CHEMICAL AND SPECTRAL STUDIES IN MODIFIED STEROIDS

RESUME

THESIS SUBMITTED FOR THE DEGREE OF
Doctor of Philosophy
IN
CHEMISTRY

SUHAIL AHMAD

DEPARTMENT OF CHEMISTRY
ALIGARH MUSLIM UNIVERSITY
ALIGARH (INDIA)
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Dated 16.4.91

This is to certify that the work embodied in this thesis entitled "Chemical and Spectral Studies in Modified Steroids" is the original work done by Mr. Suhail Ahmad under my supervision. The Thesis is suitable for submission for the award of the degree of Doctor of Philosophy in Chemistry.

(Dr. SHAFIULLAH)

ACKNOWLEDGMENT

I wish to express my heartful gratitude to Prof. M.S. Ahmad for his persistent interest, valuable suggestions and encouragement through out the course of work.

I want to record my sincere thanks to Prof. Shafiullah for his guidance, constant support and trust throughout the course of the work.

I am grateful to Prof.M.A.Beg, Chairman, Department of Chemistry, Aligarh Muslim University, for providing the necessary facilities.

I am also grateful to Dr M. Mushfiq and Dr I Naseem for their suggestions when they were needed most and my sincere thanks to all my friends especially to Dr Shahreer Ahmad and colleagues for their friendly cooperation all through.

Financial assistant provided by University Grants Commission is thankfully acknowledged.

Mr Suhail Ahmad deserves praise for his excellent wordprocessing.

A special token of deep appreciation to my family for their patience and interest in persual of my work.

(SUHAIL AHMAD)

To,
My parents

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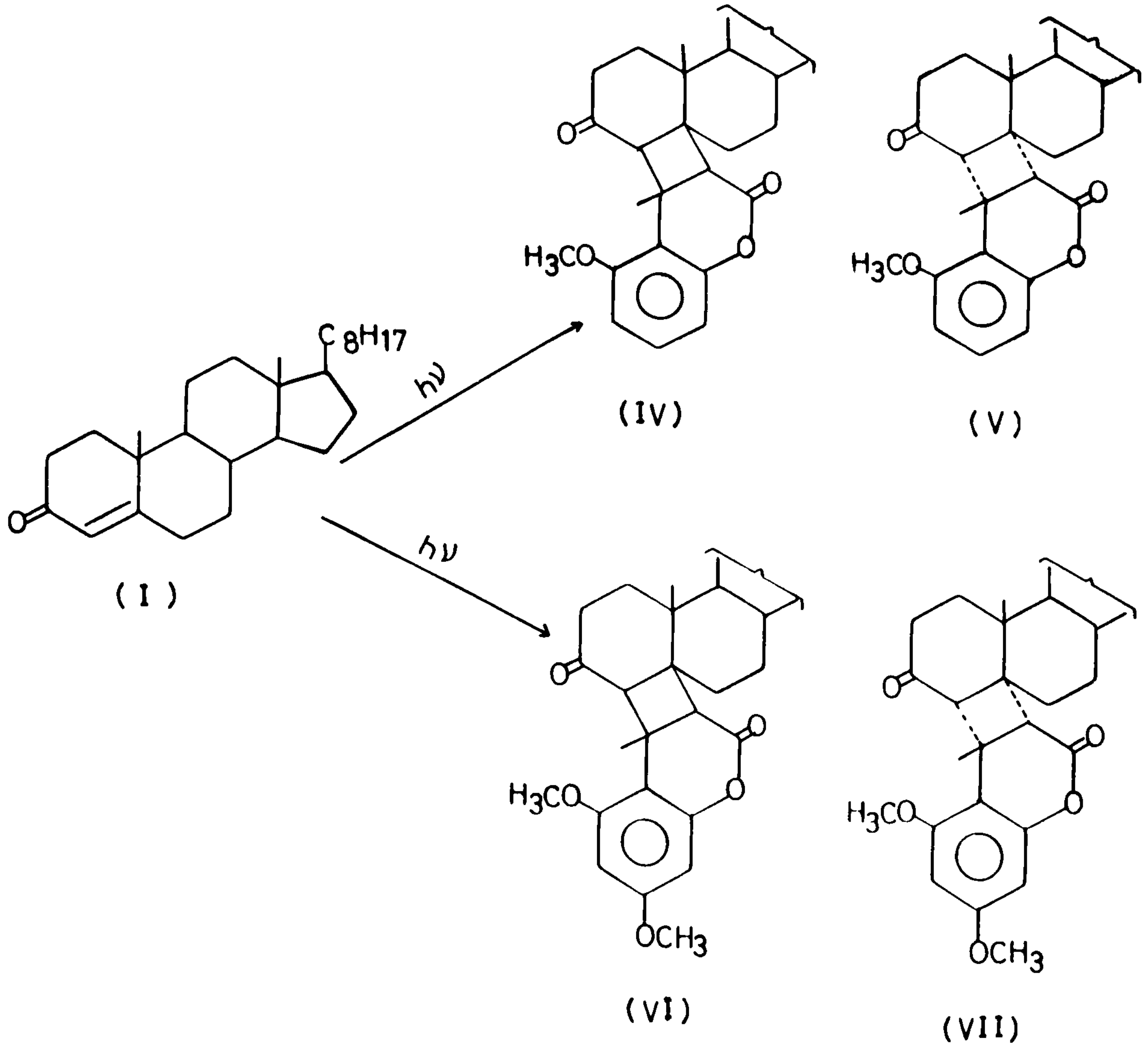
SUMMARY

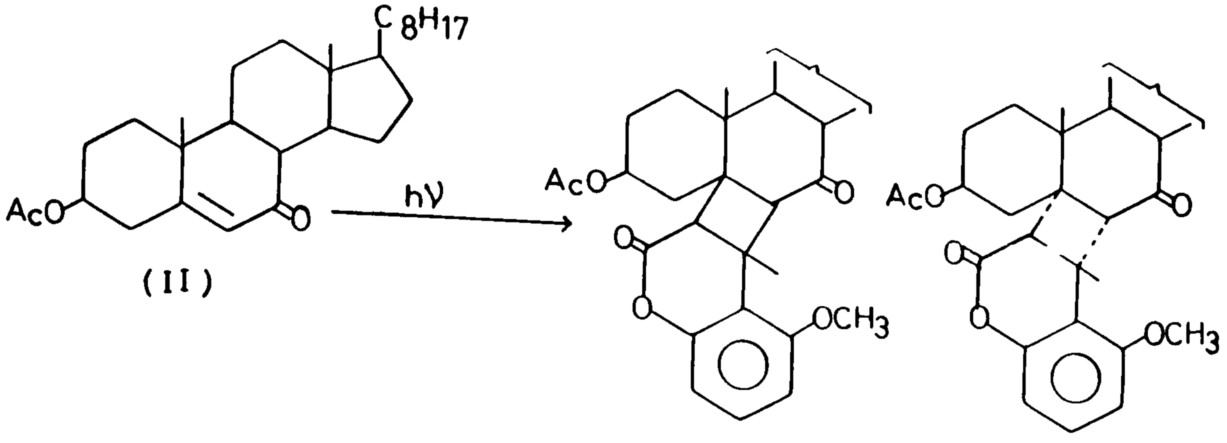
The chemistry of steroids became a matter of paramount interest in recent past because of their immense use in research and industry owing to their broad spectrum of biological properties. In this thesis, the synthesis of some important hetero steroids are described. The products obtained are characterized on the basis of analytical and spectral studies and chemical transformations. The results are summarized as below:

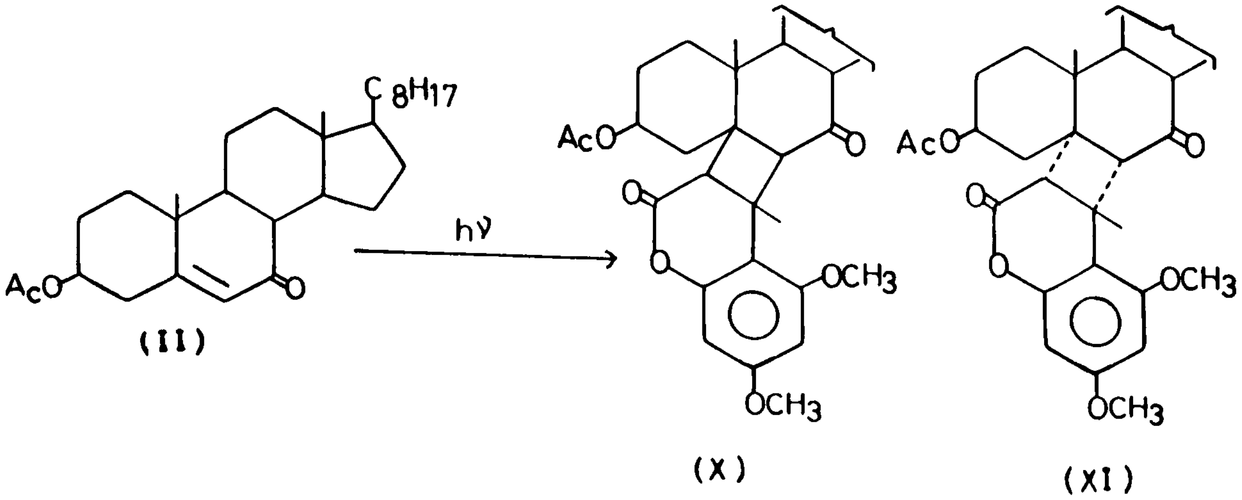
CHAPTER-ONE

PHOTOCHEMICAL ADDITION OF α,β-UNSATURATED STEROIDAL KETONES WITH SUBSTITUTED COUMARINS

Psoralens are known to photoreact with pyrimidine bases in DNA and various physiological actions are attributed with this photoreactions. There are also some of the most effective agents used in photochemotherapy of a number of skin diseases, but their use in limited due to the carcinogenicity. Recently it has been proved that psoralens formed covent C_4-photoadduct with unsaturated fatty acids, in an attempt to design safer psoralens. These therapeutic benefits prompted us to take up the syntheses of these types of photoadducts in steroids. The steroidal enones (I-III) were irradiated with 4-methyl-5-methoxycoumarin and 4-methyl-5,7-dimethoxycoumarin and obtained the following photoadducts (IV-XV).


C_8H_{17}
hν
hν
H_3CO
H_3CO
H_3CO
OCH_3
H_3CO
OCH_3
(I)
(IV)
(V)
(VI)
(VII)


C_8H_{17}
AcO
hν
AcO
OCH_3
AcO
OCH_3
(II)
(VIII)
(IX)


C8H17
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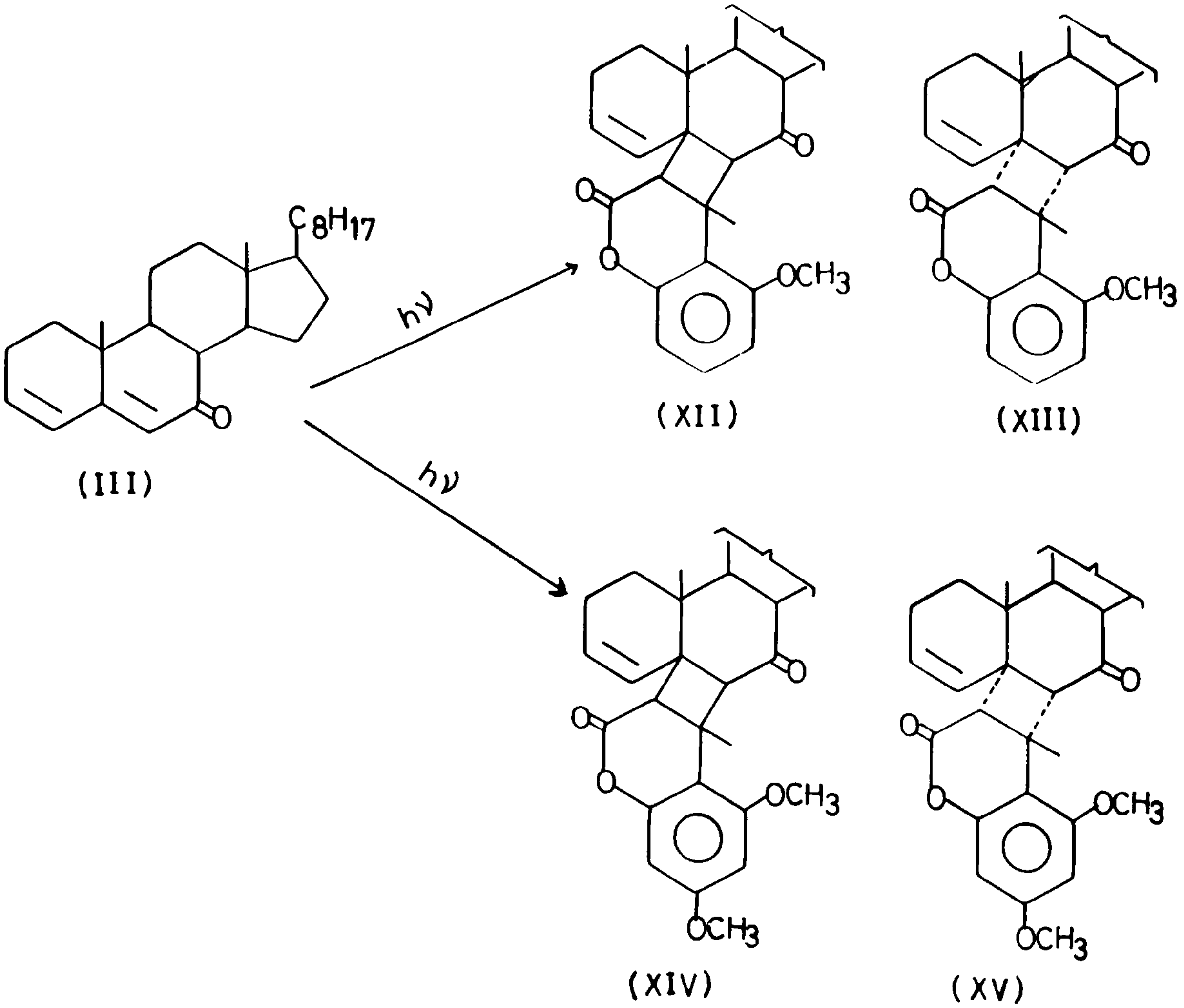
(II)
hν
AcO
OCH3
OCH3
(X)
AcO
OCH3
OCH3
(XI)


C8H17
(III)
hν
hν
OCH3
(XII)
OCH3
(XIII)
OCH3
OCH3
(XIV)
OCH3
OCH3
(XV)

CHAPTER-TWO

OXIDATION OF STEROIDAL OLEFINS

The oxidation of olefins has been utilized in the synthesis and transformation of different natural products and steroids. In most of the cases, chromium (VI), lead (IV) acetate, permanganate ion and selenium dioxide have been used as the oxidants and varying results were obtained. In the present investigation, the easily available steroidal olefins such as 3β-hydroxycholest-5-ene (XVI) its 3β -chloro (XVIII), 3β -acetoxy-(XIX) analogues, cholest-5-ene (XX), β-sitosterol (XXIV), 3β -chlorostigmst-5-ene (XXVI), 3β - -acetoxystigmast-5-ene (XXVII) and stigmasterol (XXX) have been subjected to react with silver chromate-iodine in dry dichlormethane to obtain different oxidation products.

Steroidal olefins (XVI) and (XXV) on treatment with silver chromate-iodine in dichloromethane gave ketones (XVII) and (XXV) respectively but when the olefins (XVIII-XX, XXVI and XXVII) were subjected with same reagent in same reaction conditions, they provided α-iodo ketones (XXI-XXIII, XXVIII and XXIX) and olefin (XXX) provided both α,β-unsaturated ketone as well as α-iodoketone (XXXI).

Silver chromate-iodine has proved itself an efficient and mild reagent to convert cholesterol, β-sitosterol and stigmasterol directly and quantitatively into their respective 3β -hydroxy-4-en-6-one[a] analogue, which other wise have been obtained through many step reactions.

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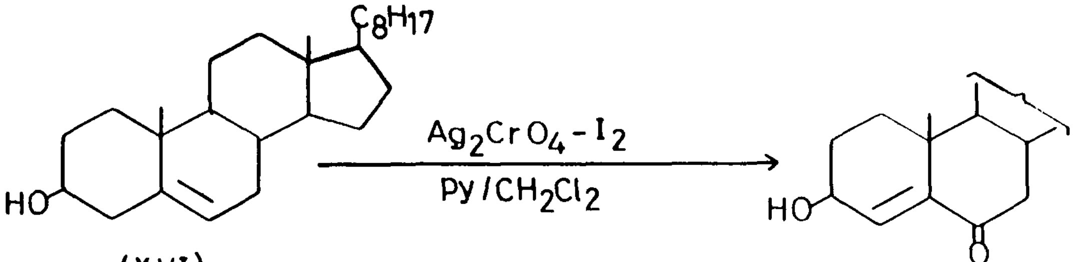
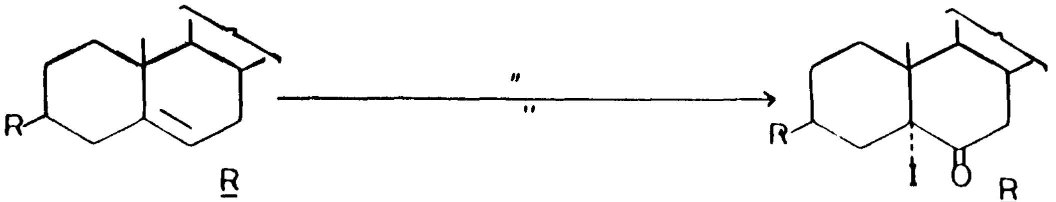
a: A convenient method for the synthesis of 3β-hydroxy-4-en-6-one steroids. J. Org. Chem., 1991, 56, 1936-37.

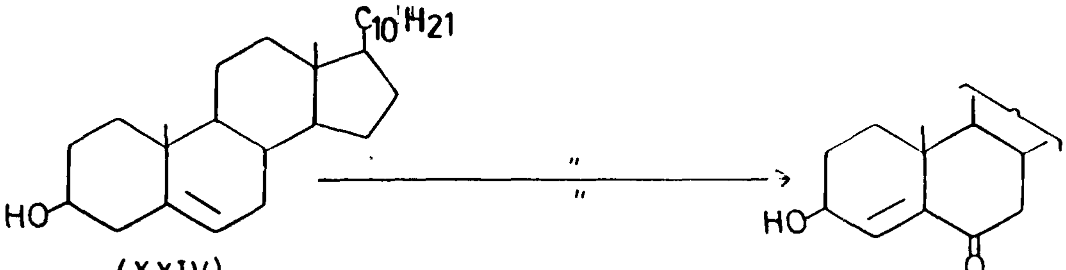


(XVI) (XVII)

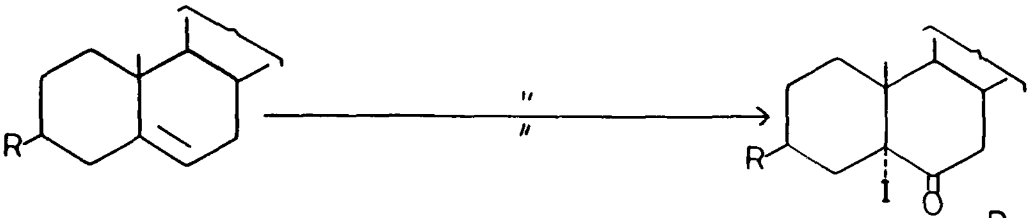


	R
(XVIII)	Cl
(XIX)	OAc
(XX)	H

	R
(XXI)	Cl
(XXII)	OAc
(XXIII)	H

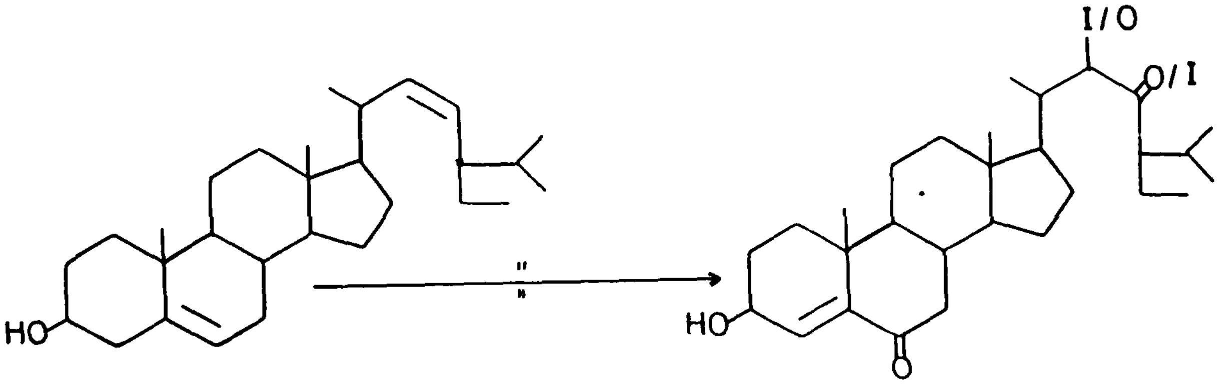


(XXIV) (XXV)



	R
(XXVI)	Cl
(XXVII)	OAc

	R
(XXVIII)	Cl
(XXIX)	OAc

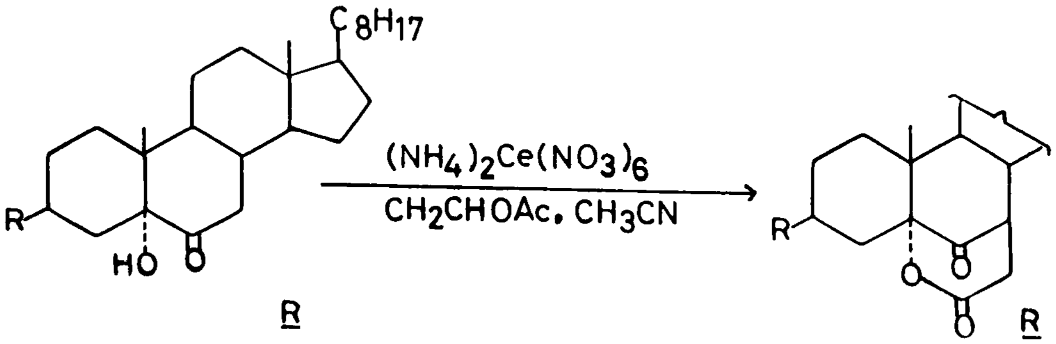


(XXX) (XXX1)

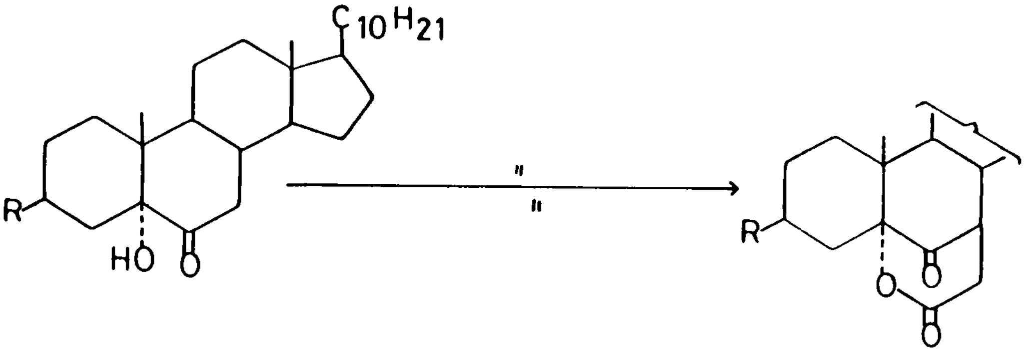
CHAPTER-THREE

SYNTHESIS OF δ-LACTONES

In recent years the addition of carbonyl compounds to alkenes promoted by one electron oxidants has attracted the attention of several research groups as a very efficient method for the synthesis of a variety of compounds. This chapter deals with the similar reactions on α-hydroxy ketones in cholestane and stigmastane series with vinyl acetate and Ce(IV) ammonium nitrate. When 5-hydroxy-5α-cholestane (XXXII), 3β-chloro-5-hydroxy-5α-cholestane (XXXIII), 3β-acetoxy-5-hydroxy-5α-cholestane (XXXIV), 5-hydroxy-5α-stigmastane (XXXVIII), 3β-chloro-5-hydroxy-5α-stigmastane (XXXIX), and 3β-acetoxy-5-hydroxy-5α-stigmastane (XL) were treated with vinyl acetate and Ce(IV) ammonium nitrate in acetonitrile, following δ-lactones (XXXV-XXXVII and XLI-XLIII) were obtained. The structure of these lactones was established on the basis of analytical and spectral data.



	R		R
(XXXII)	H	(XXXV)	H
(XXXIII)	Cl	(XXXVI)	Cl
(XXXIV)	OAc	(XXXVII)	OAc



	R		R
(XXXVIII)	H	(XLI)	H
(XXXIX)	Cl	(XLII)	Cl
(XL)	OAc	(XLIII)	OAc

CHAPTER-FOUR

SYNTHESIS OF STEROIDAL TETRAZOLE

Steroidal tetrazoles became of interest in recent past, because of the discovery of various biological activities associated with a number of tetrazoles. As a result of this realization, synthesis of tetrazole became a matter of interest.

The present work describes the preparation of tetrazoles from various steroidal olefins (XVIII-XX) and steroidal oxiranes (L-LII). When steroidal olefins such as cholest-5-ene (XX), and its 3β-chloro (XVIII) and 3β-acetoxy (XIV) analogues were treated with bromine and sodium azide in presence of anhydrous aluminium chloride using acetonitrile as solvent α-bromo tetrazoles (XLIV-XLVI)[b] alongwith α-bromoamides (XLVII-XLIX)[b] were obtained. In the similar manner when steroidal oxiranes such as $5,6\alpha$-epoxy-5α-cholestane (L), its 3β-chloro (LI) and 3β- acetoxy (LII) analogues were treated with sodium azide in presence of anhydrous aluminium chloride using acetonitrile as solvent -hydroxy tetraoles (LII-LV)[c] were obtained.

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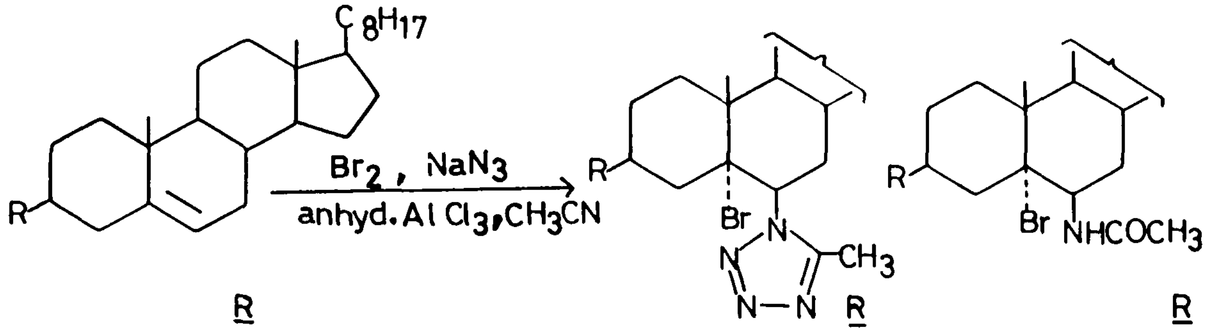
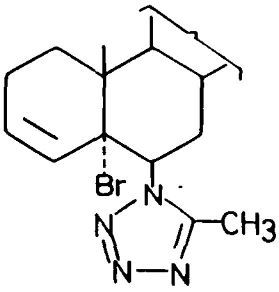
[b] Synthesis of steroidal tetrazoles; Ind. J.Chem, 1988, **27B**, 1136-1137.

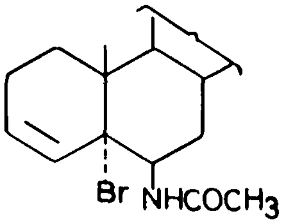
[c] Synthesis of steroidal substituted tetrazoles; Acta, Chimica, Hung; 1990, 127(3). 391-393.



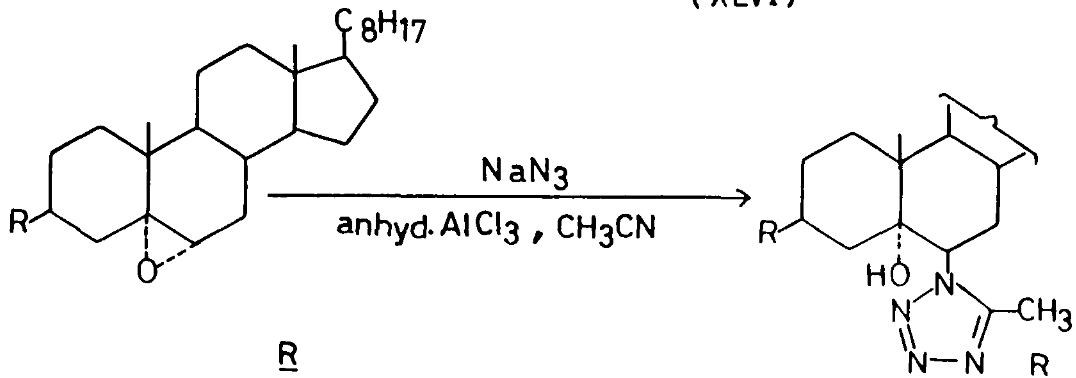
	R		R		R
(XX)	H	(XLIV)	H	(XLVII)	H
(XVIII)	Cl	(XLV)	Cl	(XLVIII)	Cl
(XIX)	OAc				



(XLVI)



(XLIX)



	R		R
(L)	H	(LIII)	H
(LI)	Cl	(LIV)	Cl
(LII)	OAc	(LV)	OAc

INTRODUCTION

The close association of steroids with the physiological phenomena of life imparted the significant picture in the field of organic chemistry. Steroids are found wide spread in nature, for instance cholesterol, sex hormones, adrenal cortex, hormones, bile salts, oestrogens, Vitamin D, sapogenin and some other important metabolites. They are numerously occurred and show a wide range of properties. The incentive feature of steroids is that they can be prepared easily in laboratory and can even be synthesized in large scale. The emergence of the field of steroids as a research area, actually was the impact of the discovery of testosterone which showed marked biological properties. The interest of scientists diverted towards the other steroids and the work on isolation as well as on synthesis started with great enthusiasm. Thereafter researchers diversified their efforts to evaluate the structural and stereo-chemical problems of steroidal skeleton. This particular area of research was proved to be of much interest because of the unique spatial requirements of the steroid molecule. Structure elucidation and the aspects of reaction mechanism in steroids became a matter of immense interest later on.

The fusion of any heterocylic ring system to steroids or to introduce any hetero atom such as sulpher, oxygen, nitrogen or halogen found to augment the biological and industrial range of them. Hence innumerable methods started developing across the world to find the better substitutes for already existing steroids. As a matter of fact steroid chemistry was always proved to be much inviting to chemists and industries fascinated us to under take the work in this direction.

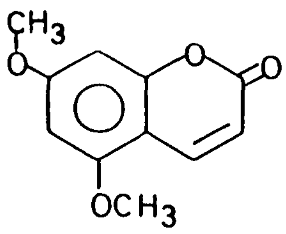
CHAPTER ONE

Photochemical addition of α,β-unsaturated steroidal ketones with substituted coumarins

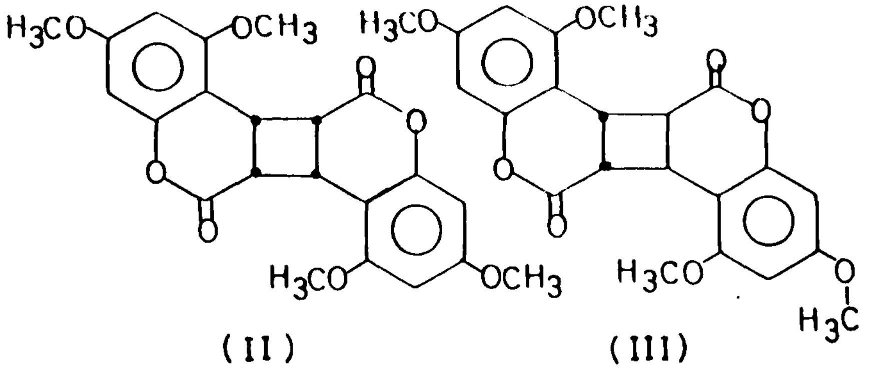
THEORETICAL

The photon has played a role in the synthesis since the beginnings of organic chemistry. In the earliest photochemical experiments, ordinary sunlight was used as the source of radiant energy and consequently, with few exceptions, complex mixtures of products were formed. This feature no doubt contributed significantly to the reluctance of organic chemists, until recently, to utilise photochemical methods in synthesis. The experimental technique has become more sophisticated now compared to the beginnings (i.e. precise excitation wave length and mercury vapour lamps are used routinely), combined with improved methods of products isolation and structure determination. These features have resulted in more and more synthetic chemists treating the photon as a routine 'Off-the-shelf' reagent. Reactions such as the Paterno-Buchi reaction[1] and photoannelation of cyclohexenones[2] with simple olefins afford numerous examples of compounds accessible at best with difficulty by other routes. The formation of α-truxillic vs β-truxinic acid from different crystals modifications of cinnamic acid is a landmark of our knowledge of chemistry of the organic solid state.[3,4] The dimerization of pyrimidine residues such as thymine is one of the principal reactions responsible for UV inactivation of genetic material in vivo.[5] The [2+2] photocycloaddition reactions are extensively reviewed.[6-8]

Shim et al.[9] reported, dimerization of 5,7-dimethoxycoumarin (I) through C_4-photo cycloaddition of 3,4-double bond and obtained the following cycloadducts (II and III).

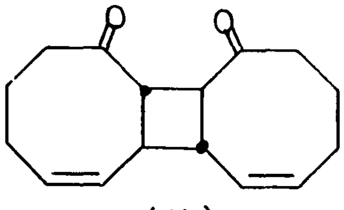


(I)

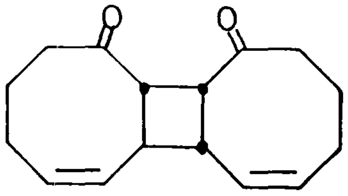


(II) (III)

Lange and Neidert[10] irradiated 2,4-cyclooctadienone (IV) and afforded following photoproducts (V-IX).



(V)



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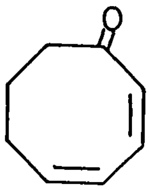

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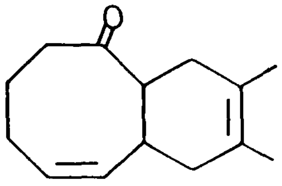

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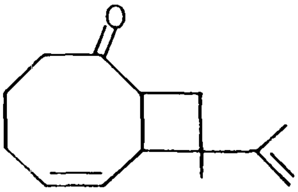

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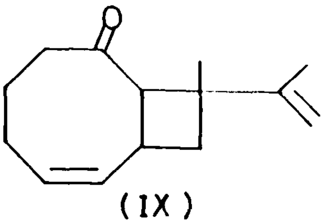
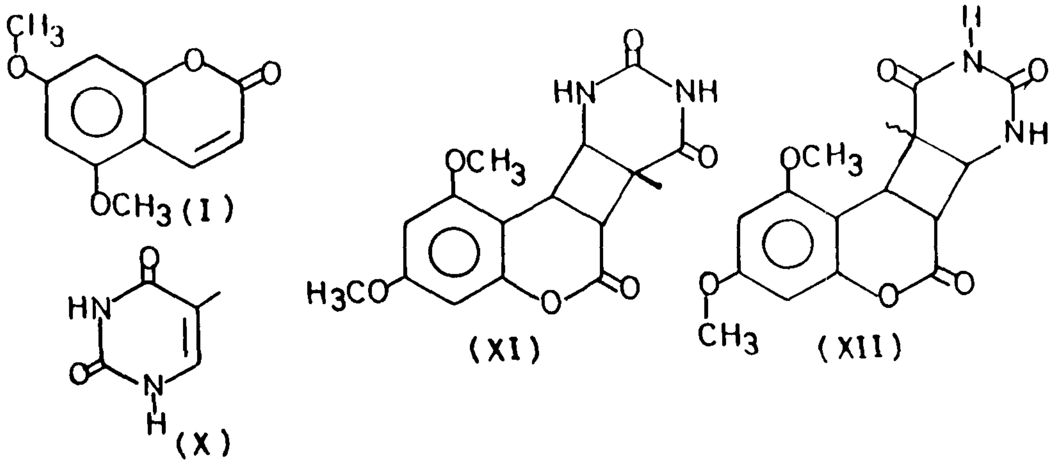


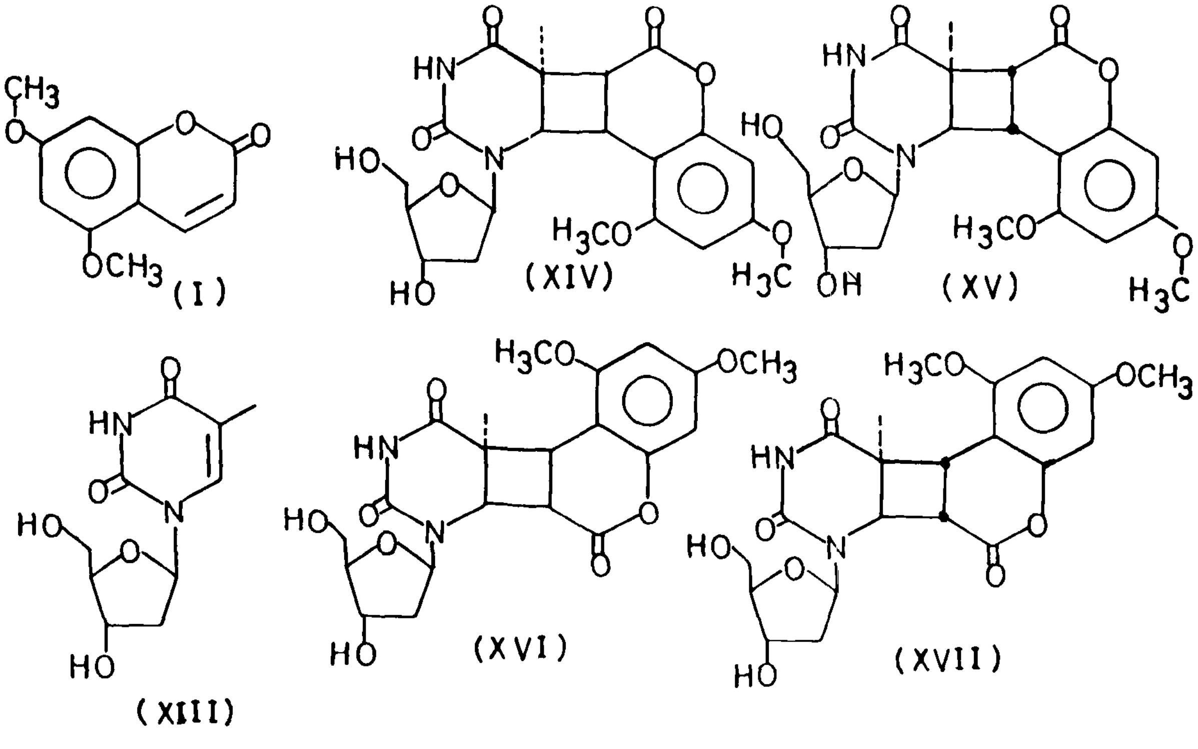
(IX)

Photocycloaddition of 5,7-dimethyoxycoumarin (I) to thymine (X) furnished 1:1 C_4-cycloadduct[11] of DMC and thymine (XI or XII).



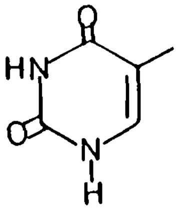
(I) (X) (XI) (XII)

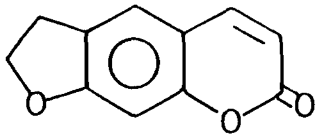
Photocyloaddition reaction of 5,7-dimethoxycoumarin (I) to thymidine (XIII) afforded four different stereoisomers (XIV-XVII).[12]



(I) (XIII) (XIV) (XV) (XVI) (XVII)

The photocycloaddition reaction of 4', 5'-dihydropsoralen (XVIII) with thymine (X) furnished a 1:1 C_4-cycloaddition product (XIX).[13]


(X)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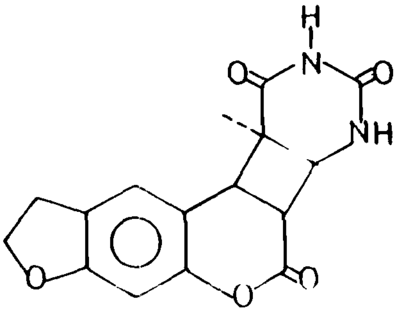
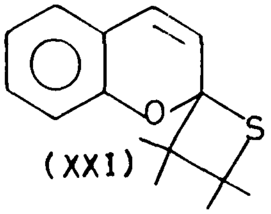
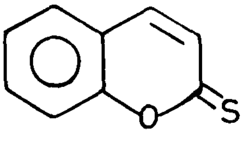

(XIX)

Devanathan and Ramamurthy[14] irradiated thiocoumarin (XX) with electon-rich and electron-deficient olefins from T_1 and obtained C_4-cycloadduct (XXI-XXVIII), formed through [2+2] addition reaction between C=S of thiocoumarin and olefin, instead of 4,5-double bond of thiocoumarin and olefin.


(XXI)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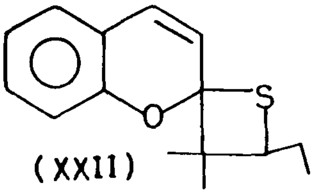
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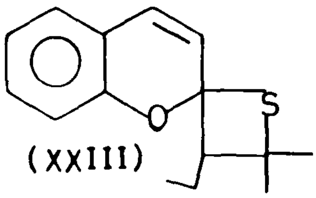
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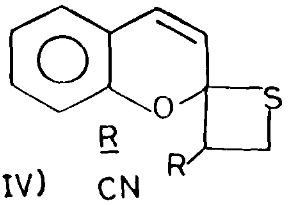
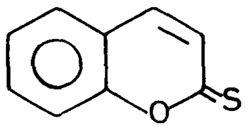


	R
(XXIV)	CN
(XXV)	$COOCH_3$
(XXVI)	$OCOCH_3$



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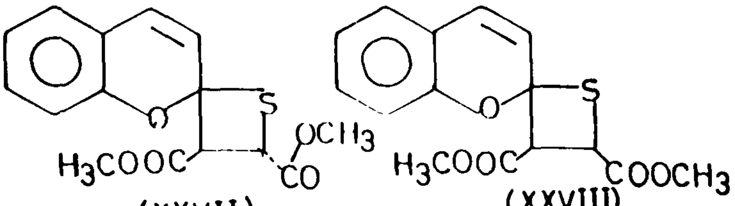
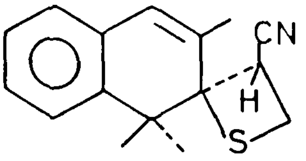


(XXVII) (XXVIII)

Rao and Ramamurthy[15] reported the photocycloaddition of α,β-unsaturated thione (XXIX) with electron deficient olefins from higher excited states and obtained the following cycloadducts (XXX-XLIII).



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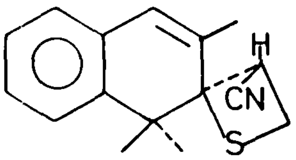

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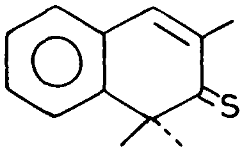

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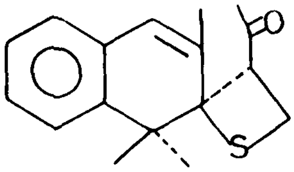

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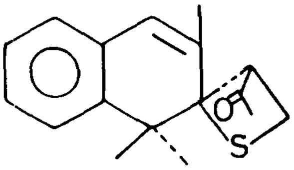
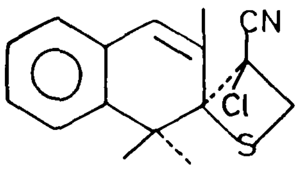
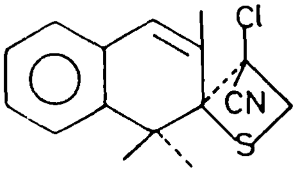


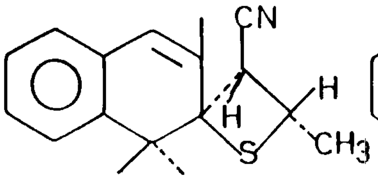
(XXIII)



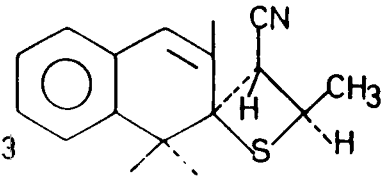
(XXXIV)



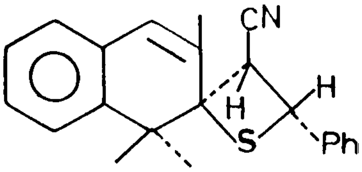
(XXXV)



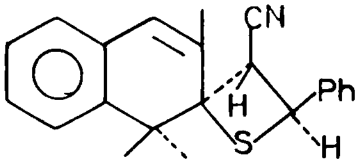
(XXXVI)



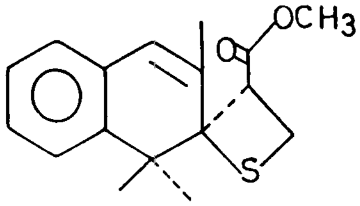
(XXXVII)



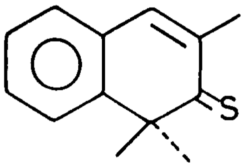
(XXXVIII)



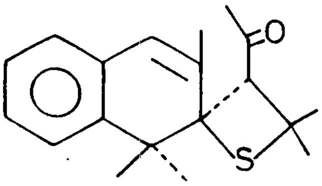
(XXXIX)



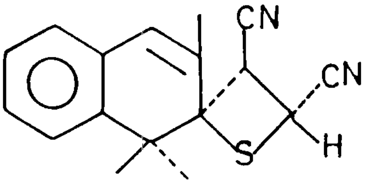
(XL)



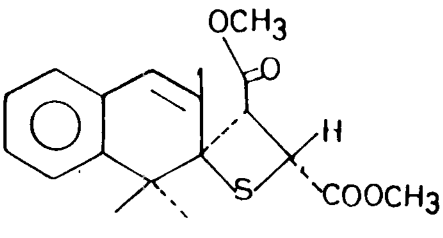
(XXIX)



(XLI)

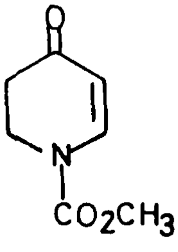


(XLII)

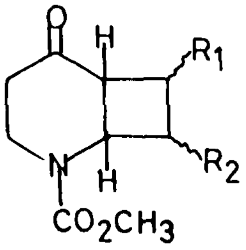


(XLIII)

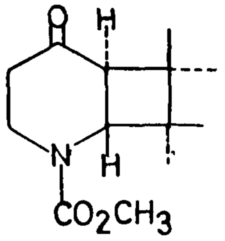
Guerry and Neier[16] reported the photochemical [2+2] cycloaddition to N-methoxycarbonyl-5,6-dihydro-4-pyridone (XLIV) with olefins and obtained following C_4-cycloadducts (XLV-XLVII).



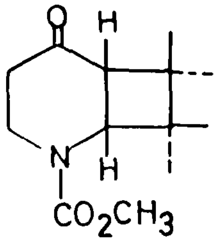
(XLIV)



(XLV)

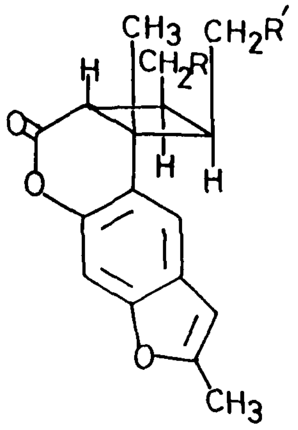


(XLVI)

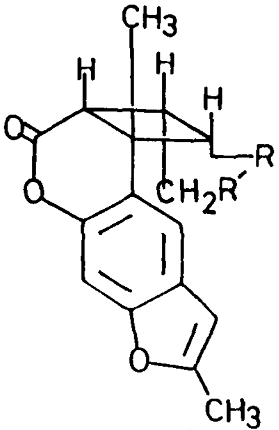


(XLVII)

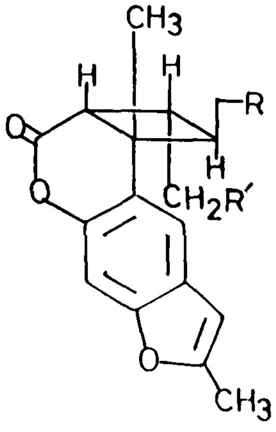
Photocycloaddition of 4,5',8-trimethylpsoralen and oleic acid methyl ester furnished following C_4-cycloadducts (XLVIII-LI).[17]



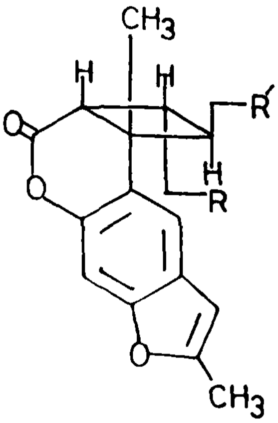
(XLVIII)



(XLIX)



(L)

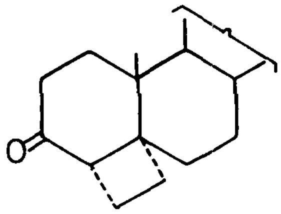


(LI)

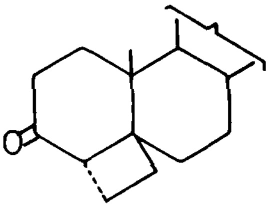
$R = -(CH_2)_6COOCH_3$

$R' = -(CH_2)_6CH_3$

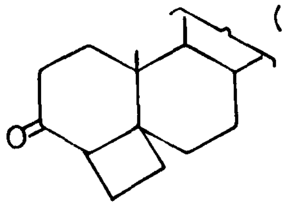
The photocycloaddition of 3-keto-4-ene steroid (LII) to cyclic and acylic olefins were reported by Lenz.[18] In this way following [2+2] photocycloadducts (LIII-LXX) were obtained.



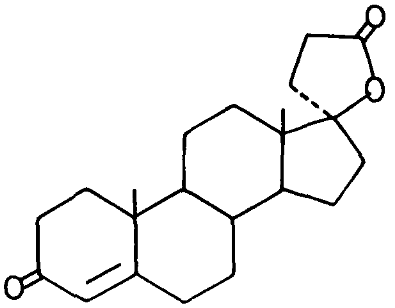
(LIII)



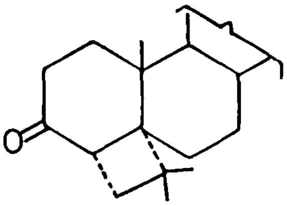
(LIV)



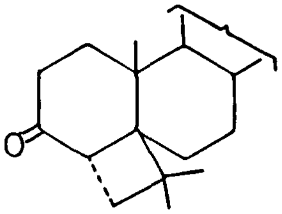
(LV)



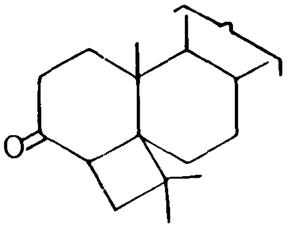
(LII)



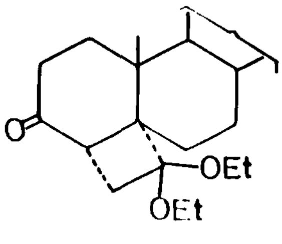
(LVI)



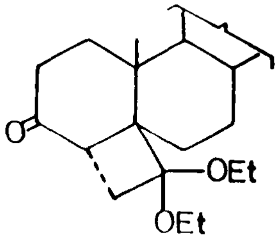
(LVII)



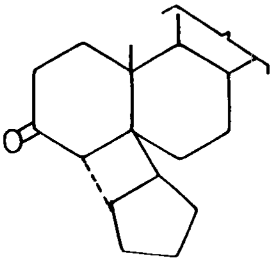
(LVIII)

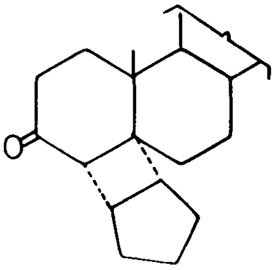


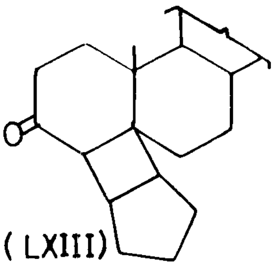
(LIX)

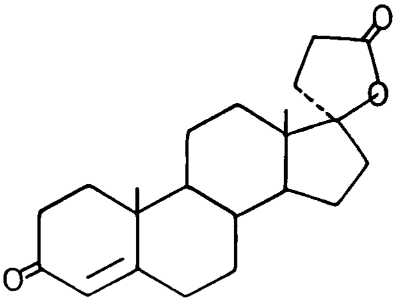


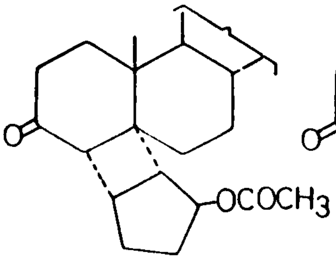
(LX)

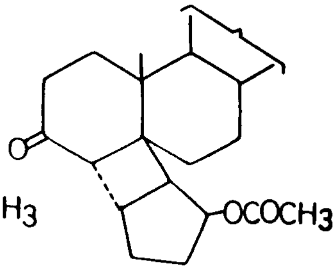

(LXI)

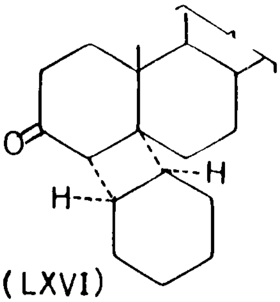

(LXII)

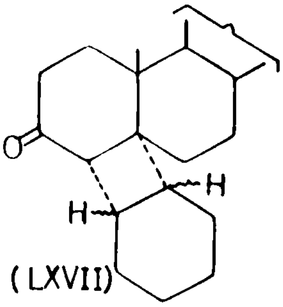

(LXIII)

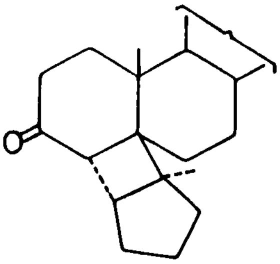

(LII)

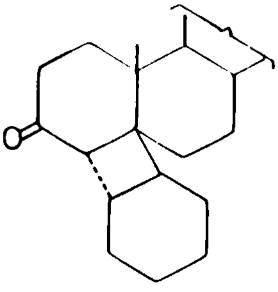

(LXIV)

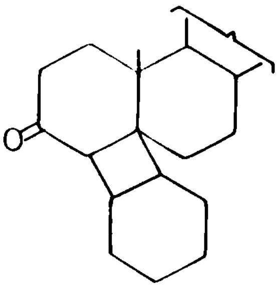

(LXV)


(LXVI)

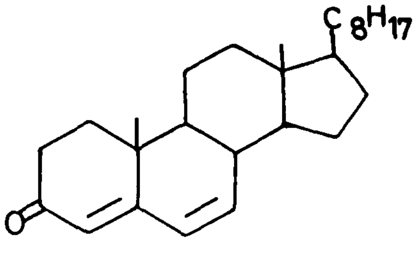

(LXVII)


(LXX)

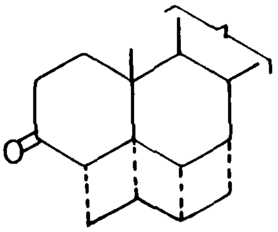

(LXVIII)


(LXIX)

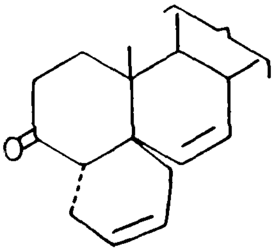
Lenz[19] described the photocycloaddition of 3-keto-4,6-diene (LXXI) to butadiene and obtained the following products (LXXII-LXXVI).



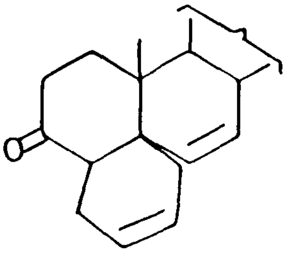
(LXXI)



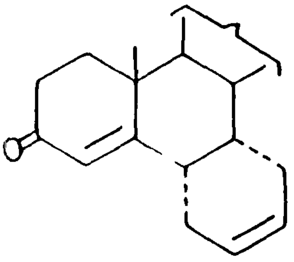
(LXXII)



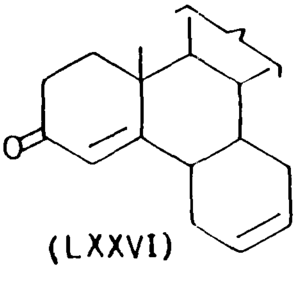
(LXXIII)



(LXXIV)

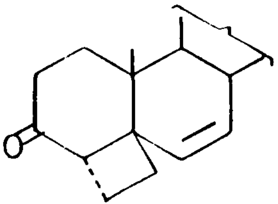


(LXXV)

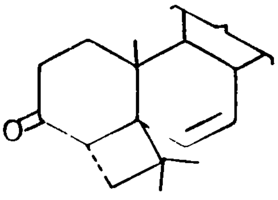


(LXXVI)

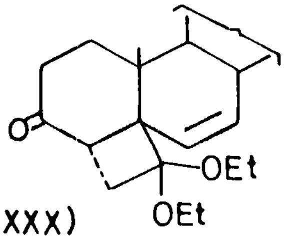
The singlet photocycloaddition of 3-keto-4,6-dienic steroids (LXXVII) to cyclic and acyclic olefins afforded only 4 , 5 -trans-substituted cyclobutanes as the head-to-tail adducts (LXXVIII-LXXXVI). [20]



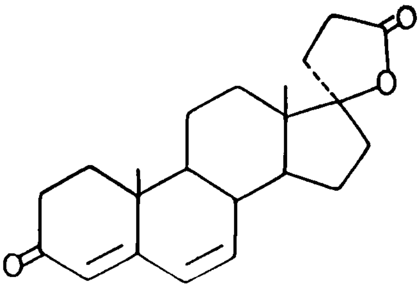
(LXXVIII)



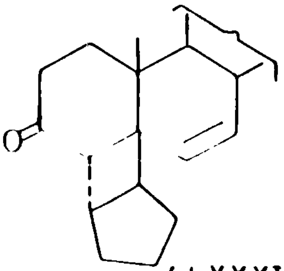
(LXXIX)



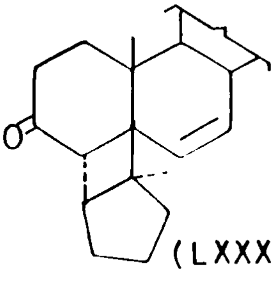
(LXXX)



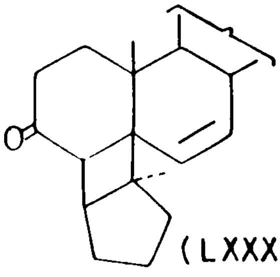
(LXXVII)



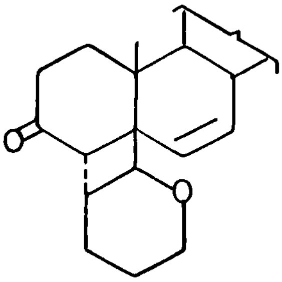
(LXXXI)



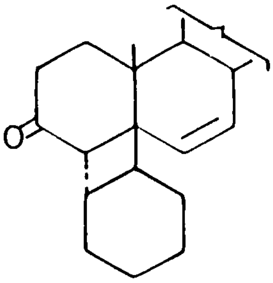
(LXXXII)



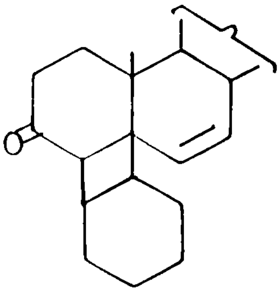
(LXXXIII)



(LXXXVI)

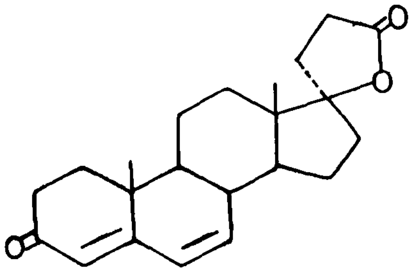


(LXXXIV)

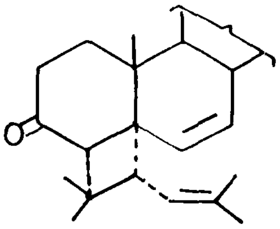


(LXXXV)

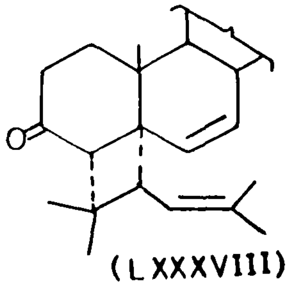
Lenz[21] studied the photocycloaddition of 3-keto-4,6-dienic steroids (LXXVII, XCI) to dienes incapable of undergoing Diels-Alder reaction and yielded these [2+2] adducts (LXXXVII-XCV).



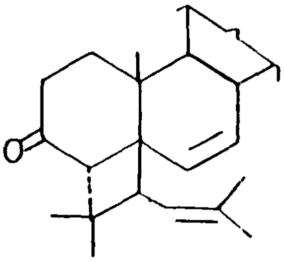
(LXXVII)



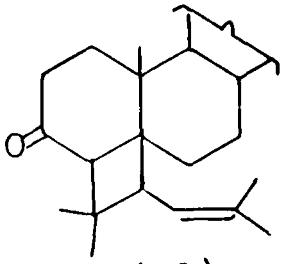
(LXXXVII)



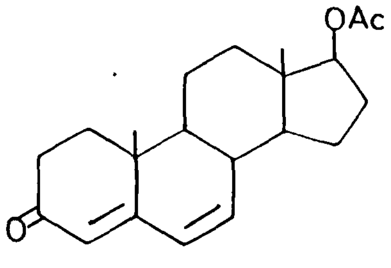
(LXXXVIII)



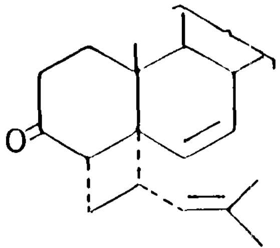
(LXXXIX)



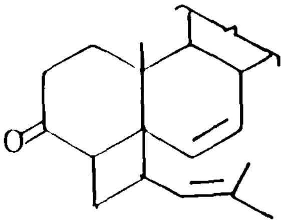
(XC)



(XCI)



(XCII)



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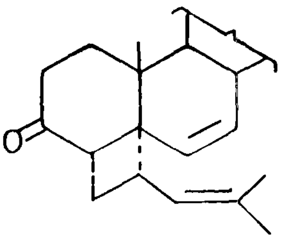
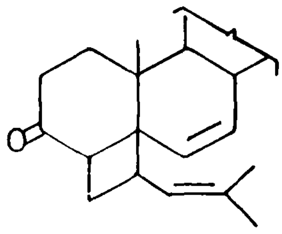
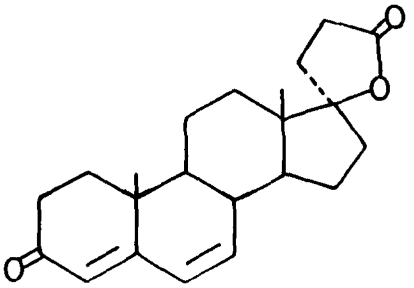


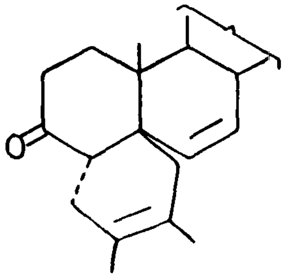
(XCIV)

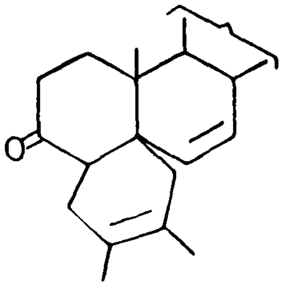


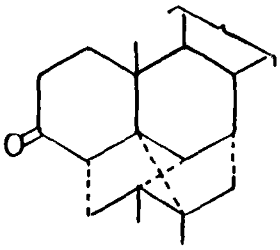
(XCV)

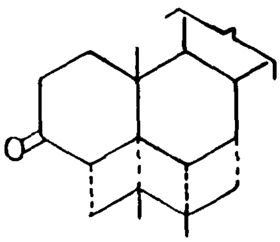
Lenz[22] reported the photocycloaddition of cyclopropylenones, and cyclodienones to dienes and obtained $[\pi 2 + \pi 2 + \pi 2 + \pi 2]$ addition products (XCVI-C).

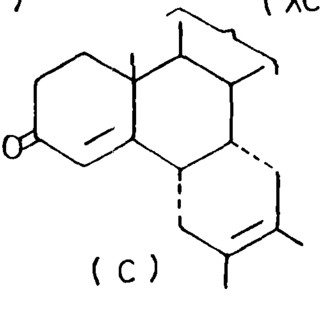

(LXXVII)


(XCVI)

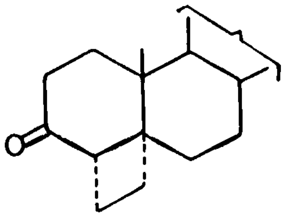

(XCVII)

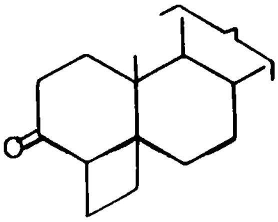

(XCVIII)


(XCIX)


(C)

Farwaha et al.[23] reported photocycloaddition of enone (CI) to olefins on silica gel and alumina and obtained following photoadducts (CII-CX).


(CII)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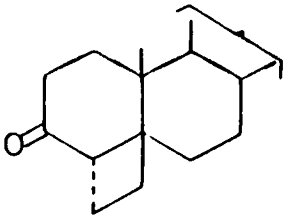
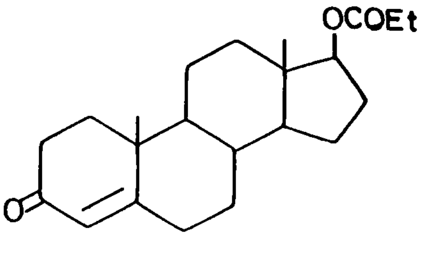
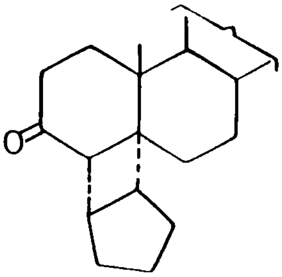
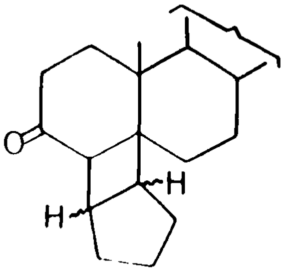

(CIV)

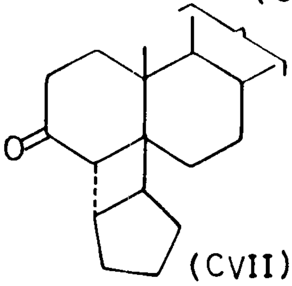


(CI)


(CV)



(CVI)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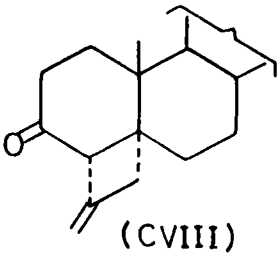
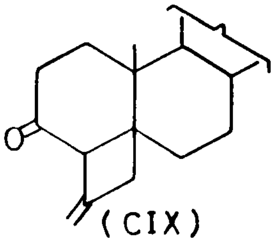
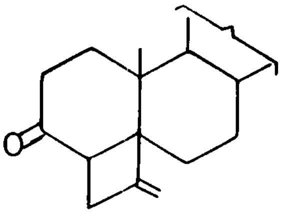

(CVIII)

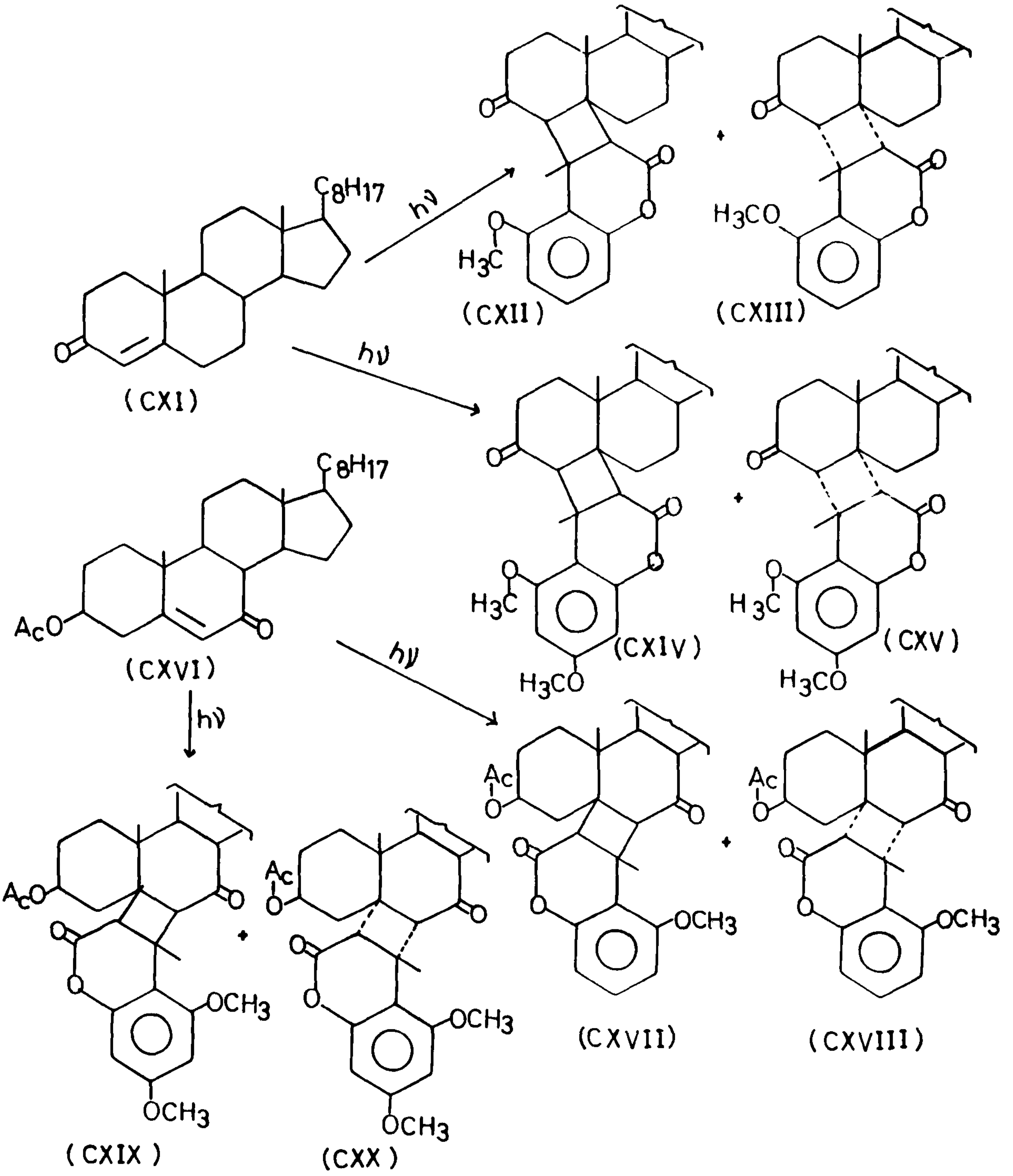

(CIX)

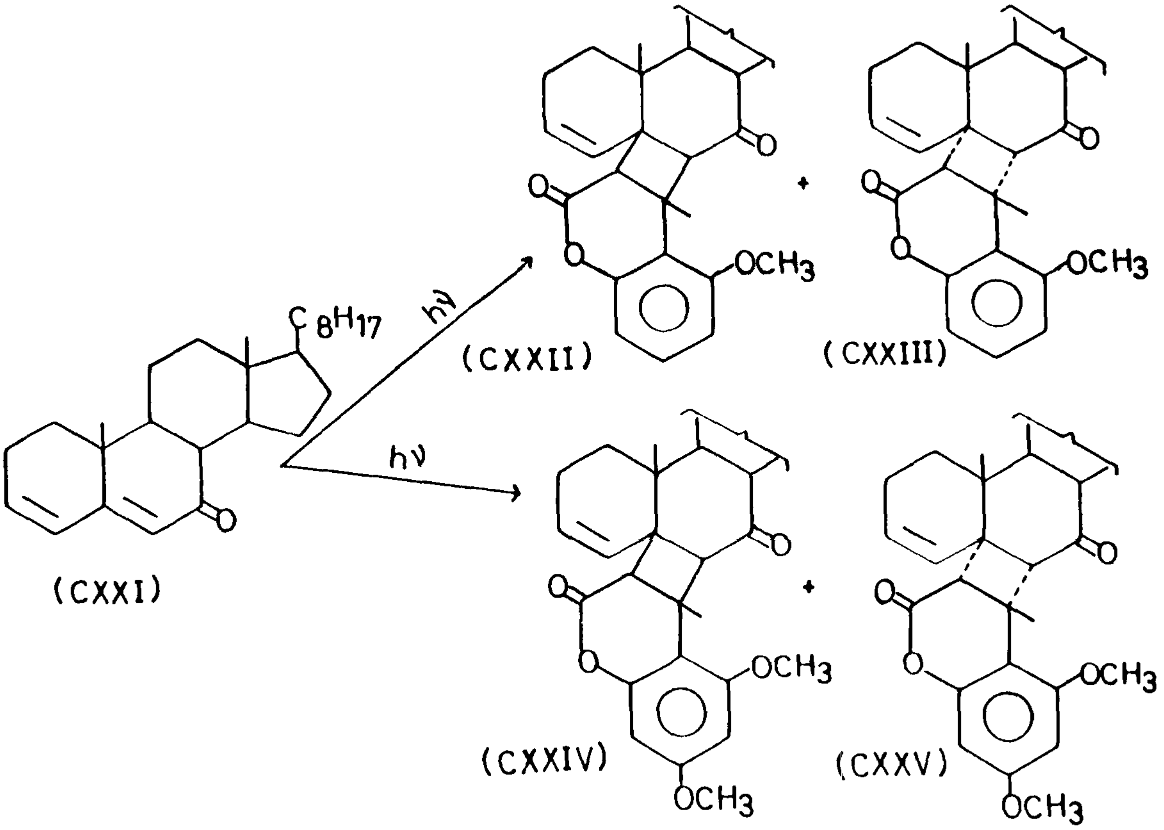

(CX)

DISCUSSION

Psoralens, naturally occurring coumarin derivatives are known to photoreact with pyrimidine bases in DNA under irradiation with near UV light. Various physiological actions such as erythema on human and guinea pig skin, mutagenic and lethal effects in bacteria, inactivation of DNA viruses, inhibition of tumor transmitting capacity of various tumor cells, and disorder in the development of sea urchin eggs fertilized with sperm have been attributed to this photoreaction[24,25]. Psoralens are some of the most effective agents available for the photochemotherapy of a number of skin diseases such as psoriasis and vitiligo.[26] The therapeutic benefit of this treatment is thought to be due to the inhibition of hyperproliferation of skin keratinocytes. The use of Psoralens is limited due to the carcinogenicity.[27] Psoralens photochemically add to the unsaturated function of pyrimidines bases in DNA forming cyclobutyl-linked adduct.[28-32] Recently it has been proved that psoralens also formed covalent C_4-photoadduct with unsaturated fatty acid[33-35], in an attempt to design safer psoralens that lack the ability to bind to DNA and the associated carcinogenicity while retaining the ability to bind with lipids and the therapeutic benefit.

These therapeutic benefits prompted us to take up the synthesis of these types of photoadducts in steroids. The steroidal enones (CXI, CXVI and CXXI) on irradiation with 4-methyl-5,7-dimethoxy coumarin and 4-methyl-5-methoxy coumarin furnished the following C_4-cyclobutyl-linked steroidal adducts (CXII-CXV, CXVII-CXX and CXXII-CXXV).

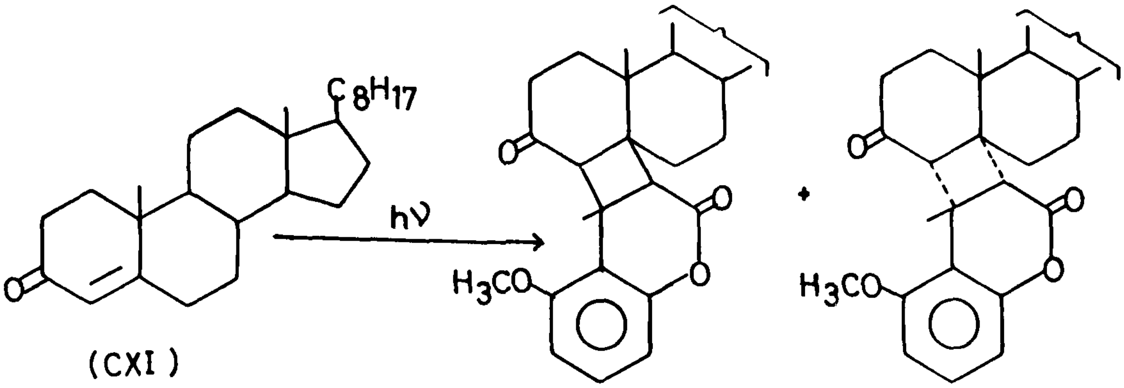




Photochemical Reaction of α,β-unsaturated ketones with substituted coumarins

Reaction of cholest-4-en-3-one (CXI) with 4-methyl-5-methoxy coumarin

In a petri-dish silica gel G was taken and cholest-4-en-3-one (CXI) and 4-methyl-5-methoxy coumarin were added along with dry dichloromethane. The resulting solution was concentrated quickly to dryness. The thin and dry film of the substance was obtained. The dry substance in the petri-dishes were placed under 450-W medium pressure Hg lamp arranged at a 15 cm distance in horizontal position. After irradiating for 30 min. the dry substances were dissolved in dry dichloromethane and the solvent was evaporated to form a dry film again and irradiated. This process was repeated several times and progress of reaction was monitored by TLC. After the irradiation, the mixture was taken in dichloromethane and filtered and the solvent was evaporated. The crude photolysis products were chromatographed over a silica gel column to afford two major photoproducts having m.p.s. 139-140°C and 160-161°C.



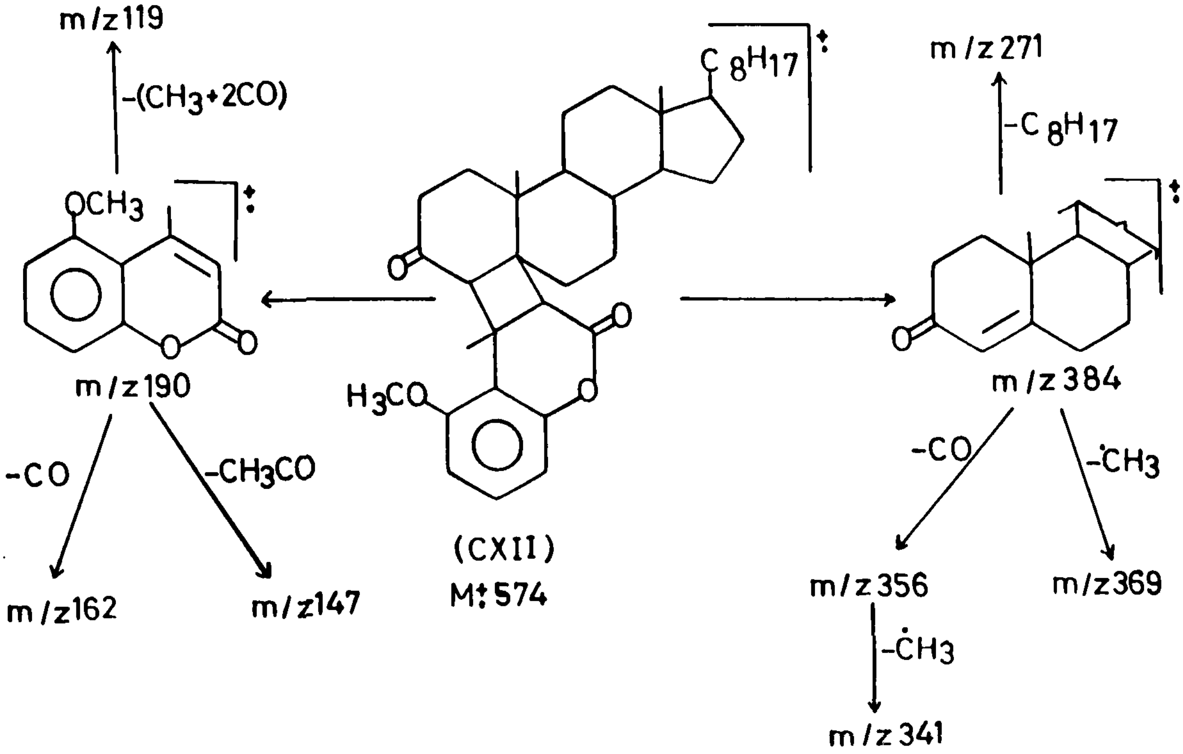
(CXI)

(CXII) (CXIII)

Characterization of the compound having m.p. 139-140°C as 1:1 C_4-photoadduct (CXII) of 4-methyl-5-methoxy coumarin and cholest-4-en-3-one

The compound with m.p. 139-140°C was analysed for $C_{38}H_{54}O_4$. In its IR spectrum the bands appeared at 1750 (carbonyl of coumarin), 1715 (C=O), 1595 (C=C, aromatic), and 830 cm^{-1} (cyclobutane). The ^1H-NMR spectrum exhibited a multiplet at δ 6.4 integrating for three protons and was assigned to the aromatic protons. A sharp singlet for three protons appeared at δ 3.9, and was assigned to the methoxy protons. Two singlets appeared at δ 3.8 and 3.72 integrating for one proton each and were assigned to the cyclobutane protons. These singlets show that the [2+2] addition is head-tail. The methyl protons of cyclobutane ring appeared at δ 1.5 as a singlet. The other methyl protons appeared at δ1.15 (C10-CH_3), 0.69 (C13-CH_3), 0.93 and 0.81 (other side chain methyl protons). The sign and magnitude of cotton effect in circular dichroism was $[\theta]_{293}=-1457$. The mass spectrum of (CXII) shows molecular ion peak and other fragment ion peaks at m/z 574 ($M^{+\cdot}$), 384, 369, 356, 341, 271, 190, 162, 147 and 119 as rationalized in scheme. On the basis of above evidences, the compound having m.p. 139-140°C was characterized as 1:1 C_4-photoadduct (CXII).

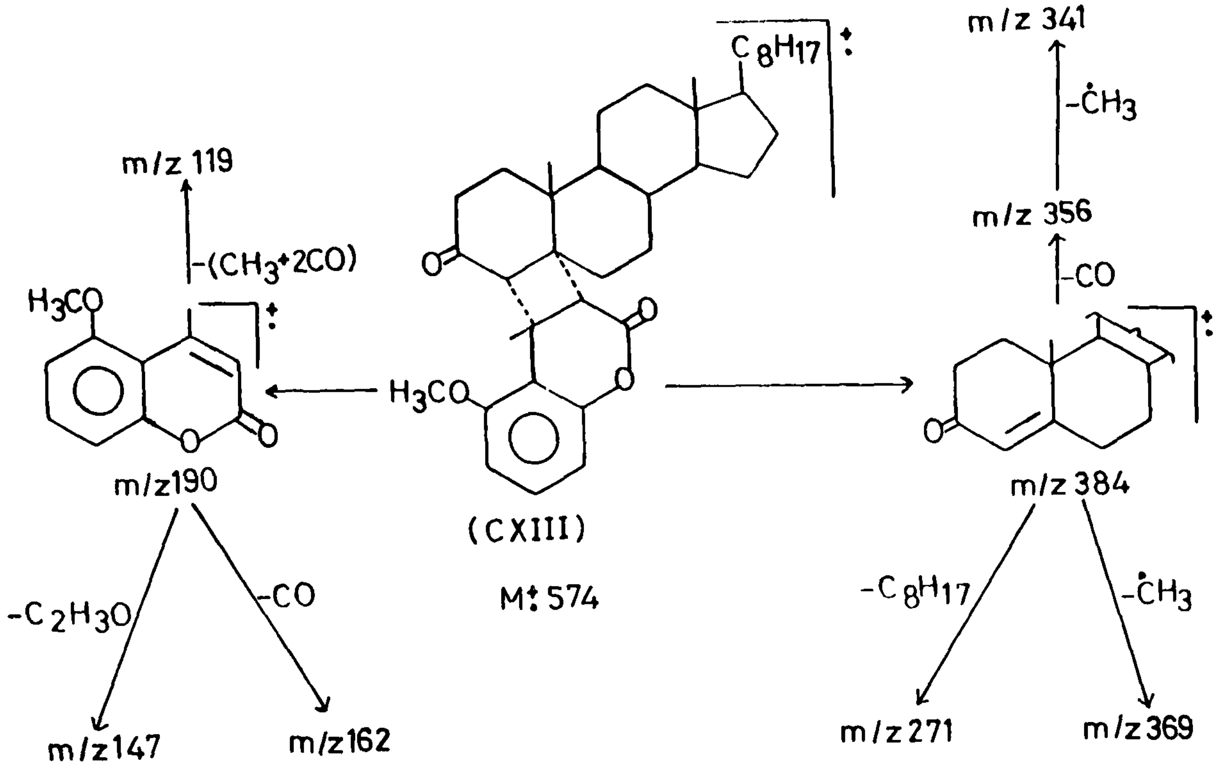
Scheme



Characterization of the compound with m.p. 160-161°C as 1:1 C_4-photoadduct (CXIII) of 4-methyl-5-methoxy coumarin and cholest-4-en-3-one

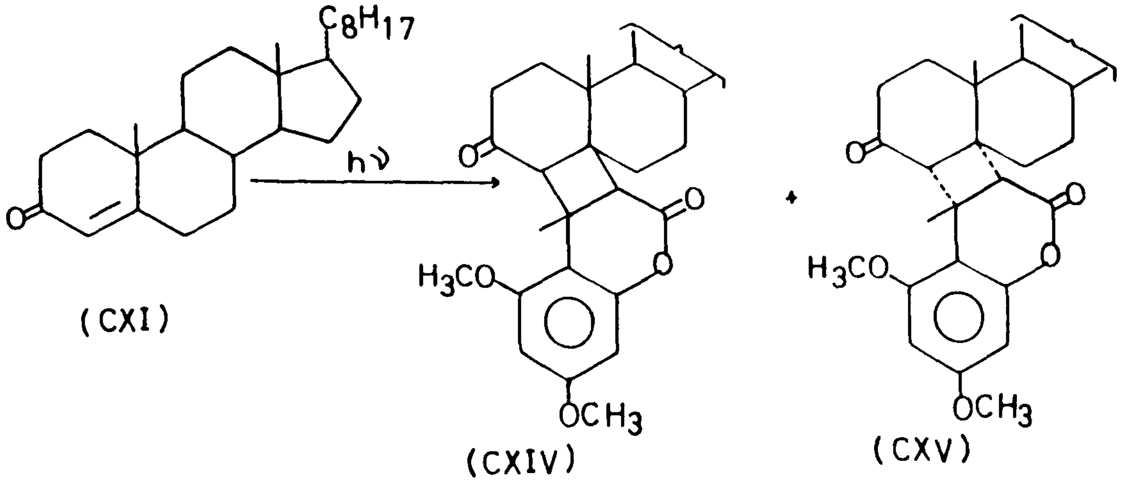
The compound having m.p. 160-161°C was analysed for $C_{38}H_{54}O_4$. In its IR spectrum, the bands appeared at 1760 (carbonyl of coumarin), 1710 (C=O), 1600 (C=C, aromatic), and 840 cm^{-1} (cyclobutane). The ^1H-NMR spectrum exhibited a multiplet centered at δ6.5 integrating for three protons and was assigned to the aromatic protons. The methoxy protons appeared as a singlet at δ 3.95. Two singlets appeared at δ3.85 and 3.78 for one proton each and were assigned to cyclobutane protons, suggesting that the adduct is head-tail. The methyl protons of cyclobutane ring appeared at δ 1.4 as a singlet. The remaining methyl protons appeared at δ 1.2 ($C10-CH_3$), 0.67 ($C13-CH_3$), 0.9 and 0.84 (other side chain methyl protons). The sign and magnitude of cotton effect in circular dichroism was $[\theta]_{291}= +2328$. The mass spectrum of (CXIII) showed molecular ion peak and other fragment ion peaks at m/z 574 ($M^{+\cdot}$), 384, 369, 356, 341, 271, 190, 162, 147 and 119 as rationalized in scheme. On the basis of above evidences, the compound having m.p. 160-161°C was characterized as 1:1 C_4-photoadduct (CXIII).

Scheme



Reaction of cholest-4-en-3-one (CXI) with 4-methyl 5,7-dimethoxycoumarin

Cholest-4-en-3-one (CXI) and 4-methyl-5,7-dimethoxycoumarin were absorbed on silica gel G. The resulting thin and dried film in petri-dishes were irradiated as usual. After irradiating for 30 min, the film was reformed and irradiated. This process was repeated several times and progress of reaction was monitored by TLC. After the irradiation, the mixture was taken in dichloromethane, filtered and chromatographed over silica gel column as described earlier. Two major photocycloadducts were obtained having m.p.s. 152-153°C and 164-165°C.



(CXI)

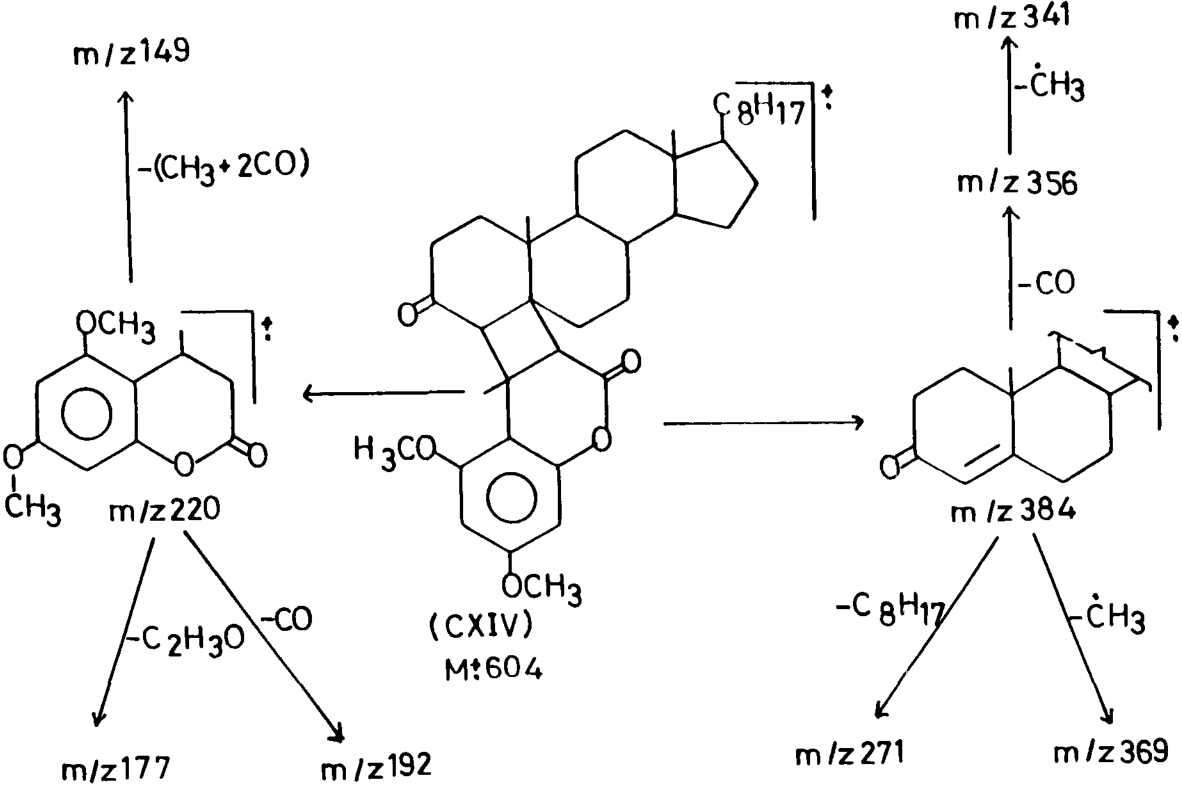
(CXIV)

(CXV)

Characterization of the compound with m.p. 152-153°C as 1:1 C_4-photoadduct (CXIV) of cholest-4-en-3-one and 4-methyl-5,7-dimethoxy coumarin

The compound having m.p. 152-153°C was analysed for $C_{39}H_{56}O_5$. The IR spectrum of the adduct exhibited two strong absorption bands at 1755 and 1720 cm^{-1} indicating the loss of 3,4-double bond of 4-methyl-5,7-dimethoxycoumarin and 4,5-double bond of cholest-4-en-3-one. Other absorption bands were observed at 1605 (C=C, aromatic) and 850 cm^{-1} (cyclobutane). In its ^1H-NMR spectrum, a multiplet centered at δ 6.7 for two protons appeared and was assigned to the aromatic protons. Two singlets for one proton each appeared at δ 3.92 and 3.87 and were assigned for cyclobutane protons suggesting that the adduct is head-tail. Two sharp singlets were exhibited at δ 3.81 and 3.79 for three protons each and were assigned to 7-methoxy and 5-methoxy protons. The methyl signal of cyclobutane appeared at δ 1.41. The other methyl protons appeared at δ 1.12 (C10-CH_3), 0.79 (C13-CH_3), 0.93 and 0.81 (other side chain methyl protons). The sign and magnitude of cotton effect in circular dichroism was $[\theta]_{293}$=-2614. The mass spectrum of cycloadduct (CXIV) exhibited molecular ion peak and some other fragment ion peaks at m/z 604 ($M^{+\cdot}$), 384, 369, 356, 341, 271, 220, 192, 177 and 149 as rationalized in scheme. On the basis of foregoing discussion, the adduct having m.p. 152-153°C was characterized as 1:1 C_4-photoadduct (CXIV).

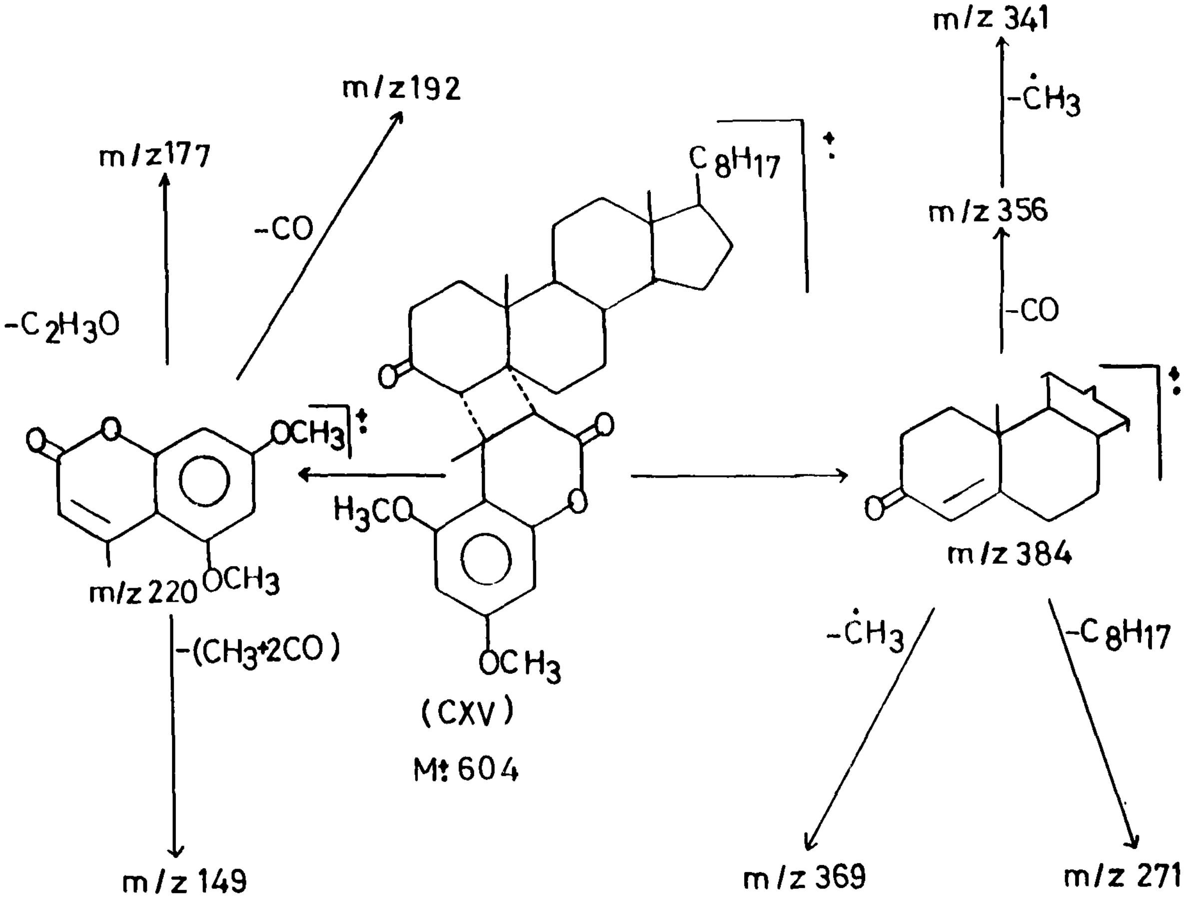
Scheme



Characterization of the photoadduct with m.p. 164-165°C as 1:1 C_4-photoadduct (CXV) of cholest-4-en-3-one and 4-methyl-5,7-dimethoxycoumarin

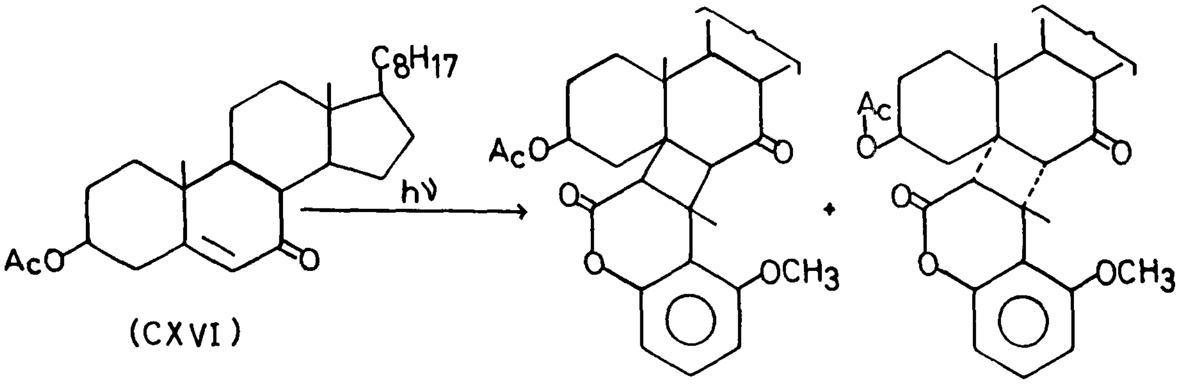
The elemental analysis of the photoadduct having m.p. 164-165°C corresponded to the molecular formula $C_{39}H_{56}O_5$. The IR spectrum of the adduct exhibited bands at 1750 (carbonyl of coumarin moiety), 1715 (C=O), 1600 (C=C, aromatic), and 855 cm^{-1} (cyclobutane). The ^1H-NMR spectrum of the photoadduct exhibited a multiplet centered at δ 6.7 integrating for two protons and was assigned to the aromatic protons. Two sharp singlets for two protons appeared at δ 3.97 and 3.91 and were assigned to the protons of cyclobutane ring of the adduct. The 5-methoxy and 7-methoxy protons appeared at δ 3.76 and 3.82 as singlets. The methyl protons of cyclobutane ring appeared at δ 1.35. Other methyl protons appeared at δ 1.02 (C10-CH_3), 0.67 (C13-CH_3), 0.95 and 0.81 (other side chain methyl protons). The sign and magnitude of cotton effect in circular dichroism was $[\theta]_{295}=+2714$. The mass spectrum of the adduct (CXV) showed molecular ion peak and some important fragment ion peaks at m/z 604 ($M^{+\cdot}$), 384, 369, 356, 341, 271, 220, 192, 177 and 149 as rationalized in scheme. On the basis of evidences, the adduct with m.p. 164-165°C was characterized as 1:1 C_4-photoadduct (CXV).

Scheme



Reaction of 3β-acetoxycholest-5-en-7-one (CXVI) with 4-methyl-5-methoxycoumarin

3β-Acetoxycholest-5-en-7-one (CXVI) and 4-methyl-5-methoxycoumarin were absorbed on silica gel G as described earlier. The resulting thin and and dried film in petri-dishes were irradiated. After irradiating for 30 min. the film was reformed and irradiated. This process was repeated several times to get better result and the progress of reaction was monitored by TLC. After the irradiation, the mixture was taken in dichloromethane, filtered and chromatographed over a column of silica gel. Two major photocycloadducts, having m.p.s. 172°C, and 183-185°C were isolated.

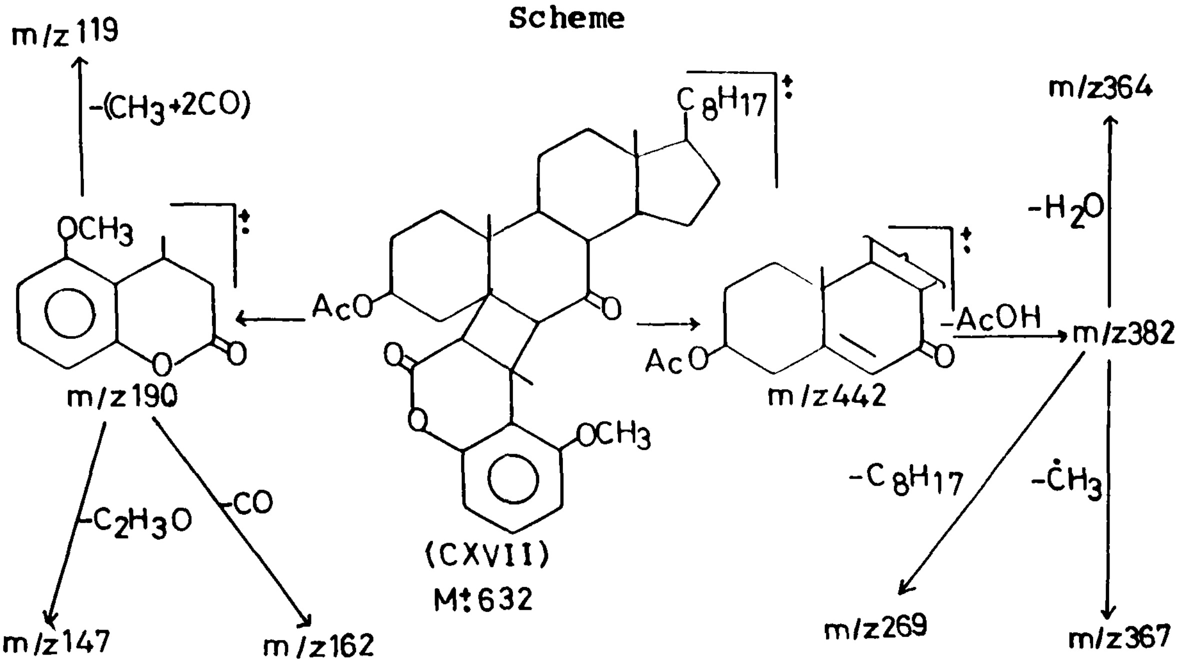


(CXVI) (CXVII) (CXVIII)

Characterization of the photoadduct having m.p. 172°C as 1:1 C_4-photoadduct (CXVII) of 3β -acetoxy-cholest-5-en-7-one 4-methyl-5-methoxycoumarin

The photoadduct with m.p. 172°C was analysed for $C_{40}H_{56}O_6$. The IR spectrum of the photoadduct exhibited two strong bands at 1760 and 1715 cm^{-1} indicating the loss of 3,4-double bond of 4-methyl-5-methoxycoumarin and 5,6-double bond of 3β -acetoxycholest-5-en-7-one.Other absorption bands were observed at 1725 (CH_3COO), 1600 (C=C, aromatic), 1050 (C-O), and 850 cm^{-1} (cyclobutane). In its ^1H-NMR spectrum a multiplet centered at δ 6.8 for three protons was observed and was assigned to aromatic protons. A multiplet centered at δ5.2 integrating for one proton was assigned to C3 -αH, (W 1/2 = 4.5 Hz, ring junction A/B cis).[36] Two singlets for one proton each appeared at δ 3.95 and 3.8 and were assigned to cyclobutane protons indicating that [2+2] photoadduct is head-tail. A sharp singlet for three protons appeared at δ3.76 and was assigned to the methoxy protons. The acetoxy protons appeared at δ 2.01 and the cyclobutyl methyl protons at δ 1.3. Other methyl protons appeared at δ 1.15 ($C10-CH_3$), 0.71 ($C13-CH_3$), 0.91 and 0.8 (other side chain methyl protons). The sign and magnitude of cotton effect in circular dichroism was $[\theta]_{294}=-6214$. The mass spectrum of the compound (CXVII) exhibited molecular ion peak and some other important fragment ion peaks at m/z 632 ($M^{+\cdot}$), 442, 382, 367, 364, 269, 190, 162, 147, and 119 as rationalized in scheme. On the basis of the above evidences, the adduct having m.p. 172°C was characterized as 1:1 C_4-photoadduct (CXVII).

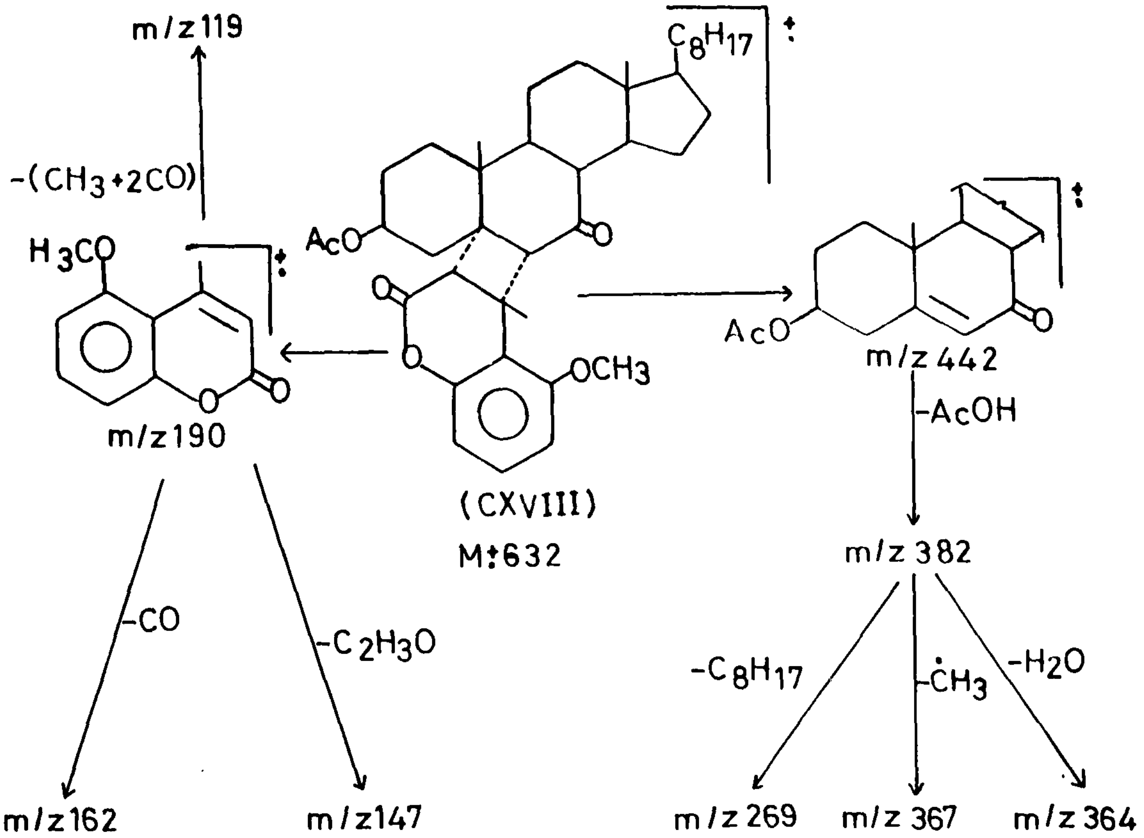
Scheme



Characterization of the photoadduct with m.p. 183-185°C as 1:1 C_4-photoadduct (CXVIII) of 3β-acetoxycholest-5-en-7-one and 4-methyl-5-methoxycoumarin

The elemental analysis of the photoadduct having m.p. 183-185°C corresponded to the molecular formula $C_{40}H_{56}O_6$. The IR spectrum of the adduct exhibited bands at 1760 (carbonyl of coumarin moiety), 1730 (CH_3COO), 1710 (C=O), 1595 (C=C, aromatic), 1040 (C-O), and 850 cm^{-1} (cylobutane). The ^1H-NMR spectrum displayed two multiplets centered at δ6.7 and 4.9 integrating for three protons and one proton and were assigned to aromatic protons and C3-α H, (W 1/2 = 16 Hz, A/B junction trans)[36] respectively. Two singlets for cyclobutane protons appeared at δ 3.87 and 3.81. The 5-methoxy protons appeared at δ 3.75 as singlet. Two sharp singlets for acetoxy protons and methyl protons of cyclobutane appeared at δ 1.9 and 1.25 respectively. Other methyl protons appeared at δ 1.12 ($C10-CH_3$), 0.69 ($C13-CH_3$), 0.92 and 0.83 (other side chain methyl protons). The sign and magnitude of cotton effect in circular dichroism was $[\theta]_{295}=+6728$. The mass spectrum of the adduct (CXVIII) showed the molecular ion peak and other important fragment ion peaks at 632 ($M^{+\cdot}$), 442, 382, 367, 364, 269, 190, 162, 147, and 119 as rationalized in scheme. On the basis of the above evidences, the adduct with m.p. 183-185°C was characterized as 1:1 C_4-photoadduct (CXVIII).

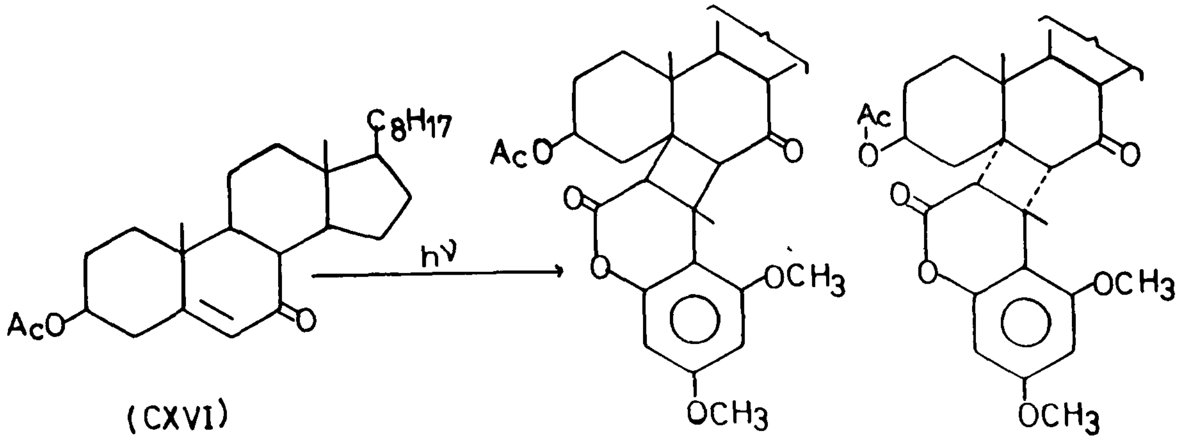
Scheme



Reaction of 3β-acetoxycholest-5-en-7-one (CXVI) with 4-methyl-5,7-dimethoxycoumarin

3β- Acetoxycholest-5-en-7-one (CXVI) and 4-methyl-5,7-dimethoxycoumarin were adsorbed on silica gel G. After evaporation of the solvent, the resulting thin and dried film in petri-dishes were irradiated in usual manner.

After irradiating for 30 min the dry film was formed again and irradiated. After the irradiation the mixture was taken in dichloromethane, filtered and chromatographed as usual. Two major photoadducts m.p.s. 179-180°C and 194°C were isolated.

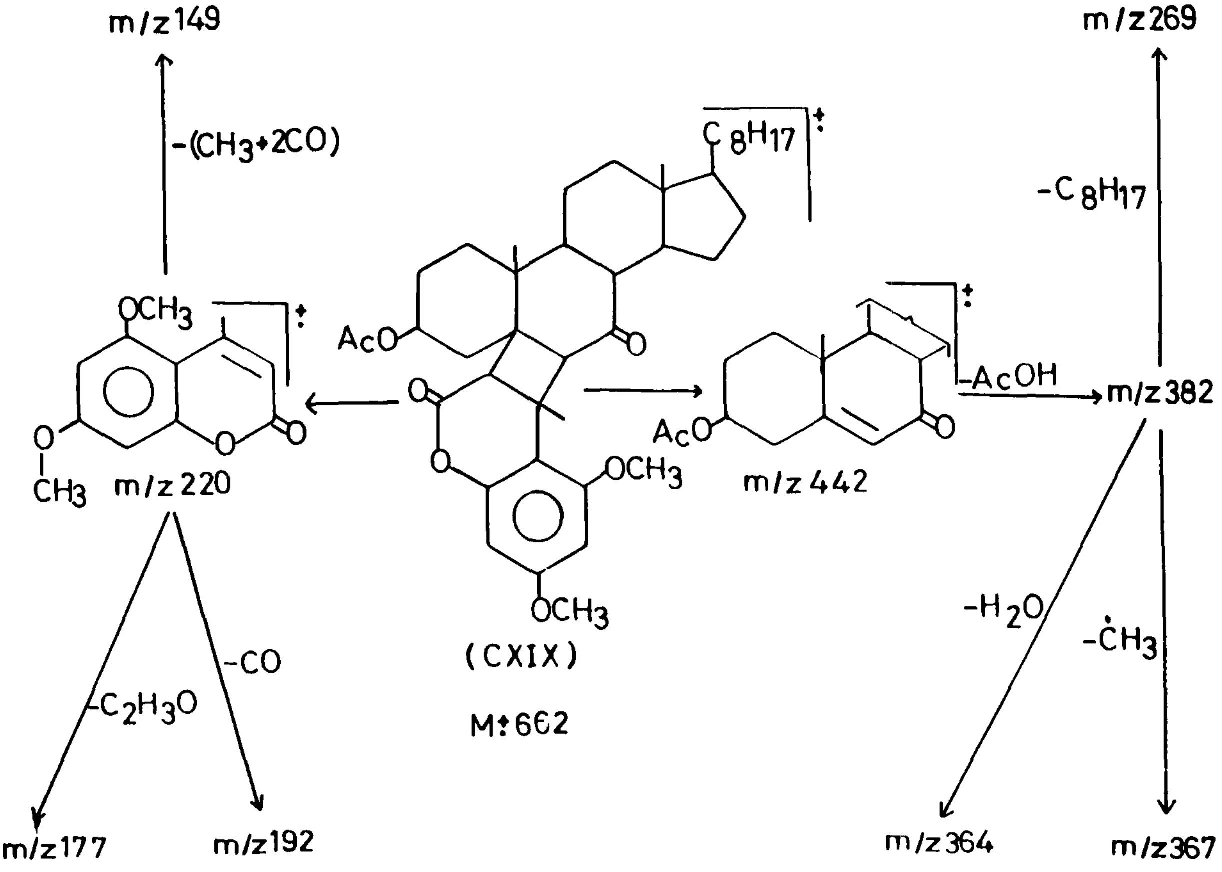


(CXVI) (CXIX) (CXX)

Characterization of the photoadduct with m.p. 179-180°C as 1:1 C_4-photoadduct (CXIX) of 3β-acetoxycholest-5-en-7-one and 4-methyl-5,7-dimethoxycoumarin

The photoadduct having m.p. 179-180°C was analysed for $C_{41}H_{58}O_7$. Its IR spectrum exhibited bands at 1750 (carbonyl of coumarin moiety), 1720 (CH_3COO), 1710 (C=O), 1605 (C=C, aromatic), 1055 (C-O) and 840 cm^{-1} (cyclobutane). The ^1H-NMR spectrum displayed two multiplets for two protons and one proton centered at δ 6.66 and 5.01 and were assigned to aromatic protons and C3-αH (W 1/2 = 4 Hz, A/B ring junction cis)[36] respectively. Two singlets for one proton each appeared at δ 3.94 and 3.86 and were assigned to cyclobutane protons, confirming the adduct as head-tail. The 5-methoxy and 7-methoxy protons appeared at δ 3.75 and 3.83 as singlets. The acetoxy and cyclobutane methyl protons appeared at δ2.0 and 1.35 as singlets. Other methyl protons appeared at δ 1.02 (C10-CH_3), 0.71 (C13-CH_3) 0.90 and 0.80 (other side chain methyl protons). The sign and magnitude of cotton effect in circular dichroism was $[\theta]_{293}=-4780$. The mass spectrum of the compound exhibited peaks for molecular ion and some important fragment ions at m/z 662 ($M^{+\cdot}$), 442, 382, 367, 364, 269, 220, 192, 177 and 149 as rationalized in scheme. On the basis of above evidences, the adduct with m.p. 179-180°C was characterized as 1:1 C_4-photoadduct (CXIX).

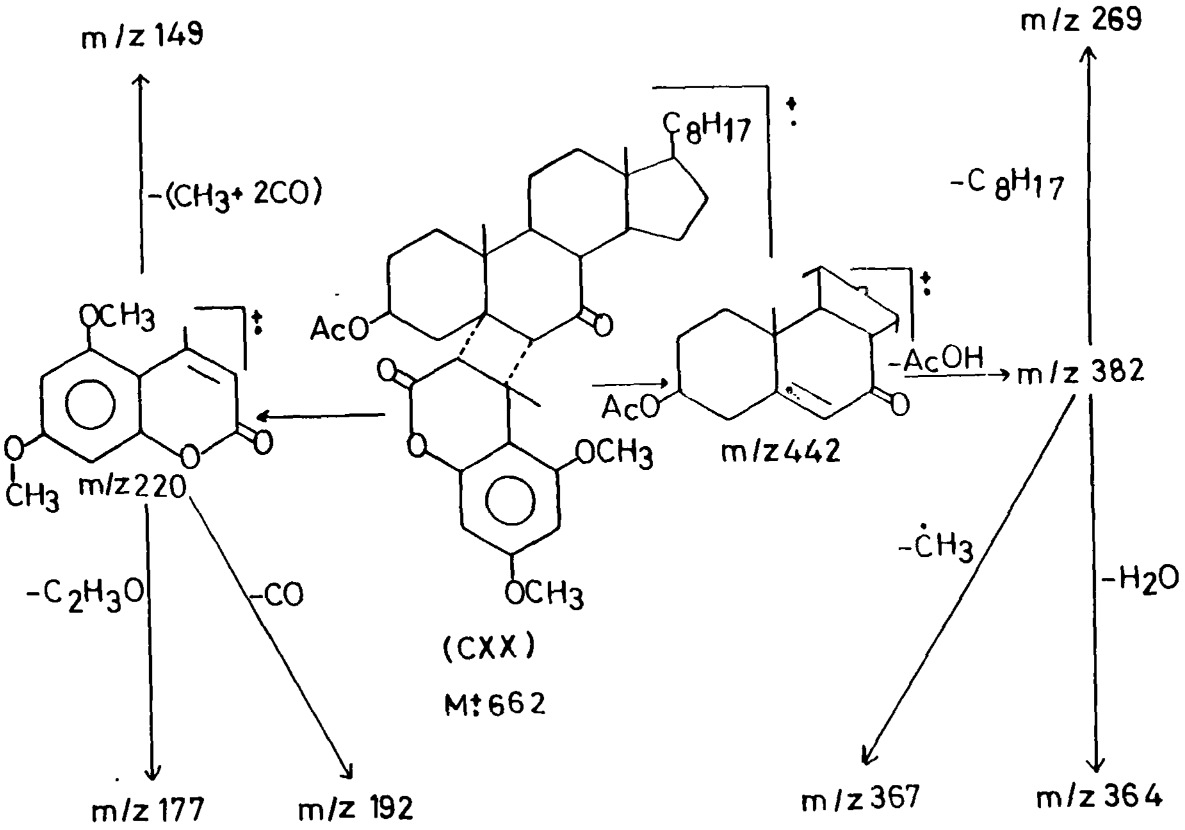
Scheme



Characterization of the photoadduct having m.p. 194°C as 1:1 C_4-photoadduct (CXX) of 3β-acetoxycholest-5-en-7-one and 4-methyl-5,7,-dimethoxycoumarin

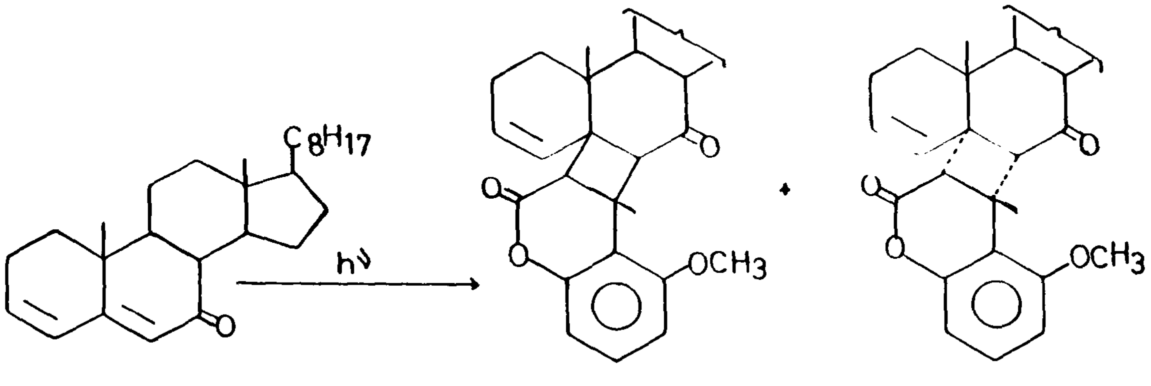
The elemental analysis of the photoadduct with m.p. 194°C corresponded to the molecular formula $C_{41}H_{58}O_7$. The IR spectrum of the adduct exhibited bands at 1750 (carbonyl of coumarin moiety), 1725 (CH_3COO), 1710 (C=O), 1600 (C=C, aromatic), 1050 (C-O) and 860 cm^{-1} (cyclobutane). The ^1H-NMR spectrum displayed two multiplets centered at δ 6.8 and 4.9 integrating for two protons and one proton and were assigned to aromatic protons and C3-αH (W 1/2 = 15 Hz, A/B ring junction trans)[36] respectively. Two singlets for one proton each appeared at δ 3.97 and 3.89 and were assigned to cyclobutane protons. The 5- and 7-methoxy protons appeared at δ3.75 and 3.84 as singlets. The acetoxy and methyl protons of cyclobutane appeared at δ 2.0 and 1.3 respectively as singlets. Other methyl protons appeared at δ 1.15 (C10-CH_3), 0.69 (C13-CH_3), 0.92 and 0.84 (other side chain methyl protons). The sign and magnitude of cotton effect in circular dichroism was $[\theta]_{294}$=+5214. The mass spectrum of the adduct (CXX) showed the molecular ion peak and other important ion peaks at m/z 662 (M^{+}), 442, 382, 364, 367, 269, 220, 192, 177 and 149 as rationalized in scheme. On the basis of above evidences, the adduct having m.p. 194°C was characterized as 1:1 C_4-photoadduct (CXX).

Scheme



Reaction of cholesta-3,5-dien-7-one (CXXI) with 4-methyl-5-methoxycoumarin

Cholesta-3,5-dien-7-one (CXXI) and 4-methyl-5-methoxycoumarin were absorbed on silica gel G and the resulting thin and dried film in petri dishes were irradiated as usual. After irradiating for 30 min., the dry film was formed again and irradiated. This process was repeated several times. After the irradiation the mixture was dissolved in dichloromethane, filtered and chromatographed as usual. Two major photoadducts having m.p.s. 132°C and 145°C were isolated.

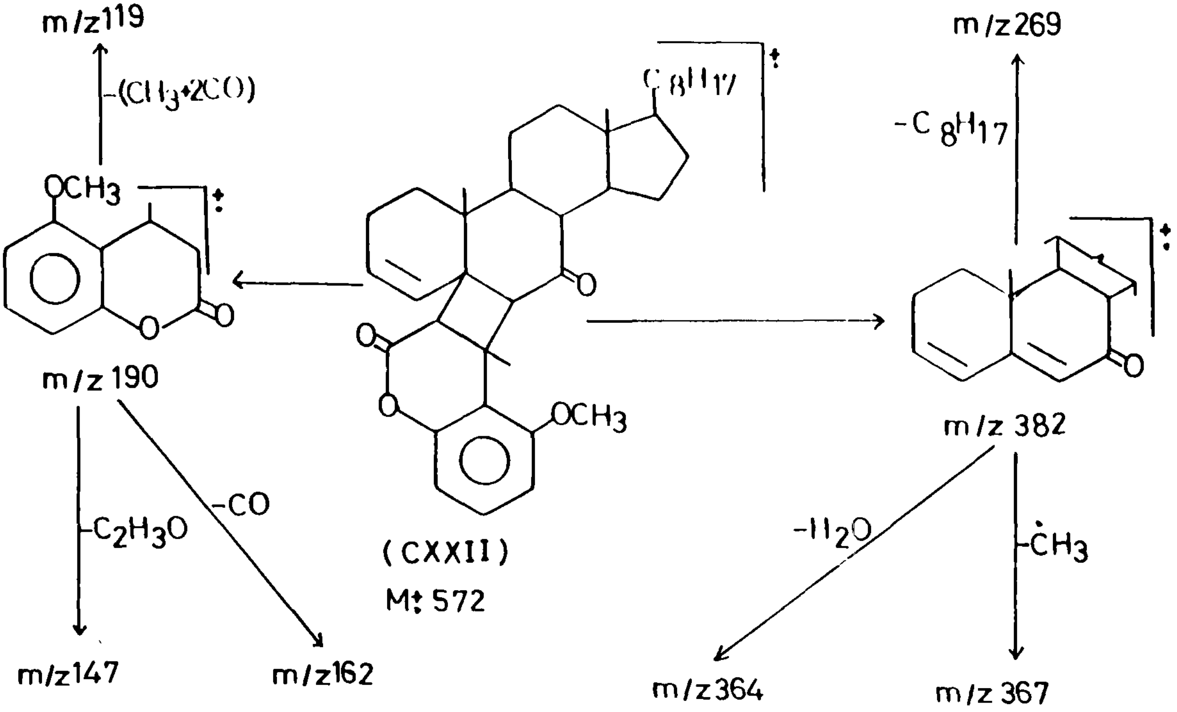


(CXXI) (CXXII) (CXXIII)

Characterization of the photoadduct with m.p. 132°C as 1:1 C_4-photoadduct (CXXII) of cholesta-3,5-dien-7-one and 4-methyl-5-methoxycoumarin

The photoadduct having m.p. 132°C was analysed for $C_{38}H_{52}O_4$. The IR spectrum of the photoadduct exhibited two strong bands at 1750 and 1720 cm^{-1} indicating the loss of 3,4-double bond of 4-methyl-5-methoxycoumarin and 5,6-double bond of cholest-3,5-dien-7-one. Other absorption bands appeared at 1610 (C=C), 1595 (C=C, aromatic), and 850 cm^{-1} (cyclobutane). In its ^{1}H-NMR spectrum appeared a multiplet centered at δ 6.7 for three protons and was assigned to the aromatic protons. A broad multiplet at δ 5.54 - 5.43 for two protons was assigned to C3 and C4 vinylic protons. Two singlets for one proton each appeared at δ 3.91 and 3.84 and were assigned to cyclobutane protons indicating that the adduct is head-tail. Two singlets for three protons each appeared at δ 3.7 and 1.4 and were assigned to the methoxy protons and methyl protons of cyclobutane. Other methyl protons appeared at δ 1.05 (C10-CH_3), 0.67 (C13-CH_3) 0.91 and 0.83 (other side chain methyl protons). The sign and magnitude of cotton effect in circular dichroism was $[\theta]_{290}$=-3712. The mass spectrum of the adduct (CXXII) exhibited molecular ion peak and some other important fragment ion peaks at m/z 572 ($M^{+\cdot}$), 382, 367, 364, 269, 190, 162, 147, and 119 as rationalized in scheme. On the basis of foregoing evidences, the photoadduct with m.p. 132^oC was characterized as 1:1 C4-photoadduct (CXXII).

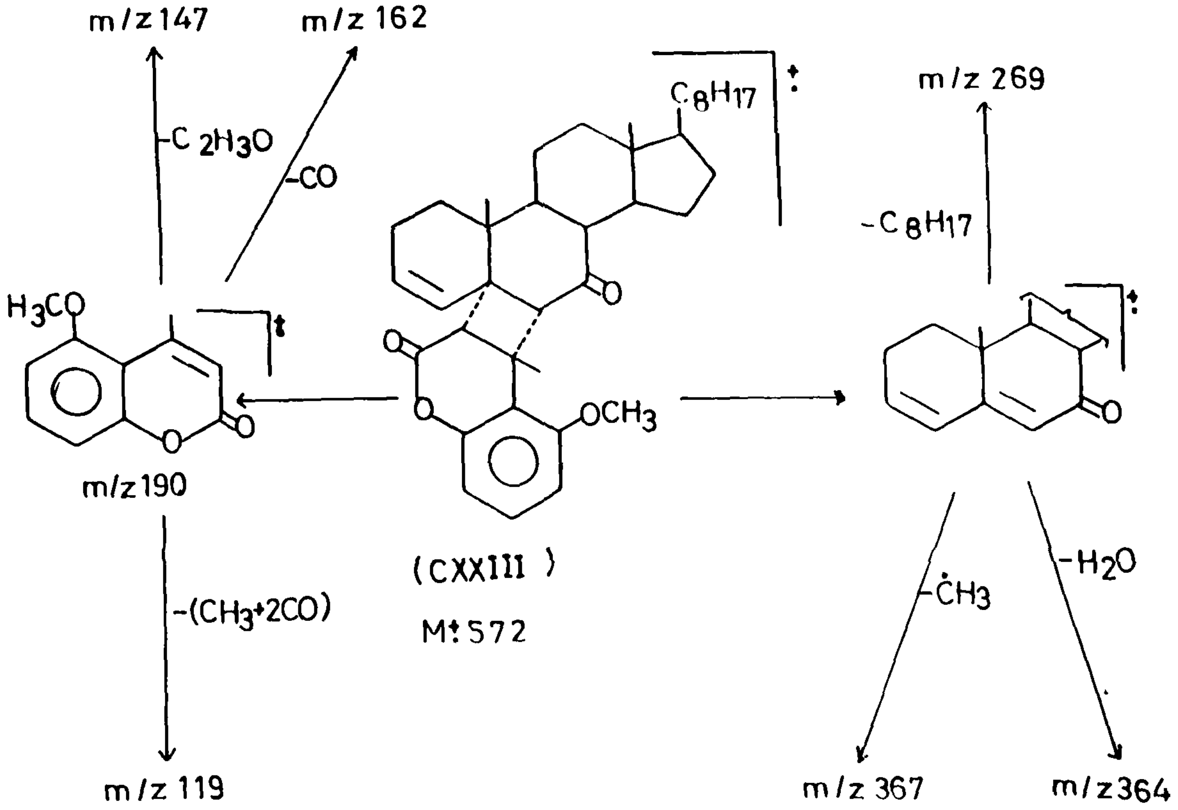
Scheme



Characterization of the photoadduct having m.p. 145°C as 1:1 C_4-photoadduct (CXXIII) of cholesta-3,5-dien-7-one and 4-methyl-5-methoxycoumarin

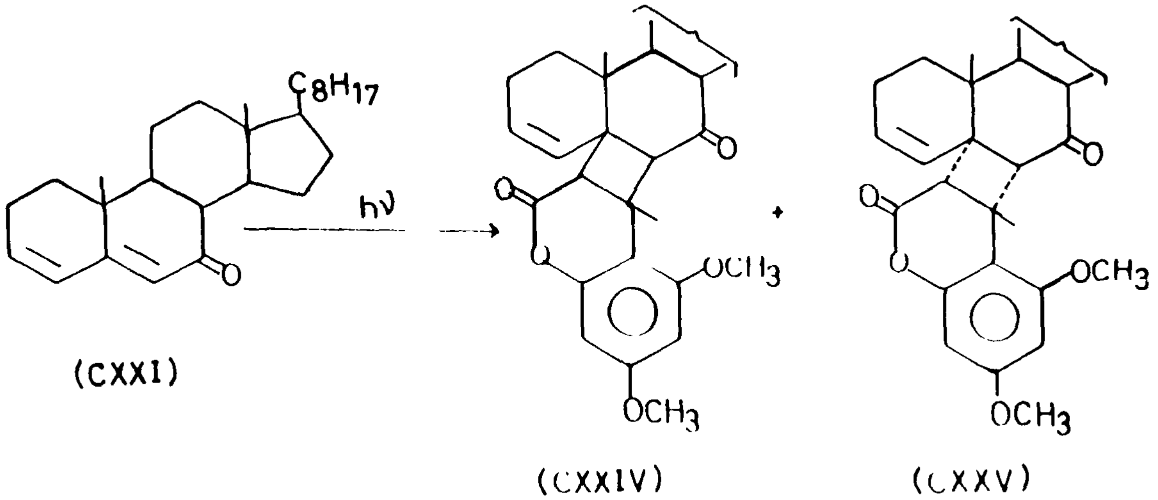
The elemental analysis of the photoadduct with m.p. 145°C corresponded to the molecular formula $C_{38}H_{52}O_4$. Its IR spectrum showed bands at 1760 (carbonyl of coumarin moiety), 1710 (C=O), 1615 (C=C), 1600 (C=C, aromatic) and 840 cm^{-1} (cyclobutane). The ^1H-NMR spectrum displayed a multiplet centered at δ 6.8 for three protons and was assigned to the aromatic protons. A broad multiplet for two protons appeared at δ 5.57-5.41 and was assigned to C3- and C4-vinylic protons. Two singlets for one proton each appeared at δ 3.89 and 3.80 and were assigned to cyclobutane protons, indicating the adduct is head-tail in nature. Two singlets for three protons each appeared at δ 3.76 and 1.25 and were assigned to the methoxy protons and methyl protons of cyclobutane respectively. Other methyl protons appeared at δ 1.1 (C10-CH_3), 0.74 (C13-CH_3), 0.95 and 0.80 (other side chain methyl protons). The sign and magnitude of cotton effect in circular dichroism was $[\theta]_{290}$=+4172. The mass spectral studies of the photoadduct (CXXIII) exhibited the molecular ion peak and some other important fragment ion peaks at m/z 572 ($M^{+\cdot}$), 382, 367, 364, 269, 190, 162, 147 and 119 as shown in scheme. On the basis of above evidences, the photoadduct having m.p. 145°C was characterized as 1:1 C4-photoadduct (CXXIII).

Scheme



Reaction of cholesta-3,5-dien-7-one (CXXI) with 4-methyl-5,7-dimethoxycoumarin

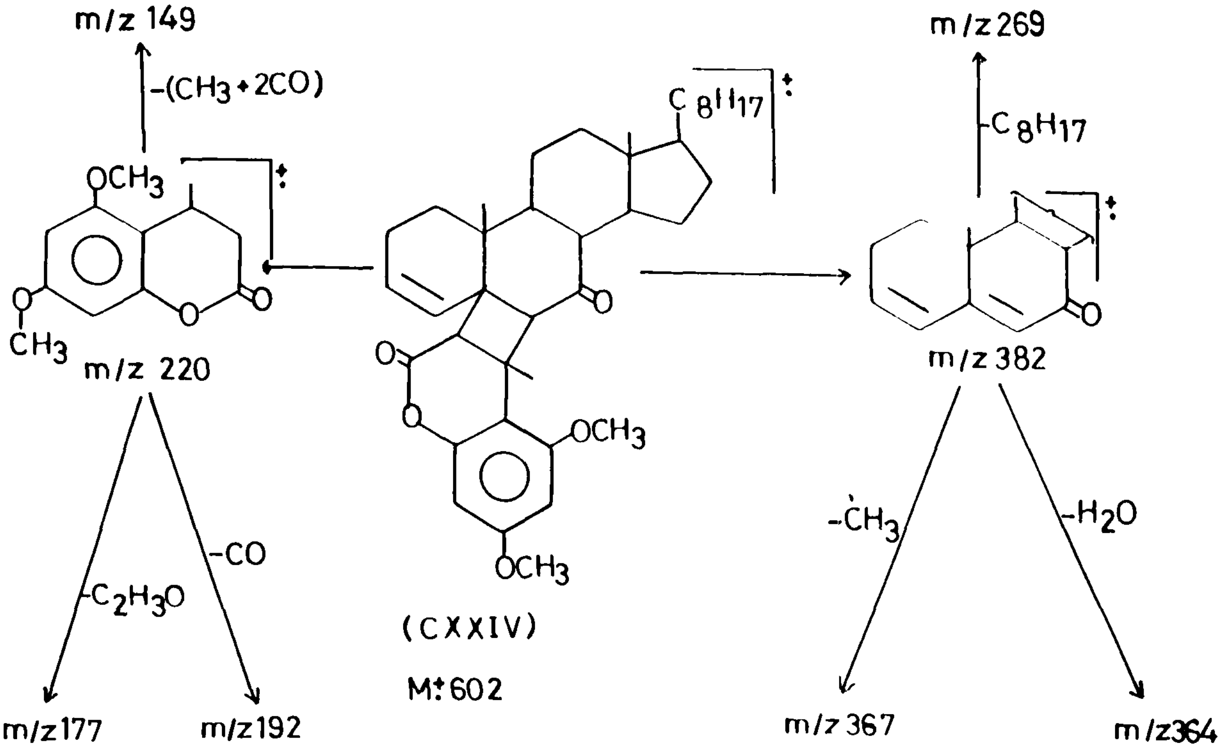
Cholesta-3,5-dien-7-one (CXXI) and 4-methyl-5,7-dimethoxycoumarin were absorbed on silica gel G.The resulting thin and dried film in petri-dishes irradiated as described earlier. After irradiating for 30 min., dry film was reformed and irradiated. This process was repeated several times. After the irradiation the mixture was taken in dichloromethane, filtered and chromatographed as usual. Two major photoadducts having m.p.s. 141-142°C and 150-151°C were isolated.



Characterization of the photoadduct with m.p. 141-142°C as 1:1 C_4-photoadduct (CXXIV) of cholesta-3,5-dien-7-one and 4-methyl-5,7-dimethoxycoumarin

The photoadduct with m.p. 141-142°C was analysed for $C_{39}H_{54}O_5$. Its IR spectrum exhibited bands at 1755 (carbonyl of coumarin moiety), 1720 (C=O), 1610 (C=C), 1600 (C=C, aromatic) and 850 cm^{-1} (cyclobutane). The ^1H-NMR spectrum exhibited a multiplet centered at δ 6.7 integrating for two protons and was assigned to aromatic protons. A broad multiplet appeared at δ 5.5 - 5.41 for two protons and was assigned to C3- and C4-vinylic protons. Two singlets for one proton each appeared at δ 3.91 and 3.87 and were assigned to the cyclobutane protons. The 5-methoxy and 7-methoxy protons appeared as singlets at δ 3.72 and 3.80 respectively. The methyl protons appeared at δ 1.32 (cyclobutane methyl protons), 1.14 (C10-CH_3), 0.67 (C13-CH_3), 0.95 and 0.81 (other side chain methyl protons). The sign and magnitude of cotton effect in circular dichroism was $[\theta]_{291}=-4761$. The mass spectrum of the photoadduct (CXXIV) showed peaks for molecular ion and some important fragment ions at m/z 602 ($M^{+\cdot}$), 382, 367, 364, 269, 220, 192, 177 and 149 as rationalized in scheme. On the basis of these evidences, the photoadduct with m.p.141-142°C was characterized as 1:1 C4-photoadduct (CXXIV).

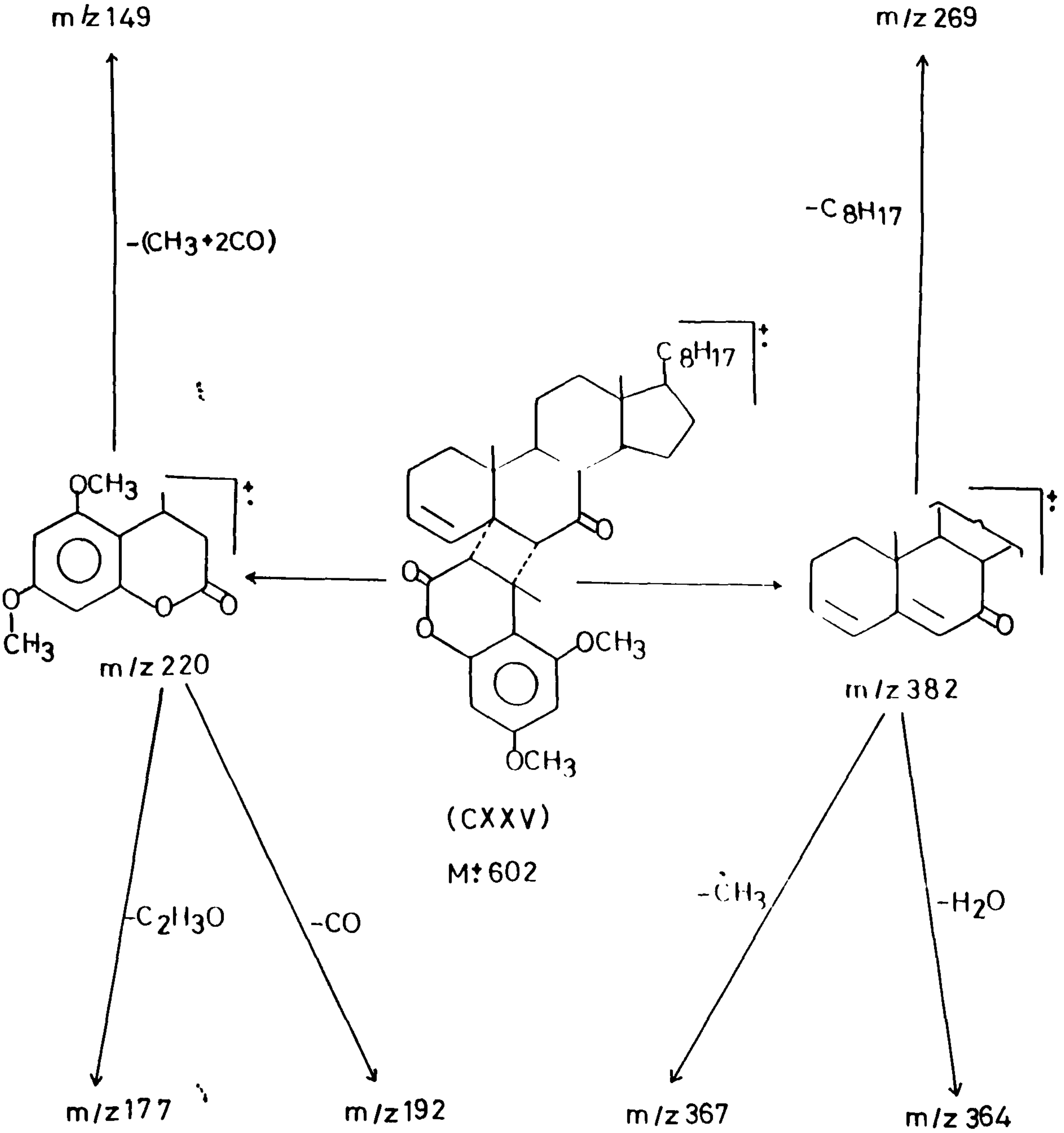
Scheme



Characterization of the photoadduct having m.p. 150-151°C as 1:1 C_4-photoadduct (CXXV) of cholesta-3,5-dien-7-one and 4-methyl-5,7-dimethoxycoumarin

The elemental analysis of the photoadduct with m.p. 150-151°C corresponded to the molecular formula $C_{39}H_{54}O_5$. The IR spectrum of the adduct exhibited bands at 1760 (carbonyl of coumarin moiety) 1715 (C=O), 1610 (C=C), 1595 (C=C, aromatic), and 860 cm^{-1} (cyclobutane). The ^1H-NMR spectrum displayed a multiplet at δ 6.5 for two aromatic protons. A broad multiplet at δ 5.5-5.4 for two protons was observed for C3-and C4-vinylic protons. Two sharp singlets for one proton each appeared at δ 3.95 and 3.87 and were assigned to the cyclobutane protons showing the adduct is head-tail. Two singlets for 5-methoxy and 7-methoxy protons appeared at δ3.74 and 3.81. The cyclobutane methyl protons were observed at δ 1.3. Other methyl protons appeared at 1.05 $(C10-CH_3)$, 0.71 $(C13-CH_3)$, 0.94 and 0.80 (other side chain methyl protons). The sign and magnitude of cotton effect in circular dichroism was $[\theta]_{297}=+5621$. The mass spectrum of the photoadduct (CXXV) displayed peaks for molecular ion and some important fragment ions at m/z 602 ($M^{+\cdot}$), 382, 367, 364, 269, 220, 192, 177, and 149 as rationalized in scheme. On the basis of these evidences, the photoadduct m.p. 150-151°C was characterized as 1:1 C4-photoadduct (CXXV).

Scheme


m/z 149
-(CH3+2CO)
m/z 269
-C8H17
C8H17
OCH3
O
CH3
m/z 220
OCH3
OCH3
(CXXV)
M+ 602
m/z 382
-C2H3O
-CO
-CH3
-H2O
m/z 177
m/z 192
m/z 367
m/z 364

EXPERIMENTAL

All melting points were observed on a kofler hot block and are uncorrected. IR spectra were obtained in KBr/Nujol with a Perkin-Elmer 237 spectrophotometer and its values are given in cm^{-1}. The ^1H-NMR spectra were run in $CDCl_3$ on a varian A60D instrument with Me_4 Si as an internal standard and its values are given in ppm (δ) (s, singlet; br, broad, and mc, multiplet centred at). Mass spectra were measured on JMS D-300 spectrometer. The values (m/z) of molecular ion and fragment ions from various compounds are given, in parenthesis, which are the relative abundance (%) of the peaks with respect to the base peak as 100%. CD spectra were measured on Jobin Yvon III.Thin layer chromatographic (TLC) plates were coated with silica gel and sprayed with 20% aqueous solution of perchloric acid. Silica gel (20g) was used for each gram of the material to be separated by column chromatography. Light petroleum refers to a fraction of b.p. 40-60°C. Sodium sulphate (anhydrous) was used as the drying agent. Dichloromethane was dried over calcium hydride before use.

3β-hydroxy - 5, 6β - dibromo-5α-cholestane

The solution of cholesterol (14 g) in ether (100 ml) was added gradually to a solution of bromine (9.6g) in glacial acetic (100 ml) and anhydrous sodium acetate (1.0g) with stirring. The solution turned yellow and promptly set to stiff paste of dibromide. The mixture was cooled to 20°C and stirred with glass rod for 5 min. to ensure complete crystallization. The product thus obtained was filtered under suction and washed with cold ether-acetic acid mixture (3:7) until the filterate was completely colourless and air dried to obtain 3β -hydroxy-5,6β -dibromo-5α -cholestane (15g) m.p. 110^{o} (reported m.p. 113^{o}).

5,6β-dibromo-5α - cholest-3-one

3 β -Hydroxy-5, 6β -dibromo-5α-cholestane (10g) was suspended in acetone (300 ml, distilled over $KMnO_4$) in a three necked round bottam flask fitted with a stirrer and dropping funnel. Jone's reagent (15 ml) was then added in small portions from dropping funnel in a course of 30 min. The temperature of the reaction mixture, during the oxidation was maintained between 0-5^{o}C by external cooling. After the oxidation was completed, the stirring was continued for additional 15 min. and cold water (200 ml) was added. The product thus obtained was filtered under suction, washed with water and methanol and air dried to afford dibromoketone (8g) m.p. 73^{o}C (reported[37] m.p. 73-75^{o}C).

Cholest-5-en-3-one

To a solution of 5, 6β -dibromo-5α-cholest-3-one (5g) in ether (100 ml) and acetic acid (2.5 ml) was added zinc dust (7.5g) in small portions during 30 min. with continuous shaking. After the complete addition the ethereal layer having suspended zinc dust was filtered. The organic layer was washed with water, sodium bicarbonate (5%) and again with water and dried. The oily residue obtained after removal of the solvent was crystallized from methanol to give (3g) cholest-5-en-3-one, m.p. 127°C (reported[37] 129°C).

Cholest-4-en-3-one (CXI)

Cholest-5-en-3-one (4.0g) was dissolved in ethanol (40 ml) and to this was added a solution of oxalic acid (0.5g) in ethanol (5ml). The reaction mixture was refluxed for 15 min, then allowed to stand at room temperature. Crystallization occurred after 1 hr and to ensure complete crystallization it was cooled at 0-4°C and filtered. The crude product was recrystallized from methanol to give ketone (3.0g) m.p. 80°C (reported[37] 81-82°C).

Reaction of cholest-4-en-3-one (CXI) with 4-methy-5-methoxycoumarin: 1:1 C4-photoadduct (CXII) and 1:1 C4-photoadduct (CXIII).

Cholest-4-en-3-one (4.0g; 10.39 m mol) and 4-methyl-5-methoxy coumarin (1.0g; 5.26 m mol) were adsorbed on silica gel G (10g) by dissolving them in dry dichloromethane (35 ml). After the evaporation of the solvent the resulting thin and dried film in petri-dishes were irradiated by placing them at a distance of 15 cm from the 450-W medium pressure by lamp arranged in horizontal manner.

After irradiating for 30 min. the dry substance was dissolved in dry dichloromethane and the solvent was evaporated to form dry film again and irradiated. This process was repeated several times in order to get better yield.The progress of the reaction was monitered by TLC.After the irradiation,the mixture was taken in dichloromethane and filtered. The filterate was chromatographed over a column of silica gel. Elution with light petroleum / ether (2:1) yielded a solid compound which was recrystallized from methanol to afford a 1:1 C4-photoadduct (CXII) (1.2g; 2.08 m mol), m.p. 139-140°C.

Analysis found : C, 79.37; H, 9.42

$C_{38}H_{54}O_4$ requires : C, 79.40; H, 9.47%

IR : ν max 1750 (carbonyl of coumarin moiety), 1715(C=0),1595 (C=C, aromatic) and 830 cm^{-1} (cyclobutane).

^{1}H-NMR : δ 6.4 (mc, 3H, aromatic protons), 3.9 (s, 3H, OCH_3), 3.8 (s, 1H, cyclobutane proton), 3.72 (s, 1H, cyclobutane proton), 1.5 (s, 3H, methyl protons of cyclobutane), 1.15 (C10-CH_3), 0.69 (CH13-CH_3), 0.93 and 0.81 (other methyl protons).

CD (methanol) : $[\theta]_{293}$-1457.

MS : $M^{+\cdot}$ 574 (2.50; $C_{38}H_{54}O_4$), 384 (100; $C_{27}H_{44}O$), 369 (35.20; $C_{26}H_{41}O$), 356 (20.30; $C_{26}H_{44}$), 341 (10.50), 271 (15.75), 270 (11.20), 269 (25.50), 258 (9.75), 257 (27.00; $C_{18}H_{25}O$), 244 (15.00; $C_{17}H_{24}O$), 243 (20.50), 230 (14.80), 229 (30.50), 228 (6.40), 226 (4.80), 225(5.00), 215 (21.80), 210 (9.60), 208 (14.40), 207 (16.00), 206 (17.50), 201 (4.80), 200 (4.80), 195 (9.60), 194 (6.40), 193 (11.20), 192

(6.40), 191 (5.50), 190 (80.75; $C_{11}H_{10}O_3$), 189 (10.00), 182 (8.00), 181 (8.50), 177 (11.20), 175 (16.40); $C_{12}H_{15}O$), 170 (4.80), 169 (19.20), 168 (3.50), 167 (30.40), 166 (17.00), 165 (6.40), 164 (11.20), 163 (4.50), 162 (25.00; $C_{10}H_{10}O_2$), 161 (5.50), 154 (11.20), 153 (40.50), 152 (16.00), 151 (9.60), 150 (30.40), 148 (9.60), 147 (25.75; $C_9H_7O_2$), 140 (16.00), 139 (8.00), 138 (5.60), 137 (17.50), 136 (20.00), 135 (8.00), 134 (8.00), 130 (4.80), 128 (9.60), 126 (16.00), 124 (19.60), 122 (9.60), 119 (24.00; C_8H_7O), 118 (10.50), 117 (7.50), 116 (4.00), 115 (6.40), 114 (4.90), 112 (20.80), 110 (8.00), 109 (19.50), 99 (11.20), 98 (38.40), 95 (4.80), 94 (36.85), 88 (11.20), 87 (7.20), 86 (32.00), 85 (11.20), 84 (33.60), 82 (35.00), 81 (4.50), 80 (12.75), 73 (35.80), 72 (9.60), 71 (46.50), 70 (8.00), 69 (35.50), 58 (52.00), 57 (12.50), 56 (61.40), 55 (5.00), 54 (6.50), 45 (5.00), 44 (49.60), 43 (60.50), 42 (19.60), 41 (72.00), 40 (67.20).

Continued elution with light petroleum / ether (1:1) afforded 1:1 C4-photoadduct (CXIII) which was recrystallized from methanol (0.98; 1.70 m mol), m.p. 160-161° C.

Analysis found : C, 79.35; H, 9.45

$C_{38}H_{54}O_4$ requires : C, 79.40; H; 9.47%

IR : ν max 1760 (carbonyl of coumarin moeity), 1710 (C=O), 1600 (C=C, aromatic) and 840 cm^{-1} (cyclobutane).

^{1}H-NMR : δ 6.5 (mc, 3H, aromatic protons), 3.95 (s, 3H, OCH_3), 3.85 (s, 1H, cyclobutane proton), 3.78 (s, 1H, cyclobutane proton), 1.4 (s, 3H, methyl protons of cyclobutane), 1.2 (C10-CH_3), 0.67 (C13-CH_3), 0.9 and 0.84 (other methyl protons).

CD (methanol) : $[\theta]_{291}$+2328

MS : $M^{+\cdot}$ 574 (3.10; $C_{38}H_{54}O_4$), 384 (100.00; $C_{27}H_{44}O$), 369(42.20; $C_{26}H_{41}O$), 356 (24.30, $C_{26}H_{44}$), 341 (16.20; $C_{25}H_{41}$), 271 (15.00), 270 (9.20), 269 (12.90), 258 (11.75), 257 (30.00; $C_{18}H_{25}O$), 244 (17.25; $C_{17}H_{24}O$), 243 (27.00), 230 (12.00), 229 (25.70), 228 (5.00), 226 (5.00), 225 (5.00), 215 (19.20), 210 (10.75), 208 (13.25), 207 (12.25), 206 (15.00), 201 (4.80), 195 (9.60), 194 (9.60), 193 (10.00), 192 (4.80), 191 (4.80), 190 (83.25; $C_{11}H_{10}O_3$), 182 (8.00), 181 (15.00), 177 (14.20), 175 (18.50; $C_{12}H_{15}O$), 170 (5.20), 169 (17.00), 168 (4.80), 167 (24.40), 166 (16.00), 165 (5.00), 164 (9.60), 163 (4.80), 162 (29.90; $C_{10}H_{10}O_2$), 161 (5.75), 154 (9.60), 153 (37.20), 152 (14.40), 151 (9.60), 150 (32.40), 148 (9.60), 147 (30.30; $C_9H_7O_2$), 140 (17.25), 139 (9.60), 138 (4.80), 137 (12.25), 136 (19.00), 135 (9.60), 134 (9.60), 130 (5.00), 128 (5.00), 126 (12.25), 125 (5.50), 124 (17.50), 123 (9.60), 122 (9.60), 121 (4.80), 120 (4.80), 119 (24.25; C_8H_7O), 118 (8.50), 117 (7.00), 116 (4.20), 115 (4.20), 114 (6.20), 112 (21.25), 110 (7.50), 109 (22.20), 99 (9.60), 98 (32.20), 95 (4.80), 94 (30.00), 88 (9.60), 87 (6.40), 86 (31.00), 85 (9.60), 84 (30.25), 82 (32.00), 81 (4.80), 80 (10.00), 73 (30.00), 72 (10.50), 71 (36.25), 70 (25.20), 69 (30.20), 58 (47.70), 57 (10.25), 56 (58.20), 55 (10.25), 54

(10.25), 45 (5.60), 44 (45.00), 43 (55.50), 42 (22.50), 41 (69.90), 40 (58.00).

Reaction of cholest-4-en-3-one (CXI) with 4-methyl-5,7-dimethoxy coumarin: 1:1 C4-photoadduct (CXIV) and 1:1 C4-photoadduct (CXV).

Cholest-4-en-3-one (4.0g; 10.39 m mol) and 4-methyl-5,7- dimethoxycoumarin (1.0g; 4.54 m mol) were adsorbed on silica gel G (10g) by dissolving them in dry dichloromethane (35 ml). After the evaporation of the solvent the resulting thin and dried film in petri-dishes were irradiated by placing them at a distance of 15 cm from the 450-W medium pressure Hg lamp arranged in a horizontal manner. After irradiating for 30 min, the film was formed again and irradiated. This process was repeated several times and the progress of the reaction was monitered by TLC. After irradiation the mixture was dissolved in dichloromethane and filtered. The filterate was chromatographed over a column of silica gel. Elution with light petroleum ether/ether (3:1) afforded a 1:1 C_4-photoadduct (CXIV), recrystallized from methanol (0.91g; 1.50 m mol), m.p. 152-153°C.

Analysis found : C, 77.41; H, 9.29,

$C_{39} H_{56} O_5$ requires : C, 77.44; H, 9.33%

IR : ν max 1755 (carbonyl of coumarin moiety), 1720 (C=O), 1605 (C=C, aromatic) and 850 cm^{-1} (cyclobutane).

^{1}H-NMR : δ 6.7 (mc, 2H, aromatic protons), 3.92 (s, 1H, cyclobutane proton), 3.87 (s, 1H, cyclobutane proton), 3.81 (s, 3H, 7-OCH_3), 3.79 (s, 3H, 5-OCH_3), 1.41 (s, 3H, methyl protons of cyclobutane), 1.12 (C10-CH_3), 0.79 (C13-CH_3), 0.93 and 0.81 (other methyl protons).

CD (methanol) : $[\theta]_{293}$-2614

MS : $M^{+\cdot}$ 604(2.72; $C_{39}H_{56}O_5$), 384 (100.00; $C_{27}H_{44}O$), 369 (38.00, $C_{26}H_{41}O$), 356 (18.50; $C_{26}H_{44}$), 341 (15.25; $C_{25}H_{41}$), 271 (17.50), 270 (10.10), 269 (22.50), 258 (10.50), 257 (30.25;$C_{18}H_{25}O$), 244 (15.25; $C_{17}H_{24}O$), 243 (19.40), 230 (21.75), 229 (25.40), 220 (75.80; $C_{12}H_{12}O_4$), 215 (23.20), 192 (42.00; $C_{11}H_{12}O_3$), 179 (6.50), 178 (7.25), 177 (31.75; $C_{10}H_9O_3$), 175 (27.50; $C_{12}H_{15}O$), 174 (13.00), 164 (12.50), 163 (7.50), 162 (12.00), 161 (8.25), 160 (9.00), 153 (7.50), 152 (6.25), 151 (4.80), 150 (12.50), 149 (23.25; $C_9H_9O_2$), 148 (7.50), 147 (6.25), 146 (10.00), 140 (8.80), 139 (4.50), 138 (10.30), 137 (12.10), 136 (14.25), 135 (8.75), 134 (11.60), 130 (4.80), 129 (8.75), 128 (6.50), 126 (6.50), 124 (14.75), 123 (20.25), 121 (22.00), 120 (8.50), 119 (11.30), 118 (4.50), 117 (7.25), 116 (10.00), 115 (4.30), 114 (5.75), 113 (10.30), 110 (6.50), 109 (12.30), 108 (5.00), 99 (10.00), 98 (20.50), 95 (4.80), 94 (25.00), 88 (9.75), 87 (7.30), 86 (10.40), 85 (12.10), 84 (4.50), 83 (7.75), 82 (6.50), 81 (4.40), 80 (15.50), 79 (21.00), 78 (10.30); 77 (16.30), 76 (5.00), 75 (6.50), 74 (3.25), 73 (2.50), 72 (15.00), 71 (4.50), 67 (2.25), 66 (8.50), 65 (5.30), 64 (3.50), 59

(12.75), 58 (7.75), 57 (17.00), 56 (4.50), 55 (5.90), 53 (5.00), 52 (10.30), 51 (7.25), 46 (5.00), 45 (19.10), 44 (30.80), 43 (7.50), 42 (20.25), 41 (36.10), 40 (18.85).

Further elution with light petroleum ether/ether (1:1) afforded the 1:1 C4-photoadduct (CXV) which was recrystallized from methanol (1.1 g; 1.81 m mol) m.p. 164-165^oC.

Analysis Found : C, 77.42; H, 9.31

$C_{39} H_{56} O_5$ requires : C, 77.44; H, 9.33%

IR : ν max 1750 (carbonyl of coumarin moiety), 1715 (C=0), 1600 (C=C, aromatic), and 855 cm^{-1} (cyclobutane).

^{1}H-NMR : δ 6.7 (mc, 2H, aromatic), 3.97 (s, 1H, cyclobutane proton), 3.91 (s, 1H, cyclobutane proton), 3.82 (s, 3H, 7-OCH_3), 3.76 (s, 3H, 5-OCH_3), 1.35 (s, 3H, methyl protons of cyclobutane), 1.02 (C10-CH_3), 0.67 (C13-CH_3), 0.95 and 0.81 (other methyl protons).

CD (methanol) : $[\theta]_{295}$+2714

MS : M^{+} 604 (2.40, $C_{39} H_{56} O_5$), 384 (100.00, $C_{27} H_{44} O$), 369 (45.30; $C_{26} H_{41} O$), 356 (25.00; $C_{26} H_{44}$), 341 (17.75; $C_{25} H_{41}$), 271(15.50), 270 (9.60), 269 (18.25), 258 (11.50), 257 (27.75; $C_{18} H_{25}O$), 244 (17.30; $C_{17} H_{24}O$), 243 (28.00), 230 (22.20), 229 (29.90), 220 (81.00; $C_{12} H_{12} O_4$), 215 (20.30), 192 (37.50; $C_{11} H_{12} O_3$), 179 (6.50), 178 (7.25), 177 (40.20; $C_{10} H_9 O_3$), 176 (12.00), 175 (21.30; $C_{12} H_{15}O$), 174 (9.60), 164 (10.30), 163 (6.50), 162 (10.25), 161 (7.00), 160 (8.70), 153 (7.20), 152 (4.80), 151 (4.80), 150 (10.00), 149 (29.10;

$C_9H_9O_2$), 148 (6.60), 147 (6.60), 146 (9.60), 140 (10.00), 139 (5.50), 138 (12.50), 137 (14.00), 136 (13.25), 135 (7.25), 134 (13.60), 133 (7.25), 132 (9.60), 130 (5.00), 129 (10.50), 128 (7.20), 127 (5.50), 126 (7.20), 125 (7.20), 124 (15.50), 123 (19.00), 121 (20.50), 120 (9.60), 119 (7.25), 118 (5.50), 117 (6.50), 110 (7.50), 109 (12.30), 108 (14.30), 107 (6.50), 99 (11.50), 98 (25.25), 95 (5.50), 94 (20.00), 88 (10.00), 87 (8.50), 86 (9.60), 85 (10.75), 84 (5.00), 83 (8.20), 82 (7.00), 80 (16.00), 79 (22.25), 78 (12.30), 77 (17.70), 76 (5.90), 75 (7.20), 72 (16.00), 71 (5.50), 66 (5.50), 65 (7.20), 59 (14.00), 58 (10.25), 57 (14.70), 56 (5.50), 55 (7.20), 52 (12.30), 47 (5.50), 46 (5.50), 45 (21.10), 44 (32.75), 43 (10.50), 42 (25.00), 41 (37.10), 40 (23.25).

3 β - Acetoxycholest-5-ene

A mixture of cholesterol (50g), pyridine (75 ml, freshly distilled over KOH) and freshly distilled acetic anhydride (50 ml) was heated on a water bath for 2 hrs. The resulting brown solution was poured into crushed ice-water mixture with stirring. A light brown solid was obtained which was filtered under suction, washed with water until free from pyridine and air dried. The crude product on recrystallization from acetone gave pure 3 β - acetoxycholest-5-ene (45.0g) m.p. 112°C (reported[38] m.p. 113°C).

3 β -Acetoxycholest-5-en-7-one (CXVI)

A solution of t-butyl chromate [t-butyl-alcohol (60 ml], CrO_3 (20g), acetic acid (84 ml)] and acetic anhydride (10 ml) was added at 0^oC to a solution of 3 β -acetoxycholest-5-ene (8g) in carbon tetrachloride (150 ml), acetic acid (30 ml) and acetic anhydride (10 ml). The contents were refluxed for 3 hrs and then diluted with water. The organic layer was washed successively with sodium bicarbonate (5%) and water and dried. Evaporation of the solvent under reduced pressure furnished an oil which was crystallized from methanol to give the desired ketone (4g), m.p. 162^oC (reported[39] m.p. 164^oC).

Reaction of 3 β -acetoxycholest-5-en-7-one (CXVI) with 4-methyl-5-methoxycoumarin: 1:1 C4-photoadduct (CXVII) and 1:1 C4-photoadduct (CXVIII).

3 β -Acetoxycholest-5-en-7-one (4.0g; 9.04 m mol) and 4-methyl-5-methoxy coumarin (1.0g; 5.26 m mol) were adsorbed on silica gel G (10g) by dissolving in dry dichloromethane (35 ml). The solvent was evaporated and the resulting thin and dried film in petri-dishes were irradiated by placing them at a distance of 15 cm from the 450-W medium pressure Hg lamp.

After irradiating for 30 min. the substance was dissolved and film was formed again and irradiated. This process is repeated several times. After irradiation, the mixture was taken in dichloromethane, filtered and chromatographed over a column of silica gel. Elution with light petroleum ether/ether (3:1) furnished a 1:1 C4-photoadduct (CXVII) which was recrystallized from methanol (1.14 g; 1.80 m mol), m.p. 172°C.

Analysis Found : C, 75.87; H, 8.88

$C_{40}H_{56}O_6$ requires : C, 75.91; H, 8.92%

IR : ν max 1760 (carbonyl of coumarin moiety), 1725 (CH_3COO), 1715(C=O), 1600 (C=C, aromatic), 1050 (C-O), and 860 cm^{-1} (cyclobutane).

^1H-NMR : δ6.8 (mc, 3H, aromatic), 5.2 (mc, 1H, C3-α H, W 1/2 = 4.5H_z, A/B junction cis)[36], 3.95 (s, 1H; cyclobutane proton), 3.8 (s, 1H, cyclobutane proton); 3.76 (s, 3H, OCH_3), 2.01(s, 3H, CH_3COO), 1.3 (s, 3H, methylprotons of cyclobutane), 1.15 (C10-CH_3), 0.71 (C13-CH_3), 0.91 and 0.8 (other methyl protons).

CD (methanol) : $[\theta]_{294}$-6214

MS : M^{+} 632 (3.10; $C_{40}H_{56}O_6$), 442 (15.80; $C_{29}H_{46}O_3$) 382(72.25; $C_{27}H_{42}O$), 367 (19.50; $C_{26}H_{39}O$), 364 (9.50), 340 (15.75), 269 (19.75; $C_{19}H_{25}O$), 255 (9.60), 254 (5.25), 253 (5.68), 252 (15.00), 251 (4.80), 250 (12.40), 249 (23.50), 248 (35.00), 246 (30.75), 245 (4.80), 244 (4.80), 243 (3.60), 240 (4.80), 239 (9.60), 238 (4.80), 235 (7.20), 234 (9.60), 232 (14.40), 231 (9.60), 230 (4.80), 229 (7.20), 228 (12.20), 227 (7.20), 225 (30.25), 224 (3.75), 214 (9.60), 213 (40.20), 212 (7.50), 211 (22.20), 210 (30.80), 209 (4.80), 208 (4.80), 206 (4.80), 205 (4.80), 200 (9.60), 199 (7.20), 198 (20.10), 197 (12.00), 196 (25.25), 195 (9.60), 194 (9.60), 193 (9.60), 191 (4.50), 190 (74.20; $C_{11}H_{10}O_3$), 189 (5.50), 188 (7.80), 187 (42.40; $C_{13}H_{15}O$), 186 (12.00), 185 (10.50), 183 (18.60), 182 (9.60). 180 (15.25), 178 (9.60), 177 (4.50), 176 (12.00), 175 (4.80), 174 (100.00; $C_{12}H_{14}O$), 173 (12.00), 172 (12.00), 171 (13.50), 170 (25.75), 169 (13.50), 168 (20.20), 166 (12.20), 165 (7.20), 164 (10.40), 162 (33.30; $C_{10}H_{10}O_2$), 161 (37.00; $C_{11}H_{13}O$), 160 (24.25), 159 (25.00), 158 (18.75), 157 (40.25), 156 (12.00), 150 (12.25), 149 (13.50), 148 (7.20), 147 (21.75; $C_9H_7O_2$), 146 (17.80), 145 (7.50), 144 (9.80), 142 (10.75), 141 (12.50), 140 (7.20), 139 (12.00), 137 (7.20), 136 (12.00), 135 (14.40), 134 (20.50; $C_9H_{10}O$), 133 (12.00), 132 (20.75), 131 (9.60), 130 (7.25), 129 (14.40), 128 (12.25), 123 (15.25), 122 (13.00), 120 (22.20), 119 (30.10; C_8H_7O), 118 (18.00), 117 (12.50), 116 (7.20), 115 (13.25), 110 (25.25), 109 (30.20), 108 (15.75), 107 (20.30), 106 (15.00), 105 (10.50), 104 (20.25), 103 (7.20), 97 (20.25), 96 (45.50), 95 (20.00), 94 (15.10), 85 (9.60), 84 (12.00), 83 (40.50), 82 (22.10), 81 (27.30), 80 (20.30), 79 (25.25), 78 (16.25), 77 (7.60), 76 (35.00), 71 (48.80), 70 (32.00), 69 (62.00), 68 (28.80), 67 (50.30), 66 (12.00), 63 (50.50), 62 (5.50), 59 (16.80), 58 (5.20), 57 (18.10), 56 (7.50), 55 (25.70), 54 (16.80), 53 (30.20), 52 (9.60), 51 (12.00), 50 (9.60), 46 (19.20), 45 (10.50), 44 (27.00), 43 (37.50), 42 (29.30).

Further elution with light petroleum ether/ether (1:1) provided a 1:1 C4-photoadduct (CXVIII) which was recrystallized from methanol (0.96g; 1.52 m mol) m.p. 183-85°C.

Analysis Fond : C, 75.88; H, 8.89

$C_{40}H_{56}O_6$ requires : C, 75.91; H, 8.92%

IR : νmax 1760 (carbonyl of coumarin moiety), 1730 (CH_3COO), 1710 (C=O), 1595 (C=C, aromatic), 1040 (C-O), and 850 cm^{-1} (cyclobutane).

^1H-NMR : δ 6.7 (mc, 3H, aromatic protons), 4.9 (mc, 1H, C3-H, W 1/2 = $16H_z$, A/B ring junction trans)[36], 3.87 (s, 1H, cyclobutane proton), 3.81 (s, 1H, cyclobutane proton), 3.75 (s, 3H, OCH_3), 1.9 (s, 3H, CH_3COO), 1.25 (s, 3H, methyl protons of cyclobutane), 1.12 (C10-CH_3), 0.69 (C13-CH_3), 0.92 and 0.83 (other methyl protons).

CD (methanol) : $[\theta]_{295}+6728$

MS : $M^{+\cdot}$ 632 (3.00; $C_{40}H_{56}O_6$), 442 (10.00, $C_{29}H_{46}O_3$), 382 (82.50; $C_{27}H_{42}O$), 367 (25.25; $C_{26}H_{39}O$), 364 (10.00), 340 (11.10), 269 (22.40; $C_{19}H_{25}O$), 255 (8.40), 254 (4.80), 253 (4.80), 252 (12.00), 251 (5.00), 250 (13.75), 249 (20.25), 248 (31.10), 247 (4.80), 246 (27.25), 245 (4.80), 244 (8.20), 240 (5.50), 239 (10.50), 238 (5.50), 235 (9.60), 234 (9.60), 231 (7.20), 230 (7.20), 229 (9.60), 228 (10.40), 227 (10.00), 226 (4.80), 225 (29.00), 224 (4.80), 214 (8.00), 213 (35.00), 212 (8.60), 211 (20.75), 210 (25.50), 209

(4.80), 208 (4.80), 201 (4.80), 200 (10.50), 199 (6.50), 198 (17.60), 197 (12.00), 196 (27.25), 195 (8.40), 194 (8.40), 193 (8.40), 192 (4.80), 191 (4.80), 190 (80.20; $C_{11} H_{10} O_3$), 189 (5.00), 188 (9.60), 187 (47.30; $C_{13} H_{15}O$), 186 (11.10), 185 (9.60), 184 (5.00), 183 (16.60), 182 (8.40), 181 (4.80), 180 (13.25), 179 (7.20), 178 (9.60), 177 (5.00), 176 (14.20), 175 (4.80), 174 (100.00; $C_{12} H_{14} O$), 173 (8.60), 171 (12.00), 170 (23.00), 169 (10.25), 168 (17.00), 167 (5.00), 166 (12.00), 165 (5.50), 164 (8.40), 163 (5.50), 162 (37.30; $C_{10} H_{10} O_2$), 161 (42.00; $C_{11} H_{13} O$), 160 (2.00), 159 (21.50), 158 (13.00), 148 (10.00), 147 (25.00; $C_9 H_7 O_2$), 146 (7.00), 145 (6.50), 144 (7.20), 143 (9.80), 142 (10.50), 141 (8.50), 140 (15.00), 136 (9.60), 135 (12.50), 134 (22.50; $C_9 H_{10} O$), 133 (14.25), 132 (19.10), 131 (9.60), 130 (6.50), 121 (5.00), 120 (20.00), 119 (34.00; $C_8 H_7O$), 118 (17.00), 117 (13.50), 116 (8.40), 110 (23.00), 109 (27.25), 107 (18.00), 106 (15.00), 105 (9.60), 104 (17.50), 103 (8.40), 97 (18.00), 96 (40.50), 95 (19.20), 94 (14.30), 83 (38.40), 82 (20.10), 81 (29.10), 80 (17.50), 79 (23.00), 79 (23.00), 78 (14.50), 77 (6.60), 76 (27.00), 71 (35.40), 70 (28.40), 69 (45.20), 68 (25.25), 67 (47.75), 66 (9.60), 65 (5.00), 57 (13.50), 56 (7.90), 55 (20.25), 54 (15.10), 53 (29.00), 52 (10.00), 51 (9.60), 50 (8.60), 46 (18.20), 45 (9.60), 44 (29.30), 43 (39.20), 42 (35.50).

Reaction of 3β -acetoxycholest-5-en-7-one (CXVI) with 4-methyl-5,7- dimethoxy coumarin: 1:1 C4-photo adduct (CXIX) and 1:1 C4-photoadduct (CXX).

3β -Acetoxycholest-5-en-7-one (4.0g; 9.04 m mol) and 4-methyl-5,7-dimethoxy coumarin (1.0g; 4.54 m mol) were adsorbed on silica gel G (10g) by dissolving them in dry dichloromethane (35 ml). Evaporation of the solvent left a thin and dried film in petri-dishes which were placed at a distance of 15 cm from the lamp arranged in horizontal manner and irradiated.

After irradiating for 30 min. the film was formed again and irradiated. This process was repeated several times. After the irradiation, the mixture was dissolved in dichloromethane, filtered and chromatographed over a column of silica gel. Elution with light petroleum ether/ether (3:1) furnished a 1:1 C4-photoadduct (CXIX) which was recrystallised from methanol (1.08g; 1.63 m mol) m.p. 179-80°C.

Analysis Found : C, 74.25; H, 8.17

$C_{41}H_{58}O_7$ requires : C, 74.28; H, 8.19%

IR : ν_{max} 1750 (carbonyl of coumarin moeity), 1720 (CH_3COO), 1710 (C=O), 1605 (C=C, aromatic), 1055 (C-O) and 840 cm^{-1} (cyclobutane)

^1H-NMR : δ 6.66 (mc, 2H, aromatic), 5.01 (mc, 1H, C_3-αH, W 1/2 = 4Hz, A/B ring junction cis)[36], 3.94 (s, 1H, cyclobutane proton), 3.86 (s, 1H, cyclobutane, proton), 3.83 (s, 3H, 7-OCH_3), 3.75 (s, 3H, 5-OCH_3), 2.0(s, 3H, CH_3 COO), 1.35(s, 3H, methyl protons of cyclobutane), 1.02 (C10-CH_3), 0.71 (C13-CH_3), 0.91 and 0.80 (other methyl protons).

CD (methanol) : $[\theta]_{293}$-4780

MS : $M^{\ddagger}$ 662 (3.40; $C_{41}H_{58}O_7$), 442 (19.20; $C_{29}H_{46}O_3$), 382 (69.50; $C_{27}H_{42}O$), 367 (17.00; $C_{26}H_{39}O$), 364 (8.20), 340 (8.50), 269 (20.50; $C_{19}H_{25}O$), 255 (10.50), 254 (7.20), 253 (6.90), 252 (12.30), 251 (5.25), 250 (12.30), 249 (22.75), 248 (32.30), 246 (26.90), 245 (5.60), 244 (5.80), 243 (4.10), 240 (5.00), 239 (10.10), 238 (4.80), 235 (7.90), 234 (10.20), 232 (15.25), 231 (10.00), 230 (5.50), 229 (8.10), 228 (13.10), 227 (6.90), 225 (27.20), 224 (4.30), 220 (87.50; $C_{12}H_{12}O_4$), 214 (11.25), 213 (37.40), 212 (8.60), 211 (20.10), 210 (32.40), 209 (4.80), 207 (3.90), 206 (4.80), 205 (4.80), 204 (12.75), 200 (10.00), 199 (6.90), 198 (21.10), 197 (6.90), 196 (12.25), 195 (9.20), 194 (9.20), 193 (5.00), 192 (18.75; $C_{11}H_{12}O_3$), 191 (4.20), 190 (4.20), 189 (5.75), 188 (8.80), 187 (38.50; $C_{13}H_{15}O$), 186 (13.80), 185 (9.75), 184 (5.00), 183 (17.00), 182 (6.90), 181 (4.80), 180 (14.25), 179 (9.10), 178 (9.10), 177 (27.30; $C_{10}H_9O_3$), 176 (10.30), 175 (5.40), 174 (100.00; $C_{12}H_{14}O$), 173 (15.00), 172 (12.40), 171 (13.25), 170 (22.30), 169 (10.00), 168 (18.75), 167 (10.90), 165 (7.70), 164 (10.25), 163 (5.40), 162 (4.80), 161 (39.00; $C_{11}H_{13}O$), 160 (24.90), 159 (27.40), 158 (14.50), 157 (32.75), 156 (10.00), 150 (12.00), 149 (25.50; $C_9 H_9 O_2$), 148 (7.40), 147 (12.40), 146 (7.40), 145 (10.75), 144 (9.00), 143 (8.75), 142 (4.80), 141 (4.80), 140 (5.20), 137 (8.20), 136 (10.00), 135 (15.25), 134 (17.50; $C_9 H_{10} O$), 133 (11.10), 132 (17.40), 131 (8.80), 130 (6.90), 129 (14.90), 128 (12.10), 123 (16.75), 122 (14.20), 120 (24.00), 119 (13.75), 118 (16.25), 117 (9.20), 116 (7.20), 115 (12.00), 110 (21.50), 109 (18.00), 108 (12.40), 107 (21.20), 106 (15.00), 105 (9.60), 104 (17.20), 103 (7.30), 97 (20.90), 96 (45.50), 95 (17.00), 94 (15.90), 85 (10.20), 84 (11.75), 83 (41.10), 82 (20.20), 81 (25.60), 80 (19.90), 79 (26.25), 78 (14.75), 77 (7.60), 76 (32.90), 71 (48.00), 70 (32.90), 69 (61.20), 68 (29.00), 67 (47.30), 66 (8.00), 63 (49.20), 62 (5.50), 59 (16.00), 58 (4.80), 57 (16.10), 56 (6.80), 55 (21.75), 54 (16.00), 53 (32.10), 52(10.00), 51 (11.20), 50 (10.40), 48 (19.40), 47 (32.50); 46 (9.00), 44 (35.70), 43 (12.30), 42 (25.00), 41 (34.50).

Further elution with light petrolem ether/ether (1:1) provided 1:1 C4-photoadduct (CXX) which was recrystallized from methanol (0.84 g; 1.27 m mol) m.p. 194°C.

Analysis Found : C, 74.30; H, 8.16

$C_{41} H_{58} O_7$ requires : C, 74.28; H, 8.19%

IR : ν max 1750 (carbonyl of coumarin moiety), 1725 (CH_3COO), 1710 (C=O), 1600 (C=C, aromatic), 1050 (C-O) and 860 cm^{-1} (cyclobutane).

^{1}H-NMR : δ 6.8 (mc, 2H, aromatic), 4.9 (mc, 1H, C3-αH, $W_{1/2}$ = 15 Hz, A/B ring junction trans)[36], 3.97 (s, 1H, cyclobutane proton), 3.89 (s, 1H, cyclobutane proton), 3.84 (s, 3H, 7-OCH_3), 3.75 (s, 3H, 5-OCH_3), 2.0 (s, 3H, CH_3COO), 1.3 (s, 3H, methyl proton of cyclobutane), 1.15 (C10-CH_3), 0.69 (C13-CH_3), 0.91 and 0.84 (other methyl protons).

CD (methanol) : $[\theta]_{294}$+5214

MS : M^{+} 662 (2.75; $C_{41}H_{58}O_7$); 442 (15.10; $C_{29}H_{46}O_3$), 382 (66.90; $C_{27}H_{42}O$), 367 (20.25; $C_{26}H_{39}O$), 364 (9.00), 340 (7.60), 269 (22.00; $C_{19}H_{25}O$), 255 (11.50), 254 (8.40), 253 (7.20), 252 (10.75), 251 (5.00), 250 (14.40), 249 (20.25), 248 (30.30), 247 (4.80), 246 (27.25), 245 (6.60), 244 (6.60), 243 (5.00), 242 (5.00), 241 (4.80), 240 (5.00), 239 (12.25), 238 (5.20), 235 (10.00), 234 (9.50), 232 (16.20), 231 (9.60), 230 (6.50), 229 (9.60), 228 (13.00), 227 (8.00), 226 (8.00), 225 (24.40), 224 (5.00), 220 (72.20; $C_{12}H_{12}O_4$), 214 (10.00), 213 (35.50), 212 (9.60), 211 (17.50), 210 (30.00), 209 (5.50), 208 (9.60), 207 (9.60), 206 (4.80), 205 (5.50), 204 (10.50), 200 (12.00), 199 (8.00), 198 (19.25), 197 (7.20), 196 (10.25), 193 (4.80), 192 (20.75; $C_{11}H_{12}O_3$), 191 (4.80), 188 (10.00), 187 (32.50; $C_{13}H_{15}O$), 186 (13.00), 185 (10.25), 184 (7.20), 183 (15.00), 182 (7.40), 181 (7.40), 180 (13.50), 179 (4.80), 178 (10.75), 177 (29.30; $C_{10}H_9O_3$), 176 (12.25), 175 (6.60), 174 (100.00; $C_{12}H_{14}O$), 173 (16.20), 172 (13.00), 171 (12.25), 170 (20.20), 169 (9.60), 168 (17.30), 167 (9.60), 166 (8.40), 165 (8.40), 164

(9.60), 163 (7.20), 162 (5.00), 161 (41.25; $C_{11}H_{13}O$), 160 (26.20), 159 (25.00), 158 (12.20), 157 (30.00), 156 (8.40), 150 (11.00), 149 (27.25; $C_9H_9O_2$), 148 (22.20), 147 (10.50), 146 (9.60), 145 (9.60), 144 (8.40), 143 (8.40), 142 (5.50), 141 (5.50), 140 (6.20), 137 (8.00), 136 (12.00), 135 (13.00), 134 (23.75; $C_9H_{10}O$), 133 (9.80), 132 (15.25), 131 (8.90), 123 (18.00), 122 (18.00), 121 (5.00), 120 (27.25), 119 (15.00), 118 (14.50), 117 (10.50), 116 (6.60), 115 (12.75), 114 (9.60), 107 (22.50), 106 (16.25), 105 (10.50), 104 (16.60), 103 (8.40), 85 (17.25), 84 (12.75), 83 (39.50), 82 (16.20), 81 (23.30), 80 (17.50), 79 (27.10), 78 (12.00), 77 (8.40), 76 (35.00), 71 (45.25), 70 (29.10), 69 (57.20), 68 (27.30), 67 (42.10), 66 (10.50), 65 (12.10), 64 (9.60), 63 (38.80), 62 (10.00), 61 (9.60), 60 (9.60), 59 (17.00), 58 (5.00), 57 (19.50), 56 (9.50), 55 (19.25), 54 (17.30), 53 (29.10), 52 (7.20), 51 (7.20), 50 (10.40), 49 (10.40), 48 (19.20), 47 (25.25), 46 (8.60), 45 (8.60), 44 (35.00), 43 (15.30), 42 (27.75), 41 (39.10), 40 (32.25).

Cholesta-3,5 - dien-7-one (CXXI)

To a solution of 3β-acetoxycholest-5-en-7-one (4.0g) in ethanol (100 ml) was added hydrochloric acid (5 ml, 12 N) and the reaction mixture was refluxed for 2 hrs. The reaction mixture was allowed to cool, and the separated pellets of dienone was filtered and recrystallized from ethanol (3.5 g) m.p. 114°C (reported[40] m.p. 113-114°C).

Reaction of cholesta-3,5-dien-7-one (CXXI) with 4-methyl-5-methoxycoumarin: 1:1 C4-photoadduct (CXXII) and 1:1 C4-photoadduct (CXXIII)

Cholesta -3,5-dien-7-one (4.0g; 10.45 m mol) and 4-methyl-5-methoxy coumarin (1.0g; 5.26 m mol) were adsorbed on silica gel G (10g) by dissolving them in dry dichloromethane (35 ml). Evaporation of the solvent furnished a thin and dry film in petri-dishes which were placed at a distance of 15 cm from the lamp arranged in horizontal manner and irradiated. After irradiating for 30 min. the film was reformed as usual and irradiated again. This process was repeated several times. After the irradiation, the mixture was taken in dichlorometane, filtered and chromatographed over a column of silica gel. Elution with light petroleum ether/ ether (3:1) furnished, 1:1 C4-photoadduct (CXXII), which was recrystallized from methanol (1.21 g; 1.266 m mol) m.p. 132°C.

Analysis Found : C, 79.65; H, 9.11

$C_{38}H_{52}O_4$ requires : C, 79.68; H, 9.15%

IR : νmax 1750 (carbonyl of coumarin moeity), 1720 (C=0), 1610 (C=C), 1595 (C=C, aromatic), and 850 cm^{-1} (cyclobutane).

^{1}H-NMR : δ 6.7 (mc, 3H, aromatic protons), 5.54-5.43 (m, 2H, C3 and C4 vinylic protons), 3.91 (s, 1H, cyclobutane proton), 3.84 (s, 1H, cyclobutane proton), 3.7 (s, 3H, OCH_3) 1.4 (s, 3H, methyl protons of cyclobutane), 1.05 (C10-CH_3), 0.67 (C13-CH_3), 0.91 and 0.83 (other methyl protons).

CD (methanol) : $[\theta]_{290} -3712$

MS : $M^{+\cdot}$ 572 (4.00; $C_{38} H_{52} O_4$), 382 (79.25; $C_{27} H_{42} O$), 367 (20.00; $C_{26} H_{39} O$), 364 (7.70), 340 (17.20), 269 (27.30; $C_{19} H_{15} O$), 252 (14.80), 251 (5.00), 250 (11.20), 249 (25.00), 248 (34.00), 247 (5.40), 246 (30.75), 245 (4.80), 244 (4.80), 239 (10.20), 238 (4.80), 235 (7.00), 234 (8.20), 233 (5.00), 232 (14.00), 231 (10.00), 230 (5.50), 229 (7.90), 228 (10.50), 227 (6.90), 225 (30.90), 224 (4.80), 214 (10.00), 213 (37.20), 212 (7.00), 211 (20.75), 210 (27.75), 209 (5.20), 208 (5.20), 207 (4.20), 206 (4.80), 205 (4.80), 200 (11.20), 199 (8.40), 198 (20.40), 197 (11.25), 196 (24.00), 195 (8.40), 194 (8.40), 193 (8.40), 191 (4.70), 190 (77.00; $C_{11} H_{10} O_3$), 189 (6.20), 188 (7.70), 187 (40.20; $C_{13} H_{15} O$), 186 (11.50), 185 (11.50), 184 (7.40), 183 (18.50), 182 (10.00), 180 (15.00), 178 (9.60), 177 (14.40), 176 (12.20), 175 (4.80), 174 (100.00; $C_{12} H_{14} O$), 173 (14.20), 172 (14.20), 171 (12.50), 170 (25.00), 169 (10.75), 168 (20.00), 166 (13.20), 165 (8.20), 164 (9.60), 163 (7.40), 162 (40.00; $C_{10} H_{10} O_2$), 161 (35.30; $C_{11} H_{13} O$), 160 (24.00), 159 (25.25), 158 (17.25), 157 (36.00), 156 (8.90), 150 (13.75), 149 (13.90), 148 (7.50), 147 (25.25; $C_9 H_7 O_2$), 146 (16.00), 145 (8.20), 144 (10.00), 143 (11.00), 142 (12.75), 141 (8.00), 140 (11.50), 137 (6.60), 136 (12.40), 135 (14.00), 134 (31.00); $C_9 H_{10} O$), 133 (13.20), 132 (20.00), 131 (10.00), 130 (7.00), 129 (13.75), 128 (11.60), 123 (14.00), 122 (12.25), 121 (9.60), 120 (21.75), 119 (37.20; $C_8 H_7 O$), 118 (17.20), 117 (14.20), 116 (7.40), 115 (12.75), 110 (24.00), 109 (27.20), 108 (14.00), 107 (19.50), 106 (14.00), 105 (11.20), 104 (22.20), 103 (6.90), 96 (40.20), 95 (17.70), 94 (11.20), 85 (10.00), 84 (9.60), 83 (32.25), 82 (20.00), 81 (25.20), 80 (19.10), 79(26.60), 78 (13.60), 77 (8.20), 76 (32.00), 71 (42.00), 70 (32.40), 69 (51.70), 68 (24.00), 67 (42.00), 66 (12.25), 62 (45.00), 61 (9.60), 59 (12.50), 58 (6.00), 57 (18.70), 56 (8.40), 55 (24.30), 54 (14.25), 53 (32.75), 52 (10.00), 51 (9.90), 50 (7.25), 49 (7.25), 46(10.50), 45 (20.00), 44 (10.50), 43 (29.30), 42 (40.00), 41 (32.20).

Further elution with light petroleum ether/ether (1:1) afforded 1:1 C4-photoadduct (CXXIII) which was recrystallized from methanol (1.05 g; 1.10 m mol) m.p. 145°C.

Analysis Found : C, 79.64; H, 9.11

$C_{38}H_{52}O_4$ requires : C, 79.68; H, 9.15%

IR : νmax 1760 (carbonyl of coumarin group), 1710 (C=0), 1615 (C=C), 1600 (C=C, aromatic), and 840 cm^{-1} (cyclobutane).

^{1}H-NMR : δ 6.8 (mc, 3H, aromatic protons), 5.57-5.41 (m, 2H, C3 and C4 vinylic protons), 3.89 (s, 1H, cyclobutane proton), 3.80 (s, 1H, cyclobutane proton), 3.76 (s, 3H, OCH_3), 1.25 (s, 3H, methyl protons of cyclobutane), 1.1 (C10-CH_3), 0.74 (C13-CH_3), 0.95 and 0.80 (other methyl protons).

CD (methanol) : $[\theta]_{290}+4172$

MS : M^{+} 572 (3.10; $C_{38}H_{52}O_4$), 382 (84.50; $C_{27}H_{42}O$), 367 (24.00); $C_{26}H_{39}O$), 364 (4.80), 340 (6.60), 269 (31.70;

$C_{19} H_{25} O$), 255 (10.00), 254 (5.10), 253 (5.10), 252 (12.40), 251 (6.60), 250 (12.60), 249 (23.30), 248 (35.50), 247 (5.00), 246 (27.70), 245 (5.00), 244 (5.00), 243 (4.20), 240 (5.60), 239 (12.30), 238 (5.60), 235 (9.60), 234 (7.20), 233 (6.00), 232 (14.50), 231 (9.60), 230 (7.20), 229 (8.40), 228 (12.40), 227 (7.40), 225 (25.25), 224 (4.80), 214 (12.40), 213 (32.20), 212 (6.00), 211 (17.10), 210 (29.20), 209 (6.40), 208 (6.40), 207 (5.50), 206 (5.50), 205 (5.50), 200 (12.20), 199 (9.60), 198 (19.20), 197 (9.60), 196 (22.00), 195 (9.60), 194 (9.60), 193 (9.60), 192 (8.40), 191 (8.40), 190 (75.25; $C_{11} H_{10} O_3$), 189 (7.40), 188 (9.60), 187 (38.75; $C_{13} H_{15} O$), 186 (12.25), 184 (4.80), 183 (19.00), 182 (9.40), 180 (16.20), 179 (6.40), 178 (10.25), 177 (14.00), 176 (10.40), 175 (5.50), 174 (100.00; $C_{12} H_{14} O$), 173 (11.10), 172 (10.40), 171 (10.40), 170 (14.25), 166 (15.00), 165 (9.40), 164 (9.40), 163 (5.00), 162 (41.25; $C_{10} H_{10} O_2$), 161 (34.50; $C_{11} H_{13} O$), 160 (22.10), 159 (20.00), 158 (15.00), 157 (22.20), 156 (10.25), 155 (9.60), 150 (14.25), 149 (14.25), 148 (6.60), 147 (26.00; $C_9 H_7 O_2$), 146 (12.00), 145 (7.40), 144 (8.40), 143 (9.60), 142 (13.50), 141 (6.60), 140 (10.00), 139 (5.00), 138 (5.00), 137 (7.40), 136 (14.25), 135 (14.75), 134 (35.40; $C_9 H_{10} O$), 133 (12.20), 132 (17.20), 131 (9.40), 130 (6.60), 129 (12.00), 123 (15.50), 122 (13.00) 121 (8.40), 120 (19.90), 119 (36.00; $C_8 H_7 O$), 118 (14.20), 117 (13.00), 116 (6.50), 115 (11.50), 114 (4.80), 110 (20.25), 109 (24.40), 108 (13.40), 107 (17.50), 106 (12.00), 105

(10.50), 104 (21.00), 103 (8.50), 102 (5.40), 99 (5.40), 98 (6.20), 97 (18.40), 96 (35.50), 95 (16.20), 94 (9.60), 83 (29.50), 82 (18.40), 81 (17.50), 80 (19.10), 79 (24.25), 78 (11.50), 77 (6.40), 76 (24.50), 75 (8.40), 74 (6.40), 71 (37.50), 70 (30.00), 69 (41.20), 68 (22.40), 67 (39.50), 66 (10.50), 59 (14.00), 58 (7.40), 57 (14.50), 56 (9.60), 55 (25.50), 54 (13.25), 53 (30.00), 52 (9.60), 57 (9.60), 50 (6.60), 45 (22.25), 44 (9.40), 43 (30.25), 42 (42.50), 41 (35.00).

Reaction of cholesta-3,5-dien-7-one (CXXI) with 4-methyl-5,7-dimethoxy coumarin: 1:1 C4-photoadduct (CXXIV) and 1:1 C4-photoadduct (CXXV)

Cholesta-3,5-dien-7-one (4.0g; 10.45 m mol) and 4-methyl-5,7-dimethoxy coumarin (1.0g; 4.54 m mol) were adosrbed on silica gel G (10g) by dissolving them in dry di chloromethane (35 ml). After evaporation of the solvent. The resulting thin and dried film was placed 15 cm away from the lamp arranged in horizontal manner and irradiated. After irradiating for 30 min. The film was dissolved and reformed as described earlier and irradiated. This process was repeated several times. After the irradiation the mixture was dissolved in dichloromethane, filtered and chromatographed over a coloum of silica gel. Elution with light petroleum / ether (3:1) afforded 1:1 C4-photoadduct (CXXIV) which was recrystallized from methanol (1.28g; 2.12 m mol) m.p. 141-42°C.

Analysis Found : C, 77.68; H, 9.01

C_{39} H_{54} O_5 requires : C, 77.70; H, 9.03%

IR : ν max 1755 (carbonyl of coumarin moiety), 1720 (C=O), 1610 (C=C), 1600 (C=C, aromatic) and 850 cm^{-1} (cyclobutane).

^1H-NMR : δ 6.7 (mc, 2H, aromatic protons), 5.5-5.41 (m, 2H, C3- and C4- vinylic protons), 3.91 (s, 1H, cyclobutane proton), 3.87 (s, 1H, cyclobutane proton), 3.80 (s, 3H, 7-OCH_3), 3.72 (s, 3H, 5-OCH_3), 1.32 (s, 3H, methyl protons of cyclobutane), 1.14 (C10-CH_3), 0.67 (C13-CH_3), 0.95 and 0.81 (other methyl protons).

CD (methanol) : $[\theta]_{291}{}^{-476}$]

MS : $M^{\dot{+}}$ 602 (2.90; C_{39} H_{54} O_5), 382 (84.50; C_{27} $H_{42}O$), 367 (22.50; C_{26} H_{39} O), 364 (7.50), 340 (10.00), 269 (27.40; C_{19} $H_{25}O$), 254 (8.00), 253 (7.00), 252 (13.50), 251 (5.00), 250 (12.00), 249 (20.75), 248 (31.20), 247 (9.60), 246 (30.20), 245 (7.20), 244 (5.40), 243 (5.00), 242 (5.00), 241 (4.60), 240 (5.00), 239 (11.90), 238 (4.80), 237 (6.60), 236 (6.60), 235 (7.90), 234 (11.20), 233 (4.80), 232 (17.00), 231 (12.25), 230 (6.20), 229 (8.00), 228 (12.50), 225 (25.20), 224 (5.50), 223 (5.50), 221 (4.80), 220 (80.00; C_{12} H_{12} O_4), 219 (5.00), 218 (5.00), 214 (12.40), 213 (31.00), 212 (8.50), 211 (21.60), 210 (32.60), 209 (4.80), 207 (6.40), 200 (12.00), 199 (7.40), 198 (20.50), 197 (6.60), 196 (12.25), 195 (10.00), 194 (10.00), 193 (4.80), 192 (32.00; C_{11} H_{12} O_3), 191 (4.20), 190 (4.20), 189 (6.25), 188 (9.10), 187 (38.50; C_{13} $H_{15}O$), 186 (12.25), 185 (10.00), 184 (6.20), 183 (18.10), 182 (7.40), 181 (5.00), 180 (15.50), 179 (6.40), 178 (10.00), 177 (16.25; C_9 H_7 O_2), 176 (11.10), 175 (5.00), 174 (100.00; C_{12} H_{14} O), 173 (17.40), 172 (14.10), 171 (12.00), 170 (25.25), 169 (9.60), 168 (17.25), 167 (11.20), 166 (6.50), 165 (8.20), 164 (10.00), 163 (6.20), 162 (4.80), 161 (42.00; C_{11} H_{13} O), 160 (25.75), 159 (29.10), 158 (12.00), 157 (33.50), 156 (9.50), 150 (10.75), 149 (15.90); C_9 H_9 O_2), 148 (7.00), 147 (11.25), 146 (7.40), 145 (11.50), 144 (9.80), 143 (7.20), 142 (4.80), 141 (4.80), 140 (5.90), 137 (8.10), 136 (9.60), 135 (15.00), 134 (20.50; C_9 H_{10} O), 133 (10.50), 132 (15.00), 131 (9.60), 130 (5.50), 129 (14.00), 128 (11.50), 123 (16.00), 122 (15.10), 120 (22.25), 119 (12.20), 118 (14.00), 117 (10.00), 116 (8.20), 115 (11.25), 110 (20.00), 109 (16.40), 108 (12.00), 107 (20.25), 106 (14.30), 105 (10.00), 104 (16.30), 103 (7.30), 97 (22.25), 96 (45.00), 95 (15.50), 94 (14.75), 86 (12.25), 85 (10.00), 84 (11.00), 83 (40.20), 82 (19.20), 81 (26.25), 80 (20.25), 79 (25.00), 78 (13.70), 77 (8.20), 76 (30.00), 70 (47.50), 69 (35.20), 68 (56.10), 67 (24.25), 66 (41.30), 63 (47.50), 62 (6.20), 59 (13.75), 58 (4.80), 57 (15.50), 56 (6.00), 55 (20.00), 54 (15.50), 53 (31.00), 52 (9.60), 51 (10.75), 50 (10.75), 49 (20.00), 48 (30.50), 47 (9.00), 44 (37.70), 43 (15.40), 42 (29.00), 41 (34.50).

Further elution with light petroleum ether/ether (1:1) furnished 1:1 C4-photoadduct (CXXV) which was recrystallized from methanol (0.97 g; 1.62 m mol) m.p. 150-51^{o}C.

Analysis Found : C, 77.64; H, 8.98

$C_{39} H_{54} O_5$ requires : C, 77.70; H, 9.03%

IR : ν max 1760 (carbonyl of coumarin moiety), 1715 (C=0), 1610 (C=C), 1595 (C=C, aromatic), and 860 cm^{-1} (cyclobutane).

^{1}H-NMR : δ 6.5 (mc, 2H, aromatic protons), 5.5-5.4 (m, 2H, C3-and C4-Vinylic protons), 3.95 (s, 1H, cyclobutane proton), 3.87 (s, 1H, cyclobutane proton), 3.81 (s, 3H, 7-OCH_3), 3.74 (s, 3H, 5-OCH_3), 1.3 (s, 3H, methyl protons of cyclobutane), 1.05 (C10-CH_3), 0.71 (C13-CH_3), 0.94 and 0.80 (other methyl protons).

CD (methanol) : $[\theta]_{297}$+5621

MS : M^{+} 602 (3.30;$C_{39} H_{54} O_5$), 382 (80.50; $C_{27} H_{42} O_3$), 367 (27.25; $C_{26} H_{39} O$), 364 (6.50), 340 (9.60), 269 (30.00; $C_{19} H_{25} O$), 258 (5.50), 257 (5.50), 256 (8.40), 255 (8.40), 254 (10.00), 253 (7.50), 252 (15.25), 251 (7.50), 250 (10.00), 249 (22.70), 248 (19.40), 247 (8.40), 246 (24.30), 245 (9.20), 244 (6.60), 243 (6.60), 240 (7.20), 239 (12.40), 238 (5.00), 237 (5.00), 235 (10.00), 234 (10.50), 233 (8.50), 232 (15.25), 231 (11.50), 230 (7.40), 229 (9.60), 228 (14.40), 225 (23.50), 224 (6.50), 223 (5.00), 220 (78.75; $C_{12} H_{12} O_4$), 219 (6.60), 218 (5.00), 217 (4.50), 214 (10.75), 213

(30.00), 212 (9.40), 211 (22.60), 210 (32.00), 209 (5.00), 208 (4.00), 200 (13.50), 199 (9.60), 198 (17.50), 197 (8.50), 196 (14.00), 195 (11.25), 194 (11.25), 193 (4.00), 192 (35.25; $C_{11} H_{12} O_3$), 191 (4.50), 190 (4.50), 189 (7.20), 188 (10.00), 187 (40.00; $C_{13} H_{15} O$), 186 (13.25), 185 (10.50), 183 (16.60), 182 (6.60), 181 (4.80), 180 (12.50), 178 (12.50), 177 (19.50; $C_{10} H_9O$), 176 (13.00), 175 (5.00), 174 (100.00; $C_{12} H_{14} O$), 173 (19.00), 172 (13.40), 171 (10.00), 170 (19.50), 169 (22.25), 168 (17.40), 164 (12.50), 163 (9.60), 162 (6.60), 161 (45.25; $C_{11} H_{13} O$), 160 (24.50), 159 (25.50), 158 (10.00), 157 (30.00), 156 (10.50), 150 (13.00), 149 (17.40); $C_9 H_9 O_2$), 148 (6.20), 147 (10.00), 146 (7.40), 145 (13.00), 144 (8.40), 143 (10.00), 142 (5.00), 141 (6.20), 140 (7.40), 139 (7.40), 137 (8.10), 136 (9.60), 135 (12.50), 134 (17.25; $C_9 H_{10} O$), 133 (8.40), 132 (12.50), 131 (10.00), 130 (7.20), 129 (14.00), 128 (11.50), 123 (18.50), 122 (12.75), 121 (9.60), 120 (24.25), 119 (10.50), 118 (12.50), 117 (9.40), 116 (10.00), 115 (10.00), 107 (24.00), 106 (16.50), 105 (10.50), 104 (17.70), 103 (9.80), 102 (6.60), 97 (19.50), 96 (27.30), 95 (35.25), 94 (15.40), 93 (10.50), 92 (9.50), 87 (9.00), 86 (13.00), 85 (8.80), 84 (14.00), 83 (30.25), 82 (16.60), 81 (20.00), 80 (20.25), 79 (22.50), 78 (10.50), 77 (10.50), 76 (25.00), 75 (14.20), 74 (13.00), 73 (12.00), 72 (9.40), 71 (40.00), 70 (31.00), 69 (40.50), 68

(20.25), 67 (27.25), 66 (9.00), 59 (17.20), 58 (7.40), 57 (15.50), 56 (7.40), 55 (25.00), 54 (10.50), 53 (27.25), 52 (10.00), 51 (10.00), 50 (10.00), 49 (22.25), 48 (26.50), 47 (9.40), 46 (7.20), 45 (15.00), 44 (42.50), 43 (10.40), 442 (38.25), 41 (25.20).

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CHAPTER TWO

Oxidation of steroidal olefins

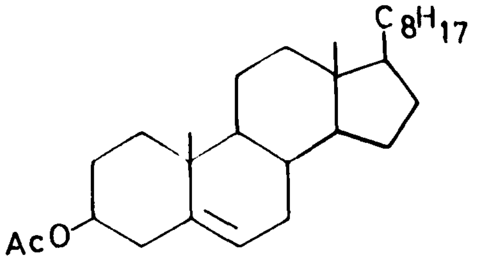
THEORETICAL

The development of novel reaction routes in synthetic organic chemistry by oxidation methods[1] have been very lucrative for organic chemists. Susceptibility of alkenes to electrophilic attack and their capability to reduce most of the oxidants motivated the chemists to study the oxidizing effects of transition metal ions and oxides on alkenes. The importance of metal ion as oxidants is indubitable because of their low cost, stability and considerable selectivity with respect to functional groups by virtue of their action.

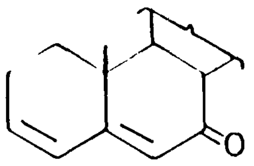
The most commonly used inorganic oxidants are potassium permanganate, osmium tetraoxide, ruthenium tetraoxide, palladium chloride, potassium peroxydisulfate and certain chromium and mercury salts.

Alkenes undergo either exhaustive oxidation or allylic oxidation depending upon the reaction conditions, reagents used and on the nature of the oxidant. In some cases, these reactions are carried out even at room temperature but in most of the cases elevated temperatures are required. The products of these oxidations from olefins are ketones, diols, α-ketols and other degraded products.

Windus and Naggatz[2] reported the oxidation of cholesteryl acetate (I) with chromic acid in acetic acid, which yielded cholesta-3,5-dien-7-one (II).

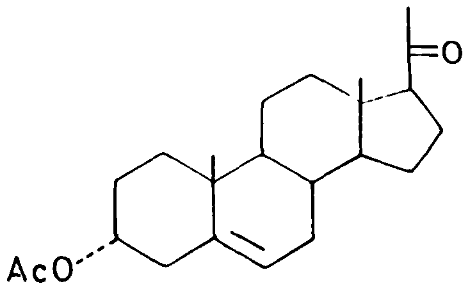


(I)

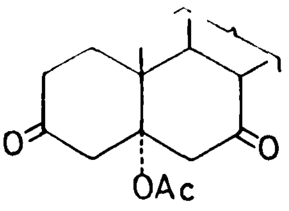


(II)

Fieser et al.[3,4] identified the oxidation product obtained by Windus and Naggatz by chromic acid oxidation of epicholesteryl acetate (III) as 5-acetoxy-5α-cholestan-3,7-dione (IV) and suggested the intramolecular C3-C5 acyl migration.



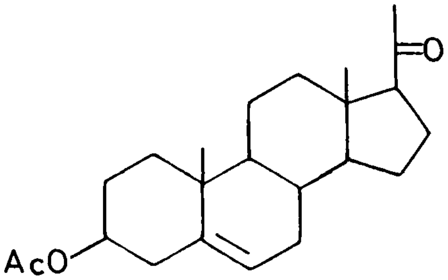
(III)



(IV)

The formation of α,β-unsaturated ketones has also been reported from the oxidation of steroidal alkenes with chromic acid. Marshall et al.[5] reported the introduction of ketone (VI) at C-7 of pregnolone acetate (V) using sodium chromate in acetic acid-acetic anhydride solution. Wintersteiner and Moore[6] treated (Δ^{8-14}) - cholesteryl acetate (VII) with CrO_3-AcOH and obtained five products (VIII-XII). Elks et al.[7]

obtained 5,6-seco product (XIII) by treating cholesteryl acetate (I) with chromic acid.



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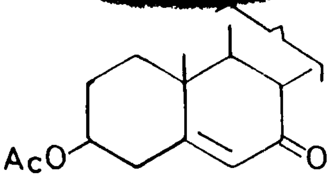

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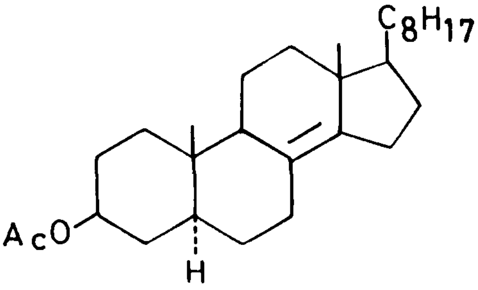

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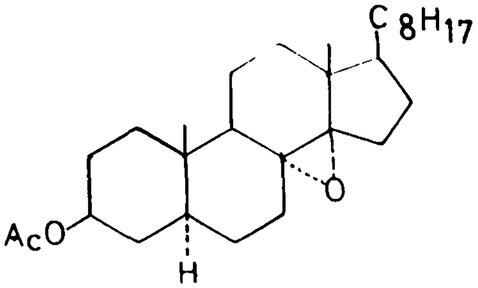

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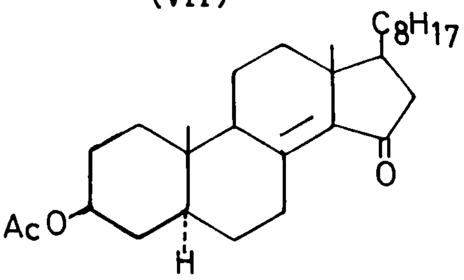

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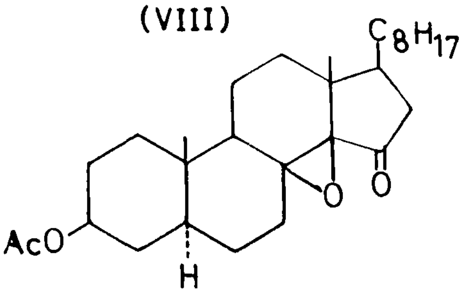

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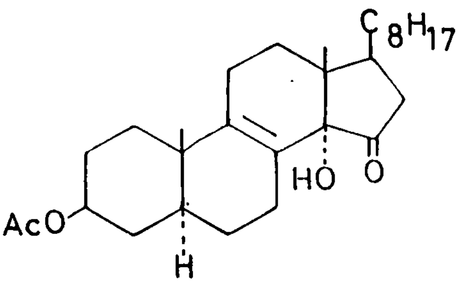

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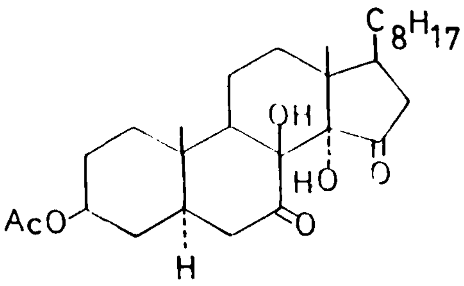

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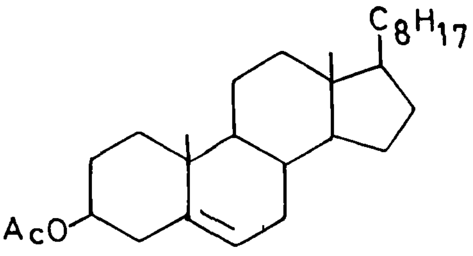

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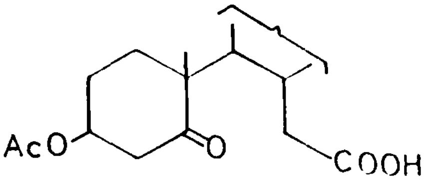
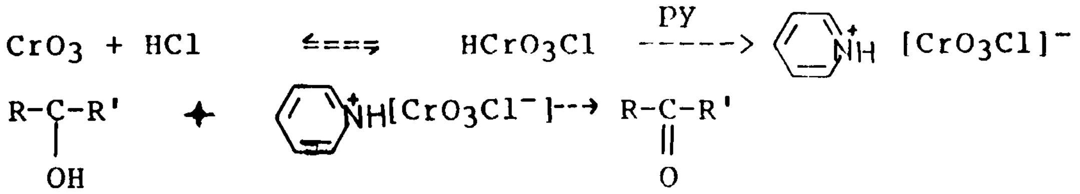
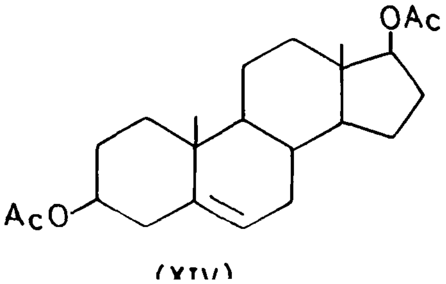
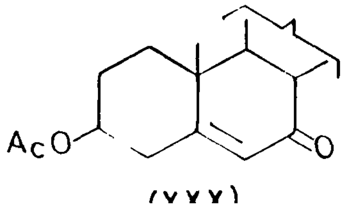


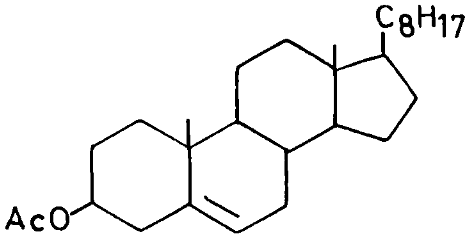
(XIII)

Corey and Suggs[8] have studied the use of pyridinium chlorochromate as oxidant. They reported the advantage of this reagent over others and showed that it can be prepared easily, safely and also possesses high capability to convert primary alcohols into aldehydes in better yield.



William and co-workers[9] reported the oxidation of olefins (I, XIV-XXIX) with chromium trioxide-pyridine complex at room temperature and obtained the following products (XXX-LV) in good to moderate yield.

Olefin	Ketone
 (XIV)	 (XXX)



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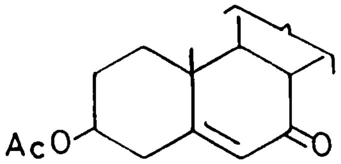

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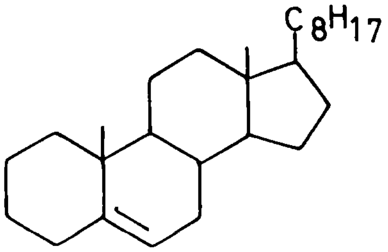

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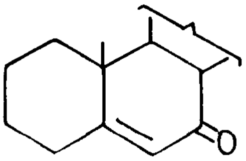

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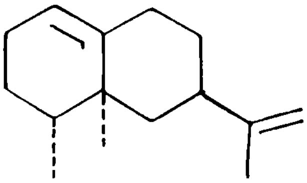

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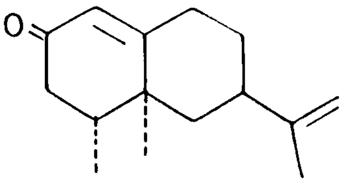

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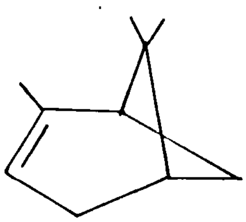

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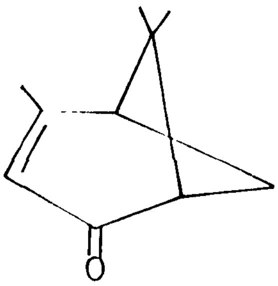
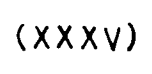


(XXXIV)

(XVIII)



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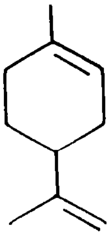

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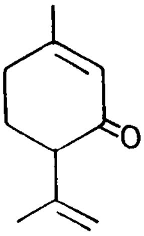

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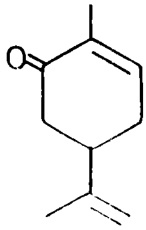

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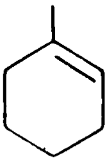

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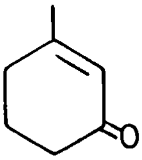

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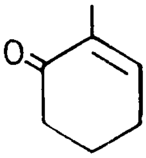

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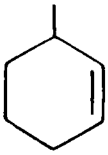
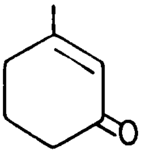


(XXI)



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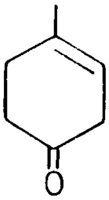

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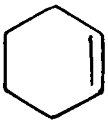

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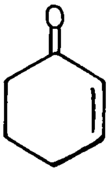

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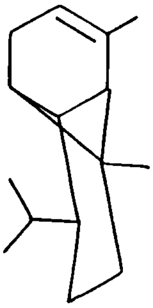

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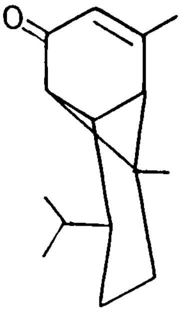

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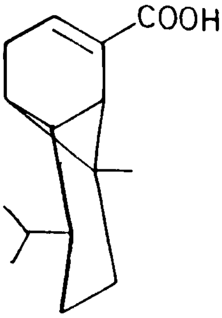

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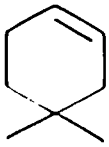

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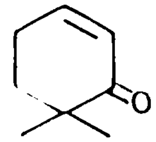

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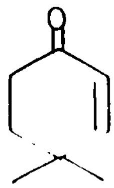

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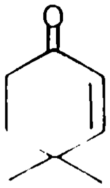

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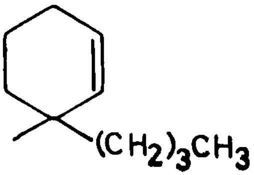

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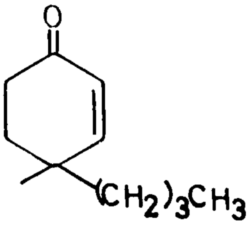

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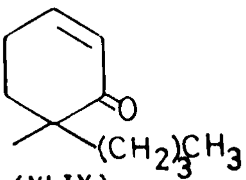

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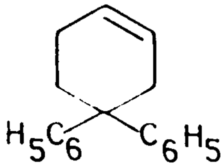

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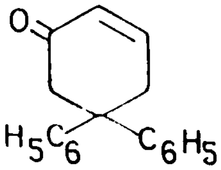

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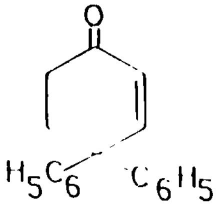

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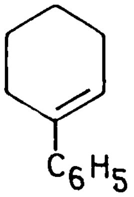

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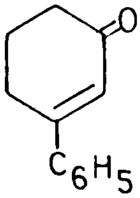

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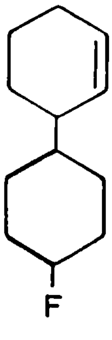

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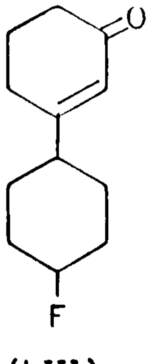

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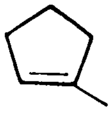

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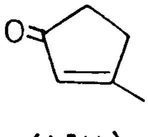

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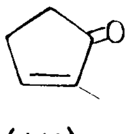
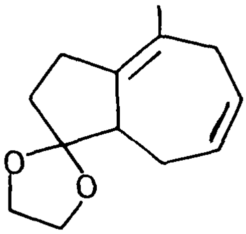


(LV)

Wender et al.[10] reported the oxidation of 1,4-diene (LVI) by pyridinium chlorochromate and obtained dienones (LVII) and (LVIII). Marshall and Wuts[11] reported an analogous behaviour of 1,4,-diene (LIX) with pyridinium chlorochromate which yielded two products (LX and LXI).



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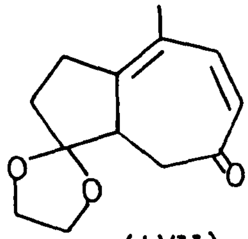

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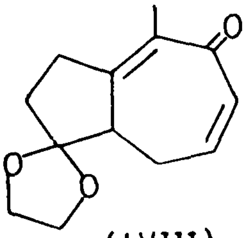

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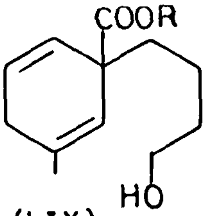

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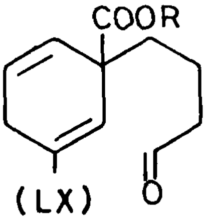

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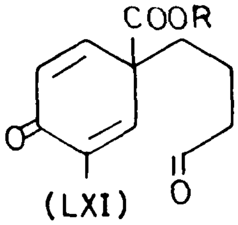
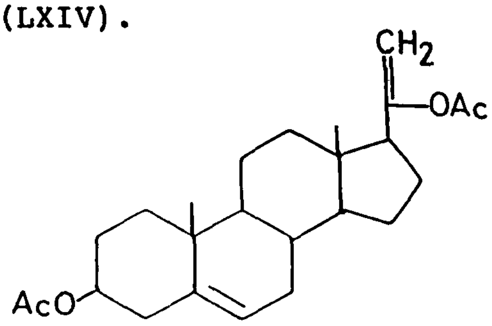


(LXI)

Djerassi and Lenk[12] reported the use of N-iodosuccinimide for the synthesis of iodoketones. They treated steroidal enol acetate (LXII) with N-iodosuccinimide and obtained 21-iodopregnenolone acetate (LXIII). Muller and Jones[13] prepared, α-iodoketone (LXV) from the enol acetate (LXIV).



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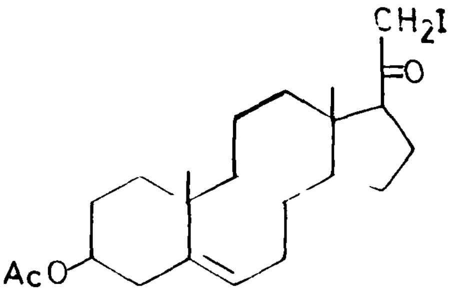

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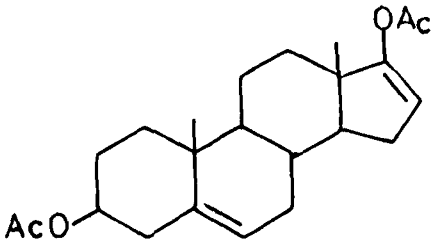

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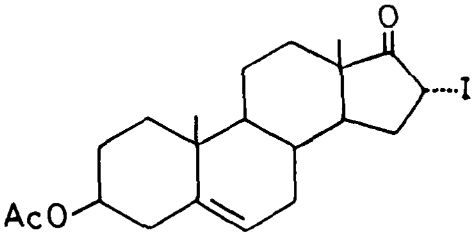
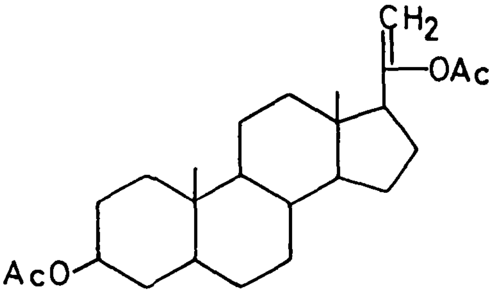


(LXV)

Djerassi and Lenk[14] treated unsaturated enol acetate such as 20-acetoxy- $\Delta^{16,20}$-diene (LXVI) with N-iodosuccinimide in dioxane and obtained the iodoketone (LXVII). They observed that the double bond present in ring D did not interfere in the reaction.



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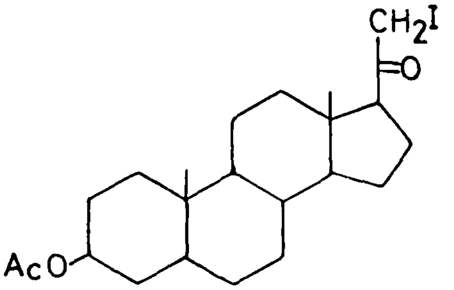


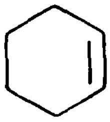
(LXVII)

Ascoli et al.[15] summarized the preparation of α-iodoketones (LXXIII-LXXVII) by the reaction of pyridinium dichromate-iodine with the cyclic olefins (LXVIII-LXXII). They treated different cyclic olefins with pyridinium dichromate-iodine and afforded the corresponding α-iodoketones (table-I).

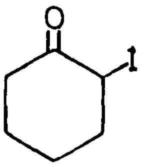
Table-I

Olefin	α-Iodoketone	Yield in %
1-Cyclohexene (LXVIII)	2 α- Iodocyclohexanone (LXXIII)	50
1-Cyclooctene (LXIX)	2- Iodocyclooctanone (LXXIV)	60
4t-Butyl-1-cyclohexene (LXX)	<u>Trans</u> 2α-iodo-4-t-butyl-cyclohexanone (LXXV)	62
1-Phenyl-1-cyclohexene (LXXI)	<u>Cis</u> 1-phenyl-2α-Iodo-cyclohexanol (LXXVI)	60
2-Cholestene (LXXII)	3α-Iodocholestan-2-one (LXXVII)	70

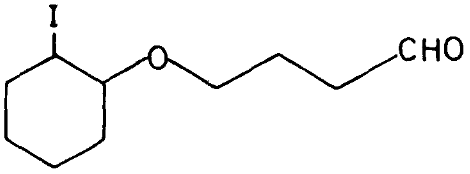
Cardillo and Shimizu[16] reported that the oxidation of olefins by silver chromate can be carried out in different solvents but the best yield of α-iodoketone was obtained in CH_2Cl_2 in the presence of pyridine (table-2). The oxidation of olefins can be carried out in THF also but in this case, ether (LXXX) was also obtained as a minor product.



(LXXVIII)

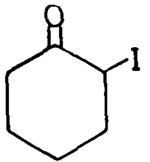
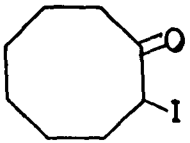


(LXXIX)

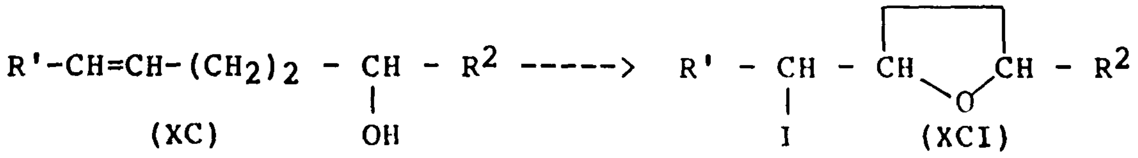


(LXXX)

Table-2

Olefin	Iodoketone	Yield in %
Cyclohexene (LXXVIII)	 (LXXIX)	60
Cyclooctene (LXXXII)	 (LXXXIII)	65
1-Octene (LXXXVI)	C_6H_{13}-CO-CH_2 I (LXXXV)	74
1-Octadecene (LXXXVI)	$C_{16}H_{33}$-CO-CH_2 I (LXXXVII)	65
Styrene (LXXXVIII)	Ph-CO-CH_2 I (LXXXIX)	86

The synthesis of 13-iodo-9,12-epoxyoctadecanoic acid (XCI) by the action of Ag_2CrO_4-Iodine pyridine complex on isoricinoleic acid (XC) was also reported[17]



$$\underset{(XC)}{R'\text{-}CH{=}CH\text{-}(CH_2)_2 - \underset{OH}{\underset{|}{CH}} - R^2} \dashrightarrow R' - \underset{I}{\underset{|}{CH}} - \underset{(XCI)}{CH\underset{O}{\diagdown\!\diagup}CH} - R^2$$

$R' = CH_3 - (CH_2)_4,\quad R^2 = (CH_2)_7 - COOH$

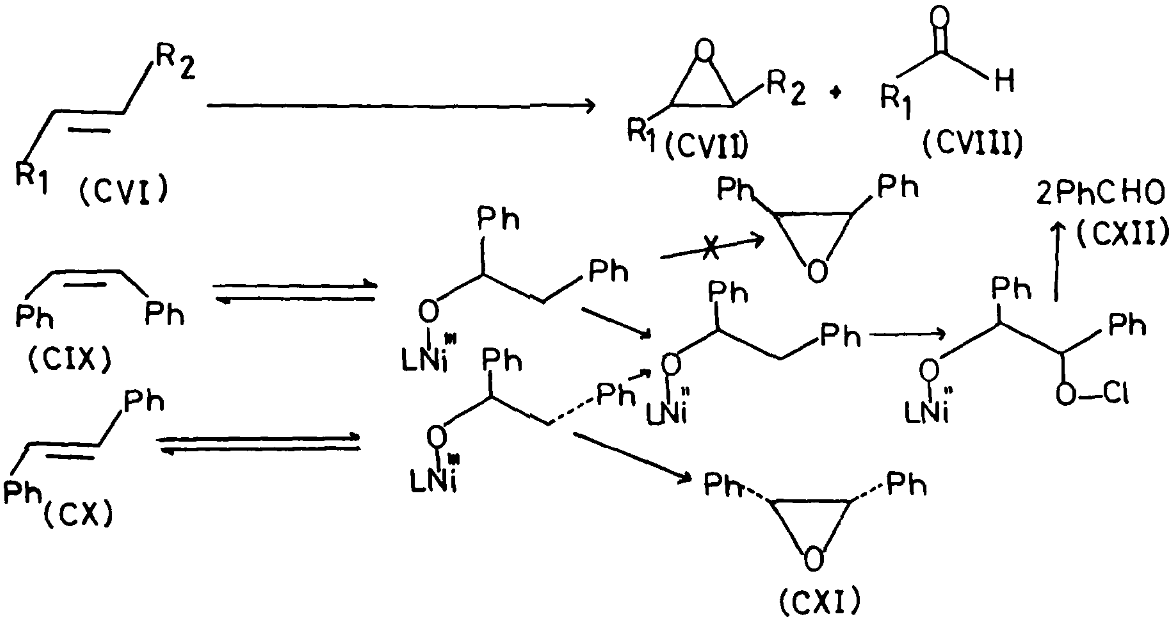
Bregeault, Jean Marie et al.[18] reported the oxidation of 1-octene and 1-hexene with O_2in anhyd. ethanol containing $PdCl_2$-$BiCl_3$-LiCl in the ratio of 1:2:2 to afford the corresponding ketones. The selectivity for 2-octanone is 57%. Hosokawa et al.[19] reported the oxidation of terminal olefins (LXXXVIII, XCII-XCVII) with molecular oxygen using palladium (II) catalyst and obtained the following products (XCVIII-CV).

$$\mathrm{RCH{:}CH_2} \xrightarrow[\mathrm{CuCl\ and\ PdCl_2}]{\mathrm{O_2,\ Me_2C{:}NOH}} \mathrm{RCOMe}$$

(XCII)	$Me\ (CH_2)_7-$	(XCVII)	$Me\ (CH_2)_7-$
(XCIII)	$Me\ (CH_2)_{11}-$	(XCIX)	$Me\ (CH_2)_{11}-$
(XCIV)	$EtO_2\ (CH_2)_8-$	(C)	$EtO_2\ (CH_2)_8-$
(XCV)	$MeCOCH{:}CH(CH_2)_8-$	(CI)	$MeCOCH{:}CH(CH_2)_8-$
(XCVI)	$MeCO(CH_2)_2-$	(CII)	$MeCO(CH_2)_2-$
(XCVII)	$PhOCH_2-$	(CIII)	$PhOCH_2-$

$$\underset{\text{(LXXXVIII)}}{\mathrm{PhCH{:}CH_2}} \xrightarrow[\mathrm{CuCl\ and\ PdCl_2}]{\mathrm{O_2,\ Me_2C{:}NOH}} \underset{\substack{\text{major}\\ \text{(CIV)}}}{\mathrm{PhCOMe}} + \underset{\substack{\text{minor}\\ \text{(CV)}}}{\mathrm{Ph\ CH_2\ CHO}}$$

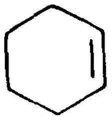
Yoon and Burrows[20] reported the oxidation of aryl-substituted olefins using NOCl as terminal oxidant under phase-transfer conditions to yield epoxides, aldehydes and carboxylic acids. The reaction was catalysed efficiently by 2.5 mol % of Ni(II) (salem) complex. Aliphatic olefins produce mixture of epoxide and chlorinated product.



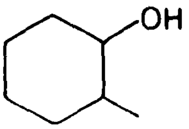
The oxidation of olefins (LXXVIII, LXXXVIII and CXV) with oxygen and sodium borohydride catalysed by managanese meso-tetrakis (p-sulfonatophenyl) porphin was conducted by Shimizu and co-worker[21] and afforded the corresponding alcohols (CXIII, XIV and CXVI).

(LXXVIII) (CXIII)
$PhCH:CH_2$ ----------------> PhCH(OH)Me
(LXXXVIII) (CXIV)
PhCH:CHMe ---------------> PhCH(OH)Et
(CXV) (CXVI)

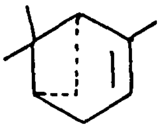
Erdik and Matheson[22] reported the kinetics of osmium tetraoxide catalysed trimethyl-amine N-oxide oxidations of cyclohexene (LXXVIII) and α-pinene (CXVIII) and obtained the respective diols (CXVII and CXIX).



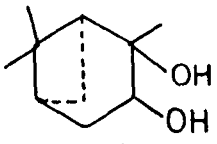
(LXXVIII)



(CXVII)



(CXVIII)

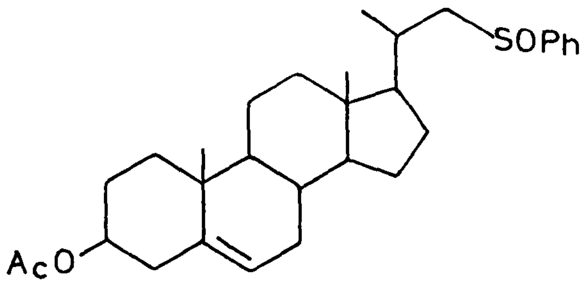


(CXIX)

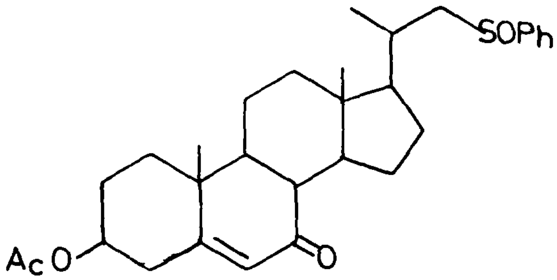
Formation of alcohol (CXXI) from respective olefin (CXX) by **bis** [(trifluoroacetyl) acetanato] cobalt (II) catalysed oxidation-reduction was reported by Inoki et al.[23]

$$\underset{\text{(CXX)}}{CH_2{:}CMe(CH_2)_8\,H} \xrightarrow[\text{Co }[CH(COMe)\ CoCF_3]_2]{\text{mol. O}} \underset{\text{(CXXI)}}{HOCMe_2\ (CH_2)_8H}$$

Siemann et al.[24] reported the preparation of 3β-substituted (20S)-20-[(benzenesulfonyl) methyl] pregn-5-en-7-one (CXXIII) from respective 3β -substituted (20S)-20-[(benzenesulfonyl)methyl] pregen-5-ene (CXXII).

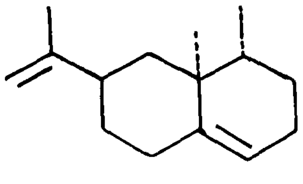


(CXXII)

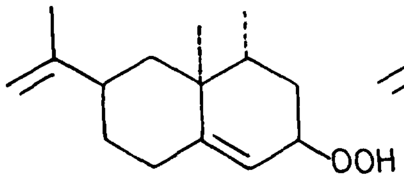


(CXXIII)

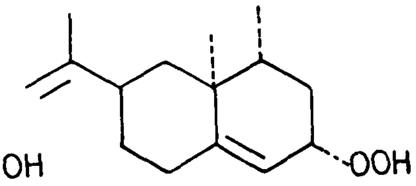
Davies and Davidson[25] carried out the oxidation of (+)-valencene (CXXIV) with triplet and singlet oxygen and observed the following results (CXXV-CXXVII).



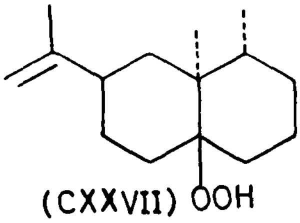
(CXXIV)



(CXXV)

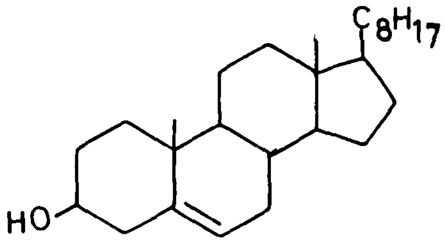


(CXXVI)

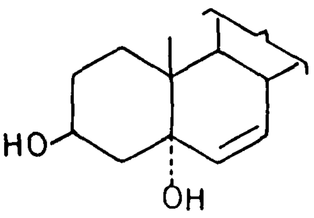


(CXXVII)

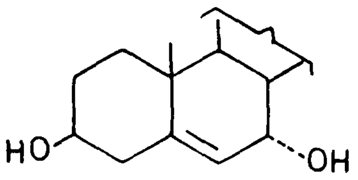
Schenck[26] reported that 5α -hydroperoxy-3β -hydroxycholest-6-ene (CXXIX) was formed from cholesterol and singlet oxygen, rearranged in a non-polar solvent to 7α -hydroxycholest-5-ene (CXXX).



CXXVIII

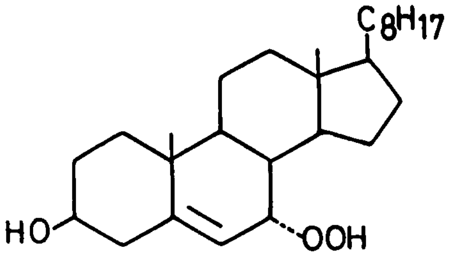


(CXXIX)

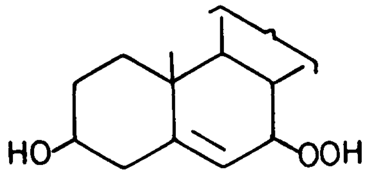


(CXXX)

Smith et al.[27] reported that 7α -hydroperxoy-cholest-5-ene (CXXXI) underwent a slow epimerization to 7β-hydroperoxycholest-5-ene (CXXXII).

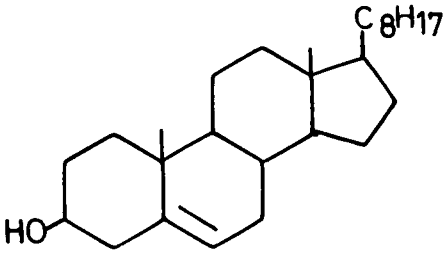


(CXXXI)

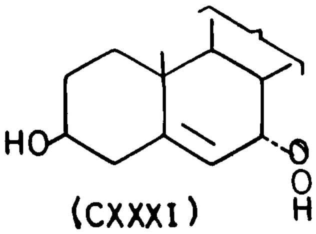


(CXXXII)

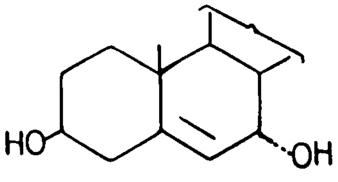
Cholesterol (CXXVIII) ubiquitously present in mammalian tissues is subjected to autoxidation by air, peroxidation _in vivo_ and metabolism. These intriguing events and biologically active oxysterols (LXXXI, CXXX-CXLV) thus produced, were reviewed in detail.[28-30]



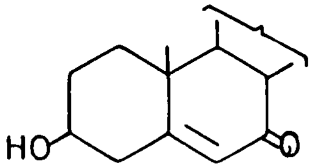
(CXXVIII)



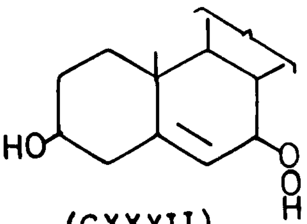
(CXXXI)



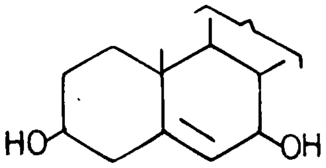
(CXXX)



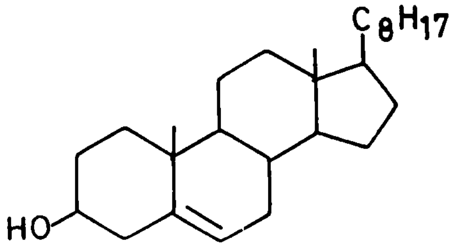
(CXXXIII)

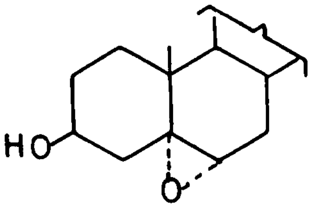


(CXXXII)



(CXXXIV)


(CXXVIII)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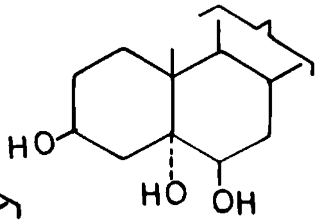
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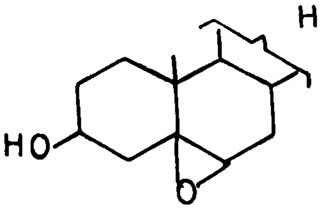
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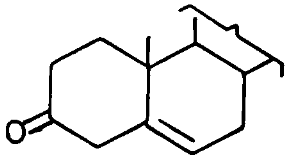
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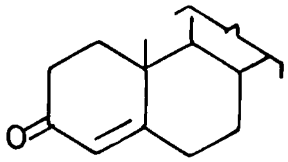
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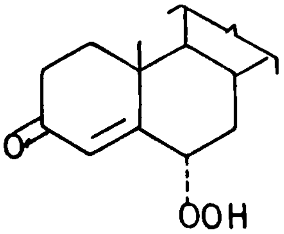
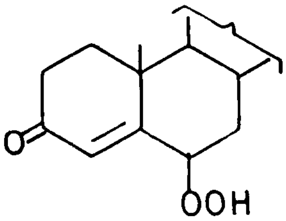
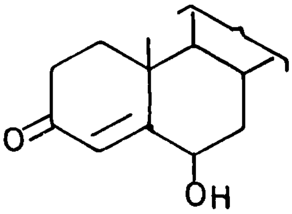
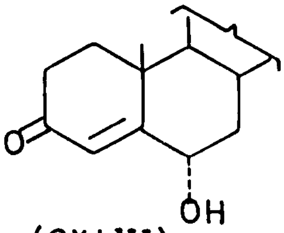
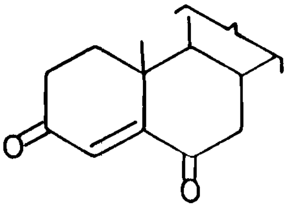
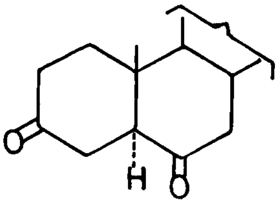

(CXL)


(CXXXVIII)


(CXLII)


(CXLIII)

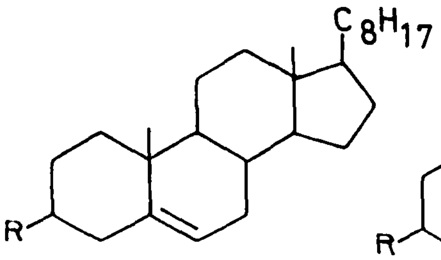

(CXLI)


(CXLIV)

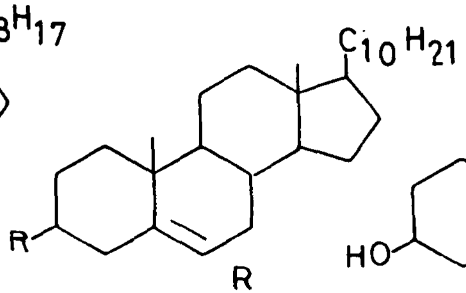
DISCUSSION

The oxidation of olefins has been utilized in the synthesis and in the transformation of natural products and steroids. In most of the cases lead (IV) acetate, Mn(III) acetate, Cr(VI), permanganate ion and selenium dioxide were the oxidants used. Different results were obtained depending upon the reagent used and the conditions employed.

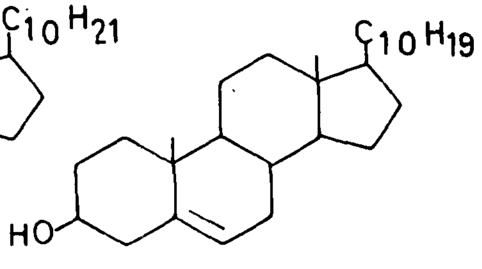
We have made an attempt to carry out the oxidation of some easily accessible steroidal olefins such as 3β-hydroxycholest-5-ene (CXXVIII), 3β-chlorocholest-5-ene (CXLV), 3β-acetoxycholest-5-ene (I), cholest-5-ene (XV), β-sitosterol (CXLVI), 3β-chlorostigmast-5-ene (CXLVII), 3β-acetoxystigmast-5-ene (CXLVIII) and stigmastrol (CXLIX) by silver chromate-iodine and pyridine in dichloromethane.



	R
(CXXVIII)	OH
(CXLV)	Cl
(I)	OAc
(XV)	H



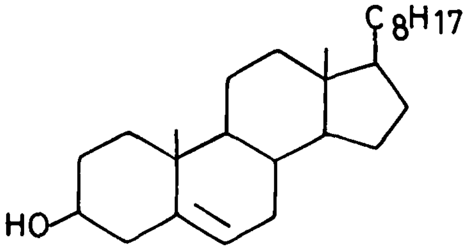
	R
(CXLVI)	OH
(CXLVII)	Cl
(CXLVIII)	OAc



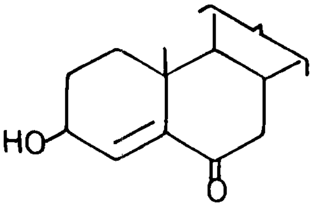
(CXLIX)

Reaction of 3β-hydroxycholest-5-ene (CXXVIII) with silver chromate-iodine in dichloromethane

To a suspension of silver chromate in dry dichloromethane, iodine and a solution of pyridine in dry dichloromethane was added at 0°C and stirred for 5 min. To this mixture a solution of 3β-hydroxycholest-5-ene (CXXVIII) in dry dichloromethane was added dropwise for 10 min. and was further stirred for 20 min. at 0°C. Then the cooling bath was removed and the reaction was stirred for an additional hour at room temperature and filtered. The filterate was washed with 5% aqueous sodium thiosulphate, saturated aqueous NaCl and dried over anhydrous sodium sulphate. After column chromatography over silica gel a compound (CL) having m.p. 149-150°C was isolated.



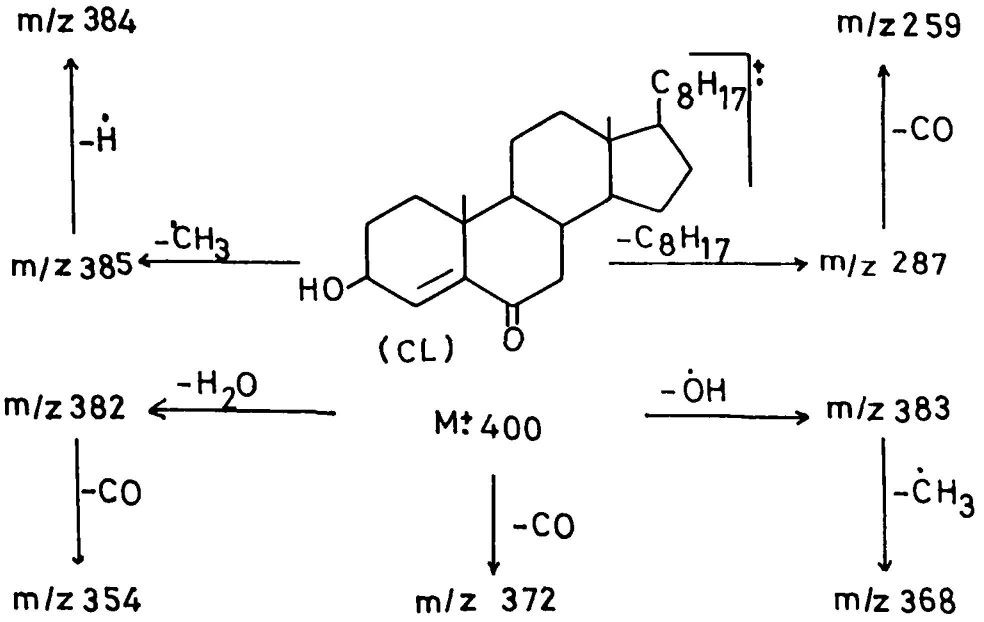
(CXXVIII)



(CL)

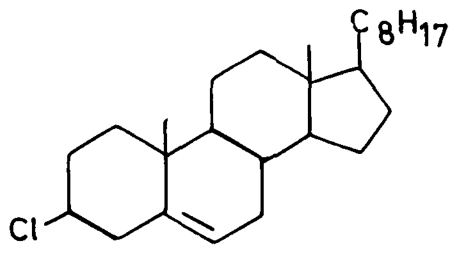
Characterization of the compound having m.p. 149-150°C as 3β -hydroxycholest- 4-en-6-one (CL)

The compound with m.p. 149-150°C was correctly analyzed for $C_{27}H_{44}O_2$. The IR spectrum of the compound showed bands at 3400 (OH), 1685 and 1620 cm^{-1} (C=C-C=O). Its ^1H-NMR spectrum exhibited a doublet integrating for one proton at 6.02 and was assigned to the C4-vinylic proton. A multiplet centered at 4.3 for one proton was assigned to C3-αH, (W 1/2=12 Hz, axial)[32]. The hydroxy proton (exchangeable with deuterium) was appeared at 2.18 as a broad singlet. Methyl protons were observed at 1.15 (C10-CH_3), 0.70 (C13-CH_3), 0.95 and 0.81 (other methyl protons). The mass spectrum of the compound gave molecular ion and some important fragment ions at m/z 400 (M^+), 385, 384, 383, 382, 372, 368, 359, 354, 287, and 259. The formation of these fragment ions were explained in Scheme which is tentative in nature. On the basis of these values and by comparison with its authentic sample (reported[31] m.p. 150°C) the compound, m.p. 149-150° C was identified as 3β-hydroxycholest-4-en- 6-one (CL).

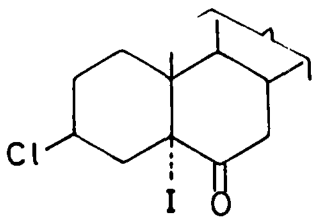


Reaction of 3β -chlorocholest-5-ene (CXLV) with silver chromate-iodine in dichloromethane

To a stirred solution of silver chromate-iodine and pyridine in dichloromethane, the solution of 3β -chlorocholest-5-ene (CXLV) in dichloromethane was gradually added with stirring. After completion of reaction, it was worked up in usual fashion and chromatographed over silica gel column to obtain a compound melting at 82°C.



(CXLV)

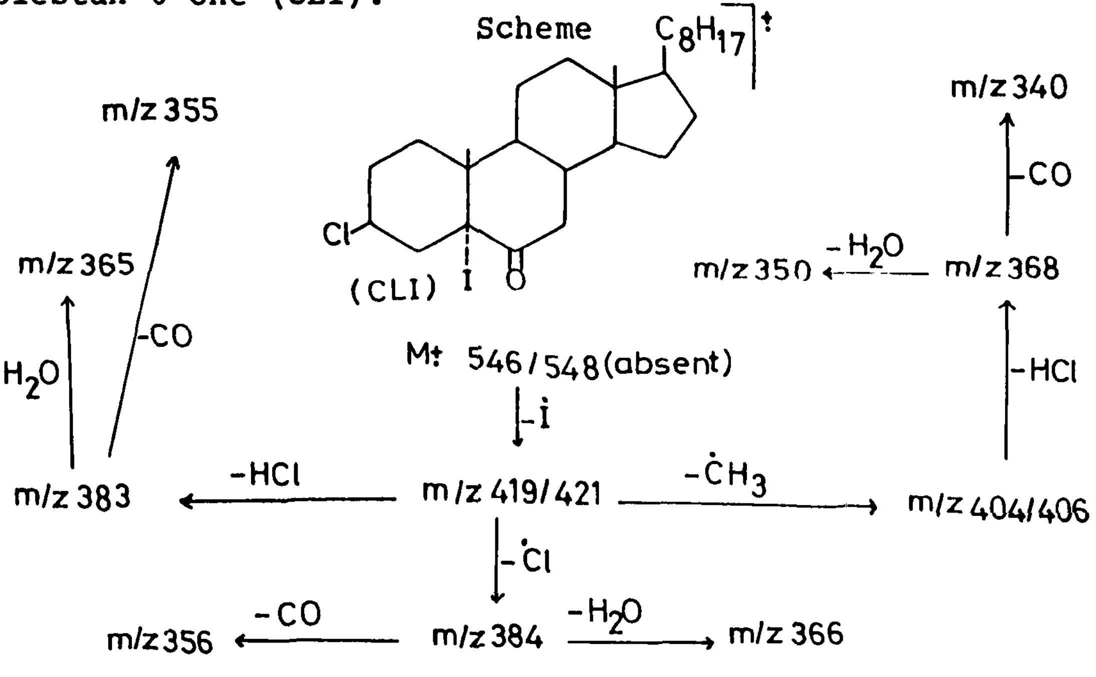


(CLI)

Characterization of the compound with m.p. 82°C as 3β-chloro-5-iodo-5α-cholestan-6-one (CLI)

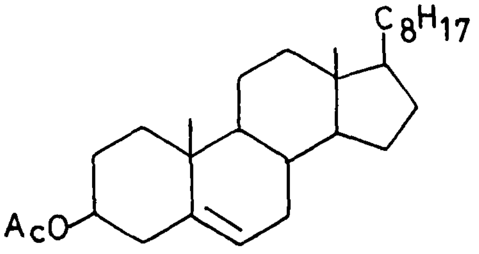
The elemental analysis of the compound corresponded to the molecular composition of $C_{27}H_{44}OCI$ (positive Beilstein test). The band at 1715 cm^{-1} in IR spectrum of (CLI) suggested the presence of carbonyl group. Other bands at 750 and 510 cm^{-1} were ascribable to C-Cl and C-I respectively. The ^{1}H-NMR spectrum of the compound displayed a multiplet centered at δ 4.1 for C3-αH, (W 1/2=15 Hz, axial, A/B ring junction trans).[32] Methyl protons appeared at δ 1.15 (C10-CH_3), 0.65 (C13-CH_3), 0.92 and 0.84 (other methyl protons). In the mass spectrum of the compound, the molecular ion peak was absent. The other significant peaks in the mass spectrum were observed at m/z 419/421, 404/406, 384, 383, 368, 366, 365, 356, 355, 350, and 340 as given in Scheme. On the basis of above elemental and spectral data, the compound with m.p.82°C was characterized as 3β-chloro-5-iodo-5α-cholestan-6-one (CLI).

Scheme

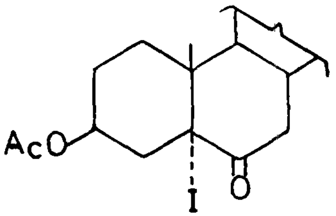


Reaction of 3β -acetoxycholest-5-ene (I) with silver chromate-iodine in dichloromethane

To a well stirred solution of silver chromate-iodine and pyridine in dichloromethane, a solution of 3β-acetoxycholest-5-ene (I) in dichloromethane was added gradually at 0°C. After completion of reaction, the mixture was worked-up as usual and chromatographed over silica gel to get a compound with m.p. 77°C (decomposed).



(I)

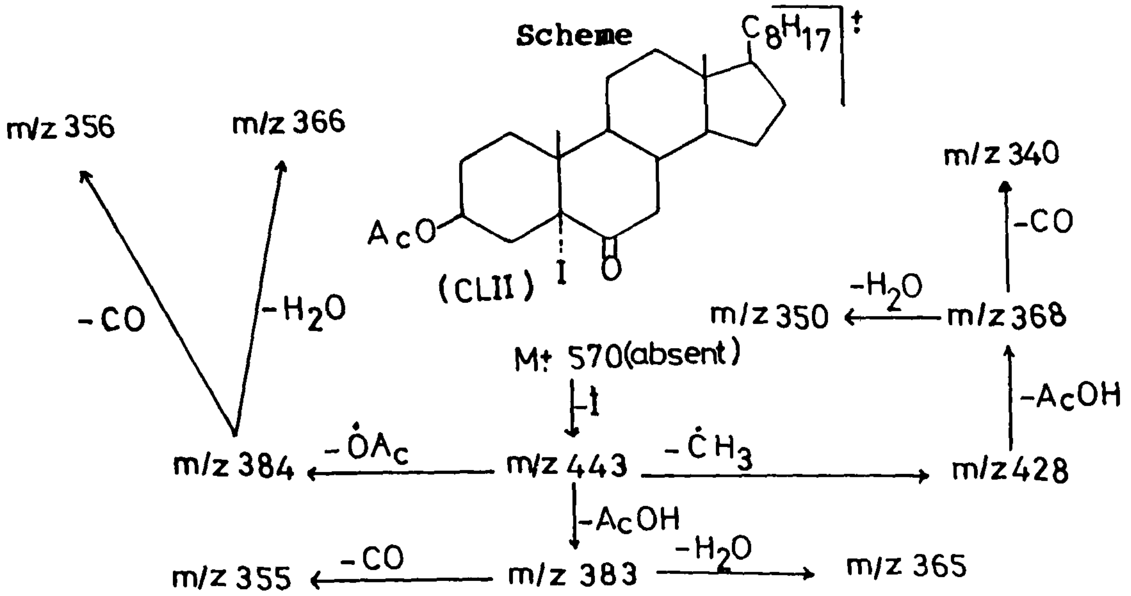


(CLII)

Characterization of the compound with m.p. 77°C (decomposed) as 3β -acetoxy-5-iodo-5α -cholestan-6-one (CLII)

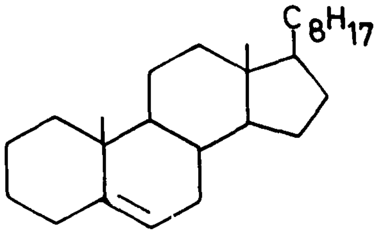
The compound with m.p. 77°C (decomposed) was analyzed for $C_{29}H_{47}O_3I$ (positive Beilstein test). IR spectrum of the compound exhibited absorption bands at 1730 (CH_3-COO), 1710 (C=O), 1050 (C-O)[33] and 520 cm^{-1} (C-I). ^1H-NMR spectrum displayed a multiplet centered at δ 4.7 for one proton and was assigned to C3- α H (W 1/2 = 14 Hz, axial)[32] which suggested the ring junction A/B is trans. A sharp singlet for the methyl protons of acetoxy moiety was appeared at δ 2.0. The methyl protons were observed at δ 1.05 (C10-CH_3), 0.76 (C13-CH_3), 0.97 and 0.81 (other methyl protons). The mass spectrum of the compound did not give the molecular ion peak (M^{+} 570). Significant fragment peaks were observed at m/z 443, 428, 384, 383, 368, 366, 365, 356, 355, 350, and 340 as rationalized in Scheme. On the basis of foregoing discussion, the compound with m.p. 77°C may be regarded as 3β-acetoxy-5-iodo-5α-cholestan-6-one (CLII).

Scheme

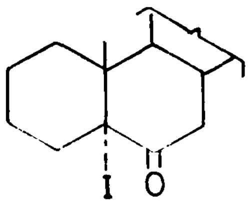


Reaction of cholest-5-ene (XV) with silver chromate-iodine in dichloromethane

To an ice-cooled solution of silver chromate-iodine and pyridine in dichloromethane, the solution of cholest-5-ene (XV) in dichloromethane was added gradually with stirring. After work up and column chromatography over silica gel a semi solid compound was obtained.



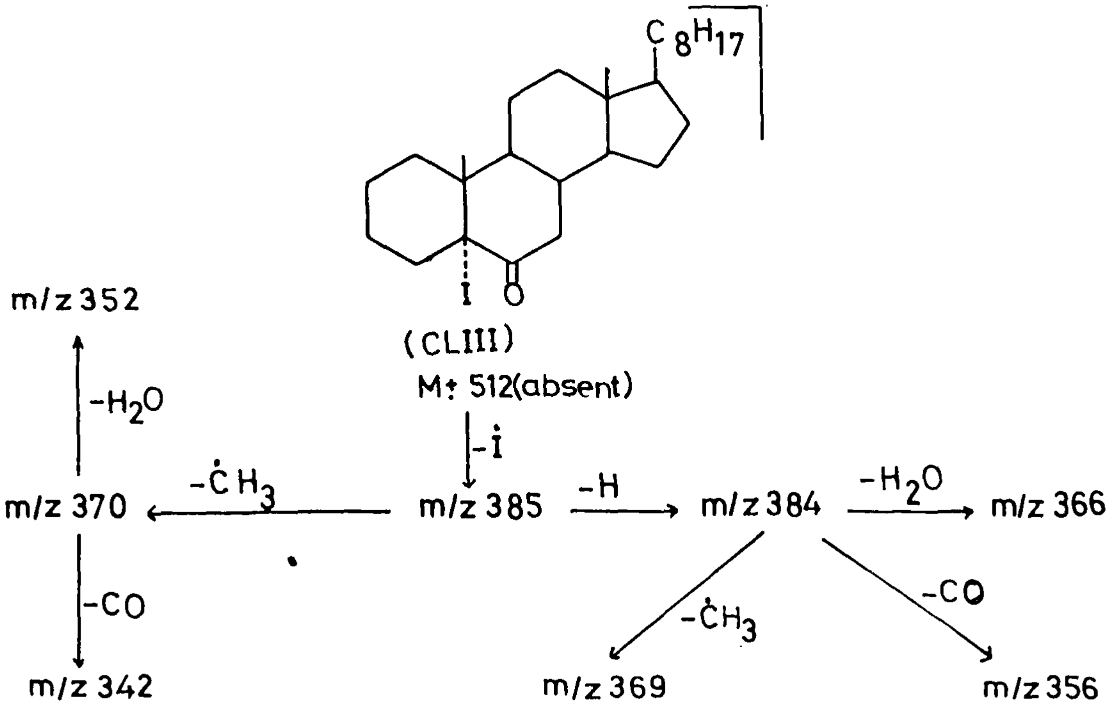
(XV)



(CLIII)

Characterization of the semi-solid compound as 5-iodo-5α-cholestan-6-one (CLIII)

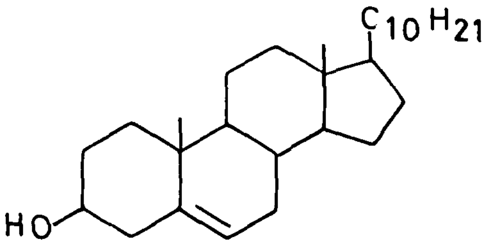
The semi-solid compound showed molecular composition $C_{27}H_{45}OI$ (positive Beilstein test). From the molecular composition, it is evident that iodine and oxygen atoms were added to the parent compound and the bands at 1715 and 525 cm^{-1} in its IR spectrum suggested the presence of carbonyl group and carbon iodine bond respectively. In the ^{1}H-NMR spectrum of the compound only methyl protons were observed at δ 1.10 ($C10-CH_3$), 0.68 ($C13-CH_3$), 0.91 and 0.80 (other methyl protons). From these observations, the compound (CLIII) was characterized as 5-iodo-5α-cholestan-6-one (semi-solid). Mass spectrum of the compound further supported the structure. The molecular ion peak was absent. Some prominent fragment ion peaks were observed at m/z 385, 384, 370, 369, 366, 356, 352 and 342 as shown in Scheme.



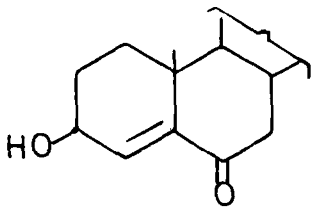
(CLIII)

Reaction of β-sitosterol (CXLVI) with silver chromate-iodine in dichloromethane

To a stirred solution of silver chromate-iodine and pyridine in dichloromethane, a solution of β-sitosterol (CXLVI) in dichloromethane was added gradually at 0°C. After usual work up and column chromatography over silica gel a compound with m.p. 162°C was isolated.



(CXLVI)

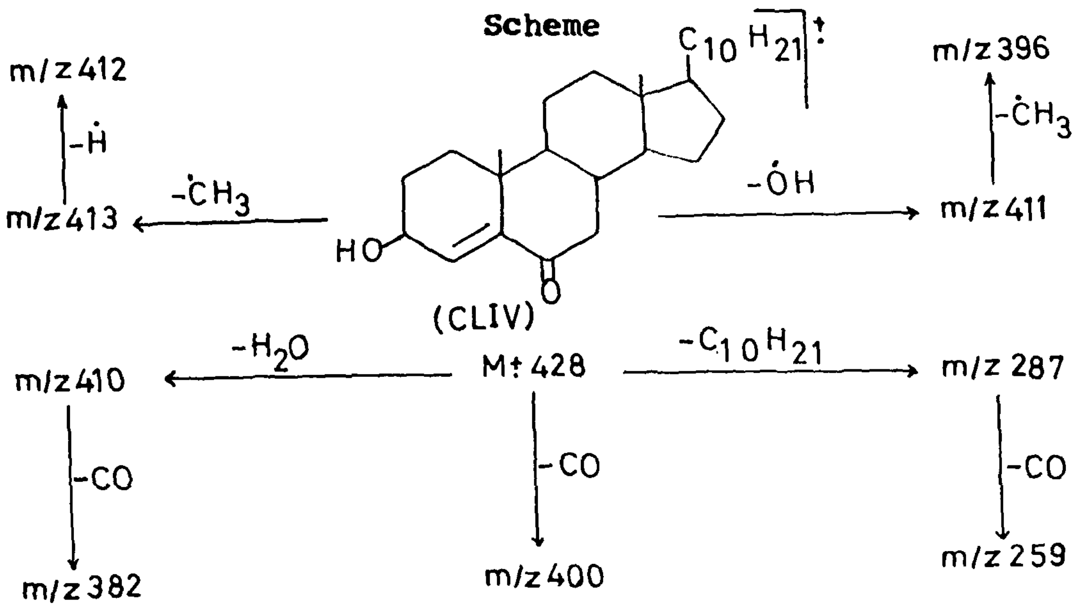


(CLIV)

Characterization of the compound, melting point 162° C as 3β -hydroxystigmast-4-en-6-one (CLIV)

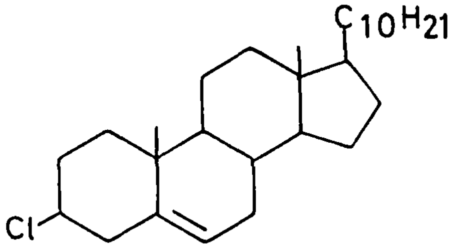
The compound m.p. 162°C was analyzed for $C_{29}H_{48}O_2$. The IR spectrum of the compound showed bands at 3450 (OH), 1690, 1615 cm^{-1} (C=C-C=O). In its ^1H-NMR spectrum a doublet at δ 6.12 for one proton was found and assigned to C4 vinylic proton. A multiplet centered at δ 4.35 integrating for one proton was due to C3 -αH (W 1/2 = 15 Hz, axial)[32]. The hydroxyl proton (exchangeable with deuterium) was appeared at δ 2.2 as a broad singlet. Methyl protons appeared at δ 1.12 ($C10-CH_3$), 0.68 ($C13-CH_3$), 0.94, 0.80 (other methyl protons).On the basis of above discussion,the compound with a m.p. of 162°C was characterized as 3β -hydroxystigmast-4-en-6-one (CLIV). The mass spectral studies of the compound further supported the above structure. The mass spectrum gave the molecular ion peak at m/z 428 ($M^{+\cdot}$) and some important fragment ion peaks at m/z 413, 412, 411, 410, 400, 396, 382, 287, and 259 as rationalized in Scheme.

Scheme

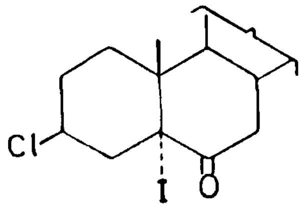


Reaction of 3β -chlorostigmast-5-ene (CXLVII) with silver chromate-iodine in dichloromethane

3β -chorostigmast-5-ene (CXLVII) solution in dichloromethane was added to a well stirred solution of silver chromate-iodine and pyridine in dichloromethane at 0°C. After usual work up and column chromatography over silica gel, an oily compound was isolated.



(CXLVII)

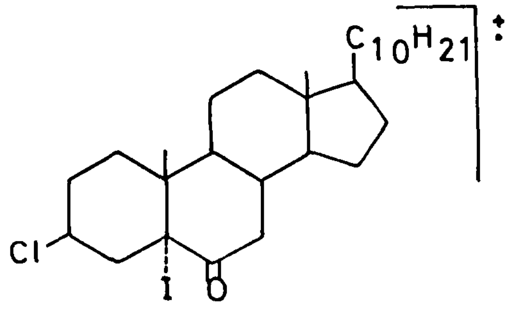


(CLV)

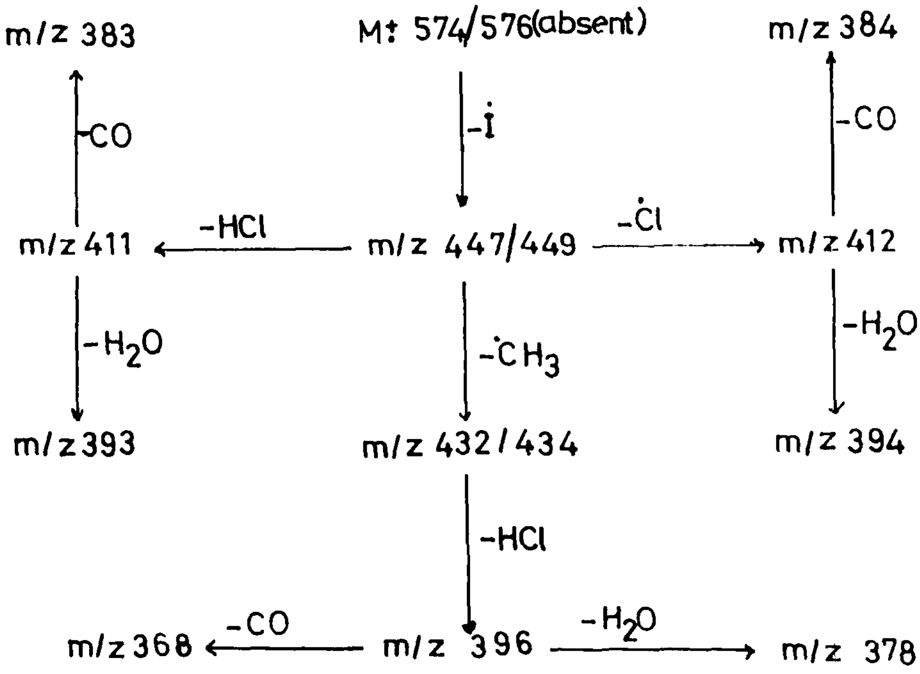
Characterization of the oily compound as 3β -chloro-5- iodo-5 α-stigmastan-6-one (CLV)

The oily compound was analyzed for $C_{29}H_{48}OClI$ (positive Beilstein test). Its IR spectrum showed bands at 1715 (C=O), 750 (C-Cl) and 510 cm^{-1} (C-I). The ^{1}H-NMR exhibited a multiplet centered at δ 3.8 for one proton and was assigned to C3-αH (W 1/2 = 14 Hz, axial)[32]. The methyl protons were observed at δ 1.15 (C10-CH_3), 0.67 (C13-CH_3), 0.94 and 0.83 (other methyl protons). In the mass spectrum of above compound the molecular ion was absent and the important fragment ions appeared at m/z 447/449, 432/434, 412, 411, 396, 394, 393, 384, 383, 378 and 368 as given in Scheme. On the basis of above data, it is evident that the oily compound is 3β-chloro-5-iodo-5α-stigmastan-6-one (CLV).

Scheme



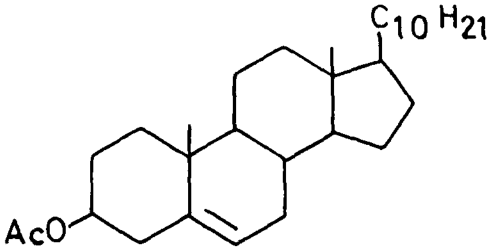
(CLV)



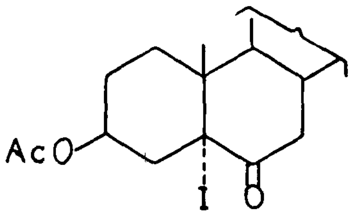
Reaction of 3β-acetoxystigmast-5-ene (CXLVIII) with silver chromate-iodine in dichloromethane

To a well stirred solution of silver chromate-iodine and pyridine in dichloromethane a solution of 3β -

-acetoxystigmast-5-ene (CXLVIII) in dichloromethane was added at 0°C. After the completion of reaction, the reaction mixture was worked up in usual manner and chromatographed over silica gel column. A compound melting at 97°C was obtained.



(CXLVIII)



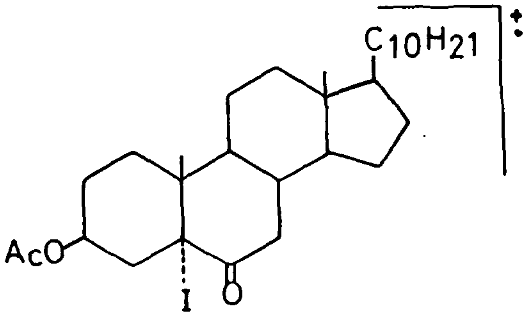
(CLVI)

Characterization of the compound with melting point 97°C as 3β-acetoxy-5-iodo-5α-stigmastan-6-one (CLVI)

Elemental analysis of the compound (CLVI) showed the molecular composition $C_{31}H_{51}O_3I$ (positive Beilstein test). The IR spectrum exhibited bands at 1725 ($-OCOCH_3$), 1715 (C=O), 1030 (-O-C)^{33} and 510 cm^{-1} (C-I). The ^1H-NMR spectrum of the compound exhibited a multiplet centered at δ 4.6 for one proton and was assigned to C3-αH (W 1/2 = 16 Hz, axial).^{32} A sharp singlet for three protons appeared at δ 1.9 for methyl protons of acetoxy group. The methyl protons were observed at δ 1.15 ($C10-CH_3$), 0.65 ($C13-CH_3$), 0.95 and

0.82 (other methyl protons). In the mass spectrum of the compound molecular ion was absent and but important fragment ions peaks appeared at m/z 471, 456, 412, 411, 396, 394, 393, 384, 383, 378 and 368 as shown in Scheme. On the basis of these evidences, the compound with m.p. 97°C was characterized as 3β -acetoxy-5-iodo-5α-stigmastan-6-one (CLVI).

Scheme



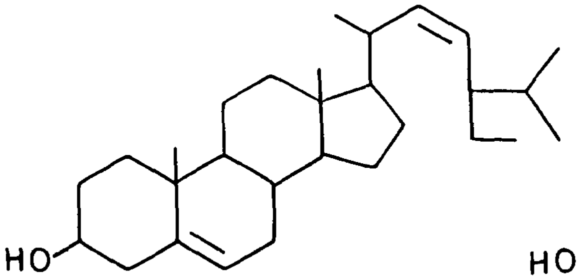
(CLVI)

$$\begin{tikzcd}
m/z\,383 & M^{+\cdot}\,598\ \text{(absent)} \arrow[d, "-\dot{I}"] & m/z\,384 \\
m/z\,411 \arrow[u, "-CO"] \arrow[d, "-H_2O"] & m/z\,471 \arrow[l, "-AcOH"'] \arrow[r, "-\dot{O}Ac"] \arrow[d, "-\dot{C}H_3"] & m/z\,412 \arrow[u, "-CO"] \arrow[d, "-H_2O"] \\
m/z\,393 & m/z\,456 \arrow[d, "-AcOH"] & m/z\,394 \\
m/z\,368 & m/z\,369 \arrow[l, "-CO"'] \arrow[r, "-H_2O"] & m/z\,378
\end{tikzcd}$$

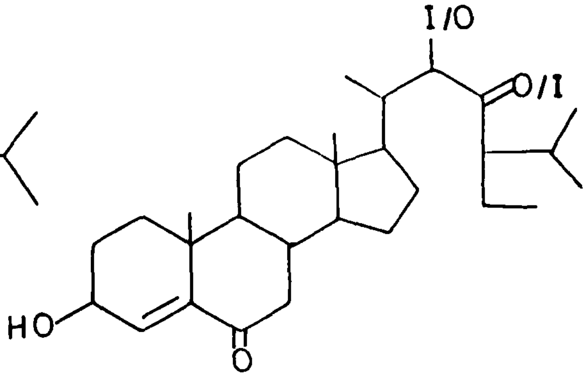
Reaction of stigmasterol (CXLIX) with silver chromate-iodine in dichloromethane

To a suspension of silver chromate-iodine and pyridine in dichloromethane was added a solution of stigmasterol

(CXLIX) in dichloromethane at 0°C. After the completion of reaction, the mixture was worked up in the same manner as described earlier and column chromatographed over silica gel. A semi-solid compound was obtained.



(CXLIX)



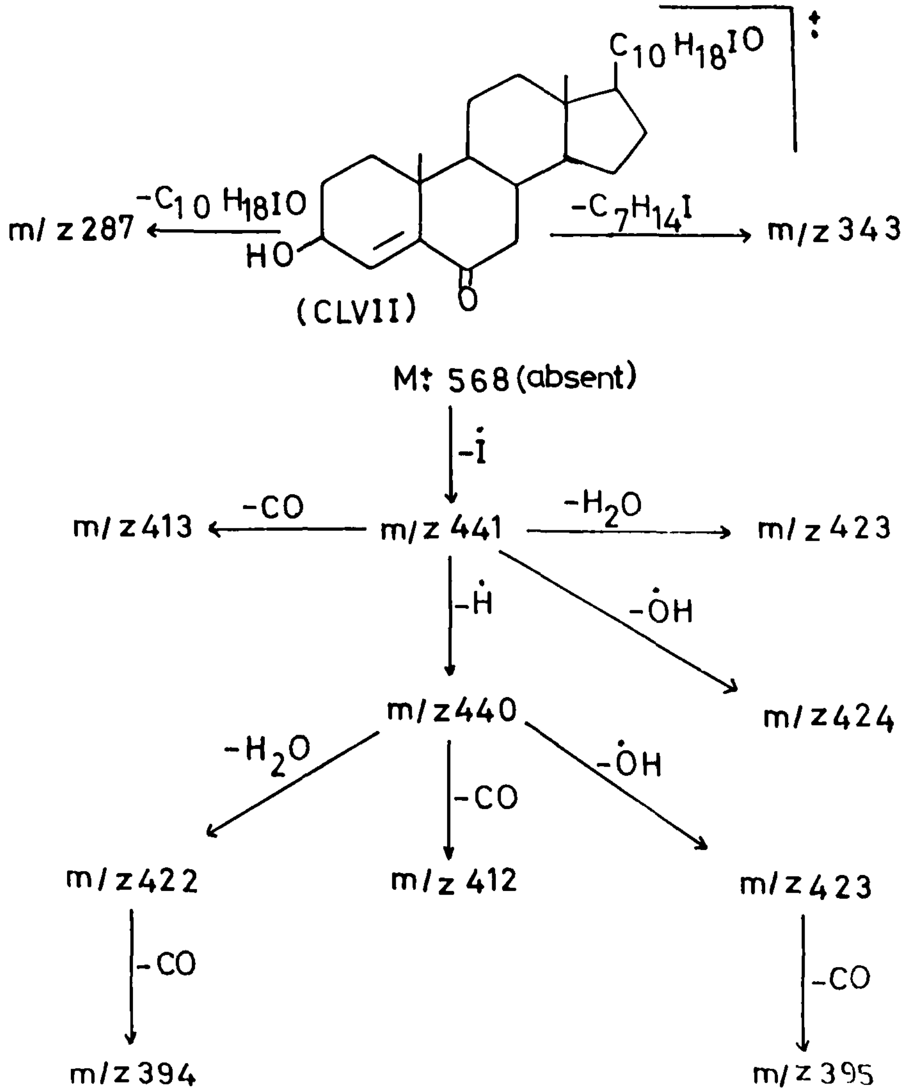
(CLVII)

Characterization of the semi-solid compound as 3β-hydroxy - 22/23-iodostigmast-4-en-6, 23/22-dione (CLVII)

Elemental analysis of the compound (CLVII) showed the molecular composition $C_{29}H_{45}O_3I$ (positive Beilstein test). The IR spectrum of the compound exhibited bands at 3420 (OH), 1720 (C=O), 1680, 1610 (C=C-C=O) and 520 cm^{-1} (C-I). The ^1H-NMR spectrum displayed two doublets for one proton each at δ 6.2 and 4.4 which were assigned to C4-vinylic proton and C-22/23-H respectively. A multiplet centered at δ 4.1 integrating for one proton was assigned to C3-α H (W 1/2 = 16 Hz, axial)[32]. The deuterium exchangeable hydroxyl proton appeared at δ 1.9 as a broad singlet. The methyl protons were observed at δ 1.14 (C10-CH_3), 0.71 (C13-CH_3), 0.96 and 0.81

(other methyl protons). In the mass spectrum of the compound the molecular ion was absent. The important fragment ions were observed at m/z 441, 440, 424, 423, 422, 413, 412, 395, 394, 343, and 287 as shown in Scheme. On the basis of foregoing discussion, the semi-solid compound was characterized as 3β-hydroxy-22/23-iodostigmast-4-en-6, 23/22-dione (CLVII).

Scheme



(CLVII)

EXPERIMENTAL

Preparation of Silver Chromate

A solution of silver nitrate (17.0g) in 200 ml of distilled water was stirred vigorously with a solution of potassium chromate (9.7g) in 200 ml of water at room temperature. Reddish brown silver chromate precipitated promptly[34]. The precipitate was filtered, washed successively with water, dried _in vacuo_, finely pulverized, and dried again _in vacuo_ at 90°C overnight.

Oxidation of 3β-hydroxy cholest-5-ene (CXXVIII) with silver chromate-iodine: 3β-Hydroxycholest-4-en-6-one (CL)

To a suspension of silver chromate (1.1 g; 3.3 mmol) in 15 ml of dry dichloromethane was added iodine (1.14g; 4.5 mmol) and a solution of pyridine (0.12g; 1.5 mmol) in 0.75 ml of dry dichloromethane at 0°C and stirred for 5 min. A solution of 3β - hydroxycholest - 5 - ene (CXXVIII) (0.77g; 2.0 mmol) in 5 ml of dry dichloromethane was added dropwise for 10 min. to the ice-cooled suspension and stirred for 20 min. at 0°C. Then the cooling bath was removed and the reaction mixture was stirred for an additional hour at room temperature. The reaction mixture was filtered. The filterate was washed with aqueous sodium thiosulphate (50%) and saturated aqueous sodium chloride and dried (Na_2SO_4). The crude product obtained after removal of solvent was chromatographed over silica gel (40g). Elution with light petroleum/ether (4:1) gave a solid product, 3β-

-hydroxycholest-4-en-6-one (CL) which was recrystallized from light petroleum (0.578, 1.44mmol), m.p 149-150°C (negative Beilstein test).

Analysis Found : C, 80.90; H, 10.98

$C_{27}H_{44}O_2$ requires : C, 80.94; H, 11.07%

IR : ν max. 3400 (OH), 1685 and 1620 cm^{-1} (C=C-C=O)

^1H-NMR : δ 6.02 (d, 1H, C4-H), 4.3 (mc, 1H, C3-αH, W 1/2 = 12 Hz, axial)[32], 2.18 (br,. 1H, OH), 1.15 (C10-CH_3), 0.70 (C13-CH_3), 0.95 and 0.81 (other methyl protons).

MS : $M^{+\cdot}$. 400 (100.00; $C_{27}H_{44}O_2$), 385 (13.75; $C_{26}H_{41}O_2$); 384 (15.00; $C_{26}H_{40}O_2$), 383 (16.50; $C_{27}H_{43}O$), 382 (29.50; $C_{27}H_{42}O$), 372 (7.00), 368 (5.00), 367 (10.00), 365 (3.50), 364 (2.00), 363 (1.50), 362 (3.00), 359 (7.50), 356 (5.00), 354 (5.50), 331 (15.50), 330 (50.00), 329 (1.50), 328 (7.50), 292 (5.50), 290 (4.50), 289 (4.50), 288 (6.50), 287 (22.50), 286 (4.00), 267 (2.50), 266 (5.00), 265 (7.50), 261 (5.50), 260 (6.00), 259 (7.50), 248 (10.50), 247 (31.00), 246 (22.50), 245 (41.20), 155 (7.40), 154 (6.00), 153 (4.80), 152 (15.40; $C_9H_{12}O_2$), 123 (4.00), 122 (9.60), 121 (23.50), 120 (7.20), 111 (20.00), 110 (10.50), 109 (15.00), 108 (17.50), 107 (30.25), 105 (16.20), 95 (40.00), 94 (27.25), 93 (18.00), 92 (5.00), 83 (6.50), 81 31.00), 79 (22.25), 71 (17.75), 68 (25.00), 67 (16.50), 66 (4.80), 57 (51.50), 56 (10.50), 55 (18.50), 43 (67.50), 42 (11.75), 41 (7.50), 40 (10.00).

3β-Chlorocholest-5-ene (CXLV)

Freshly purified thionyl chloride (75 ml) was added gradually to cholesterol (100g) at room temperature. A vigorous reaction ensued with the evolution of gaseous products. When the reaction slackened, the mixture was gently heated at temperature of 50-60°C on a water bath. The yellow solid thus obtained was filtered, washed several times with ice cooled water and air dried. Recrystallization of the crude product from acetone gave 3β-chlorocholest-5-ene (95.5 g), m.p. 95-96°C (reported[35] m.p. 96-97°C). It gave positive Beilstein test and a yellow colour with tetranitromethane in chloroform.

Oxidation of 3β-Chlorocholest-5-ene (CXLV) with silver chromate-iodine: 3β-Chloro-5-iodo-5α-cholestan-6-one (CLI)

To a suspension of silver chromate (1.1g; 3.3 m mol) in 15 ml of dry dichloromethane was added iodine (1.14g; 4.5 m mol) and a solution of pyridine (0.12g; 1.5 m mol) in 0.75 ml of dry dichloromethane at 0°C and stirred for 5 min. A solution of 3β-chlorocholest-5-ene (CXLV) (0.81g; 2.0 m mol) in 5 ml of dry dichloromethane was added dropwise for 10 min to the ice-cooled suspension and was stirred for 20 min at 0°C. Then the cooling bath was removed and the reaction mixture was stirred for an hour at room temperature. The reaction mixture was filtered, the filterate was washed with aqueous sodium thiosulphate (50%) and saturated aqueous sodium chloride and dried (Na_2SO_4). The crude product obtained was chromatographed over silica gel (40g). Elution with light petroleum/ether (10:1) gave a solid product, 3β-chloro-5-iodo-5α-cholestan-6-one (CLI) which was recrystallized from light petroleum (0.85g, 1.55 m mol), gave m.p. 82° (Positive Beilstein test).

Analysis found : C, 59.25; H, 8.07
$C_{27}H_{44}OICl$ requires : C, 59.28; H, 8.11%

IR : ν max 1715 (C=O), 750 (C-Cl) and 510 cm^{-1} (C-I)
^{1}H-NMR : δ 4.1 (mc, IH, C3-αH, W 1/2 = 15 Hz, axial),[32] 1.15 (C10-CH_3), 0.65 (C13-CH_3), 0.92 and 0.84 (other methyl protons)
MS : M^{+} 546/548 (not observed; $C_{27}H_{44}OICl$), 419/421 (8.40/2.79; $C_{27}H_{44}OCl$), 418/420 (9.60/3.19), 404/406 (7.20/2.39; $C_{26}H_{41}OCl$), 403/405 (5.50/1.83), 384(80.00; $C_{27}H_{44}O$), 383 (68.50; $C_{27}H_{43}O$), 382 (9.00), 369 (14.50; $C_{26}H_{41}O$), 368 (27.25), 367 (6.50), 366 (20.00; $C_{27}H_{42}$), 365(62.50; $C_{27}H_{41}$), 356 (12.00), 355 (14.20; $C_{26}H_{43}$), 354 (6.60), 351 (19.50), 350 (17.25), 349 (6.20), 348 (4.20), 340 (5.00), 339 (7.40), 337 (7.30), 306/ 308 (10.50/3.40), 305/307 (11.00/3.66), 250 (5.00), 249 (7.50), 248 (6.20), 247 (10.00), 246 (5.50), 245 (5.50), 244 (8.40), 243 (9.50), 242 (8.40), 241 (6.00), 240 (5.50), 230 (6.40), 229 (14.30), 228 (20.00), 227 (17.00), 226 (7.20), 225 (5.00), 216 (5.70), 215 (10.40), 214 (6.50), 213 (6.50), 212 (5.50), 176 (7.20), 175

(12.00), 174 (8.50), 161 (15.50), 160 (30.00), 159 (10.40), 158 (8.50), 157 (6.60), 152 (19.25), 151 (7.50), 150 (7.50), 149 (12.50), 148 (6.60), 147 (9.60), 146 (8.20), 145 (6.60), 139 (5.0), 138 (9.60), 137 (12.20), 136 (100.00), $C_9H_{12}O$), 135 (7.40), 134 (6.60), 128 (12.00), 127 (14.25), 126 (10.00), 125 (4.80), 124 (8.40), 123 (15.30), 122 (17.20), 121 (27.20), 98 (6.40), 97 (9.00), 96 (12.25), 95 (47.50), 94 (14.00), 93 (29.40), 92 (21.00), 91 (10.20), 90 (6.50), 83 (35.00), 82 (15.30), 81 (47.50), 80 (10.50), 79 (37.00), 78 (12.25), 70 (30.40), 69 (14.25), 68 (49.50), 67 (21.90), 66 (41.10), 65 (10.25), 60 (9.60), 59 (20.00), 58 (17.50), 57 (60.00), 56 (15.75), 55 (70.00), 54 (25.25), 46 (27.50), 43 (40.50), 42 (25.25).

Oxidation of 3β -acetoxycholest-5-ene (I) with silver chromate-iodine: 3β -Acetoxy-5-iodo-5α -cholestan-6-one (CLII)

To a suspension of silver chromate (1.1g; 3.3 m mol) in 15 ml of dry dichloromethane iodine (1.14g; 4.5 m mol) and a solution of pyridine was added (0.12 g; 1.5 m mol) in 0.75 ml of dry dichloromethane at 0°C and stirred for 5 min. A solution of 3β- acetoxycholest-5-ene (I) (0.86g; 2.0 m mol) in 5 ml of dry dichloromethane was added dropwise for 10 min. to the ice-cooled suspension and was stirred for 20 min. at 0°C. Then the cooling bath was removed and the reaction mixture was stirred for an hour at room temperature. The reaction mixture was filtered, the filterate was worked up as usual and chromatographed over silica gel (40g). Elution with light petroleum/ ether (10:1) gave a solid product, 3β-acetoxy-5-iodo-5α -cholestan-6-one (CLII) which was recrystallised from light petroleum (0.87g, 1.52 m mol), m.p. 77°C (decomposed) (positive Beilstein test).

Analysis found : C, 59.98; H, 8.34

$C_{29}H_{47}O_3I$ requires : C, 61.04; H, 8.31%

IR : ν max 1730 (CH_3COO), 1710 (C=O), 1050 (C-O) and 520 cm^{-1} (C-I).

^{1}H-NMR : δ 4.7 (mc, 1H, C3-αH, W 1/2 = 14 Hz, axial)[32], 2.0 (s, 3H, CH_3COO-), 1.05 (C10-CH_3), 0.76 (C13-CH_3), 0.97 and 0.81 (other methyl protons).

MS : $M^{+\cdot}$ 570 (not observed), 443 (9.60; $C_{29}H_{47}O_3$), 442 (10.50; $C_{29}H_{46}O_3$), 428 (5.50; $C_{28}H_{44}O_3$), 427 (4.50), 400 (35.50; $C_{27}H_{44}O_2$), 399 (5.50), 398 (6.60), 385 (12.50), 384 (85.50; $C_{27}H_{44}O$), 383 (71.00; $C_{27}H_{43}O$), 382 (9.60), 369 (10.40; $C_{26}H_{41}O$), 368 (22.75; $C_{26}H_{40}O$), 367 (5.00), 366 (24.00; $C_{27}H_{42}$), 365 (70.50; $C_{27}H_{41}$), 364 (4.80), 356 (12.50; $C_{26}H_{44}$), 355 (13.75), 354 (7.40), 351 (18.75), 300 (16.00), 340 (5.50), 332 (4.50), 331 (4.50), 330 (9.00), 329 (10.20), 247 (8.50), 246 (5.00), 245 (6.20), 244 (7.50), 243 (9.60), 242 (8.40), 241 (10.40), 240 (6.60), 229 (11.25), 228 (16.50), 227 (9.60), 217 (6.20), 216 (7.00), 215 (8.40), 214 (5.40), 176 (5.00), 175 (9.40), 174 (7.20), 173 (5.40), 166 (10.40), 165 (38.00), 164 (38.00), 160 (25.00), 159 (12.40), 158 (7.40), 157 (7.40), 156 (12.20), 153 (8.40), 152 (15.00), 151 (9.60), 149 (10.56), 148 (7.20), 147 (10.50), 138 (10.00), 137 (12.50), 136 (100.00; $C_9H_{12}O$), 135 (9.50), 134 (8.40), 128 (10.50), 127 (12.50), 123 (19.30), 122 (15.40), 121 (22.25), 120 (13.40), 119 (17.50), 97 (10.20), 96 (14.20), 95 (52.50), 94 (7.40), 93 (35.00), 92 (28.25), 91 (14.00), 83 (17.00), 82 (47.20), 81 (24.00), 80 (44.40), 79 (14.00), 72 (10.00), 71 (17.25), 70 (50.50), 69 (16.00), 68 (45.25), 67 (28.00), 66 (32.50), 65 (14.00), 59 (20.25), 58 (19.00), 57 (9.50), 56 (60.50), 55 (28.00), 54 (46.50), 53 (18.50), 44 (9.70), 43 (26.00), 42 (45.50), 41 (16.25).

Cholest-5-ene (XV)

3β -Chlorocholest-5-ene (15.0g) was dissolved in warm amyl alcohol (300 ml) and sodium metal (35.0g) was added in small portions to the solution with continuous stirring over a period of 8 hrs. The reaction mixture was heated now and then during the course of the reaction in order to keep the sodium metal dissolved. The reaction mixture was poured into water acidified with HCl and allowed to stand over night. A white crystalline solid was obtained which was filtered under suction, washed thoroughly with water and air dried. Recrystallization of the crude product from acetone gave the desired compound as cubes (10.8g), m.p. 93°C (reported[36], m.p. 89.5-91.2°C).

Oxidation of cholest-5-ene (XV) with silver chromate-iodine: 5-Iodo-5α-Cholestan-6-one (CLIII)

To a suspension of silver chromate (1.1g; 3.3 m mol) in 15 ml of dry dichloromethane was added iodine (1.14g; 4.5 m mol) and a solution of pyridine (0.12 g; 1.5 m mol) in 0.75 ml of dry dichloromethane at 0°C and stirred for 5 min. A solution of cholest-5-ene (XV) (0.74g; 2.0 m mol) in 5 ml of dry dichloromethane was added for 10 min. to the ice cooled suspension and was stirred for 20 min. at 0°C. The cooling bath was removed and the reaction mixture was stirred for an hour at room temperature. The reaction mixture was filtered and worked-up as usual and chromatographed over silica gel (40g). Elution with light petroleum/ ether (10:1) gave a semi solid product, 5-iodo-5α- cholestan-6-one (CLIII) (0.73g, 1.43 m mol) (positive Beilstein test).

Analysis found : C, 63.24; H, 8.81

$C_{27}H_{45}OI$ requires : C, 63.27; H, 8.85%

IR : ν max 1715 (C=O) and 525 cm^{-1} (C-I)

^{1}H-NMR : δ 1.10 (C10-CH_3), 0.68 (C13-CH_3), 0.91 and 0.80 (other methyl protons).

MS : M^{+} 512 (not observed), 385 (10.00; $C_{27}H_{45}O$), 384 (100.00; $C_{27}H_{44}O$), 370 (9.50; $C_{26}H_{42}O$), 369 (25.25), 366 (15.00), 356 (15.00), 352 (8.40), 351 (7.20), 342 (14.50), 341 (7.75), 272 (6.40), 271 (15.20), 247 (16.10), 246 (9.60), 245 (17.00), 244 (6.10), 243 (19.25), 242 (10.00), 241 (6.50), 231 (10.20), 229 (24.25), 228 (16.50), 215 (10.00), 214 (9.20), 213 (8.00), 201 (15.75), 188 (11.00), 187 (14.20), 186 (7.70), 175 (14.75), 174 (12.20), 173 (9.00), 172 (6.20), 162 (10.20), 161 (25.70), 160 (10.00), 159 (8.40), 158 (5.00), 157 (10.75), 143 (10.25), 142 (9.60), 141 (11.00), 140 (20.20), 138 (9.60), 137 (25.50), 136 (60.20), 135 (10.80), 134 (8.40), 128 (15.20), 127 (18.40), 126 (17.50), 125 (12.00), 124 (14.40), 123 (67.00), 122 (80.00), 121 (42.00), 120 (25.20), 119 (10.00), 118 (6.60), 112 (5.40), 111 (12.25), 110 (8.20), 109 (20.25), 108 (20.25), 107 (22.00), 106 (12.40), 105 (9.60), 98 (10.70), 97 (8.40), 96 (19.50), 95 (59.00), 94 (38.40), 93 (12.20), 92 (6.60), 91 (12.20), 81 (11.00), 80 (17.70), 79 (62.00), 78 (22.25), 77 (15.50), 55 (22.75), 54 (12.25), 53 (9.00), 52(50.00), 51 (15.50), 50 (9.60), 45 (17.50), 44 (25.20), 43 (40.00), 42 (19.50), 41 (10.70), 40 (9.60).

Oxidation of β-sitosterol (CXLVI) with silver chromate-iodine: 3β-Hydroxystigmast-4-en-6-one (CLIV)

To a well stirred solution of silver chromate (1.1g; 3.3 m mol), iodine (1.14g; 4.5 m mol) and pyridine (0.12 g; 1.5 m mol) in 15.75 of dry dichloromethane was added a solution of β-sitosterol (CXLVI) (0.83g; 2.0 m mol) in 5 ml of dry dichloromethane at 0°C for 10 min. The suspension was stirred for 20 min. at 0°C and one hour at room temperature.

The reaction mixture was filtered and the filterate was worked up as usual. The crude product thus obtained was chromatographed over silica gel (40g). Elution with light petroleum/ether (4:1) furnished a solid compound, 3β - hydroxystigmast-4-en-6-one (CLIV) which was recrystallized from light petroleum (0.597g, 1.39 m mol) m.p. 162°C (negative Beilstein test).

Analysis found : C, 81.27; H, 11.25

$C_{29} H_{48} O_2$ requires : C, 81.25; H, 11.29%

IR : ν max 3450 (OH), 1690 and 1615 cm^{-1} (C=C-C=O).

^{1}H-NMR : δ 6.12 (d, 1H, C4-H), 4.35 (mc, 1H, C3-αH, W 1/2 = 15 H_2, axial)^{32}, 2.2 (br, 1H, OH), 1.12 (C10-CH_3), 0.68 (C13-CH_3), 0.94 and 0.8 (other methyl protons).

MS : M^{+} 428 (100.00; $C_{29} H_{48} O_2$), 413 (10.00; $C_{28} H_{45} O_2$), 412 (13.50; $C_{28} H_{44} O_2$), 411 (9.20; $C_{29} H_{47} O$), 410 (15.50, $C_{29} H_{46} O$), 400 (8.40), $C_{28} H_{48} O$), 396 (7.00; $C_{28} H_{44} O$), 382 (6.50), 287 (21.50), 286 (17.25), 272 (20.20), 271 (13.25), 270 (6.40), 269 (9.40), 260 (5.50), 259 (6.50), 248 (9.60), 247 (24.50), 246 (7.40), 245 (12.25), 231 (10.40), 230 (5.00), 178 (10.20), 177 (14.25), 176 (8.40), 175 (13.75), 174 (11.20), 161 (9.20), 160 (8.40), 159 (6.20), 153 (7.20), 152 (16.40; $C_9 H_{12} O_2$), 151 (10.20), 150 (9.50), 139 (25.00), 138 (12.50), 137 (17.20), 136 (8.40), 135 (22.50), 134 (6.50), 123 (6.60), 122 (10.50), 121 (21.00), 120 (5.40), 119 (17.25), 118 (5.00), 111 (25.00), 110 (9.60), 109 (19.10), 108 (25.20), 107 (40.00), 106 (15.50), 105

(20.00), 104 (8.50), 96 (10.50), 95 (42.00), 94 (21.50), 93 (17.00) 92 (10.00), 91 (8.40), 83 (15.75), 82 (8.20), 81 (37.20), 80 (11.00), 79 (29.00), 72 (10.40), 71 (22.20), 70 (12.00), 69 (27.25), 68 (32.50), 67 (20.00), 58 (9.20), 57 (48.50), 56 (12.00), 55 (10.75), 49 (17.00), 48 (12.50), 47 (20.50), 46 (45.75), 45 (36.00), 44 (24.50), 43 (62.40), 42 (24.50), 41 (42.20).

3β -Chlorostigmast-5-ene (CXLVI)

Freshly purified thionyl chloride (40 ml) was added gradually to β-sitosterol (50g) at room temperature. A vigorous reaction ensured with the evolution of gaseous products. When the reaction slackened, the mixture was gently heated at a temperature of 50-60°C on water bath for 1 hr and then poured onto crushed ice with stirring. The yellow solid thus obtained was filtered under suction, washed several times with ice cooled water and air dried. Recrystallization from acetone gave 3β -chlorostigmast-5-ene (45 g), m.p. 82°C (reported,[37] m.p. 82°C).

Oxidation of 3β -chlorostigmast-5-ene (CXLVII) with silver chromate-iodine: 3β -Chloro-5-iodo-5α -stigmastan-6-one (CLV)

To a suspension of silver chromate (1.1g; 3.3 m mol) in 15 ml of dry dichloromethane iodine (1.14g; m mol) and a solution of pyridine was added (0.12 g; 1.5 m mol) in 0.75 ml of dry dichloromethane at 0°C and stirred for 5 min. A solution of 3β -chlorostigmast-5-ene (CXLVII) (0.87g; 2.0

mmol) in 5 ml of dry dichloromethane was added for 10 min. to the ice-cooled suspension and was stirred for 20 min. at 0^oC. Then the cooling bath was removed and the mixture was stirred for an hour at room temperature. The reaction mixture was filtered, the filterate was worked-up as usual and chromatographed over silica gel (40g). Elution with light petroleum/ether (10:1) gave an oily compound, 3β--chloro-5-iodo-5α-stigmastan-6-one (CLV), (0.92g, 1.6 mmol) (positive Beilstein test).

Analysis found : C, 60.51; H, 8.37

$C_{29}H_{48}$ OClI requires : C, 60.57; H, 8.41%

IR : ν max 1715 (C=O), 750 (C-Cl) and 510 cm^{-1} (C-I).

^1H-NMR : δ 3.8 (mc, 1H, C3-αH, W 1/2 = 14 Hz, axial)[32], 1.15 (C10-CH_3), 0.67 (C13-CH_3), 0.94 and 0.83 (other methyl protons).

MS : M^{+} 574 (not observed), 447/449 (15.20/ 5.06; $C_{29}H_{48}$ OCl), 446/448 (13.70/4.56), 432/434 (8.60/2.86; $C_{28}H_{45}$ OCl), 431/433 (6.50/2.16), 412 (77.50; $C_{29}H_{48}O$), 411 (65.20), 410 (12.50), 397 (25.20), 396 (27.50; $C_{28}H_{44}O$), 395 (8.50), 394 (19.75), 393 (58.50), 384 (17.25; $C_{28}H_{48}$), 383 (20.00), 382 (10.25), 378 (18.50), 377 (14.00), 306 / 308 (11.00/3.66), 305/307 (13.50/4.50), 247 (13.25), 246 (10.00), 245 (6.60), 244 (10.25), 243 (12.70), 242 (14.00), 241 (10.10), 240 (7.40), 239 (7.40), 238 (5.00), 229 (17.00), 228 (25.50), 227 (21.00), 226 (10.00), 225 (6.60), 224 (5.40), 217 (6.40), 216 (6.40), 215 (12.00), 214 (8.20), 175 (16.50), 174 (9.00), 162 (10.50), 161 (17.25), 160 (28.00), 159 (11.00), 158 (7.40), 153 (5.60), 152 (16.00), 151 (11.00), 149 (13.25), 140 (5.50), 139 (5.50), 138 (12.25), 137 (21.20), 136 (100.00; $C_9 H_{12}O$), 135 (13.30), 134 (9.75), 133 (10.50), 129 (8.40), 128 (9.90), 127 (12.75), 126 (10.0), 125 (6.40), 124 (11.20), 123 (20.20), 122 (18.50), 121 (32.50), 120 (16.20), 119 (12.00), 96 (19.10), 95 (51.00), 94 (12.50), 86 (8.40), 85 (10.00), 84 (45.00), 83 (20.25), 82 (15.50), 81 (40.20), 80 (20.20), 79 (9.50), 78 (31.40), 77 (15.50), 76 (10.20), 70 (26.50), 69 (18.25), 68 (54.00), 67 (17.50), 66 (40.00), 65 (17.50), 62 (10.20), 61 (10.20), 60 (8.40), 59 (17.50), 58 (10.00), 57 (47.50), 56 (11.25), 55 (55.40), 54 (20.00), 46 (32.50), 45 (10.40), 44 (10.40), 43 (54.00), 42 (29.25), 41 (9.00), 40 (14.50).

3β-Acetoxystigmast-5-ene (CXLVII)

A mixture of β-sitosterol (100g), pyridine (150 ml) and freshly distilled acetic anhydride (100 ml) was heated on a water bath for 2 hrs. A brown solution was obtained which after cooling was poured onto crushed ice water mixture with stirring. The white precipitate thus obtained was filtered under suction, washed with water and air dried. The crude acetate was recrystallized from acetone (90 g), m.p. 120°C (reported[37], m.p. 120°C).

Oxidation of 3β -actoxystigmast-5-ene (CXLVIII) with silver chromate-iodine: 3β -Acetoxy-5-iodo-5α -stigmastan-6-one (CLVI)

To a well stirred solution of silver chromate (1.1g, 3.3 m mol), iodine (1.14g, 4.5 m mol) and pyridine (0.12g; 1.5 m mol) in 15.75 ml of dry dichloromethane, was added a solution of 3β -acetoxystigmast-5-ene (CXLVIII) (0.91g; 2.0 m mol) in 5 ml of dry dichloromethane at 0^{o}C for 10 min. The suspension was stirred for 20 min. at 0^{o}C and one hour at room temperature. The reaction mixture was filtered and the filterate was worked-up as usual. The crude product thus obtained was chromatographed over silica gel (40g). Elution with light petroleum ether/ether (10:1) gave a solid product, 3β -acetoxy-5-iodo-5α -stigmastan-6-one (CLVI) which was recrystallized from light petroleum (0.92, 1.54 m mol) m.p. 97^{o}C (positive Beilstein test).

Analysis found : C, 62.22; H, 8.54

$C_{31}H_{51}O_3I$ requires : C, 62.19; H, 8.59%

IR : ν max 1725 (CH_3COO), 1715 (C=O), 1030 (C-O), and 510 cm^{-1} (C-I).

^{1}H-NMR : δ 4.6 (mc, 1H, C3-α H, W 1/2 = 16Hz, axial)^{32}, 1.9 (s, 3H, CH_3 COO) 1.15 (C10-CH_3), 0.65 (C13-CH_3), 0.95 and 0.82 (other methyl protons).

MS : $M^{+\cdot}$ 598 (not observed), 471 (10.00; $C_{31}H_{51}O_3$), 470 (9.50), 456 (7.40), 455 (5.00), 428 (41.00), 427 (6.50), 426

(7.40), 413 (13.20), 412 (87.40; $C_{29}H_{48}O$), 411 (69.90), 410 (8.40), 397 (13.00), 396 (27.20), 395 (4.80), 394 (31.50), 393 (67.50; $C_{29}H_{45}$), 392 (5.70), 384 (10.74), 383 (12.20), 379 (20.20), 378 (17.00), 368 (4.80), 330 (9.60), 329 (10.50), 247 (14.20), 246 (6.40), 245 (5.40), 244 (9.50), 243 (9.50), 242 (10.90), 229 (17.50), 228 (15.00), 227 (11.25), 226 (9.40), 225 (7.00), 216 (9.50), 215 (12.00), 214 (7.30), 213 (5.40), 212 (5.40), 180 (10.25), 179 (9.00), 178 (12.50), 177 (8.75), 176 (5.40), 175 (12.20), 174 (9.60), 173 (5.60), 167 (7.50), 166 (10.90), 165 (28.50), 164 (12.25), 160 (29.50), 159 (21.00), 158 (10.40), 157 (5.50), 156 (5.50), 154 (10.20), 153 (7.30), 152 (19.10), 149 (12.50), 148 (6.50), 147 (12.50), 137 (14.00), 136 (100.00; $C_9H_{12}O$), 135 (27.20), 134 (10.50), 130 (6.40), 129 (8.00), 128 (13.20), 127 (17.50), 126 (10.20), 125 (7.40), 123 (25.50), 122 (20.00), 121 (24.00), 120 (12.25), 98 (5.40), 97 (7.75), 96 (17.20), 95 (56.00), 94 (17.20), 93 (31.20), 92 (24.25), 91 (11.50), 82 (14.50), 81 (40.20), 80 (26.50), 79 (8.80), 72 (10.40), 71 (8.40), 70 (26.60), 69 (14.00), 68 (20.10), 67 (40.50), 66 (25.50), 65 (29.00), 59 (30.10), 58 (22.25), 57 (12.25), 56 (57.30), 55 (27.50), 54 (45.00), 53 (20.20), 52 (12.50), 46 (9.60), 45 (13.00), 44 (29.25), 43 (50.00), 42 (12.40), 41 (10.50).

Oxidation of stigmasterol (CXLIX) with silver chromate - iodine: 3β -Hydroxy-22/23-iodostigmast-4-en-6, 23/22-dione (CLVII)

To a suspension of silver chromate (1.43g; 4.3 m mol) in 15 ml of dry dichloromethane was added iodine (1.22g; 4.8 m mol) and a solution of pyridine (0.12g; 1.5 m mol) in 0.75 ml of dry dichloromethane at 0°C and stirred for 5 min. A solution of stigmasterol (CXLIX) (0.83g; 2.0 m mol) in 5 ml of dry dichloromethane was added for 10 min to the ice-cooled suspension and was stirred for 20 min at 0°C. Then the cooling bath was removed and the mixture was stirred for an hour at room temperature. The reaction mixture was filtered. The filterate was worked-up as usual and chromatographed over silica gel (40g). Elution with light petroleum/ether (4:1) provided 3β -hydroxy- 22/23- iodostigmast-4-en-6, 23/22 -dione (CLVII) as semi-solid (0.668g, 1.18 m mol) (positive Beilstein test).

Analysis found : C, 61.21; H, 7.95

$C_{29} H_{45} O_3$ I requires : C, 61.26; H, 7.98%

IR : ν max 3420 (OH), 1720 (C=O), 1680, 1610 (C=C-C=O) and 520 cm^{-1} (C-I).

^{1}H-NMR : δ 6.2 (d, 1H, C4-H), 4.4 (d, 1H, C 22/23-H), 4.1 (mc, 1H, C3-αH, W 1/2 = 16 Hz, axial)[32], 1.9 (br, 1H, OH), 1.14 (C10-CH_3), 0.71 (C13-CH_3), 0.96 and 0.81 (other methyl protons).

MS : M$^{\dot{+}}$ 568 (not observed) 441 (75.00); $C_{29} H_{45} O_3$), 440 (68.50; $C_{29} H_{44} O_3$), 424 (12.00), 423 (7.50), 422 (15.50; $C_{29} H_{42} O_2$), 413 (6.50), 412 (10.00), 395 (5.50), 394 (7.50; $C_{28} H_{42}O$), 343 (21.50); $C_{22} H_{31} O_3$), 342 (7.40), 341 (10.20), 340 (6.60), 287 (42.50; $C_{19} H_{27} O_2$), 286 (17.50), 272 (27.25), 271 (10.00), 270 (7.40), 261 (7.00), 260 (6.40), 259 (7.00), 258 (7.00), 248 (10.75), 247 (29.20), 246 (8.00), 245 (11.10), 244 (5.00), 231 (14.20), 230 (6.40), 157 (10.40), 156 (8.40), 155 (5.50), 154 (7.70), 153 (7.70), 152 (20.00; $C_9 H_{12} O_2$). 151 (12.50), 150 (8.40), 149 (5.00), 148 (8.40), 140 (10.40), 139 (32.25), 138 (9.60), 137 (19.20), 136 (10.50), 135 (20.00), 134 (9.40), 128 (15.00), 127 (19.50), 126 (8.20), 125 (6.00), 124 (6.60), 123 (10.20), 122 (10.20), 121 (25.00), 120 (7.40), 119 (21.25), 118 (7.00), 117 (7.00), 116 (5.50), 111 (22.25), 110 (12.00), 109 (13.75), 108 (27.20), 107 (24.10), 106 (40.25), 105 (45.00), 104 (9.60), 98 (10.20), 97 (10.20), 96 (14.00), 95 (32.25), 94 (20.00), 93 (12.50), 92 (50.50), 91 (10.00), 90 (9.60), 89 (13.30), 82 (17.90), 81 (22.25), 80 (39.40), 79 (21.00),78 (27.20), 77 (9.00), 71 (29.00), 70 (24.50), 69 (17.50), 68 (38.00), 67 (14.20), 66 (12.50), 61 (19.00), 60 (10.75), 59 (41.20), 57 (55.50), 56 (17.70), 55 (21.00), 54 (21.00), 53 (13.50), 46 (20.50), 45 (28.25), 44 (32.00), 43 (100.00), 42 (62.10), 41 (25.50).

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CHAPTER THREE

Synthesis of δ-lactones

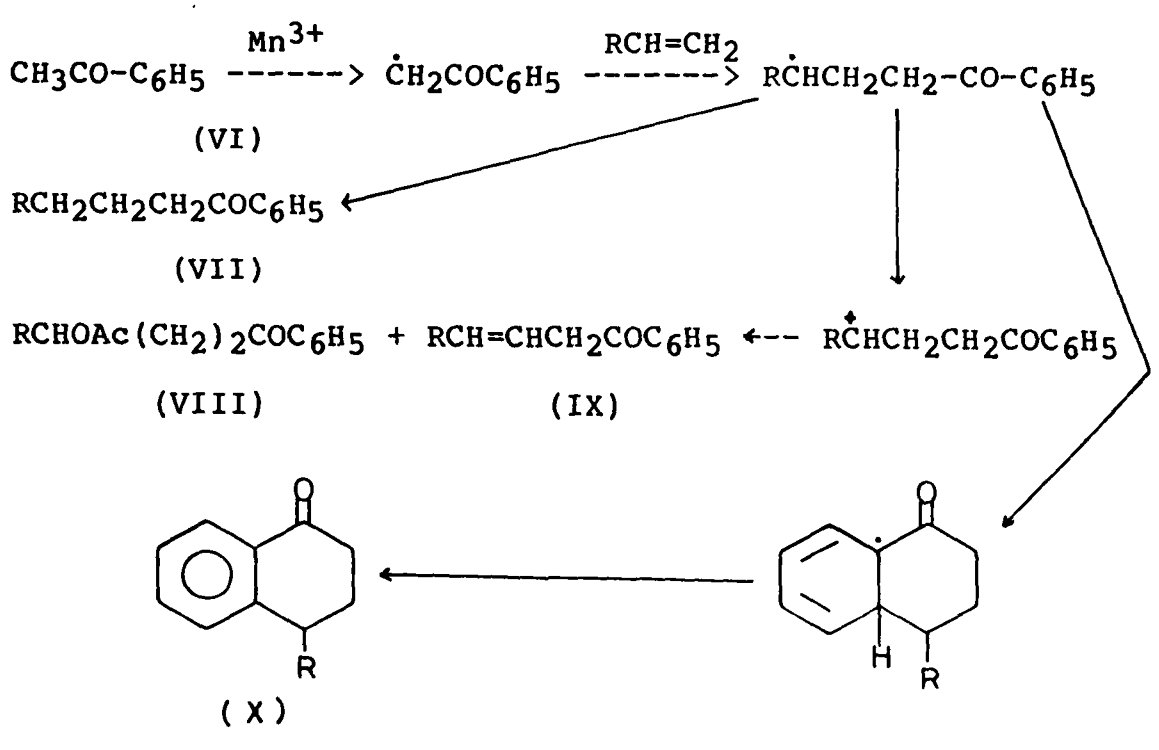
THEORETICAL

Oxidative addition of enolizable carbonyl compound to alkenes promoted by one electron oxidant is a well-known reaction which received considerable attention in recent years. Heiba and Dessau reported[1] the oxidative addition of acetone (I) to an olefin (II) through Mn(III) acetate or Ce(IV) acetate and obtained the following results (III-V).

$$\underset{(I)}{CH_3\,CO\text{-}CH_3} + \underset{(II)}{C_6H_{13}\text{-}CH{=}CH_2} \xrightarrow[HOAc]{Ce(OAc)_4 \text{ or } Mn(OAc)_3} \underset{(III)}{C_9H_{19}\,CO\text{-}CH_3} +$$

$$\underset{(IV)}{C_6H_{13}CH{=}CHCH_2CO\text{-}CH_3} + \underset{(V)}{C_6H_{13}\text{-}CHOAc\text{-}CH_2CH_2\text{-}CO\text{-}CH_3}$$

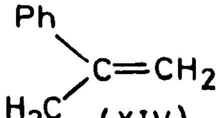
Heiba and Dessau reported[2] the oxidative addition of acetophenone (VI) through Mn(III) acetate but here instead of three products, they isolated four major products (VII-X).



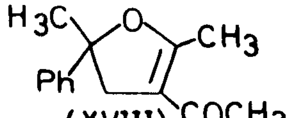
Dihydrofurans (XVIII-XXIV) were formed[3a] in high yields by the reaction of readily enolizable ketones, such as β-diketones (XI,XII) and β-ketoester (XIII), with olefins (II,XIV-XVII) in presence of manganic acetate.

$CH_3-CO-CH_2-CO-CH_3$

(XI)



(XIV)



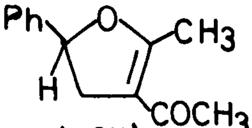
(XVIII)

$CH_3-CO-CH_2CO-CH_3$

(XI)

$Ph-CH=CH_2$

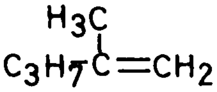
(XV)



(XIX)

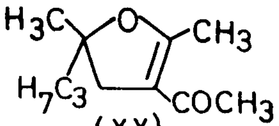
$CH_3CO-CH_2CO-CH_3$

(XI)



$C_3H_7-\overset{H_3C}{C}=CH_2$

(XVI)



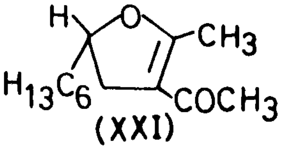
(XX)

$CH_3CO-CH_2CO-CH_3$

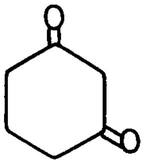
(XI)

$C_6H_{13}-CH=CH_2$

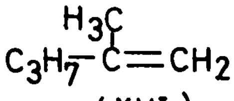
(II)



(XXI)

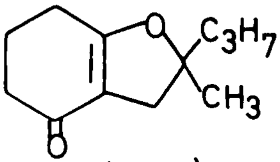


(XII)

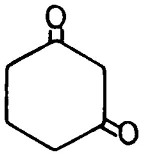


$C_3H_7-\overset{H_3C}{C}=CH_2$

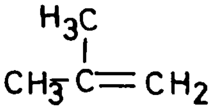
(XVI)



(XXII)

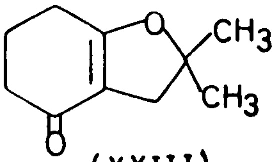


(XII)



$CH_3-\overset{H_3C}{C}=CH_2$

(XVII)



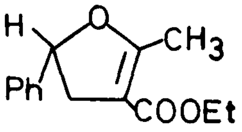
(XXIII)

$CH_3CO-CH_2-COOEt$

(XIII)

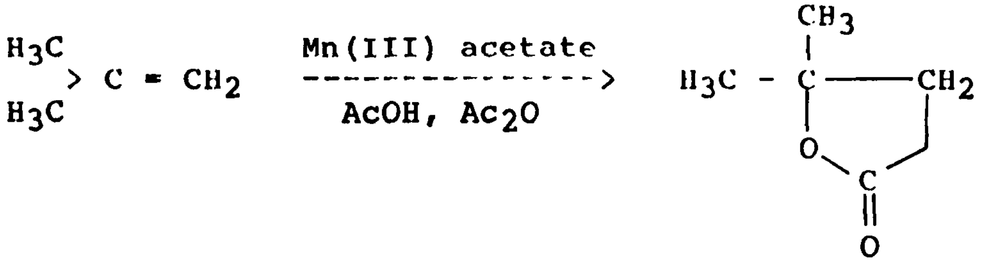
$Ph-CH=CH_2$

(XV)

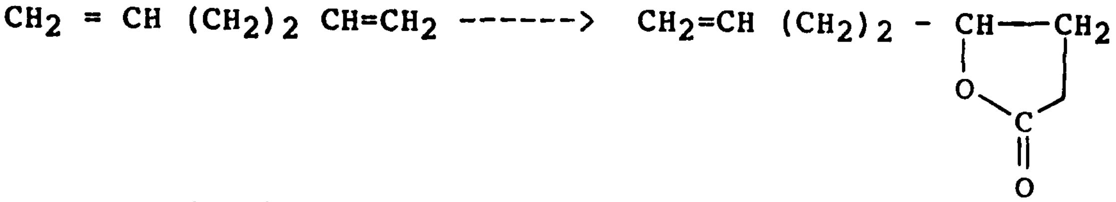


(XXIV)

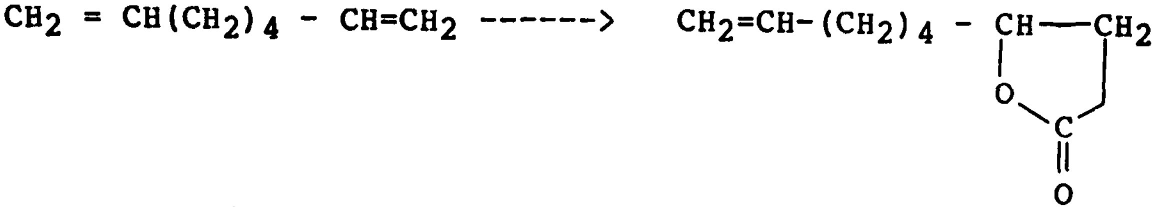
Heiba et al.[3b] reported the synthesis of γ- lactones from olefins with acetic acid. They allowed various olefins (XVII, XXV-XXVII) to react with Mn(III) acetate in presence of acetic acid and acetic anhydride and obtained the corresponding γ- lactones (XXVIII-XXI).



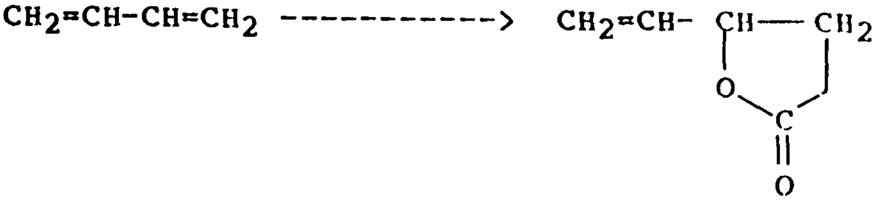
(XVII) (XXVIII)



(XXV) (XXIX)

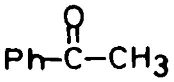


(XXVI) (XXX)

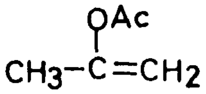


(XXVII) (XXXI)

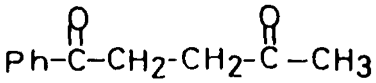
1,4-diketones (XXXVI-XL) were synthesized[4] in one step by the reaction of enol esters (XXXV) with ketones (VI, XXXII-XXXIV) in the presence of manganic acetate.


$Ph-\overset{O}{\overset{\|}{C}}-CH_3$

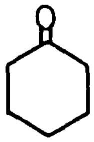
(VI)


$CH_3-\overset{OAc}{\overset{|}{C}}=CH_2$

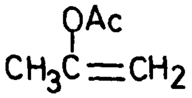
(XXXV)


$Ph-\overset{O}{\overset{\|}{C}}-CH_2-CH_2-\overset{O}{\overset{\|}{C}}-CH_3$

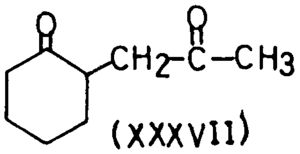
(XXXVI)



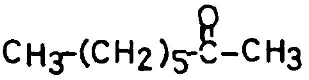
(XXXII)


$CH_3\overset{OAc}{\overset{|}{C}}=CH_2$

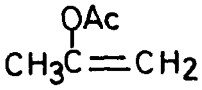
(XXXV)



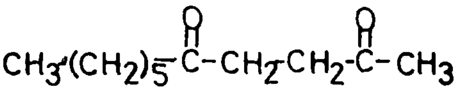
(XXXVII)


$CH_3-(CH_2)_5-\overset{O}{\overset{\|}{C}}-CH_3$

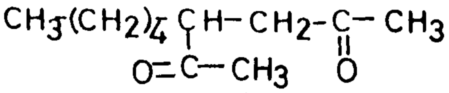
(XXXIII)


$CH_3\overset{OAc}{\overset{|}{C}}=CH_2$

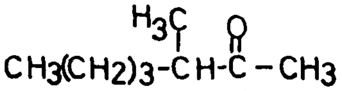
(XXXV)


$CH_3-(CH_2)_5-\overset{O}{\overset{\|}{C}}-CH_2-CH_2-\overset{O}{\overset{\|}{C}}-CH_3$

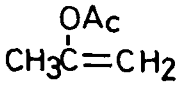
(XXXVIII)


$CH_3-(CH_2)_4-\underset{O=C-CH_3}{\underset{|}{C}}H-CH_2-\underset{O}{\underset{\|}{C}}-CH_3$

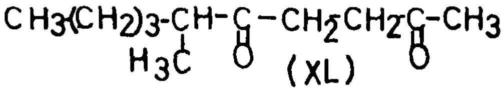
(XXXIX)


$CH_3(CH_2)_3-\overset{H_3C}{\overset{|}{C}}H-\overset{O}{\overset{\|}{C}}-CH_3$

(XXXIV)

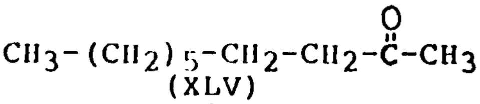
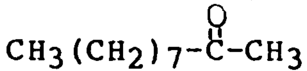
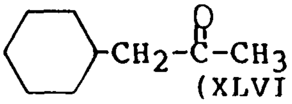
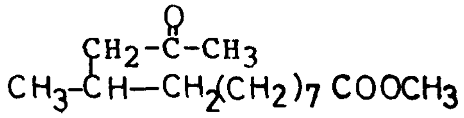

$CH_3\overset{OAc}{\overset{|}{C}}=CH_2$

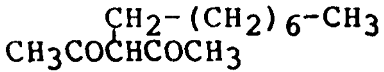
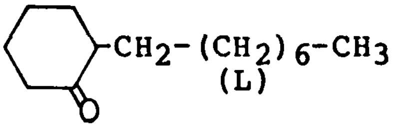
(XXXV)


$CH_3(CH_2)_3-\underset{H_3C}{\underset{|}{C}}H-\underset{O}{\underset{\|}{C}}-CH_2CH_2-\underset{O}{\underset{\|}{C}}-CH_3$

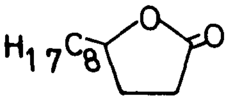
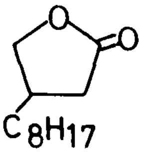
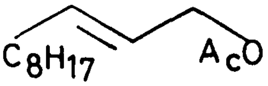
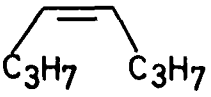
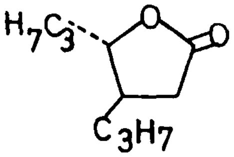
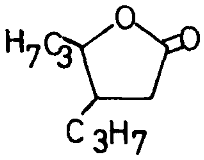
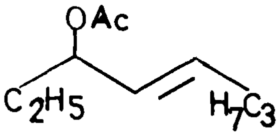
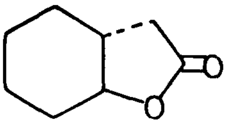
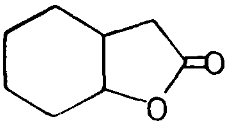
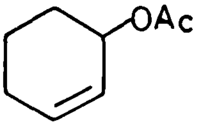
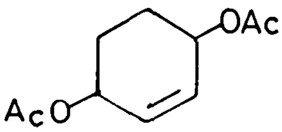
(XL)

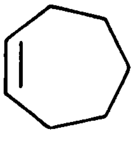
Cittero et al. reported[5] the addition of ketones (I, XLI and XXXII) to olefins (II, XLII-XLIV) by Ag^+-catalysed decomposition of peroxydisulphate and obtained the following results (XLV-L).

CH_3CO-CH_3 (I)	Oct-1-ene (II)	 $CH_3-(CH_2)_5-CH_2-CH_2-\overset{O}{\overset{\|}{C}}-CH_3$ (XLV)
CH_3CO-CH_3 (I)	Hept-1-ene (XLII)	 $CH_3(CH_2)_7-\overset{O}{\overset{\|}{C}}-CH_3$ (XLVI)
CH_3CO-CH_3 (I)	Cyclohexene (XLIII)	 (XLVII)
CH_3CO-CH_3 (I)	Methyl undec-9-enoate (XLIV)	 $CH_3-\overset{CH_2-\overset{O}{\overset{\|}{C}}-CH_3}{\overset{|}{C}}H-CH_2(CH_2)_7COOCH_3$ (XLVIII)

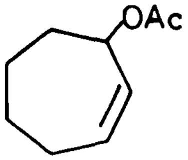
Acetylacetone (XLI)	Oct-1-ene (II)	 $CH_3CO\overset{CH_2-(CH_2)_6-CH_3}{C}HCOCH_3$ (XLIX)
Cyclohexanone (XXXII)	Oct-1-ene (II)	 (L)

The annulation of a γ-lactone ring onto an alkene by Mn(III) acetate oxidation of acetic acid was reported by Fristad and Petersan.[6] This way the alkenes (LI-LXI) provided following products (LXII-CVI).

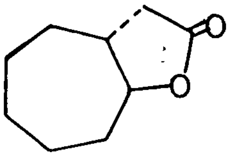
Alkene	Products		
$C_8H_{17}\text{-}CH{=}CH_2$ (LI)	 (LXII)	 (LXIII)	 (LXIV)
 (LII)	 (LXV)	 (LXVI)	 (LXVII)
 (XLIII)	 (LXVIII)	 (LXIX)	
	 (LXX)	 (LXXI)	



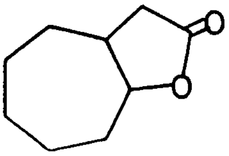
(LIII)



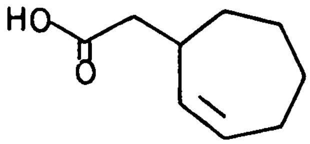
(LXXII)



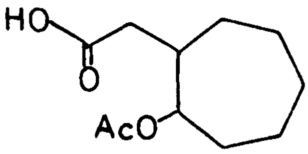
(LXXIII)



(LXXIV)



(LXXV)



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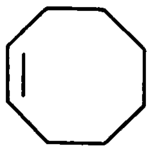

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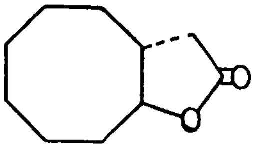

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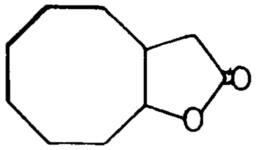

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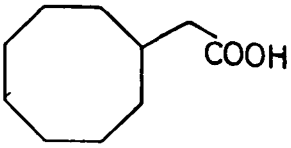

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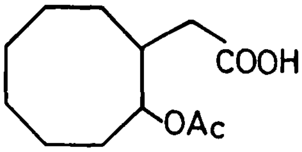

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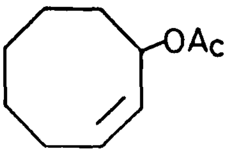

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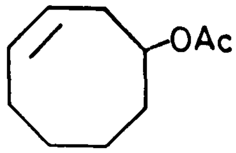

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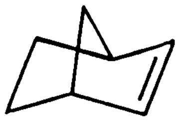

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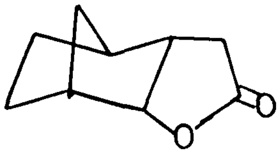

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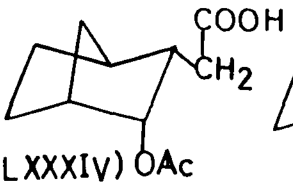

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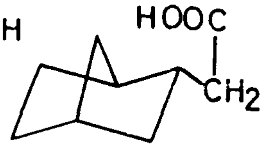

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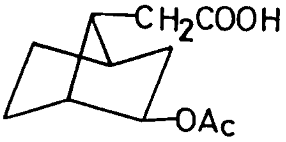

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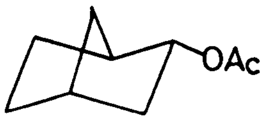

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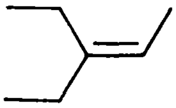

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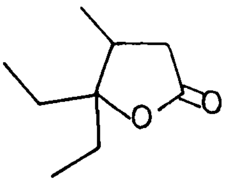

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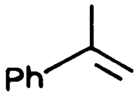
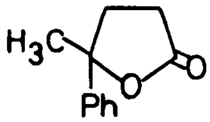


(LVII)



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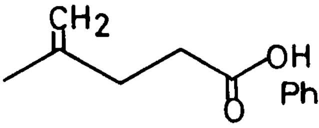
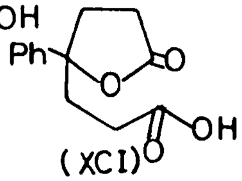


(XC)



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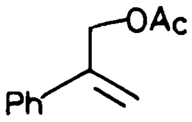

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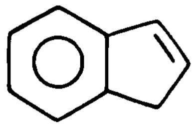

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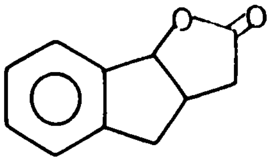

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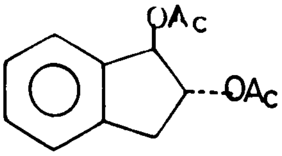

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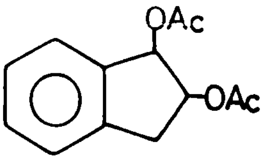

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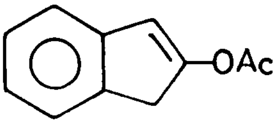

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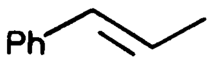

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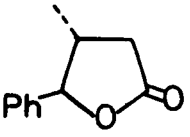

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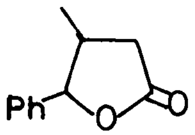

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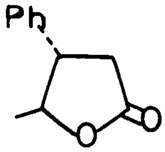

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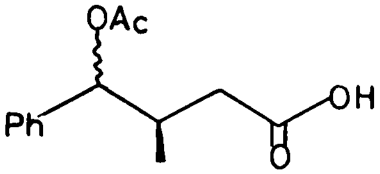
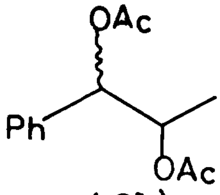


(C)



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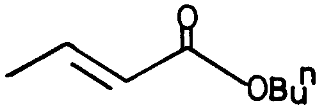
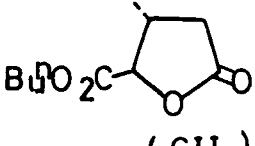


(LX)



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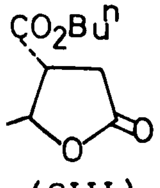

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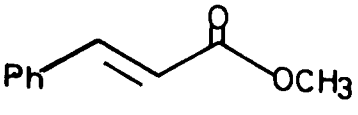

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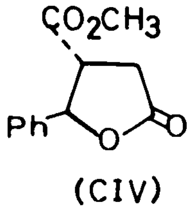

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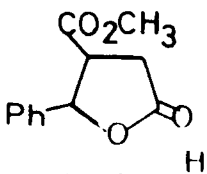
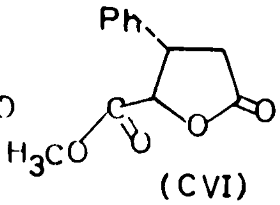
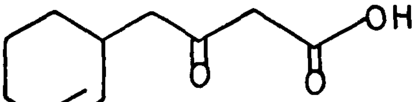


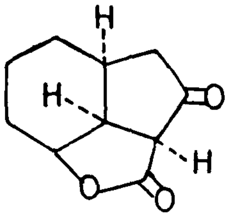
(CV)

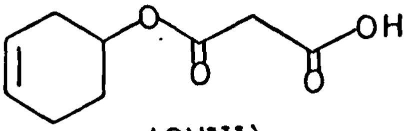


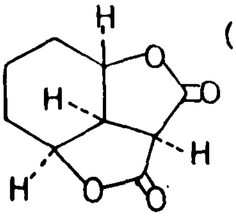
(CVI)

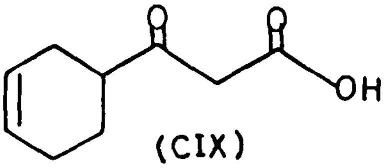
Corey and Kang reported[7] the synthesis of γ-lactones by the reaction of keto-acid with $Mn_3O(OAc)_7$ in presence of acetic acid. In this way 4-(2-cyclohexenyl)-o-oxobutanoic acid (CVII) was converted into ketolactone (CXII). The half malonate ester of 2-cyclohexen-1-ol (CVIII) furnished the bis (γ-lactone) (CXIII). Similarly ketoacid (CIX) afforded tricylic bridged lactone (CXIV), keto acid (CX) gave the ketolactone (CXV) and the keto acid (CXI) furnished the tricylic lactone (CXVI).

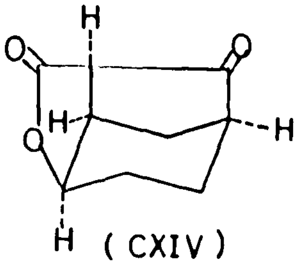

(CVII)

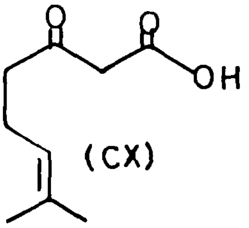

(CXII)

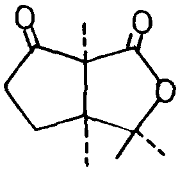

(CVIII)


(CXIII)

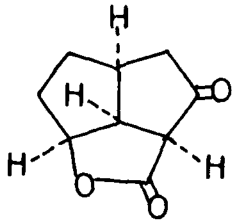

(CIX)


(CXIV)


(CX)


(CXV)


(CXI)


(CXVI)

Trahanovsky and Cromer[8] reported the oxidation of methyl-, ethyl-, isopropyl-, and tert-butyl-phenylcarbinols (CXVII-CXX) by ceric ammonium nitrate affording the respective ketones (CXXI-CXXVIII).

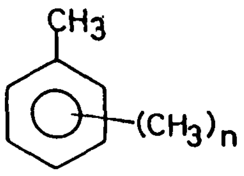
$$\text{PhCHOH-R} \xrightarrow{2\text{Ce}^{IV}} \text{PhCOR}$$

$$\text{PhCHOH-R} \xrightarrow{2\text{Ce}^{IV}} \text{PhCH} = \text{O} + \text{products of R+}$$

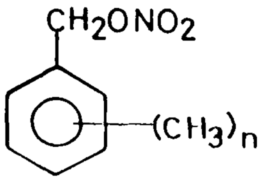
	R
(CXXI)	$-CH_3$
(CXXII)	$-C_2H_5$
(CXXIII)	$-CH(CH_3)_2$
(CXXIV)	$-C(CH_3)_3$

	R		R
(CXVII)	$-CH_3$	(CXXV)	$-CH_3$
(CXVIII)	$-C_2H_5$	(CXXVI)	$-C_2H_5$
(CXIX)	$-CH(CH_3)_2$	(CXXVII)	$-CH(CH_3)_2$
(CXX)	$-C(CH_3)_3$	(CXXVIII)	$-C(CH_3)_3$

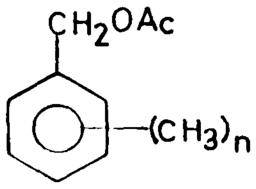
Baciocchi et al.[9] reported the oxidation of alkylaromatic compounds (CXXIX) by ceric ammonium nitrate in acetic acid and obtained the following products (CXXX, CXXXI).



(CXXIX)

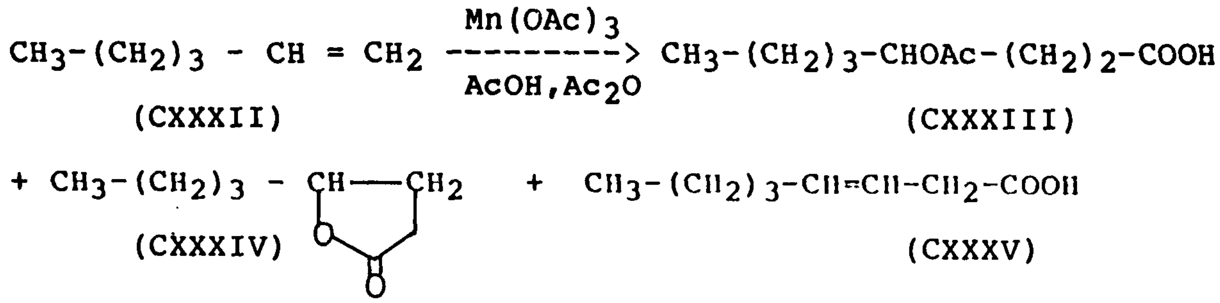


(CXXX)



(CXXXI)

Okano[10] reported the oxidation of 1-hexene (CXXXII) and 2-methyl-2-pentenene (CXXXVIII) with Mn(III) acetate in presence of acetic acid and propionic acid . 1-Hexene (CXXXII) afforded 4-acetoxy-octanoic acid (CXXXIII), the γ-lactone of 4-hydroxyoctanoic acid (CXXXIV), 3-octanoic acid (CXXXV), 4-octanoic acid (CXXXVI) and octanoic acid (CXXXVII) in presence of acetic acid. 2-Methyl-2-pentene (CXXXII) gave 4-acetoxy-3-ethyl-4-methyl-pentanoic acid (CXXXIX), γ-lactone of 3-ethyl-4-hydroxy-4-methyl pentanoic acid (CXL), 3-isopropenyl pentanoic acid (CXLI) and 3-ethyl-4-methylene heptanedioic acid (CXLII).



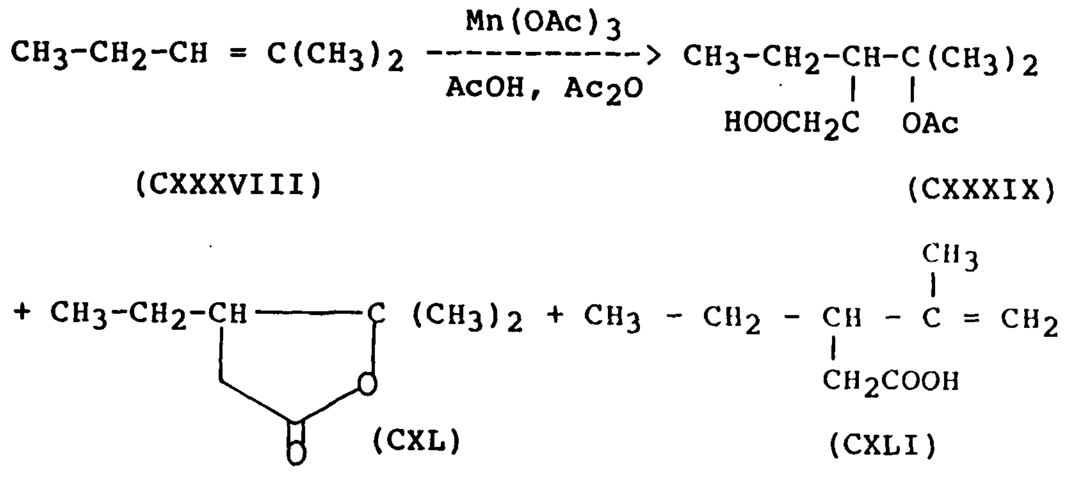
$CH_3-(CH_2)_3-CH=CH_2 \xrightarrow[AcOH, Ac_2O]{Mn(OAc)_3} CH_3-(CH_2)_3-CHOAc-(CH_2)_2-COOH$

(CXXXII) (CXXXIII)

(CXXXIV) $+ CH_3-(CH_2)_3-CH=CH-CH_2-COOH$ (CXXXV)

$+ CH_3-(CH_2)_2-CH=CH-(CH_2)_2-COOH + CH_3-(CH_2)_6-COOH$

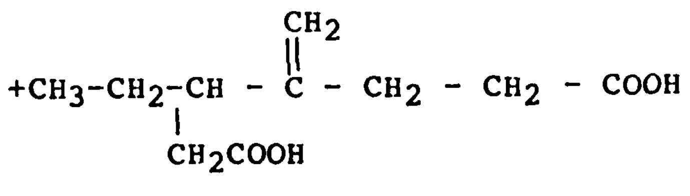
(CXXXVI) (CXXXVII)



$CH_3-CH_2-CH=C(CH_3)_2 \xrightarrow[AcOH,\ Ac_2O]{Mn(OAc)_3} CH_3-CH_2-CH(CH_2COOH)-C(CH_3)_2(OAc)$

(CXXXVIII) (CXXXIX)

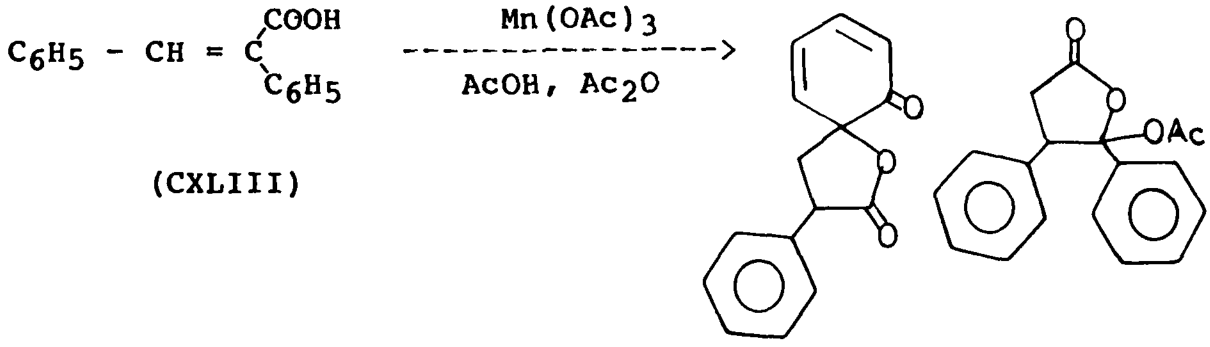
(CXL) $+ CH_3-CH_2-CH(CH_2COOH)-C(CH_3)=CH_2$ (CXLI)



$$+CH_3-CH_2-\underset{\displaystyle CH_2COOH}{\underset{|}{CH}} - \overset{\displaystyle CH_2}{\overset{\|}{C}} - CH_2 - CH_2 - COOH$$

(CXLII)

Oishi and Kurosawa[11] reported the reaction of α-phenylcinnamic acid (CXLIII) with Mn(III) acetate in presence of acetic acid and acetic anhydride yielding spirolactone (CXLIV) and 5-acetoxy-4,5 diphenyl-2(5H)-furanone (CXLV).



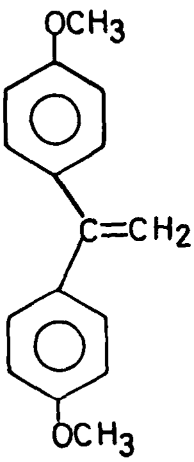
$$C_6H_5 - CH = C\begin{matrix}COOH\\C_6H_5\end{matrix} \xrightarrow[AcOH,\ Ac_2O]{Mn(OAc)_3}$$

(CXLIII)

(CXLV)

(CXLIV)

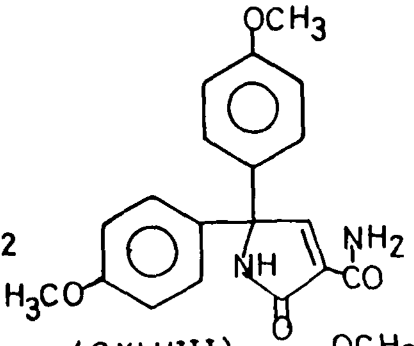
The oxidation of 1,1-bis (4-methoxyphenyl)-ethene (CXLVI) with Mn(III) acetate in the presence of malonamide (CXLVII) afforded α, β-unsaturated -γ-lactams such as 3-carbamoyl-5,5-bis (4-methoxyphenyl)-1H-pyrrol-2(5H)-one (CXLVIII) and 3-carbamoyl-4-hydroxy-5,5-bis (4-methoxyphenyl) -1H-pyrrol-2(5H) -one (CXLIX) rather than the corresponding 2-butene-4-olide (CL).[12]



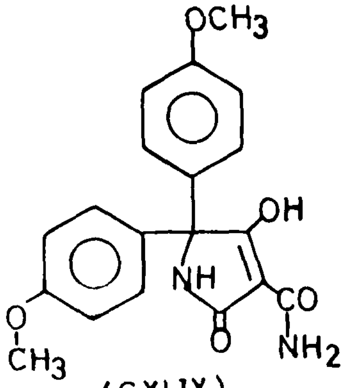
(CXLVI)

$CH_2(CONH_2)_2$

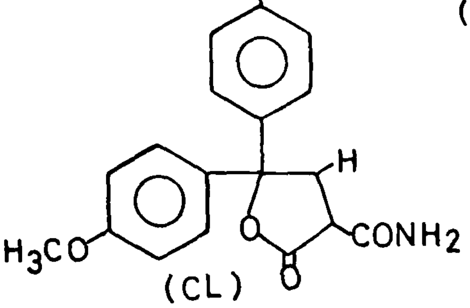
CXLVII



(CXLVIII)

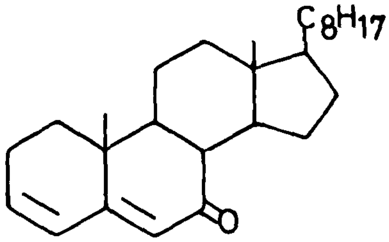


(CXLIX)

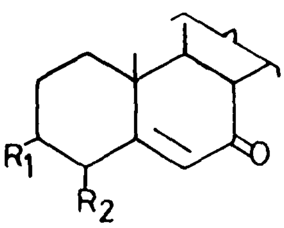


(CL)

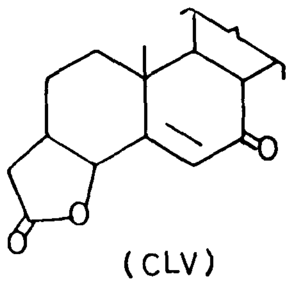
The oxidation of cholesta-3,5-dien-7-one (CLI) with Mn(III) acetate in presence of acetic acid and acetic anhydride yielded 4β-hydroxy-7-oxocholest-5-en-3β-yl acetic acid γ-lactone (CLV). On similar treatment cholest-5-en-7-one (CLII) and 3β-chlorocholest-5-en-7-one (CLIII) furnished lactone (CLV), 7-oxocholest-5-en-4β-yl acetate (CLIV) and lactone (CLV), ketone (CLI) respectively.[13]



(CLI)

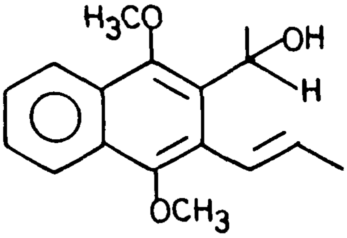


	R_1	R_2
(CLII)	H	H
(CLIII)	Cl	H
(CLIV)	H	OAc

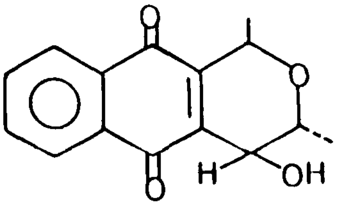


(CLV)

Charn et al.[14] reported the synthesis of naphtho (2,3-C) pyran-5,10-quinones (CLVII) using ceric ammonium nitrate from (CLVI).

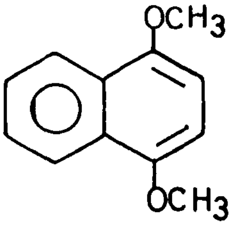


(CLVI)

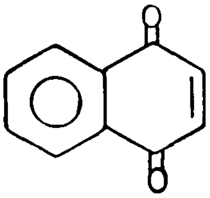


(CLVII)

Jacob et al.[15] reported the synthesis of quinone (CLIX) from hydroquinone dimethyl ether (CLVIII) using ceric ammonium nitrate.

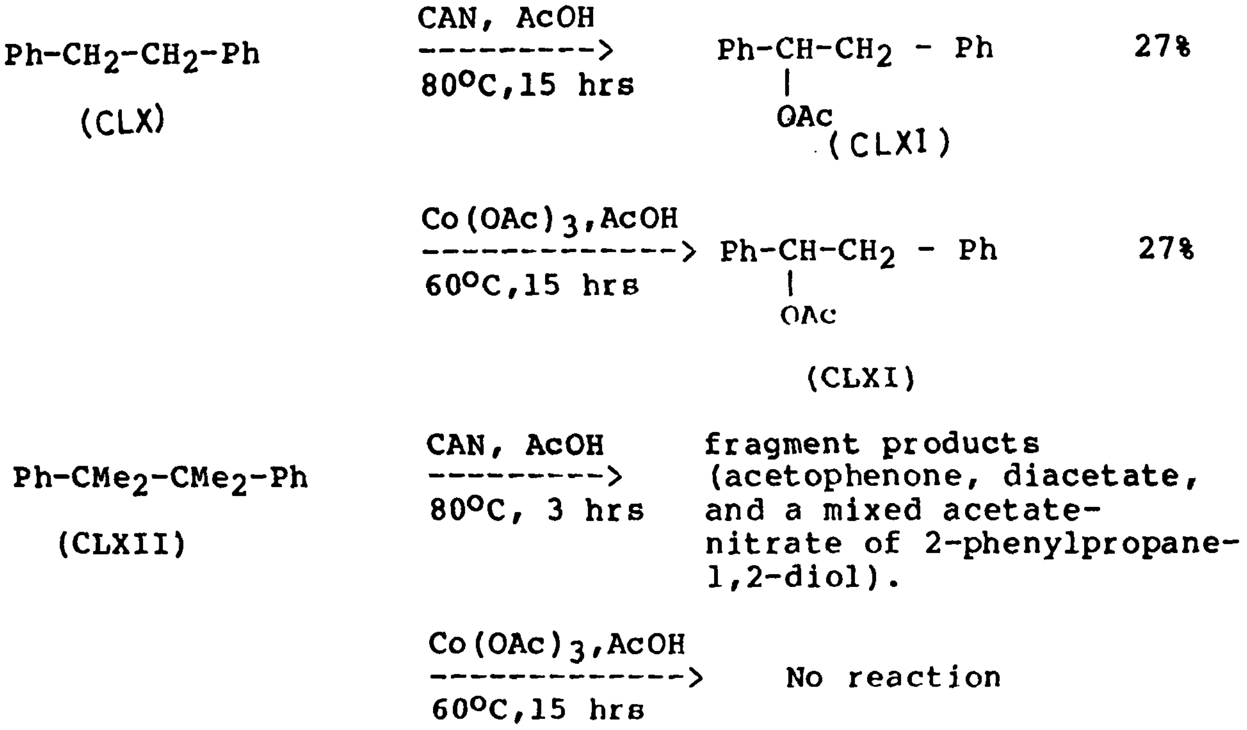


(CLVIII)



(CLIX)

Baciocchi and Ruzziconi[16] reported the oxidation of 1,2-diphenylethane (CLX) and 2,3-dimethyl-2,3-diphenylbutane (CLXII) by cerium (IV) ammonium nitrate and $Co(OAc)_3$ in acetic acid. In this way (CLX) provided (CLXI) but (CLXII) provided fragment products with CAN and no reaction takes place while using $Co(OAc)_3$.



$$\underset{\text{(CLX)}}{\mathrm{Ph{-}CH_2{-}CH_2{-}Ph}} \xrightarrow[80^{\circ}\mathrm{C,\,15\ hrs}]{\mathrm{CAN,\ AcOH}} \underset{\text{(CLXI)}}{\mathrm{Ph{-}\underset{OAc}{CH}{-}CH_2 - Ph}} \quad 27\%$$

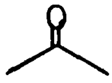
$$\xrightarrow[60^{\circ}\mathrm{C,15\ hrs}]{\mathrm{Co(OAc)_3,AcOH}} \mathrm{Ph{-}\underset{OAc}{CH}{-}CH_2 - Ph} \quad 27\%$$

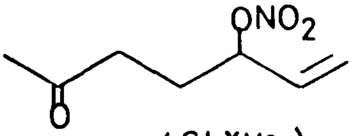
(CLXI)

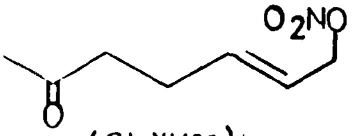
$$\underset{\text{(CLXII)}}{\mathrm{Ph{-}CMe_2{-}CMe_2{-}Ph}} \xrightarrow[80^{\circ}\mathrm{C,\ 3\ hrs}]{\mathrm{CAN,\ AcOH}}$$ fragment products (acetophenone, diacetate, and a mixed acetate-nitrate of 2-phenylpropane-1,2-diol).

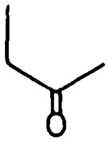
$$\xrightarrow[60^{\circ}\mathrm{C,15\ hrs}]{\mathrm{Co(OAc)_3,AcOH}}$$ No reaction

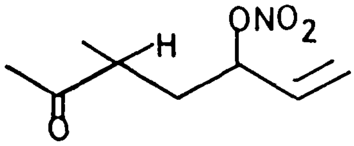
Baciocchi and Ruzziconi[17] reported the oxidative additions of acetone (I), 2-butanone (CLXIII), 3-methyl-2-butanone (CLXIV) and ethyl acetoacetate (CLXV) to 1,3-butadiene by cerium (IV) ammonium nitrate. Acetone (I) afforded 6-oxo-1-hepten-3-ol-nitrate (CLXVI) and 6-oxo-2(E)-hepten-1-ol- nitrate (CLXVII). 2-Butanone (CLXIII) gave 5-methyl-6-oxo-1-hepten- 3-ol-nitrate (CLXVIII) and 5-methyl-6-oxo-2(E)-hepten-1-ol-nitrate (CLXIX), 3-Methyl-2-butanone (CLXIV) yielded 5,5-dimethyl-6-oxo-2(E)-hepten-1-ol nitrate (CLXX), 6-oxo-1-octen-3-ol-nitrate (CLXXI), 7-methyl-6-oxo-2(E)-octen-1-ol-nitrate (CLXXII) and 2-methyl-3-oxobutan-2-ol nitrate (CLXXIII). Ethyl actoacetate (CLXV) furnished 5-carbethoxy-6-oxo-1-hepten-3-ol nitrate (CLXXIV) and 5-carboethoxy-6-oxo-2(E)-hepten-1-ol nitrate (CLXXV).

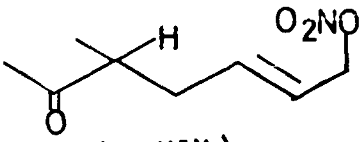

(I)

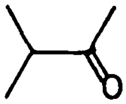

(CLXVI)

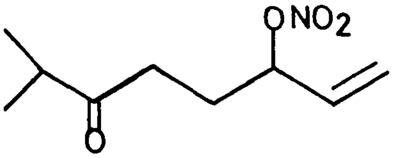

(CLXVII)

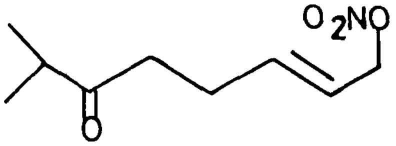

(CLXIII)

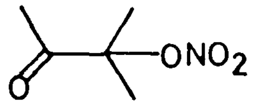

(CLXVIII)

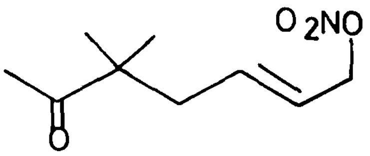

(CLXIX)


(CLXIV)


(CLXX)


(CLXXI)


(CLXXII)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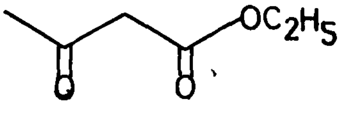
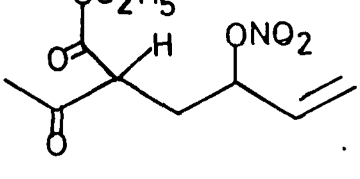
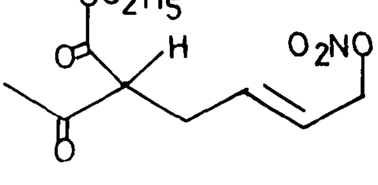
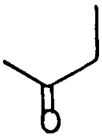
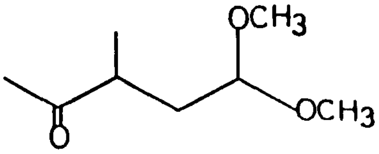
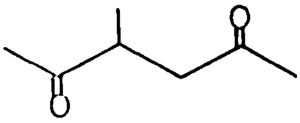
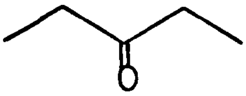
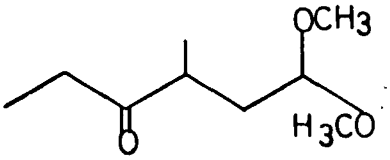
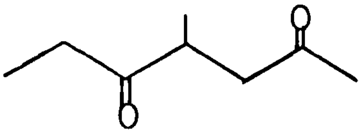
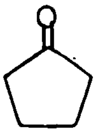
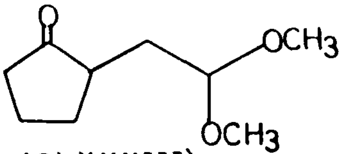
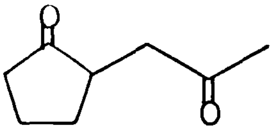
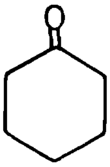
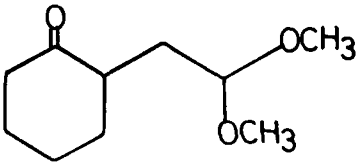
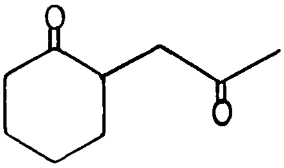
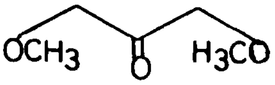
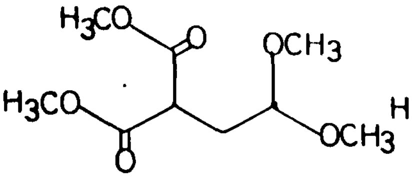
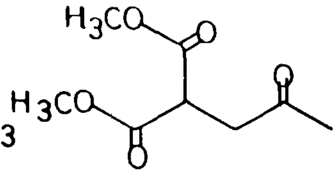

(CLXV)


(CLXXIV)


(CLXXV)

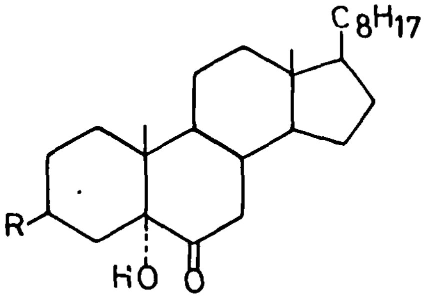
Baciocchi et al.[18] reported the synthesis of 1,4-dicarbonyl compounds (XXXVIII, CLXXIX-CLXXXVII) by ceric ammonium nitrate promoted reaction of ketones (XXXII , CLXIII, CLXXVI-CLXXVIII) with vinyl and isopropanyl acetate.

Carbonyl compound	Product yield (%) Reaction with⫽⟍OAc	 Reaction with⫽⅄OAc
 (CLXIII)	 (CLXXIX)	 (CLXXX)
 (CLXXVI)	 (CLXXXI)	 (CLXXXII)
 (CLXXVII)	 (CLXXXIII)	 (CLXXXIV)
 (XXXII)	 (CLXXXV)	 (XXXVIII)
 (CLXXVIII)	 (CLXXXVI)	 (CLXXXVII)

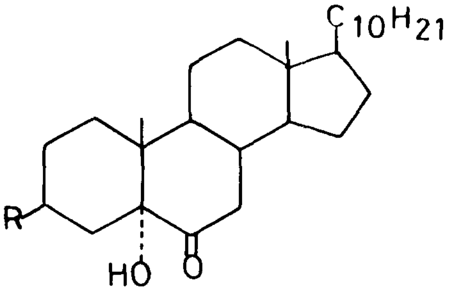
DISCUSSION

In recent years the addition of carbonyl compounds to alkenes promoted by one electron oxidants has attracted the attention of several research groups as a very efficient method for the synthesis of a variety of compounds.

This chapter deals with the similar reactions[7,10] on hydroxy ketones in cholestane and stigmastane series with vinyl acetate and Ce(IV) ammonium nitrate. For the present study 5-hydroxy-5α-cholestan-6-one (CLXXXVIII), 3β-chloro-5-hydroxy-5α-cholestan-6-one (CLXXXIX), 3β-acetoxy-5-hydroxy-5α-cholestan-6-one (CXC), 5-hydroxy-5α-stigmastan-6-one(CXCI), 3β-chloro-5-hydroxy-5α-stigmastan-6-one (CXCII), and 3β-acetoxy-5-hydroxy-5α-stigmastan-6-one (CXCIII) were selected.



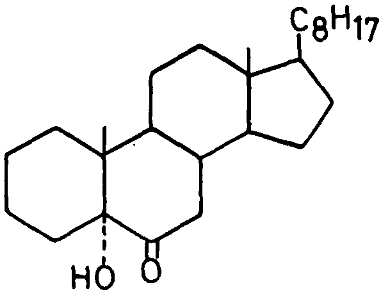
	R
(CLXXXVIII)	H
(CLXXXIX)	Cl
(CXC)	OAc



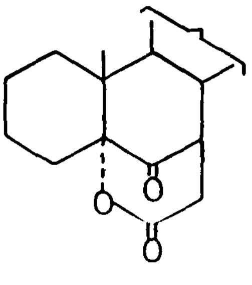
	R
(CXCI)	H
(CXCII)	Cl
(CXCIII)	OAc

Reaction of 5-hydroxy-5α-cholestan-6-one (CLXXXVIII) with vinyl acetate and Ce(IV) ammonium nitrate

The 5-hydroxy-5α-cholestan-6-one (CLXXXVIII) was dissolved in acetonitrile and to it was added Ce(IV) ammonium nitrate and vinyl acetate. The mixture was stirred for 1 hr at room temperature and then refluxed for 1 hr on a steam bath. An aqueous solution of sodium bicarbonate (20%) was added and the content was refluxed for another 30 min. with stirring. After completion of the reaction, solvent was removed under reduced pressure and the residue was worked up in chloroform. The organic layer was washed with water and dried. The solvent was removed under reduced pressure and the crude product, thus obtained was chromotographed over a column of silica gel affording an oily compound.



(CLXXXVIII)

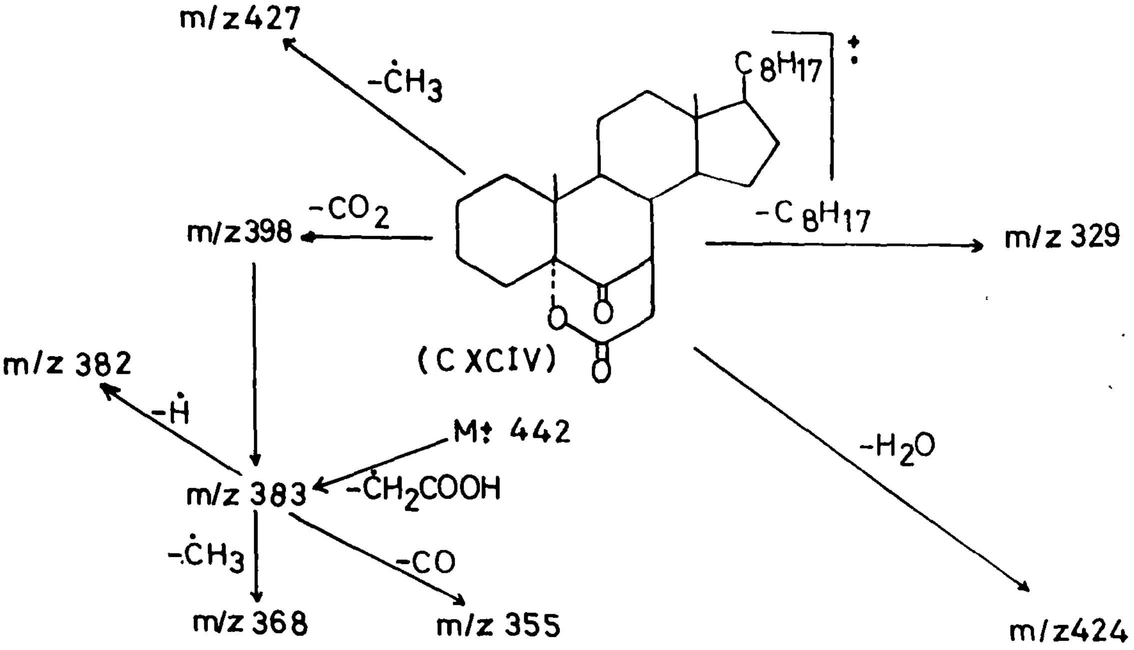


(CXCIV)

Characterization of the oily compound as 7β-yl-acetic acid-5-hydroxy-6-oxo-5α-cholestan- δ-lactone (CXCIV)

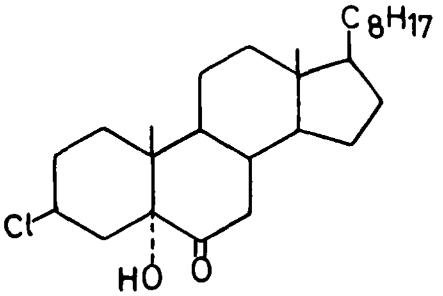
The elemental analysis of the compound (CXCIV) corresponded to the molecular formula $C_{29}H_{46}O_3$. The IR spectrum of the compound exhibited bands at 1735, 1220 (δ-lactone) and 1710 cm^{-1} (C=O). Its ^1H-NMR spectrum displayed a multiplet centered at δ 2.4 integrating for three protons and was assigned to the methylene protons of δ-lactone and the C7-αH. Methyl protons were observed at δ 1.2 ($C10-CH_3$), 0.67 ($C13-CH_3$), 0.91 and 0.83 (other methyl protons). The mass spectrum of the compound gave the molecular ion peak at m/z 442 ($M^{\dot{+}}$) and some important fragment ion peaks at 427, 424, 398, 383, 382, 355 and 329, as rationalized in scheme. On the basis of the foregoing evidences, the oily compound (CXCIV) was characterized as 7β-yl-acetic acid-5-hydroxy-6-oxo-5α-cholestan δ-lactone (CXCIV).

Scheme

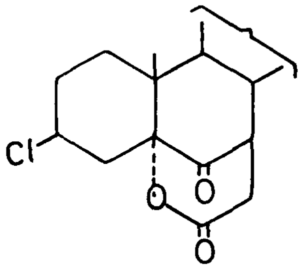


Reaction of 3β-chloro-5-hydroxy-5α-cholestan-6-one (CLXXXIX) with vinyl acetate and Ce(IV) ammonium nitrate.

3β-Chloro-5-hydroxy-5α-cholestan-6-one (CLXXXIX) was taken in acetonitrile and to it was added vinyl acetate and Ce(IV) ammonium nitrate. The content was stirred for 1 hr at room temperature and refluxed for 1 hr on a steam bath. An aqueous solution of sodium bicarbonate was added and the mixture was refluxed while being stirred for 30 min. The solvent was removed in vacuo and the residue was chromatographed over a silica gel column to afford a compound having m.p. 194-195°C.



(CLXXXIX)

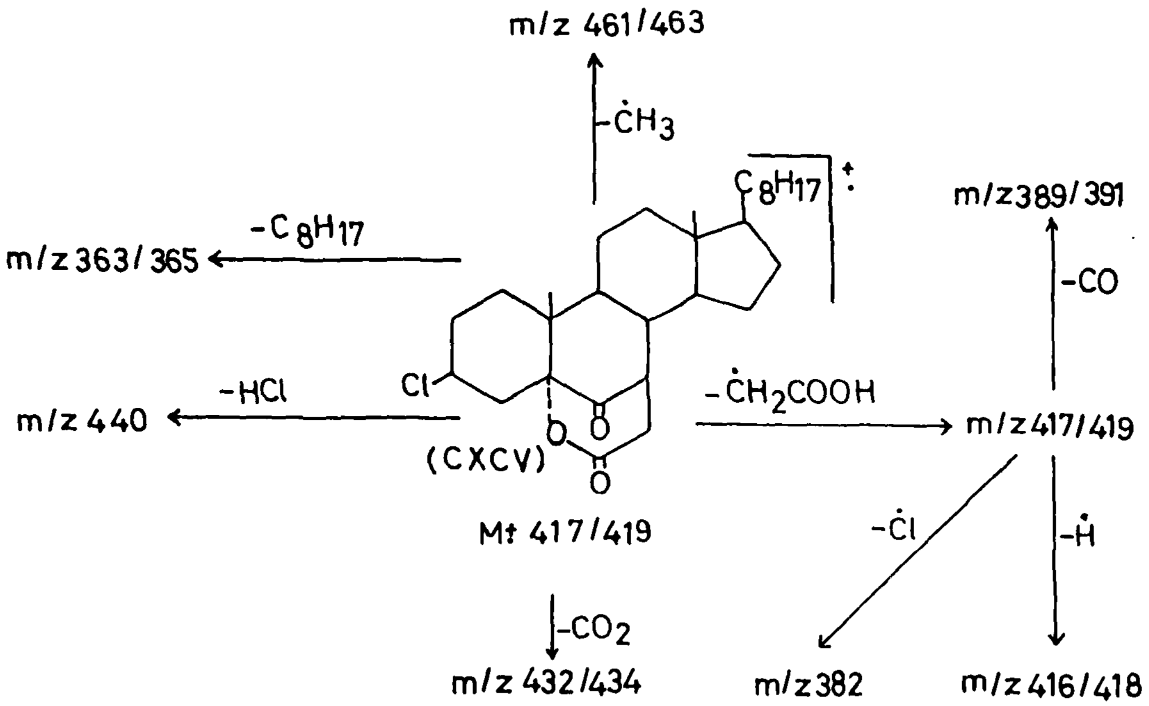


(CXCV)

Characterization of the compound having m.p. 194-195°C as 3β-chloro-7β-yl-acetic acid-5-hydroxy-6-oxo-5-α cholestan δ-lactone (CXCV).

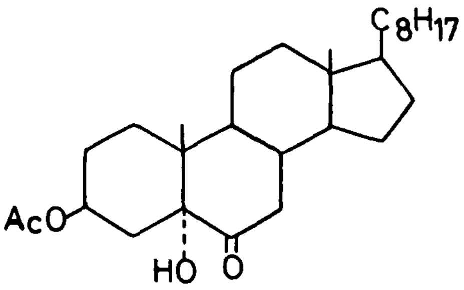
The compound with m.p. 194-195°C was analysed for $C_{29}H_{45}O_3Cl$ (positive Beilstein test). The IR spectrum of the compound gave bands at 1740, 1215 (δ-lactone), 1715 (C=O) and 740 cm^{-1} (C-Cl). The ^{1}H-NMR spectrum of the compound exhibited a signal at δ 3.8 as a multiplet for one proton and was assigned to C3 -αH (W 1/2 = 16 Hz).[19] A multiplet was observed at δ 2.3 integrating for three protons, which was attributed to the methylene protons of δ-lactone and C7 -αH. Methyl protons were observed at δ 1.15 (C10-CH_3), 0.71 (C13-CH_3), 0.95 and 0.81 (other methyl protons). The mass spectrum of the compound displayed the molecular ion peak and some other important, fragment ion peaks at m/z 476/478 ($M^{+\cdot}$), 461/463, 440, 432/434, 417/419, 416/418, 389/391, 382, and 363/365, as rationalized in scheme. On the basis of these analytical and spectral evidences, the compound having m.p. 194-195°C was characterized as 3β-chloro-7β-yl-acetic acid -5-hydroxy-6-oxo-cholestan δ-lactone (CXCV).

Scheme

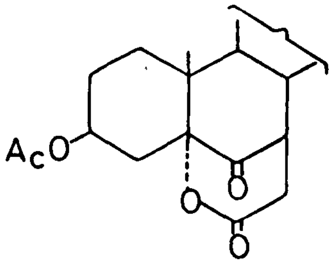


Reaction of 3β-acetoxy-5-hydroxy-5α-cholestan-6-one (CXC) with vinyl acetate and Ce(IV) ammonium nitrate

3β-Acetoxy-5-hydroxy-5α-cholestan-6-one (CXC) and vinyl acetate were taken in acetonitrile and to this was added Ce(IV) ammonium nitrate. The content was stirred at room temperature for 1 hr and refluxed for 1 hr and an aqueous solution of sodium bicarbonate was added and refluxed again for 30 min. After completion of reaction the content was worked up. After column chromatography over silica gel, a compound m.p. 207°C was isolated.



(CXC)



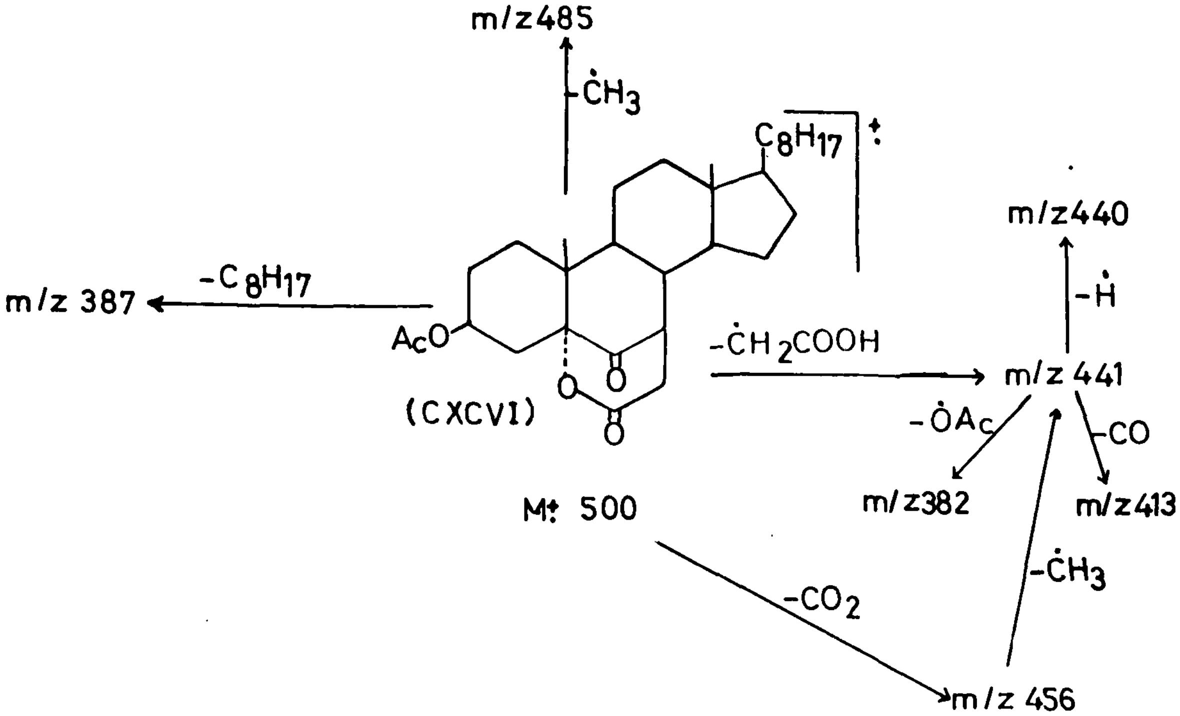
(CXCVI) .

Characterization of the compound with m.p. 207°C as 3β-acetoxy-7β-yl-acetic acid-5-hydroxy-6-oxo-cholestan-δ-lactone (CXCVI)

The elemental analysis of the compound having m.p.207°C corresponded for the molecular formula $C_{31}H_{48}O_5$. The IR spectrum of the compound exhibited bands at 1740 (δ-lactone), 1725 (CH_3COO), 1710 (C=O), 1050 cm^{-1} (C-O). The

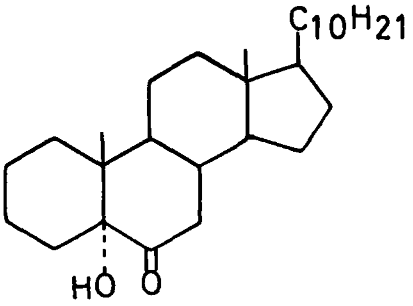
^{1}H-NMR spectrum of the compound displayed a multiplet centered at δ 5.2 integrating for one proton and was assigned to C3-αH, (W 1/2 = 17 Hz, axial).[19] A multiplet at δ 2.45 for three protons was observed and was attributed to the methylene protons of δ-lactone and C7-αH. The methyl protons of acetoxy group appeared at δ 2.01 as a singlet. Methyl protons were observed at δ 1.05 ($C10-CH_3$), 0.69 ($C13-CH_3$), 0.95 and 0.82 (other methyl protons). The mass spectrum of the compound gave molecular ion peak and some other important fragment ion peaks at m/z 500 ($M^{+\cdot}$), 485, 456, 441, 440, 413, 387 and 382, as rationalized in the scheme. On the basis of these evidences, the compound having m.p. 207°C was characterized as 3β-acetoxy-7β-yl-acetic acid-5-hydroxy-6-oxo-5α-cholestan-δ-lactone (CXCVI).

Scheme

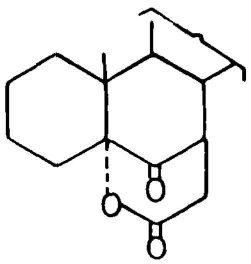


Reaction of 5-hydroxy-5α-stigmastan-6-one (CXCI) with vinyl acetate and Ce(IV) ammonium nitrate

5-Hydroxy-5α-stigmastan-6-one (CXCI) and vinyl acetate were dissolved in acetonitrile and to it was added Ce(IV) ammonium nitrate. The mixture was stirred for 1 hr at room temperature and refluxed for 1 hr. A solution of aqueous sodium bicarbonate was added and the content was refluxed for another 30 min. After usual worked up and column chromatography a compound with m.p.82°C was isolated.



(CXCI)

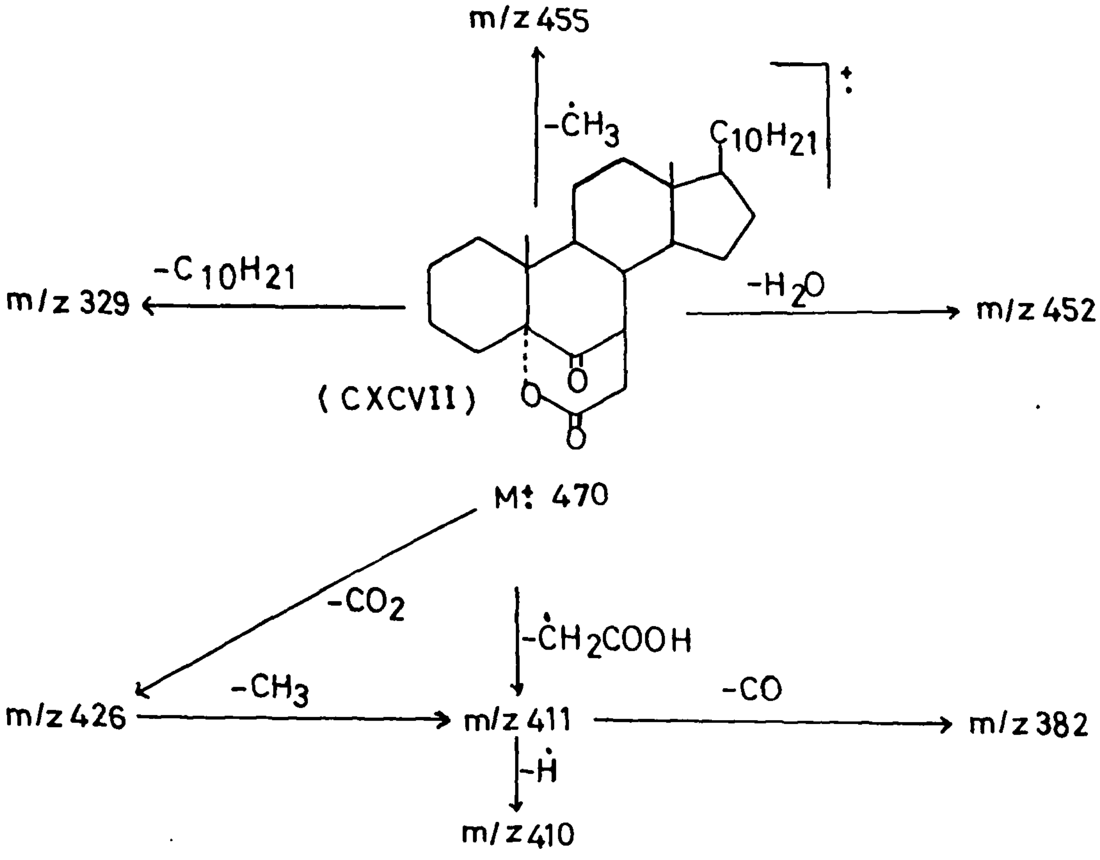


(CXCVII)

Characterization of the compound having m.p.82°C as 7β-yl-acetic acid-5-hydroxy-6-oxo-5α-stigmastan-δ-lactone (CXCVII)

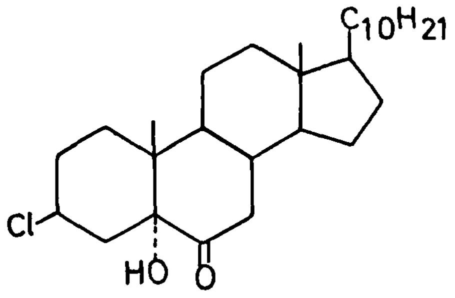
The elemental analysis of the compound (CXCVII) corresponded to the molecular formula $C_{31}H_{50}O_3$. The IR spectrum of the compound exhibited bands at 1740, 1220 (δ-lactone) and 1705 cm^{-1} (C=O). Its ^{1}H-NMR spectrum displayed a multiplet for three protons at δ 2.3 and was assigned to the methylene protons of δ-lactone and the C7-αH. The methyl protons appeared at δ 1.15 ($C10-CH_3$), 0.71 ($C13-CH_3$), 0.95 and 0.80 (other methyl protons). The mass spectrum of the compound gave molecular ion peak and some other important fragment ion peaks at m/z 470 ($M^{+\cdot}$), 455, 452, 426, 411, 410, 382 and 329 as shown in scheme. On the basis of these evidences, the compound having m.p. 82°C was characterized as 7β-yl-acetic acid-5-hydroxy-6-oxo-5α-stigmastan-δ-lactone (CXCVII).

Scheme

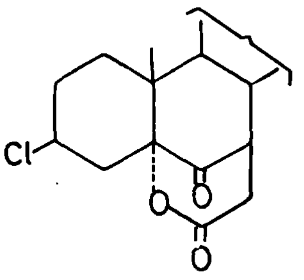


Reaction of 3β-chloro-5-hydroxy-5α-stigmastan-6-one (CXCII) with vinyl acetate and Ce(IV) ammonium nitrate

3β-Chloro-5-hydroxy-5α-stigmastan-6-one (CXCII) and vinyl acetate were allowed to react with Ce(IV) ammonium nitrate in acetonitrile. The content was stirred at room temperature for 1 hr and refluxed for 1 hr on a steam bath. To this was added an aqueous solution of sodium bicarbonate and refluxed for another 30 min. After the usual work up and column chromatography over silica gel, an oily compound was obtained.



(CXCII)

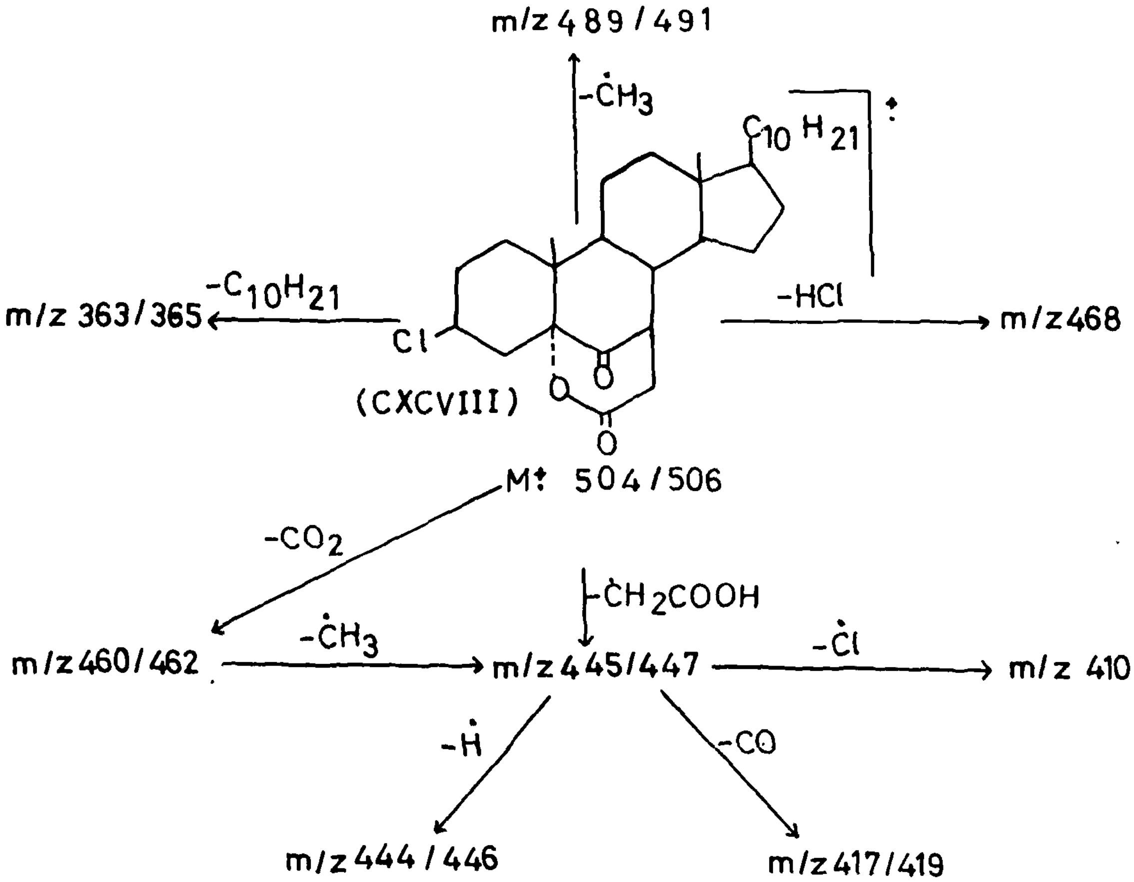


(CXCVIII)

Characterization of the oily compound as 3β-chloro-7β-yl- acetic acid-5-hydroxy-6-oxo-5α-stigmastan- δ-lactone (CXCVIII)

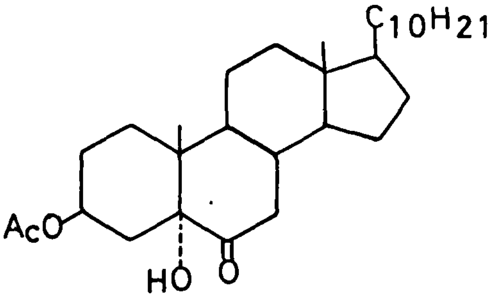
The oily compound (CXCVIII) was analysed for $C_{31}H_{49}O_3$ Cl (positive Beilstein test). Its IR spectrum displayed bands at 1745, 1210 (δ-lactone), 1720 (C=O), and 740 cm^{-1} (C-Cl). ^1H-NMR spectrum of the compound displayed two multiplets centered at δ 3.9 and 2.4 integrating for one proton and three protons respectively and were assigned to C3- α H, (W 1/2 = 15 Hz, axial)[19] and the methylene protons of the δ-lactone moiety along with C7-αH. The methyl signals appeared at δ 1.2 (C10-CH_3), 0.68 (C13-CH_3), 0.91 and 0.84 (other methyl protons). In the mass spectrum of the compound (CXCVIII), the molecular ion peak and some important fragment ion peaks were observed at m/z 504/506 ($M^{+\cdot}$), 489/491, 468, 460/462, 445/447, 444/446, 417/419, 410, and 363/365 as rationalized in the scheme. On the basis of these analytical as well as spectral evidences, the oily compound (CXCVIII) was characterized as 3β-hydroxy-7β-yl -acetic acid-5- hydroxy- -6-oxo-5α-stigmastan- δ -lactone (CXCVIII).

Scheme

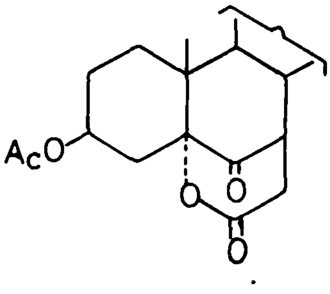


Reaction of 3β-acetoxy-5-hydroxy-5α-stigmastan-6-one (CXCIII) with vinyl acetate and Ce(IV) ammonium nitrate

3β-Acetoxy-5-hydroxy-5α-stigmastan-6-one (CXCIII) and vinyl acetate were taken in acetonitrile while being stirred and to it was added Ce(IV) ammonium nitrate. The stirring was continued for 1 hr at room temperature and then the content was refluxed for 1 hr on a steam bath. An aqueous solution of sodium bicarbonate was added and the mixture was refluxed while being stirred for another 30 min. After the usual work up and column chromatography, a compound having m.p. 109°C was isolated.



(CXCIII)

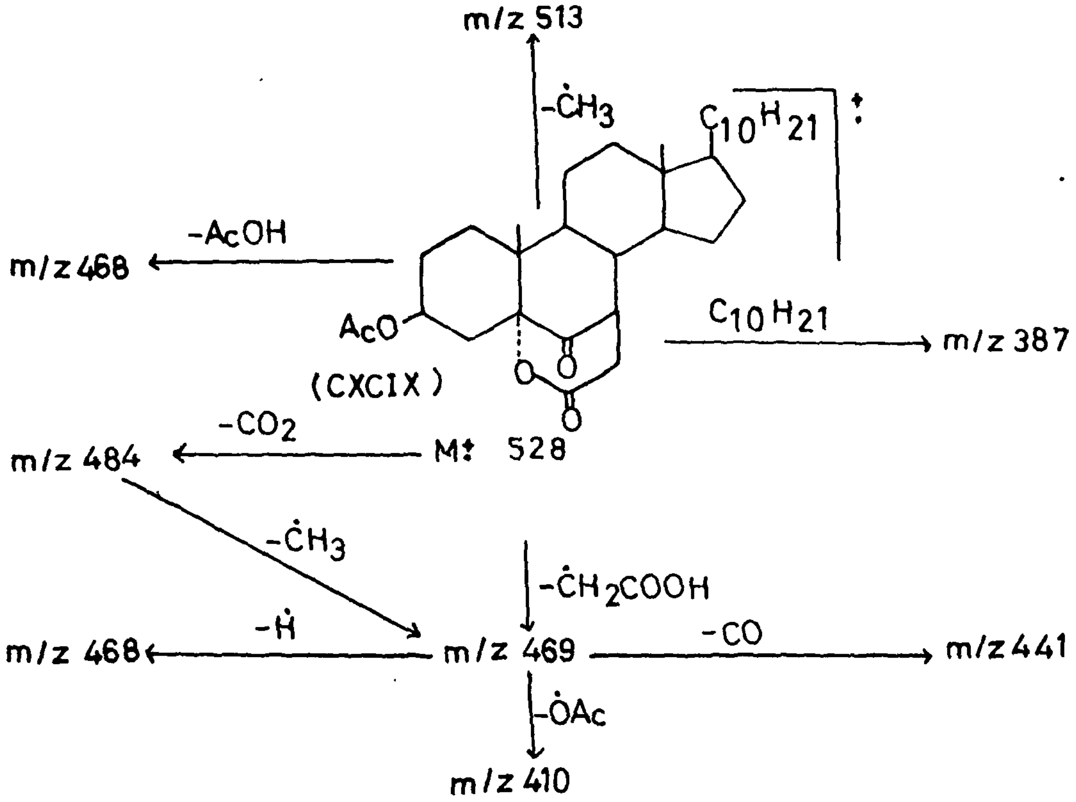


(CXCIX)

Characterization of the compound with m.p. 109°C as 3β-acetoxy-7β-yl-acetic acid-5-hydroxy-6-oxo-5α-stigmastan-δ-lactone (CXCIX)

The elemental analysis of the compound (CXCIX) corresponded to the molecular formula $C_{33}H_{52}O_5$. The IR spectrum of the compound exhibited bands at 1735 (δ-lactone), 1725 (CH_3COO), 1710 (C=O), 1040 cm^{-1} (C-O). The ^{1}H-NMR of the compound displayed two multiplets for one and three protons at δ 5.2 and 2.4, and were assigned to the C3-αH ($W1/2$ = 16 Hz; axial)[19] and the methylene protons of δ-lactone moiety along with C7-αH. The methyl protons of acetoxy group were observed at δ 1.9 as a singlet. The methyl protons appeared at δ 1.05 (C10-CH_3), 0.71 (C13-CH_3), 0.93, and 0.81 (other methyl protons). In the mass spectrum of the compound, the molecular ion peak and some important fragment ion peaks were observed at m/z 528 ($M^{+\cdot}$), 513, 484, 469, 468, 441, 410, and 409, as shown in scheme. On the basis of these evidences, the compound having m.p. 109°C was characterized as 3β-acetoxy-7β-yl-acetic acid-5-hydroxy-5α-stigmastan-δ-lactone (CXCIX).

Scheme



EXPERIMENTAL

5, 6β-Dihydroxy-5α-cholestane

To a suspension of cholest-5-ene (2g) in formic acid (88%, 2 ml) was added H_2O_2 (30%, 2 ml). The mixture was shaken at room temperature for 10 hrs then it was diluted with water (200 ml) and extracted with ether. The ethereal solution was washed with sodium hydroxide solution (2N), water and dried over anhydrous sodium sulphate. To the residue, obtained after removal of the solvent, methanolic KOH (25%, 22 ml) was added and the mixture was refluxed for 1 hr then the reaction mixture was acidified with HCl and the organic matter was extracted with ether. Usual work up and removal of the solvent gave an oil, which was chromatographed over silica gel (40 g). Elution with light petroleum ether/ ether (10:1) gave the diol which was crystallized from methanol (1.1g), m.p. 126°C (reported[20] m.p. 125-126°C).

5-Hydroxy-5α-cholestan-6-one (CLXXXVIII)

The 5,6β-dihydroxy-5α-cholestane (1g) was suspended in acetone (10 ml) in a three necked flask fitted with a stirrer and a dropping funnel. The suspension was stirred for 5 min. and Jone's reagent (2 ml) was then added dropwise from the dropping funnel in a course of 15 min. The temperature of the reaction mixture during the oxidation was maintained between 0-5°C by external cooling. After the addition was complete, stirring was continued for additional

15 min. and cold water (200 ml) was then added. The product thus obtained was filtered, washed throughly with water and air dried to give an oil which was recrystallized from acetone to furnish 5-hydroxy-5α-cholestan-6-one (800 mg), m.p. 152°C (reported m.p. 153-154°C).

Reaction of 5-hydroxy-5α-cholestan-6-one (CLXXXVIII) with vinyl acetate and Ce (IV) ammonium nitrate: 7β-yl-acetic acid-5-hydroxy-6-oxo-5α-cholestan δ-lactone (CXCIV).

To a mixture of 5-hydroxy-5α-cholestan-6-one (CLXXXVIII) (1 g; 2.26 m mol) and vinyl acetate (0.19g; 2.26 m mol) in acetronitrile (50 ml) was added Ce (Iv) ammonium nitrate (3.72 g; 6.78 m mol). The mixture was stirred at room temperature for 1 hr and refluxed for 1 hr on a steam bath. An aqueous solution of sodium hydrogen carbonate (20%) (25 ml) was added and the content was reflux for another 30 min. with stirring. After cooling the mixture was poured into water and extracted with chloroform. The organic layer was washed with water and dried. Removal of chloroform under reduced pressure gave an oily residue which was chromatographed over a column of silica gel. Elution with light petroleum ether/ether (5:1) furnished an oily compound, 7β-yl-acetic acid 5-hydroxy-6-oxo-5α-cholestan-δ- lactone (CXCIV) (0.72g; 1.63 m mol).

Analysis found : C, 78.61; H, 10.46

$C_{29}H_{46}O_3$ requires : C, 78.68; H, 10.48%

IR : ν max 1735, 1220 (δ-lactone) and 1710 cm^{-1} (C=O).

^{1}H-NMR : δ 2.4 (mc, 3H, methylene protons of δ-lactone and (C7 - α H), 1.2 (C10-CH$_3$), 0.67 (C13-CH$_3$), 0.91 and 0.83 (other methyl protons).

MS : $M^{+\cdot}$ 442 (19.60; $C_{29}H_{46}O_3$), 427 (8.50), 425 (5.00), 414 (15.70; $C_{28}H_{46}O_2$), 398 (17.25), 396 (12.00), 386 (15.00; $C_{27}H_{46}O$), 383 (10.50), 382 (10.50), 368 (8.40), 355 (24.25; $C_{26}H_{43}$), 329 (19.00), 328 (14.20), 314 (20.20), 302 (10.40), 301 (12.50; $C_{19}H_{25}O_3$), 288 (13.50), 287 (15.20; $C_{18}H_{23}O_3$), 273 (16.00), 232 (22.50; $C_{13}H_{16}O_3$), 217 (27.00; $C_{12}H_{13}O_3$), 216 (8.75), 205 (6.00), 204 (5.20), 203 (9.50), 190 (7.60), 179 (10.25), 178 (5.40), 177 (14.00), 176 (6.50), 165 (10.40), 164 (17.20), 163 (10.75), 162 (5.00), 161 (7.20), 152 (7.50), 151 (4.80), 150 (6.25), 149 (16.25), 148 (3.25), 147 (6.60), 137 (7.50), 136 (17.25), 135 (13.50), 134 (6.00), 124 (7.50), 123 (7.50), 122 (27.75), 121 (20.00), 120 (7.10), 119 (9.60), 118 (4.80), 110 (5.00), 109 (37.25), 108 (40.20), 107 (37.25), 106 (10.00), 105 (17.20), 104 (5.40), 97 (10.00), 96 (7.50), 95 (37.50), 94 (13.25), 93 (27.70), 92 (8.40), 91 (16.25), 83 (10.00), 82 (11.25), 81 (37.50), 80 (7.50), 79 (27.25), 78 (7.40), 787 (10.00), 71 (15.00), 70 (7.60), 69 (25.20), 68 (15.75), 67 (30.00), 57 (30.00), 56 (15.00), 55 (45.50), 54 (9.60), 53 (17.25), 46 (10.00), 45 (14.20), 44 (100.00), 43 (63.50), 42 (37.30), 41 (27.00), 40 (48.25).

3β-Chloro-5, 6β-dihydroxy-5α-cholestane

3β-Chlorocholest-5-ene (28g) in hot acetic acid (600 ml) was treated with hydrogen peroxide (12 ml, 30%) and the reaction mixture was heated at 95°C for 30 min. Removal of the solvent under reduced pressure gave an oily product which was extracted with ether. Evaporation of the solvent provided an oil (ca 29g) which was chromatographed on alumina oxide (600 g). Elution with benzene/pentane (3:7) gave unreacted 3β-chlorocholest-5-ene (3.3g). Elution with ether gave 3β-chloro-5,6β-dihydroxy-5α-cholestane (15 g), which was crystallized from ether : pentane, m.p. 126°C (reported[21] m.p. 126°C).

3β-Chloro-5-hydroxy-5α-cholestan-6-one (CLXXXIX)

3β-Chloro-5,6β-dihydroxy-5α-cholestane (2.0g) was dissolved in ether (40 ml), methanol (10 ml) and water (10 ml) and treated with N-bromosuccinimide (1g). After 1 hr ether (50 ml) was added and the solution was washed with water, sodium metabisulphite solution (10%) and water and dried. Evaporation of the solvent gave the crude ketone (CLXXXIX) which was recrystallized from acetone to afford 3β-chloro-5-hydroxy-5α-cholestan-6-one (1.4 g), m.p. 181°C (reported[21] m.p. 182°C).

Reaction of 3β-chloro-5-hydroxy-5α-cholestan-6-one (CLXXXIX) with vinyl acetate and Ce (IV) ammonium nitrate: 3β Chloro-7β-yl-acetic acid-5-hydroxy-6-oxo-5α-cholestan-δ-lactone (CXCV).

To a solution of 3β-chloro-5-hydroxy-5α-cholestan-6-one (CLXXXIX) (1g; 2.10 m mol) and vinyl acetate (0.18g; 2.10 m mol) in acetonitrile (50 ml) was added Ce (IV) ammonium nitrate (3.45g; 6.3 m mol). The mixture was stirred at room temperature for 1 hr and refluxed for 1 hr on a steam bath. An aqueous solution of sodium hydrogen carbonate (20%, 25 ml) was added and the mixture was refluxed for 30 min. with stirring. After cooling to room temperature, the content was poured into water and extracted with chloroform. After usual work up and evaporation of the solvent provided an oily residue, which was chromatographed over a column of silica gel. Elution with light petroleum ether/ ether (5:1) yielded a semi-solid which was recrystallized from acetone to afford 3β-chloro-7β-yl-acetic acid-5-hydroxy-6-oxo-5α-cholestan-δ-lactone (CXCV) (0.6g; 1.26 m mol) m.p. 194-195°C.

Analysis found : C, 72.95; H, 9.47

$C_{29}H_{45}O_3Cl$ requires : C, 73.00 ; H, 9.51%

IR : ν max 1740, 1215 (δ-lactone), 1715 (C=0) and 740 cm^{-1} (C-Cl).

^{1}H-NMR : δ 3.8 (mc, 1H, C3-αH, W 1/2 = 16 Hz, axial)[19], 2.3 (mc, 3H, methylene protons of δ-lactone and C7- αH), 1.15 (C10-CH_3), 0.71 (C13-CH_3), 0.95, and 0.81 (other methyl protons).

MS : $M^{+\cdot}$ 476/478 (5.40/1.81; $C_{29}H_{45}O_3Cl$), 461/463 (7.40/ 2.44), 448/450 (10.00/3.31), 440 (24.20; $C_{29}H_{44}O_3$), 432/434 (15.50/5.14), 420/422 (14.20/4.70), 417/419 (13.25/4.42), 416/418 (15.50/5.14), 412 (9.80, $C_{28}H_{44}O$), 402/404 (9.80/3.25), 396 (27.20; $C_{28}H_{44}O$), 394 (8.40), 389/391 (17.20/5.71), 384 (10.20), 382 (19.00), 381 (24.25), 380 (27.00), 372 (27.50), 367 (14.70), 366 (12.00), 363/365 (10.00/3.32), 362/364 (12.30/4.10), 353 (12.70), 348/350 (13.50/4.39), 336/338 (12.00/3.97), 335/337 (14.40/4.80), 327 (12.40), 322/324 (15.75/5.23), 321/323 (19.00/6.30), 307/309 (20.60/6.80), 276 (14.20), 275 (19.00), 266/268 (19.50/6.47), 262 (15.60), 261 (20.00), 251/253 (22.00/7.31), 247 (21.75), 228 (12.20), 227 (15.00), 226 (7.25), 225 (4.80), 219 (5.40), 218 (4.20), 216 (35.75), 215 (9.60), 214 (4.50), 212 (3.25), 211 (8.50), 207 (10.00), 206 (40.20), 205 (14.25), 192 (4.80), 191 (47.70), 190 (15.75), 189 (9.00), 188 (5.20), 169 (11.78), 168 (8.20), 150 (7.75), 149 (20.20), 134 (7.60), 133 (6.00), 132 (7.60), 131 (10.00), 130 (8.20), 123 (4.60), 122 (9.60), 121 (6.50), 120 (12.30), 119 (9.00), 118 (8.50), 112 (10.20), 111 (14.70), 110 (13.90), 109 (13.90), 108 (8.50), 107 (17.60), 106 (14.30), 105 (40.25), 74 (35.50), 73 (16.00), 72 (9.50), 70 (17.00), 69 (39.20), 68 (7.40), 67

(22.50), 58 (10.00), 57 (42.60), 56 (18.40), 55 (60.25), 45 (25.75), 44 (100.00), 43 (76.00), 42 (13.50), 41 (46.20), 40 (51.00).

3β,5,6β-Trihydroxy-5α-cholestane

A suspension of cholesterol (20g) in formic acid (88%; 28 ml) was heated to 70-80°C with stirring for 5 min to form the 3-formate derivative, which separated as on oily layer, and cooled to 25°C. The resulting thick paste of solidified formate was treated with hydrogen peroxide (30%, 20 ml) and shaken occasionally. The temperature of the reaction mixture was raised to 35-40°C. After 45 min. the solid was dissolved, a foam subsided and a blue fluorescent solution resulted, but the temperature remains a few degrees above of room temperature for about 4 hrs. After a total reaction time between 6-15 hrs, the mixture was treated with boiling water (300 ml), stirred and allowed to cool down. A granular white solid appeared which was collected and dried superficially and dissolved in methanol (600 ml). The solution was treated with a aqueous solution of sodium hydroxide (2.5%; 20 ml), warmed on a steam bath for 10 min. filtered, acidified and diluted with water (200 ml). The white solid that precipitated was collected after cooling, washed with water and dried to afford 3β,5,6β-trihydroxy-5α-cholestane m.p. 236-237°C (reported[22] m.p. 236-238°C).

3β,5-Dihydroxy-5α-cholestan-6-one

To a solution of 3β,5,6β-trihydroxy-5α-cholestane (10g) in 1,4-dioxan (90 ml) was added N-bromosuccinimide (4.5 g) at about 25°C. After 15 min the reaction mixture was cooled in an ice bath and diolone which crystallized out was collected by filteration and washed thoroughly with methanol/water (1:1) to obtain 3β,5-dihydroxy-5α-cholestan-6-one (6.5 g) m.p. 231-233°C (reported[22] 231-233°C).

The mother liquor was diluted with water and extracted with ether. The ethereal solution was washed with water and dried, to obtain an additional quantity of 3β,5-dihydroxy-5α-cholestan-6-one (2.3 g) m.p. 231-233°C (reported[22] m.p. 231-233°C).

3β-Acetoxy-5-hydroxy-5α-cholestan-6-one (CXC).

A mixture of 3β,5-dihdroxy-5α-cholestan-6-one (10g), pyridine (15 ml, freshly distilled) and acetic anhydride (10 ml) was refluxed for 2 hrs. The reaction mixture was allowed to cool at room temperature and treated with water. The reaction product consisting of colourless needles, was filtered washed with a little methanol and dried. Recrystallization from methanol gave 3β-acetoxy-5-hydroxy-5α-cholestan-6-one m.p. 230°C (reported[22] 232°C).

3β-Acetoxy-5,6α-epoxy-5α-cholestane

3β-Acetoxycholest-5-ene (10g) in chloroform (100 ml) was treated with a solution of perbenzoic acid (1.1 mol equivalent) in chloroform and left for 20 hrs at -8°C. The reaction mixture was then washed successivley with ice-cold aqueous solution of sodium bicarbonate (5%), water, sodium thiosulphate solution (aqueous 5%) and again with water. Evaporation of the solvent gave an oil which was chromatographed over silica gel coloumn. Elution with light petroleum ether/ether (10:1) gave a solid compound which was recrystallized from acetone as needles to afford epoxide (8.0g) m.p. 97°C (reported[23] m.p. 97°C).

3 β -Acetoxy-5, 6 β-dihydroxy-5 α-cholestane

3 β -Acetoxy-5, 6 α -epoxy-5 α -cholestane (8g) was dissolved in acetone (140 ml) and to this hydroiodic acid (16 ml) was added and the mixture was refluxed for 1 hr. After the completion of the reaction, the solvent was removed under reduced pressure and the residue was extracted with ether. The organic layer was washed with water, sodium bicarbonate (5%) and again with water and dried. Evaporation of the solvent gave a solid which was recrystallized from methanol to afford 3 β -acetoxy-5,6 β -dihydroxy-5α -cholestane m.p. 203°C (reported[22] m.p. 203-205°C).

3 β -Acetoxy-5-hydroxy-5 α-cholestan-6-one (CXC)

3 β -Acetoxy-5, 6 β -dihydroxy-5 α-cholestane (4.0g) was dissolved in acetone (30 ml) and was kept in ice bath. To this solution, Jone's reagent (35 g of chromium trioxide in 100 ml of water and 30 ml of H_2SO_4) was added dropwise with

stirring till the colour of the solution persisted. The solution was further stirred for 30 min. The reaction mixture was diluted with water and the precipitated solid was filtered, dried and recrystallized from acetone to give the ketone (CXC) (3.0g) m.p. 232°C (reported[22], 232-233°C).

Reaction of 3β -acetoxy-5-hydroxy-5α -cholestan-6-one (CXC) with vinyl acetate and Ce (IV) ammonium nitrate: 3β -Acetoxy-7β -yl-acetic acid-5-hydroxy-6-oxo-5α -cholestan -δ -lactone (CXCVI).

To a solution of 3β -acetoxy-5-hydroxy-5α-cholestan -6-one (CXC) (1g; 2.00 m mol) and vinyl acetate (0.17 g; 2.00 m mol) in acetonitrile (50 ml) was added Ce (IV) ammonium nitrate (3.29 g; 6.00 m mol). The content was stirred at room temeprature and refluxed for 1 hr each. To this solution, was added an aqueous solution of sodium hydrogen carbonate (20%, 25 ml) and the mixture was refluxed for another 30 min with stirring. After cooling upto room temperature, the mixture was poured into water and worked up with chloroform. Evaporation of the solvent provided an oily residue which was chromatographed over a column of silica gel. Elution with light petroeum ether/ether (5:1) yielded a solid which was recrystallized from acetone to afford 3β--acetoxy-7β -yl-acetic acid-5-hydroxy-6-oxo-5α -cholestan-δ-lactone (CXCVI) (0.64g; 1.28 m mol) m.p 207°C.

Analysis found : C, 74.32; H, 9.63

$C_{31} H_{48} O_5$ requires : C, 74.36; H, 9.66%

IR : νmax 1740 (δ-lactone), 1725 (CH_3 COO), 1710 (C=0), 1050 cm^{-1} (C-0).

^{1}H-NMR : δ 5.2 (mc, 1H, C3-α H, W 1/2 = 17 Hz, axial)[19], 2.45 (mc, 3H, methylene protons of δ-lactone moiety and C7-αH), 2.01 (s, 3H, CH_3 COO), 1.05 (C10-CH_3), 0.69 (C13-CH_3), 0.95 and 0.82 (other methyl protons).

MS : $M^{+\cdot}$ 500 (7.30; $C_{31} H_{48} O_5$), 485 (10.60), 472 (13.30), 456 (15.50; $C_{30} H_{48} O_3$), 454 (12.50), 444 (12.00), 441 (15.75), 440 (20.00; $C_{29} H_{44} O_3$), 426 (17.20), 413 (17.30), 412 (16.20), 396 (23.00; $C_{28} H_{44}$ O), 394 (9.60), 387 (10.80), 386 (12.50), 384 (11.00), 382 (14.20), 381 (22.50), 380 (24.20), 372 (22.00), 367 (20.00), 366 (10.20), 360 (14.50), 359 (17.00), 353 (12.25), 346 (16.20), 345 (17.00), 331 (18.25), 327 (13.25), 290 (20.75), 276 (15.20), 275 (20.00), 274 (3.25), 262 (16.00), 261 (18.10), 260 (9.60), 259 (4.75), 247 (15.20), 246 (10.00), 245 (5.40), 230 (7.40), 229 (4.10), 228 (4.10), 220 (10.25), 219 (10.25), 218 (15.00), 217 (6.20), 216 (27.20), 215 (7.50), 206 (29.50), 205 (9.10), 204 (7.25), 203 (8.75), 202 (8.75), 191 (37.00), 190 (14.30), 189 (19.25), 165 (10.00), 164 (7.30), 163 (3.40), 151 (12.50), 150 (6.30), 149 (6.30), 148 (4.75), 109 (12.50), 108 (12.50), 107 (14.10), 95 (13.75), 94 (10.30), 93 (20.20), 90 (4.10), 89 (3.80), 83 (5.25), 82 (4.80), 80 (3.75), 71 (12.00), 70 (6.10), 69 (5.25), 68 (9.10), 57

(16.25), 56 (12.00), 55 (29.75), 47 (21.25), 46 (14.10), 45 (29.75), 44 (100.00), 43 (22.30), 42 (41.00), 41 (10.50), 40 (12.75).

Stigmast-5-ene

3β -Chlorostigmast-5-ene (10g) was dissolved in warm amyl alcohol (230 ml) and sodium metal (20g) was added to the solution with continuous stirring over a period of 8 hrs. The reaction mixture was warmed occasionally, when all the sodium metal dissolved. The reaction mixture was poured into water, acidified with hydrochloric acid and then allowed to stand overnight. A white crystalline solid thus obtained was filtered under suction and washed throughly with water and air dried. The crude material was recrystallized from acetone to provide stigmast-5-ene (8g), m.p. 75°C (reported[24] m.p. 75°C).

5-Hydroxy-5 α -stigmastan-6-one (CXCI)

To a suspension of stigmast-5-ene (2g) in formic acid (88%, 2 ml), hydrogen peroxide (30%, 2 ml) was added. The mixture was shaken at room temperature for 10 hrs, then it was diluted with water (200 ml) and extracted with ether. The ehterial solution was washed with sodium hydroxide (2N), water and dried. The residue obtained after removal of the solvent, was dissolved in methanolic KOH (25%, 22 ml) and the mixture was refluxed for 1 hr, acidified with hydrochloric acid, extracted with ether and worked up. Removal of the solvent gave an oil, which was suspended in acetone (10 ml) in a three necked flask fitted with a stirrer and a dropping funnel. The suspension was stirred for 5 min. and Jone's reagent (2 ml) was added dropwise in a course of 15 min. The temperature of the reaction mixture during the oxidation was maintained between 0-5°C by external cooling. After the complete addition, the stirring was continued for additional 15 min. and cold water (200 ml) was then added. The product thus obtained was filtered, washed throughly with water and air dried to give the ketone (CXCI) recrystallized from acetone (750 mg), m.p. 142°C.

IR : νmax 3450 (OH), 1715 cm^{-1} (C=0)

^1H-NMR : δ 2.5 (br, 1H, OH), 2.13 (mc, 2H, C7-H_2), 1.1 (C10-CH_3), 0.7 (C13-CH_3), 0.96, 0.90 and 0.8 (other methyl protons).

Reaction of 5-hydroxy-5α-stigmastan-6-one (CXCI) with vinyl acetate and Ce (IV) ammonium nitrate: 7β-yl-acetic acid-5-hydroxy-6-oxo-5α-stigmastan-δ-lactone (CXCVI)

To a mixture of 5-hydroxy-5α-stigmastan-6-one (CXCI) (1.0g; 2.12 m mol) and vinyl acetate (0.18g; 2.12 m mol) in acetonitrile (50 ml) was added Ce (IV) ammonium nitrate (3.49g; 6.36 m mol). The content was stirred at room temperature for 1 hr and then refluxed on a steam bath for 1hr. An aqueous solution of sodium bicarbonate (20%, 25 ml) was then added and the mixture was refluxed for another 30 min with stirring. After cooling to room temperature, the content was poured into water and extracted with chloroform. After usual work up and evaporation of the solvent, an oily residue was obtained, which was chromatographed over a column of silica gel. Elution with light petroleum ether/ether (5:1) provided a solid which was recrystazllized from acetone to afford 7β -yl-acetic acid-5-hydroxy-6-oxo-5α -stigmastan-δ-lactone (CXCVII) (0.7g; 1.49 m mol) m.p. 82°C.

Analysis found : C, 79.07; H, 10.66

$C_{31}H_{50}O_3$ requires : C, 79.10; H, 10.71%

IR : νmax 1740, 1220 (δ-lactone) and 1705 cm^{-1} (C=O).

^{1}H-NMR : δ 2.3 (mc, 3H, methylene protons of the δ-lactone and C7-α H), 1.15 (C10-CH_3), 0.71 (C13-CH_3), 0.95 and 0.80 (other methyl protons).

MS : $M^{+\cdot}$ 470 (17.30; $C_{31}H_{50}O_3$), 455 (7.40), 452 (6.25), 442 (13.25), 426 (19.00; $C_{30}H_{50}$), 424 (14.40), 414 (17.80), 411 (20.50), 410 (22.20), 396 (17.40), 383 (24.00), 329 (15.30), 328 (17.25), 302 (12.00), 301 (13.70), 288 (16.70), 287 (18.50), 273 (20.00), 232 (29.25), 220 (3.40), 219 (6.20), 218 (8.25), 217 (25.00), 216 (10.50), 215 (5.00), 192 (4.20), 191 (10.25), 190 (12.40), 179 (13.50), 177 (16.30), 176 (9.20), 175 (4.80), 174 (4.80), 164 (20.00), 163 (13.75), 162 (7.40), 161 (8.50), 160 (5.40), 159 (3.60), 150 (6.00), 149 (12.25), 148 (7.40), 147 (9.10), 146 (5.50), 137 (7.50), 136 (19.25), 135 (16.30), 134 (10.70), 133 (5.10), 132 (4.20), 124 (4.50), 123 (4.50), 122 (10.25), 121 (19.50), 120 (17.25), 119 (12.00), 118 (9.60), 117 (6.60), 116 (12.75), 109 (23.25), 108 (40.00), 107 (48.25), 106 (32.10), 105 (20.90), 104 (15.50), 103 (6.00), 95 (42.00), 94 (19.75), 93 (17.23), 92 (10.00), 91 (17.70), 90 (7.40), 82 (34.75), 81 (20.00), 80 (17.25), 79 (30.00), 78 (10.50), 77 (6.70), 76 (6.70), 69 (31.30), 68 (13.25), 67 (21.00), 66 (10.00), 65 (7.20), 57 (25.10), 56 (30.50), 55 (21.90), 54 (11.75), 53 (20.00), 52 (8.30), 47 (29.25), 46 (16.00), 45 (12.75), 44 (100.00), 43 (74.30), 42 (40.50), 41 (30.20), 40 (37.75).

3β-Chloro-5-hydroxy-5α-stigmastan-6-one (CXCII).

3β-Chlorostigmast-5-ene (28g) in hot acetic acid (600 ml) was treated with hydrogen peroxide (30%, 12 ml) and the reaction mixture was heated at a temperature of 95°C for 30 min. Removal of the solvent in vacuum gave an oily product, which was extracted with ether. Evaporation of the solvent provided an oil, which was chromatographed on aluminium oxide (600g). Elution with petroleum ether / ether (10:1) gave the unreacted 3β-chlorostigmast-5-ene (3.3g). Further elution with ether furnished on oil, which was suspended in acetone (100 ml) and Jone's reagent (35 g of chromium trioxide in 10 ml of water and 30 ml of sulphuric acid) was added dropwise with stirring till the colour of the reagent persisted at 0-5°C. The solution was further stirred for 30 min. The reaction mixture was diluted with water and the precipitated solid was filtered, dried and recrystallized from acetone to give the hydroxy ketone (CXCII) (12.0g) m.p. 178°C.

IR : νmax 3500 (OH), 1710 (C=O) and 740 cm^{-1} (C-Cl).

^1H-NMR : δ 3.85 (mc, 1H, C3-α H, W 1/2 = 16 Hz, axial)[19], 2.45 (br, 1H, OH), 2.1 (mc, 2H, C7-H_2), 1.15 (C10-CH_3), 0.69 (C13-CH_3), 0.98, 0.92 and 0.81 (other methyl protons).

Reaction of 3β-chloro-5-hydroxy-5α-stigmastan-6-one (CXCII) with Vinyl acetate and Ce(IV) ammonium nitrate: 3β-chloro-7β-yl-acetic acid-5-hydroxy-6-oxo-5α-stigmastan- δ-lactone (CXCIII).

To a solution of 3β-chloro-5-hydroxy -5α-stigmastan-6-one (CXCII) (1.0g; 1.98 m mol) and vinyl acetate (0.17g; 1.98 m mol) in acetonitrile (50 ml) was added Ce(IV) ammonium nitrate (3.26 g; 5.94 m mol) and was stirred for 1 hr at room temperature and refluxed for 1 hr. To this sodium bicarbonate solution (20%, 25 ml) was added and was refluxed for another 30 min. with stirring. After cooling, it was poured into water and extracted from chloroform. Usual work up and evaporation of the solvent provided an oil, which was chromatographed over silica gel column. Elution with light petroleum ether/ether (5:1) furnished an oily compound, 3β--chloro-7β -yl-acetic acid-5-hydroxy-6-oxo-5α -stigmastan lactone (CXCVIII) (0.71g; 1.41 m mol).

Analysis found : C, 73.68; H, 9.74

$C_{31}H_{49}O_3Cl$ requires : C, 73.30; H, 9.78%

IR : νmax 1745, 1210 (δ-lactone), 1720 (C=O), and 740 cm^{-1} (C-Cl).

^{1}H-NMR : δ 3.9 (mc, 1H, C3-α H, W 1/2 = 15 Hz, axial)^{19}, 2.4 (mc, 3H, methylene protons of δ-lactone and C7-αH), 1.2 (C10-CH_3), 0.68 (C13-CH_3), 0.91 and 0.84 (other methyl protons).

MS : $M^{+\cdot}$ 504/506 (6.40/2.11; $C_{31}H_{49}O_3Cl$), 489/491 (5.00/1.60), 476/478 (10.50/3.48), 468 (27.60; $C_{31}H_{48}O_3$), 460/462 (14.50/4.80; $C_{30}H_{49}OCl$), 448/450 (9.75/3.24), 445/447 (12.75/4.24), 444/446 (15.00/4.97), 440 (17.50), 430/432 (11.00/3.65), 424 (17.60; $C_{30}H_{48}O$), 422 (10.20), 417/419 (17.00/5.65),412 (13.00), 410 (27.70), 409 (21.25), 408 (27.70), 400 (21.20), 394 (13.75), 381 (15.20), 336/338 (9.20/3.05),335/337 (10.50/3.49), 327 (16.00), 322 (11.00), 321 (13.10), 307/309 (12.75/4.25), 300 (12.00), 299 (13.10), 286 (12.75), 285 (14.30), 271 (15.00), 266/268 (17.25/5.74), 251/253 (20.00/6.66), 230 (27.25), 219 (7.20), 218 (4.20), 217 (25.20), 216 (10.0), 215 (45.30), 214 (13.75), 213 (3.70), 212 (3.70), 211 (6.40), 208 (10.20), 207 (14.30), 206 (26.25), 205 (13.10), 204 (9.60), 195 (7.10), 194 (6.40), 193 (6.40), 192 (3.25), 191 (22.25), 190 (40.30), 189 (12.00), 188 (7.40), 187 (4.80), 186 (7.40), 150 (9.60), 149 (27.20), 148 (7.40), 147 (7.40), 145 (12.50), 132 (17.10), 131 (13.75), 130 (9.60), 129 (5.70), 128 (3.75), 127 (3.75), 125 (6.25), 124 (6.25), 123 (4.80), 122 (12.60), 121 (8.50), 120 (16.10), 119 (10.50), 111 (15.50), 110 (12.75), 109 (14.25), 108 (14.25), 107 (35.70), 106 (40.10), 105 (10.00), 104 (6.40), 103 (5.00), 74 (30.25), 73 (32.30), 72 (16.50), 71 (10.25), 70 (19.00), 69 (25.00), 68 (8.50), 59 (16.70), 58 (13.00), 57 (31.25), 56 (30.75), 55 (62.20), 54 (33.50), 45 (40.00), 44 (100.00), 43 (80.10), 42 (39.25), 41 (27.20), 40 (30.50).

3 β -Acetoxy-5-hydroxy-5 ∝ -stigmastan-6-one (CXCIII).

A mixture of β-sitosterol (20g) and formic acid (88%; 20 ml) was heated on a water bath at 70-80°C for 5 min. and then allowed to attain room temperature. Hydrogen peroxide (30%; 20 ml) was added to the mixture and was kept at room temperature for 12 hrs with occasional shaking. Boiling water (300 ml) was added to the mixture with stirring and the reaction mixture was allowed to attain room temperature. A white solid seperated which was filtered under suction and air dried. The solid was dissolved in methanol (600 ml) and was heated with sodium hydroxide solution (25%; 20 ml) for 10 min. on a steam bath, acidified with hydrochloric acid and diluted with boiling water (300 ml). A solid was obtained on cooling, which was dissolved in 1,4-dioxane (180 ml). To this N-bromosuccinimide (8g) was added at 25°C. After 15 min. the reaction was cooled in an ice bath. The solid which crystallized out was collected and washed throughly with 50% methanol. This solid was taken in pyridine (15 ml) and acetic anhydride (10 ml) and was heated under reflux for 2 hrs. The reaction mixture was allowed to cool to room temperature and treated with water. The reaction product consisting of colourless needles was filtered, washed with a little methanol and air dried. Recrystallization from methanol gave the hydroxy ketone (CXCIII) (7g) m.p. 220^{o}C.

IR : ν max 3400 (OH), 1725 (CH_3 COO), 1710 (C=O) and 1050 cm^{-1} (C-O).

^{1}H-NMR : δ 4.5 (mc, 1H, C3-αH, W 1/2 = 17 Hz, axial)[19], 2.5 (br, 1H, OH), 2.15 (mc, 2H, C7-H_2), 1.9 (s, 3H, CH_3 COO), 1.05 (C10-CH_3), 0.71 (C13-CH_3), 0.95, 0.91 and 0.82 (other methyl protons).

Reaction of 3β-acetoxy-5-hydroxy-5α-stigmastan-6-one (CXCIII) with vinyl acetate and Ce(IV) ammonium nitrate: 3β-Acetoxy-7β-yl-acetic acid-5-hydroxy-6-oxo-5α-stigmastan-δ-lactone (CXCIX).

To a solution of 3β-acetoxy-5-hydroxy-5α-stigmastan-6-one (CXCIII) (1.0 g; 1.89 m mol) and vinyl acetate (0.16g; 1.89 m mol) in acetonitrile (50 ml) was added Ce (IV) ammonium nitrate (3.11g; 5.67 m mol) and was stirred at room temperature for 1 hr and refluxed on a steam bath for 1 hr. An aqueous solution of sodium bicarbonate (20%, 25 ml) was added and the content was refluxed for another 30 min. After cooling, the mixture was poured into water and extracted with chloroform. Evaporation of chloroform gave an oily residue which was chromatographed over a column of silica gel. Elution with light petroleum ether/ ether (5:1) provided 3β -acetoxy-7β -yl-acetic acid-5-hydroxy-6-oxo-5α-stigmastan- δ-lactone (CXCIX), which was recrystallized from acetone (0.67g; 1.27 m mol). m.p. 109°C.

Analysis found : C, 74.93; H, 9.88

$C_{33}H_{52}O_5$ requires : C, 74.96; H, 9.91%

IR : ν max 1735 (δ-lactone), 1725 (CH_3COO), 1710 (C=O) and 1040 cm^{-1} (C-O).

^{1}H-NMR : δ 5.2 (mc, 1H, C3-α H, W 1/2 = 16 Hz, axial)[19], 2.4 (mc, 3H, methylene protons of δ-lactone and C7- α H), 1.09 (s, 3H, CH_3COO), 1.05 (C10-CH_3), 0.71 (C13-CH_3), 0.93 and 0.81 (other methyl protons).

MS : $M^{+\cdot}$ 528 (6.10; $C_{33}H_{52}O_5$), 513 (7.50), 484 (14.00), 482 (4.80), 472 (6.80), 469 (15.25), 468 (29.00; $C_{31}H_{48}O_3$), 452 (13.40), 441 (14.70), 440 (11.50), 424 (12.50), 422 (7.40), 412 (9.80), 410 (20.30), 409 (24.50; $C_{29}H_{45}O$), 408 (26.00), 400 (25.00), 394 (12.70), 392 (15.20), 381 (11.00), 360 (11.40), 359 (12.70), 346 (13.50), 345 (15.00), 331 (16.20), 327 (20.50), 300 (15.50), 299 (17.00), 290 (17.00), 286 (14.30), 285 (16.00), 275 (16.25), 271 (17.10), 230 (32.50), 218 (7.40), 217 (9.60), 216 (31.70), 215 (37.30), 214 (16.60), 213 (8.30), 205 (8.10), 204 (6.75), 203 (6.75), 191 (20.20), 190 (15.50), 189 (17.30), 188 (7.20), 187 (4.80), 167 (10.40), 166 (6.40), 165 (12.30), 164 (8.10), 163 (3.90), 149 (8.50), 148 (11.75), 147 (11.75), 146 (5.60), 111 (10.25), 110 (7.90), 109 (14.25), 108 (7.75), 107 (12.25), 106 (7.20), 105 (5.10), 95 (17.30), 94 (25.25), 93

(10.50), 92 (27.10), 91 (8.50), 90 (4.00), 89 (4.00), 83 (15.00), 82 (6.20), 81 (7.90), 80 (5.10), 72 (12.00), 71 (9.10), 70 (10.75), 69 (4.80), 68 (4.80), 58 (20.00), 57 (14.75), 56 (10.00), 55 (37.10), 54 (29.25), 46 (27.50), 45 (30.25), 44 (100.00), 43 (41.70), 42 (37.00), 41 (17.25), 40 (35.50).

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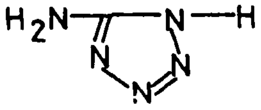
CHAPTER FOUR

Synthesis of steroidal tetrazoles

THEORETICAL

The five membered doubly unsaturated heterocycle with one carbon and four nitrogen atoms is known as tetrazole. The first tetrazole was recognised in 1885 by Bladin[1] during an investigation of dicyanophenylhydrazine. An excellent review covering methods of synthesis of tetrazoles and almost all aspects of tetrazole chemistry, is given by Benson.[2]

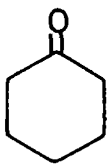
Tetrazoles have important biological as well as non-biological applications. These have been applied in various explosives and in propellants. Nitrocellulose propellant powder is rendered flashless without loss of ballistic potential by incorporation of 5-aminotetrazole (I). They have also been used as binders in composite propellants and match compositions. They are of use in fibre, dye-stuff and textile industries and have application in photography too. It is also used in the shock treatment of certain psychosis to produce convulsions. Such convulsive effects produced by tetrazoles are of significant importance, as they are used as bird management chemical. The best known biologically active tetrazole is pentamethylenetetrazole (III), which is used in clinics to overcome intoxications owing to over dosage of barbiturates.[3] Stimulant, depressant, sedative and analgesic activities are shown by certain tetrazoles. Anticonvulsant, hypertensive and adrenergic blocking actions are also exhibited by a number of 5-monosubstituted tetrazoles.[2]



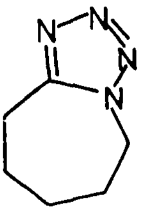
(I)

The synthesis of tetrazoles may be carried out by various methods like (i) oxidative ring closure, (ii) hydrazineazide reaction, (iii) rearrangements, (iv) acylhydrazine diazonium reaction, (v) addition of hydrazoic acid to compounds having carbon-nitrogen unsaturation, such as nitriles, cyanates, isothiocyanates and cyanamides, and (vi) hydrazine nitrite reaction. One of the most valuable method for preparation of tetrazole is the rearrangement reaction between ketones and an excess of hydrazoic acid in presence of strong acids as catalyst, a modification of the Schmidt-reaction.[4,5]

The reaction has found its most extensive applications with cyclic ketones, with which yields are generally better than with acyclic ketones. Champman et al.[6] obtained pentamethylenetetrazole (III) from cyclohexanone (II). Benson[2] synthesized the same tetrazole (III) from cyclohexanoneoxime (IV).



(II)



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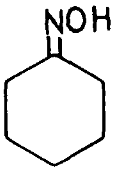
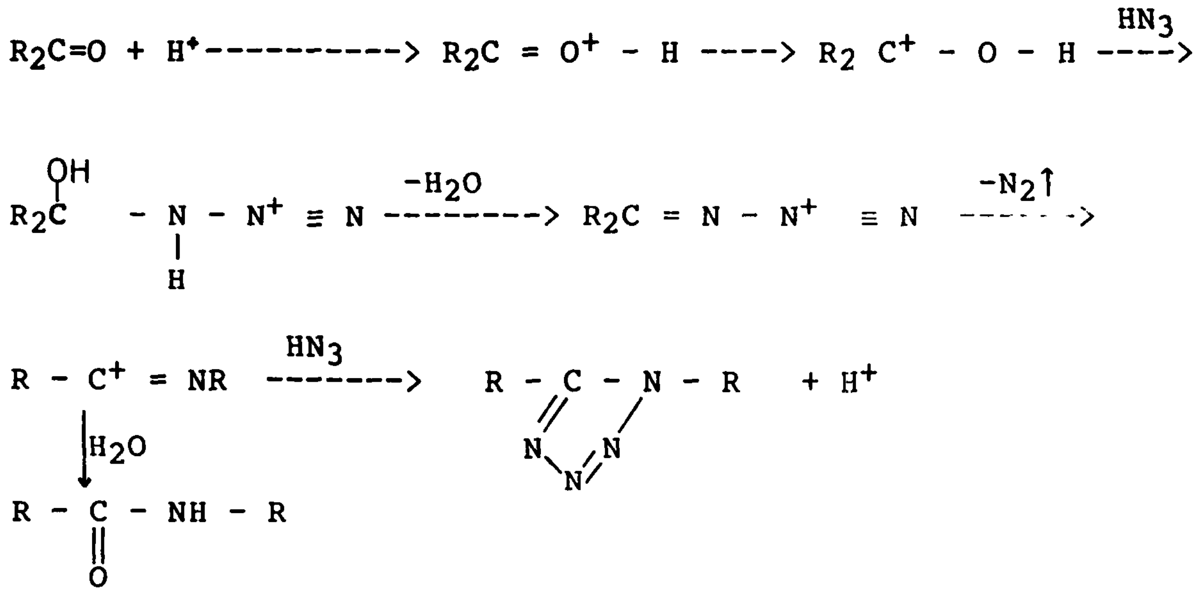
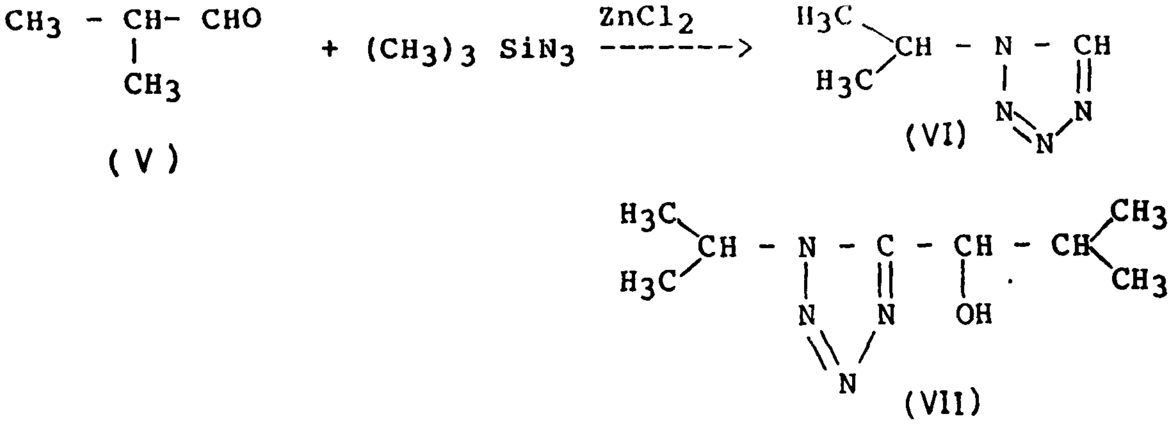


(IV)

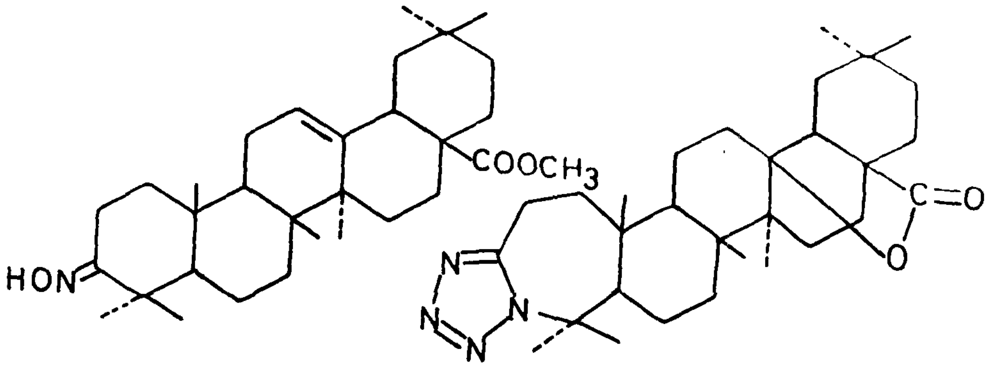
A probable mechanism for this transformation was given by Smith[7], in which the first step was the conversion of the compound to a carbonium ion under the influence of acid catalyst. This was followed by combination with one molecule of hydrazoic acid, dehydration of the intermediate and rearrangement to an imido-carbonium ion with a simultaneous loss of nitrogen. The formation of tetrazole took place with a reaction of second molecule of hydrazoic acid and imidocarbonium ion, the positive charge being lost as a proton. But instead of tetrazole a lactam was obtained if water molecule reacted with the imidocarbonium ion in place of a second molecule of hydrazoic acid. The mechanism accounted satisfactorily for the necessity of using strong acid as catalyst.



When a mixture of 2-methylpropanal (V), trimethylsilyl azide (3 equiv.) and zinc chloride (1 equiv.) was stirred at room temperature, yielded 1- (1-methylethyl)-1H-tetrazole (VI) and 5-(1-hydroxy-2-methylpropyl)-1-(1-methylethyl)-tetrazole (VII).[8]

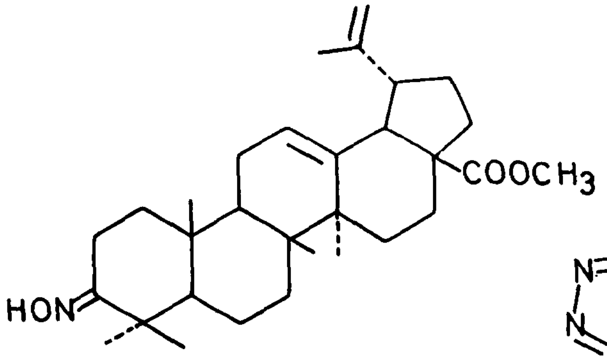


The reaction of sodium azide on the oximes of methyl oleanonate (VIII) and methyl betulonate (IX) in methylene-dichloride in presence of chlorosulphonic acid furnished 4-aza-A-homo-olean-28(13) lactone [3,4-d] tetrazole (X) and 4-aza-A-homo-28-oxoallobetulin [3,4-d] tetrazole (XI)[9].

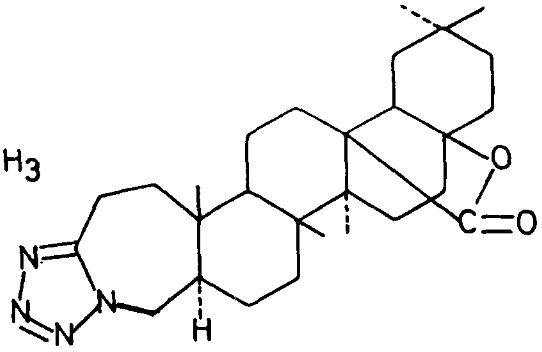


(VIII)

(X)

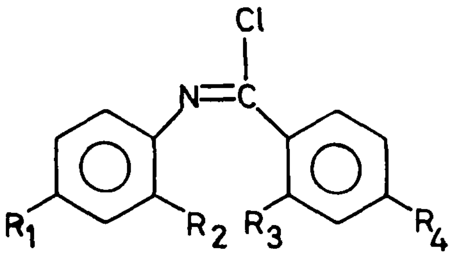


(IX)

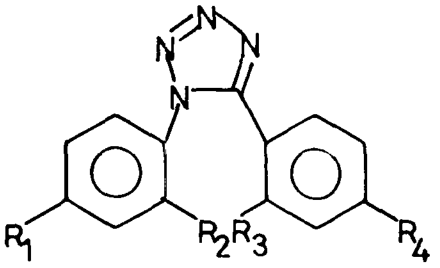


(XI)

Haughton et al.[10] prepared 1,5-diaryltetrazole (XIII) by the reaction of imidoyl chlorides (XII) with sodium azide in N,N-dimethylformamide.

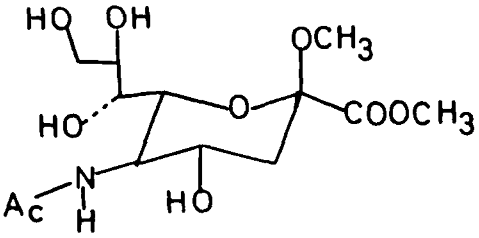


(XII)

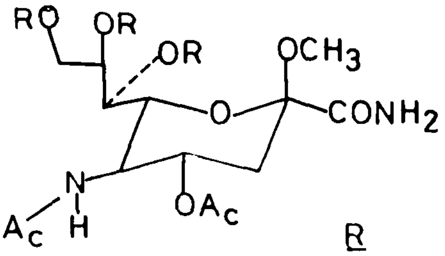


(XIII)

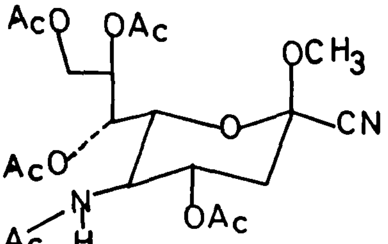
Methyl-5-(acetylamino)-3,5-didesoxy- β - Δ -glycero-D-galacto-2-nonulo-pyranosidonic methyl ester (XIV)[11] was transformed into the corresponding amides (XV, XVI), the peracetylated (XV, XVI) were converted with $POCl_3$ into the nitrile derivative (XVII) which on reaction with ammonium azide furnished (XVIII, XIX) with a bioisosteric tetrazole function.



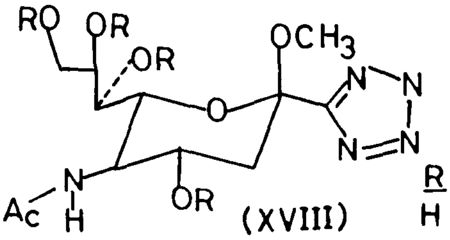
(XIV)



	R
(XV)	H
(XVI)	CH_3CO

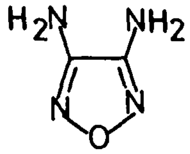


(XVII)

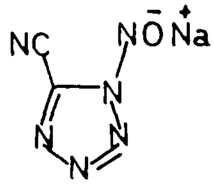


	R
(XVIII)	H
(XIX)	CH_3CO

Chnrakov et al.[12] prepared the sodium salt of 1-oxy-5-cyanotetrazole (XXI) from aminoazidofurazane (XX).

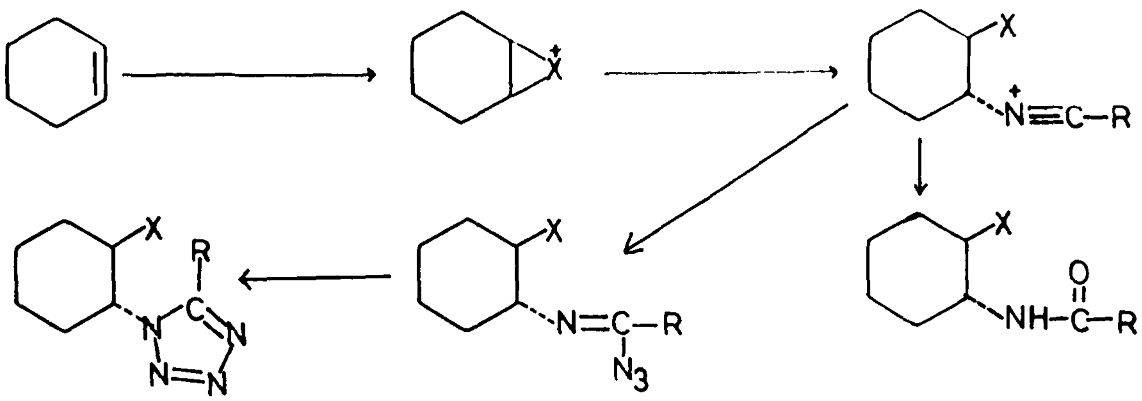


(XX)



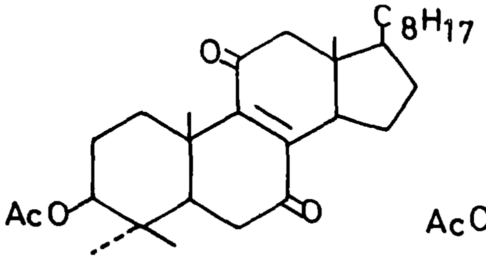
(XXI)

Hassner et al.[13] reported one of the most valuable method for the preparation of 1,5-disubstituted tetrazoles. In which a carbon carbon double bond was made to react with halogen and sodium azide using nitriles as solvent and proposed the following mechanism for the formation of tetrazole.

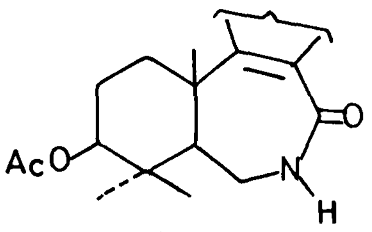


Steroidal tetrazoles

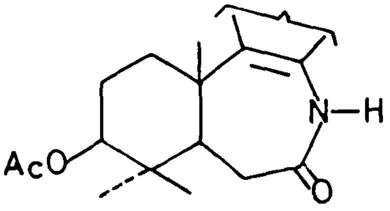
The first example of the formation of a tetrazole in steroid and triterpenoid was given by Barnes et al.[14] in 1952. Treatment of 3β -acetoxy-7,11, dioxolanost-8-ene (XXII), with hydrazoic acid gave two isomeric monolactams (XXIII, XXIV), and a tetrazole, which was considered to be formed by the reaction with 7-oxo-function, having the structure (XXV) or (XXVI). The structure of the tetrazole could not be established very accurately.



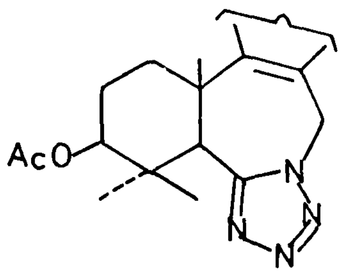
(XXII)



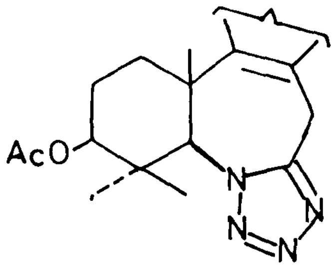
(XXIII)



(XXIV)

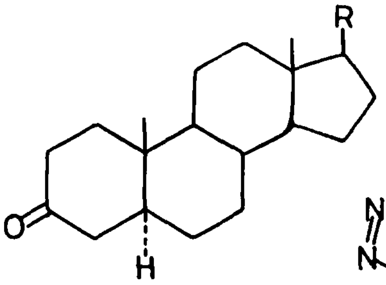


(XXV)



(XXVI)

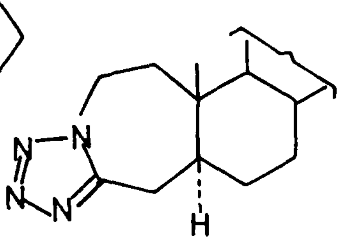
Steroidal tetrazoles did not attract the attention of synthetic organic chemists until 1968, when Mechoulam[15] reported the synthesis of a number of ring A fused steroidal tetrazoles and claimed that some of them possessed antifertility and antispermatogenic activities. From the Schmidt reaction of 5α-cholestan-3-one (XXVII) and 17β-hydroxy-5α-androstan-3-one (XXVIII) using excess of hydrazoic acid, Mechoulam obtained mixtures of isomeric tetrazoles (XXIX, XXXI and XXX, XXXII), respectively.



R

(XXVII) C_8H_{17}

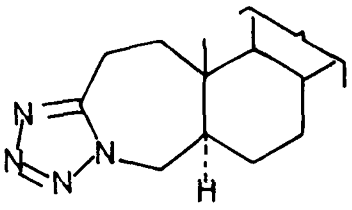
(XXVIII) OH



R

(XXIX) C_8H_{17}

(XXX) OH

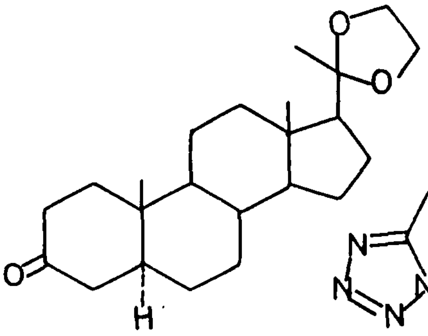


R

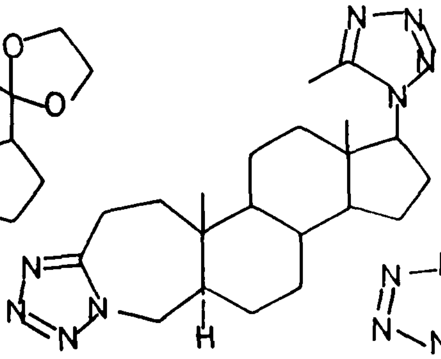
(XXXI) C_8H_{17}

(XXXII) OH

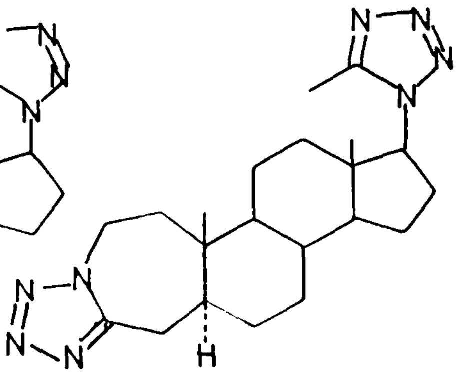
Similar treatment of 20,20-ethylenedioxy-5α-pregnan-3-one (XXXIII) afforded a mixture of 17β -(5-methyltetrazine— 1-yl) 3-aza-A-homo-5α-androstano [3,4-d] tetrazole (XXXIV) and its 4-aza, isomer (XXXV).[15]



(XXXIII)

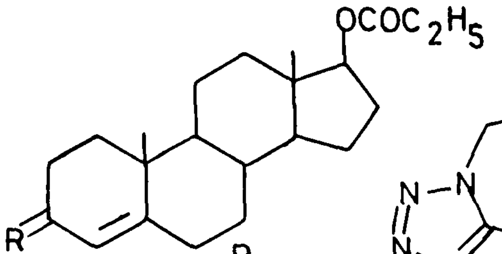


(XXXIV)

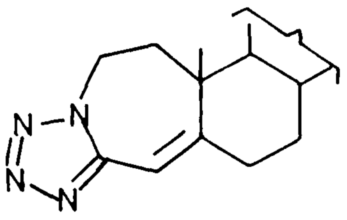


(XXXV)

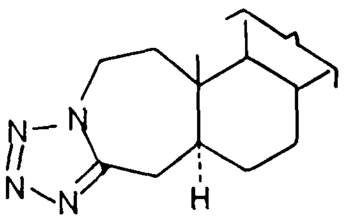
In 1970, Moural and Syhora[16] reported the synthesis of a series of 3-aza-A-homo-4a-eno [3,4-d] tetrazole analogues from the corresponding 3-oxo-4-eno steroids by the reactions of hydrazoic acid. The reaction of 3-oxoandrost-4-en-17β-propionate (XXXVI) has been reported to yield tetrazole (XXXVIII) which on hydrogenation gave the corresponding dihydro derivatives (XXXIX). A tetrazole (XXXVIII) was also obtained when 3β -hydroximinoandrost-4-en-17β -propionate (XXXVII) was treated with hydrazoic acid. Similarly, 3-oxocholest-4-ene (XL) yielded 3-aza-A-homocholest-4a-eno [3,4-d] tetrazole (XLI).



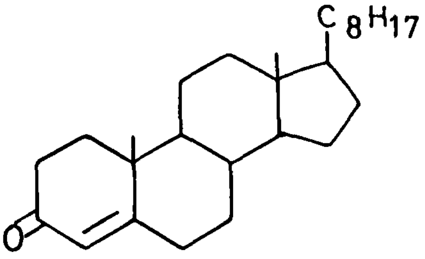
	R
(XXXVI)	O
(XXXVII)	NOH

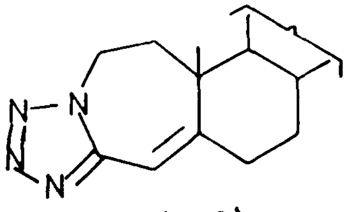


(XXXVIII)

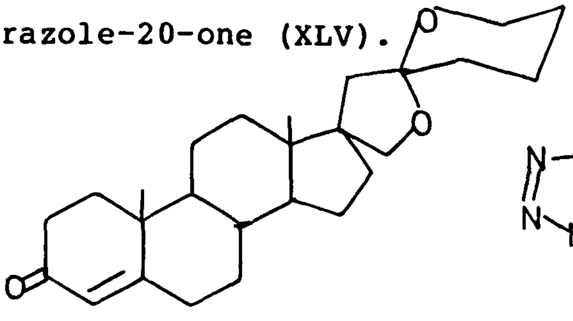


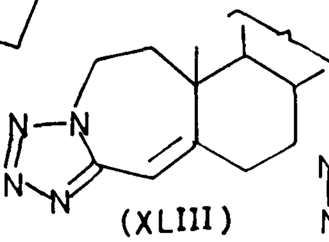
(XXXIX)

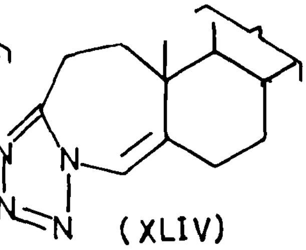

(XL)

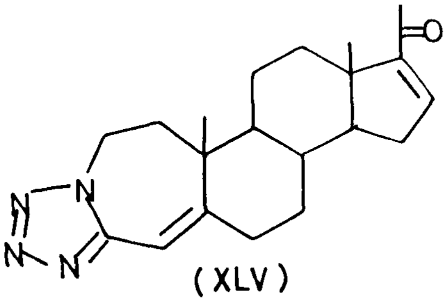

(XLI)

Singh et al.[17] obtained 3-aza-A-homo-(25R)-spirost-4a-eno [3,4-d] tetrazole (XLIII) in preference to the isomer (XLIV) on treating (25R)-siprost-4-en-3-one (XLII) with hydrazoic acid in the presence of BF_3-etherate as catalyst. The structure (XLIII) was confirmed on the basis of spectral data. The observation was that, the Schmidt reaction of 4-en-3-one or the Beckmann rearrangement of the corresponding oxime generally afforded lactam, with 3-aza-A-homo-4a-eno-one system, which also supported the structure (XLIII) in preference to (XLIV). Marker's degradation of the tetrazole (XLIII) gave 3-aza-A-homopregna-4a,16-dieno [3,4-d] tetrazole-20-one (XLV).

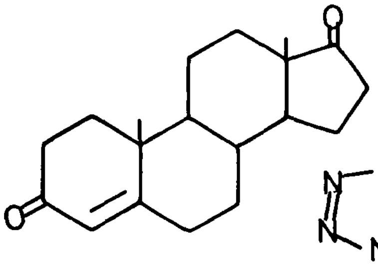

(XLII)

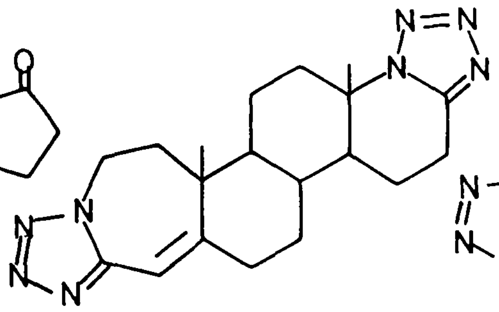

(XLIII)


(XLIV)

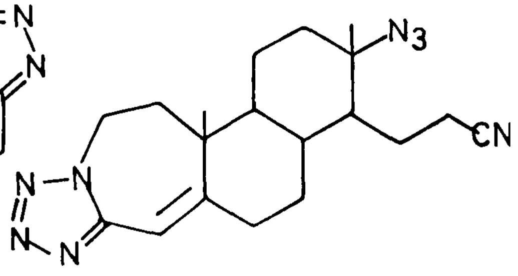

(XLV)

Singh et al.[18,19] have reported the reaction of androst-4-ene-3,17-dione (XLVI) with hydrazoic acid and BF_3-etherate in chloroform to get the expected 3,17a-diaza-A,D-bishomoandrost-4a-eno [3,4-d:17a, 17-d] bistetrazole (XLVII) and an unusual product 13,17-seco-13——azido-A-homoandrost-4a-eno [3,4-d] tetrazole-17-nitrile (XLVIII). The azido-nitrile (XLVIII) cyclizes on heating to (XLVII). The structures were unequivocally established on spectral evidences. The example is claimed to be the first of its kind for the formation of azidonitrile in Schmidt reaction and its thermal cyclization to a tetrazole.


(XLVI)

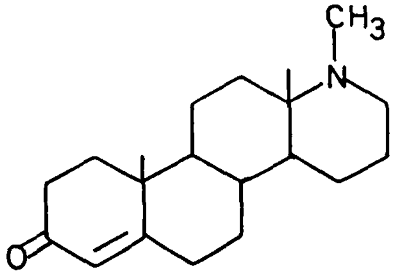


(XLVII)

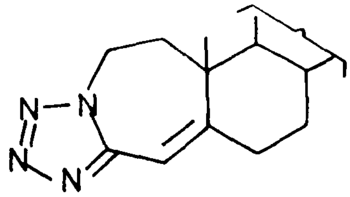


(XLVIII)

It has been reported by Singh and Paul[20] that the treatment of 17a-methyl-17a-aza-D-homoandrost-4-en-3-one (XLIX) with an excess of hydrazoic acid in the presence of BF_3-etherate afforded 17a-methyl-3, 17a-diaza-A,D-bishomoandrost-4a-eno [3,4-d] tetrazole (L).

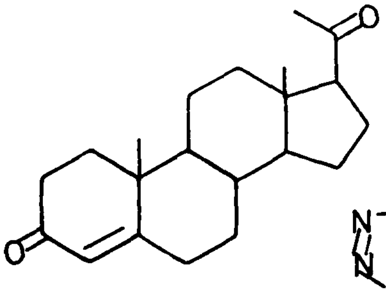


(XLIX)

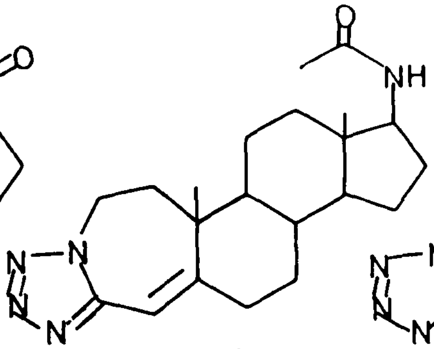


(L)

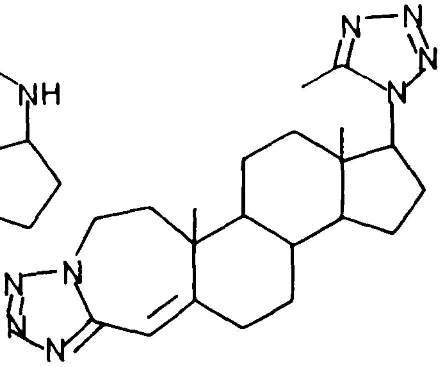
Singh et al.[21] have reported the synthesis of tetrazole from reaction of progesterone with hydrazoic acid and BF_3-etherate. Progesterone (LI) was shown to afford 17β-acetamido-3-aza-A-homoandrost-4a-eno [3,4-d] tetrazole (LII) and 17β (5'-methyl-tetrazol-1'-yl) 3-aza-A-homoandrost-4a-eno [3,4-d] tetrazole (LIII). The structure (LII) was further confirmed when the same was obtained by the reaction of 17β - acetamidoandrost-4-en-3-one (LIV) with hydrazoic acid and BF_3-etherate.



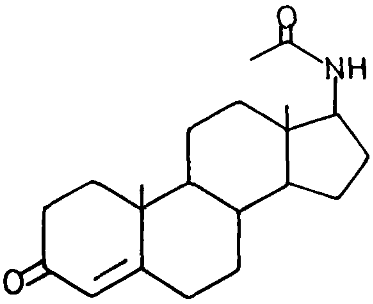
(LI)



(LII)

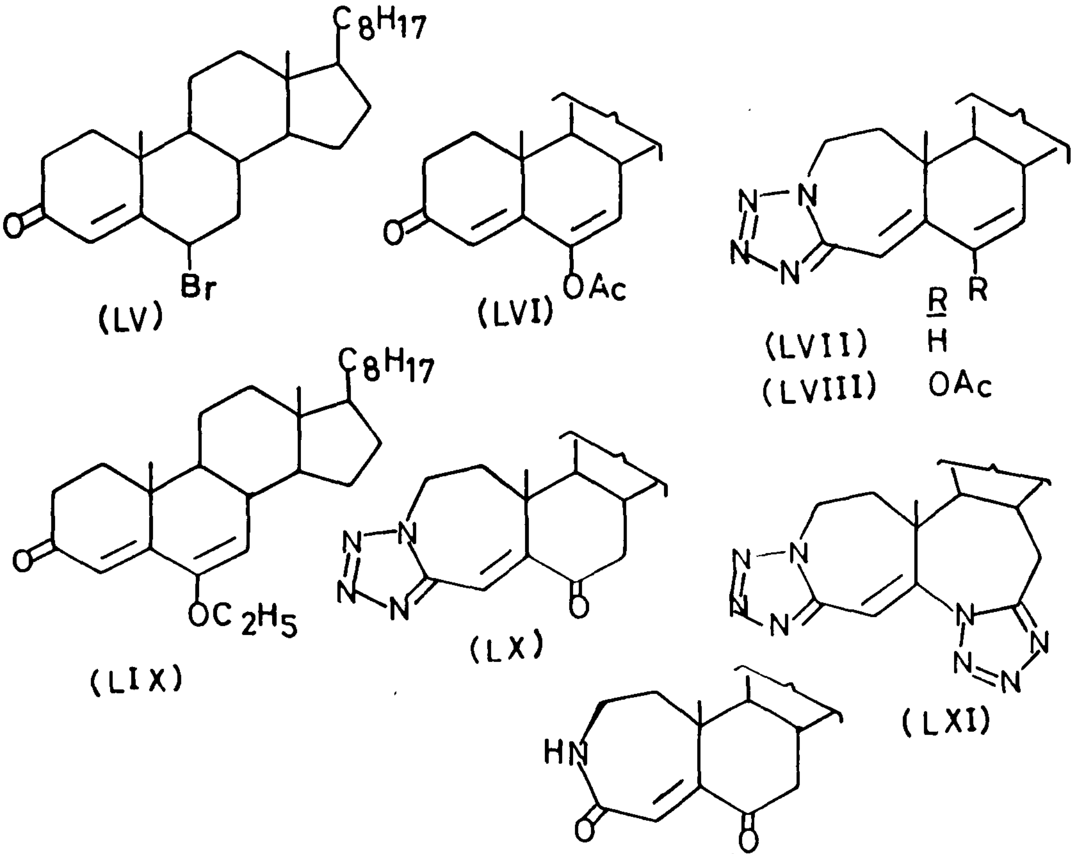


(LIII)



(LIV)

The reactions of 6β-bromocholest-4-en-3-one (LV), 6-acetoxycholesta-4,6-dien-3-one (LVI) and 6-ethoxycholesta-4,6-dien-3-one (LIX) with an excess of hydrazoic acid in the presence of BF_3-etherate were also studied[22,23]. The reaction of (LV) provided exclusively 3-aza-A-homocholesta-4a,6-dieno [3,4-d] tetrazole (LVII). Under similar reaction conditions, (LVI) furnished 6-acetoxy-3-aza-A-homocholesta-4a,6-dieno [3,4-d] tetrazole (LVIII) and (LIX) provided (LX), (LXI) and (LXII).



(LV)

(LVI)

	R
(LVII)	H
(LVIII)	OAc

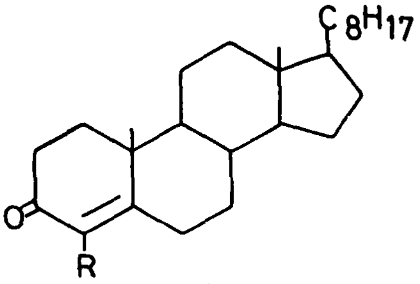
(LIX)

(LX)

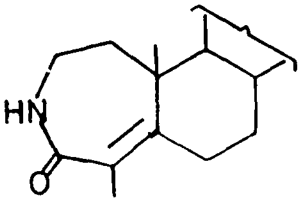
(LXI)

(LXII)

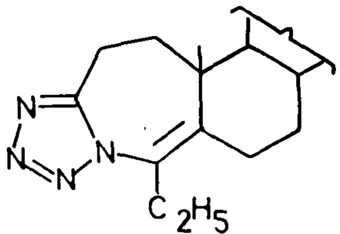
Reaction of 4-methylcholest-4-en-3-one (LXIII) with an excess of hydrazoic acid provided 3-aza-A-homo-4a-methylcholest-4a-en-4-one (LXV) and 3-aza-A-homo-4a-methylcholest-4a-eno-[3,4-d] tetrazole (LXVI). 4-Ethylcholest-4-en-3-one (LXIV) afforded 3-aza-A-homo-4a-ethylcholest-4a-eno [3,4-d] tetrazole (LXVII) and its 4-aza isomer (LXVIII).Under similar reaction conditions 4,4-dimethylcholest-5-en-3-one (LXIX) provided 4,4-dimethyl-5α -cholestane-3,6-dione (LXXI) and 4-aza-A-homo-4a,4a-dimethylcholest-5-eno [4,3-d] tetrazole (LXXII). Where as, the 4,4-diethylcholest-5-en-3-one (LXX) furnished 4-aza-A-homo-4a,4a-diethylcholest-5-eno [4,3-d] tetrazole (LXXIII) and 4,4-diethyl-3,4-seco-4β -azidocholest-5-en-3-nitrile (LXXIV).[24]



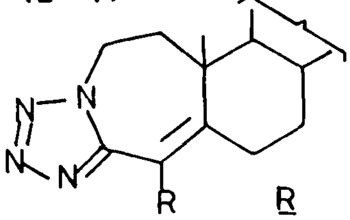
	R
(LXIII)	CH_3
(LXIV)	C_2H_5



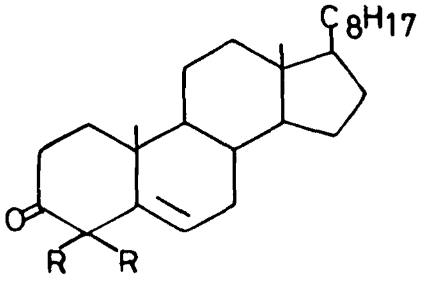
(LXV)



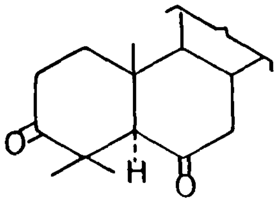
(LXVIII)



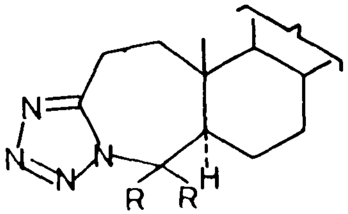
	R
(LXVI)	H
(LXVII)	C_2H_5



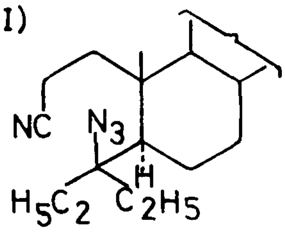
	R
(LXIX)	CH_3
(LXX)	C_2H_5



(LXXI)

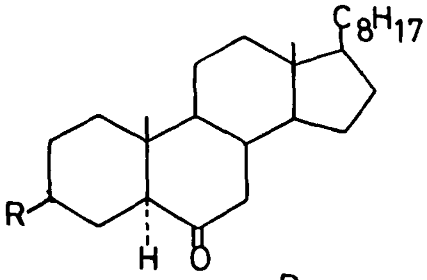


	R
(LXXII)	CH_3
(LXXIII)	C_2H_5

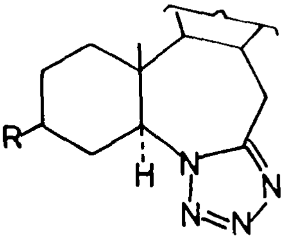


(LXXIV)

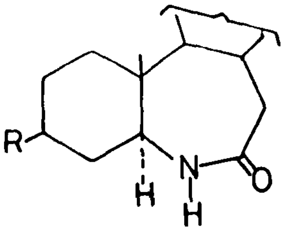
A number of tetrazoles have been reported[25] possessing the 6-aza-B-homo-5α-cholestano [6,7-d] tetrazole functionalities from the corresponding 5α-cholestan-6-ones. Under the usual reaction conditions 5α-cholestan-6-one (LXXV), its 3β-acetoxy (LXXVI), 3β-hydroxy (LXXVII) and 3β-chloro (LXXVIII) analogues furnished the corresponding tetrazoles (LXXIX-LXXXII) and the lactams (LXXXIII-LXXXVI). Similar types of ketones (LXXXVII-XVC) in stigmastane series also furnished the corresponding tetrazoles (XCVI-CIV).[26]



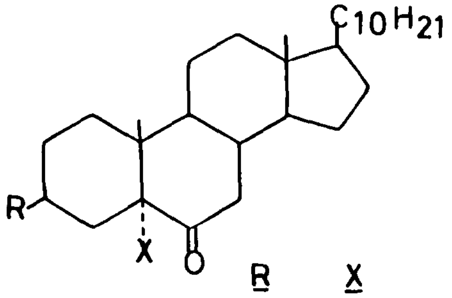
	R
(LXXV)	H
(LXXVI)	OAc
(LXXVII)	OH
(LXXVIII)	Cl



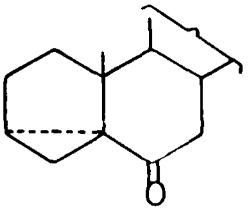
	R
(LXXIX)	H
(LXXX)	OAc
(LXXXI)	OH
(LXXXII)	Cl



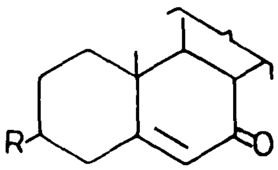
	R
(LXXXIII)	H
(LXXXIV)	OAc
(LXXXV)	OH
(LXXXVI)	Cl



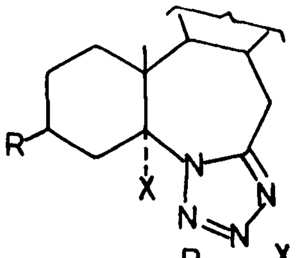
	R	X
(LXXXVII)	H	H
(LXXXVIII)	OH	H
(LXXXIX)	Cl	H
(XC)	OAc	H
(XCI)	OAc	Br



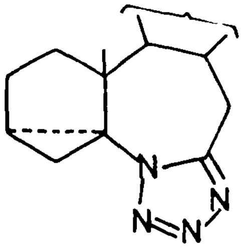
(XCII)



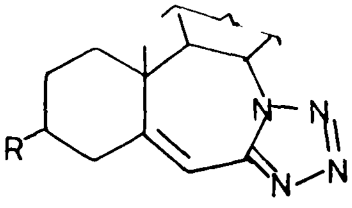
	R
(XCIII)	H
(XCIV)	Cl
(XCV)	OAc



	R	X
(XCVI)	H	H
(XCVII)	OH	H
(XCVIII)	Cl	H
(XCIX)	OAc	H
(C)	OAc	Br

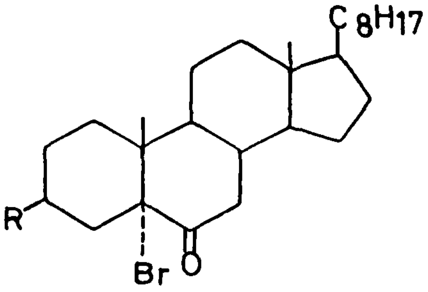


(CI)

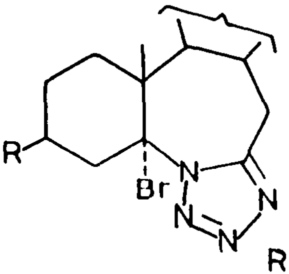


	R
(CII)	H
(CIII)	Cl
(CIV)	OAc

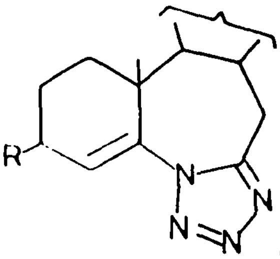
The reaction of 5-bromo-5α-cholestan-6-one (CV) and its 3β-acetoxy analogue (CVI) with hydrazoic acid afforded the corresponding tetrazoles, 6-aza-5-bromo-B-homo-5α-cholestano [6,7-d] tetrazole (CVII), its 3β-acetoxy (CVIII) and 3β-hydroxy (CIX) analogues. Dehydrobromination of these tetrazoles (CVII-CIX) afforded 6-aza-B-homocholest-4-eno [6,7-d] tetrazole (CX), its 3β-acetoxy (CXI) and 3β-hydroxy (CXII) analogues. Jone's oxidation of (CXII) gave 6-aza-3-oxo-B-homocholest-4-eno [6,7-d] tetrazole (CXIII).[27]



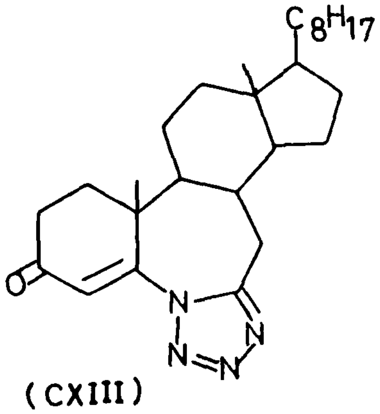
	R
(CV)	H
(CVI)	OAc



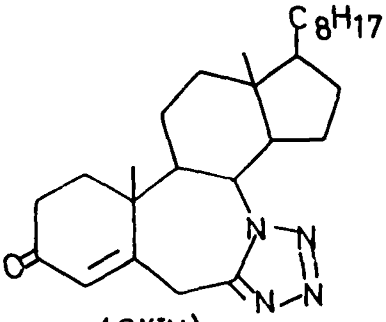
	R
(CVII)	H
(CVIII)	OAc
(CIX)	OH

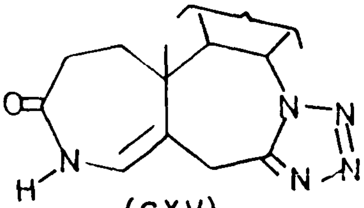


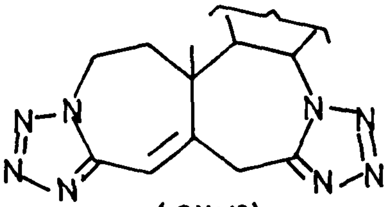
	R
(CX)	H
(CXI)	OAc
(CXII)	OH

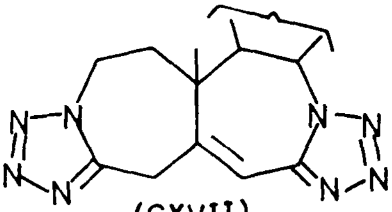

(CXIII)

The reaction of 7a-aza-B-homocholest-4-eno [7a,7-d] tetrazole-3-one (CXIV) with equimolar quantity of sodium azide in polyphosphoric acid gave 4,7a-aza-A,B-bishomocholest-4a-eno [7a,7-d] tetrazole-3-one (CXV). With an excess of hydrazoic acid, (CXIV) provided a bistetrazole which could be either 3,7a-diaza-A,B-bishomocholest-4a-eno [3,4-d:7a,7-d] bistetrazole (CXVI) or its Δ^5 isomer (CXVII).[28]

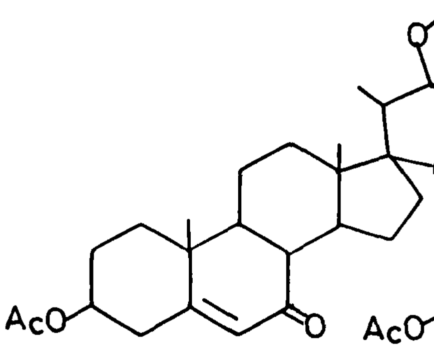

(CXIV)


(CXV)

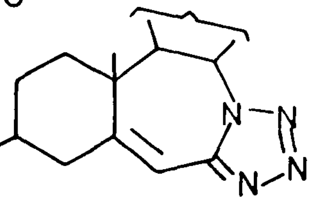

(CXVI)


(CXVII)

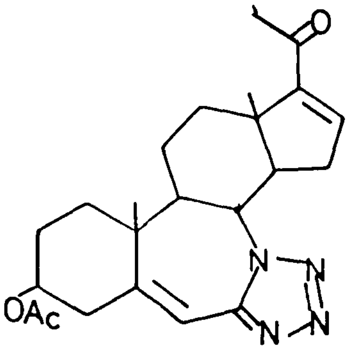
Reaction of (25R)-7-oxospirost-5-en-3β -yl acetate (CXVIII) with hydrazoic acid afforded the corresponding tetrazole (CXIX). Marker's degradation followed by selective hydrogenation of (CXIX) yielded 20-oxo-7a-aza-B-homopregna-5,16-dieno [7a,7-d] tetrazole-3β -yl acetate (CXX). The tetrazole (CXX) on hydrolysis followed by oppenauer oxidation afforded 7a-aza-B-homopregen-4-eno [7a,7-d] tetrazole-3,20-dione (CXXIV). The treatment of 7-oxoandrost-5-en-3β , 17β-diol diacetate (CXXI) with hydrazoic acid afforded 7a-aza-B-homoandrost-5-eno [7a, 7-d] tetrazole-3β , 17β -diol diacetate (CXXII). This tetrazole (CXXII) afforded 3-oxo-7a-aza-B-homoandrost-4-eno [7a,7-d] tetrazole-17β -yl acetate (CXXIII) on hydrolysis followed by oppenauer oxidation.[29]



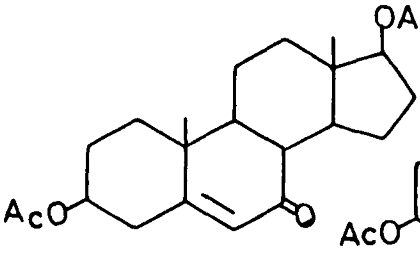
(CXVIII)



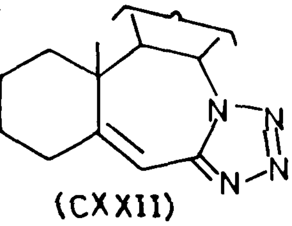
(CXIX)



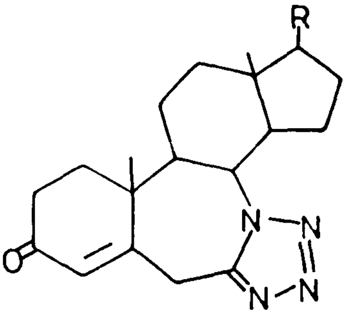
(CXX)



(CXXI)

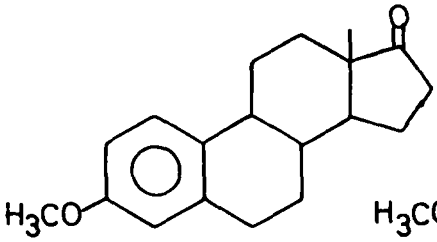


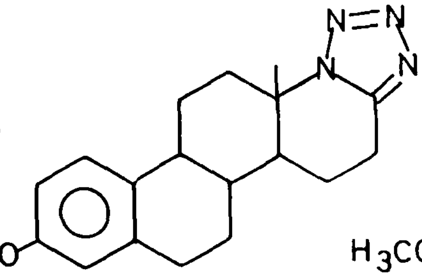
(CXXII)

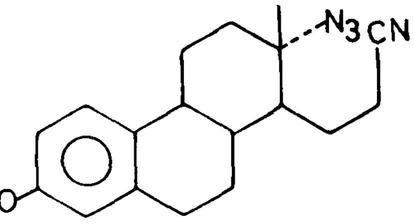


	R
(CXXIII)	OAc
(CXXIV)	Ac

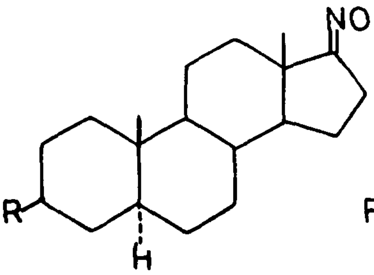
Singh et al.[30] reported the formation of 3-methoxy-17a-aza-D-homo-1,3,5(10)-estratrieno [17a,17-d] tetrazole (CXXVI) and 3-methyoxy 13,17-seco-13α-azido-1,3,5 (10)-estratrieno-17-nitrile (CXXVII) from estrone methyl ether (CXXV) using an excess of hydrazoic acid. The azido nitrile (CXXVII) on thermal cyclization provided tetrazole (CXXVI).


(CXXV)

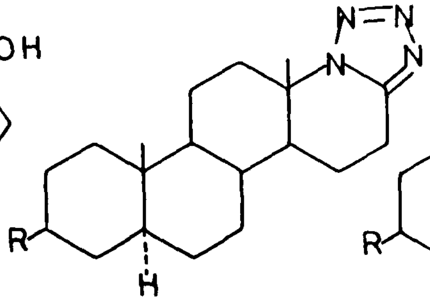

(CXXVI)


(CXXVII)

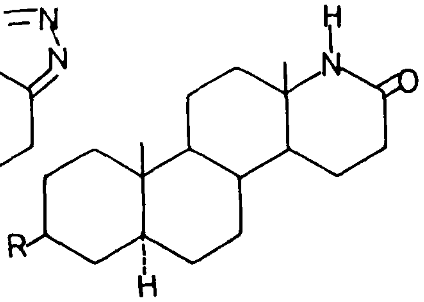
Cervantes et al.[31] reported the formation of ring D fused tetrazoles from the reaction of 17-ketoximes with an excess of sodium azide in the presence of sulphuric acid. The reaction of 5α-androstan-17-one oxime (CXXVIII) was shown to afford 17a-aza-D-homo-5α-androstano [17a,17-d] tetrazole (CXXX) and D-homo lactam (CXXXIII). Similarly the oxime (CXXIX) furnished 3β-acetoxy-17a-aza-D-homo-5α -androstano [17a,17-d] tetrazole (CXXXI), it 3β -hydroxy analogue (CXXXII) and the lactam (CXXXIV). Similarly the oxime (CXXXV) yielded 17a-aza-3-hydroxy-D-homoestra-1,3,5(10)-trieno [17a, 17-d] tetrazole-3-methyl ether (CXXXVI) alongwith the lactam (CXXXVII) and seconitrile (CXXXVIII).



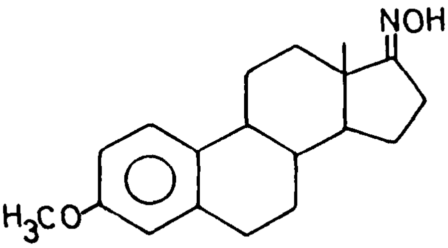
	R
(CXXVIII)	H
(CXXIX)	OAc



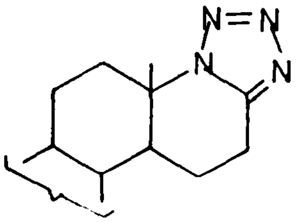
	R
(CXXX)	H
(CXXXI)	OAc
(CXXXII)	OH



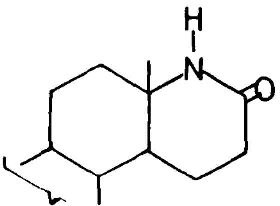
	R
(CXXXIII)	H
(CXXXIV)	OAc



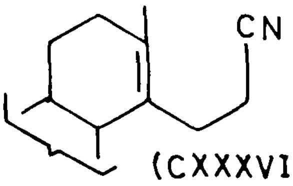
(CXXXV)



(CXXXVI)

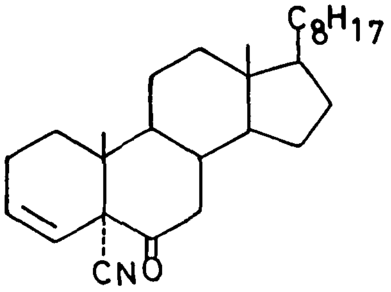


(CXXXVII)

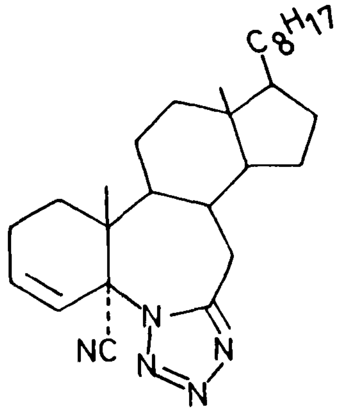


(CXXXVIII)

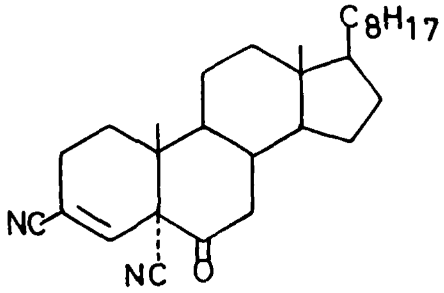
When 5α-cyanochclest-3-en-6-one (CXXXIX) and 3,5-dicyano-5α-cholest-3-en-6-one (CXL) were treated with an excess of hydrazoic acid and BF$_3$-etherate (as catalyst) afforded 5α-cyano-6-aza-B-homocholest-3-eno [6,7-d] tetrazole (CXLI) and 3,5-dicyano-6-aza-B-homocholest-3-eno [6,7-d] tetrazole (CXLII) respectively.[32]



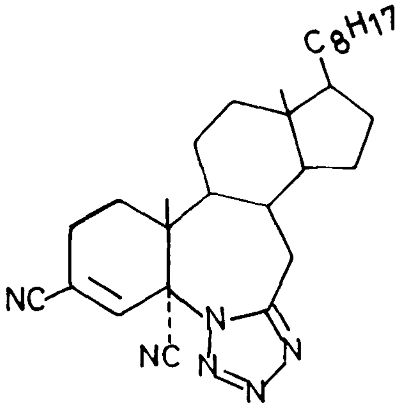
(CXXXIX)



(CXLI)

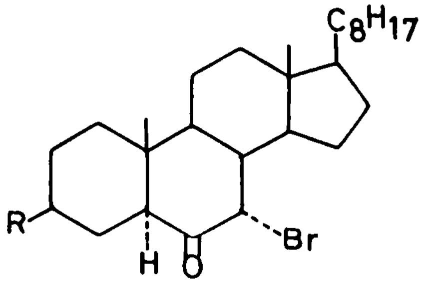


(CXL)

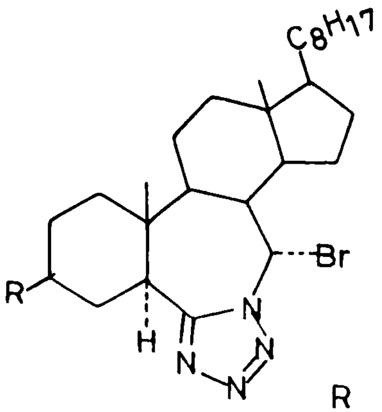


(CXLII)

Synthesis of bromo tetrazoles (CXLVI-CXLVIII) by the reaction of respective α-bromo ketones (CXLIII-CXLV) with hydrazoic acid in presence of BF_3-etherate was also reported.[33]



	R
(CXLIII)	H
(CXLIV)	Cl
(CXLV)	OAc

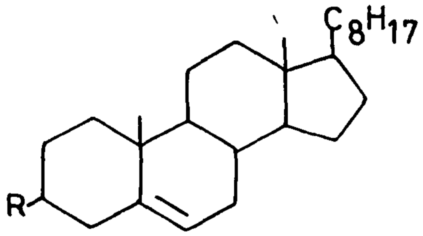


	R
(CXLVI)	H
(CXLVII)	Cl
(CXLVIII)	OAc

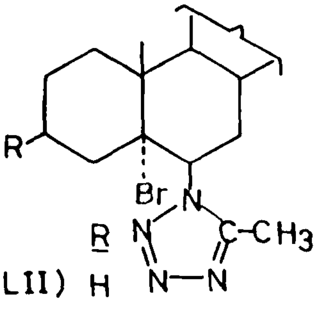
DISCUSSION

Steroidal tetrazoles became of interest in recent past, because of the discovery of various biological activities such as hypertensive[2], anticonvulsant[2,34], antiallergic[35], antiulcer[36], antibacterial[37], antiviral[37], antifungal[37] and analgesic[38], associated with a number of substituted tetrazoles. As a result of this realization, synthesis of steroidal tetrazoles became a matter of interest and consequently a number of papers appeared describing the preparation of steroidal tetrazoles from various steroidal ketones.

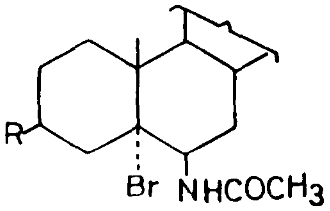
The present work describes the preparation of ∝-bromotetrazoles (CLII-CLIV) along with ∝-bromoamides (CLV-CLVII) from the steroidal olefins such as cholest-5-ene (CXLIX), 3β-chlorochest-5-ene (CL) and 3β-acetoxy cholest-5-ene (CLI) and also the preparation of ∝-hydroxy tetrazoles (CLXI-CLXIII), from the respective steroidal oxiranes (CLVIII-CLX).



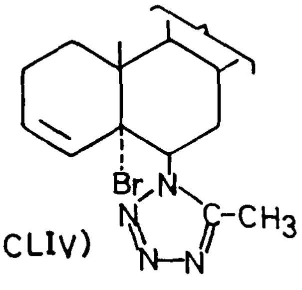
	R
(CXLIX)	H
(CL)	Cl
(CLI)	OAc



	R
(CLII)	H
(CLIII)	Cl



	R
(CLV)	H
(CLVI)	Cl



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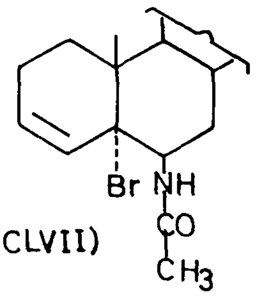
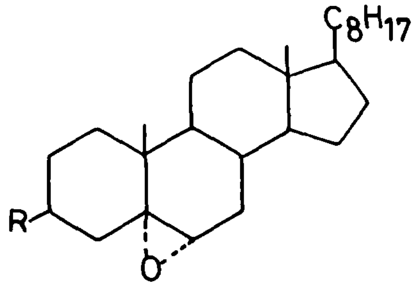
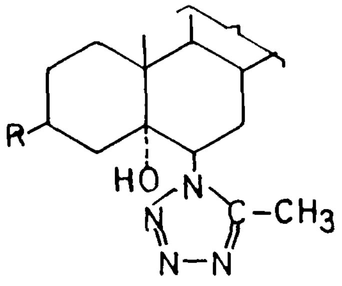


(CLVII)

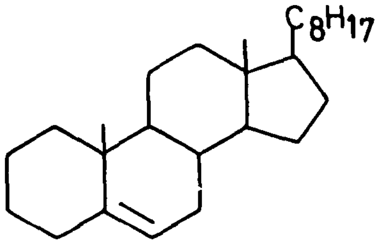




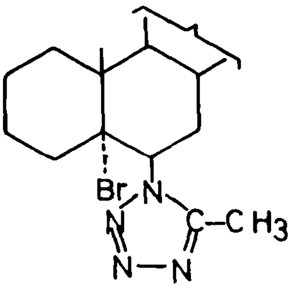
REACTIONS OF STEROIDAL OLEFIN WITH BROMINE, ACETONITRILE AND SODIUM AZIDE

Reaction of cholest-5-ene (CXLIX) with bromine, acetonitrile and sodium azide in the presence of anhydrous aluminium chloride

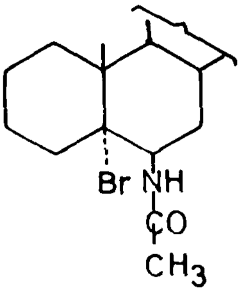
Cholest-5-ene (CXLIX) in acetonitrile, was treated with bromine and sodium azide in the presence of anhydrous aluminium chloride. The suspension was stirred at 0°C and room temperature for 2 hrs each. The progress of the reaction was monitored by TLC. The solvent was removed and the residue was extracted with chloroform. The organic layer was washed with water, sodium bicarbonate solution and again with water and dried over anhydrous sodium sulphate. The removal of solvent provided an oily residue, which was chromatographed over silica gel to furnish two compounds, having m.p.s. 156°C and 172°C.



(CXLIX)



(CLII)



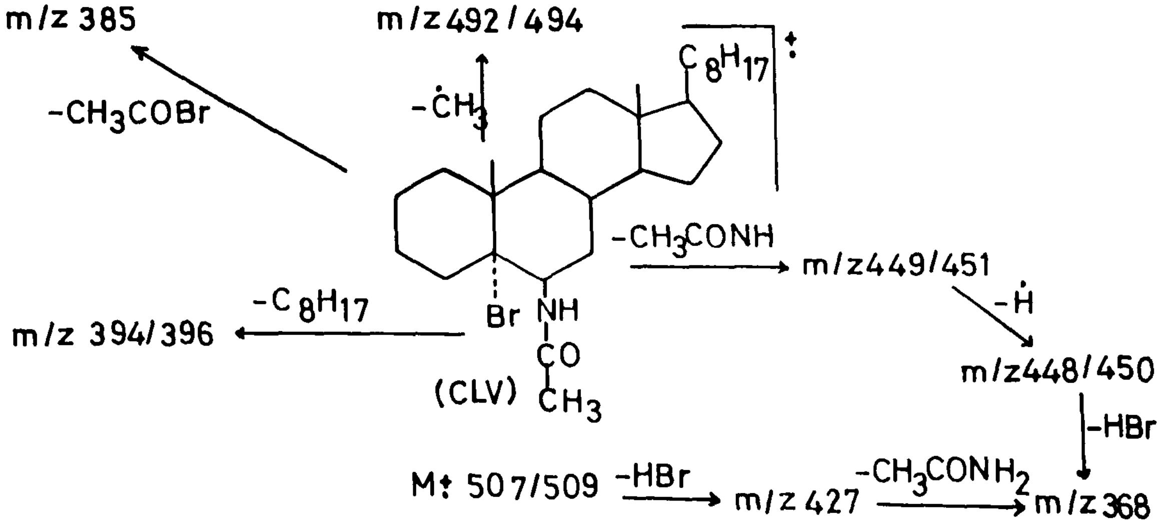
(CLV)

Characterization of the compound having m.p. 172°C as 5-bromo-6β-acetamido-5α-cholestane (CLV)

The compound with m.p. 172°C was correctly analysed for $C_{29}H_{50}NOBr$ (positive Beilstein test). Its IR spectrum gave bands at 3420 (NH), 1670 (-CO-NH) and 730 cm^{-1} (C-Br). The ^{1}H-NMR spectrum of the compound exhibited a broad singlet centered at δ 5.8 integrating for one proton (deuterium exchangeable) and was assigned to N-H proton. A multiplet centered at δ 3.2 integrating for one proton was assigned to C6- α H. A sharp singlet integrating for three protons appeared at δ 2.1 due to methyl group of the amide moiety. Other methyl protons appeared at δ 1.2 (C10-CH_3), 0.72 (C13-CH_3), 0.97 and 0.84 (other side chain methyl protons). In the light of above observations,the compound having m.p. 172°C may therefore be regarded as 5-bromo-6β-acetamido-5α-cholestane (CLV). The mass spectral studies further supported the above structure for the compound (CLV). The mass spectrum of (CLV) gave the molecular ion peaks at m/z

507/509 (M$^{+\cdot}$) followed by other significant peaks at m/z 492/494, 449/451, 448/450, 427, 394/396, 385, 368, and lower mass fragment ion peaks. Formation of some significant fragment ions has been explained in scheme which is tentative in nature.

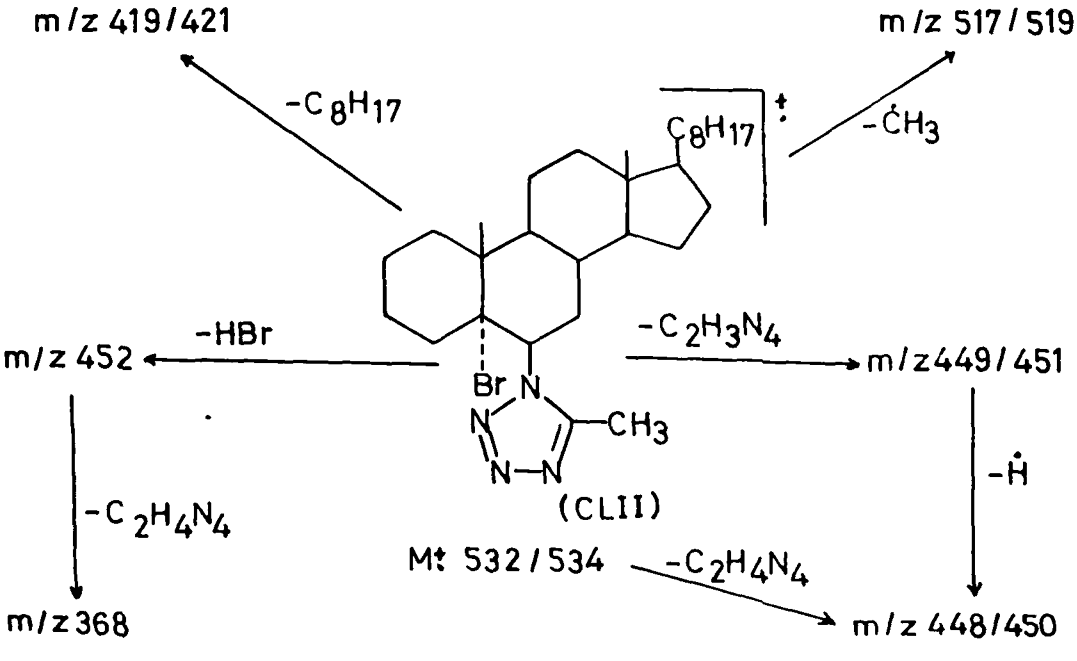
Scheme



Characterization of the compound having m.p. 156°C as 5-bromo-5α-cholest-6β(1')-5'-methyltetrazole (CLII)

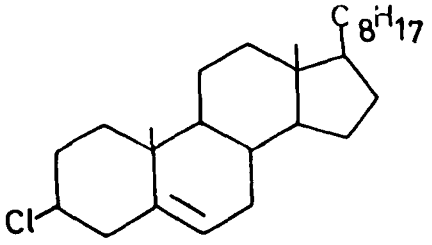
The compound (CLII) with m.p. 156°C was analyzed correctly for $C_{29}H_{49}N_4Br$. The IR spectrum of the compound exhibited bands at 1530, 1460, 1380 (C=N and N=N)^{17} and 740 cm^{-1} (C-Br). The ^{1}H-NMR spectrum of the compound exhibited a broad signal centered at δ 3.1 integrating for one proton and was assigned to C6-αH. A sharp singlet appeared at δ 2.5 integrating for three protons, was assigned to 5'-methyl protons of tetrazole moiety. Other methyl protons appeared at δ1.02 $(C10-CH_3)$, 0.7 $(C13-CH_3)$, 0.96 and 0.81 (other side chain methyl protons). These observations suggested the compound to be 5-bromo-5α-cholest-6β (1')-5'- methyltetrazole (CLII). This structure was further supported by mass spectral studies. The mass spectrum of (CLII) gave the molecular ion peak at m/z 532/534 $(M^{+\cdot})$ followed by other significant peaks at m/z 517/519, 452, 449/451, 448/450, 419/421, 368, and lower mass fragment ion peaks. Formation of some of the significant fragment ions have been rationalized in scheme.

Scheme

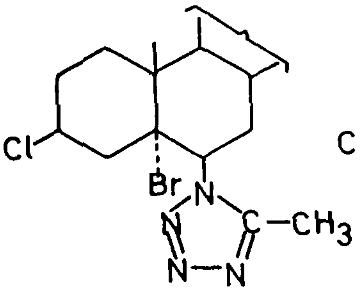


Reaction of 3β -chlorocholest-5-ene (CL) with bromine, acetonitrile and sodium azide in presence of anhydrous aluminium chloride

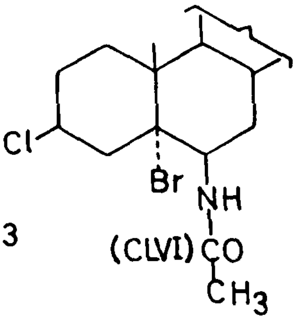
3β -Chlorocholest-5-ene (CL) in acetonitrile, was treated with bromine and sodium azide in presence of anhydrous aluminium chloride. The suspension was stirred and worked up as described earlier. After column chromatography two oily compounds were obtained.



(CL)



(CLIII)

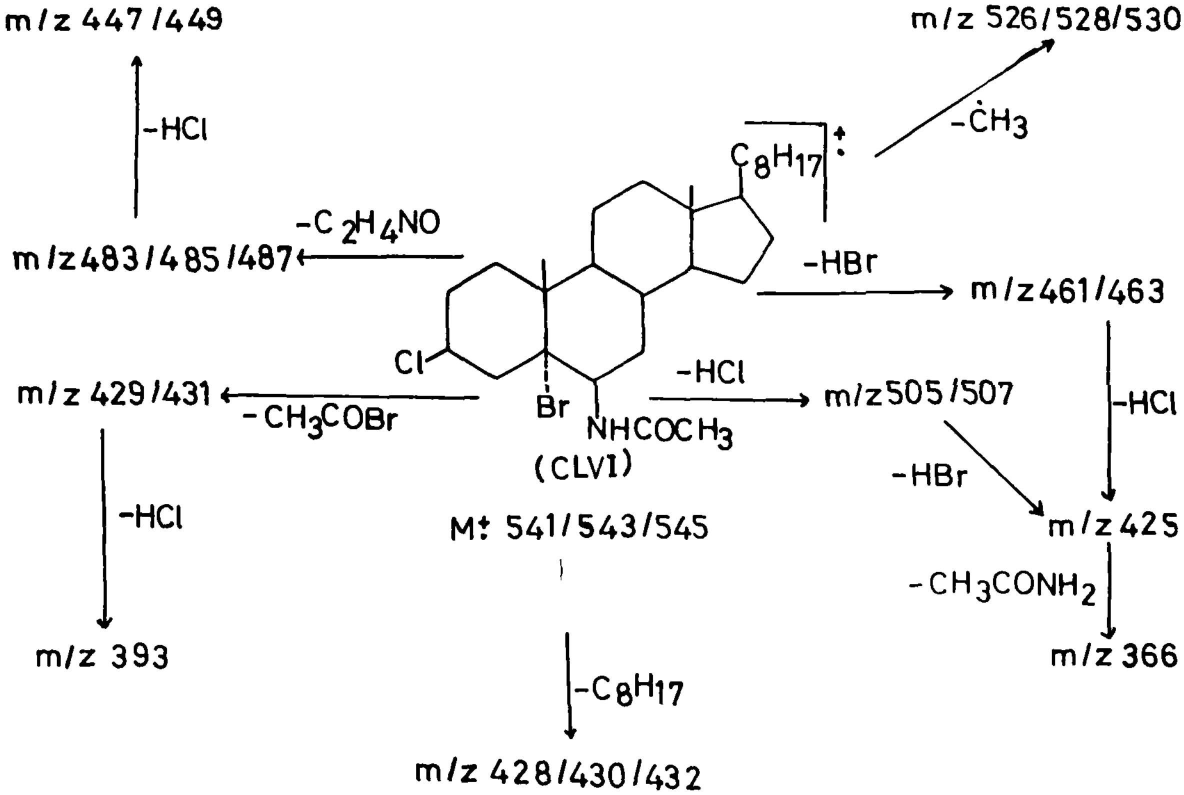


(CLVI)

Characterization of the oily compound (CLVI) as 3β-chloro-5-bromo-6β-acetamido-5α-cholestane

The elemental analysis of the oily compound (CLVI) corresponded to the molecular formula $C_{29}H_{49}NOBrCl$ (positive Beilstein test). The IR spectrum of the compound exhibited bands at 3410 (NH), 1660 (-NH-CO-), 740 and 715 cm^{-1} (C-Cl and C-Br). The ^{1}H-NMR spectrum of the compound exhibited a broad singlet for one proton at δ 5.8 which was assigned to the NH proton (deuterium exchangeable). Two multiplets centered at δ 4.41 and 3.76 integrating for one proton each, were assigned to C_3-αH (W 1/2 = 16 Hz, axial)[39] and C6- αH (W 1/2 = 4.5 Hz, equatorial)[38] respectively. A sharp singlet for three protons appeared at δ 2.01 which was assigned to NH-CO-CH_3. Other methyl protons were observed at δ 1.26 (C10-CH_3), 0.68 (C13-CH_3), 0.95 and 0.82 (other side chain methyl protons). These values suggested the compound to be 3β--chloro-5-α bromo-6β-acetamido-5α-cholestane (CLVI). This structure was further supported by its mass spectral studies. In the mass spectrum of (CLVI), molecular ion peak appeared at m/z 541/543/545 ($M^{+\cdot}$) followed by some other prominent fragment ions at m/z 526/528/530, 505/507, 483/485/487, 461/463, 447/449, 429/431, 428/430/432, 425, 393, 366 and were rationalized in scheme.

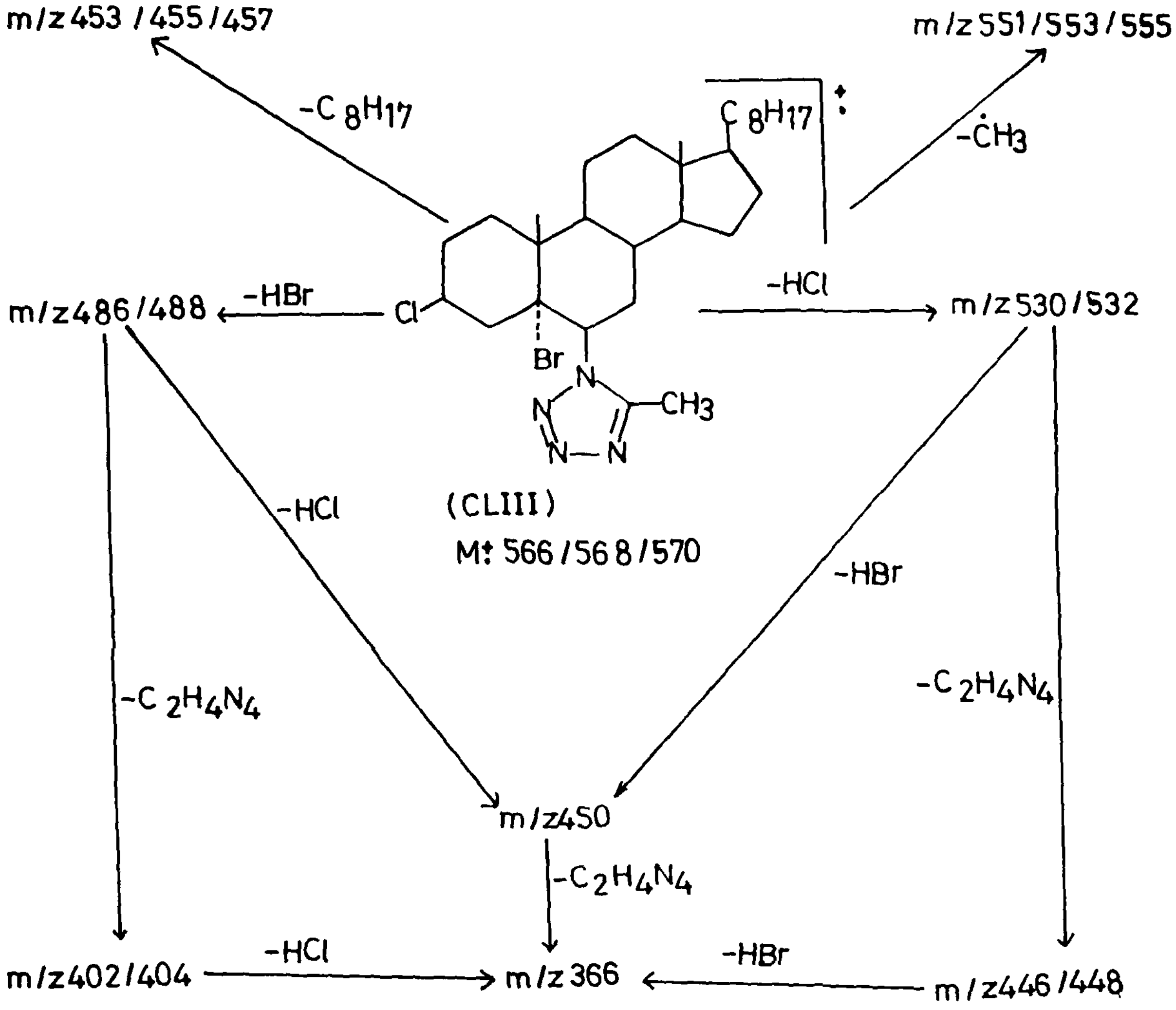
Scheme



Characterization of the second oily compound as 3β -chloro-5-bromo-5-α cholest-6β (1')-5'-methyltetrazole (CLIII)

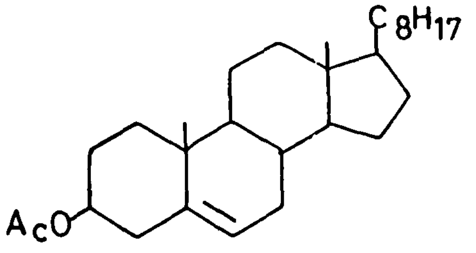
The oily compound (CLIII) was analysed for $C_{29}H_{48}N_4BrCl$ (positive Beilstein test). The IR spectrum of the compound showed bands at 1525, 1460, 1375 (C=N and N=N)[16,17], 740 and 720 cm^{-1} (C-Cl, and C-Br). The ^1H-NMR spectrum of the compound exhibited a multiplet at δ 3.95 for one proton and was assigned to C3-αH (W 1/2 = 16 Hz, axial).[39] Another multiplet for one proton appeared at 3.6 which was assigned to C6-α H (W 1/2 = 4 Hz, equatorial).[39] A sharp singlet integrating for three methyl protons of tetrazole moiety appeared at δ 2.52. Other methyl protons appeared at δ 1.2 (C10-CH_3), 0.7 (C13-CH_3), 0.91 and 0.80 (other side chain methyl protons). The mass spectrum of the compound showed signals at m/z 566/568/570 ($M^{+\cdot}$), 551/553/555, 530/532, 453/455/457, 450, 446/448, 402/404 and 366 as given in scheme. On the basis of above analytical and spectral data, the oily compound was characterized as 3β-chloro-5-bromo-5α-cholest-6β(1')-5'-methyltetrazole (CLIII).

Scheme

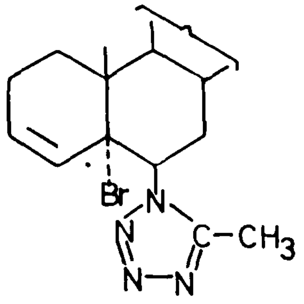


Reaction of 3β - acetoxy cholest-5-ene (CLI) with bromine, acetonitrile and sodium azide in presence of anhydrous aluminium chloride

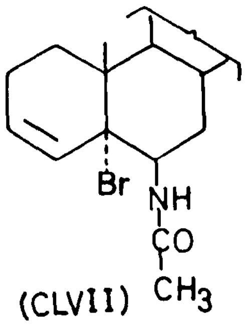
3β - Acetoxycholest-5-ene (CLI) was dissolved in acetonitrile, and was treated with bromine, sodium azide in presence of anhydrous aluminium chloride. After the completion of the reaction, the reaction mixture was worked up as usual and the solvent was removed. The crude product thus obtained was chromatographed over silica gel affording two products having m.ps. 159°C and 178°C.



(CLI)



(CLIV)

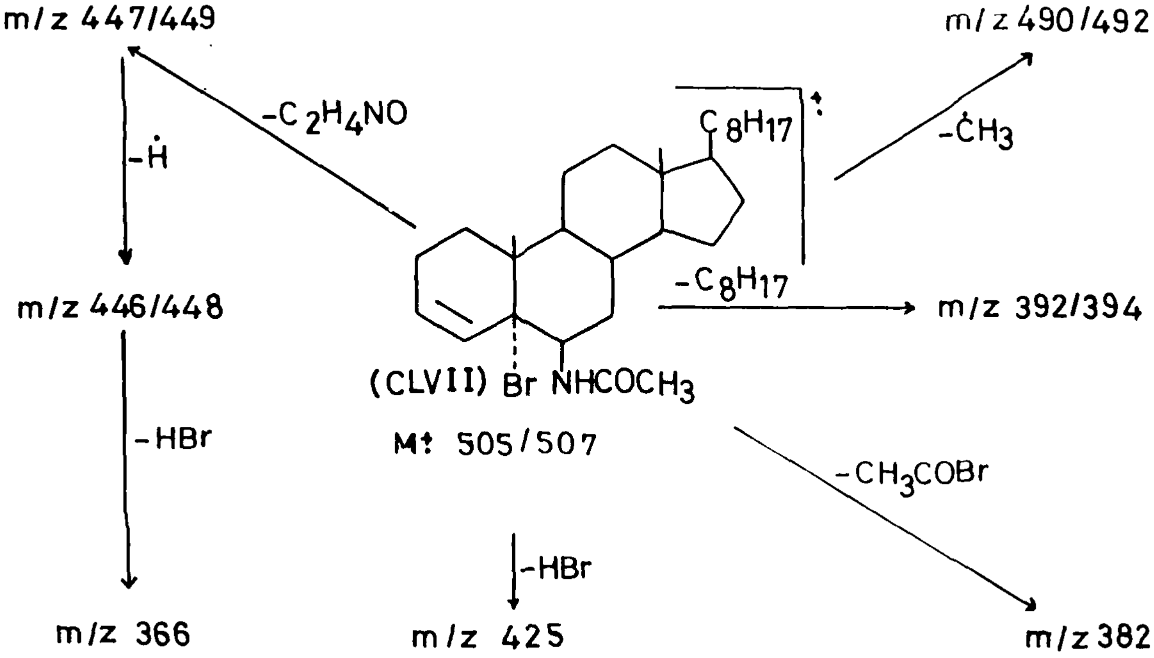


(CLVII)

Characterization of the compound having m.p. 159°C as 5-bromo- 6β - acetamido-5α -cholest-3-ene (CLVII).

The elemental analysis of the compound with m.p. 159°C corresponded to the molecular formula $C_{29}H_{48}NOBr$ (positive Beilstein test). Its IR spectrum exhibited bands at 3430 (NH), 1670 (-NH-CO-), 1625 (C=C), and 730 cm^{-1} (C-Br). The ^1H-NMR spectrum of the compound displayed a broad singlet centered at δ 6.2 (deuterium exchangeable) for one proton and was assigned to NH proton. A broad multiplet for two protons appeared at δ 5.5-5.4 due to C3 and C4 Vinylic protons. A signal at δ 3.2 for one proton was found for C6-αH (W1/2 = 5Hz, equatorial).[39] A sharp singlet for the methyl protons of the amide moiety appeared at δ 2.1. Other methyl protons were observed at δ 1.2 ($C10-CH_3$), 0.7 ($C13-CH_3$), 0.97 and 0.83 (other side chain methyl protons). The mass spectrum of the compound gave molecular ion peak at m/z 505/507 ($M^{+\cdot}$) and some prominent ion peaks at m/z 490/492, 447/449, 446/448, 425,392/394, 382 and 366 as rationalized in scheme. On the basis of these values,the compound with m.p. 159°C was characterized as 5-bromo-6β -acetamido-5α -cholest-3-ene (CLVII).

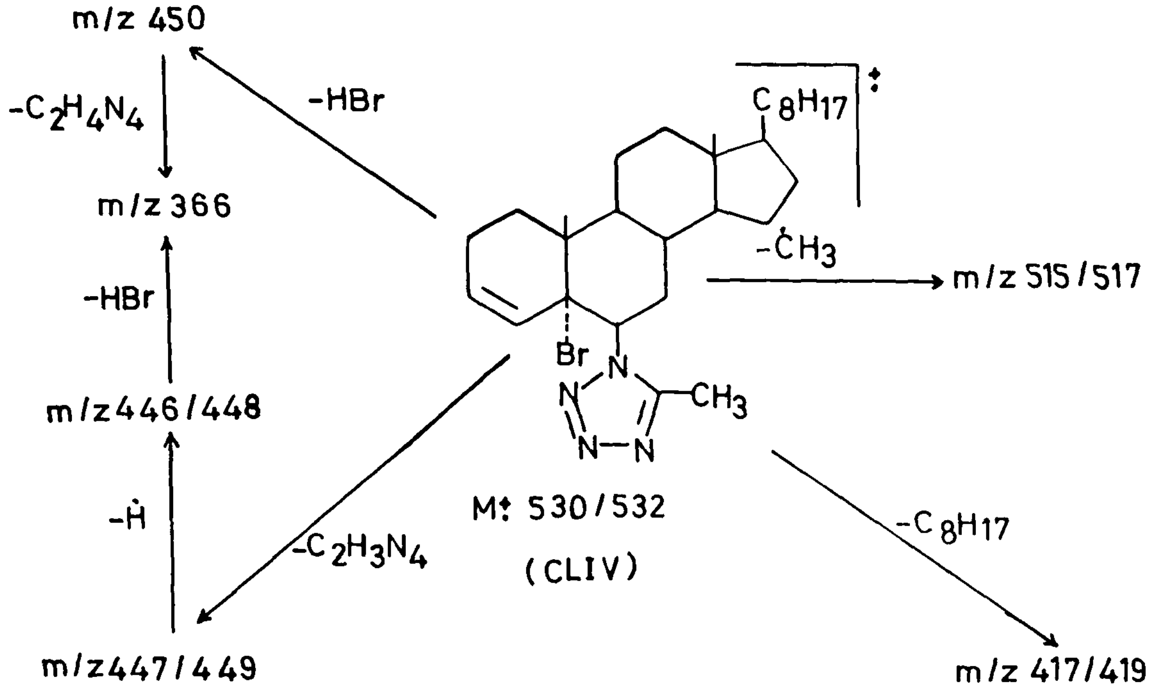
Scheme



Characterization of the compound with m.p. 178°C as 5-bromo-5α - cholest-3-en-6β (1')- 5'-methyltetrazole (CLIV).

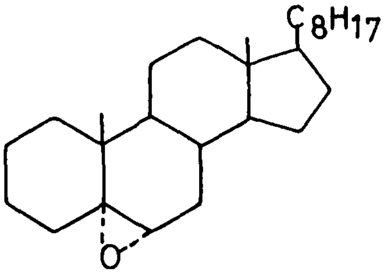
The compound having m.p. 178°C showed the molecular composition $C_{29}H_{47}N_4Br$. The IR spectrum of the compound exhibited bands at 1520, 1465, 1380 (C=N and N=N)[16,17], 1620 (C=C) and 730 cm^{-1} (C-Br). The ^{1}H-NMR spectrum of the compound displayed a broad multiplet at δ 5.53-5.45 integrating for two protons and was assigned to C3 and C4 vinylic protons. A multiplet centered at δ 3.06 for one proton was assigned to C6-αH (W1/2 = 4.5 Hz, equatorial).[39] The methyl protons of tetrazole moiety appeared at δ 2.56. Other methyl protons were observed at δ 1.15 (C10-CH_3), 0.71 (C13-CH_3), 0.92 and 0.80 (other side chain methyl protons). In the mass spectrum the molecular ion peak observed at m/z 530/532 ($M^{+\cdot}$) and other prominent ion peaks were appeared at m/z 515/517, 447/449, 446/448, 450, 417/419 and 366 as given in scheme. On the basis of these data, the compound having m.p. 178°C was characterized as 5-bromo-5α- cholest-3-en- 6β (1') -5'-methyltetrazole (CLIV).

Scheme

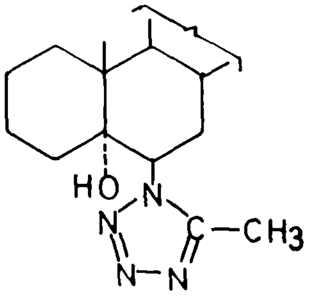


Reaction of 5,6 α-epoxy-5α-cholestane (CLVIII) with acetonitrile and sodium azide in presence of anhydrous aluminium chloride.

5,6 α-Epoxy-5α-cholestane (CLVIII) was taken in dry acetonitrile and were added anhydrous aluminium chloride and sodium azide. The mixture was stirred for 6 hrs at room temperature. After completion of reaction, the solvent was evaporated and the residue was extracted with chloroform. The organic layer was washed with water, aqueous solution of soidum bicarbonate (5%) and again with water, and dried. Removal of chloroform left an oil which was chromatographed on a silica gel column and a compond with m.p. 181°C was obtained.



(CLVIII)

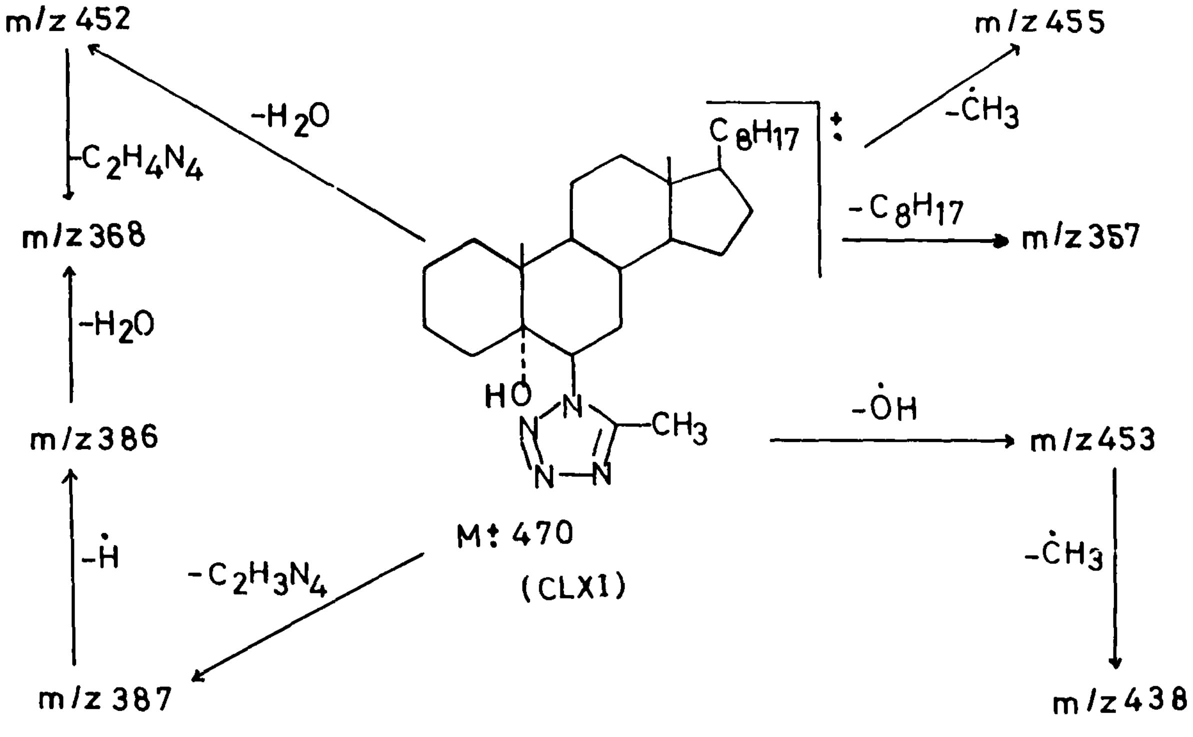


(CLXI)

Characterization of the compound meting at 181°C as 5-hydroxy-5 α-cholest-6β (1')-5'-methyltetazole (CLXI).

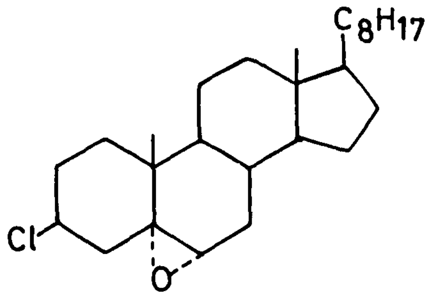
The elemental analysis of the compound, m.p.181°C corresponded to the molecular formula $C_{29}H_{50}N_4O$. The IR spectrum of the compound exhibited bands at 3300 (OH), 1510, 1460 and 1375 cm^{-1} (C=N, N=N)[16,17]. These values suggested the presence of tetrazole moiety. The ^{1}H -NMR spectrum of the compound displayed a multiplet for one proton centered at δ 4.21 which was assigned to C6-α H (W1/2 = 5Hz, equatorial).[39] A sharp singlet integrating for three protons appeared at δ 2.57 due to the methyl protons of the tetrazole moiety. The hydroxyl proton (exchangeable with deuterium) appeared at δ 2.11 as a broad singlet. Other methyl protons were observed at δ 1.05 (C10-CH_3), 0.67 (C13-CH_3), 0.95 and 0.84 (other side chain methyl protons). The mass spectrum of the compound showed the molecular ion peak at m/z 470 ($M^{+\cdot}$). Some other characteristic fragment ion peaks were recorded at m/z 455, 453, 452, 387, 386, 368, 357 and 438. The fragmentation pattern of these ions were given in scheme. On the basis of above evidences, the compound having m.p. 181°C was characterized as 5-hydroxy-5α -cholest-6β (1')-5'-methyltetrazole (CLXI).

Scheme

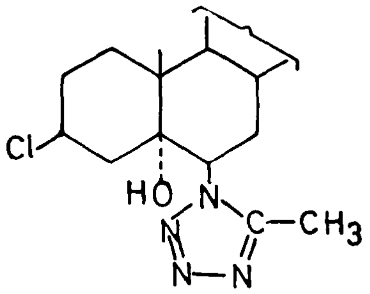


Reaction of 3β-chloro-5,6α-epoxy-5α-cholestane (CLIX) with acetonitrile and sodium azide in the presence of anhydrous aluminium chloride.

To a solution of 3β-chloro-5,6α- epoxy 5α-cholestane (CLIX) in acetonitrile were added anhydrous aluminium chloride and sodium azide. After usual work up of the reaction mixture and chromatography over silica gel, a compound having m.p. 174° was isolated.



(CLIX)

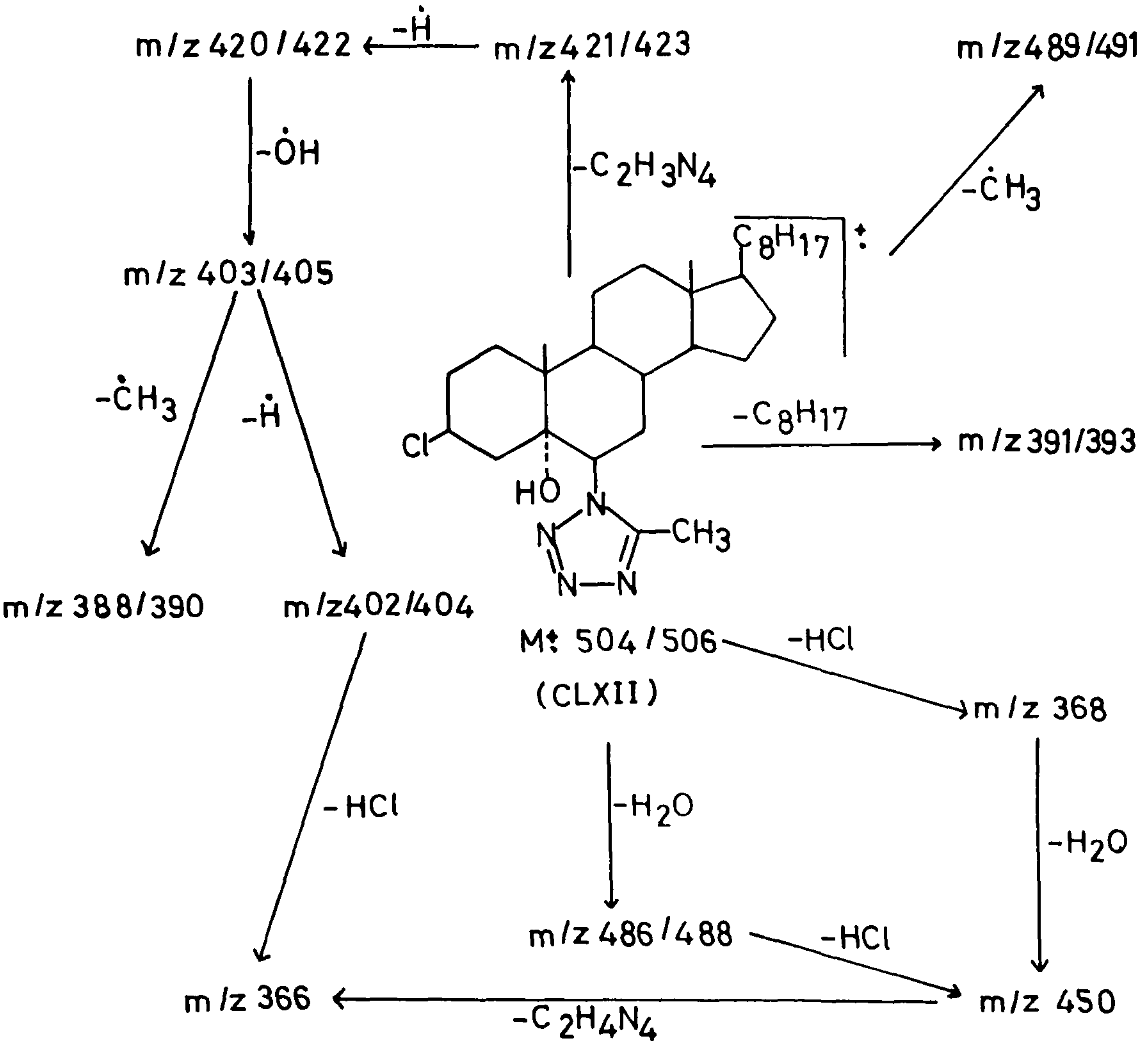


(CLXII)

Characterization of the compound with m.p. 174°C as 3β--chloro-5-hydroxy-5α-cholest- 6β (1')-5'-methyltetrazole (CLXII).

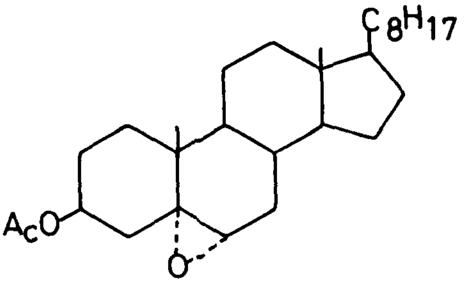
The compound having m.p. 174°C showed the molecular composition $C_{29}H_{49}N_4OCl$ (positive Beilstein test). The IR spectrum of the compound exhibited bands at 3400 (OH), 1515, 1475, 1380 (C=N, N=N)[16,17] and 760 cm^{-1} (C-Cl). The ^1H-NMR spectrum of the compound displayed two multiplets for one proton each at δ 4.46 and 4.22 and were assigned to C3-α H (W 1/2=16Hz, axial)[39] and C6-α H (W 1/2=4.5Hz, equatorial)[39] respectively. Signal for the methyl protons of tetrazole moiety appeared at δ 2.62 as a sharp singlet. The hydroxyl proton (exhangeable with deuterium) appeared at δ 2.28 as a broad singlet. Other methyl protons were observed at δ 1.08 (C10-CH_3), 0.76 (C13-CH_3), 0.95 and 0.84 (other side chain methyl protons). On the basis of above values, the compound melting at 174°C was characterized as 3β - chloro-5-hydroxy-5α-cholest-6β (1')-5'-methyltetrazole (CLXII). This structure was further supported by mass spectral studies. The mass spectrum showed the molecular ion peak at m/z 504/506 ($M^{+\cdot}$) and other important fragment ions peaks at m/z 489/491, 486/488, 468, 450, 421/423, 420/422, 403/405, 402/404, 391/393, 388/390 and 366 as shown in scheme.

Scheme

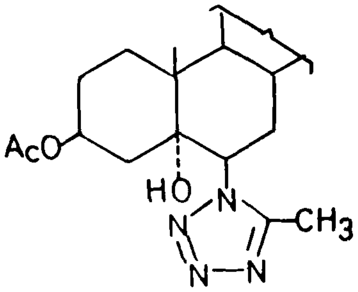


Reaction of 3β-acetoxy-5,6α-epoxy-5α-cholestane (CLX) with acetonitrile and sodium azdie in presence of anhydrous aluminium chloride.

To a stirred solution of 3β -acetoxy-5,6α -epoxy-5α-cholestane (CLX) in acetonitrile was added sodium azide and anhydrous aluminium chloride. After usual work up and column chromatography a compound having m.p. 221°C was isolated.



(CLX)

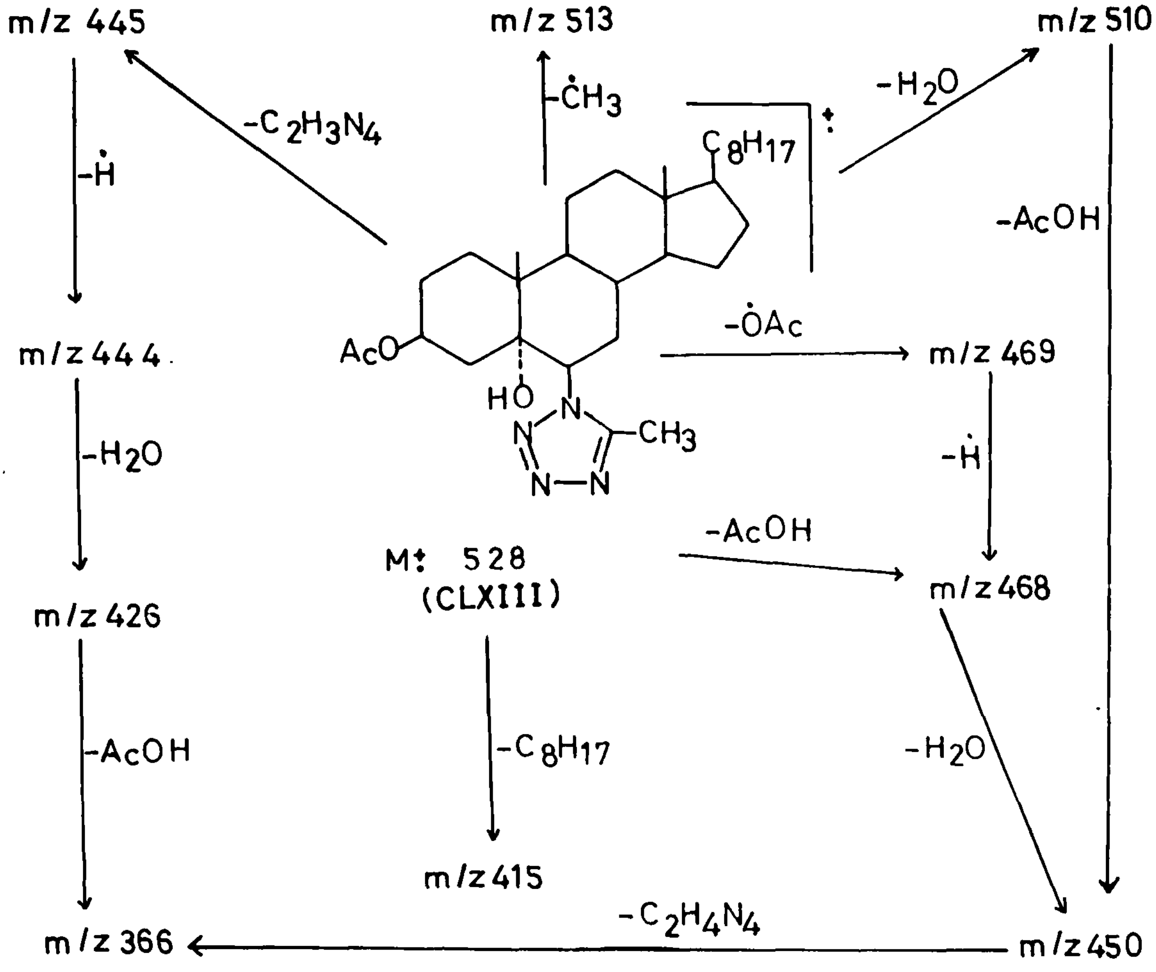


(CLXIII)

Characterization of the compound having m.p.221°C as 3β--acetoxy-5-hydroxy-5α -cholest-6β (1')-5'-methyl tetrazole (CLXIII).

The elemental analysis for the compound having m.p. 221°C corresponded to the molecular composition $C_{31}H_{52}N_4O_3$. Its IR spectrum exhibited bands at 3375 (OH), 1720 (CH_3COO), 1520, 1465, 1375 (C=N, N=N)[16,17] 1250 and 1030 cm^{-1} (C-O). The ^1H-NMR spectrum of the compound showed two multiplets for one proton each at δ 5.1, 4.23 and were assigned to C3-αH (W 1/2=16 Hz, axial)[39] and C6-αH (W 1/2=4Hz, equatorial)[39] respectively. A sharp singlet exhibited at δ 2.57 integrating for three protons was due to the methylprotons of the tetrazole moiety. The hydroxyl proton (exchangeable with deuterium) appeared at δ 2.24 as a broad singlet. The methyl protons of the acetoxy group appeared at δ 2.01 as a sharp singlet. Other methyl protons were observed at δ 1.21 ($C10-CH_3$), 0.72 ($C13-CH_3$), 0.91 and 0.83 (other side chain methyl protons). The mass spectrum of the compound gave molecular ion peak at m/z 528 ($M^{+\cdot}$) followed by other important fragment ion peaks at m/z 513, 510, 469, 468, 450, 445, 444, 426, 415 and 366 as shown in scheme. On the basis of all these data, the compound having m.p, 221°C was characterized as 3β-acetoxy-5-hydroxy-5α - cholest-6β (1')-5'-methyltetrazole (CLXIII).

Scheme



EXPERIMENTAL

Reaction of cholest-5-ene (CXLIX) with bromine, acetonitrile and sodium azide: 5-Bromo-6β-acetamido-5α-cholestane (CLV) and 5-bromo-5α-cholest-6β (1')-5'-methyltetrazole (CLII).

Cholest-5-ene (2g; 5.4 m mol) was taken in acetonitrile (40 ml) and to this was added anhydrous aluminium chloride (2g, 15.0 m mol). The suspension was cooled in ice-salt bath, while being stirred magnetically when the content has cooled down to 0°C, bromine (0.8g; 50m mol) then sodium azide (1.5g; 23.2 m mol) were added successively. The stirring was continued for 2 hrs at 0°C and again 2 hrs at room temperature. The prgoress of reaction was monitored by TLC. The solvent was removed under reduced pressure and residue was extracted with chloroform. Chloroform layer was washed with water, sodium bicarbonate (5%) again with water and dried (anhyd. Na_2SO_4). Chloroform was evaporated under reduced pressure and the residue was chromatographed over silica gel. Elution with light petroleum ether/ether (5:1) provided a solid compound which was recrystallized from acetone to yield 5-bromo-6β-acetamido-5α-cholestane (CLV) (0.45g; 0.88 m mol), m.p. 172°C.

Analysis found : C, 68.4; H, 9.9; N, 2.6

$C_{29}H_{50}NOBr$ required : C, 68.50; H, 9.84; N, 2.75%

IR : ν max 3420 (NH), 1670 (-CO-NH-) and 730 cm^{-1} (C-Br).

^{1}H-NMR : δ 5.8 (br, 1H, NH), 3.2 (m, 1H, W 1/2=4.5 Hz, C6-α H)[39], 2.1 (s, 3H, -CO-CH_3), 1.2 (C10-CH_3), 0.72 (C13-CH_3), 0.97 and 0.84 (other methyl protons).

MS : $M^{+\cdot}$ 507/509 (5.40/5.38; C_{29} H_{50} NO Br), 492/404 (6.10/6.09), 449/451 (8.40/8.38), 448/450 (10.90/10.99), 428 (9.50), 427 (12.25, C_{29} H_{49} NO), 394/396 (7.60/7.59), 385 (10.25), 368 (20.25; C_{27} H_{44}), 367/369 (6.50/6.48), 353/355 (9.60/9.57), 352/354 (13.75/13.72), 338/340 (8.40/8.39), 308/310 (10.50/10.47), 307/309 (12.00/11.97), 294/296 (8.50/8.49), 293/295 (10.00/9.98), 287 (11.00), 286 (14.20) 280/282 (10.20/10.19), 279/281 (13.10/13.09), 273 (12.10), 272 (15.25), 270 (4.80), 259 (9.60), 258 (12.25), 251 (10.00), 250 (8.20), 249 (5.00), 246 (5.00), 245 (10.25), 244 (5.00), 218 (4.80), 217 (4.80), 189 (6.10), 188 (3.80), 177 (4.70), 176 (8.10), 175 (4.60), 174 (3.25), 164 (4.50), 163 (9.60), 162 (7.25), 161 (4.75), 160 (3.20), 158 (5.00), 147 (10.20), 146 (7.45), 145 (10.20), 144 (4.00), 135 (11.75), 134 (7.60), 133 (5.00), 130 (13.70), 129 (6.00), 121 (10.50), 120 (80.00), 119 (9.75), 118 (11.60), 117 (6.75), 106 (16.75), 105(7.20), 104 (17.20), 103 (9.00), 95 (36.80), 94 (18.40), 93 (36.80), 92 (10.20), 91 (23.00), 90 (8.50), 83 (10.30), 82 (18.10), 81 (29.90), 80 (18.60), 79 (30.10), 78 (12.0), 77 (12.30), 71 (12.30), 70 (6.10), 69 (26.20), 68 (12.50), 67 (30.90), 56 (35.70), 55 (14.00), 54 (47.60), 53 (10.25), 45 (40.10), 44 (30.75), 43 (100.00), 42 (58.25), 41 (14.30), 40 (41.25).

Further elution with light petroleum ether/ether (3:1) furnished a solid which was recrystallized from acetone to afford 5-bromo-5 α -cholest- 6β -(1')-5'-methyltetrazole (CLII) (1.1g, 2.06 m mol), m.p. 156^{o}C.

Analysis found : C, 65.39; H, 9.2; N, 10.4

C_{29} H_4 Br requires : C, 65.290; H, 9.19; N, 10.54%

IR : ν max 1530, 1460, 1380 (C=N, N=N)^{16,17} and 740 cm^{-1} (C-Br).

^{1}H-NMR : δ3.1 (m, 1H, W1/2 = 5Hz, C6-α H)^{39}, 2.5 (s, 3H, -N-CN-CH_3), 1.02 (C10-CH_3), 0.7 (C13-CH_3), 0.96 and 0.81 (other methyl protons).

MS : $M^{+\cdot}$ 532/534 (5.20/5.18; C_{29} H_{49} H_4 Br), 517/519 (5.00/4.99), 453 (10.00), 452 (12.75; C_{29} H_{48} N_4), 449/451 (6.40/6.38), 448/450 (9.50/9.47; C_{27} H_{45} Br), 438 (11.20), 419/421 (5.40/5.37), 392/394 (8.30/8.28), 391/393 (9.75/9.73), 378/380 (8.70/8.69), 377/379 (13.10/13.08), 368 (14.25; C_{27} H_{44}), 312 (12.80), 311 (14.00), 308/310 (9.75/9.74), 307/309 (11.90/11.88), 305 (9.00), 298 (10.00), 297 (13.30), 294/296 (11.20/11.18), 293/295 (15.30/15.29), 270 (3.80), 269 (5.40), 268 (7.45), 267 (5.00), 252 (5.50), 251 (10.25), 250 (6.10), 248 (4.80), 246 (4.60), 245 (4.60), 217 (4.10), 216 (10.25), 215 (4.10), 189 (5.10), 188 (7.50), 187 (3.80), 178 (3.50), 177 (5.75), 175 (6.20), 174 (5.00), 173 (3.10), 162 (3.25), 161 (5.75), 160 (7.20), 159 (4.20), 158 (10.40), 147 (9.80), 146 (5.50), 145 (9.80), 135 (10.00), 134 (6.10), 133 (7.50), 130 (14.10), 129 (8.50), 121 (17.75), 120 (10.00), 119 (6.20), 118 (14.70), 106 (24.25), 105

(12.50) 104 (19.30), 103 (7.20), 95 (42.10), 94 (23.75), 93 (38.50), 92 (10.00), 91 (25.50), 84 (8.40), 83 (12.10), 82 (19.00), 81 (31.00), 80 (19.80), 79 (34.30), 77 (12.40), 71 (12.40), 70 (7.25), 69 (29.00), 68 (10.25), 67 (32.10), 58 (24.30), 57 (30.10), 56 (15.75), 55 (10.25), 54 (47.20), 45 (30.25), 44 (10.00), 43 (27.25), 42 (100.00), 41 (41.00), 40 (17.25).

Reaction of 3β -chlorocholest-5-ene (CL) with bromine, acetonitrile and sodium azide: 3β -Chloro-5-bromo-6β -acetamido-5α -cholestane (CLVI) and 3β -chloro-5-bromo-5α -cholest-6β(1')-5' - methyltetrazole (CLIII).

To a suspension of 3β -chlorocholest-5-ene (2g, 4.9 m mol) in acetonitrile (40 ml) was added anhydrous aluminium chloride (2g, 15.0 m mol). The suspension was cooled in ice-salt bath with continuous stirring. To this mixture, bromine (0.8g; 5.0 m mol) and sodium azide (1.5g; 23.1 m mol) were added successively and the stirring continued at 0°C and room temperature for 2 hrs each. After the completion of reaction, it was worked up as described earlier and chromatographed over silica gel. Elution with light petroleum ether/ether (10:1) provided 3β-chloro-5-bromo-6β-acetamido-5α--cholestane (CLVI), (0.5g; 0.92 m mol) as an oil.

Analysis found : C, 64.1; H, 9.1; N, 2.5

$C_{29}H_{49}NOBrCl$ requires : C, 64.14, H, 9.09, N, 2.58%

IR : ν max 3410 (NH), 1860 (NH-CO-CH_3) and 715 cm^{-1} (C-Cl and C-Br).

^1H-NMR : δ4.41 (mc, 1H, W 1/2 = 16 Hz, C3- α H)[40], 3.76 (mc, 1H, W 1/2 = 4.5 Hz, C6- α H), 2.01 (s, 3H, -CO-CH_3), 1.26 (C10-CH_3), 0.68 (C13-CH_3), 0.95 and 0.82 (other methyl protons).

MS : $M^{\dagger}$ 541/543/545 (3.80/4.92/1.20; $C_{29}H_{49}$NOBrCl), 526/528/530 (4.90/6.35/1.54), 505/507 (7.10/7.09) 483/485/487 (6.00/7.77/1.90), 462/464 (6.20/2.00), 461/463 (8.50/2.81), 447/449 (7.40/7.37), 446/448 (9.50/9.48), 429/431 (8.30/2.74), 428/430/432 (4.00/5.18/1.23), 426 (6.10), 425 (20.25; $C_{29}H_{47}$NO), 393 (14.40), 366 (24.30), 351 (16.00), 319 (4.50), 318 (5.10), 317 (4.50), 308 (4.50), 307 (5.00), 306 (6.10), 305 (4.50), 304 (17.70), 303 (6.00), 256 (3.80), 255 (3.80), 254 (5.20), 250 (11.30), 249 (6.30), 228 (5.00), 226 (12.20), 225 (14.10), 212 (13.75), 211 (15.00), 198 (5.00), 197 (5.00), 176 (3.40), 175 (5.10), 1745 (6.60), 173 (5.30), 172 (4.10), 160 (7.50), 159 (6.10), 158 (5.00), 156 (6.20), 149 (9.00), 148 (7.10), 147 (5.25), 146 (10.25), 145 (4.80), 134 (8.70), 133 (6.00), 132 (10.00), 131 (5.00), 130 (6.30), 120 (11.20), 119 (8.00), 118 (11.30), 106 (10.00), 105 (7.50), 104 (17.50), 103 (15.10), 102 (15.00), 94 (30.00), 93 (11.20), 92 (27.50), 91 (20.00), 90 (15.75), 84 (14.75), 82 (29.25), 81 (27.25), 80 (29.30), 79 (27.50), 78 (20.00), 77 (10.50), 76 (7.50), 70 (12.50), 69 (6.30), 68 (22.50), 67 (8.70), 66 (20.00), 56 (32.20), 55 (10.00), 54

(30.25), 52 (24.00), 44 (35.75), 43 (24.80), 42 (100.00), 41 (52.20), 40 (15.50).

Further elution with light petroleum ether/ether (5:1) afforded 3β -chloro-5-bromo-5α-cholest-6β (1')-5'-methyl-tetrazole (CLIII), (1.0g; 1.76 m mol) as an oil.

Analysis found : C, 61.3; H, 8.5; N, 9.8

$C_{29}H_{48}N_4BrCl$ requires : C, 61.31, H, 8.52, N, 9.86%

IR : ν max 1525, 1460, 1375 (C=N, N=N)[16,17], 740 and 720 cm^{-1} (C-Cl and C-Br).

^1H-NMR : δ 3.95 (mc, 1H, W 1/2 = 16 Hz, C3-αH)[39], 3.6 (mc, 1H, W 1/2 = 4 Hz, C6-αH)[40], 2.52 (s, 3H, -N-CN-CH_3), 1.2 (C10-CH_3), 0.7 (C13-CH_3), 0.91 and 0.80 (other methyl protons).

MS : $M^{+\cdot}$ 566/568/570 (3.50/4.51/1.08; $C_{29}H_{48}N_4BrCl$), 551/553/555 (4.90/6.35/1.54), 531/533 (6.50/6.45), 530/532 (7.20/7.18), 483/485/487 (5.20/6.74/1.61), 482/484/486 (6.75/8.75/2.13), 472/474 (8.00/2.64, 453/455/457 (3.75/4.85/1.17), 452 (9.25), 451 (3.75), 450 (13.00), 446/ 448 (8.80/8.78), 402/404 (10.25/3.39), 366 (17.20), 350 (12.75), 344 (7.50), 334 (5.10), 318 (5.10), 317 (5.25), 3.08 (5.00), 307 (4.50), 306 (4.50), 305 (9.20), 304 (6.20), 303 (10.50), 257 (4.80), 256 (7.30), 255 (4.80), 254 (5.20), 250 (14.25), 249 (5.40), 226 (8.40), 225 (9.75), 212 (10.00), 211 (11.25), 188 (5.00), 187 (5.00), 186 (3.25), 160 (17.25), 159 (8.50), 158 (5.00), 156 (10.25), 147 (9.00), 146 (9.10), 134 (10.00), 133 (8.40), 132 (5.25), 131 (5.25), 130 (7.70), 129 (6.10), 120 (10.25), 119 (9.60), 118 (11.30), 117 (10.90),. 105 (12.25), 104 (20.75), 103 (4.80), 102 (3.75), 96 (34.20), 95 (39.50), 94 (42.00), 93 (14.30), 92 (30.50), 91 (12.75), 84 (15.30), 83 (17.00), 82 (25.00), 81 (20.25), 80 (25.50), 79 (30.00), 78 (17.75), 77 (25.30), 76 (7.60), 69 (6.30), 68 (29.50), 67 (17.20), 66 (9.60), 65 (20.25), 64 (10.00), 55 (32.25), 54 (10.74), 53 (19.80), 52 (40.30), 45 (30.25), 44 (10.00), 43 (35.35), 42 (100.00), 41 (42.00), 40 (12.20).

Reaction of 3β-acetoxycholest-5-ene (CLI) with bromine acetonitrile and sodium azide: 5-Bromo-6β-acetamido-5α-cholest-3-ene **(CLVII) and** 5-bromo-5α-cholest-3-en-6β **(1')-5' methyltetrazole (CLIV).**

The 3β-acetoxycholest-5-ene (2g, 4.67 m mol) was dissolved in acetonitrile (40 ml) and to this mixture was added anhydrous aluminium chloride (2g; 15.0 m mol). The suspension was cooled to 0°C in an ice-salt bath while being stirred magnetically. To this suspension, bromine (0.8g; 5.0m mol) and sodium azide (1.5g; 23.1 m mol) were added successively. The stirring was continued for 2 hrs at 0°C and 2 hrs at room temperature. After the completion of the reaction, the mixture was worked-up as usual and chromatographed over silica gel. Elution with light petroleum ether/ether (5:1) provided a solid compound which was recrystallized from acetone to yield 5-bromo-6β-acetamido-5α-cholest-3-ene (CLVII) (0.3g; 0.592 m mol) m.p. 159°.

Analysis found : C, 68.7; H, 9.5; N, 2.8

$C_{29}H_{48}NOBr$ requires : C, 68.75; H, 9.55; N, 2.76%

IR : ν max 3430 (NH), 1670 ($-NH-CO-CH_3$), 1625 (C=C) and 730 cm^{-1} (C-Br).

^1H-NMR : δ6.2 (br, 1H, NH), 5.5-5.4 (mc, 2H, C3 and C4 vinyl protons), 3.2 (mc, 1H, W 1/2 = 5Hz, C6-αH)[39], 2.1 (s, 3H, $-CO-CH_3$); 1.2 ($C10-CH_3$), 0.7 ($C13-CH_3$), 0.97 and 0.83 (other methyl protons).

MS : $M^{+\cdot}$ 505/507 (6.75/6.73; $C_{29}H_{48}NOBr$), 490/192 (5.00/4.97), 447/449 (8.75/8.74), 446/448 (9.80/9.77), 426 (10.30), 425 (9.60, $C_{29}H_{47}NO$), 411 (14.25), 392/394 (5.75/5.72), 383 (11.30), 382 (14.25), 368 (12.20), 366 (24.40; $C_{27}H_{42}$), 332 (4.40), 331 (6.20), 330 (7.50), 329 (5.00), 328 (9.20), 327 (4.10), 302 (4.20), 301 (7.50), 300 (4.20), 276 (10.25), 275 (12.30), 274 (8.20), 273 (4.10), 268 (3.50), 267 (3.50), 263 (2.50), 262 (2.10), 255 (4.50), 254 13.75), 246 (5.75), 245 (10.20), 244 (5.00), 228 (8.10), 227 (9.75), 226 (9.75), 225 (13.10), 214 (9.10), 213 (11.70), 212 (10.00), 211 (14.10), 200 (6.40), 199 (9.60), 198 (7.00), 197 (4.30), 188 (7.20), 187 (6.90), 186 (6.50), 185 (6.90), 184 (4.00), 174 (7.30), 173 (5.75), 172 (5.75), 171 (3.60), 162 (4.90), 161 (4.90), 160 (7.60), 159 (5.00), 158 (8.30), 157 (7.10), 157 (7.10), 146 (10.25), 145 (13.00), 144 (10.25), 143 (6.00), 142 (3.75), 134 (9.30), 132 (12.50), 130 (10.00), 120 (13.30), 119 (11.25), 118 (10.10), 111 (4.80), 106 (15.75), 105 (10.25), 104 (17.00), 103 (6.60), 94 (27.90), 93

(20.25), 92 (35.10), 91 (10.75), 89 (18.75), 88 (10.20), 82 (10.10), 81 (35.00), 80 (10.25), 79 (35.90), 78 (9.25), 70 (19.25), 69 (21.00), 68 (10.10), 676 (27.20), 66 (27.10), 65 (18.80), 59 (14.10), 58 (17.25), 56 (32.25), 54 (37.00), 53 (42.10), 52 (10.00), 45 (12.20), 44 (35.10), 43 (100.00), 42 (37.25), 41 (35.25), 40 (42.00).

Further elution with light petroleum ether/ ether (3:1) furnished a solid compound, which was recrystallized from acetone to afford 5-bromo-5 α -cholest-3-en-6 β (1')-5'-methyltetrazole (CLIV) (1.2g; 2.26 m mol) m.p. 178^{o}C.

Analysis found : C, 65.5; H, 8.9; N, 10.5

C_{29} H_{47} N_4 Br requires : C, 65.52; H, 8.91; N, 10.54%

IR : ν max 1520, 1465, 1380 (C=N, N=N)[16,17], 1620 (C=C) and 730 cm^{-1} (C-Br).

^{1}H-NMR : δ 5.53-5.45 (mc, 2H, C3 and C4-vinyl protons), 3.06 (mc, 1H, W 1/2 = 4.5 Hz, C6-αH)[39], 2.56 (s, 3H, -N-CN-CH_3), 1.15 (C10-CH_3), 0.71 (C13-CH_3), 0.92 and 0.80 (other methyl protons).

MS : $M^{+\cdot}$ 530/532 (5.75/5.73; C_{29} H_{47} N_4 Br), 515/517 (6.00)/5.98), 451 (7.20), 450 (8.30; C_{29} H_{46} N_4), 447/449 (8.50/ 8.47), 446/448 (10.00/9.98), 436 (14.25), 417/419 (5.50/5.48), 368 (17.70), 367 (8.10), 366 (27.20; C_{27} H_{42}), 330 (7.50), 329 (5.00), 328 (3.75), 301 (3.30), 300 (6.40), 299 (3.30), 298 (3.70), 276 (4.00), 275 (8.20), 274 (6.10), 273 (5.00), 268 (5.00), 267 (5.00), 266 (9.60), 265 (4.75), 262 (3.50), 255 (5.40), 254 (10.10), 253 (7.30), 252 (4.25), 246 (6.20), 245 (5.00), 240 (5.30), 239 (10.25), 238 (5.10), 228 (7.40), 227 (10.00), 226 (8.10), 225 (13.30), 214 (8.30), 213 (10.10), 212 (8.75), 211 (14.60), 210 (6.50), 202 (5.40), 201 (5.40), 200 (6.75), 199 (4.80), 188 (6.40), 187 (6.20), 186 (6.20), 185 (4.80), 184 (3.25), 175 (7.40), 174 (6.10), 173 (6.10), 172 (4.25), 171 (4.20), 162 (5.20), 161 (5.90), 159 (6.75), 158 (7.20), 157 (6.10), 156 (3.75), 155 (3.50), 146 (10.50), 145 (14.25), 144 (17.00), 143 (8.40), 133 (15.25), 132 (19.30), 131 (10.00), 130 (13.70), 129 (4.75), 120 (21.20), 119 (9.60), 118 (10.75), 117 (5.60), 111 (5.60), 110 (5.50), 106 (17.30), 105 (5.40), 104 (19.25), 103 (7.10), 94 (27.25), 93 (34.50), 92 (14.00), 91 (8.10), 89 (15.00), 88 (7.40), 84 (17.80), 83 (20.00), 82 (19.75), 81 (33.10), 80 (20.10), 79 (33.50), 69 (16.60), 68 (10.50), 67 (19.20), 66 (20.25), 65 (6.00), 61 (5.00), 56 (30.00), 55 (12.25), 54 (35.00), 53 (9.75), 44 (41.20), 43 (100.00), 42 (10.25), 41 (47.00), 40 (14.00).

5,6 α-Epoxy-5 α -cholestane (CLVIII)

Cholest-5-ene (6g) in chloroform (40 ml) was treated with a solution of perbenzoic acid (1.1 mol equivalent) in chloroform and left at -8°C for 20 hrs. The reaction was washed successively with ice-cold aqueous soidum bicarbonate solution (5%), water, aqueous sodium thiosulphate solution (5%) and again with water and dried over anhydrous sodium sulphate. Evaporation of the solvent yielded (CLVIII) as an oil which was crystallized from acetone as needles (4.5g), m.p. 76°C (reported[40], m.p. 76°).

Reaction of 5,6 α -epoxy-5 α -cholestane (CLVIII) with acetonitrile and sodium azide: 5-Hydroxy-5 α -cholest-6β (1') - 5'-methyltetrazole (CLXI).

To a stirred solution of 5,6 α -expoxy-5 α -cholestane (CLVIII) (2.0g; 5.18 m mol) in acetonitrile (20 ml) were added anhydrous aluminium chloride (catalytic amount) and sodium azide (equimolar). Stirring was continued for 6 hrs at room temperature. After completion of the reaction, the solvent was evaporated at reduced pressure and the residue was extracted with chloroform. The organic layer was washed with water, 5% aqueous solution of sodium bicarbonate and again with water, and dried. Removal of chloroform left an oil which was chromatographed on a silica gel (40 g) column.

Elution with light petroleum ether/ether (5:1) provided a solid compound which was recrystallized from acetone to yield, 5-hydroxy-5 α -cholest-6 β (1')-5'-methyltetrazole (CLXI), (1.6g; 3.4 m mol), m.p. 181°C.

Analysis found : C, 74.1; H, 10.7; N, 11.0

$C_{29}H_{50}N_4O$ requires : C, 73.99, H, 10.71; N, 11.9%

IR : ν max 3300 (OH), 1510, 1460 and 1375 cm^{-1} (C=N, N=N)[16,17].

^1H-NMR : δ4.21 (mc, 1H, W 1/2 = 5Hz, C6-αH)[39], 2.57 (s, 3H,

-N-CN-CH_3), 2.11 (br, 1H, OH), 1.05 (C10-CH_3), 0.67 (C13-CH_3), 0.95 and 0.84 (other methyl protons).

MS : M^{+} 470 (7.00; $C_{29}H_{50}N_4O$), 455 (8.10), 453 (8.50), 452 (9.30), 438 (7.70), 387 (12.25), 386 (14.30; $C_{27}H_{46}O$), 368 (13.10; $C_{27}H_{44}$), 357 (7.50), 330 (7.20), 329 (9.50), 316 (8.50), 315 (10.00), 283 (3.90), 282 (3.50), 281 (5.20), 267 (4.40), 266 (4.40), 265 (10.25), 264 (5.30), 263 (8.75), 249 (6.40), 248 (4.40), 247 (10.75), 246 (5.00), 228 (8.70), 227 (9.90), 214 (8.90), 213 (10.30), 212 (2.40), 211 (8.75), 194 (8.00), 193 (4.30), 192 (14.20), 136 (6.40), 135 (3.20), 134 (17.50), 133 (10.00), 132 (9.90), 131 (4.00), 130 (10.50), 129 (8.10), 120 (12.00), 119 (5.00), 118 (14.30), 117 (20.70), 116 (9.20), 115 (4.80), 108 (16.75), 107 (6.40), 106 (20.00), 105 (5.10), 104 (21.50), 103 (11.25), 94 (33.30), 93 (7.50), 92 (28.60), 91 (4.90), 90 (26.75), 89 (4.50), 84 (10.00), 83 (20.00), 82 (19.10), 81 (9.60), 80 (40.50), 79 (12.20), 70 (21.50), 69 (12.00), 68 (34.60), 67 (35.30), 66 (23.80), 65 (8.90), 57 (52.40), 56 (11.50), 55 (54.80), 54 (17.30), 53 (10.50), 45 (41.20), 44 (35.30), 43 (100.00), 42 (15.30), 41 (42.10), 40 (19.00).

3β -Chloro-5,6α-epoxy-5α-cholestane (CLIX)

3β -Chlorocholest-5-ene (11g) in chloroform (100 ml) was treated with a solution of perbenzoic acid (1.1 molequivalent) and left for 20 hrs at -8°C. The reaction mixture was then washed successively with ice-cold sodium bicarbonate solution (5%), water, sodium thiosulphate solution (50%) and again with water and dried. Evaporation of the solvent yielded (CLIX) as oil which was crystallized from acetone as needle (8.1g), m.p. 89°C (reported[41] m.p. 89.5-90.5°C).

Reaction of 3β-chloro-5,6α-epoxy-5α-cholestane (CLIX) with acetonitrile and sodium azide: 3β-Chloro-5-hydroxy-5α-cholest-6β(1')-5'-methyltetrazole (CLXII).

To a stirred solution of 3β-chloro-5,6α-epoxy-5α-cholestane (CLIX) (2.0g, 4.74 m mol) in acetonitrile (20 ml) was added anhydrous aluminium chloride (catalytic amount) and sodium azide (equimolar). Stirring was continued for 6 hrs. at room temperature. After completion of the reaction, the reaction mixture was worked up as usual and chromatographed over silica gel coloumn. Elution with light petroleum ether/ether (5:1) provided a compound which was crystallized from acetone to yield 3β-chloro-5-hydroxy-5α-cholest-6β(1')-5'-methyltetrazole (CLXII), (1.75g, 3.46 m mol), m.p. 174°C.

Analysis found : C, 70.1; H, 9.6; N, 11.0

$C_{29}H_{49}N_4OCl$ requires : C, 68.94; H, 9.77; N, 11.09%

IR : νmax 3400 (OH), 1515, 1475, 1380 (C=N, N=N)[16,17], and 760 (C-Cl).

^{1}H-NMR : δ4.46 (mc, 1H, W 1/2 = 16 Hz, C3-αH)[40], 4.22 (mc, 1H, W 1/2 = 4.5 Hz, C6-αH)[39], 2.62 (s, 3H,-N-CN-CH_3) 2.28 (br, 1H, OH), 1.08 (C10-CH_3), 0.76 (C13-CH_3), 0.95 and 0.84 (other methyl protons).

MS : $M^{+\cdot}$ 504/506 (5.00/1.64; $C_{29}H_{49}N_4OCl$), 489/491 (6.20/2.03), 486/488 (7.10/2.35), 468 (9.80; $C_{29}H_{48}N_4O$), 450 (12.00; $C_{29}H_{46}N_4$), 421/423 (7.50/2.48), 420/422 (10.20/3.39; $C_{27}H_{45}OCl$), 403/405 (6.75/2.22), 402/404 (10.50/3.48), 391/393 (7.10/2.33), 288/290 (8.50/2.80), 366 (23.75; $C_{27}H_{42}$), 351 (8.70), 267 (11.60), 266 (5.40), 260 (8.10), 259 (12.75), 258 (8.10), 257 (4.80), 256 (4.80), 255 (13.90), 254 (7.10), 246 (8.10), 245 (8.10), 244 (3.75), 230 (8.10), 229 (4.75), 228 (7.40), 227 (8.00), 226 (7.40), 225 (8.50), 214 (7.10), 213 (9.25), 212 (8.00), 211 (10.10), 200 (11.70), 199 (6.50), 193 (37.20), 192 (12.25), 191 (5.50), 163 (9.30), 162 (9.75), 161 (10.50), 160 (12.80), 159 (9.00), 158 (11.60), 157 (7.20), 150 (5.80), 149 (8.00), 148 (12.75), 147 (5.20), 146 (8.20), 145 (8.20), 144 (16.25), 135 (16.30), 134 (10.20), 125 (21.00), 124 (16.30), 123 (15.10), 122 (7.25), 118 (16.30), 117 (25.50), 116 (15.80), 115 (6.75), 95 (19.80), 94 (22.75), 93 (42.10), 92 (15.20), 91 (27.30), 90 (44.20), 84 (14.10), 83 (21.75), 80 (15.20), 79 (35.30), 78 (39.70), 77 (10.25), 76 (26.90), 75 (8.30), 65 (19.75), 57 (16.30), 56 (30.10), 55 (37.00), 54 (42.25), 53 (10.00), 44 (42.25), 43 (100.00), 42 (47.00), 41 (31.25), 40 (30.00).

Reaction of 3β-acetoxy-5,6α-epoxy-5α-cholestane (CLX) with acetonitrile and sodium azide: 3β-Acetoxy-5-hydroxy-5α-Cholest-6β(1')-5'-methyltetrazole (CLXIII).

To a stirred solution of 3β-acetoxy-5,6α-epoxy-5α-cholestane (CLX) (2.0g; 4.51 m mol) in acetonitrile (20 ml) was added anhydrous aluminium chloride (catalytic amount) and sodium azide (equimolar). Stirring was continued for 6 hrs. at room temperature. After completion of reaction, the reaction mixture was worked up as usual and chromatographed over silica gel column. Elution with light petroleum ether/ether (5:1) provided a solid compound which was recrystallized from acetone to afford, 3β-acetoxy- 5-hydroxy-5α-cholest-6β(1')-5'-methyltetrazole (CLXIII), (1.70 g; 3.22 m mol), m.p. 221°c.

Analysis found : C, 70.3; H, 9.9 ; N, 10.7

$C_{31}H_{52}N_4O_3$ requires : C, 70.41; H, 9.91; N 10.59%

IR : ν max 3375 (OH), 1720 (CH_3COO), 1520, 1465, 1375 (C=N, N=N)[16,17], 1250 and 1030 cm^{-1} (C-O).

^1H-NMR : δ 5.1 (mc, 1H, W 1/2 = 16 Hz, C3-αH)[40], 4.23 (mc, 1H, W 1/2 = 4 Hz, C6-αH)[39], 2.57 (s, 3H, -N-CN-CH_3), 2.24 (br, 1H, OH), 2.01 (s, 3H, $OCOCH_3$), 1.21 (C10-CH_3), 0.72 (C13-CH_3), 0.91 and 0.83 (other methyl protons).

MS : $M^{+\cdot}$ 528 (7.60; $C_{31}H_{52}N_4O_3$), 513 (7.00), 510 (8.25), 469 (10.50), 468 (12.10; $C_{29}H_{48}O$), 450 (15.30; $C_{29}H_{46}$), 445 (8.40), 444 (9.75), 426 (10.75; $C_{29}H_{46}O_2$), 415 (7.80), 410 (16.20), 366 (23.00; $C_{27}H_{42}$), 339 (6.20), 338 (9.60), 337 (5.75), 254 (4.80), 253 (6.10), 252 (5.00), 246 (5.20), 245 (5.25), 228 (7.40), 227 (9.75), 226 (8.25), 225 (12.00), 214 (8.50), 213 (9.90), 212 (9.50), 211 (14.50), 210 (4.20), 206 (2.75), 205 (5.75), 204 (10.20), 203 (6.00), 201 (4.30), 200 (7.40), 199 (4.50), 198 (4.50), 197 (3.75), 162

(5.00), 161 (5.20), 160 (5.50), 159 (4.10), 158 (6.40), 157 (4.10), 156 (7.20), 155 (3.75), 148 (6.50), 147 (5.10), 146 (6.00), 145 (5.10), 144 (12.00), 143 (10.00), 142 (7.10), 135 (9.60), 134 (13.25), 133 (7.50), 122 (14.50), 121 (9.75), 120 (14.75), 119 (14.75), 118 (20.25), 117 (40.00), 116 (10.50), 106 (24.30), 105 (60.10), 104 (37.30), 103 (15.25), 95 (11.90), 94 (20.25), 93 (29.00), 92 (35.30), 91 (10.75), 90 (40.30), 89 (12.25), 84 (15.25), 83 (25.75), 80 (13.70), 79 (12.25), 78 (32.10), 77 (30.00), 76 (19.25), 75 (9.60), 61 (17.25), 60 (14.00), 59 (11.20), 44 (10.50), 43 (100.00), 42 (19.30), 41 (41.20), 40 (38.70).

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11.2 Hz, PhCHCH*H*OAc), 4.23 (dd, *J* = 4.5, 11.8 Hz, C-4 H), 3.96 (dd, *J* = 8.0, 11.7 Hz, CMe_2CHC*H*HOAc), 3.36 (dd, *J* = 4.4, 8.0 Hz, CMe_2CHCH*H*OAc), 2.09 (s, $COCH_3$), 2.00 (s, $COCH_3$), 1.30 (s, C-3 CH_3), 1.20 (s, C-3 CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) 173.8, 170.6, 170.2, 136.3, 128.9, 128.3, 127.4, 64.0, 63.8, 61.6, 56.7, 51.9, 22.4, 20.7, 20.6, 16.5; IR (CCl_4) 1755, 1752 cm^{-1}; MS (CI) *m/z* 334 (MH$^+$, 100), 274 (11), 264 (10), 163 (8), 128 (12).

3,3-Dimethyl-4(*S)-(hydroxymethyl)-1-[2-hydroxy-1-(*S**)-phenylethyl]-2-azetidinone (12).** According to the method of Mori,[13] a solution of diacetate 11 (17 mg, 0.051 mmol), EtOH (1 mL), and a catalytic amount of KCN (~1 mg) was stirred at 23 °C for 7 h. This solution was then diluted with CH_2Cl_2 (5 mL), filtered through Florisil, and concentrated. The residue was purified by flash chromatography (silica gel, 9:1 $CHCl_3$–EtOH) to give 12 mg (92%) of 12 as an oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.31–7.40 (m, Ph), 4.61 (dd, *J* = 3.8, 8.0 Hz, NC*H*Ph), 4.40 (br s, OH), 4.06–4.13 (m, PhCHC*H*HOH), 3.92–3.99 (m, PhCHCH*H*OH), 3.51–3.62 (m, CMe_2CHC*H*HOH), 3.43–3.49 (m, CMe_2CHCH*H*OH), 3.34 (dd, *J* = 4.6, 5.6 Hz, C-4 H), 2.05 (br s, OH), 1.30 (s, CH_3), 1.26 (s, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) 175.6, 137.6, 129.0, 128.4, 127.4, 65.6, 64.3, 62.0, 61.4, 51.2, 22.7, 16.6; IR (film) 3387, 1718 cm^{-1}.

1-[2-[(*p*-Bromobenzoyl)oxy]-1(*S)-phenylethyl]-3,3-dimethyl-4(*S**)-[[(*p*-bromobenzoyl)oxy]methyl]-2-azetidinone (13).** A solution of 12 (7 mg, 0.028 mmol), *p*-bromobenzoyl chloride (34 mg, 0.16 mmol), and pyridine (0.5 mL) was stirred at 23 °C for 10 h. The resulting slurry was diluted with H_2O (2 mL) and extracted with Et_2O (3 × 2 mL). The combined organic extracts were washed with 1 M HCl (3 mL), 1 M $KHCO_3$ (3 mL), saturated aqueous $CuSO_4$ (3 mL), and saturated aqueous NaCl (3 mL). After drying (Na_2SO_4) and concentration, the residue was purified by flash chromatography (silica gel, 3:1 hexanes–EtOAc) to give 15 mg (88%) of 13 as a colorless crystalline solid.

An analytical sample of this material prepared from (*R*)-(−)-2-phenylglycine afforded X-ray quality crystals from a mixture of EtOAc–hexane–EtOH: mp 82–83 °C; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.54–7.91 (m, 8 H, C_6H_4), 7.27–7.34 (m, Ph), 5.02 (dd, *J* = 4.8, 10.0 Hz, NC*H*Ph), 4.92 (app t, *J* = 10.0 Hz, CHC*H*HO), 4.69 (dd, *J* = 4.9, 10.7 Hz, CHCH*H*O), 4.44 (dd, *J* = 4.5, 12.0 Hz, CHC*H*HO), 4.22 (dd, *J* = 7.1, 12.0 Hz, CHCH*H*O), 3.50 (dd, *J* = 4.5, 7.1 Hz, C-4 H), 1.32 (s, CH_3), 1.25 (s, CH_3); IR (CCl_4) 1730, 1760 cm^{-1}. Anal. Calcd for $C_{28}H_{25}NO_5Br_2$: C, 54.66; H, 4.10; N, 2.28; Br, 25.97. Found: C, 54.58; H, 4.15; N, 2.28; Br, 25.87.

3(*S)-(Acetylamino)-1-[2-(benzyloxy)-1(*S**)-phenylethyl]-4(*S**)-[(1,1-dimethylethoxy)methyl]-2-azetidinone (16) and 3(*R**)-(Acetylamino)-1-[2-(benzyloxy)-1(*S**)-phenylethyl]-4(*S**)-[(1,1-dimethylethoxy)methyl]-2-azetidinone (17).** To a solution of LDA (2.0 mmol, formed as described for the preparation of 10) were added dropwise at −20 °C a solution of silyl glycinate 15[3] (0.46 g 1.9 mmol) and 6 mL of THF. After 2 h at −20 °C, a solution of imine 14 (0.56 g, 1.7 mmol) and 2 mL of THF was added dropwise. The reaction mixture was allowed to warm to 23 °C and after 10 h was quenched with AcOH (2 mL of a 1.0 M THF solution), and AcCl (0.60 g, 7.6 mmol) was then added. After 10 h at 23 °C the solvent was removed in vacuo, and the residue was partitioned between saturated $KHCO_3$ (5 mL) and EtOAc (3 × 5 mL). The combined organic layers were dried (Na_2SO_4) and concentrated to give a 1:5 mixture (by GLC analysis) of β-lactams 16 and 17, respectively. Flash chromatography (silica gel, EtOAc) gave 124 mg (17%) of pure 16 as a clear oil and 305 mg (42%) of pure 17 also as a clear oil.

16: ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.27–7.42 (m, Ph), 6.58 (br d, *J* = 8.5 Hz, NH), 5.45 (dd, *J* = 5.2, 9.5 Hz, C-3 H), 4.52 (AB q, *J* = 11.7 Hz, Δν = 28 Hz, C*H*$_2$Ph), 4.55–4.59 (m, NC*H*Ph), 4.23 (app t, *J* = 9.5 Hz, C*H*HOBn), 3.81 (app quintet, *J* = 2.7 Hz, C-4 H), 3.74 (dd, *J* = 5.9, 10 Hz, CH*H*OBn), 3.49 (dd, *J* = 2.2, 10.4 Hz, C*H*HOBu^t), 3.29 (dd, *J* = 2.9, 10.4 Hz, CH*H*OBu^t), 1.93 (s, $COCH_3$), 1.02 (s, $C(CH_3)_3$); ^{13}C NMR (75 MHz, $CDCl_3$) 169.7, 167.2, 137.9, 137.4, 128.5, 128.4, 127.9, 127.8, 73.3, 70.8, 59.2, 58.5, 58.3, 56.5, 27.2, 27.1, 23.3; IR (CCl_4) 1758, 1740, 1691 cm^{-1}; HRMS (EI) *m/z* 424.2354 (424.2362 calcd for $C_{25}H_{32}N_2O_4$).

17: ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.27–7.44 (m, Ph), 6.02 (br d, *J* = 6.3 Hz, NH), 4.82 (dd, *J* = 5.9, 9.4 Hz, NC*H*Ph), 4.61 (dd, *J* = 2.1, 6.3 Hz, C-3 H), 4.59 (s, CH_2Ph), 4.24 (app t, *J* = 9.6 Hz, C*H*HOBn), 3.80 (dd, *J* = 5.9, 9.8 Hz, CH*H*OBn), 3.64 (dd, *J* = 2.5, 9.57 Hz, C*H*HOBu^t), 3.52 (app dt, *J* ~ 2, 7 Hz, C-4 H), 3.36 (dd, *J* = 7.3, 9.5 Hz, CH*H*OBu^t), 1.93 (s, $COCH_3$), 1.02 (s, $C(CH_3)_3$); ^{13}C NMR (75 MHz, $CDCl_3$) 170.4, 166.6, 138.1, 137.2, 128.4, 128.3, 127.8, 127.8, 127.6, 73.0, 70.8, 62.6, 62.1, 58.7, 57.2, 27.1, 27.1, 22.7; IR (CCl_4) 1744, 1683 cm^{-1}; HRMS (EI) *m/z* 424.2384 (424.2364 calcd for $C_{25}H_{32}N_2O_4$).

Alternatively, with toluene as the solvent, 14 (0.56 g, 1.7 mmol) and 15 (0.46 g, 1.9 mmol) gave a 1:10 ratio of 16 and 17, respectively (determined by GC analysis).

Epimerization of the Cis β-Lactam 16. To a solution of LDA (0.36 mmol, ca. 0.5 M in THF) at −70 °C was added a solution of β-lactam 16 (73 mg, 0.17 mmol) and THF (0.5 mL). After 1 h at −70 °C, Me_3SiCl (~30 μL, 0.24 mmol) was added dropwise, and the reaction was allowed to warm to 0 °C over 1 h. The reaction was then recooled to −70 °C and quenched with AcOH (0.3 mL of a 1.3 M solution in THF, 0.39 mmol). Upon warming to 23 °C, H_2O (2 mL) was added, and the mixture was extracted with EtOAc (3 × 1 mL). The combined organic extracts were washed with saturated aqueous K_2CO_3 (2 mL), dried (Na_2SO_4), and concentrated. The crude residue contained a 2:1 mixture of 17 and 16 as well as two other low boiling products (determined by GC analysis). This crude mixture was dissolved in EtOAc (2 mL) and stirred with 1 M HCl (2 mL) for 1 h. The aqueous layer was removed and washed with EtOAc (2 × 2 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated to give 44 mg (60%) of a 2.2:1 mixture of 17 and 16 as the only products observable by GC and ^{1}H NMR analysis.

3(*S)-(Acetylamino)-4(*S**)-[(1,1-dimethylethoxy)methyl]-1-(2-hydroxy-1(*S**)-phenylethyl)-2-azetidinone (18).** A mixture of 16 (54 mg, 0.13 mmol), 10% Pd/C (~10 mg), and EtOH (2 mL) was rapidly stirred under an atmosphere of H_2 for 12 h and then filtered through a bed of Celite. Concentration and purification of the residue by flash chromatography (silica gel, 20:1 CH_3Cl–EtOH) gave 28 mg (65%) of 18 as a colorless crystalline solid. An analytical sample was obtained by recrystallization from CH_2Cl_2–hexane: mp 147 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.28–7.37 (m, Ph), 6.98 (br d, *J* = 9.5 Hz, NH), 5.45 (dd, *J* = 5.3, 9.5 Hz, C-3 H), 4.83 (dd, *J* = 3.9, 8.6 Hz, NC*H*Ph), 3.97–4.07 (m, C*H*HO*H*), 3.88–3.93 (m, C-4 H and CH*H*OH), 3.57 (dd, *J* = 2.8, 10.6 Hz, C*H*HOBu^t), 3.43 (dd, *J* = 2.7, 10.6 Hz, CH*H*OBu^t), 2.00 (s, $COCH_3$), 1.15 (s, $C(CH_3)_3$); ^{13}C NMR (75 MHz, $CDCl_3$) 170.0, 168.5, 136.0, 128.8, 128.2, 127.7, 74.6, 63.4, 60.0, 58.5, 57.5, 56.7, 27.2, 23.1; IR (CCl_4) 3317, 3306, 2875, 1744, 1667 cm^{-1}; MS (CI) *m/z* 335 (MH$^+$, 100), 279 (10), 236 (12). Anal. Calcd for $C_{18}H_{26}N_2O_4$: C, 64.65; H, 7.84; N, 8.38. Found: C, 64.58; H, 7.86; N, 8.34.

Acknowledgment. The support of the National Science Foundation (CHE-86-18451) is gratefully acknowledged. NMR, MS, and X-ray analyses employed instrumentation purchased with the assistance of the NSF Shared Instrumentation Program. We particularly wish to thank Dr. J. Ziller of the UCI Crystallography Laboratory for X-ray analyses.

Supplementary Material Available: Details of the single-crystal X-ray analyses of 13 and 18 (13 pages). Ordering information is given on any current masthead page.

A Convenient Method for the Synthesis of 3β-Hydroxy 4-En-6-one Steroids

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Received September 6, 1990

In view of the synthetic utility of the title compounds and their multistep syntheses,[1] we report a convenient and

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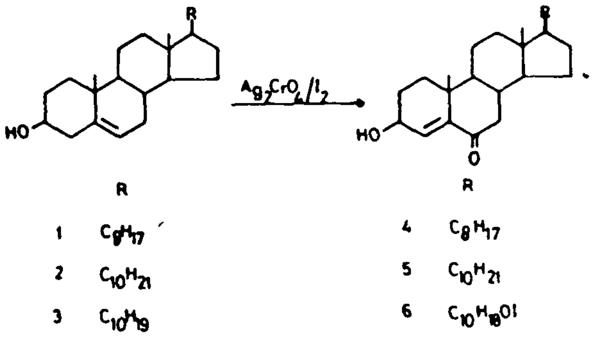
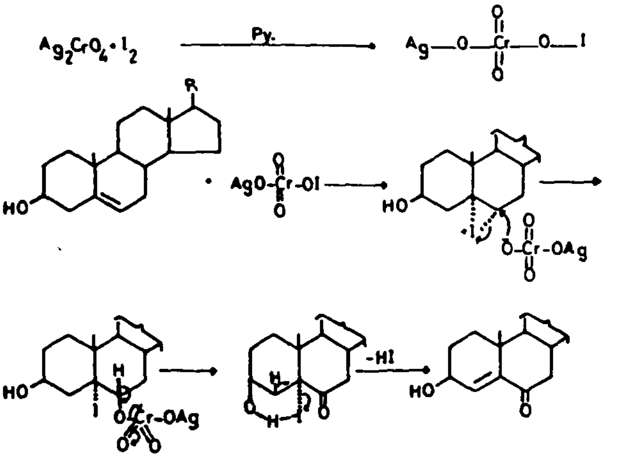
(1) Heilbron, I. M.; Jones, E. R. H.; Spring, P. S. *J. Chem. Soc.* 1937, 801.

0022-3263/91/1956-1936$02.50/0

Scheme I



Scheme II



single-step preparation of the title compounds with quantitative yields. Our synthetic strategy involves the reaction of silver chromate–iodine and pyridine with cholesterol (1), β-sitosterol (2) and stigmasterol (3) affording 3β-hydroxycholest-4-en-6-one (4), 3β-hydroxystigmast-4-en-6-one (5), and 3β-hydroxy-22/23-iodostigmast-4-en-6,23/22-dione (6), respectively (Scheme I). The novelty of this reaction lies in its simplicity and its clean, one-step character (Scheme II). The formation of hydroxy iodo ketones from olefins is rationalized according to the mechanism described by Cardillo and Shimizu.[2] In these hydroxy iodo ketones a n-σ charge transfer takes place from the nonbonding electrons of oxygen (C3–OH) to the bond C5-I,[3] increasing the bond length[4] and heteropolarity[5] of this bond. As a consequence of this, the hydrogen atom of the hydroxyl group chelates to the iodine atom. The stability of the complex so formed is further increased by back donation[6] of electron density from the C5–I bond, increasing the positive charge at C5. All of these processes weaken the C–I bond, leading to its rupture to give I^- and a carbocation, which leads to the formation of the α,β-unsaturated ketone (Scheme II). The role of pyridine is presumably that of facilitating the formation of the supposed hypoiodous chromic acid mixed anhydride. In fact, addition of pyridine to a silver chromate–iodine mixture caused an immediate change of color.

Some other steroidal olefins, such as the 3β-acetoxy and 3β-chloro analogues of cholesterol and β-sitosterol, were subjected to the same treatment, but they instead provided the respective α-iodo ketones.

Thus, the above results as well as the mild reaction conditions, which provide 3β-hydroxy 4-en-6-one steroids (4, 5, and 6) in quantitative yields from their respective olefins (1, 2, and 3), make the present method highly useful for the synthesis of these unsaturated ketones which otherwise have been obtained by many steps.

Experimental Section

Melting points were recorded on a Kofler hot block apparatus and are uncorrected. IR data were obtained on a Pye-Unicam SP3-100 spectrometer. ^1H NMR were run in $CDCl_3$ on a Varian A60-D instrument with TMS as the internal standard, and its values are given in ppm (δ). Mass spectra were recorded by using a JMS-300 spectrometer. Elemental analysis was carried out at the Instrumentation Centre of the Department. Methylene chloride was freshly dried over calcium hydride.

General Procedure for Synthsis of 3β-Hydroxy 4-En-6-one Steroids from Their Respective Steroidal Olefins. To a suspension of silver chromate (3.3 mmol) in 15 mL of dichloromethane was added iodine (4.5 mmol) and a solution of pyridine (1.5 mmol) in 0.75 mL of dichloromethane at 0 °C, and the mixture was stirred for 5 min. A solution of steroidal olefin (2.0 mmol) in 5 mL of dichloromethane was added dropwise during 10 min to the ice-cooled suspension and was stirred for 20 min at 0 °C. Then the cooling bath was removed and the reaction mixture was stirred for an additional hour at room temperature. The reaction mixture was filtered, and the filtrate was successively washed with 5% aqueous $Na_2S_2O_3$ and saturated aqueous NaCl and dried over anhydrous sodium sulfate. The crude product obtained after removal of the solvent was purified by column chromatography (ca. 18 g of silica gel; elutant petroleum ether/ether, 4/1) to give the respective α,β-unsaturated ketones (4–6), recrystallized from petroleum ether (4 and 5).

3β-Hydroxycholest-4-en-6-one (4): yield 0.578 g (75%); mp 149–150 °C; IR (KBr) 3400 (OH), 1685, 1620 cm^{-1} (C=C—C=O); ^1H NMR ($CDCl_3$/TMS) δ 6.02 (d, 1 H, C4-H), 4.3 (mc, 1 H, C3α-H, $W_{1/2}$ = 12 Hz, axial), 2.18 (br, 1 H, OH), 1.15 (s, 3 H, C10-CH_3), 0.70 (s, 3 H, C13-CH_3), 0.91 and 0.81 (other methyl protons); MS (*m*/*e*, intensity), 400 ($M^{\cdot+}$, 100), 385 (13.75), 384 (15.0), 383 (5.5), 382 (12.5), 372 (7.0), 368 (5.0), 354 (5.5), 287 (17.5), 259 (7.5), 152 (15.4). Anal. Calcd for $C_{27}H_{44}O_2$: C, 80.94; H, 11.07. Found: C, 80.90; H, 10.98.

3β-Hydroxystigmast-4-en-6-one (5): yield 0.597 g (72%); mp 162 °C; IR (KBr) 3450 (OH), 1690, 1615 cm^{-1} (C=C—C=O); ^1H NMR ($CDCl_3$/TMS) δ 6.12 (d, 1 H, C4-H), 4.35 (mc, 1 H, C3α-H, $W_{1/2}$ = 15 Hz, axial), 2.2 (br, 1 H, OH), 1.12 (s, 3 H, C10-CH_3), 0.68 (s, 3 H, C13-CH_3), 0.94 and 0.82 (other methyl protons); MS (*m*/*e*, intensity) 428 ($M^{\cdot+}$, 100), 413 (10.0), 412 (13.5), 411 (9.2), 410 (15.5), 400 (8.4), 396 (7.0), 382 (6.5), 287 (21.5), 259 (6.5), 152 (17.4). Anal. Calcd for $C_{29}H_{48}O_2$: C, 81.24; H, 11.28. Found: C, 81.39; H, 11.22.

3β-Hydroxy-22/23-iodostigmast-4-ene-6,23/22-dione (6): yield 0.668 g (81%) semisolid; IR (Nujol) 3420 (OH), 1720 (C=O), 1680, 1610 (C=C—C=O), 520 cm^{-1} (C—I); ^1H NMR ($CDCl_3$/TMS) δ 6.2 (d, 1 H, C4-H), 4.4 (d, 1 H, C22/23-H), 4.1 (mc, 1 H, C3α-H, $W_{1/2}$ = 16 Hz, axial), 1.9 (br, 1 H, OH), 1.14 (s, 3 H, C10-CH_3), 0.71 (s, 3 H, C13-CH_3), 0.91 and 0.83 (other methyl protons); MS (*m*/*e* intensity) 568 ($M^{\cdot+}$, not observed), 441 (75.0), 440 (68.5), 424 (12.0), 423 (7.5), 422 (15.5), 413 (6.5), 412 (10.0), 395 (5.5), 394 (7.5), 343 (21.5), 287 (42.5), 152 (20.0). Anal. Calcd for $C_{29}H_{45}O_3I$: C, 61.25; H, 7.97. Found: C, 61.20; H, 7.93.

Acknowledgment. We are thankful to Prof. M. S. Ahmad and Dr. P. M. Qureshi for their valuable suggestions. Financial support from the CSIR and UGC, New Delhi, is gratefully acknowledged.

Registry No. 1, 57-88-5; 2, 83-46-5; 3, 83-48-7; 4, 570-91-2; 5, 130798-13-9; 6, 130798-14-0.

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Indian Journal of Chemistry
Vol 27B, December 1988, pp 1136-1137

Syntheses of Steroidal Tetrazoles

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Received 29 *July* 1987, *accepted* 1 *February* 1988

Cholest-5-ene (**1**) and its 3β-substituted derivatives (**2**, **3**) on treatment with acetonitrile bromine and sodium azide afford amides (**4-6**) and tetrazoles (**7-9**) The structures of the products have been established on the basis of their analytical and spectral data (IR, PMR and mass)

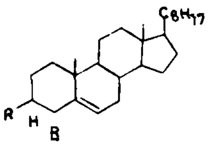
The known biological activities$^{1-3}$ of tetrazoles prompted us to prepare the steroidal tetrazoles by the reaction of cholest-5-ene^4 (**1**), 3β-acetoxycholest-5-ene^6 (**3**) with bromine, acetonitrile and sodium azide in the presence of anhydrous aluminium chloride as a trapping agent for $\bar{\mathrm{Br}}$ **1** afforded the amide (**4**) and a tetrazole (**7**) while **2** and **3** furnished the amides (**5**) and (**6**) and tetrazoles (**8**) and (**9**) respectively The amides (**4-6**) and tetrazoles (**7-9**) were characterized on the basis of their elemental analysis and spectral data.

The mechanism for their formation has already been reported in literature^7 The diaxial opening of the bromonium ion is analogous to the diaxial opening of epoxides^8 and the formation of dibromide from the steroidal olefins^9

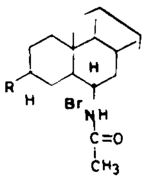
Reaction of olefins (**1-3**) *with bromine, acetonitrile and sodium azide in presence of anhydrous aluminium chloride General procedure*

The olefin (2 g) was taken in acetonitrile (40 ml) and to the mixture was added anhydrous aluminium chloride (2 g) The suspension was cooled in ice-salt bath while being stirred magnetically When the content had cooled down to 0°, bromine (0 8 g) was added and then sodium azide (1 5 g) added immediately The stirring was continued for 2 hr in cold and 2 hr at room temperature The solvent was removed under reduced pressure and the residue extracted with chloroform The chloroform layer was washed with water, sodium bicarbonate solution (5%), again with water and dried (anhyd Na_2SO_4) The chloroform was removed under reduced pressure and the residue chromatographed over silica gel (40 g)

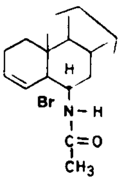
The cholest-5-ene (**1**) furnished 5-bromo-6β-acetamido-5α-cholestane (**4**), on elution with light pet ether-ether (5 1) which recrystallized from acetone (0 45 g), m p 172° (Found C, 68 4, H, 9 9, N, 2 6 $C_{29}H_{50}NOBr$ requires C, 68 50, H, 9 84, N, 2 75%), IR(KBr) 3420(NH), 1670($-CO-NH$) and 730 cm^{-1} ($C-Br$), PMR($CDCl_3$) δ5 8(1H, *b*s, NH, deuterium exchangeable), 3 2(1H, m, $W_{1\ 2}$ = 4 5 Hz, $C_6-\alpha H$), 2 1(3H, s, $-NH-CO-CH_3$), 1 2, 0 9, 0 85 and 0 72 (CH_3), MS *m/z* 508(M^+), 427($M-HBr$), 369($M-C_2H_5NOBr$) and 5-bromo-5α-cholest-6β(1′)-5′-methyltetrazole (**7**) on elution with light pet ether (3 1), **7** recrystallized from acetone (1 1 g), m p 156° (Found C, 65 3, H, 9 0, N, 10 4 $C_{29}H_{49}N_4Br$ requires C, 65 29, H, 9 19, N, 10 54%), IR(KBr) 1530, 1460, 1380($C=N$ and $N=N$)$^{10\ 11}$ and 740 cm^{-1}($C-Br$), PMR($CDCl_3$) δ3 1 (1H *m* W_1 2 = 5Hz, C_6-αH), 2 5(3H, *s*, $-N-CN-CH$), 1 02 0 91, 0 81 and 0 7 (CH_3), MS *m/z* 533(M^+), 452($M-HBr$), 369($M-C_2H_4N_4Br$)



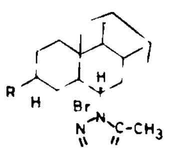
	R
(1)	H
(2)	Cl
(3)	OAc



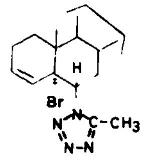
	R
(4)	H
(5)	Cl



(6)



	R
(7)	H
(8)	Cl



(9)

Under the same reaction conditions and column chromatography **2** provided 3β-chloro-5-bromo-6β-acetamido-5α-cholestane (**5**), an oil (0 5 g) (Found C, 63 3, H, 9 1, N, 2 4 $C_{29}H_{49}NOBrCl$ requires C, 63 27, H, 9 0, N, 2 6%), IR(nujol) 3410(NH), 1660($-NH-CO$), 740 and 715 cm^{-1}($C-Cl$ and $C-Br$), PMR(CDCl) δ5 8(1H *b*s, NH, deuterium exchangeable) 4 41(1H, m, W_1 2 = 16Hz, $C_3-\alpha H$), 3 76(1H, m W_1 = 4 5Hz, $C_6-\alpha H$), 2 01(3H, s, $-CO-CH$), 1 26 0 9, 0 83 and 0 68 (CH ,) and 3β-chloro-5-bromo-5α-cholest-6β(1′)5′-methyltetrazole (**8**), an oil (1 g) (Found C, 61 2, H, 8 4, N, 9 8 $C_{29}H_{48}N_4BrCl$ requires C, 61 4, H, 8 6, N 9 9%), IR(nujol) 1525, 1460, 1375($C=N$ and $N=N$), 740 and 720 cm^{-1}($C-Cl$ and $C—Br$), PMR($CDCl_3$): δ3.95 (1H, m, $W_{1/2} = 16Hz$, $C_3-\alpha H$), 3.6(1H, m, $W_{1/2} = 4Hz$, $C_6-\alpha H$), 2.52(3H, s, $-N-CN-CH_3$), 1.2, 0.83 and 0.7(CH_3).

Compound **3** provided 6β-acetamido-5α-cholest-3-ene (**6**), recrystallized from acetone (0.3 g), m.p. 159° (Found: C, 68.7; H, 9.3; N, 2.8. $C_{29}H_{48}NOBr$ requires C, 68.8; H, 9.5; N, 3.0%); IR(KBr): 3430(NH), 1670 ($-NH-CO-$), 1625($C=C$), and 730 cm^{-1} ($C-Br$); PMR($CDCl_3$): δ6.2 (1H, *bs*, NH, deuterium exchangeable), 5.5-5.4(2H, *bm*, C_3 and C_4 vinyl protons), 3.2 (1H, m, $W_{1/2} = 5Hz$, C_6—αH), 2.1(3H, s, $-CO-CH_3$), 1.2, 0.92, 0.8 and 0.7(CH_3) and 5-bromo-5α-cholest-3-en-6β(1′)-5′-methyltetrazole (**9**), recrystallized from acetone (1.2 g), m.p. 178° (Found: C, 65.4; H, 8.7; N, 10.4. $C_{29}H_{47}N_4Br$ requires C, 65.5; H, 8.9; N, 10.5%); IR(KBr): 1520, 1465, 1380 ($C=N$ and $N=N$), 1620($C=C$) and 730 cm^{-1} ($C-Br$); PMR($CDCl_3$): δ5.53-5.45 (2H, *bm*., C_3 and C_4 vinyl protons), 3.06(1H, m, $W_{1/2} = 4.5Hz$, $C_6-\alpha H$), 2.56(3H, s, $-N-CN-CH_3$), 1.15, 0.91, 0.83 and 0.71(CH_3). Elimination of C_3 acetate in presence of sodium azide is a well known process[12].

The authors are thankful to Prof M S Ahmad, Chairman, Department of Chemistry for providing the necessary research facilities.

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Acta Chimica Hungarica 127 (3), pp. 391—393 (1990)

SYNTHESES OF STEROIDAL SUBSTITUTED TETRAZOLES

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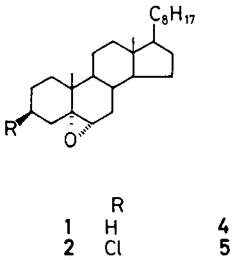
Received March 18, 1988
In revised form August 16, 1988
Accepted for publication October 13, 1988

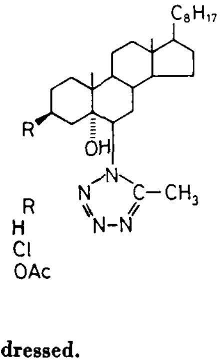
The reaction of 5,6α-epoxy-5α-cholestane (**1**) with acetonitrile and sodium azide provides 5-hydroxy-5α-cholest-6β-(1')-5'-methyltetrazole (**4**). Under similar reaction conditions the epoxides **2** and **3** afford 3β-chloro-5-hydroxy-5α-cholest-6β-(1')-5'-methyltatrazole (**5**) and 3β-acetoxy-5-hydroxy-5α-cholest-6β-(1')-5'-methyltetrazole (**6**) respectively. The structures of these products (**4**, **5** and **6**) have been established on the basis of their spectral and analytical data.

Several biological activities have been associated with substituted tetrazoles such as antiallergic [1], anticonvulsant [2], antiulcer [3], antibacterial, antiviral, antifungal [4], antiinflammatory [5], analgesic [6] and hypertensive [7] effects. Prompted by these physiological observations, we undertook the synthesis of substituted steroidal tetrazoles. Steroidal epoxides (**1**, **2** and **3**) were made to react with acetonitrile and sodium azide in the presence of anhydrous aluminium chloride in order to prepare the unknown steroidal hydroxytetrazoles (**4**, **5** and **6**).

The reaction of 5,6α-epoxy-5α-cholestane (**1**) [8] in acetonitrile with NaN_3 and anhydrous $AlCl_3$ afforded the cholestanyl tetrazole **4** in a good yield. Under similar reaction conditions 5β-chloro-5,6α-epoxy-5α-cholestane (**2**) [9] and 3β-acetoxy-5,6α-epoxy-5α-cholestane (**3**) [10] furnished the cholestanyl tetrazololes **5** and **6**, respectively, in quantitative yields. The forma-



	R
1	H
2	Cl
3	OAc



	R
4	H
5	Cl
6	OAc

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tion of these steroidal tetrazololes might be explained by assuming that first a Ritter reaction takes place between the epoxide and acetonitrile and the product reacts then with the azide ion by dipolar cycloaddition.

Compound **4**, m.p. 181 °C, analyzed for $C_{29}H_{50}N_4O$ (M^{+} 470) and had characteristic mass signals at *m/z* 387 ($M-C_2H_3N_4$), 386 ($M-C_2H_4N_4$), 369 ($M-C_2H_5N_4O$) and 84 ($C_2H_4N_4$). The ir spectrum showed characteristic absorption bands at 3300 (OH), 1510, 1460 and 1375 cm^{-1} (C=N, N=N) [11, 12]. The ^1H nmr spectrum of **4** displayed a broad multiplet for *one proton* at δ 4.21 ($W_{1/2} = 5$ Hz), which was assigned to the C-6 *equatorial* (α) proton [13]. *A sharp singlet integrating for three protons* appeared at δ 2.57 and was assigned to the methyl protons of the tetrazole moiety. The hydroxyl proton (exchangeable with deuterium) appeared at δ 2.11 as a broad multiplet. The angular and side chain methyl protons were seen at δ 1.05 (10-CH_3), 0.67 (13-CH_3) and 0.9, 0.81 (side chain methyl protons). Thus, the above data *confirmed the structure of compound* **4** as 5-hydroxy-5α-cholest-6β(1')5'-methyltetrazole.

Table I

Spectral (ir, ^1H nmr and mass) *data of tetrazololes* **5** *and* **6**

Compound	Mass (*m/z*)	Ir max cm^{-1}	^1H nmr, ppm (δ)
5	504/506 (M^{+}) 468 ($M^{+}-HCl$), 421/423 ($M-C_2H_3N_4$), 420/422 ($M-C_2H_4N_4$), 403/405 ($M-C_2H_5N_4O$), 384 (468-$C_2H_4N_4$), 84 ($C_2H_4N_4$).	3400(OH), 1515, 1475 1380 (C=N, N=N) and 760 (C—Cl).	4.46 (m, 3α-*H*, $W_{1/2} = 16$ Hz, *axial)*, 4.22 (m, 6α-*H*, $W_{1/2} = 4.5$ Hz, *equatorial)*, 2.62 (s, tetrazole-CH_3), 2.28 (m, exchangeable with deuterium, O*H*), 1.08 (10-CH_3), 0.76 (13-CH_3 and 0.90, 0.81 (side chain methyl protons).
6	528 (M^{+}), 468 ($M-AcOH$), 445 ($M-C_2H_3N_4$), 444 ($M-C_2H_4N_4$), 427 ($M-C_2H_5N_4O$), 384 (468— $C_2H_4N_4$), 84 $C_2H_4N_4$).	3375(OH); 1720 (CH_3COO); 1520, 1465, 1375 (C=N, N=N); 1250 and 1030 (C—O).	5.1 (m 3α-*H*, $W_{1/2} = 16$ Hz, *axial)*, 4.23 (m, 6α-*H*, $W_{1/2} = 4$ Hz, *equatorial)*, 2.57 (s, tetrazole-CH_3); 2.24 (m, exchangeable with deuterium, O*H*), 2.01 (OCOCH_3), 1.21 (10-CH_3), 0.72 (13-CH_3) and 0.94, 0.81 (side chain methyl protons).

Similarly, the structures of products **5**, m.p. 174 °C, and **6**, m.p. 221 °C, were established on the basis of their spectral data (ir, ^1H nmr, mass) (Table I) and elemental analyses (Table II) as 3β-chloro-5-hydroxy-5α-cholest-6β(1')-5'-methyltetrazole and 3β-acetoxy-5-hydroxy-5α-cholest-6β(1')-5'-methyltetrazole, respectively.

Table II

Product	M.p., °C	Yield, %	Elemental analysis		
5	174	68.7	$C_{29}H_{49}N_4OCl$	Calcd.	C 68.94; H 9.77; N 11.09
			(505.20)	Found	C 70.1; H 9.6; N 11.0%
6	221	73.8	$C_{31}H_{52}N_4O_3$	Calcd.	C 70.41; H 9.91; N 10.59
			(528.76)	Found	C 70.3; H 9.9; N 10.7%

Experimental

All melting points are uncorrected. Ir spectra were determined in KBr on a Perkin-Elmer 237 spectrophotometer (νmax in cm^{-1}), ^{1}H nmr spectra in $CDCl_3$ on a Varian A-60D instrument with TMS as internal standard (chemical shift in ppm, δ) (s = singlet, m = multiplet, br = broad), and mass spectra on a JMS D-300 mass spectrometer at 70 eV using direct insertion technique at a source temperature of 250 °C. Light petroleum refers to a fraction of b.p. 60—80 °C. Anhydrous sodium sulfate was used as the drying agent.

Reaction of acetonitrile and sodium azide with steroidal epoxides; General Procedure

To a stirred solution of the epoxide (2.0 g) in acetonitrile (20 mL) were added anhydrous aluminium chloride (catalytic amount) and sodium azide (equimolar). Stirring was continued for 6 h at room temperature. After completion of the reaction the solvent was evaporated under reduced pressure and the residue extracted with chloroform. The organic layer was washed with water, 5% sodium hydrogen carbonate solution, and again with water, and dried. Removal of chloroform left an oil, which was chromatographed on a silica gel (40 g) column [light petroleum ether (5 : 1) as eluant]. In this way the epoxide **1** furnished the tetrazole **4**, m.p. 181 °C (1.6 g; 3.4 mmol) (yield 65.7%).

$C_{29}H_{50}N_4O$ (470.72). Calcd. C 73.99; H 10.71; N 11.9. Found C 74.1; H 10.7; N 11.0%.

Similarly, epoxides **2** and **3** gave the tetrazololes **5** and **6** respectively. The spectral (ir, ^{1}H nmr, mass) data of these products (**5** and **6**) are shown in Table I and their m.p.'s, yields and elemental analyses are given in Table II.

The authors are thankful to Professor S. M. Osman, Chairman, Department of Chemistry, for providing the necessary research facilities. Financial support from the CSIR and UGC, New Delhi, is gratefully acknowledged.

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