Synthesis of Terpenoids And Steroids

A Thesis Submitted to the
University Of Poona
For the Degree Of
Doctor Of Philosophy
(In chemistry)

by

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A C K N O W L E D G M E N T S

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My thanks are due to all my colleagues for their generous help and cheerful co-operation.

The services of the co-workers from the microanalysis, spectroscopy and gas chromatographic sections are gratefully acknowledged.

I am grateful to the Director, National Chemical Laboratory, Poona, India for allowing me to submit this work in the form of a thesis.

(A.S. VAIDYA)

March 1969.

C O N T E N T S

		Pages
PART – 1		
Synthesis of saussurea lactone	..	1 – 64
PART – 2		
CHAPTER I		
Degradation of bile acid side-chain with lead tetra-acetate	..	65 – 119
CHAPTER II		
Debromination of diaxial vicinal dibromosterols with potassium-t-butoxide-dimethyl sulphoxide	..	120 – 152

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GENERAL REMARKS

1. The melting points and boiling points are uncorrected.

2. All temperatures are recorded on the Centigrade scale.

3. The ultraviolet spectra were recorded on Beckman DK-II ratio recording spectrophotometer.

4. The infrared spectra were recorded on a Perkin-Elmer infracord spectrophotometer, Model 137B and Model 221 with sodium chloride optics.

5. The NMR spectra were measured in carbon-tetrachloride solution unless otherwise mentioned using tetramethylsilane as internal reference on A-60 Varian instrument and the chemical shifts were measured in τ units.

6. The acid washed activated alumina standardised as per Brockmann's procedure was employed for column chromatography.

7. Gas liquid chromatographic analysis were carried out on a Griffin and George GLC apparatus MK IIA employing hydrogen as carrier gas.

8. The list of references pertaining to each part has been given at the end of that part.

9. The numbers given to the charts and numbers given to the figures in each Chapter of the thesis refer to that particular part only.

10. All the IR spectra and NMR spectra are given ~~at~~ the end of ~~the thesis.~~ each chapter.

11. Silica gel (200 mesh; prepared in the Fine Chemical Project, National Chemical Laboratory) with 15% of plaster of Paris (200 mesh; commercial qualtity) as binder, was used for TLC.

PART - I

Synthesis of Saussurea Lactone.

SUMMARY

A new synthesis of saussurea lactone having the elemanic carbon skeleton, is reported . The syntheses of saussurea lactone and other elemanic compounds reported so far, involve the scission of C_2- C_3 bond of santonin. The novelty of the synthesis of saussurea lactone described in this Chapter lies in the fact that it has been achieved by fission of the C_3- C_4 linkage. (CHART FIVE)

Baeyer-Villiger oxidation of the keto oxide (XIX) prepared by known literature method furnishes the ε-lactone (XL); (XL) on saponification and acetylation of resulting hydroxy acid affords (XLVI). The key step in the synthesis is the base oxidative decarboxylation of (XLVI) with lead tetraacetate and cupric acetate to furnish (XLVII). The hydrolysis of (XLVII) and Jones oxidation of the resulting alcohol (XLVIII) gave the unsaturated ketone (XLIX). Treatment of (XLIX) with methyl magnesium iodide furnished the tertiary alcohol (L) which on dehydration with phosphorus oxychloride in pyridine yielded the oxide (LI), identical with an authentic sample prepared from saussurea lactone (VI). Since the oxide (LI) can be oxidised to saussurea lactone the above sequence of reactions constitutes a new synthesis of saussurea

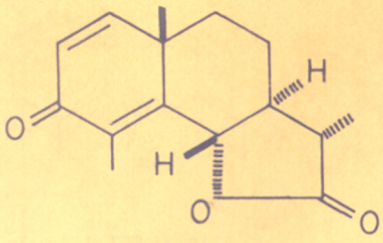
lactone (VI).

Transformations have also been carried out with the intention of preparing 2-keto oxide (LXI), a potential intermediate in the synthesis of saussurea lactone.

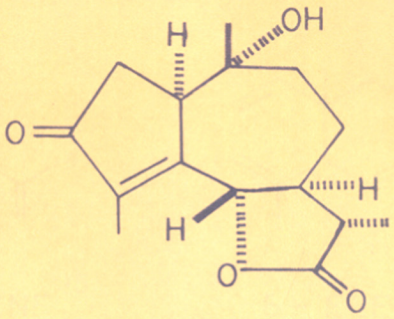
The name "terpenoid" is applied in a general sense to certain substances derived from vegetable kingdom, the great majority of which possess a carbon skeleton which can be regarded as built up of two or more isoprene units, usually in a head-to-tail arrangement[1].

(-)α-Santonin (I) is one of the most thoroughly investigated terpenoids. Its absolute configuration has been established by X-ray studies[2] and other data[3]. X-ray crystallographic analysis[4] of isophoto-α-santonic lactone (II) as well as detailed studies[5] of the chemistry of lactone (III) have shown that (-)α-santonin has the stereochemistry shown in (I). Its configuration at C-11 is also supported by its degradation[6] to (+)-benzoyl alanine. This configuration is the reverse of what had been widely accepted earlier, based[7] on the studies on the stereochemistry of the desmotropo-santonin (III).

Recently a number of sesquiterpenes having the elemanic carbon skeleton (IV) have been isolated from the natural sources[8]. Probably many of them are artifacts formed by the thermal rearrangement of corresponding germacrane (V) derivatives[9,12]. However it has been established that the tumour inhibitor, vernolepin (Chart 1) a dilactone based on elemane



I



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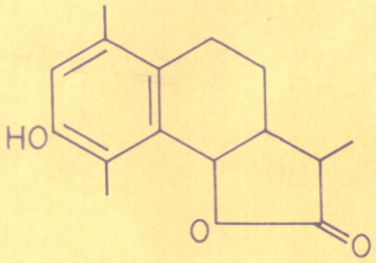

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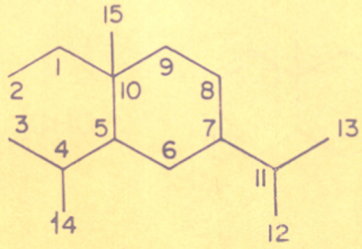

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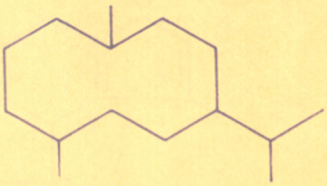

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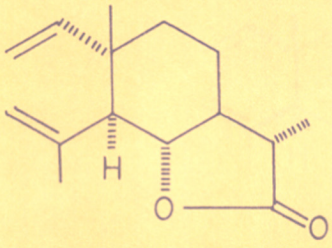

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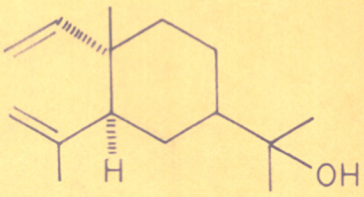
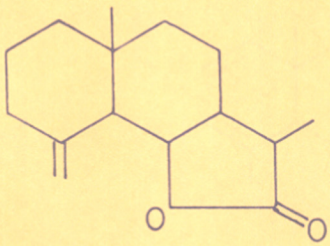


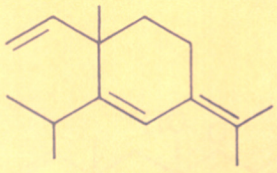
VII



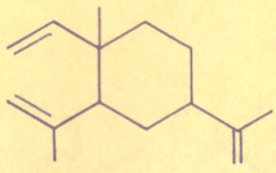
VIII

CHART ONE

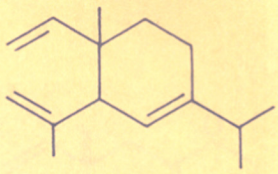
NATURALLY OCCURING COMPOUNDS WITH ELEMANIC SKELETON



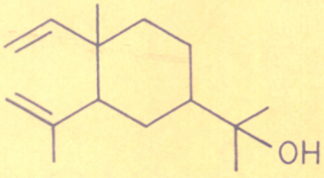
∝-ELEMENE [14]



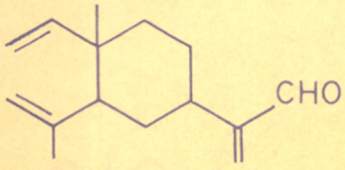
β-ELEMENE [15]



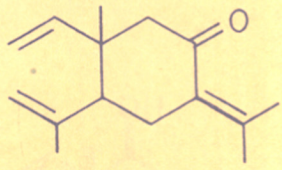
δ-ELEMENE [16]



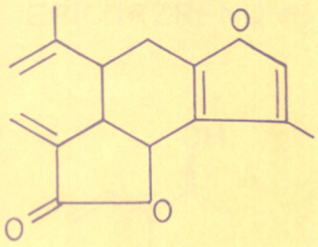
ELEMOL



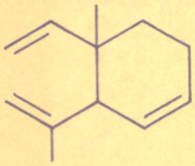
ELEMENAL [17]



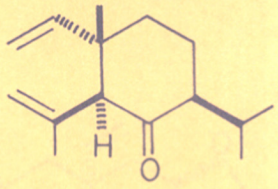
β-ELEMENONE [14]



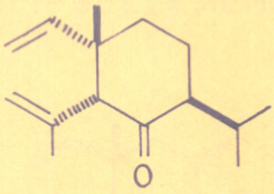
ISOLINDERALACTONE [18]



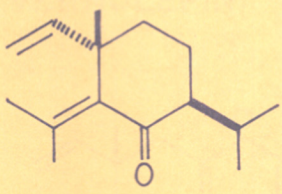
GEIJERENE [19]



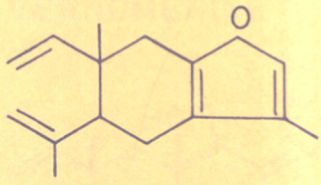
SHYOBUNONE [20]



EPISHYOBUNONE [20]

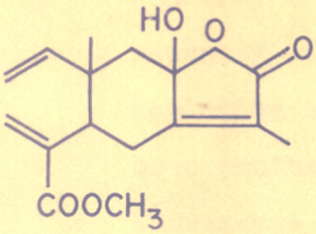


ISOSHYOBUNONE [20]

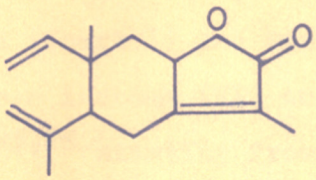


ISOSERICENINE [21]

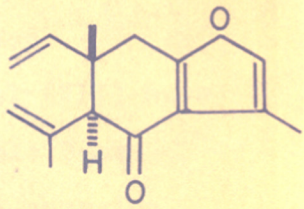
CHART ONE CONTD.



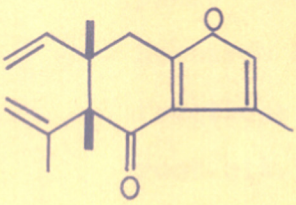
SERICEALACTONE[21]



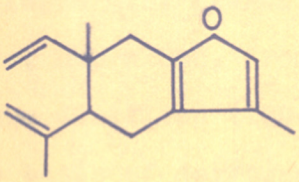
DEOXYSERICEALACTONE[21]



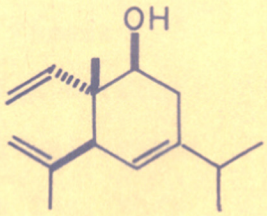
CURZERENONE[22]



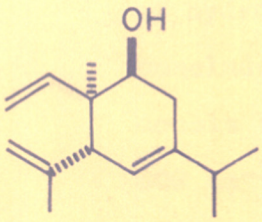
EPICURZRENONE[22]



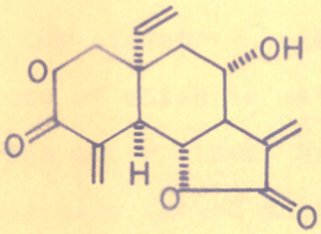
ISOFURANOGERMACRENE[22]



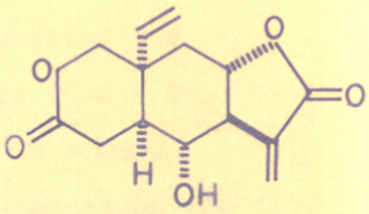
δ-ELEMENOL[23]



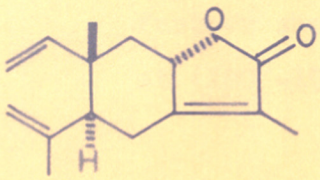
EPI-δ-ELEMENOL[23]



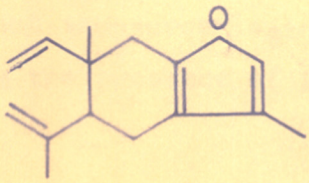
VERNOLEPIN[13]



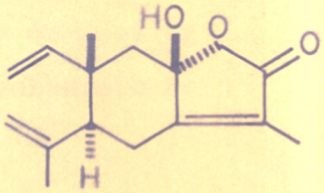
VERNOMENINE[13]



ISOGERMAFURENOLIDE[24]



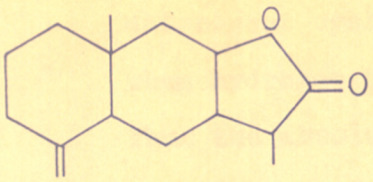
CURZERENE[39]



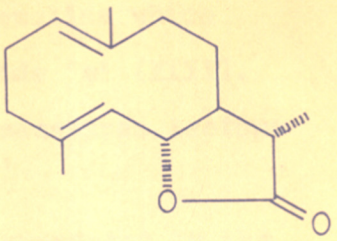
HYDROXYISOGERMA-FURENOLIDE[24].

skeleton is indeed a naturally occurring compound[13]. A number of compounds having elemanic skeleton are recently reported (Chart 1) and many of them including saussurea lactone (VI) and elemol (VII) have been synthesised[25,26] starting from suitable 3-oxo eudesmanes which are readily available and carrying out the fission of the C_2 - C_3 bond.

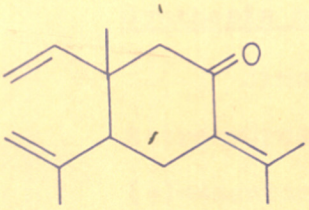
Saussurea lactone (VI) was isolated for the first time by Rao and Varma[10] from the roots of the plant saussurea lappa C.B. Clarke at the Forest Research Institute, Dehra Dun, from the high boiling fractions of vacuum distilled (180-200°/11 mm) costus root oil. On the basis of degradative studies, they proposed a tentative bicyclic structure[11] (VIII) or (IX) for this lactone. However these structures were disproved by Bhattacharyya et al.[12] who on the basis of hydrogenation studies and spectral evidences concluded that saussurea lactone contains two double bonds, one of which is methylenic (R-C = CH_2, 892 cm^{-1}) and the other vinyl type (R-CH = CH_2, 909 cm^{-1}). They also showed that dihydrocostunolide (X) on pyrolysis (200-220°/50 mm) furnishes saussurea lactone (VI). This is analogous with the formation of pyrogermacrone (XI) from germacrone[27] (XII). They further showed that saussurea lactone (VI) on heating at (180°-190°) in the presence of paranitrobenzoic acid



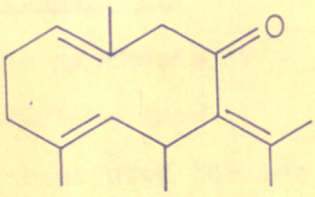
IX



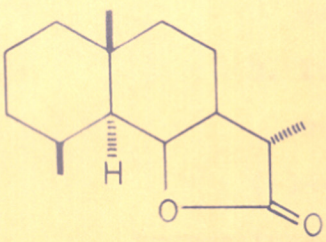
X



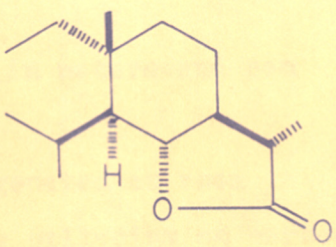
XI



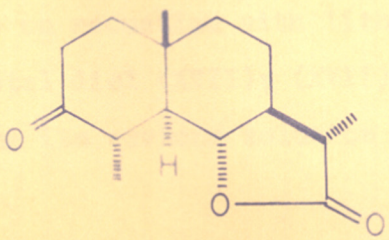
XII



XIII



XIV



XV

underwent cyclisation forming santenolide which when hydrogenated afforded santanolide 'c' (XIII). Thus the absolute configuration of saussurea lactone is represented by (VI).

This configuration was also supported by the total synthesis of tetrahydrosaussurea lactone[28] (XIV) and saussurea lactone itself[25] (VI).

Synthesis of tetrahydrosaussurea lactone (XIV)

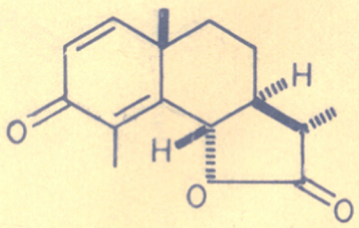
Simonovic et al.[28] achieved the synthesis of tetrahydrosaussurea lactone (XIV) starting from (-)α-santonin (I) (-)α-santonin has been used for the synthesis of several compounds because

1. It is readily available.
2. Its stereochemistry has been rigorously established both by physical and chemical methods.
3. It is highly crystalline in nature and can be very easily purified.

(-)α-Santonin (I) was hydrogenated at room temperature in acetone medium using palladium on carbon catalyst. The resulting α-tetrahydrosantonin (XV) was ketalised by azeotropic distillation with ethylene glycol, toluene and paratoluene sulphonic acid. The ketal (XVI) on reduction with lithium aluminium hydride afforded ketal diol (XVII); (XVII) was then deketalised by refluxing its acetone solution with sulphuric acid.

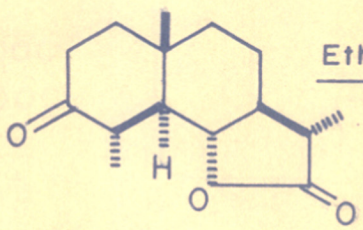
CHART TWO

SYNTHESIS OF TETRAHYDROSAUSSUREA LACTONE.



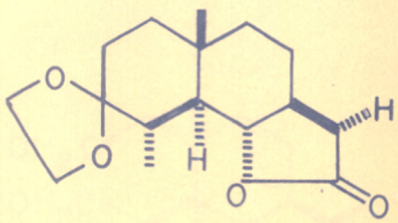
I

$H_2/Pd-C$



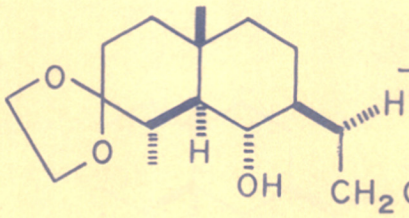
XV

Ethylene glycol



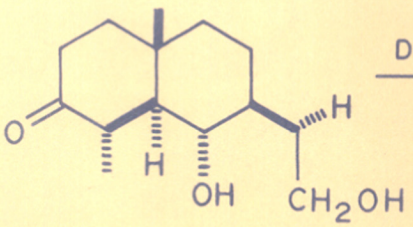
XVI

LAH



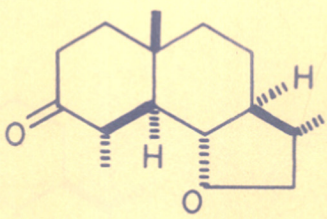
XVII

H_2SO_4 Acetone



XVIII

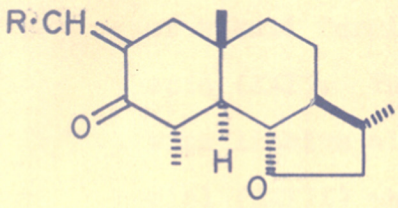
Dehydration



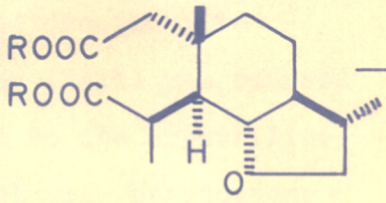
XIX

C_6H_5CHO NaOH

CHART TWO CONTD.



Alkaline
H_2O_2



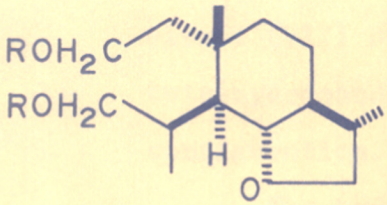
LAH
Tosylation

XX R = 

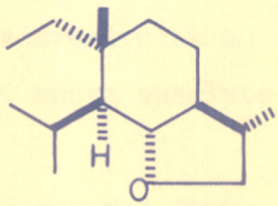
XX A R = ∅

XXI R ≡ H

XXII R ≡ CH_3



LAH

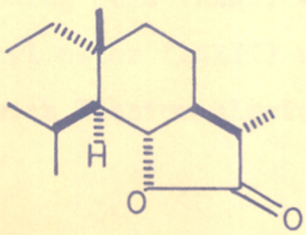


CrO_3

XXIII R ≡ H

XXIV R ≡ Ts

XXV



XIV

The keto diol (XVIII) on acid catalysed dehydration furnished the keto oxide (XIX). The keto oxide (XIX) was converted to the furfurilidine derivative (XX) which on treatment with hydrogen peroxide in presence of alkali furnished the desired dicarboxylic acid (XXI). The dimethyl ester (XXII) was reduced with lithium aluminium hydride to the crystalline diol (XXIII) which on treatment with paratoluene sulphonyl chloride in pyridine solution formed the ditosylate (XXIV). The ditosylate on reduction with lithium aluminium hydride afforded the oxide (XXV); (XXV) on oxidation with chromic acid gave tetrahydrosaussurea lactone (XIV).

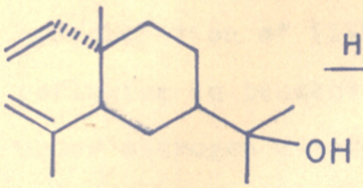
Synthesis of tetrahydrosaussurea lactone from elemol

To determine the absolute configuration of elemol (VII) Bhattacharyya et al.[29] converted it to tetrahydrosaussurea lactone (XIV) of known absolute configuration.

The hydrocarbon (XXVIII) was prepared from elemol (VII) by a known procedure; (XXVIII) on treatment with perbenzoic acid gave the epoxide (XXIX) which on isomerization with BF_3-etherate under controlled conditions afforded the aldehyde (XXX); (XXX) was oxidised to the corresponding acid (XXXI) with $KMnO_4$ or silver oxide; the methyl ester (XXXII) was reduced to the alcohol (XXXIII) with lithium aluminium hydride.

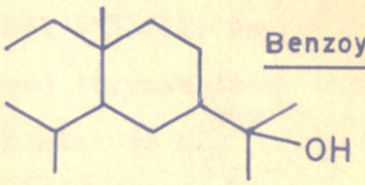
CHART THREE

SYNTHESIS OF TETRAHYDROSAUSSUREA LACTONE FROM ELEMOL.



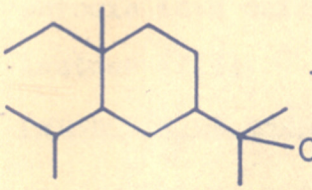
VII

Hydrogenation →



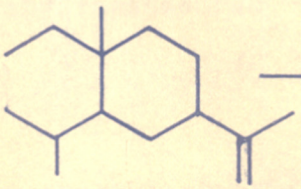
XXVI

Benzoylation →



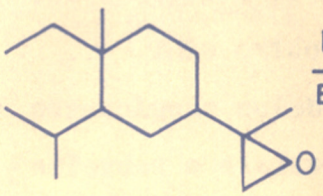
XXVII

Pyrolysis →



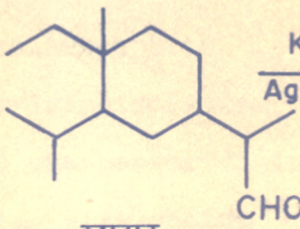
XXVIII

PBA →



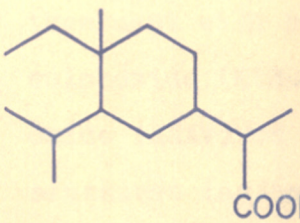
XXIX

Isomerization
BF_3 – etherate →



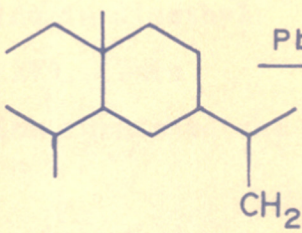
XXX

$KMnO_4$ or
Ag.-oxide →



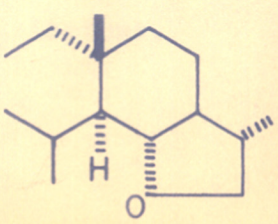
XXXI R ≡ H
XXXII R ≡ CH_3

LAH →



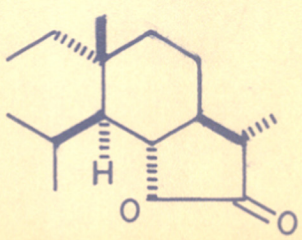
XXXIII

$Pb(OAc)_4$
C_6H_6 →



XXV

CrO_3 →



XIV

This alcohol can be more conveniently prepared by hydroboration of (XXVIII). The alcohol (XXXIII) on refluxing in benzene solution with lead tetraacetate under nitrogen atmosphere furnished a mixture of epimeric oxides which were separated by chromatography. One of the epimers was the oxide (XXV) which on chromic acid oxidation afforded tetrahydrosaussurea lactone (XIV).

Synthesis of saussurea lactone (VI)

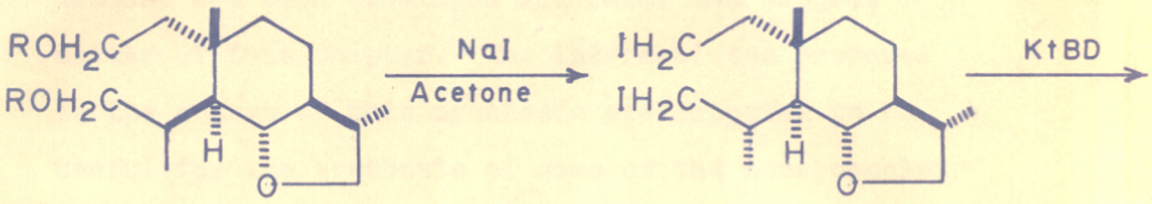
Honwad and Rao synthesised saussurea lactone[25] from the oxido diol (XXIII) which is an intermediate in the synthesis of tetrahydrosaussurea lactone (XIV).

This oxido diol (XXIII) on treatment with paratoluene sulphonyl chloride in pyridine solution afforded a ditosylate (XXIV); (XXIV) was converted into a diiodo compound (XXXIV) by refluxing with sodium iodide in acetone. The diiodo compound (XXXIV) on treatment with potassium-tert-butoxide in dimethyl sulphoxide (KtBD) gave the oxide (XXXV). This oxide (XXXV) on chromic acid oxidation furnished the saussurea lactone (VI).

We now describe the new synthesis of saussurea lactone (VI). This synthesis was initiated before Honwad and Rao completed their synthesis of saussurea lactone.

CHART FOUR

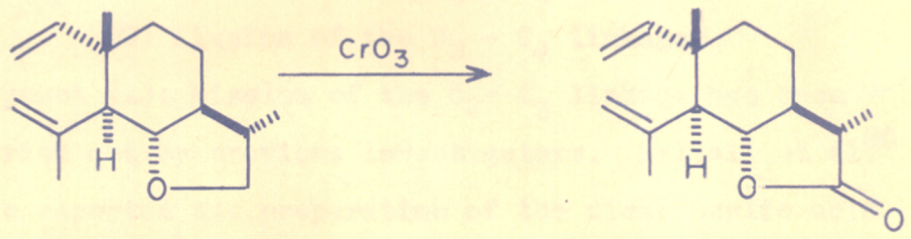
SYNTHESIS OF SAUSSUREA LACTONE BY HONWAD & RAO



XXIII R ≡ H

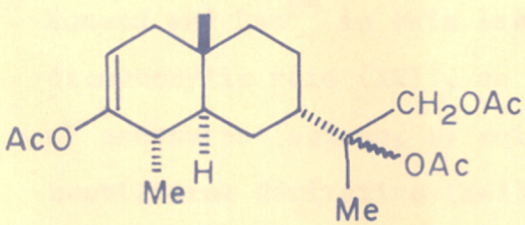
XXIV R ≡ Ts

XXXIV

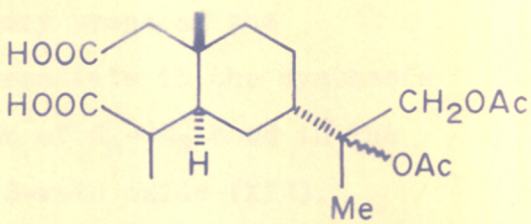


XXXV

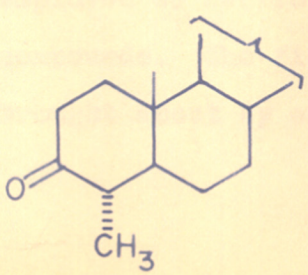
VI



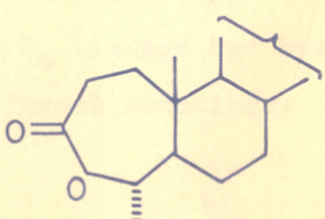
XXXVI



XXXVII



XXXVIII



XXXIX

PRESENT WORK

A new route for the synthesis of saussurea lactone has been developed and forms the subject matter of this Chapter. The intermediates prepared in the course of this synthesis are expected to be useful for the synthesis of some of the more complex elemanic compounds isolated recently.

The presence of a keto function in the oxide (XIX) furnishes two types of approaches which can be used for the synthesis of compounds related to elemane.

Approach (1) Fission of the C_2 - C_3 linkage.

(2) Fission of the C_3 - C_4 linkage.

Approach (1): Fission of the C_2- C_3 linkage has been carried out by previous investigators. Halsall et al.[30] have reported the preparation of the dicarboxylic acid (XXXVII) by ozonolysis of the enol acetate (XXXVI) followed by oxidative fission of the ozonide with H_2O_2. Honwad and Rao[25] in this laboratory prepared the dicarboxylic acid (XXI), an intermediate in the synthesis of saussurea lactone, by scission of C_2- C_3 bond in the benzilidine derivative (XXA) of 3-keto oxide (XIX).

Approach (2): This approach does not appear to have been employed so far for the synthesis of elemane type compounds. The fission of the C_3- C_4 linkage has been brought about by employing two different reactions:

a) Baeyer-Villiger oxidation.

b) Beckmann rearrangement.

(a) Baeyer-Villiger oxidation of the ketone such as (XIX) can be expected to proceed along two different directions.

i) Oxygen insertion between C-3 and C-4.

ii) Oxygen insertion between C-2 and C-3.

The former possibility is more likely since it is known that for unsymmetrical ketones oxygen insertion generally takes place between the more substituted carbon atom adjacent to C=O group and the carbonyl group. As a typical example, the oxidation of the closely related 4α-methyl cholestan-3-one (XXXVIII) may be cited[31]. A solution of (XXXVIII) and m-chloroperbenzoic acid in chloroform when allowed to remain at 25° for 18 hrs. furnished 4-oxa-4aα-methyl-A-homocholestan-3-one (XXXIX) in high yield; (XXXIX) gave a single peak on VPC. NMR spectrum showed methyl signal as doublet centred at τ 8.71 (J = 7 cps) indicating methyl attached to the carbon bearing acyloxy substituent.

In agreement with expectation[31] Baeyer-Villiger oxidation of the keto oxide (XIX) with perbenzoic acid furnished ε-lactone (XL). The structure assigned to the ε-lactone (XL) which was obtained as a sharp melting crystalline solid is consistent with its IR spectrum (band at 1740 cm^{-1} due to ε-lactone) and NMR spectrum

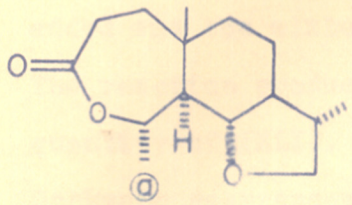
(a doublet centred at 8.66 τ (J = 7 cps) due to (a) in (XL).

Conclusive proof for the structure of the ε-lactone being (XL) and not (XL)A is provided by its conversion to saussurea lactone by employing the sequence of reactions described in sequel. Baeyer-Villiger oxidation of α-tetrahydrosantonin lactone (XV) furnished in moderate yields the expected dilactone (XLI) (IR bands at 1770 cm^{-1} and 1739 cm^{-1} due to γ and ε-lactones respectively). Since the ε-lactone (XL) was obtained in higher yields than (XLI) and its purification was also comparatively easier, further transformations were carried out with (XL).

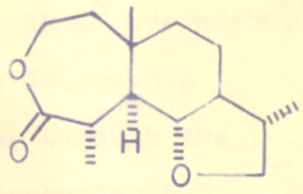
(b) The Beckmann rearrangement of (XLII) was carried out by adding phosphorusoxy chloride to a solution of oxime (XLII) in pyridine at 0° and keeping at room temperature for one hour[32]. The rearrangement furnished the expected product (XLIII) (IR band at 1770 cm^{-1} for γ-lactone at 1653 cm^{-1} for C^{O} - NH grouping.

Transformation of the lactam (XLIII) to the ε-lactone (XLI) was attempted according to the procedure of Bladon and McMeekin[33] who prepared hecolactone acetate (XLV) from the lactam acetate (XLIV) without isolation of the nitroso derivative and without heating. To a solution of the lactam (XLIII) in acetic

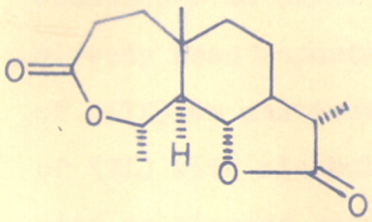
CHART FOUR CONTD.



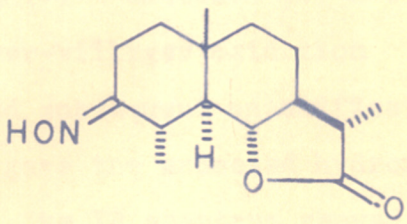
XL



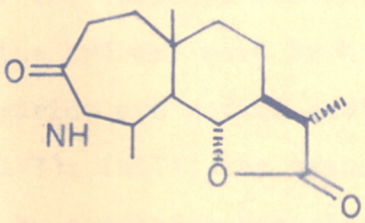
XL A



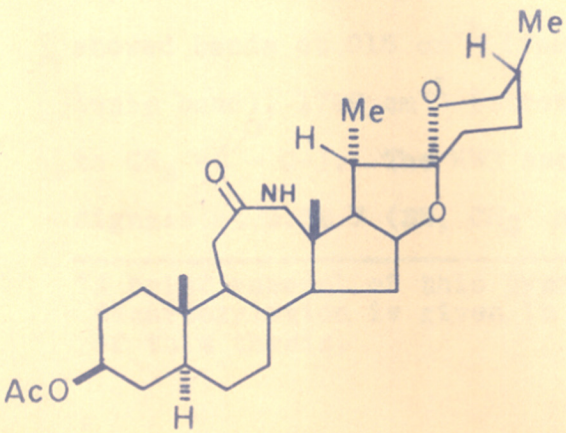
XLI



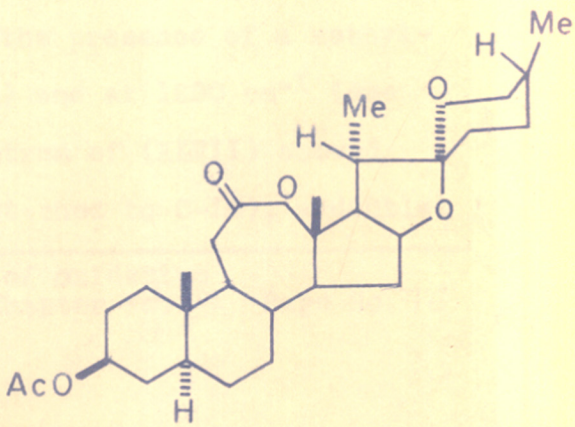
XLII



XLIII



XLIV



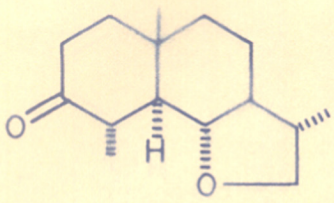
XLV

anhydride and acetic acid at 0° sodium nitrite was added and the mixture was maintained at 0° overnight. The reaction product did not contain detectable quantity of (XLI). Hence this route, through the Beckmann rearrangement of ∝-tetrahydrosantonin oxime (XLII), for the C_3- C_4 scission was not useful.

Synthesis of 3-oxo-5,7∝ (H), 4,6,11β(H)-eudesman-6:13 oxide (XIX) from (-) ∝-santonin (I) has already been reported[28]. Baeyer-villiger oxidation of (XIX) as mentioned above and subsequent saponification of (XL) with alcoholic alkali gave the expected hydroxy acid as viscous brown liquid. The IR spectrum showed absorption due to the -OH group and a strong band at 1724 cm^{-1} for the carbonyl absorption. The acetylation of the hydroxy acid by heating under reflux with acetic anhydride and sodium acetate yielded the acetoxy acid (XLVI); (XLVI) was transformed to the acetate (XLVII) by oxidative decarboxylation[34] with lead tetraacetate in benzene solution in presence of cupric acetate and pyridine*. The IR spectrum of (XLVII) showed bands at 915 cm^{-1} (for the presence of a methylenic band), 1739 cm^{-1} (strong) and at 1250 cm^{-1} (due to CH_3 -C(=O)- O-). The NMR spectrum of (XLVII) showed signals at 9.02 τ (3H, CH_3 attached to C-10), a doublet

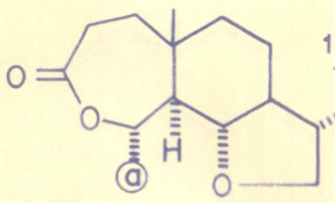
*A brief account of this type of oxidative decarboxylation is given in Chapter No. II Page No. 76 of this thesis.

CHART FIVE



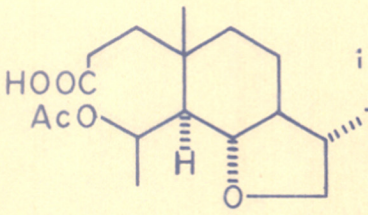
XIX

Baeyer Villiger Oxidation



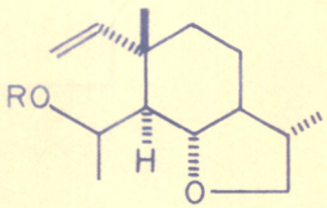
XL

1) Alcoholic alkali
2) Acetylation



XLVI

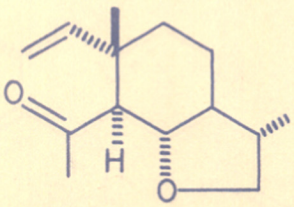
i) Oxidative decarboxylation
ii) Hydrolysis



XLVII R ≡ $CH_3-C(=O)-$

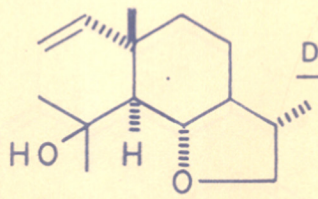
XLVIII R ≡ H

Jones oxidation



XLIX

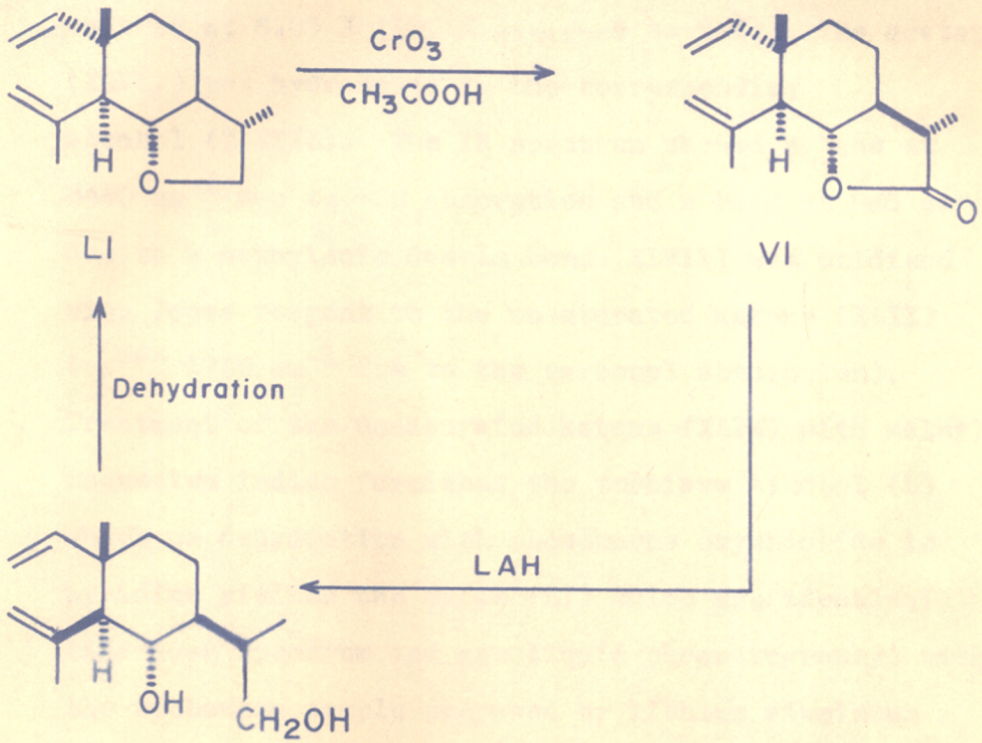
CH_3 Mg I



L

Dehydration

CHART FIVE CONTD.



centred at 8.96 τ (3H, CH_3 attached to C-11), a doublet centred at 8.75 τ (3H, CH_3 attached to C-4). A sharp signal at 8.1 τ (singlet due to methylenic double bond), a multiplet centred at 6.53 τ (2H, -O-CH_2), a triplet centred at 6.05 τ (1H, H attached to C-6). The acetate (XLVII) was hydrolysed to the corresponding alcohol (XLVIII). The IR spectrum showed a band at 3450 cm^{-1} due to -OH absorption and a band at 925 cm^{-1} due to a methylenic double bond; XLVIII was oxidised with Jones reagent to the unsaturated ketone (XLIX) (λ_{max} 1720 cm^{-1} due to the carbonyl absorption). Treatment of the unsaturated ketone (XLIX) with methyl magnesium iodide furnished the tertiary alcohol (L) which on dehydration with phosphorus oxychloride in pyridine yielded the oxide (LI) which was identical (infrared spectrum and gas liquid chromatography) with the authentic sample prepared by lithium aluminium hydride reduction of saussurea lactone and subsequent dehydration of the resulting diol (LII). Since the oxide (LI) can be oxidised to the saussurea lactone (VI) by a method reported in literature[25], the above transformations constitute a new synthesis of saussurea lactone (VI).

Below are described some of the attempts for the preparation of 2-keto oxide (LXI) a potential

intermediate* for the synthesis of saussurea lactone. However these approaches were abandoned without reaching the final goal, since we could synthesis saussurea lactone (VI) through the approach presented above.

The preparation of the above 2-keto oxide (LXI) from 3-keto oxide (XIX) can be accomplished by three different methods:

I Method

First method for the preparation of 2-keto oxide (LXI) involves an important intermediate 6:13-oxidoeudesm-2-ene (LV). Two different approaches have been explored to synthesise it and both of them have been successful.

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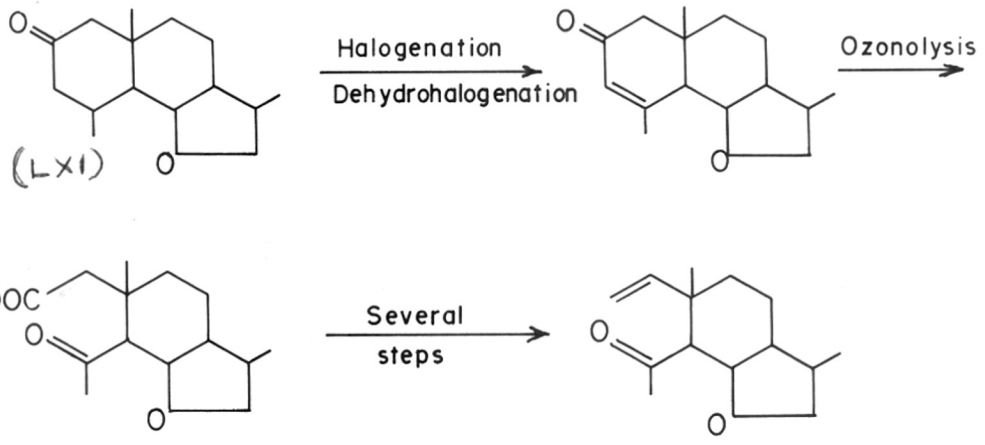
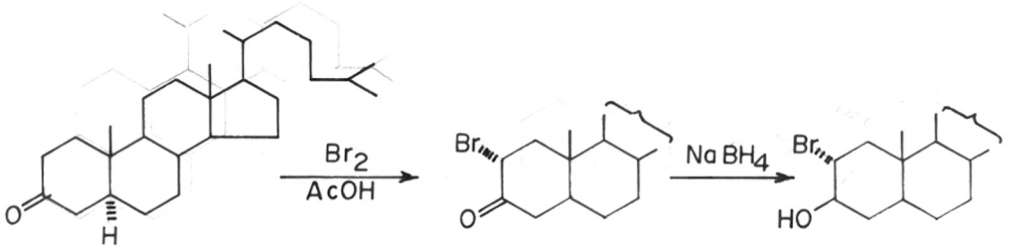
*

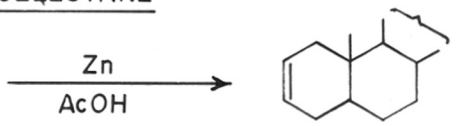


However this work has not been carried out.

First approach described below is based on similar sequence of reactions carried out for the synthesis of Δ^2-cholestene free from Δ^3-cholestene[35] cholestanone



CHOLESTANE

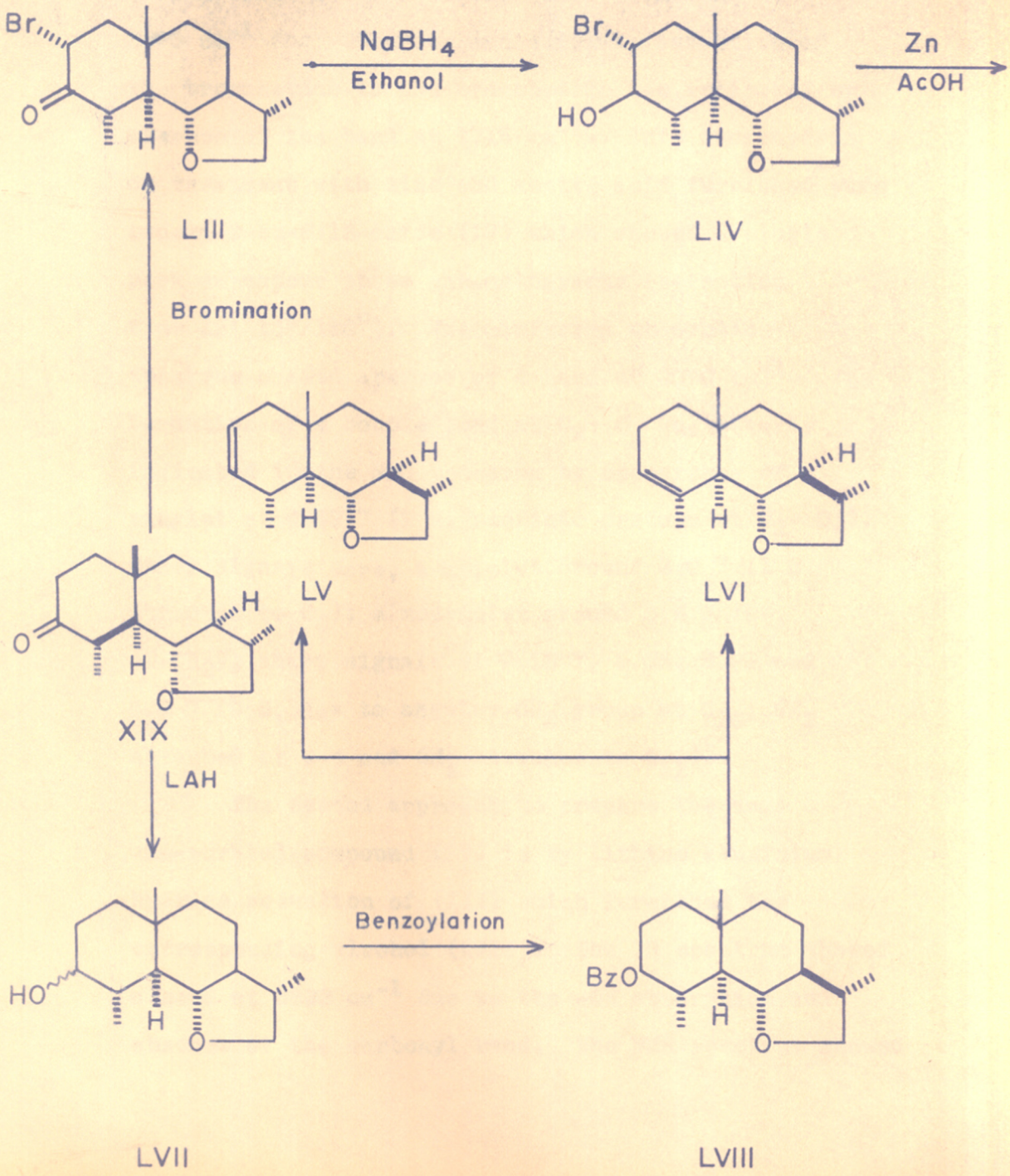


Δ^2 —CHOLESTENE

It was anticipated that a similar sequence should be useful in the transformation of 3-keto oxide (XIX) to 6:13 oxido-eudesm-2-ene (LV). The first step in the transformation is the bromination of (XIX). Formation of 2-bromocompound (LIII) was anticipated since the closely related α-tetrahydrosantonin is known to furnish (LXV) on bromination. Yanagita and Tahara[36] and W. Cocker and T.B.H.McMurry[37] have prepared the bromocompound (LXV) by brominating α-tetrahydrosantonin (XV).

3-Oxo-5,7α(H),4,6,11 β(H)-eudesman-6:13-oxide (XIX) was brominated in glacial acetic acid solution in presence of HBr in acetic acid. The

CHART FIVE CONTD.



resulting bromoketone (LIII) when reduced with sodium borohydride in ethanolic solution furnished the bromohydrin (LIV). The IR spectrum of the bromohydrin showed a strong absorption band at 3390 cm^{-1} for -OH group and complete reduction of the bromoketone to the bromohydrin was indicated by absence of the band at 1715 cm^{-1}. This bromohydrin on treatment with zinc and acetic acid furnished pure eudesm-2-en-6:13-oxide (LV) which showed a single peak on vapour phase chromatography (retention time 12' 15"/180°). The infrared absorption spectrum showed absence of a band at 3390 cm^{-1}. The formation of a double bond at C_2- C_3 was clearly indicated in the NMR spectrum by appearance of a singlet at 4.58 τ (2 H, olefinic protons at C_2- C_3). Other signals were, a triplet around 6.0 τ (1 H attached to C_6); a multiplet around 6.6 τ (2H, -O-CH_2), sharp signals at 9.15 τ, 9.05, 8.91 and 8.8 τ (9 H, due to angular CH_3 group at C_{10}, CH_3 attached at C-4 and CH_3 attached to C_{11}).

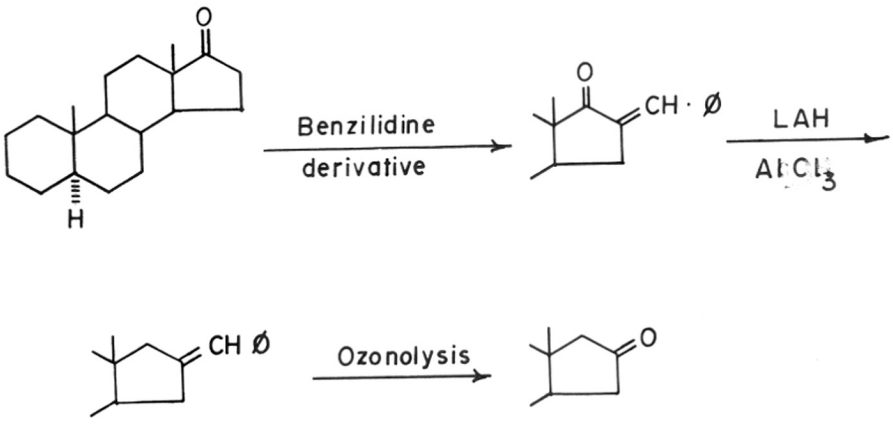
The second approach to prepare the same unsaturated compound (LV) is by lithium aluminium hydride reduction of (XIX) which furnished the corresponding alcohol (LVII). The IR spectrum showed a band at 3333 cm^{-1} due to the -OH absorption and absence of the carbonyl band. The NMR spectrum showed

signals at 9.1, 9.05, 8.93 and 8.85 τ (9H protons due to angular methyl group at C-10; methyl group attached at C-4 and the methyl group at C-11), a triplet centred at 6.08 τ (1H, H attached to C-6) and a multiplet centred at 6.7 τ due to (2H protons $O-CH_2-$); (LVII) on benzoylation with benzoyl chloride in pyridine afforded the benzoate (LVIII). The IR spectrum showed absence of hydroxyl absorption. The benzoate on pyrolysis at 330° afforded a mixture of 5,7α(H), 4,6,11 β(H)-eudesm-2-en-6:13-oxide (LV) and 5,7α(H)-4,6,11 β(H)-eudesm-3-en-6:13-oxide (LVI). The GLC analysis of the pyrolysed product showed Δ^2-en (LV) as the major component and Δ^3-en (LVI) 20% (retention time 13' 33" and 16' 18" at 178°-179°/9 sec/ 10 ml polyester column 12"/hr). Presence of Δ^2-en (LV) as the major component was confirmed by comparing its GLC with an authentic sample under identical conditions. However preliminary attempts to prepare 2-keto oxide (LXI) from Δ^2-en (LV) by hydroboration and Jones oxidation of the resulting alcohol were not successful.

II Method

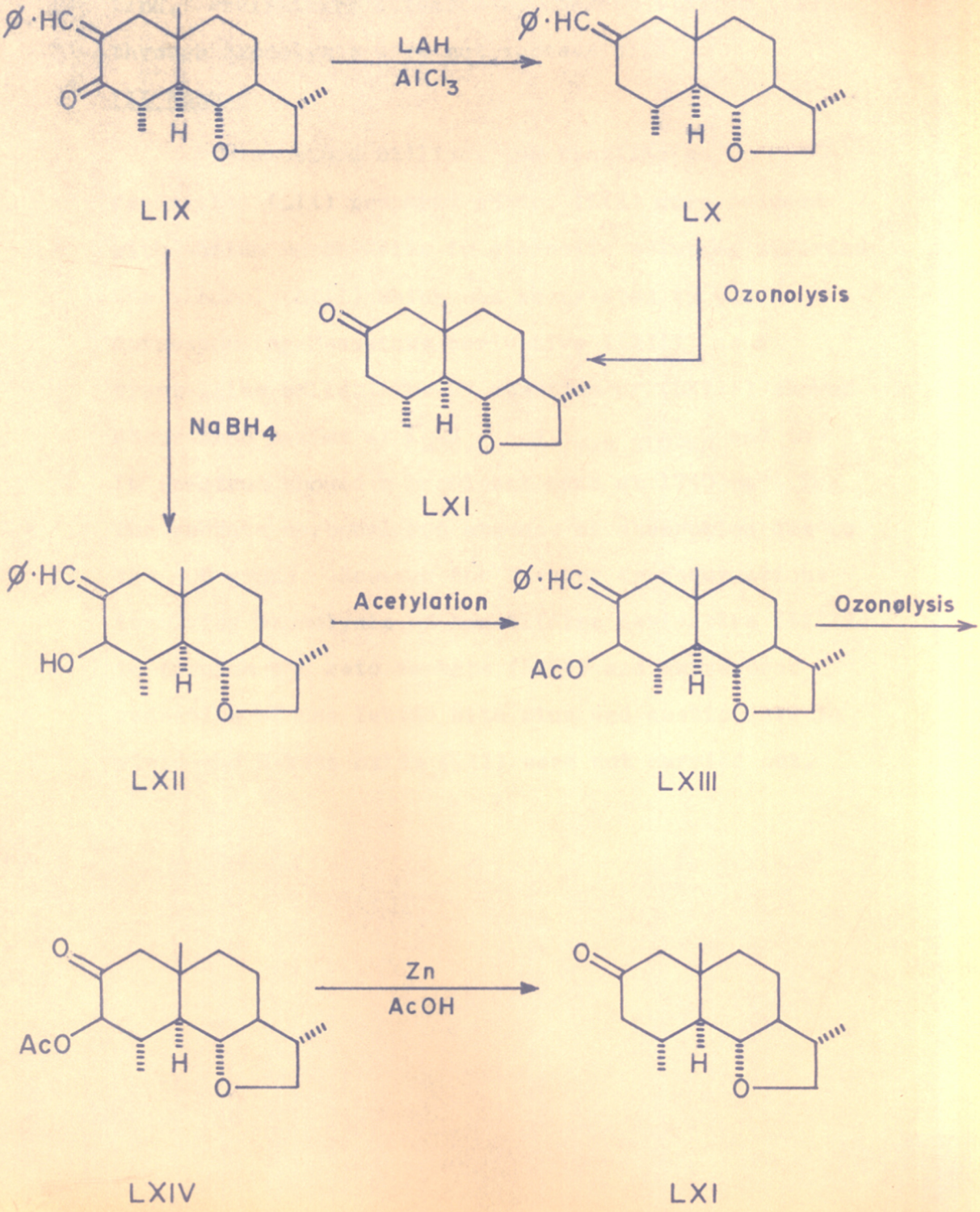
The second method was planned taking into consideration the work of Jones et al.[38] describing a convenient method for the conversion of 17-oxosteroids

to 16-oxosteroids as shown below:



On similar lines 6:13-oxido-3-keto eudesmane (XIX) was subjected to the same sequence of reactions. A methanolic solution of (XIX) when treated with benzaldehyde in presence of alkali furnished the benzilidine derivative (LIX). The infrared spectrum showed prominent bands at ~~1710 cm^{-1}~~, 1667 cm^{-1}, 1587 cm^{-1} and 757 cm^{-1} indicating the presence of a conjugated carbonyl group and a phenyl group. The UV spectrum showed absorption maxima at λ293 mμ and λ224 mμ (ε 20590 and 8882 respectively) (lit. value[28]: λ_{max} 290 mμ ε 14200 - 17500). The benzilidine derivative (LIX) when subjected to lithium aluminium hydride reduction in presence of aluminium chloride furnished 6:13-oxido-2-benzilidine eudesmane (LX). The IR spectrum of which indicated

CHART FIVE CONTD.



absence of absorption due to the conjugated ketone at 1667 cm^{-1} and retention of the aromatic absorption band. Preliminary attempts to convert (LX) to (LXI) through ozonolysis were not successful.

III Method

This method utilizes the benzilidine derivative (LIX) prepared above; (LIX) when reduced with sodium borohydride in ethanolic solution afforded the alcohol (LXII) which was acetylated to the corresponding 3-acetoxy derivative (LXIII) obtained as a crystalline solid. The UV spectrum of (LXIII) showed absorption maxima at $\lambda_{236.5}$ and λ_{max} 212 mμ and the IR spectrum showed a prominent band at 1740 cm^{-1} for the acetate carbonyl and absence of absorption due to the -OH group. However the further transformations involving ozonolysis of benzilidine derivative (LXIII) to furnish the keto acetate (LXIV) and subsequent reduction of the latter with zinc and acetic acid to yield the 2-keto oxide (LXI) were not carried out.

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E X P E R I M E N T A L

Preparation of 3-oxo eudesman-6:13 oxide (XIX)

3-Oxo-eudesman-6:13 oxide (XIX) was prepared starting from (-) ∝-santonin[28] (I). (-)∝-Santonin (I) was catalytically hydrogenated to ∝-tetrahydro-santonin (XV) in acetone medium. The ketal (XVI) of the latter on reduction with lithium aluminium hydride afforded the ketal-diol (XVII). The ketal-diol was deketalized by refluxing with dilute H_2SO_4 to keto-diol (XVIII) and then dehydrated by refluxing with toluene and 20% hydrochloric acid. The resulting 3-keto oxide (I) was crystallised from petroleum ether (40^o-60^o).

Melting point - 85^o- 86^o (lit value[40] 84^o-85^o)

Specific rotation - $\alpha)_D$ - 7.5^o (C, 4.98% in $CHCl_3$).

Analysis - C, 76.42; H, 10.22; $C_{15}H_{24}O_2$

requires C, 76.22; H, 10.24%

Vapour phase chromatography - using a polyester column maintained at 220^o and hydrogen as carrier gas, showed a single peak at 22' 28" (150 M- amp. 8.5 sec./10 cc).

TLC - TLC over a glass plate coated with a mixture of silicic acid and plaster of paris (85:15; 200 mesh) and activated at 120^o for 2 hrs. showed a single spot using petroleum ether - 5% ethyl acetate system.

IR spectrum (Nujol film) Showed bands at 2899, 2299, 1770, 1695, 1471, 1370, 1333, 1316, 1274, 1190, 1163, 1117, 1075, 1058, 1031, 1000, 971, 943, 926, 901, 885, 840, 781, 725 and 704 cm^{-1}.

2:4 DNP derivative of 6:13 oxido-3-keto eudesmane

To a solution of dinitrophenyl hydrazine (0.226 g) in ethanol (25 ml), concentrated HCl (0.25 ml) was added. The solution was boiled and filtered through flutted filter paper. To the clear filtrate, a solution of 3-keto oxide (XIX; 0.113 g) in ethanol (2 ml) was added and the solution was boiled for two minutes. It was kept at room temperature for 4 days when a solid separated. It was filtered and washed with ice-cold ethanol. Dried under vacuum to get red crystals.

M.P. - 176^{o}-177^{o}

Analysis - Found: C, 60.77; H, 6.64; N, 14.0

$C_{21}H_{23}O_5N_4$ requires : C, 60.56; H, 6.68; N, 13.45%.

IR spectrum (Nujol film) Showed bands at 2559, 1626, 1600, 1527, 1462, 1379, 1342, 1307, 925, 833, 746 and 724 cm^{-1}.

Oxime of 3-keto oxide

To a solution of 3-keto oxide (XIX; 0.29 g) in ethanol (12 ml), a solution of hydroxylamine hydrochloride (0.8 g) in water (3 ml) and a solution of NaOH (10%; 3 ml) was added and the mixture refluxed

over steam bath for two hrs. It was diluted with water (50 ml) and ethanol was removed under suction. The separated solid was filtered out and washed with water until free of alkali. Dried under vacuum and crystallised from petroleum ether-acetone mixture (1:1).

M.P. - 138°-139°.

Specific rotation - $\alpha)_D^{25^\circ}$ - 92° (C, 2.04% in $CHCl_3$).

Analysis - Found: C, 72.13; H, 9.41

$C_{15}H_{25}O_2N$ requires: C, 71.71; H, 9.95%.

IR spectrum (Nujol film) showed bands at 3226, 2874, 1770, 1653, 1502, 1370, 1342, 1227, 1193, 1175, 1124, 1126, 1000, 980, 943, 847, 840, 787, 763 and 704 cm^{-1}.

Semicarbazone derivative of (XIX)

The semicarbazone derivative of (XIX) was prepared by treating its ethanolic solution with semicarbazide hydrochloride. The resulting solid derivative was crystallised from alcohol and dried over P_2O_5.

M.P. - 200°.

Analysis - Found: N, 14.27%

$C_{16}H_{27}O_2N_3$ requires: N, 14.32%.

Baeyer-Villiger oxidation of 3-oxo eudesman-6:13 oxide (XIX)

(XIX), (3.5 g) was dissolved in chloroform (60 ml) and a solution of perbenzoic acid (1.14 N; 45 ml) in chloroform was added. The mixture was allowed to stand overnight at 0°, and at room temperature for 6 hrs. It was then washed with saturated sodium carbonate solution

water and dried over anhydrous sodium sulphate. Evaporation of the solvent furnished the ε-lactone (XL, 2.904 g) which was crystallized from petroleum ether and acetone mixture (80:20).

M.P. - 139°-140°.

Specific rotation - $[\alpha]_D^{33^\circ}$ - 72° (C, 2.9%, $CHCl_3$).

Analysis - Found : C, 70.73; H, 9.22.

$C_{15}H_{24}O_3$ requires: C, 71.39; H, 9.59%.

IR spectrum - (in Nujol) Showed a prominent band at 1760 cm^{-1} due to C=O group and other bands at 2930, 2880, 1555, 1480, 1395, 1360, 1318, 1310, 1295, 1280, 1230, 1215, 1200, 1180, 1160, 1135, 1095, 1070, 1025, 965, 932, 895, 885 and 720 cm^{-1}.

3,4-Seco-4-acetoxy-6:13-oxidoeudesman-3-oic acid (XLVI)

A mixture of lactone (XL) (0.473 g) and ethanolic potassium hydroxide (3%; 10 ml) was heated under reflux for 5 hrs.;cooled, dilute with water (100 ml) and extracted with ether. The ether extract on solvent removal left no residue. The aqueous part on acidification with hydrochloric acid, extraction with ether (25 ml x 3), washing with water, drying and evaporation of the solvent afforded the corresponding hydroxy acid (0.479 g) as viscous brown liquid.

A mixture of the above hydroxy acid (0.470 g), acetic anhydride (5 ml) and sodium acetate (anhydrous) (0.05 g) was refluxed in oil bath for 2 hrs. Cooled,

diluted with water (30 ml) and extracted thrice with ether (25 x 3). The combined ether extract was repeatedly washed with saturated sodium carbonate solution. The ether extract on solvent removal furnished 0.239 g of solid m.p. 138°-139°C identified as (XL) through IR and mixed m.p. The sodium carbonate extracted material on acidification, extraction with ether, washing with water, drying and evaporation of the solvent furnished the acetoxy acid XLVI (0.177 g).

6:13-Oxido-2,3-seco-4-acetoxy eudesm-1-ene (XLVII)

A mixture of XLVI (0.177 g), dry benzene (5 ml), cupric acetate (0.02 g) and pyridine (one drop) was magnetically stirred at room temperature for 0.5 hr. Lead tetraacetate (0.5 g) was then added followed by remainder of benzene (15 ml). The stirring was continued for one hr. in dark. The mixture was then refluxed for one hr. over steam bath under a slow current of nitrogen in dark. After cooling the reaction mixture, excess of lead tetraacetate was destroyed by ethylene glycol. The reaction mixture was washed with saturated sodium carbonate solution to separate the unreacted acid. The neutral part after the usual work up left a residue (0.086 g) which was chromatographed over Gr. II alumina (1:20). The petroleum ether-benzene fraction (1:1) was distilled at 140°(bath)/0.2 mm.

Analysis - Found: C, 72.19; H, 9.92

$C_{16}H_{26}O_3$ requires: C, 72.18; H, 9.77%.

IR spectrum - The spectrum showed two prominent bands at 1724 and 1242 cm^{-1}. Other bands were at 2941, 1639, 1449, 1370, 1325, 1183, 1156, 1130, 1081, 1026, 1000, 970, 952, 934, 917, 854 and 833 cm^{-1}.

6:13-Oxido-2,3-seco-4-hydroxy eudesm-1-ene (XLVIII)

XLVII, (0.215 g) was refluxed with alcoholic potassium hydroxide (5%, 5 ml) for 5 hrs. Cooled, diluted with water (50 ml) and extracted with ether (15 ml x 3). The combined ether extract was washed with water till neutral, dried over anhydrous sodium sulphate and evaporated to furnish (XLVIII, (0.106 g).

IR spectrum - (Nujol film) Showed bands at 3448, 2941, 2326, 1695, 1626, 1449, 1408, 1370, 1342, 1176, 1149, 1075, 1026, 970, 952, 885, 869, 850, 833, 781, 763, 740, 699 and 671 cm^{-1}.

6:13-Oxido-2,3-seco-4-oxo eudesm-1-ene (XLIX)

Jones reagent was added dropwise at room temperature to a solution of alcohol (XLVIII) (0.106 g) in acetone till the chromic acid colour persisted. The reaction mixture was kept for 30 minutes at room temperature, diluted with water (50 ml) and extracted with ether (20 ml x 3). The ether extract on working up furnished the ketone (XLIX) (0.097 g).

B.P. - 140°(bath)/0.5 mm.

IR spectrum showed prominent bands at 3448 and 1695 cm^{-1}. Other bands were observed at 2941, 2326, 1625, 1449, 1408, 1370, 1342, 1260, 1212, 1176, 1149, 1075, 1026, 970, 952, 929, 885, 869, 849, 833, 781, 763, 740, 699 and 671 cm^{-1}.

5,7α(H)-4,6,11 β(H)-6:13-oxido-2,3-seco-eudesm-1,3-diene (LI)

To an ice-cooled solution of methyl magnesium iodide (prepared from methyl iodide (2.1 ml), and magnesium (0.95 g) in dry ether (20 ml) was added dropwise under stirring a solution of keto oxide (XLIX) (0.038 g) in dry ether (5 ml). The reaction product was heated under reflux for 1.5 hrs. and decomposed with saturated aqueous NH_4Cl (5 ml). The reaction mixture was extracted with ether and the extract washed with water until neutral, dried and evaporated to get a brown coloured residue (0.044 g).

To a solution of this residue (L; 0.04 g) in pyridine (3 ml), phosphorus oxychloride (0.2 ml) was added and the mixture was heated on steam bath for 2 hrs. The reaction product was diluted with water and extracted once with chloroform (5 ml) and with ether (10 ml x 3). The combined extract was washed with dilute hydrochloric acid, saturated aqueous solution of $NaHCO_3$, water and dried over anhydrous Na_2SO_4 and distilled to get the diene (LI).

B.P. - 140°(bath)/0.2 mm.

VPC - VPC on a polyester column maintained at 216° and using hydrogen as carrier gas, the diene showed a single peak at 2' 42". Injection of an authentic sample of diene under identical conditions had a retention time of 2' 48".

TLC - TLC on a glass plate coated with silicic acid and plaster of paris (85:15) showed a single spot.

IR spectrum - (liquid film) was exactly identical with that of authentic sample.

Oxide (LI) from saussurea lactone (VI)

Saussurea lactone m.p. 139°-141°, $\alpha)_D$ + 60° (0.250 g) was reduced with lithium aluminium hydride (0.5 g) as usual. The diol (LII) (0.203 g) thus obtained was refluxed with dry benzene (20 ml) and p-toluene-sulphonic acid (0.05 g) for 0.5 hr. on steam bath. The reaction product obtained after usual working up was chromatographed over alumina (Gr. II); petroleum ether eluted fraction (0.1 g) gave the required oxide on evaporation of the solvent.

6:13-Oxido-3ξ-hydroxy eudesmane (LVII)

A solution of the 3-keto oxide (XIX; 0.4416 g) in dry ether (15 ml) was added to a suspension of LAH (0.348 g) in dry ether (30 ml). The mixture was refluxed for 3 hrs., cooled and carefully treated with ethanol and then with water to decompose excess of LAH. It was

acidified with dilute HCl aqueous (1:1) and extracted with ether. The ether extract was washed with water and dried. The removal of solvent furnished the 3ξ-hydroxy oxide (LVII) (0.4554 g).

B.P. 160°-170°(bath)/0.15 mm.

Specific rotation - $[\alpha]_D^{29^\circ}$ - 5 (C, 3.44%; $CHCl_3$).

Analysis - Found: C, 75.68; H, 11.03

$C_{15}H_{26}O_2$ requires: C, 75.63; H, 10.92%.

IR spectrum (Nujol film) showed a prominent band at 3333 cm^{-1}. Other bands were at 2941, 2326, 1460, 1379, 1117, 1058, 1031, 1010, 980, 952 and 854 cm^{-1}.

6:13-Oxido-Δ^2-eudesmene - (LV) from 3-keto oxide (XIX)

(a) 2-Bromo-3-keto oxide (LIII)

The keto oxide (XIX; 0.2654 g) was dissolved in acetic acid (3 ml). To this solution, HBr (30%) in acetic acid (0.1 ml) was added. This was followed by a dropwise addition of solution of bromine (0.38 g) in acetic acid (1 ml), at room temperature under stirring. Reaction mixture was stirred at 40° for 15 minutes. Excess of bromine was destroyed by adding ethanol (2 ml). The reaction mixture was then poured in ice-cold water (50 ml) and extracted with ether (15 ml x 3). The combined ether extract was washed with water, dried and solvent evaporated to get the crude bromoketone (LIII).

(b) Bromohydrin (LIV)

The solution of above bromoketone (LIII) in

ethanol (30 ml) was treated with sodium borohydride (0.150 g) by shaking vigorously during addition and kept at room temperature for 20 hrs. It was then poured into water and extracted with ether. The ether extract was washed with water until neutral. Dried over anhydrous Na_2SO_4 and ether evaporated to get the bromohydrin (LIV; 0.3151 g).

IR spectrum - (liquid film) Showed absorption bands at 3390, 2899, 2326, 1923, 1724, 1613, 1449, 1370, 1266, 1190, 1163, 1124, 952, 909, 885, 862, 800, 775, 724 and 709 cm^{-1}.

(c) 6:13-Oxido-Δ^2-eudesmene (LV)

Zinc powder (1.2 g) was added to a solution of (LIV; 0.3151 g) in acetic acid (25 ml) and the mixture was refluxed for 0.5 hr. The reaction product on cooling was filtered through a flutted filter paper, acetic acid removed. The residue was dissolved in ether and the ethereal solution was washed with saturated Na_2CO_3 solution and water, dried over anhydrous sodium sulphate and concentrated to get the crude hydrocarbon (0.2376 g). This crude product was purified by passing over alumina (Gr. I, 1:25) and eluted with petroleum ether, petroleum-ether-benzene (1:1), benzene and ether. The petroleum ether concentrate was distilled.

B.P. - 115-125°(bath temp.)/0.1 mm.

Specific rotation - $\alpha)_D^{29°}$ - 19° (C, 4.4%; $CHCl_3$).

Analysis - Found: C, 81.69; H, 10.98.

$C_{15}H_{24}O$ requires : C, 82.02; H, 10.91%.

VPC - VPC on a polyester column maintained at 180° and using H_2 as a carrier gas, showed a single peak at 12' 15".

IR spectrum - (Liquid film) showed bands at 2857, 2299, 1639, 1439, 1361, 1316, 1282, 1258, 1235, 1176, 1149, 1117, 1047, 1020, 980, 961, 939, 877, 833, 813, 729 and 689 cm^{-1}.

Benzoate of 6:13-oxido-3ξ-hydroxy eudesmane (LVIII)

A mixture of alcohol (LVII; 0.1146 g) pyridine (4 ml) and benzoyl chloride (0.8 ml) was kept at room temperature for 48 hrs. It was then poured into ice-cold water (50 ml) and extracted with ether. The ethereal extract was washed successively with HCl, Na_2CO_3 solution and water, dried over anhydrous Na_2SO_4. The crude benzoate (LVIII) obtained on evaporation of ether was chromatographed over Gr. II alumina (1:25) and eluted by petroleum ether, benzene and alcohol. The petroleum ether eluate on concentration gave benzoate.

IR spectrum - (liquid film) Showed prominent bands at 2857, 1770, 1695, 1587, 1439, 1370, 1299, 1258, 1198, 1163, 1111, 1064, 952, 800, 785 and 709 cm^{-1}.

Pyrolysis of the benzoate of 6:13 oxido-3ξ hydroxy-eudesmane (LVIII)

The benzoate (0.2347 g) was heated at 350° for

one hr. in nitrogen atmosphere. The product of pyrolysis was extracted with ether, and washed with saturated Na_2CO_3 solution and water, dried over anhydrous Na_2SO_4. The residue (0.0991 g) obtained on evaporation of the solvent was chromatographed over alumina (Gr. I; 1:20). The petroleum ether eluted fraction was distilled at 145° (bath)/0.7 mm.

VPC - VPC of this distilled product at 180° on polyester column 12"/hr., and H_2 as carrier gas showed two peaks at 13' 33" (major) and 16' 18". Injection of an authentic sample of 6:13-oxido-Δ^2-eudesmene (LV) under identical conditions showed a retention time 13' 30".

6:13-Oxido-2-benzilidine-3-acetoxy-eudesmane (LXIII)

To a boiling solution of 3-keto oxide (XIX; 2.0 g) in methanol (100 ml) freshly distilled benzaldehyde (1.2 g) was added, followed by NaOH solution (33%, 10 ml). Above mixture was maintained at 40°-50° for 72 hrs. under N_2- atmosphere. The mixture was then diluted with water and extracted with ether. The ether extract was washed with water, till neutral, dried over anhydrous Na_2SO_4 and solvent evaporated. The residue thus obtained was chromatographed over Gr. I alumina (1:20) and eluted successively with petroleum ether (200 ml), petroleum-ether-benzene (1:1) (200 ml); petroleum ether-benzene (1:2; 200 ml); benzene (200 ml) and benzene-ethyl acetate (5:1; 200 ml).

UV of petroleum ether + benzene (1:1) fraction

UV Spectrum (in ethanol) λ_{max} at 293 mμ (ε value 20590) λ_{max} at 224 mμ (ε value 8882).

The petroleum ether-benzene (1:1) fraction (LIX) (0.6499 g) was dissolved in ethanol (30 ml) and sodium borohydride (0.1 g) was added. The mixture was kept at room temperature overnight. The reduction product after usual working up afforded a resinous material (LXII) which could not be crystallised.

UV spectrum - (in ethanol) λ_{max} at 239 mμ (ε 85550)

A mixture of crude alcohol (LXII) (0.360 g), acetic anhydride (0.5 ml) and pyridine (4 ml) was kept at room temperature for 12 hrs. It was then poured into water and extracted with ether. The ether extract was thoroughly washed with HCl, Na_2CO_3 solution, followed by water till neutral and dried over anhydrous Na_2SO_4. On evaporation of the solvent a solid (0.3181 g) was obtained (LXIII). Crystallised from petroleum ether.

M.P. 163°-164°.

Specific rotation - $\alpha)_D^{25^\circ}$ - 32° (C, 3.94%, $CHCl_3$).

Analysis - Found: C, 77.85; H, 8.81.

$C_{24}H_{32}O_3$ requires: C, 78.22; H, 8.75%.

IR spectrum (Nujol film) showed bands at 2941, 1731, 1653, 1587, 1460, 1379, 1235, 1183, 1117, 1070, 1036, 1015, 971, 893, 862, 847, 758 and 699 cm^{-1}.

UV spectrum (in ethanol) λ_{max} at 236.5 mμ. and 212 mμ.

Oxime of ∝-tetrahydrosantonin (XLII)

To a solution of ∝-tetrahydrosantonin (XV) (2.017 g) in a mixture of methanol (70 ml) and ethanol (50 ml), aqueous NaOH (10%, 20 ml) and hydroxylamine hydrochloride (5.07 g) in 20 ml water was added. The mixture was refluxed for 2 hrs. It was diluted with water (100 ml) and most of the alcohol was removed under suction. It was further diluted with water (500 ml), cooled in ice and filtered. The solid was washed with water (150 ml) and dried under vacuum over KOH pellets. Crystallised from methanol-acetone mixture (1:1).

M.P. 228°-229°.

Specific rotation - $\alpha)_D^{25^\circ}$ + 67.5° (0.77% in $CHCl_3$).

Analysis - Found: C, 68.45; H, 8.56.

$C_{15}H_{23}O_3N$ requires: C, 67.94; H, 8.68%.

IR spectrum (Nujol film) showed bands at 2899, 1739, 1453, 1374, 1224, 1205, 1182, 1129, 1022, 980, 943, 893, 855, 787 and 730 cm^{-1}.

Beckman rearrangement of the oxime (XLII)

To the solution of oxime (XLII; 2.929 g) in pyridine (25 ml) maintained at 0°, $POCl_3$ (5 ml) was added and the mixture was kept at room temperature for 1 hr. The mixture was poured into water when a white solid separated. Solvents were removed under suction. The solid material on crystallization from methanol furnished (XLIII).

M.P. - 216°-218° (mixed m.p. with starting oxime depressed to 190°-195°).

Analysis - Found: C, 67.56; H, 8.81; N, 5.35

requires : C, 67.94; H, 8.68; N, 5.28%

IR spectrum (Nujol film) showed bands at 3226, 2899, 1770, 1653, 1274, 1258, 1370, 1282, 1248, 1232, 1214, 1199, 1147, 1114, 1087, 1058, 1015, 980, 934, 900, 862, 847, 819, 781 and 719 cm^{-1}.

Preparation of the ε-lactone (XLI) from the lactam (XLIII)

To a solution of the lactam (XLIII, 0.609 g) in acetic anhydride (32 ml) and acetic acid (8 ml), cooled to 0°, sodium nitrite (6.6 g) was added in four equal lots with vigorous manual shaking and cooling in ice. The reaction mixture was maintained at 0° for 48 hrs. It was occasionally disturbed by glass rod. It was then poured into water and extracted thrice with ether. The combined ether extract was washed with sodium carbonate solution to separate it into acidic and neutral parts. The neutral part on usual work up, and prolonged cooling did not furnish the expected solid ε-lactone (XLI).

6:13-Oxido-2-benzilidine eudesmane (LX)

Aluminium chloride (9.9 g) was added to a suspension of LAH (1.552 g) in dry ether (60 ml). When the vigorous reaction subsided, a solution of benzilidine derivative (LIX, 1.4 g) in dry ether (20 ml)

was added dropwise in 5 minutes. The reaction mixture was stirred under reflux for 1 hr. and then decomposed by ethyl acetate at 0°. It was acidified by dil. H_2SO_4, extracted with ether, washed with water till free of acid, dried over anhydrous Na_2SO_4, and ether evaporated to furnish crude benzilidine derivative (LX) (1.323 g) which was chromatographed over Gr. I alumina. The petroleum ether eluted fraction (0.427 g) ~~showed~~ had

Analysis - Found: C, 84.20; H, 9.74

$C_{22}H_{32}O$ requires: C, 84.61; H, 9.61%.

IR spectrum (smear) showed prominent bands at 2880, 1590, 1490, 1450, 1370, 1280, 1185, 1130, 1075, 1035, 1020, 970, 885, 835, 750 and 700 cm^{-1}.

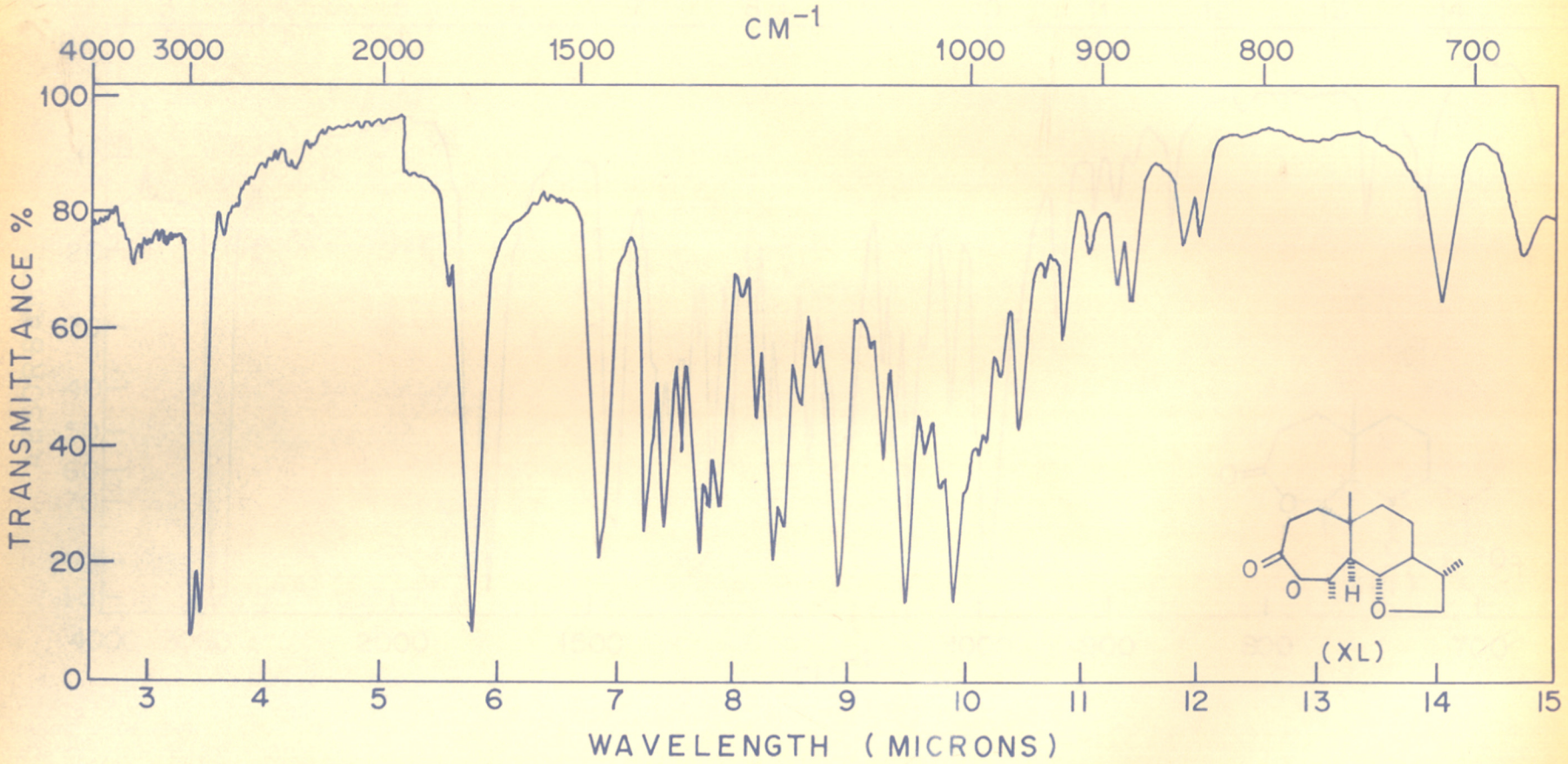


FIG. 1. IR SPECTRUM (NUJOL) OF LACTONE OF 3,4-SECO-4-HYDROXY-6,13 OXIDOEUDESMAN-3-OIC ACID

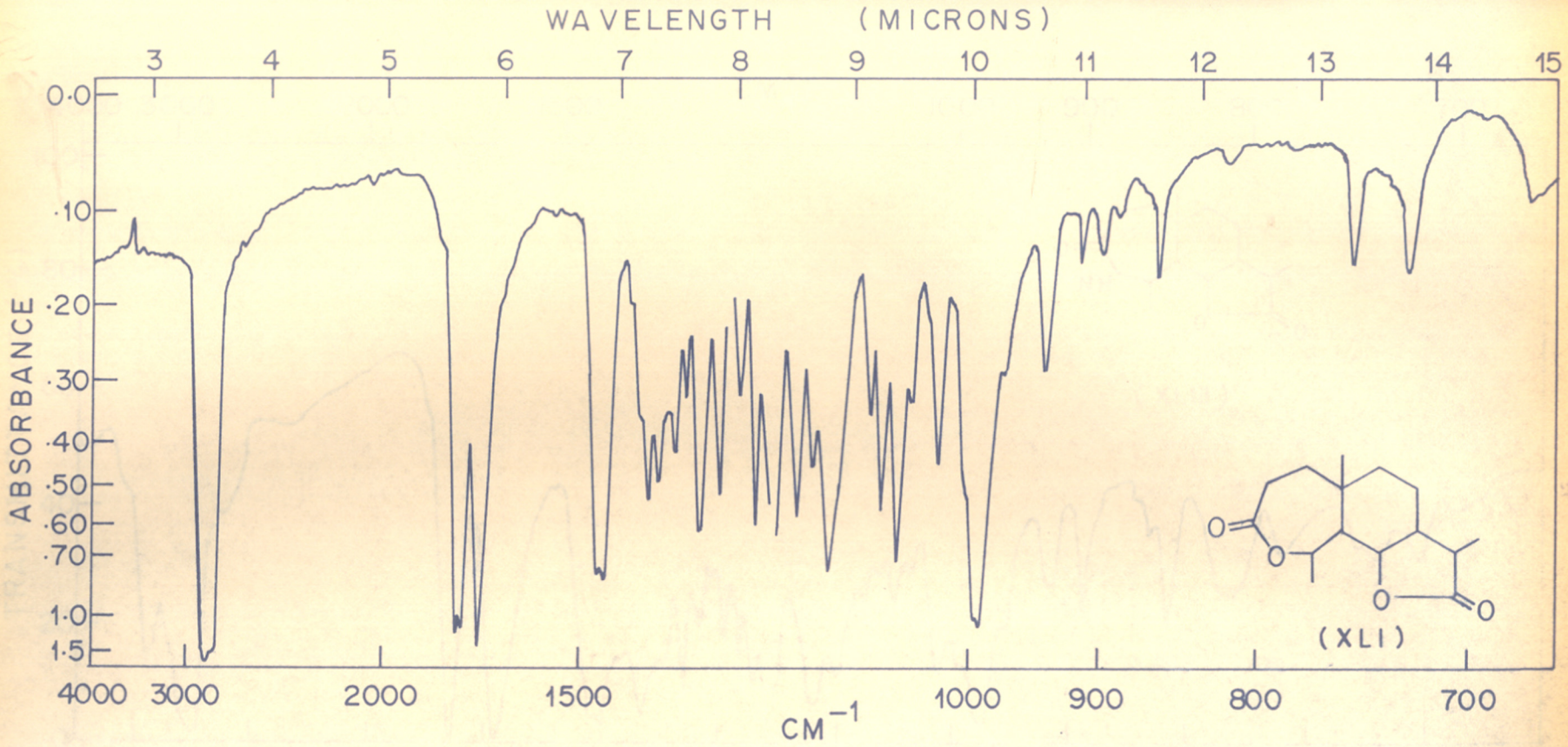


FIG. 2. IR SPECTRUM (NUJOL) OF ϵ-LACTONE FROM α-TETRAHYDROSANTONIN

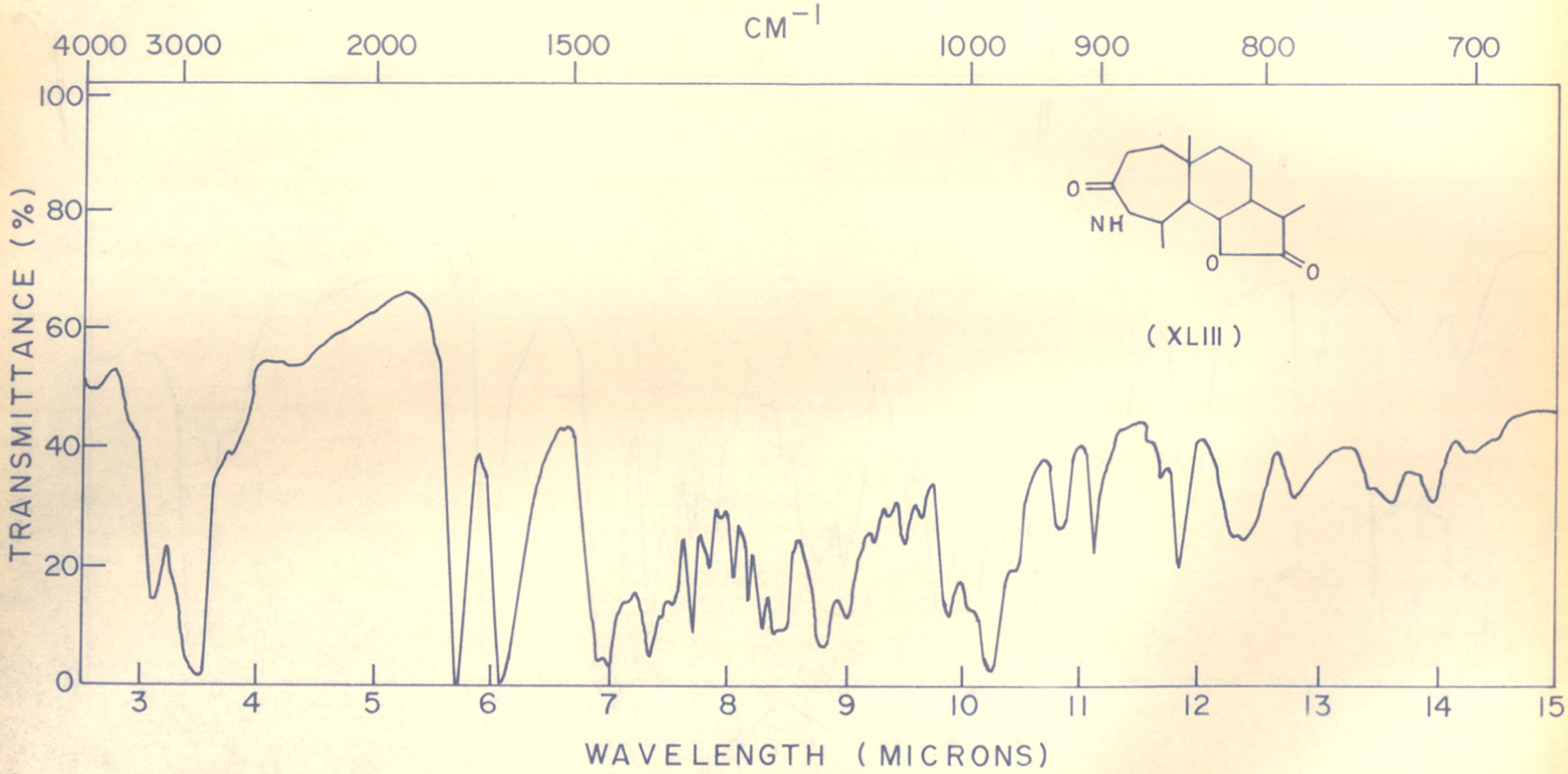


FIG. 3. IR SPECTRUM (NUJOL) OF LACTAM OF 3,4-SECO-6,13-SECO-4-AMINO 6-HYDROXYEUDESMAN-3,13-DIOIC ACID

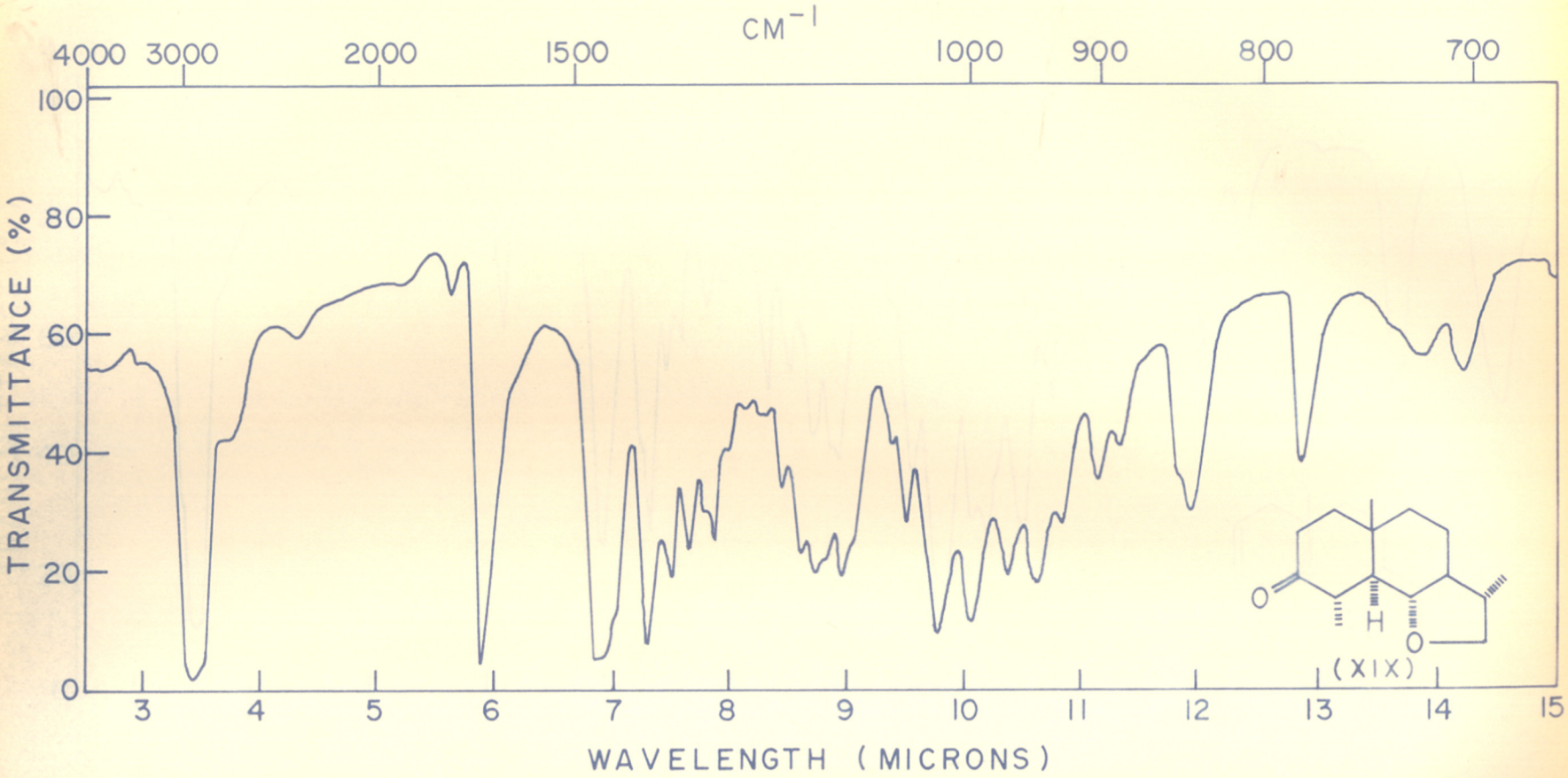


FIG. 4. IR SPECTRUM (NUJOL) OF 6:13-OXIDO-3-KETO EUDESMANE

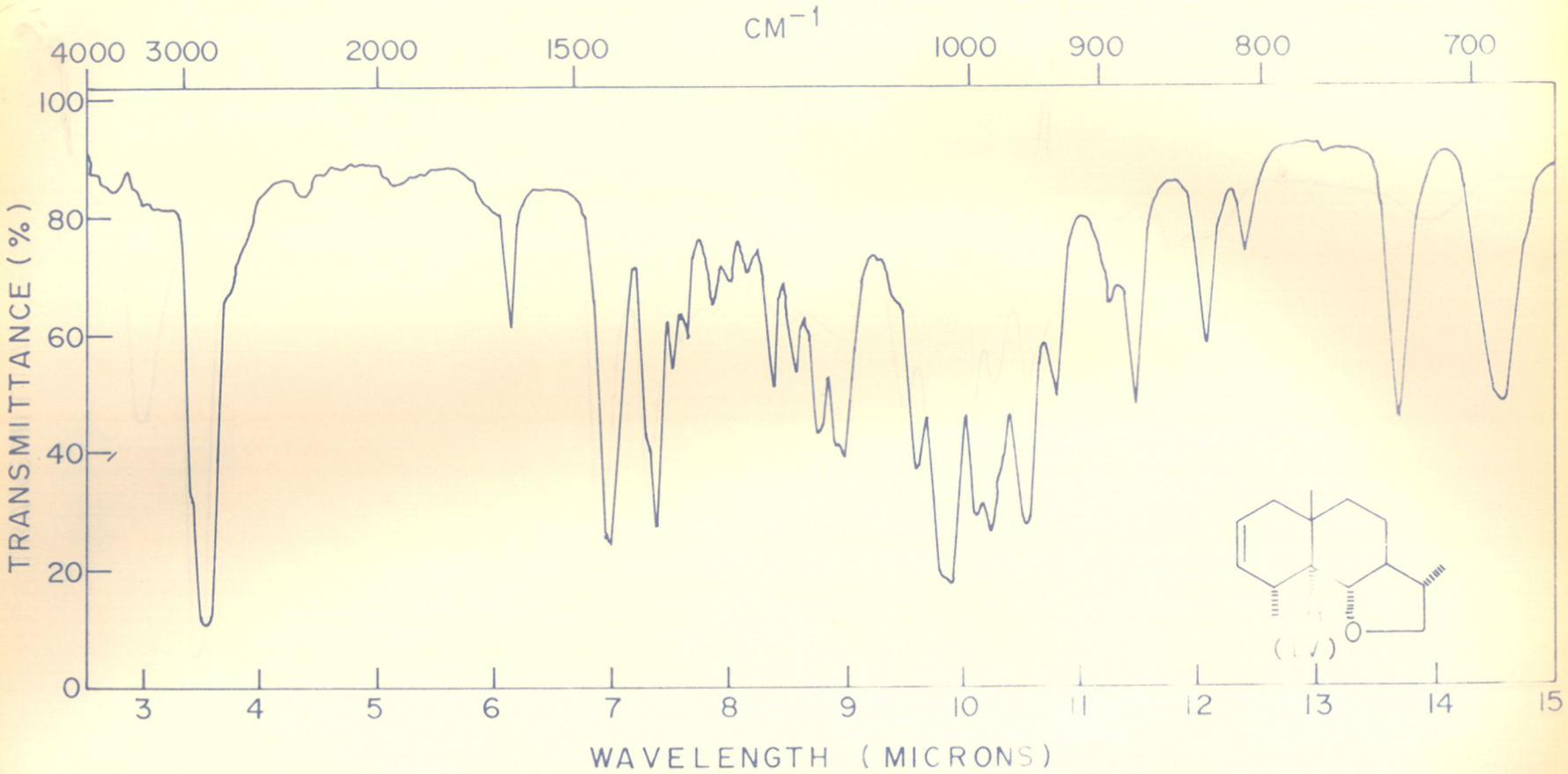


FIG. 5. IR SPECTRUM (LIQ. FILM) OF 6:13-OXIDO-Δ^2-EUDESMENE

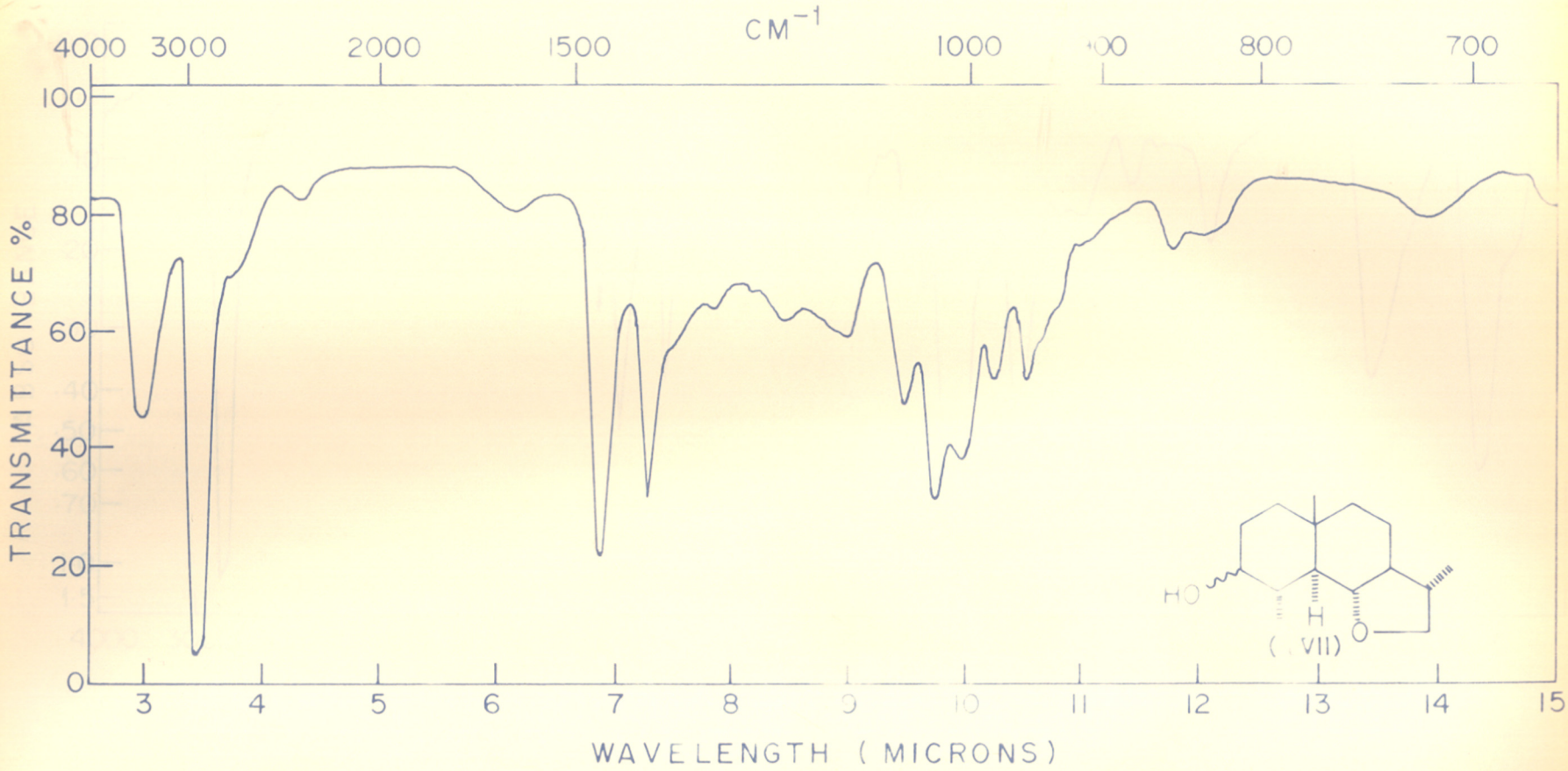


FIG. 6 IR SPECTRUM (NUJOL) OF 6:13-OXIDO-3ξ-HYDROXY EUDESMANE

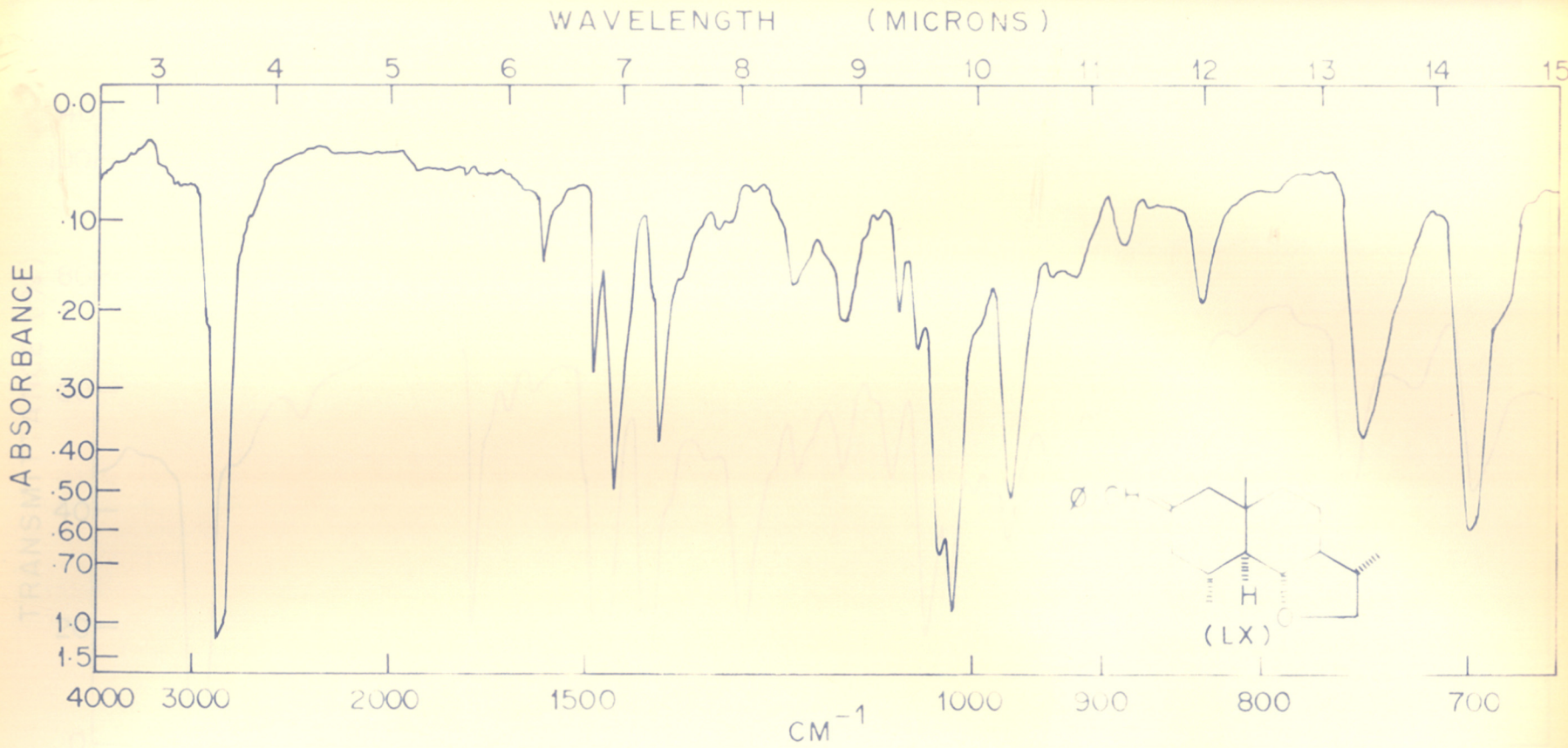


FIG. 7. IR SPECTRUM (SMEAR) OF 6:13-OXIDO-2-BENZILIDINE EUDESM NE

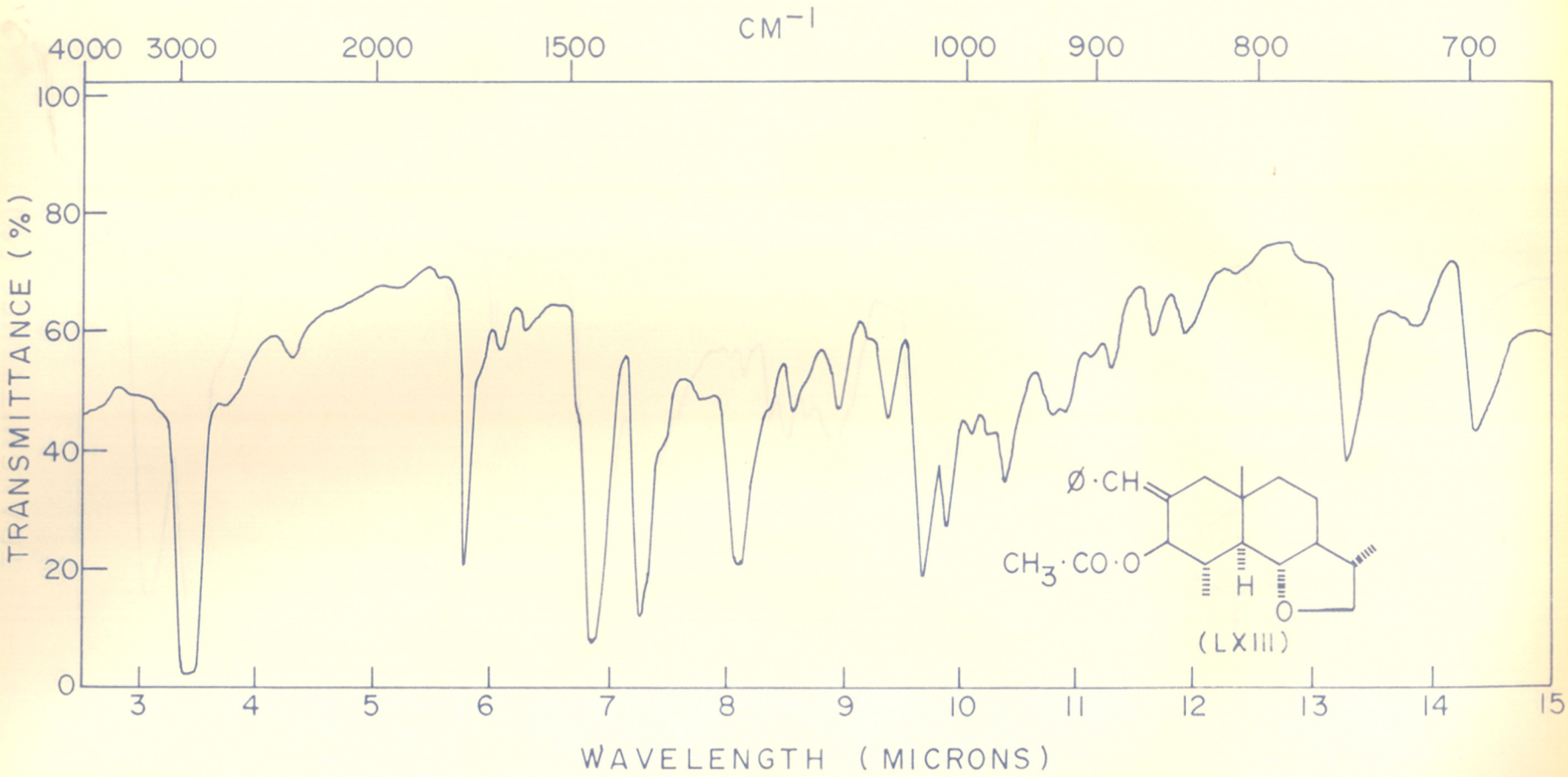


FIG. 8. IR SPECTRUM (NUJOL) OF 6:13-OXIDO-2-BENZILIDINE-3-ACETOXY EUDESMAN

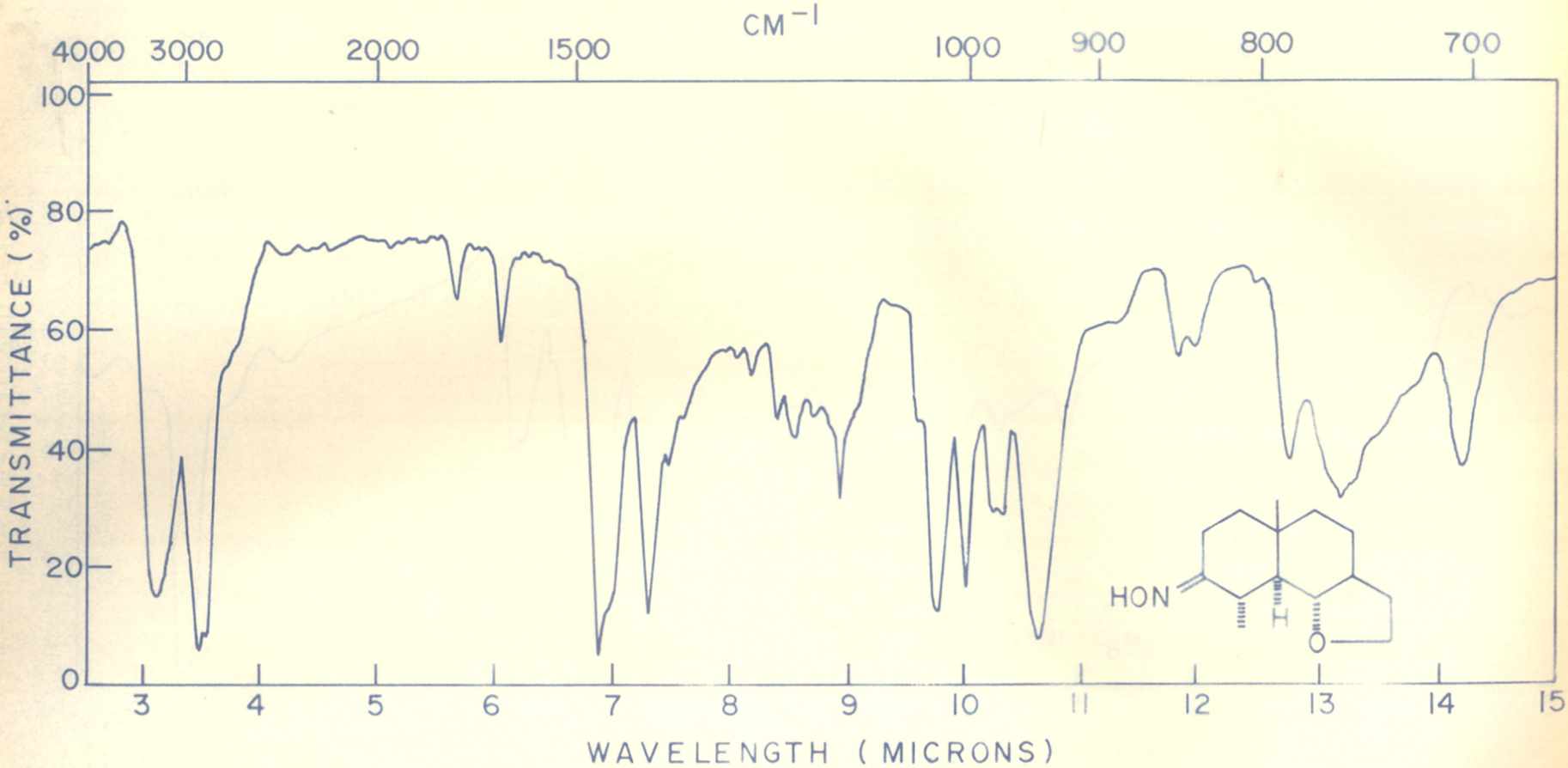


FIG. 9. IR SPECTRUM (NUJOL) OF OXIME OF 6:13-OXIDO-3-KETO EUDESMANE

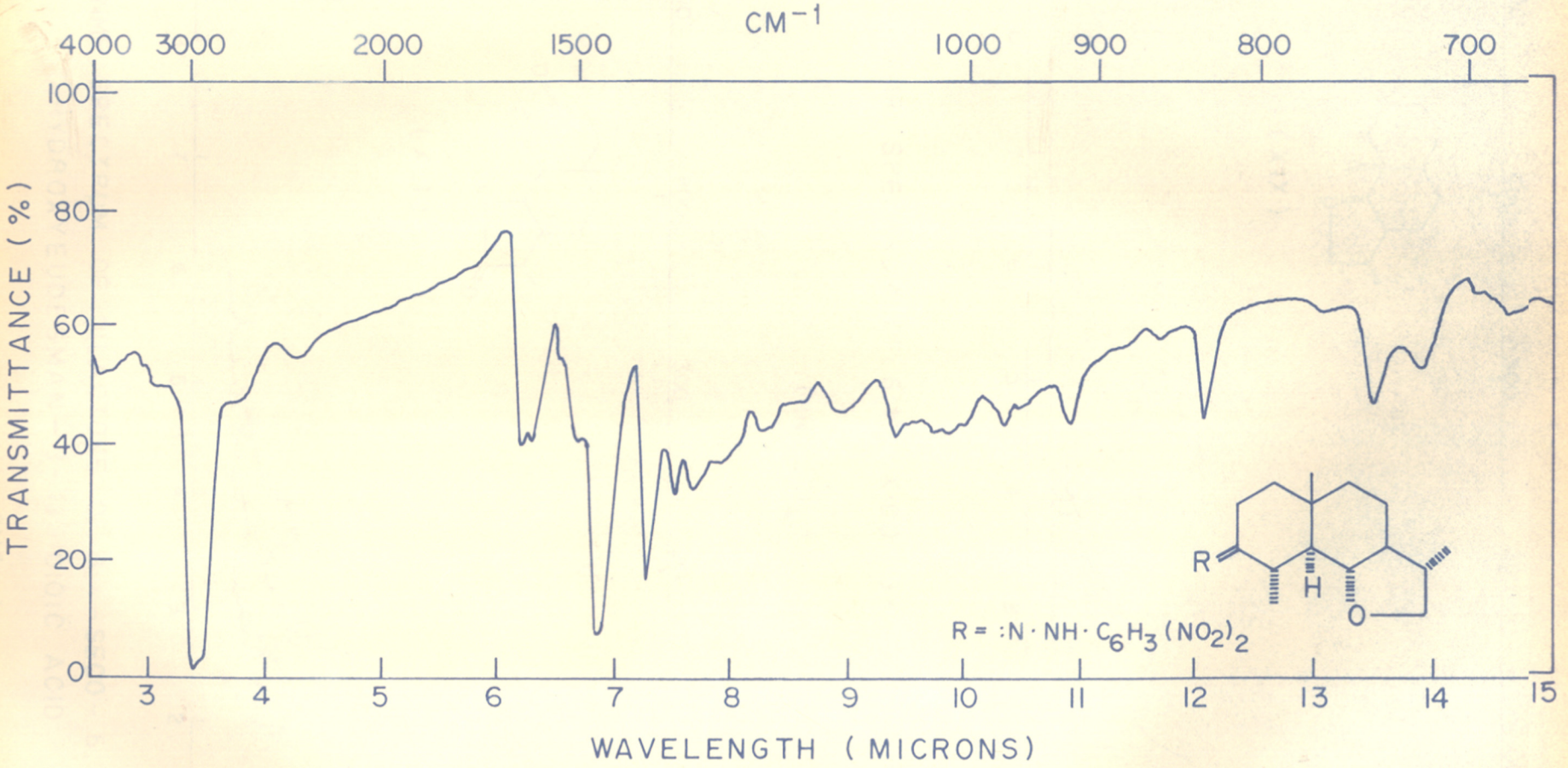
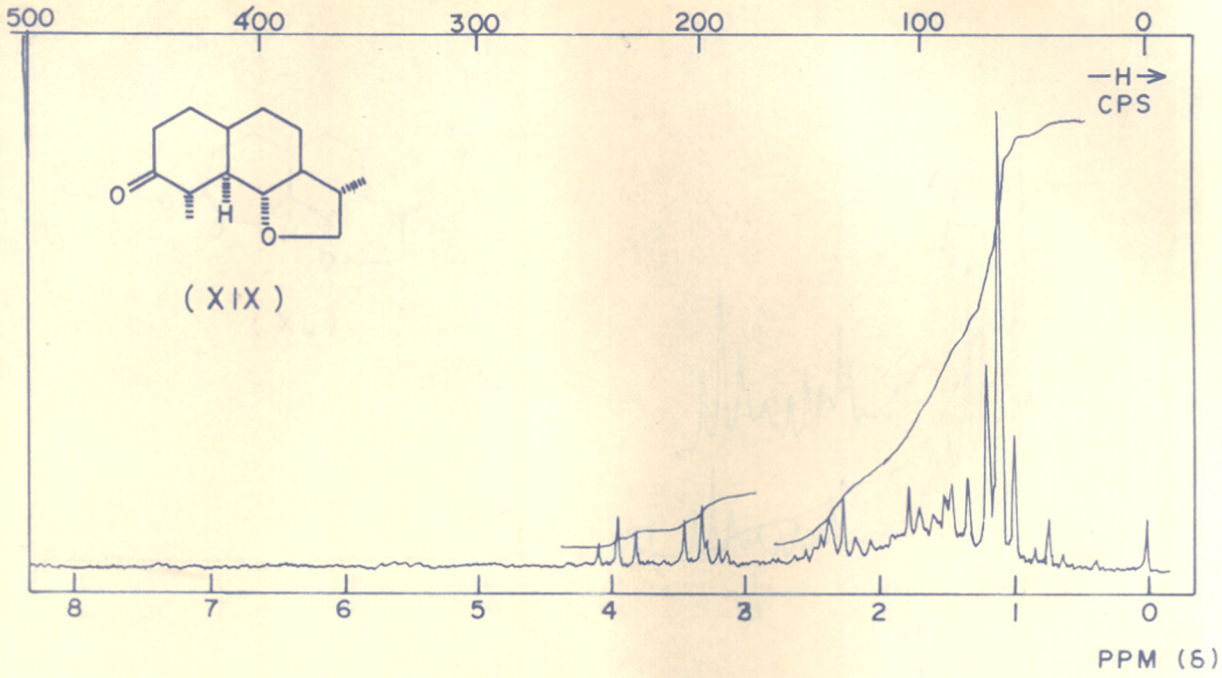


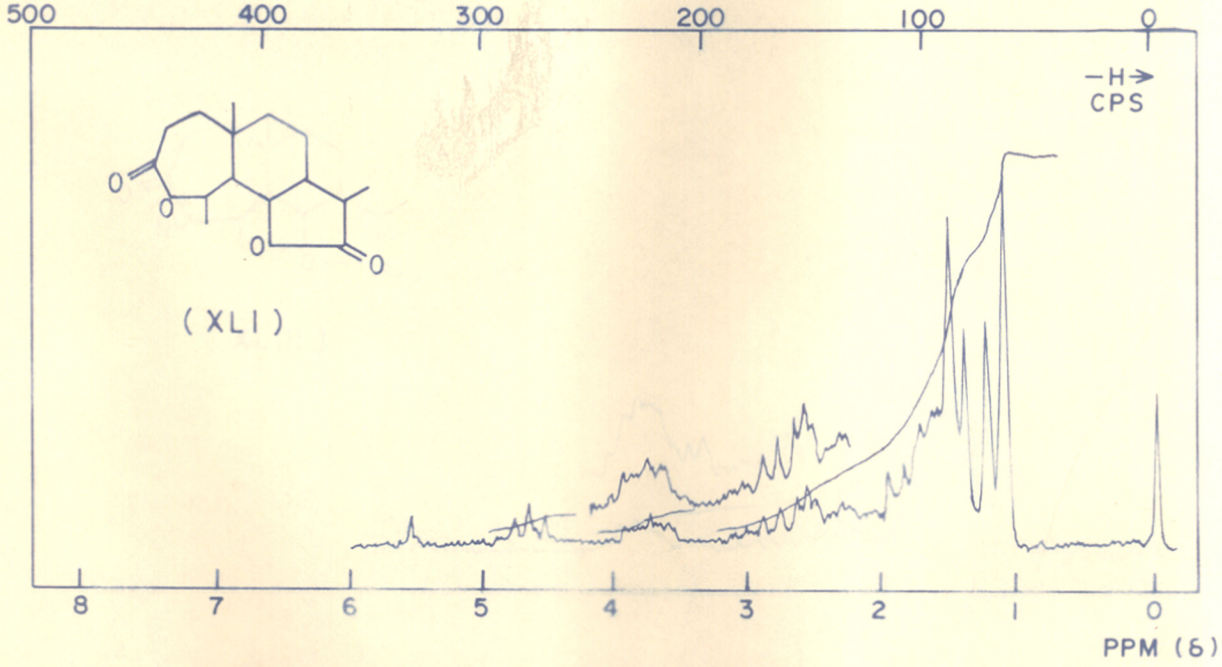
FIG. 10. IR SPECTRUM (NUJOL) OF 2:4 D.N.P. DERIVATIVE OF 6:13-OXIDO-3-KETO EUDESMANE



(XIX)

NMR SPECTRUM OF 6:13-OXIDO-3-KETO EUDESMANE

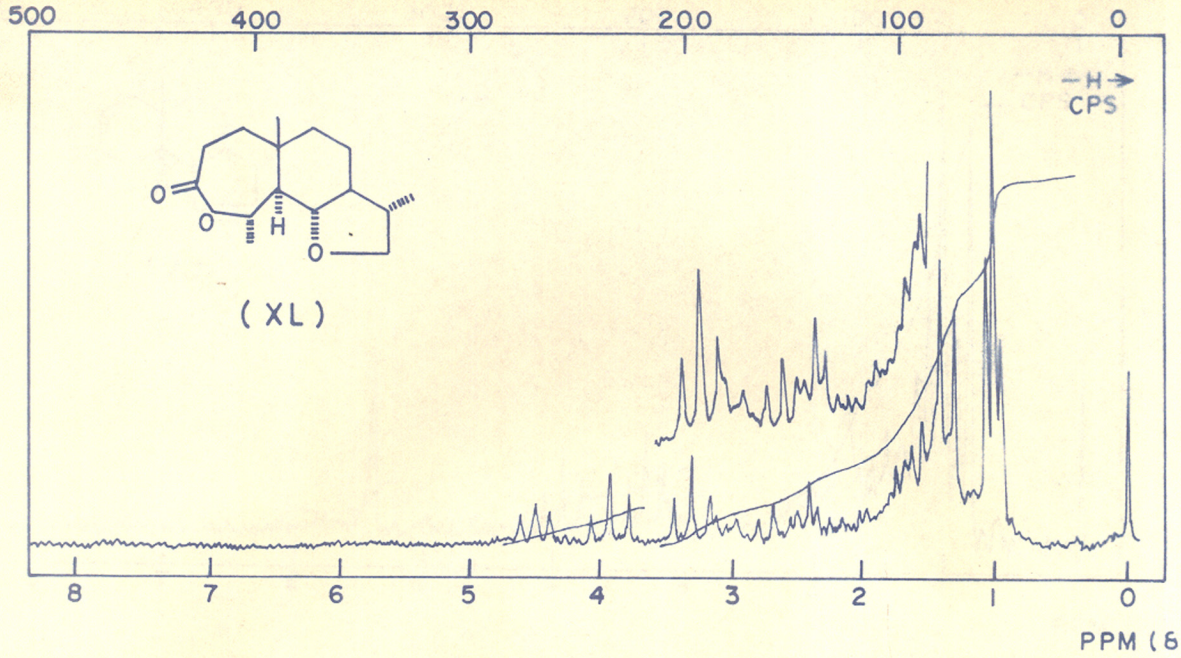
(IN CCl_4)



(XLI)

NMR SPECTRUM OF DILACTONE OF 3,4-SECO-6,13-SECO-4,6-DIHYDROXYEUDESMAN-3-13-DIOIC ACID

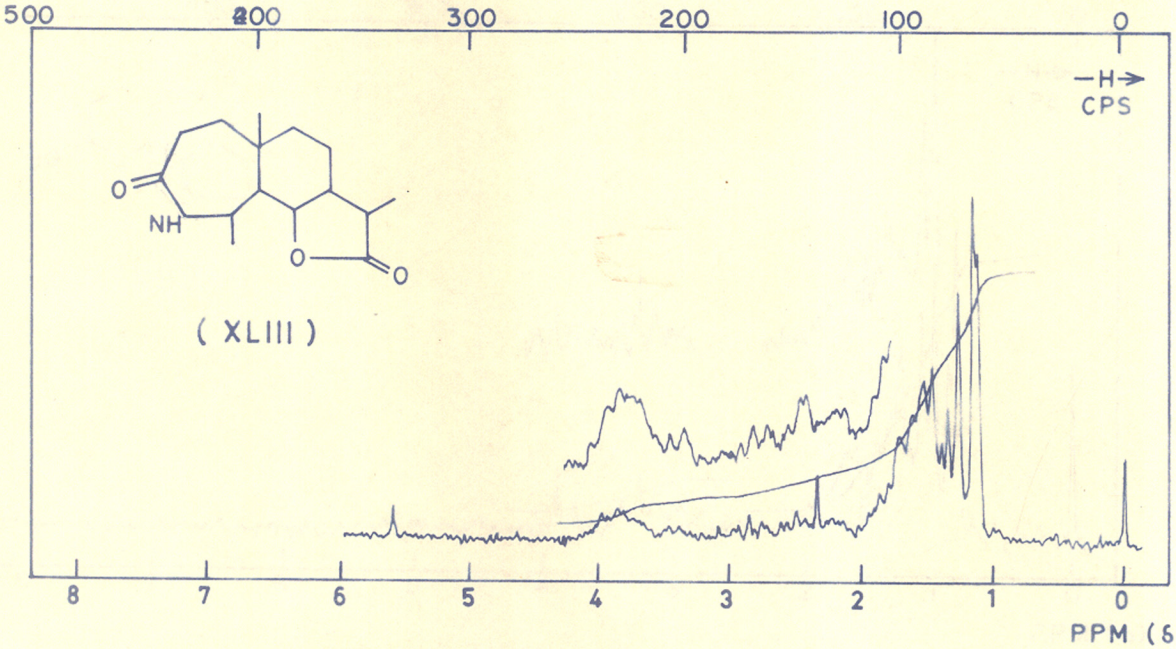
(IN $CHCl_3$)



(XL)

NMR SPECTRUM OF LACTONE OF 3,-4-SECO-4-HYDROXY-
—6,13-OXIDOEUDESMAN-3-OIC ACID

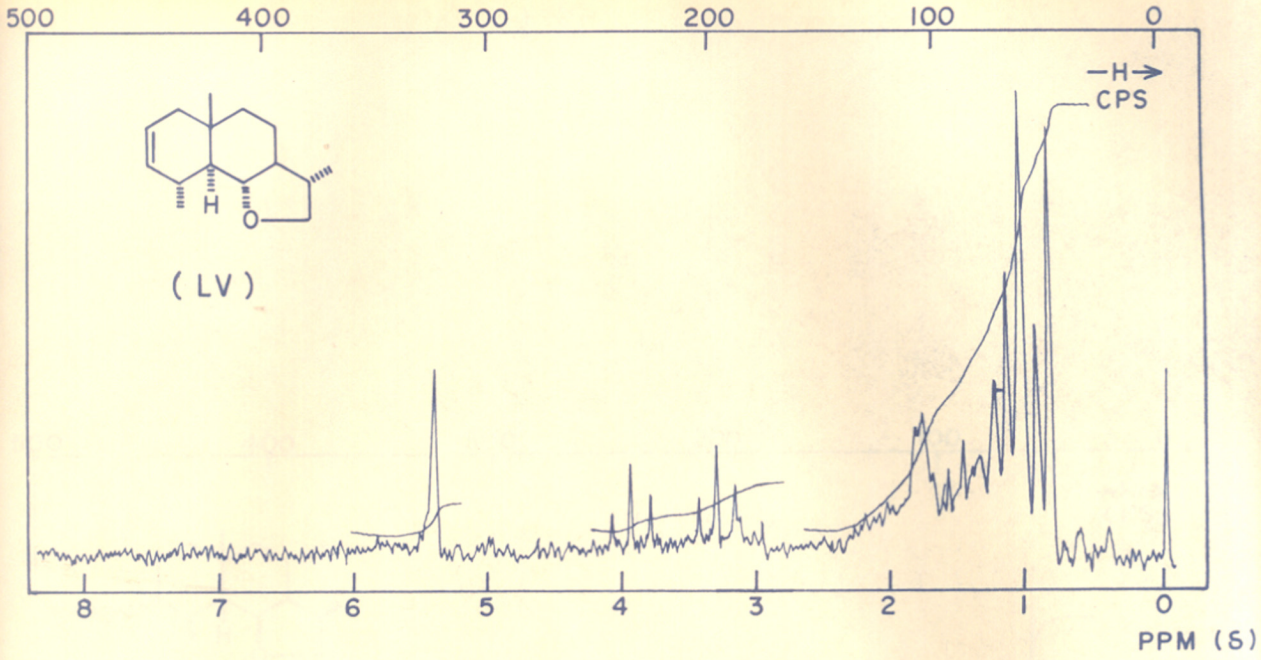
(IN CCl_4)



(XLIII)

NMR SPECTRUM OF LACTAM OF 3,4-SECO-6,13-SECO-4-
-AMINO-6-HYDROXYEUDESMAN—3,13-DIOIC ACID

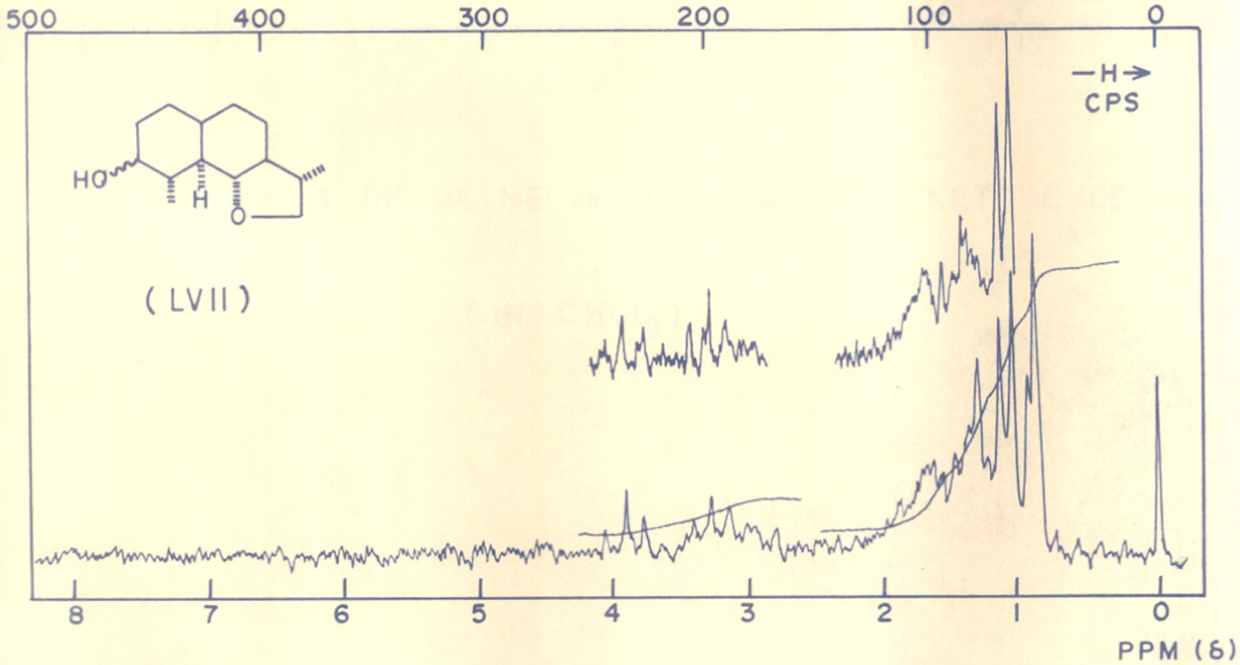
(IN $CHCl_3$)



(LV)

NMR SPECTRUM OF 6 : 13 – OXIDO – Δ^2 – EUDESMENE

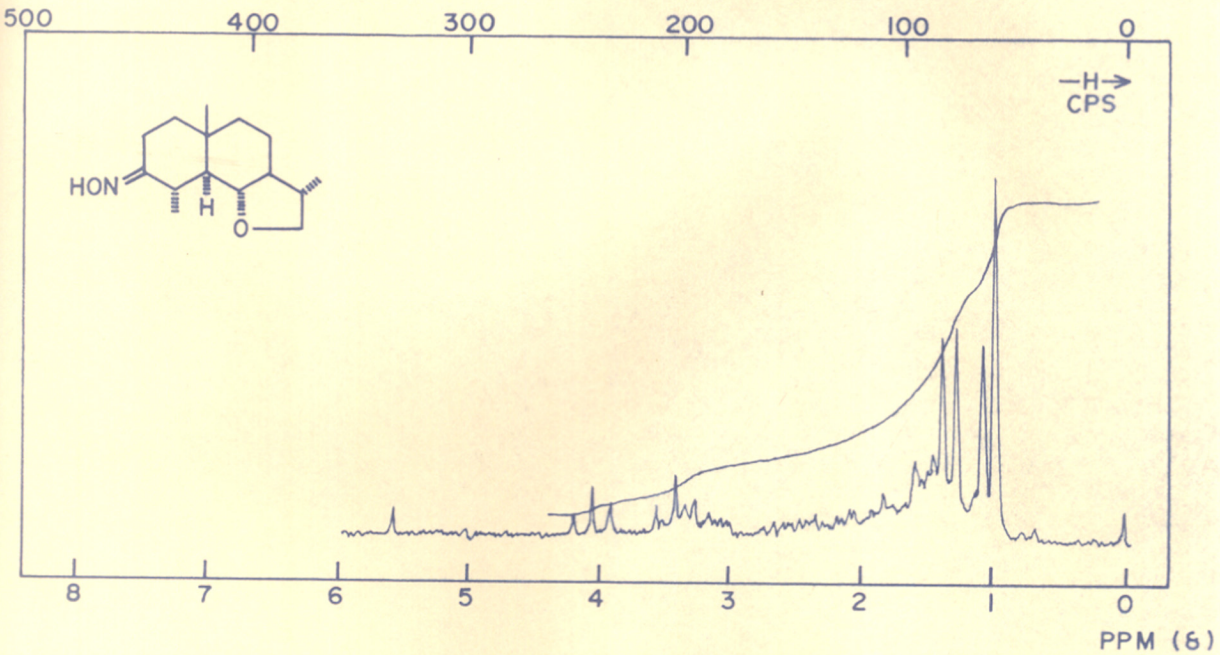
(IN CCl_4)



(LVII)

NMR SPECTRUM OF 6 : 13 – OXIDO – 3ξ – HYDROXY EUDESMANE

(IN CCl_4)



NMR SPECTRUM OF OXIME OF 6:13 OXIDO-3-KETO EUDESMANE

(IN $CHCl_3$)

PART - II

Chapter - I

Degradation of Bile Acid Side Chain with Lead Tetra Acetate.

SUMMARY

One of the important problems in the synthesis of medicinally important 11-oxygenated steroids from bile acid is the degradation of the side-chain. This Chapter deals with a new method of degrading the bile acid side-chain to obtain Δ^{22}-alkenes in good yields. The reagent employed is lead tetraacetate in presence of catalytic amounts of cupric acetate and pyridine. The resulting Δ^{22}-alkenes have been characterized. The values of C-19 and C-18 methyl signals in the NMR spectra of these alkenes are consistent with the values calculated for these compounds with the help of Zurcher's tables.

Further transformations have been carried out on one of the above alkenes, 3α, 12α-dihydroxy- Δ^{22}-24-norcholene (XV). The purpose of these transformations was to convert the bile acids to the derivatives of pregnane (XXXVI) and androstane (XXXV).

The degradation of the side chain of bile acids is one of the important problems in the synthesis of the physiologically active compounds like cortisol, cortisone and other 11-oxygenated steroids.

Wieland, the pioneer worker in this field, in his attempts to elucidate the structure of ring D in sterols and bile acids sought to stepwise degradation of the bile acid side-chain. After the failure of number of known methods, Wieland, Schlichting and Jacobi achieved it in 1926 by application of a general method described earlier by Barbier and now known as the Barbier-Wieland degradation. The method deals with the successive oxidation of the carbinols obtained by the Grignard reaction on the esters of cholanic acid and its lower homologues as shown in (Chart I).

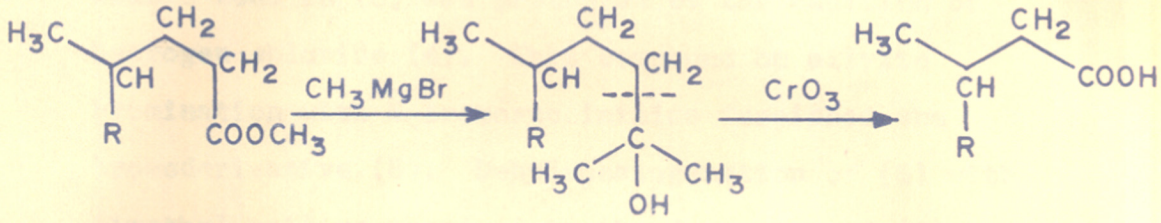
This method is not commercially feasible as it involves a large number of steps and overall yields are poor. Meystre and Miescher in 1944 described a highly efficient new method for degrading the bile acid side-chain and in 1946 they reported the partial synthesis of progesterone (8) from 3β-hydroxy-Δ^5-cholenic acid (Chart II).

The methyl ester of 3β-hydroxy-Δ^5-cholenic acid (1) when subjected to Grignard reaction with phenyl magnesium bromide followed by treatment with acetic anhydride furnished Δ^5, 3β-acetoxy-24, 24-diphenyl

CHART I

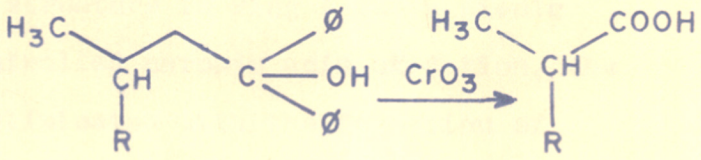
BARBIER–WIELAND DEGRADATION OF CHOLANIC ACID ESTER.

(1)



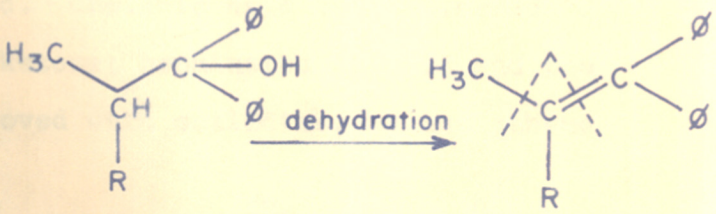
Cholanic acid ester — Norcholanic acid

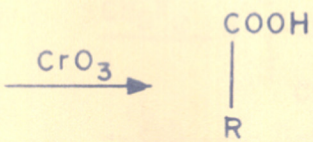
(2) Ester → C_6H_5MgBr



Bisnorcholanic acid

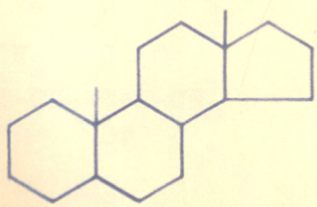
(3) Ester → C_6H_5MgBr





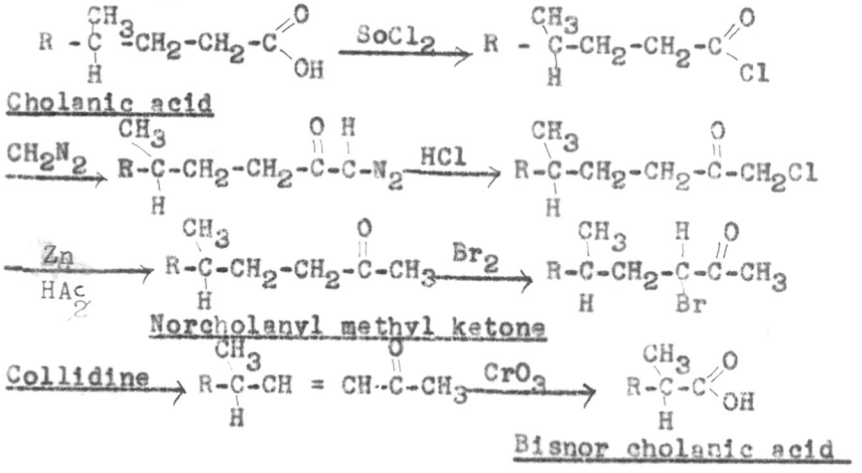
Etiocholanic acid

R =



carbinol (2); (2) on dehydration afforded the diphenyl ethylene (3). The more reactive nuclear double bond in (3) was protected by the addition of hydrogen chloride (4). This compound on allylic bromination with N-bromosuccinimide furnished the bromoderivative (5). Dehydrohalogenation of (5) with dimethyl aniline resulted in the formation of (6) by elimination of hydrogen bromide and hydrogen chloride:(6) on hydrolysis and oppenauer oxidation afforded (7) having the desired structure in ring A and a dienic side-chain. By controlled chromic acid oxidation, the dienic system was eliminated with the formation of progesterone (8).

In 1946, Hollander and Gallagher[1] developed a procedure for the degradation of the bile acid side-chain by the elimination of two carbon atoms to furnish bisnor cholanic acid. Cholanic acid was converted to norcholanyl methyl ketone; brominated at C-23 and the elements of HBr removed with collidine, by the scheme shown below:



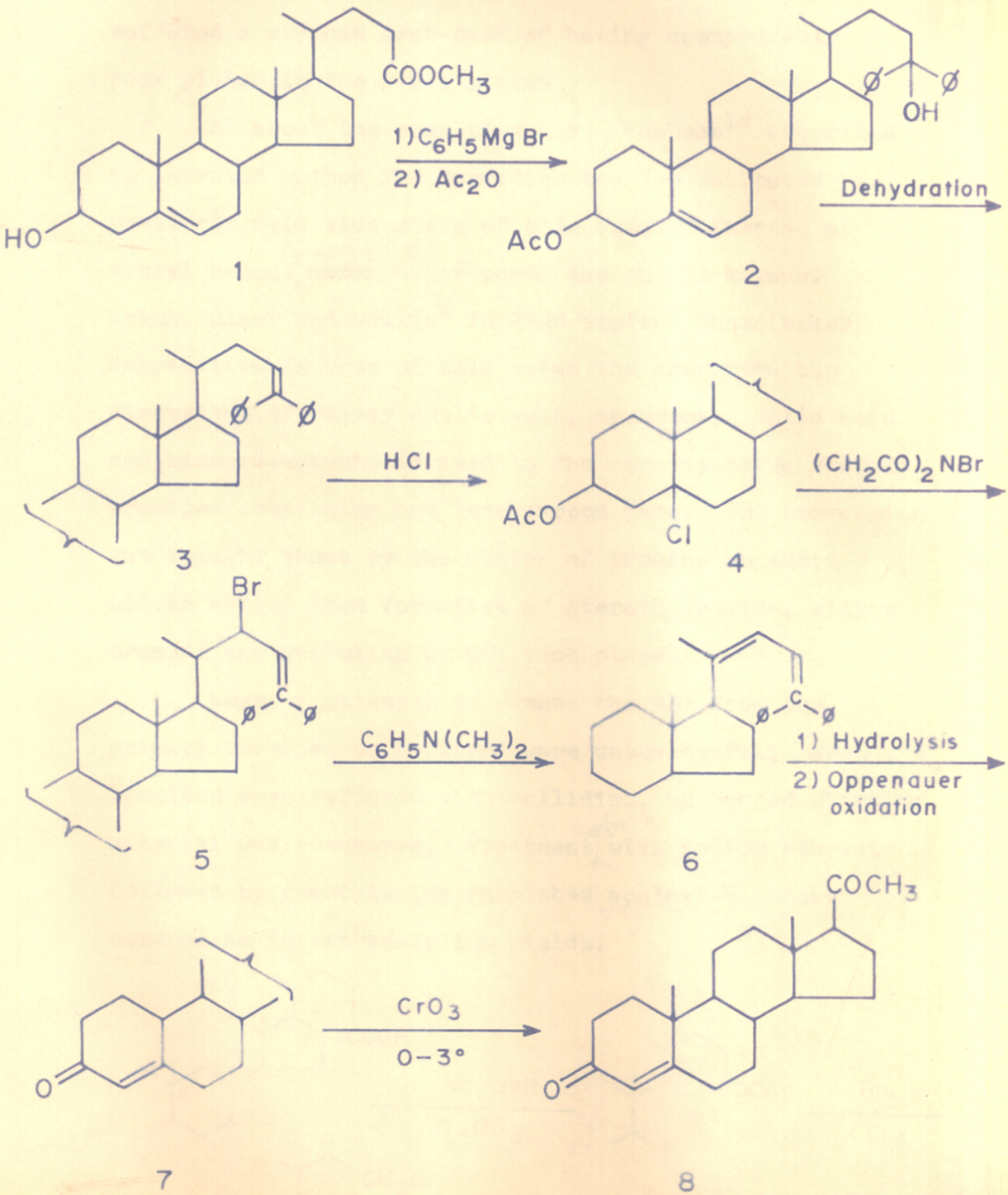
Cholanic acid

Norcholanyl methyl ketone

Bisnor cholanic acid

CHART II

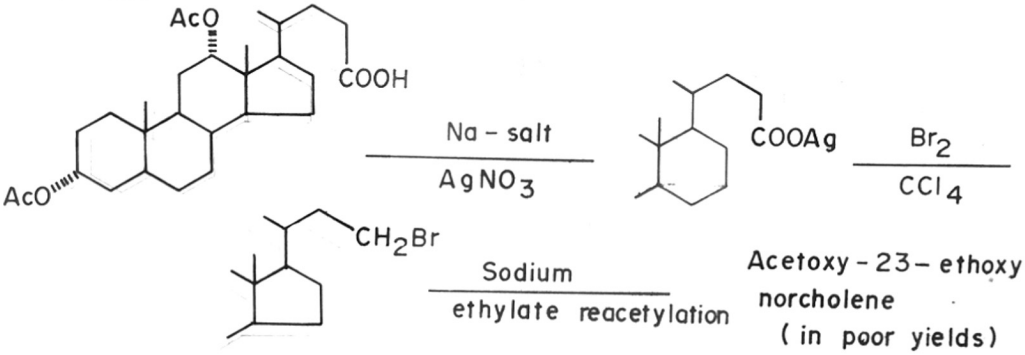
PARTIAL SYNTHESIS OF PROGESTERONE (8) BY MEYSTRE AND MIESCHER.



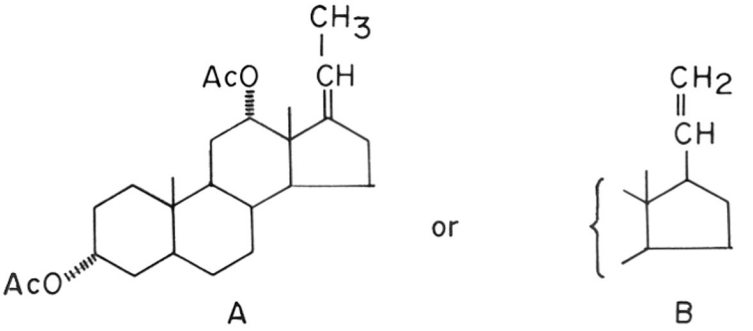
Although the authors succeeded in degrading the side-chain by two carbon atoms without the necessity of using the Grignard reaction, the method suffered a serious draw-back of having unexpectedly poor yields in the final stages.

At about the same time R.P. Jakobson[1a] described an improved method for degrading the Y-substituted n-valeric acid side-chain of bile acids. Instead of methyl ketone ~~above~~ he ~~prepared~~ the phenyl ketone. Brink, Clark and Wallis[2] in 1946 studied Hunsdiecker degradation in case of bile acids and converted the diacetates of desoxy cholic acid, nordesoxy cholic acid and bisnordesoxycholic acid to the corresponding steroid bromides containing one less carbon atom. The conversion was brought about by the action of bromine on their silver salts, when formation of steroid bromide, silver bromide and evolution of CO_2 took place.

However attempts to remove the HBr from the primary bromides so prepared were unsuccessful; When the bromides were refluxed with collidine, unchanged starting material was recovered, ~~treatment~~ with sodium ethylate followed by reacetylation furnished acetoxy-23-ethoxy norcholene in extremely low yields.



The secondary C-20 bromide was stable towards collidine but when refluxed over piperidine, HBr was removed with the formation of diacetoxypregnene (A) or (B).



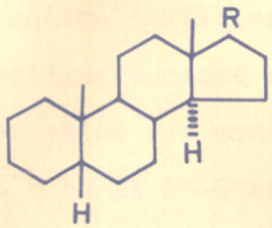
The oxidative decarboxylation of diacetate of desoxycholic acid carried by us furnished far better yields of the expected alkene (XIV).

Dr. Rao and co-workers[3] in this laboratory attempted to prepare ∝,ß-unsaturated acid (XXIII) from cholanic acid (I) through an approach similar to the formation of unsaturated acid from dodecanoic acid according to the following scheme.

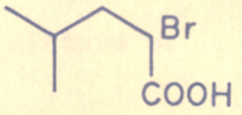
$$\underset{\text{Dodecanoic acid}}{n\text{-}C_8H_{17}CH_2\cdot CH_2\cdot CH_2\cdot COOH} \xrightarrow[PCl_3]{Br_2} \underset{\text{∝-bromo acid}}{n\text{-}C_8H_{17}CH_2\cdot CH_2\cdot CHBrCOOH}$$

$$\xrightarrow{KOC(CH_3)_3} \begin{matrix} n\text{-}C_8H_{17}CH_2CH = CHCOOK \\ + \\ n\text{-}C_8H_{17}CH = CH.CH_2.COOK \end{matrix} \xrightarrow{H^+} \text{Unsaturated acids}$$

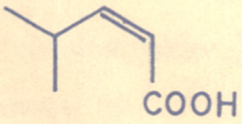
The latter on bromination in presence of phosphorus trichloride affords ∝-bromo acid which on subsequent



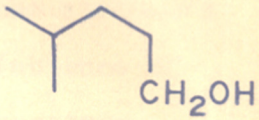
(XXII) R =



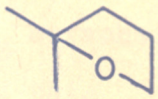
(XXIII) R =



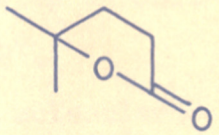
(XXIV) R =

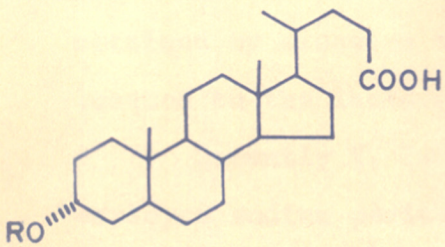


(XXV) R =



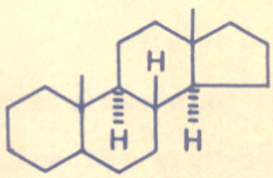
(XXVI) R =



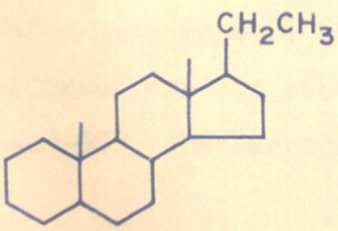


(XXXIII) R = Ac

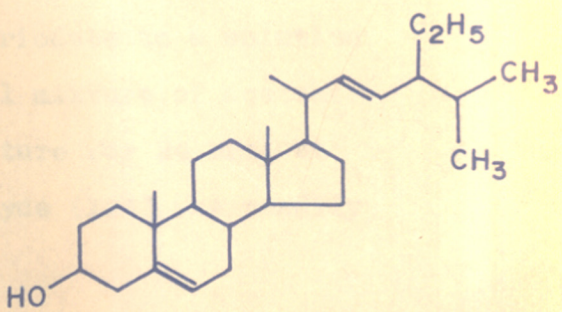
(XXXIV) R = H



(XXXV)



(XXXVI)



(XXXVII)

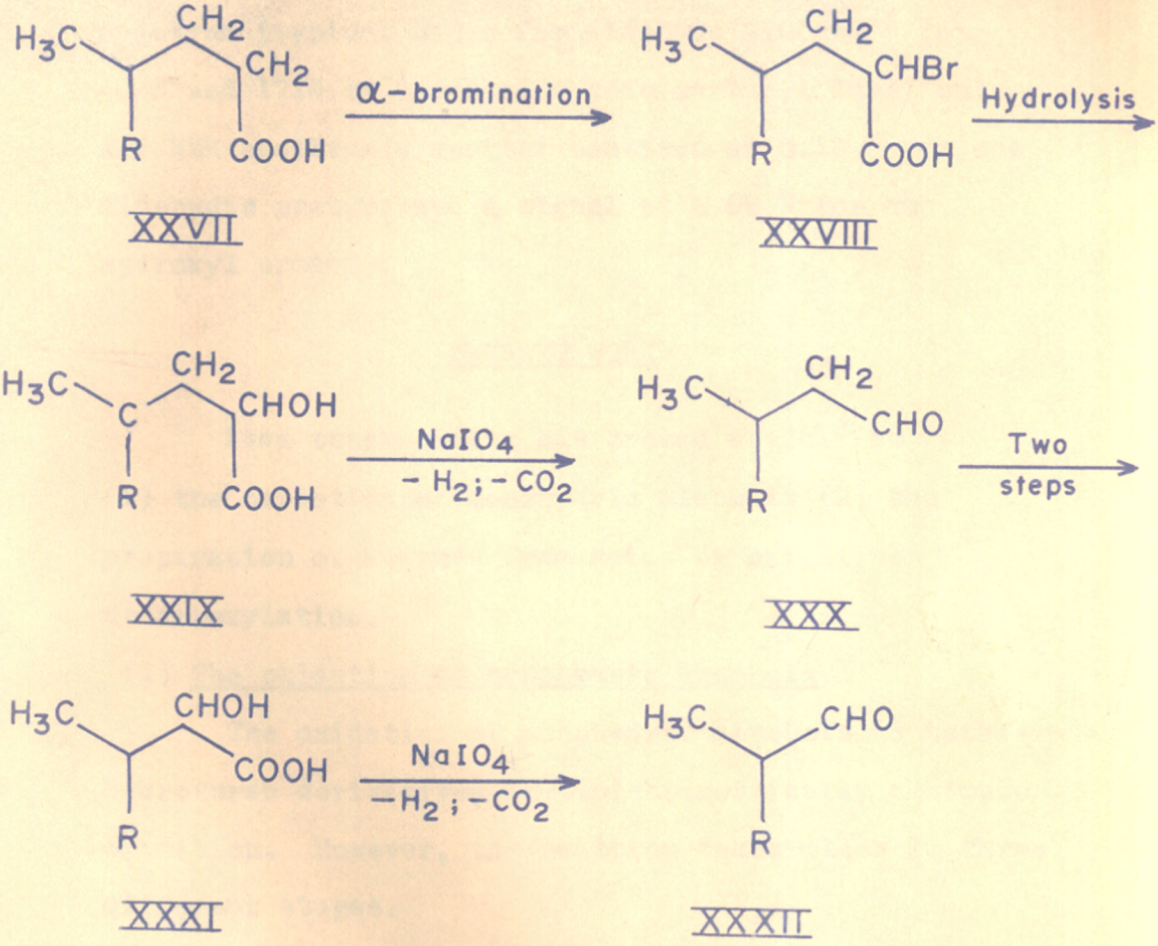
dehydrobromination in presence of potassium tertiary butoxide followed by acidification gives a mixture of two acids.

In a new approach to degrade the bile acid side-chain they prepared the oxide (XXV)[4]. 24-Hydroxy-cholane (XXIV) on oxidation with lead tetraacete in boiling benzene solution furnished (XXV), the structure of which was confirmed by its IR spectrum (absence of a band at 3400 cm^{-1} of -OH group) and NMR spectrum which showed a singlet at 8.83 τ due to CH_3 attached to C-20. Further support for the structure of this oxide (XXV) was provided by itsoxidation with chromic acid to give the Y-lactone (XXVI) (m.p. 153°, $\nu_{max}^{CS_2}$ 1760 cm^{-1} (Y-lactone); mass spectrum molecular ion peak at m/e 358; base peak at m/e 99 (fragment obtained by cleavage at C_{17-20} and positive charge located on the lactone moiety).

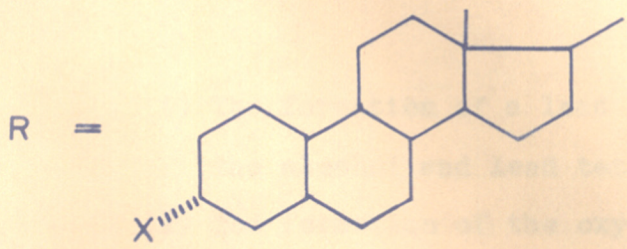
Recently Y. Yanuka et al.[5] have successfully employed sodium periodate for shortening the side-chain of α-hydroxy bile acids to the corresponding aldehydes. The stepwise degradation is shown in the Chart III.

The sodium periodate oxidation was carried out by adding an excess of sodium periodate to a solution of α-hydroxy acid (XXIX) in 4:2:1 mixture of acetone: ACOH:water. On stirring the mixture for 24 hrs. at 40°-50°, the corresponding aldehyde (XXX) was readily

CHART III



XXVII XXVIII XXIX XXX XXXI XXXII



X = H or OH

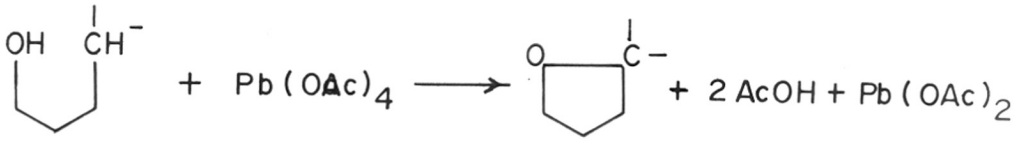
isolated in pure form. The structure of the aldehyde (XXX) was confirmed by studying the IR spectrum (typical bands for aldehyde 2700 cm^{-1} for $-\overset{O}{\overset{\|}{C}}-H$ and 1715 cm^{-1} for aldehydic carbonyl function) and NMR spectrum (a quartet centered at 0.19 τ for one aldehydic proton; and a signal at 6.58 τ for one hydroxyl proton).

PRESENT WORK

Lead tetraacetate has proved useful[6] in (1) the oxidation of monohydric alcohols (2) the preparation of alkenes from acids by oxidative decarboxylation.

(1) The oxidation of monohydric alcohols

The oxidation of monohydric alcohols to tetrahydrofuran derivatives is stoichiometrically a simple oxidation. However, the reaction takes place in three different stages.



i) The formation of a lead alkoxide from the alcohol and lead tetraacetate.

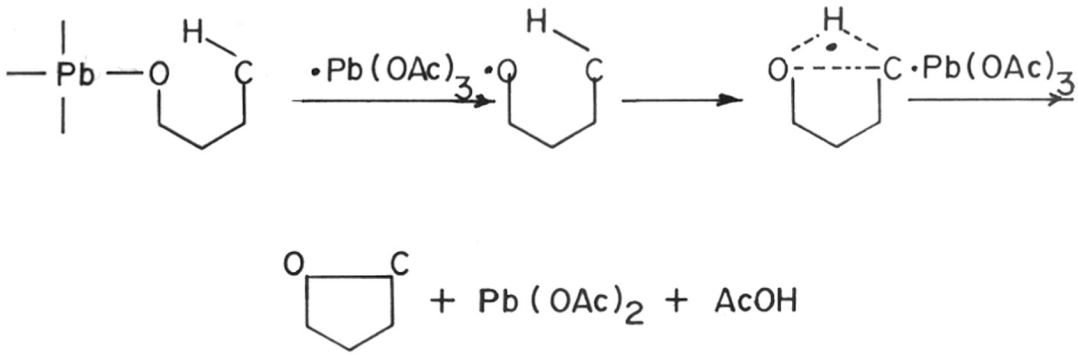
ii) The formation of the oxy-radical.

iii) The formation of the ether. Thus

i) $ROH + Pb(OAcyl)_4 \rightleftharpoons RO\text{-}Pb(OAcyl)_3 + HOAcyl$

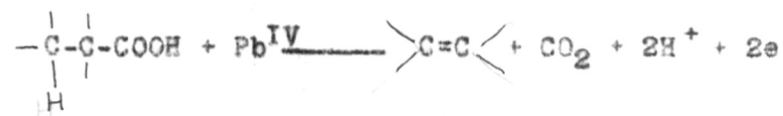
ii) Cleavage of Pb-O bond.

iii) Ether formation



(2) Preparation of alkenes from acids by oxidative decarboxylation

J.K. Kochi et al.[7] reported the thermal or photochemical decarboxylation of aliphatic acids by lead tetraacetate. High yields of oxidation products such as alkenes and esters were obtained from tertiary and α-benzilic acids with Pb^{IV}. In contrast, primary and secondary acids only slowly decarboxylated by Pb^{IV} and generally afforded poor to mediocre yields of oxidation products. Thus -



Presence of catalytic amounts of cupric salts markedly catalysed the decarboxylations as they are

particularly effective oxidants of alkyl radicals. Copper salts and pyridine conjunctively catalyse the decomposition at an extraordinary rate. However, the decarboxylations are strongly inhibited by oxygen. If no precaution is excercised to remove oxygen from the system, the decomposition is interminably reluctant. Similarly if oxygen is added to the reaction at an intermediate juncture, the decomposition is interrupted instantaneously and remains dormant for a relatively long period. It then resumes at a rate similar to that before inhibition.

In the present work, we applied this reaction to prepare terminal alkenes from bile acids.

Oxidative decarboxylation of cholanic acid (I)

Cholanic acid (I) when heated on steam bath for one hr. in nitrogen atmosphere with a mixture of benzene, lead tetraacetate, cupric acetate and pyridine gave the expected $\triangle^{22}$-24-norcholene (VI). The IR spectrum of VI showed strong absorption at 910 cm^{-1} and also at 990 and 1640 cm^{-1} indicating the presence of (-CH = CH_2) grouping. The NMR spectrum showed a signal at 9.32 τ (3H, singlet due to C-18 CH_3), 9.07 τ (3H, singlet, due to C-19 CH_3). [These assignments of C-18 and C-19 methyl groups have been made taking into account the reported values for 5β, 14α-androstane (C_{18}-0.692 δ, 41.5 cps; C_{19}-0.925 δ, 55.5 cps) in Zurcher's tables for C_{18} and

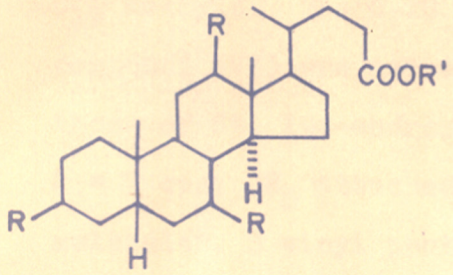
C-18 and C-19 Proton signals for the compounds reported in this Chapter

	C-18		C-19	
	Calcd.	Found	Calcd.	Found
1.* Δ^{22}-24 Norcholene		9.32 τ		9.07 τ
2. 3-Keto-Δ^{22}-24-norcholene	9.278 τ	9.29 τ	8.953 τ	8.99 τ
3. 3α-Hydroxy-Δ^{22}-24-norcholene	9.31 τ	9.32 τ	9.062 τ	9.07 τ
4. 3α-Acetoxy-Δ^{22}-24-norcholene	9.31 τ	9.33 τ	9.05 τ	9.06 τ
5. 3α-12α-Diacetoxy-Δ^{22}-24-norcholene	9.23 τ	9.27 τ	9.07 τ	9.09 τ
6. 3α-12α-Dihydroxy-Δ^{22}-24-norcholene	9.27 τ	9.31 τ	9.07 τ	9.1 τ
7. 3-12-Diketo-Δ^{22}-24-norcholene	8.903 τ	8.92 τ	8.853 τ	8.87 τ
8. 3α,7α-12α-Triacetoxy Δ^{22}-24-norcholene	9.23 τ	9.25 τ	9.062 τ	9.08 τ
9.@ 3-Carbethoxy-12-keto-Δ^{22}-24-norcholene	8.94 τ	8.95 or 8.97 τ	8.95 τ	8.95 or 8.97 τ
10.@ 3-Carbethoxy-12-hydroxy-Δ^{22}-24-norcholene	9.27 τ	9.30 τ	9.05 τ	9.08 τ

*Values of Δ^{22}-24-norcholene are taken as standard values. Since there are no substituents in the rings A B C, C_{19} proton signal can be expected in the same region as in 5β-14α-androstane. In case of C-18 protons, although the side-chain is in the vicinity, it does not apparently affect the value appreciably.

@The C-18 and C-19 proton values of compound numbers (2-10) are calculated with the help of Zurcher's table, given in "Applications of NMR spectroscopy in organic chemistry" - N.S. Bhacca and D.H. Williams, Holden-Day Inc., San Francisco 1964.

@3α-Carbethoxy group has been taken as equivalent to 3α-acetoxy group which does not appreciably affect the C_{18} and C_{19} proton signals.



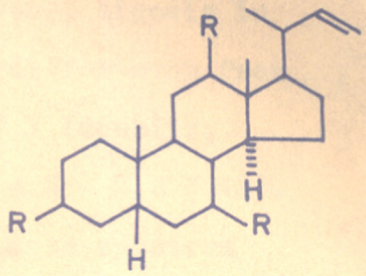
I) R = R' = H

II) R = ---- OH ; R' = H

III) R = O ; R' = H

IV) R = ---- OAc ; R' = Me

V) R = ---- OAc ; R' = H

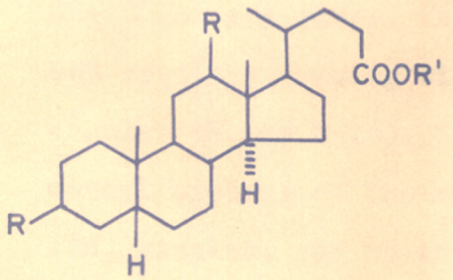


VI) R = H

VII) R = OAc

VIII) R = O

IX) R = ---- OH

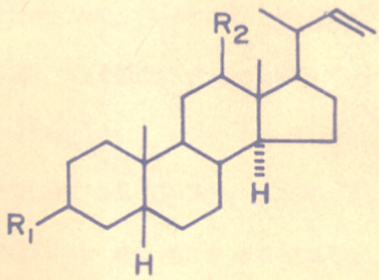


X) R = ---- OH ; R' = H

XI) R = ---- OAc ; R' = H

XII) R = O ; R' = H

XIII) R = ---- OAc ; R' = Me



XIV) $R_1 = R_2 =$ ---- OAc

XV) $R_1 = R_2 =$ ---- OH

XVI) $R_1 = R_2 =$ O

XVII) R_1 = O·COO·Et ; R_2 = OH

XVIII) R_1 = O·COO·Et ; R_2 = O

XIX) R_1 = ---- OH ; R_2 = H

XX) R_1 = ---- OAc ; R_2 = H

XXI) R_1 = O ; R_2 = H

C_{19} methyls. The C-18 and C-19 methyl signals in compound (VI) are not expected to differ much from those of 5β, 14α-androstane[7]. 8.97 τ (doublet, J = 7 cps; CH_3 attached to C-20); 4.3 - 5.3 τ (3H, multiplet, 3 vinyl protons). The mass spectrum recorded M^+ 314 (calculated value 314).

Preparation of 3α, 12α-diacetoxy-Δ^{22}-24-norcholene (XIV)

The diacetoxy cholanic acid (XI) prepared by acetylation of desoxycholic acid (X) on oxidative decarboxylation furnished (XIV) which showed in the IR spectrum bands at 920, 1010 and 1645 cm^{-1} (due to -CH = CH_2 grouping) and at 1250 and 1740 cm^{-1} due to $CH_3.C(=O)-O-$ grouping. This was further supported by the NMR spectrum showing signals at 9.27 τ (3H, singlet, angular CH_3 at C-13), 8.06 τ (3H, singlet, due to the methyl protons of the acetate function at C-3), 7.96 τ (3H, singlet, due to the methyl protons of the acetate function at C-12*) and a multiplet in the region 4.15 τ - 5.3 τ (due to -CH = CH_2 grouping). The mass spectrum recorded the mol. wt. 430 (calculated value: 430).

---

*3-Acetoxy-Δ^{22}-norcholene (XX) shows a singlet at 8.07 τ due to C-3-acetate group. Therefore the remaining singlet at 7.96 τ has been assigned to C-12 acetate.

Following above procedure, the bile acids mentioned below were subjected to oxidative decarboxylation to furnish the corresponding terminal alkenes.

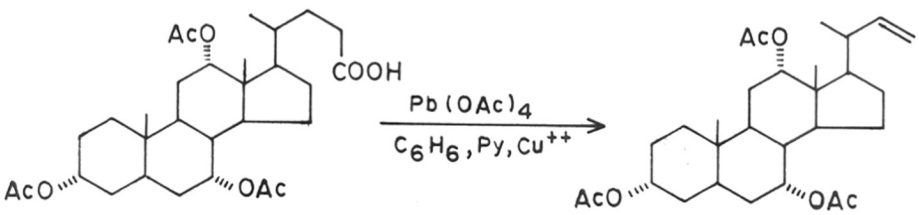
1) 3∝,7∝,12∝-Triacetoxycholanic acid (V)

2) 3,7,12-Triketocholanic acid (III)

3) 3,12-Diketocholanic acid (XII)

The results have been represented in a tabular form for each of the acids separately.

Preparation of 3∝,7∝,12∝-triacetoxy-Δ^{22}-24-norcholene (VII) from 3∝, 7∝, 12∝-triacetoxy cholanic acid (V) by oxidative decarboxylation

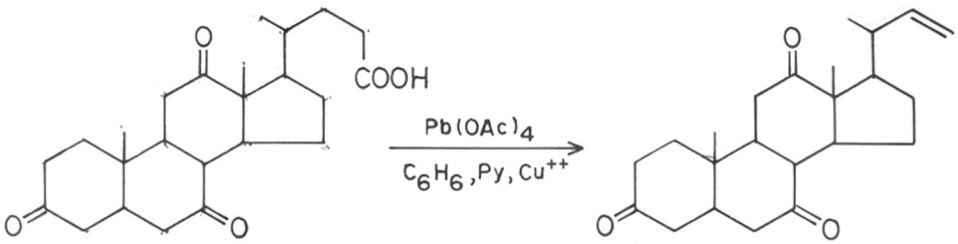


(V) (VII)

Yield	45%
M.P.	Did not solidify. Corresponding trihydroxy-Δ^{22}-24-norcholene (IX) obtained on saponification melted at 178°-180°
IR Spectrum	ν_{max}^{nujol} 1640 cm^{-1} and 915 cm^{-1} due to the double bond at C_{22}.
	ν_{max}^{nujol} 1250 cm^{-1} (due to acetate groups)
NMR Spectrum CCl_4	8.04 τ (3H, singlet due to the methyl protons of the acetate function at C-3).
	7.95 τ (3H, singlet due to the methyl protons of the acetate function at C-12)
	*7.92 τ (3H, singlet due to the methyl protons of the acetate function at C-7)
	4.5-5.3 τ (multiplet due to the vinyl protons)

*Signal at 7.92 τ is assigned to C-7 acetate as the signals at 8.04 τ and 7.95 τ have been shown to be due to C-3 and C-12 acetates respectively.

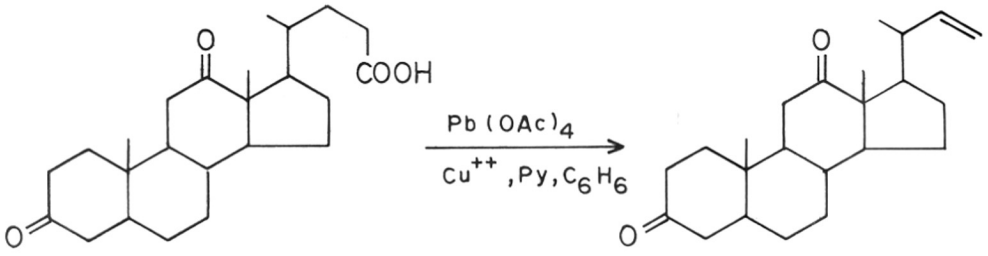
Preparation of 3,7,12-triketo-Δ^{22}-norcholene (VIII) from 3,7,12-triketo cholanic acid (III) by oxidative decarboxylation



(III) (VIII)

Yield	44%
M.P.	245°
IR Spectrum	ν_{max}^{nujol} 918 cm^{-1}, 1012 and 1626 cm^{-1} due to the terminal alkene group at C-22 ν_{max} 1695 cm^{-1} due to the carbonyl function.

Preparation of 3,12-diketo-Δ^{22}-norcholene (XVI) 3,12-diketo cholanic acid (XII) by oxidative decarboxylation



(XII) (XVI)

Yield	32%
M.P.	160° - 161°
IR Spectrum	ν_{max}^{nujol} 915, 990 and 1640 cm^{-1} (due to $-CH = CH_2$)
	ν_{max}^{nujol} 1720 cm^{-1} (due to the carbonyl function)
NMR Spectrum in $CHCl_3$	4.25 - 5.3 τ (multiplet due to $-CH = CH_2$ grouping)
	8.92 τ (singlet due to C-18 methyl protons)
	8.87 τ (singlet due to C-19 methyl protons)

3α, 12α-Diacetoxy-Δ^{22}-24-alkene (XIV) when hydrolysed by refluxing with alkali furnished the alkene diol (XV), whose IR spectrum showed a strong band at 3330 cm^{-1} (-OH group) and bands at 909, 990 and 1631 cm^{-1} for the terminal alkene group attached at C-22. The completion of hydrolysis was also indicated by the absence of bands at 1740 and 1250 cm^{-1}. The NMR spectrum of (XV) showed the absence of sharp singlets at 8.06 τ and 7.96 τ due to the methyl protons of acetate functions at C-3 and C-12. Other signals were 9.31 τ (a singlet due to C-18 methyl protons); 9.10 τ (a singlet due to C-19 methyl protons) and a doublet centred at 9.01 τ due to the methyl group attached to C-20.

Saponification of 3α, 7α, 12α triacetoxy-Δ^{22}-24-norcholene (VII) by refluxing over alcoholic alkali yielded the corresponding triol (IX), whose IR spectrum showed a strong absorption for -OH grouping at 3260 cm^{-1}, prominent bands at 910, 990 and 1645 cm^{-1} due to the terminal alkene group and absence of a band due to the acetate group.

After studying the applicability of oxidative decarboxylation reaction on different compounds mentioned above, further transformations were carried on 3α,12α-dihydroxy-Δ^{22}-24-norcholene (XV)which was prepared from desoxycholic acid (X) as mentioned earlier in this thesis.

Desoxycholic acid has been obtained in good yields from cholic acid[8] (II), a major constituent of bile acids mixture.

The purpose of these transformations was to convert the bile acids to the C-3 oxygenated derivatives of pregnane (XXXVI) and androstane (XXXV). To achieve this we undertook the conversion of (XV) to 3-hydroxy-Δ^{22}-24-norcholene (XIX) as the double bond in this compound is located in the same position as in case of stigmasterol (XXXVII). It may be mentioned that the conversion of stigmasterol (XXXVII) to pregnane derivatives in very high yields is well known.[9]

As 3α, 12α-dihydroxy-Δ^{22}-24-norcholene (XV) has the C-3α-hydroxy function in equatorial position and the C-12 hydroxyl in axial position, the C-3 hydroxyl group was selectively* carbethoxylated by adding ethylchloroformate to the dioxan solution of (XV) in presence of pyridine as a base. The resulting

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*Ethylchloroformate (cathyl chloride or ethyl chloro-carbonate), because of resonance involving the ester function, is less reactive than acetyl chloride. The reactivity in fact is such as to render the substance an ideal reagent for the selective acylation of saturated steroid secondary alcohols of equatorial orientation, axial groups if present, remain unreacted.

3α-carbethoxy-12α-hydroxy-Δ^{22}-24-norcholene (XVII) showed the IR bands at 3571 cm^{-1} for the hydroxyl function at C-12, a band at 1709 cm^{-1} for the carbonyl group of carbethoxy function at C-3 and bands at 909, 1000 and 1640 cm^{-1} due to the terminal alkene group at C-22. The NMR spectrum showed a quartet centred at 5.95 τ (J = 7 cps) due to the CH_2 function of the carbethoxyl group introduced at C-3, 8.75 τ (triplet J = 7 cps methyl of $O.COOC_2H_5$).

Jones oxidation of (XVII) gave 3α-carbethoxy-12-keto-Δ^{22}-24-norcholene (XVIII) which showed IR bands at 1739 cm^{-1} and 1695 cm^{-1} due to the carbonyl group of carbethoxy function located at C-3 and carbonyl group at C-12; ~~The~~ bands at 909 cm^{-1}, 1000 cm^{-1} and a shoulder at 1640 cm^{-1} (due to $-CH = CH_2$ grouping). The NMR spectrum showed retention of quartet centred at 5.91 τ (J = 7 cps) due to the CH_2 group of the carbethoxy function at C-3, triplet at 8.76 τ ($CH_3.CH_2-$) a multiplet in the region 4.3 τ - 5.3 τ due to the protons attached to the terminal alkene group.

(XVIII) When subjected to Huang-Minlon reduction afforded 3α-hydroxy-Δ^{22}-norcholene (XIX). The IR spectrum showed a strong absorption at 3330 cm^{-1} due to the hydroxyl function and absence of carbonyl band and also sharp bands at 915 cm^{-1}, 1000 and 1640 cm^{-1} due to $-CH = CH_2$ grouping(absence of a carbethoxy group at C-3

in the NMR Spectrum
was shown by absence of a quartet around 6 ℑ.

3α-Hydroxy-Δ^{22}-24-norcholene (XIX) on oxidation with Jones reagent furnished the 3-keto-Δ^{22}-24-norcholene (XXI). The infrared spectrum of XXI which showed bands at 915, 1000 and 1640 cm^{-1} due to the terminal alkene grouping at C-22. Presence of a carbonyl function at C-3 was indicated by sharp band at 1720 cm^{-1}. The NMR spectrum showed a multiplet in the region 4.3 - 5.3 ℑ due to the vinyl protons attached to the double bond at C-22.

3-Hydroxy-Δ^{22}-24-norcholene (XIX) on acetylation furnished 3-acetoxy-Δ^{22}-norcholene (XX) which was characterised by the bands at 910, 992, 1640 cm^{-1} in the IR spectrum due to (-CH = CH_2); (absence of a band at 3390 cm^{-1} due to absence of hydroxy function) and presence of a band at 1245 cm^{-1} due to the acetate group. The NMR spectrum showed a multiplet in the region 4.35 ℑ - 5.35 ℑ (due to -CH = CH_2) and a sharp singlet at 8.07 ℑ (methyl protons of acetate at C-3).

This acetoxy compound*(XX) prepared starting from desoxycholic acid (X) is obtained in better yields than preparation of the same compound by oxidative decarboxylation of the acetate of lithocholic acid (XXXIII).

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*The acetate (XX) prepared from desoxycholic acid (X) was found to be identical in all respects (m.p., mixed m.p. and spectral data) with the same acetate prepared by Chaudhari and Rao in this laboratory starting from lithocholic acid (XXXIV). The conversion of (XX) to androstane and pregnane derivatives has been carried out by Chaudhari and Rao in this laboratory.

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EXPERIMENTAL

Preparation of triketocholanic acid (III)

To a solution of cholic acid (II) (10 g) in acetone (800 ml), Jones reagent was added dropwise till the colour of the reagent persisted. The solution was kept at room temperature for 30 minutes. The excess of reagent was destroyed by ethanol and the reaction mixture was diluted with water (400 ml). The solvents were removed under suction, when triketocholanic acid (III) separated as solid. It was filtered and washed with ice-cold ethanol (m.p. 236°). The mother liquor was then extracted with ether, the latter on usual work up gave the same acid (m.p.233° 236°). Literature reports m.p. 237°.

IR Spectrum (Page No.—) (in Nujol) showed bands at 3030, 2940, 1724, 1710, 1450, 1370, 1350, 1316, 1299, 1282, 1220, 1170, 1117, 1110, 980, 952 and 720cm^{-1}.

Huang-Minlon reduction of triketocholanic acid

A mixture of triketocholanic acid (III) (7 g), 80% hydrazine hydrate solution (21 ml) and diethylene glycol (140 ml) was maintained at 120° for two hrs. in N_2 atmosphere. The reaction mixture was then cooled to 60° and potassium hydroxide pellets (42 g) was added. The temperature of the reaction was again raised to 120° and maintained at that temperature for 1 hr. After

1 hr., the condenser was removed and the temperature of the reaction was raised to 170°. At 170°, the air condenser was fitted and the temperature was raised to 200° and maintained there for 6 hrs. The flask was then cooled to room temperature and the reaction product was poured in water and acidified with hydrochloric acid to get cholanic acid (I).

M.P. 161°C.

Literature value: 164°C.

IR Spectrum (Page No.—) (in nujol) showed bands at 3030, 2940, 2865, 1724, 1470, 1447, 1374, 1253, 1176, 1100 and 952 cm^{-1}.

Preparation of Δ^{22}-24-norcholene (VI)

A mixture of cholanic acid (I) (1.059 g, 2.944 m.mols), cupric acetate (0.120 g, 0.663 m.mols), pyridine (0.1 g, 1.099 m.mols) and dry benzene (20 ml) was magnetically stirred for 40 minutes. Lead tetra-acetate (2.6 g 5.384 m.mols) and remainder of benzene (50 ml) was then added and the mixture was stirred in dark for 1 hr. under nitrogen atmosphere. It was then refluxed over water-bath for 1 hr. in nitrogen atmosphere. The reaction product was cooled and ethylene glycol (0.5 ml) was added to it, to destroy the unreacted lead tetraacetate. The solution was filtered and the residue on the funnel was washed with hot benzene. The filtrate along with the combined

washings was extracted with saturated solution of Na_2CO_3 to separate the acidic fraction, from which unreacted acid was liberated on acidification with hydrochloric acid. The liberated acid was extracted thrice with ether and combined ether extract washed with water till neutral dried over anhydrous Na_2SO_4 and evaporated to get unreacted acid (0.151 g).

The neutral part was washed with water, dried and evaporated to get the residue (0.773 g). It was chromatographed over Gr. II alumina (1:20) and eluted with petroleum ether, petroleum ether-benzene (1:1) and alcohol. The petroleum ether fraction on concentration afforded (VI) as solid.

M.P. 74°.

Specific rotation - $\alpha)_D^{29^{\circ}} + 16^{\circ}$ (5.2 $CHCl_3$).

Analysis : Found: C, 87.68; H, 12.40

$C_{23}H_{38}$ requires : C, 87.82; H, 12.18%.

IR Spectrum (Page No.103) (in nujol) showed bands at 3000, 2820, 1640, 1460, 1440, 1375, 1295, 1275, 1165, 1000, 990, 950 and 910 cm^{-1}.

3α,7α,12α-Triacetoxycholanic acid (V)

Cholic acid (II) (10 g) was dissolved in acetic anhydride (50 ml) and sodium acetate (anhydrous (8.0 g) was added. The mixture was refluxed for 5 hrs; cooled and poured in water; kept overnight. Next day the sticky solid material at the bottom was extracted with ether

and washed with saturated aqueous Na_2CO_3 to separate into acid and neutral parts. The alkaline extract on acidification with dil. hydrochloric acid (1:1) liberated the triacetoxy acid (V). The latter was extracted with ether, washed with water dried over anhydrous Na_2SO_4 and evaporated (12.778 g).

Methyl ester of 3∝,7∝,12∝-triacetoxy cholanic acid (IV)

The methyl ester of triacetoxy cholanic acid (IV) was prepared by reacting it with diazomethane. To an ice-cooled ether solution of the triacetoxycholanic acid (V, 0.317 g), ether solution of diazomethane was added till the reaction mixtured showed permanent yellow colour to show an excess of diazomethane. After 30 minutes the excess diazomethane was destroyed by adding a few drops of acetic acid. The reaction mixture was then transferred to a separating funnel and washed with 20% KOH solution to remove unreacted acid. The ethereal layer was then washed with water until neutral, dried over anhydrous sodium sulphate and concentrated. IR of the residue clearly showed the absence of OH absorption.

IR Spectrum (Page No. —) (liquid film) showed bands 2910, 1740, 1480, 1450, 1390, 1260, 1200, 1125, 1030, 970, 950, 895 and 868 cm^{-1}.

Preparation of 3∝,7∝,12∝-triacetoxy-Δ^{22}-24-norcholene (VII)

To a solution of 3∝,7∝, 12∝-triacetoxycholanic

acid (V, 1.006 g) in dry benzene (20 ml), cupric acetate (0.1 g) and pyridine (0.1 ml) was added and the mixture was stirred for 40 minutes. The lead tetraacetate (2.6 g) and benzene (50 ml) was added and the mixture was stirred in dark for 1 hr. It was then refluxed on steam bath for 1 hr. under nitrogen atmosphere. Cooled and worked up as in case of oxidative decarboxylation of cholanic acid to get a neutral part (0.812 g). Chromatography of the neutral part over 20 times Gr. II alumina was done and following fractions were collected. Petroleum-ether-benzene (1:1) fraction (0.187 g); benzene fraction (0.151 g) and alcohol fraction (0.364 g).

The petroleum ether-benzene fraction furnished (VII). IR Spectrum (Page No. 105) (liquid film) showed bands at 2900, 1730, 1640, 1480, 1440, 1380, 1240, 1215, 1200, 1160, 1135, 1070, 1030, 970, 940, 915, 895, 865, 825, 805 and 772 cm^{-1}.

3α,7α,12α-Trihydroxy-Δ^{22}-norcholene (IX)

KOH pellets (1.0 g) were added to a solution of above Δ^{22}-24-norcholene (VII, 0.276 g) in ethylene glycol (10 ml) and the mixture was refluxed for 16 hrs. in N_2 atmosphere. The solution was then cooled, poured in water and extracted with ether (15 ml x 3). The combined ether extract was washed with water till neutral, dried and evaporated. The residue (0.206 g) was

crystallised from dilute acetone to get (IX).

M.P. 178°-180°.

IR Spectrum (Page No. 109) (nujol film) showed bands at 3260, 2850/1645, 1460, 1385, 1305, 1200, 1155, 1130, 1080, 1050, 1025, 1000, 990, 960, 920, 910, 860 and at 820 cm^{-1}.

3α,12α-Diacetoxycholanic acid (XI)

A mixture of desoxycholic acid (X, 10.0 g), anhydrous sodium acetate (8.0 g) and acetic anhydride (70.0 ml) was refluxed for 5 hrs, cooled and poured into ice-cold water. The solution was allowed to stand overnight. It was then extracted with ether. The ether extract was washed with saturated solution of Na_2CO_3 till alkaline. The latter liberated the diacetoxy acid on acidification with dilute hydrochloric acid. The acidic solution was extracted with ether, washed with water, dried over anhydrous sodium sulphate and evaporated to get (XI) as white resinous ~~solid~~ (11.77 g).

IR Spectrum (Page No. —) (liquid film) showed bands at 3050, 2850, 1740, 1470, 1425, 1375, 1250, 1165, 1120, 1100, 1075, 1030, 970, 960, 920, 895, 855, 805 and 760 cm^{-1}.

3α,12α-Diacetoxy methyl cholanate (XIII)

Methyl ester of diacetoxy cholanic acid (XIII) was prepared by treating (XI) with diazomethane at 0° and working up as in case of triacetoxy methyl cholante.

IR Spectrum (Page No. —) (liquid film) showed bands

at 2920, 1745, 1710, 1560, 1480, 1390, 1340, 1260, 1200, 1180, 1125, 1100, 1040, 980, 960, 912, 892, 860, 835, 805, 785 and 715 cm^{-1}.

3α,12α-Diacetoxy-Δ^{22}-24-norcholene (XIV)

Pyridine (0.1 ml) and cupric acetate (0.1 g) were added to a solution of 3α, 12α-diacetoxycholanic acid (XI, 0.991 g) in dry benzene (20 ml) and the mixture was stirred for 40 minutes. Lead tetraacetate (2.6 g) was then added followed by dry benzene (50 ml) and the stirring was continued for another 1 hr. in dark. It was then refluxed on the steam bath for 1 hr, Cooled and excess of lead tetraacetate was destroyed by adding ethylene glycol. The reaction product was worked out as in case of cholanic acid. The crude Δ^{22}-24-norcholene (XIV) was purified by chromatography over Gr. II alumina. The petroleum ether-benzene (1:1) fraction had

M.P. 129°- 130°.

Specific rotation - $[\alpha]_D^{29°}$ + 77.8° (3.34, in $CHCl_3$).

Analysis: Found: C, 75.48; H, 9.73.

$C_{27}H_{42}O_4$ requires: C, 75.31; H, 9.83%.

Mol. wt. 430 by mass spectrum.

IR Spectrum (Page No. 104) (nujol film) showed bands at 2880, 1740, 1645, 1460, 1370, 1320, 1300, 1250, 1195, 1160, 1120, 1090, 1065, 1040, 1010, 980, 958, 920 and 880 cm^{-1}.

3,12-Diketocholanic acid (XII)

Jones reagent was added dropwise at room temperature to a solution of 3α,12α-dihydroxycholanic acid (X, 5 g) in acetone (600 ml) till the chromic acid colour persisted. The reaction mixture was kept for 30 minutes at room temperature. It was then diluted with water and acetone removed under suction. The aqueous solution was filtered and the solid (XII) was washed with water till free of acid. M.P. of crude diketo compound - 180°-184°C.

Oxidative decarboxylation of 3,12-diketocholanic acid (XII)

A mixture of 3,12-diketocholanic acid (XII, 1.184 g), cupric acetate (0.1 g), pyridine (0.1 ml) and benzene (50 ml) was magnetically stirred for 40 minutes. Lead tetraacetate (4.0 g) and remainder of benzene (100 ml) was then added and stirring continued in dark for 1 hr. It was then refluxed over water-bath in nitrogen atmosphere for 1 hr., cooled and excess of lead tetraacetate was destroyed by ethylene glycol. The reaction product was worked up as in previous cases. The crude diketo alkene (XVI) was crystallised from acetone.

M.P. 160-161°.

Analysis - Found: C, 80.72; H, 10.00.

$C_{23}H_{34}O_2$ requires: C, 80.65; H, 10.01%.

IR Spectrum (Page No.107) IR spectrum showed bands at 2900, 1720, 1640, 1460, 1445, 1380, 1340, 1310, 1285,

1265, 1245, 1220, 1170, 1158, 1130, 1110, 1095, 1042, 1025, 1015, 1005, 990, 958, 948, 930, 915 and 880 cm^{-1}.

3α,12α-Dihydroxy-Δ^{22}-24-norcholene (XV)

3α,12α-Diacetoxy-Δ^{22}-norcholene (XIV) (2.8 g) was treated with 10% ethanolic KOH (50 ml) and refluxed on the water-bath for 11 hrs. The reaction product was cooled and poured into ice-cold water, the solid separated was extracted with ether and ether extract continuously washed with water until neutral, dried over anhydrous Na_2SO_4 and evaporated, to get crude dihydroxy alkene (XV) (2.3 g). It was crystallised from petroleum ether-acetone mixture (2:1).

M.P. 159-160°.

Specific rotation - $(\alpha)_D^{28^\circ}$ + 25° (2.5% in $CHCl_3$).

IR Spectrum (Page No.108) (nujol film) showed bands at 3330, 2924, 2326, 1805, 1631, 1449, 1374, 1295, 1243, 1222, 1189, 1149, 1114, 1087, 1064, 1042, 1013, 990, 980, 970, 943, 909, 847, 793 and 757 cm^{-1}.

Preparation of 3,7,12-triketo-Δ^{22}-24-norcholene (VIII)

To a suspension of triketocholanic acid (III, 1.392 g) in benzene (dry, 75 ml), cupric acetate (0.160 g) and pyridine (0.1 g) were added and the resulting green coloured suspension was magnetically stirred. To it lead tetraacetate (4.0 g) and dry benzene (150 ml) was added and mixture was stirred for

another one hour in N_2 atmosphere at room temperature in dark. It was then refluxed over steam-bath under N_2 atmosphere for 1 hr, cooled and treated with ethylene glycol to destroy unreacted lead tetraacetate. It was then worked up as usual. The crude triketo compound (VIII) was chromatographed over Gr. II alumina (1:20) and eluted successively by petroleum ether (100 ml), petroleum ether-benzene (1:1, 100 ml), benzene (100 ml), ether (150 ml) and alcohol-chloroform mixture (1:1, 70 ml). The ether fraction (0.113 g) was crystallised from acetone-petroleum ether mixture. M.P. - 245°

Analysis - Found: C, 77.25; H, 9.26.

$C_{23}H_{32}O_3$ requires: C, 77.49; H, 9.05%.

IR Spectrum (Page No. 106) (nujol film) showed bands at 2857, 1695, 1626, 1460, 1370, 1333, 1316, 1266, 1121, 1012, 962 and 918 cm^{-1}.

3α-Carbethoxy- 12α-hydroxy-Δ^{22}-24-norcholene (XVII)

A mixture of 3α, 12α-dihydroxy-Δ^{22}-24-norcholene (XV, 1.9 g), dioxan (15 ml) and pyridine (2.5 ml) was cooled in ice and ethyl chloroformate (3.0 ml) was added to it dropwise. During addition, the reaction mixture was agitated by swirling (2 minutes). A white, solid separated and at the end of the addition all the reaction mixture solidified. It was allowed to stand at room temperature for 0.5 hr. To the reaction mixture

was then added water (36 ml) containing hydrochloric acid (36%, 1.5 ml) and heated on water-bath for 0.5 hr. Cooled and extracted thrice with ether. The combined ether extract was washed with water, dried over anhydrous Na_2SO_4 and evaporated. The residue (2.1 g) was chromatographed over Gr. II alumina (1:15) and eluted with petroleum ether, petroleum ether-benzene (0.9341 g) benzene (0.511 g) and ether.

The petroleum ether-benzene fraction and benzene fraction were identical with each other on IR basis. The latter was crystallised from petroleum ether to furnish (XVII).

M.P. - 107°-108°.

Specific rotation - $[\alpha]_D^{28^\circ}$ + 39° (2.41% $CHCl_3$).

Analysis - Found: C, 74.04; H, 10.45.

$C_{26}H_{43}O_4$ requires: C, 74.47; H, 10.27%.

IR Spectrum (Page No.110) showed bands at 3571, 2941, 1709, 1449, 1370, 1316, 1266, 1163, 1117, 1087, 1042, 1020, 1000, 970, 934, 909, 900, 885, 862, 793 and 757 cm^{-1}.

Jones oxidation of 3α-carbethoxy-12α-hydroxy-Δ^{22}-24-norcholene (XVII)

To a solution of 3α-carbethoxy 12α-hydroxy alkene (XVII, 0.9341 g) in acetone (20 ml), Jones reagent was added dropwise at room temperature till the colour of the reagent persisted. The reaction mixture

was kept at room temperature for 20 minutes. It was then diluted with ~~enough of~~ water and extracted with ether. The ether extract was washed with water until neutral, dried and evaporated. The residue was crystallised from petroleum ether to afford (XVIII).

M.P. - 95°-96°.

Analysis - Found: C, 75.09; H, 10.07

$C_{26}H_{40}O_4$ requires: C, 74.96; H, 9.68%.

IR Spectrum (Page No. 111) The IR spectrum showed bands at 2941, 2857, 2326, 1739, 1695, 1613, 1460, 1370, 1316, 1266, 1235, 1111, 1000, 970, 952, 934, 909, 877, 800, 793 and 729 cm^{-1}.

Huang-Minlon reduction of 3α-carbethoxy-12-keto--Δ^{22}-24-norcholene (XVIII)

A mixture of (XVIII) (0.837 g), diethylene glycol (18 ml) and hydrazine hydrate 80% (3 ml) in a 50 ml round bottom flask fitted with water condenser was heated at 120° in oil bath for 2 hrs. in nitrogen atmosphere. After 2 hrs. the reaction mixture was cooled to 60° and KOH pellets (4.5 g) were added. The temperature was again raised to 120° and maintained at 120° for 1 hr. The water condenser was then removed and temperature raised to 170°. At 170°, the air condenser was placed and the temperature of reaction was raised to 200°. It was maintained at 200° for 6 hrs. The flask was then cooled and the product was diluted with water, extracted with ether. The ether extract was washed with

water until neutral, dried over anhydrous Na_2SO_4 and evaporated to furnish crude XIX (0.662 g; m.p. 118°-123°). It was crystallised from acetone.

M.P. - 125°-126°.

Analysis - Found: C, 83.85; H, 11.81.

$C_{23}H_{38}O$ requires: C, 83.57; H, 11.59%.

Mol. Wt. by mass spectrum 330 (~~lit.~~ calcd. value 330).

IR Spectrum (Page No. 112) (nujol film) showed bands at 3390, 2857, 2353, 1661, 1468, 1389, 1316, 1274, 1220, 1174, 1121, 1096, 1075, 1049, 1020, 1000, 952, 917 and 924 cm^{-1}.

Jones oxidation of 3α-hydroxy-Δ^{22}-24-norcholene (XIX)

To a solution of 3α-hydroxy-Δ^{22}-24-norcholene XIX (2.897 g) in acetone (150 ml), Jones reagent was added dropwise at room temperature till the colour of the reagent persisted. The reaction mixture was allowed to stand at room temperature for 30 minutes. It was then diluted with water and extracted with ether. The ether extract was washed with water until neutral, dried over anhydrous Na_2SO_4 and evaporated to get the crude ketone (2.6 g). The crude ketone (XXI) on crystallization from petroleum ether-acetone mixture (80:20) showed

M.P. 131°-132°C.

Analysis - Found: C, 83.58; H, 11.02

$C_{23}H_{36}O$ requires: C, 84.08; H, 11.05

Specific rotation - $[\alpha]_D^{28°}$ + 28° (3.272% in $CHCl_3$).

IR Spectrum (Page No.113) (nujol film) showed bands at 2924, 1724, 1639, 1453, 1389, 1277, 1220, 1179, 1126, 1081, 1047, 1000/960, 912, 844 and 755.

3α-Acetoxy-Δ^{22}-24-norcholene (XX)

To a solution of 3α-hydroxy-Δ^{22}-24-norcholene (XIX, 0.251 g) in pyridine (3 ml), acetic anhydride (0.2 ml) was added and the reaction mixture was kept at room temperature for 24 hrs. It was then diluted with iced water, and extracted with ether. The ether extract was washed successively with dilute hydrochloric acid and aqueous Na_2CO_3 sol; washed with water till neutral and dried over anhydrous Na_2SO_4. On evaporation of ether, crude acetate (XX) was obtained which was purified by chromatography over Gr. III alumina (1:20).

M.P. - 91°C (mixed m.p. of this sample with the sample prepared by Chaudhari and Rao in this laboratory by another route mentioned earlier, remains undepressed.

IR Spectrum (Page No. 114) The IR spectrum showed main bands at 3000, 1748, 1648, 1468, 1380, 1250, 1170, 1075, 1040, 955, 910 and 890 cm^{-1}.

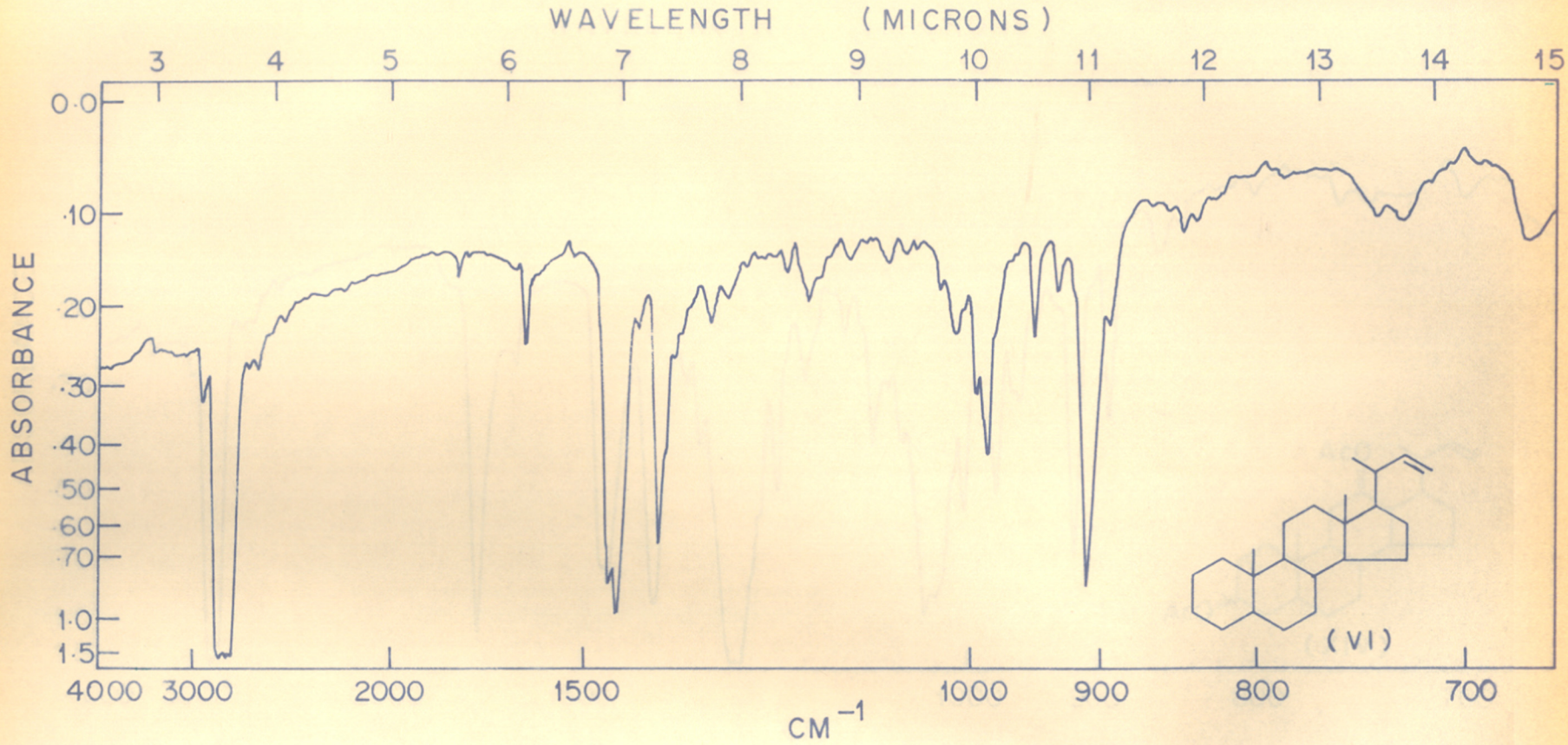


FIG. 1. IR SPECTRUM (NUJOL) OF Δ^{22} – 24 – NORCHOLENE

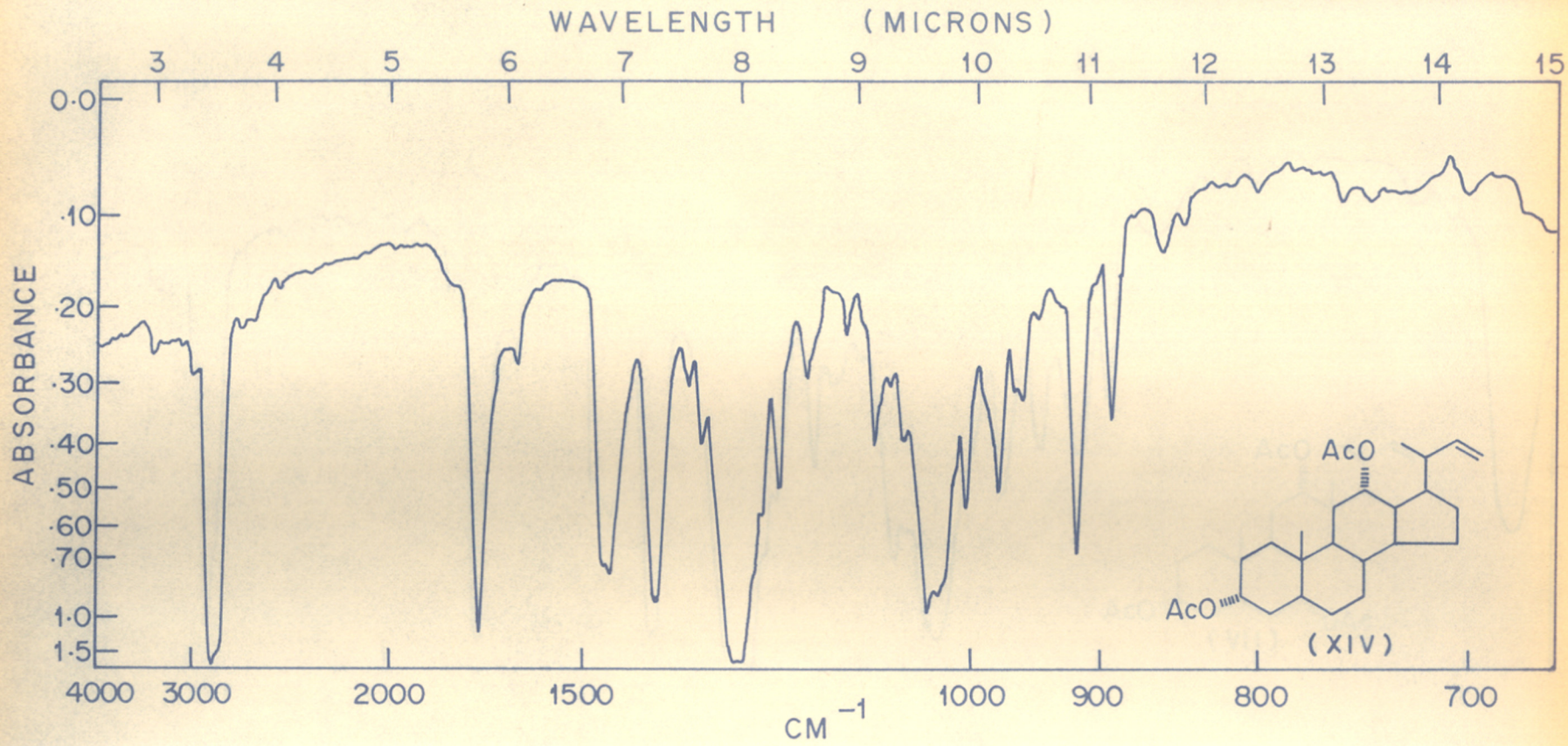


FIG. 2. IR SPECTRUM (NUJOL) OF 3α, 12α-DIACETOXY-Δ^{22}-24-NORCHOLENE

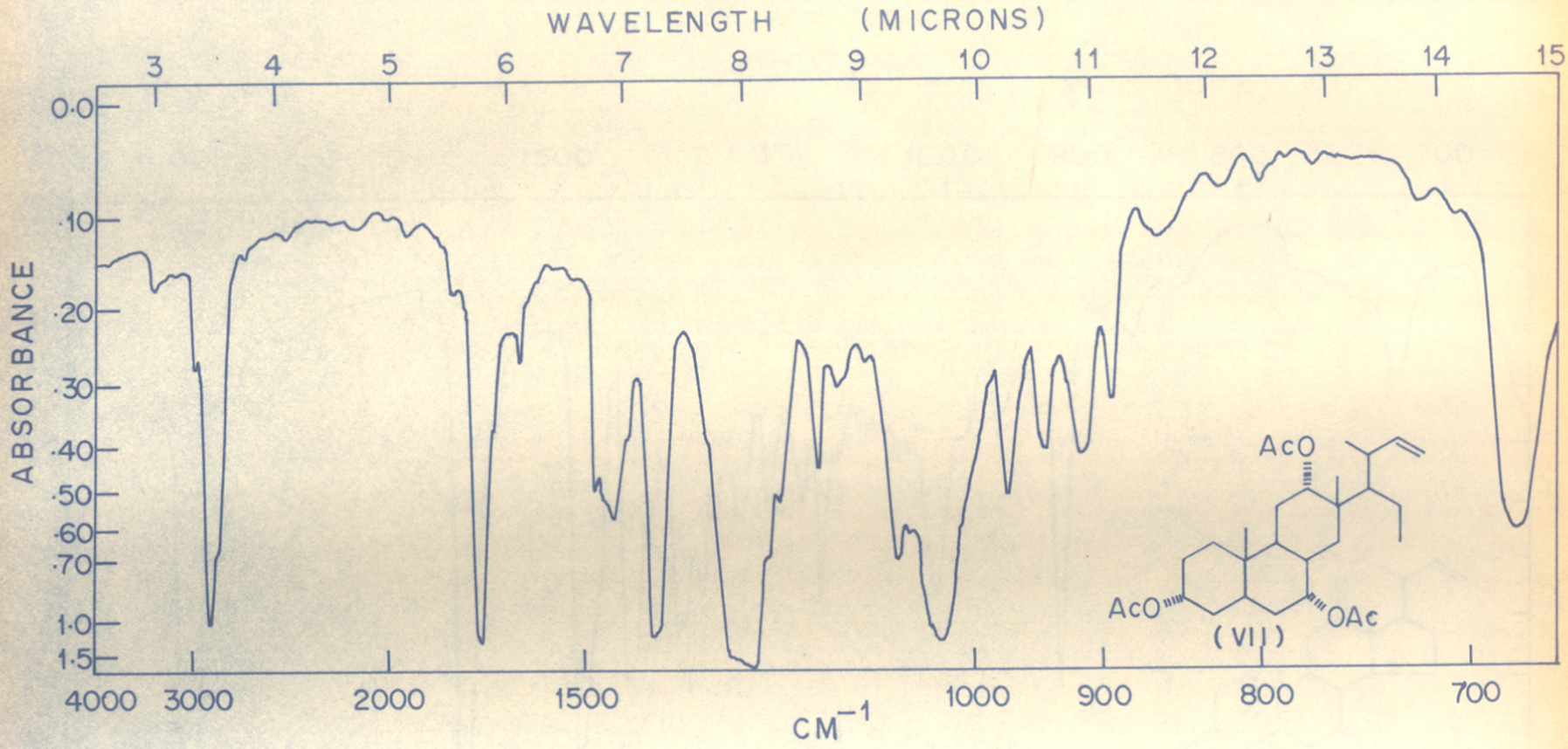


FIG. 3 IR SPECTRUM (LQ. FILM) OF 3α, 7α, 12α-TRIACEOXY-Δ^{22}-24-NORCHOLENE

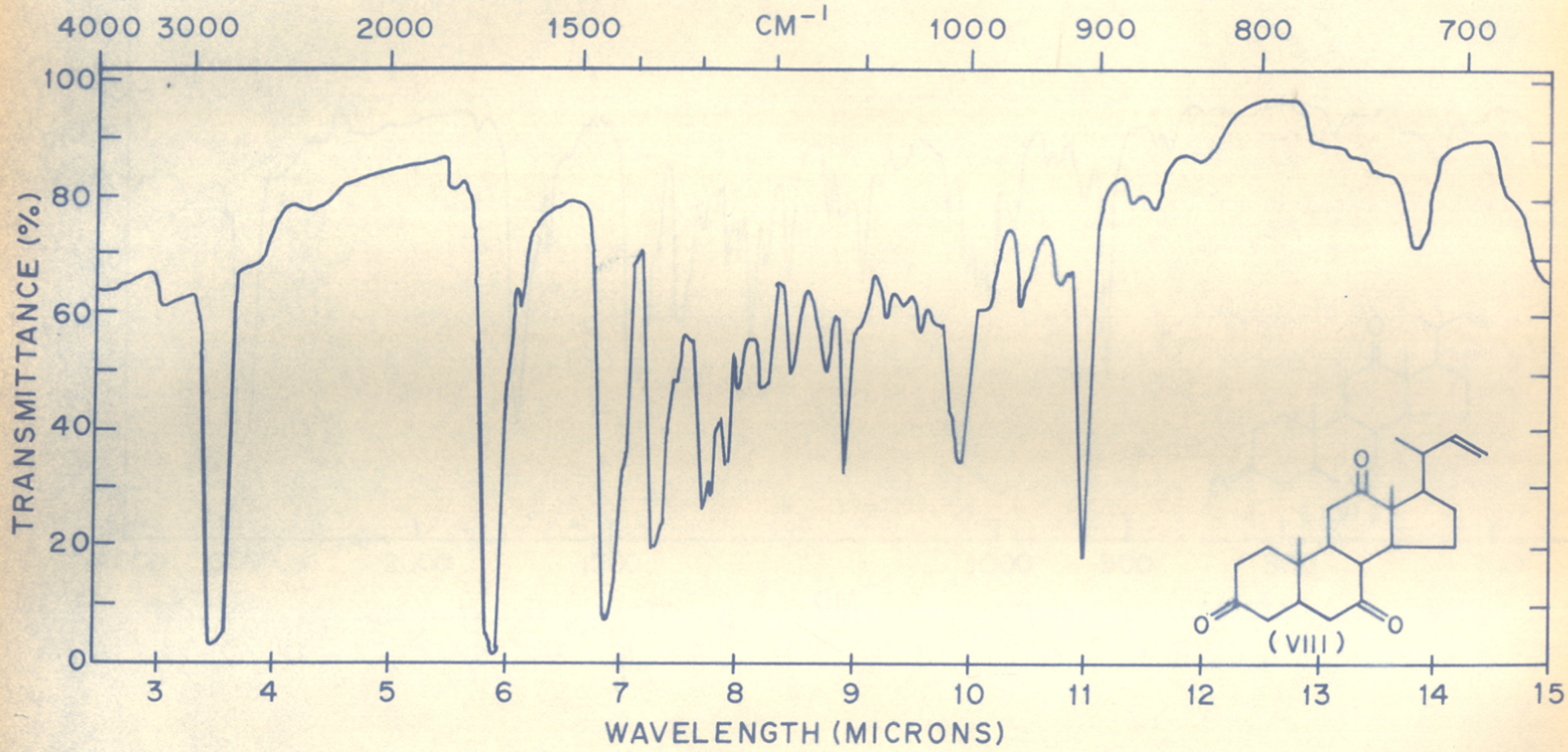


FIG. 4. IR SPECTRUM (NUJOL) OF 3,7,12-TRIKETO-Δ^{22}-24-NORCHOLENE.

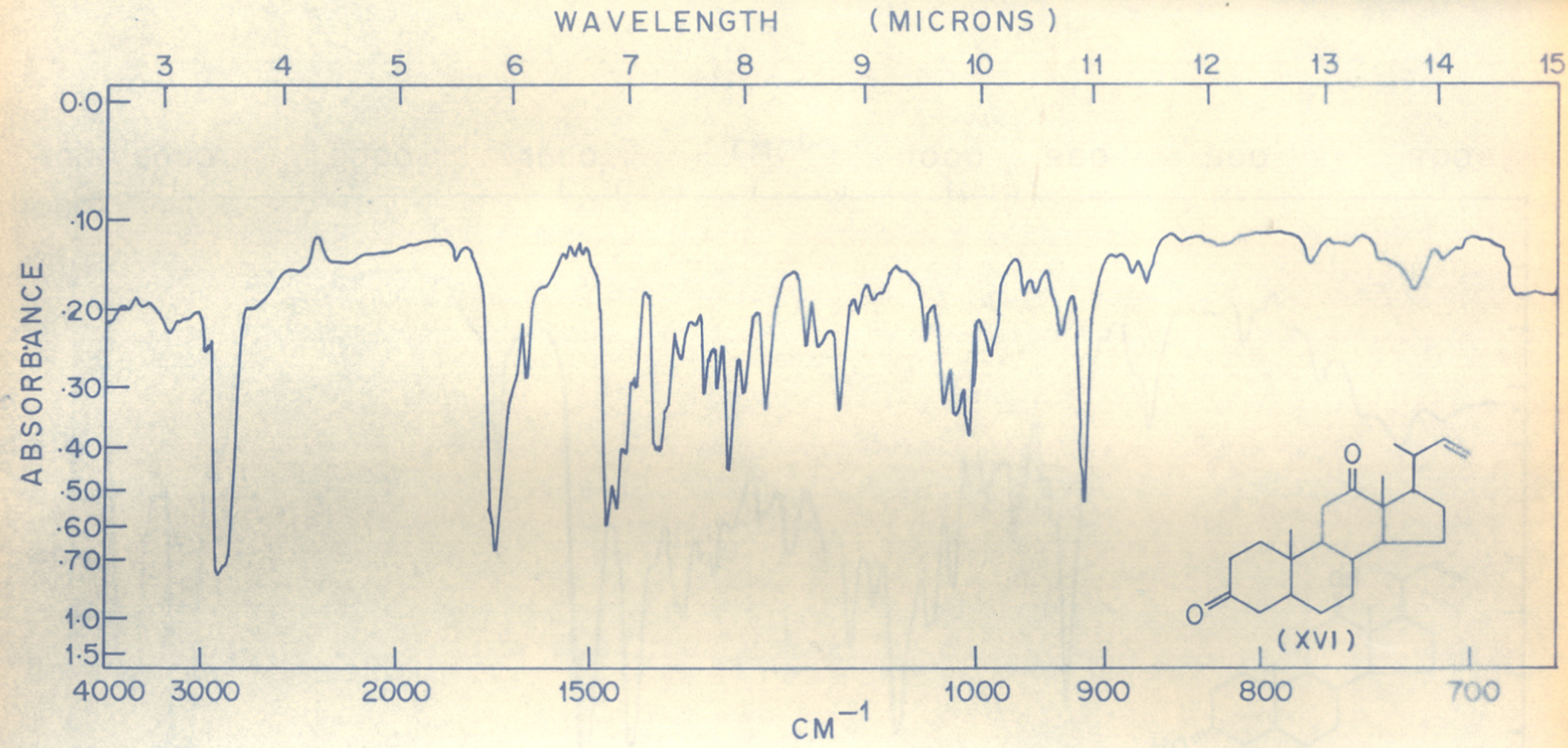


FIG. 5. IR SPECTRUM (NUJOL) OF 3,12-DIKETO-Δ^{22}-24-NORCHOLENE

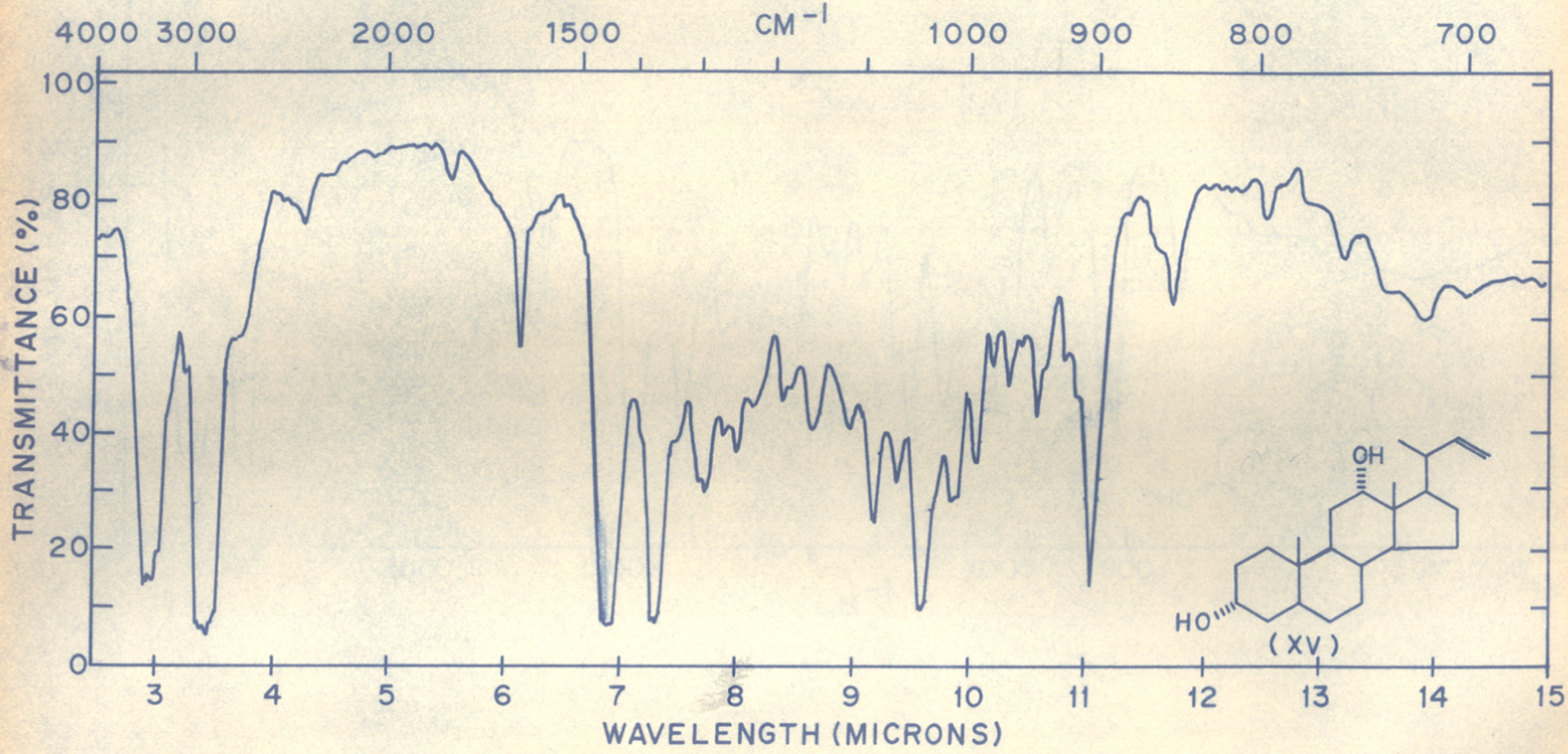


FIG. 6. IR SPECTRUM (NUJOL) OF 3α,12α-DIHYDROXY-Δ^{22}-24-NORCHOLENE.

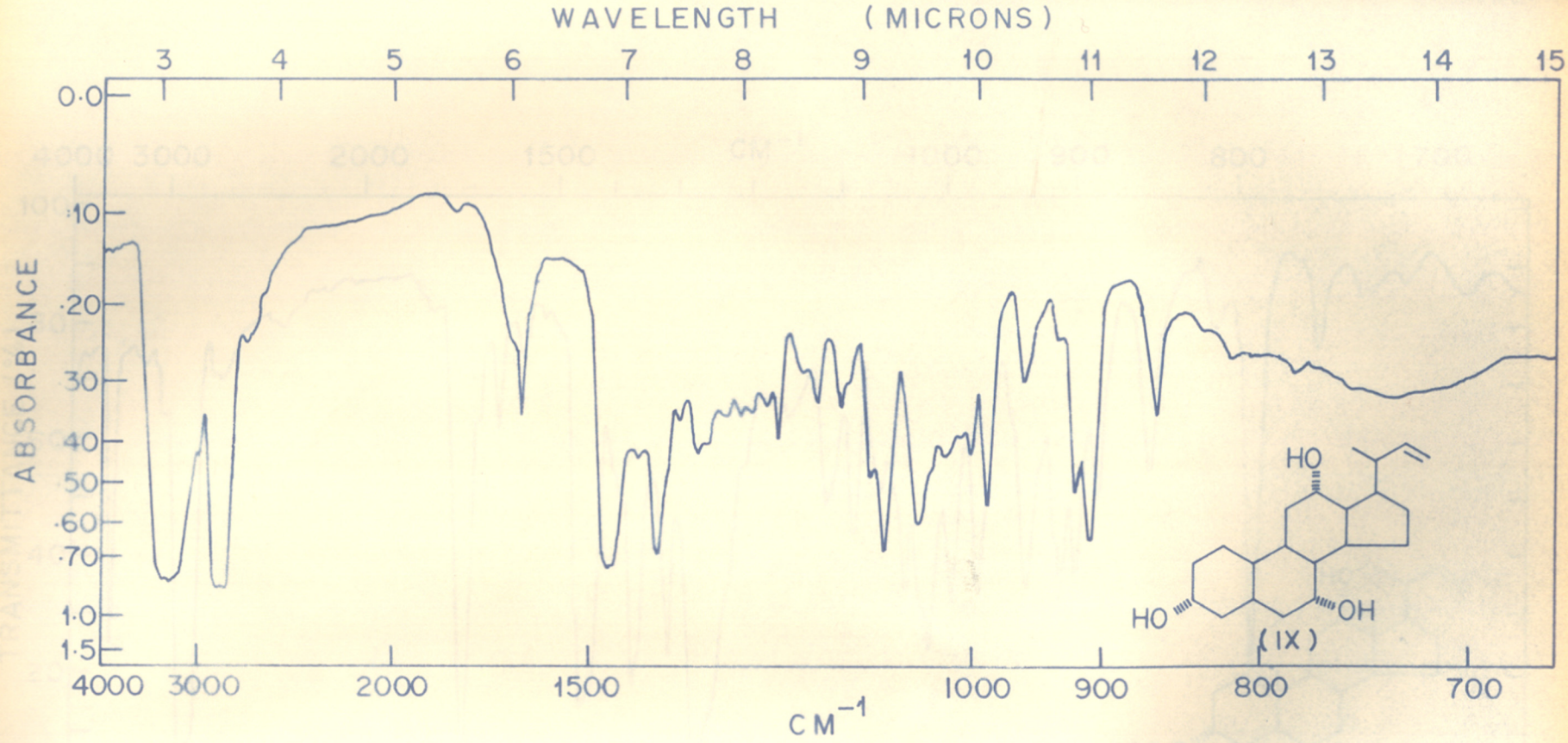


FIG. 7 IR SPECTRUM (NUJOL) OF 3α; 7α, 12α-TRIHYDROXY-Δ^{22}-24-NORCHOLENE

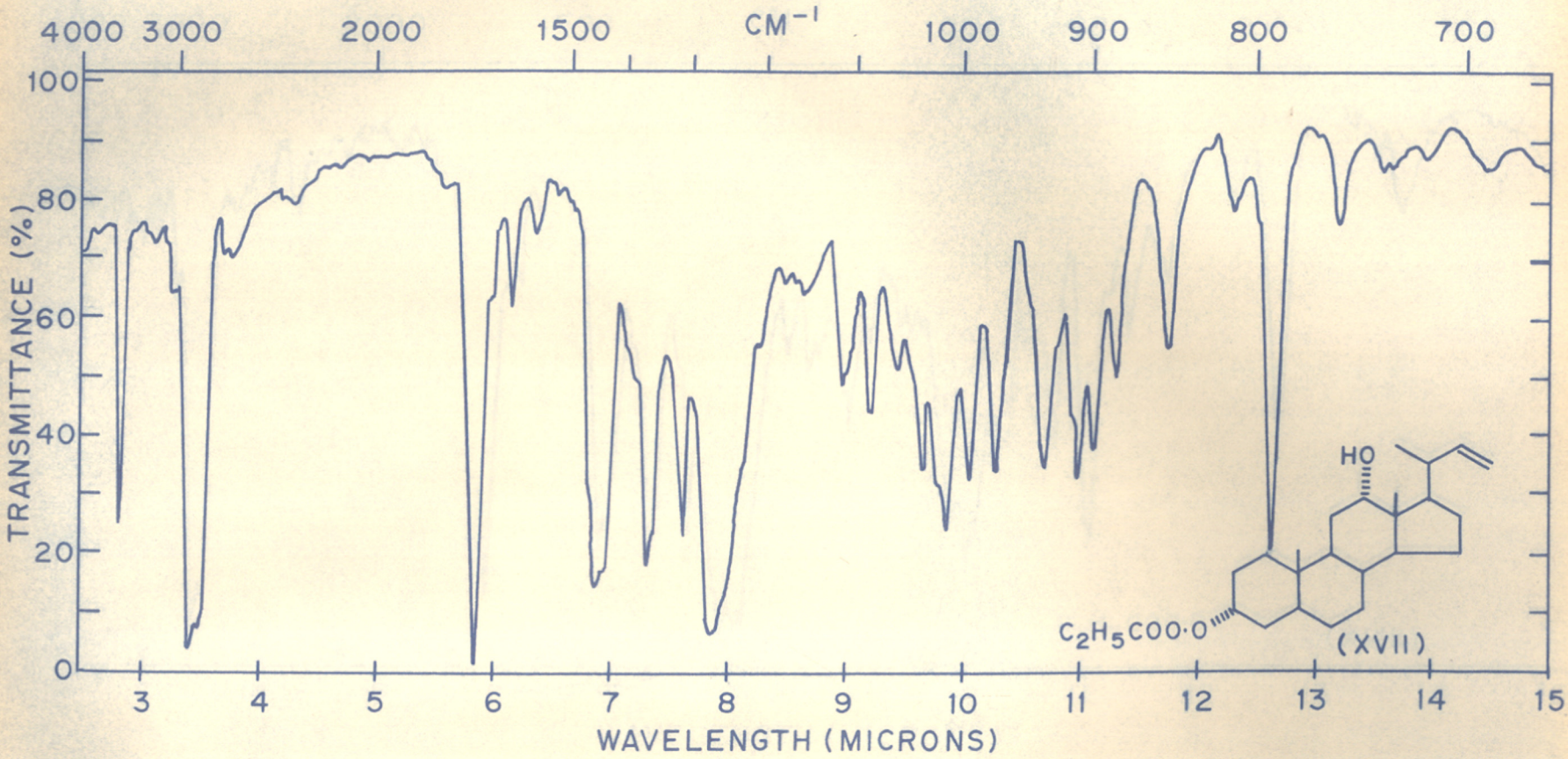


FIG. 8, IR SPECTRUM (NUJOL) OF 3α-CARBETHOXY-12α-HYDROXY-Δ^{22}-24-NORCHOLENE.

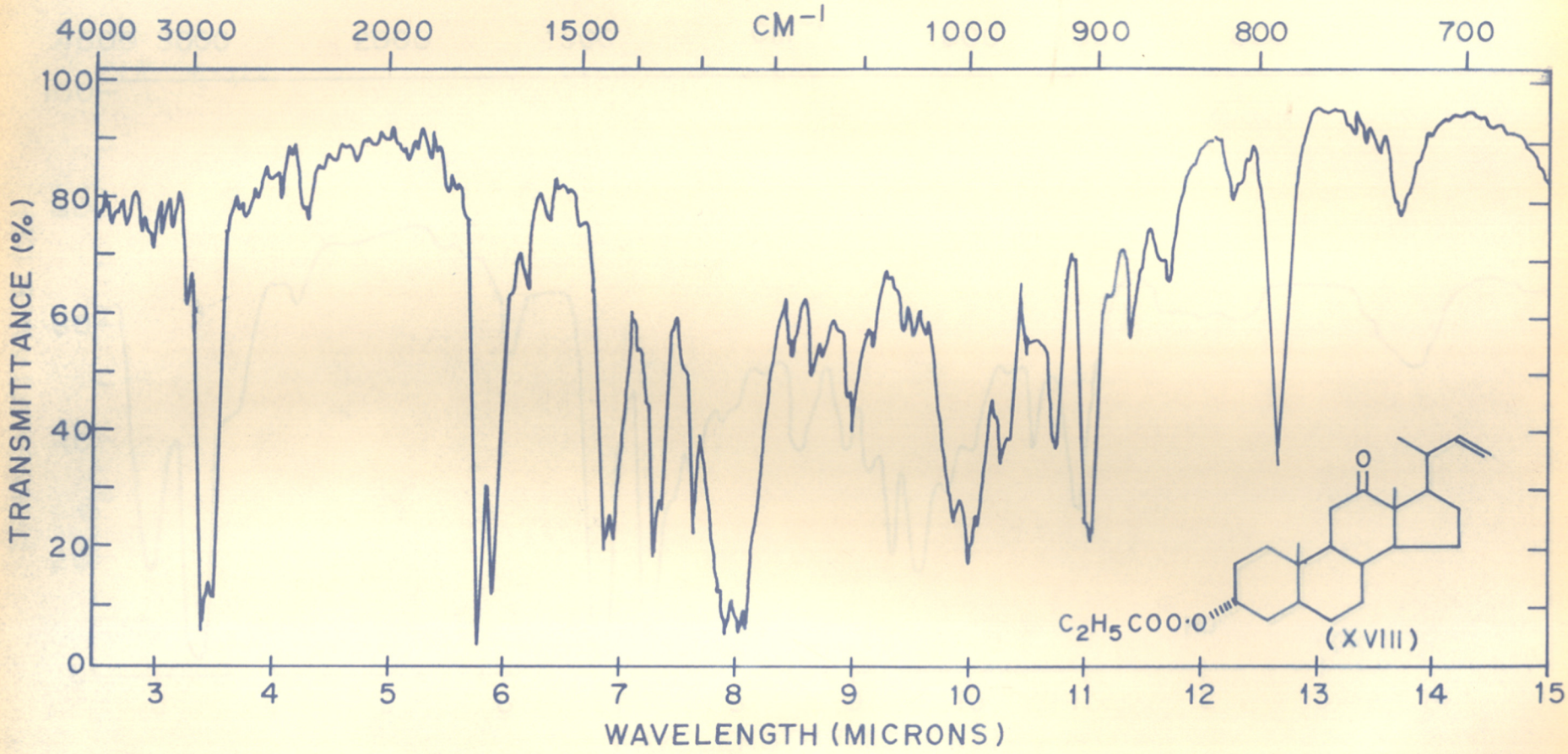


FIG. 9. IR SPECTRUM (NUJOL) OF 3α-CARBETHOXY-12-KETO-Δ^{22}-24-NORCHOLENE.

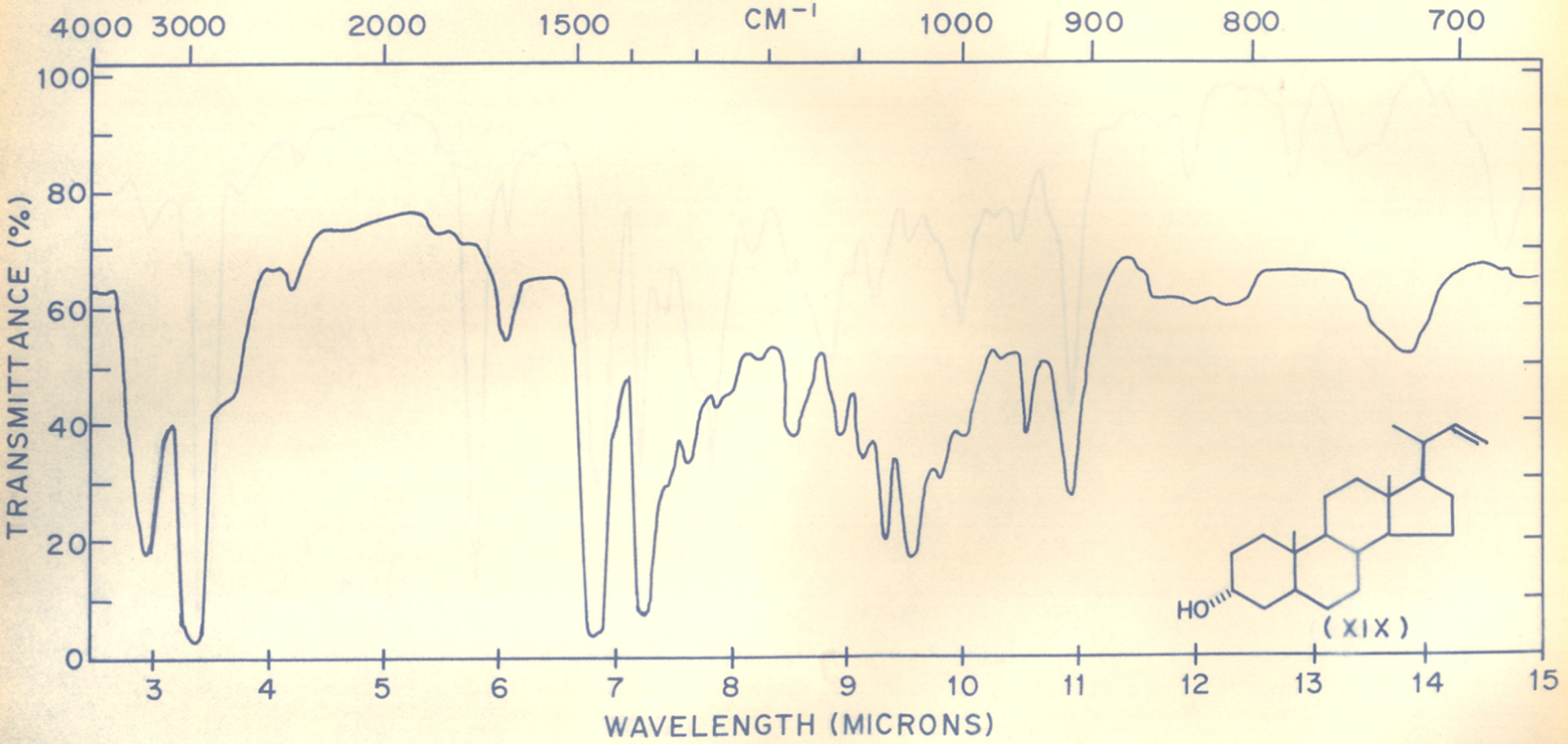


FIG. 10. IR SPECTRUM (NUJOL) OF 3α-HYDROXY-Δ^{22}-24-NORCHOLENE.

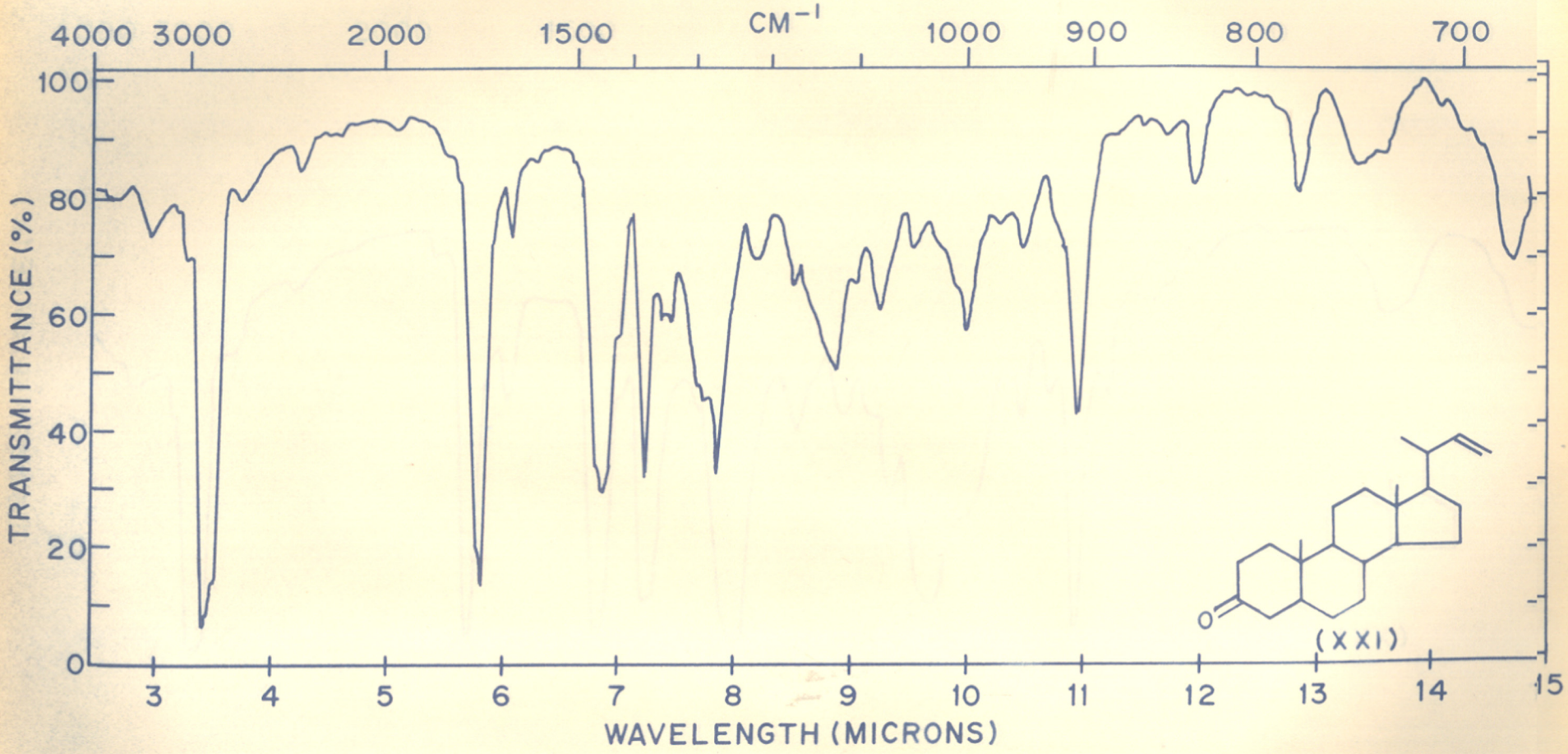
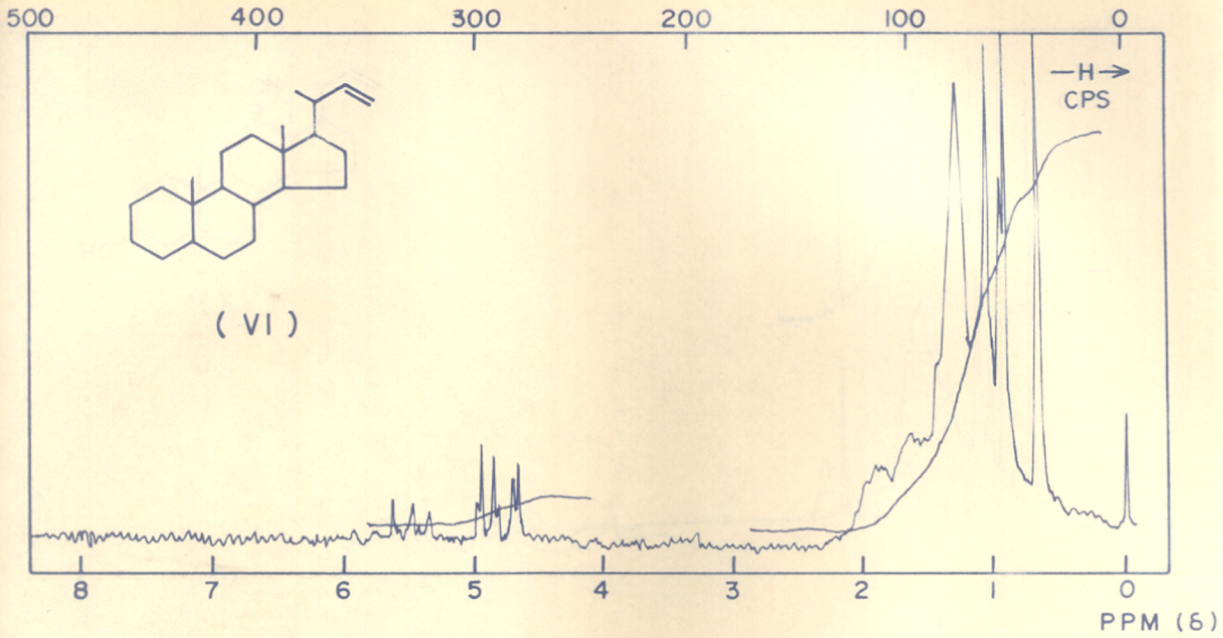
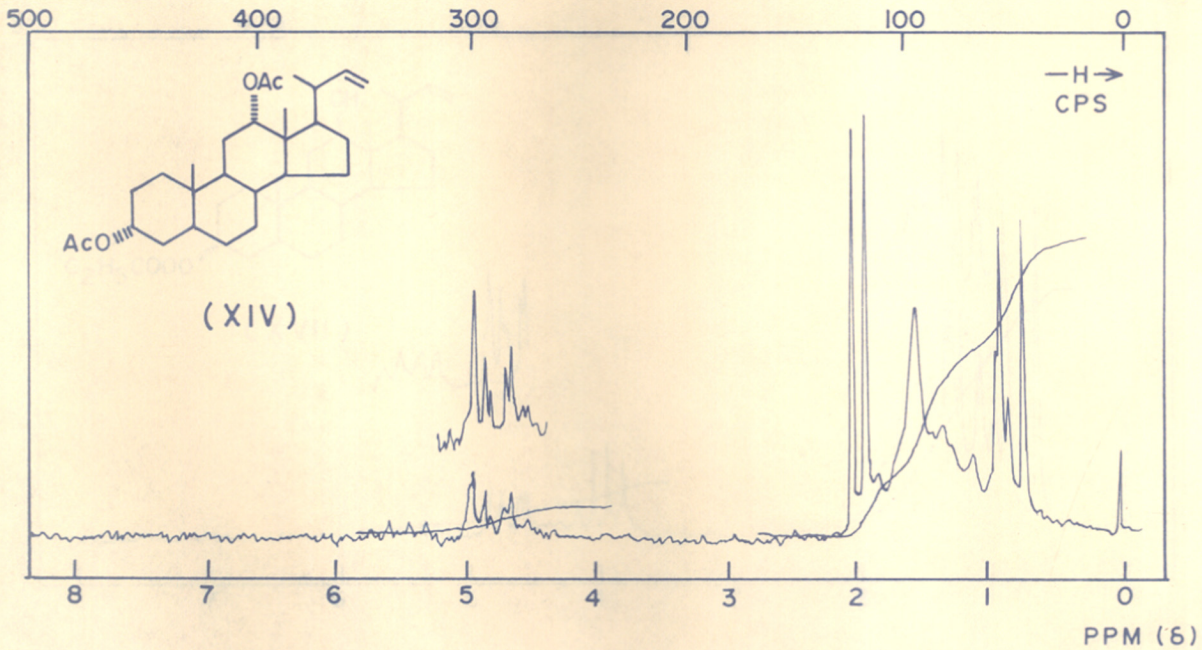


FIG. 11. IR SPECTRUM (NUJOL) OF 3-KETO-Δ^{22}-24-NORCHOLENE.



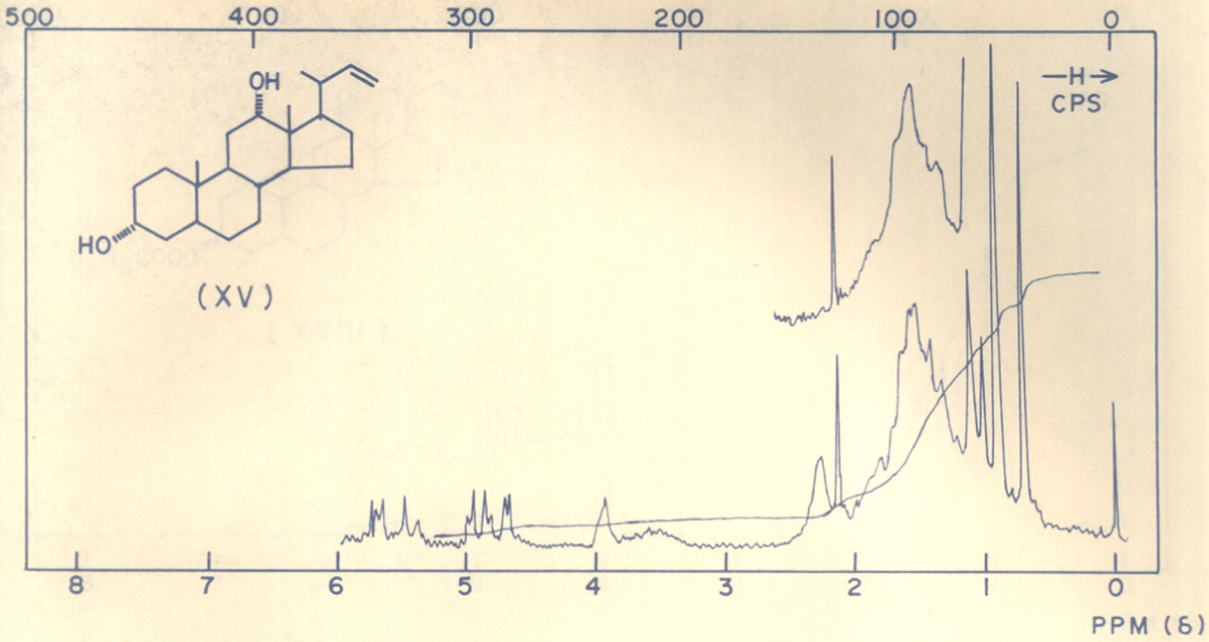
NMR SPECTRUM OF Δ^{22} – 24 – NORCHOLENE

(IN CCl_4)



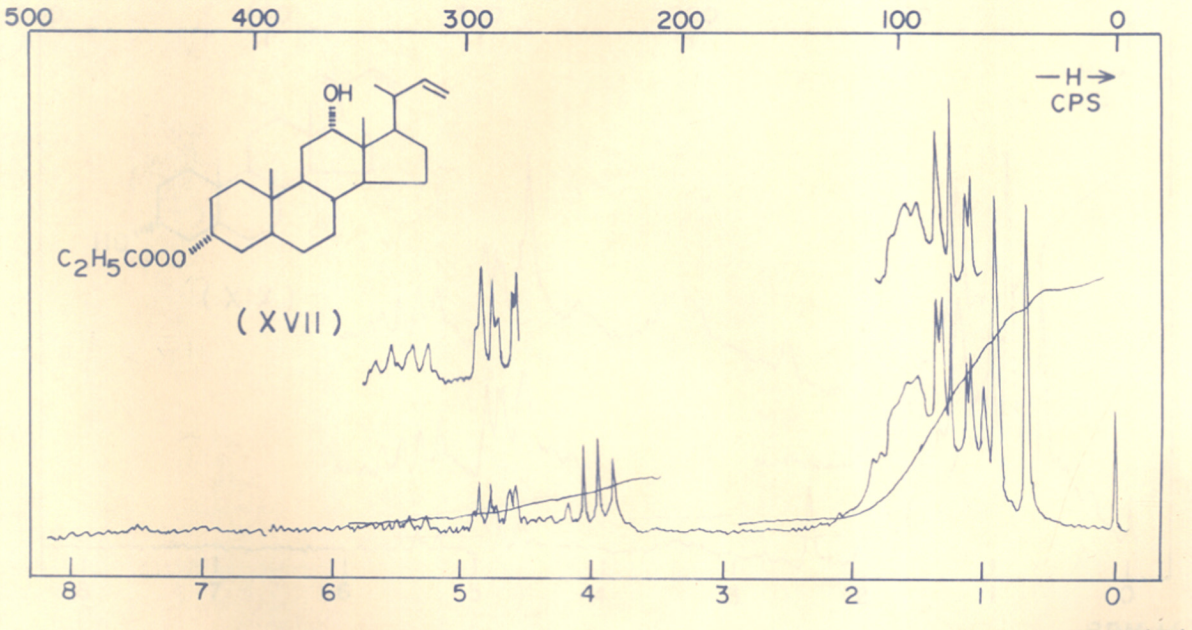
NMR SPECTRUM OF 3α, 12α – DIACETOXY – Δ^{22} – 24 – NORCHOLENE

(IN CCl_4)



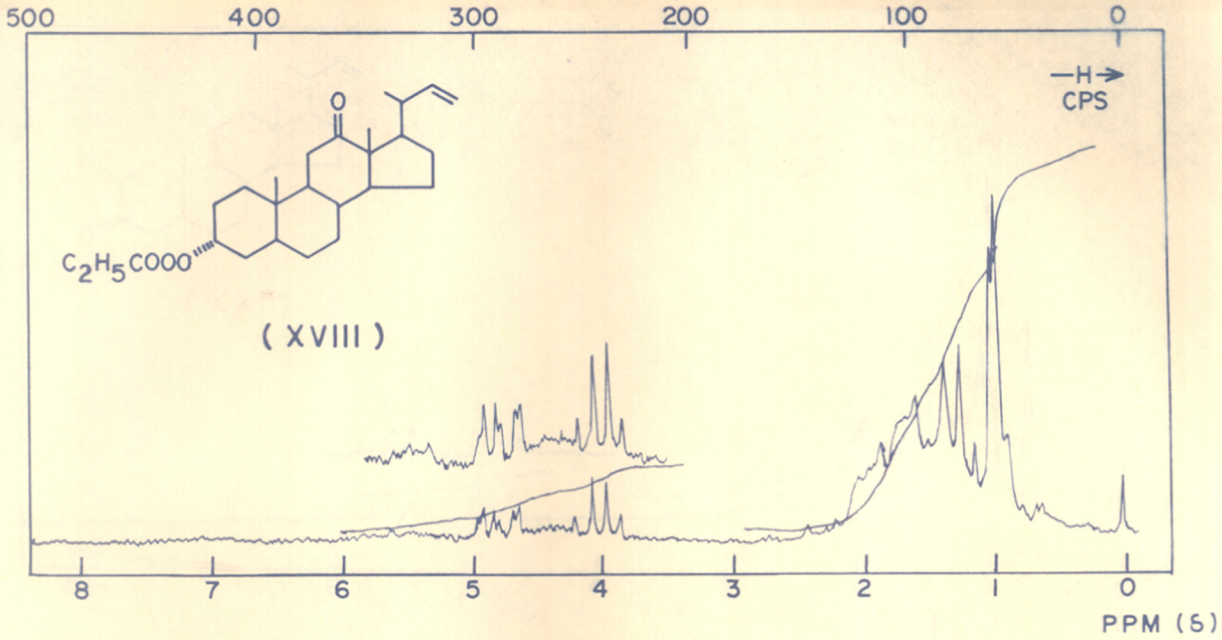
NMR SPECTRUM OF 3α, 12α - DIHYDROXY - Δ^{22} - 24 - NORCHOLENE

(IN $CHCl_3$)



NMR SPECTRUM OF 3α - CARBETHOXY - 12α - HYDROXY - Δ^{22} - 24 - NORCHOLENE

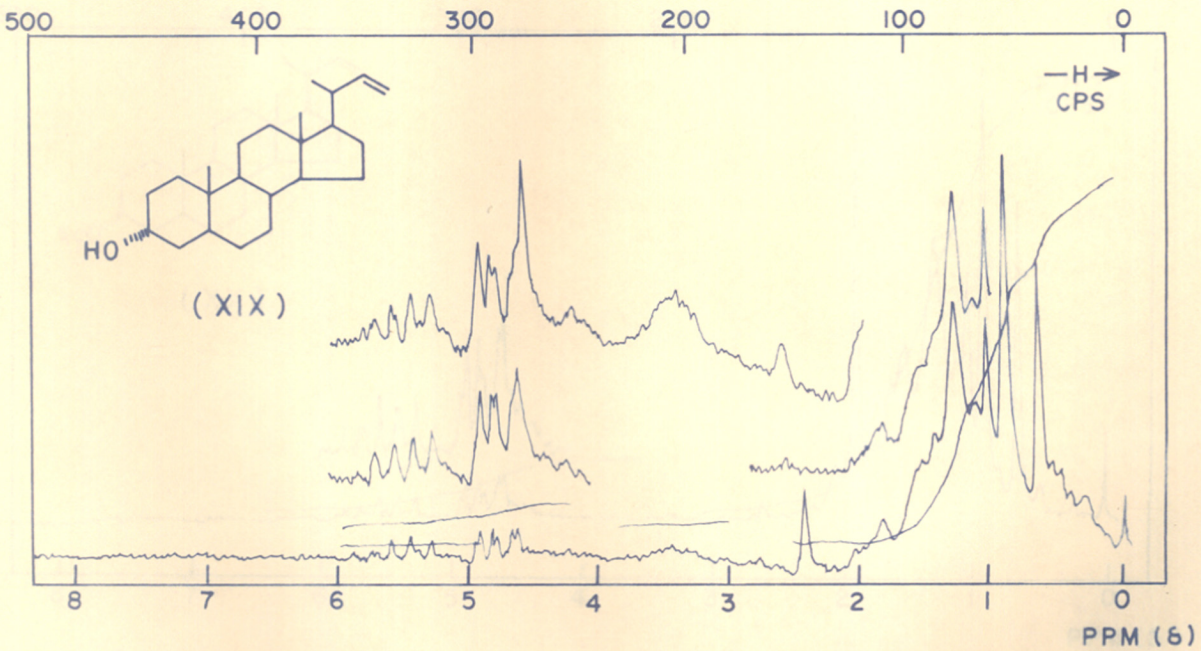
(IN CCl_4)



(XVIII)

NMR SPECTRUM OF 3α-CARBETHOXY-12-KETO-Δ^{22}-24-NORCHOLENE

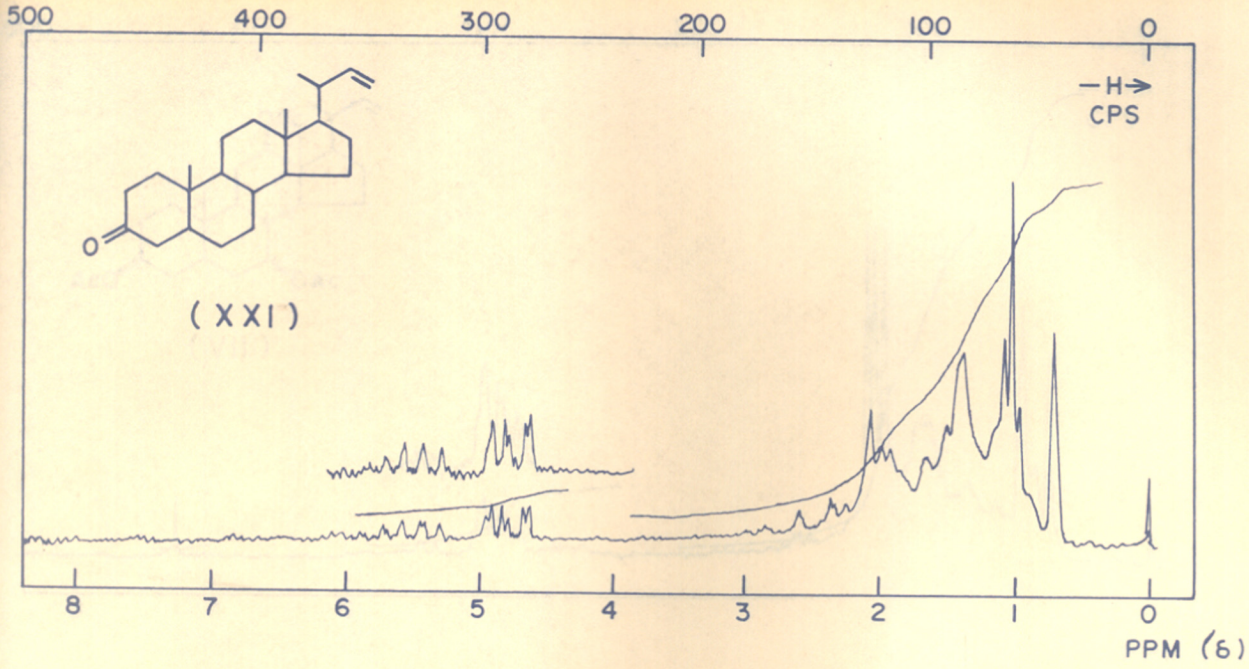
(IN CCl_4)



(XIX)

NMR SPECTRUM OF 3α-HYDROXY-Δ^{22}-24-NORCHOLENE

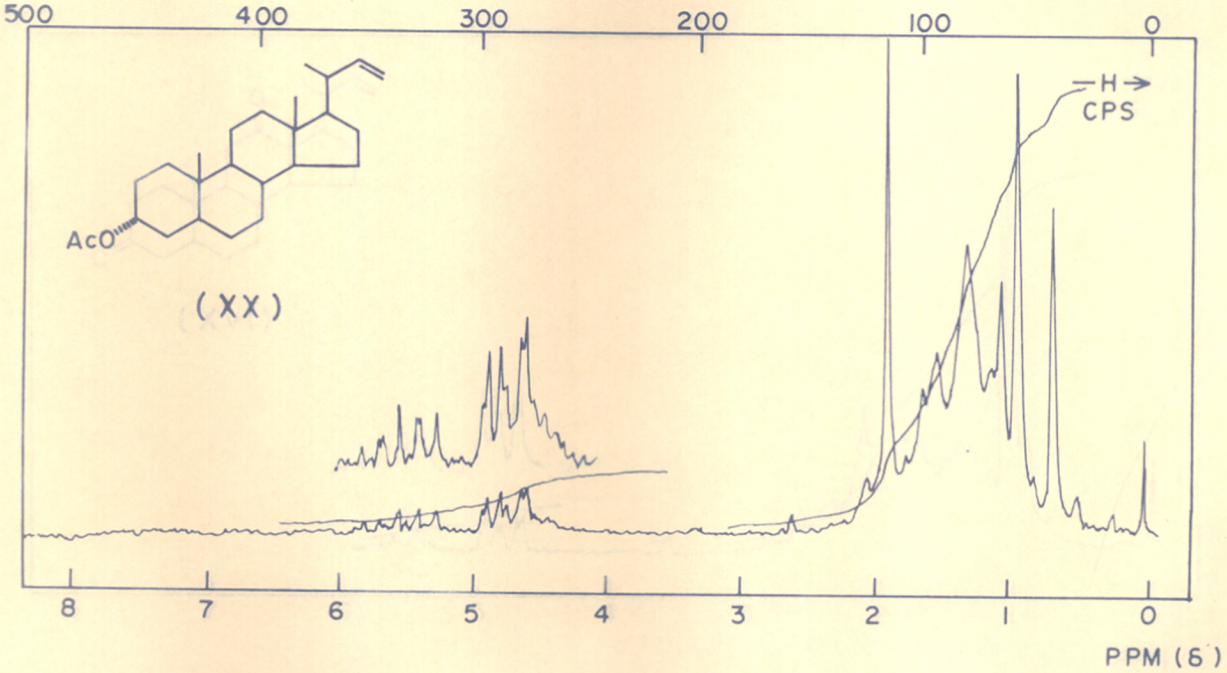
(IN CCl_4)



(XXI)

NMR SPECTRUM OF 3-KETO-Δ^{22}-24-NORCHOLENE

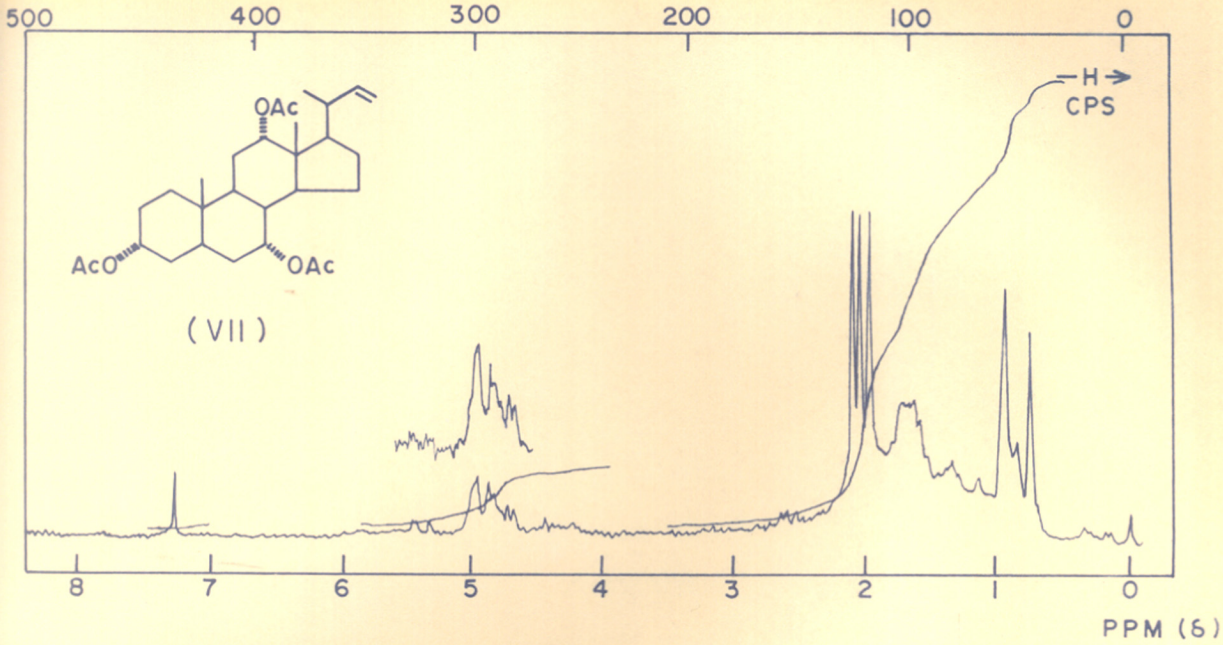
(IN CCl_4)



(XX)

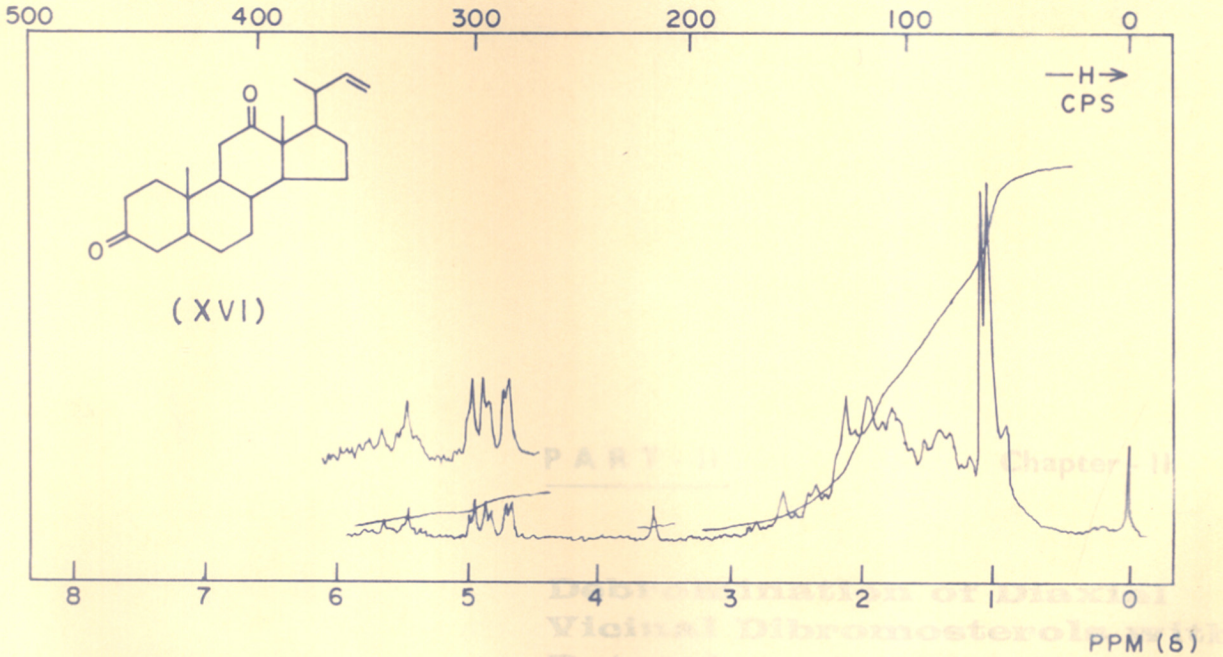
NMR SPECTRUM OF 3α,-ACETOXY-Δ^{22}-24-NORCHOLENE

(IN CCl_4)



NMR SPECTRUM OF 3α, 7α, 12α – TRIACETOXY – Δ^{22} – 24 – NORCHOLENE

(IN CCl_4)



NMR SPECTRUM OF 3, 12 – DIKETO – Δ^{22} – 24 – NORCHOLENE

(IN $CHCl_3$)

PART - II

Chapter - II

Debromination of Diaxial Vicinal Dibromosterols with Potassium t- Butoxide - Di - Methyl Sulphoxide.

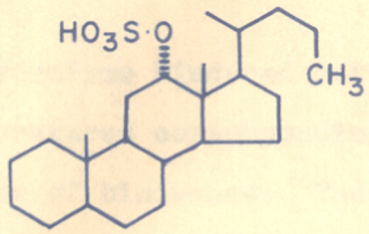
SUMMARY

In this Chapter the action of strong basic reagent, potassium-tert-butoxide in dimethyl-sulphoxide (KtBD) on diaxial, vicinal, dibromo-sterols has been investigated. KtBD is known as a strong dehydrohalogenating agent. However in case of above mentioned dibromosterols, e.g. 5α, 6β-dibromocholestan-3β-ol KtBD has been shown to bring about debromination to afford cholesterol. The possible mechanism for such type of elimination has been described.

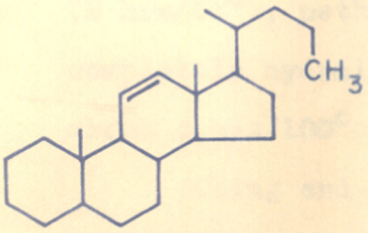
The reagent, potassium-t-butoxide in dimethyl sulphoxide (KtBD) has been used in a number of recently reported notable reactions[1].

Alkaline hydrolysis of asymmetric sulphonate esters usually yields inverted or racemised alcoholic products accompanied by varying proportions of olefinic material. Chang[2] for the first time carried out the alkaline room temperature hydrolysis of mesylates of equatorial conformation to alcohols of original configuration. When 12α-mesyloxy cholane[3] (I) is treated with KtBD reagent at room temperature, $\triangle^{11}$-cholene (II) is obtained smoothly and in good yields (65%) accompanied by 12α-cholenol (III) in substantial yield (29%). Methyl desoxycholate dimesylate (IV) on reaction with KtBD was expected to yield principally 3α-hydroxy-11-cholenic acid (V). Surprisingly however, the main product proved to be 3,11-choladienic acid (VI) (thus affording an excellent method of preparing the dienic acid from desoxycholic acid).

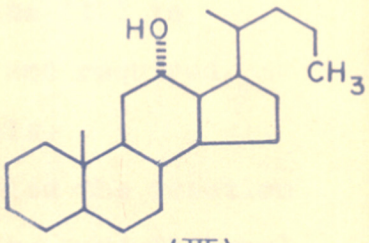
The cleavage of the sulphur-oxygen bond of a methane sulphonate group by KtBD suggested that the reagent might be effective for hydrolysing esters of hindered acids through alkyl-oxygen fission[4], under conditions less drastic or less restrictive than those employed in existing methods. It was found that KtBD



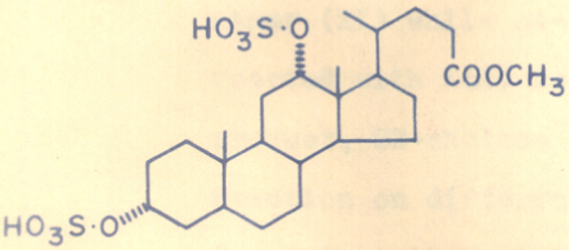
(I)



(II)



(III)



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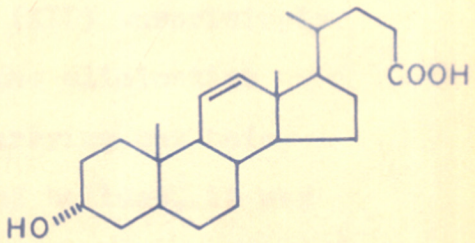

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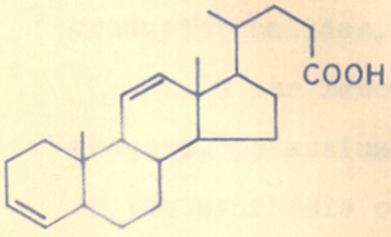
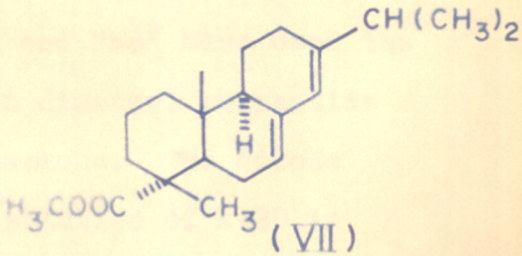
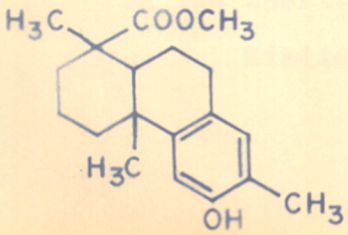


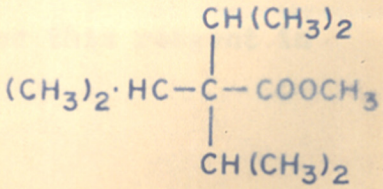
(VI)



(VII)



(VIII)



(IX)

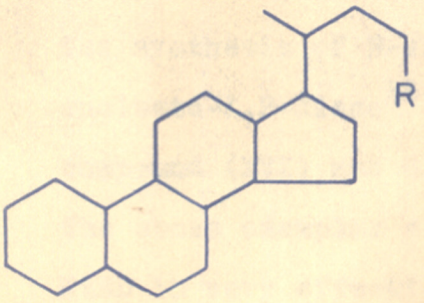
does indeed hydrolyse hindered esters, with required reaction temperatures corresponding roughly to the apparent degree of hindrance. Thus in comparison studies, following esters hydrolysed as, methyl dehydroabietate (VII) (less than one hour at room temperature), methyl orthomethyl podocarpate (VIII) (2 hrs/56°), methyl triisopropyl acetate (IX) in completely hydrolysed in (20 hrs/56°) and required about 4 hrs/100° for complete hydrolysis.

Chang and co-workers[5] also studied the reaction of KtBD on primary tosylates and halides. 24-Cholanyl tosylate (X) yielded predominently the tertiary butyl ether (XI) while 24-chlorocholane (XII) surprisingly reacted with KtBD to give mainly the elimination product, 23-cholene (XIII). On carrying out this reaction on different tosylates and halides, it was found that this difference in behaviour was a general one: tosylates give predominently the substitution products; halides, chiefly products of elimination.

In our laboratory Honwad and Rao[9] have used the reagent, potassium t-butoxide in dimethyl sulphoxide in the synthesis of saussurea lactone. The diiodo compound (XIV) when added to a solution of KtBD in nitrogen atmosphere furnished the diene (XV) as shown in the Chart.

Similarly Patil and Rao employed this reagent in

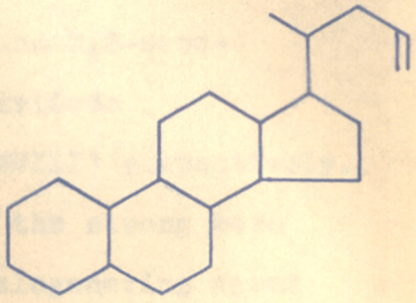
CHART II.



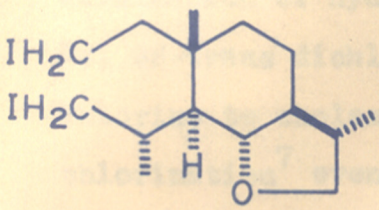
X R = CH_2OTs

XI R = $CH_2O(CH_3)_3$

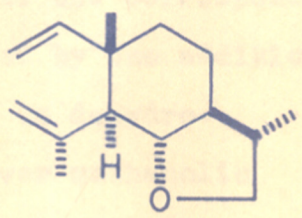
XII R = CH_2Cl



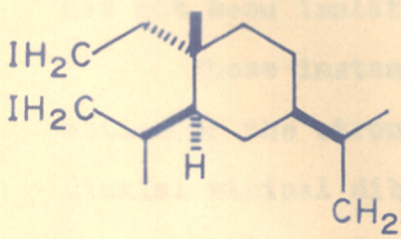
(XIII)



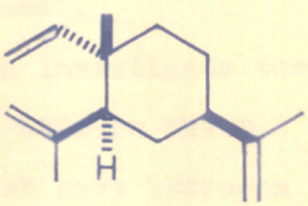
KtBD
N_2 atm.



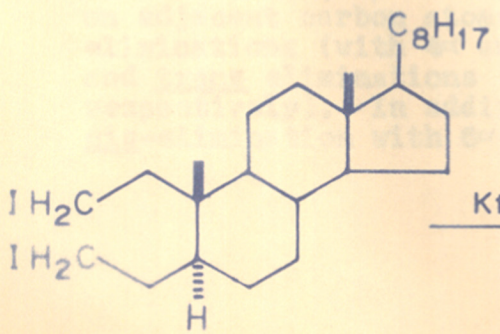
(XIV) (XV)



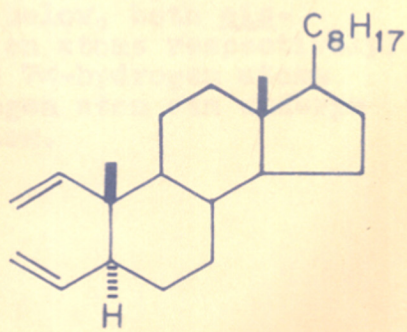
KtBD



(XVI) (XVII)



KtBD



(XVIII) (XIX)

the synthesis of β-elemene[10] (XVII) and 2,3-seco-cholesta-1,3-diene[11] (XIX) from the triiodo compound (XVI) and diiodo compound (XVIII) respectively. The above examples clearly show that the strong base KtBD is very effective as a dehydrohalogenating agent even when a primary halide is the reactant.

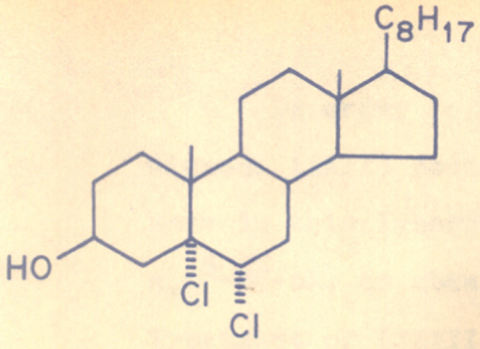
It has been reported[6] that 5α, 6α-dichloro-cholestan-3β-ol (XX) prepared by the action of iodo-benzene dichloride on cholesterol undergoes facile elimination of hydrogen chloride while the corresponding 5α, 6β-trans dichloride (XXI) prepared by the addition of chlorine to cholesterol is resistant to dehydro-chlorination[7] even after refluxing over methanolic caustic potash. 5α, 6β-Dibromocholestan-3β-yl-benzoate consumes nearly two equivalents of alkali during the course of two days at 25° but the product has not been isolated and characterised[8].

These instances prompted us to investigate the action of the stronger basic reagent KtBD on these diaxial vicinal dibromosterols[15] which have hydrogen atoms on adjacent carbon atoms*.

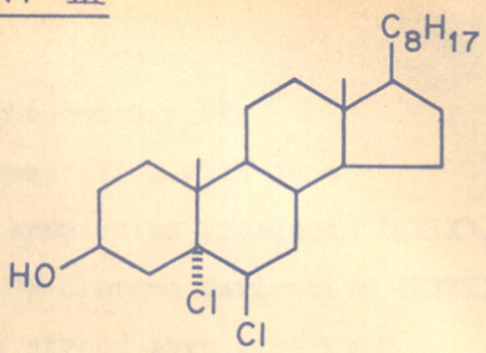
---

*In case of 5α, 6β-dibromosterols with hydrogen atoms on adjacent carbon atoms discussed below, both cis-eliminations (with 4α and 7β-hydrogen atoms respectively) and trans eliminations (with 4β and 7α-hydrogen atoms respectively). In addition 5α-halogen atom can undergo cis-elimination with 6α-hydrogen atom.

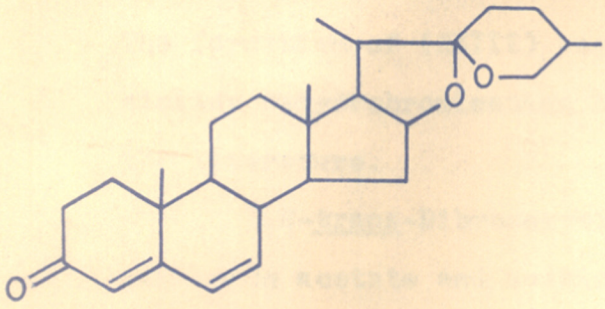
CHART III



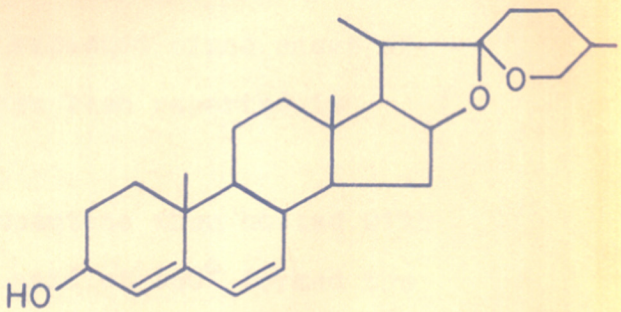
(XX)



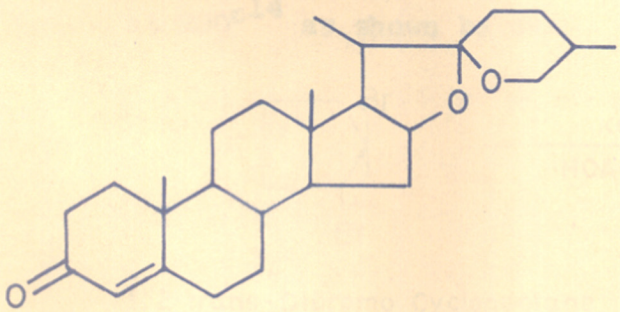
(XXI)



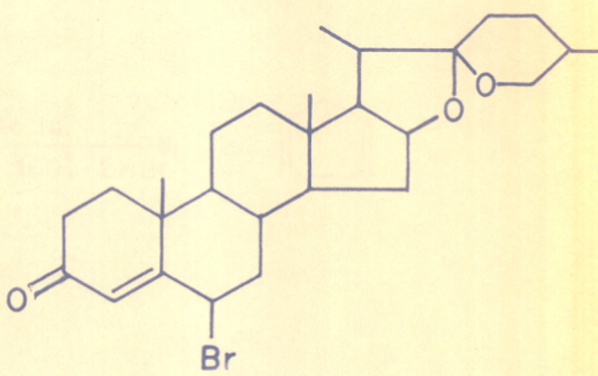
(XXII)



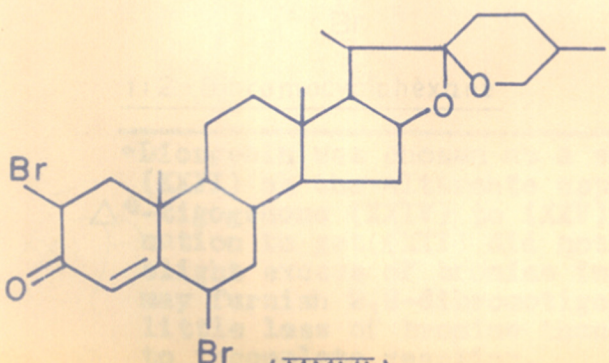
(XXIII)



(XXIV)



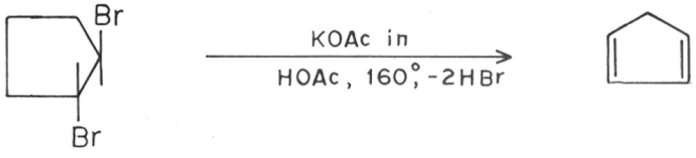
(XXV)



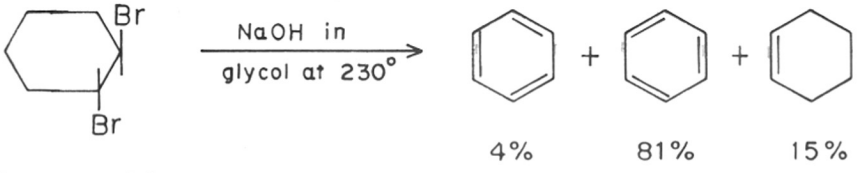
(XXVI)

In order to prepare the conjugated dienone (XXII) required in connection with some work in this laboratory, we brominated diosgenin (XXIX), a Δ^5-3β-ol, to obtain a 5α, 6β-dibromo derivative (XXXIII). Treatment of (XXXIII) with a strong base like KtBD was expected to furnish (XXIII) as one of the products*. The formation of (XXIII) was expected since cases of similar dehydrobromination have been reported in the literature.

1,2-trans-Dibromocyclopentane when heated with potassium acetate and acetic acid at 160° formed the conjugated diene by elimination of two HBr molecules[13], and 1,2-dibromocyclohexane affords the conjugated diene in very high yields when heated with NaOH and glycol at 230°[14] as shown below:



1:2 trans-Dibromo Cyclopentane



1:2-Dibromocyclohexane

*Diosgenin was chosen as a starting material to prepare (XXII) as the alternate approach involving bromination of Δ^4-tigogenone (XXIV) to (XXV) and subsequent dehydrobromination to get (XXII) did not appear attractive since a slight excess of bromine in bromination of Δ^4-tigogenone may furnish 2,6-dibromotigogenone (XXVI) and addition of a little less of bromine than calculated quantity will lead to incomplete reaction.

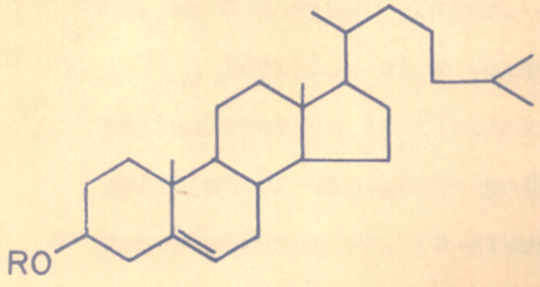
The oxidation of (XXIII) with MnO_2 will afford (XXII). However, when a solution of 5α,6β-dibromotigogenin (XXXIII) in DMSO was treated with potassium-tert-butoxide, (XXIII) underwent debromination instead of the expected dehydrobromination. The debromination of diaxial vicinal dibromosterols with KtBD has not been reported so far in the literature to our knowledge except the one reported by Turner[12].

In support of above observation the reaction of KtBD was also studied in case of following dibromides:

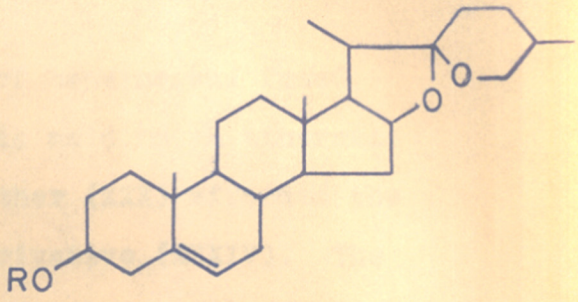
1. 5α, 6β-Dibromocholestan-3β-ol (XXXI)
2. 3β-Methoxy-5α, 6β-dibromocholestane (XXXII)
3. 5α, 6β-Dibromotigogenin methyl ether (XXXIV)
4. 2β, 3α-Dibromocholestane (XXXVI)

A solution of diosgenin (XXIX) in dry benzene when refluxed with potassium furnished the corresponding potassium salt which on refluxing with freshly distilled methyl iodide formed diosgenin methyl ether (XXX), the IR spectrum of which showed absence of a band due to the hydroxy group, and appearance of a pair of bands at 840 and 806 cm^{-1} due to trisubstituted double bond in a cyclic system. The NMR spectrum showed signals at 9.25 τ (C-18 methyl protons) and 9.0 τ (due to C-19 methyl protons), a sharp singlet at 6.75 τ (due to $-O-C\underline{H}_3$) and a multiplet in the region 4.3 τ - 4.8 τ

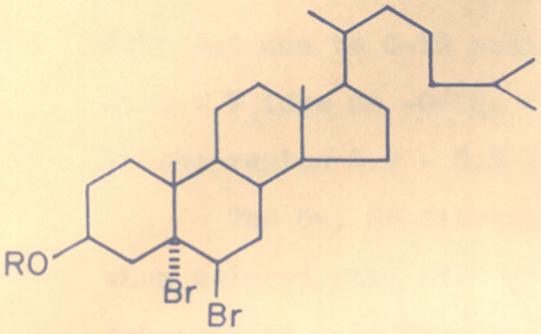
CHART IV



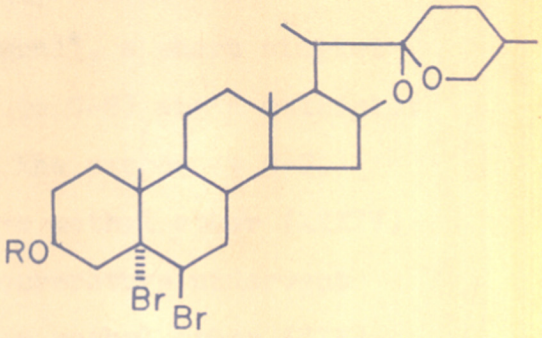
(XXVII) R = H
(XXVIII) R = Me



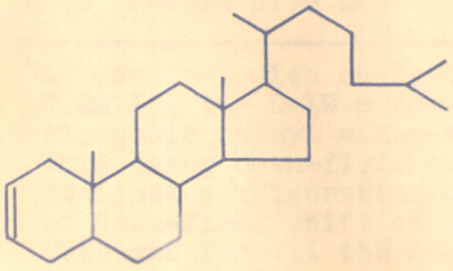
(XXIX) R = H
(XXX) R = Me



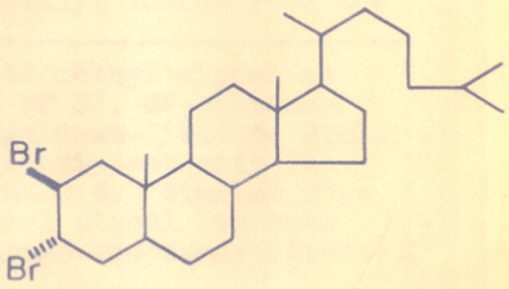
(XXXI) R = H
(XXXII) R = Me



(XXXIII) R = H
(XXXIV) R = Me



(XXXV)



(XXXVI)

due to C-6 vinyl proton.

Addition of a solution of bromine and fused sodium acetate in glacial acetic acid to an ethereal solution of diosgenin methyl ether (XXX) afforded the corresponding 5α, 6β-dibromoderivative (XXXIV). The IR spectrum indicated absence of a pair of bands between the region 850-800 cm^{-1} due to trisubstituted double bond. The NMR spectrum showed signals at 9.22 τ (due to C-18 methyl protons) and at 8.6 τ (singlet due to C-19 methyl protons)*, a sharp singlet at 6.7 τ (due to -O-CH_3 attached to C-3) and a multiplet in the region 5.2 - 5.3 τ due to the proton at C-6.

The 5α, 6β-dibromotigogenin methyl ether (XXXIV) when stirred with KtBD at room temperature underwent debromination to furnish diosgenin methyl ether (XXX). This was confirmed by melting point and mixed melting point with authentic sample of (XXX).

Cholesterol (XXVII) as in case of diosgenin (XXIX) when treated with potassium and methyl iodide gave the

---

*As compared with cholestane (C-19 methyl signal at 9.22 τ), the C-19 methyl signal of 5α, 6β-dibromotigogenin methyl ether is shifted down-field to 8.6τ. This large down-field shift is consistent with the assigned configuration at C-5 and C-6. Similar type of down-field shift of C-19 methyl signal has been observed for all the 5α, 6β-dibromo compounds reported in this Chapter.

corresponding 3β-methyl ether (XXVIII), the IR spectrum of which showed band at 806 and 840 cm^{-1} due to the trisubstituted double bond, a doublet at 1460 cm^{-1} and 1379 cm^{-1} due to the gem dimethyl group and absence of a band near 3500 cm^{-1} due to absence of -OH function. The NMR spectrum showed bands at 4.78 τ (C-6 vinyl proton); 6.78 τ (C-3β-methyl ether) and at 7.0 - 7.3 τ (C-3α-H). This methyl ether when treated with bromine in acetic acid solution afforded 3β-methoxy-5α,6β-dibromocholestane (XXXII). The IR spectrum showed absence of a trisubstituted double bond and NMR spectrum besides signals at 9.32 τ and 8.58 τ for the angular methyl groups at C-18 and C-19 respectively, showed a singlet at 6.7 τ due to $-OCH_3$. When 3β-methoxy-5α,6β-dibromocholestane (XXXII) in dimethyl sulphoxide solution was stirred with KtBD at room temperature it underwent debromination to afford cholesterol methyl ether (XXVIII) identified by m.p. and mixed m.p. and comparison of IR spectra and TLC behaviour.

An ethereal solution of diosgenin (XXIX) on bromination by adding bromine in acetic acid solution yielded 5α,6β-dibromotigogenin (XXXIII), the IR spectrum of which showed absence of the trisubstituted double bond. The NMR spectrum showed singlet at 9.17τ (due to C-18 methyl protons) and at 8.52 τ (due to C-19 methyl

protons).

An ethereal solution of (XXXIII) when treated with KtBD at room temperature underwent facile debromination to form diosgenin (XXIX). M.p. and mixed m.p. with an authentic sample of diosgenin remained undepressed.

Similarly 5α, 6β-dibromocholestane-3β-ol (XXXI) underwent debromination to give cholesterol (XXVII).

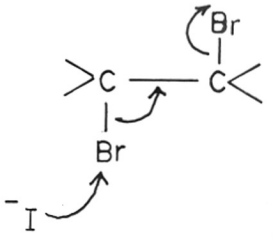
All the compounds discussed so far involved C-5 and C-6 dibromo derivatives and uniformly underwent debromination with KtBD. Similar reaction was also tried with 2β, 3α-dibromocholestane (XXXVI) prepared by known literature method.

An ethereal solution of (XXXV) when treated with a solution of bromine in acetic acid furnished the dibromoderivative (XXXVI). M.p. 121° $(\alpha)_D$ + 73° (lit. value $(\alpha)_D$ + 76°). The latter when stirred with KtBD at room temperature furnished Δ^2-cholestene (XXXV) identified by m.p. and mixed m.p. with an authentic sample of (XXXV).

Probable mechanism of debromination

The elimination of bromine from diaxial vicinal dibromo compounds under the influence of iodide ion is regarded[8] as involving a four-centre

type transition state as illustrated below:



For a minimization of activation energy, quantum mechanical theory indicates that the four centres must lie in one plane. When rotation about the C-C bond is possible, as for example in 1,2-dibromo-ethane, the two halogen atoms are easily able to take up the necessary conformation for activation energy minimization.

In cyclohexane derivatives, the necessary coplanarity is achieved by two trans substituents when both are axial. cis-Substituents are unable to take up this conformation on geometrical grounds.

In the reactions reported above pot-tert-butoxide has been used in presence of dimethyl sulphoxide. Hence the debromination may involve either t-butoxide ion or methyl sulphinyl carbanion[4].

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EXPERIMENTAL

Cholesterol methyl ether (XXVIII)

Cholesterol (XXVII; 11.37 g) was dissolved in dry benzene (450 ml) and potassium metal (3.6 g) was added. The mixture was refluxed for 1 hr with vigourous shaking at intervals to disperse the molten potassium into small globulets. Freshly distilled methyl iodide (22 ml) was then added and refluxing was continued further for 3 hrs. The reaction mixture was then cooled to room temperature and methanol was cautiously added to destroy the unreacted potassium. The solvents were removed under suction and the residue was diluted with water and extracted with petroleum ether (150 ml x 3). The combined petroleum ether extract was then acidified, washed free of acid with water, dried and passed through a column of alumina (Gr. III). The petroleum ether fraction on concentration furnished (XXVIII) as a white solid.

M.P. - 85° (lit. value 84.5°).

IR Spectrum (Page No. 146) IR spectrum showed bands at 2899, 2353, 1587, 1538, 1460, 1379, 1333, 1282, 1250, 1190, 1176, 1163, 1099, 1031, 1000, 980, 961, 943, 926, 901, 885, 862, 840, 806, 769 and 746 cm^{-1}.

3β-Methoxy-5α,6β-dibromocholestane (XXXII)

The cholesterol methyl ether (XXVIII; 1.11 g)

was dissolved in dry ether (15 ml) and the solution was cooled to 15° in iced water. A solution of fused sodium acetate (0.05 g) and bromine (0.15 ml) in glacial acetic acid (6 ml) was then added dropwise to it under stirring and stirring continued for 15 minutes. The reaction mixture on dilution with water, extraction with ether and usual work up gave the dibromo compound (XXXII; 1.509 g). Crystallised from petroleum ether-acetone mixture (1:1).

M.P. 106-108° (lit. value 107°).

Specific rotation $[\alpha]_D^{27°}$ - 54° (c, 3.16 in benzene) (lit. value $[\alpha]_D^{20°}$ - 52.96°).

Analysis - Found: C, 60.37; H, 8.81; Br, 28.55 $C_{28}H_{47}OBr_2$ requires: C, 60.1; H, 8.4; Br, 28.55%).

IR Spectrum (Page No. 147) IR spectrum showed bands at 2941, 2326, 1460, 1370, 1307, 1258, 1235, 1205, 1183, 1163, 1105, 1047, 1026, 1010, 980, 970, 952, 926, 893 and 833 cm^{-1}.

Debromination of 3β-methoxy-5α,6β-dibromocholestane

Potassium metal (0.4 g) was added to dry tert. butyl alcohol (30 ml) and mixture was refluxed till all the potassium reacted (3 hr.). Tertiary butyl alcohol was then removed on water-bath under suction and the dry white potassium-tert-butoxide was added to a solution of the dibromo compound (XXXII; 0.4078 g) in dimethyl sulphoxide (30 ml). The reaction mixture

was stirred overnight at room temperature. Next day, the reaction product was poured into ice cold water and extracted with ether. The ether extract was washed with water and dried over anhydrous sodium sulphate. The residue obtained after the evaporation of the solvent was chromatographed over alumin (Gr. II). The petroleum ether fraction (XXVIII) (0.255 g) was crystallised from acetone to furnish long needles of (XXVIII).

M.P. 85°-87°. The mixed m.p. with cholesterol methyl ether was undepressed and infrared spectra also were identical with each other.

5α, 6β-Dibromocholestane-3β-ol (XXXI)

Cholesterol (10 g) was dissolved in absolute ether (65 ml) and cooled to 20°. A solution of fused sodium acetate (0.3 g) and bromine (4.6 g) in acetic acid (40 ml) was then added dropwise with stirring. The solution was filtered and solid dibromo compound was washed with acetic acid, dried under vacuum.

M.P. - 114°-115° (lit. value 114°).

Specific rotation - $(\alpha)_D^{26^\circ}$ - 45° (c, 4.8 in $CHCl_3$), (lit. value - 44°).

IR Spectrum (Page No. 148) - IR spectrum showed bands at 3390, 3175, 2899, 2564, 1695, 1449, 1370, 1299, 1274, 1205, 1176, 1156, 1111, 1075, 1073, 1042, 1005, 961, 952, 926, 893 and 870 cm^{-1}.

Debromination of 5α, 6β-dibromocholestane-3β-ol

A mixture of 5α, 6β-dibromocholestane-3β-ol (XXXI; 1.98 g), dimethyl sulphoxide (dried over calcium hydride, 110 ml) and potassium-tert-butoxide (2.5 g) was stirred at room temperature for 33 hrs. The reaction product obtained by usual work up was identified as cholesterol through m.p. and mixed m.p. comparison of IR spectra and TLC using 6% ethyl-acetate in benzene. The identity was fully confirmed by converting the reaction product to its acetate and comparing it (m.p., mixed m.p. and IR) with authentic cholesteryl acetate. The acetates were prepared by adding pyridine and acetic anhydride to the reaction product and to the standard sample of cholesterol.

Diosgenin methyl ether (XXX)

To a solution of diosgenin (XXIX; 10.9 g) in sodium dry benzene (450 ml), potassium metal (4.4 g) was added and the mixture was refluxed for one hr. with occasional shaking to pulverise the molten potassium. Freshly distilled methyl iodide (26 ml) was then added and refluxing continued for 4.5 hrs. Cooled and unreacted potassium metal was destroyed by methanol. All the solvents were removed under suction and the residue was worked out as in case of methyl ether of cholesterol. The crude methyl ether of diosgenin thus obtained was crystallised from petroleum ether-acetone

mixture.

M.P. 179°-180° (lit. value 180-182°).

Analysis - Found: C, 78.52; H, 10.07

$C_{28}H_{44}O_3$ requires: C, 78.50; H, 10.28%.

IR Spectrum (Page No.144) IR Spectrum showed bands at 2941, 2336, 1667, 1562, 1449, 1370, 1342, 1282, 1242, 1190, 1176, 1147, 1106, 1081, 1070, 1052, 1010, 980, 901, 943, 934, 917, 892, 869, 840, 806 and 724 cm^{-1}.

5α, 6β-Dibromotigogenin methyl ether (XXXIV)

To a solution of diosgenin methyl ether (XXX; 3.114 g) in dry ether (45 ml), a solution of bromine (0.4 ml) and fused sodium acetate (0.150 g) in glacial acetic acid (18 ml) was added dropwise at room temperature. After stirring for 15 minutes a white solid separated which was filtered out (m.p.160-165°) and crystallised from carbon tetrachloride.

M.P. 165°

Analysis - Found: C, 57.18; H, 7.45.

$C_{28}H_{44}O_3Br_2$ requires: C,57.14;H, 7.48%.

IR spectrum (Page No.145) showed bands at 2941, 1460, 1374, 1302, 1242, 1198, 1176, 1156, 1109, 1075, 1053, 1020, 1010, 980, 961, 943, 925, 900, 869 and 724 cm^{-1}.

Debromination of 5α, 6β-dibromotigogenin methyl ether (XXXIV)

Dry potassium-tert-butoxide (4.6 g) was added to a solution of 5α, 6β-dibromotigogenin methyl ether

(XXXIV; 2.004 g) in freshly distilled dimethyl sulphoxide (115 ml). The mixture was agitated overnight at room temperature. Next day it was diluted with water and extracted with ether. The ether extract was washed with water, dried and evaporated to afford a crude debromination product. It was chromatographed over Gr. II alumina (1:20) and eluted by petroleum ether, petroleum ether-benzene (80:20) and benzene. The petroleum ether-benzene fraction on evaporation furnished (XXX)×

M.P. 180° (mixed m.p. with diosgenin-methyl- ether remained undepressed.

IR Spectrum (Page No.—) showed bands at 2924, 2353, 1667, 1456, 1379, 1342, 1302, 1285, 1247, 1193, 1176, 1163, 1139, 1109, 1081, 1073, 1053, 1012, 980, 961, 943, 934, 917, 900, 885, 869, 840, 806, 781 and 729 cm^{-1}.

Δ^2-Cholestene (XXXV)

To a solution of cholestan-3-one (4.8 g) in glacial acetic acid (125 ml) HBr/acetic acid (2 drops) was added followed by a dropwise addition of a solution of bromine (2.3 g) in acetic acid (10 ml). The homogeneous solution was stirred at room temperature for 30 minutes. The bromo-ketone separated, was filtered and washed with water till free of acid, dried over KOH pellets under vacuum.

The above bromo ketone was dissolved in ethanol (350 ml) and to the clear solution sodium borohydride (2 g)

was added and the flask was kept at room temperature for 20 hrs. The product was poured into the water (1.2 L) and extracted with chloroform. This extract was washed with water and dried over anhydrous sodium sulphate. The chloroform was recovered under suction. The crude bromohydrin obtained was directly utilised for preparation of Δ^2-cholestene. To a solution of 2-bromocholestan-3β ol (4.54 g) in acetic acid (200 ml) zinc dust (8.5 g) was added and the mixture was refluxed for 1/2 hr, cooled, filtered and acetic acid recovered under suction. The product was then taken in ether and washed with saturated Na_2CO_3 solution and water, dried over anhydrous sodium sulphate and solvent evaporated to get crude Δ^2-cholestene (XXXV) which was purified by chromatography over Gr. III alumina (1:20). The petroleum ether fraction afforded Δ^2-cholestene (1.9 g).

M.P. 68° (lit. value 69°) Crystallized from acetone-ether mixture.

Preparation of 2β 3α-dibromocholestane (XXXVI)

To a solution of Δ^2-cholestene (XXXV; 0.73 g) in dry ether (45 ml), a solution of bromine (0.31 ml) in glacial acetic acid (1 ml) was added dropwise under stirring, the reaction mixture was stirred for 2 hrs. The usual work up afforded the dibromo compound (XXXVI, 0.935 g).

M.P. 121° (lit. value 122°-4°).

Specific rotation - $(\alpha)_D$ + 73° (c, 4.8% $CHCl_3$).

(lit. value $(\alpha)_D$ + 76°).

Debromination of 2β, 3α-dibromocholestane (XXXVI) with KtBD

Potassium-tert-butoxide (1.13 g) was added to a solution of 2β, 3α-dibromocholestane (0.42 g) in DMSO (25 ml) and the mixture was stirred at room temperature for 16 hrs. The reaction product was then poured into water and extracted thrice with ether. The combined ether extract was washed with water until neutral, dried over anhydrous Na_2SO_4 and evaporated. Crude debromination product was chromatographed over Gr. II alumina (1:20). The petroleum ether fraction on evaporation furnished a solid (m.p. 63°-69°) found to be identical with a standard sample of Δ^2-cholestene ~~in all respects~~ (m.p., mixed m.p., IR).

Preparation of 5α,6β-dibromotigogenin (XXXIII)

Diosgenin (2.9 g) was dissolved in a mixture of dry ether (150 ml) and acetic acid (15 ml). To the clear solution, a solution of bromine (0.5 ml) in acetic acid (2 ml) was added dropwise and the reaction mixture was stirred at room temperature for 1 hr. The ether was evaporated and the solid was washed with cold acetone to remove the colour of bromine and crystallised from acetone.

M.P. 126°-128°C.

Specific rotation - $[\alpha]_D^{25}$ - 104° (c, 1.64 in benzene).

Debromination of 5α, 6β-dibromotigogenin (XXXIII)

A mixture of 5α, 6β-dibromotigogenin (XXXIII; 0.462 g), dimethyl sulphoxide (25 ml) and potassium-tert-butoxide (1.7 g) was magnetically stirred at room temperature for 17 hrs. The reaction product on usual work up furnished a solid (0.273 g) idential with (XXIX) on the basis of IR and TLC.

TLC with benzene + 6% ethyl acetate	Diosgenin	Rf value - 0.282
	Diosgenin Dibromide	Rf value - 0.381
	KtBD product	Rf value - 0.282

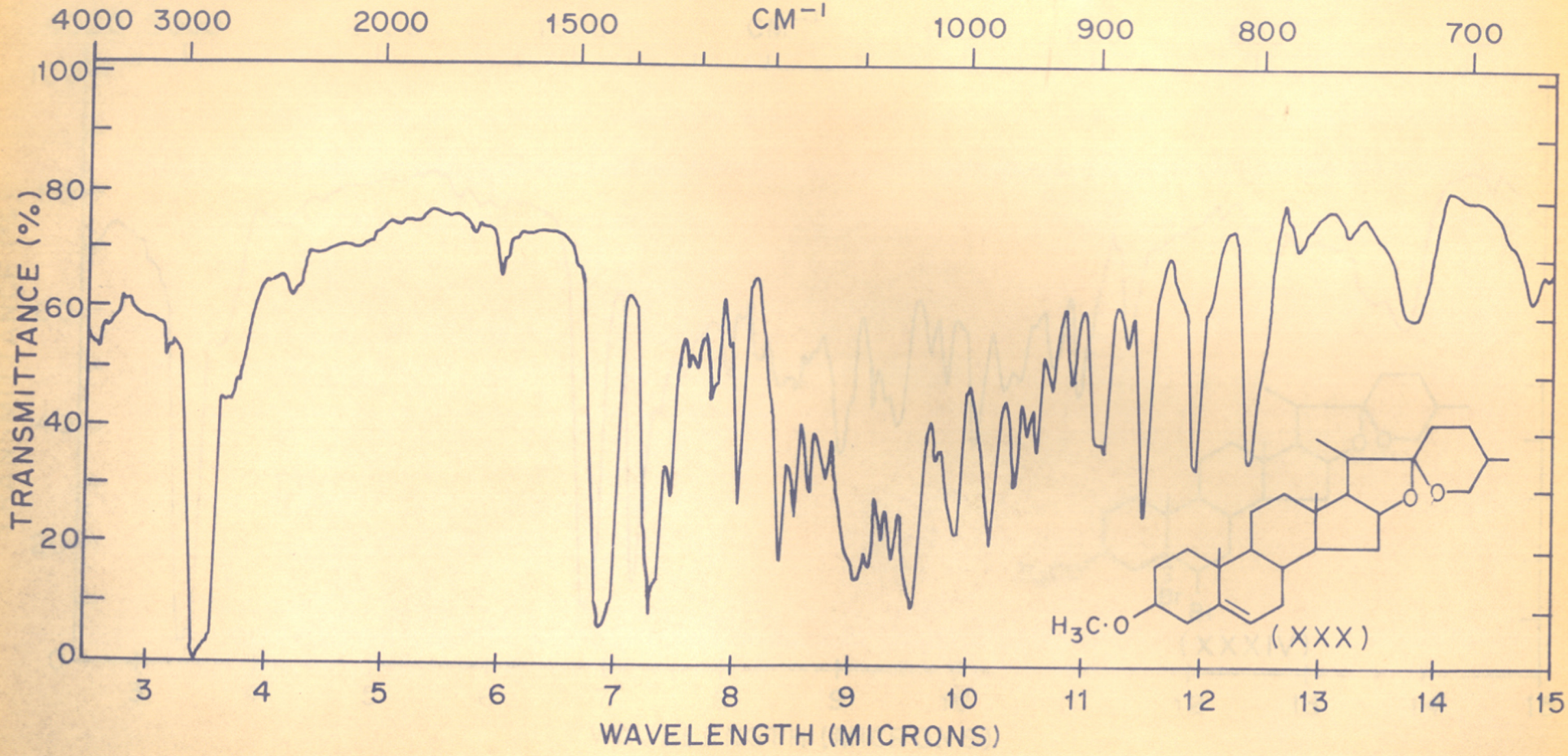


FIG. 1. IR SPECTRUM (NUJOL) OF DIOSGENIN METHYL ETHER.

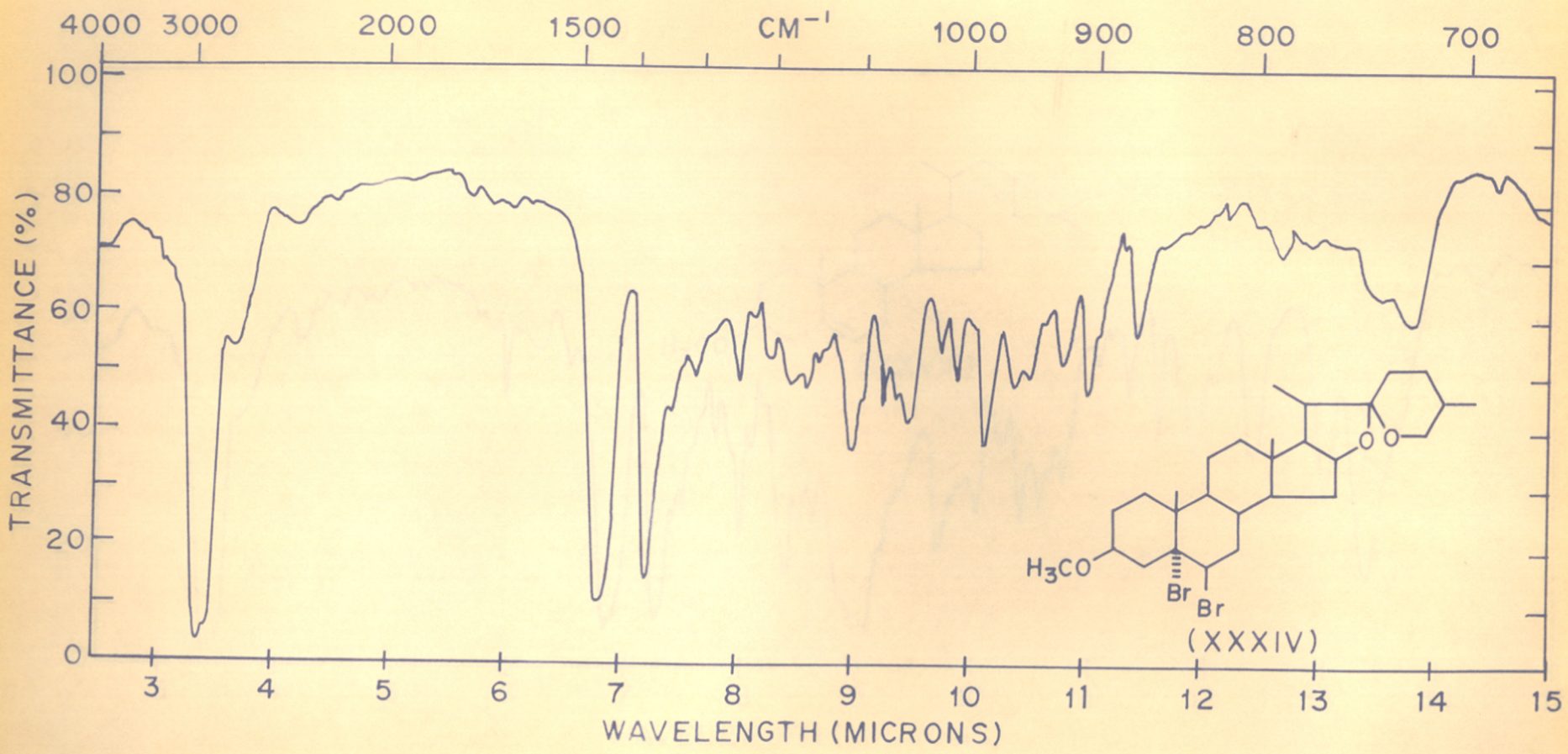


FIG. 2. IR SPECTRUM (NUJOL FILM) OF 5α,6β-DIBROMOTIGO-GENIN METHYL ETHER.

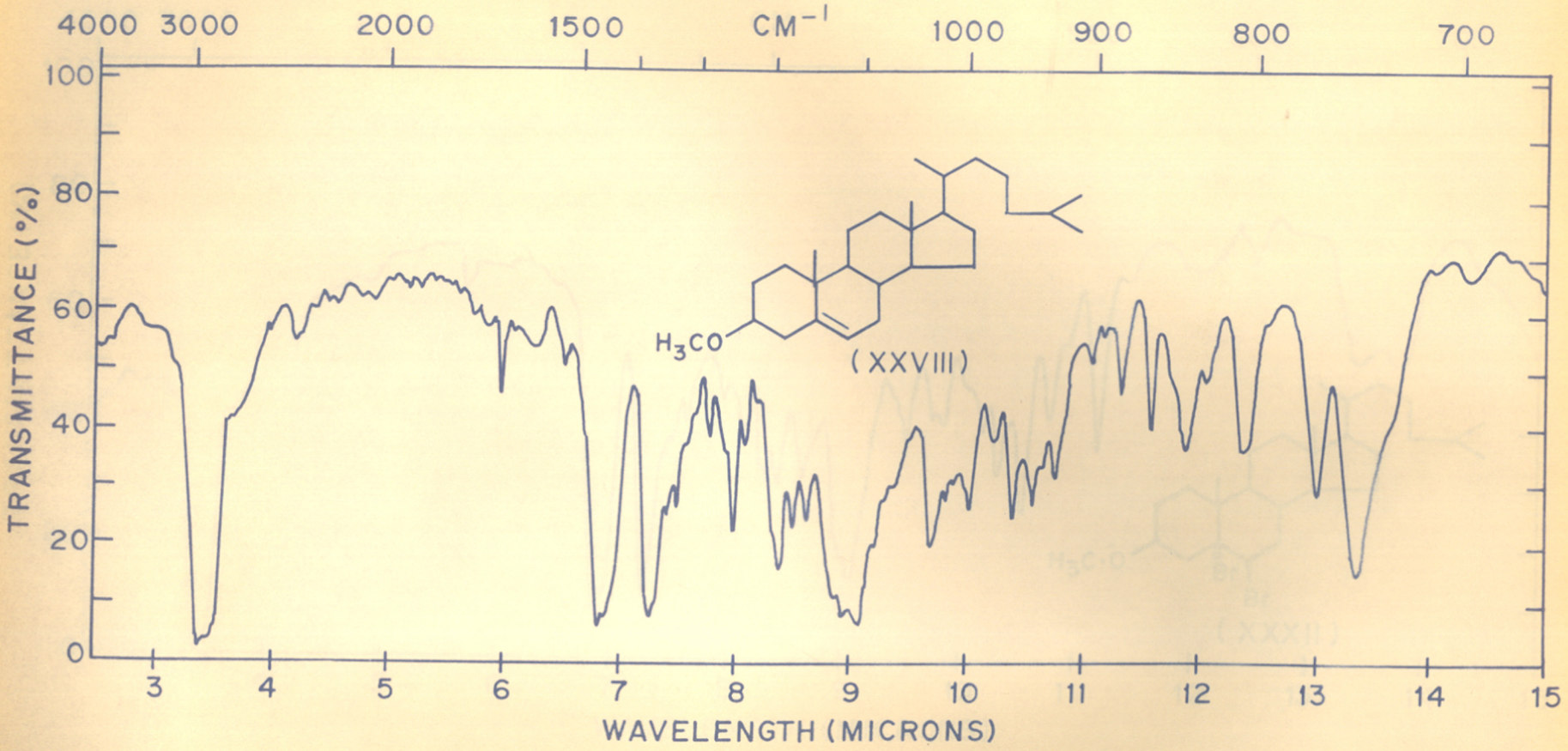


FIG. 3. IR SPECTRUM (NUJOL) OF CHOLESTEROL METHYL ETHER.

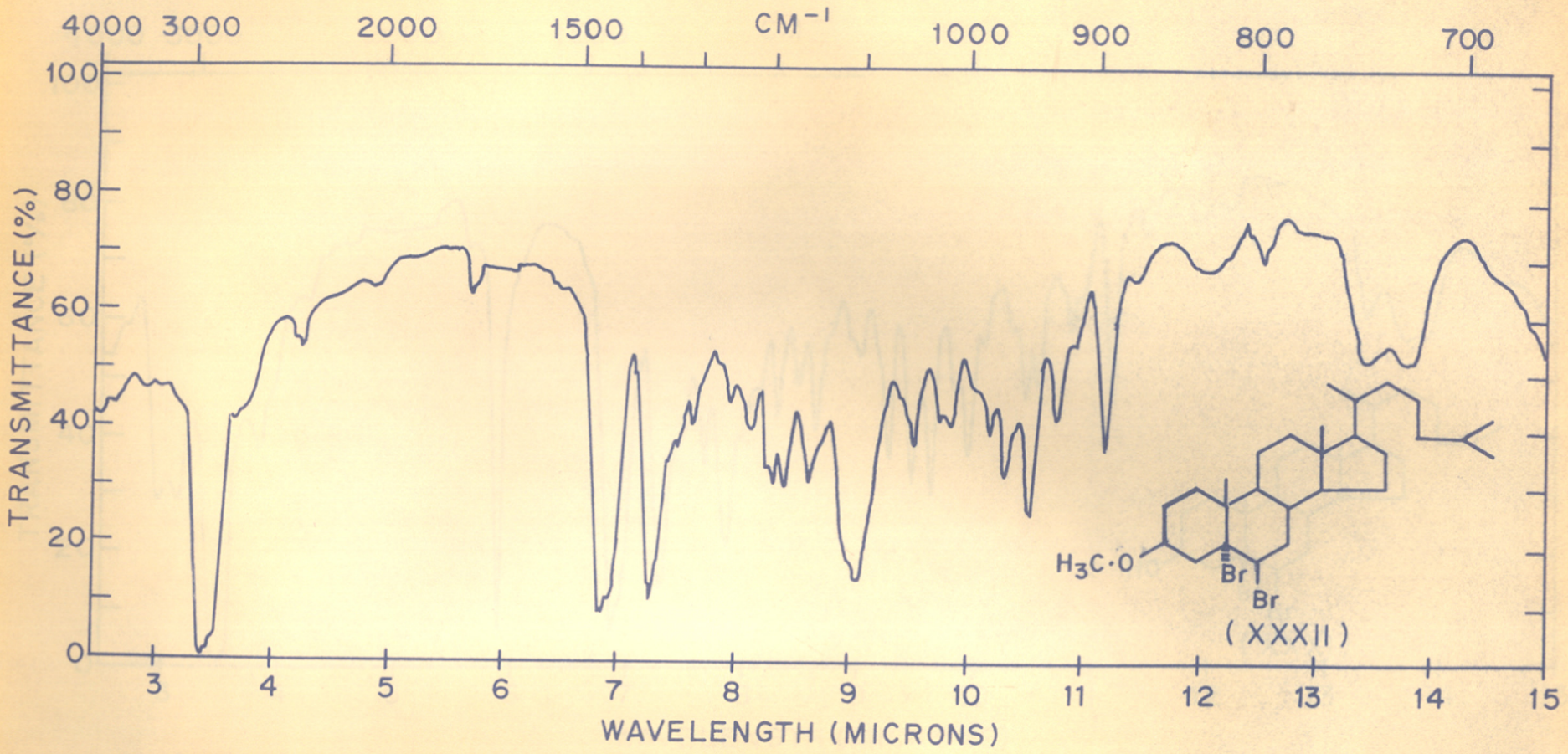


FIG. 4. IR SPECTRUM (NUJOL) OF 3β-METHOXY-5α,6β-DIBROMOCHOLESTANE.

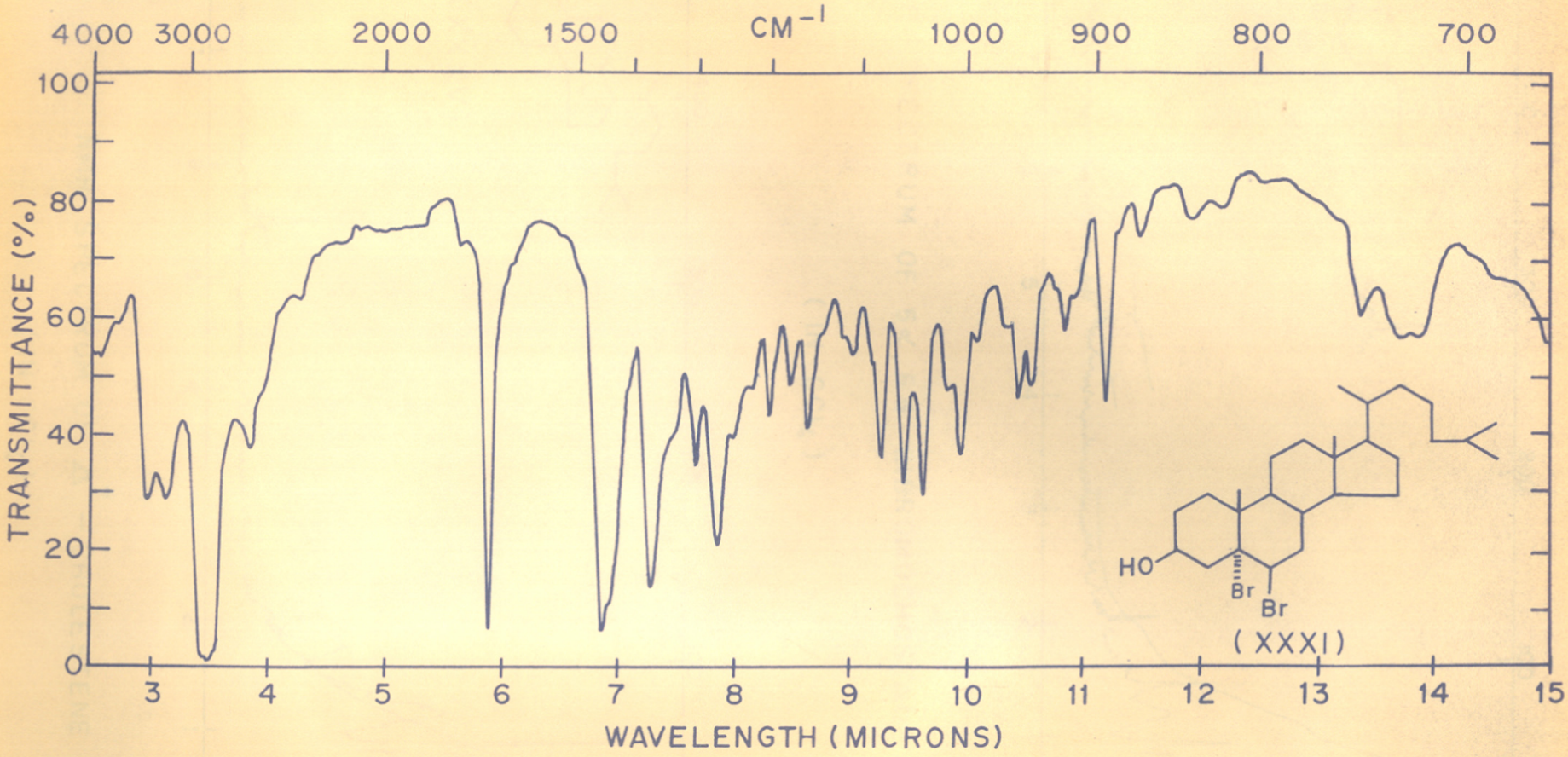
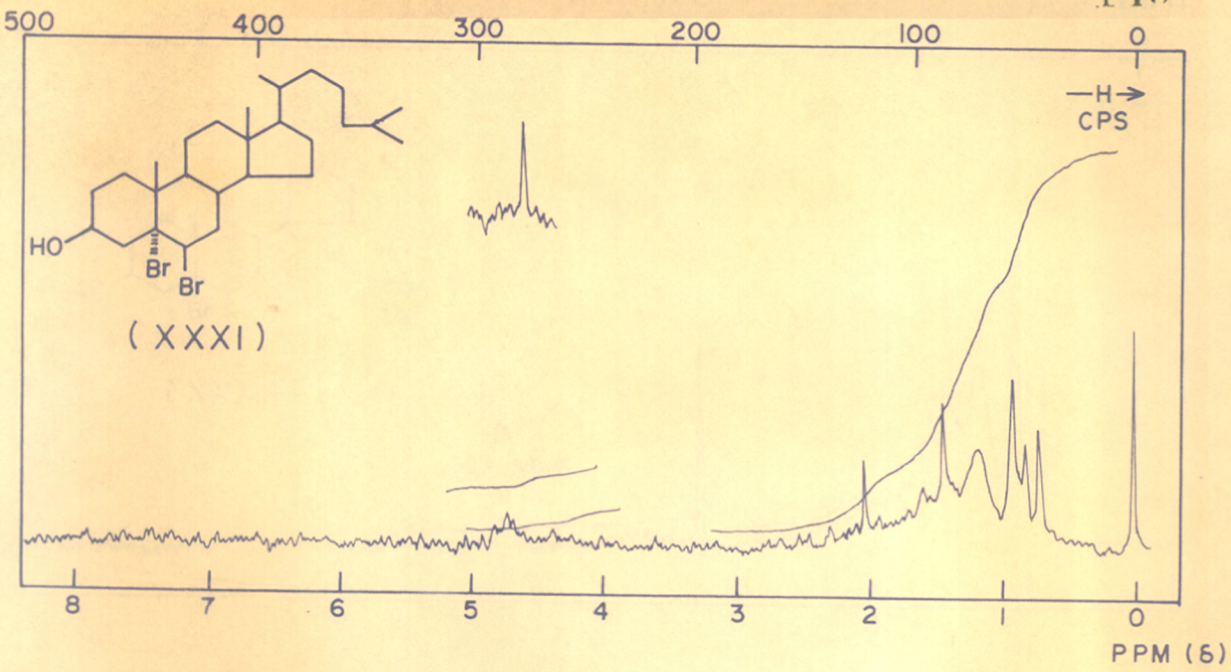


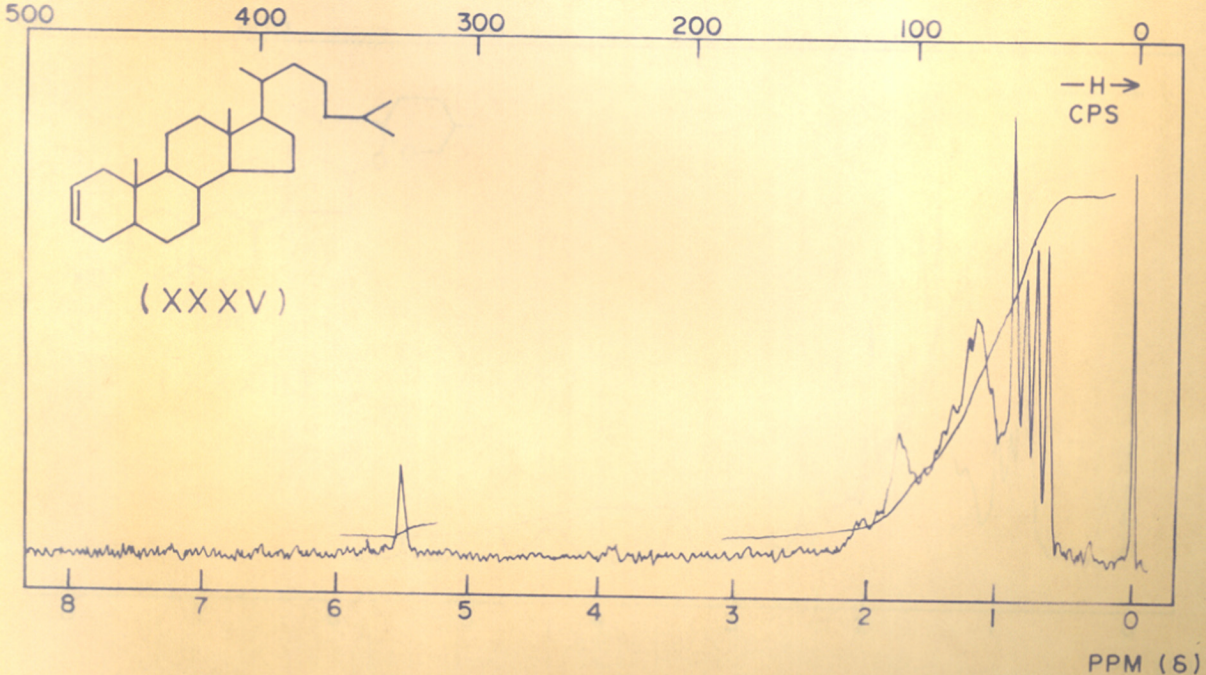
FIG. 5. IR SPECTRUM (NUJOL FILM) OF 5α,6β-DIBROMOCHOLESTANE-3β-OL.



(XXXI)

NMR SPECTRUM OF 5α, 6β-DIBROMOCHOSTANE-3β-OI

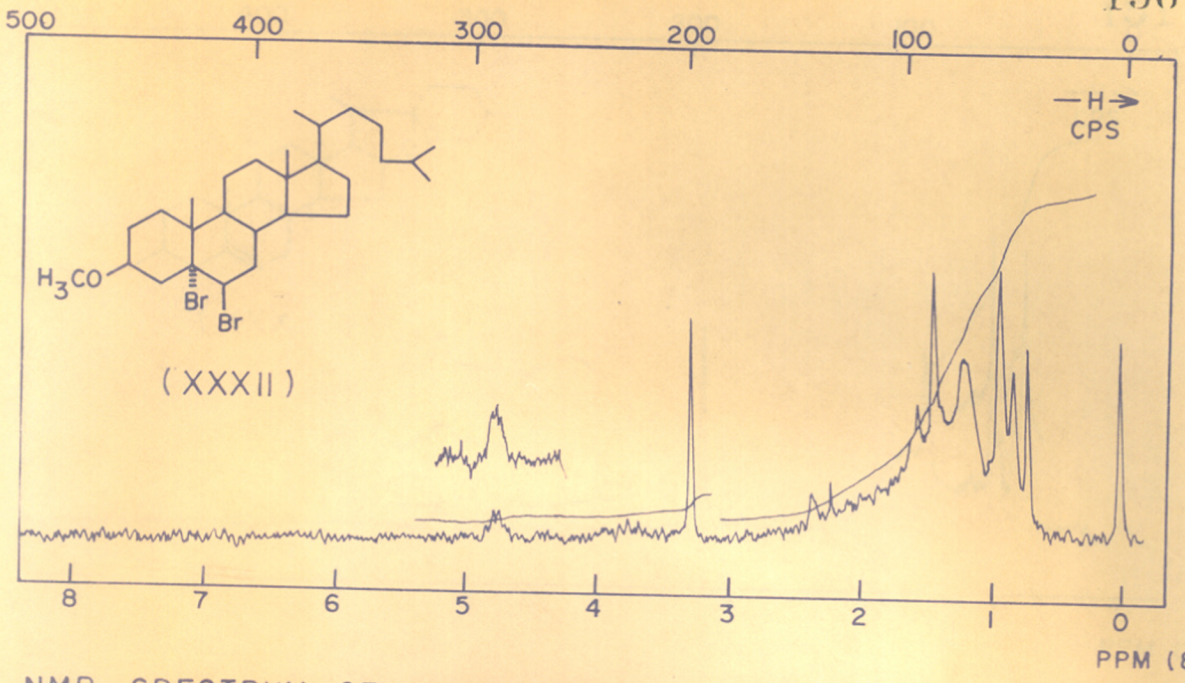
(IN CCl_4)



(XXXV)

NMR SPECTRUM OF Δ^2-CHOLESTENE

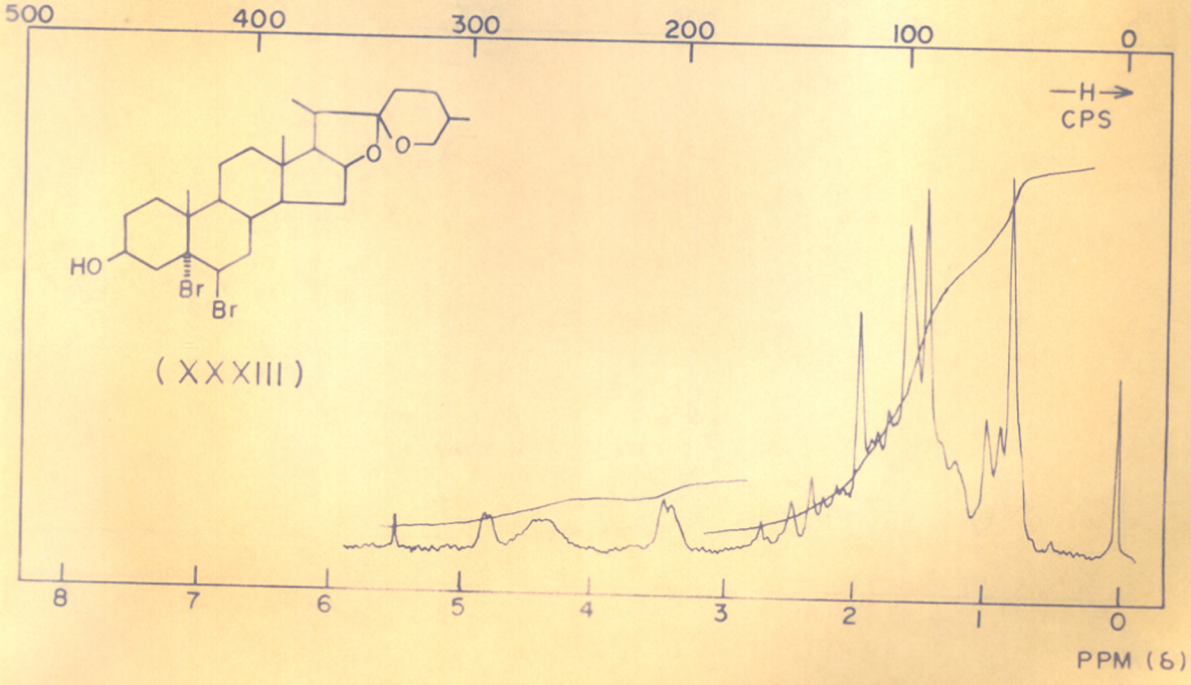
(IN CCl_4)



(XXXII)

NMR SPECTRUM OF 3β-METHOXY-5α,6β-DIBROMOCHOLESTANE

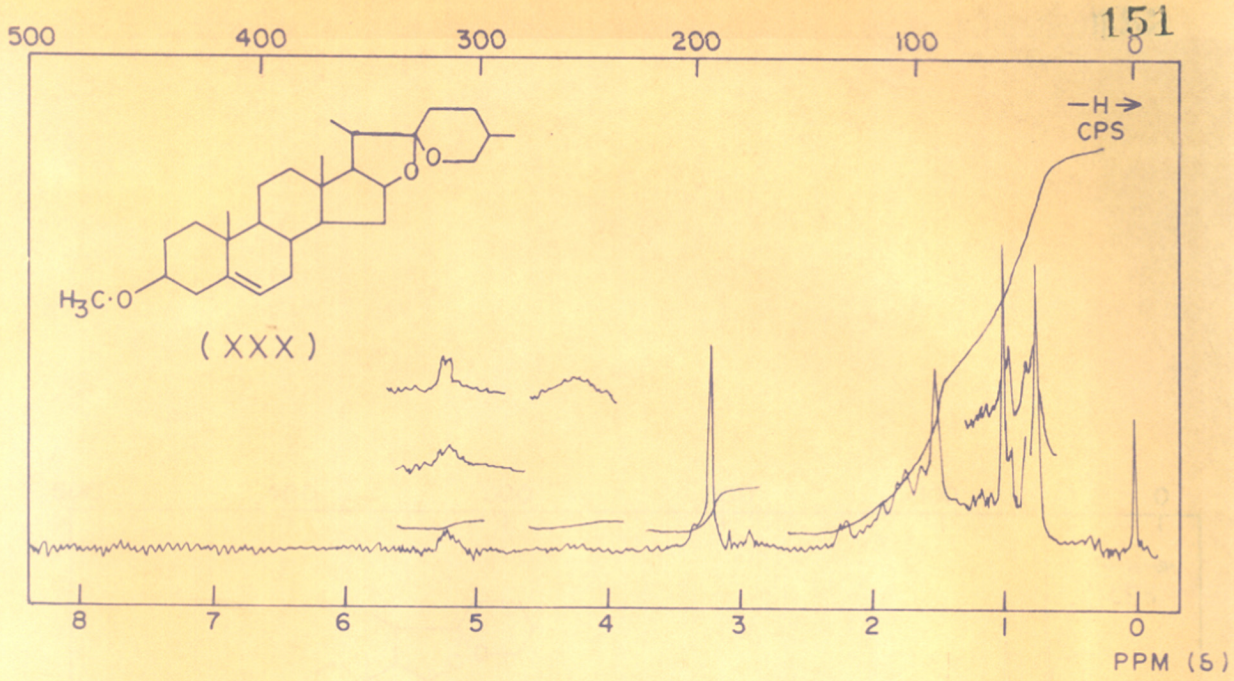
(IN CCl_4)



(XXXIII)

NMR SPECTRUM OF 5α,6β-DIBROMOTIGOGENIN

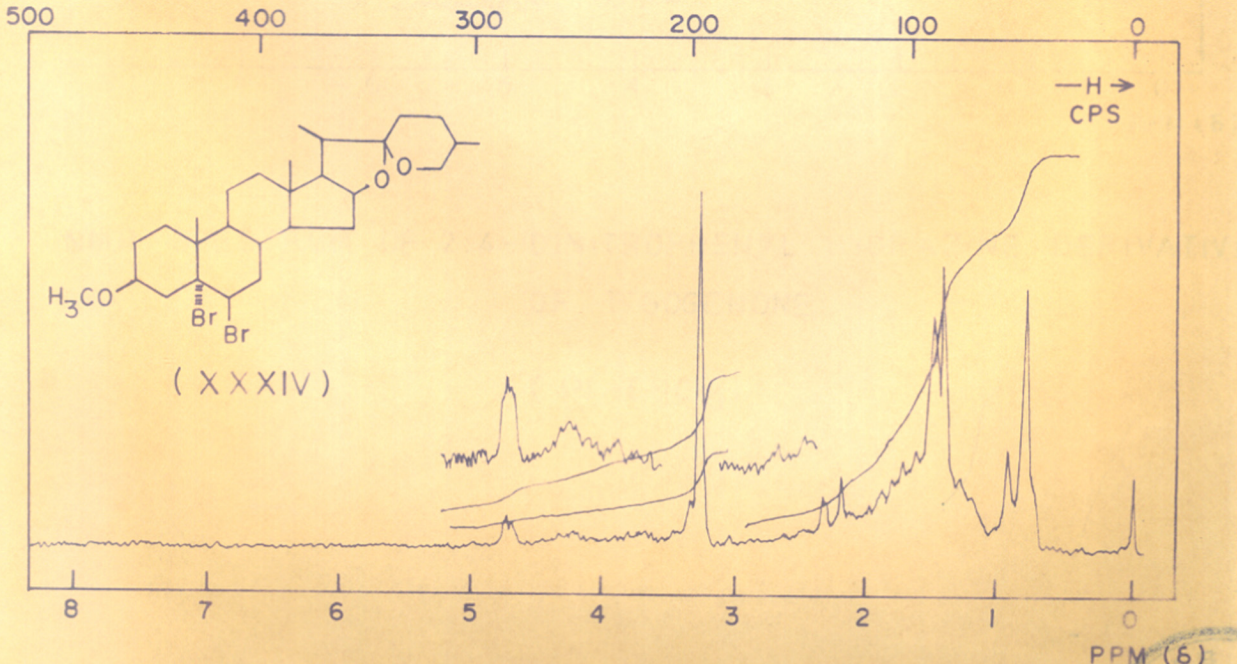
(IN $CHCl_3$)



(XXX)

NMR SPECTRUM OF DIOSGENIN METHYL ETHER

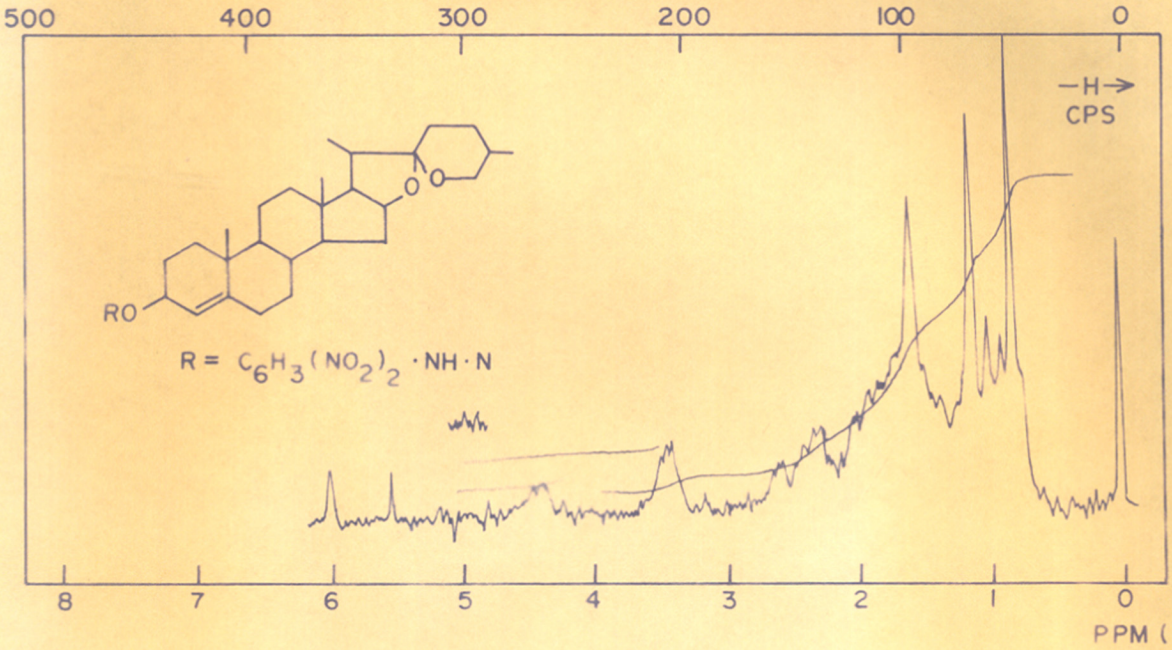
(IN CCl_4)



(XXXIV)

NMR SPECTRUM OF 5α, 6β-DIBROMOTIGOGENIN-METHYL ETHER

(IN CCl_4)



NMR SPECTRUM OF 2:4-DINITROPHENYL HYDRAZINE DERIVATIVE OF TIGOGENONE

(IN $CHCl_3$)