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STUDIES IN SESQUITERPENES

A THESIS SUBMITTED TO AGRA UNIVERSITY FOR
DEGREE OF DOCTOR OF PHILOSOPHY

BY

RAMA KANT GUPTA, M.Sc.

NATIONAL CHEMICAL LABORATORY

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PART I

SYNTHESIS OF A DEGRADATION PRODUCT OF PATCHOULI ALCOHOL

CONTENTS

CHAPTER I

TRICYCLIC SESQUITERPENES

(INTRODUCTION)

TRICYCLIC SESQUITERPENES

During the last two decades the development in the field of sesquiterpenes has been truly remarkable. A large number of new types have been discovered and the synthesis of several interesting compounds has been achieved. It is not possible to cover the entire field in a reasonable space and hence this Introductory Chapter is restricted to a brief review on tricyclic sesquiterpenes* with special emphasis on their synthesis, a theme relevant to present work. Chart 1 summarises the various tricyclic systems discovered in Nature so far.

CEDRANE

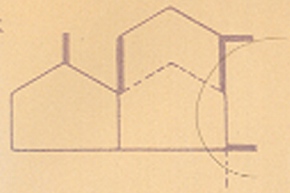
Quite a few members of this class have been isolated and studied. Table 1 and Chart 2 summarise the present position in this field.

TABLE 1 - Cedrane type Sesquiterpenes

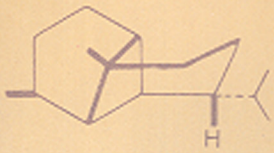
No.	Name	b.p./mm	n_D	m.p.	$[\alpha]_D$	Ref.
1	α-Cedrene	100°/3	1.4982	-	-31.3°	2,3,4
2	β-Cedrene	-	1.5047	-	11.3°	2,6
3	Cedrol	-	-	86-87°	9.9° ± 5 0.4°	
4	Shellolic acid	-	-	206-207°	18.0°	8,9,10,11
5	Epi-shellolic acid.	-	-	232-233°	49.0°	10
6	Jalaric acid	-	-	178-180°	36.8°	7

*The survey covers literature available in this Laboratory upto January 1965.

‡

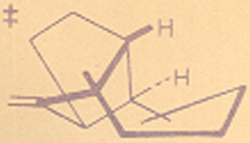


CEDRANE

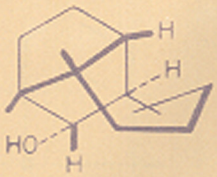


COPANE

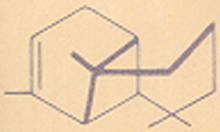
‡



LONGIFOLENE

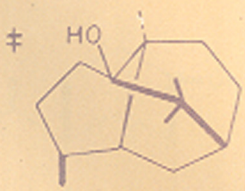


LONGIBORNEOL

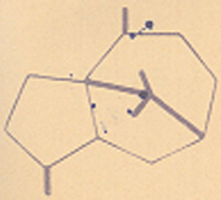


∝ – LONGIPINENE

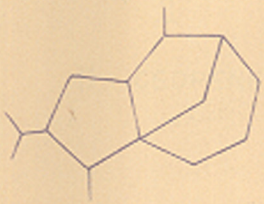
‡



PATCHOULI ALCOHOL



ISOPATCHOULANE



TRICYCLOVETIVANE

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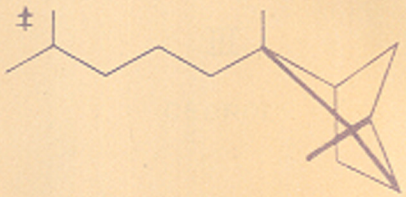
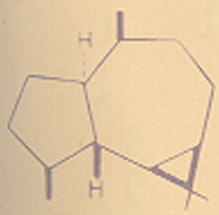


∝ – SANTALANE

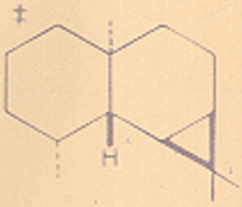


AROMADENDRANE

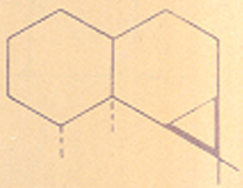
‡

ALLOAROMADENDRANE

‡

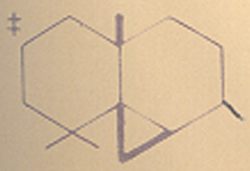


MAALIANE

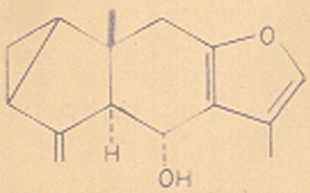


CALARANE

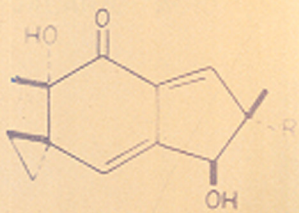
‡



THUJOPSANE



LINDERENE



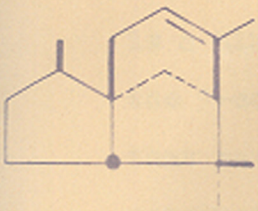
ILLUDIN-S R = CH_2OH

ILLUDIN-M R = CH_3

CHART - 1*

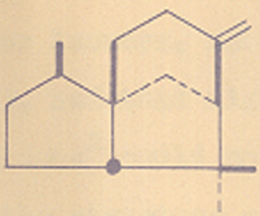
* When only one member is known in a class its structure has been given

‡ Sesquiterpene-type whose synthesis has been reported in the litreture



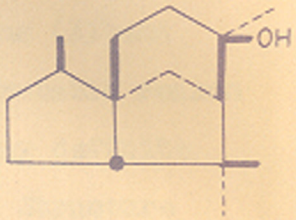
I

∝ - CEDRENE



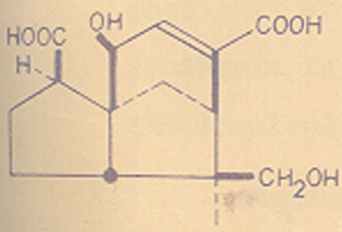
II

β - CEDRENE



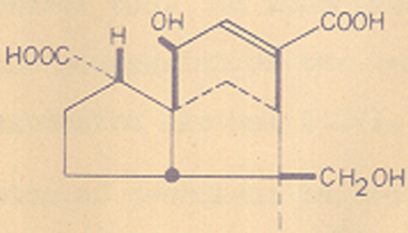
III

CEDROL



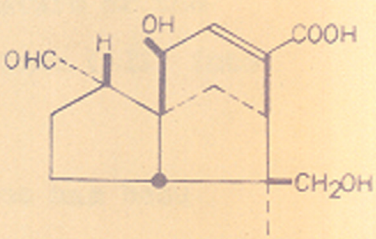
IV

SHELLOLIC ACID



V

EPI SHELLOLIC ACID



VI

JALARIC ACID

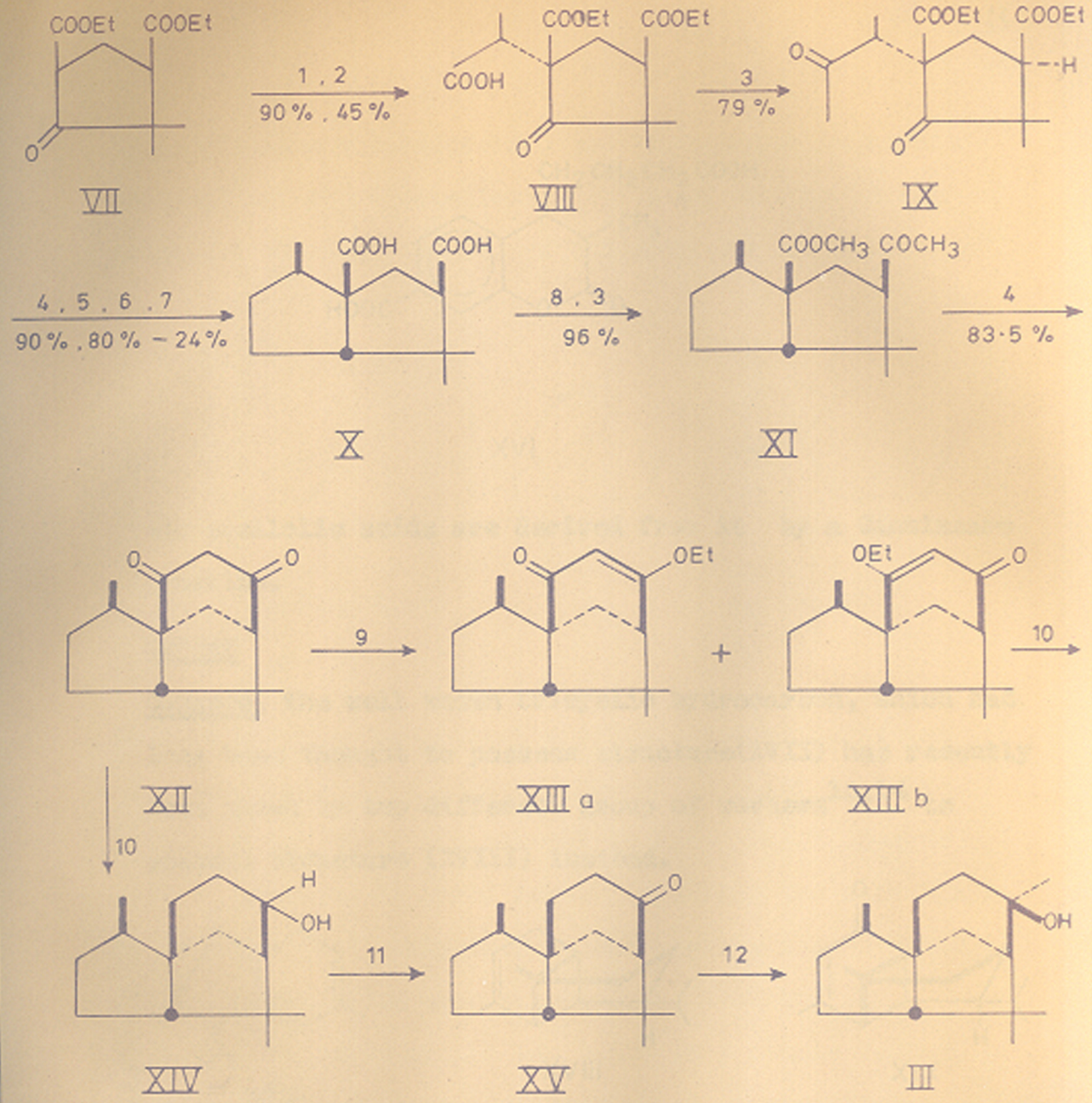
CHART – 2.

CEDRANE - TYPE SESQUITERPENES

Cedrene and Cedrol. The hydrocarbon cedrene and the corresponding alcohol cedrol were first isolated by Walter[1] in 1843. The naturally occurring hydrocarbon is a mixture of two isomers, namely α-cedrene (I) and the β-cedrene (II), and that might be the probable reason that earlier work done[2] could not lead to any definite conclusion about the structure of cedrene. Structure of α-cedrene (I) was finally elucidated independently by Stork and Berslow[3] and by Plattner et al.[4]. A brilliant synthesis of cedrol, outlined in Chart 3, has been reported by Stork and Clarke[5]. The synthesis is unique in the sense that it established the stereochemistry of cedrol too. An important feature of the synthesis is the conversion of the β-diketone (XII) into the required saturated alcohol (XIV).

Conversion of α-cedrene to β-cedrene has been reported by Goryaev and Tolstikov[6].

Jalaric acid, one of the products of alkaline hydrolysis of shellac, has been shown[7] to possess structure VI by its correlation with shellolic acid which has been assigned the cedrane type structure (IV)[8] on the basis of its chemical degradations and especially its base catalysed degradation to (XVI).[8] It has been further demonstrated[12] that jalaric acid is the primary product of hydrolysis and



REAGENTS —

1 $CH_3CHCOOCH_2C_6H_5$ (Br), NaH

2 H_2 / Pd – C, EtAC

3 $(COCl)_2$, CH_2N_2, HCl & Zn–AcOH

4 ^tBuOK & ^tBuOH

5 $p-CH_3C_6H_4SO_3H$, C_6H_6

6 Li, liq. NH_3

7 CH_2SH / CH_2SH, Raneynickel & KOH – MeOH

8 CH_2N_2 & MeOH, KOH

9 $p-CH_3C_6H_4SO_3H$, EtOH

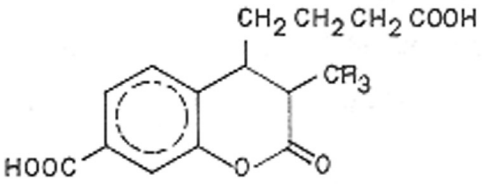
10 $LiAlH_4$

11 CrO_3, Py

12 CH_3Li

CHART – 3.

SYNTHESIS OF CEDROL

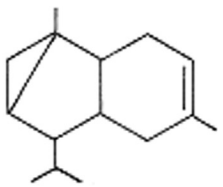


XVI

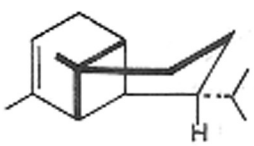
the shellolic acids are derived from it by a Cannizzaro reaction.

COPAENE

Copaene, the well known tricyclic hydrocarbon, which had long been thought to possess structure(XVII) has recently been shown by two different group of workers[13,14] to possess structure (XVIII) instead.



XVII

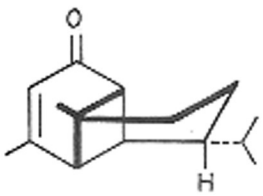


XVIII

b. p. 114-115°/10 mm

n_D 1·4864

$[\alpha]_D$ −6·3°



XIX

b.p.128-129°/ 1 mm

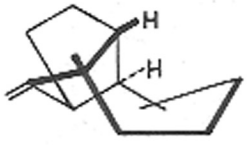
$[\alpha]_D$ ·34°

Mustakone, an $\alpha\beta$-unsaturated ketone, isolated from Cyperus rotundus Linn[13] has been assigned the structure (XIX).

LONGIFOLENE and LONGIBORNEOL

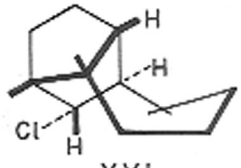
The tricyclic hydrocarbon, longifolene, was isolated from the essential oil of Pinus longifolia[2]. The structure(XX)

of longifolene was determined by X-ray crystallographic studies[15] of its hydrochloride (XXI) as well as by the brilliant chemical studies of Ourisson and his coworkers[16].

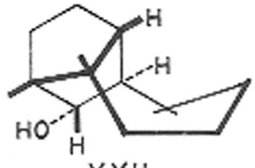


XX

LONGIFOLENE
b.p. 150-151°/36 mm
n_D 1.4950
$[\alpha]_D$ 42.7°



XXI

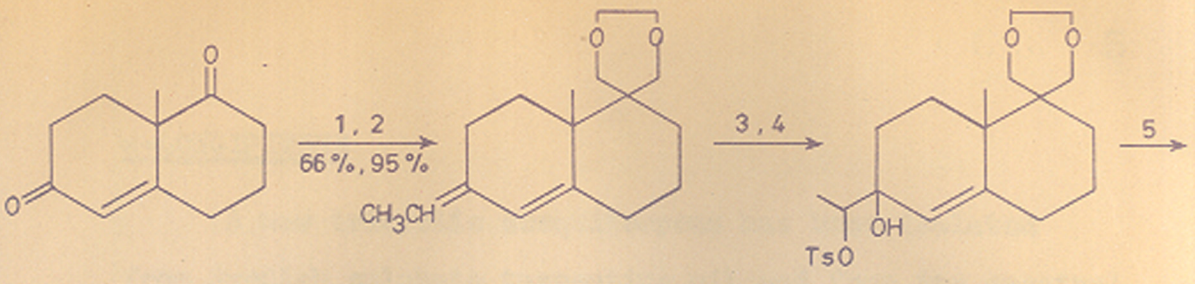


XXII

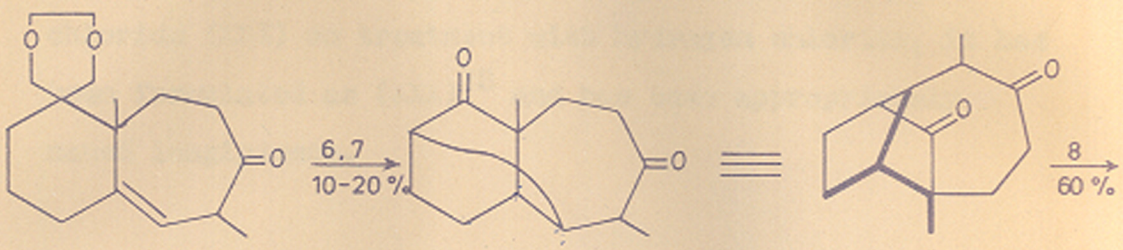
LONGIBORNEOL
m.p. 106-107°
$[\alpha]_D$ 21°

Longifolene has been recently synthesised by Corey and his coworkers[17] by a scheme outlined in Chart 4. This brilliant synthesis has several features which deserve special mention. A novel scheme involving the solvolysis of tosylate (XXV) was used for elaborating the required seven membered ring with appropriate functionality. From this the tricyclic system was built in a simple fashion by an internal Michael addition, which is reminiscent of the transformation of santonin to santonic acid[18,19]. The resulting tricyclic diketone (XXVII) could then be converted into longifolene.

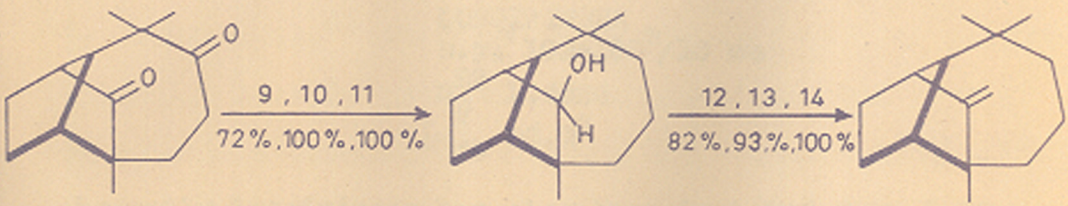
Longiborneol, a crystalline tricyclic alcohol, having structure (XXII) was first prepared by Ourisson[16] from longifolene, and has since then been identified in a number of essential oils[20,21,22].



XXIII XXIV XXV



XXVI XXVII



XXVIII XXIX XX

REAGENTS —

1 CH_2OH , C_6H_6 & $p\text{-}CH_3C_6H_4SO_3H$
CH_2OH

2 CH_3CH_2 . P Br ϕ_3 & ^nBuLi

3 OsO_4

4 $p\text{-}CH_3C_6H_4SO_2Cl$, CH_2Cl_2 & Py

5 $LiClO_4$, $CaCO_3$ & THF

6 2N . HCl

7 $(C_2H_5)_3N$, CH_2OH
CH_2OH

8 ϕ_3CNa , CH_3I

9 CH_2SH , BF_3
CH_2SH

10 $LiAlH_4$

11 H_2N . NH_2

12 CrO_3 , ACOH

13 CH_3Li

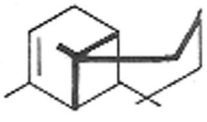
14 Py , SO_2Cl_2

CHART–4.

SYNTHESIS OF LONGIFOLENE

α-LONGIPINENE

A new tricyclic sesquiterpene has been isolated from Swedish sulphate turpentine oil and from its spectral characteristics along with its conversion to longibornyl chloride (XXI) on treatment with hydrogen chloride, it has been formulated as (XXX)[23] and has been appropriately named longipinene.



XXX

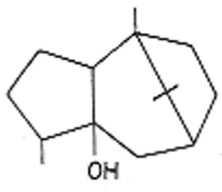
LONGIPINENE
b.p. 102-106°/10 mm
n_D^{22} 1.4924
$[\alpha]_D$ 36.9°

Recently longipinene has also been isolated from Indian turpentine oil[24].

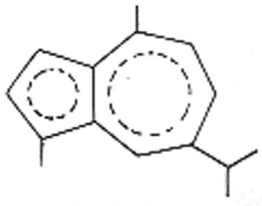
PATCHOULI ALCOHOL

Patchouli alcohol, a crystalline constituent of patchouli oil, was first isolated by Gal[25] from the essential oil of leaves of Pogostemon patchouli var. suavis. Structure (XXXI) was given to patchouli alcohol by Triebs[26] and this was based on two important experiments: (i) dehydrogenation of patchouli alcohol gave S-guaiazulene (XXXII) (ii) acid catalysed dehydration of patchouli alcohol furnished a hydrocarbon (α-patchoulene) which on ozonolysis followed by oxidation with potassium permanganate gave homocamphoric

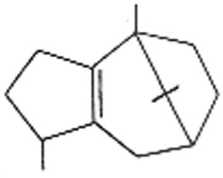
acid (XXXIV) and camphoric acid (XXXV) and on this basis was formulated as XXXIII.



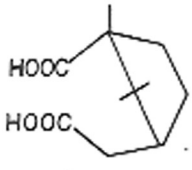
XXXI



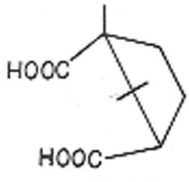
XXXII



XXXIII

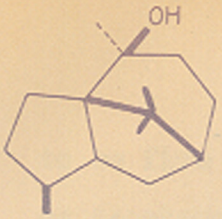


XXXIV

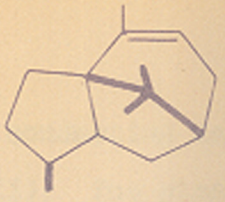


XXXV

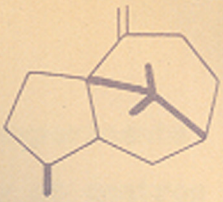
The structure of patchouli alcohol was reinvestigated by Büchi et al.[27] who proposed structure XXXVI for patchouli alcohol. Acetate pyrolysis of patchouli alcohol gave a mixture of α-patchoulene (XXXVII) and γ-patchoulene (XXXVIII) accompanied by small amount of β-patchoulene (XXXVIII), which was further degraded to a norketone (XXXIX). The low reactivity of norketone towards 2:4-dinitrophenyl hydrazine ascertained the environment of hydroxyl group. Oxidation of α,γ-patchoulenes (XXXVII, XXXVIII) gave nor-patchoulidicarboxylic acid (XL), the anhydride of which had infra-red bands attributable to substituted glutaric anhydride (1786 and 1764 cm^{-1}). This established the size of ring C. Further degradation of diacid (XL) furnished bicyclic keto ester (XLI) whose infrared spectrum indicated the size of ring B as five membered and the size of ring A was ascertained



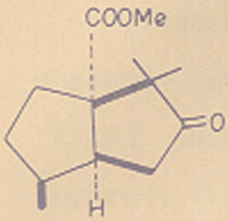
XXXVI



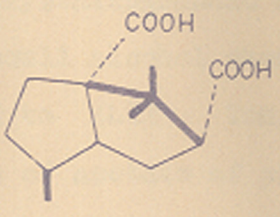
XXXVII



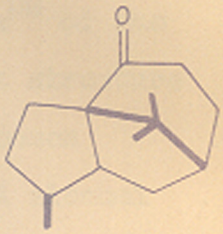
XXXVIII



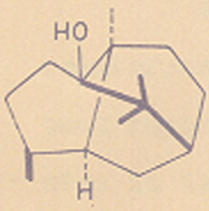
XLI



XL



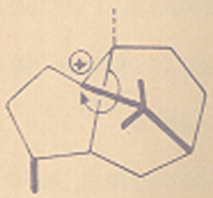
XXXIX



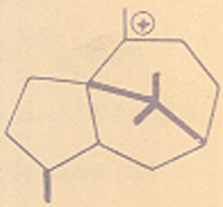
XLII

mp. 55 - 56°

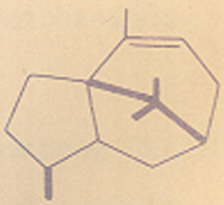
$[\alpha]_D$ - 129°



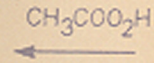
XLIII

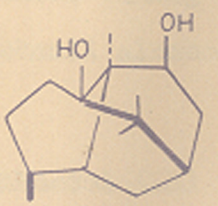


XLIV



XLV





XLVI

CHART – 5.

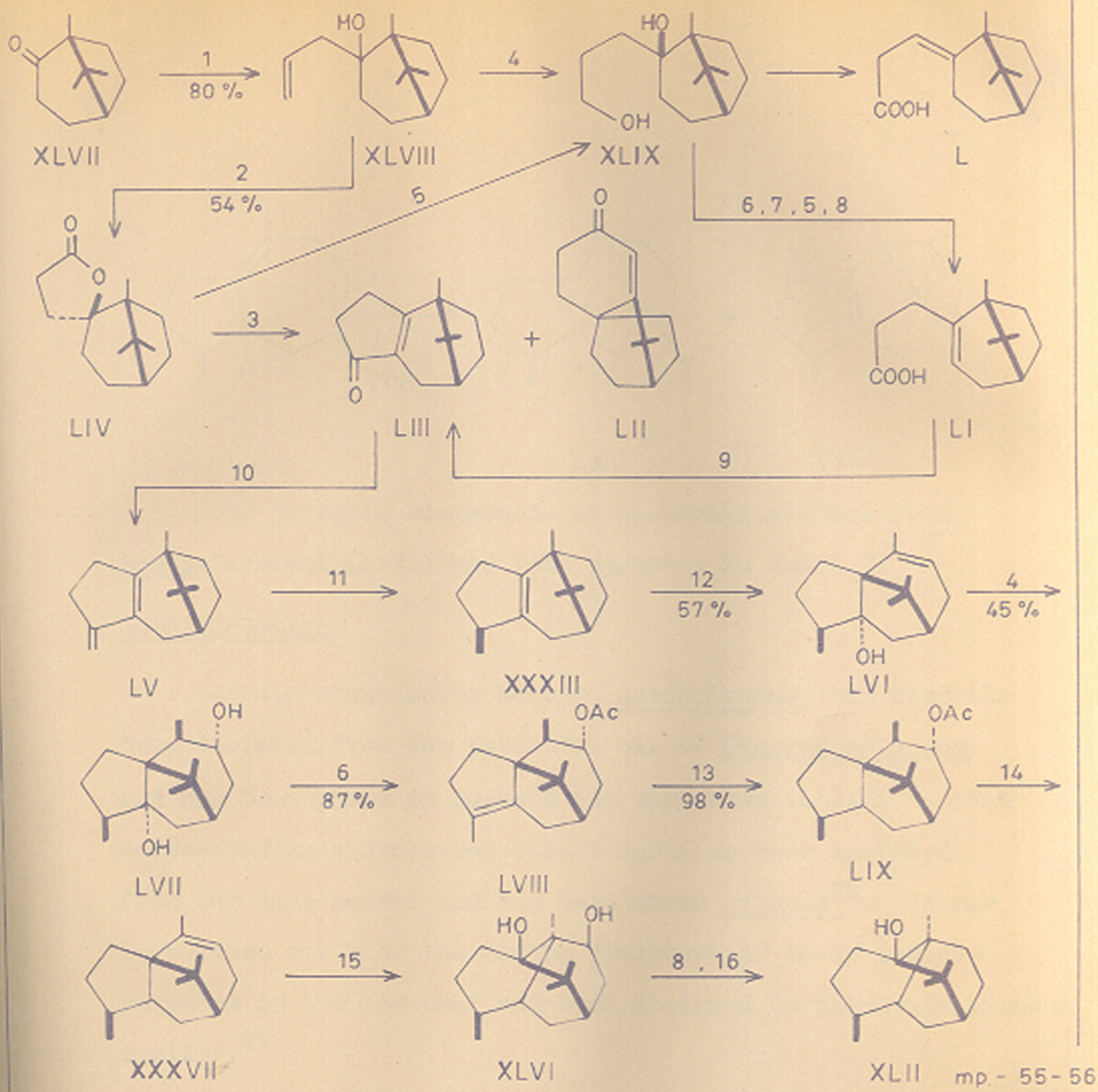
TRANSFORMATIONS OF PATCHOULI ALCOHOL

to be five membered by conducting degradation experiments on β-patchoulene (XXXIII). The stereochemistry at centres C_1, C_{3a}, C_4, C_7 and C_{8a} was also established by chemical means coupled with spectroscopic data.

Recently X-ray crystallographic analysis[28] of the chromate ester of patchouli alcohol showed that structure XXXVI must be revised to XLII. Thus it becomes apparent that pyrolysis of acetate of patchouli alcohol is accompanied by an unprecedented rearrangement to give α- (XXXVII) and γ-patchoulene (XXXVIII).

A synthesis of patchouli alcohol, with some reinterpretation of earlier communicated results[29], has been reported by Büchi et al.[30] (Chart 6). The interesting step in the synthesis is the peracetic acid oxidation of α-patchoulene (XXXVII) to give the 1:3 diol (XLVI) instead of anticipated 1:2 diol. The formation of 1:3 diol is due to a surprising rearrangement taking place to give the required skeleton of patchouli alcohol from α-patchoulene (XXXVII).

A conversion of bulnesol (LX) to β-patchoulene (XXXIII) and β-bulnesene (LXI) on heating with alumina and pyridine constitutes an indirect synthesis of patchouli alcohol[31], as β-patchoulene (XXXIII) has been transformed into patchouli alcohol[29,30].



mp. - 55 - 56°

$[\alpha]_D$ - 129°

REAGENTS —

1 $CH_2=CH.CH_2MgBr$

2 B_2H_6; CrO_3, H_2SO_4 & acetone.

3 Ac_2O, Py & $ZnCl_2$

4 B_2H_6 . H_2O_2

5 $LiAlH_4$

6 Ac_2O, Py

7 $POCl_3$, Py

8 CrO_3

9 $AlCl_3$, CS_2

10 $CH_2=P\phi_3$

11 H_2 / Raney Ni W_2

12 CH_3CO_3H & BF_3 - etherate

13 H_2/PtO_2

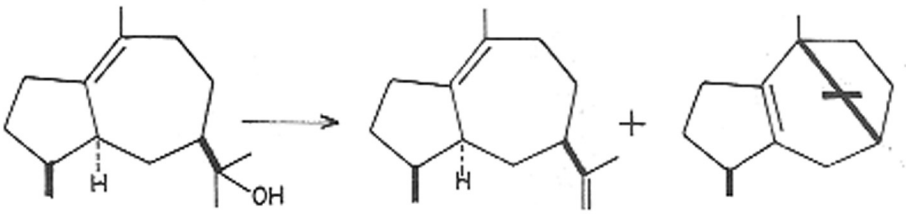
14 Heat

15 CH_3CO_3H

16 $H_2N.NH_2$, KOH, CH_2OH | CH_2OH

CHART – 6

SYNTHESIS OF PATCHOULI ALCOHOL

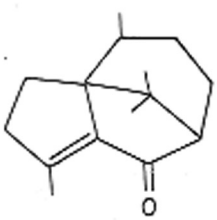


LX LXI XXXIII

The probable biogenesis of patchouli alcohol from trans-farnesol (LXII) has been depicted in Chart 7.

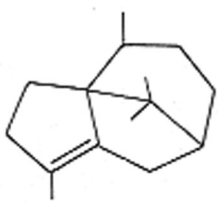
ISOPATCHOULANE

An α,β-unsaturated ketone, patchulenone, has recently been isolated from the essential oil of Cyperus rotundus and has been shown to possess the structure (LXIII)[32]. The corresponding hydrocarbon (LXIV) has also been isolated from the same source and has been named cyprene[33]. It may be pointed out that the carbon framework of these sesquiterpenes is the one that had been assigned to patchouli alcohol earlier.[27]



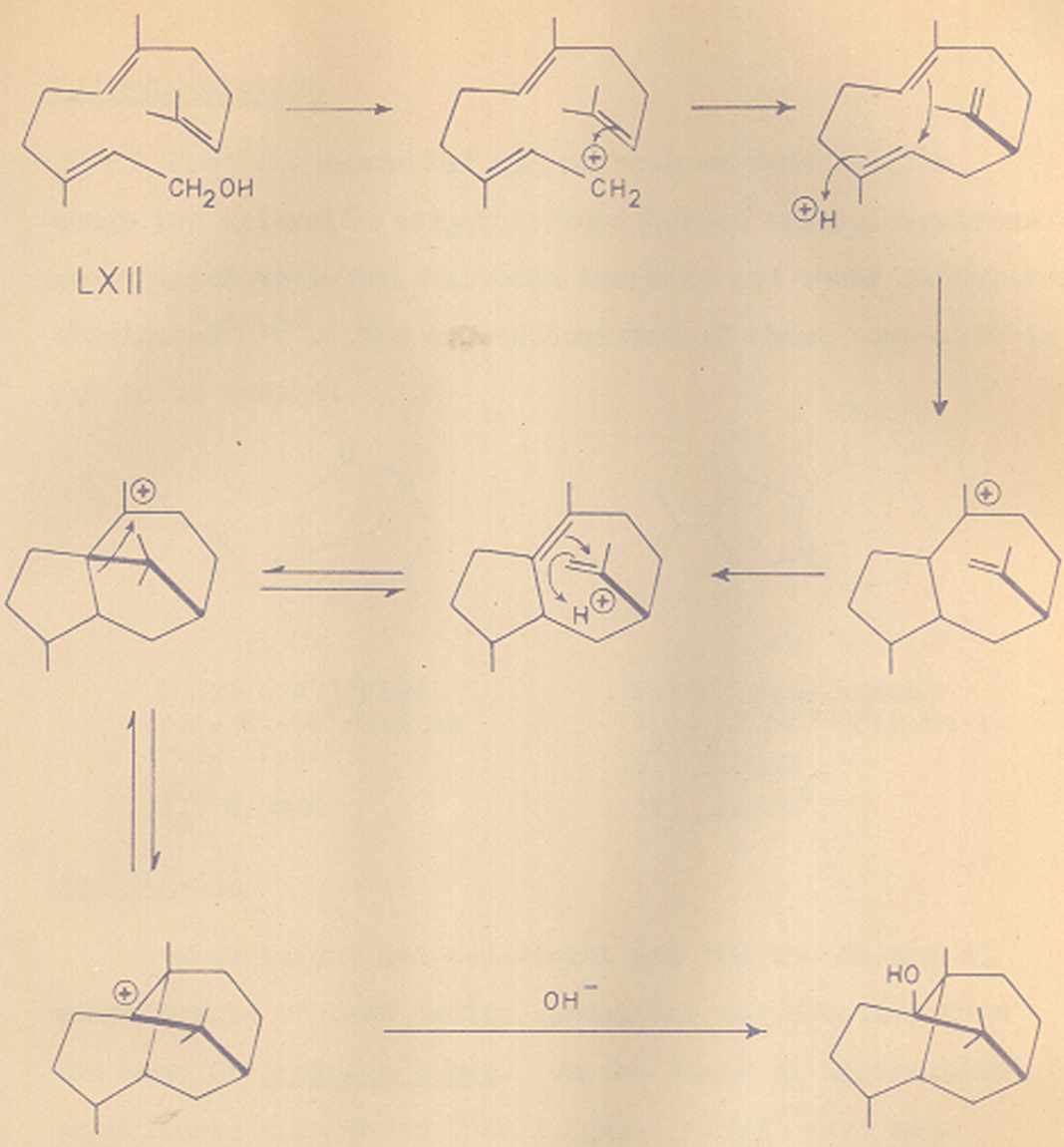
LXIII

PATCHOULENONE
m.p. 52.5°
$[\alpha]_D$ -97.1°



LXIV

CYPRENE
b.p. 104°/5 mm
n_D^{20} 1.5058
$[\alpha]_D$ -20°



LXII

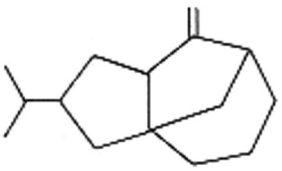
XLVI

CHART – 7.

BIOGENESIS OF PATCHOULI ALCOHOL

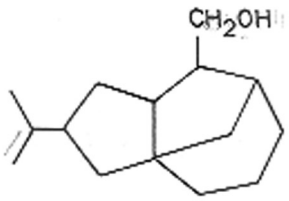
TRICYCLOVETIVANE

From the essential oil of vetiver from Belgian congo two tricyclic sesquiterpenes termed tricyclovetivene and tricyclovetivenol has been isolated and their structures elucidated[34,35]. The stereochemistry of these compounds is yet to be settled.



LXV

TRICYCLOVETIVENE
b.p. 81-82°/0.6 mm
$[\alpha]_D$ 13.11°
d_4^{20} 0.9340

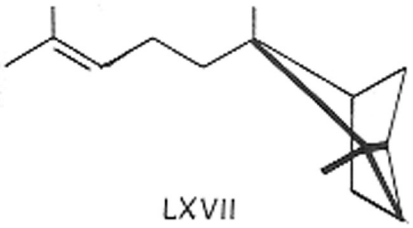


LXVI

TRICYCLOVETIVENOL
b.p. 171-174°/12 mm
n_D^{20} 1.5204
$[\alpha]_D$ 28.80°

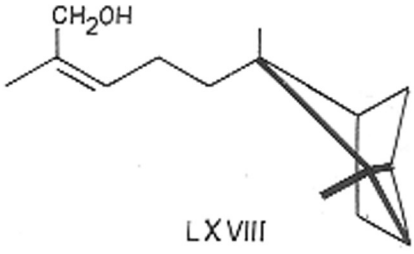
α-SANTALANE

α-Santalene and α-Santalol are the two important constituents of East Indian sandalwood oil obtained from the wood of Santalum album. On the basis of degradation experiments structures (LXVII) and (LXVIII) have been assigned to α-santalene and α-santalol respectively[2].



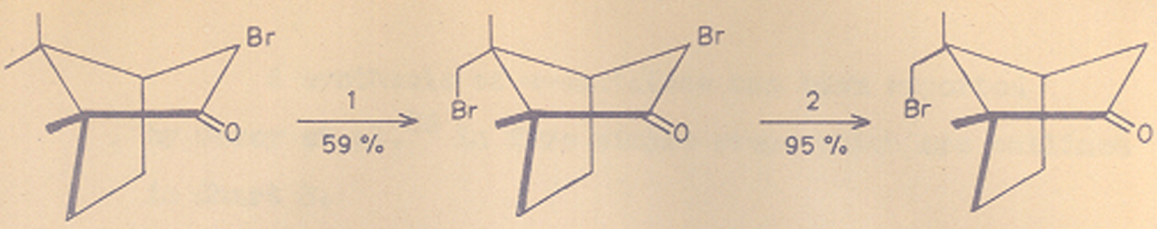
LXVII

α-SANTALENE
b.p.116-120°/8 ± 2 mm
n_D^{25} 1.4822; $[\alpha]_D$ 18.4°

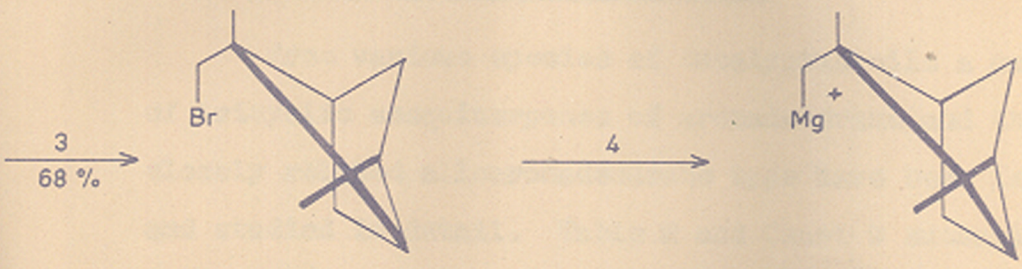


LXVIII

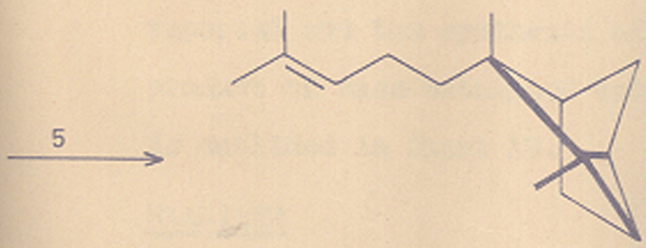
α-SANTALOL
b.p. 166-167°/14 mm
n_D 1.5017 ; $[\alpha]_D$ 9.0°



LXIX LXX LXXI



LXXII LXXIII



LXVII

REAGENTS —

1 $Br_2 - HSO_3Cl$

2 Zn – HBr

3 $H_2N.NH_2$ & HgO

4 Mg

5 $(CH_3)_2 = CH.O.COC_9H_{11}$

CHART – 8.

SYNTHESIS OF α – SANTALENE

A synthesis of α-santalene has been reported by Corey et al.[36] in five simple steps which are outlined in Chart 8.

Conversion of α-santalol to α-santalene has also been reported[37].

AROMADENDRANE and ALLO-AROMADENDRANE

From various species of Eucalyptus oils a number of tricyclic sesquiterpenes of aromadendrane and the closely related alloaromadendrane type have been isolated and studied in detail. Table 2 and Chart 9 summarise the sesquiterpenes of this group reported in the literature so far.

Some synthetic work in this series has been reported and the synthesis of epicyclocolorenone[55], the product of base catalysed epimerisation of cyclocolorenone[53], is outlined in Chart 10.

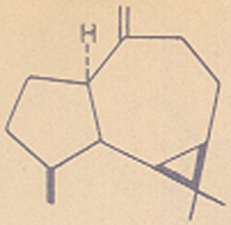
MAALIANE

Maaliol, a saturated tricyclic sesquiterpene alcohol, was first isolated from the resin from Canarium samonense by some chemist of Schimmel and Company[56] and more recently from Valeriana officinalis[57]. Dehydrogenation yielded cadalene along with a little vetivalene (XCIII). The presence of a cyclopropane ring was shown by spectroscopic data and confirmed by chemical evidence[58]. All these led to the establishment of structure (XCII) for maaliol.

TABLE 2 - Sesquiterpenes of Aromadendrane and Alloaromadendrane type.

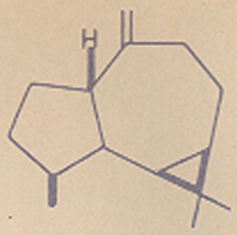
No.	Name	Sources	Structure	b.p./mm	n_D	m.p.	$[\alpha]_D$	Refs.
1	Aromadendrene.	Eucalyptus globulus E. nova anglica Metrosideros scandens.	(LXXIV)	122°/10	1.4953	-	24.5°	38,39,42, 44-47.
2	Alloaromadendrene.	Eucalyptus globulus Verosia serophulariaefolia.	(LXXV)	115°/7	1.4934	-	-21.6°	42,44-46
3	Ledol	Ledum palustre L.	(LXXVI)	-	-	104-105°	8.0°	39,40,42, 44-47, 54
4	Palustrol	Ledum palustre L.	(LXXVII)	130-32°/3	1.4916	-	-17.1°	48
5	Viridiflorol	Melaleuca viridiflora Juniperus oxycedrus.	(LXXVIII)	-	-	75°	4.0°	42,44,45,46
6	Globulol	Eucalyptus globulus	(LXXIX)	-	-	87°	-42°	42,44-47, 49
7	Spathulenol	Eucalyptus spathulata var. grandiflora.	(LXXX)	-	-	148°*	56°	50
8	α-Gurjunene	Dipterocarpus dyeri Pierre.	(LXXXI)	76-77°/3	1.5101	-	-227	51
9	Cyclocolorenone.	Pseudowintara colorata.	(LXXXII)	136-38°/5	1.5270	-	-400	52

*Melting point of 3,5-dinitrobenzoate is reported.



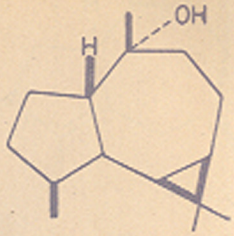
LXXIV

AROMA–DENDRENE



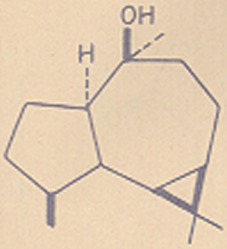
LXXV

ALLO AROMADENDRENE



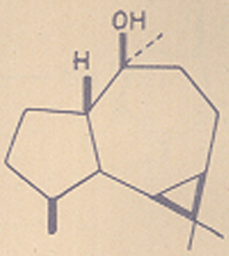
LXXVI

LEDOL



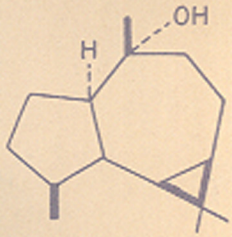
LXXVII

PALUSTROL



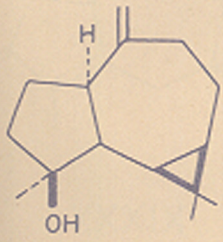
LXXVIII

VIRIDIFLOROL



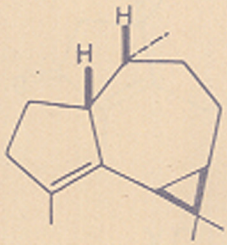
LXXIX

GLOBULOL



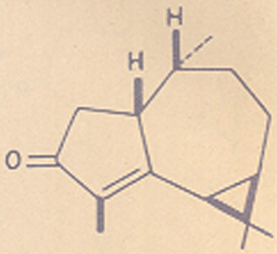
LXXX

SPATHULENOL



LXXXI

α-GURJUNENE

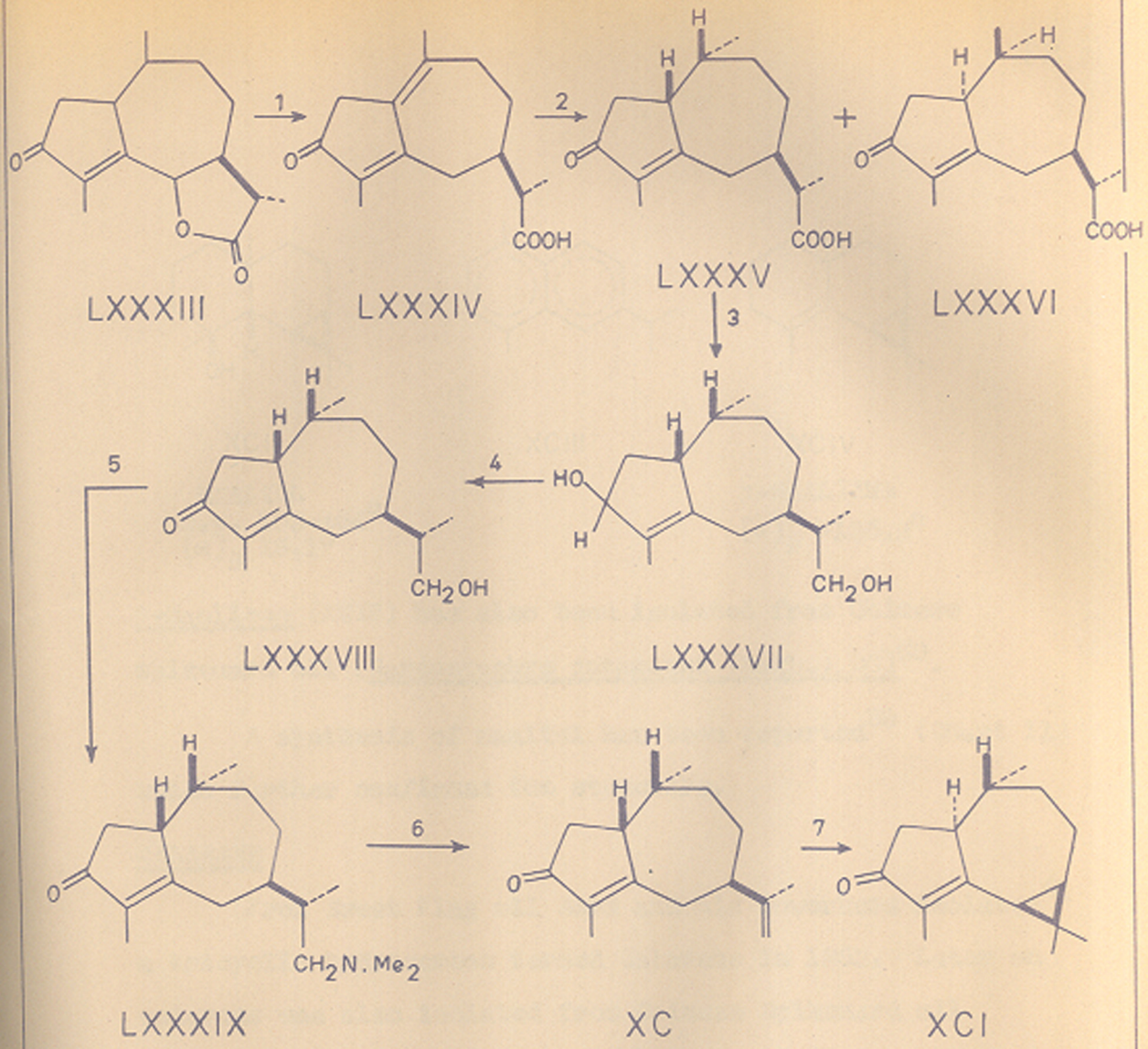


LXXXII

CYCLOCOLORENONE

CHART – 9.

AROMADENDRANE AND ALLOAROMADENDRANE TYPE SESQUITERPENES

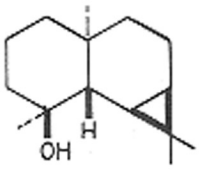


REAGENTS —

1 $CrCl_2$
2 H_2
3 $LiAlH_4$
4 2,3-dichloro 5,6 dicyano benzoquinone
5 $p\text{-}CH_3C_6H_4SO_2Cl$; py ; $(CH_3)_2NH$, CH_3CN
6 Heat
7 HBr ; KOH ; MeOH

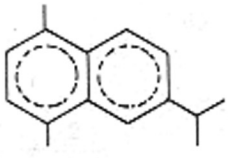
CHART - 10.

SYNTHESIS OF EPICYCLOCOLORENONE

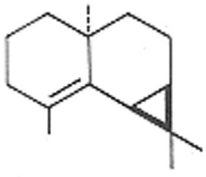


XCII

MAALIOL
m.p. 103-104°
$[\alpha]_D$ 18.1°



XCIII



XCIV

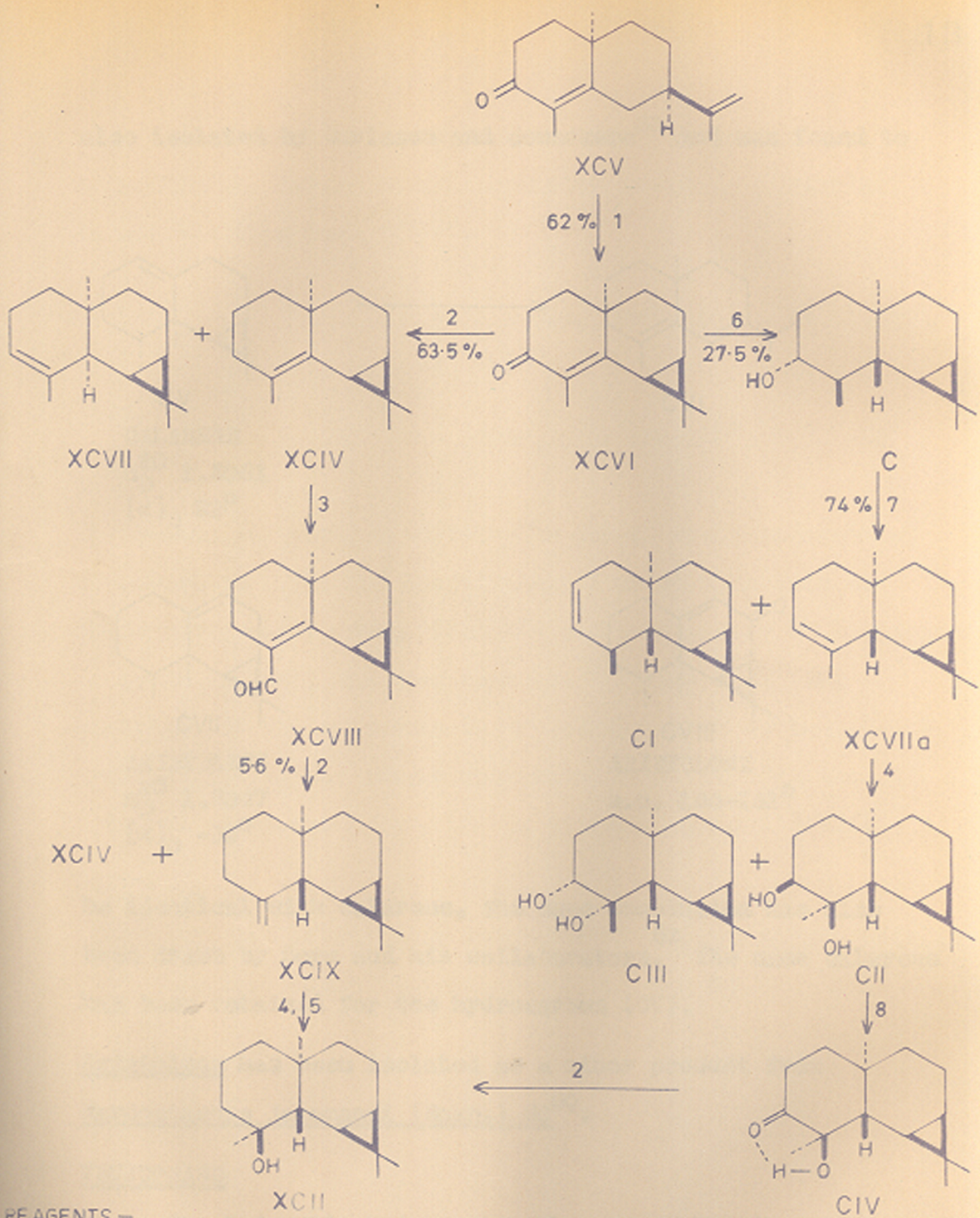
β-MAALIENE
$[\alpha]_D$ -136.2°

α-Maaliene (XCIV) has also been isolated from Chinese spikenard oil [Nardostachys jatamansi (Roxb.) DC][60].

A synthesis of maaliol has been reported[59] (Chart 11) which further confirmed the structure.

CALARANE

From Sweet Flag oil Corm and his coworkers isolated[61] a tricyclic hydrocarbon termed Calarene in 1953. Later on calarene was also isolated from Chinese Spikenard oil [Nardostachys jatamansi (Roxb.) DC] and was assigned structure (CV)[60]. The structural derivations were based on spectroscopic data, biogenetic consideration and the acid catalysed dehydration of calarene to a diene (CVI). The same diene is obtained by dehydration of maaliol (XCII). In their later communication Corm et al.[62] reported that the calarene isolated by them earlier was a mixture of two hydrocarbons, namely β-Gurjunene and aristolene (CVII), derived from the α,β-unsaturated ketone, Aristolone (CVIII)[64]. β-Gurjunene was



REAGENTS –

1 HBr, KOH, MeOH

2 $H_2N.NH_2$, KOH & diethylene glycol

3 SeO_2

4 OsO_4

5 $p-CH_3C_6H_4SO_2Cl$, $LiAlH_4$

6 Li, liq. NH_3 & EtOH

7 Ac_2, Py & heat

8 CrO_3, Py

CHART – 11

SYNTHESIS OF MAALIOL

also isolated by Ourisson and coworkers[63] and was found to

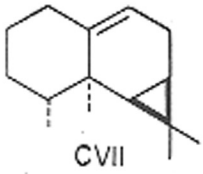
CV

CALARENE

n_D^{20} 1.5051

$[\alpha]_D$ 82°

CVI

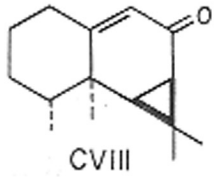


CVII

ARISTOLENE

n_D^{20} 1.5047

$[\alpha]_D$ -99°



CVIII

ARISTOLONE

m.p. 100-101°

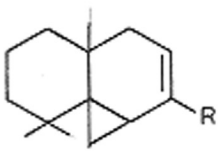
be identical with calarene, The same conclusion has also been drawn by Gorm and his collaborators.[62] The name calarene has been retained for the hydrocarbon (CV).

Aristolene has been isolated as a minor product from Hardostachys jatamansi (Roxb.) DC[60].

THUJOPSANE

The tricyclic hydrocarbon thujopsene (CIX) and the related hinokiic acid (CX) were isolated from the oil of Japanese Hiba tree [Thujopsis dolabrata (l.f.) Sieb, et, Zucc][65,66]. The presence of a cyclopropane ring in conjunction

with the double bond was established from molecular refractivity, catalytic hydrogenation, conjugate addition, IR and NMR spectrum[67,68,69].



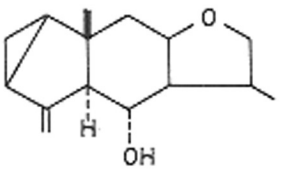
CIX R = CH_3, b.p. 120°C/10 mm, n_D^{25} 1.5031 $[\alpha]_D$ -110°

CX R = -COOH, m.p. 169-170°, $[\alpha]_D$ -86°

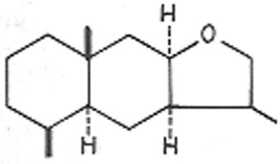
Systematic degradation experiments led to the establishment of structure (CIX) for thujopsene. A total synthesis of thujopsene, which establishes the stereochemistry of thujopsene as shown in (CXV) has been reported[70] (Chart 12). The highlight of the synthesis is the construction of the cyclopropane ring in one single operation, that too with the required stereochemistry, in the bicyclic alcohol (CXII).

LINDERENE

Linderene, the crystalline component of Lindera strychinifolia Vill, has been shown[71] to possess structure (CXVI). The

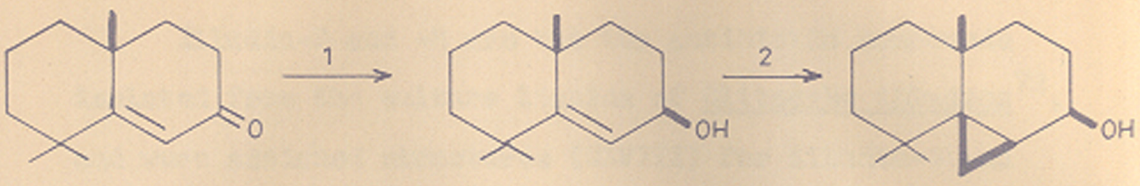


CXVI

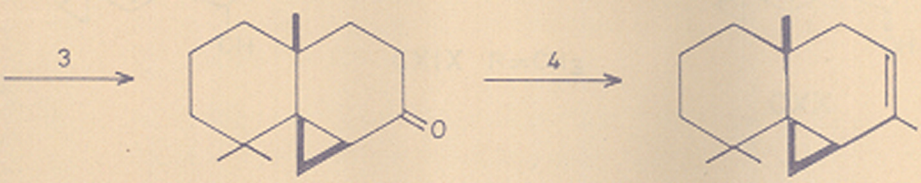


CXVII

structural derivation rests mainly on the spectroscopic data and its conversion to the known hexahydroanhydrolone (CXVII).



CXI CXII CXIII



CXIV CXV

REAGENTS —

1 $LiAlH_4$

2 CH_2I_2, Zn- Cu Couple

3 CrO_3

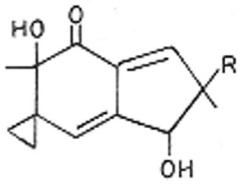
4 MeMgI, NH_4Cl

CHART – 12.

SYNTHESIS OF THUJOPSENE

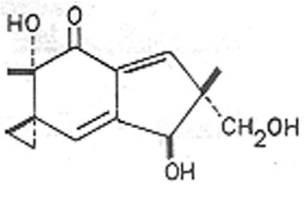
ILLUDIN-S and M

Illudin-S and -M are the two antibiotic compounds isolated from the culture liquids of Clitocybe illudens[72], and were assigned structures (CXVIII) for illudin-S and (CXIX) illudin-M[73]. Recently Japanese workers isolated an



CXVIII R=CH_2OH

CXIX R=CH_3



CXX

alcohol under the name Lampterol, an antitumor factor, from Lampteromyces Japonicus which was found to be identical with illudin-S[74]. The stereochemistry of illudin-S as depicted in structure (CXX) has been established by X-ray crystallography[75].

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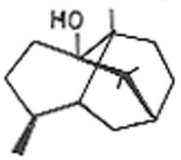
CHAPTER II

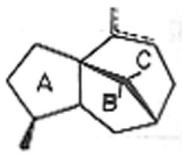
SYNTHESIS OF 2,2,6-TRIMETHYL-3-OXI-1-CARBOMETHOXY BICYCLO [0,3,3] OCTANE, A DEGRADATION PRODUCT OF PATCHOULI ALCOHOL

SYNTHESIS OF 2,2,6-TRIMETHYL-3-OXO-1-CARBOMETHOXY-BICYCLO [0,3,3]-OCTANE, A DEGRADATION PRODUCT OF PATCHOULI ALCOHOL.

In the structure determination of patchouli alcohol (I)[1,2,3] the bicyclo keto ester (III) obtainable by the degradation of patchoulenes (II), the dehydation products of patchouli alcohol, provided the important clue to the size of ring B in the patchoulenes. Since, the bicyclo keto ester III contains twelve carbon atoms of patchouli alcohol* it was thought worthwhile to seek synthetic support for its structure. The present Chapter describes a total synthesis of this compound.



I



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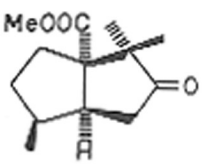

III

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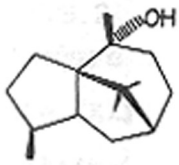
*The bicyclo keto ester (III) appeared attractive for elaborating further the molecule of patchouli alcohol, which was considered at the time this work was started, to possess the structure IV[1,2].



IV

The scheme which was followed successfully is outlined in Fig.1.

Preparation of 2-carbethoxy-5-methyl-cyclopentanone (V)

Since 2-carbethoxy-5-methyl-cyclopentanone (V) forms the starting material for the synthesis it was necessary to evolve a rapid and efficient method for its preparation. The compound is known to be available in yields of 70 - 80% by the Dieckmann cyclisation of diethyl α-methyl-adipate (XVI)[4-7] which in turn has been prepared in overall yield of 62% from diethyl adipate (via XIV → XV → XVI)[5]. In the earlier stages of this work, the above route was followed with suitable modifications (Fig.2) to get diethyl α-methyl-adipate in overall yields of 65%. However, it was considered

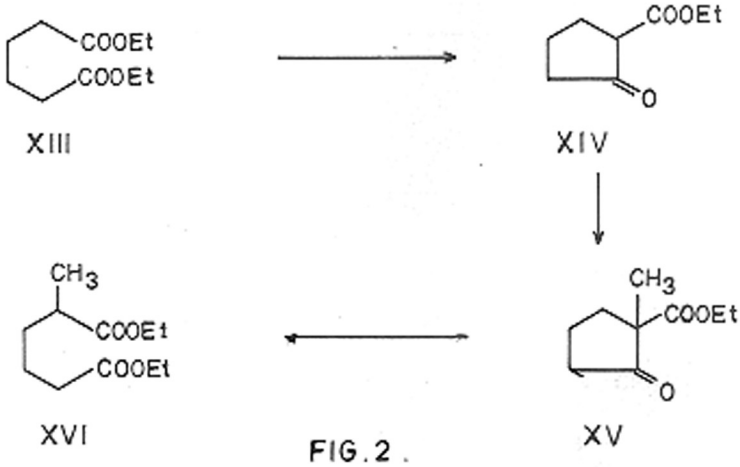
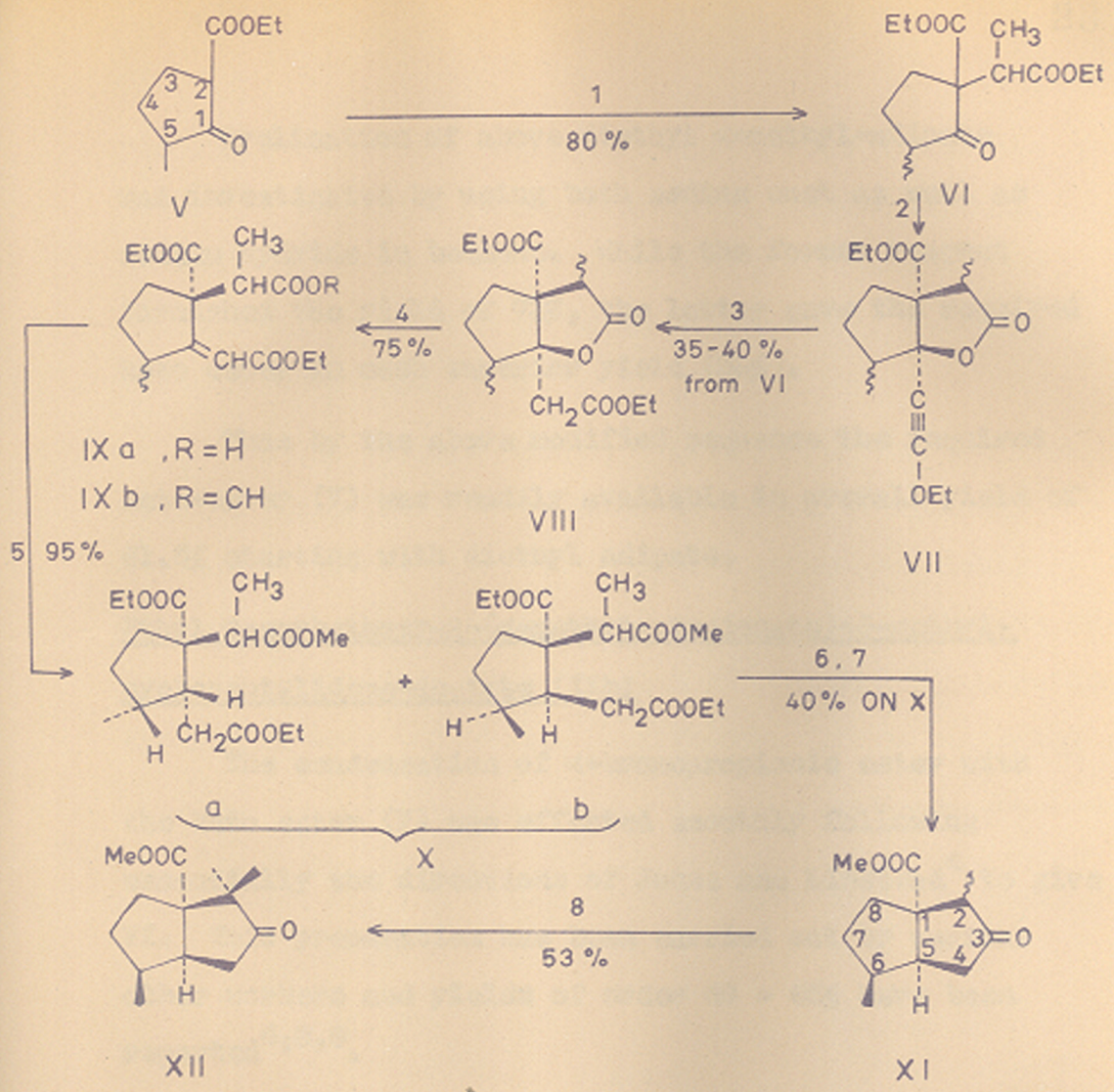


FIG. 2.

desirable to work out a procedure by which XVI could be prepared from diethyl adipate (XIII) without isolating the intermediates XIV and XV. Ultimately, a procedure could be worked out which furnished diethyl α-methyl-adipate in 73% yield from diethyl adipate without isolating the intermediates.



REAGENTS —

1 $CH_3CH(Br)COOC_2H_5$, Na

2 $BrMgC{\equiv}C-OEt$, NH_4Cl

3 Aq · H_2SO_4, dioxan

4 NaOH, MeOH ; CH_2N_2

5 H_2, Rh – Pt, AcOH

6 NaH, C_6H_6

7 Aq·HCl,-AcOH ; CH_2N_2

8 Ph_3CNa, CH_3I

FIG. 1

SYNTHESIS OF 2,2,6-TRIMETHYL-3-OXO-1-CARBOMETHOXY-BICYCLO [0,3,3] OCTANE

Cyclisation of above diethyl α-methyl-adipate was investigated by using both sodium dust as well as sodium hydride in benzene. While the former reagent furnished the yield of 73%, the latter gave the required keto ester in much superior yield (88%).

Thus by the above modified sequence the required keto-ester (V) was readily available in overall yield of 61.5% starting with diethyl adipate.

Ethyl 2-carbethoxy-2-(α-methyl-propionate)-5-methyl-cyclopentylidene-acetate (IXb)

The condensation of α-bromopropionic ester with the keto ester (V) was effected smoothly following essentially the directions of Jones and Linstead[4] to give VI. This preparation has been carried out by various other workers and yields of order 49 - 65% have been reported[4,8,9].

The elaboration of the carbonyl function in VI into the desired methylidene carboxylic ester side chain, as in IXb could, in principle, be achieved by a variety of reactions: e.g., Reformatsky[14,15], Knoevenagel[16,17] or via condensation with ethoxyacetylene[18]. However, in view of the great dependence of Reformatsky and Knoevenagel

reactions to steric* factors it was decided to use the procedure involving condensation with ethoxyacetylene, a method first reported by Shchukina and Rubtsov[19] and successfully used even in cases of sterically hindered carbonyl compounds[20-25].

Of the various methods available for the preparation of ethoxyacetylene[18] the method described by Eglinton[26] and involving the reaction of sodium amide and diethyl chloroacetal in liquid ammonia was selected. Inspite of detailed directions being available[27] for this preparation, the yields were not at all satisfactory in the beginning and

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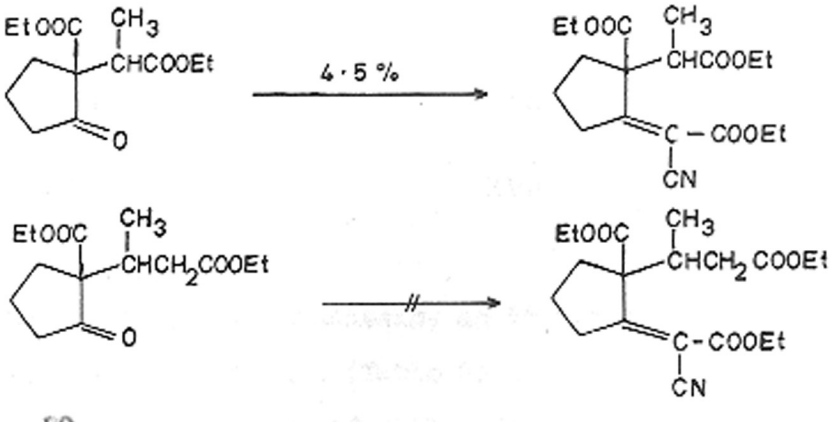
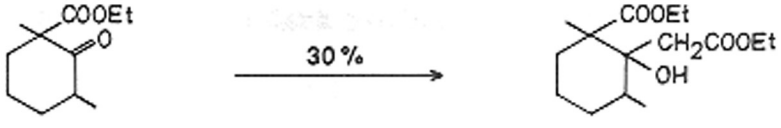
*Thus, for example, either failure or very poor yields for the following cases have been reported:

Knoevenagel[28,29]

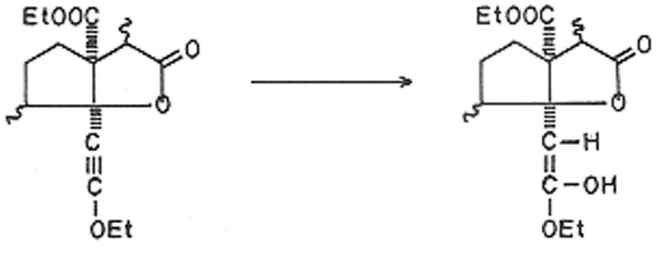


Reformatsky[30]



it was only after following strictly the procedure described in the Experimental that reproducible yield (48-56%) could eventually be obtained. Table 1 summarises results of several runs made to standardise this preparation.

The condensation of ethoxyacetylene with the keto-ester VI was patterned after the procedure described by Barett and co-workers[24,25] for similar condensations. Condensation of ethoxyacetylene magnesium bromide with keto ester (VI) yielded the acetylenic lactone (VII) which, without further purification, was hydrated (XVII) with aqueous sulphuric acid to furnish the lactone (VIII). However, this step proved to be



VII XVII

crucial in the projected synthesis, as it was only after considerable experimentation (Table 2) that somewhat acceptable (35-40%) and reproducible yields of lactone (VIII) could be obtained. In the course of this work it was found that the crude dark product of hydration must be

TABLE 1: PREPARATION OF METHOXYACETYLENE

[Runs with 38 g (1.65 g. atom) of sodium and 76.25 g (0.50 mole) of chloroacetal]

No.	Yield*		Remarks
	g.	%	
1	6.0	17.1	Insufficient cooling (!)
2	6.9	19.6	Addition of brine was not rapid; this resulted in decomposition.
3	5.5	15.7	A solution of calcium chloride, instead of brine, used for quenching[34].
4	8.7	24.8	No special reason.
5	4.8	13.7	"
6	18.3	52.7	Conditions, as described in Experimental, strictly followed.
7	11.0	31.4	"
8	19.4	55.4	"
9	15.0	42.8	"
10	17.5	50.0	"
11	17.0	48.6	"

*Yields of 58-61.6% have been reported[27].

TABLE 2: CONDENSATION OF METHOXYACETYLENE WITH KETOESTER (VI)

No.	Methoxy-acetylene g.	Keto-ester (VI) g.	Molar ratio.	Crude product g.	Total distil-late. g.	Lactone (VIII) g.	Yield* %	Remarks
1	5.6	7.5	3.0:1	7.3				-
2	6.6	10.4	2.6:1	10.4	23.1	15.2	30.6	Product from Expt. No.1,2,and 3 were combined and processed.
3	18.0	25.0	2.9:1	28.0				
4	4.0	5.8	2.6:1	-	3.6	2.67	39.8	-
5	8.7	15.0	2.2:1	14.0	11.1	4.32	24.8	-
6	4.8	9.4	2.0:1	-	4.0	2.36	21.7	-
7	17.0	30.0	2.2:1	38.0	26.0	20.9	60.2+	-
8	19.0	50.0	1.5:1	35.0	20.4	3.5	6.1	Large amount of VI gives poor yield; mostly unreacted VI is obtained.
9	15.5	27.0	2.2:1	21.0	15.7	11.6	36.9	-
10	15.4	27.0	2.2:1	25.2	19.0	12.9	39.8	-

*Yield based on ketoester (VI).

+Yield could not be reproduced.

rapidly distilled in a preliminary distillation before attempting its final fractionation.

The product from the above reaction analysed for $C_{16}H_{24}O_6$ and showed in the IR spectrum (Fig.3) bands at 1779 cm^{-1} (γ-lactone) and 1740-1730 cm^{-1} (ester). These data are in accord with the expected structure VIII. The stereochemistry for the ring junction, as shown in structure VIII, is derived from the fact that cis- bicyclo [0,3,3]octane is far more stable than the trans-bicyclo [0,3,3]octane*[31,32], and consequently the ready lactonisation of hydroxy acetylenic ester is consistent only with a cis ring closure. However, as will be discussed later, the stereochemistry at various asymmetric centres in lactone (VIII) is of no consequence for further follow up of the synthetic sequence.

The above lactone on ring-opening with sodium hydroxide in methanol underwent, being a β-hydroxy acid derivative, smooth elimination† to the required unsaturated acid IXa which, on treatment with diazomethane, gave the unsaturated ester (IXb). The compound analysed for $C_{17}H_{26}O_6$

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*The trans-isomer has a higher heat of combustion by 6 Kcal/mole[31].

†For similar cases see: (a) W.S.Johnson, R.G. Christiansen and R.E. Ireland, J. Am. Chem. Soc., 79, 1995 (1957); (b) B. Belleau, J. Am. Chem. Soc., 73, 5149 (1951); (c) W.E. Bachmann and G.D. Johnson, J. Am. Chem. Soc., 71, 3463 (1949).

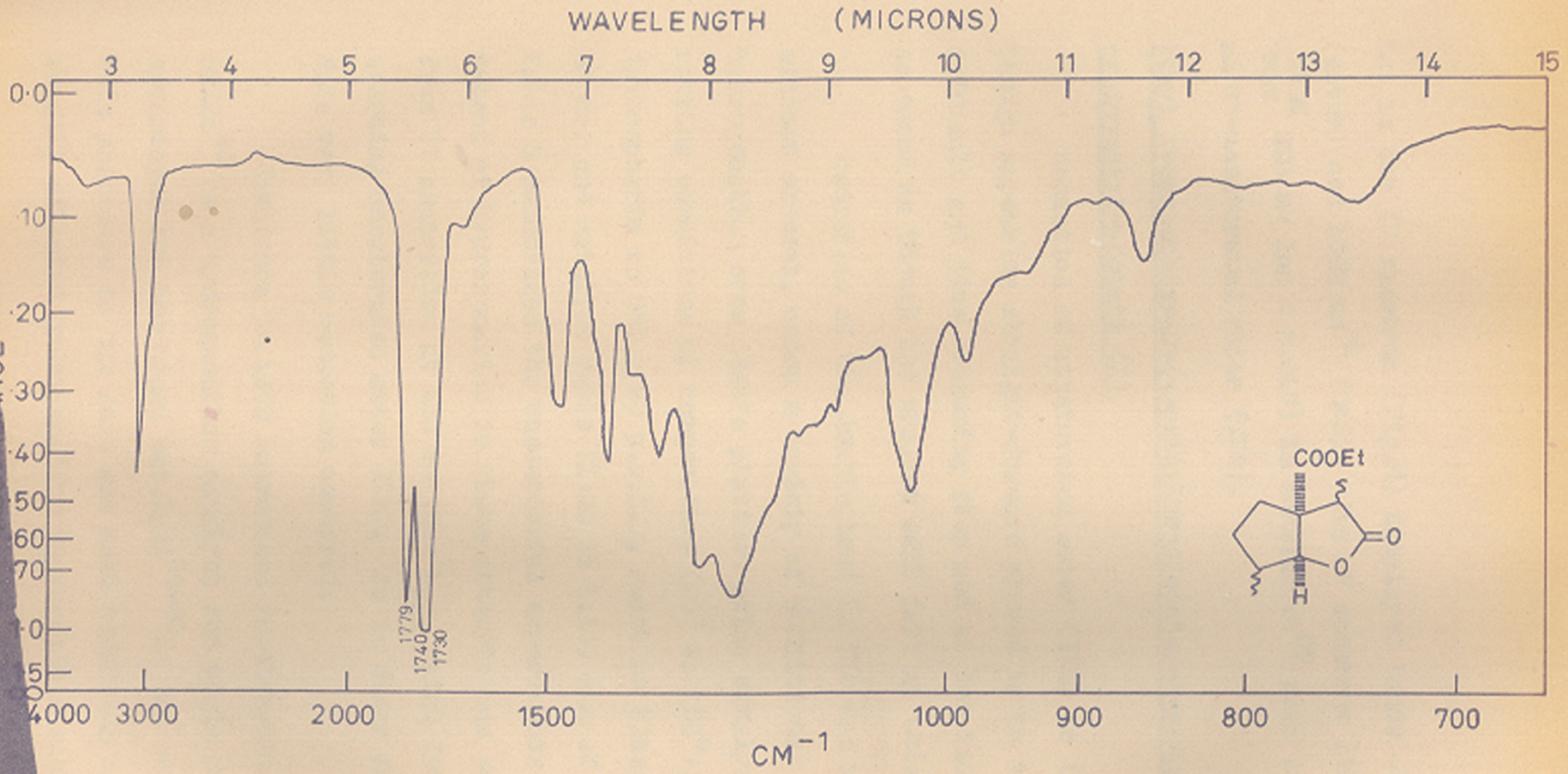


FIG. 3. IR SPECTRUM OF LACTONE (VIII)

and in the IR spectrum (Fig.4) displayed bands at 1728 cm^{-1} (ester) and 1642 cm^{-1} (C=C). Its UV spectrum [(Fig.5); λ_{max}^{EtOH} 222 mμ log ε 3.917] is consistent[33] with its being an α,β-unsaturated ester (IXb).

Ethyl 3-carbethoxy-2-(α-methylpropionate)-5-methyl-cyclopentyl-acetate (X)

Reduction of unsaturated ester (IXb) to (X) though appearing straight-forward proved to be the most difficult and time consuming step and at one time it appeared as though the project will fall at this stage.

Reduction of the double bond in IXb was attempted, without success, under a variety of conditions. Thus, hydrogenation over Adam's platinum oxide catalyst, under varying conditions of temperature (20° to 150°), pressure (atmospheric to 880 ± 20 p.s.i.), reaction times (7 hr to 48 hr) and catalyst ratio (1:20 to 1:10) was of no avail. Table 3 summarises the unsuccessful experiments; the extent of hydrogenation in these attempts was evaluated from UV absorption at 222 mμ (the λ_{max} value for the starting unsaturated ester IXb). As is clear from these data very little reduction occurred.

Nishimura in 1960 introduced rhodium-platinum (3:1) oxide[35] as a hydrogenation catalyst and claimed several advantages for the mixed catalyst[36-42]. The application of this procedure to our case was most rewarding as this readily effected hydrogenation to furnish a mixture of

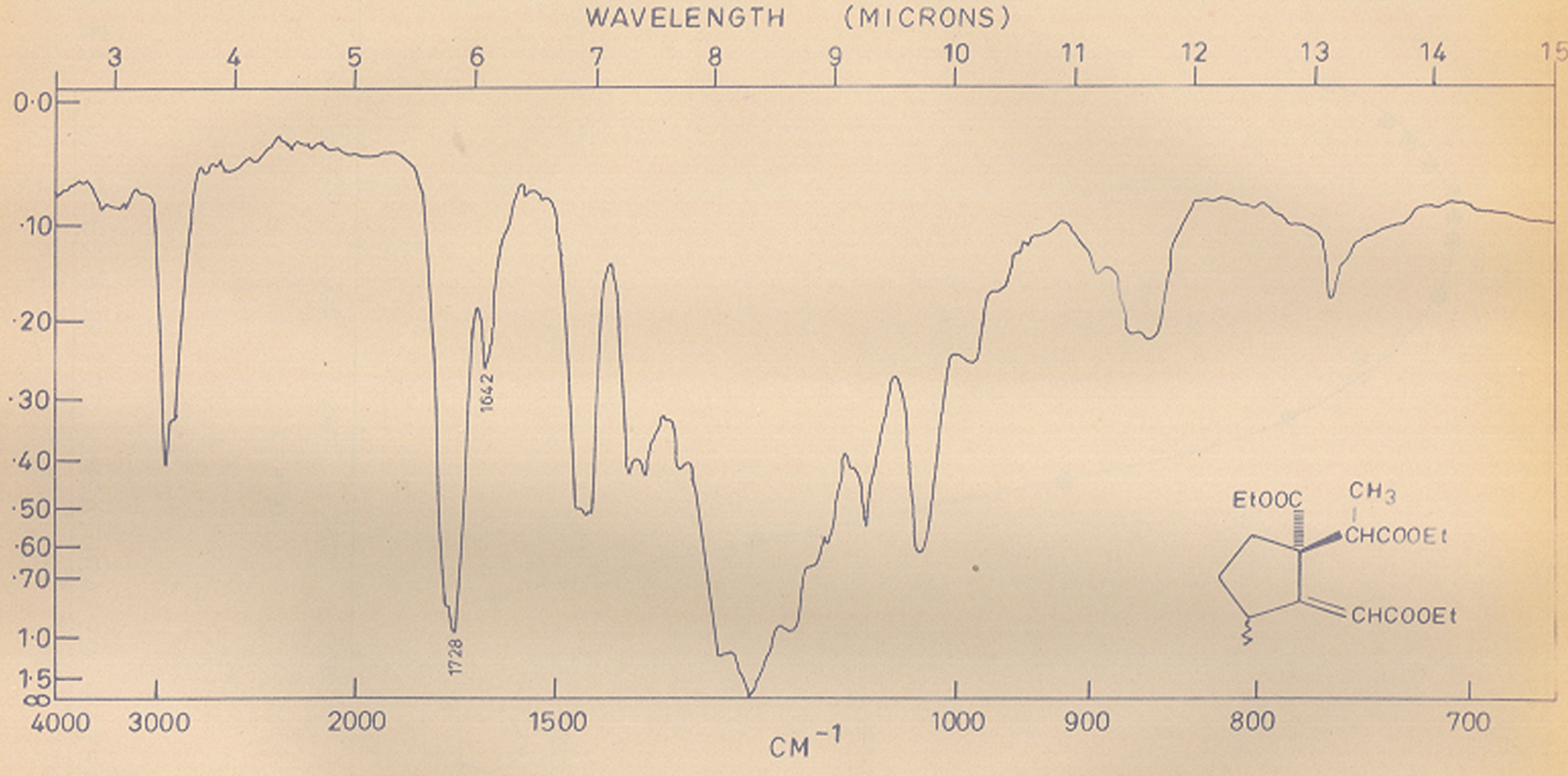


FIG. 4. IR SPECTRUM OF UNSATURATED ESTER (IXb)

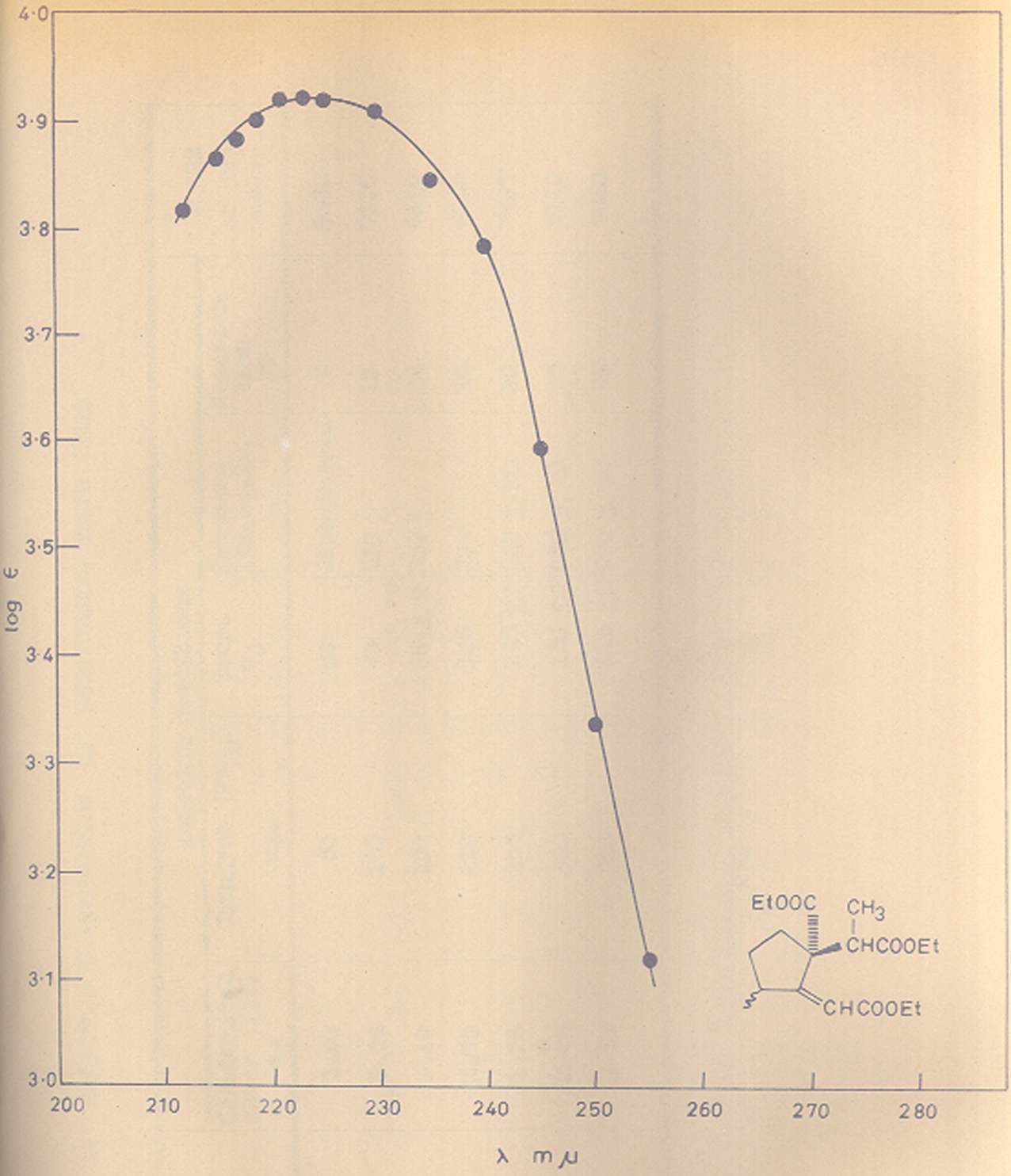


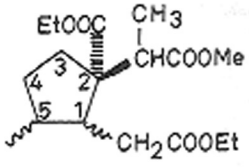
FIG. 5 UV SPECTRUM OF UNSATURATED ESTER (IX b)

TABLE 3: ATTEMPTED HYDROGENATION OF UNSATURATED ESTER (IXb)

Expt. No.	Reaction conditions					* ε 222 of product.
	Unsaturated ester (IXb) g.	Catalyst (PtO_2) mg.	Temp. ^oC	Pressure lbs/sq.in.	Reaction time hr	
1	0.50	50	20	Atmospheric	7	8260
2	3.44	150	70	520	12	7112
3	3.10	100	68 ± 4	850	24	6110
4	2.90	100	125	720	24	6350
5	3.25	200	145 ±2	830 ± 20	28	7487
6	2.83	200	150 ±3	830 ± 10	45	6110
7	2.19	230	150 ±3	880 ± 20	48	7650

*(IXb has ε_{222} = 8260)

of saturated ester (XVIII) in high yield. Fig.6 shows the IR spectrum of the product; in the UV it did not show

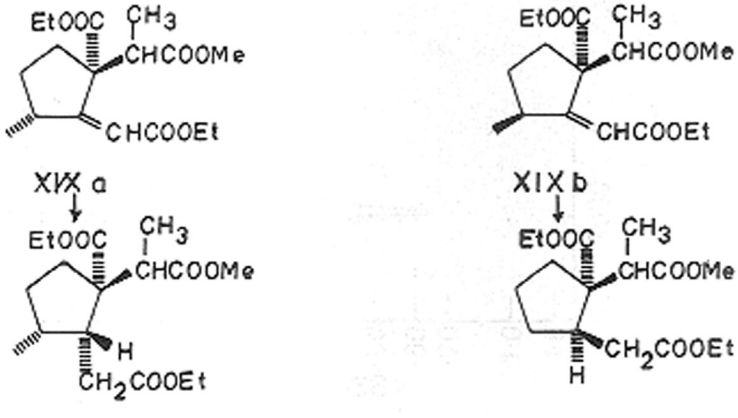


XVIII

any absorption peak in the 215 to 230 mμ region.

2,2,6-Trimethyl-3-oxo-1-carbomethoxy-bicyclo [0,3,3]octane(XII)

It was important at this stage to have some idea about the stereochemistry of the ester (XVIII). It appears to be fairly well established that catalytic hydrogenation at room temperature and pressure involves the addition of two atoms of hydrogen from the same side, i.e. from the sterically less hindered side of the unsaturated substrate[43-47]. On this basis it was anticipated that the stereochemistry of the resulting ester (XVIII) would be dependent on the configuration of methyl at C_5 in the unsaturated ester (IXb). Thus, the product of catalytic hydrogenation was expected



Xa FIG. 7. Xb

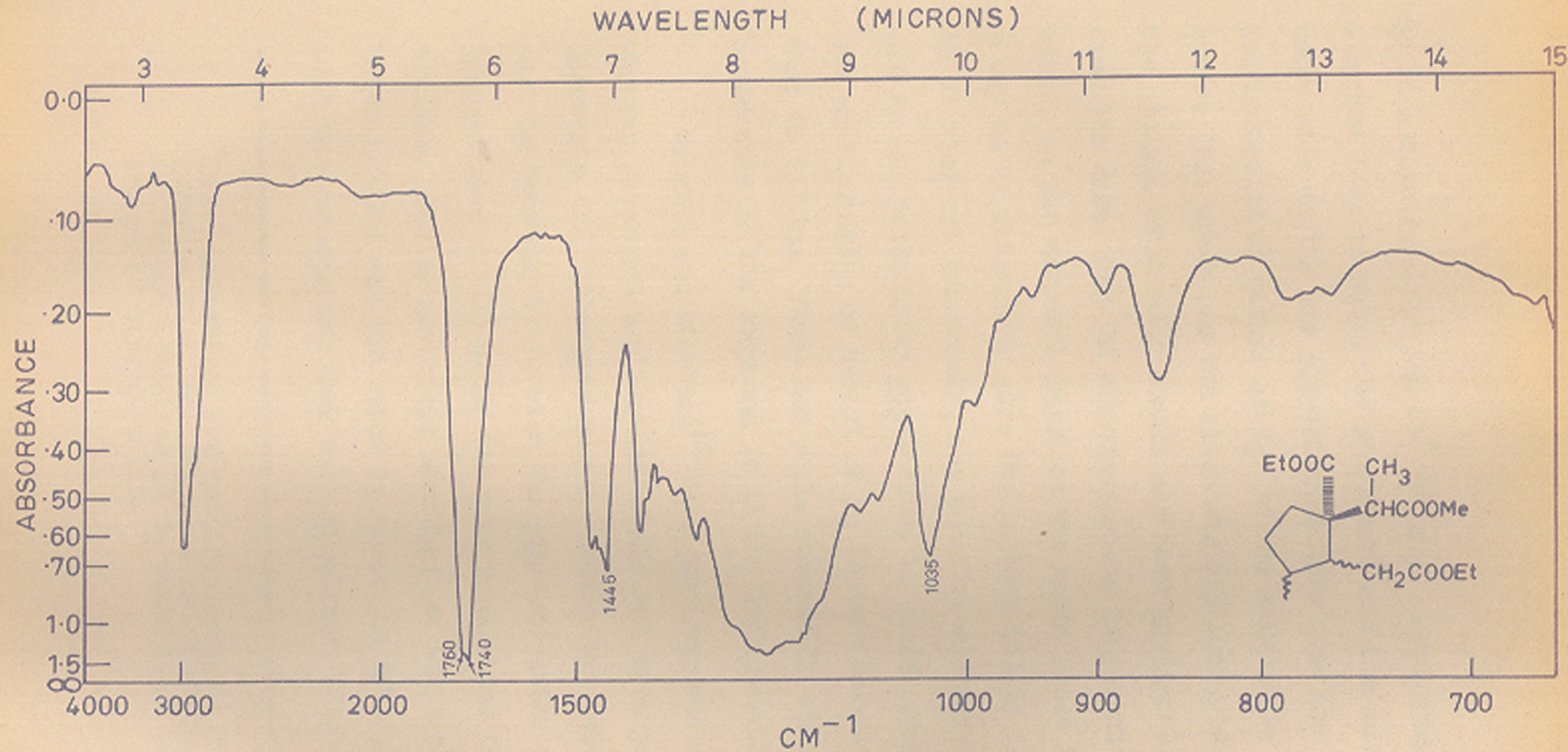


FIG. 6. IR SPECTRUM OF SATURATED ESTER (XVIII)

to be a mixture of Xa and Xb* (Fig.7). Furthermore, compound (Xb) in which the propionate and the acetate ester side chains are cis-oriented have also the desired configuration of methyl at C_5; in the only other alternative (Xa) which has the alternate configuration at C_5 the vicinal ester side chains are also trans-oriented. From the fact, that in ethoxyacetylene condensation the attack on the carbonyl function has taken place in such a way as to ultimately give the lactone (VIII) in which, as pointed out previously, the two five-membered rings are in all probability cis-locked, it would appear that the configuration of methyl at C_5 is more likely to be that in (XIXb). Thus, one could reasonably expect a preponderance of the compound Xb in the hydrogenation product.

Barrett and Linstead[31] have demonstrated that whereas Dieckmann cyclisation of diethyl cyclopentyl-1,2-diacetate (XX) undergoes smooth cyclisation (with sodium dust in benzene) to furnish the cis-keto ester (XXI), the trans-isomer (XXII) under the same conditions fails to cyclise. Taking advantage of this fact the saturated ester (XVIII) was subjected to Dieckmann cyclisation with the expectation that only cis-isomer (Xb) would undergo

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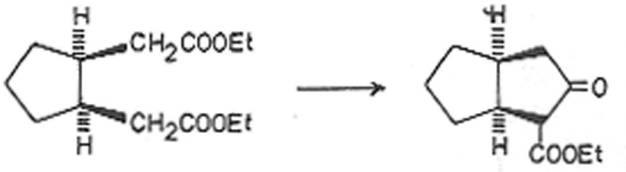
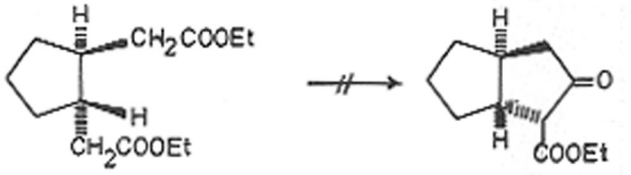
*These deductions are not dependent on the configuration at C_2 in XIX, as a consideration of the alternative configuration at C_2 would lead to the mirror images of structure XIX.



XX XXI



XXII XXIII

cyclisation under these conditions. The crude product was hydrolysed with aqueous AcOH-HCl and the resulting material was re-esterified (diazomethane) and fractionated to give desired keto-ester (XI) in an over all yield of 40% (based on XVIII). In the IR (Fig.8) it showed ν^{cso} at 1750-1728 cm^{-1} as required by structure XI; a peak at 1408 cm^{-1}, assignable to scissoring frequency of a methylene α to carbonyl, is also present.

The compound XI showed a single peak in a GLC under a variety of conditions. However, it is clear from its PMR spectrum (Fig.9) that the above product is more or less a 1:1 mixture (as disclosed by two signals for $-COOCH_3$ protons at 216 and 221 cps) of two isomers; this is also required by the CH_3-CH-signals centred at 56 cps, 58 cps and 62 cps (J = 9 cps, 7 cps and 8 cps respectively). Since the fusion of rings in the keto ester(XI)

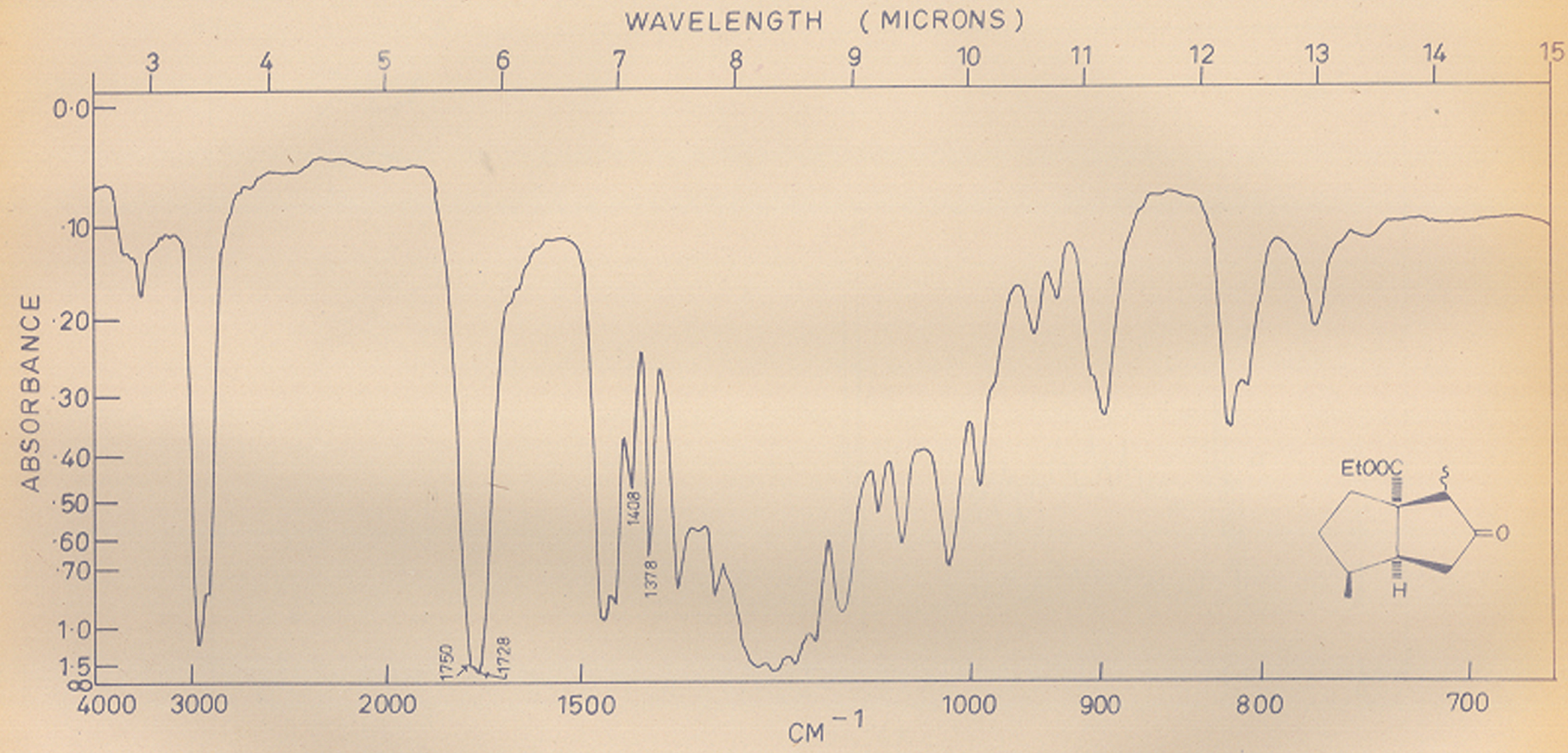


FIG. 8 IR SPECTRUM OF KETO-ESTER (XI)

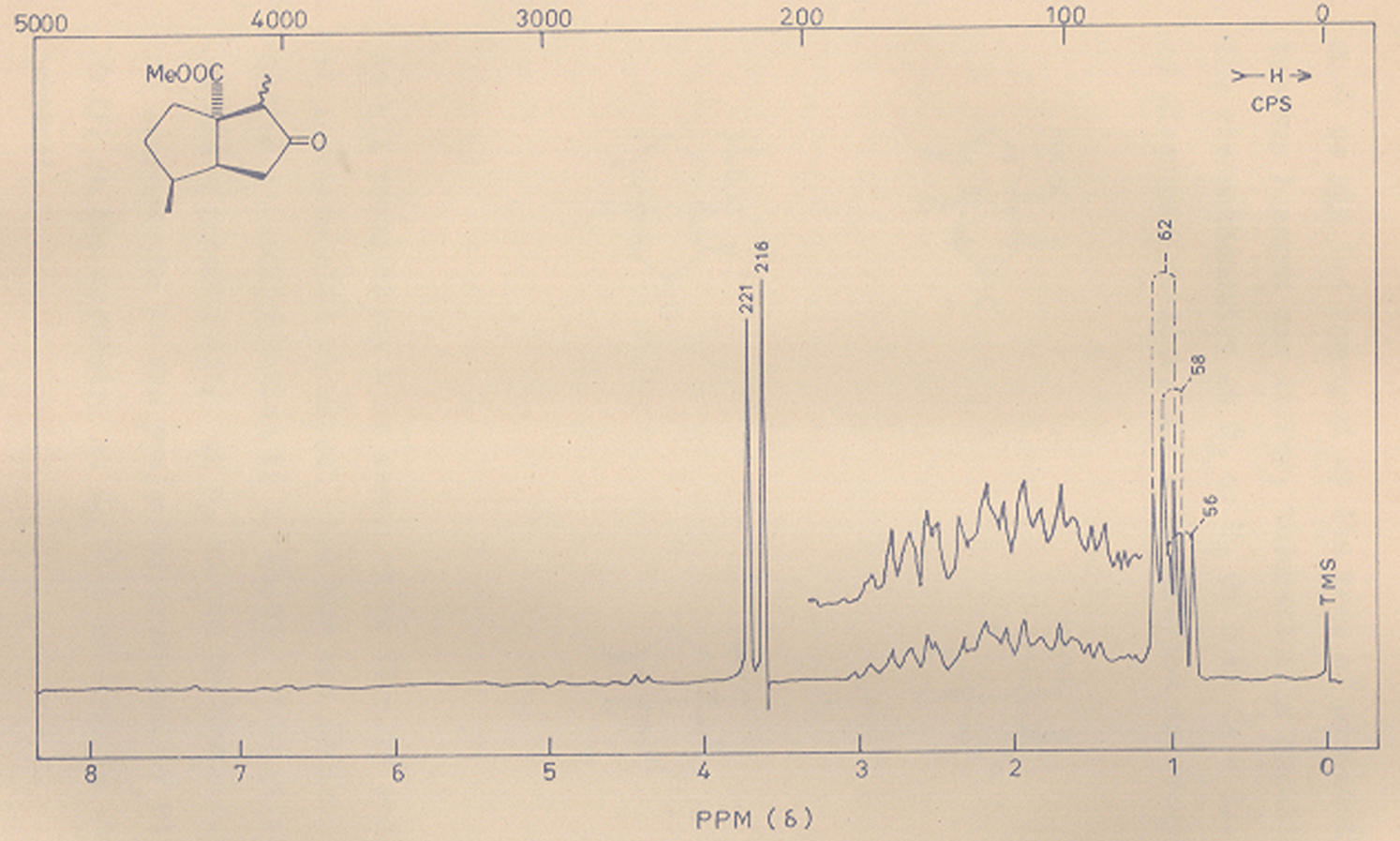
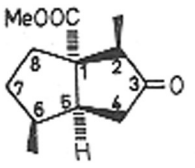
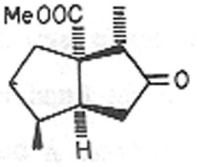


FIG. 9. PMR SPECTRUM OF KETO-ESTER (XI)

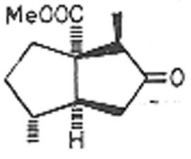
must be cis (as required by its mode of preparation); the two isomers can differ, theoretically speaking, in the stereochemistry at C_2 or C_6 or both (a - d). However, as discussed earlier, the configuration of methyl at C_5 is,



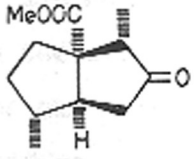
a



b



c



d

in all probability β as shown in Xb (Fig.7) and hence it is reasonable to expect that the two isomers of XI differ in configuration at C_2 (a,b). This difference in the stereochemistry at C_2, as can be visualised, is of no consequence in the projected synthesis of the keto-ester (XII) as the asymmetry at C_2 will be lost in the final product.

The last step in the synthesis of (XII), viz. the introduction of a methyl at C_2 in (XI), could be

achieved smoothly by a procedure patterned after the work of Corey and Cantrall[48]. Thus, the keto ester (XI) on treatment with trityl sodium and methyl iodide readily furnished a monomethylated product, $C_{13}H_{20}O_3$. The fact that the methylation has gone in the right direction to furnish XII was clear from its IR spectrum (Fig.10), in which the band at 1408 cm^{-1} (CH_2 α to C=O) is still present and a doublet at 1380 and 1360 cm^{-1} (the absence of this doublet in Fig.8 may be noted), which is characteristic of gemianl dimethyl group[49] appears. The PMR spectrum (Fig. 11) is fully consistent with the structure (XII) and provides evidence in support of our previous contention that the isomers of (XI) differ only in the stereochemistry at C_8, as the PMR spectrum (Fig.11) does not show any evidence* for the presence of isomers.

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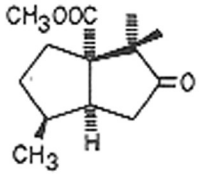
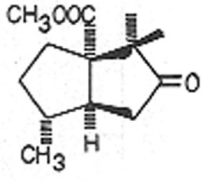
*Had the isomers of (XI) differed in configuration of methyl at C_8, it is reasonable to expect that the mixture of (i) and (ii) should show at least some difference in the chemical shift of $COOCH_3$ or CH_3-CH- in the PMR spectrum of XII.



(i)



(ii)

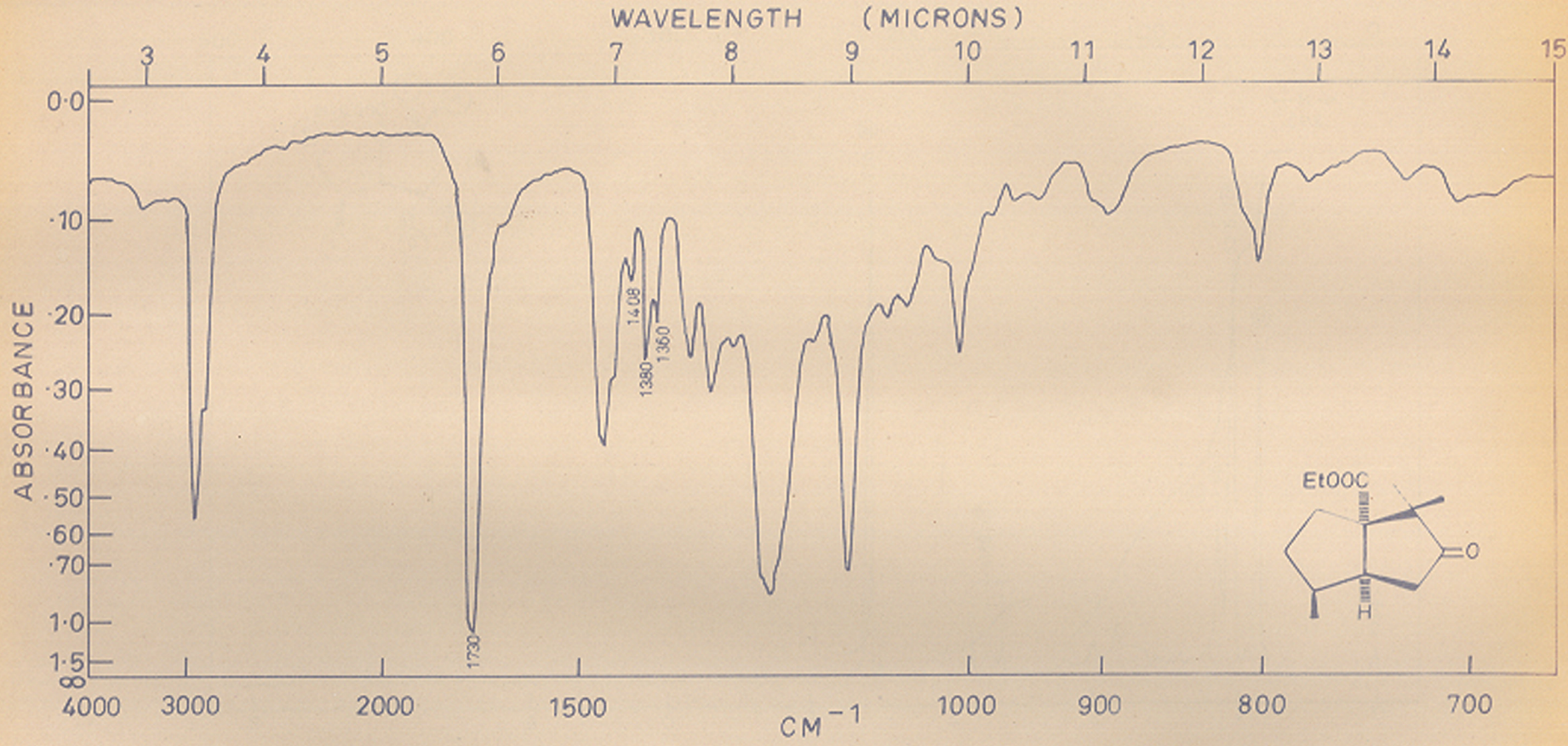


FIG. 10. IR SPECTRUM OF KETO-ESTER (XII)

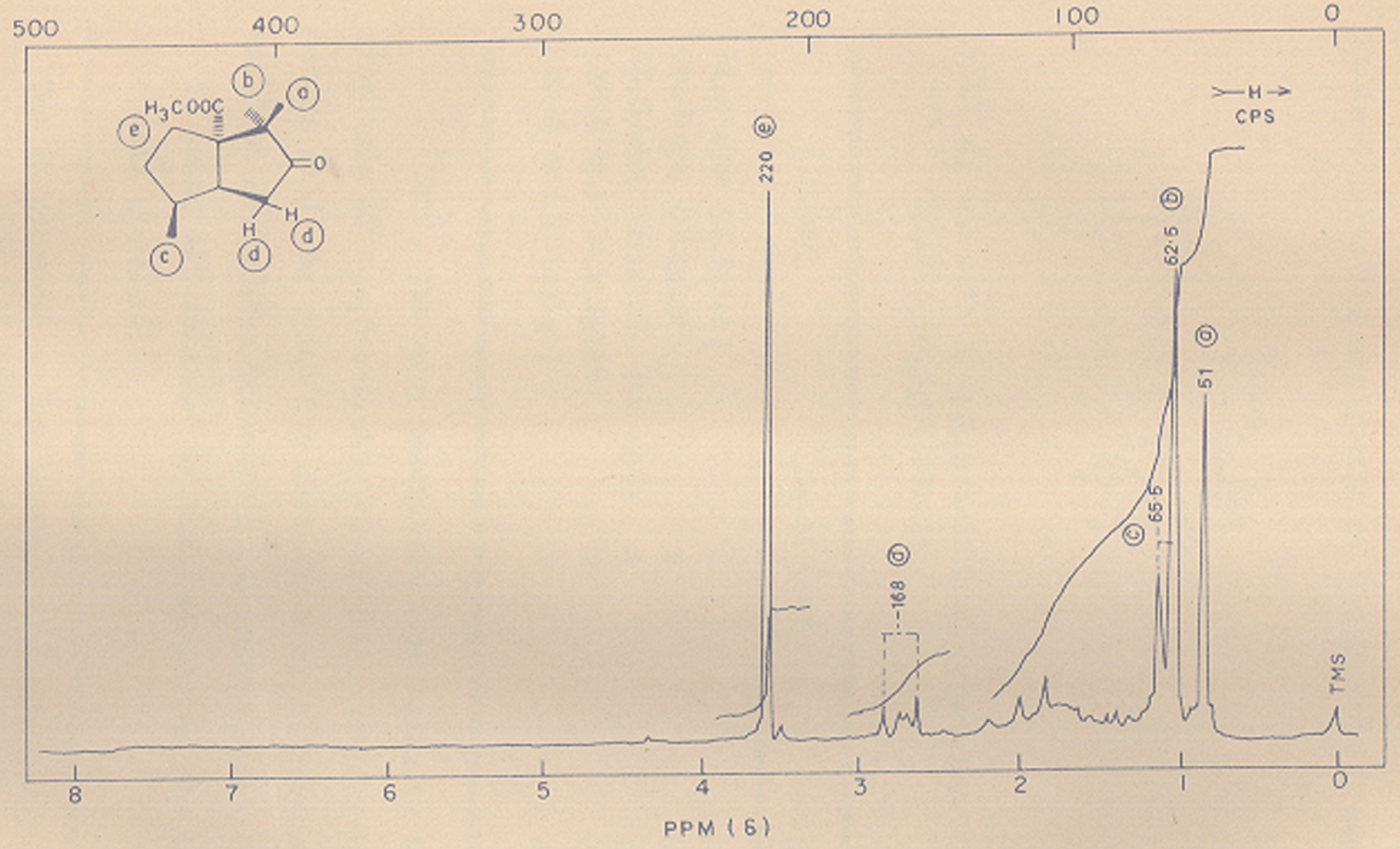


FIG. 11. PMR SPECTRUM OF KETO ESTER (XII)

Table 4 gives the assignment of the important signals of XII.

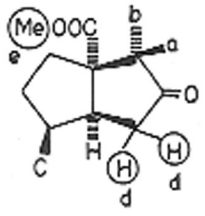


TABLE 4: PMR DATA OF 2,2,6-TRIMETHYL-3-OXO-1-CARBOMETHOXY-BICYCLO [0,3,3] OCTANE.

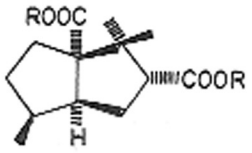
Signal	No.of protons	Assignment
51.0 cps (Singlet)	3	a
62.5 cps (Singlet)	3	b
65.5 cps (Doublet, J=6 cps)	3	c
168.0 cps (Multiplet)	2	d
220.0 cps (Singlet)	3	e

Thus, the work described above leads to the total synthesis of 2,2,6-trimethyl-3-oxo-1-carbethoxy-bicyclo[0,3,3] octane (XII) in which the assignment of stereochemistry is based on reasonable deductions and should represent the ± form of compound III obtained by Büchi et al. by the degradation of patchouli alcohol*.

*The IR spectrum of our synthetic compound was sent to Prof. G. Büchi for comparison with his product, who kindly informed us (Feb.20, 1963) though the curves are very similar they are not superimposable. He further pointed out that their sample was never absolutely pure as there was neither VPC nor thin-layer chromatography those days. But further observed that all important peaks are identical though.

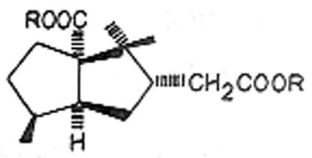
DEGRADATION OF PATCHOULI ALCOHOL

As pointed out previously, the keto-ester (III), appeared attractive for elaborating further the molecule of patchouli alcohol which was considered, at the time this work was started, to possess the structure IV. Two routes starting from the keto ester (XII) and passing either through the dimethyl bis-nor-patchouli dicarboxylate (XXIVb) or dimethyl nor-patchouli dicarboxylate (XXVb) were envisaged for the purpose. Since, while this work was in



XXIV a, R=H

XXIV b, $R=CH_3$



XXV a, R=H

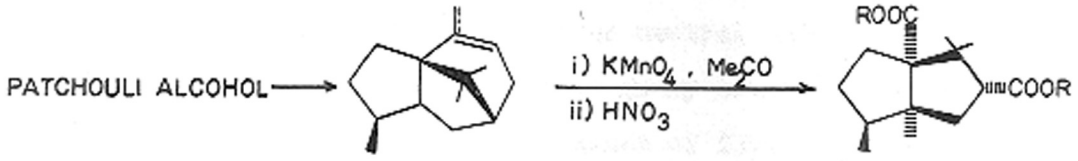
XXV b, $R=CH_3$

progress the structure of patchouli alcohol underwent revision to I, it became apparent that the projected synthetic routes from keto ester (XII), via XXIVb or XXVb, to patchouli alcohol were no longer feasible. However, concurrently with the synthetic work discussed earlier, some degradation experiments on patchouli alcohol were carried out to get XXIVb and XXVb for use as relays in the projected syntheses. The following pages contain a brief outline of some of the interesting results obtained

during the course of these degradation studies.

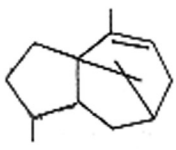
Dimethyl bis-nor-patchouli dicarboxylate (XXIVb)

The procedure followed by Büchi, Erickson and Wakabayashi[2] for the degradation of patchouli alcohol to bis-nor diester (XXIVb) is outlined below (II → XXIVa → XXIVb), however no yields were specified.

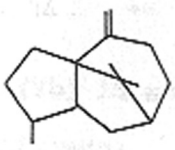


I II XXIV a, R = H
XXIV b, R = CH_3

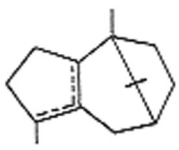
In the first instance the procedure of Büchi and co-workers[2] was investigated. Dehydration of patchouli alcohol with pyridine and phosphorous oxychloride, following details of these workers, furnished a mixture of isomeric hydrocarbons. The distribution of isomers in this mixture was estimated by GLC to be: α-patchoulene ~ 68%, γ-patchoulene ~ 13% and β-patchoulene ~ 16%. This mixture was used in all subsequent experiments



IIa



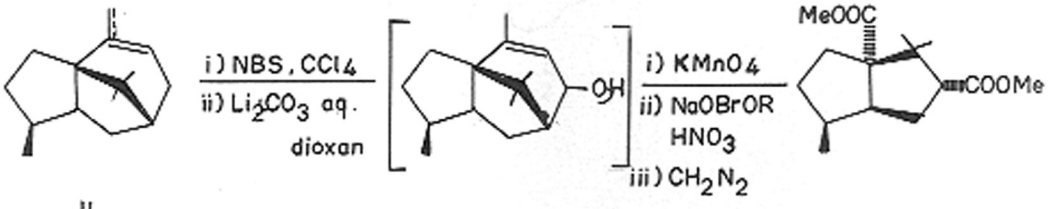
IIb



IIc

planned for the degradation of α-patchoulene (IIa). Oxidation of this with potassium permanganate, followed by nitric acid oxidation, according to reported procedure of Büchi and co-workers[2], furnished a gum (8-10% by weight on II); but all efforts to isolate the crystalline diacid (XXIVa) from this gum ended in failure. The gummy acidic material was converted into its methyl esters (diazomethane) and chromatographed over neutral alumina. Benzene eluted an oil (15% by weight on gummy esters) which on GLC (Fig.12) indicated the presence of four components, of which the required compound (peak No.3) formed only a minor constituent, as revealed by a mixed GLC with an authentic sample*.

Since, the reported procedure did not prove successful in our hands, attention was directed to the following sequence of reactions (Fig.14) by which it became possible



II

FIG. 14.

to get us required diester (XXIVb) in an over all yield of 7.4% from the patchoulene mixture.

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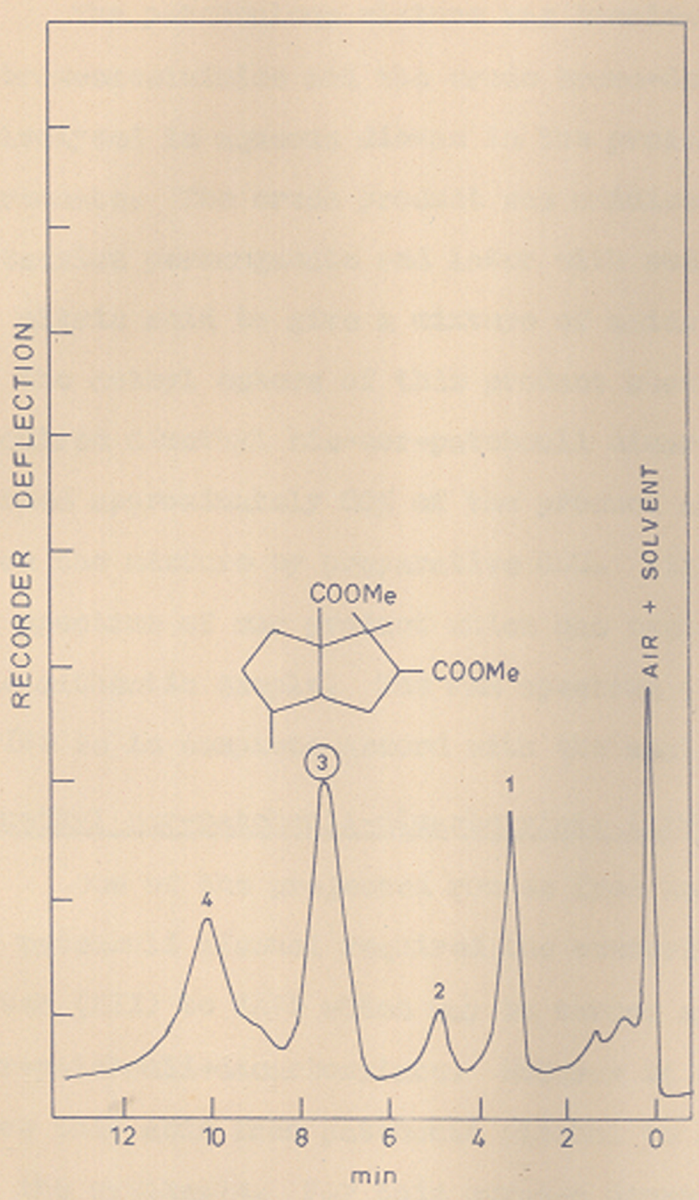
*We are thankful to Prof. G. Büchi for providing an authentic sample of the diacid XXIVa.



GLC OF METHYL ESTERS OBTAINED BY THE DEGRADATION OF PATCHOULENES BY BÜCHI'S METHOD.

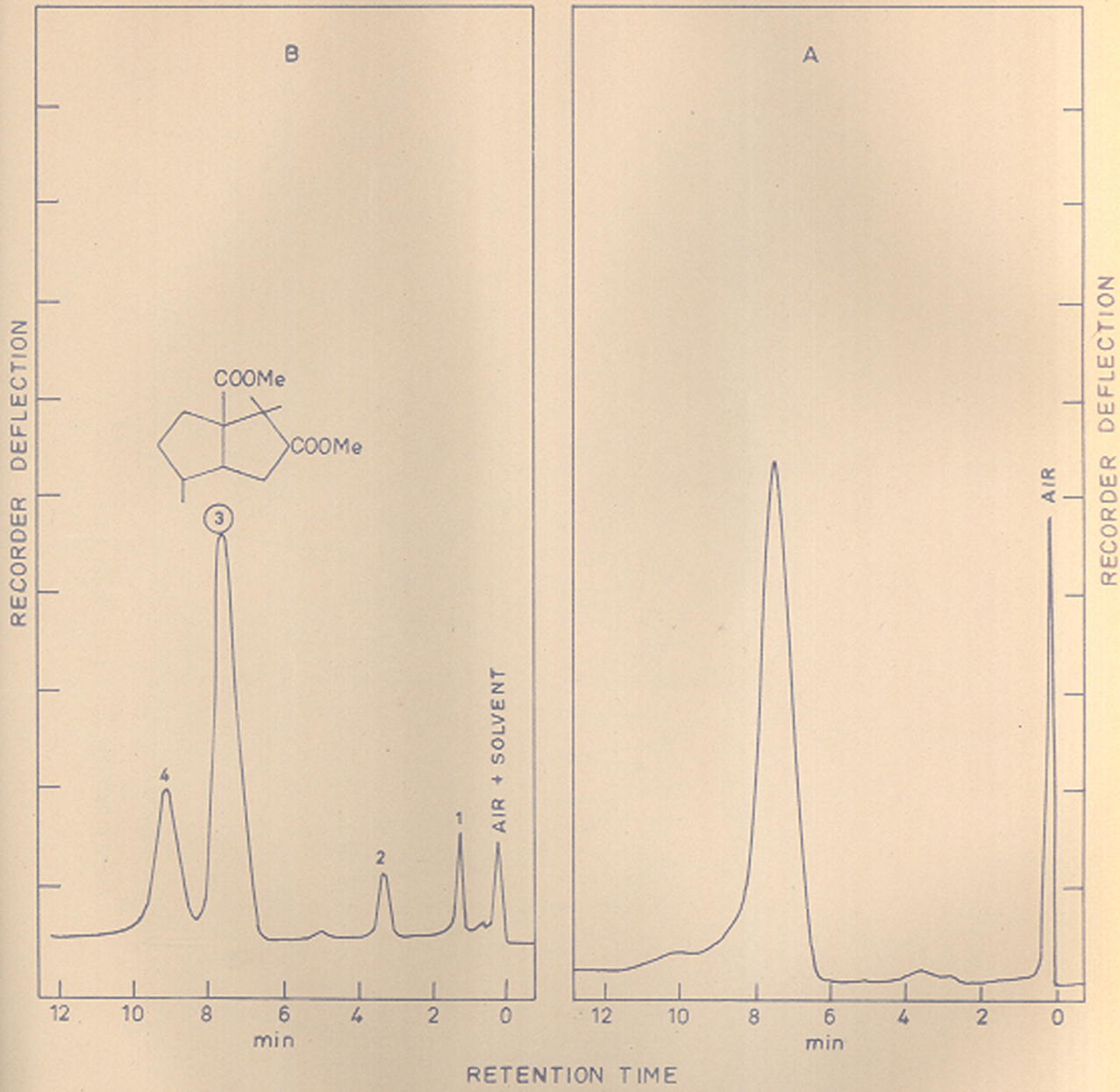
Column, 20% diethylene glycol polysuccinate on chromosorb W; length 5 ft. Temp. 200°. Flow rate, 50 ml/min

FIG. 12.

The patchoulene mixture was brominated with N-bromosuccinimide and the crude bromo-derivative was solvolysed in aqueous dioxan in the presence of lithium carbonate. The crude product was oxidised first with potassium permanganate and later with sodium hypo-bromite or nitric acid to give a mixture of acids. GLC (Fig.13) of the methyl esters of this product showed that the required dimethyl bis-nor-patchouli dicarboxylate (XXIVb) formed approximately 60% of the product and was separated from the mixture by preparative GLC. Fig.15 shows the IR spectrum of our product which has been compared with the authentic sample. The PMR spectrum (Fig.16) of XXIVb is in complete accord with the assigned structure.

Dimethyl nor-patchouli-dicarboxylate (XXVb)

One of the projected routes from keto ester (XII) to patchouli alcohol required the conversion of keto-ester (XII) to XXVb which may be termed as dimethyl nor-patchouli-dicarboxylate. However it was necessary to have this acid from patchouli alcohol to act as a relay in the synthesis. For this purpose degradation of patchouli alcohol was investigated. Ozonolysis of patchoulenes mixture followed by oxidative cleavage of the ozonide yielded an acidic product which was oxidised further with nitric acid. The resulting material on crystallisation from formic acid gave a dicarboxylic acid, m.p. 242-244°, analysing for $C_{14}H_{22}O_4$. That this compound is the required



GLC OF METHYL ESTERS OBTAINED BY THE DEGRADATION OF PATCHOULENES BY PRESENT METHOD

A – PREPARATIVE GLC SEPARATED ESTER (XXIV b)

B – TOTAL MIXTURE

Column, 20 % diethylene glycol polysuccinate on chromosorb W, length, 5 ft.

Temp. 200°. Flow rate, 50 ml/min

FIG 13.

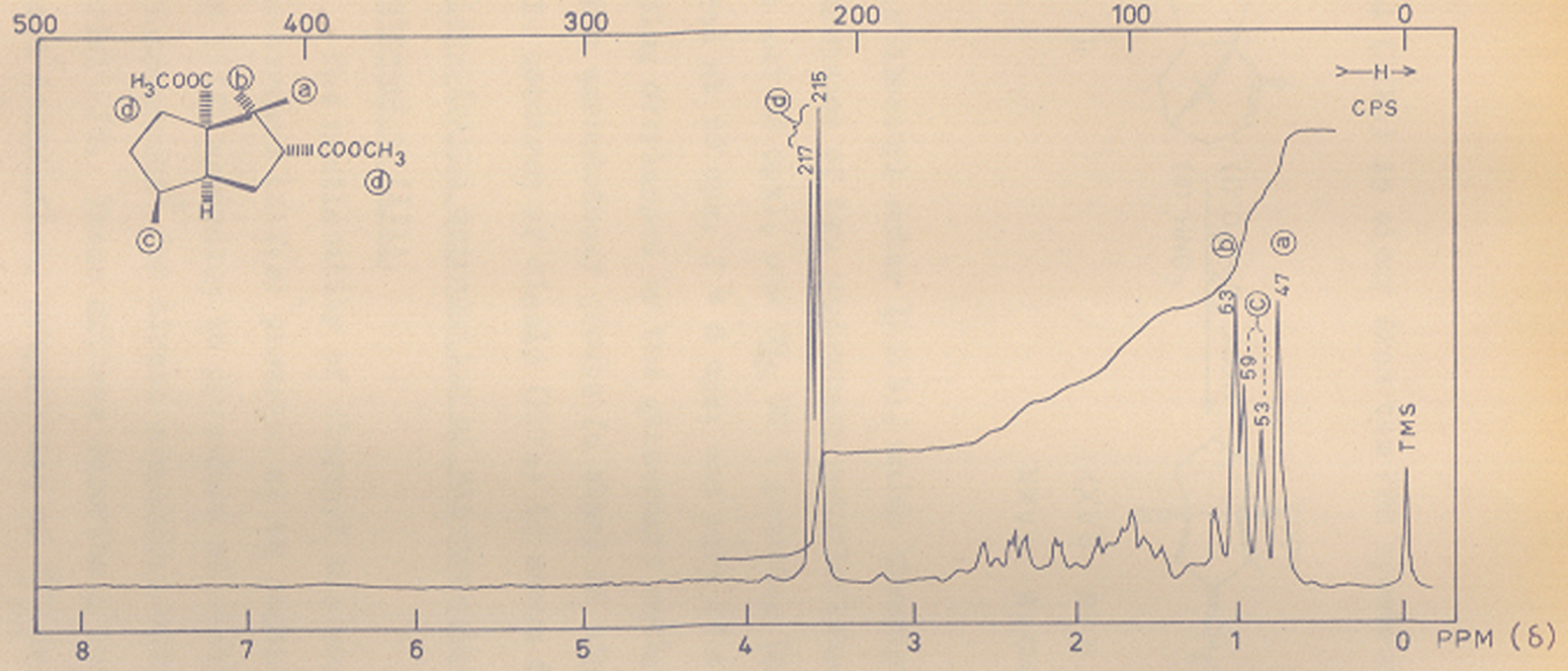
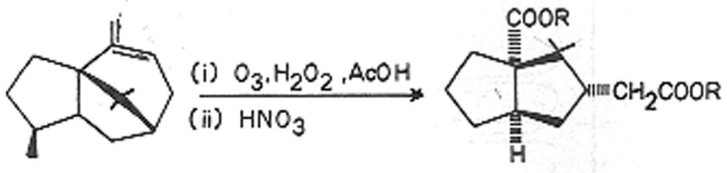


FIG. 16. PMR SPECTRUM OF DIMETHYL BIS-NOR-PATCHOULI-DICARBOXYLATE (XXIV b)

diacid (XXVa) is clear from the PMR spectrum (Fig.17)



II

XXV a R= H

XXV b R= CH_3

of its dimethyl ester (XXVb), which clearly indicates the presence of two quaternary methyls (sharp 3H signals at 41 and 63 cps), one CH_3 CH < grouping (a 3H doublet centred at 59 cps, J = 6 cps; one part of the doublet is being overlapped by the quaternary methyl signal) and two carbomethoxy groups (a sharp 6H signal at 218 cps). The IR spectrum of diacid (XXVa) is shown in Fig.18.

Barbier-Wieland degradation of bis-nor-diester (XXIVb) to keto-ester (III).

The availability of dimethyl bis-nor-patchouli-dicarboxylate (XXIVb) prompted us to degrade it to keto-ester (III) according to procedure of Büchi, Erickson and Wakabayashi[2] for direct comparison with our synthetic material XII. These authors describe a two stage (Barbier-Wieland degradation) preparation of III from XXIVb passing through diphenylethylene ester (XXVI), which was isolated as a solid melting at 154-155° and having λ_{max}^{EtOH} 227 mμ (ε, 11,200). By following the procedure of these authors

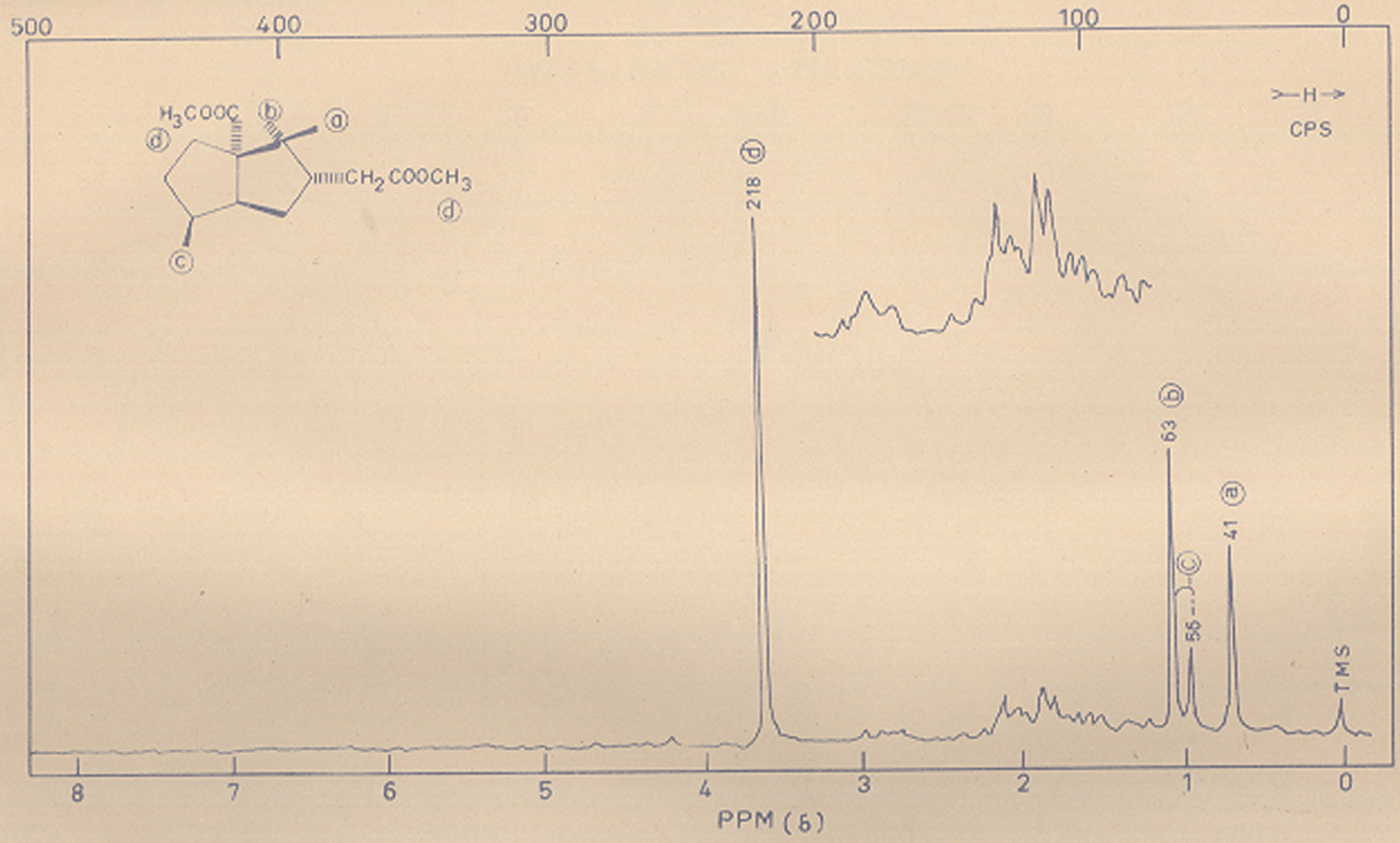


FIG. 17 PMR SPECTRUM OF DIMETHYL NOR-PATCHOULI DICARBOXYLATE (XXVb)

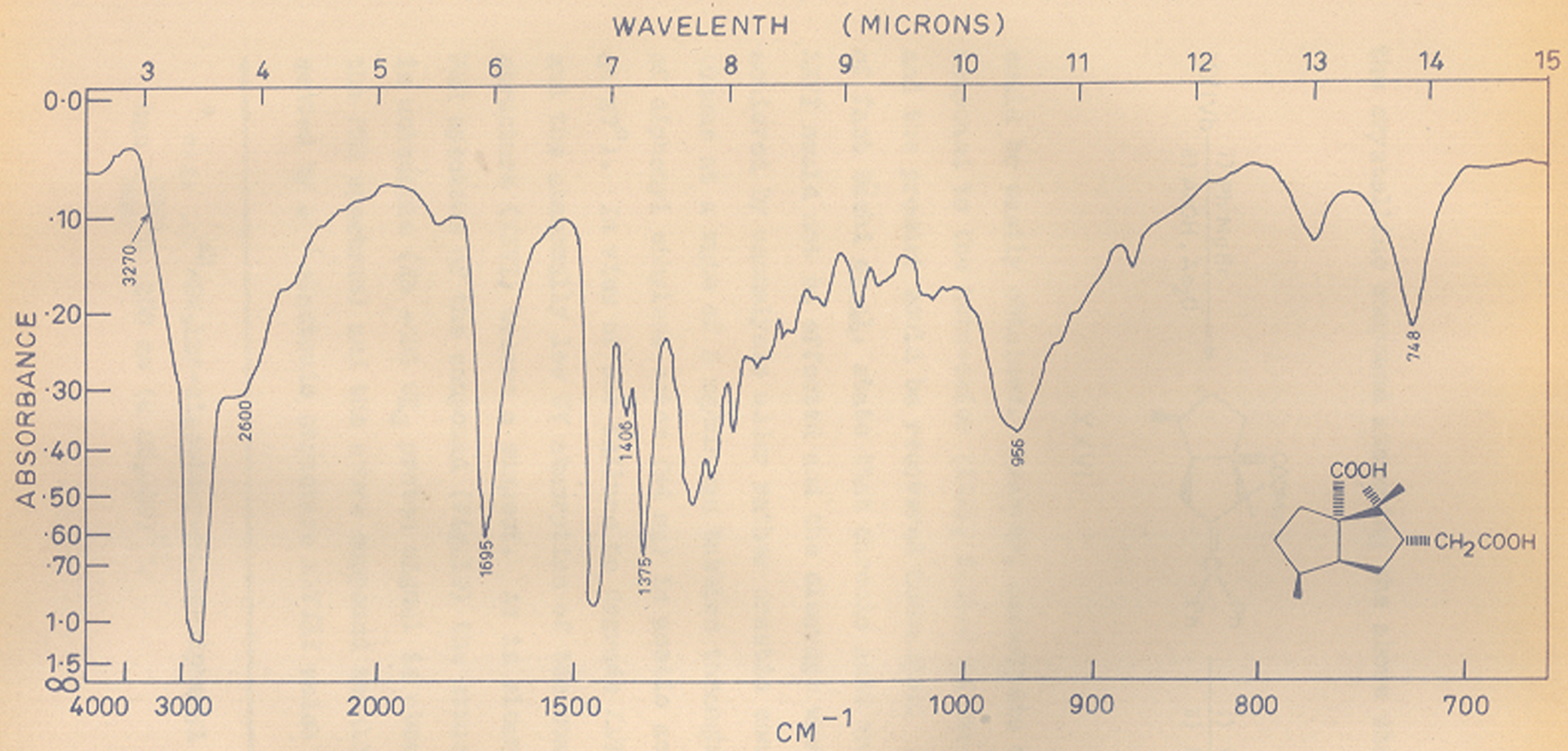
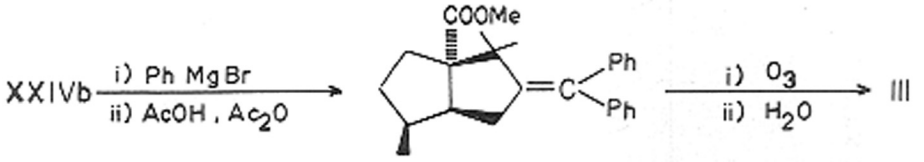


FIG. 18. IR SPECTRUM OF NORPATCHOULI DICARBOXYLIC ACID (XXVa)

the crystalline compound answering the above characteristics



XXVI

could be easily obtained. However, ozonolysis of this compound to the keto-ester (III), failed in our hands and the product could be recovered unchanged. As a matter of fact Büchi et al. state that chromic acid oxidation of XXVI could not be effected and the cleavage was ultimately achieved by ozonolysis under rather drastic conditions. (Ozone at a rate of 3 mg/min was bubbled through a solution of diphenyl ethylene ester (84 mg) in acetic acid for 7 hr at 27°). In view of our failure to degrade XXVI further and the abnormally low UV absorption of the compound* the structure (XXVI) became a suspect. As is clear from the PMR spectrum of the compound (Fig.19) the structure XXVI is untenable (No -COO CH_3 proton signal is observed in the PMR spectrum) and the above compound should be represented by a δ-lactonic structure XXVIII which can originate

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* e.g. Δ^{23}-3α,12β-diacetoxy-24,24-diphenyl cholene has $\lambda_{max}^{CHCl_3}$ 250 mμ (ε 25,000)[51].

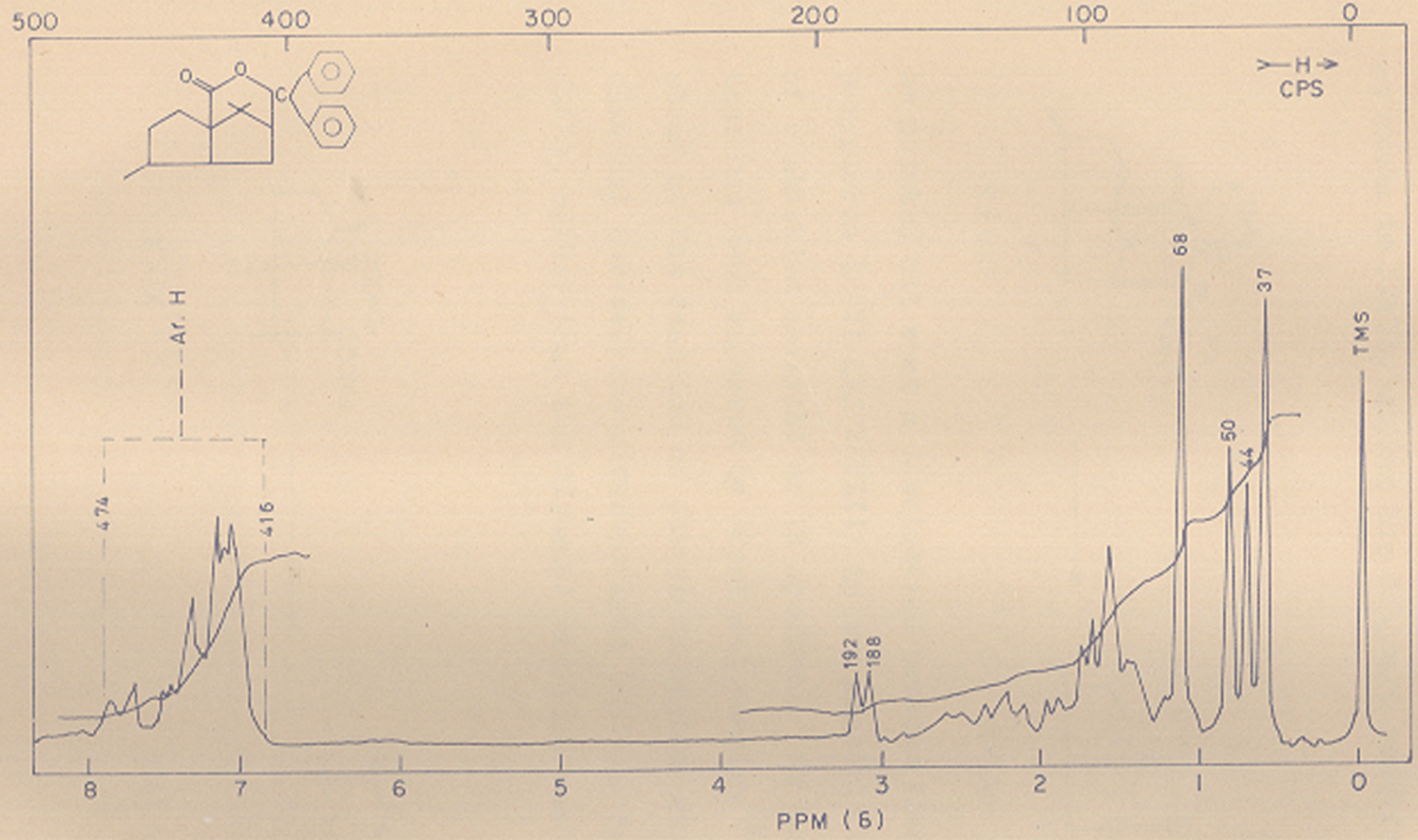


FIG. 19. PMR SPECTRUM OF δ-LACTONE (XXVIII)

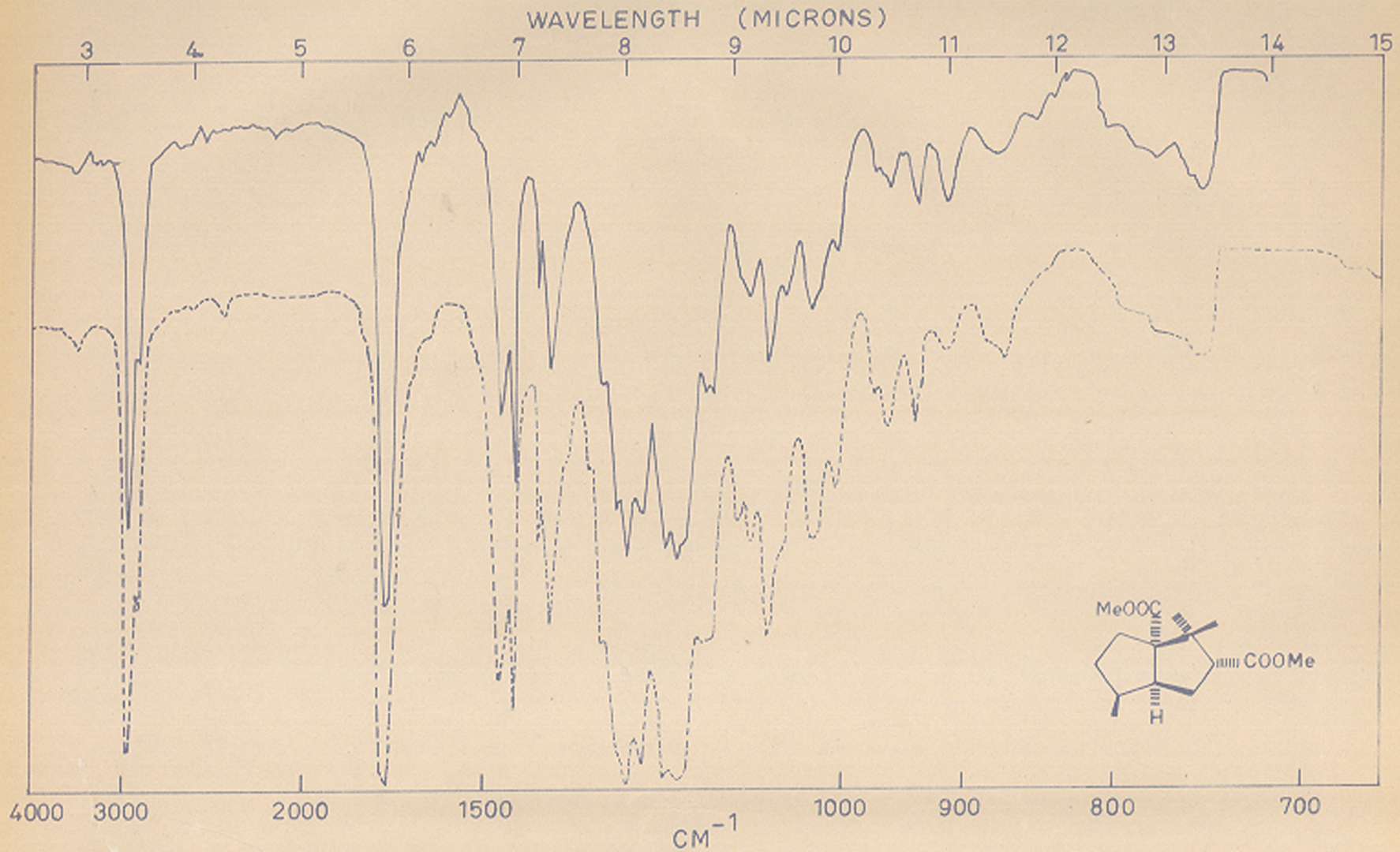
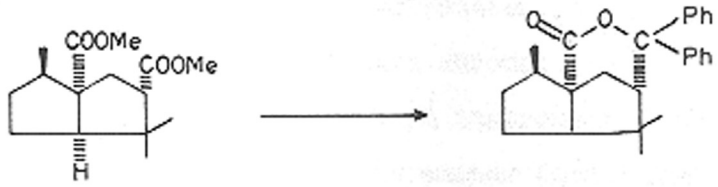


FIG. 15. IR SPECTRUM (CCl_4) OF DIMETHYL BIS-NOR-PATCHOULI-DICARBOXYLATE (XXIVb)

as shown in XXVII, during the Grignard reaction. It must

XXVII XXVIII

be pointed out that a distinction between these two structures (XXVI and XXVIII) is not possible on the basis of combustion analysis or IR spectrum. An exactly parallel case has been reported by Stork and Berslow[50] during their study of the reaction of phenyl magnesium bromide on dimethyl nor-cedrene-dicarboxylate (XXIX), when the δ-lactone (XXX), rather than the diphenyl ethylene was obtained.



XXIX XXX

EXPERIMENTAL

All the boiling points are uncorrected. Melting points were determined on a Koffler hot stage microscope and are uncorrected. Pet. ether refers to the fraction b.p. 40-60°. All solvent extracts were finally washed with brine, before drying (Na_2SO_4). Rotations were taken in chloroform on an automatic polarimeter (Perkin-Elmer model 141).

IR spectra were taken on a Perkin-Elmer Infracord (model 137E) and Perkin-Elmer Infrared spectrophotometer (model 221) either as smears (liquids) or in nujol (solids), unless stated to contrary. UV spectral measurements were made on a Beckman Ratio Recording Spectrophotometer (model DK 2) and a Perkin-Elmer spectrophotometer (model 350) in 95% ethanol. All PMR spectra were taken in a ~10% solution in CCl_4 with tetramethylsilane as the internal standard, on a Varian Associates A-60 spectrometer; signals are reported in cps values. Gas liquid chromatography (GLC) analyses were carried on Aerograph instrument (model A-350B) or on a Perkin-Elmer Vapour Fractometer (model 154-D); with H_2 as carrier gas.

Alumina used in this investigation was washed with 10% aqueous nitric acid, made neutral by washing with distilled water and activated at 460° for 6 hours[52]. The various grades were prepared and checked according to reported

procedure of Brockmann[53]. Thin-layer chromatography (TLC) was carried out on silica gel (-200 mesh) containing 15% plaster of paris as binder, using the equipment and procedure of Gupta and Dev[54]. Either concentrated sulphuric acid or a mixture of sulphuric acid and nitric acid (1:1) was used for spraying and visualisation of spots.

Diethyl adipate (XIII)

Adipic acid (450 g, 3.08 moles), absolute ethanol (600 ml), dry carbon tetrachloride (260 ml) and sulphosalicylic acid (5 g) were taken in a flask fitted with a Dean Stark trap to which was attached a reflux condenser. The contents were refluxed (waterbath) for 15 hr, after that no more water separated. The reaction mixture was allowed to attain room temperature and poured into water (1 litre). The two layers were separated, worked up in usual manner and fractionated to give diethyl adipate as colourless mobile liquid, b.p. 98-99°/1 mm, n_D^{30} 1.4230 (Lit. b.p.: 134°/14 mm[55]), yield 580 g (93%); IR spectrum: $-COOC_2H_5$ 1730 cm^{-1}.

2-Carbethoxycyclopentanone (XIV)[5,10,11,12]

Pulverised sodium was prepared from sodium (51.75 g, 2.25 g.atoms) under refluxing xylene. Xylene was decanted off, the pulverised sodium washed with dry S-free benzene (2 x 100 ml) and covered with benzene (1 litre).

Diethyl adipate (303 g, 1.5 moles) was added to it from the top of a reflux condenser, which was attached to a mercury pop valve. The reaction was started by adding dry ethanol (5 ml) followed by gentle warming (steam-bath). A very vigorous reaction started within a very short time which was maintained under control by occasional cooling in an ice-bath. When all the vigour of reaction had subsided, the contents were refluxed (heating mantle) for 8 hr (anhydrous conditions) in the atmosphere of hydrogen (evolved). Dilute aqueous acetic acid (600 ml, 1:1) was added to the reaction mixture under external cooling (ice-salt) and left overnight (12 hr) to break the complex. The product worked up in the usual way and dried. Removal of solvent (under suction) and fractionation furnished 2-carbethoxycyclopentanone as colourless mobile liquid; b.p. 140°/63 mm; n_D^{30} 1.4460 (Lit. b.p.: 102°/1 mm[11]), yield 190 g (81%); IR spectrum: C=O in five-membered ring 1751 cm^{-1}; $-COOC_2H_5$ 1721 cm^{-1}.

2-Methyl-2-carbethoxycyclopentanone (XV)[5]

2-Carbethoxycyclopentanone (78 g, 0.5 mole) was added to a well stirred suspension of powdered sodium (12.7 g, 0.55 g.atoms) in dry benzene (300 ml) at -10° (ice-salt). After the addition was complete, the contents were stirred for 2 hours and methyl iodide (85.2 g, 0.6 mole) was added to it slowly. The reaction product was heated under gentle

reflux (heating mantle) for 68 hours, cooled in an ice-salt bath and dilute hydrochloric acid (50 ml, 22%) was added. The reaction mixture was worked up in the usual fashion, dried and solvent removed. Fractionation of the residue gave 2-methyl-2-carbethoxycyclopentanone; b.p. 88°/4 mm, n_D^{30} 1.4410 (Lit.[56]: b.p. 94-95°/8 mm; n_D^{20} 1.4460), yield 76 g (90%).

Diethyl α-methyladipate (XVI)[5-7,13]

(a) From XV: To a solution of sodium (0.6 g, .025 g.atom) in dry ethanol (46 ml), 2-methyl-2-carbethoxycyclopentanone (40 g, .23 mole) was added quickly in one lot. The reaction mixture was heated (waterbath) under gentle reflux (anhydrous conditions) for 30 min. Aqueous acetic acid (40 ml, 1:1) was then added to the cooled (ice-salt) reaction product and the required ester was extracted with benzene (3 x 50 ml); the combined benzene extracts were washed with 5% aqueous sodium bicarbonate solution and dried. Solvent was removed and the product fractionated to give diethyl α-methyladipate; b.p. 118°/6.5 mm, n_D^{27} 1.4285 (Lit.[57]: b.p. 132-34°/15 mm), yield 45 g (88.5%); IR spectrum: $COOC_2H_5$ 1733 cm^{-1}.

(b) Without isolating the intermediates. Diethyl adipate (50.5 g, .25 mole) was added to a suspension of 50% sodium hydride (14.6 g, .3 mole) in benzene (300 ml). The flask was then fitted with a reflux condenser the top of which, through a calcium chloride guard, was connected to a mercury

pop valve. The reaction was started by adding a small amount of alcohol (1 ml) followed by gentle warming. Within a short time a vigorous reaction started, which was kept under control by occasional cooling in an ice bath. When there was no more evolution of hydrogen gas, the contents of the flask were refluxed (waterbath) for 5 hr. 50 ml of benzene-ethanol mixture was distilled off from the reaction vessel in a stream of nitrogen and freshly distilled methyl iodide (60 g, 0.4 mole) was added and then left aside at room temperature till the solid cake completely dissolved (manual swirling was required to break the cake in the beginning). The reaction mixture was now refluxed (18 hr), cooled down to room temperature and dry ethanol (75 ml) and sodium (1 g) was added. After the complete dissolution of sodium, the product refluxed for another 90 min. and worked up as in previous case. Removal of solvent (under suction) and fractionation furnished the desired diethyl α-methyl-adipate; b.p. 101-02°/1.2 mm, n_D^{28} 1.4290, yield 41.4 g (77%; based on diethyl adipate).

2-Carbethoxy-5-methylcyclopentanone (V)[4-7]

It was prepared following essentially the directions of Jones and Linstead[4]. To the pulverised sodium (8.3 g, 0.35 mole) in dry benzene (150 ml) was added diethyl α-methyl adipate (50 g, .23 mole) in one lot. The reaction was started by adding a small amount of dry ethanol (1 ml)

followed by gentle warming. A brisk reaction had started with the evolution of hydrogen. When the evolution of hydrogen had subsided, the reaction mixture was heated (waterbath) under reflux for 21 hr and then chilled in an ice-salt bath. Dilute hydrochloric acid (100 ml; 22%) was added to it to break the complex, the two layers separated and processed as usual. The solvent was stripped off in vacuo (water pump) and the residual oil fractionated to give the desired keto-ester V; b.p. 80-81°/1.5 mm, n_D^{30} 1.4451 (Lit.[56]; b.p. 108-09°/13 mm), yield 28.5 g (73%). IR spectrum: >=O in five-membered ring 1751 cm^{-1}; $COOC_2H_5$ 1721 cm^{-1}.

When sodium hydride was substituted for sodium dust in the above experiment the yields were improved to 88%. Thus, from 50% sodium hydride (5.3 g, 0.11 mole), dry benzene (75 ml) and diethyl α-methyl adipate (21.6 g, 0.1 mole) and following essentially the conditions described above, 15 g (88%) of keto-ester (V) was obtained; b.p. 85-86°/2 mm, n_D^{20} 1.4451.

Ethyl 2-carbethoxy-2-(α-methyl-propionate)-5-methyl-cyclopentanone (VI)[4,8,9]

The above keto-ester (42.5 g, 0.25 mole) was added slowly to a well stirred suspension of pulverised sodium (6.9 g, 0.32 mole) in dry toluene (200 ml) at 1-4° (ice bath) and then allowed to attain room temp.(28°).

The reaction mixture was then heated on a steam bath for 3 hr and then in an oil bath (110-15°) for 1 hr; cooled down to 3-5° (ice bath) and ethyl α-bromo-propionate (54.3 g, 0.3 mole; prepared from propionic acid by bromination followed by esterification with ethanol) was added dropwise under brisk stirring. After the addition of bromo ester, the reaction mixture was allowed to attain room temperature, heated under reflux (2-1/2 hr) in an oil bath (138-43°) and was kept aside for 3 days (28°). After refluxing for additional 2 hr, the contents were chilled (ice-salt bath) and water (150 ml) was added slowly under stirring. The two layers, so formed, were separated and the organic layer was washed with water (2 x 50 ml). All aqueous portions were combined, acidified with dilute acetic acid and extracted with toluene. All combined toluene layers were then washed successively with dilute acetic acid (2 x 50 ml) 25%, brine (2 x 50 ml), 5% aqueous sodium bicarbonate (1 x 100 ml) and dried. The solvent was removed (under suction) and product fractionated to give the desired keto-ester (VI); b.p. 136-38°/2.5 mm, n_D^{26} 1.4540 (Lit.[4]: b.p. 171-73°/19 mm), yield 53.1 g (80%). IR spectrum: >=O in five-membered ring 1751 cm^{-1}; $COOC_2H_5$ 1727 cm^{-1}.

Ethoxyacetylene[26,27]

In 1-litre three necked flask fitted with an efficient stirrer, a soda lime-potassium hydroxide guard

tube and an inlet tube, liquid ammonia (600 ml) was transferred from an ammonia gas cylinder and crystalline powdered ferric nitrate (0.6 g) was added to it. Sodium (38 g, 1.65 g.atom; B.D.H. laboratory reagent) was sliced into small pieces of approximate size 1/4" x 1/4" x 3/4". One such piece of sodium was cautiously and carefully introduced into liquid ammonia which reacted immediately (formation of blue colour). The contents of the flask were stirred slowly till blue colour disappeared (the colour at this stage is grey due to formation of sodium amide). Another piece of sodium was now added to the flask and above procedure repeated. Thus, one by one, all pieces of sodium were dissolved one after the other*. After the addition of entire amount of sodium, the contents of the flask were gently swirled for 75 min. (volume of liquid ammonia was maintained around 450 ml). The guard tube was now replaced with a dropping funnel with a pressure equaliser and diethyl chloroacetal (76.25 g, 0.5 mole; prepared by chlorination of vinyl acetate[59]) was added dropwise (30 min.) under gentle stirring. The inlet tube was then connected to a nitrogen

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*During the addition of sodium care had to be taken that volume of liquid ammonia should not fall below 300 ml under any circumstances. To compensate the loss due to evaporation, more of liquid ammonia should be introduced as and when required. The preferred volume of ammonia should be maintained around 450 ml.

cylinder, through a sulphuric acid bubbler and the ammonia was slowly evaporated (8 hr) in a continuous stream of nitrogen and then left overnight in an atmosphere of nitrogen. Next day the inlet tube was quickly replaced with a 500 ml pressure equalising dropping funnel having a wide bore (1 cm), stop-cock and containing precooled (-20°) brine (325 ml). The flow of nitrogen was now directed from the top of this funnel; the flask cooled* down to -80° (dry ice-acetone) and the precooled brine was added rapidly in less than a minute's time (prolonged addition of brine resulted sometimes in decomposition of ethoxy-acetylene). The flask was allowed to attain room temp. slowly and the product was then distilled, through a Vigreux column (30 cm) attached to a double surface condenser, from a temperature controlled waterbath slowly heated to 80°. The distillate was collected in a receiver cooled to -30° and any uncondensed material was trapped in a chilled (ice-salt) trap. The condensed material from the trap (if any) as well as from the receiver was transferred to a separatory funnel and washed (till neutral) with a cold saturated aqueous solution of

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*The flow of nitrogen during the cooling process was considerably increased to exclude the possibility of air getting into the flask. The sodium salt of ethoxyacetylene is extremely pyrophoric.

sodium dihydrogen phosphate, brine (2 x 10 ml) and dried. Fractionation through a short (5 cm) column furnished ethoxyacetylene; b.p. 50-51°/715 mm, n_D^{27} 1.3700 (Lit.[27]: b.p. 49-51°/749 mm; n_D^{25} 1.3700), yield 18.3 g (52.7%).

3-Methyl-1-carbethoxy-2-carbethoxylmethyl-2-hydroxy-cyclopentyl-α-propionic acid lactone (VIII).

To a solution of ethyl magnesium bromide, prepared from magnesium (5.8 g, .24 mole) and ethyl bromide (30 g, .27 mole) in absolute ether (200 ml) under the envelope of nitrogen, ethoxyacetylene (15.4 g, 0.22 mole) in dry ether (100 ml) was added slowly under brisk mechanical stirring. When the evolution of ethane had ceased, dry S-free benzene (100 ml) was added to this milky suspension of ethoxyacetylene magnesium bromide to form a clear solution. The reaction flask was cooled (ice-salt) and refilled with fresh dry nitrogen. The keto-ester (VI; 27.0 g, .1 mole) in benzene (100 ml) was then added slowly dropwise (2 hr) under brisk stirring. A light brown colour developed which went on deepening as time lapsed. Stirring was continued for 5 hr at this temperature (ice-salt) and the reaction mixture was then left overnight (12 hr) at room temperature (25°). The stirring was repeated for another 2 hr under cooling of ice-salt bath and the complex broken by adding a cold saturated aqueous solution of ammonium chloride (200 ml). The ether benzene layer was

separated and washed with water (2 x 75 ml). All combined aqueous portions were thoroughly extracted with ether (5 x 50 ml) and the ethereal extracts were combined with ether-benzene layer, washed with brine (3 x 50 ml), dried and solvent removed. The residue obtained was dissolved in peroxide free pure dioxan (200 ml) and aqueous sulphuric acid (20 ml, ~ 3.6N H_2SO_4) was added. The reaction started by the immediate evolution of heat, however, never proved violent. The hydration was allowed to proceed (18 hr) at room temperature and then the excess sulphuric acid was neutralised with 10% aqueous solution of sodium bicarbonate. Most of the dioxan water was removed (trapping the vapours in an ice-salt chilled trap) under suction of a water pump at 74-76°, water (100 ml) added to the residue and organic material thoroughly extracted with ether (6 x 50 ml). The combined ether extract was washed with water (2 x 50 ml), dried and solvent removed. The dark brown residue (25.2 g), so obtained, was rapidly distilled with the free flame of a burner through a short (5 cm) Vigreux column at a vacuum of 1 mm or less to give a yellow oil (19.0 g) which was fractionated and the following fractions were collected.

Fr.No.	b.p./mm	n_D^{30}	Yield g.	Yield %
1	85-132°/0.7	1.4624	4.36	
2	132-170°/0.6 mostly 157-162°/0.6	1.4759	12.10	37.4
3	158-160°/0.6 (middle cut)	1.4748	0.83	2.6

Fractions 2 and 3 constituted the desired lactone (VIII). Fr.3 was analysed: (Found: C, 61.62; H, 7.3. $C_{16}H_{24}O_6$ requires: C, 61.53; H, 7.7%). IR spectrum: (Fig.3).

Ethyl 2-carbethoxy-2-(α-methyl-propionate)-5-methyl cyclopentylidene-acetate (IXb).

A mixture of above γ-lactone (12.0 g, .038 mole), methanol (500 ml) and 10% aqueous sodium hydroxide (30 ml, .075 mole) was heated (waterbath) under reflux for 2-1/2 hr under protection from carbon dioxide (KOH guard). Most of the methanol was removed under suction (water pump) at a bath temperature below 50°. Water (100 ml) was added to the residue and the organic material extracted with ether (3 x 40 ml). The combined ether extract was washed with 10% sodium bicarbonate solution (1 x 25 ml), water and dried. Removal of solvent gave a neutral liquid (0.8 g) which was not investigated further.

All alkaline washings and the aqueous portions were combined, neutralised with dilute hydrochloric acid and the liberated acidic material was taken in ether (4 x 50 ml). The ether extract was washed with water (2 x 20 ml), dried and treated with a slight excess of ethereal solution of diazomethane. After 2 hr the excess diazomethane was destroyed with the aid of few drops of acetic acid, worked up as usual and dried. Removal of solvent gave a mobile liquid which was fractionated and the following fractions were collected.

Fr.No.	b.p./mm	n_D^{30}	Yield	
			g	%
1	Upto 121°/0.6	1.4560	0.54	
2	121-135°/0.6 mostly 132-133°/0.6	1.4635	8.62	60.3
3	132-133°/0.6	1.4642	0.68	5.7

Fractions 2 and 3 constituted the desired product (IXb). Fraction 3 was analysed: (Found: C, 61.9; H, 7.85. $C_{17}H_{26}O_6$ requires: C, 62.5; H, 7.97%); IR spectrum (Fig.4); UV spectrum (Fig.5).

Attempted hydrogenation of ethyl 2-carbethoxy-2-(α-methyl-propionate)-5-methyl-cyclopentylidene-acetate (IXb) over PtO_2.

Several unsuccessful attempts were made to reduce the

double bond in the ester IXb, some of which have been summarised in Table 3. The details of a typical experiment follow: the unsaturated ester (IXb; 3.26 g, .01 mole) was dissolved in A.R. grade glacial acetic acid (250 ml) and was transferred to a Parr high pressure reaction autoclave*. Adams platinum oxide catalyst (300 mg) was added and the autoclave closed. The reaction vessel was flushed with hydrogen and then filled with hydrogen till the gauge indicated the inside pressure around 750 p.s.i. The reaction vessel was heated (electrically) to a temperature of 145 ± 2°C. During heating and thereafterwards the hydrogen pressure inside the vessel was maintained around 820 p.s.i. either by releasing the excess pressure or by introducing more of hydrogen, depending upon the requirements. After attaining the desired conditions the contents of reaction vessel were stirred (28 hr); then cooled down to room temperature and the pressure released. The product was transferred to a R.B. flask and the autoclave thoroughly rinsed with acetic acid. The catalyst was filtered off and the filterate was concentrated (~ 10 ml) in vacuo. Water (50 ml) was added to the residue, which was then extracted with ether (4 x 50 ml) and the combined ether

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*Supplied by Parr Instrument Co., Inc., Molina, Illinois, U.S.A.

extract was washed free of acid with sodium bicarbonate solution and dried. Removal of solvent left a liquid (3.1 g), which was distilled; b.p. 139-42°/0.3 mm, n_D^{27} 1.4740, yield 2.88 g (88% by weight); UV spectrum: λ_{max} 222 mμ, ε 7487.

Ethyl 2-carbethoxy-2-(α-methylpropionate)-5-methyl-cyclopentyl-acetate (X)

Preparation of catalyst. Rhodium chloride (1.0 g; Fischer Scientific Company, U.S.A.), chloroplatinic acid (0.52 g; Johnson and Matthey, London) and analytical grade sodium nitrate (20 g; E.Merck, Germany) were mixed in a 100 ml pyrex beaker. Water (5 ml) was added to it and mixed well with a clean glass rod to an almost homogeneous mass. The contents of beaker were first heated slowly with a free flame to dryness and then heated strongly (about 1-1/2" high flame of a burner) when the fusion started. Heating was continued at this temperature till there was practically no more evolution of fumes; heating was continued for an additional 20 min. The product was allowed to cool and the catalyst isolated and dried as usual[60]: pale brown powder, yield 0.75 g.

Hydrogenation. The unsaturated ester (IXb; 2.45 g, .0075 mole) was hydrogenated at room temperature (27°) and pressure (710 mm) in glacial acetic acid (50 ml) over pre-reduced rhodium platinum (3:1) oxide catalyst. The hydrogen uptake came to close after absorption of 194 ml of hydrogen (0.99 mole

equivalent of gas) in 10 hr. The catalyst was filtered off and most of the acetic acid from the filterate was removed under suction (water pump) on a steam bath. Water (30 ml) was added to the residue and the organic material extracted with ether (4 x 25 ml). The combined ether extracts were washed free of acetic acid and dried. Removal of solvent gave a mobile liquid which was distilled; b.p. 143-45°/0.6 mm, n_D^{30} 1.0842, d_4^{30} 1.0842, MR_D 83.03 (Calculated for X: MR_D 83.49); yield 2.35 g (35%). (Found: C, 61.98; H, 8.82. $C_{17}H_{28}O_6$ requires: C, 62.2; H, 8.6%); IR spectrum (Fig.6).

2,6-Dimethyl-3-oxo-7-carbomethoxy-bicyclo [0,3,3] octane (XI).

The above saturated ester (X; 5.43, .016 mole) was taken up in dry benzene (50 ml) and 50% sodium hydride (2.3 g, 0.48 mole) was added to it. The reaction was started by adding a few drops of anhydrous ethanol followed by heating on a steam bath; a brisk reaction had set in with the evolution of hydrogen. When the evolution of gas had ceased, the contents were heated (water bath) under reflux (6 hr) in the atmosphere of hydrogen (evolved). The reaction mixture was worked up as usual, dried and solvent removed. The residue so obtained was taken up in acetic acid (25 ml) and hydrochloric acid (50 ml) diluted with water (25 ml) was added in one lot, and the product refluxed for 3 hr in the atmosphere of evolved carbon dioxide. Most of the acids were

removed in vacuo on a steam bath, water (20 ml) was added to the residue and the reaction mixture was extracted with ether (3 x 50 ml). The combined ether extracts were washed with 5% aqueous sodium hydroxide (5 x 10 ml), water (2 x 10 ml) and dried. Solvent was removed and the product distilled to give a mobile liquid; b.p. 140-45°/0.5 mm, yield 0.63 g (8.6% based on X).

All the basic extracts were combined together, neutralised with dilute hydrochloric acid under external cooling (ice-salt) and extracted with ether (5 x 20 ml). The combined ether layer was dried (Na_2SO_4) and treated with a slight excess of ethereal solution of diazomethane. The excess diazomethane and ether were removed in vacuo (water pump) and the residue left behind was fractionated:

Fr.No.	b.p./mm	n_D^{30}	$FeCl_3$ test	Yield	
				g	%
1	96-105°/0.5 mostly 96-97°/0.5	1.4660	-ve	1.40	40
2	105-130°/0.5 mostly 130°/0.5	1.4664	-ve	1.42	30*

*Yield based on trimethyl ester of X.

Fr. 1 constituted the desired compound.

Semicarbazone from fraction 1: Semicarbazide hydrochloride (1.5 g) was dissolved in minimum amount of water and diluted with pyridine (1.4 ml); to this the above fraction 1 (1.4 g)

was added and the mixture diluted with alcohol till just homogeneous. The mixture was left overnight and the semicarabazone, so formed, was filtered off, washed with a little alcohol and dried; m.p. 172-76° dec., yield 1.15 g (71%).

2.19 g of above crude semicarbazone was crystallised from ethanol; m.p. 176-78° dec., yield 1.88 g (85%). (Found: N, 15.7. $C_{13}H_{21}O_3N_3$ requires: N, 15.53%).

Regeneration of Keto-ester (XI) from semicarbazone. The crystallised semicarbazone (1.85 g) was powdered and mixed intimately with powdered oxalic acid (3.6 g). The mixture was placed in a flask fitted with a reflux condenser and an efficient stirrer, and was covered with toluene (35 ml) and water (20ml). The contents of the flask were heated (oil-bath) under reflux and stirring for 3 hr and then allowed to attain room temperature. The two layers were separated and worked up as usual. The solvent was removed and product distilled to give pure keto-ester XI; b.p. 94°/0.6 mm, n_D^{30} 1.4630, yield .896 g (91%). (Found: C, 68.25; H, 8.59. $C_{12}H_{18}O_3$ requires: C, 68.5; H, 8.57%); IR spectrum (Fig.8); PMR spectrum (Fig.9). GLC (Perkin-Elmer) indicated one peak on different columns: (i) Column, 20% diethylene glycol on celite; column length, 2 metre; temperature 200°; gas pressure, 35 p.s.i.; retention time, 3 min 52 sec. (ii) Column 20% Carbowax 1500 on celite; column length, 2 metre; temperature 200°; gas pressure, 25 p.s.i.; retention time, 7 min. 36 sec.

2,2,6-Trimethyl-3-oxo-1-carbomethoxy-bicyclo [0,2,3]octane (XII)

Preparation of trityl sodium[61]. About 2% (W/W) sodium amalgam was prepared as following.

Sodium (1.2 g) was cut into small pieces of approximate size 2 mm x 2 mm. One such piece of sodium was hooked into a sharpened edge of a glass rod and dipped into distilled mercury (60 g). The flask was swirled gently till the sodium piece completely dissolved in mercury. After this the procedure described above was repeated with remaining pieces of sodium. During the addition of sodium pieces care was taken not to expose the sodium amalgam to atmospheric moisture as far as was practicable.

Triphenyl chloromethane (5 g) was taken in dry ether (100 ml) in a R.B. flask fitted with a decantation device. The air of the flask was replaced with dry nitrogen and the above 2% sodium amalgam was added quickly in one lot to this ethereal solution. The reaction mixture was chilled (ice-salt), filled with fresh dry nitrogen and shaken manually. After 10 min. a faint red colour, indicating the formation of trityl sodium, appeared. As the reaction was exothermic the inside temperature was maintained in the vicinity of 5°. Manual shaking was continued for one hour more; after which there was no further deepening of red colour. 7 ml of this red solution was added to water (10 ml) and the alkali formed was estimated by titrating it against .2N oxalic acid solution. Strength of trityl sodium was found to be .13N.

Caution. Trityl sodium is extremely reactive and reacts instantaneously with moisture, air, oxygen and carbondioxide even during transfers. Therefore, all reactions with this reagent, should be performed under strict anhydrous conditions in the inert atmosphere of nitrogen and the transfer of this reagent should be made quickly to avoid undesired exposure. For small scale addition a nitrogen gas flushed hypodermic syringe should be used.

Methylation. To a solution of keto-ester (XI; 330 mg, 1.57 m.mole) in dry ether (10 ml) was added the above solution of trityl sodium (20 ml, 2.6 m.mole) slowly under brisk stirring (magnetic) in the atmosphere of dry nitrogen. The reaction mixture was stirred for 1 hr, when a faint red colour, indicating the presence of slight excess of reagent, persisted*. At this stage methyl iodide (3 ml) was added in one lot and stirring continued for 18 hr at room temperature (27°). Excess of methyl iodide and solvent were removed (under suction) at room temperature, water (10 ml) added to the residue and extracted with ether (5 x 15 ml). The combined ether extracts were washed with water (2 x 10 ml)

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*The persistence of red colour is the necessary requirement of this reaction which marks the complete enolisation. It was required to add 1 m.mole of the trityl sodium in excess to achieve this condition. This might be, perhaps, due to the fact that part of reagent got attacked during transfer, even though all the care was taken to avoid exposure.

and dried. Removal of solvent furnished a product (1.32 g) which was chromatographed over alumina gr.II (15 g, 20 cm x 1 cm).

Chromatogram

Fr.No.	Eluent	Volume	Wt.of compd.(g)	Remarks.
1	Pet.ether	1 x 50 ml	0.825	Discarded.
2	"	4 x 25 ml	0.077	"
3	"	2 x 25 ml	0.028	Contains required compd.
4	Benzene-pet.ether (1:1)	1 x 25 ml	0.217	"
5	"	2 x 25 ml	0.037	"
6	2% MeOH in C_6H_6.	2 x 25 ml	0.023	Discarded.
7	"	2 x 25 ml	0.041	"

Fractions 3 to 5 were combined together and distilled (bath) at a temperature below 150° at 1 mm. The mobile distillate was redistilled to give pure keto-ester XII; b.p.(bath) 108-13°/ 0.5 mm, yield 187 mg (53%). (Found: C, 69.61; H, 8.84. $C_{12}H_{20}O_3$ requires: C, 69.61; H, 8.92%); IR spectrum: (Fig.10); PMR spectrum: (Fig.11); GLC (Column, 20% diethylene glycol polysuccinate on celite; length, 2 metre; temp. 200°; gas pressure, 25 p.s.i.) exhibited single peak (retention time 2 min. 54 sec.).

Isolation of patchouli alcohol (I)

Patchouli oil (1030 g; a product of Sumatra supplied by T.A. Hye, Penang, Malaya) was fractionated through a 30 cm long Vigreux column and following fractions were collected:

Fr.No.	b.p./mm	Yield	
		g	%
1	115-40°/8	595	57.7
2	127-34°/2.5	15	1.4
3	136-40°/2.5	234	22.7
4	143-47°/3	111	10.7
5	Undistillable residue.		7.2

Fractions 3 and 4 solidified on keeping at -15° for 48 hr. The two fractions (3 and 4) were mixed and crystallised from pet. ether at -15° to give patchouli alcohol (95 g), m.p. 55-56°. The mother liquors were combined with fraction 2, concentrated, and chilled at -15° to give another crop (20 g) of patchouli alcohol. Total yield 115 g (11%).

Patchoulenes (II)[2]

Patchouli alcohol (6.12 g, .027 mole) was taken up in dry pyridine (100 ml) in a 250 ml R.B. flask fitted with a reflux condenser carrying a calcium chloride guard tube. Freshly distilled phosphorus oxychloride (70 ml) was added slowly and cautiously from the top of the condenser and the contents were heated (isomantle) under reflux for 6 hr. The

purple coloured reaction mixture was allowed to attain room temperature and percolated slowly through a 15 cm column of crushed ice (more ice added when necessary to avoid over heating). The material so collected was extracted with ether (4 x 60 ml), washed with 10% hydrochloric acid (till washings were acidic), water (1 x 50 ml), 5% aqueous solution of sodium bicarbonate (2 x 50 ml) and dried. Removal of solvent (under suction of a water pump) furnished a mobile oil (5.2 g, 91%) which was distilled through a short (6 cm) Vigreux column to give 11; b.p. 103-105°/2.5 mm (Lit.[2]; b.p. 141-42°/17 mm), n_D^{30} 1.5034, yield 4.83 g (84%); GLC (Column, 20% carbowax 1500 on celite; column length, 2 metre; temperature 160°; gas pressure 15 p.s.i.) exhibited four peaks. γ-patchoulene (peak No.1; retention time 4 min. 32 sec.; 13%), α-patchoulene (peak No.3; retention time 8 min; 69%) and β-patchoulenes (peak No.2 and 4; retention times 7 min. and 10 min. 50 sec. respectively; 16%).

Dimethyl bis-nor-patchouli-dicarboxylate (12,IVb)

(a) Büchi's method. To a suspension of patchoulenes (8.4 g, .041 mole), obtained above, in water (5 ml) and acetone (distilled over $KMnO_4$; 20 ml) powdered potassium permanganate (10.5 g, .066 mole) was added, in small lots, under brisk mechanical stirring. Stirring was continued for 2 hr and then the mixture was left overnight (15 hr) at room temp. The reaction mixture was diluted with water (25 ml) and saturated with sulphur dioxide gas (until practically colourless). It was then thoroughly extracted with ether (5 x 25 ml)

and the combined ether extracts were washed with 5% aqueous sodium bicarbonate (3 x 25 ml). The basic extracts were neutralised with cold dilute hydrochloric acid and the organic acid liberated was extracted with ether (4 x 20 ml). This ethereal solution was washed with water (2 x 10 ml) and dried. Removal of solvent furnished a yellow gum (1.0 g).

The ether extract containing the neutral product of oxidation on drying and solvent removal gave a viscous yellow oil (7.3 g) which deposited crystals on prolonged storage in a refrigerator.

Water (4 ml) was added to the above gummy acid (1.0 g) and heated under mild reflux in an oil bath (133 ± 3°). Nitric acid (6 ml) was added to it slowly and cautiously from the top of the condenser. Heating was continued at this temperature (1 hr); the contents of the flask were then cooled down to room temperature and diluted with water (10 ml). The organic material was extracted with ether (5 x 20 ml), the ether extract washed with small portions of water (5 x 5 ml) till neutral and dried. Removal of solvent (under suction) gave a gum (0.92 g; 10.9% based on II). It was dissolved in formic acid (3 ml) and stored in a refrigerator. No crystalline bis-nor-patchouli-dicarboxylic acid (XXIVa) separated out even on prolonged (15 days) storing. The formic acid was then stripped off in vacuo and the gum esterified with an ethereal solution of diazomethane. Drying and solvent removal gave a crude mixture (0.81 g) which was chromatographed

over alumina grade I (13 g, 12 cm x 1.4 cm).

Chromatogram

Fr.No.	Eluent	Vol.(ml)	Wt.of compd. (mg).	Remarks.
1	Pet. ether	200	5	
2	Benzene	450	127	Further investigated.
3	0.5% MeOH in C_6H_6.	150	13	
4	"	250	130	

Fraction 2 was distilled at 1 mm. GLC (Fig.12) indicated the presence of at least four components, out of which the desired diester XXIVb (peak No.3) constituted ca.35%.

(b) Present method. Patchoulenes (5.1 g, .025 mole), N-bromosuccinimide (4.9 g, .027 mole), benzoyl peroxide (250 mg) and dry carbon tetrachloride were taken in a 250 ml R.B. flask and heated (water bath) under reflux for 2 hr (anhydrous conditions). The insoluble succinimide was filtered off and washed well with carbon tetrachloride. Solvent was removed (under suction) from the filtrate and the brown residue obtained was dissolved in dioxan (80 ml). Water (20 ml) was added to it followed by lithium carbonate (0.92 g, .012 mole) and the mixture refluxed on a steam bath for 18 hr. The unreacted lithium carbonate was filtered off, washed with water, ether and dried. It weighed 127 mg (1.5 mmole

The filterate was diluted with water (50 ml) and extracted with ether (3 x 50 ml). The combined ether extracts were washed with water (2 x 30 ml) and dried. Removal of solvent (under suction) left behind a brown residue which was distilled; b.p. 88-120°/0.6 to 0.8 mm, yield 4.57 g.

The above product (4.57 g) was suspended in aqueous acetone (60 ml; 5 parts acetone and 1 part water) in a 250 ml three-necked R.B. flask fitted with a reflux condenser, an efficient stirrer and a stopper. Powdered potassium permanganate (13.4 g, .084 mole) was added to it in small lots of about 1 g each, under brisk stirring, in the course of 1 hr. Stirring was continued for 3 hr and then the reaction mixture was left overnight (16 hr) at room temperature (26°). The precipitated MnO_2 was filtered off and washed successively with water (2 x 25 ml), ether (2 x 25 ml) and 10% aqueous sodium carbonate (1 x 15 ml). The combined filterates were made acidic with dilute hydrochloric acid; two layers separated and the lower aqueous layer extracted with ether (2 x 25 ml). The combined ether layers were extracted with 10% aqueous sodium carbonate (3 x 15 ml) and the combined basic extracts were neutralised with dilute hydrochloric acid. The organic acidic material, so liberated, was extracted with ether (4 x 25 ml), washed with water (2 x 10 ml) and dried. Removal of solvent furnished a gum (2 .54 g).

Work up of the neutral portion gave a yellow oil (1.99 g) which was not investigated further.

(44) HNO_3 oxidation of acid: Water (6 ml) was added to the above gummy acid (2.54 g) and heated under reflux in an oil bath (138 ± 2°). Nitric acid (15 ml) was added slowly and cautiously (from the top of condenser) to this refluxing mixture. After 30 min. of reflux, more nitric acid (3 ml), was added and the refluxing continued for another 30 min. The reaction mixture was allowed to attain room temperature and poured into cold water (50 ml). The milky suspension so formed was extracted with ether (4 x 25 ml) and the combined ether extracts were washed with small portions (~ 7 ml) of water until the washings were almost neutral. The ether solution was dried and esterified with a slight excess of ethereal solution of diazomethane and processed as usual. Removal of solvent furnished a mobile liquid (1.84 g) which was distilled; b.p. 150-172°/4 mm, yield 1.3 g. GLC (Fig. 13) of the distilled material indicated the presence of four components out of which the required compound (peak No.3) constitutes the major (60%) component. The required dimethyl bis-nor-patchouli-dicarboxylate (XXIVb) was isolated from this mixture by preparative GLC.

The above mixture (1.25 g) was diluted with acetone (1.5 ml) and was injected (3 injections) into a "preparative column"* at 200°C (N_2, 25 lbs/sq.in., R.R.1) and only two

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*Supplied by Perkin-Elmer Corporation, Norwalk, Connecticut, U.S.A. Made up of aluminium tubing, length 9 ft (6 x 1-1/2 ft tubes), diameter 1 inch, column packed with 20% diethylene glycol polysuccinate on Chromosorb W.

fractions, corresponding to peak No.3 and 4 (Fig.13), were collected and were designated as 'A' and 'B'. A, 605 mg (48.4%; by weight on mixture) and B, 266 mg (20.8%).

Fraction A was distilled to give the desired diester XXIVb; b.p. 121°/2 mm, n_D^{30} 1.4750, yield 560 mg (7.4%; by weight on II). (Found: C, 67.11; H, 9.16. $C_{15}H_{24}O_4$ requires: C, 67.13; H, 9.02%). IR spectrum (Fig.15); PMR spectrum (Fig.16); GLC (Fig.13; block A).

Dimethyl nor-patchouli-dicarboxylate (XXVb)

A solution of patchoulenes (8.1 g, .04 mole) in purified ethyl acetate (100 ml) was ozonised at -10° (ice-salt) with a current of ozonised oxygen (output of ozone ~ 80 mg/hr) till no more of ozone was absorbed (10 hr; potassium iodide-acetic acid test). The solvent was removed by suction at a temperature below 30°. The residual pale yellow coloured ozonide was taken up in acetic acid (30 ml), mixed with an 17% aqueous solution of hydrogen peroxide (25 ml), and left at room temperature for 90 min. The mixture was then heated (60 ± 2°) for one hour in a temperature controlled waterbath and finally for 2 hr on a steam bath. The reaction mixture was allowed to attain room temperature, water (100 ml) added and extracted thoroughly with ether (5 x 40 ml). All combined ether layers were extracted with 10% aqueous sodium carbonate (3 x 25 ml), washed with water (2 x 25 ml) and dried. Solvent removal (under suction) furnished a gum (3.1 g).

The basic extracts were combined together, acidified with 10% hydrochloric acid (under ice-salt cooling) and the liberated organic material was taken up in ether (3 x 50 ml), washed with water (1 x 25 ml) and dried. Removal of solvent in vacuo furnished a gum which was suspended in water (10 ml) and heated under reflux in an oil bath (125°). Nitric acid (25 ml) was added to it slowly and cautiously from the top of the condenser and refluxing continued for 15 min. More of nitric acid (5 ml) was added at this stage and refluxing continued for another 1 hr. The product was cooled down to room temperature, poured into cold water (100 ml) and extracted with ether. The combined ether extract was washed with water (4 x 10 ml) and dried. Solvent was stripped off under suction to give a gum (2.2 g). It was dissolved in formic acid (5 ml) and stored in the freezer of a refrigerator for two days (48 hr). The crystals so separated were filtered off, washed with a little of formic acid and dried; m.p. 238-42°, yield 130 mg. Recrystallisation from ethanol-petrol mixture yielded pure nor-patchouli dicarboxylic acid (XXVa); m.p. 242-44°, yield 140 mg. (Found: C, 65.91; H, 8.86. $C_{14}H_{22}O_4$ requires: C, 66.14; H, 8.66%). Mixed m.p. with an authentic sample of bis-nor-patchouli dicarboxylic acid (XXIVa) is 190-97°; IR spectrum (Fig.18).

80 mg of above diacid was converted to its dimethyl ester (diazomethane) and distilled to give the corresponding dimethyl nor-patchoulidicarboxylate; yield 73 mg. (Found:

C, 68.14; H, 9.39. $C_{16}H_{26}O_4$ requires: C, 68.05; H, 9.38%); PMR spectrum (Fig.17); GLC (column, 20% diethylene glycol polysuccinate on chromosorb W, length 5 ft; temperature 200°; flow, 50 ml/min; retention time, 7 min. 52 sec.) exhibited a single peak of +97% purity.

Barbier-Wieland degradation of dimethyl bis-nor-patchouli-dicarboxylate (XXIVb).

A solution of phenyl magnesium-bromide was prepared from magnesium (.52 g, .021 mole) and bromobenzene (3.08 g, .02 mole) in dry ether (20 ml) under nitrogen. On titration against 0.1N H_2SO_4 it was found to contain 180 mg of phenyl magnesium bromide per ml. To the stirred (magnetic) solution of phenyl magnesium bromide (5.3 ml, 5.2 m.mole) in dry ether (10 ml) was added a solution of dimethyl bis-nor-patchouli dicarboxylate (500 mg, 1.87 m.mole) in dry ether (5 ml) under the inert atmosphere of nitrogen. The reaction mixture was stirred (2-1/2 hr) under gentle reflux, cooled down in an ice-salt bath and the complex broken by adding an aqueous solution of ammonium chloride (5 g of NH_4Cl in 15 ml of H_2O). The ether layer was separated and the aqueous layer extracted once with ether. The combined ether extracts were washed with water (2 x 10 ml) and dried. Removal of solvent in vacuo furnished an oil which was taken up in acetic acid (2.5 ml) and acetic anhydride (1.5 ml) and refluxed (2 hr) in an oil bath. Removal of acetic acid and acetic anhydride gave

a product (800 mg) which was chromatographed over alumina grade I (30 g, 19 cm x 1.6 cm).

Chromatogram

Fr.No.	Eluent	Vol.(ml)	Wt.of compd.(mg)	Remarks.
1	Pet.ether 60-80	150	7.0	Fr.1 to 4 rejected.
2	"	50	6.0	
3	Benzene-pet.ether (1:1)	50	69.0	
4	"	50	5.3	
5	"	50	29.3	Contains desired compound.
6	"	50	32.4	"
7	"	75	27.1	"
8	"	75	15.0	"
9	Benzene-pet.ether (7:3)	75	29.0	"
10	"	75	26.3	"
11	"	150	23.0	"
12	"	50	7.0	"
13	Benzene	50	5.0	"
14	"	450	102.0	Discarded.
15	1% MeOH in C_6H_6	200	116.0	"
16	5% MeOH in C_6H_6	500	10.0	"
17	10% aq. Na_2CO_3	50	185.0 (as ester)	Rechromatographed.

Fr.5 to 13 were combined together on the basis of their TLC (5% EtAc in C_6H_6), dissolved in pet. ether (60-80°) and stored in refrigerator (overnight). A white amorphous solid (m.p.142-46°)

separated out and was filtered off. Crystallisation from pet. ether (60-80°) furnished a crystalline solid; m.p. 152-54°, yield 142 mg (20.5%).

An analytical sample, prepared by recrystallisation of the above sample from n-hexane, had m.p. 153-54°, $[\alpha]_D$ +111° (c, 1.3%). (Found: C, 83.75; H, 7.86. $C_{25}H_{28}O_2$ requires: C, 83.33; H, 7.77%). UV spectrum: λ_{max} 227 mμ; ε 10760; IR spectrum: >C=O 1740 cm^{-1}; PMR spectrum (Fig.19).

Rechromatography of fraction 17 over alumina grade I (5 g) furnished more of the above δ-lactone (25 mg; 3.5%).

Ozonolysis of the δ-lactone. A solution of the above δ-lactone (100 mg, .28 m.mole) in acetic acid (30 ml) was ozonised at room temperature (27°) with a current of ozonised oxygen (750 mg/hr, output of a Welsbach Ozoniser, model T 24) for 1 hr and 45 min. The solution was concentrated in vacuo, suspended in water (25 ml) and heated under reflux for 30 min. The organic material was extracted with ether (4 x 25 ml); the ether extract washed with water (2 x 10 ml), 5% aqueous sodium bicarbonate (3 x 10 ml) and dried. Removal of solvent left behind a solid (36 mg) which was crystallised from hexane; m.p. 153-54°, yield 30 mg. No depression in m.p. when mixed with an authentic sample of δ-lactone.

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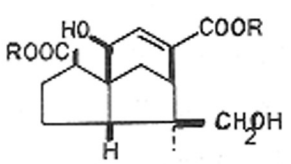
PART II

CORRELATION OF SHELLOLIC ACID WITH CEDRENE

C O N T E N T S

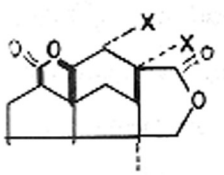
CORRELATION OF SHELLOLIC ACID WITH CEDRENE

Shellolic acid, one of the products of alkaline hydrolysis of shellac, the resin secreted by lac insect Laccifer lacca, was first isolated by Harries and Nagel in 1922[1]. Earlier work[1,2,3] had established shellolic acid as an unsaturated dihydroxy dicarboxylic acid of molecular formula $C_{15}H_{20}O_6$. However, till recently, practically nothing else was known about the structure of shellolic acid and it was only in 1960 that Yates and Field[4], based on sound degradative studies, put forward the structure Ia for shellolic acid. Through a series of standard reactions, supported by IR and PMR spectroscopic data, the relationship between the various functional groups was established. One such striking reaction is the ease with which γ- and δ -lactones



Ia, R=H

Ib, R=CH_3

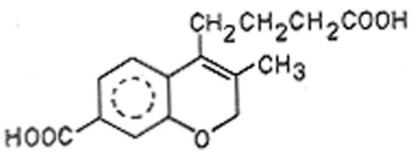


IIa, X=H

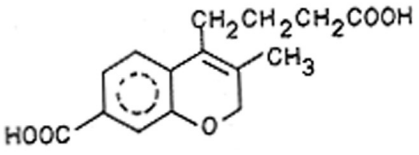
IIb, X=OH

are formed whenever the double bond in shellolic acid is hydrogenated (IIa) or hydroxylated (IIb).

The carbon framework of the acid was deduced from the structure of the diacid (III) obtainable by alkali fusion of shellolic acid; dehydrogenation of III furnished the coumarin derivative (IV) whose structure



III

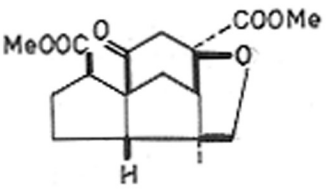


IV

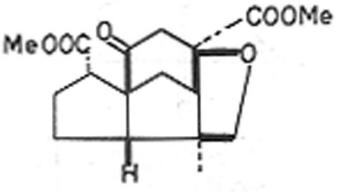
was confirmed by an unambiguous synthesis.

The above structure of shellolic acid has been used by another group of workers[5] for interpreting reactions of shellolic acid carried out by them.

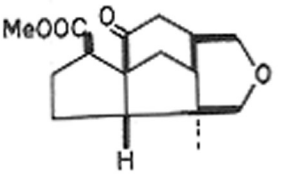
The stereochemistry of shellolic acid, as indicated in Ia, tentatively suggested by Yates and Field[4], has been confirmed by Cookson et al.[6,7]; this involved, besides some degradative studies, a critical analysis of PMR spectra of dimethyl shellolate (Ib) and some of its transformation products. The optical rotatory dispersion of three ketones (V, VI and VII)[6] support the absolute configurations written and hence structure Ia also represents the absolute stereochemistry of shellolic acid.



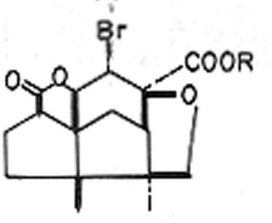
V



VI



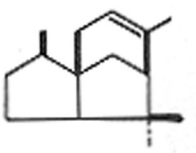
VII



VIII

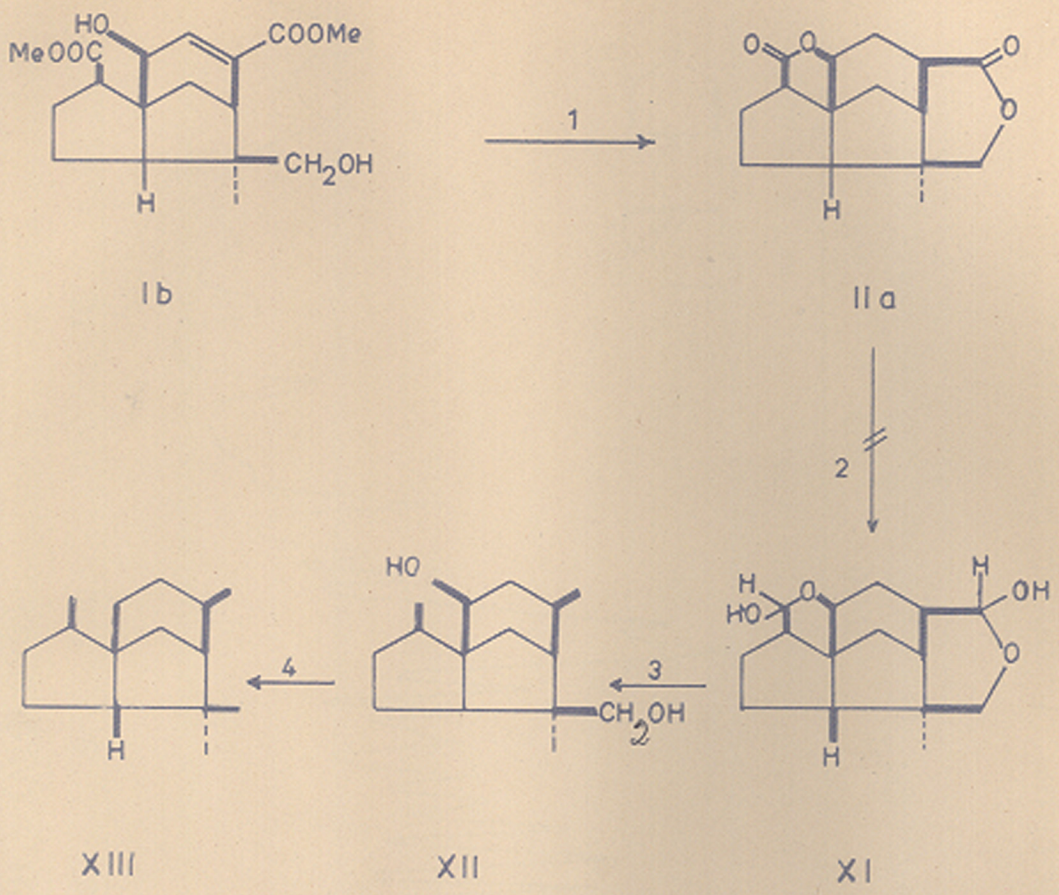
The above conclusions have been confirmed by an X-ray analysis of the bromolactone (VIII)[8].

The above work, thus, conclusively establishes (+)-shellolic acid as a derivative of (-)-cedrene (IX), the structure[9,10,11] and absolute stereochemistry[12] of which have been known for quite sometime. It appeared of interest to effect a direct chemical correlation between



IX

shellolic acid and cedrene, as this would provide a direct chemical proof for the absolute stereochemistry of shellolic acid, which, as can be seen from the above, rests only on



REAGENTS —

1 H_2/PtO_2, AcOH

2 $NaBH_4$

3 WOLFF-KISHNER REDUCTION

4 OXIDATION AND WOLFF-KISHNER REDUCTION

FIG. 1.

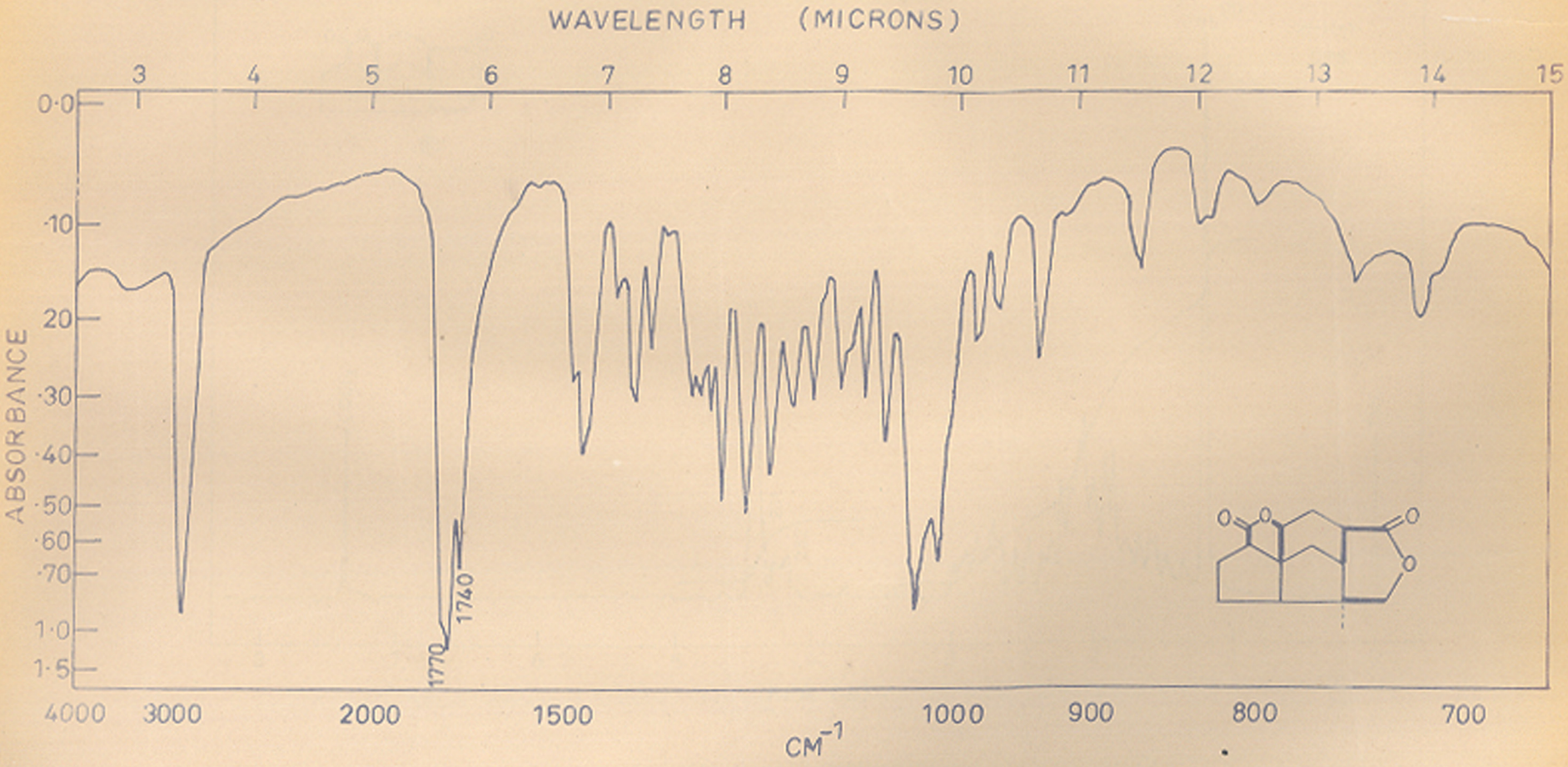


FIG. 4. IR SPECTRUM OF DILACTONE (IIa)

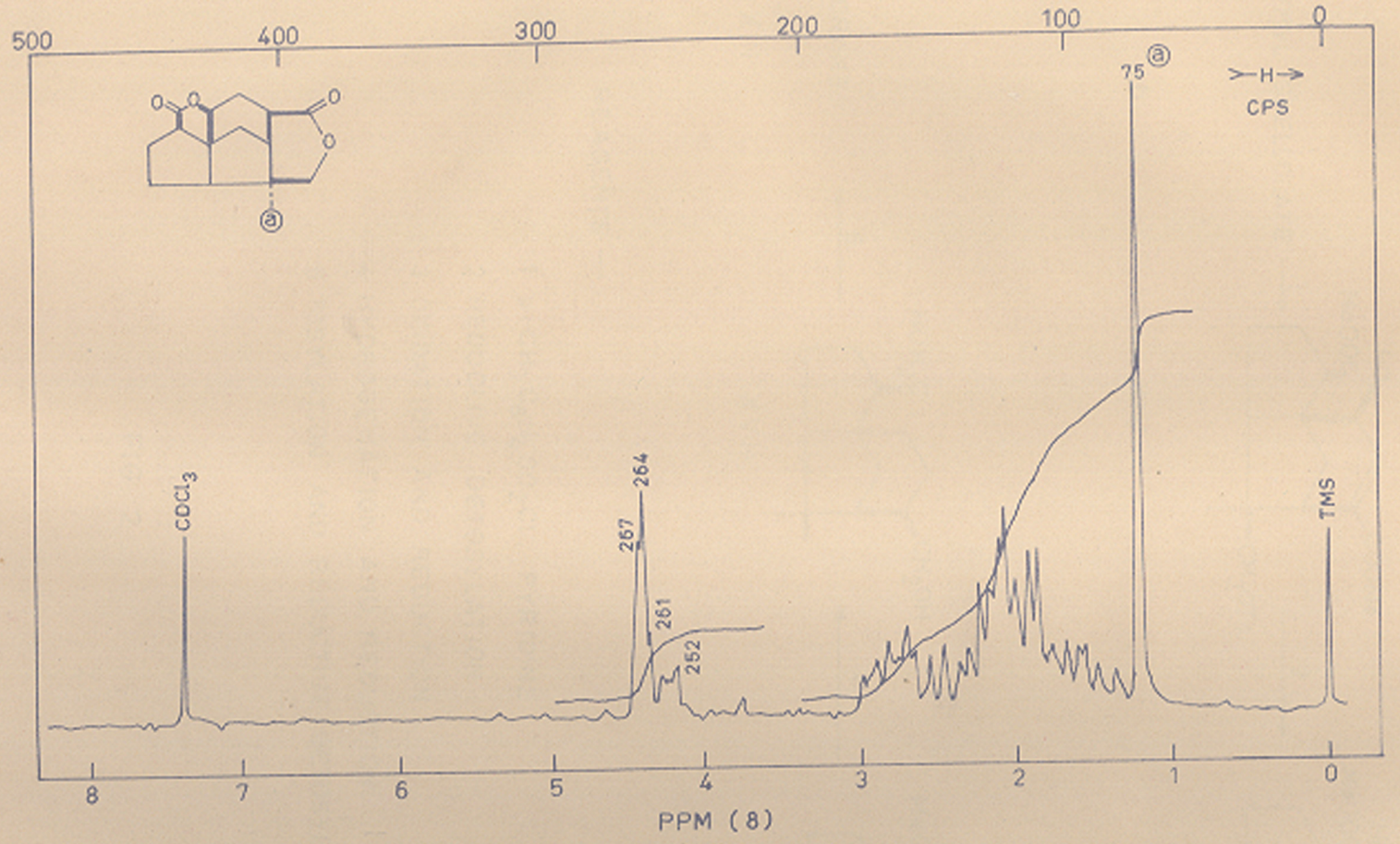
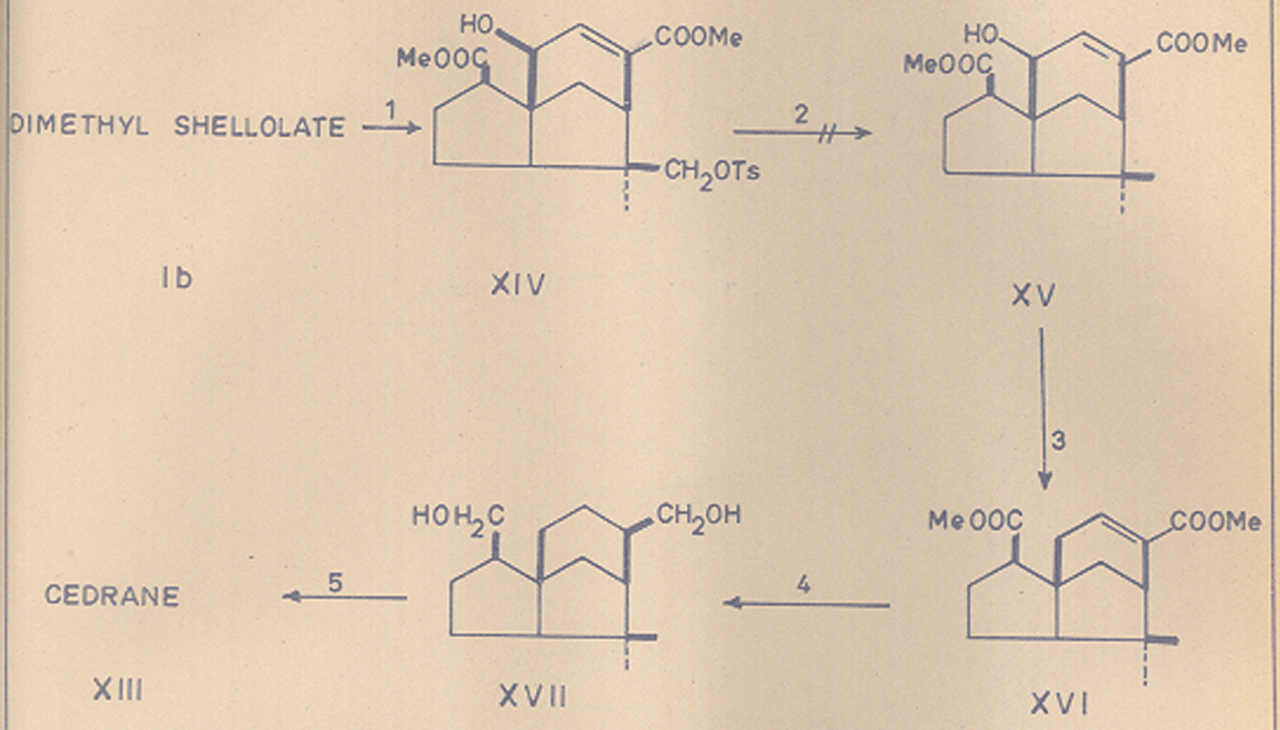


FIG. 5. PMR SPECTRUM OF DILACTONE (IIa)



REAGENTS —

1 p·$CH_3C_6H_4SO_2Cl$, PYRIDINE

2 REDUCLIVE DETOSYLATION

3 OXIDATION AND REDUCTION

4 HYDROGENATION AND REDUCTION

5 TOSYLATION AND REDUCTIVE DETOSYLATION

FIG. 2.

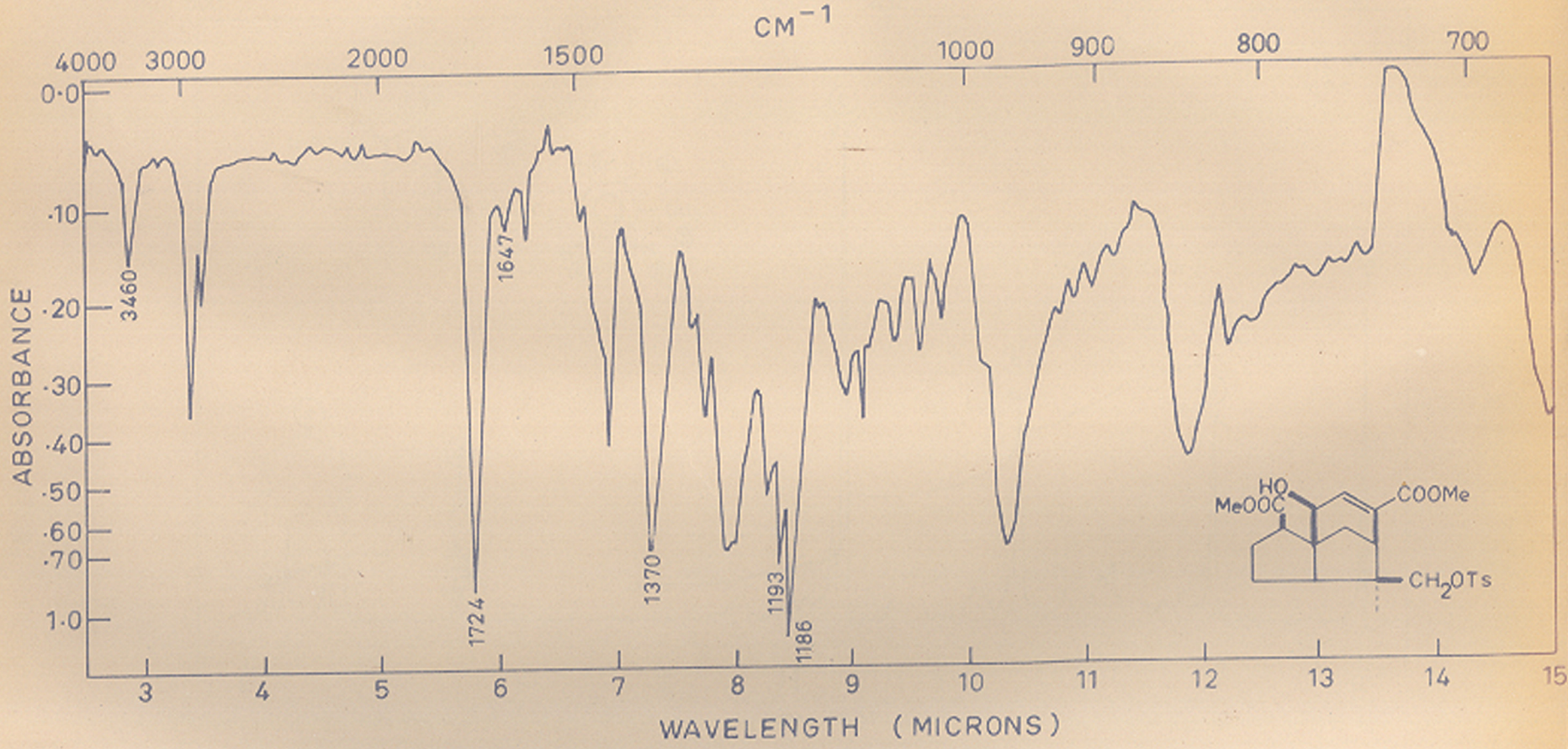


FIG. 6. IR SPECTRUM OF MONOTOSYLATE (XIV)

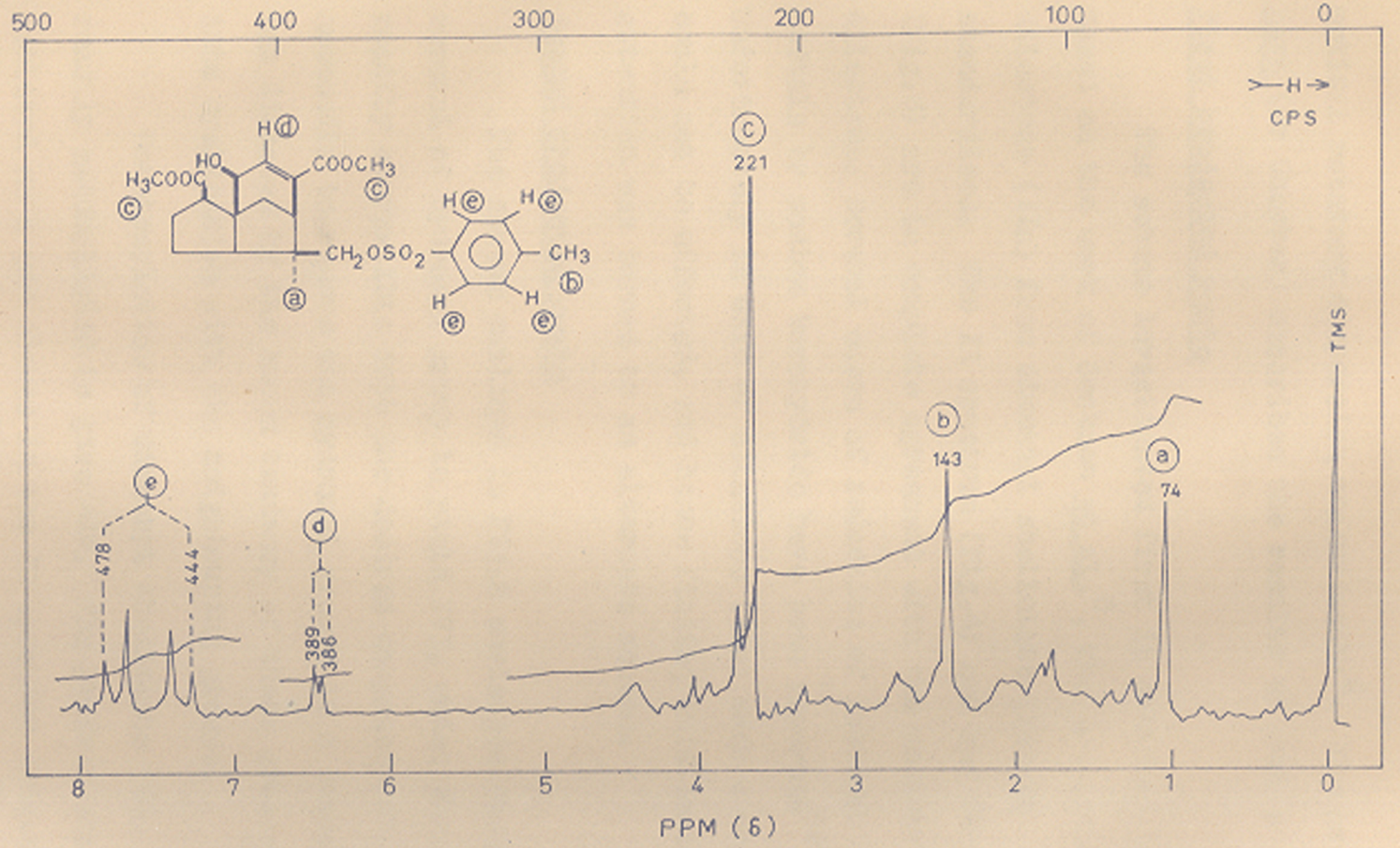


FIG. 7. PMR SPECTRUM OF MONOTOSYLATE (XIV)

optical rotatory dispersion measurements[6]. The present part (or Chapter) describes the results of such a study.

First projected route

The scheme investigated first is outlined in Fig.1. Based on the work of Cookson et al.[6], the preparation of dilactone (IIa) from dimethyl shellolate (Ib) was readily standardised. The IR spectrum (Fig.4) and the PMR spectrum (Fig.5) are in complete agreement with the structure IIa for dilactone. Several cases of reduction of lactones to hemi-acetals by sodium borohydride have been reported[13,14,15]. Unfortunately in case of dilactone (IIa) such a conversion could not be effected, and hence finding this route blocked, attention was turned to an alternate scheme.

Second projected route

The scheme outlined in Fig.2 envisages stepwise removal of hydroxyl group to yield XVI, which should be readily convertible into the desired compound XIII. The necessity to remove the hydroxyl groups in a stepwise manner was dictated by the known tendency of these groups to enter into cyclisation with the neighbouring groups.

Monotosylation of dimethyl shellolate (Ib) could be readily accomplished to give XIV. The product which was isolated as a gum showed in the IR spectrum (Fig.6) bands for: OH 3460 cm^{-1}; OSO_2[17] 1370, 1193, 1186 cm^{-1}; COOMe 1724 cm^{-1} and C=C 1647 cm^{-1}. The structure XIV is further

supported by its PMR spectrum (Fig.7) wherein the proton assignments have been indicated.

Treatment of the monotosylate (XIV) either with sodium iodide in acetic acid[16] or in methyl ethyl ketone[17] led only to the recovery of unchanged tosylate. Next, reductive detosylation, *via* benzyl thioether[18] was investigated. Treatment of monotosylate (XIV) with benzyl mercaptan in dimethyl formamide in presence of metallic sodium at reflux temperature yielded a product which was treated with Raney-nickel (W-2) catalyst without further purification. The IR spectrum of the product, so obtained, indicated the absence of any hydroxyl group, double bond and tosylate functions. Thus, these reaction conditions, appeared to be rather drastic. In a reinvestigation the product from the interaction of monotosylate (XIV) with benzyl mercaptan was analysed by thin layer chromatography. Two major products appeared to have been formed which were separated by careful chromatography. However, spectral characteristics (IR, PMR; vide Experimental) of these compounds, showed the absence of hydroxyl and olefinic bands, and hence it was concluded that the reaction with benzyl mercaptan had taken an unexpected course, and this was not investigated further.

Route III

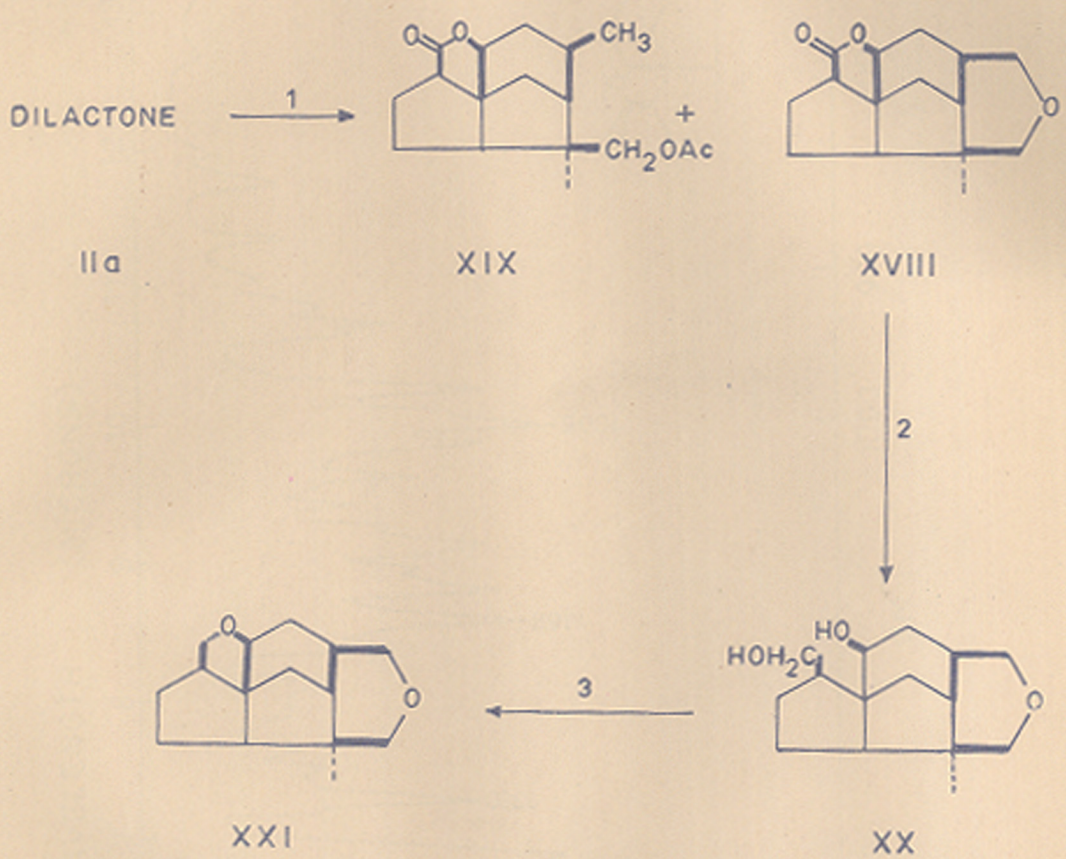
Partial success, in as much as the GLC evidence

for the formation of cedrane can be relied upon, has been achieved by this route.

The central idea in this scheme was the preparation of diether (XXI) which on catalytic deoxygenation[19,20,21] was expected to furnish cedrane (XIII). Catalytic deoxygenation has been claimed to give high conversion of methyl tetrahydrofuran to n-pentane[19] and as a matter of fact it has been claimed[20,21] that the carbon skeleton of ethers (and a variety of other compounds) can be established by this reaction as adapted to GLC. As will be seen in the sequel this reaction proved quite disappointing and only traces of hydrocarbons were obtained.

Conversion of dimethyl shellolate into diether (XXI). The route successfully followed for the preparation of diether (XXI) is shown in Fig.3. Hydrogenation of dilactone (IIa) over platinum oxide in acetic acid in presence of catalytic amounts of perchloric acid[22] ceased after the uptake of 2.4 mole equivalents of hydrogen. TLC of the product indicated the presence of at least three components, two of which appeared to be major. The two major compounds (A and B) were isolated by careful chromatography over silica gel.

Compound A, $C_{15}H_{20}O_2$ (m.p. 90-91°) is clearly a γ-lactone (1775 cm^{-1}) from its IR spectrum (Fig.8). Its PMR spectrum (Fig.9) showed the presence of a quaternary methyl (a 3H singlet at 48 cps), two $-CH_2-O$ groups (a 4H



IIa XIX XVIII

XXI XX

REAGENTS —

1 $H_2/PtO_2.AcOH$ AND $HClO_4$

2 $LiAlH_4$

3 $p-CH_3C_6H_4SO_2Cl$ PYRIDINE

FIG. 3.

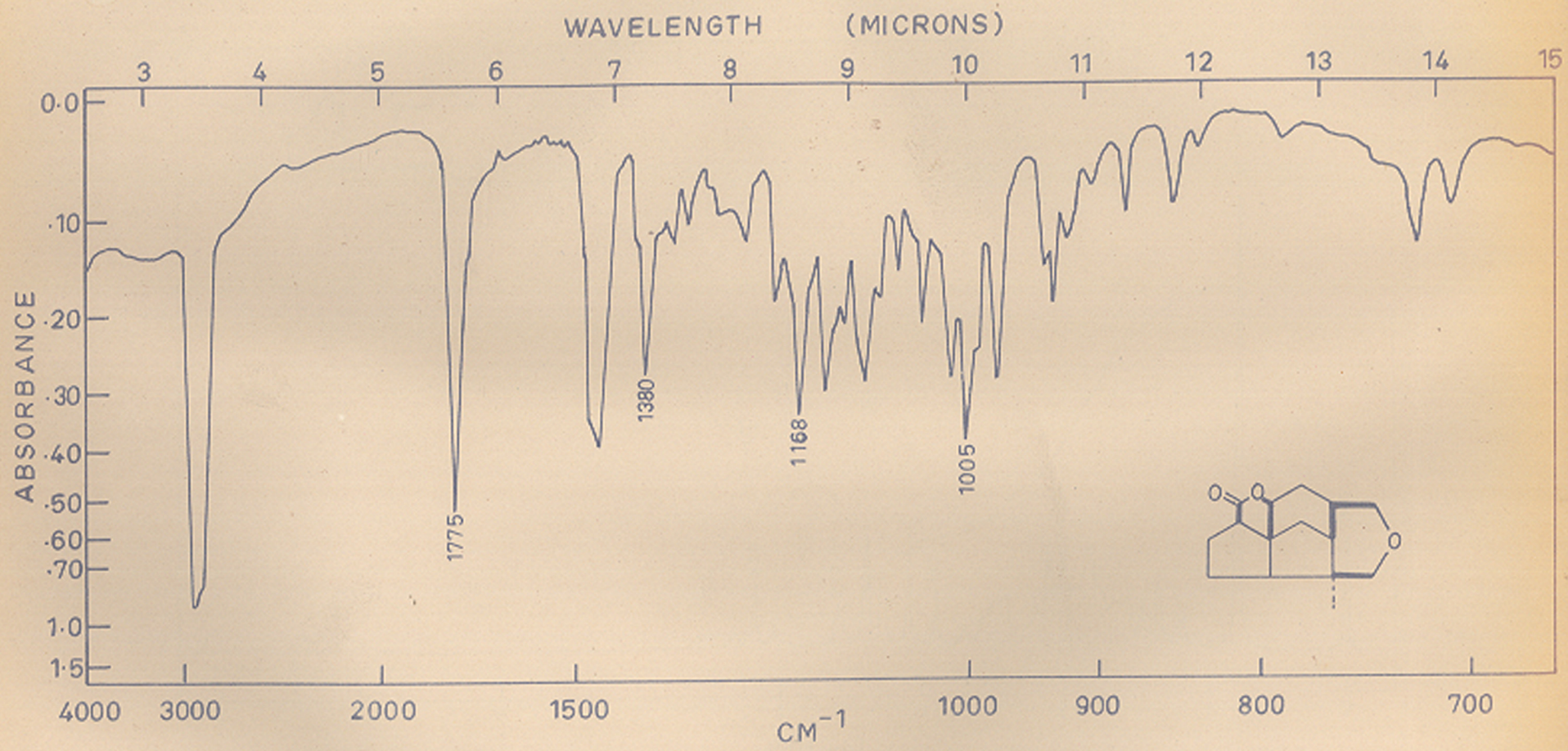


FIG. 8. IR SPECTRUM OF γ-LACTONE ETHER (XVIII).

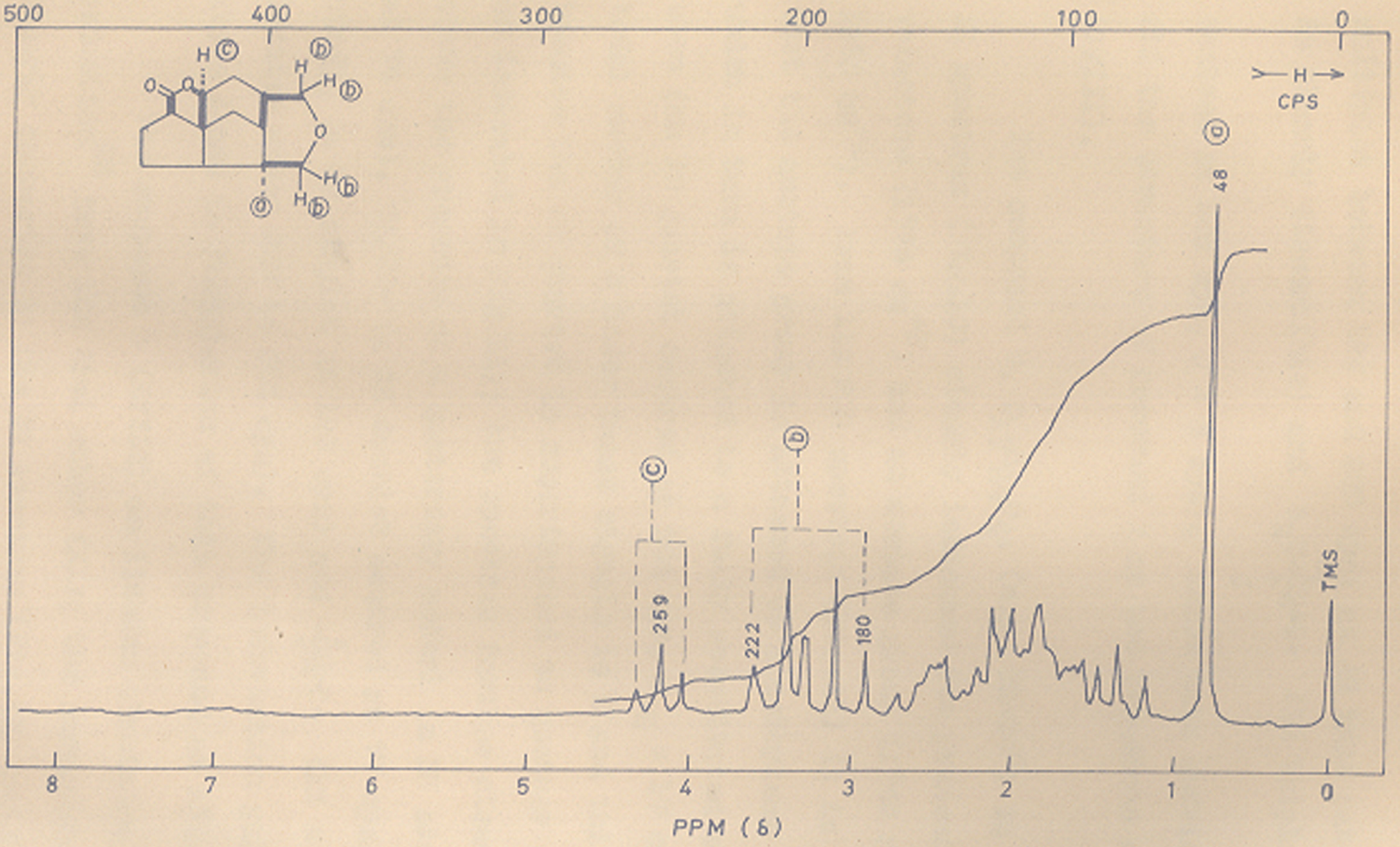


FIG. 9. PMR SPECTRUM OF L γ-LACTONE ETHER (XVIII)

multiplet between 180 and 220 cps; an AB type pattern is clearly discernible) and $H_2C\text{-}\underset{\underset{C}{|}}{CH}\text{-}O\text{-}$ (1H triplet centred at 269 cps, J = 8 cps). These data suffice to fix the structure of compound A as the γ-lactone ether (XVIII).

The compound B, $C_{17}H_{24}O_4$, (m.p. 98-99°) in its IR spectrum (Fig.10) clearly indicated the presence of a γ-lactone (1776 cm^{-1}) and an acetate group (1745 and 1250 cm^{-1}). From its PMR spectrum (Fig.11) it is clear that the acetate group is attached to a methylene carbon which in turn is attached to a fully substituted carbon atom (an AB quartet centred at 244 cps, J_{AB} = 17 cps; the total number of H under these signals is 3 and this is because the AB quartet is superimposed on another signal as indicated in Fig.11); the spectrum further clearly shows the presence of a quaternary methyl (a 3H singlet at 74 cps), CH_3CH- (a 3H doublet centred at 77 cps, J = 6 cps), $OCOCH_3$ (a 3H singlet at 120 cps) and $\text{-}\underset{|}{CH}\text{-}O\text{-}$ (1H multiplet located under 229 to 256 cps). The information gained above leads to formulation of this compound as XIX.

The compound A (XVIII) on lithium aluminium hydride reduction[23] gave the diol ether (XX); the structure is clearly supported by its IR spectrum (Fig.12) and the PMR data (vide Experimental). The diol ether (XX) on treatment with p-toluenesulphonyl chloride in dry pyridine[24,25]

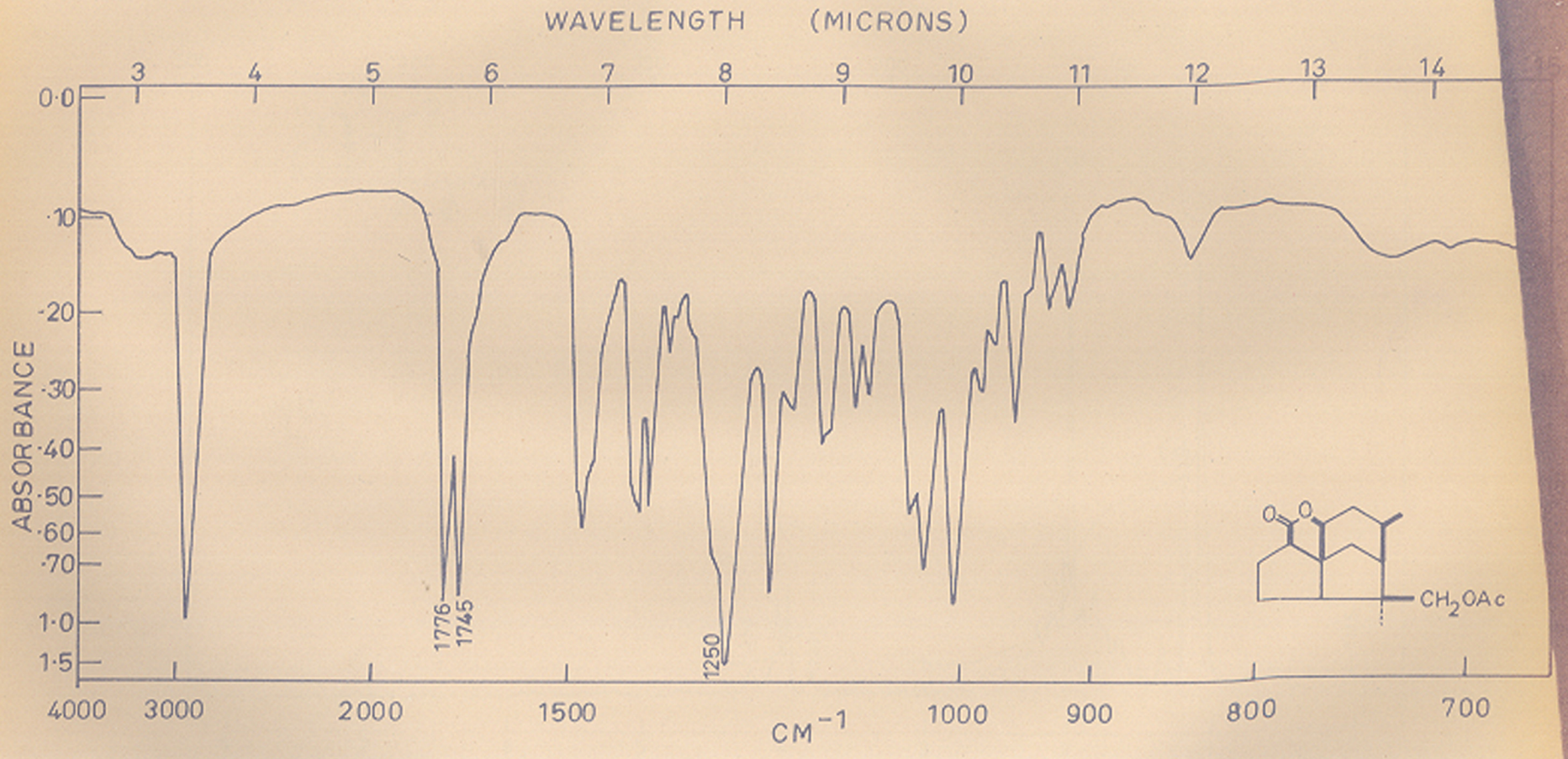


FIG. 10 . IR SPECTRUM OF γ - LACTONE ACETATE (XIX)

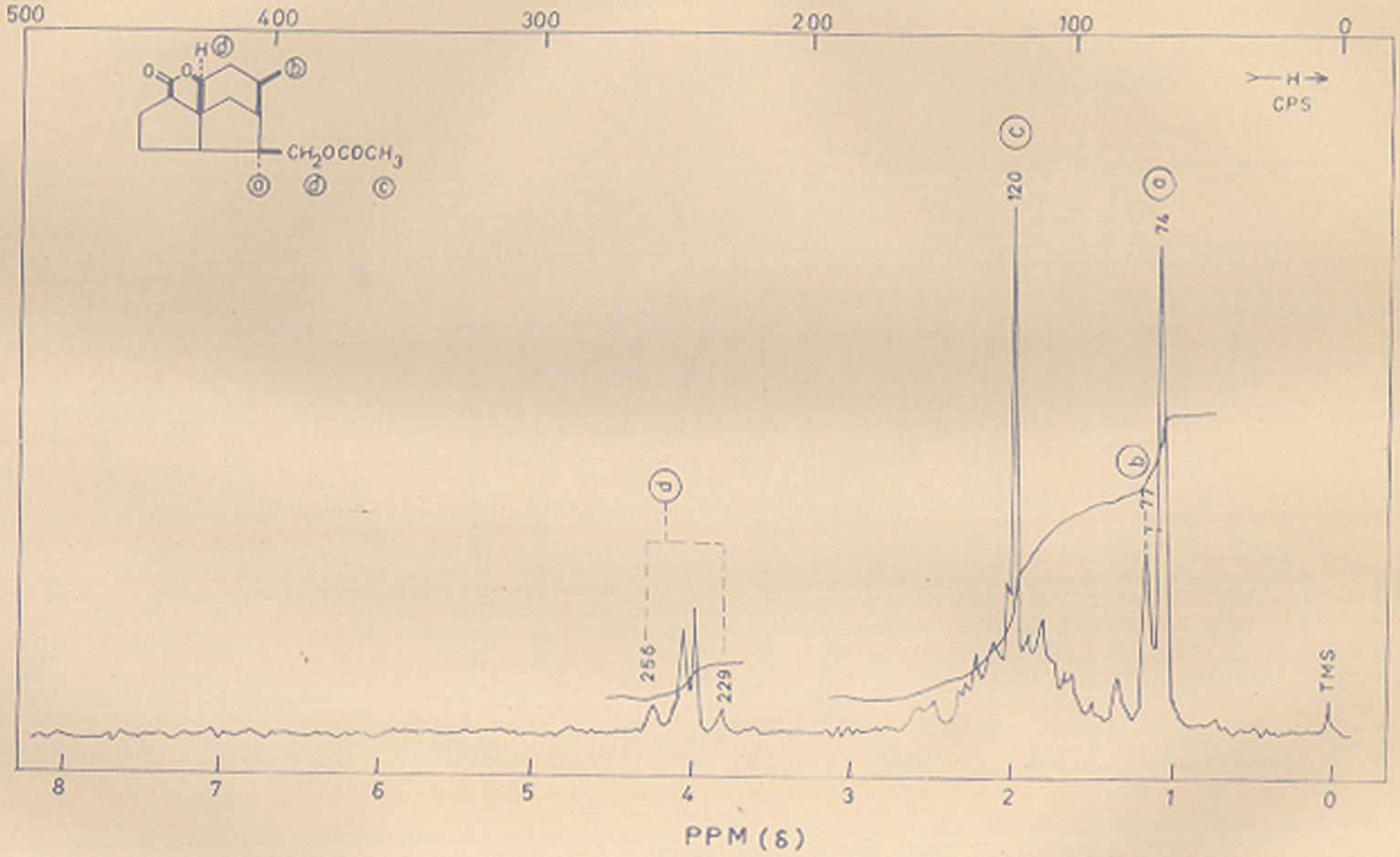


FIG. 11. PMR SPECTRUM OF γ-LACTONE ACETATE (XIX)

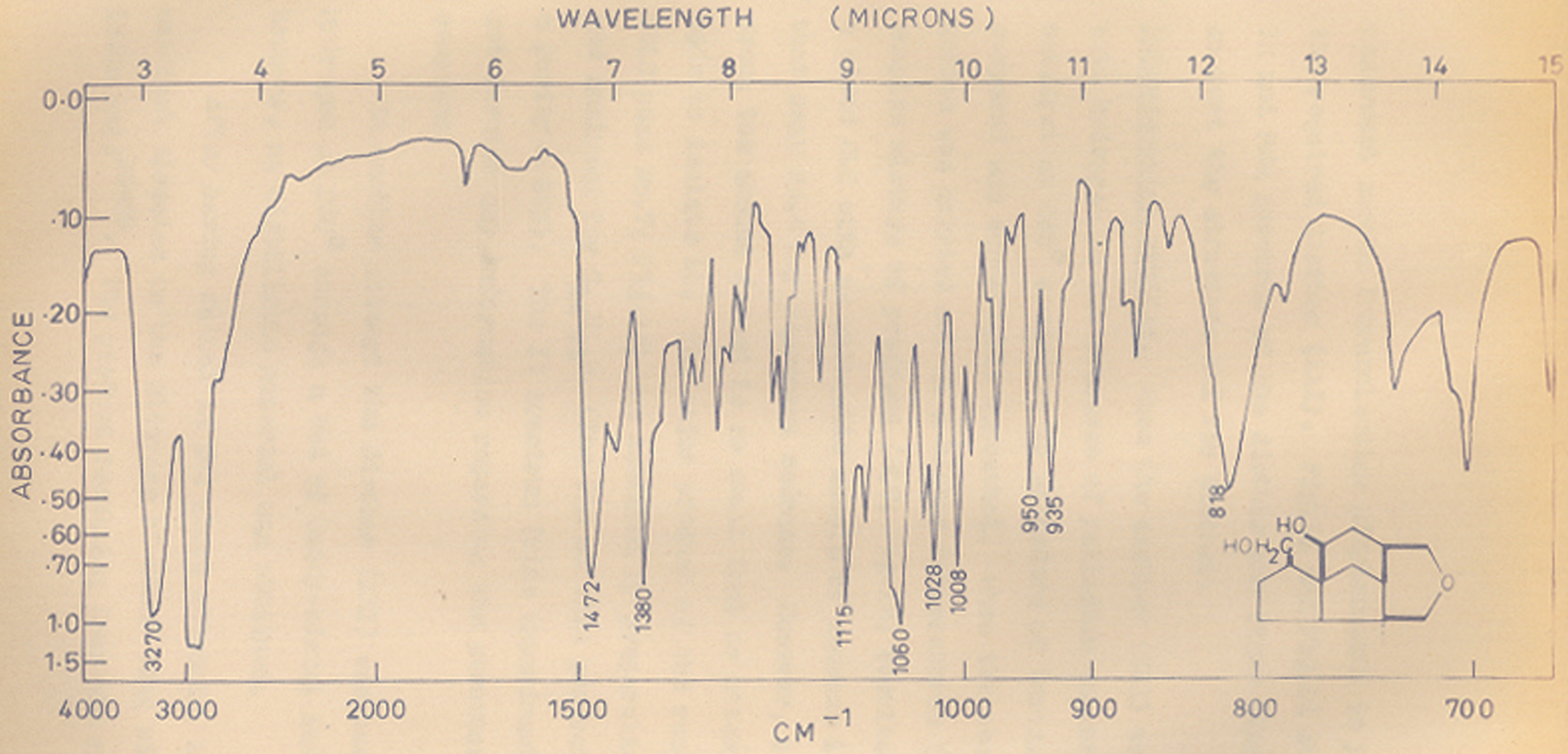


FIG. 12. IR SPECTRUM OF DIOL ETHER (XX).

underwent smooth intramolecular displacement to yield the required diether (XXI). Fig.13 and Fig.14 show the IR and PMR spectrum of the diether and these clearly support the structure XXI for diether.

Deoxygenation studies. When the diether (XXI) was treated with hydrogen in the presence of palladium on chromosorb W catalyst at 295° according to procedure of Beroza[20,21] the compound was essentially unscathed. When the above reaction was carried out at a higher temperatures (325°) a complex mixture of products (GLC; Fig.15) resulted. By a mixed GLC with an authentic sample of cedrane it was shown that peak No.4 may represent cedrane. However, as can be seen, the amount formed is so small that no attempt was made to isolate it. The major product of the reaction (GLC peak No.7; Fig.15) was isolated by preparative TLC and analysed for $C_{14}H_{21}O$. (The GLC of this product showed a purity ~ 85%). The IR spectrum (vide Experimental) could not furnish any information regarding the structure of this compound.

In another attempt the diether (XXI) was passed alongwith hydrogen at 250° through a bed of Raney-nickel and chromosorb W, however, no distillable material was obtained.

After having failed in the above attempts, attention was next directed to the cleavage of ether ring with hydroiodic acid[26-29]. The product resulting from the reaction of

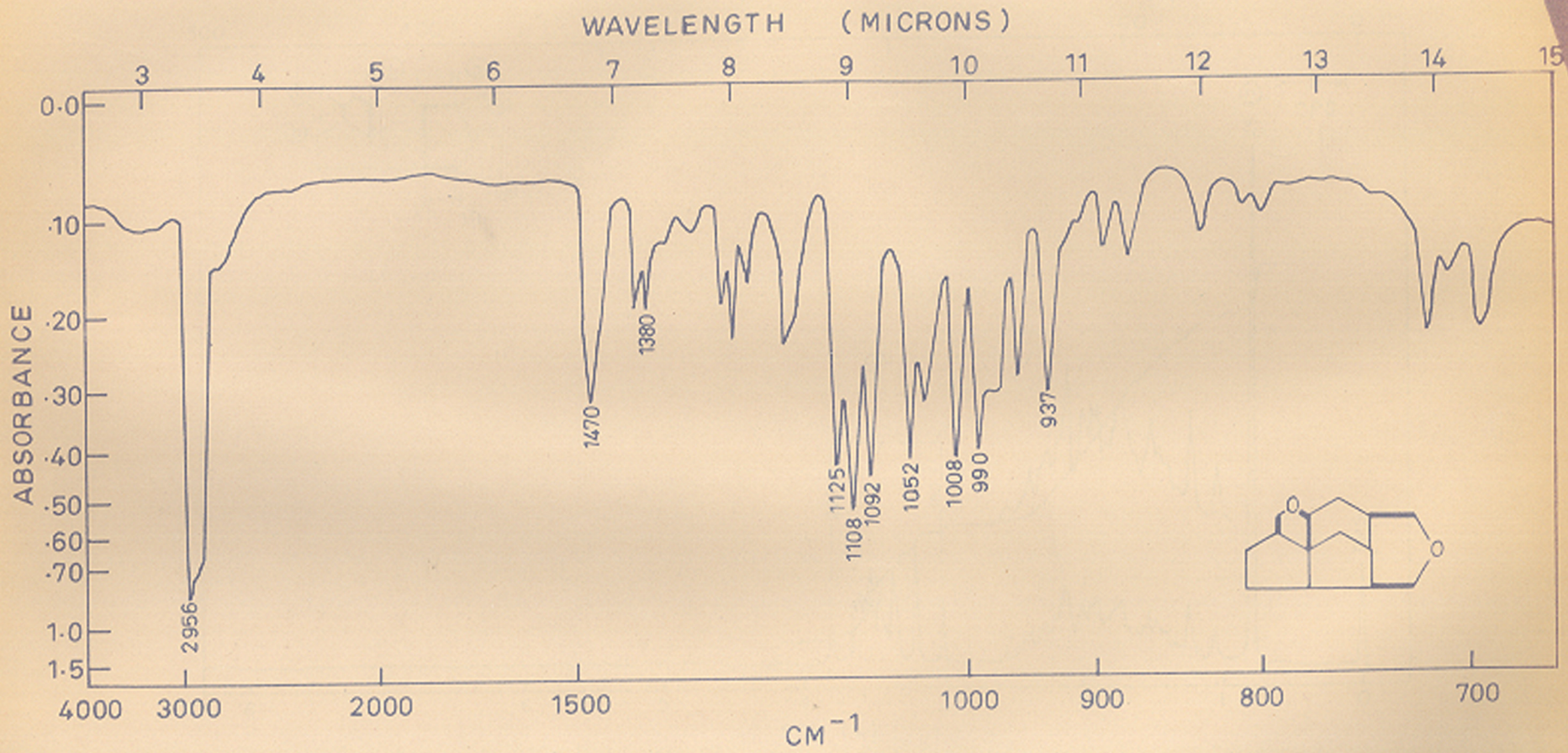


FIG. 13. IR SPECTRUM OF DIETHER (XXI)

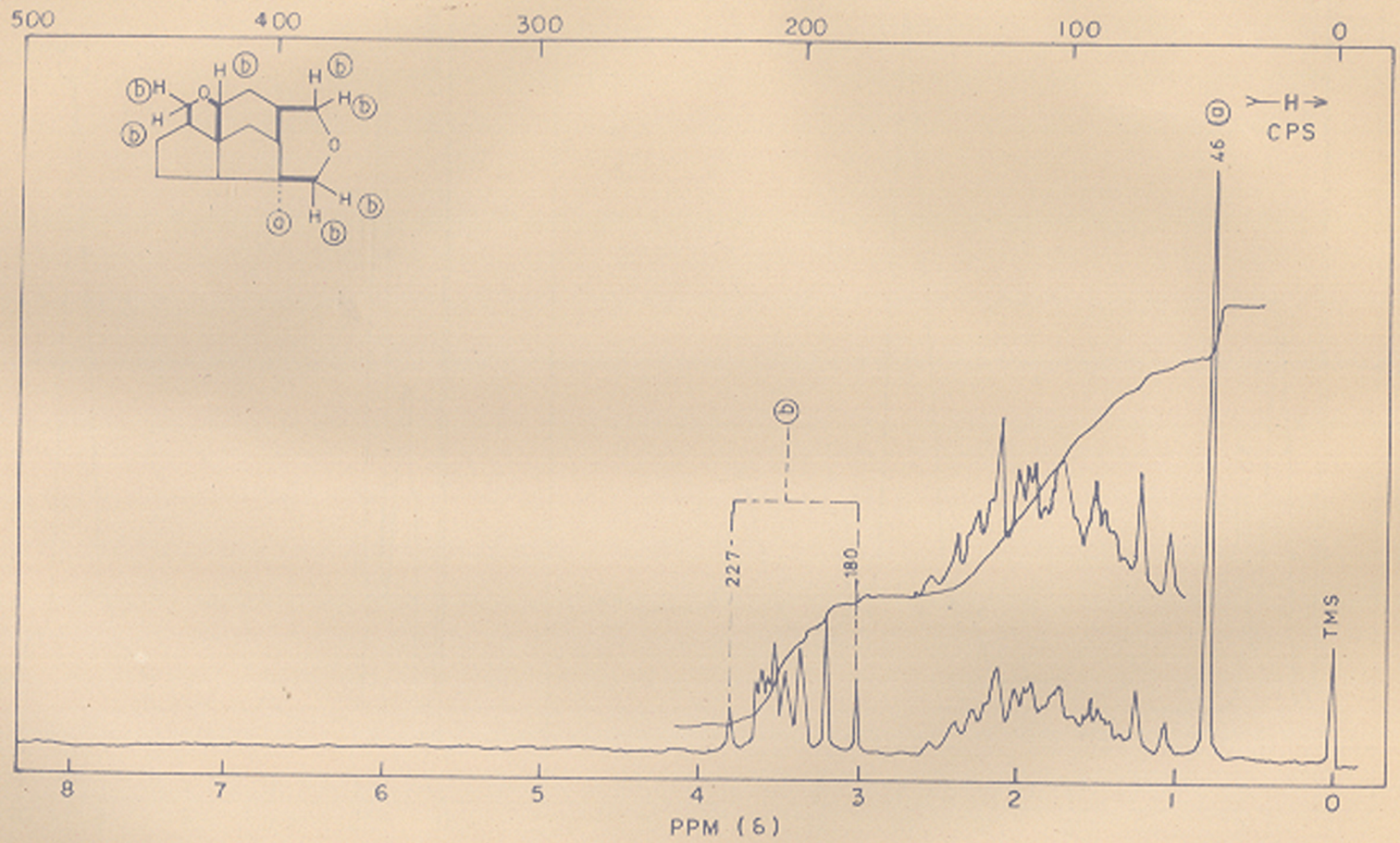
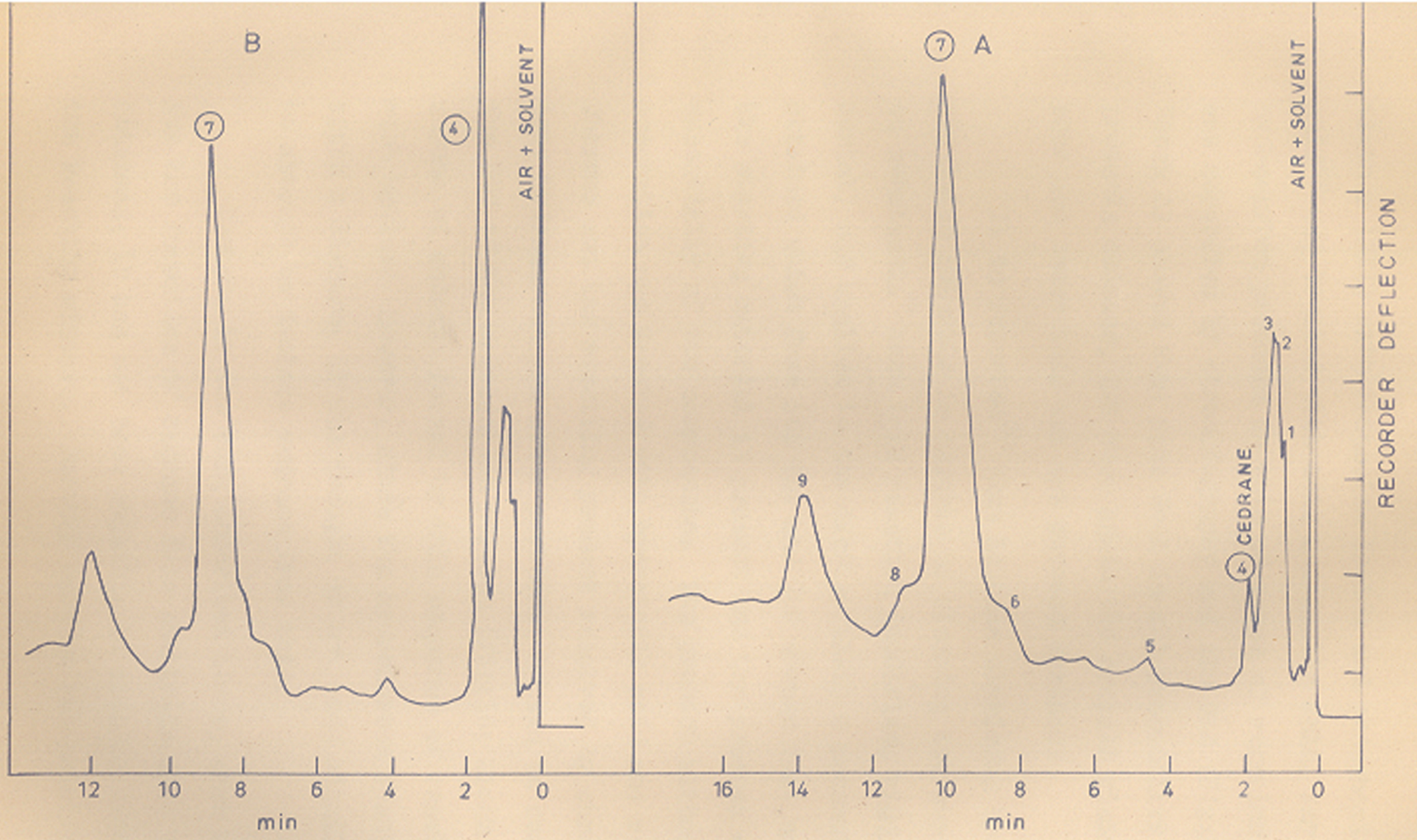


FIG. 14. PMR SPECTRUM OF DIETHER (XXI)



RETENTION TIME

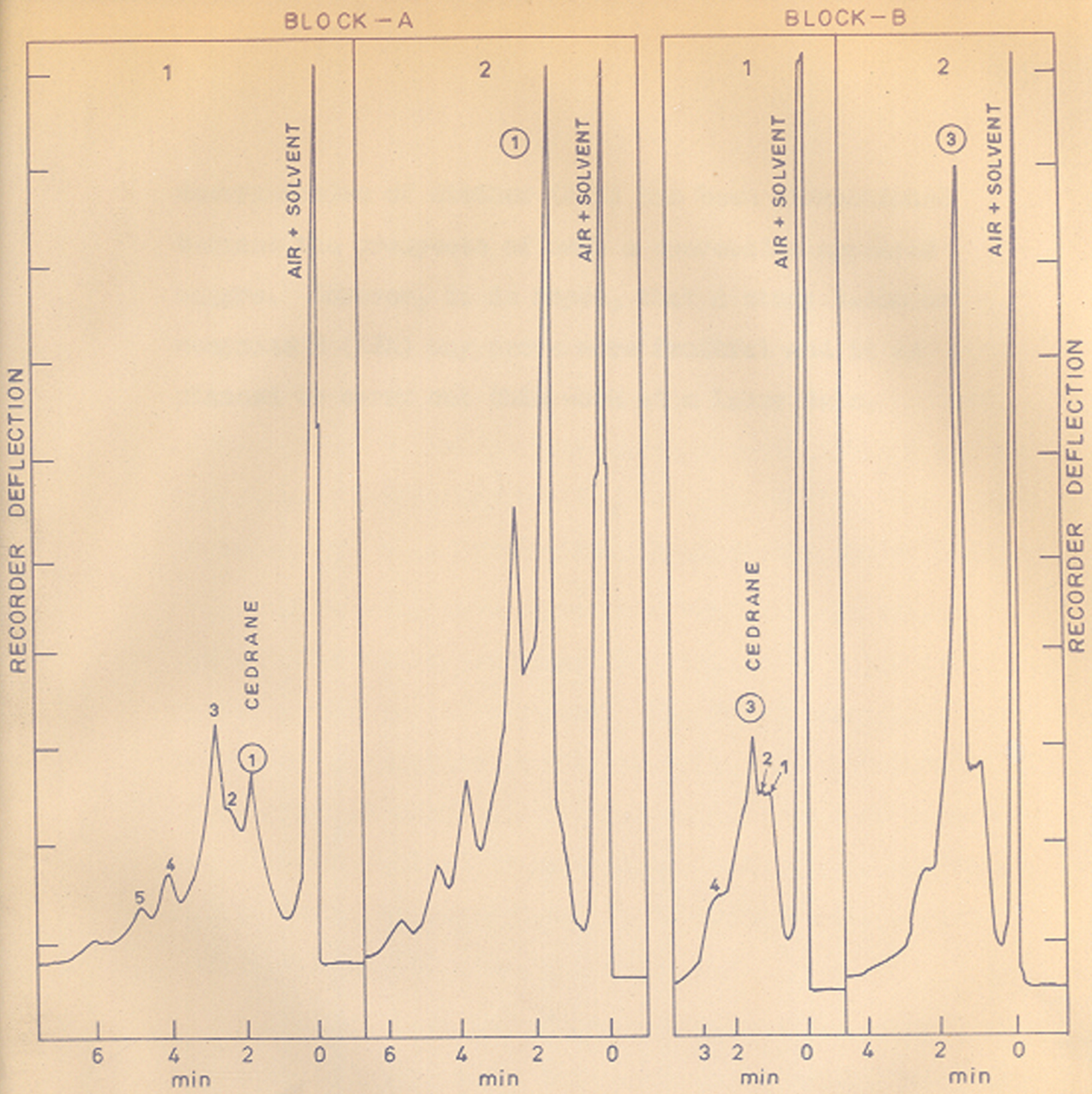
GLC OF DEOXYGENATION PRODUCT OF DIETHER (XXI)
A) TOTAL MIXTURE (TEMP. 125°) B) TOTAL MIX + CEDRANE (TEMP. 130°)
Column , 20 % diethylene glycol polysuccinate on chromosorb W, Length 5 ft
Flow rate , 50 ml /min.

FIG 15 .

diether (XXI) with potassium iodide and phosphoric acid[28] was treated with zinc and acetic acid. Any hydrocarbon produced in this sequence of reactions was separated by chromatography and its GLC (Fig.16; Block A) showed that peak No.1 in all probability represents cedrane, but once again the overall yield was poor and hence this was not pursued further.

It is reported[30] that lithium aluminium hydride-aluminium chloride is capable of cleaving tetrahydrofuran to n-butanol. When this reaction (modified, *vide* Experimental) was applied to the diether (XXI) a product was obtained which from its TLC and GLC showed that none of the starting material is present and the product consists essentially of two components. The product without further separation was treated with hydroiodic acid and red phosphorous and the resulting product resolved by chromatography into hydrocarbon and other portion. As can be seen from the GLC of the hydrocarbon portion (Fig.16; Block B) the amount of cedrane formed by this sequence of reaction is much better. However, since the hydrocarbon fraction is again a mixture, it was thought of not much significance to attempt to isolate cedrane from this.

Though, in the work described above, some evidence for the formation of cedrane from shellolic acid has been obtained, it has not been possible to isolate cedrane from the reaction mixture. Further work on the catalytic



BLOCK A. GLC OF THE PRODUCT OBTAINED BY KI AND H_3PO_4
CLEAVAGE OF DIETHER (XXI)
1) TOTAL HYDROCARBONS 2) TOTAL HYDROCARONS + CEDRANE
Column, 20 % diethylene glycol polysuccinate on chromosorb W;
length, 5 ft., Temp. 160°, Flow rate, 30 ml / min

BLOCK B. GLC OF THE PRODUCT OBTAINED BY $LiAlH_4 - AlCl_3$
CLEAVAGE OF DIETHER (XXI)
1) TOTAL HYDROCARBONS 2) TOTAL HYDROCARBONS + CEDRANE
Column, 20 % diethylene glycol polysuccinate on chromosorb W;
length, 5 ft. Temp. 135°, Flow rate, 50 ml/min

FIG. 16.

deoxygenation of diether (XXI) has been discontinued because the prospects of such a conversion appeared meagre. However, it is hoped, that a study based on compound B (XIX) may prove more fruitful and it is planned to carry out this work at a later date.

EXPERIMENTAL

All the boiling points are uncorrected. Melting points were determined on a Koffler hot stage microscope and are uncorrected. Pet. ether refers to the fraction of b.p. 60-80°. All solvent extracts were finally washed with brine, before drying (Na_2SO_4). Rotations were taken in chloroform on a Perkin-Elmer Polarimeter (model 141).

IR spectra were taken on a Perkin-Elmer Infracord (model 137E) either as smear (liquid) or in nujol (solids), unless stated to the contrary. All PMR spectra were taken in a ca. 10% solution in CCl_4 or $CDCl_3$ with tetramethylsilane as internal standard on a Varian Associates A-60 spectrometer; signals are reported in cps values. Gas liquid chromatography (GLC) was carried out on 'Aerograph' (model A-350-B) with H_2 as carrier gas.

Alumina used in this investigation was washed with 10% aqueous nitric acid, made neutral by washing with distilled water, and activated at 460° for 6 hr[31]. The various grades were prepared and checked according to the reported procedure of Brockmann[32]. Silica gel (-120 to +200 mesh) used in this investigation for column chromatography was activated at 120-130° for 8 hr. Thin-layer chromatography (TLC) was carried out on silica gel (-250 mesh) containing 15% plaster of Paris as binder, using the equipment and

procedure of Gupta and Dev[33]. A mixture of concentrated sulphuric acid and nitric acid (1:1) was used for spraying and visualisation of spots.

Isolation of Dimethyl Shellolate (Ib)

Although various methods are available in the literature[1,2,5,6,34-37] for the isolation of shellolic acid (Ia) or its methylester (Ib), the procedure developed by Wadia, Bhaskar and Dev[38] in this Laboratory was preferred because of its simplicity.

To dewaxed 'blonde' shellac* (300 g) was added a cold solution of sodium hydroxide (70 g) in water (1500 ml). This was swirled by hand in a bath maintained at 20-22°, till the resin had dissolved and then kept for 5 hr in the same bath with regular hand shaking. The reaction mixture was then acidified with ice-cold dilute phosphoric acid (300 ml, 1:1) when a sticky mass separated. The water-soluble portion was decanted off and the sticky mass washed with water (3 x 400 ml).

The water-soluble portion and the washings were mixed and extracted with ethyl acetate (1 x 1200 ml + 2 x 450 ml). The combined ethyl acetate extracts were washed with water

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*Supplied by Angelo Brothers, Calcutta (India).

(3 x 300 ml) and dried. The dried extract was concentrated to 150 ml in vacuo in a stream of nitrogen and cooled down to room temperature when a solid (7.5 g; m.p. 168-170°) separated.

The above solid (5 g) was mixed with 20% aqueous sodium hydroxide (20 ml) and kept at room temperature for 10 days; the reaction mixture was acidified with dilute hydrochloric acid and extracted with ethyl acetate (2 x 100 ml). The combined extract washed with water (3 x 10 ml) and dried. Removal of solvent furnished an acidic mixture (4.4 g, 86%). The gummy acidic mixture was dissolved in ethanol and treated with a slight excess of ethereal solution of diazomethane and worked up as usual. TLC (solvent system: toluene, 7 parts; ethylacetate, 4 parts; and acetone, 4 parts) indicated four major components corresponding to epi-laksholate (Rf .13), laksholate (Rf .23), epi-shellolate (Rf .35) and dimethylshellolate (Rf .42).

30 g of the above mixture of methylesters was chromatographed over alumina II (700 g).

Chromatogram

Fr.No.	Eluent	Vol.(l)	Wt. of compd.(g)	Remarks.
1	Benzene	3.0	.015	Discarded.
2	1% MeOH in C_6H_6	2 x .75	.100	"
3	"	"	12.302	Mostly shellolate.
4	"	"	3.062	Mostly epishellolate.
5	"	"	0.124	"
6	3% MeOH in C_6H_6	"	0.591	Essentially laksholate and epilaksholate.
7	"	"	2.472	
8	"	"	1.328	
9	"	"	1.615	
10	5% MeOH in C_6H_6	"	2.566	
11	"	"	.300	

Fraction 3 crystallised from benzene to give a crystalline solid (6.6 g) which was recrystallised from ethylacetate to give pure dimethyl shellolate; m.p. 148-149° (Lit.[6]: m.p. 149-50°), yield 5.6 g.

Rechromatography of the above mother liquors followed by crystallisation from benzene gave another crop of pure dimethyl shellolate (1.4 g). Total yield 7.0 g (23%) by weight on methylesters mixture. (Found: C, 63.23; H, 7.60.

$C_{17}H_{24}O_6$ requires: C, 62.96; H, 7.41%). IR spectrum: OH 3440 cm^{-1}; COOMe 1710 cm^{-1}; C=C 1645 cm^{-1}.

Preparation of dilactone (IIa)

Dimethyl shellolate (1.94 g, .06 mole) was hydrogenated at room temperature (27°) and pressure (710 mm) in glacial acetic acid (15 ml) over pre-reduced platinum oxide (50 mg) catalyst. The hydrogenation was stopped after absorption of 157 ml of hydrogen (1 mole equivalent of H_2). The catalyst was filtered off and most of the acetic acid from the filterate was removed (under suction) on a steam bath. Water (10 ml) was added to the residual gum and the mixture extracted with ethylacetate (4 x 20 ml). The combined ethylacetate extracts were washed with 5% aqueous sodium bicarbonate and dried. Removal of solvent furnished a gum (0.76 g) which was crystallised from ethylacetate to give the desire dilactone; m.p. 151-53°, yield .67 g (83.7%). An analytical sample prepared by recrystallisation of the above dilactone had: m.p. 152-53°, $[\alpha]_D$ -60°, (c, .42%) (Lit.[6]: m.p. 152-53°; $[\alpha]_D$ -57°). (Found: C, 68.71; H, 6.97. $C_{15}H_{18}O_4$ requires: C, 68.7; H, 6.9%).

Attempted sodiumborohydride reduction of dilactone (IIa) to hemiacetal (XI)

Dilactone (IIa; 80 mg, .3 m.mole) was dissolved in anhydrous methanol (5 ml) and cooled down to -5° (ice-salt). A solution of sodiumborohydride (9 mg, .25 m.mole) in dry methanol (1.8 ml) was added to it slowly under stirring (magnetic)

in the course of 3 min. The reaction mixture was stirred for 1 hr at -5° and then for another 1 hr at room temperature, and then left overnight (20 hr). Acetic acid (0.1 ml) was added to the product followed by water (5 ml). The organic material was extracted with ethylacetate (3 x 10 ml), the combined extract washed with water (2 x 5 ml) and dried. Removal of solvent furnished a gum (72 mg) which was crystallised from ethylacetate to give a crystalline solid; m.p. 150-52°, yield 40 mg. No depression in the m.p. when mixed with an authentic sample of IIa; IR spectrum was superimposable on that of dilactone.

Tosylation of dimethyl shellolate (Ia)

Dimethyl shellolate (600 mg, 1.54 m.mole) was dissolved in dry pyridine (5 ml) and cooled in an ice bath. To this cold solution, p-toluenesulphonyl chloride (600 mg, 3.14 m.mole) was added in one lot and the reaction mixture kept in a refrigerator for 24 hr. Water (15 ml) was added to it and the milky suspension so formed was extracted with ether (5 x 20 ml). The combined ether solution washed with dilute hydrochloric acid (2 x 10 ml, 2%), water (2 x 20 ml), 5% aqueous sodium bicarbonate (3 x 10 ml) and dried. Removal of solvent (under suction) furnished the desired mono tosylate as a gum (730 mg, 97%); all attempts to obtain crystalline mono tosylate from this

gum were of no avail. TLC (solvent system: toluene-ethylacetate-acetone in the ratio 7:4:2) showed a single spot of ~95% purity. A pure sample (TLC) was obtained by chromatography of the above mono tosylate (220 mg) over silica gel (6 g).

Fr.No.	Eluent	Volume (ml)	Wt.of compd.(mg)	Remarks.
1	Benzene	100	9.0	Rejected.
2	1.5% MeOH in C_6H_6	10	39.1	
3	"	10	69.6	Purest fraction.
4	"	10	71.7	"
5	"	10	31.4	

Fraction 3 and 4 constituted the purest sample of required mono tosylate (XIV). IR spectrum (Fig.6); PMR spectrum (Fig.7).

Attempted reductive detosylation of mono tosylate (XIV)

(a) Treatment with sodium iodide and acetic acid. Mono-tosylate (275 mg) was dissolved in acetic acid (10 ml) and sodium iodide (1.0 g) was added to it. The reaction mixture was heated under gentle reflux (6 hr), cooled down to room temperature and diluted with water (40 ml). The organic material was taken up in ether (3 x 50 ml); washed successively with aqueous sodium bicarbonate solution,

water, 10% aqueous sodium thiosulphate, water and dried. Removal of solvent furnished a gum (256 mg), which was identified (TLC and IR spectrum) as unreacted mono tosylate (XIV).

(b) Treatment with sodium iodide in butanone-2. Sodium iodide (330 mg, 2.2 m.mole) was added to a solution of mono tosylate (XIV; 262 mg, .55 m.mole) in butanone-2 (10 ml) and the contents were heated under reflux for 18 hr. Water (25 ml) was added to the cooled (10°) reaction mixture, and the product worked up as above. Removal of solvent (under suction) furnished a gum (240 mg, 91% by weight on XIV) which from its TLC and IR spectrum was found to be identical with mono tosylate.

(c) Reaction of mono tosylate (XIV) with benzyl mercaptan followed by Raney nickel. Benzyl mercaptan (346 mg, 2.8 m.mole) and sodium (65 mg, 2.8 mg atom) was added to a solution of mono tosylate (XIV; 380 mg; .8 m.mole) in dimethyl formamide (10 ml). The reaction mixture was heated under reflux for 4 hr, cooled down to room temperature, diluted with water and acidified with dilute hydrochloric acid. Unreacted excess benzyl mercaptan was steam distilled from this and the non-volatile portion was extracted with ether (4 x 15 ml), washed with water (2 x 10 ml) and dried. Removal of solvent furnished a gum (300 mg) which was dissolved in ethanol (35 ml) and Raney-nickel (W-2; 3 g) added to it. The contents were heated (steambath) under

reflux for 8 hr, the catalyst filtered off, and the filtrate concentrated in vacuo to give an oil (60 mg). IR spectrum (crude product) in $CHCl_3$: 2907, 1754 (Sh), 1718, 1587, 1536, 1439, 1395, 1258, 1093, 1010 cm^{-1}. TLC (solvent system: 40% ethylacetate in benzene) showed it to be a mixture, the major component having the Rf .81.

The above crude product (90 mg; from two lots) was chromatographed over alumina II (3 g).

Chromatogram

Fr.No.	Eluent	Volume (ml)	Wt.of compd. (mg)	Remarks.
1	Pet. ether	30	20.7	Corresponds to spot of Rf .81
2	25% C_6H_6 in pet. ether	25	1.0	
3	50% " "	25	0.5	
4	Benzene	25	4.4	
5	"	10	0.3	
6	5% MeOH in C_6H_6	10	6.8	
7	"	10	10.0	
8	Ether	50	12.2	

IR spectrum (CCl_4) of fraction 1 could not give any information regarding the structure of compound and has bands at 2907, 1543, 1460, 1250, 1193, 1002 cm^{-1}.

(d) Reinvestigation of reaction between benzyl mercaptan and monotosylate (XIV). Benzyl mercaptan (640 mg, 5.1 m.mole) and sodium (130 mg, 5.7 m.mole) in pure dimethyl formamide (15 ml) were heated under reflux till all the sodium had dissolved. To this refluxing solution, monotosylate (XIV; 1.1 g, 2.3 m.mole) in dimethyl formamide (7 ml) was added slowly during 3 min. The reaction mixture was then refluxed for 6 hr, diluted with water and acidified with hydrochloric acid. The product was processed as above and dried. Removal of solvent (under suction) gave a gum (1.00 g) whose TLC (5% MeOAc in C_6H_6) indicated it to be a complex mixture having two main components of Rf .4 and .56 respectively.

The two main spots, designated as 'A' (Rf .4) and 'B' (Rf .56) were isolated by chromatography of above gum (1.0 g) over silica gel (40 g, 12 cm x 2.8 cm).

Fr.No.	Eluent	Volume (ml)	Wt.of compd. (mg)	Remarks.
1	Benzene	300	122.0	Discarded
2	5% EtAc in C_6H_6	50	0.9	"
3	"	"	6.6	Fr.3 to 5 combined (TLC).
4	"	"	53.2	
5	"	"	60.6	
6	"	"	59.5	Fr.6 to 10 combined
7	"	"	53.7	(TLC). Constituted Compound B.
8	"	"	44.3	
9	"	"	44.3	
10	"	"	44.0	
11	"	"	34.0	Fr.11 to 14 combined
12	"	150	69.1	(TLC)
13	"	"	37.9	
14	15% EtAc in C_6H_6	50	11.5	
15	"	"	45.2	Fr.15 to 20 combined
16	"	"	37.7	(TLC). Constituted Compound A.
17	"	"	29.0	
18	"	"	22.8	
19	"	"	10.0	
20	"	"	10.0	
21	"	150	35.0	Fr.21 to 24 discarded.
22	"	250	21.0	
23	25% EtAc in C_6H_6	200	12.0	
24	MeOH	150	124.0	

Combined fractions (6 to 10) corresponds to compound B (246 mg). IR spectrum (CCl_4): 2924, 1773 (sh), 1739, 1724, 1431, 1408, 1374, 1361, 1242, 1198, 1176, 1152, 1133, 1103, 1087, 1031 cm^{-1}. PMR spectrum: a quaternary methyl (unsplit signal at 73 cps), two carbomethoxy groups (sharp signals at 215 and 216 cps); methyl of the tosylate group missing (no sharp signal around 140 cps) and no vinylic protons (no signal in the vicinity of 330 cps). Besides this, the PMR spectrum also indicated the presence of some aromatic protons.

Combined fractions (15 to 20) constituted compound A (155 mg). IR spectrum (CCl_4): 2941, 1742, 1653, 1499, 1460, 1443, 1395, 1250, 1170, 1110 and 1031 cm^{-1}; the PMR spectrum has a very bad pattern and has signals at 72, 172, 179, 214 and 218 cps, besides some signals in the aromatic protons region (430 to 439 cps).

Hydrogenation of dilactone (IIa)

Dilactone (IIa; 2.0 g, .0076 mole) was hydrogenated at room temperature (27°) and pressure (710 mm) in glacial acetic acid (20 ml), containing perchloric acid (.05 ml, 60%), over pre-reduced platinum oxide (200 mg). The hydrogen absorption came to a close after uptake of 482 ml of hydrogen (2.4 mole equivalents of H_2) in 30 hr. The catalyst was filtered off and the filtrate concentrated (ca. 5 ml) in vacuo on a steam bath.

Water (25 ml) was added to the residue and the product extracted with ethylacetate (5 x 20 ml) and worked up as usual. Removal of solvent (under suction) furnished a gum (1.8 g) whose TLC (25% EtOAc in C_6H_6) indicated the presence of three components: yellow spot (compound A, Rf .33), violet spot (compound B, Rf .46) and a light brown spot (minor constituent, Rf .63). The above gum (1.75 g) was chromatographed over a column of silica gel (55 g, 20 cm x 3 cm).

Chromatogram

Fr.No.	Eluent	Volume (ml)	Wt.of compd. (mg)	Remarks.
1	Benzene	500	80.0	
2	2% EtOAc in C_6H_6	250	10.0	
3	5% "	30	Nil	
4	"	"	Nil	
5	"	"	12.0	
6	"	"	208.5	Rich in compd. B
7	"	"	248.0	"
8	"	"	119.2	Rich in compd. A
9	"	"	238.5	"
10	"	"	146.5	"
11	"	"	95.7	"
12	"	"	68.0	"
13	"	50	54.0	"
14	"	"	65.0	"
15	"	"	56.8	"
16	"	"	20.6	"
17	"	"	12.6	Fr.17 to 20 combined
18	"	"	10.4	
19	"	"	Nil	
20	EtOAc	150	230.6	

All the fractions from 6 to 17 were found to be mixtures (TLC) of compound 'A' and 'B'.

(i) Fractions 5 and 6 were combined and crystallised from benzene-pet. ether to give a crystalline compound (m.p. 75-92°). Recrystallisation of this solid from hexane furnished pure compound B (XIX); m.p. 98-99°, yield 80 mg, $[\alpha]_D$ -108° (c, 0.4%). (Found: C, 69.88; H, 8.35. $C_{17}H_{24}O_4$ requires: C, 69.86; H, 8.21%). IR spectrum (Fig.10); PMR spectrum (Fig.11).

(ii) Fractions 7 to 16 were combined and twice crystallised from pet. ether to give pure compound A (XVIII); m.p. 90-91°, yield 500 mg, $[\alpha]_D$ -104° (c, .5%). (Found: C, 72.78; H, 8.19. $C_{15}H_{20}O_3$ requires: C, 72.58; H, 8.06%). IR spectrum (Fig.8); PMR spectrum (Fig.9).

The mother liquors from the above crystallisations were combined and chromatographed over silica gel (25 g) to give more of compound B (80 mg) and compound A (120 mg).

Lithium aluminium hydride reduction of γ-lactone ether (XVIII) to diol ether (XX)

To a well stirred suspension of lithium aluminium hydride (750 mg) in anhydrous ether (50 ml), a solution of γ-lactone ether (XVIII; 740 mg) in ether (15 ml) was introduced at room temperature (25°) during 10 min. After stirring for 2 hr, the reaction mixture was left overnight (16 hr). This was chilled in ice-salt bath and with stirring, cautiously

treated, with a cold aqueous saturated solution of sodium potassium tartrate. The ether was separated, and the aqueous layer extracted with ether (3 x 15 ml). The combined ether extracts were washed with water and dried. Removal of solvent furnished a crystalline residue (720 mg) which was crystallised from ethyl acetate to give pure diol ether (XX); m.p. 171-172°, yield 640 mg (85%), $[\alpha]_D$ +11° (c, 0.5%). (Found: C, 71.2; H, 9.69. $C_{15}H_{24}O_3$ requires: C, 71.42; H, 9.52%). IR spectrum (Fig.12). The PMR spectrum of diol ether indicated the presence of: a quaternary methyl (a 3H singlet at 51 cps); one $-H_2C-\overset{HC}{\underset{C}{\overset{|}{\underset{|}{C}}}}H$ (a 1H triplet centred at 152 cps, J = 8 cps); two $-CH_2-O-$ (a 4H multiplet between 185 to 220 cps); one $>CH-OH$ (a broad 1H singlet at 258 cps) and a 4H multiplet ranging from 231 to 241 cps.

Cyclisation of diol ether (XX) to diether (XXI)

p-Toluenesulphonyl chloride (126 mg, .66 m.mole) was added to a solution of diol ether (XX; 56 mg, .22 m.mole) in dry pyridine (2.5 ml) at room temperature. After 6 hours the progress of reaction was checked (TLC) and was found to be complete. Water (10 ml) was added to the reaction mixture and the required product extracted with ether (5 x 10 ml). The ether extract was washed with dilute hydrochloric acid, water, 5% aqueous sodium carbonate and dried. Removal of solvent (under suction) furnished a liquid (65 mg) which

was filtered through a column of alumina II (2.5 g). Benzene eluted an oil (44 mg, 85%) which was distilled to give the desired diether (XXI); b.p. (bath) 178-183°/3 mm, n_D^{30} 1.5276, $[\alpha]_D$ -201° (c, .22%). (Found: C, 76.72; H, 9.67. $C_{15}H_{22}O$ requires: C, 76.32; H, 9.40%). IR spectrum (Fig.13); PMR spectrum (Fig.14).

Attempted catalytic deoxygenation of diether (XXI) to cedrane (XIII).

(a) Over palladium catalyst

Preparation of catalyst[21,22] Chromosorb W (5 g) was added to a solution of palladium chloride (89 mg) in water containing 40 mg of sodium hydroxide (5 ml of .2N NaOH solution). The contents were mixed well with the help of a glass rod and evaporated to dryness (water bath) with regular stirring. The catalyst was finally dried (oven) at 110° for two hr.

Deoxygenation. A column (20 cm x 1 cm) of the above catalyst was prepared in a glass tube and the catalyst bed heated (electrically) in a stream of hydrogen (flow of hydrogen ca. 100 ml/min.) first at 125° (1 hr), then at 200° (1 hr), and finally at 295° (30 min). Diether (XXI; ca. 125 mg) was dropped over this heated bed of catalyst, in a stream of hydrogen, in five equal instalments; every instalment was added after an interval of 20 min. (total dropping time 80 min). The vapours emerging out were trapped in a

well-chilled (ice-salt) receiver. TLC (20% EtOAc in C_6H_6) of the trapped material (51 mg) indicated the major spot corresponding to unreacted diether. On washing the catalyst bed and the tube with pet. ether (40-60°) more of a mobile liquid (53 mg) was obtained which had the same pattern on TLC as the trapped condensate.

When the reaction was performed at elevated temperature (325°) on a catalyst bed of the dimension 40 cm x 1 cm, a colourless mobile liquid (40 mg) was obtained from 60 mg of diether (XXI). TLC of this mobile liquid showed the complete absence of starting material, however, GLC (Fig.15) indicated it to be a complex mixture. The major component (peak No.7, Fig.15) was isolated by carrying out the preparative TLC of mixture (30 mg) on silica gel (layer of dimensions 20 cm x 20 cm x 0.1 cm). The main component (16 mg) was isolated and distilled. (Found: C, 82.00; H, 10.23. $C_{14}H_{21}O$ requires: C, 81.95; H, 10.24%). GLC (column, 20% diethylene glycol polysuccinate on chromosorb W; column length, 5 ft. temperature 130°; flow, 50 ml/min.) indicated one major compound (corresponding to peak No.7, Fig.11) of ca. 85% purity. IR spectrum: 2980, 1722, 1475, 1460, 1380, 1300, 1180, 1116, 1050, 990, 965 cm^{-1}.

(b) Over Raney-nickel catalyst: Raney-nickel catalyst (5 g) under ethanol was mixed, as intimately as possible, with

chromosorb W (5 g). A column of 1 cm diameter was packed with this catalyst. It was slowly heated to 250° in a stream of hydrogen (ca. 100 ml/min.). Hydrogen was passed at this temperature for 2 hr to sweep away any possible vapours of ethanol. Diether (XXI; ca. 60 mg) was dropped over this catalyst in three equal instalments in the course of 1 hr. The vapours emerging out from the other end were trapped in a well-chilled (ice-salt) receiver. After the addition was complete, the reaction tube was allowed to attain room temperature and then thoroughly washed with pet. ether (40-60°). These washings were combined with the trapped condensate and dried. On removing the solvent (under suction), no distillable material could be traced and hence no further investigation was possible.

Potassium iodide and phosphoric acid cleavage of diether (XXI).

A mixture of potassium iodide (670 mg), phosphoric acid (0.2 ml; 80%), phosphorus pentoxide (12 mg) and the diether (60 mg) were heated under reflux, under scrupulously anhydrous conditions, in an oil bath (140 ± 2°) for 6 hr. The reaction mixture was allowed to attain room temperature and the complex broken by adding a small amount (ca. 3 g) of crushed ice. The organic material was extracted with ether (4 x 10 ml) washed successively with 5% aqueous solution of sodium thiosulphate, water, 5% sodium carbonate and dried.

Removal of solvent furnished a yellow gum (73 mg) which was dissolved in acetic acid (10 ml) and zinc dust (5 g) was added to it. The contents of the flask were heated ($95^{\circ} \pm 1^{\circ}$) under stirring (magnetic) for 6 hr. The solid material was filtered off and washed thoroughly with ether. The filtrate was diluted with water (30 ml), extracted with ether (4 x 20 ml), washed with 5% aqueous sodium bicarbonate until washings were basic and dried. Removal of solvent furnished a pale coloured product (52 mg) which was filtered through a column of alumina I (3 g). Pet. ether (20 ml) eluted a mobile liquid (8 mg). GLC (Fig.16, block A) of this product indicated it to be a mixture of at least five components out of which peak No.1 (Fig.16, block A) corresponds to cedrane (mixed GLC). However, it was not possible to isolate cedrane from this mixture.

Lithium aluminium hydride - aluminium chloride cleavage of diether (XXI)

To a well stirred suspension of lithium aluminium hydride (1.2 g) and powdered aluminium chloride (1.3 g) in anhydrous ether (25 ml) and S-free benzene (15 ml), a solution of diether (XXI; 115 mg) in ether (10 ml) was added, under nitrogen envelope, during 5 min. The reaction mixture was stirred (48 hr) under mild reflux. This was chilled in an ice-salt bath and with stirring, cautiously treated with 25 ml of 10% H_2SO_4. The ether-benzene layer

was separated, and the aqueous phase extracted with ether (4 x 15 ml). The combined organic extracts were washed with water, saturated aq. sodium bicarbonate, water, and dried. Removal of solvent (under suction) furnished a liquid (130 mg). GLC (column, 20% diethylene glycol polysuccinate; column length, 5 ft; temperature, 160°; flow, 50 ml/min.) of the material indicated the presence of four products of which two were major components corresponding to peaks No.1 and 2 (retention time; 1 min and 1 min. 20 sec respectively). Analysis of the mixture (Found: C, 82.39; H, 10.82. $C_{15}H_{24}O$ requires: C, 81.8; H, 10.9%). IR spectrum: 3041, 1460, 1389, 1366, 1111, 1042 cm^{-1}.

The above crude product (120 mg) was mixed with red phosphorus (260 mg) and hydriodic acid (1.5 ml; d, 1.7), and heated under gentle reflux for 18 hr. The reaction mixture was allowed to attain room temperature, diluted with water (5 ml), and extracted with ether (4 x 15 ml). The combined ether extracts were washed with 10% aq. sodium thiosulphate, water, saturated aq. sodium bicarbonate, water and dried. Removal of solvent furnished a yellow liquid which was passed through a column of alumina I (5 g). Pet. ether (30 ml) eluted a colourless mobile liquid (80 mg) which was rechromatographed over a column of silver nitrate impregnated silica gel[33] (3 g). Elution with pet. ether (3 ml) gave a mobile liquid; yield 24 mg. GLC (Fig.16, block B)

of this product indicated the presence of four components out of which peak No.3 corresponded to cedrane (mixed GLC). As could be seen from GLC (Fig.16, block B) the formation of cedrane by this procedure is better, but again, due to poor yields it was not possible to isolate it.

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