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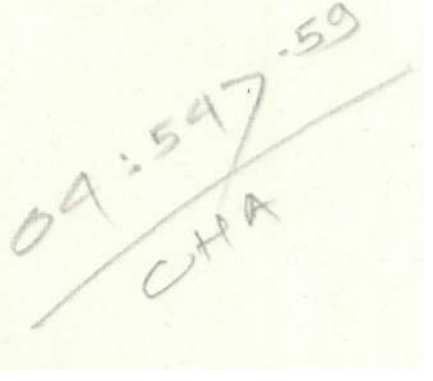
STUDIES IN TERPENOIDS

chemical examination of the constituents of the resin from ailanthus malabarica dc

thesis submitted to the university of poona for the degree of doctor of philosophy



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Page

chapter one
introduction
triterpenoid
types

TRITERPENOID TYPES

Modern physical methods of isolation and structure determination, coupled with a better understanding of biogenetic and organic mechanistic basis that is available today, have revolutionised the study of the chemistry of natural products. One of the fields in which the impact has been very impressive is the field of terpenoids.

The triterpenoids[1-13] constitute by far the largest terpenoid class. They are widely distributed in the vegetable kingdom; their occurrence in the animal kingdom, is, however much more limited[6,7,9,10]. In plants, the triterpenes have been found to occur in all parts of the plant[13], in the free state[6,7,9,10] and in combination with sugars as glycosides[6,7,9,10] and with acids as esters[6,7,9,10]. Though the triterpenoids have been known and investigated for over hundred years, it is only during the last fifteen years that serious progress has been made about their structures and absolute stereochemistry. Excellent monographs have appeared on triterpenoids in general[1-7] and on tetracyclic[7-10] and pentacyclic triterpenoids[2,7,11,12] from time to time. It is the purpose of this introductory Chapter to survey the recent developments in the field of triterpenoids. Since it is not possible to cover the entire field in a limited space, it is planned to deal mainly with the

classification of triterpenoids and a note on their possible biogenesis.

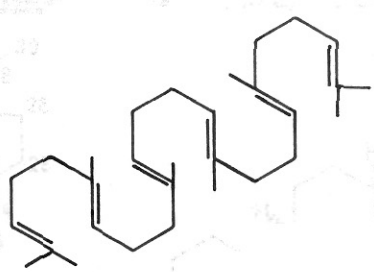
The triterpenoids can be classified into four major classes viz.

1. acyclic
2. tricyclic
3. tetracyclic and
4. pentacyclic

A brief survey of our present knowledge of these types follows.

1. ACYCLIC TRITERPENOIDS[7,10,14,15]

The only member of this group known, thus far, is squalene, $C_{30}H_{50}$, which has been isolated from animal source and formulated as I (all-trans) on the basis of classical researches by Heilbron et al.[16] and supported by its synthesis by Karrer and Helfenstein[17].



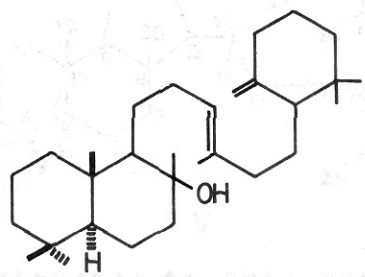
I

2. TRICYCLIC TRITERPENOIDS[6,7]

The occurrence of tricarbocyclic triterpenoids is rare. This class of triterpenoids can further be divided into three groups, viz. : a) ambrein[6,7], b) obelane[21,22] and c) malabaricane[23].

a) AMBREIN[6,7]

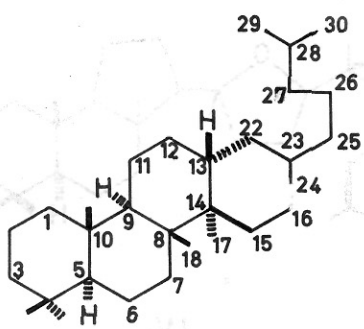
The only member of this group is ambrein (II), a tertiary alcohol, isolated from an animal source, ambergris by Pelletier and Carventon[18]. Its structure elucidation has been briefly surveyed[6,19,20].



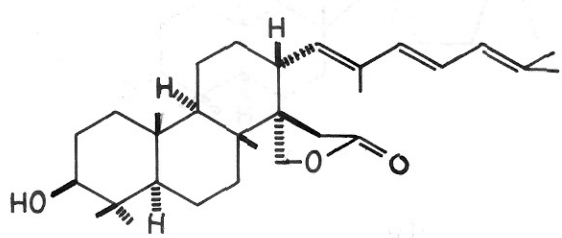
II

b) OBELANE (III)[21,22]

This is a new tricarbocyclic skeleton recently reported by Rade et al.[21,22]. Only one compound of this



III

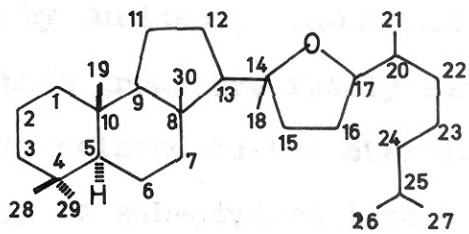


IV

group, ebelin lactone (IV)[22] is known as yet, which was obtained by the acid hydrolysis of a crude saponin from Emmenospermum alphitonioides F. Muell. The structure of this lactone is based upon chemical evidence and X-ray analysis of the bromoacetate of hexahydro ebelin lactone.

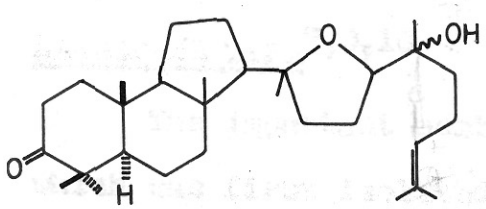
c) MALABARICANE (V)[23]

This is a new tricarbocyclic skeleton, reported very recently by us, from the exudate of Ailanthus malabarica DC.

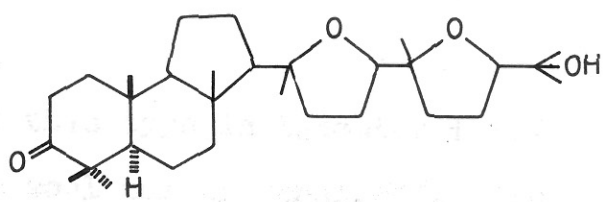


V

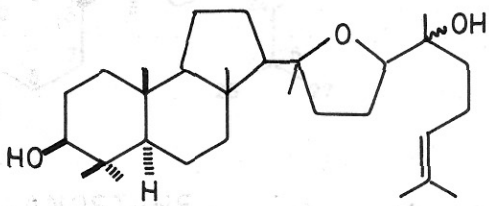
Ten compounds belonging to this group have been isolated by us, and to four of these, structures have been assigned (VI - IX). This work forms the basis of the present thesis.



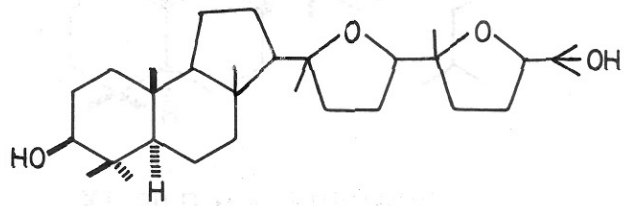
VI



VII



VIII



IX

3. TETRACYCLIC TRITERPENOIDS[6-10]

The chemistry of tetracyclic triterpenoids has been reviewed by Ourisson, Crabbe and Rodig (1964)[10]. The compounds of this group are fairly similar in structure and are closely related to the steroids. The tetracyclic triterpenes may be sub-divided into two main groups (Chart 1).

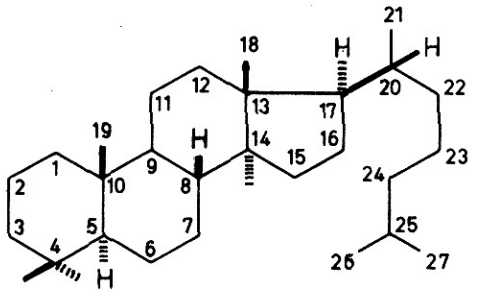
GROUP I

Most of the compounds in this group contain a perhydrocyclopentanophenanthrene skeleton, analogous to that of the steroids but with varying substitution patterns.

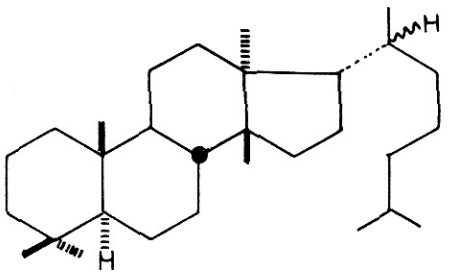
LANOSTANE TYPE[7,9,10]

The important member of this type is lanosterol (XV), which was first isolated from wool wax by Schulze[24]. Its structure elucidation has been briefly surveyed by Halsall[25] and by Barton[4]. The conversion of cholestrol to lanosterol

GROUP – I.

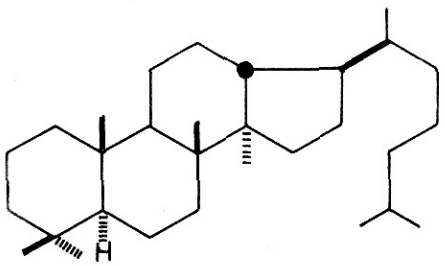


X LANOSTANE



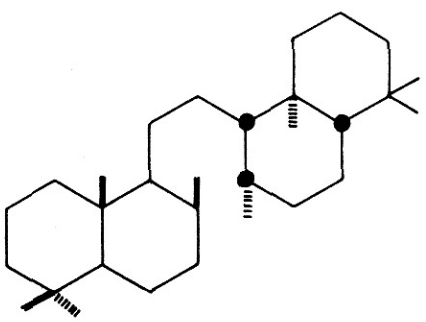
XI 20 β H – EUPHANE

XII 20 α H – TIRUCALLANE



XIII DAMMARANE

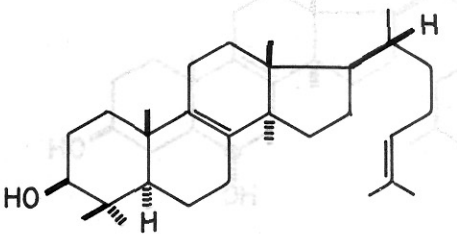
ROUP – II



XIV ONOCERANE

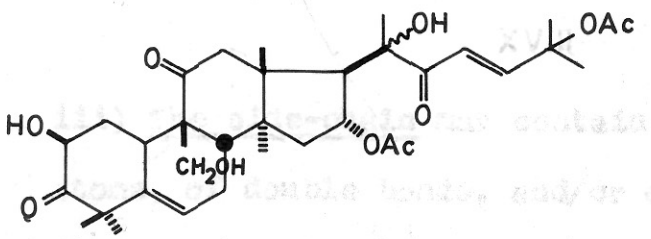
CHART – 1. TETRACYCLIC TRITERPENOID TYPES

constitutes, in effect, a total synthesis of the latter[26] since the total synthesis of cholesterol has already been achieved[27]. Its structure has also been confirmed by radiocrystallography[28,29].

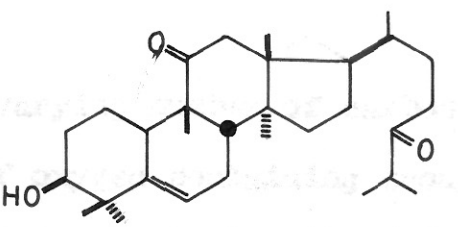


XV

The glycosides have been encountered only with the bitter substances present in many Curcurbitaceae[10]: these are for the most part glucosides of substances called "curcurbitacins" A (XVIa)[30,31], B[30,32], C[30], D[30,33], E[34], I[35], G and H. Bryogenin (XVIb) is "Aglycone 157"[36].

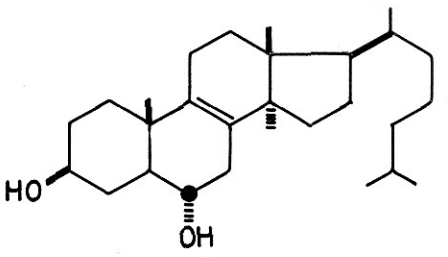


XVI a



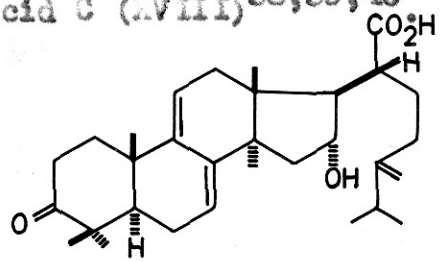
XVI b

Variations in lanostane type[10]. i) Ring A may be modified by the absence of one or more of the methyl groups e.g. macdougallin[37] (XVII).



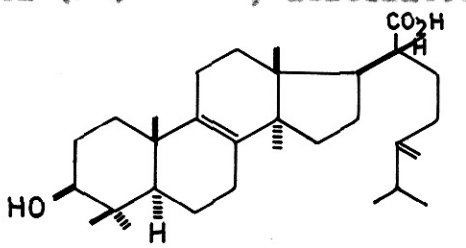
XVII

ii) The ring system may contain different functional group(s) and/or additional double bond(s); occasionally, the methyl groups may occur at different positions e.g. polyporenic acid C (XVIII)[38,39,40]



XVIII

iii) The side-chain may contain varying number of carbon atoms, of double bonds, and/or of oxygen containing groups (hydroxy, carbonyl or carboxyl) e.g. eburicoic acid (XIX)[41-43] citrostadienol (XX)[44,45a], abieslactone (XXI)[45b].



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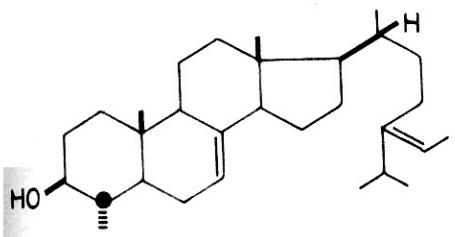

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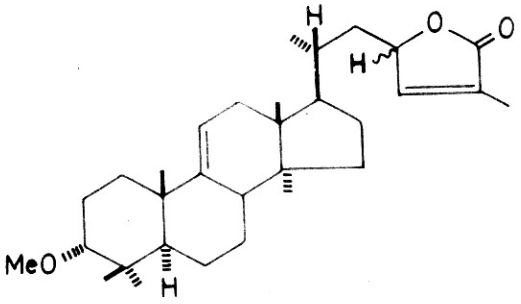
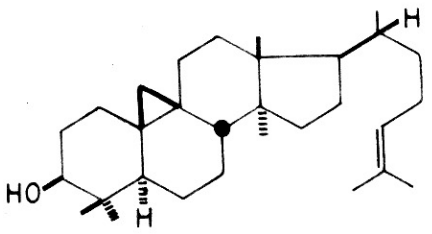
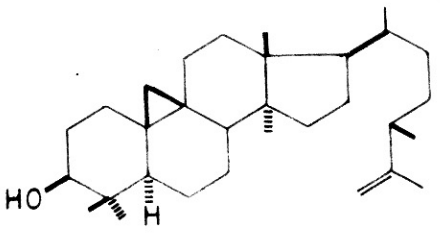


XXI

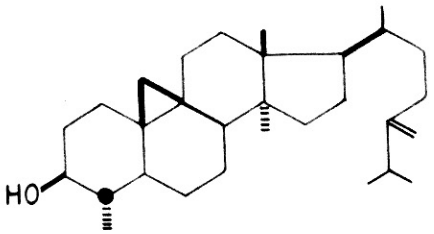
iv) A cyclopropane ring may be present e.g. cycloartenol (XXII)[46-49], cyclolaudenol (XXIII)[50,51], cycloeucalenol (XXIV)[52-54a], cimigenol (XXV)[54b].



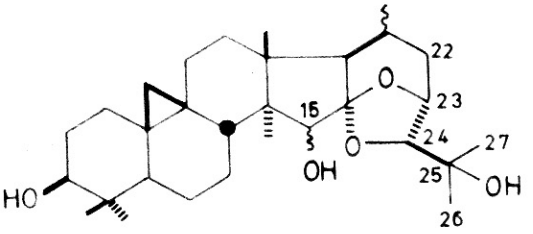
XXII



XXIII



XXIV

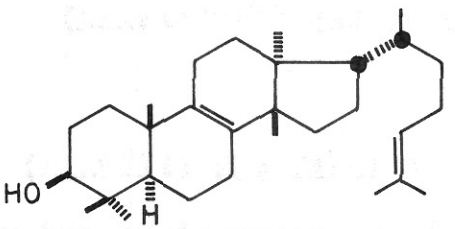


XXV

The conversion of lanosterol derivatives into cycloartane constitutes a formal total synthesis of cycloartane[55].

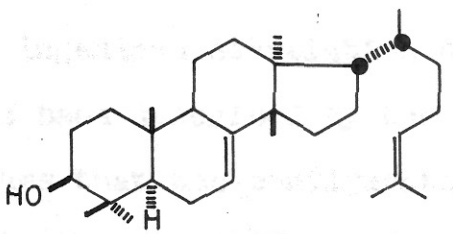
EUPHANE TYPE[9,10]

Euphol (XXVI)[56,57] is the parent compound of euphane type, first isolated by Newbold and Spring[56] from euphorbium resin. The structure elucidation[57] of euphol has been briefly surveyed by Gascoigne and Simes[9].



XXVI

Butyrospermol (XXVII)[58-60] is another very important member of this type which was discovered[58] in attempts to reisolate the presumed tetracyclic triterpene "basseol" from shea-nut fat from Butyrospermum parkii. Its structure has been established by Irvine et al.[59]

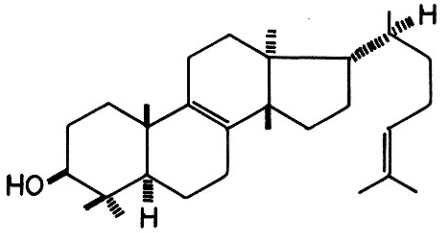


XXVII

Butyrospermol has been known to be a progenitor of TETRANORTRITERPENOIDS[60] which are degraded tetracyclic compounds. This interesting subgroup of compounds is associated with the i) oxidative cleavage of ring D e.g. gedunin (XXXVIII)[61-63], anthotheeol (XXXIX)[64,65] and khivorin (XXXX)[66-68], ii) cleavage of rings D and A e.g. limonin (XXXXI)[69-71], nomilin (XXXXII)[70a-73,75] and obacunone (XXXXIII)[70a-76], and iii) cleavage of rings D and E e.g. andirobin (XXXXIV)[77,81], swietenolide (XXXXV)[78-80], methyl angolensate (XXXXVI)[81,82] and swietenine (XXXXVII)[83-86]. (Chart 2).

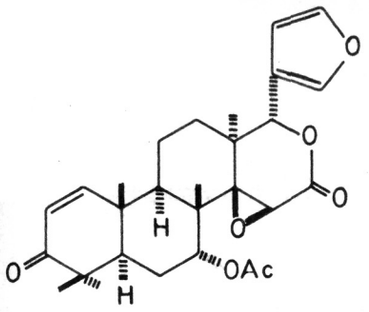
TIRUCALLOL TYPE

Tirucallol (XXXXVIII) was first isolated by Haines and Warren[87] from the resin of Euphorbia tirucalli. Its structure has been elucidated by degradation method as in

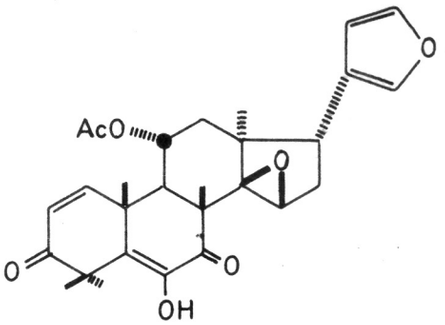


XXXVIII

euphol[88]. An ingenious correlation of tirucallol with lanosterol has been described by the Zurich group[89] and this establishes that the configuration at C_{17} in euphol and tirucallol (the two differ only in their configuration at C_{20}) is opposite to that in lanosterol.



XXVIII



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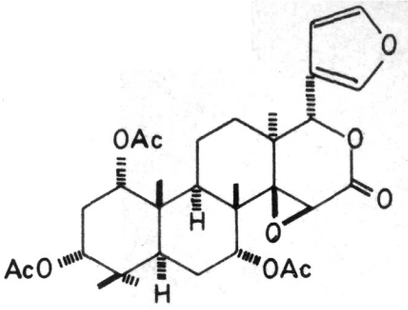
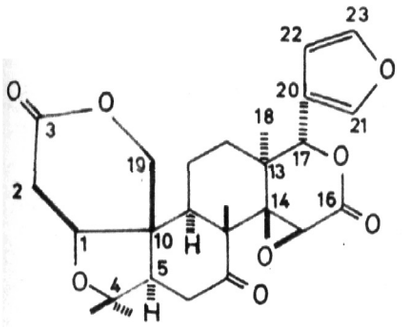
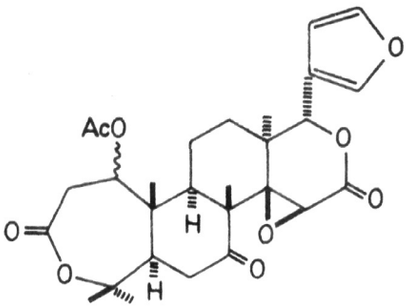


XXX



XXXI



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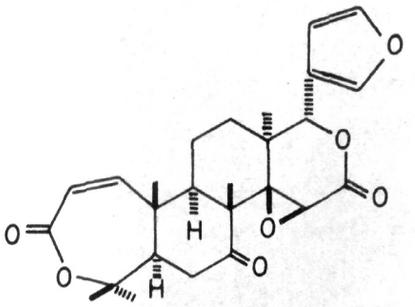

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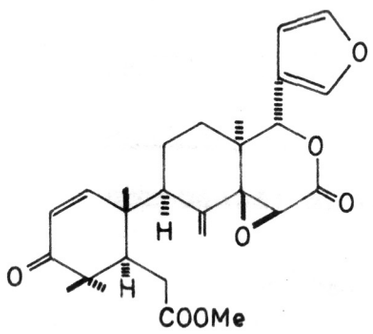
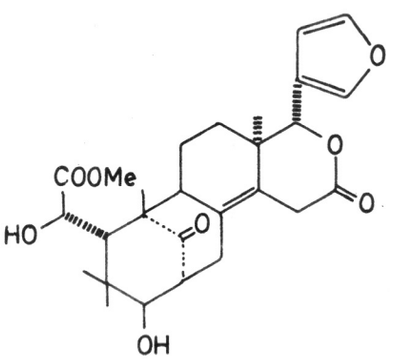


XXXIV



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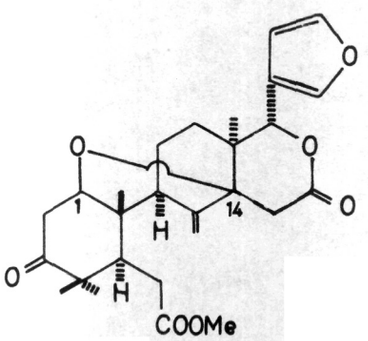

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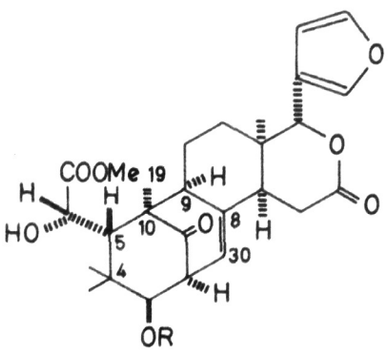


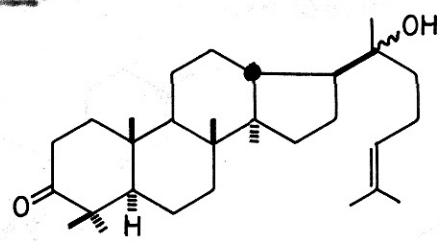
R = tigloyl

XXXVII

CHART 2. TETRANORTRITERPENOIDS

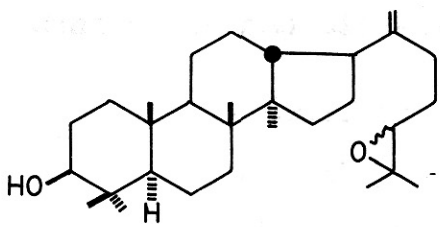
DAMMARANE TYPE[6-10]

The parent compound of this type is dipterocarpol (XXXIX) isolated by van Itallie[90] from the balsam of D.hasseltii and D. trinervis. The structure and stereochemistry was later established by Mills et al.[91] and Durisson et al.[92]

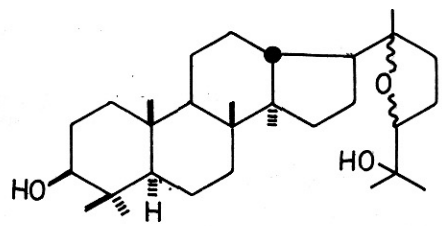


XXXIX

Variations in the dammarane type: 1) Modifications in the side chain has been recently observed in two important compounds: aglaiol (XL)[93] and ocotillol (XLI)[94,95].



XL



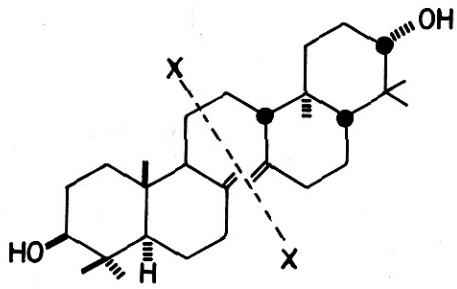
XLI

GROUP II

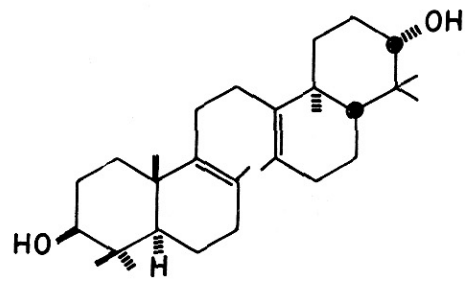
ONOCERANE TYPE

α-Onocerin (XLII), the first member of this type, was isolated in 1855 by Hiasiwetz[96] from the roots of

Ononis spinosa. Its structure was elucidated by Barton and Overton[97] by chemical degradation a hundred years after its isolation and confirmed by total synthesis by Stork et al. (1959)[98]. β-Onocerin (XLIII) is a double bond isomer of α-onocerin, perhaps an artefact obtained by the isomerization of α-onocerin[99].



XLII



XLIII

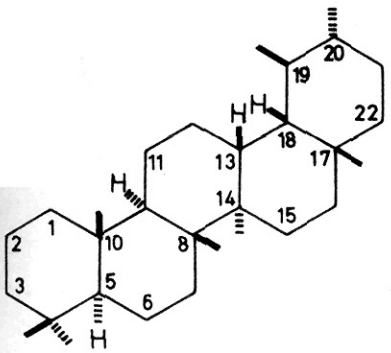
Remarkable feature of this type is its symmetry about the X-X axis. This structure is interesting both chemically and biogenetically[7].

4. PENTACYCLIC TRITERPENOID[2,7,11,12]

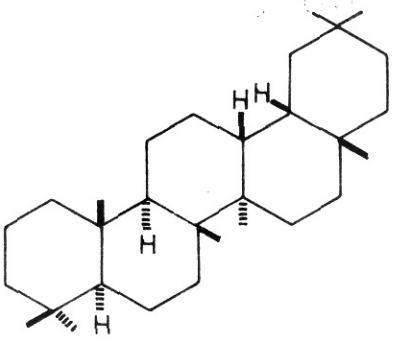
The chemistry of pentacyclic triterpenoids has been reviewed by T.G. Halsall and A.T. Aplin (1964)[12]. This group is by far the largest and is normally divided into six types (Chart 3).

URSANE TYPE[6,7,12]

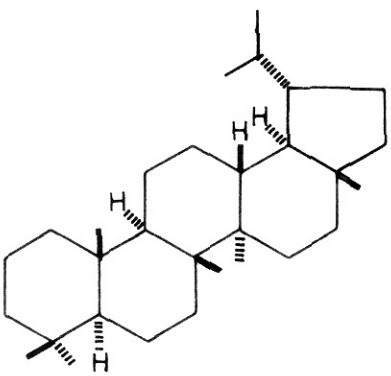
This group is characterised with trans-anti-trans-syn-cis backbone. One of the important members of this group is



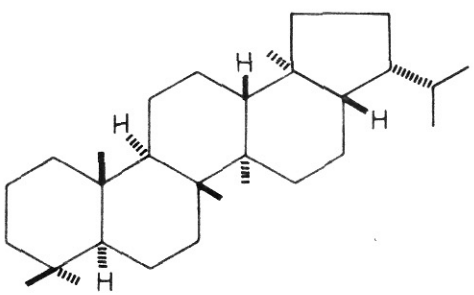
XLIV URSANE



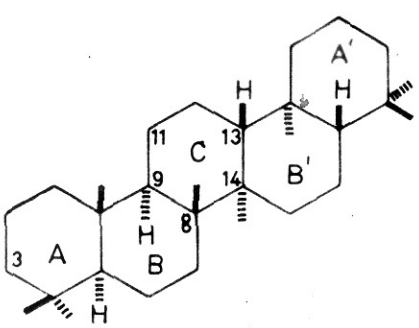
XLV OLEANANE



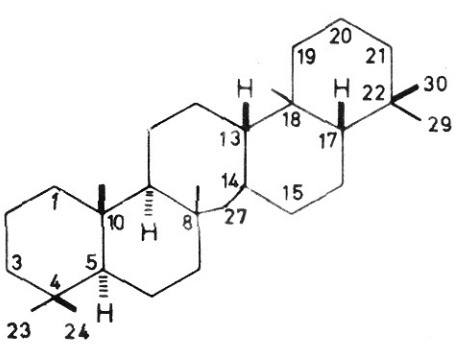
XLVI LUPANE



XLVII HOPANE



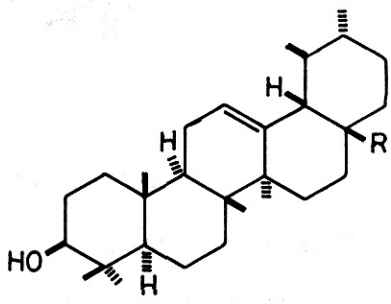
XLVIII GAMMACERANE



XLIX SERRATANE

CHART - 3. PENTACYCLIC TRITERPENOID TYPES

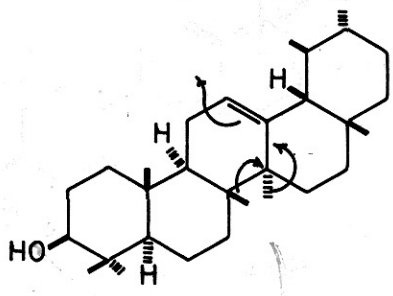
∝-amyrin (L), the main triterpenoid component of the latex from the milk tree (Brosium galactodendron). Its structure[100] was proposed by Spring et al.[101] and Jones et al.[102]. Ursolic acid (LI)[103] is another member of this type.



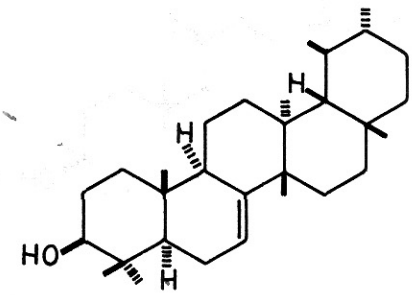
L R = CH_3

LI R = COOH

Baurenol (LII)[104,105] can be derived from ∝-amyrin (L) by the methyl migration.



L

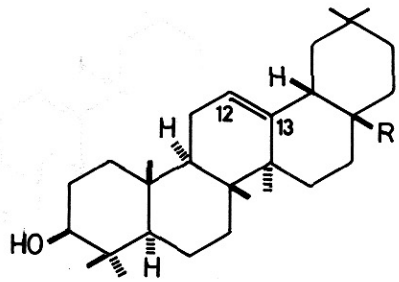


LII

OLEANANE TYPE[5-7,12]:

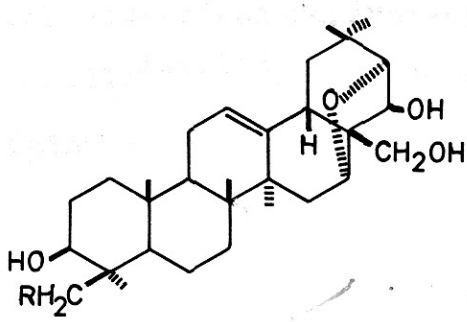
The basic skeleton of this group is with trans-anti-trans-syn-cis backbone. Some of the important members are β-amyrin (LIII) (isolated by Rose[106] from elemi resin and Baup[107] was the first to use the name "amyrin". Its structure has also been established by X-ray analysis) and

oleanolic acid (LIV)[5].

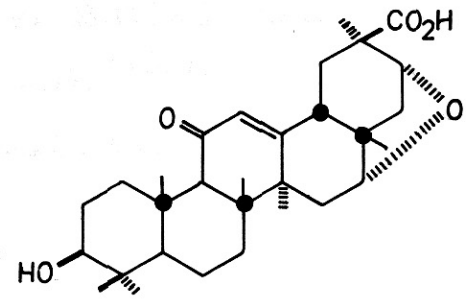


LIII R = CH_3
LIV R = COOH

Ethereal linkages in the "right" side of the molecule. In pentacyclic triterpenes with Δ^{12}-double bond has so far been encountered in only three cases, e.g. aescigenin (LV)[108,109], barringtogenol D (LVI)[108,109] and liquoric acid (LVII)[110].



LV R = OH
LVI R = H



LVII

Variations in Oleanane type: i) Ring A may be modified by simple C-C bond fission e.g. nyctanthic acid (LVIII)[111,112] Fission of C_2-C_3 bond on the oleanane skeleton is found in an acid (LIX) isolated by Crowley[113] from Bursera graveolens.

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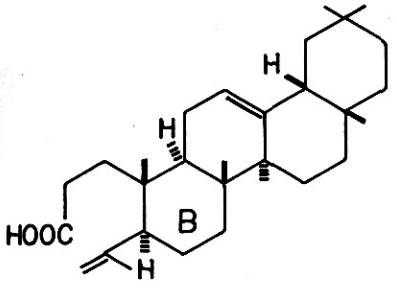
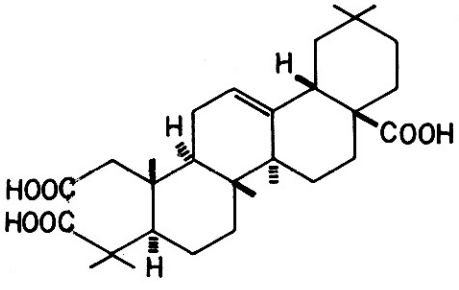
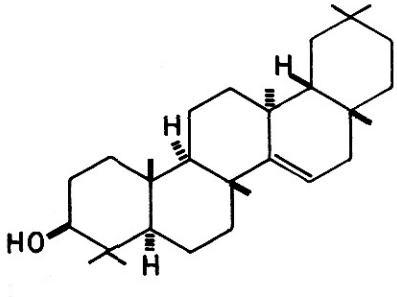


LVIII

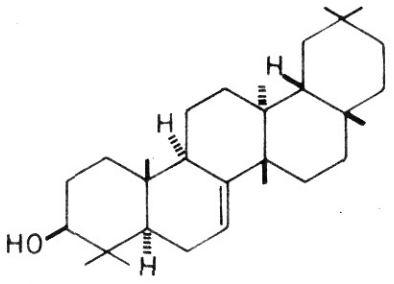


LIX

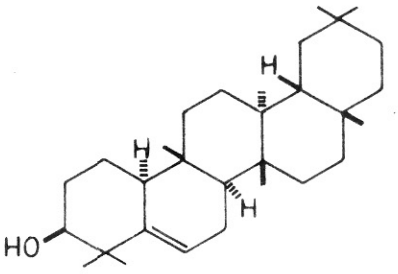
ii) <u>The ring system</u> may be modified by methyl group migration, (a) D-friedo-derivatives e.g. taraxerol (LVI)[114,115] (b) D:C-friedo-derivatives e.g. multiflorenol (LVII)[116,117] (c) D:B-friedo-derivatives e.g. glutinol (LVIII)[117], celasterol (LVIII)[118,119], pristimerin (LVIV)[118,119] and (d) D:A-friedo-derivatives e.g. friedelin (LVV)[5].



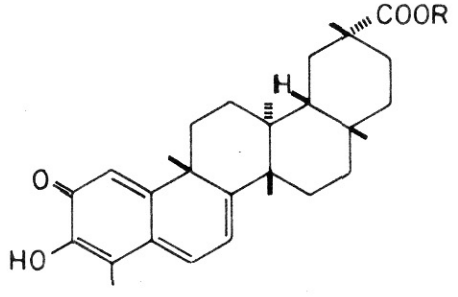
LX



LXI

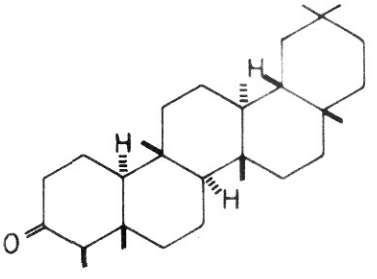


LXII



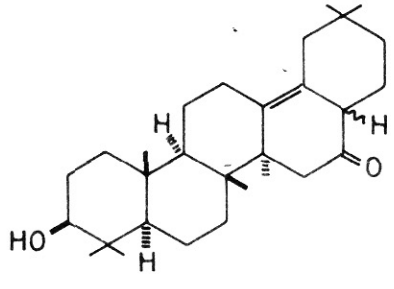
LXIII R = H

LXIV R = CH_3

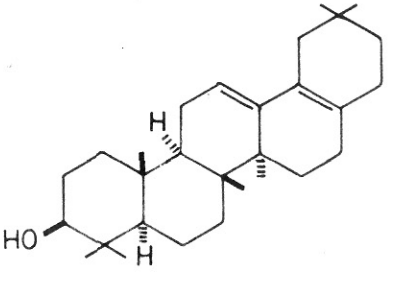


LXV

ii) Another group in which C_{28} has been lost (nor-riterpene) e.g. albigenin (LXVI)[120] and aegiceradienol LXVII)[121,122].



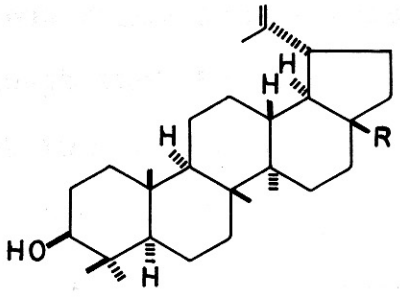
LXVI



LXVII

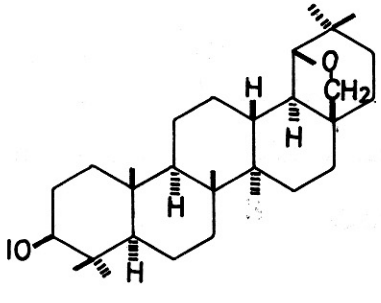
LUPANE TYPE

In this group all the rings are trans-fused and ring E is five membered. Some of the important members of this group are lupeol (LXVIII)[5] (isolated by Schulze and Steiger in 1889[123] from the seeds of the lupinetree, Lupinus albus. and its structure was elucidated by Jones et al.)[124], Betulinic acid (LXIX)[125] and Betulin (LXX)[5,126].

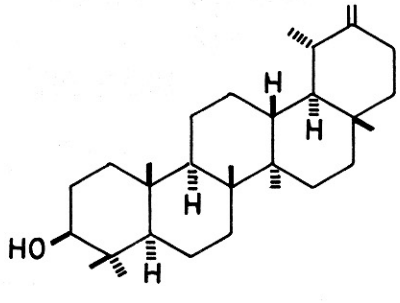


LXVIII R = CH_3
LXIX R = COOH
LXX R = CH_2OH

Variations in Lupane Type: i) The ring system may be modified by methyl group migration e.g. allobetulin (LXXI)[127,128] and taraxasterol (LXXII)[5,11,129].

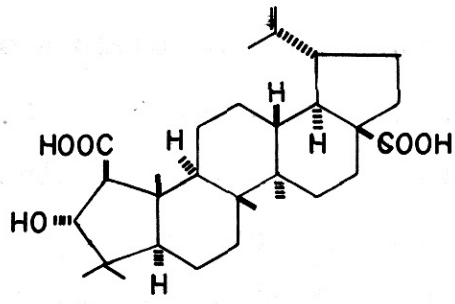


LXXI



LXXII

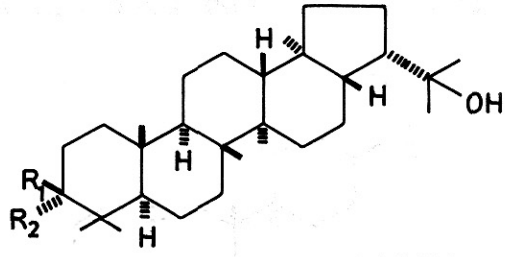
ii) The ring A may be modified to a five membered ring e.g. Ceanothic acid (LXXIII)[130-132].



LXXIII

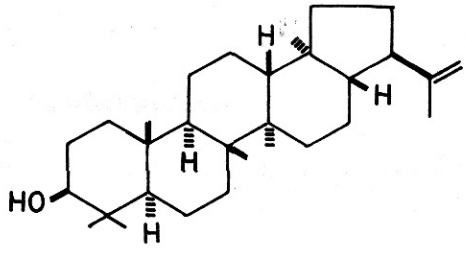
HOPANE TYPE

The carbon framework of this type is very similar to lupane, except that the isopropyl chain is attached at C-21. Some of the important members are hydroxyhopanone (LXXIV)[133-135] and hopan-3β-, 22-diol-3β-monoacetate (LXXV)[12].



LXXIV $R_1 = R_2 = O$
LXXV $R_1 = OAc$
$R_2 = H$

Variations in Hopane Type: i) The ring system may have a different configuration at C_{21} e.g. moretenol (LXXVI)[136] has isohopane skeleton (21αH).

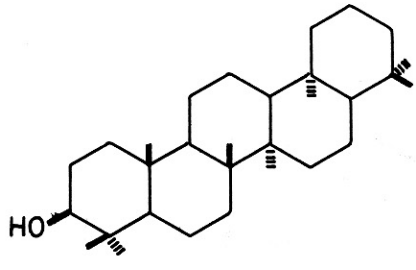


LXXVI

ii) The hopane skeleton may be rearranged by methyl group migration. a) E:C-friedo e.g. fernene (LXXVII)[137,138] and davallic acid (LXXVIII)[139] and arundoin (LXXIX)[140,141]. b) E:A-friedo e.g. adiantoxide (LXXX)[142]. c) D:C-friedo-derivative e.g. arborinol[143] (LXXXI). d) E:B-friedo e.g. simiarenol[144] (LXXXII). (Chart 4).

GAMMACERANE TYPE

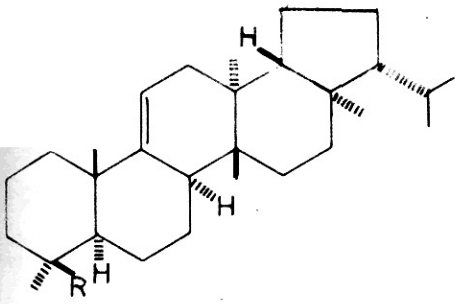
Tetrahymanol (LXXXIII) is the first pentacyclic triterpenoid alcohol isolated from an organism of animal kingdom by Mallory et al.[145]. Its structure and synthesis have been reported by Tsuda et al.[146]. The isolation of the hydrocarbon has been reported by Hills et al.[147a,b]



LXXXIII

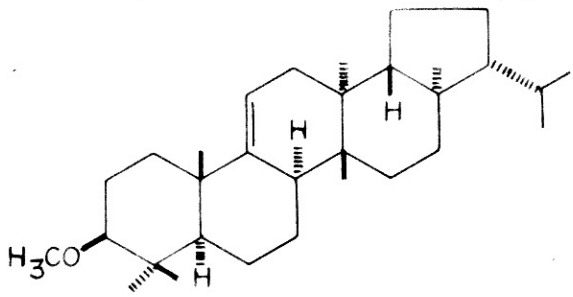
SERRATANE TYPE

This new skeleton with ring C as seven membered has been recently reported by Imubushi et al.[148a,b]. The first member reported was serratenediol (LXXXIV)[148a,b], later 21-episerratenediol (LXXXV)[149,150], tohogenol (LXXXVI)[151] and tohogeninol (LXXXVII)[151] were reported.

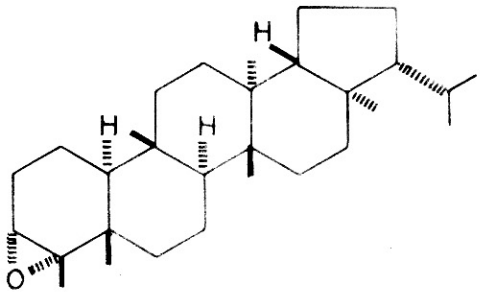


LXXVII R = CH_3

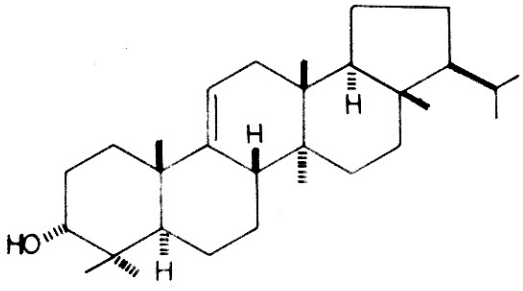
LXXVIII R = COOH



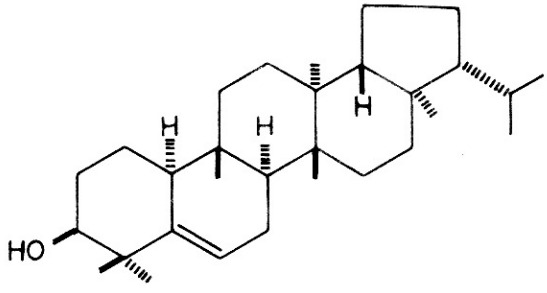
LXXIX



LXXX

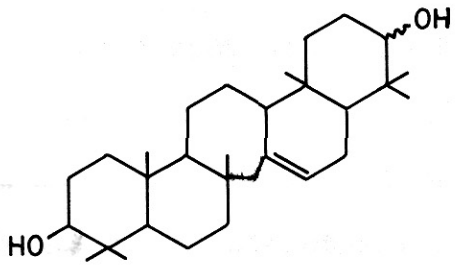


LXXXI

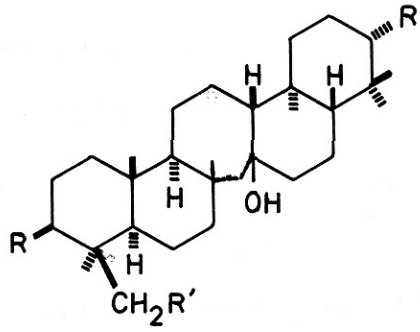


LXXXII

CHART - 4.



LXXXIV β-OH
LXXXV ∝-OH



LXXXVI R=OH, R'=H
LXXXVII R=R'=OH

The isolation of the hydrocarbon serratene has been recently reported by Berti et al.[152].

BIOGENESIS OF TRITERPENOIDS[7,10,12,153-158]

Stimulated by the brilliant deduction of Woodward and Bloch[159] that the steroids and triterpenoids came from squalene (I) with its terminal isoprenoid units forming their terminal rings (or side-chain), Ruzicka et al.[157-158] have proposed a comprehensive scheme for the biogenesis of the triterpenoids. Stork and Burgstahler[160] have independently proposed a similar theory. Both groups have stated that a somewhat different path is required for the steroids and lanosterols and for the other triterpenoids. Convincing report for the essential correctness of the postulated pathways comes from labelling studies on β-amyrin[161], lupeol, betulin and betulinic acid[162].

The various triterpenoids known today can be derived from different basic representatives*, which may differ from each other in the carbon skeleton, in the position of the double bond, or in configuration. The derivation from squalene of these basic representatives with all their structural and configurational details rests on the assumption of a few reasonable postulates[157]:

1) The cyclisation of squalene takes place in the all-trans-configuration and in a well-defined sequence of chair and boat conformations.

2) The transformation from squalene to the triterpenes proceeds according to the rules of anti-planar (=anti-parallel) cationic 1,2-addition, 1,2-rearrangement (1,2 shift) and 1,2-elimination.

3) All steps on the route from squalene to the final product proceed in a non-stop reaction i.e. no intermediates produced by neutralisation of the formal cationic charge should occur.

---

*The term "basic representative" is meant to indicate those triterpenes in which the sum of the number of carbon rings and of double bonds (actual and pontentia) is equal to six. In 1955, 14 such representatives were known, but δ-amyrin was overlooked in the paper[158]. Since then, three new representatives have been found (glutinone, bauerenol and hydroxy hopanone), which all conform to the biogenetic isoprene rule.

The biogenetic reactions are arranged in nine Charts (5 - 13). The large dots in the formulae represent methyl groups, the smaller dots hydrogen atoms.

CYCLISATION OF ALL-TRANS-SQUALENE IN CHAIR-BOAT-CHAIR-BOAT CONFORMATIONAL SEQUENCE - The biogenesis of lanosterol[163-166] (Chart 5) requires this conformational sequence of all-trans-squalene. The boat conformation of ring B, in contrast to its chair conformation in squalene in Chart 6 , is the condition for the formation of the configuration of the four asymmetric centres in ring D and the long side chain of lanosterol. For the same reason the boat conformation of ring D in the intermediate (LXXXIX) must change to a chair conformation (XC) before the formation of the intermediate (XCI).

CYCLISATION OF ALL-TRANS-SQUALENE IN CHAIR-CHAIR-CHAIR-BOAT CONFORMATIONAL SEQUENCE - This second cyclisation mode is subdivided into three Charts (6,7,8).

It should be recalled that lanosterol and tirucallol are enantiomeric at the four asymmetric centres in ring D and the long side-chain. The reaction sequence (LXXXVIII) → (LXXXIX) → (XC) → (XCI) in Chart 5 can therefore be considered as a parallel to the sequence (XCIII) → (XCIV) → (XCV) → (XCVI) in Chart 6 . The intermediate (XCIV) undergoes a rearrangement to the bridged cation (XCVII), from which euphol can be derived. The two dammarenediols, differing

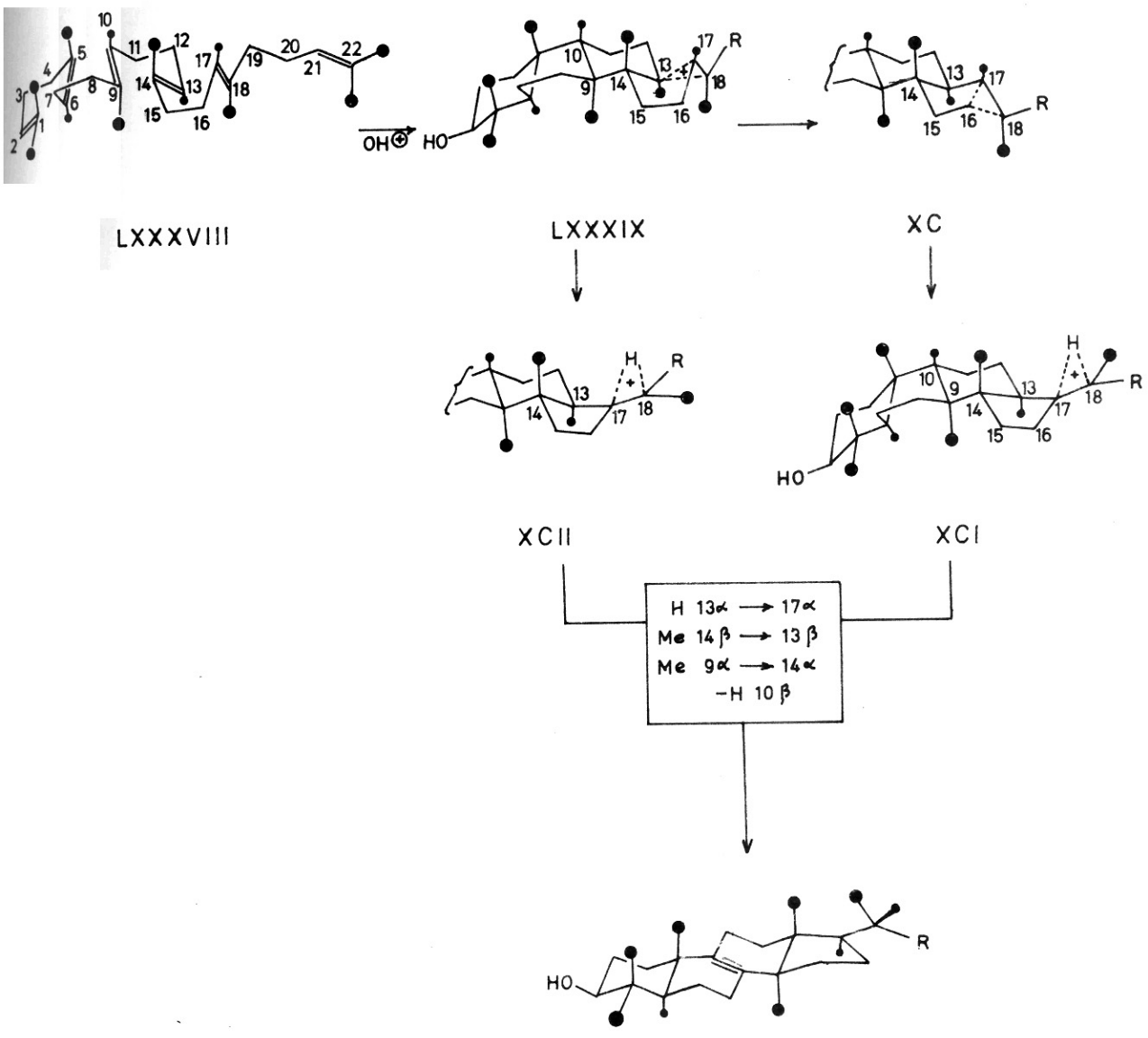
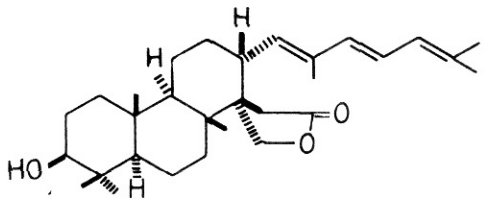

LXXXVIII
LXXXIX
XC
XCII
XCI
H 13α → 17α
Me 14β → 13β
Me 9α → 14α
−H 10β
HO
R
LANOSTEROL

CHART – 5.



EBELIN LACTONE

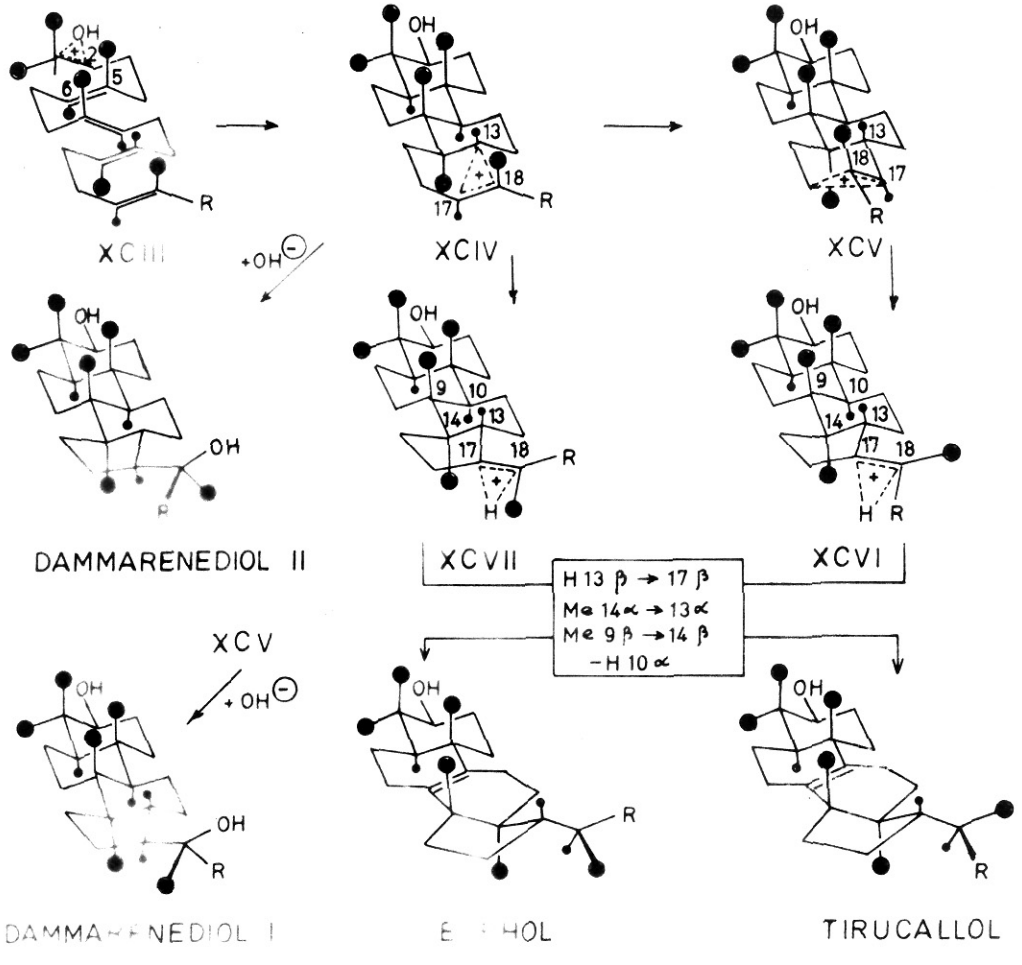


CHART - 6.

from each other only in the configuration of the long side chain, are produced directly from the intermediates (XCIV) and (XCV) respectively by antiplanar addition of OH^-.

The ebelin lactone is probably produced by oxidative cleavage of ring D in (XCIV).

All the pentacyclic triterpenes are derived from the non-classical cation (XCV) by cyclisation of the long side-chain in its boat conformation (Chart 7). The intermediate (XCVIII) so produced gives rise to lupeol by elimination of hydrogen.

On the otherhand the formation of all the triterpenes with a six-membered ring E requires the rearrangement of the same ring E in the intermediate (XCVIII) to a chair conformation (XCIX). These triterpenes exist in two structural types. One type is characterised by the presence of the gem-dimethyl group in ring E (cf. Chart 8), whereas in the other type ring E carries two isolated methyl groups (Chart 7). In two representatives of the latter type (taraxasterol and ψ-taraxasterol) the methyl group at position 21 has α-configuration, in the other two representatives [α-amyrin and bauerenol][167] its configuration is β. This difference in configuration requires two additional intermediates (C) and (CI).

Chart 8 contains the pentacyclic triterpenes with the gem-dimethyl group in ring E. Three basic representatives

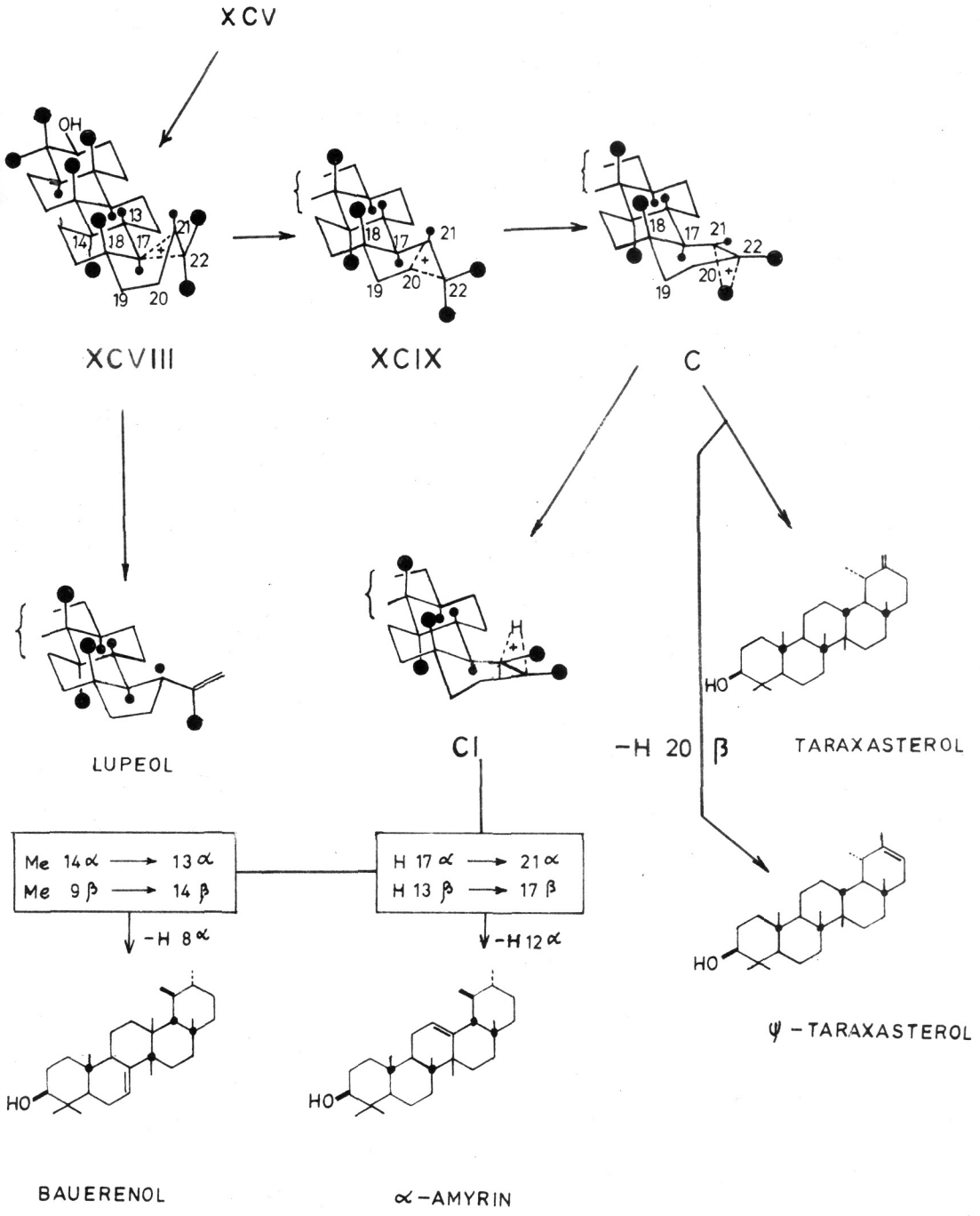

XCV
OH
XCVIII
XCIX
C
LUPEOL
CI
-H 20 β
TARAXASTEROL
Me 14α → 13α
Me 9β → 14β
H 17α → 21α
H 13β → 17β
-H 8α
-H 12α
HO
BAUERENOL
α-AMYRIN
ψ-TARAXASTEROL

CHART - 7 .

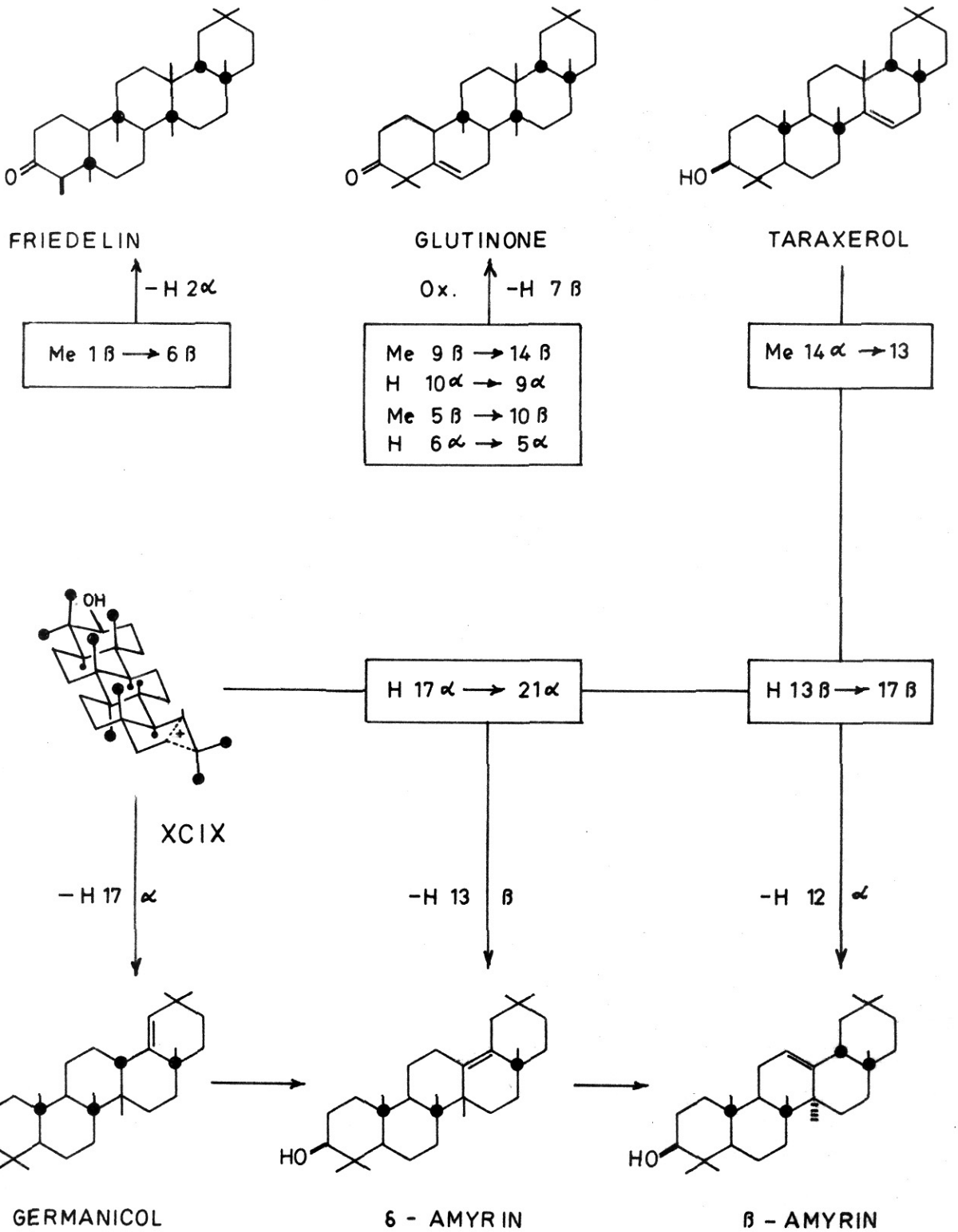

FRIEDELIN
GLUTINONE
TARAXEROL
−H 2α
Ox.
−H 7 β
Me 1 β → 6 β
Me 9 β → 14 β
H 10α → 9α
Me 5 β → 10 β
H 6α → 5α
Me 14α → 13
OH
H 17α → 21α
H 13 β → 17 β
XCIX
−H 17 α
−H 13 β
−H 12 α
HO
HO
HO
GERMANICOL
δ - AMYRIN
β - AMYRIN

CHART – 8.

of this type are derived from the bridged cation (XXI) without rearrangement, by hydrogen shifts and a final hydrogen elimination. Thus germanicol, δ-amyrin[168] and β-amyrin are produced. They all have the same carbon skeleton and differ only in the position of the double bond in ring E, D and C respectively. The formation of the other three basic representatives taraxerol, glutinone[139] and friedelin, requires shifts of methyl groups in addition to further hydrogen shifts.

CYCLISATION OF ALL-TRANS-SQUALENE IN CHAIR-CHAIR-CHAIR-CHAIR-CHAIR CONFORMATIONAL SEQUENCE - This cyclisation mode leads to the gammacerane and the hopane ring system, the simplest biogenetically, of the pentacyclic triterpenes and thence by a non-concerted rearrangement to the carbon skeletons of fernane group[137,138], simiarenol and adiantoxide (Chart 9).

CYCLISATION OF ALL-TRANS-SQUALENE IN CHAIR-CHAIR-CHAIR-CHAIR-BOAT CONFORMATIONAL SEQUENCE - This mode of cyclisation leads to 22α (H) hopane derivative, moretenol (Chart 10).

CYCLISATION OF ALL-TRANS-SQUALENE IN CHAIR-BOAT-CHAIR-CHAIR-CHAIR CONFORMATIONAL SEQUENCE - This cyclisation mode shown in Chart 11 leads to arborane derivatives.

CYCLISATION OF ALL-TRANS-SQUALENE SIMULTANEOUSLY FROM BOTH ENDS - Three natural triterpenes, ambrein, onocerin and

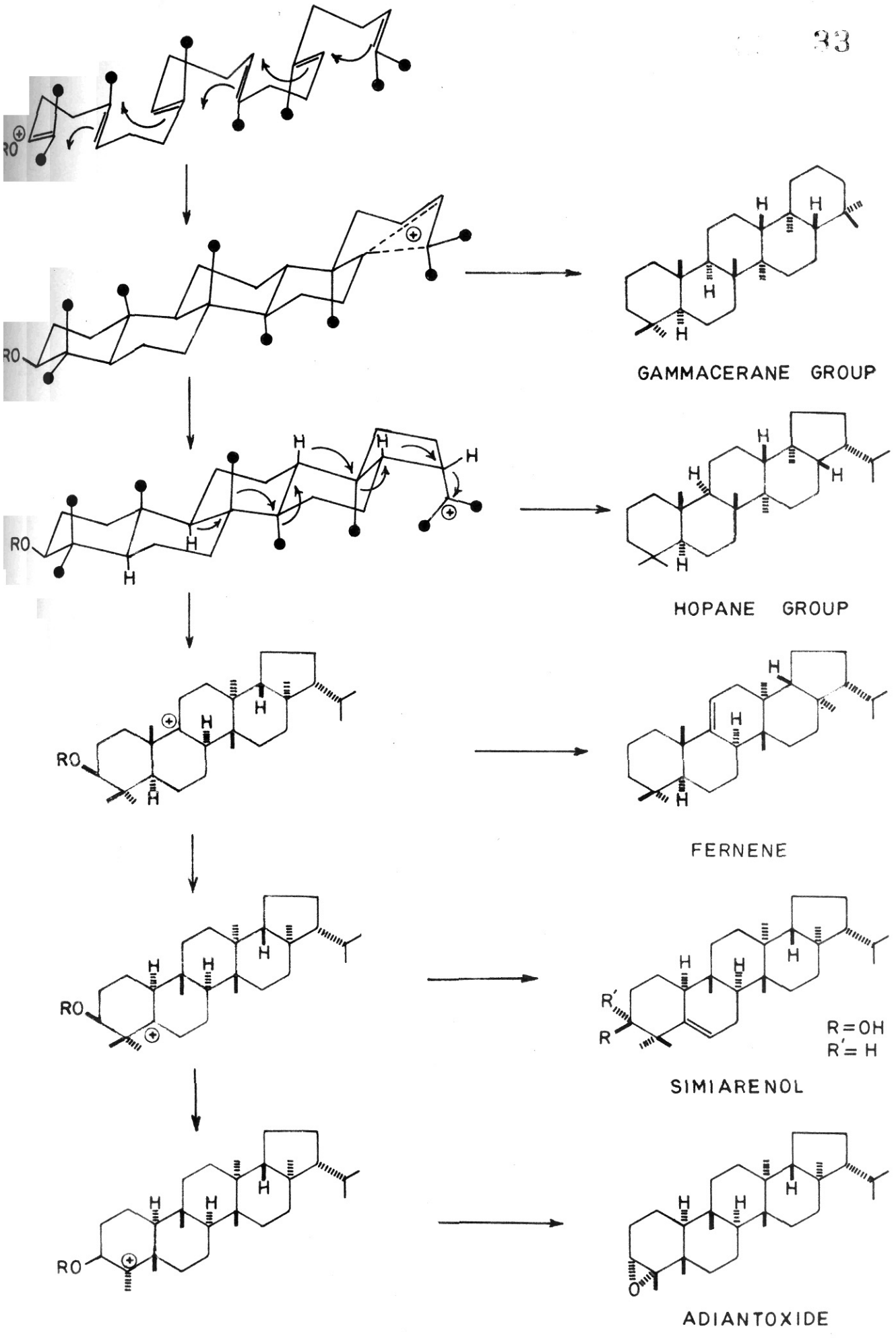
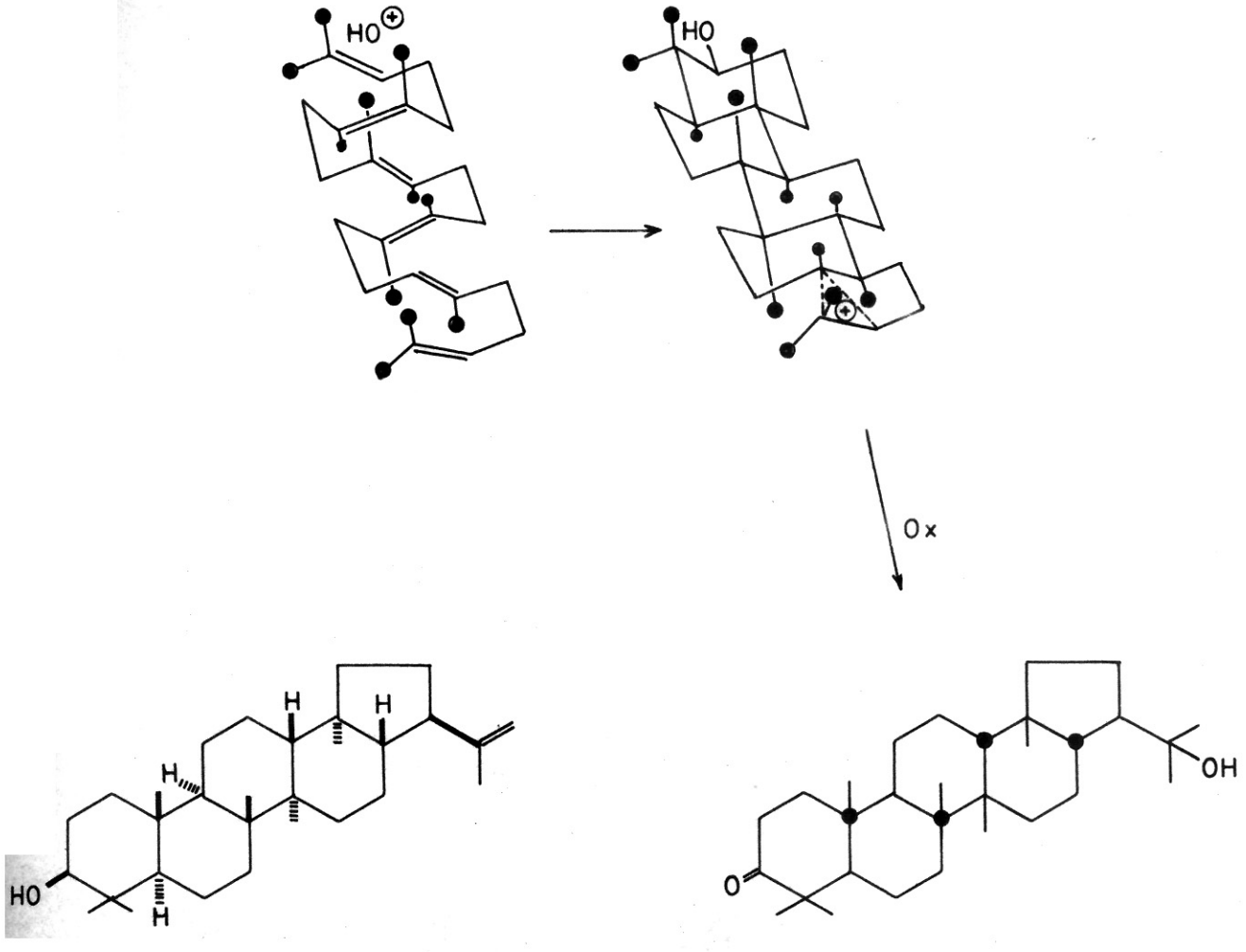

RO
GAMMACERANE GROUP
HOPANE GROUP
FERNENE
R=OH
R'=H
SIMIARENOL
ADIANTOXIDE

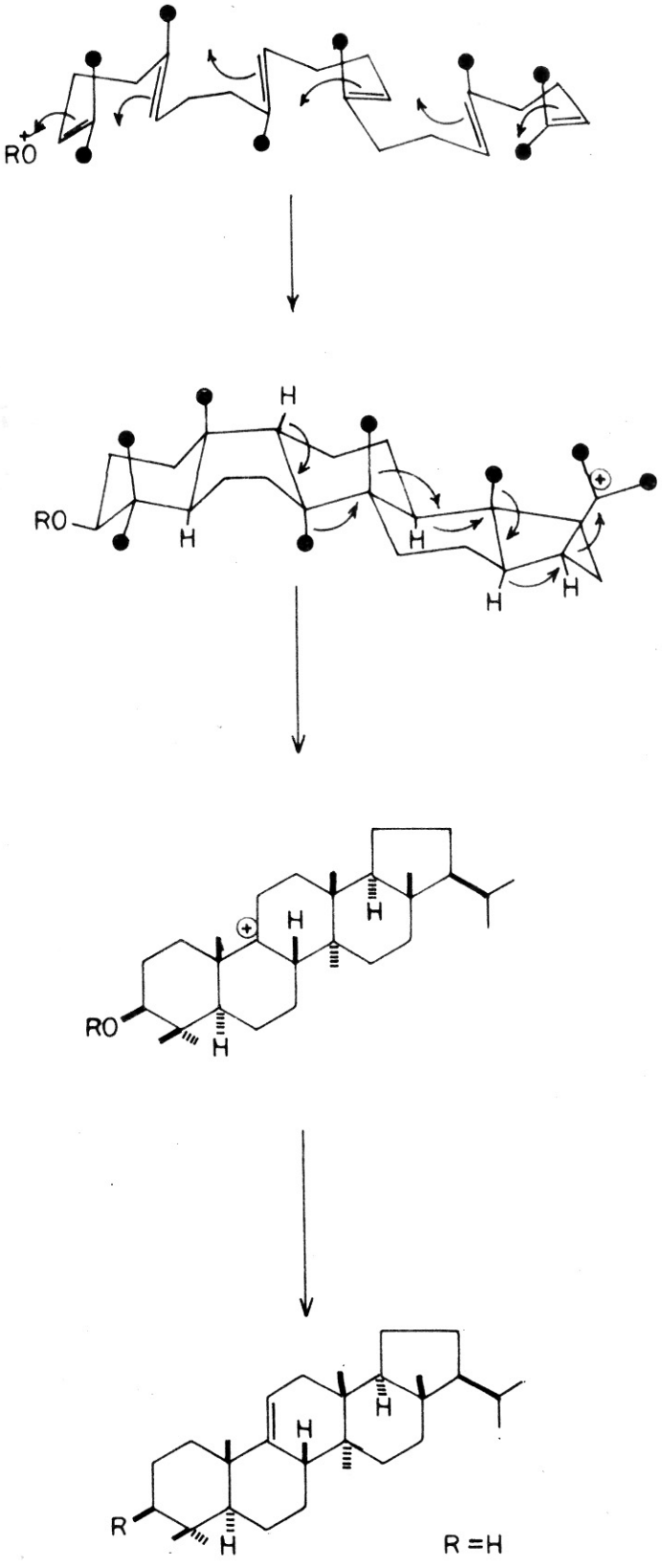
CHART – 9.



MORETENOL

HYDROXYHOPANONE

CHART - 10.

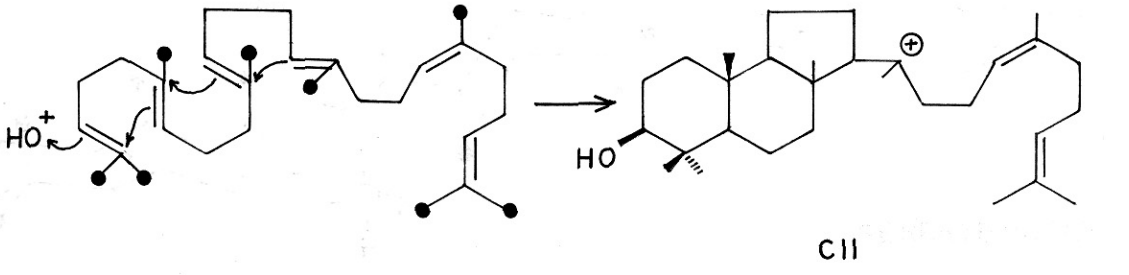


ARBORANE GROUP

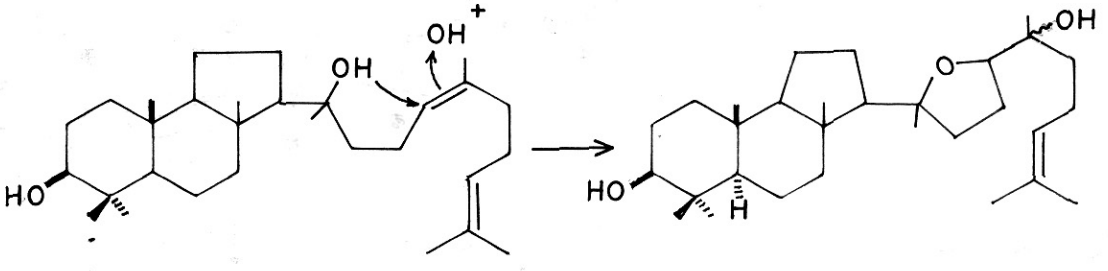
CHART – 11.

serratane derivatives are derivable from all-trans-squalene with the ends folded in the chair-chair conformation by a simultaneous attack of OH^+ at both ends (Chart 12).

CYCLISATION OF ALL-TRANS-SQUALENE WITH CLOSURE OF RING C MARKOWNIKOF-WISE - Usually the closure of the rings of squalene follows anti-Markownikoff rule. If the folding for ring C takes place in Markownikoff fashion, the resulting species (CII) is eminently suited for incorporating the malabaricane group e.g. malabaricanediol.



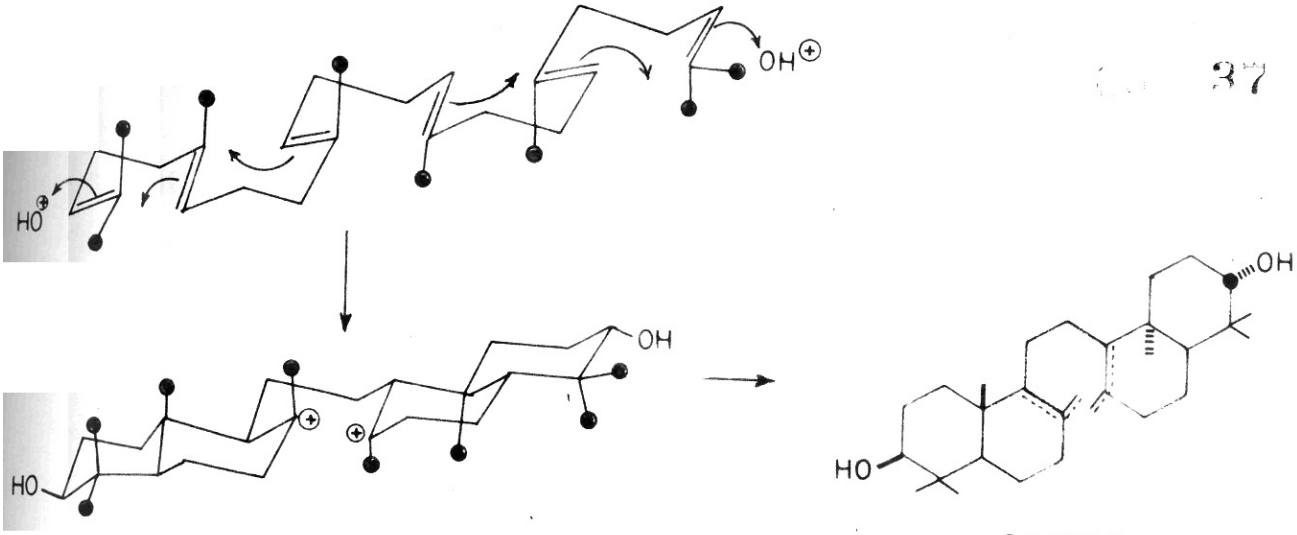
CII



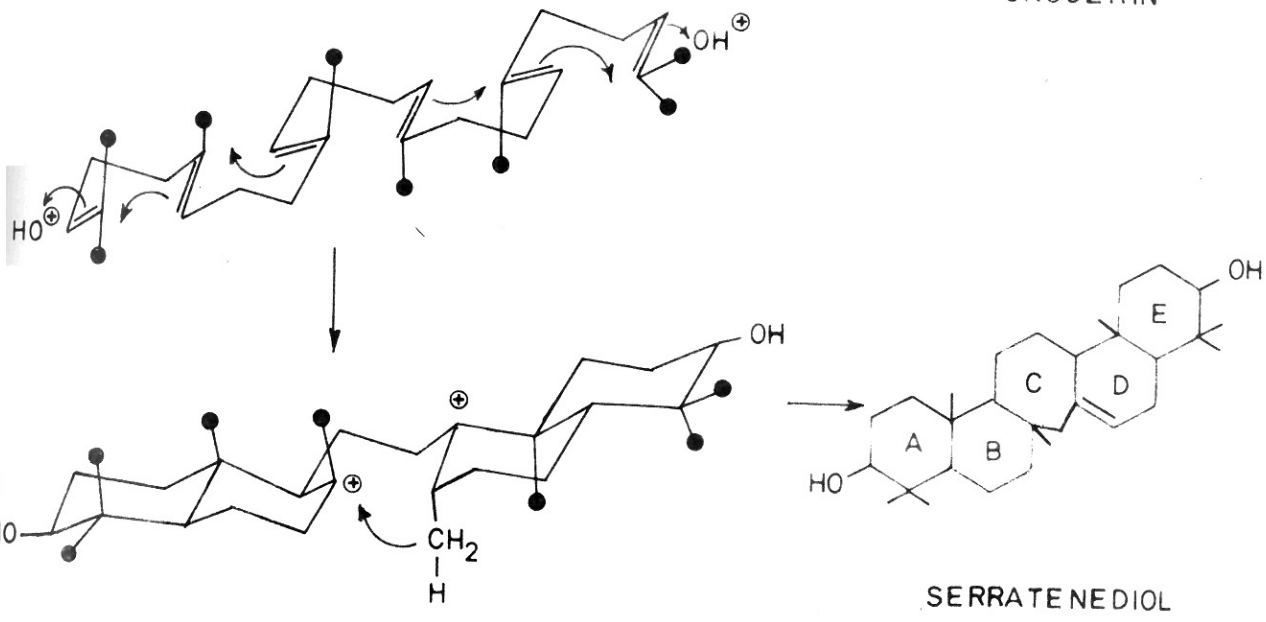
Malabaricanediol

BIOGENESIS OF TETRANORTRITERPENOIDS

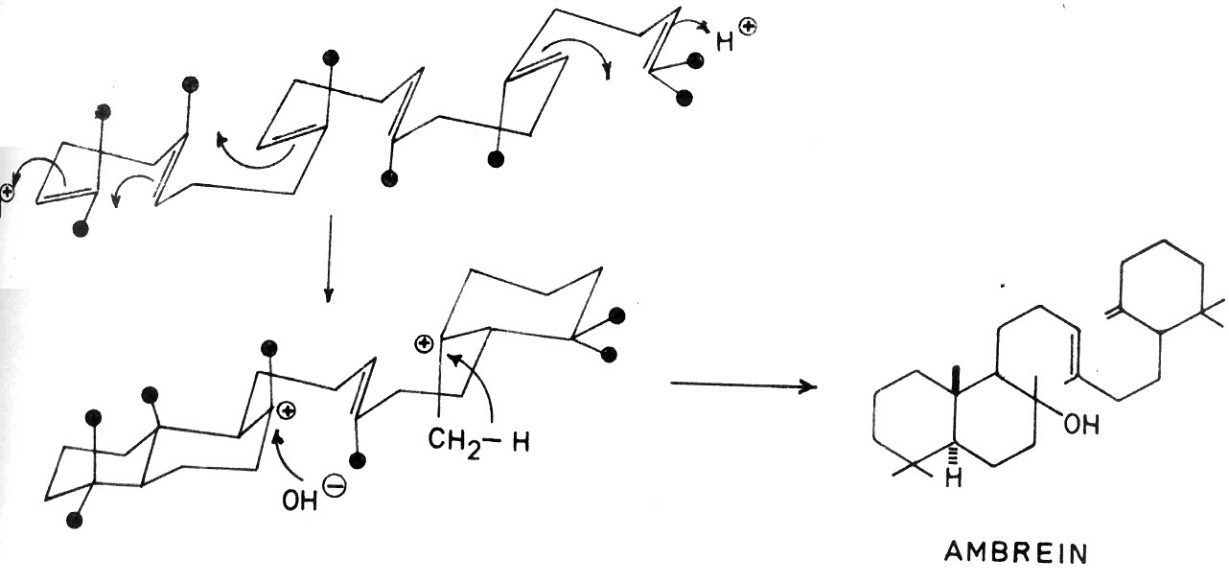
Tetranortriterpenoids may be derived from bytyrospermol with the formation of a furan ring by the cyclisation



ONOCERIN



SERRATENEDIOL



AMBREIN

CHART – 12.

of C-20 to C-23 followed by the loss of four carbon atoms at the end of the chain (C-24 - C-27) leading thereby to an intermediate (CIII) which gives rise to cedrelone, anthothecol and nimbin. In this connection the isolation of turraenthin[170] from Meliaceae family needs mention as it supplies the missing link in the same stereochemical compounds with a 17-β'-furyl substituent. The formation of α,β-epoxy- -lactone moiety may be explained by the biochemical equivalent of the Baeyer-Villiger oxidation of a C-16 ketone derived from (CIII), to furnish the D-lactone which with the migration of a methyl group from C-14 to C-8 gives rise to a precursor (CIV) of these furanolactone. Such a reaction is known to occur in dihydrobutyrospermyl acetate[171] (CV) which furnishes a product[172] (CVI) of the same partial structure as gedunin and the related products. Moreover, it is notable that ketonic acid[173], a pentacyclic terpenoid which occurs in the Meliaceae family, can also be built up from the same branch skeleton generated from squalene. Thus a tentative biosynthetic scheme covering the skeletally related to C-26 modified triterpenes has been outlined in Chart 13 .

HYL ANGOLENSATE

ANDIROBIN

7-DEACETOXY-7-KETOGEDUNIN

GEDUNIN

KHIVORIN

OXID . CLEAV.
bet. C-7 & C-8

OXID. CLEAV. BET. C-3 & C-4 AND OXID.
CYC. OF C-3 CARBOXYL WITH C-19

LIMONIN

CIV

TURRAENTHIN

BUTYROSPERMOL

1. OXID. CLEAV.
2. HYDRATION
3. ALLYLIC REARRANG.

NIMBIN

ANTHOTHECOL

MICHAEL
ADDITION
BETWEEN C-2 & C-30

TENOLIDE AND
ED BICYCLONONANOLIDES

CEDRELONE

CVI

SQUALENE

MEVALONIC ACID

CHART 13.

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chapter two
isolation

Ailanthus Malabarica D C

I S O L A T I O N

Ailanthus Desf.[1] belongs to a genus Simaroubaceae which includes about 8 species of trees and shrubs distributed in Southern Asia and Australia. Four species occur in India viz. Ailanthus glandulosa Desf [= Ailanthus altissima (Mill) swingle], Ailanthus malabarica DC, Ailanthus grandis Prain and Ailanthus excelsa Roxb.

Ailanthus malabarica DC* [2,3,4,5] is a lofty tree with a tall cylindrical trunk and thick rough bark, often with bright red colored grains of resin. It is found in the evergreen forests of the western ghats[1] (from North Kanara and Mysore to Travancore: upto 5,000 feet), in Pegu Yoma (Burma) and in Ceylon[1]. It is often planted in South India for ornamental purposes.

Leaves are very large[2], 1.5 - 2 ft, crowded, spreading and pinnate; flowers white, small; and the seed is much compressed and circular. The leaves are the source of a black dye used for coloring satin[4].

Its bark is bitter and is employed in the indigenous systems of medicine[6] in the treatment of dyspepsia, chronic

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*Various local names[5]: Marathi - Guggula-dhup; Tamil - Perumaram; Telugu - Maddipalu.

bronchitis, asthma and diarrhoea, and is recommended as a tonic and febrifuge[2].

On incision the bark yields a dark colored, highly viscous aromatic resin known as Mattipal[3], which in turn hardens into a brittle resin with a strong balsamic odour. It is collected for local use as incense and forms an ingredient of agar-battis[1].

The wood[7] is white, very light, soft and spongy. The timber is used for packing cases, fishing floats, boats, spear sheaths, sword handles, toys and drums[1].

PREVIOUS WORK

Ailanthus malabarica and Ailanthus glandulosa have been the subject of investigations by a number of groups. The summary of the earlier work is given below.

In 1928 Scherzer[8] reported the isolation of ceryl alcohol, an unidentified hydrocarbon, palmitic and stearic acids from the EtOH extract of Ailanthus glandulosa.

Wasicky and Oeriu[9] have isolated a bitter principle, Ailanthin, $C_{36}H_{50}O_{10}$, m.p. 223-24° from the bark of the glandulosa species.

From the leaves of Ailanthus glandulosa, tannins and from the wood, phytosterol, high molecular weight alcohols, saponins, quassin and quercetin, sugars and vanillins have

been reported by Bernasconi[10].

In a reinvestigation of glandulosa species by Casinovi[11,12] et al. and Polonsky et al.[13], bitter principles related to quassin (I) viz. chaparrinone (II), ailanthone (III), amarolide (IV) and its derivatives have been reported.

From Ailanthus malabarica Hooper[14] obtained ailanthic acid.

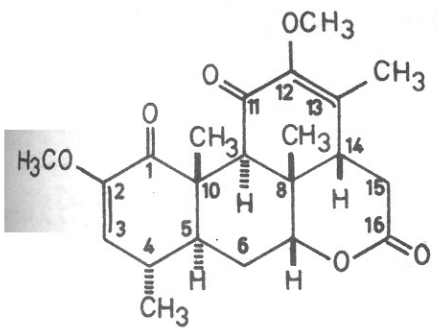
In a reinvestigation of Ailanthus malabarica Dhar and coworkers[15,16] isolated a steroidal compound, malanthin ($C_{21}H_{30}O_4$) m.p. 152-6°, for which they have assigned tentative partial structure (V).(Chart 1)

PRESENT WORK

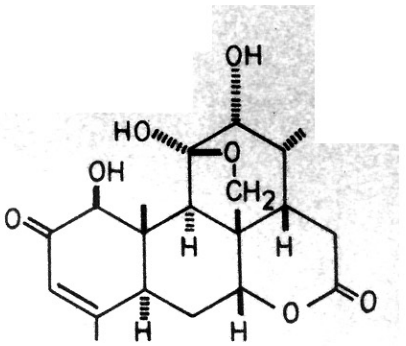
The above work prompted us to undertake a systematic investigation of the oleo resin of Ailanthus malabarica DC.

In the first instance the resin was separated into acid (~22%) and neutral (~76%) fractions. A preliminary thin layer chromatoplate of the neutral portion (Fig.1) revealed it to be mixture of at least 15 compounds, ten of which have been separated by column, preparative layer and IDCC[20] chromatographies.

The scheme finally worked out for the isolation of



I



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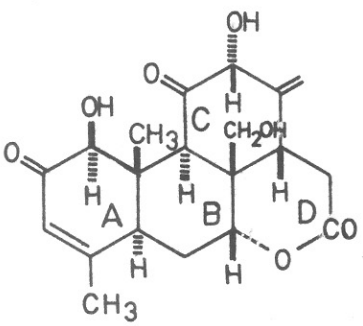

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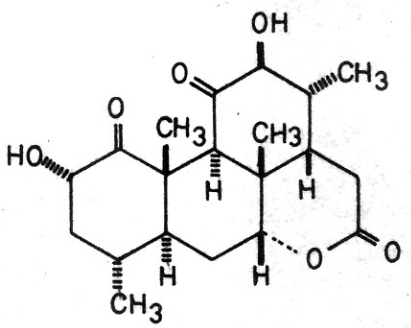

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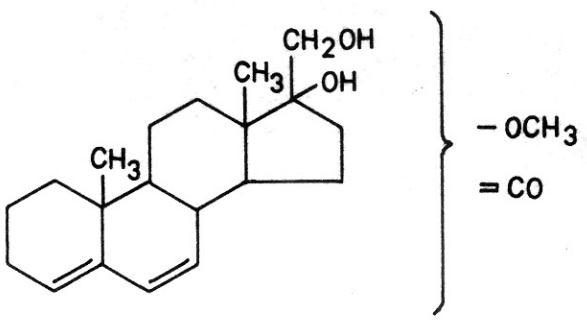
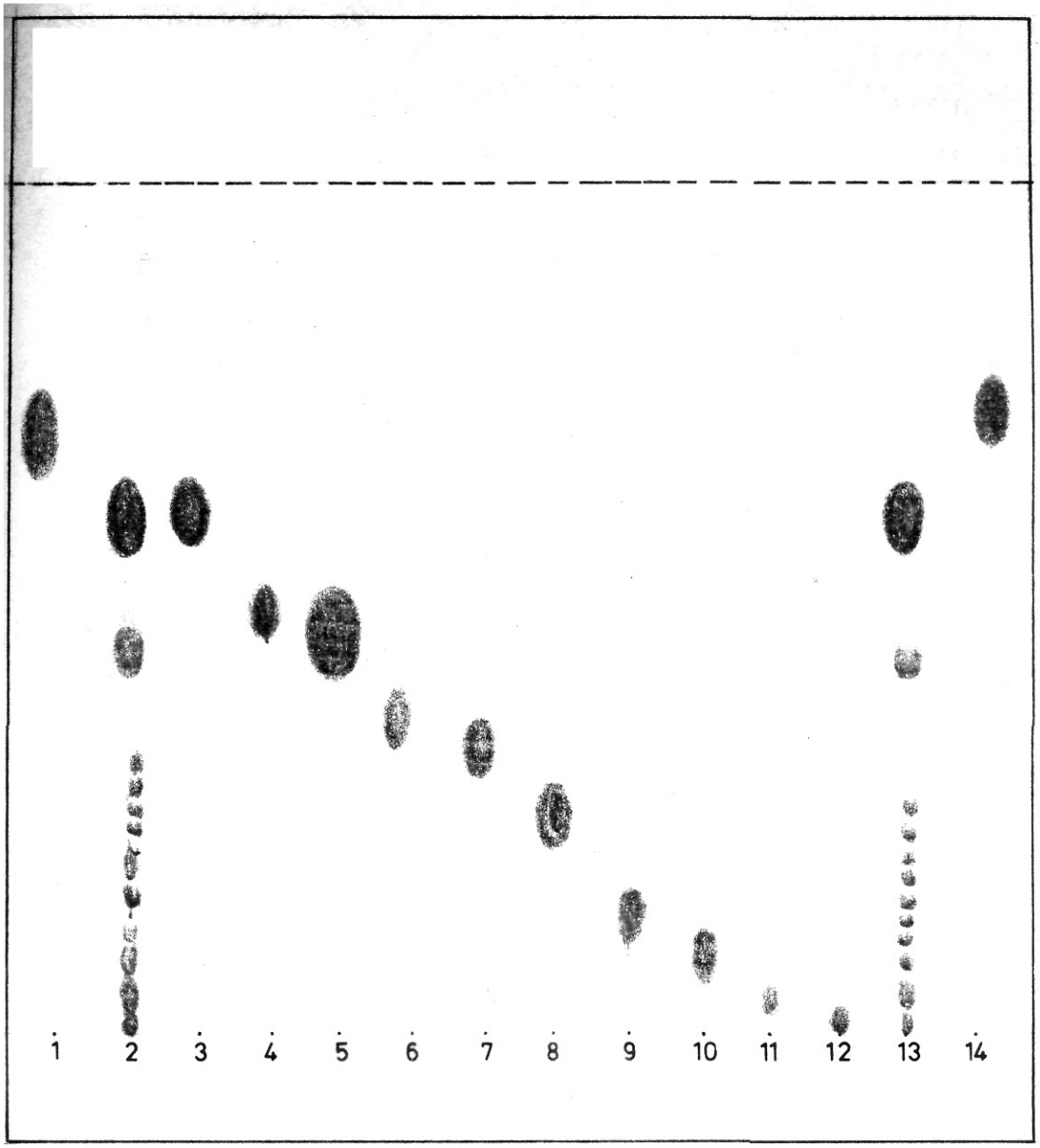


V

CHART – 1.



SILICA GEL G PLATE SOLVENT SYSTEM – BENZENE + ETHYLACETATE (75:25)
SPRAYING REAGENT – 0·5% VANILLIN IN PHOSPHORIC ACID (1:1)

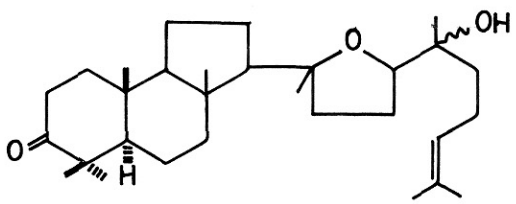
SPOTS – 1 & 14 - SUDAN RED , 2 & 13 TOTAL NEUTRAL FRACTION
3 MALABARICOL, 4 COMPOUND B_1, 5 MALABARICANE DIOL B_2
6 EPOXYMALABARICOL, 7 COMPOUND C_2
8 EPOXYMALABARICANE DIOL 9 COMPOUND E_1
10 COMPOUND F_1 11 COMPOUND G 12 COMPOUND G_2

FIG. 1. THIN LAYER CHROMATOGRAM OF TRITERPENOIDS OF NEUTRAL FRACTION OF AILANTHUS MALABARICA DC

these compounds is outlined in Fig.2. Initially the neutral fraction is roughly chromatographed over SiO_2 gel column into seven fractions (Fig.3a and b) and each fraction, next, systematically recharged.

5% EtOAc in benzene eluate A

This fraction amounted to ca. 52.5% of the total neutral portion, which was further separated into three pure compounds according to scheme shown in Fig.2. Compound A_1, [$C_{30}H_{50}O_3$, m.p. 68-69.5°, $[\alpha]_D$ +36.09°, (~ 45.25% of the total neutral extract)] being the major component, its structure elucidation was undertaken first and as a result of the work discussed in Chapter III, its structure has been established to be (VI) and has been named malabaricol.



VI

Of the other two compounds (Fig.4), B_2 (~ 70%) has been shown to possess structure (VII) and has been designated malabaricanediol (discussed in Chapter IV).

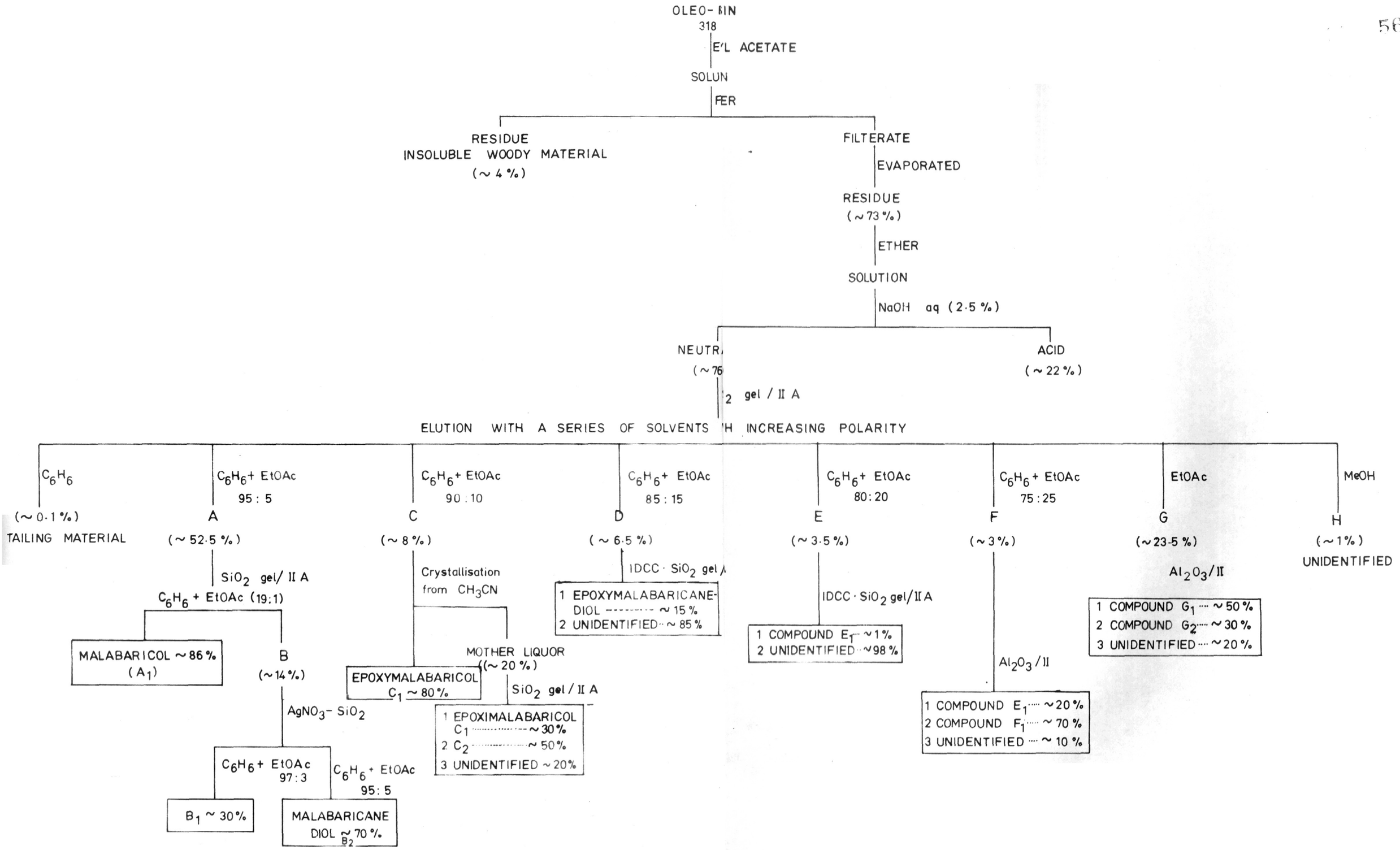
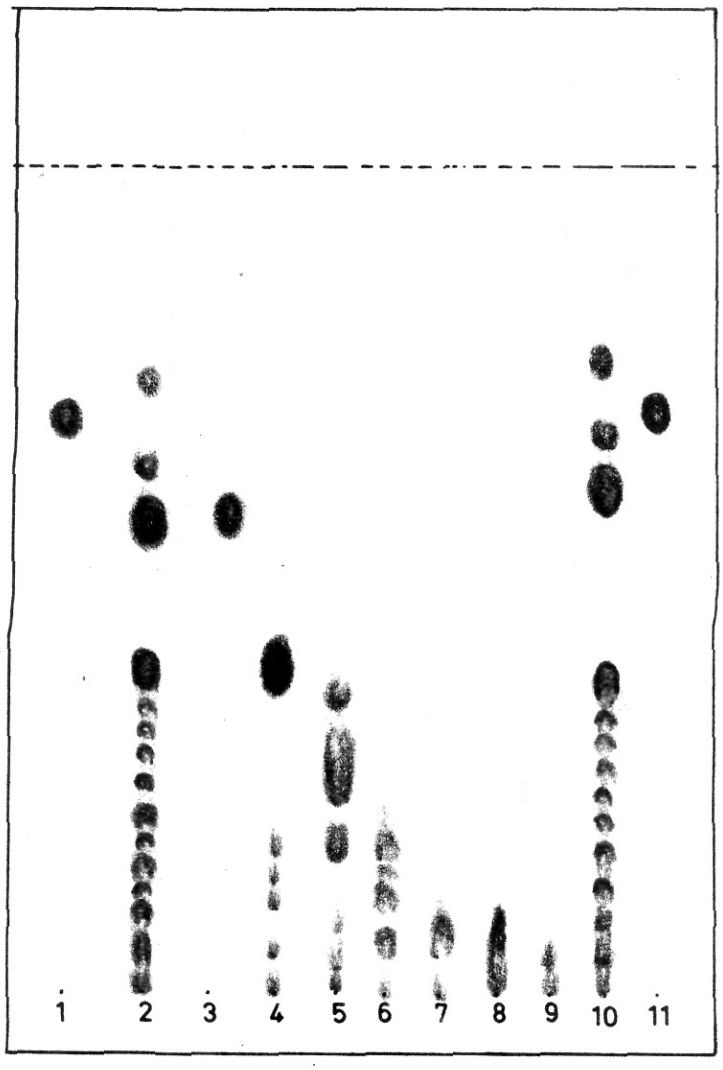


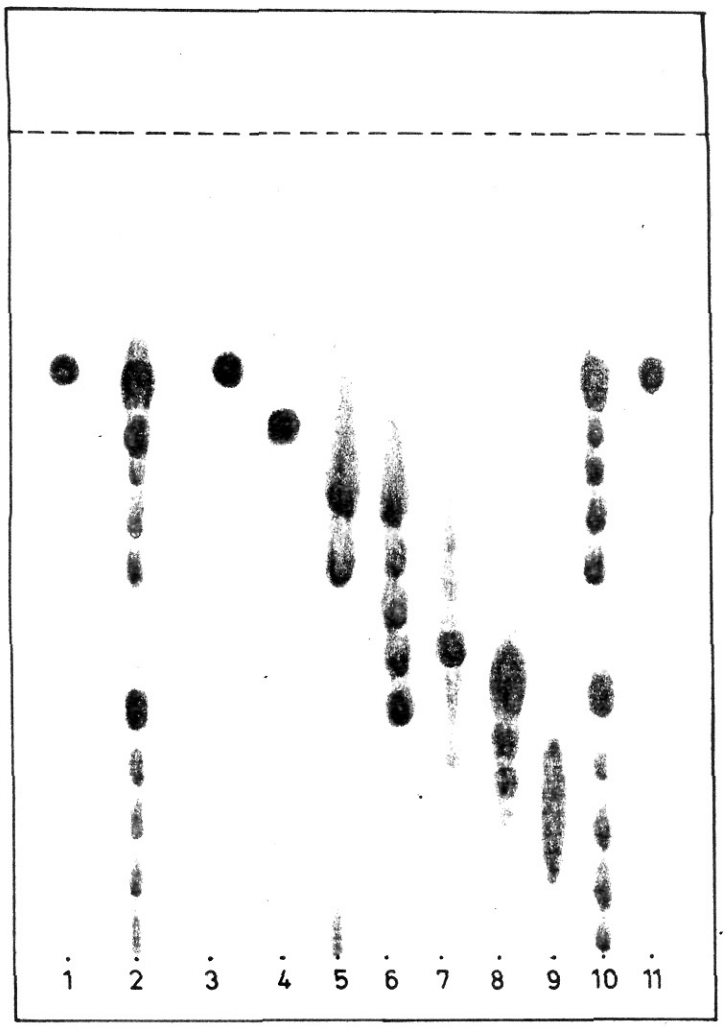
FIG. 2. SCHEME FOR THE SEPARATION OF VARIOUS CONSTITUTS OF AILANTHUS MALBARICA DC.



SOLVENT SYSTEM – BENZENE + ETHYL ACETATE (75 : 25)

SPOTS – 1 & 11 SUDAN RED, 2 & 10 TOTAL NEUTRAL FRACTION
3 FRACTION A, 4 FRACTION C, 5 FRACTION D
6 FRACTION E, 7 FRACTION F, 8 FRACTION G
9 FRACTION H

FIG. 3a. THIN LAYER CHROMATOGRAM OF DIFFERENT FRACTIONS



SOLVENT SYSTEM - BENZENE + ETHYL ACETATE (25 : 75)

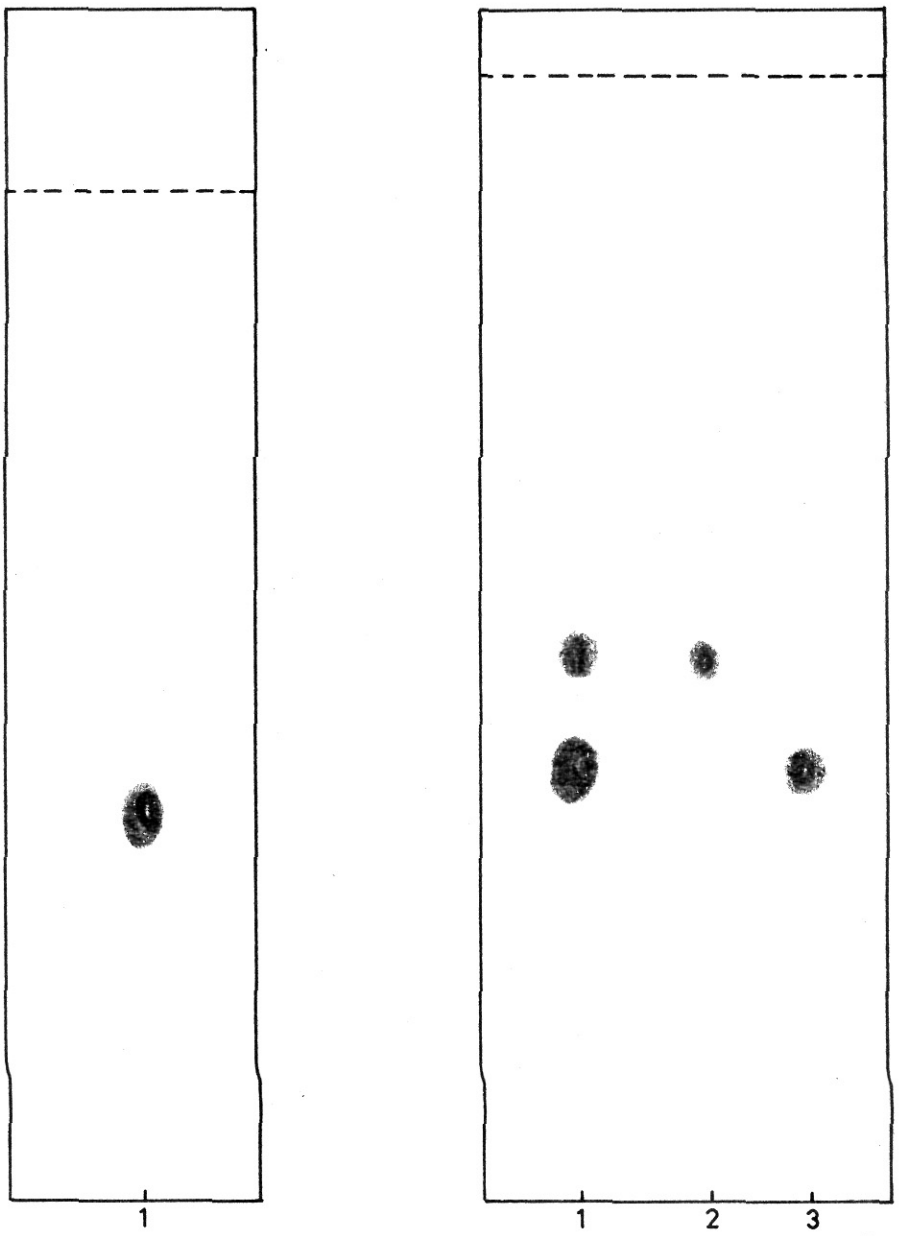
SPOTS - 1 & 11 SUDAN RED 2 & 10 TOTAL NEUTRAL FRACTION

3 FRACTION A 4 FRACTION C 5 FRACTION D

6 FRACTION E 7 FRACTION F 8 FRACTION G

9 FRACTION H

3 b. THIN LAYER CHROMATOGRAM OF DIFFERENT FRACTION



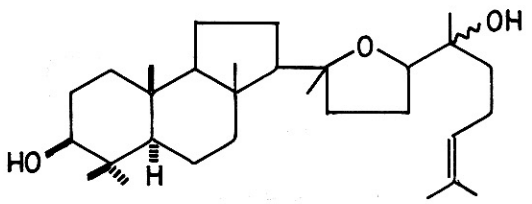
SOLVENT SYSTEM – BENZENE + ETHYL ACETATE 75 : 25

SPRAYING REAGENT – SULPHURIC ACID CONC.

a) SILICA GEL G PLATE
SPOT – FRACTION B

b) $AgNO_3$ – SiO_2 GEL PLATE
SPOTS – 1 FRACTION B
2 COMPOUND B_1
3 MALABARICANE DIOL (B_2)

4. THIN LAYER CHROMATOGRAM OF FRACTION B

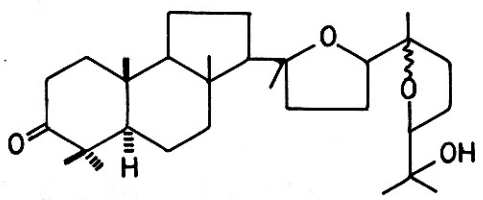


VII

Compound B_1 (~30%) analyses for $C_{30}H_{52}O_3$ and has m.p. 161.5 - 162.5°, $[\alpha]_D$ +62.69°. Its tentative structure on the basis of physical data has been discussed in Chapter IV.

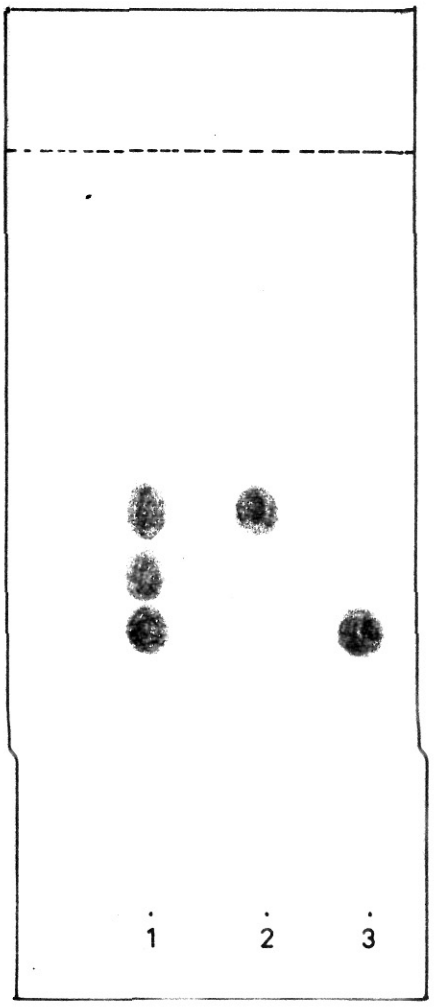
10% Ethylacetate in benzene eluate C

This fraction (~8%) readily crystallised from acetonitrile and gave a homogenous compound C_1 which analysed for $C_{30}H_{50}O_4$, m.p. 143-44°, $[\alpha]_D$ +24.6°. As a result of the work discussed in Chapter IV, it has been assigned the structure (VIII) and has been named epoxymalabaricol.



VIII

The mother liquor left after crystallisation of the above fraction showed atleast three compounds on thin layer chromatoplate (Fig.5) one of which happened to be epoxy-malabaricol. Of the other two, C_2 was isolated in very small



SILICA GEL G PLATE

SOLVENT SYSTEM - BENZENE + ETHYL ACETATE (75:25)

SPRAYING REAGENT — 0·5 % VANILLIN IN PHOSPHORIC ACID (1:1)

SPOTS — 1 MOTHER LIQUOR 2 EPOXYMALABARICOL
3 COMPOUND C_2

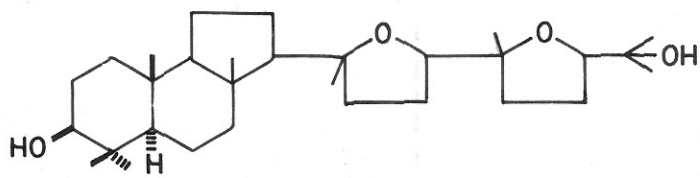
FIG. 5. THIN LAYER CHROMATOGRAM OF THE MOTHER-LIQUOR OF EPOXY-MALABARICOL

amounts as discussed in Fig.2.

15% Ethylacetate in benzene eluate D

This fraction (~6.5%) though appearing homogenous on TLC (Fig.2) was found to be a mixture of five compounds by changing the resolving solvent systems (Fig.6).

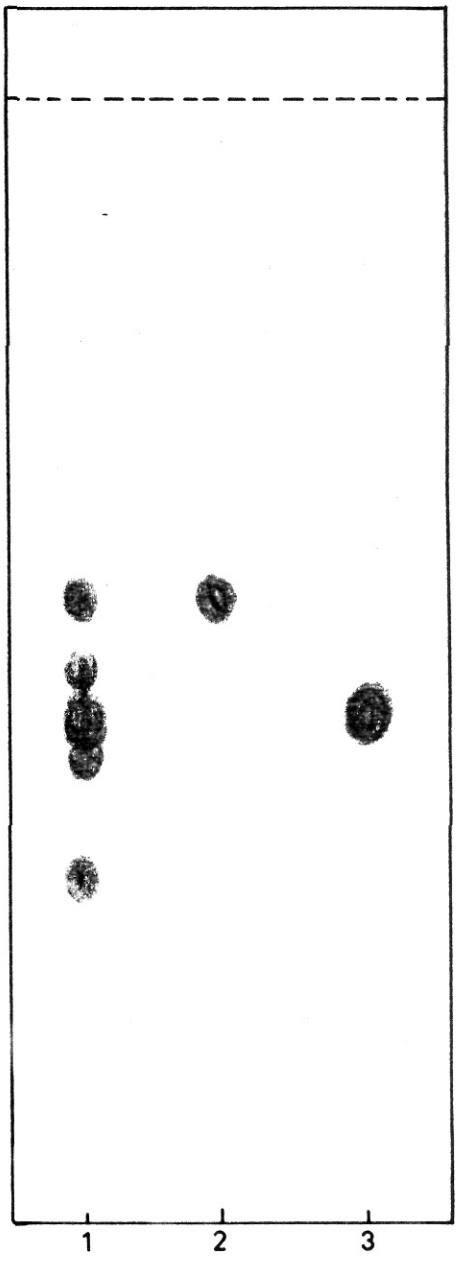
After repeated column, preparative layer and LSCC chromatographies over silica gel only one compound (~15%) was obtained in pure crystalline form and its homogeneity was checked on TLC over SiO_2. This compound, $C_{30}H_{52}O_4$, m.p. 134-136.5°, $[\alpha]_D$ +4.9° ($CHCl_3$) has been assigned structure (IX) as discussed in Chapter IV and has been named as epoxymalabaricanediol.



IX

20% Ethylacetate in benzene eluate E

This fraction (~3.5%) on further work-up as shown in Fig.2 furnished a crystalline compound E_1, by repeated chromatography (LSCC). The spectral data of this compound, m.p. 182-183.5°, $[\alpha]_D$ -70.18 ($CHCl_3$) have been discussed in Chapter IV and its probable structure thereby assigned.



SILICA GEL G PLATE

SOLVENT SYSTEM – HEXANE + ETHER (16 : 84)

SPRAYING REAGENT - 0·5 % VANILLIN IN PHOSPHORIC ACID (1:1)

SPOTS - 1 FRACTION D. 2 COMPOUND C_2

3 EPOXYMALABARICANE DIOL

5. THIN LAYER CHROMATOGRAM OF FRACTION D

25% Ethylacetate in benzene eluate F

Rechromatography of this fraction (~ 3%) over neutral Al_2O_3/II gave two crystalline compounds, one of which corresponded to compound E_1 (discussed above). The other compound F_1, m.p. 38-39°, $[\alpha]_D$ +30.1 ($CHCl_3$) has been assigned a tentative structure on the basis of spectral data (discussed in Chapter IV).

Ethylacetate eluate G

Further workup of this fraction (~ 23.5%) over neutral Al_2O_3/II yielded two homogenuous compounds (TLC) G_1 and G_2. All attempts to crystallise G_1 ($[\alpha]_D$ +26.02° ($CHCl_3$)] proved abortive while G_2 (gum) could be crystallised from acetonitrile, m.p. 144-45°, $[\alpha]_D$ +71.39° ($CHCl_3$). The tentative structures of these compounds have been discussed in Chapter IV.

The Methanol eluate of the neutral fraction was not investigated further.

Thus, as a part of present investigations, a number of new triterpenes could be isolated and their structures established. Table I enlists the physical constants and the percentages of these compounds based upon total neutral fraction.

TABLE 1 - NEUTRAL CONSTITUENTS OF AILANTHUS MALABARICA OLEO RESIN

No.	Constituent	Mol. formula	m.p.	$[\alpha]_D$ $CHCl_3$	Structure	Approx. % on the neutral extract.
1	Malabaricol	$C_{30}H_{50}O_3$	68-69.5°	+36.09°	VI	45.25
2	Compound B_1	$C_{30}H_{52}O_3$	161.5-162.5°	+62.69°	ocotillone	2.2
3	Malabaricanediol		Gum	+23.03°	VII	5.2
4	Epoxymalabaricol	$C_{30}H_{50}O_4$	143-44°	+24.6°	VIII	6.23
5	Epoxymalabaricanediol.	$C_{30}H_{52}O_4$	134-135.5°	+ 4.9°	IX	0.95
6	Compound E_1		182-183.5°	-70.18°	-	0.62
7	Compound F_1	$C_{30}H_{52}O_4$	98-99°	+30.1°	Hydroxymalabaricol	1.35
8	Compound G_1		Gum	+26.02°	-	11.5
9	Compound G_2	$C_{30}H_{52}O_4$	144-145°	+71.39°	-	6.9

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

All melting points were determined on Kofler block and are uncorrected. All solvent extracts were finally washed with brine and dried over anhydrous sodium sulphate. Rotations were taken in chloroform (unless stated otherwise) on a Perkin-Elmer Polarimeter (model 141). For tetranitromethane (TNM) tests, compound dissolved in minimum quantity of chloroform and equal amount of 10% solution of the reagent in $CHCl_3$ were mixed.

The IR spectra were taken on a Perkin-Elmer Infracord, model 137B, either as nujol mull or as KBr disc. The PMR spectra were determined in 10-20% CCl_4 solutions with tetramethylsilane (TMS) as internal standard on a Varian A-60 spectrometer. The signal positions are reported in cycles per second (cps) units starting from TMS as zero.

Alumina used during this investigation was washed with nitric acid[17] and activated at 460° for 6 hr. The various grades were prepared and standardised according to Brockmann procedure[18]. Thin layer chromatographies (TLC) were carried out by using silica gel (~ 250 mesh) containing 15% gypsum. Silica gel used for column chromatography was standardised according to the procedure

of Hernandez et al.[19] Method followed for IDCC (Inverted Dry Column Chromatography) was that of Sukh Dev et al.[20] Silver nitrate-silica gel for column and TLC was prepared according to the procedure described by A.S.Gupta and Sukh Dev[21]. Visualization of the spots, after development, was done by spraying with conc. H_2SO_4 or a weaker phosphoric acid-vanillin reagent[22], and heating at about 100° for 10-15 minutes.

All chromatographies were monitored by TLC.

Fractionation of the exudate of Ailanthus malabarica DC

Oleoresin (318 g) was dissolved in ethylacetate (500 ml; kept at room temp. for 2 days) and filtered. The filterate was evaporated to dryness to give a dark brownish gummy material (238 g; ~ 73%). The insoluble woody material (13 g; ~ 4%) was discarded.

The gummy material was dissolved in ether (600 ml) and extracted with 2.5% aqueous NaOH (100 ml x 3). The ethereal layer was washed with water (50 ml x 2) and the aqueous wash added to the alkali extract. The ethereal layer was dried and the solvent flashed off to yield a yellowish gummy neutral fraction (180 g; ~ 76%).

The combined aqueous NaOH extracts were acidified with dil. HCl at 5-10° and extracted with ether (150 ml x 4). The combined ether extracts were washed with water (100ml x 2),

brine (100 ml) and dried. Removal of solvent furnished dark brown gummy material (52 g; ~ 22%).

The neutral fraction was fractionated further by chromatography over silica gel as shown in Chromatogram 1.

CHROMATOGRAM 1

Substance: 61 g of neutral portion.

Adsorbent: 1.2 kg silica gel/IIA.

Column : 41 cm x 8 cm.

No.	Eluent	Ratio	Vol. (ml)	Eluate (g)	Fr. No.	Remarks
1	Benzene	-	1000x14	0.0731		Dark yellow liquid.
2	Benz. + EtOAc	95:5	1000x15	32.5732	A	Yellow gum.
3	"	90:10	1000x21	3.8100	C	White crystalline solid m.p.135-140°.
4	"	85:15	1000x16	3.9608	D	Gummy material.
5	"	80:20	1000x11	2.0000	E	" "
6	"	75:25	1000x15	1.7000	F	" "
7	Ethyl Acetate	-	1000x6	14.3881	G	" "
8	Methanol	-	1000x2	0.6888		
			Total:	59.1940 g (~ 97%)		

Fractions 1 and 8 were not studied further.

Fraction 2 (A of Chromatogram 1)

This fraction was not homogeneous over TLC and was

rechromatographed over silica gel.

CHROMATOGRAM 2

Substance: 32 g of fraction 2(A)

Adsorbent: 1 kg SiO_2 gel/IIA

Column : 36 cm x 8 cm

No.	Eluent	Ratio	Vol. (ml)	Fluate (g)	Remarks
1	Benzene	-	1000x3	0.0081	top tailing, discarded.
2	Benz.+ EtOAc.	19:1	500x10	26.0098	Malabaricol (A_1) gummy material, crystallised on keeping, m.p.59-65°.
3	""	19:1	500x3	1.0032	Mixed fractions.
4	""	"	500x7	3.5500	Gum (B).
			Total:	30.5711 (≈ 94%).	

Malabaricol (A_1, fraction 2) - This fraction was crystallised four times from acetonitrile at 0° to give a crystalline compound, m.p. 68-69.5°, $[\alpha]_D$ +36.09° (0.9% $CHCl_3$), TLM: clear yellow colour. [Found: C, 78.81; H, 11.24. $C_{30}H_{50}O_3$ requires: C, 78.55; H, 10.99%].

Fraction 4 - This fraction though homogeneous over silica gel chromatoplate (Fig.4a) showed two spots on $AgNO_3$-SiO_2 gel chromatoplate[(Fig.4b), solvent system - 25% EtOAc in C_6H_6]. This was chromatographed over a column of $AgNO_3$-SiO_2 gel.

CHROMATOGRAM 3

Substance: 3.5 g of fraction 4, Chromatogram 2.

Adsorbent: 180 g $AgNO_3$-SiO_2 gel.

Column : 45 cm x 2.5 cm.

No.	Eluent	Ratio	Vol. (ml)	Eluate (g)	Remarks.
1	Benzene	-	200x5	0.0600	Top tailing impurity, rejected.
2	Benz.+ EtOAc	97:3	100x10	0.7663	Solid, m.p. 155-61° (B_1).
3	" "	96:4	100x3	0.2987	Gum, mixed fractions.
4	" "	95:5	100x8	1.9648	Gum (B_2), malabaricanediol.
5	" "	90:10	100x4	0.2211	Tailing, discarded.
			Total:	3.2807 (~ 93%)	

Fraction 2 (B_1) - This fraction on crystallising three times from acetonitrile gave colourless fluffy crystals (480 mg), m.p. 161.5 - 162.5°, $[\alpha]_D$ +62.69° (c, 1.0%, $CHCl_3$). TNM: negative [Found: C, 78.07; H, 11.01; $C_{30}H_{52}O_3$ requires: C, 78.2 ; H, 11.38%.

Malabaricanediol (B_2, fraction 4) - This fraction did not crystallise with any solvent. $[\alpha]_D$ +23.03° (c, 1.0% $CHCl_3$), TNM test: distinct pale yellow.

Epoxymalabaricol (C_1, fraction 3 of Chromatogram 1) - This fraction was crystallised from acetonitrile four times to furnish a white crystalline compound (C_1, 2.5 g), m.p. 143-44°, $[\alpha]_D$ +24.6° (c, 1.0% $CHCl_3$) [Found: C, 76.0; H, 10.14. $C_{30}H_{50}O_4$ requires: C, 75.90; H, 10.62%].

The mother liquors left after crystallisation of epoxymalabaricol were evaporated to furnish a gummy material (1.25 g) whose TLC (Fig.5, solvent system - 25% EtOAc in C_6H_6) showed it to be a mixture of at least three compounds which were separated over a column of SiO_2 gel.

CHROMATOGRAM 4

Substance: 1.2 g of mother liquor residue.

Adsorbent: 50 g SiO_2 gel/ IIA.

Column : 44 cm x 1.6 cm.

No.	Eluent	Ratio	Vol. (ml)	Eluate (g)	Remarks
1	Benzene	-	50x3	0.0149	Waxy material, rejected.
2	C_6H_6 + EtOAc	95:5	50x3	0.0081	" "
3	"	90:10	50x5	0.5011	Epoxymalabaricol (C_1) m.p. 135-40°.
4	"	"	50x2	0.2008	Mixed fractions.
5	"	"	50x4	0.2059	Gummy material.
6	"	75:25	50x2	0.0881	Tailing material rejected.
			Total:	1.0189 g (~ 84%).	

Fraction 5 on crystallisation from acetonitrile gave epoxymalabaricol (C_1) m.p. 143-44°.

Fraction 6 on repeated crystallisations from acetonitrile gave a crystalline compound (C_2, 15 mg) m.p. 105-107°.

Fraction 4 (D) of Chromatogram 1

This fraction though appearing homogeneous on TLC (Figs.3a and 3b) was resolved into five compounds (Fig.6) on changing the solvent system (16% P.E. in ether). This mixture was separated by LSC over SiO_2 gel.

CHROMATOGRAM 5

Substance: 2.0 g

Adsorbent: 500 SiO_2 gel/IIA

Column : 25 cm x 6.6 cm.

Solvent system: 16% Pet. Ether in Ether.

Fr.No.	Wt. of the fraction (g)	Remarks
1	0.4034	Solid, unstable decomposed on keeping.
2	0.5258	
3	0.3986	Mixed fraction.
4	0.1962	Epoxymalabaricanediol m.p. 132-6°.
5	0.1071	
6	0.0182	Tailing material rejected.
7	0.0078	
8	0.0056	
Total:	1.7627 g (~ 88%)	

Epoxymalabaricanediol: Fractions 4 and 5 were mixed and crystallised three times from acetonitrile to give crystalline solid (150 mg), m.p. 134-135.5°, $[\alpha]_D$ +4.9 (c, 0.9% $CHCl_3$). [Found: C, 75.90; H, 11.02. $C_{30}H_{52}O_4$ requires: C, 75.58; H, 11.00%].

Fraction 5, Chromatogram 1 (E)

This fraction was purified further by LSCC over silica gel.

CHROMATOGRAM 6

Substance: 1.3 g

Adsorbent: 500 g SiO_2 gel/III B

Column : 25 cm x 6.6 cm.

Solvent system: 50% Ethyl acetate in benzene.

No.	Fraction No.	Wt. of the fraction (g)	Remarks
1	1-7	0.0887	Tailing material rejected.
2	8-12	0.2591	E_1 solid, m.p. 160-175°
3	13-14	0.1320	Gummy material did not crystallise.
4	15-17	0.5088	Mixed fractions.
5	18	0.1497	Top tailing.
	Total:	1.1387 g (≈ 88%)	

Compound E_1 - Fractions 8-12 on repeated crystallisations

from acetonitrile furnished a white crystalline compound m.p. 182-83.5°, $[\alpha]_D$ -70.18°. [Found: C, 76.60 ; H, 11.48%.

Fraction 6, Chromatogram 1 (F)

This fraction was further purified by rechromatography over neutral alumina.

CHROMATOGRAM 7

Substance: 1.5 g of fraction 6, Chromatogram 1

Adsorbent: 60 g neutral Al_2O_3/ II

Column : 21cm x 2 cm

No.	Eluent	Ratio	Vol. (ml)	Eluate (g)	Remarks.
1	Benzene	-	100x6	0.0131	Rejected.
2	C_6H_6 + MeOH	99:1	60x3	0.0063	"
3	"	"	30x4	0.7831	F_1 solid m.p. 85-95°.
4	"	"	30x10	0.1290	Gum, TLC same as F_1 but does not crystallise.
5	"	97:3	30x2	0.1691	F_1
6	MeOH	-	100	0.2431	Tailing impurities at base (deep yellow).
			Total:	1.3437 g	(≈ 89%).

Compound F_1 - Fraction 3 on repeated crystallisations from acetonitrile gave fine needle shaped crystals, m.p.98-99°,

$[\alpha]_D$ +30.1° (c, 0.5% $CHCl_3$) [Found: C, 75.30 ; H, 11.73; $C_{30}H_{52}O_4$ requires: C, 75.58 ; H, 11.0%].

Fraction 7, Chromatogram 1 (G)

This fraction was further chromatographed over neutral alumina/II.

CHROMATOGRAM 8

Substance: 5.5 g fraction 7, Chromatogram 1

Absorbent: 200 g neutral Al_2O_3/II

Column : 41 cm x 2.7 cm.

No.	Eluent	Ratio	Vol. (ml)	Eluate (g)	Remarks.
1	Benzene	-	200x10	0.0147	Rejected.
2	C_6H_6 + MeOH	99.5: 0.5	100x10	0.0196	"
3	" "	99:1	100x19	0.0351	"
4	" "	98:2	100x1	0.0114	"
5	" "	"	100x2	1.5815	Mixed fraction.
6	" "	"	100x2	0.7335	G_1 with little tailing.
7	" "	"	100x22	0.3622	G_1 gum
8	" "	97:3	100x1	0.0039	G_1 "
9	" "	"	100x2	0.7946	G_1 with little impurity of G_2
10	" "	"	100x2	0.1165	Mixture G_1+G_2
11	" "	"	100x13	0.1783	G_2 m.p. 140-45°
12	" "	95:5	100x12	0.7776	G_2
13	" "	"	100x6	0.0716	Tailing impurity.
14	MeOH	-	200	0.1013	Rejected.
			Total:	4.3651 g (≈ 31%).	

Compound G_1 - Fractions 7 and 8 failed to crystallise. $[\alpha]_D$ +26.02° (c, 1% $CHCl_3$).

Compound G_2 - Fractions 11 and 12 were mixed and crystallised from acetonitrile to give white crystalline solid m.p. 144-5°, $[\alpha]_D$ +71.39°. (c, 0.9% $CHCl_3$). [Found: C, 75.32 ; H, 11.38 $C_{30}H_{52}O_4$ requires: C, 75.58 ; H, 11.0%].

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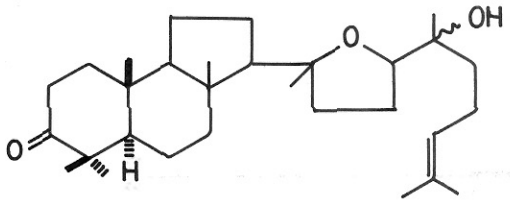
chapter three
structure of malabaricol

STRUCTURE OF MALABARICOL

In the preceding Chapter, we described the isolation of several new triterpenoids from the resinous exudate from the trunk of Ailanthus malabarica DC. Work on the structural elucidation of the major component, malabaricol, was taken up first. The present Chapter describes, in detail, the evidence which establishes its structure as I.



I

Malabaricol, m.p. 68-69.5°, $[\alpha]_D$ +36.1° ($CHCl_3$) analyses for $C_{30}H_{50}O_3$ and shows in its mass spectrum (Fig.1) the molecular ion peak (M^+) at m/e = 458 which is in accord with the above molecular formula. Its IR spectrum (Fig.2) exhibits absorption bands at 3550 cm^{-1} (sharp, OH), 1700 cm^{-1} (C=O), 1435 cm^{-1} (CH_2 scissoring next to carbonyl)[1] and at 1380, 1390 cm^{-1} (gem-dimethyl)[2]. In the UV spectrum, besides the end-absorption (ϵ_{220} 263, ϵ_{225} 120), a low intensity maximum at 280 mμ (ε 46) is exhibited. The UV data require that the C=O group in

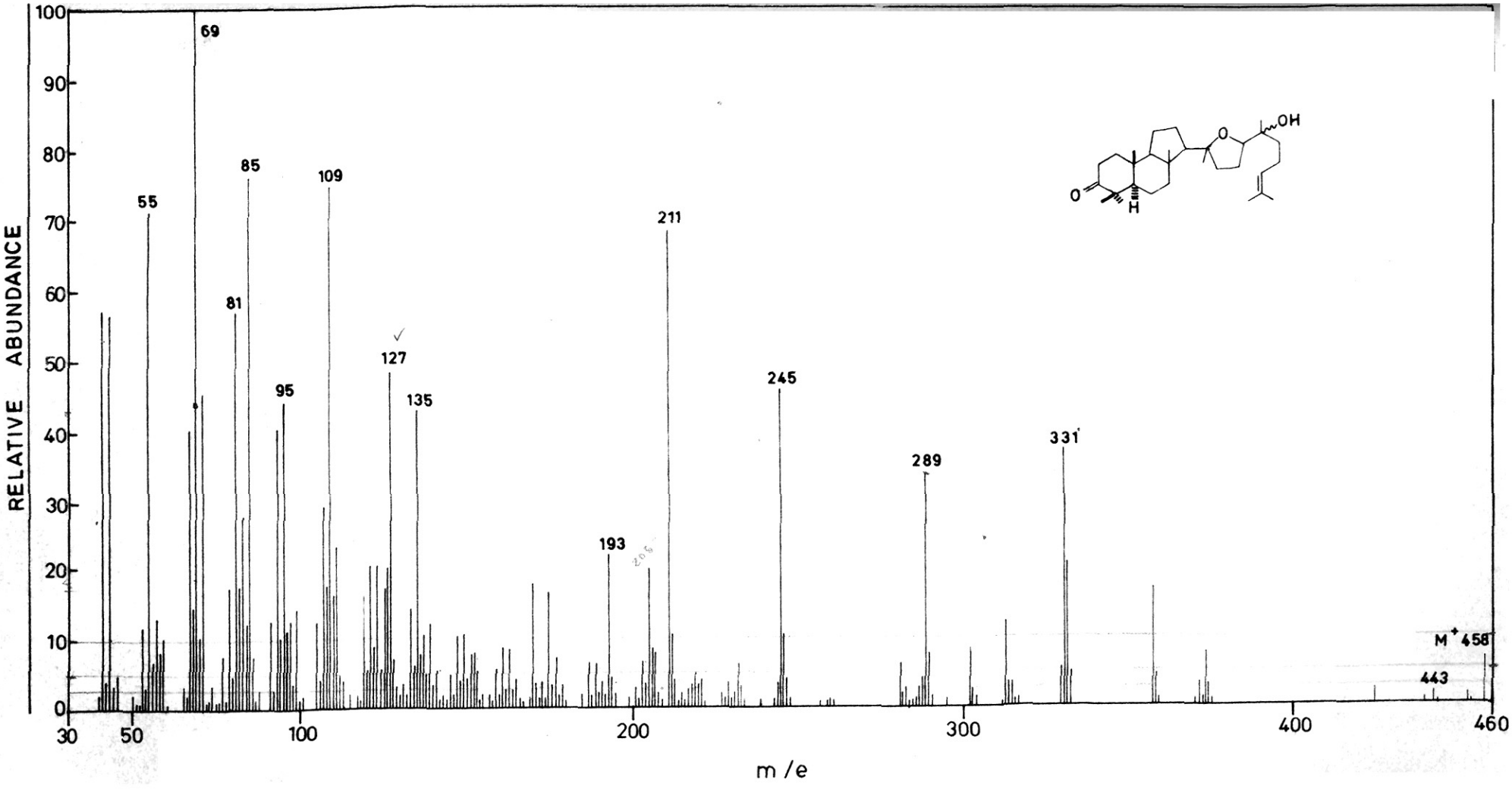


FIG. 1. MASS SPECTRUM OF MALABARICOL

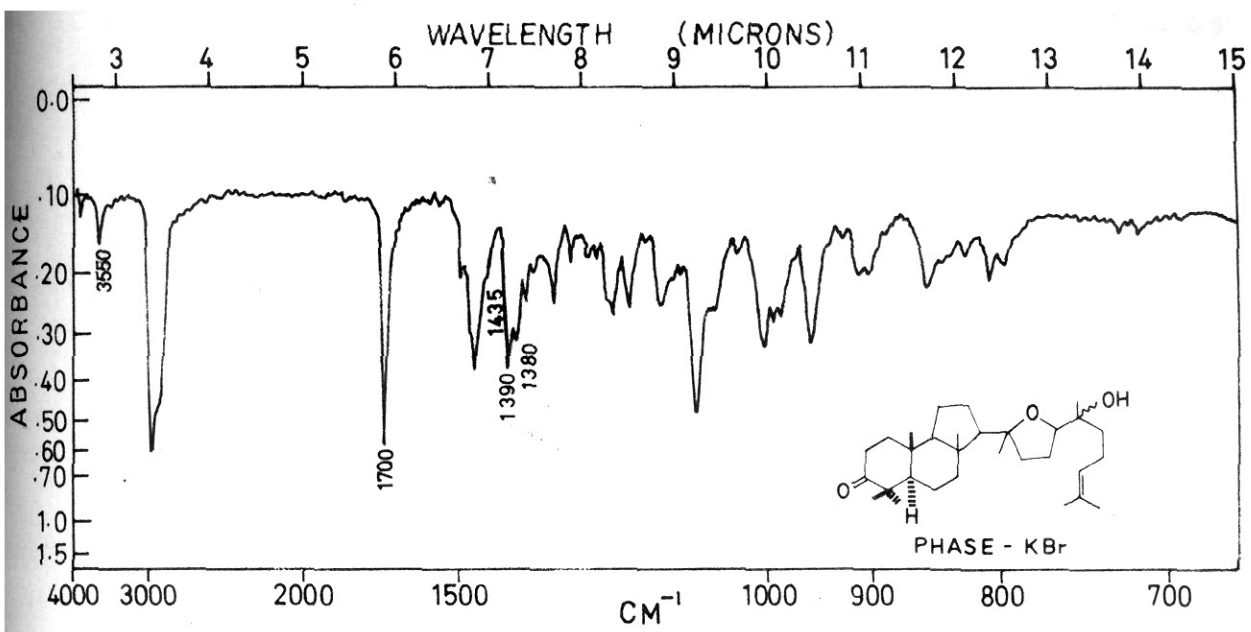


FIG. 2. IR SPECTRUM OF MALABARICOL

malabaricol should be that of a ketone (acyclic or larger than 5-membered) and its intensity is consistent[3] with the presence of only one such group. Thus, the third oxygen function of malabaricol must be located as an ether or another OH. The compound is not acetylated by Ac_2O-pyridine (20-25°, one week) and is not attacked by CrO_3-pyridine[4] (20-25°, one week), hence the OH group(s) must be tertiary.

Its PMR spectrum (Fig.3) shows signals for six quaternary methyls (58.5, 58.5, 58.5, 61, 65 and 70 c/s), two vinylic methyls (95 and 98 c/s), one olefinic proton (1H triplet centred at 298 c/s, J = 6 c/s) and a 2H multiplet centred at 138 c/s, the pattern and position of which are reminiscent[5] of the C_2-methylene of 3-ketotriterpenoids; the methyl signals separate far clearer, when the spectrum is taken in C_6H_6 solution (Fig.4) (46.5, 50, 58.5, 68, 68, 76.5, 98 and 102 c/s). The PMR spectrum also displays a 1H triplet (J = 7 c/s) centred at 212 c/s (221 c/s, in C_6H_6 solution), which is assigned to $-CH_2-\underset{\underset{C}{|}}{CH}-O-$, and since, it has been demonstrated earlier that there is no oxidisable (pyridine-CrO_3) hydroxyl function in malabaricol, this oxygen function must be located as an ether: $-CH_2-\underset{\underset{C}{|}}{CH}-O-C$.

From the above, it is clear that malabaricol must be a triterpenoid with a keto, a tertiary-OH and an ether

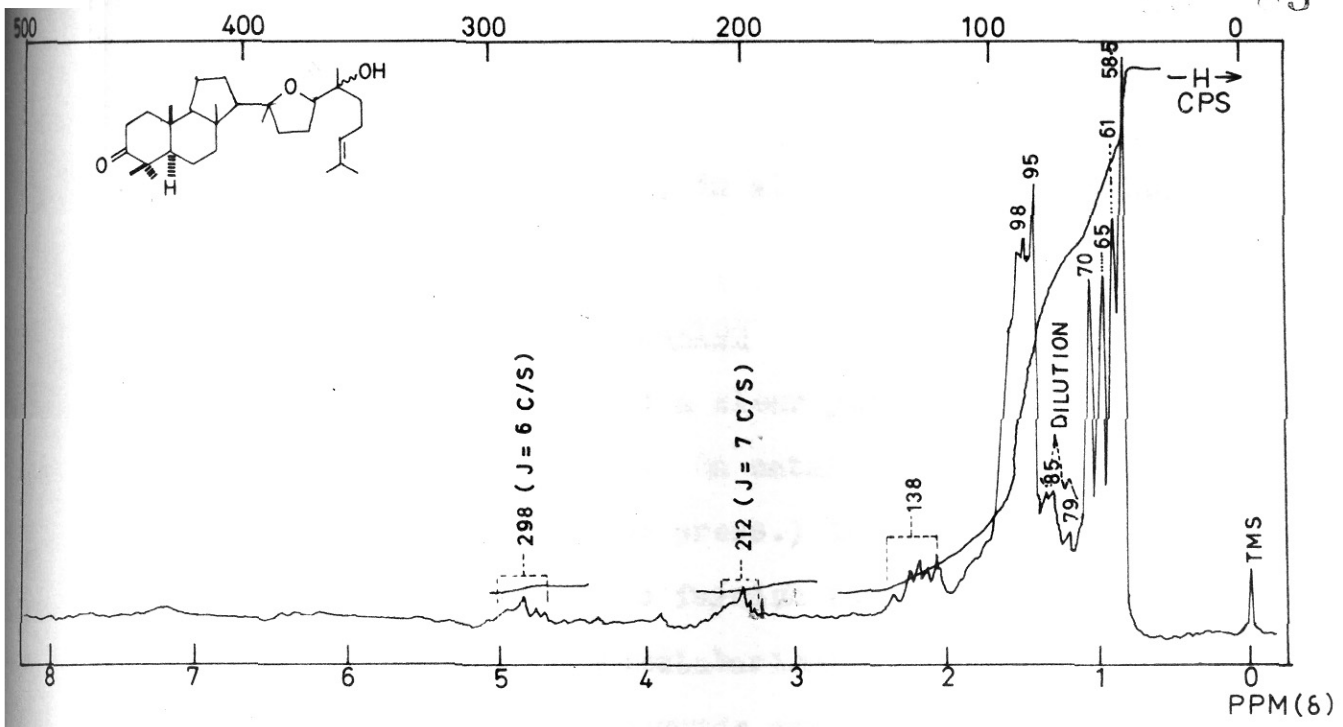


FIG. 3. PMR SPECTRUM OF MALABARICOL (IN CCl_4)

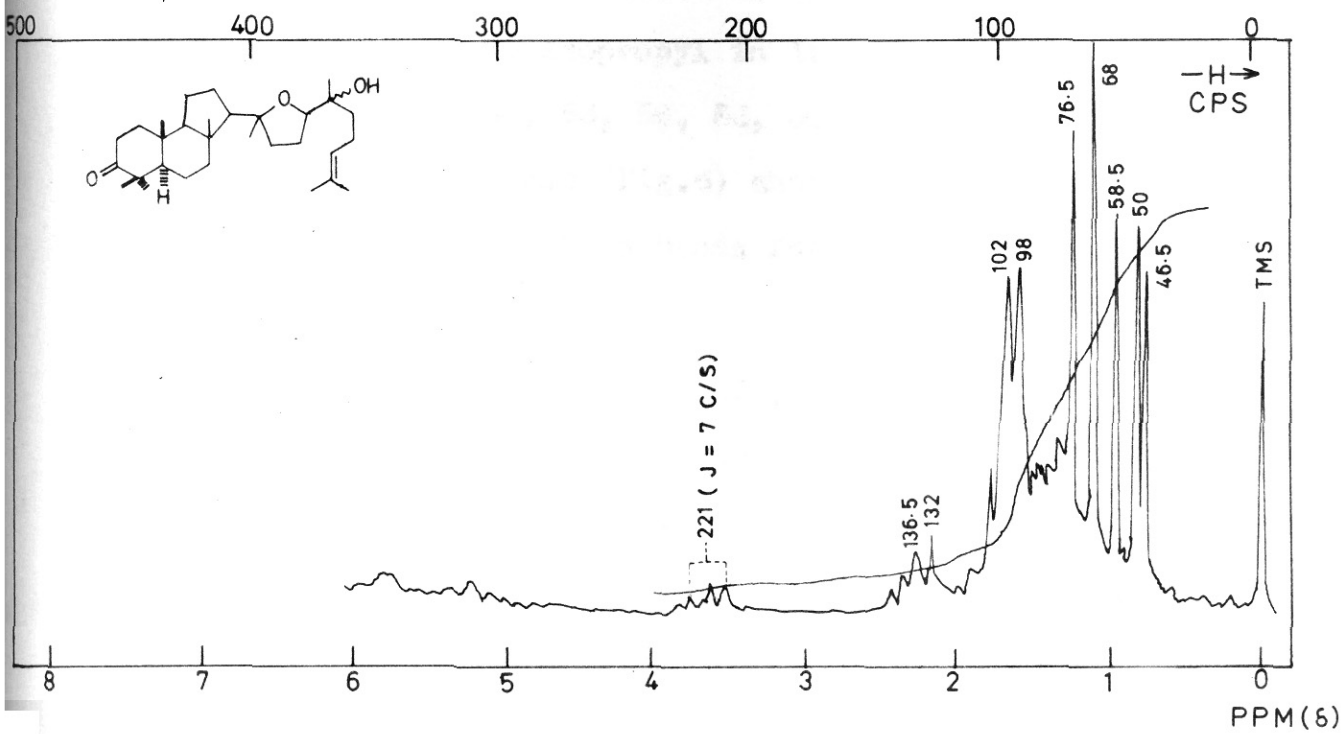


FIG. 4. PMR SPECTRUM OF MALABARICOL (IN BENZENE)

function, the keto group, in all probability, being located at C_3.

NATURE OF THE CARBON SKELETON

Malabaricol gives a clear yellow colour with tetranitromethane (TNM). On catalytic hydrogenation (PtO_2, AcOH; 30°, 708 mm press.) it took up 1.5 to almost 2 mole equivalent of H_2 to furnish two diols (C-3 axial and equatorial) and dihydromalabaricol. Confirmatory evidence for the above three compounds came from their respective spectral data.

The PMR spectrum (Fig.5) of dihydromalabaricol (~30%) (II, $C_{30}H_{52}O_3$, m.p. 98-99°, $[\alpha]_D$ +31.7°, is consistent with the saturation of an isopropylidene group in malabaricol to isopropyl in its dihydroderivative (Me signals at 48, 54, 56, 56, 56, 60, 63 and 69 c/s; no vinyl H). Its IR spectrum (Fig.6) shows the absence of olefinic absorption and exhibits bands for OH (3560, 1086 cm^{-1}) and C=O (1700 cm^{-1}).

The C-3 axial diol (III, ~15%), $C_{30}H_{54}O_3$, m.p. 101-102.5°, $[\alpha]_D$ +1.30°, shows in its PMR spectrum (Fig.7) signals for eight methyls at 50.5, 50.5, 50.5, 56, 56, 56, 56, 66.5 and 72.5 c/s. Its IR spectrum (Fig.8) exhibits absorption at 3550, 3500, 1006, 1081 cm^{-1} and reveals the absence of keto group.

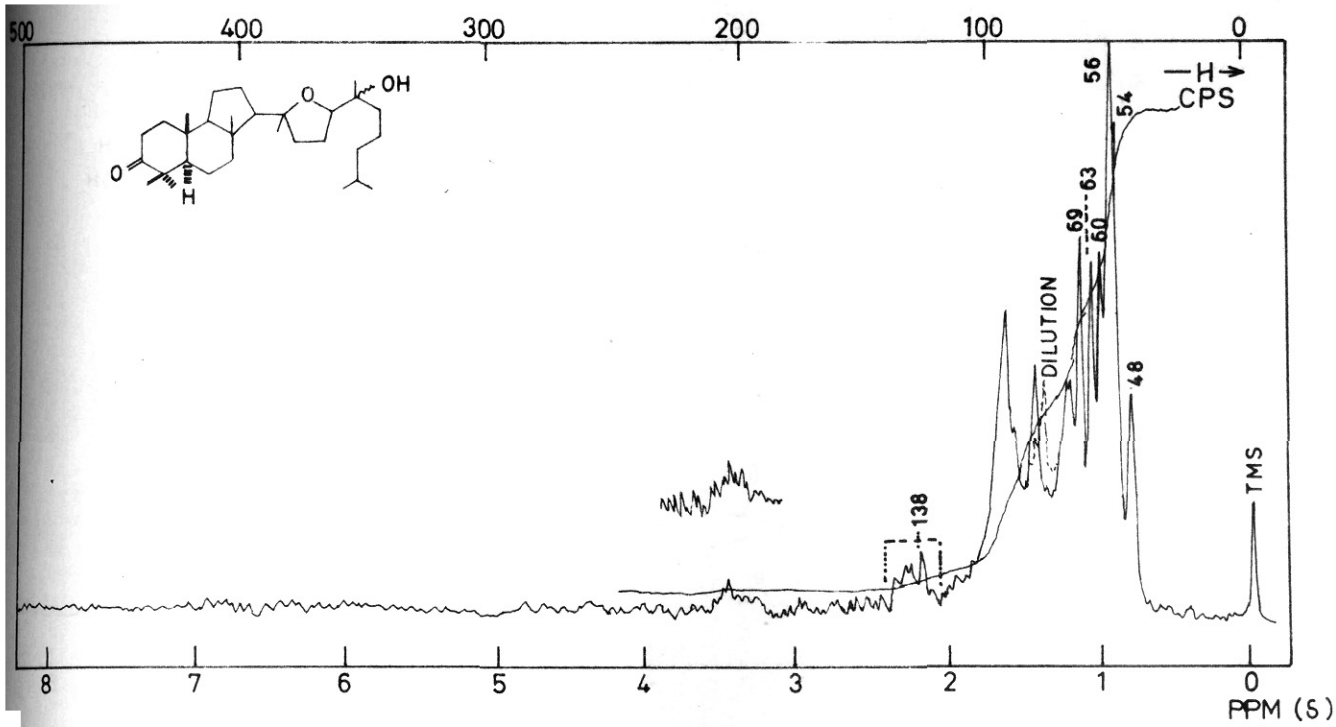


FIG. 5. PMR SPECTRUM OF DIHYDROMALABARICOL

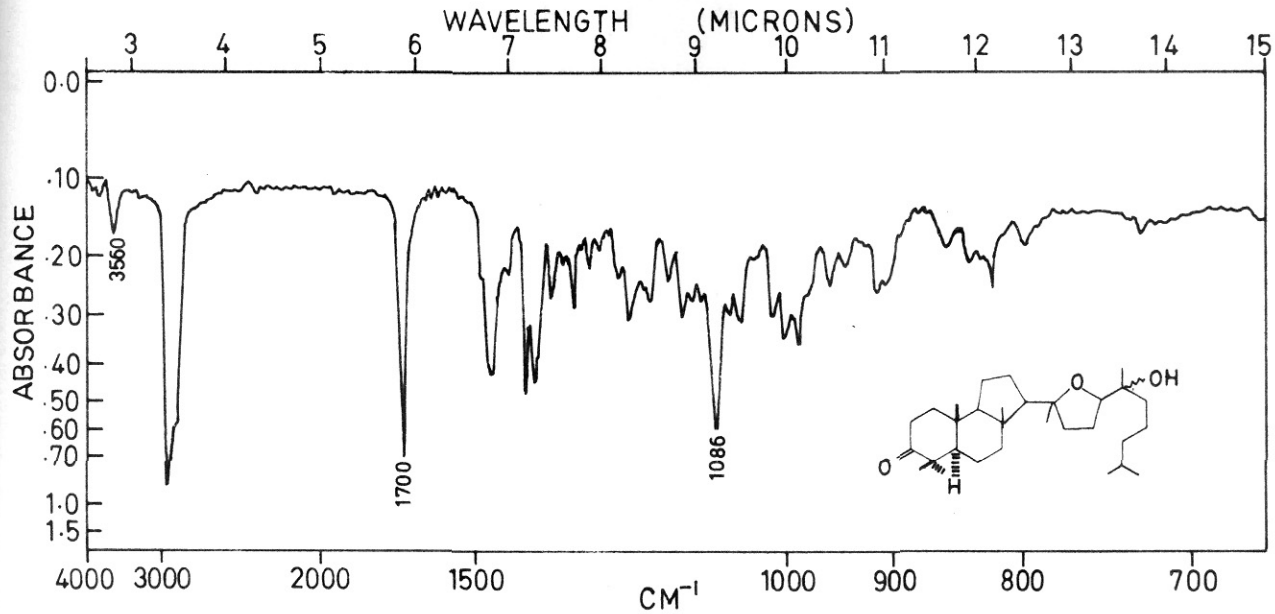


FIG. 6. IR SPECTRUM OF DIHYDROMALABARICOL

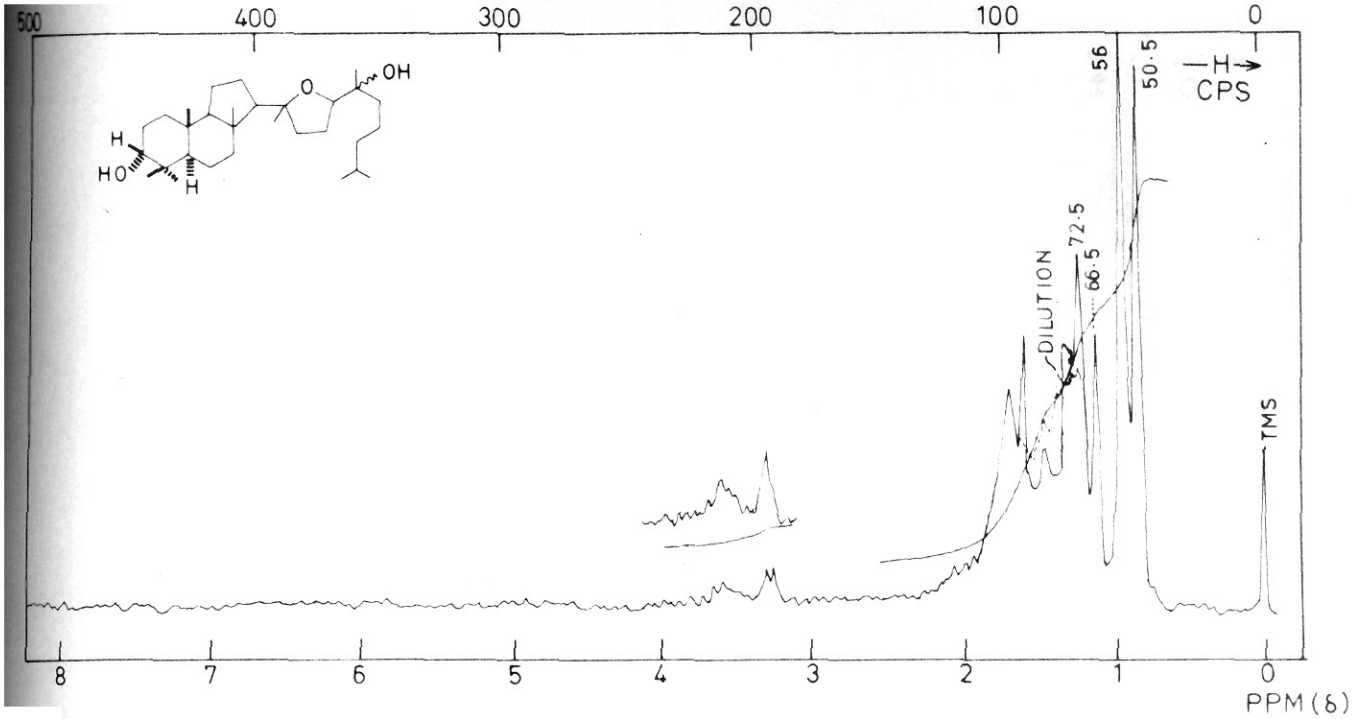


FIG. 7. PMR SPECTRUM OF COMPOUND C-3 AXIAL DIOL III.

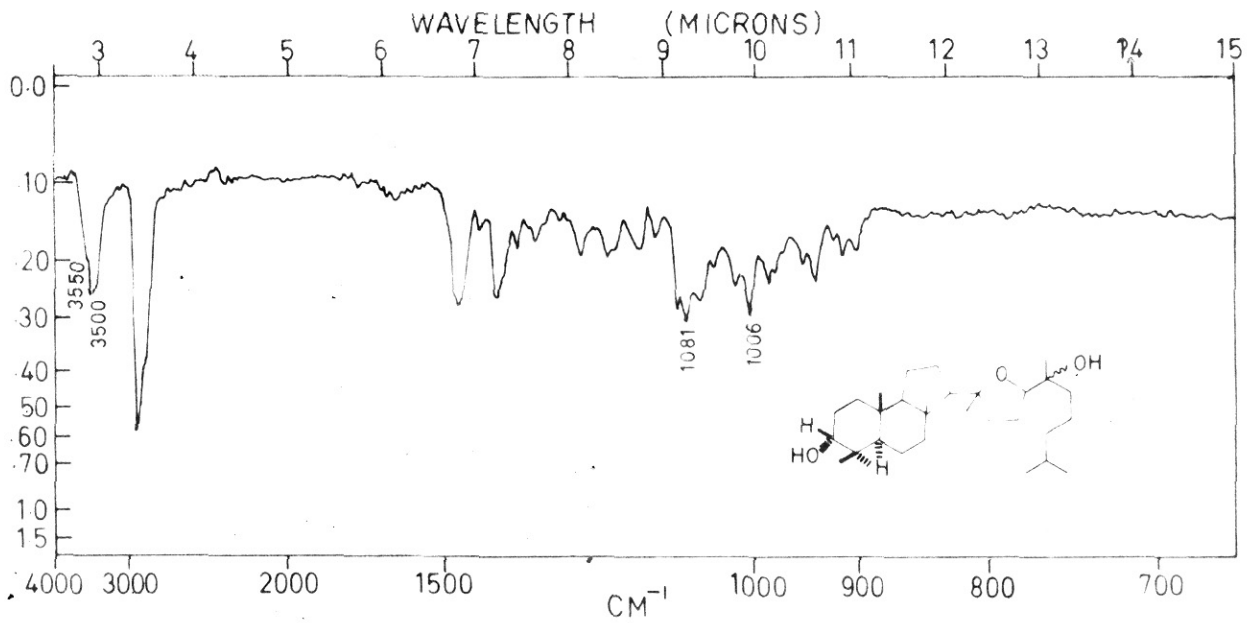


FIG. 8. IR SPECTRUM OF COMPOUND C-3 AXIAL DIOL III.

The C-3 equatorial diol (gum) (IV, ~ 45%), $[\alpha]_D$ +13.94°, shows in its PMR spectrum (Fig.9) signals for eight quaternary methyls: 45.5, 50.5, 50.5, 56.5, 56.5, 56.5, 76 and 71.5 c/s. Its IR spectrum (Fig.10) exhibits absorption bands at 3450, 3350, 1025, 1048 cm^{-1} and reveals the absence of keto group.

The configuration of hydroxyl group at C_3 in these compounds was clear from their PMR spectrum. The PMR spectrum of the solid diol (III, m.p. 101-102.5°) shows the $C_3 <^{OH}_{H}$ essentially as ill-resolved triplet (J = 3 c/s) centred at 198 c/s (the signal centred at 216 c/s is to be assigned to the proton linked to the carbon carrying the ether function; this signal again occurs at 216 c/s in the PMR spectrum of the other epimer and also shows the same multiplicity); this small coupling is consistent with the proton being equatorial[6]. On the other hand the second isomer (gum) shows the $C_3 <^{OH}_{H}$ signal as a quartet centred at 188 c/s (J_1 = 6.5 c/s, J_2 = 8 c/s) which is again in accord with the proton being axial[6]. This has been further corroborated by the result of $LiAlH_4$ reduction of dihydromalabaricol. It is fairly well established that $LiAlH_4$ reduction of 3-keto steroids and triterpenoids yield compounds with equatorial hydroxyl predominating[7]. The product obtained by this reaction was identical (IR, PMR, TLC) with the C-3 equatorial diol (IV).

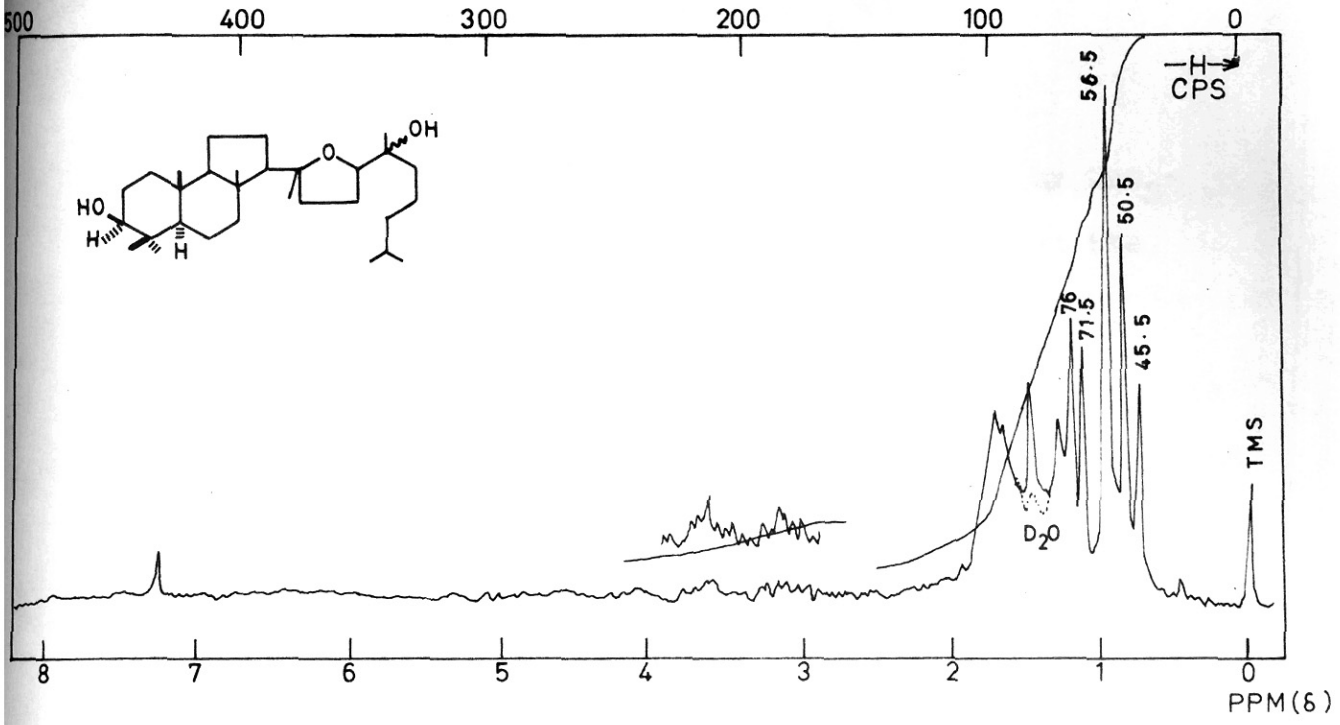


FIG. 9. PMR SPECTRUM OF C-3 EQUATORIAL DIOL IV.

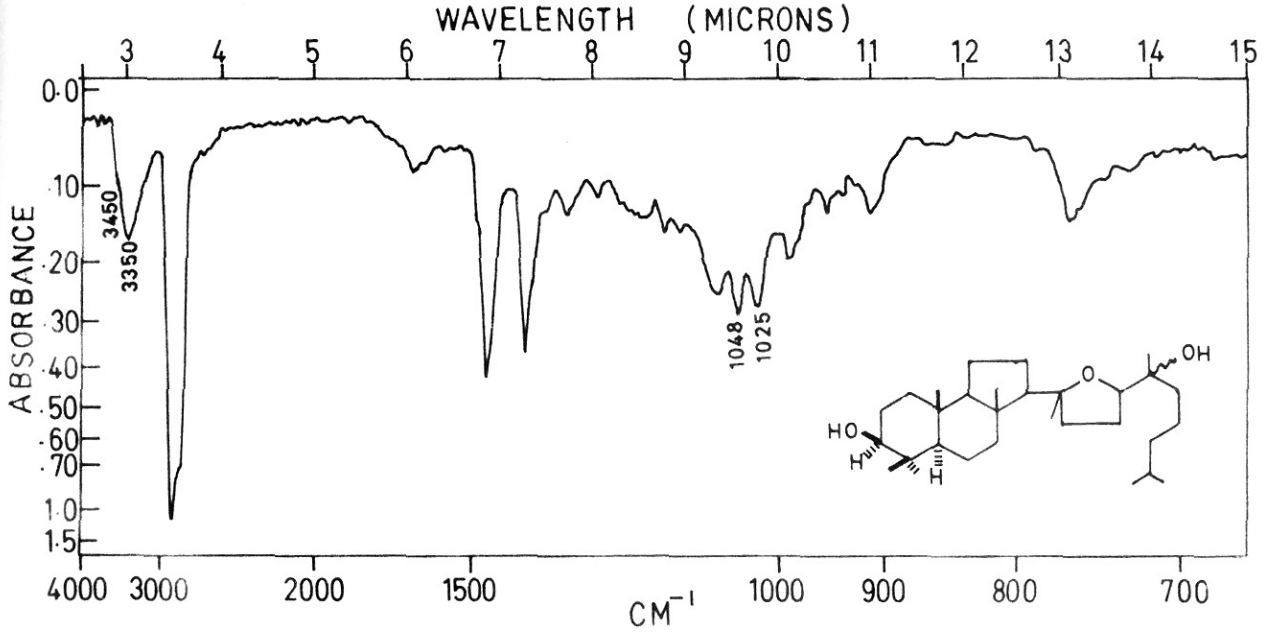


FIG. 10. IR SPECTRUM OF C-3 EQUATORIAL DIOL IV.

Both the diols were readily oxidised by CrO_3-pyridine to dihydromalabaricol. The diols and the dihydroketone give a negative TNM test.

Malabaricol and dipterocarpol were subjected to percamphoric acid oxidation[8] under identical conditions (5°, toluene). Table 1 gives the kinetic data of this reaction which are summarised in Fig.11. This study reveals that the degree of unsaturation in malabaricol is the same as in dipterocarpol.

Thus, malabaricol is only mono-olefinic and from its molecular formula and functionality discussed above, must be either tetracarbocyclic with an acyclic ether linkage or tricarbocyclic with a cyclic ether function.

The key reaction in the structure determination of malabaricol turned out to be its oxidation with Jones reagent[9], which readily furnished in good yield (~95%), a compound (m.p. 145-146°, $[\alpha]_D$ +29.4°) characterised as an octa nor-γ-lactone which analysed for $C_{22}H_{34}O_3$ (XVI). The molecular formula was confirmed from its mass spectrum (Fig.12; M^+, m/e = 346). It can be converted to a water-soluble Na salt, which regenerates the parent lactone on acidification. Its PMR spectrum (Fig.13) shows the presence of only five methyls (all quaternary): 59, 61, 62, 63.5 and 83 c/s (in benzene Fig.14, 44, 46, 58, 63 and

TABLE 1 - PERCAMPHORIC ACID REACTION OF DIPTEROCARPOL AND MALABARICOL.

No.	Solution	0.093 N $Na_2S_2O_3$	Time (hr)
DIPTEROCARPOL			
1	1 ml	0.73 ml	5 mins.
2	"	0.52 "	1 hr
3	"	0.4 "	2 "
4	"	0.54 "	4 "
5	"	0.44 "	8 "
6	"	0.41 "	22 "
7	"	0.33 "	46 "
8	"	0.39 "	70 "
9	"	0.33 "	94 "
10	"	0.32 "	118 "
MALABARICOL			
1	1 ml	0.82 ml	0
2	"	0.64 "	1 hr
3	"	0.55 "	2 "
4	"	0.42 "	4 "
5	"	0.5 "	8 "
6	"	0.41 "	22 "
7	"	0.4 "	46 "
8	"	0.34 "	70 "
9	"	0.29 "	94 "
10	"	0.34 "	118 "

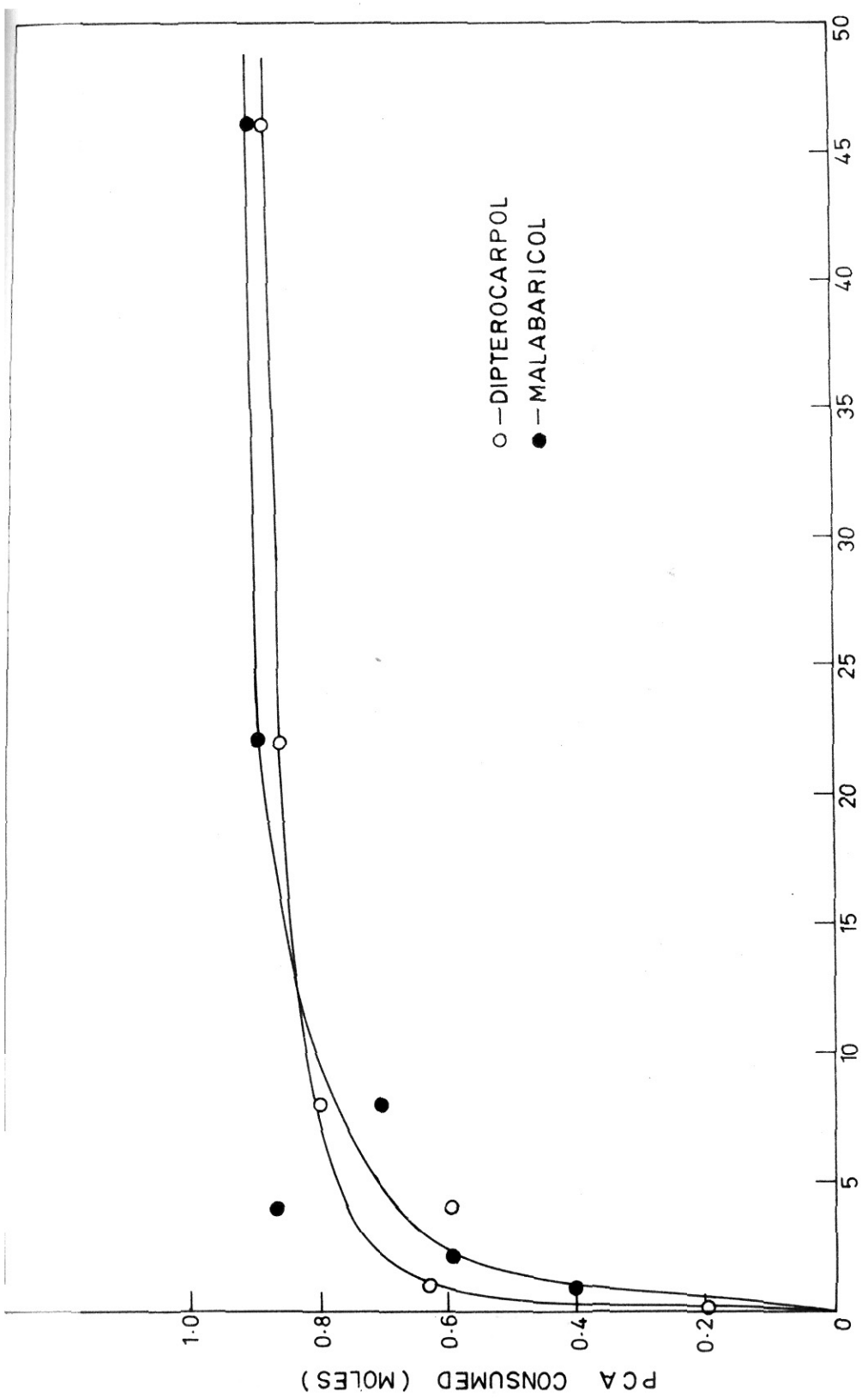


FIG. 11. ESTIMATION OF UNSATURATION BY PERCAMPHORIC ACID

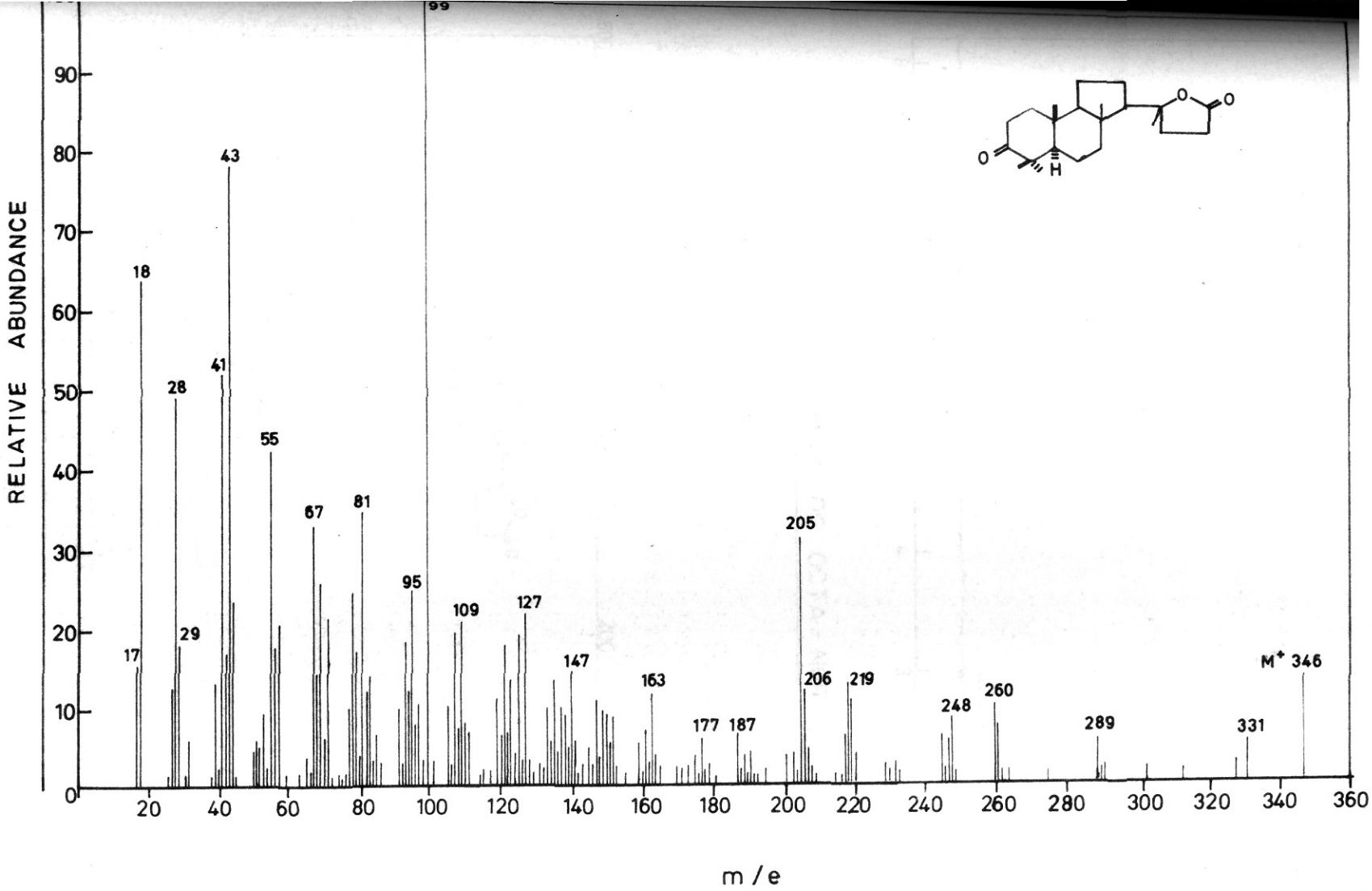


FIG. 12. MASS SPECTRUM OF OCTA-NOR-γ-LACTONE XVI.

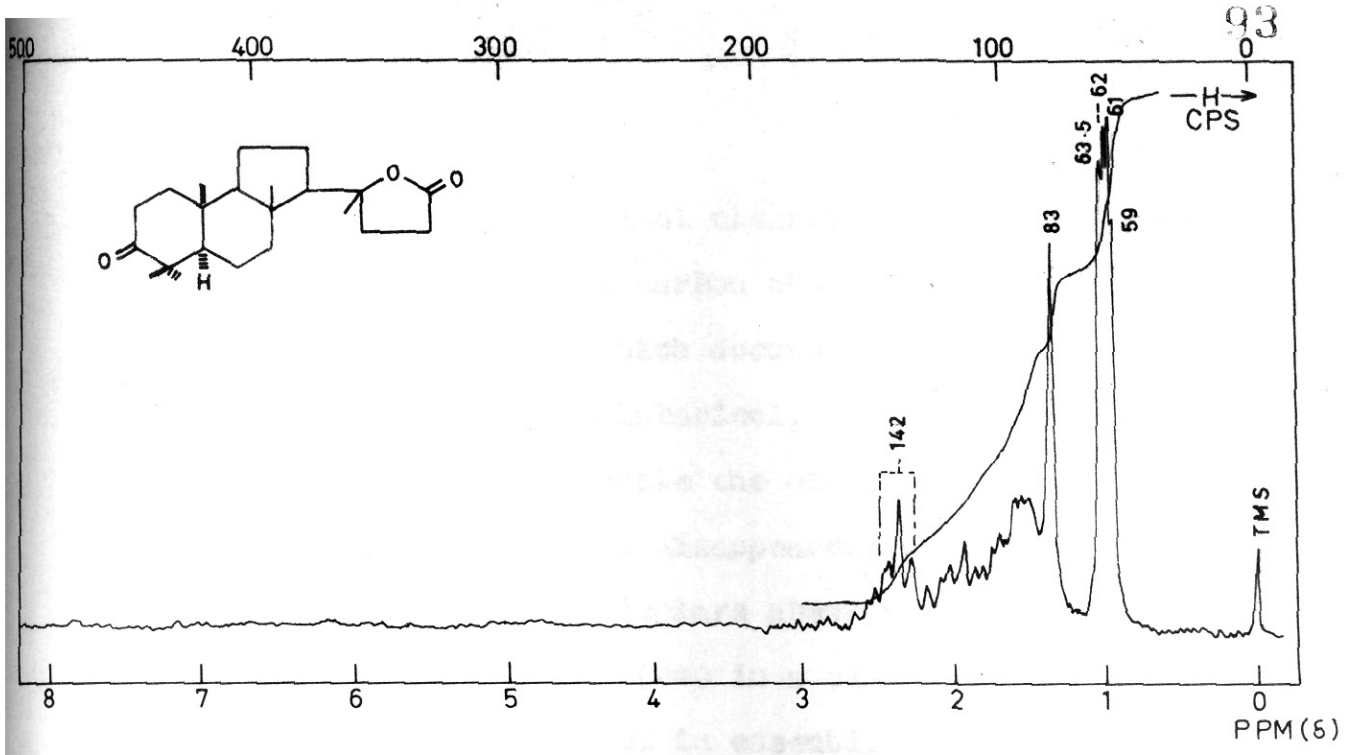


FIG. 13. PMR SPECTRUM OF OCTA-NOR-γ-LACTONE XVI (IN CCl_4)

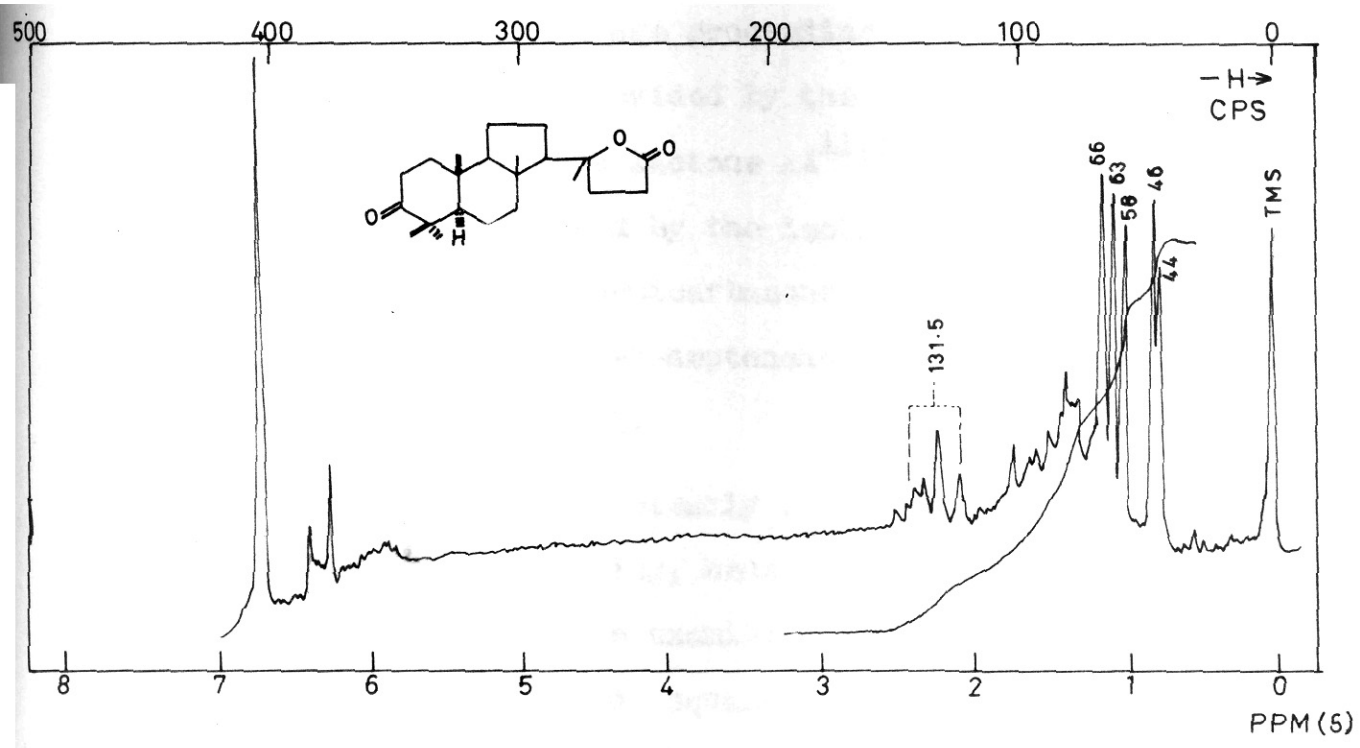


FIG 14. PMR SPECTRUM OF OCTA-NOR-γ-LACTONE XVI (IN BENZENE)

66 c/s), the 83 c/s signal clearly arising due to a quaternary methyl on a carbon atom linked to oxygen; the $-CH_2-C=O$ signal, which occurs centred at 138 c/s in the PMR spectrum of malabaricol, is still present (now centred at 142 c/s), while the other two downfield signals of malabaricol have now disappeared in the lactone. Its IR spectrum (Fig.15) displays absorption bands at 1775 cm^{-1} (γ-lactone), 1702 cm^{-1} (C=O in a six membered ring). The same lactone is produced in essentially the same yield by Jones oxidation or RuO_4[10] oxidation of dihydromalabaricol (or the diols III and IV). These results can be rationalised in terms of the part structure V (which is fully consistent with its PMR spectrum discussed earlier), for malabaricol the cleavage proceeding through VI → VIII. A close analogy is provided by the CrO_3 acid cleavage of ocotillol (X) to the lactone XI[11,12]. The part structure V is further supported by the isolation and identification (n_D, b.p., IR, VPC, semicarbazone derivative - m.p. 134-35°C and m.m.p.) of methyl-2-heptenone (IX) as the other cleavage product of malabaricol.

The above work clearly formulates the ether linkage of malabaricol in a ring, hence the compound can only be tricarbocyclic. While examining theoretically the possible modes of cyclisation of squalene, the well-established[13]

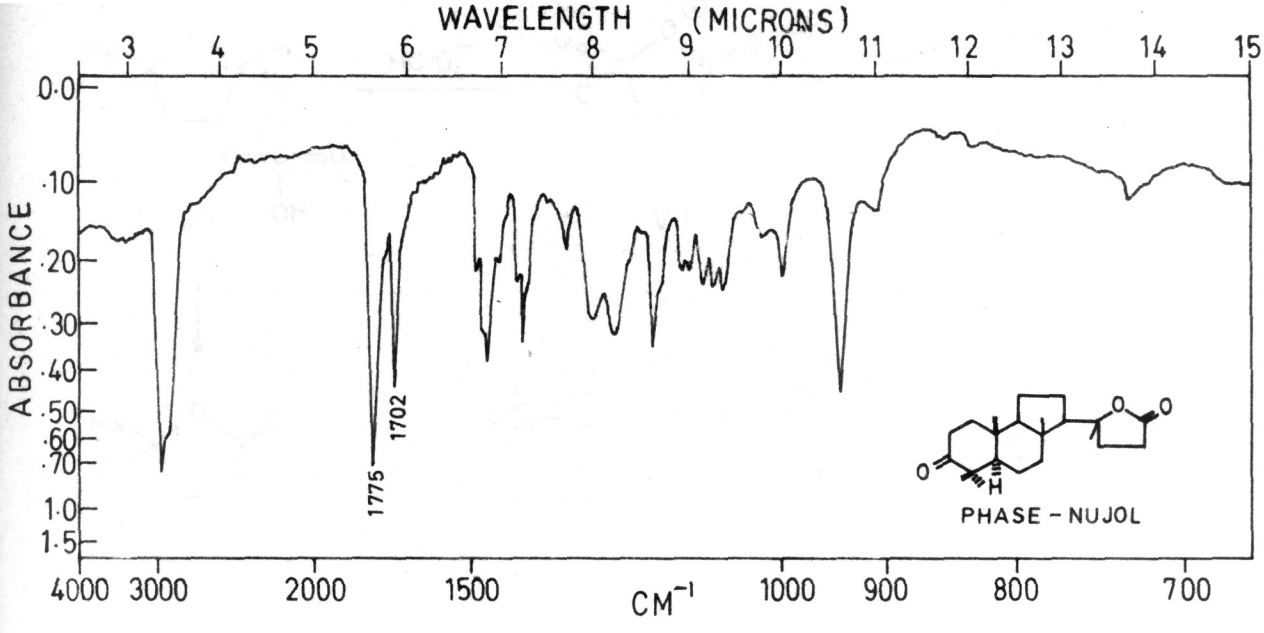
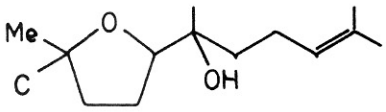
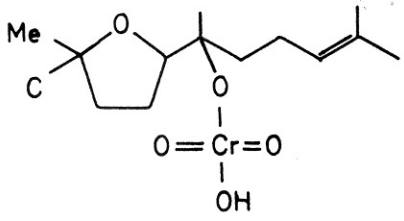


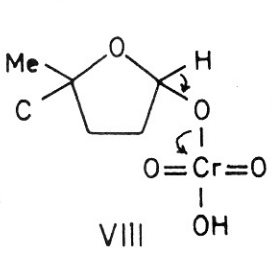
FIG. 15. IR SPECTRUM OF OCTA-NOR-γ-LACTONE XVI



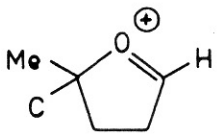
V



VI

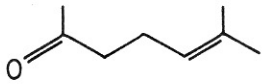


VIII

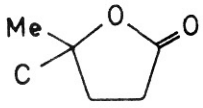


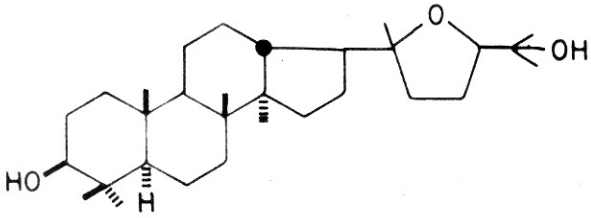
VII

+

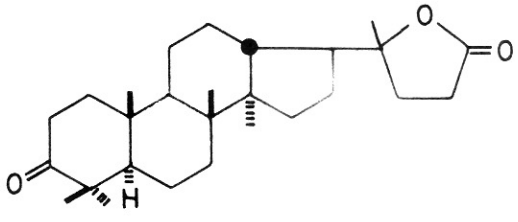


IX





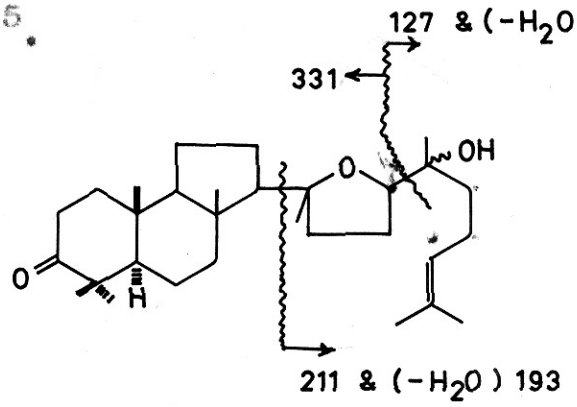
X



XI

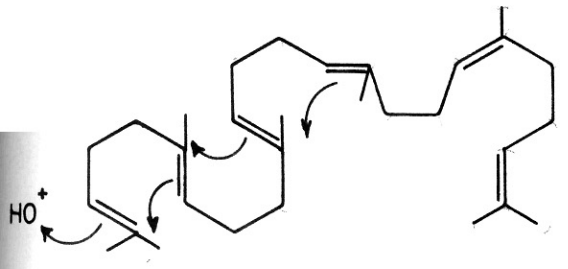
precursor of triterpenoids and steroids, to arrive at a tricyclic system suitable for incorporation in malabaricol structure, it was noted that if ring C is closed Markownikoff-wise (XII), rather than the usual anti-Markownikoff-wise so far observed for all naturally occurring triterpenes the resulting species (XIII) is eminently suited for incorporating the part structure (cf. XIV)[14] to finally give I, as the possible structure of malabaricol. (Chart 1).

Malabaricol, if correctly represented by I, should show, on electron impact, the fragmentation depicted in XV the characteristic α-fission of α-substituted tetrahydrofurans[15].

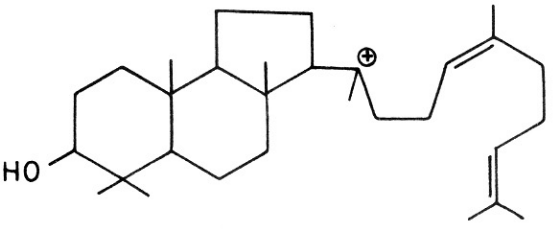


XV

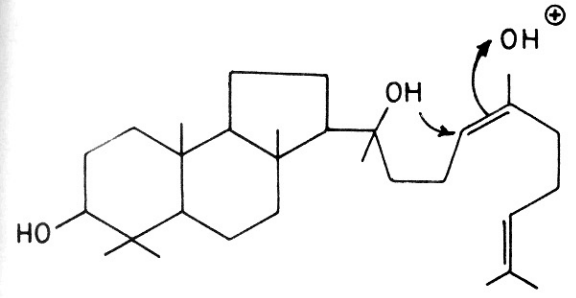
As can be seen from Table 2, all these are important fragments in the mass spectrum (Fig.1) of malabaricol.



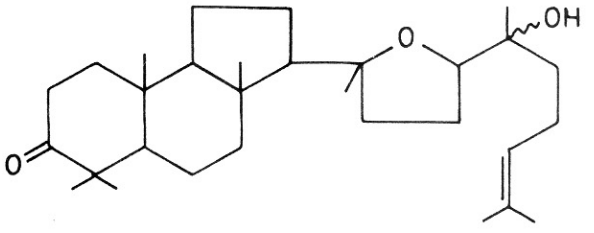
XII



XIII



XIV



I

CHART – 1.

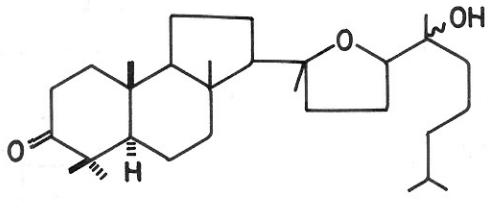
TABLE 2 - IMPORTANT PEAKS IN THE MASS SPECTRUM OF MALABARICOL

m/e	% base peak	$\% \sum_{40}$
458	8	0.3
443	2	0.1
321	36	1.8
289	33	1.6
245	44	2.2
211	67	3.3
193	22	1.1
165	41	2.0
127	47	2.3
109	74	3.6
95	43	2.1
85	75	3.7
81	57	2.8
69	100	4.9
55	71	3.5

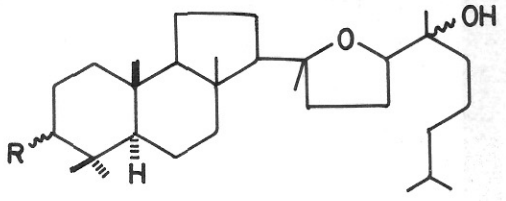
Thus, structure I for malabaricol is clearly supported by its mass spectrum.

If malabaricol is correctly represented by I then the hydrogenation products, dihydromalabaricol and the diols

may be represented by II, III and IV.



II



III R =  C-3 axial diol

IV R =  C-3 equet diol

SYSTEMATIC DEGRADATION OF MALABARICOL

Though the assigned structure I for malabaricol is based upon quite sound evidence viz. spectral data, biogenetic considerations and some chemical reactions, it was considered essential to degrade it to compound XIA in order to get a direct proof for the size of ring C. The scheme envisaged for this purpose is outlined in Fig.16.

The octa-nor-γ-lactone (which may now be represented by XVI) on reduction with $LiAlH_4$ furnished a triol (~ 96%, $C_{22}H_{40}O_3$, m.p. 190-91°. IR spectrum, Fig.17. OH 3370, 1075, 1050, 1033 and 1008 cm^{-1}), which on acetylation (Ac_2O-pyridine 12 hr at 25°) gave in good yield an hydroxy diacetate ($C_{26}H_{44}O_5$, m.p. 61-64°, $[\alpha]_D$ +7.34°) formulated as XVII. This structure is consistent with its spectral data; PMR spectrum (Fig.18): five quaternary methyls at

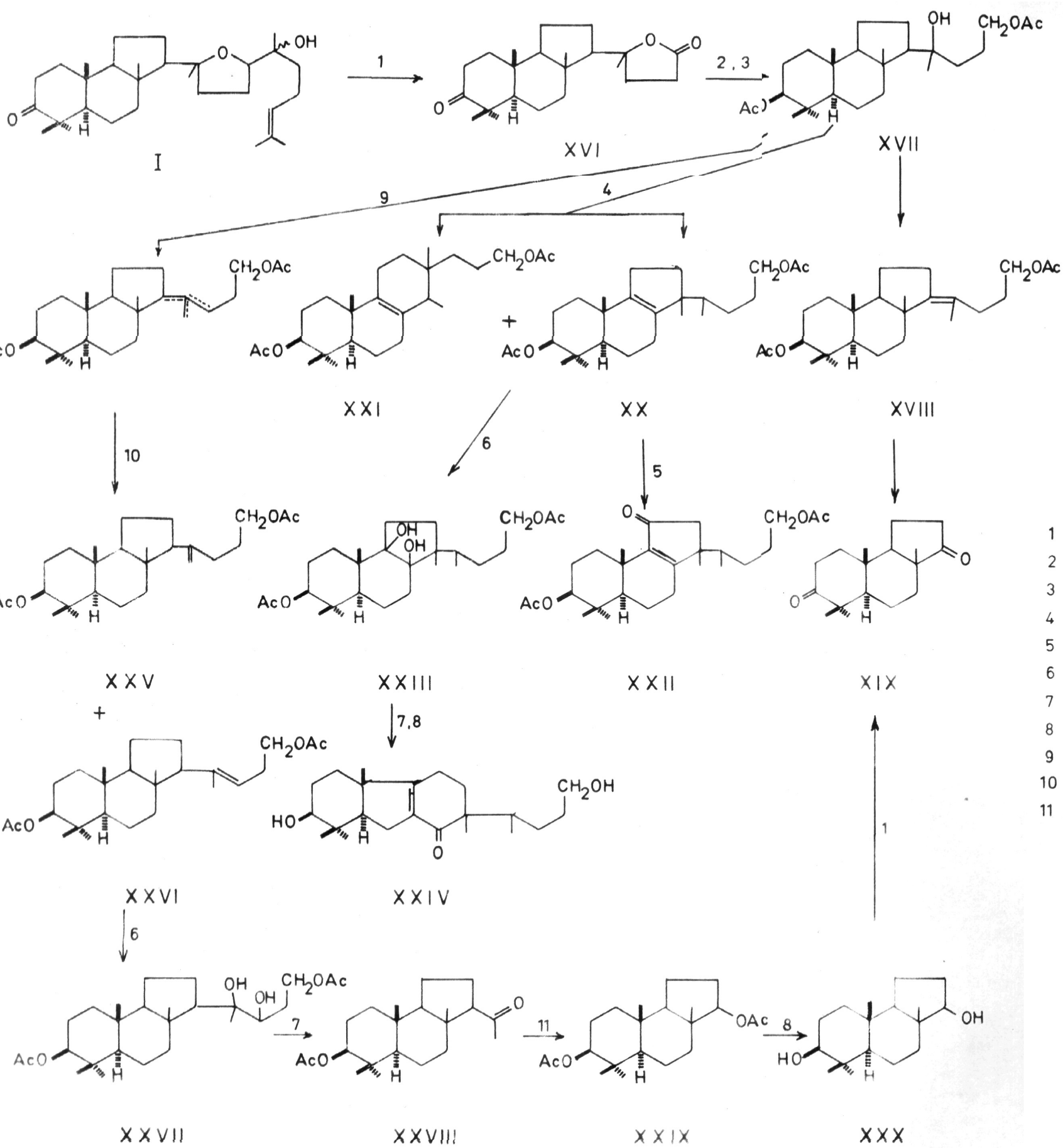


FIG. 16. SCHEME FOR THE DEGRADATION OF MALABARICOL (I) TO DIKETONE XIX.

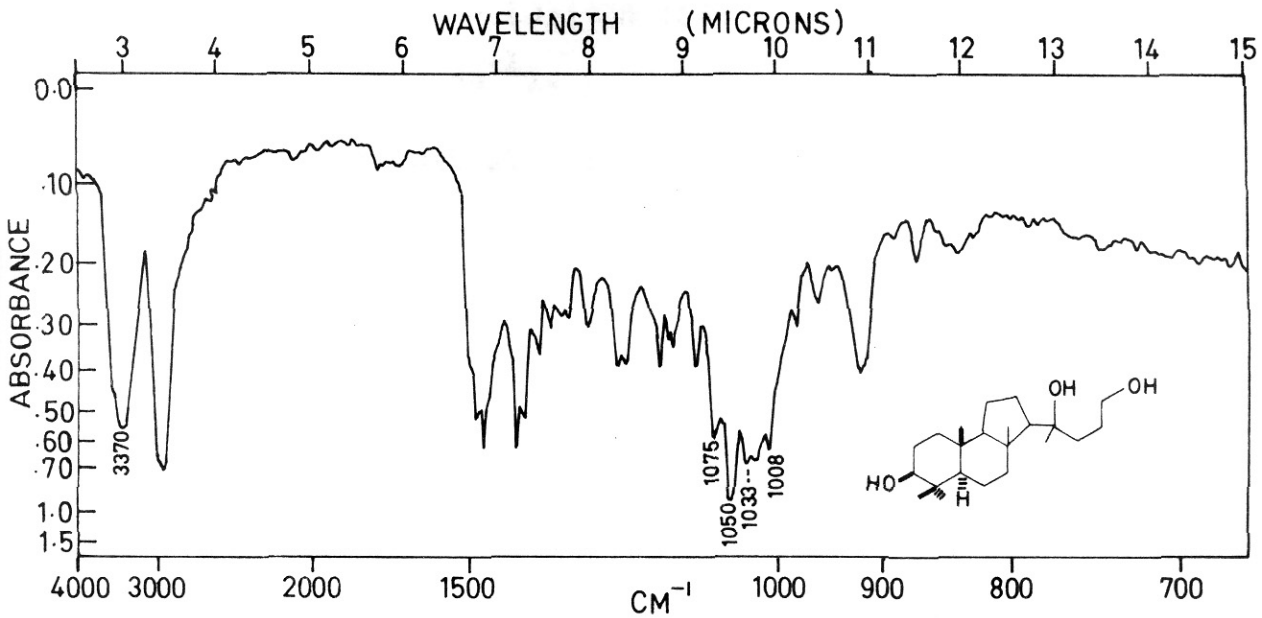


FIG. 17. IR SPECTRUM OF TRIOL

52.5 c/s (3H), 57 c/s (3H) and 71 c/s (3H); CH_3COO, 6H signal at 120 c/s; $-CH_2.OAc$, 2H triplet centred at 241 c/s (J = 6 c/s); $CHOAc$, 1H broad signal centred at 268 c/s. IR spectrum (Fig.19): OH (3500, 1045 cm^{-1}), -OAc (1750, 1730 and 1250 cm^{-1}).

The next step involved in the degradation was the dehydration of hydroxy diacetate (XVII) to olefin XVIII. It was first attempted using iodine as the dehydrating agent[16]. Instead of obtaining the required product (XVIII) two rearranged olefins (XX and XXI) in almost equal amounts were obtained (TLC test positive) which have been formulated on the basis of their spectral data.

The PMR spectrum (Fig.20) of (XXI) displays two sharp signals at 54 (6H) and 59 c/s (6H) for four quaternary methyls and a doublet centred at 43 c/s (J = 6 c/s) for a secondary methyl group. It further shows a sharp singlet at 119 c/s (6H) for two acetate groups, a triplet centred at 240 c/s (J = 6 c/s, 2H) for $-CH_2-OAc$ and a triplet centred at 269 c/s (J = 7 c/s, 1H) for C-3 axial proton. Its IR spectrum (Fig.21) exhibits absorption at 1750 and 1250 cm^{-1} (-OAc). The PMR spectrum (Fig.22) of (XX) reveals the presence of four quaternary methyls (12H signal at 54 c/s), a secondary methyl (doublet centred at 58.5 c/s, J = 2 c/s) and two acetate groups (a sharp singlet

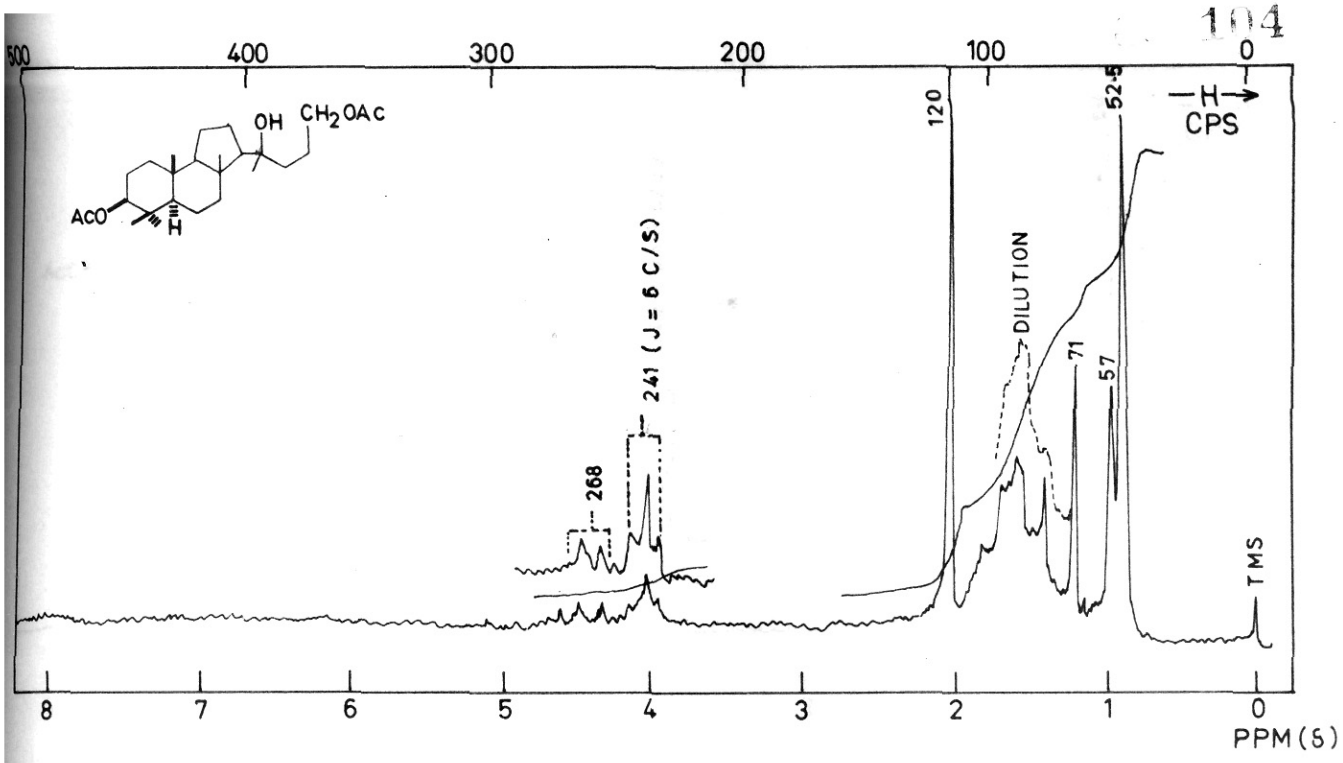


FIG. 18. PMR SPECTRUM OF HYDROXY DIACETATE

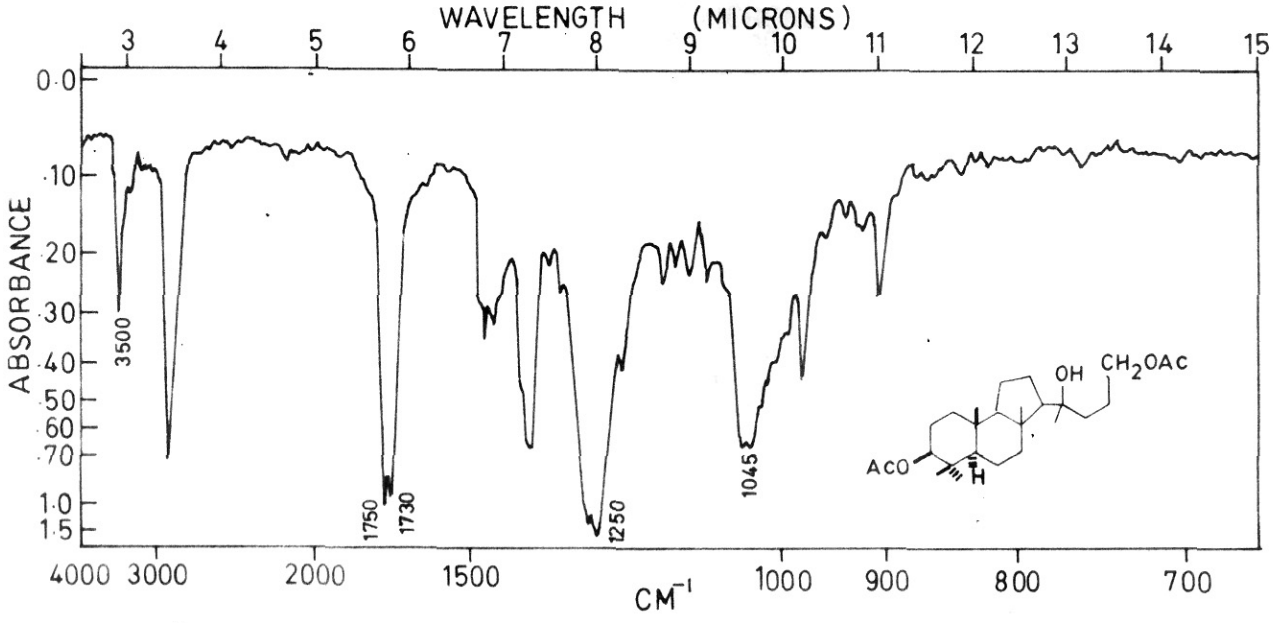


FIG. 19. IR SPECTRUM OF HYDROXY DIACETATE

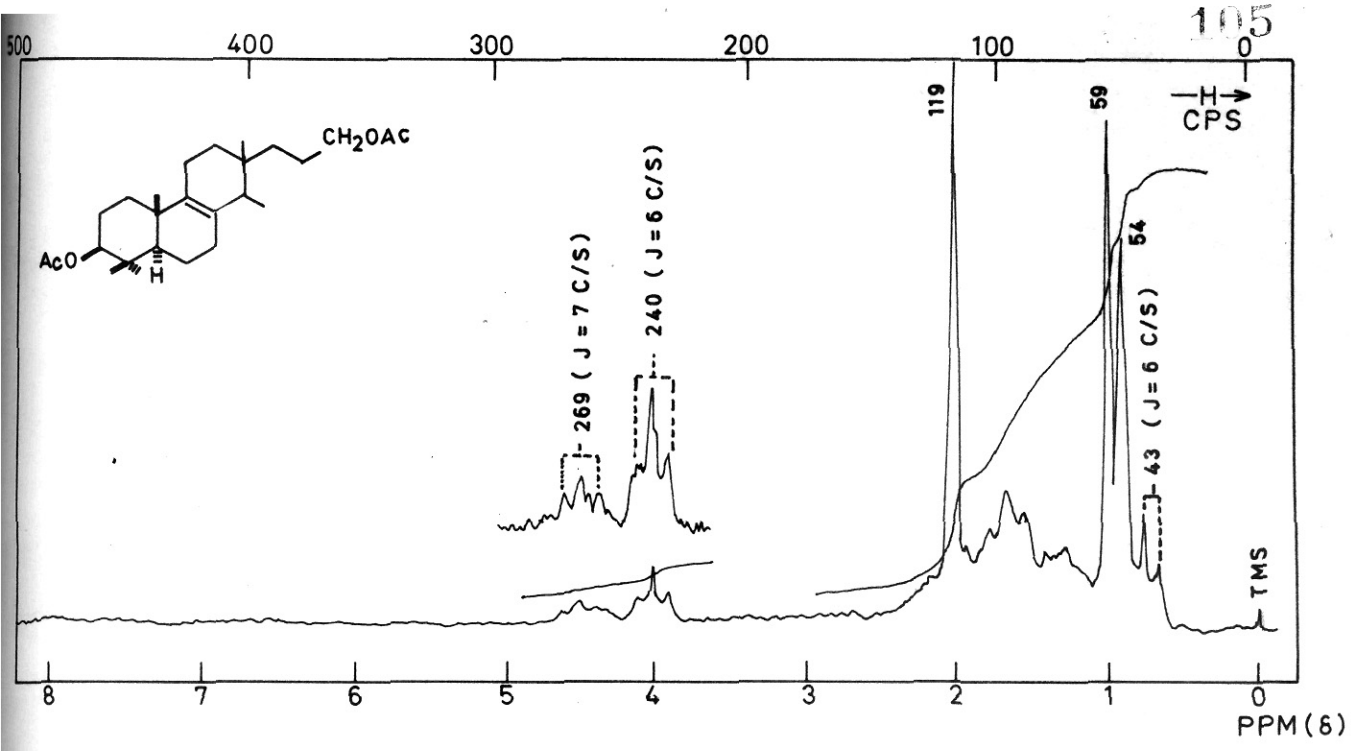


FIG. 20. PMR SPECTRUM OF XXI.

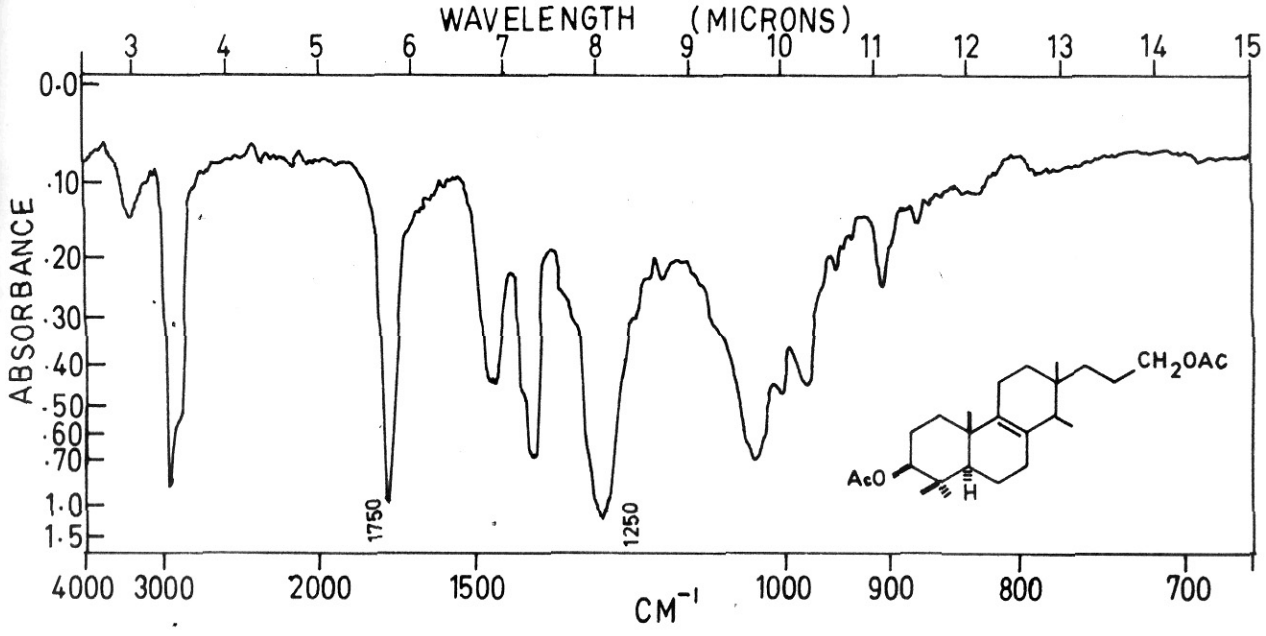


FIG. 21. IR SPECTRUM OF XXI.

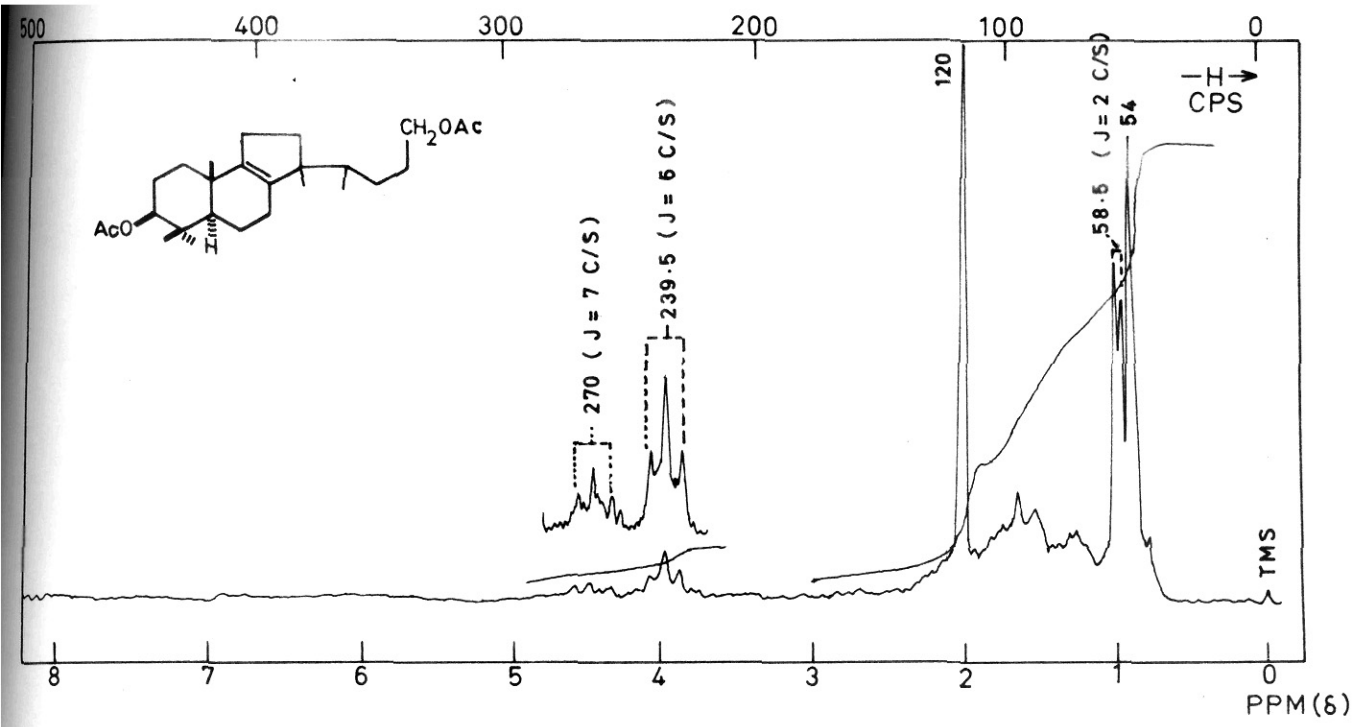


FIG. 22. PMR SPECTRUM OF XX.

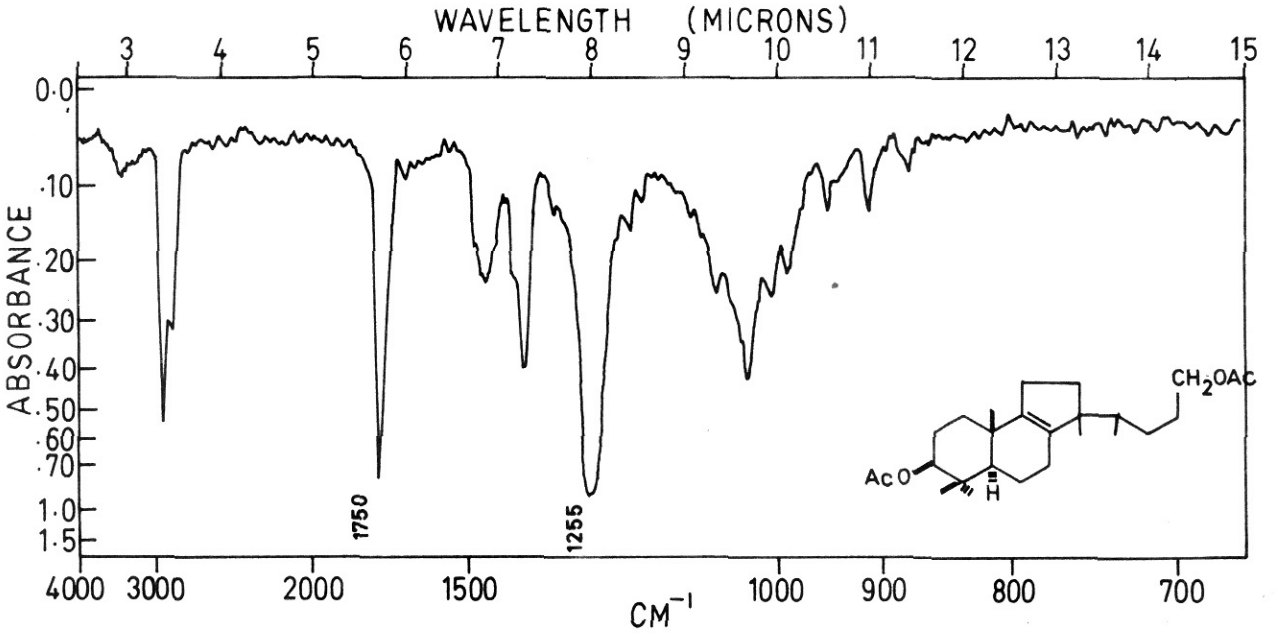
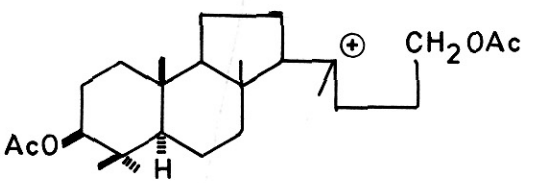


FIG. 23 IR SPECTRUM OF XX.

at 120 c/s, 6H). Further it shows a triplet centred at 239.5 c/s (J = 6 c/s) for 2H (-C<u>H</u>$_2$-OAc) and a triplet centred at 270 c/s (J = 7 c/s) for 1H (-C<u>H</u>-OAc). Its IR spectrum (Fig.23) displays absorption bands at 1750 and 1255 cm^{-1} for acetate groups.

These two olefinic compounds are conceivable <u>via</u> the intermediate cation XXII**a**.



XXII a

Chromium trioxide-acetic acid oxidation[17] of the latter (XX) furnished essentially a ketone (XXII) along with a very minor second compound which was separated by preparative layer chromatography over silica gel. Its UV (Fig.24; λ_{max} 259 mμ, ε 10,800), IR (Fig.25, 1690 cm^{-1} for 5-membered α,β-unsaturated ketone) and PMR (Fig.26; a doublet centred at 57.5 c/s; J = 7 c/s fora secondary methyl; 58 c/s (3H), 73 c/s (3H), 78 c/s (3H) for four quaternary methyls; 120 c/s (6H) for two acetate groups; a triplet centred at 241 c/s, J = 6 c/s, 2H for -C<u>H</u>$_2$-OAc and a triplet at 271 c/s, J = 7 c/s, 1H for -C<u>H</u>-OAc) are fully consigned with the designated size of the ketone ring.

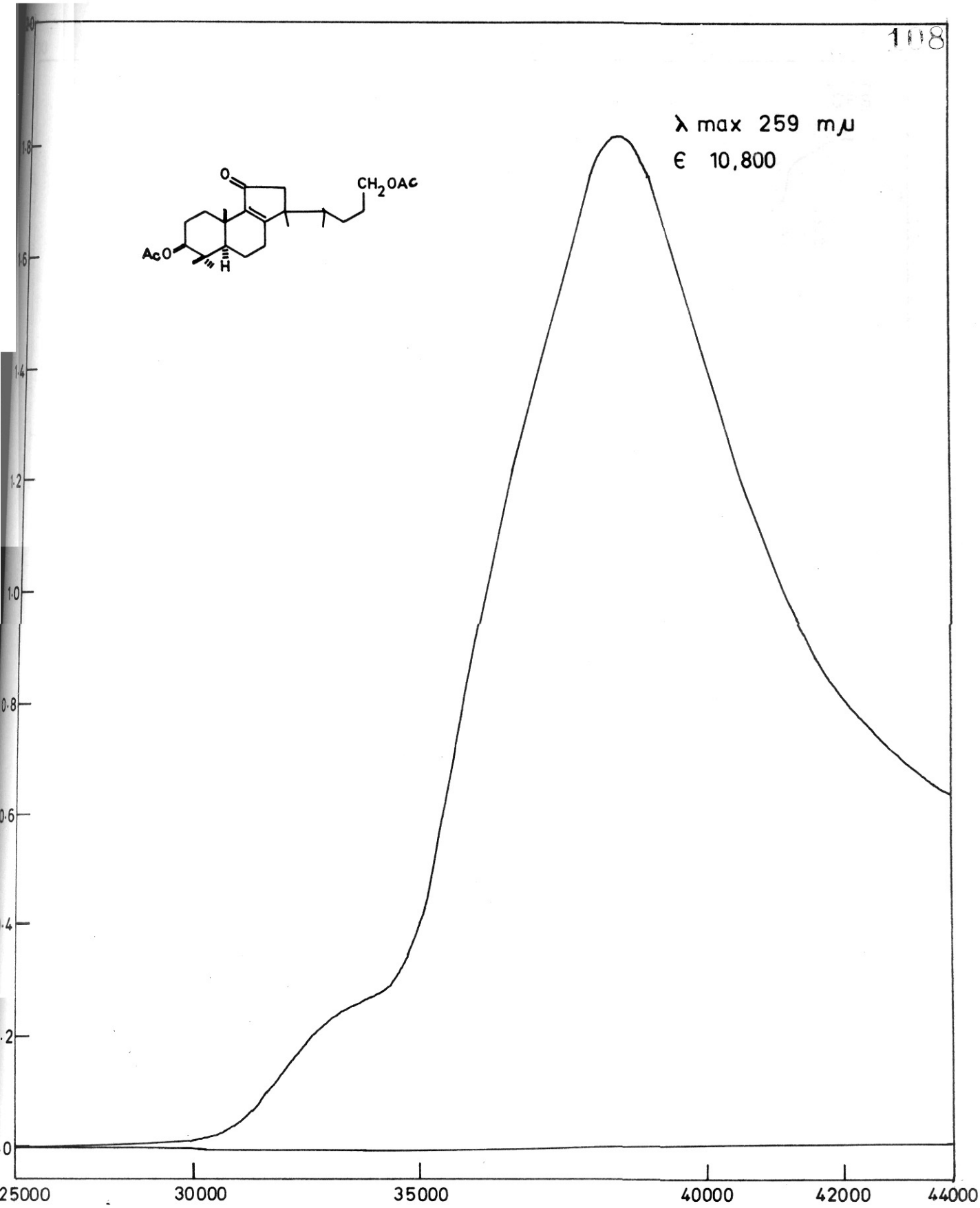


FIG. 24. UV SPECTRUM OF XXII

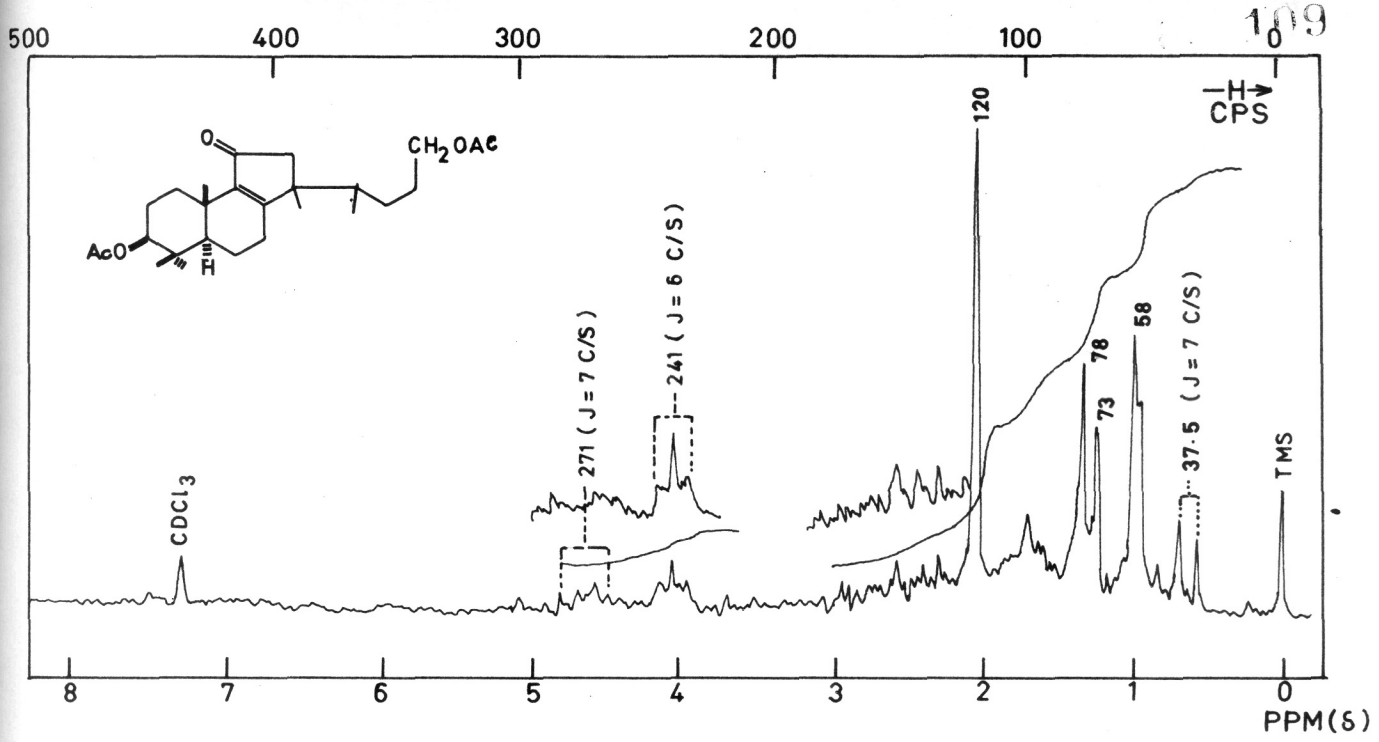


FIG. 26. PMR SPECTRUM OF XXII.

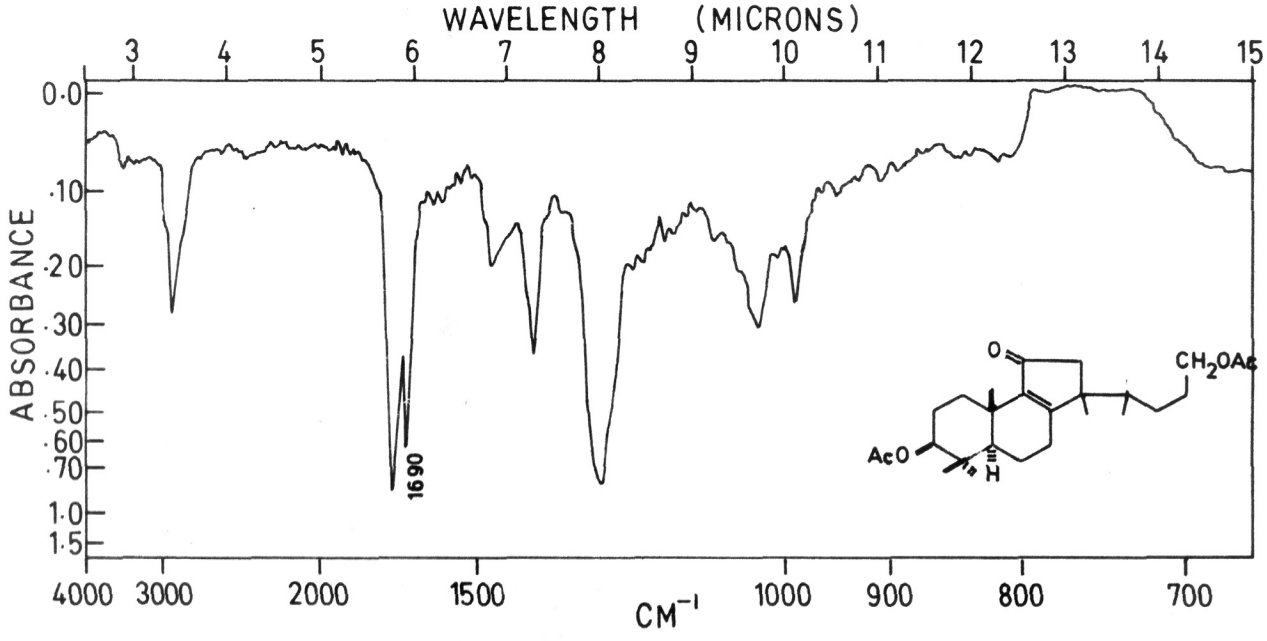


FIG. 25. IR SPECTRUM OF XXII.

The osmylation[18] of XX gave a diol (XXIII, $C_{26}H_{44}O_6$, m.p. 143-144°, IR spectrum: Fig.27, 3200, 3400 cm^{-1} for OH 1750 and 1260 cm^{-1} for acetate, PMR spectrum: Fig.28, displays five methyls 45, 51, 51, 58, 58, 61.5 c/s, one of which is secondary; and two acetate groups: a sharp singlet at 121 c/s for 6H, $-CH_2-OAc$, a 2H triplet at 242 c/s, J = 6 c/s; and $-CH-OAc$, a 1H triplet at 269 c/s, J = 7 c/s, for 3-β axial proton) which underwent a cleavage on reaction with $Pb(OAc)_4$ in benzene[19]. This product was cyclised to furnish an α,β-unsaturated ketone, formulated as XXIV. This structure is consistent with its spectral data (UV: λ_{max} 248, IR: Fig.29: 3430 cm^{-1} (OH), 1650 (α,β-unsaturated six membered ketone), PMR: Fig.30: a doublet for secondary methyl centred at 49.5 c/s, J = 3 c/s; four quaternary methyls at 58.5, 58.5, 59.5 and 62.5 c/s.

Since the required olefin (XVIII) could not be obtained by I_2 dehydration it became imperative to choose a reagent by which the elimination should take place by E_2 mechanism. For this purpose $SOCl_2$/Pyridine[20] was selected. Dehydration of hydroxydiacetate with this reagent (-15°, 12 hr) furnished a mixture of two olefins (TLC; very minor amounts of a third isomer were also present) one of them predominating considerably (~ 70%). The mixture was separated on SiO_2-gel and the major component identified as XXV on the basis of its spectral data. Its PMR spectrum

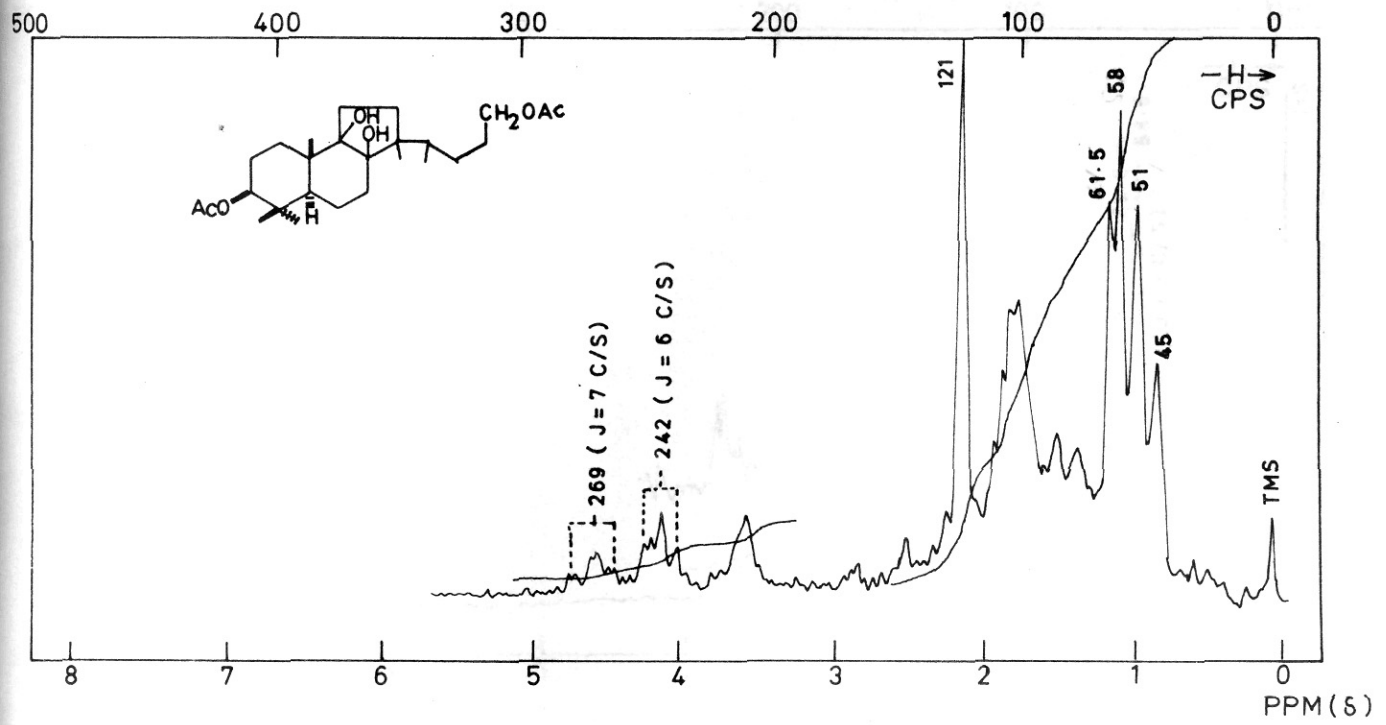


FIG. 28. PMR SPECTRUM OF XXIII.

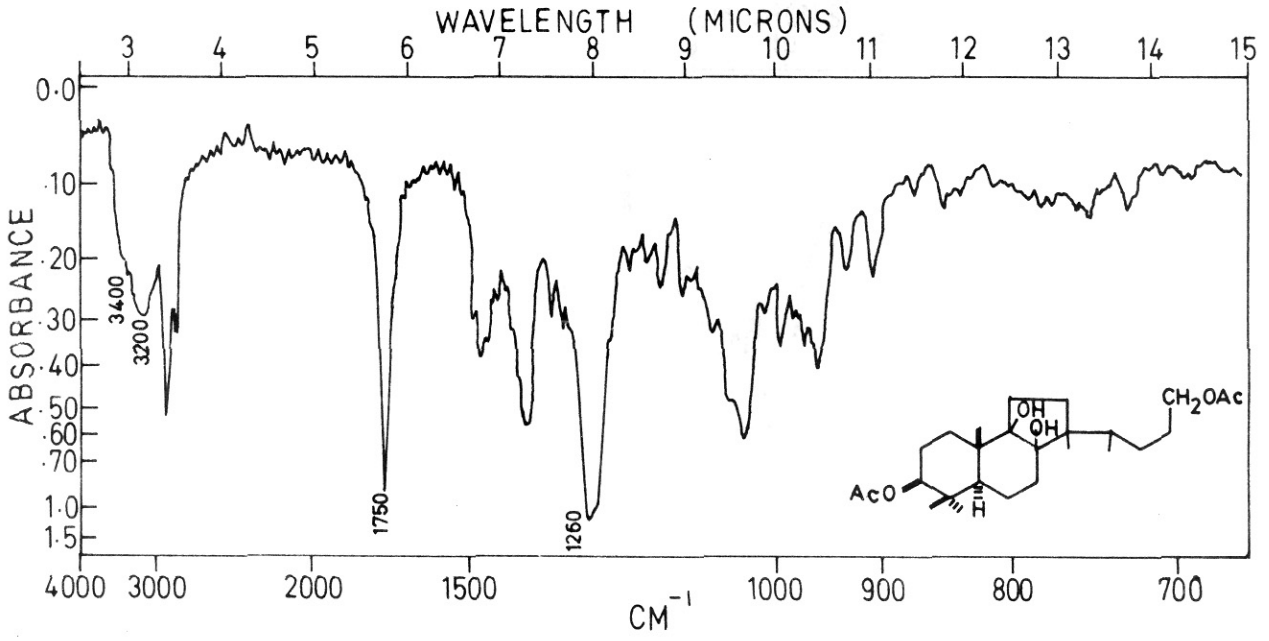


FIG. 27. IR SPECTRUM OF XXIII.

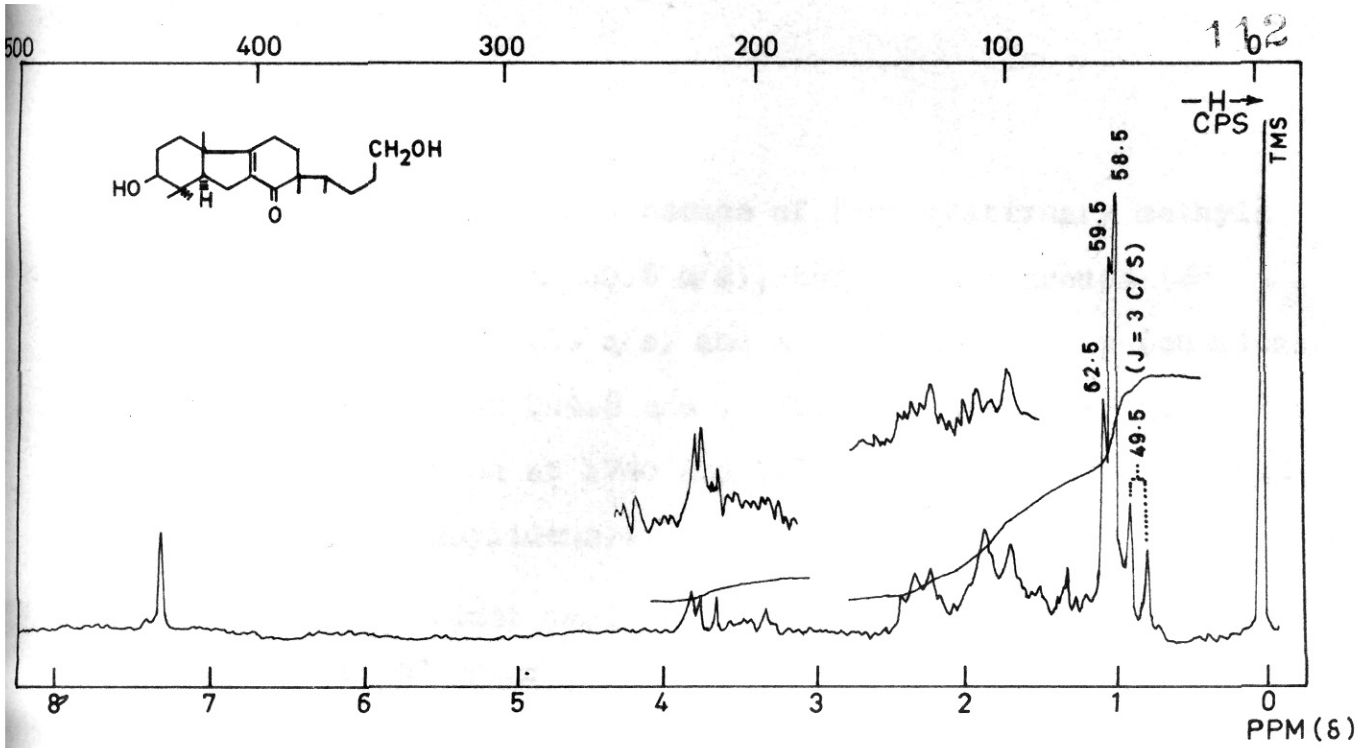


FIG. 30. PMR SPECTRUM OF XXIV.

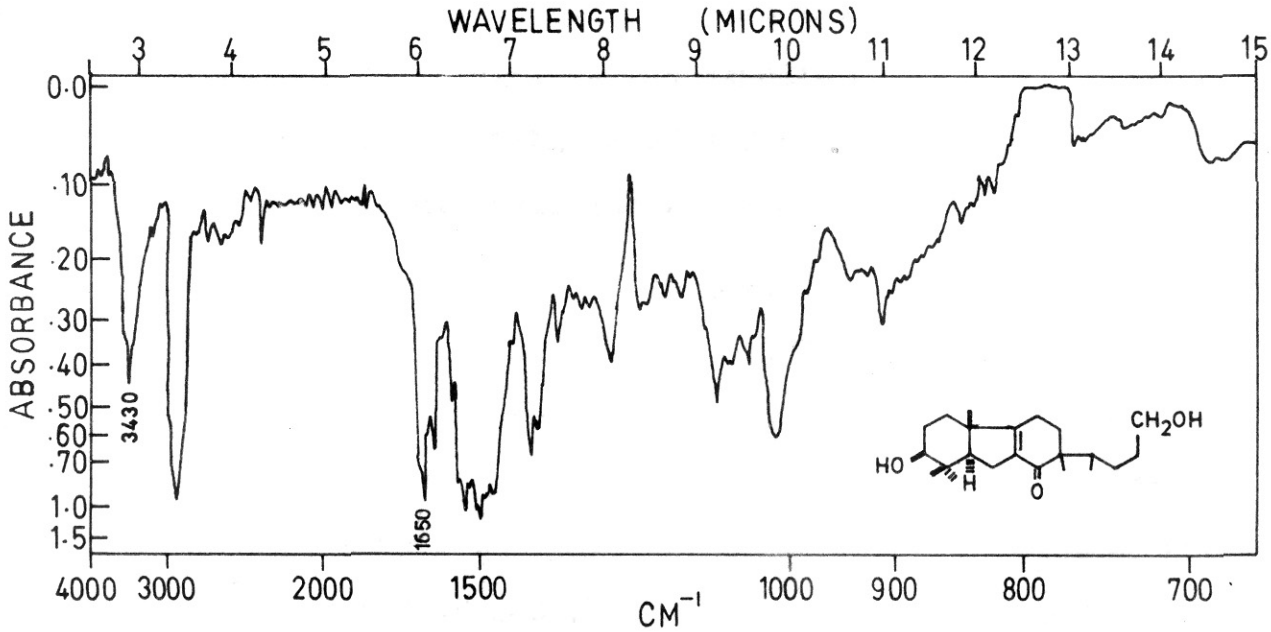


FIG. 29. IR SPECTRUM OF XXIV.

(Fig.31) reveals the presence of four quaternary methyls (51.5, 51.5, 53 and 60.5 c/s), two acetate groups (6H sharp singlet at 120 c/s) and a vinylidene group (chemical shift at 278 and 294.5 c/s). Its IR spectrum (Fig.32) shows absorption at 1740 and 1255 cm^{-1} (acetate), 905 and 1650 cm^{-1} (vinylidene).

The minor product, $C_{26}H_{42}O_4$, m.p. 110-112°, $[\alpha]_D$ +17.35° ($CHCl_3$), was shown from its PMR spectrum (Fig.33; four quaternary methyls, 51, 51, 53.5 and 59 c/s; one vinylic methyl, 98.5 c/s; two CH_2COO signals at 119, 120 c/s; CH_2OAc, 2H triplet centred at 244 c/s, J = 6.5 c/s; $CHOAc$, 1H triplet centred at 300 c/s, J = 7 c/s) to be the desired isomer (XXVI). Its IR spectrum (Fig.34) displays absorption at 1745 and 1260 cm^{-1} (acetate). The required compound XXVI was expeditiously obtained by isomerising the total olefin mixture with Li in ethylene diamine[21], when this isomer predominated.

Osmylation of XXVI gave the corresponding α-glycol XXVII, $C_{26}H_{44}O_6$, m.p. 175.5 - 177° with the expected spectral data. Its PMR spectrum (Fig.35) shows the presence of four quaternary methyls at 52, 52, 52, 57 c/s and one methyl on carbon bearing oxygen at 65 c/s, two acetates (122.5 and 124 c/s). Its IR spectrum (Fig.36) exhibits absorption at 3550 and 3440 cm^{-1} (OH); 1750 and

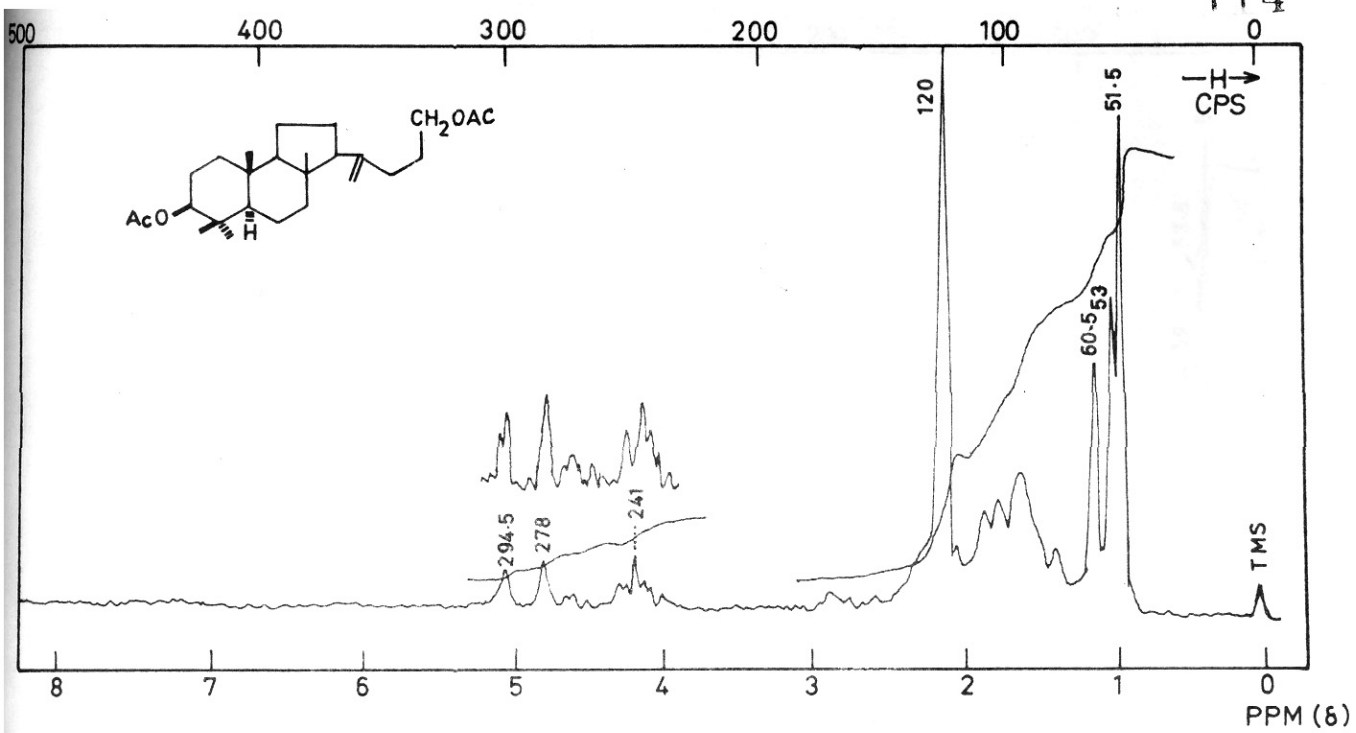


FIG. 31. PMR SPECTRUM OF OLEFIN XXV.

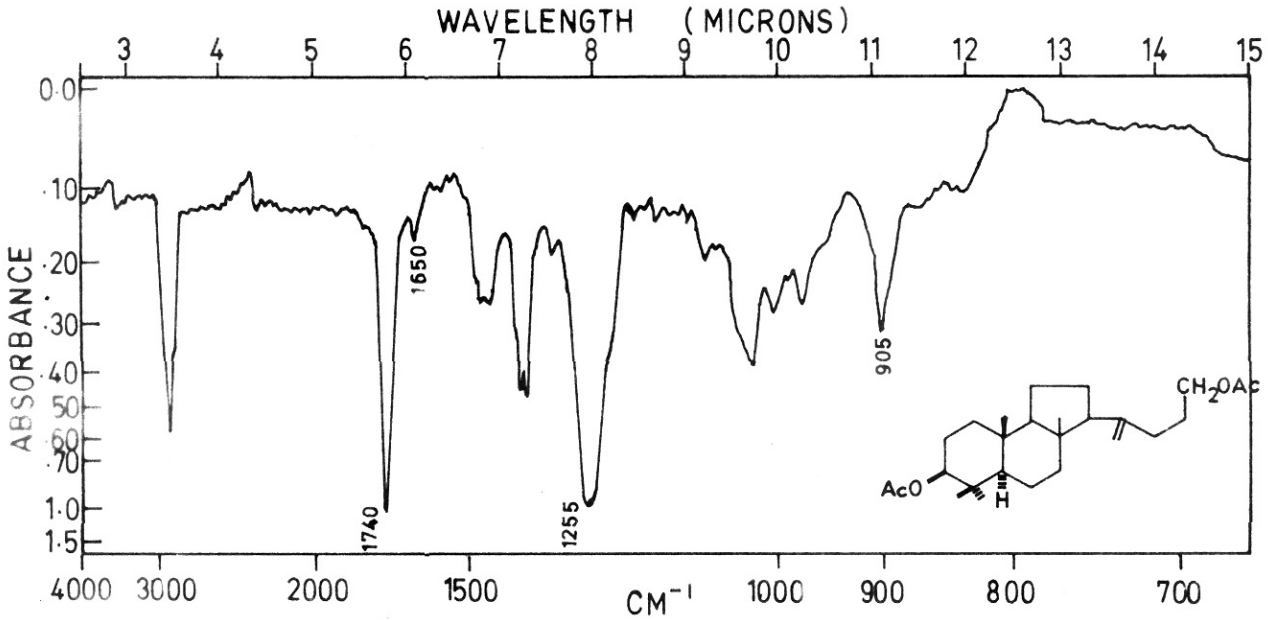


FIG. 32. IR SPECTRUM OF OLEFIN XXV.

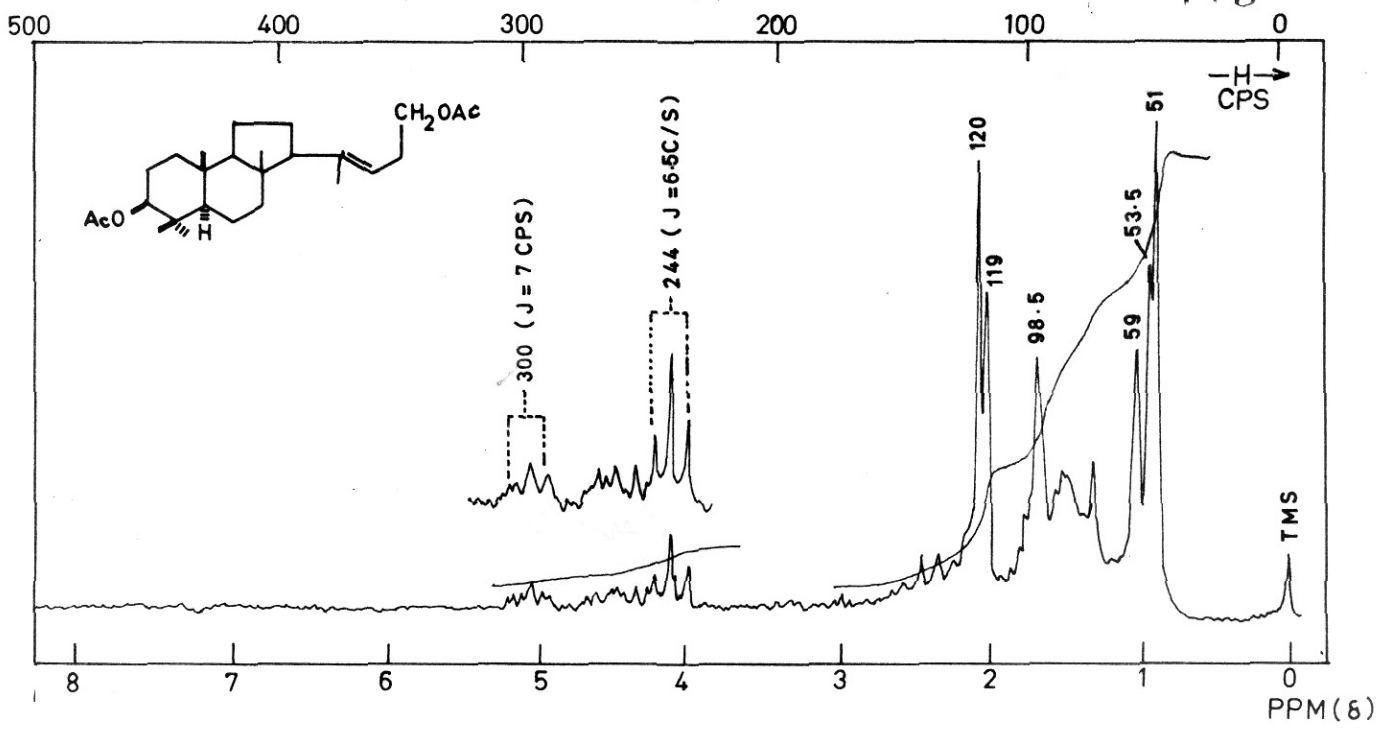


FIG. 33. PMR SPECTRUM OF XXVI.

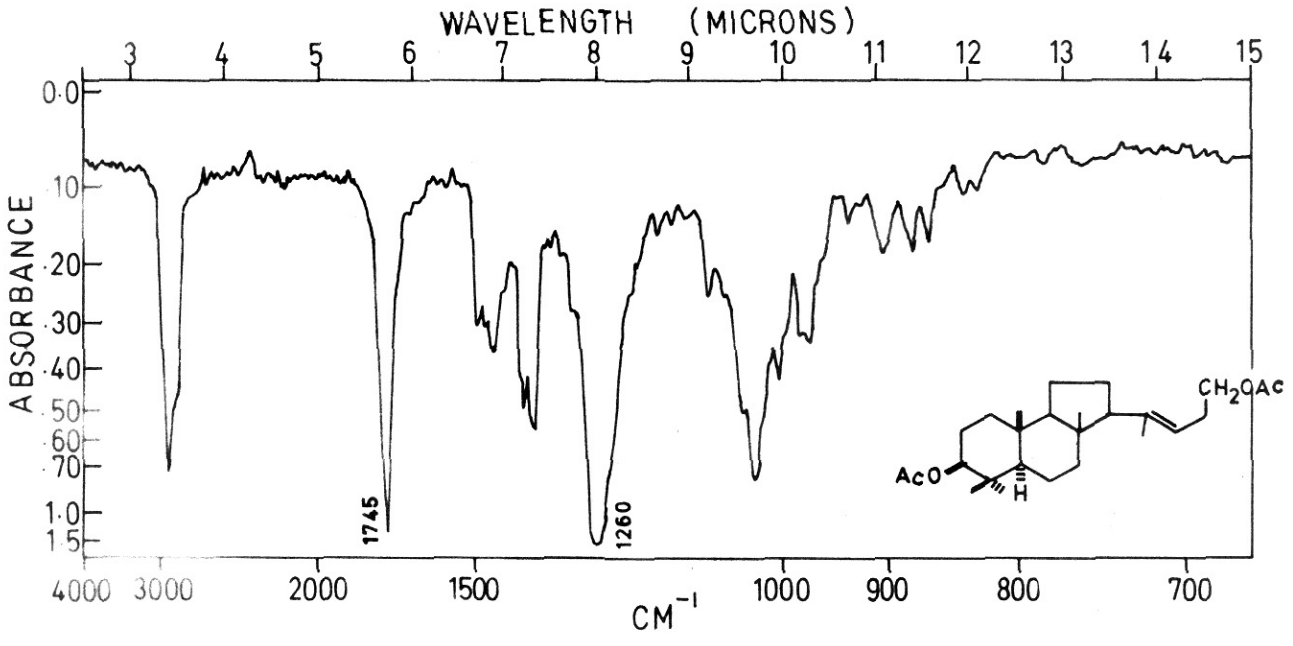


FIG. 34. IR SPECTRUM OF XXVI.

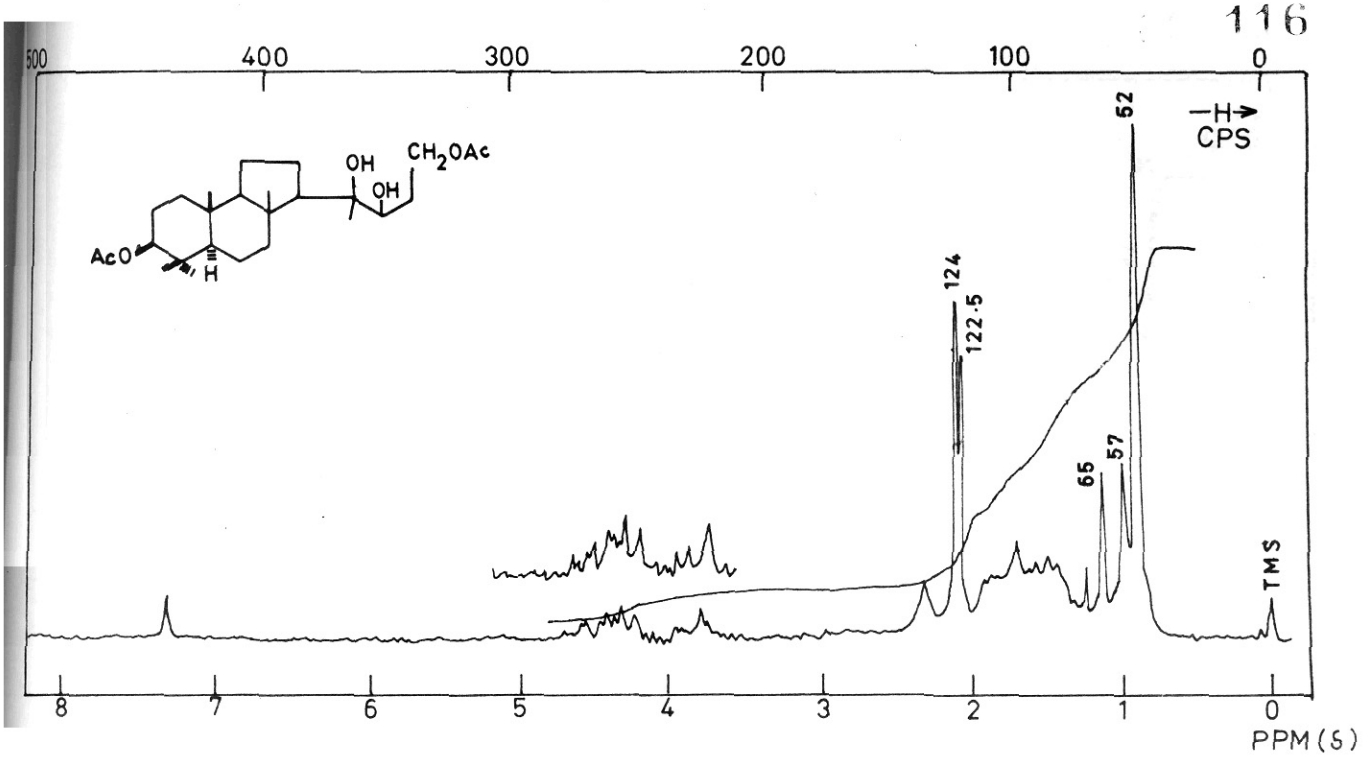


FIG. 35. PMR SPECTRUM OF XXVII.

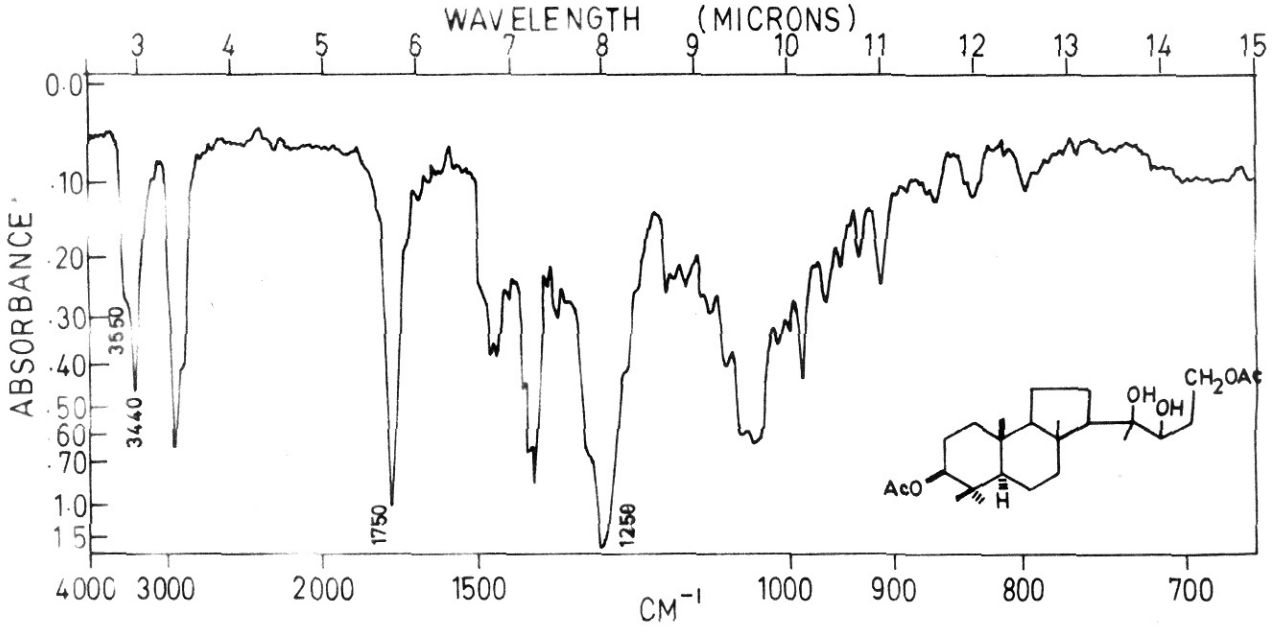


FIG. 36. IR SPECTRUM OF XXVII.

1250 cm^{-1} (acetate). The glycol was cleaved with $Pb(OAc)_4$ (C_6H_6 solution, ~25°, 3 hr) to furnish the desired methyl ketone (XXVIII $C_{21}H_{34}O_3$, m.p. 126-127°). Its structure was confirmed from its spectral data. The PMR spectrum (Fig.37) shows the resonance signals for four quaternary methyls (51, 51, 52 and 62 c/s), an acetate signal (118 c/s) and a methyl on carbonyl (122 c/s) its IR spectrum (Fig.38) shows absorption at 1725 and 1245 cm^{-1} (acetate) and 1705 cm^{-1} (-CO-CH_3).

The methyl ketone XXVIII was oxidised with perbenzoic acid[22] (C_6H_6 solution, ~25°, 3 days) to yield a diacetate (XXIX, $C_{21}H_{34}O_4$, 151.5 - 152°). This product had all the spectral requirements of XXIX. Its PMR spectrum (Fig.39) displays a sharp singlet at 53.5 c/s (12H, four quaternary methyls), a sharp signal at 120 c/s (6H, 2- -OCOCH_3 groups) and a multiplet located between 260 and 284 c/s (2H for 2- -CH-OAc). Its IR spectrum (Fig.40) exhibits absorptions at 1735, 1725 and 1250 cm^{-1} for acetate groupings. The hydrolysis of this product with 10% alc. KOH (2 hr) gave a solid diol (XXX, $C_{17}H_{30}O_2$, m.p. 210-11°; IR spectrum, Fig.41, 3350 and 3200 cm^{-1} for OH).

The diol (XXX) was oxidised with Jones reagent to give a diketone (XXI, $C_{17}H_{26}O_2$, m.p. 64-66°, M^+ m/e = 262). Its structure was confirmed from its spectral data.

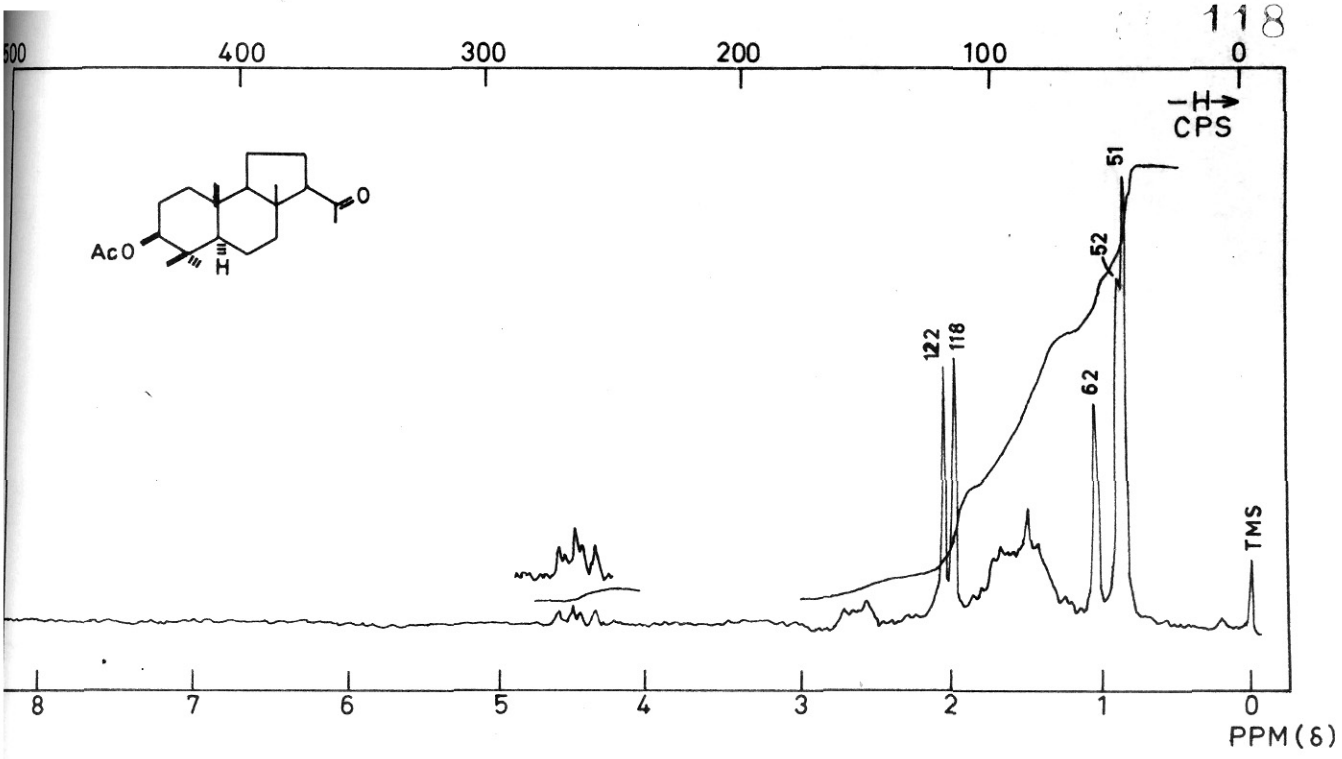


FIG. 37. PMR SPECTRUM OF METHYL KETONE XXVIII.

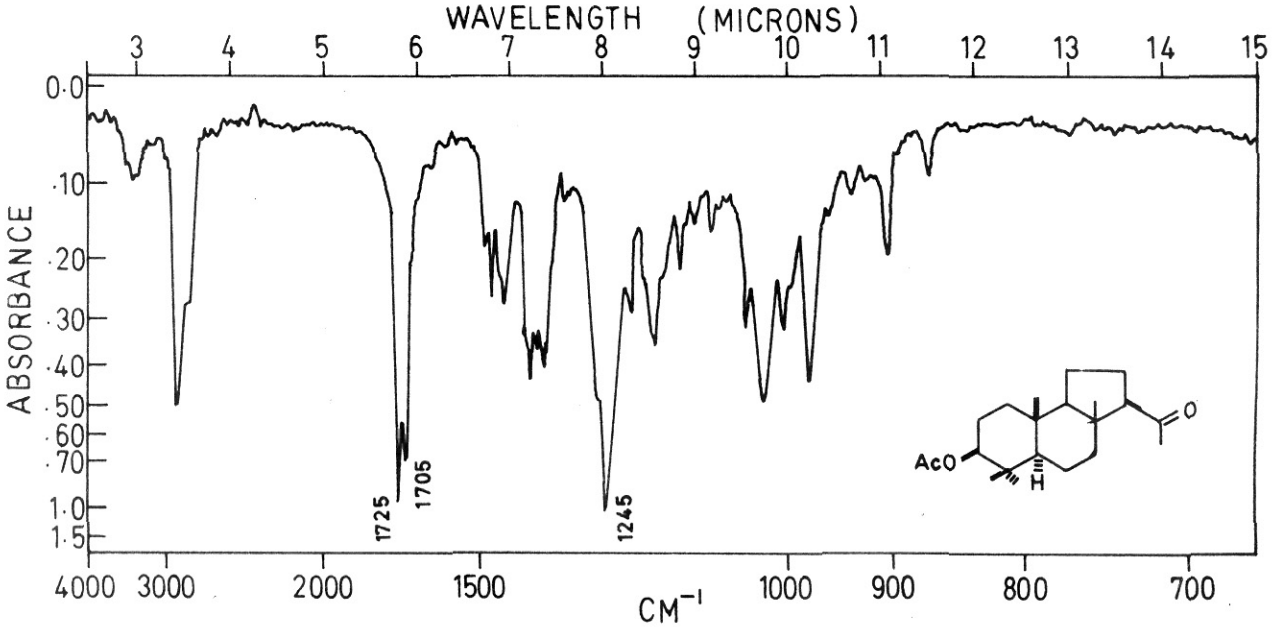


FIG. 38. IR SPECTRUM OF METHYL KETONE XXVIII.

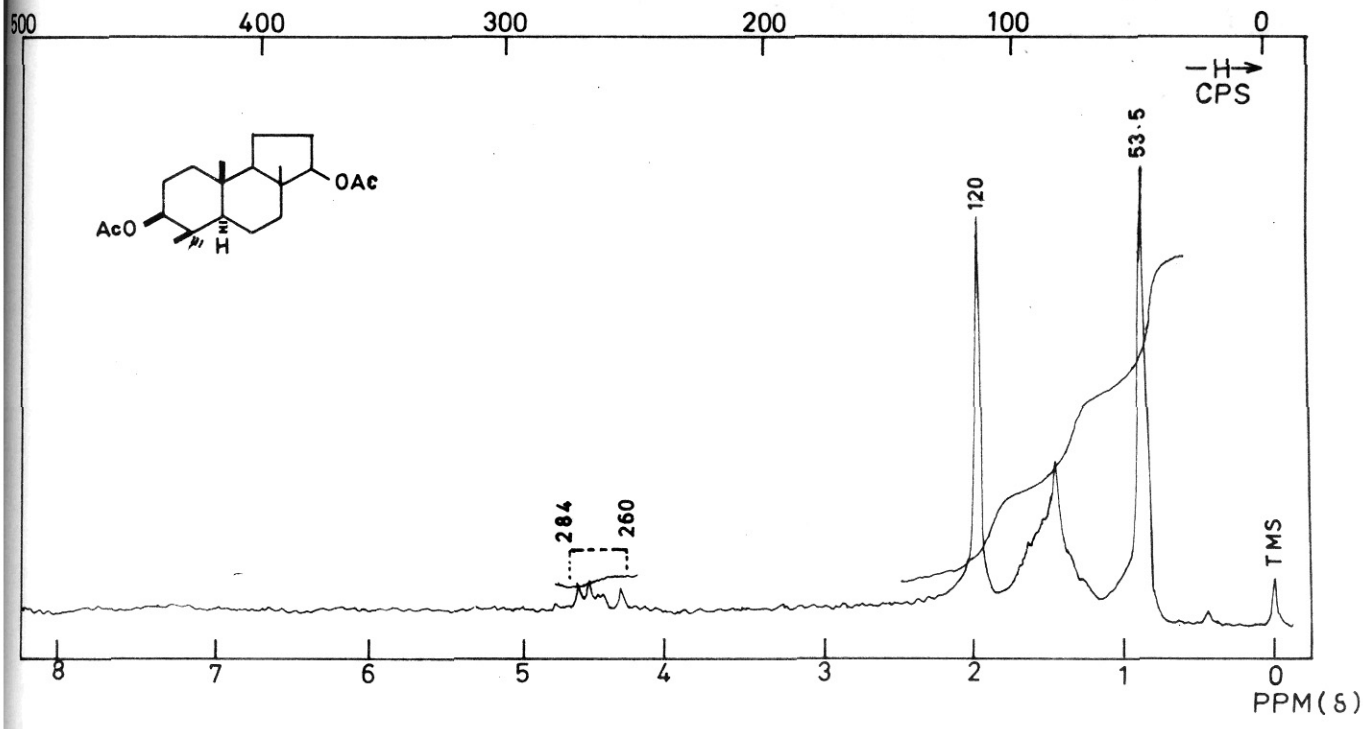


FIG. 39. PMR SPECTRUM OF XXIX.

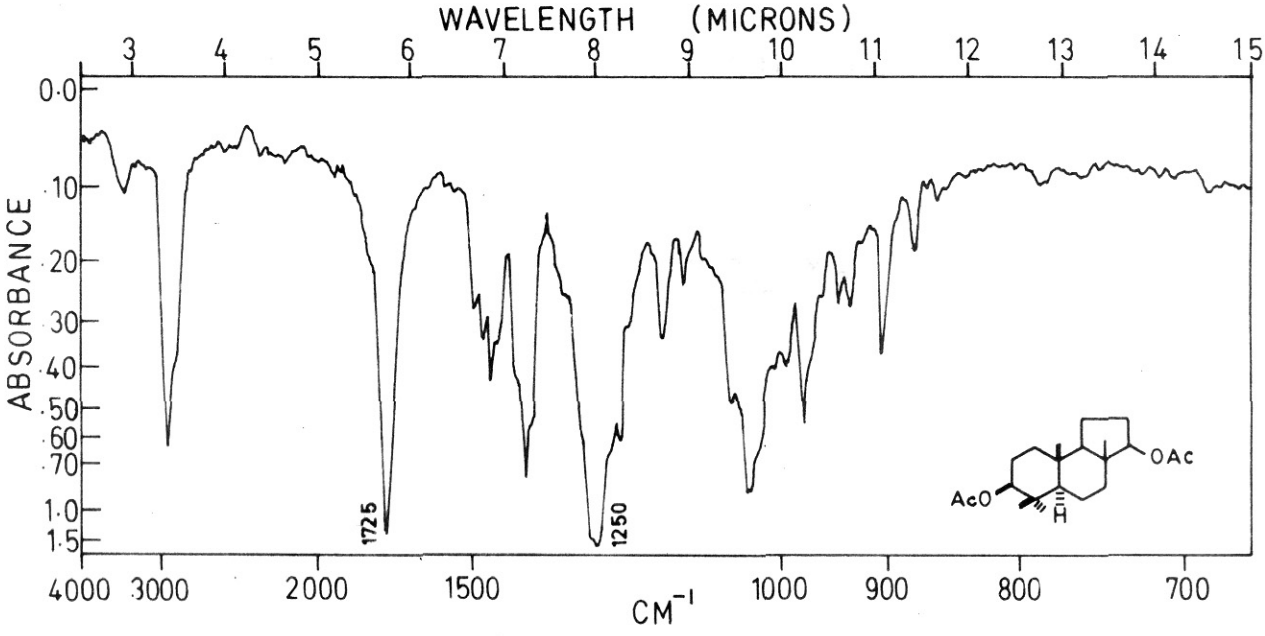


FIG. 40. IR SPECTRUM OF XXIX.

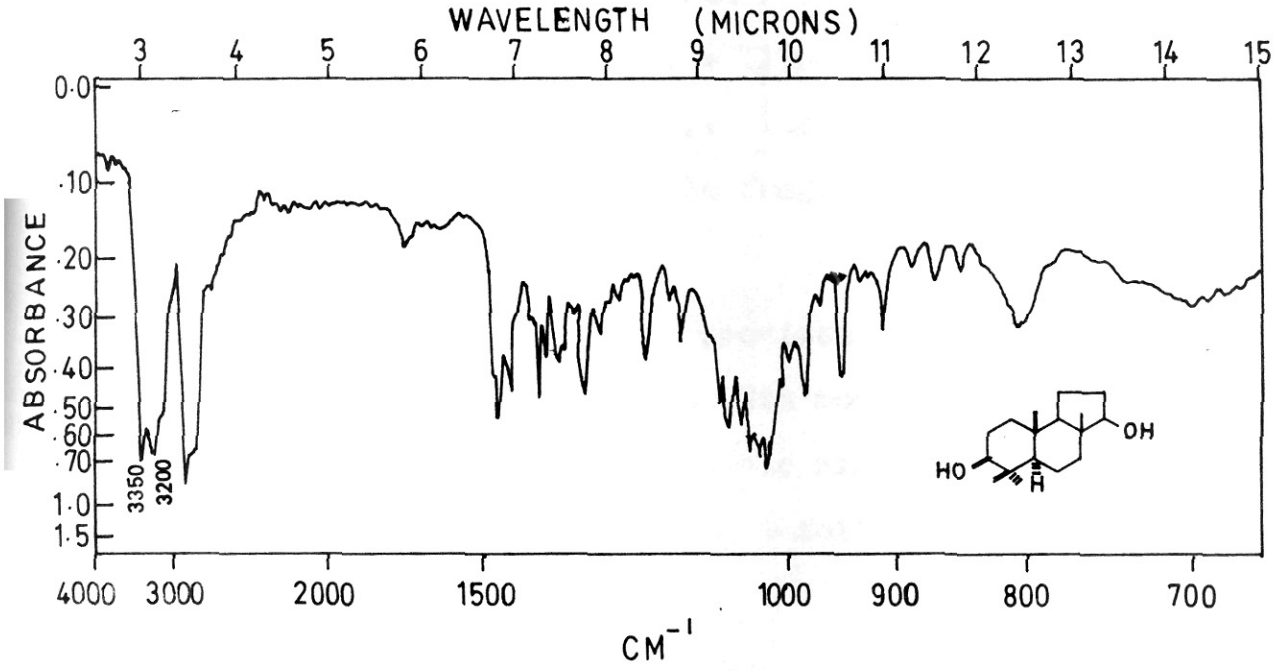


FIG. 41. IR SPECTRUM OF DIOL XXX.

Its PMR spectrum (Fig.42) shows the presence of four quaternary methyls (58, 61, 63 and 63 c/s); $-CH_2CO$, one 2H multiplet centred at 144 c/s (cf. PMR of malabaricol) and another 2H multiplet centred at 120 c/s. Its IR spectrum (Figs. 43 and 44 - CCl_4) clearly reveals the presence of a five-membered ring ketone (1738 cm^{-1}) and a six membered ring ketone (1703 cm^{-1}), both bands being of almost equal intensity. Its mass spectrum is shown in Fig.45 and its probable fragmentation pattern is shown in Fig.46.[23]

This degradation provides unequivocal evidence for the size of ring C and its mode of linking to the tetrahydrofuran moiety. Since ring A must be six-membered (IR, PMR), the size of ring B follows, which also must be six-membered.*

STEREOCHEMISTRY OF MALABARICOL

Malabaricol and the lactone (XVI), both show a positive Cotton-effect (Fig.47a,b). This may be compared with those of dipterocarpol (XXXI) or the trinor-lactone (XI) in which the A/B ring junction has been shown to be <u>trans</u> and hence malabaricol should have the same absolute stereochemistry at the A/B ring junction. On the basis of biogenetic grounds (discussed earlier) the B/C ring junction should also be <u>trans</u>.

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*It should be mentioned here that van Tamelen and co-workers[23] have recently demonstrated that one of the products of nonenzymic cyclisation of squalene-2,3-epoxide has the same gross carbon framework as I.

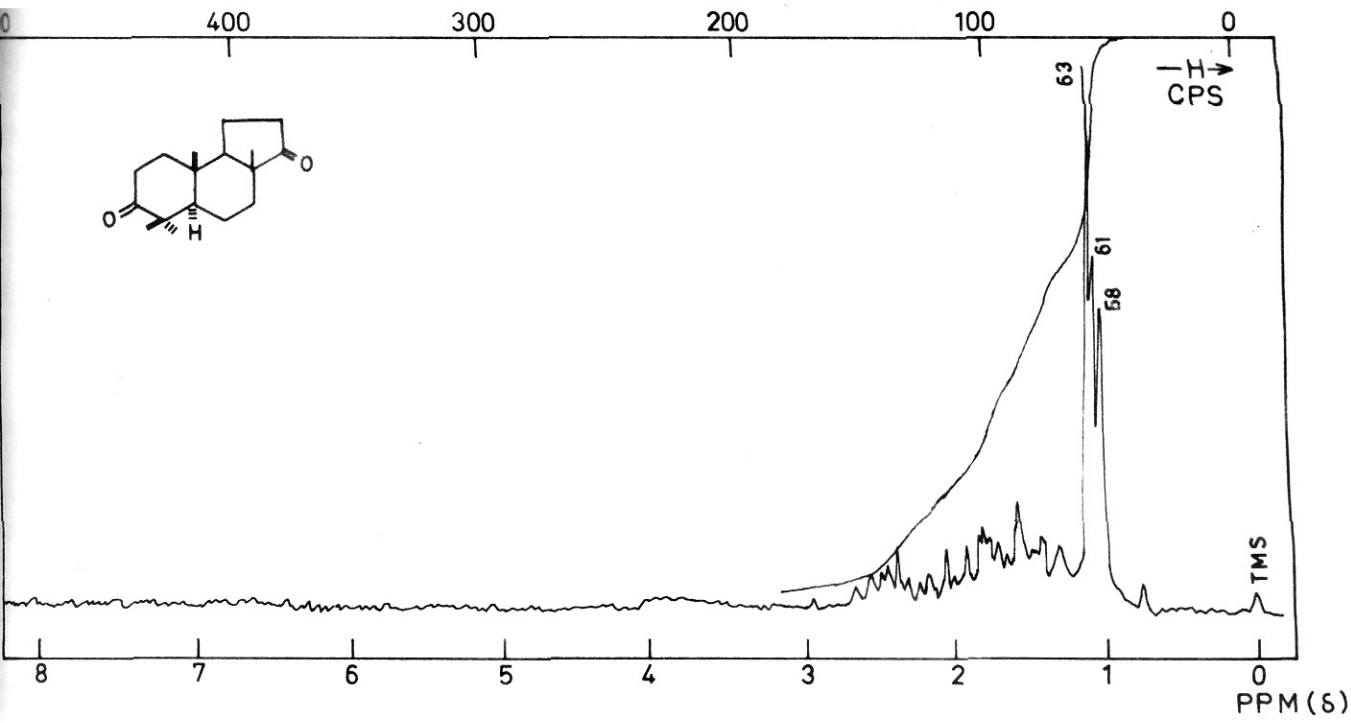


FIG. 42. PMR SPECTRUM OF XIX.

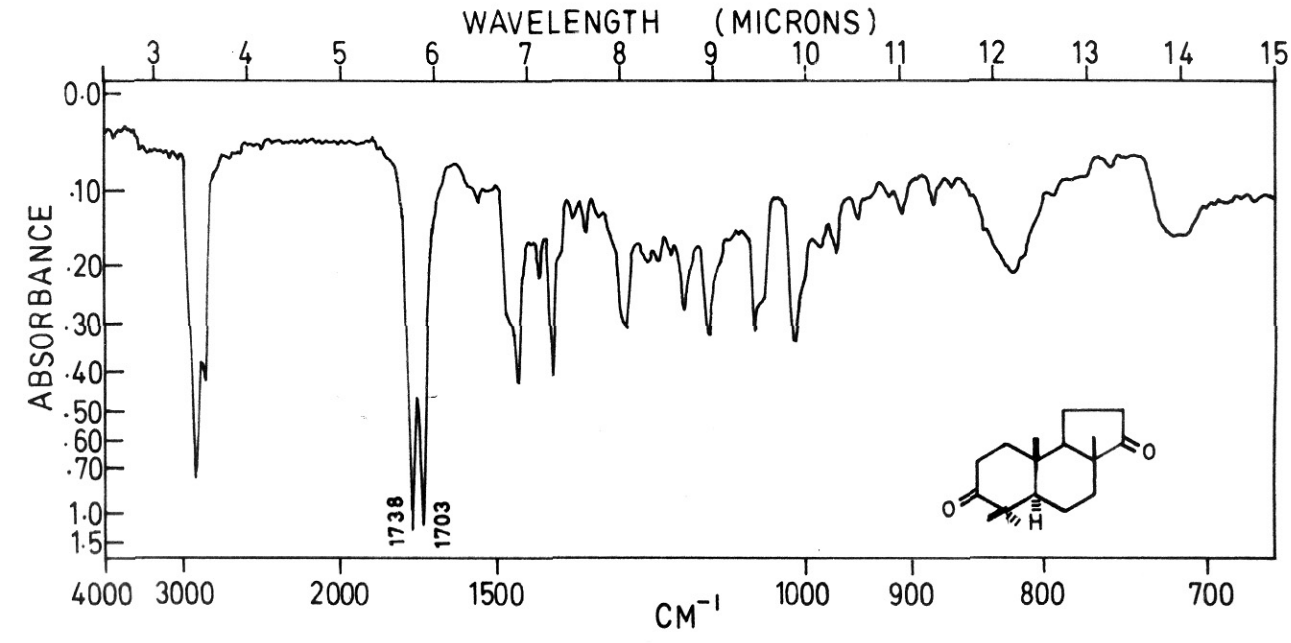


FIG. 43. IR SPECTRUM OF XIX.

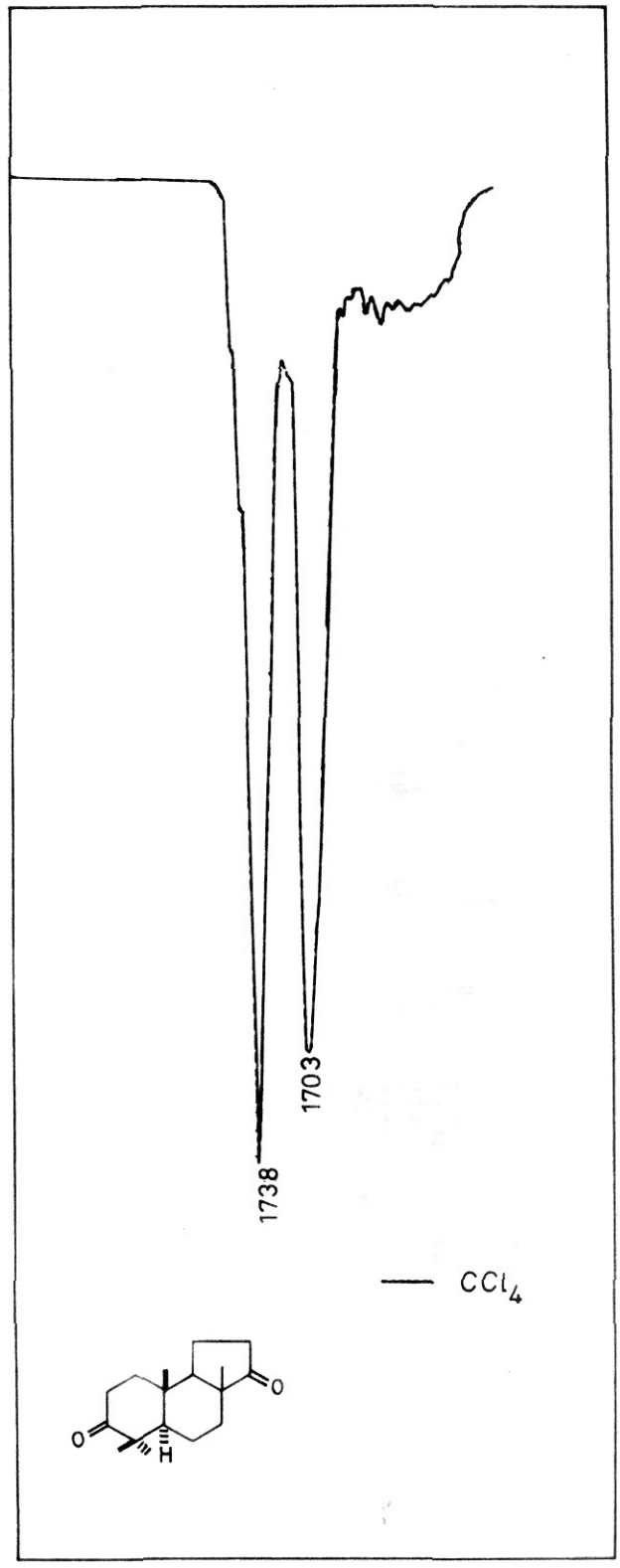


FIG. 44. IR SPECTRUM OF XIX

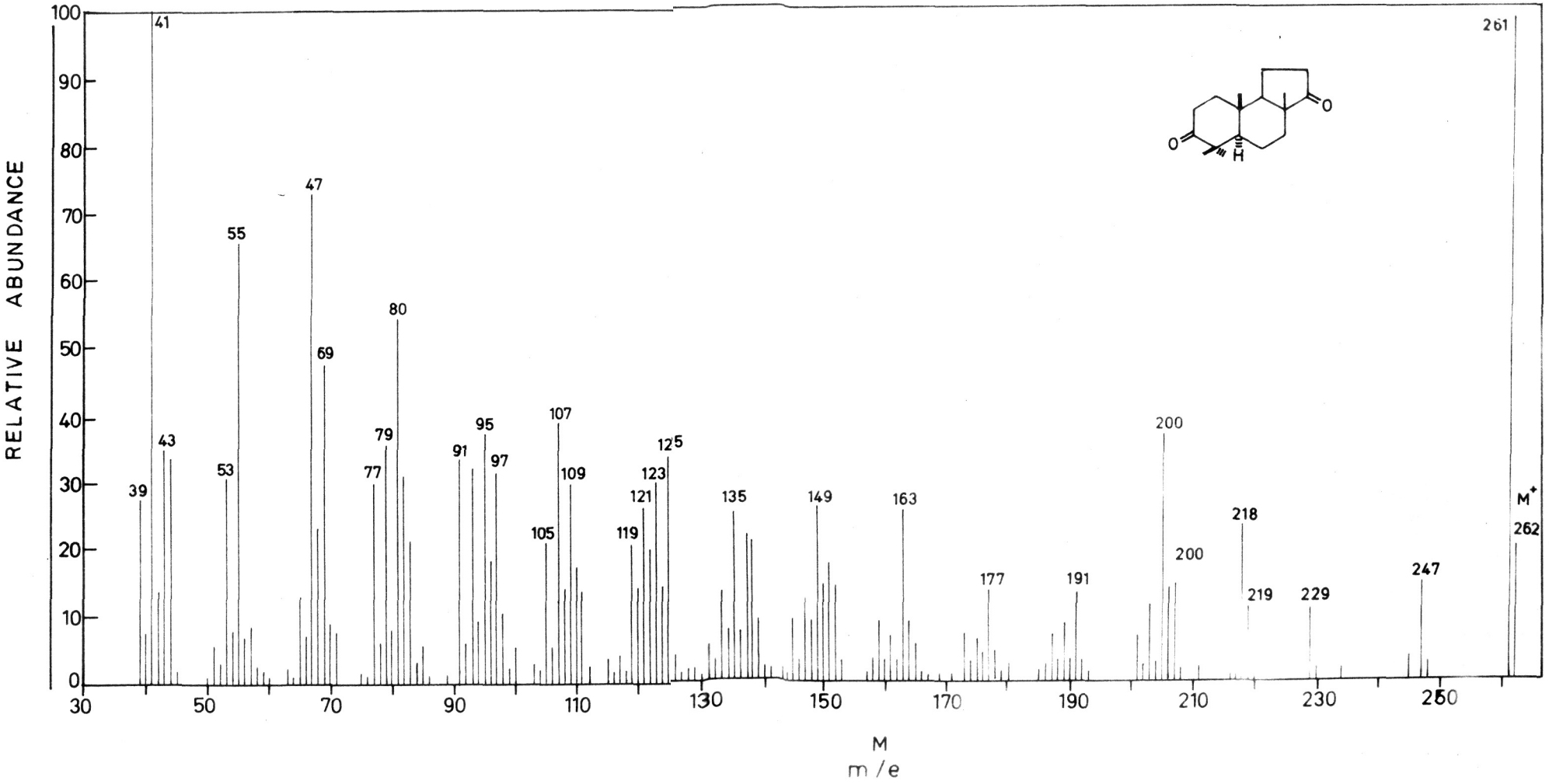
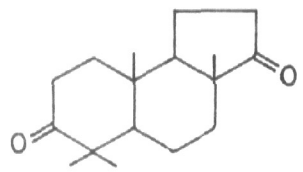


FIG. 45. MASS SPECTRUM OF DIKETONE (XIX)

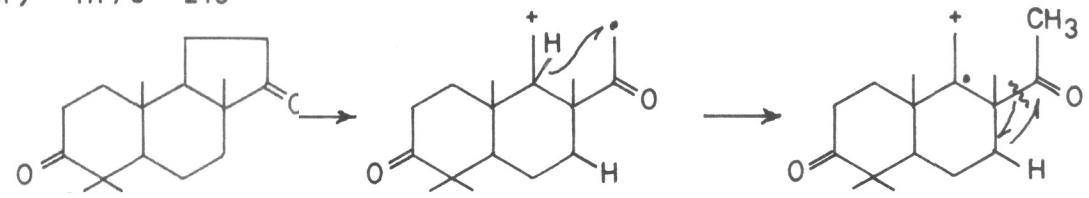
i)



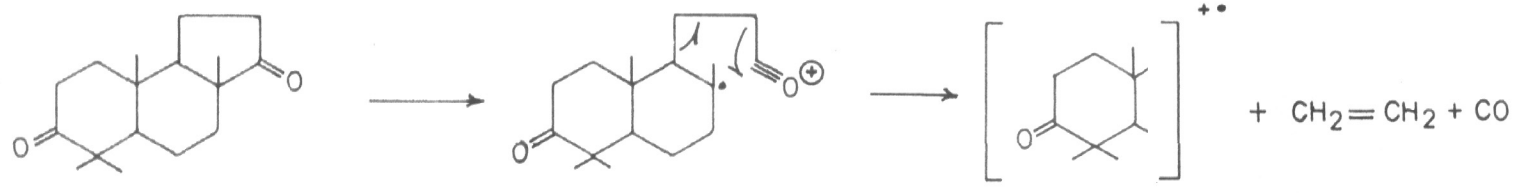
$C_{17}H_{26}O_2$

M^+ 262, BASE PEAK

ii) m/e 218

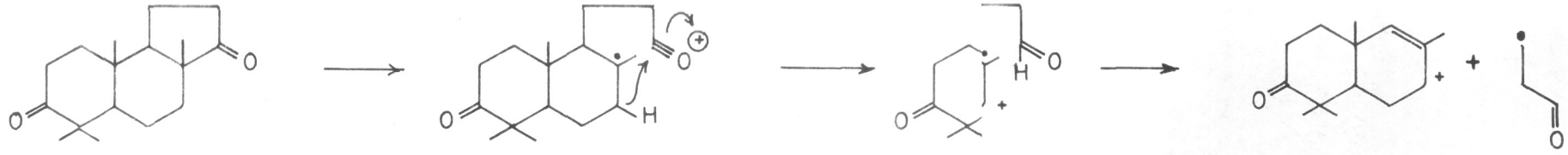


iii) m/e 206 (M-56)



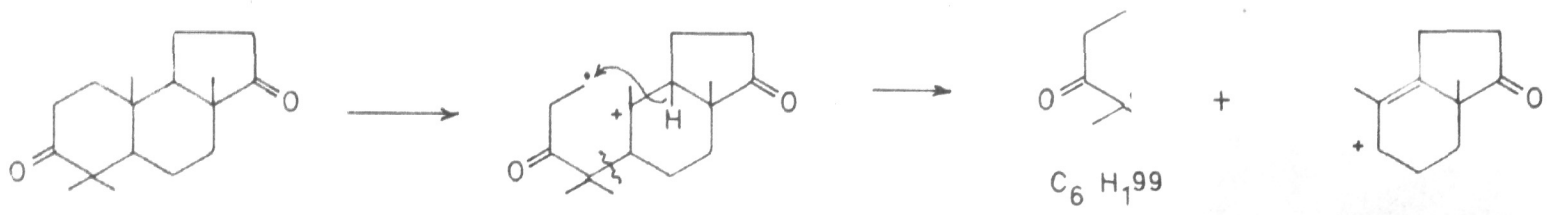
M − 56 ($C_{15}H_{22}O$ = 218) + $CH_2=CH_2$ + CO

iv) m/e 205 (M-57)



M − 57 (205) + CH_3CHO 44

v) m/e 163 and 99



$C_6H_{1}99$

$C_{11}H_{15}O$ = 163

(M - 99)

FIG. 46. FRAGMENTATION PATTERN OF DIKE XIX.

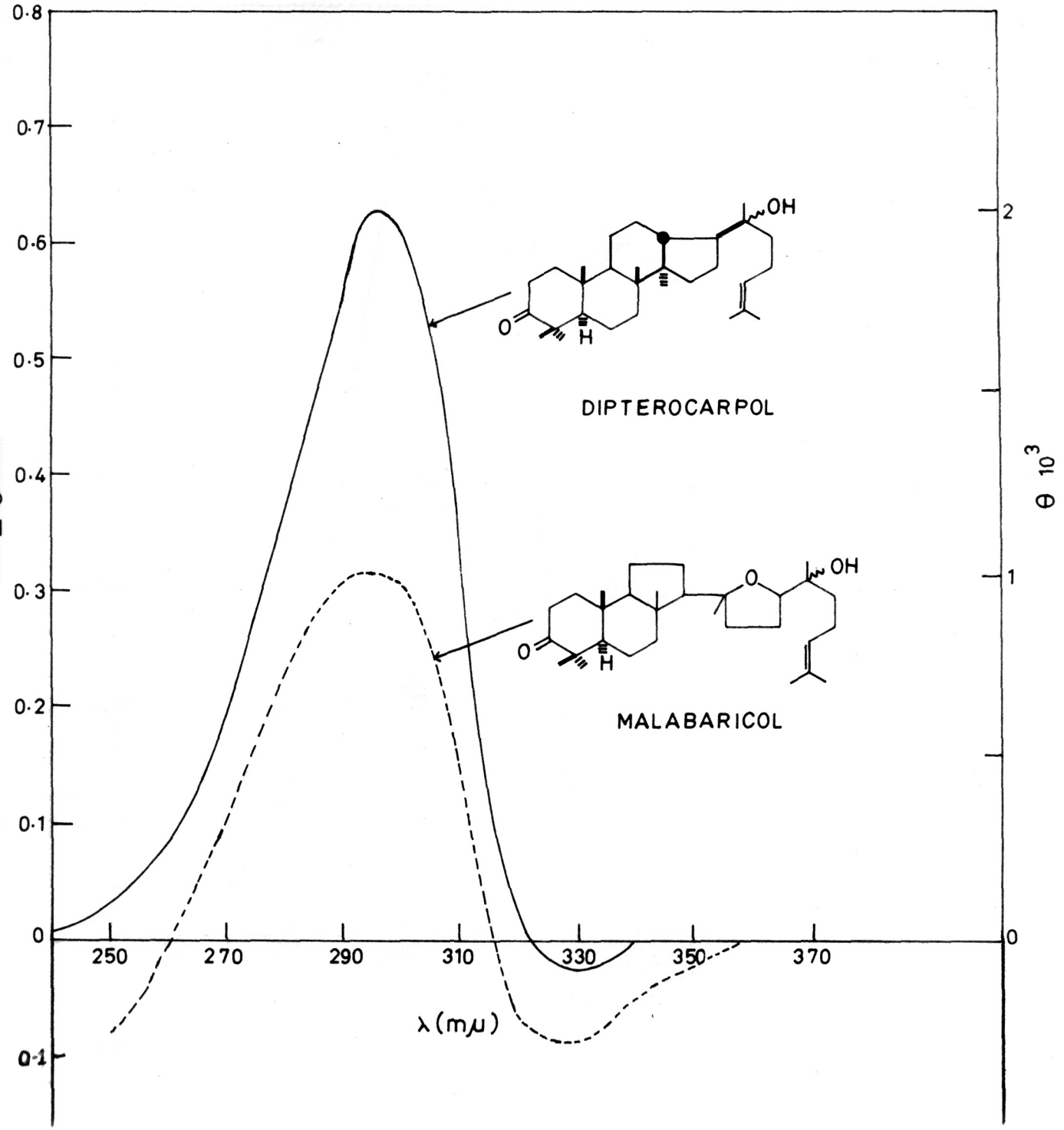


FIG. 47 a. C.D. CURVES OF MALABARICOL AND DIPTEROCARPOL.

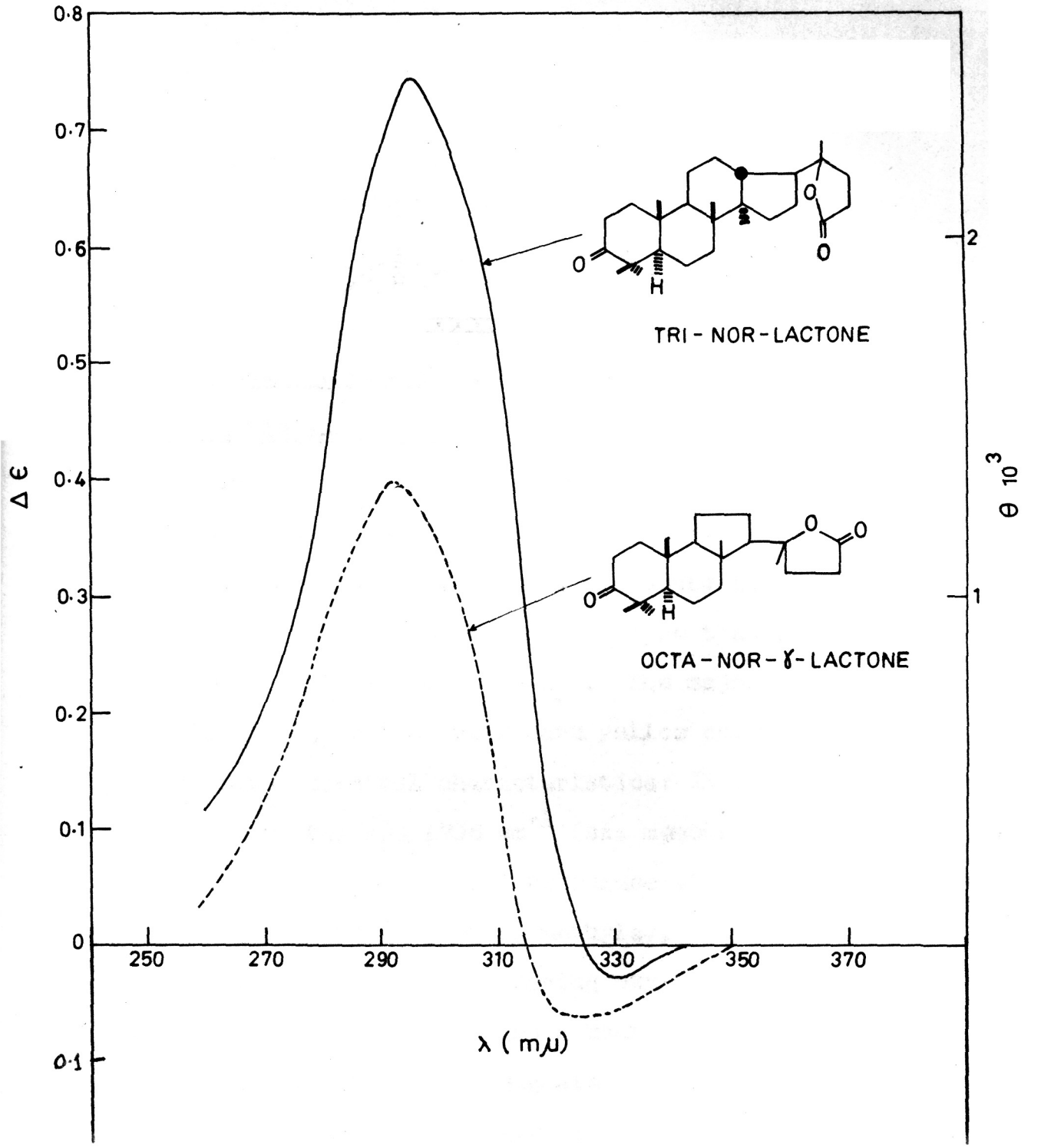
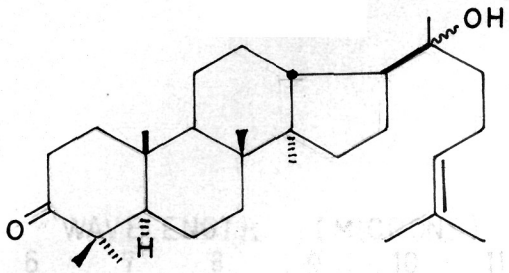


FIG. 47 b. COMPARISON OF C.D. CURVES OF OCTA-NOR-γ-LACTONE (XVI) AND TRINOR-LACTONE (XI).



XXXI

REACTIONS OF MALABARICOL

1. Acetic anhydride-Pyridine[24]: Although it has been mentioned earlier that malabaricol is not acetylated with Ac_2O/Pyridine (20-25°, one week) however under drastic conditions (160°, 24 hrs) it furnishes two products with one predominating considerably (more than 80%). (Minor product $[\alpha]_D^{32}$ +34.61° ($CHCl_3$). The major product ($[\alpha]_D^{32}$ +25.5°($CHCl_3$); TNM: very dark yellow colour) has the following spectral characteristics: IR (Fig.48): 1730 cm^{-1} (C=O acetate) and 1706 cm^{-1} (six membered C=O). PMR spectrum (Fig.49 - CCl_4) resonance signals at 58, 58, 59.5, 61.5 c/s (four quaternary methyls), 71.5 and 78.5 c/s (two methyls on carbon bearing oxygen), 95 and 99.5 c/s (two olefinic methyls) and a sharp signal at 114.5 c/s (acetate). The methyl signals are more clearly separated in benzene solution (Fig.50): 31.5, 35.5, 43.5, 51, 52 (five quaternary methyls), 74.5 c/s (methyl on carbon bearing oxygen) and 90 c/s (two olefinic methyls), 117 c/s

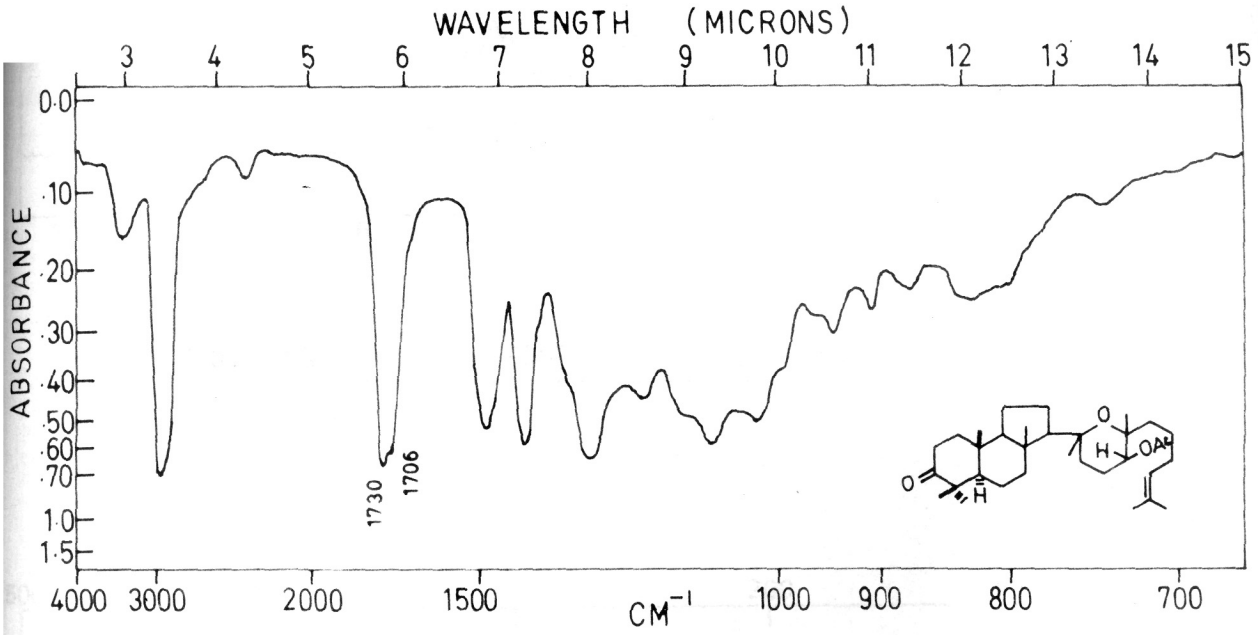


FIG 48. IR SPECTRUM OF XXXII.

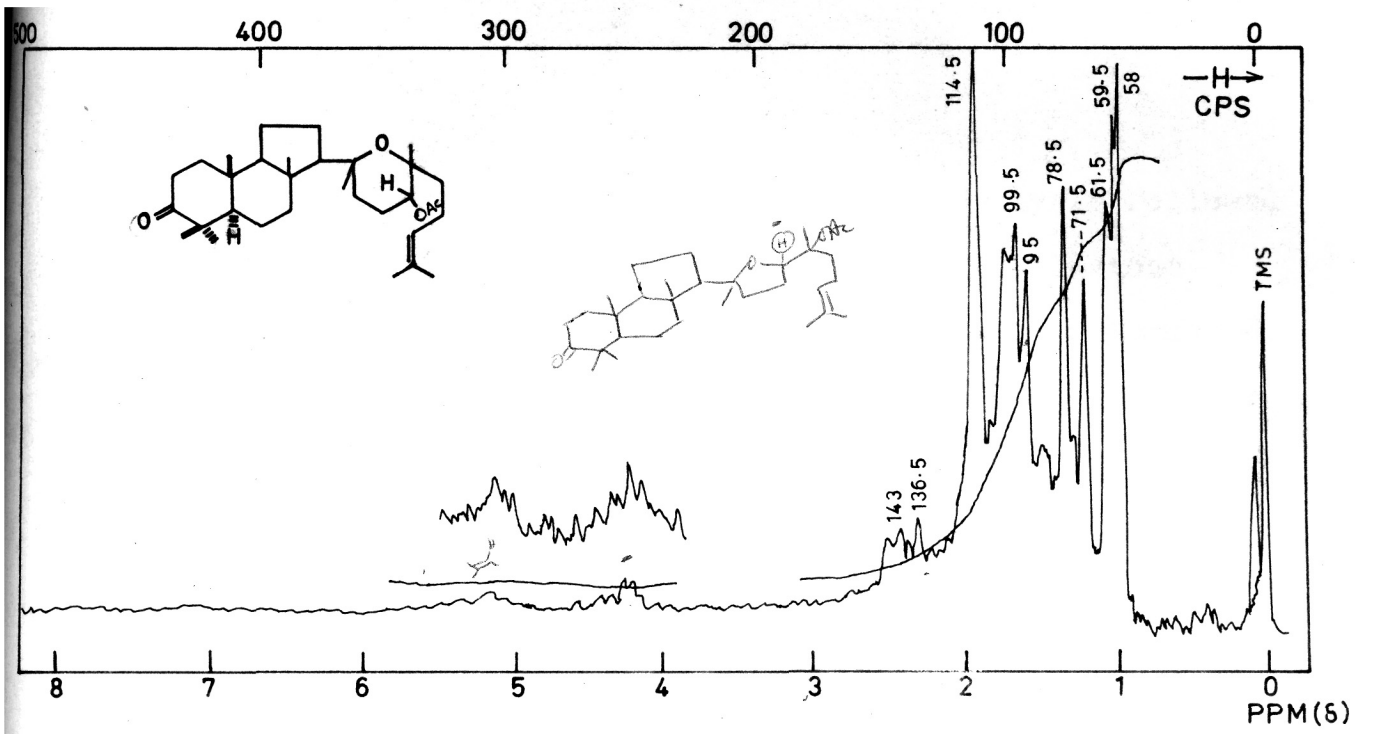


FIG. 49. PMR SPECTRUM OF XXXII (IN CCl_4).

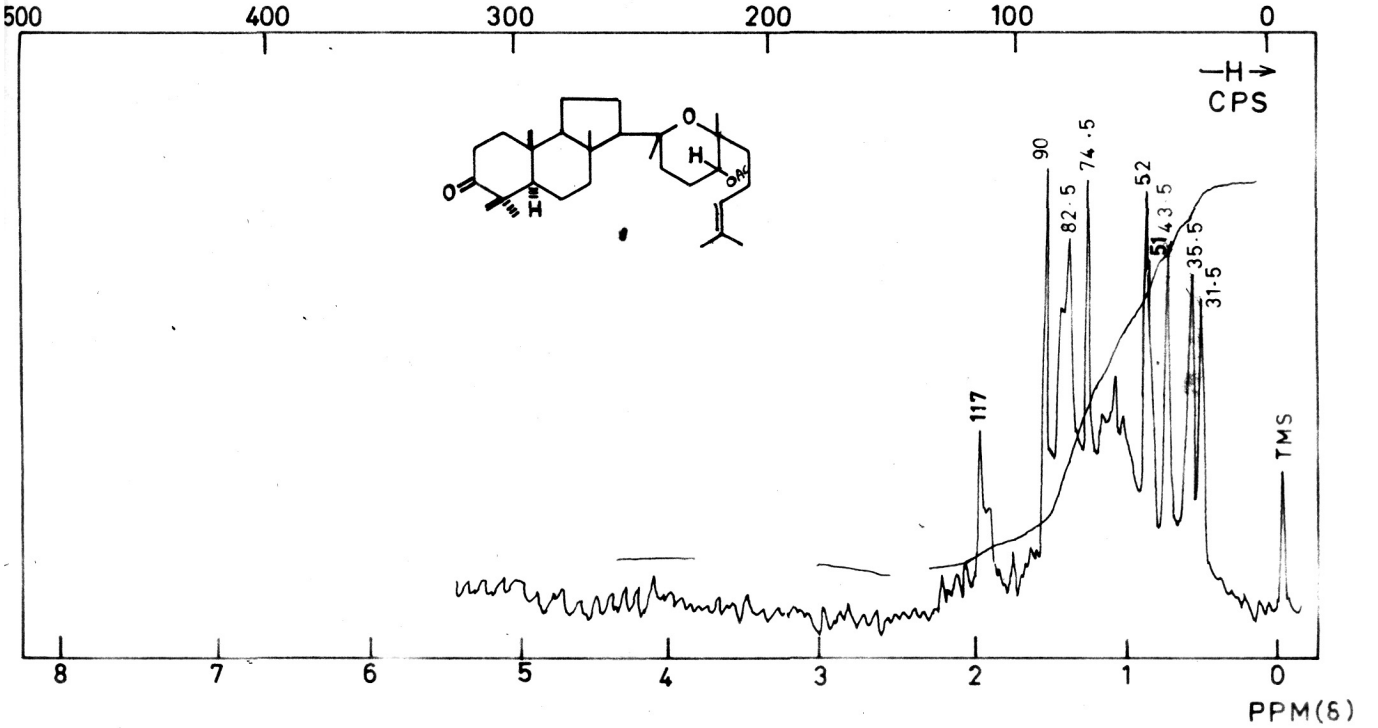
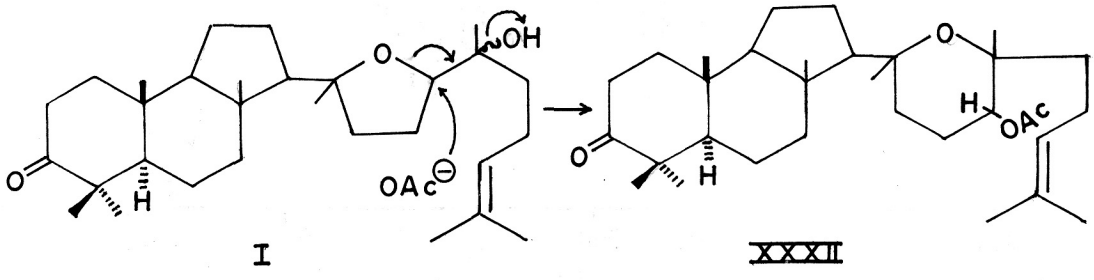


FIG. 50. PMR SPECTRUM OF XXXII (IN BENZENE).

(acetate). This product on alkaline hydrolysis followed by Jones oxidation furnished the octa-nor-γ-lactone identical (m.p., m.m.p., IR) with the lactone discussed earlier XVI. These data suggest the probable structure of the reaction product to be XXXII which can arise from malabaricol by the mechanistic path shown below.



I XXXII

2. KBH_4 reduction of lactone: It was attempted to reduce the octa nor-γ-lactone (XVI) with KBH_4 (aq.dioxan, room temp. 24 hrs). In the reaction product the lactone ring remained intact and only 3-keto was reduced to OH (IR Fig.51, 3400 cm^{-1} OH; 1775 cm^{-1} γ-lactone). This alcohol (XXXIII, $C_{22}H_{36}O_3$, m.p. 138.5-140°, $[\alpha]_D^{28}$ +5.5° ($CHCl_3$) on acetylation furnished a monoacetate ($C_{26}H_{38}O_4$, m.p. 187-188°, $[\alpha]_D^{28}$ +11.81° ($CHCl_3$). The spectral data is in complete accord with the assigned structure (XXXIV) (PMR spectrum, Fig.52, four quaternary methyls: 51, 51, 51 and 57.5 c/s; one methyl on carbon bearing oxygen:

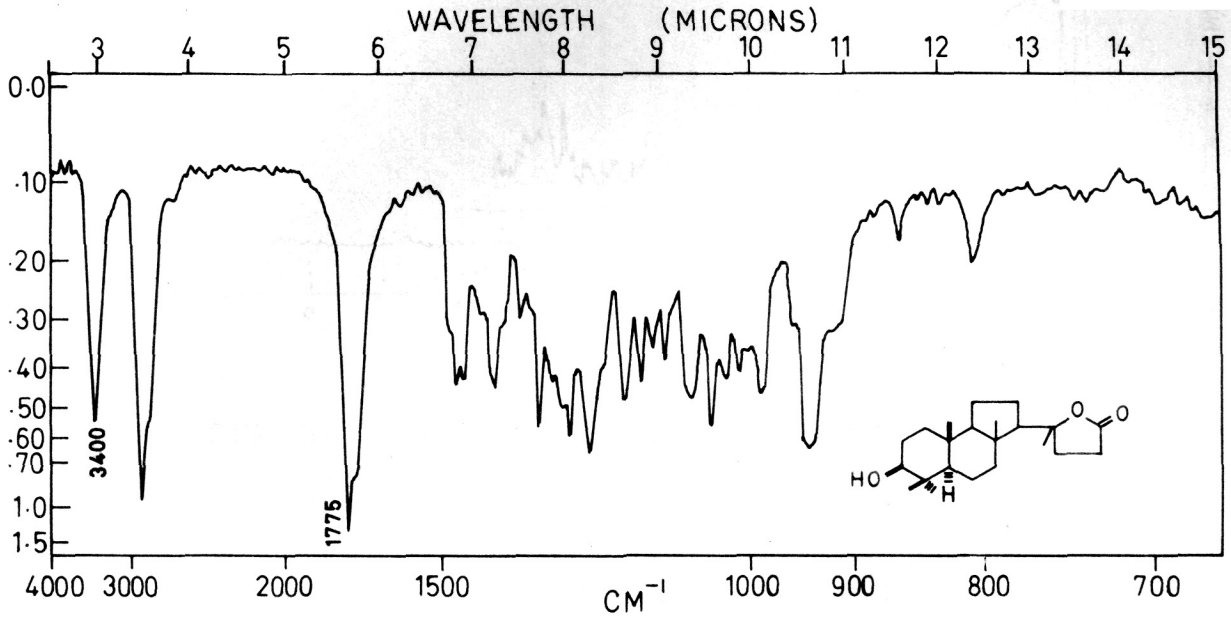


FIG. 51. IR SPECTRUM OF XXXIII.

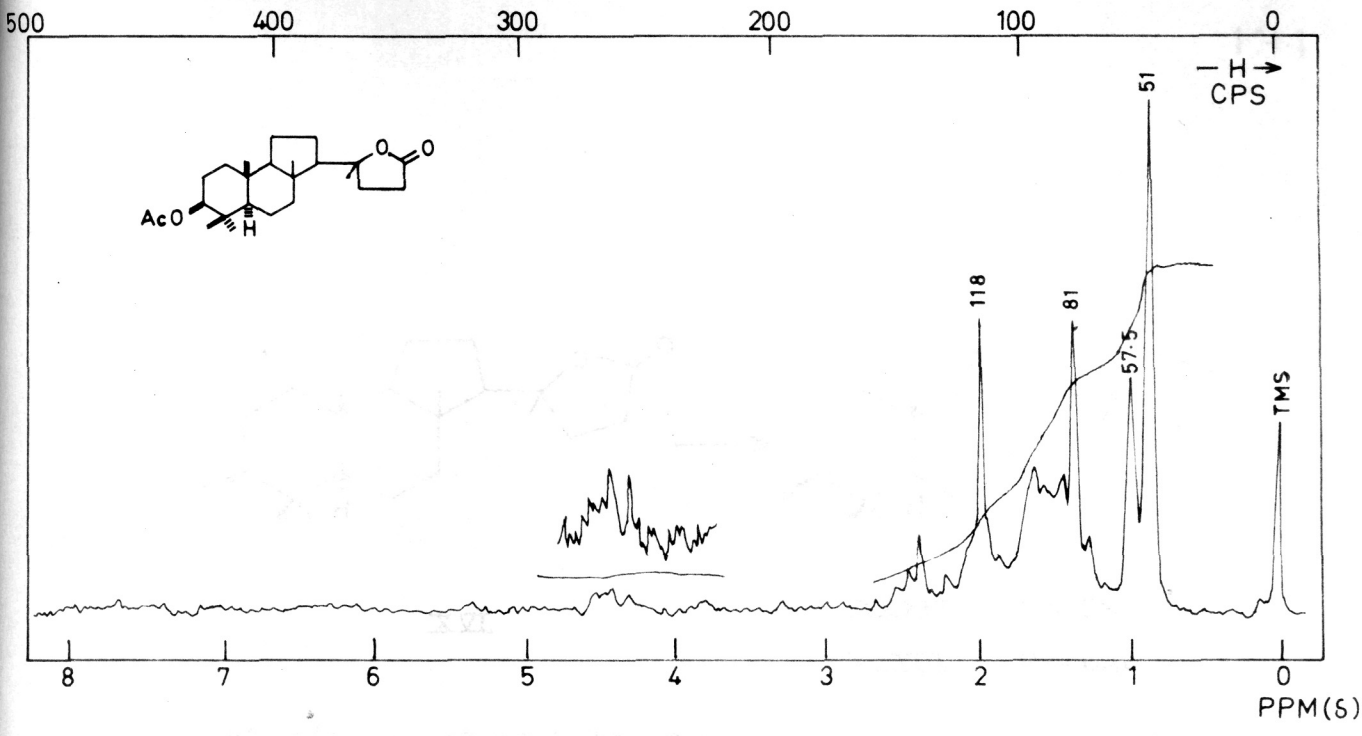


FIG. 52. PMR SPECTRUM OF XXXIV.

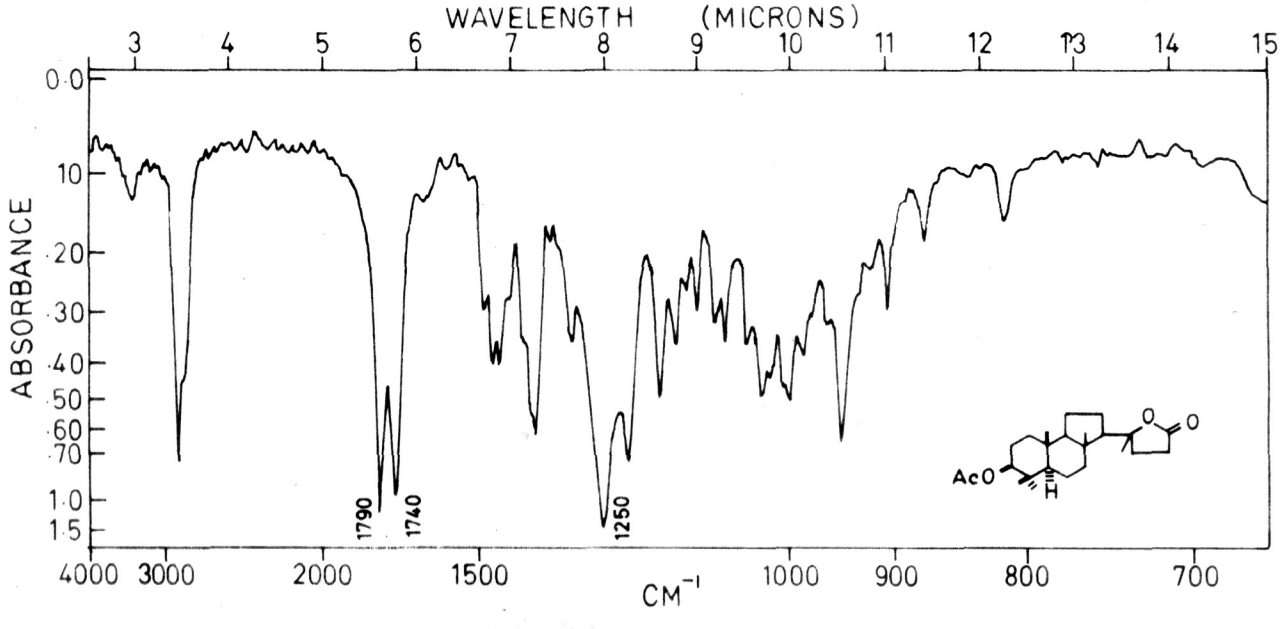
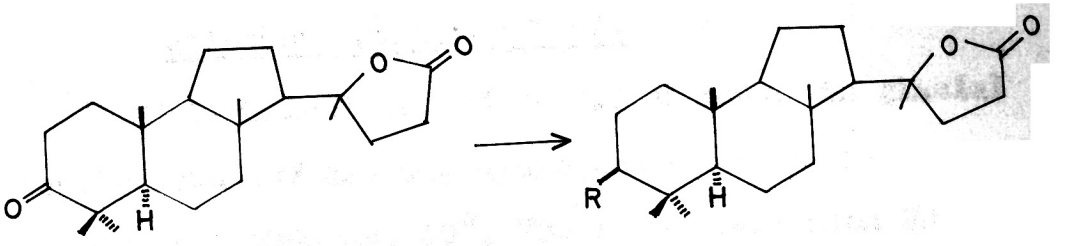


FIG. 53. IR SPECTRUM OF XXXIV.



XVI

XXXIII R = OH

XXXIV R = OAc

81 c/s and an acetate group at 118 c/s. IR spectrum, Fig.53: 1790 cm^{-1}, γ-lactone; 1740, 1255 cm^{-1}, acetate).

EXPERIMENTAL

For general remarks, see p.

Hydrogenation of malabaricol (I)

Malabaricol (1.096 g; 0.0043 mole) in glacial acetic acid (27 ml) was hydrogenated over prereduced Adam's PtO_2 (200 mg, 30°, 708 mm press.) when 221 ml (1.75 moles) of hydrogen was absorbed during 3 hr. The reaction product was filtered, aqueous Na_2CO_3 added (till free from acid) and extracted with ether (50 ml x 3). The combined extracts were washed with water (50 ml x 2), brine (50 ml) and dried. Removal of solvent gave a gummy residue (1.0696 g; ~ 98%). Its TLC over SiO_2 gel (solvent system: 25% ethyl acetate in benzene) showed it to be a mixture of atleast three compounds with R_f 0.85, 0.7, 0.7 (two spots overlapping each other).

The compounds were separated by chromatography over a column of SiO_2 gel.

CHROMATOGRAM

Substance: 1.84 g

Adsorbent: 70 g, SiO_2 gel/IIA

Column : 23 cm x 2.8 cm.

No.	Eluent	Ratio	Vol. (ml)	Eluate (g)	Remarks
1	Benzene	-	30x3	0.0089	Rejected.
2	C_6H_6 + EtOAc	95:5	30x5	0.0037	"
3	"	"	30x4	0.5435	Dihydromalabaricol m.p. 96-99°.
4	"	"	30x2	0.1791	Mixed fractions.
5	"	"	30x11	0.6896	Gum, 3-equat. diol IV.
6	"	"	30x6	0.0910	Gum, 3-equat. diol IV.
7	"	90:10	30x4	0.0835	
8	"	85:15	60x5	0.2268	3-axial diol m.p. 100-102°.
			Total:	1.8261 g (~ 97%).	

Dihydromalabaricol (II). Fraction 3 was crystallised from acetonitrile to give white shining crystals (400 mg), m.p. 98-99°, $[\alpha]_D$ +31.75° (c, 0.9%, $CHCl_3$). [Found: C, 77.96; H, 11.15. $C_{30}H_{52}O_3$ requires: C, 78.2; H, 11.38%].

C-3 equatorial diol (IV). Fractions 5-7 did not crystallise $[\alpha]_D$ +13.95° ($CHCl_3$).

C-3 axial diol (III). Fraction 8 on crystallisation from acetonitrile gave flaky crystals (150 mg) m.p. 101-102.5°, $[\alpha]_D$ +1.30° ($CHCl_3$). [Found: C, 77.57; H, 11.44. $C_{30}H_{54}O_3$ requires: C, 77.86; H, 11.76%].

$LiAlH_4$ reduction[7] of dihydromalabaricol (II)

Dihydromalabaricol (48 mg, 0.0001 mole) in dry ether (10 ml) was added to a stirred suspension of $LiAlH_4$ (38 mg) in dry ether (10 ml) during 15 min. at 0° under anhydrous conditions. The stirring was continued for 5 hr at room temp., refluxed for 2 hr and left overnight. The complex was broken by a saturated solution of potassium sodium tartarate (4 ml) at 0°C while stirring was continued for another 3 hr and left overnight. The product was taken up in a separatory funnel and ether layer removed. The aqueous portion was extracted with ether (10 ml x 3). The combined ether extracts were washed with brine (15 ml) and dried. Removal of solvent gave a gum (46 mg, ~ 92%) identical with 3-equatorial diol (IV) (IR, TLC, PMR).

CrO_3-Pyridine oxidation[4] of 3-equatorial diol (IV)

Alcohol (IV, 46 mg, 0.0001 mole) in pyridine (0.5 ml) was added to a suspension of CrO_3 (50 mg) in pyridine (1 ml). The reaction mixture was swirled from time to time and allowed to stand at room temp. (~ 28°C) for 24hr. After adding water (5 ml), the reaction mixture was filtered through celite, and the filterate extracted with ether (5 ml x 4), which were then washed with water (5 ml x 4), brine (10 ml) and dried. Removal of solvent yielded 39 mg

(~ 86%) of a gum, which was purified to remove tailing by preparative layer chromatography over SiO_2 gel (solvent system: 25% ethyl acetate in benzene) yield of pure compound 28 mg, m.p. 94-97°. It was crystallised from acetonitrile to give 21 mg of crystalline compound m.p. 97.5 - 98.5°, identical with dihydromalabaricol (II, m.m.p., IR, TLC).

CrO_3-Pyridine oxidation[4] of 3-axial diol (III)

Alcohol (III, 51 mg, 0.0001 mole) in pyridine (0.5 ml) was added to a suspension of CrO_3 (50 mg) in pyridine (1 ml). The reaction mixture was stirred from time to time and allowed to stand at room temp. (~ 28°) overnight (24 hr). After adding water (5 ml), the reaction product was filtered through celite and extracted with ether (5 ml x 4), which was then washed with water (5 ml x 4), brine (10 ml) and dried. Removal of the solvent yielded 41 mg (~ 84%) of the gum, which was purified by preparative layer chromatography (solvent system: 25% ethyl acetate in benzene). Yield, 29 mg, m.p. 95-97.5°. It was crystallised from acetonitrile to give 24 mg of crystalline compound m.p. 97-98.5°, identical (m.m.p., IR, TLC, PMR) with the oxidation product of 3-equatorial diol.

Octa-nor-γ-lactone (XVI)

Jones reagent[9] (prepared from 25 g CrO_3 + 15 ml H_2O + 10 ml H_2SO_4) was added dropwise while stirring to a

solution of malabaricol[(I); 45.8 g, 0.1 mole] in acetone (350 ml) at 5-10° during 30 min. It was stirred at this temp. for another 2 hr. The excess of reagent was destroyed by the addition of a few drops of MeOH (changes from yellow to green colour). The reaction mixture was poured in cold water (500 ml) and extracted with ether (200 ml x 4) which was then washed with water (250 ml x 2), brine (200 ml) and dried. Flashing off the solvent gave 46.3 g (~ 97%) of very viscous light yellow material which solidifies on cooling. The reaction product gave a strong characteristic smell of methyl-2-heptenone.

Methyl-2-heptenone (IX) was removed from the reaction product by steam distillation, dried and distilled at 112-14°/30 mm, yield 10.5 g, n_D^{20} 1.443, semicarbazone m.p. 134-5°. IR of methyl-2-heptenone was superimposable on an authentic IR spectrum. [Found: C, 76.20; H, 11.18. $C_8H_{14}O$ requires: C, 76.14; H, 11.18%].

The product left behind after steam distillation was filtered, yield 34.5 g, m.p. 138-146°. It was crystallised twice from hexane:C_6H_6 to give transparent crystalline material (XVI, 25 g) m.p. 145-6°, $[\alpha]_D$ +29.4° ($CHCl_3$). [Found: C, 76.23; H, 9.56. $C_{22}H_{34}O_3$ requires: C, 76.23; H, 9.52%].

Jone's oxidation[9] of dihydromalabaricol (II)

Jone's reagent was added dropwise with stirring to a solution of dihydromalabaricol (55 mg, 0.00011 mole) in acetone (5 ml) at 5-10° till yellow colour persisted. The reaction mixture was stirred for another 1 hr (5-10°) and worked up as usual to yield a crystalline solid (40 mg, ~ 72%) m.p. 140-145°. It was crystallised from hexane (2 ml) to give white shining crystals (25 mg) m.p. 145-146°, identical with octa-nor-γ-lactone (XVI) (m.m.p., TLC, IR, PMR).

Ruthenium tetroxide[10] oxidation of dihydromalabaricol (II)

Dihydromalabaricol (II) (95 mg, 0.0002 moles) dissolved in acetone (8 ml) was treated at ~ 28°C with a freshly prepared solution of RuO_4 in CCl_4 (51 mg RuO_2 + 425 mg $NaIO_4$) when black RuO_2 precipitated, another portion of $NaIO_4$ (25 mg in 1 ml water) was added to dissolve the precipitate and stirring was continued for another 12 hr. A few drops of isopropanol were added and stirred for 30 mins to destroy the excess of reagent. It was filtered, precipitate washed with acetone and solvent removed under suction to give 72 mg (~ 75%) pale yellow gummy material which on adding a drop of pet. ether (40-60°) crystallised out. m.p. (crude) 140-46°. This was crystallised from hexane-benzene to give a beautiful white crystalline compound (34 mg, m.p. 144-146°) identical (m.m.p., TLC, IR, PMR) with octa-nor-γ-

lactone (XVI).

Triol from octa-nor-,-lactone (XVI)

To a suspension of $LiAlH_4$ (3.46 g) in dry ether (100 ml) was added dropwise a solution of lactone (XVI, 3.46 g, 0.01 mole) in dry ether (150 ml) while stirring during 30 min. under perfectly anhydrous conditions. After the addition was complete the reaction mixture was stirred for another 4 hr and refluxed for 5 hr. The complex was broken by the slow addition of a saturated solution of Rochele's salt (100 ml) with stirring under ice-cold conditions. The stirring was continued for another 4 hr and allowed to stand at room temp. overnight. The reaction mixture was transferred to a separatory funnel and ether layer separated. The aqueous portion was extracted with ether (30 ml x 4). The combined ether extracts were washed with water (50 ml x 2), brine (50 ml) and dried. Removal of solvent gave 3.15 g (~ 93%) of a solid m.p. 187-190°C. It was crystallised from ethylacetate to give white shining feathery crystals 2.68 g, m.p. 190-91°. [Found: C, 74.75; H, 11.40. $C_{22}H_{40}O_3$ requires: C, 74.95; H, 11.44%].

Hydroxy diacetate (XVII)

The above triol (2 g) was acetylated with acetic anhydride (5 ml) and pyridine (5 ml) at room temp. (~ 28°) After 24 hr it was poured over a mixture of ice and water

(10 ml) and extracted with ether (10 ml x 4) which was washed with water (20 ml x 5), brine (25 ml) and dried. Flashing off the solvent gave 2.45 g (~ 99%) of gummy material which solidifies on keeping. m.p. (crude) 57-60°. On crystallising twice from pet. ether it gave a crystalline compound 1.8 g, m.p. 61-64°, $[\alpha]_D$ +7.343° (c, 0.9% $CHCl_3$). [Found: C, 71.83; H, 10.37. $C_{26}H_{44}O_5$ requires: C, 71.52; H, 10.16%].

Iodine dehydration[16] of hydroxy diacetate (XVII)

To XVII (1.09 g, 0.0025 mole) in thiophene-free dry benzene (5 ml), iodine (32 mg, 0.00025 mole) was added and refluxed for 5 min. The completion of the reaction was checked by TLC (solvent system: 5% ethyl acetate in benzene). TLC revealed the formation of essentially two products with R_f 0.41 and 0.5 with the former predominating. The reaction mixture was washed with aqueous $Na_2S_2O_3$ (10%, 5 ml x 2) followed by a washing with water (5 ml) and brine (5 ml). After drying the solvent was removed to give 0.985 g (~ 95%). The mixture was separated by DCC over SiO_2 gel/IIA.

CHROMATOGRAM

Substance: 920 mg

Adsorbent: 250 g SiO_2 gel/IIA.

Column : 25 cm x 4.7 cm.

Solvent system: 5% Ethyl acetate in benzene.

S.No.	Frac.No.	Wt. of the frac. (g)	Remarks
1	1-2	0.0600	Tailing.
2	3-5	0.4580	AA Rf:0.41
3	6-7	0.1070	Mixed fractions.
4	8-10	0.2510	AA1 Rf: 0.5
5	11-12	0.0157	
	Total	0.8917 (~ 97%).	

CrO_3-acetic acid oxidation[17] of AA

AA (50 mg) was added to CrO_3 (50 mg) in glacial acetic acid (5 ml) and stirred for 3 hr at 65-70°C. The reaction mixture was poured into ice cold aqueous Na_2CO_3 (10%, 25 ml) and extracted with ether (10 ml x 3) which was washed with water (10 ml x 2), brine (10 ml) and dried. Removal of solvent gave 45 mg of gummy material.

TLC showed the formation of two compounds with Rf: 0.42, 0.55 (solvent system: 25% ethyl acetate in benzene). The mixture was separated by preparative layer chromatography over SiO_2 gel. Spot with Rf: 0.42 - 28.4 mg and Rf: 0.55 - 10 mg.

The major compound was characterised as AAII (UV, IR, PMR).

Osmylation[18] of AA

To AA (135 mg, 0.00032 mole) in pet.ether + ether

(1:1 - 4 ml) containing pyridine (0.2 ml) was added OsO_4 solution (85 mg in pet. ether + ether 4.2 ml). It was swirled and left in dark at room temp. After 5 days some solid separated which was very little to be filtered. The solvent was removed under suction and the residue was dissolved in benzene + methanol (1:1, 5 ml). H_2S Black precipitate separated on bubbling H_2S through the solution till saturation. The precipitate was filtered and washed well with benzene + methanol (1:1, 5 ml). The solvent was stripped off from the filterate to give a solid (XXIII) (137 mg, ~ 98%) m.p. 136.5 - 142° with shrinking at 125°. It was crystallised from pet. ether to give shining flaky crystals, 80 mg, m.p. 143-44°. [Found: C, 68.76; H, 9.95. $C_{26}H_{44}O_6$ requires; C, 68.99; H, 9.80%].

Lead tetra-acetate[19] cleavage of the diol (XXIII)

To XXIII (27 mg, .0006 mole) in dry benzene (3 ml) $Pb(OAc)_4$ (35 mg) was added and stirred for 3.5 hr at 28°C. The completion of the reaction was checked by TLC (solvent system: 25% ethyl acetate in benzene). To the reaction mixture water (2 ml) was added and benzene layer separated. The aqueous portion was extracted with ether (3 ml x 2) and the combined organic extracts were washed with water (5 ml), brine (5 ml) and dried. Removal of solvent gave 25.8 mg of a solid (m.p. 142 - 144.5°C) which was refluxed without purification with 10% alcoholic KOH (2 ml) for 2 hr. The

The reaction mixture was diluted with water (5 ml) and extracted with ether (5 ml x 3), which was washed with water (5 ml x 2), brine (5 ml) and dried. Stripping off the solvent gave 18.8 mg of a gummy material which showed in its TLC (solvent system - 25% Ethyl acetate in benzene) the presence of two compounds. The reaction mixture was separated over a column of SiO_2 gel.

CHROMATOGRAM

Substance: 18 mg

Adsorbent: 2 g SiO_2 gel/IIA

Column : 7 cm x 0.8 cm.

No.	Eluent	Ratio	Vol. (ml)	Eluate (g)	Remarks
1	Benzene	-	5	0.0014	Rejected.
2	C_6H_6 + EtOAc	75:25	5 x2	0.0140	XXIV
3	" "	50:50	5 x2	0.0010	Rejected.
			Total:	0.0154 (~ 90%)	

Fraction 2 - This fraction did not crystallise. It was characterised as XXIV from its spectral data (UV, IR, PMR).

Thionylchloride-Pyridine[20] dehydration of hydroxy diacetate (XVII)

To XVII (1.99 g, 0.0025 mole) in pyridine (5 ml) at -15°C was added a solution of $SOCl_2$ (0.39 ml, 0.005 mole) in

pyridine (5 ml) dropwise during 45 min. It was stirred for 1 hr and left overnight at room temp. The completion of the reaction was monitored by TLC (solvent system: 5% ethyl acetate in benzene) which revealed the formation of a mixture of two olefins one of them predominating considerably; a third isomer was also present in very minor amounts. The reaction was worked up by taking the reaction mixture in ether (20 ml) and adding water (20 ml) to it. The ethereal layer was separated and the aqueous layer extracted with ether (15 ml x 4). The combined ether extracts were washed with water (20 ml x 5), brine (25 ml x 2) and dried. Flashing off the solvent gave 1.01 g (~ 95%) of gummy material which was purified by chromatographying it over a column of silica gel.

CHROMATOGRAM

Substance: 627 mg.

Absorbent: 30 g, SiO_2 gel/IIA

Column : 32 x 1.6 cm.

No.	Eluent	Ratio	Vol. (ml)	Eluate (g)	Remarks

No.	Eluent	Ratio	Vol. (ml)	Eluate (g)	Remarks.
4	P.E.+C_6H_6	70:30	30x10	0.0121	Gum, tailing, rejected.
5	"	60:40	30x8	0.0053	" " "
6	"	40:60	15x2	0.0022	" " "
7	"	"	15x5	0.0788	Gum with top minor impurity.
8	"	"	15x6	0.2100	Gum XXV
9	"	"	15x20	0.1070	Mixed fractions of (XXV) and (XXVI).
10	"	"	15x6	0.0388	Solid 107-112
11	"	30:70	20x25	0.0550	" XXVI
12	Benzene	-	20x10	0.0187	"
13	Methanol	-	50	0.0240	Base impurity and tailing.
				Total: 0.5730	(~ 92%).

XXV - Fraction 8 did not crystallise and was identified from its spectral data as XXV.

XXVI - Fractions 10-12 were combined and crystallised from pet. ether to give colorless spiny crystals (75 mg) m.p. 110-112°, $[\alpha]_D$ +17.35 ($CHCl_3$). [Found: C, 74.95; H, 10.23. $C_{26}H_{42}O_4$ requires: C, 74.60; H, 10.11%].

Isomerisation of XXV to XXVI by Li/Ethylenediamine[21]

Li metal (200 mg) was added to ethylene diamine (5 ml) at 110° under anhydrous conditions in an atmosphere of nitrogen. The heating was continued with stirring till

all the Li dissolves (indicated by the change in color from blue to yellow). To this olefin (XXV; 400 mg) in ethylene diamine (5 ml) was added and stirred at 110° for another 2 hr. It was left overnight at room temp. (15 hr). The reaction mixture was chilled in ice and water (20 ml) added to dissolve the solid. It was extracted with ether (15 ml x 4) which was washed with dil. HCl (10%, 10 ml x 2), brine (15 ml) and dried. Stripping off the solvent left 320 mg (~ 80%) of gummy material. The crude reaction product was acetylated with acetic anhydride (2 ml) and pyridine (2 ml) at room temp. (12 hr). The usual work-up gave 345 mg of gummy substance, whose TLC on silica gel (solvent system - 5% EtOAc in C_6H_6) showed the formation of XXVI and the presence of some starting material (very minor). The mixture was separated on a column of silica gel.

CHROMATOGRAM

Substance : 340 mg

Silica gel : 20 g, SiO_2 gel/IIA

Column : 25 cm x 1 cm.

No.	Eluent	Ratio	Vol. (ml)	Eluate (g)	Remarks
1	Pet.ether	-	20 x3	0.0050	Rejected.
2	Pet.ether + Benz.	70:30	20x10	0.0045	"
3	"	40:60	20x5	0.0057	"
4	"	"	10x3	0.0357	Gum, XXV
5	"	"	10x6	0.0571	Mixed fractions.
6	"	"	10x15	0.1153	Solid m.p. 107-111° XXVI.
7	Benzene	-	20x10	0.0828	Solid (same).
8	MeOH	-		0.0285	Base impurity and tailing.
			Total:	0.3346 g (~ 98%).	

Fraction 4 was readily identified as starting material (XXV, TLC, IR).

XXVI - Fraction 6 and 7 are mixed (196.1 mg) and crystallised from pet. ether to give 143 mg of crystalline material m.p. 110-12°, identical with XXVI (m.m.p. and TLC).

Osmylation[18] of XXVI to diol (XXVII)

To olefin (XXVI, 418 mg, 0.001 mole) in pet. ether + ether (1:1, 10 ml) containing pyridine (0.5 ml) was added OsO_4 solution (280 mg in pet. ether + ether 10 ml, 0.0011 mole). It was swirled and left in dark at room temp. After 3 days (very little solid had separated) the solvent was

removed under suction to yield a dark brown gummy material which was dissolved in a mixture of benzene + methanol (1:1; 15 ml). H_2S was bubbled through it till saturation. The black precipitate thus formed was filtered and washed well with benzene + methanol (1:1, 10 ml). Removal of solvent from the filterate gave a solid (430 mg, 91% m.p. 172-175°). It was crystallised from ethyl acetate + pet. ether mixture to give crystalline solid (XXVII) (345 mg) m.p. 175.5 - 177°, [Found: C, 68.96; H, 9.99. $C_{26}H_{44}O_6$ requires: C, 68.99; H, 9.80%].

Methyl Ketone (XXVIII) from diol (XXVII)

To diol (XXVII; 226 mg, 0.0005 mole) in dry benzene (20 ml), $Pb(OAc)_4$ (350 mg, 0.00055 mole) was added and stirred for 3 hr at 28°C. The completion of the reaction was checked by TLC (solvent system: 25% ethyl acetate in benzene). Water (10 ml) was added to the reaction mixture and benzene layer was separated. The aqueous portion was extracted with ether (5 ml x 2). The combined organic extracts were washed with water (10 ml x 2), brine (10 ml) and dried. Removal of the solvent gave 195 mg of solid material. TLC showed two spots with one predominating. The mixture was purified by passing through a column of silica gel.

CHROMATOGRAM

Substance: 190 mg

Adsorbent: 10 g SiO_2 gel/IIA

Column : 20 cm x 0.7 cm

No.	Eluent	Ratio	Vol. (ml)	Eluate (g)	Remarks
1	Pet. ether	-	10x2	0.0010	Rejected.
2	Pet.ether + Benzene	1:1	10x2	0.0022	"
3	C_6H_6 + EtOAc	97:3	5x4	0.0038	"
4	""	97:3	5x10	0.1350	Solid XXVIII m.p. 149-152°
5	""	95:5	5x5	0.0155	Mixed fractions.
6	Benzene	-	20	0.0213	Base impurity, tailing rejected.
			Total:	0.1786	(93%)

Methyl ketone XXVIII Fraction 4 (135 mg) was crystallised from pet. ether to give crystalline solid (112 mg), m.p. 126-127°, [Found: C, 75.18; H, 10.36. $C_{21}H_{34}O_3$ requires: C, 75.40; H, 10.25%].

Diacetate (XXIX) from methyl ketone (XXVIII)

PBA solution[22] in benzene (15 ml containing 200 mg of PBA) was added to methyl ketone (100 mg in benzene, 5 ml)

while cooling (~ 10%). It was swirled and left in dark at ~ 28°C. The reaction was monitored by TLC from time to time and worked up after three days (solvent system: 15% ethyl acetate in benzene) by washing the benzene solution with saturated Na_2CO_3 solution (10 ml x 4), water (10 ml x 2), brine (10 ml) and dried. Flashing off the solvent gave a crystalline material (105 mg, ~ 95%) m.p. 148-150° which was crystallised from methanol to give 95 mg of white crystalline solid m.p. 151.5 - 152°, [Found: C, 72.08; H, 9.75. $C_{21}H_{34}O_4$ requires: C, 71.95; H, 9.78%].

Diol (AAA) from diacetate (AcAcA)

Diacetate (AcAcA, 90 mg) was hydrolysed with 10% alc. KOH (2 ml) by refluxing for 2 hr. It was diluted with water (5 ml) and extracted with ether (5 ml x 3) which was washed with water (5 ml x 2), brine (5 ml) and dried. Removal of solvent gave a solid (78 mg) m.p. 208-210°. It was crystallised from aqueous alcohol to yield a crystalline solid (AAA) (58 mg), m.p. 210-211° [Found: C, 76.44; H, 11.45. $C_{17}H_{30}O_2$ requires: C, 76.64; H, 11.35%].

Diketone (AcAcA) from diol (AAA)

Jone's reagent[9] was added dropwise to diol (AAA, 40 mg) in acetone (5 ml) at 5-10° while stirring (till yellow colour persists). Stirring was continued for

another 1 hr (5-10°). The excess of reagent was destroyed by the addition of a few drops of methanol (colour changes from yellow to green). The reaction mixture was poured over ice-cold water (10 ml) and extracted with ether (5 ml x 3) which was washed with water (5 ml x 2), brine (5 ml) and dried. Removal of solvent gave 35 mg of solid material m.p. 59-64° which was crystallised from pet. ether to give 22 mg of a crystalline solid m.p. 64-66°. [Found: C, 77.59; H, 9.76. $C_{17}H_{26}O_2$ requires: C, 77.82; H, 9.99%].

Acetic anhydride-Pyridine[24] reaction of malabaricol

Malabaricol (1, 1.054 g), acetic anhydride (7 ml) and pyridine (7 ml) were refluxed for 24 hr at 160° (bath temp.). It was allowed to stand at room temp. overnight. The reaction mixture was poured into cold water (20 ml) and extracted with ether (20 ml x 4) which was washed with water (25 ml x 5), brine (25 ml) and dried. Removal of solvent gave a gummy residue (2.242 g). Its TLC on $AgNO_3$-SiO_2 gel plate (solvent system: 10% Ethyl acetate in benzene) revealed essentially the formation of one compound with a very minor second compound. It was purified over a column of $AgNO_3$-SiO_2 gel.

CHROMATOGRAM

Substance: 2 g

Adsorbent: 90 g $AgNO_3$-SiO_2 gel.

Column : 40 cm x 2.6 cm.

No.	Eluent	Ratio	Vol. (ml)	Eluate (g)	Remarks
1	Pet. ether	-	90x5	0.0061	Rejected.
2	Pet.ether + benzene.	90:10	90x5	0.0040	"
3	" "	80:20	90x5	0.0017	"
4	" "	70:30	90x10	0.0275	Gum, minor compound. TLC: single spot.
5	" "	60:40	90x20	0.5250	Mixed fractions.
6	" "	50:5	90x6	0.7500	Gum, minor compound. TLC: single spot.
7	Benzene		45x10	0.4540	Gum, major compound.
8	Methanol		200	0.1416	Base impurity, tailing.
			Total:	1.3000	(~ 95%).

Fraction 4 was identified as the minor product (TLC) which did not crystallise from any solvent, $[\alpha]_D$ +34.61° ($CHCl_3$).

Fractions 6 and 7 were combined and identified as XXXII, $[\alpha]_D$ +25.5° ($CHCl_3$) on the basis of its spectral data (IR, PMR). However it did not crystallise from any solvent.

KBH_4 reduction of octa-nor-1-lactone (XVI)

To a solution of lactone (XVI; 200 mg) in dioxan (8 ml), a solution of KBH_4 (75 mg) in aqueous dioxan (1:1, 4 ml) was added and allowed to stand at room temp. (overnight). Excess of reagent was destroyed by the addition of a few drops of dilute acetic acid. The reaction mixture was diluted with water (10 ml) and extracted with ether (10 ml x 3) which was washed with water (15 ml x 2), brine (15 ml) and dried. Removal of solvent gave a solid (199 mg) m.p. 135-138°. It was crystallised from ether to furnish a crystalline alcohol (XXIII) (140 mg) m.p. 138.5 - 140°; $[\alpha]_D$ +5.5 ($CHCl_3$), [Found: C, 75.95; H, 10.52. $C_{22}H_{36}O_3$ requires: C, 75.81; H, 10.41%]. 100 mg of this alcohol was acetylated (Ac_2O-pyridine, room temp. 15 hr) to furnish a monoacetate (XXIV) (105 mg m.p. 182-187°) which was crystallised from acetonitrile to give flaky crystals (75 mg) m.p. 187-188°, $[\alpha]_D$ +11.81° ($CHCl_3$) [Found: C, 75.80; H, 8.89. $C_{26}H_{38}O_4$ requires: C, 75.69; H, 8.80%].

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chapter four
minor constituents of the resin of ailanthus malabarica

MINOR CONSTITUENTS OF THE RESIN OF AILANTHUS MALABARICA DC

In Chapter II we have described the isolation of nine minor constituents besides malabaricol (major component constituting 45.25 %) from the neutral portion of the exudate of Ailanthus malabarica DC. This Chapter discusses the structures of three derivatives of malabaricol, which we have now designated as epoxymalabaricol, malabaricanediol and epoxymalabaricanediol. The tentative structures of some of the remaining related compounds are given on the basis of spectral data.

EPOXYMALABARICOL

This compound analyses for $C_{30}H_{50}O_4$, m.p. 143-44°, $[\alpha]_D$ +24.6° ($CHCl_3$). It displays bands for OH (3500, 1082 cm^{-1}) and c=o (1703 cm^{-1}) in the IR spectrum (Fig.1). Its PMR spectrum (Fig.2) shows signals for: eight quaternary methyls (56, 59, 59, 59, 62, 65, 68 and 74 c/s), and CH_2-C=O (a 2H multiplet centred at 142 c/s); a 2H multiplet located between 212-240 c/s is considered to arise from two overlapping triplets due to two protons of type $-CH_2-\underset{O}{\underset{|}{C}}H-O-$. The methyl signals separate far clearer when the spectrum (Fig.3) is taken in benzene solution (46, 50.5, 53.5, 61.5, 61.5, 61.5, 71.5 and 84.5 c/s), the multiplet centred at 142 c/s shifts slightly upfield to 137.5 c/s and

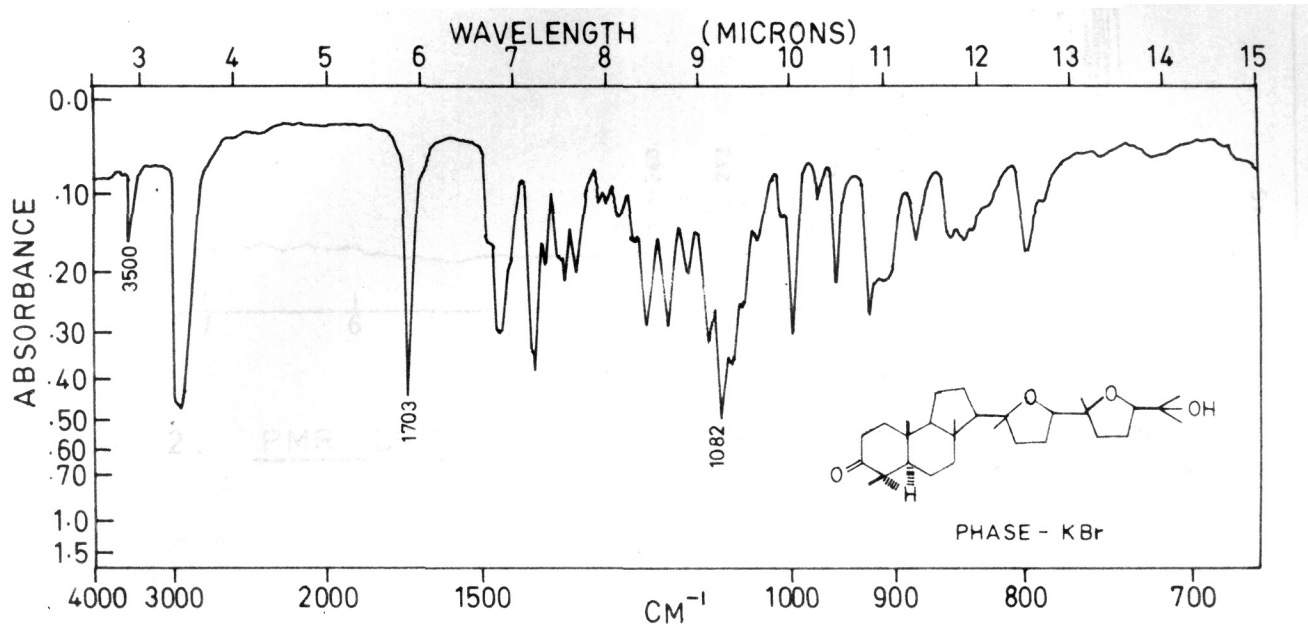


FIG. 1. IR SPECTRUM OF EPOXYMALABARICOL

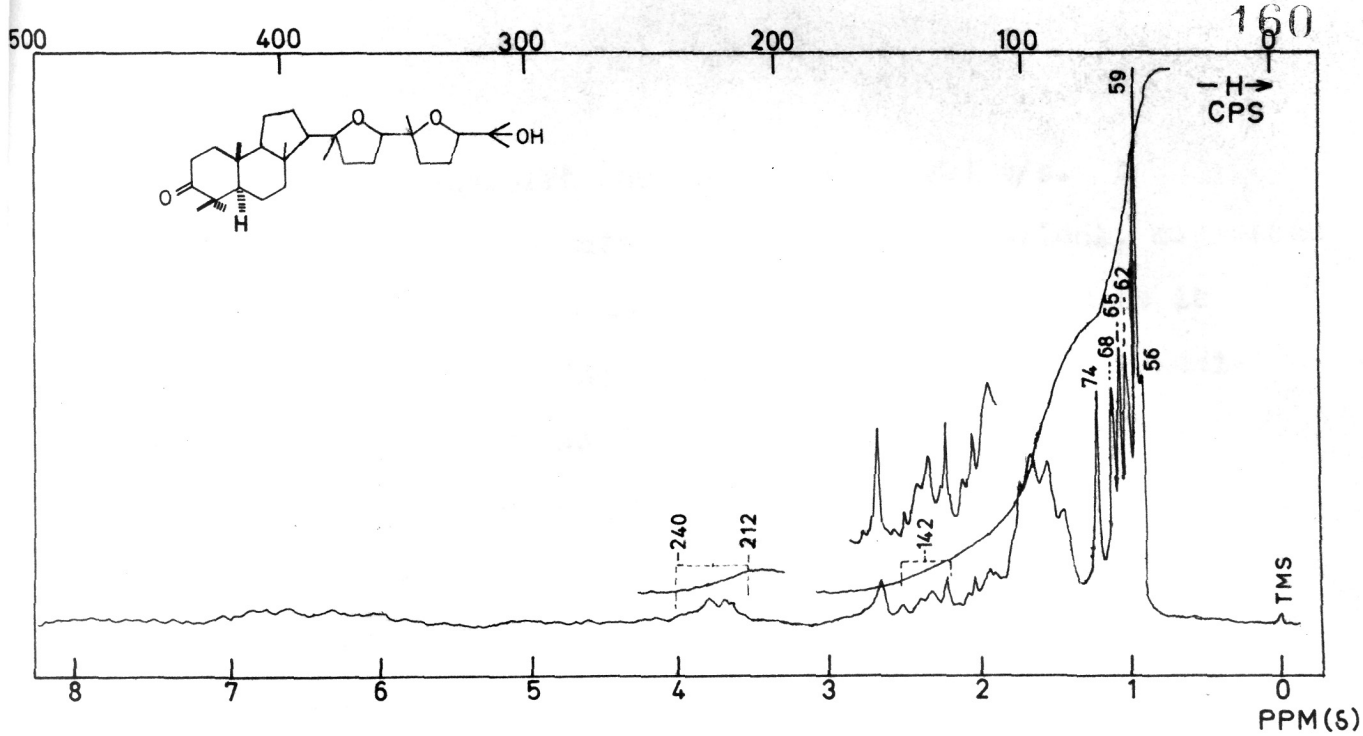


FIG. 2. PMR SPECTRUM OF EPOXYMALABARICOL (IN CCl_4)

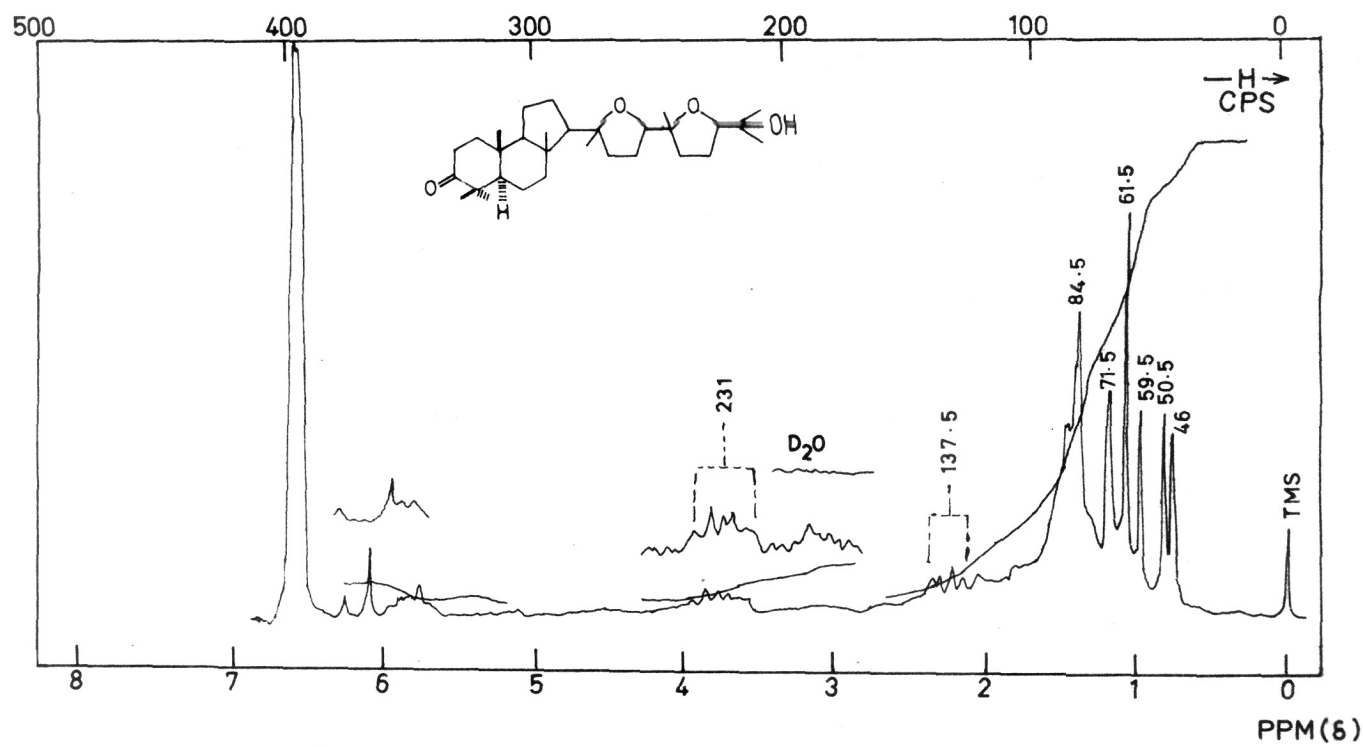
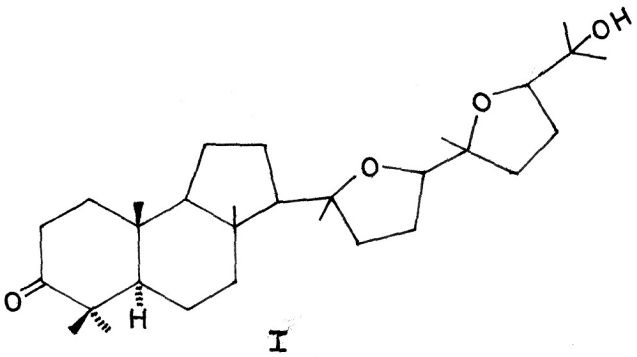


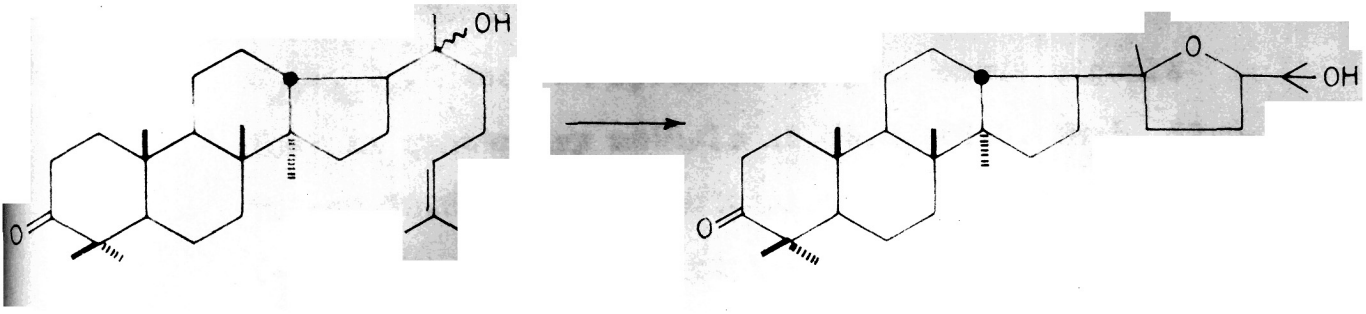
FIG. 3. PMR SPECTRUM OF EPOXYMALABARICOL (IN BENZENE)

the 225 c/s multiplet now resonates at 231 c/s. A comparison of these data with that of malabaricol, suggested that the new compound is clearly closely related to it and could have possibly arisen from malabaricol by additional oxygenation involving the side-chain olefinic linkage. In clear support of this, percamphoric acid oxidation of malabaricol, furnished a product indistinguishable (m.p., m.m.p., IR, PMR, $[\alpha]_D$) from the new compound, which was then named epoxy-malabaricol. This compound is assigned the structure I, rather than an oxirane structure



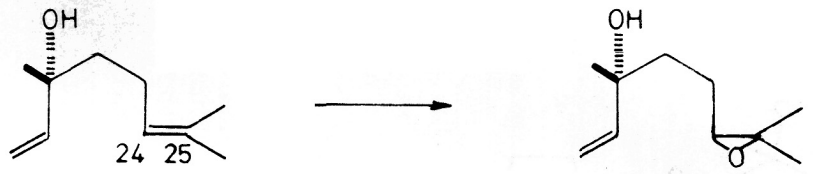
I

because the newly generated proton of type $-CH_2-\underset{\underset{C}{|}}{CH}-O-C$, shows its PMR signal, well outside the range of a secondary proton located on an oxirane ring[1]. There are several analogies[2] for such an epoxidation with a per acid, the closest being the conversion of dipterocarpol (II) into ocotillone (III) by percamphoric acid[3]. This course of

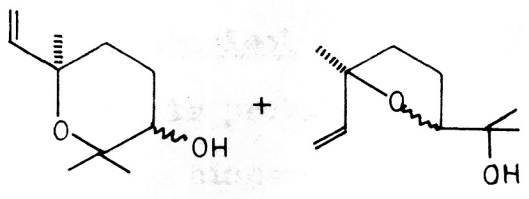


III

events is elegantly demonstrated by the conversion of linalool (IV) to linalool-oxide (VI) via the 1,2-epoxide (V).



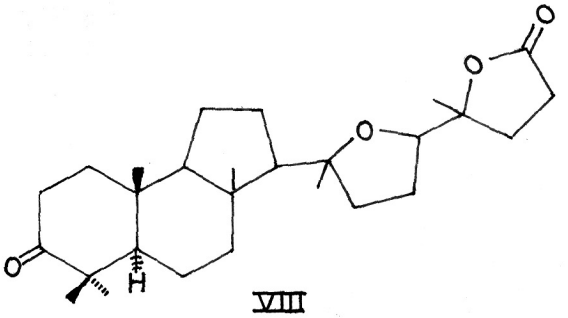
IV V



VII VI

1 9

Oxidation of epoxymalabaricol with Jones reagent[4] furnished a γ-lactone, m.p. 155-156°, $C_{27}H_{42}O_4$. Its PMR spectrum (Fig.4) shows signals for six quaternary methyls at 56.5, 58.5, 58.5, 62.5, 72 and 78.5 c/s, a 2H multiplet centred at 142 c/s ($-CH_2-C=O$) and a 1H multiplet centred between 225 and 242 c/s ($-CH_2-\underset{\underset{C}{|}}{CH}-O-$). The methyl signals separate far clearer when the spectrum is taken in benzene (Fig.5) (46, 50, 60, 62, 62 and 70 c/s). Its IR spectrum (Fig.6) exhibits absorptions at 1705 cm^{-1} (six membered ketone) and 1776 cm^{-1} (γ-lactone). These data for the lactone are in complete accord with the trisnor lactone (VIII) formed by RuO_4 oxidation[5] of malabaricol.



VIII

Biogenesis of epoxymalabaricol

Epoxymalabaricol is probably formed in the plant from malabaricol by the biogenetic equivalent of 1,2-epoxidation at $C_{24} = C_{25}$ with subsequent oxide opening at C_{24} by the C-20 hydroxyl group. Although oxide ring

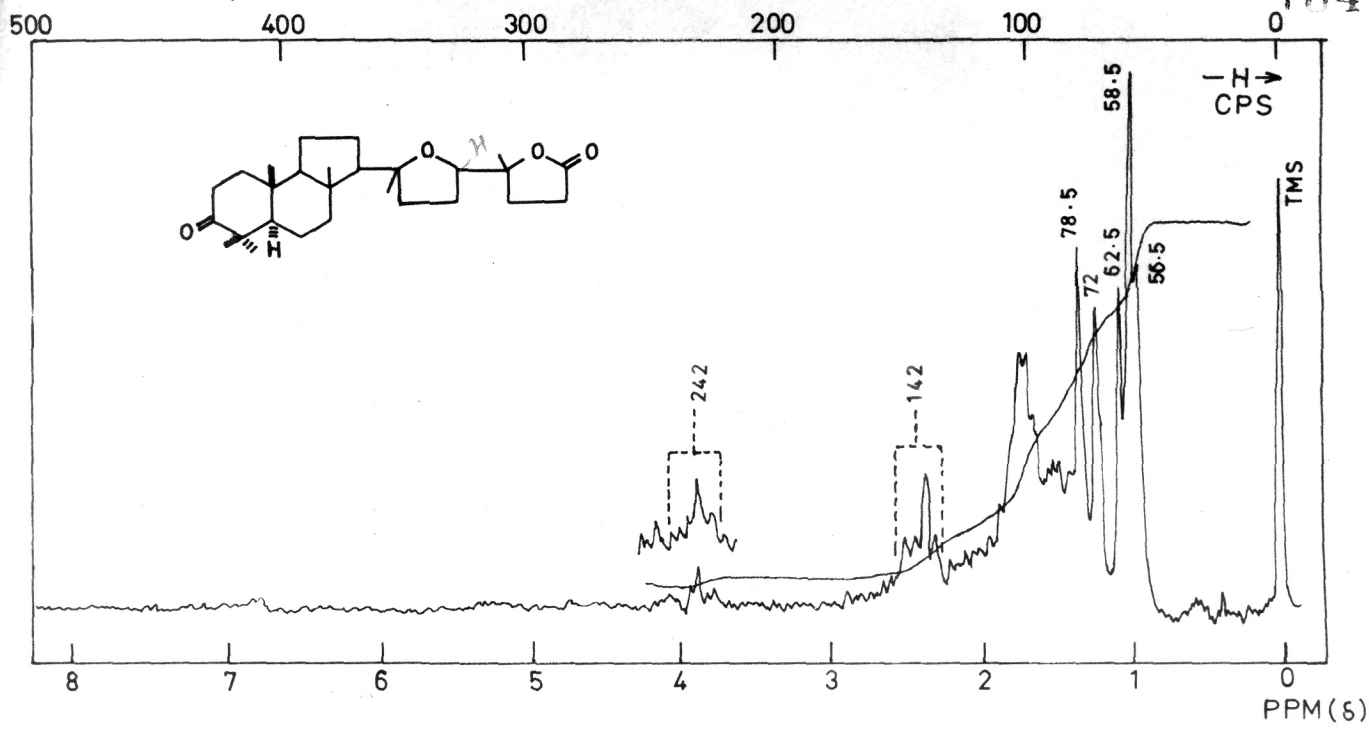


FIG. 4. PMR SPECTRUM OF TRIS-NOR LACTONE (VIII) (IN CCl_4)

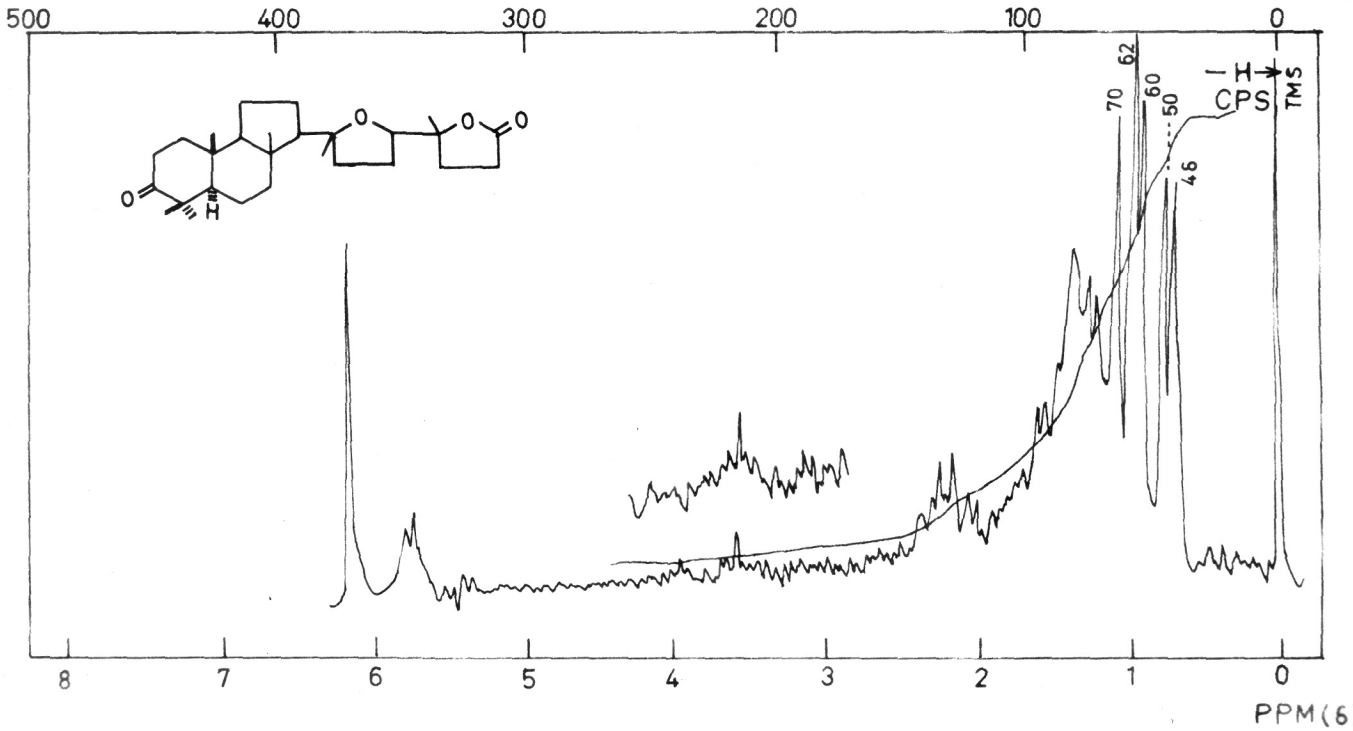


FIG. 5 PMR SPECTRUM OF TRIS-NOR LACTONE (VIII) (IN BENZENE)

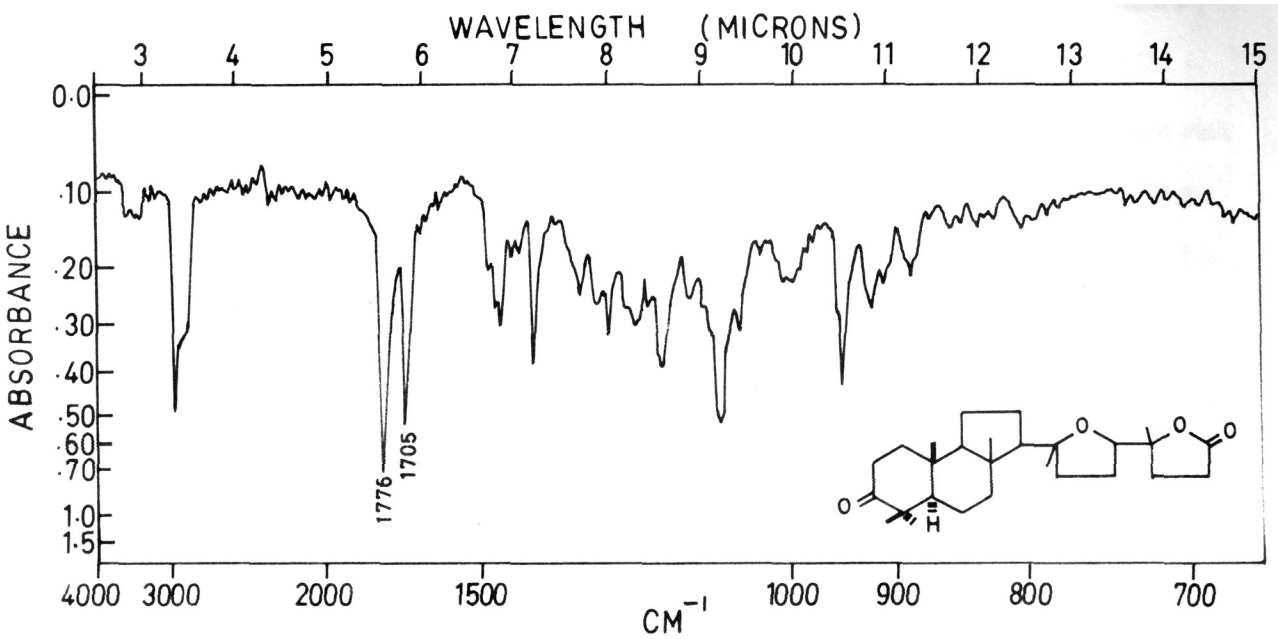
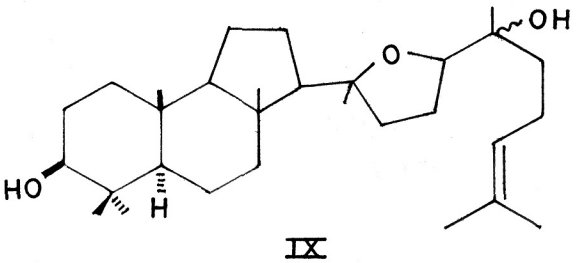


FIG. 6. IR SPECTRUM OF TRIS-NOR LACTONE VIII.

opening might occur at C-25, particularly in acid medium, five membered rings are usually formed more rapidly than six-membered rings.

MALABARICANEDIOL

This compound could not be obtained in crystalline form and has $[\alpha]_D$ +25.0° ($CHCl_3$). Its PMR spectrum (Fig.7) reveals the presence of six quaternary methyls (signals at 44.5, 50, 57, 57, 69, 71), two olefinic methyls (3H signals at 96 and 99 c/s), a 2H multiplet located between 175 - 217 c/s arising from two overlapping triplets due to protons of type $-CH_2-\underset{O}{CH}-O-$ and $CH_2-\underset{O}{CH}-$, one olefinic proton (1H triplet centred at 305 c/s, J = 7 c/s). Its IR spectrum (Fig.8) exhibits absorption for OH (3480 cm^{-1}). These spectral data suggest it to be C_3-alcohol corresponding to malabaricol which has been obtained by $NaBH_4$ reduction[6] of malabaricol and thus has been designated as malabaricanediol (IX).



IX

EPOXYMALABARICANEDIOL

This compound analyses for $C_{30}H_{50}O_4$ and has m.p. 134-135.5°, $[\alpha]_D$ +4.9 ($CHCl_3$). Its PMR spectrum (Fig.9)

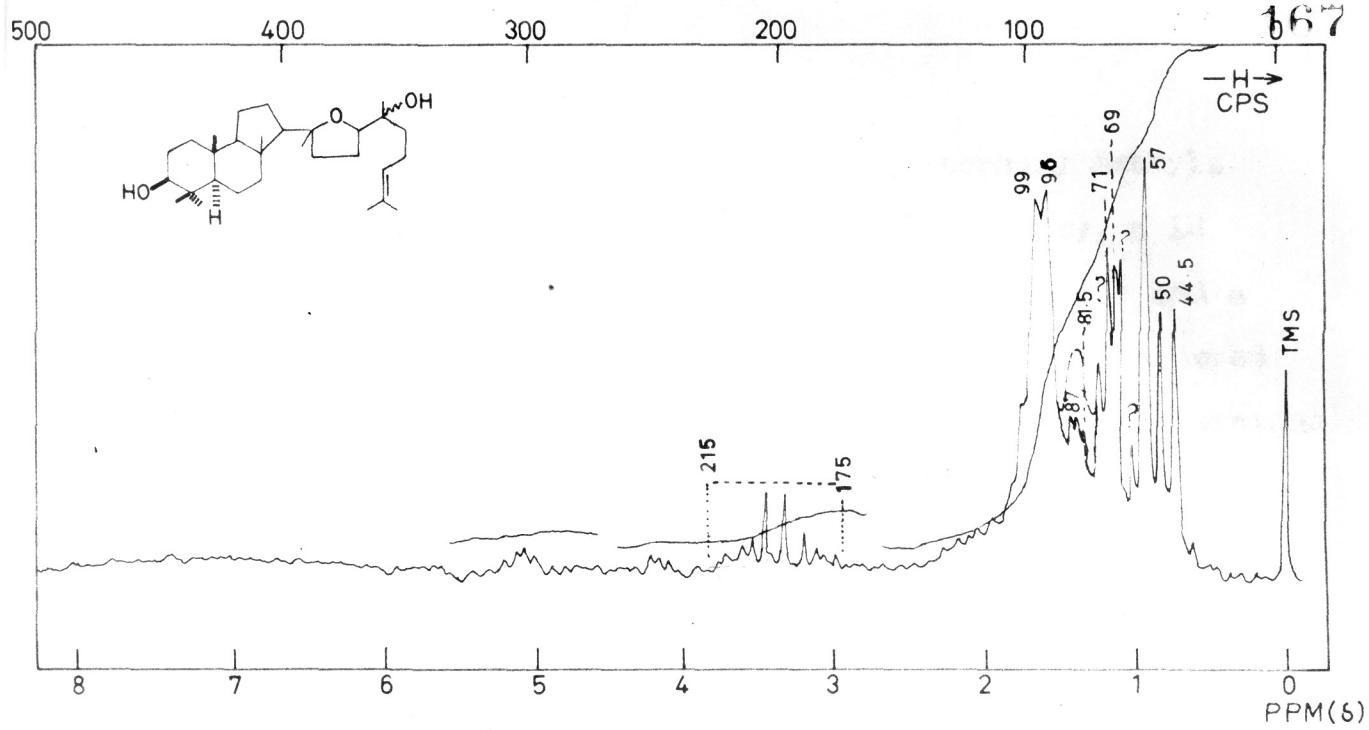


FIG. 7. PMR SPECTRUM OF MALABARICANEDIOL IX.

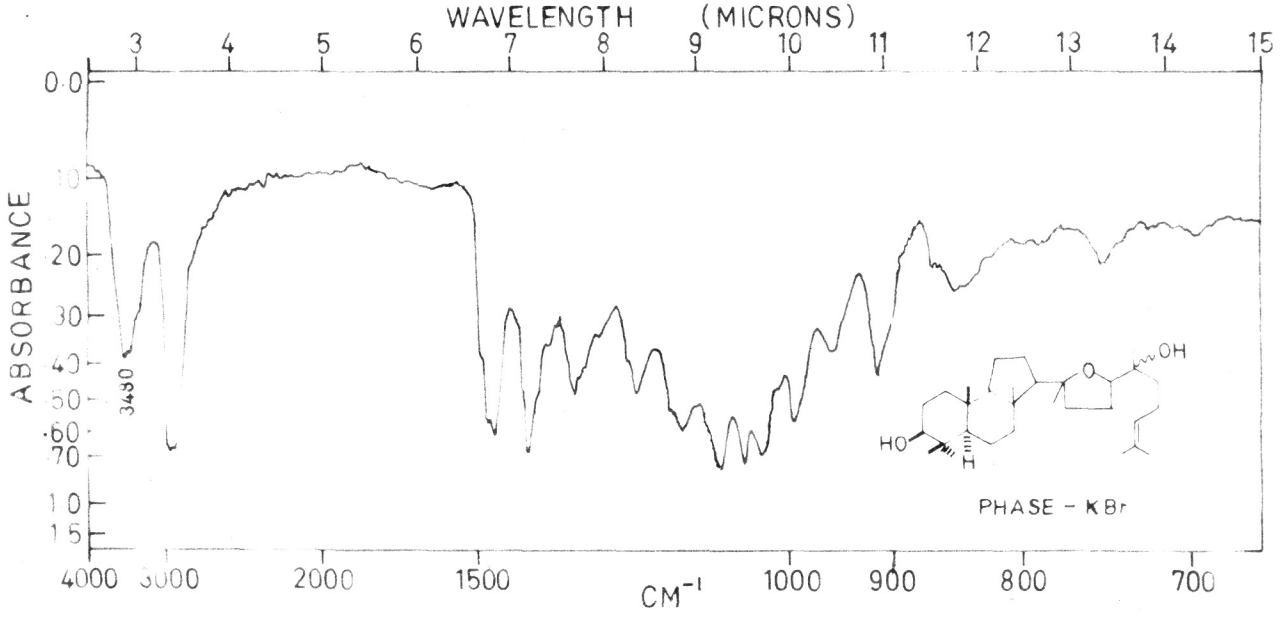
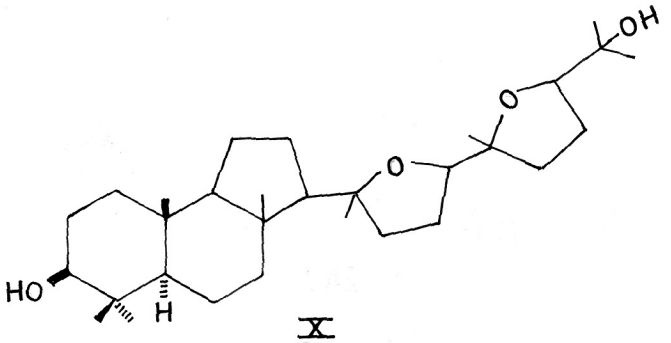


FIG. 8. IR SPECTRUM OF MALABARICANEDIOL IX

shows resonance signals for eight quaternary methyls (45, 50.5, 58, 58, 61, 66, 69.5 and 73.5 c/s), a 1H triplet centred at 186 c/s (J = 7 c/s ; $-C\underline{H}-O$) and a 2H multiplet located between 214-238 c/s is considered to arise from two overlapping triplets due to two protons of type $-CH_2-\underset{C}{\underline{C}H}-O$. Its IR spectrum (Fig.10) displays absorption for OH (3490, 3400 cm^{-1}). A comparison of these data with that of epoxymalabaricol, suggested that the new compound may be the C_3-alcohol corresponding to epoxymalabaricol. This has been confirmed by its identity (m.m.p., IR, PMR, TLC, $[\alpha]_D$) with an alcohol (A) obtained by $NaBH_4$ reduction of epoxymalabaricol. This naturally occurring compound has been named epoxymalabaricanediol.



X

OTHER MINOR COMPONENTS

From a critical examination of the spectral data of the minor constituents, it has been possible to arrive at plausible structures of three of these. It has not been

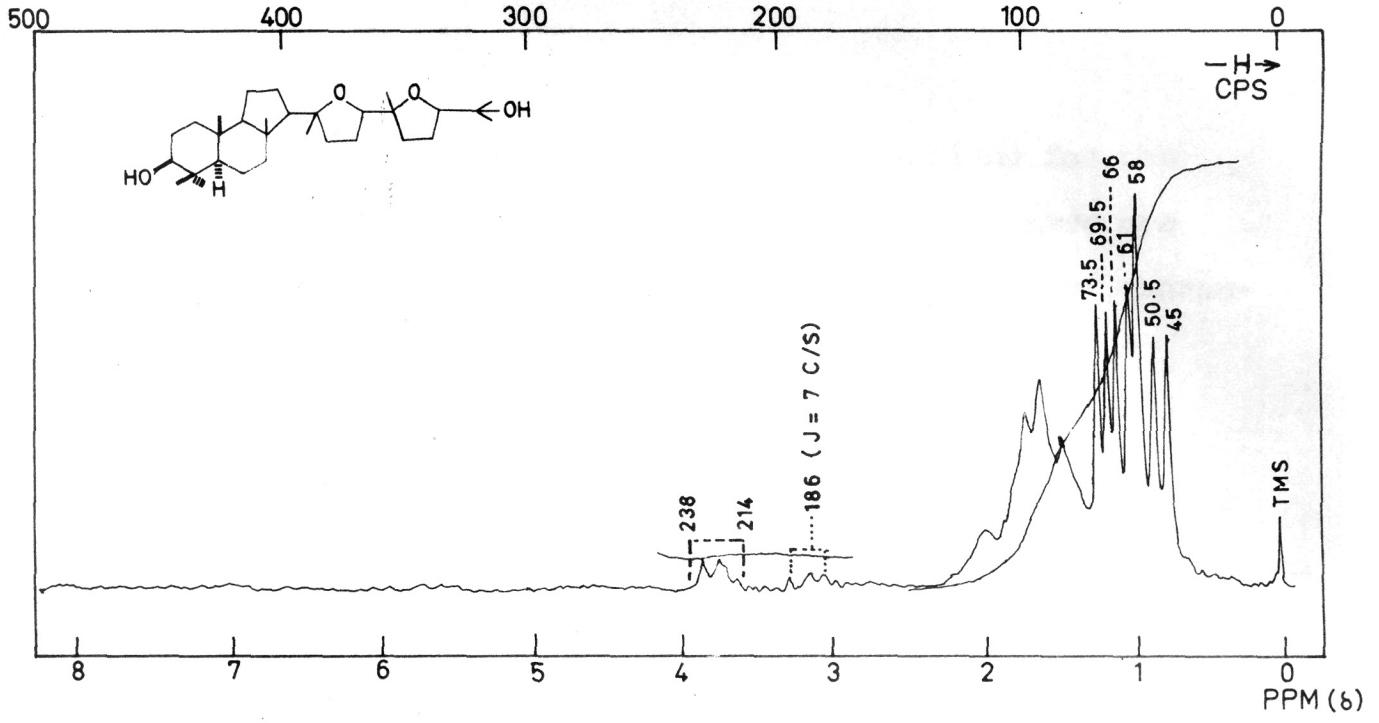


FIG. 9. PMR SPECTRUM OF EPOXYMALABARICANEDIOL X.

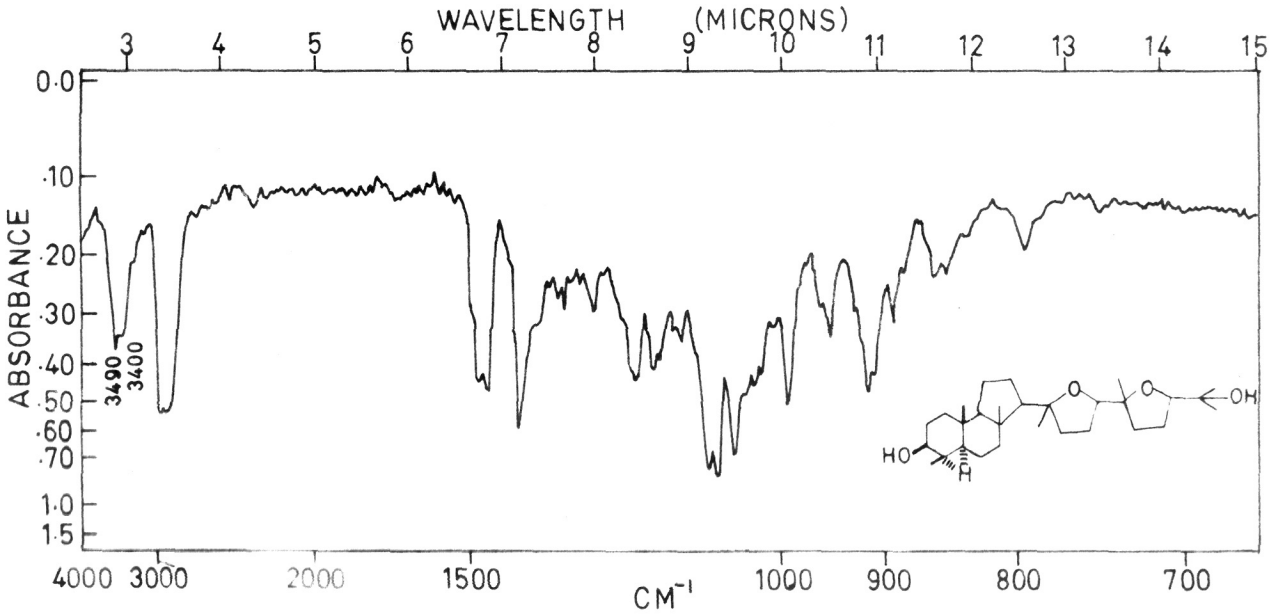


FIG. 10. IR SPECTRUM OF EPOXYMALABARICANEDIOL X

possible to deduce any likely formulations for the other minor constituents; the spectra of these are appended at the end of this Chapter, by way of characterisation of these compounds.

COMPOUND B_1

This compound, m.p. 161.5 - 162.5°, $[\alpha]_D$ +62.69 analyses for $C_{30}H_{52}O_3$. Its PMR (Fig.11), IR (Fig.12) and mass spectra (Fig.13) are given. Its PMR spectrum shows signals for eight quaternary methyls (53.5, 57, 60.5, 60.5, 62.5, 62.5, 66 and 68 c/s), 1H triplet centred at 215.5 (J = 6 c/s) for $-\underset{\overset{\|}{O}}{C}H-$ and a 2H multiplet of C_2-methylene next to 3-keto compounds[8]. The pattern and positions of quaternary methyls and C_2-methylenes are reminiscent of malabaricol type compounds. The IR spectrum displays absorption for OH (3520 cm^{-1}) and carbonyl (1704 cm^{-1}). Moreover PMR spectrum clearly reveals the absence of any olefinic proton as well as vinylic methyls. These data suggest two possible structures (XI and XII) which appear to be supported by the mass spectrum of this compound (Fig.13). The molecular ion could not be detected and the base peak appears at m/e 145, the genesis of which is indicated in XIII.

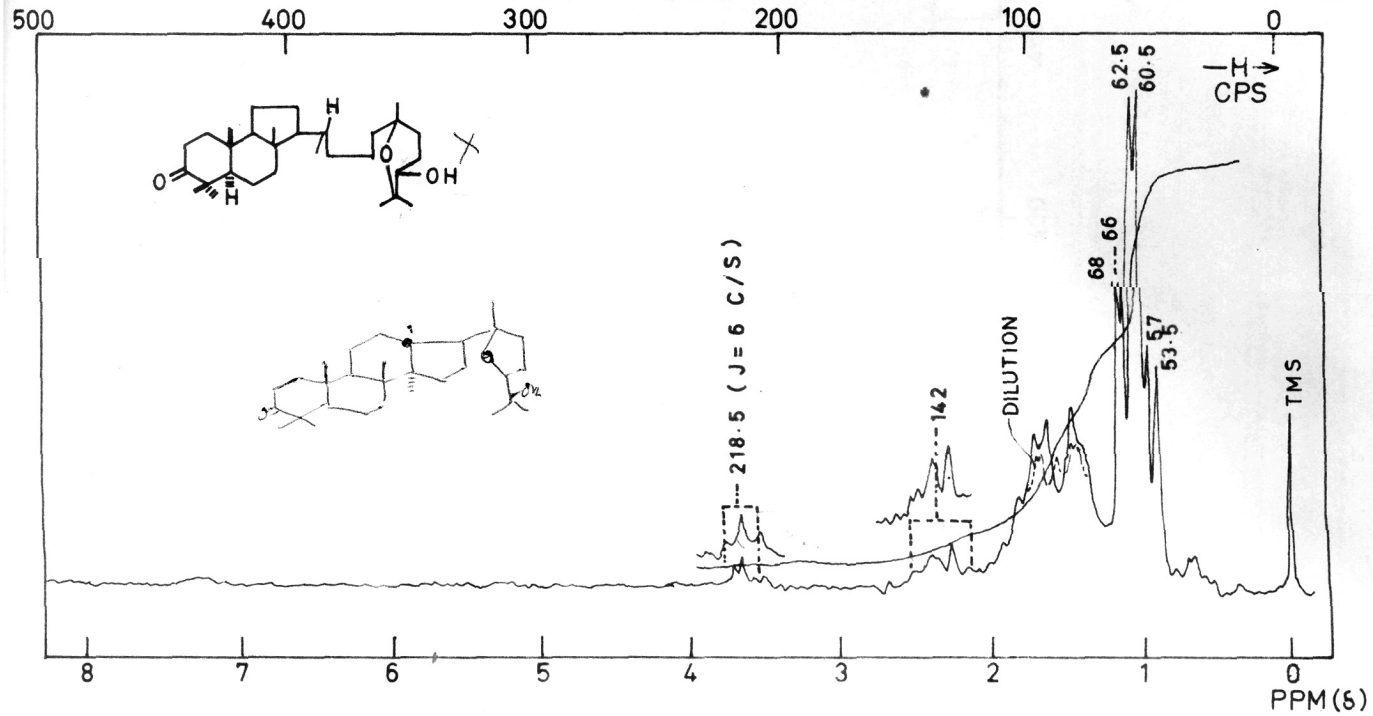


FIG. 11. PMR SPECTRUM OF COMPOUND B_1 XI

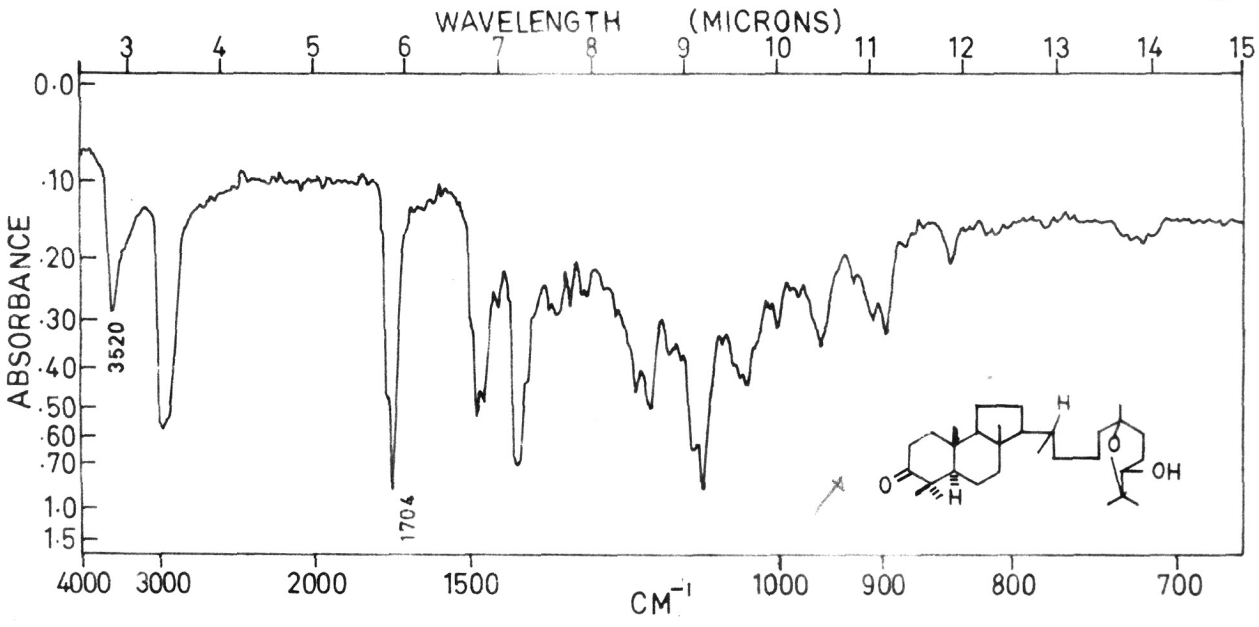


FIG. 12. IR SPECTRUM OF COMPOUND B_1 XI

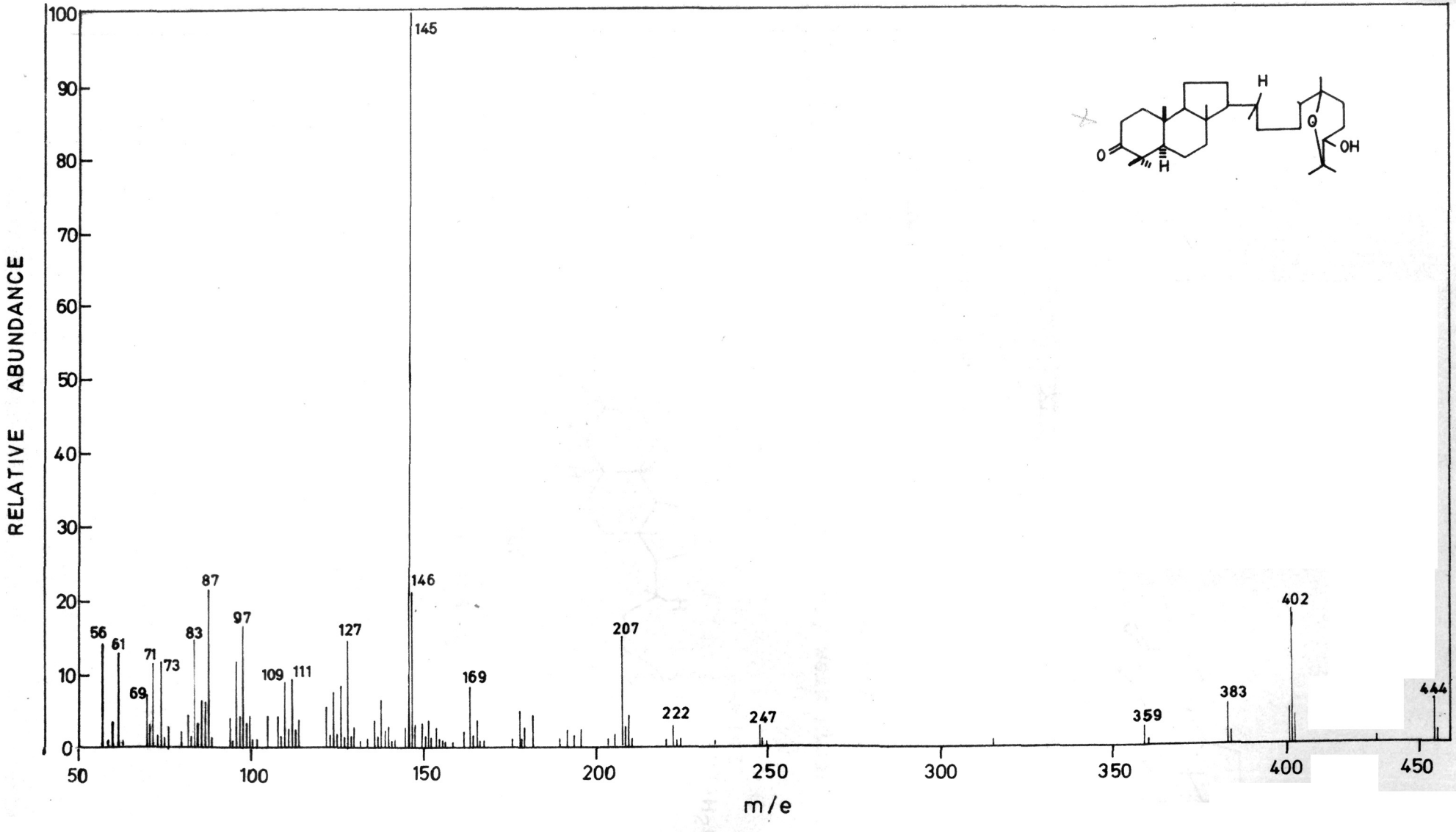
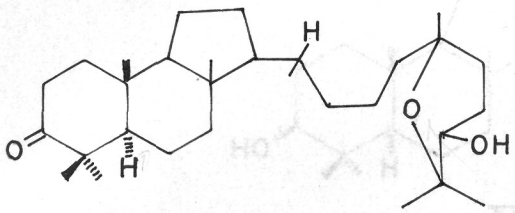
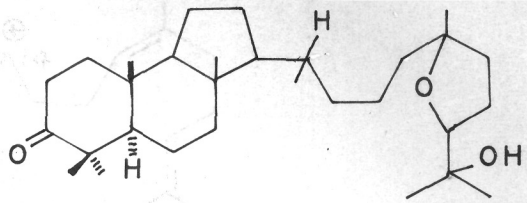


FIG. 13. MASS SPECTRUM OF COMPOUND B_1 XI.

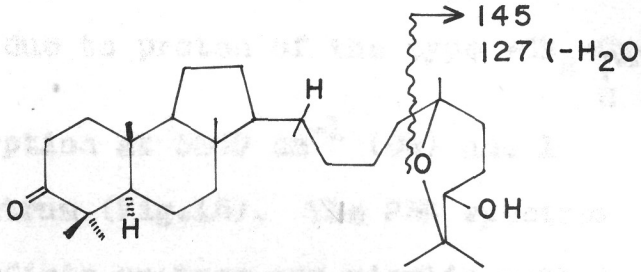


XI



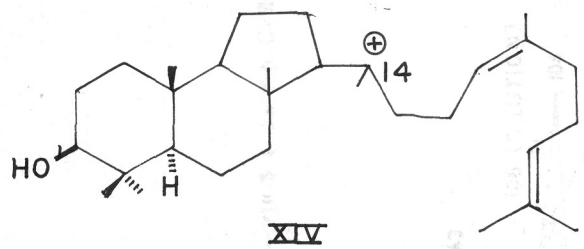
XII

However due to strong absorption of OH in the infrared region structure XI seems to be more plausible as the tertiary hydroxyl in malabaricane series (as well as ocotillone[3]) displays a very weak absorption (cf. Fig.1 Chapter 3).



XIII

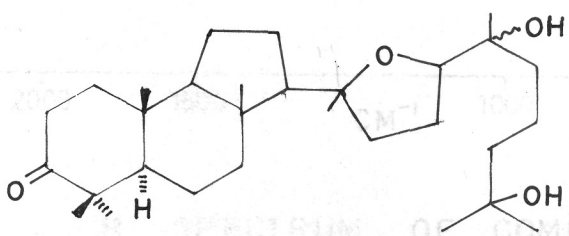
Biogenetically compound B_1 is conceivable from the ion XIV by hydride attack at C-14 followed by hydroxylation-epoxidation of the side chain double bonds.



XIV

COMPOUND K_1

This compound, m.p. 98-99°, $[\alpha]_D$ +30.1° analyses for $C_{30}H_{52}O_4$. Its PMR spectrum (Fig.14) displays signals for eight quaternary methyls (59, 60, 63.5, 67.5, 70, 70, 71 and 83 c/s), a 2H multiplet centred at 143 c/s, the pattern and position of which are reminiscent of the C_2-methylene of 3-keto triterpenoids, and a 1H triplet centred at 218 c/s (J = 7.5 c/s) due to proton of the type $-CH_2-\underset{C}{CH}-O-$. It displays absorption at 3350 cm^{-1} (OH) and 1703 cm^{-1} (C=O) in the IR spectrum (Fig.15). The PMR spectrum shows no signal for olefinic protons and vinylic methyls. Comparison of these data with that of malabaricol suggested that the new compound is likely to have structure (XV).



XV

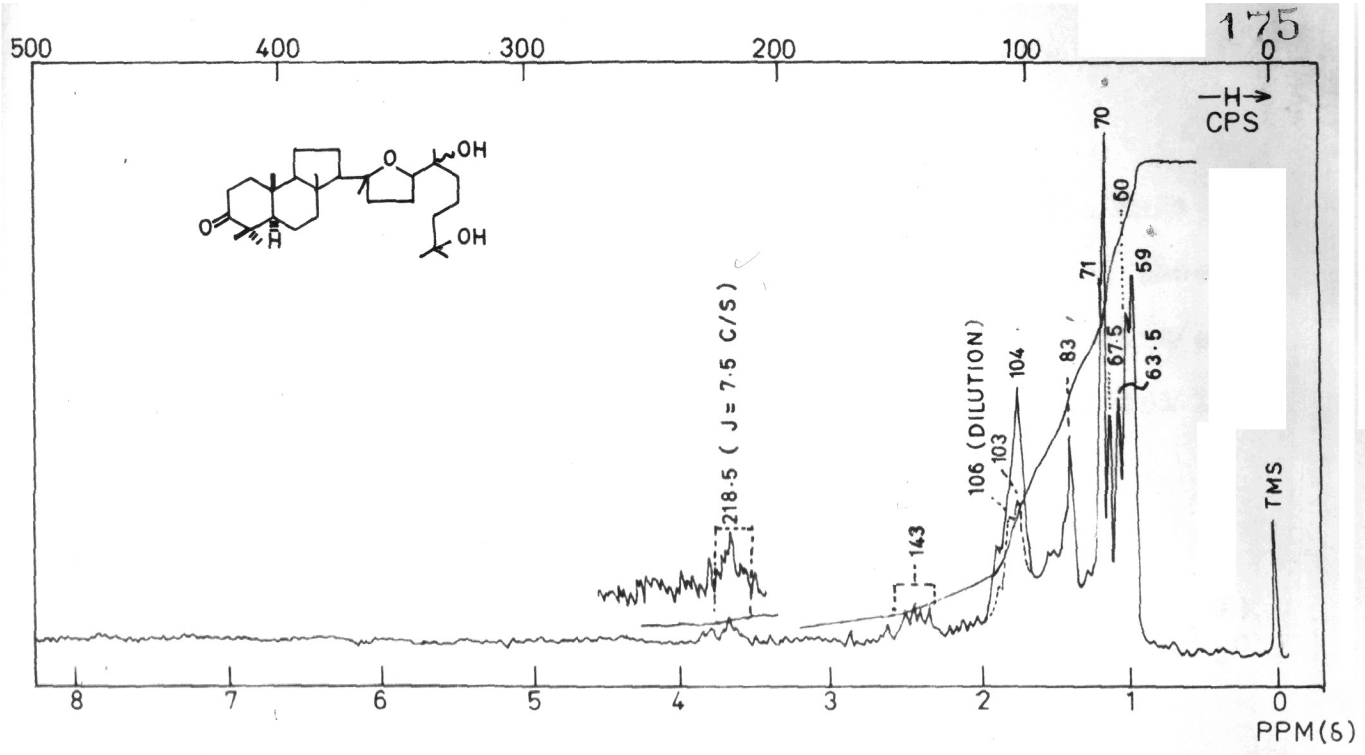


FIG. 14. PMR SPECTRUM OF COMPOUND F_1 XV.

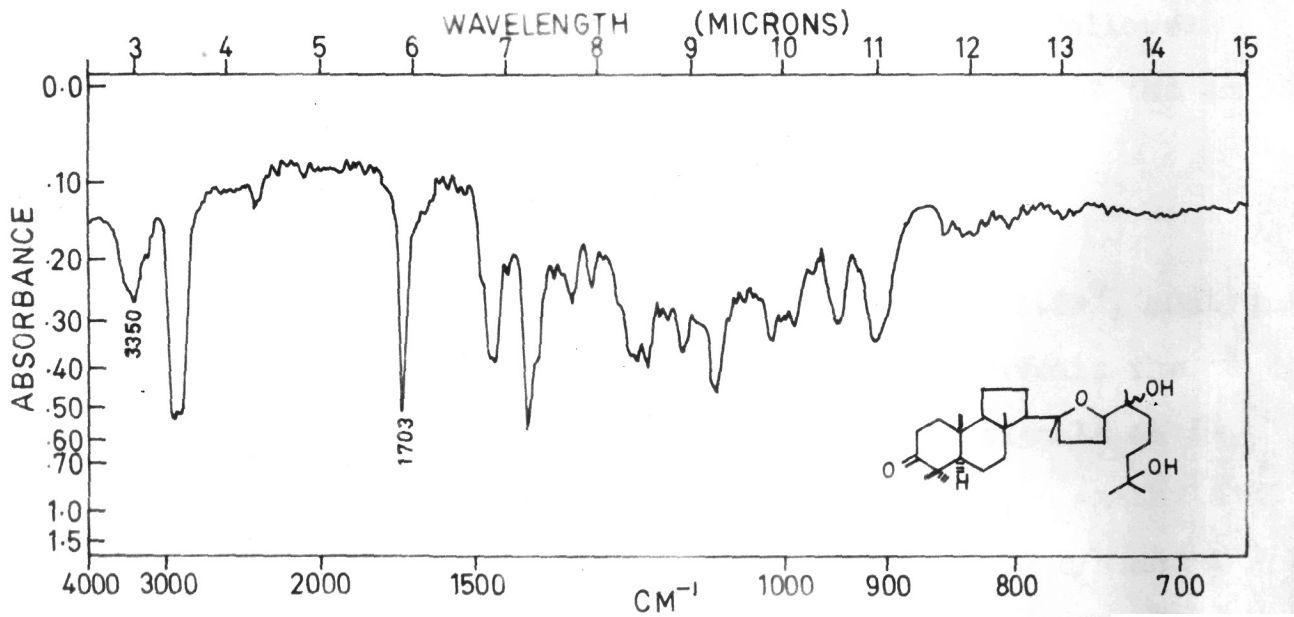
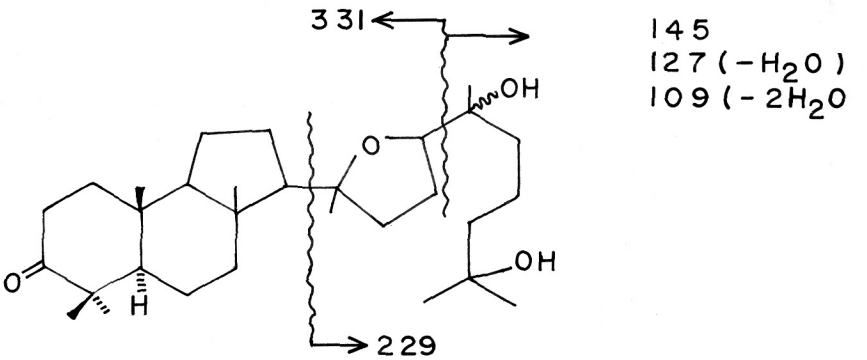


FIG. 15. IR SPECTRUM OF COMPOUND F_1 XV.

This structure is well supported by its mass spectrum (Fig.16). The mass spectrum does not show the molecular ion peak and shows a base peak at m/e 127. The fragmentation pattern of F_1 is depicted in the following figure XVI.



XVI

Biogenetically this structure (XV) is conceivable from squalene via the intermediate ion (XIV) followed by oxygenative ring closure and hydroxylation of the double bonds.

COMPOUND G_2

This compound, m.p. 144-145°, $[\alpha]_D$ +71.39°, analyses for $C_{30}H_{52}O_4$. Its PMR spectrum (Fig.17) reveals the presence of eight quaternary methyls (3H signals at 54, 57, 60.5, 63, 65, 70.5, 70.5 and 73.5 c/s), C_2-methylene next to 3 keto as a multiplet centred at 147 c/s and 1H multiplet centred at 200 c/s for $-CH_2-\underset{C}{CH}-O$. Its IR spectrum (Fig.18) exhibits strong OH absorption at

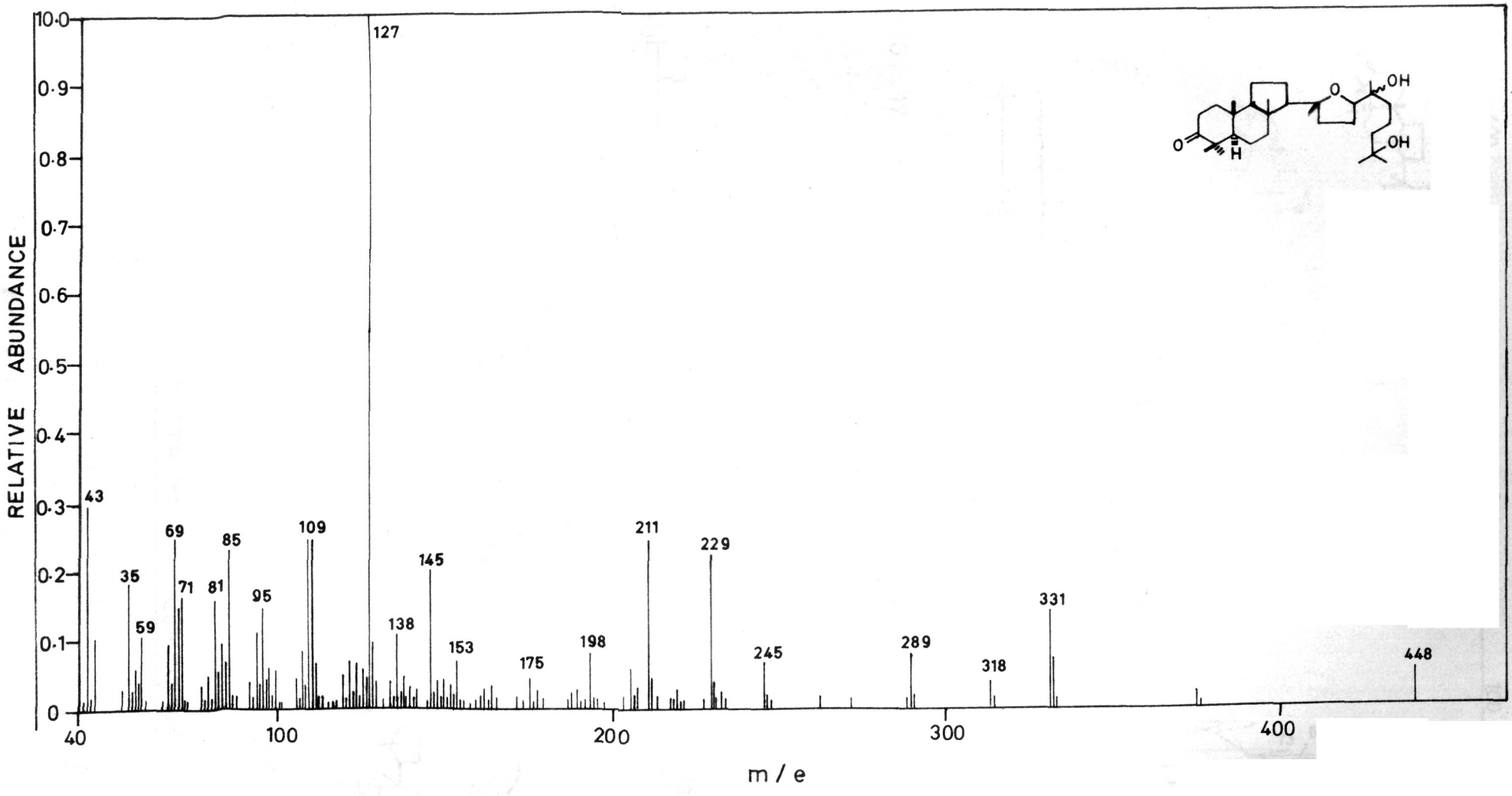


FIG. 16. MASS SPECTRUM OF COMPOUND F_1 XV.

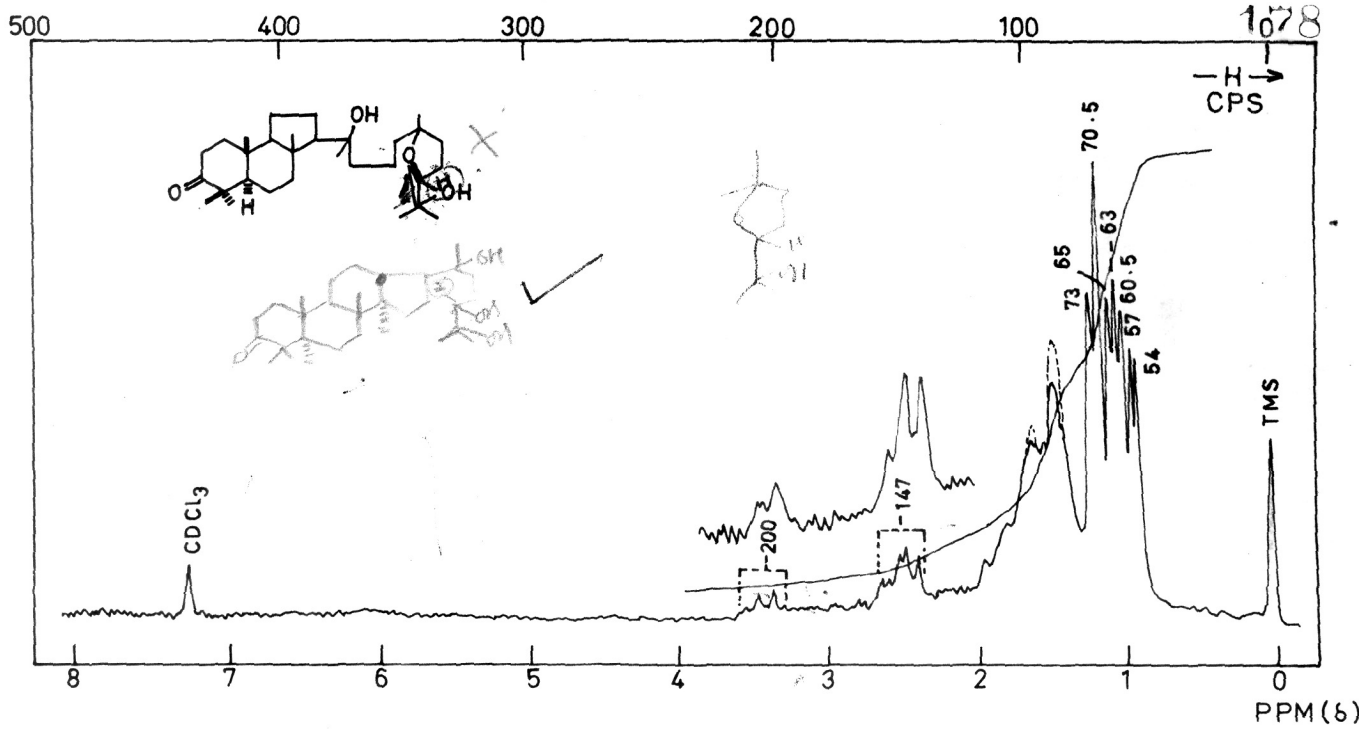


FIG. 17. PMR SPECTRUM OF COMPOUND G_2 XVII

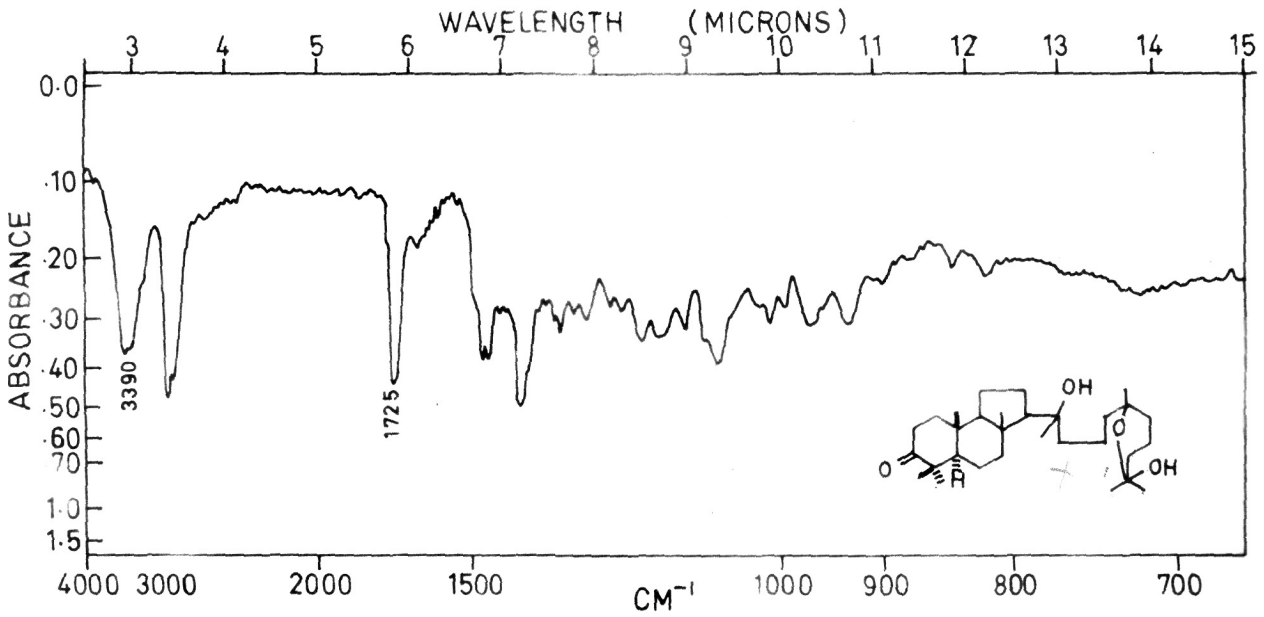
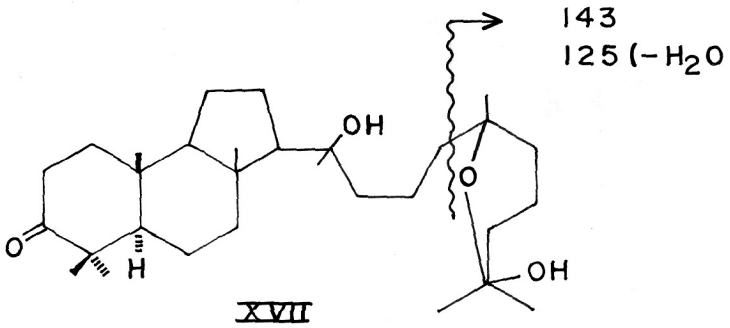


FIG. 18. IR SPECTRUM OF COMPOUND G_2 XVII

3390 cm^{-1} and carbonyl absorption at 1725 cm^{-1}. A comparison of these spectral data with those of malabaricol and other related compounds suggested a new compound having formula (XVII).



XVII

The mass spectrum of this compound is shown in Fig.19 in which the molecular ion peak has not been recorded. The highest peak (m/e 458) is conceivably the $(M-H_2O)^+$. The base peak at m/e 143 possibly arises via the fragmentation pathway depicted (XVII).

Biogenetically compound C_2 is conceivable from squalene via the intermediate ion XIV by hydroxylation at C_{14} and hydroxylation-epoxidation of the side chain double bonds.

REMAINING COMPOUNDS

Since it has not been possible to arrive at any definite conclusions from their spectral data only their spectra are appended.

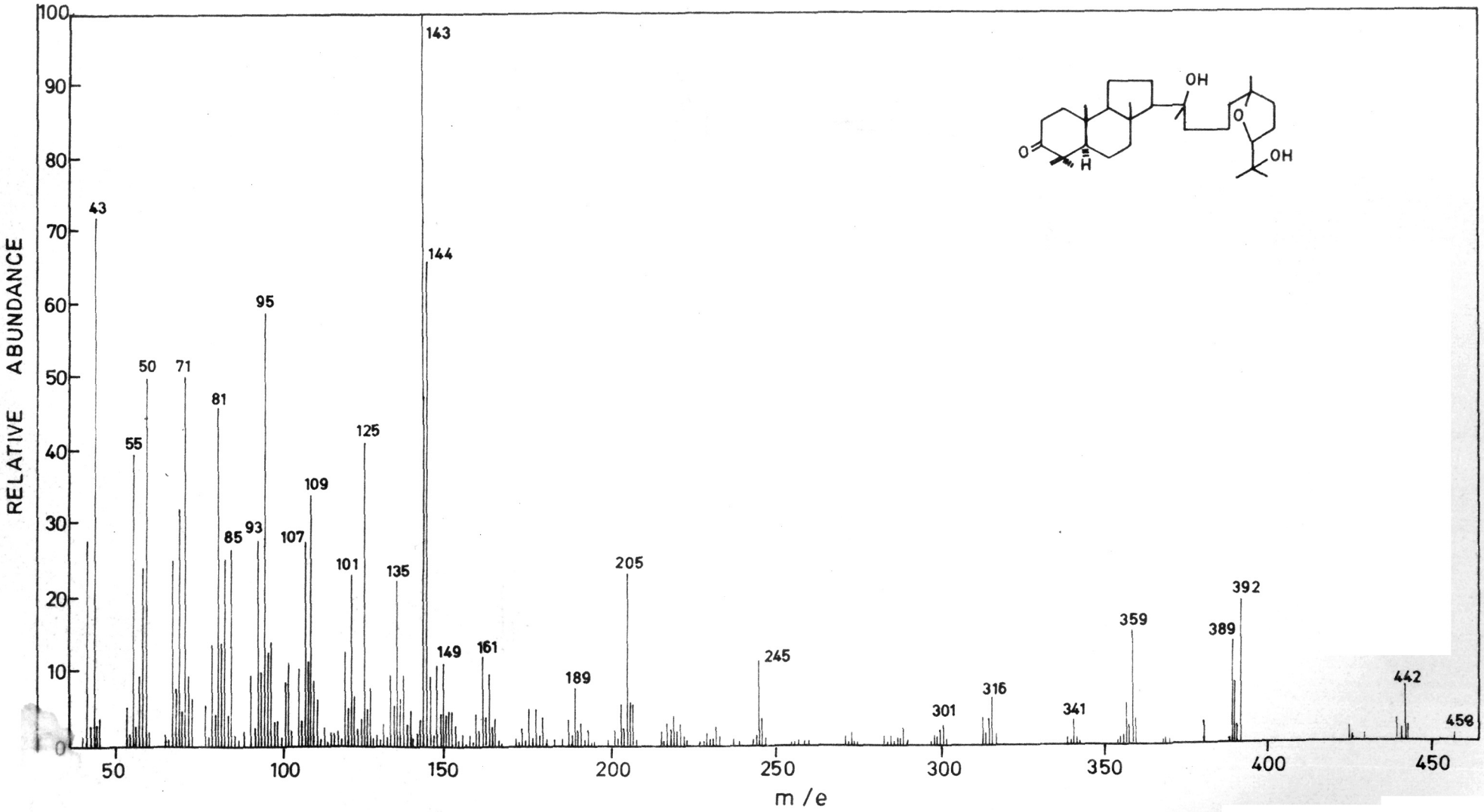


FIG. 19. MASS SPECTRUM OF COMPOUND G_2 XVII.

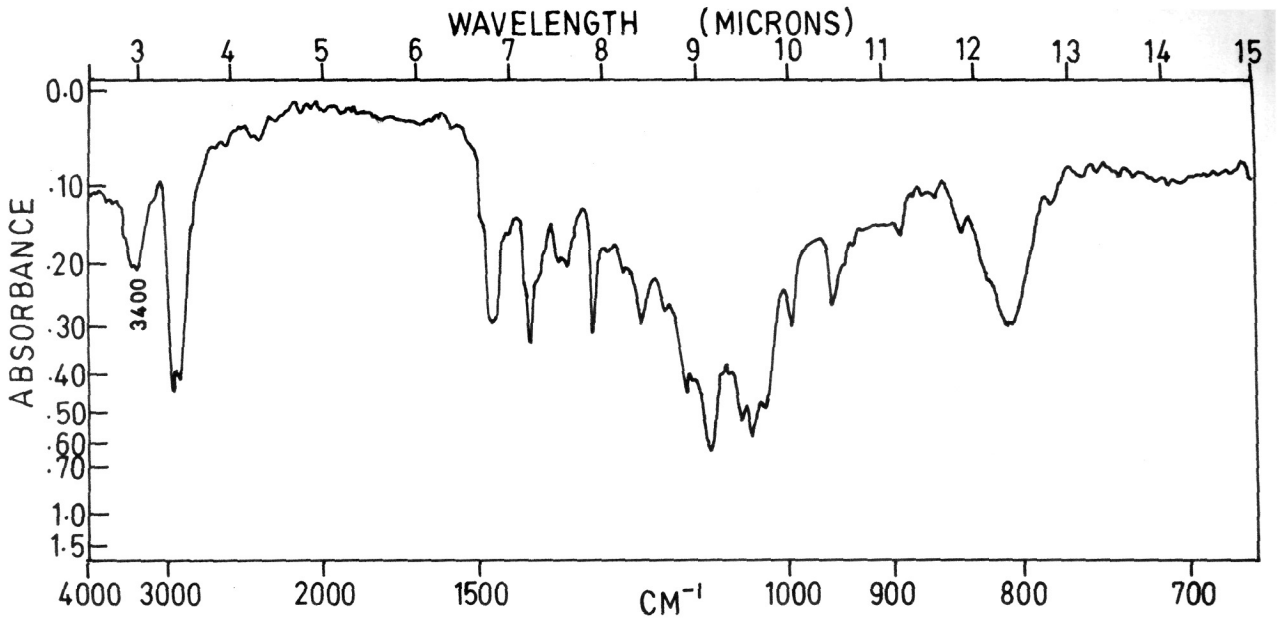


FIG. 20. IR SPECTRUM OF COMPOUND C_2.

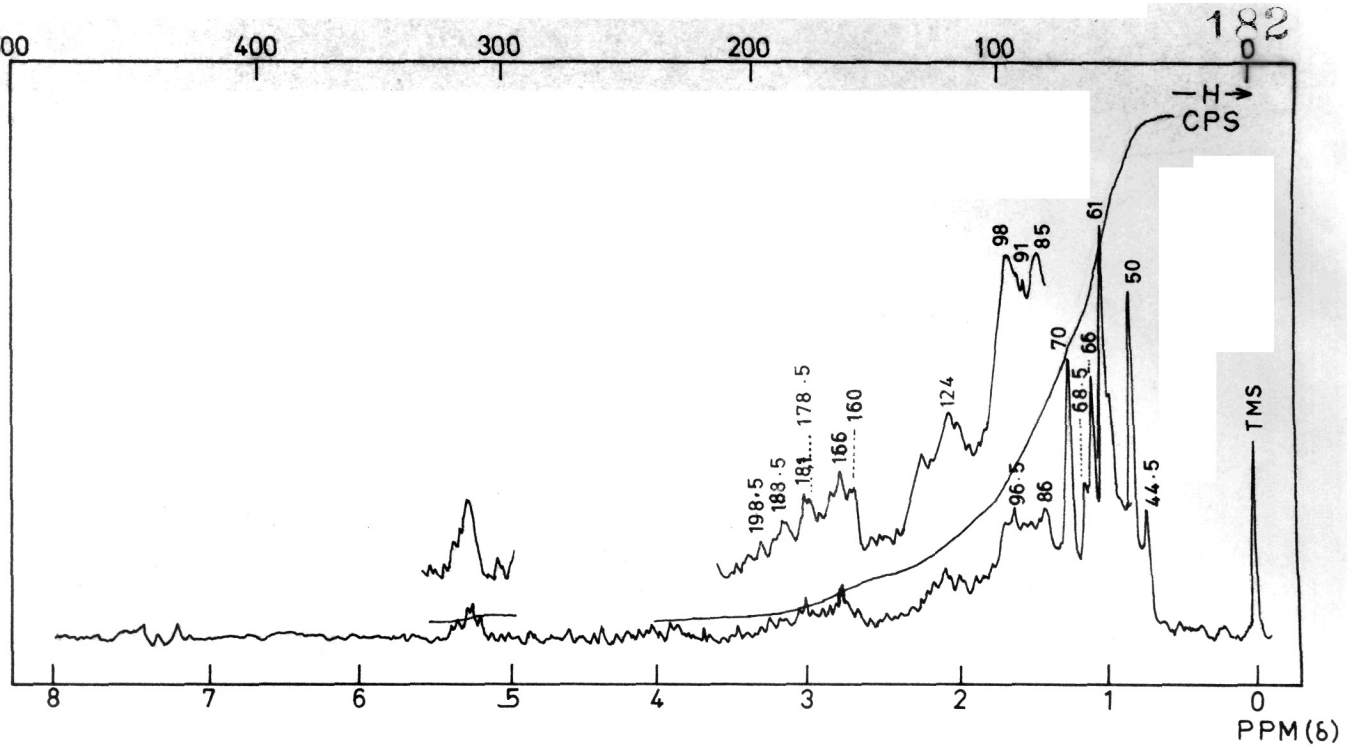


FIG. 21. PMR SPECTRUM OF COMPOUND E_1

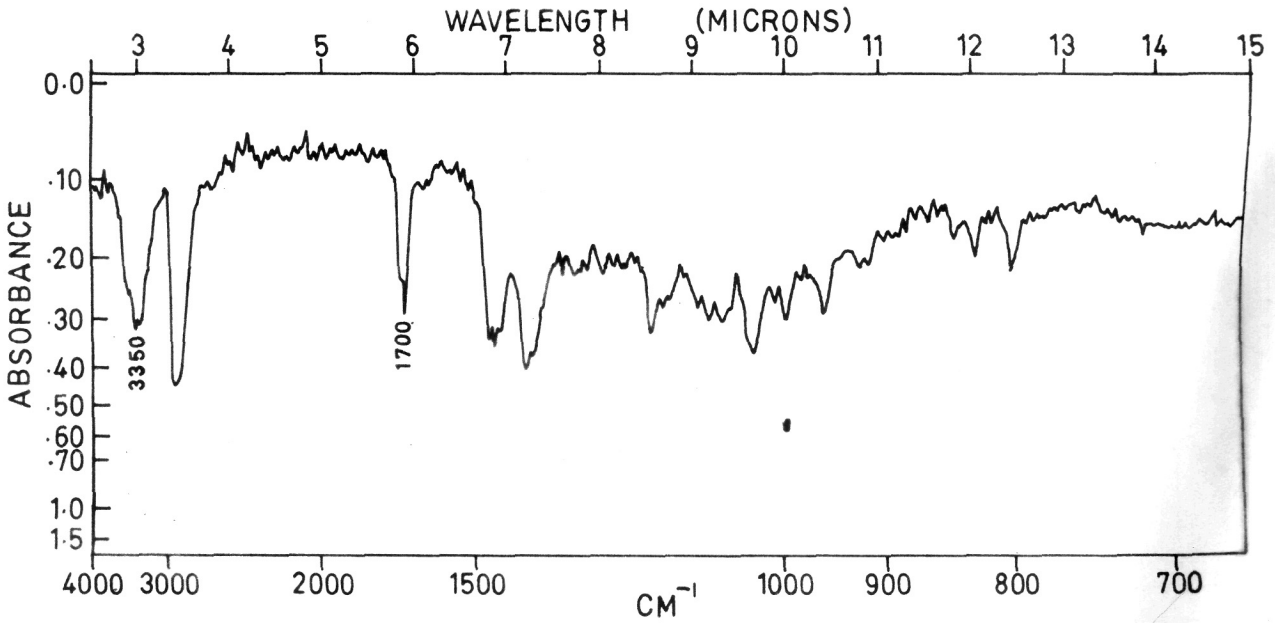


FIG. 22. IR SPECTRUM OF COMPOUND E_1

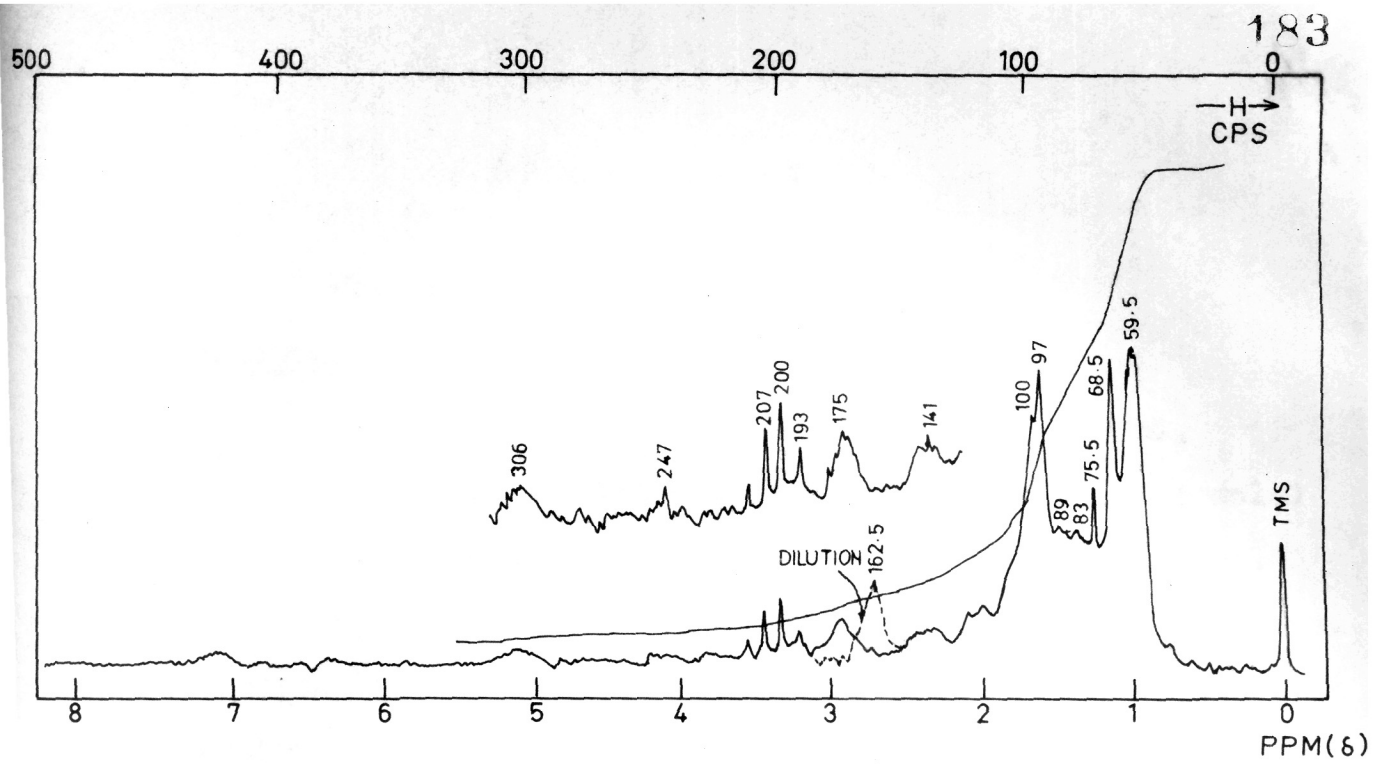


FIG. 23. PMR SPECTRUM OF COMPOUND G_1

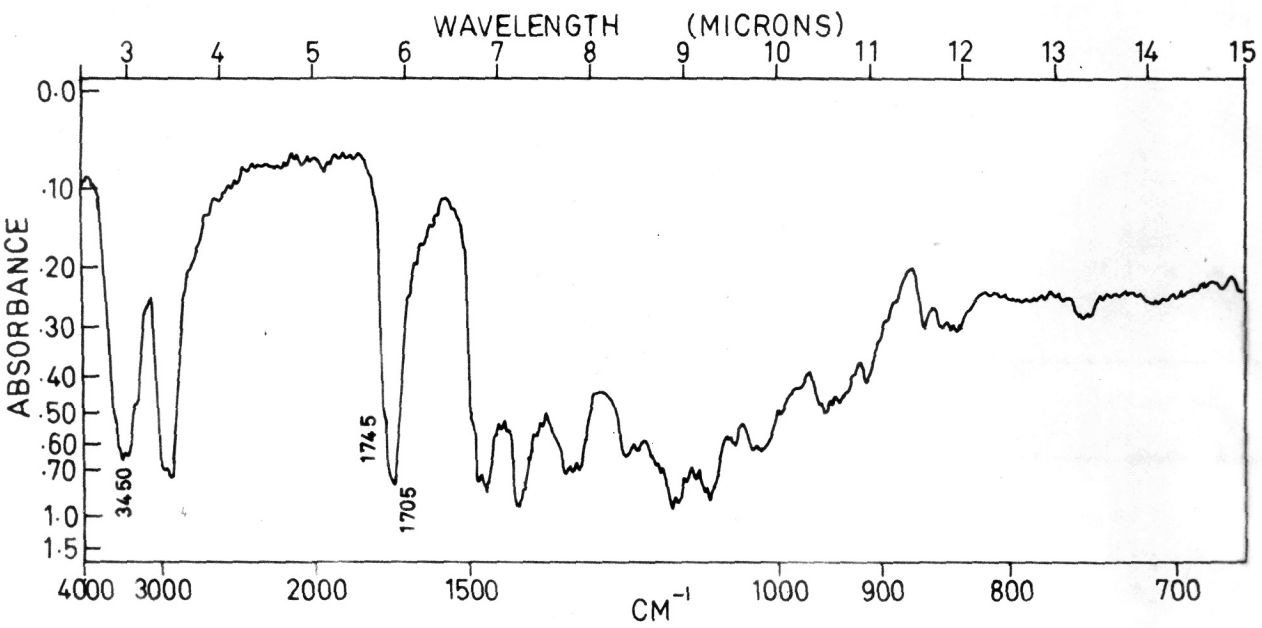


FIG. 24. IR SPECTRUM OF COMPOUND G_1

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

For general remarks, see page

Epoxymalabaricol (I) from malabaricol

Percamphoric acid[9] in benzene (0.125N, 36 ml, 0.0015 mole) was added to malabaricol (458 mg, 0.001 mole) in thiophene-free benzene (10 ml) at 5-10° with shaking. The reaction mixture was kept in fridge (~ 7°C) for 10 days. The reaction was monitored by TLC from time to time (solvent system: benzene + ethylacetate 75:25). It was washed with aqueous Na_2CO_3 (10%, 20 ml x 4), water (20 ml x 2), brine (20 ml) and dried. The solvent was stripped off to yield 445 mg (~ 95%) of solid material which showed two spots on TLC with R_f 0.35 and 0.44 of nearly same intensity. The mixture was separated over a column of silica gel.

CHROMATOGRAM

Substance: 400 mg

Adsorbent: 20 g SiO_2 gel/IIA

Column : 20 cm x 1.2 cm.

No.	Eluent	Ratio	Vol. (ml)	Eluate (g)	Remarks
1	Benzene	-	20 x5	0.0016	Rejected.
2	C_6H_6 + EtOAc	95:5	20x10	0.1438	Solid. Epoxymalabaricol m.p.140-43.
3	"	90:10	20x5	0.1037	Mixed fraction.
4	"	"	20x12	0.1116	Spot R_f 0.35
5	Methanol	-	50	0.0250	Base impurity.
			Total:	0.3857	(~ 96%).

Epoxymalabaricol (I) - Fraction 2 was crystallised from acetonitrile to furnish white crystalline compound (95 mg) m.p. 143-44°, $[\alpha]_D$ +24.6° (c, 1.0% $CHCl_3$). [Found: C, 76.15; H, 10.23. $C_{30}H_{50}O_4$ requires: C, 75.90; H, 10.62%]. It was found identical (m.m.p., IR, TLC, PMR) with the naturally occurring substance.

Fraction 4 - m.p. 126.5 - 127°, PMR spectrum: eight quaternary methyls (58, 58, 62, 62, 62 and 72 c/s), a 2H multiplet between 132.5 and 148 c/s ($-CH_2-\overset{\overset{O}{\|}}{C}-$); multiplet (2H) located between 218-234 c/s ($-\underset{\overset{|}{O}}{CH}-C$). IR spectrum: bands at 3800 cm^{-1} (OH), 1700 (C=O). The compound was not studied further.

Tris-nor lactone (VIII)

Jone's reagent[4] (prepared from 128 mg CrO_3, 0.07 ml con. H_2SO_4, 0.3 ml water) was added dropwise to a stirred solution of epoxymalabaricol (I, 94 mg, 0.0002 mole) in acetone (10 ml) at 8-10°C. Stirring was continued for another 1.5 hr. A few drops of methanol were added and stirred to destroy excess reagent and the reaction mixture was poured into cold water (25 ml) and extracted with ether (15 ml x 4) which was then washed with $NaHCO_3$ (15 ml), water (15 ml x 2), brine (20 ml) and dried. Flashing off the solvent gave 88 mg of solid m.p. 147-53°. It was crystallised from benzene:hexane to give 62 mg of

crystalline substance m.p. 155-56°. [Found: C, 75.16; H, 9.02. $C_{27}H_{42}O_4$ requires: C, 75.31; H, 9.83%].

RuO_4 oxidation[5] of malabaricol

CCl_4 solution of RuO_4 (prepared from 30 mg RuO_2, 240 mg $NaIO_4$) was added dropwise with stirring to malabaricol (100 mg) in acetone (10 ml). Black precipitate of RuO_2 was continuously formed during addition. After the addition $NaIO_4$ (50 mg dissolved in 1 ml water) was added while stirring to convert RuO_2 to RuO_4 (indicated by yellow coloration of reaction mixture). Stirring was continued for another 2 hr. The excess of reagent was destroyed by the addition of a few drops of isopropanol and stirred for 30 min. RuO_2 precipitate was filtered and washed with acetone. The filterate was diluted with water (20 ml) and extracted with ether (15 ml x 3), which was washed with water (20 ml), brine (20 ml) and dried. Removal of solvent gave a solid. Yield 75.3 mg (~ 78%). Its TLC on silica gel chromatoplate (solvent system: 25% EtOAc in C_6H_6) showed it to be a mixture of at least five compounds with one constituting more than half (R_f 0.68). The major compound was separated by preparative layer chromatography. Yield: 38 mg, m.p. 135-142°. Repeated crystallisation from pet. ether + benzene gave white crystalline compound 19 mg, m.p. 155-56°. [Found: C, 75.43; H, 9.31.

$C_{27}H_{42}O_4$ requires: C, 75.31; H, 9.83%]. It was found identical (m.m.p., IR, PMR, TLC) with tris-nor lactone (VIII) obtained by Jone's oxidation of epoxymalabaricol (I).

Malabaricanediol (IX) from malabaricol

To a solution of malabaricol (100 mg) in methanol (7 ml) was added $NaBH_4$[6] (30 mg). The reaction mixture was swirled from time to time and allowed to stand at room temp. (28°C) for 28 hr. The reaction was monitored by TLC from time to time (solvent system: 25% ethyl acetate in benzene). The reaction mixture was poured into water (5 ml) and extracted with ether (10 ml x 3), which was then treated with acetic acid (4-5 drops, to remove excess $NaBH_4$). The ether extract was then washed with water (10 ml x 2), brine (10 ml) and dried. Flashing off the solvent gave a gummy material (103 mg, $[\alpha]_D$ +23.03) which showed a single spot (R_F 0.45) on TLC. The product however did not crystallise from any solvent. It was found identical (IR, PMR, TLC, $[\alpha]_D$) with the naturally occurring substance (malabaricanediol, IX).

Epoxymalabaricanediol (X) from epoxymalabaricol (I)

To epoxymalabaricol (98.8 mg) in dioxan (2 ml) was added dropwise a solution of BH_4K[7] (43 mg) in aqueous dioxan (1:1, 2 ml). The reaction mixture was swirled from time to time (till a clear solution formed) and allowed to stand at

room temp. (28°C) for about 3 hr. The reaction was monitored by TLC from time to time (solvent system: 25% ethyl acetate in benzene), water (7 ml) was added to the reaction mixture and the excess $NaBH_4$ destroyed by the addition of acetic acid (4-5 drops). It was extracted with ether (10 ml x 3) which was then washed with water (10 ml x 2), brine (10 ml) and dried. Stripping off the solvent gave a solid material (99.9 mg) m.p. 130-32°. It was crystallised from acetonitrile to give shining crystals (70 mg) m.p. 134-135.5°, $[\alpha]_D$ +4.9° ($CHCl_3$). [Found: C, 75.83; H, 11.05. $C_{30}H_{52}O_4$ requires: C, 75.58; H, 11.0%]. It was found identical (m.m.p., TLC, IR, PMR, $[\alpha]_D$) with the naturally occurring epoxymalabaricanediol (X).

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