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

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C O N T E N T S

"STUDIES IN NATURAL PRODUCTS"

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SUMMARY

This thesis consists of a General Introduction dealing briefly with the biogenesis of terpenoids and ten chapters. Chapters I to VI are concerned with the chemistry of tetranortriterpenoids, a group of modified triterpenoids from the Meliaceae and Rutaceae families. The present state of knowledge of these compounds is reviewed in Chapter I. This is followed by discussions of the result of an investigation into the attempted conversion of the tetranortriterpenoid gedunin, to a simple decanortriterpenoid related to quassin (Chapter II). Although the desired compound was not obtained some success was achieved in the introduction of an oxygen in ring C (C-12). Chapter III describes the structural elucidation of two new 3,4-secotirucallane derivatives and 2'-hydroxyrohitukin from the bark of Guarea cedrata. A partial synthesis of the seco-acids from elemonic acid is also described. The structures of four complex tetranortriterpenoids from Trichilia dregeana form the subject matter of Chapter IV. This is followed by a discussion of an investigation into the tetranortriterpenoid constituents of the bark of Turrea floribunda. Two new compounds were isolated from this source (Chapter V). A reexamination of a rearrangement of mexicanolide is the subject matter of Chapter VI.

Chapter VII is concerned with the structure of roxburghilin and compound (13), both bis-amides of 2-aminopyrrolidine, from the leaves of Aglaia roxburghiana and Chapter VIII with the structure of a labdane dialdehyde from Afromomum daniellii (Zingiberaceae). Detailed consideration of spectroscopic properties of these compounds and correlation with synthetic derivatives led to the structures indicated.

Three sesquiterpenoid lactones, a guaianolide and two germacranolides from Vicoa indica form the subject matter of Chapter IX. Detailed consideration of the spectroscopic properties of these compounds led to biogenetically acceptable structures. The final details of conformation and stereochemistry remain to be determined.

The last chapter deals with neolignans from Myristica fragrans. The structures were assigned by ^{1}H and ^{13}C n.m.r. and those of the phenyl coumarane type compounds were confirmed by partial synthesis from isoeugenol.

INTRODUCTION

Natural product chemistry has continued to grow rapidly since the middle of this century. The potential use of natural compounds and their biogenetic relationship make the study of natural products and of terpenoids in particular, a subject of fascination for organic chemists. Structural elucidation, with its inherent tendency to diverge, has provided many interesting inroads into the chemistry of carbocyclic compounds in general. Despite the vituperative assertions of Cookson,[5] this type of research will continue to be pursued with undiminished vigour owing to Nature's unique ability to construct exotic structures. The wealth of information derived from studying the diverse structural types and biosynthetic pathways has played a significant role in the development of general chemical concepts.[4]

In the terpenoid field, findings led to the generalization known as the 'Isoprene rule', first proposed by Wallach in 1887 and later developed by Robinson,[6] which states that terpenoids have a carbon skeleton formed by isoprene units linked head to tail. This was later modified by Ruzicka[7] who proposed a 'Biogenetic Isoprene Rule' to account for a number of substances whose skeleta cannot be constructed from intact isoprene units. The 'Biogenetic Isoprene Rule' proposed that they can arise from isoprenoid precursors by removal or addition of one or more fragments or by molecular rearrangements or by a combination of these processes.

To attempt an exhaustive classification of natural products which covers almost all types of organic molecules would be beyond the scope of this work. It is sufficient for our purpose to say that classifications are generally based on either one or a combination of the following criteria. (a) Molecular skeleton[1] (b) Physiological activity (c) Taxonomy[2] and (d) Biogenesis.[3,15]

Terpenoid biosynthesis.[8,15] The recognition of acetic acid, in the form of acetyl coenzyme A, as the fundamental biogenetic progenitor of all terpenoids is now well-established, and a major breakthrough in the search of the proposed C_5 precursor was provided by the discovery of mevalonic acid (3)[9] in 1956. It was found that the labelled R-isomer is incorporated quantitatively into cholesterol on incubation with cell free rat liver homogenate. Under anaerobic conditions 2-^{14}C-mevalonic acid is converted to squalene (10). In all cases it was observed that C-1 is lost as CO_2. Decarboxylation is known to occur prior to the formation of the terpenoid chain and a discrete five-carbon unit is formed.

The biosynthesis of mevalonate from ^{14}C-acetate has been the subject of many biochemical studies.[10] The current view can be summarised as follows (Scheme 1). Mevalonic acid (3) is derived from S-3-hydroxy-3-methylglutaryl coenzyme A (2) by NADPH reduction. (2) arises by an aldol condensation of acetoacetyl coenzyme A (1) with acetyl coenzyme A. The formation of isopentenyl pyrophosphate (IPP) (4) and the isomeric dimethyl allyl pyrophosphate (DMAPP) (5) from mevalonic acid (3) can be visualised as in Scheme 2. The subsequent conversion of (4) and (5) to acyclic terpenoid precursors is represented by Scheme 3. It is noteworthy that most natural acyclic polyisoprenoids are 'all trans'.[11] For the purpose of this work it would be pertinent to discuss briefly, only the accepted biogenesis of the triterpenoids in general and the diterpenoids with particular reference to labdane.

The cyclisation of geranylgeraniol to diterpenoids probably conforms with the stereochemical postulates of Eschenmoser et al.[12] These were originally applied to triterpenoids, but in principle can be extrapolated

to the other polyisop renoids. The main conclusions derivable from Eschenmoser's work are:

i) The acyclic precursor is folded at the enzyme surface, into a specific conformation.

ii) Concerted cyclisation occurs by trans-planar addition to the double bonds.

iii) All subsequent rearrangements and/or eliminations proceed in accordance with optimal stereoelectronic requirements, i.e. the affected groups are trans-antiparallel. Thus cyclisation of geranylgeraniol or the isomer geranyllinalool can occur to form the antipodal bicyclic alcohols (8) or (9) (Scheme 4). The naturally occurring labdanes are based on the enantiomeric bicyclic alcohols (8) and (9) with a trans-anti backbone.

Squalene (10), the progenitor of triterpenes and steroids, is derived from two farnesyl pyrophosphate (11) units joined in the unusual head to head fashion.[13,10] The process is believed to occur via the intermediate presqualene alcohol (12)[14] and its stereochemistry has been elucidated by tracer studies. A reasonable mechanism is shown in Scheme 5. The polycyclic structures formed from squalene can be rationalized in terms of the ways in which squalene may be folded on the enzyme surface. For instance, the formation of euphol (13) (or tirucallol), the putative precursor of the tetranortriterpenoids, involves cyclisation of squalene in the chair-chair-chair-boat conformation (14) (see Scheme 6). The corresponding chair-boat-chair-boat folding leads to lanosterol (15) and hence the steroids. Cyclisation is usually initiated by acid opening of squalene monoepoxide (14). Only the (3S)-enantiomer is used by a wide variety of biological systems.[11]

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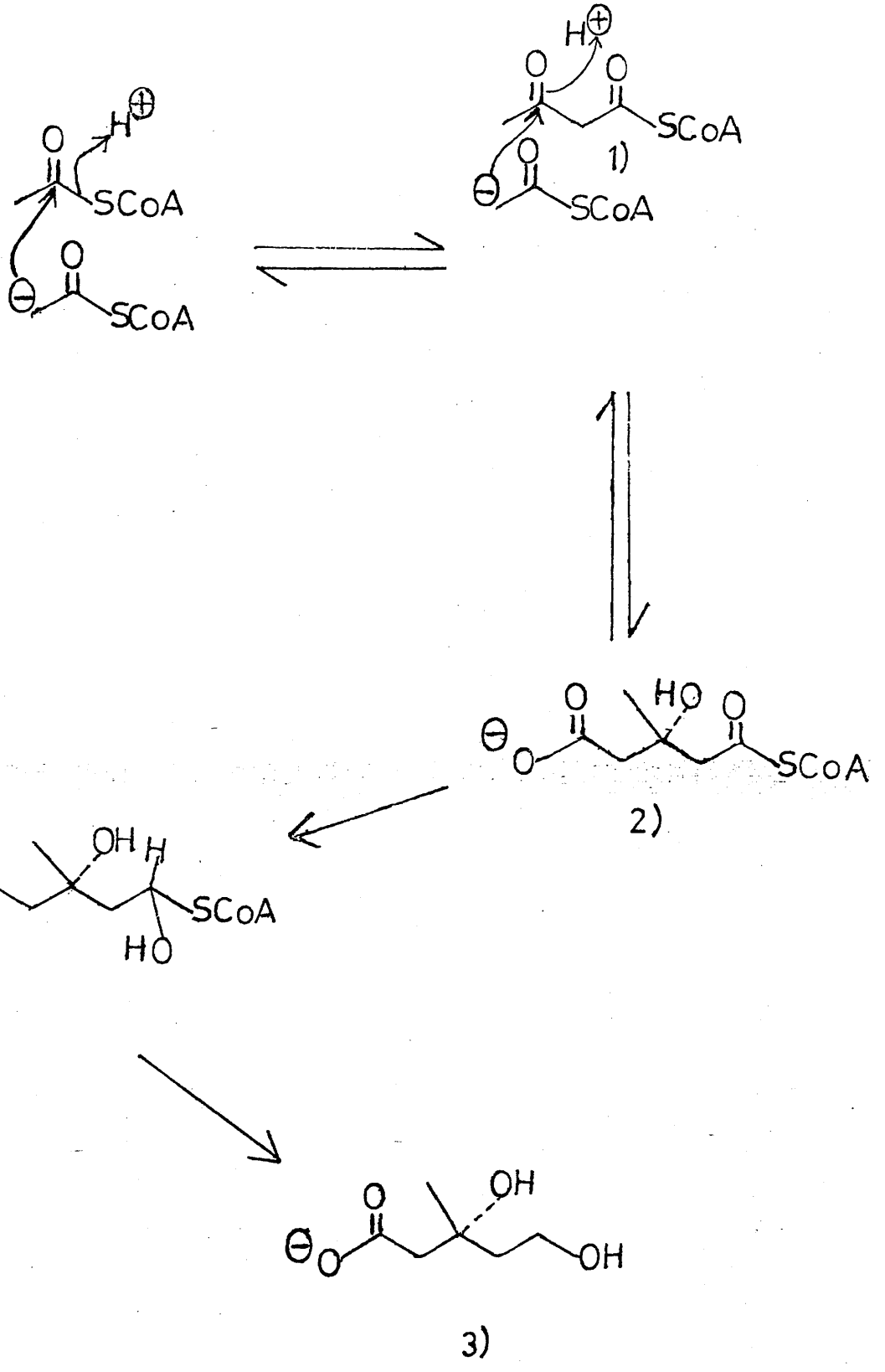
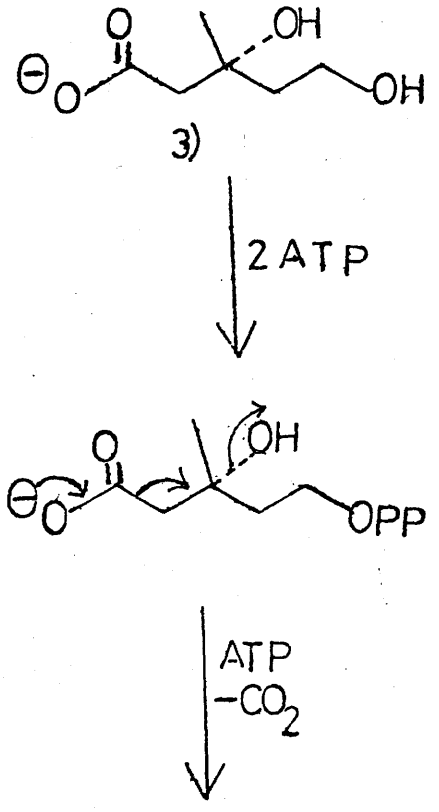
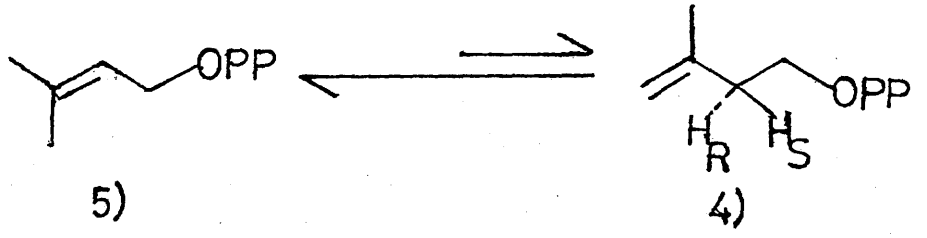
Scheme 1

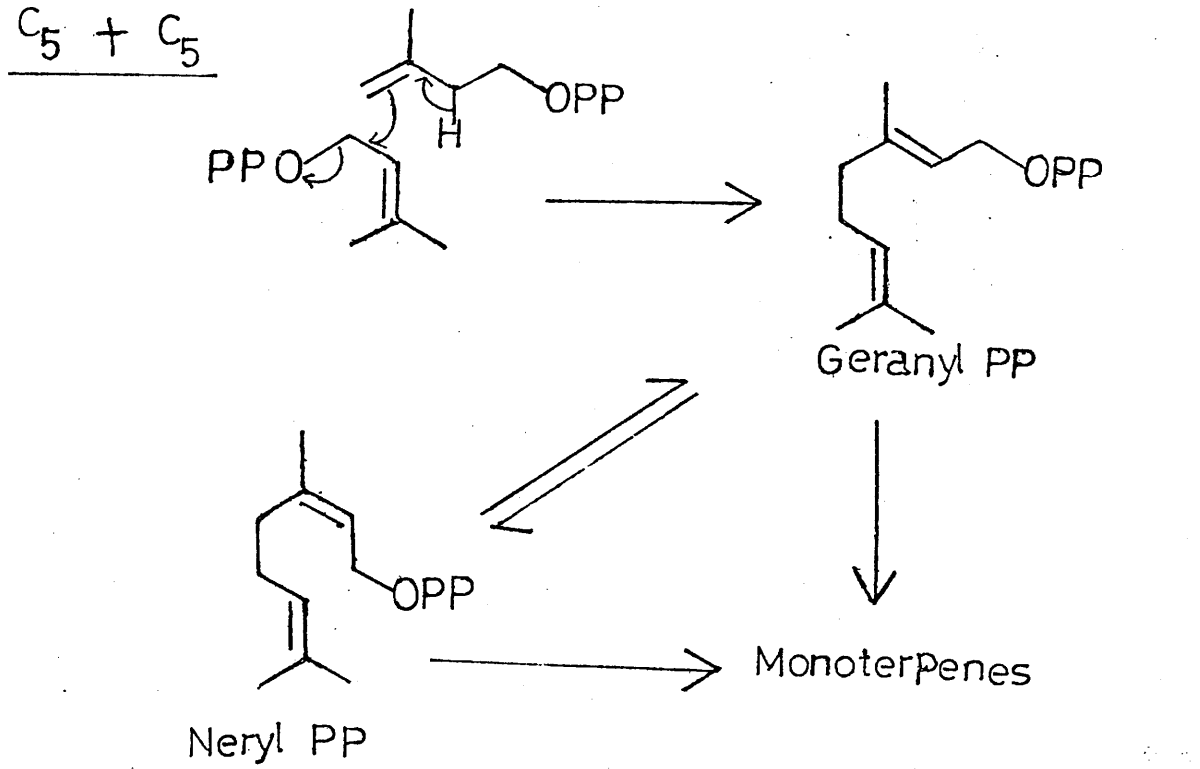


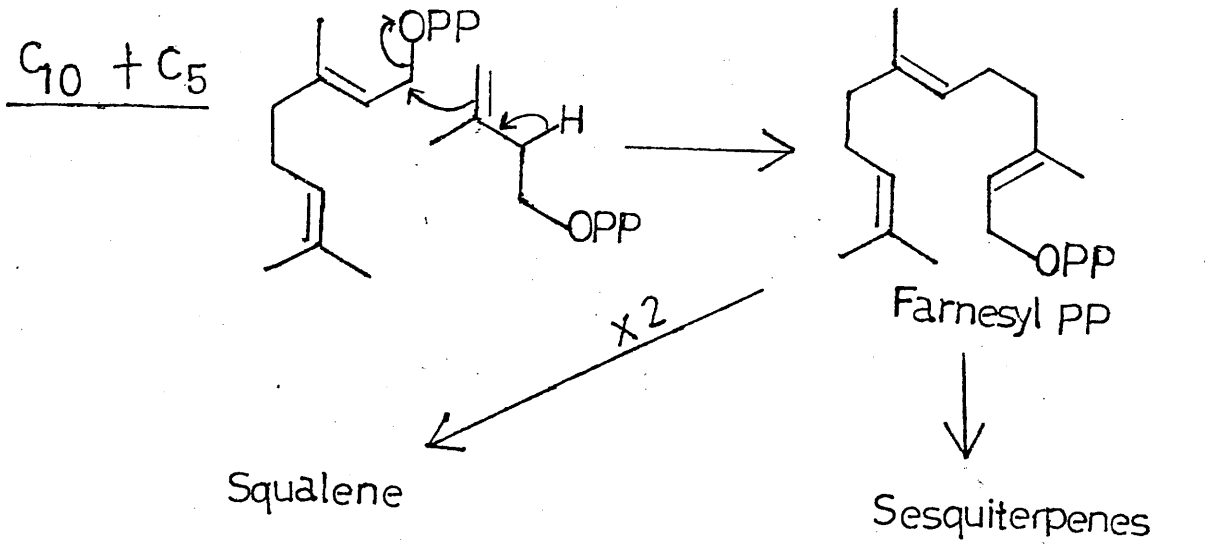
Scheme 2

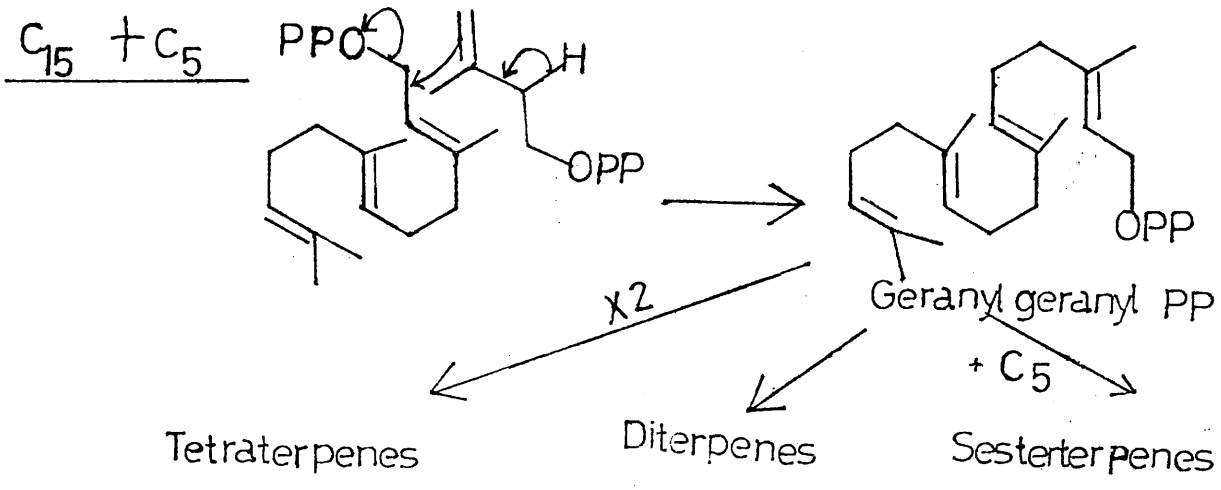




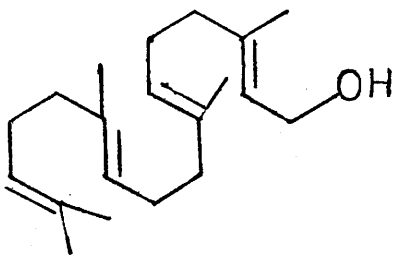
Scheme 3


C5 + C5
OPP
H
PPO
OPP
Geranyl PP
OPP
Neryl PP
Monoterpenes

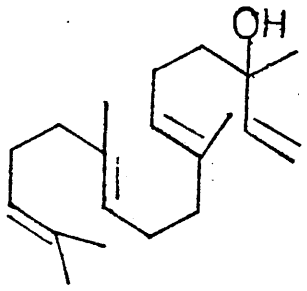

C10 + C5
OPP
H
OPP
OPP
Farnesyl PP
x2
Squalene
Sesquiterpenes


C15 + C5
PPO
H
OPP
OPP
Geranyl geranyl PP
x2
+ C5
Tetraterpenes
Diterpenes
Sesterterpenes

Scheme 4



6)



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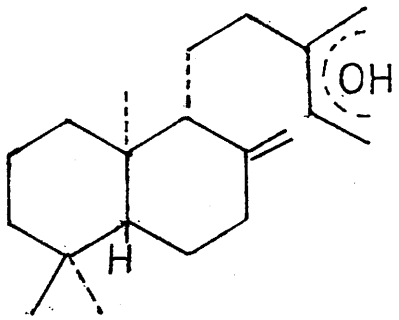

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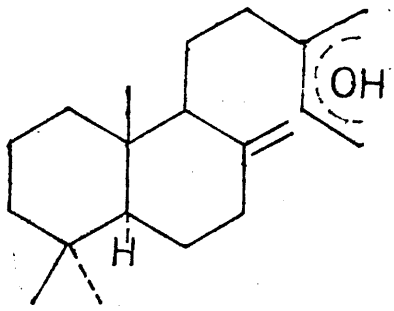
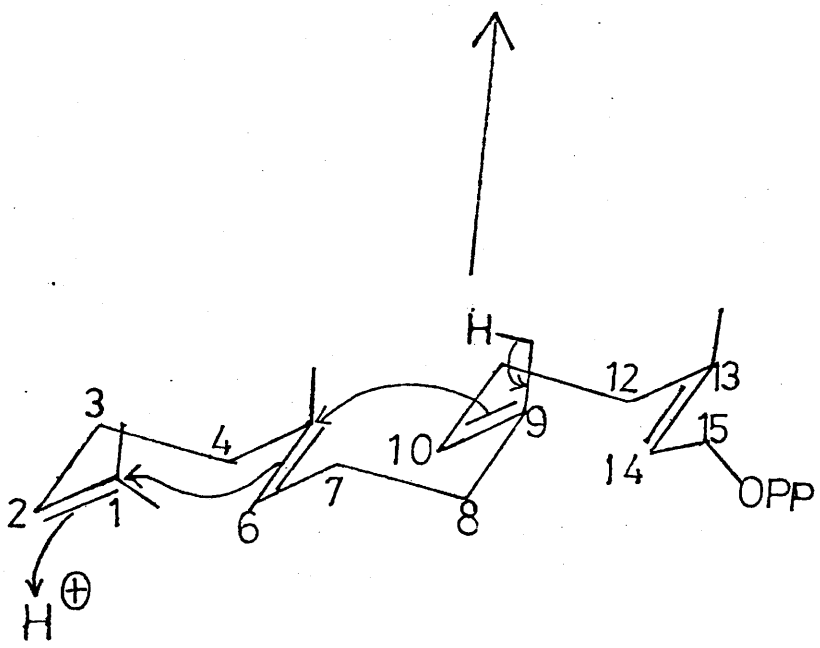
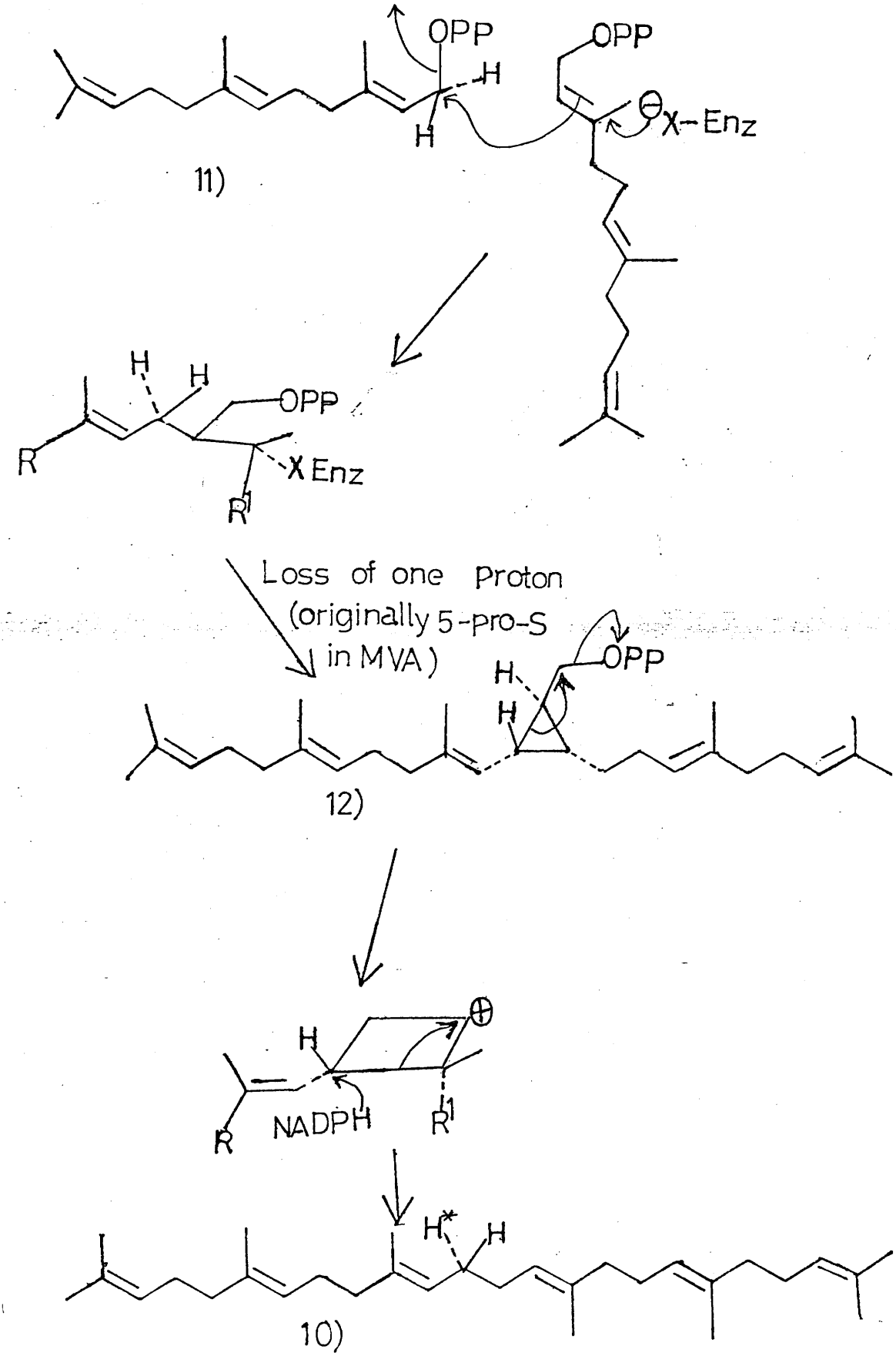


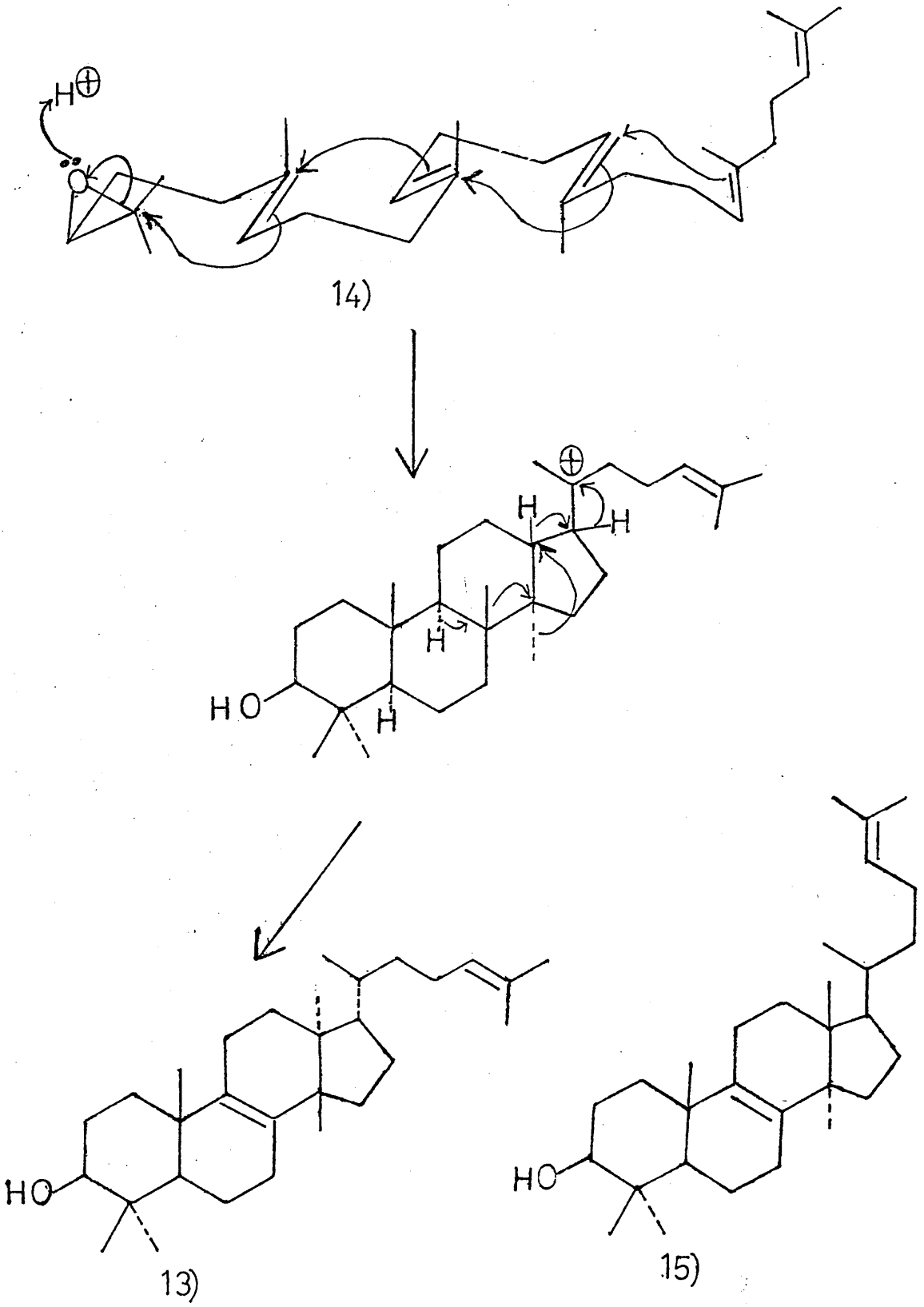
8)



Scheme 5


OPP
OPP
H
H
X–Enz
11)
H
H
OPP
R
X Enz
R'
Loss of one Proton
(originally 5-pro-S
in MVA)
H
H
OPP
12)
H
NADPH
R'
R
H*
H
10)

Scheme 6



CHAPTER I

REVIEW OF TETRANORTRITERPENOIDS

The tetranortriterpenoids or limonoids form a class of diverse structural types based on a C_{26} carbon skeleton containing a β-substituted furan. They are found mainly in the Rutaceae, Cneoraceae and Meliaceae[1,2] and some have interesting biological activity. Investigations in this field were stimulated by the elucidation[3] of the constitution and configuration of limonin (1) in 1960.

By 1964 it had become apparent[4] that quassinoids, a group of C_{19} and C_{20} compounds related to quassin (2) whose structure was established[5] in 1962, probably share a biosynthetic pathway with limonin and its relatives. The first direct evidence for this hypothesis came in 1966 from the incorporation[6] of labelled mevalonate into glaucarubinone (3) and glaucarubolone (4).

A biogenetic derivation of limonoids from euphol (5) (or tirucallol) was first proposed by Arigoni, Barton, Corey, Jeger, and their collaborators, who suggested[7] that limonoids are formed from the hypothetical apoeuphol intermediate (6) which arises from euphol by a skeletal rearrangement, during which a methyl group migrates from C-14 to C-8 and oxygen is introduced at C-7. Oxygenation of the side chain may precede or follow the apoeuphol rearrangement, since both melianone (7)[8] and grandiofoliolenone (8)[9] have been isolated. However, oxidative modification eventually results in removal of the four terminal side chain carbon atoms and formation of a β-substituted furan ring. The simple tetranortriterpenoid (9) thus formed can undergo further oxidations, Baeyer-Villiger ring cleavages and rearrangement to produce the wide variety of structural types which have been reported. Further degradation of (9) can lead to pentanortriterpenoids e.g. (10) found in the Cneoraceae[10] and quassinoids e.g. (2) found in the Simaroubaceae[1,11] (see Scheme 1). The subject divides naturally into three major areas: tetranortriterpenoids,

C_{26} compounds related to limonin (1); pentanortriterpenoids, C_{25} compounds related to cneorin C (68); and decanortriterpenoids, C_{19} or C_{20} compounds related to quassin (2). Several reviews dealing with certain aspects of the subject have appeared: Limonoids in the Citrus Species,[12] Limonoid Bitter Principles,[13] Simaroubaceous Bitter Principles[14] and Beiträge zur Biologie der Pflanzen.[75]

This short review is intended to give a broad picture of the present state of knowledge in these series. For convenience these compounds will be considered in groups according to the extent of ring cleavage. It is pertinent to discuss beforehand some of the C_{30} tirucallol and apotirucallol derivatives which often co-occur with the tetranortriterpenoids and which appear the likely forerunners.

(1) C_{30} Precursors.- Turreanthin (11)[15] is one example of the group of compounds with a pattern of side chain oxygenation which may represent an intermediate stage between tirucallol and the furan ring of tetranortriterpenoids. The isolation of (12),[16] and several other apotirucallol derivatives, with an intact side chain suggests that skeletal rearrangement precedes furan formation. Halsall and his colleagues[17] demonstrated the possible intermediacy of these C_{30} compounds in the biogenesis of tetranortriterpenoids by the in vitro conversion of turreanthin into the simple limonoid (13) (see Scheme 2). The 7α,8α-epoxide (14) is smoothly converted, by Lewis acid, into the apo-derivative (15) with the desired oxygen substituent at C-7.

(2) Intact C_{26} Skeleton.- At the stage of the simplest limonoid (13), further oxidations can occur in ring D giving rise to a variety of compounds with oxygen functions at carbons 14, 15, 16[22] and even 17. Epoxidation of the ring D double bond as in trichilenone (16)[18] is sometimes accompanied by a ketonic carbonyl at C-16 as in nimbinin (17).[19] The isolation of azadiradione (18)[20] and other similar compounds (e.g. 17β-hydroxyazadiradione

(21)[21]) suggests that functionalization of the C-16 occurs prior to epoxidation of the double bond. Other oxidations can occur in rings A, B and C at carbons 1, 2, 6, 11 and 12. Examples include (19) and (20)[23], vepinin (22)[24] with an ether between C-7 and C-15, and the highly oxygenated compounds sendanin (23)[25] from Melia azedarach, amoorstatin (24),[26] 12α-hydroxyamoorstatin (25)[27] and the related aphanastatin (26),[26b] from Aphanamixis grandifolia. These aphanamixis compounds are of considerable interest because of their antitumour activity. The presence of a hydroxyl group at C-6 may lead to the formation of an ether bridge with the 4α methyl group, as in nimbidin (28)[28] and vilasinin 1,3-diacetate (27).[16]

(3) Ring D Cleaved.- The next step in the elaboration of the tetranortriterpenoids skeleton leads to the formation of the characteristic ring D epoxy lactone by biochemical Baeyer-Villiger oxidation of a 16-oxo-precursor. Two of the most abundant tetranortriterpenoids gedunin (29)[29] and khivorin (30)[30] belong to this group. Both have been prepared in vitro by Baeyer-Villiger oxidation of the supposed precursors nimbinin (17) and khayanthone (31)[31,32] respectively. They often co-occur with complex ring B cleaved tetranortriterpenoids. It is therefore reasonable that compounds of this type represent an intermediate stage in their biosynthesis.

(4) Ring B Cleaved.- Many members of this group have also undergone cleavage of ring D. The typical ring B cleaved system exemplified by andirobin (32)[31] can arise by formal Baeyer-Villiger oxidation of a 7-oxo-compound followed by hydrolytic opening of the lactone and dehydration of the tertiary hydroxyl group to give the 8,30 exomethylene group. The corresponding diene lactone deoxyandirobin (33)[32] has also been isolated. Methyl angolensate (34)[33] has the interesting 1,14 ether which presumably arises by addition of a 1α-hydroxyl group to the α,β-unsaturated ring D

lactone. Both andirobin and methyl angolensate have been prepared *in vitro* by partial synthesis[34] from khivorin.

The first examples of simple ring B cleaved tetranortriterpenoids with an intact ring D are toonacilin (35) and its 6-acetoxy derivative (36) from *Toona ciliata*. They are of special interest because of their potent antifeedant activity against the Mexican bean beetle.[35]

This group of tetranortriterpenoids is unique in that the initial cleavage of ring B can be obscured by subsequent carbon-carbon bond formation between C-2 and C-30 to give the bicyclononane ring system as in mexicanolide (37).[34,36] The first representative of the latter group is swietenine (38) from *Swietenia macrophylla*.[37] The residual double bond is also found at 8,14 as in mexicanolide (37) and swietenolide (39) and at 14,15 as in carapin.[38] Increasing oxidation level in this series is represented by 2α-hydroxyangustdienolide (40)[39] and xyloccensin A (41)[40] and leads to the highly complex compounds like utilin (42)[41] and bussein (43).[42] Two new features apparent in these structures are (a) the formation of a new carbocyclic ring between the 4α-methyl group and C-1; and (b) the introduction of the orthoacetate at 1, 8 and 9 or 8, 9 and 14. The reaction of an unactivated methyl group and a ketonic carbonyl is unusual and finds analogy in photochemistry. The occurrence of compounds of this type is so far restricted to *Entandrophragma* and *Chukrasia* species.[43]

(5) *Ring A Cleaved*.- Compounds in this group have the characteristic ring D epoxylactone system and most came from citrus species.[12] This group is of historic significance, since the development of the chemistry of the tetranortriterpenoid dates from the elucidation of the structure of limonin.[3] In limonin, the initial ring cleavage is obscured by subsequent reactions. The simple Baeyer-Villiger cleavage of ring A is more obvious in obacunone (44)[44] and nomilin (45)[45]. Harrisonin (46)[46]

from Harrisonii abyssinica has an interesting hemiacetal function at C-7. Nomilinic acid (47)[47] represents the opened form of the ring A ε-lactone and may be regarded as a precursor of the C-19 oxidised derivatives inchangin (48)[48] and limonin (1). Veprisone (49)[49] is a simpler example of the C-1, C-4 ether which is probably formed by addition of the C-4 tertiary hydroxyl group to the unsaturated ester [or lactone as in limonin (1)]. Alternatively, dehydration and epoxidation leads to spathelin (50)[50].

(6) Ring C Cleaved.- This group of compounds is restricted to Melia azedarach and Azadirachta indica. Nimbin (51),[51] nimbolide (52)[52] and salaninin (53)[53] illustrate the common features. Sendanal (54)[54] isolated from M. azedarach, has the appropriate functionality for transformation into the above compounds. Ochinal (55)[55] is biogenetically interesting since it represents simple ring C cleavage of a 12-hydroxy precursor (e.g. sendanal). The most interesting and most complex member of this group is azadirachtin (56)[56] a powerful locust antifeedant.

(7) Rings A and B Cleaved.- The first member of this interesting group is prieurianin (57)[57] from Trichilia prieuriana. Other members of this group, isolated from Trichilia and Guarea species have also been reported.[58]

(8) Modified Side Chains.- A growing number of tetranortriterpenoids with modification of the usual furan ring have appeared recently. These include the isomeric γ-hydroxybutenolides (58) and (59),[59] the methoxybutenolide (60),[69] the butenolide (61)[61] and the γ-lactone (62).[62] It is uncertain whether all these compounds are genuine natural products or artefacts formed by the action of light and oxygen on the furan ring. Photooxidation of several tetranortriterpenoids is known to give the corresponding γ-hydroxybutenolides.[63]

(9) Pentanortriterpenoids.- This is a fascinating group of highly cleaved C_{25} terpenoids which has been isolated from the Cneoraceae.[76] Initially these compounds e.g. cneorin C (73) were considered to be sesterterpenoids, but with the structural elucidation of cneorin B (74)[77] the biogenetic relationship with tetranortriterpenoids became more apparent. More representatives of this group of compounds are beginning to emerge. Further structural variants are represented by tricoccins S_4 (75), S_{33} (76),[69] S_{14} (77) and R_9 (78). The latter was transformed into cneorin B_{III} (79). The carbon framework (80) helps to illustrate the relationship between this group and the tetranortriterpenoids; and it has now been proposed[77] that the cneorins and related compounds are pentanortriterpenoids with the same biogenetic origins as the tetranortriterpenoids with which they co-occur.

(10) Decanortriterpenoids, C_{20} Compounds related to Quassin.- Further degradation of an apo-tirucallol precursor leads to quassin (2) and related C_{20} and C_{19} compounds. Simarolide (72),[74] the corresponding ring A diosphenol methyl ether[74] and soulameolide (63), recently isolated from Soulamea tomentosa,[64] represent an intermediate stage on this pathway. There has been a recent revival of interest in quassinoids because of their biological activity. Undulatone (64) from Hannoa undulata,[65] 6α-tigloyl chapparinone (65) from Ailanthus integrifolia[66] and 6α-senecioyl chapparinone (66) from Simaba multiflora[66] have antileukemic activity which is due in part to the presence of the 6α-oxygen function. Other active compounds include bruceoside A (67) and bruceoside B (68) from the seeds of Brucea javanica.[68] The structural requirements for antineoplastic activity have been disclosed.[68]

Quassinoids have a clear structural relationship with merogedunin (70) and it is tempting to view (70) as a convenient starting material for partial synthesis. Our efforts in this area are described in the sequel.

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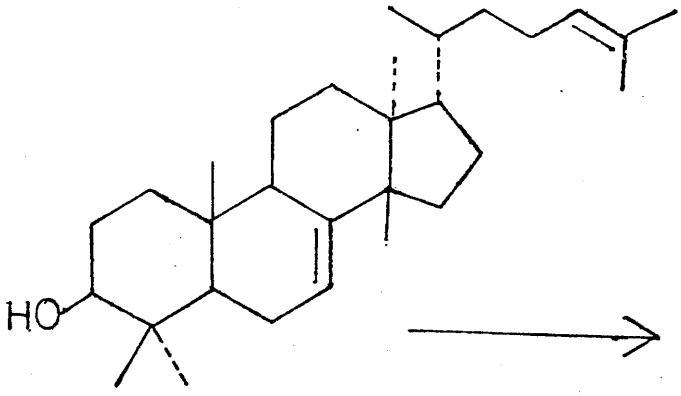
Scheme 1



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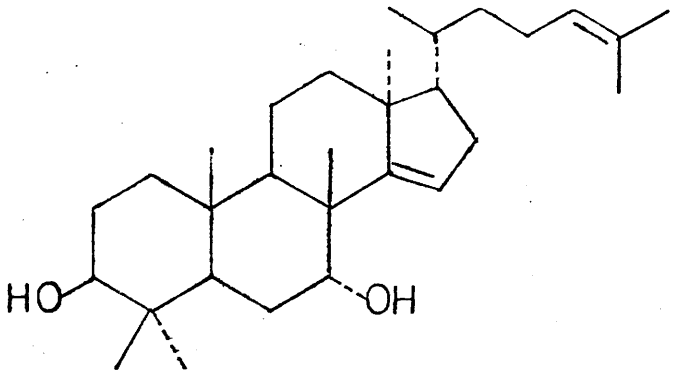
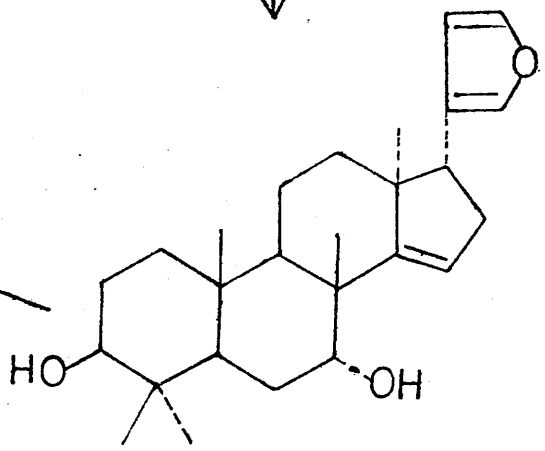


(6)

Cleavage of rings
A, B, C and D



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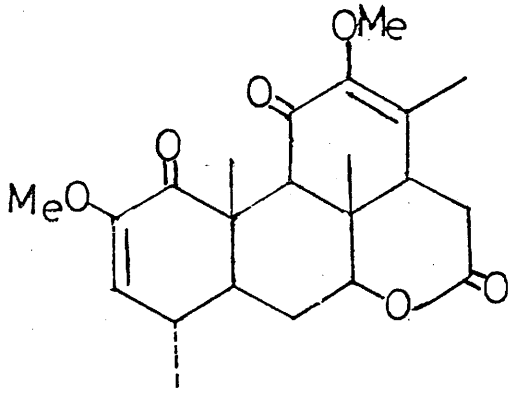

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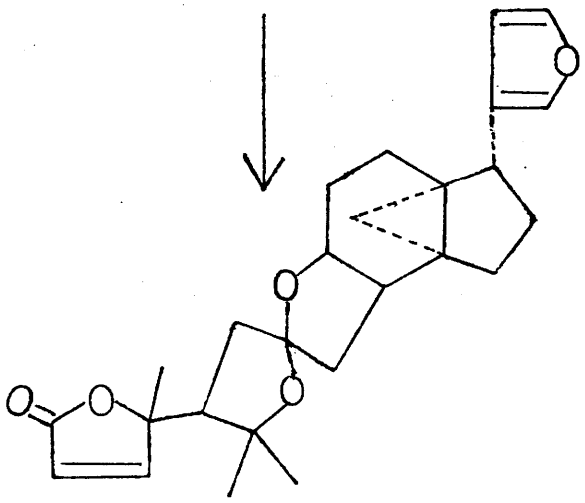

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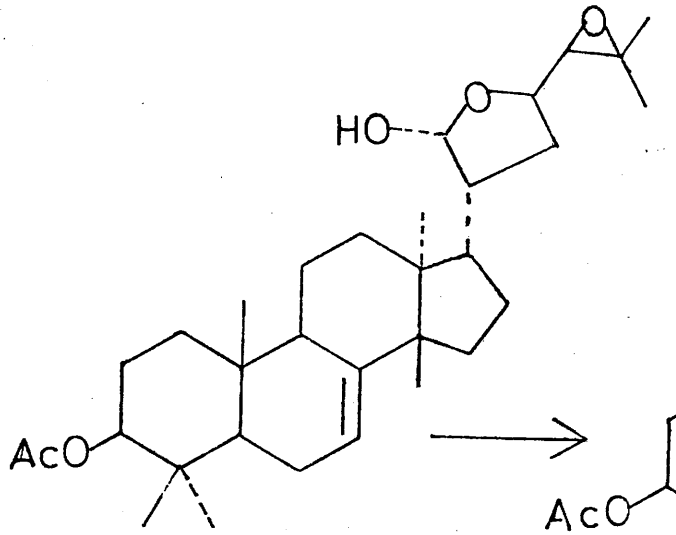
Scheme 2



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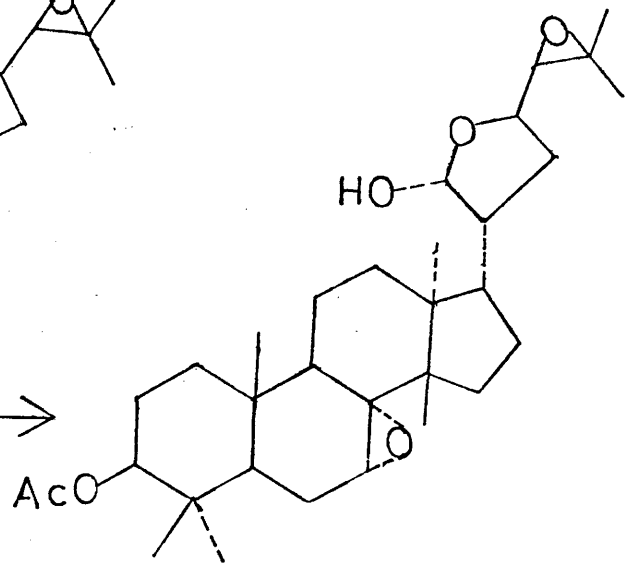

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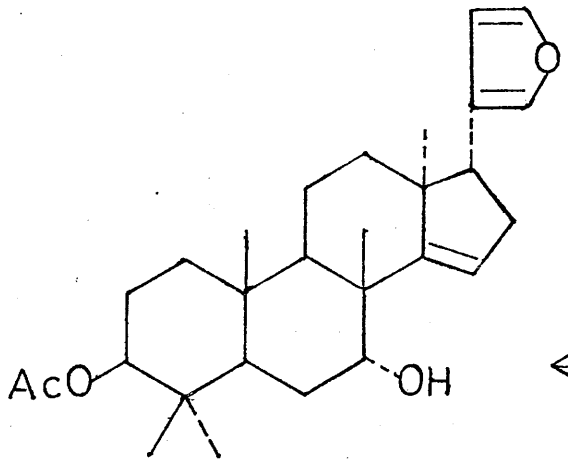

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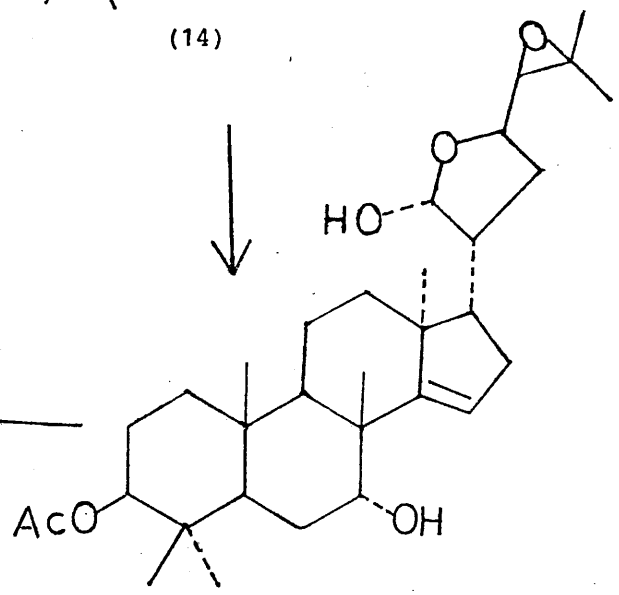

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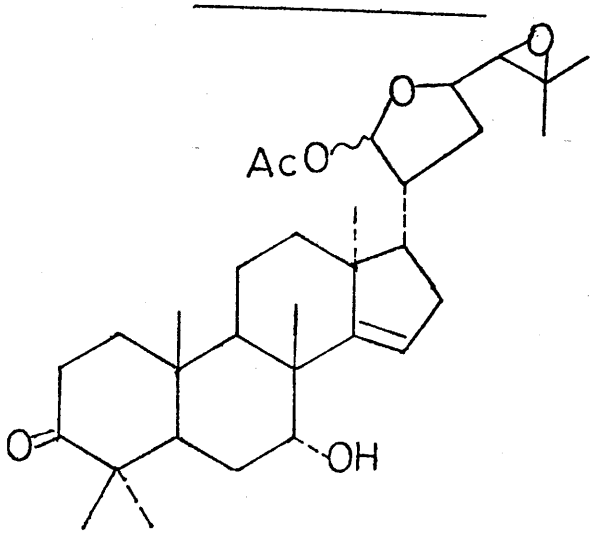

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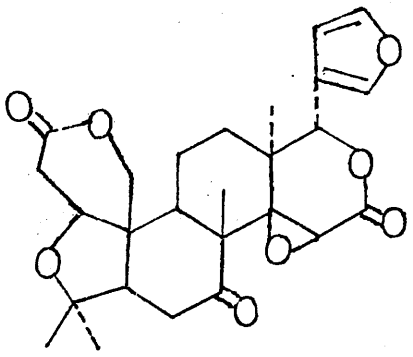
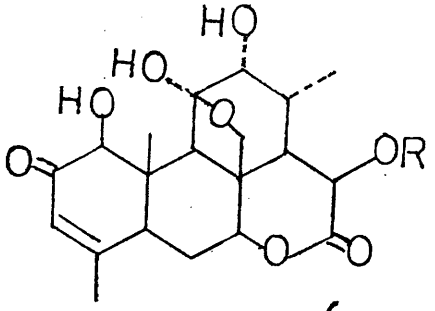
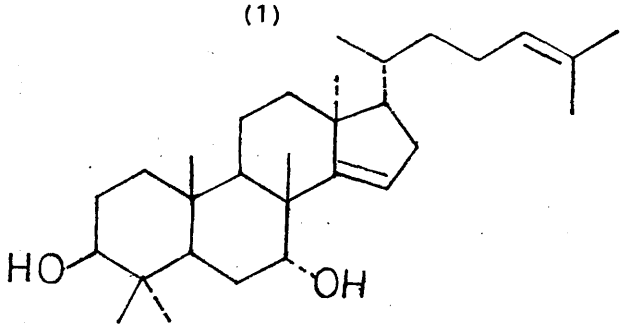


(1)



3) R = OC(OH)(C)C

4) R = H



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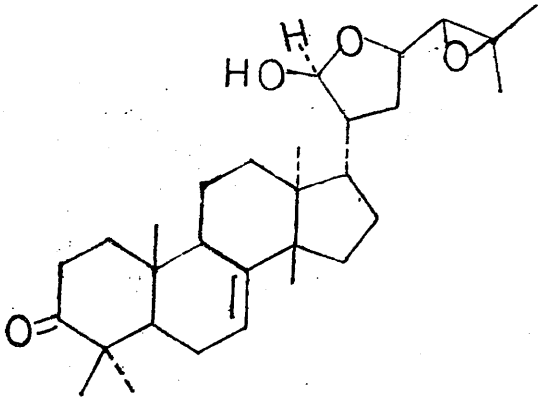

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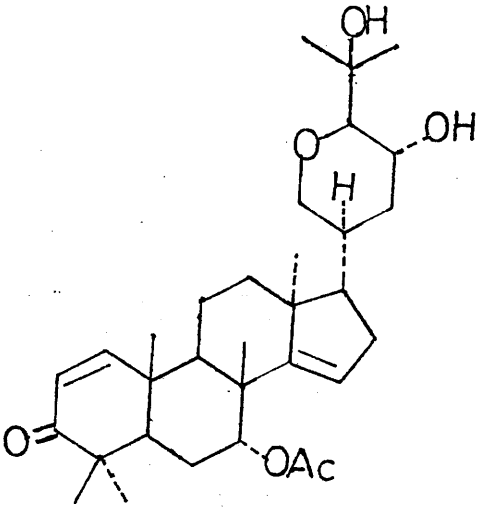

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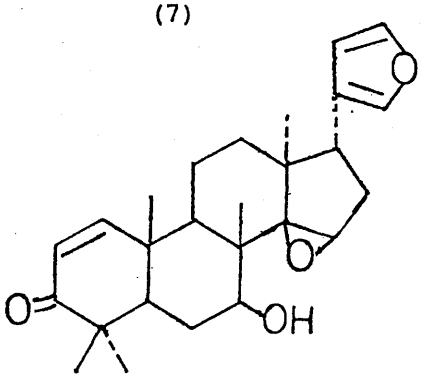

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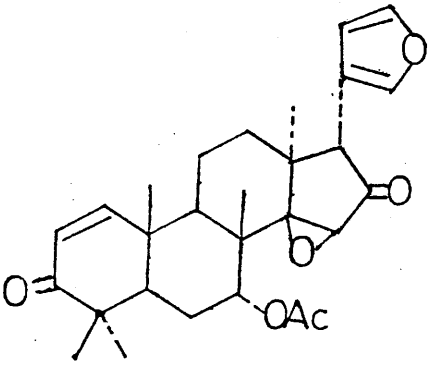

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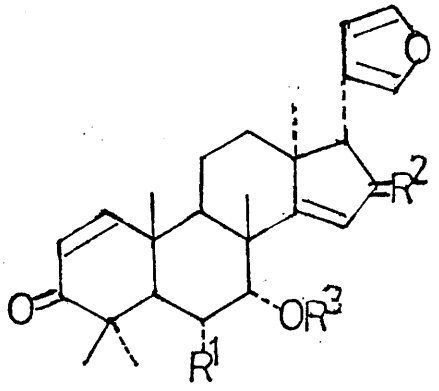
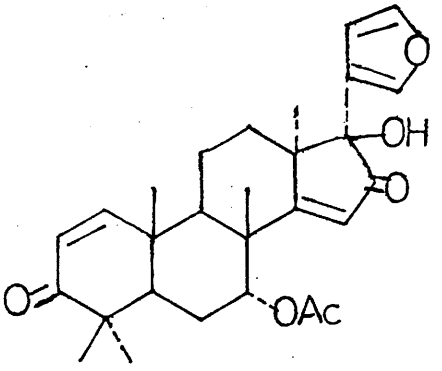


18) R^1=H ; R^2=O ; R^3=Ac

19) R^1=OAc ; R^2=H,H ; R^3=Ac

20) R^1=OAc ; R^2=O ; R^3=Ac



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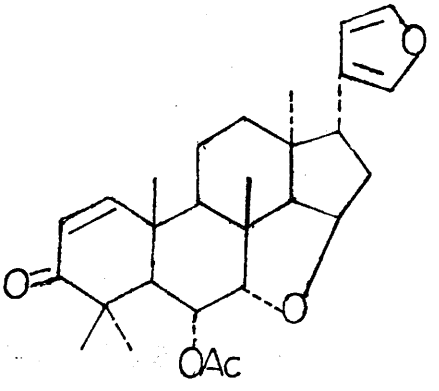

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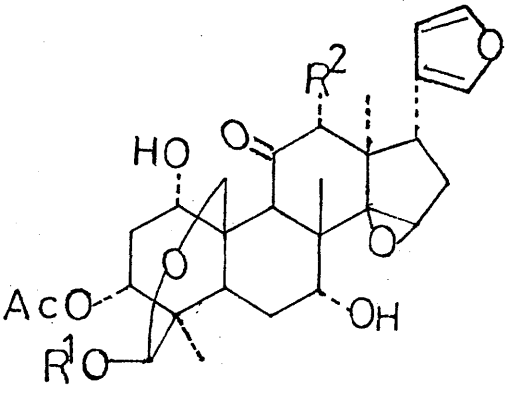
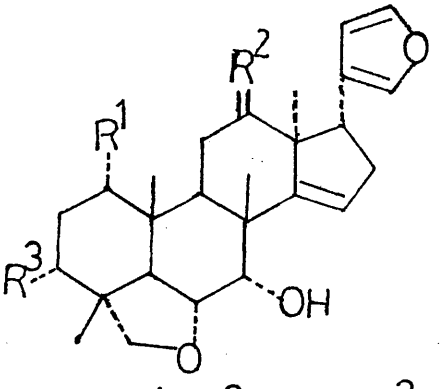


23) R^1=Ac ; R^2=OAc

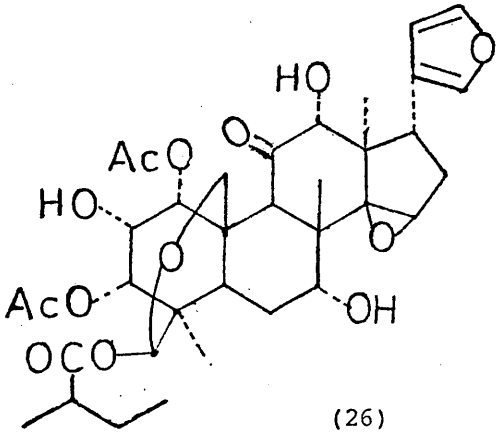
24) R^1= R^2= H

25) R^1= H ; R^2= OH



27) R^1= R^3=OAc ; R^2=H,H

28) R^1= R^3=OH ; R^2= O



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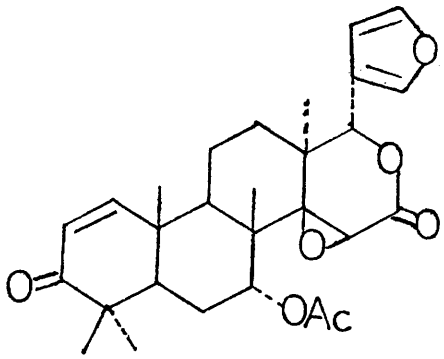

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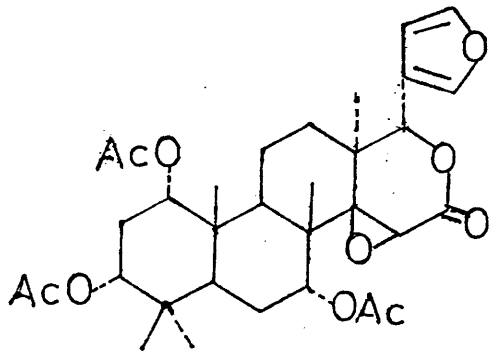

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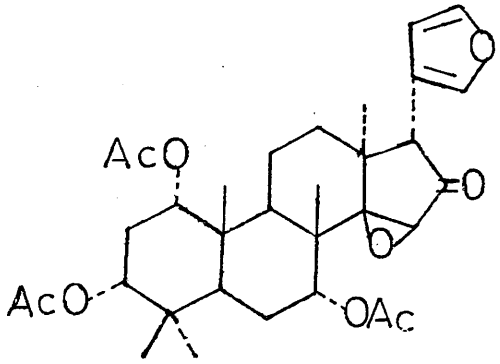

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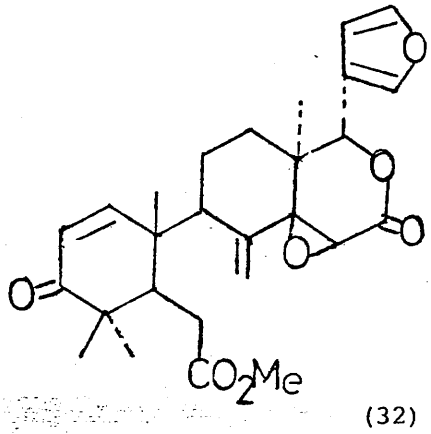

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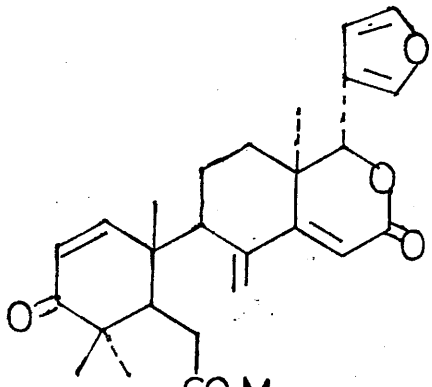

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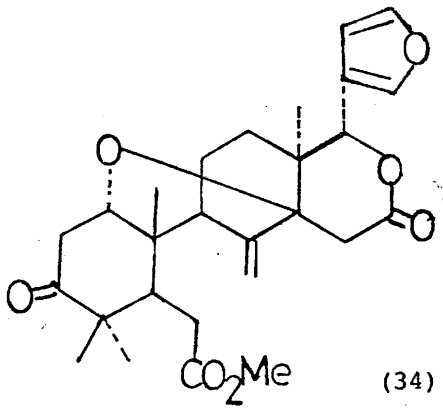

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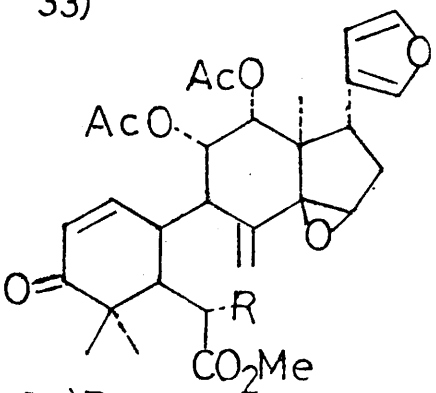
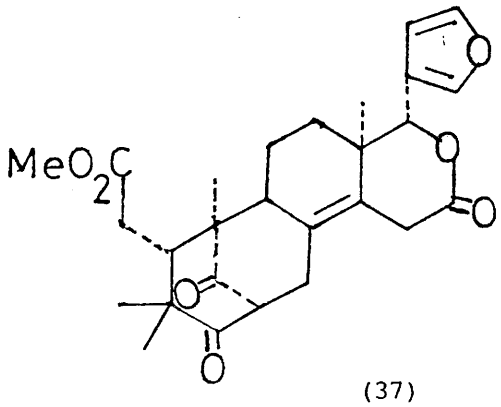


35)R=H

36)R=OAc



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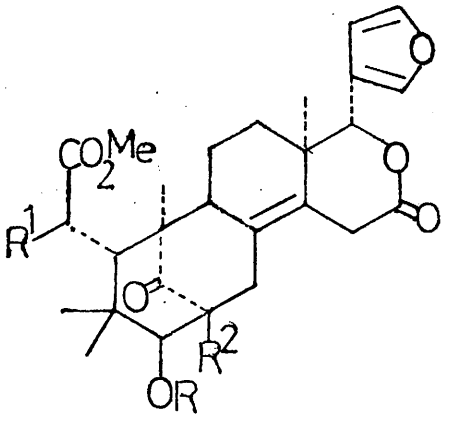
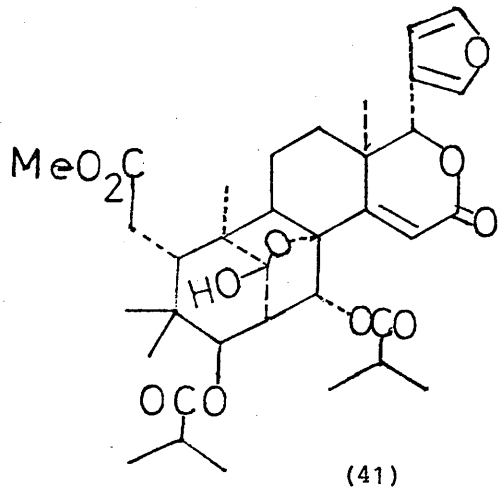


38) R = Tg ; R^1 = OH; $\Delta^{8(30)}$;
R^2 = H.

39) R = R^2 = H ; R^1 = OH

40) R = Ac ; R^1 = H ; R^2 = OH; $\Delta^{8(30),14(15)}$



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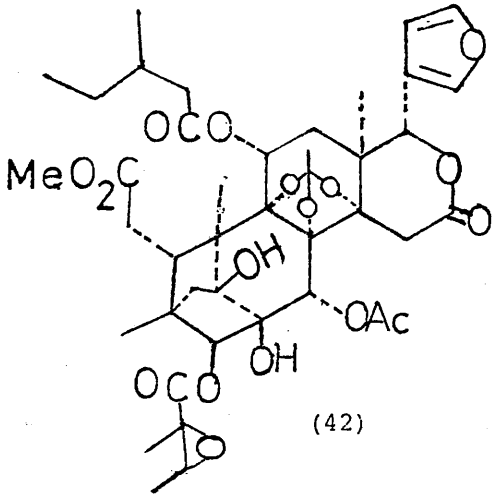

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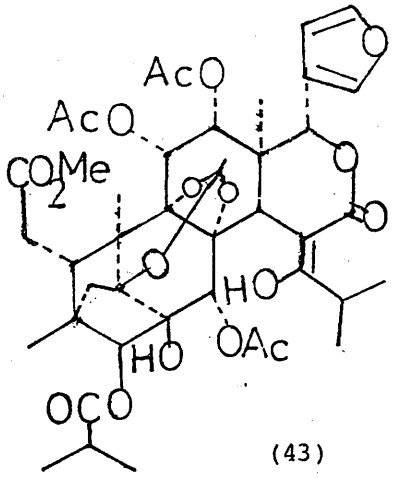

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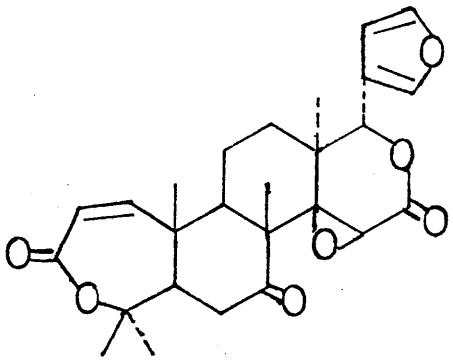

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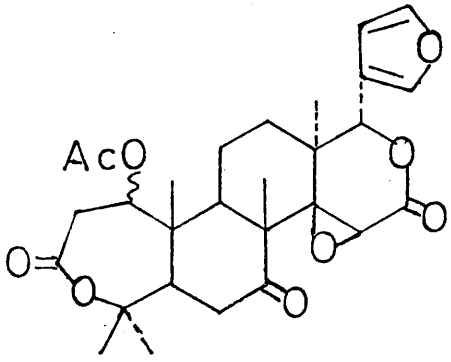

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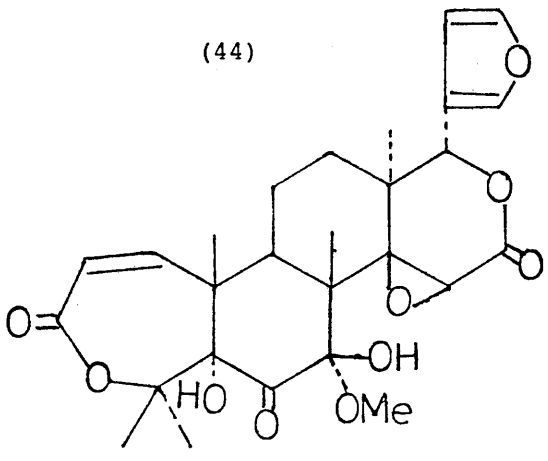

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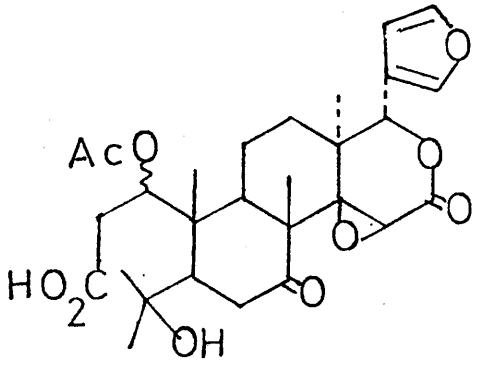

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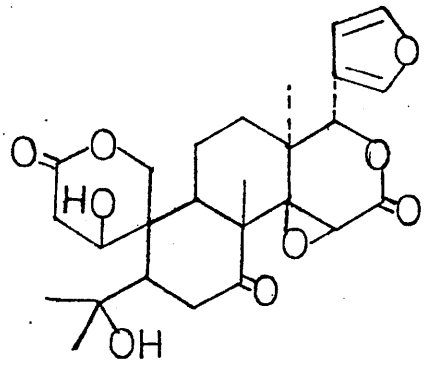

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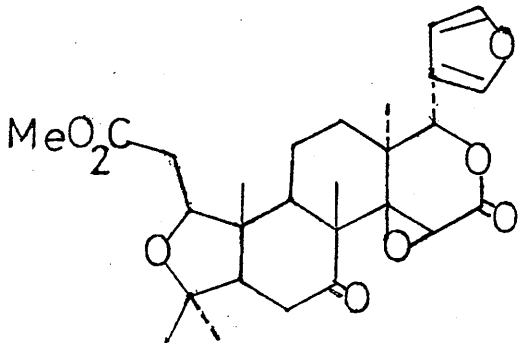

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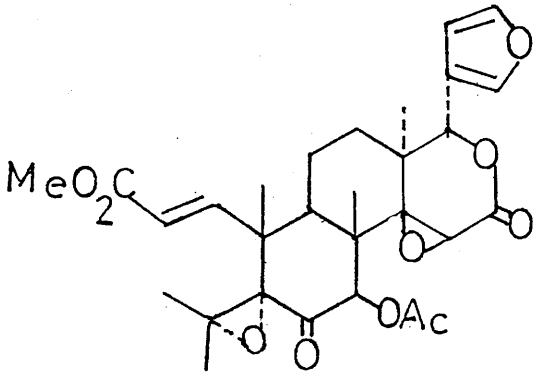

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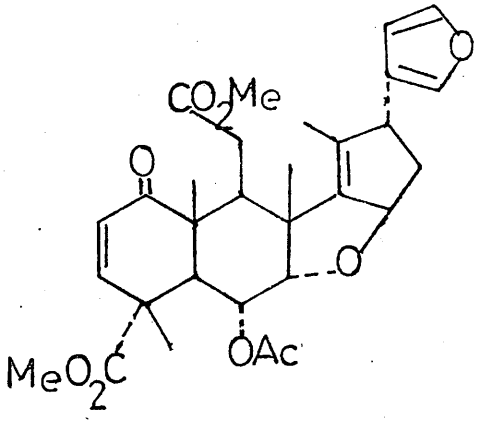

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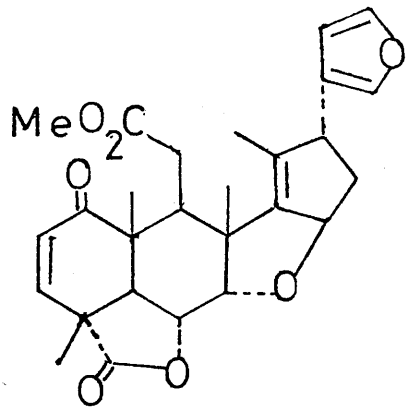

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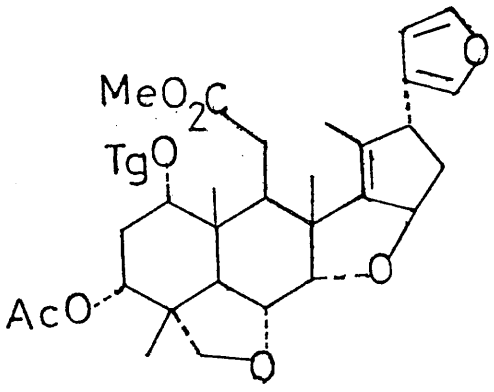

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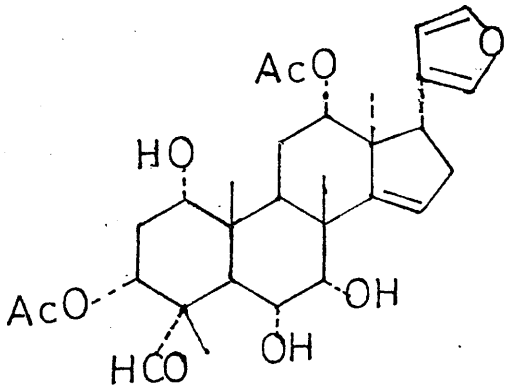

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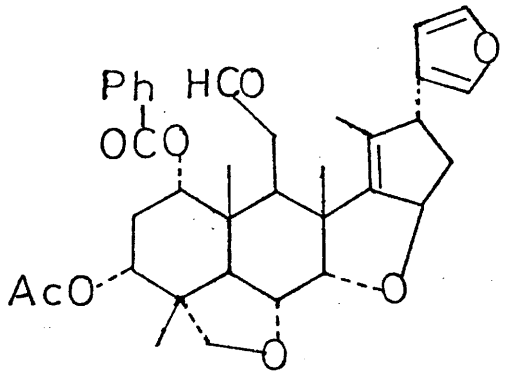

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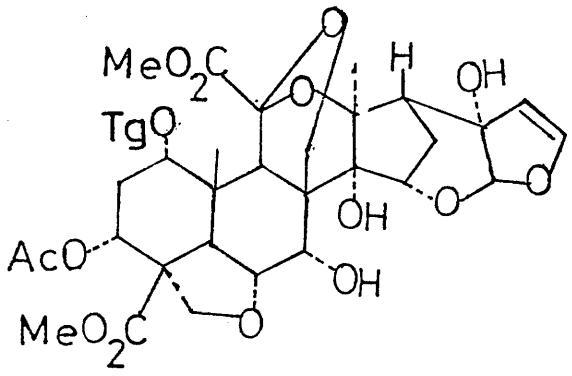

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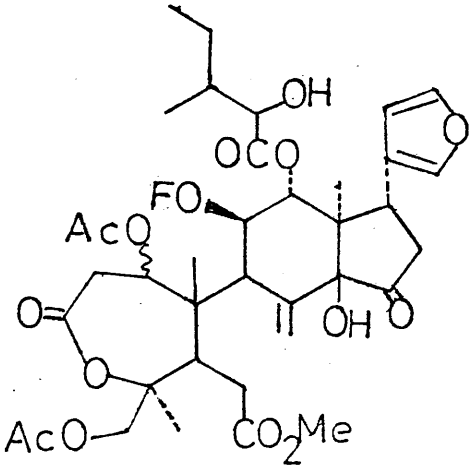

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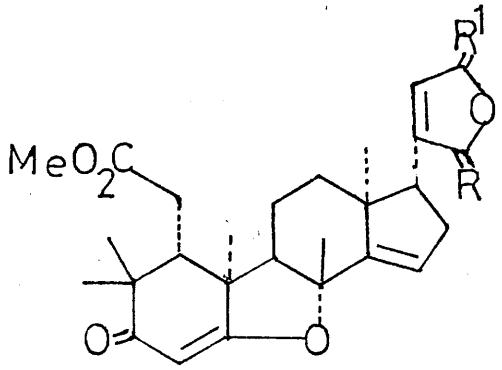

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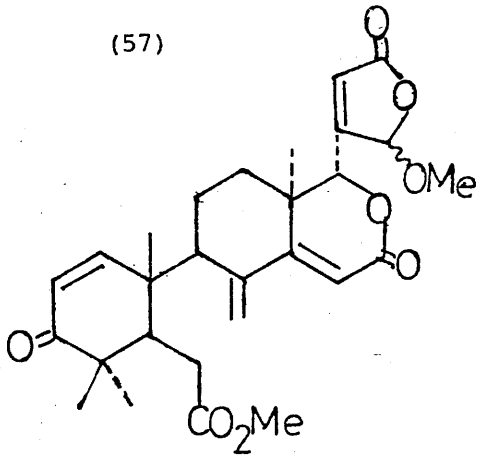
59) $R=OH, H$; $R^1=O$



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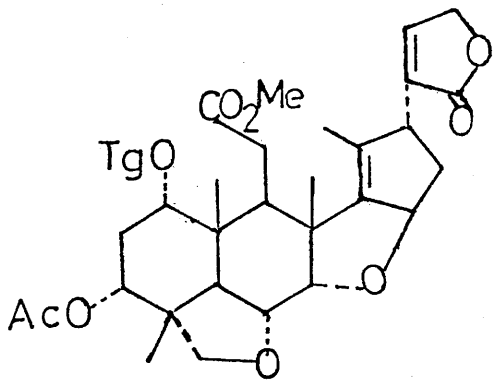

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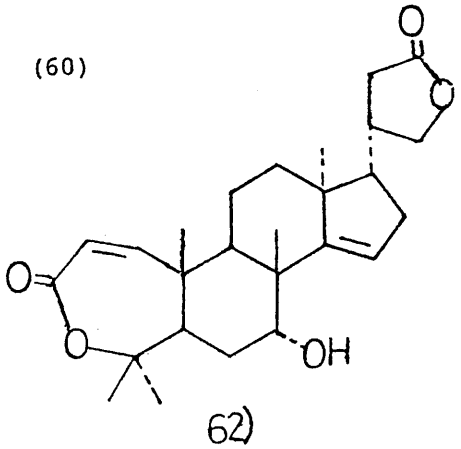

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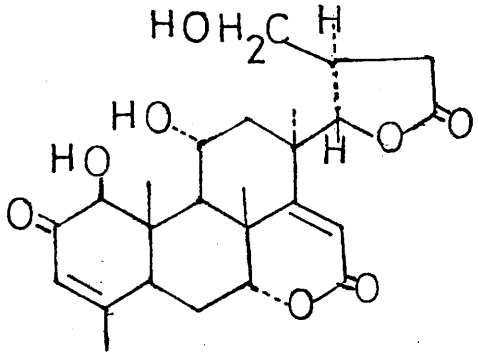

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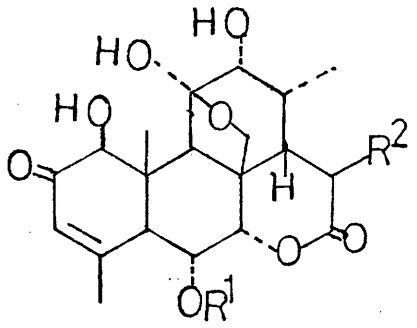
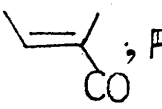
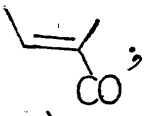
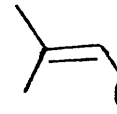
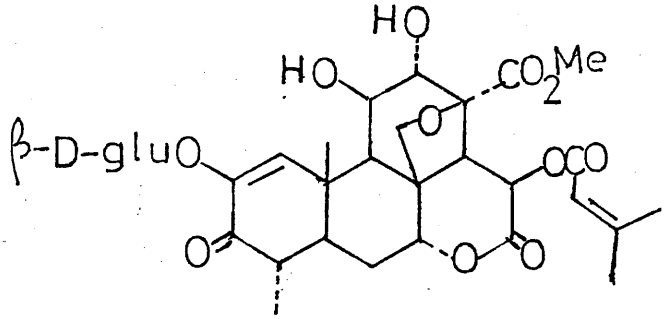


64) R^1 =  ; R^2 = OAc

65) R^1 =  ; R^2 = H

66) R^1 =  ; R^2 = H



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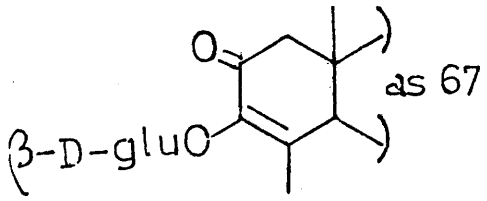

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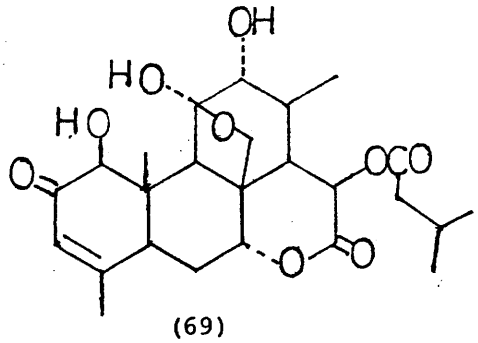

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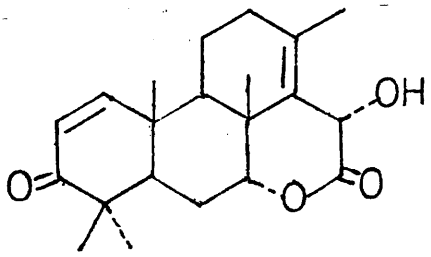

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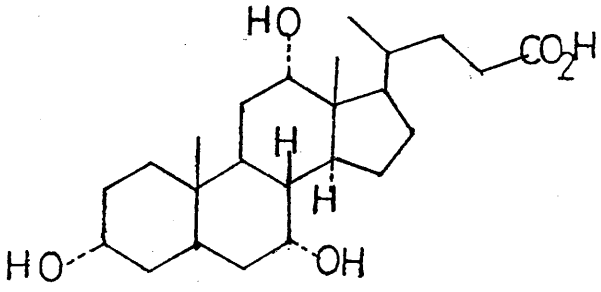

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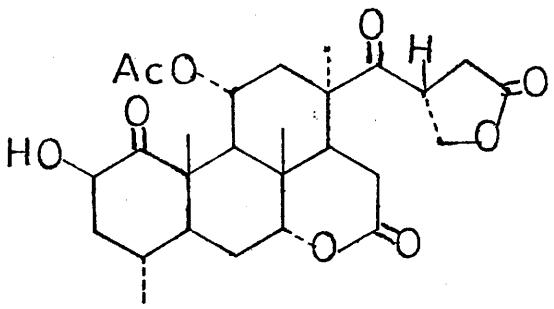

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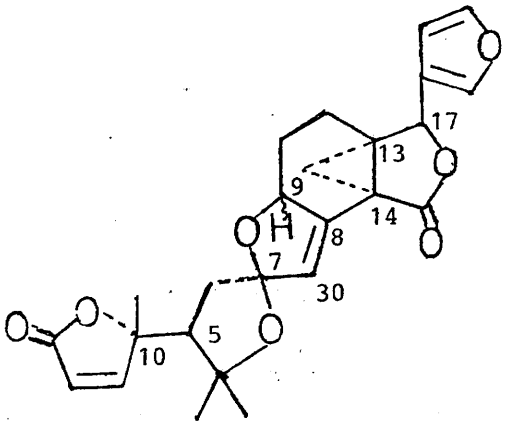

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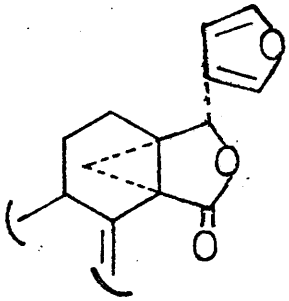

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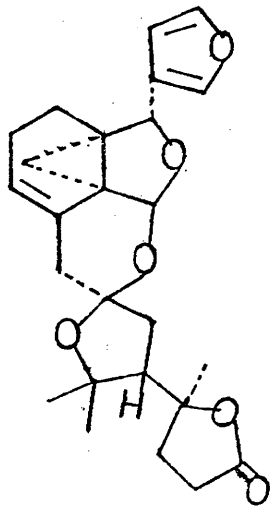

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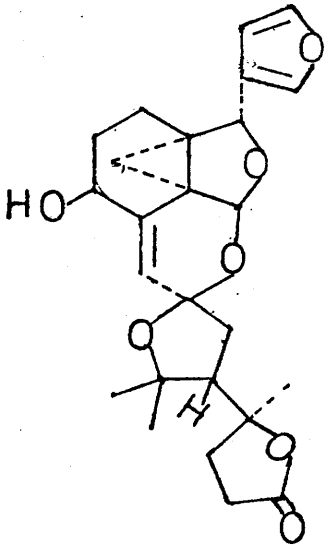

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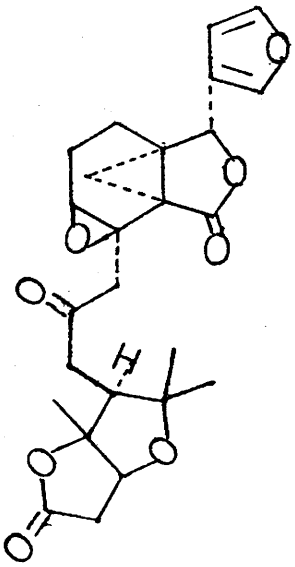

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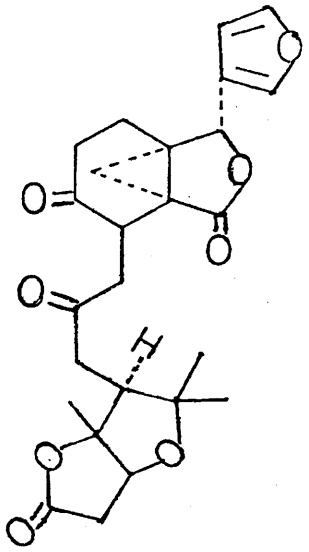

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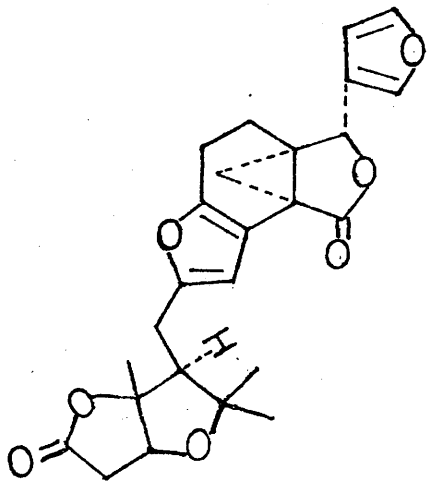

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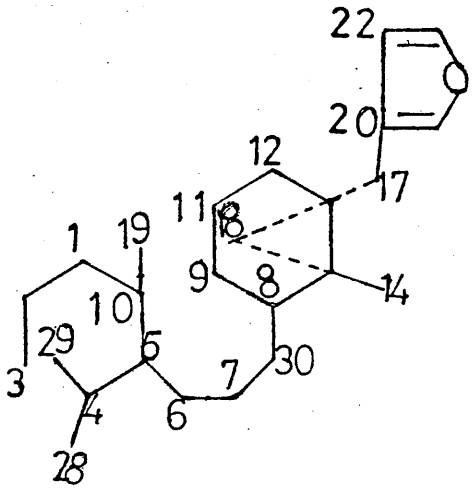

80)

CHAPTER II

ATTEMPTED CONVERSION OF LIMONOIDS TO QUASSINOIDS

MODIFICATION OF GEDUNIN

INTRODUCTION

The chemistry of quassinoids[1] dates back to the isolation of quassin (1) from Quassia amara[2] and since that time many quassinoids have been isolated. Apart from their inherent chemical interest the quassinoids are important because of their biological activity. Bruceantin[3] (2), undulatone (3) from Hannoa undulata,[4] 6α-tigloyloxy-chapparinone (4) from Ailanthus integrifolia,[5] 6α-senecioylchapparinone (5) from Simaba multiflora,[6] bruceoside A (6) and bruceoside B (7) from the seeds of Brucea javanica[7] are some examples of antileukemic quassinoids.

The quassinoids are complex molecules and this probably accounts for the limited number of synthetic studies which have appeared. Recently Grieco et al[9] have synthesised 1β-hydroxy-9β-picras-12-en-16-one (8) using a Diels-Alder strategy. The key intermediate dienophile (9) was obtained via a six step sequence from the decalol (10) and subsequently converted to the tricyclic ketone (11). Various δ-lactones, e.g. (12), have been prepared from D-ring secoderivatives of cholic acid.[8] An approach which involved the Robinson annulation[10] of bicyclic β-ketoester (13) to give the tricyclic enone (14)[8] a potentially useful intermediate was unsuccessful.

It is well established that limonoids with a ring D epoxylactone as in gedunin (15),[11] khivorin (16)[12] and limonin (17)[13] rearrange on treatment with alkali. For example gedunin is converted into merogedunol (18). This is structurally related to the quassin skeleton but has an extra methyl group at C-4 and lacks oxygen functionality. It was our intention to use gedunin or merogedunol (18) as starting material for a partial synthesis of the simple quassinoid (19) and (20) using recorded procedures[14,15] and subsequently to introduce oxygen functionality at C-11 and C-12. Further modification would lead finally to quassinoid (21).

D I S C U S S I O N

The proposed plan (Scheme 1) was to monodemethylate dihydrogedunin and rearrange the demethylated compound (22) with alkali to the mero-derivative (23). It was anticipated that functionality could be introduced at C-12 by allylic oxidation or bromination or by migration of the double bond to the 12 (13) position followed by epoxidation. The target molecule of this scheme was the enone (20).

Monodemethylation of 4,4-dimethyl systems has received much attention in the literature.[14,15] Cohen et al[15] had converted dihydrolanosterol into the corresponding desmethyl-derivative using the sequence of reaction in Scheme 2. The method makes use of the 'abnormal' Beckmann reaction which 3-hydroxyimino-4,4-dimethyl steroids undergo to yield 3,4-seco-nitriles. Epoxidation of the 4 methylene group, followed by treatment of the 3,4-seco-epoxy-nitrile with boron trifluoride in refluxing toluene afforded the desmethyl compound.

The initial efforts to demethylate gedunin were based on the above method. 'Abnormal' Beckmann reaction of dihydrogedunin (25) using toluene p-sulphonyl chloride in pyridine afforded the seconitrile (26) which was converted to the epoxynitrile (27) with m-chloro perbenzoic acid. Unlike the lanostane series above there was no evidence for the presence of a mixture of C-4 epimeric epoxides. The epoxide protons and the C-4 methyl group appear as singlets at δ 2.65 and δ 1.23 respectively. Unfortunately treatment of the epoxynitrile (27) with boron trifluoride etherate in refluxing toluene under nitrogen followed by aqueous acid work up resulted in decomposition. The explanation for this probably lies in the sensitivity of the ring D epoxide and the furan ring to boron trifluoride. Successful conversion to the desired aldehyde (28)

was achieved using toluene-p-sulphonic acid in refluxing benzene, but the yield was so low that this route had to be discarded.

An alternative approach followed the method published by Kazlauskas et al,[14] using the sequence of reaction in Scheme 3. This involved the Baeyer-Villiger procedure of Rosenthal, Niedermeyer and Fried[19] to convert 3-oxo-4,4-dimethyl-compounds to 4-methyl-4-methylene-3,4-seco acids. Esterification followed by selenium dioxide oxidation in refluxing dioxan resulted in a conversion of the 4-methyl-4-methylene moiety into the α,β-unsaturated aldehyde, which was further oxidised into the carboxylic acid by treatment in t-butyl alcohol with selenium dioxide and 90% hydrogen peroxide.[18] Esterification followed by treatment of the diester with sodium hydride in refluxing tetrahydrofuran, hydrogenation and alkaline hydrolysis led to the desmethyl compound. Dihydro gedunin was converted into the methyl ester (29) in almost quantitative yield by Baeyer-Villiger oxidation followed by treatment of the resulting lactone (30) with 10% sulphuric acid in glacial acetic acid and methylation with diazomethane.

Selenium dioxide oxidation of (29) in refluxing dioxan resulted in a smooth conversion (90%) into the α,β-unsaturated aldehyde (31). This compound was resistant to all known reagents for the oxidation of aldehydes. Treatment with selenium dioxide and (90%) hydrogen peroxide in t-butyl alcohol resulted in total loss of starting material. Since, again, the furan ring seemed the likely source of the problem it was decided to remove it prior to the oxidation step. The lactone (30) was allowed to undergo the mero-rearrangement by refluxing with 20% ethanolic KOH. Acidification, esterification with diazomethane, and dehydration of the ensuing ester with 10% H_2SO_4 conc. in glacial acetic acid afforded the methyl ester (33) which was resubmitted to the procedure described above.

The resulting aldehyde (34) proved to be as stubborn to oxidation as compound (31) above. Selenium dioxide, hydrogen peroxide afforded a mixture of esters, after treatment with diazomethane, which was difficult to purify by preparative t.l.c. Attempted ring closure of the mixture with sodium hydride in THF was unsuccessful. However the carboxylic acid (32) cyclised on treatment with hot acetic anhydride containing sodium acetate. Esterification of product with diazomethane and hydrogenation afforded compounds (35) and (36) in sequence. These compounds were not useful for our purpose.

While the monodemethylation experiments were going on, functionalisation of the 11 and 12 positions of merogedunol (18) was being explored. The mero compound (18) or its acetate or its dihydro derivative was resistant to all known reagents capable of inducing allylic oxidation or halogenation. The reason for this is not very clear. In separate experiments, the diene (38), obtained quantitatively from dihydromerogedunol (39) by treatment of the latter with 10% H_2SO_4 in glacial acetic acid, an improvement on the $POCl_3$ route, afforded the 12α,13α epoxide (39) on treatment with anhydrous sodium chromate in acetic acid acetic anhydride mixture. Evidence for (39) being a mixture could not be found. Analytical t.l.c. showed a single spot; and in the ^1H n.m.r. spectrum, the epoxide ring proton appears as a triplet at δ 3.26 (J 3Hz). The signal due to C-18 methyl group is a singlet at 1.50. On treatment with trifluoroacetic acid in thiophene free benzene compound (39) yields the alcohol (40). This was readily identified by the appearance in the i.r. spectrum of a band at 3620 for the OH. The ^1H m.r. spectrum shows the disappearance of the signal at δ 3.26 and 1.5 and the appearance of new signals δ 5.18 and 5.09 (brs, each) for the C-18 exomethylene and δ 4.52 (1H, t, J 3Hz $CH_2\underline{CH}$-OH, H-12). When treated with Jones

reagent compound (40) afforded two compounds (41) and (42). Both compounds were identified by the ^{1}H m.r. spectra [(41) δ 9.58 (1H, s, CHO), 6.96 (1H, t, J 4Hz, vinyl proton H-12); (42) δ 3.92 (2H, brs, CH_2OH), 3.60 (1H, narrow doublet, J 3Hz, epoxide ring proton, H-12)]. Lack of material prevented further work.

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

(1) Dihydrogedunin (25)[11].- To gedunin (1 g) in ethyl acetate (70 ml) was added 10% palladium charcoal (100 mg) and hydrogenation was allowed to continue at room temperature until there was no more uptake of hydrogen. Filtration and evaporation of solvent under reduced pressure afforded dihydrogedunin (25) (980 mg); [δ_H 0.93, 0.95, 1.0, 1.05 and 1.18 C-Me; 2.06 acetate, 3.48 (1H, s, epoxide ring proton), 4.52 (1H, t, J 3 Hz, H-7), 5.58 (1H, s, H-17) and the usual furan protons at 6.30 and 7.36.]

(2) Dihydrogedunin oxime (43).- Dihydrogedunin (3.6 g) in dry ethanol (372 ml) was added to anhydrous sodium acetate (1.19 g) and hydroxyl amine hydrochloride (744 mg). The mixture was refluxed overnight. Work up afforded the oxime (43) (2.24 g), recrystallised from ethanol. M.p. 231°-232°C, m/e = 499. (Found: C, 67.24; H, 7.50; N, 2.79; $C_{28}H_{37}O_7N$ requires C, 67.31; H, 7.47; N, 2.80.)

[δ_H 1.0 (9H), 1.05, 1.16 (C-Me); 2.03 acetate, 3.48 (1H, s, epoxide ring proton), 4.52 (1H, t, J 3 Hz, H-7), 5.58 (1H, s, H-17) and the furan protons at 6.30 and 7.36.]

(3) Gedunin 3,4-seconitrile (26).- The oxime from above (3.47 g) was dissolved in anhydrous pyridine (216 ml). To the solution was added tosyl chloride (10.78 g) and the mixture was refluxed overnight. Treatment with 3N hydrochloric acid (540 ml) and extraction 3 x with ether (50 ml) followed. The ether extract was dried over Na_2SO_4 anhydrous and evaporated under reduced pressure to give the seconitrile (26) (3.0 g), an oil. M/e = 481. [δ_H 0.92, 1.1, 1.23 (C-Me), 1.7 vinyl methyl, 2.1 acetate, 3.5 (1H, s, epoxide ring proton) 4.48 (1H, t, J 3 Hz, H-7), 4.7 and 4.88 (brs, each 1H, $\Delta^{4,28}$ exomethylene), 5.58 (1H, s, H-17) and the furan protons at δ 6.3 and 7.38.]

(4) Seconitrile epoxide (27).- To the seconitrile (26) (1.5 g) in methylene chloride (199 ml) was added m-chloroperbenzoic acid (1.42 g) and the mixture kept at 0°C for 2 days. The mixture was then flooded with water, extracted with chloroform and filtered through a column of grade IV alumina to remove m-chlorobenzoic acid. Evaporation of solvent under reduced pressure afforded the epoxide (27) (1.42 g), an oil. M/e = 497; [δ_H 1.0, 1.06, 1.2 (C-Me), 1.23 (3H, s, C-29 methyl), 2.08 acetate, 2.65 (2H, s, 2H-28 epoxide ring proton); 3.5 (1H, s, H-15 epoxide ring proton), 4.53 (1H, t, J 3 Hz, H-7), 5.56 (1H, s, H-17) and the furan ring protons at 6.32 and 7.38.]

(5) Dihydrogedunin ring A ε-lactone (30).- To dihydrogedunin (1.1 g) in dry methylene chloride (20 ml) was added anhydrous disodium hydrogen orthophosphate (800 mg) and peroxyacetic acid (2 ml) at 0°C, and the solution allowed to stir for 8 hrs at room temperature. The reaction mixture was then flooded with water and extracted with chloroform. The chloroform extract was dried over anhydrous sodium sulphate, and then evaporated under reduced pressure to give the lactone (30) (1.06 g) after recrystallisation from methanol. M.p. 155°-156°C, m^+/e = 500. (Found: C, 54.62; H, 6.03; $C_{28}H_{36}O_8.H_2O.CHCl_3$ requires C, 54.58; H, 6.12%).

[δ_H 1.06, 1.10, 1.18, 1.33 and 1.36 (C-Me), 2.1 (acetate), 3.48 (1H, s, H-15), 4.48 (1H, t, J 3 Hz, H-7), 5.58 (1H, s, H-17) and the furan ring proton at 6.30 and 7.36.]

(6) 3,4-Secodihydrogedunin methyl ester (29).- The ring A lactone from above (407.8 mg) was treated with a 10% H_2SO_4/glacial acetic acid mixture at room temperature for 15 minutes, with good stirring. The mixture was then flooded with water, extracted with chloroform, dried in the usual way and evaporated under reduced pressure. The crude product, on treatment with diazomethane in methanol gave the secocompound (29)

(383.8 mg) after preparative t.l.c. (1.5% MeOH/$CHCl_3$). This was an oil; m/e = 514.

[δ_H 0.9, 1.08, 1.2 (C-Me), 1.68 (3H, brs, vinyl methyl), 2.08 (acetate), 3.5 (1H, s, H-15 epoxide ring proton), 3.63 (3H, s, CO_2Me), 4.46 (1H, t, J 3 Hz, H-7), exomethylene protons at δ 4.7 and 4.83 (brs, each), 5.58 (1H, s, H-17) and the furan ring protons at δ 6.3 and 7.36.]

(7) The epoxide (44).- To the solution of the ester (29) (100 mg) in methylene chloride (20 ml), was added m-chloroperbenzoic acid (60 mg) and the mixture kept at 0°C for 2 days. Work up afforded the epoxide (44) (72 mg) after preparative t.l.c. (2% MeOH/$CHCl_3$). This is an oil. M/e = 530.

[δ_H 1.0, 1.05, 1.16 for (C-Me); 1.20 (3H, s, C-29 methyl), 2.06 (acetate), 2.65 (2H, s, 2H-28 epoxide ring protons), 3.50 (1H, s, H-15), 3.66 (3H, s, CO_2Me), 4.53 (1H, t, J 3 Hz, H-7), 5.56 (1H, s, H-17), δ 6.3 and 7.36 for the furan ring protons.]

(8) SeO_2 Oxidation of the 3,4-secodihydrogedunin methyl ester (29).- To the methyl ester (29) (472.4 mg) in dioxan (25 ml) was added 3 drops of de-ionized water and selenium dioxide (103.6 mg) and the mixture stirred mechanically at 90°C for 4 hrs. Work up, and preparative t.l.c. (2% MeOH/$CHCl_3$) afforded compound (31) (328 mg) as an oil. M^+/e = 528.

[δ_H 0.85, 1.1 and 1.23 (C-Me), 2.1 (acetate) 3.5 (1H, s, H-15 epoxide ring proton), 3.63 (3H, s, CO_2Me), 4.46 (1H, t, J 3 Hz, H-7), 5.58 (1H, s, H-17), two exomethylene protons at 6.16 and 6.28 (1H, s) respectively, the furan ring protons at 6.30 and 7.38, δ 9.43 (1H, s, CHO aldehyde)].

(9) The cyclised compound (35).- The ester (29) was initially hydrolysed to the acid (32) by treatment with anhydrous K_2CO_3 in wet methanol at room temperature for 18 hr. A mixture of the crude acid (200 mg) with acetic anhydride (5 ml) and anhydrous sodium

acetate (100 mg) was maintained at 100°C overnight. Work up followed by preparative t.l.c. (16% EtOAc/CCl_4) afforded compound (35) (198 mg) recrystallised from ether, after esterification with diazomethane. M.p. 181°-182°C; m/e 510. (Found: C, 67.99; H, 6.87; $C_{29}H_{34}O_8$ requires C, 68.22; H, 6.71).

[δ_H 0.78, 1.06, 1.23 (C-Me), 2.06 (acetate), 3.52 (1H, s, H-15 epoxide ring proton), 3.73 (3H, s, CO_2Me), 4.58 (1H, t, J 3 Hz, H-7), 5.08 (brs) and 5.26 (brs) (exomethylene protons), 5.60 (1H, s, H-17), the furan ring protons at 6.33 and 7.40, δ 7.22 (1H, m, H-3 vinyl proton)].

(10) Hydrogenation of compound (35).- Compound (35) (200 mg), in an ethanol-benzene mixture (1:0.2 v/v) containing 10% palladinized charcoal (40 mg) was hydrogenated until uptake of hydrogen had ceased. Filtration and evaporation of solvent under reduced pressure afforded compound (36) (180 mg) recrystallised from ether. M.p. 202°-203°C, m/e = 512. (Found: C, 67.68; H, 6.80; $C_{29}H_{36}O_8$ requires C, 67.95; H, 7.08.)

[δ_H 0.85, 1.06, 1.22 (C-Me), 0.98 (3H, d, J 7 Hz, secondary methyl attached to C-4), 2.06 (acetate), 3.50 (1H, s, epoxide ring proton H-15), 3.70 (3H, s, CO_2Me), 4.52 (1H, t, J 3 Hz, H-7), 5.58 (1H, s, H-17), furan ring protons at δ 6.30 and 7.36, δ 6.95 (1H, m, vinyl proton H-3)].

(11) 3,4-Secoanhydrodihydromerogedunol methyl ester (33).- The dihydrolactone (30) (800 mg) was refluxed with 10% ethanolic KOH (200 ml) for 2 hrs. The ensuing solution was acidified with dilute sulphuric acid and extracted with chloroform. The chloroform extract was dried, and evaporated under reduced pressure. Esterification with diazomethane, followed by treatment with 10% H_2SO_4/AcOH afforded compound (33) (468 mg) after work up and column chromatography of the crude product over

grade IV alumina. The fraction collected at elution with 50% $CHCl_3$/ petroleum ether contains (33), as an oil. M^+/e = 358.

[δ_H 0.98, 1.13 (C-Me), 1.80 (3H, brs) and 1.86 (3H, brs) (for two vinyl methyls), 3.66 (3H, s, $CO_2\underline{Me}$), 4.30 (1H, t, J 3 Hz, H-7), 4.68 and 4.98 (1H, each, brs, exomethylene protons), 5.66 (2H, brs, vinyl protons H-12 and H-15)].

(12) $\underline{SeO_2}$ Oxidation of (33).- Compound (33) (224 mg) in dioxan (25 ml) containing selenium dioxide (68 mg) was oxidised as described for (29). Work up and purification by column chromatography over grade IV alumina, elution with 80% $CHCl_3$/petroleum ether afforded the aldehyde (34) (186 mg) crystallised from chloroform light petroleum. M.p. 165°-166°C, m/e = 372. (Found: C, 71.2; H, 7.59; $C_{22}H_{28}O_5$ requires C, 70.94; H, 7.58%).

[δ_H 0.90, 1.13 (C-Me), 1.85 (3H, brs vinyl methyl), 3.60 (3H, s, $CO_2\underline{Me}$), 4.30 (1H, t, J 3 Hz, H-7), 5.76 (2H, brs, vinyl protons H-12 and H-15), 6.23 and 6.33 (exomethylene), 9.46 (1H, s, $C\underline{H}O$ aldehyde)].

(13) Alkaline hydrolysis of gedunin[11].- Gedunin (1.5 g) was refluxed with 20% ethanolic KOH (600 ml) for 1½ hrs. The mixture was allowed to cool, and then acidified with dilute hydrochloric acid. Extraction with chloroform and column chromatography over grade IV alumina (eluate from 50% $CHCl_3$-light petroleum) gave the desired mero compound (18) (600 mg).

(14) Anhydromerogedunol (45)[11].- To compound (18) (117 mg), dissolved in pyridine (26 ml), was added phosphorous oxychloride ($POCl_3$) (4 ml) and the mixture was refluxed for 2 hrs. Solvent was evaporated to dryness under reduced pressure, and azeotroping three times with chloroform, the anhydro compound (45) (69 mg) identical with authentic sample was obtained. Yield was improved to (102 mg) by the use of 10% H_2SO_4/AcOH at room temperature for 15 minutes as described for compound (33).

[δ_H 1.08, 1.13, 1.18 (6H) (C-Me), 1.85 (3H, brs, vinyl methyl), 4.36 (1H, t, J 3 Hz, H-7), 5.73 (1H, s, vinyl proton H-15), 5.8 (1H, brs, vinyl proton H-12), 5.85 ~ 6.88 (ABq, 2H, J 9 Hz, H-1 and H-2 conjugated enone)].

(15) Anhydrodihydromerogedunol (38)[11].- To anhydromerogedunol (45) (406 mg) in dry methanol (30 ml) was added $NaBH_4$ (50 mg) and the mixture allowed to stir at room temperature for 3 hrs. Excess borohydride was destroyed with acetic acid. Addition of water, and extraction with chloroform followed by evaporation of solvent under reduced pressure, after drying over anhydrous sodium sulphate, gave the alcohol which was oxidised with Jones reagent in acetone at ice temperature. Preparative t.l.c. of the crude product (2% MeOH/$CHCl_3$) afforded the dihydro compound (38).

[δ_H 1.03, 1.10 (9H) (C-Me), 1.82 (3H, brs, vinyl methyl), 4.35 (1H, t, J 3 Hz, H-7), 5.70 (2H, brs, vinyl protons H-12 and H-15)].

(16) Anhydrous sodium chromate oxidation of anhydrodihydromerogedunol.- To the dihydro compound (38) (180 mg) was added 3 ml of glacial acetic acid-acetic anhydride mixture (2:1 v/v) and sodium chromate (140 mg) which had been predried at 150°C under vacuum for 18 hrs. The mixture was allowed to stir at 30°C overnight; then flooded with water and extracted with chloroform. Solvent was dried and evaporated under reduced pressure. Preparative t.l.c. of product (50% EtOAc/CCl_4) afforded the 12α,13α-epoxide (39) (126 mg) recrystallised from ether. M.p. 253°-254°C, m /e = 344, i.r. (CCl_4) showed absence of an OH. (Found: C, 73.05; H, 8.12; $C_{21}H_{28}O_4$ requires C, 73.22; H, 8.19%).

[δ_H 1.02, 1.03, 1.06, 1.13 (C-Me), 1.50 (3H, s, H-30), 3.25 (1H, brt, epoxide ring proton H-12), 4.35 (1H, t, J 3 Hz, H-7), 6.10 (1H, s, vinyl proton H-15)].

(17) Trifluoroacetic acid ring opening of the epoxide (39).- The epoxide (39) was dissolved in thiophene free benzene (20 ml), containing trifluoroacetic acid (0.02 ml). The mixture was refluxed overnight. The solvent was evaporated to dryness under reduced pressure and the crude product was refluxed with aqueous methanol (20 ml) (methanol:water 20:0.5 v/v) for 6 hrs. Evaporation of solvent and preparative t.l.c. (56% EtOAc/CCl_4) afforded the allylic alcohol (40) (30 mg) which was recrystallised from ether-light petroleum. M.p. 192°-193°C, m/e = 344, 326 (P-18). (Found: C, 73.30; H, 8.08; $C_{21}H_{28}O_4$ requires C, 73.22; H, 8.19%). I.r. (CCl_4) 3620 (OH), 1730 and 1715 cm^{-1}.

[δ_H 0.98, 1.03, 1.06 and 1.10 (C-Me), 4.33 (1H, t, J 3 Hz, H-7), 4.52 (1H, t, J 3 Hz, H-12) 5.09 (brs) and 5.18 (brs) (exomethylene), 5.74 (1H, s, vinyl proton H-15)].

(18) Jones oxidation of the alcohol (40).- The alcohol (40) (14.3 mg) was dissolved in acetone, Jones reagent (2 drops) added and the solution allowed to stir for 5 minutes at 0°C. Work up afforded a mixture of two compounds (12 mg). This was separated by repetitive preparative t.l.c. (56% EtOAc/CCl_4). The less polar compound (41), $C_{21}H_{26}O_4$, was an oil; m/e = 342.

[δ_H 1.10 (6H), and 1.15 (6H) (C-Me), 4.46 (1H, t, J 3 Hz, H-7), 6.37 (1H, brs, vinyl proton H-15), 6.96 (1H, t, J 4 Hz, vinyl proton H-12), 9.58 (1H, s, CHO)].

The more polar compound (42), $C_{21}H_{28}O_5$, was also an oil; m/e = 360.

[δ_H 1.07, 1.09, 1.13, 1.17 (C-Me), 3.60 (1H, narrow d, J 3 Hz, H-12 epoxide ring proton), 3.92 (2H, brs, CH_2OH), 4.39 (1H, t, J 3 Hz, H-7), 6.19 (1H, s, vinyl proton H-15)].

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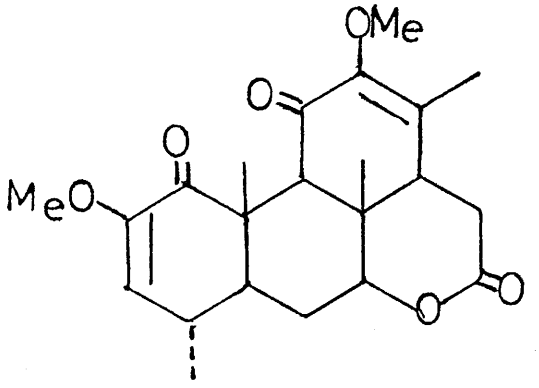

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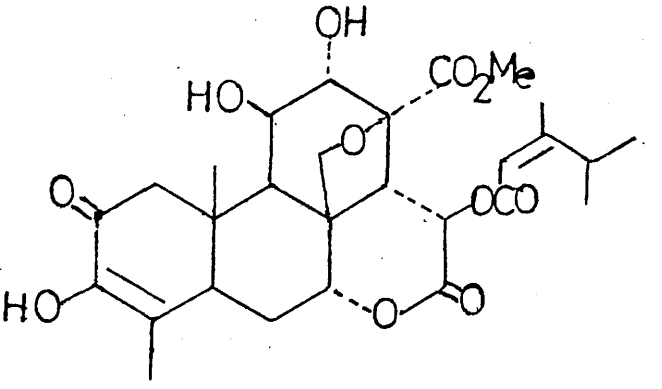

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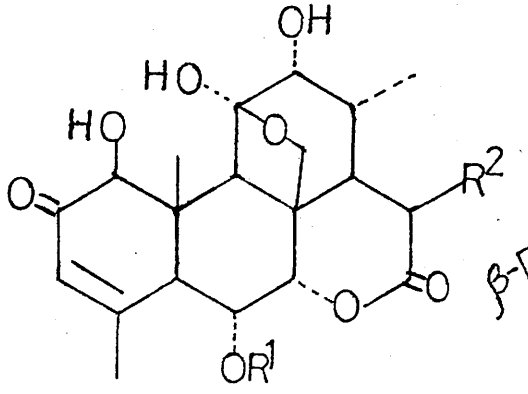
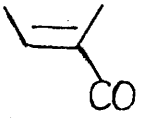
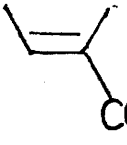
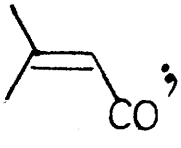
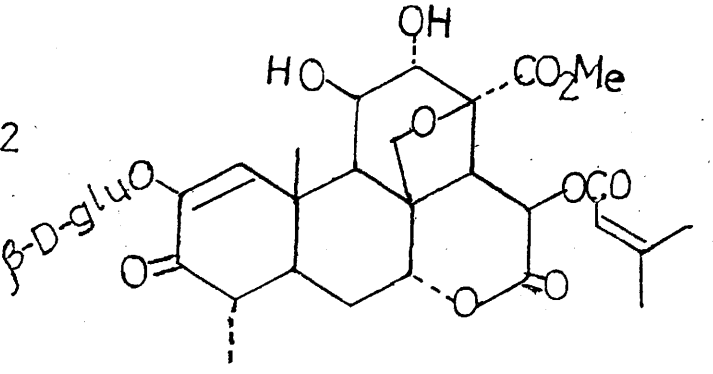


3) R^1 =  ; R^2 = OAc

4) R^1 =  ; R^2 = H

5) R^1 =  ; R^2 = H



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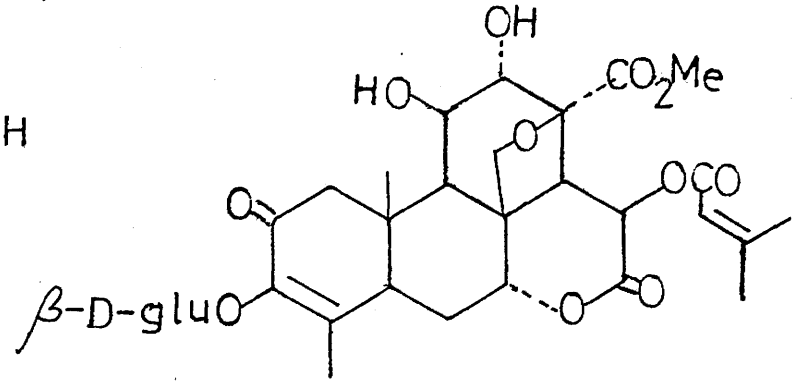

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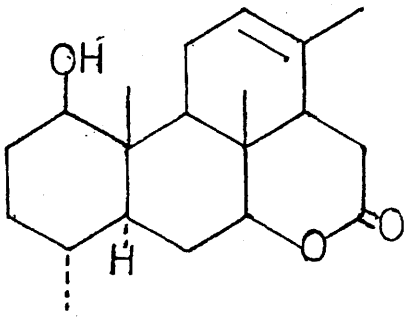

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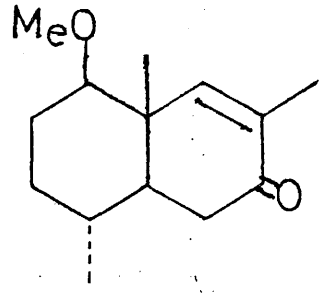

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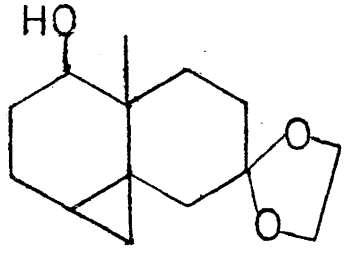

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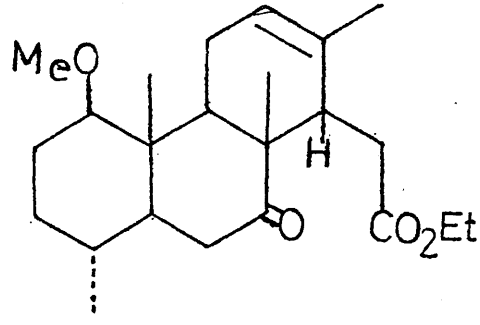

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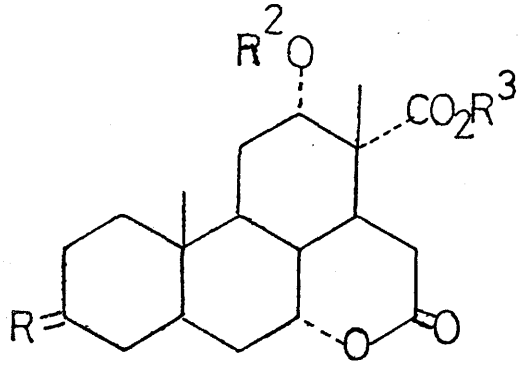

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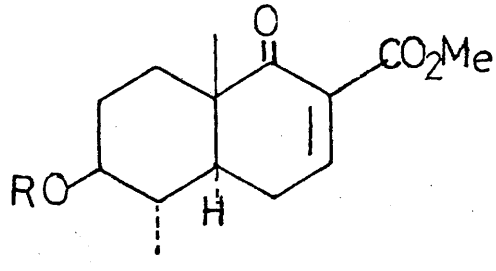

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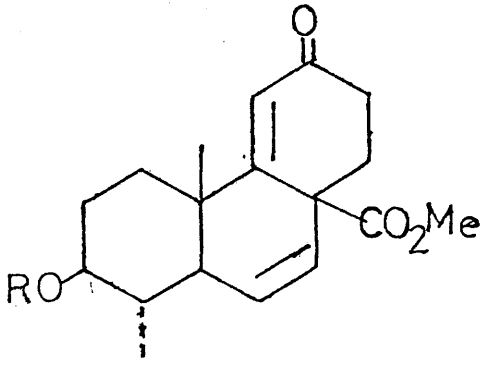

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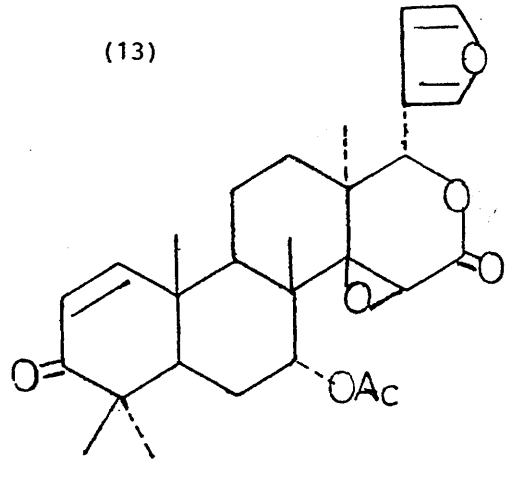

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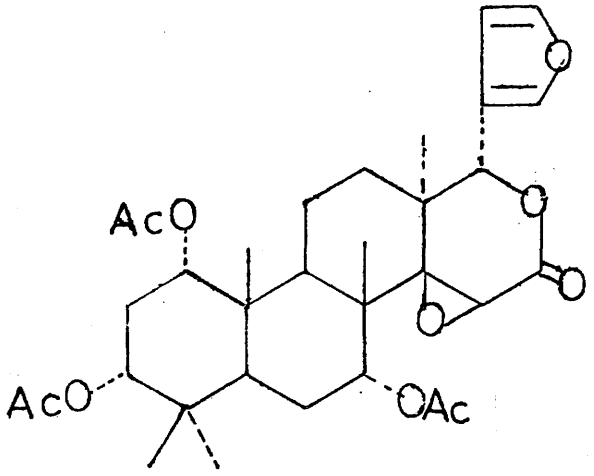

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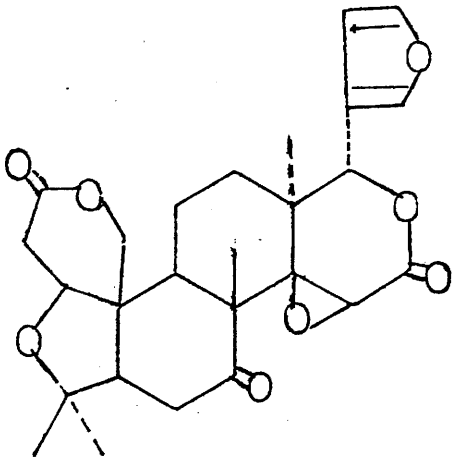

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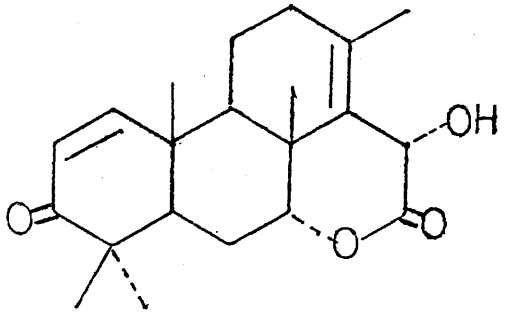

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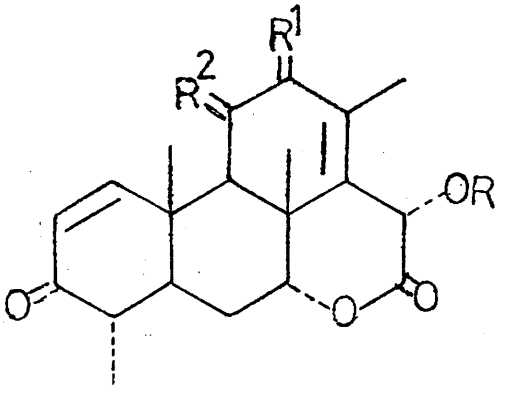

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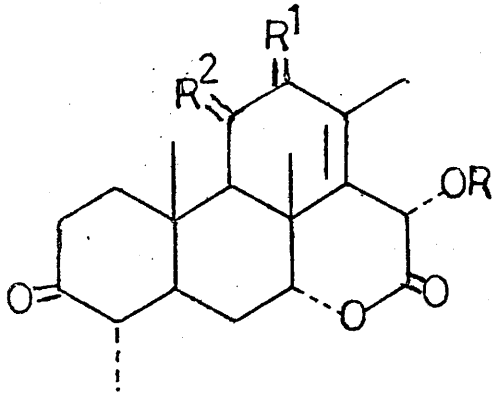

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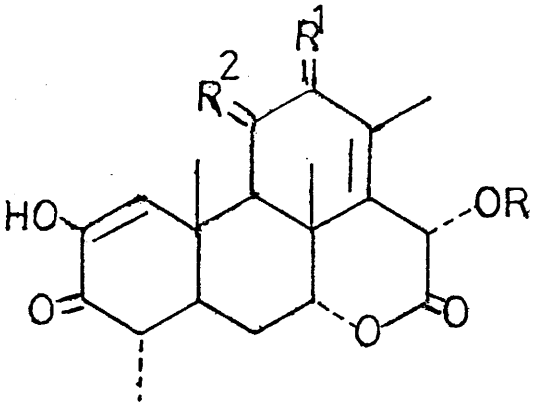

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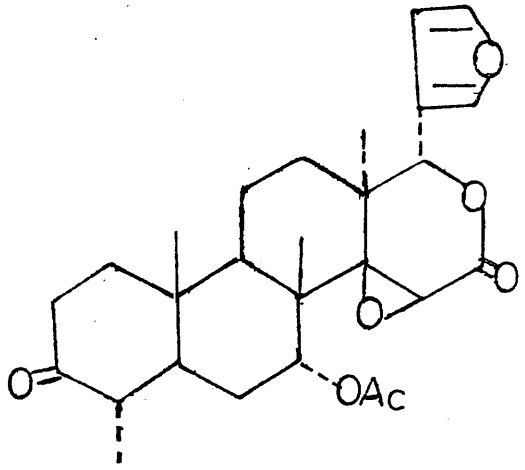

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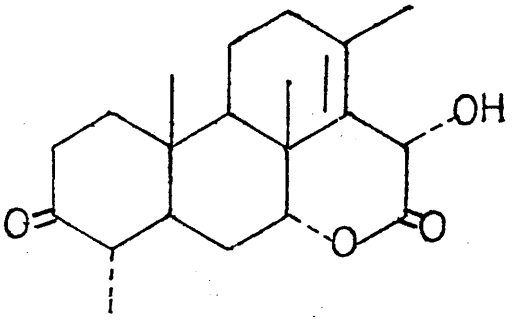

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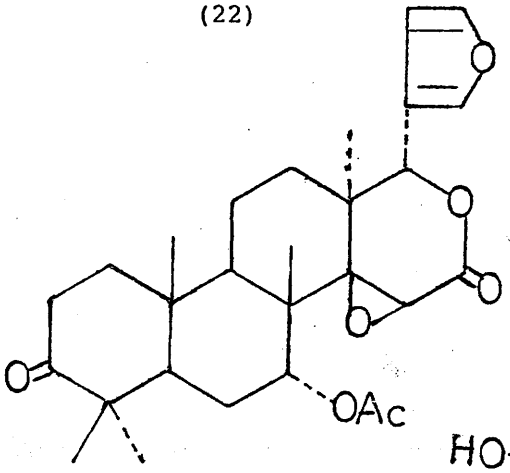

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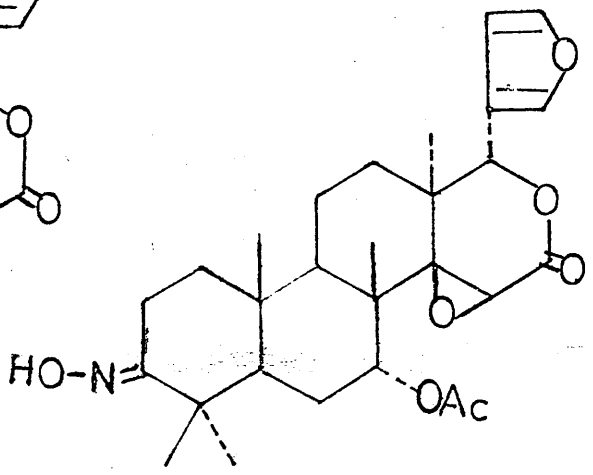

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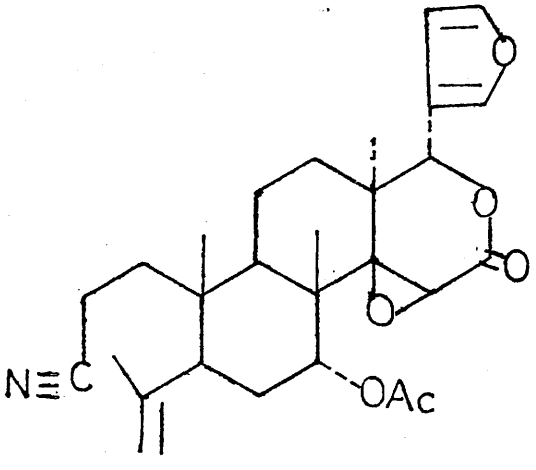

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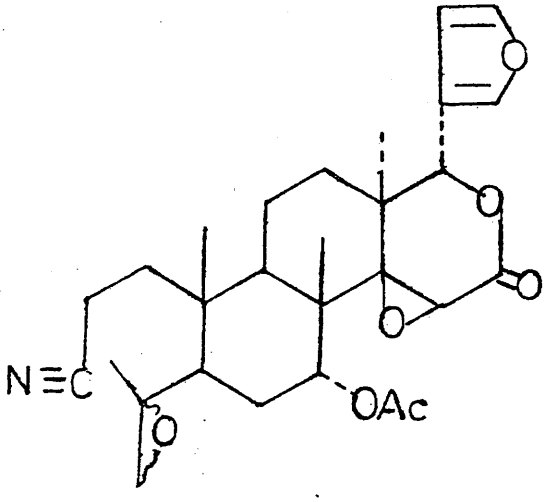

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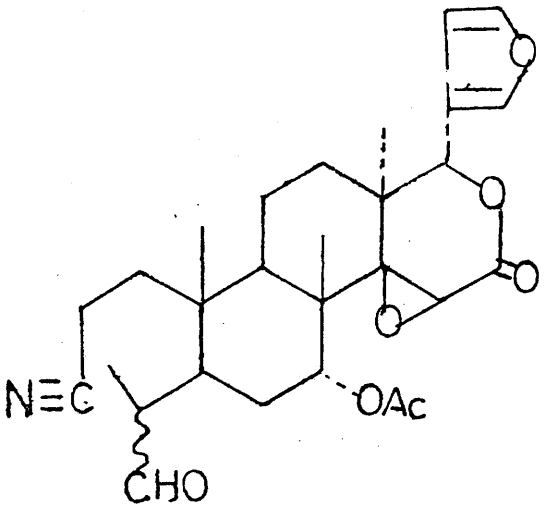

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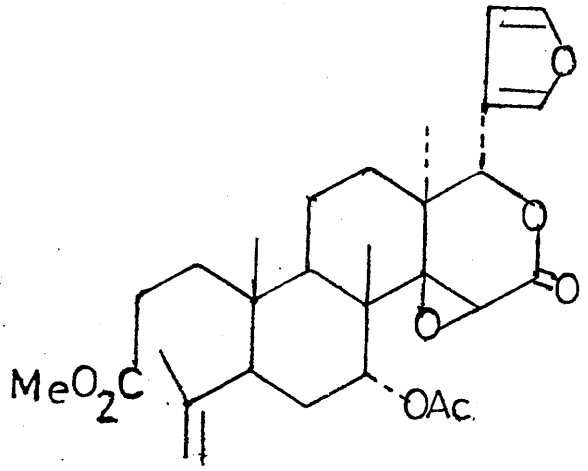

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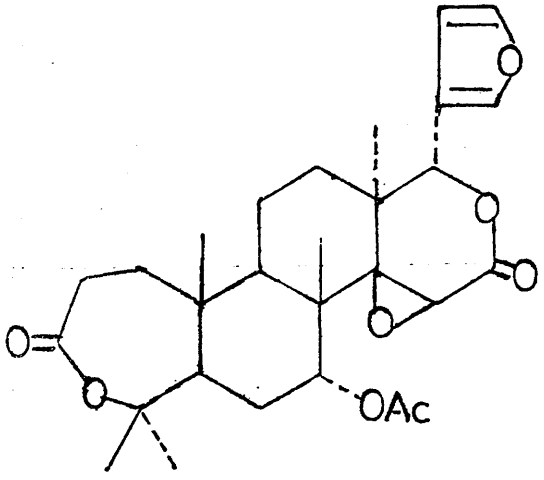

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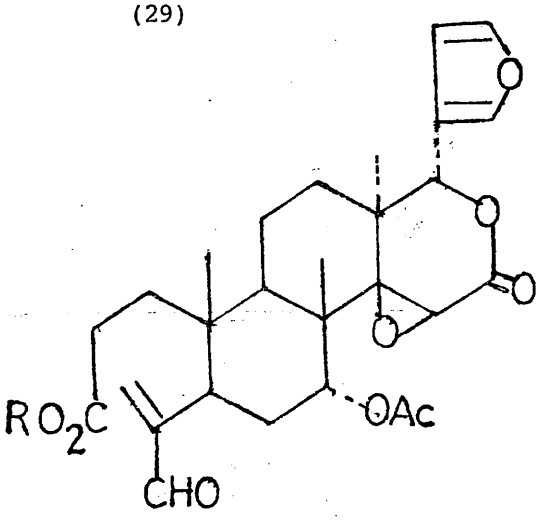
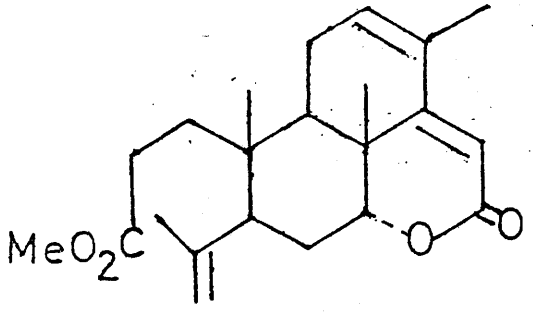


31) R = Me

32) R = H



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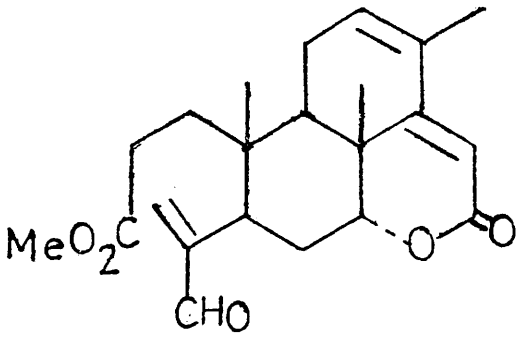

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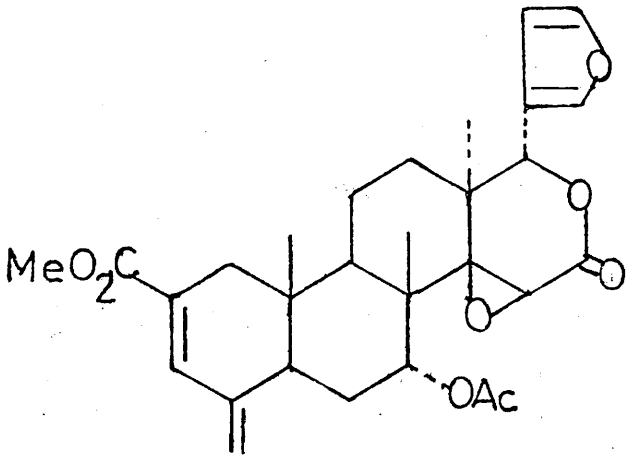

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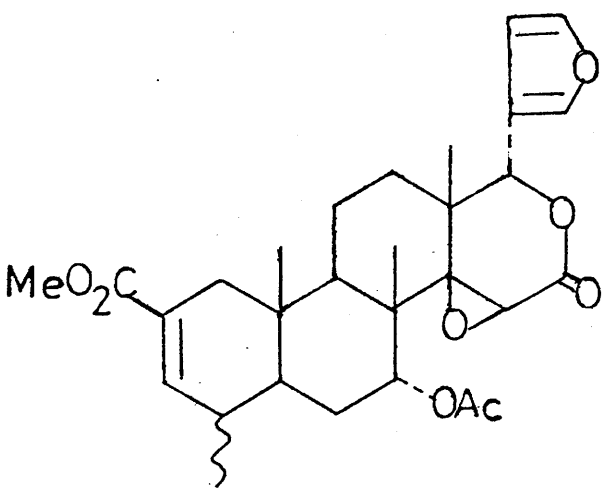

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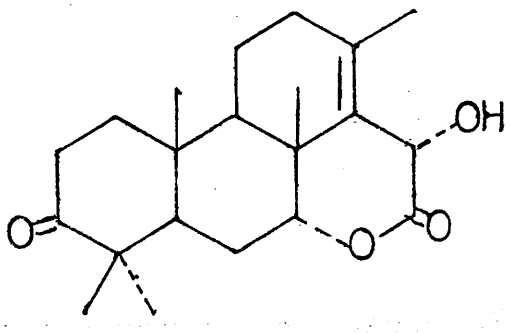

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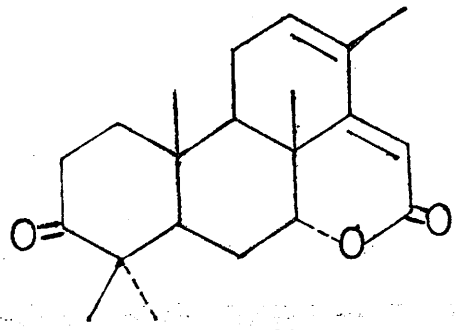

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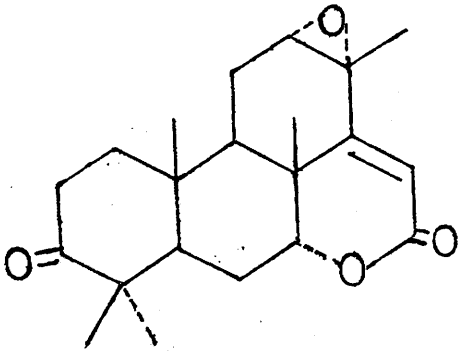

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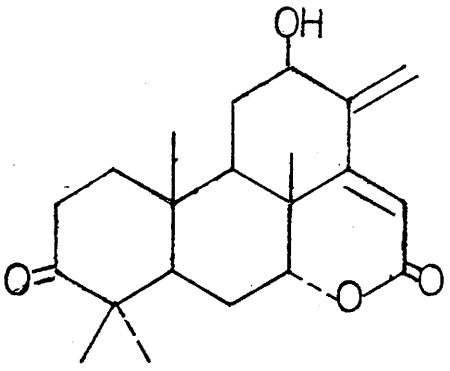

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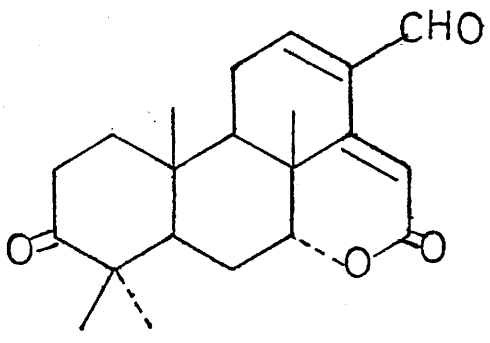

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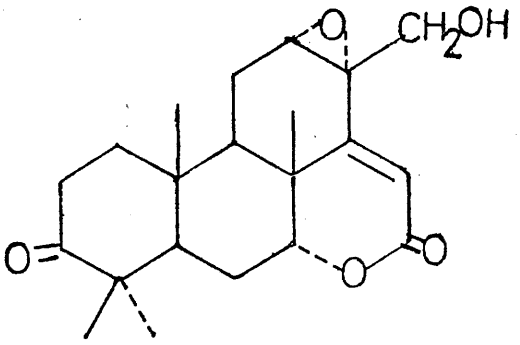
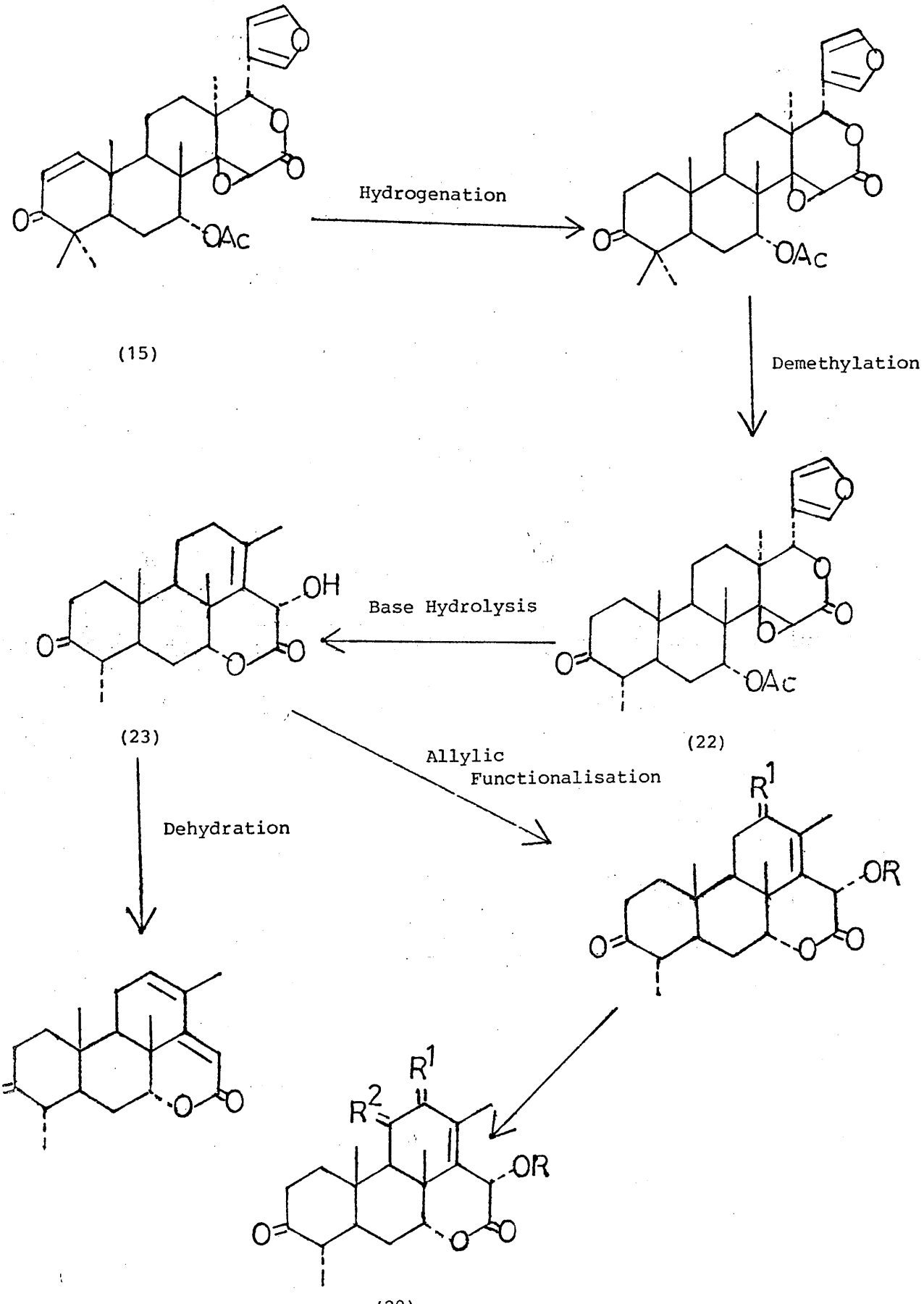
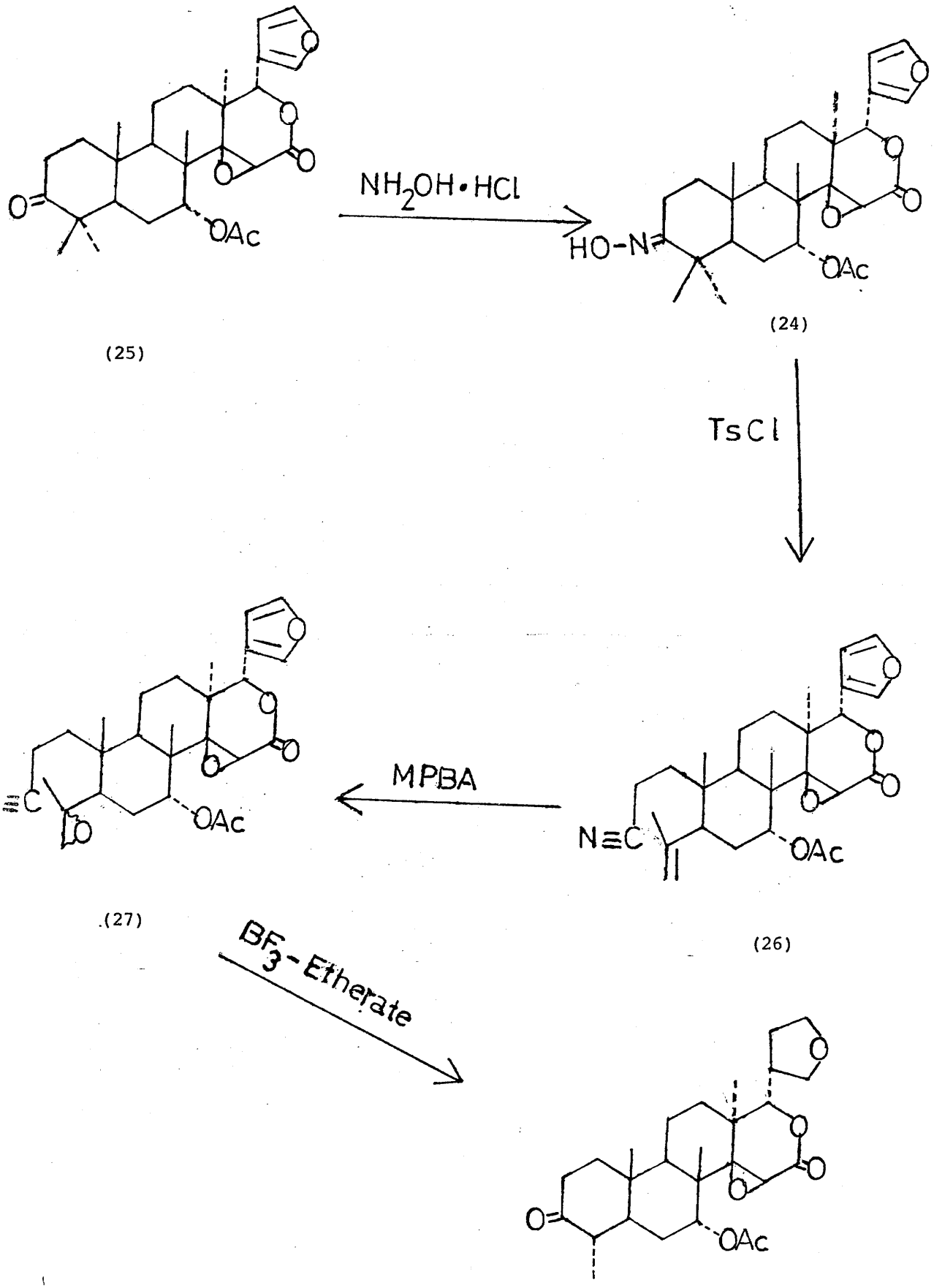


(42)

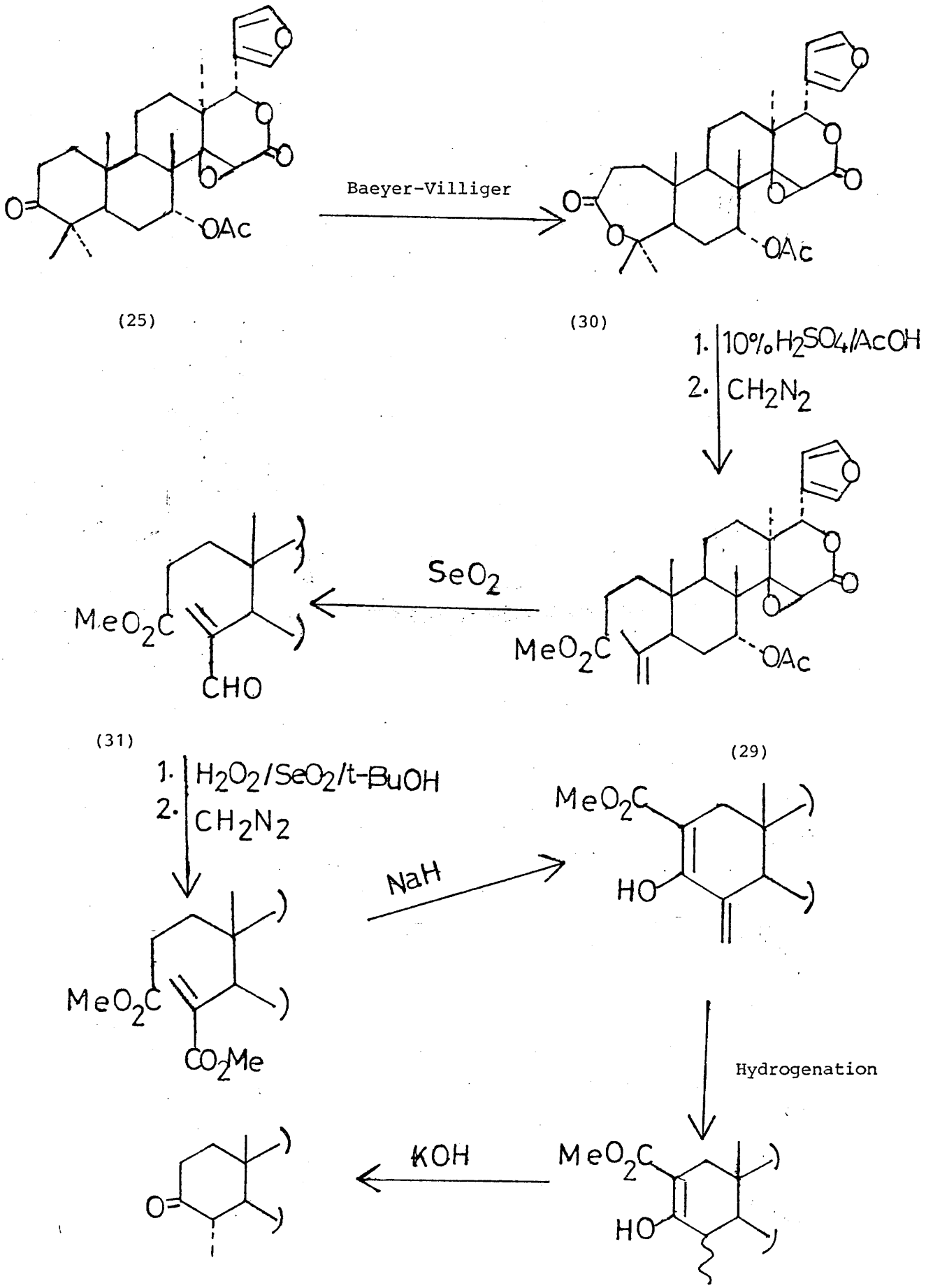
Scheme 1


Hydrogenation
OAc
(15)
Demethylation
OH
Base Hydrolysis
OAc
(23)
(22)
Allylic
Functionalisation
Dehydration
R1
OR
R2
R1
OR
(20)

Scheme 2


NH2OH•HCl
HO-N
OAc
(25)
(24)
TsCl
MPBA
N≡C
OAc
(27)
(26)
BF3-Etherate
O
OAc
(22)

Scheme 3


Baeyer-Villiger
OAc
(25)
(30)
1. 10% H_2SO_4/AcOH
2. CH_2N_2
SeO_2
MeO_2C
CHO
(31)
(29)
1. H_2O_2/SeO_2/t-BuOH
2. CH_2N_2
NaH
HO
CO_2Me
Hydrogenation
KOH
O

CHAPTER III

3,4-SECOTIRUCALLANE DERIVATIVES AND 2'-HYDROXYROHITUKIN FROM THE BARK OF GUAREA CEDRATA (MELIACEAE)

INTRODUCTION

The Meliaceae family embraces many species, which can be conveniently grouped into tribes. The Guareae is one such tribe. This tribe has been considerably investigated.

Cabralea eichleriana[1] contains dammarane triterpenoids related to aglaiol,[2] protolimonoids and a range of limonoids with a ring D epoxylactone as gedunin (1) and khivorin (2) and with ring B cleaved. Guarea trichiliodes[3] yielded fissinolide (3). A series of interesting cyclopropanoid triterpenoids related to glabretal (4) has been obtained from G. glabra.[4] Previous work on G. thompsonii and G. cedrata[5,6,7] produced several highly oxygenated compounds of the prieurianin (5) and rohitukin (6).

This chapter is concerned with the structural elucidation of three new compounds, the ring A secotirucallane A (7) and B (8) and 2'-hydroxy rohitukin (9), isolated from the bark of G. cedrata.

Prieurianin (5) and rohitukin (6) belong to the small group of complex tetranortriterpenoids from Trichilia, Guarea and Aphanamixis species, which unexpectedly exist in solution as a mixture of slowly interconverting sterically hindered conformational isomers. This results in broadening of the ^{13}C and ^{1}H n.m.r. spectra (and even in the absence of some ^{13}C resonances) at room temperature and makes interpretation more difficult. No progress was made with this group until it was realised that a conformational problem existed and the spectra were run at elevated temperature. Prieurianin, $C_{38}H_{50}O_{16}$, from the wood of T. prieuriana, was isolated in 1965,[16] but its structure remained unresolved until 1975 when it was assigned[17] the structure (5) on

the basis of chemical and spectroscopic evidence, and X-ray analysis.[18] The functional groups revealed spectroscopically (^{1}H and ^{13}C n.m.r.) include a ketone, two acetates, a formate, a carbomethoxy, a lactone, a 2'-hydroxy-3'-methylpentanoate, and an exomethylene. The remaining oxygens are accounted for by a β-substituted furan ring and a tertiary hydroxyl group. Thus prieurianin is bicarbocyclic and has two rings of the typical tetracyclic apotirucallol nucleus cleaved.

At ambient temperature only one tertiary methyl signal is apparent in the ^{1}H n.m.r. spectrum of prieurianin.[17] However at 67°C in deuterioacetone, the spectrum is well defined and three tertiary methyls are observed. Detailed analysis, with spin decoupling, of the high temperature spectrum suggested the partial structure (10) for rings C and D. It is perhaps not without significance that several uncleaved tetranortriterpenoids from other Trichilia species also have oxygenation at C-11 and C-12. These include the heudelottins[19] [e.g. heudelottin F (11)] from T. heudelottii and hirtin (12) from T. hirta.[20] Other features of the ^{1}H n.m.r. spectrum of prieurianin include two acetates, one primary and one secondary and two ABX spin systems, one involving the secondary acetate. These structural units taken in conjunction with the carbomethoxyl and lactone were readily assembled to give the biogenetically reasonable structure (5) for prieurianin. An X-ray analysis of prieurianin 2'-p-bromobenzenesulphonate confirmed structure (5) and established the full stereochemistry.[18]

The reasons for the conformational problems of prieurianin and related compounds are not yet clear. The atoms whose n.m.r. resonances are affected are all in the vicinity of the C-9, C-10 bond. The simplest explanation is that of restricted rotation about this bond. The ring A

ε-lactone seems to be necessary for this effect since ring B cleaved compounds with a carbocyclic ring A, e.g. toonacilin (13), have not been reported to suffer from conformational problems.

Rohitukin (6) from T. rokka is very similar to prieurianin with the C-7 carbonyl lactonised to C-29 to form a δ-lactone. The ester attached to C-12 was identified as 3-methylbutanoate.

Cleavage of ring A is a common feature in terpenoid chemistry. Kadsurdic acid (14), a secolanostane isolated from the stem of Kadsura japonica,[8] eichlerianic acid (15) and the lactone (16) isolated from Cabralea eichleriana[9] and sebiferic acid (17) from Sapium sebiferum[10] are representative examples. Entandrolide (18) isolated from the seeds of Entandrophragma species[11] is a simple tirucallane ring A lactone. Alnuseric acid (19) has been obtained in vitro from the 3-oxo compound (20)[12] with which it cooccurs.

The biogenetic derivation of these ring A cleaved compounds presumably involves Baeyer-Villiger oxidation of a 3-ketone followed by hydrolytic ring opening of the lactone and the dehydration of the tertiary hydroxyl group to give the 4,28-exomethylene group (Scheme 1).

D I S C U S S I O N

Chromatography of the extract of the bark of G. cedrata afforded three new compounds A, B and C which were assigned structures (7), (8) and (9) respectively on the following evidence.

Compound A (7), $C_{30}H_{46}O_4$, has spectroscopic properties consistent with the presence of two carboxyl groups [i.r.: 3200-2500 (br), 1709 cm^{-1}; δ_C 183.5 and 181.3], an exomethylene [δ_H 4.80 (2H, bs); δ_C 132.4 (s) and 114.1 (t)] and two trisubstituted double bonds [δ_H 5.23 (m, H-7) and 5.09 (bt, H-24); δ_C 123.5 (d, C-24), 147.5 (s, C-25) and 118.0 (d, C-7), 145.8 (s, C-8)]. The molecule is therefore tricarbocyclic. In addition there are three tertiary methyls (δ_H 0.81, 0.87 and 0.95) and three vinyl methyls (δ_H 1.55, 1.65 and 1.75). Hydrogenation over palladium charcoal of the dimethyl ester (21) obtained by reaction of (7) with diazomethane, afforded the tetrahydro-derivative (22) whose ^{13}C n.m.r. spectrum [δ_C 118.3 (d, C-7) and 145.6 (s, C-8)] clearly showed that one of the trisubstituted double bonds was resistant to hydrogenation under normal conditions. On treatment with dry hydrogen chloride in chloroform the tetrahydro dimethyl ester (22) was converted into the isomeric compound (23) with a tetrasubstituted double bond ^{13}C n.m.r. spectrum [δ_C 147.3 and 137.6 (C-8 and C-9)]. Under similar conditions the dimethyl ester (21) gave the chlorodiene (24) [δ_C 70.8 (s, C-25), 147.3, 137.6 both s, C-8 and C-9), 129.8 (s, C-4), 113.8 (t, C-28)]. This acid-induced isomerisation of a hindered trisubstituted to a tetrasubstituted double bond is reminiscent of the behaviour of Δ^7 tetracyclic triterpenoids, e.g. odoratol (33), and, taken in conjunction with the above spectroscopic evidence, led us to (7) as a biogenetically acceptable structure for compound A. This was confirmed in the following way.

Methyl 3-oxotirucalla-8,24-dien-21-oate (25), isolated from elemi resin according to the procedure of Halsall and his colleagues[14] was hydrogenated over palladium charcoal to give the non-crystalline 24,25-dihydro-derivative (26). Baeyer-Villiger oxidation of (26) with peracetic acid afforded a mixture of the lactone (27) and the epoxy-lactone (28), separable by preparative t.l.c. The former was converted into the diene dimethyl ester (30), via the hydroxy dimethyl ester (29) by alkaline hydrolysis, methylation and dehydration with thionyl chloride. Hydrogenation of (30) yielded dimethyl 3,4-secotirucall-8-en-3,21-dioate (23) identical in all respects with the product of acid isomerisation of dimethyl tetrahydro-A (22). This series of transformations confirmed that compound A is 3,4-secotirucalla-4(28),7,24-trien-3,21-dioic acid (7). Hydrolysis, methylation and dehydration of the epoxylactone (28) in sequence afforded (30) and (32) respectively.

The spectroscopic properties of compound B (8) $C_{31}H_{48}O_4$ suggested that it is a mono methyl ester of compound A. This was readily established by methylation with diazomethane to give the dimethyl ester (21). Comparison of the ^{13}C n.m.r. spectra of the three compounds (7), (8) and (21) indicated that the free carboxyl group of B (δ_C 183.5) is associated with the downfield carbomethoxyl group (δ_C 176.4) of the dimethyl ester (21). It is therefore assigned as the C-21 carboxyl group on the basis of normal ^{13}C substitution rules.[15] Thus compound B is 3,4-secotirucalla-4(28), 7,24-trien-3,21-dioic acid 3-methyl ester (8).

Compound C from the extract is a new complex tetranortriterpenoid, 2'-hydroxyrohitukin (9), $C_{34}H_{42}O_{14}$, belonging to the small group of compounds, related to prieurianin (5) and rohitukin (6)[7] which give broad ^1H n.m.r. spectra at room temperature as a result of conformational

processes occurring at an intermediate rate on the n.m.r. time scale. At 60°C the ^{1}H n.m.r. spectrum of (9) is well resolved and readily revealed the structural features. Thus it has resonances for a β-substituted furan, an acetate, a formate, two hydroxyl groups (δ 5.21 and 2.45, exchangeable with D_2O), 2H-29 (δ 4.17, bs), H-17 (δ 3.98, t, J 9Hz), an exomethylene (δ 5.90 and 5.49, both s, 2H-30), H-1 (δ 5.10, m), H-2' (δ 3.13, d, J 4Hz), three tertiary (δ 0.95, 1.73 and 1.78) and two secondary methyl groups (δ 0.83 and 0.65, both d, J 7Hz). Decoupling experiments identified the characteristic ring C system involving H-9 (δ 3.76, d, J 7Hz), H-11 (δ 5.45, dd, J 12, 7Hz) and H-12 (δ 6.13, d, J 12Hz). The ^{13}C n.m.r. spectrum confirmed the presence of the ε- and δ-lactones and the ketol system in ring D. The above data suggested that (9) only differed from rohitukin (6) in the nature of the ester function attached to C-12. This was confimed by comparison of their ^{13}C spectra[22] (Table 1) which are virtually identical with the exception of the resonances associated with the ester functions. It is apparent that the 3-methyl butanoate (34)[15] of rohitukin has been replaced by a 2-hydroxy-3-methylbutanoate (35) in (9). As expected the introduction of a hydroxyl substituent on C-2' causes a large downfield shift of C-2', smaller downfield shifts of C-1' and C-3' and differential upfield shifts of C-4' and C-5'.

GENERAL EXPERIMENTAL

All melting points were determined on a Kofler hot-stage apparatus and are uncorrected. Proton nuclear magnetic resonance spectra were recorded on Varian XL-100 or Perkin-Elmer R-32 spectrometers using tetramethylsilane as internal reference in deuteriochloroform, except where otherwise stated. Proton noise decoupled pulsed FT ^{13}C n.m.r. spectra width $\leq$ 1.52 Hz per data point were obtained at 25.2 MHz on a Varian XL-100 spectrometer, operated by Dr. D.S. Rycroft, for solutions in $CDCl_3$ at room temperature (ca 25°C), unless otherwise stated. Shifts are given as positive downfield (p.p.m.) from internal tetramethylsilane. Assignments are based on chemical shift rules, multiplicities in the off-resonance-decoupled spectra, correlation with ^1H chemical shifts using two off-resonance-decoupled spectra, and by comparison with similar compounds.

Mass spectra were routinely determined by Mr. A. Ritchie and staff on an AEI-GECMS-12 mass spectrometer. Microanalysis were carried out by Mrs. W. Harkness and staff.

U.V. and I.R. were carried out by Mrs. F. Lawrie and staff.

Columns were run using Grade IV acid alumina and t.l.c. on silica gel plates of 0.5 mm thickness, except where otherwise stated.

EXPERIMENTAL

Extraction.- Powdered bark (6 kg) of G. cedrata collected in Okonolinga (Cameroon) was extracted with hexane in a Soxhlet. A solid (1.2 g) which separated during extraction was shown by preparative t.l.c. (benzene-ethyl acetate, 3:1), to be mainly one compound. Crystallisation from methanol afforded 2'-hydroxy-rohitukin (9) (0.6 g), m.p. 231-237°C; m/e 614 (P-60); i.r. (CCl_4); 3620, 3440, 1750, 1740 and 1720 cm^{-1}; [^{13}C n.m.r. δ (60°C) see Table I]. (Found: C, 58.9; H, 6.3; $C_{34}H_{42}O_{14}.H_2O$ requires C, 58.95; H, 6.35%). A further crop of solid (0.5 g) was shown by t.l.c. (methylene chloride-methanol, 19:1) to contain a second compound as a major component. Chromatography over silica gel and elution with hexane-ether (19:1) yielded compound B, 3,4-secotirucalla-4(28),7,24-trien-3,21-dioic acid 3 methyl ester (8) (300 mg) m.p. 190° (ex methanol), [α_D] + 11° (c, 0.5 in methanol); m/e 484; i.r. (CCl_4): 3500-2500, 1741, 1703 and 1640 cm^{-1}; [^1H n.m.r. δ 0.78, 0.89 and 0.97 (C-Me), 1.75, 1.65 and 1.55 (vinyl Me), 3.62 (CO_2Me), 4.8 (2H, bs, CH_2=C<), 5.09 (1H, bt, H-24) and 5.23 (1H, m, H-7); ^{13}C n.m.r. δ 183.4 (C-21), 174.4 (C-3), 147.3 (c-25), 123.6 (C-24), 145.9 (C-8), 118.3 (C-7), 132.3 (C-4), 113.9 (C-28), 51.4 (CO_2Me), 51.3, 43.3 and 36.8 (s), 50.0, 49.3, 47.5 and 40.6 (d), 33.6, 32.2, 32.0, 30.2, 30.1, 28.1, 27.4, 26.1 and 18.1 (t) and 27.4, 25.7, 22.5, 21.7, 17.6 and 15.8 (q).] (Found: C, 76.85; H, 9.70; $C_{31}H_{48}O_4$ requires C, 76.8; H, 10.0%). Concentration of the hexane extract gave an oily solid which was washed with benzene and chloroform. The solid residue (8 g) was dissolved in methanol-chloroform and adsorbed on a silica gel column. Elution with benzene gave compound A, 3,4-secotirucalla-4(28), 7,24-trien-3,21-dioic acid (7) (5.75 g) m.p. 170° (ex benzene),

[α_D] + 18° (c, 1.4 in methanol); m/e 470; [^{13}C n.m.r. δ 51.4, 43.3 and 36.4 (s), 50.3, 50.0, 48.8, 40.7 (d), 33.6, 32.2, 30.5, 30.1, 30.1 and 27.2, 27.2, 26.0 and 18.1 (t), 27.0, 25.7, 21.7, 21.4, 17.7 and 16.2 (q)]. (Found: C, 75.0; H, 10.3; $C_{30}H_{46}O_4.H_2O$ requires C, 75.3; H, 10.0%).

Dimethyl,3,4-secotirucalla-4(28),7,24-trien-3,21-oate (21).- Reaction of either compound A (7) or compound B (8) with diazomethane in methanol followed by purification by preparative t.l.c. yielded the non-crystalline dimethyl ester (21); m/e 498; [^{1}H n.m.r. δ 0.78, 0.83 and 0.94 (C-Me), 1.74, 1.64, and 1.53 (vinyl Me), 3.63 (2 x CO_2Me), 4.80 (2H, bs, (CH_2=C<), 5.05 (1H, bt, H-24) and 5.23 (1H, m, H-7); ^{13}C n.m.r. δ 176.5 (C-21), 174.3 (C-3), 147.3 (C-25), 123.7 (C-24), 145.9 (C-8), 118.3 (C-7), 132.0 (C-4), 113.9 (C-28), 51.5 and 51.1 (2 x CO_2Me), 51.1, 43.1 and 36.8 (s), 49.8 49.4, 47.6 and 40.6 (d), 33.8, 32.4, 31.8, 30.2, 30.2, 28.1, 27.4, 26.1 and 17.8 (t) and 27.1, 25.7, 22.4, 21.9, 17.6 and 15.9 (q)].

Dimethyl 3,4-secotirucall-7-en-3,21-dioate (22).- The dimethyl ester (21) (146 mg) in ethyl acetate solution was hydrogenated over 10% palladium charcoal until uptake of hydrogen ceased. Normal work up afforded the non-crystalline tetrahydro dimethyl ester (22) (140 mg); m/e 502; [^{1}H n.m.r. δ 3.64 (2 x CO_2Me) and 5.26 (1H, m, H-7); ^{13}C n.m.r. δ 176.6 (C-21), 174.6 (C-3), 145.6 (C-8), 118.3 (C-7), 51.5 and 51.1 (2 x CO_2Me)].

Dimethyl 3,4-secotirucall-8-en-3,21-dioate (23).- Dry hydrogen chloride gas was bubbled through a chloroform solution of the tetrahydrodimethyl ester (22) (100 mg) for ten minutes and the reaction left for one hour at room temperature. Dimethyl 3,4-secotirucall-8-en-3,21-dioate (23) (90 mg) obtained on work up, was crystallised from ether-

light petroleum and had m.p. 92-94°C, m/e 502; cd $\Delta\varepsilon$ value -2.37 (223 nm) -4.75 (200 nm); [^{1}H n.m.r. δ 3.64 (2 x $CO_2\underline{Me}$) no vinyl protons.] (Found: C, 76.3; H, 10.85; $C_{32}H_{54}O_4$ requires C, 76.45; H, 10.85%).

Dimethyl 25-chloro-3,4-secotirucall-4(28),8-dien-3,21-dioate (24).- On treatment with dry hydrogen chloride gas under the above conditions the dimethyl ester (21) (100 mg) was converted into the chlorodiene (24) (87 mg); m.p. 114-115°C (ex ether-light petroleum). M/e 498 (P-HCl); [^{1}H n.m.r. δ 0.80, 0.86, 0.90 (C-$\underline{Me}$), 1.52 (6H, Cl-$C\underline{Me}_2$), 1.73 (vinyl $\underline{Me}$), 3.68 (2 x $CO_2\underline{Me}$), 4.68 and 4.89 (each 1H, bs, $\underline{CH}_2$=C<)]. (Found: C, 71.85; H, 9.8; Cl, 6.7; $C_{32}H_{51}O_4Cl$ requires C, 71.85; H, 9.55; Cl, 6.65%).

Methyl 3-oxotirucall-8-en-21-oate (26).- Methyl 3-oxotirucall-8,24-dien-21-oate (25) (150 mg) m.p. 110-113°C isolated from elemi resin, was dissolved in ethyl acetate and hydrogenated over 10% palladium charcoal. Normal work up afforded the non-crystalline methyl 3-oxotirucall-8-en-21-oate (26) (130 mg). M/e 470; [^{1}H n.m.r. δ 3.66 ($CO_2\underline{Me}$)].

Baeyer Villiger Oxidation of (26).- Acetic anhydride (20 ml) was added dropwise over a period of twenty minutes to a stirred, ice-cold solution of methylene chloride (20 ml) containing hydrogen peroxide (90%, 6 ml) and a drop of concentrated sulphuric acid. Stirring was continued for thirty minutes at room temperature. Excess of this peracetic acid was added dropwise to a stirred, ice-cold solution of the dihydro derivative (26) (130 mg) in dry methylene chloride (20 ml) in the presence of anhydrous disodium hydrogen phosphate (160 mg) and the reaction allowed to stand overnight at room temperature. The mixture was flooded with water and extracted into chloroform which was evaporated under reduced pressure. Analytical t.l.c. of the crude

product showed the presence of two products which were separated by preparative t.l.c. (13% ether-benzene). The lactone (27) (50 mg) was crystallised from ether-light petroleum and has m.p. 135-137°; m/e 486; [^{1}H n.m.r. δ 3.66 ($CO_2\underline{Me}$); ^{13}C n.m.r. δ 176.7 (C-21), 174.3 (C-3), 134.2 and 133.5 (C-8 and C-9), 86.0 (C-4) and 51.0 ($CO_2\underline{Me}$)]. (Found: C, 76.5; H, 10.45; $C_{31}H_{50}O_4$ requires C, 76.5; H, 10.35%). The epoxy lactone (28) (40 mg) was crystallised from ether-light petroleum and has m.p. 169-170°C; m/e 502; [^{1}H n.m.r. δ 3.63 ($CO_2\underline{Me}$), ^{13}C n.m.r. δ 176.6 (C-21), 173.3 (C-3), 85.5 (C-4), 69.6 and 68.8 (C-8 and C-9), 51.5 ($CO_2\underline{Me}$)]. (Found: C, 74.25; H, 10.0; $C_{31}H_{50}O_5$ requires C, 74.05; H, 10.05%).

Dimethyl 4-hydroxy-3,4-secotirucall-8-en-3,21-dioate (29).- The lactone (27) (50 mg) was refluxed in ethanolic KOH (5%) for two hours. Acidification with acetic acid, extraction with chloroform, methylation with diazomethane in methanol and purification by preparative t.l.c. (13% ether-benzene) yielded the hydroxy dimethyl ester (29) (40 mg) m.p. 97-98°C (ex ether-light petroleum); m/e 500 (P-18); i.r. (CCl_4): 3501 and 1735 cm^{-1}; [^{1}H n.m.r. δ 3.66 (2 x $CO_2\underline{Me}$); ^{13}C n.m.r. δ 176.8 (C-21), 176.0 (C-3), 138.5 and 130.8 (C-8 and C-9), 75.3 (C-4), 51.7 and 51.0 (2 x $CO_2\underline{Me}$)]. (Found: C, 74.4; H, 10.6; $C_{32}H_{54}O_5$ requires C, 74.1; H, 10.5%).

Dimethyl 4-hydroxy-3,4-secotirucall-8α,9α-epoxy-3,21-dioate (30).- The epoxylactone (28) (40 mg) was treated as described above. This afforded compound (30) (36 mg) m.p. 104-106°C (ex ether-light petroleum), m/e 516 (P-18). (Found: C, 71.81; H, 10.29; $C_{32}H_{54}O_6$ requires C, 71.87; H, 10.18%). I.r. (CCl_4): 3501 and 1735 cm^{-1}.

Dimethyl 3,4-secotirucall-4(28),8-dien-3,21-dioate (31).- An ice-cold solution of the hydroxy dimethyl ester (29) (28 mg) in dry pyridine (3 ml) was treated with thionyl chloride (three drops) and allowed to stand for five minutes. Water was added and the solution extracted with chloroform and evaporated to dryness under reduced pressure. The crude product was purified by preparative t.l.c. (13% ether-benzene) to give the diene dimethyl ester (31) (25 mg) m.p. 105-106°C (ex ether-light petroleum); m/e 500; [^{1}H n.m.r. δ 4.68 and 4.89 (each 1H, bs, CH_2=C<), 3.66 (2 x CO_2Me), 1.72 (vinyl Me)]. (Found: C, 74.2; H, 10.5; $C_{32}H_{52}O_4.H_2O$ requires C, 74.4; H, 10.5%).

Dimethyl 3,4-secotirucall-4(28)-en-8α,9α-epoxy-3,21-dioate (32).- The hydroxy dimethyl ester (30) (30 mg) was treated as described for (31), and resulted in (32) (25 mg). M.p. 119-120°C (ex ether-petroleum ether); m/e 516. (Found: C, 74.15; H, 9.96; $C_{32}H_{52}O_5$ requires C, 74.37; H, 10.14%).

Hydrogenation of compound (31).- The diene dimethyl ester (31) (25 mg) was dissolved in ethyl acetate and hydrogenated over 10% palladium charcoal as above. Preparative t.l.c. of the crude product and crystallisation from ether-light petroleum gave dimethyl 3,4-secotirucall-8-en-3,21-dioate (23) (21 mg) m.p. 92-93°C, cd, Δε -1.89 (223 nm), -5.50 (203 nm) identical in all respects (n.m.r., mass spectrum, cd, mixed m.p., and t.l.c.) with the compound obtained by hydrogenation and acid isomerisation of the dimethyl ester (21) derived from compound A (7) and (8). (Found: C, 76.4; H, 11.0; $C_{32}H_{54}O_4$ requires C, 76.45; H, 10.85%).

Table 1

^{13}C n.m.r. spectra of rohitukin and related compounds.

Carbon No.	6^h	9^h	Carbon No.	6^h	9^h
1	71.8	71.3	1'	172.2	175
2	37.6	37.5	2'	42.9	73
3	169.5	169.4	3'	24.9	31.2
4	81.2	81.1	4'	22.5	19.1
5	42.8	42.7	5'	22.5	15.5
6	32.2	32.1	HC(O)	160.3	160.3
7	173.3	173.3	OAc	21.2	21.2
8	139.2	138.9	C-Me	23.3	23.3
9	52.0	51.9		21.4	21.4
10	49.7	49.8		12.9	13.0
11	75.7	74.9	CH_3COO	169.3	169.4
12	75.8	75.6			
13	46.4	46.3			
14	79.5	79.4			
15	206.6	206.4			
16	42.0	42.0			
17	35.4	35.4			
20	124.7	124.9			
21	140.8	140.9			
22	110.8	110.6			
23	142.9	143.3			
29	78.0	78.1			
30	123.0	122.8			

(h) at 60°C

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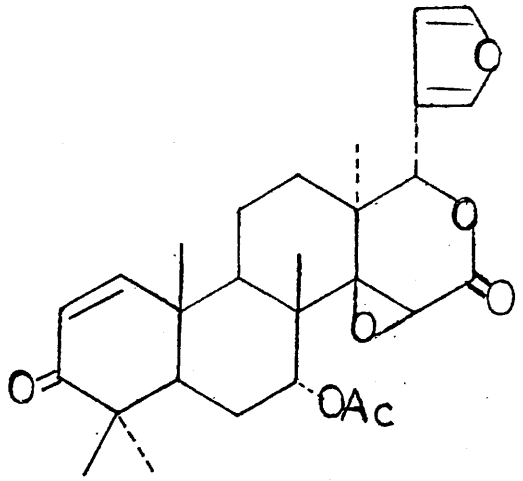
22. See Table 1.



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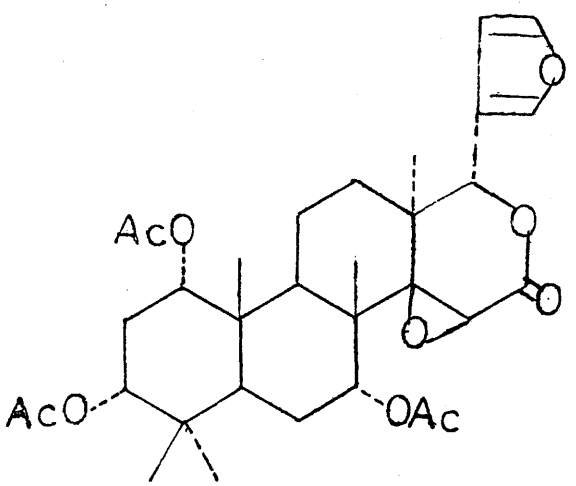

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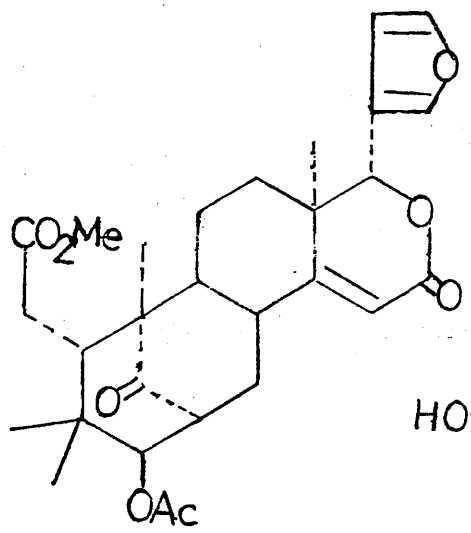

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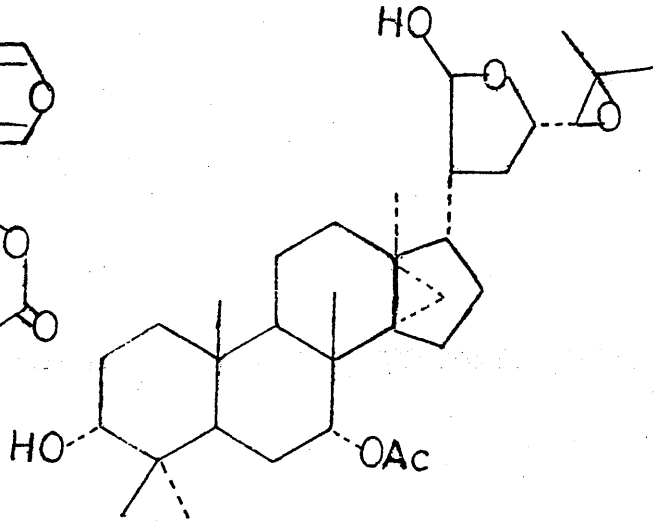

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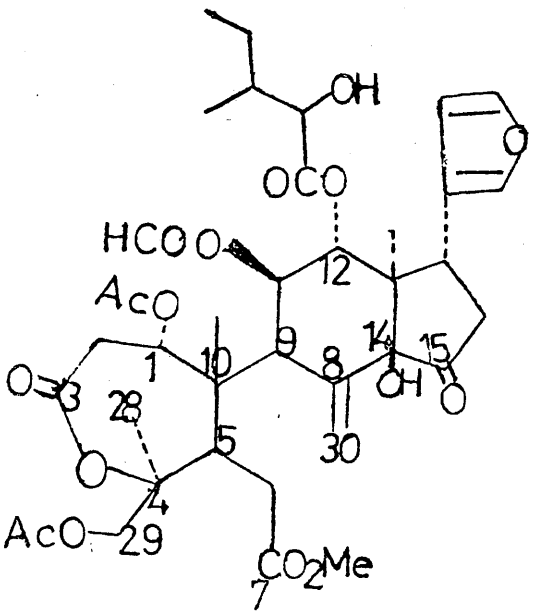

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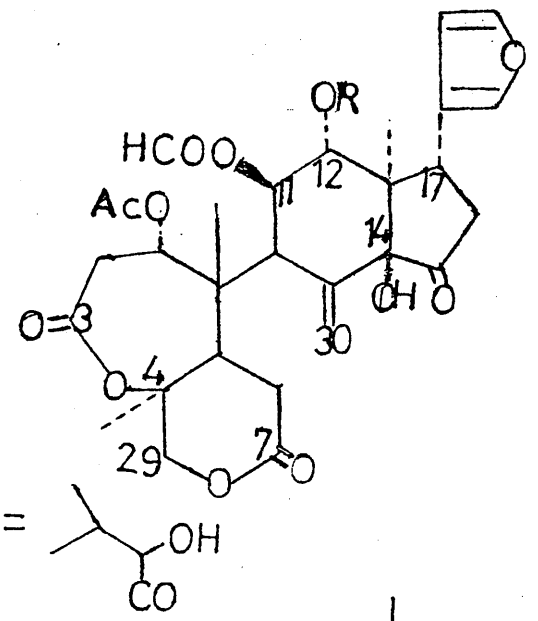
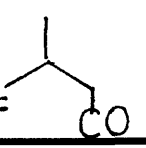
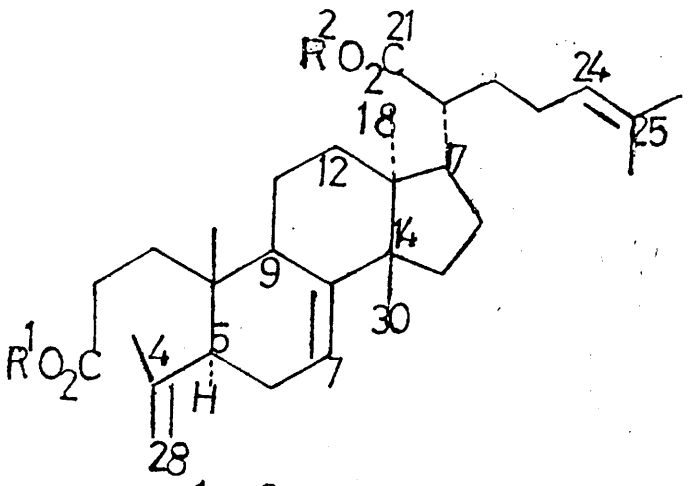


(9) R =

(6) R =

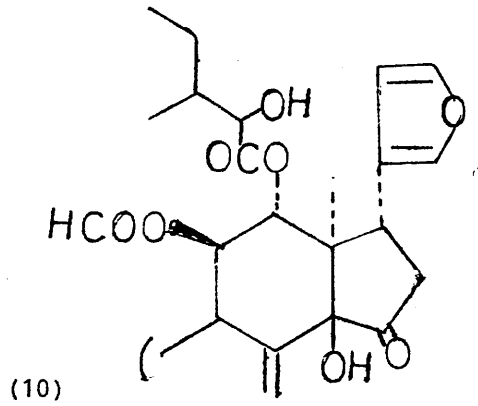




7) $R^1 = R^2 = H$

8) $R^1 = Me$, $R^2 = H$

21) $R^1 = R^2 = Me$



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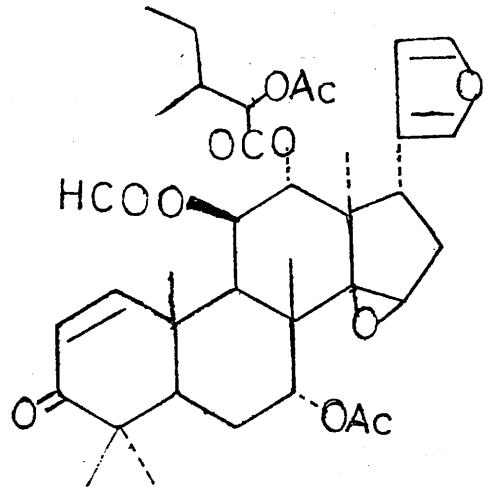

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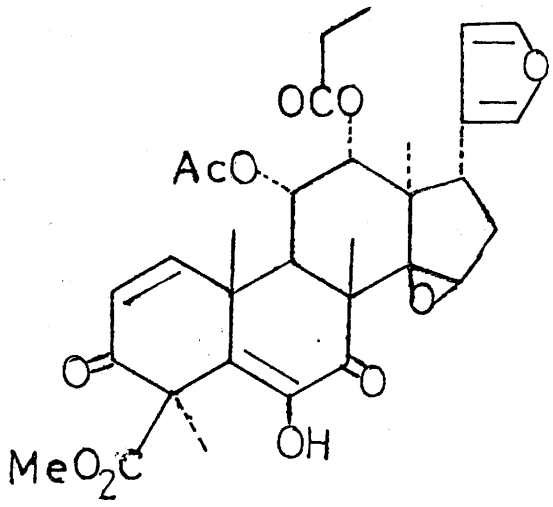

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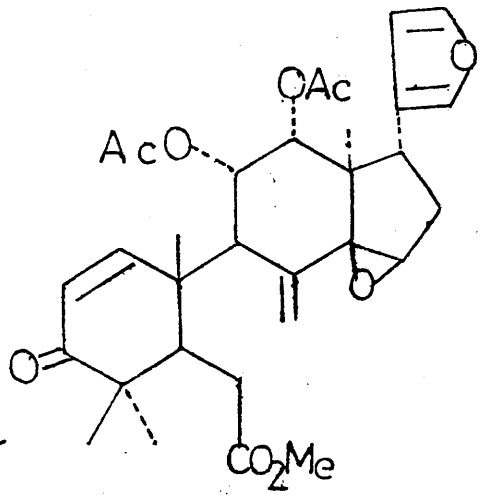

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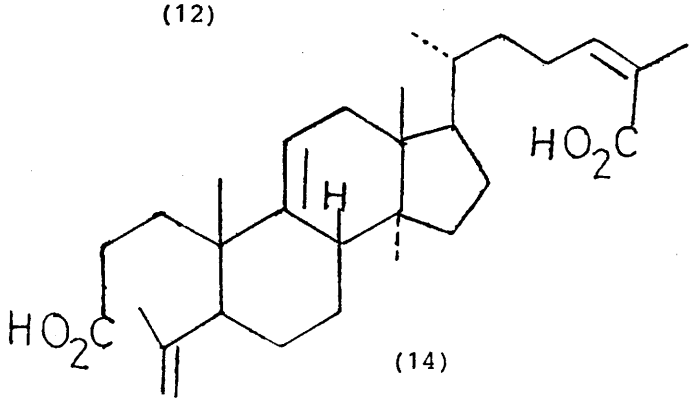

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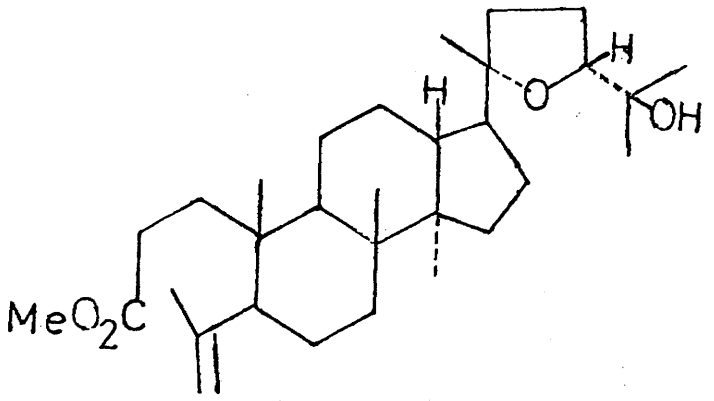

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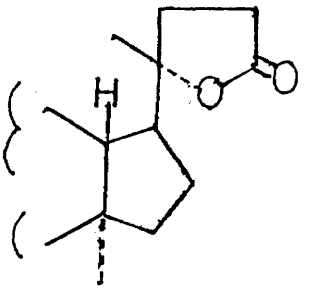

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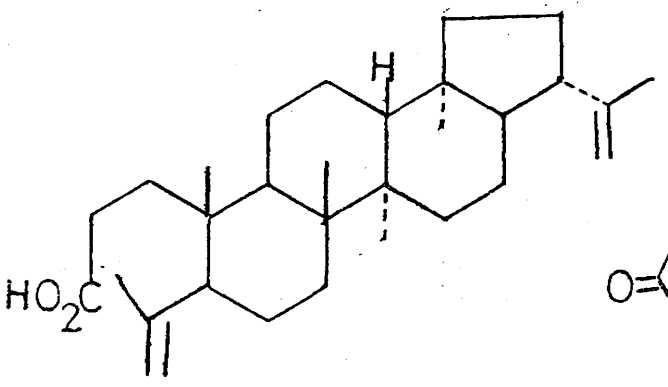

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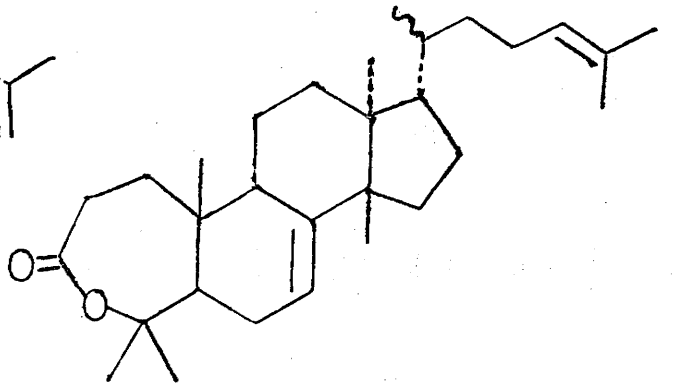

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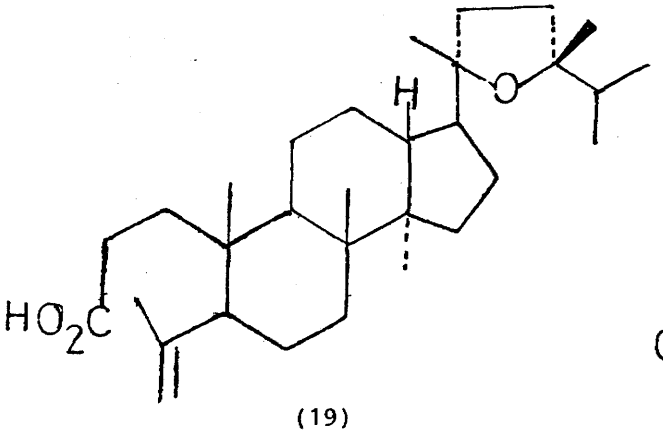

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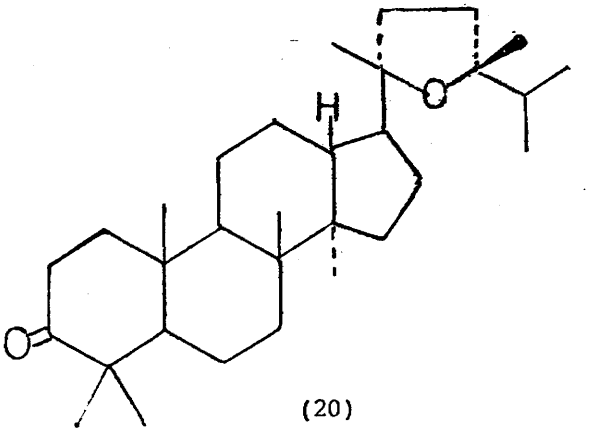

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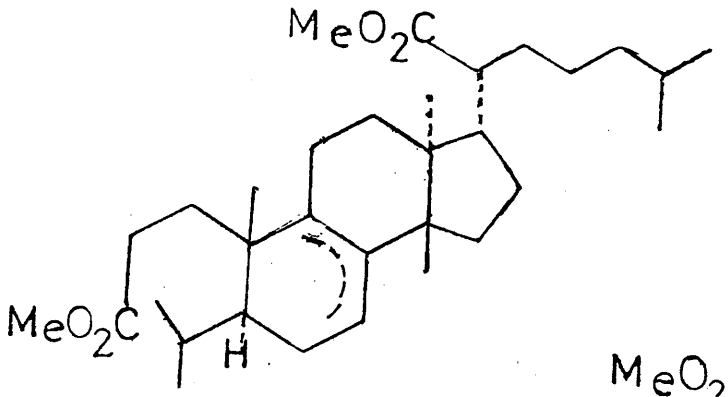

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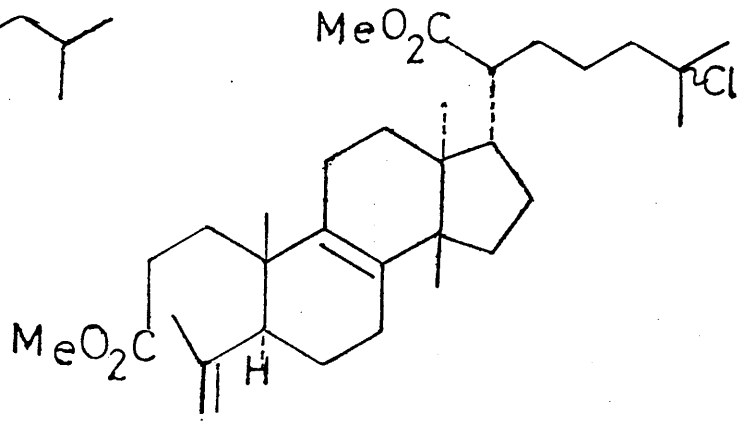

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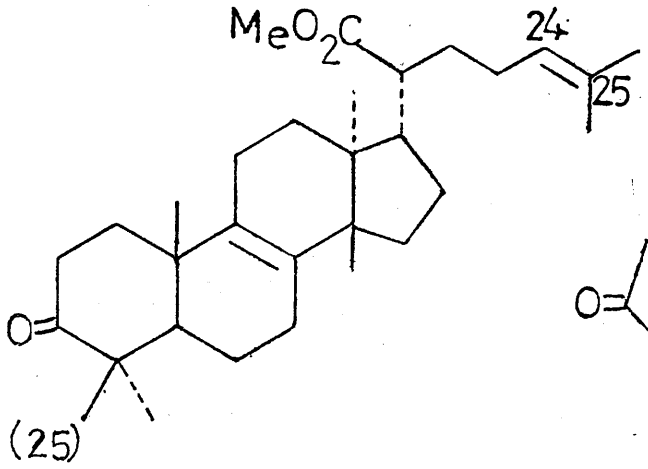
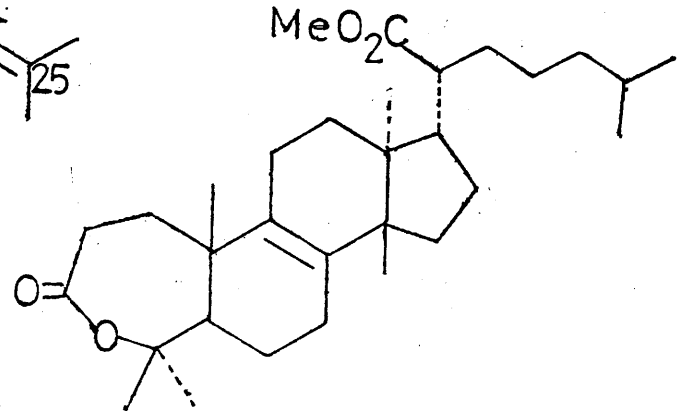


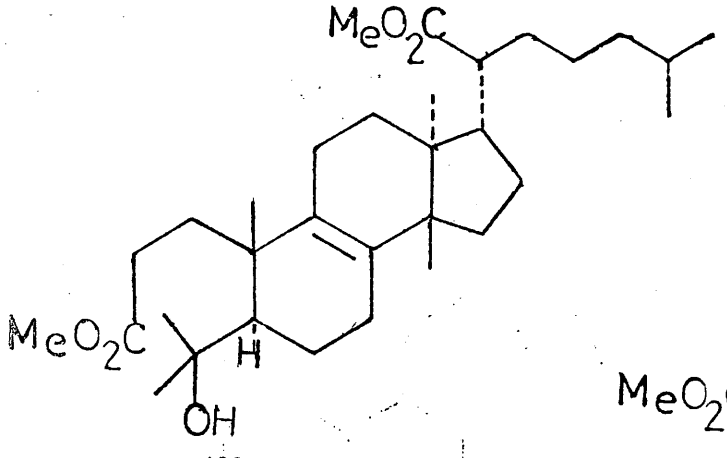
(25)

26) 24,25-dihydro (25)



(27)

(28) 8α,9α epoxide



(29)

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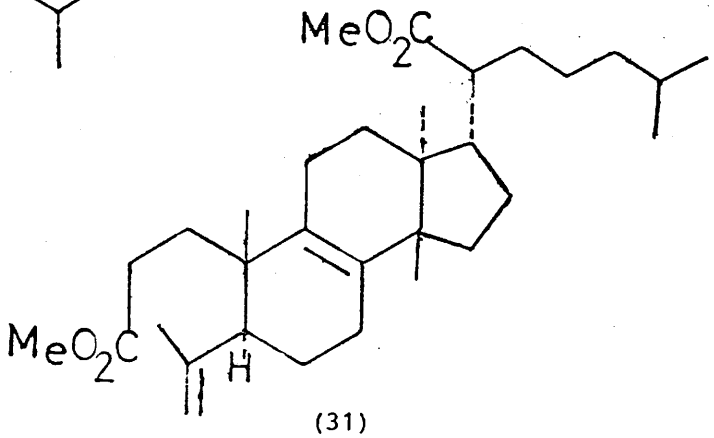

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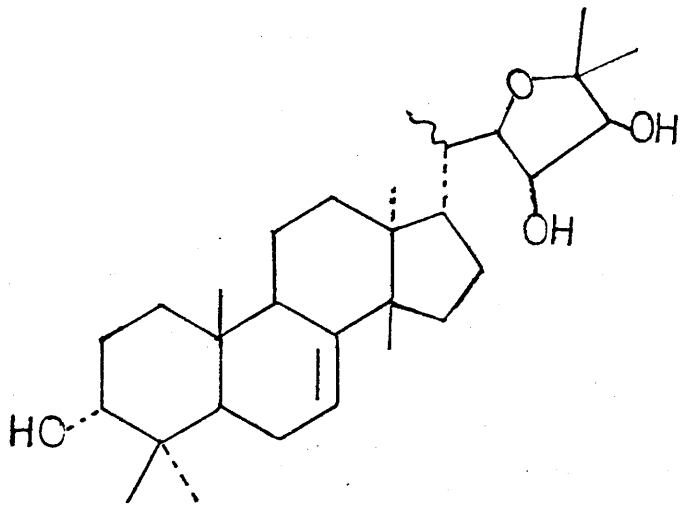
(32) 8α,9α epoxide



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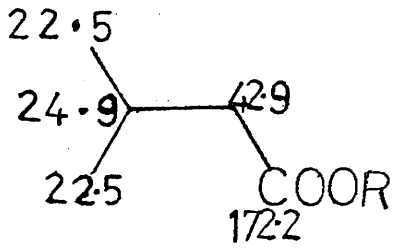

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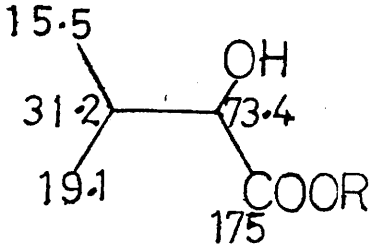
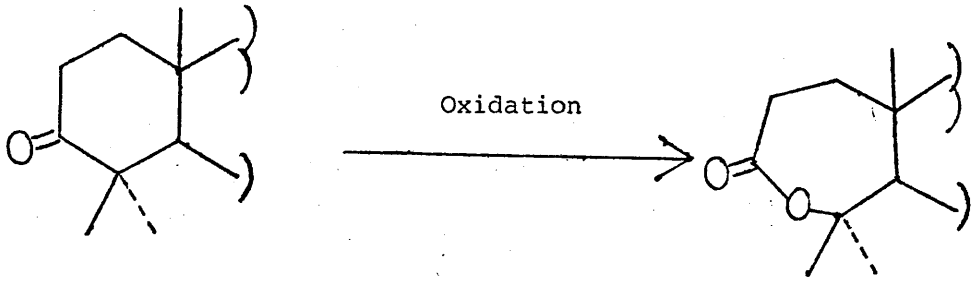
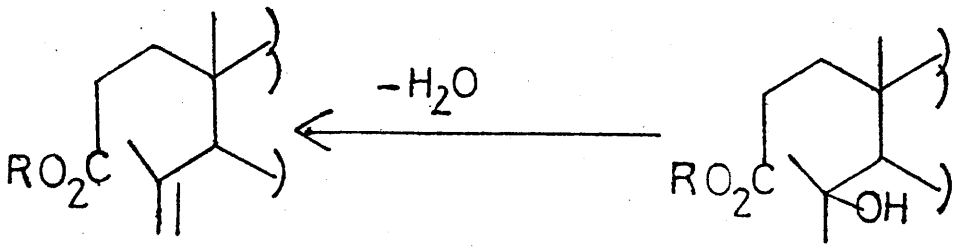


(35)

Scheme 1



(36) (37)



(40) R = H

(41) R = Me

(38) R = H

(39) R = Me

CHAPTER IV

EXTRACTIVES FROM THE SEED OF TRICHILIA DREGEANA (MELIACEAE)

INTRODUCTION

The *Trichiliae* is one of the genera of the *Meliaceae* family. It is apparently the second most widely studied. Representative compounds include havenensin (1) from *Trichilia havanensis*,[1] heudelottin (2) from *T. heudelotti*,[2] hirtin (3) from *T. hirta*[3] and prieurianin (4) from *T. prieuriana*.[4] *T. dregeana*, also known as *T. splendida*, a medium to large tree often planted for shade, is found extending northwards from South Africa to tropical Africa. The timber from the tree has been found to contain dregeanin (5),[5,6] and the bark has been found to yield a similar compound, which has not yet been identified.

This chapter is concerned with four more compounds which were isolated from the seed of *T. dregeana*. The seeds were collected from the shade trees of the cricket ground of Durban High School (S. Africa). The hexane extract of the seeds is a formidable mixture but repetitive preparative t.l.c. eventually afforded small amounts of four compounds, dregeana 1 (6), dregeana 2 (7), dregeana 3b (8) and rohituka 7 (9) whose structures are based entirely on the spectroscopic evidence described below.

D I S C U S S I O N

Dregeana 1 (6), $C_{33}H_{40}O_{12}$, has spectroscopic properties (see Tables 1 and 2) which are very similar to those of polystachin (10) from Aphanamixis polystacha.[7] Its ^{1}H n.m.r. spectrum shows resonances for a β-substituted furan, a formate, an exomethylene, an AB quartet (δ 4.26 and 4.09, J 12 Hz, 2H-29) and three tertiary methyls. Decoupling experiments readily revealed the characteristic H-9, H-11, H-12 coupled system. The presence of a 2-hydroxy-3-methylpentanoate is suggested by two unresolved methyl signals at δ ca. 0.8 and a secondary carbinol proton at δ 3.36 (d, J 4 Hz, H-2'). The ^{13}C spectrum of (6) has appropriate resonances for this ester moiety and, in addition, shows characteristic carbonyl signals associated with a C-15 ketone, two lactones (C-3 and C-7), a formate and the C-12 ester. These functional groups account for all but one of the oxygen atoms. This oxygen must be present as an ether to accommodate the remaining double bond equivalent. The secondary-tertiary nature of this ether follows from the fact that there are two unassigned oxygen-bearing carbons, a singlet and a doublet, in the ^{13}C off-resonance spectrum. The ^{1}H resonance for the secondary terminus appears at δ 3.87 (m). These functional groups can be assembled to give the biogenetically acceptable structure (6) for dregeana 1 which is, therefore, closely related to polystachin and differs only in the nature of the C-12 ester function. Unlike most of the other compounds in this series dregeana 1 gives sharp spectra at room temperature presumably because the 1,14-oxide prevents rotation about the C-9, C-10 bond. There is no firm evidence for the configuration at C-1 which is drawn in the biogenetically usual α-configuration.

The structure of rohituka 7 (9), $C_{35}H_{44}O_{13}$, is readily assigned from its spectroscopic properties. It gives broad spectra at room temperature which are characteristic of prieurianin (4) and related compounds.[6] At 60°C the spectra are well resolved. The functional groups include two lactones, one α,β-unsaturated, a formate, an exo-methylene, a 2'-hydroxy-3-methylpentanoate, a tertiary hydroxyl and a β-substituted furan. These indicate a close relationship with D-4 (11), an α,β-unsaturated ring A lactone from T. prieuriana.[6] The only difference concerns C-14 and C-15. The epoxide of D-4 (11) is absent in (9) and is replaced by a tertiary hydroxyl and a secondary acetate group. Thus rohituka 7 has structure (9). Unlike the other compounds discussed in this chapter rohituka 7 is crystalline. It has also been isolated from Aphanamixis polystacha.[8]

The third compound dregeana 2 (7) has the molecular formula $C_{33}H_{42}O_{13}$. Its n.m.r. spectra are broad at ambient temperature indicating that it is a ring B cleaved tetranortriterpenoid related to prieurianin. The structural units revealed spectroscopically include a ring A lactone, a carbomethoxyl, an exomethylene, a coupled system involving H-9, H-11, and H-12 with ester functions attached to 11 and 12, a ring D ketol and a β-substituted furan. Dregeana 2 is distinguished from prieurianin by the absence of a formate and a C-29 methylene group. The ^{13}C spectrum has resonances for three acetates and four tertiary methyl groups. Thus dregeana 2 must have a gem-dimethyl system at C-4 and acetates at C-1, C-11 and C-12. The chemical shift of one of the acetates is at abnormally high field (δ 1.63). This is consistent with a 12α-acetate which is shielded by the furan ring. Other examples of this type of shielding have been reported.[9,10] The above evidence leads to structure (7) for dregeana 2 which is the first example of this group of highly oxygenated tetranortriterpenoid without oxygenation at C-29.

The fourth compound, dregeana 3b (8) has a parent ion at m/e 642 corresponding to the molecular formula $C_{36}H_{50}O_{10}$. Its lack of an exomethylene group suggested an intact C_{26} skeleton. The methyl region of the proton spectrum is complex but contains at least five tertiary methyls and two secondary methyls. Its complexity is due to the fact that dregeana 3b is a mixture of esters. Two acetates are present and therefore dregeana 3b must have a C_6 ester group attached, presumably, to C-12. The ^{13}C spectrum clearly shows four carbonyl groups, including a C-3 lactone, a ring D double bond, and four secondary oxygen bearing carbons in addition to the tertiary lactone terminus. In the ^{1}H n.m.r. spectrum the four secondary carbinol protons (C-1, C-7, C-12 and C-2') appear as triplets and thus suggests that the C_6 ester is a 2'-hydroxy-4-methylpentanoate instead of the more common 2'-hydroxy-3-methyl-pentanoate. The methyl region of the ^{13}C spectra is complex and suggests that some of the latter is also present. The above evidence leads to the tentative structure (8) for dregeana 3b. A compound, dregeana 3 (12), with the same carbon skeleton but bearing a 2'-acetoxy-3'-methylpentanoate at C-12 has been reported from the same extract.[7]

EXPERIMENTAL

Isolation.- Minced seeds of T. dregeana were extracted with hexane. The extract, an oil, was partitioned between light petroleum and methanol to give a limonoid fraction. A sample (3 g) of this fraction was sent to us by Professor D.A.H. Taylor, University of Natal. It was subjected to repetitive preparative t.l.c. (40% EtOAc/CCl_4). Four bands were detected on spraying with water. The least polar band, band 1, was a mixture of esters which was discarded because of the small quantity. Band 2 afforded impure dregeana 2, band 3 a mixture of dregeana 3b and dregeana 1 and band 4 impure rohituka 7.

Dregeana 2 (7).- Band 2 from above was resubmitted to repetitive preparative t.l.c. (40% EtOAc/CCl_4) and afforded dregeana 2 (7) (30 mg) $C_{33}H_{42}O_{13}$, m/e 646, as an oil. (Found M^+ 646.2674, $C_{33}H_{42}O_{13}$ requires 646.2674).

^1H and ^{13}C n.m.r. chemical shifts (see Tables 1 and 2).

Dregeana 1 (6) and dregeana 3b (8).- Band 3 from the previous separation was resubmitted to repetitive preparative t.l.c. (60% EtOAc/CCl_4). The less polar band afforded dregeana 3b (8) (30 mg) $C_{36}H_{50}O_{10}$, m/e 642, as a fluffy solid which could not be crystallised. [^1H and ^{13}C n.m.r. data (see Tables 1 and 2)].

The more polar band yielded dregeana 1 (6) (45 mg) $C_{33}H_{40}O_{12}$, m/e 628, again as a fluffy solid which could not be crystallised.

^1H and ^{13}C n.m.r. chemical shifts (see Tables 1 and 2).

Rohituka 7 (9).- Repetitive preparative t.l.c. of band 4 of the initial separation gave rohituka 7 (9) (60 mg), $C_{35}H_{44}O_{13}$, m/e 672, as a crystalline solid m.p. 237-238°C (ex methanol-chloroform). ^1H and ^{13}C n.m.r. data (see Tables 1 and 2).

Table 1

^{1}H n.m.r. chemical shifts of dregeana 1 (6) and related compounds.

^{1}H	(6)	(7)	(8)	(9)
1	3.87 (m)	5.51 (bt, 7)	4.72 (t, 3)	7.46 (AB, 12)
2	- -	- -	- -	6.04 (AB, 12)
7	- -	- -	5.38 (bt, 3)	- -
9	2.73 (d, 6)	3.65 (d, 9)	- -	ca. 3.85 (obs)
11	5.37 (dd, 11, 6)	5.22 (dd, 11, 9)	- -	ca. 5.5 (obs)
12	6.15 (d, 11)	5.94 (d, 11)	5.07 (t, 7)	6.16 (d, 11)
15	- -	- -	5.50 (bt)	ca. 5.5 (obs)
17	3.82 (dd, 9, 6)	3.95 (t, 9)	- -	ca. 3.85 (obs)
CH_2=	5.52 (s)	6.07, 5.77 (each s)	- -	5.22, 5.20 (each s)
29	4.26, 4.09 (AB, 12)	- -	- -	4.25, 4.02 (AB, 12)
2'	3.36 (m)	- -	4.03 (bt)	3.19 (m)
CO_2Me	-	3.76	-	-
t-Me	1.02 0.90 0.86	1.56 1.49 1.45 0.92	1.48 1.36 1.22 1.18 0.92	1.63 1.23 0.97
Formate	8.09	-	-	7.88
OAc	-	2.08 2.01 1.63	2.04 1.90	2.07
OH	N.A.	4.52	N.A.	N.A.
Sec-Me	- - - -	- - - -	1.04 (d, 7) 0.83 (d, 7)	- - - -
Furan	7.38 7.25 6.22	7.32 7.21 6.26	7.30 7.25 6.22	7.31 7.15 6.22
	esters obscured			esters obscured

obs = obscured

N.A. = not assigned

Table 2

^{13}C n.m.r. chemical shifts of dregeana 1 (6) and related compounds.

Carbon Type	6	7	8	9
C-15	205.0	206.4	-	-
C-7	174.9	176.0	-	174.9
C-1'	172.4	-	173.9	172.0
C-3	167.5	169.6	170.8	166.7
HCO (d)	160.4	-	-	159.9
CH_3CO (s)	-	170.8	169.9	169.5
	-	170.4 (x 2)	169.6	-
C-21	143.3	142.6	142.2	143.1
C-23	140.7	140.5	140.3	140.8
C-20	121.9	123.4	124.2	123.7
C-22	110.3	110.8	111.6	110.7
C-8	134.3	138.9	-	140.6
C-30	119.3	125.6	-	119.4
C-1	-	-	-	153.2
C-2	-	-	-	120.5
C-15	-	-	122.2	-
C-14	-	-	155.4	-
OMe	-	52.9	-	-
C-2'	75.1	-	75.4	76.2
C-3'	36.9	-	37.2	37.9
C-4'	23.2	-	23.7	23.3
C-5'	11.5	-	11.7	11.4
C-6'	15.2	-	15.3	15.3
-C-O	87.3	83.7	85.1	84.8
	78.6	80.9	-	79.2
CH-O	75.1	72.9	75.4	75.1
	74.3	72.7	70.8	72.5
	73.6	71.0	76.7	71.5
	72.2	-	-	-
$-CH_2-O$	74.4	-	-	74.7
(s)	50.1	-	51.23	51.0
	49.2	49.2	49.9	-
	-	47.9	-	-
	-	-	44.2	44.0
(d)	55.2	51.5	51.2	52.3
	41.1	49.0	44.0	51.0
	40.8	35.4	38.4	39.7
	32.8	-	37.2	37.9
(t)	38.4	38.0	36.7	36.8
	38.1	34.3	34.9	30.2
	32.8	41.3	34.4	-
	-	-	29.7	-
(q)	29.1	31.9	28.3	27.1
	22.2	21.4	26.2	24.1
	-	21.1	25.2	-
	-	20.4	22.8	20.8
	-	19.0	21.3	13.5
	12.3	12.8	20.7	-
	-	-	19.3	-
	-	-	15.7	-
	-	-	15.0	-
	-	-	14.6	-

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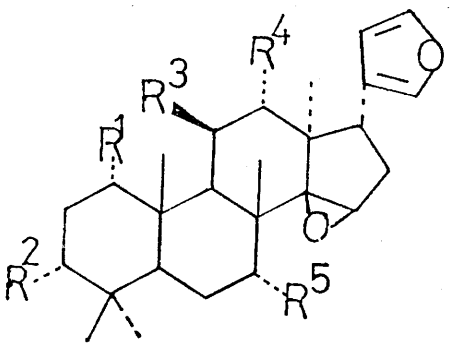
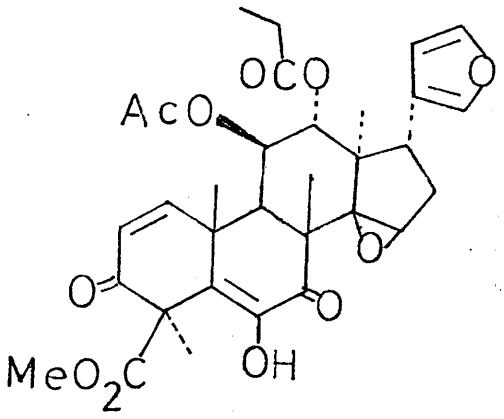
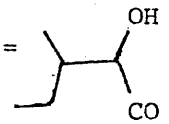
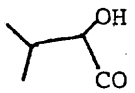
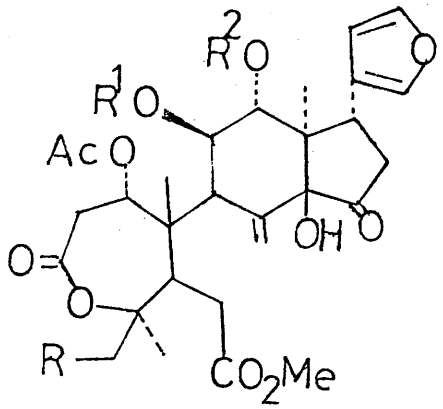


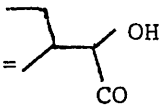
(1) $R^1 = R^2 = R^5 = OH$
$R^3 = R^4 = H$

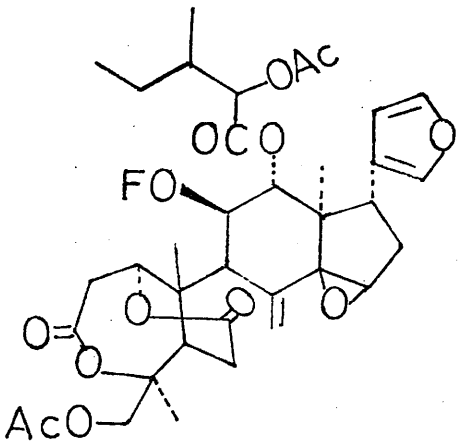


(3)

(2) $R^2 = O$, $\Delta^{1,2}$; $R^3 = HCOO$, $R^4 =$ 
$R^5 =$ 

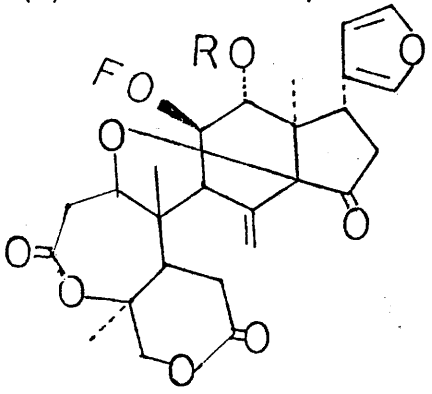


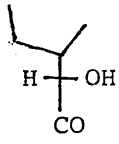
(4) $R^1 = F$, $R^2 =$ 
$R = AcO$

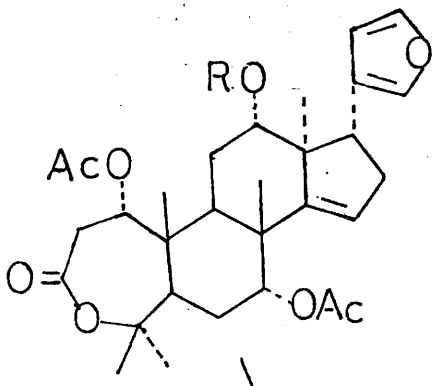


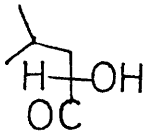
(5)

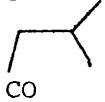
(7) $R^1 = R^2 = AcO$, $R = H$

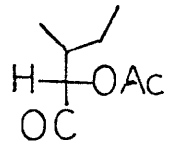


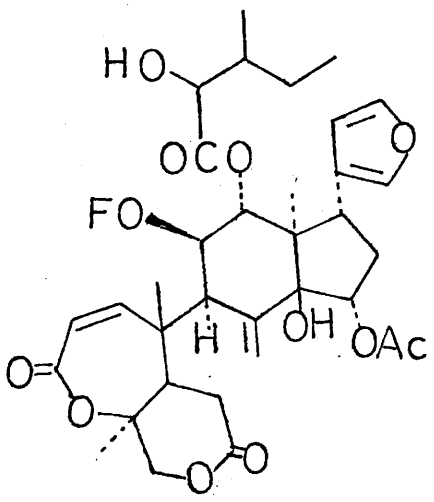
(6) $R =$ 



(8) $R =$ 

(10) $R =$ 

(12) 



(9)

(11) 14β,15β epoxide

CHAPTER V

NEW TETRANORTRITERPENOIDS FROM THE BARK OF TURREA FLORIBUNDA (MELIACEAE)

INTRODUCTION

Although the *Turreae* is a tribe of the widely investigated subfamily, *Melioideae*, of the *Meliaceae*, its study has been seemingly neglected. Only *Naregamia alata*[1] has been examined and has not yielded limonoids or protolimonoids.

In this chapter, we report the isolation of two new compounds A (1) and B (2) from the bark of *Turrea floribunda* and discuss the spectroscopic and chemical evidence that led to their structural elucidation.

D I S C U S S I O N

Column chromatography of the extract of the bark of Turrea floribunda followed by careful repetitive preparative t.l.c. and crystallisation afforded two crystalline compounds A and B which were assigned structures (1) and (2) respectively on the following evidence.

Compound A (1) $C_{33}H_{44}O_{12}$, has bands in the i.r. arising from ester and hydroxyl functional groups [ν_{max} (CCl_4) 3600, 1730 cm^{-1}]. Its ^1H and ^{13}C n.m.r. spectra (see Tables 1 and 2) indicate the presence of a β-substituted furan, two hydroxyl groups (δ_H 3.43; exchangeable with D_2O), a carbomethoxyl group, a trisubstituted epoxide, three acetates and four tertiary methyls. These functional groups account for all the oxygens in the molecule which is therefore tetracarbocyclic. This eliminates the possibility of a cleaved ring system and suggests a normal uncleaved tetranortriterpenoid carbon skeleton with a ring D epoxide and one tertiary methyl group oxidised to a carbomethoxyl. The structural problem is thus reduced to one of establishing the oxygenation pattern (i.e. the placing of five secondary oxygen functions and a carbomethoxyl group).

The two secondary hydroxyl protons overlap at δ_H 3.75. However addition of a few drops of benzene causes differential solvent shifts and reveals them as narrow triplets (δ_H 3.79 and 3.69, J 3 Hz). Double resonance experiments indicate that one of these (H-11) is coupled to a secondary acetate proton at δ 4.36 (d, J 3 Hz, H-12) and to a methine doublet (J 3 Hz, H-9) at δ 3.00. The remaining two secondary ester protons are also narrow triplets [δ 5.12 (J 3 Hz, H-1) and 4.65 (J 3 Hz, H-7)]. The observed coupling pattern can be

satisfactorily accommodated by placing the oxygen functions at carbons 1, 3, 7, 11 and 12. The alternative arrangement 1, 3, 6, 7, 12 can be excluded on the basis of the oxidation product (5) to be discussed below. The size of the coupling constants indicates the usual configuration of the oxygen substituents at C-1, C-3 and C-7. The coupling constants of the H-9, H-11, H-12 system are consistent with 11β and 12α oxygen substituents. Precedent for such an arrangement can be found in the heudelottins, which are esters based on the alcohol (9), from Trichilia heudelottii,[2] and which have the same coupling constants for H-9, H-11 and H-12. These data suggest structure (1) for compound A. The carbomethoxyl group is assumed to be attached to C-4 and is equatorial (α) in view of the absence of the usual downfield signal for a 4α-methyl group in the ^{13}C spectrum.

Acetylation of compound A afforded the pentaacetate (3) in which the resonances for H-1 and H-11 have, as expected, moved downfield to δ4.97 (t, J 3 Hz) and δ 5.2 (t, J 3 Hz) respectively. Valuable structural evidence was obtained by Collins' oxidation of compound A. The product was the diketone (5) whose spectroscopic data readily revealed the presence of a ring A enone [δ_H 7.82 (d, J 10 Hz, H-1) and 5.92 (d, J 10 Hz, H-2)] and a C-11 keto group [δ_H 5.32 (s, H-12) and 3.56 (s, H-9)]. In addition to this change in multiplicity the resonances for H-12 and H-9 move downfield from δ 4.88 and 3.38 respectively in the pentaacetate (3). The chemical shift of H-1 (δ 7.82) is at lower field than normal (ca. δ 7.3) for similar ring A enones as a result of the deshielding effect of the 11-ketone. This observation confirms the oxygenation pattern as in (1) and excludes the alternative 1, 3, 6, 7, 12 arrangement. The formation of the enone is readily rationalised in terms of oxidation of the 3α-hydroxyl group followed by β-elimination of the 1α-acetate.

Unsuccessful attempts were made to prove the presence of the carbomethoxyl group at C-4 by alkaline hydrolysis of (5). It was not possible to determine whether decarboxylation occurred since no characterisable product was obtained. The reasons for this lack of stability to alkali are not clear. Fortunately the oxidation product of compound B (see below) proved more amenable to this reaction.

Treatment of compound A (1) with mineral acid afforded a rearranged ketone whose spectroscopic properties accord with structure (8). This rearrangement is well documented for other 14β,15β-epoxides in this series e.g. havanensin (10)[4] and the heudelottins.[3]

The spectroscopic properties (see Tables 1 and 2) of compound B (2), $C_{37}H_{50}O_{13}$ [ν_{max} (CCl_4) 3600, 1740, 1745 sh, 1760 sh cm^{-1}] indicate that it is closely related to compound A (1). Thus it has resonances for four tertiary methyls, three acetates, a secondary hydroxyl group (δ_H 3.43 exchangeable with D_2O), a carbomethoxyl, a trisubstituted epoxide and a β-substituted furan. The presence of an isobutyrate is obvious in both the ^1H and ^{13}C spectra [δ_C 176.4, 34.3 (d), 19.0 (q) and 18.8 (q)]. Decoupling experiments revealed H-9 (δ_H 3.3, d, J 3 Hz), H-11 (δ_H 5.15, t, J 3 Hz) and H-12 (δ_H 4.86, d, J 3 Hz). The chemical shifts indicate that both C-11 and C-12 bear ester substituents. The isobutyrate is placed at C-12 by biogenetic analogy. Comparison of the chemical shifts of the remaining oxygen substituent with those of A (1) suggested that the free hydroxyl group is attached to C-3. Thus compound B was assigned structure (2).

Acetylation of B afforded the tetraacetate (4) whose spectroscopic properties are virtually identical to those of A pentaacetate (3), with the exception of the resonances associated with the isobutyrate, thus confirming that both A and B have the same carbon framework and

oxygenation pattern. Oxidation of B (2) with Collins' reagent yielded the enone (6) which has the expected spectroscopic properties. Alkaline hydrolysis of (6) followed by acetylation gave the desired product (7) which lacks the carbomethoxyl group. Although the new compound was crystalline it was accompanied by a small amount of a second product which could not be removed by crystallisation or preparative t.l.c. The obvious features of the ^{1}H n.m.r. spectrum of (7) include a secondary methyl group (δ_H 1.05, d, J 7 Hz) and a doublet of quartets (δ_H 4.14, J 7, 3 Hz) which must arise from H-4. The formation of the decarboxylated product (7) provides definite evidence for the attachment of the carbomethoxyl group to C-4 in compounds A and B.

The ^{13}C chemical shifts of compounds (1) to (6) are listed in Table 2. The assignments are based on chemical shift rules, multiplicities and residual splittings in off resonance spectra, and comparison with related molecules. Comparison of the shifts of A (1) and its acetate (3) reveals normal acetylation shifts of C-2 ($\Delta\delta$ - 3.2 ppm), C-4 ($\Delta\delta$ - 1.9 ppm) and C-9 ($\Delta\delta$ - 1 ppm). The more dramatic shift of C-12 ($\Delta\delta$ - 8.1 ppm) must be due to the removal of H-bonding effects. A similar explanation accounts for the shift of the carbomethoxyl carbonyl group ($\Delta\delta$ - 1.5 ppm) and the anomalous acetylation shifts of C-3 ($\Delta\delta$ - 1.1 ppm) and C-11 ($\Delta\delta$ + 0.4 ppm).

Others esters isolated from the extract are mixtures, as shown by their n.m.r. spectra. Acetylation afforded compounds identical in all respects to the acetylated products of either compound A or B. This suggests that the components of the mixtures have the same skeletal framework, but differ from one another in the number and type of acyl groups attached to the secondary hydroxyl groups. For example, the most polar material consists of several diacetates. On acetylation it gave the pentaacetate (3).

EXPERIMENTAL

Isolation.- The extract (30 g) from the bark of Turrea floribunda was chromatographed over a column of Spence alumina grade H, deactivated by treatment with aqueous acetic acid (acid: H_2O, 1:9, v/v; 5 ml for every 100 g of alumina). The column was eluted with light petroleum ether containing increasing amounts of chloroform. The fraction eluted with 60% chloroform-light petroleum ether contained a mixture of compounds A (1) and B (2). This fraction (1.5 g) was subjected to careful repetitive preparative t.l.c. (44% EtOAc/CCl_4). The major band was subjected to partial crystallisation from ether. The first crop was compound A (268 mg) and the second crop was compound B (158 mg).

Compound A (1): m.p. 251-252°C (ex ether), m/e 632, 614 (P-18), 572 (P-60). (Found: C, 62.34; H, 7.34. $C_{33}H_{44}O_{12}$ requires C, 62.65; H, 6.96%).

Compound B (2): m.p. 233-234°C (ex ether), m/e 702, 642 (P-60), 614 (P-88), 554 (P-148). (Found: C, 63.06; H, 7.60. $C_{37}H_{50}O_{13}$ requires C, 63.23; H, 7.17%).

Acetylation of compound A (1) and B (2).-

(a) Compound A (1) (40 mg) was acetylated in the usual way at room temperature overnight. The crude product on preparative t.l.c. (44% EtOAc/CCl_4) afforded the pentaacetate (3) (38 mg) which was recrystallised from ether. M.p. 290-291°C, m/e 716, 656 (P-60), 596 (P-120), 536 (P-180). (Found: C, 62.13; H, 6.49. $C_{37}H_{48}O_{14}$ requires C, 62.01; H, 6.70%). ^1H and ^{13}C n.m.r. data (see Tables 1 and 2).

(b) Compound B (2) (40 mg) was acetylated in the usual manner. This gave the tetraacetate (4) (38 mg) which was crystallised from ether. M.p. 214-215°C; m/e 744, 684 (P-60), 624 (P-120) and 656 (P-88)

596 (P-148). (Found: C, 62.72; H, 6.78. $C_{39}H_{52}O_{14}$ requires C, 62.89; H, 7.04%). ^{1}H and ^{13}C n.m.r. data (see Tables 1 and 2).

Collins' oxidation of compounds A (1) and B (2).-

(a) Compound A (1) (60 mg) was dissolved in freshly distilled DMF (1 ml), and pyridinium dichromate complex (238 mg) added. The mixture was allowed to stir at room temperature for 30 hrs. The crude product was purified by preparative t.l.c. (40% EtOAc/CCl_4) and afforded the diketone (5) (33 mg). M.p. 204-205°C (ex ether); m/e 568, 508 (P-60), 448 (P-120); i.r. ν_{max} (CCl_4) 1680, 1725, 1755 cm^{-1}. (Found: C, 65.20; H, 6.45. $C_{31}H_{36}O_{10}$ requires C, 65.48; H, 6.38%). ^{1}H and ^{13}C n.m.r. data (see Tables 1 and 2).

(b) The solution of compound B (2) (60 mg) in freshly distilled DMF (1 ml) was treated with pyridinium dichromate complex (360 mg) as described from compound A (1). Work up and preparative t.l.c. afforded the enone (6) which was recrystallised from ether. M.p. 209-210°C; m/e 640, 580 (P-60), 552 (P-88) and 492 (P-148); i.r. ν_{max} (CCl_4) 1680, 1745 cm^{-1}. (Found: C, 65.72; H, 6.98. $C_{35}H_{44}O_{11}$ requires C, 65.61; H, 6.92%). ^{1}H and ^{13}C n.m.r. date (see Tables 1 and 2).

Alkaline hydrolysis of the enone (6).- Enone (6) (50 mg) was refluxed with 1.2% ethanolic KOH (25 ml) for 1½ hrs. The solution was allowed to cool, and was then acidified with acetic acid and extracted into chloroform. The crude product was acetylated and purified by preparative t.l.c. (50% EtOAc/CCl_4) to give the decarboxylated product (7) (28 mg), m.p. 135-136°C (ex ether); m/e 554, 494 (P-60); i.r. ν_{max} (CCl_4) 1748, 1685 cm^{-1}. (Found: M^+, 554.25119. $C_{31}H_{38}O_9$ requires M^+, 554.25155). (Found: C, 66.82; H, 7.18. $C_{31}H_{38}O_9$ requires C, 67.13; H, 6.91%).

[δ_H 7.27 (1H, d, J 10 Hz, H-1), 5.92 (1H, d, J 10 Hz, H-2), 5.94 (1H, t, J 5 Hz, H-11), 5.12 (1H, t, J 5 Hz, H-12), 4.77 (1H, t, J 3 Hz,

H-7), 4.17 (1H, dq, J 7, 3 Hz, H-4), 3.68 (1H, s, H-15), 2.95 (1H, d, J 5 Hz, H-9), 7.33, 7.14 and 6.40 (furans), 2.17, 2.15 and 2.09 (acetates), 1.40, 1.41, 0.98 (t-methyls) and 1.08 (3H, d, J 7 Hz, C-4 methyl)].

Acid rearrangement of compound A (1).- Compound A (1) (100 mg) was heated in 0.05 M-HCl in methanol (80 ml) and allowed to reflux for 1 hr. The solution was extracted with ether. The crude product was purified by preparative t.l.c. (50% EtOAc/CCl_4). This afforded the rearranged ketone (8) (18 mg). M/e 632, 572 (P-60), 554 (P-78, loss of H_2O and AcOH), 494 (loss of two moles of AcOH and 1 mole of H_2O). I.r. ν_{max} (CCl_4) 3590, 3510, 1735, 1740 sh, 1715 sh cm^{-1}. (Found: M^+ 632.28298. $C_{33}H_{44}O_{12}$ requires M^+ 632.28324.) [δ_H (at 60°C) 5.16 (1H, t, J 3 Hz, H-1), 4.60 (1H, t, J 3 Hz, H-7), 4.43 (2H, m, H-11 and H-12), 3.85 (1H, br, H-3), 3.55 (3H, s, $CO_2\underline{Me}$), 3.2 (1H, d, J 3 Hz, H-9), 2.18, 2.10 and 2.0 (acetates), 1.38, 1.33, 1.23 and 1.03 (t-methyls) and 7.26, 7.13 and 6.43 (furans)].

Table 1

^{1}H n.m.r. chemical shifts of compounds A (1) and B (2) and related compounds.

1	2	3	4	5	6	Protons
5.12 (t, 3)	4.86 (t, 3)	4.97 (t, 3)	4.98 (t, 3)	7.82 (d, 10)	7.30 (d, 10)	H-1
- -	- -	- -	- -	5.92 (d, 10)	5.95 (d, 10)	H-2
3.75 (t, 3)	3.75 (brs)	4.65 (brm)	4.66 (brs)	- -	- -	H-3
4.65 (t, 3)	4.68 (t, 3)	4.65 (t, 3)	4.66 (t, 3)	4.72 (t, 3)	4.68 (t, 3)	H-7
3.00 (m)	3.30 (d, 3)	3.38 (d, 3)	3.39 (d, 3)	3.56 (s)	2.96 (d, 3)	H-9
3.75 (t, 3)	5.15 (t, 3)	5.20 (t, 3)	5.20 (t, 3)	- -	5.88 (t, 3)	H-11
4.36 (d, 3)	4.86 (d, 3)	4.88 (d, 3)	4.88 (d, 3)	5.32 (s)	5.06 (d, 3)	H-12
3.60 (s)	3.63 (s)	3.60 (s)	3.60 (s)	3.62 (s)	3.61 (s)	H-15
3.65	3.63	3.55	3.56	3.65	3.65	CO_2Me
2.13	2.10	2.10 (x 2)	2.08	2.22	2.10	OAc
2.12	2.12	2.13	2.15	2.08	2.02	
2.05	2.02	2.03	2.05	-	-	
-	-	1.90	1.92	-	-	
7.26	7.23	7.26	7.26	7.26	7.25	β-substituted furan
7.13	7.03	7.08	7.08	7.10	7.06	
6.43	6.38	6.40	6.40	6.30	6.35	
- -	1.18 (d, 7)	- -	1.20 (d, 7)	- -	1.26 (d, 7)	3H-3'
- -	1.16 (d, 7)	- -	1.16 (d, 7)	- -	1.16 (d, 7)	3H-4'
1.4	1.30	1.30	1.32	1.40	1.41	C-Me
1.32	1.21	1.20	1.23	1.35	1.35	
1.20	1.15	1.16	1.18	1.30	1.31	
1.0	1.02	1.03	1.08	1.0	0.95	

Note: Letters and figures in parenthesis represent the multiplicities and coupling constants respectively. Coupling constants (J) are in Hz.

Table 2

^{13}C n.m.r. chemical shifts of compound A (1) and B (2) and related compounds.

Carbon No.	1	2	3	4	5	6
1 (d)	74.3	74.2	73.3	73.3	159.6	156.3
2 (t)	27.8	27.1	24.6	24.6	125.0 (d)	125.5 (d)
3 (d)	73.4	73.2	72.3	72.3	196.9 (s)	197.2 (s)
4 (s)	51.5	51.5	49.6	49.6	58,3	58.1
5 (d)	32.2	32.5	33.3	33.3	42.0	43.8
6 (t)	25.5	25.4	25.2	25.2	24.7	24.0
7 (d)	74.6	74.2	74.0	74.1	71.3	73.4[a]
8 (s)	41.0	40.7	40.6	40.4	40.8	40.9
9 (d)	41.4[a]	40.7[a]	40.4[a]	40.4[a]	54.7	43.8
10 (s)	40.1	40.2	40.3	40.1	38.9	39.8
11 (d)	74.0	74.0	74.4	74.3	204.1 (s)	73.1[a]
12 (d)	87.3	79.2	79.6	79.2	77.9	78.4
13 (s)	48.0	48.9	48.7	49.0	48.6	48.9
14 (s)	74.0	73.8	74.0	74.0	74.9	74.3
15 (d)	63.2	63.3	63.2	63.3	63.2	63.4
16 (t)	32.5	32.5	32.6	32.6	33.6	32.7
17 (d)	41.2[a]	40.2[a]	40.3[a]	40.1[a]	42.6[a]	39.8
20 (s)	128.3	128.1	128.1	128.2	127.0	128.0
21 (d)	140.6	140.6	140.7	140.6	140.4	140.5
22 (d)	112.4	112.3	112.4	112.4	111.7	112.1
23 (d)	142.4	142.5	142.4	142.4	142.9	142.6
29 (s)	175.3	175.2	173.8	173.8	172.5	172.5
MeCOO [12]	173.3	-	170.9	-	170.4	-
[1]	170.2	170.1	170.0	170.0	-	-
[7]	169.5	169.3	169.6	169.4	169.4	169.5
[3]	-	-	169.0[b]	169.1	-	-
[11]	-	168.8	169.3[b]	169.1	-	170.2
MeCO (q)	21.4	21.4	21.5	21.4	-	-
(q)	21.4	21.4	21.3	21.4	-	21.1
(q)	20.9	21.4	21.2	21.2	21.1	21.1
	-	-	20.9	20.9	20.5	-
	-	-	20.9	-	-	-
C-1' (s)	-	176.4	-	176.4	-	176.7
C-2' (d)	-	34.3	-	34.3	-	34.3
C-3' (q)	-	19.0[b]	-	19.0[b]	-	19.2[b]
C-4' (q)	-	18.8[b]	-	18.8[b]	-	18.6[b]
MeC (q)	24.0	23.8	23.7	23.7	25.3	25.2
	18.3	17.7	17.8	17.8	21.4	21.5
	16.8	16.7	17.0	17.0	16.5	16.7
	16.8	16.7	16.5	16.6	16.5	16.3

Note:- (i) a, b, means interchangeable.

(ii) Letters in parenthesis are multiplicities in the off resonance spectra.

(iii) Figures in square brackets refer to the carbon bearing the secondary hydroxyl function of the ester.

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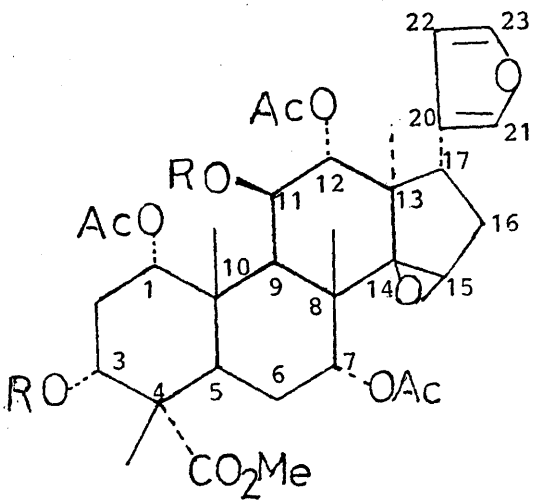

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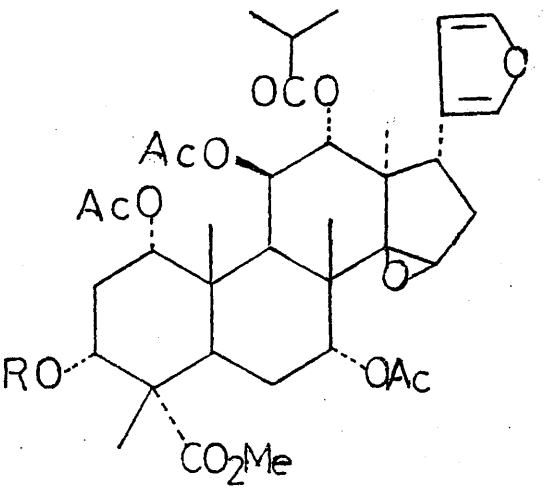

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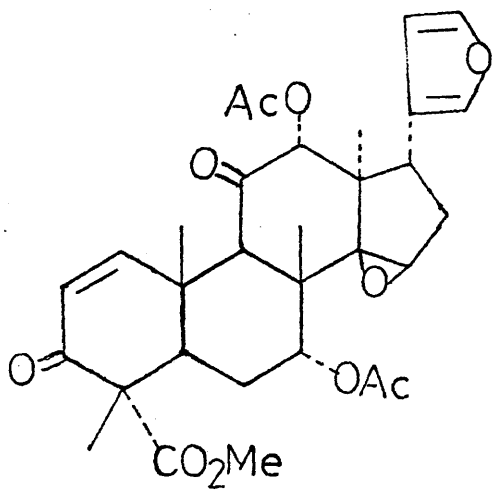

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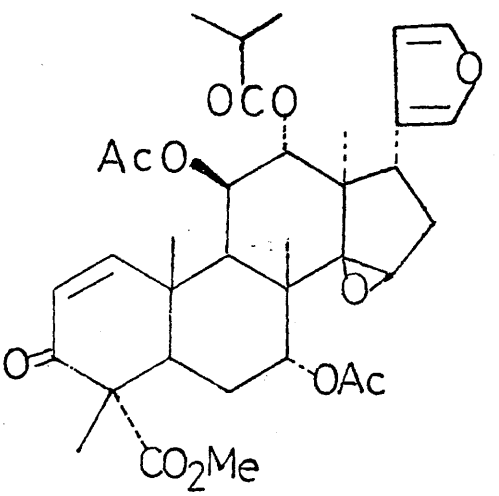

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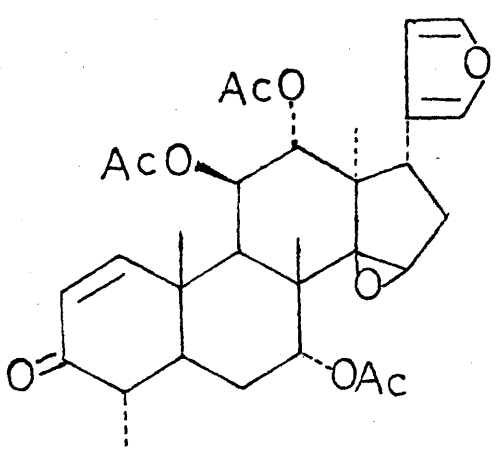

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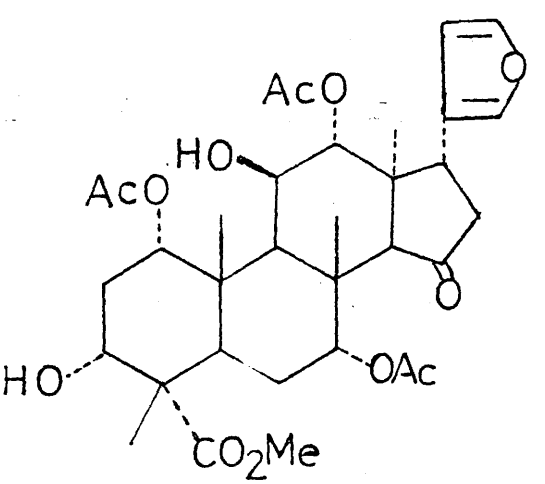

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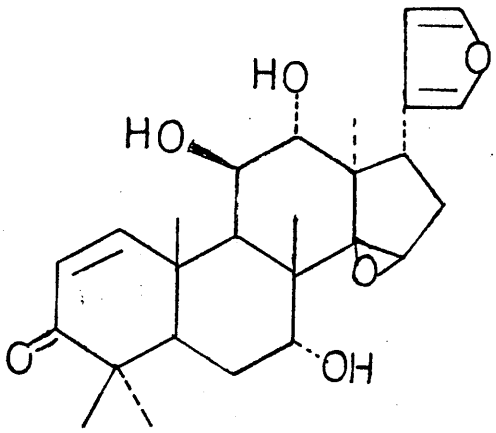

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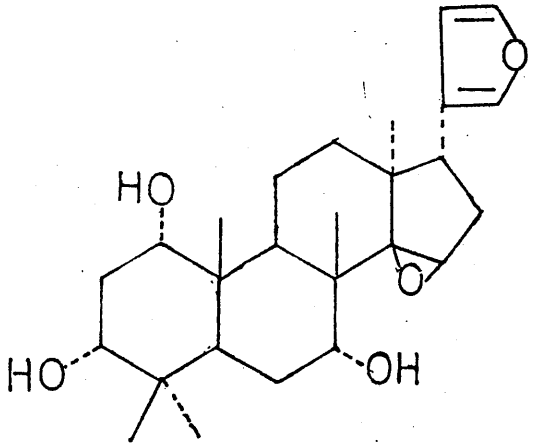

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CHAPTER VI

RE-EXAMINATION OF A REARRANGEMENT OF MEXICANOLIDE

INTRODUCTION

In 1966 Taylor reported[1] that treatment of mexicanolide (1) with 1% methanolic sulphuric acid afforded the methoxy methyl ester (2) which presumably arises by acid induced opening of the lactone ring and replacement of the allylic C-17 oxygen by a methoxyl group. Reduction of (2) with sodium borohydride gave a mixture of the 3β and 3α-hydroxy derivatives (3) and (4), the former in major amount. Attempted acetylation of (3) with toluene-p-sulphonic acid in acetic acid and acetic anhydride resulted in the formation of a rearrangement product which was assigned the cyclopropanoid structure (9). We decided to repeat these reactions and to examine the ^{13}C n.m.r. spectra of the products with a view to confirming or otherwise the structure (9).

DISCUSSION

Reduction of the methoxy methyl ester (2) with sodium borohydride gave as expected a mixture of the 3β-alcohol (3) and the 3α-alcohol (4) whose spectroscopic properties accorded with the published values. These two compounds are readily distinguished by the size of the coupling constant of H-3. In the 3β-alcohol this proton appears as a broad doublet (J 10 Hz) at δ 3.75 whereas in the 3α-alcohol it is a narrow doublet (J 3 Hz) at δ 3.4. A small amount of a third compound was obtained during the preparative plate separation of the crude reaction product. Its proton n.m.r. spectrum indicated the presence of three protons attached to oxygen-bearing carbons [δ_H 4.15 (s, H-17), 3.78 (d, J 6 Hz, H-3) and 4.39 (dd, J 4, 2 Hz, H-1)] and only one carbomethoxyl group. It is tempting to suggest that this compound has the structure (6) and arises by the reduction of the carbonyl group at C-1 followed by lactonisation with the C-7 carbonyl group. Inspection of models favours structure (6) over the alternative structure with a lactone between C-7 and C-3 (α). The probability of a long range W coupling between H-1 and H-5 is apparent. This would explain the multiplicity of H-1 (dd, J 4, 2 Hz) which, at first sight, is unexpected. The assignment of structure (6) is also supported by its ^{13}C n.m.r. spectrum (see Table 1). Reduction of the C-1 carbonyl as in (3) results in n.m.r. γ-gauche interactions between the resultant hydroxyl group and C-3 and C-5. These carbons move upfield with respect to (1). Reduction of the carbonyl also causes upfield shifts of C-2 and C-10. Reduction of the C-1 carbonyl group in this series is unusual in view of its hindered environment.

Acetylation of the 3β-hydroxyl compound (3) with acetic anhydride in pyridine on the steam bath yielded the normal acetate (5) [δ_H 4.93 (d, J 10 Hz, H-3)]. In the previous work Taylor reported that (3) was stable to these reagents. The results of acetylation with toluene-p-sulphonic acid in acetic acid-acetic anhydride varied with the quantity of the acid catalyst. Using the published procedure acetylation of (3) afforded the rearranged product (9) with the expected spectroscopic properties. It was readily identified by the resonance properties. [δ_H 7.39 and 6.36 (both d, J 2 Hz) and 2.46 (3H, s, $\underline{CH_3}CO$)] for the acetyl furan.

The reaction was repeated using one-fifth of the quantity of toluene-p-sulphonic acid. Two new compounds were obtained. The ^1H n.m.r. spectrum of the less polar product, $C_{28}H_{34}O_7$, was similar to that of the rearrangement product (9) above. The major difference was the replacement of the signals for the acetyl furan by those of the normal β-substituted furan. This compound was therefore assigned structure (8). This result showed that the reduction in the amount of toluene-p-sulphonic acid had permitted the rearrangement to occur without acylation of the furan. The virtual identity of the ^{13}C n.m.r. spectra (see Table 1) of (8) and (9), with the exception of the furan resonances, supports this conclusion.

The ^1H n.m.r. spectra of the more polar product, $C_{32}H_{42}O_{10}$, showed the presence of two acetates, one of which is attached to C-3 (β) [δ 4.93 (d, J 10 Hz)]. The downfield chemical shift of H-17 [δ 6.32 (s)] and H-21 [δ 7.72 (brs)] suggested that the second acetate is attached to C-17. Thus the more polar compound was assigned structure (7). Its formation involves simple acetylation of the 3β-hydroxyl group and replacement of the C-17 methoxyl by an acetate.

The ^{13}C chemical shifts of compounds (1), (3), (5), (6), (8) and (9) are shown in Table 1. The assignments are based on chemical shifts, multiplicities in off resonance spectra and comparison with literature values for (1) and (5).[1] The ^{13}C data support the previously assigned structure for the rearrangement product (9) and hence its desacetyl derivative (8). The formation of the 3β,8β-ether is confirmed by the chemical shifts of C-3 and C-8. This results, in addition, in upfield γ-effects on C-11 and C-5 and a downfield β-effect on C-9. The high-field chemical shift values of C-13, C-14 and C-17 provide good evidence for the presence of the cyclopropane ring.

EXPERIMENTAL

Methoxy methyl ester (2).- Mexicanolide (1) (200 mg) was dissolved in analaR methanol (20 ml) and concentrated sulphuric acid (0.2 ml) was added. The mixture was refluxed for thirty minutes and distilled water (20 ml) was added to the hot solution. On cooling crystals of the methoxy methyl ester (2) were deposited, and were recrystallised from methanol. M.p. 171-173°C identical in all respects with the reported compound.[1] (^{1}H n.m.r.)

Sodium borohydride reduction of (2).- Sodium borohydride (195 mg) was added to a solution of compound (2) (130 mg) in anhydrous ethanol (6 ml) and analaR chloroform (3 drops). The mixture was stirred for two hours at 25°C. Water (4 ml) was added and the product extracted with chloroform (5 x 2 ml). The extract was then washed with water, dried and evaporated to dryness. Preparative t.l.c. of the crude product (40% EtOAc/CCl_4) afforded three compounds, (3), (4) and (6).

(i) The 3β-hydroxyl compound (3). [δ_H 7.47 (1H, brs) 7.42 (1H, m) and 6.53 (1H, m) (β-substituted furan protons), 4.5 (1H, s, H-17), 3.6 (3H, CO_2Me) and 3.65 (3H, CO_2Me), 3.23 (3H, OMe), 1.1, 0.97, 0.90, and 0.73 (C-Me)]. M.p. 179-180°C (lit.[1] 179°).

(ii) The 3α-hydroxyl compound (4). $C_{29}H_{40}O_8$. [δ_H 7.43 (2H, brs) and 6.48 (1H, brs) (β-substituted furan), 4.65 (1H, s, H-17), 4.6 and 4.7 (3H, each, CO_2Me), 3.23 (3H, OMe), 1.1, 1.0, 0.95 and 0.65 (C-Me)]. M.p. 188-189°C (lit.[1] 188-196°).

(iii) The lactone (6). [δ_H 7.4 (1H, m), 7.25 (1H, m) and 6.35 (1H, brs) (β-substituted furan), 4.15 (1H, s, H-17), 3.66 (3H, s, CO_2Me), 3.02 (3H, OMe), 1.3 (6H), 1.15 and 0.85 (C-Me)]. $C_{28}H_{38}O_7$ m/e 486.

(Found M^+ 486. $C_{28}H_{38}O_7$ requires 486.)

Acetylation of the 3β-alcohol (3).

(a) With acetic anhydride in pyridine.- The alcohol (3) (32 mg) was dissolved in acetic anhydride-pyridine mixture (10 ml), (2:1 v/v), and the mixture kept at steam temperature for 2 hrs. Usual work up afforded the 3β-acetate (5) (30 mg); m.p. 195-196°C (ex chloroform-light petroleum ether). $C_{31}H_{42}O_9$, m/e 558. [δ_H 7.6 (1H, m), 7.42 (1H, m) and 6.55 (1H, m) (β-substituted furan), 4.93 (1H, d, J 10 Hz, H-3), 4.70 (1H, s, H-17), 3.63 (3H, s, $CO_2\underline{Me}$), 3.53 (3H, s, $CO_2\underline{Me}$), 3.15 (3H, O$\underline{Me}$), 2.12 (acetate), 1.10, 1.0 and 0.76 (6H) (C-$\underline{Me}$)]. (Found M^+ 558. $C_{31}H_{42}O_9$ requires 558).

(b) With a catalytic amount of toluene-p-sulphonic acid in acetic acid/acetic anhydride mixture.- To the solution of the 3β-alcohol (3) (32 mg) in a mixture of acetic anhydride (2 drops) and glacial acetic acid (1.3 ml) was added toluene-p-sulphonic acid (32 mg). The reaction mixture was allowed to stand at room temperature overnight. Work up and preparative t.l.c. of the crude product afforded compounds (7) and (8), (21 mg) and (9 mg) respectively.

(i) diacetate (7): $C_{32}H_{42}O_{10}$ m.p. 178-180°C (ex ether), m/e 586. [δ_H 7.72 (1H, brs), 7.40 (1H, m), 6.60 (1H, m), (β-substituted furan), 6.32 (1H, s, H-17), 4.93 (1H, d, J 10 Hz, H-3), 3.66, 3.56 (3H, each, $CO_2\underline{Me}$), 2.13 and 2.02 (3H, each, acetate), 1.12 (6H), 0.80 (6H) (C-$\underline{Me}$)].

(ii) rearrangement product (8): recrystallised from chloroform-light petroleum ether, m.p. 161-162°C. $C_{28}H_{34}O_7$, m/e 482. (Found M^+ 482.23099. $C_{28}H_{34}O_7$ requires 482.23042). [δ_H 7.3 (1H, m), 7.2 (1H, m) and 6.25 (1H, m) (β-substituted furan), 3.93 (1H, d, J 7 Hz, H-3), 3.65, 3.60 (3H, each, $CO_2\underline{Me}$), 1.06 (6H), 0.85 and 0.56 (C-Me)].

(c) With published amount of toluene-p-sulphonic acid in acetic acid/ acetic anhydride mixture.- The 3β-alcohol (3) (54.7 mg) was dissolved in a mixture of glacial acetic acid (2 ml) and acetic anhydride (0.6 ml). Toluene-p-sulphonic acid (54.7 mg) was added and the mixture was stored at 22°C overnight. The mixture was flooded with water and extracted with chloroform (4 x 6 ml). Evaporation of the solvent afforded the rearrangement compound (9) (32 mg), recrystallised from benzene-light petroleum ether, m.p. 199-200°C (lit.[1] 196-199°C).

Table 1

^{13}C n.m.r. spectra of mexicanolide and related compounds.

Carbon No.	1	3	5	6	8	9
1	212.0	221	218.9	87.4	216.7	216.8
2	58.0	56.1	56.5	51.4	58.0	57.5
3	210.9	78.8	77.4	73.0	87.2	87.4
4	49.4	39.5	38.1	37.0	37.5	37.5
5	50.5	49.7	47.7	44.0	43.2	43.3
6	32.3	32.8	33.4	32.2	33.0	32.9
7	173.5	173.9	173.8	172.6	173.7	173.2
8	133.8	135.0	133.8	136.9	82.8	82.7
9	40.2	40.1	41.1	40.6	51.7	51.7
10	54.3	52.0	51.7	33.5	51.4	51.7
11	18.6	20.4	20.1	20.1	17.8	18.3
12	28.8	34.2	35.7	33.3	33.7	33.2
13	37.8	42.9	43.1	42.7	29.9	29.8
14	125.3	133.7	133.7	126.5	26.7	27.9
15	32.9	35.0	35.5	33.3	34.9	35.1
16	169.7	172.5	172.0	171.7	174.5	174.3
17	80.6	78.8	79.0	81.1	20.5	22.6
20	120.4	123.3	123.9	122.9	120.7	129.8
21	142.7	142.9	143.0	142.8	142.4	151.0
22	109.8	110.7	110.7	110.7	112.9	115.6
23	141.5	141.8	142.1	141.3	140.5	144.2
30	36.4	36.2	34.2	37.8	43.5	43.3
OMe	52.1	56.6	56.2	56.6	51.8	51.7
	-	51.7	51.8	51.9	51.8	51.7
	-	51.7	51.7	-	-	-
MeCO	-	-	170.4	-	-	187.8
C-Me	21.9	25.1	23.7	27.8	20.5	27.1
	17.8 x 2	20.8	21.1	27.8	19.0	20.6
	17.4	20.1	20.8	25.5	16.9	17.7
	-	17.5	19.4	24.6	-	17.0
	-	-	16.6	-	-	-

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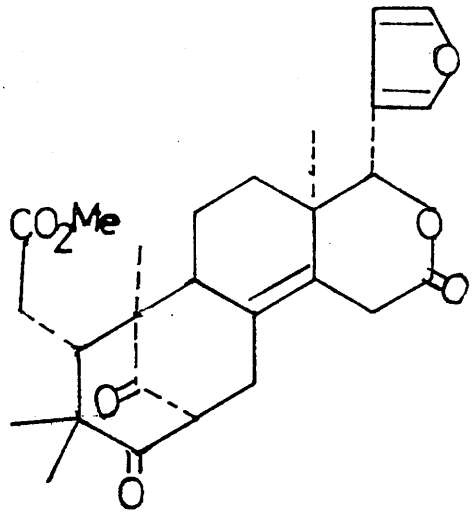
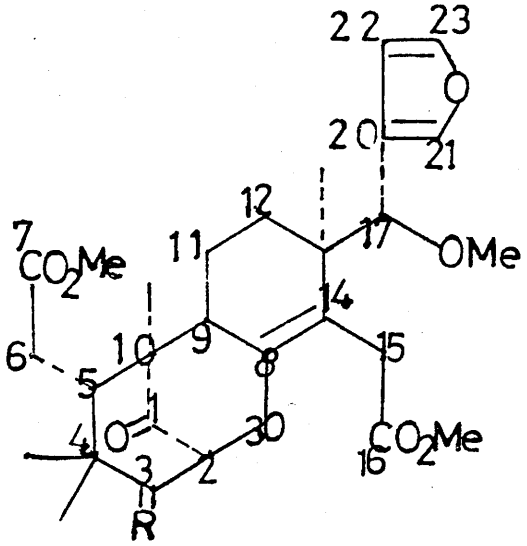


(1)

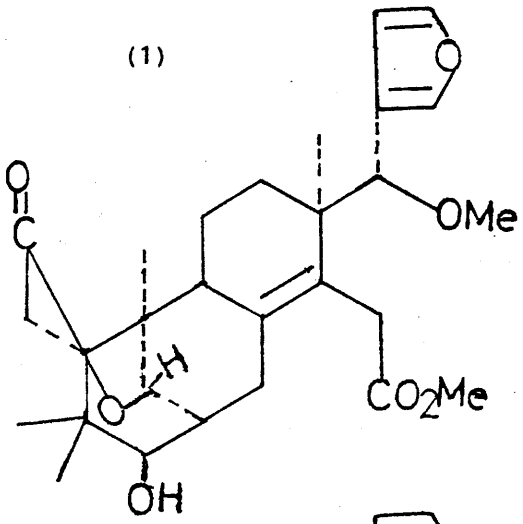


(2) R = O

(3) R = H, β-OH

(4) R = H, α-OH

(5) R = H, β-OAc



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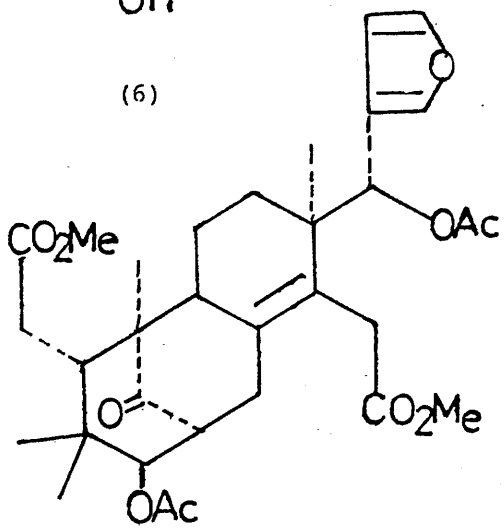

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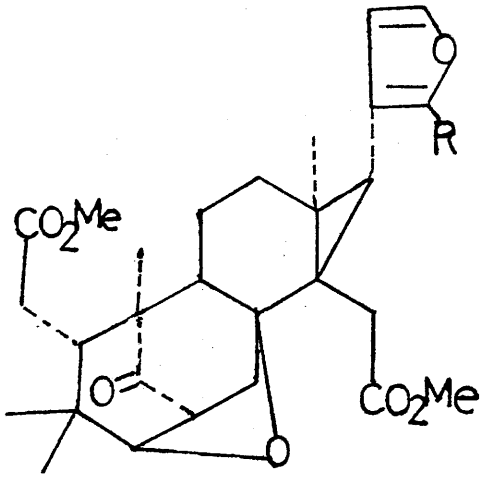

(8) R = H

(9) R = $COCH_3$

CHAPTER VII

THE STRUCTURE OF ROXBURGHILIN, A BIS-AMIDE OF 2-AMINOPYRROLIDINE, FROM THE LEAVES OF AGLAIA ROXBURGHIANA AND THE SYNTHESIS OF THE CORRESPONDING DIHYDRO-DERIVATIVE FROM L-PROLINE

INTRODUCTION

Despite the intensive investigation of the Meliaceae family over the past twenty years very few nitrogen containing compounds have been reported. One example is phragmalin (23) which occurs as an ester of nicotinic acid.[1] This chapter is concerned with an investigation of the leaves of Aglaia roxburghiana. Previous work had resulted in the isolation of β-sitosterol from the roots of this plant.[5] In the present work two bis-amides, roxburghilin (1) and the closely-related compound (13), have been isolated. Roxburghilin has been shown to be N-cinnamoyl-2-(2'S-methylbutanoylamino)-pyrrolidine (1) by a combination of chemical and spectroscopic evidence and by synthesis of the corresponding dihydro-derivative (4) from L-proline. The structure of (13) is based on spectroscopic evidence and comparison with roxburghilin.

While the paper describing this investigation was in press, Shienthong et al. published the structure of odorin and odorinol from the leaves of A. odorata.[6] These are undoubtedly identical to roxburghilin and compound (13) respectively.

D I S C U S S I O N

Roxburghilin (1), $C_{18}H_{24}O_2N_2$, $[\alpha]_D$ + 34° has bands in the i.r. at 3442, 3280 (NH), 1686 and 1660 cm^{-1} (amide). The ^1H n.m.r. spectrum indicated the presence of cinnamoyl [δ 6.94 and 7.64 (ABq, J 16 Hz) and ca. 7.4 (5H, m)] and 2-methyl-butanoyl [δ 0.76 (t, J 7 Hz, $CH_2\underline{Me}$), 1.12 (d, J 7 Hz, CH$\underline{Me}$) and 1.49 (2H, m, $\underline{CH_2}$Me) residues and one NH (δ6.60, d, J 8 Hz; disappeared on addition of D_2O-CF_3CO_2H]. Alkaline hydrolysis of (1) afforded cinnamic acid and (+)-2-methylbutanoic acid. The latter was characterised as its p-bromoanilide. The two acid residues and the remaining carbons were also readily identified in the ^{13}C n.m.r. spectrum of (1). The shifts of the 2-methylbutanoyl moiety [δ_c 175.9 (s), 42.9 (d), 27.0 (t), 17.6 (q) and 11.9 (q)] are in perfect agreement with literature values[7] (see Table 1); while those of the cinnamoyl group [δ_c 165.7 (s), 142.8 (d), 118.2 (d), 134.8 (s), 129.9(2) (d), 128.8(2) (d) and 128.2 (d)] accord with the values observed in model compounds. The remaining carbons appear at δ 62.8 (d) (C-2), 46.2 (t) (C-5), 34.5 (t) (C-3) and 21.6 (t) (C-4) (see Table 2). Thus roxburghilin is a secondary-tertiary bis-amide of a monocyclic unit $C_4H_8N_2$, comprising two methylenes, a methylene bearing nitrogen and a methine bearing two nitrogens. The corresponding ^1H resonances appear at δ 2 (4H, m), 3.62 (2H, m, $\underline{CH_2}$N) and 6.12 (1H, m, N-$\underline{CH}$-N). Irradiation at δ 2, the methylene resonance, resulted in simultaneous collapse of the CH_2-N multiplet to an AB quartet (δ 3.48 and 3.74, J 12 Hz) and the N-CH-N signal to a doublet (J 8 Hz), coupled with the NH doublet at δ 6.60. These results can be satisfactorily interpreted in terms of a 2-aminopyrrolidine nucleus and lead to structure (1) or (2) for roxburghilin.

The mass spectrum of roxburghilin has strong peaks at m/e 169 and 131, and 215 and 85 resulting from loss of the cinnamoyl and 2-methylbutanoyl fragments. In addition there is a peak at m/e 199 (M^+, 199.09968. $C_{13}H_{13}NO$ requires M^+ 199.09970) corresponding to loss of 2-methylbutanoic acid amide, presumably by a McLafferty rearrangement (Scheme 1). This result indicated that the 2-methylbutanoic acid is associated with the secondary amide function and confirmed the structure of roxburghilin as N-cinnamoyl-2-(2'-methylbutanoyl-amino)-pyrrolidine (1). The configuration at C-2 was not determined. The isolation of (+)-2-methylbutanoic acid on hydrolysis of (1) indicated that the configuration at C-2' is (s).[2] The biogenetic origin of roxburghilin is not known, but it may be derived from ornithine via an acylated putrescine intermediate (Scheme 2).

On standing in chloroform solution roxburghilin underwent partial epimerisation at C-2. This is apparent in both the ^1H n.m.r. spectrum which shows two sets of methyl signals and in the ^{13}C n.m.r. spectrum which exhibits doubling of some of the resonances.* For example, C-2 appears as two signals at δ_C 62.8 and 62.7, C-4 (δ_C 21.6) has an unresolved shoulder and the secondary amide carbons C-2' and C-5' appear at δ_C 42.9, 42.7 and 17.6 and 17.3 respectively. In addition two spots are observed on analytical t.l.c. The equilibration is accelerated by addition of a drop of trifluoroacetic acid, and presumably proceeds via a ring-opened intermediate e.g. (3). Careful preparative t.l.c. of the equilibrium mixture resulted in the isolation of 2-epiroxburghilin which has the same ^{13}C spectrum as roxburghilin as a result of equilibration at C-2 during spectrum accumulation.

Depending on the conditions, hydrogenation of roxburghilin yields not only dihydroroxburghilin (4) but also the ring-cleaved product

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* In a "non-acidic" solvent like CD_3OD doubling of signals is not observed (see Table 2).

tetrahydroroxburghilin (5). Reductive cleavage of a similar system (6) with sodium borohydride, to give compound (7) has been reported recently.[3] Treatment with acid caused equilibration at C-2 in dihydroroxburghilin, and the presence of epimers was detected by ^{13}C n.m.r. In the tertiary amide moiety C-3' appears at δ_c 31.3 (t) and 31.0 (t) while carbons C-3' and C-4' of the secondary amide group resonates at δ_c 27.2 and 27.0 and 17.6 and 17.3 respectively. The epimers have identical ^{1}H n.m.r. spectra and chromatographic properties and could not be separated. Hydrogenation of an equilibrium mixture of roxburghilin afforded an apparently single dihydro product indistinguishable from dihydroroxburghilin (4) (t.l.c. and ^{1}H n.m.r.).

The ^{13}C n.m.r. spectrum of dihydroroxburghilin (4) unlike that of roxburghilin exhibits two sets of signals for the pyrrolidine ring carbons due to restricted rotation about the tertiary amide (see Table 2). As expected only one set of signals was observed at 100°C in [$^{2}H_8$]toluene. It is interesting to note that in dihydroroxburghilin and the simple amides N-cinnamoyl- and N-dihydrocinnamoyl-pyrrolidine the chemical shift difference between C-3 and C-4, ($\Delta\delta$ 1.8 and 1.7) of the rotameric form is greater than that between C-2 and C-5, ($\Delta\delta$ 0 and 0.2). The corresponding piperidine derivatives show the opposite effect (see Table 3).

Derivatives of 2-aminopyrrolidine have been synthesised[4] but roxburghilin (1) appears to be the first example isolated from a natural source. In their approach Murato et al. employed a modified Curtius rearrangement of N-benzyloxycarbonyl-L-proline (21) with diphenylphosphorazidate (DPPA) in tertiary butanol containing triethylamine. This afforded the allophanate (22) accompanied by the carbamate (6). Similar results were obtained using a normal Curtius rearrangement of the azide of (21) in tertiary butanol. The azide was prepared using the mixed anhydride method developed by Weinstock.[8]

The structure of roxburghilin was confirmed by synthesis of its dihydro-derivative (4) following the route summarised in Scheme 3. L-Proline (20) was converted in good yield into the azide (8) by acylation with dihydrocinnamoyl chloride, methylation with diazomethane, treatment with hydrazine hydrate and reaction of the resulting hydrazide with nitrous acid. Curtius rearrangement of the azide (8) yielded the optically active isocyanate (9) which was immediately subjected to a Grignard reaction with 2-butyl magnesium bromide. Chromatography of the crude product gave dihydroroxburghilin identical in all respects with an authentic sample derived from roxburghilin. It is probable that the synthesised compound is totally racemic as a result of equilibration at C-2 during the acidic conditions of the work-up of the Grignard reaction. A second product of the reaction was the urethane (10). The butan-2-ol necessary for the formation of (10) presumably arose by reaction of the Grignard reagent with oxygen. In the course of this work model compounds (11) and (12) were also prepared by standard methods. Their ^{13}C data appear in Table 2.

A second bis-amide, $C_{18}H_{24}N_2O_3$ (m/e 316); ν_{max} (CCl_4) 3622, 3420, 3300, 1680 and 1660 cm^{-1}, isolated from the extract in minor amount has been assigned structure (13). Its spectroscopic properties are similar to those of roxburghilin (see Experimental). The obvious differences in the ^1H n.m.r. spectra are the replacement of the secondary methyl signal of (1) by a methyl singlet at δ 1.33 and the appearance of a tertiary hydroxy proton (exchangeable with D_2O) at δ 2.48. The above data clearly indicate the presence of a 2'-hydroxy-2'-methylbutanoyl residue.

EXPERIMENTAL

(1) Extraction.- Coarsely powdered leaves of Aglaia roxburghiana were successively extracted with hexane and chloroform in the cold. The hexane extract contained β-sitosterol and several tetracyclic triterpenoids. The chloroform extract was chromatographed over Grade IV alumina in benzene. The fractions eluted with benzene were combined and crystallised from ethyl acetate to give roxburghilin (1), m.p. 205°C. (Found: C, 71.8; H, 8.2; N, 9.2. $C_{18}H_{24}O_2N_2$ requires C, 72.0; H, 8.0; N, 9.3%). Preparative t.l.c. of the mother liquors afforded a small quantity of compound (13) [δ 0.90 (t, J 7 Hz, $CH_2\underline{Me}$), 2.0 (4H, m, ring methylenes), 3.62 (2H, m, $\underline{CH_2}$-N), 6.12 (1H, m, N-$\underline{CH}$-N), 6.94 and 7.66 (ABq, J 16 Hz, Ph-CH=CH-CO) and ca. 7.4 (5H, m, phenyl)]. (Found: M^+ 316.17849. $C_{18}H_{24}O_3N_2$ requires M^+ 316.17867).

(2) Hydrolysis of roxburghilin.- Roxburghilin (300 mg) was refluxed for 6 hrs in 5% ethanolic potassium hydroxide solution (15 ml). The ethanol was removed in vacuo and the residue acidified with 5 M hydrochloric acid, extracted with dichloromethane and the crude product was chromatographed over silica gel. The fraction eluted with benzene yielded a solid which was crystallised from water to give cinnamic acid, m.p. 133°C, identical with the authentic specimen.

Roxburghilin (1 g) was hydrolysed as above. The dichloromethane extract was distilled off and the fraction boiling at 180°C was redistilled to give 2-methylbutanoic acid, b.p. 177°C. This was characterised as its p-bromoanilide, prepared in the usual way and recrystallised from ether-hexane, m.p. 132-134°C, $[\alpha]_D$ + 32° (c 0.08, acetone); m/e 257 and 255, identical with authentic specimen [lit.[1] m.p. 132-134°C, $[\alpha]_D$ + 32° (acetone)].

(3) Hydrogenation of roxburghilin.- Roxburghilin (37 mg) in ethyl acetate (20 ml) was hydrogenated over 10% Pd-C for 5 minutes. The catalyst was filtered off and the solvent removed to give a quantitative yield of dihydroroxburghilin (4) which was crystallised from chloroform-ether m.p. 105-106°C; $[\alpha]_D \pm 0$; m/e 302; ν_{max} (CCl_4) 3442, 3300, 1685 and 1662 cm^{-1}; [δ_H 0.78 (3H, t, J 7 Hz, MeCH$_2$), 1.02 (3H, d, J 7 Hz, MeCH), ca. 2.6 and 2.95 (each 2H, m, PhCH$_2$CH$_2$CO), 3.45 (2H, m, CH$_2$-N), 5.65 (1H, m, N-CH-NH), 6.06 (1H, m, NH) and 7.18 (5H, brs, phenyl)]. (Found: C, 71.5; H, 8.8; N, 9.3. $C_{18}H_{26}O_2N_2$ requires C, 71.5; H, 8.7; N, 9.3%). Prolonged hydrogenation under the above conditions afforded tetrahydro roxburghilin (5) which was crystallised from ethyl acetate-ether, m.p. 133-137°C. ν_{max} (CCl_4) 3560, 3325, 1681 and 1672 (sh) cm^{-1}; [δ_H 0.91 (3H, t, J 7 Hz, MeCH$_2$), 1.15 (3H, d, J 7 Hz, MeCH), 2.47 and 2.96 (each 2H, m, PhCH$_2$CH$_2$CO), 3.2 (4H, m, 2 x CH$_2$N), 5.95 (2H, m, 2 x NH, exchangeable with D_2O-CF_3CO_2H), and 6.19 (5H, m, phenyl)]. (Found: M^+ 304.21482; $C_{18}H_{28}O_2N_2$ requires M^+ 304.21507). The amount of tetrahydro compound formed varied with the batch of catalyst used. In some experiments the yield was very low even after overnight reaction.

(4) Equilibration of roxburghilin.- Roxburghilin (20 mg) in chloroform solution was stirred with trifluoroacetic acid (2 drops) in water (5 drops) for a few minutes. Analytical t.l.c. of the product showed two spots of similar R_F values. Careful repetitive preparative t.l.c. afforded two compounds. The more polar was roxburghilin. The less polar was 2-epiroxburghilin (7 mg) which was recrystallised from chloroform-light petroleum, m.p. 171-172°C; [δ_H 0.9 (3H, t, J 7 Hz, MeCH$_2$), 1.06 (3H, d, J 7 Hz, MeCH), ca. 1.97 (4H, m, CH$_2$CH$_2$), 3.54 (2H, m, CH$_2$N), 6.14 (1H, m, N-CH-NH), 6.86 (1H, brd, J 8 Hz, NH), 6.92 and 7.68 (ABq, J 16 Hz, PhCH=CHCO) and ca. 7.4 (5H, m, phenyl)]. (Found: M^+ 300,

$C_{18}H_{24}O_2N_2$ requires M, 300). Hydrogenation of the equilibrium mixture afforded a product identical with dihydroroxburghilin (4) (t.l.c. and ^1H n.m.r.).

(5) Synthesis of dihydroroxburghilin (4).- (-)-L-Proline (20) (8.7 g) was dissolved in 7 M sodiumhydroxide solution (20 ml) and dihydrocinnamoyl-chloride (12.8 g) added with stirring. After 5 minutes the mixture was acidified and left overnight in the refrigerator. The precipitated N-dihydrocinnamoyl-L-proline (14) (8 g) was filtered off and recrystallised from chloroform-light petroleum, m.p. 98-100°C; $[\alpha]_D$ - 110° (water); [δ_H 2.1 (4H, m, CH_2-CH_2), 2.65 and 3.0 (each 2H, m, $PhCH_2CH_2CO$), 3.45 (2H, m, 2H-5), 4.58 (1H, m, H-2), 7.25 (5H, brs, phenyl) and 10.3 (1H, s, CO_2H)]. The corresponding methyl ester (15), prepared in the usual way by reaction with diazomethane in methanol, was obtained as an oil, m/e 261; ν_{max} (thin film) 1737, 1640 cm^{-1}; [δ_H 2.0 (4H, m, CH_2CH_2); 2.58 and 3.0 (each 2H, m, $PhCH_2CH_2CO$), 3.51 (2H, m, 2H-5), 3.71 (3H, s, CO_2Me), 4.48 (1H, m, H-2) and 7.3 (5H, brs, phenyl)]. The methyl ester (6.0 g) in ethanol solution, was allowed to stand overnight at room temperature with an excess of hydrazine hydrate. The hydrazide (16) (5.4 g), obtained on removal of solvent in vacuo was suspended in a mixture of concentrated hydrochloric acid-acetic acid (10:1, v/v) and cooled in a salt-ice bath. An aqueous solution of sodium nitrite was added dropwise with stirring. The reaction mixture was extracted with ethanol free chloroform and the organic layer dried over anhydrous sodium sulphate-sodium carbonate. The formation of the azide (8) (5 g) was confirmed by the presence of a band in the i.r. spectrum at 2130 cm^{-1}. Conversion of the azide into the isocyanate (9) was achieved by warming the chloroform solution at 50-60°C in an oil bath for 2.5 hr. The reaction was monitored by the appearance of the isocyanate band in the

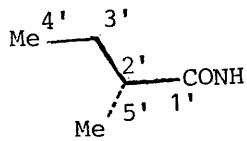
i.r. at 2,260 cm^{-1}, and the disappearance of the azide band at 2130 cm^{-1}. The isocyanate (9) (4.8 g) [$[\alpha]_D$ - 17.6° (ca 0.7, chloroform)], in dry tetrahydrofuran, was treated with 2-butylmagnesium bromide in a nitrogen atmosphere and refluxed overnight. The reaction was worked up by addition of saturated aqueous ammonium chloride solution and extracted with chloroform. The crude product was chromatographed over Grade IV alumina. Elution with 30% chloroform-light petroleum afforded dihydroroxburghilin (4) (500 mg), which was further purified by preparative t.l.c. and crystallised from chloroform-light petroleum as needles, m.p. 108-109°C $[\alpha]_D$ 0°. The spectroscopic properties of the synthetic product were identical with those of naturally derived compound. A less polar product from the column, eluted with 20% chloroform-light petroleum, was the non-crystalline urethane (10) (200 mg); m/e 318; ν_{max} (CCl_4) 3450, 3300, 1664, and 1724 cm^{-1}; [δ_H 0.87 (3H, t, J 7 Hz, MeCH_2), 1.2 (3H, d, J 7 Hz, MeCH), 3.5 (2H, m, 2H-5), 4.8 (1H, m, CH-O, H-2'), 5.16 (1H, m, NH), and 5.53 (1H, m, H-2)].

(6) Model compounds (11) and (12).- N-Acetyl-L-proline (17) was subjected to Curtius rearrangement as above. The resulting isocyanate (28) was reacted with ethanol to give the urethane (11); m/e 228; ν_{max} (CCl_4) 3340, 3282, 1725 and 1660 cm^{-1}; [δ_H (at 65°C in $CDCl_3$) 1.20 (3H, t, J 7 Hz, MeCH_2), 2.07 (3H, s, MeCO), 3.45 (2H, m, 2H-5), 4.11 (2H, q, J 7 Hz, MeCH_2O), and 5.5 (2H, m, H-2 and NH)]. In a separate experiment the isocyanate was treated with 2-butyl magnesium bromide to yield the bis-amide (12) which was crystallised from chloroform-light petroleum, m.p. 118-120°C; m/e 212; ν_{max} (CCl_4) 3445, 3300, 1680 and 1664 cm^{-1}. [δ_H 0.90 (3H, t, J 7 Hz, MeCH_2), 1.13 (3H, d, J 7 Hz, MeCH), 2.08 (3H, s, MeCO), 3.47 (2H, m, 2H-5), 5.85 (1H, m, H-2) and 6.93 (H, brd, J 8 Hz, NH)]. (Found: C, 62.05; H, 9.25; N, 13.15. $C_{11}H_{20}N_2O_2$ requires C, 62.25; H, 9.5; N, 13.2%).

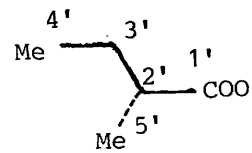
(7) N-Acetyl-L-proline (17).- Procedure as described for N-dihydrocinnamoyl-L-proline. The product was crystallised from ethyl acetate and had m.p. 104-105°C (lit.[5] 103-104°C).

Table 1

A



B



Carbon No.	δ_C A	δ_C B
1'	175.9	176.31
2'	42.9	41.62
3'	27.0	26.67
4'	11.9	11.52
5'	17.6	16.40

Table 2

^{13}C n.m.r. spectra of roxburghilin and related compounds (in $CDCl_3$ at room temperature).

	1	1[c]	4[a]	4[b]	12[y]	11[y]
C-2	62.8 62.7[x]	64.0	63.5 (65.0)	64.6	64.3	66.2
C-3	34.5	35.0	34.4 (36.7)	34.0[x]	34.6	34.6
C-4	21.6[x]	22.5	21.5 (23.8)	22.4[x]	21.6	21.4
C-5	46.2	47.2	47.2 (45.7)	46.5	45.8	45.5
Tertiary	165.7 s	167.5	172.1	171.8	170.4	170.5
amide	142.8 d	143.8	35.6	36.2	22.0	22.0
	118.2 d	119.6	31.3 31.0[x]	31.7		
	134.8 s	136.3	140.9	142.0		
	129.9 d	131.1	126.1	126.0		
	128.8(2) d	129.9	128.4(4)	128.9(2)		
	128.3(2) d	129.3		128.7(2)		
						Urethane
Secondary	175.9 s	178.3	175.6	175.4	175.6	155.3
amide	42.9 d 42.7[x]	43.6	42.9[x]	43.0	42.8	61.0
	27.3 t 27.0	28.1	27.2 27.0[x]	27.4 27.7[x]	27.0	14.6
	17.6 17.3[x] q	17.9	17.6 17.3[x]	17.5 17.4[x]	17.4	
	11.9 q	12.3	11.9	11.9	11.9	

(a) Figures in parentheses represent minor rotamer.

(b) [$^2H_8$]Toluene at 100°C. (c) CD_3OD at room temperature.

(x) Presence of epimers indicated by two resonances or unresolved shoulder.

(y) Major rotamer.

Table 3

^{13}C n.m.r. chemical shift differences of ring carbons in amide rotamers.

Compound	C-2, C-5	Δδ	C-3, C-4	Δδ
Dihydroroxburghilin[a]	64.6	0.8	36.9	2.1
	63.8		34.8	
	46.9	0.8	23.8	2.2
	46.1		21.6	
N-Dihydrocinnamoyl-pyrrolidine[a]	46.0	0.2	26.1	1.7
	45.8		24.4	
N-Cinnamoylpyrrolidine[a]	46.0	0	26.2	1.8
			24.4	
	C-2		C-3	
	C-6		C-5	
N-Dihydrocinnamoyl-piperidine[b]	47.0	3.7	26.7	1.0
	43.3		25.7	
N-Cinnamoylpiperidine[b]	46.6	3.9	26.4	0.9
	42.7		25.5	

[a] $[^2H_8]$Toluene. [b] In $CDCl_3$. The Δδ value for NN-dimethylacetamide in $CDCl_3$ is 3.0 ppm.

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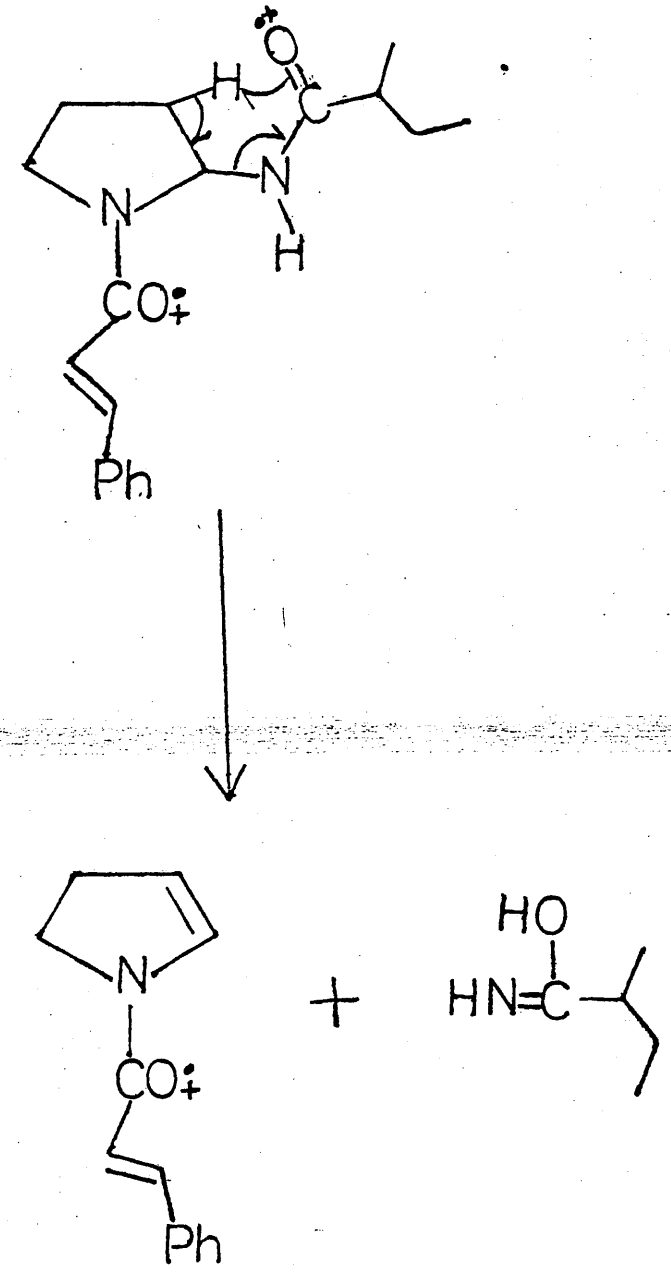
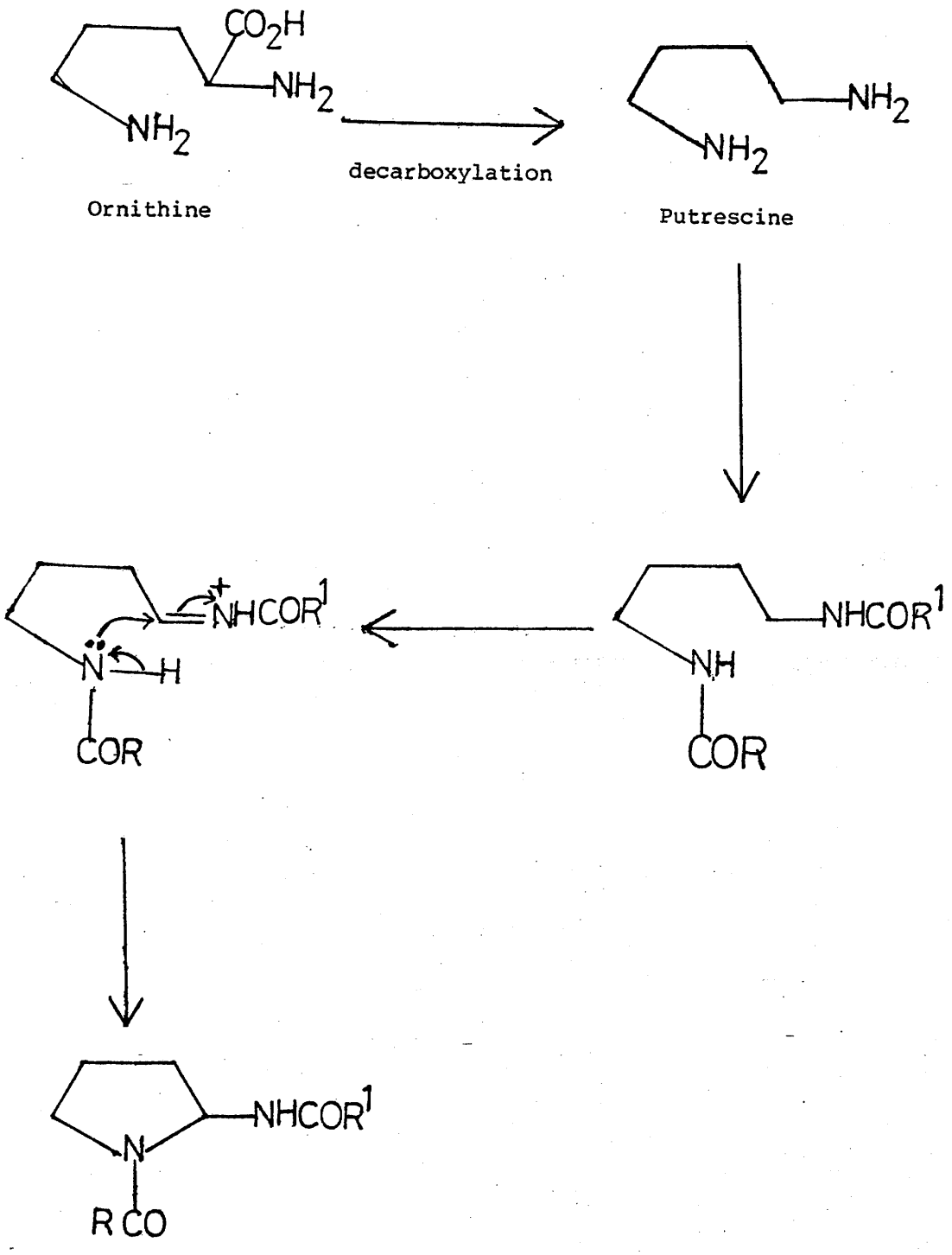
Scheme 1

McLafferty Rearrangement in Fragmentation of Roxburghilin.



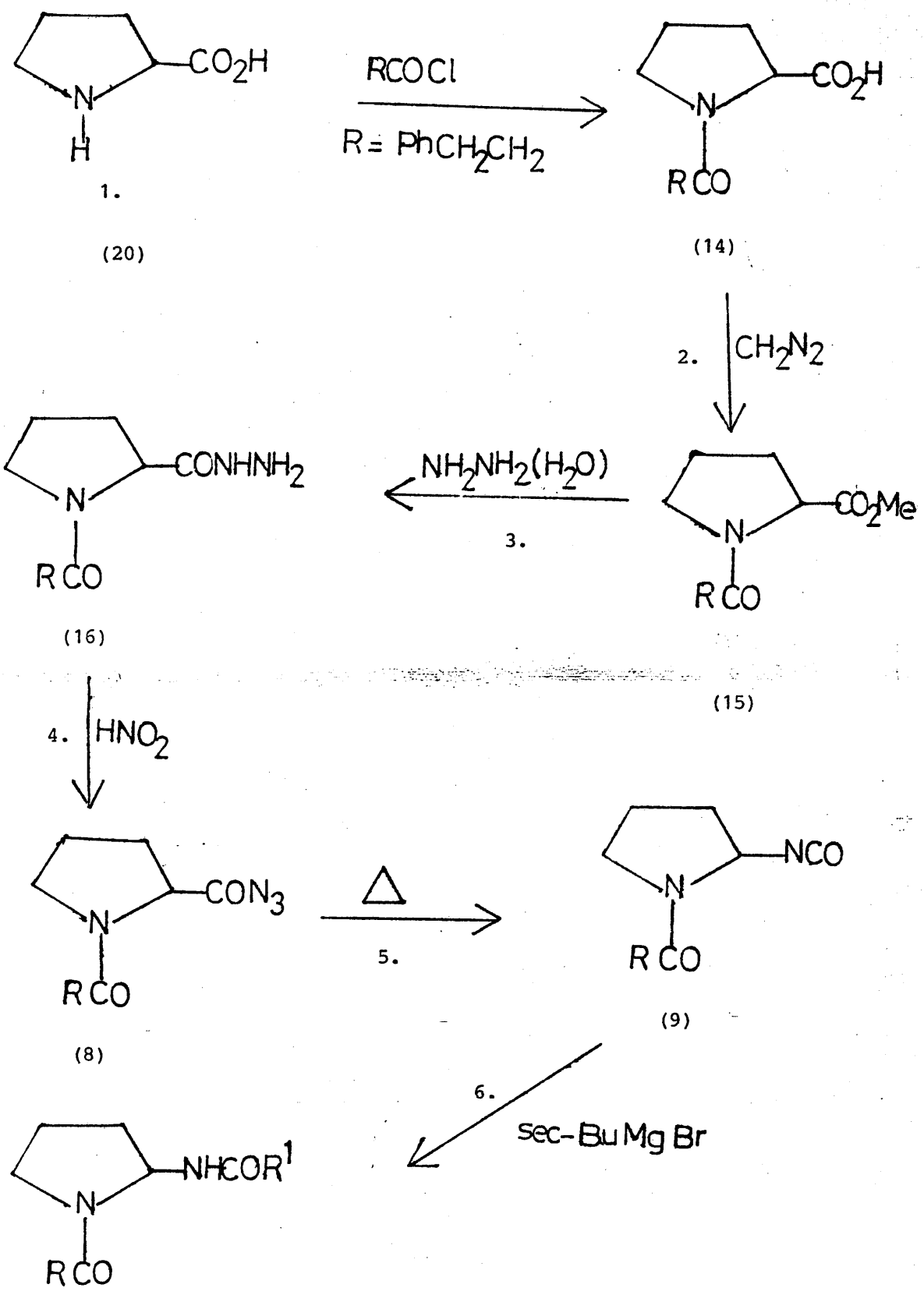
Scheme 2

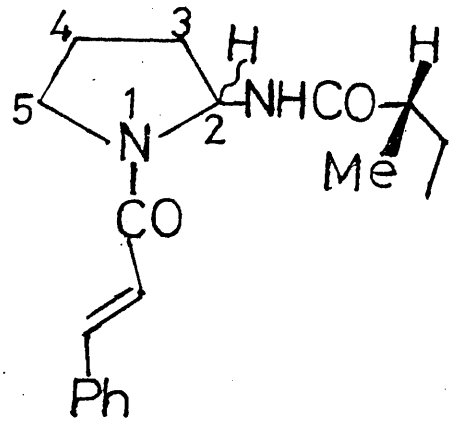


Ornithine

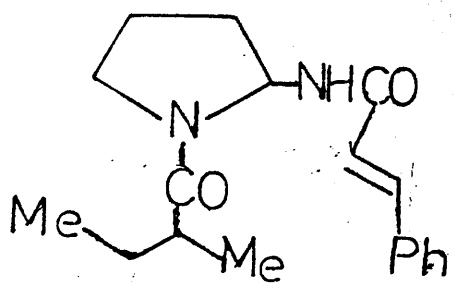
Putrescine

Scheme 3


CO2H
N
H
1.
(20)
RCOCl
R = PhCH2CH2
CO2H
N
RCO
(14)
2.
CH2N2
CONHNH2
N
RCO
(16)
NH2NH2(H2O)
3.
CO2Me
N
RCO
(15)
4.
HNO2
CON3
N
RCO
(8)
Δ
5.
NCO
N
RCO
(9)
6.
sec-Bu Mg Br
NHCOR1
N
RCO



(1)



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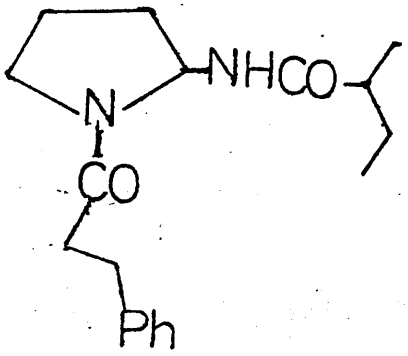

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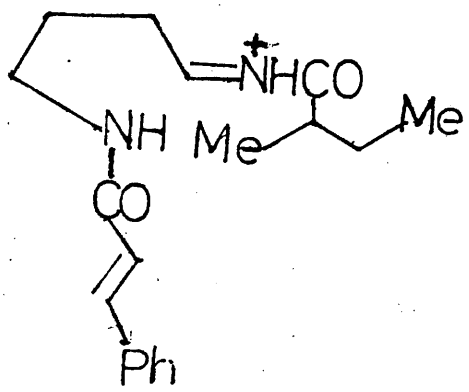

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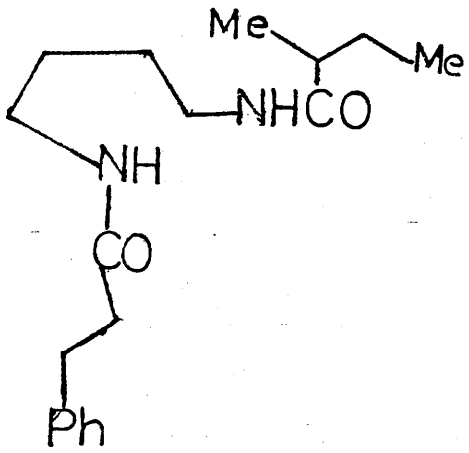

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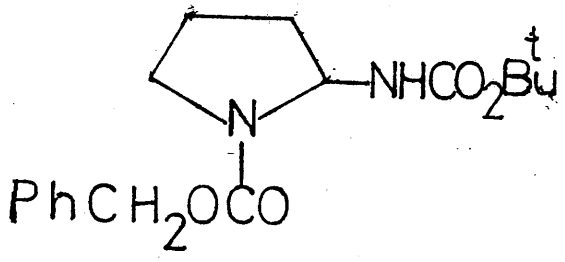
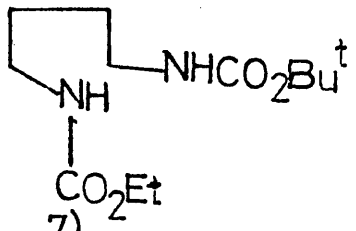


(6)



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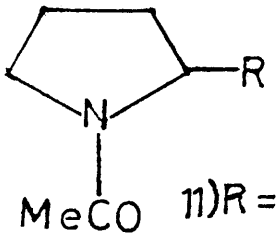
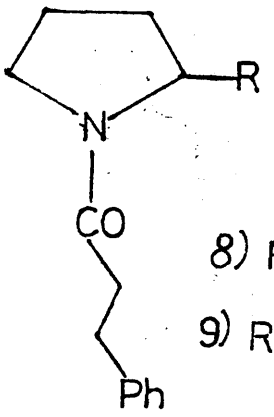
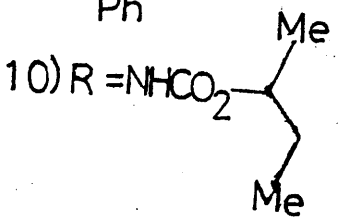


11) R = $NHCO_2Et$

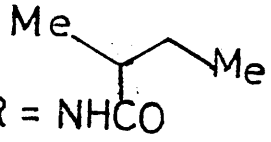


8) R = CON_3

9) R = NCO



10) R = $NHCO_2$



12) R = NHCO

17) R = CO_2H

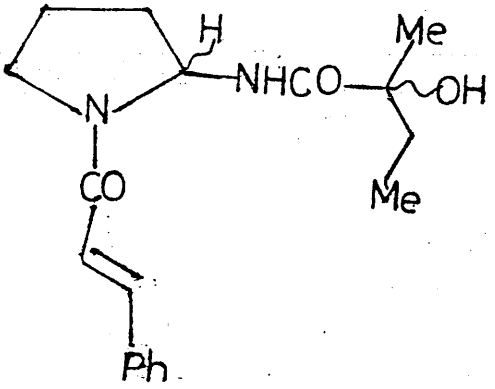
18) R = CO_2Me

19) R = $CONHNH_2$

14) R = CO_2H

15) R = CO_2Me

16) R = $CONHNH_2$



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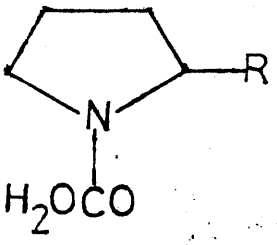
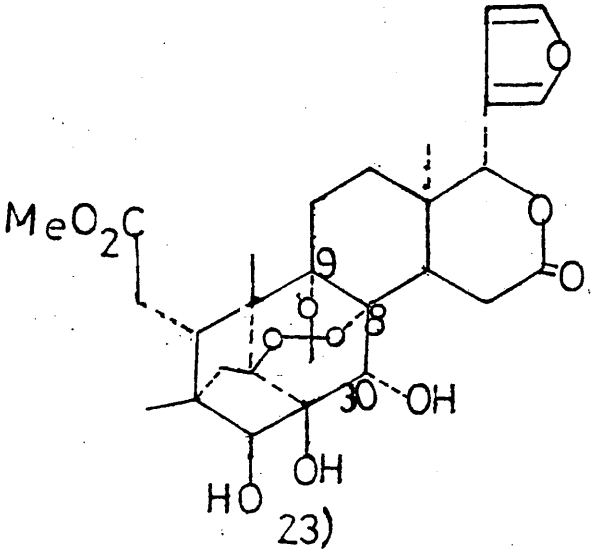


21) R = CO_2H

22) R = $NHCONHCO_2Bu^t$



23)

CHAPTER VIII

THE STRUCTURE OF A LABDANE DIALDEHYDE FROM AFROMOMUM DANIELLII (ZINGIBERACEAE)

INTRODUCTION

The plant Afromomum daniellii (Zingiberaceae) is a perennial herb which grows in many regions of Cameroon. It is known locally as "Achoh" and the seeds produce a hot taste on chewing. Like other members of its family which have been found useful, the roots of this plant are used as a purgative. Afromomum angustifolium from the same locality, and Curcuma angustifolia, a native of East India, are known to be a rich source of arrowroot. The medicinal properties of other members of this family, and this species in particular, stimulated our interest. Extraction of the seeds with hexane afforded a diterpenoid dialdehyde $C_{20}H_{30}O_3$ to which we assigned the structure (E)-8β,17-epoxylab-12-ene-15,16-dial (1) on the basis of its spectroscopic properties and by correlation with cis-12-norambreinolide (6). Natural dialdehydes are not very common, though in general they have interesting biological activity. Linaridial (3), a cis-clerodane from Linaria japonica,[1] warburganal (9), ugandensidial (10), and poligodial (11) from the bark of East African Warburgia species (W. stuhlmannii and W. ugandensis)[2] are representative examples. Compounds (9), (10) and (11) exhibit strong insect antifeedant activity in African army worms Spodoptera littoralis and S. exempta and have been synthesised,[3,4] albeit in low yield. It is attractive to regard (1) as a starting point for partial synthesis of the above sesquiterpenoid dialdehydes. Unfortunately preliminary attempts to cleave the C-11, C-12 bond proved unsuccessful. The biological activity of (1) is, however, under investigation.

D I S C U S S I O N

The ^{1}H n.m.r. spectrum of (1) has signals for three tertiary methyls (δ_H 0.9, 0.87, and 0.84), an epoxide methylene [δ 2.27 and 2.42 (ABq, J 3.5 Hz)], an allylic methylene [(δ 3.38 (brs)], a saturated aldehyde [δ 9.58 (t, J 1 Hz)] and an α β-unsaturated aldehyde [δ 9.36 (s); 6.64 (brt, J 7 Hz, vinyl H-12)]. The i.r. [ν_{max} (CCl_4) 2712, 1731, 1690, 1640 cm^{-1}] and u.v. [λ_{max} 234 nm (ε 14,400)] spectra confirmed the presence of two aldehyde groups. The above data account for the functionality of (1) which is therefore bicarbocyclic. The relationship between the two aldehyde groups was established by double resonance experiments. Irradiation of the allylic methylene resonance at δ 3.38 caused the collapse of the saturated aldehyde triplet at δ 9.58 to a singlet and simultaneously sharpened the vinyl proton triplet at δ 6.64. This suggested the partial structure (2). Irradiation at δ 6.64, the resonance frequency of the vinyl proton, resulted in a 20% increase in the integrated intensity of the unsaturated aldehyde proton and thus established the (E)-configuration of the double bond. The partial structure (2) corresponds to the side chain of linaridial (3), a cis-clerodane from Linaria japonica,[1] and there is a good agreement between the above spectroscopic data and those reported for linaridial. The remaining features of the dialdehyde were readily accommodated in a labdane skeleton, leading to structure (1). The ^{13}C resonances of rings A and B of (1) (see Table 1) were similar to published data.[5] Confirmation of the structure and absolute stereochemistry was obtained as follows (Scheme 1).

Reduction of (1) with $LiAlH_4$ afforded the triol (4). The ^1H spectrum [δ_H 0.83, 0.86, 0.96, 1.09 (C-Me), 2.44 (t, J 6 Hz, 2H-14); 3.73 (t, J 6 Hz, $\underline{CH_2}OH$, 2H-15), 4.0 (brs, $\underline{CH_2}$-OH, 2H-16) and 5.48 (t, J 6 Hz, H-12)] fully supported its structure. Reaction of (4) with OsO_4 and periodate cleavage of the resulting pentaol yielded the non-crystalline hemiacetal (5) [δ_H 4.95 (t, J 5 Hz, H-12)]. This was converted by Jones oxidation into cis-12-norambreinolide (6) ($[\alpha]_D$ - 28°[6]) m.p. 94-95°C (lit. 93-94.5°C). ^1H n.m.r. [δ_H 0.86, 0.92 (6H) C-Me, 1.32 (C-8 Me) and 2.55 (2H, m, 2H-11)]. Trans-12-Norambreinolide (7)[7] was obtained by chromium trioxide oxidation of sclareol (8)[8] and was epimerised under acidic conditions[6] to cis-12-norambreinolide (6) ($[\alpha]_D$ - 33°), identical in all respects with the degradation product of (1). This correlation confirms the structure and absolute configuration of the labdane dialdehyde (1).

Compound (7) probably arose via an initial dehydration of the tertiary hydroxyl group of sclareol to give the diene (14), followed by oxidative cleavage of the C-12, C-13 double bond with formation of the carboxylic acid (15) which lactonised with the C-8 hydroxyl group under the acidic conditions. It is reasonable to assume that the epimerisation occurred by acid opening of the lactone ring to generate the exomethylene derivative (16), protonation and relactonisation.

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

Extraction.- Dried seeds (1 kg) of A. daniellii collected from Evodoula in the Central South Province of Cameroon in December were powdered and Soxhlet-extracted with hexane for 24 hrs. The extract was concentrated and set aside for several days. The solid which was deposited was filtered off through a column of alumina in hexane to give (1) (20 g). Recrystallisation from chloroform-light petroleum afforded the pure (E)-8β,17-epoxylab-12-ene-15,16-dial (1) m.p. 90-92°C; $[\alpha]_D$ + 28.1° (C 1.41). (Found: C, 73.65; H, 9.65. $C_{20}H_{30}O_3.\frac{1}{2}H_2O$ requires C, 73.4; H, 9.55%).

Reduction of (1).- (a) The aldehyde (1) (300 mg) in dry ether (20 ml) was treated with excess of $LiAlH_4$ (500 mg) and the solution refluxed for 4 hrs. The excess of $LiAlH_4$ was destroyed by dropwise addition of saturated brine and the inorganic residue removed by filtration. Evaporation of the ether afforded the (E)-lab-12-ene-8,15,16-triol (4) which was crystallised from light petroleum as needles, m.p. 98-99°C [δ_H 0.83, 0.86, 0.96, 1.09 (C-Me), 2.44 (t, J 6 Hz, 2H-14), 3.73 (t, J 6 Hz, $\underline{CH_2}OH$, 2H-15), 4.0 (brs, $\underline{CH_2}$-OH, 2H-16), and 5.48 (t, J 6 Hz, H-12)]. (Found: C, 74.3; H, 11.10. $C_{20}H_{36}O_3$ requires C, 74.0; H, 11.2%).

(b) The aldehyde (1) (200 mg) in dry methanol (20 ml) was treated with a stoicheometric amount of $NaBH_4$ (23.9 mg) and the mixture allowed to stir for 2 hrs, after which acetic acid was added. The solution was flooded with water and extracted with chloroform. Evaporation under reduced pressure gave the (E)-8β,17-epoxylab-12-ene-15,16-diol (17), crystallised from benzene-light petroleum ether, m.p. 78-79°C, m/e 322; (Found: C, 74.3; H, 10.37. $C_{20}H_{34}O_3$ requires C 74.49; H, 10.63%).

[δ_H 0.80, 0.86 (6H) (C-Me), an epoxide methylene δ 2.22 and 2.55 (ABq, J 3.5 Hz), 5.38 (brt, J 7 Hz (vinyl H-12); 4.0 (brs, $\underline{CH_2}OH$, 2H-16); 3.70 (t, J 6 Hz, $\underline{CH_2}OH$, 2H-15), and 2.36 (t, J 6 Hz, 2H-14)].

Hemiacetal (5).- The triol (4) (100 mg) was dissolved in ether (40 ml) containing a few drops of pyridine and osmium tetroxide (100 mg) was added. The reaction mixture was set aside in the dark for 24 hr., stirred with aqueous sodium metabisulphite solution and extracted with ethyl acetate. The product, a single polar spot on analytical t.l.c. without further purification was stirred overnight in aqueous methanol (20 ml) with excess $NaIO_4$. Addition of water and extraction with ethyl acetate afforded the hemiacetal (5) as a gum, m/e 234; [δ_H 0.86 (6H), 0.88, 1.27 (C-Me) and 4.95 (t, J 5 Hz, H-12)].

Lactone (6).- The hemiacetal (5) (20 mg) in acetone was oxidised with Jones reagent. The lactone cis-12-norambreinolide (6) was obtained, and was recrystallised from light petroleum as needles i.r. ν_{max} (CCl_4) 1780 cm^{-1}; m.p. 94-95°C.

Oxidation of sclareol (8).- A stirred solution of sclareol (8) (2 g) in glacial acetic acid (20 ml) was treated with CrO_3 (4.4 g) in 10% aqueous acetic acid (20 ml) during 30 min.; and stirring was continued for 24 hrs. Extraction with ether and removal of acidic products with aqueous Na_2CO_3 afforded trans-12-norambreinolide (7) m.p. 123-125°C (ex light petroleum) (lit.[7] 123-125°C) ν_{max} (CCl_4) 1778 cm^{-1}; [δ_H 0.85, 0.88, 0.92 and 1.33 (C-Me)].

Epimerisation of trans-12-norambreinolide (7).- The trans lactone (7) (51 mg) was heated at 70°C in glacial acetic acid (2 ml) containing 50% H_2SO_4 (0.2 ml) for 6 hrs. and set aside overnight. Addition of water and extraction with ether gave cis-12-norambreinolide (6) which crystallised from light petroleum ether as needles, m.p. 93-94.5°C (lit.[6] 95°C);

$[\alpha]_D$ - 33° (C, 0.57) identical in all respects with the degradation product of the natural aldehyde (1).

Attempted synthesis of warburganal (9) and related compounds.- Treatment of the diol (17) or its diacetate (18) with the following reagents resulted in total failure to isolate any products.

(a) Bromination of the double bond in CCl_4, $CHCl_3$, and ether respectively, with a view to generating the dibromide (22).

(b) Iodine and silver benzoate in dry benzene with the hope of obtaining the iodobenzoate, or dibenzoate (23) and (24) respectively.

(c) Selenium dioxide in dioxane which could lead to the 11-oxo or 11,14-dioxo derivatives (25) or (26).

(d) Diphenyl diselenide in the presence of t-butyl hydroperoxide which might afford the allylic alcohol (27) or (28).

The epoxide is resistant to dilute sulphuric acid and metal-dialkyl amide complexes such as lithium diethyl amide.

Table 1

^{13}C n.m.r. of compound (1) and related compounds

Carbon	(1)	(19)
1	39.6 (t)	39.8
2	18.4 (t)	18.5
3	42.0 (t)	42.1
4	33.6 (s)	33.3
5	52.8 (d)	56.2
6	20.0 (t)	20.6
7	39.6 (t)	40.9
8	57.6 (s)	74.4
9	55.2 (d)	62.5
10	40.0 (s)	39.2
11	22.4 (t)	24.0
12	161.2 (d)	44.3
13	136.0 (s)	30.6
14	36.0 (t)	39.8
15	198.0 (d)	60.3
16	194.0 (d)	20.1
17	48.8 (t)	23.2
18	33.6 (q)	33.5
19	21.6 (q)	21.5
20	14.8 (q)	15.5

Assignments are based on chemical shift rules, multiplicity in the offresonance spectra and comparison with published data.[5]

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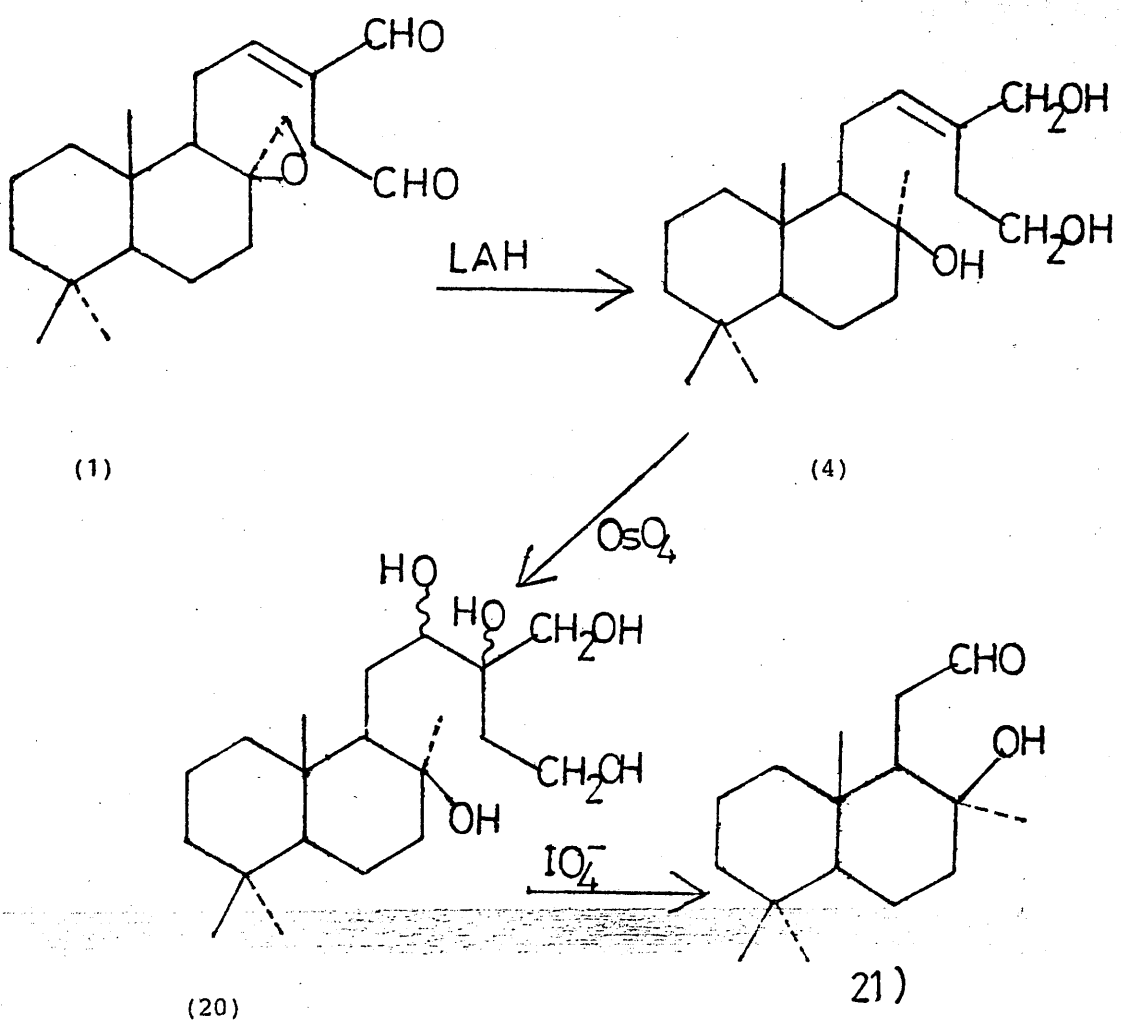
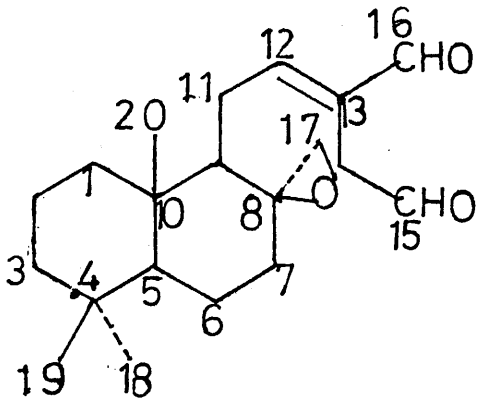
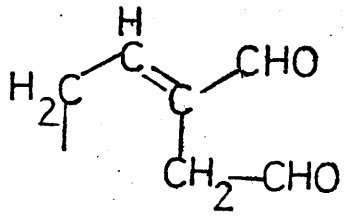
Scheme 1



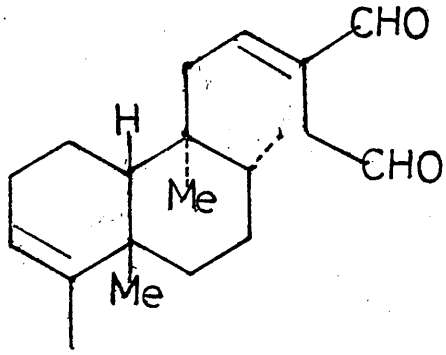
(1) (4) (20) 21) (6) (5) (8) (7)


16
CHO
12
11
20
17
13
1
10
8
O
CHO
15
3
4
5
6
7
19
18

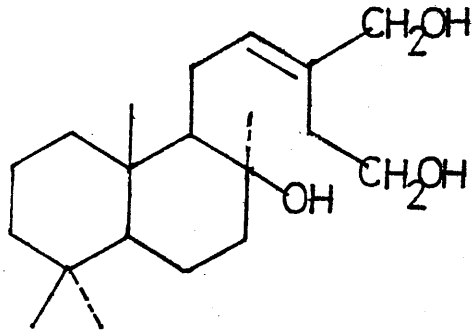
1)


H
C
CHO
H2C
C
CH2—CHO

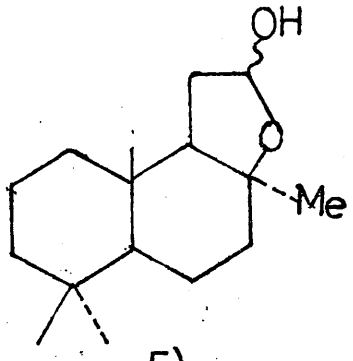
2)


CHO
H
CHO
Me
Me

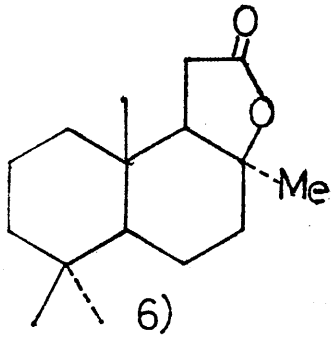
3)


CH2OH
CH2OH
OH

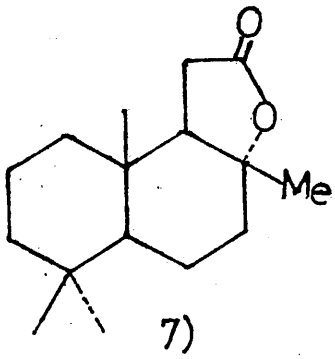
4)


OH
O
Me

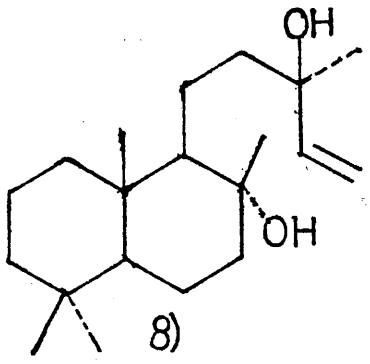
5)


O
O
Me

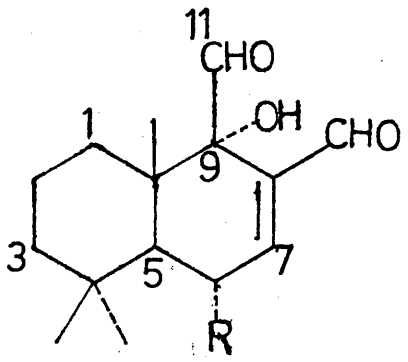
6)


O
O
Me

7)

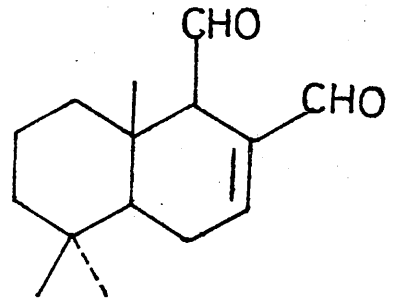

OH
OH

8)

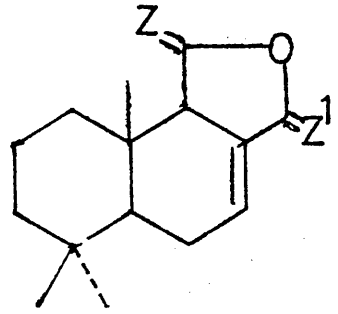


9) R = H

10) R = OAc

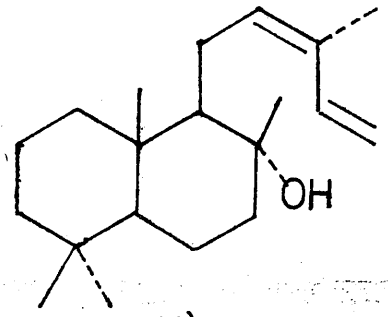


11)

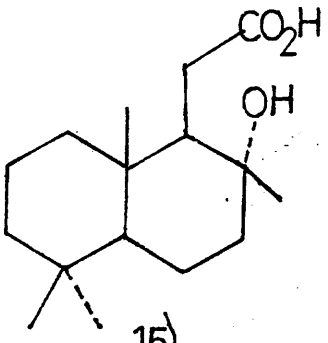


12) $Z = H_2, Z^1 = O$

13) $Z = O, Z^1 = H_2$



14)



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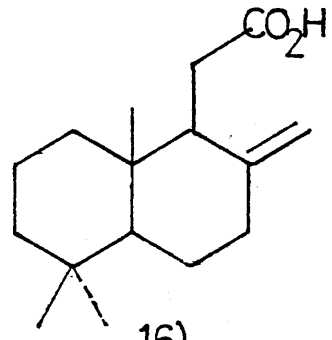
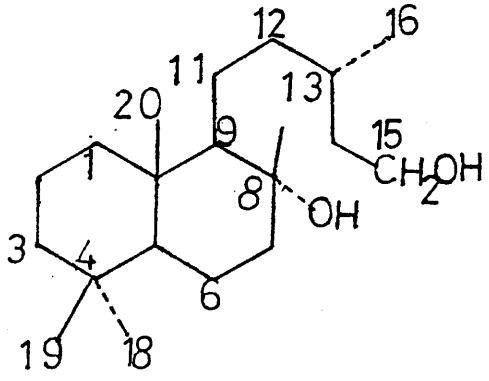
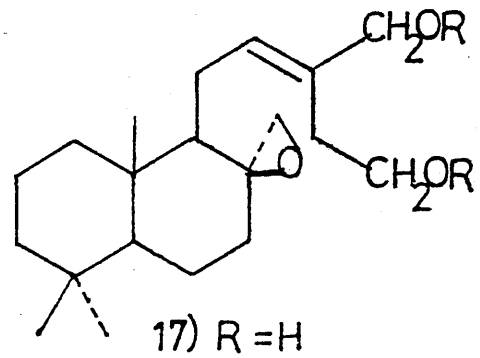


16)

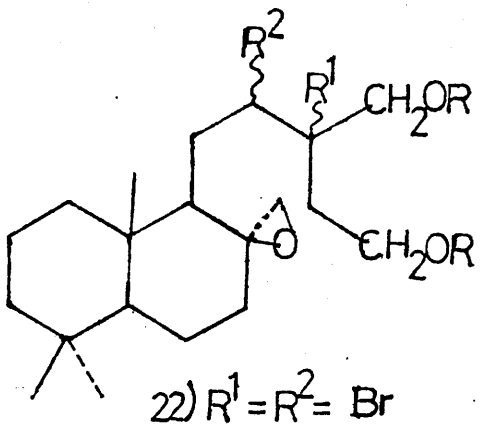


19)



17) R = H

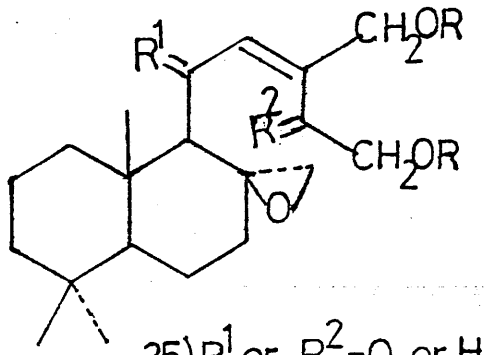
18) R = Ac



22) $R^1 = R^2 =$ Br

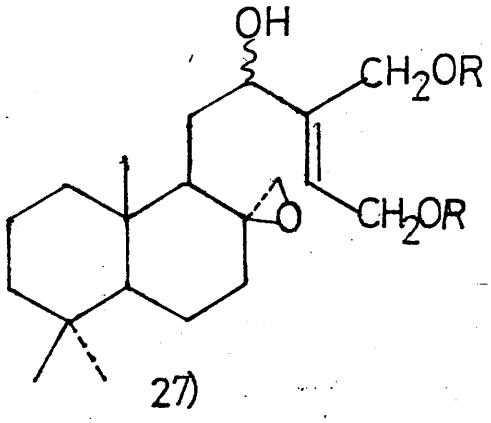
23) R^1 or R^2 = I or OBz

24) $R^1 = R^2 =$ OBz

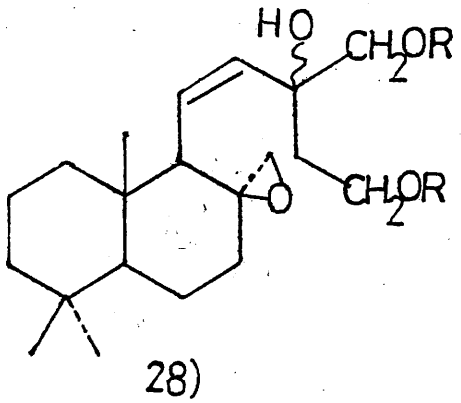


25) R^1 or R^2 = O or H_2

26) $R^1 = R^2 = O$



27)



28)

CHAPTER IX

NEW SESQUITERPENOID LACTONES FROM VICOA INDICA (COMPOSITAE)

INTRODUCTION

The vast field of sesquiterpenoid lactones has been the subject of a recent extensive review.[1] Interest in these natural products is still great, probably because of their successful use as markers in biochemical systematic studies (Chemotaxonomy), mainly in the Compositae,[2] and their various biological activities.[3]

A detailed review of the biogenesis and chemistry of sesquiterpenoid lactones will be beyond the scope of this thesis. It is sufficient to repeat the generally accepted assumptions that these sesquiterpenoid lactones are derived from farnesyl-pyrophosphates[4] and that the majority of the skeletal types are biogenetic derivatives of germacranolide (1). Some of the presently known structural classes and their presumed biogenet relationships are as shown in Scheme 1. The germacranolides are divided into subgroups on the basis of the configuration of the 1,10 and 4,5 double bonds (see Scheme 2).

This chapter deals with three new sesquiterpenoid lactones isolated from Vicoa indica, a shrub belonging to a small tribe of the Compositae family. Extraction of V. indica, collected near Madras, afforded two sesquiterpenoid lactones A and B which are assigned the guaianolide structure (2) and the germacranolide structure (7) respectively on the basis of spectroscopic evidence. In an effort to obtain more material the same plant, gathered in a different region near Poona, was extracted and yielded a third sesquiterpenoid lactone, the germacranolide (11). The evidence for these assignments is discussed below.

D I S C U S S I O N

Compound A (2), $C_{20}H_{24}O_6$, [m/e 360; ν_{max} (CCl_4) 3605, 3460 br, 1782, 1727 sh, 1710 and 1649 w cm^{-1}; λ_{max} 224 nm] has spectroscopic properties (see Tables 1 and 2) consistent with the presence of an $\alpha\beta$-unsaturated cyclopentenone, an angelate,[5] a secondary hydroxyl group, an exomethylene γ-lactone, a vinyl methyl group and a secondary methyl group. These functional groups account for all the oxygen atoms and hence the molecule is bicarbocyclic. Extensive homonuclear proton decoupling experiments at 360 MHz enabled the constitution of the entire molecule to be established as follows. Irradiation of H-5 (δ 3.19, bdd, J 10.9, 7.2 Hz) resulted in the removal of a small allylic coupling to the vinyl proton H-3 (δ 6.11, dq, J 2.0, 1.3 Hz), which is also coupled to the vinyl methyl group, and simultaneously removed doublet splittings from H-1 (δ 2.90, dd, J 7.2, 3.9 Hz) and H-6 (δ 4.43, dd, J 9.6, 10.9 Hz). H-6 is coupled in turn to H-7 (δ 2.94, tt, J 10.0, 3.1 Hz). On irradiation of H-7 the exomethylene protons collapsed to singlets by loss of their allylic coupling and doublet splittings were removed from H-6 and H-8 (δ 4.04, ddd, J 10.4, 9.3, 4.4 Hz). The attachment of the secondary hydroxyl group to C-8 was confirmed by D_2O exchange which caused the disappearance of the hydroxyl proton doublet (δ 2.49, J 4.4 Hz) and the loss of a doublet splitting from H-8. The third splitting of H-8 is due to coupling with H-9 (δ 5.01, dd, J 9.3, 3.3 Hz), the position of the attachment of the angelate, which is in turn coupled to the methine H-10 (δ 2.76, m) on the same carbon atom as the secondary methyl group. Decoupling of H-10, in addition to affecting H-9 and the secondary methyl, removed a doublet splitting from H-1. This decoupling sequence is

summarised in the diagram (3) and leads uniquely to the guaianolide skeleton (4) for lactone A.

Evidence for the stereochemistry of lactone A is readily available from the coupling constant information. The large allylic couplings (2.9, 3.3 Hz) of the exomethylene protons together with the large value of $J_{6,7}$ (9.6 Hz) are characteristic of a trans-fused lactone.[1] The C-7 substituent is assumed to be in the normal β configuration.[5,6] The large values of $J_{5,6}$, $J_{7,8}$, and $J_{8,9}$ (10.9, 10.4, and 9.3 Hz respectively) are consistent with antiperiplanar arrangements. The cis nature of the A,B ring junction is suggested by the magnitude of $J_{1,5}$ (7.2 Hz) which is in good agreement with the corresponding value for the model system (5)[6] (see below). The configuration of the remaining centre C-10 is not obvious at first sight. However an examination of models reveals a conformation, with the secondary methyl group β and pseudo-axial, which accommodates the observed values of $J_{9,10}$ (3.3 Hz) and $J_{10,1}$ (3.9 Hz). In this conformation the secondary methyl group lies close to H-6. The observation of a nuclear Overhauser enhancement (~ 10%) of H-6 on irradiation of the secondary methyl protons provides supportive evidence for this assignment. The alternative arrangement with the C-10 methyl group α (pseudo-axial) and a trans AB ring junction (i.e. H-1β) which could also accommodate the observed coupling constants is excluded by the nuclear Overhauser effect. Thus lactone A is assigned the structure and stereochemistry depicted in (2).

Acetylation of A afforded the monoacetate (6) in which the resonance for H-8 has, as expected, moved downfield (Δδ 1.44). Comparison of the ^{13}C chemical shifts (see Table 2) of the acetate (6) in relation to the parent compound (2) reveals β-acetylation shifts of C-9 (Δδ - 3.6)

and C-7 ($\Delta\delta$ - 2.7) although C-8 itself remains relatively unchanged. An upfield shift ($\Delta\delta$ + 1.6) of the angelate carbonyl group is presumably due to H-bonding removal which may also negate the anticipated positive α-acetylation shift of C-8.

Lactone B (7), $C_{20}H_{26}O_6$, [m/e 362; ν_{max} (CCl_4) 3612, 3518, 1780, 1712, 1688 and 1634 cm^{-1}; λ_{max} 221 nm] has spectroscopic properties which are strikingly similar to those of A (2) and which indicate the same functional groups. The two additional hydrogens in the molecular formula together with the change in the enone carbonyl frequency suggest that it is a germacranolide and not a guaianolide. This conclusion is supported by the ^{13}C off resonance spectrum which has two methylene triplets and two methine doublets.

Decoupling experiments and consideration of coupling constant values [see (8)] permitted the assembly of the part structure (9) on the assumption that $J_{7,8}$ is zero. This part structure is readily expanded to (7) for compound B which is thus the germacranolide equivalent of lactone A. The same stereochemistry as (2) is assumed although further work is required to determine the exact conformation of the molecule.

Acetylation of B (7) yielded the acetate (10) in which the resonance for H-8 has moved to lower field ($\Delta\delta$ 1.62) and overlaps with H-9 to give a two proton singlet at δ 5.52. The ^{13}C chemical shifts of B (7) and its acetate (10) (Table 2) are generally similar to those of A (2) and its acetate (6). The most striking change concerns C-4 which exhibits a dramatic upfield shift of 34 ppm on changing from the guaianolide to the germacranolide. The methyl groups are also affected, the vinyl methyl moving downfield by 6.3 ppm and the secondary methyl by 8.6 ppm. It is interesting to note that the ketonic carbonyl of

lactone B appears at δ 206.2, a slightly lowfield position for an unsaturated ketone. This suggests that there may be some departure from planarity in the enone system. Comparison of the shifts of B (7) and its acetate (10) reveals upfield shifts of C-9 ($\Delta\delta$ - 3.1) and the angelate carbonyl ($\Delta\delta$ - 1.8) although, in this case, C-7 and C-8 are relatively unchanged. Small changes in the shifts of several other carbons suggest that a slight conformational change has occurred.

The spectroscopic properties (see Tables 1 and 2) of lactone C (11), $C_{22}H_{32}O_9$, [m/e 440; ν_{max} (CCl_4) 3610, 3485, 1755 and 1790 cm^{-1}] revealed the presence of two secondary esters, an acetate and a 2-methylbutanoate, two secondary hydroxyl groups, a trisubstituted epoxide (δ_H 2.83 (bs, H-3); δ_C 70.0 (d, C-3) and 65.3 (s, C-4), an exomethylene lactone, and two methyl groups, one secondary and one tertiary. The molecule is therefore monocarbocyclic and presumably a germacranolide. The ^{13}C spectrum shows only one methylene and two methine signals in addition to the carbons associated with the above functional groups.

Once again homonuclear proton decoupling studies provided useful information. The two secondary ester protons, H-8 and H-9, are vicinal. Irradiation at H-10 (δ 2.5) causes the simultaneous collapse of the secondary methyl doublet and the sharpening of H-9. There is no evidence which permits a decision on which position bears the acetate and which the 2-methylbutanoate. For convenience and by analogy with the lactone A and B the 2-methylbutanoate is assumed to be attached to C-9. This leads to part structure (12). The allylic coupling (~ 3 Hz) of the exomethylene protons and the large $J_{6,7}$ (9 Hz) indicates a trans-fused lactone. The proton attached to the lactone terminus (H-6) is coupled to a secondary hydroxyl proton (δ 4.36, d, J 9 Hz, H-5) which shows no

further coupling. These results afford the part structure (13). The remaining secondary hydroxyl proton has a small coupling to the epoxide proton (H-3) and its major coupling (9 Hz) to one of the methylene protons. The chemical shift of the tertiary methyl group (δ 1.44) indicates that it is also attached to the epoxide at C-4. The third part structure is therefore (14). On the assumption that there is a zero coupling between H-7 and H-8, as in lactone B (7), these part structures can be assembled to give (11) as the gross structure for lactone C.

Support for this gross structure was obtained from chemical transformation of lactone C. Acetylation gave the diacetate (15) and the triacetate (16). It is clear from its spectroscopic properties that, in the diacetate (15), acetylation has taken place at C-5 since H-5 has moved downfield by 1.37 ppm. In the triacetate (16) both H-2 and H-5 resonate at low field. Formation of the diacetate (15) results in acetylation shifts of C-5 (Δδ + 0.8), C-4 (Δδ - 2.1) and C-6 (Δδ - 2.8). Similarly acetylation shifts of C-2 (Δδ + 1.2), C-3 (Δδ - 3.3) and C-1 (Δδ - 2.1) are observed in the triacetate (16).

Oxidation of lactone C (11) with Jones reagent yielded the hydroxyketone (17). It was readily apparent from the ^{1}H n.m.r. spectrum that H-6 is still coupled to the secondary hydroxyl proton H-5 and hence that the hydroxyl group attached to C-2 has been oxidised to a ketonic carbonyl group. In addition the epoxide proton has moved downfield by 1.00 ppm as a sharp singlet and the resonances for the C-1 methylene group are clearly visible [δ 3.31 (dd, J 10, 15 Hz) and 1.99 (d, J 15 Hz)]. The carbon resonance of the C-1 methylene group also shows a large downfield shift (10.7 ppm). A closer examination of the ^{1}H n.m.r.

spectrum of (17) discloses further information which is of considerable value in conformational and stereochemical terms. Both H-7 and H-5 exhibit large upfield shifts (1.22 and 0.63 ppm respectively). This suggests a conformation of the molecule experience transannular shielding by the newly created carbonyl group. The conformational mobility of the medium ring makes it difficult to arrive at a unique decision for the conformation and further work is necessary. It is significant to note, however, that the coupling constants of ketone (17) are almost identical to those of lactone B (7) suggesting that they have the same stereochemistry.

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

The compounds were sent to us by an Indian colleague at Captain Srinivasa Murti Research Institute for Ayurveda in Madras.

Table 1

^{1}H n.m.r. chemical shifts of sesquiterpenoid lactones from *Vicoa indica*.

Proton	4	6	7	10	11[h]	16	15	17
I	2.90 (dd,7.2, 3.9)		2.78 (dd,10.9, 13.8)					
I_b	-		2.11 (bd,13.8)					
3	6.11 (dq,2.0, 1.3)		6.30 (bq,1.2)	6.38 (bs)	2.86 (bs)	2.95 (d,2)	2.90 (bs)	3.86 (s)
5	3.19 (dd)		3.17 (brdd, 12.4,7.7)		4.36 (d,9)	5.65 (d,9)	5.73 (d,9)	3.73 (d,9)
6	4.43 (dd,9.6, 10.9)	4.56 (dd,11,10)	4.28 (ddt,3.3, 8.8,7.7)	4.13 (dt,9,3)	4.09 (t,9)	4.21 (t,9)	4.20 (t,9)	3.96 (dd,9,8)
7	2.94 (tt,10.0, 3.1)		3.11 (dt,8.8, 3.3)		3.92 (m)	3.57 (m)	4.08 (m)	2.70 (dt,9,3)
8	4.04 (ddd,4.4, 9.3,10.4)	5.48 (t,10)		5.52 (s)	5.23 (d,10)	5.25 (d,10)	5.25 (d,10)	5.21 (d,10)
9	5.01 (dd,3.3, 9.3)	5.17 (dd,10.3)	5.29 (dd,2.4, 10.6)	5.52 (s)	5.44 (bd,10)	5.45 (bd,10)	5.51 (bd,10)	5.45 (dd,10,2)
10	2.76 (tq,3.6, 7.5)	2.67 (m)	2.64 (m)		2.5 (m)			2.58 (m)
13_a	6.50 (dd,1.1, 2.9)	6.32 (d,3)	6.39 (d,3.5)	6.38 (d,~3)	6.36 (d,~3)	6.47 (d,3)	6.44 (d,~3)	6.38 (d,~3)
13_b	6.41 (dd,1.1, 3.3)	5.70 (d,3)	5.77 (d,3.1)	5.83 (d,~3)	5.82 (d,~3)	5.89 (d,3)	5.87 (d,~3)	5.81 (d,~3)
15	2.34 (t,1.0)	2.30 (bs)	1.93 (bd,1.2)	1.97 (bs)	1.44	1.5	1.52	1.57
Angelate 3'	6.18 (qq,1.5, 7.3)	6.14 (m)	6.15 (m)	6.15 (m)	-	-	-	-

Table 1 (continued)

^{1}H n.m.r. chemical shifts of sesquiterpenoid lactones from Vicoa indica.

Proton	2	6	7	10	11[h]	16	15	17
Angel-	2.03	1.97	2.00	1.97	0.78	0.79	0.80	0.75
ate 4'	(dq,1.5, 7.3)	(d,7)	(dq,1.5, 7.3)		(t,7)	(t,7)	(t,7)	(t)
5'	1.92	1.79	1.94	1.88	0.94	0.97	1.01	1.0
	(dq,1.5, 1.5)	(d,1.5)	(dq,1.5, 1.5)		(d,7)	(d,7)	(d,7)	(d,7)
14	0.86	0.86	1.09	1.06	1.00	1.01	1.03	0.98
	(d,7.5)	(d,7)	(d,6.9)	(d,7)	(d,7)	(d,7)	(d,7)	(d,7)
-OH	2.49	-				-		3.52
	(d,4.4)	-				-		
OAc	-	2.01		1.88	1.98	2.02	2.03	2.01
						2.1	2.15	
						2.15		
2					4.64	5.73	4.71	-
					(bd,9)	(bd,9)	(bd,9)	-
5_b			2.89 (bd,12.4)					

h = 60°

Table 2

^{13}C n.m.r. chemical shifts of sesquiterpenoid lactones from *Vicoa indica*.

Carbon	2	6	7	10	11	15	16	17
1 (t)	49.7	49.6	45.4	44.8	31.4	31.2	29.3	42.1(dd)
2 (s)	206.9	206.4	206.2	206.0	65.0(d)	64.9(d)	66.2(d)	207.4(s)
3 (d)	132.8	132.9	131.0	131.2	70.0	69.6	66.7	64.4
4 (s)	179.1	178.5	145.5	145.6	65.3	63.2	62.5	65.8
5 (d)	52.0	52.0	34.1	34.7	74.5	75.3	74.3	73.7
6 (d)	77.1	77.3	77.2	76.1	79.2	76.4	76.3	77.6
7 (d)	48.7	46.0	46.4	45.8	41.8	42.2	42.9	42.4
8 (d)	71.3	71.0	70.5	69.9	70.4	70.4	69.6	69.2
9 (d)	80.5	76.9	77.2	74.1	75.7	75.5	74.8	74.2
10 (d)	35.9	36.0	33.3	33.9	27.1	27.2	28.4	33.7
11 (s)	135.3	134.2	133.4	132.7	132.9	132.3	131.7	131.9
12 (s)	169.4	168.6	168.8	168.7	169.8	168.4	167.9	167.7
13 (t)	126.9	125.4	123.2	124.1	124.1	124.2	124.9	125.1
14 (q)	11.8	11.8	20.4	20.2	22.2	22.2	22.0	20.0
15 (q)	19.8	19.6	26.1	25.9	17.9	18.6	18.6	16.8
1' (s)	167.5	165.9	168.4	166.6	176.2	176.3	176.1	176.3
2' (s)	127.0	126.8	127.3	127.0	40.9(d)	41.0(d)	40.9(d)	40.9(d)
3'	140.4	140.6	139.7	140.1	26.5(t)	26.5(t)	26.5(t)	26.5(t)
4'	20.5	20.4	20.6	20.5	11.6	11.6	11.6	11.6
5'	16.0	15.9	16.0	15.9	16.3	16.3	16.3	16.2
$CH_3\underline{CO}$	-	169.4	-	170.4	170.4	170.2	170.1	-
	-	-	-	-	-	170.2	169.5	169.9
	-	-	-	-	-	-	169.1	-
MeCO	-	20.8	-	20.5	20.8	21.0	21.0	20.6
						20.7	20.8	
							20.7	

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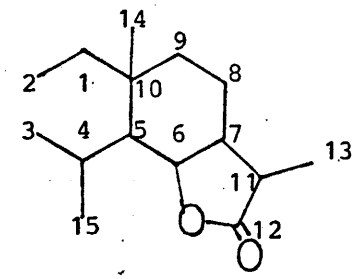
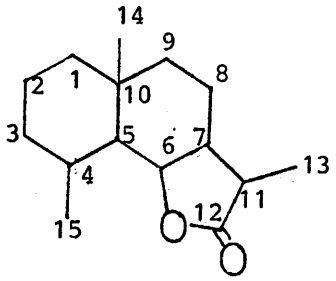
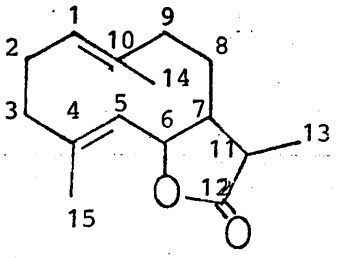
Scheme 1



elemanolide



eudesmanolide



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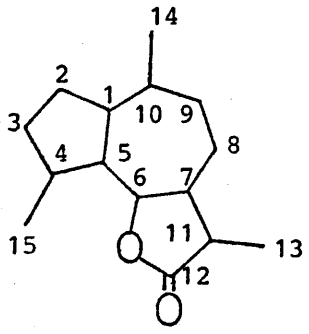
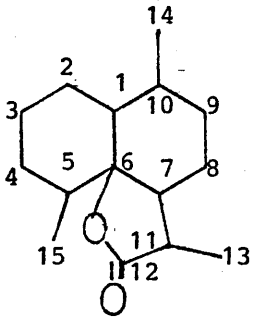
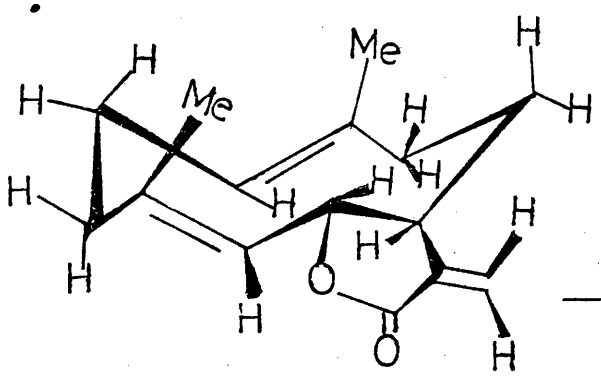


guaianolide

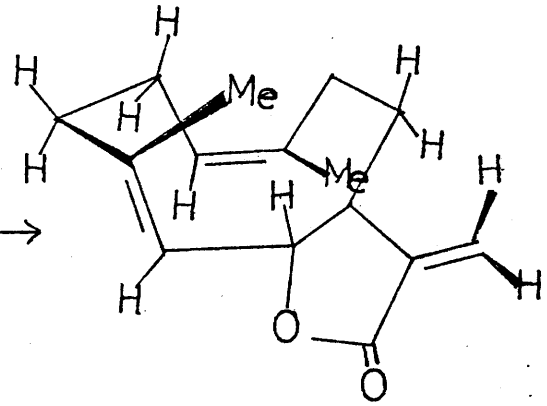


ca. dinanolide

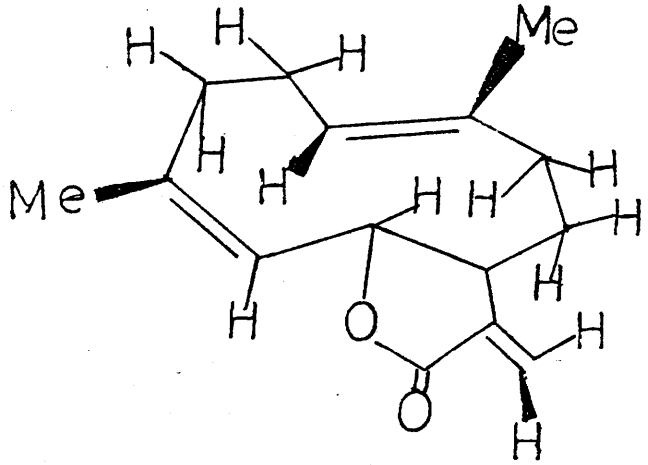
Scheme 2



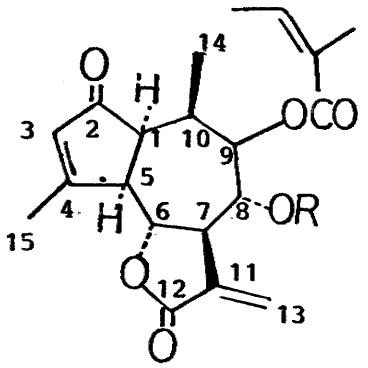
germacranolide



melampolide



heliangolide



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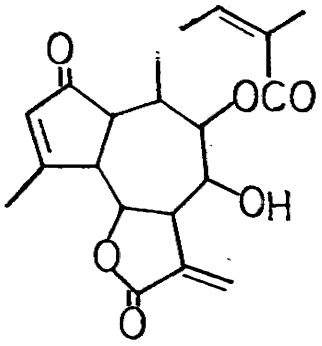
(6) R = Ac



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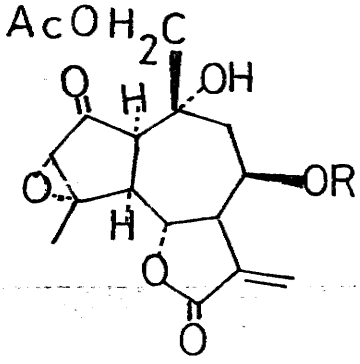

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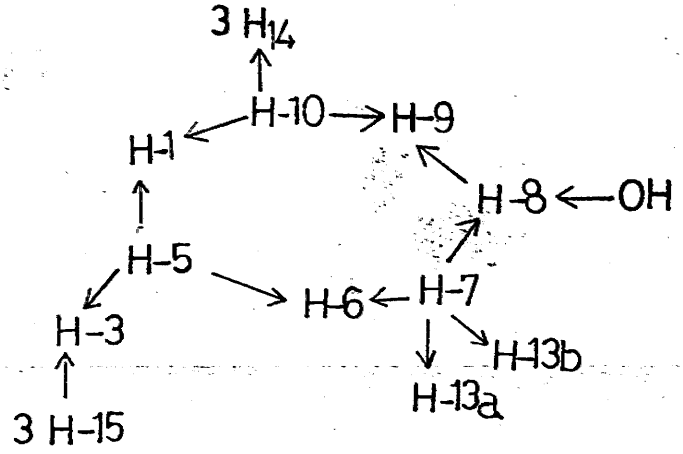

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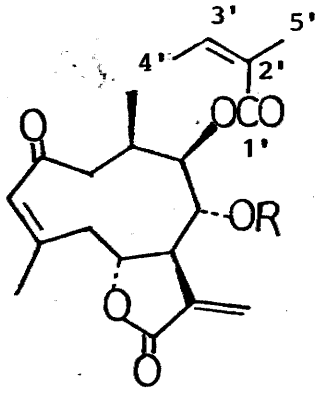

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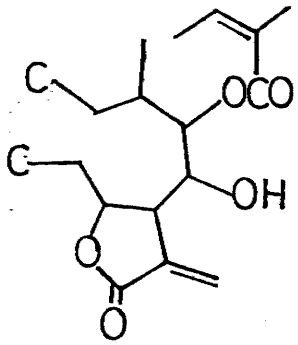

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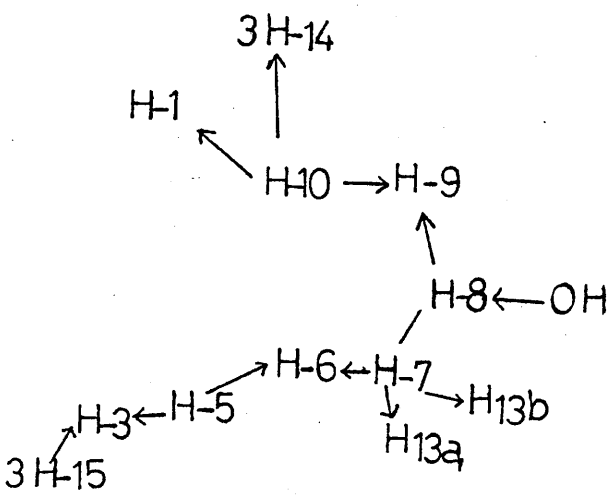

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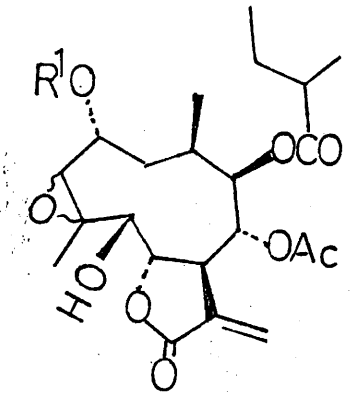
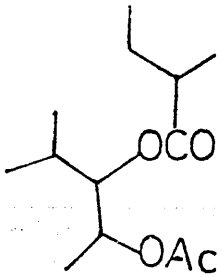


(11) R = R' = H

(15) R = Ac; R' = H

(16) R = R' = Ac



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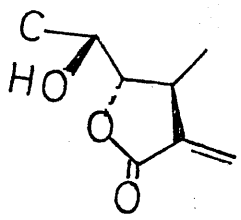
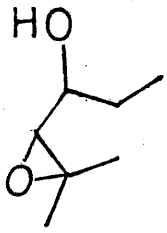
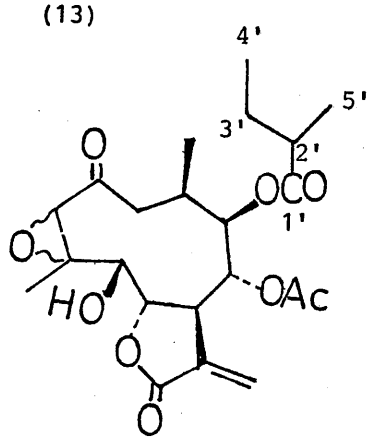


(13)



(14)



(17)

CHAPTER X

NEOLIGNANS FROM

MYRISTICA FRAGRANS

INTRODUCTION

Neolignans have been the subject of a review by Gottlieb.[1] The term "lignans" was first applied by Haworth[2,3] to plant products based on carbon skeleta having two n-propylbenzene residues linked by the β-carbon atoms of the side chains. Unlike most of the "Haworth lignans" derived by the coupling of acid and/or alcohol, the neolignans are derived by the oxidative coupling of propenyl and/or allyl derivatives.[5] There are at least fifteen skeletal types based on the coupling pattern of the monomeric precursor units.

Biogenesis. The biogenesis of most of the known neolignans can be explained by oxidative coupling of a propenylphenol derived starter with either a propenylphenol or an allylphenol derived termination unit. Other cases involve the coupling of two allylphenol derived units (Scheme 1). Couplings involving radicals (5) and (9), (7) and (9), and (6) and (9) will result in prototype compounds related to surinamensin (17), licarin (18)[12] and eusiderin (19) respectively. While the ease of oxidation of propenylphenols is to be expected in view of the higher stabilization of the derived radical, there is no evidence that all reactions represented in Scheme 1 proceed *in vivo* by radical pairing. Erdtman in his papers[7,8] postulated that the coupling step should produce a quinone methide intermediate which may add water, hydroxide, hydride or carbanions.

The ArC_3 residue is very common to lignins, lignans and neolignans and it is pertinent to assume that the monomeric precursors required for the formation of neolignans are derived from p-hydroxycinnamoylcoenzyme A (1) (see Schemes 2 and 3) via cinnamic acid (2). Biosynthetic studies

of simple neolignans are not known but there is enough evidence from structural relationship between lignans and neolignans to suggest that they are both a branch in the "shikimic acid pathway".

The function of neolignans in plants is not yet clear. This is also the case with many other secondary metabolites. However some of the plant sources of neolignans are used in native systems of medicine and have biological activity.[9,10]

This chapter is concerned with the structures of several neolignans, from an unidentified plant source, which were sent by Indian colleagues at the Captain Srinivasa Murti Research Institute for Ayurveda in Madras. After the work was completed the plant source was identified as Myristica fragrans and it was discovered that the compounds are already known. Some ^{13}C data are reported for the first time.

D I S C U S S I O N

The first compound MF1 has the molecular formula $C_{20}H_{22}O_4$. It readily formed a monoacetate and a methyl ether. Its spectroscopic properties (see Tables 1 and 2) revealed the presence of two aromatic rings, two methoxyl groups, a phenolic hydroxyl, a propenyl residue [δ_H 6.38 (1H, d, J 16 Hz), 6.19 (1H, dq, J 16, 6 Hz) and 1.85 (3H, d, J 6 Hz)] and a coupled system consisting of a secondary carbon bearing oxygen [δ 5.12 (d, J 9.6 Hz)] and a secondary methyl group [δ 3.48 (1H, dq, J 9.6, 6 Hz) and 1.36 (3H, d, J 6 Hz)]. The substitution pattern of the aromatic rings was not clear from the proton spectrum but the ^{13}C n.m.r. spectrum confirmed that there are five aromatic protons. It was obvious that the molecule consists of two phenyl propane units linked together and the structural features identified above were readily assembled to give structure (18). This is, of course, dehydrodiisoeugenol and the assignment was confirmed by comparison with an authentic sample prepared from isoeugenol. Dehydrodiisoeugenol occurs naturally as licarin A in the trunk wood of Licaria arita.[12]

The second compound MF85, $C_{20}H_{20}O_4$, has similar spectroscopic properties to (18). The major difference concerns the replacement of a methoxyl and a phenolic hydroxyl group by a methylenedioxy function [δ 5.9 (2H, s)]. Thus MF85 was assigned structure (20) and is identical to licarin B. Confirmation of this was obtained by conversion of dehydrodiisoeugenol (18) into (20) following literature procedures, by successive treatment with sodium periodate, sulphur dioxide, and diiodomethane sodium hydride. The ^{13}C chemical shifts of both (18) and (20) are identical with those reported by Wenkert and his colleagues.[4]

The mobile oil which remained after crystallisation of compounds (18) and (20) was subjected to repetitive preparative t.l.c. Three compounds designated MFG1 (26), MFG2 (27) and MFG3 (28) respectively were isolated as oils in the ratio 2:4:1.

The ^{1}H n.m.r. spectrum of MFG1 (26) $C_{24}H_{30}O_7$ is very informative (see Table 3). It shows the presence of an acetate, four methoxyl groups, five aromatic protons, two of which are equivalent, an allyl group and a coupled system consisting of a secondary acetate proton [δ 5.84 (d, J 4 Hz, H-7)] and a proton [δ 4.44 (dq, J 7, 4 Hz, H-8)] attached to a carbon bearing a secondary methyl group. These assignments were supported by double resonance experiments. The lowfield chemical shift of H-8 suggested the attachment of oxygen to the same carbon. The presence of a second secondary carbon bearing oxygen in the ^{13}C n.m.r. spectrum, in addition to the secondary acetate carbon, confirmed this. Benzene induced shifts of the methoxyl groups indicated that they each have an ortho aromatic proton (see Table 3). Thus it seemed likely that MFG1 has structure (26) consisting of two phenyl-propane units linked together via oxygen. The structure of MFG2 as (27) followed readily since, on acetylation, it yields MFG1.

Oxidation of MFG2 with Jones reagent afforded the ketone (29) which provided the first definite proof of the 1,3,4-substitution pattern of the aromatic ring A. Introduction of the ketone carbonyl in conjugation with the aromatic ring resulted in deshielding of the two ortho protons [δ 7.7 (d, J 1 Hz, H-2) and 7.85 (dd, J 8, 2 Hz, H-6)] while the meta proton remained virtually unchanged [δ 6.83 (d, J 8 Hz, H-5)]. In addition H-8 appeared as a clean quartet (J 7 Hz) at δ 5.23 coupled to the secondary methyl group at δ 1.52. Further evidence for the

structure of MFG2 as 1-(3,4-dimethoxyphenyl)-2-(4-allyl-2,6-dimethoxyphenoxy)-propan-1-ol (27) was obtained by examination of its ^{13}C chemical shifts and comparison with (17),[6] (19),[4] (26) and other related systems. Tentative assignments are presented in Table 4.

The last compound MFG3 (28), $C_{23}H_{30}O_6$, lacks hydroxyl or acetate absorption in the i.r. Its ^{1}H n.m.r. spectrum shows the presence of a secondary methyl, an allyl group, five methoxyl groups [one more than (26) and (27)] and two aromatic rings each with two equivalent aromatic protons [δ 6.38 and 6.45 (each 2H s)]. Benzene induced shifts[11] of the methoxyl groups indicated that only one of them lacks an ortho proton. This information suggested that the "new" methoxyl group is attached to C-5 in ring A. The ^{13}C chemical shifts of MFG3 (28) provided confirmation of the substitution pattern of the aromatic rings (see Table 4) and in addition revealed the residual structural features. One of the two secondary carbons bearing oxygen in MFG1 and MFG2 has been replaced by a methylene group (δ_C 43.7). The coupled system [Ar-CH_2-$CH(CH_3)$-O-Ar) is apparent in the proton spectrum. Thus MFG3 is the 7-deoxy-derivative,1-(3,4,5-trimethoxyphenyl)-2-(4-allyl-2,6-dimethoxyphenoxy)-propane (28).

Subsequent to our work on these compounds and the discovery that their plant source is Myristica fragrans, we learnt that Japanese workers had already published[13] these structures. Our conclusions are in complete agreement with the published work. In addition the ^{13}C chemical shifts are tabulated.

EXPERIMENTAL

Two crystalline compounds MF1 (18) and MF85 (20) and an oily mixture from Myristica fragrans were sent from India. MF1, $C_{20}H_{22}O_4$ had m.p. 128°C; [lit.[15] m.p. for (±)-dehydrodiisoeugenol 133-134°C (EtOH)]; m/e 326. ^1H and ^{13}C n.m.r. spectra (see Tables 1 and 2).

MF85, $C_{20}H_{20}O_4$ had m.p. 85°C (lit.[12] 91-92°C (MeOH)]; m/e 324. ^1H and ^{13}C n.m.r. data (see Tables 1 and 2).

Isolation of MFG1, MFG2 and MFG3.- The oily mixture was subjected to a careful repetitive preparative t.l.c. (35% benzene-ether). Pure samples of three compounds, MFG1 (26), MFG2 (27) and MFG3 (28) were obtained in the ratio 2:4:1. All were non-crystalline.

MFG1 (26) (1-(3,4-dimethoxyphenyl)-2-(4-allyl-2,6-dimethoxyphenoxy)-propan-1-ol acetate). $[\alpha]_D$ - 2.55° (c, 2.2, $CHCl_3$), m/e 430, 237, 195, 194, 193, and 191. (Found: M^+, 430.19903. $C_{24}H_{30}O_7$ requires M^+, 430.19903), i.r. ν_{max} (film): 1742, 1633, 1589, 1512, 1500 and 1459 cm^{-1}. ^1H and ^{13}C n.m.r. data (see Tables 3 and 4).

MFG2 (27) (1-(3,4-dimethoxyphenyl)-2-(4-allyl-2,6-dimethoxyphenoxy)-propan-1-ol). $[\alpha]_D$ + 9.13° (c, 3.1, $CHCl_3$), m/e 388, 221, 195, 193, 179, 178. (Found: M^+, 388.18826. $C_{22}H_{28}O_6$ requires M^+, 388.188575), i.r. ν_{max} (film): 3520, 1633, 1589, 1510, 1500, 1458 cm^{-1}. ^1H and ^{13}C n.m.r. data (see Tables 3 and 4).

MFG3 (28) (1-(3,4,5-trimethoxyphenyl)-2-(4-allyl-2,6-dimethoxy-phenoxy)-propane). $[\alpha]_D$ - 0.34° (c, 1.5, $CHCl_3$), m/e 402, 288, 278, 221, 193, 192, 164. (Found: M^+, 402.20406. $C_{23}H_{30}O_6$ requires M^+, 402.204224). ^1H and ^{13}C n.m.r. data (see Tables 3 and 4).

1-(3,4-dimethoxyphenyl)-2-(4-allyl-2,6-dimethoxyphenoxy)-propan-1-one (29). MFG2 (50 mg) was dissolved in acetone (20 ml). Jones reagent was added dropwise at 0°C until the solution turned green. Work up in the usual way afforded the ketone (29) (40 mg). This was obtained as an oil and purified by preparative t.l.c. (35% benzene-ether). I.r. ν_{max} (film): 1680, 1638, 1595, 1580, 1516, 1503, 1458 cm^{-1}; m/e 386, 236 (P-150), 222, 221, 194, 193, 164. (Found: M^+, 386.17259. $C_{22}H_{26}O_6$ requires M^+ 386.172926).

^1H n.m.r. data (see Table 3).

Acetylation of MFG2 (27). Acetylation of MFG2 (50 mg) with acetic anhydride-pyridine mixture in the usual manner and preparative t.l.c. of the product (35% benzene-ether) yielded the acetate (26) (45 mg) as an oil, identical in all respects (t.l.c.; ^1H and ^{13}C n.m.r.) with MFG1 (26).

(±)-Dehydrodiisoeugenol (licarin A) (18).- Commercial isoeugenol (7 ml) was added to a solution of ferric chloride (14 g) in distilled water. The reaction mixture was left in the refrigerator overnight. Dehydrodiisoeugenol (2.6 g) crystallised out. This was purified by recrystallization from 95% alcohol and had m.p. of 131-132°C. This was completely identical with MF1 (^1H and ^{13}C n.m.r. spectra).

Dehydrodiisoeugenol methyl ether (21).- Dehydrodiisoeugenol (190 mg) in dry DMSO (25 ml) was treated with sodium hydride (14 mg) followed by methyl iodide (82 mg ≡ 0.04 ml). Usual work up and purification by preparative t.l.c. (25% chloroform-light petroleum) yielded the methyl ether (21) (150 mg) m.p. 107-108°C (ex methanol) (lit.[14] 91.5-92°C); m/e 340. ^1H and ^{13}C n.m.r. data (see Tables 1 and 2).

Dehydrodiisoeugenol acetate (22).- To dehydrodiisoeugenol (212 mg) in pyridine solution (5 ml) was added acetic anhydride (10 ml). The reaction mixture was allowed to stand at room temperature overnight. Evaporation of the solvent and preparative t.l.c., using 22% chloroform-light petroleum as eluant, afforded the acetate (22) (200 mg). M.p. 110-111°C (ex EtOH) (lit.[14] 124-125°C), m/e 368.

^{1}H and ^{13}C n.m.r. data (see Tables 1 and 2).

Dihydrodehydrodiisoeugenol methyl ether (23).- The methyl ether (32 mg) in ethyl acetate (12 ml) was stirred in the presence of 10% palladinised charcoal in a hydrogen atmosphere for 30 minutes. Filtration and evaporation of solvent afforded the dihydro-derivative (23), $C_{21}H_{26}O_4$, (24 mg), m.p. 96-97°C (ex methanol), m/e 342.

^{1}H and ^{13}C n.m.r. data (see Tables 1 and 2).

A second product, separated from the mother liquors by t.l.c., was the tetrahydro derivative (30), $C_{21}H_{28}O_4$, obtained as an oil, m/e 344. [δ_H 6.7 ~ 6.56 (5H, m, Ar protons), 5.56 (1H, s, phenolic OH), 3.86 (9H, s, ArOMe), 3.46 (1H, m, H-3), 2.90 (2H, ABX J 15, 6 Hz, 2H-2), 2.48 (2H, t, J 7 Hz, 2H-α), 1.62 (2H, m, 2H-β), 1.16 (3H, d, J 7 Hz, C-3 Me), 0.88 (3H, t, J 7 Hz, γ-Me)].

Acetate of tetrahydrodehydrodiisoeugenol methyl ether (24).- Tetrahydrodehydrodiisoeugenol (30) (127 mg) was acetylated under the usual conditions and allowed to stand overnight. The crude product was purified by preparative t.l.c. (23% chloroform-light petroleum) and gave the acetate (24), $C_{23}H_{30}O_5$, (120 mg) as an oil, m/e 386.

^{1}H and ^{13}C n.m.r. data (see Tables 1 and 2).

Dihydrodehydrodiisoeugenol acetate (31).- Hydrogenation of the acetate (22) (30 mg) over Pd/C (3 mg) for 10 minutes afforded the dihydroderivative (31), $C_{22}H_{26}O_5$, (28 mg) as an oil, m/e 370;

[δ_H 7.06, 6.96 and 4.58 (5H, Ar protons), 5.13 (1H, d, J 9.6 Hz, H-2), 3.88 and 3.80 (each 3H, s, Ar-OMe), 3.48 (1H, dq, J 9.6, 6 Hz, H-3), 2.53 (2H, t, J 7 Hz, 2H-α), 2.28 (3H, s, acetate), 1.63 (2H, dq, J 18, 7 Hz, 2H-β), 0.92 (3H, t, J 7 Hz, γ-Me), 1.36 (3H, d, J 6 Hz, C-3 Me)].

Tetrahydro-MF85 (25).- Tetrahydro-MF85 (25) was obtained by hydrogenation of MF85 as above. The product, $C_{20}H_{24}O_4$, was an oil, m/e 328, i.r. ν_{max} (CCl_4) 3375 cm^{-1}, u.v. λ_{max} (MeOH) 288 nm, shifted to 293 nm on addition of NaOH solution. [δ_H 6.65 ~ 6.55 (5H, Ar protons), 5.88 (2H, s, methylene dioxy function), 5.56 (1H, s, Ar-OH), 3.85 (3H, s, Ar-OMe), 3.36 (1H, dq, J 9.6, 6 Hz, H-3), 2.80 (2H, ABX, J 15, 6 Hz, 2H-2), 2.48 (2H, t, J 7 Hz, 2H-α), 1.62 (2H, m, 2H-β), 1.15 (3H, d, J 7 Hz, C-3 Me), 0.88 (3H, t, J 7 Hz, γ-Me)].

MF-85 (20) (Licarin B).- To dehydrodiisoeugenol (521 mg) in glacial acetic acid (42 ml) was added a solution of sodium metaperiodate (339 mg) in water (11 ml) and the solution left for 2 hours. Excess SO_2 was then passed through; the resulting catechol (302 mg) was dissolved in dry DMSO (30 ml), and sodium hydride (46 mg) and diidomethane (0.08 ml) added in turn. The crude product was crystallised from methanol to give MF-85 (20) (168 mg) m.p. 85°C.

Table 1

Proton n.m.r. chemical shifts and coupling constants of MF1 (licarin A) and MF85 (licarin B) and related compounds.

	Licarin A (lit.[12])	Licarin B (lit.[12])	18	20	21	22	23	24
Me-3	1.43 d (6.7Hz)	1.35 d (7Hz)	1.36 d (7Hz)	1.35 d (7Hz)	1.33 d (7Hz)	1.34 d (7Hz)	1.37 d (7Hz)	1.15 d (7Hz)
H-2	5.14 d (9.2Hz)	5.04 d (8.9Hz)	5.12 d (9.6Hz)	5.08 d (9Hz)	5.07 d (9Hz)	5.06 d (9Hz)	5.10 d (9Hz)	2.75 ABX (15,6Hz)
H-3	3.48 dq (9.2, 6.7Hz)	3.39 m	3.48 dq (9.6, 7Hz)	3.38 m	3.33 dq (9.6, 6Hz)	3.35 m	3.47 m	3.10 m
α-CH	6.4 d (15.5Hz)	6.34 dq (16, ~1Hz)	6.38 d (16Hz)	6.35 d (16Hz)	6.37 d (16Hz)	6.35 d (16Hz)	2.55 t (7Hz)	2.50 t (7Hz)
β-CH	6.11 dq (15.5, 5.2Hz)	6.09 dq (16, 6.5Hz)	6.19 dq (16,6Hz)	6.13 dq (16,6Hz)	6.13 dq (16,6Hz)	6.12 dq (16,6Hz)	1.65 m	1.60 m
γ-CH_3	1.92 d (5.2Hz)	1.84 d (6.5, ~1Hz)	1.85 d (6Hz)	1.83 d (6Hz)	1.80 d (6Hz)	1.82 d (6Hz)	0.93 t (7Hz)	0.90 t (7Hz)
Ar-H	7.0-6.75 m 5H	6.92-6.75 m 5H	6.98-6.78 m 5H	6.90-6.75 m 5H	6.96-6.73 m 5H	6.90-6.61 m 5H	6.98-6.58 m 5H	6.75-6.55 m 5H
Ar-OMe	3.95, 3.90 s 3H each	3.85 s 3H	3.88, 3.85 s 3H each	3.86 s 3H	3.80 s 9H	3.95, 3.90 3H each	3.87 9H	3.80 3.76 (6H)
Others	5.69 s OH	5.90 s O_2CH_2	5.67 s OH	5.90 s O_2CH_2	-	2.30 Acetate	-	2.25 Acetate

Table 2

^{13}C n.m.r. chemical shifts of MF1 (licarin A) and MF85 (licarin B) and related compounds.

Carbons	Licarin A (lit.[4])	Licarin B (lit.[4])	18	20	21	22	23	24
2	93.3	93.0	93.8	93.4	93.6	93.0	93.5	35.1
3	45.2	45.5	45.6	45.8	45.6	45.8	45.8	43.0
3a	132.8	132.7	133.3	133.2	133.3	133.0	132.9	140.9
4	112.9	113.0	113.4	113.4	113.4	113.4	115.4	121.0
5	131.7[a]	131.8	132.2	132.2	132.2	132.4	136.3	135.5
6	109.0	109.2	109.3	109.5	109.4	109.5	110.8	111.0
7	143.6	143.7	144.2	144.2	144.2	144.2	143.9	150.7
7a	146.3	146.2	146.6	146.6	146.6	146.5	145.4	139.3
3-Me	17.2	17.6	17.6	17.9	17.6	17.9	17.4	19.9
OMe	55.5	55.7	55.9	56.0	55.9	55.9	55.9	55.7
	-	-	55.9	-	55.9	55.9	55.9	55.9
	-	-	-	-	55.9	-	55.9	55.9
1'	131.6[a]	134.0	132.1	134.4	132.7	132.7	132.9	133.3
2'	108.6	106.3	109.0	106.8	109.6	110.3	109.6	110.0
3'	146.1	147.5	146.7	148.0	149.2	151.3	149.1	148.6
4'	145.3	147.2	145.8	147.7	149.2	139.7	149.1	147.3
5'	113.8	107.7	114.1	108.1	112.0	122.7	111.8	112.5
6'	119.3	119.7	119.9	120.2	119.2	118.6	119.3	118.8
α	130.5	130.6	131.0	131.0	131.0	131.0	38.1	38.3
β	122.8	122.9	123.4	123.4	123.4	123.5	25.1	24.6
γ	18.0	18.1	18.4	18.3	18.4	18.3	13.9	13.9
$CH_3\underline{C}O$	-	-	-	-	-	168.9	-	169.1
$\underline{C}H_3CO$	-	-	-	-	-	20.6	-	20.5
$O\underline{C}H_2O$	-	100.7	-	101.1	-	-	-	-

(a) these values may be interchanged

Table 3

^{1}H n.m.r. chemical shifts and coupling constants of several β-aryl ether-type phenylpropanoids

	26	27	28	29
Me-8	1.25 d (7 Hz)	1.10 d (7 Hz)	1.20 d (7 Hz)	1.52 d (7 Hz)
exomethylene 2H-9'	complex m ca. 5.05	complex m ca. 5.10	complex m ca. 5.02	complex m ca. 5.08
H-7	5.84 d (4 Hz)	4.82 brs	2.90 dd (13, 6 Hz) 2.59 dd (13, 7.5 Hz)	
H-8	4.44 dq (7, 4 Hz)	4.35 dq (7, 4 Hz)	4.40 m	5.20 q (7 Hz)
2H-7'	3.30 d (7 Hz)	3.36 d (7 Hz)	3.32 d (7 Hz)	3.30 d (7 Hz)
H-8'	5.95 m	5.90 m	5.92 m	6.0 m
Ar-OMe	3.82 3.84 3.75 (x 2) 3.44 3.42 in benzene	3.85 3.88 (x 3)	3.78 (x 2) 3.82 (x 3) 3.42 (x 4) 3.82 in benzene	3.70 (x 2) 3.92 3.90
Ar-2,5,6	complex m ca. 6.85	complex m ca. 6.88	6.45 brs	6.83 d (J 8 Hz) 7.85 dd (J 8, 2 Hz) 7.7 d (1 Hz)
Ar-3',5'	6.38 (brs)	6.45 (brs)	6.38 (brs)	6.35 (brs)
Others	OAc 2.12	OH 3.08 br	-	-

Table 4

^{13}C n.m.r. chemical shifts of MFG 1-3 and related compounds.

Carbons	17 (lit.[6])	19 (lit.[4])	26	27	28
1	137.6	131.9	130.6	132.8	134.9
2	104.2	104.1	110.3	109.4	106.7
3	152.9	153.0	148.8	148.8	152.9
4	135.5	138.0	148.6	148.0	136.4
5	152.9	153.0	110.9	111.0	152.9
6	104.2	104.1	119.3	118.2	106.7
7	83.6	80.6	76.7	72.8	43.7
8	78.5	73.7	80.0	82.3	79.8
9	17.0	17.0	14.5	12.9	19.8
1'	133.3	132.1	133.8	133.1	134.5
2'	109.1	104.3	105.5	105.6	105.5
3'	150.5	148.1	153.4	153.4	153.7
4'	146.4	130.9	135.7	136.1	135.5
5'	118.6	143.8	153.4	153.4	153.7
6'	118.7	104.3	105.5	105.6	105.5
7'	130.2	39.7	40.5	40.5	40.5
8'	124.6	136.9	137.2	137.3	137.3
9'	18.2	115.3	115.9	116.1	116.0
OMe	60.6	60.4	55.9(x 4)	56.1(x 4)	60.8
	56.0(x 2)	55.8(x 2)	-	-	56.08(x 4)
	55.6	55.7	-	-	-
CH_3CO	-	-	170.0	-	-
CH_3CO	-	-	21.2	-	-

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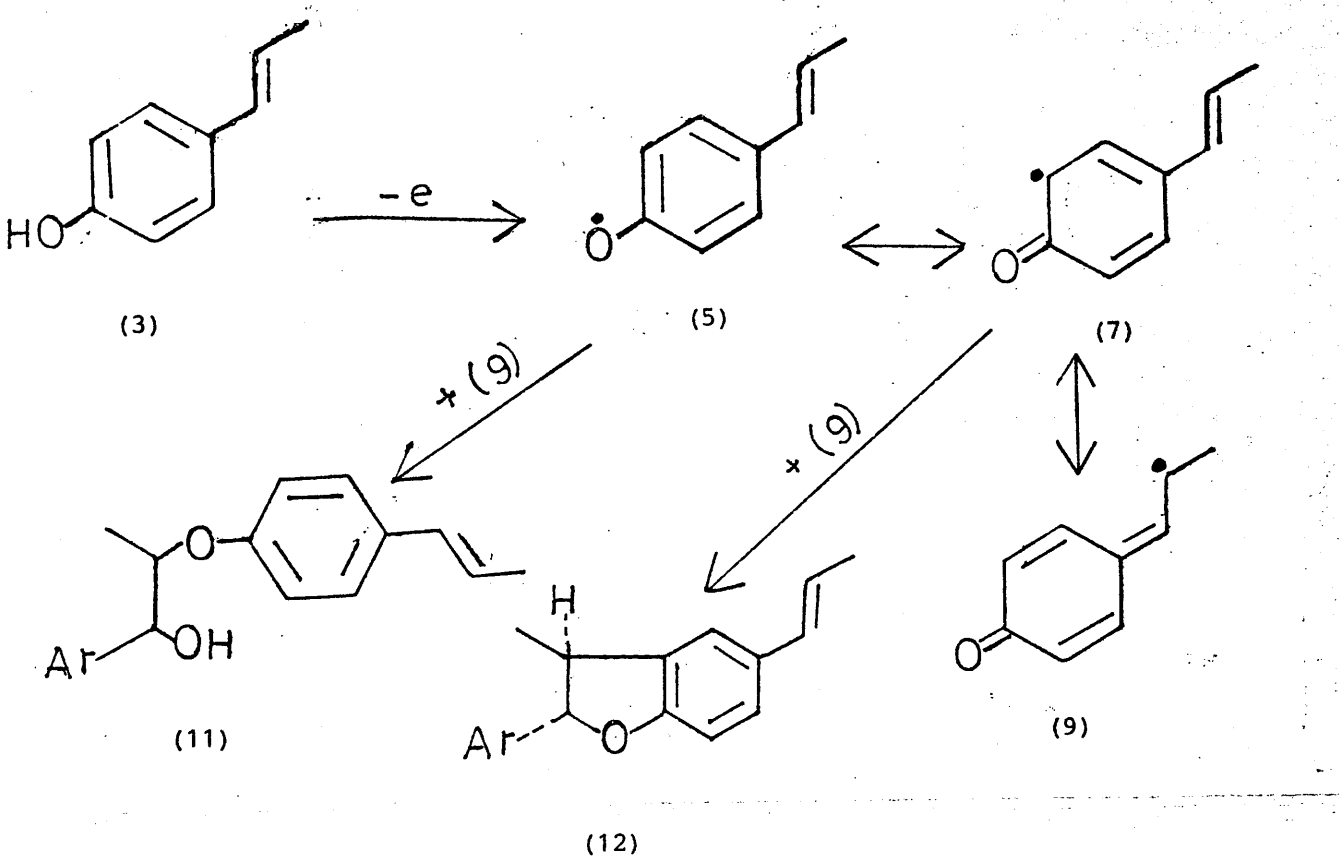
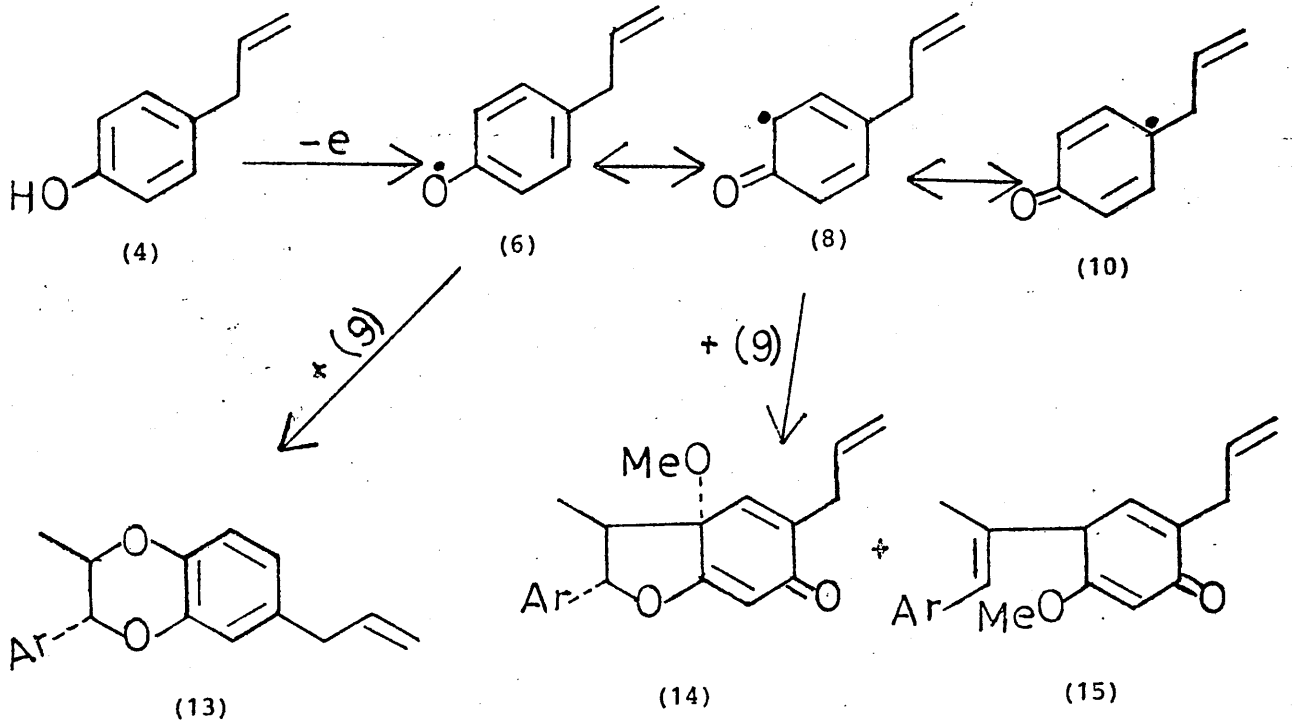
Scheme 1





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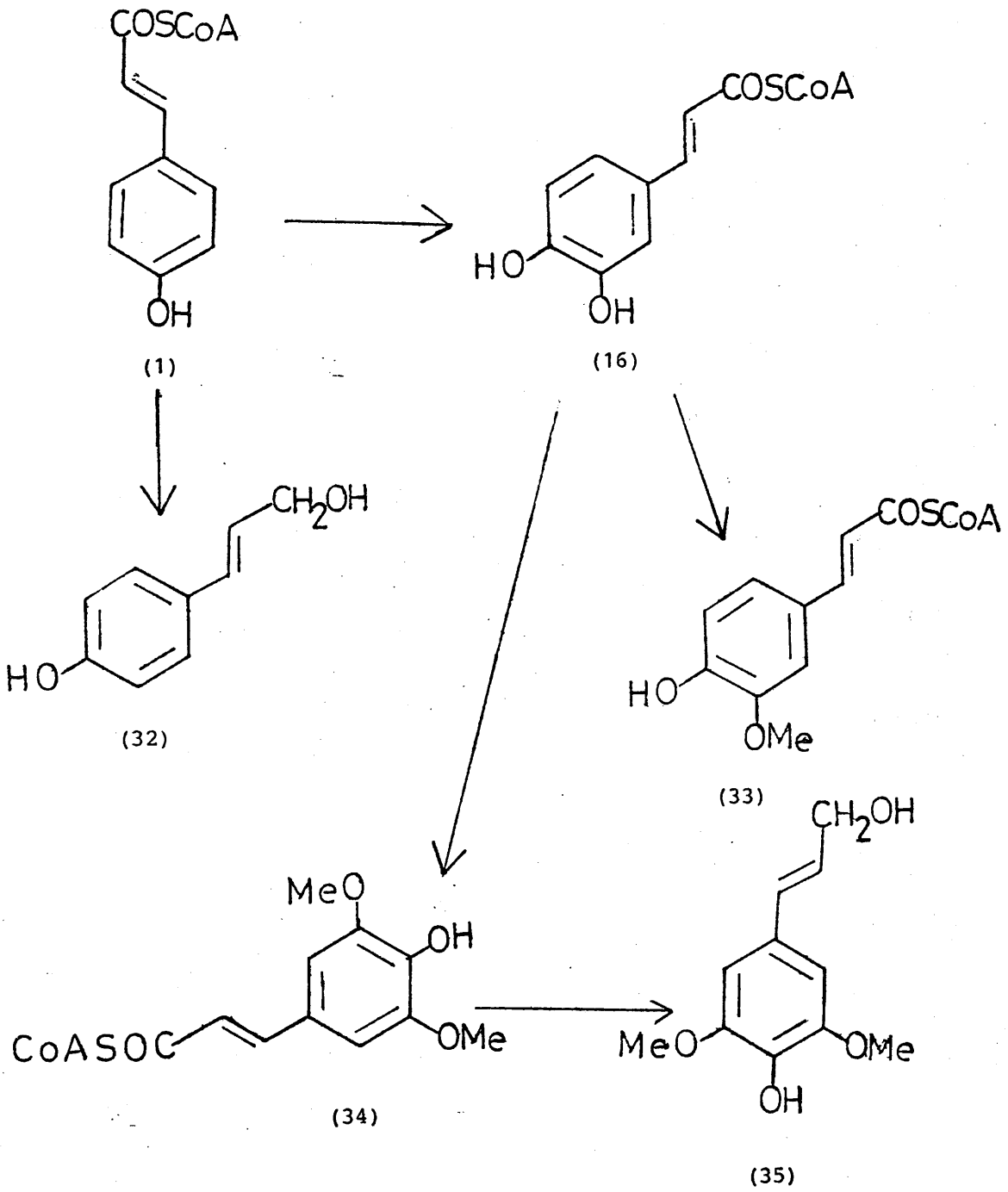
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COSCoA
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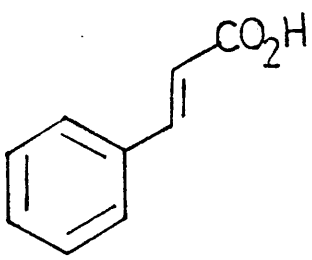
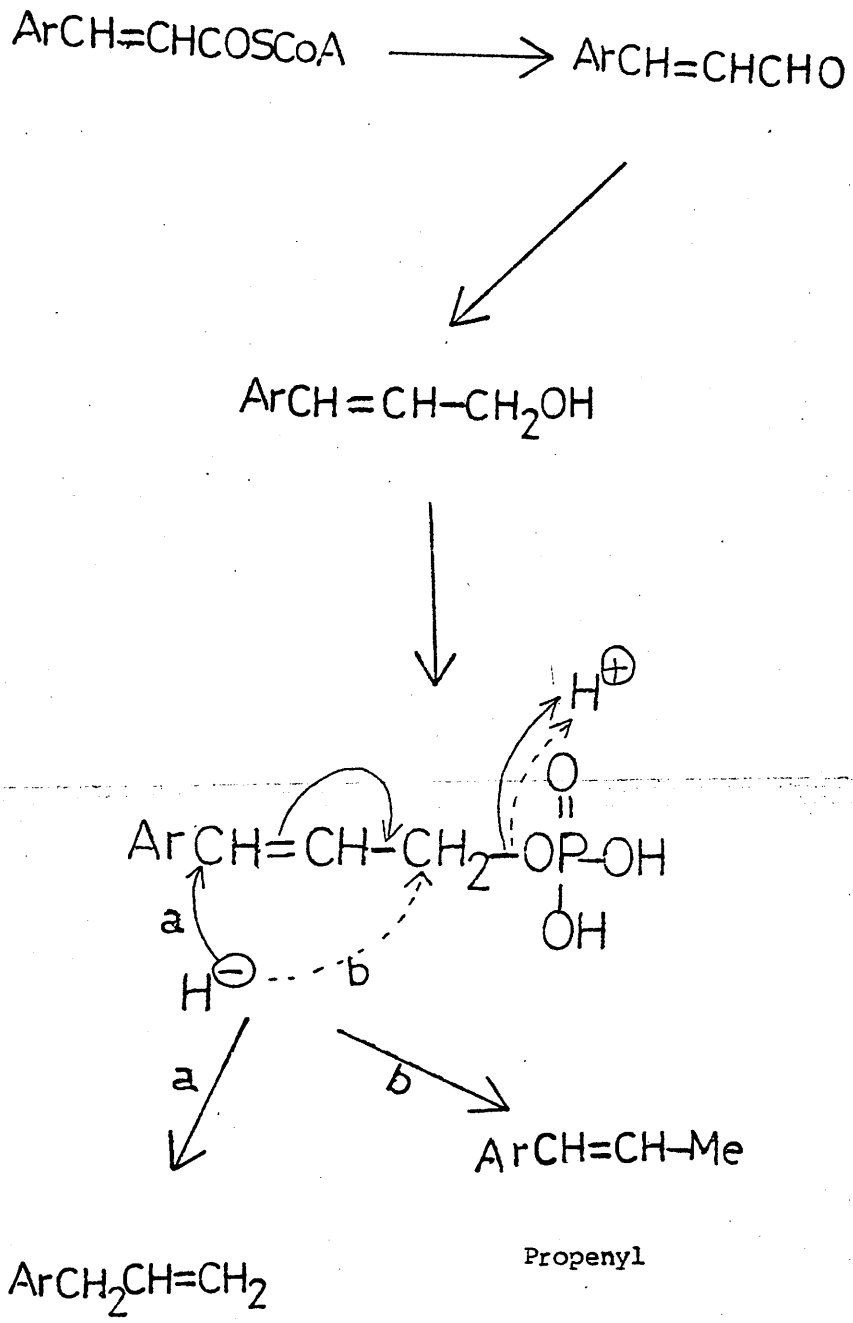

CO2H
(2)

Scheme 3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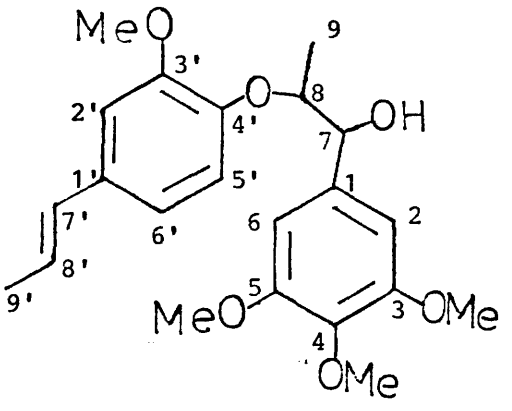
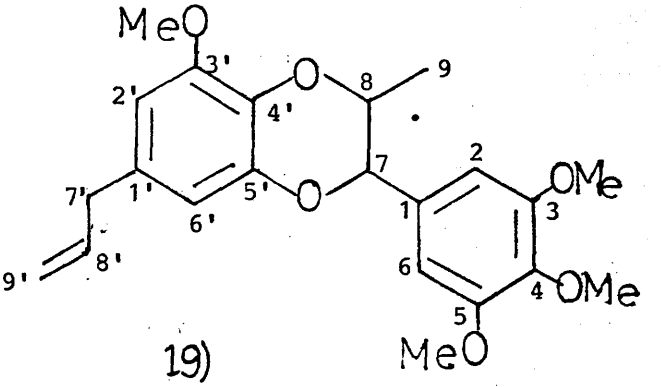
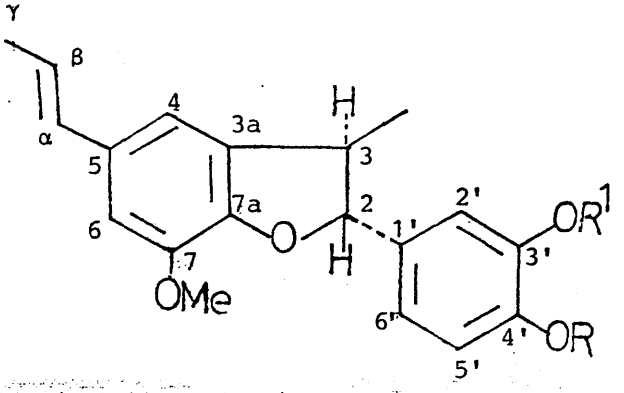


17)



19)



(18) R^1 = Me, R = H

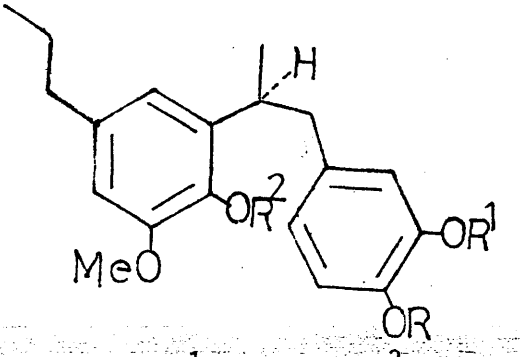
(20) R^1-R = CH_2

(21) R^1 = R = Me

(22) R^1 = Me; R = Ac

(23) dihydro (21)

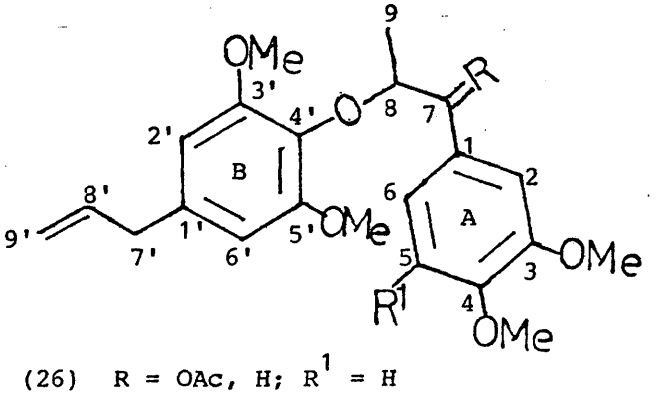
(31) dihydro (22)



(24) R^1 = R = Me, R^2 = Ac

(25) R^1-R = CH_2, R^2 = H

(30) R^1 = R = Me, R^2 = H



(26) R = OAc, H; R^1 = H

(27) R = OH, H; R^1 = H

(28) R = H,H; R^1 = OMe

(29) R = O; R^1 = H