A THESIS

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by

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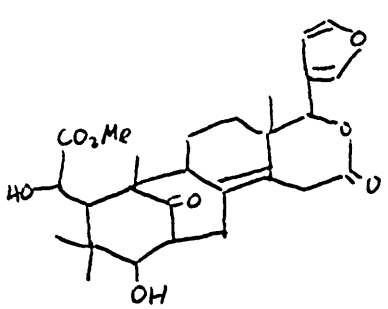
STUDIES IN NATURAL PRODUCT CHEMISTRY

by William D.C.Warnock.

SUMMARY

This thesis is concerned with the structural elucidation of three tetranortriterpenoids and interconversion studies in this field. It is prefaced by a review of the tetranortriterpenoids. The configuration and stereochemistry of two monoterpene alkaloids are also derived.

Part I. The constitution and stereochemistry of swietenolide (A), a bitter principle from the seeds of Swietenia macrophylla, a Central American timber of the family Meliaceae, are deduced from its chemical and spectroscopic behaviour and confirmed by degradative correlation with mexicanolide. The structures of two other tetranortriterpenoids from the heartwood of Khaya grandifoliola, a West African member of the same family, are shown to be 6-hydroxy methyl angolensate (B) and 6-acetoxy methyl angolensate (C) by analysis of their single and double resonance N.M.R. spectra.



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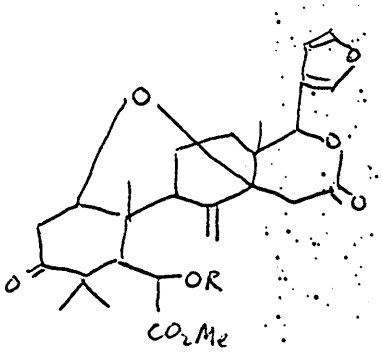
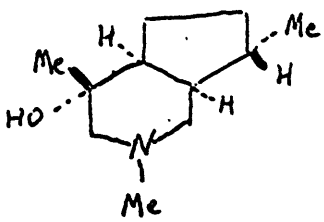


(B) R = H

(C) R = Ac

Part II. Experiments designed to support present theories on the biogenesis of tetranortriterpenoids possessing the bicyclononanolide ring system, as typified by swietenolide, are described. Attempts were made to achieve *in vitro* conversion of two naturally occurring tetranortriterpenoids into mexicanolide by formation of the C-2/C-30 bond, a key step in the proposed biogenesis.

Part III. The constitution and stereochemistry of hydroxyskytanthines I (D) and II (E), two minor alkaloids of *Skytanthus acutus*, a plant native to the Chilean Atacama desert, are established on the basis of single and double resonance N.M.R. and infrared spectroscopy and mass spectrometry. The chemistry and biosynthesis of *Skytanthus* alkaloids is also reviewed.



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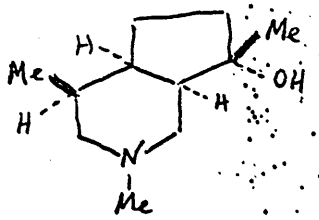

(E)

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THE MODIFIED TRITERPENES

The first two sections of this thesis describe the elucidation of the constitution and stereochemistry of swietenolide[1] (A1) 6-hydroxy methyl angolensate[2] (A2) and 6-acetoxy methyl angolensate (A3) and experiments designed to support present theories on the biogenetic origin of the bicyclononanolides. It seems appropriate to preface this with a review of the known modified triterpenes.

From a biogenetic viewpoint the modified triterpenes can be derived from a precursor possessing the carbon skeleton and stereochemistry of euphol (A4). Loss of four carbon atoms by cleavage of the C-23 — C-24 bond and oxidative cyclisation of the remainder of the side chain leads to the furan ring. The structures of flindissol[3] (A5), turraeanthin[4] (A6) and aphanamixin[5] (A7) which exhibit a potential furan ring and a carbon skeleton identical with that of euphol support this proposal. In grandifolione[6] (A8) formation of the furan is complete and the carbon skeleton and stereochemistry is that of apo-euphol (A9) where C-16 has undergone allylic oxidation and the olefinic linkage between C-14 and C-15 has been epoxidised. The migration of the methyl group from C-14 to C-8 with loss of a proton from C-15 finds precedent in

the oxidation of dihydrobutyrospermyl acetate (A10) to the 7-ketone[7]. Baeyer-Villiger cleavage of ring D can then lead to the commonly occurring epoxy δ-lactone as in khivorin[8] (A11) and gedunin[9] (A12).

Further oxidative cleavage of ring A between C-3 and C-4 and lactonisation of the carboxyl function at C-3 to the oxidised methyl C-19 with concomitant cyclisation of the hydroxyl group at C-4 to the olefinic linkage at C-1 provides a rational biogenetic route to limonin[10,11,12] (A13), the first modified triterpene to have its structure determined. Precedents for the C-3 —— C-4 cleavage are to be found in the triterpenes dammarenolic acid[13] (A14), nyctanthic acid[14] (A15) and canaric acid[15] (A16). The structure of obacunone[12] (A17), which has been related[16] to limonin, is derived similarly by ring A cleavage with formation of a seven-membered lactone.

A novel reaction of limonin which has been important as a diagnostic test in modified triterpene chemistry is the base-catalysed conversion of limonol (A18) to merolimonol (A19). Limonol is produced by Meerwein-Pondorff reduction of limonin and has accordingly an axial hydroxyl group, and when treated with base rearranges with loss of fur-

furaldehyde to merolimonol. This reaction, peculiar to the axial hydroxyl[10,12,17], has been rationalised by postulating opening of the epoxide ring to give the trimethylene oxide (A20), This then undergoes base-catalysed loss of furfuraldehyde to form the hydroxy acid (A21) which lactonises on acidification. The reaction, characteristic of a C-7 axial oxygen substituent together with an epoxy δ-lactone ring D, was used in the structural elucidation of khivorin[8] (A11) and gedunin[9] (A12).

Quassin[18,19] (A22), a bitter principle isolated in 1960, was initially assumed to be diterpenoid and biogenetically derived either from the pimarane (A23) skeleton by a series of methyl migrations and shift of a C_2 fragment or from two C_{10} units as in (A24) by oxidative coupling. It was later proposed[20,21] that quassin and the related Simaroubaceae bitter principles have a tetranortriterpenoid origin. Loss of a C_5 fragment as in the limonol-merolimonol conversion followed by oxidation and decarboxylation of one of the C-4 methyl groups and lactonisation of the C-16 carboxyl to the oxygen at C-7 provides a feasible biogenesis of the quassin skeleton. This is supported by the structural and stereochemical similarity of the mero-

limonol compounds to the Simaroubaceae terpenoids. Recent biosynthetic experiments[22] where mevalonic acid lactone-2-^{14}C has been fed to Simarouba glauca shoots have produced labelled glaucarubolone (A25) which on degradation shows incorporation of radioactivity at C-1 but not at C-4, C-10, C-12, C-13 or C-16, which accords with a biogenetic scheme via euphol.

The first example of a modified triterpene in which ring B has been cleaved is swietenine[23] (A26), which can be derived biogenetically from a precursor of the type (A27) by cleavage of the C-7 —— C-8 bond followed by Michael addition of C-2 to C-30. Cleavage between C-7 and C-8 without subsequent Michael condensation can account for the biogenesis of andirobin[24] (A28) and methyl angolensate[25,26] (A29). Further discussion of the biogenesis of ring B cleaved triterpenoids appears later (see pp. 81, 82) for swietenolide (A1) and 6-hydroxy methyl angolensate (A2).

Examples of compounds formed by cleavage of ring C of a triterpene precursor are nimbin[27] (A30) and salannin[28] (A31). These compounds can arise from a precursor of the type (A32) by cleavage of the C-12 — C-13 bond followed by attachment of the C-7 hydroxyl to C-15 and migration of the

olefinic linkage to C-13 — C-14. An additional point of interest is that they are the only modified triterpenes to date showing oxidation of one of the C-4 geminal dimethyl groups.

Allowing for different oxygenation patterns, the structural types mentioned above, derived variously by cleavages of rings A, B, C and D, comprise all the modified triterpenes reported to date with the exceptions of odoratin[29] (A33) and fraxinellone[30] (A34). The carbon skeleton of the former could arise from a precursor of the destiglcylswietenine (A35) type as shown in Figure 1 by retroaldolisation made irreversible by lactone formation, followed by a 1,5-dicarbonyl cleavage. Fraxinellone may be a substantially modified member of the series, in which rings C and D and the furan moiety remain.

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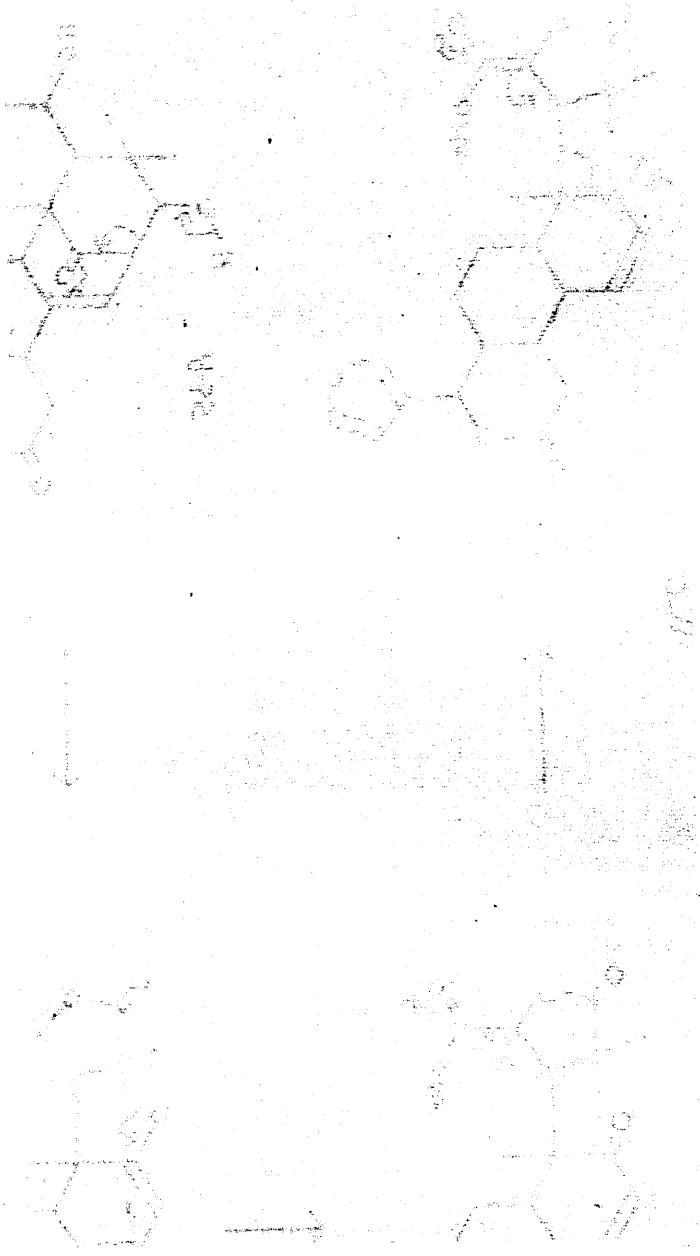


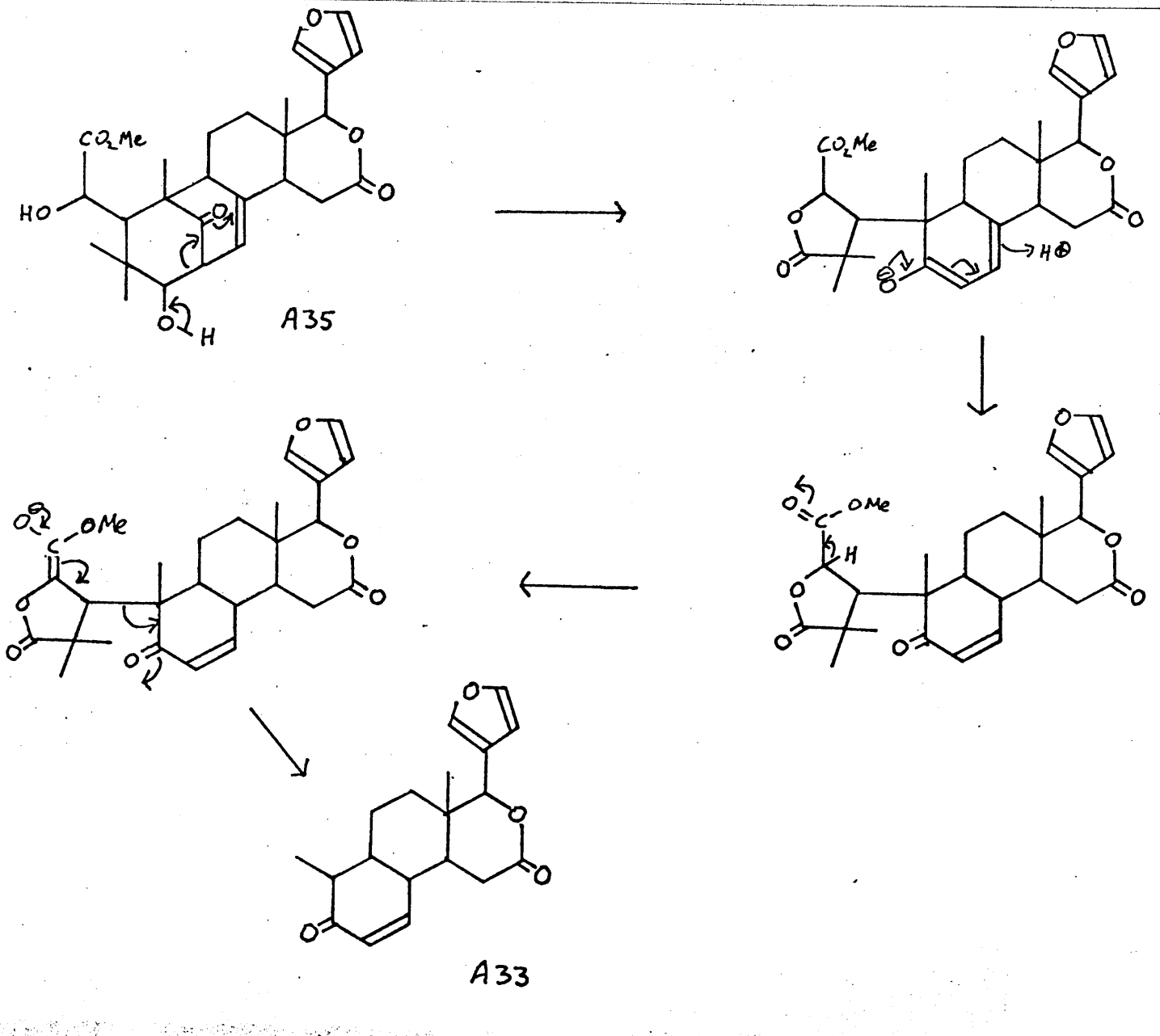
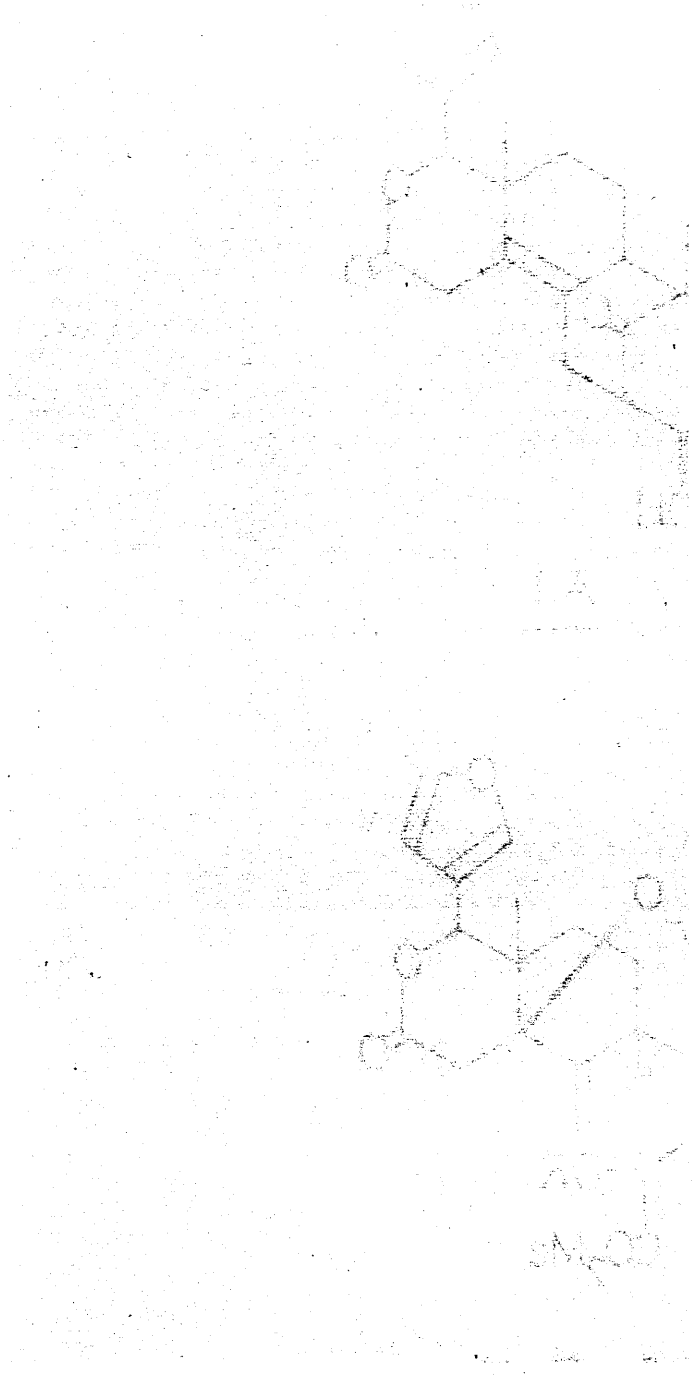
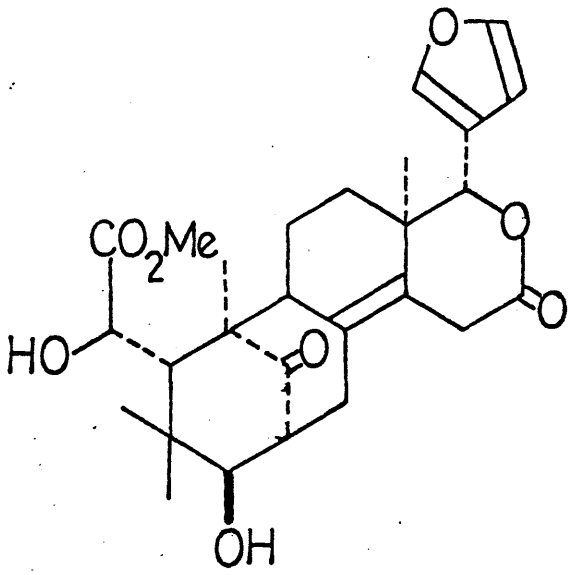


Fig. 1





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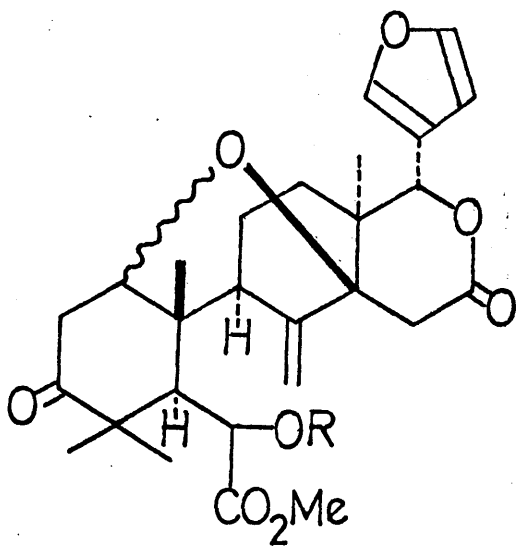
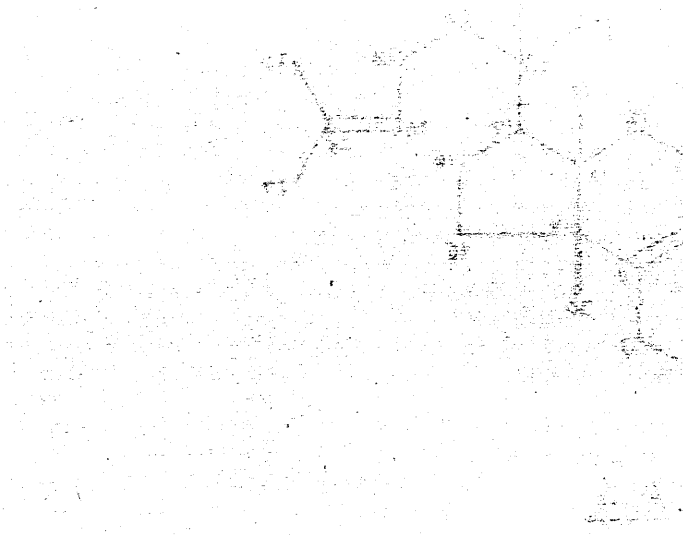
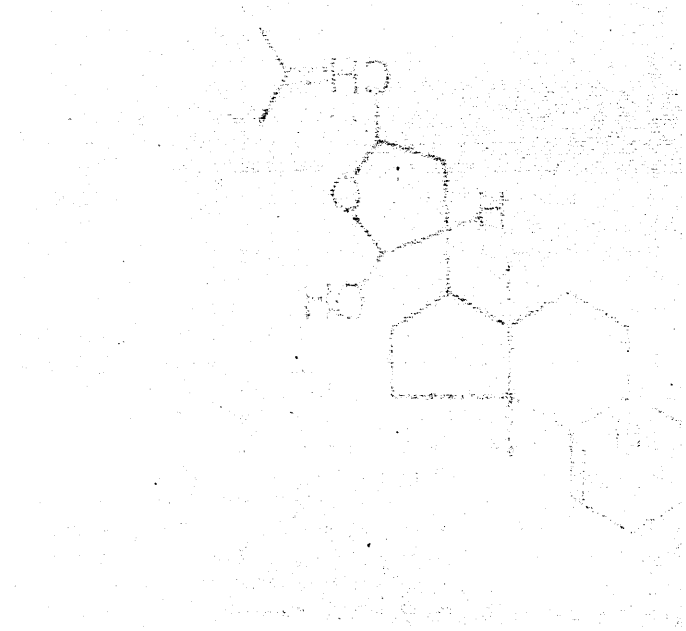
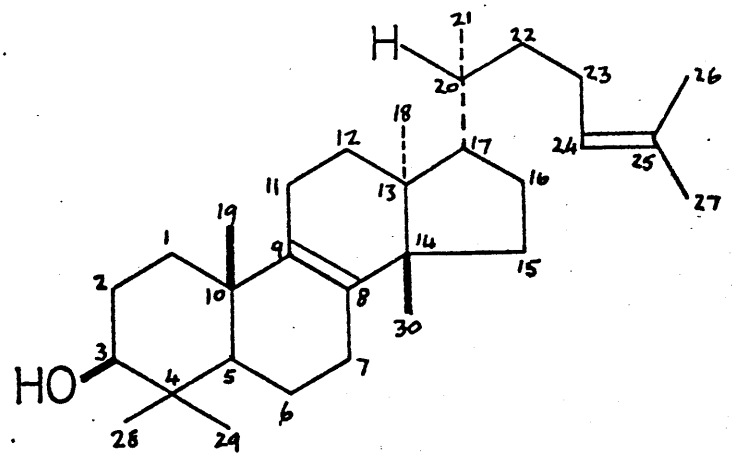


A 2 R=H

A 3 R=Ac



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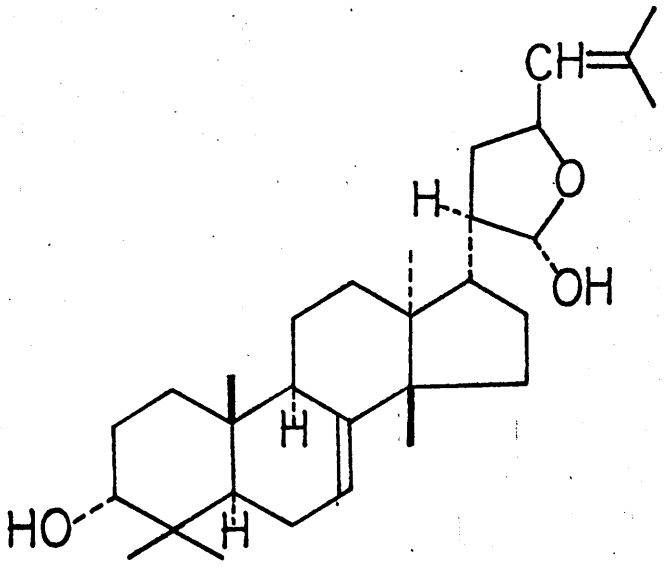
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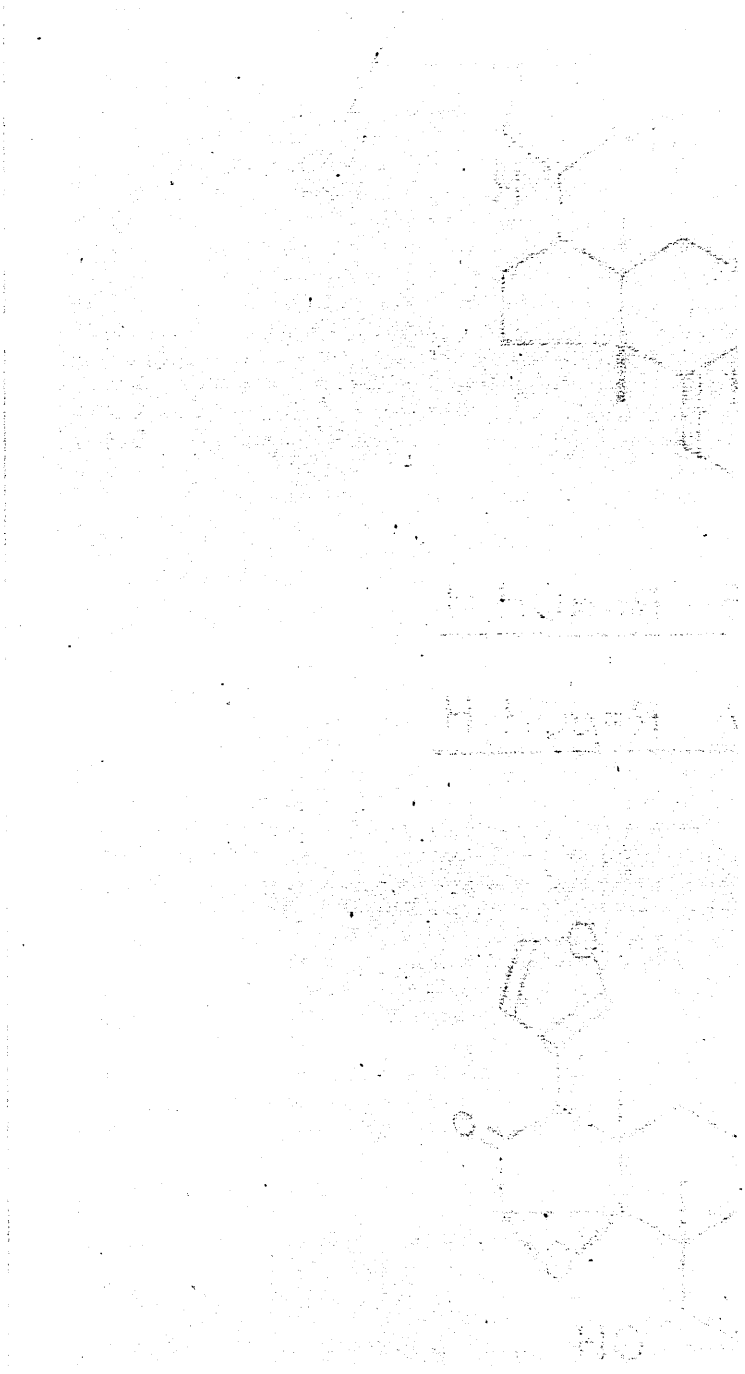
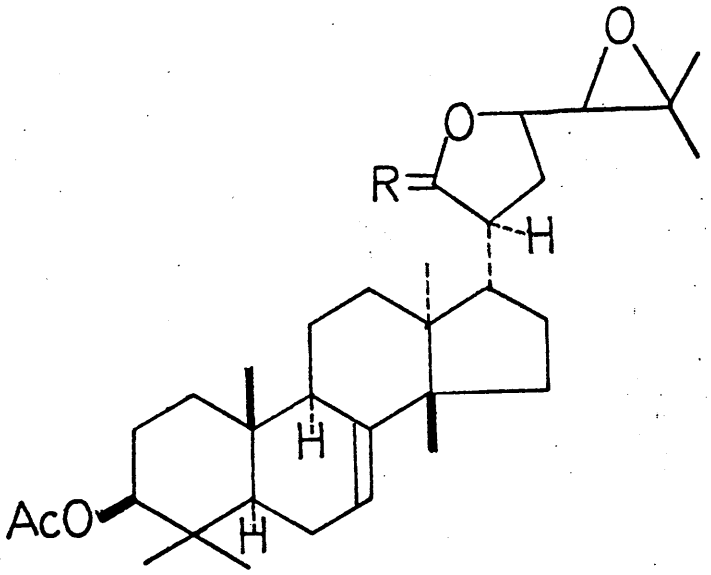
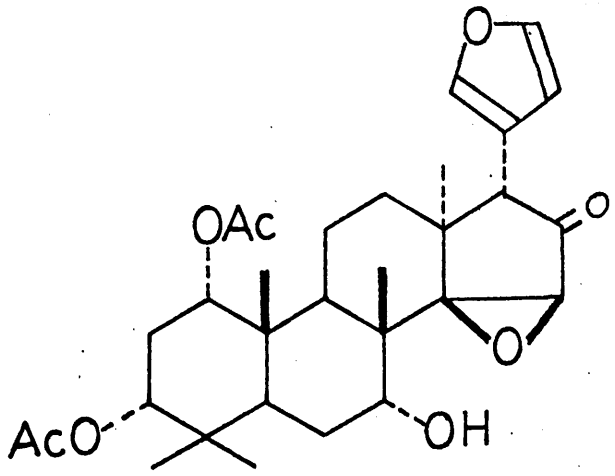




A6 R=αOH,H

A7 R=βOH,H



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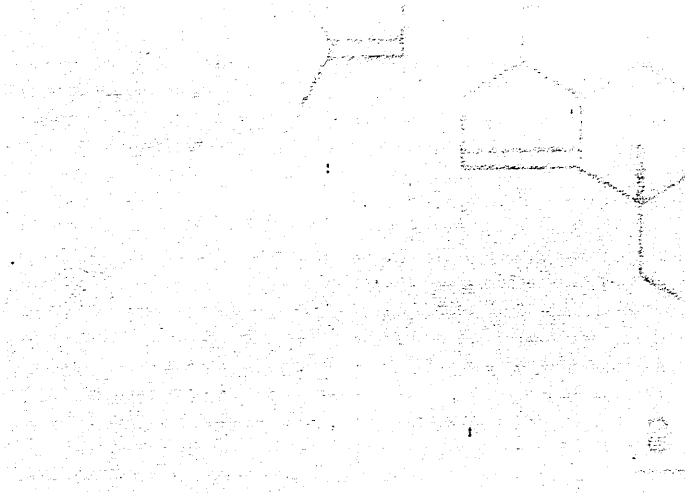

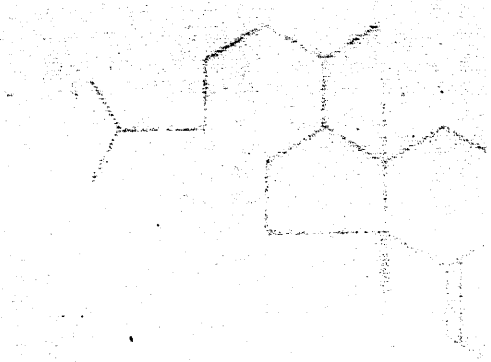

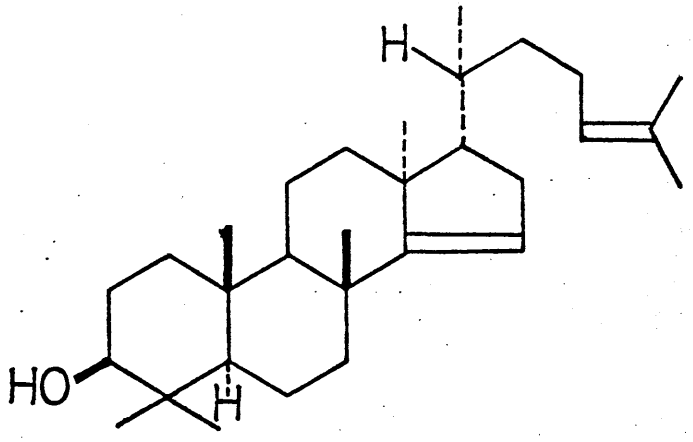

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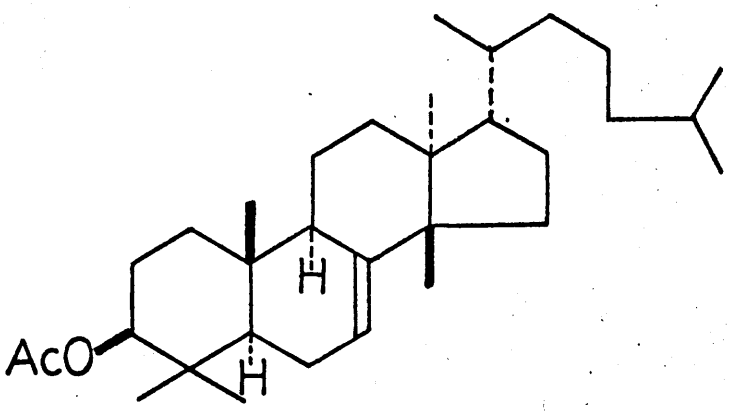

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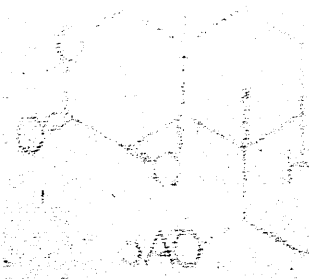

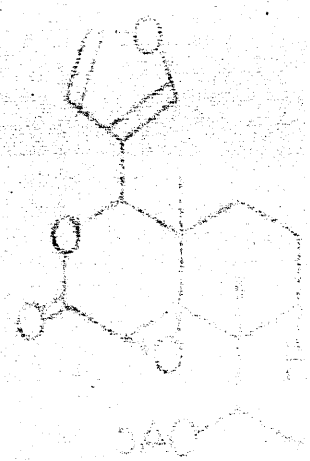

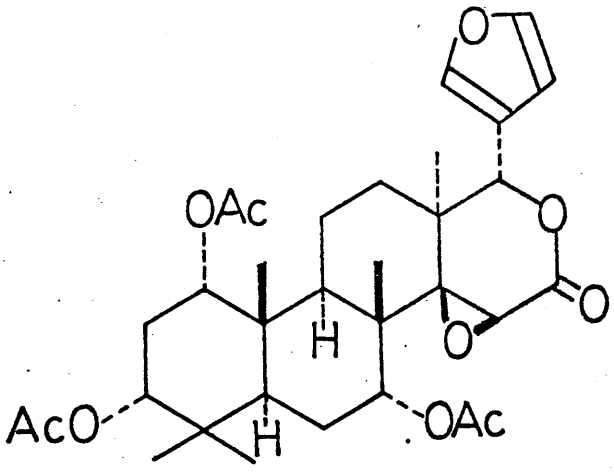

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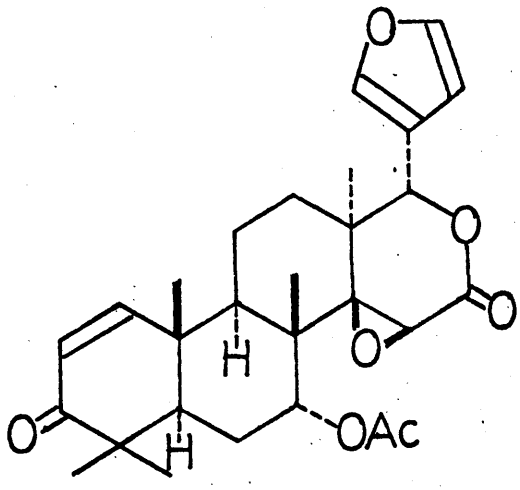

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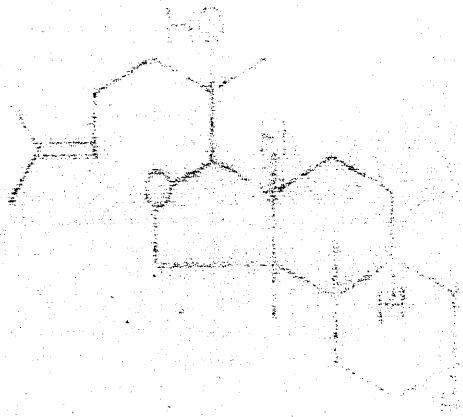

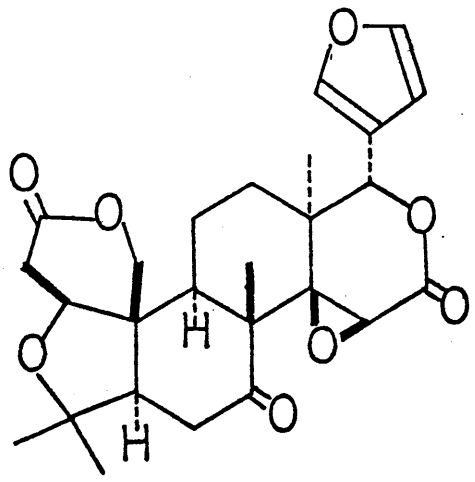

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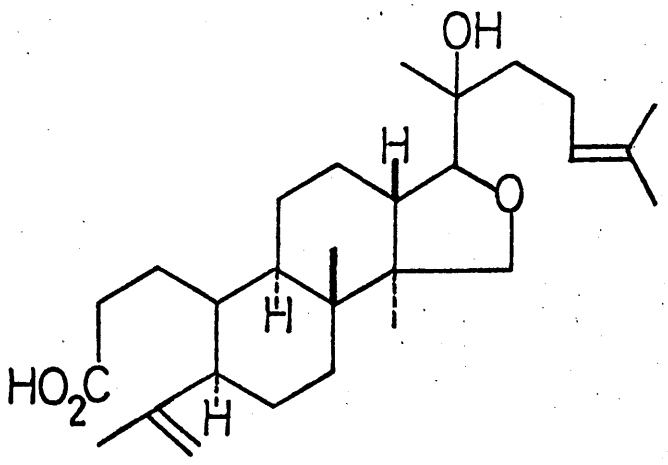

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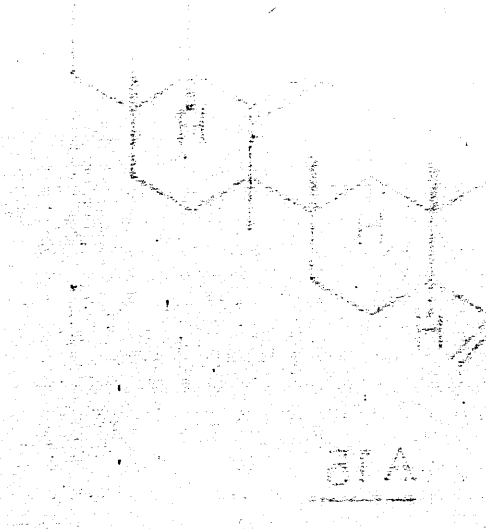

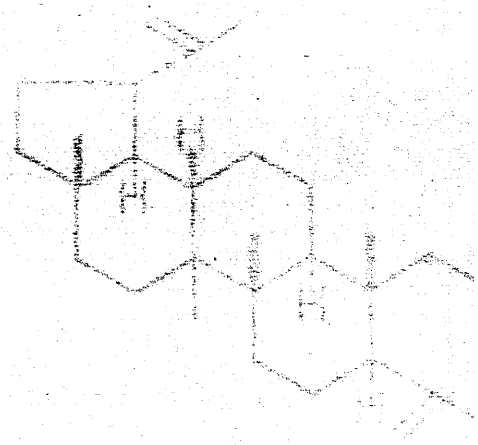

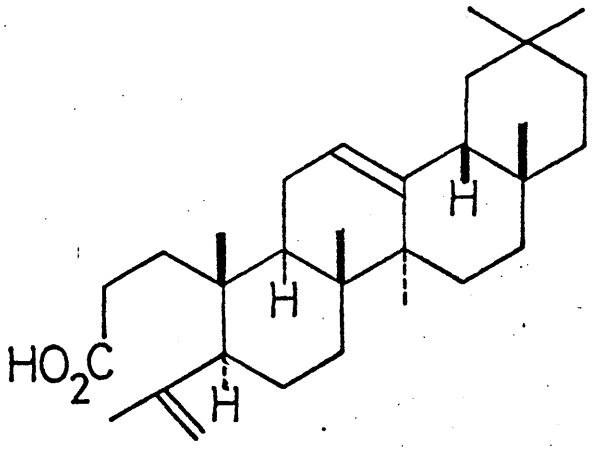

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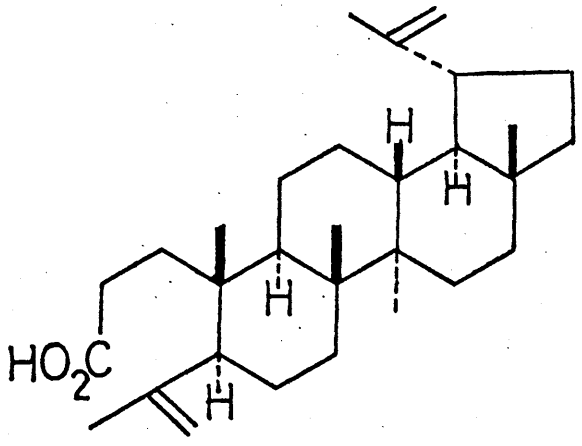

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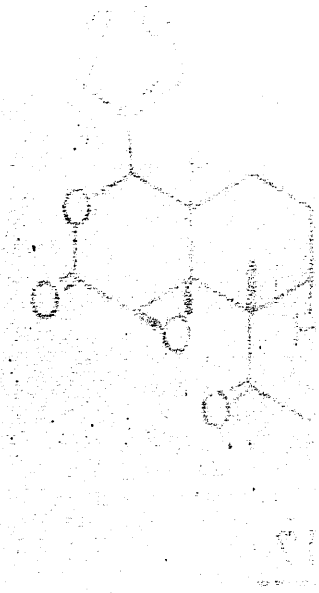

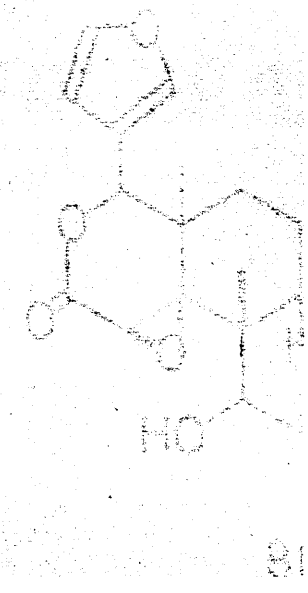
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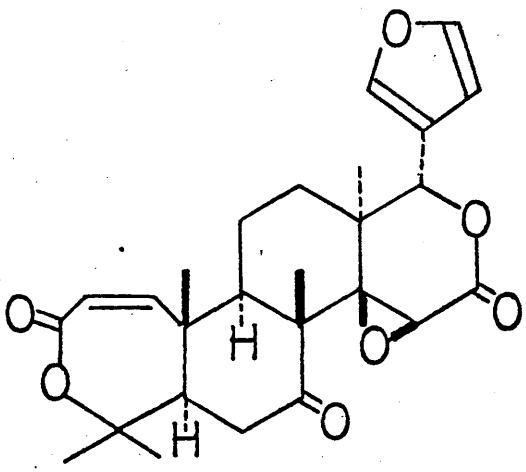

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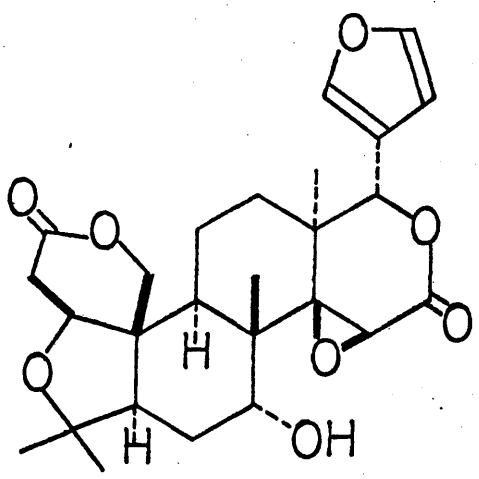

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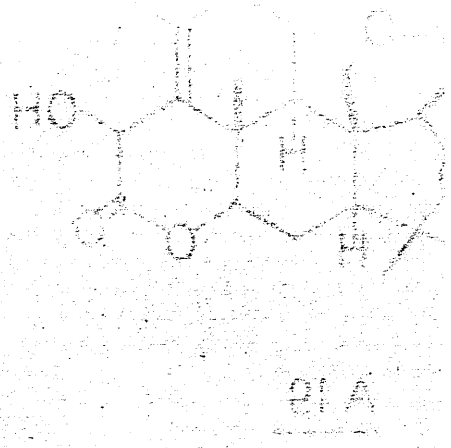

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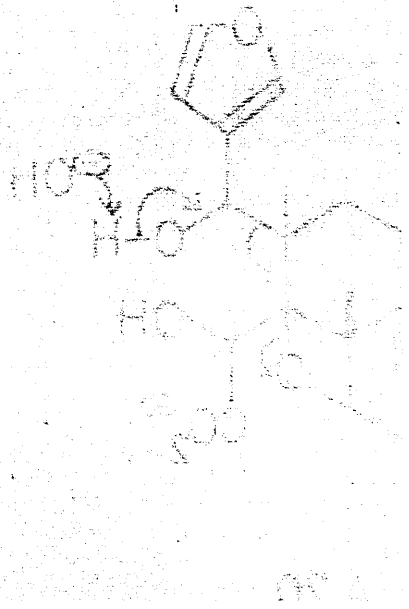

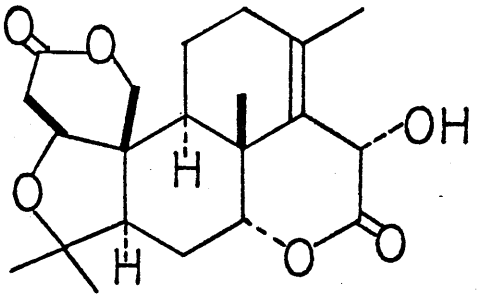

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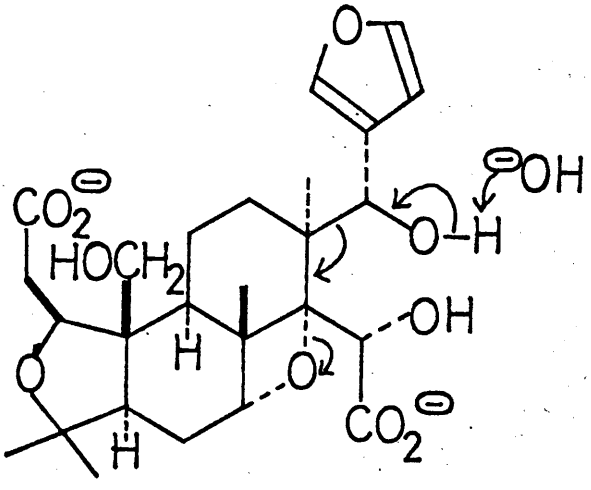

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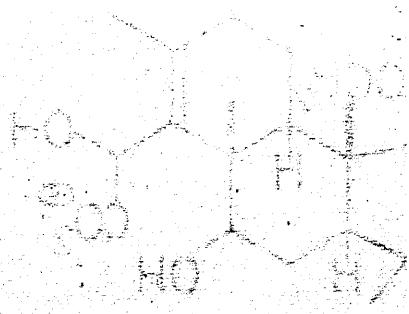

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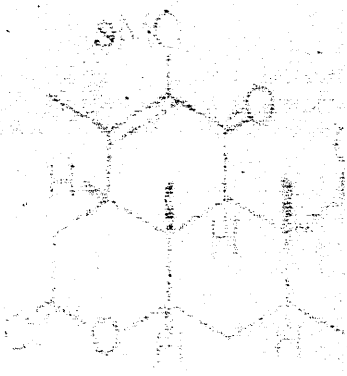

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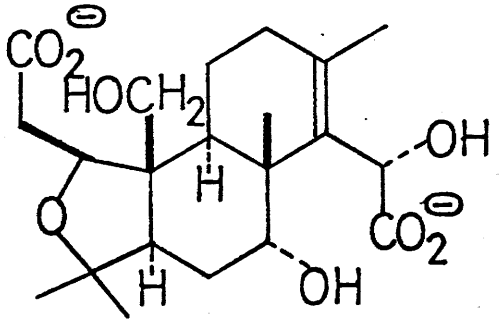

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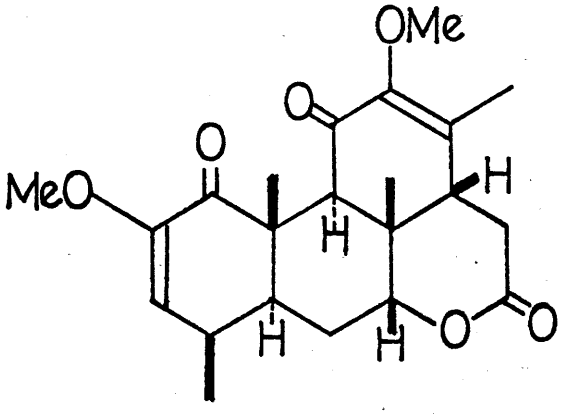

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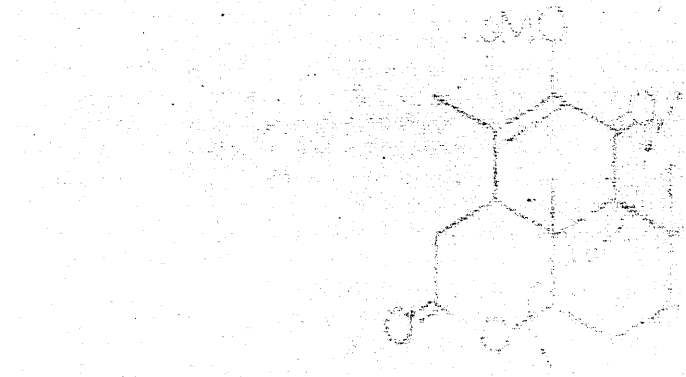

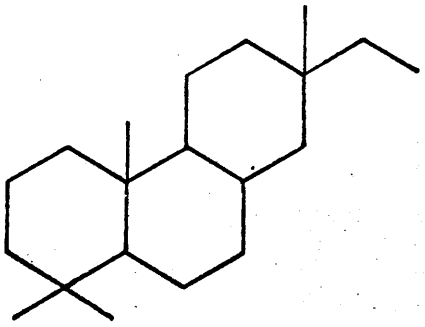

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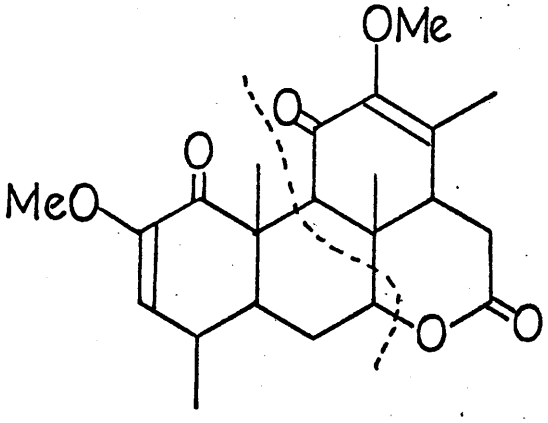

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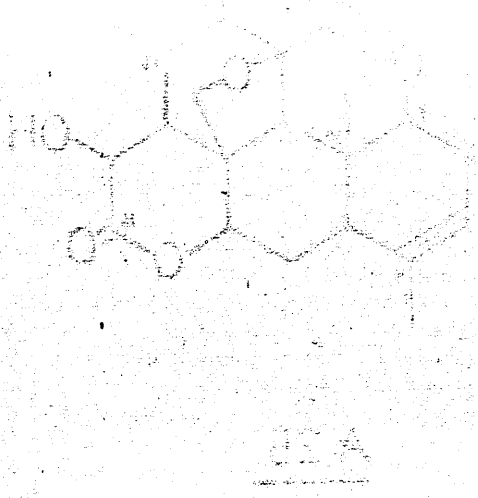

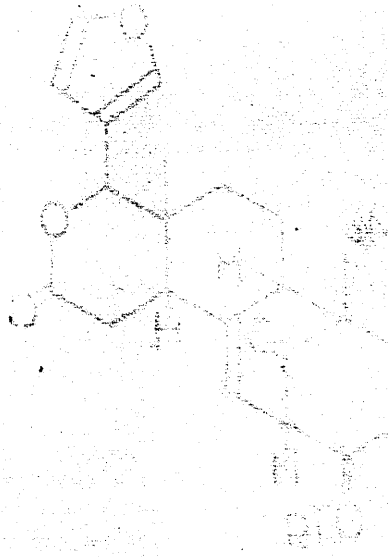

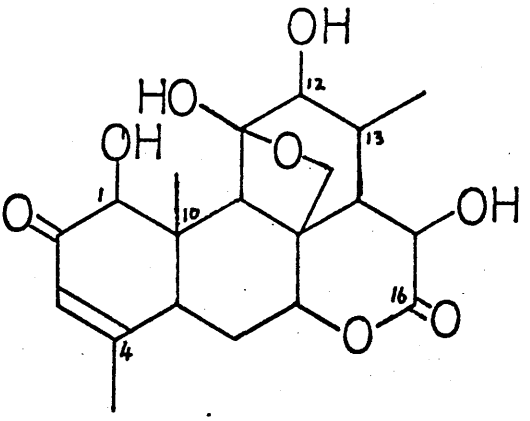

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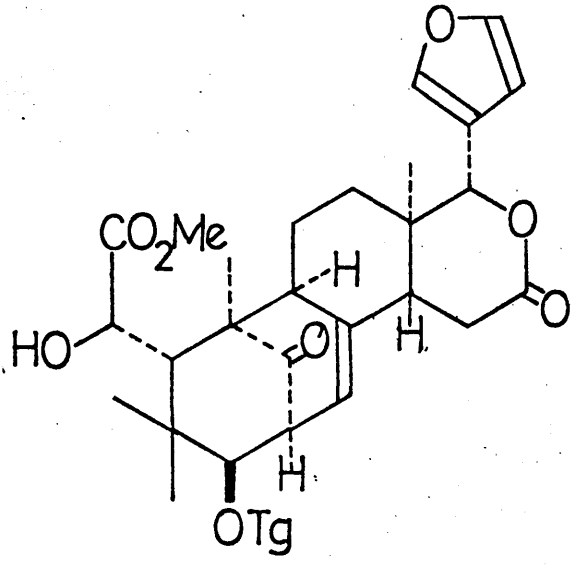

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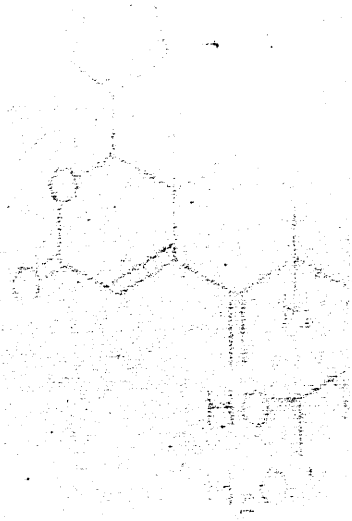

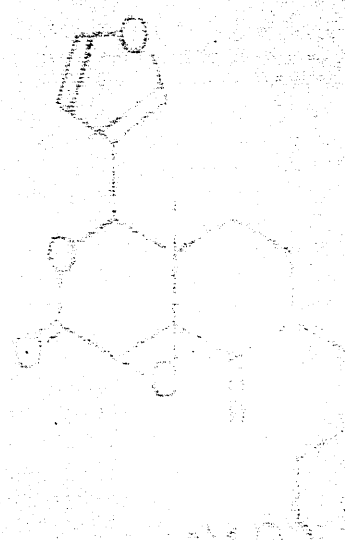

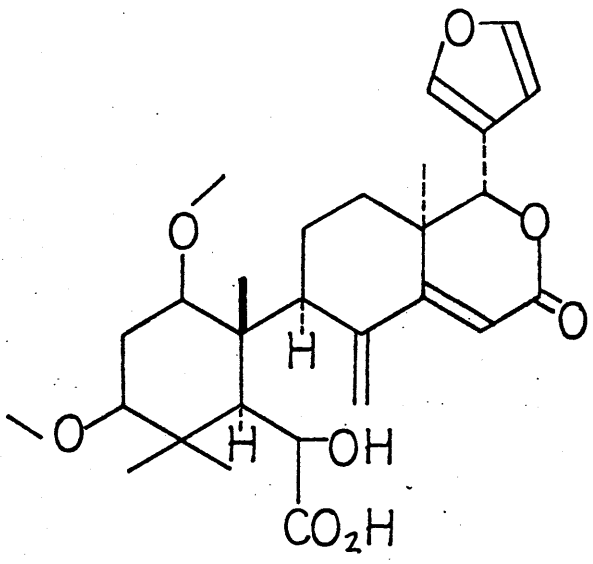

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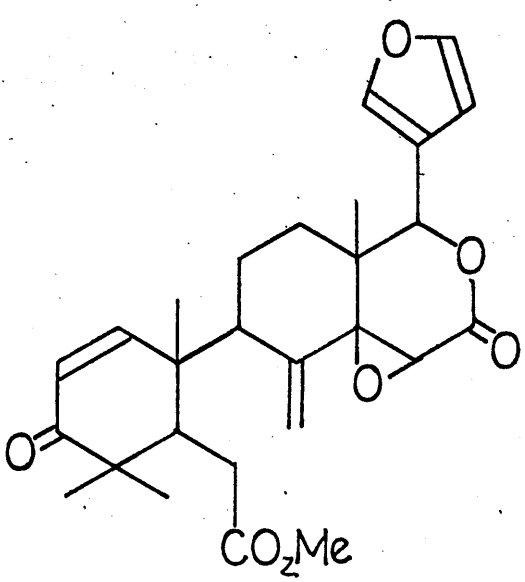

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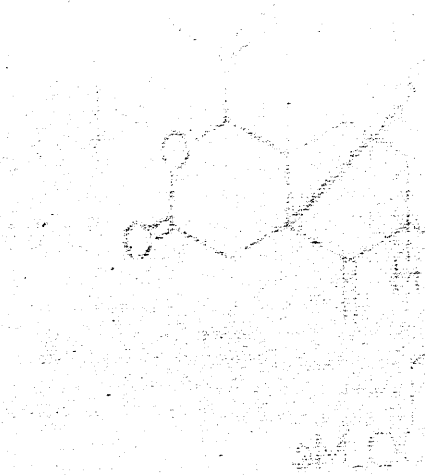

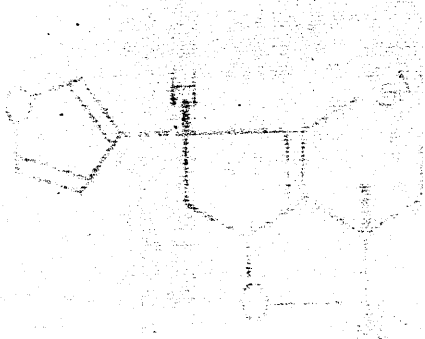

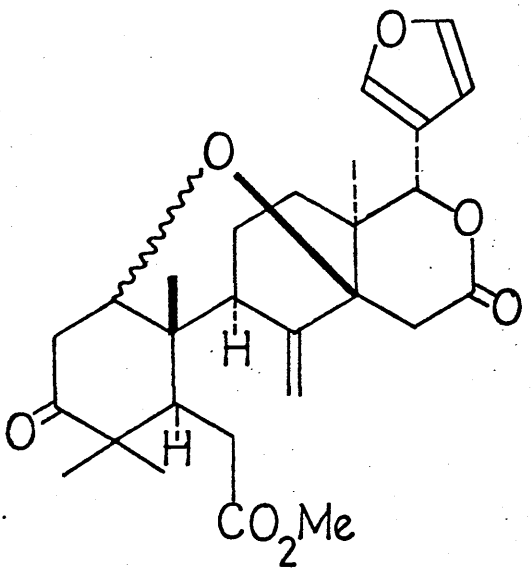

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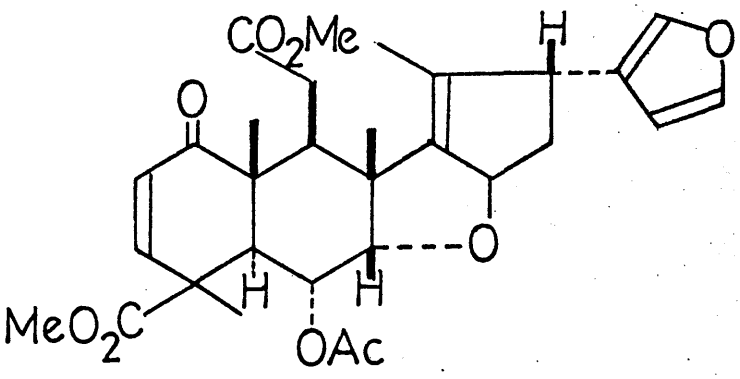

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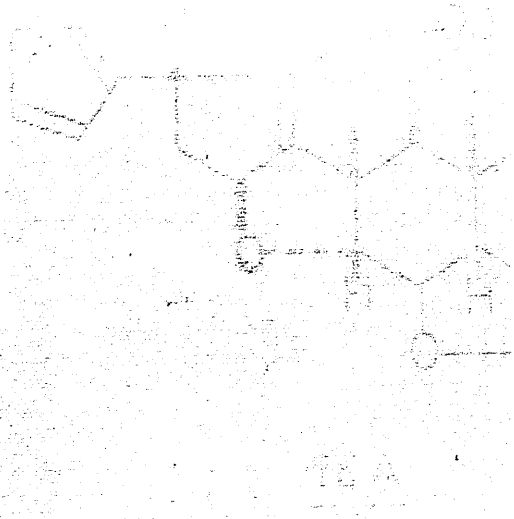

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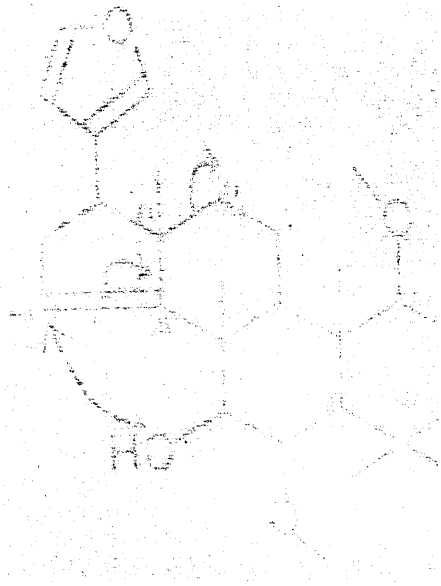

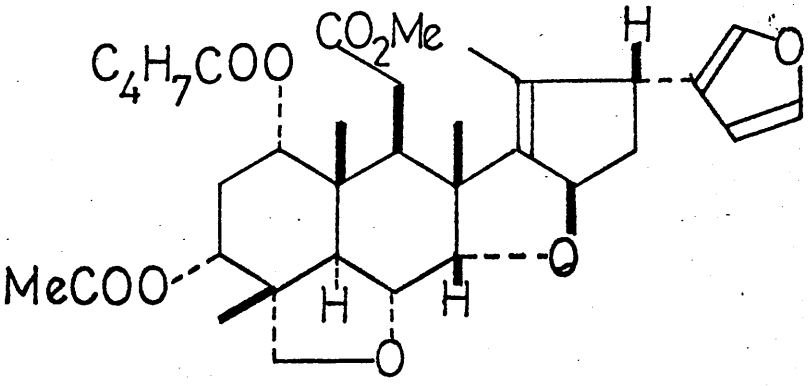

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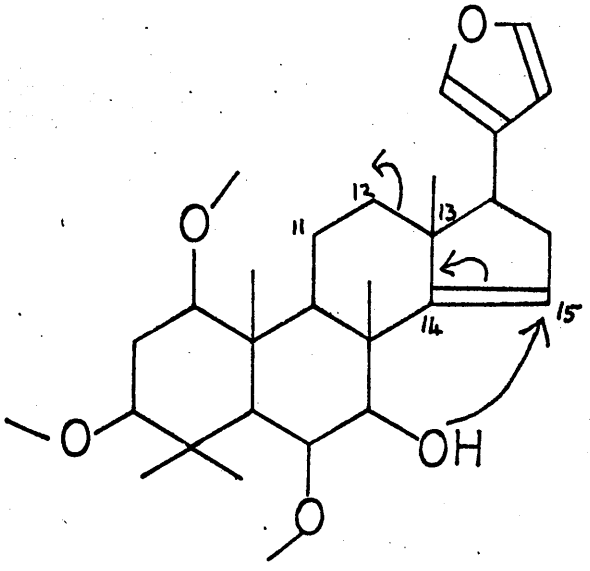

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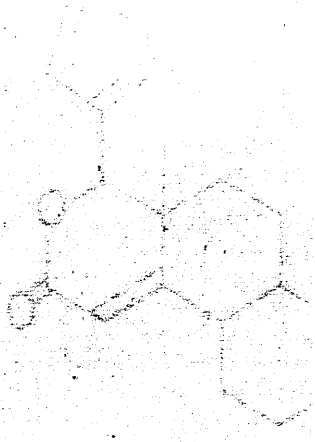

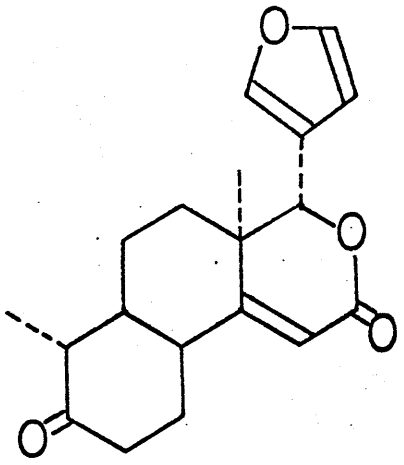

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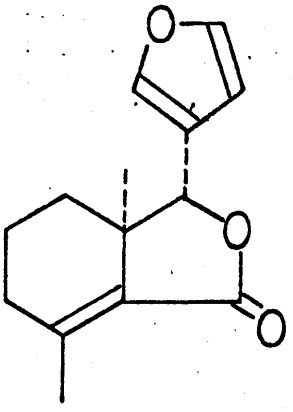

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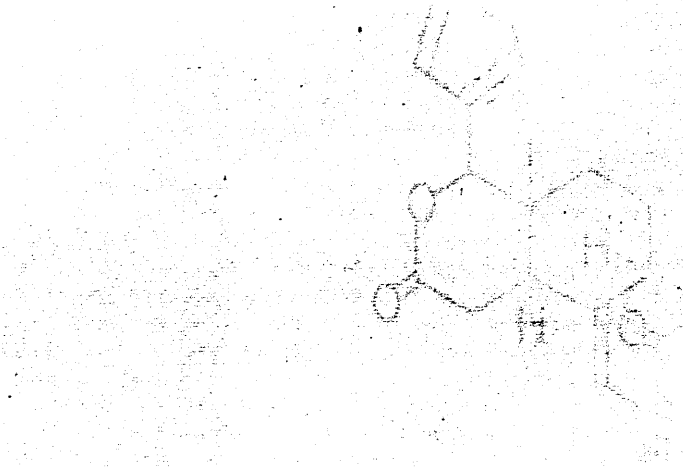

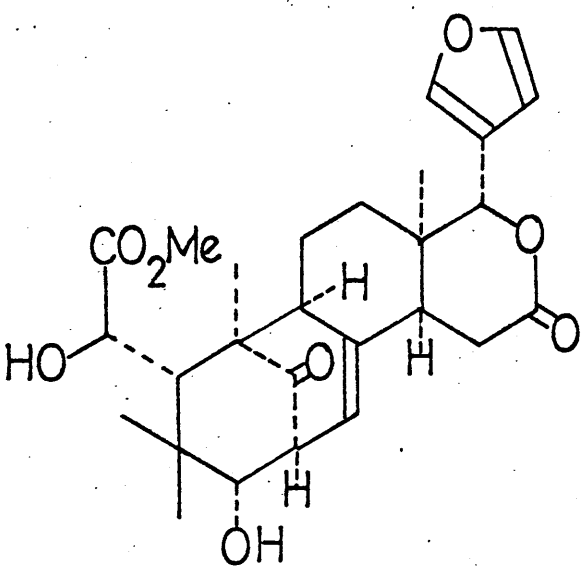

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PART IA

SWIETENOLIDE

INTRODUCTION

The constitution and stereochemistry of swietenolide, a bitter principle from the seeds of Swietenia macrophylla (Meliaceae), a mahogany tree native to Central America, are deduced from its chemical and spectroscopic behaviour and confirmed by degradative correlation with mexicanolide.

REVIEW OF THE CHEMISTRY OF SWIETENOLIDE.

The isolation of swietenolide from the seeds of Swietenia macrophylla King was initially reported[1] in 1951. Subsequent work[2] showed it to be a hygroscopic white solid, m.p. (from ethyl acetate) 218-222°, $[\alpha]_D$ -126° (methanol). Carefully dried material gave microanalyses in good agreement with the composition $C_{27}H_{34}O_8$, Kuhn-Roth oxidation detected 2.54 C-methyl groups and a modified Zeisel determination 0.96 O-methyl groups. The presence of 2.26 active hydrogens was demonstrated by the Zerewitinoff method.

Swietenolide kept in 0.05 N sodium hydroxide (ethanol/water; 1:1) consumed one equivalent of base and was regenerated on acidification, indicating the presence of a lactone ring. When heated at 95° with 0.1 N sodium hydroxide (ethanol/water; 1:1) for five hours two equivalents of base were consumed and acidification produced swietic acid, $C_{26}H_{32}O_8$, m.p. 180-181°, which was believed[2] to yield swietenolide on treatment with ethereal diazomethane (see later).

The I.R. spectrum of swietenolide and swietic acid showed $\nu_{max.}$ (Nujol) 3100-3200, 1505, 1025, 875 and 800 cm.$^{-1}$ suggesting the presence of a furan ring. This was confirmed by NMR which showed that the furan was β-substituted.

Hydrogenation of swietenolide over 10% palladised charcoal in acetic acid gave hexahydro swietenolic acid, m.p. 232-235°, $[\alpha]_D$ -59°, which on treatment with ethereal diazomethane formed the methyl ester. This suggested hydrogenolysis of the lactone and saturation of the furan ring as in limonin[3,4] and columbin[5]. The part-structure (A) was accordingly postulated.

Neither swietenolide, swietic acid nor hexahydro swietenolic acid formed an oxime, semicarbazone or 2,4-dinitrophenylhydrazone although the presence of a ketone was indicated by their U.V. spectrum ($\lambda_{max.}$ 284-288 mμ, $\varepsilon \sim 50$). The I.R. spectrum of dried swietenolide showed ν_{max} ($CHCl_3$) 3628, 3610 (shoulder) and 3535 (free and associated hydroxyl), 1751 (δ -lactone), 1740 (methyl ester) and 1721 (cyclohexanone) cm.$^{-1}$. Oxidation of swietenolide with potassium dichromate in acetic acid produced dehydro-swietenolide, $C_{27}H_{32}O_8$, which had $\nu_{max.}$ ($CHCl_3$) 3597,

3525 (associated hydroxyl) and 1710 (increased intensity) $cm.^{-1}$, showing that the free secondary hydroxyl had been oxidised to a ketone. The U.V. spectrum of dehydroswietenolide in neutral ethanol showed only end absorption. However on addition of base an intense maximum appeared at 288 mμ (log ε, 4.54), changing on acidification to 264 mμ (log ε, 4.38), which suggested the formation of an enolisable β-diketone on treatment of dehydroswietenolide with base.

Hexahydro swietenolic acid had $\lambda_{max.}$ 209 mμ (log ε, 3.81) indicative of a double bond in swietenolide which survived hydrogenation and was probably tetrasubstituted. A positive tetranitromethane test for hexahydro swietenolic acid supported this assumption and the positive Tollens test given by swietenolide and the hexahydro ester but not by the hexahydro acid suggested the location of the double bond βγ to the lactonic carbonyl (crotonic and fumaric esters give the Tollens test but the free acids do not).

On treatment with lead tetraacetate in acetic acid swietenolide and hexahydro swietenolic acid reacted only slowly whereas swietic acid consumed one equivalent rapidly. This indicated that one of the hydroxyl groups

in swietenolide was α to the carbomethoxyl group. This was confirmed by the isolation of formaldehyde (chromotropic acid) from sodium periodate treatment of the lithium aluminium hydride reduction product of swietenolide.

The above evidence was summarised[2] in part expression (B) for swietenolide which was regarded as closely related to the congeneric non-bitter principle swietenine[1,6]. Later work[7] confirmed the part-expression (B) on chemical and NMR evidence and showed the presence of a fourth C-methyl group. Hydrolysis of swietenine, which appeared to have the same functional groups as swietenolide except that one of the hydroxyl groups was tigloylated, did not however yield swietenolide, suggesting a more complex relationship between them than was formerly supposed.

THE CONSTITUTION AND STEREOCHEMISTRY OF SWIETENOLIDE

The functional groups previously determined[2,7,8] for swietenolide (B1)*, $C_{27}H_{34}O_8$, m.p. 221-225°, $[\alpha]_D$ -136°, are further supported by examination of the single and double resonance NMR spectra of swietenolide (Fig. 1) and its derivatives.

The simple diacetate (B2) of swietenolide, $C_{31}H_{38}O_{10}$, m.p. 225-228°, $[\alpha]_D$ -129°, shows in its NMR spectrum (Fig.2) four distinct singlets (3H each, tertiary methyls) at τ 9.16, 8.96, 8.93 and 8.84, a singlet (6H, 2 $-OCOCH_3$) at τ 7.85 and a singlet (3H, $-COOCH_3$) at τ 6.24. It also shows a sharp doublet (1H, J = 10Hz, $\geq$C<u>H</u>OAc) at τ 5.12 which on irradiation at τ 6.84 (1H, <u>m</u>, H-2) collapses to a singlet, and two diffuse singlets at τ 4.49 (1H, $-C\underline{H}OAc-CO_2Me$) and 6.58 (1H, H-5) each of which sharpens on irradiation at the other. The furanic protons show as diffuse singlets at τ 2.42 and 2.53 (1H each, H-21 and H-23) and τ 3.50 (1H, H-22) and there is a sharp

* For ease of exposition full structural formulae anticipate their derivation where appropriate.

singlet at τ 4.37 (1H, H-17). The remaining nine protons attached to C-9, C-11, C-12, C-15 and C-30 appear in the region τ 6.3 to 8.3 and the assignments shown (Fig. 2) are supported by double irradiation experiments and by analogy with mexicanolide reduction product monoacetate[9] (B3) (see Fig. 3 and see later).

Oxidation of swietenolide with Jones reagent affords, depending on the conditions (see Experimental), either 3-dehydroswietenolide (B4), $C_{27}H_{32}O_8$, m.p. 241-244°, or 3,6-bisdehydroswietenolide (B5), $C_{27}H_{30}O_8$, m.p. 183-185°. The latter is transformed into the former by the action of zinc dust in boiling acetic acid. The U.V. spectra of both oxidation products exhibit interesting properties[10] strikingly similar to those of mexicanolide[9] (B6). Thus 3-dehydroswietenolide has in neutral ethanol $\lambda_{max.}$ 210 mμ (log ε 3.15) which is immediately supplanted on addition of alkali by $\lambda_{max.}$ 287 mμ (log ε, 4.53), and this in turn is replaced on acidification by $\lambda_{max.}$ 265 mμ (log ε, 4.17) (shoulder at 285 mμ). These changes reflect cleavage of the C-9 - C-10 bond and formation of the β-diketone (B7) or (B8), $[\alpha]_D$ + 122°. Similarly, mexicanolide forms the β-diketone (B9) or (B10). The base-catalysed cleavage process could occur

either after isomerisation of the double bond to C-14 - C-15 [cf. (B11)] or possibly directly[11] [cf. (B12)].

Further, acetylation of swietenolide with fused sodium acetate in acetic anhydride affords[7,8] the anhydroacetate (B13), $C_{29}H_{34}O_8$, m.p. 198-201°, $[\alpha]_D$ + 249°, whose U.V. absorption [$\lambda_{max.}$ 235 mμ (log ε, 4.10), 280 mμ (log ε, 4.19)] and NMR spectrum [vinyl protons at τ 3.93 (1H, m, H-9), 4.08 (1H, s, H-3) and 4.37 (1H, s, H-15)] closely parallel those of the corresponding derivative (B14) of mexicanolide. The properties of these two pairs of compounds are compared in Table 1.

Evidently the retro-Michael fission in the above cases is rendered irreversible either by resonance stabilisation of the enolisable β-diketone system or by β-elimination of the acetate formed at C-3 to afford the enone. The latter reaction led us to suspect that swietenolide itself might react similarly under basic conditions which would favour elimination of the C-3 β-hydroxyl. This was indeed achieved, treatment of swietenolide with a 3% solution of sodium methoxide in dry refluxing methanol furnishing the non-crystalline enone (B15), $C_{27}H_{32}O_7$, which on acetylation yielded the anhydroacetate (B13).

From the similarities summarised in Table 1 taken in conjunction with the NMR spectra of swietenolide diacetate (Fig. 2), mexicanolide reduction product monoacetate (Fig. 3), 3-dehydroswietenolide (Fig. 4) and mexicanolide (Fig. 5), it is clear that 3-dehydroswietenolide must be 6-hydroxymexicanolide (B4). This is further supported by the circular dichroism (Fig. 6) and rotatory dispersion (Fig. 7) curves of swietenolide, 3-dehydroswietenolide, 3-dihydromexicanolide (B16) and mexicanolide.

Definitive support for the structure of swietenolide[12] is available from degradation of the derived β-diketone (B7) or (B8). Cleavage by sodium periodate* of an enolisable 1,3-diketone bearing an alkyl substituent at the 2-carbon atom, RCO-CR' = C(OH)R", results[13] in the formation of three carboxylic acids, RCO_2H, $R'CO_2H$ and $R''CO_2H$. Thus cleavage of the β-diketone (B7) or (B8) from 3-dehydroswietenolide provides, after methylation, the γ-lactone diester (B17) and the diene lactone monoester (B19), which are uniquely defined by their analytical and spectroscopic properties.

* We are indebted to Professor R. A. Raphael, F.R.S., for bringing this reaction to our notice.

The oily γ-lactone diester (B17), $C_{12}H_{18}O_6$, $[\alpha]_D$ -8°, has $\nu_{max.}$ (CCl_4) 1743 (methyl esters) and 1798 (γ-lactone) cm.$^{-1}$. Its NMR spectrum (benzene) has signals at τ 5.65 (1H, d, J = 8 Hz, H-6), 6.70 (6H, two closely spaced s, methyl esters), 7.15 (1H, q, J = 8, 9Hz, H-5), 7.70 (1H, m, H-10), 8.88, 9.08 (3H each, s, tertiary methyls) and 9.04 (3H, d, J = 6Hz, secondary methyl). Since only one lactone is formed we prefer the less crowded isomer (B17) to the alternative (B18).

The diene lactone monoester (B19), $C_{17}H_{18}O_5$, m.p. 147-149°, $[\alpha]_D$ + 387°, has $\lambda_{max.}$ 272 mμ (log ε, 4.18), 212 mμ (log ε, 3.95) and $\nu_{max.}$ (CCl_4) 1740 (methyl ester), 1730 (doubly unsaturated δ-lactone) cm.$^{-1}$. The NMR spectrum has well-separated signals at τ 2.5 (2H, diffuse s, H-21 and H-23), 3.5 (1H, diffuse s, H-22), 3.75 (1H, m, H-9) 4.17 (1H, s, H-15), 4.82 (1H, s, H-17), 6.27 (3H, s, methyl ester), 6.70 (2H, broadened s, 2H-30), 7.6 (2H, m, 2H-11), 8.5 (2H, m, 2H-12) and 8.92 (3H, s, 3H-18).

Periodate cleavage of the corresponding β-diketone (B9) or (B10) from mexicanolide[9,12] affords, as anticipated, the same diene lactone monoester (B19) and an oily triester (B20), $C_{13}H_{22}O_6$, $[\alpha]_D$ -26°, ν_{max} (CCl_4) 1738 (methyl esters) cm.$^{-1}$, NMR signals ($CDCl_3$) at τ 6.30 (9H, s, methyl esters),

7.0 - 7.7 (4H, m, H-5, 2H-6, H-10), 8.8 (6H, s, tertiary methyls) and 8.95 (3H, d, J = 6Hz, secondary methyl).

Hydrolysis of swietenolide with a 5% solution of potassium hydroxide in refluxing ethanol for one hour produces desmethylisoswietenolide (B21), $C_{26}H_{32}O_8$, m.p. 182-184°, $[\alpha]_D$ -129°, which on methylation with ethereal diazomethane affords 3-episwietenolide (B22), $C_{27}H_{34}O_8$, m.p. 213-217°, $[\alpha]_D$ -114°, and not swietenolide as previously reported[2]. Oxidation of 3-episwietenolide with Jones reagent leads to the same 3-dehydro- (B4) and 3,6-bisdehydroswietenolide (B5) as are obtained from swietenolide (see above).

Epimerisation at C-3 by retroaldolisation and realdolisation involving the C-1 carbonyl group (see Fig. 8) has previously been encountered with swietenine[14] (B23) and it appears that here, as in swietenine, the C-3 oxygen substituent has the less stable β (quasi-axial) configuration and on reaction with base is completely transformed into the more stable α (quasi-equatorial) epimer. This is clearly seen from the NMR spectra of swietenolide diacetate (B2) and 3-episwietenolide diacetate (B24). The H-3 resonance in the former appears as a clean doublet centred at τ 5.12

whose observed coupling constant ($J_{2,3}$ = 10Hz) is in agreement[15,16] with the dihedral angle $\theta_{2,3} \sim 0^{\circ}$ (Fieser models) when the C-3 hydroxyl is β-oriented. In the latter, H-3 is a doublet centred at τ 5.69 whose coupling constant ($J_{2,3}$ = 3Hz) is similarly in accord with the dihedral angle $\theta_{2,3} \sim 120^{\circ}$ when the hydroxyl group is α-oriented.

It was previously observed[2] that the hydrolysis product of swietenolide rapidly consumed one equivalent of lead tetraacetate. Treatment of desmethylisoswietenolide (B21) with one equivalent of lead tetraacetate in acetic acid furnishes the noraldehyde (B25), $C_{25}H_{30}O_6$, m.p. 194-197°, $[\alpha]_D$ -31°. Its NMR spectrum shows a doublet (J = 6Hz) centred at τ 0.15 (-C<u>H</u>O) arising from vicinal coupling with H-5 (τ 7.41, <u>d</u>, J = 6Hz). The I.R. spectrum ($CHCl_3$) has $\nu_{max.}$ 3623 (free hydroxyl), 1741 (δ-lactone) and 1718 (aldehyde, cyclohexanone) $cm.^{-1}$.

One point not readily accessible from direct evidence is the configuration at C-6 in swietenolide. In swietenine (B23), whose absolute configuration was established[17] by Bijvoet's anomalous-dispersion method[18], C-6 has the (R)-configuration[19]. Removal of the asymmetric centre C-6 in the 3,6-dioxoswietenolide and 3,6-dioxoswietenine series

(B26) during transformation of the α-hydroxy ester into (a) the pyruvate ($-CHOH-CO_2Me \longrightarrow -CO-CO_2Me$) and (b) the noraldehyde ($-CHOH-CO_2Me \longrightarrow -CHO$) results in the following molecular rotation changes: swietenolide - $[\varphi]_D$ (a) + 129°, $[\varphi]_D$ (b) + 411°; swietenine[20] - $[\varphi]_D$ (a) + 596°, $[\varphi]_D$ (b) + 483°. Accordingly it seems likely that C-6 has the (R)-configuration in swietenolide.

The absolute configuration of swietenolide as depicted in (B1) then follows from that of mexicanolide (B6), defined by circular dichroism measurements[9b] and supported by an X-ray determination[21] of the iodoacetate (B27) derived from " Cedrela odorata substance B " which is identical to mexicanolide. From the circular dichroism curves (Fig.6) of swietenolide (B1) and 3-dihydromexicanolide (B16) it appears* that the bicyclononanone system is twisted. According to an octant projection, ring C is in a negative octant as is the 3-hydroxyl, whereas the acidic side-chain falls into either a positive octant or into the third nodal

* We warmly thank Dr. Günther Snatzke for measuring the CD curves and for this interpretation.

plane (on average). The three methyl groups are also in nodal planes. From this a CD of not greater than about -1 would be expected and therefore some twist of the bicyclononanone system would seem to be responsible for the high negative CD's. Such a twist is indicated in the X-ray structures for swietenine p-iodobenzoate[17] and the iodoacetate (B27)[21] in the crystalline state and if one assumes that a similar conformation is present in solution this would explain the relatively high negative CD's.

Several attempts were made to relate swietenolide directly to mexicanolide. Hydrogenation of swietenolide over 10% palladised charcoal in acetic acid and methylation of the product afforded the hexahydro ester (B28) m.p. 196-199°, which was oxidised to the triketone (B29). This triketone (B 29) and mexicanolide hexahydro ester (B30) which are identical except at C-6 were each subjected under similar conditions to a modified[22] Wolff-Kishner reduction. TLC examination showed a very complex mixture of products in each case and no direct comparisons were possible.

Formation of the mesylate (B31), ν_{max} (CCl_4) 1180 and 1370 (SO_2) cm.$^{-1}$, from 3-dehydroswietenolide offered an attractive route to mexicanolide by reductive removal of the mesyloxy ($-OSO_2CH_3$) group. This was attempted using: (a) zinc in acetic acid; (b) sodium iodide in ethanol; (c) sodium benzyl mercaptide in ethanol; (d) lithium aluminium hydride in tetrahydrofuran; (e) collidine followed by hydrogenation and methylation; (f) chromous acetate in acetic acid; (g) chromous chloride in acetic acid. In no case however was mexicanolide or the expected product obtained.

Correlation of swietenolide with swietenine (B23) was also attempted by treatment of 3-episwietenolide (B22) and destigloylisoswietenine (B32) with hydrogen chloride in chloroform. Although reaction readily occurred in both instances TLC showed the absence of a common product and the structures of the reaction products were not investigated.

An interesting difference in reactivity in strongly basic conditions between swietenolide (B1) and swietenine (B32) was noticed in the course of this work. As mentioned above, swietenolide when refluxed in a 3% solution of sodium methoxide in methanol affords the

enone (B15) by cleavage of the C-9 — C-10 bond as in (B11) or (B12) followed by β-elimination of the hydroxyl group. Swietenine, however, when treated with a 5% solution of potassium hydroxide in ethanol under reflux affords, on methylation, destigloylisoswietenine (B32) and an enone (B33) which is formed by cleavage of the C-2 — C-3 bond followed by hemiacetal formation between the hydroxyl at C-6 and the C-3 carbonyl as in (B34) and (B35). Oxidation of the enone hemiacetal (B33) with Jones reagent affords the enone γ-lactone (B36), m.p. 246-253°. The different situation of the isolated double bond in these molecules thus probably explains the contrasting cleavage reactions, but it should be noted that C-2 — C-3 cleavage occurs in swietenolide as in swietenine during epimerisation of the C-3 hydroxyl group (see Fig. 8).

EXPERIMENTAL

Melting points were determined on a Kofler hot-stage apparatus. Specific rotations refer to chloroform solutions except where otherwise specified. Infra-red solution spectra were obtained by Mrs. F. Lawrie on a Unicam SP 100 Mark II spectrophotometer with a prism grating monochromator operated with evacuated optics, or on a Unicam SP 257 spectrophotometer. Ultra-violet spectra were measured in ethanol on a Unicam SP 800A spectrophotometer. Microanalyses were performed by Mr. J.M.L. Cameron, B.Sc., and his staff. Mass spectral data were obtained by Miss J. Wilkie on an A.E.I. MS 9 spectrometer. Woelm alumina deactivated according to the Brockmann[23] scale of activity was used for column chromatography and Merck Kieselgel G for thin-layer chromatography unless otherwise indicated. R_f values were not recorded; where necessary known compounds were run concurrently for identification purposes. Circular dichroism curves were recorded by Dr. G. Snatzke and rotatory dispersion curves by Professor W. Klyne. Nuclear magnetic resonance spectra were obtained by

Miss S. Price and Mr. J. Gall on a Perkin Elmer R 10 60 MHz and a Varian Associates HA 100 100 MHz spectrometer using approximately 0.3M solutions in deuteriochloroform with tetramethylsilane as internal standard. Double irradiation experiments were performed with the latter using a Muirhead D 890 A oscillator and calibration was checked with a Hewlett-Packard 5212 A electronic counter. Light petroleum refers to the fraction boiling between 60 and 80°C.

Extraction of Swietenolide from Swietenia macrophylla Seeds

The seeds used in this investigation were collected in Trinidad during March, through the courtesy of Mr. W.S. Chalmers, Assistant Conservator of Forests, Port of Spain, whose help we gratefully acknowledge. The milled seeds (8 kg.) were defatted by extraction with light petroleum in a Soxhlet apparatus. The dried meal (3.7 kg.) was extracted with chloroform, the resulting extract evaporated to 1 l. and filtered from insoluble material. After removal of solvent from the filtrate the residue was chromatographed on alumina. Subsequent purification by preparative TLC afforded, inter alia, swietenolide (18 g.)

which was crystallised from ethanol/water, m.p. 218-222°, $[\alpha]_D$ - 126° (c, 2.40, methanol); rotatory dispersion (methanol): $[\varphi]_{400}$ - 2,900, $[\varphi]_{306}$ - 12,100, $[\varphi]_{270}$ + 7,400, $[\varphi]_{240}$ + 4,650, $[\varphi]_{233}$ + 5,800°; circular dichroism (dioxan): $\Delta\varepsilon_{313}$ - 1.70, $\Delta\varepsilon_{301}$ - 3,20, $\Delta\varepsilon_{294}$ - 3.22; $\nu_{max.}$ ($CHCl_3$): 3628, (3610 shoulder), 3535, 1751, 1740 and 1721 $cm.^{-1}$. (Found: C, 66.7; H, 7.25. $C_{27}H_{34}O_8$ requires: C, 66.65; H, 7.05).

Acetylation of Swietenolide: The Diacetate (B2)

Swietenolide (80 mg.) was dissolved in dry pyridine (2 ml.) and acetic anhydride (2 ml.). The solution was heated at 60° for 4 hr. and worked up by addition of water (20 ml.) and extraction with chloroform (2 x 10 ml.). The product was separated by preparative TLC (2% methanol/chloroform) affording (from chloroform/ether/light petroleum) swietenolide diacetate (B2) (28 mg.), m.p. 225-228°, $[\alpha]_D$ - 129° (c, 1.1). (Found: C, 65.3; H, 6.7, $C_{31}H_{38}O_{10}$ requires: C, 65.3; H, 6.7%).

3-Dehydroswietenolide (B4)

(a) Swietenolide (99 mg.) in acetone (100 ml.) and Jones reagent (1 ml.) was kept at -20° for 5 min. Chromatography of the product obtained in the usual way afforded

3-dehydroswietenolide (50 mg.), m.p. (from chloroform/light petroleum) 241-244°; rotatory dispersion (methanol): $[\varphi]_{400}$ -1,280, $[\varphi]_{315}$ -5,980, $[\varphi]_{272}$ + 3,140, $[\varphi]_{250}$ + 3,000, $[\varphi]_{227}$ + 7,260°; circular dichroism (dioxan): $\Delta\varepsilon_{315}$ -1.33, $\Delta\varepsilon_{302}$ -2.30, $\Delta\varepsilon_{294}$ -2.08. (Found: C, 66.7; H, 6.8. $C_{27}H_{32}O_8$ requires: C, 66.9; H, 6.7%).

(b) 3-Episwietenolide (see below) (50 mg.) oxidised as in (a) afforded 3-dehydroswietenolide (20 mg.), m.p. and mixed m.p. 240-244°.

(c) 3,6-Bisdehydroswietenolide (see below) (250 mg.) and zinc dust (3 g.) were refluxed in acetic acid (20 ml.) for 1½ hr. Solids were removed by filtration, solvent by evaporation under reduced pressure and the product extracted from water into chloroform. Preparative TLC furnished 3-dehydroswietenolide (180 mg.); m.p. (from chloroform/light petroleum) 240-244°, undepressed on admixture with material obtained in (a).

3,6-Bisdehydroswietenolide (B5)

(a) To swietenolide (97 mg.) in acetone (50 ml.) Jones reagent (5 ml.) was added dropwise and the mixture kept at 20° for 3 min. The reaction was then poured into

water and the product recovered in the usual way. Preparative TLC afforded 3,6-bisdehydroswietenolide (69 mg.), m.p. (from chloroform/light petroleum) 183-185°, $[\alpha]_D$ -4° (c, 1.00). (Found: C, 67.0; H, 6.0. $C_{27}H_{30}O_8$ requires: C, 67.2; H, 6.25%).

(b) 3-Episwietenolide (B22) (93 mg.) oxidised under comparable conditions gave 3,6-bisdehydroswietenolide (66 mg.), m.p. (from chloroform/light petroleum) 182-185°, mixed m.p. 182-185°.

Treatment of Swietenolide with Strong Alkali: The Enone (B15).

Swietenolide (200 mg.) was refluxed in a 3% solution of sodium methoxide in dry methanol for 4½ hr. The product, obtained by dilution, acidification and extraction into chloroform, was esterified with ethereal diazomethane and separated by preparative TLC (2% methanol/chloroform; 50% ethyl acetate/light petroleum) to give the non-crystalline enone (B15), $\lambda_{max.}$ 235 mμ (log ε, 4.15), 278 mμ (log ε, 4.20); $\nu_{max.}$ (CCl_4) 3520 (bonded hydroxyl), 1730 (shoulder at 1738) (diene lactone, methyl ester), 1680 (enone) $cm.^{-1}$. (Found: C, 69.2; H, 7.2. $C_{27}H_{32}O_7$ requires: C, 69.2; H, 6.9%). Acetylation as

above afforded the anhydroacetate (B13) m.p. and mixed m.p. (from chloroform/light petroleum) 198-200° indistinguishable by TLC.

Alkali Treatment of 3-Dehydroswietenolide: The β-Diketone (B7) or (B8).

3-Dehydroswietenolide (B4) (250 mg) was kept in a mixture of ethanol (50 ml.) and 1N sodium hydroxide (1 ml.) at 20° for 2 min. The product (170 mg.), obtained on dilution with water, acidification and extraction into chloroform, was isolated by preparative TLC (2% methanol/chloroform) as the non-crystalline β-diketone (B7) or (B8), $[\alpha]_D$ + 122°. For U.V., I.R. and NMR data see Table 1. (Found: C, 66.7; H, 6.6. $C_{27}H_{32}O_8$ requires: C, 66.9; H, 6.7%).

Periodate Cleavage of the β-Diketones (a) (B7) or (B8) from Swietenolide and (b) (B9) or (B10) from Mexicanolide

(a) The β-diketone obtained above (170 mg.) in water (20 ml.) containing sodium hydroxide (1 equivalent) and sodium metaperiodate (380 mg.; 5 equivalents) was stirred at 20° for 18 hr. Separation of the product as usual afforded acidic (48 mg.) and neutral (108 mg.) fractions. Esterification of the acid fraction in

methanol (5 ml.) with ethereal diazomethane afforded, on preparative TLC, (i) the γ-lactone diester (B 17) (21 mg.) which was distilled at 160°/0.1 mm., $[\alpha]_D$ - 8° (c, 1.20). (Found: C, 55.8; H, 6.8. $C_{12}H_{18}O_6$ requires: C, 55.8; H, 7.05%) and (ii) the diene lactone monoester (B19) (20 mg.), m.p. (from chloroform/ether) 147-149°, $[\alpha]_D$ + 387°. (Found: C, 67.35; H, 6.2. $C_{17}H_{18}O_5$ requires: C, 67.55; H, 6.0%).

(b) To the β-diketone (B9) or (B10) (900 mg.) in tert.-butanol (100 ml.) was added sodium metaperiodate (10 g.) in water (30 ml.) and the mixture stirred at 20° for 72 hr. The product was separated as before into acidic (200 mg.) and neutral (520 mg.) fractions. Methylation of the acid fraction and separation by preparative TLC afforded (i) the diene lactone monoester (B19) (60 mg.), identical with the lactone obtained in (a) (m.p., mixed m.p. and NMR) and (ii) the triester (B20) (50 mg.), $[\alpha]_D$ - 26°, which was distilled at 155°/0.05 mm. (Found: C, 56.15; H, 7.95. $C_{13}H_{22}O_6$ requires: C, 56.9; H, 8.1%).

3-Episwietenolide (B22)

Swietenolide (1.0 g.) in ethanolic potassium hydroxide (100 ml.; 5%) was refluxed in a nitrogen atmosphere

for 1 hr. Dilution, acidification and extraction into chloroform afforded acidic material (930 mg.), desmethylisoswietenolide (B21) m.p. (from ethanol/water) 178-184°. Methylation with ethereal diazomethane followed by preparative TLC (2% methanol/chloroform) afforded 3-episwietenolide (B22)(410 mg.), m.p. (from chloroform/light petroleum) 213-217°, $[\alpha]_D$ - 114° (c, 1.32). (Found: C, 66.5; H, 7.05. $C_{27}H_{34}O_8$ requires: C, 66.7; H, 7.05%).

3-Episwietenolide Diacetate (B24)

3-Episwietenolide (46 mg.) was treated with pyridine/acetic anhydride as for swietenolide (see above). The least polar constituent obtained by preparative TLC. was an amorphous white solid, 3-episwietenolide diacetate. (Found: C, 65.0; H, 6.8. $C_{31}H_{38}O_{10}$ requires C, 65.3; H, 6.7%).

Lead Tetraacetate Oxidation of Desmethylisoswietenolide: The Noraldehyde (B25)

Desmethylisoswietenolide (480mg.) and lead tetraacetate (650 mg.) in acetic acid (40 ml.) were stored in the dark at 20° for 58 hr. Dilution with water and extraction into chloroform afforded on preparative TLC

(chloroform, run twice) the noraldehyde (B25) (130 mg.), m.p. (from chloroform/light petroleum) 194-197°, $[\alpha]_D$ - 31° (c, 1.04). (Found: C, 70.2; H, 7.3. $C_{25}H_{30}O_6$ requires: C, 70.4; H, 7.1%).

Hydrogenation of Swietenolide: The Hexahydro Ester (B28)

Swietenolide (100 mg.) in acetic acid (25 ml.) was shaken with 10% Pd/C under hydrogen for 1½ hr, when hydrogen uptake was complete. 15 ml. (3.2 moles) hydrogen was taken up. The acidic product obtained by filtration and evaporation under reduced pressure was methylated with ethereal diazomethane. Preparative TLC afforded the hexahydro ester (74 mg.), m.p. (from chloroform/light petroleum) 196-199°.

Wolff-Kishner Reduction of the Triketone (B29) and Mexicanolide Hexahydro Ester (B30).

Swietenolide hexahydro ester (B28) (74 mg.) from the above reaction was oxidised with Jones reagent (1 ml.) in acetone (25 ml.) at 20° for 5 min. and the reactions worked up in the usual way. Preparative TLC afforded the non-crystalline triketone (B29) (51 mg.). This triketone (51 mg.) and mexicanolide hexahydro ester (50 mg.) were each treated in triethylene glycol (5 ml.)

with hydrazine hydrate (5 ml.) and potassium hydroxide (20 mg.). The solutions were refluxed at 90-100° for 1 hr. and then heated to 200° and kept at that temperature for 20 min. Addition of water and extraction into chloroform afforded in each case a complex mixture of products on TLC examination. No common major product was detected.

Treatment of 3-Dehydroswietenolide with Mesyl Chloride: The Mesylate (B31).

3-Dehydroswietenolide (B4) (200 mg.) was treated with mesyl chloride (1 ml.) in pyridine (5 ml.) at 20° for 12 hr. Addition of water and extraction into chloroform which was washed with saturated sodium bicarbonate solution yielded, on preparative TLC the non-crystalline mesylate (B31) (120 mg.), $\nu_{max.}$ ($CHCl_3$) 1180, 1370 (SO_2) $cm.^{-1}$.

Attempted Elimination of the Mesylate

(a) Zinc in Acetic Acid.. The mesylate (B31) (50 mg.) from the above reaction was dissolved in acetic acid (5 ml.), zinc dust (300 mg.) added and the mixture refluxed for 18 hr. After filtration water (15 ml.) was added and the solution extracted with chloroform.

Examination of the product by TLC and I.R. showed it to be largely unchanged starting material. The product was redissolved in acetic acid (5 ml.) zinc dust (100 mg.) added and the solution refluxed for 25 hr. Zinc dust (~15 mg.) was added every 40 min. for the first 6 hr. The mixture was worked up as before and examination by TLC showed the absence of mexicanolide but presence of a more polar compound. This was isolated and showed retention of the I.R. maxima at 1180 and 1370 $cm.^{-1}$.

(b) Sodium Iodide in Acetic Acid. Mesylate (B31) (5 mg.) and dried sodium iodide (100 mg.) were refluxed in acetic acid (5 ml.) for 30 min. The solution was poured into water (50 ml.) containing sodium thiosulphate (4g.) and extracted with chloroform. TLC examination showed substantially unreacted starting material. The reaction product was redissolved in acetic acid (5 ml.), dried sodium iodide (150 mg.) added and the solution refluxed for 6 hr. and worked up as before. TLC examination showed a complex mixture of products which included neither starting material nor mexicanolide.

(c) Sodium Benzyl Mercaptide in Ethanol. Mesylate (B31) (5 mg.) was dissolved in absolute ethanol (5 ml.) at 0^{o}

and sodium benzyl mercaptide (5 mg.) added. The reaction was allowed to heat to 20° over 1 hr., diluted with water and extracted with chloroform. TLC examination showed a complex mixture of products.

(d) Lithium Aluminium Hydride in Tetrahydrofuran. Mesylate (B31) (5 mg.) in dry tetrahydrofuran (4 ml.) was refluxed with lithium aluminium hydride (5 mg.) for 1 hr. The solution was cooled, saturated sodium sulphate solution added, diluted with water and extracted with chloroform. After methylation with ethereal diazomethane TLC examination showed a complex mixture of products.

(e) Collidine and Hydrogenation. Mesylate (B31) (20 mg.) was refluxed in collidine (10 ml.) for 1 hr. The solvent was removed under reduced pressure and the product hydrogenated in acetic acid over 10% Pd/C as described above. Methylation with ethereal diazomethane and examination by TLC showed a complex mixture of products none of which corresponded to the hexahydro ester (B30).

(f) Chromous Acetate in Acetic Acid. Mesylate (B31) (35 mg.) was dissolved in acetic acid (3 ml.) and water (1 ml.) in an atmosphere of nitrogen and chromous

acetate (200 mg.) added. The solution was stirred at 30° for 19 hr., diluted with water and extracted with chloroform. TLC examination showed the product to be largely (~95%) starting material.

(g) Chromous Chloride in Acetic Acid. The unchanged mesylate from the above reaction (30 mg.) was dissolved in acetic acid (5 ml.) in a nitrogen atmosphere and 0.75 N chromous chloride (2 ml.) added. The solution was left at 20° for 15 min. and worked up as before. TLC examination showed a mixture of starting material and more polar products and absence of mexicanolide. The mixture was oxidised in acetone (20 ml.) with Jones reagent (0.5 ml.) at 20° for 5 min. and worked up in the usual way. TLC examination showed a complex mixture of products which did not include mexicanolide.

Treatment of 3-Episwietenolide (B22) and Destigloylisoswietenine (B33) with Hydrogen Chloride

3-Episwietenolide (20 mg.) and destigloylisoswietenine (20 mg.) were separately dissolved in dry chloroform (20 ml.) and dry hydrogen chloride gas bubbled through the solutions for 20 min. After standing for 4 hr. the solvent was removed and the products examined by TLC. In each case at least three less polar components were formed but no two were identical.

Treatment of Swietenolide in strong Alkali.

The Enone Hemiacetal (B33)

Swietenine (200 mg.) in ethanol (48 ml.) containing potassium hydroxide (2.5 g.) in water (2 ml.) was refluxed for $1\frac{1}{2}$ hr. The acidic material obtained by dilution, acidification and extraction with chloroform was methylated with ethereal diazomethane. Preparative TLC afforded the non-crystalline enone hemiacetal (B33) (24 mg.), NMR signals at τ 3.52, (2H, q, H8 and H30), 4.29 (1H, s, H-17), 5.22 (1H, s, H-3), 5.41 (1H, d, J = 7Hz, H-6), 6.86 (1H, d, J = 7Hz, H-5).

The Enone γ-Lactone (B36)

The enone hemiacetal (B33) (24 mg.) from the above reaction in acetone (15 ml.) was treated with Jones reagent (0.3 ml.) at 20° for 3 min. Preparative TLC afforded the enone γ-lactone (B36) (18 mg.), m.p. (from methanol/water) 246-253°, $\nu_{max.}$ ($CHCl_3$) 1788 (γ-lactone), 1730 (δ-lactone, methyl ester), 1694 (enone) $cm.^{-1}$. (Found: C, 67.1; H, 6.8. $C_{27}H_{32}O_8$ requires: C, 66.9; H, 6.7%).

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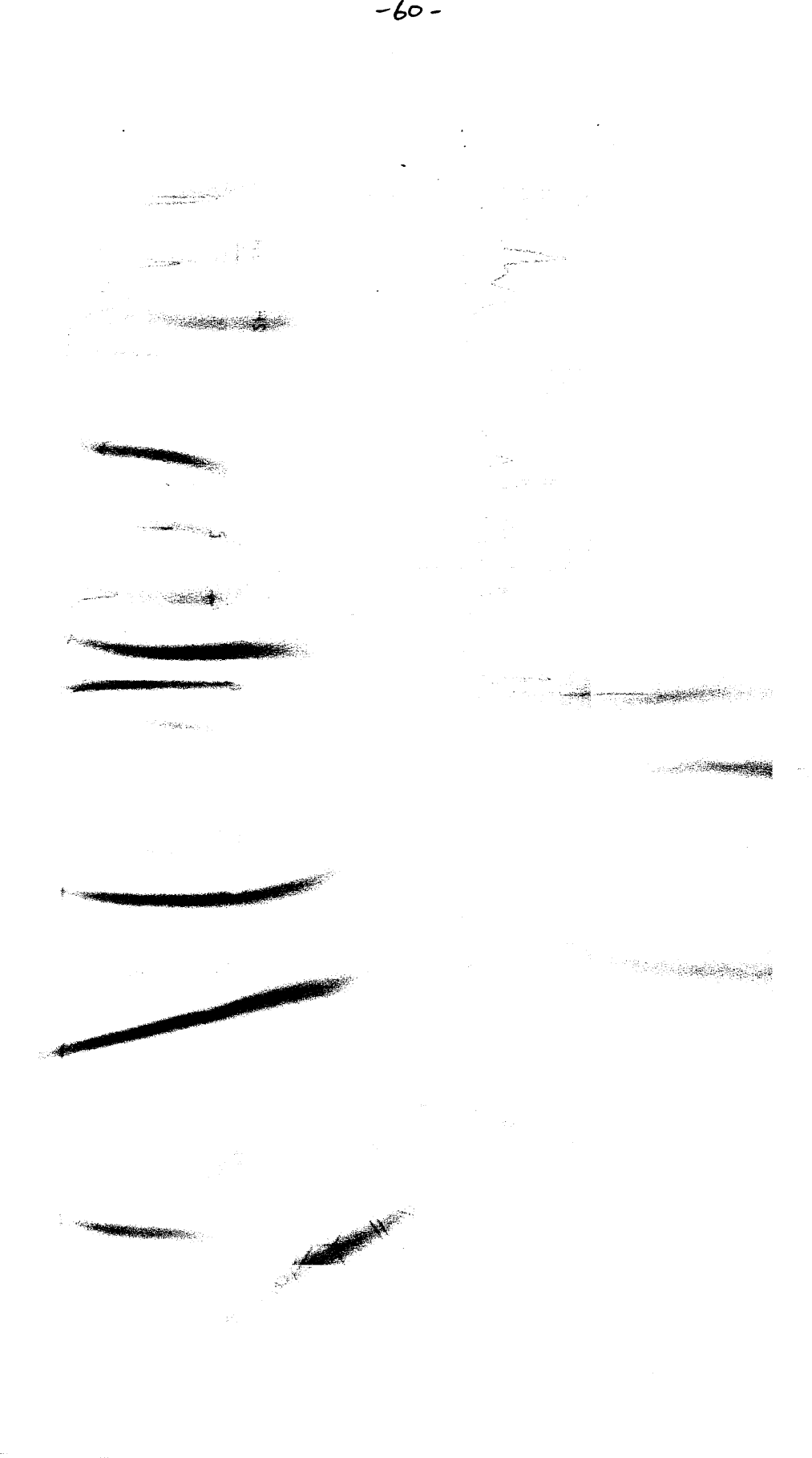
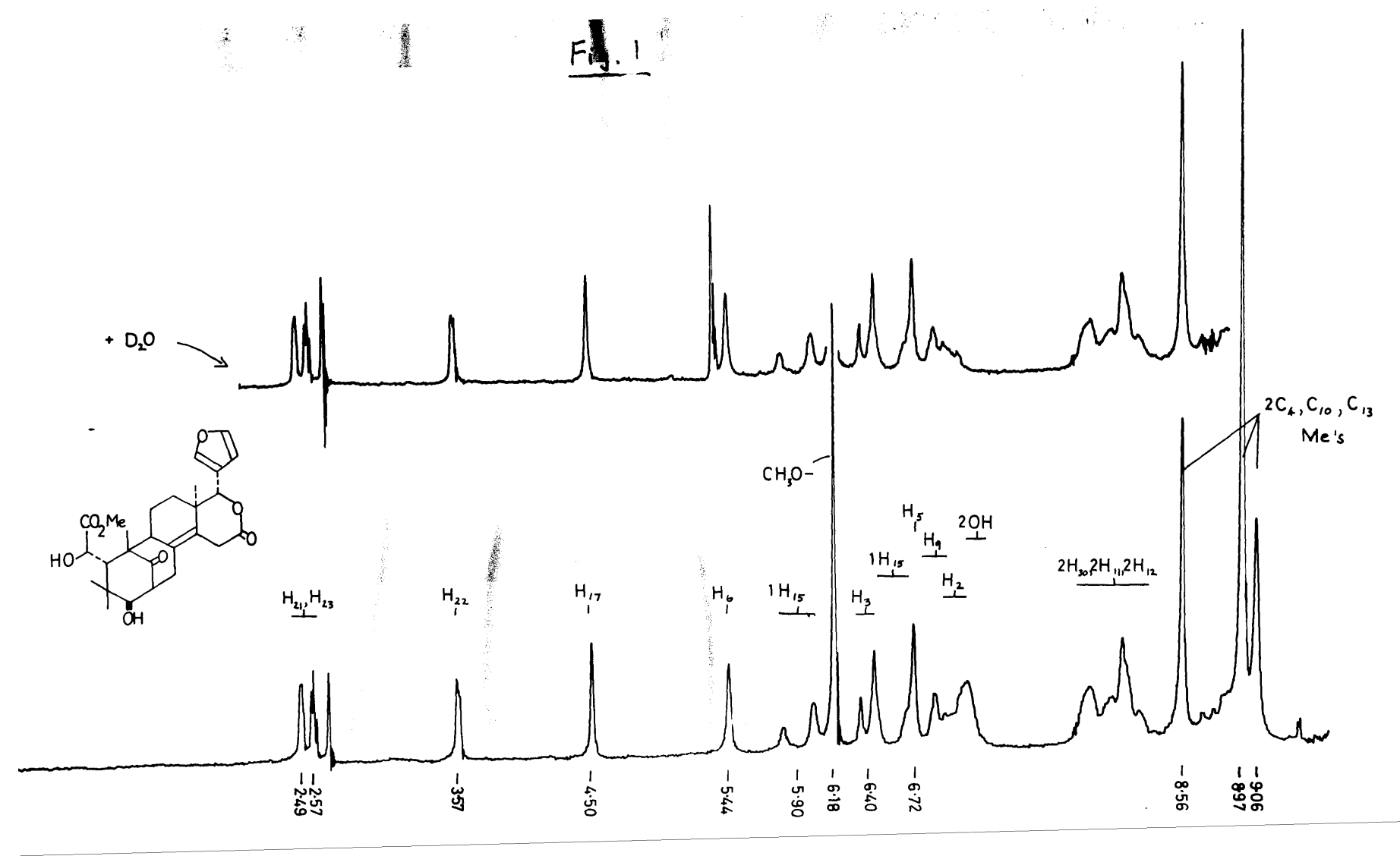


Fig. 1


+ D2O
CH3O-
2C4, C10, C13 Me's
H5
2OH
H9
1H15
H2
2H6, 2H11, 2H12
H21, H23
H22
H17
H6
1H15
H3
-2·49
-2·57
-3·57
-4·50
-5·44
-5·90
-6·18
-6·40
-6·72
-8·56
-8·97
-9·06

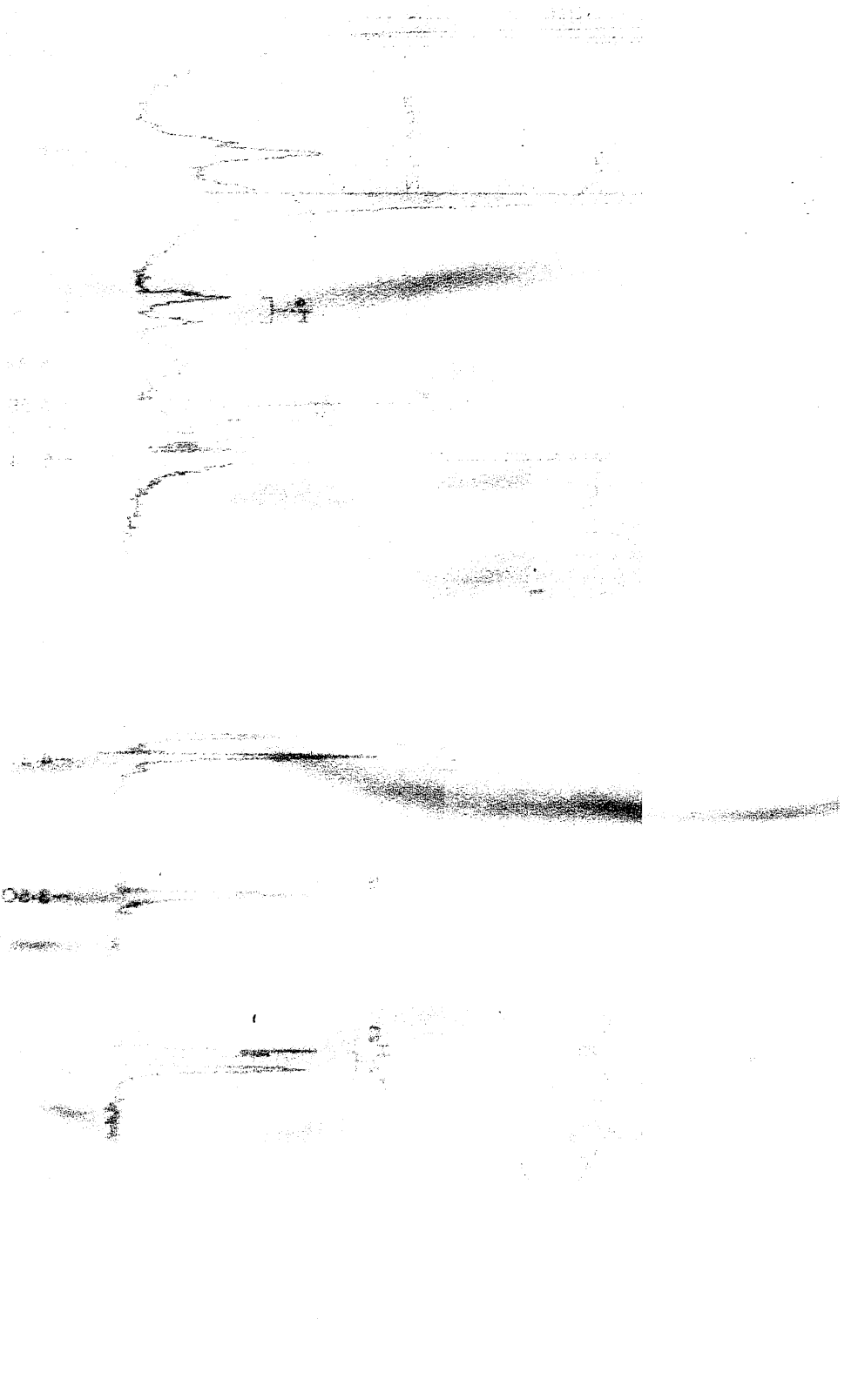
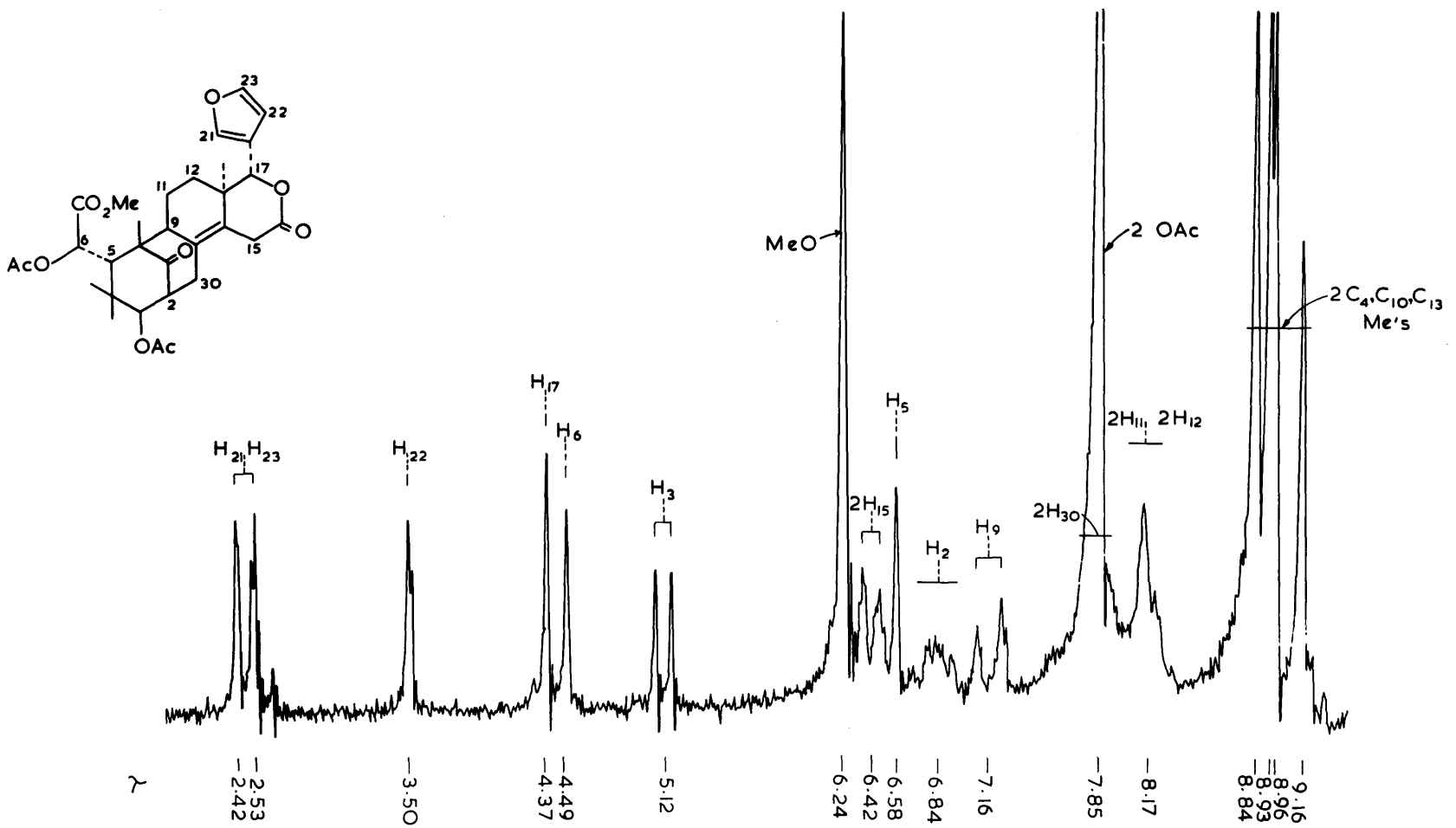


Fig. 2


23
22
21
17
12
11
9
6
5
15
30
2
CO2Me
AcO
OAc
MeO
2 OAc
2 C4,C10,C13 Me's
H21,H23
H22
H17
H6
H3
H5
2H15
H2
H9
2H30
2H11, 2H12
τ
2.42
2.53
3.50
4.37
4.49
5.12
6.24
6.42
6.58
6.84
7.16
7.85
8.17
8.84
8.93
8.96
9.16

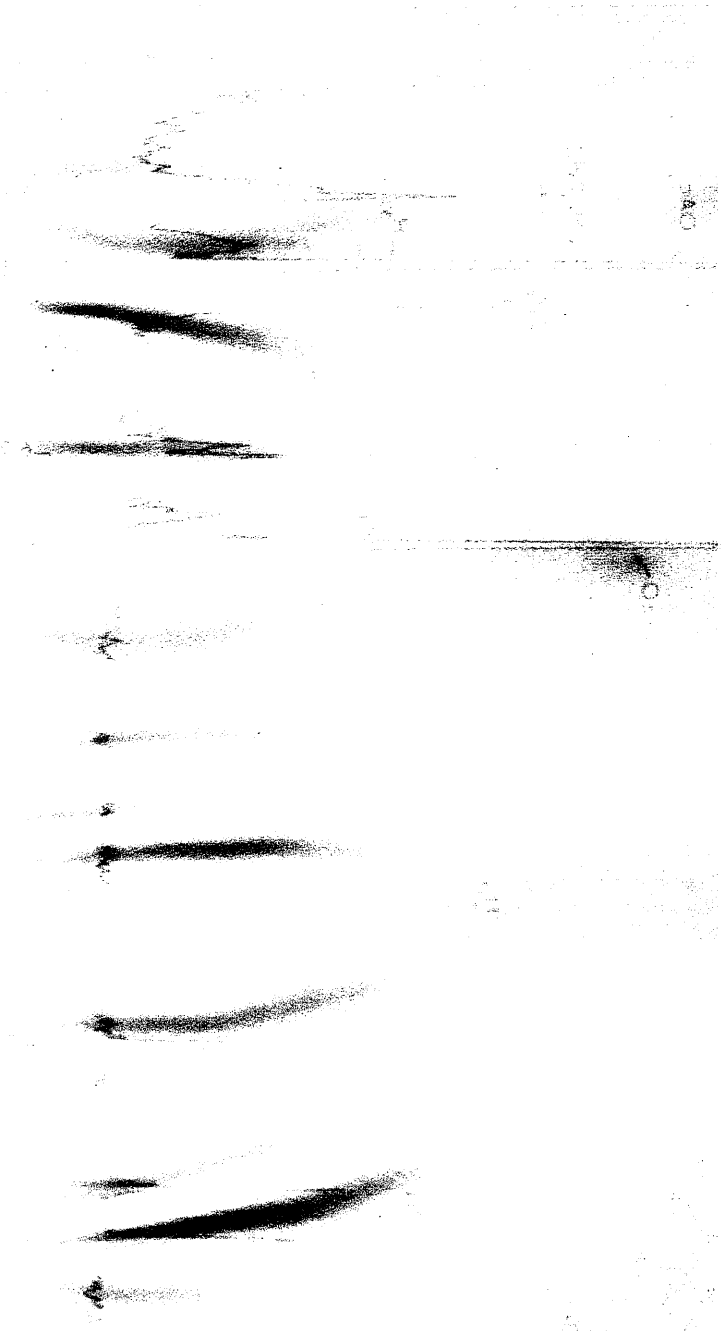
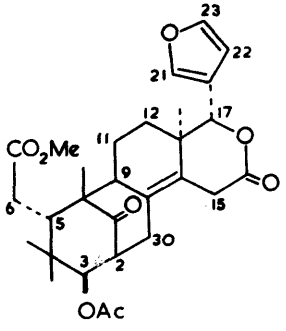


Fig. 3


23
22
21
17
12
11
9
CO_2Me
6
5
3
2
30
15
OAc

MeO
OAc
$2C_4, C_{10}, C_{13}Me's$
H_{21}, H_{23}
H_{22}
H_{17}
H_3
$2H_{15}$
H_2
H_5
H_9
$2H_6$
$2H_{11}, 2H_{12}$
$2H_{30}$
τ
2.48
2.64
3.36
4.34
4.97
6.32
6.42
6.72
7.08
7.65
7.70
8.14
8.66
8.76
9.05
9.11

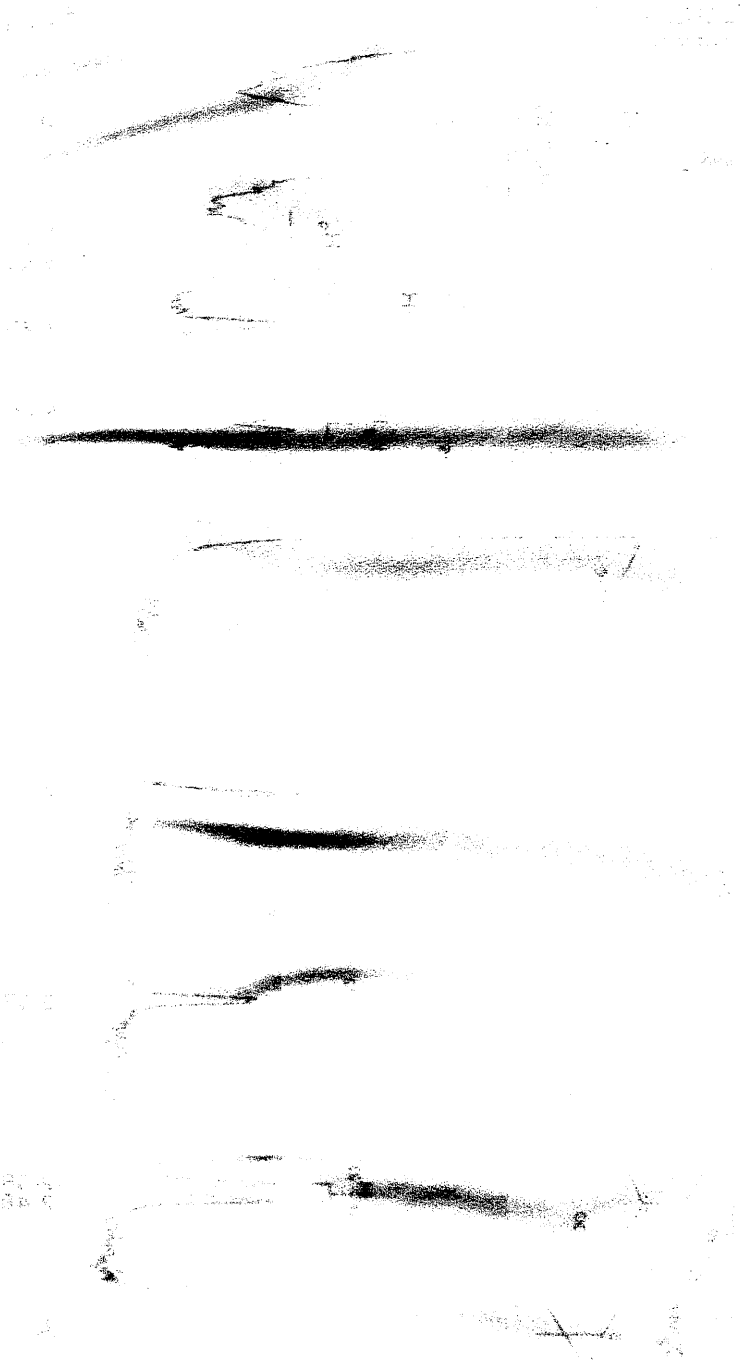
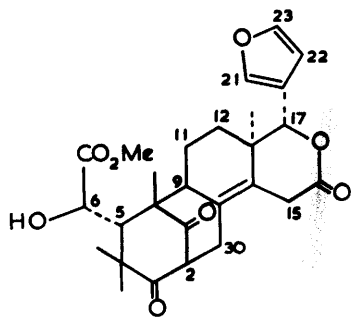


Fig. 4


23
22
21
12
17
11
CO_2Me
9
6
5
HO
15
30
2
O

$2C_4, C_{10}, C_{13}$ Me's
OMe
$2H_{11}$ $2H_{12}$
$2H_{15}$
H_{17}
H_2 H_{30}
H_5
$-OH$
H_{21} H_{23}
H_{22}
H_6
$1H_{30}$ H_9
τ
2.48
2.58
3.57
4.71
5.32
6.08
6.50
6.74
7.05
7.23
7.57
7.73
8.40
8.76
8.88
8.94

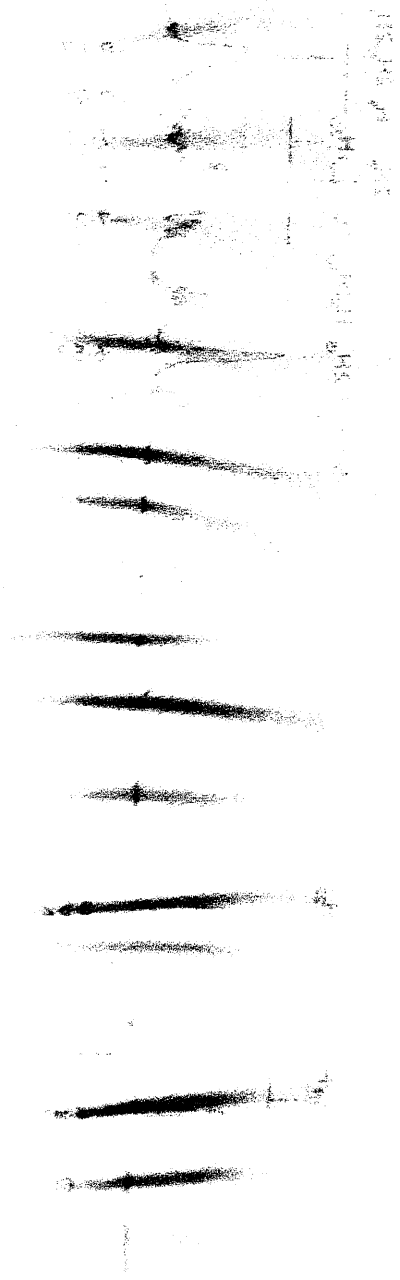
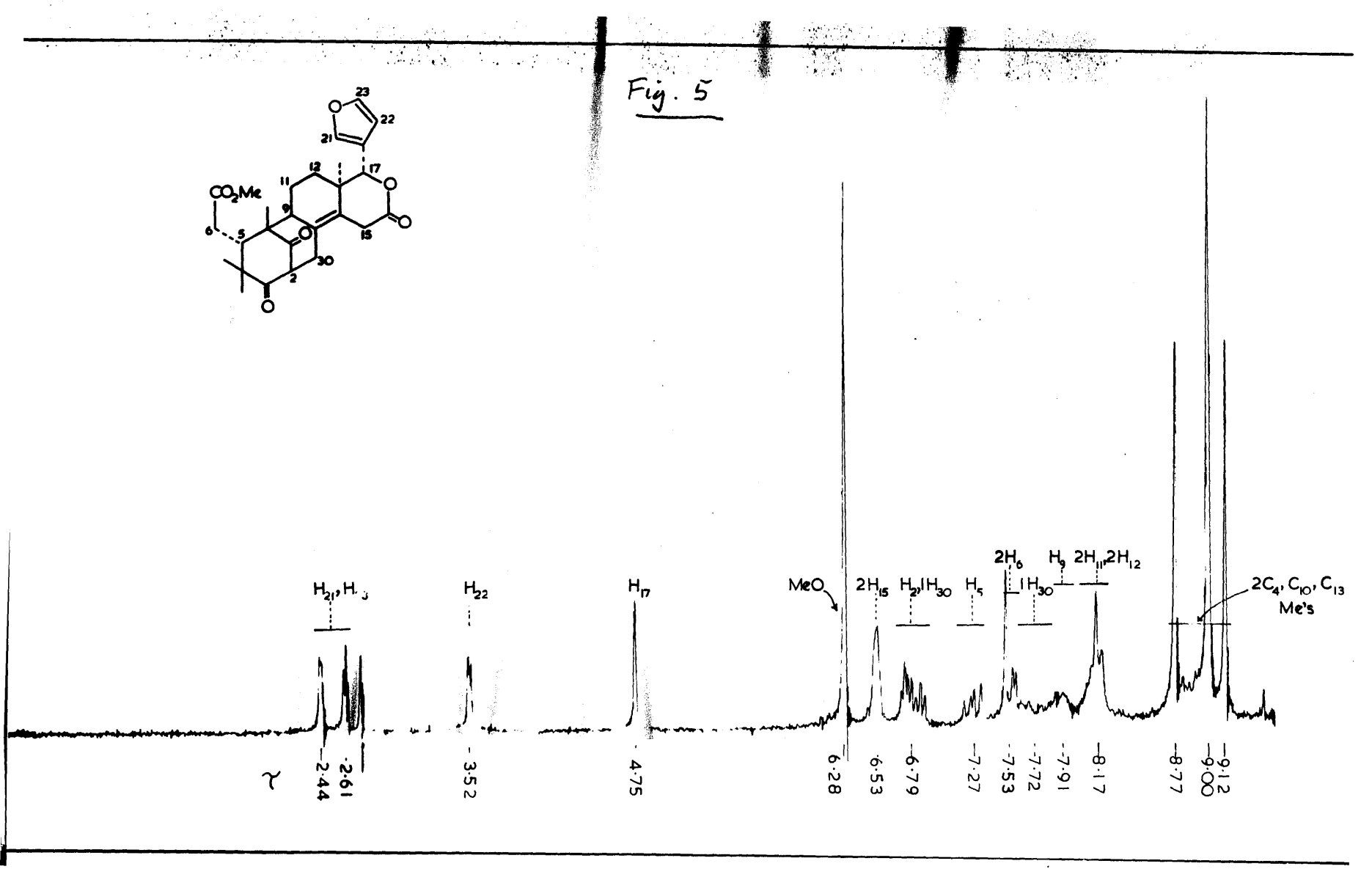


Fig. 5


23
22
21
17
12
11
9
CO2Me
6
5
15
30
2
O
H21, H23
H22
H17
MeO
2H15
H2, 1H30
H5
2H6
1H30
H9
2H11, 2H12
2C4, C10, C13
Me's
τ
2·44
2·61
3·52
4·75
6·28
6·53
6·79
7·27
7·53
7·72
7·91
8·17
8·77
9·00
9·12

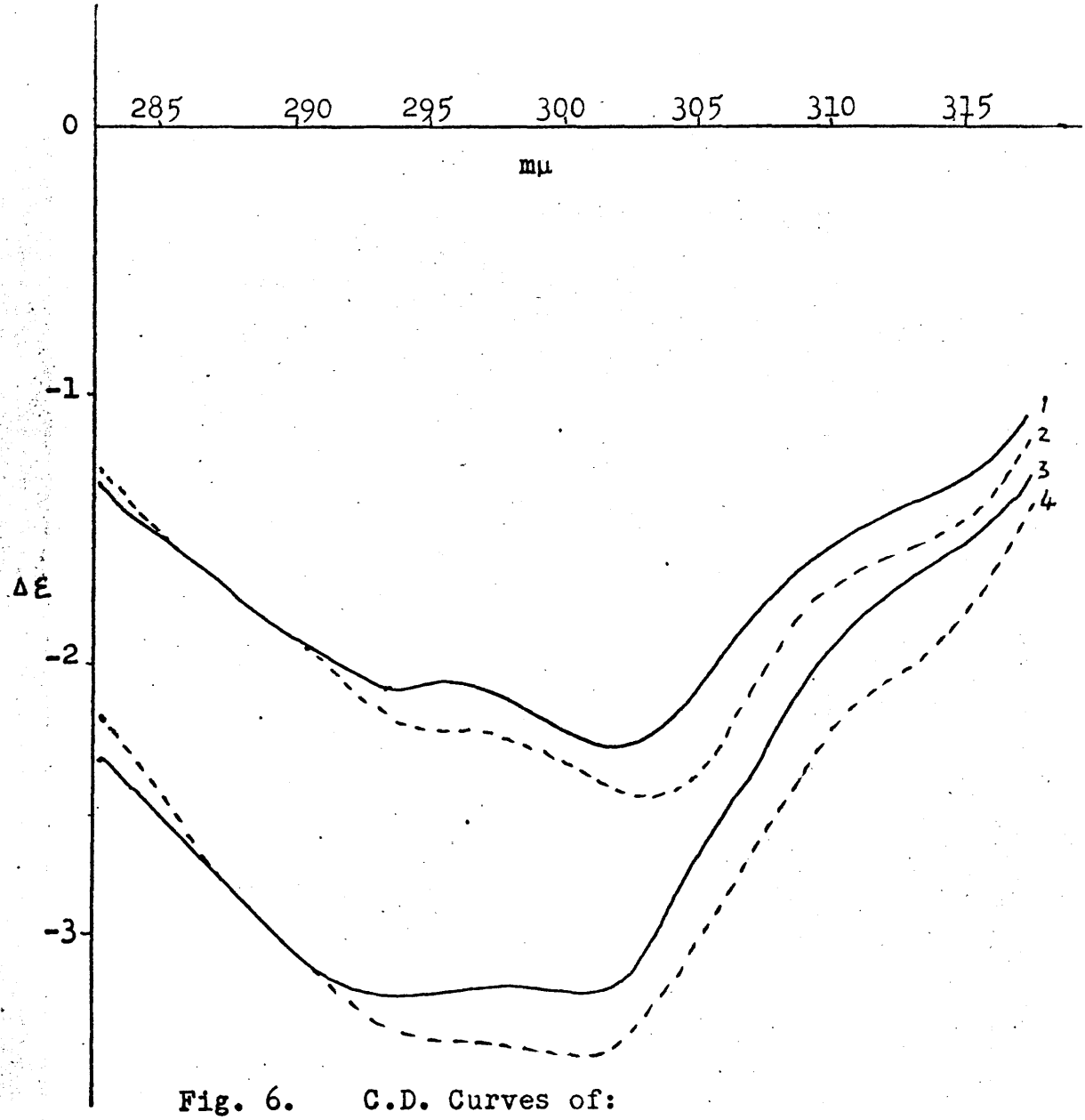
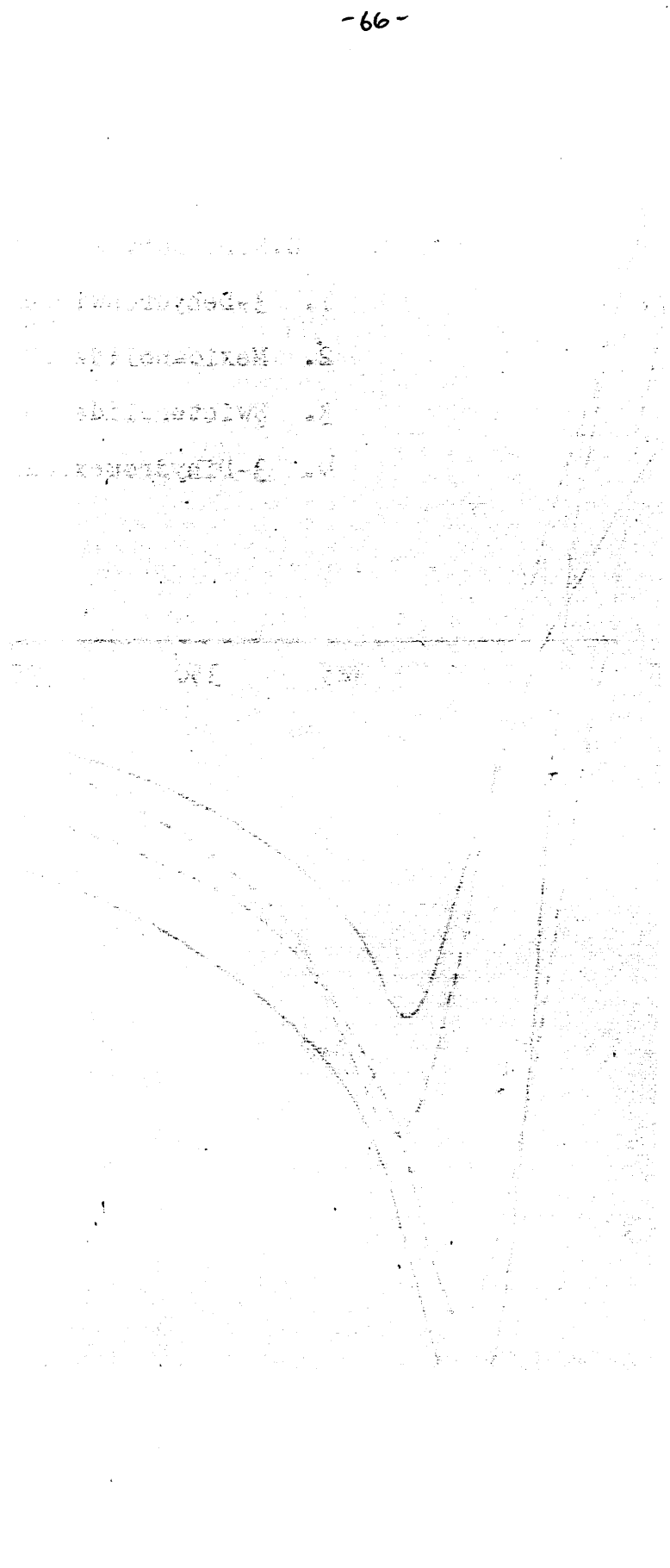


Fig. 6. C.D. Curves of:

1. 3-Dehydroswietenolide (B4)
2. Mexicanolide (B6)
3. Swietenolide (B1)
4. 3-Dihydromexicanolide (B16).



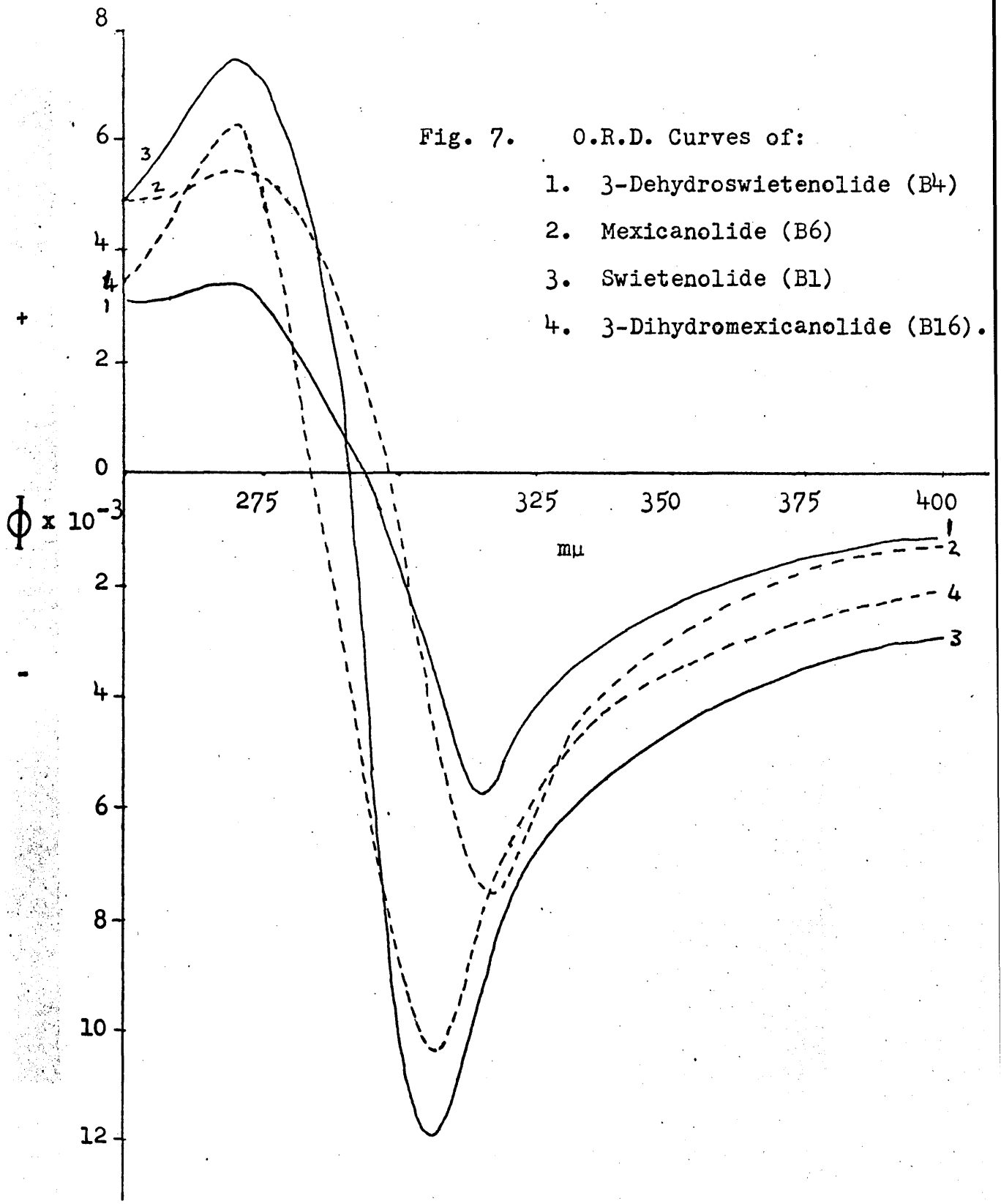
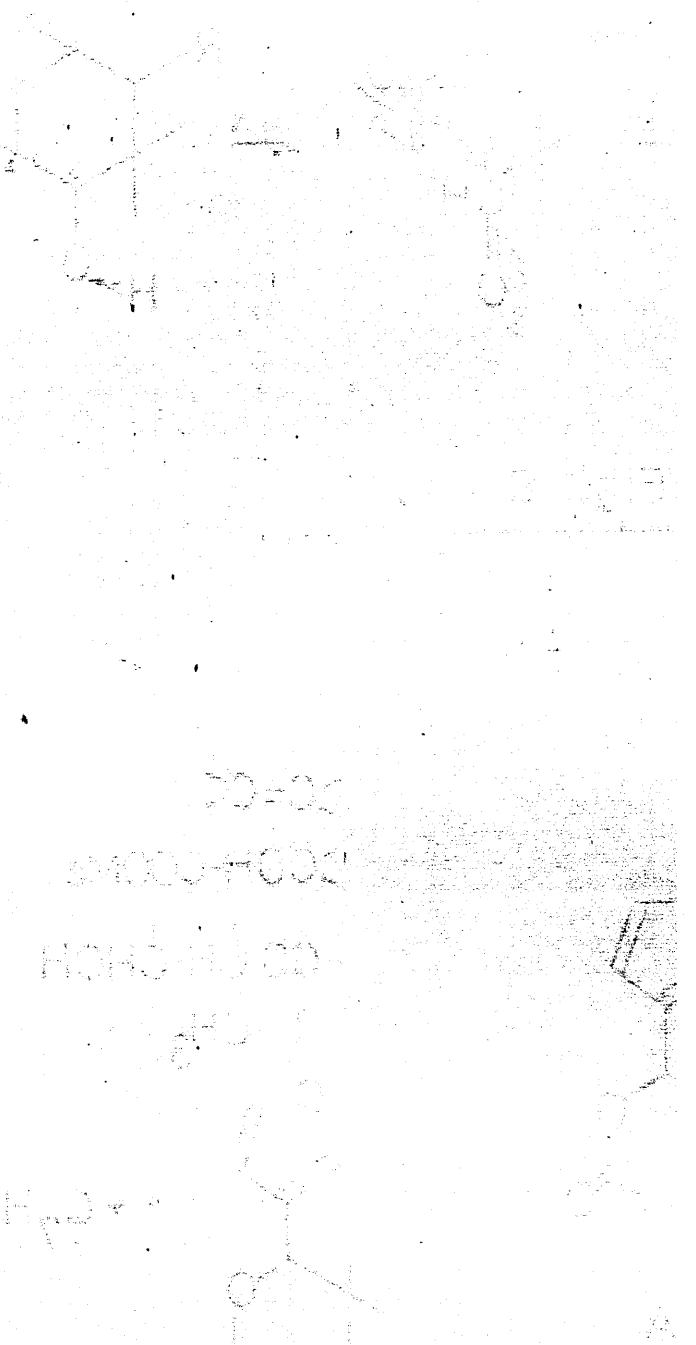


Fig. 7. O.R.D. Curves of:

1. 3-Dehydroswietenolide (B4)
2. Mexicanolide (B6)
3. Swietenolide (B1)
4. 3-Dihydromexicanolide (B16).



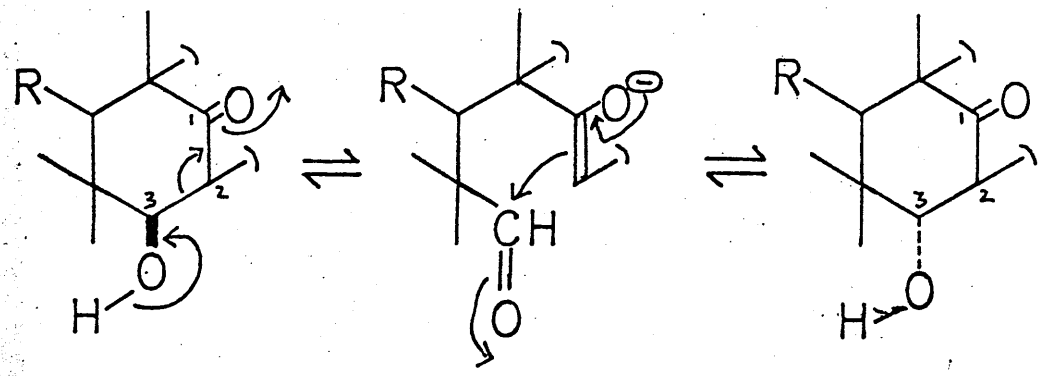
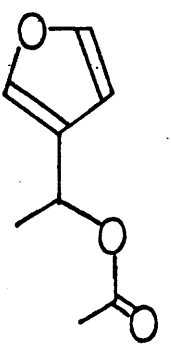


Fig. 8



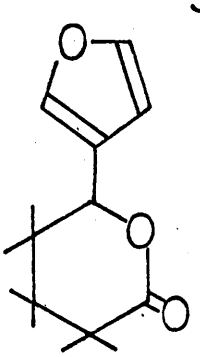
A

>C=C<

>COH-COOMe

-CO-CH-CHOH

3 -CH_3



+ C_7H_{14}

B

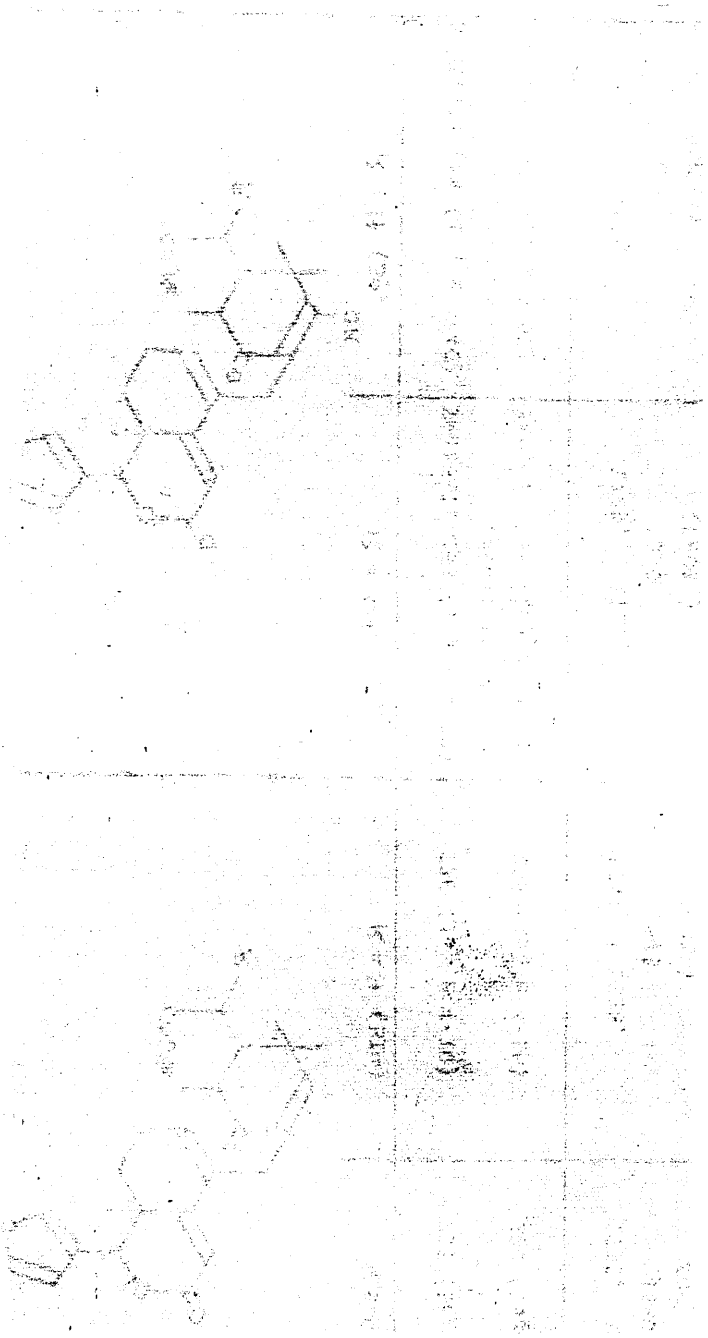
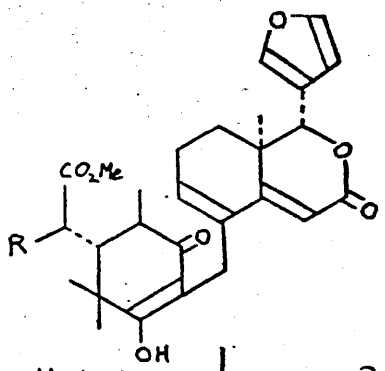
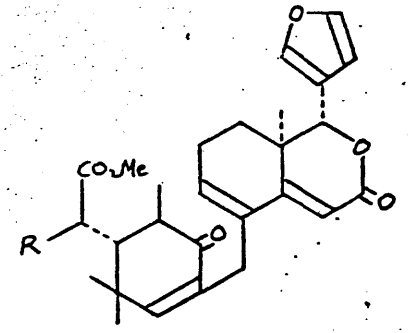


TABLE 1.



R = H (B9)

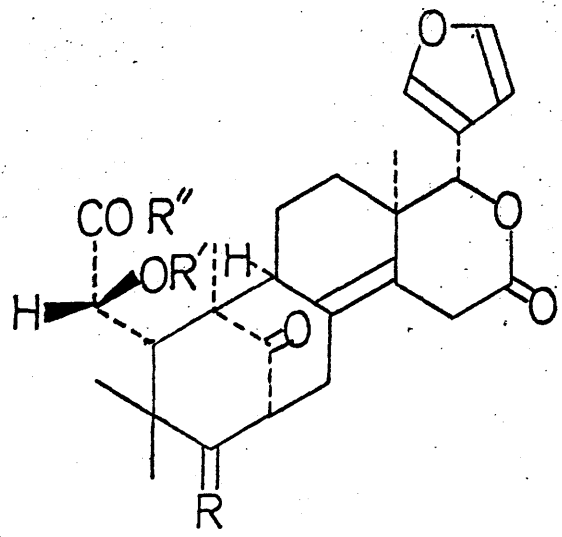
R = OH (B7)



R = H (B14)

R = OAc (B13)

	R = H (B9)	R = OH (B7)	R = H (B14)	R = OAc (B13)
U.V. $\lambda_{max.}$ (mμ) in EtOH	Neutral: 264 (log ε 4·40) (shoulder at 285) Basic: 287 (log ε 4·57)	Neutral: 265 (log ε 4·17) (shoulder at 285) Basic: 287 (log ε 4·53)	236 (log ε 4·10) 278 (log ε 4·16)	235 (log ε 4·10) 280 (log ε 4·19)
I.R. $\nu_{max.}$ ($cm.^{-1}$)	1734, 1710 1626 ($CHCl_3$)	1729, 1711, 1630 ($CHCl_3$)	1741, 1728, 1678 (CCl_4)	1755, 1729, 1680 (CCl_4)
N.M.R. τ in $CDCl_3$	4·02 (s, H-15) 4·09 (m, H-9) 8·74 (d, C-19 Me)	3·96 (s, H-15) 3·97 (m, H-9) 8·80 (d, C-19 Me)	3·73 (s, H-3) 3·89 (m, H-9) 4·21 (s, H-15)	4·08 (s, H-3) 3·93 (m, H-9) 4·37 (s, H-15)



B1 R=βOH,H; R′=H; R″=Me

B2 R=βOAc,H; R′=Ac; R″=Me

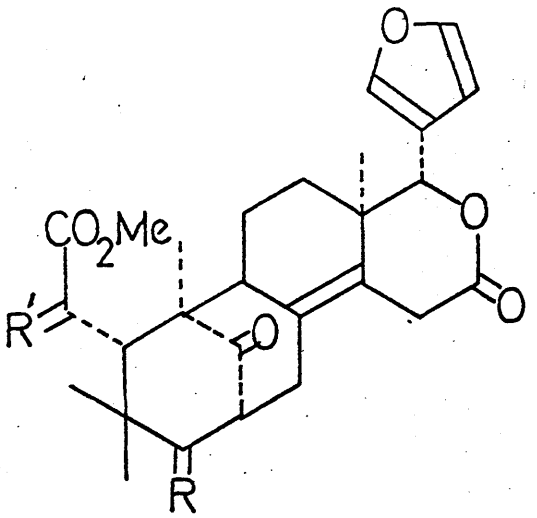
B4 R=O; R=H; R=Me

B21 R=αOH,H; R′=R″=H

B22 R=αOH,H; R′=H; R″=Me

B24 R=αOAc,H; R′=Ac; R″=Me

B31 R=O; R′=SO_2CH_3; R″=Me

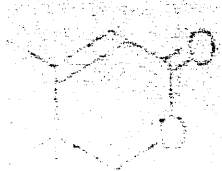


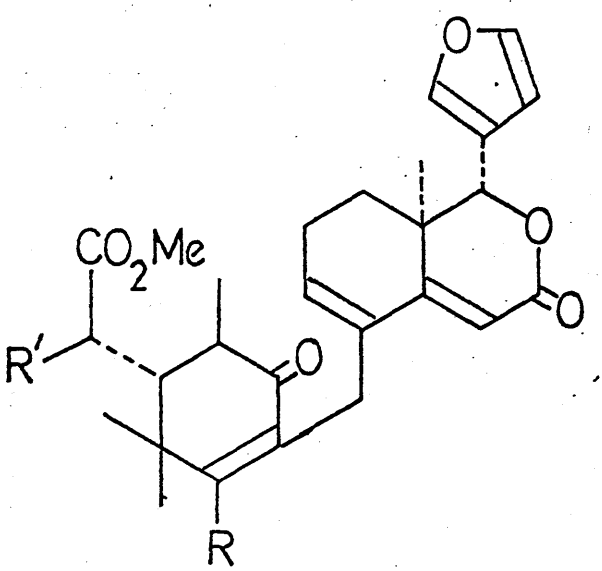
B 3 R= βOAc,H ; R'=H$_2$

B 5 R= R'=O

B6 R=O ; R'=H$_2$

B16 R= βOH,H ; R'=H$_2$





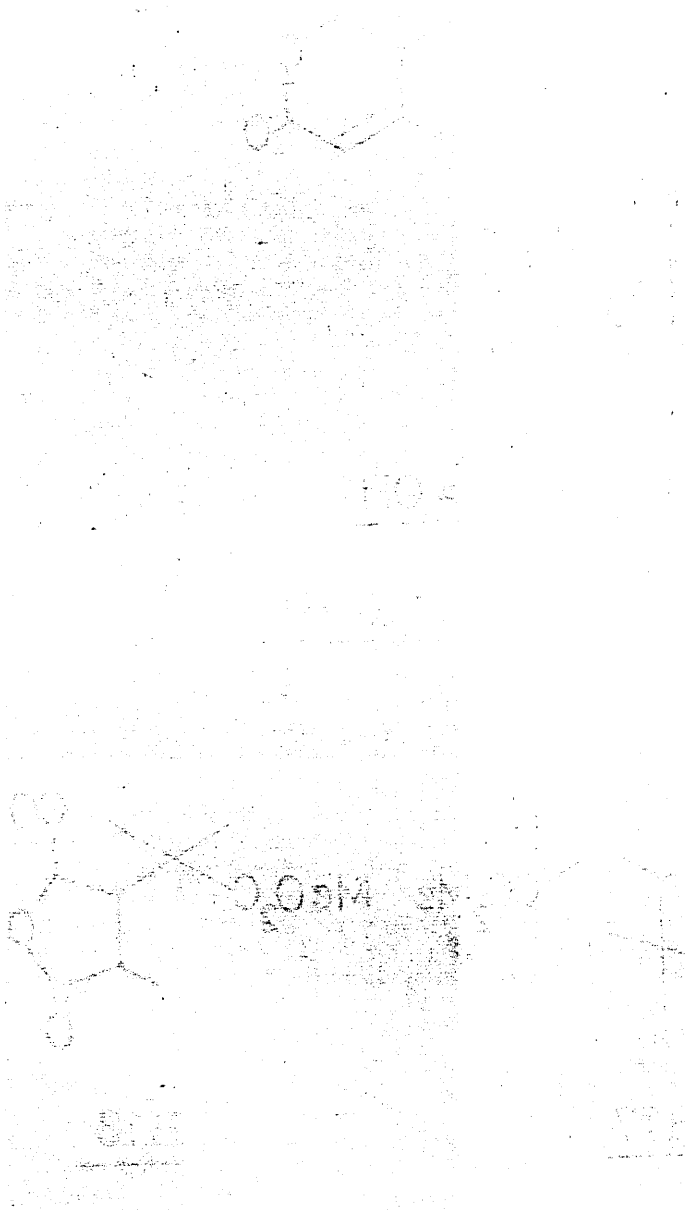
B7 R = R' = OH

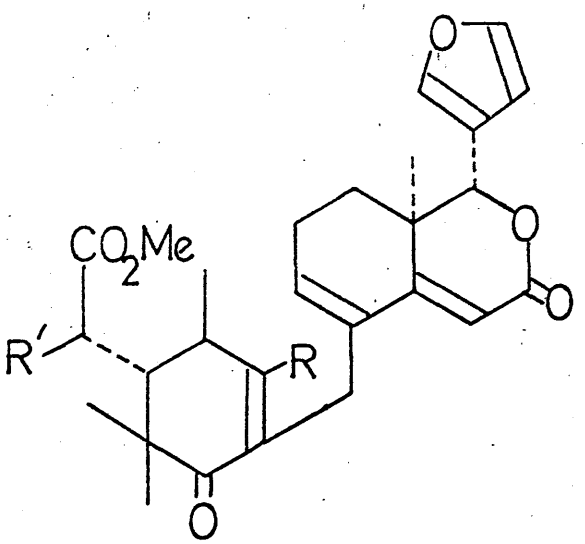
B9 R = OH ; R' = H

B13 R = H ; R' = OAc

B14 R = R' = H

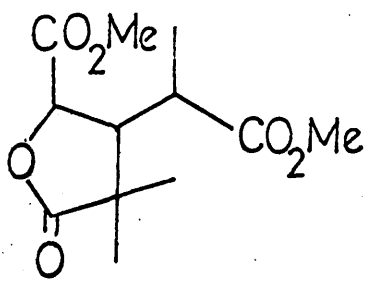
B15 R = H ; R' = OH



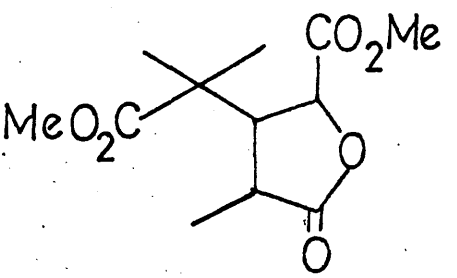


B8 R = R′ = OH

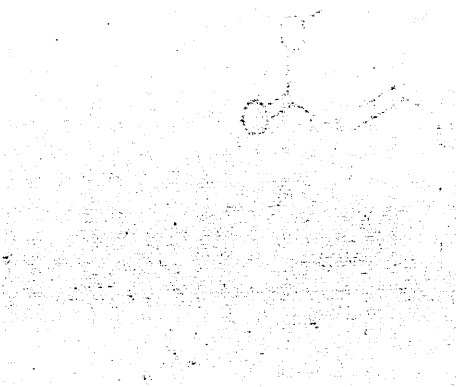
B10 R = OH ; R′ = H

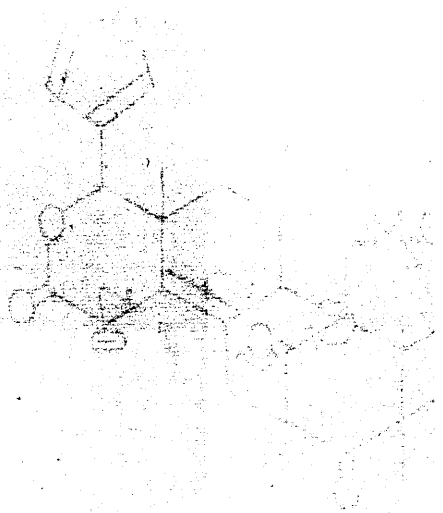


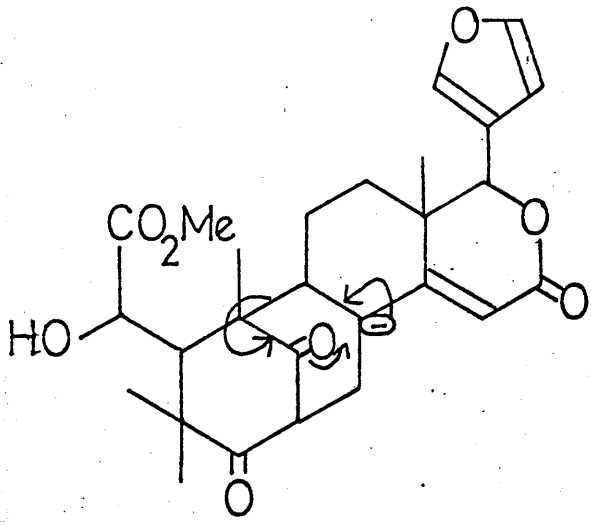
B17



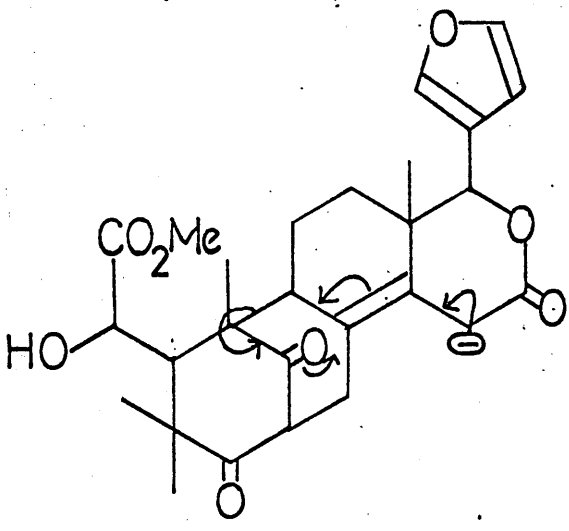
B18



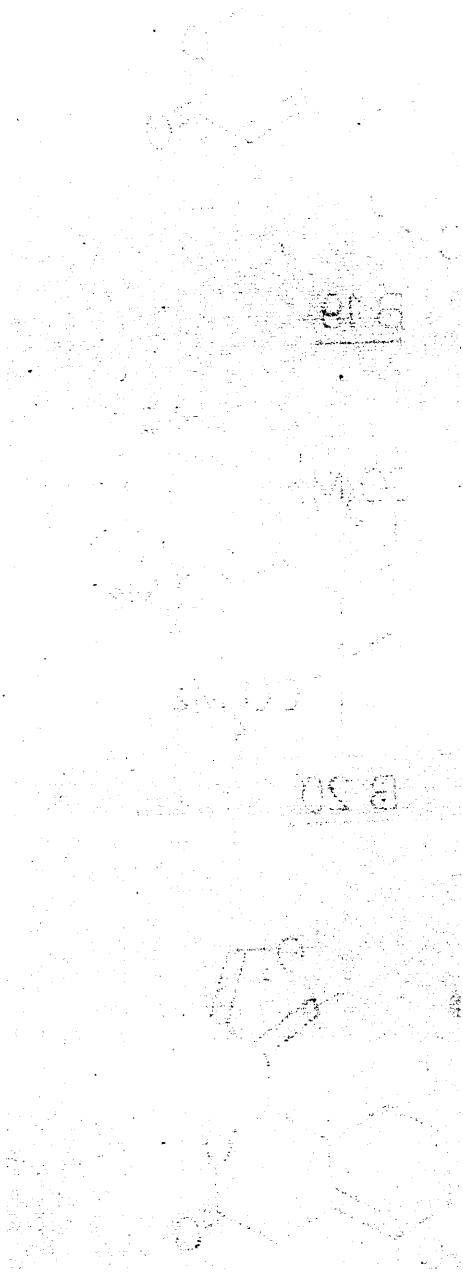


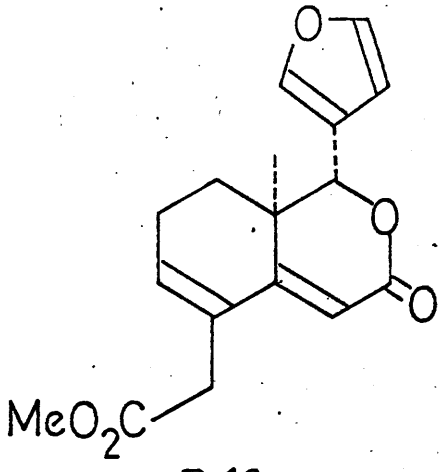


B11

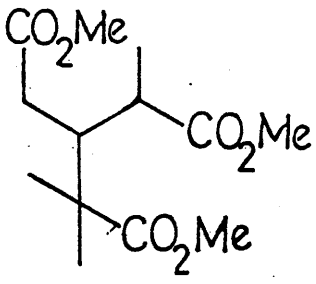


B12

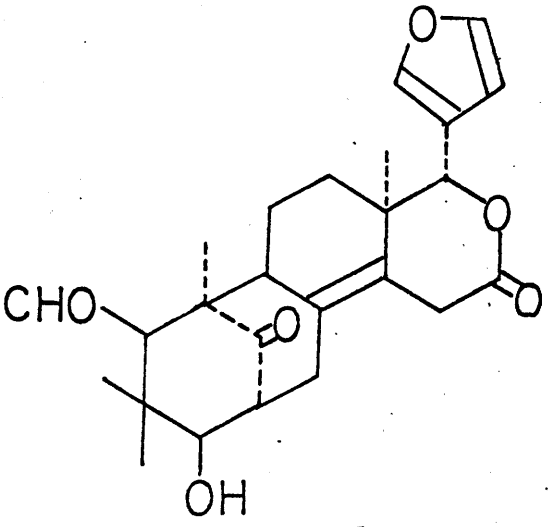




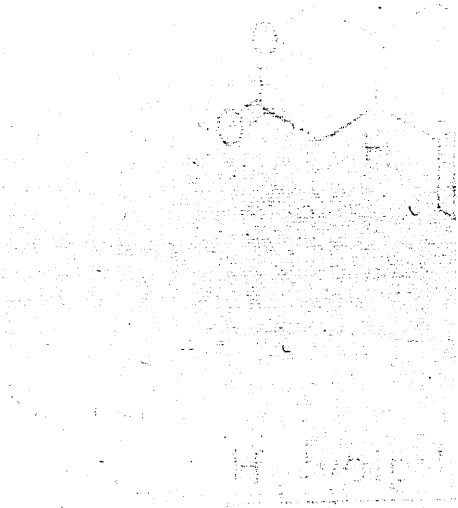
B 19

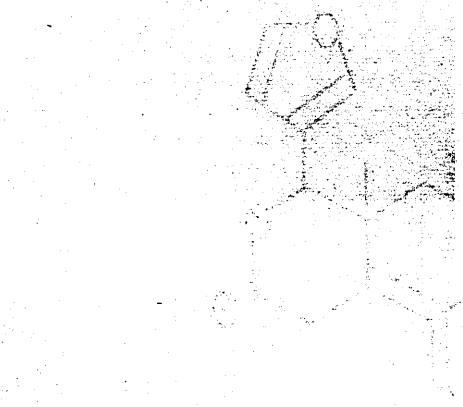


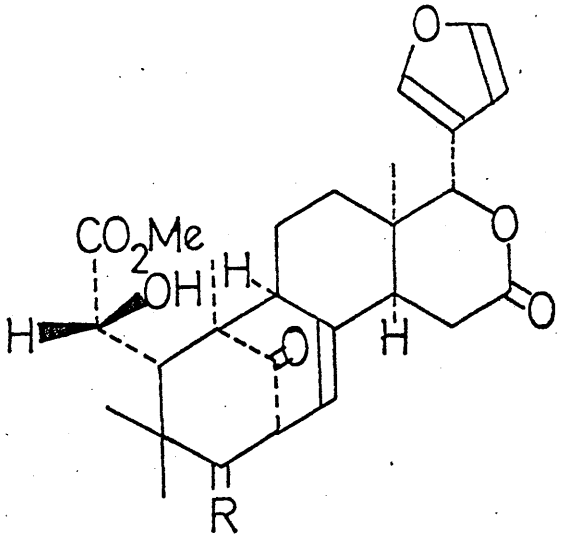
B 20



B25

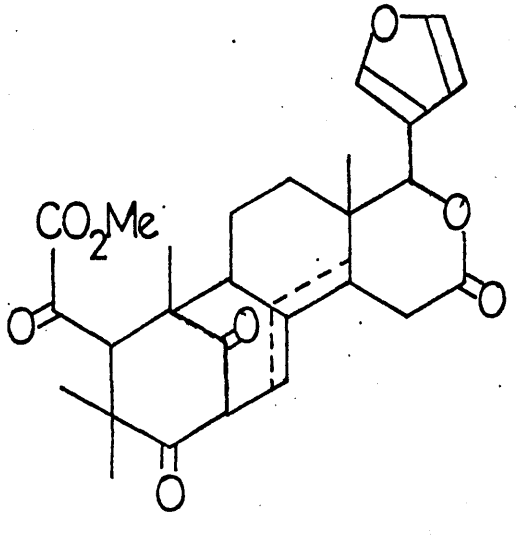

H



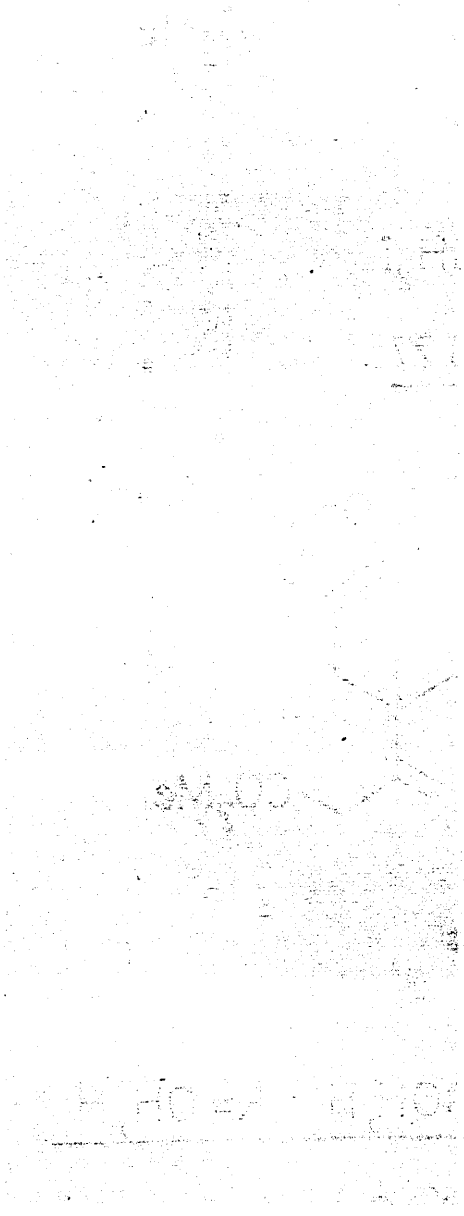


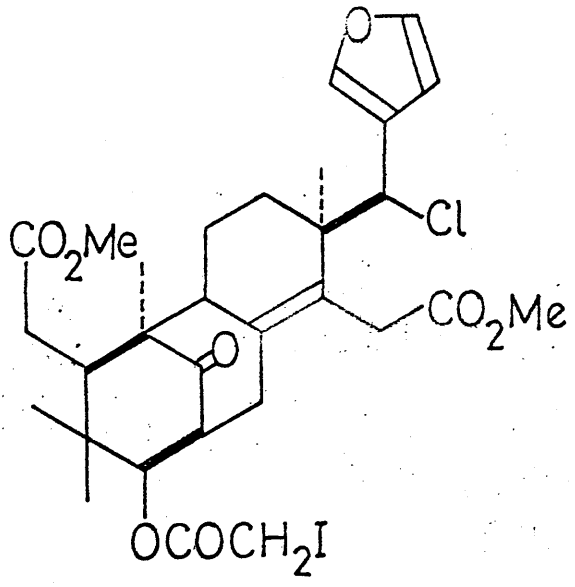
B23 R=βOTigloyl, H

B32 R=αOH, H

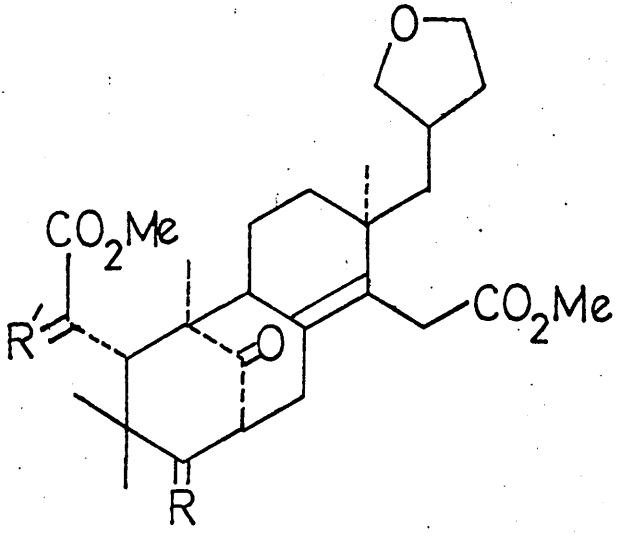


B26





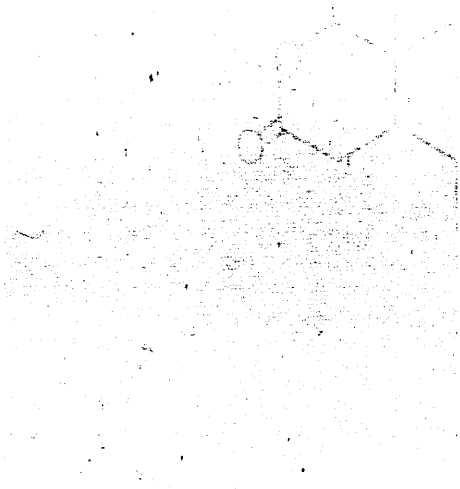
B 27

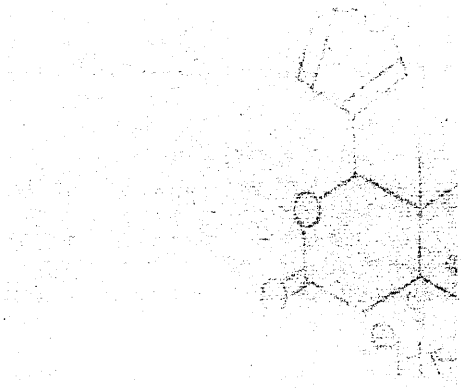


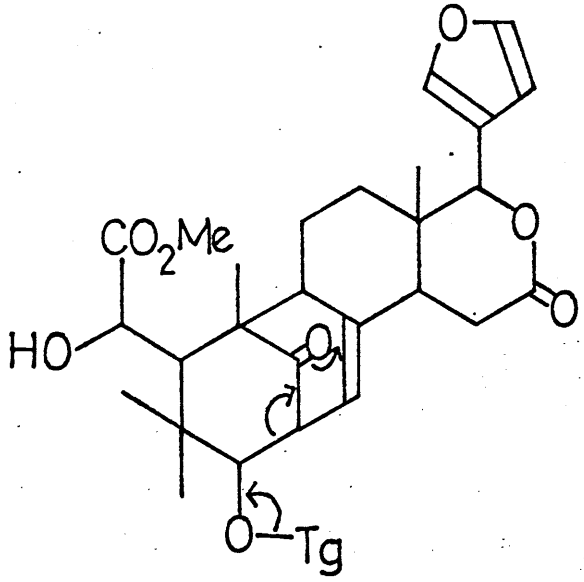
B 28 R= βOH, H ; R'= OH, H

B 29 R= R'= O

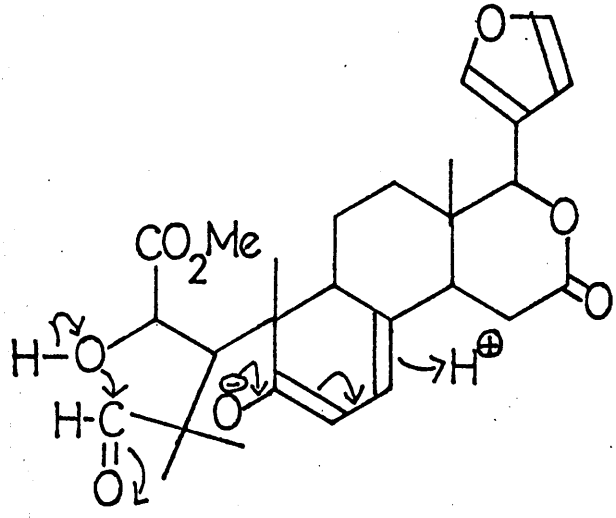
B 30 R= O ; R'= H_2



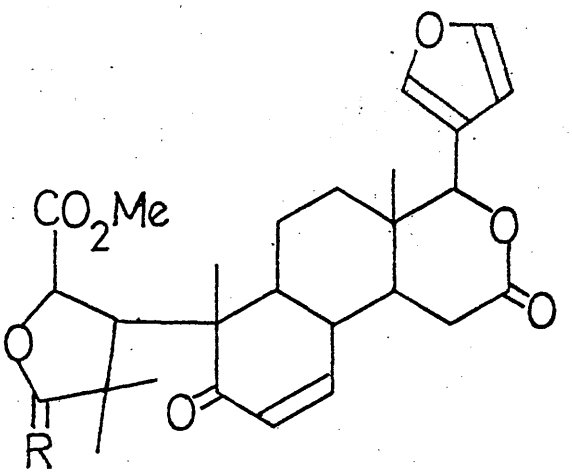




B34



B35



B33 R=OH,H

B36 R=O

PART IB

6-HYDROXY AND 6-ACETOXY METHYL ANGOLENSATE

INTRODUCTION

Two tetranortriterpenoids from the heartwood of Khaya grandifoliola, a West African timber of the family Meliaceae, are shown to be 6-hydroxy methyl angolensate and 6-acetoxy methyl angolensate by analysis of their N.M.R. single and double resonance spectra.

THE CONSTITUTION OF 6-HYDROXY AND 6-ACETOXY METHYL ANGOLENSATE

Methyl angolensate (C1) has been isolated from various members[1] of the family Meliaceae, notably Guarea thompsonii, Entandrophragma angolense, E. utile and Cedrela odorata, and its structure has been determined by two groups[2,3,4]. From the heartwood of Khaya grandifoliola we have obtained, inter alia, an alcohol (C2), $C_{27}H_{34}O_8$, m.p. 235-238°, $[\alpha]_D$ -85° and an acetate (C3), $C_{29}H_{36}O_9$, m.p. 172-174°, $[\alpha]_D$ -82°, which on the basis of spectroscopic evidence we have identified[5] as 6-hydroxy methyl angolensate and its acetate 6-acetoxy methyl angolensate.

These two compounds together with methyl angolensate and andirobin[6] (C4) represent to date the only known modified triterpenes exhibiting a cleaved ring B which have not undergone subsequent cyclisation. This class represents an intermediate stage in the biogenesis of swietenolide[7] (C5) and the other bicyclononanolides and in turn arises biogenetically from compounds with the carbon skeleton of gedunin[8] (C6) and khivorin[9,10] (C7). Interrelation of gedunin, methyl angolensate and andirobin via

a common transformation product has been reported[11] recently and section II of this thesis describes attempts to convert ring B-seco-triterpenoids to bicyclononanolides. It is possible that 6-hydroxy methyl angolensate (C2) could be converted directly <u>in vivo</u> into swietenolide (C5) along a pathway similar to those shown in Fig. 1.

The NMR spectra at 100 MHz of methyl angolensate (C1) (Fig. 2), 6-hydroxy methyl angolensate (C2) (Fig. 3) and 6-acetoxy methyl angolensate (C3) (Fig. 4) immediately show several suggestive similarities. For clarity we shall discuss these spectra in terms of the configurations already expressed. Each compound shows signals characteristic of two α and one β furanic protons, a C-17 proton, two vinyl proton singlets at $\sim \tau$ 5, characteristic of an exocyclic methylene group, an AB quartet assignable to the isolated protons at C-15 and five three-proton singlets, attributable to one methyl ester and four tertiary methyls.

Assignments in the region between τ 6.3 and 8.0 can be made more readily in the spectra of the alcohol (C2) and the acetate (C3) than in the spectrum of methyl angolensate (C1) as would be expected upon removal of the complex multiplet arising from the geminal C-6 protons.

The alcohol (C2) (Fig. 3) loses upon exchange with D_2O a broad singlet at τ 6.87 which can accordingly be attributed to the alcoholic -O<u>H</u> proton. The two C-15 protons form an AB quartet centred at τ 7.08, 7.44 (J = 18 Hz) and the C-5 proton appears as a slightly broadened singlet at τ 7.25, which sharpens on irradiation at τ 5.57 (H-6). There remains in the τ 6-8 region a clearly discernible ABX system arising from the three protons attached to C-1 and C-2. The H-1 (A) signal is a quartet centred at τ 6.42 whose couplings (by inspection) with the two protons at C-2 (B,X) (J = 5.5 and 3Hz) are supported by double irradiation experiments. Both C-2 protons form quartets, that centred at τ 6.89 (B) having J = 14 and 5,5Hz and the other centred at τ 7.63 (X) having J = 14 and 3Hz. Double irradiation in turn at A, B and X simplifies the other resonances in accordance with expectation, although complete decoupling of A when irradiating B (and the reverse) is not readily accomplished since $W^{\frac{1}{2}}$ for B (22Hz) is almost one half of $\Delta\delta_{AB}$ (47Hz). It is further possible to locate the C-13 methyl resonance at τ 8.55 since irradiation at this frequency sharpens the singlet at τ 4.45 (H-17) by removing the ^4J coupling between these two groups. The

unresolved region between τ 7.6 and 8.5 contains the signals from the five protons attached to C-9, C-11 and C-12.

The single and double resonance spectra of the acetate (C3) (Fig 4.) can be interpreted similarly. The C-6 acetate methyl protons ($\underline{CH_3}$-CO-O-) appear as a sharp singlet at τ 7.82 and the C-6 proton, which is shifted ~1 τ downfield as compared with its position in the alcohol (C2) as expected, is a slightly broadened singlet at τ 4.56, sharpening on irradiation at τ 7.02 (H-5). As before, the resonances of the two C-15 protons, an AB quartet, are centred at τ 7.08, 7.44 (J = 18Hz) and those of the C-1 and C-2 protons, an ABX system, appear at τ 6.51 (H-1, A), 6.94 (H-2, B) and 7.64 (H-2, X) with J_{AB} = 5.5, J_{AX} = 3 and J_{BX} = 14Hz (by inspection). These assignments are supported by double irradiation (see Fig. 4).

The information available from these studies does not allow decisions to be made concerning the configurations at C-6 and C-1 and the latter indeed remains undefined in the case of methyl angolensate.

EXPERIMENTAL

For general experimental see Part IA.

Extraction of the heartwood of Khaya grandifoliola.

The wood used was obtained from the Forestry Division, Kumasi, Ghana, through the good offices of Mr. A.G. Kenyon, Tropical Products Institute, London, to whom we express our gratitude

The powdered heartwood (7 kg.) was continuously extracted with ethyl acetate in a Sohxlet extractor. The resulting extract was evaporated to 1 l, mixed with chloroform (2 l.) and filtered from insoluble material. After removal of solvent from the filtrate the residue was chromatographed on alumina [Spence, Grade H, deactivated with 5% of acetic acid : water (1:9)]. The material obtained (6.6 g.) was further purified by preparative TLC on silica gel. Subsequent crystallisations yielded, inter alia, 6-acetoxy methyl angolensate (C3) (180 mg.), needles from methanol/water, m.p. 172-174°, $[\alpha]_D$ -82° (c, 1.60), $\nu_{max.}$ (CCl_4) 1751 (δ-lactone, α-acetoxy methyl ester, acetate) and 1725 (cyclohexanone) $cm.^{-1}$ (Found C, 65.64; H, 7.03. $C_{29}H_{36}O_9$ requires: C, 65.89; H, 6.87%) and

6-hydroxy methyl angolensate (C2) (1.62 g.), needles from methanol/water, m.p. 235-238°, $[\alpha]_D$ -85° (c, 0.95), $\nu_{max.}$ (CCl_4) 3600 (free hydroxyl), 3510 (bonded hydroxyl) 1751 (δ-lactone), 1724 (methyl ester) and 1716 (cyclohexanone) $cm.^{-1}$ (Found: C, 66.51; H, 6.92. $C_{27}H_{34}O_8$ requires: C, 66.65; H, 7.04%).

Alkaline hydrolysis of 6-acetoxy methyl angolensate (C3)

It was found convenient to separate 6-acetoxy methyl angolensate (C3) from the methyl angolensate (C1) also present in the extract by hydrolysis of a mixture of the two followed by separation and reacetylation of 6-hydroxy methyl angolensate (C2). A mixture of methyl angolensate and 6-acetoxy methyl angolensate (2.1 g.) was dissolved in a 2% solution of potassium hydroxide in methanol:water (99:1) (50 ml.) and left for 3 hr. at 20°. Water (50 ml.) was added, the solution acidified with 6N hydrochloric acid and extracted with chloroform. Separation of the products by preparative TLC yielded methyl angolensate (1.2 g.) and 6-hydroxy methyl angolensate (600 mg.).

Acetylation of 6-hydroxy methyl angolensate (C2).

6-Hydroxy methyl angolensate (C2) (100 mg.) was dissolved in pyridine (5 ml.) and acetic anhydride (5 ml.) and the solution left at 60° for 18 hr. Water (120 ml.) was added and the solution extracted with chloroform. The product was purified by preparative TLC to afford 6-acetoxy methyl angolensate (68 mg.). This was identical with the acetate obtained from the extract as above by column and TLC, as judged by m.p., mixed m.p., NMR and IR.

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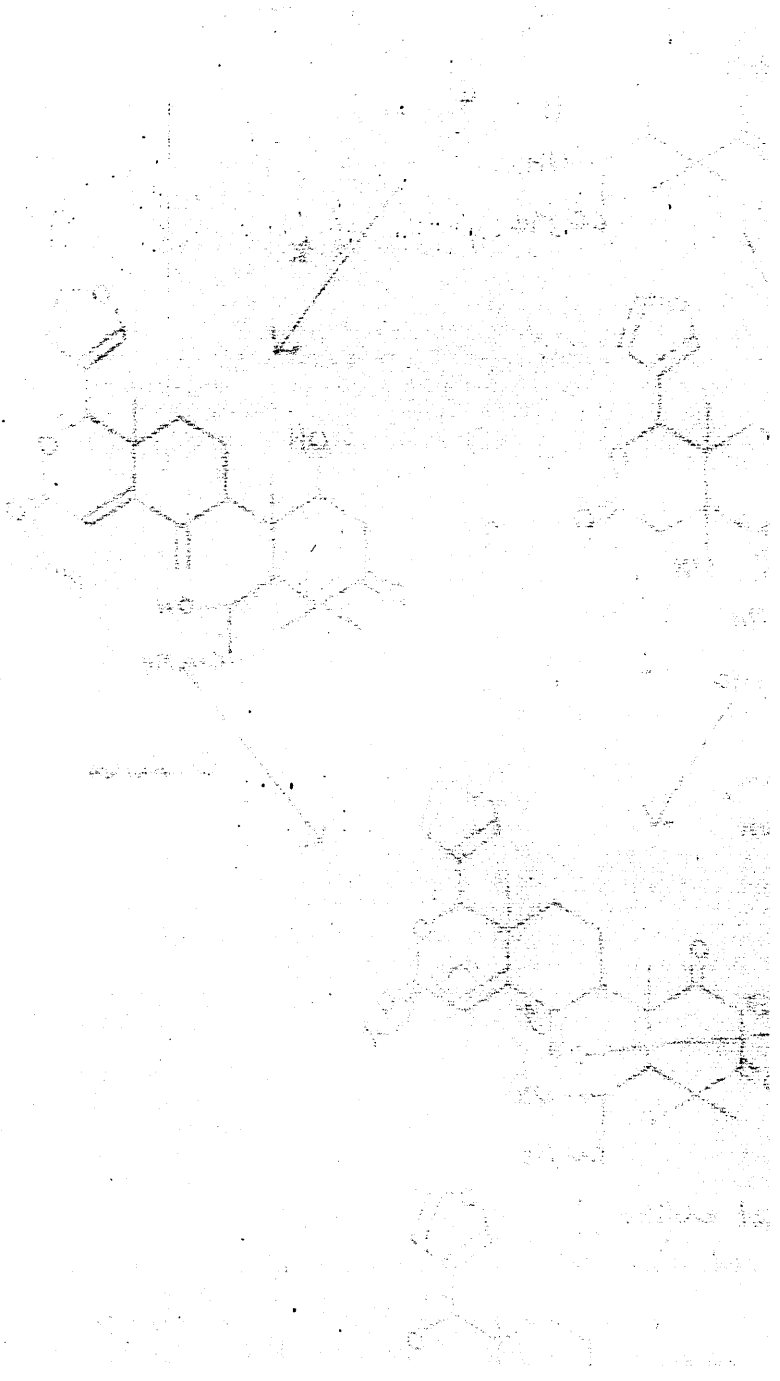


Fig. 1

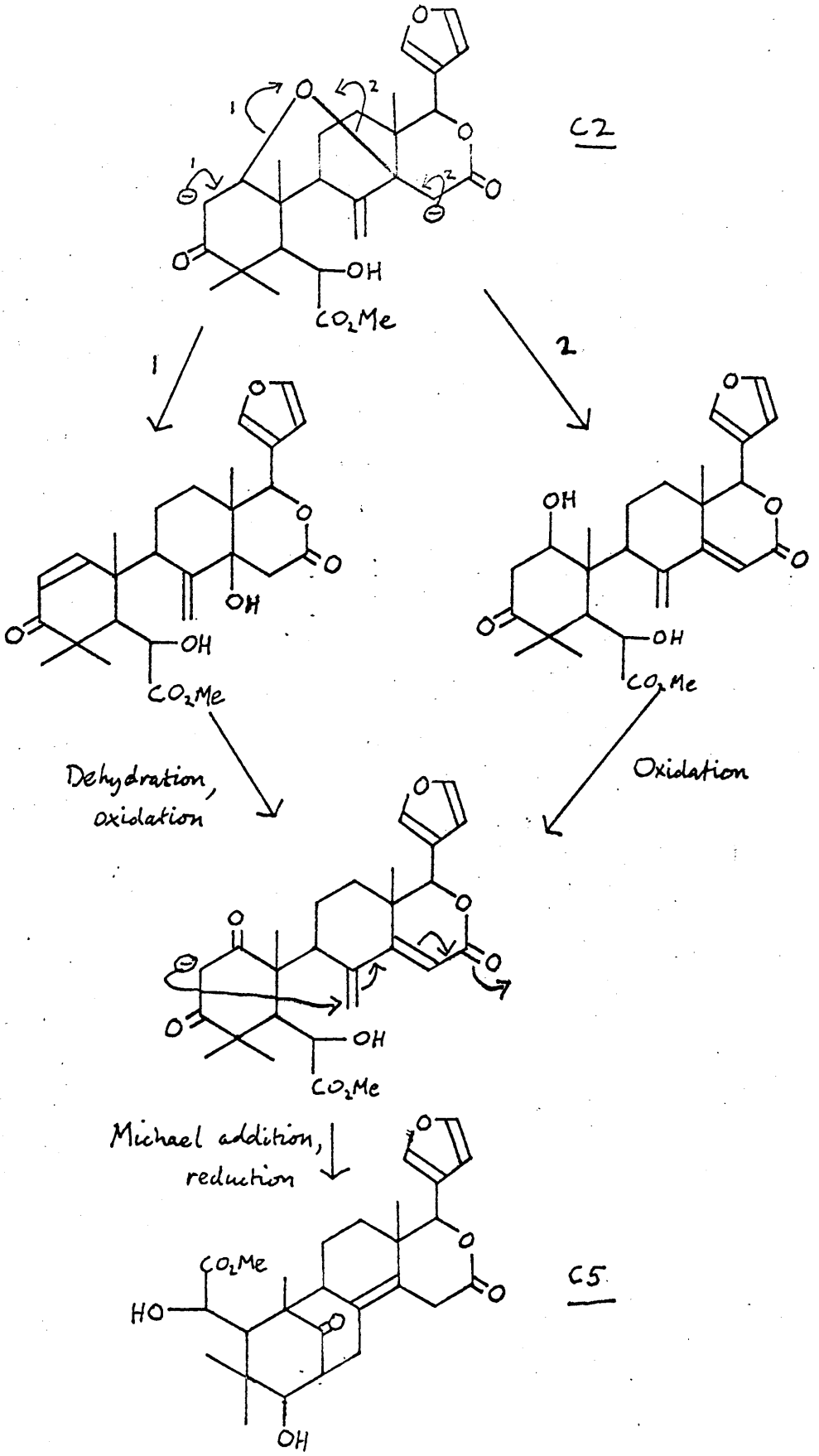
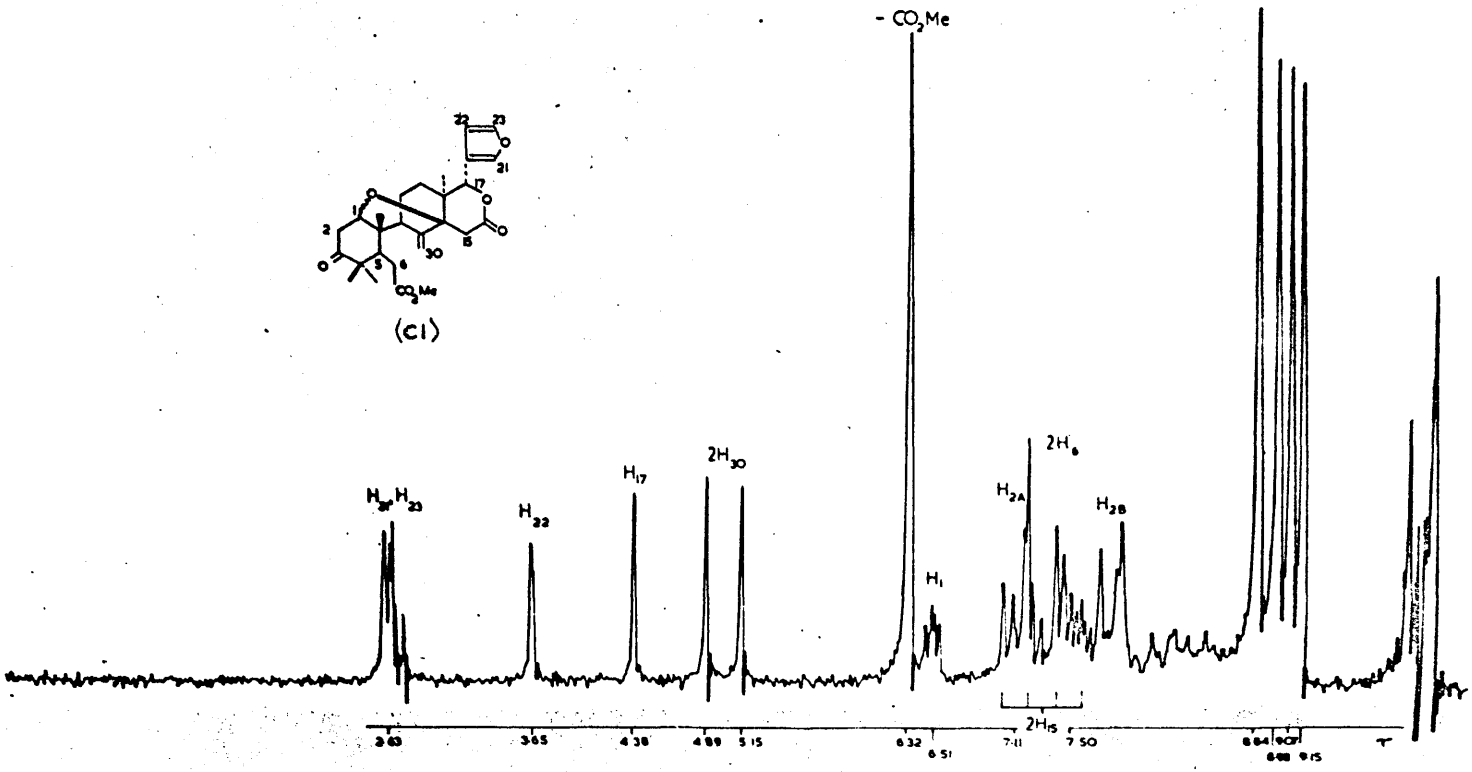

C2
1
2
Dehydration, oxidation
Oxidation
Michael addition, reduction
C5

Fig. 2.


- CO₂Me
H₂₃
H₂₂
H₁₇
2H₃₀
H₁
H₂A
2H₆
H₂B
2H₁₅
2·63
3·65
4·38
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5·15
6·32
6·51
7·11
7·50
8·64
8·88
9·15
τ

(C1)

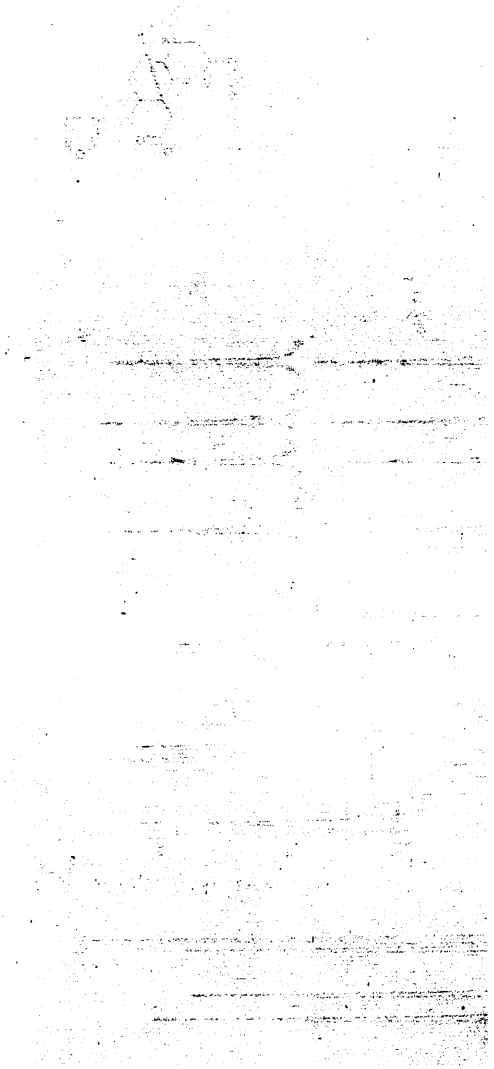
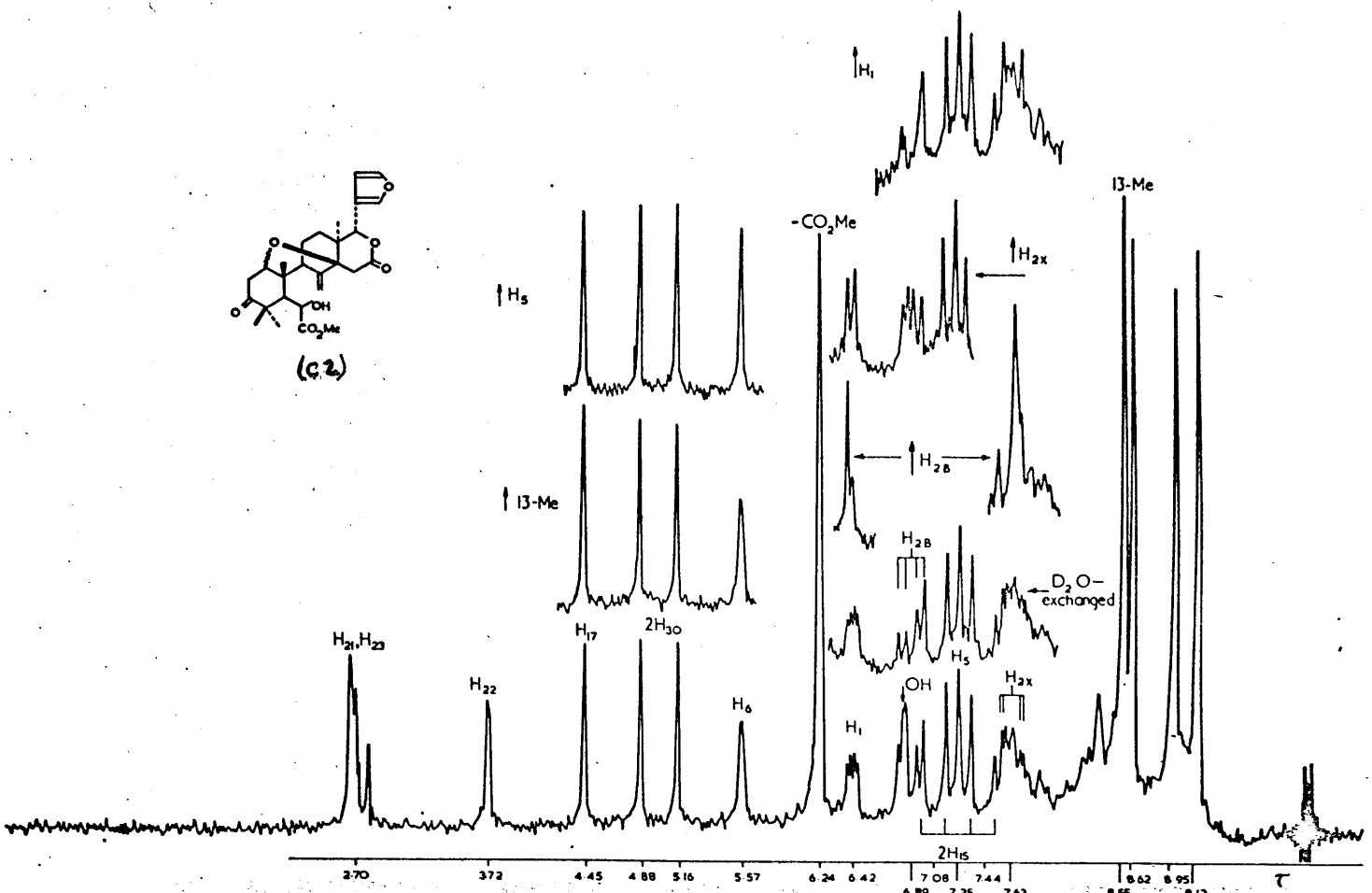


Fig. 3


H1
13-Me
-CO2Me
H2x
H5
H2B
13-Me
H2B
D2O-exchanged
H21,H23
H22
H17
2H30
H6
H1
OH
H5
H2x
2H15
2·70
3·72
4·45
4·88
5·16
5·57
6·24
6·42
7·08
6·89
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8·55
8·62
8·95
9·12
τ

(C2)

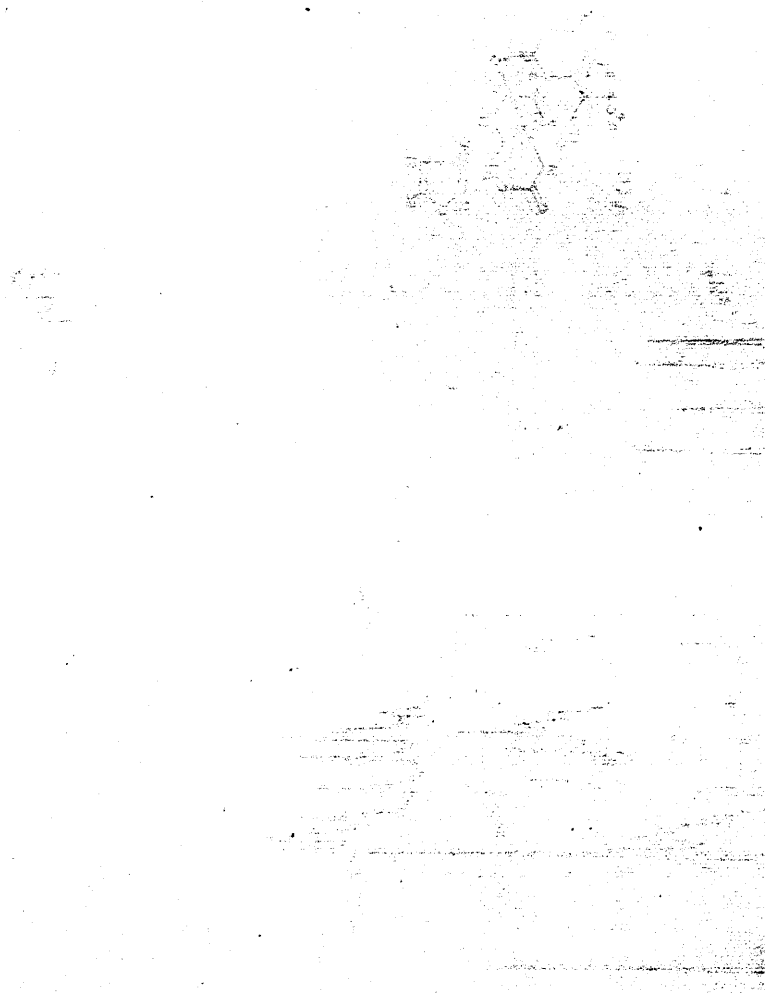
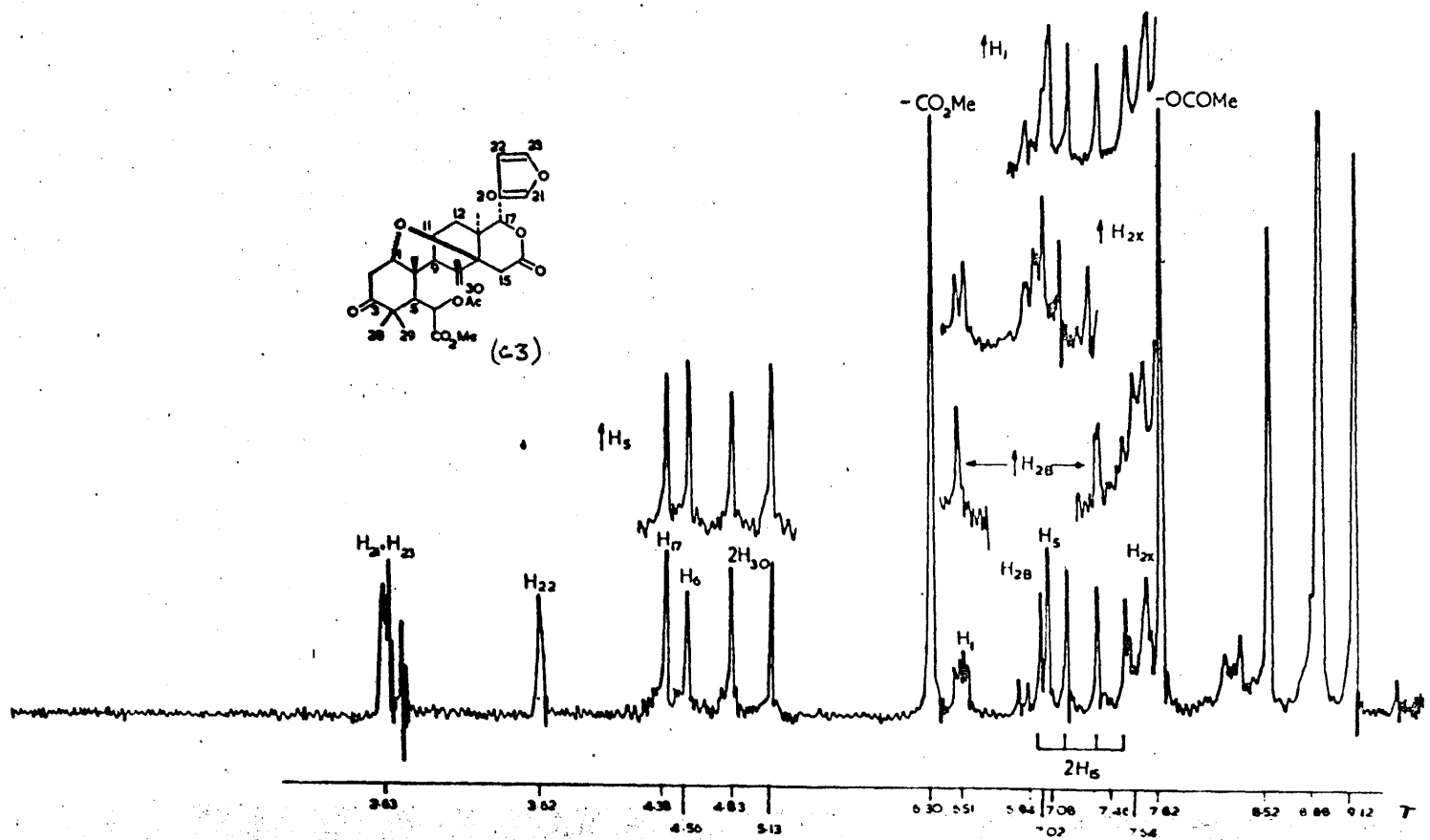
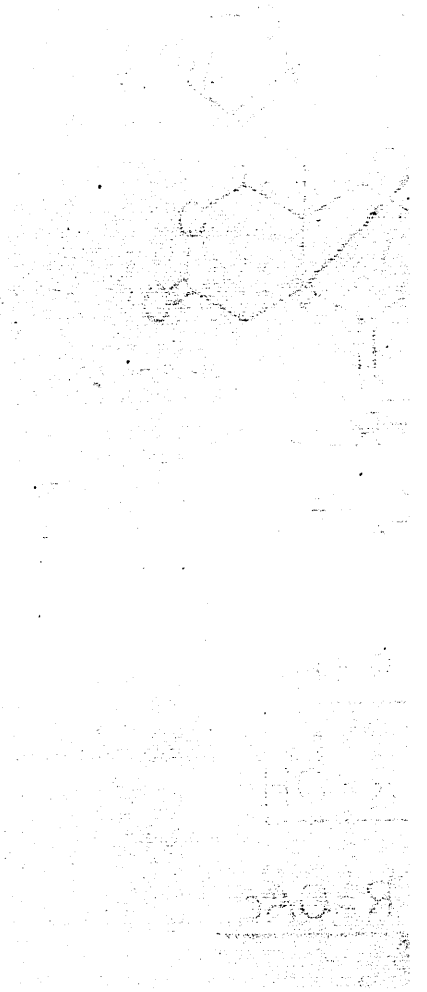
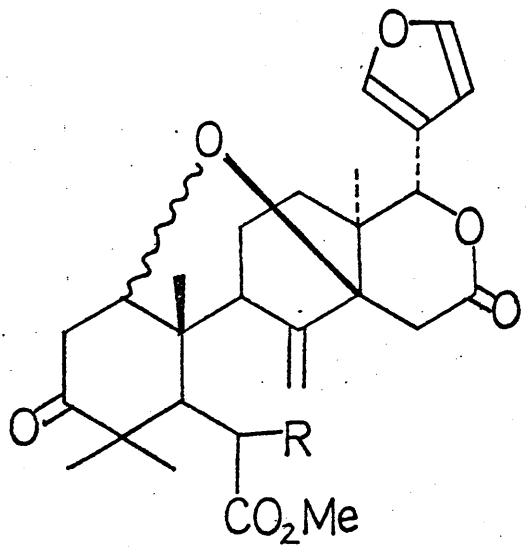


Fig. 4.


(c-3)
H1
-CO2Me
-OCOMe
H2x
H5
H28
H17
H6
2H30
H2a, H23
H22
2H5
3.63
3.62
4.38
4.83
4.56
5.13
6.30
5.51
5.84
7.08
7.02
7.46
7.56
7.82
8.52
8.86
9.12
τ

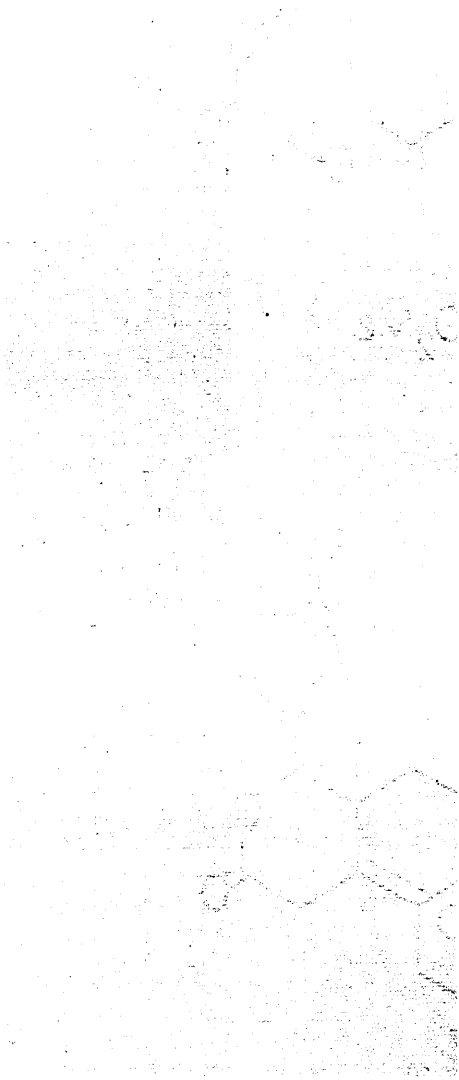


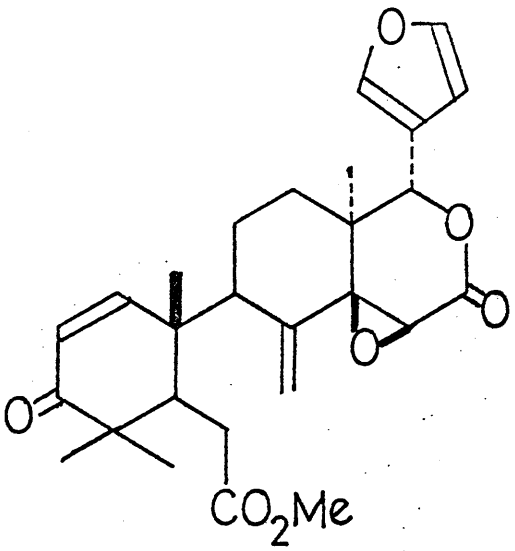


C1 R=H

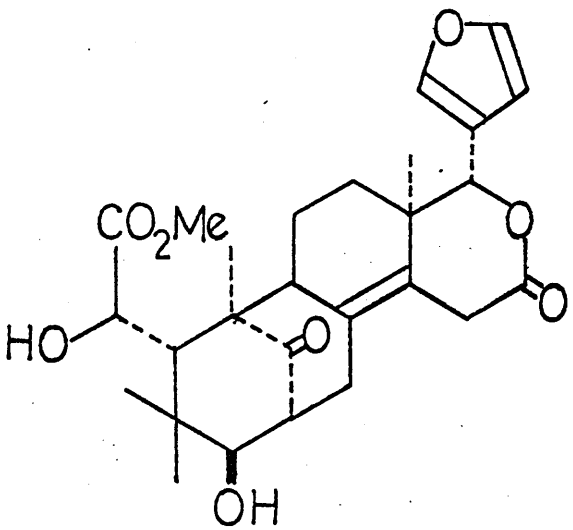
C2 R=OH

C3 R=OAc

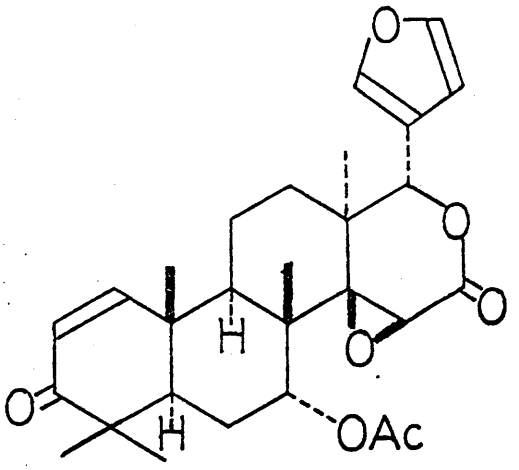




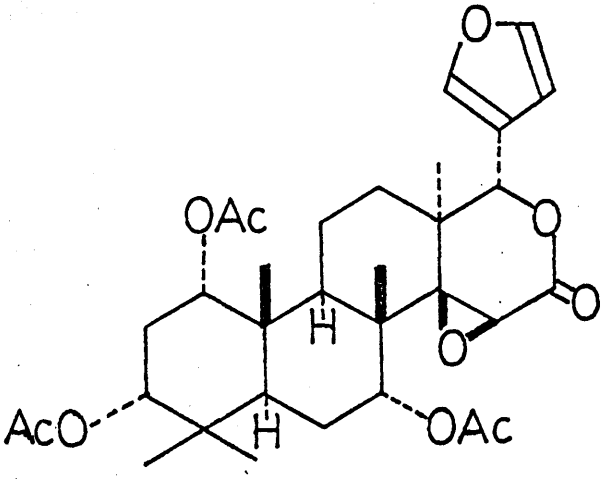
C 4



C 5



C6



C7

PART II

INTERCONVERSIONS IN THE TETRANORTRITERPENOID SERIES : ATTEMPTED FORMATION OF THE BICYCLO-NONANOLIDE RING SYSTEM.

INTRODUCTION

Attempts to achieve *in vitro* conversion of two naturally occurring tetranortriterpenoids into mexicanolide by formation of the C-2 —— C-30 bond, a key step in the proposed biogenesis of bicyclononanolides, are described.

ACKNOWLEDGEMENT

We gratefully acknowledge a generous gift of methyl angolensate from Dr. W.R. Chan, University of the West Indies.

ATTEMPTED CONVERSION OF METHYL ANGOLENSATE INTO MEXICANOLIDE

The first part of this thesis describes the structural elucidation of some bicyclononanolide and ring B-cleaved tetranortriterpenoids. The latter class is believed to be a biogenetic precursor of the former and a pathway of the kind illustrated in Fig. I, (p. 89) provides a rational biogenetic route to the bicyclononanolide skeleton. The key intermediate in this route is a compound of the type (D1), which by a Michael-type addition of C-2 to C-30 as shown could give rise to mexicanolide (D2) or its double bond isomer carapin[1,2] (D3). It is perhaps more likely that cyclisation would produce mexicanolide, since carapin may be isomerised to mexicanolide by chromatography on alumina.*

* Although this reaction has been reported,[2] work in this department has failed to confirm that this isomerisation occurs.[3]

It is interesting to note that of the known bicyclononanolides, which are presumably formed by a similar cyclisation process, swietenine (D4) alone has an isolated trisubstituted double bond between C-8 and C-30. No isomerisation of this double bond to the tetrasubstituted position C-8 — C-14 as in mexicanolide or alternatively to C-8 — C-9 has been observed. We have endeavoured to achieve in vitro conversion of methyl angolensate (D5), a ring B cleaved triterpenoid to the intermediate (D1) and hence to mexicanolide (D2) in an attempt to support the feasibility of the proposed biogenetic pathways.

Hydrolysis of methyl angolensate to angolensic acid (D6) and subsequent treatment with a solution of sodium isobutoxide in either toluene[4,5] or isobutanol[6] cleaves the ether linkage in the expected direction to afford the enone acid (D7) which is esterified by ethereal diazomethane to the methyl ester (D8). Care must be taken in handling the products (D7) and (D8) since in acidic media the ether ring readily re-forms. Dehydration of the tertiary hydroxyl group in (D8) to produce deoxyandirobin[7] (D9) is achieved by reflux with sodium methoxide in dry methanol.[8] Deoxyandirobin can also be obtained directly from methyl angolensate by treatment with a refluxing solution of sulphuric acid in methanol.[9]

Ring A in the αβ-unsaturated ketones (D8) and (D9) is similar to that of cedrolide (≡ 7-oxo-7-deacetoxy-gedunin[1]) (D10). Because of the limited quantities of methyl angolensate available to us, pilot reactions, followed spectroscopically, were first carried out on cedrolide. It was found that alkaline hydrogen peroxide converted cedrolide to the epoxide (D11) and this in turn was transformed by chromous acetate in acetic acid to the β-ketol (D12) which was oxidised by Jones reagent to the β-diketone (D13). Transformations of αβ-epoxy ketones to β-diketones have also been achieved by ultra-violet irradiation.[10,11] For example, irradiation of a 0.5% solution of 17-acetoxy-1α,2α-epoxy-5α-androstan-3-one (D14) in dioxan for eight hours followed by evaporation of the solvent and chromatography of the residue affords 17-acetoxy-5α-androstan-1,3-dione (D15). β-Diketones can also be prepared from αβ-epoxy ketones by lithium aluminium hydride reduction followed by Jones oxidation.[12,13] Thus 1α,2α-epoxy-5α-cholestan-3-one (D16) treated in ether with a suspension of lithium aluminium hydride during 30 minutes followed by reflux for three hours yields, on chromatography, 5α-cholestan-1α,3α-diol (D17) and 5α-cholestan-1α,3β-diol (D18). Either diol on treatment

with Jones reagent in acetone then affords 5α-cholestan-1,3-dione (D19). Thus a number of routes to the desired intermediate (D1) are available via epoxidation of the αβ-unsaturated ketone in deoxyandirobin (D9). Surprisingly, however, we have been unable to effect epoxidation of deoxyandirobin using hydrogen peroxide in methanol at concentrations of up to 80% in the presence of sodium hydroxide of various normalities for periods of from one to seventy-two hours at 20°. Nor has it proved possible to epoxidise the αβ-unsaturated ketone (D8) from methyl angolensate under similar conditions, with a view to subsequent dehydration of the hydroxyl group at C-14.

Several attempts were made to introduce the desired functionality at C-1 by hydrating the αβ-unsaturated ketone system under various acidic and basic conditions. It was anticipated that in aqueous acid or base an equilibrium would be established between the enone and the corresponding β-hydroxy ketone. Efforts to oxidise the β-hydroxy ketone in aqueous acidic and basic media to the β-diketone in the hope of driving the reaction irreversibly in this direction were unsuccessful (see Experimental).

The base-catalysed cleavage of the ether linkage resulting in the formation of the Δ^1-3-ketone proceeds by the

mechanism shown in (D20), the proton at C-2 being, as expected, more acidic than that at C-15. Attempts were made to cleave the ether linkage in the opposite direction as in (D22) by protecting the 3-ketone as the ethylene ketal. Methyl angolensate when refluxed with ethylene glycol in the presence of β-naphthalene sulphonic acid afforded the required ketal (D21). Treatment of this ketal under a variety of basic conditions failed however to produce the desired alcohol (D23) (see Experimental). Reduction of methyl angolensate with sodium borohydride in methanol afforded 3-dihydro methyl angolensate (D24) which formed the acetate (D25). Acidic and basic treatment of these compounds also failed to effect cleavage of the ether linkage.

It is debatable whether in the above reactions cleavage of the ether linkage fails to occur or whether this is followed by its reversal. The enone alcohol (D8) obtained by the alternative cleavage reaction readily reverts to methyl angolensate in acidic media by addition of the hydroxyl to the terminus of an αβ-unsaturated ketone. The facile occurrence of this reaction can be understood from examination of a three-dimensional (Fieser) model of the compound (D8), when it can be seen

that in a sterically unstrained conformation (as in D26) the oxygen attached to C-14 is appropriately placed for addition to C-1. It seems less likely that the hydroxyl at C-1 in (D23) would undergo addition to the central double bond of a doubly saturated lactone system, but such a process may be favoured sterically and cannot be discounted.

Another method of forming β-diketones from the corresponding αβ-unsaturated ketones has recently come to our notice. Treatment[14] of 17β-acetoxy-Δ^1-androsten-3-one with perchloric acid and N-bromosuccinimide in dioxan forms the bromohydrin (D27) which on debromination and oxidation affords 17-acetoxy-androsten-1,3-dione (D28). Lack of time has prevented us from applying similar conditions to the enones (D8) and (D9).

ATTEMPTED CONVERSION OF 7-OXO-7-DEACETOXY KHIVORIN INTO MEXICANOLIDE

7-Oxo-7-deactoxy khivorin (D29) has been isolated from Khaya senegalensis[1] and Khaya grandifoliola[15] and characterised by correlation with khivorin.[1,16] Its structure in rings B, C and D is identical with those of cedrolide (D10) and limonin[17,18] (D30) and a series of reactions carried out on the latter[18] suggested a possible means of converting 7-oxo-7-deacetoxy khivorin into a ring B cleaved derivative which could in turn be transformed into the desired intermediate (D1).

Limonin was converted by chromous chloride reduction to deoxylimonin (D31) which on treatment with base yielded the ring B cleaved deoxylimonic acid (D32). This reaction series was further extended[18] by hydrogenation of deoxylimonin to deoxytetrahydrolimonin (D33) which was similarly cleaved by base to deoxytetrahydrolimonic acid (D34). Treatment of this compound with chlorine in carbon tetrachloride followed by bisdehydrochlorination afforded a mixture of the cisoid and transoid diene lactones (D35) and (D36).

A similar reaction sequence, together with hydrolysis of the acetate groups at C-1 and C-3 and oxidation of the resulting hydroxyl groups, applied to 7-oxo-7-deacetoxy khivorin could be expected to provide the compound (D37) which is a tetrahydro derivative of the required intermediate (D1). This intermediate cannot be prepared directly however, since the chlorination and dehydrochlorination reactions cannot be safely carried out in the presence of the furan ring. Further, the overall yield in the sequence limonin — cisoid diene lactone (D35) was at best somewhat less than 10%, which in view of the limited quantity of 7-oxo-7-deacetoxy khivorin available to us made the route less attractive. However, limonin was converted to deoxylimonic acid (D32) in about 45% yield. It was thus decided to attempt to prepare the corresponding compound (D38) from 7-oxo-7-deactoxy khivorin.

Treatment of 7-oxo-7-deacetoxy khivorin (D29) in acetone and acetic acid with 1N chromous chloride at 45° for 41 hours followed by preparative TLC and crystallisation yielded 14,15-deoxy-7-oxo-7-deacetoxy khivorin (D39), m.p. 253-257°. This compound was then treated with base under conditions analogous to those employed in the conversion of deoxylimonin into deoxylimonic acid.

It was found that reaction did not occur and basic conditions were made gradually more vigorous until cleavage was finally achieved with a 3% solution of potassium hydroxide in refluxing ethanol. As expected under these conditions the acetate groups at C-1 and C-3 were hydrolysed and esterification with ethereal diazomethane followed by preparative TLC afforded the product (D40).

It now remained to find a means of transforming the βγ-unsaturated lactone system in (D40) into the desired cisoid diene lactone system as in (D41) whilst leaving the furan ring intact. As before, a model compound (D42) on which pilot reactions were first carried out was prepared from cedrolide. Treatment of (D42) with chlorine followed by dehydrochlorination confirmed that this method was unsuitable (NMR showed loss of furan ring). It was possible however to achieve allylic bromination of C-15 with one equivalent of N-bromosuccinimide in refluxing carbon tetrachloride and subsequent dehydrobromination afforded, inter alia, a compound whose NMR and UV spectra were consistent with the desired structure (D43). Precisely similar treatment of the βγ-unsaturated lactone (D40) from 14,15-deoxy-7-oxo-deacetoxy khivorin however did not provide the anticipated cisoid diene lactone (D41) but yielded an intractable mixture of products which could not be resolved.

EXPERIMENTAL

For general experimental see Part IA

Angolensic Acid (D6)

Methyl angolensate (D5) (800 mg.) in methanol (100 ml.) containing potassium hydroxide (5 g.) in water (5 ml.) was refluxed for 1 hr. Dilution, acidification and extraction into chloroform yielded on preparative TLC (5% MeOH/$CHCl_3$) angolensic acid (752 mg.), m.p. (from EtOH/H_2O) 262-266° (lit.[6] m.p. 265-267°). Treatment of a small sample in methanol with ethereal diazomethane afforded methyl angolensate, m.p. and mixed m.p. 201-204° (lit.[6] m.p. 204-205°).

Cleavage of the Ether Linkage: The αβ-Unsaturated Ketone (D8).

Angolensic acid (D6) (200 mg.) in dry toluene (15 ml.) and isobutanol (15 ml.) was treated with sodium (200 mg.) and stirred under nitrogen at 20° for 16 hr. Dilution with aqueous buffer of pH6 and extraction with chloroform yielded acidic material (183 mg.) which was treated in methanol (10 ml.) with excess ethereal diazomethane. Preparative TLC afforded the αβ-unsaturated ketone (D8) (106 mg.), m.p. (from EtOH/H_2O) 190-193°

(lit.[6] m.p. 192-193.5°). NMR signals at τ 2.35, 4.10 (2H, q, H-2 and H-1), 4.34 (1H, s, H-17), 4.95 (2H, d, J = 17 Hz, 2H-30), 6.36 (3H, s, methyl ester).

Deoxyandirobin (D9)

(a) αβ-Unsaturated ketone (D8) (50 mg.) was refluxed in dry methanol (20 ml.) containing sodium (110 mg.) for 16 hr. Dilution, acidification and extraction into chloroform afforded, on preparative TLC deoxyandirobin (29 mg.), m,p. (from EtOH/H_2O) 162-164°, NMR signals at τ 3.34, 4.04 (2H, q, H-2 and H-1), 3.93 (1H, s, H.-7), 4.42 (1H, diffuse s, H-15), 4.82 (2H, m, 2H-30), 6.25 (3H, s, methyl ester). (Found: C, 71.4; H. 7.2, $C_{27}H_{32}O_6$ requires: C, 71.7; H, 7.1%).

(b) Methyl angolensate (100 mg.) in methanol (25 ml.) containing sulphuric acid (0.5 ml., 2%) was refluxed for 24 hr. The usual work up afforded, on preparative TLC, desoxyandirobin identical with that obtained in (a) (m.p., mixed m.p., NMR).

Epoxidation of Cedrolide: The Epoxide (D11)

Cedrolide (D10) (480 mg.) in methanol (100 ml.) containing 2N sodium hydroxide (10 ml.) and 30% hydrogen

peroxide solution (12 ml.) was kept at 20° for 40 min. Dilution with aqueous buffer solution of pH6 and extraction with chloroform afforded, on preparative TLC the epoxide (D11) (260 mg.), NMR signals at τ 4.51 (1H, s, H-17), 6.14 (1H, s, H-15), 6.49 (2H, q, H-1 and H-2).

The β-Ketol (D12)

Epoxide (D11) (100 mg.) (from the previous reaction) in acetone (10 ml.) containing sodium acetate (0.7 g.), acetic acid (0.5 ml.) and water (2.5 ml.) was treated with a suspension of chromous acetate (144 mg.) in acetone (4 ml.) and water (1 ml.) under nitrogen at 20° for 5 hr. Dilution and extraction into chloroform afforded, on preparative TLC, the β-ketol (58 mg.), $\nu_{max.}$ ($CHCl_3$) 3595 (hydroxyl), 1730 (cyclohexanones, δ -lactone).

The β-Diketone (D13)

The β-ketol (D12) (55 mg.) obtained as above in acetone (20 ml.) was treated with Jones reagent (0.5 ml.) at -20° for 5 min. The usual separation yielded β-diketone (32 mg.), NMR signals at τ 4.49 (1H, s, H-17), 6.32 (1H, s, H-15), 6.50 (2H, diffuse s, 2H-2), $\lambda_{max.}$ 265 mμ rising to 285 mμ on addition of base.

Attempted Epoxidation of Deoxyandirobin (D9) and the αβ-Unsaturated Ketone (D8)

Deoxyandirobin (50 mg.) in methanol (20 ml.) containing 2N sodium hydroxide (2 ml.) and 30% hydrogen peroxide solution (2.5 ml.) was left at 20° for periods of 1, 4, 16 and 72 hr. and worked up at pH6 as before. In each case only deoxyandirobin was recovered (TLC, m.p. and mixed m.p.).

Deoxyandirobin (20 mg.) in methanol (10 ml.) containing 2N sodium hydroxide (1 ml.) and 60% hydrogen peroxide solution (5 ml.) was left at 20° for periods of 16 and 72 hr. Work up as before yielded only deoxyandirobin (TLC, m.p. and mixed m.p.).

Deoxyandirobin (20 mg.) in methanol (10 ml.) containing 2N sodium hydroxide (1 ml.) and 85% hydrogen peroxide solution (10 ml.) was left at 20° for 72 hr. Work up as before afforded only deoxyandirobin (TLC, m.p. and mixed m.p.

Deoxyandirobin (20 mg.) was shaken with 85% hydrogen peroxide solution (10 ml.) and 2N sodium hydroxide (1 ml.) at 20° for 24 hr. Work up as above yielded only deoxyandirobin, (m.p. and mixed m.p.).

Deoxyandirobin (20 mg.) in methanol (10 ml.) containing 0.5 N sodium hydroxide (0.5 ml.) and 40% hydrogen peroxide solution (5 ml.) was left at 20° for 24 hr. Work up as before yielded only deoxyandirobin (TLC, m.p. and mixed m.p.).

Deoxyandirobin (20 mg.) in methanol (10 ml.) containing 5N sodium hydroxide (2 ml.) and 85% hydrogen peroxide solution (5 ml.) was left at 20° for 72 hr. Work up as before yielded deoxyandirobin (TLC, m.p. and mixed m.p.) and a little acidic material which on esterification with ethereal diazomethane yielded deoxyandirobin (TLC).

αβ-Unsaturated ketone (D8) was treated with various proportions of alkaline hydrogen peroxide as above for periods of up to 72 hr. In each case the product consisted of unchanged αβ-unsaturated ketone and methyl angolensate (TLC, NMR, IR).

Attempted Hydration and Oxidation of the αβ-Unsaturated Ketone (D8).

αβ-Unsaturated ketone (D8) (20 mg.) in dioxan (5 ml.) containing 1N sodium hydroxide (5 ml.) was left at 20° for 30 mins., potassium dichromate (10 mg.) added and the solution left for 1 hr. Work up at pH6 as before afforded unchanged αβ-unsaturated ketone (TLC, IR). The above

conditions were varied by using 5N sodium hydroxide with both potassium dichromate and potassium permanganate. Work up as before afforded in each case unchanged αβ-unsaturated ketone and small amounts of methyl angolensate (D5) and angolensic acid (D6), (TLC, IR).

αβ-Unsaturated ketone (20 mg.) in dioxan (5 ml.) containing Jones reagent (5 drops) and water (5 ml.) was left at 20° for 24 hr. The usual work up afforded unchanged αβ-unsaturated ketone and methyl angolensate (TLC, IR).

Ketalisation of Methyl Angolensate: The Ketal (D21).

Methyl angolensate (D5) (40 mg.) in benzene (5 ml.) containing ethylene glycol (3 drops) was added to β-naphthalene sulphonic acid (8 mg.) in refluxing benzene (10 ml.) in a Dean and Stark apparatus and refluxed for 3 hr. Dilution with water and removal of the benzene layer afforded, on preparative TLC, ketal (D21) (27 mg.), NMR signals at τ 4.14 (1H, s, H-17), 5.00 (2H, d, J = 16 Hz, 2H-30), 6.00 (4H, m, ethylene ketal protons), 6.30 (3H, s, methyl ester),

Attempted Cleavage of the Ether Linkage in the Ketal (D21)

Ketal (20 mg.) from the above reaction was refluxed for 24 hr. in 15 ml. of (a) a 1% solution of sodium methoxide in methanol; (b) a 5% solution of sodium isobutoxide in toluene; (c) a 7½% solution of sodium isobutoxide in toluene. In each case the usual work up afforded only unchanged ketal (TLC, IR).

Ketal (20 mg.) was refluxed in 15 ml. of a 3% solution of sodium methoxide in methanol for 12 hr. and worked up as before to give a mixture of products including unchanged starting material and the corresponding acid. None of the product was hydroxylic (IR).

Methyl Angolensate Reduction Product (D24).

Methyl angolensate (100 mg.) in methanol (10 ml.) was treated at 0° with sodium borohydride (10 mg.) for 5 min. Dilution, acidification and extraction into chloroform afforded, on preparative TLC, the alcohol (D24) (55 mg.), NMR signals at τ 4.50 (1H, s, H-17), 4.95 (2H, d, J = 16 Hz, 2H-30), 6.32 (3H, s, methyl ester), 6.68 (1H, m, H-3).

Acetylation of Methyl Angolensate Reduction Product (D24): The Acetate (D25).

The alcohol (D24) (50 mg.) from the above reaction was dissolved in acetic anhydride (2 ml.) and pyridine (2 ml.) and left at 50° for 16 hr. Dilution and extraction into chloroform afforded, on preparative TLC, the acetate (D25) (42 mg.), NMR signals at τ 4.21 (1H, s, H-17), 4.98 (2H, d, J = 16Hz, 2H-30), 6.29 (3H, s, methyl ester), 7.89 (3H, s, acetate methyl).

Attempted Cleavage of the Ether Linkage in the Alcohol (D24) and the Acetate (D25).

The alcohol (D24) (20 mg.) was refluxed in methanol (20 ml.) containing sulphuric acid (0.4 ml., 2%) for 18 hr. Work up as usual afforded only starting material (TLC, NMR).

The alcohol (D24) (20 mg.) in dry chloroform (10 ml.) was treated with a stream of hydrogen chloride gas for 6 min. and the solution left stoppered for 1 hr. Evaporation of the solvent afforded unchanged starting material (TLC, NMR).

The alcohol (D24) (20 mg.) was refluxed with (a) 3% (b) 6% solution of sodium isobutoxide in toluene (15 ml.) for 24 hr. In each case the usual work up yielded only unchanged starting material (TLC, NMR).

The acetate (D25) (20 mg.) was treated with a 2% solution of sulphuric acid in methanol as above. Work up as before afforded a mixture of unchanged starting material and the alcohol (D24) (TLC, NMR).

The acetate (D25) (20 mg.) was treated with hydrogen chloride in chloroform as above. Work up yielded only unchanged starting material.

14,15-Deoxo-7-oxo-7-deacetoxy Khivorin (D39)

7-Oxo-7-deacetoxy khivorin (D29) (1.1g) in acetone (150 ml.) and acetic acid (60 ml.) was treated under nitrogen with 1N chromous chloride solution (50 ml.) at 45° for 41 hr. Dilution and extraction with chloroform afforded, on preparative TLC, 14,15-deoxo-7-oxo-7-deacetoxy khivorin (670 mg.), m.p. (from ethanol/water) 253-257°, NMR signals at τ 3.44 (1H, s, H-15), 5.00 (1H, s, H-17), 5.26 (2H, m, H-1 and H-3), 7.98, 8.02 (each 3H, s, acetate methyls), 8.45, 8.78, 8.84, 9.00, 9.17 (each 3H, s, tertiary methyls). (Found: C, 68.2; H, 7.15. $C_{30}H_{38}O_8$ requires: C, 68.4; H, 7.3%).

The βγ-Unsaturated Lactone (D40)

14,15-deoxo-7-oxo-7-deacetoxy khivorin (D39) (620 mg.) was refluxed in ethanol (100 ml.) containing

potassium hydroxide (3 g.) in water (3 ml.) for 1½ hr. Dilution, acidification and extraction with chloroform yielded acidic material which was esterified in methanol with excess ethereal diazomethane. Preparative TLC afforded βγ-unsaturated lactone (D40) (320 mg.), NMR signals at τ 4.76 (1H, s, H-17), 6.34 (3H, s, methyl ester), 6.43 (2H, m, H-1 and H-3), 8.21 (3H, s, vinyl methyl), 8.85, 8.98 (3H each, s, tertiary methyls), 9.04 (6H, s, 2 tertiary methyls).

The βγ-Unsaturated Lactone (D42)

Cedrolide (D10) (550 mg.) in methanol (50 ml.) containing sodium borohydride (50 mg.) was left at 0° for 5 min. Dilution, acidification and extraction with chloroform afforded a mixture of alcohols which was oxidised with Jones reagent (1 ml.) in acetone (50 ml.) at 20° for 5 min. The usual work up afforded, on preparative TLC, the ketone (D44) (375 mg.). Treatment of this ketone epoxide (D44) with chromous chloride as above yielded the αβ-unsaturated lactone (D45) which was cleaved and esterified as before to yield on preparative TLC the βγ-unsaturated lactone (D42) (150 mg.), NMR signals at τ 5.04 (1H, s, H-17), 6.33 (3H, s, methyl ester), 8.27 (3H, s, vinyl methyl), 8.85 (6H, s, 2 tertiary methyls), 8.87,

9.00 (3H each, s, tertiary methyls), $\nu_{max.}$ (CCl_4) 1740 (methyl ester, δ-lactone), 1713 (cyclohexanone) $cm.^{-1}$.

Treatment of the βγ-Unsaturated Lactone (D42) with Chlorine

The βγ-unsaturated lactone (D42) (50 mg.) was treated in the dark with 2 ml. of a solution of chlorine in carbon tetrachloride (2.0 m.moles in 28 ml.) at 20° for 16 hr. Removal of solvent and heating at 100° at 15 mm. pressure for 30 mins. afforded, on preparative TLC, two main products. NMR examinations showed loss of the furan ring in each case (no signals below 4 τ).

The Cisoid Diene Lactone (D43)

βγ-Unsaturated lactone (D42) (97 mg.) in carbon tetrachloride (20 ml.) was refluxed with N-bromosuccinimide (38 mg., 1 equivalent) for 30 mins. The solution was filtered and the solvent evaporated under reduced pressure. The residue was heated at 100° under 15 mm. pressure for 15 mins. and purification by preparative TLC (2% MeOH/$CHCl_3$ on Kieselgel G; 50% $CHCl_3$/light petroleum on Fluka alumina) afforded cisoid diene lactone (D43) (18 mg.), NMR signals at τ 4.07 (1H, s, H-17), 4.56 (1H, diffuse s, H-15), 4.82 (2H, m, 2H-30), 6.30 (3H, s, methyl ester), 8.82, 8.87, 8.92, 8.97 (3H each, s, tertiary

methyls), λ_{max} 257 mμ (log ε, 3.84), ν_{max} 1738 (methyl ester, unsaturated δ -lactone), 1722 (shoulder) cyclohexanone) cm.$^{-1}$.

Treatment of the βγ-Unsaturated Lactone (D40) with N-Bromosuccinimide

βγ-Unsaturated lactone (D40) (320 mg.) was refluxed in carbon tetrachloride (60 ml.) containing N-bromosuccinimide (120 mg., 1 equivalent) for 30 min. Extraction and treatment as in the previous experiment yielded a gum which showed on TLC examination as a complex mixture of products, none of which could be isolated and identified.

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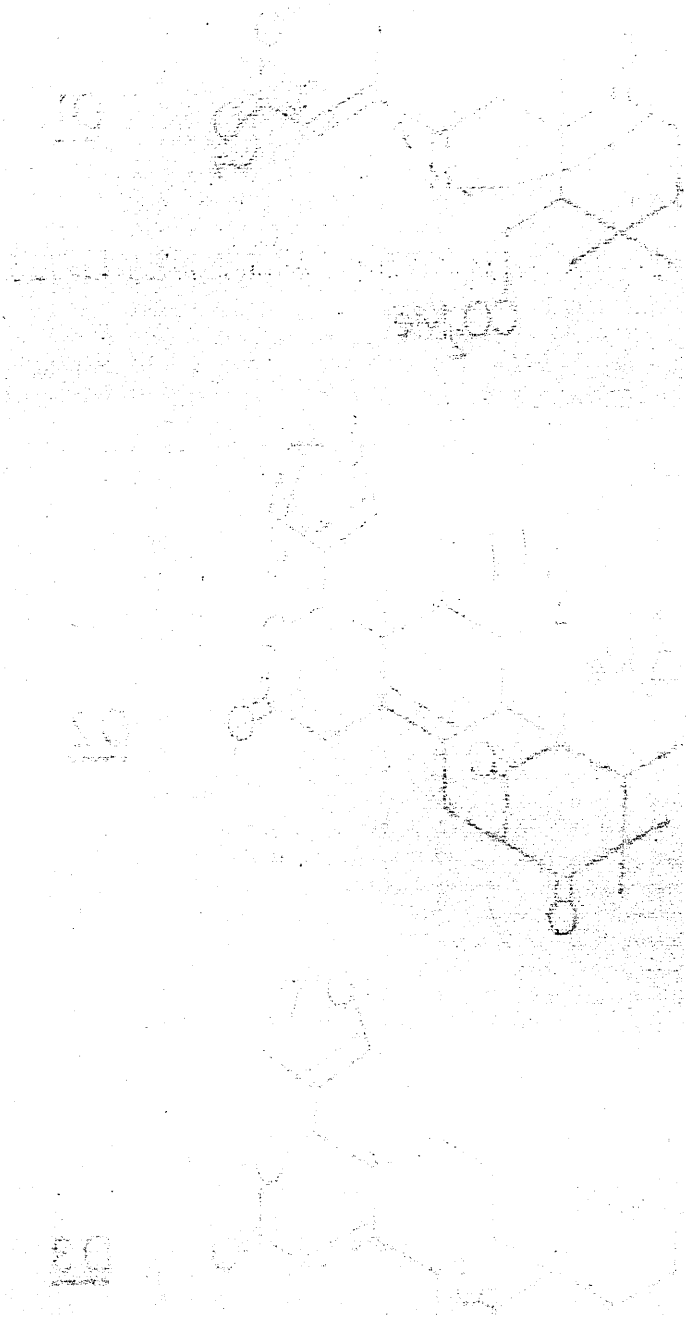

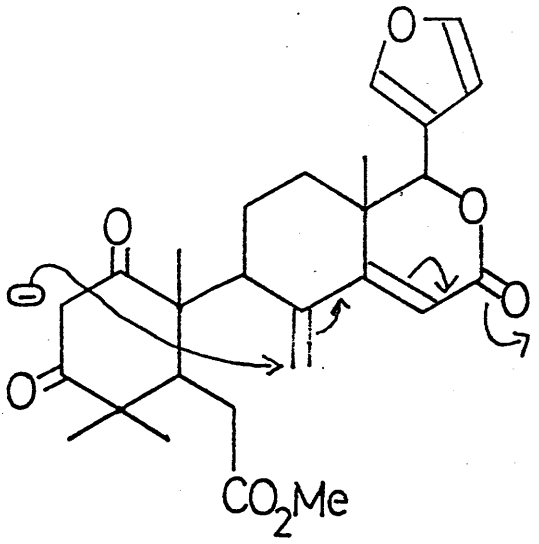

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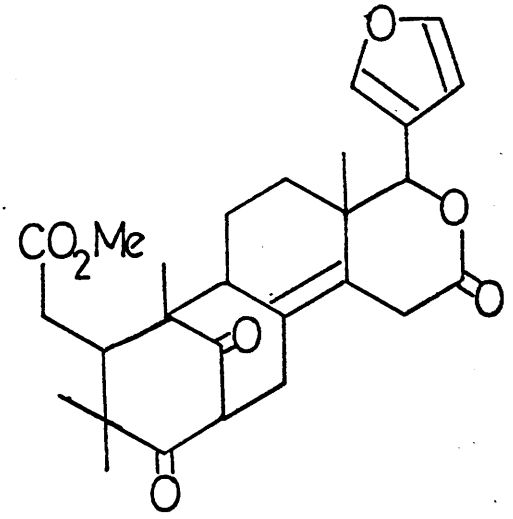

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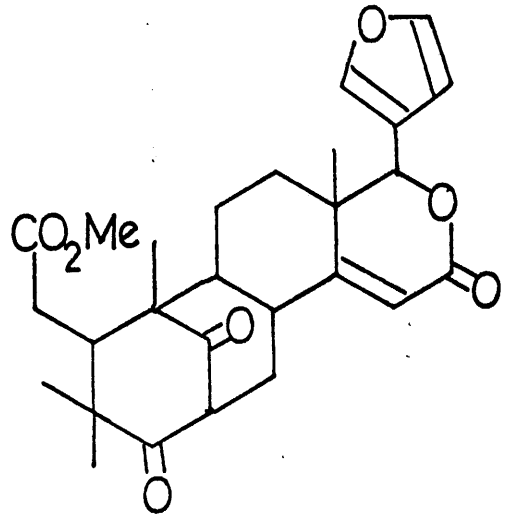

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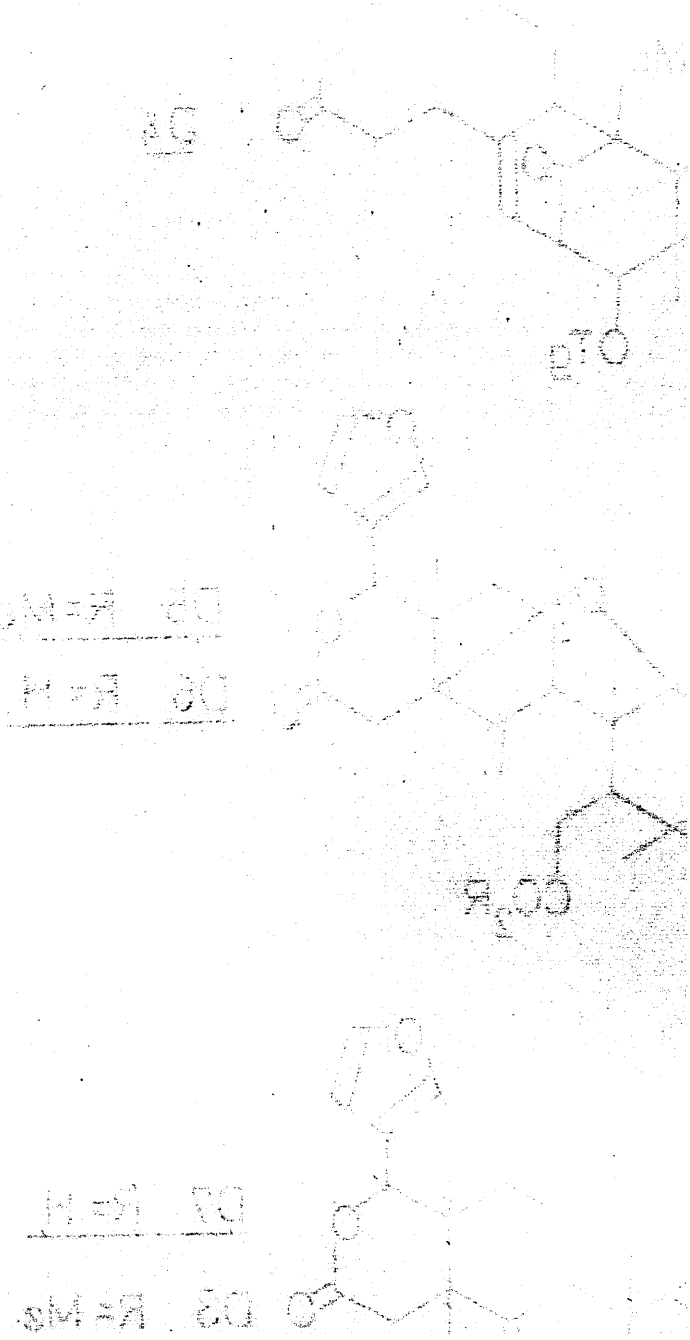

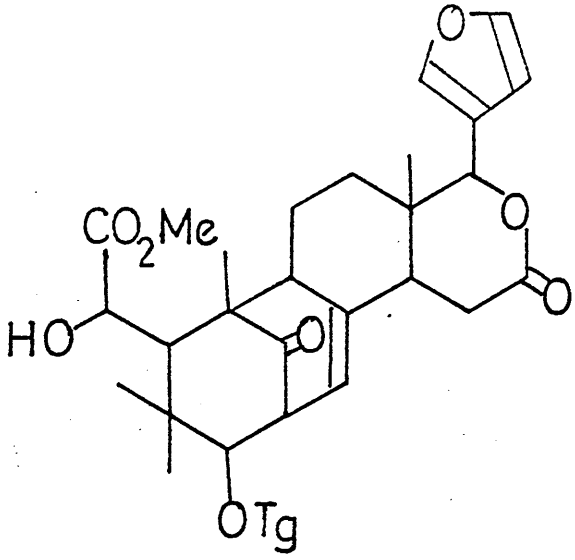

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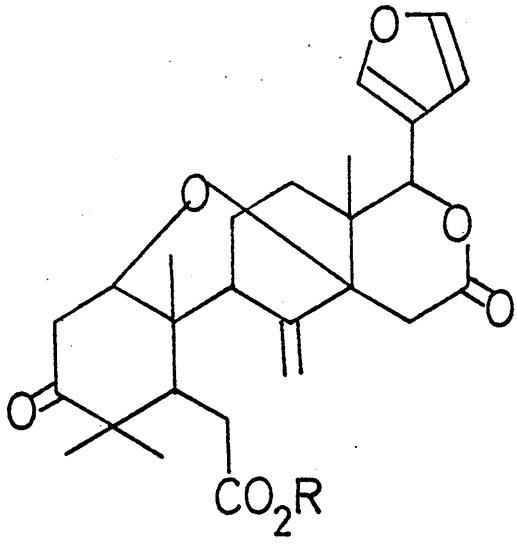

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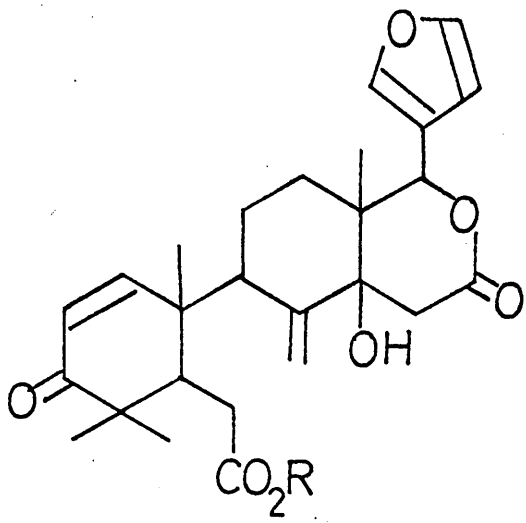
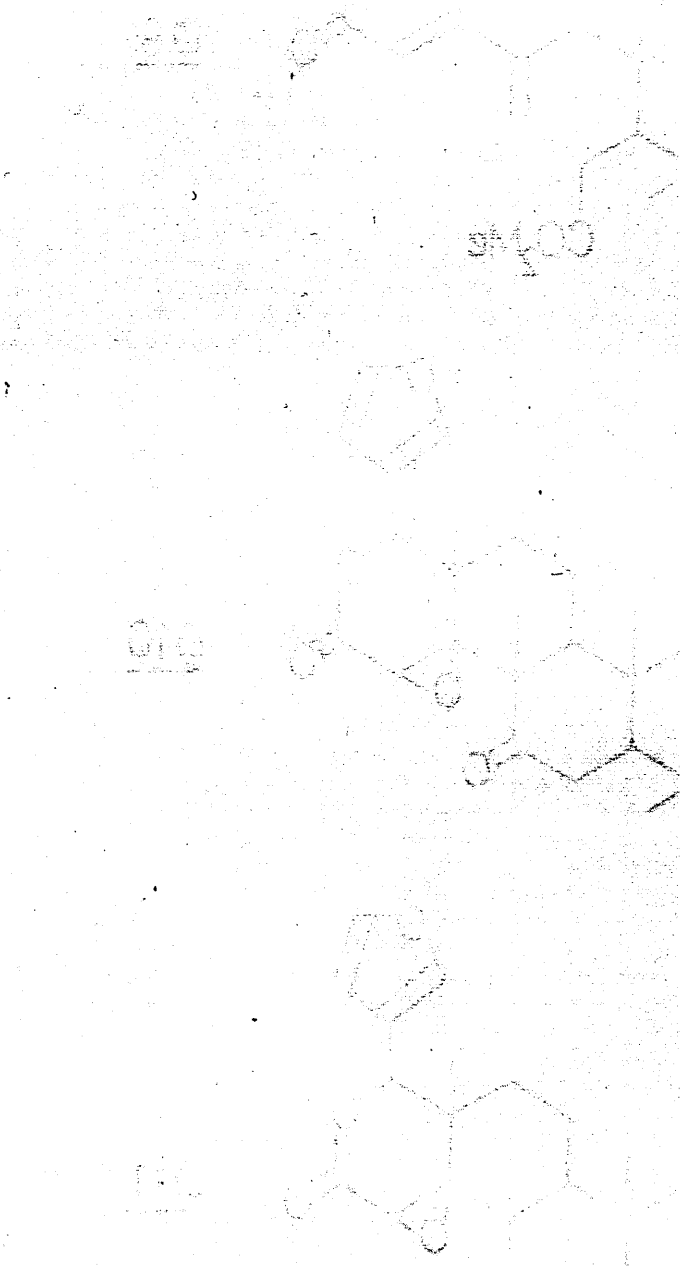
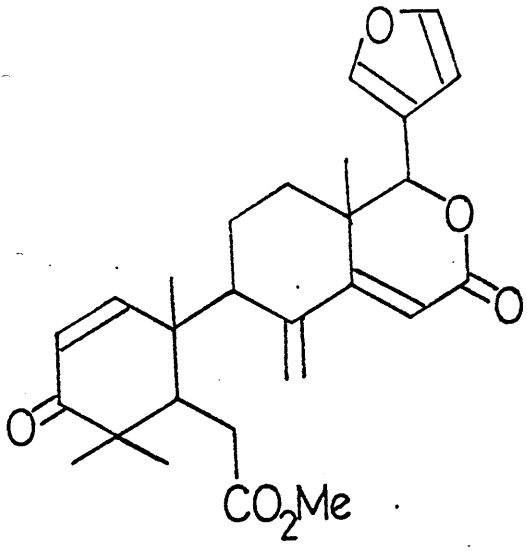
D6 R= H



D7 R= H

D8 R= Me





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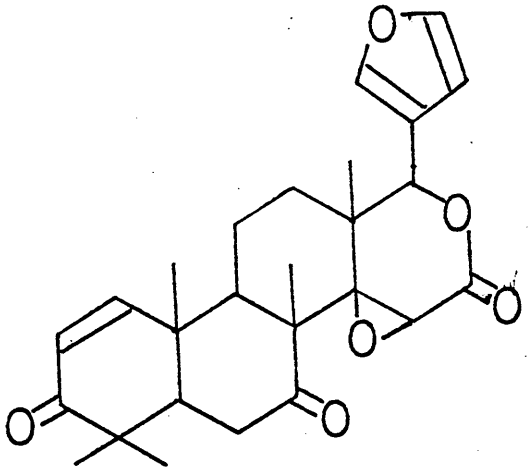

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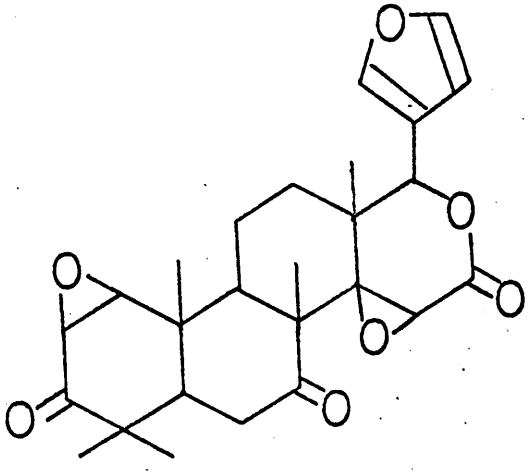

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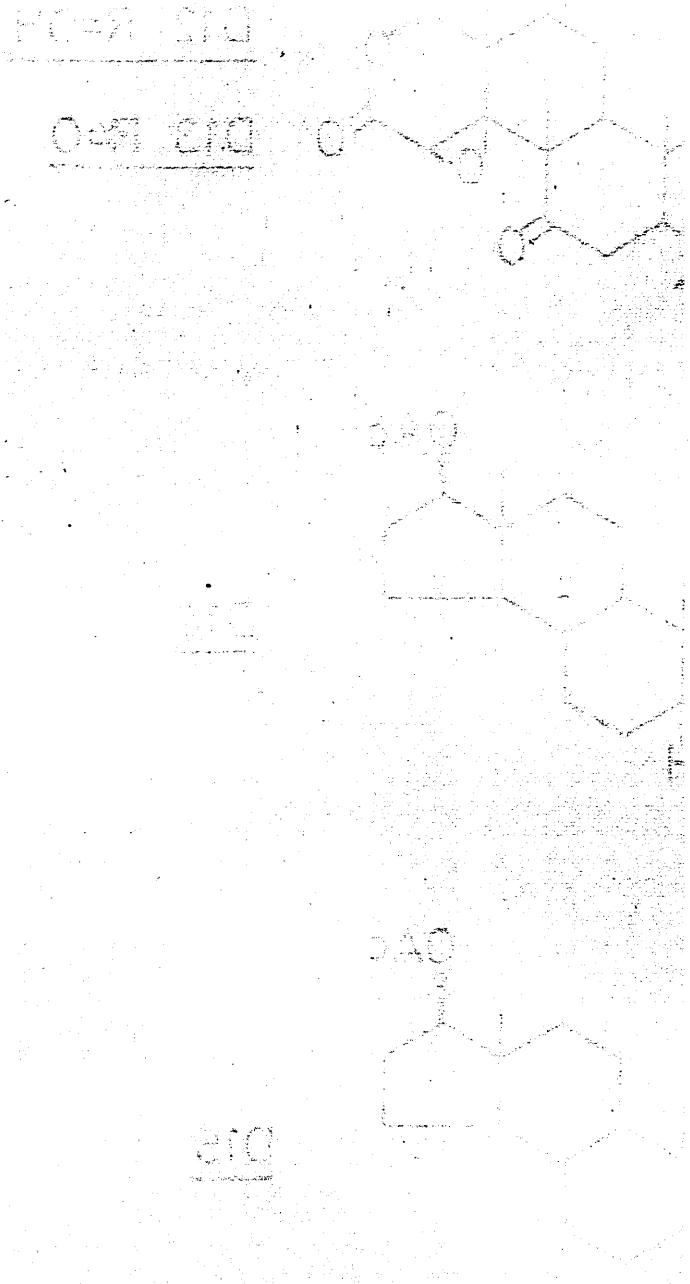
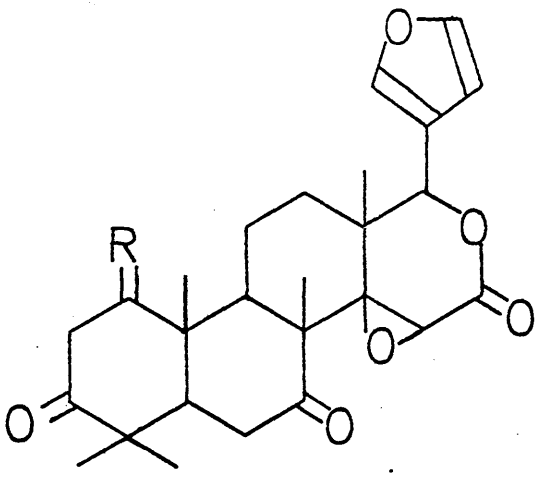
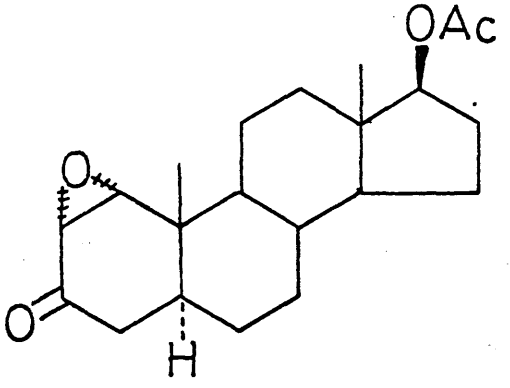




D12 R=OH,H

D13 R=O



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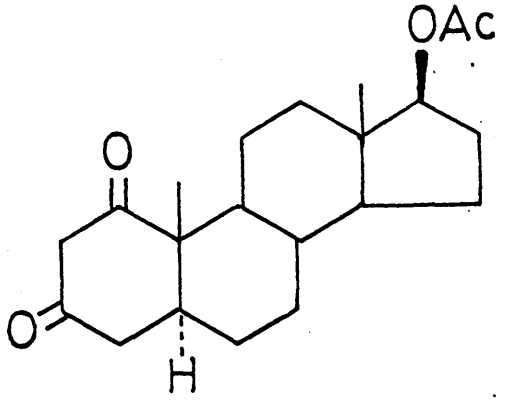

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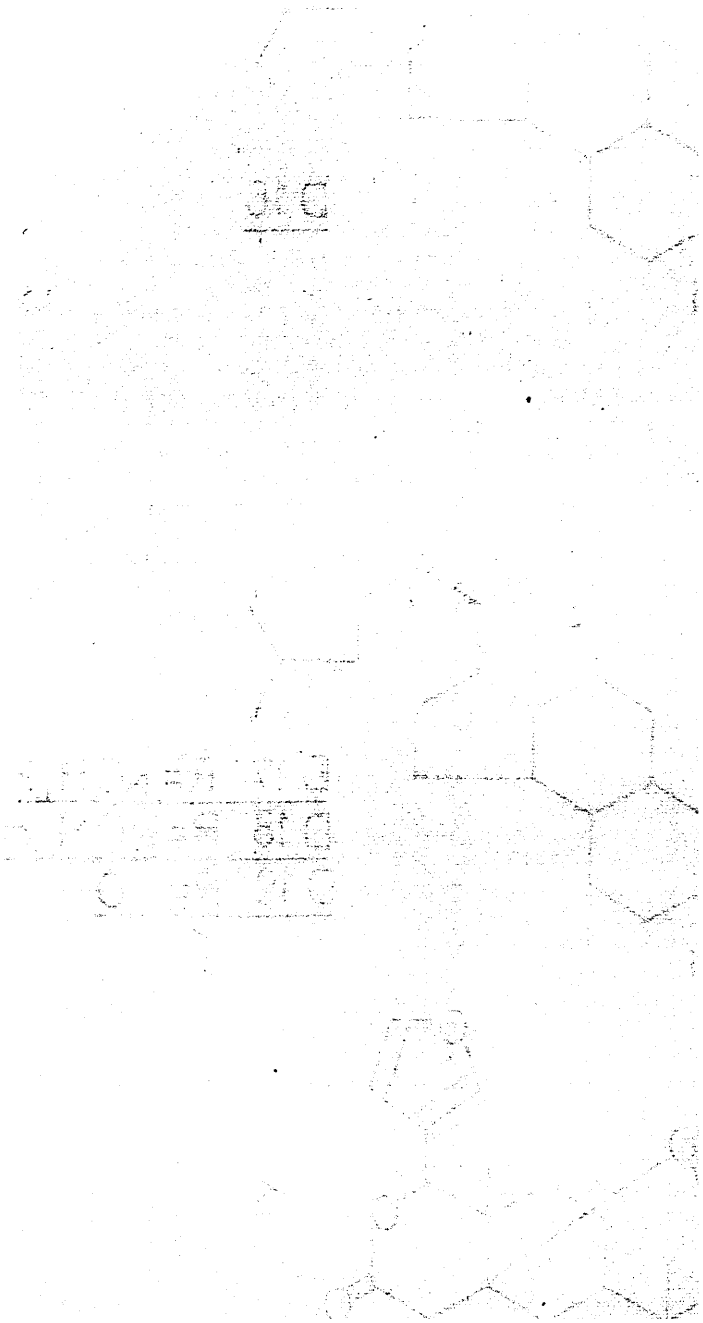
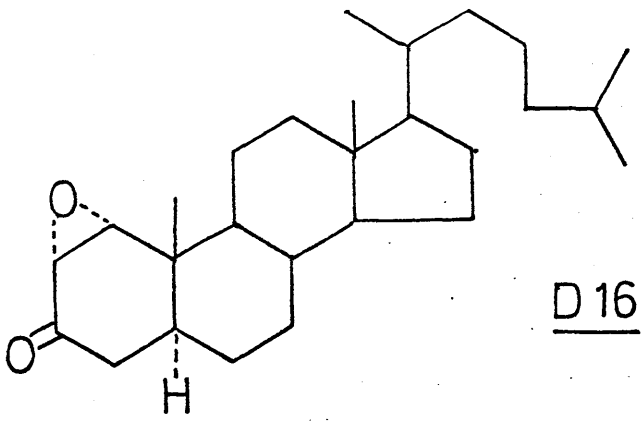
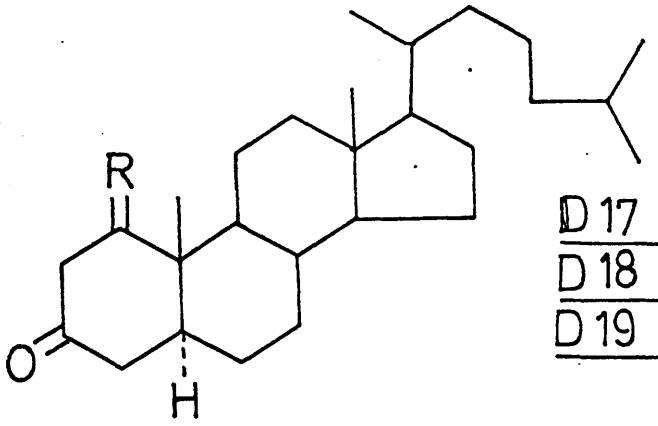
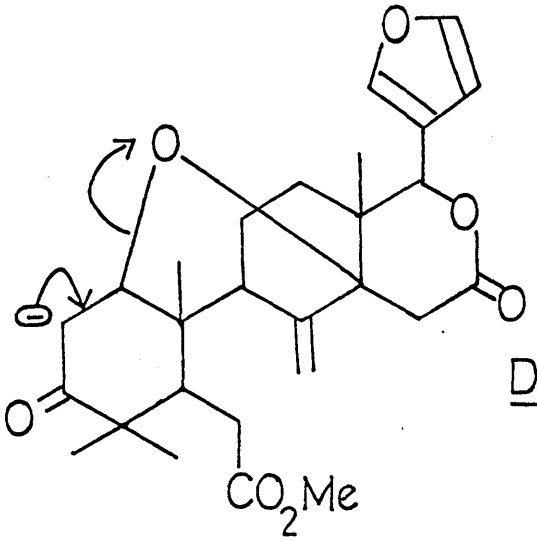




D 16



D 17 R= αOH, H
D 18 R= βOH, H
D 19 R= O



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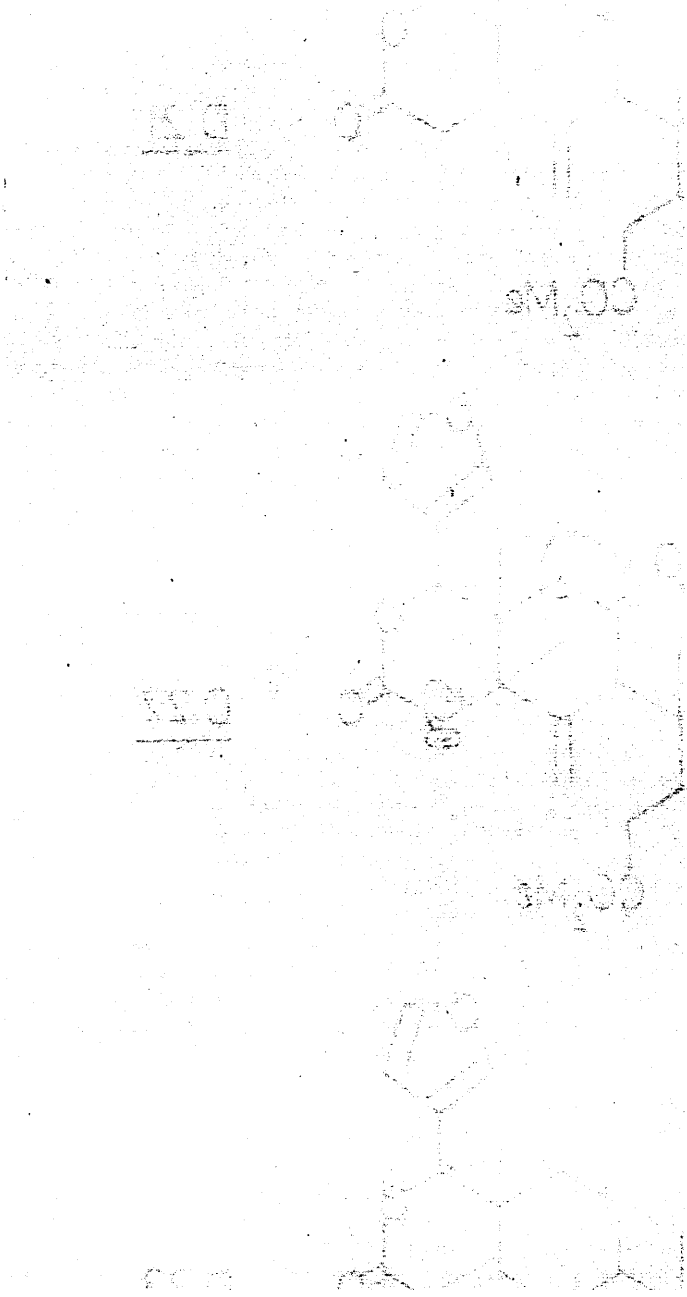

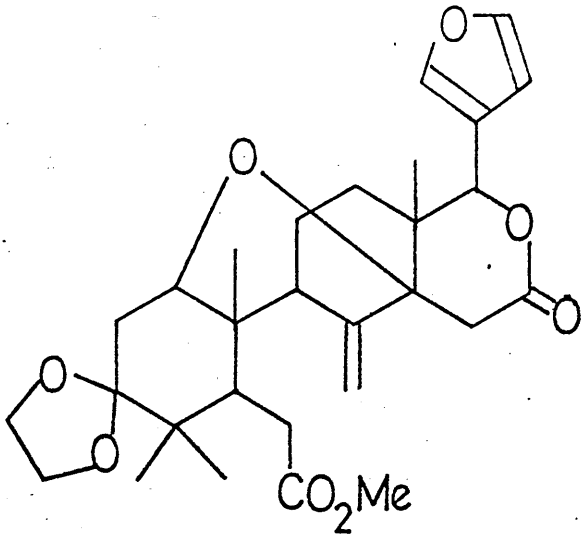

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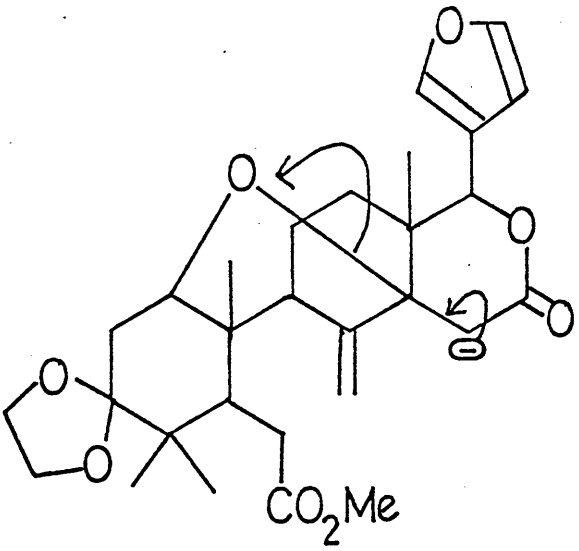

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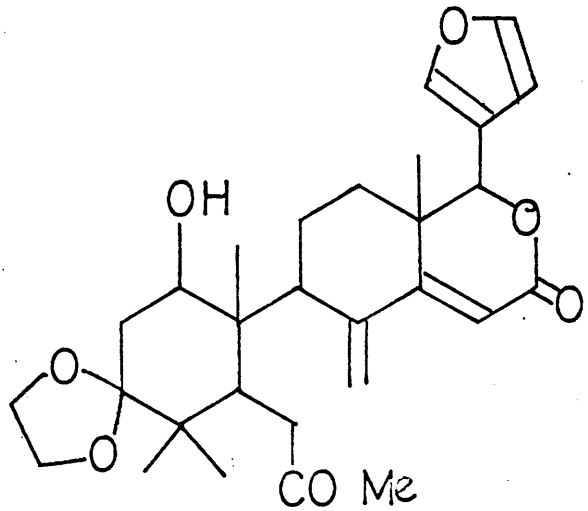
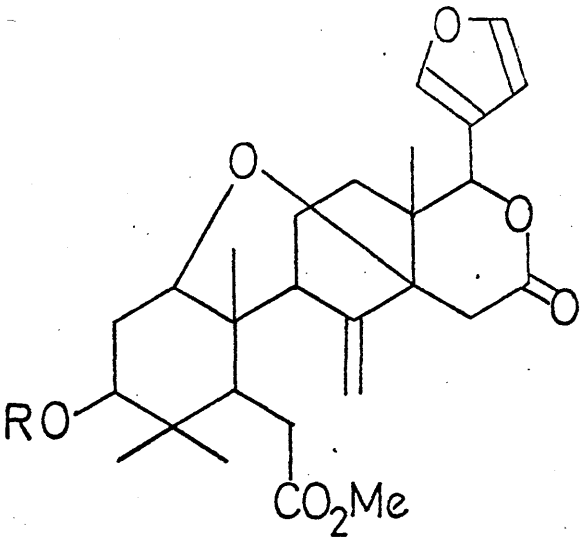
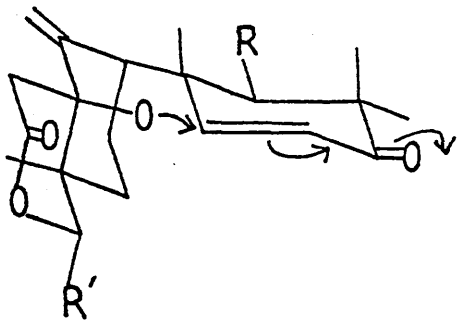


D 23



D 24 R = H

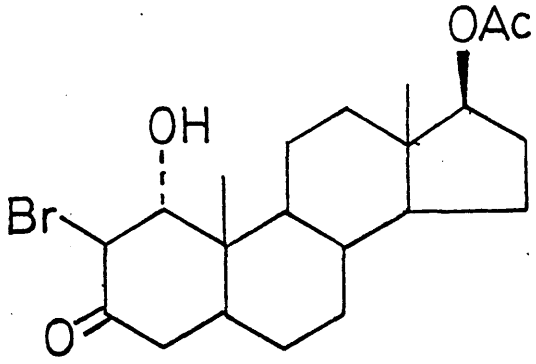
D 25 R = Ac



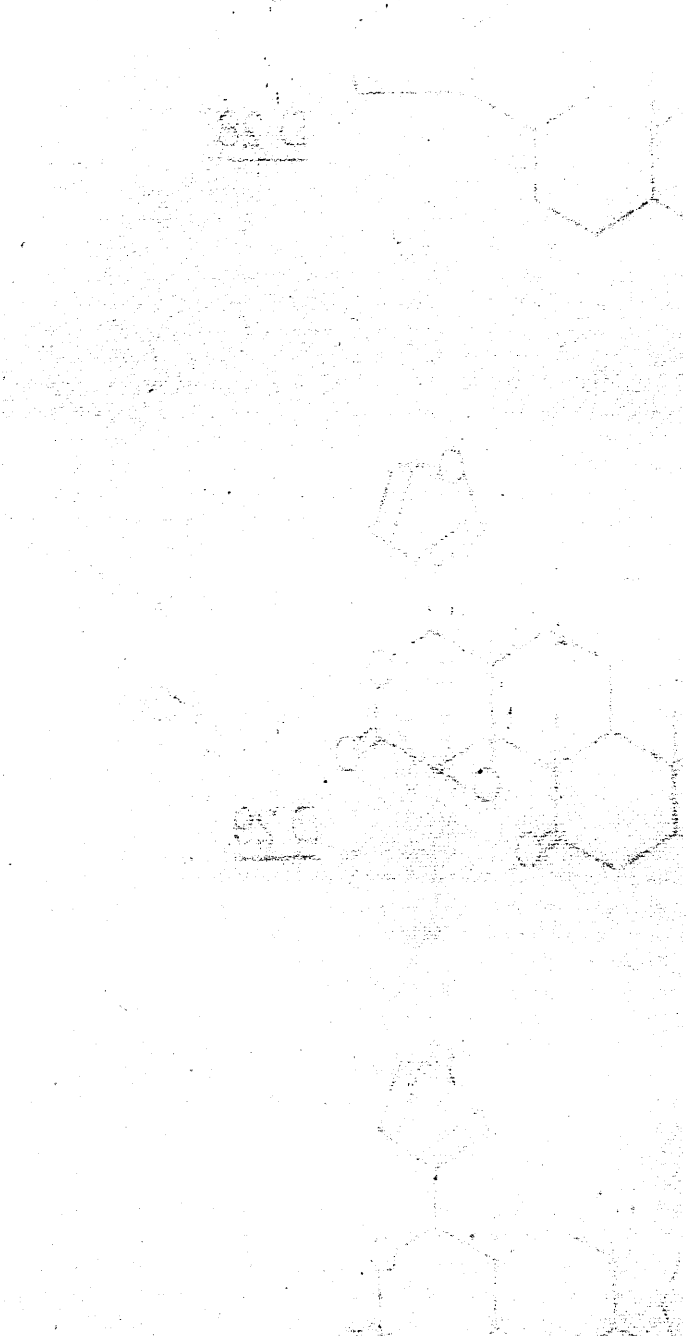
D 26

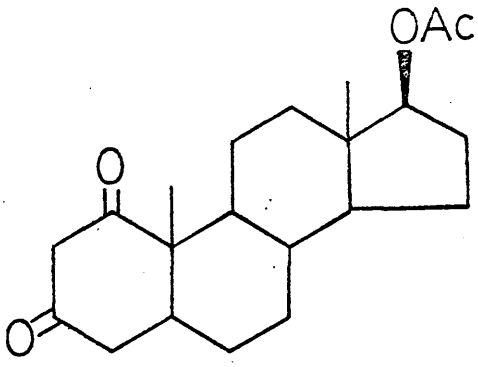
R = CH_2CO_2Me,

R′ = β-Furan.



D 27





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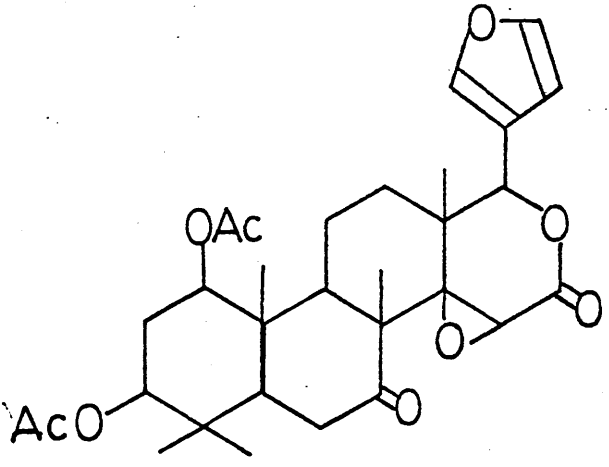

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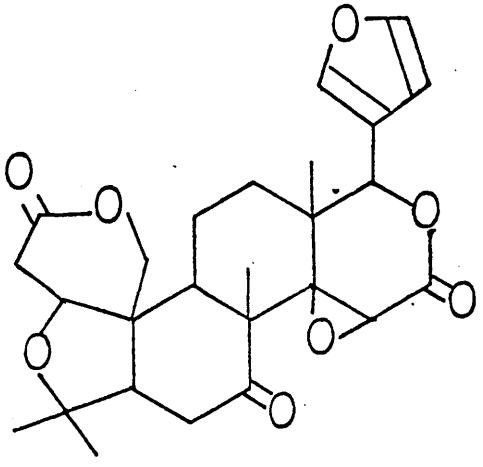

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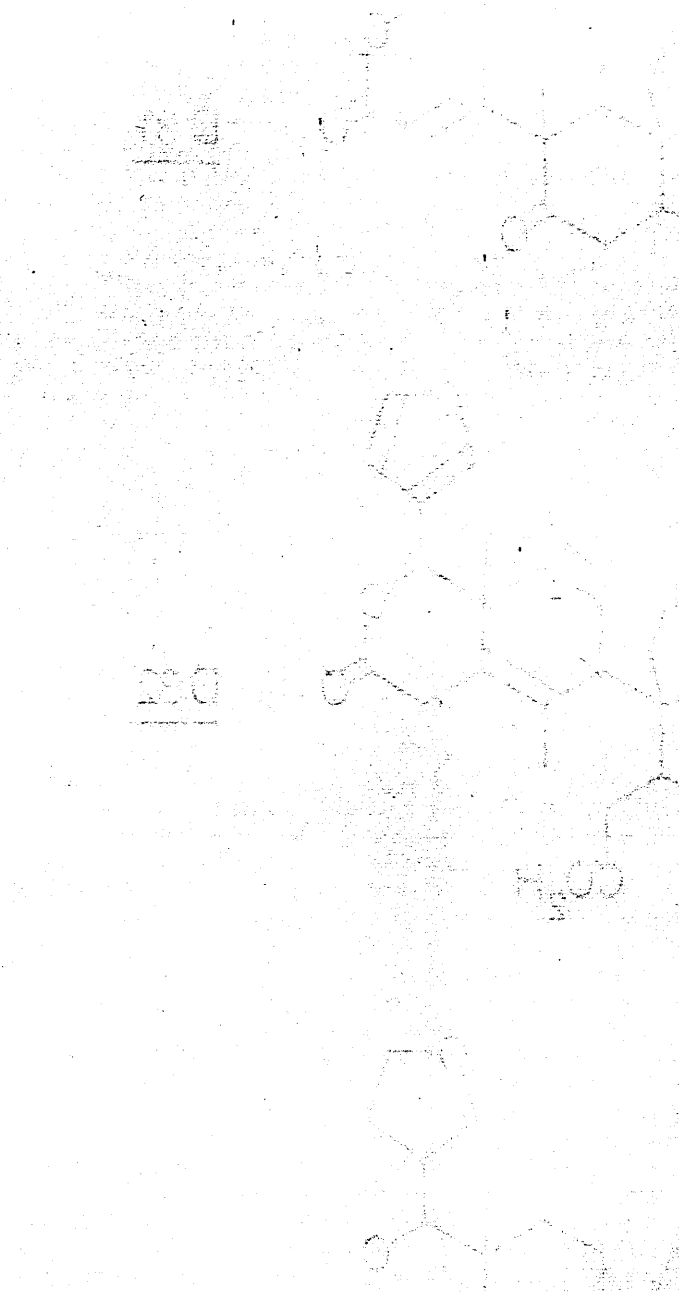
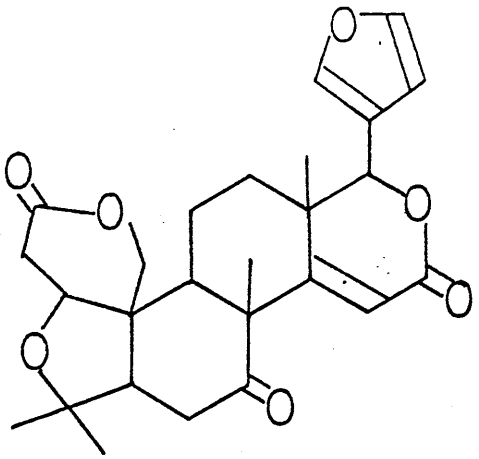
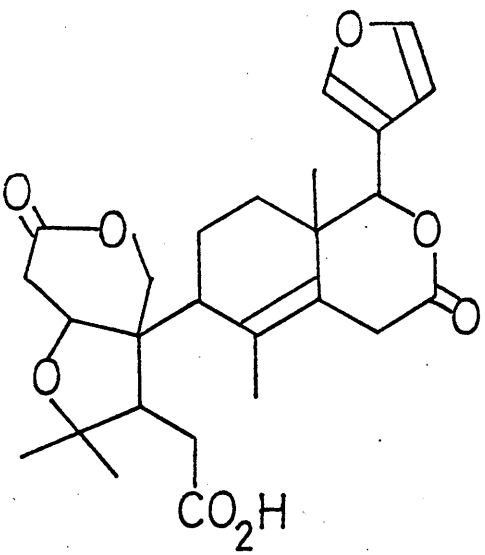
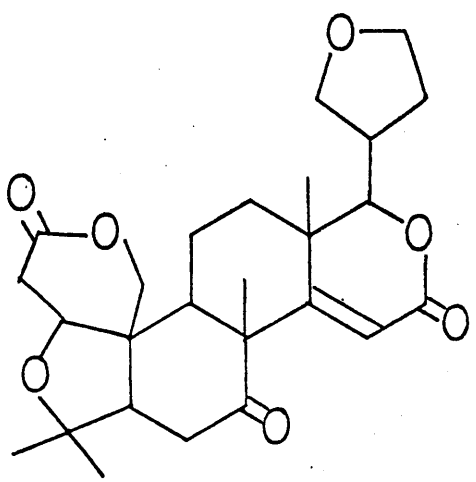




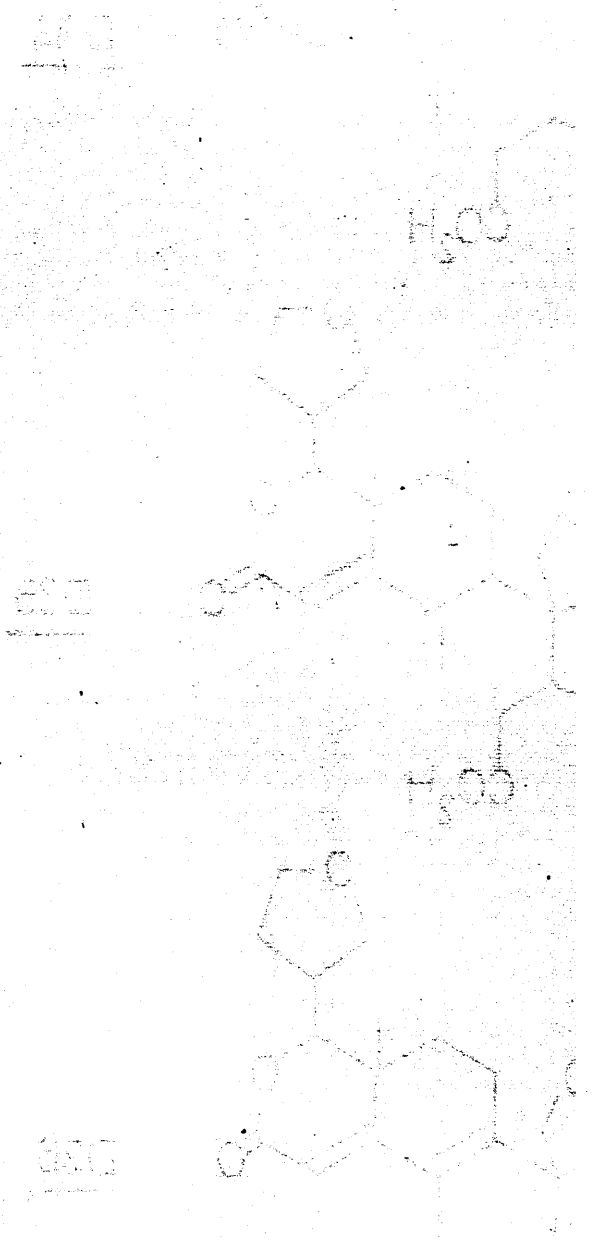
D 31

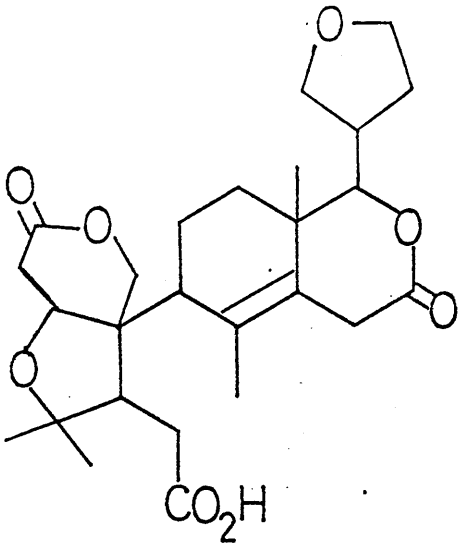


D 32

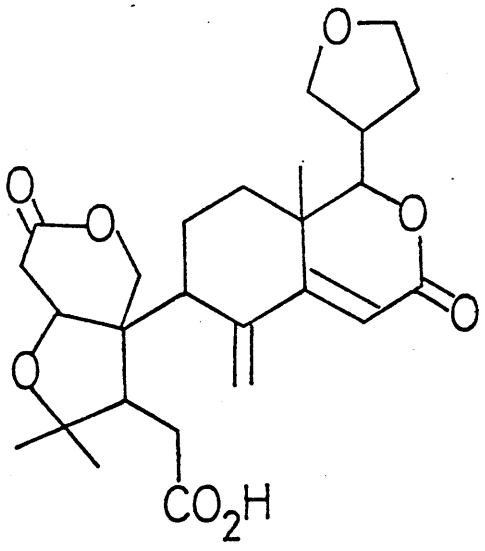


D 33





D34



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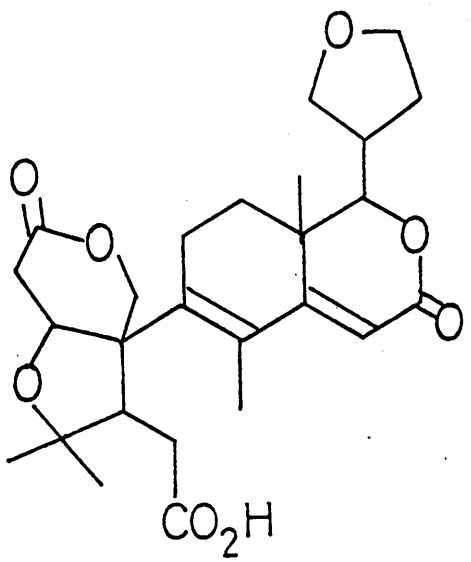
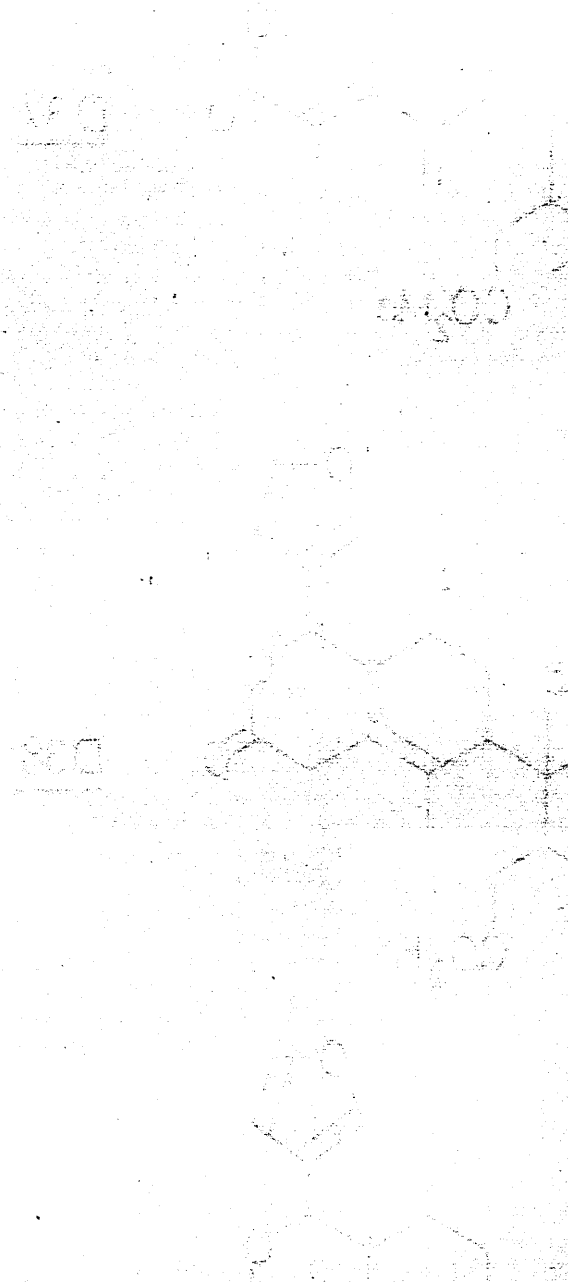
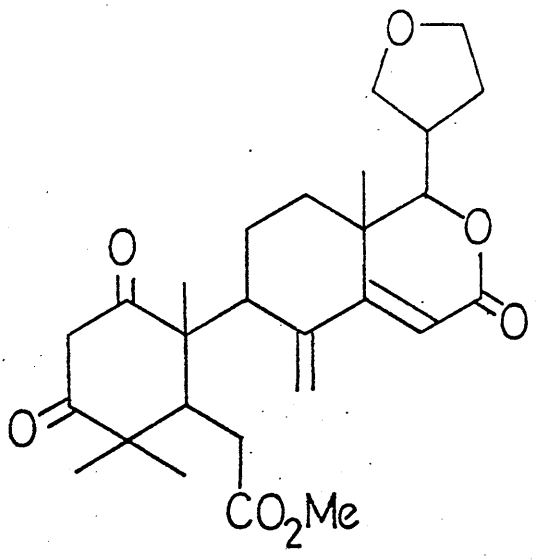
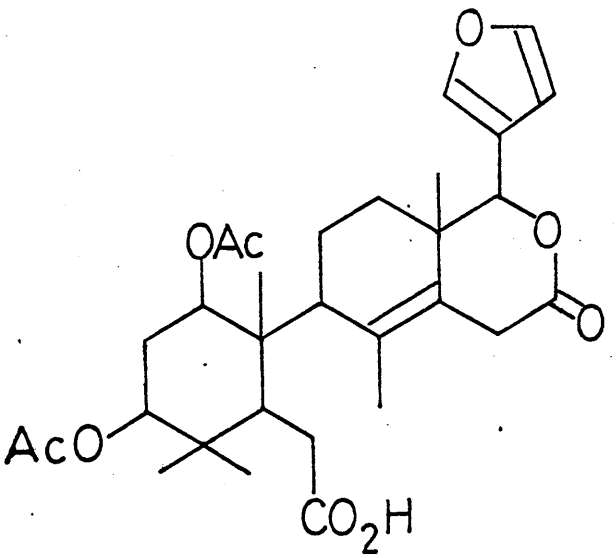


D36





D37



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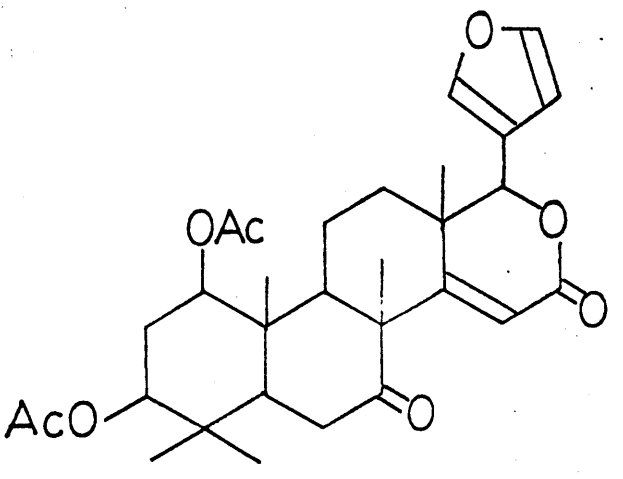
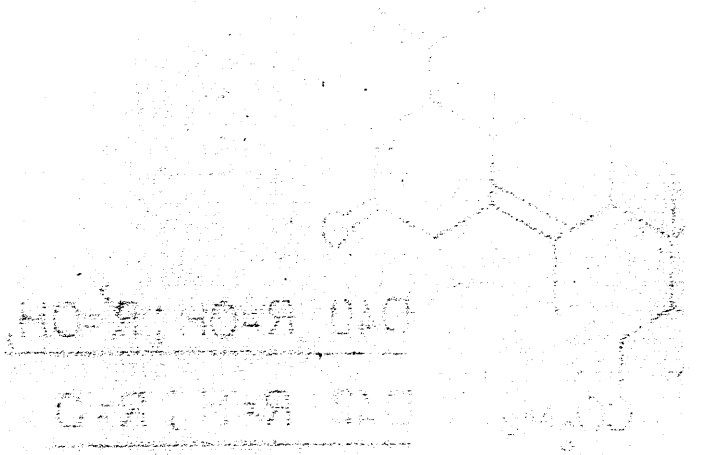
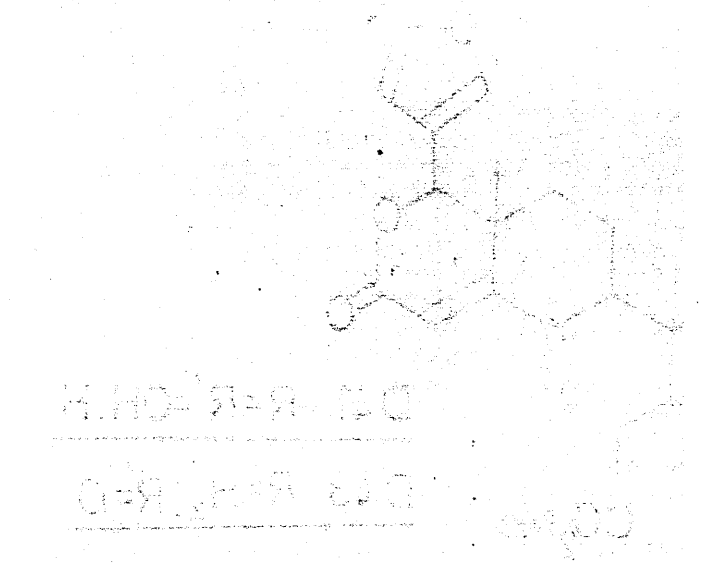
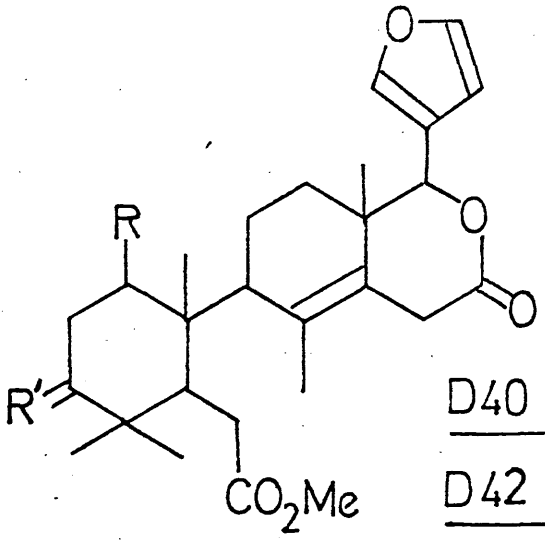


D39

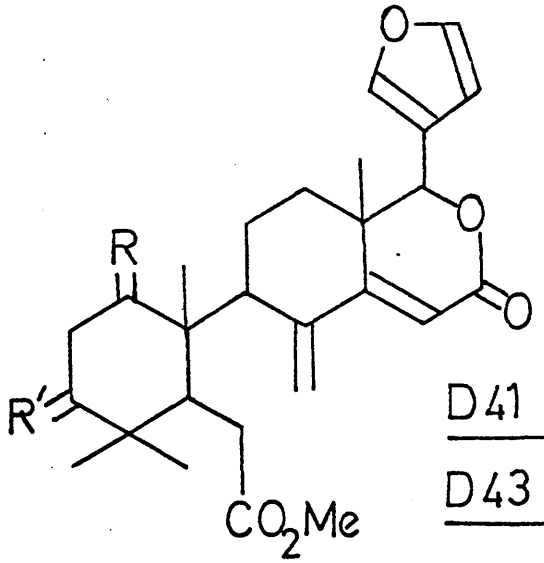






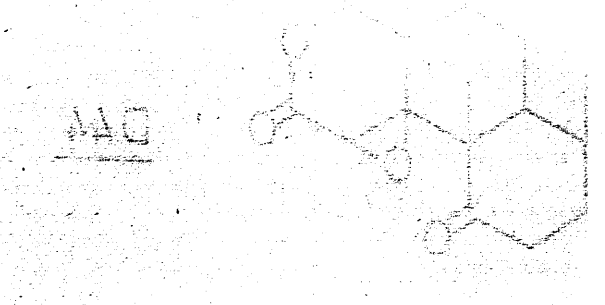
D40 R=OH ; R′=OH,H

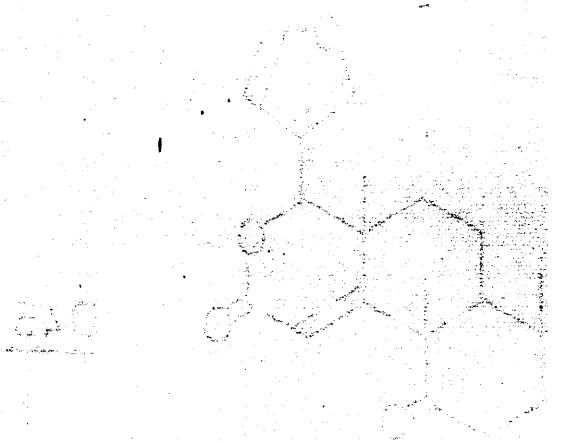
D42 R=H ; R=O

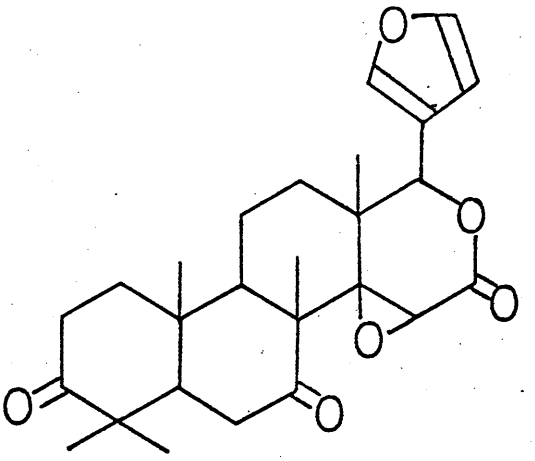


D41 R=R′=OH,H

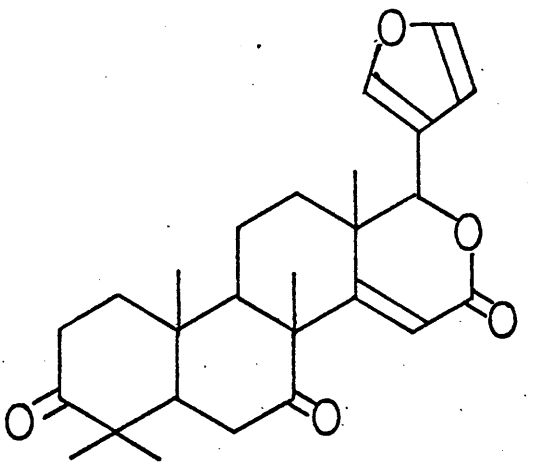
D43 R=H2 ; R′=O







D44



D45

PART III

HYDROXYSKYTANTHINES I and II

INTRODUCTION

Skytanthus acutus Meyen is a member of the sub-family Plumieroideae, native to the Chilean Atacama desert. A number of alkaloids belonging to the rare monoterpene class have been isolated from various parts of the plant. Recent biosynthetic studies confirm that these have an isoprenoid origin. The structure and stereochemistry of two minor Skytanthus leaf alkaloids, hydroxy-skytanthines I and II, are discussed here.

ACKNOWLEDGEMENT

It is a pleasure to thank Professor H.H. Appel, Universidad Tecnica Federico Santa Maria, Valparaiso, Chile, who supplied us with pure samples of hydroxyskytanthines I and II.

REVIEW OF THE CHEMISTRY AND BIOSYNTHESIS OF SKYTANTHUS ALKALOIDS

Extraction of Skytanthus acutus Meyen was reported by various groups[1,2,3] in 1961. A liquid alkaloid, skytanthine, was isolated, b.p. 54°/1.5 mm., $[\alpha]_D$ + 42°, molecular formula $C_{11}H_{21}N$, containing one N-methyl and two C-methyl groups. It was purified via the picrate, m.p. 135-136°, from which it was regenerated by mild base or chromatography on basic alumina. No hydrogen uptake was observed even under vigorous conditions, indicating that the molecule was bicyclic.

Hofmann degradation furnished a basic methine (E2), $C_{12}H_{23}N$, showing the nitrogen atom to be part of a ring. Ozonolysis of the methine (E2) produced formaldehyde and a compound (E3), $C_{11}H_{21}NO$, which gave a positive iodoform test. When treated with peroxytrifluoroacetic acid[4], the ozonolysis product (E3) yielded a liquid (E4), $C_{11}H_{21}NO_2$, which on hydrolysis gave a secondary alcohol (E5), $C_9H_{19}NO$. Jones oxidation of this alcohol produced a ketone (E6), whose I.R. spectrum indicated a cyclopentanone.

Summation of these reactions led to part expression (E1) for skytanthine. . .

The positions of the remaining two carbon atoms and the size of the second ring were established by dehydrogenation of skytanthine over palladised charcoal, which yielded a substituted pyridine. Modified Kuhn-Roth oxidation[5] of this compound gave only acetic acid, indicating that the pyridine ring substituents can be only methyl groups or branched chains. Microanalysis together with NMR established the structure of this pyridine as (E7 a or b) and hence skytanthine as (E8) or (E9). Biogenetic considerations favoured (E8) and (E7a) and these were verified by a direct comparison of the picrate of (E7a) with authentic racemic actinidine picrate[6]. The structure of skytanthine was accordingly established as (E8).

Further investigations[7,8] revealed that skytanthine as previously extracted was a mixture of isomers. Purification of the major isomer via the picrate was possible as before[1,2,3] but thin layer or vapour phase chromatography furnished three isomeric skytanthines. These were identified by stereospecific conversion of α, β, γ and δ nepetalinic acids (E10) of established structure[9,10,11] and

stereochemistry[12] to the corresponding alkaloids (E11). This was accomplished by lithium aluminium hydride reduction of each acid to the corresponding diol which was tosylated and then cyclised by heating with methylamine in a sealed vessel at 100° for 18 hours. Direct comparison (mixed m.p. of picrates) showed that the skytanthine previously isolated via the picrate was the β-isomer. β-skytanthine purified by vapour phase chromatography and regeneration from its picrate had b.p. 88°/10 mm., $[\alpha]_D$ + 16.4°. The other naturally-occurring diastereoisomers were identified as α-skytanthine, $[\alpha]_D$ + 79°, and δ-skytanthine, $[\alpha]_D$ + 9°.

Both thin layer and vapour phase chromatography showed the presence of another volatile component in natural skytanthine oil and this was isolated[13] and identified as a dehydroskytanthine. Hydrogenation of this compound over platinum oxide in acetic acid produced δ-skytanthine and this, together with its NMR spectrum (τ 8.50, 3H, s, vinyl methyl) shows dehydroskytanthine to be (E12) or (E13).

A non-volatile alkaloid isolated originally by Appel[1] as Alkaloid D, m.p. 93-95°, $C_{11}H_{21}NO$, showed[13] hydroxyl absorption in the I.R., and NMR signals in deuteric-

chloroform at τ 9.18 (3H, d, J = 6.5 Hz, secondary methyl), 8.76 [3H, s $>C(OH)CH_3$] and 7.7 (3H, s, N-methyl). Treatment with thionyl chloride gave an unsaturated compound identical with the dehydroskytanthine (E12) or (E13) above, and Alkaloid D was thus assigned the structure (E14) or (E15). We have subsequently studied Alkaloid D (hydroxyskytanthine I) and an isomeric congener (hydroxyskytanthine II) and established their structures and stereochemistry (see later).

The biosynthesis of Skytanthus alkaloids is of interest because (i) they are terpenoid in nature and (ii) they may serve as a link to higher alkaloids[15,16,17,18]. The structure suggests that the piperidine nucleus could be formed from an isoprenoid precursor. Present evidence on the biogenesis of piperidine rings, recently reviewed by Leete[19], has suggested two pathways: (a) from lysine, which gives rise to the piperidine rings of anabasine[20,21] (E17), homostachydrine[22] (E18) and pipecolic acid[23,24,25,26] (E19); (b) from acetate and ammonia, which are the precursors of coniine (E20) and conhydrine[27,28] (E21).

An isoprenoid biogenesis of the skytanthines thus points to a third pathway for the formation of piperdine rings. A preliminary report[29] established that mevalonic acid is indeed a precursor of β-skytanthine. More recent work[30] has confirmed and extended these results. Incorporation of radioactivity from DL-mevalonic acid-2-^{14}C, together with lack of incorporation from DL-lysine-2-^{14}C, showed that the skytanthine skeleton arises from an isoprenoid precursor and not from lysine. Labelling experiments also showed that L-methionine methyl-^{14}C is the precursor of the N-methyl group in skytanthine.

A novel phenomenon in these experiments was the randomisation of the label between the terminal methyl carbon atoms of the monoterpenoid (e.g. geranyl pyrophosphate) intermediate which occurred in 16-month old plants [as in (E22)] but not in 3-year old plants [as in (E23)]. This could possibly be due to enzymatic differences with age but will require further study.

THE CONSTITUTION AND STEREOCHEMISTRY OF HYDROXYSKYTANTHINES I and II

The first non-volatile, crystalline alkaloid to be isolated from Skytanthus acutus was initially[1] assigned the name Alkaloid D and later[13] allocated the structure (E14) or (E15) on the basis of its dehydration to the naturally-occurring dehydroskytanthine (E12) or (E13). Alkaloid D, which is now[14] named hydroxyskytanthine I, and the congeneric hydroxyskytanthine II, are assigned the structures (E24) and (E25) respectively. The structural and stereochemical deductions leading to configurations (E24) and (E25) are based largely on a detailed examination of the NMR spectra of these compounds.

Hydroxyskytanthine I [HS I] (E24), $C_{11}H_{21}NO$, obtained[14] in 0.005% yield from the leaves of Skytanthus acutus, has m.p. 94-95° after purification by sublimation and recrystallisation from cyclohexane, $[\alpha]_D$ + 35.8° (methanol). Hydroxyskytanthine II [HS II] (E25), obtained in 0.001% yield and purified similarly, has m.p. 119-120° $[\alpha]_D$ -38.5° (methanol).

Mass spectral measurements of the two substances show the base peak (100%) in each spectrum at m/e 58, attributable[31] to the ion (E26). Each spectrum also exhibits a peak at m/e 44 (24% in HS I; 53% in HS II) corresponding to the fragment (E27). Peaks at m/e 84 (8%) and 110 (7%) however only appear in the spectrum of HS II and are attributable to the ions (E28) and (E29) respectively.

The NMR spectrum of each compound (Figs. 1 and 2) shows evidence of an N-methyl group (τ 7.75 in HS I; 7.83 in HS II; each 3H, s), a methyl group attached to the carbon of a tertiary carbinol (τ 8.77 in HS I; 8.89 in HS II; each 3H, s) and a secondary methyl group (τ 9.20 in HS I; 9.00 in HS II; each 3H, d, J = 6Hz). The equatorial (β) protons at C-1 and C-3 appear in both compounds as doublets 0.8 to 1.3 τ downfield from the axial (α) protons at these positions, as is the case with N-methyl piperidine[32], showing the N-methyl group to be equatorial. In HS II both of these low-field doublets exhibit a further minor and probably vicinal coupling (see below), whereas in HS I only one of the doublets is so coupled. Accordingly, the tertiary hydroxyl group must be situated at C-4 in HS I and at C-7 in HS II.

These conclusions are readily supported by double irradiation experiments. Thus in HS I strong irradiation at τ 8.3 (1α and 3α protons) collapses the two low-field doublets to a singlet (τ 7.36, H-3β) and a broadened singlet (τ 7.20, H-1β; small vicinal coupling to H-7a). Conversely, irradiation at τ 7.20 (H-1β) produces a broadened singlet at τ 8.32 (H-1α; small vicinal coupling to H-7a) and leaves a doublet at τ 8.25 (H-3α; geminal coupling to H-3β, J = 11Hz). Similarly, irradiation at τ 7.36 (H-3β) results in a singlet at τ 8.25 (H-3α) and a broadened doublet at τ 8.32 (H-1α; geminal coupling to H-1β, J = 9Hz, and small vicinal coupling to H-7a).

In HS II, H-1β and H-3β show as broadened doublets at τ 7.12 (geminal coupling to H-1α, J = 9Hz, and small vicinal coupling to H-7a) and τ 7.42 (geminal coupling to H-3α, J = 11Hz, and small vicinal coupling to H-4). Likewise, H-1α and H-3α show as multiplets at τ 8.37 (geminal coupling to H-3β, vicinal coupling to H-4) and τ 8.09 (geminal coupling to H-1β, small vicinal coupling to H-7a). Double irradiation results are analogous to those for HS I (see above and see Fig.2).

These results clearly show that the α proton attached to C-1 has in each case only a small vicinal coupling to the proton at C-7a and therefore that these protons cannot be trans diaxial. Of the four possible configurations a, b, c and d (Fig. 3) in one antipodal series (that related to δ-skytanthine is shown), b alone satisfies this condition. Accordingly, both HS I and HS II must be cis-fused and exist in conformation b.

Further stereochemical information is derived from the I.R. solution spectra of these compounds, since neither spectrum shows evidence of intramolecular hydrogen bonding. HS I has $\nu_{max.}$ (CCl_4) 3608 cm.$^{-1}$ (shoulder at 3595, possibly two rotamers of -OH) whereas 3-hydroxy-piperidine, which approximates to HS I with a C-4 β hydroxyl, has[33] $\nu_{max.}$ (tetrachloroethane) 3620 (free hydroxyl) and 3534 (bonded hydroxyl cm.$^{-1}$, $\Delta\nu_{OH}$ being 86 cm.$^{-1}$. This indicates that the hydroxyl group in HS I is not bonded and hence is equatorial (α). In the case of HS II, if the hydroxyl at C-7 is axial (β), the shortest -OH....N distance (from Fieser models) is 1.5Å and a strong hydrogen bond would be expected. In fact HS II [$\nu_{max.}$ (CCl_4) 3605 cm.$^{-1}$] shows no hydrogen bonding and the hydroxyl group at C-4 must accordingly be equatorial (α).

The configurations of HS I and HS II are therefore unequivocally established as (E24) and (E25) and it follows that dehydroskytanthine, obtained both naturally[13] and as a dehydration product of HS I, must be formulated as (E13).

EXPERIMENTAL

For general experimental see Part IA.

Isolation of Hydroxyskytanthines I and II*

The extract from the leaves of Skytanthus acutus was prepared as previously described[1] and the greater part of the skytanthines separated by steam distillation. Chloroform extraction of the remaining solution gave a mixture of bases (yield 0.1%) which was chromatographed on alumina, affording successively hydroxyskytanthines I and II. Hydroxyskytanthine I (0.005%) purified by sublimation had m.p. (from cyclohexane) 94-95°; $[\alpha]_D$ + 38.5° (c, 1.50 in cyclohexane), + 35.8° (c, 1.80 in methanol). It had NMR signals at τ 9.20 (3H, d, J = 6Hz, C-7 methyl), 8.77 (3H, s, C-4 methyl), 7.75 (3H, s, N-methyl), 8.32 (1H, d, J = 9Hz, C-1αH), 8.25 (1H, d, J = 11Hz, C-3αH), 7.36 (1H, d, J = 11Hz, C-3βH), 7.20 (1H, d, J = 9Hz, C-1βH). Hydroxyskytanthine II (0.001%) purified by sublimation had m.p. (from cyclohexane)

* This work was carried out by Professor H.H. Appel and Dr. G. Adolphen, who supplied us with pure samples of HS I and HS II.

119-120°, $[\alpha]_D$ -38.5° (c, 1.00 in methanol). Mixed m.p. with HS I showed a strong depression. It had NMR signals at τ 9.00 (3H, d , J = 6Hz, C-4 methyl), 8.89 (3H, s, C-7 methyl), 7.83 (3H, s, N-methyl), 8.37 (1H, d, J = 9Hz, C-1αH), 8.09 (1H, d, J = 11Hz, C-3αH), 7.42 (1H, d, J = 11Hz, C-3βH), 7.12 (1H, d, J = 9Hz, C-1βH).

TLC on Kieselgel G prepared with 0.1 N sodium hydroxide using methanol/chloroform (1:1) as eluant gave for HS I R_f 0.56-0.59 and for HS II R_f 0.30-0.33.

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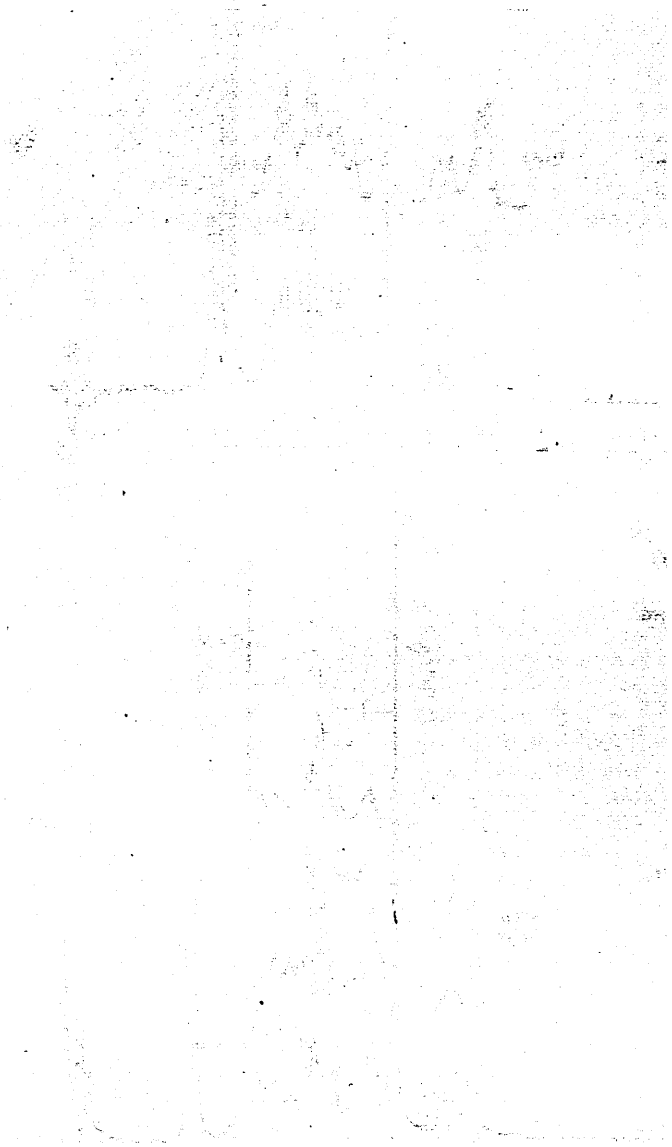
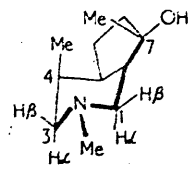
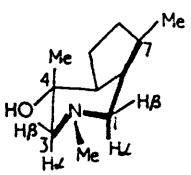




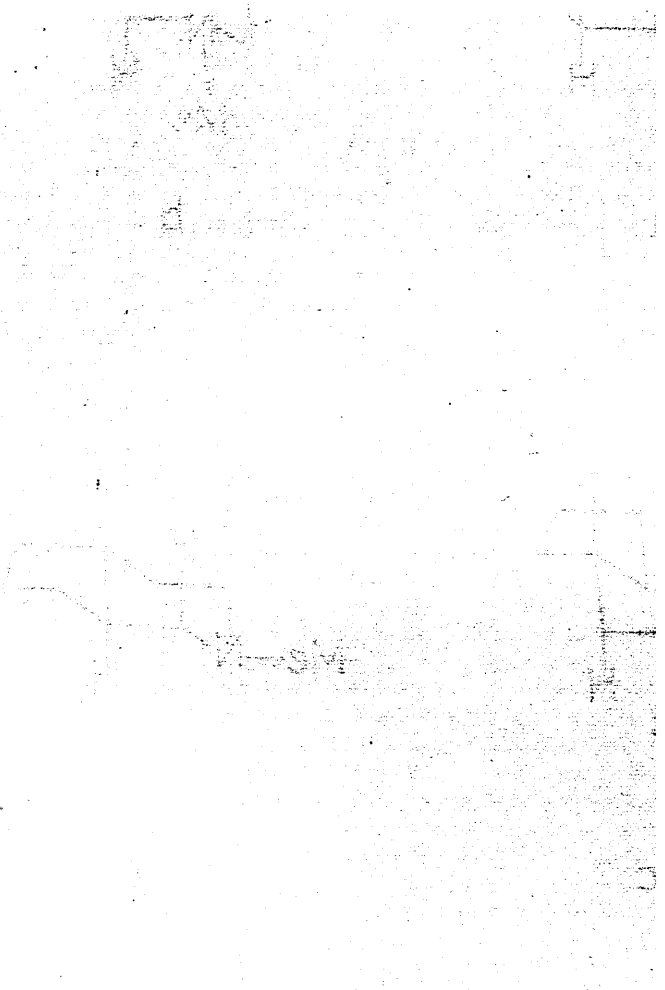
HS-II

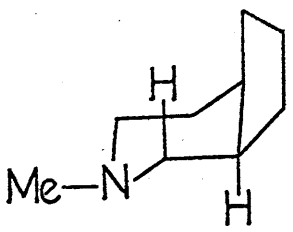
Fig. 2.



HS-I

Fig. 1





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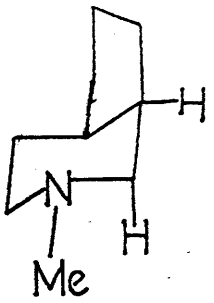

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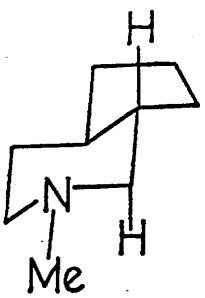

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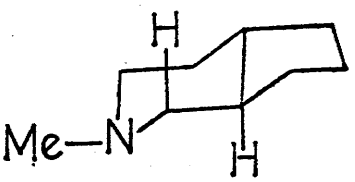
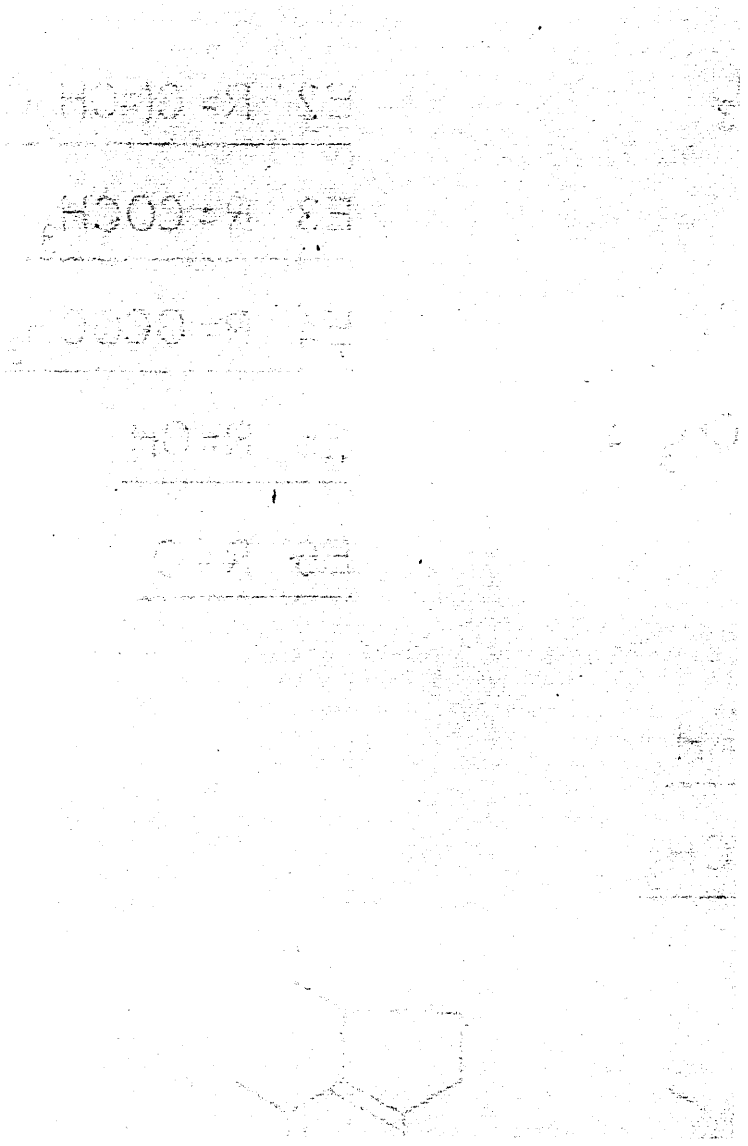
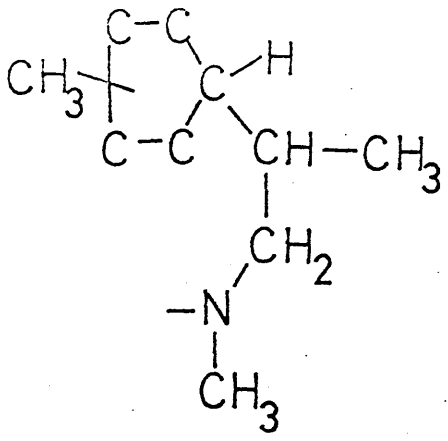


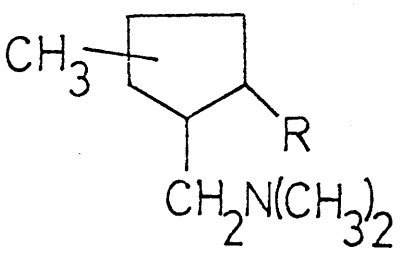
d

Fig. 3





E1



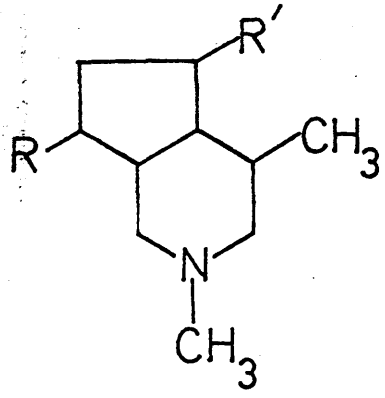
E2 R= $C(=CH_2)CH_3$

E3 R= $COCH_3$

E4 R= $OCOCH_3$

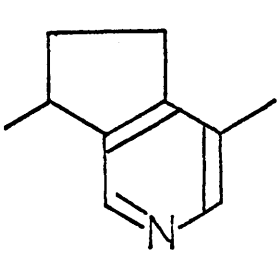
E5 R=OH

E6 R=O



E8 R= CH_3 ; R'=H

E9 R=H ; R'= CH_3



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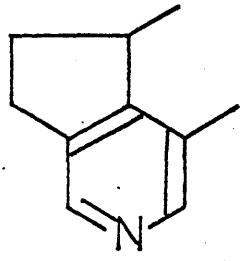
E7



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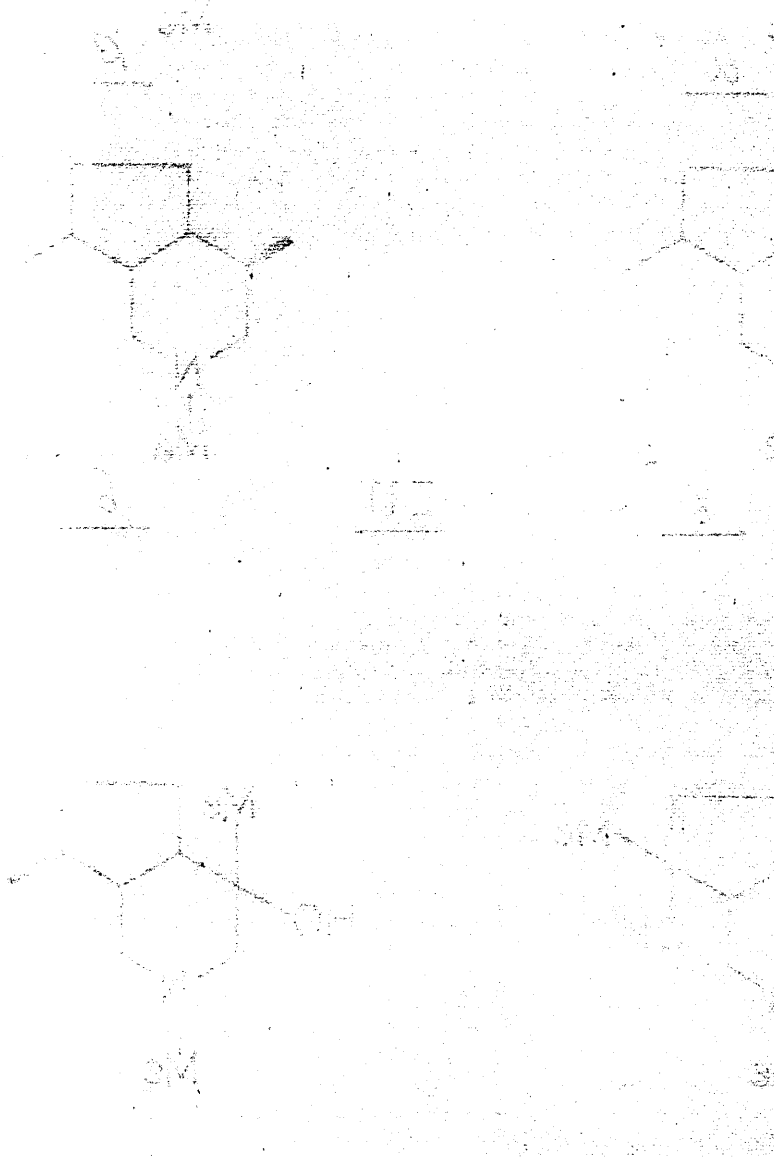
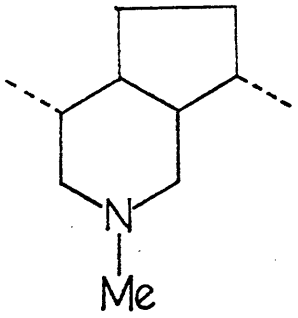
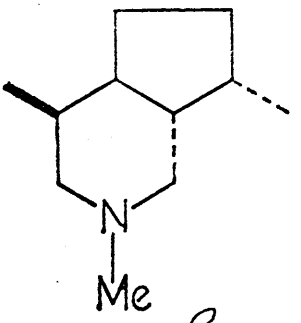




α



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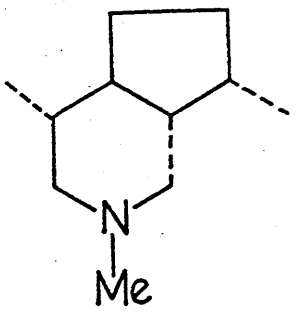
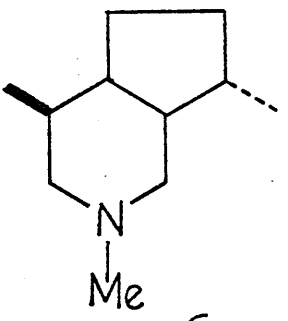


γ

E11



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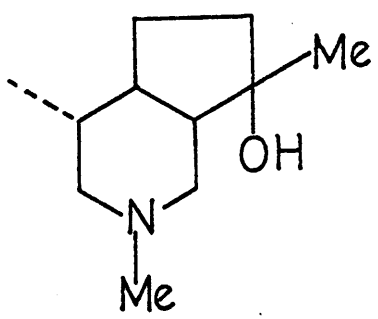

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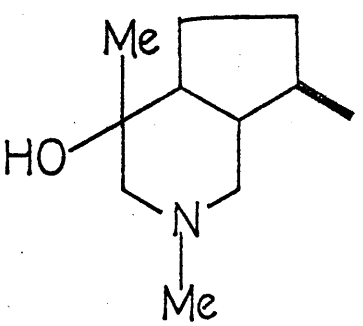

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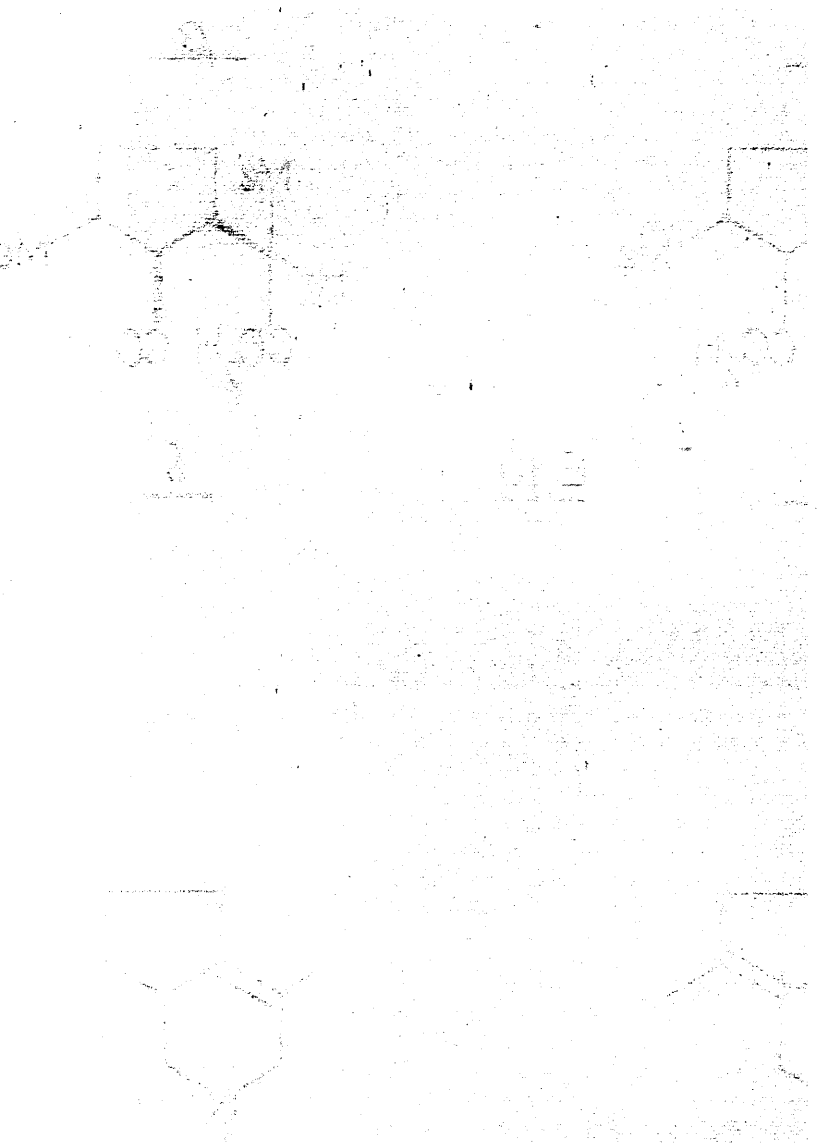

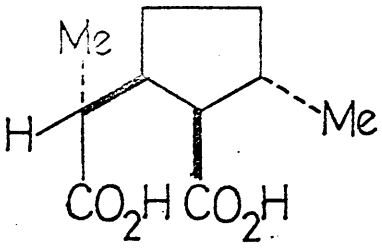

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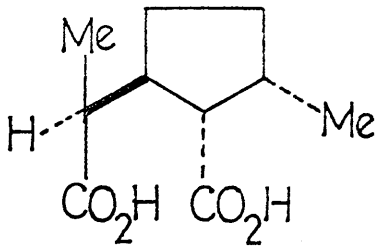

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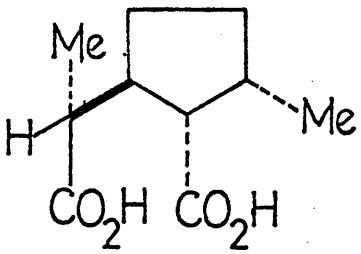
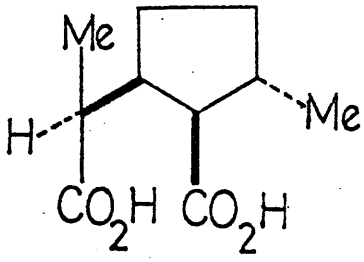


γ

E 10



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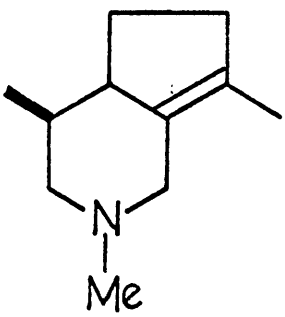

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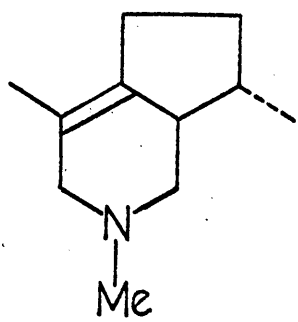

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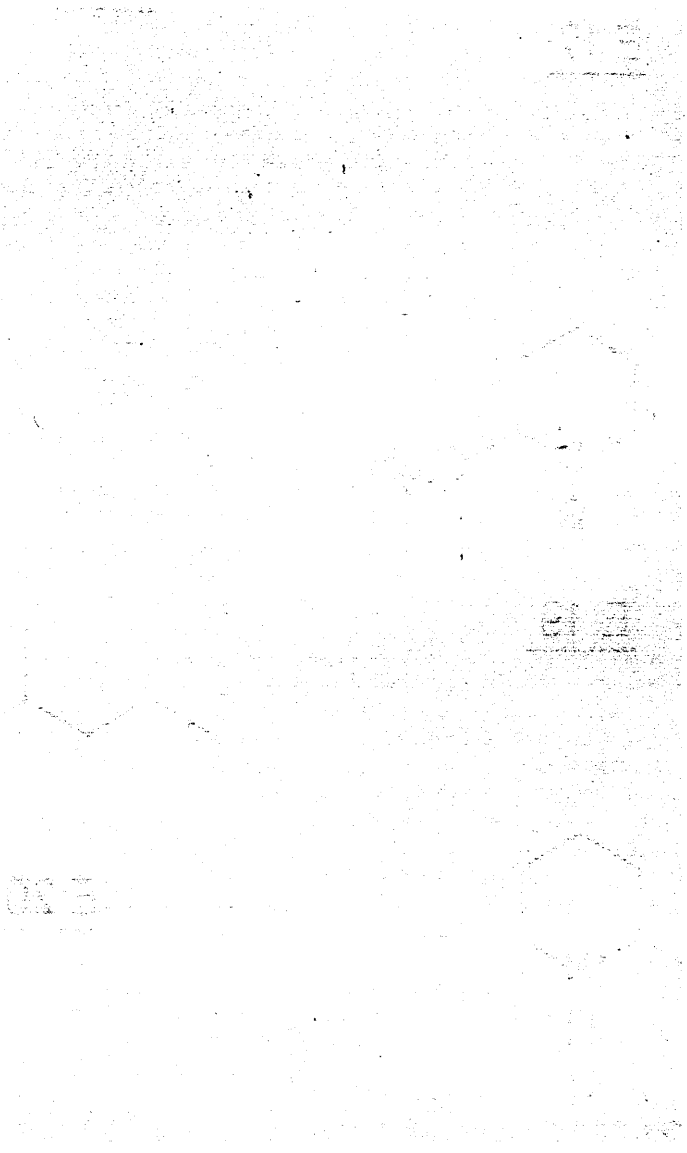

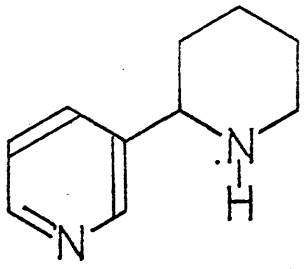

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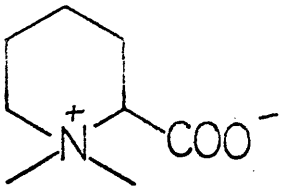

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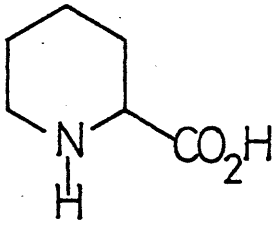

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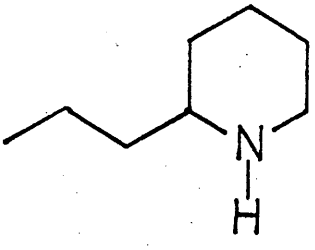

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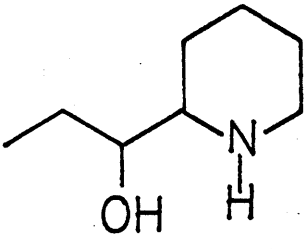

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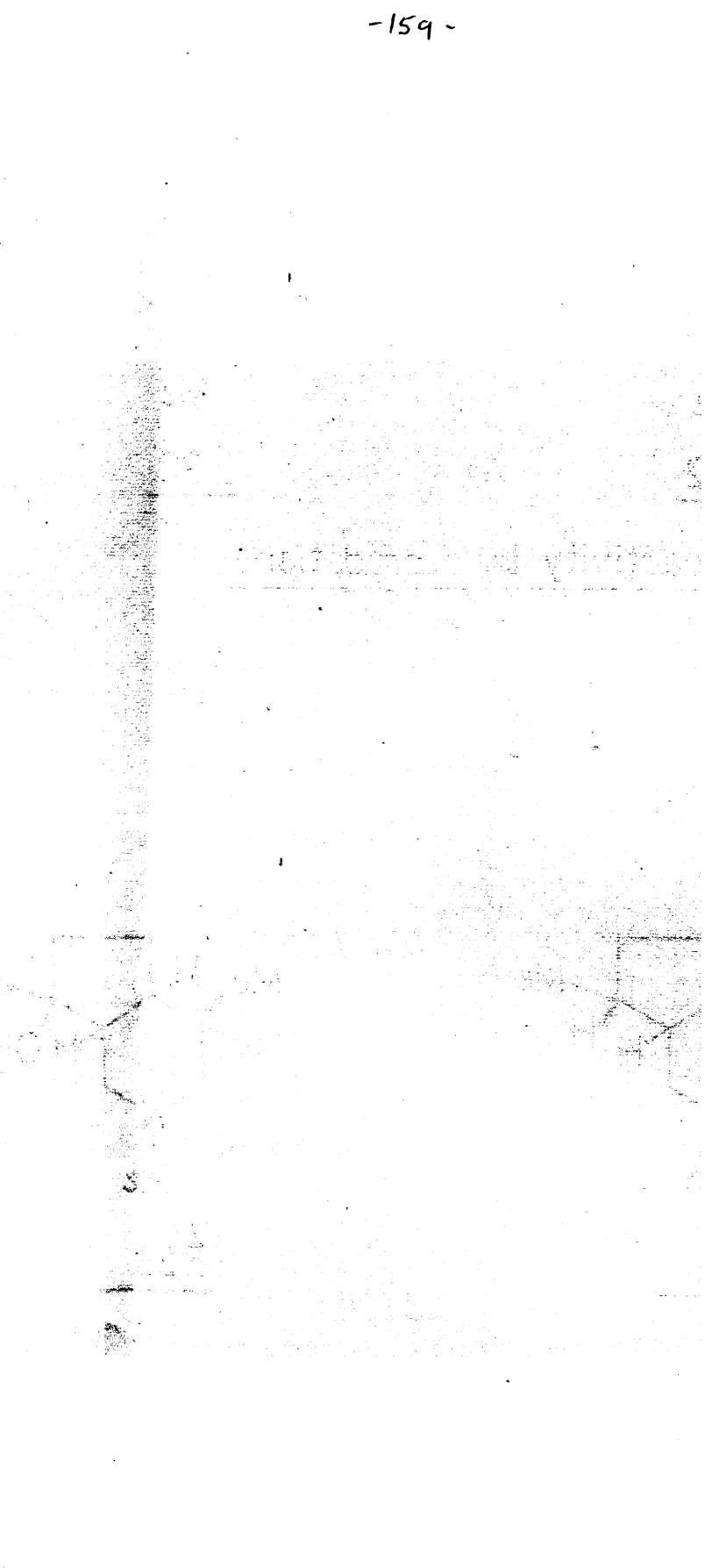

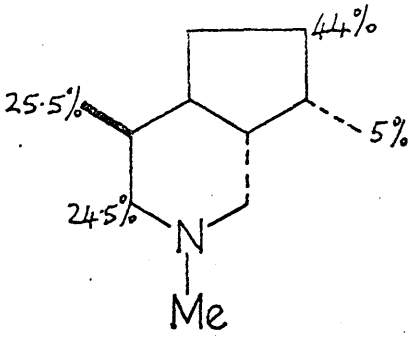

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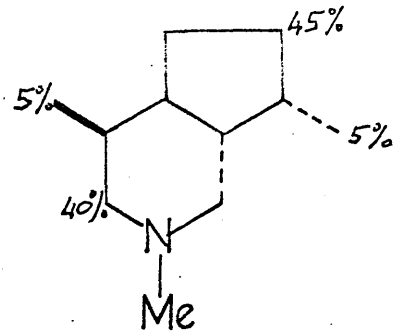
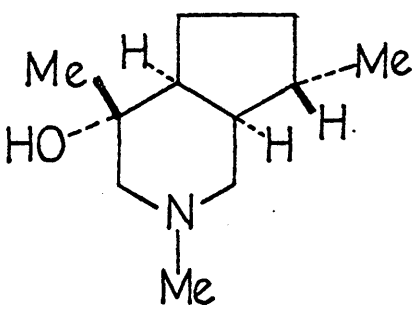


E 23

% Radioactivity by degradation.



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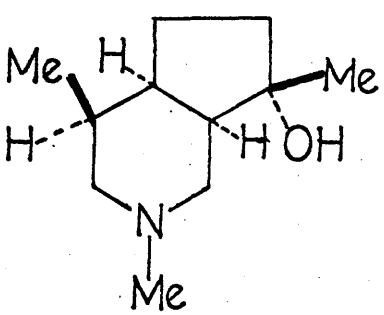

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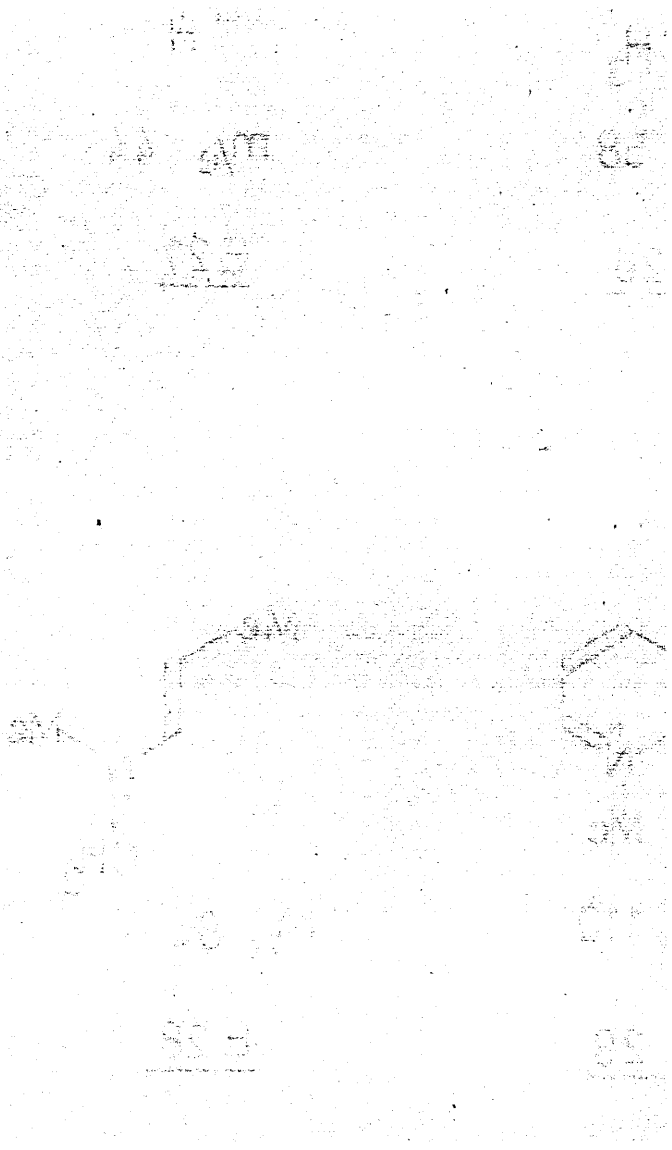
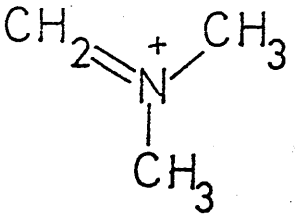
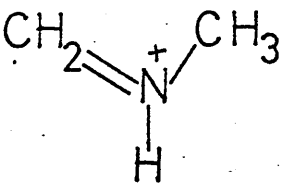




m/e 58

E 26



m/e 44

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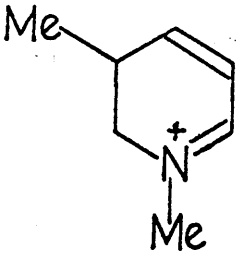

m/e 110

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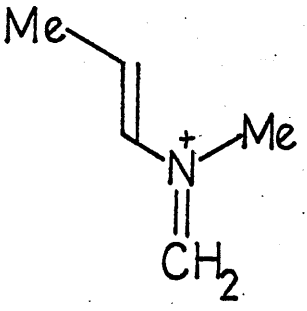

m/e 84

E 28