ISOLATION, STRUCTURAL and STEREOCHEMICAL STUDIES in the TERPENOID FIELD

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by

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SUMMARY

This thesis consists of three sections, each concerned with an aspect of terpenoid chemistry. The first is devoted to the stereochemistry of the diterpenoid lactone, marrubiin. The gross structure of this compound has been secure for some time, but the stereochemistry, apart from the A:B ring junction has been a matter of controversy. Two approaches to the problem were used: the more facile method was felt to be by X-ray analysis of a heavy atom derivative, but attempts to prepare a suitable derivative proved unsuccessful; the other approach was by spectroscopic studies of various derivatives of marrubiin. Combined with information obtained by previous workers, the interpretation of these studies permitted a firm assignation of the stereochemistry of marrubiin.

The second section is concerned with the examination of extractives of the heartwood of Guarea Globra. The compounds isolated proved to be new triterpenoids. The first one described was shown to be a mixture of C_{28}, C_{29} and C_{30} homologues, not readily separable by chromatographic methods. On the basis of chemical and spectroscopic evidence, tentative suggestions as to the structure of these compounds have been made. Eight other compounds were isolated, of which four were closely related, and tentative

structures for them proposed, while for the other four compounds, only in the case of one, was sufficient information obtained to allow a tentative assignment of structure.

The X-ray Crystallographic analysis of the p-iodobenzoate of triol Q acetonide is described in the final section. Triol Q is a diterpene triol from Erythroxylon Monogynum Roxb., isolated as the acetate acetonide, which was converted to the p-iodobenzoate. The structure was solved by Patterson and Fourier syntheses using the heavy atom method of determining the phase angles in the Fourier summations. The atomic parameters were refined by the method of least squares to an R value of 14.4, and since the purpose of the analysis had been achieved, i.e. the determination of the stereochemistry of triol Q, the refinement was terminated. The molecular parameters and geometry are detailed in the tables and figures at the end of this section.

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MARRUBIIN

Marrubiin (I) a crystalline bitter principle of Marrubium vulgare Linne was first isolated in 1842 by Mein[1]. Before 1908, little progress was made in the structure elucidation of the compound, although the extraction procedure was improved[2,3,4,5]. The presence of the γ-lactone was first demonstrated by Gordin[6], hydrolysis of marrubiin in 10% alcoholic sodium hydroxide giving marrubiic acid (IIa), (reported yield, 98%). This compound was reconverted into marrubiin by distillation in vacuo, and it was deduced from the relative ease of hydrolysis to the hydroxy acid, that marrubiin contained a γ-lactone, a proposal subsequently confirmed by infra-red studies[7].

The correct molecular formulae for marrubiin and marrubiic acid were first proposed by Lawson and Eustice[8], as $C_{20}H_{28}O_4$ and $C_{20}H_{30}O_5$ respectively. This evidence, coupled with the production of agathaline (III) by selenium hydrogenation, led to the conclusion that marrubiin was a diterpenoid, probably belonging to the same class as agathic acid, manoyl oxide and sclareol, and having the skeleton (IV). The presence of a hydroxyl group in marrubiin was demonstrated by the Zerewittinoff method[9], and also by dehydration with

thionyl chloride or phosphorus trichloride to a compound $C_{20}H_{26}O_3$ (m.p.98°C) in only moderate yield[8]. Because of the inertness of the hydroxyl group to acetic anhydride and to benzoyl chloride it was concluded to be tertiary.

Hydrogenation of marrubiin over Adam's catalyst in acetic acid gave[8] a moderate yield of tetrahydro-marrubiin (V) (m.p. 134°C), which could be converted by alkaline hydrolysis to tetrahydromarubiic acid (VI). The presence of the furan ring in the side chain was deduced by Cocker et al.[9] on the basis of infra-red and ultra-violet spectral data, and colour reactions. Chromic acid oxidation resulted in oxidative cleavage of the furan ring and production of the dilactone (VII), demonstrating that the tertiary hydroxyl was in the γ-position with respect to the furan residue. Upon ozonolysis of anhydrotetrahydromarrubiin (VIII), hydrolysis yielded a hydroxy-keto acid which proved to be stable in refluxing aqueous sodium hydroxide, eliminating the possibility of the keto acid being a β-keto acid. This left C-4 as the only possible location of the carboxyl group. Since marrubin was known to be γ-lactone C-2 and C-6 are the only possible

positions of attachment of the ether oxygen. The keto acid (IX), available from alkaline permanganate oxidation of marrubiic acid was converted by refluxing in acetic anhydride to an enol-lactone (X)[7]. Since formation of an enol-lactone to C-2 (XI) would be contrary to Bredt's rules, the lactone must be attached to C-6 in marrubiin. This evidence enables the gross structure of marrubiin to be written as (I).

More recently, evidence[10,11], which supports the structure (I) has been obtained, and in addition determines the stereochemistry of the Ring A:B junction. The keto acid (IX) was converted via the corresponding acid chloride by Stephen's reduction to the aldehyde ketone (XII), which on Huang-Minlon reduction gave a mixture of two compounds: the saturated lactone (XIII) and the unsaturated acid (XIV). The same two compounds have been obtained by acid treatment of ambreinolide[12], which has the stereochemistry as shown in (XV). This allows the assignment of stereochemistry at C-10 (β-methyl), and with the proviso that no inversion at C-5 had taken place due to enolisation of the C-6 ketone during the Huang-Minlon reaction, the hydrogen at C-5 as α.

The fact that the two lactones (XIII), the one from marrubiin, the other from ambreinolide, were identical, prompted the conclusion that a knowledge of the stereochemistry at C-8 and C-9 in this lactone would permit assignation of the stereochemistry at C-8 and C-9 in marrubiin[13]. Consequently the hydroxy ketone (XVI) obtainable by permanganate oxidation of sclareol[14], was dehydrated by refluxing in benzene with iodine to give the unsaturated ketone (XVII) which was oxidised to the unsaturated acid (XIV) with sodium hypobromite. This acid was treated with an excess of perphthalic acid, and on acid hydrolysis yielded two lactones (XVIII) and (XIX), due to trans-diaxial opening of the resulting α (or β) epoxides, and subsequent closure of the lactone rings. Dehydration of (XIX) in pyridine and thionyl chloride yielded the unsaturated lactone (XX), which demonstrates the C-8 hydroxyl in (XIX) to be axial, otherwise dehydration would have given the exomethylene compound (XXI). Assuming the two hydroxyls have a trans-diaxial relationship, then the hydroxyl at C-9 is also axial, and α-orientated. Osmylation of the unsaturated acid (XIV) yielded a diol-acid[15] (XXII) which was converted by acid treatment to the lactone (XXIII)

and this was dehydrated with pyridine and thionyl chloride to give the unsaturated lactone (XXI). For dehydration to have taken place exo to the ring, the hydroxyl at C-8 must have been equatorial, and α-oriented. Since osmium tetroxide forms cis-diols, this provides additional support for the assumption that the hydroxyl at C-9 in (XXIII) and also (XXI) is axial and α-oriented. Hydrogenation of the unsaturated lactone (XX) gave predominantly the same saturated lactone (XIII) as that obtained by isomerisation of ambreinolide, and since addition of hydrogen from the α-face seemed probable, the methyl group at C-8 was assigned the β-orientation. Hydrogenation of the other unsaturated lactone (XXI) resulted in predominantly the C-8 epimer of (XIII) which was clearly different in its physical properties from (XIII). On the basis of the above evidence it was claimed that marrubiin had a β-oriented side chain at C-9, and a β-oriented methyl group at C-8.

A synthetic scheme has been recently proposed[16] which is based on the conversion of the keto-ester (XXIV), via the diene-lactone (XXV), to the keto-lactone (XXVI) which is available by oxidation of anhydromarrubiin[11]. This route, however, has been abandoned because

unwanted rearrangements were more facile than was anticipated. Attempts to alkylate the keto-function at C-9 in (XXVI), obtained from marrubiin, using Grignard reagents and lithium alkyls failed, but addition of acetylene and ethyl propiolate gave a moderate yield of the corresponding acetylenic alcohols. This latter product gave on hydrogenation and chromatography, 8% of a compound (m.p. 220 - 225°C) whose structure was given as (VII), but which was not, however, identical with the dilactone obtained from marrubiin.

Marrubium vulgare L. is the principal source of marrubiin, although it is present to a small extent in Ballota foetida, and has recently been found[17] in Leonotis Leonurus R.Br.

DISCUSSION

The Stereochemistry of Marrubiin.

Since the absolute stereochemistry of marrubiin (I) at C-5 and C-10 had been established[11] previously, the problem now remaining was to determine the stereochemistry at C-4, C-6, C-8 and C-9. Two possible approaches to this end were envisaged. The first method was by X-ray crystallographic analysis of a suitable heavy atom derivative: the second was by spectroscopic studies of various derivatives of marrubiin. The attempts to form a heavy atom derivative of marrubiin have met with no success, but the spectroscopic work has been much more fruitful, although the stereochemistry at C-8 and C-9 has not been rigorously proved.

The stereochemistry of the γ-lactone fusion was shown to be cis and β in the following manner. The N.M.R. spectra of marrubiin (I), tetrahydromarrubiin (VIII and the ether (XXVII), m.p. 124-125°C, showed poorly resolved triplets for the C-6 proton at τ 5.25, 5.30 and 5.80 respectively (multiplet width 10-14 c.p.s.)

Furthermore, marrubenol (XXVIIIa), marrubanol (XXIX) and the oily mono-acetate (XXVIIIb) $[\alpha]_D = -6^\circ$ showed

broadened singlets for the proton C-6 at τ 5.78, 5.78 and 5.66 respectively ($W_{\frac{1}{2}}$ = 6-8 c.p.s.). This narrow range of resonance is indicative of an equatorial (α) proton at C-6, since it would experience only two axial-equatorial couplings, plus one equatorial-equatorial coupling, as it has two neighbouring axial protons, at C-5 and C-7, plus an equatorial one at C-7.

The keto-aldehyde (XXX), m.p. 110-111°C, showed an absorption in the N.M.R. at τ -0.45 for the aldehyde proton, which is considerably lower than the values quoted for either an axial (~ τ 0.2) or an equatorial (~ τ 0.5) aldehyde[18]. The shift is probably due to the deshielding effect of the carbonyl at C-6. A similar downfield shift was apparent in the spectrum of the only keto-acetate (XXXI), $[\alpha]_D$ = +6°, which showed a quartet (J = 12 c.p.s.) centred at τ 5.30 ($-C\underline{H}_2OAc$), which is lower than that anticipated for an axial (τ 5.70 - 5.90) or an equatorial (τ 6.15 - 6.35) primary acetate[19]. The mono-acetate (XXVIIIb) showed a quartet (J = 12 c.p.s.) centred at τ 5.44 ($-C\underline{H}_2OAc$), the downfield shift in this case being caused by the axial hydroxyl at C-6. The magnitude of this downfield shift would be better rationalised as deriving from an axial rather than an equatorial primary acetate being deshielded by the axial C-6 hydroxyl.

This reasoning, however, led only to tentative conclusions, and to resolve the problem, attempts were made to remove the deshielding oxygen function at C-6. The first route tried was by hydride reduction of the tosylate of marrubiic acid (IIa), but all attempts to tosylate the hydroxyl at C-6 led to marrubiin, or to the recovery of starting material. Similarly, tosylation of marrubenol yielded only the ether (XXVI) and this route was abandoned.

Attempts to reduce the keto-acid (IX) by the Wolff-Kishner method led to a cyclic hydrazide (XXXII)[10]. Consequently the keto-acetate (XXXI) was treated with hydrazine and potassium hydroxide in ethylene glycol in the Huang-Minlon method (2 hrs. at 180°) but only the starting material was obtained on methylation. More vigorous conditions[20,21], produced a mixture of products, all more polar than the starting material, and no further attempts were made in this direction.

The keto-acetate (XXXI) was subjected to thio ketalisation in varying conditions. The milder methods resulted in recovery of the starting material, while more vigorous conditions resulted in decomposition to complex mixtures. Attempts to form a thioketal

of the keto-acid (XXXIIIa), m.p. 158-159°C, or its methyl ester (XXXIIIb) also met with no success.

Previously, the enol-lactone (X) had been prepared from the keto-acid (IX)[7] by refluxing in acetic anhydride with a little fused sodium acetate. Attempts to form the enol-lactone (XXXIV) corresponding to the keto-acid (XXXIIIa) were unsuccessful using the reported conditions[7,11]. Under these conditions, only the mixed anhydride (XXXIIIc), m.p. 156-157°C, was obtained. However, conversion to the enol-lactone (XXXIV), m.p. 154-156°C, (90% yield) was achieved by using a much larger proportion of sodium acetate in the reaction mixture. The N.M.R. spectrum of this compound showed the absence of olefinic protons, favouring the structure as written, rather than with the Δ^6 double bond. Upon hydrogenation of the enol-lactone (XXXIV) over Adam's catalyst in acetic acid, hydrogenolysis of the vinyl oxygen occurred, giving the desoxy-acid (XXXVa), m.p. 140-142°C, as the main product. Two other products were obtained, corresponding to saturation of the double bond. One was tetrahydromarrubiin (V), arising from addition of hydrogen to the α-side, while the other corresponded to an isomer of tetrahydromarrubic

acid, probably due to hydrogenation from the β-side. Examination of models shows that the lactone produced by hydrogenation from the β-side would be highly strained, and this probably opened to give the stericly more favourable dihydroxy acid (XXXVI) m.p. 103-105°C. In one hydrogenation of several, using a different batch of catalyst, the oily bis-desoxy-acid (XXXVIIa) was afforded as the major product, along with the desoxy-lactone (XXXVIII), m.p. 94-98°C, corresponding to an additional hydrogenolysis of the hydroxyl at C-9. The desoxy-acid (XXXVa) was methylated, and the product converted as an oily alcohol (XXXVb), $[\alpha]_D = -3.3^\circ$, by hydride reduction. The corresponding oily acetate (XXXVc), $[\alpha]_D = +4.4^\circ$, was prepared by treatment of the alcohol with acetic anhydride in pyridine, and in the N.M.R. showed a quartet (J = 12 c.p.s.) centred at τ 5.90 ($C\underline{H}_2OAc$) as expected (τ 5.70 - 5.90)[19] for an axial primary acetate. Furthermore, oxidation of the alcohol (XXXVb) with Sarett reagent provided the unstable oily aldehyde (XXXVd) P m/e = 322, the N.M.R. of which showed a resonance resulting from the aldehydic proton at τ 0.14 (1 H singlet) which is in good agreement with that expected for an axial aldehyde group[18].

The bis-desoxy-acid (XXXVIIa) was converted to the corresponding acetate (XXXVIIb), m.p. 76-77°C, and the oily aldehyde (XXXVII.), $[\alpha]_D$ = +12.2°, by the same route, and a study of their N.M.R. spectra (τ 5.90; $C\underline{H}_2OAc$: τ 0.14; -$C\underline{H}$O) led to the same stereochemical conclusions, i.e. that the lactone fusion is cis and β-oriented.

Confirmation of the stereochemistry at C-4 and C-6 was available from pK^*_{mcs} measurements, and infra-red spectroscopic studies. The pK^*_{mcs} of marrubiic acid (6.66) and tetrahydro marrubiic acid (6.71) are both well below that expected[22] for either an axial or equatorial carboxyl group, the effect probably arising from stabilization of the carboxylate anion by hydrogen bonding to the secondary hydroxyl group at C-6. The two acids and the corresponding methyl esters all showed strong intramolecular hydrogen bonding in their infra-red spectra. Similar compounds[23] of known stereochemistry, namely 6α-hydroxy-12-deoxyenantiopodocarpic acid (XXXIXa) and the methyl ester (XXXIXb) showed[24] closely analgous behaviour in the infra-red, while the acid (XLa) and methyl ester (XLb), epimeric at C-6 showed different infra-red

results thus confirming the cis (β) lactone fusion in marrubiin - See Table I.

This orientation of the lactone ring was suggested earlier[7], but refuted by more recent workers[25], whose evidence consisted of lithium in liquid ammonia, and sodium borohydride in methanol reductions of the keto-acid (XXXIIIa) which led to better than 70% yields of tetrahydromarrubiic acid (VI). Hydride reduction would be expected to yield the β-hydroxyl at C-6, due to attack of the hydride ion from the α-face[26], but it was claimed that the carboxyl function at C-4 was α-oriented, and would exert an electrostatic shielding effect which would prevent attack of the hydride ion from the α-face, resulting in the reduction yielding the α-hydroxyl at C-6, and hence it was claimed that marrubiin should have a cis (α) lactone fusion. This evidence, however, would be more in accordance with a cis (β) lactone fusion, the β-carboxyl function at C-4 adding to the hindrance of the β-face, and hydride ion attack being directed from the α-face as expected.

There is further purely chemical evidence, consonant with the assignment of a cis (β) lactone ring. Thus: (a) the ready formation of the ether (XXVII) on attempted

brosylation of marrubenol (XXXVIIIa) removes a 1,3-diaxial non-bonded interaction; (b) the observation[11] that the olefin (XLI) results in at least 50% yield from treatment of the hydroxy-acid (XLII) with tosyl chloride and pyridine at 20°C, would indicate a facile trans-diaxial elimination of p-toluene sulphonic acid from the intermediate ester; (c) hydrogenation of the enol-lactone (XXXIV) yielded a larger proportion of tetra-hydromarrubiin (V) than the dihydroxy acid (XXXVI) corresponding to the greater ease of hydrogenation in the less hindered (α) side of the molecule; (d) the secondary hydroxyl in marrubenol (XXVIIIa) is fairly resistant to acetylation, giving mainly the mono-acetate (XXVIIIb) which is, however, readily oxidised to the keto-acetate (XXXI)- showing reactivity typical of an axial secondary alcohol.

From a study of the unusually high absorptions of the tertiary hydroxyl in the infra-red spectra of marrubiin (I) (ν_{OH} 3626 cm.$^{-1}$ free; 3587 cm.$^{-1}$ bonded), tetrahydromarrubiin (V) (ν_{OH} 3630 cm.$^{-1}$ free), the mono-acetate (XXVIIIb) (ν_{OH} 3625 cm.$^{-1}$ free; 3585 cm.$^{-1}$ bonded) and the keto-acetate (XXXI) (ν_{OH} 3630 cm.$^{-1}$ free; 3583 cm.$^{-1}$ bonded), it seems likely that there is a

similar steric situation around C-8, C-9 and C-10 in these four compounds. It would be expected, that if the secondary methyl group at C-8 were axial, the change from the mono-acetate to the keto-acetate would produce a similar upfield shift in the N.M.R. of about 15 - 20 c.p.s.[27], for the resonances of the C-8 and C-10 methyl groups. Although the C-10 methyl group is shifted upfield as expected (22 c.p.s.), the secondary methyl group at C-8 shifts downfield by 3.5 c.p.s., and is therefore probably equat-orial. This configuration at C-8 was previously suggested[7] on the basis of the keto-lactone (XXVI) being unchanged by refluxing caustic soda, although if the methyl group were axial, it would easily epimerise, perhaps even under the conditions of formation.

Marrubiin (I) and tetrahydromarrubiin (V) were found to be fairly resistant to dehydration in conditions favourable for ionic elimination, and in fact required to be refluxed in phosphorus oxychloride and pyridine for three hours, and even then, dehydration did not go to completion. It was at first thought[28], that this low rate of dehydration was due to the fact that the hydroxyl at C-9 was equatorial, since we had shown that the C-8 proton was very probably axial. The product of

dehydration was one spot on t.l.c. but was shown by N.M.R. to consist of two compounds, anhydromarrubiin (XLIII) (33%) and the uncharacterised anhydromarrubiin (XLIV) (67%). With the proviso that (XLIII) is not an intermediate in the function of (XLIV), this shows that the hydroxyl at C-9 is axial and α-oriented. Previously, the only compound isolated from the dehydration of marrubiin was (XLIII) which prompted the conclusion that the C-9 hydroxyl was equatorial, and could dehydrate only exo to the ring[7], but it was pointed out[11], that the major dehydration product was an oil which had not been characterised, and that the above conclusion was unsound. It now seems possible, that since the hydroxyl is axial, the reason for such a slow dehydration is that the axial proton at C-8 is relatively inaccessible to base.

The axial (α) orientation of the hydroxyl at C-9 is confirmed by Mangoni's[13] conclusions concerning the stereochemistry of the iso-ambreinolide (XIII) to which marrubiin can be degraded[11]. The reasoning of the Italian workers for the stereochemistry at C-9 seems reasonably acceptable, although we disagree with the conclusions about C-8. The structures of the two unsaturated lactones (XX) and (XXI) seem reasonably

secure. Hydrogenation of (XX) over Adam's catalyst in acetic acid gave mainly the iso-ambreinolide (XIII) which is available by degradation of marrubiin, while hydrogenation of (XXI) in the same conditions gave predominantly the C-8 epimer. In the former case, it was claimed that addition of hydrogen had occurred from the α-side of the molecule, but examination of models indicates that α-face hydrogenation is much more likely in the exo (XXI) rather than the endo (XX) isomer, and it would appear likely that the assignments of these workers[13] should be reversed. Thus, iso-ambreinolide possesses an equatorial (α) methyl at C-8. The conclusion gains support from the conversion of ambreinolide (XV) to the iso-ambreinolide (XIII) available by degradation of marrubiin. The isomerisation is effected in 70% sulphuric acid at 60°C [12], probably via the unsaturated acid (XIV) which is protonated and relactonised (at C-9) in a trans-diaxial fashion, yielding an equatorial methyl group at C-8, and an equatorial β-oriented side chain at C-9.

Further confirmation of the conclusions concerning C-9, is available from synthetic studies[16]. The keto-lactone (XXVI) from marrubiin, upon treatment with ethyl propiolate, followed by hydrogenation, and chromato-

graphic purification afforded a dilactone (VII) m.p. 220-225°C in 8% yield overall, which was not identical with that obtained by oxidation of marrubiin. This difference might be due to epimerisation of the C-8 methyl, but this seems unlikely because it is already equatorial in the present compound. More probably, the two are epimers at C-9, since attack of the propiolate ester would be favoured from the unhindered α-side of the molecule, giving a β-hydroxyl, which would subsequently lactonise with the α-side chain ester. This confirms the α-orientation of the hydroxyl at C-9 in marrubiin, and on the basis of the above arguments, the stereochemistry of marrubiin may be formulated as (XLV),

The Hydrogenation of Marrubiin and its Derivatives.

Previous workers[7,8,9] have prepared tetrahydromarrubiin (V) by hydrogenation of marrubiin (I) over Adam's catalyst in acetic acid in poor yield. Hydrogenation under these conditions yielded[11] tetrahydromarrubiin (V) plus two hexahydromarrubiins, m.p. 150° and 80°C respectively. In our hands hydrogenation of marrubiin over Adam's catalyst in ethyl acetate

afforded, in addition to the compounds previously mentioned, octahydromarrubiin (XLVI) m.p. 88-89°C which showed only one absorption below τ 7.5 in the N.M.R. which was the broadened triplet at τ 5.36 (J = 5 c.p.s.) corresponding to the C-6 proton. Furthermore a single peak at τ 8.76 (6 H) corresponded to the tertiary methyls, at C-4 and C-10; two doublets at τ 9.05 (J = 5 c.p.s.) and τ 9.12 (J = 5 c.p.s.) plus a triplet at τ 9.10 (J = 5 c.p.s.) corresponded to the methyl group at C-8 and the secondary and primary methyl groups in the saturated side chain. This compound is formed as a result of hydrogenolysis on each side of the furan oxygen.

The two hexahydromarrubiins were found to be closely similar in chromatographic polarity, but were eventually separated by repeated thin layer chromatography. The more polar of the two, hexahydromarrubiin II, m.p. 150-152°C, analysed for $C_{20}H_{34}O_4$, showed a triplet in the N.M.R. at τ 6.28 (2 H; J = 6 c.p.s.) due to the system CH_2-$C\underline{H}_2$-OH, and can thus be formulated as (XLVIIa). Difficulty was experienced in crystallising hexahydromarrubiin I, and it was characterised as its acetate (XLVIIIb), m.p. 121-123°C which analysed for $C_{22}H_{36}O_5$, and showed a doublet in the N.M.R. centred at τ 6.06

(2 H; J = 6 c.p.s.) due to CH-C$\underline{H}_2$-OAc. Therefore, hexahydromarrubiin I can be represented as (XLVIIIa).

Recent work[29] has shown that tetrahydromarrubiin, as obtained by hydrogenation of marrubiin, is not a single compound, but the expected mixture of two forms, epimeric at the point of attachment of the tetrahydrofuran. The two epimers were separated by fractional crystallisation, affording the two epimers which had m.p. 139° and 116°C respectively. In all probability, therefore, octahydromarrubiin (XLVI) and both hexahydromarrubiins (XLVIIa), (XLVIIIa), consist of epimeric mixtures, but no effort has been made to separate them.

Marrubanol (IL) was obtained[7] by hydrogenation of marrubenol (XXVIIIa) in about 40% yield giving needles m.p. 175°C, $[\alpha]_D^{20}$ = 15.15°. In our hands, hydrogenation of marrubenol afforded two compounds. The less polar, major component, m.p. 142-144°C, $[\alpha]_D^{25}$ = 37.2°, analysed for $C_{20}H_{36}O_4$, and had N.M.R. corresponding to marrubanol (IL) (two isomers epimeric at C-13). The more polar component analysed for $C_{20}H_{38}O_4$, had m.p. 178-180°C, $[\alpha]_D^{25}$ = 7.15° and fit for a hexahydromarrubenol, (four isomers - isomeric in

the position of the side chain primary alcohol and epimeric at C-13).

Attempts at the Formation of a Heavy Atom Derivative.

In attempting to form a heavy atom derivative of marrubiin, the necessity to retain stereochemical identity at all relevant centres was always considered. The most attractive site for introduction of a heavy atom was the furan ring, and attempts to functionalise it were made. Experiments aimed at Friedel-Crafts acetylation of the furan led to elimination of the tertiary hydroxyl at C-9, and a poor yield of mixed products. No Diels-Alder adduct could be obtained satisfactorily. Bromination reactions using N-bromosuccinimide were tried, but were unsuccessful.

The second site considered for appending a heavy atom group was the γ-lactone, which was opened by alkaline hydrolysis, yielding marrubiic acid (IIa) which was recyclised to marrubiin to show that no stereochemical change had occurred on hydrolysis. Acetyl marrubiic acid (IIb) was known to be a crystalline compound[8] (m.p. 112°C), and preparation of the corresponding iodoacetate was attempted. Treatment of marrubiic

acid with chloroacetic anhydride in dry pyridine at room temperature (the conditions used for cedrelone[30],) afforded only unchanged starting material, while refluxing afforded the mixed anhydride (IIc), $\nu_{max.}^{CCl_4}$ = 1515, 1750 cm.$^{-1}$. Attempts to form the m- and p-iodobenzoates using the corresponding acid chlorides in pyridine were also unsuccessful. When marrubiic acid was treated with brosyl chloride in pyridine, the only product obtained was marrubiin, due to closure of the lactone. The silver salt of marrubiic acid was prepared, but precipitated from solution as a flocculent solid, which showed a strong absorption in the infra-red at 1550 cm.$^{-1}$ typical of the carboxylate anion. The silver marrubiate (L) could not be crystallised in suitable form.

Marrubiin was reduced to marrubenol by refluxing with lithium aluminium hydride in dry tetrahydrofuran the reported[7] method proving much less satisfactory owing to the very low solubility of marrubiin in ether. Both the p-iodobenzoate (XXVIIIc) and the 3,5-dibromobenzoate (XXVIIId) of marrubenol were prepared, but in spite of exhaustive thin layer chromatography, neither could be induced to crystallise. On treatment of marrubenol with brosyl chloride in pyridine, the ether (XXVII)

was obtained as the sole product, the formation of this compound probably being due to the C-6 hydroxyl acting as a nucleophile, replacing the first formed brosylate on the primary alcohol

The brosylate and p-iodobenzoate of hexahydro-marrubiin (II) (XLVIIb) and (XLVIIc) respectively were prepared, but neither compound was obtained in crystalline form.

EXPERIMENTAL

All m.p.s were determined on a Kofler block. Specific rotations refer to chloroform solutions at room temperature unless otherwise stated. Infra-red solution spectra were kindly recorded by Mrs. F. Lawrie on a Unicam SP.100 Mark II spectrophotometer with a prism grating monochromator, and operated with evacuated optics. Liquid film and nujol spectra were recorded on a Unicam SP.200 spectrophotometer. Microanalyses were by Mr. J.M.L. Cameron and his staff. Nuclear magnetic resonance spectra were run on a Perkin-Elmer R.10 and a Varian Associates HA.100 spectrometer. Mass spectra were run on a MS.9 double focussing instrument. $pK^{*}_{mcs.}$ measurements were made by microtitration in the solvent system methyl cellosolve:water (4:1) by the courtesy of Professor W. Simon, Eidg. Technische Hochschule Zurich. Woelm Grade I alumina deactivated according to the Brockmann[31] scale of activity was used for chromatography. Chromatoplates were prepared by the method of Stahl[32] using Kieselgel G (Merck). For preparative purposes the plates used were either 0.25 mm. or 0.50 mm. in thickness.

Extraction of Marrubium vulgare L.

The coarsely chopped, dried whole plant (5 Kg.) was extracted with acetone (20 litres) for 48 hours in a Soxhlet apparatus. The acetone solution was then evaporated under reduced pressure, and the resulting oil (80 gm.) digested in benzene. The supernatant solution was decanted, and the residue digested with benzene twice more. The combined solutions were reduced in volume (to 100 ml.) and chromatographed over acid alumina(2Kg;Spence Grade 0) using a gradient elution technique. Marrubiin (I) was eluted with chlorophyll in chloroform-benzene (approx. 1:2). The crude marrubiin thus obtained - a green solid (12 g.) - was rechromatographed over acid alumina (600 g. Grade III), and after two crystallisations from ethyl acetate-light petroleum formed colourless needles m.p. 159-160° $[\alpha]_D$ = 33.5° (C = 1) $\nu_{max.}^{CCl_4}$ 3626, 3587, 1778, 873 cm.$^{-1}$ $\lambda_{max.}^{EtOH}$ = 214 mμ (log ε = 3.93).

Hydrolysis of Marrubiin (I).

Marrubiin (100 mg.) was hydrolysed in refluxing ethoxyethanol (10 ml.) containing potassium hydroxide (100 mg.) and a little water (6 drops) for 20 minutes. The hot reaction mixture was poured on to ice, and after

adjusting the pH of the aqueous layer to 12, neutral products were extracted with ethyl acetate. The aqueous layer was made just acid to Congo red with hydrochloric acid (10 $\bar{N}$) and extracted with ethyl acetate (2 x 50 ml.). The combined extracts were washed with water, dried over anhydrous sodium sulphate, and evaporated to dryness. The marrubiic acid (IIa) obtained (65 mg.) crystallised from aqueous ethanol as needles m.p. 188-193°C, and after one more crystallisation from ethyl acetate-light petroleum gave m.p. 193-194°C (lit.[8] m.p. 205°C).

Lactonisation of Marrubiic Acid (IIa).

Marrubiic acid (51.5 mg.) and dicyclohexylcarbodiimide (65 mg.) were dissolved in dry benzene (30 ml.) and the solution refluxed for 24 hours. The solution was evaporated to dryness, and the product purified by preparative thin layer chromatography (t.l.c.), affording needles (43 mg.) from ethyl acetate-petrol m.p.159-160°C, which were shown to be identical with marrubiin (m.p., mixed m.p., i.r., and $[\alpha]_D$).

Marrubenol (XXVIIIa)

Marrubiin (I) (60 mg.) was treated with a large excess of lithium aluminium hydride in refluxing tetrahydrofuran (20 ml.) for 1 hour. The solution was cooled, and a saturated solution of sodium sulphate added dropwise till no further effervescence was noticed. The solution was filtered through a cotton wool plug, the residue washed with ethyl acetate, and the solvent removed to afford marrubenol (XXVIIIa) (58 mg.) crystallising from aqueous ethanol as needles m.p. 144-146°C, $[\alpha]_D$ = 20.4° (C = 1.2), (lit.[7] m.p. 138°C, $[\alpha]_D$ = 19.9°).

Oxidation of Marrubenol (XXVIIIa)

Marrubenol (50 mg.) was dissolved in dry pyridine (10 ml.) and 'AnalaR" chromium trioxide (80 mg.) added with chilling. The flask was stoppered and allowed to stand at room temperature for 14 hours. Methanol (2 ml.) was added, and the mixture evaporated almost to dryness under reduced pressure. To the residual oily solid ethyl acetate (20 ml.) and water (20 ml.) were added, and after 30 minutes the mixture was filtered and the residue washed with ethyl acetate (2 x 10 ml.). The ethyl acetate extract was washed with water (2 x 25 ml.) dried

and evaporated to dryness to afford the crude keto-aldehyde m.p. 108-110°C, which was filtered through a short column of acid alumina (Grade III) in benzene. Crystallisation from chloroform-light petroleum gave the keto-aldehyde (XXX) as needles (29 mg.) m.p. 110-111°C $\nu_{max.}^{CCl_4}$ = 1713, 1704, 872 cm.$^{-1}$. (Found: C = 72.36; H = 8.51; $C_{20}H_{28}O_4$ requires C = 72.26; H = 8.49).

Marrubenol mono-acetate (XXVIIIb).

Marrubenol (XXVIIIa) (150 mg.) was taken up in dry pyridine (10 ml.), chilled to 0°C, 'AnalaR'® acetic anhydride (6 ml.) added, and the resulting solution allowed to stand at room temperature for 14 hours. The reaction mixture was poured on to ice, and after 30 minutes extracted with ethyl acetate (2 x 20 ml.). The combined ethyl acetate layers were washed with water (3 x 20 ml.), dried over anhydrous sodium sulphate, and evaporated to dryness. A chromatoplate showed two products which were separated by preparative t.l.c. (chloroform as solvent). The less polar product (18 mg.) which could not be made to crystallise was marrubenol diacetate (XXVIIIe). The major product (118 mg.), the mono-acetate (XXVIIIb), also failed to crystallise. $[\alpha]_D$ = -6.0° (C = 2), $\nu_{max.}^{CCl_4}$ = 3625, 3590, 3565, 1752, 1738, 1237, 8.73 cm.$^{-1}$. (Found: C = 69.82; H = 9.21; $C_{22}H_{34}O_5$ requires C = 69.81; H = 9.05).

Attempted Brosylation of Marrubenol (XXVIIIa).

Marrubenol (80 mg.) was dissolved in dry pyridine and p-bromobenzene - sulphonyl chloride (200 mg.) added. After 12 hours the solution was poured on to ice and extracted with ethyl acetate (2 x 20 ml.). The combined extracts were washed with water (2 x 20 ml.) dried over anhydrous sodium sulphate and evaporated to dryness under reduced pressure. The major product was purified by chromatography over silica using benzene as eluant. The ether (XXVII) crystallised from chloroform-light petroleum as colourless needles (50 mg.) m.p. 124-125°C $\nu_{max.}^{CCl_4}$ 3628, 3588, 873 cm.$^{-1}$, $\lambda_{max.}^{EtOH}$ = 213 mμ (log ε = 3.94. (Found: C = 75.54, H = 9.48; $C_{20}H_{30}O_3$ requires C = 75.43, H = 9.50).

Hydrolysis of Tetrahydromarrubiin (V).

Tetrahydromarrubiin (V) (300 mg.) was hydrolysed in the same way as marrubiin. The product was crystallised from aqueous methanol to give needles (210 mg.) of tetrahydromarrubiic acid (VI) m.p. 179-180°C (lit.[9] m.p. 187°C) which had $\nu_{max.}^{CHCl_3}$ = 3625, 3600, 1714, 1684 cm.$^{-1}$.

Oxidation of Tetrahydromarrubiic acid (VI).

The acid (140 mg.) in dry pyridine (20 ml.) was treated with 'AnalaR'' chromium trioxide (150 mg.). The mixture was left at room temperature for 12 hours and worked up in the manner described above. The coloured impurities were removed by preparative t.l.c. (chloroform containing 2% methanol as solvent) affording the keto-acid (XXXIIIa) as needles (120 mg.) from ethyl acetate-light petroleum m.p. 158-159°C (lit.[25] m.p. 157-159°C), $\nu_{max.}^{CCl_4}$ = 3630, 3000 (br.), 1752, 1680 cm^{-1}. (Found: C = 68.34, H = 9.28; $C_{20}H_{32}O_5$ requires C = 68.15, H = 9.15).

Tetrahydro-enol-lactone (XXXIV).

The keto-acid (XXXIIIa) (100 mg.) was refluxed in ''AnalaR'' acetic anhydride (10 ml.) under nitrogen for 1 hour, and then for a further 2 hours after the addition of fused sodium acetate (30 mg.). The acetic anhydride was removed under reduced pressure and the residue extracted with ethyl acetate (30 ml.). The extract was washed with sodium bicarbonate solution (2 x 20 ml.), then with water (2 x 20 ml.), dried over anhydrous sodium sulphate and evaporated to dryness,

furnishing the enol-lactone (XXXIV) which crystallised from ethyl acetate-light petroleum as needles (90 mg.) m.p. 154-156°C $\nu_{max.}^{CCl_4}$ = 3630, 1813, 1713 cm.$^{-1}$. (Found: C = 72.04, H = 9.35; $C_{20}H_{30}O_4$ requires C = 71.82, H = 9.04).

Hydrogenation of the enol-lactone (XXXIV).

The enol-lactone (65 mg.) was hydrogenated in acetic acid (40 ml.) over Adam's catalyst (Johnson, Matthey & Co.; 15 mg.) for 2½ hours. The catalyst was filtered off, and the solvent removed under reduced pressure, leaving an oil (83 mg.) which consisted of one major plus two minor products (t.l.c.). These were separated by preparative t.l.c. (chloroform containing 3% methanol as solvent). The least polar product crystallised from ethyl acetate-light petroleum giving needles (16 mg.) m.p. 120-122°C of tetrahydromarrubiin(V), identical (m.p., mixed m.p., i.r., N.M.R.) with an authentic sample. The major product (intermediate polarity) crystallised from ethyl acetate-light petroleum, furnishing needles (56 mg.) of the desoxy-acid (XXXVa) m.p. 140-142°C, $\nu_{max.}^{CCl_4}$ = 3630, 1727 cm.$^{-1}$. (Found: C = 70.96, H = 10.36; $C_{20}H_{34}O_4$ requires C = 70.97, H = 10.13). The most polar product crystallised

from aqueous methanol giving the dihydroxy acid (XXXVI) as needles (9 mg.) m.p. 103-105°C., $\nu_{max.}^{CCl_4}$ = 3623, 3530, 1736 cm.$^{-1}$. (Found: C = 66.37, H = 9.35; $C_{20}H_{34}O_5$ $\frac{1}{2}H_2O$ requires C = 66.13, H = 9.70).

Reduction of the desoxy-acid (XXXVa).

The acid (50 mg.) was methylated with diazomethane and the product filtered through a short column of acid alumina (Grade III) to remove diazomethane polymer. The oily methyl ester (XXXVc) (50 mg.) was dissolved in dry ether (15 ml.), lithium aluminium hydride (65 mg.) added, and the solution refluxed for 90 minutes. Work up in the manner previously described, afforded the oily diol (XXXVb) (44 mg.) which failed to crystallise, and had $[\alpha]_D$ = -3.3° (C = 2.5) P m/e = 324.

Acetylation of the diol (XXXVb).

The above diol (24 mg.) in dry pyridine (5 ml.) was treated with acetic anhydride (5 ml.) for 14 hours. Work up in the manner previously described gave the crude acetate (XXXVc) (22 mg.) as an oil. Purification by preparative t.l.c. (chloroform as solvent) yielded 18 mg. of pure (one spot on t.l.c.) acetate (XXXVc)

$[\alpha]_D$ = +4,4° (C = 1.3), which could not be induced to crystallise. $\nu_{max.}^{CCl_4}$ = 3630, 1741 cm.$^{-1}$. P m/e = 306 (Found:C = 71.76, H = 10.68; $C_{22}H_{38}O_4$ requires C = 72.09, H = 10.45).

Oxidation of the diol (XXXVb).

The above diol (26 mg.) in dry pyridine (5 ml.) was treated with " AnalaR" chromium trioxide (25 mg.) for 10 hours, and worked up in the usual manner. The residue proved to be a mixture of products (t.l.c.), the preponderant one was separated from the others by preparative t.l.c. (chloroform as solvent), furnishing the aldehyde (XXXVd) (8 mg.) as an oil. P m/e = 322

Bis desoxy Series

The enol-lactone (XXXIV) (45 mg.) on hydrogenation in acetic acid (30 ml.) over Adam's catalyst (Englehard Industries; 8 mg.) afforded two compounds (t.l.c.), which were separated by preparative t.l.c. (chloroform as solvent). The minor product crystallised from petrol as needles (5 mg.) m.p. 94-98° C of desoxy-tetrahydromarrubiin (XXXVIII) $\nu_{max.}^{CCl_4}$ = 1778 cm.$^{-1}$ (no absorption between 3100 - 4000 cm.$^{-1}$). The major

product, a carboxylic acid (XXXVIIa) (35 mg.) was treated with diazomethane, and reduced as before to the primary alcohol (XXXVIId) which was converted as before to the corresponding acetate (XXXVIIb) m.p. 76-77°C $[\alpha]_D$= 23.6° (C = 2). $\nu_{max.}^{CCl_4}$ 1742 cm.$^{-1}$ (no absorption between 3100 - 4000 cm.$^{-1}$. P m/e 290 (Found: C = 75.23, H = 11.32; $C_{22}H_{38}O_3$ requires C = 75.38, H = 10.93). Oxidation of the alcohol (XXXVIId) (12 mg.) as before afforded the oily aldehyde (XXXVIIc) (8 mg.) $[\alpha]_D$ = +13° (C = 0.8) $\nu_{max.}^{CCl_4}$ = 1718 cm.$^{-1}$.

Dehydration of marrubiin (I).

Marrubiin (50 mg.) was refluxed in dry pyridine (3 ml.) containing phosphorus oxychloride (1 ml.) for 3 hours. The reaction mixture was poured on to ice and extracted with ethyl acetate (2 x 15 ml.). The combined ethyl acetate extracts were washed with water (2 x 20 ml.), dried over anhydrous sulphate, and the solvent removed, affording an oil (48 mg.) which was a mixture of two spots on t.l.c. - unchanged starting material plus product. The product was separated by preparative t.l.c. and was shown by careful integration in the N.M.R. to be a 2:1 mixture of two anhydro-marrubiins (XLIV) and (XLIII)

respectively, which were not separated. The oily mixture had P m/e = 314, $\nu_{max.}^{CCl_4}$ = 1776 cm.$^{-1}$. (No absorption between 3100 - 4000 cm.$^{-1}$.

Hydrogenation of Marrubiin.

Marrubiin (1.12 g.) was hydrogenated in "AnalaR" ethyl acetate (50 ml.) over Adam's catalyst (100 mg.) - final uptake 162 ml. (2.2 moles). The catalyst was filtered off, and the solution evaporated to dryness, affording a solid crystalline mass (1.10 g.) which was shown by t.l.c. to be a mixture of four components, which were separated by chromatography over acid alumina (50 g.; Grade III). Benzene eluted the first component, octahydromarrubiin (XLVI) as a waxy solid (19 mg.) which crystallised from light petroleum as needles, m.p. 88-89°C $[\alpha]_D$ = +38° (C = 1.1) $\nu_{max.}^{CCl_4}$ = 3630, 1780 cm.$^{-1}$. (Found: C = 74.43, H = 10.76; $C_{20}H_{34}O_3$ requires C = 74.49, H = 10.63). The major component was eluted with chloroform-benzene (1:2), and crystallisation from ethyl acetate-light petroleum furnished needles (810 mg.) of tetrahydromarrubiin (V) m.p. 122-124°C., $\nu_{max.}^{CCl_4}$ = 3630, 1780cm.$^{-1}$. The final two components were eluted with chloroform-benzene (1:1) with almost no separation of one from the other, and only the last fraction proved

to be crystalline. Repeated crystallisation of this fraction from ethyl acetate-light petroleum gave needles of hexahydromarrubiin II (XLVIIa) m.p. 150-152°C. $[\alpha]_D$ = 17.4° (C = 1.2), (Found: C = 70.84, H = 9.95; $C_{20}H_{34}O_4$ requires C = 70.97, H = 10.13). Hexahydromarrubiin I (XLVIIIa) was separated from slightly earlier fractions, which contained both isomers, by preparative t.l.c., but failed to crystallise, and was therefore treated with acetic anhydride and pyridine in the usual manner to afford hexahydromarrubiin I acetate (XLVIIIb) as needles from ethyl acetate-light petroleum, m.p. 121-123°C. (Found: C = 69.84, H = 9.65; $C_{22}H_{36}O_5$ requires C = 69.44, H = 9.54).

Hydrogenation of marrubenol (XXVIIIa).

Marrubenol (320 mg.) was hydrogenated in "AnalaR" ethyl acetate (40 ml.) over Adam's catalyst (35 mg.) until uptake of hydrogen ceased (final uptake 53 ml.: 2.3 moles). Filtration of the catalyst and removal of the solvent afforded a crystalline mass (310 mg.) which was shown (t.l.c.) to be a mixture of two components, which were separated by chromatography over acid alumina (15 gm. Grade IV). The first

component was eluted with chloroform-benzene (1:4) and crystallised from chloroform-light petroleum as needles (210 mg.) of marrubanol (IL) m.p. 142-144°C, $[\alpha]_D$ = 37.2° (C = 1.3) (lit.[7] m.p. 175°C $[\alpha]_D$ = 15.15). (Found: C = 70.26, H = 10.24; $C_{20}H_{36}O_4$ requires C = 70.54, H = 10.66). The second component was eluted with chloroform-benzene (1:1) and crystallised from ethyl acetate or chloroform as prisms (68 mg.) of hexahydro-marrubenol m.p. 178-180°C $[\alpha]_D$ = +7.15°. (Found: C = 69.81, H = 11.22; $C_{20}H_{38}O_4$ requires C = 70.13, H = 11.18).

Reduction of tetrahydromarrubiin (V).

Tetrahydromarrubiin (60 mg.) was treated with lithium aluminium hydride in refluxing dry tetrahydrofuran for 90 minutes. The reaction was worked up in the usual manner to afford marrubanol (IL) as needles (from chloroform-light petroleum) m.p. 142-144°C, which was identical (m.p., mixed m.p., $[\alpha]_D$) with a sample obtained by the previous reaction.

Attempted acetylation of marrubiin (I).

Marrubiin (50 mg.) in benzene (2.7 ml.) and acetic anhydride (20 mg.) were stirred at -5°C for 30 minutes. Two drops of boron trifluoride etherate were added and the reaction was then allowed to warm up to room temperature. The reaction mixture was poured into water (15 ml.) and extracted with chloroform (20 ml.). The chloroform extract was washed with water (2 x 15 ml.), dried, and the solvent removed, yielding an oily residue (40 mg.) which was shown by t.l.c. to be a complex mixture of a large number of compounds, the only one present in appreciable amount being the least polar component. Preperative t.l.c. yielded this compound as an oil (6 mg.) $\nu_{max.}^{film}$ = 1776, 1683, 873 cm.$^{-1}$, $\nu_{max.}^{EtOH}$ = 215 (log ε = 3.96). This compound was not further investigated.

Attempted formation of a Diels-Alder adduct.

(a) Marrubiin (I) (10.9 mg.: 0.03 m.moles) in benzene (2.0 ml.) was added to a solution of maleic anhydride (3.6 mg.:0.04 m.moles) in dry ether (1.5 ml.). The flask was sealed and left at room temperature for 4 days. Evaporation of solvent and crystallisation of the residue

from ethyl acetate-light petroleum (both at room temperature) afforded unchanged marrubiin m.p. 159-160°C. $\nu_{max.}^{Nujol}$ = 870 cm.$^{-1}$.

(b) Marrubiin (25.6 mg.: 0.08 m.moles) and maleic anhydride (8.7 mg.: 0.09 m.moles) were refluxed in dry benzene (6 ml.) for 21 hours. Removal of solvent and crystallisation from ethyl acetate-light petroleum gave unchanged marrubiin m.p. 159-160°C. $\nu_{max.}^{Nujol}$ = 870 cm.$^{-1}$.

(c) Marrubiin (25.9 mg.: 0.08m.moles) and maleic anhydride (26.8 mg.: 0.3m.moles) were refluxed in dry benzene (5 ml.) for 24 hours. T.l.c. showed a near-complete absence of starting material, but on work up, only marrubiin and maleic anhydride were isolated.

(d) Marrubiin (20 mg.) and acetylene dicarboxylic acid (20 mg.) were refluxed in dry benzene (7 ml.) for 6 hours. Removal of the solvent left an oil, from which marrubiin (18 mg.) m.p. 157-159°C. was recovered by preparative t.l.c.

(e) Marrubiin (28 mg.) and diethyl acetylene dicarboxylate (65 mg.) were refluxed in toluene for 24 hours. Removal of the toluene under reduced

pressure afforded an oil which consisted (t.l.c.) mainly of unchanged marrubiin, plus three minor products. Preparative t.l.c. afforded only unchanged marrubiin (23 mg.) m.p. 158-160°C.

Attempted brosylation of marrubiic acid (IIa).

Marrubiic acid (42 mg.) in dry pyridine (5 ml.) was treated with p-bromobenzene-sulphonyl chloride at room temperature for 48 hours. Work up in the usual manner afforded an oil, which was shown to consist (t.l.c.) of unchanged marrubiic acid (IIa) and one other major component. These were separated by preparative t.l.c. (chloroform containing 2% methanol as solvent), and the product shown to be marrubiin (I) m.p. 157-159°C (m.m.p. 157-159°C).

Preparation of silver marrubiate (L).

Marrubiic acid (40 mg.: 0.11 m.moles) was dissolved in 0.1$\bar{N}$ sodim hydroxide (1 ml.) and dioxan (1ml To this solution was added dropwise, a 0.06$\bar{M}$ solution of silver nitrate (1.7 ml.: 0.11 m.moles). The white precipitate which formed was filtered off, and had $\nu_{max.}^{Nujol}$ = 3640, 1550, 875 cm.$^{-1}$. Crystallisation

from aqueous ethanol, and aqueous dioxan failed to produce crystals of suitable size.

Preparation of marrubenol p-iodobenzoate (XXVIIIc).

Marrubenol (XXVIIIa) (45 mg.) in dry pyridine (10 ml.) was treated with p-iodobenzoyl chloride (200 mg.) for 18 hours at room temperature. The reaction mixture was poured into water (20 ml.) and after 30 minutes, extracted with ethyl acetate (2 x 20 ml.). The combined extracts were washed with water (2 x 20 ml.), dried, and the solvent removed. The crystalline residue (200 mg.) was mainly p-iodobenzoic anhydride (t.l.c.), and was separated from the ester by chromatography over acid alumina (10 gm. Grade III). Benzene eluted p-iodobenzoic anhydride (130 mg.) which crystallised from ethyl acetate as large flat plates m.p. 192-194°C. Benzene-chloroform (2:1) eluted the oily marrubenol p-iodobenzoate (XXVIIIc) $\nu_{max.}^{CCl_4}$ = 3640, 1700, 1595, 872 $cm.^{-1}$ which despite a further purification by preparative t.l.c., did not crystallise.

Preparation of marrubenol 3,5-dibromobenzoate (XXVIIId).

Marrubenol (XXVIIIa) (35 mg.) in dry pyridine

(5 ml.) was treated with 3,5-dibromobenzoyl chloride at room temperature for 24 hours. Work up in the usual manner afforded the oily marrubenol 3,5-dibromobenzoate (XXVIIId) (40 mg.) $\nu_{max.}^{CCl_4}$ = 3638, 1709, 1596, 873 cm.$^{-1}$.

Preparation of hexahydromarrubiin II brosylate (XLVIIb).

Hexahydromarrubiin II (XLVIIa) (25 mg.) in dry pyridine (5 ml.) was treated with an excess of p-bromobenzene-sulphonyl chloride (150 mg.) for 16 hours. Work up in the usual manner afforded the only brosylate (XLVIIb) (30 mg.), $\nu_{max.}^{film}$ = 3640, 1780, 1600, 870 cm.$^{-1}$, which, despite repeated (X 4) purification by preparative t.l.c. did not crystallise.

Preparation of hexahydromarrubiin II p-iodobenzoate (XLVIIc)

Hexahydromarrubiin II (XLVIIa) (30 mg.) in dry pyridine (10 ml.) was treated with p-iodobenzoyl chloride for 18 hours. Work up as above afforded the oily p-iodobenzoate (XLV IIc) (32 mg.) $\nu_{max.}^{CCl_4}$ = 3630, 1776, 1700, 1600 cm.$^{-1}$ which did not crystallise.

Oxidation of the mono-acetate (XXVIIIb).

The above acetate (65 mg.) was taken up in dry pyridine (8 ml.) and 'AnalaR' chromium trioxide (85 mg.) added with chilling. The flask was stoppered and allowed to sit at room temperature for 4 hours. Work up in the manner described above furnished an oil (58 mg.) from which the oily keto-acetate (XXXI) was isolated by preparative t.l.c. (chloroform as solvent). The compound had $[\alpha]_D = +6.1^\circ$ (C = 5.5), $\nu_{max.}^{CCl_4} = 3630, 3583, 1740, 1713, 1236, 873$ cm.$^{-1}$. (Found: C = 70.00, H = 8.89; $C_{20}H_{32}O_5$ requires C = 70.18, H = 8.57).

REFERENCES

1. Harms, Arch. Pharm.,(1842), 83, 144; (1851), 116, 141.
2. Kroymeyer, Arch. Pharm., (1849), 108, 258.
3. Hertel, Amer. J. Pharm., (1890), 273.
4. Morrison, Amer. J. Pharm., (1890), 327.
5. Matusc , Amer. J. Pharm., (1897), 201.
6. Gordin, J. Amer.Chem. Soc., (1908), 30, 265.
7. Cocker, Cross, Duff, Edward and Holley, J.Chem.Soc., (1953), 2540.
8. Lawson and Eustice, J. Chem. Soc., (1939), 587.
9. Hollis, Richards and Robertson, Nature, (1939), 143, 604.
10. Hardy, Rigby and Moody, J. Chem. Soc., (1957), 2955.
11. Burn and Rigby, J. Chem. Soc., (1957), 2964.
12. Collin-Asselineau, Lederer, Mercier and Polonsky, Bull. Soc. Chim., France, (1950), 720.
13. Mangoni and Balardini, Gazzetta, (1963), 93, 465.
14. Ruzicka, Seidel and Engel, Helv. Chim. Acta, (1942), 25, 621.
15. Dietrich, Lederer and Mercier, Helv. Chim. Acta, (1954), 37, 705.
16. Moody, Chem. and Ind., (1965), 88.
17. Rivett, J. Chem. Soc., (1964), 1857.

18. For leading references see Murray and McCrindle, Chem. and Ind., (1964), 500.

19. Gaudemer, Polonsky and Wenkert, Bull Soc. Chim., France, (1964), 407.

20. Cram, Sahyun and Knox, J. Amer. Chem. Soc., (1962), 84, 1734.

21. Ruyle, Erickson, Lovell and Chamberlin, J.Org.Chem., (1960), 25, 1260.

22. Pascual Rigau, Ph.D. Thesis, Zurich, (1965).
Sommer, Rigau, Arya, and Simon, Helv. Chim. Acta., (1963), 46, 1734.
Rigau and Simon, Helv. Chim. Acta.,(1964), 47, 683.
Oki and Hirota, Bull. Chem. Soc., Japan, (1961), 34, 374; (1962), 35, 1048; (1964), 37, 213.

23. Tahara and Hirao, Chem. Pharm. Bull. (Japan), (1964), 12, 984.

24. Bennet, Eglinton, Fulke, Hirao, McCrindle, Simon and Tahara - unpublished results.

25. Castine, Wheeler and Wheeler, Chem. and Ind., (1961), 1832.

26. Barton, J. Chem. Soc., (1953), 1027.

27. Bhacca and Williams, Applications of N.M.R. Spectroscopy in Organic Chemistry, Holden-Day, San Francisco, (1964), p.19.

28. Fulke and McCrindle, Chem. and Ind., (1965), 647.

29. Boyle, Chem. and Ind., (1966), 33.

30. S.G. McGeachan, Ph.D. Thesis, Glasgow, (1963).

31. Brockmann and Schodder, Ber., (1941), 74, 73.

32. Stahl, Chem. Ztg., (1958), 82, 323.

Table I

$pK^{*}_{mcs.}$ and infra-red data for the acids (IIa), (VI), (XXXIXa), (XLa) and their methyl esters.

Acid	$pK^{*}_{mcs.}$	Ester Carbonyl ν_{CO}(cm.$^{-1}$)	ε^{a}	Assignment	$\Delta\nu_{CO}$ (cm.$^{-1}$)	%
(IIa)	6.66	1736	70	C-6-OH--- O-C- (R, O)	-8	15
		1708	470	C-6-OH---O=C-OR	20	85
(VI)	6.71	1736	50	C-6-OH---O-C- (R, O)	-8	10
		1706	490	C-6-OH---O=C-OR	22	90
(XXXIXa)	6.35	1741	50	C-6-OH---O-C- (R, C)	-13	10
		1712	545	C-6-OH---O=C-OR	16	90
(XLa)	7.13	1733	200	Free Ester	-6	35
		1711	570	C-6-OH---O=C-OR	9	65
(XLc)	8.45	1728	610	Free Ester	-	-

$\Delta\nu_{CO}$ values = 1728 - ν_{CO} (substance)

All spectra were run on carbon tetrachloride at about 0.002 with cell paths of 0.5 - 2.00 mm. for ν_{CO}.

Table II.

N.M.R. data for marrubiin derivatives.

Compound	Furan	C-6 H	C_4 function		Methyls
I	2·69 - 2H 3·69 - 1H	5·25 - 1H triplet J = 8 cps			8·70, 8·90, 9·04 doublet, J = 6 cps
XXVII	2·68 - 2H 3·69 - 1H	5·85 - 1H triplet J = 7 cps	6·32 - 2H triplet J = 9 cps	7·50 - 2H quartet J = 7 cps	8·80, 8·88, 9·07 doublet, J = 6 cps
XXVIIIa	2·69 - 2H 3·69 - 1H	5·78 - 1H broad singlet	6·25 - 2H broad singlet	6·82 - 1H doublet J = 10cps 7·53 - 2H quartet J = 7 cps	8·70, 8·97, 9·04 doublet, J = 6 cps
XXVIIIb	2·68 - 2H 3·68 - 1H	5·66 - H broad singlet.	5·44 - 2H quartet J = 12cps	7·54 - 2H quartet J = 8 cps	7·92, 8·72, 8·98, 9·04, doublet, J = 6 cps
XXXI	2·67 - 2H 3·66 - 1H		5·30 - 2H quartet J = 10cps	6·90 - 1H 7·50 - 2H quartet J = 8 cps	7·92, 8·93, 9·09, 8·97, doublet, J = 6 cps
XXX	2·69 - 2H 3·69 - 1H		-0·45 - 1H	6·71 - H	8·84, 9·16, 8·92 doublet, J = 6 cps
XXVIIIc	2·69 - 2H 3·68 - 1H	5·58 - 1H broad	5·11 - 2H quartet J = 11cps	7·51 - 2H quartet J = 8 cps	8·69, 8·88, 9·04, doublet, J = 6 cps
IIc	2·6 - 2H 3·6 - 1H	6·65 - 1H		7·68 - 2H (due to $COCH_2Cl$)	8·7 8·93, 9·0 doublet, J = 6 cps

Table III.

N.M.R. data for tetrahydromarrubiin derivatives.

Compound	Tetra-hydro-furan	C-6-H	C-4 function		Methyls
V	6·26 – 3H 6·74 – 1H	5·25 – 1H triplet J = 8 cps			8·70, 8·94, 9·09 doublet, J = 6 cps
XXXIIIa	6·18 – 3H 6·64 – 1H			7·24 – 2H doublet J = 12cps 7·62 – 2H quartet J = 10cps	8·69, 9·10, 8·94 doublet, J = 6 cps
XXXIV	6·23 – 3H 6·70 – 1H			7·23 – 1H triplet J = 12cps	8·74, 9·15, 8·97 doublet, J = 6 cps
XXXVc	6·28 – 3H 6·76 – 1H		6·44 – 3H due to $COOCH_3$		8·84, 9·25, 9·16 doublet J = 6 cps
XXXVc	6·24 – 3H 6·74 – 1H		5·86 – 3H quartet J = 10cps	7·96 – 3H due to CH_3CO	9·02, 9·14, 9·13 doublet, J = 6 cps
XXXVd	6·24 – 3H 6·74 – 1H		9·15 – 1H due to CHO		8·86, 9·20, 9·10 doublet J = 6 cps
XXXVe	6·25 – 3H 6·70 – 1H		6·42 – 3H		8·85, 9·25, 9·15 doublet, J = 6 cps
XXXVd	6·22 – 3H 6·68 – 1H		5·22 – 2H broad		9·06, 9·20, 9·05 doublet, J = 6 cps
XXXVb	6·19 – 3H 6·68 – 1H		5·90 – 2H quartet J = 12cps	7·98 – 3H due to CH_3CO	9·04, 9·14, 9·12 doublet, J = 6 cps
XXXVc	6·20 – 3H 6·68 – 1H		0·14 – 1H due to CHO		8·98, 9·28, 9·07 doublet, J = 6 cps

Table IV.

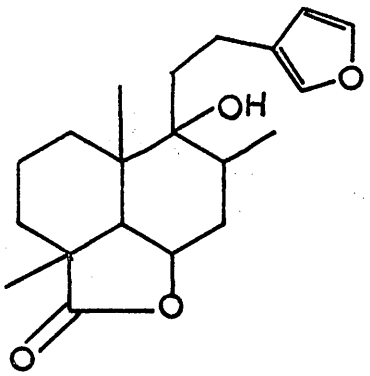
N.M.R. data for marrubiin hydrogenation products

Compound	Low field protons		Methyls
XLVI	5·36 - 1H triplet J = 6 cps due to C6 - H	7·83 - 2H doublet J = 5 cps	8·76 - 6H methyls at C-4, C-10 9·05, 9·12, doublets, J = 6 cps 9·10 triplet, J = 5 cps.
XLVIIa	5·20 - 1H triplet J = 6 cps 6·28 - 2H triplet J = 6 cps	7·71 - 2H doublet J = 5 cps	8·71, 8·94 methyls at C-4, C-10. 9·06, 9·08, doublets, J = 5·5 cps
XLVIIIa	5·22 - 1H triplet J = 6 cps. 6·38 - 2H broad singlet.	7·71, doublet J = 5 cps.	8·70, 8·93 methyls at C-4, C-10. 9·03 doublet, J = 5 cps. 9·07 triplet, J = 5 cps.
XLVIIIb	5·35 - 1H triplet J = 6 cps 6·06 - 2H doublet J = 4·5 cps	7·99 - 3H singlet.	8·74, 8·96 methyls at C-4, C-10. 9·10 doublet, J = 6 cps. 9·12 triplet, J = 5 cps.

Table V.

N.M.R. data for marrubiin dehydration mixture.

Proton Assignments	Position (τ)	Integration (Scale Units)	Integration (Protons)	Compound Assignable
2 α-furan	2·80	14·0	2·0	(XLIII) plus (XLIV)
1 β-furan	3·82	6·8	1·0	(XLIII) plus (XLIV)
1 vinyl	4·77 (triplet J = 6 cps)	2·24	0·33	(XLIII)
1 C-6 H	5·16	7·0	1·0	(XLIII) plus (XLIV)
2 C-12 H	6·92	4·50	0·66	(XLIII)
1 C-8 CH_3	8·40	14·2	2·00	(XLIV)



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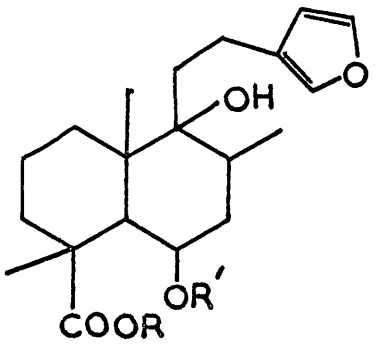
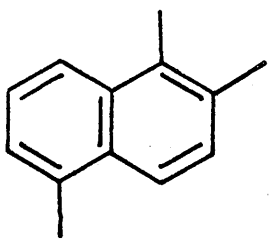


II A ; R = R' = H

B ; R = H ; R' = CO.CH$_3$

C ; R = CO.CH$_2$Cl ; R' = H



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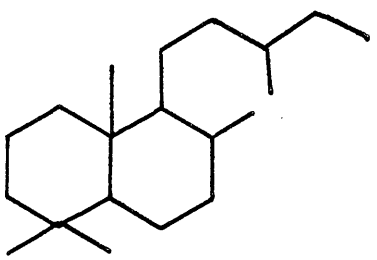

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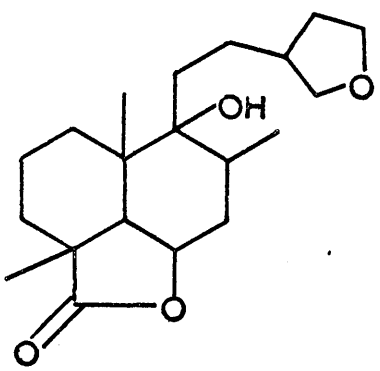

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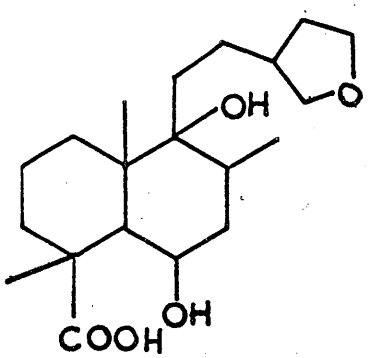

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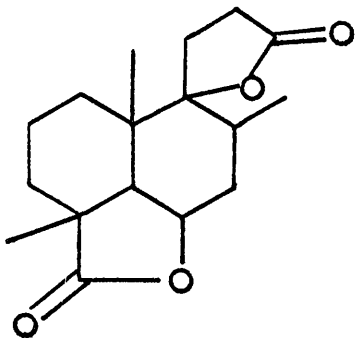

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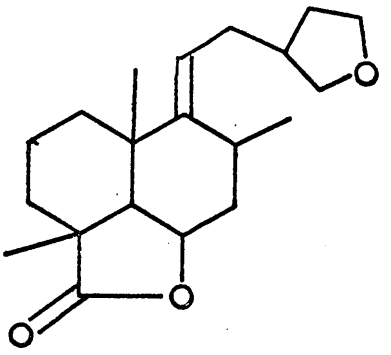

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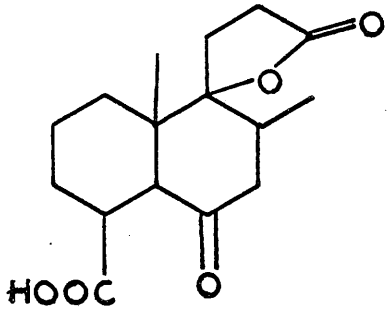

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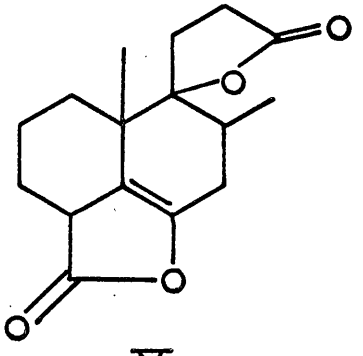

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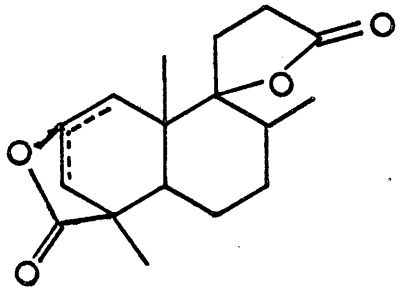

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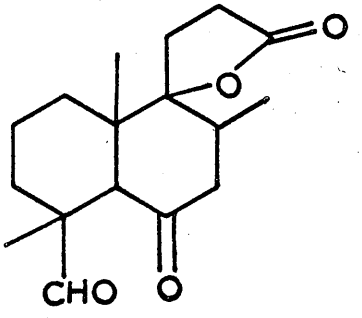

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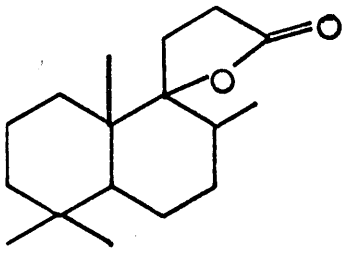

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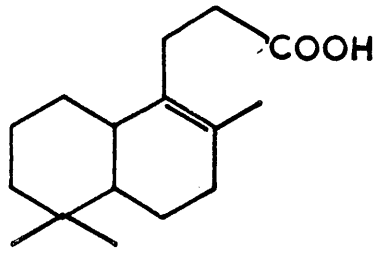

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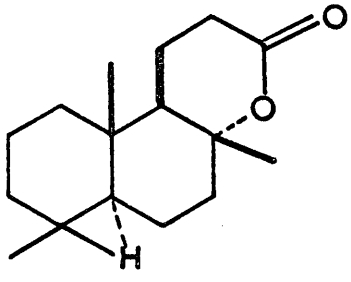

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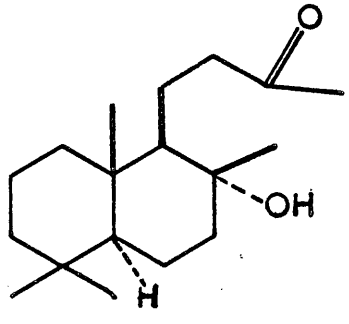

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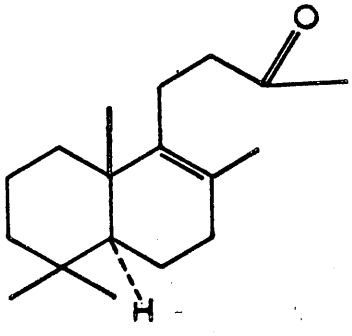

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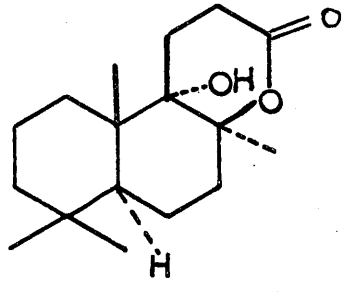

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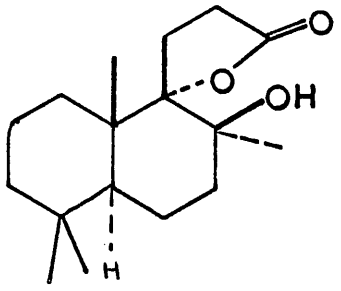

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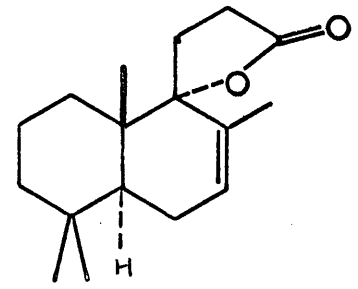

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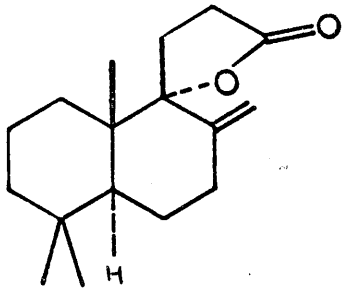

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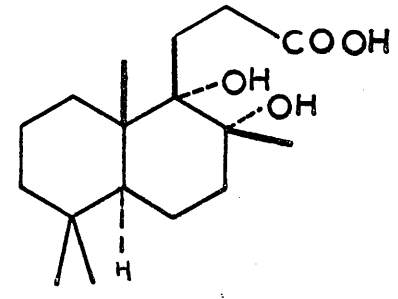

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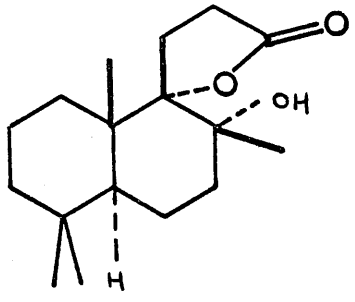

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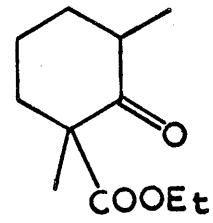

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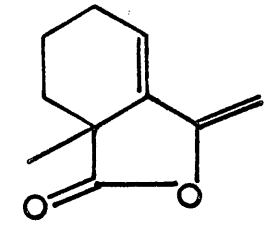

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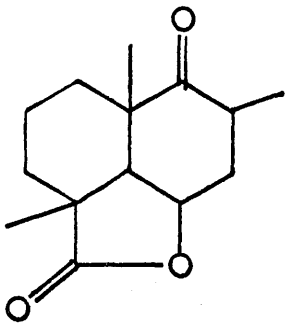

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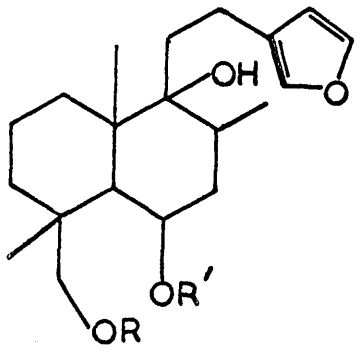


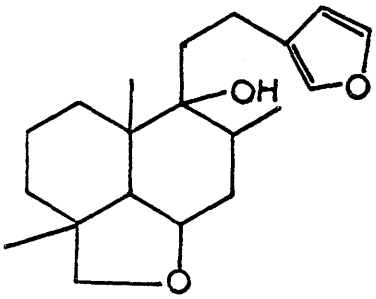
XXVIII A ; R = R′ = H

B ; R = CO.CH$_3$; R′ = H

C ; R = CO-C$_6$H$_4$-I ; R′ = H

D ; R = CO-C$_6$H$_3$(Br)$_2$; R′ = H

E ; R = R′ = CO.CH$_3$



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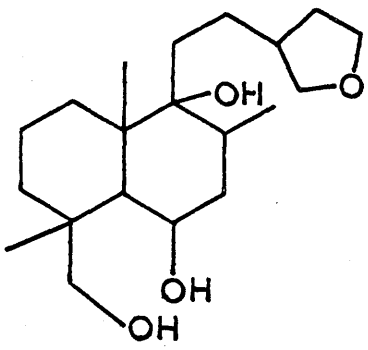

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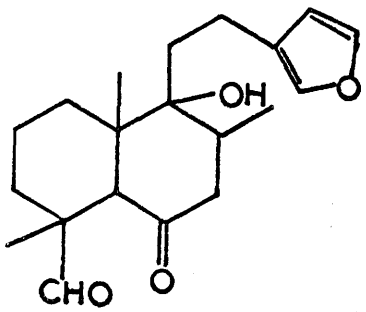

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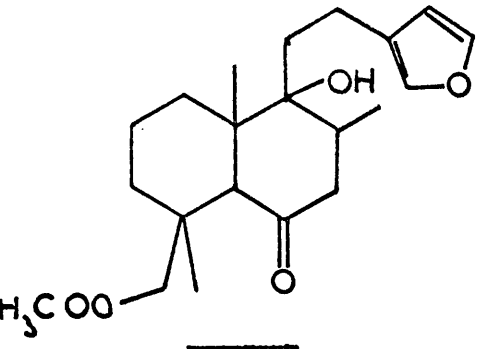

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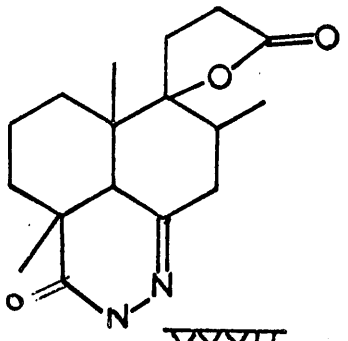

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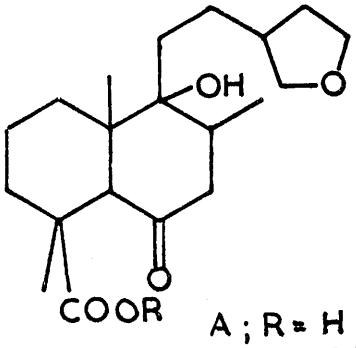
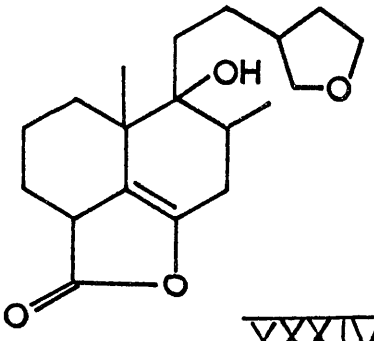
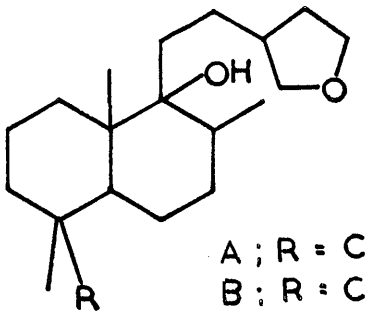


A ; R = H
B ; R = CH3
C ; R = COCH3

XXXIII

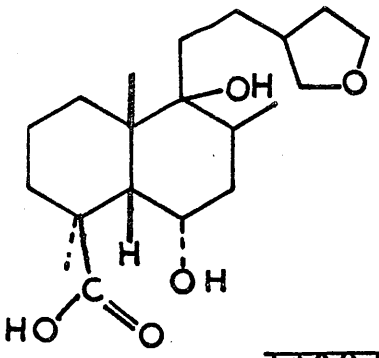


XXXIV



A ; R = COOH
B ; R = CH2OH
C ; R = CH2OOC.CH3
D ; R = CHO
E ; R = COOCH3

XXXV



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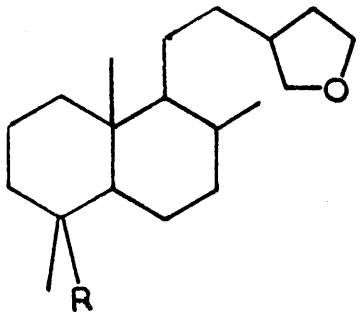
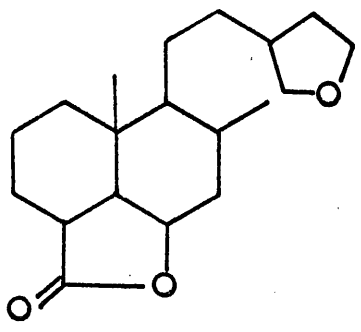
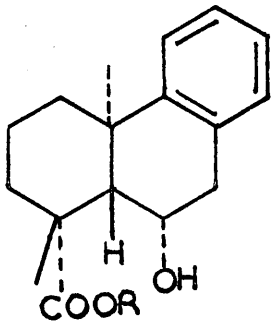


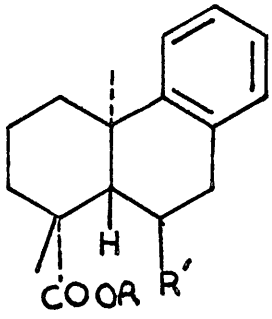
XXXVII A ; R = COOH
B ; R = $CH_2OOC.CH_3$
C ; R = CHO
D ; R = CH_2OH
E ; R = $COOCH_3$



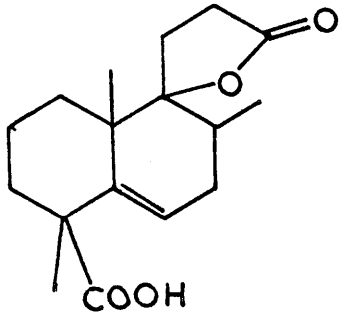
XXXVIII



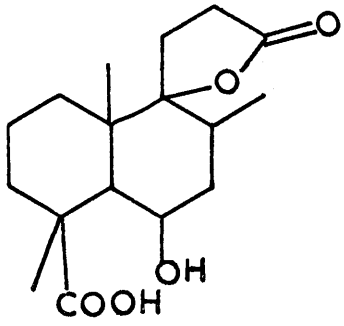
XXXIX A ; R = H
B ; R = CH_3



XL A ; R = H ; R' = OH
B ; R = CH_3 ; R' = OH
C ; R = R' = H
D ; R = CH_3 ; R' = H



XLI



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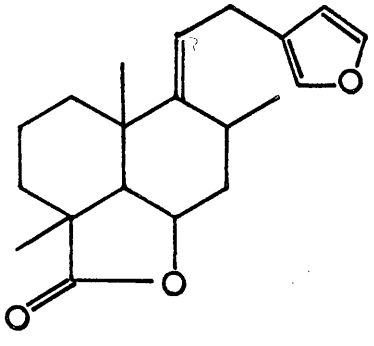

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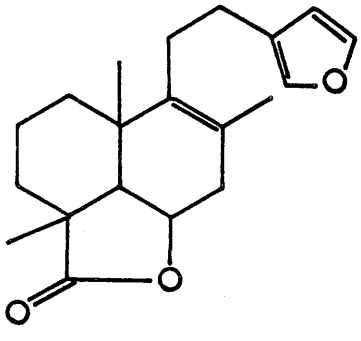

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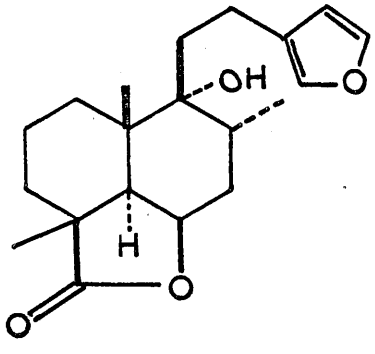
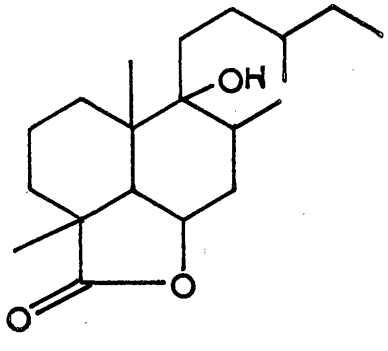
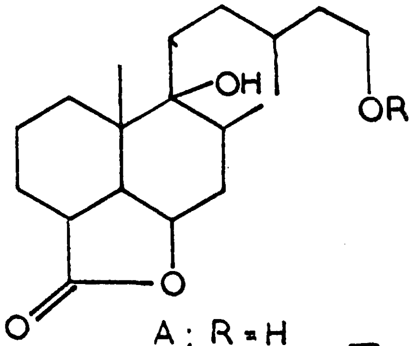


XLV



XLVI

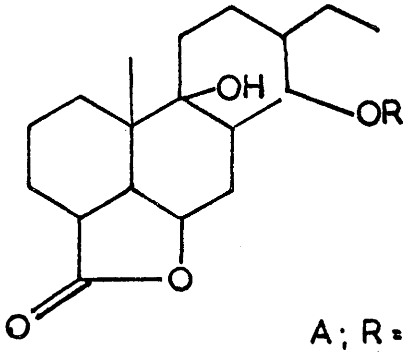


XLVII

A; R = H

B; R = $-SO_2C_6H_4Br$

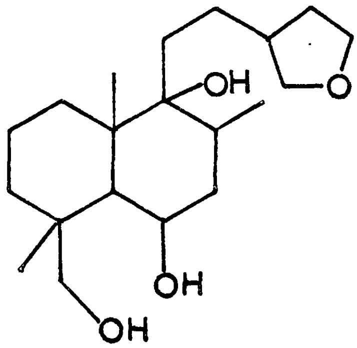
C; R = COC_6H_4I



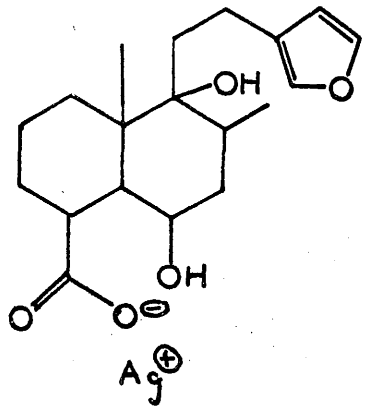
XLVIII

A; R = H

B; R = $COCH_3$



IL



L

TETRACYCLIC TRITERPENES

In the past two decades, the rapid improvement of separation techniques and the increased availability of physical methods to the organic chemist have led to a renewed interest in compounds of complex structure. The triterpene field is one of the outstanding examples of this recent development. It appears likely that all triterpenes are derived biogenetically by cyclisation of squalene (1A) folded in a suitable manner[1,2,3,4]. Cyclisation of squalene in a chair-chair-chair-chair-chain arrangement (1B) leads to the carbonium ion (2) which is the precursor of the dammarane series [e.g. dammaradienol (3)]. Isomerisation of the carbonium ion (2; arrows) leads to the tirucallane [e.g. tirucallol (4)] and euphane [e.g. euphol (5)] series of triterpenes. The lanostane series [e.g. lanosterol (6)] can be thought of as arising from cyclisation of squalene in a chair-boat-chair-chair-chain conformation, followed by a series of 1,2-hydride and methyl group shifts, similar to that proposed for the derivation of the euphane series[4].

Dammaradienol (3) and dammarenediol (7) have been isolated from commercial Dammar resins of the Dipterocarpaceae[5], although perhaps the most interesting

compound of this series is dammarenolic acid[5,6](8A) which probably results from oxidative cleavage of the 3-ketone [c.f. nyctanthic acid[6](8B)] Aglaiol (9), the epoxide corresponding to dammaradienol (3) with which it was correlated, has recently been isolated from Aglaia odorata Lour.[6], which is a member of the Meliaceae.

The lanostane series shows quite a wide structural variety. Since lanosterol (6) is known to be an intermediate in the biogenesis of cholesterol (10), a great deal of interest has centred on the isolation and identification of demethylated forms of lanosterol, and recently such compounds as macdougallin[8](11) and peniocerol[9](12) have been isolated from the cactus Peniocereus macdougalli, while 4α-methylcholest-8-en-3-ol[10] and 4α-methylcholest-7-en-3-ol[11] have been isolated from animal sources. The last of these compounds has also been found in the cactus Lophocereus schotti[12]. An interesting structural feature which occurs in certain members of the lanosterol-related group is the C-9,10 cyclopropane ring, found in the cycloartanol (13) series, in which the cyclopropane ring is β-fused, and the ring B:C fusion is cis. The lanostane series also contains compounds with "extra" carbon atoms, such as eburicoic

acid (14), cycloläudenol (15) and 24-methylenecycloartenol (16). It has been shown that the additional alkylation in such systems is not acetate derived, but can come from formate, or from methionine[13], and is probably best envisaged as an electrophilic attack of CH_3^+ on the C-24 double bond.

In the euphane-tirucallane series, euphol (5) and tirucallol (4) have been known for quite some time, but more recently, the related compound flindissol[14](17) has been isolated from a member of the family Rutaceae, and its structure elucidated. Since then, turraeanthin[15] (18)and melianone[16](19) have been isolated from members of the closely related family Meliaceae. From Flindersia bourjotiana (Rutaceae) a similar series of compounds has been obtained[17], namely bourjotinolone A, B and C (20A, B, C) and bourjotone (18 D).

Flindissol (17) and turraeanthin (18) would appear to represent two possible steps in the biogenetic degradation of the tirucallol side chain to a β-furan, a feature of the limonin (21 A) -like compounds. The next step is possibly the isomerisation of the epoxide in turraeanthin to the ketone, which could then, by oxidative cleavage and dehydration be converted to the

furanoid intermediate (22 A), although no compound corresponding to this structure has yet been detected. Migration of the C-14 methyl group to C-8, followed by loss of a proton from C-15 and introduction of a ketone at C-7 results in (23A) [c.f. the oxidation of dihydrobutyrospermyl acetate (22B) to the 7-ketone[18](23B)]. Epoxidation of the olefinic linkage in ring D of (23A), followed by oxidation at other centres of the molecule leads to cedrelone[19](24A), anthothecol[20](24 B) and hirtin[21](24C). Allylic oxidation in (23A), followed by epoxidation of the ring D double bond, leads, with appropriate functionalisation to grandifolione[22](25). A Baeyer-Villiger type cleavage of grandifolione (25) leads directly to khivorin (26 A) which has the familiar glycidic δ-lactone in ring D, typical of the limonoid types. Another member of this series, isolated originally from Entandophragma angolense[24] is gedunin (27 A) whose structure was elucidated by chemical methods[25] and confirmed by X-ray analysis[26], and to which khivorin has been related[27]. Several other closely related compounds from trees of the Meliaceae family are known, such as cedrolide[28](27B), 11-acetoxygedunin (27C) and 6,11-diacetoxygedunin[29](27D) which are all found in Carapa guayanensis, 7-oxodeacetoxykhvorin[28] (26 B), 1,2-dihydrogedunin[28,30](26C) and 7-oxodeacetoxy-1,2-dihydrogedun-3-ol[30] (26 D).

A further series of compounds is arrived at by oxidative cleavage of ring B in 7-oxodeacetoxygedunin (27 B) leading to andirobin[31] (28) then to methyl angolensate[32](29) by reductive opening of the epoxide ring, followed by cyclisation of the C-14 hydroxyl group to C-1. Gedunin (27A) has recently been related[33] to methyl angolensate (29) and andirobin (28) via dihydrodeoxyandirobin (30). By a Michael type cyclisation of C-2 to C-30 in a cleaved ring B precursor, the formation of swietenine (31) can be envisaged. Following the elucidation[34] of this structure, the structures of other related compounds were published, namely swietenolide[35](32 A), mexicanolide[36](32B) and carapin[37](33). Recently, the structure of odoratin (34) has been established[38], and it has been suggested that it may derive biogenetically from carapin (33) by a reverse Michael reaction, followed by β-diketone cleavage.

A Baeyer-Villiger type cleavage of 7-oxodeacetoxy-gedunin leads to (35) which is in fact obacunone[39], isolated from citrus species (Rutaceae). Opening of the ring A lactone, followed by cyclisation of the C-4 hydroxyl group to C-1 and reduction affords veprisone (36) which has been isolated from Vepris bilocularis[40], a member of the family Rutaceae. Lactonisation of the carbo-

methoxyl group in veprisone to the angular methyl group at C-10 and epimerisation at C-1 leads to the familiar structure of limonin (21A), elucidated by chemical[40] and X-ray methods[41]. Several related compounds from citrus trees have been subsequently reported, such as nomilin[42] (37A), deacetyl nomilin[43](37B), deoxylimonin[43](38), evodol[44](39) and ichangin[45](40).

One reaction in particular is common to these triterpenes which are modified in ring D; it is the base catalysed limonol (21B) to merolimonol (41) conversion. Limonin (21A), on Meerwein-Ponndorf reduction gives limonol (21B) which has an axial (α) hydroxyl group, in keeping with its mode of formation. Base treatment causes limonol to undergo rearrangement with loss of β-furfuraldehyde and the formation of merolimonol (41). The reaction apparently occurs only when a 7α-hydroxyl group is present, and has been rationalised by postulating opening of the epoxide ring to give the fairly unusual trimethylene oxide (42) which then undergoes base-catalysed loss of β-furfurladehyde as shown, with the formation of the hydroxy acid (43). Lactonisation of this compound on acidification then gives merolimonol (41). The reaction has subsequently been observed in many other liminoid compounds, notably gedunin (27A) and khivorin (26A).

Initially it was thought[46] that quassin (44) a bitter principle of the Simaroubaceae family was biogenetically derived from a diterpenoid precursor with a pimarane skeleton (44a) by a series of methyl group shifts, and a shift of a two carbon fragment, or by oxidative coupling of two identical C_{10} units as shown in (44b). In the light of the limonol-merolimonol reaction however, it was proposed[47,48] that the C_{26} triterpenoids are precursors of the C_{20} simaroubaceae bitter principles, their derivation involving loss of a C_5 fragment as described above, with subsequent loss of a methyl group at C-4, presumably by oxidation and decarboxylation. This proposal is reinforced by the above structural resemblance and stereochemical similarity of the Simaroubaceae C_{20} compounds to the merolimonol type of compounds.

Further confirmation that the quassin-type bitter principles are derived from a limonoid precursor is afforded by the structure of simarolide[49](44) which has a C_{25} skeleton. The absolute stereochemistry of simarolide suggests that its precursor may indeed be a tetracyclic triterpene of the euphol (5) type, from which one of the C-4 methyl groups has been oxidatively

removed. Oxidative cleavage of the C-23, C-24 bond with subsequent lactonisation on to C-20 would produce a side chain of the requisite structure and stereochemistry. The biogenesis probably also involves migration of the C-14 methyl group to C-8, with the introduction of a hydroxyl group at C-7. Baeyer-Villiger cleavage of ring D followed by relactonisation to the hydroxyl group at C-7 and oxidation of the resulting hydroxyl group at C-17 then leads to simarolide (45). Two other members of this series closely related to quassin (44) are chaparrin[50](46) and glaucarubin[51](47). They can be envisaged as deriving from simarolide (45) by cleavage of the C-13, C-17 bond. Two further compounds of this series, samaderine[52](48A) and cedronoline[53](48B) are C_{19} compounds, and probably arise by the additional loss of C-16. The presence of an oxygen atom at C-13 in both compounds suggests an oxidative cleavage of the C-13, C-17 bond in the precursor.

One of the most interesting compounds of the modified triterpene series is fraxinellone[53](49) recently isolated from Dictamnus albus L. (Rutaceae). Both the stereochemistry and source of this compound are similar to those of limonin (21A) and it seems likely that

fraxinellone (49) arises from a limonoid precursor by cleavage of rings A and B, and oxidative decarboxylation of ring D.

As yet, only two triterpenoids related to limonin, are known with a cleaved ring C; they are nimbin[54](50) and salannin[55](51), both obtained from Melia azadirachta. Biogenetically they can be envisaged as deriving from a precursor such as (23A) by oxidative cleavage of the C-12, C-13 bond, followed by oxidation and etherification. A further point of interest in these compounds is that salannin (51) is so far the only example of a triterpenoid of this type with an oxidised C-4 methyl group.

A great deal of interest centres on the ecology of these compounds, especially since so many possible biogenetic routes can be envisaged. Distinguishing experimentally between the various possible pathways of biogenesis however is fraught with difficulties, because in most cases the source of these compounds are trees, and the effective feeding of isotopically labelled compounds to higher plants is much less readily accomplished than to lower plants.

DISCUSSION

Triterpenes of Guarea Globra

Recently a large number of modified triterpenes such as gedunin (27A), nimbin (50), methyl angolensate (29) and limonin (21A) have been isolated from members of the family Meliaceae or the closely related Rutaceae. The possibility of isolating biogenetically important relatives of these compounds prompted examination of the heartwoods of other members of the Meliaceae, and one which has proved very fruitful in terms of the number of compounds isolated is Guarea globra. Examination by t.l.c. of the chloroform-soluble fraction of an ethyl acetate extract of powdered heartwood showed a large number of fairly polar compounds plus two less polar components. Separation by column chromatography over acid alumina using a gradient elution technique was only partly successful, and each component had to be further purified by repetitive t.l.c, on a preparative scale. The compounds obtained will be discussed in the order of increasing chromatographic polarity (on silica gel).

Globrenone (G 1)

Globrenone was eluted in benzene, and after purification by preparative t.l.c. and several crystallisations from methanol, had m.p. 92-94°C. Infra-red ($\nu_{max.}^{CCl_4}$ = 1678, 1618 cm.$^{-1}$) and ultra-violet ($\lambda_{max.}^{EtOH}$ = 242 mμ, log ε = 4.2) spectral data indicated the presence of an α,β-unsaturated ketone. The N.M.R. spectrum showed a singlet at τ 4.37, integrating for about 0.7H, and a multiplet at τ 5.00 corresponding to 0.3H. From this, it appeared evident that globrenone was a mixture. Confirmatory evidence on this point was available from mass spectral data - globrenone showed a parent, which was also the base peak of the spectrum, at m/e = 412 (100%) with two homologous peaks at m/e = 426 (38%); 398 (12%), corresponding to a major component of molecular formula $C_{29}H_{48}O$ with its C_{30} and C_{28} homologues present as impurities. From the ultra-violet spectrum, it seemed likely that a very small percentage of dienone was also present in the mixture ($\lambda_{max.}^{EtOH}$ = 304 mμ). Separation of these compounds by further preparative t.l.c. was only partially successful, the less polar fractions, m.p. 93-94°C, containing none of the C_{30} compound (P m/e = 412, no peak at 426), although the more polar fractions, m.p. 92-93°C, were still a mixture of

C_{28}, C_{29} and C_{30} compounds [m/e = 398 (13%), 412 (54%), 426 (21%)].

Hydride reduction of the original mixture afforded two products in proportions of about 3:1. The major one (G 2A), m.p. 111-113°C, was shown to be an unsaturated alcohol from the infra-red absorptions at 3622, 3606cm.$^{-1}$ (-OH) and 1647 cm.$^{-1}$ (C = C). The mass spectrum of the compound showed a parent at m/e = 414 (76%) with a strong peak at m/e = 396 (65%; loss of water from parent) and two weaker ones at m/e = 400 (10%), 382 (10%; loss of water from m/e = 400), corresponding to a major component of molecular formula $C_{29}H_{50}O$ with its C_{28} homologue as an impurity. The N.M.R. spectrum showed a singlet at τ 4.75 (0.7H) and a multiplet at τ 4.94 (0.3H), both due to olefinic protons. Thus it seems probable that this product is also a mixture of compounds, possibly isomeric with respect to the position of the double bond(confirmed by the ultra-violet end absorption of globrenone at 198 mμ, typical of an isolated trisubstituted double bond), A broad multiplet at τ 5.86 (1 H; $W_{\frac{1}{2}}$ = 16 c.p.s.) which, on formation of the acetate, was shifted downfield to τ 4.95 (1H; $W_{\frac{1}{2}}$ = 16 c.p.s.), was ascribed to a proton on carbon bearing oxygen. From the fact that reduction

of the carbonyl in (G1) causes the olefinic singlet to move upfield from τ 4.37 to τ 4.75, it seems likely that this proton is attached to the α-carbon, and since this shows very little coupling, it is reasonable to suppose that this is an equatorial alcohol, the axial proton, and its neighbouring olefinic proton having a dihedral angle of about 70° in any of the positions which a normal tetracyclic triterpene skeleton would allow. Manganese dioxide oxidation of this alcohol afforded a crystalline solid, m.p. 92-94°C, which had the same mixed m.p. and infra-red absorption as the parent enone. The minor product from hydride reduction (G3), m.p. 104-108°C, which is possibly $C_{30}H_{52}O$, showed a doublet in the N.M.R. at τ 4.60 (J = 5.5 c.p.s.) due to an olefinic proton, and a multiplet at τ 6.00 ($W_{\frac{1}{2}}$ = 15 c.p.s.; C<u>H</u>-OH). Also present were two weak absorptions at τ 5.00 and τ 6.34 which integrated for only about 0.15 H. It appears, that in this case, the doublet at τ 4.60 is probably due to the olefinic proton next to an axial alcohol, the dihedral angle between the two protons in this case being near to 40°.

Hydrogenation of globrenone (G1) in ethyl acetate over Adam's catalyst afforded three products, which were

separated by preparative t.l.c. The predominant one (G4) (intermediate polarity), m.p. 136-137°C, showed a parent peak in the mass spectrum at m/e = 416 (21%) with two others at m/e = 401 (13%), 398 (57%), corresponding to the saturated alcohol of molecular formula $C_{29}H_{52}O$, and loss of CH_3 and H_2O respectively. This compound was no longer contaminated with the C_{28} and C_{30} homologues. The most polar compound (G5), m.p. 132-135°C, was also isolated, but the least polar fraction was not. Both products (G4) and (G5), appeared to be saturated equatorial alcohols ($\nu_{max.}^{CCl_4}$ = 3610; 3610 $cm.^{-1}$), each showing a broad multiplet at τ 6.38 (C<u>H</u>-OH; width ~30 c.p.s), Such a spread of resonance would be expected for an axial proton with one equatorial and two axial neighbours.

Dehydration of globrenol (G2A) in phosphorus oxychloride and pyridine afforded a mixture of two dienes which were partially separated by t.l.c. on silver nitrate-silica gel. The crude predominant diene (G6) had $\lambda_{max.}^{EtOH}$ = 230, 237, 245 mμ., which is more closely similar to the absorptions found for the diene from melianone[16] (G7), $\lambda_{max.}^{EtOH}$ = 231.5, 239, 247 mμ, than those found for the corresponding lanostadiene[56], $\lambda_{max.}^{EtOH}$ = 236, 242, 249 mμ. The crude minor product had $\lambda_{max.}^{EtOH}$ = 260, 268, 275 mμ,

probably due to a homoannular diene. Conjecture on the formation of these dienes at the present would be meaningless, since it is evident from the spectral data that the starting material was a mixture, and it is impossible to tell whether each component of the mixture gave a single product.

Accepting the validity of Woodward's rules, and a normal tetracyclic triterpene skeleton, location of the enone system of globrenone (G1) in the side chain or in ring A seems unlikely, bearing in mind the fact that the N.M.R. spectrum shows no methyl groups below τ 8.90 and an absence of spin-spin coupling of the olefinic proton. Similarly, it does not appear likely that the enone is situated in ring D, leaving rings B and C as the only possible sites. In the case of a euphane skeleton, there are three possibilities consonant with the ultraviolet and N.M.R. spectral data: in ring B, a 7-en-6-one or a 5-en-7-one; in ring C, a 9(11)-en-12-one. The last site is excluded on the basis of the proton on the hydroxylic carbon in globrenol (G2A) showing considerable further coupling than that experienced by the olefinic proton. Further, the ease of dehydration of globrenol (G 2A) to the hetero-annular diene might be more easily rationalised on the basis of a 7-en-6-ol rather than a 5-en-7-ol structure.

Assuming that (G 2A) is an equatorial alcohol, and that the minor product of hydride reduction (G 3) is an axial alcohol of the C_{30} homologue, it is possible in the latter case, that hydride ion approach would come from the α-face, leading to an axial β-hydroxyl, while in the former case, if the axial C-4 methyl group were absent, β-face approach of hydride ion is feasible. On this basis, the structures (G1A) and G1B) are proposed very tentatively for the major component ($C_{29}H_{48}O$) and its C_{30} homologue respectively. In accord with this proposal, methyl region in the N.M.R. of (G 4) integrates for about 21 H, and shows peaks corresponding to three tertiary methyl groups, τ 9.35, 9.11, 9.08, while that of (G 5) integrates for 24 H, and shows peaks corresponding to five tertiary methyl groups, τ 9.35, 9.20 (6 H), 9.14, 9.11. This can only arise from (G 4) being the C-4 desmethyl-(G 5), since loss of a methyl group from any other site on a tetracyclic triterpene nucleus would leave four tertiary methyl groups, not three.

Further structural elucidation will depend firstly on the successful separation of the compounds which are present in "globrenone". This is a mixture of three homologues, on mass spectral evidence, each of which in

turn is very probably also a mixture of 7-en-6-one and another isomer. The most effective separation obtained so far was that of the hydrogenation products.

β-sitosterol (G 8)

The second compound eluted, crystallised as needles from chloroform, and had m.p. 134-136°C. Its staining with ceric sulphate solution and mobility on t.l.c. prompted direct comparison with an authentic specimen of β-sitosterol (G 8), with which it was indeed found to be identical (m.p., mixed m.p.).

Globral I (G 9)

The first of the group of polar compounds was named globral I (G 9), m.p. 137-139°C and in keeping with its chromatographic polarity it showed evidence of considerable oxygenation; $\nu_{max.}^{CCl_4}$ = 3611 (OH), 1732 (acetate), 1715, 1642, 1635 (mixed α,β-unsaturated esters) $cm.^{-1}$; $\lambda_{max.}^{EtCH}$ = 223 mμ (log ε = 4.11) (α,β-unsaturated ester). The mass spectrum showed a parent at m/e = 612, and a lower homologue at m/e = 598, which explained the difficulty in obtaining satisfactory analytical figures, globral I being in fact a mixture of compounds of molecular formulae

$C_{37}H_{56}O_7$ and $C_{36}H_{54}O_7$. N.M.R. data confirmed this inhomogeneity, two multiplets at τ 3.86 ($W_{\frac{1}{2}}$ = 6 c.p.s.) and 4.42 ($W_{\frac{1}{2}}$ = 6 c.p.s.) due to olefinic protons integrating for 0.5 H and 1.0 Hrespectively.

On the basis of this, and the two C = C stretching frequencies observed in the infra-red spectrum, it seems likely that globral I (G 9) is a mixture of methacrylate and β-methylcrotonate esters. Hydrogenation of globral I (G 9) over Adam's catalyst in ethyl acetate afforded the oily dihydroglobral I (G10A), in which the infra-red absorption at 1715 cm.$^{-1}$ had moved to 1730 cm.$^{-1}$, confirming the unsaturated nature of the ester. Kupchan cleavage of globral I (G 9) affords an easily hydrolysed ester as the major product, which, on hydrolysis, showed no trace of homologues in the neutral fraction (P m/e = 530). This reinforces the conclusion that globral I (G 9) is a mixture of methacrylate and β-methylcrotonate esters.

Sarett oxidation of globral I gave globral I lactone (G 10C), m.p. 200-202°C., which shows an infra-red absorption at 1782 cm.$^{-1}$, characteristic of a γ-lactone. In the N.M.R., the doublet at τ 4.60 (J = 6 c.p.s.) disappeared due to the oxidation of a cyclic hemi-

acetal to the corresponding lactone [cf. flindissol[14](17)]. A doublet at τ 7.18 (J = 6 c.p.s) in globral I (G 9) was assigned to an epoxide proton, its coupling to a broad multiplet at τ 6.10 (1 H) being confirmed by nuclear magnetic double resonance. On oxidation to the lactone, this multiplet shifted downfield to τ 5.81, prompting the conclusion that the system (G 11) must be present on the side chain, similar to that found in turraeanthin of recently assigned[15] structure (18).

Two peaks in the mass spectrum of globral I (G 9) at m/e = 552 and 548 corresponding to loss of the elements of acetic acid from the parents m/e = 612 and 598 respectively, the infra-red absorptions at 1732, 1249 $cm.^{-1}$, and the N.M.R. absorptions at τ 8.00 (3 H, singlet) and τ 4.98 (1 H, multiplet; $W_{\frac{1}{2}}$ = 6 c.p.s.) strongly suggest the presence of an axial secondary acetate. The N.M.R. absorption at τ 5.31 (1 H, multiplet; $W_{\frac{1}{2}}$ = 7 c.p.s.) is assigned to the proton on the carbon bearing the unsaturated ester.

The absence of the expected double bond in the nucleus is accounted for by the doublets centred at τ 9.66, 9.34 (J = 6 c.p.s.) diagnostic of a methylene group in a cyclopropane ring, which is probably 9,10-fused.

Furthermore, globral I shows only four tertiary methyl groups in the N.M.R. at τ 9.22, 9.11, 9.07, 8.89. On the basis of this evidence, the skeleton of globral I is proposed as that shown (G 9A).

Hydrolysis of globral I or globral I lactone in mild conditions resulted only in recovery of starting material. Refluxing in methanolic potassium hydroxide was found necessary to ensure any hydrolysis, and this led to rather complex mixtures of products which on N.M.R. evidence still contained the grouping H-C-OAc. Assuming that there is oxygenation at C-3, this can only be the point of attachment of the unsaturated ester, since an acetate at C-3 would be expected to hydrolyse in refluxing methanolic potassium hydroxide. As the multiplet at τ 5.31 in the N.M.R. spectrum of globral has a width of only 7 c.p.s., and appears to be a triplet, the unsaturated ester must be axial, the equatorial proton at C-3 experiencing only two small couplings from the neighbouring protons at C - 2. The 3α-hydroxyl orientation, although less common than the 3β, is also found in flindissol[14] (17). The multiplet for the C<u>H</u>-OAc in globral I and its lactone at τ 4.98 ($W_{\frac{1}{2}}$ = 6 c.p.s.) appears to be a triplet, which suggests that this proton has two neighbours. In the

proposed skeleton, this leaves only four possible positions for this proton: C-1, C-11, C-12 and C-15. Since the acetate is resistant to hydrolysis, this excludes C-1 and C-15, and leaves the hindered C-11 and C-12 positions as the possible locations. The very small coupling observe is indicative of an axial acetate, the proton experiencing an axial equatorial (2-3.5 c.p.s.) and an equatorial-equatorial coupling (2-3.5 c.p.s.). On the evidence available, we therefore suggest, very tentatively, for globral I the structures (G 9A) and (G 9B), although on biogenetic grounds, (G 9A) is probably more favoured. For the sake of convenience, all structural formulae refer to (G 9A) as the structure of globral I. Concerning the stereochemistry at C-8, this is written as involving an α-hydrogen for two reasons: in the cyclolanostane series [e.g. cycloartanol (13)] the proton at C-8 is β, corresponding to addition of the hydrogen from the steric less hindered side, and in the euphol series, the less hindered side is the α-face; examination of models shows a 8α-hydrogen orientation to be sterically much more favourable in the case of a cyclo-euphol type.

Hydrolysis of globral I lactone (G 10C) in refluxing ethanolic sulphuric acid afforded two compounds by

opening of the epoxide. According to N.M.R. and infra-red spectral data, the other functional centres were intact in both cases. The amorphous major product showed three absorptions in the hydroxyl region of the infra-red at 3608, 3582, 3536 $cm.^{-1}$ due to a free hydroxyl, and two bonded forms respectively. The minor product, less polar on t.c.l. showed no absorption corresponding to a free hydroxyl in the infra-red, but peaks at 3576 and 3535 $cm.^{-1}$, corresponding to two bonded forms. In both cases, the peak at $\sim$ 3535 $cm.^{-1}$ is due to hydrogen bonding of the C-25 hydroxyl group to the ethereal oxygen of the γ-lactone (O-O distance $\sim$ 2.0 Å). Bonding from the C-24 hydroxyl group to the lactone ethereal oxygen is much less feasible (O-O distance $\sim$2.6 Å). In the case of the major product, the absorption at 3582 $cm.^{-1}$ shows a frequency shift ($\Delta\nu_{OH}$ = 26 $cm.^{-1}$) comparable with that found for erythro- and trans-1,2-diols[58]. While the absorption at 3576 $cm.^{-1}$ observed in the minor product corresponds to a shift ($\Delta\nu_{OH}$ = 32 $cm.^{-1}$) which is closely similar to that found for 2-methoxyethanol ($\Delta\nu_{OH}$ = 31 $cm.^{-1}$)[5]. On this basis, the structures of the major and minor products are written as (G 12A) and (G 12B) respectively. The structures proposed are in keeping

with their mode of formation; the protonated epoxide being subjected to nucleophilic attack at C-24 by a molecule of water [giving (G 12A)] or a molecule of ethanol [giving (G 12B)]. A similar epoxide ring opening was observed in acetic acid, leading to a mixture of acetate and diacetate.

In one hydrogenation of globral I, in ethyl acetate over Adam's catalyst (18 hours), a crystalline product (G 13), m.p. 176-178°C which corresponded to a tetrahydroglobral I (P m/e = 616, 602), was obtained. According to spectral evidence the hemiacetal ring had been reduced to the corresponding diol (G 13), [$\nu_{max.}^{CCl_4}$ = 3639, 3600, 3483 cm.$^{-1}$; O-C<u>H</u>-O at τ 4.60 absent; new peak at τ 6.42 (2 H; doublet; J = 5 c.p.s.)]. On oxidation, this diol gives the same dihydroglobral I lactone (G 10B) as that obtained by oxidation of dihydroglobral I (G 10A).

<u>Globral II (G 14A)</u>

the second compound of the polar group was referred to as globral II (G 14A), and had m.p. 165-167°C. From mass spectral (P m/e = 528) and combustion analysis data, the molecular formula of $C_{32}H_{48}O_6$ was deduced. The compound was nearly transparent in the ultra-violet

above 200 mμ, but the infra-red spectrum showed the presence of a hydroxyl group (3610 $cm.^{-1}$), an acetate (1735, 1246 $cm.^{-1}$) and a cyclohexanone (1709 $cm.^{-1}$). The N.M.R. spectrum showed globral II to be similar to globral I. Thus, it has a similar hemiacetal-epoxide side chain, a cyclopropane ring, and an axial acetate (see tables). Oxidation with Sarett's reagent afforded globral II lactone (G 14 B) (P m/e = 526) which was shown to be the γ-lactone ($\nu_{max.}^{CCl_4}$ = 1783 $cm.^{-1}$) corresponding to the hemiacetal.

The optical rotary dispersion curve of globral II (G 14 A) showed a positive Cotton effect; $\alpha_{213} = 343^{o}$, $\alpha_{263} = -151^{o}$, $\alpha_{300} = 319^{o}$, $\alpha_{400} = -47^{o}$. This is opposite in sign to the curve obtained for cycloartenone[57]. The effect of the acetate group and difference in stereochemistry at C-8 on the Cotton curve is not certain, and since no suitable model compounds are available, no conclusions can be reached on this basis at present.

Attempted hydrolysis of globral II in mild conditions led to recovery of the starting material, but refluxing in strong base afforded a moderate yield of an oil (G 15), which showed no sharp singlet at τ 8.00 in

the N.M.R., and in the mass spectrum showed a parent ion at m/e = 486, corresponding to hydrolysis of the acetate. Acid hydrolyses opened the epoxide ring, leaving the acetate intact, and were not further investigated.

Since the cyclopropane methylene protons and the CH-OAc proton all absorb at frequencies in the N.M.R. similar to the corresponding absorptions observed for globral I, it seems reasonable to assume that these are in the same positions in globral II. Based on this, the structure of globral II is proposed as (G 14A).

Globral III (G 16)

The third compound, globral III had m.p. 198-200°C; and on the basis of mass spectral (P m/e = 630) and combustion analysis data, was assigned the molecular formula $C_{37}H_{58}O_8$. The ultra-violet spectrum showed the absence of olefinic linkages, and this was confirmed by the N.M.R. and infra-red spectra. Study of the spectral data showed that globral III had a hemiacetal-epoxide side chain as found in the two compounds, globral I and globral II, previously described, and as before, oxidation yielded a γ-lactone ($\nu_{max.}^{CCl_4}$ = 1782 cm.$^{-1}$). A broadened singlet at τ 5.00 ($W_{\frac{1}{2}}$ = 6 c.p.s.) and a

sharp singlet at τ 7.99 (3H) in the N.M.R. spectrum of globral III suggested the presence of an axial secondary acetate analogous to that found in the previous two compounds. Two doublets at τ 9.62, 9.35 (J = 5 c.p.s.) showed the presence of a cyclopropane ring. A broadened singlet at τ 5.22 ($W_{\frac{1}{2}}$ = 6 c.p.s.), and two secondary methyls at about τ 9.10 in the N.M.R., bearing in mind the molecular formula $C_{37}H_{58}O_8$, suggested the presence of an axial C_5 ester. Upon shaking the N.M.R. sample with deuterium oxide, the multiplet at τ 6.05 collapsed to a sharp doublet (J = 4 c.p.s.). Double resonance experiments showed that this doublet did not arise from coupling with any of the low field protons, but rather with a proton observed in the methylene envelope. This shows that a C<u>H</u>-OH proton with only one adjacent proton must be present in globral III. Such a sequence cannot be accommodated on the proposed skeleton (G 9A) except perhaps with the hydroxyl at C-12, i.e. adjacent to the acetate. This possibility is however excluded by the double resonance results, and the hydroxyl group must be located in the C_5 ester. Further, this ester can only be a 3-methyl-2-hydroxybutyrate to accord with the CH-CH-OH requirement. For comparison, the N.M.R.

spectrum of ethyl lactate was recorded, and this showed a quartet due to the proton on the α-carbon centred at τ 5.95, a chemical shift close to that found for the analogous proton in globral III (τ 6.05).

Thus the structure of globral III, on the above evidence is written as (G 16). Confirmatory evidence for the hydroxy ester is available from the infra-red spectrum of the keto-lactone (G17 A), m.p. 213-215°C, which shows a broad absorption at about 1730 $cm.^{-1}$, due to the acetate, and the α-keto-ester.

Acetylation of globral III (G 16) afforded an oily diacetate, which was hydrolysed on basic alumina to the acetate (G 17B), m.p. 185-187°C, which in turn was oxidised to the lactone acetate (G 17 C), m.p. 202-204°C. In an attempt to form a heavy atom derivative, the corresponding iodoacetoxy compounds were made, but none of these were of suitable crystalline form for X-ray analysis.

Globral IV (G 18A)

The fourth compound of the polar group was isolated as an oil, globral IV, and was assigned the molecular formula $C_{32}H_{50}O_6$ on the basis of its mass spectrum

(P m/e = 530). The spectral data were in accord with the presence of a hemiacetal-epoxide side chain, a cyclopropane ring, and an axial secondary acetate, in common with the three previous compounds. A multiplet at τ 6.55 ($W_{\frac{1}{2}}$ = 7 c.p.s.) in the N.M.R., plus an absorption at 3626 cm.$^{-1}$ in the infra-red suggested the presence of an axial secondary hydroxyl group in globral IV. Oxidation afforded a keto-γ-lactone which was found to be identical with globral II lactone (G 14B). On this basis, globral IV may be written as (G 18A).

Globral IV was converted to the oily diacetate by treatment with acetic anhydride and pyridine. Hydrolysis by adsorption on basic alumina to the monoacetate, followed by oxidation gave the lactone acetate (G 14B) m.p. 220 - 222°C which had absorptions in the infra-red at 1784 cm.$^{-1}$ (γ-lactone) and 1733 cm.$^{-1}$ (two acetates). The corresponding lactone iodoacetate (G 14C) m.p. 184-188°C, was made, but did not crystallise in a form suitable for X-ray analysis.

If the conclusions reached as to the structures of these first four compounds are correct, then their correlation should prove quite simple. Globral II and globral IV have already been correlated, and from mass

spectral and N.M.R. evidence, the product from Kupchan cleavage of globral I is globral IV. No further work in this direction has yet been done.

Globral V

The fifth compound of the polar group, an oil, globral V appeared to be considerably different according to the spectral data: in the N.M.R. it showed a series of multiplets at low field, each due to one proton at τ 4.64, 5.00, 5.55, 6.20, 6.44, 6.60, 6.88, with an acetate methyl group at τ 7.99. The methyl region, even at 100 M.c.s. was poorly resolved, but a singlet at τ 8.76 (6 H) was easily distinguishable, while the rest of the upfield region consisted of three tertiary methyl groups at τ 8.90, 9.10 and 9.18, with a secondary methyl group centred at τ 9.02 (J = 7 c.p.s.). The presence of an acetate group was confirmed by the infra-red spectrum (1731 $cm.^{-1}$) which shows a large hydroxyl absorption [3615, 3510 (broad) $cm.^{-1}$]. Attempts to oxidise this compound using Sarett's reagent failed to afford any isolable product. N.M.R. data suggest that the epoxide ring, and the hemiacetal found in the side chain of the previous compounds are both absent but even tentative conclusions as to the structure of this compound cannot be drawn at present.

Globral VI

The sixth compound, globral VI seemed totally different from all of the previous compounds. It had m.p. 194-200°C, and showed two hydroxyl absorptions in the infra-red (3640, 3625 cm.$^{-1}$) and a small peak at 1634 cm.$^{-1}$ suggestive of an isolated double bond. The ultra-violet spectrum showed $\lambda_{max.}^{EtOH}$ = 209 mμ; log ε = 3.91, typical of an isolated tetrasubstituted double bond. Only a small amount of material (6-8 mg.) was available, and consequently the quality of the N.M.R. spectrum was poor and of very little diagnostic value.

Globral VIII

Globral VIII was obtained as an oil by repeated preparative g.l.c. of the fractions eluted with ethyl acetate from the chromatogram column. In the infra-red it showed two free hydroxylic absorptions (3630, 3610 cm.$^{-1}$) assigned to a primary and a secondary alcohol respectively. A strong hydrogen bonding peak at about 3450 cm.$^{-1}$ was also observed, the shift ($\Delta \nu_{OH}$ = 170 cm.$^{-1}$) being characteristic[58] of 1,4-diols. The infra-red spectrum also showed the presence of an acetate group (1737, 1249 cm.$^{-1}$) and a cyclohexanone (1710 cm.$^{-1}$). Six tertiary methyl groups

were clearly visible in its N.M.R. spectrum, at τ 8.77 (6 H), 8.92 (3 H) and 9.03 (9 H), as was an acetate methyl group at τ 8.01, the corresponding HC-OAc proton being at τ 5.03. Also present were multiplets at τ 6.20 (1H), 6.38 (2 H) and 6.62 (1H), assigned to CH-OH, CH_2OH and CH-OR respectively.

Oxidation of globral VIII with Sarett's reagent gave a crystalline product, m.p. 174-178°C, which showed no hydroxylic absorption in the infra-red, but instead a new peak at 1790 $cm.^{-1}$ corresponding to a γ-lactone. The N.M.R. spectrum of this compound proved very revealing. The methyl region consisted of six tertiary methyl groups at τ 9.02 (15 H) and 8.90 (3 H). The improved quality of this spectrum allowed observation of two doublets at τ 9.64 and 9.35 (one proton each; J = 6 c.p.s.) arising from a methylene group in a cyclopropane ring. A multiplet at τ 5.00 ($W_{\frac{1}{2}}$ = 6 c.p.s.) was assigned to the CH-OAc proton, whose coupling with a broadened singlet at τ 8.28 (2 H) was demonstrated by double resonance experiments. By irradiation at either of these frequencies, the other signal collapsed to a sharp singlet, showing that there was no further coupling. This coupling pattern requires a CH-OAc proton with only two adjacent hydrogen atoms,

each of which has no further hydrogen neighbours. On the basis of the proposed skeleton, the only location for the acetoxy group which fits this requirement is at either C-11 or C-12. Its attachment to C-11 is more likely on biogenetic grounds. Further, the narrow spread of resonance is diagnostic of an axial acetate group.

Two more low field absorptions were observed; a triplet at τ 6.02 (1H; J = 8 c.p.s.) and a diffuse triplet at τ 5.64 (width ~ 26 c.p.s.). These two protons were mutually coupled, since on irradiation at τ 6.02 the multiplet at τ 5.64 collapsed to a quartet (separation 4 c.p.s.) and on irradiation at τ 5.64, the triplet at τ 6.02 collapsed to a doublet (J = 8 c.p.s.). Irradiation at τ 7.54 caused the multiplet at τ 5.64 to collapse to a doublet (J = 8 c.p.s.), while the reverse experiment caused visible simplification of the multiplet at τ 7.54. The proton at τ 6.02 was also coupled with a multiplet at τ 7.72, since on irradiation at τ 6.02, the multiplet at τ 7.72 collapsed to a doublet (J = 3.5 c.p.s.), while irradiation at τ7.72 resulted in the collapse of the of the triplet at τ 6.02 to a doublet (J = 8 c.p.s.). Taking into account the chemical shifts, such a coupling

pattern requires the system (G 19) to be present. This can only be accommodated in the side chain of a tetracyclic skeleton, and bearing in mind the fact that this compound contains a γ-lactone, and no secondary methyl groups the structure (G 20) is proposed for this oxidation product. This structure fully explains the couplings observed, estimated values for these being, $J_{17,21}$ = 4 c.p.s., $J_{21,22}$ = 8 c.p.s., $J_{22,23}$ = 8 c.p.s., $J_{23,24}$ = 8 c.p.s., which are in complete agreement with those found. The stereochemistry as shown assumes a tirucallol (4)-type precursor.

The mode of formation of this lactone probably involves oxidation of the primary alcohol in the precursor to the corresponding hydroxy-aldehyde, which is then oxidised to the γ-lactone (G 20), possibly via the corresponding hemiacetal. On this basis, therefore, the structure (G 21) is proposed for globral (VIII). An analogous pattern of oxidation in the side chain is found in bourjotinolone A[17] (20 A). Such a side chain may be derived biogenetically from a tirucallol (4) side chain by allylic oxidation at C-23, formation of an other linkage between C-22 and C-25 and additional oxygenation of C-20.

EXPERIMENTAL

Extraction of Guarea globra.

The powdered heartwood of Guarea globra (10 Kg.) was extracted with ethyl acetate (20 litres) in a Soxhlet apparatus for 48 hours. The solvent was reduced in bulk (to 1 litre), chloroform (1.5 litres) added, and after cooling, the waxy precipitate filtered off. The precipitation process was repeated twice with chloroform and twice with benzene. Removal of the solvent afforded a benzene soluble oil (160 g.) which was shown to be a mixture of about ten main components (t.l.c.).

Separation of components.

The above oil (40 g.) was dissolved in benzene (180 ml.) and chromatographed over acid alumina (2 Kg.; Spence, Grade 0) using a gradient elution technique. Benzene eluted a yellow wax A (6 g.), followed by a pale yellow oil B (2.5 g.) which crystallised on cooling. Washing with benzene-chloroform (20:1) brought off a white crystalline solid C (5.8 g.). Small amounts of amorphous material were eluted, followed by a crystalline solid D (2.3 g.) [chloroform (approx. 2:1)]. Thereafter, each fraction was oily, and consisted of a mixture of

components (t.l.c.). In all, a further 17g. of these oily fractions E were eluted.

The yellow wax A was shown by t.l.c. (light petroleum as solvent) to consist of a large number of compounds, and was not further investigated. The crystalline solid B, was purified by preparative t.l.c. (chloroform as solvent), crystallisation from methanol affording needles of globrenone (G 1), which had m.p. 92-94°C, $\nu_{max.}^{CCl_4}$ = 1678, 1618 cm.$^{-1}$, $\lambda_{max.}^{EtOH}$ = 197, 242, 304 mμ (log ε_{242} = 4.2). Found: C = 84.01, H = 11.76; $C_{29}H_{48}O$ requires, C = 84.40, H = 11.72. P m/e = 426 (412).

The solid C crystallised from chloroform in needles m.p. 134-136°C and had the same m.p. and mixed m.p. as an authentic sample of β-sitosterol supplied by Dr. J. Connolly.

Crystallisation of solid D from ethyl acetate-light petroleum or methanol, furnished needles, m.p. 128 - 130°C. Repeated crystallisation from methanol afforded needles of globral I (G 9A), which had m.p. 137 - 139°C, $[\alpha]_D$ = -61.3° (c = 1), $\nu_{max.}^{CCl_4}$ = 3611, 1732, 1715, 1652, 1635, 1249 cm.$^{-1}$, $\lambda_{max.}^{EtOH}$ = 223 mμ (log ε = 4.11). Found: C = 71.83, H = 8.65. $C_{37}H_{56}O_7$ requires, C = 72.51, H = 9.21 ($C_{36}H_{54}O_7$ requires, C = 72.21, H = 9.09). P m/e = 612 (598).

The oil E was chromatographed over acid alumina (800g.; Grade III), using a gradient elution technique. Benzene eluted a little amorphous material (1.4g.) which was not further investigated. Benzene-chloroform (3:1) eluted more globral I (G 9A) (1.3g.) identified by t.l.c., which crystallised from methanol as needles, m.p.129-132°C. Benzene-chloroform (2:1) eluted a slightly more polar compound (t.l.c.) which crystallised slowly from ethyl acetate-light petroleum as needles (2.6g.) of globral II (G 15A), m.p. 133-136°C. Repeated crystallisation from di-isopropyl ether afforded needles m.p. 140-143; 165-167°C, $[\alpha]_D$ = -3.1° (C = 1), $\nu_{max.}^{CCl_4}$ = 3610, 1735, 1709, 1246 cm.$^{-1}$, Found: C = 73.81, H = 9.40; $C_{30}H_{48}O_6$ requires, C = 72.69, H = 9.40. P m/e = 528.

Further elution with benzene-chloroform (2:1) afforded <u>globral III</u> (G 17A), which deposited needles (3.1g.) from methanol, m.p. 129-135°C. Repeated crystallisation from ethyl acetate-light petroleum afforded needles which had m.p. 104-110; 198-200°C, $[\alpha]_D$ (C = 1.5), $\nu_{max.}^{CCl_4}$ = 3610, 3540, 3430 (broad), 1732, 1250 cm.$^{-1}$. Found: C = 69.93, H = 9.03; $C_{37}H_{58}O_8$ requires, C = 70.44, H = 9.27. P m/e = 630.

Continued elution produced mixed fractions, and the remaining compounds were separated by preparative t.l.c. The next compound in order of polarity was separated from globral III by preparative t.l.c. (chloroform containing 3% methanol as solvent), affording globral IV (G 18A) as an oil, which had $\nu_{max.}^{CCl_4}$ = 3634, 3611, 3530, 1731, 1250cm.$^{-1}$ P m/e = 530. Globral V was isolated in crude form as an oil, and had $\nu_{max.}^{CCl_4}$ = 3608, 3505, 1731, 1710, 1250, 1220cm.$^{-1}$. Preparative t.l.c. (chloroform containing 5% methanol as solvent) afforded globral VI as a solid, crystallising from ethyl acetate-light petroleum as flat plates m.p. 194-200°C, which had $\nu_{max.}^{CCl_4}$ = 3640, 3625, 1634 cm.$^{-1}$, $\lambda_{max.}^{EtOH}$ = 209 mμ ($\varepsilon \sim$ 8000). The next compound in order of polarity (t.lc.) was not isolated in a sufficiently high state of purity to warrant even spectral study. The most polar compound, globral VIII (G 21) was isolated from the ethyl acetate washings of the column by preparative t.l.c. as an oil, which had $\nu_{max.}^{CCl_4}$ = 3630, 3610, 1738, 1712 cm.$^{-1}$.

Reduction of globrenone (G 1)

Globrenone (120mg.) was refluxed in dry ether (20 ml.) with excess lithium aluminium hydride (150 mg.). Work up in the usual manner afforded a crystalline residue

which consisted of two products, which were separated by preparative t.l.c. (chloroform as solvent). The more polar, major, product which crystallised from light petroleum as needles, was globrenol (G 2A) (89 mg.), m.p. 111-113°C, $\nu_{max.}^{CCl_4}$ = 3622, 3606, 1647 cm.$^{-1}$. Found: C = 83.87, H = 12.21; $C_{29}H_{50}O$ requires, C = 83.99, H = 12.15. P m/e = 414. The other component also crystallised from light petroleum to give needles, m.p. 104-108°C.

Oxidation of globrenol (G 2A).

The above compound (10 mg.) in chloroform (10 ml.) was stirred with activated manganese dioxide for 36 hours. Filtration, and removal of the solvent afforded a crystalline residue (9 mg.), which crystallised as needles from methanol m.p. 92-94°C, $\nu_{max.}^{CCl_4}$ = 1678, 1618 cm.$^{-1}$. This was identical with a sample of globrenone (G 1) (m.p., m.m.p., i.r.), but had P m/e = 412.

Globrenol acetate (G 2B).

Globrenol (40 mg.) in dry pyridine (10 ml.) was treated with acetic anhydride (6 ml.) at room temperature for 14 hours. The reaction mixture was poured on to

ice, and extracted with ether (2 x 15 ml.), the combined extracts washed with water (2 x 15 ml.), dried and evaporated to dryness to afford a yellow oil (41 mg.), which consisted almost entirely of globrenol acetate (t.l.c.) which was purified by preparative t.l.c. (benzene-chloroform [1:2] as solvent) to afford globrenol acetate (G 2B) as needles from methanol m.p. 92-94°C, $\nu_{max.}^{CCl_4}$ = 1732 cm.$^{-1}$. Found: C = 82.00, H = 11.02; $C_{31}H_{52}O_2$ requires, C = 81.52, H = 11.42.

Hydrogenation of globrenone (G.1).

Globrenone (G 1) (68 mg.) was hydrogenated in ethyl acetate (20 ml.) over Adam's catalyst (10 mg.) for 14 hours (slow uptake of hydrogen). The catalyst was filtered off, and the solvent removed to afford an oil (64 mg.) which contained three products (t.l.c.), the two more polar products having a polarity similar to globrenol The major product, second in order of t.l.c. polarity, was separated by preparative t.l.c. (chloroform as solvent and crystallised from light petroleum giving needles of globral (G 4), m.p. 136-137°C, $\nu_{max.}^{CCl_4}$ = 3608 cm.$^{-1}$. Found: C = 83.52, H = 12.43; $C_{29}H_{52}O$ requires, C = 83.58, H = 12.58, P m/e = 416. The most polar component was crystallised from light petroleum, m.p. 132-135°C, $\nu_{max.}^{CCl_4}$ = 3605 cm.$^{-1}$.

Globrenol p-iodobenzoate (G 2C).

Globrenol (G 2A) (24 mg.) in dry pyridine (6 ml.) was treated with p-iodobenzoyl chloride (110 mg.) for 16 hours. The mixture was poured into water (15 ml.) and after 30 minutes, extracted with ether (2 x 15 ml.). The combined extracts were washed with water (2 x 20 ml.), dried, and evaporated to dryness. The solid residue was extracted with light petroleum, evaporation of which left a solid residue (43 mg.) which consisted of the p-iodobenzoate plus p-iodobenzoic anhydride. Separation was achieved by chromatography over acid alumina (3 gm. Grade II), benzene-chloroform (7:1) eluting the p-iodobenzoate (G 2C) which was crystallised from methanol-ether, m.p. 112-115°C. A suitable crystal was mounted on a glass fibre, and set up about the needle axis, but showed no symmetry in the first oscillation photograph. The first Weissenberg photograph showed that the crystal was triclinic and also showed no strong spots, except those of low $\sin\theta$.

The minor product of the hydride reduction was treated in a similar manner but afforded only fine felted needles, m.p. 119-120°C, and was not further investigated.

Separation of globrenone and homologues.

Crude globrenone (100 mg.) was run four times on a t.l.c. plate 0.5 mm. thick [chloroform-light petroleum (2:1) as solvent], split into two bands, and each band run four times on t.l.c. plates 0.25 mm. thick, in the same solvent as before. The plate containing the front fraction was split into two bands, and the front one extracted to afford globrenone, crystallising from methanol with m.p. 92-94°C. P m/e = 412. The plate containing the rear fraction was also split into two bands, and the rear one extracted to give needles from methanol, m.p. 92-94°C. P m/e = 412 (426).

Dehydration of globrenol (G 2).

The alcohol (G 2) (10 mg.) in dry pyridine (2 ml.) was treated with phosphorus oxychloride (6 drops) for 1 hour. The reaction mixture was poured into water and extracted with ether (2 x 10 ml.). The ether extract was washed with water (2 x 10 ml.), dried and evaporated to afford an oil (8 mg.) which was shown by t.l.c. (silver nitrate silica, petrol containing 1% ether as solvent) to consist of two products. These were partially separated by preparative t.l.c. The less polar

(t.l.c.) fraction was an oil (4 mg.) which had $\lambda_{max.}^{EtOH}$ = 230, 237, 245 mμ. The more polar one, also an oil (~ 1 mg.), had $\lambda_{max.}^{EtOH}$ = 260, 268, 275 mμ.

Oxidation of globral I (G 9A).

The above compound (100 mg.) in dry pyridine (10 ml.) was treated with "AnalaR" chromium trioxide (130 mg.) for 14 hours. The reaction was worked up in the usual manner to afford the lactone (G 11), (70 mg.), needles from ethyl acetate-light petroleum, m.p. 200-202°C, $\nu_{max.}^{CCl_4}$ = 1782, 1734, 1717, 1642, 1635, 1249, 1160 $cm.^{-1}$. Found C = 72.40, H = 8.54; $C_{37}H_{54}O_7$ requires, C = 72.75, H = 8.91 ($C_{36}H_{52}O_7$ requires, C = 72.45, H = 8.78) P m/e = 610 (596).

Acetylation of globral I (G 9A).

The above compound (153 mg.) in dry pyridine (10 ml.) at 0°C was treated with acetic anhydride (5 ml.) and set aside at room temperature for 12 hours. Work up in the usual manner afforded an oily residue, which was shown (t.l.c.) to consist of a mixture of two compounds of very similar polarity, plus starting material. Preparative t.l.c. (chloroform containing 2% methanol) proved ineffective in separating the two acetates, and these appeared to be

decomposing steadily. After four days, it appeared that the mixture had hydrolysed to the extent of 80% (t.l.c.), and the remaining acetate fraction was mainly the less polar isomer, which was separated from the starting material by preparative t.l.c. [ethyl acetate-light petroleum (1:2) as solvent] affording needles from ethyl acetate-light petroleum of globral I acetate (G 9B). m.p. 99-100°C, P m/e = 594 (580).

Hydrogenation of globral I (G 9A).

The above compound (124 mg.) was hydrogenated in ethyl acetate (40 ml.) over Adam's catalyst (10 mg.). After the fairly rapid uptake of hydrogen (5 ml.: 1.1 moles) had ceased, the catalyst was filtered off and the solvent removed to afford an oil, which consisted of mainly one product (t.l.c.) of similar polarity to the starting material. Purification by preparative t.l.c. (chloroform containing 2% methanol as solvent) afforded dihydroglobral I (G 10A) as an oil (106 mg.) which failed to crystallise, $\nu_{max.}^{CCl_4}$ = 3610, 1731, 1249 cm.$^{-1}$, P m/e = 614 (600). The oil (100 mg.) in dry pyridine (10 ml.) was treated with "AnalaR" chromium trioxide (140 mg.) for 15 hours. Work up in the usual manner afforded

dihyrdroglobral I lactone (G 10B) (72 mg.) as needles from ethyl acetate-light petroleum m.p. 200-201°C $\nu_{max.}^{CCl_4}$ = 1783, 1731, 1249 cm.$^{-1}$ P m/e = 612 (598).

Globral I (G 9) (63 mg.) was hydrogenated under similar conditions as before, except that it was left on for 18 hours. Work up as before yielded a mixture of products (t.l.c.) the major component, being considerably more polar than the starting material. Preparative t.l.c. (chloroform containing 4% methanol as solvent) afforded tetrahydroglobral I (G 14) as needles (48 mg.) from ethyl acetate-light petroleum. m.p. 176-178°C $\nu_{max.}^{CCl_4}$ = 3639, 3600, 3483, 1730, 1249 cm.$^{-1}$. Found: C = 71.61, H = 9.51; $C_{37}H_{60}O_7$, requires, C = 72.04, H = 9.80 ($C_{36}H_{58}O_7$ requires C = 71.72, H = 9.70) P m/e = 616 (602). This compound (4 mg.) in dry pyridine (1 ml.) was treated with "AnalaR" chromium trioxide (10 mg.). Work up in the usual manner afforded a brown oil (4 mg.) which was purified by preparative t.l.c. affording needles of the dihydroglobral I lactone (G 10B) from ethyl acetate-light petroleum m.p. 197-199°C $\nu_{max.}^{CCl_4}$ 1783, 1721, 1248 cm.$^{-1}$ P m/e = 612 (598).

Acid hydrolysis of globral I lactone (G 11).

The lactone (G 11) (48 mg.) was refluxed in ethanol (15 ml.) containing 30% sulphuric acid (3 ml.) for 50 minutes. The reaction mixture was neutralised with sodium bicarbonate, the ethanol removed under reduced pressure, and the aqueous residue extracted with ethyl acetate (2 x 12 ml.). The combined extracts were washed with water (15 ml.), dried, and evaporated to dryness to afford an oil (41 mg.) which consisted of a polar (major) product, and two less polar products (t.l.c.). These were separated by preparative t.l.c. (chloroform containing 3% methanol as solvent) to afford the major product as a glass (G 13A), which had $\nu_{max.}^{CCl_4}$ = 3608, 3582, 3536, 1781, 1734, 1715, 1653, 1637, 1248 cm.$^{-1}$. The less polar product (G 13B) failed to crystallise, and had $\nu_{max.}^{CCl_4}$ = 3580, 3528, 1786, 1735, 1717, 1652, 1635, 1249, 1160 cm.$^{-1}$.

Kupchan cleavage of globral I (G 9).

Globral I (85 mg.) in ether (2 ml.) and dry pyridine (1 ml.) was added to osmium tetroxide (100 mg.) and left at room temperature for 16 hours. Work up in the usual manner afforded an oil (85 mg.) which consisted

of two polar compounds (t.l.c.). The crude product (26 mg.) in methanol (3 ml.) was treated with sodium periodate (40 mg.) in water (1 ml.) and afforded, on work up, an oil containing one major product (t.l.c.), which was isolated by preparative t.l.c. [ethyl acetate-light petroleum (3:2) as solvent] as an oil (18 mg.). This oil (18 mg.) in aqueous methanol (1:2; 6 ml.) was treated with sodium bicarbonate for 2 hours. The mixture was evaporated almost to dryness, extracted with ethyl acetate (20 ml.) and the extract washed with water (2 x 10 ml.). Evaporation of the solvent afforded an oil (G 10D) (16 mg.) which was purified by t.l.c., but failed to crystallise, and had P m/e = 530; $\nu_{max.}^{CCl_4}$ = 3604, 1734 cm.$^{-1}$.

Oxidation of globral II (G 14A).

Globral II (63 mg.) in dry pyridine (12 ml.) was treated with "AnalaR" chromium trioxide (100 mg.) for 17 hours. Work up in the usual manner afforded a brown solid (58 mg.) which was purified by preparative t.l.c. (chloroform containing 2% methanol as solvent), crystallisation from ethyl acetate-light petroleum affording needles (49 mg.) of globral II lactone (G 14B), m.p.

210-213°C, $[\alpha]_D$ = -34.8° (C = 1.5) $\nu_{max.}^{CCl_4}$ = 1783, 1735, 1708, 1245 cm.$^{-1}$. Found: C = 73.11, H = 8.84; $C_{32}H_{46}O_6$ requires, C = 72.97, H = 8.80, P m/e = 526.

Hydrolysis of globral II (G 14A).

Globral II (100 mg.) in aqueous methanol (1:1; 24 ml.) was refluxed with potassium hydroxide (2:5 g.) for 90 minutes. The reaction mixture was then extracted with ether (3 x 20 ml.), and the combined extracts washed with water (3 x 20 ml.), dried and evaporated to dryness, affording an oil (85 mg) which was shown (t.l.c.) to consist of three major products, one less polar than starting material, the other two more polar. Separation was achieved by preparative t.l.c. (chloroform containing 3% methanol as solvent), and the major, most polar product isolated as an oil (40 mg.) which had P m/e 486, corresponding to deacteylglobral II (G 15).

Oxidation of globral III (G 16).

Globral III (47 mg.) in dry pyridine (10 ml.) was treated with "AnalaR" chromium trioxide (58 mg.) for 16 hours. Work up in the usual manner afforded a brown crystalline mass (43 mg.) which was purified by preparative

t.l.c. (chloroform containing 2% methanol as solvent) to give globral III lactone (G 17A) which crystallised from ethyl acetate-light petroleum as needles (37 mg.) m.p. 213-215°C, $[\alpha]_D$ = -79.4° (c = 1.1). $\nu_{max.}^{CCl_4}$ = 1782, 1733, 1725, 1270, 1240 cm.$^{-1}$, P m/e = 626.

Acetylation of globral III (G 16).

Globral III (70 mg.) in dry pyridine (10 ml.) was treated with acetic anhydride (6 ml.) for 20 hours. Work up in the usual manner afforded a gummy oil (72 mg.) which consisted mainly of the diacetate, with a little mono-acetate and starting material. This oil, in benzene, was adsorbed on basic alumina (10 gm. Grade III) and washed slowly with benzene for 24 hours. Unchanged diacetate was recycled through the column. Washing the column with chloroform afforded a mixture which consisted (t.l.c.) mainly of globral III and its mono-acetate, which were separated by preparative t.l.c. (chloroform containing 3% methanol as solvent), affording globral III acetate (G 17B) as needles (24 mg.) from ethyl acetate-light petroleum m.p. 185-187°C, $[\alpha]_D$ = -39.2° (= 1). $\nu_{max.}^{CCl_4}$ = 3615, 1742, 1735, 1250, 1243 cm.$^{-1}$. Found: C = 69.42, H = 9.04; $C_{39}H_{60}O_9$ requires, C = 69.61, H = 8.99 P m/e = 672.

Oxidation of globral III acetate (G 17B).

Globral III acetate (10 mg.) in dry pyridine (2 ml.) was treated with "AnalaR" chromium trioxide (15 mg.) for 14 hours. Work up in the usual manner afforded a brown solid (8 mg.) which was purified by preparative t.l.c. to afford globral III lactone acetate (G 17C) (6 mg.) as needles from ethyl acetate-light petroleum, m.p. 202-204°($\nu_{max.}^{CCl_4}$ = 1782, 1737, 1248, 1232 cm.$^{-1}$. P m/e = 670.

Globral III p-iodobenzoate lactone (G 17D).

Globral III (65 mg.) in dry pyridine (15 ml.) was treated with a large excess of p-iodobenzoyl chloride (210 mg.) for 24 hours. Work up in the usual manner afforded a crystalline mass, which was mainly p-iodobenzoic anhydride, but also contained a mixture of mono- and di-odobenzoates of globral III. The iodobenzoic anhydride was removed by chromatography over acid alumina (10 gm. Grade III), and the crude di-p-iodobenzoate obtained was hydrolysed on a column of basic alumina in the manner previously described. The crude mono-p-iodobenzoate thus obtained (14 mg.) was treated with chromium trioxide (15 mg.) in dry pyridine (4 ml.), and work up in the usual manner afforded a yellow oil (12 mg.) which

was purified by preparative t.l.c. to afford feathery needles of the p-iodobenzoate lactone (G 17D) m.p. 197-201°C $\nu_{max.}^{CCl_4}$ = 1782, 1732, 1700 cm.$^{-1}$. Crystallisation from ethyl acetate-light petroleum, ether, ether-light petroleum, aqueous methanol, and aqueous ethanol afforded similar feathery needles, which were not suitable for X-ray analysis.

Globral III bis iodoacetate (G 17E).

Globral III (47 mg.) in dry dioxan (10 ml.) containing dry pyridine (3 drops) was chilled to 0°C, and chloroacetyl chloride (2 ml.) dropwise. The flask was then stoppered and left at room temperature for 16 hours. The reaction mixture was poured on to ice, and after 1 hour extracted with ethyl acetate (2 x 10 ml.). The combined extracts were washed with sodium bicarbonate solution (2 x 10 ml.) and with water (3 x 10 ml.), dried, and the solvent removed to afford an oil (40 mg.) which consisted of one major component (t.l.c.) which had a polarity similar to globral III lactone. The major product was isolated by preparative t.l.c. (chloroform as solvent) and crystallised as five feathery needles (19 mg.), m.p. 176-181°C, from ethyl acetate-light

petroleum, $\nu_{max.}^{CCl_4}$ = 1750, 1732, 1276, 1250 cm.$^{-1}$. This compound was refluxed in "AnalaR" acetone (3 ml.) containing sodium iodide (60 mg.) in an atmosphere of nitrogen for 6 hours. The solvent was evaporated, the residue extracted with ethyl acetate (10 ml.), the extract washed with water (2 x 10 ml.), dried and evaporated to dryness to afford the bis iodoacetate (G 17E) (8 mg.) which crystallised as small rosettes from ethylacetate-light petroleum, and as fine needles from ether, or ether-light petroleum.

Oxidation of globral IV.

Globral IV (48 mg.) in dry pyridine (10 ml.) was treated with "AnalaR" chromium trioxide (80 mg.) for 12 hours. Work up in the usual fashion afforded a brown oil (45 mg.), containing (t.l.c.), one major product, which was isolated by preparative t.l.c. (chloroform containing 1% methanol as solvent). This product, globral IV lactone (36 mg.), crystallised from ethyl acetate-light petroleum as needles; m.p. 210-212°C, $[\alpha]_D$ = 35.5° (C = 1.5), $\nu_{max.}^{CCl_4}$ = 1782, 1736, 1708, 1245 cm P m/e = 526. Direct comparison of this compound with globral II lactone (G 14B) showed that they were identical (m.p., mixed m.p., $[\alpha]_D$, i.r., N.M.R., mass spec.).

Globral IV lactone acetate (G 18B).

Globral IV (105 mg.) in dry pyridine (10 ml.) was treated with acetic anhydride (10 ml.) for 12 hours. Work up in the usual manner afforded an oil (100 mg.) which consisted mainly of the diacetate (t.l.c.) (No $\nu_{max.}$ between 3200-4000 $cm.^{-1}$). This oil, in benzene was converted on basic alumina (10 gm. Grade III) as before, into the monoacetate, which was purified by preparative t.l.c. (chloroform containing 2% methanol as solvent) and the resulting oil (42 mg.) in dry pyridine (8 ml.) treated with "AnalaR" chromium trioxide (60 mg.) for 12 hours. Work up in the usual manner afforded a brown oil which consisted of one major component, and a more polar minor one (t.l.c.). On standing, the proportion of the minor product seemed to be increasing, and after 72 hours, the two products were separated by preparative t.l.c. to afford the major product globral IV lactone acetate (33 mg.) as needles from ethyl acetate-light petroleum, m.p. 220-222°C (with weeping from 210°C), $[\alpha]_D = -68.5^{\circ}$ (c = 1.6), $\nu_{max.}^{CCl_4} = 1783, 1732, 1249\ cm.^{-1}$, Found: C = 71.57, H = 8.69; $C_{34}H_{48}O_7$ requires, C = 71.80, H = 8.51; P m/e = 570.

Oxidation of globral VIII.

Globral VIII (14 mg.) in dry pyridine (3 ml.) was treated with "AnalaR" chromium trioxide (15 mg.) for 15 hours. Work up in the usual manner afforded a brown solid, which was purified by preparative t.l.c. (chloroform containing 2% methanol as solvent) and crystallisation from ethyl acetate-light petroleum furnished needles of globral VIII lactone (10 mg.) m.p. 174-178°C, $[\alpha]_D$ = -24.2° (c = 0.7) $\nu_{max.}^{CCl_4}$ = 1790, 1737, 1710, 1247 cm.$^{-1}$.

Unsuccessful oxidations.

Globral V, globral VI and globral VII were treated with chromium trioxide in dry pyridine as described previously, but in each case, no isolable product (t.l.c.) was obtained.

Globral I p-iodobenzoate.

Globral I (32 mg.) in dry pyridine (10 ml.) was treated with p-iodobenzoyl chloride (100 mg.) for 16 hours. Work up in the manner previously described afforded a solid crystalline mass (103 mg.) which consisted mainly of p-iodobenzoic anhydride. Separation was achieved by

filtration through a short column of acid alumina (5 gm. Grade III), and after further purification by preparative t.l.c. (chloroform as solvent), globral I iodobenzoate (one spot on t.l.c.) was crystallised from ethyl acetate-light petroleum as feathery needles, m.p. 128-132°C. $\nu_{max.}^{CCl_4}$ = 1734, 1716, 1700, 1610 cm.$^{-1}$. Crystallisation from methanol-ether, chloroform-light petroleum, aqueous methanol, all afforded feathery needles unsuitable for X-ray analysis.

Attempted bromination of globral III lactone (G 16A).

Globral III lactone (5 mg.) was stirred in ether (5 ml.) and acetic acid (1 ml.) at 0°C, and bromine in ether added dropwise till the brown colouration persisted. After 45 minutes, the starting material had disappeared (t.l.c.) affording a product of greater polarity. Removal of the solvent afforded an oil, which did not crystallise even after purification by preparative t.l.c. and had $\nu_{max.}^{CCl_4}$ = 3570, 1783, 1730 cm.$^{-1}$.

REFERENCES

1. Woodward and Bloch, J. Amer. Chem. Soc., (1953), 75, 2023.
2. Clayton and Bloch, J. Biol. Chem., (1956), 218, 305, 319.
3. Tchen and Bloch, J. Amer. Chem. Soc., (1956), 78, 1516. J. Biol. Chem., (1957), 226, 921.
4. Eschenmoser, Ruzicka, Jeger and Arigoni, Helv. Chim. Acta, (1955), 38, 1890.
5. Mills and Werner, J. Chem. Soc., 1955, 3132.
6. Arigoni, Barton, Bernasconi, Djerassi, Mills and Wolff, Proc. Chem. Soc., (1959), 306.
7. Shiengthong, Verasarn, Na Nonggai-Suwanrath and Warnhoff, Tetrahedron, (1965), 21, 917.
8. Djerassi, Knight and Wilkinson, J.Amer.Chem.Soc., (1963), 85, 835.
9. Djerassi, Murray and Villotti, J. Chem. Soc., (1965), 1160.
10. Kandutsch and Russell, J. Biol. Chem. (1959), 234, 2037.
11. Neiderhiser and Wells, Arch. Biochem. Biophys., (1959), 81, 300.
12. Djerassi, Krakower, Lemin, Liu, Mills and Villotti, J. Amer. Chem. Soc., (1958), 80, 6284.

13. Dauben, Fonkin and Boswell, J.Amer.Chem.Soc., (1957), 79, 1000.

14. Birch, Turnbull, Muhammad and Collins, J.Chem.Soc., (1963), 2762.

15. Bevan, Ekong, Halsall and Toft, Chem.Comm. (1965), 636.

16. Lavie, Mahendra, Jain and Kirson, Tetrahedron Letters, (1966), 2049.

17. Breen, Ritchie, Sidwell and Taylor, Aust.J.Chem., (1966), 19, 455.

18. Lawrie, Hamilton, Spring and Watson, J.Chem.Soc., (1956), 3272.

19. Grant, Hamilton, Hanor, Hodges, McGeachin, Raphael, Robertson and Sim, Proc.Chem.Soc., (1961), 444.

20. Bevan, Rees and Taylor, J.Chem.Soc., (1963), 983.

21. Chan and Taylor, Chem.Comm., (1966), 206.

22. Connolly, McCrindle and Overton, in press.

23. Bevan, Halsall, Nwaji and Taylor, J.Chem.Soc., (1962), 768.

24. Akisanya, Bevan, Hirst, Halsall and Taylor, J.Chem.Soc., (1960), 3827.

25. Akisanya, Bevan, Halsall, Powell and Taylor, J.Chem.Soc., (1961), 3705.

26. Sutherland, Sim and Robertson, Proc.Chem.Soc., (1962), 222.

27. Akisanya, Arene, Bevan, Ekong, Nwaji, Okogun, Powell and Taylor, J.Chem.Soc.C.,(1966), 507.

28. Bevan, Powell and Taylor, J.Chem.Soc., (1963), 980.

29. Connolly, McCrindle, Overton and Feeney, Tetrahedron, (1966), 22, 891.

30. Housely, King, King and Taylor, J.Chem.Soc., (1962), 5095.

31. Ollis, Ward and Zellnik, Tetrahedron Letters, (1964), 207.

32. Bevan, Powell, Taylor, Toft, Welford, Chan, Mootoo and Halsall, Chem. and Ind., (1964), 1751.

33. Ekong and Olagbemi, J.Chem.Soc.C., (1966), 944.

34. Connolly, Henderson, McCrindle, Overton and Bhacca, Tetrahedron Letters, (1964), 2593).
McPhail and Sim, Tetrahedron Letters, (1964), 2599.
Connolly, Henderson, McCrindle, Overton and Bhacca, J.Chem.Soc., (1965), 6935.

35. Connolly, McCrindle, Overton and Warnock, Tetrahedron Letters, (1965), 2937.

36. Connolly, McCrindle and Overton, Chem.Comm.(1965),162.

37. Arene, Bevan, Powell and Taylor, Chem.Comm.(1965),302.

38, Chan, Taylor and Aplin, Chem. Comm., (1966), 567.

39. Govindachari, Joshi and Sundararajan, Tetrahedron, (1964), 20, 2985.

40. Arigoni, Barton, Corey, Jeger, et al., Experientia, (1960), 16, 41.

41. Arnott, Davie, Robertson, Sim and Watson, Experientia, (1960), 16.

42. Kubota, Matsuura, Tokoroyama and Matsumoto, Tetrahedron Letters, (1961), 325.

43. Dreyer, J.Org.Chem., (1965), 30, 749.

44. Hirosi, Bull.Pharm.Soc. Japan, (1963), 11, 535.

45. Dreyer, J.Org.Chem., (1966), 31, 2279.

46. Valenta, Gray, Papadopoulos and Podesva, Tetrahedron, (1962), 18, 1433.

47. Dreyer, Experientia, (1964), 20, 297.

48. Bredenberg, Chem. and Ind., (1964), 73.

49. Polonsky, Proc.Chem.Soc., (1964), 292.
Brown and Sim, Proc.Chem.Soc., (1964), 293.

50. Giessman and Ellestad, Tetrahedron Letters, (1962), 1083.
Davidson, Hollands and de Mayo, Tetrahedron Letters, (1962), 1089.

51. Polonsky, Fouquey and Gaudemer, Bull.Soc.Chim. France, (1964), 1827.

52. Polonsky, I.U.P.A.C. Symposium, Kyoto, Japan, (1964).

53. Pailer, Schaden, Spiteller and Fenzl, Monatsh., (1965), 1324.

54. Narayanan, Pachapurkar, Pradhan, Shah and Narayanan, J.Ind.Chem.Soc., (1964), 2, 108.

55. Henderson, McCrindle, Overton and Melera, Tetrahedron Letters, (1964), 3969.

56. Scott, 'Interpretation of Ultraviolet Spectra of Natural Products', Pergamon Press, (1964), P.51.

57. Djerassi, 'Optical Rotatory Dispersion', McGraw Hill, (1960), P.90.

58. See Tichy, in 'Advances in Organic Chemistry', Vol. 5, Interscience Publishers, New York, (1965).

Table I

N.M.R. data for globral I derivatives

Compound	Cyclopropane	Methyls	H-C-O	H C=C
(G9)	9.66,9.34 doublets; J = 6 cps	9.22,9.11,9.07, 8.89,8.70 broad (9H), 8.00, (acetate)	7.18(1H; D; J = 6cps) 6.10(1H; M; $W_{\frac{1}{2}}$=27cps) 5.31(1H; M; $W^2_{\frac{1}{2}}$= 8cps) 4.98(1H; M; $W^2_{\frac{1}{2}}$= 6cps) 4.60(1H; D; J^2= 6cps)	3.86(0.8H) 4.50(0.6H)
(G10C)	9.64,9.31 doublets; J = 6 cps	9.22,9.11,9.07, 8.88,8.73 broad (9H), 7.99, (acetate)	7.20(1H; D; J = 6cps) 5.81(1H; M; $W_{\frac{1}{2}}$=30cps) 5.30(1H; M; $W^2_{\frac{1}{2}}$= 7cps) 4.97(1H; M; $W^2_{\frac{1}{2}}$= 7cps)	3.86(0.9H) 4.44(0.6H)
(G10A)	9,62,9.32 doublets;	9.22,9.12,9.07, 8.89,8,79 (d; J = 6cps) 8.70, (6H), 7.98, (acetate)	7.16(1H; D; J = 7cps) 6.10(1H; M; $W_{\frac{1}{2}}$=25cps) 5.23(1H; M; $W^2_{\frac{1}{2}}$= 6cps) 4.98(1H; M; $W^2_{\frac{1}{2}}$= 6cps) 4.56(1H; M; $W^2_{\frac{1}{2}}$= 6cps)	
(G13)	9.58,9.30 doublets; J = 5 cps	9.22,9.11,9.09, 8.91,8.79 (d; J = 7cps) 8.67, (6H), 7.98, (acetate)	7.20(1H; D; J = 7cps) 6.60(1H; M; $W_{\frac{1}{2}}$=12cps) 6.40(2H; M; $W^2_{\frac{1}{2}}$=10cps) 5.32(1H; M; $W^2_{\frac{1}{2}}$= 6cps) 4.98(1H; M; $W^2_{\frac{1}{2}}$= 6cps)	
(G10B)	9.60,9.31 doublets; J = 6 cps	9.22,9.10,9.07, 8.89,8.76 (d; J = 7cps) 8.65, (6H), 7.98, (acetate)	7.20(1H; D; J = 7cps) 5.86(1H; M; $W_{\frac{1}{2}}$=30cps) 5.30(1H; M; $W^2_{\frac{1}{2}}$= 8cps) 4.97(1H; M; $W^2_{\frac{1}{2}}$= 6cps)	
(G10D)	9.66,9.35 doublets J = 5 cps	9.18,9.14,9.09, 8.89,8.70 (6H) 7.95 (acetate)	7.12(1H; D; J = 7cps) 6.55(1H; M; $W_{\frac{1}{2}}$= 8cps) 6.10(1H; M; $W^2_{\frac{1}{2}}$=25cps) 4.96(1H; M; $W^2_{\frac{1}{2}}$= 8cps) 4.50(1H; M; $W^2_{\frac{1}{2}}$= 6cps)	

D = doublet T = triplet M = multiplet Q = quartet

Table II

N.M.R. data for globral II and globral III derivatives

Compound	Cyclopropane	Methyls	H-C-O	Others
(Gl4A)	9.65,9.30 doublets; J = 6 cps	8.98,(9H),8.86, 8.69,(6H),7.95 (acetate)	7.13(1H; D; J = 7cps) 6.15(1H; M; $W_{\frac{1}{2}}$=26cps) 4,90(1H; M; $W_{\frac{1}{2}}$= 6cps) 4.56(1H; M, $W_{\frac{1}{2}}$= 6cps)	7.55 (2H; Q; peak separation 6 cps)
(Gl4B)	9.66,9.34 doublets; J = 6 cps	8.97,(9H),8.84, 8.63 (6H),7.95 (acetate)	7.20(1H; D; J = 7cps) 5.90(1H; M; $W_{\frac{1}{2}}$=25cps) 4.91(1H; M; $W_{\frac{1}{2}}$= 6cps)	7.55 (2H; Q; peak separation 6 cps)
(Gl5)		9.06,8.98,8.94, 8.72,8.69	6.75(1H; D; J = 8cps) 6.24(1H; M; $W_{\frac{1}{2}}$= 8cps) 6.09(2H; M; $W_{\frac{1}{2}}$=30cps)	7.57(2H; Q; peak separation 6 cps)
(Gl8A)	9.63,9.34 doublets; J = 6 cps	9.09,(9H),8.89, 8.70,(6H),7.94 (acetate)	7.12(1H; D; J = 7cps) 6.54(1H; M; $W_{\frac{1}{2}}$= 8cps) 6.18(1H; M; $W_{\frac{1}{2}}$=23cps) 4.96(1H; M; $W_{\frac{1}{2}}$= 7cps) 4.55(1H; M; $W_{\frac{1}{2}}$= 7cps)	
(Gl4B) (ex Gl4A)	9.66,9.38 doublets; J = 6 cps	9.02,(9H),8.90, 8.70,8.68,8.00, (acetate)	7.20(1H; D; J = 7cps) 5.90(1H; M; $W_{\frac{1}{2}}$=24cps) 5.00(1H; T; J=2.5cps)	

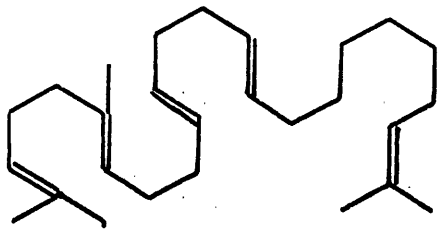
D = doublet T = triplet M = multiplet Q = quartet

Table III

N.M.R. data for globral III, globral VIII and their oxidation products

Compound	Cyclopropane	Methyls	H-C-O	Others
(G16)	9.65,9.35 doublets; J = 5 cps	9.20,9.10,9.07, 8.89,8.69,(6H), 7.99 (acetate) 9.1[illegible],8.92 (D; J = 6 cps)	7.21(1H; D; J = 7cps) 6.20(1H; M; W_1=24cps) 5.92(1H; D; J^2= 4cps) 5.22(1H; M; W_1= 6cps) 5.00(1H; M; $W_{\frac{1}{2}}$= 6cps) 4.55(1H; M; $W_{\frac{1}{2}}$= 6cps)	
(G17A)	9.62,9.34 doublets; J = 6 cps	9.20,9.08,9.05, 8.89,8.63,(6H), 7.96 (acetate) 8.95,8.80 (D; J = 6 cps)	[illegible].21(1H; D; J = 6cps) 5.81(1H; M; W_1=26cps) 5.17(1H; M; $W_{\frac{1}{2}}$= 5cps) 5.00(1H; M; $W_{\frac{1}{2}}$= 6cps)	
(G21)		9.03 (9H) 8.92 (3H) 8.77 (6H) 8.01(acetate)	6.62(1H; M) 6.36(2H; M) 6.20(1H; M) 5.02(1H; M)	7.62(2H;M) 6.87(1H) 6.81(1H)
(G20)	9.64,9.35 doublets; J = 6 cps	9.02(15H) 8.90, 8.00 (acetate)	6.02(1H; T; J = 8cps) 5.64(1H; M; W_1=24cps) 5.00(1H; T; J^2= 3cps)	7.72(2H;M) 7.62 7.54

D = doublet T = triplet M = multiplet Q = quartet



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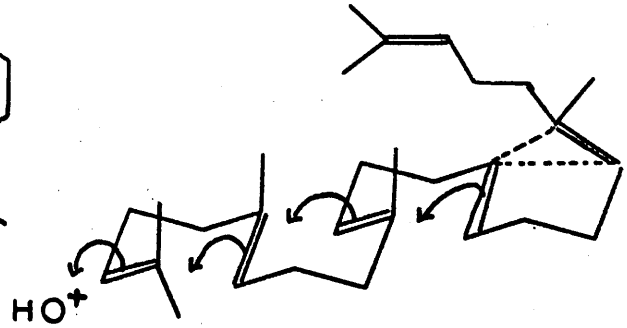

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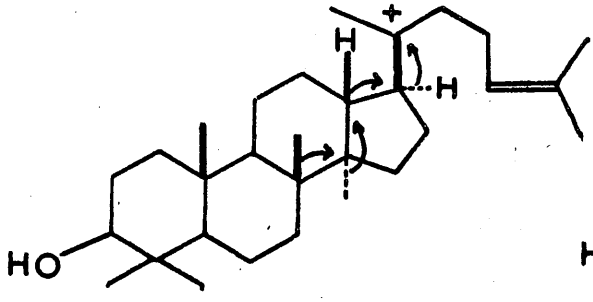

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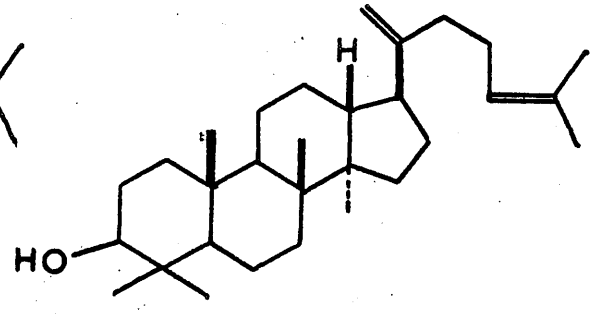

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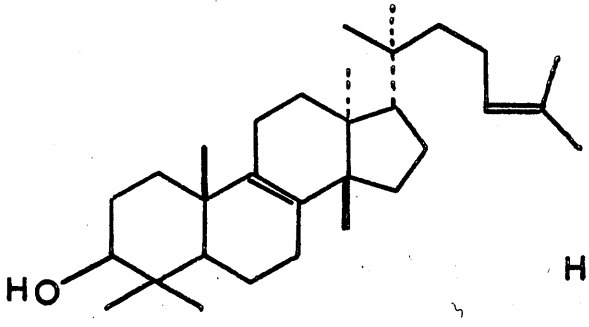

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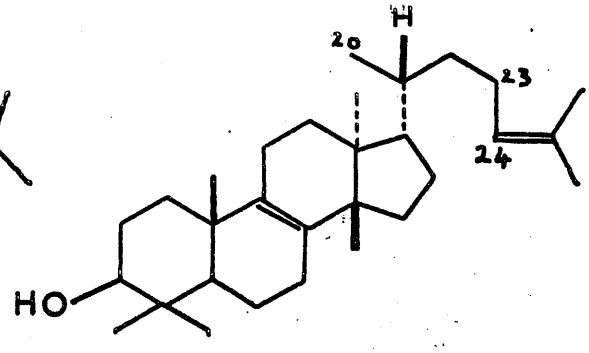

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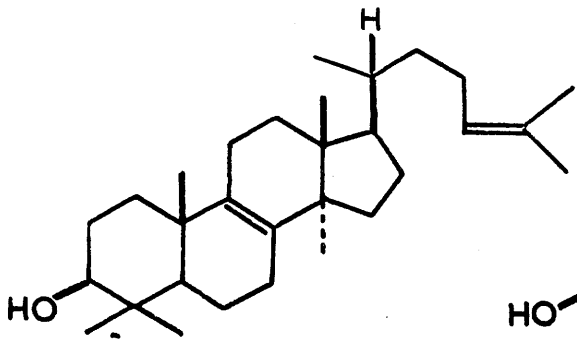

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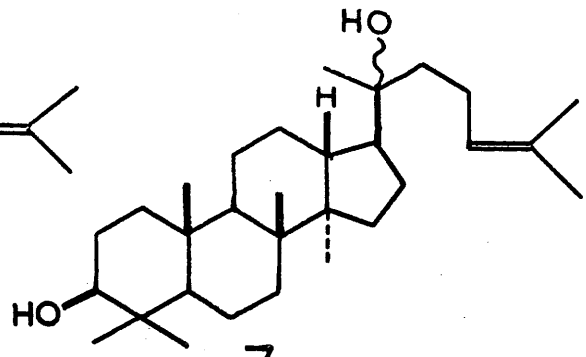

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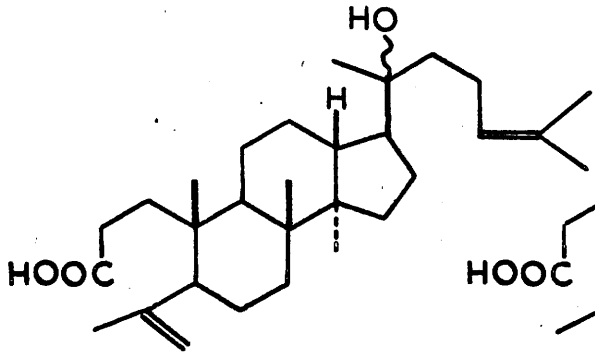

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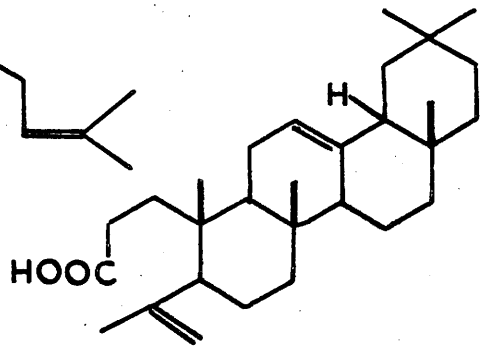

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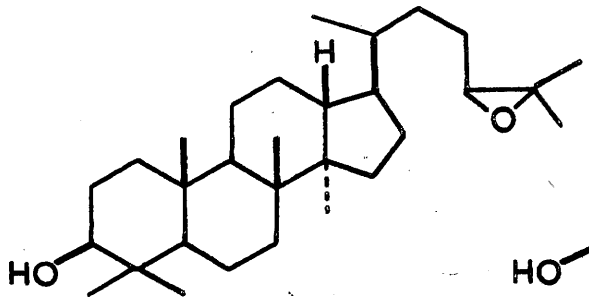

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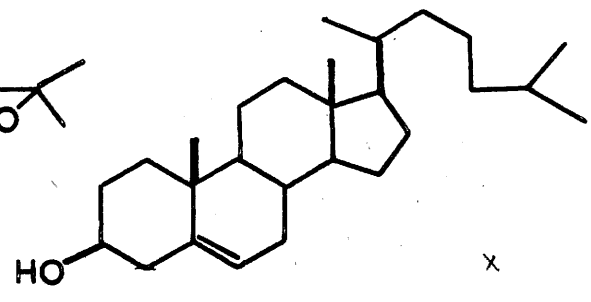

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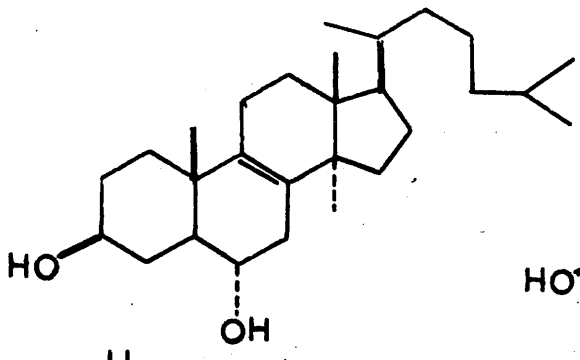

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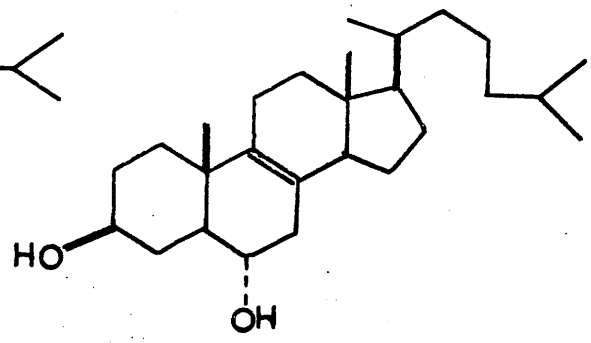

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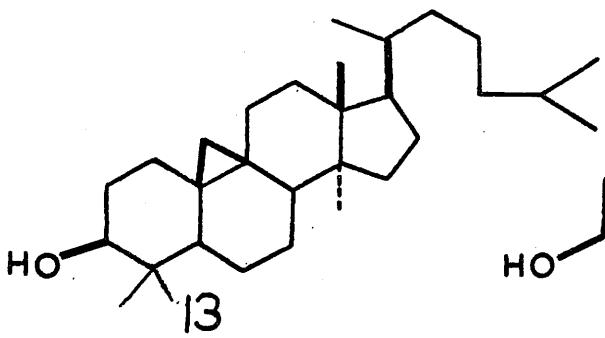

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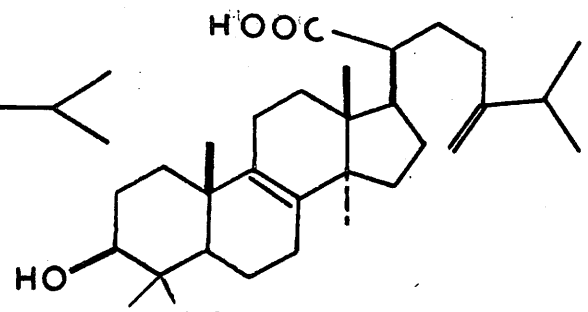

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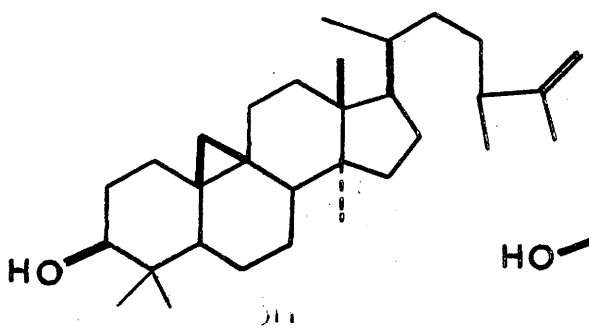

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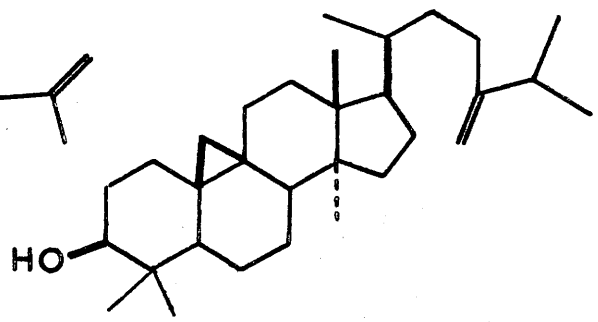

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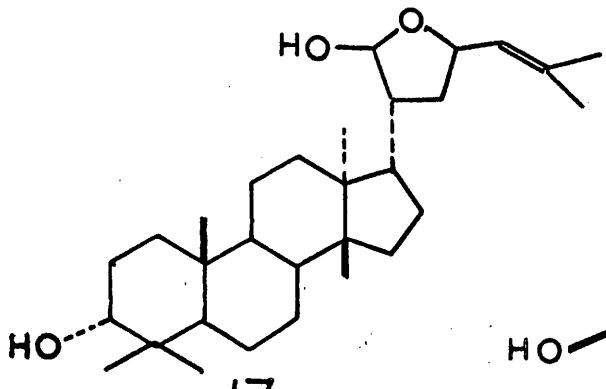

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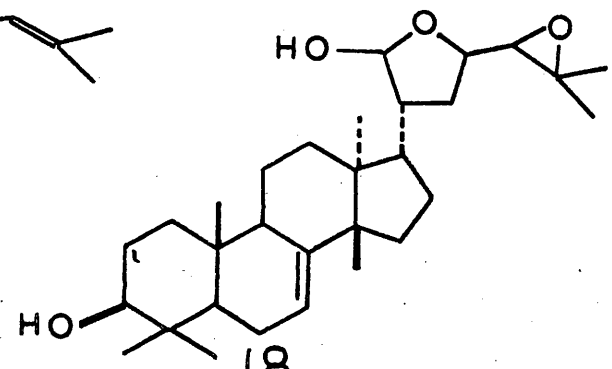

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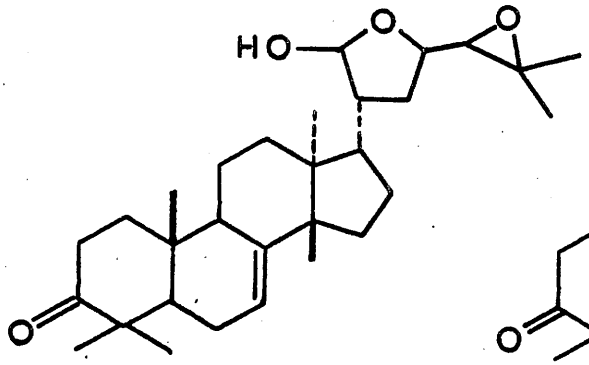

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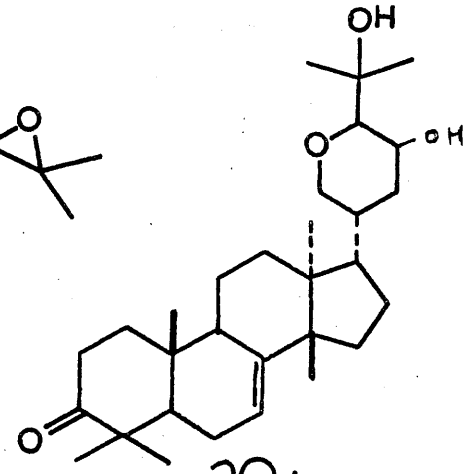
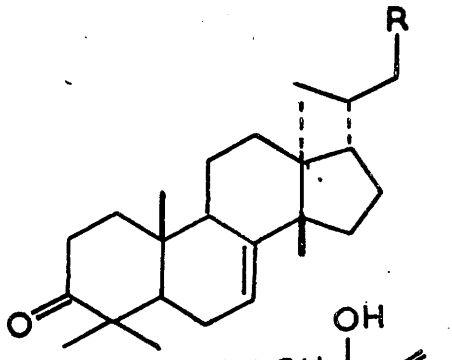


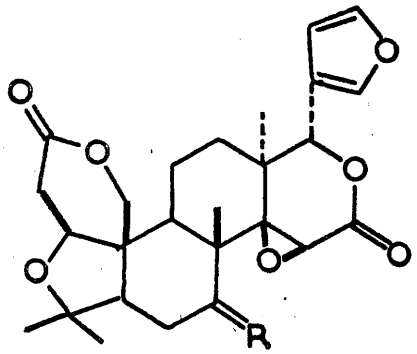
20A



20 B; R = CH_2OH (OH)

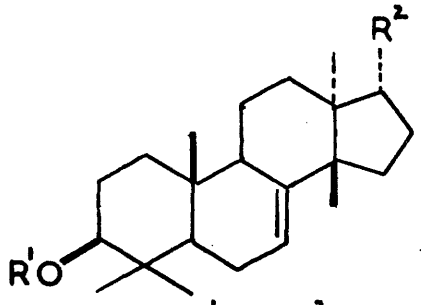
C; R = CHOH (OH, Cl)

D; R = $CO.CH_3$

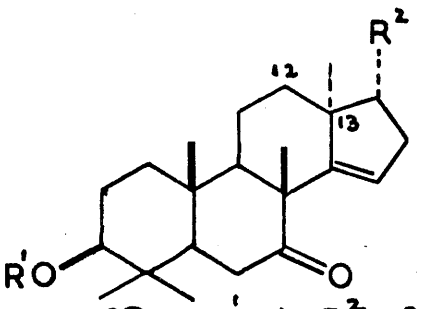


21 A; R = O

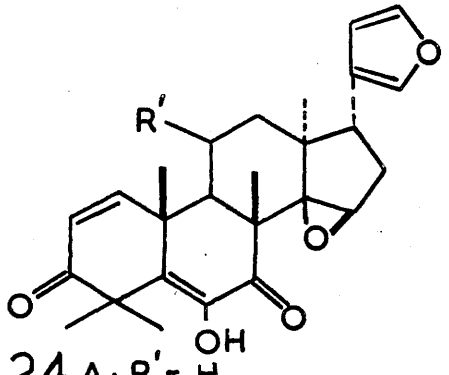
B; R = H, α-OH



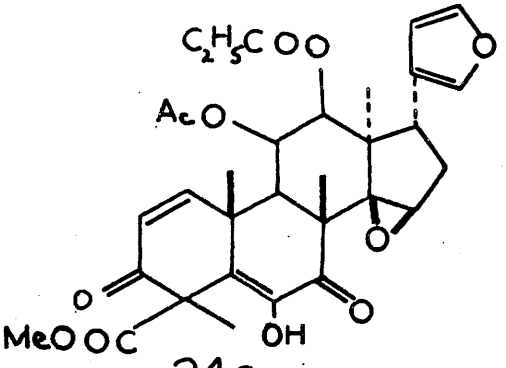
22 A; $R^1 = H$; $R^2 = \beta$ FURAN
B $R^1 = Ac$; $R^2 = C_8H_{17}$



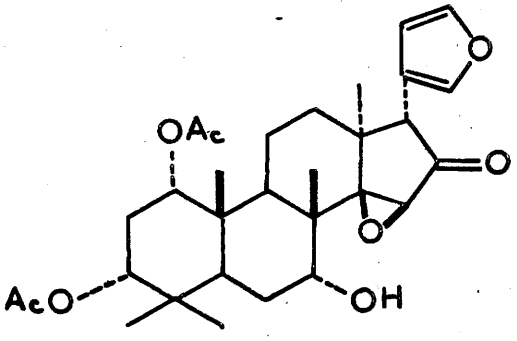
23 A; $R^1 = H$; $R^2 = \beta$ FURAN
B $R = Ac$; $R^2 = C_8H_{17}$



24 A; $R' = H$
B; $R' = \alpha OAc$



24C



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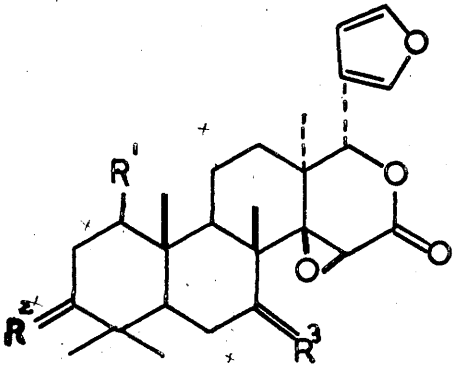
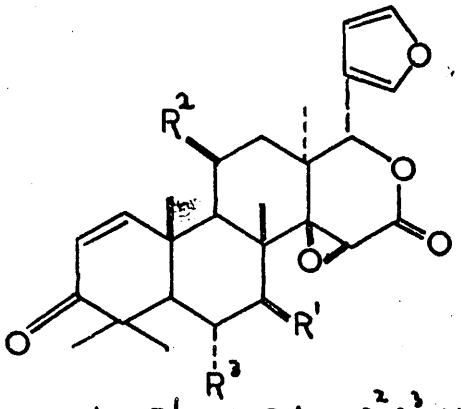
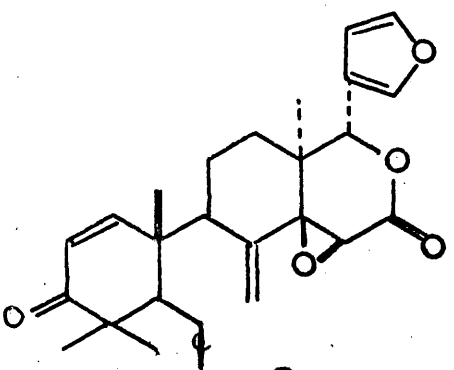


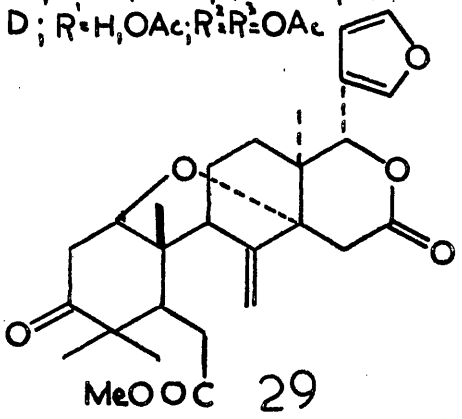
26 A; $R^1 = OAc$; $R^2 = R^3 = H, \alpha OAc$
B; $R^1 = OAc$; $R^2 = H, \alpha OAc$; $R^3 = O$
C; $R^1 = H$; $R^2 = O$; $R^3 = H, \alpha OAc$
D; $R^1 = H$; $R^2 = H, OH$; $R^3 = O$



27 A ; R^1 = H, OAc ; $R^2 = R^3$ = H
B ; R^1 = O ; $R^2 = R^3$ = H
C ; R^1 = H, OAc ; R^2 = OAc ; R^3 = H
D ; R^1 = H, OAc ; $R^2 = R^3$ = OAc



MeOOC 28



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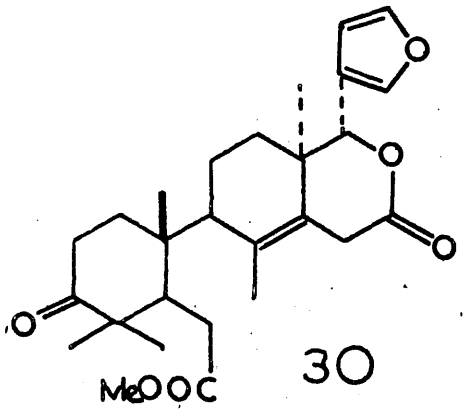

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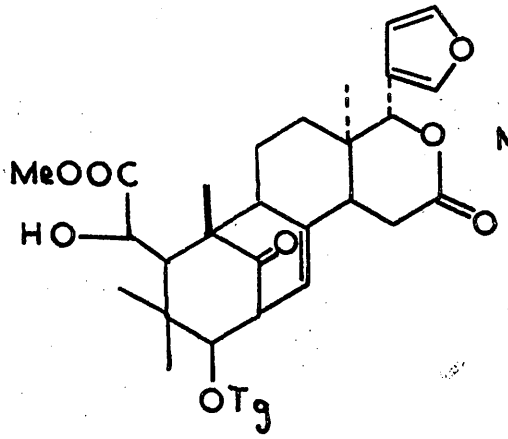

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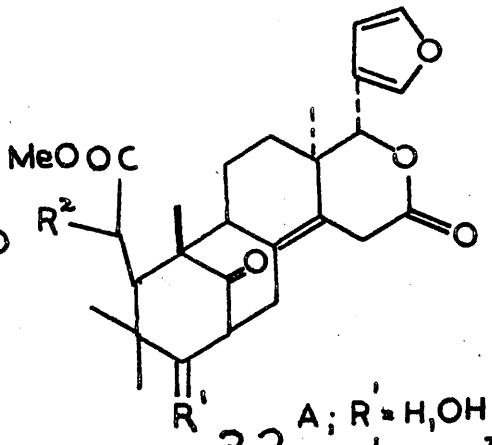
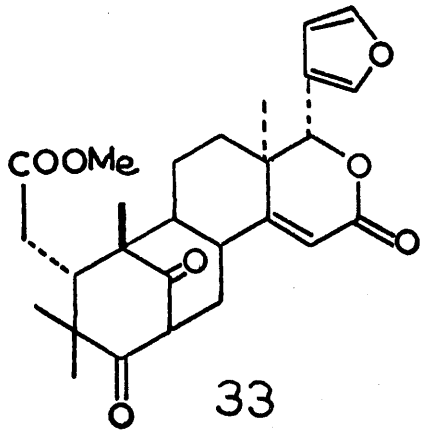


32 A ; R^1 = H, OH ; R^2 = OH
B ; R^1 = O ; R^2 = H



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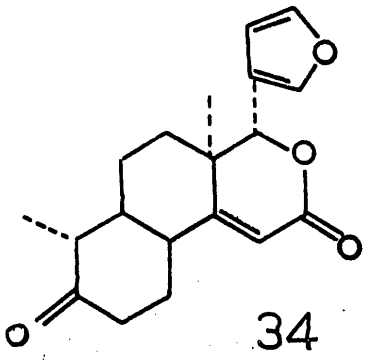

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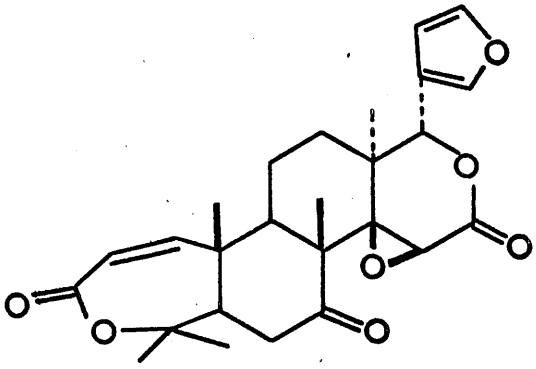

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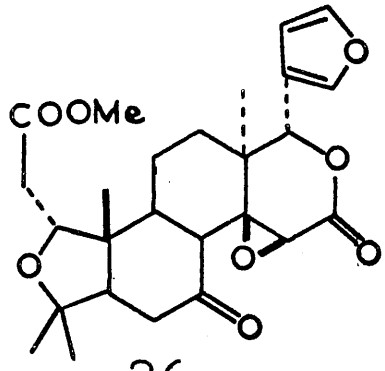

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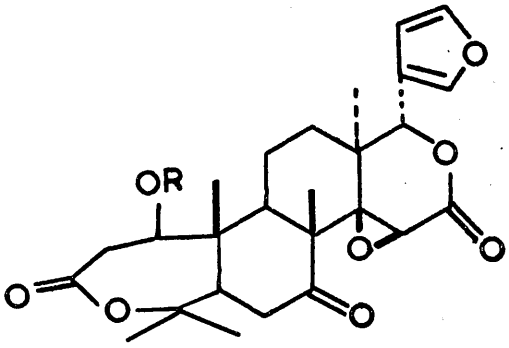
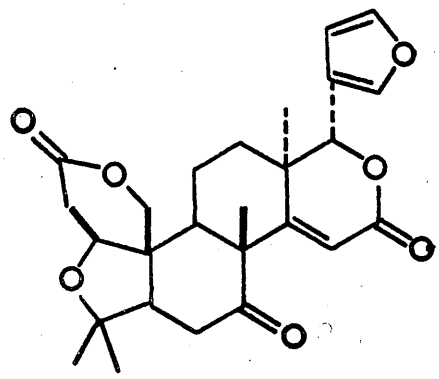


37 A ; R = Ac
B ; R = H



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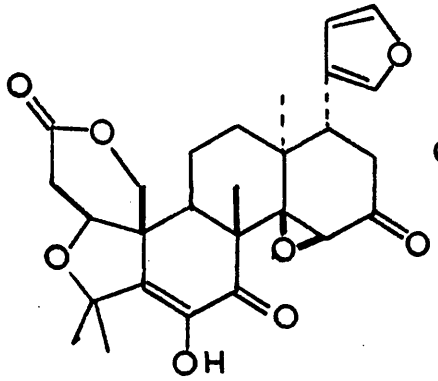

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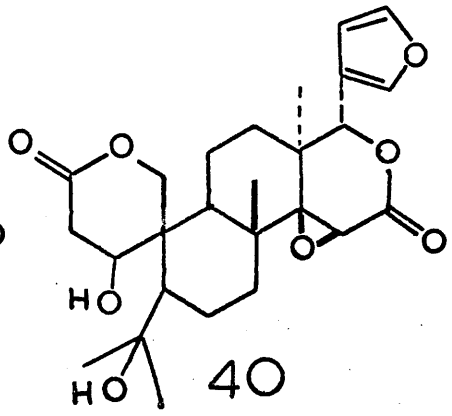

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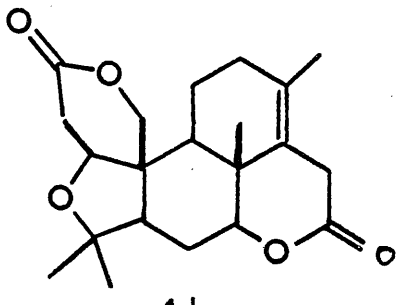

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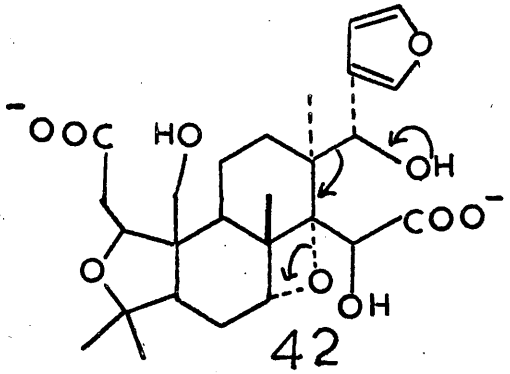

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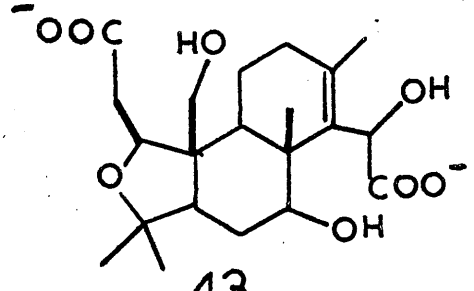

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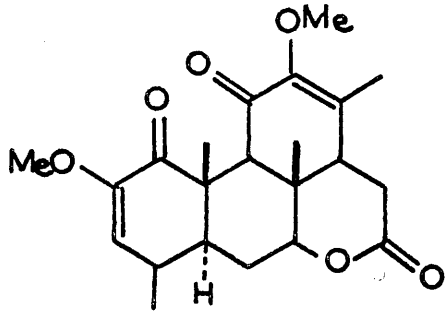

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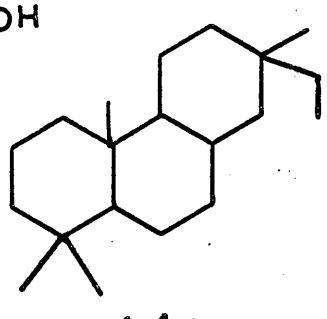
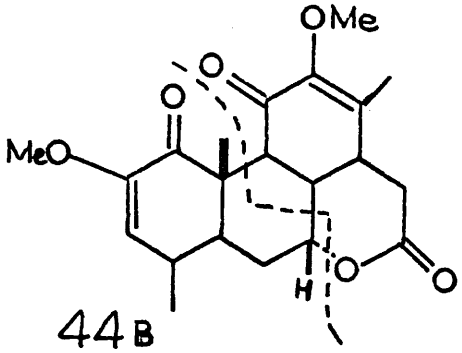


44A



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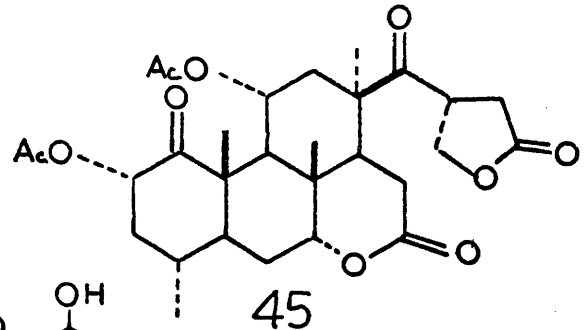

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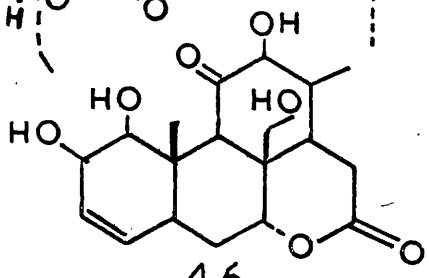

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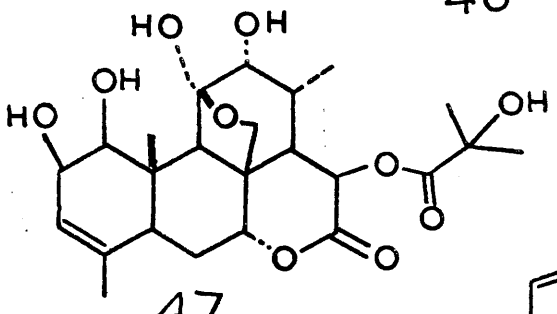

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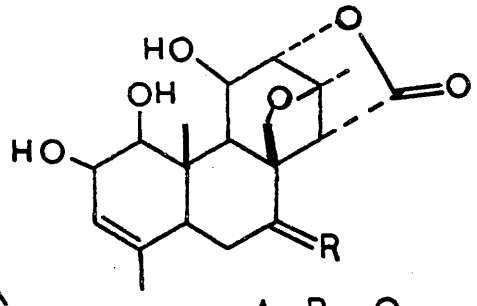
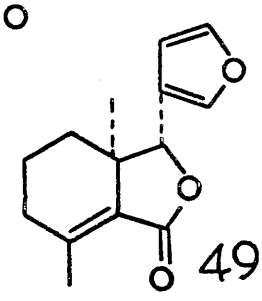


48 A ; R = O
B ; R = H, OH



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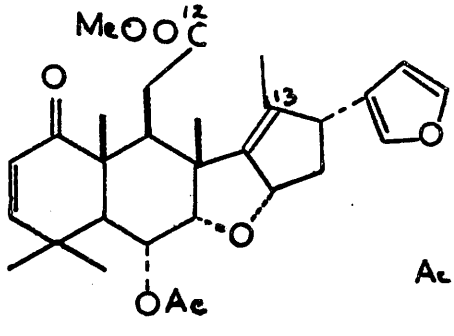

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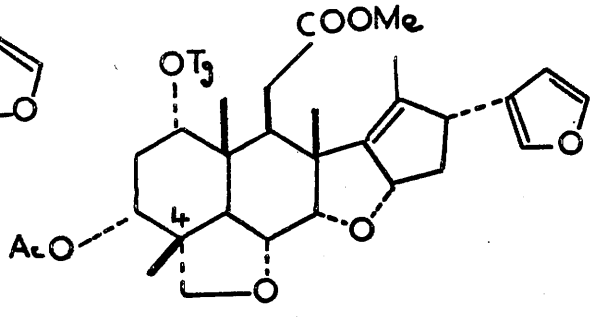
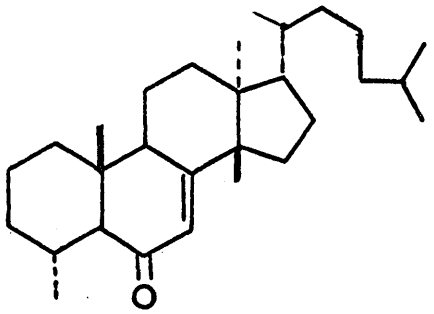
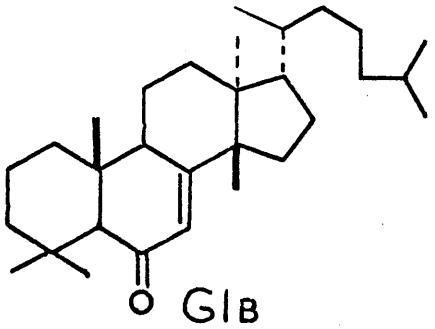


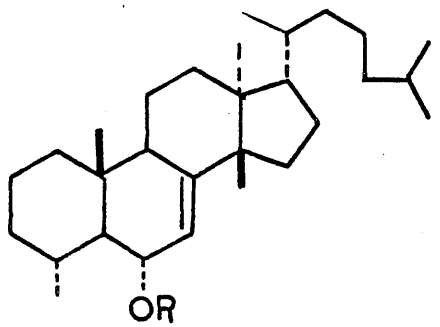
51



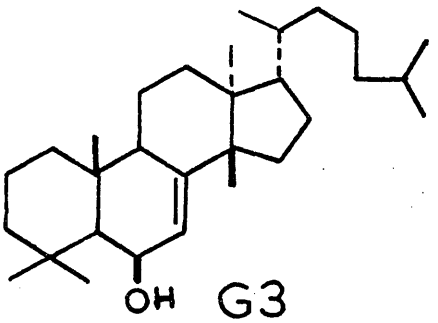
G1A



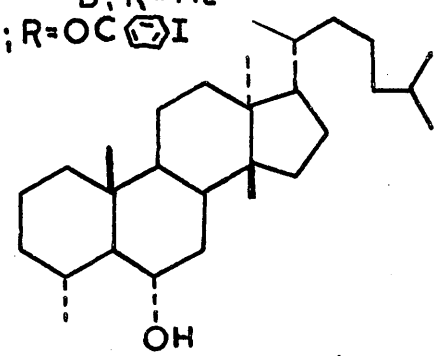
G1B



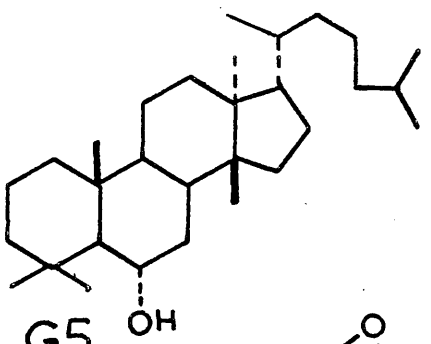
G 2 A; R = H
B; R = Ac
C; R = OC⟨⟩I



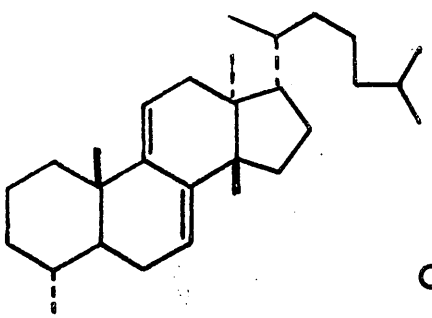
G3



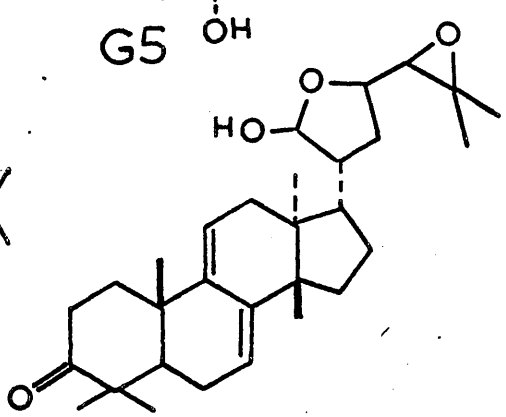
G4



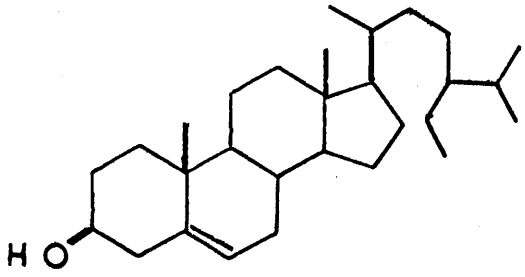
G5



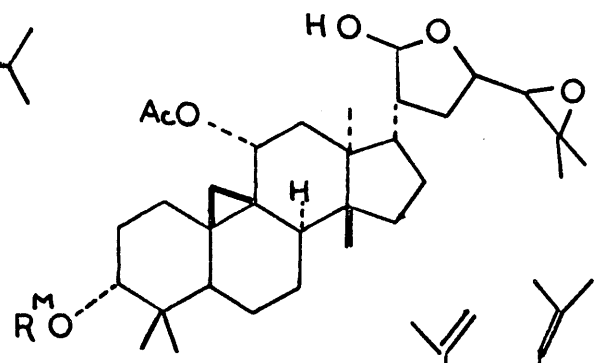
G6



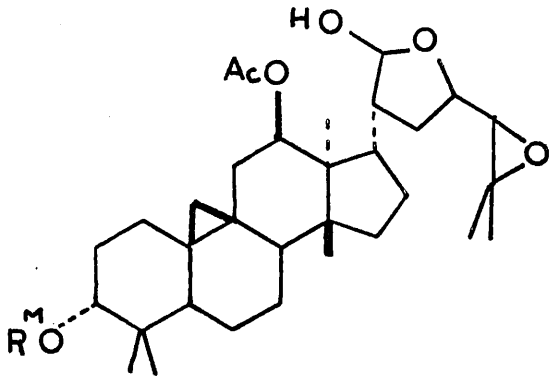
G7



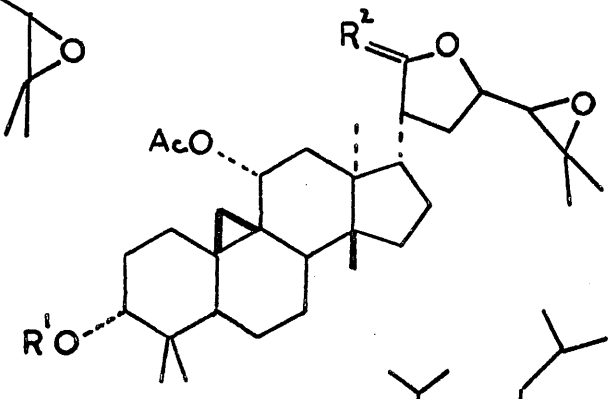
G8



G9 A ; R^M = OC + OC



G9 B

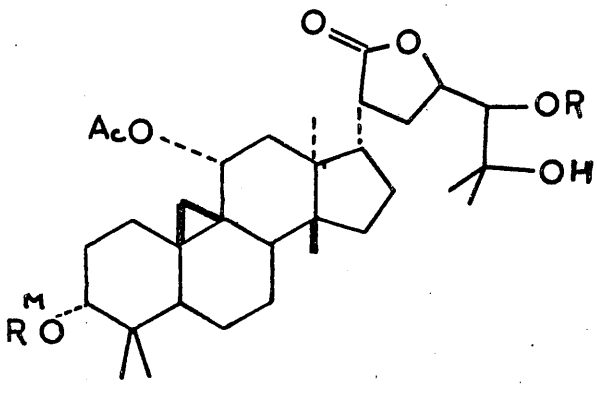


G10 A ; R^1 = OC + OC ; R^2 = H, OH

B ; " " " ; R^2 = O

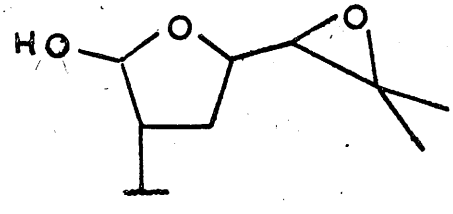
C ; $R^1 = R^M$; R^2 = H, OH

D ; R^1 = H ; R^2 = H, OH

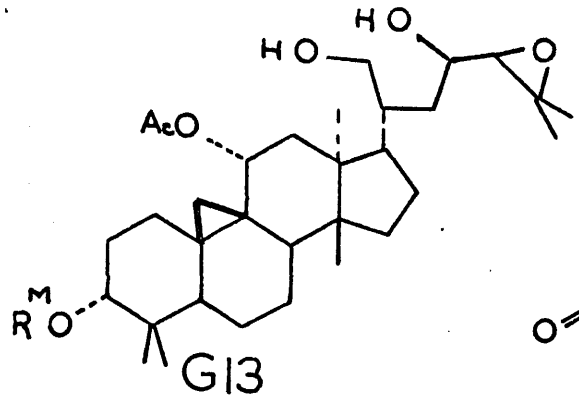


G12 A ; R = H

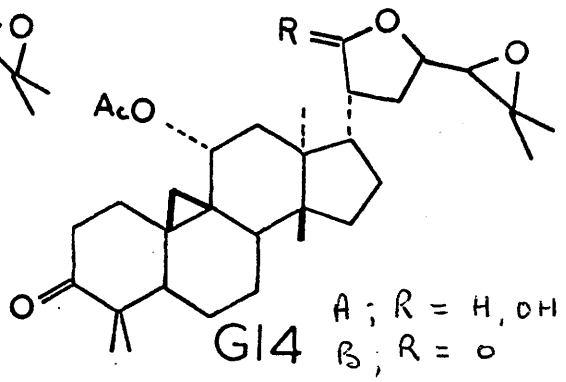
B ; R = C_2H_5



G11

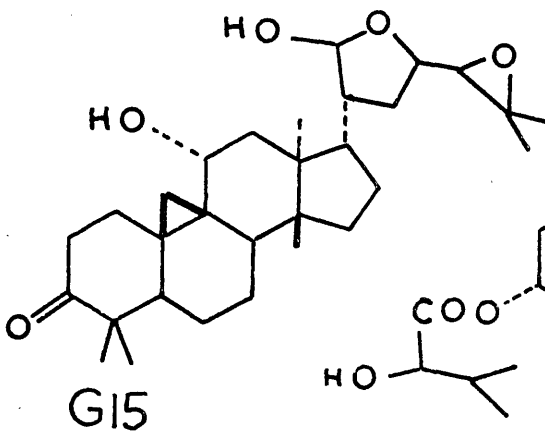


G13

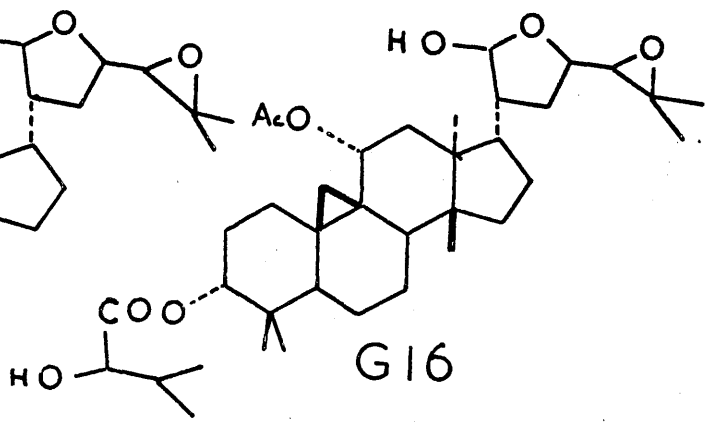


G14

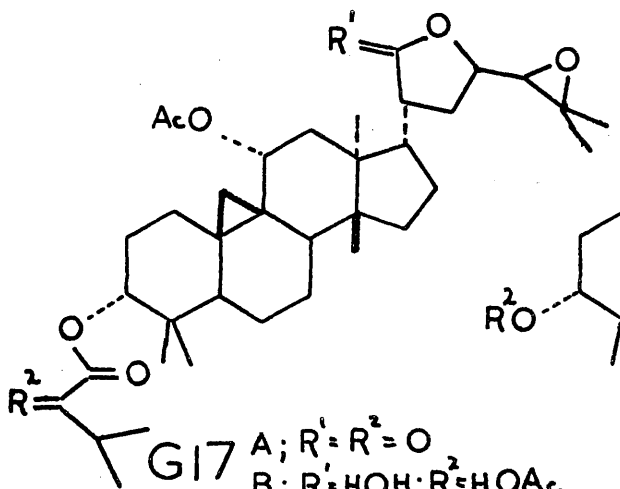
A ; R = H, OH
B ; R = O



G15

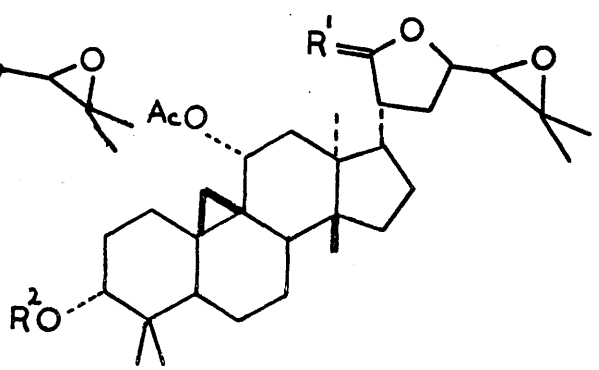


G16



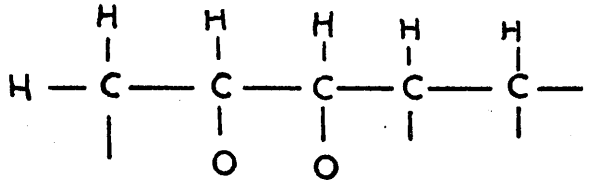
G17

A ; R' = R² = O
B ; R' = H, OH ; R² = H, OAc
C ; R' = O ; R² = OAc
D ; R' = O ; R² = H, OOC  I
E ; R' = R² = H, OOC.CH₂I

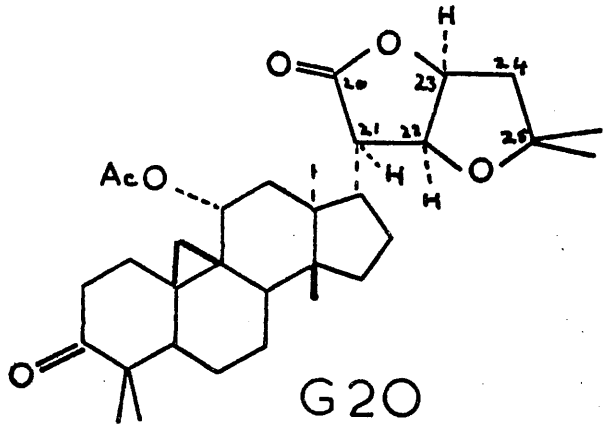


G18

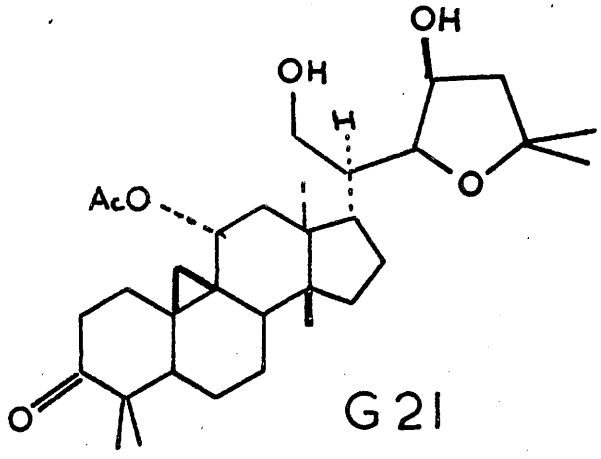
A ; R' = H, OH ; R² = H
B R' = O ; R² = Ac
C R' = O ; R² = COCH₂I



G19



G20



G21

INTRODUCTION

Up to 1912, a great deal of knowledge had been amassed concerning crystal habit and symmetry, but little was known of the internal arrangement of the atoms within the crystal structure. It was in that year that von Laue suggested that the three-dimensional array of atoms in a crystal might diffract x-rays. The experiment was carried out by Frederich and Knipping and after an initial disappointing result, showed von Laue's suggestion to be correct.

Following this discovery, W.L. Bragg elucidated the fundamental equation, which bears his name, by treating the diffraction phenomenon as one of reflection of the x-ray beam by the crystal planes. Diffraction theory has subsequently been expanded, allowing x-ray crystallography to be placed on a firm mathematical basis. Any detailed and rigorous treatment of diffraction theory is outside the scope of this thesis, but some of the salient features are mentioned below.

The phenomenon of x-ray diffraction maxima and minima is caused by an x-ray beam impinging upon an electron, causing it to become excited and emit secondary radiation. It can be shown that in any particular

direction, for constructive interference to occur the relationship

$$\lambda = 2 d \sin \theta$$

must hold, where d is the perpendicular distance between the scattering planes. θ is the angle which the x-ray beam makes with the scattering planes and λ is the wavelength of the x-ray beam. This equation is a formulation of Bragg's Law.

Since electrons occupy a finite space, phase differences exist between rays scattered from different points in this space, subsequently causing a reduction in intensity of the resultant beam. The scattering factor $f(h\ k\ \ell)$ for an atom whose electron density is $(u\ v\ w)$ is given by

$$f(hk\ell) = \int_{\infty}^{\infty}\int\int \rho(uvw) \exp\left[2\pi i(hu + kv + \ell w)\right] du\, dv\, dw$$

where (uvw) are coordinates referred to the centre of the atom. The scattering power of the atom is thus a function of the distribution of the electrons in the atom, and of the angle of scattering. For small angles of diffraction the phase differences are small, and the scattered amplitudes will approach Z, the atomic number.

The larger the angle however, the greater the phase differences become, and thus the scattered beam becomes weaker, the scattering factor being less than Z. This factor is known as the atomic scattering factor, and if the atom is assumed to have spherical symmetry, this factor is constant for a given angle of diffraction.

Atoms in crystals however, vibrate at ordinary temperatures, with frequencies much lower than those of X-rays, causing the electron density of an atom to be distorted from spherical symmetry. This has the effect of causing atoms which should scatter in phase to scatter slightly out of phase, resulting in a reduction in intensity and a modification of the atomic scattering factor. Approximate allowance for this can be made by using the factor

$$f = f_o . \exp(- B \sin^2 \theta/\lambda^2)$$

where θ is the Bragg angle, f_o is the atomic scattering factor for the atom at rest and B the Debye temperature factor is a constant. A relationship between B and $\bar{u}^2$, the mean square displacement of the atoms from their positions, thus

$$B = 8\pi^2 U \quad (\text{where } U = \bar{u}^2)$$

implies that all atoms vibrate with equal amplitudes. This is not strictly true, each crystallographically independent atom in a unit cell generally having a thermal vibration different from the others. A further implication of the above expression is that the thermal vibrations are isotropic, but in many cases they are markedly anisotropic. In this case, the vibrations are described such that the mean square amplitude if vibration in the direction of a unit vector $\underline{l}$ is

$$\bar{u}^2 = \sum_{i=j}^{3} \sum_{j=1}^{3} U_{ij} \cdot \ell_i \ \ell_j$$

More commonly, the temperature factor is written in the alternative devised by Cruickshank[1],

$$f = f_o \cdot \exp\left[-2\pi^2(u_{11}h^2a^{*2} + u_{22}k^2b^{*2} + u_{33}\ell^2c^{*2} + 2u_{23}k\ell b^*c^* + 2u_{31}\ell hc^*a^* + 2u_{12}hka^*b^*)\right]$$

The relation between intensity and structure amplitude is given by I, the total energy reflected in the course of passing the crystal through the region of Bragg reflection,

$$I = K.L.p. |F|^2$$

where K is a proportionality constant dependent on the intensity of the incident radiation, the volume of the

crystal, the number of cells per unit volume and the angular velocity of the crystal; L is the "Lorentz" factor and p is the polarisation factor. Such an expression should hold only for infintesimal crystals, but it is found to be applicable to many comparatively large crystals, due to the crystal behaving as a mosaic of small blocks. The Lorentz factor is a measure of the different lengths of time which different crystal planes spend in the reflecting position. The polarisation factor p is generally applied, since in most experiments the x-ray beam is unpolarised. This causes a reduction in intensity of the x-ray beam by the factor p, which is equal to $\frac{1 + \cos^2 2\theta}{2}$. Further reductions in the reflected intensity are caused by absorption and extinction. All of these effects may be taken into account when converting the observed intensities to the structure amplitudes.

In most cases, crystals do not have all their atoms arranged on lattice points, but have a certain arrangement of the N atoms within the unit cell. Each of these atoms within the unit cell, can be regarded as being on a lattice point on the lattice which is generated by the crystallographically related atoms,

thus giving rise to a set of N congruent lattices, each of which will obey the Bragg reflection conditions, although the different lattices will in general scatter out of phase. The intensities of the scattered rays will thus depend on the atomic arrangement within the cell. The structure factor F, the expression for the complete wave scattered by the crystal is thus

$$F = \sum_{j=1}^{N} f_j \exp 2\pi i(hx_j + ky_j + \ell z_j)$$

F is therefore a complex quantity, which can be represented by a modulus $|F(hkl)$, known as the structure amplitude and a phase constant $\alpha(hk\ell))$. The structure factor can be calculated by means of the expressions

$$|F(hk\ell)| = \sqrt{A^2 + B^2}$$

$$\alpha(hk\ell) = \tan^{-1} \frac{B}{A}$$

where $A = \sum_{j=1}^{N} fj.\cos 2\pi(hx_j + ky_j + \ell z_j)$

and $B = \sum_{j=1}^{N} fj.\cos 2\pi(hx_j + ky_j + \ell z_j)$

In the general case, the number of electrons in a volume element dx dy dz is given by $\rho(xyz) \frac{V}{abc}$ - dx dy dz, where V is the volume of the unit cell. Thus the structure factor expression may be written.

$$F(hk\ell) = \frac{V}{abc} \iiint_{abo}^{abc} \rho(xyz) \exp 2\pi i\ (hx + Ky + \ell z)\ dx\ dy\ dz$$

A periodic function can be represented by a Fourier series, and since a crystal is periodic in three dimensions, its electron density can be neatly represented by such a series in the form

$$\rho(xyz) = \sum_{-\infty}^{+\infty}\sum\sum \frac{|F(hk\ell)|}{V} \cos\,[2\pi(hx + ky + \ell z) - \alpha(hk\ell)]$$

where $A(hk\ell)$ is the Fourier coefficient which must be determined in order to evaluate the series and obtain the electron density at any point in the crystal. It can be shown that $A(\overline{hk\ell}) = F(hk\ell)/V$. The electron density can therefore be written

$$\rho(xyz) = \sum\sum\sum \frac{|F(hk\ell)|}{V} \cos\,[2\pi(hx + ky + \ell z) - \alpha(hk\ell)]$$

where $\alpha(hk\ell)$ is the phase angle associated with each structure factor. The structure amplitudes $F(hk\ell)$, can be readily derived from the observed intensities, but no experimental means exist for recording the phases. This constitutes the phase problem.

Patterson[2] in 1934 developed the vector representation of a crystal structure, in which he used the squares of the structure amplitudes as coefficients, and temporarily ignored the phases of the structure factors. The Patterson function can be written as

$$A(uvw) = \frac{1}{V}\int_0^1\int\int_0^1 \rho(xyz)\cdot\rho(x + u,\ y + v,\ z + w)\,dx\,dy\,dz$$

or, by expressing (xyz) and (x + u, y + v, z + w) in terms of the corresponding Fourier series

$$A(uvw) = \frac{1}{V}\sum_{-\infty}^{+\infty}\sum\sum |F(hk\ell)|^2 \exp 2\pi i (hu + kv + \ell w)$$

Thus A(uvw) will be large only when both the electron density distributions are large. This situation arises if an atom is situated at both (xyz) and (x + u, y + v, z + w). Consequently every pair of atoms in the unit cell will give rise to a peak in the Patterson map. It can be seen in the case of a unit cell of N atoms, that there will be N peaks superimposed at the origin, and a further $\frac{N(N-1)}{2}$ peaks, in the Patterson function. The general solution of such a function would prove extremely difficult, and in general, this method is used in conjunction with the heavy atom method.

In the case where a unit cell contains a small number of atoms of high atomic number, the height of the peaks associated with the interatomic vectors between those atoms will be large and these peaks will stand out against the background of smaller peaks. If the heavy atom positions are simply related to the symmetry of the crystal, the co-ordinates of these atoms can be readily determined. With these co-ordinates, it is then

possible to calculate the phase angles for each reflection, and since the contribution of the heavy atoms outweighs the contribution of the light atoms, these phase angles (α_H) will be good aproximations to the (unknown) phase angles for the molecules as a whole.

Using the observed values of the structure amplitudes and the calculated phase angles (α_H), it is possible to compute a Fourier series. From this summation it is usually possible to pick out some of the structural features of the molecule. New phase angles can be calculated at this point. These should be a better approximation to the correct phase angles, and can be used in the computation of a further electron density distribution. This process can be repeated until the structure analysis is complete.

Once a structure has been fully determined, an effort is made to obtain the closest possible agreement between the observed and calculated structure amplitudes. A measure of the agreement is expressed as the R factor

$$R = \frac{\sum \left| |Fo| \right|}{\sum |Fo|}$$

which should decrease with refinement. This agreement can usually be improved by adjusting the thermal and

positional parameters already obtained for the structure.

When the structure parameters differ by only small amounts from their true values, these parameters may be systematically adjusted in such a way that the discrepancy between the observed and calculated structure factors is minimised. The method of "least squares" was introduced by Hughes[3] in 1941.

The Glasgow S.F.L.S. program minimises the function

$$R = \frac{\sum w(|Fo| - |Fd)^2}{\sum w |Fo|^2}$$

where w, a weighting factor for each term, is used because the accuracy with which each $|F_o|$ value has been determined varies. The various weighting schemes are designed to make w inversely proportional to the variance of $|F_o|$. If R is close to a minimum, then it is minimised in the following way. If p_1, p_2, pn are the n parameters upon which $|Fc|$ is dependent, then for R to be a minimum

$$\frac{\partial R}{\partial pj} = 0 \qquad (j = 1, 2, \ldots\ldots n)$$

that is

$$\sum w\Delta \frac{\partial |Fc|}{\partial pj} \Big/ \sum w |Fo|^2 = 0 \quad \ldots\ldots \quad (1)$$

where $\Delta = \big||F|o - |Fc|\big|$. For a set of pj

close to the correct values. Δ may be expanded as a function of the parameters

$$\Delta(p + e) = \Delta(p) - \sum_{j=1}^{n} e_j \left| \frac{\partial Fd}{\partial pj} \right| \quad \ldots\ldots\ldots (2)$$

where e is the error which, when added to the parameters gives the true value. By suitable rearrangement of equations (1) and (2) we get a set of n equations, known as the normal equations which must be solved for the values of e. Successive applications of this procedure refine the parameters of the structure to values compatible with the accuracy of the original data.

DISCUSSION

This analysis unambiguously determines the structure of Triol Q acetonide p-iodobenzoate as I.[4] The effect of anomalous dispersion of the iodine atom could not be detected on the Weissenberg film, but fortunately the stereochemistry of the triol Q has been related to Rosenonolactone[5] whose absolute stereochemistry is known; all the diagrams refer to the absolute stereochemistry.

The cyclopropane fusion on ring A causes considerable distortion of this ring from the cyclohexane chair-form (Fig. I). The mean plane through the atoms of ring A shows it to be a half chair, atoms C(1) and C(2) being those most displaced from the mean plane of the ring (-0.39Å and 0.33Å respectively). The dihedral angle between the plane of the cyclopropane ring and the plane through atoms C(3), C(4), C(5) and C(10) is 71°.

Rings B and C have normal cyclohexane chair conformations, but have a definite dihedral angle between each other. The angle between the planes of ring A and ring B is 14°, while that between ring B and ring C is 90°. In the absence of distortion, the planes of these rings would be parallel.

The plane through atoms O(3), O(4) and C(28) of the acetonide ring show atoms C(15) and C(16) to be displaced considerably (0.75Å and 0.72Å respectively) from the plane, showing that the acetonide ring is envelope shaped.

The dihedral angle between the plane of the benzene ring and the plane of the carboxyl groups is 1.2°. The distortion may be explained in terms of intermolecular forces; C(18) has a fairly close intermolecular contact with O(2), the carbonyl oxygen, of 3.48Å.

From the figures given in Table I, the mean e.s.d.s in bond lengths are C-C = 0.05, C-O = 0.03, C-I = 0.03Å. None of the carbon-carbon single bonds differ significantly from the typical $C_{sp^3} - C_{sp^3}$ distance given by Sutton *et al.*[6], of 1.541Å. The average $C_{sp^3} - C_{sp^3}$ distance over the whole molecule is 1.536Å. The mean C-C distance in the benzene ring is 1.355Å, not significantly different from the usual distance of 1.397Å![7] Similarly, the C_{sp^3}-O and C_{sp^2}-O distances of 1.424Å and 1.32Å do not differ greatly from the accepted values[7] of 1.43Å and 1.36Å respectively. The C(21) - C(22) distance of 1.50Å is close to the accepted value[7] of 1.47Å, although the C(25) - I distance of

2-13Å is somewhat larger than the accepted average value[7] of 2.05Å.

All intermolecular contacts less than 4.0Å were calculated. They all correspond to normal Van der Waals contacts. The proximity of C(18) of one molecule to O(2) of a neighbouring molecule causes the carboxyl group to be rotated out of the benzene plane. Such rotations are not uncommon, e.g. in the determination of the crystal structure of a p-bromobenzoate derivative of a Taxine rearrangement product[8], the carboxyl group is found to be rotated 8° out of the benzene plane by intermolecular packing forces. Figure III shows the crystal structure as viewed in projection down the C axis.

EXPERIMENTAL

Preparation of Triol Q acetonide p-iodobenzoate

Triol Q acetonide acetate (IIA) (30 mg.) in refluxing ether (10 ml.) was treated with an excess of lithium aluminium hydride (60 mg.) for 2 hours. The reaction was worked up in the usual manner with a saturated solution of sodium sulphate, to afford Triol Q acetonide (IIB) (24 mg.) as needles from aqueous methanol m.p. 116°C. Found: C = 75.95 ; H = 10.81 ; $C_{23}H_{38}O_3$ requires C = 76.19; H = 10.57.

Triol Q acetonide (IIB) (18 mg.) in dry pyridine (4 ml.) was treated with an excess of p-iodobenzoyl chloride (200 mg.) for 20 hours. The mixture was worked up by pouring on to ice and extracting with ethyl acetate (2 x 10 ml.). The ethyl acetate extract was washed with water (3 x 10 ml.), dried, and evaporated to dryness to afford a crystalline mass, which consisted mainly of p-iodobenzoic anhydride. Repeated digestion of this residue with light petroleum 60-80, afforded the crude p-iodobenzoate ester, which was purified by preparative t.l.c. (benzene/chloroform, 1/1 as solvent) to afford triol Q acetonide p-iodobenzoate (I) as needles (16 mg.) from methanol/ether. m.p. 177-179°C.

Found: C = 60.90, H = 7.15; $C_{30}H_{41}I\,O_4$ requires C = 60.95; H, 6.95%. The colourless needles were elongated along *c*.

The unit cell parameters and space group were obtained from oscillation, Weissenberg and precession photographs.

Crystal Data

Triol Q acetonide p-iodobenzoate, $C_{30}H_{41}O_4I$, M = 592. Orthorhombic, a = 10.34, b = 25.84, c = 10.44Å. U = 2790Å^3, D_m not measured (insufficient material), z = 4, D_C = 1.35. Absent spectra: *h* o when *h* is odd, $ok\,o$ when *k* is odd, $oo\,l$ when *l* is odd. Space group: $P2_12_12_1(D_2^4)$.

The intensity data collection was by the equi-inclination Weissenberg method using Cu Kα radiation, with a small crystal rotating about *c*. The reciprocal lattice nets hko,--- hk7 were surveyed. The intensities were estimated visually by comparison with a calibrated scale, and appropriate corrections were made for Lorentz, polarisation and rotation factors. Absorption was small and no corrections were applied. The 1326 measured amplitudes were placed on an absolute scale during the least squares refinement by including the

appropriate layer scale factors K_ℓ in the normal equations.

Results

Structure Analysis

The iodine atom was found from the three-dimensional Patterson function as (0.0, 0.2669, 0.6755) and with $^{x}/a = 0$, half of the data are inadequately phased by the heavy atom. In the first Fourier summation based on the phase angles derived from the iodine aton position and the measured structure amplitudes, the weighting scheme devised by Sim was applied. The first electron density distribution was complicated by the inevitable presence of pseudo-mirror planes at $x = 0, \frac{1}{2}$, etc. Fortunately, the benzoate portion of the iodobenzoate, and ring C to which it is attached were clearly resolved from their mirror images. Their acceptance and inclusion in the second structure factor calculation served to destroy the phasing ambiguity and the second electron density map revealed 22 of the 35 non-hydrogen atoms. Two more rounds of structure factor and electron density calculations progressively revealed the entire structure. In the structure factor calculation, the

atomic scattering factors of International Tables, Vol. III[9] were used; all atoms were assigned a U_{iso} of 0.05 Å^2. In the final three-dimensional electron density distribution (Fig. II) only the methyl carbon atoms of the acetonide group are not well defined, possibly attributable to high thermal vibration.

The positional parameters were further refined by Fourier methods, using both F_o and F_c syntheses and applying back-shift corrections to allow for termination of series errors. Final refinement was by the method of least squares. A weighting scheme of the form

$$w = \left[1 - \exp\left(-p_1\left(\frac{\sin\theta}{\lambda}\right)^2\right)\right] \Big/ \left[1 + p_2|F_o| + p_3|F_o|^2\right]$$

was employed. The scale factors necessary to place the various sets of reflections on a common absolute scale were included in the isotropic least squares refinement. The limitation of storage capacity in the Glasgow KDF9 computer necessitated using a block diagonal approximation to the normal equation matrix. For the first cycle, the parameters, p_1, p_2, p_3 were given values such that unit weights would be obtained. The Glasgow KDF9 least squares program outputs an analysis of the weighting scheme used in a least squares cycle so that one may judge the appropriateness of the weighting scheme and the

parameters employed in it. The values of p_1, p_2 and p_3 were adjusted as necessary throughout the refinement; the final values for p_1, p_2 and p_3 are 200, 0.01 and 0.001 respectively.

After five rounds of refinement the atoms were allowed to vibrate anisotropically and from this point onwards an overall scale factor was refined instead of layer scale factors. The progress of the refinement is shown in Table VI.

At the last cycle, the co-ordinate shifts were much smaller than the σ,s,d,s, and as the purpose of the analysis, the determination of the stereochemistry of triol Q acetonide, had been achieved, refinement was terminated. The measured and calculated structure amplitudes obtained during the final least squares cycles are shown in Table VIII.

Molecular Parameters and Dimensions

The co-ordinates employed in the last S.F. calculation and their standard derivations are listed in Table I. The thermal parameters are listed in Table II, they are the values of U_{ij} in the expression

$$\exp[-2\pi^2(u_{11}h^2a^{*2} + u_{22}k^2b^{*2} + u_{33}k^2c^{*2}$$

$$+ 2u_{23}klb^*c^* + 2u_{31}lhc^*a^* + 2u_{12}hka^*b^*)]$$

the bond lengths and valence angles calculated from the co-ordinates of Table I are listed in Table III and Table IV respectively. All intra- and inter- molecular distances less than 4Å were calculated and are listed in Table V. The results of some mean molecular plane calculations are given in Table VII.

REFERENCES

1. Cruickshank, Acta.Cryst., 1965, 19, 153
2. Patterson, Phys. Rev. 1934, 46, 372
   Z. Kryst., 1935, 90, 517
3. Hughes, J.Amer.Chem.Soc., 1941, 63, 1737
4. Ferguson, Fulke and McCrindle, Chem.Comm. 1966, 691
5. Connolly, McCrindle, Murray, Overton and Melera, Tetrahedron Letters, 1964, 1859; Connolly, McCrindle, Murray, Renfrew, Overton and Melera, J.Chem.Soc.(C), 1966, 268
6. Allen and Sutton, Acta. Cryst., 1949, 3, 46
7. 'Tables of Interatomic Distances and Configuration in Molecules and Ions', Chem.Soc. Special Publication No. 11, 1958
8. Chan, Halsall, Hornby, Oxford, Sabel, Bjamer, Ferguson and Robertson, Chem. Comm., 1966, 923
9. 'International Tables for X-ray Crystallography', Kynoch Press, Birmingham, 1962.

TABLE I

Atomic Coordinates and e.s.d.s.*

Origin as in "International Tables Vol. I"[9]. For numbering scheme see I.

Atom	x/a	y/b	z/c
I	0.5115 (03)	0.7334 (01)	0.1662 (03)
$O_{(1)}$	0.2618 (16)	0.4891 (06)	0.0197 (19)
$O_{(2)}$	0.1298 (21)	0.5380 (07)	-0.1016 (22)
$O_{(3)}$	-0.1380 (20)	0.4418 (08)	0.2265 (24)
$O_{(4)}$	-0.2924 (25)	0.3827 (08)	0.2316 (26)
$C_{(1)}$	0.4510 (27)	0.4384 (10)	-0.1502 (30)
$C_{(2)}$	0.5276 (21)	0.4313 (10)	-0.2732 (37)
$C_{(3)}$	0.6220 (31)	0.3848 (10)	-0.2605 (37)
$C_{(4)}$	0.5600 (34)	0.3370 (11)	-0.2112 (40)
$C_{(5)}$	0.4241 (29)	0.3400 (10)	-0.1356 (32)
$C_{(6)}$	0.3402 (26)	0.2929 (10)	-0.1355 (33)
$C_{(7)}$	0.2487 (32)	0.2954 (12)	-0.0265 (32)
$C_{(8)}$	0.1876 (34)	0.3490 (10)	-0.0226 (33)
$C_{(9)}$	0.2742 (28)	0.3987 (10)	-0.0071 (31)
$C_{(10)}$	0.3563 (23)	0.3921 (09)	-0.1422 (30)
$C_{(11)}$	0.1908 (21)	0.4435 (08)	-0.0013 (31)
$C_{(12)}$	0.0885 (33)	0.4448 (12)	0.0847 (32)
$C_{(13)}$	0.0007 (34)	0.3936 (11)	0.0912 (35)
$C_{(14)}$	0.0831 (26)	0.3443 (09)	0.0876 (32)
$C_{(15)}$	-0.0744 (40)	0.3929 (12)	0.2210 (42)
$C_{(16)}$	-0.1802 (31)	0.3517 (10)	0.2203 (34)

TABLE I - contd.

Atom	x/a	y/b	z/c
$C_{(17)}$	-0.0826 (31)	0.3987 (11)	-0.0261 (36)
$C_{(18)}$	0.3568 (33)	0.3914 (10)	0.1146 (37)
$C_{(19)}$	0.5507 (30)	0.3324 (11)	-0.0580 (32)
$C_{(20)}$	0.5793 (42)	0.2887 (14)	-0.2831 (42)
$C_{(21)}$	0.2201 (32)	0.5324 (10)	-0.0325 (32)
$C_{(22)}$	0.2949 (28)	0.5792 (10)	0.0093 (32)
$C_{(23)}$	0.2556 (31)	0.6273 (11)	-0.0150 (34)
$C_{(24)}$	0.3133 (34)	0.6709 (10)	0.0282 (40)
$C_{(25)}$	0.4230 (34)	0.6650 (15)	0.0927 (38)
$C_{(26)}$	0.4773 (34)	0.6180 (12)	0.1134 (32)
$C_{(27)}$	0.4084 (34)	0.5784 (10)	0.0764 (41)
$C_{(28)}$	-0.2623 (30)	0.4334 (11)	0.2795 (35)
$C_{(29)}$	-0.3483 (29)	0.4725 (12)	0.2190 (42)
$C_{(30)}$	-0.2590 (52)	0.4405 (20)	0.4354 (45)

*The estimated standard deviations for each value is shown in brackets. The bracketed figures refer to the third and fourth decimal places e.g. 0.5115 (03) refers to a co-ordinate of 0.5115 with an e.s.d. of 0.0003.

TABLE II

Temperature factors

Atom	U_{11}	U_{22}	U_{33}	$2U_{32}$	$2U_{31}$	$2U_{12}$
I	0.1106	0.0846	0.0962	0.0027	0.0223	-0.0668
O_1	0.0280	0.0408	0.0296	-0.0101	0.0105	0.0010
O_2	0.0641	0.0557	0.0489	-0.0110	0.0007	0.0268
O_3	0.0487	0.0653	0.0715	-0.0171	0.0134	-0.0173
O_4	0.0842	0.0538	0.0774	-0.0189	0.0106	0.0059
C_1	0.0465	0.0451	0.0312	-0.0369	-0.0638	-0.0041
C_2	0.0330	0.0431	0.0838	0.0279	0.0197	0.0325
C_3	0.0553	0.0431	0.0732	-0.0212	0.0304	-0.0097
C_4	0.0597	0.0452	0.0933	-0.0158	-0.0167	0.0213
C_5	0.0466	0.0495	0.0450	-0.0109	-0.0308	0.0045
C_6	0.0305	0.0608	0.0472	-0.0204	0.0328	0.0484
C_7	0.0780	0.0700	0.0232	-0.0188	-0.0421	-0.0455
C_8	0.0855	0.0395	0.0395	-0.0326	-0.0083	0.0371
C_9	0.0422	0.0610	0.0267	0.0135	0.0094	-0.0273
C_{10}	0.0162	0.0447	0.0353	-0.0029	-0.0287	0.0169
C_{11}	0.0121	0.0183	0.0572	-0.0135	-0.0339	0.0036
C_{12}	0.0642	0.0671	0.0289	-0.0057	0.0282	-0.0395
C_{13}	0.0713	0.0488	0.0617	0.0421	-0.0078	-0.0100
C_{14}	0.0327	0.0353	0.0552	0.0381	-0.0350	-0.0447
C_{15}	0.0907	0.0523	0.0854	0.0504	0.0698	0.0334
C_{16}	0.0559	0.0446	0.0563	0.0555	0.0549	0.0342
C_{17}	0.0528	0.0579	0.0610	0.0209	-0.0295	-0.0540
C_{18}	0.0686	0.0376	0.0637	-0.0046	0.0023	-0.0198
C_{19}	0.0444	0.0537	0.0412	0.0092	0.0088	0.0589
C_{20}	0.1022	0.0693	0.0758	-0.0216	0.0292	0.0749

TABLE II - contd.

Atom	U_{11}	U_{22}	U_{23}	$2U_{32}$	$2U_{31}$	$2U_{12}$
C_{21}	0.0662	0.0554	0.0286	-0.0703	0.0746	-0.0374
C_{22}	0.0459	0.0460	0.0388	0.0497	0.0467	0.0069
C_{23}	0.0716	0.0529	0.0390	0.0075	0.0229	-0.0021
C_{24}	0.0644	0.0416	0.0865	-0.0366	0.0557	-0.0079
C_{25}	0.0445	0.1108	0.0602	-0.0171	0.0352	0.0452
C_{26}	0.0738	0.0702	0.0228	0.0354	0.0098	0.0148
C_{27}	0.0430	0.0414	0.0220	-0.0016	0.0147	-0.0263
C_{28}	0.0459	0.0581	0.0549	-0.0160	0.0187	-0.0711
C_{29}	0.0262	0.0713	0.0933	-0.0073	0.0398	-0.0358
C_{30}	0.1419	0.1627	0.0423	0.0958	0.0286	-0.1208

TABLE III

Bond Lengths.

Atoms	Dist. (Å)	Atoms	Dist. (Å)	Atoms	Dist. (Å)
C_1-C_2	1.52	C_9 -C_{10}	1.66	C_{21}-C_{22}	1.50
C_1-C_{10}	1.55	C_9 -C_{11}	1.44	C_{12}-C_{23}	1.34
C_2-C_3	1.55	C_9 -C_{18}	1.54	C_{22}-C_{27}	1.37
C_3-C_4	1.49	C_{11}-C_{12}	1.39	C_{23}-C_{24}	1.34
C_4-C_5	1.61	C_{11}-O_1	1.41	C_{24}-C_{25}	1.33
C_4-C_{19}	1.61	C_{12}-C_{13}	1.61	C_{25}-C_{26}	1.36
C_4-C_{20}	1.47	C_{13}-C_{14}	1.53	C_{25}- I	2.13
C_5-C_6	1.49	C_{13}-C_{15}	1.56	C_{26}-C_{27}	1.38
C_5-C_{10}	1.52	C_{13}-C_{17}	1.50	C_{28}-O_3	1.42
C_5-C_{19}	1.55	C_{15}-C_{16}	1.53	C_{28}-O_4	1.44
C_6-C_7,	1.48	C_{15}-O_3	1.43	C_{28}-C_{29}	1.49
C_7-C_8	1.52	C_{16}-O_4	1.42	$C_{28}C_{30}$	1.64
C_8-C_9	1.58	C_{21}-O_1	1.32		
C_8-C_{14}	1.58	C_{21}-O_2	1.19		

TABLE IV

Valence Angles

C(2)	C(1)	C(10)	106°	C(1)	C(10)	C(5)	113°
C(1)	C(2)	C(3)	110°	C(1)	C(10)	C(9)	107°
C(2)	C(3)	C(4)	114°	C(5)	C(10)	C(9)	107°
C(3)	C(4)	C(5)	120°	C(9)	C(11)	C(12)	120°
C(3)	C(4)	C(19)	116°	C(11)	C(12)	C(12)	116°
C(5)	C(4)	C(19)	58°	C(12)	C(13)	C(14)	112°
C(5)	C(4)	C(20)	114°	C(12)	C(13)	C(15)	109°
C(19)	C(4)	C(20)	117°	C(12)	C(13)	C(17)	103°
C(4)	C(5)	C(10)	115°	C(14)	C(13)	C(15)	108°
C(4)	C(5)	C(19)	61°	C(14)	C(13)	C(17)	112°
C(6)	C(5)	C(10)	117°	C(15)	C(13)	C(17)	111°
C(6)	C(5)	C(19)	113°	C(13)	C(14)	C(8)	110°
C(10)	C(5)	C(19)	122°	C(13)	C(15)	C(16)	111°
C(5)	C(6)	C(7)	110°	C(13)	C(15)	O(3)	105°
C(6)	C(7)	C(8)	109°	C(16)	C(15)	O(3)	107°
C(7)	C(8)	C(9)	121°	C(15)	C(16)	O(4)	101°
C(7)	C(8)	C(14)	104°	C(4)	C(19)	C(5)	61°
C(9)	C(8)	C(14)	112°	O(1)	C(21)	O(8)	128°
C(8)	C(9)	C(10)	97°	O(1)	C(21)	C(22)	113°
C(8)	C(9)	C(11)	109°	O(2)	C(21)	C(22)	119°

Valence Angles - contd.

C(8)	C(9)	C(18)	107°	C(21)	C(22)	C(23)	123°
C(10)	C(9)	C(11)	115°	C(21)	C(22)	C(27)	121°
C(10)	C(9)	C(18)	114°	C(22)	C(23)	C(24)	125°
C(11)	C(9)	C(18)	113°	C(23)	C(24)	C(25)	117°
C(24)	C(25)	C(26)	122°	O(3)	C(28)	C(30)	111°
C(24)	C(25)	I(1)	117°	O(4)	C(28)	C(29)	110°
C(26)	C(25)	I	121°	O(4)	C(28)	C(30)	117°
C(25)	C(26)	C(27)	118°	C(11)	O(1)	C(21)	118°
C(22)	C(27)	C(26)	121°	C(15)	O(3)	C(28)	107°
O(3)	C(28)	O(4)	102°	C(16)	O(4)	C(28)	112°
O(3)	C(28)	C(29)	106°				

TABLE V

Intermolecular Contacts

Atom A	Atom B	E P*	Cell	A-B(Å)
C(1)	O(3)	2	(0 1 -1)	3.87
C(2)	C(12)	2	(0 1 -1)	3.73
C(2)	C(21)	2	(0 1 -1)	3.84
C(2)	C(30)	1	(1 0 -1)	3.77
C(2)	O(2)	2	(0 1 -1)	3.84
C(2)	O(3)	2	(0 1 -1)	3.47
C(3)	C(17)	1	(1 0 0)	3.93
C(3)	C(30)	1	(1 0 -1)	3.70
C(6)	C(16)	3	(0 1 0)	3.85
C(6)	C(24)	2	(0 1 -1)	3.97
C(7)	C(19)	3	(-1 1 0)	3.99
C(14)	C(20)	3	(-1 1 0)	4.00
C(17)	C(26)	2	(0 1 -1)	3.94
C(18)	C(29)	1	(1 0 0)	3.86
C(18)	O(1)	2	(0 1 0)	3.48
C(18)	O(4)	1	(1 0 0)	3.83
C(19)	O(4)	1	(1 0 0)	3.67
C(26)	C(30)	2	(0 1 -1)	3.77
C(27)	C(29)	1	(1 0 0)	3.94

Intermolecular Contacts - cont.d.

Atom A	Atom B	E P*	Cell	A-B(Å)
C(27)	C(30)	2	(0 1 -1)	3.93
C(29)	C(30)	2	(-1 1 -1)	3.88
C(30)	O(2)	2	(-1 1 0)	3.89

*The integers in this column refer to the following equivalent positions:

1, x, y, z ;

2, $\frac{1}{2}$ - x, - y, $\frac{1}{2}$ + z;

3, $\frac{1}{2}$ + x, $\frac{1}{2}$ - y, - z.

For any distance, the triple set of integers given under the column 'Cell' indicate the unit cell translation which must be added to the appropriate equivalent position operation to derive the coordinates of the atom given under 'Atom B' from those given in Table I.

TABLE VI

Progress of Refinement

Operation	R	$\Sigma w \Delta^2$	R'	Comment
1st SF	51.14			Iodine only
2nd SF	42.12			I, O_2, C_{13}
3rd SF	36.19			I, O_2, C_{19}
4th SF	34.91			I, O_2, C_{26}
4th SF	32.47			Used reestimated data
5th SF	26.97			All atoms included
6th SF	24.11			"
7th SF	22.66			"
ASS isotropic L.S. (1st cycle)	19.79	7525.6		Unit weights
2nd cycle	19.65	6601.1		"
Main S.F.L.S. 1st cycle	19.02	99674.8	3.67	$p_3 = 0.0001$
2nd cycle	19.02	54910.4	5.10	$p_3 = 0.0005$
3rd cycle	18.76	40969.0	6.08	Anisotropic $p_3 = 0.001$
4th cycle	15.68	29298.7	4.14	$p_3 = 0.001$
5th cycle	14.37	18336.5	3.73	$p_3 = 0.01$

TABLE VII

Mean Molecular Planes

Atoms are listed with their displacement (Å) from the planes.

	Plane I		Plane II		Plane III		Plane IV	
Atoms in Plane	C(22)	-0.014	O(1)	-0.006	C(4)	0.000	C(3)	-0.029
	C(23)	0.035	O(2)	-0.007	C(5)	0.000	C(4)	0.054
	C(24)	-0.016	C(21)	0.017	C(19)	0.000	C(5)	-0.052
	C(25)	-0.023	C(22)	-0.005			C(10)	0.027
	C(26)	0.041						
	C(27)	-0.023						
Atoms out of Plane	I	-0.164	C(11)	-0.134	C(3)	-1.[illegible]	C(1)	-0.572
	C(21)	-0.069	C(23)	-0.210	C(6)	1.293	C(2)	0.254
			C(27)	0.177	C(10)	-1.260	C(6)	0.575
					C(20)	1.278	C(9)	-0.887
							C(19)	-1.284
							C(20)	0.890

	Plane V		Plane VI		Plane VII		Plane VIII	
Atoms in Plane	C(1)	-0.389	C(5)	-0.264	C(8)	0.273	O(3)	0.00[illegible]
	C(2)	0.330	C(6)	0.163	C(9)	-0.229	O(4)	0.00[illegible]
	C(3)	-0.101	C(7)	-0.177	C(11)	0.168	C(28)	0.00[illegible]
	C(4)	-0.037	C(8)	0.269	C(12)	-0.134		
	C(5)	-0.010	C(9)	-0.300	C(13)	0.170		
	C(10)	0.207	C(10)	0.309	C(14)	-0.248		
Atoms out of Plane	C(6)	0.603	C(1)	-0.121	C(1)	-0.315	C(15)	-0.749
	C(9)	-0.589	C(4)	-0.477	C(7)	-0.045	C(16)	-0.75[illegible]
	C(19)	-1.332	C(11)	0.251	C(10)	0.617	C(29)	1.29[illegible]
	C(20)	0.682	C(14)	-0.015	C(15)	-0.669	C(30)	-1.259
			C(18)	-1.839	C(17)	1.659		
			C(19)	-1.707	C(18)	-1.758		

The components of the unit vectors normal to these planes are as follows:

I	0.509,	0.039,	-0.860	V	-0.505,	-0.145,	-0.851
II	0.610,	-0.126,	-0.783	VI	-0.597,	0.074,	-0.799
III	-0.100,	-0.992,	-0.080	VII	-0.464,	0.044,	-0.885
IV	-0.430,	-0.210,	-0.878	VIII	-0.418,	0.409,	-0.811

TABLE VIII

Calculated and observed structure factors

H	K	L	|Fo|	|Fc|
0	4	0	54.1	32.7
0	6	0	183.9	175.7
0	8	0	54.7	55.4
0	10	0	88.6	90.2
0	12	0	7.1	15.7
0	14	0	28.1	24.8
0	16	0	19.5	15.1
0	18	0	78.4	85.1
0	20	0	14.8	10.5
0	22	0	30.2	29.2
0	24	0	26.5	30.5
0	26	0	23.5	24.2
0	28	0	9.7	8.2
0	30	0	16.6	13.8
1	1	0	86.2	95.7
1	2	0	61.1	60.7
1	3	0	27.1	15.6
1	4	0	45.0	40.7
1	5	0	54.6	45.2
1	6	0	32.3	34.1
1	7	0	20.6	22.0
1	8	0	114.7	132.2
1	9	0	8.6	8.5
1	10	0	84.9	90.8
1	11	0	26.6	30.0
1	12	0	112.2	117.6
1	13	0	4.8	2.9
1	14	0	93.8	90.1
1	15	0	5.3	4.8
1	16	0	87.2	75.2
1	17	0	29.1	21.6
1	18	0	55.0	56.0
1	19	0	14.0	9.3
1	20	0	52.2	49.5
1	21	0	6.6	5.0
1	22	0	45.4	45.9
2	0	0	95.0	98.1
2	1	0	14.9	8.9
2	2	0	189.5	236.7
2	3	0	2.9	4.4
2	4	0	106.5	109.9
2	5	0	56.4	58.7
2	6	0	125.2	133.9
2	7	0	63.2	53.3
2	8	0	69.7	72.7
2	9	0	4.1	1.4
2	10	0	83.8	74.7
2	11	0	88.1	57.9
2	12	0	67.2	65.5
2	13	0	7.9	1.9
2	14	0	31.8	26.5
2	15	0	5.5	2.1
2	16	0	22.1	18.1
2	17	0	32.6	28.2
2	18	0	33.8	35.7
2	19	0	6.4	11.8
2	20	0	25.4	23.1
2	21	0	6.7	1.3
2	22	0	21.5	15.7
2	23	0	21.7	23.6
2	24	0	26.5	21.6
2	25	0	6.7	12.4
2	26	0	20.7	18.4
3	1	0	26.5	28.4
3	2	0	46.9	42.9
3	3	0	42.5	23.8
3	4	0	27.0	31.5
3	5	0	69.5	55.3
3	6	0	22.2	31.4
3	7	0	26.5	14.4
3	8	0	143.7	136.1
3	9	0	109.6	98.4
3	10	0	184.4	194.9
3	11	0	4.8	6.5
3	12	0	34.8	18.9
3	13	0	5.3	5.0
3	14	0	61.6	62.2
3	15	0	18.1	20.1
3	16	0	79.1	83.7
3	17	0	6.1	2.4
3	18	0	36.2	35.3
3	19	0	6.5	0.5
3	20	0	38.1	34.2
3	21	0	6.8	1.2
3	22	0	28.7	20.2
3	23	0	6.8	9.3
3	24	0	32.1	30.8
4	0	0	102.6	120.0
4	1	0	4.0	6.0
4	2	0	103.9	107.6
4	3	0	11.2	5.5
4	4	0	103.5	105.0
4	5	0	38.1	38.4
4	6	0	90.2	89.1
4	7	0	46.4	38.4
4	8	0	94.6	81.5
4	9	0	17.2	3.1
4	10	0	21.1	22.3
4	11	0	5.2	8.0
4	12	0	50.0	47.1
4	13	0	20.6	17.2
4	14	0	5.8	7.2
4	15	0	19.0	6.6
4	16	0	29.5	22.6
4	17	0	24.8	14.3
4	18	0	6.6	5.8
4	19	0	27.2	20.5
4	20	0	25.4	27.1
4	21	0	21.7	17.5
4	22	0	15.3	16.8
4	23	0	24.9	22.5
5	1	0	16.4	13.2
5	2	0	18.1	18.9
5	3	0	48.1	43.4
5	4	0	66.0	64.9
5	5	0	7.7	7.3
5	6	0	32.6	28.6
5	7	0	63.8	59.4
5	8	0	35.8	40.0
5	9	0	36.6	32.2

H	K	L	|Fo|	|Fc|
5	10	0	59.8	58.4
5	11	0	20.9	19.0
5	12	0	62.7	61.9
5	13	0	19.0	13.5
5	14	0	53.4	52.5
5	15	0	36.2	35.7
5	16	0	44.8	47.7
5	17	0	14.8	14.7
5	18	0	30.2	23.0
5	19	0	6.8	4.7
5	20	0	37.6	24.6
5	21	0	6.8	5.1
5	22	0	21.4	16.1
5	23	0	6.6	1.2
5	24	0	17.5	13.0
6	0	0	22.9	26.5
6	1	0	8.3	9.7
6	2	0	70.0	66.7
6	3	0	54.4	57.6
6	4	0	65.7	63.5
6	5	0	13.4	16.4
6	6	0	63.8	62.7
6	7	0	12.6	19.6
6	8	0	44.7	45.9
6	9	0	9.3	11.2
6	10	0	33.5	30.1
6	11	0	28.8	25.9
6	12	0	14.1	4.1
6	13	0	14.4	2.0
6	14	0	28.1	25.4
6	15	0	33.9	29.7
6	16	0	6.8	6.9
6	17	0	18.7	1.4
6	18	0	6.9	6.2
6	19	0	6.8	0.9
6	20	0	6.8	7.0
6	21	0	18.9	15.1
6	22	0	14.6	15.1
6	23	0	24.4	18.4
6	24	0	16.4	16.8
6	25	0	12.6	14.5
7	1	0	13.2	16.5
7	2	0	5.9	6.7
7	3	0	6.0	8.1
7	4	0	21.2	20.8
7	5	0	37.6	35.6
7	6	0	19.4	23.0
7	7	0	6.2	1.4
7	8	0	14.1	13.9
7	9	0	27.8	23.6
7	10	0	28.2	27.1
7	11	0	16.7	22.8
7	12	0	34.6	35.3
7	13	0	21.3	23.7
7	14	0	26.3	20.0
7	15	0	15.3	21.3
7	16	0	28.3	25.2
7	17	0	6.8	2.3
7	18	0	27.1	26.6
7	19	0	6.7	9.2
7	20	0	14.6	14.6
7	21	0	6.3	1.9
8	0	0	27.4	26.8
8	1	0	35.3	34.8
8	2	0	6.5	4.4
8	3	0	6.5	9.4
8	4	0	43.7	43.6
8	5	0	14.7	16.6
8	6	0	44.3	44.8
8	7	0	6.7	10.4
8	8	0	39.1	41.2
8	9	0	6.8	6.9
8	10	0	6.8	10.2
8	11	0	6.8	8.5
8	12	0	6.8	8.8
8	13	0	26.6	31.9
8	14	0	15.3	14.2
8	15	0	6.8	6.0
8	16	0	21.2	17.4
8	17	0	14.8	13.8
9	1	0	6.8	13.2
9	2	0	6.8	5.5
9	3	0	6.8	2.9
9	4	0	6.8	11.8
9	5	0	16.8	12.2
9	6	0	11.9	13.9
9	7	0	30.7	28.1
9	8	0	6.9	14.3
9	9	0	30.6	35.4
9	10	0	6.8	1.7
9	11	0	13.6	14.6
9	12	0	18.4	17.0
9	13	0	29.8	35.8
9	14	0	14.6	14.3
0	2	1	39.0	33.6
0	3	1	126.3	113.5
0	4	1	225.7	184.7
0	5	1	126.7	126.9
0	6	1	100.1	90.4
0	7	1	45.1	36.6
0	8	1	166.8	135.1
0	9	1	61.0	53.3
0	10	1	58.9	53.7
0	11	1	40.2	45.3
0	12	1	102.1	100.4
0	13	1	6.5	3.6
0	14	1	122.3	94.2
0	15	1	10.2	7.6
0	16	1	69.8	55.1
0	17	1	32.6	29.4
0	18	1	66.5	52.8
0	19	1	8.6	6.2
0	20	1	26.5	21.6
0	21	1	94.7	76.7
0	22	1	9.2	7.5
0	23	1	14.8	15.4
0	24	1	24.8	15.6
0	25	1	9.3	9.9
0	26	1	24.0	16.8
1	0	1	51.7	43.9

H	K	L	|Fo|	|Fc|
1	1	1	80.6	51.8
1	2	1	185.6	145.1
1	3	1	137.9	116.0
1	4	1	169.7	190.0
1	5	1	60.2	54.9
1	6	1	95.5	103.1
1	7	1	51.3	42.6
1	8	1	114.7	128.6
1	9	1	40.8	47.7
1	10	1	37.6	43.2
1	11	1	45.0	28.2
1	12	1	24.3	22.5
1	13	1	77.0	69.6
1	14	1	29.1	31.2
1	15	1	54.1	39.2
1	16	1	10.8	9.5
1	17	1	49.2	46.1
1	18	1	18.6	17.1
1	19	1	36.0	34.6
1	20	1	57.5	45.3
1	21	1	20.4	16.3
1	22	1	56.7	54.2
1	23	1	9.4	6.3
1	24	1	20.9	14.5
1	25	1	9.2	13.0
1	26	1	23.9	19.5
2	0	1	47.6	37.4
2	1	1	108.7	86.0
2	2	1	160.1	124.5
2	3	1	177.9	124.2
2	4	1	87.8	71.6
2	5	1	109.6	79.6
2	6	1	116.0	95.6
2	7	1	68.2	69.7
2	8	1	48.1	60.4
2	9	1	68.2	47.2
2	10	1	108.0	99.4
2	11	1	24.1	15.8
2	12	1	133.7	113.9
2	13	1	23.2	12.4
2	14	1	65.2	68.4
2	15	1	10.6	16.2
2	16	1	74.3	58.8
2	17	1	8.2	5.6
2	18	1	82.0	63.7
2	19	1	8.7	9.5
2	20	1	18.0	15.7
2	21	1	18.4	9.8
2	22	1	20.8	18.8
2	23	1	20.9	23.1
2	24	1	29.5	22.8
2	25	1	9.2	8.1
2	26	1	8.9	6.8
3	0	1	102.4	97.5
3	1	1	86.2	61.3
3	2	1	184.6	160.6
3	3	1	22.9	16.6
3	4	1	104.4	98.7
3	5	1	64.5	59.0
3	6	1	125.1	89.0
3	7	1	24.0	25.2
3	8	1	90.3	76.3
3	9	1	33.6	12.2
3	10	1	55.0	46.3
3	11	1	123.0	89.1
3	12	1	47.8	40.1
3	13	1	53.6	48.0
3	14	1	7.5	7.5
3	15	1	37.6	31.0
3	16	1	8.1	10.1
3	17	1	40.9	31.7
3	18	1	8.7	9.8
3	19	1	44.7	24.6
3	20	1	9.1	10.2
3	21	1	37.7	24.1
3	22	1	29.6	23.0
3	23	1	20.9	9.2
3	24	1	29.2	16.0
4	0	1	26.1	18.0
4	1	1	98.6	68.9
4	2	1	52.0	39.1
4	3	1	26.8	29.4
4	4	1	28.2	17.0
4	5	1	51.9	44.3
4	6	1	107.8	82.4
4	7	1	77.5	63.0
4	8	1	23.3	23.4
4	9	1	42.3	37.0
4	10	1	60.4	58.1
4	11	1	49.5	44.7
4	12	1	101.2	73.3
4	13	1	37.0	39.2
4	14	1	52.1	50.2
4	15	1	8.3	14.1
4	16	1	49.7	46.9
4	17	1	8.8	6.7
4	18	1	40.2	35.7
4	19	1	9.2	5.0
4	20	1	41.6	36.6
4	21	1	9.4	19.0
4	22	1	35.0	23.6
4	23	1	11.3	3.2
4	24	1	20.2	9.9
4	25	1	16.4	14.2
5	0	1	135.2	110.7
5	1	1	42.7	43.1
5	2	1	97.0	75.3
5	3	1	49.1	38.7
5	4	1	73.2	49.9
5	5	1	28.0	27.1
5	6	1	79.4	81.1
5	7	1	39.9	30.3
5	8	1	77.7	59.5
5	9	1	50.0	43.0
5	10	1	44.8	33.8
5	11	1	12.3	11.2
5	12	1	22.0	18.4
5	13	1	33.0	22.2
5	14	1	32.9	24.4
5	15	1	44.4	36.8

H	K	L	|Fo|	|Fc|
5	16	1	19.9	9.3
5	17	1	32.8	25.7
5	18	1	20.6	24.0
5	19	1	25.5	22.4
5	20	1	9.4	7.6
5	21	1	24.7	18.2
5	22	1	9.2	7.5
5	23	1	20.1	12.4
6	0	1	7.2	5.7
6	1	1	44.3	36.2
6	2	1	39.8	30.0
6	3	1	44.6	39.1
6	4	1	10.5	11.6
6	5	1	20.6	17.5
6	6	1	25.9	24.3
6	7	1	46.9	36.3
6	8	1	50.1	51.5
6	9	1	34.8	30.1
6	10	1	34.0	29.9
6	11	1	37.7	33.9
6	12	1	42.2	32.6
6	13	1	29.8	28.0
6	14	1	31.7	21.3
6	15	1	9.1	7.5
6	16	1	34.6	27.2
6	17	1	20.8	23.5
6	18	1	41.9	35.8
6	19	1	9.3	5.2
6	20	1	25.4	17.7
6	21	1	9.1	5.7
6	22	1	20.8	16.3
6	23	1	8.5	5.7
6	24	1	16.3	12.9
7	0	1	38.3	34.0
7	1	1	12.8	13.1
7	2	1	52.0	42.8
7	3	1	18.3	20.4
7	4	1	48.7	44.4
7	5	1	29.4	23.2
7	6	1	20.6	16.3
7	7	1	19.0	16.9
7	8	1	40.0	31.1
7	9	1	31.5	24.8
7	10	1	39.7	30.7
7	11	1	28.5	31.5
7	12	1	37.0	32.7
7	13	1	9.2	4.9
7	14	1	20.8	12.8
7	15	1	20.9	17.7
7	16	1	9.4	15.2
7	17	1	14.8	13.6
7	18	1	9.2	2.7
7	19	1	24.1	23.9
7	20	1	8.9	9.1
7	21	1	19.2	17.1
7	22	1	8.2	3.8
7	23	1	17.5	14.4
8	0	1	19.8	16.5
8	1	1	21.7	20.0
8	2	1	8.9	5.9
8	3	1	8.9	5.3
8	4	1	8.9	15.4
8	5	1	37.1	26.7
8	6	1	14.3	10.6
8	7	1	18.2	17.0
8	8	1	37.8	24.0
8	9	1	45.2	34.7
8	10	1	36.0	30.3
8	11	1	31.0	26.8
8	12	1	20.9	17.7
8	13	1	14.8	11.5
8	14	1	14.8	12.4
8	15	1	18.5	18.4
8	16	1	18.3	16.8
0	2	2	112.1	111.8
0	3	2	73.4	69.2
0	4	2	68.0	66.3
0	5	2	21.9	13.9
0	6	2	94.1	104.9
0	7	2	66.2	62.9
0	8	2	54.5	55.1
0	9	2	120.9	125.8
0	10	2	30.2	38.5
0	11	2	50.8	70.8
0	12	2	17.6	19.9
0	13	2	79.4	85.4
0	14	2	8.8	2.6
0	15	2	56.4	63.8
0	16	2	9.6	14.7
0	17	2	61.2	70.6
0	18	2	16.5	17.8
0	19	2	36.8	39.2
0	20	2	11.2	18.5
0	21	2	30.3	24.6
0	22	2	11.6	5.4
0	23	2	23.4	25.7
0	24	2	16.5	20.8
1	0	2	39.0	38.4
1	1	2	389.4	341.9
1	2	2	100.5	68.6
1	3	2	98.2	71.6
1	4	2	59.8	50.3
1	5	2	94.5	103.6
1	6	2	25.0	43.2
1	7	2	39.9	51.4
1	8	2	34.0	39.0
1	9	2	56.7	74.6
1	10	2	53.0	59.6
1	11	2	75.8	74.2
1	12	2	45.6	57.8
1	13	2	23.1	20.6
1	14	2	29.4	39.2
1	15	2	20.8	14.1
1	16	2	37.7	40.0
1	17	2	26.8	34.0
1	18	2	23.6	22.6
1	19	2	36.1	29.7
1	20	2	37.2	35.7
1	21	2	22.9	16.0
1	22	2	23.3	16.5

H	K	L	|Fo|	|Fc|
1	23	2	16.6	12.6
2	0	2	217.9	178.6
2	1	2	90.0	63.4
2	2	2	109.0	82.6
2	3	2	62.9	53.4
2	4	2	89.3	103.1
2	5	2	38.3	33.5
2	6	2	66.3	54.2
2	7	2	88.5	105.2
2	8	2	45.4	42.6
2	9	2	110.7	103.3
2	10	2	16.8	23.6
2	11	2	86.5	112.6
2	12	2	22.8	24.0
2	13	2	50.9	63.4
2	14	2	18.3	15.9
2	15	2	55.7	55.7
2	16	2	10.0	10.0
2	17	2	46.3	43.2
2	18	2	10.7	14.7
2	19	2	42.8	36.2
2	20	2	11.3	9.0
2	21	2	20.0	25.1
2	22	2	11.7	13.6
2	23	2	26.2	25.3
3	0	2	20.0	14.0
3	1	2	136.1	125.4
3	2	2	40.0	36.0
3	3	2	88.8	90.7
3	4	2	75.2	71.1
3	5	2	65.8	60.4
3	6	2	40.5	37.9
3	7	2	100.8	110.9
3	8	2	44.0	40.3
3	9	2	49.1	58.8
3	10	2	39.7	40.6
3	11	2	46.4	43.0
3	12	2	41.0	34.8
3	13	2	30.5	30.5
3	14	2	38.4	35.4
3	15	2	15.8	15.0
3	16	2	43.2	36.0
3	17	2	10.7	9.4
3	18	2	44.1	30.4
3	19	2	25.3	24.2
3	20	2	18.2	17.3
3	21	2	11.7	9.3
3	22	2	11.7	12.3
3	23	2	18.4	17.3
4	0	2	33.3	18.6
4	1	2	15.7	9.6
4	2	2	80.5	76.8
4	3	2	33.8	26.2
4	4	2	46.5	51.2
4	5	2	39.1	41.1
4	6	2	70.3	63.0
4	7	2	31.9	39.0
4	8	2	43.2	40.3
4	9	2	88.4	88.3
4	10	2	60.8	62.3
4	11	2	61.4	67.2
4	12	2	42.4	33.1
4	13	2	28.6	37.7
4	14	2	16.0	18.0
4	15	2	49.7	58.3
4	16	2	10.8	12.8
4	17	2	38.4	32.6
4	18	2	11.3	8.1
4	19	2	33.6	27.6
4	20	2	18.5	17.3
4	21	2	26.2	25.3
4	22	2	11.7	14.9
4	23	2	19.9	11.2
4	24	2	11.2	11.0
4	25	2	18.7	14.1
5	0	2	28.7	18.2
5	1	2	61.6	62.2
5	2	2	44.0	37.5
5	3	2	85.7	79.5
5	4	2	39.8	40.3
5	5	2	57.8	58.7
5	6	2	33.7	33.7
5	7	2	76.9	72.3
5	8	2	20.4	24.4
5	9	2	59.3	50.4
5	10	2	48.2	38.1
5	11	2	9.9	7.1
5	12	2	10.2	10.1
5	13	2	23.4	26.7
5	14	2	41.7	43.0
5	15	2	11.0	13.2
5	16	2	25.2	12.7
5	17	2	11.5	3.0
5	18	2	18.4	11.8
5	19	2	11.7	4.8
5	20	2	26.2	22.7
5	21	2	11.6	12.2
5	22	2	19.8	18.6
6	0	2	71.3	68.3
6	1	2	22.6	16.3
6	2	2	18.5	10.9
6	3	2	20.9	22.3
6	4	2	39.5	38.6
6	5	2	15.1	10.4
6	6	2	34.3	33.7
6	7	2	22.1	20.5
6	8	2	40.9	31.4
6	9	2	36.3	30.2
6	10	2	25.7	29.4
6	11	2	23.9	29.9
6	12	2	18.9	18.2
6	13	2	27.3	26.5
6	14	2	25.3	21.3
6	15	2	39.8	35.4
6	16	2	11.6	13.5
6	17	2	34.1	33.3
6	18	2	11.7	6.2
6	19	2	26.1	21.6
6	20	2	11.5	7.2
6	21	2	25.3	16.7

H	K	L	|Fo|	|Fc|
6	22	2	11.0	5.7
6	23	2	19.7	12.5
7	0	2	34.0	33.4
7	1	2	23.0	28.7
7	2	2	20.6	24.7
7	3	2	46.4	40.2
7	4	2	23.4	21.8
7	5	2	40.8	41.9
7	6	2	27.2	26.2
7	7	2	45.8	47.0
7	8	2	17.3	13.1
7	9	2	20.7	20.5
7	10	2	11.2	9.2
7	11	2	22.7	22.3
7	12	2	39.0	41.9
7	13	2	25.9	17.1
7	14	2	28.6	25.5
7	15	2	26.2	18.2
7	16	2	23.4	17.3
7	17	2	11.6	2.0
7	18	2	23.0	13.5
0	2	3	72.7	58.0
0	3	3	184.7	180.8
0	4	3	32.8	31.5
0	5	3	152.1	143.4
0	6	3	22.4	29.7
0	7	3	103.7	100.6
0	8	3	15.6	12.9
0	9	3	61.9	56.5
0	10	3	34.6	31.5
0	11	3	18.7	26.0
0	12	3	17.3	11.3
0	13	3	10.1	19.6
0	14	3	5.3	1.1
0	15	3	20.4	13.1
0	16	3	5.8	4.0
0	17	3	9.6	4.3
0	18	3	6.3	13.4
0	19	3	19.5	14.2
0	20	3	10.5	6.4
0	21	3	6.8	9.5
0	22	3	6.9	1.0
0	23	3	34.4	37.1
1	0	3	95.1	67.7
1	1	3	67.5	41.6
1	2	3	67.0	26.1
1	3	3	116.5	87.5
1	4	3	26.6	20.8
1	5	3	57.1	62.0
1	6	3	39.2	32.4
1	7	3	72.3	72.6
1	8	3	39.4	39.5
1	9	3	87.8	105.2
1	10	3	9.7	8.0
1	11	3	86.6	93.2
1	12	3	15.3	11.4
1	13	3	79.0	74.6
1	14	3	5.4	3.6
1	15	3	72.1	76.2
1	16	3	5.9	9.8
1	17	3	65.6	59.5
1	18	3	6.3	8.4
1	19	3	31.9	27.8
1	20	3	14.9	11.7
1	21	3	26.4	26.9
1	22	3	28.8	24.4
1	23	3	30.8	26.8
2	0	3	33.1	28.6
2	1	3	168.4	147.6
2	2	3	20.1	25.7
2	3	3	147.7	122.9
2	4	3	35.3	34.0
2	5	3	96.7	93.4
2	6	3	3.7	6.4
2	7	3	107.0	106.3
2	8	3	15.9	21.3
2	9	3	60.6	67.2
2	10	3	19.1	14.5
2	11	3	26.3	28.3
2	12	3	18.9	23.3
2	13	3	23.6	22.6
2	14	3	12.4	13.1
2	15	3	18.2	19.3
2	16	3	22.1	16.3
2	17	3	13.9	11.6
2	18	3	6.4	12.5
2	19	3	27.6	28.9
2	20	3	26.1	25.5
2	21	3	41.1	43.8
2	22	3	21.8	21.4
2	23	3	13.7	10.8
2	24	3	6.8	6.0
2	25	3	21.9	19.6
3	0	3	65.8	37.4
3	1	3	12.8	15.2
3	2	3	60.5	42.5
3	3	3	31.9	32.0
3	4	3	29.4	24.1
3	5	3	69.3	55.4
3	6	3	42.4	28.8
3	7	3	63.9	61.3
3	8	3	47.5	44.5
3	9	3	48.8	52.0
3	10	3	32.0	32.3
3	11	3	60.8	60.2
3	12	3	16.9	12.4
3	13	3	69.7	78.3
3	14	3	20.9	23.8
3	15	3	54.5	55.2
3	16	3	9.8	9.7
3	17	3	58.2	54.8
3	18	3	14.7	8.3
3	19	3	39.8	46.7
3	20	3	26.4	22.1
3	21	3	25.3	24.2
3	22	3	16.9	21.7
3	23	3	21.5	16.0
4	0	3	13.5	15.1
4	1	3	138.1	124.4
4	2	3	38.3	29.3

TABLE VIII (cont.)

H	K	L	|Fo|	|Fc|
4	3	3	79.1	82.2
4	4	3	24.4	29.0
4	5	3	83.0	81.4
4	6	3	21.0	19.8
4	7	3	67.7	66.6
4	8	3	5.0	8.2
4	9	3	34.6	34.7
4	10	3	16.9	18.7
4	11	3	24.7	19.5
4	12	3	27.4	24.0
4	13	3	20.9	23.2
4	14	3	24.4	20.5
4	15	3	14.1	12.0
4	16	3	27.0	22.8
4	17	3	6.6	9.0
4	18	3	21.3	15.9
4	19	3	24.2	24.0
4	20	3	6.9	4.3
4	21	3	6.9	10.8
4	22	3	15.2	12.8
4	23	3	18.3	19.0
4	24	3	17.7	19.1
5	0	3	23.3	19.7
5	1	3	4.9	1.0
5	2	3	19.2	13.6
5	3	3	20.9	20.0
5	4	3	18.0	15.3
5	5	3	33.7	43.1
5	6	3	45.6	44.6
5	7	3	40.0	48.5
5	8	3	5.5	1.8
5	9	3	32.3	41.0
5	10	3	31.9	28.9
5	11	3	68.6	71.7
5	12	3	50.4	54.9
5	13	3	28.1	26.9
5	14	3	10.2	16.6
5	15	3	31.2	29.8
5	16	3	6.7	11.7
5	17	3	30.4	34.8
5	18	3	6.9	14.1
5	19	3	25.3	21.9
5	20	3	15.3	12.9
5	21	3	22.5	20.5
5	22	3	6.6	6.9
5	23	3	20.3	17.8
6	0	3	21.5	26.6
6	1	3	35.2	41.5
6	2	3	26.5	28.8
6	3	3	41.8	48.5
6	4	3	5.7	7.9
6	5	3	35.3	39.4
6	6	3	13.1	24.5
6	7	3	32.0	34.3
6	8	3	30.3	32.7
6	9	3	39.0	45.1
6	10	3	34.4	32.8
6	11	3	43.5	45.4
6	12	3	10.3	11.3
6	13	3	23.5	10.7
6	14	3	6.7	7.9
6	15	3	15.2	15.0
6	16	3	20.6	14.0
6	17	3	6.9	9.0
6	18	3	21.7	16.2
6	19	3	6.8	5.4
6	20	3	15.0	13.8
6	21	3	14.6	16.1
6	22	3	14.1	13.6
7	0	3	6.2	4.1
7	1	3	6.2	8.7
7	2	3	13.9	8.0
7	3	3	19.7	20.4
7	4	3	19.8	18.2
7	5	3	14.1	15.5
7	6	3	30.3	32.2
7	7	3	24.2	20.8
7	8	3	25.3	27.1
7	9	3	39.1	47.5
7	10	3	28.8	24.9
7	11	3	15.1	12.6
7	12	3	6.8	5.7
7	13	3	20.0	22.3
7	14	3	16.9	17.0
7	15	3	16.9	20.1
7	16	3	15.3	13.9
7	17	3	16.6	15.3
8	0	3	6.7	7.2
8	1	3	25.8	28.9
8	2	3	25.9	27.3
8	3	3	22.2	25.8
8	4	3	22.3	24.5
8	5	3	20.8	21.1
8	6	3	6.8	10.2
8	7	3	21.5	20.2
0	1	4	30.7	27.7
0	2	4	114.9	103.2
0	3	4	27.1	26.7
0	4	4	66.9	67.6
0	5	4	51.7	59.5
0	6	4	44.3	41.1
0	7	4	67.8	65.7
0	8	4	27.8	28.8
0	9	4	90.2	83.9
0	10	4	38.6	28.5
0	11	4	105.8	95.8
0	12	4	7.1	10.1
0	13	4	25.1	30.0
0	14	4	26.4	24.0
0	15	4	55.1	59.0
0	16	4	16.6	15.3
0	17	4	28.1	24.4
0	18	4	6.5	5.5
0	19	4	31.7	32.1
0	20	4	6.8	4.8
0	21	4	27.6	26.9
1	0	4	68.0	69.3
1	1	4	85.9	84.6
1	2	4	12.6	12.5
1	3	4	166.2	115.7
1	4	4	47.7	43.4
1	5	4	104.5	87.1
1	6	4	29.8	19.6
1	7	4	83.9	88.5
1	8	4	38.7	40.4
1	9	4	47.4	48.8
1	10	4	51.1	46.7
1	11	4	24.2	28.9
1	12	4	37.8	34.9
1	13	4	27.6	29.8
1	14	4	32.0	33.4
1	15	4	5.9	7.3
1	16	4	26.6	22.3
1	17	4	11.0	11.7
1	18	4	36.4	40.1
1	19	4	10.6	14.7
1	20	4	10.8	13.2
1	21	4	10.9	11.3
1	22	4	6.9	5.3
1	23	4	28.0	30.4
2	0	4	242.0	184.8
2	1	4	76.7	55.0
2	2	4	39.4	36.5
2	3	4	28.8	14.2
2	4	4	42.5	24.0
2	5	4	71.6	57.8
2	6	4	39.5	38.6
2	7	4	71.1	62.1
2	8	4	47.6	42.9
2	9	4	74.0	73.9
2	10	4	30.4	34.6
2	12	4	55.2	24.2
2	12	4	17.6	24.2
2	13	4	64.4	63.5
2	14	4	14.7	12.5
2	15	4	41.4	43.7
2	16	4	6.2	13.2
2	17	4	41.5	47.3
2	18	4	6.6	14.7
2	19	4	35.2	38.1
2	20	4	6.9	6.2
2	21	4	15.5	17.6
3	0	4	105.8	88.3
3	1	4	142.6	129.7
3	2	4	76.1	66.9
3	3	4	84.1	85.4
3	4	4	20.4	17.8
3	5	4	86.9	87.4
3	6	4	36.4	37.9
3	7	4	48.7	39.5
3	8	4	33.6	37.7
3	9	4	48.3	50.6
3	10	4	17.1	18.0
3	11	4	22.8	21.5
3	12	4	37.5	45.1
3	13	4	21.8	22.3
3	14	4	25.2	27.1
3	15	4	6.2	6.0
3	16	4	29.5	29.6
3	17	4	6.6	4.1
3	18	4	23.4	18.1
3	19	4	24.7	26.6
3	20	4	6.9	8.6
3	21	4	21.9	25.5
3	22	4	13.7	15.7
3	23	4	10.7	8.9
3	24	4	13.1	10.9
4	0	4	25.8	17.5
4	1	4	10.1	10.9
4	2	4	52.8	59.0
4	3	4	51.5	62.6
4	4	4	27.8	29.6
4	5	4	34.0	34.6
4	6	4	42.5	37.6
4	7	4	46.7	48.0
4	8	4	29.9	31.5
4	9	4	30.9	33.1
4	10	4	33.1	34.1
4	11	4	38.8	42.7
4	12	4	15.2	14.8
4	13	4	42.2	47.3
4	14	4	16.8	13.5
4	15	4	33.8	36.6
4	16	4	6.7	12.7
4	17	4	28.4	26.7
4	18	4	6.9	2.5
4	19	4	24.5	24.5
4	20	4	6.9	4.9
4	21	4	20.6	15.7
4	22	4	6.8	9.1
4	23	4	16.1	13.2
5	0	4	29.9	27.4
5	1	4	62.3	64.2
5	2	4	8.2	12.4
5	3	4	57.0	57.6
5	4	4	17.7	18.5
5	5	4	51.4	50.5
5	6	4	5.5	5.3
5	7	4	22.9	20.5
5	8	4	29.4	29.3
5	9	4	57.6	59.2
5	10	4	39.5	39.7
5	11	4	29.8	39.6
5	12	4	14.2	11.2
5	13	4	6.5	14.3
5	14	4	22.5	20.9
5	15	4	9.5	13.6
5	16	4	30.6	29.5
5	17	4	6.9	4.4
5	18	4	18.3	23.0
5	19	4	6.9	4.6
5	20	4	15.3	14.1
6	0	4	30.5	40.5
6	1	4	27.0	27.2
6	2	4	18.5	19.0
6	3	4	5.9	8.4
6	4	4	24.9	28.7
6	5	4	26.9	31.9
6	6	4	29.9	31.8
6	7	4	25.1	19.4
6	8	4	37.7	41.8
6	9	4	20.2	11.6
6	10	4	29.8	40.8
6	11	4	42.8	53.1
6	12	4	6.7	9.3
6	13	4	45.6	54.1
6	14	4	23.8	24.8
6	15	4	20.7	16.8
6	16	4	6.9	5.7
6	17	4	16.9	18.3
6	18	4	6.9	4.6
6	19	4	24.3	24.1
7	0	4	18.6	15.2
7	1	4	26.8	36.0
7	2	4	14.3	21.4
7	3	4	25.4	27.8
7	4	4	6.5	8.3
7	5	4	22.2	22.1
7	6	4	6.6	7.4
7	7	4	26.6	23.7
7	8	4	6.7	9.3
7	9	4	10.7	14.6
7	10	4	6.8	2.3
7	11	4	24.3	21.6
7	12	4	18.9	14.2
7	13	4	15.5	13.5
7	14	4	15.5	12.7
7	15	4	10.9	14.7
0	1	5	23.7	37.3
0	2	5	38.2	45.1
0	3	5	60.2	72.7
0	4	5	10.9	10.2
0	5	5	28.9	32.3
0	6	5	61.9	58.3
0	7	5	48.4	51.7
0	8	5	30.7	36.6
0	9	5	4.9	3.0
0	10	5	84.6	84.1
0	11	5	21.4	23.6
0	12	5	41.1	53.6
0	13	5	6.1	4.3
0	14	5	27.5	32.4
0	15	5	6.7	1.2
0	16	5	32.4	40.7
0	17	5	7.1	0.5
0	18	5	28.8	32.8
1	0	5	83.8	88.3
1	1	5	14.1	18.6
1	2	5	140.7	93.4
1	3	5	30.9	16.8
1	4	5	73.9	68.7
1	5	5	49.4	43.2
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1	11	5	34.3	41.6
1	12	5	13.2	15.2
1	13	5	27.3	30.3
1	14	5	6.4	11.9
1	15	5	29.2	35.1
1	16	5	6.9	9.0
1	17	5	11.3	10.9
1	18	5	11.6	17.2
1	19	5	11.8	16.8
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2	4	5	68.9	50.9
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2	6	5	36.5	34.5
2	7	5	43.5	29.7
2	8	5	57.4	57.6
2	9	5	21.5	22.5
2	10	5	36.1	38.3
2	11	5	20.6	15.3
2	12	5	49.2	52.8
2	13	5	23.8	23.6
2	14	5	37.2	39.0
2	15	5	15.3	10.1
2	16	5	38.8	42.0
2	17	5	7.3	12.4
2	18	5	19.6	18.4
2	19	5	11.9	9.1
2	20	5	24.0	23.0
2	21	5	21.4	18.3
2	22	5	22.5	19.9
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3	2	5	87.2	70.9
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3	5	5	23.2	28.4
3	6	5	47.3	42.9
3	7	5	26.4	28.1
3	8	5	35.9	40.0
3	9	5	27.5	23.3
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0	5	7	5.5	2.3
0	6	7	33.8	31.0
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0	8	7	33.2	35.8
0	9	7	32.1	39.6
0	10	7	17.6	17.7
0	11	7	8.3	9.7
0	12	7	41.1	38.0
0	13	7	9.0	12.6
0	14	7	22.8	23.8
0	15	7	9.6	11.6
0	16	7	28.4	33.3
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1	1	7	20.6	27.9
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1	3	7	14.5	12.0
1	4	7	34.7	40.7
1	5	7	5.8	3.2
1	6	7	43.5	43.5
1	7	7	28.2	30.1
1	8	7	23.8	25.2
1	9	7	32.3	26.4
1	10	7	25.3	22.0
1	11	7	23.0	29.5
2	0	7	21.3	10.4
2	1	7	34.0	34.3
2	2	7	9.0	6.1
2	3	7	28.2	24.8
2	4	7	19.7	12.0
2	5	7	32.8	26.5
2	6	7	30.9	34.7
2	7	7	17.8	18.5
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2	9	7	12.7	18.9
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2	12	7	20.1	18.9
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2	15	7	9.7	8.2
2	16	7	22.1	23.7
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4	11	7	9.5	10.8
4	12	7	21.7	20.1
5	0	7	41.4	34.3
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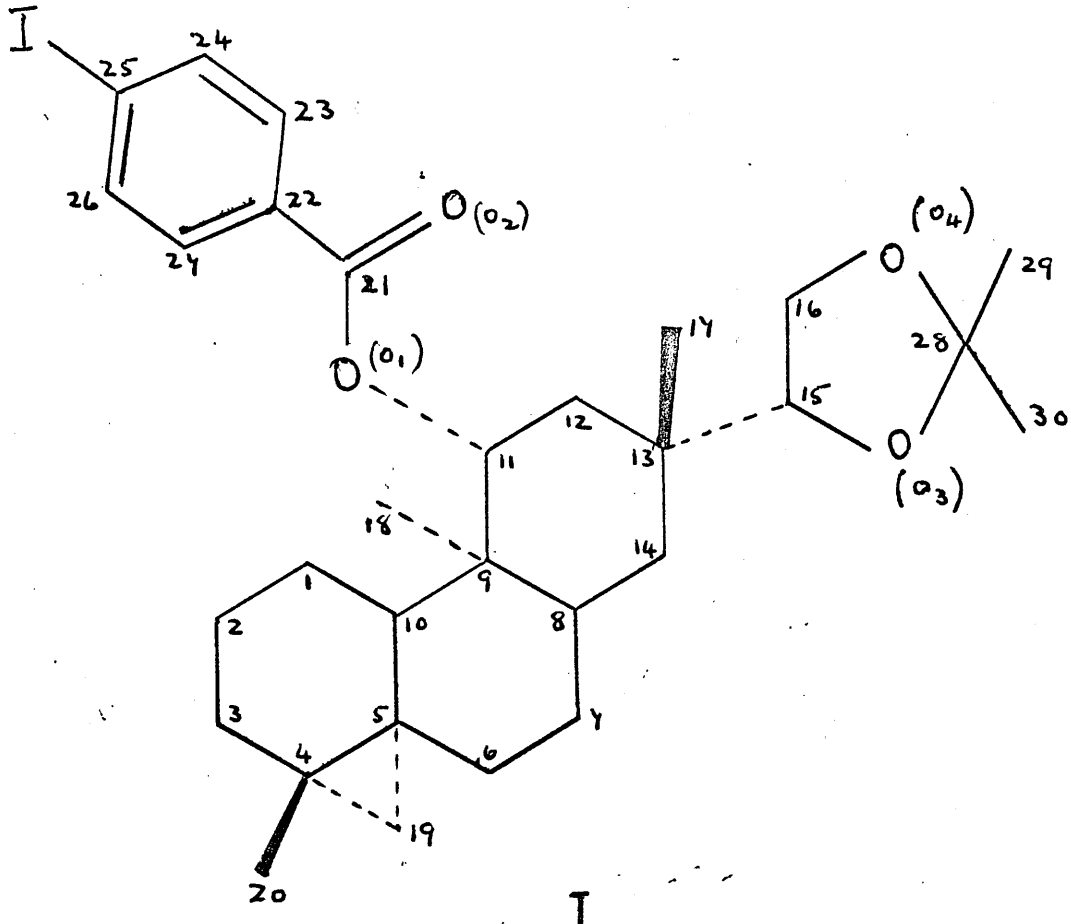
5	4	7	42.8	40.1



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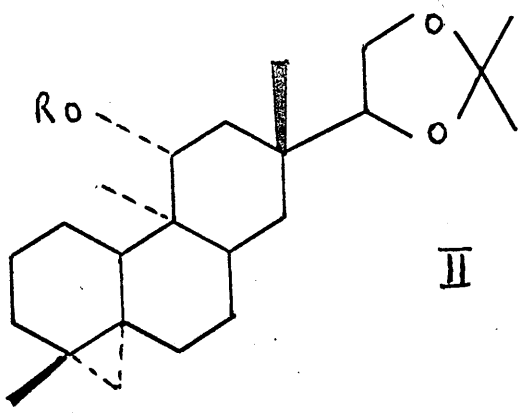

II A ; R = $COCH_3$

B ; R = H.

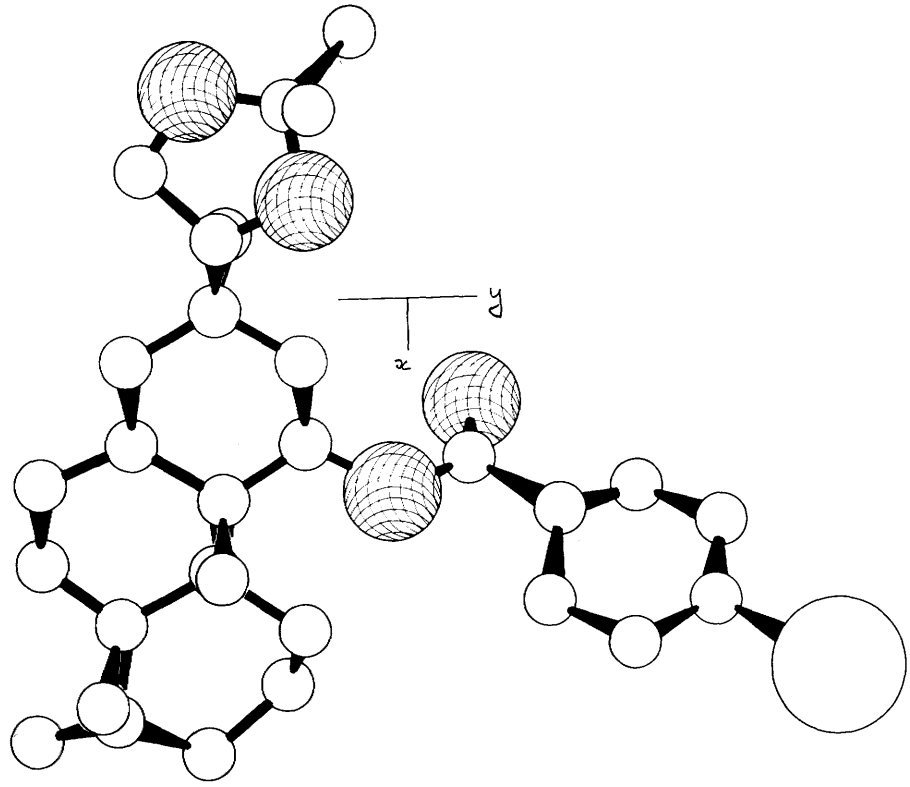

FIGURE I

Structure of the triol Q iodobenzoate molecule as viewed along the c axis.

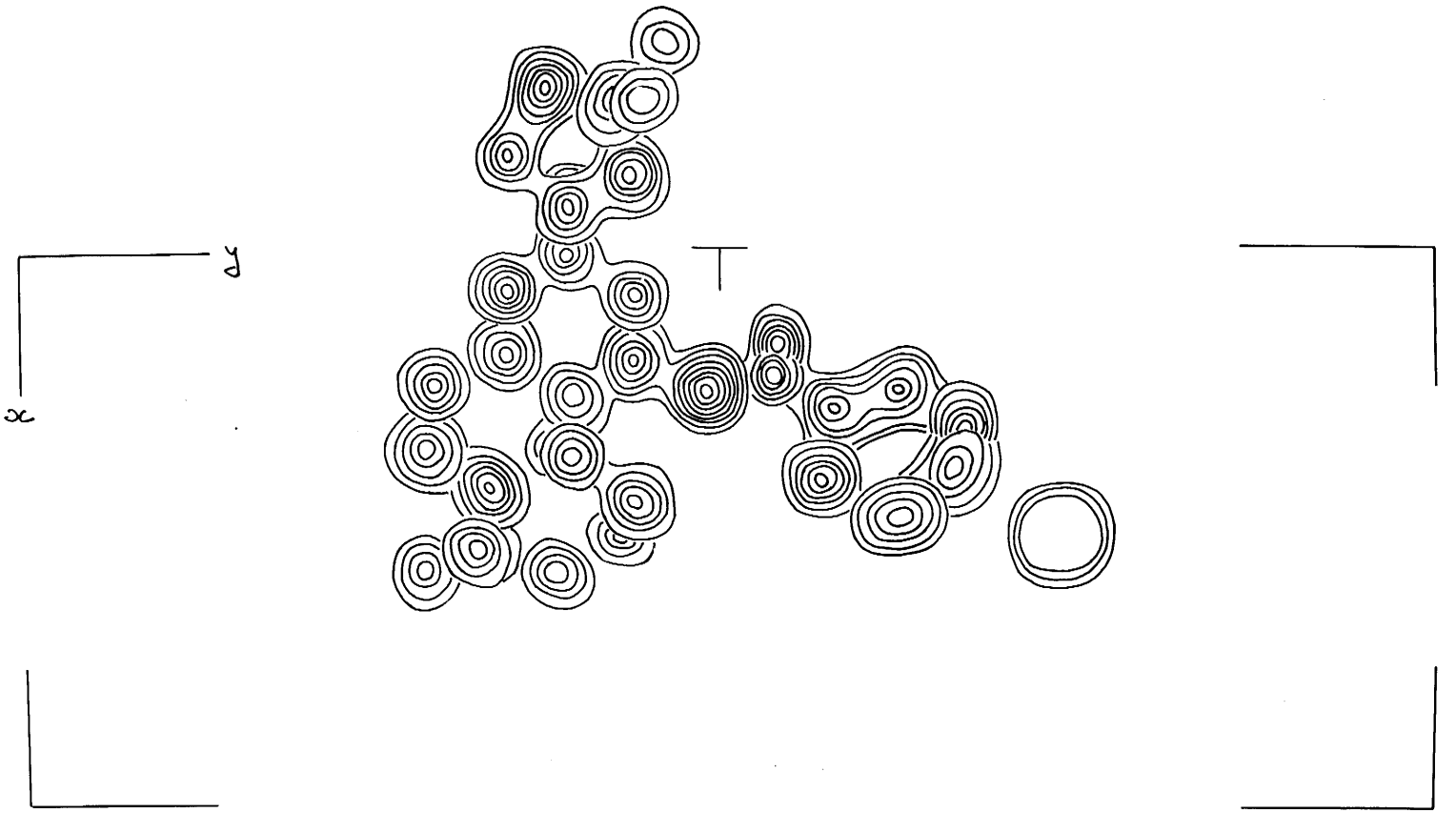

FIGURE II

Fourier diagram in projection along the c axis.

FIGURE III