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SESQUITERPENOIDS OF *WARBURGIA* SPECIES—II
UGANDENSOLIDE AND UGANDENSIDIAL (CINNAMODIAL)

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Abstract—Two crystalline sesquiterpenoids of drimane type, ugandensolide (I) and ugandensidial (II) have been isolated from the heartwood of *Warburgia ugandensis* Sprague (Canellaceae), and their structures determined. Ugandensidial proved to be identical with cinnamodial from *Cinnamosma fragrans* Baillon (Canellaceae). An interesting example of isomerization during GLC has been observed for the α-acetoxy-ketones (VII and XIV).

A SUPPLY of *Warburgia* heartwood, considered to be *W. ugandensis* Sprague, was received from Kenya through the Tropical Products Institute of London. This wood was paler in colour and less aromatic than that previously examined.[1] Solvent extraction and chromatography of the resulting oil afforded two new crystalline sesquiterpenoids; a lactone, ugandensolide (I) and a dialdehyde, ugandensidial (II). A trace amount of warburgin, the major sesquiterpenoid constituent of the previously examined heartwood oil,[1] was tentatively identified by GLC and TLC. Its presence was not confirmed by isolation.

Ugandensolide (I)

Ugandensolide crystallized as colourless needles from ethanol, with m.p. 218° and $[\alpha]_D$ +23° ($CHCl_3$). Elemental analysis and the mass spectrum indicated the formula $C_{17}H_{24}O_5$. The IR spectrum in carbon tetrachloride showed an OH band at 3600 cm^{-1} (unaltered on dilution) and CO bands at 1734 (tentatively assigned to an acetate), 1769 and 1751 cm^{-1}. In chloroform solution these bands appeared at 1750, 1760 (shoulder of slightly weaker intensity) and 1731 cm^{-1} (acetate). Similar complex shapes and solvent dependence of the CO absorption have been reported in studies of γ-lactones.[2] In the UV region ugandensolide showed absorption in ethanol at λ_{max} 214 mμ (ε, 13,000). Taken in conjunction with the IR data this suggested the presence of an αβ-unsaturated γ-lactone function.

The 100 Mc/s NMR spectrum (Fig. 1) afforded considerable structural information. The presence of an acetate was supported by a peak at 7·97 τ (3H). The OH proton at 6·43 τ was coupled, with J = 5·5 c/s, to a proton at 5·83 τ, which proved the OH to be secondary. (Exchange of the OH with deuterium oxide gave a singlet at 5·83 τ). Three tertiary Me groups were apparent from signals at 9·00 and 8·98 τ (6H) and 8·57 τ. A broadened singlet at 4·66 τ was assigned to the proton on the carbon bearing the acetate (—C<u>H</u>—OAc). Two doublets at 5·39 τ (1H) and 5·15 τ (1H), strongly coupled with J = 17·0 c/s, were assigned to the lactone methylene protons (—O—C<u>H</u>$_2$—) evidently in a dissymmetric environment. A doublet of multiplets due to a single proton at 7·47 τ with a coupling constant of approximately 12 c/s could not at first be explained.

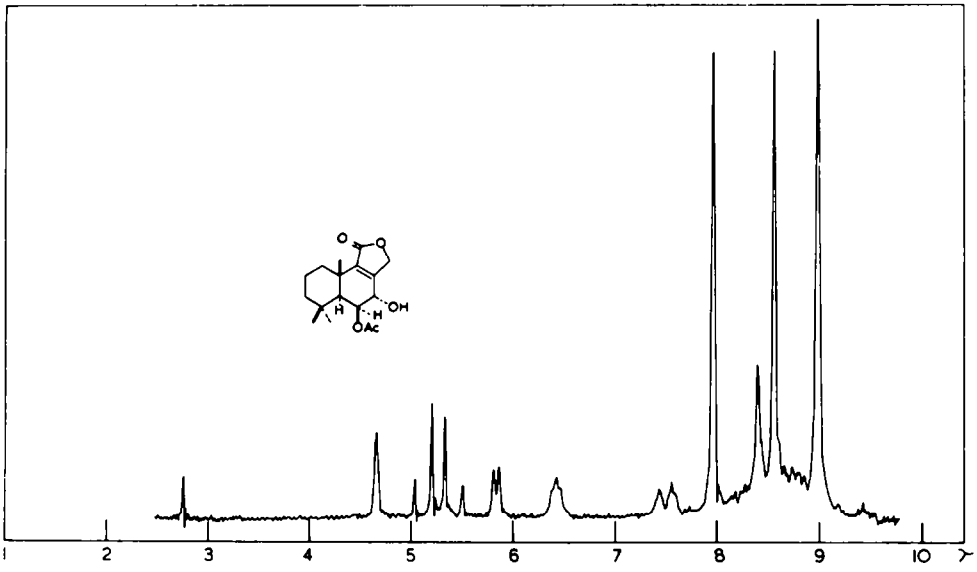


FIG. 1 100 Mc/s NMR spectrum of ugandensolide in $CDCl_3$.

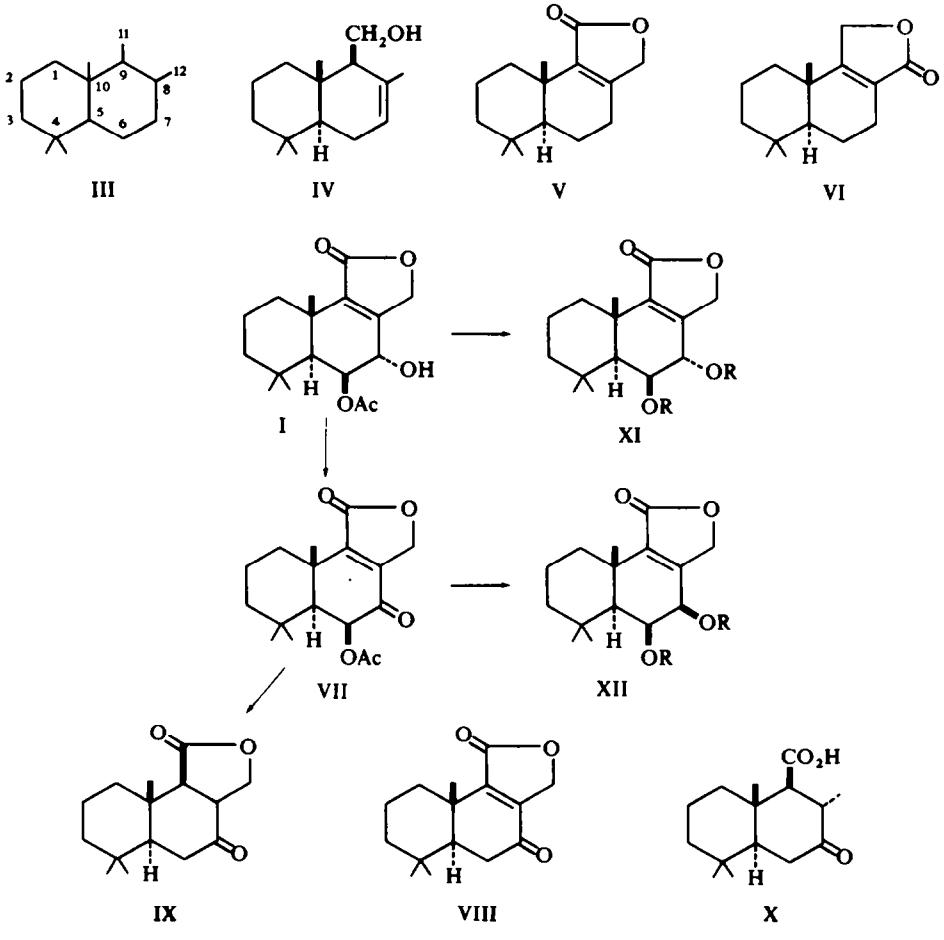
On the above rationale there were no olefinic protons and the butenolide was assumed to have a tetrasubstituted double bond. This is consistent with the resistance of ugandensolide to catalytic hydrogenation. Of the six double bond equivalents implied by the formula, $C_{17}H_{24}O_5$, the butenolide and acetate accounted for four, leaving two carbocyclic rings. The absence of secondary and vinylic Me groups virtually excluded the eremophilane carbon skeleton.[1] Three angular Me groups and a butenolide seemed best accommodated in a bicyclofarnesane (III) structure. The isolation of drimenol (IV) from extraction of the first supply of heartwood lent biogenetic support to this proposal. We therefore assigned to ugandensolide, as a working hypothesis, the basic isodrimenin (V) or confertifolin (VI)[3] skeleton with additional secondary OH and acetate functions.

The doublet of multiplets at 7·47 τ, unassigned above, was shown by double irradiation to be coupled to an unseen resonance at 8·72 τ (J ca. 12 c/s). We observed similar doublets in the spectra of butenolide degradation products of ugandensolide. Assuming the isodrimenin skeleton, the lower field doublet could be assigned to the C-1β equatorial proton in the plane of, and deshielded by, the lactone CO. The α-proton, out of this plane, is then slightly shielded, accounting for the signal at 8·72 τ. Similar data are recorded for 5α-androstan-11-one in which a coupling of 12 c/s between the C-1β proton at 7·55 τ and the shielded 1α proton at 9·22 τ is observed.[4] The spectrum of isodrimenin also shows a diffuse doublet at 7·52 τ with J ca. 13 c/s.

The C-10 angular Me resonance in isodrimenin is at 8·92 τ. In ugandensolide this Me signal is shifted to 8·57 τ implying a marked deshielding due either to the acetate or OH functions. The lactone methylene in isodrimenin gives rise to a sharp singlet at 5·58 τ. The coupling of 17·0 c/s between these protons in ugandensolide was again presumed to be due to the effect of the acetate or OH functions.

Jones' oxidation of ugandensolide gave a ketone of molecular formula $C_{17}H_{22}O_5$ (analysis and mass spectrum). IR absorption at 1698 cm^{-1} suggested a conjugated CO function. This received support from the UV absorption at 250 mμ (ε, 10,000). In the NMR spectrum the secondary acetate proton (—CHOAc) appeared as a doublet at 4·11 τ with J = 2·0 c/s proved, by double irradiation, to be coupling with a proton at 8·13 τ. This latter signal was clearly distinguishable from the saturated methylene resonances and was assigned to the 5α-(ring junction) proton. If we assume the basic isodrimenin structure and absolute stereochemistry, these observations strongly support structure VII for this ketone. The assignment of the C-6β-axial acetate is indicated by the weak coupling (2·0 c/s) between the 5α- and 6α-protons, consistent with a dihedral angle of about 60°.[4]

The signal due to the lactone methylene in the NMR spectrum of VII appeared as a singlet at 5·10 τ. The dissymmetry at this position in ugandensolide was therefore evidently mainly due to the effect of the OH function. The most significant feature of the NMR spectrum of the ketoacetate was the additional deshielding of the C-10 angular Me group to 8·35 τ. In ugandensolide this signal was at 8·57 τ and in isodrimenin at 8·92 τ. However if Zürcher's rules[4] are applied using isodrimenin as the



parent compound a value of 8·46 τ is predicted for the angular Me resonance in VII [8·92–0·183 (6β-OAc)—0·275 (7-keto group) = 8·46] which is in moderately good agreement with the observed value.

In the CO region of the IR spectrum (CCl_4 solution), bands at 1761 and 1774 cm^{-1} were assigned to the acetate and lactone respectively. The increase of 27 cm^{-1} in the acetate frequency when compared with ugandensolide can be accounted for by interaction between the ketone and acetate function as e.g. in 2α-acetoxy-5α-cholestan-3-one and the 2β-acetoxy-3-one.[5]

We considered that a correlation of the ketoacetate (VII) with either oxoisodrimenin (VIII) or its zinc and acetic acid reduction product (IX)[3] should provide a simple proof of structure VII. Reaction of VII in refluxing acetic acid with zinc dust gave a single crystalline product of molecular formula $C_{15}H_{22}O_3$ (analysis and mass spectrum) with IR maxima in carbon tetrachloride at 1712 (cyclohexanone) and 1778 cm^{-1} (butanolide). This product proved to be identical with a sample of dihydro-oxoisodrimenin by mixed m.p. determination and comparison of IR and mass spectra, optical rotation and GLC data.

Appel *et al.* had assigned a *cis*-fused lactone structure (IX; 8α-H) to dihydro-oxoisodrimenin.[3] The NMR spectrum of dihydro-oxoisodrimenin revealed a coupling of 12·5 c/s between the C-8 and C-9 ring junction protons. The C-9 proton gave a sharp doublet at 7·16 τ. The C-8 proton at 6·70 τ appeared as a complex multiplet due to additional coupling with the C-12 methylene at 5·54 τ. Irradiation at this methylene resonance gave a doublet with J = 12·5 c/s for the C-8 proton. The dihedral angle between the C-8 and C-9 protons in the *cis*-fused lactone (IX; 8α-H) is close to zero. From the Karplus equation the coupling constant should therefore have a maximum value of 10 c/s.[4] The observed coupling of 12·5 c/s better fits the *trans*-fused structure IX (8β-H) implying an epimerization at C-8 under the reaction conditions. This is supported by the coupling of 12·0 c/s between the C-8 and C-9 protons of the 8α-Me ketoacid (X).* Regardless of the configuration of dihydro-oxoisodrimenin at C-8, the identity of our product with that obtained from isodrimenin, together with the physical data cited, determined the structure and absolute configuration of the ketoacetate as VII, and of ugandensolide as I or its C-7 epimer.

The following evidence permits assignment of the 7α-OH configuration in ugandensolide. Hydrolysis of ugandensolide with sulphuric acid in methanol gave a diol XI (R = H), $C_{15}H_{22}O_4$ (analysis and mass spectrum). The IR spectrum in chloroform showed two bands due to the lactone in the CO region, at ν_{max} 1761 and 1751 cm^{-1}. Reacetylation with acetic anhydride in pyridine gave the diacetate XI (R = Ac) also obtained by acetylation of I. Treatment of the ketoacetate (VII) with sodium borohydride in methanol resulted in reduction and hydrolysis to a second diol XII (R = H) characterized by elemental analysis, IR and mass spectra. Acetylation of XII (R = H) gave the diacetate XII (R = Ac). Examination of the crystallization mother liquors from diol XII (R = H), by acetylation of a portion for GLC, suggested that the isomeric diol XI (R = H) accounted for not more than 5% of the total hydride reduction product.

The distinction between diols XI (R = H) and XII (R = H) could have been due

* A sample of (X) was available from previous work.[12]

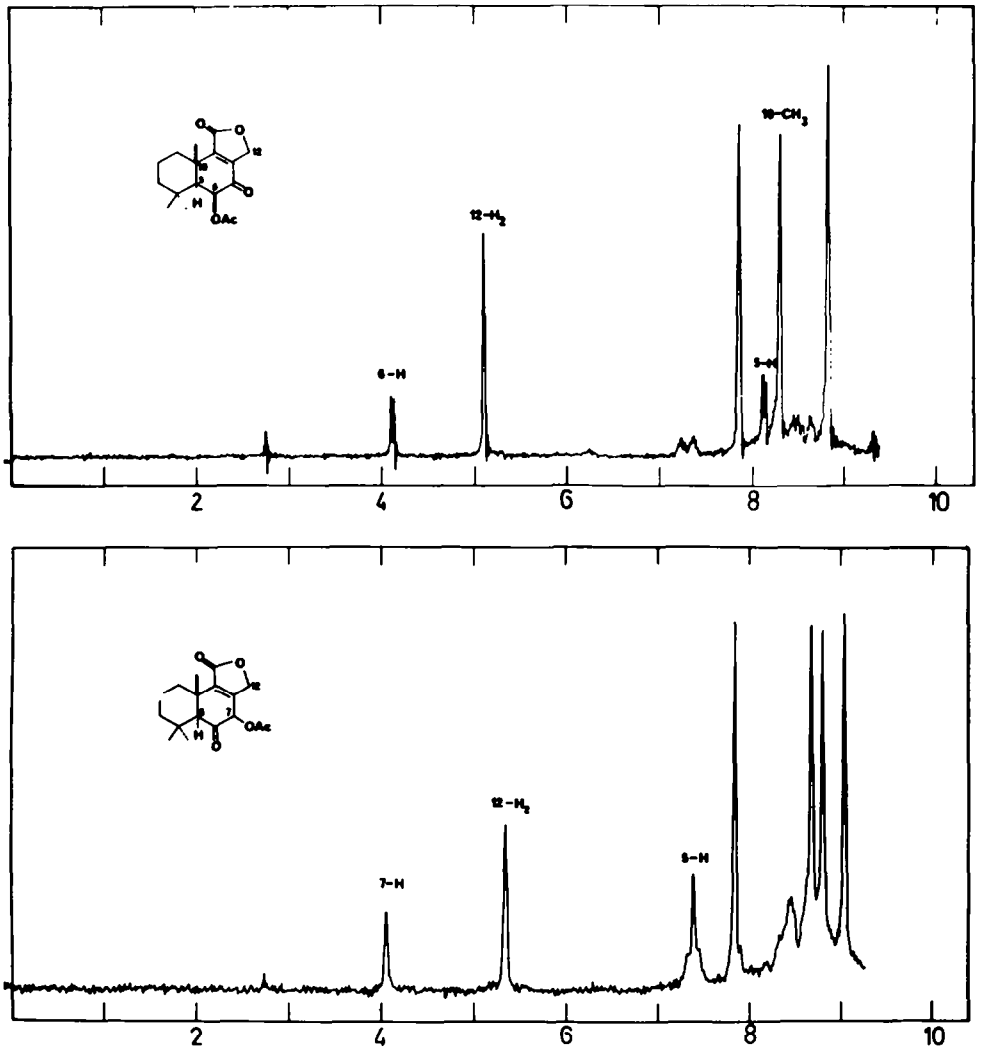
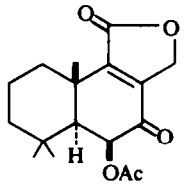


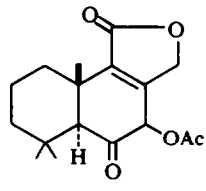
FIG. 2 100 Mc/s NMR spectra of isomeric keto-acetates VII and XIV in $CDCl_3$.

to their isomeric nature at either or both the C-6 and C-7 positions. However the NMR spectra of the corresponding diacetates showed no significant coupling between the C-5α- and C-6 protons, proving the axial nature of the C-6 OH substituent, and indicating that no epimerisation had taken place at C-6 in the borohydride reduction of VII. The diols XI (R = H) and XII (R = H) were therefore epimeric at C-7. Hydride attack on the ketoacetate (VII) would be expected to occur predominantly from the less hindered α-face leading to the *cis*-6β,7β-diol (XII). Ugandensolide (I) and diol XI (R = H) therefore have the *trans*-6β-7α-stereochemistry implied in the formulae.

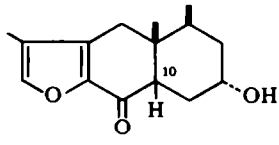
Evidence supporting the stereochemical assignments to diols XI (R = H) and XII (R = H) was obtained from their reaction with phenylboronic acid.[6] A cyclic boronate ester was formed from the *cis*-6β,7β-diol XII (R = H) and was identified by GC–MS. In accordance with the diaxial geometry assigned to diol XI (R = H) no cyclic ester formed in this instance.



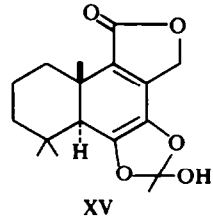
VII



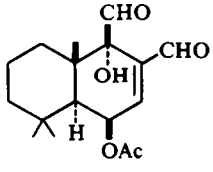
XIV



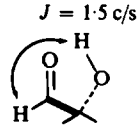
XIII



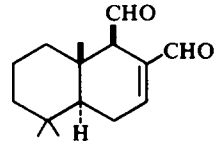
XV



II



XVII



XVI

Rearrangement of the keto-acetate (VII)

GLC of the ketoacetate (VII) on the phase 1% QF-1 at 200° revealed an "impurity" of 15% which was proved to be isomeric with VII by GC–MS. Repeated crystallization did not reduce the relative amount of this second component. Convincing proof that its presence was due to a thermal isomerization came from injection of VII into the volatilization zone, kept at 240°, at zero gas flow. After thirty seconds the gas flow was restored and it was found that the original ratio of 85:15 had become 30:70. We had previously observed isomerization under GLC conditions of the *cis*-furano-ketoalcohol (XIII; 10β-H) to the *trans*-isomer (XIII; 10α-H). We inferred that an

explanation of the above results might be the conversion of VII to its C-6 equatorial acetate isomer.

Several attempts to reproduce this isomerization on a preparative scale were made. Treatment of VII under mild basic conditions resulted in hydrolysis and some decomposition. Reacetylation returned VII unchanged. Heating in a sealed capillary tube for one minute at 150° produced nearly complete isomerization but with substantial decomposition. The ketoacetate was also heated in various high-boiling solvents but no clearly-defined increase in isomer content was observed by GLC. An isomerization procedure based on GLC conditions proved more successful. The ketoacetate was absorbed on to GLC support, placed in a Pyrex glass tube, sealed under a vacuum of 0·05 mm and heated at 175° for 45 min. Preparative TLC led to separation of starting material from the slightly more polar product, which was found to have the molecular formula $C_{17}H_{22}O_5$ (analysis and mass spectrum) and was therefore isomeric with VII. It was, however, immediately obvious that it was not the C-6 epimer. The IR spectrum in carbon tetrachloride showed bands at 1773, 1768 and 1745 cm^{-1}, showing the absence of a conjugated ketone function. This was confirmed by UV absorption at 210 mμ (ε, 11,000) which corresponded to the butenolide chromophore alone. The rearranged ketoacetate (XIV) seemed a possible structure. Non-bonded dipolar interaction between the ketone and acetate could account for the high values of their infrared carbonyl frequencies. There was no obvious driving force for the transformation VII to XIV. Nevertheless a comparison of the NMR spectra of the two compounds showed that the isomer XIV was in fact the product (Fig. 2). The 5α-proton signal, a doublet at 8·13 τ in the spectrum of VII, was in XIV a singlet at 7·39 τ superposed on the doublet of multiplets due to the C-1β proton. A slightly broadened singlet at 4·05 τ was assigned to the C-7 proton coupling with the C-12 lactone methylene protons at 5·35 τ (confirmed by double irradiation). The geminal Me signals in the spectrum of XIV had different chemical shifts, due to the anisotropy of the C-6 ketone function. No reliable assignment of the three tertiary methyl resonances at 8·68, 8·81 and 9·04 τ could be made.

Rearrangement of 2α-acetoxy-cholestan-3-one to the 3β-acetoxy-2-one (in 20% yield) occurs on active alumina.[5] Similarly 4α-acetoxy-cholest-5-en-3-one is isomerized to the 3β-acetoxy-4-one.[7] In both cases the conversion is considered to occur by enolisation followed by acyl migration probably via a cyclic intermediate. If reaction of VII to XIV goes via an intermediate of type XV assignment of configuration at C-7 is not justified. However XIV proved to be resistant to deacetoxylation with zinc and acetic acid under conditions which readily reduced the 6β-acetoxy-7-ketone (VII). Elimination of the function α- to the ketone in reactions of this type occurs most readily if this substituent is axial, or can adopt a conformation in which it is perpendicular to the plane of the C=O double bond.[8] This therefore suggests a 7β-oriented acetate function in XIV.

Ugandensidial (*cinnamodial*) (II)

The dialdehyde ugandensidial, a major component of the heartwood extract, was eluted after ugandensolide during chromatography. The structure as II was deduced as outlined below from spectrometric data together with an assumed biogenetic relationship with ugandensolide. At this stage we learned through Dr. K. H. Overton of the then unpublished work[9] of Professor L. Canonica, Dr. G. Jommi and their

co-workers, on the structure of cinnamodial isolated from *Cinnamosma fragrans* Baillon (Canellaceae).* The two compounds proved to be identical, and the name cinnamodial is adopted.

The molecular formula from elemental analysis was $C_{17}H_{24}O_5$. This was confirmed by the mass spectrum although the molecular ion was extremely weak, being less than 1% of the base peak. Single proton resonances at 0·24 and 0·54 τ in the NMR spectrum (Fig. 3) led to the conclusion that the compound was a dialdehyde. CO bands in the IR spectrum at 1746, 1724 and 1698 cm^{-1} were assigned to acetate, saturated aldehyde and conjugated aldehyde functions respectively. The presence of an intramolecularly H-bonded OH function was indicated by a band at 3469 cm^{-1} (for CCl_4 soln) unaffected by dilution. The UV spectrum in cyclohexane showed λ_{max} 219 mμ (ε, 14,000).

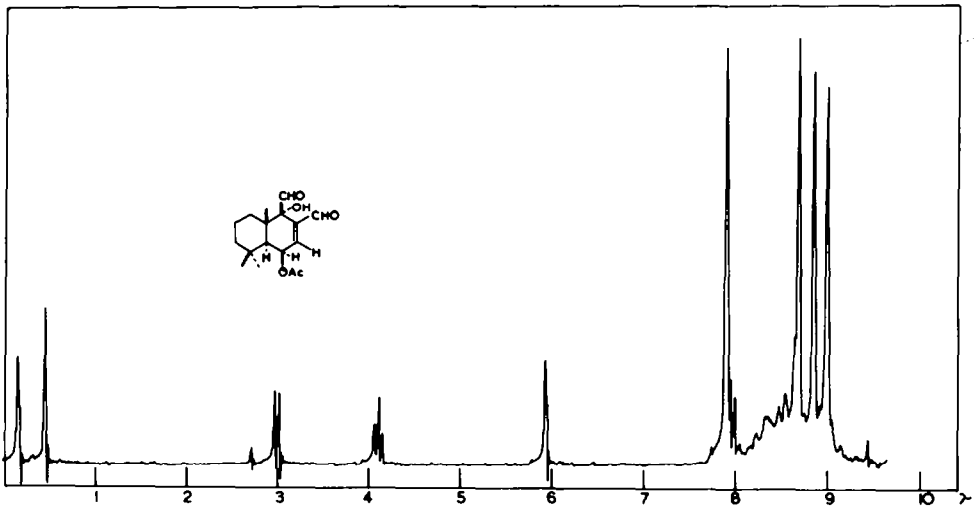


FIG. 3 100 Mc/s NMR spectrum of ugandensidial (cinnamodial) in $CDCl_3$.

Returning to the NMR spectrum,† the presence of three tertiary Me groups (8·69, 8·85 and 9·00 τ) and an acetate (7·91 τ) suggested a relationship with ugandensolide. Conjugated and non-conjugated aldehyde functions could then only be accommodated at C-8 and C-9 as in polygodial (XVI).[10] The acetate and OH functions were assigned as represented in formula II. The C-6 proton appeared as a triplet at 4·10 τ due to identical couplings of 5·0 c/s with each of the C-5α- (7·97 τ) and C-7 (ethylenic) protons (2·99 τ). The magnitude of the coupling constant between the protons at C-5 and C-6 made probable the assignment of the C-6 acetate as axial.[4]

The most striking feature of the NMR spectrum was a coupling of 1·5 c/s between the OH proton at 5·93 τ and the lower field aldehyde resonance (0·24 τ). This seemed best explained by a coupling with the proton of the tertiary aldehyde function in the

* Through the courtesy of Dr. Jommi, comparisons of physical data for samples of ugandensidial and cinnamodial were made in Milan.

† Double irradiation experiments confirmed all the couplings discussed.

planar but "non-W" conformation (XVII) which also accounted for the strong intramolecular H-bonding of the OH function.

The phylogenetic status of the Magnoliales, as putative progenitors of the other orders of angiosperms,[13,14] lends interest to their chemical constituents as possible taxonomic characters. Drimenol and its congeners have hitherto been found principally in the genus *Drimys* (Winteraceae): indeed, the only other instances known to us of the occurrence of drimenol are that cited in the present work,[1] and its isolation

TABLE 1. ISOMERIZATION OF KETOACETATE (VII) DURING GLC[a]

Period of stopped gas flow (min. after injection)[b]	Estimated ratio of VII to XIV from relative peak areas
0	85:15
0·5	30:70
2·0	20:80
8·0[c]	5:95

[a] Effected with a 4-ft column packed with 1% QF-1 on silanized Gas-Chrom P (100–120 mesh) 200°: gas flow rate 40 ml/min, established after the intervals indicated. Pye Argon Chromatograph.

[b] Injection into preheater zone at 240°.

[c] The chromatogram showed minor peaks of shorter retention, evidently due to decomposition.

from the livermoss *Bazzania trilobata* L.[15] There are relatively few reported examples of bicyclofarnesane-type sesquiterpenoids occurring outside the Magnoliales: examples are polygodial[10] (tadeonal[16]) in *Polygonum hydropiper* (Polygonaceae), and the fungal products tauranin[17] and pebrolide.[18] The finding of drimanic sesquiterpenoids in two genera of the Canellaceae, *Warburgia* and *Cinnamosma*[9,11] therefore appears to strengthen the somewhat tentative[13,14] taxonomic association of the Canellaceae and Winteraceae. The co-occurrence of drimane and eremophilane derivatives in *Warburgia* is an unusual example of the production of different skeletal types within one genus, in that eremophilane sesquiterpenoids have not previously been found in the Magnoliales, and although discovered originally in the Myoporaceae, appear to be characteristic constituents mainly of certain non-woody plants, notably in the Compositae and Valerianaceae. Recent discoveries of new natural eremophilane derivatives[19] suggest that this class of sesquiterpenoids is more widely distributed than was formerly apparent.

EXPERIMENTAL

General experimental details are given in the preceding paper.[1]

Isolation of ugandensolide and ugandensidial

Dried powdered heartwood of *Warburgia ugandensis* Sprague (6·5 kg) was extracted with EtOH (35 l.) for 6 days at room temp. The EtOH soln was evaporated and the extract taken up in $CHCl_3$ leaving an insoluble residue (26·0 g). The $CHCl_3$ extract was dried and evaporated giving an oil (90·0 g). GLC (1% QF-1) and GC–MS of the cold EtOH extract indicated a complex mixture and the presence of 3 principal

sesquiterpenoid components not observed in an earlier examination of a different sample of *Warburgia ugandensis* heartwood.[1] One of these substantially decomposed during preparation of the large scale extract and chromatography as noted below was directed specifically at the isolation of the two remaining principal constituents.

The total oil (90·0 g) was chromatographed on silicic acid (500 g): 8 fractions were taken as follows: pet ether (1 × 2·0 l.), benzene (1 × 2·0 l.), benzene–$CHCl_3$ (1:1) (1 × 2·0 l.), $CHCl_3$ (3 × 2·0 l.), $CHCl_3$–EtOAc (1:1) (1 × 2·0 l.), EtOAc (1 × 2·0 l). Ugandensidial was present in the $CHCl_3$ fractions 4, 5 and 6 while ugandensolide was the major component of fraction 6. Fraction 6 (19·2 g) was rechromatographed on alumina (1·0 kg, grade III) with an EtOAc–pet ether gradient elution. Ugandensolide (4·55 g) crystallized from fractions eluted by EtOAc–pet ether (3:7) and was recrystallized from EtOH as colourless needles: m.p. 218°; $[\alpha]_D$ +23°; λ_{max} (EtOH) 214 mμ (ε, 13,000); ν_{max} (CCl_3) 3600 (unaltered on dilution), 1769, 1751 and 1734 cm^{-1}; ν_{max} ($CHCl_3$), 1760, 1750 and 1731 cm^{-1}. (Found: C, 66·12; H, 7·79. $C_{17}H_{24}O_5$ requires: C, 66·21; H, 7·84%).

Ugandensidial (2·7 g) separated from fractions eluted by EtOAc–pet ether (1:1) and was recrystallized from EtOAc–pet ether as colourless needles: m.p. 137–140°; $[\alpha]_D$ −407°; λ_{max} (cyclohexane) 219 mμ (ε, 14,000); ν_{max} (CCl_4) 1746, 1724 and 1698 cm^{-1}. (Found: C, 66·45; H, 7·85. $C_{17}H_{24}O_5$ requires: C, 66·21; H, 7·84%).

Attempted catalytic hydrogenation of ugandensolide

Ugandensolide was recovered unchanged [as judged by GLC on the phase 1% SE-30 and TLC with the system MeOH—$CHCl_3$ (3:97)] after attempted hydrogenation under the following conditions:

(a) in EtOAc with 10% Pd–C catalyst for 6 hr

(b) in MeOH with PtO_2 catalyst for 14 hr

(c) in EtOH at 45° and 4 atm press with PtO_2 catalyst for 24 hr

Hydrogenation in AcOH with PtO_2 catalyst for 20 hr gave a mixture comprising about 60% of starting material with two other main products, not further examined.

trans-6β,7α-*Diol* (XI, R = H) *and diacetate* (XI, R = Ac)

Ugandensolide (60 mg) was dissolved in MeOH (10 ml) with 3N H_2SO_4 aq (0·8 ml) and refluxed for 48 hr, when TLC with EtOAc–pet ether (1:1) showed nearly complete conversion to XI (R = H), R_f 0·15; cf. ugandensolide, R_f 0·45. The soln was concentrated, diluted with water (10 ml), extracted with ether, washed, dried and evaporated. Crystallization of XI (R.= H) from EtOH gave colourless needles (36 mg) of m.p. 260–264° (sealed capillary); ν_{max} ($CHCl_3$) 1761, 1751 cm^{-1}; ν_{max} (Nujol) 3250–3500, 1725 cm^{-1}. (Found: C, 67·51; H, 8·34, $C_{15}H_{22}O_4$ requires: C, 67·65; H, 8·33%).

A small scale reacetylation of XI (R = H) with pyridine–Ac_2O (1:2) at 60° for 20 hr gave a single product, not distinguishable by GLC (1% QF-1) and TLC with EtOAc–pet ether (1:1) from that obtained below (XI, R = Ac) by acetylation of ugandensolide.

Ugandensolide (50 mg) was heated at 60° in pyridine (1 ml) and Ac_2O (2 ml) for 20 hr. The bulk of the solvent was evaporated and the mixture diluted with water, extracted with ether; the extract was washed, dried and evaporated to give an oil [(XI, R = Ac); 55 mg]. This was crystallized from pet ether–EtOAc as colourless prisms and had m.p. 104–105°; ν_{max} (CCl_4) 1769, 1752 cm^{-1}. 100 Mc/s NMR ($CDCl_3$) τ values: 8·97 (6H), 8·51 (3 H), 7·95 (3 H), 7·90 (3 H), 7·44 (1 H, d of multiplets J ca. 13 c/s), 5·36 (2 H, incompletely resolved d), 4·84 (1 H, broad s), 4·45 (1 H, broad s). (Found: C, 65·18; H, 7·36. $C_{19}H_{26}O_6$ requires: C, 65·13; H, 7·48%).

Ketoacetate (VII)

Ugandensolide (1·20 g) was dissolved in acetone (15 ml). CrO_3 in dil H_2SO_4 aq (Jones' reagent)[20] (1·5 ml) was added over 1 hr with stirring at 0°. Reaction was continued for a further 2 hr at 0°. Addition to ice and water (100 ml) was followed by ether extraction. The ethereal soln was washed, dried and evaporated to give a solid product VII (1·15 g). Recrystallization from EtOH gave colourless prisms: m.p. 135–138°; ν_{max} (CCl_4) 1774, 1761 and 1698 cm^{-1}; λ_{max} (EtOH) 250 mμ (ε, 10,000); λ_{max} (0·05 N NaOH in EtOH) initially 230 mμ (ε, 5000) shifting to 245 mμ (ε, 8500 after 30 min); λ_{max} (reacidified—HCl) 224 mμ (ε, ca. 5000) and 250 mμ (ε, ca. 2500). 100 Mc/s NMR ($CDCl_3$) τ values: 8·89 (6 H), 8·35 (3 H), 8·13 (1 H, d J = 2·0 c/s), 7·90 (3 H), 7·29 (1 H, d of multiplets J ca. 13 c/s), 5·10 (2 H), 4·11 (1 H, d J = 2·0 c/s). MS M^+ ion m/e 306 (14%), base peak m/e 43. (Found: C, 66·39; H, 7·02. $C_{17}H_{22}O_5$ requires: C, 66·65; H, 7·24%).

cis-6β,7β-*Diol* (XII, R = H) *and diacetate* (XII, R = Ac)

Ketoacetate VII (180 mg) was dissolved in MeOH (10 ml). $NaBH_4$ (100 mg) was added in portions over 30 min. The mixture was stirred for 20 hr at room temp, diluted with water, extracted with ether and dried. Evaporation of the ether gave a colourless solid XII (R = H; 140 mg), recrystallized as colourless needles from MeOH to m.p. 240–245° (sealed capillary); ν_{max} ($CHCl_3$) 1760 (sh), 1751 cm^{-1}. MS M^+ ion 266 (base peak). (Found: C, 67·51; H, 8·34. $C_{15}H_{22}O_4$ requires: C, 67·65; H, 8·33%).

Diol XII (R = H; 25 mg) was dissolved in pyridine (0·5 ml) with Ac_2O (1 ml) and heated for 20 hr at 60°. The solvents were removed; water was added and the mixture extracted with ether. The ethereal soln was washed, dried and evaporated to give a colourless solid XII (R = Ac; 24 mg) recrystallized from MeOH as colourless needles: m.p. 222–223°; ν_{max} (CCl_4) 1771 and 1750 cm^{-1}; 100 Mc/s NMR ($CDCl_3$) τ values: 8·99, 8·96 (6 H); 8·43 (3 H), 7·96 (3 H), 7·92 (3 H), 7·47 (1 H, d of multiplets, J ca. 13 c/s), 5·37 (2 H, incompletely resolved d), 4·27 (1 H, incompletely resolved d, J ca. 5 c/s), 4·09 (1 H, d J = 5·0 c/s). (Found: C, 65·08; H, 7·56, $C_{19}H_{26}O_6$ requires: C, 65·13; H, 7·48%).

Acetylation of the crystallization liquors from diol XII (R = H; ca. one third of the total reduction product) gave 80% XII (R = Ac), 15% of a component indistinguishable from XI (R = Ac) and 5% of an unidentified component as judged by GLC (1% QF-1).

Zinc and acetic acid reduction of ketoacetate (VII)

Ketoacetate VII (200 mg) was dissolved in AcOH (15 ml) and Zn dust (400 mg) added. The mixture was refluxed for 2 hr then filtered: cold Na_2CO_3 aq was added to make the soln just basic. This was then extracted with ether and the extract washed and dried. Evaporation of the solvent gave a colourless solid product IX (170 mg). This was recrystallized from benzene–pet ether: m.p. 123–126°; $[\alpha]_D$ −119° (benzene); ν_{max} (CCl_4) 1778, 1712 cm^{-1}; 100 Mc/s NMR spectrum ($CDCl_3$) τ values: 9·14 (3 H) 9·07 (6 H), 7·54 (2 H, complex m), 7·16 (1 H, d J = 12·5 c/s), 6·70 (1 H, complex m), 5·54 (2 H, complex m). MS M^+ ion at *m/e* 250 (3%), base peak *m/e* 85. (Found: C, 71·91; H, 8·73. $C_{15}H_{22}O_3$ requires: C, 71·97; H, 8·86%). Identity of IX with dihydrooxoisodrimenin[3] was proved by their undepressed mixed m.p., by comparison of IR (KCl disc) MS and $[\alpha]_D$ data. The two samples were also found to have identical GLC behaviour on the phases 5% QF-1, 5% Apiezon L and 2% Carbowax 20M.

Treatment of diols (XI, R = H) *and* (XII, R = H) *with phenylboronic acid*

A stock solution of phenylboronic acid (10 mg/ml in acetone) was prepared. Solutions of XI (R = H) and XII (R = H) in pyridine were prepared in concentrations suitable for GLC, and 1·5 molar equivs of phenylboronic acid soln added to each. After 2 hr at room temp, the reaction mixtures were examined directly by GLC, and later GC–MS, on the phase 1% SE-30. A cyclic boronate ester was formed from XII (R = H). MS M^+ ion ($C_{21}H_{25}BO_4$) at *m/e* 352 (65%), base peak *m/e* 41. No corresponding component was recorded from the reaction of XI (R = H).

Conversion of the 6β-*acetoxy-7-ketone* (VII) *to the* 7β-*acetoxy-6-ketone* (XIV)

Injection of pure (TLC) ketoacetate VII on 1% QF-1 at 200° resulted in partial conversion to the isomer XIV. GC–MS confirmed the isomeric nature of the two peaks recorded. That the ratio of VII to XIV was thermally dependent was shown by injection into the pre-heater zone (240°) with the gas flow stopped for various times (Table 1). The progress of subsequent attempts to prepare the isomer XIV could be followed by GLC.

Unsuccessful attempts were made to isomerize VII to XIV by means of base or acid catalysis and by heating at 160° in a variety of high-boiling solvents.

Ketoacetate VII (2 mg) in a sealed capillary was heated at 150° for 30 sec. The material immediately darkened on melting. GLC (1% QF-1) indicated almost complete conversion to XIV. However TLC revealed extensive decomposition to polar products not recorded on GLC.

Ketoacetate VII (250 mg) was dissolved in ether (50 ml) and a packing from a discarded column (1·5 g–5% QF-1 on Gas Chrom Q) was added. The solvent was evaporated and the compound was thus evenly absorbed on the packing. The mixture was placed in a Pyrex glass tube which was sealed under a vacuum of 0·05 mm and heated for 45 min at 175°. The products (295 mg), contaminated with QF-1 phase, were recovered by elution with ether. GLC indicated a marked enhancement in concentration of isomer XIV. TLC with EtOAc–pet ether (1 : 2) indicated two major components: starting material, R_f 0·45 and product XIV, R_f 0·30 together with at least three minor components, estimated as 10% of the total material recovered. Preparative TLC allowed the separation of starting material (150 mg) and product (55 mg). The

recovered starting material was pyrolysed again, and crude product (30 mg) and starting material (90 mg) were recovered in a similar manner.

Crystallization of XIV from EtOH gave colourless needles: m.p. 179–181°; ν_{max} (CCl_4) 1773, 1768 and 1745 cm^{-1}; λ_{max} (EtOH) 210 mμ (ε, 11,000); λ_{max} (0·05 N NaOH in EtOH) 243 mμ (ε, 13,000 after 10 min) and 455 mμ (ε, ca. 1500); λ_{max} (reacidified—HCl) 223 mμ (ε, ca. 11,000) 252 mμ (ε, ca. 4000) and 347 mμ (ε, ca. 2000). MS M^+ ion *m/e* 306 (base peak). 100 Mc/s NMR ($CDCl_3$) τ values: 9·04 (3 H), 8·81 (3 H), 8·68 (3 H), 7·83 (3 H), 7·39 (1 H), 7·38 (1 H, d of multiplets *J*, ca. 12 c/s), 5·35 (2 H, slightly broadened s), 4·05 (1 H, slightly broadened s). (Found: C, 66·48; H, 6·99. $C_{17}H_{22}O_5$ requires: C, 66·65; H, 7·24%).

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