Structure of the Diterpene Clerodendrin A

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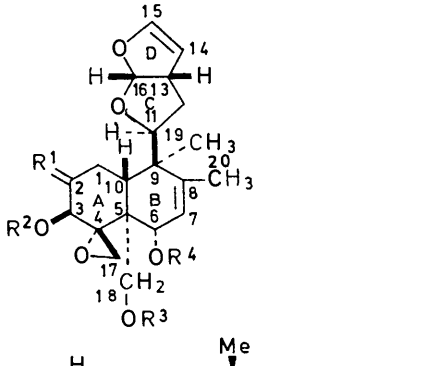
Clerodendrin A (I), a bitter principle of *Clerodendron tricotomum* Thunb. and an antifeeding repellent, is a diterpene with the clerodon skeleton as in clerodin (II). On oxidation with sodium periodate the dihydro-tetraol (XXVI) gave the acetal (XXVII). The formation of the acetal revealed the relative configuration of the epoxide ring and the 18-hydroxy-group. The c.d. and o.r.d. curves of the αβ-unsaturated ketone (XXXII), obtained by treatment of (XXVII) with manganese dioxide, showed a positive Cotton sign. Therefore, compound (I) has the configuration antipodal to that of clerodin. This was confirmed by *X*-ray analysis of the *p*-bromobenzoate of the chlorohydrin (XXII).

CLERODENDRIN A (I),[1] a bitter principle of *Clerodendron tricotomum* Thunb. and an antifeeding repellent for the larvae of *Spodoptera litura* F.,[2] is a diterpene which has the clerodon skeleton. Strong evidence for its constitution was provided by chemical and physicochemical data. The constitution and absolute configuration of clerodendrin A have been confirmed as (I) by *X*-ray crystallographic studies.[3]

Clerodendrin A, m.p. 164—165°, $C_{31}H_{42}O_{12}$, is a neutral compound with a hydroxy-group and ester carbonyl groups [$\nu_{max.}$ (KBr) 3600 and 1740 cm^{-1}]. In the n.m.r. spectrum † of (I), there were signals for three acetyl groups at δ 1·98—2·11 for one tertiary methyl and one vinyl methyl group at δ 1·22(s) and 1·69(s), respectively. Two triplets at δ 4·79 and 6·43 were attributed to the protons of the vinyl ether group.[4] These data suggested a structure closely related to clerodin (II) a bitter principle of *Clerodendron infortunatum*.[5]

Alkaline hydrolysis of (I) under mild conditions gave clerodendrin A tetraol (III), m.p. 250° (decomp.), acetic acid, and a hydroxy-acid (IVa), m.p. 71—72°. The hydroxy-acid was converted to its *p*-bromophenacyl ester (IVb), m.p. 86—87°. Although the molecular ion peak of the ester was not detected in the mass spectrum, the ester was shown to be *p*-bromophenacyl 2-hydroxy-2-methylbutyrate from i.r. and n.m.r. spectra, $\nu_{max.}$ (KBr) 1730 and 1695 cm^{-1}, δ 0·82 (3H, t, *J* 7·5 Hz, CH_2CH_3), 1·45 [3H, s, $C(OH)CH_3$], 1·74 (2H, m due to adjacent asymmetric carbon atom,[6] CH_2CH_3), 2·90 (1H, s, OH), 5·26 (2H, s, OCH_2CO), and 7·54 and

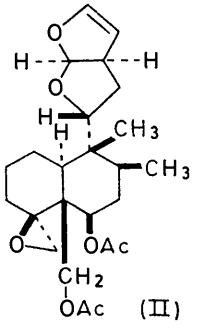


(I) R^1 = H/OH, R^2 = Et—C(Me)(OAc)—CO, R^3 = R^4 = Ac

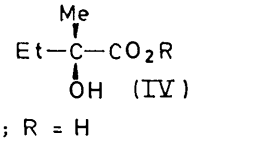
(III) R^1 = H/OH, R^2 = R^3 = R^4 = H

(XXIV) R^1 = H/OAc, R^2-R^4 as (I)

(XXV) R^1 = O, R^2-R^4 as (I)



(II)



(IV)

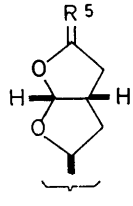
a; R = H

b; R = $CH_2COC_6H_4Br$

(V) R^1-R^4 as (I), R^5 = H_2.

(VI) R^1-R^4 as (I), R^5 = O

(VII) R^1-R^4 as (I), R^5 = H/OMe



(XXVI) R^1 = H/OH, R^2 = R^3 = R^4 = H, R^5 = H_2

(XXXVI) R^1 = O, R^2-R^4 as (I), R^5 = H_2

† Detailed n.m.r. data are listed in Supplementary Publication SUP No. 20462 (7 pp.). For details of supplementary publications see Notice to Authors No. 7 in *J. Chem. Soc.* (*A*), 1970, Issue 20.

[1] For a preliminary account see N. Kato, S. Shibayama, K. Munakata, and C. Katayama, *Chem. Comm.*, 1971, 1632.

[2] N. Kato, M. Shibayama, M. Takahashi, and K. Munakata, *Agric. Biol. Chem. Japan*, 1972, **36**, 2577.

[3] N. Kato, K. Munakata, and C. Katayama, *J.C.S. Perkin II*, 1973, 69.

[4] L. M. Jackmann and S. Sternhell, 'Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry,' Pergamon, Oxford, 1969, pp. 187, 316

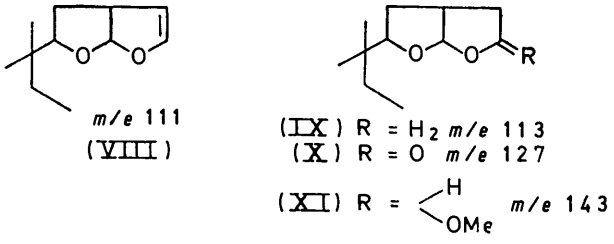
[5] D. H. R. Barton, H. T. Cheung, A. D. Cross, L. M. Jackman, and M. Martin-Smith, *Proc. Chem. Soc.*, 1961, 76; *J. Chem. Soc.*, 1961, 5061; G. A. Sim, I. C. Paul, T. A. Hamor, and J. M. Robertson, *ibid.*, p. 75; I. C. Paul, G. A. Sim, T. A. Hamor, and J. M. Robertson, *ibid.*, 1962, 4133.

[6] P. M. Nair and J. D. Roberts, *J. Amer. Chem. Soc.*, 1957, **79**, 4565.

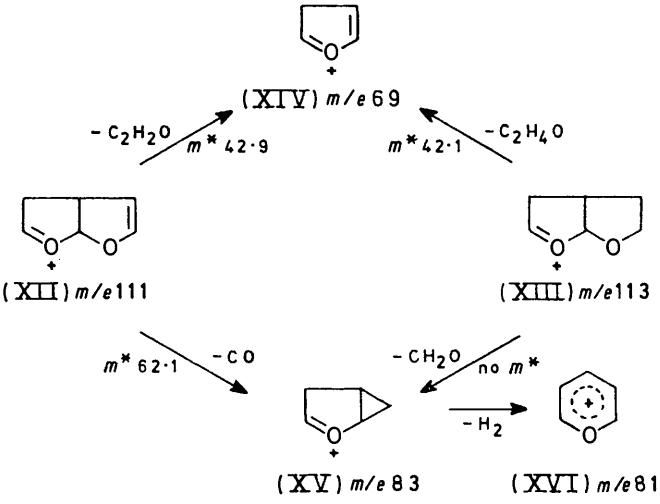
7·68 (4H, dd of A_2B_2, J 9·0 Hz, ArH). The absolute configuration of this acid was determined as *R*-(—) from the specific rotations of the free acid, $[\alpha]_D$ —7·1° ($CHCl_3$), and its phenacyl ester, $[\alpha]_D$ —3·1° ($CHCl_3$), by comparison with data reported for authentic samples of known absolute stereochemistry.[7] The same acid with the *S*-configuration has been obtained from the bitter principle of glaucarubin [8] and from the veratrum alkaloids.[9]

The n.m.r. spectra of (I) and its derivatives showed two well resolved triplets for vinyl ether protons at δ *ca.* 4·7 and 6·4 (J 2·6 Hz) and one multiplet at *ca.* 3·5. The interactions of these protons were revealed by spin-decoupling experiments. Irradiation of H-13 of (I), which appeared as a broad signal at δ 3·56, eliminated couplings of 2·6 Hz to 14- and 15-H (t, J 2·5 Hz) of the enol double bond and the coupling of 6·1 Hz to 16-H at δ 6·05. The signal for H-16 shifted upfield [5] *ca.* 0·4 p.p.m. in the dihydro-derivative (V), m.p. 174—176°, which was obtained by catalytic hydrogenation of (I). Thus, this proton suffered a large deshielding effect due to the anisotropy of the O–C–O system [5,10] and the enol double bond.[5] The dihydrofuran group gave a hemiacetal intermediate by treatment with acetic acid followed by rapid hydrolysis with water and oxidation of this by chromic acid afforded a γ-lactone (VI), m.p. 169·5—170·5°, $\nu_{max.}$ (KBr) 1790 cm^{-1}.[11] A similar reaction of the enol ether double bond was found in the case of catalytic hydrogenation of (I) in methanol, when the methanol adduct (VII), m.p. 187·5—188·5°, was obtained.*

Mass spectral analyses have been of assistance in extending the partial structure from the dihydrofuran ring to a tetrahydrofurofuran ring [C, D rings in (I)]. An intense peak containing rings C and D at *m/e* 111 in



the spectra of (I) and its derivatives was shifted to an intense peak of *m/e* 113 in the dihydro-derivative (V) while the derivatives (VI) and (VII) showed corresponding fragment ions at *m/e* 127 and 143, respectively. These characteristic ions suggested the bond between these fragments [(VIII)—(XI)] and the remainder of the molecule is labile towards electron bombardment. Similar fragment ions were also observed in other derivatives. These fragmentations are rationalized by formation of stable oxonium ions by characteristic α-fission of α-substituents in the saturated furan ring [12] and also by a structure in which the C(9)–C(11) bond is allylic and C-9 is fully substituted. It is noteworthy



SCHEME 1

that the oxonium ion (XII) which results from (I) and (XIII) which comes from (V) gave the same fragment ion (XIV; *m/e* 69) which process occurred by loss of a neutral molecule C_2H_2O and C_2H_4O, respectively (Scheme 1). Those transitions were substantiated by the observation of metastable ions at *m/e* 42·9 and 42·1, respectively. Furthermore, both oxonium ions gave the same fragment ion (XV) at *m/e* 83. This ion lost hydrogen to form the pyrylium ion (XVI) with *m/e* 81. The transition (XII) ⟶ (XV) was substantiated by a metastable ion at *m/e* 62·1. The extended partial structure was confirmed by the n.m.r. spectrum in which the C-11 methine proton appeared as the X part of an ABX system at δ *ca.* 4·0 in most derivatives.

That the hydroxy-group of the C_5 hydroxy-acid was acetylated in (I) was elucidated by mass spectrometry. Compound (I) and its derivatives [(V)—(VII) and (XXIV)] gave a characteristic fragment ion (XVII) at *m/e* 143 (Scheme 2). This ion expelled 28 mass units to afford an ion (XVIII) at *m/e* 115, which then lost a keten group to give (XIX) at *m/e* 73. These degradation pathways were supported by the presence of appropriate metastable ions at *m/e* 92·5 and 46·3,

* When 10% Pd–C preserved for a few years was used as catalyst, the methanol adduct (VII) was obtained. By using a fresh sample, the dihydro-derivative (V) was obtained quantitatively.

[7] B. W. Christensen and A. Kjær, *Acta Chem. Scand.*, 1962, **16**, 2466; S. C. Nyburg, G. L. Walford, and P. Yates, *Chem. Comm.*, 1965, 203.

[8] G. Kartha and D. J. Haas, *J. Amer. Chem. Soc.*, 1964, **86**, 3630; J. Polonsky, C. Fougney, A. Gaudmer, Z. Baskevitch, N. Bourguignon, and F. Prestat-Gaudmer, *Bull. Soc. chim. France*, 1964, 1827.

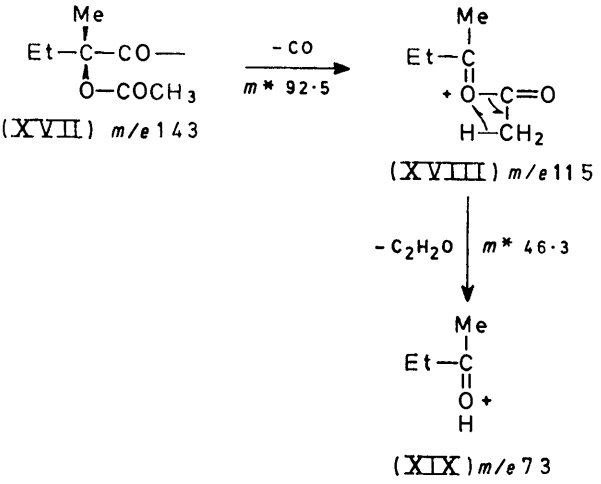
[9] H. A. Nash and R. M. Brooker, *J. Amer. Chem. Soc.*, 1953, **75**, 1942; A. Stoll and E. Seebeck, *Helv. Chim. Acta*, 1953, **36**, 718.

[10] S. Shibata, M. Aimi, and M. Watanabe, *Tetrahedron Letters*, 1964, 1991.

[11] L. J. Bellamy, 'The Infrared Spectra of Complex Organic Molecules,' John Wiley, New York, 1958, 2nd edn.

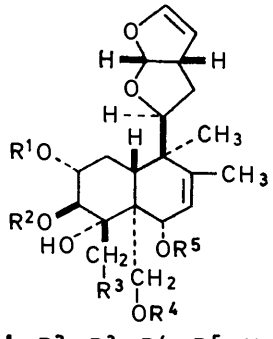
[12] G. Spiteller, *Adv. Heterocyclic Chem.*, 1966, **7**, 327; Q. N. Porter and J. Baldas, 'Mass Spectrometry of Heterocyclic Compounds,' Wiley-Interscience, New York, 1971, p. 39.

respectively.[13] In contrast to these observations, the fragment and metastable ion peaks were not present in the mass spectra of the alcohol derivatives.



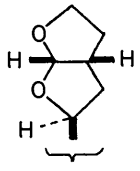
SCHEME 2

The 17- and 18-methylene protons exhibited two typical AB quartets. The latter in compound (I)



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

(XXII) $R^1 = p\text{-}BrC_6H_4CO-$, $R^2 = Et-C(Me)(OAc)-CO-$, $R^3 = Cl$, $R^4 = R^5 = Ac$



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

(XXIII) $R^1 = R^2 = CO_2Et$, $R^3 = Cl$, R^4, $R^5 = >C=O$

appeared at δ_A 4·61 and δ_B 4·45 with J 12·5 Hz, and the former at δ_A 3·82 and δ_B 3·62 with J 4·4 Hz. No significant change of chemical shift or multiplicity of the 18-H_2 signal occurred in esterified derivatives,[14] but the shift difference between the A and B parts of the AB system was smaller ($\delta_A - \delta_B$ 0—0·08) in the alcohols than in the esterified compounds.[15] The chemical shifts, δ 2·5—4·0, and coupling constants, J 4—5 Hz, of the upfield quartet are typical values for primary epoxide protons.[5,16] In the pentaol derivatives (XX) and (XXI), which were obtained by reduction with $LiAlH_4$ of (I) and (V), the AB quartet for the primary epoxide ring disappeared and, instead, a sharp singlet at δ 1·3—1·8 appeared for a *C*-methyl group on a tertiary carbon atom attached to a hydroxy-group. The epoxide ring is easily cleaved by addition of hydrochloric acid, as in clerodendrin A *p*-bromobenzoate chlorohydrin (XXII), m.p. 146—148°, and in the cyclic carbonate (XXIII), m.p. 184—186°. The methylene protons of the chlorohydrin group showed an AB quartet centred at δ 3·82 and 4·51 with large splittings of J 12·2 and 11·8 Hz,[14,17] respectively.

Acetylation of (I) with acetic anhydride and pyridine quantitatively yielded an acetate (XXIV), m.p. 120—121°. No hydroxy-absorption was observed in the i.r. spectrum but four acetyl signals appeared in the n.m.r. spectrum. The 2-proton signal at δ 3·52 in (I) shifted downfield to δ 4·98 on acetylation. These findings were used as probes for assigning other protons by decoupling experiments. Irradiation at δ 3·52 in (I) removed the coupling of a doublet (3-H) at δ 5·47 and altered the shape of a multiplet (1-H) at δ 2·65. In a decoupled spectrum of (I), similar observations were made for signals at δ 4·98 and 5·49 with J 10·6 Hz. Removal of the ester groups by hydrolysis or reduction caused an upfield shift of the 3-H signal of *ca.* 1 p.p.m. On oxidation with chromium trioxide–pyridine, (I) gave clerodendrin A monoketone (XXV), m.p. 98—101°. This product shows a weak absorption at $\lambda_{max.}$ 278 nm (ε 70) and carbonyl absorption at 1740 cm^{-1} overlapping with the ester carbonyl bands. In the n.m.r. spectrum of (XXV), the multiplet at δ 3·52 in (I) disappeared and the signal for 3-H appeared as a singlet at δ 5·95. The signal for 1-H_2 was shifted downfield by a neighbouring carbonyl group and appeared as a double doublet at δ 3·22 (J 4·8 and 14·2 Hz) and 2·88 (J 14·2 and *ca.* 13 Hz). The spectrum for [$^2H_5$]pyridine solution relative to $CDCl_3$ enabled a more definitive analysis of the ABX system of 1-H_2 and 10-H. The 1*ax*-proton at δ 3·45[18] coupled with 1*eq*-H (δ 3·14) with J 14·4 Hz and, furthermore, these protons coupled with 10-H with J 12·8 and 4·8 Hz,[19] respectively; 10-H was axial on the basis of the coupling constants.[20]

The configuration of 2- and 3-H of the glycol system

[13] H. Budzikiewicz, C. Djerassi, and D. H. Williams, 'Structure Elucidation of Natural Products by Mass Spectrometry,' Holden-Day, San Francisco, 1964, p. 204.

[14] J. A. Pople and A. A. Bothner-By, *J. Chem. Phys.*, 1965, **42**, 1339.

[15] J. A. Pople, *Molecular Phys.*, 1958, **1**, 3.

[16] K. L. Williamson, C. A. Landford, and C. R. Nicholson, *J. Amer. Chem. Soc.*, 1964, **86**, 762; S. L. Manatt, D. D. Ellman, and S. J. Brois, *ibid.*, 1965, **87**, 2220.

[17] L. M. Jackman, 'Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry,' Pergamon, London, 1959, p. 53.

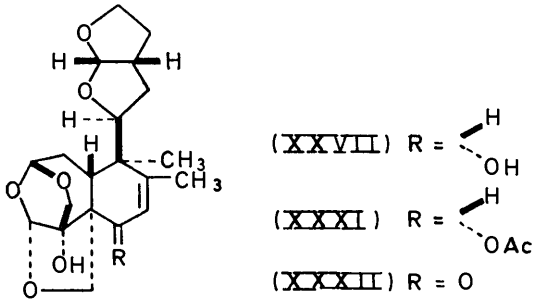
[18] K. M. Wellman and F. G. Bordwell, *Tetrahedron Letters*, 1963, 1703.

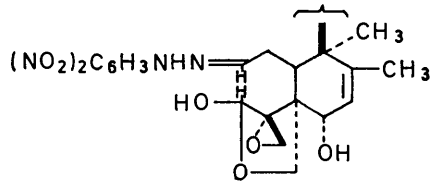
[19] D. H. Williams and N. S. Bhacca, *J. Amer. Chem. Soc.*, 1964, **86**, 2742.

[20] M. Karplus, *J. Chem. Phys.*, 1959, **30**, 11.

was assigned as *trans*-diaxial from their coupling constants (J 9—10 Hz) and the half-band width of the 2-H signal ($W_{\frac{1}{2}}$ *ca.* 18 Hz).[21] On periodate oxidation in aqueous solution, one mole of periodate was consumed in less than three minutes per mole of the tetraol derivative (XXVI), m.p. 240° (decomp.), which was obtained by hydrolysis of (V). One mole of (XXI) rapidly consumed two moles of periodate. The findings provide information regarding the relationship of the glycol and the epoxide ring. The relationship has been verified from the chemical-shift differences of the various protons in the tetraol and the pentaol derivatives. Only the signal for 3-H was shifted upfield by 0·17—0·3 p.p.m. on cleavage of the epoxide ring, while the other protons were almost unaffected. The shift was probably due to the influence of the neighbouring epoxide ring [22] and also the axial position of the 3-proton.

On a preparative scale, periodate oxidation of (XXVI) gave a viscous liquid which showed an aldehyde carbonyl absorption at 1723 cm^{-1} in the i.r. spectrum. During purification by column chromatography on silica gel or by crystallization from ethyl acetate–light petroleum, this liquid decomposed to give several compounds, and finally dihydroclerodendrin A acetal (XXVII), m.p. 223—225°, was obtained, which did not show any carbonyl absorption in the i.r. spectrum nor signals of any aldehydic protons in the n.m.r. spectrum. These observations suggested that it was an acetal or hemiacetal. Since the results of mass





(XXXIII)

spectrometry and elemental analysis were in accord with the expected dialdehyde derivative, (XXVII) may be formed by intramolecular cyclization. In the n.m.r. spectrum of (XXVII), a singlet at δ 5·74 and a doublet at 5·46 (J 6·5 Hz) were assigned to 3-H and 2-H, respectively, since these chemical shifts are typical of methine protons adjacent to the oxygen atoms of an acetal or hemiacetal group.[23]

The AB quartet of the epoxide protons disappeared in the spectrum of (XXVII), whereas two AB quartets appeared in the region of the methylenoxy protons (δ 4—5) with large splittings (J 10·6 and 9·5 Hz). The two quartets were assigned to 17- and 18-H_2 as follows. The downfield doublet of 18-H_2 appeared as a broad signal with half-band width *ca.* 2·6 Hz and the upfield signal was a sharp doublet. A zigzag geometry is required for long-range coupling over four bonds,[24] and one of the protons at C-18 bears such a relationship to a C-6 proton. Long-range coupling of the doublet with the C-6 proton was revealed by decoupling experiments. The other quartet may be assigned to the signal for 17-H_2; the half band width of the upfield quartet for 17-H_2 was *ca.* 1·4 Hz as for 19-H_3. The downfield shift of *ca.* 1 p.p.m. of the 17-H_2 signal compared with that for (I) and the large splitting were not due to the effects of bond anisotropy but a result of re-forming a primary alcohol or an oxide ring by cleavage of the epoxide by an intramolecular alkoxylation reaction. The most striking aspect of the result was that the cleavage must occur concertedly with acetal formation initiated by 18-OH.

We suggest that the acetal was produced *via* either path a or b of Scheme 3. The possibility of three- or four-membered oxide ring formation has been excluded from the Scheme, since it is unlikely that such a strained ring is formed by concerted alkoxylation under such mild conditions.

Therefore, three paths can be envisaged for the reaction.

The partial structure (XXVIII) formed through path b is more strained than (XXIX) and (XXX) (by inspection of Dreiding models). The results [25] seem to indicate that cleavage of the epoxide ring takes place by attack of the C-2 alkoxide anion at C-17 (path c) rather than at C-4 (path d). Proof that (XXIX) was formed predominantly by path a ⟶ c was deduced from the following. Acetylation of the acetal with acetic anhydride and pyridine at room temperature or 70 °C for 10 h yielded an acetal monoacetate (XXXI), m.p. 209—210·5°. The chemical shifts of its acetal ring protons were very similar to those of (XXVII). They were not deshielded by the acetoxy-group at δ 2·02, whereas 6-H shifted downfield by *ca.* 1 p.p.m. The half band width of the AB quartet for 18-H_2 was *ca.* 1·8 Hz for the upfield part and *ca.* 2·5 Hz for the downfield. The long-range coupling of the latter signal with the C-6 proton was eliminated by irradiation at δ 6·03.

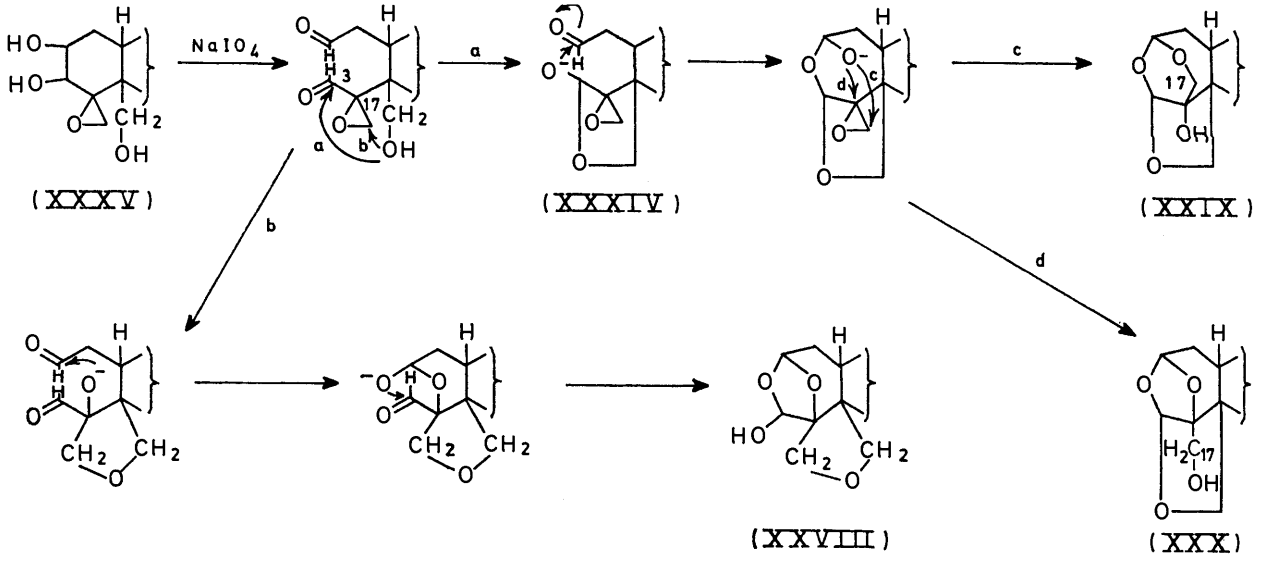
In addition, oxidation of (XXVII) with manganese dioxide in 5% methanol–chloroform gave an acetal

[21] A. Hassner and C. Heathcock, *J. Org. Chem.*, 1964, **29**, 1350.
[22] K. Tori, A. Aono, K. Kitahonoki, R. Muneyuki, Y. Takano, H. Tanida, and T. Tsuji, *Tetrahedron Letters*, 1966, 2291.
[23] L. F. Fieser and T. Goto, *J. Amer. Chem. Soc.*, 1960, **82**, 1697; G. Albers-Schönberg and H. Schmid, *Helv. Chim. Acta*, 1961, **44**, 1447; D. Lavie, M. K. Jain, and I. Kirson, *J. Chem. Soc.* (*C*), 1967, 1347.
[24] S. Sternhell, *Rev. Pure Appl. Chem.*, 1964, **14**, 15.
[25] G. A. Haggis and L. N. Owen, *J. Chem. Soc.*, 1950, 2250.

αβ-unsaturated ketone (XXXII), m.p. 237—240°, $\lambda_{max.}$ 248 nm (ε 8900). Only the signal for 6-H disappeared from the n.m.r. spectrum of (XXXII) and other signals may easily be assigned by comparison with those of (XXVII) and (XXXI). Replacement of H-6 by a carbonyl group caused elimination of the long-range coupling with 18-H. The i.r. spectrum of (XXXII) showed an absorption band at 3600 cm^{-1} (4-OH) for dilute chloroform solution [26] and αβ-unsaturated carbonyl bands at 1645 and 1630 cm^{-1}. The low frequency

These facts lead to the conclusion that the partial structure of the acetal is expressed as (XXIX) and the acetal was formed *via* the route a ⟶ c. The formation of the acetal (XXVII) is important because it not only reveals the structure of ring A but decides the relative configuration of C-18 to the epoxide ring as (XXXV) or its enantiomer.

A double bond in ring B was assigned as trisubstituted from the absorption intensity (ε 5090) at λ 203 nm [28] of (V), whereas it resisted catalytic reduction over platinum



SCHEME 3

of the carbonyl band may be attributed to hydrogen bonding with 4-OH.[27] Since the acetal derivative was produced quantitatively by reduction of (XXXII) with $NaBH_4$, the 6-OH group may be in a (quasi-)-equatorial position. The viscous liquid obtained by periodate oxidation of (XXVI) gave a phenylhydrazone (XXXIII), m.p. 225—227°, in low yield. The i.r. spectrum of (XXXIII) showed no carbonyl absorption but a hydroxy-absorption at 3400 cm^{-1}. Since in the n.m.r. spectrum of (XXXIII) the 2-H signal shifted to δ 7·30, the 2-formyl group had formed a phenylhydrazone. Since 3-H appeared at δ 5·76 as a sharp singlet, the 3-formyl group was converted into a hemiacetal with 18-OH. An AB quartet at δ 4·99 and 4·82 was too far downfield to be assigned to 17-H_2 of the epoxide ring. However, the coupling constant, J 6·0 Hz, corresponded to that of geminal protons of an epoxide ring. On the other hand, one of the C-18 protons shifted upfield to δ 3·30 with J 12·5 Hz. This unusual shift can be attributed to the diamagnetic anisotropy of the phenylhydrazone group which may be in a fixed conformation owing to hydrogen bonding with 4-OH. This is evidence, therefore, that (XXIX) cyclized *via* the intermediate (XXXIV).

oxide even at 100 atm and 100 °C. In the case of (I), one of the two methyl groups appeared as a doublet ($W_{\frac{1}{2}}$ *ca.* 5·0 Hz) with a small coupling, J 1·2 Hz, at δ 1·69, and 6- and 7-H appeared as broad singlets with a half-band width of 6·0 and 4·4 Hz at δ 5·23 and 5·03, respectively. Irradiation of 6-H reduced the half-band width to *ca.* 2·3 and 1·8 Hz for the 6- and 7-H, respectively. Also, irradiation of 6-H removed the 1·2 Hz coupling and of 7-H eliminated the half-band width of *ca.* 2·3 Hz of 20-H_3. Hence, the existence of the couplings $J_{20,6}$ 1·8 and $J_{20,7}$ 0·5 Hz was confirmed. Furthermore, $J_{6,7}$ 1 Hz was confirmed and also $J_{6,18}$ 0·5 Hz.

The broad singlet of 6-H, which shifted upfield *ca.* 1 p.p.m. in the tetraol and pentaol derivatives, was assigned to a methine proton of an allylic alcohol. On the other hand, the signal for the vinyl 7-H shifted downfield *ca.* 0·5 p.p.m. The long-range couplings are those expected for a homoallylic alcohol, C(OH)–C=CMe, rather than an allylic alcohol C(OH)–CMe=C.[29] The n.m.r. spectrum of (XXXII) in [$^2H_5$]-pyridine exhibited sharp singlets for 7-H and 20-H_3 at δ 6·15 and 1·83. For solution in $CDCl_3$ they appeared as a doublet (J 1·2 Hz) and a broad singlet ($W_{\frac{1}{2}}$ *ca.* 2·5

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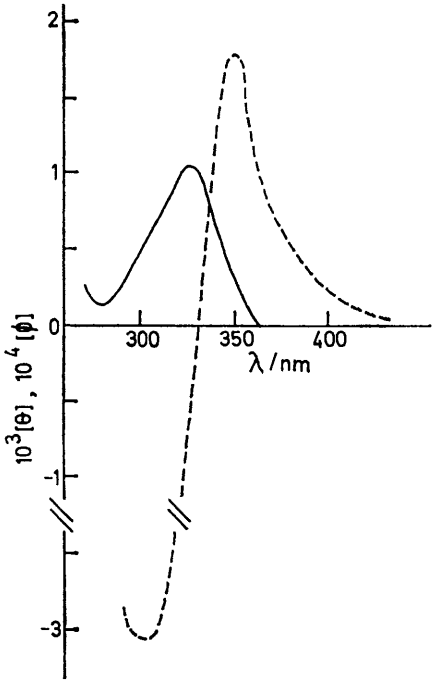
[28] P. S. Ellington and G. D. Meakins, *J. Chem. Soc.*, 1960, 697.
[29] Values of $J_{20,6}$, $J_{20,7}$, and $J_{7,8}$ are in the range of the values found for the similar enone systems, S. Sternhell, *Rev. Pure Appl. Chem.*, 1964, **14**, 15; R. F. C. Brown, I. D. Rae, and S. Sternhell, *Austral. J. Chem.*, 1965, **18**, 61.

Hz), the values of which are in good agreement with those found by Davis and Woodgate [30] for 3-methylcyclohex-2-enone (in CCl_4).

The functionality at C-6 and C-18 was characterized by forming a cyclic carbonate. The cyclic carbonate (XXIII) was prepared by the treatment of (XXVI) with ethyl chloroformate in pyridine. The carbonyl absorptions, 1757 and 1740 cm^{-1}, indicate a carbonate formed from a 1,3-glycol. Therefore, this glycol must have the *cis*-configuration.[31] The 6-OH group must be (quasi-)equatorial, since (XXXII) regenerated the original acetal (XXVII) by reduction, and 6- and 7-H coupled with a small J value.



C.d. (——) and o.r.d. (– – – –) curves of dihydroclerodendrin A acetal αβ-unsaturated ketone (XXXII)

Consequently, we consider that the bulky furofuran ring, together with a methyl group, is attached to C-9. Therefore, the furofuran ring has a (quasi-)equatorial orientation.

Since clerodendrin A is very unstable to acid and base, partial hydrolysis did not proceed satisfactorily under various conditions. The location of the 2-acetoxy-2-methylbutyryl group at C-3 and not at 6- or 18-OH was established by its effect on the oxidation and esterification of the 2-OH group. Oxidation of (I) with CrO_3–pyridine gave only the monoketone (XXV) in *ca.* 40% after 24 h at room temperature. *p*-Bromobenzoyl chloride in pyridine did not react with the 2-OH group at room temperature, but gave the ester after reaction at 70 °C for 11 h.

This established the relative configuration of clerodendrin A apart from that of some asymmetric centres. The absolute configuration was shown to be the antipode of clerodin from the following considerations. The Cotton effect exhibited by the n–π^* transition of compound (XXXII) was positive, as shown by the o.r.d. and c.d. curves in the Figure. The general features of the o.r.d. curve of the αβ-unsaturated ketone are similar to those of 3β-acetoxycholest-5-en-7-one and the Cotton sign is opposite to that of cholest-2-en-1-one.[32] Examination of the geometry of such acetals with Dreiding models did not indicate substantial distortions in the conformation of ring B due to the enone chromophore. We conclude that the AB ring junction is antipodal to that of clerodin and the other configurations may also be antipodal. Since both the monoketone (XXV) and the dihydro-monoketone (XXXVI), obtained from (V) by oxidation by CrO_3–pyridine, showed plain curves in the o.r.d. and since it is not known to what extent the acetal ring affects the o.r.d. curve of (XXXII), we have no definite assignment of the absolute configuration of these compounds.

Therefore, in order to establish the constitution and configuration, an *X*-ray analysis of the *p*-bromobenzoate chlorohydrin (XXII) was undertaken. The *X*-ray analysis is in agreement with the chemical and physicochemical observations discussed above. It should be noted that clerodendrin A has a carbon skeleton antipodal to that of clerodin, except for the C-2, -3, and -8 atoms.

EXPERIMENTAL

I.r. spectra were obtained with a JASCO IR-G spectrophotometer. N.m.r. spectra were taken with Varian HA-100 and JEOL 4H-100 spectrometers (tetramethylsilane as internal standard). Mass spectra were obtained with a Hitachi RMU-6C spectrometer. O.r.d. and c.d. curves were measured with a JASCO ORD/UV-5 instrument.

Extraction of Clerodendron tricotomum *Thunb.*—Dry, ground leaves of the shrub (4·7 kg) were extracted three times with hot benzene. The filtered solution was concentrated under reduced pressure to *ca.* 300 ml. The extract was chromatographed over neutral alumina (2 kg). Elution with benzene and with 1% methanol–benzene afforded a diterpenoid fraction. Rechromatography of this fraction over silica gel (2 kg) using n-hexane–ethyl acetate (5 : 2) as eluant gave *clerodendrin A* (I) (2 g), prisms, m.p. 164—165° (from ether), $[\alpha]_D$ +7·4° (*c* 3·25; $CHCl_3$), $\lambda_{max.}$ (MeOH–N_2) 203 nm (ε 10,700), $\nu_{max.}$ (KBr) 3540, 3420, 1742, 1718, and 1620 cm^{-1}, M^+ 606 (Found: C, 61·25; H, 6·95. $C_{31}H_{42}O_{12}$ requires C, 61·35; H, 7·0%).

Alkaline Hydrolysis of Clerodendrin A (I).—(a) *Clerodendrin A tetraol* (III). A solution of clerodendrin A (I) (500 mg) in methanol (10 ml) was added to a solution of potassium carbonate (230 mg, 4 equiv.) in methanol (50 ml) and water (0·5 ml) with stirring. After stirring at room temperature for 2 h, the solution was concentrated under reduced pressure. The residue was dissolved in water (10 ml) saturated with diethyl ether (20 ml), and after

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[31] L. F. Fieser, J. E. Herz, M. W. Klohs, M. A. Romero, and T. Utne, *J. Amer. Chem. Soc.*, 1952, **74**, 3309.

[32] C. Djerassi, R. Riniker, and B. Riniker, *J. Amer. Chem. Soc.*, 1956, **78**, 6377.

being set aside at −10 °C overnight the solution deposited *clerodendrin A tetraol* (III) as needles (270 mg). A sample for analysis was recrystallized several times from water–ether, m.p. 250° (decomp.), $[\alpha]_D$ +19° (*c* 0·28, pyridine), $\nu_{max.}$ (KBr) 3500—3350, 1640, 1620, and 1150—950 (complex) cm^{-1}, M^+ 380 (Found: C, 61·75; H, 7·55. $C_{20}H_{28}O_7$,-0·5MeOH requires C, 62·1; H, 7·6%).

(b) *2-Hydroxy-2-methylbutyric acid* (IVa). The aqueous solution from the preceding experiment (15 ml) was acidified to pH 1 with N-hydrochloric acid and, after being saturated with sodium chloride, extracted with diethyl ether. The solution was dried (Na_2SO_4) and concentrated under reduced pressure at 30 °C. The residue was purified by sublimation at 70 °C and 20 mmHg and yielded 2-hydroxy-2-methylbutyric acid (26 mg) as needles, m.p. 71—72°, $[\alpha]_D$ −7·1° (*c* 1·4, $CHCl_3$), $\nu_{max.}$ (KBr) 3460, 2960, and 1733 cm^{-1}.

(c) p-*Bromophenacyl 2-hydroxy-2-methylbutyrate* (IVb). The aqueous solution (60 ml) from which (III) was extracted was concentrated to small volume (2 ml) and adjusted to pH 6 by the addition of 1N-hydrochloric acid. *p*-Bromophenacyl bromide (615 mg) was added, and the mixture was dissolved in the minimum quantity of alcohol and refluxed for 1·5 h. The solution was concentrated to small volume and the precipitated product was collected. The product, after chromatography over silica gel with chloroform, gave two kinds of crystals. One was the *p*-bromophenacyl ester of acetic acid and the other was the p-*bromophenacyl ester* of *2-hydroxy-2-methylbutyric acid* (IVb) (280 mg), needles, m.p. 86—87°, $[\alpha]_D$ −3·1° (*c* 0·95, $CHCl_3$), $\nu_{max.}$ (KBr) 3520, 1733, and 1698 cm^{-1} (Found: C, 49·9; H, 4·95; Br, 25·6. $C_{13}H_{15}BrO_4$ requires C, 49·55; H, 4·8; Br, 25·35%).

Dihydroclerodendrin A (V).—Clerodendrin A (I) (300 mg) was dissolved in 95% ethanol (100 ml), and 5% palladium–charcol (150 mg) or platinum oxide (50 mg) was added. Hydrogenation proceeded with stirring and 1 equiv. of H_2 was absorbed in 10 min. After filtration and evaporation the residue was recrystallized from diethyl ether to give *dihydroclerodendrin A* (V) (300 mg) as prisms, m.p. 174—176°, $[\alpha]_D$ +30·4° (*c* 1·30, $CHCl_3$), $\lambda_{max.}$ (MeOH–N_2), 203 nm (ε 5090), $\nu_{max.}$ (KBr) 3550, 3430, 1748, 1720, 1640br, and 1270 cm^{-1}, M^+ 608 (Found: C, 61·15; H, 7·4. $C_{31}H_{44}$-O_{12} requires C, 61·25; H, 7·3%).

Clerodendrin A γ-Lactone (VI).—Clerodendrin A (I) (116 mg) in glacial acetic acid (4 ml) was kept at room temperature for 7 h. Water was added to the solution, and the mixture was kept at room temperature overnight. After addition of an excess of $NaHCO_3$, the product was extracted with chloroform, the solvent was removed, and the residue in glacial acetic acid (2 ml) was treated with $Na_2Cr_2O_7$ (50 mg) in acetic acid (2 ml) at room temperature overnight. The solution was neutralized with $NaHCO_3$ and extracted with ether. Chromatography over silica gel gave the *γ-lactone* (VI) (29·6 mg) as prisms, m.p. 169·5—170·5°, $[\alpha]_D$ +33° (*c* 1·00, $CHCl_3$), $\nu_{max.}$ (KBr) 3440, 1790, 1740, and 1640 cm^{-1}, M^+ 622 (Found: C, 59·55; H, 6·85. $C_{31}H_{42}O_{13}$ requires C, 59·85; H, 6·95%).

Clerodendrin A–Methanol Adduct (VII).—Using an old sample of 10% palladium–charcol (100 mg) as catalyst, clerodendrin A (I) (1 g) in methanol (100 ml) was hydrogenated with stirring for 10 min. The mixture was filtered and the solvent was removed under reduced pressure. After chromatography over silica gel with n-hexane–ethyl acetate (1 : 3·5), two products were obtained. One was identical with (V) (343 mg) and the other was the *adduct* (VII) which, after recrystallization from ether and light petroleum, gave needles (542 mg), m.p. 187·5—188·5°, $[\alpha]_D$ +73·3° (*c* 0·88, $CHCl_3$), $\nu_{max.}$ (KBr) 3520, 3450, 1740, and 1718 cm^{-1}, M^+ 638 (Found: C, 60·15; H, 7·3. $C_{32}H_{46}O_{13}$ requires C, 60·25; H, 7·25%).

Clerodendrin A Pentaol (XX).—Lithium aluminium hydride (400 mg) in dry ether (20 ml) was added dropwise to a stirred solution of (I) (205 mg) in dry ether (25 ml). After 30 min at room temperature, the excess of lithium aluminium hydride was decomposed by the dropwise addition of water. The ether was removed under reduced pressure and the residue was chromatographed over silica gel with chloroform–methanol (1 : 1). The crude product was recrystallized from chloroform–methanol and yielded *clerodendrin A pentaol* (XX) as needles (93 mg), m.p. 250° (decomp.), $[\alpha]_D$ +39·7° (*c* 0·92, pyridine), $\nu_{max.}$ (KBr) 3550, 3370, 1630br, 1620, and 1170—850 (complex) cm^{-1}, M^+ 382 (Found: C, 62·75; H, 7·9. $C_{20}H_{30}O_7$ requires C, 62·8; H, 7·65%).

Dihydroclerodendrin A Pentaol (XXI).—After a similar reduction of compound (V) and work-up, recrystallization from chloroform–methanol–ether yielded *dihydroclerodendrin A pentaol* (XXI) as needles, m.p. 225—227°, $[\alpha]_D$ +68° (*c* 0·27, pyridine), $\nu_{max.}$ (KBr) 3560, 3400, 1630, and 1170—900 (complex) cm^{-1}, M^+ 384 (Found: C, 61·1; H, 7·95. $C_{20}H_{32}O_7$,MeOH requires C, 60·85; H, 8·2%).

Clerodendrin A p-*Bromobenzoate Chlorohydrin* (XXII).—To a solution of clerodendrin A (I) (100 mg) in pyridine was added *p*-bromobenzoyl chloride (2 mmol) at 0 °C and the solution was stirred at 70 °C for 11 h. After pyridine was removed under reduced pressure at 45 °C, the residue was chromatographed over silica gel with n-hexane–ethyl acetate–chloroform (1 : 2 : 2). The product was recrystallized from ethanol and yielded the p-*bromobenzoate chlorohydrin* (XXII) as prisms (48 mg), m.p. 146—148°, $[\alpha]_D$ +1·3° (*c* 0·40, $CHCl_3$), $\nu_{max.}$ (KBr) 3300, 1748, 1712, 1620, and 1590 cm^{-1} (Found: C, 55·45; H, 6·15; Br, 8·85; Cl, 3·9. $C_{38}H_{46}BrClO_{13}$,EtOH requires C, 55·1; H, 6·0; Br, 9·15; Cl, 4·05%).

Dihydroclerodendrin A Cyclic Carbonate (XXIII).—The dihydrotetraol (XXVI) (70 mg) in pyridine, when added to an excess of ethyl chloroformate at −10 °C, and kept at 0 °C for 1 h, gave, after chromatography over silica gel with n-hexane–ethyl acetate–chloroform (1 : 2 : 2) and crystallization from ethyl acetate–ether, the *carbonate* (XXIII) (42 mg) as prisms, m.p. 184—186°, $[\alpha]_D$ +34·3° (*c* 1·72 pyridine), $\nu_{max.}$ (KBr) 3360, 1757, 1740, 1640br, 1270, and 1243 cm^{-1} (Found: C, 55·05; H, 6·75; Cl, 6·0. $C_{27}H_{37}ClO_{12}$ requires C, 55·05; H, 6·35; Cl, 6·05%).

Clerodendrin A Acetate (XXIV).—Clerodendrin A (I) (45 mg) was acetylated by treatment with dry pyridine (10 ml) and acetic anhydride (1 ml) overnight at room temperature. The solvent was removed under reduced pressure at 45 °C. The residue, after chromatography over silica gel with n-hexane–ethyl acetate–chloroform (1 : 2 : 2) and crystallization from ethyl acetate–light petroleum, gave *clerodendron A acetate* (XXIV) (44·5 mg) as needles, m.p. 120—121°, $[\alpha]_D$ +11·4° (*c* 0·88, $CHCl_3$), $\nu_{max.}$ (KBr) 1745 and 1620 cm^{-1}, M^+ 648 (Found: C, 61·0; H, 6·55. $C_{33}H_{44}O_{13}$ requires C, 61·25; H, 6·85%).

Clerodendrin A Monoketone (XXV).—Compound (I) (200 mg) in dry pyridine (10 ml) was added dropwise to CrO_3 (300 mg) in dry pyridine (15 ml) at 0 °C and the mixture was stirred at room temperature for 24 h. The solution

was diluted with ether (100 ml) and ethyl acetate (10 ml) and, after being filtered through Celite, was concentrated to dryness under reduced pressure at 40 °C. After chromatography over silica gel with n-hexane–ethyl acetate–chloroform (1 : 2 : 2), *clerodendrin A monoketone* (XXV) was obtained as amorphous solid (95 mg), m.p. 98—101°, $[\alpha]_D$ +31·9° (*c* 0·91, $CHCl_3$), $\lambda_{max.}$ (MeOH) 278 nm (ε 70), $\nu_{max.}$ (KBr) 1740, 1618, and 1240 cm^{-1} (Found: C, 61·95; H, 6·6. $C_{31}H_{40}O_{12}$ requires C, 61·6; H, 6·65%).

Dihydroclerodendrin A Tetraol (XXVI).—Compound (V) (300 mg) in methanol (30 ml) was added, with stirring, to potassium carbonate (145 mg, 4 mmol) in methanol (50 ml) and water (0·5 ml). After 1 h at room temperature, the solution was concentrated under reduced pressure. The residue was dissolved in water (5 ml), saturated with ether (20 ml), and kept at −10 °C overnight; the *dihydrotetraol* (XXVI) was obtained as needles (150 mg). A sample for analysis was recrystallized several times from water–ether, m.p. 240° (decomp.), $[\alpha]_D$ +61° (*c* 0·28, pyridine), $\nu_{max.}$ (KBr) 3500, 3350, 1630, and 1150—900 cm^{-1}, M^+ 382 (Found: C, 62·75; H, 8·0. $C_{20}H_{30}O_7$ requires C, 62·8; H, 7·9%).

Periodate Oxidation of Dihydroclerodendrin A Tetraol (XXVI).—(a) *Titration.* Titration of the dihydrotetraol (XXVI) by the Fleury–Lange procedure was carried out by use of 0·356M-sodium periodate solution. The consumption of periodate was 1·00 (3 min), 1·62 (1 h), 1·75 (3 h), 1·90 (6 h), and 3·00 equiv. (20 h). The procedure was as follows. The dihydrotetraol (XXVI) (38·4 mg) was dissolved in water (8 ml). A solution (2 ml) of sodium periodate in water (76·3 mg ml^{-1}) was added to the sample. A portion (1 ml) of the sample solution was added to a mixture of 0·106N-sodium arsenite solution (3 ml) and aqueous 20% potassium iodide (0·2 ml) at regular intervals. After 10 min, the excess of sodium arsenite was titrated with 0·103N-iodine solution.

(b) *Isolation of dihydroclerodendrin A acetal* (XXVII). An aqueous solution (1·5 ml) of sodium periodate (0·356 mol) was added to the dihydrotetraol (XXVI) (200 mg) in water (20 ml). After 5 min stirring at room temperature the solution was saturated with sodium chloride (10 g) and extracted with ethyl acetate (4 × 25 ml). The combined extracts were concentrated under reduced pressure to give an oil (190 mg). The product decomposed on attempted crystallization from ethyl acetate–light petroleum or purification by chromatography over silica gel. Finally, the *acetal* (XXVII) was obtained as a stable product (72 mg). A sample for analysis crystallized from ethyl acetate as prisms, m.p. 223—225°, $[\alpha]_D$ +44° (*c* 0·77, pyridine), $\nu_{max.}$ (KBr) 3310, 3150, 1640, and 1180—880 (complex) cm^{-1}, M^+ 380 (Found: C, 62·9; H, 7·5. $C_{20}H_{28}O_7$ requires C, 63·15; H, 7·4%).

Dihydroclerodendrin A Acetal Monoacetate (XXXI).—The acetal (XXVII) (18 mg) was acetylated by treatment with dry pyridine (5 ml) and acetic anhydride (0·8 ml) overnight at room temperature. The solvent was removed under reduced pressure at 40 °C and the residue was chromatographed over silica gel with ethyl acetate–n-hexane (1 : 1). Recrystallization of the product from ethyl acetate and light petroleum yielded the *acetal monoacetate* (XXXI) as prisms (18 mg), m.p. 209—210·5°, $[\alpha]_D$ +62° (*c* 1·64, $CHCl_3$), $\nu_{max.}$ (KBr) 3500, 3450, 1732, 1620, 1250, and 1150—880 cm^{-1}, M^+ 422 (Found: C, 62·5; H, 7·3. $C_{22}H_{30}O_8$ requires C, 62·55; H, 7·05%).

Dihydroclerodendrin A Acetal αβ-Unsaturated Ketone (XXXII).—Active manganese dioxide (500 mg) was added, with stirring, to the acetal (XXVII) (47 mg) in 5% methanol–chloroform (25 ml). After 4 h at room temperature, the solution was filtered through Celite and the filtrate was concentrated under reduced pressure. After chromatography over silica gel with chloroform–methanol (1 : 1), the product was recrystallized from ethyl acetate and light petroleum and the *acetal αβ-unsaturated ketone* (XXXII) was obtained as prisms (46 mg), m.p. 237—240°, $[\alpha]_D$ −38° (*c* 0·84, pyridine), $\lambda_{max.}$ (MeOH) 248 nm (ε 8900), c.d. (*c* 0·0032, dioxan) $[\theta]_{364}$ 0, $[\theta]_{325}$ +1060, and $[\theta]_{282}$ +100, o.r.d. (*c* 0·0032, dioxan) $[\phi]_{470}$ 0, $[\phi]_{350}$ +18,000, $[\phi]_{332}$ 0, and $[\phi]_{304}$ −30,800, $\nu_{max.}$ (KBr) 3450, 3300, 1645, 1630, and 1170—880 (complex) cm^{-1}, $\nu_{max.}$ ($CHCl_3$; 0·004 mol), 3600 and 1660 cm^{-1}, M^+ 378 (Found: C, 63·2; H, 7·0. $C_{20}H_{26}O_7$ requires C, 63·5; H, 6·95%).

Dihydroclerodendrin A Hemiacetal Phenylhydrazone (XXXIII).—The viscous liquid obtained by the sodium metaperiodate oxidation of the dihydro-tetraol (XXVI) (75 mg) was dissolved in water (3 ml), and an acetic acid solution of phenylhydrazine (3 ml, 3 mmol) was added. The solution was kept for 30 min and, after chromatography over silica gel with n-hexane–ethyl acetate–chloroform (1 : 2 : 2), the product was crystallized from ethyl acetate–light petroleum to give the *phenylhydrazone* (XXXIII) (7·5 mg) as needles, m.p. 225—227°, $[\alpha]_D$ +4·4° (*c* 1·1, pyridine), $\lambda_{max.}$ (MeOH) 243 (ε 10,200) and 288 (1480) nm, $\nu_{max.}$ (KBr) 3400, 3300, 1620br, 1600, and 1495 cm^{-1}, M^+ 470 (Found: C, 66·2; H, 7·35; N, 6·1. $C_{26}H_{34}N_2O_6$ requires C, 66·3; H, 7·3; N, 5·95%).

Sodium Borohydride Reduction of the Acetal αβ-Unsaturated Ketone (XXXII).—Sodium borohydride (10 mg) was added to a stirred solution of the acetal αβ-unsaturated ketone (XXXII) (10 mg) in dry dioxan (3 ml). After 1 h at room temperature, the excess of sodium borohydride was decomposed by addition of hydrochloric acid and the mixture was chromatographed over silica gel (2 g). Elution with chloroform–methanol (1 : 1) gave a product (5 mg) which was identified as dihydroclerodendrin A acetal (XXVII) by comparison of the i.r. spectrum and R_F values with those of the authentic sample.

Dihydroclerodendrin A Monoketone (XXXVI).—A solution of (V) (250 mg) in dry pyridine (10 ml) was added to CrO_3 (350 mg) in dry pyridine (15 ml) and kept for 24 h at room temperature. The solution was filtered through Celite and concentrated under reduced pressure. After chromatography over silica gel with n-hexane–ethyl acetate, the residue gave the *dihydro-monoketone* (XXXVI) (167 mg) as needles, m.p. 167—169°, $[\alpha]_D$ +70·1° (*c* 1·57, $CHCl_3$), $\nu_{max.}$ (KBr) 1764, 1737, 1250, and 1245 cm^{-1} (Found: C, 61·3; H, 7·0. $C_{31}H_{42}O_{12}$ requires C, 61·35; H, 7·0%).

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