Structure of the Diterpene Clerodendrin A

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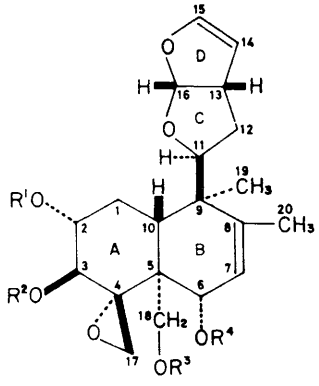
Summary Clerodendrin A, the bitter principle and antifeeding repellent, is shown to be a diterpene of clerodon skeleton with the structure (I).

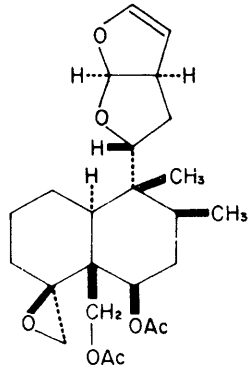
CLERODENDRIN A, a bitter principle of *Clerodendron tricotomum* Thunb,, and the antifeeding repellent for the larvae of *Spodoptera littoralis* Boisd.,[1] is shown to be (I) with the clerodon skeleton as in clerodin (II).[2]

Clerodendrin A, m.p. 164—165°, $C_{31}H_{42}O_{12}$, contains one hydroxy-group, one tertiary methyl, and one vinyl methyl group, three acetate residues, and a *R*-(−)-2-hydroxy-2-methylbutyrate residue (the free acid has m.p. 71—72° and $[\alpha]_D$ − 7·1°). The n.m.r. spectrum of (I) exhibits the presence of a tetrahydrofuro-furan ring, which was readily reduced to give a dihydro-derivative (III), m.p. 164—165°. Treatment of (I) with acetic acid followed by chromic acid oxidation afforded, through a hemiacetal intermediate, a γ-lactone (IV), m.p. 169·5—170·5°. A methanol adduct (V), m.p. 187·5—188·5°, was obtained as the by-product of catalytic hydrogenation. Furthermore, the furo-furan ring was confirmed by the observation of intense mass spectral peak at *m/e* 111, 113, 127, and 143 for (I), (III), (IV), and (V), respectively.

Mild alkaline hydrolysis and $LiAlH_4$ reduction of (III) gave the dihydrotetraol (VI), m.p. 240° (decomp.), and the dihydropentaol (VII), m.p. 225—227°, respectively. The vicinal coupling constant (*J* 9·4 Hz) between the C-2 and C-3 protons indicates a *trans* di-equatorial arrangement of the C-2, C-3-glycol. The arrangement of the glycol and the epoxide ring is revealed from the results of the periodate oxidation and the downfield shift, *ca.* 0·2 p.p.m., of the C-3 proton signal of (VI) compared with that of (VII). Oxidation with sodium periodate followed by purification through silica-gel chromatography or by crystallization from ethyl acetate (VI) afforded the acetal (VIII), m.p. 223—225°, which may be formed *via* intramolecular alkoxylation. The structure is deduced from the following spectral data: n.m.r., C-17 protons [δ 4·14 and 4·59, d, *J* 14·4 Hz; in (I), δ 3·00 and 2·68, d, *J* 4·0 Hz] and C-18 protons [δ 4·30 and 4·86, d, *J* 9·5 Hz; in (I), δ 4·72 and 4·58, d, *J* 11·8 Hz]; i.r. 4-OH (ν_{max} 3600 cm^{-1}, $CHCl_3$). That the configuration of the epoxide ring is retained in acetal intermediates is



(I) R^1=H, R^2=$C_2H_5C(CH_3)(OAc)CO$-, R^3=R^4=Ac



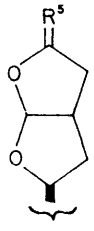
(II)

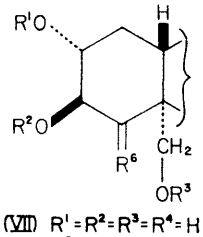
(III) R^1~R^4=same groups as in (I), R^5=H_2

(IV) R^1~R^4=same groups as in (I), R^5=O

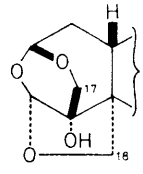
(V) R^1~R^4=same groups as in (I), R^5=H, OCH$_3$

(VI) R^1=R^2=R^3=R^4=H, R^5=H_2

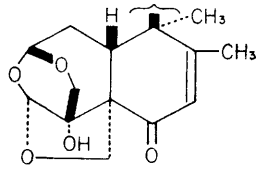




(VII) R^1=R^2=R^3=R^4=H, R^5=H_2, R^6=CH$_3$, OH

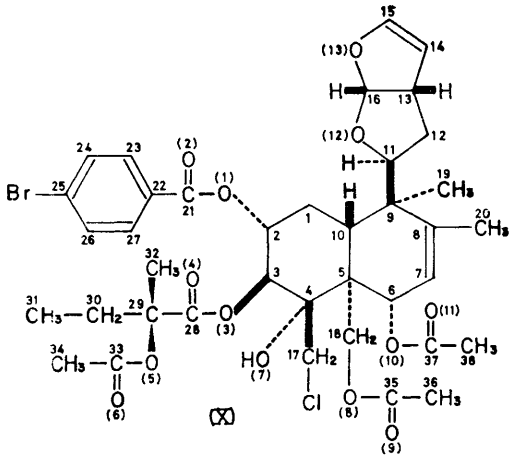


(VIII) R^4=H, R^5=H_2



(IX) R^5=H_2

shown by inspection of a Dreiding model. The formation of (VIII) shows the arrangement and the relative configuration of the epoxide ring and the C-18 primary alcohol group. With oxidation by manganese dioxide of (VIII) the allylic alcohol system was converted into the $\alpha\beta$-unsaturated ketone (IX), m.p. 237—240°, [ν_{max} 1645 and 1630 cm^{-1}, λ_{max} 248 nm (ϵ 8900)].



The absolute configuration of clerodendrin A is deduced to be (I), since (IX) had o.r.d. and c.d. curves similar to those of the cholestenone derivatives. Therefore, clerodendrin A is an antipode of clerodin, except for the C-2, C-3, and C-8 carbon atoms.

In order to confirm the constitution and configuration, an *X*-ray analysis of the *p*-bromobenzoate chlorohydrin (X) was undertaken.

The crystals are orthorhombic, space group $P2_12_12_1$ with four molecules of $C_{38}H_{46}O_{13}BrCl{\cdot}C_2H_5OH$, $M = 872{\cdot}21$, in a unit cell of dimensions $a = 18{\cdot}95$, $b = 22{\cdot}74$, $c = 10{\cdot}06$ Å. A total of 2924 reflections were collected by the multiple-film technique using a Weissenberg camera and Cu radiation. The structure was solved by Patterson and Fourier methods and refinement by block-diagonal least-squares techniques with anisotropic temperature factors for bromine and chlorine atoms has reduced R to 9·88%.

The molecule has structure (X). The chlorohydrin group at C-4 and C-17 is derived from the original epoxide ring by adding hydrochloride. The results confirm the constitution of clerodendrin A which was originally suggested.

The absolute configuration was established by Bijvoet's anomalous dispersion method and this confirms the spectral evidence. It should be noted that in (X), there is a 2-acetoxy-2-methylbutyrate group at C-3. The absolute configuration of this acid, obtained by hydrolysis of (I), was determined as *R*-(−) by comparison of $[\alpha]_D$ with the reported value of the authentic sample of known absolute stereochemistry.[3] This result agreed with that from the *X*-ray analysis.

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[1] N. Kato, M. Takahashi, S. Shibayama, and K. Munakata, to be published.
[2] 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, T. A. Hamor, I. C. Paul, and J. M. Robertson, *ibid.*, p. 75; I. C. Paul, G. A. Sim, T. A. Hamor, and J. M. Robertson, *ibid.*, 1962, 4133.
[3] B. W. Christensen and A. Kjær, *Acta Chem. Scand.*, 1962, **16**, 2466.