The Structure of Entandrophragmin

By D. A. H. TAYLOR and K. WRAGG

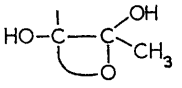
(*Department of Chemistry, University of Ibadan, Nigeria*)

ENTANDROPHRAGMIN, $C_{43}H_{56}O_{17}$, was first isolated from Sapele mahogany, the timber of *Entandrophragma cylindricum*.[1] It has since been isolated from the timber of *E. bussei* and *E. caudatum*,[2] and provisionally identified chromatographically in *E. spicatum* and *E. palustre*.[3] On hydrolysis it gives one mol. each of 2,3-epoxy-2-methylbutyric acid, 2-methylbutyric acid, isobutyric acid, and acetic acid.[4] Utilin[1] has the same structure, except that it gives two mols. of acetic acid and no isobutyric acid.[4]

We now suggest the structure (I) as a hypothesis which accounts for the observed properties and reactions of entandrophragmin, and present a

brief account of the principal evidence and reasoning that has led us to this structure.

Alkaline hydrolysis of entandrophragmin gives β-furfuraldehyde;[1] titration shows the presence of a lactone and a nuclear carboxyl group, seen as a methoxycarbonyl group in the n.m.r. spectrum. No acetyl group is seen in the n.m.r. spectrum, hence it must be concealed, probably as an orthoacetate, or as an acetal of a *C*-acetyl group.[5] The n.m.r. shows two tertiary hydroxyl groups. Lead tetra-acetate oxidation gives a compound $C_{43}H_{54}O_{17}$, which no longer contains any hydroxyl groups, but shows an acetyl in the n.m.r. The hydroxyl groups must therefore be present in an α-glycol system of the type



representing the concealed acetyl group.

Subtraction of these structural elements leaves a C_{26} nucleus, as in gedunin, and two oxygen atoms and five double-bond equivalents unaccounted for. The ultraviolet absorption spectrum (λ_{max} 214 mμ, ϵ $4{\cdot}4 \times 10^3$; 267 mμ, ϵ 64) suggests the presence of a furan ring and at least one ketone group; the other oxygen may be present as a second ketone group or an ether. This leaves a nucleus with three carbocyclic rings, or two rings and a double bond.

Entandrophragmin shows eight *C*-methyl groups in the n.m.r. spectrum, five of which are accounted for above, leaving three in the nucleus. In agreement, of the two methanolysis products,[4] one (A), an alcohol $C_{22}H_{30}O_{10}$, has lost the furan ring and the cyclic acetate, and shows three methyl groups (one secondary); the other, isolated as a tetra-acetate (B), $C_{37}H_{42}O_{16}$, still retains the furan ring and the cyclic acetate, and shows four tertiary methyl groups (one in the cyclic acetate). Both are unsaturated lactones [(A) λ_{max} 216 mμ, ϵ 8×10^3; (B) λ_{max} 216 mμ, ϵ $1{\cdot}4 \times 10^4$].

The n.m.r. spectrum of entandrophragmin at 100 Mc./sec. is very well resolved and very informative. In deuterochloroform (+D_2O) it shows three furan protons (δ 7·72, 7·38, 6·68), three singlets (δ 6·12, 5·74, 4·84; W_H 2·0, 1·5, 1·2 c./sec.)[6] the X part of an ABX multiplet at δ 5·4 ($J_{AX} + J_{BX}$ = 15 c./sec.), a methoxycarbonyl group at δ 3·56, a quartet at δ 3·68 (J = 5 c./sec.), coupled with a secondary methyl group at δ 1·26, a doublet at δ 3·35 (J = 19 c./sec.) coupled with one at δ 2·53, and another doublet at δ 2·77, (J = 10 c./sec.) coupled with one at δ 2·17.

The quadruplet at δ 3·68 is due to the proton in the epoxy-acid residue, and has the same chemical shift in the epoxy-amide isolated on ammonolysis. This chemical shift suggests that the acid is the *threo*-isomer.[7]

The band width of the δ 6·12 singlet shows that it is due to (C-17)–H; the other two singlets are too sharp for this.[6] In the spectrum of the acetate (B) the furan protons are at δ 7·46, 7·40, 6·40, there are singlets at δ 6·56, 5·72 (W_H 1·6, 1·6 c./sec.) 5·20, 5·16 (not clearly resolved), there is the X part of an ABX multiplet at δ 5·43 ($J_{AX} + J_{BX}$ = 8 c./sec.), and a methoxycarbonyl group at δ 3·65. The doublet at δ 2·74 is still present (J = 12 c./sec.), the other half of the system is now hidden under the acetyl groups. The pair of doublets at δ 3·68, 2·53, have disappeared in (B), so we ascribe these to the hydrogen atoms at C-15, and the singlet at δ 6·56 in (B) to (C-15)–H in the new unsaturated lactone.[6] The band width of this is much too narrow for there to be any allylic coupling, so C-8 must be fully substituted. It suggests some degree of coupling, possibly with a 7β-proton.[6]

There must then be a substituent at C-14 in entandrophragmin, presumably an oxygen function, which is lost to produce the double bond in (B). This cannot be the cyclic acetate, which is present in (B), so we suppose that it is an acyl group. If β, this will account for the downfield shift of (C-17)–H and of one of the furan protons [normal in (B)]. To explain the elimination of β-furfuraldehyde on alkaline hydrolysis of entandrophragmin [(B) does not give this reaction] we consider that there is an α-oxygen function at C-7 which can displace the 14β-acyloxy-group by internal attack to give an intermediate similar to that involved in the fragmentation of limonol.[8]

Were the cyclic acetyl group at C-7, there is no sterically credible place to attach the other end of it. Hence we place an acyloxy-group at 7α and a hydrogen atom at 7β. For this to be a singlet, C-6 must be doubly substituted; available for this are the *C*-end of the cyclic acetate or a keto-group. If a carbonyl function were at C-6, it is unlikely that the 7-substituent would remain in the α-configuration necessary for fragmentation, hence we place the *C*-end of the cyclic acetate at C-6. In agreement with this reasoning, the lead tetra-acetate oxidation product, with a keto-group at C-6, does not eliminate β-furfuraldehyde. To account for the second pair of AB doublets at δ 2·77, 2·17, we place a keto-group at C-11 and assign the doublets to C-12.

It remains to locate one acyl group, the oxygen end of the cyclic acetyl, an oxygen atom, and the methoxycarbonyl group. Two angular methyl groups have to be lost, and in the n.m.r. spectrum,

we have to account for the downfield X proton of an ABX group, and a singlet at δ 4·84. Sterically, the oxygen end of the acetyl group can only be located at C-30, which must then be an acetal, as there is no $-CH_2O-$ group. Hence, the last oxygen must be present as an ether ring, one end being at C-30. The other end must be on a tertiary carbon (from the n.m.r. spectrum), only the 5β-position is suitable. We then locate the X proton at C-3, in agreement with its splitting pattern, and place the methoxycarbonyl group at position-4β where it will account for the down-field position of (C-3)–H. This completes the diagnosis, leading to the structure (I). There is no evidence to assign the R groups to the different acylated positions.

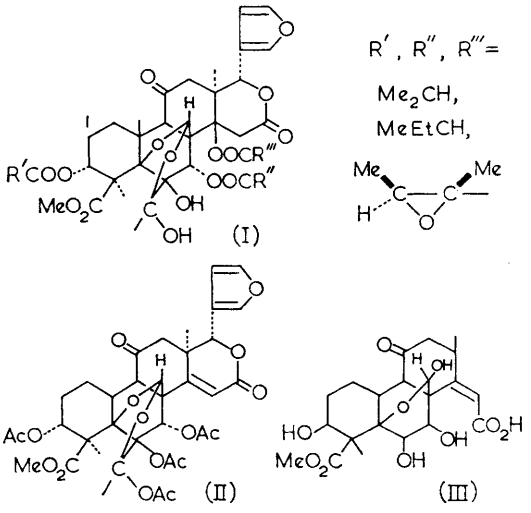
Compound (B) we consider to have the structure (II), compound (A) we consider to be the acid (III).

Biogenetically, such a structure might arise from an intermediate similar to 7-oxo-7-deacetyl-14,15-deoxygedunin, such as is involved in the biosynthesis of methyl angolensate. The 5β-oxygen may suggest a C-5–C-6 double bond being involved at some stage.

The stereochemistry at C-3 is of interest. In (B) $J_{AX} + J_{BX}$ for (C-3)–H is 8 c./sec., suggesting an axial acetyl group, while in entandrophragmin itself $J_{AX} + J_{BX}$ is 15 c./sec., suggesting an equatorial acyl group.

Although it is possible to imagine epimerisation at C-3 through a reversed aldol condensation, it is not clear why this should go in what appears to be an unfavourable direction. Provisionally, we suggest that the acyloxy-group is α, but that on account of the considerable steric hindrance, ring-A in entandrophragmin is in a boat conformation, in which the 3β-proton has a considerable coupling constant. In the less crowded acetate (B), ring-A returns to the chair conformation, in which (C-3)–H is equatorial.

We are grateful to Dr. A. Melera for 100 Mc./sec. spectra, and decoupling experiments.



(*Received, November 2nd*, 1966; *Com.* 844.)

[1] A. Akisanya, C. W. L. Bevan, J. Hirst, T. G. Halsall, and D. A. H. Taylor, *J. Chem. Soc.*, 1960, 3827.
[2] D. A. H. Taylor, *J. Chem. Soc.*, 1965, 3495.
[3] Unpublished work.
[4] E. O. Arene, C. W. L. Bevan, J. W. Powell, D. A. H. Taylor, and K. Wragg, *Chem. Comm.*, 1966, 627.
[5] W. Merz, W. A. Rohde, K. Rabindran, P. Jayaraman, and N. Viswanathan, *J. Amer. Chem. Soc.*, 1962, **84**, 3857.
[6] N. S. Ohochuku and J. W. Powell, *Chem. Comm.*, 1966, 422.
[7] B. E. Nielsen and J. Lemmich, *Acta Chem. Scand.*, 1965, **19**, 1810.
[8] *Cf.* A. D. Cross, *Quart. Rev.*, 1960, **14**, 326.