Acid-catalysed Cyclisation Reactions of the Lignan Cubebin

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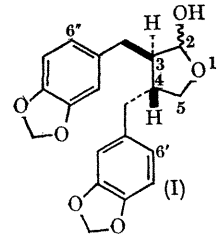
Summary The structures of the acid-catalysed reaction products from cubebin have been elucidated.

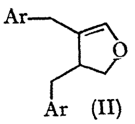
CUBEBIN (I)[1,2] is reported to be dehydrated to 'cubebinic ether' (II)[2] when treated with halogen acids in acetic acid; this ether is said to be reduced to 'cubebinol' (III) by sodium and alcohol.[2,3] On the other hand, cubebin gives a compound of unknown structure 'isocubebinic ether' when treated with sulphuric acid–acetic acid.[3] Surprisingly, this gives 'cubebinol' with methanolic hydrochloric acid.[3] Re-investigation now shows that all three named products are in fact cyclisation products, and the accepted chemistry[4] of this lignan must be superseded.

N.m.r. and other spectral data for cubebin are compatible with structure (I) and show that it exists, in chloroform, almost entirely as the hemiacetal. 'Isocubebinic ether', $C_{20}H_{18}O_5$, m.p. 156—157°, $[\alpha]_D^{26} + 26{\cdot}9°$ ($CHCl_3$) was chromophorically similar to cubebin in the u.v. region, λ_{max} 292 (ϵ 8300) and 237 (7300) nm. The three aromatic protons of one piperonyl unit gave a broad singlet (τ 3·32) whilst those from the second unit formed a singlet (τ 3·45) integrating for only two protons: aromatic cyclisation at

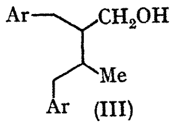
C(6′) or C(6″) is thus indicated. Two structures (IV) and (VII) involving a 2-carbonium ion from the tetrahydrofuran (I) enter into consideration, and only (IV) is consistent with n.m.r. and other data. The three protons on carbon atoms adjacent to oxygen are clearly observable: H(2) resonated as a singlet at τ 5·60 and no coupling could be observed, in accord with a measured C-H(2)–C-H(3) dihedral angle of ~80°. The 5-methylene protons are nonequivalent with τ 6·34 and 5·7—6·1 for H(5a) and H(5b) respectively. Coupling constants $J_{5a,5b}$ 8 and $J_{4,5a}$ ~0 Hz were observed and a measured C-H(4)–C-H(5a) dihedral angle of ~95° would again lead to near zero coupling. In structure (VII), the coupling of H(2) to its neighbour in a *cis*- (or *trans*-) fused five-membered system would be appreciable (*cis* ~8 Hz from the Karplus equation, though its accuracy here is disputable: a model is dihydrosterimatocystin[5] with *J* 5·8 Hz). Similarly, neither 5-proton in the geometry (VII) is likely to display near-zero vicinal coupling.



(I)

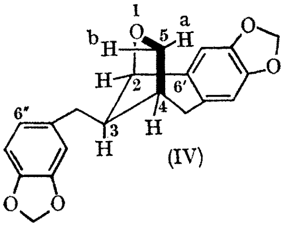


(II)

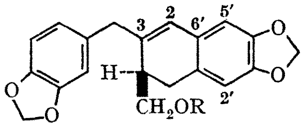


(III)

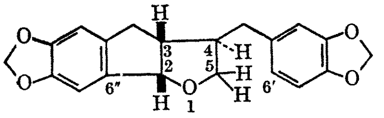
[Ar=3,4-methylenedioxyphenyl]



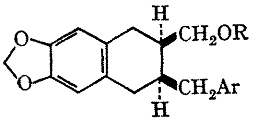
(IV)



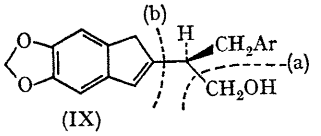
(V) R=Ac (VI) R=H



(VII)



(VIII)



(IX)

'Cubebinic ether' (m.p. 59° and 71°, dimorphic), $C_{22}H_{20}O_6$, $[\alpha]_D^{20}$ + 23·0° ($CHCl_3$), ν_{max} 1730 cm.$^{-1}$ is in fact an acetate ester. Hydrolysis gives a primary alcohol ν_{max} 3637 cm.$^{-1}$ (CCl_4, *c* > 0·005M), re-acetylateable to 'cubebinic ether'. This alcohol answers the description of 'cubebinol', having m.p. 92°, $[\alpha]_D^{23}$ + 35·1°: it is thus not a reduction product. Cubebinol and its acetate both showed styryl chromophores, λ_{max} 291 (ε 13,050) and 309 (9830) nm. for the former. Cubebinol is clearly (VI), formed by proton-catalysed opening of the bridged ether (IV). It shows three aromatic protons in the n.m.r. as a singlet (τ 3·32) with the remaining aromatic hydrogens H(2′) and H(5′) in (VI) as singlets at τ 3·53 and 3·42. The vinyl proton and the two methylenedioxy-groups give rise to singlets at τ 3·91, 4·13, and 4·18. The methylene of the dihydronaphthalene gives a doublet at τ 7·18 (*J* 5 Hz) and the two side-chain methylenes produce a multiplet, τ 6·45—6·7: the single methine proton is represented by a multiplet at τ 7·5—7·9. Hydrogenation of cubebinol gives the same compound (VIII) as is produced by hydrogenolysis of 'isocubebinic ether', confirming the relationship.

Mass-spectral and o.r.d. information will be reported in full elsewhere, but two points bear on the acceptance of structure (IV). Were the correct structure of 'isocubebinic ether' (VII), ether opening (unexpected in dilute acids) would give (IX). No significant cleavages leading to fragments *m/e* 307, or *m/e* 159 or 179, corresponding to scissions (a) or (b) are found in the mass spectrum. Further, a strong negative Cotton effect at 323—256 nm. (*a* 314) is found in the o.r.d. spectrum of cubebinol. With a quasi-equatorial disposition for the hydroxymethylene, this is expected for the inherently dissymmetric (skewed styrene) chromophore in (VI).[6] The indene (IX) has a dissymmetrically perturbed chromophore involving a flexible system (or at most, a homoconjugated chromophore).[6] The authentic compound (II) is readily prepared from cubebin ($POCl_3$–pyridine) and is quite different from 'cubebicic ether'.

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[1] E. Mameli, *Gazzetta*, 1935, **65**, 886; R. D. Haworth and W. Kelly, *J. Chem. Soc.*, 1937, 384; *Chem. and Ind.*, 1936, 901.
[2] T. Ishiguro, *J. Pharm. Soc. Japan*, 1936, **56**, 444.
[3] E. Mameli, *Gazzetta*, 1909, **39**(I), 477; 1912, **42**(II), 546.
[4] W. M. Hearon and W. S. MacGregor, *Chem. Rev.*, 1955, **55**, 957; H. Erdtman, "Moderne Methoden der Pflanzenanalyse", ed. K. Paech and M. V. Tracey, 1955, vol. 3, p. 428.
[5] E. Bullock, J. C. Roberts, and J. G. Underwood, *J. Chem. Soc.*, 1962, 4179.
[6] P. Crabbé and W. Klyne, *Tetrahedron*, 1967, **23**, 3449.