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AN 11β, 12β-EPOXY CARDIAC GLYCOSIDE FROM CERBERA Sp.

J. Cable, R.G. Coombe and T.R. Watson,
Department of Pharmacy, University of Sydney,
Sydney, Australia.

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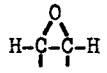
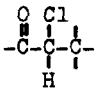
Cerbertin, $C_{32}H_{46}O_{10}$ (I) and deacetylcerbertin $C_{30}H_{44}O_9$ have been isolated from the kernels of the ripe fruit of both Cerbera floribunda and C. dilatata (1). The presence of the characteristic butenolide side chain was deduced from spectral, chemical and pharmacological evidence. The major products resulting from the hydrolysis of deacetylcerbertin with methanolic hydrochloric acid were an aglycone $C_{23}H_{33}O_5Cl$ (II) and the carbohydrate L-Thevetose. Acetylation of the chloroaglycone gave a monoacetate $C_{25}H_{35}O_6Cl$. Treatment of cerbertin (I), deacetylcerbertin or acetylcerbertin with chloroform containing hydrochloric acid gave the corresponding chlorhydrin (III). The presence of an hydroxyl group at C_{14} in the steroid nucleus was confirmed by the formation of an isolactone. The remaining oxygen function has now been shown to be present as an epoxide.

Recently Flury and Reichstein (2) have characterised tanghinigenin (from Cerbera tanghinia Hooker, = Tanghinia venenifera Poir) as 7β,8β-epoxy-digitoxigenin.

The position of the epoxide was indicated by the fact that the hydroxyl group of the derived chlorhydrin (III)

could not be acetylated but was oxidised by chromic acid to a ketone (IV) (λ_{max} 218 mμ, log ε=4.2; λ_{max} 292 mμ, log ε=1.9). The only likely position for this hydroxyl group is C 11-β.

The n.m.r. spectrum of cerbertin, deacetylcerbertin and acetylcerbertin clearly showed two doublets at 6.92τ and 7.10τ (J = 3.9 c.p.s., area 2 protons). The chemical shift and the multiplicity confirmed the presence of an epoxide of the type  which is also evidence against a tertiary structure of the derived chlorhydrin (III).

The n.m.r. spectrum of the chlorketone (IV), obtained by oxidation of the chlorhydrin from acetylcerbertin, contained no bands in the region of 7τ, but new singlet at 4.7τ (one proton), which may be assigned to the proton of an α-chloroketone of the type  . This evidence indicates the structure of the chlorketone to be an 11,keto-12,chloro-steroid.

Tori et al.(3) in their study of the n.m.r. spectra of steroidal epoxides point out that it is not possible to distinguish between the α- and β-conformations of 11,12-epoxides on the basis of coupling constants or chemical shifts, and the coupling constants of the epoxide of cerbertin, $J_{11,12}$ = 3.9, $J_{9,11}$ = 0, are in good agreement with those found by Tori.

An 11β,12β-epoxide is proposed for cerbertin since the favoured mechanism of diaxial opening (4) would lead to the 11β-hydroxy,12α-chloro compound, whereas the alternative 11α,12α-epoxide would produce the 11β-chloro,12α-hydroxy

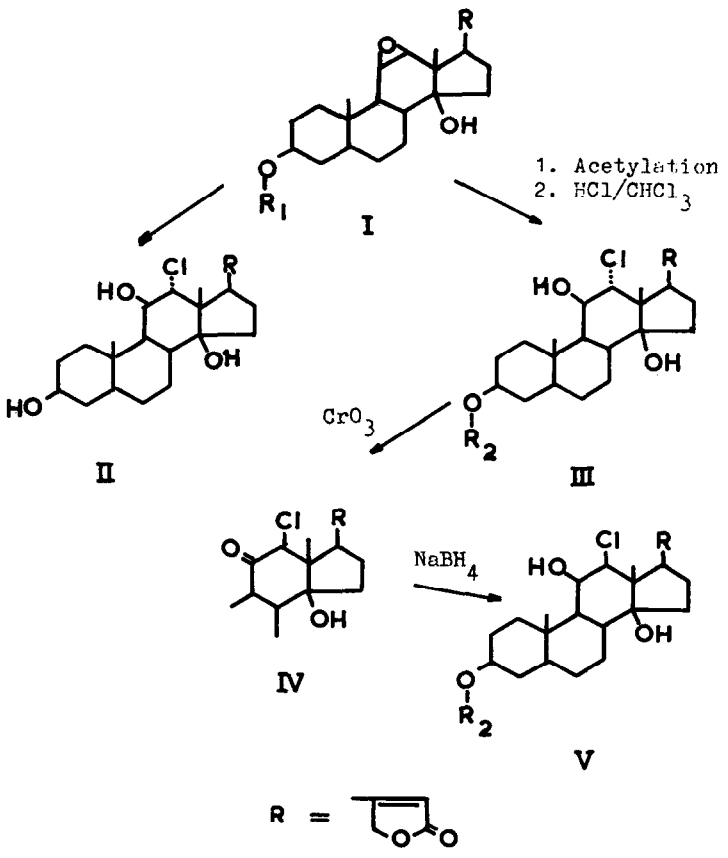
steroid. Since the hydroxyl group of the chlorhydrin could not be acetylated, the 11β-conformation is favoured for the hydroxyl group of the chlorhydrin.

As the ultraviolet absorption spectrum of the chlorketone (IV), obtained from the chlorhydrin, does not show the usual bathochromic shift associated with axial α-haloketones (5), the chlorine atom at C_{12} must be in the equatorial conformation. The epimerisation of the C_{12}-chlorine could occur during the chromic acid-acetic acid oxidation, which would allow the chlorine to occupy the preferred conformation.

The optical rotatory dispersion curve of the chlorketone (IV) shows a positive Cotton effect with the maximum of the first extremum at 320-310 mμ and the second extremum at 270 mμ. ([Ø]; 400 mμ, -255°; 320 mμ, +2130°; 310 mμ, +2260°; 270 mμ, -5270°; 251 mμ, -4000°; 240 mμ, -5700°.) The position of the first extremum agrees with the absorption maximum of the carboxyl group at 292 mμ and supports the equatorial conformation of the adjacent halogen atom. A comparison of this O.R.D. curve with those of 11,12-ketols of the 14β-OH steroids (6) shows that the chlorketone (IV) is more likely to be the 11-keto,12β-chloro compound than the 11-keto,12α-chloro compound.

Reduction of the chlorketone with sodium borohydride gives an isomeric chlorhydrin (V) which differs in physical constants (m.p. 151-156°, $[\alpha]_D^{20}$-69°(EtOH), infrared spectrum is different in the 8-12μ region) from those of the original chlorhydrin (m.p. 138-142°, $[\alpha]_D^{20}$-47°(EtOH)). This reduction product must be the 11β-hydroxy,12β-chloro compound.

These results are summarised in the following diagram:



R =

R_1 = Acetyl-L-Thevetose

R_2 = Diacetyl-L-Thevetose

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REFERENCES

1. J. Cable, R.G. Coombe and T.R. Watson, Aust. J. Chem. in press, No.12 (1964).
2. E. Flury and T. Reichstein, Ann. Chim. (Rome) 53, 23 (1963).
3. K. Tori, T. Komeno, T. Nakagawa, J. Org. Chem. 29, 1136, (1964).
4. R.E. Parker and N.S. Isaacs, Chem. Rev. 59, 737 (1959).
5. R.C. Cookson, J. Chem. Soc., 282 (1954).
6. C. Djerassi, O. Halpern, V. Halpern, O. Schindler and Ch. Tamm, Helv. Chim. Acta 41, 250 (1958).