ALTHOLACTONE, A NOVEL TETRAHYDROFURO[3,2b]PYRAN-5-ONE FROM A *POLYALTHIA* SPECIES (ANNONACEAE)

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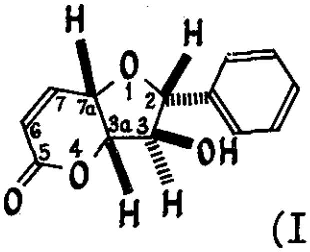
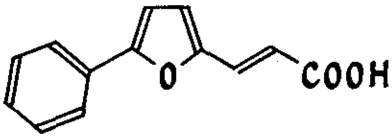
Dedicated to
Professor R.B.Woodward
on the occasion of his sixtieth birthday

Altholactone has tentatively been assigned the structure 3-hydroxy-2-phenyl-2,3,3a,7a-tetrahydro-5H-furo[3,2b]pyran-5-one (I) on the basis of its chemical reactions and physical properties.

Extracts of the bark of an unnamed *Polyalthia* species (Herbarium voucher specimen TGH 11950) from the Eastern Highlands district of New Guinea yielded a previously undescribed crystalline compound which we have named altholactone. Altholactone, mp 75°(H_2O or C_6H_6),$[\alpha]_D^{20}$ +188°



(I)



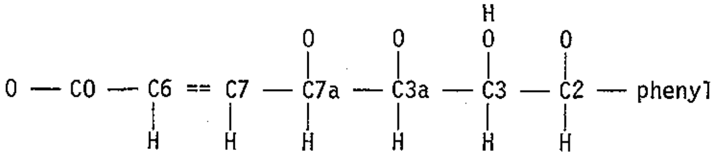
(II)

(*c*, 0.5 in EtOH), $C_{13}H_{12}O_4$ (M^+ ion, *m/e* 232) had properties in keeping with structure (I) as will be shown. Acetylation gave a *mono-O-acetate*, $C_{15}H_{14}O_5$, mp 142°, $[\alpha]_D^{23}$ +208°(*c*, 0.5 in EtOH) which on alkaline hydrolysis produced an acidic oil (as did altholactone itself) and this on standing reverted to altholactone. This behaviour is characteristic of five- and six-membered ring lactones and the carbonyl and double bond absorption at ν_{max} 1725 and 1638 cm^{-1} were in keeping with an αβ-unsaturated six-membered ring. Hydrogenation of the acetate over Pd/C ceased with the uptake of 1 mole of hydrogen to give O-*acetyl-6,7-dihydroaltholactone*, $C_{15}H_{16}O_5$, mp 99°, ν_{max} 1740 cm^{-1} (ester and unstrained saturated lactone). The isolated phenyl chromophore was evidenced by low intensity benzenoid absorption bands in the 260 nm region (ε 380) and by the formation of one mole of benzoic acid on permanganate oxidation.

The carbon backbone and position of the phenyl and carboxy groups on it were revealed by the following reactions. Altholactone gave a crystalline *mono-O-tosylate*, $C_{20}H_{18}SO_6$, mp 105°, $[\alpha]_D^{20}$ +104°(*c*, 0.5 in EtOH), which on boiling in sodium ethoxide solution afforded a yellow crystalline *acid*, $C_{13}H_{10}O_3$, (M^+ 214), mp 182°, shown to be the trans-*phenylfuranacrylic acid* (II). Thus (II) had an extended conjugated system with maxima exhibiting fine structure at λ 232 and 337 nm (ε 13,100 and 23,800) resembling a modified 7-phenyl-2,4,6-heptatrienoic acid chromophore [all *trans* isomer had maxima exhibiting fine structure at λ 241 and 335 nm (ε 7,800 and 53,100)]^1 while the nmr spectrum had one-proton olefinic doublets at δ 6.36 and 7.46 with a *trans* coupling of 16 Hz; one-proton doublets at δ 6.71 and 6.73 (*J* 4 Hz) typical of β-hydrogens on a furan ring, and a five-proton multiplet between δ 7.3-7.8 from the aromatic hydrogens. Reduction of (II) with sodium amalgam gave 3-(5'-phenyl-2'-

furyl)propionic acid, mp 117° identical with an authentic sample.[2] The previously unknown acid (II) was synthesized from *trans*-furan-2-acrylic acid and benzene diazonium chloride by Freund's method[3] in very low yield, but the product was free from structural isomers and identical with the degradation product (II) in all respects.

The exact course of the degradation sequence was obscure at this stage and structural inferences particularly uncertain on account of the severe conditions needed for the formation of (II). Nevertheless it proved a correct working hypothesis that the furan ring in (II) arose from a tetrahydrofuran in altholactone. This being so, the structural features already described were accommodated by formula (I) with the stereochemistry and position of the hydroxy group still undefined. Most of these remaining details were provided by nmr spectroscopy.



$$\mathrm{O - CO - \underset{H}{C6} = \underset{H}{C7} - \overset{O}{\underset{H}{C7a}} - \overset{O}{\underset{H}{C3a}} - \overset{\overset{H}{O}}{\underset{H}{C3}} - \overset{O}{\underset{H}{C2}} - phenyl}$$

δ 6.15 6.95 4.6 4.85 4.4 4.7

J_{67} J_{77a} J_{7a3a} J_{3a3} J_{23}

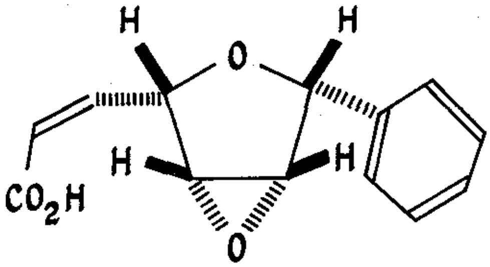
10 5 5.3 2.2 5.6 Hz

The pmr spectrum of altholactone in $CDCl_3$ solution was well resolved and consisted of six non-overlapping multiplets each of one proton, a broad signal, representing one proton, which was removed by exchanging the sample with D_2O, and a five-proton multiplet at δ 7.3 representing the aromatic protons. The chemical shifts of the six one-proton signals were all downfield of δ 4.0 suggesting that these atoms were either on carbon attached to oxygen, or on carbon double bonds. The magnitude of the coupling constants was consistent with vicinal rather than geminal couplings and long range couplings were absent. The coupling constants alone were sufficient to define uniquely the structural inter-relationships of the protons in the partial formula on the previous page. Irradiation at δ 6.9 resulted in the collapse of the δ 6.15 and 4.6 signals as expected. The spectrum in DMSO-d_6 showed the exchangeable proton of the hydroxy group as a doublet at δ 5.97 ($J \sim 5$ Hz) coupled to H3 (now a sextet, additional $J \sim 5$ Hz). Confirmation that the hydroxy group was at C3 came from an acylation shift of 0.96 ppm downfield for the H3 signal in the spectrum of the acetate.

A combination of methods was used to arrive at the relative configuration depicted in (I) because of the inherent difficulties in using coupling constants for calculating dihedral angles in furanoses. A *cis*-fused bicyclic ring system was most favoured after examination of Dreiding models of all possible isomers of (I). The *cis* model had a flexibility which allowed the dihedral angle ∠H7H7a to vary from 15 to 90° so that one would expect an averaged value for $J_{7,7a}$ together with the long range coupling $J_{6,7a}$ a minimum. The measured coupling constants collected in the table supported this, for $J_{7,7a}$ for altholactone and derivatives was

	J_{23}	J_{33a}	J_{3a7a}	J_{67}	J_{67a}	J_{77a}
Altholactone	5.6	2.3	5.3	10	0	5.0
O-Acetylaltholactone	3.6	1.3	4.3	10	0	5.4
O-Acetyldihydroaltholactone	4.5	1.4	3.8	-	0	-
O-Tosylaltholactone	-	-	4.0	10	0	5.5
Ring-opened Acid	4.0	2.0	4.3	12	1.6	7.1
Epoxy Acid	0	3.0	0	12	1.0	7.0

close to the averaged value found in the ring-opened acids and $J_{6,7a}$ was zero except in the acids where free rotation resulted in an averaged value. In contrast, the *trans*-fused model had little flexibility and the dihedral angle /H7H7a was near 90°. Predictably, $J_{7,7a}$ would be near zero, $J_{6,7a}$ measurable and $J_{3a,7a}$ much larger than observed (/H3aH7a being close to 180°). The low values found for $J_{3,3a}$ were strong but not conclusive evidence that H3 and H3a were *trans* (/H3H3a 80-135° from the model). Chemical evidence supported this, for treatment of O-tosylaltholactone with aqueous barium hydroxide at room temperature gave an *epoxy acid*, mp 114°, $C_{13}H_{12}O_4$, M^+ 232, considered to be (III). Formation of (III) occurred by a concerted process initiated by base hydrolysis of the lactone generating C3a-O^- which attacked at C3 with *trans* elimination of the p-toluene sulphonate ion and inversion of H3. The pmr spectrum of (III) had the characteristics of spectra of 2,3-anhydrofuranoses[4] with a small coupling across the epoxide and zero couplings for the epoxide protons with other protons on the tetrahydrofuran ring. Because of this peculiar feature no information on the relative stereochemistry at C2 emerged, but for chemical reasons H2 must be *cisoid* to C3-OH as the O-tosylate showed remarkable stability to boiling collidine from which it was recovered unchanged. It must be concluded that *trans* elimination cannot occur.



(III)

We are indebted to A.F.Beecham for the CD spectrum of altholactone and for his interpretation that the positive Cotton effect at 265 nm suggested that the system O=C-C=C had left handed chirality, while the strongly positive curve at shorter wavelengths (peak not reached at 220 nm) was attributable to the right-handed chirality of the allylic oxygen-ethylenic double bond system[5,6]. A positive Cotton effect for the $n \rightarrow \pi^*$ transition has been noted for a number of naturally occurring αβ-unsaturated δ-lactones and has been interpreted in terms of conformation and absolute configuration[5,7]. In the case of altholactone the CD spectrum indicated a preferred conformation consistent with the absolute configuration of (I) as shown.

Altholactone is biogenetically related to a number of α-pyrones of the Lauraceae, Annonaceae and Piperaceae families and in formal terms can be regarded as an oxygenated and cyclized derivative of the lactone of 5-hydroxy-7-phenylhepta-2,6-dienoic acid (goniothalamin)[8,9].

Acknowledgments

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