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ON THE ABSOLUTE CONFIGURATION OF TOXOL AT C-3. VICINAL H-H COUPLING CONSTANTS IN 2-ALKYL-3-HYDROXYDIHYDROBENZOFURANS.

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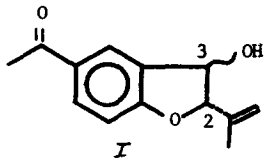
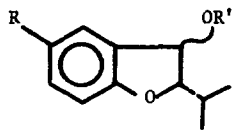
Toxol, (-)-2-iso-propenyl-3-hydroxy-5-acetyl-2,3-dihydrobenzofuran, isolated from Aplopappus heterophyllus, has been reported to have the 2S, 3S configuration (I,3α-OH)[2,3].



I



II trans:-OR'(β)

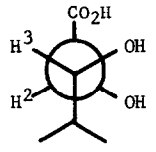
III cis:---OR'(α)

While the configurational assignment at C-2 has been correlated with several compounds of known absolute configuration[3], the assignment at C-3 was based on one experimental observation, namely, the ozonolysis of toxol to yield supposedly (+) tartaric acid[2,3]. The present work shows that the configuration of toxol at C-3 must be reassigned as R (I, 3β-OH).

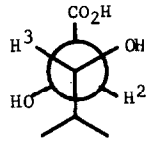
We recently reported the synthesis of racemic trans (II:R=$COCH_3$,R^1=H) and cis-2-isopropyl-3-hydroxy-5-acetyl-2,3-dihydrobenzofurans (III:R-$COCH_3$,R^1=H)[4]. The isomer, which was spectrally identical with dihydrotoxol was assigned a cis relationship at C-2,C-3. This assignment led to an unexpected consequence, namely, in synthetic dihydrotoxol and all of its precursors (III:R=Br, R^1=H; R=Br,R^1=$COCH_3$; R=CO_2H,R^1=H; R=$COCH_3$,R^1-$COCH_3$) the coupling constant for the vicinal C-2, C-3 protons was consistently smaller (J=3-4.5 vz 5-6 Hz) than in the isomeric trans series (II:R=Br,R^1=H; R=Br,R^1=$COCH_3$; R=$COCH_3$,R^1=H), in apparent violation of the Karplus equation[5]. Since it had been observed that $J_{cis} > J_{trans}$ for 2-alkyl-3-methyl-2,3-dihydrobenzofurans[6], the

unusual results mentioned above, were thought to arise from an electronegativity effect of the C-3 hydroxy (or acetoxy) group[4,7]. Recently, however, Pappas et al.[8] and Mertes and Powers[9] have shown that for 2-phenyl-3-hydroxy-2,3-dihydrobenzofurans and substituted 3-hydroxy (or 3-acetoxy)-2-methyl-2,3-dihydrobenzofurans, respectively, $J_{cis} > J_{trans}$ and the latter workers confirmed their stereochemical assignments by an x-ray diffraction study of the methiodide salt of cis-7-dimethylamino-3-hydroxy-2-methyl-2,3-dihydrobenzofuran. Thus we were prompted to seek an independent check of the stereochemical assignments in the two series II and III.

An x-ray diffraction analysis was performed on the 2-isopropyl-3-hydroxy-5-bromo-2,3-dihydrobenzofuran of m.p. 112-113°[4], belonging to the series not related to toxol[10]. The compound crystallized as orthorhombic crystals (a=16.69A, b=5.87A, and c=22.72A) of space group Pbca with eight molecules per unit cell (ρ_{obs}=1.56; ρ_{calc}=1.55 g/cm^3). Unfortunately, the crystal was unstable and decomposed after 48 hours of data collection. The structure was refined, using the 254 non-zero reflections obtained before decomposition, to an R value of 0.135; the structure obtained indicated the cis isomer III (R=Br, R'=H) and not the trans isomer as previously assumed[4]. As further support for this stereochemical assignment, this compound was shown to yield on ozonolysis threo-2,3-dihydroxy-4-methylpentanoic acid (IV), while its isomer of m.p. 44.5-45°[4,10] (II:R=Br,R'=H) gave the corresponding erythro acid V.



IV

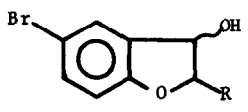


V

Racemic threo-2,3-dihydroxy-4-methyl pentanoic acid (IV:m.p.111-112°) was prepared by cis hydroxylation of trans-4-methyl-2-pentenoic acid[11] ($J_{2,3}$= 15.5 Hz)[12] according to the procedure of G. Braun[13]. Similarly, racemic erythro-2,3-dihydroxy-4-methylpentanoic acid (V:m.p. 127°) was prepared from cis-4-methyl-2-pentenoic acid[14] ($J_{2,3}$= 11.5 Hz)[12]. While isomers IV and V were prepared by stereospecific syntheses, their n.m.r. spectra further confirmed the configurational assignments. Thus, the averaged spectrum[15] (in D_2O) of IV (preferred conformer indicated) showed $J_{2,3}$= 2 Hz while that of V (preferred conformer indicated) showed $J_{2,3}$= 5.5 Hz at room temperature. The n.m.r. spectra of the crude products of ozonolysis of III (R=Br, R'=H) and II (R=Br,R'=H), respectively, clearly indicated the presence of threo IV and the absence of erythro V in the former case, while in the latter case the reverse was true. Threo IV produced in the ozonolysis

of III (R=Br,R'=H) was isolated by preparative thin-layer chromatography.

Thus, it is now quite clear that no violation of the Karplus equation exists in 2-alkyl-3-hydroxydihydrobenzofurans, and we have prepared in addition to II (R=Br,R'=H) and III (R=Br,R'=H), using the previously described procedure[4,10,16], the cis and trans 2-alkyl-3-hydroxy-5-bromo-2,3-dihydrobenzofurans VI-VIII and in each case J_{cis}= 5.5-6.5 Hz while J_{trans}=3.5-4.0 Hz (cis, trans



VI R = CH_3
VII R = C_2H_5
VIII R = nC_3H_7

assignment based on evidence presented above). While the complexity of the n.m.r. spectrum of toxol in the region of interest prevented the evaluation of $J_{2,3}$, the C-3 proton in toxol acetate was clearly visible at τ 5.93 and showed $J_{2,3}$ = 3 Hz. This observation and the derivation of racemic dihydrotoxol from the isomer now known to be trans-2-isopropyl-3-hydroxy-5-bromo-2,3-dihydrobenzofuran clearly shows that the C-2 isopropenyl group and C-3 hydroxyl groups in toxol are trans and its absolute configuration is therefore 2S, 3R. Thus the origin of (+) tartaric acid in the ozonolysis of toxol remains a mystery. Unfortunately, sufficient toxol was not available to reinvestigate this point, but the most likely explanation is that meso tartaric was actually produced in the ozonolysis and the observed optical rotation was due to a contaminant[17].

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10. Based on the results presented in this communication, the stereochemistry of the two series of dihydrobenzofurans in reference 3 should be reversed. Thus compounds III, IV, VII and VIII in reference 3 are cis, while compounds IX, X, XI, XII and XIII are trans.

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16. Whereas the previously reported conditions[4,10] gave almost pure II (R=Br, R'=H), the conditions reported for preparation of III (R=Br, R'=H) actually gave a mixture of cis and trans isomers, with the cis isomer being separated by crystallization from ethanol.

17. The "isolated" (+) tartaric acid showed $[\alpha]_D$ + 8.4° vz reported $[\alpha]_D$ + 12°[3] and its dimethyl ester showed a plain negative o.r.d. curve "similar" to that previously reported[2].