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THE ABSOLUTE CONFIGURATION OF TUTIN

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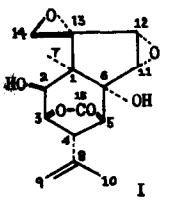
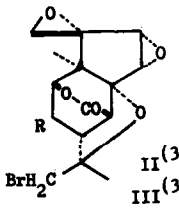
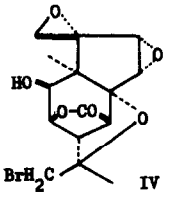
The relative configuration I has been assigned to tutin based on the X-ray crystallography of α-bromoisotutin II[1a] and α-bromoisotutinone III,[1b] and the absolute configuration has been assumed to be I only by analogy with the absolute configuration[2b] of picrotoxinin. Evidences are now presented which establish this configuration to be correct, along with observations of large downfield shifts in the N.M.R. spectra of the terminal epoxide, and the angular methyl protons, and their correlations with the stereostructure of tutin.



I



II[3b,5] R = OH
III[3b] R = O



IV

Structure I is based on the assumption that II arises from α-bromotutin IV by the isomerisation of the γ-lactone to the δ-lactone and that no other major structural change occurs upon the isomerisation of IV to II. Therefore, additional evidence which substantiates the assumption will be desirable to establish the stereostructure of tutin.

As are summarized in Table 1, tutin, dihydrotutin and α-bromotutin, which

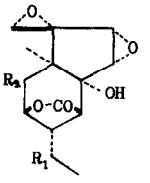
TABLE 1

Resonances of Angular Methyl and Terminal Epoxide Protons (δvalues in p.p.m.)

Compound	C_7 protons		C_{14} protons		J_{AB}(c.p.s.)
	pyridine	$CHCl_3$	pyridine		
tutin I	1.94	1.42*	4.71,**	3.10 (AB quartet)	6
dihydrotutin V	1.98	1.46	4.76,	3.08 (")	6
α-bromotutin IV	1.92	1.57	4.65,	2.99 (")	6
tutinone VI	1.73	1.30	3.07,	2.80 (")	4
α-acetyltutin VII	1.68	1.28	4.08,	3.10 (")	6
coriamyrtin VIII	1.48	1.15	3.31,	3.08 (")	4

*obtained in $CDCl_3$

**partly overlapped by the signal of 2-OH



V[3] R_1= $-CH_3$, R_2= —H, =OH

VI[3b,5] R_1= $=CH_2$, R_2 =O

VII[3] R_1= $=CH_2$, R_2= —H, =OAc

VIII[6] R_1= $=CH_2$, R_2= H_2

have a free hydroxyl group at C_2 exhibit markedly low resonances of the angular methyl and one of the terminal epoxide protons in pyridine[4] while the resonances of these protons in other analogues which lack 2-OH occur upfield. It has been reported that an angular methyl group closely situated to a hydroxyl group in a molecule shifts downfield in pyridine,[7] but the shifts observed with I and its two derivatives are markedly larger than most of those of the reported compounds. The apparently large influence of 2-OH which is trans to the angular methyl group according to the scheme, will be noticeable.

The epoxide shifts of I, IV and V in pyridine, however, are consistent with the β-configuration of 2-OH if the cyclohexane ring in tutin takes the quasi-chair conformation, for an inspection of the stereomodel[8] (Fig. 1) shows that one of the two hydrogens of the terminal epoxide in this conformation is located near the 2-OH, and that another 14-H is situated on the other side.

The preference of the quasi-chair conformation to the quasi-boat conformation in I will be reasonable when the severe interaction between the isopropenyl and the angular methyl group on the quasi-boat conformation is taken into account. The 2-OH thus shown as being trans to the adjacent methyl group is sterically not far from the methyl group on the quasi-chair conformation of the cyclohexane ring when examined with the stereomodel.[9] While various kinds of effect by the groups situated near the angular methyl group including those by 6-OH, 2-OH, 2-carbonyl, 2-OAc, 8-CH_2Br and 13,14-epoxide may be participating in producing the low shifts of the methyl signal of the compounds shown in Table 1, the large downfield shift of the methyl signal of I, IV and V in pyridine may partially be due to the pyridine molecule which is hydrogen-bonded to 2-OH in such a way to give the strong paramagnetic anisotropy effect to the angular methyl group by the steric requirements of the epoxide, the lactone and other groups.

The comparison of the observed magnitude of the coupling constant J_{2H-3H} of IV (2.5 c.p.s., in pyridine) with the coupling constant calculated by the Karplus equation,[10] $J_{2\alpha,3\alpha}\sim3.2$ c.p.s. (dihedral angle $\sim50°$), $J_{2\beta,3\alpha}\sim0$ (dihedral angle $\sim75°$) is also indicative of the β-configuration of 2-OH although the coupling constant may have been influenced by the electronegative substituents on C_2 and C_3.

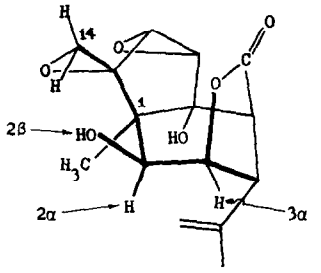
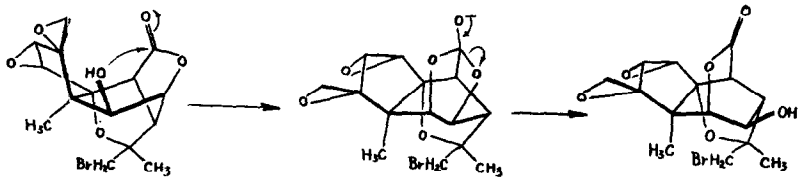


FIG. 1

Conformation of Tutin

The assignment of β-configuration to 2-OH is also favoured by the analogy of the transesterification IV⟶II carried out in alkali without neutralisation, or by treating IV with diazomethane, to the transesterification of β-bromopicrotoxinin to β-bromopicrotoxinic acid,[2a] and also by the probable mechanism of the isomerisation through an intermediate which might be formed by an intramolecular attack of 2-OH to the lactone carbonyl in IV as is shown below:



IV II

The stability of the epoxides in tutin will also be best explained by this stereostructure since the two epoxides in this conformation will be protected from the rear attack by the lactone carbonyl situated right behind both of these epoxides.

The determination of the absolute configuration of tutin has been made by the use of the optical rotatory dispersion[11] and also by the application of the benzoate rule[12] based on the relative configuration of tutin. As is exhibited in Fig. 2, α-bromoisotutinone has shown a negative rotation maximum at 346mμ([M] -4,760°, c = 0.374, dioxane), and the curve was almost superposable on that of methyl β-bromo-oxopicrotoxinate[13] ($[M]_{346}$ -5,482°, c = 0.392, dioxane). The absolute configuration of methyl β-bromo-oxopicrotoxinate is shown by IX based on the absolute configuration of picrotoxinin which was determined by the X-ray crystallography of α_1-bromopicrotoxinin,[2b] when the difference of β-bromopicrotoxinin to α-bromopicrotoxinin is regarded as being due to the configuration of the methyl and the bromomethyl group at C_8. The analogy between these two curves indicates that the absolute configuration of

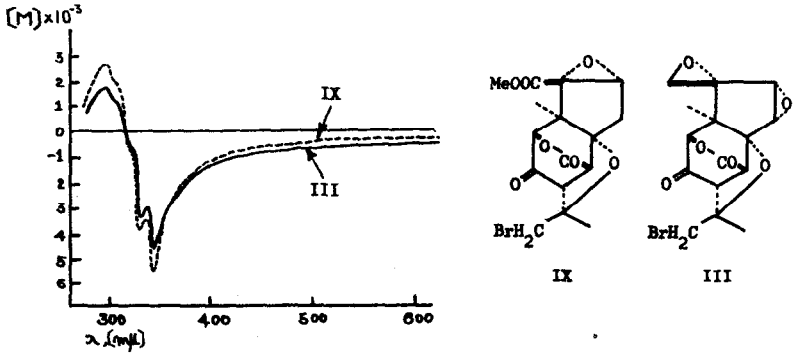


FIG. 2

ORD Curves of α-Bromoisotutinone III and Methyl β-Bromo-oxopicrotoxinate IX.

tutin is I.

The benzoate rule has been applied to α-bromotutin and tutin. Benzoyl-α-bromotutin, $C_{22}H_{21}O_7Br$, m.p. 245° (decomp.) has been obtained by the reaction of α-bromotutin with benzoyl chloride in pyridine. The infrared absorptions (Nujol) at 1780, 1715, 1600 and 720 cm^{-1} show the presence of the benzoyl group and retention of the γ-lactone group. The absence of hydroxyl group indicates that the benzoyl group has been introduced to C_2-oxygen. Besides the steric requirements of "the large group" at C_1 and "the small group" at C_3, the requirements of the terminal epoxide, the lactone and other groups which are sterically near the benzoyl group will also have to be taken into consideration in applying the benzoate rule to α-bromotutin and its benzoate. The requirements of the latter groups, when examined with the stereomodel, are regarded as being analogous to those of the former groups, so as to make the benzoyl group tend to be flanked by 2-H and C_2 to give levorotatory shift.[14] The observed molecular rotations of α-bromotutin ($[M]_D^{20}$ -502°; c = 0.85, dioxane) and benzoyl-α-bromotutin ($[M]_D^{20}$ -840°; c = 1.05, dioxane) indicates the rotation difference to be -338° showing that the absolute configuration at C_2 is in accord with the assignment of the absolute configuration IV to α-bromotutin, and I to tutin. The rotation difference between benzoyltutin[15] ($[M]_D^{20}$ +14°; c = 0.427, dioxane) and tutin ($[M]_D^{15}$ +73°; c = 0.937, dioxane) has shown to be -59°, giving a further confirmation of absolute configuration I of tutin.

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8. The Dreiding stereomodel was used.
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11. ORD curves were measured with a Japan Spectroscopic Company ORD/UV-5 spectropolarimeter at 20°.
12. J. H. Brewster, Tetrahedron 13, 106 (1961).
13. M. Sutter and E. Schlittler, Helv. Chim. Acta 33, 902 (1950); R. M. Carman, C. Hassan and R. B. Johns, J. Chem. Soc. 130 (1959).
14. The steric requirements will be predominant in this compound although the difference of polarizability between C_1 and C_3 group may give some influence.
15. First reported by K. Kinoshita (J. Chem. Soc. Japan 51, 99 (1930)) to have the molecular formula, $C_{19}H_{18}O_6$. The benzoate prepared by the authors, m.p. 182-183° has shown the molecular formula to be $C_{22}H_{22}O_7$.