Picrotoxin and Tutin. Part VII. Experiments with Tutin.*

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The infra-red spectra of tutin and its derivatives are described. Several isomerides of tutin are described and it is shown that the bromotutins are oxidised by chromic acid to the corresponding ketones.

The close similarities between the molecular formulæ of picrotoxinin, $C_{15}H_{16}O_6$, and tutin, $C_{15}H_{18}O_6$, and between the behaviour of the two substances towards bromine and hydrogen, suggest some similarity in structure. Closer examination of tutin has now shown, however, a marked difference in function of the oxygen atoms. This was foreshadowed in Part IV (*J.*, 1952, 1042) where it was shown that tutin and dihydrotutin titrate as potentially monobasic substances under conditions where picrotoxinin and dihydropicrotoxinin titrate as potentially dibasic substances. This has now been correlated with significant differences in the infra-red spectra.

Picrotoxinin and its derivatives consistently show two absorption bands in the carbonyl region of spectra of the solid substances. All the tutin derivatives examined, however, show only one carbonyl band (see Table). Since tutin has no aldehydic or ketonic properties and is potentially monobasic it may therefore be tentatively formulated as a monolactone. It cannot be a dilactone. There remain four oxygen atoms to be assigned functions. Tutin possesses four (Zerewitinoff) active hydrogen atoms, which suggests

Absorption spectra.

(Nujol pastes; bands moderate to strong, unless otherwise stated.)

	OH	CO	C:C		OH	CO
Tutin	3541, 3477	1772	1649	α-Bromotutin ...	3477	1776 (w)
*neo*Tutin	3488, 3425, 3355, 3280	1741	—	β-Bromotutin	3562, 3492, 3224	1773
β-Tutin	3344	1795	—	Bromo*iso*tutin ...	3470	1738
				Bromo*neo*tutin ...	3501	1793

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* Part VI, *J.*, 1952, 2292.

that possibly all four may be present as hydroxyl groups. Tutin forms a monoacetate, and *neo*tutin (see below) a diacetate; tutin reacts with two mols. of phenyl *iso*cyanate. This chemical evidence suggests a minimum of two hydroxyl groups. In the infra-red spectrum of tutin there are two bands in the 3-μ region. Of the bromotutins, α-bromotutin and bromo*iso*tutin (see below) have only one strong band in this region, but β-bromotutin has three well-resolved bands. *neo*Tutin has four strong bands in the 3-μ region. It seems clear that tutin is a polyhydroxy-compound, and that possibly all four unassigned oxygen atoms are present as hydroxyl groups. Unfortunately the substances of this series are not soluble in the preferred solvents and a proper evaluation of the solution spectra is therefore impossible.

As in the picrotoxinin series, the formation of monobromo-substitution products is accompanied by disappearance of the double bond. The conversion of α-bromotutin into an isomeride (now named bromo*iso*tutin) by alkali or diazomethane has already been described (Part IV, *loc. cit.*). β-Bromotutin, however, does not isomerise under these conditions. In this respect the bromotutins differ from the bromopicrotoxinins, both of which are affected (isomerisation and lactone opening) by alkali. Bromo*iso*tutin differs from all the known bromo-derivatives of both the picrotoxinin and the tutin series in being highly resistant to debromination, and the postulated *iso*tutin has not yet been prepared. We have, however, prepared *neo*tutin, the analogue of *neo*picrotoxinin. The existence of a "bromohydrotutin" isomeric with the two known bromotutins has already been established (Slater, *J.*, 1943, 50, 143) and it was suggested that this substance was possibly derived from an isomer of tutin. With the isolation of *neo*picrotoxinin (Part III, *J.*, 1949, 806) it became evident that "bromohydrotutin" must be derived from a *neo*tutin, and we have now isolated such a substance directly from the complex mixture obtained on hydrogenation of tutin in the presence of palladium and mineral acid. In passing from picrotoxinin to *neo*picrotoxinin an acylatable hydroxyl group is generated. Tutin already contains an acylatable hydroxyl group and it was therefore not unexpected that *neo*tutin, $C_{15}H_{18}O_6$, should contain two such groups and form a diacetate. In the picrotoxinin series the change to the *neo*-structure results in the disappearance of the band at 6·06 μ, due to the terminal methylene group of the *iso*propenyl system of picrotoxinin, and this is paralleled by the loss of a similar band by tutin in passage to *neo*tutin. The terminal methylene group of tutin is confirmed chemically by the isolation of formaldehyde from the products of ozonolysis.

From the reaction mixture containing *neo*tutin a second substance, $C_{15}H_{20}O_6$, was isolated, isomeric with the dihydrotutin obtained on hydrogenation of tutin with a platinum catalyst, and with "β-dihydrotutin" (*J.*, 1943, 143). It forms a diacetate, suggesting a relation to *neo*tutin rather than tutin, and can in fact be obtained directly from the former by hydrogenation. It is therefore dihydro*neo*tutin. The nature of "β-dihydrotutin" has not yet been established but we have again observed its occurrence as the main isolatable constituent of the mixture obtained by prolonged hydrogenation of tutin with a palladium catalyst in the presence of mineral acid.

Although tutin is readily degraded by hot mineral acid, short heating with N-hydrochloric acid transforms it into a saturated isomer, a change which parallels the conversion of α-picrotoxinic acid into β-picrotoxinic acid. This substance, therefore termed β-tutin, is in turn isomerised by dilute methanolic sodium methoxide to γ-tutin. In a similar way *neo*tutin with acid forms the saturated β-*neo*tutin; the amount of the latter available did not suffice for us to determine whether a γ-*neo*tutin exists. Five isomers of tutin are thus now known, and a sixth has been isolated as its bromo-derivative. The relations between them are summarised in the annexed scheme.

$$\begin{tikzcd}
\textit{neo}\text{Tutin} \arrow[d, "H^+"] & \text{Tutin} \arrow[l, "H_2\text{-Pd-}H^+"'] \arrow[d, "H^+"] \arrow[r, shift left, "Br_2"] & \alpha\text{-Bromotutin} \arrow[l, shift left, "Zn"] \arrow[r, "OH^-", "\text{or } CH_2N_2"'] & \text{Bromo}\textit{iso}\text{tutin} \\
\beta\text{-}\textit{neo}\text{Tutin} & \beta\text{-Tutin} \arrow[r, "NaOMe", "-MeOH"'] & \gamma\text{-Tutin} &
\end{tikzcd}$$

Surprisingly, although α-bromotutin reacts with diazomethane, tutin itself is unaffected. However, if the *difference* in behaviour of these two reversibly related substances is emphasised, rather than the inertness of tutin, this parallels the *difference* in behaviour of the analogous pair, picrotoxinin and bromopicrotoxinin: picrotoxinin is converted into a derivative of picrotoxic acid, whereas bromopicrotoxinin is converted into a derivative of the very different α-picrotoxinic acid (Part VI, *J.*, 1952, 2292).

Both α- and β-bromotutin are oxidised by chromic acid to dehydro-derivatives, $C_{15}H_{15}O_6Br$, which, when debrominated yield the same substance, dehydrotutin, $C_{15}H_{16}O_6$. Although no carbonyl derivatives have been prepared from them, all three substances show carbonyl absorption in the ultra-violet and are clearly ketones derived from the corresponding secondary alcohols. Bromo*iso*tutin is likewise oxidised to bromodehydro*iso*tutin, which resists debromination by zinc. Dihydrotutin is oxidised by chromic acid to the corresponding ketone, $C_{15}H_{18}O_6$.

EXPERIMENTAL

M. p.s were observed on samples placed in a bath preheated to about 10° below the observed figures.

Reaction of Tutin with Phenyl iso*Cyanate.*—Tutin (220 mg.) was heated with phenyl *iso*cyanate (1 ml.) in a sealed tube at 100° for 20 hr. On cooling, the *bisphenylurethane* was deposited, and, crystallised from toluene–methanol and then toluene, had m. p. 175—177° (Found: C, 65·9; H, 5·6; N, 4·5. $C_{29}H_{28}O_8N_2$ requires C, 65·4; H, 5·3; N, 5·3%).

neo*Tutin.*—Palladous chloride (60 mg.) in hydrochloric acid (2 drops of concentrated acid in 4 ml. of water) was added to tutin (500 mg.) in ethanol (25 ml.) and shaken in hydrogen until the first rapid absorption had ceased. The resulting solution was concentrated to 3 ml., diluted with an equal volume of water, and set aside. Pure neo*tutin* separated as the hydrate (180 mg.), m. p. 108°, $[\alpha]_D^{18}$ +51·5° (in EtOH) (Found: C, 57·7; H, 6·6. $C_{15}H_{18}O_6,H_2O$ requires C, 57·7; H, 6·4%). Bromination yielded bromo*neo*tutin. The *diacetate* (from *neo*tutin, 100 mg., acetic anhydride, 0·6 ml., and pyridine, 0·3 ml.), crystallised from aqueous ethanol, had m. p. 168° [Found: C, 59·7; H, 5·8; Ac, 24·7. $C_{15}H_{16}O_6(CO{\cdot}CH_3)_2$ requires C, 60·3; H, 5·8; 2Ac, 22·8%].

*Dihydro*neo*tutin.*—(*a*) The aqueous mother-liquors from the above preparation slowly deposited crystals of *dihydro*neo*tutin* (100 mg.), m. p. 240°, and finally after recrystallisation from water and then aqueous methanol, 277° (Found: C, 60·6; H, 6·45. $C_{15}H_{20}O_6$ requires C, 60·8; H, 6·8%). (*b*) *neo*Tutin (60 mg.) in ethanol (25 ml.) in the presence of a palladium catalyst (palladous chloride, 30 mg., in water, 2 ml., and one drop of concentrated hydrochloric acid) was hydrogenated for 90 min. (52 c.c. taken up). The resulting solution, when reduced to small volume, deposited material (40 mg.) melting initially at *ca.* 200° and finally, after three crystallisations from water, at 276—277°. It showed no depression with the above specimen.

Dihydro*neo*tutin was recovered unchanged after further hydrogenation with a palladium catalyst for 22 hr. and did not react with diazomethane. The *diacetate* (from dihydro*neo*tutin, 60 mg., acetic anhydride, 1·5 ml., and pyridine, 0·3 ml.) crystallised from methanol and had m. p. 237° [Found: C, 60·1; H, 5·9; Ac, 24·8. $C_{15}H_{18}O_6(CO{\cdot}CH_3)_2$ requires C, 60·0; H, 6·3; 2Ac, 22·6%].

Ozonolysis of Tutin.—Tutin (250 mg.) in ethyl acetate (25 ml.) was ozonised (4 hr.), then evaporated *in vacuo*, and the residual ozonide was decomposed with water overnight. The aqueous solution was distilled to yield formaldehyde, isolated and identified as the dimedone derivative.

β-*Tutin.*—Tutin (2·5 g.) was heated with N-hydrochloric acid (85 ml.) at 100° for 35 min., giving a pale yellow solution. This was continuously extracted with ether (10 hr.), and the extract distilled, to give a residual oil which rapidly deposited crystals which, recrystallised from ethanol, had m. p. 255—258° (Found: C, 61·0; H, 6·1. $C_{15}H_{18}O_6$ requires C, 61·3; H, 6·1%). β-*Tutin* is stable to bromine water and cold dilute alkaline permanganate. It reduces hot sensitised ammoniacal silver nitrate. It is rapidly decomposed by hot 1 : 1 hydrochloric acid.

γ-*Tutin.*—β-Tutin (80 mg.) in methanol (15 ml.) containing sodium methoxide (0·5 ml.; M/15) was set aside for 2 days and then acidified with glacial acetic acid (1 drop), evaporated *in vacuo*, and crystallised from methanol. γ-*Tutin* had m. p. 240° (Found: C, 60·9; H, 6·1%).

It was also obtained by treating β-tutin in methanol with ethereal diazomethane and adding one drop of 2N-sodium hydroxide.

β-neo*Tutin.*—*neo*Tutin was heated for a short period with excess of mineral acid (*ca.* N). The solution rapidly became yellow. The product was continuously extracted with ether, from which a crystalline material separated. This was recrystallised from ether (in which it is nearly insoluble) with the aid of an extraction thimble, giving β-neo*tutin*, m. p. 270° (Found : C, 61·9; H, 6·45%).

α-*Bromodehydrotutin.*—α-Bromotutin (250 mg.) in the minimum quantity of glacial acetic acid was mixed with a saturated solution of chromic acid (750 mg.) in glacial acetic acid. The mixture was set aside overnight, diluted with five volumes of water, and shaken. A crystalline precipitate rapidly formed (195 mg.). The *dehydro*-derivative crystallised from aqueous ethanol in small cubes, m. p. 174—175° (Found: C, 48·3; H, 4·0; Br, 21·3. $C_{15}H_{15}O_6Br$ requires C, 48·5; H, 4·1; Br, 21·6%), $\lambda_{max.}$ 296 mμ (log ε 1·41 in EtOH).

β-*Bromodehydrotutin.*—Oxidation of β-bromotutin (100 mg.) with chromic acid (300 as mg.) above yielded 43 mg. of crude *ketone*, m. p. 130°. It was crystallised six times from ethanol and finally obtained as small cubes, m. p. 210° (Found : C, 48·4; H, 4·25%), $\lambda_{max.}$ 304 mμ (log ε 1·44 in EtOH).

*Bromodehydro*iso*tutin.*—Bromo*iso*tutin (100 mg.) with chromic acid (300 mg.) as above yielded 95 mg. of crystalline *ketone*. Recrystallised from ethanol–dioxan it formed long needles, m. p. 280° (Found : C, 48·2; H, 4·25; Br, 21·0%), $\lambda_{max.}$ 314 mμ (log ε 1·8 in EtOH).

Dehydrotutin.—α-Bromodehydrotutin (60 mg.) in ethanol (3 ml.) was reduced at the b. p. with zinc dust (300 mg.), added gradually, followed by the addition of 15 drops of dilute acetic acid. The product was filtered and cooled. *Dehydrotutin* (30 mg.) separated in long needles and, recrystallised from ethanol, had m. p. 245° (Found : C, 61·4; H, 5·5. $C_{15}H_{16}O_6$ requires C, 61·6; H, 5·5%), $\lambda_{max.}$ 304 mμ (log ε 1·57 in EtOH).

β-Bromodehydrotutin, debrominated in the same way, yielded the same material (m. p. and mixed m. p.).

Oxidation of Dihydrotutin.—Dihydrotutin (250 mg.), oxidised as above with chromic acid (600 mg.), yielded a crystalline product (75 mg.) which recrystallised from ethanol as long flat needles, m. p. 259—260° (decomp.) (Found : C, 60·8; H, 5·75. $C_{15}H_{18}O_6$ requires C, 61·2; H, 6·1%). A further quantity (40 mg.) of the *ketone* was obtained by treating the diluted acetic acid solution with a slight excess of barium acetate, filtering, and extracting the filtrate continuously with ether for 6 hr. It had $\lambda_{max.}$ 299 mμ (log ε 1·52 in EtOH).

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