576. *Picrotoxin and Tutin. Part XII.*[1] *The Structure of Tutin.*

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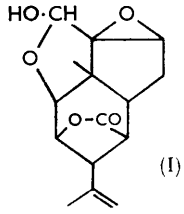
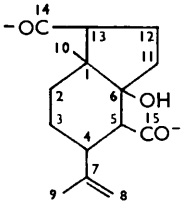
The structure of tutin is shown to be (III).

In Part XI [1] the functional groups of tutin, $C_{15}H_{18}O_6$, were defined as two γ-lactones and two hydroxyl groups, one secondary and the other tertiary, thereby accounting for all of the oxygen atoms in the molecular formula. Any attempt to position the functional groups, however, emphasised the assumed basis of tutin chemistry, *i.e.*, the lack of any experimental evidence relating the carbon skeleton to that of picrotoxinin.

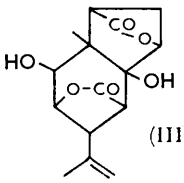
Coriarine, later identified as tutin, was isolated from the same plant as coriamyrtin [2] and since this last compound was formulated as (I), it was reasonable to assume a picrotoxinin carbon skeleton for tutin. Nevertheless, during our investigations not one transformation product could be oxidised to a ketone to which a five-membered cyclic carbonyl function could unambiguously be assigned. The molecular formula for tutin requires a bicyclic ring system, and the choice of a decalin or an indane ring system could not be made from results of chemical degradations, which in our own experience had proved



(I)



(II)



(III)

fruitless. A decision, however, was possible when it was appreciated that an indane system of the picrotoxinin type required the presence of an angular methyl group. Kuhn–Roth estimations were unhelpful, although consistent with similar determinations on picrotoxinin. The nuclear magnetic resonance spectrum of tutin * showed decisively the presence of an angular methyl group, and confirmed the presence of an isopropenyl side chain. The carbon skeleton, consequently, must be that of an indane system and it is reasonable to conclude, further, that the lactone carbonyl groups are placed similarly as in picrotoxinin. We shall develop our thesis on this basis and present evidence which justifies this assumption.

There is no free hydroxyl group alpha to a lactone carbonyl since tutin is not methylated by diazomethane; consequently the tertiary hydroxyl group, which is involved in the facile and stereospecific bromination reaction, can be placed confidently at position 6; this places the isopropenyl side chain at position 4. The similarity of the bromination in both the picrotoxinin and the tutin series enabled a partial formulation to be suggested in Part XI, and this can now be expanded to (II).† The secondary hydroxyl group must be placed in the six-membered ring since oxidation leads to tutinone,[1] a six-membered cyclic ketone (ν_{CO} 1705 cm.$^{-1}$). Tutin is not oxidised by periodic acid, consequently the two hydroxyl groups are not adjacent. From the carbon skeleton (II), the free hydroxyl group must be at position 2 or 3, and the precise position follows from the

* We are most grateful to Dr. N. Sheppard, of the University of Cambridge, for the determination of the spectra and his generous help in their interpretation.

† If coriamyrtin [1] is brominated to form a monobromo-derivative in which the double bond is saturated and the hydroxyl group has been removed, then this is sterically impossible for a compound with structure (I). It is probable that this formulation is incorrect for coriamyrtin, but the published chemistry is limited and it is not possible to suggest an alternative structure on a basis of anything better than speculation.

[1] Part XI, preceding paper.
[2] Kinoshita, *J. Chem. Soc. Japan*, 1930, **51**, 99.

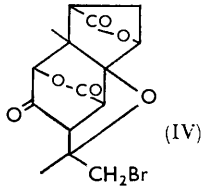
nature of the isotutin derivatives. α-Bromoisotutin is formed by alkaline isomerisation of α-bromotutin, and the view that this represents the isomerisation of a lactone [3] is supported by comparison of the infrared spectra of these compounds, particularly of the derived ketones.[1] The secondary hydroxyl group in α-bromoisotutin is unlikely to be identical with the hydroxyl in α-bromotutin, unless, in the isomerisation, a more profound rearrangement has occurred involving both lactones and leaving the original hydroxyl group unaffected. The isomerisation of monoacetyl-α-bromotutin [4] to α-bromoisotutin suggested that a new hydroxyl group arose in the transformation but was not conclusive. Stronger evidence came from the marked difference in ease of oxidation of α-bromotutin and α-bromoisotutin to the corresponding ketones. Whereas the former was readily oxidised at 37°, the latter required several hours for completion, comparable to the rate of oxidation of β-bromopicrotoxinic acid.[5] Light-absorption data emphasised the difference.[1] Ketones of the tutin series showed maxima about 1705 cm.$^{-1}$ and 3050 Å, which were raised in α-bromotutinone to 1717 cm.$^{-1}$ and 3090 Å. These values contrast with maxima for α-bromoisotutinone at 1739 cm.$^{-1}$ and 3140 Å, which were almost identical with those for oxo-β-bromopicrotoxinic acid [5] at 1740 cm.$^{-1}$ and 3140 Å. For these reasons we place the free hydroxyl group in α-bromoisotutin at position 3. In tutin, therefore, the secondary hydroxyl group is at position 2. There were other considerations, apart from a process of elimination, which also led to the same conclusion. Tutinone did not form a benzylidene derivative nor was it oxidised by selenium dioxide, which suggested that there were no methylene groups adjacent to the carbonyl. Significantly, bromination of tutinone is a reversible reaction, which would be expected if the carbonyl group were at position 2. With the free hydroxyl group in tutin at position 2, the potential hydroxyl at position 3 must be present as a lactone and since this is five-membered,[1] the lactone carbonyl will be at position 5; this agrees with the thesis that $C_{(15)}$ is placed as in picrotoxinin. Tutin, on this basis, should also possess a potential glycol unit.

Acid periodate did not react with tutin, but after alkaline hydrolysis, when two acidic centres were known to be present, sodium metaperiodate showed ready uptake of two equivalents with slower continuing oxidation, remarkably similar to periodate oxidation of hydrolysed picrotoxinic dilactone.[6,7] A 2,3-glycol in picrotoxinin derivatives did not normally show uptake greater than the expected one equivalent, which suggested a second potential glycol unit in tutin associated with structural features that permitted further oxidation. When α-bromotutin, after alkaline hydrolysis and with two acidic centres present,[1] was oxidised with sodium metaperiodate, only one equivalent of periodate reacted. The tertiary hydroxyl group is associated with the potential second glycol and, therefore, the remaining potential hydroxyl group is at position 11. This is in agreement with the placing of a carbonyl at position 13. It is possible at this stage to place all the oxygen atoms in tutin and thus derive structure (III). The free hydroxyl group at position 2 prohibits alternative closures of the lactone carbonyl groups.

The formation of α-bromoisotutin [3] is interpreted as the isomerisation of a γ-lactone to a δ-lactone. This is demonstrated most clearly in the infrared spectrum of the ketones, where the lactone maxima in α-bromotutinone at 1800 and 1775 cm.$^{-1}$ change in α-bromoisotutinone to 1780 and 1756 cm.$^{-1}$, and we suggest structure (IV) for α-bromoisotutinone. This formulation not only accounts for the remarkable similarity of light-absorption data to that for oxo-β-bromopicrotoxinic acid but predicts that debromination should take a course similar to that with the latter compound. When the debromination was carried out it was found that if the time of reaction was short, some α-bromoisotutinone was recovered, and from the mother liquors a dilactone, $C_{15}H_{16}O_6$, with infrared maxima at 1764, 1704, and 1618 cm.$^{-1}$, was obtained. From the near-identity of the relevant portion

[3] Fletcher, Hall, Richards, Slater, and Watson, *J.*, 1954, 1953.
[4] Johnson, Thesis, Victoria University of Wellington, New Zealand, 1955.
[5] Carman, Hassan, and Johns, *J.*, 1959, 130.
[6] Conroy, *J. Amer. Chem. Soc.*, 1957, **79**, 1726.
[7] Carman, Coombe, Johns, and Ward, *J.*, 1960, 1965.

of the infrared spectrum with that shown by the acid, m. p. 219°, reported in Part IX,[5] *viz.* 1764, 1708, and 1615 cm.$^{-1}$, structure (V) is suggested for this compound. If the reaction time for the debromination was increased, the product obtained in good yield was a monochloro-acid, $C_{15}H_{17}ClO_6$, showing light-absorption maxima at 1742, 1727, 1685, and 1608 cm.$^{-1}$ and 2540 and 3200 Å [cf. the acid, m. p. 251°,[5] with maxima at 1675 and 1600 cm.$^{-1}$ (unsaturated ketone) and at 2470 and 3180 Å], and structure (VI) is



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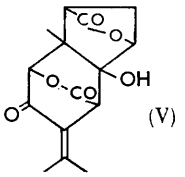

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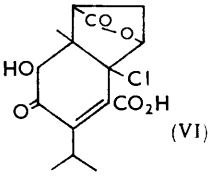
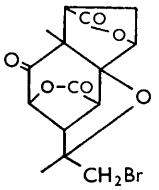


(VI)

suggested for this acid because it reacted with one equivalent of lead tetra-acetate. In working up the product, conditions similar to those for the Lucas test were employed, which accounts for the substitution by halogen. It also emphasises the lack of steric hindrance to reaction with the 6-hydroxyl group, which is a consequence of the presence of an endocyclic double bond. Of further interest is the fact that in the picrotoxinin series[5] the analogous reaction forms a lactone in which the 15-carbonyl group closes to position 12; in tutin where this is not possible, it appears as a carboxyl group.



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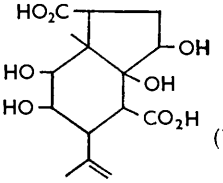


(VIII)

α-Bromotutinone may be represented as (VII). Under the same reaction conditions as were used to isomerise α-bromotutin, the ketone gave in high yield a product, $C_{15}H_{17}BrO_7$, for which lactone absorption only remained in the carbonyl region of the infrared spectrum. This reaction is interpreted as saturation of the carbonyl group with formation of a lactol, a reaction not unusual for δ-keto-acids,[8] and, in keeping with the reversibility or such reactions, with diazomethane the lactol gave a monomethyl ester monomethyl ether, $C_{17}H_{21}BrO_7$.

Tutin and tutindicarboxylic acid reacted readily with two equivalents of alkaline or acid periodate, respectively, with further uptake of reagent, and this at first appeared anomalous before structure (III) was finally derived. Further oxidation was due to subsequent attack at position 5 after initial cleavage (cf., acetoacetic acid and periodic acid [9]). When reaction with lead tetra-acetate was followed, α-bromotutin after alkaline hydrolysis reacted with one equivalent only, but tutindicarboxylic acid reacted rapidly with two equivalents with a marked drop in rate to a maximum of a third. This is in good agreement for structure (VIII) for tutindicarboxylic acid.

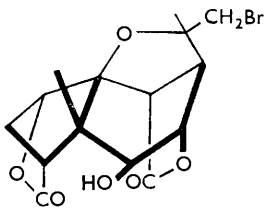
Neotutin [3] can be accounted for on the basis of structure (III) by the isomerisation of the isopropenyl side chain to an isopropylidene grouping. β-Tutin [3] is formed by addition across the double bond of the 6-hydroxyl group to give (IX; Br = H) in the same way as α-picrotoxinic acid isomerises to β-picrotoxinic acid,[3] and once the conformation is stabilised by the formation of an oxygen bridge, alkaline isomerisation of the 15-carbonyl to give a δ-lactone involving the 2-hydroxyl group, accounts for the formation of γ-tutin,[3] a member of the isotutin series.

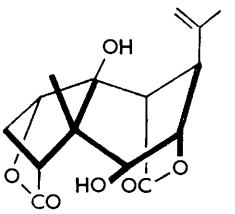
[8] W. Hückel, " Theoretical Principles of Organic Chemistry," Elsevier, Amsterdam, 1955, Vol. I, p. 291.

[9] Manners, *R.I.C. Lectures, Monographs, and Reports*, 1959, No. 2.

The conformation of tutin follows from that for α-bromotutin, which in turn must be very similar to that suggested for α-bromopicrotoxinin.[10] The hydroxyl group at position 2 must be axial to permit isomerisation to the isotutin series. The cyclohexane ring is in a half-chair conformation to permit ready bromination. If the ring junction is *cis*, then the conformation of α-bromotutin will be (IX), and hence (X) will represent tutin. This

(IX)





(X)

conformation accounts for the non-lactonisation of the 14-carbonyl with the 6-hydroxyl and also with the 2-hydroxyl group, because in this latter case the two groups are not within easy bonding distance, and finally it explains the relative stability of one lactone to hydrolysis.

Experimental

Kuhn–Roth Estimations.—Picrotoxinin, 6·0; tutin, 5·3; dihydrotutinone, 7·4; tutinone, 7·9. 1*C*-Methyl requires 9·3; 9·2; 9·2; and 9·2%, respectively.

Nuclear Magnetic Resonance Determinations.—These were made at 40 Mc./sec. and with water as a standard: tutin (in D_2O), σ at 4·05; monoacetyltutin (in $CHCl_3$), σ at 4·05, 3·45 and +0·30; picrotoxinin (in dioxan), σ at 4·15 (angular methyl), 3·45 (CH_3–[C=CH_2]) and +0·40 (doublet; >C=CH_2).

Periodic Acid Oxidations.—(*a*) Tutin (0·0241 g.) was dissolved in 0·1N-sodium hydroxide (3 ml.) and refluxed for 15 min. The solution was cooled, 0·1N-sodium metaperiodate (10 ml.) added, and the whole made up to 25 ml. Portions (3 ml.) were taken and back titrated in the usual way. Titrations after 1, 2, 6, and 7 hr. indicated that 1·8, 2·6, 3·2, and 3·3 equivalents, respectively, of periodate had reacted.

(*b*) α-Bromotutin (0·208 g.) was hydrolysed and oxidised in a similar way to (*a*). Titrations at 0·75, 1·75, 6, and 9 hourly periods showed uptake of 0·85, 0·9, 1·0, and 1·2 equivalents of periodate, respectively.

(*c*) Tutindicarboxylic acid (0·018 g.) was oxidised with periodic acid and titres, taken after 10 min., 30 min., 1·25 hr., 2 hr., and 4 hr., showed an uptake of 1·3, 2·8, 3·5, 3·5, and 3·8 equivalents of periodate, respectively. A reaction under conditions corresponding to (*a*) showed a similar rate of uptake of oxidant.

(*d*) Tutindicarboxylic acid (0·21 g.) and 0·0331N-lead tetra-acetate in glacial acetic acid (20 ml.) were made up to 50 ml. in a standard flask, with glacial acetic acid, and estimated in the usual way. Titrations after 20, 40, 70, 95, 125, 165, 290, and 325 min. showed an uptake of 1·6, 1·8, 2·1, 2·14, 2·4, 2·6, 2·8, and 2·8 equivalents of oxidising agent, respectively.

Debromination of α-Bromoisotutinone.—(*a*) α-Bromoisotutinone (0·46 g.) was debrominated in the usual way with 3 separate additions of ammonium chloride and zinc dust—the total time of reaction being *ca.* 30 min. The excess of zinc was filtered off and the filtrate taken to dryness. Water (a few ml.) was added with stirring, and after sufficient concentrated hydrochloric acid was added to bring the solution to pH 2 the initial flocculent precipitate dissolved. The solution was kept overnight and the crystals (0·12 g.) were filtered off. The filtrate was continuously extracted with ether; the first 24 hr. yielded material (0·12 g.) which later proved to be identical with the crystalline product above. This was crystallised from water, then ethyl acetate, and sublimed for analysis; the *chloro-acid* (VI) then had m. p. 226° (Found: C, 54·1; H, 5·8; Cl, 10·4. $C_{15}H_{17}ClO_6$ requires C, 54·8; H, 5·2; Cl, 10·8%); $\lambda_{max.}$ (in ethanol) 2540 and 3200 Å (log ε 3·84 and 1·85); $\nu_{max.}$ (potassium chloride disc) 3472s, 1742s, 1727s, 1685s, and 1608m cm.$^{-1}$.

(*b*) The debromination (0·4 g.) was repeated as described above, but the reaction time was cut to 10 min. The solid residue was taken up in a little water and acidified with 2N-sulphuric

[10] H. Conroy, *J. Amer. Chem. Soc.*, 1957, **89**, 5550; B. M. Craven, *Tetrahedron Letters*, 1960, **19**, 21.

acid and kept overnight. Crystalline material (0·18 g.) was filtered off and after recrystallisation from water, the first crop gave no depression of m. p. when mixed with starting material. From these mother-liquors a second product in very small yield was obtained as short needles, m. p. 238° (constant), and was the *dilactone* (V) (Found: C, 61·8; H, 5·6. $C_{15}H_{16}O_6$ requires C, 61·6; H, 5·5%); $\nu_{max.}$ (potassium chloride disc) 3534s, 1764s, 1704s, and 1618s cm.$^{-1}$. Ether extraction of the original filtrate yielded material (0·05 g.), m. p. 224° undepressed when mixed with acid (VI).

Isomerisation of α-Bromotutinone.—α-Bromotutinone (0·42 g.) was dissolved by shaking it for 1 hr. in 1 mol. of 0·1N-sodium hydroxide (the same product was formed from 2 mol. of alkali). The pale yellow solution was acidified with glacial acetic acid, becoming colourless and yielding fine needles which were collected (0·32 g.) and recrystallised from ethanol. The *lactol* had m. p. 218° (decomp.) (Found: C, 46·8; H, 4·3; Br, 20·3. $C_{15}H_{17}BrO_7$ requires C, 46·3; H, 4·4; Br, 20·6%); $\nu_{max.}$ (in Nujol) 3475, 3310, 1756, and 1741 cm.$^{-1}$. The lactol was dissolved in methanol and treated with diazomethane until a yellow colour persisted. The *methyl ester monomethyl ether* crystallised in fine yellow needles, m. p. 217° (Found: C, 49·2; H, 4·9; Br, 18·8. $C_{17}H_{21}BrO_7$ requires C, 48·9; H, 5·7; Br, 19·1%); $\nu_{max.}$ (potassium bromide disc) 3496, 3443sh, and 1723br cm.$^{-1}$.

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