18. *Tutin.*

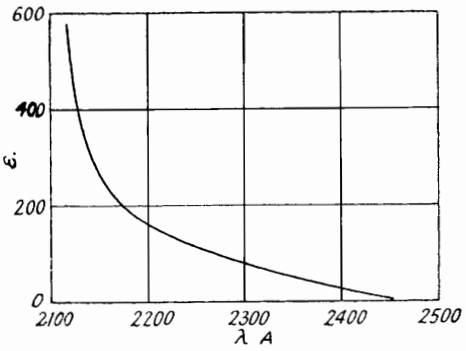
By S. N. Slater.

Tutin, $C_{15}H_{18}O_6$, yields dihydrotutin on hydrogenation and both these substances yield monobromo-substitution products. Parallel reactions have been carried out with picrotoxinin. Tutin gives an *acetyl* derivative.

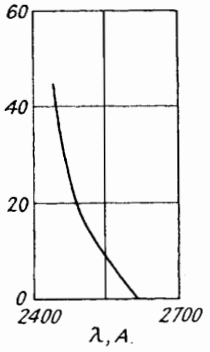
The isolation of the crystalline poison, tutin, from the leaves and seeds of the three species of *Coriaria* found in New Zealand was first reported by Easterfield and Aston (J., 1901, **79**, 120), who described it as a colourless compound, $C_{17}H_{20}O_7$, m. p. 208—209°. It was shown after hydrolysis with dilute mineral acid to reduce Fehling's solution and to give an amorphous precipitate with phenylhydrazine. Methoxy-groups were absent. Concentrated sulphuric acid gave a blood-red coloration with a saturated aqueous solution of tutin and treatment with slaked lime destroyed the poison.

Workers in Japan have since described the isolation of " coriarine " from *Coriaria japonica*, A. Gray. Kinoshita (*J. Chem. Soc. Japan*, 1930, **51**, 99; 1931, **52**, 171) gives the molecular formula $C_{12}H_{14}O_5$, m. p. 212°, and states that a mixed m. p. with tutin which has been further purified shows no depression. On acetylation with acetic anhydride and pyridine an acetyl derivative, m. p. 240°, was obtained. The benzoyl derivative melted at 170·5°. Hydrogenation with platinum in acetic acid yielded hydrotutin, m. p. 240°; acetyl derivative, m. p. 185°; benzoyl derivative, m. p. 182—185°.

Kariyone and Sato (*J. Pharm. Soc. Japan*, 1930, **50**, 659; 1930, **51**, 134) give the m. p. of coriarine as 212—213° and that of tutin from New Zealand sources as 211—212°. The crystalline forms were identical. As a



Tutin in water.



Bromopicrotoxinin in chloroform. (The ε of bromotutin is >1 at 2400A.)

result of analyses the molecular formula $C_{15}H_{18}O_6$ was suggested, which is close to that of coriamyrtin, $C_{15}H_{18}O_5$, and picrotoxinin, $C_{15}H_{16}O_6$, both of which are related pharmacologically to tutin.

Following an improved method of extraction tutin was isolated and purified by recrystallisation from alcohol, the purest specimens melting at 209—210°. Analyses agreed with the molecular formula $C_{15}H_{18}O_6$. The absorption spectrum revealed the absence of any strongly absorbing chromophore within the region examined. Acetylation with acetic anhydride and pyridine gave a *monoacetyl* derivative, m. p. 177°. Hydrogenation of tutin in alcohol with a palladised norit catalyst proceeded smoothly and yielded dihydrotutin, m. p. 190—192°. Dihydrotutin can be brominated just as readily as tutin (see below), yielding *bromohydrotutin*, m. p. 257°, and this ready bromination of the dihydro-derivative has been established also in the case of picrotoxinin. Picrotoxin was hydrogenated in alcohol with a palladised norit catalyst, and the product brominated without further purification, yielding *bromohydropicrotoxinin*, m. p. 255°.

In view of these results it seems doubtful whether the identity of coriarine and tutin has been established. The author has been unable to raise the m. p. of tutin to the figures recorded by Kariyone and Sato and by Kinoshita and there are marked differnces between the m. p.'s of the acetyl and the dihydro-derivatives of the two substances.

Tutin on treatment with bromine water readily forms a monobromo-substitution product (King, unpublished work). A closer investigation of this reaction has shown that two substances are actually produced, which have been designated α- and β-*bromotutin*. The α-form, the main product, melts at 256—257°, and the β-form at 237°. There is thus a marked similarity between this reaction and the bromination of picrotoxinin. The early literature on the bromination of picrotoxinin (Paterno and Oglialoro, *Gazzetta*, 1877, **7**, 193; Schmidt and Lowenhardt, *Ber.*, 1881, **14**, 817; Meyer and Bruger, *Ber.*, 1898, **31**, 2958) is confusing, but Horrmann (*Ber.*, 1912, **45**, 2090) states that the action of bromine on either picrotoxin or picrotoxinin yields a mixture of α- and β-bromopicrotoxinin in which the β-form (needles, decomposing at 280°) predominates. The isolation of this β-form has been confirmed.

As with tutin, the absorption spectra of β-bromopicrotoxinin and α-bromotutin revealed the absence of any strongly absorbing chromophore within the region examined. Of the two halogen derivatives, that from picrotoxinin showed the stronger absorption.

Experimental.

Isolation of Tutin.—The dried leaves and stems of *Coriaria lurida* were boiled for 3 hours with water, and the aqueous liquor concentrated in a continuous flow evaporator. After saturation with sodium chloride and filtration through sand the extract was run in a fine stream through an upwardly moving column of ether (*ca.* 8 feet) in a continuous extraction apparatus designed by Mr. C. G. Martin, M.Sc. The ethereal extract was evaporated to dryness, and the residue dissolved in the minimum quantity of water, neutralised with sodium bicarbonate, and extracted eight times with ether. The dried (sodium sulphate) extracts left on distillation a crystalline product. When this was extracted with ether (Soxhlet), practically pure tutin separated in the boiling flask, m. p. 209—210° after repeated crystallisation from alcohol (Found : C, 61·4; H, 6·2. $C_{15}H_{18}O_6$ requires C, 61·2; H, 6·1%). There was no colour produced with ferric chloride and no reaction with dinitrophenylhydrazine; alkaline permanganate was slowly decolorised and ammoniacal silver nitrate was reduced on heating. When tutin was distilled with zinc dust, extensive charring occurred and only a small quantity of distillate was obtained; this appeared to be phenolic in nature.

Acetyltutin.—Tutin (0·5 g.), acetic anhydride (2·5 c.c.), and pyridine (1 c.c.) were heated at 140° for 1½ hours, the product diluted with water, and the *acetyl* derivative recrystallised from aqueous methyl alcohol; m. p. 177° after shrinking and softening (Found : C, 60·5; H, 6·2. $C_{17}H_{20}O_7$ requires C, 60·7; H, 5·95%).

Dihydrotutin.—Tutin (0·5 g.) in ethyl alcohol was shaken with palladised norit in hydrogen (absorption, 41 c.c.; theo. for 1 double bond, 38 c.c.). After filtration and removal of the solvent the product was crystallised from methyl alcohol, yielding dihydrotutin, m. p. 190—192°, together with small quantities of material of lower m. p.

Bromohydrotutin.—Dihydrotutin (0·33 g.), dissolved in water and treated with excess of bromine water, gave a white *substance* (0·32 g.), m. p. 257° (decomp.), unchanged by recrystallisation from methyl alcohol (Found : C, 48·4; H, 5·1; Br, 21·6. $C_{15}H_{19}O_6Br$ requires C, 48·0; H, 5·1; Br, 21·3%). Mixed with α-bromotutin (see below), it melted at *ca.* 235°.

Bromohydropicrotoxinin.—Picrotoxin (0·5 g.) was shaken with palladised norit in alcohol in hydrogen and when no further contraction took place the catalyst was filtered off and the solvent removed. The residue, dissolved in water, gave with excess of bromine water a white precipitate which, after recrystallisation from alcohol, yielded *bromohydropicrotoxinin* in needles, m. p. 255° (decomp.) after softening (Found : Br, 20·9. $C_{15}H_{17}O_6Br$ requires Br, 21·4%).

Bromination of Tutin.—Tutin (1·0 g.) was dissolved in boiling water, and bromine water added in excess. The material which separated was filtered off and dried (Found : C, 48·7; H, 4·8; Br, 21·4. $C_{15}H_{17}O_6Br$ requires C, 48·3; H, 4·6; Br, 21·4%). Yield, 0·84 g.—fraction I. On standing, the aqueous mother-liquor deposited a further crop of crystalline material (0·12 g.—fraction II). The aqueous mother-liquor was evaporated to small bulk; small nodules were slowly deposited (0·08 g.—fraction III).

Fraction I : M. p. 247° (decomp.). Recrystallisation from methyl alcohol raised the m. p. to 256° (decomp.) : *α-bromotutin* (Found : Br, 21·7%).

Fraction II : M. p. 230° (decomp.). Recrystallisation from ethyl alcohol raised the m. p. to 237° (decomp.) : *β-bromotutin* (Found : Br, 21·1%).

Fraction III : M. p. *ca.* 230° (decomp.). Recrystallisation from ethyl alcohol raised the m. p. to 257° (decomp.).

Bromopicrotoxinin.—Picrotoxin (0·5 g.) was dissolved in boiling water, and bromine water added. After cooling to room temperature, the precipitate was filtered off and dried—0·29 g., m. p. wide decomposition range up to 259°. After repeated crystallisation from alcohol β-bromopicrotoxinin was obtained in fine needles, m. p. 282° (decomp.).

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