

XI.—*Tutu. Part I. Tutu and Coriomyrtin.*

By THOMAS HILL EASTERFIELD, Professor of Chemistry, Victoria College, Wellington, N.Z., and BERNARD CRACROFT ASTON, Chemist to the New Zealand Department of Agriculture.

THE monotypic natural order, *Coriariæ*, is represented in New Zealand by three species, which are known collectively as Tutu or toot. *Coriaria ruscifolia*, L. (*C. Sarmentosa*, Forst; *C. arborea*, and *C. Tutu*, Lindsay; Tutu, pohou, and tupakihi of the Maori) is commonly known as the tree-toot; it is a handsome shrub with glossy, acuminate leaves, and grows to a height of 20—25 feet. *C. thymifolia*, Humb. and Bonp. (Tutu-papa or tutu-heu-heu of the Maori), seldom exceeds three feet in height, and is known as the ground-toot. *C. angustissima*, Hook. f., is of comparatively rare occurrence. It is a small, herbaceous upland annual with a characteristic fern-like appearance.

A peculiar interest attaches to these plants in that they are all known to be highly toxic. The animals brought by Captain Cook in both his voyages died in what was to him an unaccountable manner, but as Lauder Lindsay (*B. and F. Med. and Chir. Rev.*, July, 1865, 153; October, 1868, 465; also B.A. Report, 1862, 98) has pointed out, the general description of the symptoms leaves little doubt that they died of tutu poisoning. Many instances are upon record in which upwards of 50 per cent. of a large herd of cattle has been lost in a single night from toot poisoning. The plants are very succulent and attractive to cattle, so that stock can only be driven through a tutu country at considerable risk. Cattle living in these districts appear to eat the plant with impunity, but if starved or overdriven, the apparent toleration disappears, partly, no doubt, from the fact that under these circumstances the plant is eaten in excessive quantity.

Cattle suffering from tutu poison, popularly said to be tooted, rush madly about, then stagger and fall, convulsions are of frequent occurrence, large volumes of gas appear in the stomach, and the animal eventually dies in a comatose condition. Tutu berries are of luscious appearance and taste, and are consumed in quantity by the Maoris; the seeds are, however, poisonous, and deaths from swallowing them are not uncommon, particularly amongst children. It is said that birds are not poisoned by the seeds, but cases have come under the notice of the authors in which domestic fowls have been poisoned by eating the berries, the symptoms being typical of tutu poisoning. Human beings who have recovered from toot poisoning nearly always suffer for a time from impaired memory, and permanent physical distortion sometimes accompanies severe cases. Bleeding is the usual remedy adopted by the natives and settlers, and the beneficial effect is remarkably rapid.

It is somewhat remarkable that the poisonous constituent of tutu has remained hitherto unisolated. Skey (*Trans. N.Z. Inst.*, 1869, 153, 399, 400) has shown that ether removes from the seeds a highly poisonous green oil, which, he remarks, is or contains the poison. Hughes (*Trans. N.Z. Inst.*, 1870, 237) showed that *C. ruscifolia* contained crystalline constituents soluble in alcohol or water, but did not identify them. He found that boiling with slaked lime destroyed the poisonous action of the drug. Christie (*N.Z. Med. Journ.*, July and October, 1890) has examined the physiological effect of decoctions of the plant, and denies that lime destroys the poison.

The present paper contains an account of the investigation of the three species of New Zealand *Coriaria*. It is shown that the plants all contain a highly poisonous, non-nitrogenous glucoside, $C_{17}H_{20}O_7$, for which the name tutin is proposed. *C. thymifolia* also contains quercetin

and some half-dozen well-known acids, and *C. angustissima* has yielded a volatile acid, $C_8H_8O_4$, which has not been identified.

EXPERIMENTAL.

(1). *Coriaria thymifolia*.—Eleven kilograms of the air-dried plant (root excluded) gathered at Dunedin at the time of flowering (January) were put through a chaff-cutter and boiled with successive quantities of water. The concentrated infusion was treated with a large volume of alcohol which precipitated inorganic salts, ellagic acid, and a large quantity of black, tarry matter. The residue remaining after distilling off the alcohol from the supernatant liquid was extracted with ether. When the ether was distilled off, the residue containing the characteristic glucoside tutin set to a semi-solid, crystalline mass with a pungent odour.

Acetic acid was recognised by distilling the mass with steam. From the distillate a silver salt was prepared, which, after a single recrystallisation, gave $Ag = 64.3$ per cent. Calculated for $C_2H_3O_2Ag$, $Ag = 64.7$ per cent.

Gallic acid remained in quantity when the solution, which had been distilled with steam, was evaporated to the crystallising point and the residue extracted with chloroform. It gave the usual colour reactions. After recrystallisation from water, it was dried at 150° and gave :

$C = 49.4$; $H = 3.5$ per cent.

$C_7H_6O_5$ requires $C = 49.0$; $H = 3.5$ per cent.

Quercetin, or some isomeric compound, was present in the crude gallic acid. After purification by repeated recrystallisation from water, it showed the usual colour reactions and dyeing properties, lost 2 mols. of water at 160° , and, on analysis, gave :

$C = 59.2$; $H = 3.6$ per cent.

$C_{15}H_{10}O_7$ requires $C = 59.6$; $H = 3.2$ per cent.

Quercetin has been definitely shown by Perkin to exist in *C. myrtifolia* (Trans., 1900, 77, 429).

The chloroform solution separated from the gallic acid was evaporated and the product dissolved in ether, the remaining acids were then removed by sodium carbonate.

Succinic acid was identified in the alkaline solution. It was recognised by qualitative reactions, melting point, and analysis of the silver salt.

$C = 14.3$; $H = 1.25$; $Ag = 64.8$ per cent.

$C_4H_4O_4Ag_2$ requires $C = 14.4$; $H = 1.2$; $Ag = 65.0$ per cent.

Seeds.—A kilogram and a half of the seeds of *C. thymifolia* were pul-

verised and exhausted by carbon disulphide which removed 22·6 per cent. of a green, drying oil. The seeds, freed from oil, yielded to water a small quantity of tutin which was extracted with ether, and after recrystallisation melted at 208—209°. The oil upon saponification yielded a liquid acid which was probably linoleic acid, since its calcium and barium salts were readily soluble in ether.

(2). *C. ruscifolia*.—In the examination of this plant, the juice expressed from the succulent, asparagus-like shoots (gathered at Wellington early in October) was employed. It contained the same acids as the extracts of *C. thymifolia*. The yield of tutin was 0·03 per cent. Samples of the plant gathered later in the year from the same hill-side, contained a smaller percentage of the poison. The dried seeds of *C. ruscifolia*, on extraction with carbon disulphide, yielded 22·8 per cent. of oil which was very faintly toxic. 0·18 gram administered to a small kitten produced only very mild symptoms of tutu poisoning. From the extracted seeds, water removed a few crystals of a substance which gave the characteristic bitter taste and colour reaction of tutin.

(3). *C. angustissima*.—Only 1 kilogram of the dried plant was obtainable. It was collected at Dunedin early in January. Tutin was obtained from it and identified by its melting point. This species contains an acid which was not detected in the other two; when the aqueous extract of the plant was repeatedly shaken up with ether, the later extractions contained the acid in a comparatively pure condition. It crystallised from chloroform in silky, yellowish needles which were finally sublimed at 125° under diminished pressure. It was thus obtained in colourless, iridescent plates, very readily soluble in water, alcohol, or ether. The acid has a characteristic smell, gives a transient violet colour with ferric chloride, and melts at 130° (uncorr.). On analysis:

0·1214 gave 0·2537 CO₂ and 0·0545 H₂O. C=56·99; H=4·99.

C₈H₈O₄ requires C=57·10; H=4·76 per cent.

Tutin.

The ethereal solution, from which all the acids had been removed, was evaporated and yielded almost colourless crystals which were repeatedly recrystallised from water and from alcohol. From water, the substance separates in characteristic acicular forms, from alcohol, in oblique ended prisms. The compound is perceptibly volatile, may be slowly sublimed at 120—130°, melts at 208—209° (uncorr.), and has an intensely bitter taste. It contains no nitrogen, and after hydrolysis by dilute acids reduces Fehling's solution, and with phenylhydrazine gives an amorphous precipitate which is not phenylglucosazone.

Strong sulphuric acid added to a few drops of a saturated aqueous solution of tutin gives a blood-red coloration.

Examination by Zeisel's method for methoxyl groups gave negative results. When evaporated to dryness with slaked lime, solutions of tutin yield amorphous compounds amongst which tutin can no longer be detected even when the residue has been acidified.

Some preliminary experiments upon the toxic effect of tutin were carried out by Mr. J. A. Gilruth, Chief Government Veterinary Surgeon. The compound is very poisonous. A dose of 0.129 gram killed a kitten weighing 1 kilogram in 40 minutes; 0.001 gram given to a cat weighing 2 kilograms caused a fit in 3 hours and illness for the next 24 hours. The same cat subsequently succumbed to a dose of 0.003 gram.

A dose of about a milligram produced nausea, vomiting, and incapacity for work extending over 24 hours in a healthy, full-grown man.

Three preparations were analysed, i and ii from *C. thymifolia* and iii from *C. ruscifolia*:

i. 0.1299, dried at 120—130°, gave 0.2899 CO₂ and 0.0691 H₂O. C = 60.78; H = 5.91.

ii. 0.1255, dried in desiccator, gave 0.2793 CO₂ and 0.0710 H₂O. C = 60.70; H = 6.20.

iii. 0.1264, dried at 120—130°, gave 0.2825 CO₂ and 0.0658 H₂O. C = 60.95; H = 5.78.

C₁₇H₂₀O₇ requires C = 60.71; H = 5.95 per cent.

Molecular Weight Determinations.—Calculated for C₁₇H₂₀O₇. M = 336. 0.403 gram depressed the m. p. of 10 grams of acetic acid 0.47°. M = 332. 0.319 „ „ „ „ „ 0.38°. M = 325. 0.2448 „ „ „ 8 „ phenol 0.66°. M = 333. 1.1173 grams raised the b.p. of 11.65 „ alcohol 0.35°. M = 320.

Solubilities.—One hundred grams of water at 10°, of ether at 10°, and of alcohol at 16° dissolve 1.9, 1.5, and 8.2 grams of tutin respectively. It is very soluble in acetone, but dissolves only sparingly in chloroform, and is insoluble in benzene or carbon disulphide.

The optical activity has been determined by Professor C. R. Marshall, of University College, Dundee, who reports as follows:

$\alpha_D = +0.37^\circ$; $l = 2$ dcm.; $d = 0.8$; $c = 2.5$ per cent. in alcohol; whence $[\alpha]_D^{19.5^\circ} = +9.25$.

Note on the Pharmacology of Tutin.—Professor Marshall has undertaken the pharmacology of tutin, and furnishes the following preliminary note:

“Tutin, pharmacologically, is closely allied to coriamyrtin, and

belongs to what is known as the picrotoxin group of substances. After preliminary depression, it induces salivation, a fall in the frequency of the pulse, and increased respiratory activity, followed by convulsions, for the most part clonic and limited in the earlier stages to the fore part of the body. The effect is apparently due to an action on the medulla oblongata and basal ganglia of the brain.

"It differs from coriamyrtin in being less toxic and slower in its action. On this account, the preliminary depression is more marked. Its connection with this substance, however, is close. Experiments suggest that it is broken up in the body into some substance, possibly coriamyrtin, which is the active convulsant factor.

"It ought to be stated that the coriamyrtin employed by me was obtained from Merck. After boiling for a short time with dilute hydrochloric acid (2 per cent.), it did not reduce copper sulphate solution. It melted at 224° (uncorr.), and its solubility in physiological saline solution (0.6 per cent. NaCl) was less than 0.1 per cent. Riban's coriamyrtin melted at 220°, and was soluble in water to the extent of 1.44 per cent. at 22°."

Coriamyrtin.

The physiological action of the New Zealand species of *Coriaria* and of the European species (*C. myrtifolia*) is so similar that a direct comparison of tutin with coriamyrtin, the glucoside isolated by Riban (*Bull. Soc. Chim.*, 1864, [ii], 1, 87; 1867, [ii], 7, 79), seemed desirable. A gram of coriamyrtin was obtained from Merck, of Darmstadt; the specimen melted at 225° (uncorr.),* and the melting point was not altered by recrystallisation from alcohol. Like tutin, the compound is somewhat volatile, sublimation commencing at about 150°. Analysis of the compound before and after crystallisation gave numbers agreeing closely with those obtained by Riban:

0.1389 gave 0.3288 CO₂ and 0.0822 H₂O. C = 64.56; H = 6.57.

0.1263 ,, 0.2976 CO₂ ,, 0.0734 H₂O. C = 64.25; H = 6.45.

Riban found (mean of three analyses) C = 64.07; H = 6.57.

C₃₀H₃₆O₁₀ (Riban) requires C = 64.75; H = 6.47 per cent.

C₂₁H₂₆O₇ requires C = 64.61; H = 6.66 per cent.

If the latter formula were correct, coriamyrtin would differ from tutin by C₄H₆ only, and its higher melting point, lower volatility, and solubility suggest strongly that it is a higher member of the series to which tutin belongs. Molecular weight determinations, however, indicate that the true formula is smaller than either of the above, being probably half that assigned to tutin by Riban.

* Riban gives 220°; Merck (*Chem. Centr.*, 1899, i, 706) gives 229°.

126 MELLOR : SOME α -ALKYL SUBSTITUTION PRODUCTS OF

0.2478	gram	raised the b. p. of 3.76 grams of acetone	0.46°.	M = 255.
0.3196	"	" " 6.4 " "	0.33°.	M = 265.
0.1732	"	depressed the m. p. of 8 " phenol	0.62°.	M = 250.
0.2226	"	" " 8 " "	0.80°.	M = 250.

Calculated for $C_{15}H_{18}O_5$, $M = 278$; and for $C_{21}H_{26}O_7$, $M = 390$.

The conclusion that the real formula is $C_{15}H_{18}O_4$ harmonises with the fact that, by the action of bromine, Riban obtained a crystalline derivative in which 1/18th of the hydrogen was replaced by the halogen. If, however, the compound is a glucoside, as its reactions suggest, the sugar which it yields upon hydrolysis cannot contain more than four atoms of oxygen, and the formula is remarkable in that it contains fewer oxygen atoms than that of any glucoside hitherto described.

The appended table shows the chief differences between tutin and coriamyrtin :

	Tutin, $C_{17}H_{20}O_7$.	Coriamyrtin, $C_{15}H_{18}O_5$ (E. and A.).
Solubility in 100 parts of water...	1.8 at 10°	1.44 at 22° (Riban)
Solubility in 100 parts of alcohol..	8.2 at 16°	2.00 at 22° "
Reaction with hydriodic acid, } followed by potash	Nil.	Magenta* "
With concentrated sulphuric acid..	Blood red	Dirty yellow
Initial temperature of sublimation	About 120°	About 150°

The authors desire, in conclusion, to express their thanks to Mr. J. D. Ritchie, and the other officers of the New Zealand Department of Agriculture, for their kindness in securing the raw material employed in this investigation of tutu.