152. *Alkaloids of* Toddalia aculeata: *Identity of Toddaline with Chelerythrine.*

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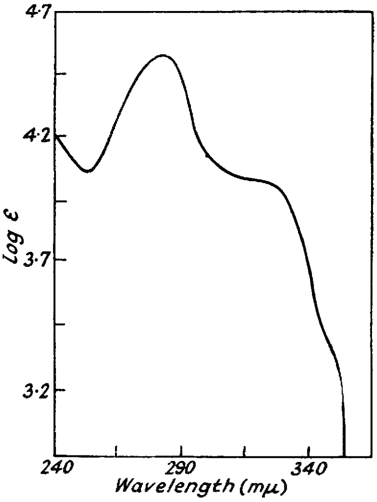
Toddaline, the major constituent of the root bark of *Toddalia aculeata*, is shown to be identical with chelerythrine, an alkaloid of the *Papaveraceae*.

From the root bark of *Toddalia aculeata*, Pers. (natural order Rutaceae), Perkin and Hummel [1] isolated a yellow alkaloid hydrochloride which they considered to be the salt of berberine. Subsequently, Dey and Pillay [2] established the absence of berberine in the root bark and isolated two bases named toddaline and toddalinine. According to them, toddaline was a tertiary base, $C_{17}H_{12}O_2(OMe)_2{>}NMe$, having m. p. 269—270° when crystallised from chloroform and being transformed into another modification, m. p. 204—206°, on contact with alcoholic ammonia. Toddalinine, obtained as an amorphous powder, m. p. 180—200°, was ascribed the formula $C_{17}H_9O_3(OMe){>}NMe$.

We have isolated from this root bark two pure crystalline alkaloids by a procedure less complicated than that of Dey and Pillay.[2] The first (m. p. 205°; from methanol) and its derivatives corresponded to toddaline and its derivatives. Elementary analyses of the base and its derivatives, however, necessitated a revision of the molecular formula to $C_{21}H_{19}O_5N$. The base was recovered unchanged after several hours' heating with methyl iodide and analyses of the hydrochloride and the picrate revealed their formation with elimination of a molecule of water, indicating the quaternary nature of the base. On treatment of the hydrochloride with aqueous potassium cyanide, it gave a colourless *pseudo*-cyanide, with phenylhydrazine a rather unstable hydrazone, and with zinc and hydrochloric acid a weakly basic compound, m. p. 167°, also obtained in better yield by reduction with lithium aluminium hydride. Oxidation with alkaline ferricyanide gave oxotoddaline, a neutral compound. The ultraviolet absorption spectrum (see Figure) of the alkaloid in ethanol showed a striking similarity to that of 9 : 10-dihydro-7 : 8 : 2′ : 3′-tetramethoxy-10-methyl-1 : 2-benzophenanthridine reported by Bailey, Robinson, and Staunton.[3]



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[1] Perkin and Hummel, *J.*, 1895, **67**, 413.

[2] Dey and Pillay, *Arch. Pharm.*, 1933, **271**, 477.

[3] Bailey, Robinson, and Staunton, *J.*, 1950, 2277.

The alkaloid and its *pseudo*cyanide did not depress the melting points of chelerythrine and chelerythrine *pseudo*cyanide, establishing the identity of " toddaline " with chelerythrine.

The isolation of an alkaloid of the 1 : 2-benzophenanthridine group from a plant of the natural order Rutaceae wherein a variety of heterocyclic structures such as quinoline, *iso*quinoline, furanoquinoline, carboline, quinazoline, and acridine is encountered lends strong support for the suggestion by Turner and Woodward [4] that alkaloids of the berberine type (widely occurring in Rutaceae) and the 1 : 2-benzophenanthridine type have a common biogenetic origin.

EXPERIMENTAL

Extraction of Toddalia aculeata.—The powdered root bark (6 kg.) was extracted by percolation with cold light petroleum (b. p. 40—60°). Removal of the solvent at ordinary pressure gave a brownish oil (300 ml.), from which distillation in steam removed essential oil (41 g.). The residue was taken up in ether and washed repeatedly with 4N-hydrochloric acid, yielding the mixed hydrochlorides (5·7 g.) of toddaline and toddalinine. The ether layer after removal of all basic material was freed from solvent and hydrolysed with 10% methanolic potassium hydroxide at room temperature. The unsaponifiable portion gave β-sitosterol (1 g.). The root bark, after extraction with light petroleum, was extracted with acetone at room temperature, and the solvent from the extracts removed at ordinary pressure. The residue was repeatedly extracted with hot 10% acetic acid, the acid extract concentrated in a vacuum, and the residue taken up in ether and washed with 4N-hydrochloric acid, giving more (2 g.) of the mixed hydrochlorides. The residue, on crystallisation from benzene, yielded toddalolactone [2] (10 g.). The residue from the acetone extract after treatment with 10% acetic acid was hydrolysed as above and afforded crude toddaline (7 g.). The alkaline mother-liquor on acidification gave a new lactonic material (1·5 g.), m. p. 120°.

Separation of toddaline and toddalinine. The mixture of hydrochlorides was separated by fractional crystallisation from methanol. Toddalinine hydrochloride separated first as citron-yellow needles, m. p. 245° (decomp.) (Found : C, 65·00; H, 5·84; N, 3·8%). Concentration of the mother-liquor afforded golden-orange needles of toddaline hydrochloride.

Toddalinine was obtained by basification of a methanolic solution of its hydrochloride with methanolic potassium hydroxide. Crystallised from methanol, it had m. p. 185° (Found : C, 71·2; H, 5·6; N, 4·1%).

Toddaline was obtained by addition of sodium carbonate to an aqueous solution of the hydrochloride and from methanol formed colourless leaflets, m. p. 204—205° (Found : C, 69·3; H, 5·6; N, 3·4. Calc. for $C_{21}H_{19}O_5N$: C, 69·1; H, 5·2; N, 3·8%). The hydrochloride crystallised readily from alcohol as golden-orange needles, m. p. 210° (decomp.) (Found : C, 65·5; H, 5·3. Calc. for $C_{21}H_{18}O_4NCl$: C, 65·5; H, 4·9%). The picrate was made from an aqueous solution of the hydrochloride and was too sparingly soluble to be crystallised from any solvent. It melted at 238° (decomp.) (Found : C, 55·9; H, 3·6. Calc. for $C_{27}H_{20}O_{11}N_4$: C, 56·2; H, 3·5%). The *pseudo*cyanide, prepared by the addition of an aqueous solution of potassium cyanide to toddaline hydrochloride, crystallised from benzene as colourless prisms, m. p. 262° (Found : C, 71·0; H, 5·0. Calc. for $C_{22}H_{18}O_4N_2$: C, 70·6; H, 4·8%). The phenylhydrazone made by Karrer's method,[5] melted at 158° and was not analysed as it decomposed rapidly.

Dihydrotoddaline.—Toddaline hydrochloride (1 g.) was added to an anhydrous ether solution of lithium aluminium hydride (1 g.) with efficient stirring. The reduction was rapid with disappearance of the strong yellow colour. The mixture was stirred for a few hours after the completion of the addition and left overnight. The excess of hydride was decomposed with moist ether. The ether layer was filtered, the solvent removed, and the residue crystallised from alcohol. Colourless needles (0·55 g.) of *dihydrotoddaline*, m. p. 167°, were obtained (Found : C, 71·9; H, 5·6. $C_{21}H_{19}O_4N$ requires C, 72·2; H, 5·4%).

Toddaline hydrochloride (0·5 g.) in hot hydrochloric acid solution was reduced with zinc dust till the solution was free from colour and the strongly acidic solution was then extracted with ether. The extract, on removal of solvent, gave a colourless compound. Crystallised from alcohol, it melted at 167° and did not depress the m. p. of the specimen obtained by employing lithium aluminium hydride.

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[4] Turner and Woodward, " The Alkaloids," Academic Press, Vol. III, 1953, p. 57.
[5] Karrer, *Ber.*, 1917, **50**, 212.

Oxotoddaline.—Toddaline hydrochloride (0·5 g.) was oxidised with alkaline ferricyanide as in the oxidation of sanguinarine nitrate.[6] *Oxotoddaline*, so obtained and recrystallised from methanol (0·2 g.), had m. p. 199° (Found : C, 69·8; H, 5·0. $C_{21}H_{17}O_5N$ requires C, 69·4; H, 4·7%).

We are grateful to Dr. R. H. F. Manske for the comparison of our specimen of toddaline *pseudo*cyanide with an authentic specimen of chelerythrine *pseudo*cyanide, and for the gift of a sample of chelerythrine. We thank the Government of India for a fellowship (to B. S. T.), Mr. Selvavinayagam for the microanalyses, and the Forest Department of the Government of Madras for roots of *Toddalia aculeata*.

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[6] Spath, Schlemmer, Schenck, and Gempp, *Ber.*, 1937, **70**, 1677.