

130. *The Alkaloids of Duboisia Leichhardtii.*

By W. MITCHELL.

Duboisia Leichhardtii has been shown to contain hyoscyamine and small amounts of *l*-hyoscine, *dl*-hyoscine, norhyoscyamine, and a new alkaloid provisionally named "*Base D*." The last was similar to but not identical with *isovaleryltropëine*, the *hydrobromide* of which has now been synthesised. The drug has been compared botanically with the *D. myoporoides* found not to contain hyoscyamine by Barger, Martin, and Mitchell (J., 1937, 1820; 1938, 1685). It is suggested that at least two distinct types of *Duboisia* have appeared in commerce.

It was shown by Barger, Martin, and Mitchell (*loc. cit.*) that Australian *Duboisia myoporoides* yielded hyoscine, and small amounts of four new alkaloids, tigloidine, valeroidine, poroidine, and *isoporoidine*. Not one of the large number of samples which they examined showed any trace of hyoscyamine, this result being at variance with those of most of the earlier workers.

A specimen of Australian material offered on the market recently as "*D. myoporoides*" was found to contain 4.1% of total alkaloids, an unusually high figure. This product was fractionated, and the following

percentages of individual alkaloids were isolated: *l*-hyoscyamine, 1.97; *l*-hyoscyne, 0.06; *dl*-hyoscyne, 0.05; norhyoscyamine, 0.01; and a new alkaloid, 0.06, all expressed on the drug.

The drug showed no well-defined macroscopic differences from the *Duboisia* previously examined by Barger, Martin, and Mitchell, but only the dried leaves were available for examination: a comparison of the flowering specimens would probably have shown some characteristic differences. Dr. Metcalfe, of the Royal Botanic Gardens, Kew, very kindly undertook the botanical examination of the drugs. In the absence of flowering material this was rendered more difficult, but as a result of consideration of the stomatal distribution on the upper and the lower leaf surfaces it was possible to state with a fair degree of certainty that the material formerly found to contain no hyoscyamine was in fact authentic *D. myoporoides*, whereas the present specimen was probably *D. Leichhardtii*. Whatever the exact botanical distinction, the important point would appear to be that these two distinct types of *Duboisia*, and possibly other intermediate forms, have appeared on the market simply as "Duboisia" or "Duboisia myoporoides." This fact, which appears to be supported by recent work on *Duboisia* referred to in the Sixteenth Annual Report of the Council for Scientific and Industrial Research, Australia, for the year ended 30th June, 1942, would account for the discrepancies between the results of various investigators, and has almost certainly led to confusion in the past.

The new alkaloid, $C_{13}H_{23}O_2N$, referred to above was similar to tigloidine, valeroidine, and the poroidines in that its hydrobromide was very soluble in chloroform. It was optically inactive and saturated. On hydrolysis it yielded tropine and a liquid acid thought to be a valeric acid. It was not possible to identify this latter with certainty, but it is probably mainly isovaleric acid. isoValeryltropine hydrobromide was synthesised but was not identical with the above hydrobromide. It is quite possible, as in the case of "Base Z," which was later shown to consist of a mixture of the isomers, poroidine and isoporoidine (*ibid.*), that this material is also an isomeric mixture, but owing to the very small amount of material available it was not possible to pursue the matter further. Since its constitution is thus not definitely established it is suggested that the material be identified by the name "Base D". It is of interest to note that whereas *D. myoporoides* yielded minor alkaloids which were esters of ψ -tropine, a dihydroxytropene, and nortropine respectively, *D. Leichhardtii* has yielded a minor alkaloid which is an ester of tropine, and that except in the case of tigloidine, which was tiglyl- ψ -tropine, they were all pantoic acid esters.

EXPERIMENTAL.

Isolation and Separation of the Alkaloids.—The drug (No. 20 powder) was extracted with cold alcohol, and the total alkaloids isolated by the usual methods. They were converted into hydrobromides, and the solution concentrated, but no crystalline material could be isolated. The hydrobromides were then converted into neutral oxalates, and the solution concentrated. Partly racemised hyoscyamine oxalate (29 g.), m. p. 190° (corr.), was separated. The mother-liquor would not yield any further crystalline material, and small amounts were therefore converted severally into hydrobromide, sulphate, neutral phosphate, borate, picrate, and *d*-camphorsulphonate. None of these solutions crystallised after concentration.

The various solutions were united, basified with ammonia, and the alkaloids extracted with chloroform. The chloroformic solution was fractionally extracted with aqueous *N*-oxalic acid, and the various fractions concentrated. These all crystallised, and yielded a total of 19.5 g. of partly racemised hyoscyamine oxalate, m. p. ranging from 188° to 194° (corr.). By repeated refractionation of the mother-liquors from this material, a further quantity of 13.5 g. was obtained, making a total of 62 g., equivalent to 1.97% of hyoscyamine alkaloid on the drug. In addition, 0.35 g. of an oxalate, m. p. 227—228° (corr.), was separated; this was norhyoscyamine oxalate (see below).

The final mother-liquors from the oxalates were united, basified with ammonia, and the alkaloids extracted with chloroform and converted into hydrobromides. The concentrated solution was extracted with two portions of chloroform (15; 15 ml.). The residue from the chloroform slowly crystallised, and the crystals were collected and washed with acetone; this was "Base D" hydrobromide (see below).

The aqueous solution of the hydrobromides so extracted was concentrated and chilled. Crystals (2.3 g.), m. p. 184° (corr.), separated. Further concentration of the mother-liquor yielded a second crop (1.9 g.), m. p. 167° (corr.); these were respectively the hydrobromides of *l*-hyoscyne and *dl*-hyoscyne (see below).

Purification of the Separate Alkaloids.—*Hyoscyamine.* The various fractions of partly racemised hyoscyamine oxalate were dissolved in water, basified with ammonia, and the alkaloid extracted with chloroform. After racemisation by the addition of a small amount of sodium hydroxide to its cold alcoholic solution (Will, *Ber.*, 1888, 21, 1723), the alkaloid was converted into hydrobromide. The resultant material crystallised from alcohol-acetone in opaque white nodules, m. p. 163.5° (corr.) not depressed by authentic atropine hydrobromide (Found: C, 55.3; H, 6.2; N, 3.9; Br, 21.0. Calc. for $C_{17}H_{23}O_2N.HBr$: C, 55.1; H, 6.5; N, 3.8; Br, 21.6%).

Norhyoscyamine. The oxalate, m. p. 227—228° (0.35 g.), was repeatedly recrystallised from acetone containing a trace of water and thereby obtained in felted needles, m. p. 249° (corr.) [Found: C, 63.2; H, 6.5; N, 4.6. Calc. for $(C_{16}H_{21}O_2N)_2.H_2C_2O_4$: C, 63.7; H, 6.9; N, 4.4%]. No authentic material was available for comparison.

Hyoscyne. Each of the two crops of hydrobromide obtained was recrystallised first from alcohol-ether and then from water; in each case colourless, efflorescent prisms were thereby obtained: From first crop, m. p. 195—196° (corr.) not depressed by authentic *l*-hyoscyne hydrobromide (Found: C, 46.9; H, 6.3; N, 3.2; Br, 18.3. Calc. for $C_{17}H_{21}O_2N.HBr.3H_2O$: C, 46.6; H, 6.4; N, 3.2; Br, 18.3%); $[\alpha]_D^{20} -24.4^\circ$ (*c*, 5.0 of anhydrous salt in water). From second crop, m. p. 185° (corr.) not depressed by authentic *dl*-hyoscyne hydrobromide (Found: N, 3.2; Br, 18.4. Calc. for $C_{17}H_{21}O_2N.HBr.3H_2O$: N, 3.2; Br, 18.3%); it was optically inactive (*c*, 5.0 of anhydrous salt in water).

"Base D." The hydrobromide crystallised from dry acetone in glistening plates, m. p. 231° (corr.) depressed to ca. 205° by tigloidine hydrobromide (m. p. 234—235°) with which it was at first thought to be identical (Found: C, 50.6; H, 7.6; N, 4.6; Br, 26.0. $C_{13}H_{23}O_2N.HBr$ requires C, 51.0; H, 7.8; N, 4.6; Br, 26.1%); it was optically inactive (*c*, 8.0 in water), and very soluble in chloroform, water, and alcohol.

Hydrolysis of "Base D."—The base from 0.4 g. of hydrobromide was boiled for 2 hours with barium hydroxide (0.75 g.) in water (10 ml.). After removal of the barium as sulphate, the acid filtrate was extracted with ether, which left 0.09 g. of an oily acid with a powerful odour of valeric acid; yield, 68%. The *p*-phenylphenacyl ester, m. p. 78° (corr.), formed dull, colourless laminae from 60% alcohol. The m. p. was depressed to ca. 68° by mixing with an equal weight of

the ester (m. p. 76°) of *isovaleric acid* and differs from those of the other three isomeric esters; the material is possibly a mixture of two of these. *p*-Phenylphenacyl tiglate was made for comparison and formed glistening laminae, m. p. 104—105° (corr.).

The solution from which the valeric acid had been extracted was neutralised with sodium hydroxide and concentrated (5 ml.). It was basified with an equal volume of 50% aqueous sodium hydroxide solution and repeatedly extracted with chloroform. The residue from the chloroform was boiled for 1 hour with acetic anhydride (5 ml.), and the product isolated and purified in the usual manner. Colourless, prismatic needles were thus obtained (from alcohol-ether), m. p. 188° (corr.) not depressed by authentic acetyltropëine hydrobromide, but depressed to 145° by acetyl- ψ -tropëine hydrobromide (m. p. 205°).

Synthesis of isoValeryl tropëine Hydrobromide.—Tropine (2.8 g.) was titrated with hydrochloric acid and the solution evaporated in a vacuum. Tropine hydrochloride so obtained was esterified with *isovaleryl chloride* (3 g.), and the product isolated and purified as in the case of tigloidine (*loc. cit.*). It formed colourless, pearly plates from alcohol-ether, and was extremely soluble in water, chloroform, and alcohol, but insoluble in ether, and was deliquescent (Found: C, 51.1; H, 7.7; N, 4.6; Br, 25.9. $C_{13}H_{22}O_2N, HBr$ requires C, 51.0; H, 7.8; N, 4.6; Br, 26.1%); m. p. 225—227° (corr.) depressed to ca. 200° by "Base D" hydrobromide; yield 60%.

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