383. *The Minor Alkaloids of* Duboisia myoporoides.

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In addition to hyoscine, the Australian drug yielded three new alkaloids. Tigloidine, $C_{13}H_{21}O_2N$, a syrup, is tiglyl-ψ-tropëine and has been synthesised. Valeroidine, $C_{13}H_{23}O_3N$, m. p. 85°, $[\alpha]_D^{20°}$ −9·0°, is the *iso*valeryl ester of a dihydroxytropane, obtained by Wolfes and Hromatka (*Merck's Jahresber.*, 1933, **47**, 45) as a by-product in the manufacture of cocaine from Peruvian coca leaves. The third alkaloid, $C_{12}H_{21}O_2N$, provisionally called base Z, is syrupy and yields a crystalline *oxalate*. The yields were respectively 0·1, 0·1, and 0·003% of the drug. The first base and the third are characterised by hydrobromides which are extracted as such from aqueous solution by chloroform. Dihydrotigloidine, dibromodihydrotigloidine, and tiglyltropëine have also been prepared. The hydrobromides of acetyltropëine and acetyl-ψ-tropëine are useful for characterising tropine and ψ-tropine respectively.

The (somewhat old) literature on *Duboisia myoporoides* is very confusing. E. Merck (*Arch. Pharm.*, 1893, **231**, 117) found hyoscine, hyoscyamine and a supposed isomeride of the latter, termed ψ-hyoscyamine. Carr and Reynolds (J., 1912, **101**, 946) isolated from *D. myoporoides* of Philippine origin 1·1% of hyoscyamine and 0·15% of a new alkaloid, norhyoscyamine; they questioned the purity of Merck's ψ-hyoscyamine and regarded it as norhyoscyamine contaminated with hyoscyamine; they did not refer to the isolation of hyoscine, presumably not found. In present-day pharmaceutical literature "duboisine," of which salts appear in commerce, is stated to be a mixture of hyoscine and hyoscyamine. Ladenburg (*Ber.*, 1880, **13**, 257) found such a commercial sample to consist largely of hyoscyamine, a later one mainly of hyoscine. The latter result (Ladenburg and Petersen, *Ber.*, 1887, **20**, 1661) appears to-day rather doubtful; the free base was not isolated, but an aurichloride corresponding fairly closely to $C_{17}H_{23}O_3N,HCl,AuCl_3$ and to Ladenburg's hyoscine formula; the true formula for hyoscine was however shown by Hesse to be $C_{17}H_{21}O_4N$, so Ladenburg's identification is very doubtful. A recent sample of "duboisine sulphate" examined by us proved to consist almost entirely of hyoscyamine sulphate and no trace of hyoscine was detectable. Since hyoscine and hyoscyamine are now well defined, the term "duboisine," applied to mixtures supposedly obtained from the Australian drug, should be abandoned. Other varieties or species may contain different alkaloids (compare *D. myoporoides* from the Philippines mentioned above). The Australian *D. Hopwoodii* contains nornicotine (Späth, Hicks, and Zajic, *Ber.*, 1935, **68**, 1388).

One of us (W. F. M.) has during recent years examined consignments of *D. myoporoides*, collected in various Australian districts at different seasons, and found considerable variation, both in the total alkaloidal content and in the proportion of the individual alkaloids; in no case could hyoscyamine be isolated. Generally the consignments consisted of carefully dried material, mostly leaves, with some small twigs and occasionally small berries. The odour was quite characteristic, not unpleasant and somewhat butyric. After the more or less complete separation of hyoscine, three new alkaloids were isolated by him; for two of these the names tigloidine and valeroidine are now suggested, since they are esters of tiglic and *iso*valeric acid respectively; the third alkaloid is provisionally referred to as base Z. None of these alkaloids gives the Vitali reaction (for tropic acid), a fact which at once distinguishes them from hyoscine or any of the alkaloids found by other workers. With the exception of a little *dl*-hyoscine, no other alkaloid could be isolated.

Tigloidine, $C_{13}H_{21}O_2N$, a thin colourless syrup, has a narcotic odour when warm and is a strong tertiary base. It is optically inactive and contains one double bond, readily reduced catalytically; it adds bromine slowly. Among various characteristic salts the *hydrobromide* is peculiar in being soluble in chloroform (1 in 3). On hydrolysis tigloidine yields tiglic acid, $C_5H_8O_2$, and ψ-tropine, $C_8H_{15}ON$, so it is tiglyl-ψ-tropëine, a fact which we have confirmed by its synthesis from tiglyl chloride and ψ-tropine hydrochloride (according to a general method employed by Jowett and Pyman, J., 1909, **95**, 1024).

Tiglic acid appears to have been obtained so far only by hydrolysis of two other alkaloids: cevadine from *Veratrum sabadilla* (Wright and Luff, J., 1878, **33**, 347) and meteloidine from *Datura meteloides* (Pyman and Reynolds, J., 1908, **93**, 2077); ψ-tropine has hitherto been obtained from one alkaloid only, tropacocaine from Javanese coca leaves (Giesel and Liebermann, *Ber.*, 1891, **24**, 2336). Since both tiglic acid and ψ-tropine have geometric isomerides, three stereoisomerides of tigloidine are conceivable; we have synthesised one of these, tiglyltropëine.

Valeroidine, $C_{12}H_{23}O_3N$, colourless nacreous plates, melts at 85° (corr.) and like tigloidine is a strong tertiary base. It has one free hydroxyl group, and is saturated. Its *hydrobromide* is only sparingly soluble in chloroform, and this difference from tigloidine is utilised in the separation of the two alkaloids (see experimental part). They can also be distinguished by Mayer's reagent, to which tigloidine behaves normally; valeroidine, on the other hand, gives a precipitate in concentrated solution only, and the precipitate is, moreover, readily soluble in dilute acids. Valeroidine is lævorotatory; its hydrobromide is dextrorotatory. On hydrolysis equimolecular proportions of *iso*valeric acid, $C_5H_{10}O_2$, and a crystalline, lævorotatory base, $C_8H_{15}O_2N$, m. p. 212° (corr.), are formed; the base was found to be identical with the dihydroxytropane separated as dibenzoyl ester from Peruvian coca leaves by Wolfes and Hromatka (*Merck's Jahresber.*, 1933, **47**, 45). We are indebted to Messrs. Merck of Darmstadt for a generous supply of this base and of the sulphate of its dibenzoyl ester, for which we tender our best thanks. Since this dihydroxytropane was obtained from the residues of the industrial partial synthesis of cocaine from ecgonine, it probably does not occur in coca leaves as such, but was formed by hydrolysis of the crude alkaloids in the manufacture of ecgonine. It is of interest to note that the chemistry of the alkaloids of *D. myoporoides* (N. O. *Solanaceæ*) resembles that of the alkaloids of *Erythroxylon Coca* (N. O. *Erythroxylaceæ*) in at least two points: both plants, widely separated taxonomically, yield ψ-tropine and dihydroxytropane, two bases not known to be produced by any other plant. Valeroidine is thus mono*iso*valeryldihydroxytropane and the first alkaloid to have yielded a pentoic acid by hydrolysis; this is represented in tigloidine by an unsaturated and in base Z apparently by a saturated acid with five carbon atoms. Gerrard (*Pharm. J.*, 1877, **8**, 787), probably the earliest worker on Australian *D. myoporoides*, already observed on hydrolysis of the total alkaloid an odour "resembling butyric acid" (not noticed by later workers). In spite of his injunction not to apply the term "duboisine" to an impure substance, this term crept into the literature.

Base Z, $C_{12}H_{21}O_2N$, a thin, colourless, strongly basic syrup, has a narcotic odour when warm. It resembles valeroidine in its behaviour to Mayer's reagent and tigloidine in forming a hydrobromide soluble in chloroform (1 in 0·4; much more even than tigloidine hydrobromide). Base Z forms a characteristic *oxalate*, used in its isolation, and is being investigated further.

Experimental.

Separation and Isolation of the Three Alkaloids.—The drug (No. 20 powder) was extracted with alcohol, and from the total alkaloids hyoscine was separated by the usual methods. The concentrated aqueous solution of the residual hydrobromides was extracted with chloroform, which removed most of the hydrobromides of tigloidine and base Z. On evaporation of the chloroform the tigloidine salt crystallised and the residual syrupy hydrobromide of base Z was converted into a neutral oxalate which slowly crystallised on concentration of its aqueous solution. The hydrobromides left in aqueous solution (from which the chloroform-soluble portion had been removed) were also converted into neutral oxalates; from their concentrated solution in water, valeroidine oxalate slowly crystallised (at first thought to be hyoscyamine oxalate). After reconversion into hydrobromides a small amount of *dl*-hyoscine was separated from the residual alkaloids, but no other base. The crude tigloidine hydrobromide was recrystallised from water. The valeroidine oxalate was converted into hydrobromide, which was recrystallised by adding ether to its warm alcoholic solution. The oxalate of base Z was recrystallised from water. A good average sample of the drug yielded: tigloidine 0·1, valeroidine 0·1, base Z 0·003%.

Tigloidine is sparingly soluble in cold water, readily in most organic solvents. The *hydrobromide*, colourless, anhydrous, tabular crystals (from water), m. p. 234—235° (corr.), is

moderately soluble in water and in alcohol, readily in chloroform (*ca.* 1 : 3), almost insoluble in ether (Found: C, 51·4; H, 7·4; N, 4·6; Br, 26·1. $C_{13}H_{21}O_2N$,HBr requires C, 51·3; H, 7·3; N, 4·6; Br, 26·3%), and is optically inactive (*c*, 5·0 in water). The methiodide was prepared from the base (0·2 g.) in dry ether (10 c.c.) and methyl iodide (0·5 c.c.), and separated overnight at room temperature; recrystallised from alcohol–ether, it formed square plates, m. p. 244—245° (corr.), readily soluble in water and in alcohol. The picrate, from the base (0·2 g.) in N/50-hydrochloric acid (5 c.c.) and saturated aqueous picric acid solution in slight excess, formed rectangular plates (from 45% alcohol), m. p. 239° (corr.), soluble in alcohol and in acetone, but very sparingly in water. The aurichloride, prepared like the picrate, formed golden-yellow plates (from aqueous acetone), m. p. 213·5—214° (corr.), readily soluble in acetone, hardly in water.

Dihydrotigloidine.—Tigloidine hydrobromide (1 g.) in water (25 c.c.) was shaken with platinum oxide (0·1 g.) in hydrogen. Absorption ceased after 50 minutes when 1 mol. had been taken up. After filtration, basification with ammonia, and extraction with chloroform, the theoretical amount (0·74 g.) of a thin syrup was obtained. The *hydrobromide* formed stout prisms (from alcohol–ether), m. p. 186—187° (corr.) (Found: C, 51·2; H, 7·9. $C_{13}H_{23}O_2N$,HBr requires C, 51·0; H, 7·8%), the methiodide was a microcrystalline powder, m. p. 209° (corr.), the picrate crystallised in plates, m. p. 134·5° (corr.), and the aurichloride in orange-yellow plates, m. p. 151° (corr.). The last two salts are rather more soluble in water than the corresponding tigloidine salts.

Dibromodihydrotigloidine.—Bromine (0·1 c.c.) was added to tigloidine hydrobromide (0·6 g.) in chloroform (10 c.c.). The solution became almost colourless in 3 days; after evaporation the faintly yellow, crystalline residue was recrystallised from a little 25% alcohol, giving stout colourless prisms, m. p. 196° (corr.; decomp.), soluble in alcohol, sparingly in water. Yield, 80%. The free base, obtained from this hydrobromide, became solid on evaporation of the chloroform. After being washed with acetone, it separated from alcohol–ether as a white microcrystalline powder, m. p. 187° (corr.; decomp.).

Hydrolysis of Tigloidine.—The base from 1 g. of hydrobromide was boiled for 1 hour with barium hydroxide (1·5 g.) in water (25 c.c.). On extraction of the solution with ether and evaporation of this solvent, the minute residue obtained neutralised 0·25 c.c. of N/10-sulphuric acid (equivalent to 0·006 g. of tigloidine). After removal of the barium as sulphate from the aqueous layer, so extracted, the acid filtrate was shaken with ether, which left 0·318 g. of an acid forming stout prisms from hot water, m. p. 64·5° (corr.), not depressed by tiglic acid (Found: equiv., 100. Calc. for $C_5H_8O_2$: equiv., 100). Yield, 97%. The dibromide, prepared in chloroform solution, formed long needles from light petroleum, m. p. 88° (corr.), not depressed by an authentic specimen.

The solution from which the tiglic acid had been extracted was freed from sulphuric acid by barium carbonate; the filtrate and washings were exactly neutralised with sulphuric acid, filtered, and evaporated. The almost colourless, distinctly hygroscopic residue (0·606 g.) gave reactions for chloride (as well as sulphate; compare the similar behaviour of teloidine, from meteloidine; Pyman and Reynolds, *loc. cit.*). Chloride and sulphate ions were removed by a slight excess of potassium hydroxide in alcohol; the filtrate then left 0·353 g. of a crystalline residue. After sublimation at 1 mm., needles were obtained from benzene–ligroin, m. p. 108° (corr.), not depressed by ψ-tropine. Yield, 76%. A portion was converted into acetyl-ψ-tropëine hydrobromide, which melted at 205° (corr.), alone and mixed with an authentic specimen.

Hydrobromides of Acetyltropëine and Acetyl-ψ-tropëine.—These compounds, which do not appear to have been described, have been found useful in identifying tropine and ψ-tropine; they are prepared by refluxing the bases with acetic anhydride for a few hours; after addition of water, basification with ammonia, and extraction with chloroform, the residue is neutralised with hydrobromic acid and crystallised from alcohol–ether. *Acetyltropëine hydrobromide* forms stout prismatic needles, m. p. 187—187·5° (corr.) (Found: N, 5·3. $C_{10}H_{17}O_2N$,HBr requires N, 5·3%). The corresponding methiodide forms glistening needles, m. p. 279—280° (corr.). The picrate, m. p. 217° (corr.), is moderately soluble in water. Acetyl-ψ-tropëine hydrobromide forms stout prisms, m. p. 205° (corr.).

Synthesis of Tigloidine.—Tiglic acid (4 g.) and phosphorus trichloride (3 g.) were heated together at 70—80° for 2 hours; the upper, slightly yellow layer was decanted from the syrupy lower layer and distilled at 64°/35 mm.; yield, 90%. Tiglyl chloride so obtained (0·25 g.) was refluxed with ψ-tropine hydrochloride (0·3 g.) for 4 hours on the water-bath. The pale yellow, syrupy product was dissolved in very dilute hydrochloric acid and washed

with ether to remove tiglic acid, then basified and extracted with chloroform. The residue on neutralisation with hydrobromic acid and evaporation yielded 0·47 g. (87%) of a crystalline hydrobromide. After solution in chloroform, filtration, and crystallisation from alcohol–ether, prisms separated, m. p. 234·5° (corr.), identical with the natural product (Found : C, 50·9; H, 7·2; N, 4·6; Br, 26·3. Calc. for $C_{13}H_{21}O_2N$,HBr : C, 51·3; H, 7·3; N, 4·6; Br, 26·3%). The methiodide had m. p. 244° (corr.), not depressed by tigloidine methiodide.

Synthesis of Tiglyltropëine Hydrobromide.—Prepared as above, from tropine hydrochloride (0·5 g.) and tiglyl chloride (0·33 g.) in 46% yield, this formed rectangular laminæ, m. p. 207° (corr.) (Found : N, 4·4. $C_{13}H_{21}O_2N$,HBr requires N, 4·6%). The substance was evidently not quite pure, but repeated recrystallisation failed to raise its m. p. The picrate formed golden-yellow plates with feathery edges, m. p. 200° (corr.), sparingly soluble in water, and the methiodide, colourless laminæ, m. p. 289—290° (corr.).

Valeroidine.—This formed soft laminar crystals, m. p. 85°, readily soluble in ether, alcohol, chloroform and water, sparingly in light petroleum. $[\alpha]_D^{20°}$ −9·0 (*c*, 5·0 in absolute alcohol) and − 4·0° (*c*, 5·0 in water). The *hydrobromide* crystallised in small needles from alcohol–ether, m. p. 170—172° (corr.) (lower figures were obtained unless the temperature was raised very slowly). $[\alpha]_D^{20°}$ + 5·0° (*c*, 20 in water) and + 2·5° (*c*, 20 in absolute alcohol) (Found : C, 48·2; H, 7·7; N, 4·3; Br, 24·4. $C_{13}H_{23}O_3N$,HBr requires C, 48·4; H, 7·5; N, 4·3; Br, 24·8%). The oxalate, prepared by neutralisation of the base with oxalic acid, formed long prismatic needles, m. p. 202° (corr.), sparingly soluble in water. The methiodide, prepared in dry ether at room temperature and recrystallised from methanol–ether, formed six-sided laminæ, m. p. 205·5° (corr.), soluble in methyl alcohol, sparingly in ethyl alcohol. The picrate separated in needles from water, m. p. 152—153° (corr.), moderately soluble in water. The aurichloride was a yellow oil.

Hydrolysis of Valeroidine.—The method was the same as that for tigloidine. The oily acid obtained (0·245 g. from 1 g. of valeroidine hydrobromide) had a powerful odour of valeric acid and was optically inactive (*c*, 2·45 in 60% alcohol) (Found : equiv., 101. Calc. for $C_5H_{10}O_2$: equiv., 102). Yield, 77%. It was characterised as the *p*-phenylphenacyl ester and the anilide. The acid (0·24 g.) was almost neutralised with sodium carbonate, and the solution concentrated (3 c.c.) and refluxed with *p*-phenylphenacyl bromide (0·5 g.) in 95% alcohol (10 c.c.). *p*-Phenylphenacyl *iso*valerate crystallised over-night and was recrystallised from 50% alcohol, forming colourless foliated masses, m. p. 76° (corr.), not depressed by a specimen prepared from authentic *iso*valeric acid. The anilide was obtained by refluxing the acid (1·5 g.) with aniline (1 g.) and repeatedly crystallised from 70% alcohol (charcoal); m. p. 114° (corr.), not depressed by an authentic specimen having the same m. p. (the literature gives m. p. 115°).

The basic fission product of valeroidine formed large, colourless, tabular crystals from alcohol–ether, m. p. 212° (corr.) (not raised by sublimation at 1 mm.). In its separation as sulphate, no trace of chloride was found. Yield, 100% (0·487 g. from 1 g. of valeroidine hydrobromide) [Found : C, 61·0; H, 9·7; N, 9·2; (N)CH_3, 7·9; active H, 1·43; equiv., 156. Calc. for dihydroxytropane, $C_8H_{15}O_2N$: C, 61·1; H, 9·6; N, 8·9; (N)CH_3, 9·5; active H, 2·0%; equiv., 157]. $[\alpha]_D^{20°}$ − 25·0° (*c*, 2·0 in absolute alcohol) and − 16·0° (*c*, 4·0 in water). The substance was in all respects similar to the dihydroxytropane from Peruvian coca leaves, supplied by Messrs. E. Merck. Both bases and their mixture melted at 212° (corr.); the Merck base had $[\alpha]_D^{21°}$ − 22·0° (*c*, 2·0 in absolute alcohol). This dihydroxytropane is a strong base, freely soluble in water and in alcohol, sparingly in ether. It is being investigated further.

Base Z.—This is a syrup, sparingly soluble in water and in ether, freely in alcohol and in chloroform. The *oxalate*, soft nacreous laminæ, m. p. 285—290° (corr.), crystallises from water, in which it is sparingly soluble in the cold [Found : C, 60·9; H, 8·6; N, 5·5; $H_2C_2O_4$, 17·6. $(C_{12}H_{21}O_2N)_2,H_2C_2O_4$ requires C, 60·9; H, 8·6; N, 5·5; $H_2C_2O_4$, 17·6%]. It is optically inactive (*c*, 1·0 in water). The hydrobromide forms similar crystals from alcohol–ether, m. p. 219—220° (corr.). It is very soluble in chloroform (*ca.* 1 in 0·4); the saturated solution is viscous.

The isolation and purification of these alkaloids were carried out by one of us (W. F. M.) in the laboratories of Messrs. T. & H. Smith, Ltd., Edinburgh, to which firm our best thanks are recorded for generous supplies both of the drug and of the separated alkaloids. The work on their constitution is by the other two authors, one of whom (W. M.) desires to express his gratitude to Messrs. T. & H. Smith, Ltd., for facilities to carry it out.

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