317. *The Minor Alkaloids of* Duboisia myoporoides. *Part II. Poroidine and* iso*Poroidine.*

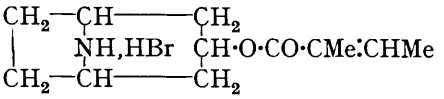
By G. Barger, Wm. F. Martin, and Wm. Mitchell.

Base Z (Part I, J., 1937, 1821), $C_{12}H_{21}O_2N$, is a mixture of about 10 parts of poroidine (*iso*valerylnortropëine) with 1 part of *iso*poroidine (*d*-α-methylbutyrylnortropëine), and has been indirectly racemised. The former constituent was separated by an indirect method, and both have been synthesised; their mixture in the above ratio was shown to be similar to base Z. A probable derivation of these bases from leucine and *iso*leucine respectively is suggested. Tiglylnortropëine, tiglyltropëine (Part I, *loc. cit.*), and *dl*-α-methylbutyryltropëine have also been prepared. The hydrobromides of all the alkaloids mentioned are freely soluble in chloroform. The *p*-phenylphenacyl esters of the butyric and valeric acids are described. A method for recovery of acid and alcohol from such esters is also given.

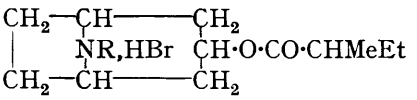
Base Z (Part I, J., 1937, 1821) is a thin, colourless syrup which partly crystallises on standing, and is dextrorotatory; it has been racemised by an indirect method. The oxalate and salicylate have no optical activity. Base Z is a strong secondary base, yields an oily nitroso-derivative, and is saturated. On hydrolysis it yields nortropine and a liquid acid, $C_5H_{10}O_2$, $[\alpha]_D^{20°}$ + 2·9°, at first thought to be partly racemised *d*-α-methylbutyric acid. *Tiglylnortropëine hydrobromide* (I) was synthesised from tiglyl chloride and nortropine hydrochloride (according to a general method employed by Jowett and Pyman, J., 1909, **95**, 1024), and catalytic reduction then yielded dl-α-*methylbutyrylnortropëine hydrobromide* (II, R = H), but this was not identical with the *hydrobromide* of racemised base Z.

Further examination of the acid $C_5H_{10}O_2$ showed it to be a mixture of *iso*valeric and *d*-α-methylbutyric acids in a ratio of about 10 to 1. iso*Valerylnortropëine hydrobromide* (III) was prepared from the corresponding hydrochloride synthesised from *iso*valeryl

chloride and nortropine hydrochloride. A mixture of 10 parts of it with 1 part of *dl*-α-methylbutyrylnortropëine hydrobromide had properties identical with those of racemised base Z hydrobromide; the melting point of the mixture was intermediate between those of its components, and was not depressed by the hydrobromide of the natural (dextrorotatory) material, the salts of which, incidentally, have the same melting points as those of the racemised base.



(I.)



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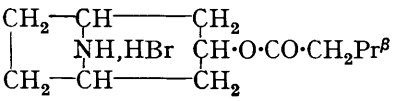

(III.)

Fractional crystallisation of various salts of base Z afforded no evidence of separation of the isomers. Chromatographic methods were equally unsuccessful. The isomers differ so slightly in structure that failure to effect direct separation is probably not surprising. An indirect separation was achieved by hydrolysis, followed by fractional precipitation of the silver salts of the acids from aqueous solution; *iso*valeric acid was thus obtained in a pure state. Esterification of this acid with the nortropine also obtained in the hydrolysis gave iso*valerylnortropëine*; this was identical with the previous synthetic material. It was not found possible to isolate the *d*-α-methylbutyric acid. Base Z is thus a mixture of much *iso*valerylnortropëine with a little *d*-α-methylbutyrylnortropëine; it is suggested that the former be named poroidine and the latter *iso*poroidine. It is probable that the two acids are derived respectively from leucine and *iso*leucine, *via* the corresponding amyl alcohols, and we thus have some indication, not otherwise available, that these aliphatic amino-acids may be used in the biogenesis of alkaloids. Usually it is only possible to infer the utilisation of aromatic amino-acids for this purpose.

dl-α-*Methylbutyryltropëine hydrobromide* (II, R = Me), made by catalytic reduction of tiglyltropëine hydrobromide (Part I, *loc. cit.*), was prepared for comparison purposes; mixtures of these two substances showed slight *elevation* of melting point.

The *p*-phenylphenacyl esters of the two butyric and the four valeric acids were prepared in the course of this work; the melting points of mixtures of the esters of the latter acids are given. Recovery of the acid from these esters cannot be effected by alkaline hydrolysis, since profound decomposition occurs. Acid hydrolysis, on the other hand, gives theoretical yields of the acid and *p*-phenylphenacyl alcohol; the method is described.

Experimental.

Base Z.—The syrup had $[\alpha]_D^{20°}$ + 2·5° (*c*, 8·0 in absolute alcohol or in chloroform). The oxalate formed colourless, diamond-shaped laminæ from water, in which it was sparingly soluble in the cold, m. p. 296—297° (corr.) [raised from the figure previously given, 285—290° (corr.), by recrystallisation] [Found : C, 60·7; H, 8·7; N, 5·7. Calc. for $(C_{12}H_{21}O_2N)_2,H_2C_2O_4$: C, 60·9; H, 8·6; N, 5·5%]. The *hydrobromide*, which formed colourless laminæ (from absolute alcohol–ether), m. p. 219—220° (corr.), was very soluble in water, in alcohol, and in chloroform (*ca.* 1 in 0·4); the last solution was viscous. $[\alpha]_D^{20°}$ + 2·9° (*c*, 6·0 in water) (Found : C, 49·4; H, 7·8; N, 4·8; Br, 27·4. $C_{12}H_{21}O_2N,HBr$ requires C, 49·3; H, 7·5; N, 4·8; Br, 27·3%). The hydrochloride separated, on addition of a large excess of ether to a concentrated absolute alcoholic solution, in long, colourless, tabular prisms, m. p. 204° (corr.); it was somewhat hygroscopic, and very soluble in water and in chloroform. The methiodide, obtained by refluxing the base (0·1 g.) in methyl alcohol (3 c.c.) with methyl iodide (0·25 c.c.) for 1 hour, formed colourless, foliated laminæ (from alcohol–ether), m. p. 301° (corr.), freely soluble in water and in alcohol. The aurichloride, prepared from the base (0·1 g.) in N/50-hydrochloric acid (2 c.c.) and auric chloride solution in slight excess, formed opaque, yellow laminæ, m. p. 203° (corr.); all attempts to recrystallise this salt resulted in its decomposition. The picrate, prepared like the aurichloride, formed tabular, yellow prisms

(from aqueous acetone), m. p. 172° (corr.). The salicylate was made by adding salicylic acid (0·85 g.) in dry ether (5 c.c.) to the base (1 g.) in dry ether (10 c.c.); colourless, glistening laminæ, m. p. 154° (corr.), separated in 75% yield after a short time. Neither the normal nor the acid phthalate was crystallisable.

The nitroso-derivative of Base Z was prepared by adding a slight excess of sodium nitrite to a solution of the base in dilute hydrochloric acid; it slowly separated as an oil which was ether-extracted, but could not be crystallised.

Hydrolysis of Base Z.—The base from 1 g. of oxalate was refluxed for 2 hours with barium hydroxide (1·5 g.) in water (20 c.c.). Ether extracted no unhydrolysed base from the mixture. After removal of barium as sulphate from the aqueous liquid, the acid filtrate was extracted with ether, yielding 0·37 g. of an oily acid with a powerful odour of valeric acid; $[\alpha]_D^{20°}$ + 2·9° (*c*, 6·2 in absolute alcohol) (Found: equiv., 103. Calc. for $C_5H_{10}O_2$: equiv., 102); yield, 95%. The *p*-phenylphenacyl ester, m. p. 69° (corr.), formed dull, colourless laminæ from 60% alcohol; the m. p. of a mixture with the ester of *dl*-α-methylbutyric acid [m. p. 71° (corr.)] was 66° (corr.). The amide, made from the chloride, formed colourless, foliated laminæ (from ether), m. p. *ca.* 120°; mixed with *dl*-α-methylbutyramide [m. p. 114° (corr.)], it melted at *ca.* 108°.

The aqueous liquid from which the 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 slightly yellow, crystalline residue gave reactions for chloride [as well as sulphate; compare the similar behaviour of tigloidine (Part I, *loc. cit.*), and meteloidine (Pyman and Reynolds, J., 1908, **93**, 2077)]. It was dissolved in water (1 c.c.), excess of 30% aqueous sodium hydroxide added, and the solution repeatedly extracted with chloroform. The residue, after evaporation of the solvent, weighed 0·32 g., m. p. *ca.* 160°; yield, 64%. It was dissolved in absolute alcohol (5 c.c.), dry ether (30 c.c.) added, and carbon dioxide bubbled through the solution for 10 minutes; the precipitated carbamate was collected, and washed with dry ether. It was an almost white, crystalline powder (0·21 g.), m. p. 166° (corr.; decomp., with evolution of carbon dioxide), not depressed by nortropine carbamate, and was optically inactive (*c*, 6·5 in water) [Found: N, 9·4. Calc. for $(C_7H_{13}ON)_2,CO_2$: N, 9·4%]. The nitroso-derivative was prepared by adding a slight excess of sodium nitrite to the base (0·1 g.) in N/20-hydrochloric acid (4 c.c.); after standing overnight, the clear solution was extracted with ether. The residue from the ether separated from a small volume of the same solvent in colourless prisms, m. p. 196° (corr.), not depressed by an authentic specimen of nitrosonortropine.

Racemisation of Base Z.—The base from 5 g. of the oxalate was hydrolysed by refluxing for 2 hours with potassium hydroxide (3 g.) in water (40 c.c.). Ether extracted 2 g. of valeric acid from the acidified mixture; yield, 100%. The aqueous liquid from which the acid had been extracted was treated with 30% of solid potassium hydroxide and repeatedly extracted with chloroform. 2·4 G. of nortropine carbamate, m. p. 166·5° (corr.; decomp., with evolution of carbon dioxide), were obtained from the extracted base by the above method; yield, 84%.

The acid was treated with potassium hydroxide (5 g.) and sufficient water for solution, and boiled for 12 hours in a nickel crucible, water being added to maintain the volume. Ether extracted 1·7 g. of acid from the diluted and acidified solution; yield, 86%. It was optically inactive (*c*, 34·0 in absolute alcohol). (This treatment was only adopted after milder methods had failed to effect racemisation.) The racemised acid (1·25 g.) and phosphorus trichloride (0·65 g.) were heated together at 80—90° for 2 hours. The upper layer was decanted from the syrupy residue and refluxed with nortropine hydrochloride (made by titrating 1·75 g. of the above carbamate with hydrochloric acid, and evaporating the solution in a vacuum) for 2 hours on the water-bath. The pale yellow, syrupy product was dissolved in very dilute hydrochloric acid, washed with ether to remove free valeric acid, then basified with ammonia, and extracted with chloroform. The residue on neutralisation with hydrobromic acid and evaporation gave 1·02 g. of a crystalline hydrobromide; yield, 28·5%. After solution in chloroform, filtration, and crystallisation from alcohol–ether, colourless, glistening laminæ were obtained, m. p. 219—220° (corr.) (Found: C, 49·5; H, 7·7; N, 4·8; Br, 27·6. Calc. for $C_{12}H_{21}O_2N,HBr$: C, 49·3; H, 7·5; N, 4·8; Br, 27·4%). It was optically inactive (*c*, 20·0 in water). The above m. p. and those of the oxalate, picrate, and methiodide were identical with those of the corresponding salts of the natural (dextrorotatory) alkaloid. (The *p*-phenylphenacyl ester and amide of the racemised acid also showed the same m. p.'s as those of the original acid.)

Synthesis of Tiglylnortropēine.—Nortropine carbamate (1·2 g.) (made from tropine; Willstätter, *Ber.*, 1896, **29**, 1580) was titrated with hydrochloric acid, and the solution evaporated in a vacuum. Nortropine hydrochloride so obtained was refluxed with tiglyl chloride (0·95 g.) (Part I, *loc. cit.*) for 2 hours on the water-bath. The syrupy product was dissolved in very dilute hydrochloric acid, and the alkaloid purified and isolated as *hydrobromide* as in the case above; weight, 1·59 g.; yield, 70%. After solution in chloroform, filtration, and crystallisation from alcohol–ether, dull, colourless laminæ were obtained, m. p. 241—242° (corr.) (Found: C, 49·4; H, 7·0; N, 4·7; Br, 27·4. $C_{12}H_{19}O_2N$,HBr requires C, 49·6; H, 6·9; N, 4·8; Br, 27·6%). The picrate formed golden-yellow, prismatic needles (from aqueous acetone), m. p. 207° (corr.), and the methiodide colourless, opaque laminæ (from alcohol–ether), m. p. 285—286° (corr.; decomp.).

Synthesis of dl-α-*Methylbutyrylnortropēine.*—Tiglylnortropëine hydrobromide (1 g.) in water (25 c.c.) was shaken with platinum oxide (0·1 g.) in hydrogen. Absorption was slow, and ceased after 6 hours when 1 mol. had been taken up. After filtration, basification with ammonia, and extraction with chloroform, the theoretical amount (0·73 g.) of a thin syrup was obtained. By titration with hydrobromic acid, evaporation, solution of the residue in chloroform, filtration, and crystallisation from alcohol–ether, the *hydrobromide* was obtained in colourless, glistening plates, m. p. 201—202° (corr.), raised to *ca.* 209° by either natural or racemised base Z hydrobromide [m. p. 219—220° (corr.)] (Found: N, 4·9; Br, 27·0. $C_{12}H_{21}O_2N$,HBr requires N, 4·8; Br, 27·4%). The *oxalate* formed colourless, glistening laminæ (from water), m. p. 296—297° (corr.), depressed to 295° (corr.) by base Z oxalate [m. p. 296—297° (corr.)] [Found: C, 60·8; H, 8·5; N, 5·5. $(C_{12}H_{21}O_2N)_2,H_2C_2O_4$ requires C, 60·9; H, 8·6; N, 5·5%]. The picrate formed golden-yellow, prismatic needles (from aqueous acetone), m. p. 188° (corr.), depressed to 180° (corr.) by base Z picrate [m. p. 172° (corr.)]. The methiodide formed dull, pearly laminæ (from alcohol–ether), m. p. 295° (corr.). (The alkaloid was independently synthesised from *dl*-α-methylbutyryl chloride and nortropine hydrochloride; the product was identical with the above. α-Methylbutyric acid is obtained in theoretical yield by shaking tiglic acid in 45% aqueous alcohol with platinum oxide in hydrogen. Sodium tiglate in water is not reduced by this method.)

p-*Phenylphenacyl Esters of the Valeric Acids.*—These were prepared from the acids by the usual method, and melted as follows: *n*-valerate, 68° (corr.); *iso*valerate, 76° (corr.); *dl*-α-methylbutyrate, 71° (corr.); trimethylacetate, 114° (corr.). The first three formed dull, felted laminæ, the fourth hard, prismatic needles. Mixtures of equal weights melted as below:

n-Valerate + *iso*valerate	*ca.* 56°	*iso*Valerate + *dl*-α-methylbutyrate ...	*ca.* 67°
,, + *dl*-α-methylbutyrate	,, 47	,, + trimethylacetate	,, 78
,, + trimethylacetate	,, 85	*dl*-α-Methylbutyrate + trimethylacetate	,, 87

Melting points of mixtures of *iso*valeric and *dl*-α-methylbutyric esters in the following ratios of former to latter were then found: 10 : 1, 69—70° (corr.), not depressed by the ester of the acid from base Z [m. p. 69° (corr.)]; 2 : 1, 66·5° (corr.). [A mixture of 10 parts of *iso*valeramide, m. p. 136° (corr.), with 1 part of *dl*-α-methylbutyramide, m. p. 112° (corr.), had m. p. *ca.* 120°, not depressed by the amide of the base Z acid, m. p. *ca.* 120°.] The *p*-phenylphenacyl esters of the butyric acids were prepared for comparison: *n*-butyrate, 82° (corr.); *iso*butyrate, 88° (corr.).

Hydrolysis of p-*Phenylphenacyl Esters.*—The ester (*ca.* 0·5 g.) in 70% aqueous acetone (10 c.c.) was refluxed for 2 hours on the water-bath with concentrated sulphuric acid (0·5 c.c.). The cooled mixture was neutralised with N-sodium hydroxide, and *p*-phenylphenacyl alcohol extracted with chloroform and recrystallised from absolute alcohol (charcoal). The aqueous liquid was then acidified with sulphuric acid, and the organic acid recovered in the usual way. The yields of acid and alcohol were quantitative. (Hydrolysis with alcoholic potassium hydroxide results in complete decomposition, resinification, and loss of both acid and alcohol.) *p*-Phenylphenacyl alcohol, so prepared, formed colourless, prismatic needles, m. p. 132° (corr.; sintering at 130°; Allen and Ball, *Canadian J. Res.*, 1932, **7**, 643, give m. p. 123—128° (Found: C, 79·1; H, 5·7. Calc. for $C_{14}H_{12}O_2$: C, 79·2; H, 5·7%).

Synthesis of iso*Valerylnortropēine.*—*iso*Valeric acid (4 g.) and phosphorus trichloride (3·5 g.) were heated together at 80—90° for 2 hours. The upper, colourless layer was decanted from the syrupy residue and distilled at 115°/760 mm.; yield, 100%. *iso*Valeryl chloride, so obtained (0·65 g.), was refluxed for 2 hours on the water-bath with nortropine hydrochloride (0·8 g.), and the alkaloid isolated as *hydrobromide* as in the previous cases; yield, 57%. After

solution in chloroform, filtration, and crystallisation from alcohol–ether, small, colourless plates were obtained, m. p. 224—225° (corr.) (Found: N, 4·8; Br, 27·2. $C_{12}H_{21}O_2N$,HBr requires N, 4·8; Br, 27·4%). Melting points of mixtures with *dl*-α-methylbutyrylnortropëine hydrobromide (assumed to have the same m. p. as the dextro-form) in various ratios were found: 10 : 1, 220° (corr.), not depressed by either natural or racemised base Z hydrobromide [m. p. 219—220° (corr.)]; 8 : 1, 217° (corr.); 4 : 1, 213—214° (corr.); 8 : 3, 210° (corr.). The *oxalate*, prepared by neutralising the base with oxalic acid, crystallised in colourless, glistening laminæ (from water), m. p. 301—302° (corr.), depressed to 296° (corr.) by *dl*-α-methylbutyrylnortropëine oxalate [m. p. 297° (corr.)] [base Z oxalate has m. p. 296—297° (corr.)] [Found: C, 60·8; H, 8·4; N, 5·6. $(C_{12}H_{21}O_2N)_2,H_2C_2O_4$ requires C, 60·9; H, 8·6; N, 5·4%]. The picrate formed golden-yellow prisms (from aqueous acetone), m. p. 172° (corr.), and the methiodide, which was only sparingly soluble in absolute alcohol, pearly laminæ from methyl alcohol–ether, m. p. 289° (corr.; darkening at 280°).

Attempted Separation of Isomers from Base Z.—(A) *Fractional crystallisation.* Base Z hydrobromide was repeatedly crystallised from alcohol–ether without sign of fractionation. The salicylate, m. p. 154° (corr.), prepared as described above, was converted into hydrobromide, m. p. 213° (corr.); this in turn yielded salicylate, m. p. 154° (corr.), identical with the starting material. The picrate was fractionally crystallised from aqueous alcohol, and aqueous acetone, fractions with m. p.'s from 167° to 172° (corr.) being obtained; these yielded hydrobromides with m. p.'s from 207° to 210° (corr.) which were evidently mixtures.

(B) *Chromatographic methods.* A 1% solution of base Z in chloroform was drawn through a column of aluminium oxide (Brockmann), followed by chloroform washings (10 of 15 c.c.). 70% of the base was unadsorbed; it was converted into hydrobromide, m. p. 215—217° (corr.), evidently a mixture. The column showed no bands under ultra-violet light, and yielded nothing to either hot alcohol, acetone, pyridine, or even dilute hydrobromic acid. Similar results were obtained with columns of kaolin and of lactose.

(C) *Hydrolysis and fractional precipitation of silver valerates.* At 20° the solubilities in water of the silver salts of *iso*valeric and *dl*-α-methylbutyric acids are respectively 1 in 540 and 1 in 137 (Beilstein). In the following separation it is assumed that the solubility of silver *d*-α-methylbutyrate is also 1 in 137. The base from 5 g. of base Z oxalate was hydrolysed by refluxing with 10% aqueous potassium hydroxide (30 c.c.); 2·31 g. of nortropine carbamate (80%) and 2·04 g. of valeric acid (100%) were isolated as in the previous hydrolysis. The acid was neutralised with sodium hydroxide solution and diluted with water to 150 c.c., and silver nitrate (3·5 g.) in water (40 c.c.) added dropwise, with constant shaking; the mixture was finally diluted with water to 200 c.c., and left overnight, the temperature being maintained at 20° throughout. The precipitated silver salt was filtered (suction), rapidly washed with water (10 c.c.), and dissolved in dilute aqueous ammonia, and the solution freed from silver by hydrochloric acid and extracted with ether. Evaporation of the solvent (dried over sodium sulphate) gave 1·14 g. of acid; yield, 56%. The *p*-phenylphenacyl ester formed colourless, foliated laminæ, m. p. 76° (corr.), not depressed by authentic *p*-phenylphenacyl *iso*valerate. The mother-liquor from the silver *iso*valerate yielded 0·75 g. of residual acid, $[\alpha]_D^{20°}$ + 4·8 (*c*, 6·0 in absolute alcohol); it was not found possible to effect further separation of this mixture.

The separated *iso*valeric acid (1 g.) was converted into chloride (1·1 g.), and esterified with nortropine hydrochloride (made from 1·4 g. of the above carbamate). The alkaloid was purified and isolated as hydrobromide as in the previous cases; yield, 36% on the acid used, and 20% on the original oxalate. After solution in chloroform, filtration, and crystallisation from alcohol–ether, small, colourless plates were obtained, m. p. 224—225° (corr.), not depressed by authentic *iso*valerylnortropëine hydrobromide. It was optically inactive (*c*, 8·0 in water) (Found: N, 4·8; Br, 27·1. Calc. for $C_{12}H_{21}O_2N$,HBr: N, 4·8; Br, 27·4%).

Synthesis of dl-α-*Methylbutyryltropëine.*—Tiglyltropëine hydrobromide (Part I, *loc. cit.*) was prepared, m. p. 208° (corr.) (Found: C, 51·5; H, 7·2; N, 4·7; Br, 26·2. Calc. for $C_{13}H_{21}O_2N$,HBr: C, 51·3; H, 7·2; N, 4·6; Br, 26·3%), and 1 g. was shaken with platinum oxide (0·1 g.) in hydrogen. Absorption ceased after 1 hour 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 colourless, glistening laminæ (from alcohol–ether), m. p. 210° (corr.); this was slightly higher than the m. p. of the unreduced alkaloid, and a mixture of the two showed a slight *elevation* to 211° (corr.) (Found: C, 50·9; H, 7·8; N, 4·4; Br, 26·1. $C_{13}H_{23}O_2N$,HBr requires C, 51·0; H, 7·8; N, 4·6; Br, 26·1%). The salt was freely soluble in chloroform. The picrate formed golden-yellow prisms

(from aqueous acetone), m. p. 225° (corr.), and the ***methiodide*** colourless, rectangular plates (from alcohol–ether), m. p. 288° (corr.; decomp.) (Found : I, 34·2. $C_{13}H_{23}O_2N,CH_3I$ requires I, 34·6%). This alkaloid is, of course, isomeric with dihydrotigloidine (*dl*-α-methylbutyryl-ψ-tropëine) (Part I, *loc. cit.*).

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