

THE MINOR ALKALOIDS OF Duboisia myoporoides.

by

William Mitchell, B.Sc. (Lond.), A.I.C.

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## P R E F A C E.

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I. I N T R O D U C T I O N.

Duboisia myoporoides, a member of the Solanaceous family, is a tall shrub or small tree. It is indigenous to Australia, being found in Queensland and New South Wales, but also occurs in New Caledonia. The following brief botanical description is given in the "Flora Australiensis", London, 1869, Vol. 4, p. 474:-

"Plant quite glabrous. Leaves alternate, from obovate-oblong to oblong-lanceolate, obtuse or rarely acute, entire, contracted into a petiole, two to four inches long. Panicles terminal, sometimes leafy at the base, usually much branched, broadly pyramidal or corymbose. Bracts minute. Calyx broadly campanulate, with broad obtuse teeth. Corolla about two lines long, white or pale lilac, the lobes rather short and obtuse. Stamens included in the tube. Berry small, nearly globular."

The chemical literature on Duboisia myoporoides is mainly rather old, and is very confusing. The earliest worker appears to have been Gerrard (Pharm. J., 1877, 8, 787) who prepared the total /

total alkaloids in a crude state. He hydrolysed these, and observed an odour "resembling butyric acid"; none of the later workers, curiously enough, seemsto have repeated this observation which, as will be shown later, was very significant. Gerrard urged that the term "duboisine" should not be applied to his preparation, which he recognised to be a mixture. Unfortunately this injunction was ignored, and the name soon appeared in the literature, while indeterminate mixtures of alkaloids, "duboisines" supposedly extracted from D. myoporoides, appeared and are still appearing in commerce. For these reasons the name cannot now be applied to any of the new alkaloids described in this work.

E. Merck (Arch. Pharm., 1893, 231, 117) examined Australian D. myoporoides and found hyoscine, hyoscyamine, and a supposed isomeride of the latter which he termed  $\Psi$ -hyoscyamine. The identity of this alkaloid was questioned by Carr and Reynolds (J.C.S., 1912, 101, 946) who isolated 1.1% of hyoscyamine and 0.15% of a new alkaloid, nor-hyoscyamine, from D. myoporoides stated to be of Philippine origin and made no reference to the presence in it of hyoscine; they regarded Merck's " $\Psi$ -hyoscyamine" as nor-hyoscyamine contaminated with a little hyoscyamine. (The author recently requested the Philippine Forestry Authorities /

Authorities to supply him with a quantity of the drug, but was informed that it did not occur there!)

Present-day pharmaceutical literature (e.g. "The British Pharmaceutical Codex") describes "duboisine", referred to above, as a mixture of hyoscyamine and hyoscine. Ladenburg (Ber., 1880, 13, 257) found a commercial sample to consist largely of hyoscyamine. Later, Ladenburg and Petersen (Ber., 1887, 20, 1661) examined another specimen and stated it to consist mainly of hyoscine. In the light of later knowledge the latter result appears very doubtful; the free base was not isolated but an aurichloride, the analysis of which corresponded fairly closely to  $C_{17}H_{23}O_3N, HCl, AuCl_3$ , and therefore to Ladenburg's hyoscine formula, isomeric with that of hyoscyamine; after considerable controversy Hesse showed the true formula of hyoscine to be  $C_{17}H_{21}O_4N$ . Possibly, therefore, this second sample of "duboisine" also consisted largely of hyoscyamine. The author examined a recent sample of commercial "duboisine" sulphate and found it to consist almost entirely of hyoscyamine sulphate; no trace of hyoscine was detectable and, in fact, the only other material found present consisted of a quantity of fibres probably derived from a brush used in the sifting of the material!

One clear fact emerges: all the quoted workers agree in finding hyoscyamine, and in some cases hyoscyne. As will be shown later, not a trace of the former well defined alkaloid has been isolable in the present work on genuine Australian D. myoporoides. It seems possible, therefore, that some of the above conflicting results are due to the authors having worked on other Solanaceous plants wrongly identified as D. myoporoides, or on other species of Duboisia having a different alkaloidal content from this Australian species. In this connection it is interesting to note that Späth, Hicks, and Zajic (Ber., 1935, 68, 1388) have recently shown the Australian D. Hopwoodii to contain nor-nicotine.

During recent years consignments of Australian D. myoporoides have been examined in the Laboratories of Messrs T. & H. Smith, Ltd., Edinburgh, by Mr Wm. F. Martin. These consignments generally consisted of material which had been collected at the time when fruiting had just commenced, and had been carefully dried. They consisted of leaves, flowering tops, and only a small proportion of small twigs; withered flowers were also present, and sometimes small berries. The odour was quite characteristic, and whilst not unpleasant was somewhat reminiscent of butyric or valeric acid. The material was /

was collected in various Australian districts at different seasons, and exhibited considerable variation both in the proportion of total alkaloid, and in the amounts of the individual alkaloids. It is to be emphasised that in no case could the presence of even a trace of hysoyamine be demonstrated.

Hyoscine was found present, and after its more or less complete separation four new alkaloids were isolated. For two of these the names tigloidine and valeroidine are suggested since they are shown below to be respectively esters of tiglic and iso-valeric acid; each occurs in average samples of the drug to the extent of about 0.1%. The other two alkaloids, which are isomeric, were isolated as a mixture, Base Z, usually found to the extent of about 0.003%. These two bases were very difficult to separate, this being only partially achieved by a very indirect method. The names poroidine and iso-poroidine are suggested for the bases; base Z contains about ten parts of the first to one part of the second.

None of these four new alkaloids gave the Vitali reaction (for tropic acid). This fact at once distinguished them from hyoscine, hyoscyamine, or any of the alkaloids described by earlier workers. Another characteristic feature was the solubility in chloroform of many of their salts, notably the hydrobromides /

hydrobromides. This property, which played an important part in the isolation of the alkaloids, is not unknown among alkaloidal salts, e.g. strychnine hydrochloride, but the degree of solubility in the present cases is quite exceptional.

Apart from a small amount of dl-hyoscyne no other definite alkaloid was separable from the drug.

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II./

II. ISOLATION AND PURIFICATION OF THE ALKALOIDS.

The isolation and purification of the alkaloids forming the subject of this thesis was performed in the Laboratories of Messrs T. & H. Smith, Ltd., Edinburgh, by Mr Wm. F. Martin, to whom the following method is due. It was subsequently repeated on a small scale by the author, and is included here for completeness. Thanks are due for permission to reproduce it, and for supplies of material for the investigation of structure described in the following sections.

The drug (No. 20 powder) was extracted with alcohol. The total alkaloids were isolated, and the hyoscine separated therefrom by the usual methods. The residual alkaloids were converted into hydrobromides and the concentrated aqueous solution of these extracted several times with chloroform; this removed most of the hydrobromides of tigloidine, poroidine, and isoporoidine (as already stated the hydrobromides of these bases are peculiar in being extremely soluble in chloroform). The solvent was completely removed, when the syrupy residue slowly deposited crystalline tigloidine hydrobromide. When the /

the maximum amount of this salt had been separated, the residual bases in the dark brown, syrupy mother liquor were extracted and converted into neutral oxalates. The aqueous solution of these was concentrated; on standing a crystalline oxalate gradually separated. This was Base Z oxalate, at first thought to be a single substance, but subsequently shown to be a mixture of the oxalates of the isomers, poroidine and isoporoidine. The small amount of dark brown, syrupy mother liquor did not yield any further crystallisable material.

The aqueous solution (from which the chloroform-soluble hydrobromides had been extracted) was basified with ammonia, and the alkaloids extracted with chloroform. These were converted into neutral oxalates, and the aqueous solution of these concentrated; valeroidine oxalate slowly crystallised on standing. After separating the maximum amount of this salt, the residual bases were extracted from the mother liquor as before, and reconverted into hydrobromides; after concentration of the aqueous solution a small amount of dl-hyoscyne hydrobromide slowly separated. No other definite base could be isolated from the considerable amount of dark brown, syrupy mother liquor. In particular, no trace of hyoscyamine was detectable at any stage.

Tigloidine /

Tigloidine hydrobromide was purified by recrystallisation from water, in which it was moderately soluble. Valeroidine oxalate was first recrystallised from water (moderately soluble). It was then suspended in water, basified with ammonia, and the base extracted with chloroform. The extract was washed with a little water, the solvent recovered, and the residual base neutralised with hydrobromic acid. The solution was slowly evaporated to dryness on the water-bath, and the residual hydrobromide crystallised by adding ether to its warm alcoholic solution. Base Z oxalate was recrystallised from water, in which it was moderately soluble.

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NOTE: At the time when these alkaloids were isolated it was assumed, from the fact that valeroidine hydrobromide was not, like the hydrobromides of the other three alkaloids, extracted by chloroform from aqueous solution, that this salt was only sparingly soluble in this solvent. The author subsequently found its solubility in chloroform at 15° to be ca. 1 in 0.5, while the chloroform solubilities of the hydrobromides of tigloidine and base Z were found to be respectively ca. 1 in 3, and 1 in 0.4. In order to ascertain how valeroidine could be separated from the other alkaloids by the above method, the following experiment /

experiment was performed:-

1 g. of each of the hydrobromides was dissolved in water (10 ml.), and each solution shaken with chloroform (10 ml.). The chloroformic extracts were separated, evaporated, and the respective residues weighed. In each case the extraction was twice repeated with chloroform (5 ml.), the extracts evaporated, and the residues weighed. The results were as follows:-

<u>Salt.</u>	<u>Residue from 1st. extraction.</u>	<u>Residue from 2nd. and 3rd. extraction.</u>
Tigloidine.	0.518 g.	0.192 g.
Valeroidine.	0.014 g.	0.011 g.
Base Z.	0.418 g.	0.150 g.

Thus the total extractions in the three cases were respectively: 71, 2.5, and 56.8%.

Evidently the water solubilities are responsible for the marked differences in partition coefficient. Tigloidine hydrobromide is only sparingly soluble in water, base Z hydrobromide is very freely soluble in this solvent, while valeroidine hydrobromide is extremely soluble.

This particular case affords an excellent example of the fact that a substance is not necessarily extracted by a solvent in which it is very soluble if already in the presence of another solvent /

solvent in which its solubility is vastly greater. In an extreme case, such as the present, this behaviour might lead to the presence of such a substance being missed altogether.

In view of the above results, the behaviour of some related alkaloids was examined. Hyoscine hydrobromide and atropine sulphate were found, for all practical purposes, to be insoluble in chloroform. Atropine hydrobromide, however, was soluble in chloroform at 15° to the extent of ca. 1 in 4, and an extraction experiment performed exactly as in the above cases gave the following results:-

<u>Residue from 1st. extraction.</u>	<u>Residue from 2nd. and 3rd extractions.</u>
0.033 g.	0.030 g.

Thus the total extraction in this case was 6.3%. Since the salt is extremely water-soluble, and is hygroscopic, extraction to this extent is quite surprising.

The above results would appear to indicate that in alkaloidal assay methods involving the preliminary extraction of fat and colouring matter from acidified solutions with chloroform the use of halogen acids should be avoided, or at least these should be employed with caution.

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### III. TIGLOIDINE.

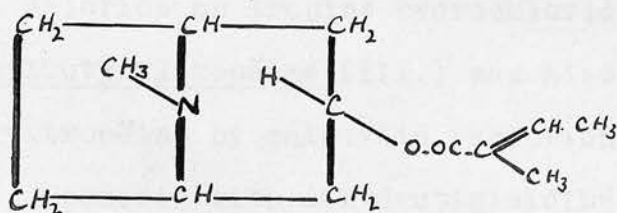
#### A. Theoretical:-

Tigloidine,  $C_{17}H_{21}O_2N$ , is a thin, colourless syrup, practically odourless in the cold, but possessing a strong "narcotic" odour when warmed. It is a strong, monacidic base, and readily forms well-defined salts of which may be mentioned the picrate, aurichloride, and hydrobromide. The last salt, as stated above the form in which tigloidine was first isolated and purified, is peculiar in its ready solubility in cold chloroform to the extent of about one in three. The alkaloid is optically inactive, as are its salts, and gives the normal reaction with Mayer's reagent, the precipitate formed not readily dissolving in excess of dilute acids.

Tigloidine is a tertiary base; it does not yield a nitroso derivative on treatment with nitrous acid, but readily forms a well-defined methiodide. The alkaloid is unsaturated, containing one double linkage which is readily reduced catalytically; the yield of the corresponding dihydro-tigloidine is theoretical. Similarly, a chloroformic solution of tigloidine slowly absorbs bromine with the formation of dibromodihydrotigloidine.

The alkaloid is moderately stable in acid /

acid solution, but is readily hydrolysed on boiling with alkalis to yield tiglic acid,  $C_5H_8O_2$ , and  $\psi$ -tropine,  $C_8H_{15}ON$ . Tigloidine is thus tiglyl-  
: $\psi$ -tropine. (I.):-



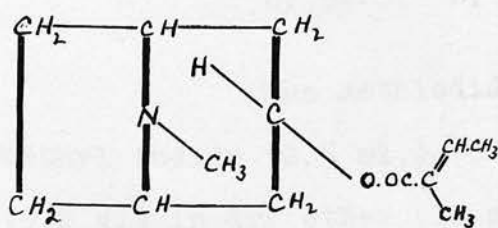
I.

This structure was confirmed by its synthesis from tiglyl chloride and  $\psi$ -tropine hydrochloride (according to a general method for the synthesis of tropëines employed by Jowett and Pyman, J.C.S., 1909, 95, 1024). The product was identical in all respects with the natural alkaloid.

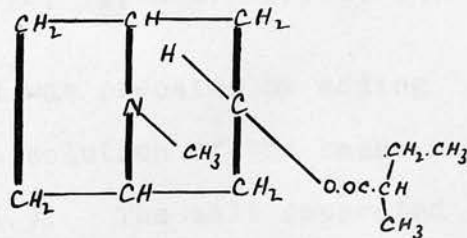
There appear to be only two recorded instances of alkaloids which have yielded tiglic acid on hydrolysis, viz. cevadine from Veratrum sabadilla (Wright and Luff, J.C.S., 1878, 33, 347), and meteloidine from Datura meteloides (Pyman and Reynolds, J.C.S., 1908, 93, 2077). Similarly, only one alkaloid appears to have so yielded  $\psi$ -tropine, viz. tropacocaine from Javanese coca leaves (Giesel and Liebermann, Ber., 1891, 24, 2336).

Since /

Since both tiglic acid and  $\psi$ -tropine have geometric isomerides, three stereoisomerides of tigloidine are conceivable. One of these, tiglyl-tropëine (II.) has now been prepared by the action of tiglyl chloride on tropine hydrochloride. dl- $\alpha$ -Methylbutyryltropëine (III.) was also prepared from tiglyltropëine by catalytic reduction; it is, of course, isomeric with dihydrotigloidine (dl- $\alpha$ -methylbutyryl- $\psi$ -tropëine) described above. It is of interest to record that the hydrobromides of these two new bases were, like tigloidine hydrobromide, extremely soluble in cold chloroform, and that the melting point of dl- $\alpha$ -methylbutyryltropëine hydrobromide was slightly higher than that of tiglyl-tropëine hydrobromide; a mixture of equal weights of the two showed a slight elevation of melting point.



II.



III.

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B...Experimental:-

a. Tigloidine and its Salts. The syrupy base, which showed no tendency to crystallise, was sparingly soluble in water, but readily in most organic solvents. It was odourless when cold, but had a very distinct "narcotic" odour when warmed, and was optically inactive (c, 5.0 in absolute alcohol).

The hydrobromide separated from water in colourless, anhydrous, tabular crystals, m.p. 234°-235° (corr.). It was moderately soluble in water and in alcohol, but readily in chloroform (ca. 1 in 3 at 15°); it was almost insoluble in ether. Like the other tigloidine salts it was optically inactive, (c, 5.0 in water).

Analysis:

Found: C, 51.4; H, 7.4; N, 4.6; Br, 26.1%.

Calculated for  $C_{13}H_{21}O_2N, HBr$ :-

C, 51.3; H, 7.2; N, 4.6; Br, 26.3%.

The methiodide was prepared by adding methyl iodide (0.5 ml.) to a solution of the base (0.2 g.) in dry ether (10 ml.). The salt separated overnight, at room temperature, and was recrystallised from absolute alcohol-ether. It thus formed square plates, m.p. 244°-245°(corr.), and was readily soluble in water and in alcohol, but almost insoluble /

insoluble in ether.

The picrate was prepared by adding slight excess of a saturated aqueous solution of picric acid to a solution of the base (0.2 g.) in n/50 hydrochloric acid (5 ml.); the precipitated salt was crystallised from 45% aqueous alcohol, separating in golden-yellow, rectangular plates, m.p. 239° (corr.). It was readily soluble in alcohol and in acetone, but almost insoluble in water.

The aurichloride, prepared like the picrate, formed golden-yellow plates from aqueous acetone, m.p. 213.5°-214° (corr.); it was readily soluble in acetone, but almost insoluble in water.

b. Preparation of Dihydrotigloidine (dl- $\alpha$ -methyl-butryl- $\psi$ -tropëine). Tigloidine was found to possess a double linkage which readily reduced acid permanganate. Tigloidine hydrobromide (1 g.) in water (25 ml.) was shaken with Adams's platinum oxide catalyst (0.1 g.) in an atmosphere of hydrogen. 1 mol. of hydrogen was taken up in 50 minutes, when absorption ceased. The solution was filtered, basified with ammonia, and the liberated base extracted with chloroform; the theoretical amount (0.74 g.) of a thin syrup was thus obtained. This was neutralised with hydrobromic acid, and the solution evaporated /

evaporated to dryness on the water-bath. The residual crystalline hydrobromide was dissolved in chloroform (in which it was freely soluble), filtered, and the solution evaporated to dryness. The purified salt was then recrystallised by adding ether to its warm solution in absolute alcohol; it formed stout, colourless prisms, m.p.  $186^{\circ}$ - $187^{\circ}$  (corr.).

Analysis:

Found: C, 51.2; H, 7.9%.

Calculated for  $C_{13}H_{23}O_2N$ , HBr:-

C, 51.0; H, 7.8%.

Other salts were prepared like the corresponding tigloidine compounds. The methiodide was a micro-crystalline powder, m.p.  $209^{\circ}$  (corr.); the picrate crystallised from aqueous acetone in golden-yellow plates, m.p.  $134.5^{\circ}$  (corr.); the aurichloride similarly formed orange-yellow plates, m.p.  $151^{\circ}$  (corr.). The last two salts were rather more soluble in water than the corresponding salts of tigloidine.

c. Preparation of Dibromodihydrodigloidine.

( $\alpha$ -methyl- $\alpha$ - $\beta$ -dibromo-butryryl- $\psi$ -tropëine.)

Bromine (0.1 ml.) was added to a solution of digloidine hydrobromide (0.6 g.) in chloroform (10 ml.). Absorption was slow, but the solution became almost colourless /

colourless after standing for three days at room temperature. The solvent was then evaporated off, and the faintly yellow, crystalline residue of dibromodihydrodigloidine hydrobromide recrystallised from a small volume of 25% aqueous alcohol. It thus formed stout, colourless prisms, m.p. 196° (corr.; decomp.), which were readily soluble in alcohol, but sparingly in water; yield, 80%.

The free base was obtained by suspending the hydrobromide in water containing excess of ammonia. After shaking well, the liberated base was extracted with chloroform, the extract washed with a small volume of water, and the solvent evaporated. The residual, syrupy base soon solidified, and was then washed with acetone, and crystallised by adding ether to its warm alcoholic solution. It separated as a white, micro-crystalline powder, m.p. 187° (corr.; decomp.).

d. Hydrolysis of Digloidine.

The base extracted from 1 g. of the hydrobromide was boiled under reflux for one hour with barium hydroxide (1.5 g.) in water (25 ml.). Ether extracted only 0.006 g. of unhydrolysed digloidine from the mixture. The aqueous liquid was then acidified to Congo Red paper with dilute sulphuric /

sulphuric acid, the precipitated barium sulphate filtered off, washed with a little warm water, and rejected. The united acid filtrates were then extracted with ether, the extract washed with a little water, and dried over anhydrous sodium sulphate. Evaporation of the solvent left 0.318 g. of an acid which formed stout prisms from hot water, m.p.  $64.5^{\circ}$  (corr.), not depressed by authentic tiglic acid; yield, 97%.

Analysis:-

Found: Equivalent by titration, 100.

Calculated for C H O :-

5 8 2

Equivalent, 100.

The dibromide was prepared by adding slight excess of bromine to a solution of the acid (0.1 g.) in chloroform (3 ml.). The solution became colourless overnight, when the solvent was evaporated, and the residue crystallised from light petroleum (b.p.  $40^{\circ}$ - $60^{\circ}$ ). It thus formed long, colourless needles, m.p.  $88^{\circ}$  (corr.), not depressed by an authentic specimen of tiglic acid dibromide.

The aqueous solution from which the tiglic acid had been ether-extracted was digested with excess of barium carbonate till faintly alkaline, filtered, the residue well washed with warm water, and rejected. The united filtrates were exactly neutralised /

neutralised with dilute sulphuric acid, filtered, and evaporated to dryness on the water-bath. 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.). It was dissolved in water (0.5 ml.), mixed with a solution of potassium hydroxide (0.18 g.) in water (0.5 ml.), warmed slightly, and absolute alcohol (20 ml.) thoroughly mixed in. After standing for thirty minutes, the mixture was filtered, the residue of potassium salts washed with absolute alcohol, and the united filtrates evaporated to dryness on the water-bath; 0.353 g. of a crystalline residue was thus obtained. After sublimation at 1 mm., colourless needles were obtained from benzene-ligroin, m.p. 108° (corr.), not depressed by authentic  $\psi$ -tropine; yield, 76%. A portion was converted into acetyl- $\psi$ -tropine hydrobromide (see below), which melted at 205° (corr.), alone and also mixed with an authentic specimen.

e. Preparation of Hydrobromides of Acetyltropine and Acetyl- $\psi$ -tropine.

These compounds, which do not appear to have been described previously, have been found useful in identifying tropine and  $\psi$ -tropine respectively. They /

They were prepared by refluxing the respective bases with excess of acetic anhydride for a few hours. The reaction mixture was then diluted with a little water, basified with ammonia with cooling, and the liberated base extracted with chloroform. The chloroformic extract was washed with a small volume of water, the solvent evaporated, and the syrupy residue neutralised with hydrobromic acid. The neutral solution was evaporated to dryness on the water-bath, and the crystalline residue recrystallised by adding ether to its warm alcoholic solution.

Acetyltropëine hydrobromide thus formed stout, prismatic needles, m.p.  $187^{\circ}$ - $187.5^{\circ}$  (corr.).

Analysis:

Found: N, 5.3%.

Calculated for  $C_{10}H_{17}O_2N$ , HBr:-

N, 5.3%.

The methiodide formed glistening needles from alcohol-ether, m.p.  $279^{\circ}$ - $280^{\circ}$  (corr.). The picrate, m.p.  $217^{\circ}$  (corr.) was moderately soluble in water.

Acetyl- $\psi$ -tropëine hydrobromide similarly formed stout prisms, m.p.  $205^{\circ}$  (corr.). Both these hydrobromides were freely soluble in chloroform.

f. Synthesis of Tigloidine.

Tiglic acid (4 g.) and phosphorus trichloride (3 g.) were heated together under reflux at /

at 70°-80° for 2 hours; the upper, slightly yellow layer was then decanted from the syrupy lower layer, and distilled at 64°/35 mm.; yield, 90%. Tiglyl chloride (0.25 g.), so obtained, was heated for 4 hours on the water-bath under reflux with  $\psi$ -tropine hydrochloride (0.3 g.). The pale yellow, syrupy product was dissolved in very dilute hydrochloric acid, and the solution washed with ether to remove free tiglic acid. The aqueous liquid was then basified with ammonia, and the liberated base extracted with chloroform. The chloroformic extract was then washed with a small volume of water, the solvent evaporated, and the syrupy residue neutralised with hydrobromic acid. Evaporation of the solution from the water-bath yielded 0.47 g. of crystalline hydrobromide; yield, 87%. This was dissolved in chloroform, filtered, the solvent evaporated, and the residue recrystallised by adding ether to its warm alcoholic solution. Tabular prisms separated, m.p. 234.5° (corr.), not depressed by the hydrobromide of the natural material.

Analysis:

Found: C, 50.9; H, 7.2; N, 4.6; Br, 26.3%.

Calculated for  $C_{13}H_{21}O_2N$ , HBr:-

C, 51.3; H, 7.2; N, 4.6; Br, 26.3%.

The methiodide had m.p. 244° (corr.), not depressed by natural tigloidine methiodide.

g. Synthesis of Tiglyltropëine. (isomeric with tigloidine.)

This was prepared as above from tiglyl chloride (0.33 g.) and tropine hydrochloride (0.5 g.) in 75% yield, and purified as the hydrobromide. This formed colourless, rectangular laminae (from alcohol-ether), m.p. 208° (corr.), and was very soluble in water and in alcohol, but insoluble in ether; like tigloidine hydrobromide it was freely soluble in cold chloroform.

Analysis:

Found: C, 51.5; H, 7.2; N, 4.7; Br, 26.2%.

Calculated for  $C_{13}H_{21}O_2N, HBr$ :-

C, 51.3; H, 7.2; N, 4.6; Br, 26.3%.

The picrate formed golden-yellow plates with feathery edges, m.p. 200° (corr.), which were sparingly soluble in water. The methiodide crystallised from alcohol-ether in colourless laminae, m.p. 289°-290° (corr.).

h. Synthesis of dl- $\alpha$ -Methylbutyryltropëine.  
(isomeric with dihydrotigloidine.)

Tiglyltropëine hydrobromide (1 g.) in water (25 ml.) was shaken with Adams's platinum oxide catalyst (0.1 g.) in an atmosphere of hydrogen. Absorption ceased after 1 hour when 1 mol. had been taken /

taken up. The filtered solution was basified with ammonia, extracted with chloroform, the extract washed with a little water, and the solvent evaporated. The residue, consisting of the theoretical amount (0.74 g.) of a thin syrup, was neutralised with hydrobromic acid, and the solution evaporated to dryness on the water-bath. The residue was dissolved in chloroform, filtered, and the solvent evaporated. The residual hydrobromide was crystallised from alcohol-ether, and thus formed colourless, glistening laminae, m.p.  $210^{\circ}$  (corr.); this was slightly higher than the m.p. of the unreduced alkaloidal hydrobromide, and a mixture of the two showed a slight elevation of m.p. to  $211^{\circ}$  (corr.). The salt was freely soluble in cold chloroform.

Analysis:

Found: C, 50.9; H, 7.8; N, 4.4; Br, 26.1%.

Calculated for  $C_{13}H_{23}O_2N, HBr$ :-

C, 51.0; H, 7.8; N, 4.6; Br, 26.1%.

The picrate formed golden-yellow prisms (from aqueous acetone), m.p.  $225^{\circ}$  (corr.), and the methiodide colourless, rectangular plates (from alcohol-ether), m.p.  $288^{\circ}$  (corr.; decomp.).

Analysis:

Found: I, 34.2%.

Calculated for  $C_{13}H_{23}O_2N, CH_3I$ :-

I, 34.6%.

#### IV. V A L E R O I D I N E.

##### A. Theoretical:-

Valeroidine,  $C_{13}H_{23}O_3N$ , crystallises in colourless, nacreous plates which melt at  $85^{\circ}$  (corr.). It differs from the other alkaloids described in this work in its ready solubility in cold water. Like tigloidine it is a strong, monacidic base, and yields characteristic salts of which the hydrobromide, oxalate, and picrate are described later; the aurichloride can only be obtained as an oil. The hydrobromide, like those of tigloidine and base Z, is readily soluble in cold chloroform (ca. 1 in 0.5), but this solvent extracts the salt from aqueous solution only to a very slight extent. This fact appears to be due to the extreme solubility of the salt in water (compare p. 10), and, as previously stated, affords a useful means of separating valeroidine from the other alkaloids of Duboisia myoporoides.

Valeroidine is laevorotatory, but the hydrobromide and other salts are dextrorotatory; in each case the nature of the solvent affects the magnitude but not the sign of the rotation. It may be distinguished from tigloidine by its behaviour with Mayer's reagent; tigloidine behaves normally, but the reagent gives a precipitate /

precipitate only with concentrated solutions of valeroidine, and the precipitate is readily dissolved by dilute acids; in this respect, as will be shown later, valeroidine resembles base Z.

Valeroidine is a tertiary base; it does not yield a nitroso derivative on treatment with nitrous acid, but readily yields a characteristic methiodide. The molecule is saturated, and has one free hydroxyl group which can readily be acetylated; the product yields a well-defined hydrobromide.

Acids do not readily hydrolyse valeroidine, but hot aqueous alkalis rapidly decompose the base with production of equimolecular proportions of isovaleric acid,  $C_5H_{10}O_2$ , and a crystalline, laevo-rotatory base,  $C_8H_{15}O_2N$ , which melts at  $212^\circ$  (corr.). The latter was found to be identical with the dihydroxytropane separated as the dibenzoyl ester from Peruvian coca leaves by Wolfes and Hromatka (Merck's Jahresber., 1933, 47, 45); both bases readily gave the same diacetyl ester which was characterised as the hydrobromide. The sulphate of this coca alkaloid is entirely analogous to the salts of the alkaloids now described in its ready solubility in cold chloroform (ca. 1 in 1.8); it is sparingly soluble in water, and chloroform readily and completely extracts it from aqueous solution. This ester of dihydroxytropane /

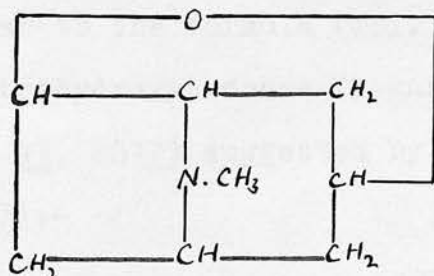
dihydroxytropine was obtained from the residues from the industrial partial synthesis of cocaine from natural ecgonine. The parent dihydroxytropine would thus probably be formed in the manufacture of the latter by hydrolysis of the crude total alkaloids of Peruvian coca leaves, in which it may have existed in some other form of combination.

It will be noted that the chemistry of the alkaloids of D. myoporoides (N.O. Solanaceae) resembles that of the alkaloids of Erythroxyton Coca (N.O. Erythroxytonaceae) in at least two points. Both plants, widely separated taxonomically, yield  $\Psi$ -tropine (as tigloidine and tropacocaine respectively), and a dihydroxytropine (as valeroidine and Merck's dibenzoyldihydroxytropine respectively); these two closely related bases are not known to be produced by any other plant.

Valeroidine is thus a monoisovaleryl-  
dihydroxytropine, and is the first alkaloid known to have yielded a pantoic acid by hydrolysis; in tigloidine this is represented by an unsaturated five carbon acid: tiglic acid. (It will be shown later that base Z also yields pantoic acids on hydrolysis). In the introduction (p. 2.) it was mentioned that the first worker on the chemistry of the alkaloids of D. myoporoides (Gerrard, loc. cit.) hydrolysed the crude /

crude total alkaloids, and observed an odour "resembling butyric acid"; evidently he had obtained a mixture of pantoic acids among his hydrolytic products. He had thus been nearer the truth than the later reported workers, who all found only alkaloids which were tropic acid esters, and made no mention of alkaloidal esters of pantoic acids such as are now described.

Wolfes and Hromatka (loc. cit.) treated their dihydroxytropene with a mixture of phosphorus pentachloride and oxychloride and from the product isolated a substance (as picrate) which they termed "tropene oxide", and for which they suggested the structure I:-

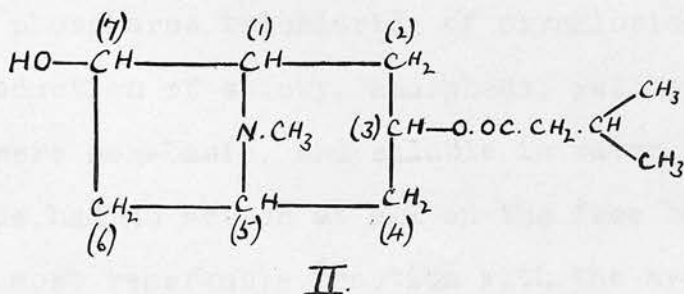


I.

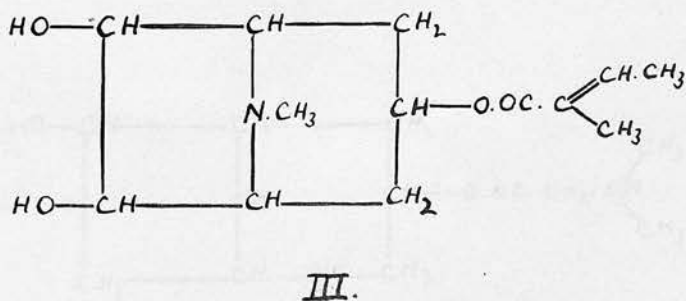
This work has been repeated both with their material and with that from valeroidine. It was only with great difficulty that a minute trace of a not very well-defined picrate was obtained. In the absence of material /

material for comparison it is not certain that this picrate was that of "tropene oxide". The formula (I.) suggests that these workers were of the opinion that the original hydroxyl groups were in positions 3 and 7.

On this basis, it was assumed at this stage that valeroidine might be 3-isovaleryl-3-7-dihydroxytropane (II.):-

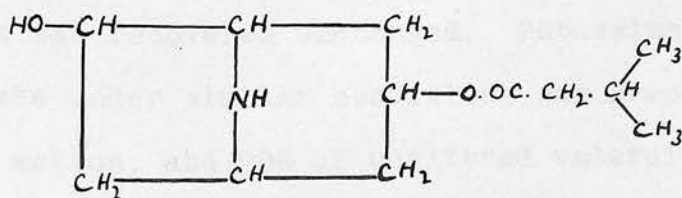


This is similar to the formula (III.) for meteloidine or monotiglyltrihydroxytropane (Pyman and Reynolds, J.C.S., 1908, 93, 2077) suggested by King (J.C.S. 1919, 115, 487):-



It was observed that if the supposed  
free /

free hydroxyl in position 7 could be replaced by hydrogen the molecule would lose its asymmetry, while subsequent removal of the isovaleryl group should yield tropine or  $\psi$ -tropine, if formula II. were correct. It was proposed to test this by replacement of the free hydroxyl in valeroidine by chlorine, followed by catalytic removal of the latter. Unfortunately all attempts to introduce the halogen were unsuccessful. The base was completely destroyed by either phosphorus trichloride or oxychloride with the production of sticky, amorphous, yellow products which were non-basic, and soluble in water. Thionyl chloride had no action at all on the free base, but gave a most remarkable reaction with the hydrobromide. On mixing this salt with thionyl chloride a quite vigorous effervescence occurred with evolution of heat, and liberation of a little bromine. After heating the mixture for a period, a base was isolated, and purified as hydrobromide,  $C_{12}H_{21}O_3N, HBr$ . This was subsequently shown to be norvaleroidine (IV.):-



IV.

It /

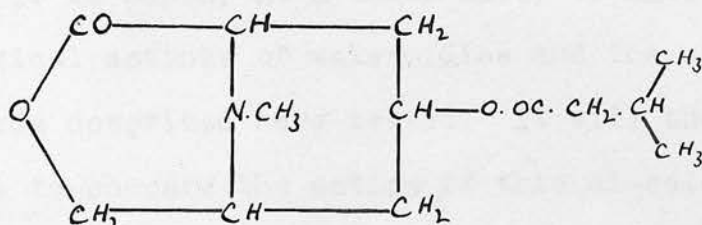
It readily formed an oily nitroso derivative on treatment with nitrous acid, and gave a good yield of valeroidine methiodide when treated with methyl iodide. This appears to be the first instance of such a demethylation occurring under the influence of thionyl chloride. At the moment no explanation of this remarkable reaction can be advanced; it is hoped to investigate it further.

Attempts to remove the free hydroxyl group in valeroidine having failed, oxidation of the alkaloid was next attempted. Still assuming the alkaloid to possess the formula II, the aim was to oxidise the secondary alcoholic to a ketonic group, or to open the pyrrolidine ring between carbon atoms 6 and 7, without removing the esterified isovaleryl group. Since the latter, as mentioned above, is readily split off by alkalis, acid oxidising agents only were applicable. As was to be expected, the alkaloid showed a fairly high resistance to oxidation. Potassium permanganate in dilute aqueous acid solution gave no recognisable new product, and 70% of the alkaloid was recovered unchanged. Potassium dichromate under similar conditions was practically without action, and 90% of unaltered valeroidine was recovered. Chromic acid in glacial acetic acid was slowly /

slowly reduced in the cold, and rapidly and quite violently on warming. In the former case 82% of the starting material was recovered, but no characteristic oxidation product was isolable. In the latter case equally, no definite product was obtained, but here no unaltered valeroidine was isolated.

Oxidation with potassium permanganate in acetone solution gave results of more promise. Besides about 50% of unaltered valeroidine, and 3% of norvaleroidine (identical with the material obtained above by the action of thionyl chloride on valeroidine hydrobromide; compare production of nortropine from tropine; Willstätter, Ber., 1896, 29, 1580), a crystalline substance was obtained; the yield of this varied in different experiments from 10 to 15%. It melted at 136° (corr.), was neutral, and more strongly laevorotatory than valeroidine,  $[\alpha]_D^{20} -16.6^\circ$ ; the analysis corresponded closely to  $C_{13}H_{21}O_4N$ . The substance was saturated, and was unchanged after attempted catalytic reduction with platinum oxide catalyst. It appeared to be a tertiary base, since no nitroso derivative could be isolated on treatment with nitrous acid. On hydrolysis with alkali it yielded equimolecular proportions of isovaleric acid and a crystalline base. So far, it has not been found possible to obtain this base in  
a /

a satisfactory state of purity, but it appears to possess the formula  $C_7H_{13}O_3N$ . This, however, does not accord well with the  $C_{13}$  formula of the parent substance, hydrolytic removal of isovaleric acid from which should, theoretically, yield a base with eight carbon atoms. It had been thought that the original oxidation product might be of the lactone structure (V.):-



V.

In order to test this hypothesis, an attempt was made to open the supposed lactone ring by esterification with alcoholic hydrochloric acid. The result was very surprising; instead of the expected ethyl ester of a hydroxy acid, norvaleroidine was obtained in good yield. This was shown to be identical with that obtained by oxidation above, and also by the action of thionyl chloride on valeroidine hydrobromide.

At the moment, no explanation of these peculiar reactions can be advanced, but it is hoped to /

to nurse this section of the work in due course, with particular reference to the peculiar demethylating action of thionyl chloride.

Di-isovaleryldihydroxytropane has been prepared by esterifying the free hydroxyl group in valeroidine with isovaleryl chloride, and a characteristic hydrobromide obtained. This salt exhibits remarkably high solubility in absolute alcohol and in water. It is hoped, at a later date, to have the pharmacological actions of valeroidine and the other new alkaloids described here tested. It will then be of interest to compare the action of this di-ester with that of valeroidine itself.

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E. /

B. Experimental:-

a. Valeroidine and its Salts.

The base crystallised in soft, colourless laminae, m.p.  $85^{\circ}$  (corr.), on adding petroleum ether (b.p.  $40^{\circ}$ - $60^{\circ}$ ) to a concentrated ethereal solution. It was readily soluble in water and in most organic solvents, but only very sparingly in petroleum ether, and was laevorotatory:  $[\alpha]_{D}^{20} -9.0^{\circ}$  (c, 5.0 in absolute alcohol) and  $-4.0^{\circ}$  (c, 5.0 in water).

The hydrobromide formed small, colourless needles (from alcohol-ether), m.p.  $172^{\circ}$  (corr.; lower figures were obtained unless the temperature was raised very slowly; material which had melted at a lower temperature on account of too rapid heating was recrystallised from alcohol-ether, and then had m.p.  $172^{\circ}$  (corr.), so that no alteration had taken place during the first melting.). The salt was extremely soluble in water, in absolute alcohol, and in chloroform; the solubility in the last solvent was ca. 1 in 0.5 at  $15^{\circ}$ , and this solution was viscous.  $[\alpha]_{D}^{20} +5.0^{\circ}$  (c, 20.0 in water) and  $+2.5^{\circ}$  (c, 20.0 in absolute alcohol).

Analysis:- /

Analysis:-

Found: C, 48.2; H, 7.7; N, 4.3; Br, 24.4%.

Calculated for  $C_{13}H_{23}O_3N$ , HBr:-

C, 48.4; H, 7.5; N, 4.3; Br, 24.8%.

The oxalate, the form in which valeroidine was first isolated, crystallised from water, in which it was sparingly soluble, in long, colourless, prismatic needles, m.p.  $205^{\circ}$  (corr.).

The methiodide was readily prepared by treating a solution of the base (0.2 g.) in dry ether (10 ml.) with methyl iodide (0.5 ml.) when it separated in good yield on standing overnight at room temperature. It was recrystallised from methanol-ether, and thus formed six-sided laminae, m.p.  $205.5^{\circ}$  (corr.), which were readily soluble in water, and in methyl alcohol, only sparingly in ethyl alcohol, and insoluble in ether.

The picrate was prepared by adding excess of saturated aqueous picric acid to a solution of the base (0.2 g.) in n/50 hydrochloric acid (5 ml.). Recrystallised from water it formed golden-yellow needles, m.p.  $152^{\circ}$ - $153^{\circ}$  (corr.). It was rather sparingly soluble in water.

The aurichloride separated as a yellow oil /

oil on adding auric chloride solution to a solution of the base in n/50 hydrochloric acid, and could not be obtained crystalline.

b. Acetylation of Valeroidine.

The base extracted from 2.5 g. of the hydrobromide was refluxed from the sand-bath for 3 hours with acetic anhydride (5 ml.). The mixture was then diluted with water (15 ml.), basified with an excess of ammonia (with cooling), and the liberated base extracted with chloroform. The chloroformic extract was washed with water (5 ml.), the solvent evaporated, and the syrupy residue neutralised with hydrobromic acid. Evaporation of the solution from the water-bath left 2.62 g. of a crystalline hydrobromide; yield, 92%. This was then dissolved in chloroform, filtered, the solvent evaporated, and the residue recrystallised from alcohol-ether. It thus formed minute, colourless needles, m.p. 197° (corr.) which were readily soluble in water, and in chloroform, but almost insoluble in ether.

Analysis:-

Found: C, 49.3; H, 7.3; N, 4.0; Br, 21.8%.

Calculated for C<sub>15</sub>H<sub>25</sub>O<sub>4</sub>N, HBr:-

C, 49.4; H, 7.1; N, 3.8; Br, 22.0%.

c. /

c. Hydrolysis of Valeroidine.

The base extracted from 1 g. of the hydrobromide was refluxed for 2 hours from the sand-bath with barium hydroxide (1.5 g.) in water (25 ml.). Ether extracted no unhydrolysed base from the cooled mixture. The aqueous liquid was acidified to Congo Red with dilute sulphuric acid, barium sulphate removed by filtration (suction), washed with a little warm water, and rejected. The united acid filtrates were then extracted with ether, this extract washed with water (10 ml.), and dried over anhydrous sodium sulphate. After evaporation of the solvent, 0.245 g. of an oily acid with a powerful odour of valeric acid was obtained; yield, 77%. This acid was optically inactive (c, 2.45 in absolute alcohol).

Analysis:-

Found: Equivalent by titration, 101.

Calculated for  $C_5H_{10}O_2$ :-

Equivalent, 102.

p-phenylphenacyl ester: The acid (0.24 g.) was almost completely neutralised with n/1 sodium hydroxide and the solution (3 ml.) refluxed from the water-bath for 1 hour with p-phenylphenacyl bromide (0.5 g.) and alcohol (10 ml.). The ester crystallised overnight, and was recrystallised from 60% aqueous alcohol. It thus formed colourless, foliated laminae, m.p. 76° (corr.), not depressed by authentic p-phenylphenacyl /

p-phenylphenacyl isovalerate, m.p. 76° (corr.).

Anilide: The acid (1.5 g. obtained from a duplicate larger-scale hydrolysis) was refluxed for 3 hours from the sand-bath with aniline (1 g.). The anilide was precipitated by dilution with water, and after repeated recrystallisation from 70% aqueous alcohol (charcoal) formed colourless, prismatic needles, m.p. 114° (corr.), not depressed by authentic isovaleranilide, m.p. 114° (corr.); the literature gives this m.p. as 115° (corr.).

The aqueous acidic liquid from which the isovaleric acid had been extracted was digested with excess of barium carbonate, filtered (suction), the residue well washed with warm water, and rejected. The slightly alkaline filtrates were exactly neutralised with dilute sulphuric acid, filtered, and evaporated to dryness on the water-bath. The crystalline residue was colourless, and weighed 0.685 g.; it gave no reaction for chloride (as did the  $\Psi$ -tropine obtained from tigloidine, p. 20.). It was dissolved in water (0.5 ml.), mixed with a solution of potassium hydroxide (0.17 g.) in water (0.5 ml.), warmed slightly, and absolute alcohol (25 ml.) mixed in. After standing for 30 minutes, the mixture was filtered, the residue washed with absolute alcohol, and the united filtrates evaporated to /

to dryness on the water-bath; 0.487 g. of a colourless, crystalline residue was thus obtained; yield, 100%. This was recrystallised from alcohol-ether, and formed large, colourless, tabular crystals, m.p.  $212^{\circ}$  (corr.) (not raised by sublimation at 1 mm.).

$[\alpha]_D^{20}$   $-25.0^{\circ}$  (c, 2.0 in absolute alcohol) and  $-16.0^{\circ}$  (c, 4.0 in water). It was freely soluble in water, and in alcohol.

Analysis:-

Found: C, 61.0; H, 9.7; N, 9.2; (N)CH<sub>3</sub>, 7.9%; active H, 1.43; equivalent by titration, 156.

Calculated for dihydroxytropane, C<sub>8</sub>H<sub>15</sub>O<sub>2</sub>N:-  
C, 61.1; H, 9.6; N, 8.9; (N)CH<sub>3</sub>, 9.5%;  
active H, 2.0; equivalent, 157.

The substance was similar in all respects to the dihydroxytropane separated from Peruvian coca leaves, and supplied by Messrs. E. Merck. This latter had m.p.  $212^{\circ}$  (corr.), not depressed by the above material, and  $[\alpha]_D^{20}$   $-22.0^{\circ}$  (c, 2.0 in absolute alcohol). Both bases yielded the same diacetyl derivative characterised as the hydrobromide, as now described.

Diacetyldihydroxytropane hydrobromide:

Dihydroxytropane (0.5 g.) was refluxed for 3 hours from the sand-bath with acetic anhydride (5 ml.). Water (15 ml.) was added, the mixture basified with ammonia (with cooling), and the liberated base extracted /

extracted with chloroform. The chloroformic extract was washed with water (5 ml.) and the solvent evaporated from the water-bath; the residue consisted of a colourless syrup which showed no sign of crystallisation after standing for 4 days. It was then neutralised with hydrobromic acid, and the solution evaporated to dryness on the water-bath. The crystalline hydrobromide was readily and completely soluble in cold chloroform, and weighed 1.0 g.; yield, 97.0%. Crystallised from alcohol-ether it formed colourless prisms, m.p.  $219^{\circ}$ - $220^{\circ}$  (corr.), which were extremely soluble in water and in chloroform, readily in alcohol, and almost insoluble in ether.

Analysis:-

Found: N, 4.3; Br, 24.7%.

Calculated for C<sub>12</sub> H<sub>19</sub> O N, HBr:-

N, 4.4; Br, 24.8%.

As stated above, both the base from valeroidine and that from Merck's alkaloid yielded this compound, m.p.  $219^{\circ}$ - $220^{\circ}$  (corr.), and a mixture of equal weights of the two salts showed no depression of m.p.

d. Note on the Solubilities of Merck's Dibenzoyl-dihydroxytropine Sulphate.

This salt was only very sparingly soluble in water, but dissolved in chloroform to the extent of /

of 1 in 1.8 at 15°.

1 g. was suspended in water (10 ml.), and the mixture shaken with chloroform (10 ml.). The separated chloroformic extract was filtered, and evaporated on the water-bath. The residue weighed 0.996 g., i.e. extraction was practically quantitative.

e. Attempted Preparation of "Tropene Oxide".

This preparation was tried both with the dihydroxytropene from valeroidine and with that from Merck's alkaloid:

The base (0.5 g.) was refluxed for 4 hours from the sand-bath with phosphorus pentachloride (1.5 g.) and phosphorus oxychloride (5 ml.). Most of the phosphorus oxychloride was distilled off in a vacuum, and the residue poured on to crushed ice. The solution was neutralised and saturated with potassium carbonate, and extracted with ether. The ethereal extract was dried over anhydrous sodium sulphate, and the solvent removed. The residue consisted of a tiny amount of a syrupy, strongly alkaline substance, which became cloudy, but did not crystallise on standing for 7 days. It was dissolved in n/50 hydrochloric acid (2 ml.), and slight excess of saturated aqueous picric acid added. The /

The bright yellow precipitate was redissolved by warming; a tiny crop separated on cooling; m.p. was indefinite, but between 250° and 280°; Wolfes and Hromatka give m.p. 277°. The yield was too tiny to allow of further purification, and despite repeated trials a larger yield could not be obtained.

f.      Attempted Replacement of Free Hydroxyl by Chlorine.

1.              Valeroidine (1 g.) in chloroform (10 ml.) was refluxed from the water-bath for 2 hours with phosphorus trichloride (2 ml.). The reaction product consisted of a colourless liquid containing yellow, flocculent material in suspension. Water (15 ml.) was added, the mixture basified with ammonia (with cooling), shaken, and the chloroformic layer separated, washed with water (5 ml.), and evaporated. The residue consisted of a very minute amount of basic material. (On rendering the mixture alkaline, the yellow material dissolved in the aqueous layer, colouring it yellow).

ii.              An exactly similar result was obtained on substituting phosphorus oxychloride for the trichloride, or valeroidine hydrobromide for the free base. /

base.

iii. In a further experiment, 1 g. of valeroidine hydrobromide in chloroform (15 ml.) was treated with phosphorus oxychloride (1 ml.) and the mixture allowed to stand in the cold for 72 hours. It then consisted of a colourless lower layer and a yellow upper layer. Water (5 ml.) was added, the mixture basified with ammonia (with cooling), shaken, and the chloroform layer separated. This extract was washed with water (5 ml.), and the solvent evaporated. The residue consisted of 0.53 g. of unaltered valeroidine; recovery, 70.5%. No other characteristic material was separable.

iv. 1 g. of valeroidine was refluxed from the water-bath for 3 hours with thionyl chloride (10 ml.). Most of the thionyl chloride was distilled off in a vacuum, and the residue poured on to crushed ice (5 g.), the mixture basified with ammonia (with cooling), and the liberated base extracted with chloroform. The residue, after evaporation of the solvent, consisted of 0.95 g. of unaltered valeroidine.

v. 1 g. of valeroidine hydrobromide was next treated with thionyl chloride (10 ml.). At once, a quite vigorous effervescence, with slight liberation of bromine, and considerable evolution of heat /

heat occurred. The mixture was then refluxed from the water-bath for 24 hours. Most of the thionyl chloride was distilled off in a vacuum, the residue poured on to crushed ice (5 g.), basified with ammonia (with cooling), and extracted with chloroform. The chloroformic extract was washed with water (5 ml.), the solvent evaporated, and the residual syrup (which crystallised on cooling) neutralised with hydrobromic acid. Evaporation of this solution yielded 0.31 g. of a crystalline hydrobromide.

The aqueous liquid from which the above base had been extracted was saturated with potassium carbonate, and extracted with chloroform. Evaporation of the solvent yielded a further quantity of base, which, treated as above, yielded 0.28 g. of hydrobromide identical with that above; total yield, 62%. The united material was crystallised from alcohol-ether, and separated in colourless, pearly laminae, m.p. 270° (corr.). This salt was freely soluble in water, in alcohol, and in chloroform; it was almost insoluble in ether.  $[\alpha]_D^{20} + 1.0^\circ$  (c, 20.0 in water).

Analysis:-

Found: C, 46.9; H, 7.1; N, 4.7; Br, 25.9%.

Calculated for  $C_{12}H_{21}O_3N, HBr$ :-

C, 46.8; H, 7.2; N, 4.6; Br, 26.0%.

Nitroso derivative: The hydrobromide (0.5 g.) was dissolved in n/l hydrochloric acid (2 ml.) and sodium nitrite (0.5 g.) in water (3 ml.) added. The mixture soon became turbid, oily drops separating. This oil was extracted with ether, the extract dried over anhydrous sodium sulphate, and the solvent evaporated. The residual yellow, viscous oil showed no sign of crystallisation after standing for 14 days.

Methylation Product: The base extracted from 0.5 g. of the hydrobromide was refluxed from the water-bath for 2 hours with methyl alcohol (5 ml.) and methyl iodide (0.5 ml.). Ether was added to the warm mixture in amount sufficient to produce a faint, permanent turbidity. Crystals separated overnight; these were collected, and recrystallised from methyl alcohol-ether. Six-sided, colourless laminae were thus obtained, m.p.  $206^{\circ}$  (corr.), not depressed by admixture of an equal weight of authentic valeroidine methiodide; yield, 60%.

g. Oxidation of Valeroidine.

i. Aqueous acid potassium permanganate:

The base extracted from 5 g. of valeroidine hydrobromide was dissolved in n/l sulphuric acid (50 ml.), potassium permanganate (1 g.) in water (150 ml.) /

(150 ml.) added, and the mixture refluxed from the sand-bath for 2 hours. (the colour of the permanganate appeared to be completely discharged before the mixture had reached the b.p.). The manganese dioxide was filtered (suction) from the cooled mixture, the filtrate concentrated (ca. 50 ml.) on the water-bath, basified with sodium carbonate, and the liberated base extracted with chloroform. The chloroformic extract was washed with water (10 ml.), and the solvent evaporated. The residual syrupy base rapidly crystallised on standing. It was neutralised with hydrobromic acid, and the solution evaporated to dryness from the water-bath. The residual hydrobromide was freely soluble in chloroform, and was recrystallised from alcohol-ether, forming colourless needles, m.p.  $170^{\circ}$  (corr.), not depressed by admixture of an equal weight of valeroidine hydrobromide; yield, 70%. No other characteristic substance was isolable.

ii. Aqueous acid potassium dichromate:

The base extracted from 5 g. of the hydrobromide was dissolved in n/5 sulphuric acid (150 ml.), 1.6 g. of powdered potassium dichromate added, and the mixture refluxed from the sand-bath for 2 hours. Very little apparent reduction of the dichromate was noticed. The mixture was neutralised with /

with potassium hydroxide, and concentrated to crystallisation from the water-bath. Potassium sulphate was removed by filtration (suction), and the filtrate basified with ammonia, and extracted with chloroform. The extract was treated exactly as described for the corresponding extract under i. above, and thus yielded 90% of valeroidine hydrobromide, m.p.  $170^{\circ}$  (corr.), identical with the starting material.

iii. Chromic Acid in Glacial Acetic Acid.

Valeroidine (1 g.) was dissolved in glacial acetic acid (20 ml.) containing chromic acid (0.4 g.), and the solution left at room temperature for 48 hours. The mixture darkened in colour and became slightly dichroic, but little reduction of the chromic acid was apparent. Water (30 ml.) was added, the mixture basified with ammonia (with cooling), and extracted with chloroform. Evaporation of the washed extract left 0.82 g. of unaltered valeroidine, characterised as the hydrobromide, m.p.  $170^{\circ}$  (corr.).

The experiment was repeated with the difference that the reaction mixture was refluxed from the sand-bath for 1 hour. As the temperature approached the b.p. a vigorous reaction occurred, and reduction of the chromic acid seemed to be more or less complete. Water (25 ml.) containing neutral ammonium /

ammonium tartrate (2 g.)(to prevent precipitation of chromic hydroxide in the subsequent basification) was added, the mixture basified with ammonia (with cooling), and extracted with chloroform. The extract was washed with water (5 ml.), the solvent evaporated, and the dark brown, syrupy base (0.65 g.) neutralised with hydrobromic acid. The solution was warmed with charcoal, filtered, and evaporated to a syrup on the water-bath. This syrup, which was completely soluble in chloroform, was dried finally in a vacuum desiccator, and was thus obtained as a glassy residue, which showed traces of crystallisation only after standing for many weeks. It probably consisted of a mixture of unaltered valeroidine hydrobromide with other products, but no definite substance could be isolated from it.

iv. Potassium Permanganate in Acetone.

Valeroidine (5 g.) was dissolved in acetone (250 ml.) and powdered potassium permanganate (9 g.) added. The mixture was refluxed from the water-bath for 48 hours. After cooling, it was filtered (suction), the residue washed with acetone, and rejected. The united filtrates were evaporated, yielding a dark brown, syrupy residue with a peculiar odour. This was dissolved in chloroform (50 ml.), and /

and the solution extracted with dilute sulphuric acid (5 of 10 ml.) and then with water (3 of 10 ml.). The united aqueous liquids were basified with ammonia, and the liberated base extracted with chloroform. The chloroformic extract was washed with water (5 ml.), the solvent evaporated, and the brown, syrupy base neutralised with hydrobromic acid. The solution was warmed with charcoal, filtered, and evaporated to dryness on the water-bath. The residue was fractionally crystallised from alcohol-ether, two main crops being thus obtained:- a. 3.5 g., m.p. 170° (corr.), not depressed by admixture of an equal weight of valeroidine hydrobromide. b. 0.22 g., m.p. 270° (corr.), not depressed by admixture of an equal weight of norvaleroidine hydrobromide (compare the preparation by the action of thionyl chloride, p.44; also that of nortropine from tropine, Willstätter, loc. cit.).

The chloroformic solution, from which the bases had been extracted, was freed from solvent on the water-bath; the dark brown, syrupy residue rapidly crystallised on cooling and stirring. A small volume of acetone was worked in, and the mixture rapidly filtered (suction), and the residue washed with small volumes of acetone. By evaporation of the filtrates, and repetition of the above process, further small /

small amounts of crystalline material were obtained. This material was recrystallised from warm acetone (charcoal), forming colourless, nacreous laminae, m.p.  $136^{\circ}$  (corr.). It was almost insoluble in water, moderately in acetone, and readily in most other organic solvents, except ether.  $[\alpha]_D^{20} -16.6^{\circ}$  (7.4 in absolute alcohol).

Analysis:

Found: C, 61.1; H, 8.4; N, 5.6%.

Calculated for  $C_{13}H_{21}O_4N$ :-

C, 61.2; H, 8.2; N, 5.5%.

It did not absorb hydrogen when shaken with platinum oxide catalyst (Adams's) in alcoholic-aqueous-acetic acid solution.

Action of Nitrous Acid: 0.1 g. was dissolved in acetone (0.5 ml.), water (5 ml.) and concentrated hydrochloric acid (0.25 ml.) added, followed by sodium nitrite (0.2 g.) in water (1 ml.); the mixture was left overnight at room temperature. Ether then extracted 0.09 g. of crystalline material, m.p.  $136^{\circ}$  (corr.), identical with the starting substance.

Hydrolysis:

1 g. was refluxed for 2 hours from the sand-bath with barium hydroxide (2 g.) in water (20 ml.). The mixture was acidified to Congo Red with dilute sulphuric acid, and the precipitated barium sulphate filtered /



filtered (suction), washed with warm water, and rejected. The united acid filtrates were extracted with ether, and the ethereal extract dried over anhydrous sodium sulphate. Evaporation of the solvent left 0.55 g. of an oily acid smelling of valeric acid; yield, greater than the theoretical 0.4 g. which was expected from the formula  $C_{13}H_{21}O_4N$  for the original substance.

p-Phenylphenacyl ester: This was made according to the method on p. 38, and formed dull, colourless laminae (from 60% aqueous alcohol), m.p.  $76^{\circ}$  (corr.), not depressed by authentic p-phenylphenacyl isovalerate.

The aqueous liquid from which the isovaleric acid had been extracted was digested on the water-bath with excess of barium carbonate, filtered (suction), the residue washed with warm water, and rejected. The united filtrates were neutralised with dilute sulphuric acid, filtered, and evaporated to dryness on the water-bath. The crystalline residue of sulphate (contained no chloride) was mixed with a solution of potassium hydroxide (0.21 g.) in water (1 ml.), warmed slightly, and absolute alcohol (25 ml.) mixed in. After standing for 30 minutes, the mixture was filtered, the residue was washed with absolute alcohol /

alcohol, and rejected. The united filtrates were evaporated to dryness on the water-bath. The faintly-yellow, crystalline residue was sublimed at 1 mm., and the almost colourless sublimate crystallised repeatedly from acetone-ether. The product consisted of slightly-yellow, tabular crystals, m.p. ca. 200° (corr.); it was not possible to obtain this substance with a really sharp m.p.

Analysis:-

Found: C, 55.2; H, 8.4; N, 8.9%.

Calculated for  $C_7H_{13}O_3N$ :-

C, 52.8; H, 8.2; N, 8.8%.

This analysis is not very satisfactory, particularly since the original formula,  $C_{13}H_{21}O_4N$ , after the removal of isovaleric acid,  $C_5H_{10}O_2$ , should lead to an 8 carbon base.

Action of Alcoholic Hydrochloric Acid:

2 g. of the oxidation product was dissolved in absolute alcohol (50 ml.) containing 4% of dry hydrogen chloride, and the mixture refluxed from the sand-bath for 3 hours. Most of the alcohol was distilled off in a vacuum, and the residue was diluted with water (50 ml.) (some ethyl isovalerate also distilled off, and was recognised by its odour). The solution was extracted with chloroform. Evaporation of the solvent left a little isovaleric ethyl /

ethyl ester, and finally a trace of varnish-like material, which was rejected. The aqueous acidic liquid was then basified with ammonia, and the liberated base extracted with chloroform. The extract was washed with water (5 ml.), and the solvent evaporated. The crystalline residue, m.p. ca. 109°, was neutralised with hydrobromic acid, and the solution evaporated to dryness from the water-bath. The crystalline residue weighed 2.32 g., and was recrystallised from alcohol-ether (charcoal). It thus formed colourless, pearly laminae, m.p. 270° (corr.), not depressed by admixture of an equal weight of authentic norvaleroidine hydrobromide. It readily yielded an oily nitrose body, and valeroidine methiodide by the methods previously given (p.46.).

h. Preparation of Di-isovaleryldihydroxytropane.

Valeroidine hydrobromide (5 g.) was refluxed from the water-bath for 3 hours with isovaleryl chloride (2.9 g.)(see p. 77). The cooled mixture was diluted with n/50 hydrochloric acid (30 ml.), and free isovaleric acid removed by washing with ether. The aqueous liquid was then basified with ammonia, and the liberated base extracted with chloroform. The chloroformic extract was washed with a little water, the solvent evaporated, and the residual /

residual syrup neutralised with hydrobromic acid. The solution was warmed with charcoal, filtered, and the filtrate evaporated to dryness on the water-bath. The residue was dissolved in absolute alcohol (3 ml.), the solution diluted with dry ether (20 ml.), filtered, and dry ether (250 ml.) added to the filtrate. The salt then separated in prismatic needles, m.p.  $176^{\circ}$ - $177^{\circ}$  (corr.). It was extremely soluble in water, in absolute alcohol, and in chloroform; it was insoluble in ether. The extreme solubility in alcohol is well illustrated by the details of crystallisation.

Analysis:-

Found: C, 53.4; H, 7.9; N, 3.6; Br, **19.5%**.

Calculated for  $C_{18}H_{31}O_4N, HBr$ :-

C, 53.2; H, 7.9; N, 3.5; Br, 19.7%.

---oOo---

V. B A S E Z.

A. Theoretical:-

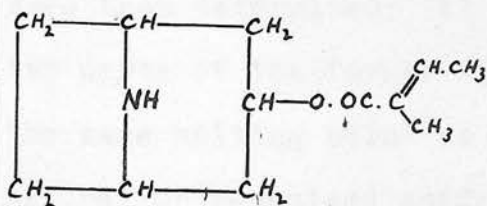
Base Z,  $C_{12}H_{21}O_2N$ , is a thin, colourless syrup which partly crystallises on standing. Like tigloidine it is almost odourless when cold, but emits a strong "narcotic" odour when warmed, and is a strong, monacidic base which readily forms characteristic salts. Besides the oxalate, the form in which it was first isolated, the hydrobromide, hydrochloride, picrate, aurichloride, and salicylate have been prepared. The hydrobromide resembles those of tigloidine and valeroidine in its ready solubility in cold chloroform (ca. 1 in 0.4); the hydrochloride and oxalate are also freely soluble in this solvent. The alkaloid is slightly dextrorotatory, as are some of its salts; others show no optical activity. Base Z resembles valeroidine in that only fairly concentrated solutions give a precipitate with Mayer's reagent, and this precipitate is readily soluble in dilute acids.

Base Z is a secondary base, readily yields an oily nitroso derivative on treatment with nitrous acid, and is saturated. It is fairly stable in /

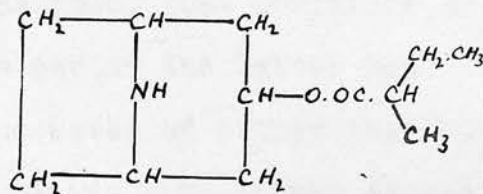
in acid solution, but rapidly hydrolyses on boiling in alkaline solutions when it yields nortropine,  $C_7H_{13}ON$ , and a liquid acid,  $C_5H_{10}O_2$ , which has  $[\alpha]_D^{20} + 2.9^\circ$ , and was thought, at first, to be partly-racemised d- $\alpha$ -methylbutyric acid; base Z was thus thought to be partly-racemised d- $\alpha$ -methylbutyryl-nortropine. On this assumption, a quantity of base Z was first racemised. This was found to be far from easy since all ordinary methods involving exposure to the mild action of alkalis resulted only in the fairly rapid hydrolysis of the alkaloid with the production of nortropine and of optically active acid. Finally the following indirect method had to be adopted:- The alkaloid was hydrolysed, and the nortropine isolated and purified as the carbamate. The acid was racemised by prolonged boiling with large excess of saturated aqueous potassium hydroxide, recovered, and converted into chloride. Nortropine hydrochloride was made from the above carbamate, and esterified with this acid chloride (general method for tropine synthesis: Jowett and Pyman, loc. cit.). The resultant alkaloid was then isolated and purified as hydrobromide; this salt was optically inactive, but had the same melting point as the hydrobromide of the natural (dextrorotatory) alkaloid; this also applied to the oxalate, and several /

several other salts prepared.

Tiglylnortropëine (I.) was next prepared from tiglyl chloride and nortropine hydrochloride, and purified as hydrobromide. The latter salt was then catalytically reduced to yield dl- $\alpha$ -methylbutyryl-nortropëine (II.) hydrobromide. This was not identical with the hydrobromide of racemised base Z.



I.

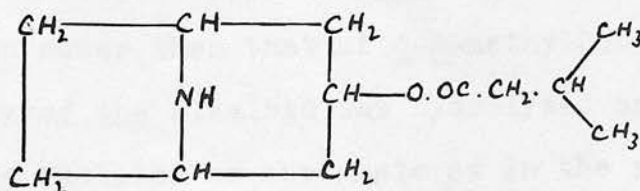


II.

The acid was examined further, when it was found that the melting points of the amides and p-phenylphenacyl esters of the natural and racemised acids were respectively identical, but showed distinct differences from those of the corresponding derivatives of synthetic dl- $\alpha$ -methylbutyric acid. It was now suspected that the acid might consist of a mixture of d- $\alpha$ -methylbutyric acid and an isomeric valeric acid. Accordingly, the p-phenylphenacyl esters of the four valeric acids were prepared, and mixed /

mixed melting points of all the possible pairs of combinations taken. (It was assumed that the melting point of the ester of dl- $\alpha$ -methylbutyric acid would not be appreciably different from that of the ester of the dextrorotatory acid). It was found that a mixture of the isovaleryl and dl- $\alpha$ -methylbutyryl esters only had a melting point in the region of that of the ester of the natural acid. The melting points of mixtures of these two esters in varying proportions were then determined; it was found that a mixture of ten parts of the former with one of the latter had the same melting point as the ester of either the natural or racemised acid; mixing with either caused no depression of melting point. A mixture of similar proportions of the amides of these two acids was likewise identical with the amide of either the natural or racemised acid.

Isovalerylnortropine (III.) was therefore prepared from isovaleryl chloride and nortropine hydrochloride, and purified as hydro-bromide.



III.

A mixture of ten parts of this salt with one part of dl- $\alpha$ -methylbutyrylnortrop $\ddot{e}$ ine hydrobromide had a melting point intermediate between those of its constituents and identical with that of the hydrobromide of either natural or racemised base Z; the melting point of this mixture was not depressed by admixture of either of the latter salts.

In order to establish more definitely that base Z consisted of a mixture of isovaleryl-nortrop $\ddot{e}$ ine and d- $\alpha$ -methylbutyrylnortrop $\ddot{e}$ ine, attempts were then made to isolate these isomers from the natural material. Fractional crystallisation of the hydrobromide, picrate, salicylate, and other salts of base Z afforded no satisfactory evidence of separation. Chromatographic methods, using various adsorbing agents, were equally unsuccessful. The isomers differ so slightly in structure and properties that failure to effect direct separation was not surprising. A partial separation was ultimately achieved by an indirect method analogous to that used in the racemisation of base Z, and depending on the fact that the silver salt of isovaleric acid is less soluble in water than that of d- $\alpha$ -methylbutyric acid. A quantity of the alkaloid was hydrolysed and the nortropine isolated as carbamate as in the racemisation. The acid was neutralised with sodium hydroxide, and the /

the theoretical amount of silver nitrate added, under controlled conditions, to the dilute aqueous solution of the sodium salts. The precipitate consisted of pure silver isovalerate, from which the acid was recovered and converted into chloride. The latter was esterified with nortropine hydrochloride made from the above carbamate; the product was identical with the previously synthesised isovalerylnortropëine. It was not found possible to isolate d- $\alpha$ -methyl-:butyric acid from the mixed acids left in the mother liquor from the silver isovalerate.

Base Z is thus a mixture of about ten parts of isovalerylnortropëine with one part of d- $\alpha$ -methylbutyrylnortropëine; it is suggested that the former be named poroidine and the latter isoporoidine. It is probable that the two valeric acids are derived respectively from leucine and isoleucine, via the corresponding amyl alcohols. This seems to constitute the first indirect evidence that these aliphatic amino-acids may be used in the biogenesis of alkaloids.

In a preliminary attempt to separate the isomeric acids, fractional crystallisation of their p-phenylphenacyl esters was attempted. There was little evidence of separation by this method. It was /

was necessary to hydrolyse these esters in the course of the work. It was found that alkaline hydrolysis was accompanied by profound decomposition and loss of both acid and alcohol. Acid hydrolysis, on the other hand, gave theoretical yields of acid and p-phenyl-phenacyl alcohol. A suitable method is described in the Experimental section (q.v.).

---oOo---

B./

B. Experimental:-

a. Base Z and its Salts.

The base was a syrup which partly crystallised on standing; it was sparingly soluble in water, but readily in most organic solvents.

$[\alpha]_D^{20} + 2.5^\circ$  (c, 8.0 in absolute alcohol or in chloroform).

The oxalate formed colourless, glistening, diamond-shaped laminae from water, in which it was sparingly soluble, m.p.  $296^\circ$ - $297^\circ$  (corr.). When examined dry under crossed Nicols these showed very fine interference effects. The salt was optically inactive (c, 4.0 in water).

Analysis:-

Found: C, 60.7; H, 8.7; N, 5.7;  $H_2C_2O_4$ , 17.6%.

Calculated for  $(C_{12}H_{21}O_2N)_2, H_2C_2O_4$ :-

C, 60.9; H, 8.6; N, 5.5;  $H_2C_2O_4$ , 17.6%.

The hydrobromide, which formed colourless, glistening laminae (from absolute alcohol-ether), m.p.  $219^\circ$ - $220^\circ$  (corr.), was very soluble in water, in alcohol, and in chloroform (ca. 1 in 0.4); the last solution was viscous. It was almost insoluble in ether.  $[\alpha]_D^{20} + 2.9^\circ$  (c, 6.0 in water).

Analysis:- /

its decomposition.

The picrate was prepared similarly to the aurichloride, and formed tabular, yellow prisms (from aqueous acetone), m.p. 172° (corr.).

The salicylate was prepared by adding salicylic acid (0.85 g.) in dry ether (5 ml.) to the base (1 g.) dissolved in dry ether (10 ml.); colourless, glistening laminae, m.p. 154° (corr.), separated in 75% yield after standing for a short time.

Neither the normal nor acid phthalate was crystallisable.

b. Nitroso Derivative of Base Z.

This was prepared by adding slight excess of an aqueous solution of sodium nitrite to a solution of the base in excess of n/10 hydrochloric acid. The solution rapidly became turbid, and oily drops separated on standing. This oil was extracted with ether, but could not be crystallised.

c. Hydrolysis of Base Z.

The base extracted from 1 g. of the oxalate was refluxed from the sand-bath for 2 hours with barium hydroxide ( 1.5 g.) in water (20 ml.). Ether extracted no unhydrolysed base from the mixture. The /

The warm aqueous liquid was acidified to Congo Red with dilute sulphuric acid, and the precipitated barium sulphate filtered (suction), washed with warm water, and rejected. The united acid filtrates were extracted with ether, the extract washed with a small volume of water, dried over anhydrous sodium sulphate, and the solvent recovered. The residue consisted of 0.37 g. of an oily acid with a powerful odour of valeric acid; yield, 95%.  $[\alpha]_D^{20} + 2.9^\circ$  (c, 6.2 in absolute alcohol).

Analysis:-

Found: Equivalent by titration, 103.

Calculated for  $C_5H_{10}O_2$ :-

Equivalent, 102.

The *p*-phenylphenacyl ester formed dull, colourless, laminae, m.p.  $69^\circ$  (corr.), from 60% aqueous alcohol; the m.p. of a mixture with an equal weight of the ester of dl- $\alpha$ -methylbutyric acid (m.p.  $71^\circ$  (corr.)) was  $66^\circ$  (corr.). The amide, made from the chloride by the action of concentrated aqueous ammonia, formed colourless, foliated laminae (from ether), m.p. ca.  $120^\circ$  (corr.); mixed with an equal weight of dl- $\alpha$ -methylbutyramide (m.p.  $114^\circ$  (corr.)), it melted at ca.  $108^\circ$ .

The aqueous acid liquid, from which the organic acid had been extracted, was digested on the water-bath /

water-bath with excess of barium carbonate until faintly alkaline to litmus paper. It was then filtered (suction), the residue washed with warm water, and rejected. The united filtrates were exactly neutralised with dilute sulphuric acid, filtered, and evaporated to dryness on the water-bath. The slightly yellow, crystalline residue gave reactions for chloride (as well as sulphate; compare the similar behaviour of  $\Psi$ -tropine from tigloidine (p. 20), and teloidine from meteloidine, Pyman and Reynolds, loc. cit.). It was dissolved in water (1 ml.), excess of 30% aqueous potassium hydroxide solution added, and the mixture repeatedly extracted with chloroform. The solvent was evaporated, and the residue leached with chloroform, a small amount of undissolved mineral matter being removed by filtration. The solvent was evaporated; the solid residue weighed 0.32 g., m.p. ca. 160° (corr.); yield, 64%. It was dissolved in absolute alcohol (5 ml.), the solution filtered, dry ether (30 ml.) added, and carbon dioxide bubbled through the solution for 10 minutes. After adding dry ether (50 ml.), and allowing to stand for 15 minutes, the precipitated carbamate was filtered (suction), and washed with dry ether. It consisted of an almost colourless, crystalline powder (0.21 g.), m.p. 166° (corr.; decomp., with evolution of carbon dioxide), not depressed by admixture of an equal weight /

weight of authentic nortropine carbamate, and was optically inactive (c, 6.5 in water).

Analysis:-

Found: N, 9.4%.

Calculated for  $(C_7H_{13}ON)_2 \cdot CO_2$  :-  
N, 9.4%.

The nitroso derivative was prepared by adding a slight excess of an aqueous solution of sodium nitrite to a solution of the base (0.1 g.) in n/20 hydrochloric acid (4 ml.); after standing overnight, the clear solution was extracted with ether, the extract dried over anhydrous sodium sulphate, and the solvent evaporated. The residue was crystallised from a small volume of dry ether, separating in colourless prisms, m.p. 196° (corr.), not depressed on mixing with an equal weight of authentic nitrosonortropine.

d. Racemisation of Base Z.

The base from 5 g. of oxalate was hydrolysed by refluxing for 2 hours from the sand-bath with potassium hydroxide (3 g.) in water (40 ml.). The cooled mixture was acidified to Congo Red with dilute sulphuric acid, extracted with ether, and the extract dried over anhydrous sodium sulphate. Evaporation of the solvent left 2 g. of valeric acid; yield, 100%.

The /

The aqueous liquid from which the organic acid had been extracted was treated with 30% of its weight of solid potassium hydroxide, and repeatedly extracted with chloroform. The extracted base yielded 2.4 g. of nortropine carbamate, m.p. 166.5° (corr.; decomp., with evolution of carbon dioxide), by the method described under the hydrolysis section (p. 67); yield, 84%.

The valeric acid was treated with potassium hydroxide (5 g.) and sufficient water for complete solution. The mixture was then gently boiled in a nickel crucible for 12 hours, water being added periodically to maintain the original volume. (this drastic method was only adopted after milder methods had failed to effect racemisation). The solution was then diluted with water (15 ml.), acidified to Congo Red with dilute sulphuric acid, and extracted with ether. The ethereal extract was dried over anhydrous sodium sulphate, and the solvent recovered. The residual acid was optically inactive (c, 34.0 in absolute alcohol), and weighed 1.7 g.; yield, 86%. The *p*-phenylphenacyl ester had m.p. 69° (corr.), and the amide ca. 120°. These figures were the same as those for the corresponding derivatives of the original (dextrorotatory) acid, and the m.p.'s were not depressed by admixture of equal weights of these corresponding derivatives.

The /

The main quantity of the racemised acid (1.25 g.) and phosphorus trichloride (0.65 g.) were heated together at 80°- 90° under reflux for 2 hours. The upper layer was decanted from the syrupy lower layer, and heated under reflux on the water-bath for 2 hours with nortropine hydrochloride (made by titrating 1.75 g. of the above nortropine carbamate with hydrochloric acid, and evaporating the solution to dryness in a vacuum). The pale yellow, syrupy product was dissolved in very dilute hydrochloric acid, and the solution washed with ether to remove free valeric acid. The aqueous solution was then basified with ammonia, and the liberated base extracted with chloroform. The chloroformic extract was washed with water (5 ml.), the solvent evaporated from the water-bath, and the residue neutralised with hydrobromic acid. The neutral solution was evaporated to dryness on the water-bath, the residue consisting of 1.02 g. of a crystalline hydrobromide; yield, 28.5% on the acid used, and 24.5% on the original oxalate after making allowance for the acid used up in making the *p*-phenylphenacyl ester and amide. The salt was dissolved in chloroform, filtered, and the solvent evaporated. The residue was dissolved in absolute alcohol, filtered, and ether added to the warm, concentrated solution; colourless, glistening laminae separated /

separated, m.p. 219°- 220° (corr.). The salt was optically inactive (c, 20.0 in water).

Analysis:-

Found: C, 49.5; H, 7.7; N, 4.8; Br, 27.6%.

Calculated for  $C_{12}H_{21}O_2N, HBr$ :-

C, 49.3; H, 7.5; N, 4.8; Br, 27.4%.

The above m.p. was identical with that of the natural (dextrorotatory) hydrobromide, and no depression of m.p. was shown on mixing equal weights of the two salts. The same applied to the oxalate, picrate, and other salts which were prepared like the natural salts described under "a" at the beginning of this Experimental section (p.63).

e. Synthesis of Tiglylnortropine.

Nortropine carbamate (1.2 g.) (made from tropine; Willstätter, Ber., 1896, 29, 1580) was neutralised with hydrochloric acid, and the solution evaporated to dryness in a vacuum. Nortropine hydrochloride, so obtained, was heated under reflux on the water-bath for 2 hours with tiglyl chloride (0.95 g.) (see synthesis of tigloidine, pp. 21, 22, for preparation of tiglyl chloride). The pale yellow, syrupy product was dissolved in very dilute hydrochloric acid, and the alkaloid purified and isolated as hydrobromide as in the case of racemic base Z above; /

above; weight, 1.59 g.; yield, 70%. The salt was dissolved in chloroform, filtered, the solvent evaporated, and the residue crystallised from alcohol-ether. It thus formed dull, colourless laminae, m.p.  $241^{\circ}$ - $242^{\circ}$  (corr.).

Analysis:-

Found: C, 49.4; H, 7.0; N, 4.7; Br, 27.4%.

Calculated for  $C_{12}H_{19}O_2N, HBr$ :-

C, 49.6; H, 6.9; N, 4.8; Br, 27.6%.

The picrate formed golden-yellow prisms (from aqueous acetone), m.p.  $207^{\circ}$  (corr.), and the methiodide colourless, opaque laminae (from alcohol-ether), m.p.  $285^{\circ}$ - $286^{\circ}$  (corr.; decomp.).

f. Synthesis of dl- $\alpha$ -methylbutyrylnortrop $\ddot{e}$ ine.

Tiglylnortrop $\ddot{e}$ ine hydrobromide (1 g.) was dissolved in water (25 ml.), and the solution shaken with Adams's platinum oxide catalyst (0.1 g.) in an atmosphere of hydrogen. Absorption was slow, and ceased after 6 hours when 1 mol. had been taken up. The solution was filtered, basified with ammonia, and the liberated base extracted with chloroform. The chloroformic extract was washed with water (5 ml.), and the solvent evaporated; the residue consisted of the theoretical amount (0.73 g.) of a thin, colourless syrup. It was neutralised with hydrobromic acid, and the /

the solution evaporated to dryness on the water-bath. The crystalline hydrobromide thus obtained was then dissolved in chloroform, filtered, the solvent evaporated, and the crystalline residue recrystallised from alcohol-ether. It formed colourless, glistening plates, m.p.  $201^{\circ}$ - $202^{\circ}$  (corr.); when the salt was mixed with an equal weight of either natural or racemised base Z hydrobromide (m.p.  $219^{\circ}$ - $220^{\circ}$  (corr.)) the m.p. was raised to ca.  $209^{\circ}$ .

Analysis:-

Found: N, 4.9; Br, 27.0%.

Calculated for  $C_{12}H_{21}O_2N, HBr:-$

N, 4.8; Br, 27.4%.

The oxalate formed colourless, glistening laminae (from water), m.p.  $296^{\circ}$ - $297^{\circ}$  (corr.), depressed to  $295^{\circ}$  (corr.) when mixed with an equal weight of either natural or racemised base Z oxalate (m.p.  $296^{\circ}$ - $297^{\circ}$  (corr.)).

Analysis:-

Found: C, 60.8; H, 8.5; N, 5.5%.

Calculated for  $(C_{12}H_{21}O_2N)_2 \cdot H_2C_2O_4 :-$

C, 60.9; H, 8.6; N, 5.5%.

The picrate formed golden-yellow, prismatic needles (from aqueous acetone), m.p.  $188^{\circ}$  (corr.); mixed with an equal weight of natural base Z picrate (m.p. /

(m.p.  $172^{\circ}$  (corr.)) the m.p. was depressed to  $180^{\circ}$  (corr.).

The methiodide formed dull, pearly laminae (from alcohol-ether), m.p.  $295^{\circ}$  (corr.).

An independent synthesis of the alkaloid was effected by esterifying dl- $\alpha$ -methylbutyryl chloride with nortropine hydrochloride; the product was identical with that described above. The dl- $\alpha$ -methylbutyryl chloride was made from dl- $\alpha$ -methylbutyric acid which latter was readily prepared in theoretical yield by catalytic reduction of tiglic acid dissolved in 45% aqueous alcohol, using Adams's platinum oxide catalyst. This method does not appear to have been previously described. Sodium tiglate in water was not reduced by this method.

g. p-Phenylphenacyl Esters of the Valeric Acids.

These, and other p-phenylphenacyl esters described in other sections were prepared by the following general method:- The acid was almost completely neutralised with n/l sodium hydroxide (aqueous), an equal volume of alcohol and  $\frac{1}{2}$  mol. of p-phenylphenacyl bromide added, and the mixture refluxed from the water-bath for 1 hour. The ester crystallised on standing /

standing for a few hours, and was filtered (suction), and recrystallised from 60% aqueous alcohol.

The valeric acids yielded the following:-

<u>p</u> -Phenylphenacyl <u>n</u> -valerate.....	m.p.	68°	(corr.).
"	<u>iso</u> valerate.....	"	76°
"	<u>dl</u> - $\alpha$ -methylbutyrate..	"	71°
"	trimethylacetate...	"	114°

The first three esters formed dull, colourless, felted laminae, the fourth hard, colourless, prismatic needles.

The m.p.'s of the first and third esters were fairly close to that of the ester of the acid from base Z (m.p. 69° (corr.)), but mixed m.p. determinations (using equal weights) showed considerable depressions. Mixtures of all the possible pairs of esters were then made, using equal weights of the constituents, and m.p.'s determined as under:-

<u>n</u> -Valerate	plus <u>iso</u> valerate.....	<sup>m.p.</sup> ca. 56°.
"	" <u>dl</u> - $\alpha$ -methylbutyrate..	" 47°.
"	" trimethylacetate....	" 85°.
<u>iso</u> Valerate	" <u>dl</u> - $\alpha$ -methylbutyrate..	" 67°.
"	" trimethylacetate....	" 78°.
<u>dl</u> - $\alpha$ -methylbutyrate	" " .....	" 87°.

The m.p. of the ester of the acid from base Z approximated only to the mixture of isovaleric and dl- $\alpha$ -methylbutyric esters; m.p.'s of mixtures in the following /

following ratios of former to latter were next determined:-

<u>Ratio.</u>	<u>M.p.</u>
10 : 1.....	69°- 70° (corr.).
2 : 1.....	66.5° " .

The m.p. of the first mixture was not depressed by admixture of an equal weight of the ester of the acid from base Z, m.p. 69° (corr.).

A mixture of 10 parts of isovaleramide, m.p. 136° (corr.), with 1 part of dl- $\alpha$ -methylbutyramide, m.p. 112° (corr.), melted at ca. 120°; this m.p. was not depressed by admixture of the amide of the acid from base Z, m.p. ca. 120°.

The p-phenylphenacyl esters of the butyric acids were prepared for comparison:-

<u>p-Phenylphenacyl n-butyr</u> ate.....	m.p. 82° (corr.).
" <u>isobutyr</u> ate.....	" 88° " .

#### h. Hydrolysis of p-Phenylphenacyl Esters.

The ester (ca. 0.5 g.) dissolved in 70% aqueous acetone (10 ml.) was refluxed from the water-bath for 2 hours with concentrated sulphuric acid (0.5 ml.). The cooled mixture was carefully neutralised with n/1 sodium hydroxide, avoiding excess, and p-phenylphenacyl /

p-phenylphenacyl alcohol extracted with chloroform. The chloroformic extract was washed with water (5 ml.), the solvent evaporated, and the residue recrystallised from absolute alcohol (charcoal); it thus separated in colourless, prismatic needles, m.p. 132° (corr.; sintering at 130°; Allen and Ball, Canadian J. Res., 1932, 7, 643, give m.p. 123°-128°).

Analysis:-

Found: C, 79.1; H, 5.7%.

Calculated for C<sub>14</sub>H<sub>12</sub>O :-

C, 79.2; H, 5.7%.

The aqueous liquid from which the p-phenylphenacyl alcohol had been extracted was then acidified to Congo Red with dilute sulphuric acid, and the organic acid extracted with ether in the usual manner.

Hydrolysis with alcoholic potassium hydroxide caused rapid colouring, resinification, and loss of both acid and p-phenylphenacyl alcohol.

i. Synthesis of isoValeryl<sup>o</sup>nortrop<sup>e</sup>ine.

isoValeric acid (4 g.) and phosphorus trichloride (3.5 g.) were heated together at 80°-90° for 2 hours under reflux. The upper, colourless layer /

layer was decanted from the lower syrupy residue, and distilled at  $115^{\circ}/760$  mm.; yield, 100%. isoValeryl chloride, so obtained, (0.65 g.) was heated for 2 hours on the water-bath under reflux with nortropine hydrochloride (0.8 g.), and the alkaloid isolated as hydrobromide as in the case of tiglylnortrop<sup>e</sup>ine hydrobromide (p.71 ); yield, 57%. The salt was dissolved in chloroform, filtered, the solvent evaporated, and the crystalline residue recrystallised from alcohol-ether. Small, colourless plates, m.p.  $224^{\circ}$ -  $225^{\circ}$  (corr.), were thus obtained. The salt was extremely soluble in water, alcohol, and chloroform.

Analysis:-

Found: N, 4.8; Br, 27.2%.

Calculated for  $C_{12}H_{21}O_2N, HBr:-$

N, 4.8; Br, 27.4%.

Melting points of mixtures of this salt with dl- $\alpha$ -methylbutyrylnortrop<sup>e</sup>ine hydrobromide (assumed to have the same m.p. as the dextrorotatory form) were then determined in the following ratios of former to latter:-

10	:	1	.....	$220^{\circ}$	m.p.	(corr.).
8	:	1	.....	$217^{\circ}$	"	.
4	:	1	.....	$213.5^{\circ}$	"	.
8	:	3	.....	$210^{\circ}$	"	.

The /

The m.p. of the first mixture was not depressed on mixing with an equal weight of either natural or racemised base Z hydrobromide, m.p. 219°- 220° (corr.).

The oxalate, prepared by neutralising the base with oxalic acid, crystallised in colourless, glistening laminae (from water), m.p. 301°- 302° (corr.), depressed to 296° (corr.) when mixed with an equal weight of dl- $\alpha$ -methylbutyrylnortropine oxalate (m.p. 297° (corr.))(base Z oxalate melts at 296°- 297° (corr.)).

Analysis:-

Found: C, 60.8; H, 8.4; N, 5.6%.

Calculated for  $(C_{12}H_{21}O_2N)_2 \cdot H_2C_2O_4$  :-  
C, 60.9; H, 8.6; N, 5.5%.

The picrate formed golden-yellow prisms (from aqueous acetone), m.p. 172° (corr.).

The methiodide, which was only sparingly soluble in absolute ethyl alcohol, formed pearly laminae (from absolute methyl alcohol-ether), m.p. 289° (corr.; darkened at 280°.).

j. Attempted Separation of the Isomers from Base Z.

1. Fractional Crystallisation:

Base Z hydrobromide was repeatedly recrystallised /

recrystallised from alcohol-ether without sign of separation; the m.p. remained constant at  $219^{\circ}$ - $220^{\circ}$  (corr.).

The salicylate, prepared as described on p. 65, was suspended in water, basified with ammonia, and the liberated base extracted with chloroform. The chloroformic extract was washed with a small volume of water, the solvent evaporated, and the residue neutralised with hydrobromic acid. The solution was evaporated to dryness from the water-bath, and the residual hydrobromide crystallised from alcohol-ether; the m.p. of the product was  $213^{\circ}$  (corr.). The base was extracted from this salt and reconverted into salicylate as before; the product had m.p.  $154^{\circ}$  (corr.), identical with that of the original salicylate.

The picrate was fractionally crystallised from aqueous alcohol and from aqueous acetone. Fractions with m.p.'s from  $167^{\circ}$  to  $172^{\circ}$  (corr.) were thus obtained. These were converted into hydrobromides with m.p.'s from  $207^{\circ}$  to  $210^{\circ}$  (corr.), and which were evidently mixtures.

## 2. Chromatographic Methods:-

A 1% solution of base Z in chloroform was /

was drawn through a column of aluminium oxide (Brockmann), followed by chloroformic washings (10 of 15 ml.). 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 ultraviolet light, and yielded no alkaloid to either hot alcohol, acetone, pyridine, or even dilute, aqueous hydrobromic acid. Similar results were obtained with columns of kaolin and of lactose.

3. Hydrolysis, followed by Fractional Precipitation of the Silver Valerates, etc.:

At 20° the solubilities in water of the silver salts of isovaleric and dl- $\alpha$ -methylbutyric acids are respectively 1 in 540 and 1 in 137 (Beilstein). In the following separation it was assumed that the water solubility of silver d- $\alpha$ -methylbutyrate was also 1 in 137.

The base extracted from 5 g. of base Z oxalate was hydrolysed by refluxing for 2 hours from the sand-bath with 10% aqueous potassium hydroxide (30 ml.); 2.31 g. of nortropine carbamate (80% yield), and 2.04 g. of valeric acid (100% yield) were isolated as in the previous hydrolysis described in the racemisation experiment (p. 68).

The /

The acid was neutralised with aqueous sodium hydroxide solution, the solution diluted with water to 150 ml., and the temperature adjusted to 20°. Silver nitrate (3.5 g.) in water (40 ml.) at 20° was added dropwise from a burette, the mixture being constantly shaken. The mixture was finally diluted with water to a volume of 200 ml., and left overnight, the temperature being maintained at 20° throughout. The precipitated silver salt was then filtered (suction), rapidly washed with water (10 ml.), and dissolved in slight excess of dilute aqueous ammonia solution. This solution was precipitated with distinct excess of dilute hydrochloric acid, added dropwise with constant stirring, filtered (suction), the residual silver chloride washed with water, and rejected. The united aqueous filtrates (acid to Congo Red) were extracted with ether, and the ethereal extract dried over anhydrous sodium sulphate. Evaporation of the solvent left 1.14 g. of oily acid which was optically inactive ( $c$ , 6.0 in absolute alcohol); yield, 56%. The *p*-phenylphenacyl ester formed colourless, foliated laminae (from 60% aqueous alcohol), m.p. 76° (corr.), not depressed by admixture of an equal weight of authentic *p*-phenylphenacyl isovalerate.

The /

The aqueous mother liquid, from which the silver isovalerate had been precipitated, was acidified to Congo Red with dilute hydrochloric acid, the precipitated silver chloride removed by filtration, and the acid filtrate extracted with ether. 0.75 g. of liquid acid,  $[\alpha]_D^{20} +4.8^\circ$  (c, 6.0 in absolute alcohol), was thus obtained; it was not found possible to effect further separation of this mixture.

The separated isovaleric acid (1 g.) was converted into chloride (1.1 g.), and esterified with nortropine hydrochloride (made from 1.4 g. of the above carbamate by neutralisation with hydrochloric acid, and evaporation to dryness in a vacuum) as described under the previous synthesis of isovaleryl-nortropine (p. 77). The alkaloid was isolated as hydrobromide as in the previous case; yield, 36% on the acid used, and 20% on the original oxalate after making allowance for the acid used in making the p-phenylphenacyl ester. The salt was dissolved in chloroform, filtered, the solvent evaporated from the water-bath, and the residue recrystallised from alcohol-ether. It thus formed small, colourless plates, m.p. 224°- 225° (corr.), not depressed by mixing with an equal weight of authentic isovaleryl-nortropine hydrobromide, and was optically inactive (c, 8.0 in water).

Analysis:- /

Analysis:-

Found: N, 4.8; Br, 27.1%.

Calculated for  $C_{12}H_{21}O_2N, HBr:-$

N, 4.8; Br, 27.4%.

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VI./

VI. S U M M A R Y.

1. The alkaloidal content of the Australian drug, Duboisia myoporoides, has been examined. Despite the claims of most of the earlier workers, no trace of hyoscyamine has been isolable from any of a large number of samples. In addition to hyoscine, four new alkaloids have been found: tigloidine (0.1%), valeroidine (0.1%), poroidine, and isoporoidine, the last two being isolated as a difficultly-separable mixture, Base Z (0.003%), at first thought to be a single substance.
  
2. Tigloidine,  $C_{13}H_{21}O_2N$ , a syrup, has been shown to be tiglyl- $\psi$ -tropëine, and has been synthesised, as has its geometric isomer, tiglyltropëine. Both these alkaloids are remarkable in possessing hydrobromides which are readily soluble in chloroform, and which can be extracted from aqueous solution by this solvent. Catalytic reduction of them has yielded respectively dl- $\alpha$ -methylbutyryl- $\psi$ -tropëine, and dl- $\alpha$ -methylbutyryltropëine. The hydrobromides of acetyltropëine and acetyl- $\psi$ -tropëine have also been prepared; they are shown to be useful in the identification of tropine and  $\psi$ -tropine respectively.

3. Valeroidine,  $C_{13}H_{23}O_3N$ , m.p.  $85^\circ$ ,  $[\alpha]_D^{20} -9.0^\circ$  has been shown to be the monoisovaleryl ester of a dihydroxytropane previously isolated as the dibenzoyl ester by Wolfes and Hromatka (Merck's Jahresber., 1933, 47, 45) from Peruvian coca leaves. The hydrobromide is readily soluble in chloroform, but unlike that of tigloidine, is not extracted from water by this solvent. An attempt has been made to determine the positions of substitution of the hydroxyl groups in the tropane molecule. In the course of this work it has been found that under certain conditions thionyl chloride possesses the remarkable property of demethylating the N-methyl group in valeroidine with production of the secondary base, norvaleroidine,  $C_{12}H_{21}O_3N$ . While very stable to oxidation, valeroidine when treated with potassium permanganate in acetone yielded a neutral product,  $C_{13}H_{21}O_4N$ , which on subsequent treatment with alcoholic hydrochloric acid also gave norvaleroidine. It is hoped to pursue this work.
4. Base Z,  $C_{12}H_{21}O_2N$ , a syrup,  $[\alpha]_D^{20} +2.5^\circ$  has been shown to be a mixture of about ten parts of poroidine (isovalerylnortropoëine) /

(isovalerylnortrop<sup>ë</sup>ine) with one part of isoporoidine (d- $\alpha$ -methylbutyrylnortrop<sup>ë</sup>ine), 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 isoleucine respectively is suggested. Tiglylnortrop<sup>ë</sup>ine,  $C_{12}H_{19}O_2N$ , has also been synthesised. The hydrobromides of the above three alkaloids are readily soluble in chloroform, which solvent also extracts them from aqueous solution. The p-phenylphenacyl esters of the butyric and valeric acids are described. A method for the recovery of acid and alcohol from such esters is also given.