214. *The Minor Alkaloids of* Duboisia myoporoides. *Part III. Valeroidine.*

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A previous statement of the chloroform solubility of valeroidine hydrobromide is corrected. Several new derivatives of valeroidine and its parent dihydroxytropane are described. Attempts to determine the positions of the hydroxyl groups in the latter have yielded results difficult to interpret. Thionyl chloride has been found to demethylate valeroidine hydrobromide to *norvaleroidine*.

VALEROIDINE has already been shown to be a mono*iso*valeryldihydroxytropane (Part I, J., 1937, 1821). The hydrobromide was then stated to be sparingly soluble in cold chloroform. It has since been found to be extremely soluble (*ca.* 1 in 0·5 at 15°); its even greater solubility in water probably explains why chloroform does not extract the salt from aqueous solution as it does the hydrobromides of tigloidine and " base Z."

The free hydroxyl group has been acetylated, and also esterified with a second *iso*-valeryl group; in each case characteristic *hydrobromides* have been obtained. The parent dihydroxytropane has yielded a *diacetyl* derivative, characterised as *hydrobromide*; the same derivative has been prepared from the dihydroxytropane isolated from Peruvian coca leaves by Wolfes and Hromatka (*Merck's Jahresber.*, 1933, **47**, 45). Attempts to determine the positions of the hydroxyl groups have been unsuccessful, any results being incapable of interpretation. In an attempted chlorination of valeroidine hydrobromide with thionyl chloride a good yield of *norvaleroidine hydrobromide* was obtained; valeroidine methiodide was readily obtained on remethylation; an oily nitroso-derivative was also prepared. This unexpected result appears to afford the first instance of such a demethylation by thionyl chloride; the reaction is being further investigated with related alkaloids.

Experimental.

Solubility of Valeroidine Hydrobromide.—10% Aqueous solutions of the hydrobromides of tigloidine, " base Z," and valeroidine yielded to an equal volume of chloroform 52, 42, and 1·5% respectively of the total salt present. Valeroidine hydrobromide is extremely soluble in cold water.

Acetylvaleroidine.—The base (2 g.) was refluxed for 3 hours with acetic anhydride (5 ml.); the product was diluted with water and basified, and the acetyl derivative extracted with chloroform and converted into *hydrobromide*; this was obtained in colourless needles, m. p. 197° (corr.), from alcohol–ether (Found: C, 49·3; H, 7·3; N, 4·0; Br, 21·8. $C_{15}H_{25}O_4N$,HBr requires C, 49·4; H, 7·1; N, 3·8; Br, 22·0%); yield, 92%. The salt was readily soluble in water and chloroform, but almost insoluble in ether.

*Di*iso*valeryldihydroxytropane.*—Valeroidine hydrobromide (5 g.) was refluxed for 3 hours with *iso*valeryl chloride (2·9 g.). The product was diluted with water, free *iso*valeric acid extracted with ether, and the base isolated as *hydrobromide* in the usual way. This salt formed colourless, prismatic needles (from alcohol–ether), m. p. 176—177° (corr.), which were very soluble in water, alcohol, chloroform, but sparingly in ether (Found: C, 53·4; H, 7·9; N, 3·6; Br, 19·5. $C_{18}H_{31}O_4N$,HBr requires C, 53·2; H, 7·9; N, 3·5; Br, 19·7%); yield, 82%.

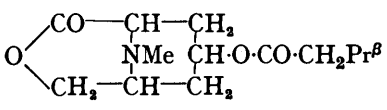
Diacetyldihydroxytropane.—This was prepared in the same way as acetylvaleroidine. The hydrobromide formed colourless prisms, m. p. 219—220° (corr.), from alcohol–ether, which were very soluble in water, alcohol, and chloroform, but sparingly in ether. The m. p. was not depressed by the similar compound prepared from the dihydroxytropane obtained from Merck's coca alkaloid.

" *Tropene Oxide.*"—Wolfes and Hromatka (*loc. cit.*) described the picrate of this substance, m. p. 277°. This preparation could not be satisfactorily repeated with either of the dihydroxytropanes. The very minute amount of picrate had an indefinite m. p. (250—280°), but repeated trials failed to give amounts capable of satisfactory purification.

Attempted Chlorination of Valeroidine.—It was hoped to remove the free hydroxyl group by chlorination, followed by catalytic reduction. Phosphorus trichloride or oxychloride with chloroformic solutions of valeroidine or its hydrobromide gave only yellow, water-soluble gums. Thionyl chloride had no action on the free base; the following result was obtained with the hydrobromide:—Thionyl chloride (10 ml.) was added to valeroidine hydrobromide (1 g.); an effervescence, considerable heat evolution, and the production of an orange colour were observed; the mixture was then refluxed for 8 hours. It was poured on ice, basified with ammonia, and extracted with chloroform. The colourless, syrupy base thus obtained was converted into *hydrobromide*, which separated from alcohol–ether in colourless, pearly laminæ, m. p. 270° (corr.), readily soluble in water, alcohol, or chloroform, but sparingly in ether. $[\alpha]_D^{20°}$ + 1·0° (*c*, 20·0 in water) (Found: C, 46·9; H, 7·1; N, 4·7; Br, 25·9. $C_{12}H_{21}O_3N$,HBr requires C, 46·8; H, 7·2; N, 4·6; Br, 26·0%); yield, 65·5%. That this substance was *norvaleroidine hydrobromide* was shown by the fact that it readily gave an oily nitroso-derivative on treatment with sodium nitrite and dilute hydrochloric acid; this was extracted with ether, but did not crystallise. Also, the base extracted from the hydrobromide (0·5 g.) in methyl alcohol (5 ml.) was refluxed for 2 hours with methyl iodide (0·5 ml.); dry ether was added to the warm mixture to produce a faint turbidity. Crystals separated overnight, and, recrystallised from methyl alcohol–ether, formed colourless, six-sided laminæ, m. p. 206° (corr.), not depressed by authentic valeroidine methiodide; yield, 60%.

Oxidation of Valeroidine.—It was hoped that oxidation would open the pyrrolidine ring, or convert the secondary alcoholic into a ketonic group. The alkaloid was very resistant to oxidation, and was recovered unchanged and almost quantitatively after refluxing in moderately concentrated solution with potassium permanganate or dichromate and dilute sulphuric acid. Similarly, chromic acid in cold glacial acetic acid was without apparent action, though on warming a vigorous action resulted; in the latter case no recognisable product could be isolated. The following method gave a new substance: Valeroidine (5 g.) in acetone (250 ml.) was refluxed for 48 hours with powdered potassium permanganate (9 g.). The liquid was filtered (suction), and the solvent recovered. The dark brown residue, of peculiar odour, was dissolved in chloroform (50 ml.) and repeatedly extracted with dilute sulphuric acid. The acid extract was basified with ammonia and extracted with chloroform, and the resultant bases converted into hydrobromides. Fractional crystallisation of these from alcohol–ether yielded 3·5 g. of valeroidine hydrobromide, and 0·22 g. of norvaleroidine hydrobromide, m. p. 270° (corr.), not depressed by authentic material (compare preparation of nortropine from tropine; Will-

stätter, *Ber.*, 1896, **29**, 1580). The original chloroformic solution, so extracted, was freed from solvent; the residue rapidly crystallised. By washing with a little cold acetone a total of 0·6 g. of crystalline material was obtained. It formed colourless, pearly laminæ, m. p. 136° (corr.), from warm acetone (charcoal), $[\alpha]_D^{20°}$ — 16·6° (*c*, 7·4 in absolute alcohol) (Found : C, 61·1; H, 8·4; N, 5·6. $C_{13}H_{21}O_4N$ requires C, 61·2; H, 8·2; N, 5·5%). It was neutral, almost insoluble in water, moderately in acetone, and readily in most other organic solvents. It did not yield a nitroso-derivative, and was unaltered by shaking with hydrogen and Adams's platinum catalyst in aqueous alcoholic solution. 1 G. was hydrolysed with barium hydroxide (2 g.) in water (20 ml.) as described for tigloidine (Part I, J., 1937, 1822). The products consisted of *iso*valeric acid (0·55 g.), characterised as the *p*-phenylphenacyl ester, m. p. 76° (corr.), not depressed by authentic material, and a crystalline base, which, after sublimation at 1 mm. and crystallisation from acetone–ether, gave faintly yellow, tabular crystals, m. p. *ca.* 200° (corr.); repeated recrystallisation failed to yield a product with a really sharp m. p. (Found : C, 55·2; H, 8·4; N, 8·9. $C_7H_{13}O_3N$ requires C, 52·8; H, 8·2; N, 8·8%. $C_8H_{13}O_3N$ requires C, 56·1; H, 7·6; N, 8·2%). The analytical figures may be partly explained by a lactone structure, whereby the original oxidation product would be represented by the annexed formula. In an attempt to open the supposed lactone ring the material (2 g.) was refluxed for 3 hours with absolute alcohol (50 ml.) containing 4% of hydrogen chloride. After removal of the alcohol, and dilution with water, the mixture was basified and extracted with chloroform. The resultant base was converted into hydrobromide, which crystallised from alcohol–ether in colourless, pearly laminæ of norvaleroidine hydrobromide, m. p. 270° (corr.), not depressed by authentic material. This unexpected result is difficult to explain.



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