631. *The Stereochemistry of the Tropane Alkaloids. Part XIII.* The Absolute Configuration and a Simplified Syntheses of Valeroidine.*

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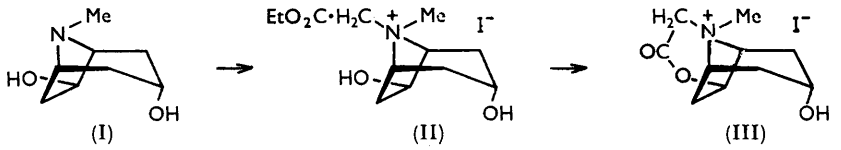
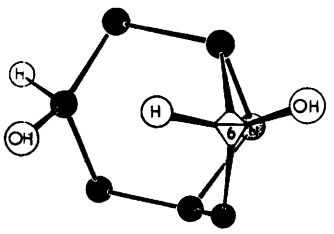
The configuration (3*R*,6*R*) has been assigned to natural valeroidine in view of the considerable dextrorotatory shift during lactonization of N_b-ethoxycarbonylmethyl-3α,6β-dihydroxytropanium iodide. Selective hydrolysis of tropane-3α,6β-diol di-isovalerate, leading to natural valeroidine, is described.

THE relative configurations of the tropane alkaloids,[1] and the absolute configurations of the majority of them, *e.g.*, of cocaine,[2] hyoscyamine, and hyoscine,[3] have been determined recently. In a preliminary report [4] we assigned the (3*R*,6*R*) absolute configuration to valeroidine by adapting Hudson's lactone rule [5] to the cyclisation of N_b-ethoxycarbonylmethyl-3α,6β-dihydroxytropanium iodide [6] (II) to the six-membered lactone (III). We give now full details of the preparative work involved and of a simpler synthesis of natural valeroidine than reported heretofore.[7]



(I) (II) (III)

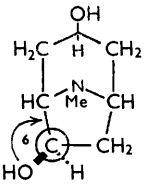
The lævorotatory form of the alkamine of natural valeroidine has been prepared both by the Stoll method [8] by resolving 6β-hydroxytropan-3-one with 3-bromo-(+)-camphor-7-sulphonic acid, and by resolving tropane-3α,6β-diol [9] with dibenzoyltartaric acid or 6β-phenylcarbamoyloxytropan-3α-ol [7] with (+)-tartaric acid. Since this lævorotatory alkamine has been converted into the same di-isovalerate [8] as was obtained by acylating tropane-3α,6β-diol, and since (+)-tropane-3α,6β-diol 6-phenylurethane has been converted stereospecifically into natural valeroidine,[7] configurational identity of (—)-valeroidine with (—)-tropane-3α,6β-diol was proved. Accordingly, extension of the conclusions reached with the alkamine to the natural alkaloid is justified. In consequence, (—)-tropane-3α,6β-diol (I) was treated with ethyl iodoacetate, giving as a first product the iodide of the lactone of N_b-carboxymethyl-3α,6β-dihydroxytropanium iodide. This proved to be strongly dextrorotatory. From the mother-liquor the ester, N_b-ethoxycarbonylmethyl-3α-dihydroxytropanium iodide (II), was obtained with a specific rotation of —23·7°. The latter compound showed m. p. 154° but resolidified, owing to lactonization, on further heating, and decomposed completely at 262°. On recrystallization from ethanol the ester was converted into the lactone.[6] A further correlation of the lactone and ester has been furnished by converting both compounds into the same betaine of m. p. 298—300°. The betaine proved to be strongly lævorotatory,



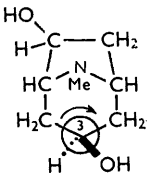
* Part XII, Dobó, Fodor, Janzsó, Koczor, Tóth, and Vincze, *J.*, 1959, 3461.

[1] Fodor, *Experientia*, 1955, **11**, 129; Fodor and his co-workers, *J.*, 1953, 721, 724, 2341; *Helv. Chim. Acta*, 1954, **37**, 892, 907.
[2] Hardegger and Ott, *Helv. Chim. Acta*, 1955, **38**, 312.
[3] Fodor and Csepreghy, *Tetrahedron Letters*, 1959, No. 7, 16.
[4] Fodor, Vincze, and Tóth, *Experientia*, 1957, **13**, 183.
[5] Hudson, *J. Amer. Chem. Soc.*, 1910, **32**, 338.
[6] Fodor, Tóth, and Vincze, *J.*, 1955, 3504.
[7] Fodor, Vincze, and Tóth, *J.*, 1957, 1349.
[8] Stoll, Lindenmann, and Jucker, *Helv. Chim. Acta*, 1953, **36**, 1506.
[9] Fodor and Kovács, *J.*, 1953, 2341.

independently of the starting material. The betaine was reconverted into the lactone by evaporation of its aqueous solution with hydriodic acid. The strongly lævorotatory ester and betaine both gave the strongly dextrorotatory lactone (III) on acid treatment. According to Hudson's rule,[5] which has been applied recently by Witkop [10] to γ- and δ-hydroxyamino-acids, *e.g.*, both to γ-hydroxy-L-lysine and to 5-hydroxypipecolic acid, it seems justified to assign the D_g-configuration (Fig. 1 †) at position 6 and the overall (3*R*,6*R*) configuration (see IV and V) to the 3α,6β-tropanediol related to valeroidine. The change of rotation seems to be mainly a consequence of a change in conformation during lactonization, which would not hold true for a tropane derivative in which both the substituents involved in ring closure were fixed rigidly to a five-membered strained ring system. However, there is a complete parallelism between the optical changes of γ-hydroxy-L-proline and 5-hydroxypipecolic acid, despite the fact that the first has a rigid ring system whilst the second has a flexible six-membered ring. Accordingly, application of Hudson's rule to the configurational problem of *N*-carboxymethyl-3α,6β-dihydroxytropanium iodide seems justified.



(IV)



(V)

Decisive evidence would be obtained by converting either a compound of known absolute configuration into (−)-tropane-3α,6β-diol or, conversely, by degrading tropane-3α,6β-diol to a compound of known absolute configuration. Unfortunately, we have not succeeded as yet in effecting the latter transformation. However, an attempt is being made to correlate values on a sounder basis than the purely empirical with absolute configurations and conformations.[11] In the laboratory of one of the authors (G. F.) application of these Brewster principles is already in progress.

The roundabout way which had to be used to realize for the first time the total synthesis of valeroidine by thermal decomposition of (−)-6β-phenylcarbamoyloxytropan-3α-ol [7] was due to the failure of other authors [8] to perform selective hydrolysis of the corresponding diol divalerate. We found recently that use of a certain concentration of aqueous sodium hydroxide in acetone led to 3α-acetoxytropan-6β-ol in very good yield from the diacetyl derivative. This method proved generally applicable to other tropane-3α,6β-diol diesters, *e.g.*, both to (±)- and to (+)-3α,6β-di-isovaleryloxytropane. In this way the racemic di-isovalerate gave a 40% yield of pure racemic valeroidine hydrochloride, and (+)-3α,6β-di-isovaleryloxytropane gave a 30% yield of natural (−)-valeroidine.

Experimental

(+)-*Lactone of* N_b-*Carboxymethyl*-3α,6β-*dihydroxytropanium Iodide and* (−)-N_b-*Ethoxycarbonylmethyl*-3α,6β-*dihydroxytropanium Iodide.*—(−)-Tropane-3α,6β-diol (0·5 g.) was dissolved in a mixture of dry ethanol (5 ml.) and benzene (7 ml.). Ethyl iodoacetate (0·75 ml.) was added and the mixture refluxed for 10 hr. After 10 min. crystallization set in. The filtered crystals of *lactone iodide* (0·4558 g.) were extracted with boiling alcohol, then having m. p. 264° (decomp.), $[\alpha]_D^{20}$ +37·5° (*c* 2 in water) (Found: C, 37·4; H, 5·3; N, 4·3; I, 38·9. $C_{10}H_{16}INO_3$ requires C, 36·9; H, 5·0; N, 4·3; I, 39·0%). The mother-liquor and the alcohol used for extraction were evaporated; the residual *ester iodide* solidified on trituration with acetone. Recrystallized from alcohol–ether it (0·4031 g.) had m. p. 154°, with resolidification and decomposition at 262°, $[\alpha]_D^{20}$ −23·7° (*c* 1 in anhydrous ethanol) (Found: C, 38·6; H, 6·2; N, 3·6;

† To derive this configuration the projection is set up, as in Fig. 1, with C-1 at the top, C-6 in the middle, and C-5 at the bottom.

[10] Witkop, *Experientia*, 1957, **12**, 372.
[11] Brewster, *J. Amer. Chem. Soc.*, 1959, **81**, 5475, 5483.

I, 34·85. $C_{12}H_{22}INO_4$ requires C, 38·9; H, 5·9; N, 3·8; I, 34·25%). The total yield was 88·7%, calculated on starting material.

(−)-N_b-*Carboxymethyltropane*-3α,6β-*diol Betaine*.—(*a*) The lactone of (+)-N_b-carboxymethyl-3α,6β-dihydroxytropanium iodide (0·292 g.) was dissolved in water (20 ml.) and shaken with moist silver oxide (0·3 g.) for 6 hr.; the silver iodide was removed and washed with aqueous methanol. After removal of silver from the solution by hydrogen sulphide the solution was filtered and evaporated, and the residue crystallized from methanol (16 ml.), yielding the *betaine* as needles (0·17 g., 64%), m. p. 299—300° (decomp.), $[\alpha]_D^{20}$ −80° (*c* 0·3 in water) (Found: C, 55·4; H, 8·4; N, 6·3. $C_{10}H_{17}NO_4$ requires C, 55·8; H, 8·0; N, 6·5%).

(*b*) N_b-Ethoxycarbonylmethyl-3α,6β-dihydroxytropanium iodide (0·0725 g.) was dissolved in water (15 ml.) and shaken with moist silver oxide for 6 hr. After filtration, washing, precipitation with hydrogen sulphide, refiltration, and evaporation, the residue was recrystallized from methanol (4 ml.) to give the pure betaine (0·0476 g.; 82%), m. p. 298—300°, $[\alpha]_D^{20}$ −79·8° (*c* 0·2 in water) (Found: C, 55·3; H, 7·6; N, 6·5%).

Lactone of (+)-N_b-*Carboxymethyl*-3α,6β-*dihydroxytropanium Iodide from the Betaine*.—(−)-N_b-Carboxymethyltropane-3α,6β-diol betaine (0·3 g.) was dissolved in water (5 ml.) and the solution was evaporated with hydriodic acid to dryness under reduced pressure at 25°. The residue, when washed with dry acetone, afforded crystals (0·28 g.), m. p. 263—264° (decomp.), $[\alpha]_D^{20}$ +37·4° (*c* 2, in water). The substance gave no m. p. depression with lactone prepared directly from (−)-tropane-3α,6β-diol.

(±)-3α,6β-*Di-isovaleryloxytropane*.—(±)-Tropane-3α,6β-diol (0·8 g.) was refluxed with isovaleryl chloride (2·4 ml.) for 5 hr. The excess of chloride was removed *in vacuo* and the residue, in water (5 ml.), was extracted with ether (4 ml.). The aqueous solution was saturated with potassium carbonate and extracted with chloroform (10 × 3 ml.); the combined extracts were dried and evaporated to an oil (0·7 g.). The derived *picrate*, crystallized from dry ethanol, had m. p. 170° (Found: C, 52·3; H, 6·2; N, 9·8. $C_{24}H_{34}N_4O_{11}$ requires C, 52·0; H, 6·2; N, 10·1%).

(±)-*Valeroidine Hydrochloride*.—(±)-Di-isovaleryloxytropane (0·52 g.) was dissolved in a mixture of acetone (29 ml.) and 0·1N-sodium hydroxide (71 ml.). The solution was kept for 6 hr. at room temperature. It was neutralised with 0·1N-hydrochloric acid and evaporated at 50° after decolorisation with charcoal. The residue was dissolved in water (4 ml.) and the solution saturated with potassium carbonate and extracted with chloroform (10 × 5 ml.). The combined chloroform extracts were dried and evaporated. A viscous, pale-yellow oil (0·25 g.) was obtained. This oil (0·19 g.) gave with dry alcoholic hydrogen chloride, after recrystallization from alcohol–ether, a product of m. p. 180—182° undepressed by (±)-valeroidine hydrochloride [7] (Found: C, 56·2; H, 9·9; Cl, 12·6. Calc. for $C_{13}H_{24}ClNO_3$: C, 56·2; H, 8·7; Cl, 12·8%).

(±)-3α,6β-*Di-isovaleryloxytropane Hydrochloride*.—(−)-Tropane-3α,6β-diol (0·03 g.) was dissolved in freshly distilled isovaleryl chloride (0·1 ml.), and the solution kept at 150° for 2 hr. Excess of chloride was evaporated and the remaining oily crystals recrystallized from alcohol–ether, to give white needles (0·0378 g.), m. p. 124—125°, $[\alpha]_D^{20}$ +2·66° (*c* 3·78 in anhydrous ethanol) (Found: C, 59·9; H, 8·7. $C_8H_{32}ClNO_4$ requires C, 59·7; H, 8·9%). The hydrobromide was prepared by Stoll, Lindenmann, and Jucker.[8]

(−)-*Valeroidine*.—(+)-3α,6β-Di-isovaleryloxytropane hydrochloride (0·03 g.) was dissolved in a mixture of acetone (1·5 ml.) and 0·1N-sodium hydroxide (3·5 ml.) and was kept at room temperature for 5 hr. The solution was neutralized with 0·1N-hydrochloric acid and evaporated at 30° *in vacuo* to about 1 ml. The solution was saturated with potassium carbonate and shaken with chloroform (6 × 1 ml.). Evaporation of the dried ($MgSO_4$) extract afforded valeroidine (0·01 g.), m. p. 80° undepressed by natural valeroidine.[12] The hydrobromide, prepared with azeotropic hydrobromic acid and recrystallized from ethanol–ether (0·0008 g.), had m. p. 170—171° alone or on admixture with the hydrobromide of authentic natural valeroidine (Found: C, 48·05; H, 7·2. Calc. for $C_{13}H_{24}BrNO_3$: C, 48·45; H, 7·5%).

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[12] Barger, Martin, and Mitchell, *J.*, 1937, 1820.