256. *The Stereochemistry of the Tropane Alkaloids. Part X.* The Total Synthesis of Valeroidine.*

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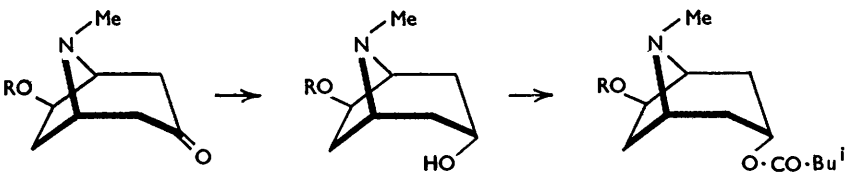
Hydrogenation of the monophenylurethane (Ib) of 6β-hydroxytropan-3-one (Ia), followed by resolution, acylation (to IIIb), and thermolysis have led to the racemic and optically active forms of 3α-*iso*valeryloxytropan-6β-ol (IIIa).† The lævorotatory form was identical with valeroidine.

Earlier work [1] has indicated that valeroidine, an alkaloid from *Duboisia myoporoides*, is (—)-3-*iso*valeryloxytropan-6-ol (IIIa). Its alkamine was identical with the (—)-tropane-diol (IIa) from Javanese coca leaves.[2] Steric correlation of scopolamine with the racemic diol (IIa), resolution of the latter,[3] and total synthesis [4] of the racemic diol (IIa) followed. Later,[5] (+)-6β-hydroxytropan-3-one (Ia) was converted into (—)-tropane-3 : 6-diol, which was also obtained from the monoester (IIIa). However, neither selective deacylation of the di*iso*valerate of the dihydroxy-compound, nor acylation of the lævorotatory diol (IIa) gave the pure alkaloid. Formation of a lactone salt [6] from the racemic diol (IIa) supported the suggested structure for valeroidine, of which we now describe the synthesis.



(I) a: R = H; b: R = CO·NHPh (II) a: R = H; b: R = CO·NHPh (III) a: R = H; b: R = CO·NHPh

The phenylurethane (Ib) of 6β-hydroxytropan-3-one (Ia) gave on hydrogenation tropane-3α : 6β-diol monophenylurethane (IIb). With *iso*valeryl chloride this gave the ester urethane (IIIb), which was cleaved by vacuum-distillation into (±)-valeroidine (IIIa).[7] Resolution of the phenylurethane (IIb) was preferred to that of (±)-valeroidine, and was effected by means of (+)-tartaric acid. The optically active phenylurethanes were converted into the optically active form of the monoester (IIIa), and the (—)-form proved to be identical with natural valeroidine.

Phenylurethane residues protecting hydroxyl groups have usually been removed by hydrolysis (*e.g.*,, in the case of hydroxyproline [8]), and the present thermal method deserves further examination.

Experimental

M.p.s are corrected.

(±)-6β-*Hydroxytropan*-3-*one Phenylurethane* (Ib).—A suspension of 6β-hydroxytropan-3-one [9] (31 g.) in ether was treated with phenyl *iso*cyanate (24 ml.) with shaking and then kept at 80° for 1 hr. The mixture was set aside for 10 hr., giving the crude product (53·8 g.), m. p. 126—129°. The contaminating diphenylurea was destroyed by the addition of N-hydrochloric

* Part IX, Fodor, Koczka, and Lestyan, *J.*, 1956, 1411.
† For nomenclature see Part I, *J.*, 1953, 721.

[1] Barger, Martin and Mitchell, *J.*, 1937, 1820; 1938, 1685; Martin and Mitchell, *J.*, 1940, 1155; Mitchell and Trautner, *J.*, 1947, 1330.
[2] Wolfes and Hromatka, *Merck's Jahresber.*, 1933, **47**, 45.
[3] Fodor, Kovács, and Mészáros, *Research*, 1952, **5**, 534; Fodor and Kovács, *J.*, 1953, 2341.
[4] Stoll, Becker, and Jucker, *Helv. Chim. Acta*, 1952, **35**, 1263.
[5] Stoll, Lindenmann, and Jucker, *ibid.*, 1953, **36**, 1506.
[6] Fodor, Tóth, and Vincze, *ibid.*, 1954, **37**, 902.
[7] Fodor, Tóth, Koczor, and Vincze, *Chem. and Ind.*, 1955, 1260.
[8] Leuchs and Brewster, *Ber.*, 1913, **46**, 986.
[9] Nedenskov and Clauson-Kaas, *Acta Chem. Scand.*, 1954, **8**, 2295.

acid (200 ml.) in water (130 ml.). The solution was filtered, extracted with chloroform, cooled, basified with potassium hydroxide (26 g.), and extracted with chloroform (8 × 50 ml.). Drying (Na_2SO_4) and evaporation afforded the crystalline *product* (38 g., 69·5%) (Found: C, 66·0; H, 6·9; N, 10·2. $C_{15}H_{18}O_3N_2$ requires C, 65·7; H, 6·6; N, 10·2%).

(±)-*Tropane*-3α : 6β-*diol* 6-*Phenylurethane* (IIb).—The above compound (25·4 g.) was hydrogenated in dry dioxan over Raney nickel at 90 atm. for 40 hr. Part of the product separated as a white crystalline powder. It was redissolved by gentle warming, the catalyst was removed, and the solution was decolorised (charcoal) and evaporated. The *product* (22·5 g., 88%), m. p. 182° (Found: C, 65·7; H, 6·9; N, 10·1. $C_{15}H_{20}O_3N_2$ requires C, 65·2; H, 7·3; N, 10·1%), began to separate during evaporation. It was collected and washed with ether.

(±)-6β-*Phenylcarbamoyloxy*-3α-iso*valeryloxytropane* (IIIb).—*iso*Valeryl chloride (2·4 g.) was added to a suspension of the urethane (IIb) (5·5 g.) in dry chloroform (10 ml.). After 7 hr. of gentle heating the solution was evaporated to dryness, leaving an oil which crystallised on trituration with ether–acetone. The *hydrochloride* (m. p. 237°, decomp.), recrystallised from dry ethanol, had m. p. 245° (Found: C, 60·1; H, 7·65; N, 7·3; Cl, 8·8. $C_{20}H_{29}O_4N_2Cl$ requires C, 60·5; H, 7·4; N, 7·1; Cl, 8·9%).

(±)-*Valeroidine Hydrochloride* (IIIa).—(±)-Valeroidine 6β-phenylurethane hydrochloride (15·2 g.) was dissolved in water (15 ml.) by gentle warming, and the solution was adjusted to pH 10 by potassium carbonate (25 g.). The precipitated base was extracted with chloroform (6 × 50 ml.), and the dried (Na_2SO_4) extract was evaporated, giving the *base* (12·1 g.). When this was heated in a Späth tube the product distilled at 220—250°/5 mm. Nine or ten distillations completed the decomposition, and the oil thus obtained was dissolved in alcohol and treated with ethanolic hydrochloric acid. Evaporation to dryness gave a crystalline solid. Repeated recrystallisation from alcohol–ether gave (±)-*valeroidine hydrochloride* (5·85 g.), m. p. 181—183° (Found: C, 56·6; H, 8·4; N, 5·0; Cl, 12·7. $C_{13}H_{23}O_3N$,HCl requires C, 56·8; H, 8·7; N, 5·0; Cl, 12·8%).

(+)-*Tropane*-3α : 6β-*diol* 6-*Phenylurethane*.—(±)-Tropane-3α : 6β-diol 6-phenylurethane (40 g.) in alcohol (450 ml.) was treated with (+)-tartaric acid (21·2 g.) in the same solvent (150 ml.). The filtered solution was evaporated to 400 ml. and set aside overnight. A crystalline product (30·4 g.) was collected [the mother-liquor, from which the (−)-compound (IIb) was isolated, was treated as described below] and recrystallised five times from ethanol (200 ml.), giving soft needles, m. p. 182—184° (decomp.), $[\alpha]_D^{20}$ 0·0° (*c* 2 in H_2O). The solution of this salt in water (420 ml.) was basified with potassium hydroxide (32 g.) and extracted with chloroform (22 × 30 ml.). Drying (Na_2SO_4), evaporation, and washing with ether gave white crystals (9·1 g.), m. p. 203—204° $[\alpha]_D^{20}$ +7·5° (*c* 2 in dry EtOH).

(−)-*Tropane*-3α : 6β-*diol* 6-*Phenylurethane*.—The mother-liquor mentioned above was evaporated to dryness, and the residue was recrystallised from alcohol (200 ml.). The first crop of crystals (2 g.) was discarded and the residue remaining after evaporation of the mother-liquor was crystallised again. Repetition of the process six times furnished crystals of the (+)-tartrate (8·3 g.), m. p. 170—171° (decomp.), $[\alpha]_D^{20}$ +14·2° (*c* 2 in H_2O), of the lævorotatory modification.

The solution of this tartrate in water (80 ml.) was basified with potassium hydroxide (15 g.), and the organic base was extracted with chloroform (20 × 20 ml.). Evaporation of the dried (Na_2SO_4) solution yielded this base (4·95 g.), m. p. 203—204°, $[\alpha]_D^{20}$ −7·5°. A mixed m. p. with the dextrorotatory form was 182°.

(+)-6β-*Phenylcarbamoyloxy*-3α-iso*valeryloxytropane*.—*iso*Valeryl chloride (3·65 g.) was added dropwise to a suspension of (+)-tropane-3α : 6β-diol 6-phenylurethane (8·3 g.) in dry chloroform (15 ml.). After 10 hr. at 80° the solution was evaporated to dryness, leaving a residue which when rubbed with ether deposited crystals. Recrystallisation from alcohol gave the *hydrochloride* (9·2 g.), m. p. 151° (decomp.), $[\alpha]_D^{20}$ −47° (*c* 1 in H_2O) (Found: C, 60·2; H, 7·6; N, 7·1; Cl, 8·5. $C_{20}H_{28}O_4N_2$,HCl requires C, 60·5; H, 7·4; N, 7·1; Cl, 8·9%).

The enantiomer was obtained in the same way, using *iso*valeryl chloride (1·01 g.), (−)-phenylurethane (2·3 g.), and dry chloroform (4 ml.). (+)-6β-*Phenylcarbamoyloxy*-3α-iso*valeryloxytropane hydrochloride* (2·7 g.) formed crystals, m. p. 151° (decomp.), $[\alpha]_D^{20}$ +47° (*c* 2 in H_2O) (Found: C, 60·1; H, 7·7; N, 7·2; Cl, 8·7%). A mixture with the lævorotatory hydrochloride showed an elevation of m. p. to 235°.

(+)-*Valeroidine*.—A solution of (−)-6β-phenylcarbamoyloxy-3α-*iso*valeryloxytropane hydrochloride (8·5 g.) in water (40 ml.) was treated with potassium hydroxide (8 g.) and extracted

with chloroform (10 × 10 ml.). Drying (Na_2SO_4) gave an oily product (6·6 g.) (Found : C, 66·9; H, 7·7. $C_{20}H_{28}O_4N_2$ requires C, 66·6; H, 7·8%) which (5·8 g.) was submitted to thermolysis at 220—230°/4—5 mm. After ninefold distillation a smoothly crystallising oil was collected. Repeated recrystallisation from ether gave (+)-valeroidine (1·92 g.), m. p. 81°, $[\alpha]_D^{20}$ +9·0° (*c* 5 in dry EtOH), which gave with constant-boiling hydrobromic acid the *hydrobromide*, m. p. 170—171° (decomp.), $[\alpha]_D^{20}$ −5·1° (*c* 3·5 in H_2O) (Found : C, 48·0; H, 7·8; N, 4·5. $C_{13}H_{23}O_3N$,HBr requires C, 48·45; H, 7·5; N, 4·35%), after crystallisation from ethanol.

(−)-*Valeroidine*.—(+)-6β-Phenylcarbamoyloxy-3α-*iso*valeryloxytropane (1·7 g.) was isolated from the hydrochloride as above and pyrolysed at 220—230°/4—5 mm. After tenfold distillation the product crystallised smoothly. Recrystallisation from ether gave (−)-valeroidine (0·28 g.), m. p. 81°, $[\alpha]_D^{20}$ −9·1° (*c* 2 in dry EtOH). A mixture with a natural specimen gave the same m. p. The hydrobromide obtained as above, after recrystallisation from alcohol–ether, had m. p. 170°, $[\alpha]_D^{20}$ +5·1° (*c* 3 in H_2O) (Found : C, 48·7; H, 7·9; N, 4·5%). It did not depress the m. p. (170°) of the hydrobromide prepared from natural valeroidine, for which specimen we are indebted to Dr. W. Mitchell.

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