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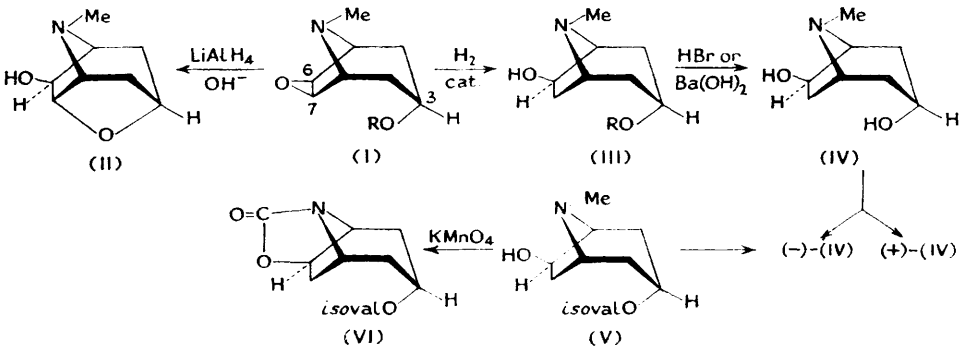
478. *The Stereochemistry of the Tropane Alkaloids. Part III.* The Configuration of Scopolamine and of Valeroidine.*

By GÁBOR FODOR and ÖDÖN KOVÁCS.

Scopolamine was converted by hydrogenolysis into (±)-3 : 6-dihydroxytropane, which was resolved. The (−)-isomer was identical with the alkamine from valeroidine (Fodor, Kovács, and Mészáros, *Research*, 1952, **5**, 534). Scopolamine and valeroidine are both β-orientated at $C_{(6)}$ since valeroidine forms a cyclic urethane and, as scopoline can be formed from scopolamine only if the $C_{(3)}$-hydroxyl group in the latter is α-orientated with respect to the nitrogen bridge, the configuration at $C_{(3)}$ in valeroidine must be the same as that in scopolamine and tropine.

WHEREAS definite steric structures can be assigned to the epimeric 2-amino-alcohols (cf. Fodor and Kiss, *J.*, 1952, 1589; Fodor and Koczka, *J.*, 1952, 850; Fodor, Kiss, and Bánfi, *Monatsh.*, 1952, **83**, 1146), to tropine and ψ-tropine (Fodor and Nádor, *J.*, 1953, 721), and to the cocaine epimers (Fodor and Kovács, *J.*, 1953, 724), the configurations of those tropane alkaloids that cannot be hydrolysed to tropines or ecgonines are uncertain. Although Willstätter and Berner (*Ber.*, 1923, **56**, 1096) indicated the four projection formulæ possible for scopolamine, no choice between them has hitherto been possible.

In alkaline solution, scopolamine (I; R = CO·CHPh·CH_2·OH) and scopine (I; R = H), but not ψ-scopine, are converted into scopoline (oscine) (II) (Willstätter and Berner, *loc. cit.*), a tetrahydrofuran derivative. It was therefore suggested (Fodor, *Nature*, 1952, **170**, 278) that the rearrangement involved a nucleophilic rearward attack by the $C_{(3)}$-oxygen atom on the $C_{(6:7)}$-epoxide ring; this seems possible if the $C_{(3)}$-hydroxyl is α and the $C_{(6:7)}$-epoxide group is β with respect to the nitrogen bridge,† the nucleophilic character of the hydroxyl group then being enhanced by the alkali present. This suggests that scopolamine and scopine are 6 : 7β-epoxy-3α-hydroxytropanes (as I) (Fodor, *Nature*, *loc. cit.*; cf. Fodor, *Proc. Chem. Acad. Sci. Hungar.*, 1952, **2**, 43).



Evidence on the stereochemistry of the epoxide group appeared to be obtainable by correlation of scopolamine with a derivative of 3 : 6-dihydroxytropane, *e.g.*, valeroidine (V) in which the β-orientation of the $C_{(6)}$-hydroxyl group is already established by the conversion of valeroidine into a cyclic derivative (VI) (Martin and Mitchell, *J.*, 1940, 1155; Mitchell and Trautner, *J.*, 1947, 1330). The details of this correlation are now described (cf. Fodor, Kovács, and Mészáros, *Research*, 1952, **5**, 534).

Attempted hydrogenolysis of scopolamine hydrobromide with lithium aluminium hydride gave only scopoline (II), presumably because of the greater nucleophilic effect of the lithium aluminium scopine complex. However, hydrogenolysis at 150 atm. with a Raney nickel catalyst at 25°, followed by hydrolysis of the ester hydrobromide mixture (III), gave (±)-3 : 6-dihydroxytropane (IV) and (−)-tropic acid. The racemate proved identical with that afforded by the Robinson synthesis (Stoll, Becker, and Jucker, *Helv.*

* Part II, *J.*, 1953, 724. † For details of the nomenclature used see *J.*, 1953, 722.

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Chim. Acta, 1952, **35**, 1263). The dibenzoate could not be resolved by use of α-bromo-(+)-camphor-π-sulphonic acid or (+)-tartaric acid, but the racemate itself was resolved in good yield by the use of (lævorotatory) dibenzoyl-(+)-tartaric acid or (+)-tartaric acid; with the former the derivative of (−)-3 : 6-dihydroxytropane separated first, with the latter that of the (+)-isomer was the less soluble. The lævorotatory form was identical with an authentic specimen * of (−)-3 : 6-dihydroxytropane, obtained by hydrolysis of valeroidine (V) (Barger, Martin, and Mitchell, *J.*, 1930, 1820).

The configurational correlations of the epoxide bridge in scopolamine and the $C_{(6)}$-hydroxyl group of valeroidine, and of the corresponding $C_{(3)}$-hydroxyl groups, are thus reasonably established. Since the β-orientation of the $C_{(6)}$-hydroxyl group in (−)-6-hydroxynor-3-tropyl *iso*valerate and in (±)-3 : 6-dihydroxytropane has been proved, the epoxide ring in scopolamine must also be β-orientated with respect to the nitrogen bridge. The $C_{(3)}$-hydroxyl group in (I) can only be α, since the formation of scopoline would otherwise be less feasible. Scopolamine (I) is therefore a 6 : 7β-epoxy-3α-hydroxytropane, as previously suggested, and valeroidine (V) the *iso*valerate of 3α : 6β-dihydroxytropane. Additional evidence on the proximity of the $C_{(6)}$-hydroxyl group and the nitrogen bridge in 3 : 6-dihydroxynortropane is now being obtained by the acyl-migration method.

The ready conversion of scopine into a tetrahydrofuran derivative, involving $C_{(3)}$ and $C_{(6)}$, suggests that the piperidine ring is in the chair form; this is supported by the difficulty of bridging the piperidine ring in *syn*-tropine derivatives. Recent investigations on N ⟶ O acyl migrations in 1-acylpiperidin-4-ols (Fodor and Lestyán, *Magy. Kém. Folyóirat*, in the press) also indicate the greater stability of the chair form in piperidines.

The stereochemistry of teloidine is now being considered.

Added in Proof.—Since this paper was submitted, Meinwald (*J.*, 1953, 712) has independently recorded the same conclusion on the configuration of scopolamine. His deductions are based in part on the formation of scopoline, in part on the structure of scopinium bromide, obtained together with scopolamine *N*-oxide (Polonovski, *Bull. Soc. Chim.*, 1928, **43**, 79). In our opinion, the suggested mechanism of this reaction and the products need further investigation.

Experimental

Hydrogenolysis of Scopolamine.—(a) *With lithium aluminium hydride.* A solution of scopolamine hydrobromide trihydrate (17·52 g., 0·04 mole) and sodium hydrogen carbonate (5·04 g.) in water (90 ml.) was shaken with chloroform (3 × 80 ml.), and the extract dried ($MgSO_4$) and evaporated *in vacuo*, giving a brown oil (12 g.). A solution of this base in dry ether (200 ml.) was added to one of lithium aluminium hydride (3·8 g., 0·1 mole) in ether (300 ml.) during 2·5 hr. at 45°, stirring was continued for 2 hr., and ice-water (8 ml.) was added. After being stirred for a further 2 hr. the ethereal solution was filtered and the residue extracted with ethanol (5 × 100 ml.); this furnished an oil (9·7 g.) on evaporation. An aqueous solution, of pH 3 (hydrochloric acid), was shaken with ether and then evaporated to dryness, giving crystals (6·4 g.); after recrystallisation from ethanol (35 ml.)–ether (45 ml.) (±)-scopoline hydrochloride (5·2 g.) had m. p. 255—257° (Found: C, 50·2; H, 7·1; N, 7·5; Cl, 18·3. Calc. for $C_8H_{13}O_2N,HCl$: C, 50·2; H, 7·2; N, 7·2; Cl, 18·3%). The picrate, m. p. 236—237°, did not depress the m. p. of a specimen from authentic (±)-scopoline (oscine).

(b) *Catalytic hydrogenation.* (i) Commercial scopolamine hydrobromide trihydrate (87·69 g., 0·2 mole) in water (300 ml.) was hydrogenated in the presence of Raney nickel [60 g.; in water (300 ml.)] for 16 hr. at 25° at atmospheric pressure; 6360 ml. (1·4 mol.) of hydrogen were absorbed. The ester hydrobromides were hydrolysed directly in solution or after removal of the solvent.

(ii) Hydrogenation over Raney nickel at 150 atm. pressure consumed the same amount of hydrogen, and gave the same product.

Acetylscopoline. Scopoline (oscine) [obtained by shaking the hydrochloride (3·9 g.) with silver oxide (5 g.) and water (60 ml.) for 30 min.] was boiled with acetic anhydride (7 ml.) for 3 hr. The acetyl derivative formed crystals (1·8 g.), m. p. 56—57°, from light petroleum (Found: C, 60·7; H, 7·6; N, 7·4; Ac, 21·1. Calc. for $C_{10}H_{15}O_3N$: C, 60·8; H, 7·6; N, 7·1; Ac, 21·4%).

The crude derivative was converted into the bromide, which had m. p. 219—220° (from

* The authors are indebted to Dr. M. Mitchell for this sample.

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chloroform–light petroleum) (cf. Hess and Wahl, *Ber.*, 1922, **55**, 1979). Neither derivative depressed the m. p. of the corresponding authentic material.

Hydrolysis of the Ester Mixture obtained by Catalytic Hydrogenation.—(a) *With* 10% *hydrobromic acid.* Water and 46% hydrobromic acid were added to the solution obtained above to give a final volume of 1700 ml., containing 170 g. of hydrobromic acid. The solution was refluxed for 16 hr., then cooled, and extracted with ether. The extracts gave (−)-tropic acid (31·8 g., 95%), m. p. 126—127° (from water), $[\alpha]_D^{25}$ −74° (*c*, 2 in H_2O) (cf. King, *J.*, 1919, **115**, 476). The residue (46·8 g.), obtained from the aqueous solution, gave (±)-3 : 6-*dihydroxytropane hydrobromide* (24·89 g., 52%), m. p. 267° (decomp.) (from ethanol–ether) (Found : C, 40·6; H, 6·6; N, 5·8; Br, 33·85. $C_8H_{15}O_2N,HBr$ requires C, 40·3; H, 6·8; N, 5·9; Br, 33·6%).

The free base, obtained by treating the hydrobromide (3·57 g.) in ethanol (30 ml.) with N-sodium hydroxide (15 ml.) and Soxhlet-extracting the product, formed crystals, m. p. 179—180° [from ethanol–ether (1 : 5)] (Found : C, 60·95; H, 9·7; N, 8·9. Calc. for $C_8H_{15}O_2N$: C, 61·1; H, 9·6; N, 8·9%). Stoll *et al.* (*loc. cit.*) record the same m. p. The picrate had m. p. 248—249° (cf. Stoll *et al.*).

(b) *With* 10% *hydrochloric acid.* The product of the hydrogenation of (−)-scopolamine hydrobromide hydrate (21·9 g.) was treated in water (80 ml.) with sodium carbonate (2·65 g.) and sodium hydrogen carbonate (5·3 g.), and the base isolated, by extraction with chloroform (10 × 20 ml.), and dried. The oil was refluxed for 16 hr. with 10% hydrochloric acid (800 ml.), tropic acid and (±)-3 : 6-dihydroxytropane hydrochloride (4·75 g., 49%), m. p. 295° (decomp.), being obtained.

(c) *With baryta.* The solution obtained from the hydrogenation of scopolamine hydrobromide hydrate (87·69 g.) was diluted with water to 1900 ml. and barium hydroxide octahydrate (110 g.) was added. After 2 hr.' refluxing, barium ions were removed by 50% sulphuric acid, and the aqueous solution extracted with ether. (±)-Tropic acid (30·2 g., 90%), $\alpha = 0°$, m. p. 98—104° (cf. Ladenburg, *Annalen*, 1881, **206**, 302), was obtained from the ether extracts. Trituration with acetone of the residue from the aqueous solution gave (±)-3 : 6-dihydroxytropane hydrobromide (33·8 g., 71%), m. p. 256° (decomp.), from which the (±)-base (20·4 g.), m. p. 177—179°, was obtained.

Barger, Martin, and Mitchell (*loc. cit.*) recorded a similar observation in the hydrolysis of tigloidine.

(±)-3 : 6-*Dibenzoyloxytropane Hydrochloride.*—The (±)-dihydroxy-compound (4·7 g.) was benzoylated with benzoyl chloride (24 g.) at 160° for 2 hr. The *derivative* formed yellow crystals (10·3 g.), m. p. 268° (Found : C, 65·5; H, 5·95; N, 3·25; Cl, 8·8. $C_{22}H_{23}O_4N,HCl$ requires C, 65·7; H, 6·0; N, 3·5; Cl, 8·8%).

Attempted Resolution of (±)-3 : 6-*Dibenzoyloxytropane Hydrochloride.*—(a) *With* α-*bromo*-(+)-*camphor*-π-*sulphonic acid.* An aqueous solution (40 ml.) of ammonium α-bromo-(+)-camphor-π-sulphonate (6·57 g.) was added to a suspension of the hydrochloride (8·03 g.) in warm water (60 ml.). The water was removed and the residue extracted with hot ethanol (80 ml.). Long white needles (8·2 g.) separated on cooling; after recrystallisation from ethanol the salt (4·4 g.) had m. p. 218—220°, $[\alpha]_D^{27}$ +59·85 (*c*, 2 in EtOH). A solution of the salt (2·0 g.) in water (20 ml.) was treated with sodium hydrogen carbonate (0·75 g.) and then extracted with chloroform (5 × 20 ml.). Removal of the solvent gave an oil, an alcoholic solution of which was treated with 9·8N-alcoholic hydrochloric acid. The hydrochloride (1·1234 g.) had m. p. 264° (decomp.), $\alpha = 0°$.

(b) *With* (+)-*tartaric acid.* An aqueous solution (200 ml.) of (±)-3 : 6-dibenzoyloxytropane [from the hydrochloride (8·03 g.)] and (+)-tartaric acid (2·95 g.) was heated to boiling; on cooling, white crystals (6·2 g.), m. p. 130—135°, separated. Repeated recrystallisation gave a salt, m. p. 155—157°, $[\alpha]_D^{27}$ +8·53° (*c*, 2·051 in 50% EtOH).

The free base, obtained from the salt (3·2 g.) and sodium hydrogen carbonate (2·6 g.) in water (40 ml.), was converted into the hydrochloride (2·32 g.), m. p. 265° (decomp.), which was optically inactive.

Resolution of (±)-3 : 6-*Dihydroxytropane with* (+)-*Tartaric Acid.*—*The* (+)-*isomer.* The (±)-base (4·71 g.) and (+)-tartaric acid (4·5 g.) were dissolved in water (60 ml.), which was then removed *in vacuo*. A solution of the residue (9·05 g.) in 78% alcohol (20·5 ml.) was set aside at 1° for 48 hr., giving rhombic crystals (*A*) (2·55 g.) (from 96% alcohol) of the (+)-3 : 6-dihydroxytropane (+)-tartrate hydrate, m. p. 150—151°, $[\alpha]_D^{27}$ +14·23° (*c*, 2·249 in H_2O) (the loss in weight at 120°/30 mm. corresponded to 1 mol. of water of crystallisation).

The anhydrous salt (1·42 g.) was converted, in water, into the picrate (1·54 g.), which was

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recrystallised from water, giving the (+)-salt, m. p. 251—252° [mixed m. p. with the (±)-salt 245—246°; Wolfes and Hromatka, *Ber.*, 1934, **47**, 45, record m. p. 153° (decomp.) for the (−)-picrate].

The (+)-picrate (1·22 g.) was converted into the (+)-sulphate by means of 0·2N-sulphuric acid (65 ml.), and the sulphate solution, after removal of picric acid by extraction with ether, shaken for 1 hr. with barium carbonate (2·6 g.). Removal of barium sulphate and evaporation of the solvent *in vacuo* gave the (+)-base (0·4156 g.). After recrystallisation from ethanol (6 ml.)–ether (30 ml.), this had m. p. 209—210°, $[\alpha]_D^{27}$ +24·14° (*c*, 1·988 in EtOH). Barger *et al.* (*loc. cit.*) record m. p. 212° (corr.), $[\alpha]_D$ −25°, for the (−)-form obtained from valeroidine.

The (−)-*isomer*. The mother liquors, left after removal of the crystal (*A*), were concentrated and the amorphous residue (5·7 g.) converted in water into the picrate, a mixture, m. p. 246—248° (from water), of the (±)- and the (−)-form being obtained. A suspension in 0·2N-sulphuric acid was extracted several times with ether (1400 ml. in all), sulphate ions were removed by barium carbonate (12 g.), and the solvent was evaporated. After four recrystallisations of the residue from alcohol–ether (5 : 1), the (−)-base, m. p. 209°, $[\alpha]_D^{27}$ −23·31° (*c*, 2·038 in EtOH), was obtained. The m. p. of this was not depressed by an authentic specimen of (−)-3 : 6-dihydroxytropane, but an admixture with the (+)-form melted at 180°.

Resolution of (±)-3 : 6-*Dihydroxytropane with* (*Lævorotatory*) OO′-*Dibenzoyl*-(+)-*tartaric Acid*.—Removal *in vacuo* of the solvent from a solution of the (±)-base (4·71 g.) and *OO′*-dibenzoyl-(+)-tartaric acid (10·74 g.) in 96% alcohol (100 ml.), and slow crystallisation of the hygroscopic solid from 96% alcohol (30 ml.) gave crystals (6·25 g.), m. p. 169—170°, $[\alpha]_D^{20}$ −78° (*c*, 2·0 in 96% EtOH). Further recrystallisation gave (−)-3 : 6-dihydroxytropane dibenzoyl-(+)-tartrate (2·9 g.), m. p. 172°, of unchanged $[\alpha]_D$.

A suspension of the finely ground salt in N-sulphuric acid (15 ml.) was repeatedly extracted with ether (300 ml. in all), N-sodium hydroxide was then added, and the solution was evaporated. Extraction of the residue with ethanol–acetone (1 : 1) and repeated recrystallisation of the extracted material from ethanol (6 ml.)–acetone (15 ml.) gave the pure (−)-base (0·34 g.), m. p. 210°, $[\alpha]_D^{20}$ −24·33° (*c*, 2·014 in EtOH). This did not depress the m. p. of an authentic specimen, kindly provided by Dr. Mitchell.

The (+)-base was similarly prepared from the first mother-liquor of the preparation of the (−)-base dibenzoyl-(+)-tartrate. The pure isomer (0·54 g.) [from ethanol–acetone (1 : 1)] had m. p. 211°, $[\alpha]_D^{20}$ +24° (*c*, 2·0 in EtOH), and depressed the m. p. of Mitchell's specimen to 180°.

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