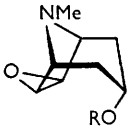
698. *The Stereochemistry of the Tropane Alkaloids. Part XII.* The Total Synthesis of Scopolamine.*

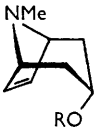
By P. Dobó, G. Fodor, G. Janzsó, I. Koczor, J. Tóth, and I. Vincze.

A stereospecific synthesis of scopolamine has been achieved, starting from tropane-3α,6β-diol, which was converted into 3α-acetoxytrop-6-ene, and thence into *O*-acetylscopine (3α-acetoxy-6β,7β-epoxytropane). Hydrolysis, followed by acylation with *O*-acetyltropoyl chloride and hydrolysis, gave (±)-scopolamine, the resolution of which has been described earlier. The biogenesis of hyoscyamine and scopolamine is discussed.

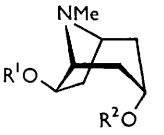
Earlier work has indicated [1] that (—)-hyoscine,[2] an alkaloid of *Hyoscyamus muticus* and *H. niger*, is an optically active form of (±)-scopolamine, an alkaloid [3] of *Scopolia atropoides*, the bases being respectively optically active and racemic forms of 6,7-epoxy-3-tropoyloxytropane (I; R = CO·CHPh·CH_2·OH).[1] The alkamine common to the two alkaloids was obtained later,[4] but could not be reconverted into scopolamine. The respective β- and α-orientations of the epoxide bridge and the acyloxy-group in the alkaloids have been proved by stereochemical considerations [5] of the conversion [4] of scopine into oscine, and by hydrogenolysis [6] of scopolamine into (—)-tropane-3α,6β-diol.[7]



(I)



(II)



(III)

Robinson-type tropinone syntheses using epoxysuccindialdehyde [8] and maleic dialdehyde [9] as the aldehyde components are attended by difficulties. It seemed to us that a valuable intermediate in the synthesis of scopolamine would be trop-6-en-3α-ol (II; R = H), a suggested common intermediate for the biogenesis of several tropane alkamines.[10] This compound should be obtainable by selective dehydration of tropane-3α,6β-diol (III; $R^1 = R^2 = H$), available synthetically,[11] and should be epoxidisable to (I; R = H).

We have now effected the total synthesis of scopolamine by a route involving these intermediates.[12] 3α-Acetoxytrop-6-ene (II; R = Ac) has been obtained by two procedures.[12a] In the first of these 6β-phenylcarbamoyloxytropan-3α-ol (III; R^1 = Ph·NH·CO, R^2 = H), obtained [13] from 6β-phenylcarbamoyloxytropinone, gave, on treatment with acetyl chloride, 3α-acetoxy-6β-phenylcarbamoyloxytropane (III; R^1 = Ph·NH·CO, R^2 = Ac), which on distillation *in vacuo* afforded 3α-acetoxytropan-6β-ol

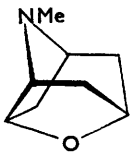
* Part X, Fodor, Tóth, and Vincze, *J.*, 1957, 1349; Part XI, Halmos, Kovács, and Fodor, *J. Org. Chem.*, 1957, **22**, 1699.

[1] For a detailed review see H. L. Holmes, in Manske and Holmes, "The Alkaloids," Academic Press, Inc., New York, 1950, Vol. I, pp. 302—305.
[2] Ladenburg, *Annalen*, 1881, **206**, 274.
[3] Schmidt, *Arch. Pharm.*, 1892, **230**, 207.
[4] Willstätter and Berner, *Ber.*, 1923, **56**, 1079.
[5] Fodor, *Nature*, 1952, **170**, 278; Meinwald, *J.*, 1953, 712; Cookson, *Chem. and Ind.*, 1953, 337.
[6] Fodor, Kovács, and Meszáros, *Research*, 1952, **5**, 534; Fodor and Kovács, *J.*, 1953, 2341.
[7] For the configuration of tropane-3α,6β-diol see Mitchell and Trautner, *J.*, 1947, 1330; Fodor, Tóth, and Vincze, *Helv. Chim. Acta*, 1954, **37**, 907.
[8] Schöpf and Schmetterling, *Angew. Chem.*, 1952, **64**, 591.
[9] Preobrashenski, Rubtsov, Dankova, and Pavlov, *J. Gen. Chem.* (*U.S.S.R.*), 1945, **25**, 952.
[10] Cromwell, *Biochem. J.*, 1943, **37**, 707, 722, and previous publications.
[11] Stoll, Becker, and Jucker, *Helv. Chim. Acta*, 1952, **35**, 1263; Stoll, Lindenmann, and Jucker, *ibid.*, 1953, **36**, 1526.
[12] Cf. preliminary reports: (*a*) Fodor, Tóth, Koczor, and Vincze, *Chem. and Ind.*, 1955, 1260; (*b*) Fodor, Tóth, Koczor, Dobó, and Vincze, *ibid.*, 1956, 754.
[13] Vincze, Tóth, and Fodor, *J.*, 1957, 1349.

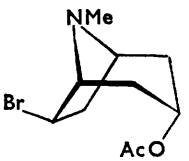
(III; R^1 = H, R^2 = Ac). The same monoester was also obtained by selective Kunz hydrolysis of 3α,6β-diacetoxytropane (III; R^1 = R^2 = Ac), and its toluene-*p*-sulphonate ester when heated with collidine yielded 3α-acetoxytrop-6-ene (II; R = Ac).

The second route involved dehydration of (±)-tropane-3α,6β-diol (III; R^1 = R^2 = H) with phosphoryl chloride to (±)-3α,6α-epoxytropane (IV),[14] by an S_N2i mechanism.[15] Acetobromolysis of the oxide (IV) afforded 3α-acetoxy-6β-bromotropane (V); dehydrobromination then yielded the acetate (II; R = Ac). The constitution of the last was proved by hydrogenation to 3α-acetoxytropane;[12a] this provides a direct correlation of the 3-hydroxyl groups of scopolamine and valeroidine with tropine. Alkaline or acid hydrolysis of 3α-acetoxytrop-6-ene gave trop-6-en-3α-ol (II; R = H).

Treatment of the acetate (II; R = Ac) with monoperphthalic acid afforded the *N*-oxide as the major product;[12a] an excess of the per-acid gave a poor yield of *O*-acetylscopine *N*-oxide (VI).[12b] The latter on hydrogenation yielded 3α-acetoxytropan-6β-ol (III; R^1 = H, R^2 = Ac), indicating *exo*-formation of the epoxide ring. Under acidic conditions no epoxidation occurred, owing to deactivation of the ethylenic bond by the positively charged tropanium nitrogen atom.[15]



(IV)



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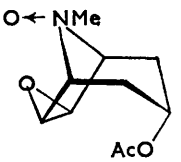

(VI)

The required epoxidation was finally effected by using trifluoroperacetic acid [16] which, with 3α-acetoxytrop-6-ene trifluoroacetate in methylenechloride–acetonitrile, gave *O*-acetylscopine (I; R = Ac), identified as the picrate.[17] A better yield was obtained by epoxidation with formic acid and 80% hydrogen peroxide. The epoxide and unchanged olefin were separated by paper chromatography in butanol–N-hydrochloric acid. An authentic specimen of *O*-acetylscopine was prepared [12b] from scopine [4] (I; R = H) by treatment of its hydrochloride with acetyl chloride.

The synthesis was completed by a Kunz [18] hydrolysis of *O*-acetylscopine to scopine (small amounts of oscine were formed simultaneously [12b]). Acylation of the carbinol base with (±)-*O*-acetyltropoyl chloride proved to be difficult. When the free base was used, only *O*-acetyloscine [19] was obtained, identified as its picrate. The observation that (−)-*O*-acetyltropoyl chloride was easily racemised by bases, possibly because of the formation of a keten as an intermediate product, prompted us to attempt the acylation of scopine hydrochloride. However, heating the salt with (±)-*O*-acetyltropoyl chloride [20] in chloroform solution gave no *O*-acetylscopolamine; paper chromatography showed the presence of some *O*-acetylscopine and a more mobile compound.* Eventually it was found that in nitrobenzene at 65° scopine hydrochloride and an excess of the acid chloride gave *O*-acetylscopolamine [21] (I; R = CO·CHPh·CH_2·OAc), accompanied by the same unidentified compound. The product was separated by partition chromatography on cellulose, with elution with butanol–N-hydrochloric acid, and then hydrolysed by acid to

* A detailed paper-chromatographic study of this and other acylation experiments is being carried out by Dr. O. Kovács.

[14] (−)-Tropene oxide has been described by Wolfes and Hromatka, *Merck's Jahresber.*, 1934, **47**, 45.
[15] Fodor, Lecture, Leipzig, October 23, 1955; *Angew. Chem.*, 1956, **68**, 153; *Tagungsber. Chem. Ges. DDR.*, 1955, 105.
[16] Emmons, *J. Amer. Chem. Soc.*, 1954, **76**, 348; Emmons and Pagano, *ibid.*, 1955, **77**, 89.
[17] Fodor, Lecture, Univ. Münster, November 3, 1955; *Angew. Chem.*, 1956, **68**, 188.
[18] Kunz and Hudson, *J. Amer. Chem. Soc.*, 1926, **48**, 1982.
[19] Schmidt, *Arch. Pharm.*, 1905, **243**, 559.
[20] Wolffenstein and Mamlock, *Ber.*, 1908, **41**, 723.
[21] Hesse, *J. pr. Chem.*, 1901, **64**, 353.

(±)-scopolamine (I; R = CO·CHPh·CH_2·OH), further purified by the same technique. The picrate [22] and tetraphenylborate of the synthetic product proved to be identical with the same derivatives of (±)-scopolamine.

Since (±)-scopolamine has been resolved into (+)- and (−)-hyoscine,[23 24] this synthesis is also a total synthesis of hyoscine.

Future work will be concerned with attempts to expoxidise 3α-tropoyloxytrop-6-ene (II; R = CO·CHPh·CH_2·OH) directly to scopolamine,[25] and with investigations concerning the rôle of 3-acyloxytrop-6-enes in biosynthesis. The ability of young *Datura ferox* plants to oxidise hyoscyamine to hyoscine [26] prompts us to study the effect of administering 3-acyloxytrop-6-enes to the plants.

Experimental

M. p.s are corrected.

3α-Acetoxy-6β-phenylcarbamoyloxytropane (III; R^1 = Ph·NH·CO, R^2 = Ac).—Acetyl chloride (85 ml.) was added to a suspension of 6β-phenylcarbamoyloxytropan-3α-ol (III; R^1 = Ph·NH·CO, R^2 = H) (276 g.) in dry chloroform (450 ml.) with cooling. After 4 hr. at 80° the crystalline *hydrochloride* was collected at the pump and washed thoroughly with acetone–ether (1 : 1). The yield was 312·5 g., and the m. p. 251—252° (decomp.). Evaporation of the filtrate afforded a second crop (20 g.; total yield 94%) (Found: C, 57·1; H, 6·1; N, 7·8; Cl, 9·8, 9·9. $C_{17}H_{23}O_4N_2Cl$ requires C, 57·5; H, 6·5; N, 7·9; Cl, 10·0%).

The salt was dissolved in water (1·4 l.), basified with potassium hydroxide (140 g.), and extracted with chloroform (5 × 250 ml.). The combined extracts were dried (Na_2SO_4) and evaporated, giving the free base (295 g.) as an oil.

3α-Acetoxytropan-6β-ol (III; R^1 = H, R^2 = Ac).—(*a*) The foregoing phenylurethane (295 g.) was pyrolysed at 205—250°/1—2 mm., decomposition being complete after ten such treatments. The oil so obtained (118·53 g.) was triturated with acetone, whereby crystallisation was induced. Recrystallisation from acetone gave colourless needles of *3α-acetoxytropan-6β-ol* (107·75 g., 63%), m. p. 117° (Found: C, 60·6; H, 9·0; N, 6·8. $C_{10}H_{17}O_3N$ requires C, 60·3; H, 8·6; N, 7·0%).

(*b*) 3α,6β-Diacetoxytropane (III; R^1 = R^2 = Ac) (24 g.) in acetone (700 ml.) was treated with 0·1N-sodium hydroxide (1·7 l.) and kept at 30° for 65 min. The solution was neutralised with N-hydrochloric acid (120 ml.) and, after evaporation of the acetone, adjusted to pH 10 with aqueous potassium hydroxide. Chloroform-extraction (total volume 650 ml.) gave, after evaporation, a partially crystalline mass. The crystals of the monoacetate (24 g.) were collected and washed with ether (yield 15·6 g., 78%; m. p. 117°).

3α-Acetoxy-6β-toluene-p-sulphonyloxytropane (III; R^1 = *p*-MeC_6H_4·SO_2, R^2 = Ac).—3α-Acetoxytropan-6β-ol (107·7 g.) and toluene-*p*-sulphonyl chloride (51·2 g.) were dissolved in chloroform (100 ml.) and kept at 100° for 3 hr. The solution was then diluted with chloroform (200 ml.) and shaken with water (5 × 50 ml.), and the combined aqueous layers were extracted with chloroform (50 ml.). The dried (Na_2SO_4) chloroform extracts were evaporated and the residue was triturated with ether. The crystals were collected (81 g., 84%); recrystallisation from acetone–ether gave plates, m. p. 80° (Found: N, 4·3. $C_{17}H_{23}O_5NS$ requires N, 4·0%). Basification of the aqueous layers with potassium hydroxide (50 g.), followed by chloroform extraction (5 × 50 ml.), gave unchanged 3α-acetoxytropan-6β-ol (47 g.), m. p. 116°. The *picrate* of the toluene-*p*-sulphonic ester crystallised from absolute ethanol and had m. p. 223—224° (Found: N, 9·8; S, 5·2, 5·3. $C_{23}H_{26}O_{12}N_4S$ requires N, 9·6; S, 5·5%).

3α-Acetoxytrop-6-ene (II; R = Ac).—A few drops of dimethylaniline were added to a suspension of the above toluene-*p*-sulphonic ester (35·3 g.) in collidine (162 ml.), and the mixture was heated at 190° for 2 hr. in a sealed tube. Evaporation at 55°/1 mm. gave an oil which was taken up in chloroform (150 ml.) and extracted with 10% potassium carbonate solution (250 ml.) several times, then with water (50 ml.). The chloroform solution was decolorised with charcoal, dried (Na_2SO_4), and evaporated, leaving *3α-acetoxytrop-6-ene*, b. p. 57—63°/1 mm. (12·1 g.) (Found: C, 66·4; H, 8·7; N, 7·8. $C_{10}H_{15}O_2N$ requires C, 66·3; H, 8·3; N,

[22] Carr and Reynolds, *J.*, 1912, **101**, 946.
[23] King, *J.*, 1919, **115**, 476.
[24] Schukina, Okun, Yurigin, and Preobrashenski, *J. Gen. Chem.* (*U.S.S.R.*), 1940, **10**, 803.
[25] Fodor, Romeike, *et al.*, Lecture, XVIth Internat. Congress Pure Appl. Chem., Paris, July 19th, 1957; *Angew. Chem.*, 1957, **69**, 678.
[26] Romeike, *ibid.*, 1956, **68**, 124.

7·7%). On catalytic hydrogenation 0·98 mol. of hydrogen was absorbed, with the formation of 3α-acetoxytropane (tropanyl acetate) [picrate, m. p. and mixed m. p. 222° (decomp.) (Found: C, 46·5; H, 4·45; N, 13·7. Calc. for $C_{16}H_{20}O_9N_4$: C, 46·8; H, 4·4; N, 13·65%)]. The *picrate* of the tropene crystallised from ethanol in needles, m. p. 210—212° (Found: N, 13·7. $C_{16}H_{18}O_9N_4$ requires N, 13·7%).

3α,6α-*Epoxytropane* (IV).—(±)-Tropane-3α,6β-diol (25 g.) was mixed with phosphoryl chloride (250 ml.) at room temperature. After 1 hr. the solution was heated at 100° for a further hour, and the excess of phosphoryl chloride removed *in vacuo*. The residue was poured on crushed ice (250 g.), and the solution decolorised (charcoal), filtered, basified to pH 9 with 10N-sodium hydroxide, and saturated with potassium carbonate. The liberated oil was isolated with ether (total volume 300 ml.), and the extracts were dried and evaporated. The residual 3α,6α-epoxytropane distilled at 50°/1 mm. (15·6 g.), as a colourless oil. The *hydrobromide* was obtained from the base (24 g.) in dry benzene (200 ml.), by treatment with acetyl bromide (13 ml.) in benzene (50 ml.). The crystalline bromide so formed was collected, washed with benzene (10 ml.), and dissolved in ethanol (200 ml.). The solution was refluxed for 20 min., decolorised (charcoal), and treated with warm ether (200 ml.). The hydrobromide, which separated as prisms (30·15 g.), m. p. 280°, was collected (Found: Br, 36·6. $C_8H_{14}ONBr$ requires Br, 36·3%).

3α-*Acetoxy*-6β-*bromotropane* (V).—The above hydrobromide (15 g.) and acetyl bromide (60 ml.) were heated in a sealed tube at 110—120° for 4 hr. Excess of acetyl bromide was removed *in vacuo*, and the residue (30 g.) dissolved in water (75 ml.). The solution was decolorised, filtered, and basified with potassium hydroxide (30 g.), and the liberated oil isolated by means of chloroform (4 × 40 ml.). The dried extracts on evaporation afforded the bromo-base, b. p. 110—115°/1 mm. (12 g.). The *picrate* crystallised from ethanol in yellow leaflets, m. p. 196° (decomp.) (Found: Br, 16·1. $C_{16}H_{19}O_9N_4Br$ requires Br, 16·3%).

Dehydrobromination of the base (8 g.) in collidine (100 ml.) containing a few drops of diethylaniline at 180° for 7 hr. under nitrogen gave, after separation of the collidine hydrobromide and removal of the excess collidine by fractionation *in vacuo*, an oil which was taken up in chloroform. The solution was washed with potassium carbonate solution and water, dried, and evaporated, yielding 3α-acetoxytrop-6-ene, b. p. 58—60°/1 mm. (2·3 g.). The picrate had m. p. 212°, alone or mixed with 3α-acetoxytrop-6-ene picrate obtained *via* the toluene-*p*-sulphonic ester (see above). On catalytic hydrogenation 3α-acetoxytropane (picrate, m. p. and mixed m. p. 222°) was obtained.

Trop-6-*en*-3α-*ol* (II; R = H).—(*a*) 3α-Acetoxytrop-6-ene (0·1 g.) in acetone (10 ml.) was mixed with 0·5N-sodium hydroxide (2 ml.) and kept at room temperature for 4 days. After removal of the solvent the oily residue was mixed with 5% ethanolic picric acid (5 ml.). *Trop*-6-*en*-3α-*ol picrate* (0·26 g.), which separated, was collected; it recrystallised from ethanol in needles, m. p. 278° (Found: C, 45·6; H, 4·55; N, 15·5. $C_{14}H_{16}O_8N_4$ requires C, 45·65; H, 4·4; N, 15·2%).

(*b*) 3α-Acetoxytrop-6-ene (1·0 g.) was refluxed for 6 hr. with 2N-hydrochloric acid (50 ml.). The solution was evaporated to dryness *in vacuo*; absolute ethanol was added and the evaporation repeated. The residual 3α-*acetoxytrop*-6-*ene hydrochloride* separated from ethanol in needles, m. p. 257—260° (decomp.) (Found: C, 54·7; H, 8·3; N, 7·8. $C_8H_{14}ONCl$ requires C, 54·7; H, 8·0; N, 8·0%). The picrate had m. p. 273°.

3α-*Acetoxytrop*-6-*ene* N-*Oxide*.—3α-Acetoxytrop-6-ene (0·1 g.) in anhydrous chloroform (1 ml.) and acetone (1 ml.) was cooled in ice and treated with 10% ethereal monoperphthalic acid (1·2 ml.). After 10 min. at 0° a sample contained 0·5 mol. of per-acid, estimated iodometrically. After 10 hr. the solvent was removed, the remaining glass dissolved in 50% potassium carbonate solution (1 ml.), and the solution extracted with chloroform (10 × 1 ml.). The combined dried extracts were evaporated and the residue was converted into the *picrate*, m. p. 168° (Found: C, 45·2; H, 5·0. $C_{16}H_{18}O_{10}N_4$ requires C, 45·1; H, 4·3%). Reaction for 20 days gave an oil which on catalytic hydrogenation (uptake: 2 mols.) afforded 3α-acetoxytropan-6β-ol, m. p. and mixed m. p. 117° (see above).

O-*Acetylscopine* (I; R = Ac) *from* 3α-*Acetoxytrop*-6-*ene* (II; R = Ac).—(*a*) 3α-Acetoxytrop-6-ene (0·362 g.), dissolved in acetonitrile (2·4 ml.), was treated with trifluoroacetic acid (2·28 g.) and cooled to 0°. A 12% solution of trifluoroperacetic acid (2·2 ml.) was added dropwise with shaking, and the mixture kept at 5° for 8 days Analysis of a sample withdrawn after 5 days showed that 80% of the peracid had been consumed. 5% Alcoholic picric acid

(10 ml.) was added, and the crude picrate [0·52 g.; m. p. 210° (decomp.)] collected and refluxed with 96% ethanol (70 ml.). The undissolved portion (m. p. 218°) was collected and crystallised from dry ethanol (10 ml.). It had m. p. 222°, alone or mixed with *O*-acetylscopine picrate obtained from natural scopolamine *via* scopine (Found: C, 45·4; H, 4·4; N, 13·3. Calc. for $C_{16}H_{18}O_{10}N_4$: C, 45·1; H, 4·3; N, 13·1%). From the mother-liquors of the crystallisation was obtained 3α-acetoxytrop-6-ene picrate, m. p. and mixed m. p. 211°.

(*b*) 3α-Acetoxytrop-6-ene (1·15 g.) was mixed with 100% formic acid (3·6 ml.), and 81% hydrogen peroxide (3 ml.) was added. After 48 hr. at 20° further hydrogen peroxide (1 ml.) was added and the mixture kept for a further 5 days. After evaporation at 20°/10 mm. to 2 ml. the residue was chromatographed in butan-1-ol–N-hydrochloric acid (5 : 1; 1 l.) on a column (175 cm. long) of cellulose powder (150 g.; Whatman Standard Grade), a 110-tube automatic fraction-collector being used. Fractions 51—100 contained *O*-acetylscopine hydrochloride (derived picrate m. p. 229°). Later fractions contained unchanged 3α-acetoxytrop-6-ene.

O-*Acetylscopine* (I; R = Ac) *from Scopolamine* (I; R = CO·CHPh·CH_2·OH).—Scopolamine was hydrolysed to scopine, m. p. 72°, as described by Willstätter and Berner.[4] Scopine (0·6 g.) was refluxed with acetyl chloride (6 ml.) for 5 hr. Evaporation gave O-*acetylscopine hydrochloride*, prisms, m. p. 231° (Found: C, 51·2; H, 7·7; N, 5·7; Cl, 14·8. $C_{10}H_{16}O_3NCl$ requires C, 51·4; H, 6·9; N, 6·0; Cl, 15·2%). The picrate had m. p. 222°.

Scopine from O-*Acetylscopine*.—(*a*) *O*-Acetylscopine was obtained from the hydrochloride by basification and chloroform-extraction. The base (1·025 g.) in acetone (50 ml.) was mixed with 0·5N-sodium hydroxide (10 ml.), and the solution filtered and kept at 25° for 10 days. Evaporation *in vacuo*, followed by treatment with ethanol (5 ml.) and 5% ethanolic picric acid, gave scopine picrate (0·638 g.), m. p. 225—232°. The picrate (0·6 g.), suspended in 96% ethanol (100 ml.), was shaken with Dowex No. 1 resin (15 g.) for 1 hr. The resin was removed and the filtrate evaporated at 35° to an oily base (0·368 g.), which was taken up in ether; the solution was dried (Na_2SO_4) and evaporated. The partly crystalline residue was collected and washed with ether, giving scopine, m. p. 72°.

(*b*) *O*-Acetylscopine (0·64 g.) in acetone (4 ml.) was treated with 0·1N-sodium hydroxide and kept at 25° for 18 hr. It was then exactly neutralised with 0·1N-hydrochloric acid and concentrated to 20 ml. Aqueous ammonia was added to pH 9·5 and the solution extracted with chloroform (5 × 10 ml.). Evaporation of the dried extracts gave a crystalline residue, which on recrystallisation from ether gave scopine, m. p. 74—76° (0·16 g., 32%).

Scopolamine from Scopine.—Scopine hydrochloride (1 g.) was powdered, suspended in nitrobenzene (7 ml.), and treated with *O*-acetyltropoyl chloride (6·5 ml.), the mixture being stirred at 50° for 38 hr. Unchanged scopine hydrochloride (0·32 g.) was removed by filtration, and the filtrate diluted with chloroform (10 ml.) and extracted with water (5 × 10 ml.). The aqueous solution, adjusted to pH 6, was extracted with chloroform (5 × 10 ml.), and the dried extracts were evaporated, leaving a viscous oil (1·15 g.). This was dissolved in butanol–hydrochloric acid and purified by chromatography on cellulose (60 g., in a column 2 m. long), as described above. Fifteen fractions of 10 ml. each, and the remainder of 5 ml., were collected. Fractions 16—25 contained *O*-acetylscopolamine; they were combined and evaporated at 50°/5 mm., leaving a yellowish oil (0·35 g.). A solution of this in N-hydrochloric acid (10 ml.) was kept at 30° for 9 hr., then evaporated to dryness at 20° *in vacuo*. The oily residue (0·24 g.) of scopolamine hydrochloride was purified by chromatography on cellulose as described above. Fractions 42—48 showed a strong mydriatic effect; they were combined and evaporated, and the residual salt treated with picric acid, giving crystalline scopolamine picrate, m. p. 175·5—176·5°, identical (mixed m. p.) with natural scopolamine picrate (Found: C, 52·1; H, 5·0; N, 11·1. Calc. for $C_{23}H_{24}O_{17}N_4$: C, 51·9; H, 4·5; N, 10·5%). The *tetraphenylborate* separated from acetone as a microcrystalline powder, m. p. and mixed m. p. 106° (decomp.) (Found: C, 78·6; H, 7·1. $C_{41}H_{42}O_4NB$ requires C, 79·0; H, 6·8%).

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Laboratory for Stereochemical Research, Hungarian Academy of Sciences, Budapest, Hungary.
Department of Organic Chemistry, The University, Szeged, Hungary.

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