ml.). A gummy impurity separated and after a few minutes was easily removed by decantation. The ether layer was washed in succession with water, sodium bicarbonate solution, water, and saturated salt solution and dried through sodium sulfate to give 25 g. (64% crude yield) of the nitrile as a yellow oil; ultraviolet spectrum: 218 (27,350); 273 (6,500); 295 (4,750); 306 (3,800); infrared spectrum: C≡N: 2240 (m); 2800? (w).

5-Methoxytryptamine. A solution of the crude 5-methoxyindole-3-acetonitrile (19 g., 0.102 mole) in 200 ml. of ether was added during 10 min. to a solution of lithium aluminum hydride (19 g.) in 1200 ml. of ether under nitrogen.

The resulting thick suspension was refluxed for 3 hr. and allowed to stand overnight. The mixture was cooled in ice and decomposed in succession with 20 ml. of water, 20 ml. of 15% aqueous sodium hydroxide, and 60 ml. of water. The resulting suspension was filtered and the cake washed well with ether.

The colorless filtrate was extracted with 5% hydrochloric acid (5 × 100 ml.). Some gummy material precipitated and was easily removed by decantation. The clear yellow extract was cooled in ice and made basic with 30% potassium hydroxide. The resulting oil was extracted three times with ether (total 500 ml.). The ether was washed with water followed by saturated salt solution; it was then dried through sodium sulfate and evaporated under reduced pressure to give a yellow solid, m.p. 119–122° (13.5 g.; 70% yield). Crystallization from benzene gave pale yellow prisms, m.p. 121.5–122.5° (lit.,[9] m.p. 121–122°); ultraviolet spectrum: 223 (25,250); 277 (6,300); 296 (5,050); f 308 (3,450); infrared spectrum: NH: 3310, 3250, 3080; aromatic C=C: 1620, 1585, 1495; C—O: 1240, 1220; aromatic substitution: 860, 850, 813, 793.

N-Acetyl-5-methoxytryptamine (I). 5-Methoxytryptamine (7.6 g.) was added to 35 ml. of acetic anhydride at room temperature. The resulting brown solution became warm and was allowed to stand under nitrogen for 23 hr. Water (200 ml.) was added and the mixture was stirred for 0.5 hr. It was then cooled in ice and neutralized partially by addition of solid sodium carbonate (28 g.). The resulting suspension was filtered and the solid washed with water. It was crystallized from benzene to give 7.6 g. (81.5% yield) of pale yellow leaflets, m.p. 116–118° unchanged on further recrystallization; ultraviolet spectrum: 223 (27,550); 278 (6,300); f. 297 (5,150); f. 308 (3,500); infrared spectrum: NH: 3240; C=O: amide I, 1627; amide II, 1555; aromatic C=C: 1620, 1587, 1492; C—O: 1217, 1180; aromatic substitution: 828, 810, 800.

Anal. Calcd. for $C_{13}H_{16}N_2O_2$: C, 67.22; H, 6.94; N, 12.06. Found: C, 67.27; H, 6.79; N, 11.89.

5-Methoxy-β-indoleninideniumethyl nitronate. A solution of 22 g. of ammonium acetate, 6.0 ml. of acetic anhydride, and 17.6 ml. of acetic acid was stirred for 20 min. and a mixture of 30.0 g. (0.18 mole) of 5-methoxyindole-3-aldehyde (Regis Chemical Co.), 100 ml. of nitromethane, and 120 ml. of acetic acid was added. The solution was brought to reflux and 14 g. of sodium acetate was added. The mixture was refluxed for 2 hr. while 20 ml. of acetic anhydride was added dropwise. The solution was allowed to cool while 45 ml. of water was added dropwise. The mixture was refrigerated and filtered. After recrystallization from alcohol the product weighed 9.6 g. (25%) and melted at 157–158°; infrared spectra: NH/OH: 3215; C=C: 1612, 1585; $-N\langle^{O}_{OH}$: 1297, 1255, 1212, 979; C—O: 1108, 1074; aromatic substitution: 954, 920, 815, 800, 783, 689; ultraviolet spectrum: 224 (19,700); 283 (9100); f. 292 (8250); f. 302 (6550); 405 (20,200).

Anal. Calcd. for $C\alpha\alpha H_{10}N_2O_3$: C, 60.54; H, 4.61; N, 12.84. Found: C, 60.07; H, 4.30; N, 12.65.

5-Methoxytryptamine. A solution of 6.0 g. (0.027 mole) of the nitronate and 50 ml. of tetrahydrofuran was added dropwise to a refluxing mixture of 5.4 g. (0.14 mole) of lithium aluminum hydride and 100 ml. of tetrahydrofuran. The mixture was refluxed for 4 hr. after the addition was complete. It was then cooled and the excess lithium aluminum hydride was decomposed with wet ether followed by concd. potassium hydroxide solution. The solution was decanted and the residue washed thoroughly with ether and added to the original filtrate. The filtrate was dried over potassium carbonate and concentrated. The residue was dissolved in ethyl acetate, refluxed with Nuchar-190-N, and filtered. An approximately equal volume of Skellysolve B was added and the solution was refrigerated overnight. Filtration yielded 1.3 g. (27%) of product which melted at 115–117°. It was identical with the sample obtained by the gramine procedure (infrared, ultraviolet) and on acetylation gave I.

5-Methoxyindole-3-acetonitrile was prepared from the Grignard derivative with chloroacetonitrile.[8]

5-Methoxyindole-3-acetic acid was prepared by hydrolysis of the crude nitrile with aqueous methanolic potassium hydroxide.[12] The acid melted at 145–146°; ultraviolet spectrum: 221 (25,150); 276 (6,300); 296 (4,800); f. 308 (3,400); infrared spectrum: NH: 3,330; OH (carboxyl): 2640, 2560; C=O: 1690, 1670; C—O: 1215, 1175.

Anal. Calcd. for $C_{11}H_{11}NO_3$: C, 64.38; H, 5.40; N, 6.82. Found: C, 64.20; H, 5.13; N, 6.62.

Methyl 5-methoxyindole-3-acetate. 5-Methoxy-3-indoleacetic acid (1.0 g.; 0.005 mole) was suspended in 100 ml. of ether and treated with three equivalents of diazomethane in ether. After 2 hr. 1.0 ml. of acetic acid was added. The solution was washed with water, sodium bicarbonate, and then with water. The solution was dried over potassium carbonate and concentrated to yield a dark red oil. This oil was subjected to distillation and the material boiling below 250°/0.03 mm. was collected. The resulting distillate solidified upon scratching. After crystallization from 50% benzene–Skellysolve B the product weighed 0.4 g. (35%) and melted at 73–74°; ultraviolet spectrum: 219 (25,800); 275 (6,350); f. 295 (4,850); f. 307 (3,500); infrared spectrum: NH: 3350; C=O: 1721; aromatic C=C: 1625, 1591, 1495; C—O: 1250, 1221, 1184, 1100, 1064, 1030; aromatic substitution: 825, 806.

Anal. Calcd. for $C_{12}H_{13}NO_3$: C, 65.74; H, 5.98; N, 6.39. Found: C, 65.61; H, 5.83; N, 6.73.

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Tropine DL-α-Methyltropate (Methylatropine) and Its Optical Antipodes

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The loss of physiological activity on the ready racemization of natural *l*-hyoscyamine (I R= H)[1–4] led us to search for more stable active anal-

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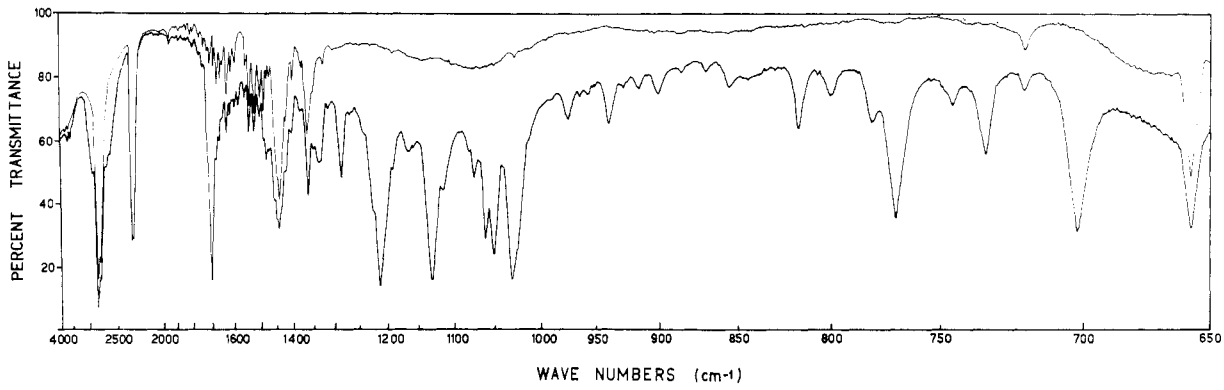


Fig. 1. Tropine *dl*-α-methyl tropate

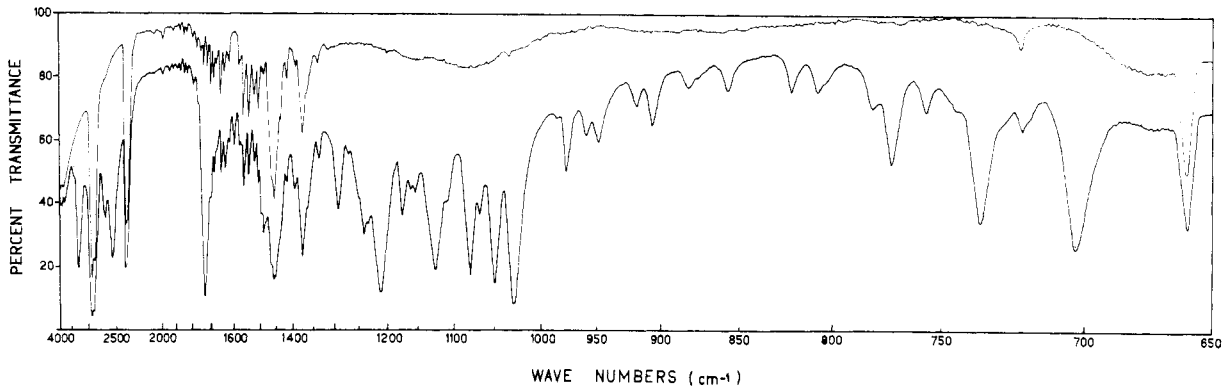
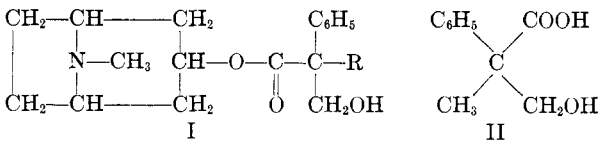


Fig. 2. Tropine (−)-α-methyl tropate

ogues. We have now resolved *dl*-α-methyltropic acid (II) the synthesis of which we recently described.[5,6a] The acids (*dl*, *d* and *l*) were converted to their *O*-acetyl chlorides, and these treated with tropine. Partial hydrolysis of the resulting ester



gave *dl*-methylatropine and the optically active α-methylhyoscyamines (I R = CH_3). Foster and Ing, who at first claimed to have synthesized α-methylatropine,[7] later recognized that they had actually synthesized the α-benzyl lactate of tropine.[8] Both racemic and optically active I (R = CH_3) are white crystals. Their infrared spectra are reported in Figs. 1 and 2. The optical dispersion curve of a 1% aqueous solution of (+) - methylhyoscyamine hydrochloride shows a gradual increase: at 700 mμ, 3°; at 500 mμ, 11°; 400 mμ, 23.5°; 375 mμ, 29°. The pharmacological activity of this product will be reported by Dr. G. Maffii and Cows. From the preliminary trials[9] α-methyl atropine seems as active as atropine and its (−) antipode [(−)-methylhyoscyamine] displays a higher activity than the (+) antipode.

(3) A. R. Cushny, *J. Pharmacol.*, **15**, 105 (1920).

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(6) (a) E. Testa, L. Fontanella, G. F. Cristiani and F. Fava, *Ann.*, **619**, 47 (1958). (b) This acid has also been prepared in very poor yield by H. E. Zaugg and R. W. De Net [*J. Org. Chem.*, **23**, 498 (1958)].

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(8) R. Foster and H. R. Ing, *J. Chem. Soc.*, 925 (1957).

EXPERIMENTAL

Resolution of α-methyltropic acid (II) *into its optical antipodes.* (a) (−)-*α-Methyltropic acid.* To 100 g. of *dl*-α-methyltropic acid,[5,6] m.p. 89–90°, and 185 g. of quinine free base dissolved in 450 ml. of warm absolute ethanol, was added 450 ml. of distilled water and the mixture heated for 5 min. on a boiling water bath. After 24 hr. at room temperature the crystalline precipitate was collected by suction, washed with 50% ethanol and dried: yield 118 g. of quinine (−)-α-methyltropate, m.p. 179.5°, $[\alpha]_D^{20}$ −120.7° (*c* = 2, ethanol). The recrystallization from 460 ml. of absolute ethanol and 460 ml. of distilled water gave 81.3 g. melting at 182–183°; $[\alpha]_D^{20}$ −123.4 (*c* = 2, ethanol). This product was further purified through a crystallization from 2350 ml. of a 9:1 mixture of ethyl acetate–95% ethanol with the addition of charcoal. The mixture was allowed to stand overnight at room temperature, then filtered. Yield, 60.5 g., m.p. 185–186°; $[\alpha]_D^{20}$ −121° (*c* = 2, ethanol). Further recrystallizations from different solvents did not raise the melting point or change the specific rotation value.

Anal. Calcd. for $C_{20}H_{24}N_2O_2;C_{10}H_{12}O_3$: N, 5.55. Found. N, 5.54.

The quinine (−)-α-methyltropate (60 g.) was suspended in 400 ml. of water and acidified to *p*H 1 with hydrochloric

(9) G. Maffii, personal communication.

acid under cooling. The solution was extracted three times with ethyl ether; the ether extracts were washed with water, dried over sodium sulfate, and evaporated to dryness. The oily residue crystallized on standing; on recrystallization from 1800 ml. of benzene–petroleum ether (1:1) 15.8 g. of (−)-α-methyltropic acid were obtained, m.p. 89–90°; $[\alpha]_D^{20}$ −28.3° (*c* = 2, ethanol).

Anal. Calcd. for $C_{10}H_{12}O_3$: C, 66.60; H, 6.71. Found: C, 66.85; H. 6.87.

(b) (+)-*α-Methyltropic acid.* To a warm solution of 13.51 g. of *dl*-α-methyltropic acid,[5,6] m.p. 89–90°, in 54 ml. of absolute ethanol was added 20.6 g. of brucine free base in 54 ml. of warm water. The mixture was refluxed until complete solution was obtained, then allowed to stand overnight. The precipitate, 10 g., was collected by suction, dried *in vacuo* and recrystallized from 250 ml. of a 1:1 mixture of ethyl acetate–95% ethanol with the addition of charcoal. After standing some hours 4.6 g. of brucine (+)-α-methyltropate were collected; m.p. 209–212°; $[\alpha]_D^{20}$ −19.22° (*c* = 2, ethanol).

Anal. Calcd. for $C_{23}H_{26}N_2O_4{\cdot}C_{10}H_{12}O_3$: N, 4.87. Found: N, 5.11.

The brucine (+)-α-methyltropate may also be prepared from the mother liquors of the first crystallization of quinine (−)-α-methyltropate after separating the free acid by acidification.

The brucine (+)-α-methyltropate (3.8 g.) was treated as described above for quinine (−)-α-methyltropate. The crude product was recrystallized from 60 ml. of benzene–petroleum ether (1:1) with addition of charcoal. Yield 0.5 g. of colorless needles melting at 88–90°; $[\alpha]_D^{20}$ +27° (*c* = 2, ethanol).

Anal. Calcd. for $C_{10}H_{12}O_3$: C, 66.60; H, 6.71. Found: C, 66.46; H, 6.69.

β-Acetoxy-α-methyl-α-phenylpropionyl chlorides. Example for dl-derivative. A mixture of 13.5 g. of *dl*-α-methyltropic acid and 27 ml. of acetyl chloride was refluxed for 0.5 hour, then the excess of acetyl chloride was removed *in vacuo*. The oily residue was treated with 70 ml. of thionyl chloride and refluxed 1 hr. The excess thionyl chloride was distilled and the residue distilled from a Claisen flask to give 11.2 g. of product, b.p. 113–116°/1 mm. The distilled compound solidified on standing and was recrystallized from 70 ml. of petroleum ether: yield 10.6 g. (59%), m.p. 66–69°.

Anal. Calcd. for $C_{12}H_{13}ClO_3$: Cl, 14.74. Found: Cl, 14.51.

The (+)- and (−)-derivative were prepared, starting from the (+)- and (−)-α-methyltropic acid respectively, as described for the *dl*-derivative. The (+)- and (−)-isomers were not distilled from the Claisen flask and isolated in a pure state but employed as such for the following condensation with tropine.

α-Methylatropine (tropine dl-α-methyltropate). *dl*-β-Acetoxy-α-methyl-α-phenylpropionyl chloride (5.8 g.) and tropine free base[10] (4.2 g.), thoroughly mixed, were heated for 5 hr. at 150°. The mixture turned to brown and gas was evolved. After cooling to room temperature, the mixture was treated with 60 ml. of warm water, then with charcoal, and filtered from the scanty undissolved residue. The filtrate was adjusted to *p*H 9 with a saturated solution of sodium carbonate, extracted with ethyl ether and the ether extract dried over sodium sulfate and filtered. The filtrate was made acidic to Congo red by treatment with a saturated ether solution of hydrogen chloride. A thick oil separated, which was decanted from the ether and dissolved in 20 ml. of water. Two drops of 10% hydrochloric acid were added to this solution and the mixture was allowed to stand 15 hr. at room temperature, in order to hydrolyze the *O*-acetyl group. A saturated solution of sodium carbonate was then added, the separated oil extracted with ethyl ether, dried over sodium sulfate, and concentrated to a final volume of 20 ml. On cooling and rubbing α-methylatropine precipitated in the form of white fine crystals. Yield 0.9 g.; m.p. 131–133°.

Anal. Calcd. for $C_{18}H_{25}NO_3$: C, 71.25; H, 8.30; N, 4.61. Found: C, 71.04; H, 8.29; N, 4.79.

(−)-*α-Methylhyoscyamine [tropine (−)-α-methyltropate].* A mixture of 3.74 g. of tropine free base, 6.24 g. of (−)-β-acetoxy-α-methyl-α-phenylpropionyl chloride and 4 ml. of anhydrous toluene was heated for 4 hr. at 120–125°, then cooled, treated with 65 ml. of water and acidified to *p*H 1 with 10% hydrochloric acid. The mixture was extracted with ethyl ether,, the aqueous layer adjusted to *p*H 8.3 with a saturated solution of sodium carbonate and extracted with ethyl ether. This ether extract was dried over sodium sulfate, and acidified to *p*H 1 with a saturated ether solution of hydrogen chloride. The ether was decanted and the oily residue treated with 35 ml. of water, acidified with 5 drops of 10% hydrochloric acid, and allowed to stand 15 hr., to hydrolyze the *O*-acetyl group. The mixture was adjusted to *p*H 8.5 with a saturated solution of sodium carbonate, extracted with ethyl ether, the extract washed with water, dried over sodium sulfate and made acidic with a saturated ether solution of hydrogen chloride. The ether was decanted, the residual oil treated with boiling ethyl acetate with the addition of charcoal and filtered. After standing some days 0.470 g. of crystalline (−)-α-methylhyoscyamine hydrochloride were collected; m.p. 210–212°; $[\alpha]_D^{20}$ −6.8° (*c* = 1, water).

Anal. Calcd. for $C_{18}H_{25}NO_3{\cdot}HCl$: C, 63.51; H, 7.42; N, 4.12; Cl, 10.4. Found: C, 64.01; H, 7.50; N, 4.09; Cl, 10.2.

(+)-*α-Methylhyoscyamine [tropine (+)-α-methyltropate]* was prepared exactly as described for (−) isomer starting from 3.99 g. of tropine free base, 6.63 g. of (+)-β-acetoxy-α-methyl-α-phenylpropionyl chloride and 4 ml. of anhydrous toluene. Yield, 0.735 g. of crystalline (+)-α-methylhyoscyamine hydrochloride, m.p. 210–211.5°: $[\alpha]_D^{20}$ +7.3° (*c* = 1, water).

Anal. Calcd. for $C_{18}H_{25}NO_3{\cdot}HCl$: C, 63.61; H, 7.42; N, 4.12; Cl, 10.4. Found: C, 63.49; H, 7.95; N, 3.70; Cl, 10.85.

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(10) Fluka, A. G., Buchs (Switzerland).

Autoxidation of Trialkylboranes

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It has been postulated by Johnson and Van Campen[1] that the oxidation of trialkylboranes to the corresponding alkylboronates (II) proceeds through an intermediate (I) containing a boron

(1) J. R. Johnson and M. G. Van Campen, *J. Am. Chem. Soc.*, **60**, 121 (1938).