Synthesis of Optically Active 10-Methoxy- and 10-Hydroxyaporphines from Apomorphine

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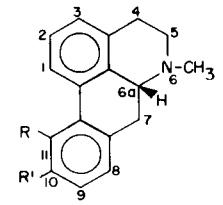
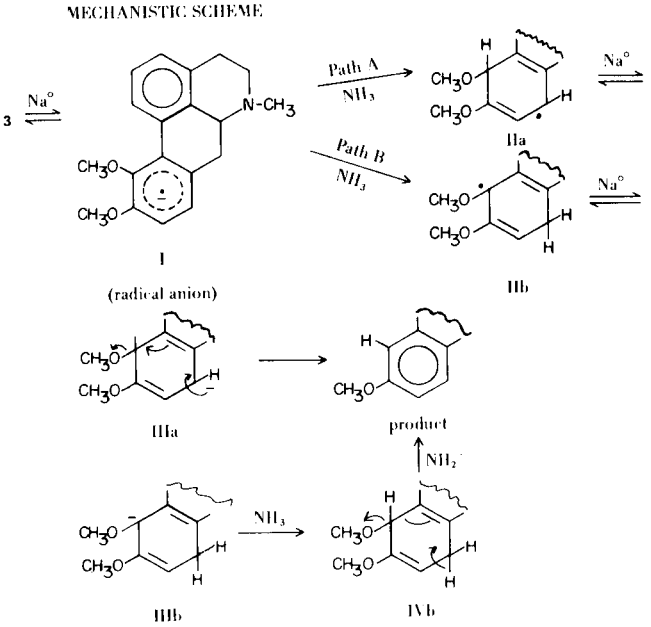
Optically active samples of the title compounds were desired to determine agonistic and/or antagonistic activity in an *in vitro* adenylate cyclase preparation of rat *corpus striatum*, and as inhibitors of striatal synaptosomal tyrosine hydroxylase. Racemic 10-methoxyaporphine (±**4**) has been previously prepared (1) in three steps by utilizing the method of Gadamer for the synthesis of aporphine (**1**). This three-step procedure provides only racemic 10-methoxyaporphine (±**4**) in ten percent yield.

It seemed probable that optically active 10-methoxyaporphine (**4**) could be prepared directly from optically active *O,O'*-dimethylapomorphine (**3**) by treating the latter with sodium in liquid ammonia. Hydrogenolysis of the C-11 methoxyl group would be in accord with a contention of Shamma (2) that a C-11 methoxyl group on an aporphine should be hydrogenolyzed by this reaction. Shamma's contention is based on the observation that similarly located C-1 methoxy groups are hydrogenolyzed by the metal-ammonia reagent. In addition, under these conditions, the chiral center at C-6a would not be racemized and therefore afford the desired product with a configuration identical (3,4) to (6a*R*)-(-)-apomorphine (**2**). Likewise, optically pure 10-hydroxyaporphine (**5**) could be obtained by cleavage of **4** with 48 percent hydrobromic acid.

Results.

Treatment of **3** with sodium in liquid ammonia afforded the expected optically active 10-methoxyaporphine (**4**) in 77 percent yield after purification. The assignment of the remaining methoxyl group to the C-10 position and the loss of the methoxyl group from C-11 can be made unequivocally by nuclear magnetic resonance spectroscopy: A single methoxyl group absorbed at δ 3.86 (3.76 for the hydrochloride salt). This value agrees with the assignment of δ 3.84 reported (5) for racemic 10-methoxyaporphine free base, prepared as discussed above. Perhaps more diagnostic is the absence of the one-proton doublet at exceptionally low field which is characteristic of aporphines with a proton on C-1 when C-11 is substituted with a methoxyl group, and *vice versa* (5). The low field doublet is clearly present in the starting material **3** at δ 8.25. Optically active 10-hydroxyaporphine (**5**) can be obtained almost quantitatively by cleavage of **4** with 48 percent hydrobromic acid. Since these compounds are prepared from (6a*R*)-(-)-apomorphine (**2**), it follows that the newly synthesized aporphines also have the *R* absolute configuration.





A plausible mechanism for the hydrogenolysis of the C-11 methoxyl group can be formulated as shown in the mechanistic scheme. The product obtained requires that the initially formed radical anion I be protonated by ammonia either at position 11 or 8 (paths A and B, respec-

tively) to form the intermediate radicals IIa and/or IIb. Further reduction by sodium would provide the corresponding anions IIIa and IIIb. Whereas intermediate IIIa could readily eliminate methoxide to form the product directly, path B requires an additional protonation step (IVb) followed by anionic elimination of methoxide by the amide anion.

Although the site(s) of initial protonation is uncertain and the driving forces responsible for the high selectivity cannot be readily derived by simple qualitative valence bond reasoning, the actual reductive pathway provides a facile, high yield method for the preparation of (6a*R*)-(-)-10-methoxy- and (6a*R*)-(-)-10-hydroxyaporphines.

EXPERIMENTAL

Melting points were determined in open glass capillaries using a Thomas-Hoover Uni-Melt apparatus and are uncorrected. Elemental analyses were performed by Gailbraith Laboratories, Knoxville, Tennessee. Infrared absorption spectra were recorded on a Beckmann Model 18A spectrophotometer. The nuclear magnetic resonance spectra were recorded on a Varian T-60 or EM-360 spectrometer using TMS as an internal standard. The ultraviolet spectra were recorded on a Cary 118 spectrophotometer. Optical rotations were determined using a Carl Zeiss Circle Polarimeter 0.01°.

(6a*R*)-(-)-*O,O'*-Dimethylapomorphine (**3**).

This compound was prepared by the procedure of Cannon (6), *et al.*, m.p. 76-78°; nmr (deuteriochloroform): δ 2.55 (s, CH_3-N), 3.71 (s, 3, CH_3-O), 3.88 (s, 3, CH_3-O), 7.06 (m, 4, ArH), 8.25 (d, 1, ArH at C-1); uv (absolute ethanol): λ max 271 nm (log ε 4.2).

(6a*R*)-(-)-10-Methoxyaporphine Hydrochloride (**4**·HCl).

Compound **3** (1 g., 3.39 mmoles) was dissolved in 20 ml. of tetrahydrofuran and then approximately 30 ml. of ammonia was condensed (dry ice/acetone) producing a homogenous solution. Then 0.34 g. of sodium was added in small amounts over 3.5 hours. After stirring an additional 3 hours the ammonia was evaporated and the crude product partitioned between water and ethyl acetate. The ethyl acetate layer was separated and the volatiles removed under reduced pressure. The crude product was purified by washing an aqueous solution of the hydrochloride salt with ether, followed by conversion back to the free base (potassium carbonate). The final hydrochloride salt was made by dissolving the base in ether-ethanol (9:1) and neutralizing with concentrated hydrochloric acid. Recrystallization from ethanol affords 0.77 g. (77 percent) of brown crystals, m.p. 255-260° dec., green at 235°; nmr (deuteriochloroform, purified base): δ 2.53 (s, CH_3-N), 3.86 (s, CH_3-O), 7.16 (m, ArH), (deuterium oxide, recrystallized hydrochloride): δ 3.20 (broad, CH_3-N), 3.76 (CH_3-O), 7.06 (m, 6, ArH); uv (water): λ max 305 nm (log ε 3.68), 287 sh, 268 (4.15), 214 (4.56); $[\alpha]_D^{27}$ -93.8° (c, 1.04, anhydrous ethanol).

Anal. Calcd. for $C_{18}H_{20}ClNO$: C, 71.76; H, 6.64; N, 4.65. Found: C, 71.68; H, 6.70; N, 4.60.

(6a*R*)-(-)-10-Hydroxyaporphine Hydrobromide (**5**·HBr).

Compound **4** (0.5 g., 1.66 mmoles) was added to 10 ml. of 48 percent hydrobromic acid. The system was flushed with nitrogen (0.5 hour) and then heated at 130° for 3 hours. After cooling, the volatiles were removed under reduced pressure and the residue recrystallized from methanol to give 0.46 g. (85 percent) of brown crystals, m.p. 265-270° dec., green at 254° (literature (7) reports a hydrochloride); ir (potassium bromide): 3145 cm^{-1} (O-H); $[\alpha]_D^{27}$ -75.4° (c, 0.557, methanol); uv (water): λ max 307 nm (log ε 3.66), 288 (3.74), 267 (4.14); nmr (trifluoroacetic acid): δ 3.23 (d, N-CH_3), 7.18 (m, 6, ArH), 8.80 (broad, 1, N-H).

Anal. Calcd. for $C_{17}H_{18}BrNO$: C, 61.45; H, 5.42; N, 4.21. Found: C, 61.58; H, 5.60; N, 4.08.

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