Preparation of 9,10-Dihydroxyaporphine ("*iso*-Amomorphine") (1)

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In the course of a continuing structure-activity study of emetic agents, 9,10-dihydroxyaporphine ("*iso*-apomorphine") (**1**) was required. The dimethyl ether **2** of this compound has been reported by Robinson and Shinoda (2) (Scheme I), who isolated it as its picrate and characterized it as its methosulfate salt. In the present work, the Robinson-Shinoda sequence was found to be satsifactory for preparation of the dimethyl ether **2** only after considerable modification of experimental conditions and reagents. Weisbach and co-workers (3) have concluded that the product of base-catalyzed condensation of *o*-nitrotoluenes with *N*-methylisoquinolinium is a 1-benzal-1,2,3,4-tetrahydroisoquinoline system (structure **5**, Scheme I), rather than a 1-benzyl-1,2-dihydroisoquinoline as represented in the older literature (7,8). The free base of **2** was isolated from the cyclization reaction mixture by column chromatography; it was extremely unstable in light and air, and it was immediately subjected to ether cleavage to obtain **1**, with no further attempt to purify it. The ether cleavage product **1** is stable and easily characterized; it has not been previously reported in the literature (4). The procedure described herein is a direct, simple preparative sequence for 9,10-dihydroxyaporphine, beginning with readily available starting materials.

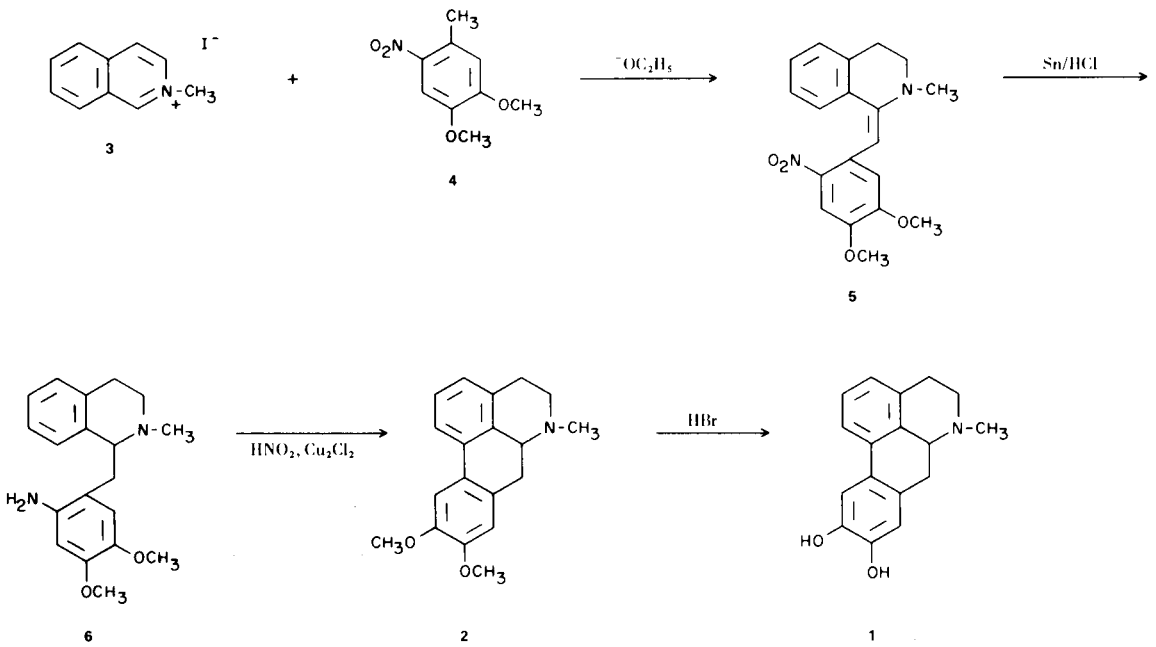
EXPERIMENTAL

Melting points were determined in open glass capillaries on a Thomas-Hoover Uni-Melt apparatus, and are corrected. Elemental analyses are by the Microanalytical Laboratory, Division of Medicinal Chemistry, The University of Iowa. The nmr spectra were recorded on a Varian Associates T-60 instrument using tetramethylsilane as the internal standard.

Isoquinoline Methiodide (**3**).

This was prepared in 80% yield from isoquinoline and methyl

SCHEME I
Preparation of 9,10-Dihydroxyaporphine



iodide, and was recrystallized from ethanol, m.p. 159-160° [lit. (5) m.p. 159°].

3,4-Dimethoxytoluene.

Method A.

The method of Luff, Perkin and Robinson (6) was used. To 2-methoxy-4-methylphenol (5.0 g., 0.036 mole, Eastman) in 10 ml. of methanol, cooled to -10°, was added 9.0 g. (0.072 mole) of dimethyl sulfate with agitation, followed by 7.5 g. (0.13 mole) of potassium hydroxide in 5 ml. of water. The reaction mixture was agitated for 0.25 hour after all the reagents had been added, then it was extracted repeatedly with ether. The combined extracts were dried (sodium sulfate), filtered, and the volatiles were removed under reduced pressure from a steam bath. The residual yellow oil was distilled at 218° (750 mm.) to afford 4.92 g. (90%) of a colorless liquid which solidified upon standing, m.p. 24° [lit. (6) m.p. 24°].

Method B.

3,4-Dimethoxybenzaldehyde (10 g., 0.06 mole, Eastman) in 200 ml. of glacial acetic acid was hydrogenated over 1 g. of 5% palladium on charcoal in a Parr shaker apparatus at room temperature and an initial pressure of 60 psig. After 1 equivalent of hydrogen was absorbed (approximately 12 hours) 10 ml. of 70% perchloric acid in 10 ml. of glacial acetic acid was added and hydrogenation was resumed at room temperature and an initial pressure of 60 psig; in 12 hours, a second equivalent of hydrogen was absorbed. The catalyst was removed by filtration, and to the filtrate was added 10 g. of potassium acetate in 35 ml. of glacial acetic acid. The precipitated potassium perchlorate was removed by filtration; the acetic acid was removed from the filtrate under reduced pressure, and the residue was treated as in Method A, yield, 7.5 g. (82%) m.p. 24°.

3,4-Dimethoxy-6-nitrotoluene (**4**).

This compound was prepared by the method of Luff, Perkin, and Robinson (6). To 4.0 g. (0.025 mole) of 3,4-dimethoxytoluene in 20 ml. of glacial acetic acid was added (with cooling) 2.5 g. of concentrated nitric acid in 8 ml. of glacial acetic acid. This mixture was permitted to stand for 5 minutes, then it was diluted with 100 ml. of water. A mass of yellow crystals separated, which was recrystallized from ethanol to afford 4.5 g. (91%) of material, m.p. 118-119° [lit. (6) m.p. 119°].

1-(3,4-Dimethoxy-6-nitrobenzal)-2-methyl-1,2,3,4-tetrahydroisoquinoline (**5**).

This compound was prepared by the method of Robinson and Robinson (7). To a solution of 2 g. (0.087 g. atom) of sodium in 80 ml. of anhydrous ethanol were added 10 g. (0.051 mole) of **4** and 7 g. (0.026 mole) of **3**. The mixture was heated to boiling, then was allowed to cool. After standing 1 hour at room temperature, the reaction mixture was again heated gently on a steam bath for 0.5 hour. A garnet-red solid which separated was collected on a filter, and the filtrate was cooled in an ice bath, resulting in separation of more solid material. The combined solids were triturated with excess dilute hydrochloric acid until no more red crystals could be seen. This solution was filtered and was then treated with excess concentrated ammonium hydroxide, resulting in separation of a brick-red oil which soon solidified. This solid was recrystallized from ethanol to yield 2.2 g. of crystals. The mother liquor afforded an additional crop, total yield, 4.5 g. (51%) m.p. 145° [lit. (7) m.p. 145°].

1-(3,4-Dimethoxy-6-aminobenzyl)-2-methyl-1,2,3,4-tetrahydroisoquinoline Dihydrochloride (**6**).

The method employed was one utilized by Gadamer *et al.* (8) for a non-methoxylated system. To a solution of 10 g. (0.029 mole) of **5** in 100 ml. of concentrated hydrochloric acid, warmed on a steam bath, was added 30 g. of granular tin in small portions. After 8 hours, the reduction was completed; the reaction mixture was permitted to stand overnight, then the aqueous phase was decanted from the heavy resinous mass which had separated. This mass was taken up in hot water, and hydrogen sulfide was passed through the hot solution until no more precipitate formed. The excess hydrogen sulfide was flushed from the solution with carbon dioxide, and the reaction mixture was filtered. The filtrate was concentrated on a steam bath under reduced pressure. The semi-solid residue was triturated with cold ethanol; a yellow solid formed, which was collected on a filter, washed with cold ethanol, and dried in a vacuum desiccator. Yield, 7.0 g. (60%) m.p. 245-246° (9); nmr (DMSO d_6) broad multiplet centered at δ 3.25 (7H, aliphatic); 2.90 (s, 3H, N-CH_3); 3.60 (s, 3H, OCH_3); 3.82 (s, 3H, OCH_3); 6.4 (d, 2H, aromatic); and a broad multiplet centered at 7.0 (4H, aromatic).

Anal. Calcd. for $C_{19}H_{26}Cl_2N_2O_2$: C, 59.22; H, 6.75; N, 7.27. Found: C, 58.97; H, 6.54; N, 7.54.

9,10-Dimethoxyaporphine (**2**).

The method of Weisbach and Douglas (10) was used. To a well-chilled (10°) solution of 5.0 g. (0.013 mole) of **6** in 52 ml. of glacial acetic acid and 3.6 ml. of concentrated sulfuric acid was added dropwise over 10 minutes, 1.66 g. (0.024 mole) of sodium nitrite in 9 ml. of water. The resulting deep red solution was stirred at 3-5° for 1 hour. To the reaction mixture was added 0.09 g. of sulfamic acid, 0.046 g. of cuprous chloride, and 100 ml. of acetone, and this mixture was refluxed for 0.75 hour. The hot solution was filtered, and the filtrate was basified with 14% ammonium hydroxide to give a green heterogeneous mixture which was extracted repeatedly with ether. The combined extracts were washed with saturated sodium chloride solution, dried over sodium sulfate, filtered, and the volatiles were removed from the filtrate under reduced pressure. The red oily residue was chromatographed on neutral alumina and eluted with ether to afford 1.49 g. (39%) of a yellow oil which was immediately utilized in the next step.

A portion of this oil was refluxed with an equal volume of dimethyl sulfate; the solid methosulfate salt which separated upon cooling was washed with ether and recrystallized several times from water then once from ethanol and was dried at 100° under reduced pressure, m.p. 236-238° [lit. (2) m.p. 246°].

A portion of the oil was converted to its methiodide salt by treatment with methyl iodide in ether solution. This salt was recrystallized from ethanol-water (charcoal), m.p. 240-241.5°; NMR (DMSO d_6) broad multiplet centered at δ 3.25 (7H, aliphatic); 3.0 (s, 6H, N-CH_3); 3.60 (s, 3H, OCH_3); 3.82 (s, 3H, OCH_3); and a broad multiplet centered at 7.5 (5H, aromatic).

Anal. Calcd. for $C_{20}H_{24}INO_2$: C, 54.91; H, 5.49; N, 3.21. Found: C, 54.64; H, 5.64; N, 3.10.

9,10-Dihydroxyaporphine Hydrobromide (**1**).

The method used was a modification of that of Thrift (11). Compound **2** (1.0 g., 0.0034 mole) was refluxed in 20 ml. of 48% hydrobromic acid under nitrogen for 2.5 hours. Volatiles were removed under reduced pressure to leave a black solid which was recrystallized several times from water (charcoal) to yield 0.7 g. (58%) of white crystals, m.p. 250-252° (dec.). This material gave a

positive test for phenolic groups with ferric chloride. NMR (DMSO d_6) δ 3.1 (s, 3H, N-C*H*$_3$); broadened signal centered at 3.4 (7H, aliphatic); multiplets centered at 6.8 and at 7.8 (5H, aromatic); and broad signals at 8.9 and 9.2 (2H, phenolic O*H*). The latter two signals dissappeared upon treatment with deuterium oxide.

Anal. Calcd. for $C_{17}H_{18}BrNO_2$: C, 58.62; H, 5.17; N, 4.02. Found: C, 58.45; H, 5.16; N, 4.14.

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