Catecholamine-related Isoquinoline Alkaloids. I. Synthesis of 4-Hydroxytetrahydroisoquinoline Analogs of Adrenaline and Metanephrine (1)

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Certain tetrahydroisoquinolines, condensation products which can form *in vitro* (2) and *in vivo* (3) from tissue catecholamines and aldehydes (acetaldehyde, formaldehyde), may be involved in the neurotoxicity of alcohol (2,4).

Similarly, isoquinolines derived from 3,4-dihydroxyphenylalanine (DOPA) and endogenous aldehydes have been suggested (5) as mediators of some of the effects observed during DOPA treatment of Parkinson's disease.

While most simple tetrahydroisoquinolines related to the catecholamine, 3,4-dihydroxyphenylethyl amine (dopamine), and to DOPA are readily synthesized by Bischler-Napieralski or Pictet-type reactions (6), the 4-hydroxylated tetrahydroisoquinoline analogs of adrenaline and metanephrine have not been synthesized on a preparative level (7).

The syntheses of these 4-hydroxylated substrates were initiated in order to obtain analytical material for pharmacological and animal behavior experiments related to alcoholism. In this report we describe the preparation of (d,l) 4,6,7-trihydroxy-1,2,3,4-tetrahydroisoquinoline (Figure 1, **4a**) and its suspected product from *in vitro* metabolism (8), (d,l) 4,7-dihydroxy-6-methoxy-1,2,3,4-tetrahydroisoquinoline (**4c**), as well as the attempted synthesis of (*cis* and *trans*) 1-methyl-4,6,7-trihydroxytetrahydroisoquinoline (**4b**) and its 6-methoxylated derivative (**4d**).

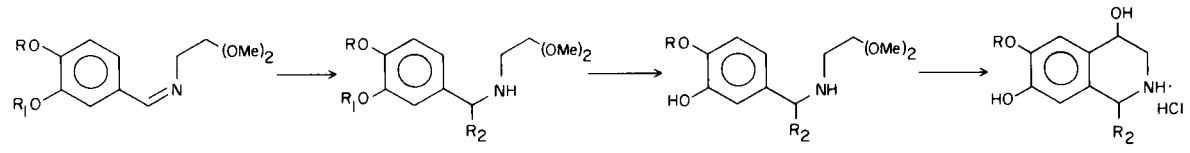
Our synthetic approach (Figure 1) was adapted from that of Bobbitt and Sih (9). Isolated in this procedure were the starting materials **1** and the products **4**.

Intermediates **2** and **3** (except **3c** as the diethyl acetal) were used as obtained. We have prepared by this method tetrahydroisoquinolines **4a** and **4c**, but have been unable to isolate **4b** and **4d** in pure form. We have isolated intermediates **2** and **3** in order to show that the impurities result from the work-up in the last step; that is, isolation of the products **4** from the acidic media.

The Schiff bases (**1a** and **b**) were readily obtained from the condensation of the corresponding benzaldehyde with aminoacetaldehyde dimethyl (diethyl) acetal in the known way.

Compounds **2a** and **b** were readily isolated as their hydrochloride salts. Compounds **2c** and **d** were obtained by reacting the Schiff base **1** with methyl magnesium chloride. It was discovered that debenzylation was a major side reaction (30%) in the Grignard reaction. Compounds **3** were obtained by catalytic (5% Pd/C) hydrogenation of the appropriate **2**. It was necessary to acid-wash (acetic or hydrochloric acid) the catalyst prior to use, since basic impurities were present and the debenzylated compounds would oxidize rapidly during removal of the catalyst and solvent.

It was evident by thin layer chromatography (tlc) that the cyclization of **3** to **4** was not going to completion under the reported conditions (9). Cyclization was accomplished by allowing **3** to stand in 3*N* hydrochloric acid for 42-48 hours. When a longer reaction time or a more concentrated acid solution was used, the solution became highly colored (red) upon standing or upon



1

a, $R = R_1 = C_7H_7$
b, $R = CH_3$, $R_1 = C_7H_7$

2

a, $R = R_1 = C_7H_7$, $R_2 = H$
b, $R = R_1 = C_7H_7$, $R_2 = CH_3$
c, $R = CH_3$, $R_1 = C_7H_7$, $R_2 = H$
d, $R = R_2 = CH_3$, $R_1 = C_7H_7$

3

a, $R = R_2 = H$
b, $R = H$, $R_2 = CH_3$
c, $R = CH_3$, $R_2 = H$
d, $R = R_2 = CH_3$

4

a, $R = R_2 = H$
b, $R = H$, $R_2 = CH_3$
c, $R = CH_3$, $R_2 = H$
d, $R = R_2 = CH_3$

Figure 1

evaporation of the solvent.

Compounds **4a** and **c** were characterized by their nmr spectrum and by chemical analysis. They did not have well-defined melting points, but tlc and gas chromatographic analysis (as their heptafluorobutyryl derivatives) (10) indicated homogeneity.

Compounds **4b** and **d** could not be obtained in a pure form (chemical analysis: C and H high, N low, Cl not done).

EXPERIMENTAL

Melting points were taken in capillary tubes and are uncorrected. Nmr spectra were taken with a Varian A-60A or T-60 spectrometer on 20-30% solutions containing tetramethylsilane or sodium 2,2-dimethyl-2-silapentane-5-sulfonate as internal standards; chemical shifts are reported in τ units.

3,4-Dibenzyloxybenzaldehyde Schiff Base (**1a**).

3,4-Dibenzyloxybenzaldehyde (15 g.) and aminoacetaldehyde dimethyl acetal (5.32 g.) were dissolved in 150 ml. of benzene and the resulting solution was refluxed for 6 hours. Water was collected in a Dean-Stark apparatus. The solution was then treated with charcoal (2 g.), refluxed for an additional hour, filtered and the solvent was removed *in vacuo*. The resulting oil was dissolved in hot hexane and allowed to stand for crystallization. The white needles were collected and air dried; (15 g., 78%), m.p. 59-61°; nmr (deuteriochloroform), 1.88 (1H s, -CH=N-); 2.46-3.18 (13H m, aromatic H); 4.84, 4.87 (4H 2s, $-CH_2-O-$); 5.35 [1H t, $-CH(OMe)_2$]; 6.27 (2H d, $N-CH_2-$); 6.61 (6H s, $-O-CH_3$).

Anal. Calcd. for $C_{25}H_{27}NO_4$: C, 74.05; H, 6.71; N, 3.45. Found: C, 73.98; H, 6.62; N, 3.30.

3-Benzyloxy-4-methoxybenzaldehyde Schiff Base (**1b**).

Compound **1b** was obtained as above using 3-benzyloxy-4-methoxy benzaldehyde (25 g.) and aminoacetaldehyde dimethyl acetal (11 g.). Crystallization from hexane afforded 26.7 g. (84%) of pale yellow needles, m.p. 61-63°; nmr (deuteriochloroform), 1.88 (1H s, -CH=N-); 2.5-3.22 (8H m, aromatic H); 4.85 (2H s, $-CH_2-O-$); 5.37 [1H t, $-CH(OMe)_2$]; 6.15 (3H s, 4-methoxy H); 6.27 (2H d, $N-CH_2-$); 6.61 (6H s, acetal CH_3-).

Anal. Calcd. for $C_{19}H_{23}NO_4$: C, 69.28; H, 7.04; N, 4.25. Found: C, 69.19; H, 7.06; N, 4.06.

3,4-(Dibenzyloxy)benzylaminoacetaldehyde Dimethyl Acetal Hydrochloride (**2a** Hydrochloride).

To the Schiff base **1a** (16.2 g.) in 150 ml. of absolute ethanol was added sodium borohydride (4 g.) portionwise with stirring and ice cooling. After the addition, the mixture was stirred at room temperature for 24 hours. The solvent was removed under reduced pressure and 100 ml. water was added to the resulting paste. The solution was extracted three times with ether. The ether extracts were dried (sodium sulfate), filtered and saturated with dry hydrogen chloride. The resulting solid was collected, air-dried and recrystallized from 2-propanol-ether to yield 12.9 g. (73%) of white plates, m.p. 153-155° dec.; nmr-free amine (deuteriochloroform), 2.74-3.14 (13H m, aromatic H); 4.88, 4.90 (4H d,d, $-CH_2-O-$); 5.53 [1H t, $-CH(OMe)_2$]; 6.27 (2H s, $Ar-CH_2-N$); 6.68 (6H s, $-O-CH_3$); 7.29 (2H d, $N-CH_2-$).

Anal. Calcd. for $C_{25}H_{30}ClNO_4$: C, 67.63; H, 6.81; N, 3.15; Cl, 7.99. Found: C, 67.59; H, 6.84; N, 2.98; Cl, 8.15.

4-Methoxy-3-benzyloxybenzylaminoacetaldehyde Dimethyl Acetal Hydrochloride (**2c** Hydrochloride).

Compound **2c** hydrochloride was prepared as above from Schiff base **1b** (9.87 g.) and sodium borohydride (2.85 g.) in 100 ml. of absolute ethanol. Recrystallization from 2-propanol-ether yielded 8.6 g. (78%) of white plates, m.p. 132-135° dec.; nmr-free amine (deuteriochloroform), 2.41-2.75 (5H m, aromatic H); 4.86 (2H s, $-CH_2-O-$); 5.52 [1H t, $-CH(OMe)_2$]; 6.18 (3H s, methoxy CH_3-); 6.30 (2H s, $Ar-CH_2-N$); 6.68 (6H s, acetal CH_3-); 7.31 (2H d, $-N-CH_2-$).

Anal. Calcd. for $C_{19}H_{26}ClNO_4$: C, 62.03; H, 7.12; N, 3.81. Cl, 9.64. Found: C, 62.04; H, 7.25; N, 3.73; Cl, 9.87.

3,4-Dibenzyloxy-α-methylbenzaldehydeaminoacetaldehyde Dimethyl (Diethyl) Acetal Hydrochloride (**2b** and **2b**-Diethyl Acetal Hydrochlorides).

The Grignard reagent was prepared in the known way using methyl iodide (8.52 g.) in dry ether (30 ml.) and magnesium (1.61 g.) in dry ether (45 ml.). After refluxing for 1 hour, the reagent was diluted with 100 ml. of dry ether. The Schiff base **1a** (8.1 g.) was placed in a dropping funnel equipped with a pressure equalizing tube and the funnel placed between the reaction vessel and reflux condenser. The ether was refluxed and stirred vigorously. After the Schiff base had been washed into the reaction vessel, the resulting mixture was refluxed for an additional 24 hours. The complex was destroyed with ammonium chloride (11 g.) in 35 ml. water and the resulting solution refluxed for ½ hour. The ether layer was removed and the aqueous layer extracted twice more with ether. The ether extracts were combined and dried (sodium sulfate). Evaporation of the solvent under reduced pressure afforded a pale yellow oil (8 g., 96%). The oil was dissolved in ether and dry hydrogen chloride was bubbled in. The solution was evaporated to dryness under reduced pressure and the resulting solid was recrystallized with difficulty from 2-propanol-ether, m.p. 156-157°; (Found: C, 68.82, Requires: C, 68.18%); nmr-free amine (deuteriochloroform), 2.33-3.16 (13H m, aromatic H); 5.46 [1H t, $-CH(OEt)_2$]; 6.00-6.74 [5H m, Ar-CH(Me)-N and acetal O-CH_2-]; 4.87 (4H d, CH_2-O-); 7.43 (2H d, $N-CH_2-$); 8.37 (1H s, NH); 8.5-9.0 (9H m, α-CH_3- and acetal CH_3-).

Compound **2b**-diethyl acetal hydrochloride was obtained in the following way. The resulting oil from the Grignard reaction was dissolved in 40 ml. of ethanol and 100 ml. of 4*N* hydrochloric acid was added dropwise with stirring and ice cooling. The resulting mixture was stirred at room temperature for 4 hours. The solvent was removed *in vacuo*. The resulting solid was recrystallized from 2-propanol-ether (71%), m.p. 131-133°; nmr-free amine (deuteriochloroform), 2.40-3.23 (13H m, aromatic H); 4.85 (4H d, $Ar-CH_2-O-$); 5.62 [1H t, $-CH(OMe)_2$]; 6.34 [1H q, Ar-CH(Me)-]; 6.66 (6H d, acetal CH_3-); 7.04 (2H d, $N-CH_2-$); 8.25 (1H s, NH); 8.70 (3H d, α-CH_3-).

Anal. Calcd. for $C_{28}H_{36}ClNO_4$: C, 69.19; H, 7.46; N, 2.88; Cl, 7.29. Found: C, 69.25; H, 7.51; N, 2.82; Cl, 7.31.

3-Benzyloxy-4-methoxy-α-methylbenzylaminoacetaldehyde Dimethyl Acetal (**2d**).

The oily product was obtained as above using Schiff base **1b** (15 g.), magnesium (4.86 g.) in 120 ml. of ether, methyl iodide (25.84 g.) in 60 ml. of ether and ammonium chloride (21.4 g.) in 64 ml. of water. The oil weighed 14.35 g. Compound **2d** was isolated as an oil in 45% yield from a silica gel column using hexane-benzene-methanol (7.5/4/1): nmr (deuteriochloroform) 2.40-2.79 (5H m, aromatic H); 2.95-3.18 (3H m, aromatic H); 4.85 (2H s, $-CH_2-O-$); 5.60 [1H t, $-CH(OMe)_2$]; 6.08-0.50 (4H m, methoxy CH_3, $-CH_2-N$); 6.69, 6.73 (6H 2s, acetal CH_3-); 7.46 (2H d, $N-CH_3$); 8.32 (1H s, NH); 8.73 (3H d, α-methyl).

Attempts to obtain the hydrochloride salts were unsuccessful. The other component from the column was shown to be identical to **3d** (32.5%) by its m.p. and nmr spectra.

3,4-Dihydroxy-α-methylbenzylaminoacetaldehyde Diethyl Acetal Hydrochloride (**3b**-Diethyl Acetal Hydrochloride).

The benzyloxyamino diethyl acetal hydrochloride (**2b**-diethyl acetal hydrochloride) (9.26 g.) was hydrogenated with acid-washed 5% Pd/C (1.11 g.) in 150 ml. of absolute ethanol at 40 psi and room temperature for 4 hours. The catalyst was filtered off and the solvent removed under reduced pressure. The resulting oil was crystallized with difficulty from 2-propanol-ether-hexane (3/4/4) at 5°, m.p. 125-127°.

Anal. Calcd. for $C_{14}H_{24}ClNO_4$: C, 54.99; H, 7.91; N, 4.58; Cl, 11.59. Found: C, 54.86; H, 8.02; N, 4.70; Cl, 11.73.

The dimethyl acetal compound (**3b**) could not be obtained as a solid ether as the free amine or as the hydrochloride salt.

3-Hydroxy-4-methoxybenzylaminoacetaldehyde Dimethyl Acetal (**3c**).

The amino-acetal hydrochloride (**2c** hydrochloride) was dissolved in water, basified wtih ammonium hydroxide and was extracted into ethyl ether. The ether extract was dried (sodium sulfate) and the solvent removed under reduced pressure. The resulting oil (7.92 g.) was hydrogenated with 5% Pd/C (0.8 g., acid-washed) at 40 psi and room temperature in 75 ml. of absolute ethanol for 8 hours. After filtering to remove the catalyst, the solvent was removed under reduced pressure. The resulting oil was dissolved in hot carbon tetrachloride, treated with charcoal and placed in the cold (5°). The resulting white solid (3.8 g., 66%) was collected and dried, m.p. 77-78°; nmr (deuteriochloroform), 3.05-3.22 (3H m, aromatic H); 5.28-5.60 (3H m -CH-, NH, OH); 6.20 (3H s, methoxy H); 6.30 (2H s, Ar-CH_2-N); 6.68 (6H s, acetal CH_3-); 7.26 (2H d, -N-CH_2-).

Anal. Calcd. for $C_{12}H_{19}NO_4$: C, 59.72; H, 7.94; N, 5.80. Found: C, 59.78; H, 7.93; N, 5.59.

3-Hydroxy-4-methoxy-α-methylbenzylaminoacetaldehyde Dimethyl Acetal (**3d**).

The oil from the Grignard reaction (**2d**) (4 g.) was hydrogenated with 5% Pd/C (1.5 g., acid washed) in 35 ml. of absolute ethanol at 40 psi and room temperature. After 6 hours, the catalyst was removed by filtering and the solvent removed under reduced pressure. The resulting solid was recrystallized from hexane (1.98 g., 67%), m.p. 93-95°; nmr (deuteriochloroform), 3.0-3.27 (3H, m, aromatic H); 5.38-5.89 [3H m, -CH(OMe)$_2$, NH, OH]; 6.08-6.37 (4H m, methoxy H, Ar-CHMe-N); 6.69 (6H d, acetal CH_3-); 7.41 (2H d, N-CH_2-); 8.67 (3H d, α-CH_3-).

Anal. Calcd. for $C_{13}H_{21}NO_4$: C, 61.16; H, 8.29; N, 5.47. Found: C, 61.02; H, 8.41; N, 5.28.

4,6,7-Trihydroxy-1,2,3,4-tetrahydroisoquinoline Hydrochloride (**4a**).

The dibenzyloxyamino-acetal hydrochloride (**3a** hydrochloride) (8 g.) was hydrogenated with 5% Pd/C (2 g., acid washed) for 8 hours at 15 psi and room temperature in 100 ml. of absolute ethanol. The catalyst was filtered off and the solvent removed under reduced pressure. The resulting oil was dissolved in 100 ml. of 3*N* hydrochloric acid, extracted three times with ether-benzene (1/1) and allowed to stand for 2 days. The acid solution was extracted three times with chloroform and concentrated *in vacuo* on the rotating evaporator at 20-25°. The solution was concentrated to about 1/3 the original volume. The resulting solid was collected, washed twice with ice cold ethanol and twice with warm (30°) chloroform, and air dried. The faint yellow crystals weighed 3.13 g. (66%). The analytical sample was dried *in vacuo* over phosphorous pentoxide at 64°, m.p. above 140°, slow dec.; nmr (deuterium oxide), 3.00, 3.22 (2H, 2s, aromatic H); 5.00 (1H t, H-4); 5.67 (2H s, H-1); 6.40 (2H t, H-3).

Anal. Calcd. for $C_9H_{12}ClNO_3$: C, 49.66; H, 5.56; N, 6.43; Cl, 16.29. Found: C, 49.57; H, 5.64; N, 6.55; Cl, 16.46.

4,7-Dihydroxy-6-methoxy-1,2,3,4-tetrahydroisoquinoline Hydrochloride (**4c**).

The hydroxy-methoxybenzylaminoacetal **4c** (4.84 g.) in 100 ml. of 3*N* hydrochloric acid was treated as above. After standing for 2 days, the solution was concentrated to 1/2 volume. Crystallization was induced by cooling with dry ice. After crystals had formed, the solution was concentrated to 1/3 volume. The crystals (2.82 g., 61%) were collected and treated as above, m.p. 107-111° dec.; nmr (deuterium oxide), 2.90, 3.25 (2H 2s, aromatic H); 4.95 (t, H-4, overlapped by -OH signal); 5.67 (2H s, H-1); (2H s, H-1); 6.05 (3H s, methoxy H); 7.40 (1H t, H-3).

Anal. Calcd. for $C_{10}H_{14}ClNO_3$: C, 51.84; H, 6.09; N, 6.05; Cl, 15.30. Found: C, 51.71; H, 5.89; N, 6.07; Cl, 15.45.

Attempts to Obtain Compounds **4b** and **4d** as Pure Material.

The compounds could not be recrystallized readily from alcohol or mixtures containing alcohol. Recrystallization, when achieved, did not change the compounds melting points or chemical analyses, agreeing with J. M. Bobbitt, *et al.* (11).

Attempts to obtain the free amines by neutralization with ammonium hydroxide or propylene oxide resulted in the rapid discoloration of the material either upon filtering or upon extraction into chloroform. The color could not be removed with activated charcoal and the material could not be recrystallized. The compounds also decomposed when chromatographed on silica gel preparative layer plates (formic acid/2-butanol/water).

Since dimers are considered to be among the side products in the cyclization with acid (11), the material was chromatographed on Sephadex G-10 (particle size 40-120μ, elutant 0.005*N* ammonium acetate). The tlc and melting point of the material obtained after freeze-drying the elutant were identical to those of the sample applied to the column.

The compounds could be obtained as colorless solutions from a Dowex 50W-X4 (H+ form) column. Impure solid material **4** (from crystallization or evaporation) was applied to the column as an aqueous solution. The column was washed with water and eluted with various hydrochloric acid solutions (0.1, 0.5, 1.0, 2.0 *N*). The compounds were eluted in the 2.0 *N* fraction. Upon concentration, the solutions became colored and the material isolated was the same as that applied to the column.

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