The Synthesis of Tetrahydroisoquinolines Related to Catecholamines

Reinhard Sarges

Pfizer Central Research Pfizer, Inc., Groton, Connecticut 06340

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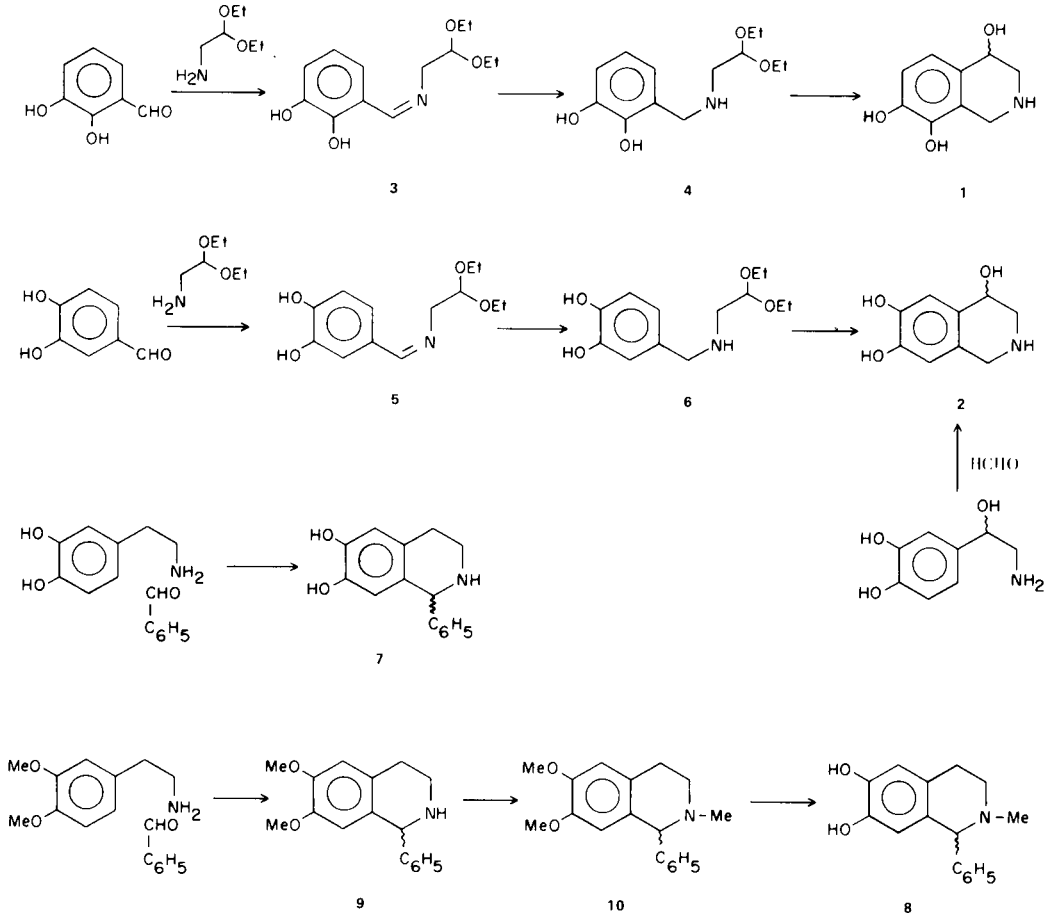
During a study of the α-adrenergic receptor (1) we required the two "cyclic" analogs, **1** and **2**, of epinephrine, in which the aminoalkyl side chain of epinephrine is connected to the 2- or the 6-position of the catechol ring to form tetrahydroisoquinolines. The synthesis of these compounds was approached by the method of Bobbitt *et al.* (2).

Condensation of 2,3-dihydroxybenzaldehyde with diethylaminoacetal to the Schiff base **3**, followed by Raney nickel reduction and cyclization with 6*N* hydrochloric acid gave in good yield the racemic 4,7,8-trihydroxyethrahydroisoquinoline (**1**). The analogous reaction starting with 3,4-dihydroxybenzaldehyde gave only moderate yields of the isomeric 4,6,7-trihydroxytetrahydroisoquioline (**2**). This prompted us to investigate on a preparative scale the previously reported (3,4) condensation of norepinephrine with formaldehyde to **2**. Indeed, treatment of an aqueous solution of norepinephrine hydrochloride with formaldehyde at room temperature gave fair yields of **2**, but the reaction mixture contained so many byproducts that multiple recrystallizations were required for the isolation of pure **2**. Hence, Bobbitt's procedure remains the method of choice for the preparation of **2**. A synthesis of this compound *via* a slightly different sequence has



appeared in the literature (5) in the meantime.

The successful condensation of norepinephrine with formaldehyde stimulated us to extend this method to the preparation of 1-phenyl-6,7-dihydroxytetrahydroisoquinoline (**7**), and its *N*-methyl derivative (**8**). We found that the condensation of benzaldehyde with 3-hydroxytyramine required much stronger conditions, *i.e.* the presence of hydrochloric acid and elevated temperatures, which gave an 88% yield of **7**. A 11% yield of **7**, using trifluoroacetic acid as the catalyst, has been reported (6). The reaction conditions using hydrochloric acid and elevated temperatures were in turn inadequate to achieve the condensation of benzaldehyde with 3,4-dimethoxyphenylethylamine. However, this reaction proceeded well by the method of Lepape (7), using phosphoric acid as the catalyst. The resulting 1-phenyl-6,7-dimethoxytetrahydroisoquinoline (**9**) (8) was methylated by the Leuckart reaction to give the known compound **10** (9), and the methoxy groups were cleaved by the reaction conditions of Yamato *et al.* (10) with 12*N* hydrochloric acid to give the desired dihydroxy derivative **8** in good overall yield.

EXPERIMENTAL

Melting points were determined with a Thomas-Hoover apparatus and are uncorrected. Elemental analyses were performed by the Analytical Department of Pfizer Central Research. Nmr spectra were obtained on Varian T-60 or A-60 instruments.

N-(2,3-Dihydroxybenzylidene)aminoacetaldehyde Diethyl Acetal (3).

A mixture of 20 g. (0.145 mole) of 2,3-dihydroxybenzaldehyde (11) and 20 g. (0.15 mole) of aminoacetaldehyde diethyl acetal in 600 ml. of benzene was heated to reflux until no more water was collected in a Dean-Stark apparatus. After evaporation, there was obtained a quantitative yield of crude **3**. A small sample was recrystallized from hexane to give an analytical sample, m.p. 67-68°; nmr (deuteriochloroform): δ 1.2 (6H, t J = 7 Hz), 3.2-4.0 (6H, m), 4.7 (1H, t J = 5.5 Hz), 6.4-7.1 (3H, m), 8.15 (1H, s), 10.2 (2H, broad s).

Anal. Calcd. for $C_{13}H_{19}NO_4$: C, 61.64; H, 7.56; N, 5.53. Found: C, 61.42; H, 7.48; N, 5.80.

N-(2,3-Dihydroxybenzyl)aminoacetaldehyde Diethyl Acetal (4).

A solution of 31.8 g. (0.125 mole) of crude **3** in 150 ml. of ether was hydrogenated over 3 g. of Raney nickel at 50 psi in a Parr apparatus overnight. The mixture was filtered, evaporated, and the residue crystallized from hexane to give 28.8 g. (90%) of **4**, m.p. 74-75°; nmr (deuteriochloroform): δ 1.2 (6H, t J = 7 Hz), 2.75 (2H, d J = 5.5 Hz), 3.3-3.9 (4H, m), 4.0 (2H, s), 4.65 (1H, t J = 5.5 Hz), 6.2-7.0 (6H, m).

Anal. Calcd. for $C_{13}H_{21}NO_4$: C, 61.15; H, 8.29; N, 5.49. Found: C, 60.99; H, 8.21; N, 5.44.

4,7,8-Trihydroxy-1,2,3,4-tetrahydroisoquinoline (1).

A solution of 24 g. (0.094 mole) of **4** in 300 ml. of 6*N* hydrochloric acid was stirred at room temperature for 90 minutes. The crystals that separated were filtered, dried, and recrystallized from water-methanol to give 14.9 g. (73%) of **1** as the hydrochloride, m.p. 196-198°; nmr (deuterium oxide): δ 3.6-4.2 (2H, m, AB part of an ABX pattern, H-3), 4.35-5.1 (2H, m, AM pattern, H-1), 5.2 (s, DOH), 5.1-5.8 (1H, m, X-part of an ABX pattern, H-4), 7.35 2H, s, H-5, H-6).

Anal. Calcd. for $C_{19}H_{11}NO_3 \cdot HCl$: C, 49.67; H, 5.56; N, 6.44. Found: C, 49.40; H, 5.49; N, 6.24.

N-(3,4-Dihydroxybenzylidene)aminoacetaldehyde Diethyl Acetal (5).

This compound was prepared by heating 30 g. (0.217 mole) of 3,4-dihydroxybenzaldehyde and 30 g. of aminoacetaldehyde diethyl acetal in 1 l. of benzene as described above for 1 hour. After cooling and evaporation, the residue was recrystallized from ethanol to give 45.6 g. (82%) of **5**, m.p. 113-115°; nmr (DMSO-d_6): δ 1.1 (6H, t J = 7 Hz), 3.2-3.8 (6H, m), 4.7 (1H, t J = 5 Hz), 6.5-7.7 (5H, m), 8.1 (1H, s).

Anal. Calcd. for $C_{13}H_{19}NO_4 \cdot 1/4H_2O$: C, 60.58; H, 7.63; N, 5.43. Found: C, 60.61; H, 7.84; N, 5.15.

N-(3,4-Dihydroxybenzyl)aminoacetaldehyde Diethyl Acetal (6).

A solution of 25.7 g. (0.1 mole) of **5** in 300 ml. of tetrahydrofuran was hydrogenated over 5 g. of Raney nickel at 50 psi for 6 hours. After filtration and evaporation, the residue was recrystallized from ethyl acetate-hexane to give 8.0 g. (31%) of **6**, m.p. 87-88°; nmr (deuteriochloroform): δ 1.1 (6H, t J = 7 Hz), 2.75 (2H, d J = 5 Hz), 3.2-3.8 (6H, m), 4.55 (1H, t J = 5 Hz), 6.3-6.9 (6H, m).

Anal. Calcd. for $C_{13}H_{21}NO_4$: C, 61.15; H, 8.29; N, 5.49. Found: C, 60.90; H, 8.27; N, 5.30.

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

A solution of 1 g. (0.0039 mole) of **6** in 5 ml. of 6*N* hydrochloric acid was stirred at room temperature under nitrogen. After 2 hours no crystals had separated yet and the mixture was kept overnight. The solids which had separated (0.58 g.) were collected, washed with acetone, and recrystallized from 10 ml. of water-90 ml. of acetone, to give 0.49 g. (58%) of **2** as the hydrochloride, m.p. 172° dec (Reference 5 gives m.p. >140°); nmr (deuterium oxide): δ 3.3-3.8 (2H, m, AB part of ABX pattern, H-3), 4.3 (2H, s, H-1), 4.9 (1H, m, X part of an ABX pattern, H-4), 6.7, 6.95 (2H, 2s, H-5, H-8).

Anal. Calcd. for $C_9H_{11}NO_3 \cdot HCl$: C, 49.67; H, 5.56; N, 6.44. Found: C, 49.38; H, 5.39; N, 6.09.

Alternatively, **2** was prepared by adding dropwise, with stirring, 4.65 g. of 36% formaldehyde to a solution of 9.22 g. (0.045 mole) of *dl*-norepinephrine hydrochloride in 15 ml. of water. The *p*H of the reaction mixture was 2.2. After stirring for an additional hour, 100 ml. of acetone was added and the precipitated solids (7.3 g.) collected. These solids were very inhomogeneous by tlc analysis (methyl ethyl ketone, acetic acid, water; 75:5:20); only trace amounts of **1** were detected. After six recrystallizations from water-acetone, there was obtained 1.2 g. (12%) of pure **2** as the hydrochloride, m.p. 169° dec.

6,7-Dihydroxy-1-phenyl-1,2,3,4-tetrahydroisoquinoline (7).

A mixture of 2.3 g. (0.012 mole) of 3-hydroxytyramine hydrochloride, 1.28 g. of (0.012 mole) of freshly distilled benzaldehyde, 20 ml. of methanol and 2 ml. of 1*N* hydrochloric acid was heated to reflux overnight. After evaporation *in vacuo*, the residue was triturated with ether, and the solids filtered and recrystallized from methanol-ether to give 3.03 g. (88%) of **7** as the hydrochloride hemihydrate, m.p. 133° dec., (lit. (6) m.p. 140-156°); nmr (deuterium oxide): δ 2.9-3.6 (4H, m, H-3, H-4), 5.6 (1H, s, H-1), 6.2,

6.7 (2H, 2s, H-5, H-8), 7.4 (5H, s).

Anal. Calcd. for $C_{15}H_{15}NO_2 \cdot HCl \cdot 1/2H_2O$: C, 62.89; H, 5.98; N, 4.89. Found: C, 63.22; H, 6.07; N, 4.70.

6,7-Dimethoxy-1-phenyl-1,2,3,4-tetrahydroisoquinoline (9).

Freshly distilled benzaldehyde (1.05 g., 0.01 mole) was combined with 1.8 g. (0.01 mole) of β-(3,4-dimethoxyphenyl)ethylamine, and 20 ml. of 85% phosphoric acid was added dropwise to this mixture. The reaction mixture was stirred at 37° overnight, cooled to room temperature, and poured into water. After washing with ether, the aqueous layer was made alkaline with sodium hydroxide and extracted with ether. The ether extract was dried, evaporated, and the residue recrystallized from ethanol to give 1.91 g. (71%) of **9** m.p. 112-114° (lit. (8) m.p. 112-113°). The hydrochloride of **9** had m.p. 278° dec, after recrystallization from methanol-ether.

Anal. Calcd. for $C_{17}H_{19}NO_2 \cdot HCl$: C, 66.76; H, 6.59; N, 4.58. Found: C, 66.38; H, 6.55; N, 4.52.

6,7-Dimethoxy-2-methyl-1-phenyl-1,2,3,4-tetrahydroisoquinoline (10).

A mixture of 5.0 g. (0.0185 mole) of **9** (free base), 3.5 g. of 36% formaldehyde, and 5.2 g. of 98% formic acid was heated on a steam bath for 2.5 hours. After cooling, 50 ml. of water was added and the mixture washed with ether. The aqueous layer was made alkaline with sodium hydroxide and extracted with ether. The ether layer was dried, evaporated and the residue crystallized from hexane to give 4.5 g. (86%) of **10**, m.p. 74-76° (lit. (9) m.p. 75-77°).

6,7-Dihydroxy-2-methyl-1-phenyl-1,2,3,4-tetrahydroisoquinoline (8).

A mixture of 2 g. (0.0071 mole) of **10** and of 10 ml. of 12*N* hydrochloric acid was heated in a sealed glass tube to 150-160° for 3 hours. After cooling and evaporation, the residue was dissolved in water, washed with ether, and the aqueous layer adjusted to *p*H 8 with sodium bicarbonate and extracted with ether. The ether extract was dried, treated with hydrogen chloride gas and evaporated. The residue was crystallized twice from methanol-ether to give 1.33 g. (60%) of **8** as the hydrochloride hydrate, m.p. 142° dec; nmr of the free base (deuteriochloroform): δ 2.05 (3H, s, N-Me), 2.2-3.2 (4H, m, H-3, H-4), 4.2 (1H, s, H-1), 5.9, 6.35 (2H, 2s, H-5, H-8), 6.9-7.5 (7H, m, OH, phenyl).

Anal. Calcd. for $C_{16}H_{17}NO_2 \cdot HCl \cdot H_2O$: C, 62.03; H, 6.50; N, 4.52. Found: C, 61.94; H, 6.90; N, 4.39.

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