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2,3-Dihydroxyphenethanolamine as an Adrenergic Agent†

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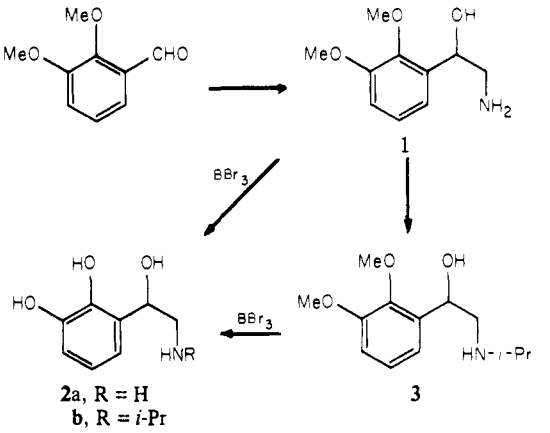
In an attempt to further define the role of the *m*-hydroxy group in adrenergic agents, 2,3-dihydroxyphenethanolamine hydrobromide and *N*-isopropyl-2,3-dihydroxyphenethanolamine hydrobromide were prepared. These agents are less active than norepinephrine in α- and β-adrenergic in vitro tests. The synthesis and conclusions from the tests are discussed.

Numerous aromatic-substituted phenethylamines have been tested for adrenergic activity; however, the demonstrated dopaminergic activity of some phenethylamines[1] makes reexamination of aromatic substitution patterns in phenethanolamines of interest. To this end, a study of the previously unreported 2,3-dihydroxyphenethanolamines **2a,b** was undertaken. These compounds, like norepinephrine, are catechols and are capable of chelating divalent metal ions (considered important in interactions with the adrenergic receptor[2] and in storage at presynaptic sites[3]). Work with alkylsulfonamide substituents on the benzene ring of phenylethanolamines has been interpreted by Larsen and co-workers[4] as indicating the importance of an acidic group at the 3 position of the ring. Consistent with Larsen's proposal, 3,5-dihydroxyisoproterenol is a direct-acting β-adrenergic agonist.[5] Its ability to chelate metal ions has not been reported. The work of Rosen et al.[6] on frog erythrocytes supports the importance of the 3-hydroxy group for β-adrenergic agents. Kappe and Armstrong[7] determined that the first proton in a catechol is more acidic than in a simple phenol, suggesting that a hydroxy group in the 2 position of **2a,b** may simultaneously increase the activity and acidity of a 3-hydroxy-substituted compound.

Buck[8] reported a low-yield (5%) synthesis of 2,3-dimethoxyphenethanolamine (1) but did not describe its *O*-demethylation. The treatment of 2,3-dimethoxybenzaldehyde with trimethylsilyl cyanide (using the procedure of Evans and coworkers[9]) followed by reduction with $LiAlH_4$ afforded an improved yield (57%) of 1. Demethylation of 1 and 3 with BBr_3 to yield **2a,b**, respectively, was more satisfactory than reaction with HBr.

Standard procedures on three animals using isolated rat vas deferens preparations and blood pressure were employed in testing for adrenergic agonist activity.[10] Compound **2a** had a slow onset of action and was $^1/_{80}$th as potent as *l*-norepinephrine (13 μg/ml of **2a** was equipotent with 0.165 μg/ml of *l*-norepinephrine) in the vas deferens preparations. Treatment of the tissue with *l*-norepinephrine potentiated the contraction. Compound **2b** produced a decrease in blood pressure but was $^1/_{800}$th as potent as *dl*-isoproterenol (120 mg/kg of **2b** was equipotent with 0.150 mg/kg of *dl*-isoproterenol). Compound **2a** produced an increase in blood pressure but was $^1/_{100}$th as potent as *l*-norepinephrine (100 mg/kg of **2a** was equipotent with 1 mg/kg of *l*-norepinephrine).

Scheme I



When compound **2a** was tested at 1.0 m*M* concentration as a substrate for catechol *O*-methyltransferase by the procedure of Nikodejevic,[11] less than 5% methylation was detected. A tenfold excess of **2a** inhibited methylation of *l*-norepinephrine by about 25%.

It is tempting to rationalize the absence of direct adrenergic activity of **2a** in terms of two proposed models[2] for the adrenergic receptor. Chelation of a divalent metal ion has been suggested as important in adrenergic agonist–receptor interactions. However, lack of information about the microenvironment of the receptor makes quantitative measurement of agonist–metal association difficult to interpret. Chelation between catecholamines and magnesium in aqueous solution is difficult to demonstrate, even at a pH greater than 9;[3] yet, in *N,N*-dimethyllaurylamide (simulating a lipid environment) chelation can be detected.[12]

Using the spectrophotometric assay of Jameson[13] the data in Figure 1 indicate that **2a** can form a complex with Cu^{2+} similar to catechol and norepinephrine. This is an indication that 2,3-dihydroxyphenethanolamines are able to participate in chelation if it is necessary for adrenergic

† Dedicated to Dr. Edward E. Smissman who was chairman of this Department from 1960 to July 1974.

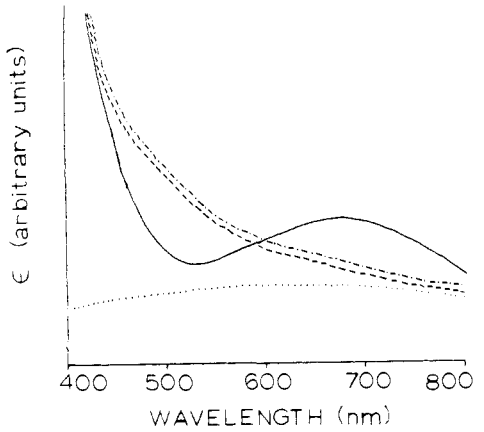


Figure 1. Spectrometric determination of chelation of catechols to a metal ion (Cu^{2+}) in the presence of base (NaOH).[14] All measurements were taken at a cation-ligand-base ratio of 1:2:4. Catechol (1×10^{-3} *M*), ——; norepinephrine hydrobromide (1×10^{-3} *M*), - - - -; 2,3-dihydroxyphenethanolamine hydrobromide (1×10^{-3} *M*), - · - · -; and phenethanolamine (1×10^{-3} *M*), · · · · ·.

activity. However, after chelation, the ethanolamine side chain may be reoriented in space, so that it can no longer interact with the side-chain binding site.

An alternative explanation for low activity is possible. The conformation of the side chain and the β-hydroxyl group at the receptor is unknown, but interactions between the β-hydroxy and the *o*-hydroxyl group may affect activity.

Experimental Section[14]

2,3-Dimethoxyphenethanolamine (1). Following the procedure of Evans et al.[9] 5.1 g (0.03 mol) of 2,3-dimethoxybenzaldehyde (Aldrich) and 3.4 g (0.035 mol) of trimethylsilyl cyanide were stirred in PhH (50 ml) with 2.0 mg of ZnI_2. After 2 hr an aliquot showed no absorbance in the carbonyl region of the ir spectrum. The reaction mixture was added to a stirred suspension of 1.50 g (0.040 mol) of $LiAlH_4$ in Et_2O (25 ml) under a N_2 atmosphere. After stirring for 3 hr the mixture was hydrolyzed by slow addition of 5 ml of H_2O and filtered and the solid continuously extracted with Et_2O in a Soxhlet apparatus. Concentration of the Et_2O solution gave a yellow solid which was recrystallized from *i*-PrOH to afford 3.4 g (57%) of 1 as a white solid: mp 95–96° (lit.[8] mp 95–96°).

2,3-Dihydroxyphenethanolamine Hydrobromide (2a). Following the procedure of McOmie[15] 0.0125 mol of BBr_3 was added to 0.50 g (0.0025 mol) of 1 in CH_2Cl_2 at −78° under an atmosphere of N_2. After stirring the mixture for 20 hr at room temperature an excess of MeOH (5 ml) was added and the solution was concentrated to afford a white solid. Crystallization from *i*-PrOH–Et_2O afforded 0.440 g (71%) of **2a** as a tan solid: mp 220–225° dec. Anal. ($C_8H_{12}NO_3Br$) C, H, N.

***N*-Isopropyl-2,3-dimethoxyphenethanolamine Hydrobromide (3).** Following the procedure of Schellenberg,[16] to a mixture of 1 (0.500 g, 0.0025 mol), $AcONa \cdot 3H_2O$ (0.78 g), AcOH (2.17 ml), Me_2CO (5.0 ml), and H_2O (6.3 ml) at 0° was added $NaBH_4$ (2.4 g) in small portions during 1 hr. Acetone (5.0 ml) was then added and the mixture stirred an additional hour. The reaction mixture was poured into 3% $NaHCO_3$ solution (100 ml) and extracted with Et_2O (3 × 50 ml). The combined Et_2O extracts were dried (Na_2SO_4); addition of HBr–Et_2O afforded a yellow solid. Recrystallization from *i*-PrOH–Et_2O gave 0.232 g (33%) of **3**: mp 217–219° dec. Anal. ($C_{13}H_{22}NO_3Br$) C, H, N.

***N*-Isopropyl-2,3-dihydroxyphenethanolamine Hydrobromide (2b).** Using the procedure described for the synthesis of **2a**, O-demethylation of **3** (500 mg, 0.0018 mol) afforded 478 mg (90%) of **2b**, after crystallization from *i*-PrOH–Et_2O: mp 243–247° dec. Anal. ($C_{11}H_{18}NO_3Br$) C, H, N.

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