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Synthesis and Evaluation of Brain Catecholamine Depletion by *N*-Alkyl Derivatives of 6-Aminodopamine†,[1]

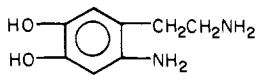
Donald E. Nerland* and Edward E. Smissman

Department of Medicinal Chemistry, School of Pharmacy, The University of Kansas, Lawrence, Kansas 66045.
Received May 8, 1975

Three analogs of 6-aminodopamine were synthesized and tested for their ability to deplete the central nervous system of norepinephrine and dopamine. The compounds were analogs in which the aliphatic nitrogen of the ethyl side chain was substituted with dimethyl, isopropyl, and methyl groups. The first two compounds showed only very weak depletion of norepinephrine stores, while having no effect on dopamine levels. The third compound was not tested due to its instability.

The isostere of 6-hydroxydopamine, 6-aminodopamine (**1**), was reported by Stone and coworkers[2a] to be an effective noradrenaline depletor in the dog heart. Similar results have also been obtained in the mouse brain after intracerebral injection of 6-aminodopamine.[2b] Subsequent studies[3,4] have shown that 6-aminodopamine is a neurotoxic agent, capable of producing a degeneration of catecholamine neurons, similar to 6-hydroxydopamine.[5]

For 6-aminodopamine to exert its neurotoxic action a critical amount of 6-aminodopamine must be taken up by the neuron. Modification of the structure of 6-aminodopamine, so as to alter its uptake, could lead to a more selective neurotoxic agent for the noradrenergic or dopaminergic neurons of the central nervous system. This report is concerned with the modification of the nitrogen of the ethylamine side chain of **1**. In order to examine the effect of alkyl substituents on the ethylamine nitrogen compounds **2–4** were prepared and examined for their ability to act as catecholamine depletors in the central nervous system.



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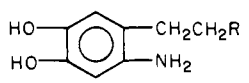
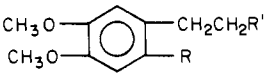


2, R = $N(CH_3)_2$
3, R = $NHCH(CH_3)_2$
4, R = $NHCH_3$

The synthesis of **2** was initiated by nitration of **5** to yield **6**, which was subsequently allowed to react under Eschweiler–Clarke conditions to yield the dimethyl derivative **7**. Reduction of the nitro group of **7** afforded the diamine **8** which was treated with 48% HBr to remove the methoxy-protecting groups.

Reductive alkylation of **5** with acetone afforded the *N*-isopropyl compound **9**. Nitration of **9** afforded **10**, which was reduced and the methoxy-protecting groups were removed as before to yield **3**.

Nitration of **11** with nitric acid afforded **12**. Catalytic reduction of **12** with platinum oxide yielded 1-(2-amino-4,5-dimethoxyphenyl)-2-(methylamino)ethane which was isolated as its diacetamide **13**. The acetate and methoxy-protecting groups were removed with 48% HBr to yield **4** as its dihydrobromide salt.



5, R = H; R' = NH_2
6, R = NO_2; R' = NH_2
7, R = NO_2; R' = $N(CH_3)_2$
8, R = NH_2; R' = $N(CH_3)_2$
9, R = H; R' = $NHCH(CH_3)_2$
10, R = NO_2; R' = $NHCH(CH_3)_2$
11, R = H; R' = $NHCH_3$
12, R = NO_2; R' = $NHCH_3$
13, R = $NHC(=O)CH_3$; R' = $NCH_3C(=O)CH_3$

Pharmacology and Discussion. Compounds **1–3** were evaluated for their ability to deplete the central nervous system of norepinephrine and dopamine. Compound **4** was so unstable that it could not be tested for biological activity. The compounds were dissolved in 0.9% saline solution containing 1 mg/ml of ascorbic acid. In a series of four experiments, white mice (15–30 g) were injected intracranially with 50 μg (calculated as free base) of test compound at intervals of 24 hr on three successive days. The animals were sacrificed 24 hr after the final injection and the brains removed. The catecholamine content of the brain was assayed according to the procedure of Shellenberger and Gordon.[6] The catecholamine content of the treated mouse brains is given in Table I and is expressed as a percentage of that found in control brains.

As can be seen from Table I, compounds **2** and **3** caused no reduction in the dopamine levels and only a very slight decrease in the levels of norepinephrine in the central nervous system. The inability of these compounds to cause a reduction in the catecholamine content of the central nervous system may be attributed to at least two reasons. It is possible these analogs were ineffective because of the inability of the uptake system to transport these compounds to the site of action within the neuron. It has been previously shown[7] that increasing bulk on the nitrogen of the ethyl side chain decreases a compound's ability to participate in the uptake process. In addition, the 6-aminodopamine analogs may be ineffective because of their ability to undergo facile cyclization and rearrangement to indoles.[8] In essence this reaction removes the ethylamine side chain from participating in the uptake process.

† Submitted in memory of Dr. Edward E. Smissman.

* Correspondence concerning this paper should be addressed to this author at the Department of Pharmacology, University of Minnesota, Minneapolis, Minn. 55455.

Table I. Catecholamine Depletion by 6-Aminodopamine Analogs

Compd	Dosage schedule	Total	Sacrifice (time after last inj)	NE, ng/g[a]	% control	DA, ng/g[a]	% control
1	3 × 50 μg	150 μg	24 hr	113 ± 17	34	566 ± 10	66
2	3 × 50 μg	150 μg	24 hr	270 ± 35	88	581 ± 40	106
3	3 × 50 μg	150 μg	24 hr	328 ± 25	81	605 ± 17	94

[a] Figures represent standard error.

Experimental Section

Melting points were determined in open glass capillaries on a Thomas-Hoover Uni-Melt apparatus and are uncorrected. Elemental analyses were performed on F & M 185 or 185-B CHN at the University of Kansas. Where analyses are indicated by symbols of the elements, the analytical results are within ±0.4% of the theoretical values. Ir and NMR spectra were obtained for all of the compounds and were consistent with the given structures. Ir spectra were recorded on Beckman IR-10 and IR-33 instruments, and NMR spectra were recorded on a Varian Associates T-60 instrument using tetramethylsilane or sodium 2,2-dimethyl-2-silapentane-5-sulfonate as internal standards. Mass spectral peak matching was performed, using a Varian Atlas CH 5B, on compounds which underwent facile autoxidation.

1-(4,5-Dimethoxy-2-nitrophenyl)ethylamine (6). Commercially available 2-(3,4-dimethoxyphenyl)ethylamine (**5**, 4.0 g, 0.018 mol) was nitrated according to the method of Mason[9] utilizing dilute nitric acid to yield 3.7 g (74%) of compound, mp 110–111° (lit.[9] 110–111°).

1-(4,5-Dimethoxy-2-nitrophenyl)-2-(dimethylamino)ethane (7). Compound **6** (5.0 g, 0.022 mol) was refluxed with formic acid (5.6 g, 0.110 mol) and 37% aqueous formaldehyde (5.0 g, 0.066 mol) for 8 hr. The reaction mixture was cooled, 5 ml of 4 *N* HCl was added, and volatiles were evaporated under reduced pressure. The residue was dissolved in 60 ml of H_2O and made basic with 8 *N* NaOH solution. The aqueous solution was extracted with ether and the combined extracts were washed with H_2O and saturated NaCl. The ether solution was dried (K_2CO_3) and the desiccant removed by filtration. The solvent was removed under reduced pressure to yield 4.5 g of a dark oil. Chromatography on silica gel, eluting with ethyl acetate, acetone, and NH_4OH (10:1:0.5), afforded 2.9 g (53%) of a yellow oil. Anal. ($C_{12}H_{18}N_2O_4$) C, H, N.

1-(4,5-Dimethoxy-2-aminophenyl)-2-(dimethylamino)ethane Dihydrochloride (8). To compound **7** (2.0 g, 7.9 mmol) in 51 ml of ethanol was added platinum oxide (200 mg) and the contents were hydrogenated at 25° under 3 atm of hydrogen. The catalyst was removed by filtration and the solution saturated with HCl. The solvent was removed under reduced pressure and the resulting solid recrystallized from ethanol to yield 1.5 g (47%) of compound, mp 244–246° dec. Anal. ($C_{23}H_{12}Cl_2N_2O_2$) C, H, N.

1-(2-Amino-4,5-dihydroxyphenyl)-2-(dimethylamino)ethane Dihydrobromide (2). To compound **8** (1.5 g, 0.005 mol) contained in a Wheaton pressure bottle was added 30 ml of 48% HBr. The system was flushed with nitrogen and the container sealed and heated at 120° for 6 hr. The volatiles were removed under reduced pressure and the residue was dried under vacuum to yield 1.4 g (70%) of compound: mp 163–167°; found M^+ 196.119, $C_{10}H_{16}N_2O_2$ requires 196.121.

1-(3,4-Dimethoxyphenyl)-2-(isopropylamino)ethane (9). To **5** (13.0 g, 0.072 mol) in 150 ml of acetone was added platinum oxide and the contents were hydrogenated at 25° under 3 atm of hydrogen. The catalyst was removed by filtration and the solvent removed under reduced pressure. The resulting yellow oil was distilled [92° (0.1 mm)] to yield 15.7 g (98%) of compound. Anal. ($C_{13}H_{21}NO_2$) C, H, N.

1-(4,5-Dimethoxy-2-nitrophenyl)-2-(isopropylamino)ethane Perchlorate (10). To a mixture of 64 ml of nitric acid and 12 ml of H_2O at 12–15° was added compound **9** (8.0 g, 0.036 mol) dropwise with stirring. The mixture was stirred for 4 hr and diluted with 50 ml of ice–H_2O. The precipitate was collected and dissolved in hot H_2O. The solution was made basic with NaOH and allowed to cool. The precipitate was removed by filtration and recrystallized as the perchlorate salt from ethanol to yield 9.7 g (73%) of compound, mp 198–200° dec. Anal. ($C_{13}H_{22}ClN_2O_8$) C, H, N.

1-(2-Amino-4,5-dihydroxyphenyl)-2-(isopropylamino)ethane Dihydrobromide (3). The free base of **10** (1.34 g, 0.005 mol) was dissolved in 50 ml of ethanol and the contents were hydrogenated over platinum oxide. The catalyst was filtered and the solvent removed under reduced pressure. The residue was dissolved in 20 ml of 48% HBr and the solution was transferred to a Wheaton bottle. The system was flushed with nitrogen and the container sealed and heated at 120° for 4 hr. The volatiles were removed under reduced pressure. The residue was dried under vacuum to yield 1.5 g (82%) of compound: mp 137–140°; found M^+ 210.134, $C_{11}H_{18}N_2O_2$ requires 210.136.

1-(3,4-Dimethoxyphenyl)-2-(methylamino)ethane Hydroiodide (11). Compound **11** was prepared according to the method of Buck[10] without modification: mp 131–132° (lit.[10] 131°).

1-(4,5-Dimethoxy-2-nitrophenyl)-2-(methylamino)ethane Hydrochloride (12). The free base of **11** (8.1 g, 0.042 mol) was nitrated under the same conditions as **10** to yield 6.8 g (67%) of compound, mp 208–209°. Anal. ($C_{11}H_{17}ClN_2O_4$) C, H, N.

1-(2-Acetamido-4,5-dimethoxyphenyl)-2-(*N*-methylacetamido)ethane (13). To compound **12** (5.0 g, 0.022 mol) dissolved in 75 ml of ethanol was added platinum oxide (500 mg) and the contents were hydrogenated at 25° under 2 atm of hydrogen. The catalyst was removed by filtration, the solvent removed under reduced pressure, and the residue dissolved in 25 ml of acetic acid. Acetic anhydride (4.2 g, 0.08 mol) was added to the solution and refluxed for 2 hr. The reaction mixture was diluted with H_2O and extracted with chloroform and the combined extracts were dried ($MgSO_4$). The desiccant was removed by filtration and the solvent removed under reduced pressure. The residue was chromatographed on silica gel (acetone) and recrystallized (benzene–hexane) to yield 2.6 g (40%) of compound, mp 102–103°. Anal. ($C_{15}H_{22}N_2O_4$) C, H, N.

Acknowledgment. We wish to thank Dr. C. L. Blank for performing the biological assays. This investigation was supported by National Institutes of Health Grants NS 90399 and GM 01341.

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