ovariectomy, each rat was subcutaneously injected with 6 μg of 17β-estradiol in 0.1 mL of corn oil at time 0. The test compound in corn oil was injected subcutaneously twice, at time 0 and at 8 h, with 2.5 mg of test compound in 0.2 mL of corn oil. Vaginal smears were obtained at 32 h, and rats showing smears with cornified epithelial cells were considered to be in estrus. The optimum conditions were established with compound **4** at 0, 8, 24, 32, 48, 56, and 72 h. Thereafter, smears were taken at 32 h for compounds **1–3**. Details of the procedures describing the competitive binding to the estrogen receptor protein are outlined in previous publications.[14,15]

Acknowledgment. This investigation was supported by Grant CA 22001, awarded by the National Cancer Institute, Department of Health, Education and Welfare.

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N-Aralkyl Substitution of 2-Amino-5,6- and -6,7-dihydroxy-1,2,3,4-tetrahydronaphthalenes. 2. Derivatives of a Hypotensive-Positive Inotropic Agent[1]

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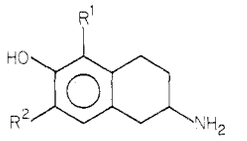
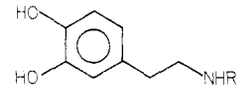
Seven derivatives of 2-[[2-(3,4-dihydroxyphenyl)-1-methylethyl]amino]-6,7-dihydroxy-1,2,3,4-tetrahydronaphthalene, an inotropic agent which also causes a decrease in blood pressure, were synthesized and tested for inotropic potency, cardioselectivity, and inotropic selectivity. The derivatives were designed to explore whether catechol moieties and rigid rotamers of dopamine are necessary for the activity which was found in the parent compound. The derivatives had phenolic functions in place of catechols, and they had phenethylamine in place of the tetrahydronaphthalene moiety. In no case was the profile of activity of the parent compound duplicated in the derivatives.

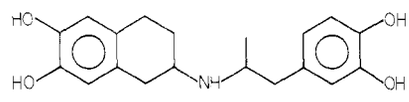
In a previous paper we described the cardiovascular properties of a series of *N*-aralkyl-substituted rigid analogues of dopamine,[2] where 2-amino-5,6-dihydroxy-1,2,3,4-tetrahydronaphthalene (A-5,6-DTN, **1**) and 2-amino-6,7-dihydroxy-1,2,3,4-tetrahydronaphthalene (A-6,7-DTN, **2**) served as rigid forms of dopamine. One goal of that research was to prepare a selective inotropic agent which was superior to either dopamine (**3**) or dobutamine (**4**). Indeed, one compound, **5**, proved to be at least as potent and inotropic selective as the standards and, unlike compounds of similar structure which increased blood pressure,[2] it caused a decrease in blood pressure at inotropic doses. This combination of hypotensive and inotropic activities has found clinical application in the treatment of congestive heart failure using the two drugs nitroprusside and dopamine.[3] We were intrigued by the unique pharmacological profile exhibited by this compound and, therefore, set out to examine the effect of structural modification on pharmacological activity.



1, R^1 = OH; R^2 = H
2, R^1 = H; R^2 = OH



3, R = H
4, R = $CH(CH_3)CH_2$-Ph·OH



5

(1) This paper has been presented. See "Abstracts of Papers", 182nd National Meeting of the American Chemical Society, New York, Aug 1981; American Chemical Society: Washington, DC, 1981; Abstr MEDI 8.
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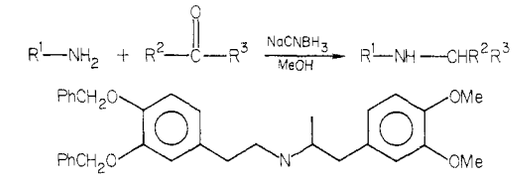
Scheme I



13

Our earlier work[2] explored two structural parameters necessary for potency, cardioselectivity and inotropic selectivity, in *N*-aralkyl-substituted rigid dopamine analogues. One parameter was the rotation of the phenyl ring relative to the ethylamine side chain (A-5,6-DTN vs. A-6,7-DTN) and the other was the chain length and branching of the aralkyl function attached to the tetralin amine. Compound **5** demonstrated that the A-6,7-DTN moiety coupled with a 2-propyl-3-(3′,4′-dihydroxyphenyl) group afforded the best spectrum of activity in the series. The present study examined the effects of the hydroxyl groups on the aromatic rings and the necessity of a rigid form of dopamine in the molecule.

Chemistry. The products (Table I) were formed by reductive amination of the 6-methoxy- and 6,7-dimethoxy-2-aminotetralin or dopamine *O*-methyl ether with the corresponding ketones using the method of Borch (Scheme I).[4] The hydroxyl groups were then deblocked in refluxing 48% hydrobromic acid. In the case of **12**, the hydroxyl groups were protected as benzyl ethers (**13**) with deblocking accomplished by hydrogenolysis. The dihydroxytetralin products were unstable in aqueous solution over a few hours; however, the compounds were stable for several hours in aqueous bisulfite solution.

Because of the sensitivity of the catechol products to air, the products were isolated after deblocking simply be removing the hydrobromic acid in vacuo, dissolving the re-

(4) Borch, R.; Bernstein, M.; Durst, H. *J. Am. Chem. Soc.* **1971**, *93*, 2897.

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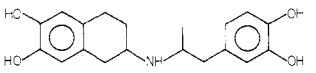
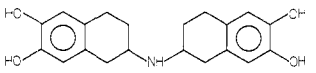
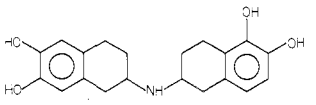
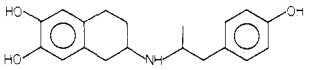
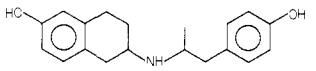
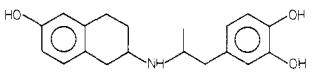
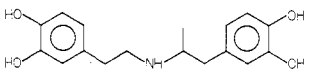
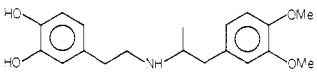
Table I. Inotropic Potency, Cardioselectivity, and Inotropic Selectivity of Test Compounds in Dogs [a]

	structure	N [a]	inotropic potency, nmol/kg		cardioselectivity: Δ BP, mmHg		inotropic selectivity: Δ HR, bpm	
			CF(50) [b]	CF(100) [b]	CF(50)	CF(100)	CF(50)	CF(100)
5		6	11.4 ± 1.7 [d]	27.0 ± 3.6	−39 ± 4	−30 ± 5	−5 ± 5	4 ± 6
6		2	961.0	2650.0	−78	84	31	62
7		4	210 ± 70	590 ± 200	−61 ± 5	−55 ± 8	24 ± 4	31 ± 9
8		4	680 ± 300	c	−25 ± 16	c	23 ± 11	c
9		2	c	c	c	c	c	c
10		4	25 ± 14	85 ± 32	−46 ± 8	−66 ± 7	30 ± 5	49 ± 7
11		4	4 ± 1.0	13 ± 2	−19 ± 3	−34 ± 3	26 ± 4	39 ± 6
12		4	490 ± 100	1100 ± 200	−24 ± 3	−31 ± 2	10 ± 6	17 ± 9

[a] N refers to number of experiments. [b] CF(50) and CF(100) are the drug doses causing a 50 and a 100% increase in right ventricular contractile force (see ref 1). [c] Indicates the CF(50) or CF(100) levels were not obtained at the highest dose tested. [d] Values are means plus or minus the standard error of the mean.

sulting solid in degassed water, clearing the solution with Norit, filtering, and removing the water in vacuo. No further purification was attempted. This procedure apparently resulted in the trapping of HBr in the waters of hydration, for in no case where this procedure was employed were single equivalents of HBr found in the combustion analysis. Mass spectral data failed to show any P + 2 peaks, which would be characteristic of bromine incorporation in the molecules. Additionally, catechol and phenol products all exhibited single spots on TLC (*n*-BuOH/HOAc/H_2O, 12:3:5). Thus, the products are apparently pure.

Though a mixture of diastereomers can theoretically exist in structures **5–10**, we were unable to detect mixtures in any of the crystallized methyl ether intermediates by TLC ($CHCl_3$/MeOH/NH_4OH, 9:0.1:0.05; EtOAc/MeOH, 2:1) or by ^{13}C NMR.

Pharmacology. The compounds were tested in vivo in mongrel dogs as previously described.[2] For comparative purposes, all in vivo data have been normalized to 50 [CF(50)] and 100% [CF(100)] increases in right ventricular contractile force. Inotropic selectivity was assessed by normalizing changes in heart rate to the CF(50) and CF(100) levels. Similarly, cardioselectivity was estimated by normalizing changes in diastolic blood pressure to the two levels of contractile force change.

Results and Discussion

Compounds **6** and **7** were designed to test the hypothesis that a preferred rotamer on the propylcatechol end of the molecule was involved in the activity of the molecule at a particular receptor. These compounds were dramatically less potent (Table I) than **5** and failed to show inotropic selectivity. The blood-pressure effects of **6** were typical of A-6,7-DTN derivatives, which are pressor agents, while **7** acted like A-5,6-DTN compounds and caused a decrease in blood pressure. Compounds **8–10** were prepared to ascertain the importance of catechol vs. *p*-phenol on the aromatic rings. The presence of at least one catechol is essential, since **9** was inactive. The potency decreased significantly when a *p*-phenol replaced the catechol (**8**); however, there was little effect on potency with this change on the tetrahydronaphthalene (**10**). Neither compound had appreciable inotropic selectivity, while both caused marked decreases in blood pressure. Compound **11** is the nonrigid congener of **5**. It was prepared to see if the activity of **5** could be duplicated in the absence of a rigid dopamine nucleus. Though the inotropic potency was greater and the blood-pressure effects were similar to **5**, the compound failed to have inotropic selectivity. Compound **12** was synthesized to see if methoxy groups could replace the hydroxy groups on the phenyl ring. Though significantly less potent than **11**, at higher doses the compound showed inotropic selectivity similar to dobutamine.[2]

The unique pharmacological profile of **5** has resisted duplication by structural analogues presented here and previously.[2] The difficulty in replicating the spectrum of activity may result from the interaction of the compound with several receptor types, both in the heart and in the vasculature. We have found that the inotropic response of **5** is due to agonist activity at β-adrenergic receptors in the myocardium, while the inotropic selectivity arises in part from sympathoinhibition mediated by cardiac α-adrenergic receptors. The vascular action of **5** involves agonist activity at postsynaptic β receptors as well as α receptors. Apparently, the strucutre of **5** is particularly suited for activity at these receptors, while slight structural modifications moderate or eliminate activity at one or more receptors. A detailed examination of the mechanism of action of **5** will be reported in due course.

Experimental Section

Melting points were determined on a Thomas-Hoover melting poing apparatus and are uncorrected. IR spectra were recorded on a Perkin-Elmer Model 283 spectrophotometer as KBr pellets. ^1H NMR spectra were determined on a Varian T-60A spectrometer in $CDCl_3$ or CD_3OD using tetramethylsilane as a standard

or in D_2O using 4,4-dimethyl-4-silapentane-5-sulfonate as a standard. ^{13}C NMR spectra were taken of an IBM NR/80 spectrometer. Mass spectra were obtained on a Hewlett Packard 5985C GC/MS by the Northwestern University Analytical Service, Evanston, IL. Elemental analyses were performed by Galbraith Laboratories, Knoxville, TN.

2-Amino-6,7-dihydroxy-1,2,3,4-tetrahydronaphthalene (A-6,7-DTN). The compound was prepared using the method of Cannon[5] or Horn,[6] mp 268–270 °C (lit.[7] mp 270–271 °C).

2-[[2-(3,4-Dihydroxyphenyl)-1-methylethyl]amino]-6,7-dihydroxy-1,2,3,4-tetrahydronaphthalene (5). The compound was prepared as reported earlier.[2]

2,2′-Iminobis[1,2,3,4-tetrahydro-6,7-naphthalenediol] (6). The compound was prepared as reported earlier.[2]

2-[(5,6-Dihydroxy-1,2,3,4-tetrahydronaphthalenyl)imino]-1,2,3,4-tetrahydro-6,7-naphthalenediol (7). A mixture of 1.00 g (4.10 mmol) of A-6,7-DTN·HCl dimethyl ether, 0.850 g (4.10 mmol) of 5,6-dimethoxy-2-tetralone,[5] and 0.260 g (4.10 mmol) of sodium cyanoborohydride in 100 mL of methanol was stirred for 3 days under a nitrogen atmosphere. The solvent was removed, water was added, and extraction of the aqueous mixture with ethyl acetate afforded 7 tetramethyl ether. The product was taken up in methanol and the solution was saturated with hydrogen chloride. The solvent was removed on a rotary evaporator, and the resulting solid was crystallized from ethanol/water (10:1). The product was dissolved in 50 mL of 48% hydrobromic acid, and the solution was heated to reflux under a nitrogen atmosphere for 24 h. The acid was removed in vacuo, the resulting solid was dissolved in water, cleared with Norit, and filtered, and the water was removed in vacuo, leaving 0.200 g (11.6%) of light brown product: mp >300 °C; NMR (CD_3OD) δ 1.4–2.4 (m, 4 H), 2.4–3.0 (m, 8 H), 3.3–4.0 (m, 2 H), 6.2–6.4 (m, 4 H). The dicatechol proved to be too unstable to afford a correct combustion analysis: however, a correct C, H, N analysis was obtained for the HCl salt of the tetramethyl ether of 7: NMR (CD_3OD) δ 1.6–2.6 (m, 4 H), 2.6–3.2 (m, 8 H), 3.80 (s, 12 H), 6.62 (s, 2 H), 6.78 (s, 2 H).

2-[[2-(4-Hydroxyphenyl)-1-methylethyl]amino]-6,7-dihydroxy-1,2,3,4-tetrahydronaphthalene (8). The reductive amination of the protected A-6,7-DTN and *p*-methoxyphenylacetone (Aldrich) was carried out as for 7, affording the HCl salt of the trimethyl ether of 8 in 89% yield. Deblocking and workup as for 7 yielded 8 in 66% yield: mp 154–155 °C; NMR (CD_3OD) δ 1.61 (d, J = 6 Hz, 3 H), 1.81–2.91 (m, 2 H), 2.91–3.64 (m, 6 H), 3.64–4.31 (m, 2 H), 6.74–6.87 (m, 2 H), 7.04 (d, J = 8 Hz, 2 H), 7.41 (d, J = 8 Hz, 2 H). Anal. ($C_{19}H_{23}NO_4 \cdot 1H_2O \cdot 1.18HBr$) C, H, N, Br.

2-Amino-6-methoxy-1,2,3,4-tetrahydronaphthalene. A mixture of 5.50 g (31.3 mmol) of 6-methoxy-2-tetralone (Aldrich) and 2.61 g (31.3 mmol) of methoxylamine hydrochloride in 3.1 mL (31 mmol) of a 10 N solution of sodium hydroxide was heated to 70 °C for 18 h. The addition of water and extraction with ethyl acetate afforded the crude *o*-methyl oxime, which was dissolved in 50 mL of THF and, under a nitrogen atmosphere, was treated with 62 mL (62 mmol) of a 1 M solution of BH_3–THF complex. The solution was heated to reflux for 6 h and quenched with water. The addition of water and extraction with ethyl acetate afforded with crude tetralinamine. The product was dissolved in methanol, and the solution was saturated with hydrogen chloride. The solvent was removed, yielding 3.36 g (50.9%) of crude 2-amino-6-methoxy-1,2,3,4-tetrahydronaphthalene: NMR (CD_3OD) δ 1.5–2.5 (m, 2 H), 2.5–3.2 (m, 4 H), 3.2–3.6 (m, 1 H), 3.75 (s, 3 H), 6.6–7.4 (m, 3 H). The product was used without further purification.

2-[[2-(4-Hydroxyphenyl)-1-methylethyl]amino]-6-hydroxy-1,2,3,4-tetrahydronaphthalene (9). The reductive amination of 2-amino-6-methoxy-1,2,3,4-tetrahydronaphthalene and *p*-methoxyphenylacetone (Aldrich) was carried out as for 7, affording the HCl salt of the dimethyl ether of 9 in 22% yield. Deblocking and workup as for 7 afforded 9 in 49% yield: mp >300 °C; NMR (CD_3OD) δ 1.32 (d, J = 6 Hz, 3 H), 1.6–2.6 (m, 3 H), 2.6–3.2 (m, 5 H), 3.2–4.1 (m, 2 H), 6.4–7.3 (m, 7 H). Anal. ($C_{19}H_{23}NO_2 \cdot 0.8H_2O \cdot 1.15HBr$) C, H, N, Br, H_2O.

2-[[2-(3,4-Dihydroxyphenyl)-1-methylethyl]amino]-6-hydroxy-1,2,3,4-tetrahydronaphthalene (10). The reductive amination of 2-amino-6-methoxy-1,2,3,4-tetrahydronaphthalene and 3,4-dimethoxyphenylacetone (Aldrich) was carried out as for 7, affording the HCl salt of the trimethyl ether of 10 in 14% yield. Deblocking and workup as for 7 afforded 10 in 95% yield: mp >300 °C; NMR (CD_3OD) δ 1.27 (d, J = 6 Hz, 3 H), 1.5–2.5 (m, 3 H), 2.5–3.2 (m, 5 H), 3.2–3.9 (m, 2 H), 6.4–7.1 (m, 6 H). Anal. ($C_{19}H_{23}NO_3 \cdot 1.8H_2O \cdot 1.25HBr$) C, H, N, Br, H_2O.

4-[2-[[2-(3,4-Dihydroxyphenyl)-1-methylethyl]amino]-ethyl]-1,2-benzenediol (11). The reductive amination of β-(3,4-dimethoxyphenyl)ethylamine (Aldrich) and 3,4-dimethoxyphenylacetone (Aldrich) was carried out as for 7, affording the HCl salt of the tetramethyl ether of 11 in 60% yield. Deblocking and workup as for 7 afforded 11 in 70% yield: mp 125 °C; NMR (D_2O) δ 1.33 (d, J = 6 Hz, 3 H), 2.5–3.7 (m, 7 H), 6.4–7.1 (m, 6 H). Anal. ($C_{17}H_{21}NO_4 \cdot 0.75H_2O \cdot 1.13HBr$) C, H, N, Br, H_2O.

4-[2-[[2-(3,4-Dihydroxyphenyl)-1-methylethyl]amino]-ethyl]-1,2-dimethoxybenzene (12). The reductive amination of 3,4-bis(benzyloxy)phenethylamine hydrochloride (Aldrich) and 3,4-dimethoxyphenylacetone (Aldrich) was carried out as for 7, affording the HCl salt 13 in 65% yield. Hydrogenolysis of the HCl salt of 13 with Pd/C in ethanol at 40 psi of hydrogen with shaking using a Paar hydrogenator for 4 h afforded 12 in 70% yield: mp 212 °C; NMR (CD_3OD) δ 1.23 (d, J = 6 Hz, 3 H), 2.7–3.7 (m, 7 H), 3.78 (s, 6 H), 6.6–7.1 (m, 6 H). Anal. ($C_{19}H_{25}NO_4 \cdot HCl$) C, H, N.

Acknowledgment. The authors express their appreciation to Lawrence A. Black and Lee Preusser for their excellent technical assistance.

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Nitro and Amino Derivatives of Lucanthone as Antitumor Agents

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Received August 6, 1981

A group of nitro and amino derivatives of lucanthone was prepared and tested for antitumor activity. Reaction of 1-chloro-4-methyl-7-nitrothioxanthenone and *N,N*-diethylethylenediamine gave the 7-amino analogue (11) directly, accompanied by 7-amino-1-chloro-4-methylthioxanthenone. The antitumor activity of 11 was inferior to that of lucanthone and 7-hydroxylucanthone. The most active compound in the series was the nitro compound 1. In the P-388 lymphocytic leukemia screen it showed a T/C = 178 at 200 mg/kg.

In a recent paper, reasons were given to support the hypothesis that hydroxylation of lucanthone at appropriate positions in the ring system might lead to compounds with enhanced antitumor activity.[1] It has been shown that

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