Structure-Activity Relationships of N-Substituted Dopamine and 2-Amino-6,7-dihydroxy-1,2,3,4-tetrahydronaphthalene Analogues: Behavioral Effects in Lesioned and Reserpinized Mice

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N,N-Disubstituted dopamine and 2-amino-6,7-dihydroxy-1,2,3,4-tetrahydronaphthalene (6,7-ADTN) analogues were synthesized and tested intraperitoneally in mice for dopamine agonism. Compounds inducing asymmetric postures in unilaterally caudectomized mice were further tested in mice treated with reserpine and α-methyl-*p*-tyrosine methyl ester. ED_{50} values determined for reversal of reserpine-induced catalepsy were used to rank drug potency and correlated with molecular structure. *N*-*n*-Propyl N-substituted compounds were more effective than other *N*,*N*-dialkyl homologues. Of these, analogues with one alkyl group larger than propyl became inactive or their dopaminomimetic effect was reduced when the propyl was replaced with a larger group. N-Monosubstituted analogues were inactive as dopamine agonists. *N*-*n*-Pr-*N*-*n*-Bu-6,7-ADTN was six times more potent than *N*-*n*-propyl-*N*-*n*-pentyl- and *N*-*n*-propyl-*N*-phenethyldopamine but ten times less potent than apomorphine. The availability of an array of structurally related dopamine analogues with dopaminomimetic properties may make it possible to test the hypothesis that there are more than one type of dopamine receptor and that stereotypy and locomotor activity may have different central nervous system loci. Moreover, they may be of potential use in the treatment of parkinsonism and other extrapyramidal disorders.

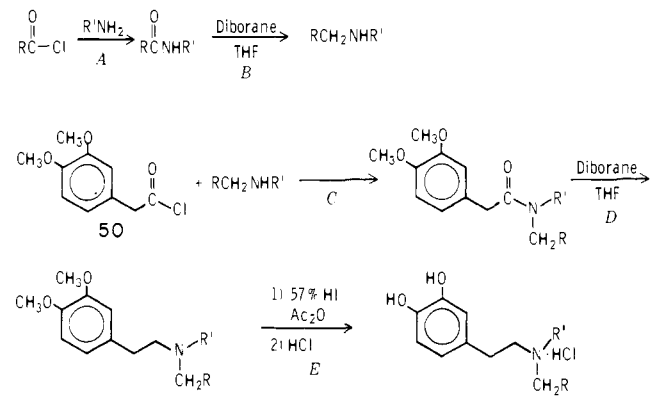
We have reported previously[1] that *N*-*n*-propyl-*N*-phenethyl-β-(3,4-dihydroxyphenyl)ethylamine hydrochloride (**29**) was the most effective among N,N-disubstituted dopamine (DA) analogues with respect to long-lasting CNS dopaminomimetic effects when given intraperitoneally to unilaterally nigra-lesioned rats and caudectomized mice. By contrast, *N*-*n*-propyl-*N*-*n*-butyl- (**39**) and *N*-*n*-propyl-*N*-*n*-pentyldopamine (**43**) were shown to be more effective in causing a DA-like increase in renal blood flow of the pentobarbital-anesthetized dog when given by arterial infusion.[2] *N*-*n*-Monosubstituted DA analogues were found to be inactive as DA agonists,[1-3] with the exception of epinine, shown to be a vascular DA agonist,[2] while *N*-methyl N-substituted analogues demonstrated little or no effect.[1-3]

Of the symmetrically N,N-disubstituted DA derivatives tested only *N*,*N*-di-*n*-propyldopamine (**23**) was shown to have dopaminomimetic properties when given by arterial infusion to anesthetized dogs,[2] by peripheral administration, or by direct intracerebral injection into the nucleus accumbens and caudate-putamen of the rat.[4] For any homologous series in the N,N-disubstituted DA analogues, the presence of the *N*-*n*-propyl group appeared to be consistently the optimum substituent for maximum behavioral effects in lesioned animals[1,3] or for DA-like vascular effects.[2] This suggests that the *N*-*n*-propyl substituent may possess unique functional importance for the drug's intrinsic DA-like activity.

In our present work, we sought supplemental evidence to support this thesis by synthesizing and testing additional appropriate N,N-disubstituted DA analogues, as well as some N,N-disubstituted derivatives of 2-amino-6,7-dihydroxy-1,2,3,4-tetrahydronaphthalene (6,7-ADTN). Furthermore, for *N*-phenylalkyl substituents, we explored the effects on DA agonism by varying the length of the alkyl chain and by replacing the phenyl moiety with a cyclohexyl group.

Newly synthesized N,N-disubstituted DA and 6,7-ADTN analogues (Tables III and IV), as well as many previously reported ones,[1,3] were screened initially in unilaterally caudectomized mice for CNS dopaminomimetic activity. Those eliciting a positive behavioral response were tested further for direct DA agonism in mice pretreated with reserpine and the hydrochloride of *dl*-α-methyl-*p*-tyrosine methyl ester (α-MTM), a tyrosine hydroxylase inhibitor.[5] ED_{50} values for reversing reserpine-induced catalepsy, a DA postsynaptic-mediated phenomenon,[6] were estimated in an effort to rank the relative potencies.

Scheme I



Chemistry. With the exception of the *N*,*N*-diphenylethyldopamine (**31**) derivative, N,N-disubstituted DA analogues were synthesized according to Scheme I. Whenever the appropriate secondary amine was commercially unavailable, it was prepared as indicated by steps A and B of Scheme I and purified either by vacuum distillation or by crystallization of its hydrochloride salt (Table I) before its use in the next step. The preparation of N-monosubstituted DA derivatives and their *N*-methyl homologues used in the present work has been reported elsewhere.[1] Compound **31** was prepared by the reaction of β-(3,4-dimethoxyphenyl)ethylamine with an excess of the phenylacetic acid-$NaBH_4$ complex according to the method of Marchini et al.[7] Although its synthesis had been previously described,[1] **29** is shown in Table IV with additional melting point data. These correspond to different crystalline forms, each obtained under different crystallization conditions. ^1H NMR and IR spectra of the three different crystalline forms were identical.

The N,N-disubstituted 6,7-ADTN derivatives were prepared according to Scheme II. The methoxylated

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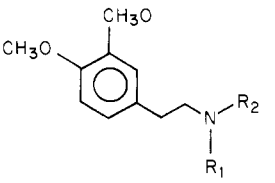
Table I. Physical Properties of N,N-Disubstituted Amines

no.	R_1	R_2	% yield	bp, °C (mmHg)	HCl salt lit. mp, °C
1	CH_3CH_2	n-$CH_3(CH_2)_2$	98	79-81 (atm pres) lit.[a] 77-80 (738)	
2	n-$CH_3(CH_2)_3$	n-$CH_3(CH_2)_4$	85	180-182 (atm pres) lit.[b] 180-182 (743)	286-288
3	n-$CH_3(CH_2)_2$	$C_6H_5CH_2$	94	40-42 (0.20) lit.[c] 47-55 (0.2)	160-161
4	n-$CH_3(CH_2)_2$	$C_6H_5CH_2CH_2$	92	104-107 (15-16) lit.[d] 102 (16)	
5	n-$CH_3(CH_2)_3$	$C_6H_5CH_2CH_2$	81	72-74 (0.5)	
6	n-$CH_3(CH_2)_2$	$C_6H_5CH_2CH_2CH_2$	99	73-76 (1.8-2.0)	
7	n-$CH_3(CH_2)_2$	2-cyclohexylethyl	97	96-100 (8-9) lit.[e] 106-107 (13)	265-267 266-267

[a] K. N. Campbell, A. H. Sommers, and B. K. Campbell, *J. Am. Chem. Soc.*, 66, 82 (1944). [b] H. R. Henze and D. J. Humphreys, *ibid.*, 64, 2878 (1942). [c] A. R. Surrey and M. K. Rukwid, *ibid.*, 77, 3798 (1955). [d] E. J. Schwoegler and H. Adkins, *ibid.*, 61, 3499 (1939). [e] F. F. Blicke and F. B. Zienty, *ibid.*, 61, 93 (1939).

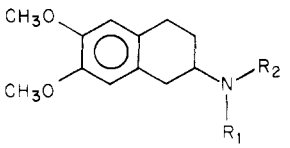
Table II. Physical Properties of the Hydrochlorides of N,N-Disubstituted β-(3,4-Dimethoxyphenyl)ethylamines



no.	R_1	R_2	% yield	mp, °C	recrystn solvent	formula[c]
8	CH_3CH_2	n-$CH_3(CH_2)_2$	91	98-99	EtOAc	$C_{15}H_{26}ClNO_3$
9	n-$CH_3(CH_2)_2$	n-$CH_3(CH_2)_2$	87	101.5-103.0	$CHCl_3$ + ether	$C_{16}H_{28}ClNO_2$
10	CH_3CH_2	n-$CH_3(CH_2)_3$	87	81-84	$CHCl_3$ + ether	$C_{16}H_{28}ClNO_2$
11	n-$CH_3(CH_2)_3$	n-$CH_3(CH_2)_4$	89	91.5-93	EtOAc + ether	$C_{19}H_{34}ClNO_2$
12	n-$CH_3(CH_2)_2$	$C_6H_5(CH_2)_2$	98	110.5-112	EtOAc	$C_{21}H_{30}ClNO_2$
13	n-$CH_3(CH_2)_3$	$C_6H_5(CH_2)_2$	75	*a*		
14	$C_6H_5(CH_2)_2$	$C_6H_5(CH_2)_2$	64	46-47[b]	pet. ether	$C_{26}H_{31}NO_2$
15	n-$CH_3(CH_2)_2$	$C_6H_5CH_2$	87	163.5-164.5	EtOH + ether	$C_{20}H_{28}ClNO_2$
16	n-$CH_3(CH_2)_2$	$C_6H_5(CH_2)_3$	98	55-57	CH_2Cl_2 + ether	$C_{22}H_{32}ClNO_2$
17	n-$CH_3(CH_2)_2$	cyclohexylethyl	55	oil[c]		$C_{21}H_{35}NO_2$
18	$CH_3CH_2(CH_3)CH$	$CH_3CH_2(CH_3)CH$	66	83-86	EtOH + ether	$C_{18}H_{32}ClNO_2$

[a] Noncrystallizable solid. TLC in three different solvent systems, D, E, and G (see Experimental Section), showed on visualization (UV and I_2 vapors) one spot. [b] Free base. The hydrochloride salt was intractable to crystallization. [c] The free base was distilled and the main fraction collected at 161-163 °C (0.15 mmHg). TLC showed 17 to be homogeneous in three different solvent systems, A, B, and C (see Experimental Section). All, with the exception of compound 17, gave satisfactory analyses for C, H, Cl, and N.

Table III. Physical Properties of the Hydrochlorides of N-Substituted 2-Amino-6,7-dimethoxy-1,2,3,4-tetrahydronaphthalenes



no.	R_1	R_2	% yield	mp, °C	recrystn solvent	formula[a]
19	H	n-$CH_3(CH_2)_3$	77	221-222	EtOH + ether	$C_{16}H_{26}ClNO_2$
20	n-$CH_3(CH_2)_2$	n-$CH_3(CH_2)_3$	80	153-155	EtOH + ether	$C_{19}H_{32}ClNO_2$
21	n-$CH_3(CH_2)_3$	n-$CH_3(CH_2)_3$	86	155-156	acetone + ether	$C_{20}H_{30}ClNO_2$

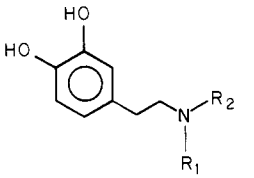
[a] All compounds gave satisfactory analyses for C, H, and N.

tetralone (steps A–C) was prepared according to the procedure of Cannon et al.[8] Amination was achieved by catalytic hydrogenation of the imine (step E) obtained by the condensation of the tetralone with n-butylamine (step D). The secondary amine thus obtained was further alkylated using the $NaBH_4$–carboxylic acid complex method[7] (step F). *N,N*-di-*n*-Pr-ADTN·HBr (**49**) used in our present study was prepared according to the method of Cannon et al.[8]

Pharmacology. (1) Postural Effects on Lesioned Mice. Swiss albino, Hale–Stoner male mice had a right caudectomy performed by suction according to the method of Lotti.[9] Such an operation was deemed successful if 4 weeks after the lesion the mice reacted to apomorphine (APO; 1.0 mg/kg) by assuming a strong asymmetric posture toward the lesion with their contralateral limbs abducted and their ipsilateral ones obducted.

(2) Reversal of Reserpine-Induced Catalepsy in

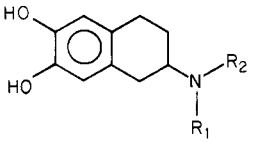
Table IV. Physical Properties of the Hydrochlorides of N,N-Disubstituted β-(3,4-Dihydroxyphenyl)ethylamines



no.	R_1	R_2	% yield	mp, °C	recrystn solvent	formula[a]
22	CH_3CH_2	n-$CH_3(CH_2)_2$	75	158-159	EtOH + ether	$C_{13}H_{22}ClNO_2$
23	n-$CH_3(CH_2)_2$	n-$CH_3(CH_2)_2$	90	138-140	EtOH + ether	$C_{14}H_{24}ClNO_2$
24	CH_3CH_2	n-$CH_3(CH_2)_3$	78	126.5-129	$CHCl_3$ + ether	$C_{14}H_{24}ClNO_2$
25	n-$CH_3(CH_2)_3$	n-$CH_3(CH_2)_4$	92	75-77	methyl ethyl ketone + ether	$C_{17}H_{30}ClNO_2$
26	$CH_3CH_2(CH_3)CH$	$CH_3CH_2(CH_3)CH$	70	136-139	EtOH + ether	$C_{16}H_{28}ClNO_2$
27	$CH_3(CH_2)_2$	$C_6H_5CH_2$	90	175-176	EtOH	$C_{18}H_{24}ClNO_2$
28	$CH_3(CH_2)_2$	$C_6H_5(CH_2)_3$	90	br range[b]	methyl ethyl ketone + ether	$C_{22}H_{32}ClNO_2$
29	n-$CH_3(CH_2)_2$	$C_6H_5(CH_2)_2$	90	51-55	EtOH + ether	$C_{19}H_{30}ClNO_2$
				142-145	CH_2Cl_2	
				161-162	methyl ethyl ketone + EtOAc	$C_{19}H_{30}ClNO_2$
30	$CH_3(CH_2)_3$	$C_6H_5(CH_2)_2$	66	169.5-171	EtOH + ether	$C_{20}H_{28}ClNO_2$
31	$C_6H_5(CH_2)_2$	$C_6H_5(CH_2)_2$	88	68-71	CH_2Cl_2 + ether	$C_{24}H_{28}ClNO_2$
32	n-$CH_3(CH_2)_2$	cyclohexylethyl	87	126-126	EtOH + EtOAc	$C_{19}H_{32}ClNO_2$

[a] All compounds gave satisfactory analyses for C, H, Cl, and N. [b] Compound 28 was obtained as an amorphous solid.

Table V. Physical Properties of the Hydrobromides of N,N-Disubstituted 2-Amino-6,7-dihydroxy-1,2,3,4-tetrahydronaphthalenes

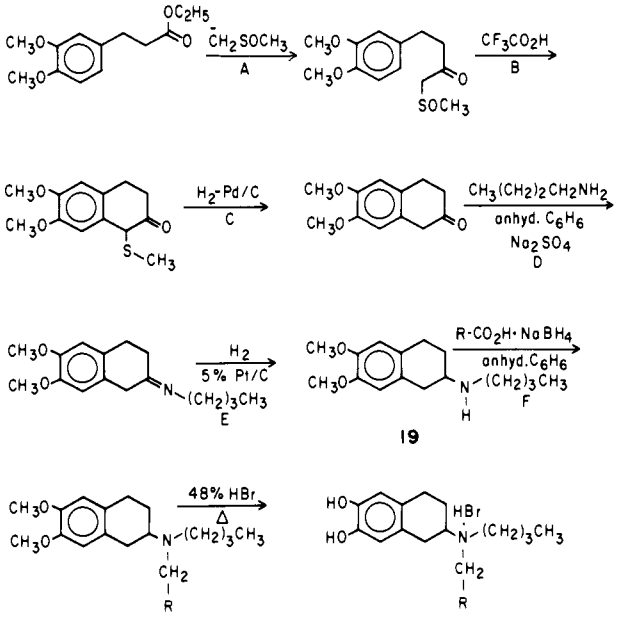


no.	R_1	R_2	% yield	mp, °C	recrystn solvent	formula[a]
33	n-$CH_3(CH_2)_2$	n-$CH_3(CH_2)_3$	88	191-193	EtOH + EtOAc	$C_{17}H_{28}BrNO_2$
34	n-$CH_3(CH_2)_3$	n-$CH_3(CH_2)_3$	86	191-193	EtOH + EtOAc	$C_{18}H_{30}BrNO_2$

[a] All compounds gave satisfactory analyses for C, H, and N.

Mice. Johnson et al.[10] used reserpinized mice to evaluate the antagonistic effects of DA agonists (α-bromocriptine, APO, and *d*-amphetamine) in the reserpine-induced cataleptic state. All three compounds reversed catalepsy, as evidenced by the emergence of movements and stereotypic behavior. Using this model in a pilot study, we were able to reproduce these results using the "rubber stopper test" for catalepsy, as formulated by Tedeschi.[11] The forepaws of the test mouse were placed on a rubber stopper (size 7), and the time required for the mouse to move off the stopper was noted. Untreated or saline-treated mice required 1–3 s to get off the stopper. Reserpinized mice in a cataleptic state remained on the stopper for as long as 65 min. Reserpinized mice reacted positively when injected intraperitoneally with APO or with *d*-amphetamine by getting off the stopper 3–6 min postinjection. However, reserpinized mice, when treated in addition with α-MTM, reacted only to APO (a direct agonist) 3–6 min after its administration. Amphetamine, an indirect agonist,[12a,b] depends for its action on the presence of newly synthesized endogenous DA. This has been virtually eliminated by treatment with the tyrosine hydroxylase inhibitor. In contrast to the unilaterally caudectomized mice, the use of this model can distinguish between direct and indirect agonists.

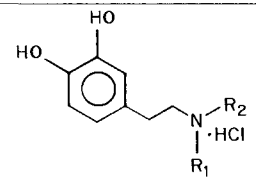
Scheme II



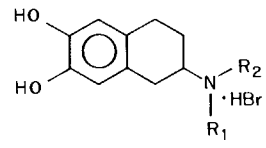
Results and Discussion

Attempting to correlate in vivo biological activities of drugs with molecular structure, in terms of intrinsic activity, is at best hazardous speculation, especially when factors such as absorption, distribution, and metabolic rates play an important role in shaping the biological potency of a drug. Nevertheless, even with the above qualifications in mind, an examination of the results in Table VI reveals that some general observations can be made with regard to the relation between CNS-mediated

Table VI. Behavioral Effects on Caudectomized and Reserpinized Mice



22-32, 35-48



33, 34, 49

compd	R_1	R_2	dose, mg/kg, ip (mmol/kg)	onset, min ± SE	duration, min ± SE	reversal of catalepsy: ED_{50}, mg/kg ± SE, ip (mmol/kg ± SE)
apomorphine hydrochloride			1.0 (3.2×10^{-3})	4.6 ± 0.6	12.8 ± 2.0	0.11 ± 0.04 ($3.6 \times 10^{-4} \pm 1.2 \times 10^{-4}$)
L-Dopa			858 (4.35)	17.7 ± 8.1	24 ± 11	248 ± 14 (1.37 ± 0.08)
35	H	CH_3 [a]	85 (0.417)	nil		
36	CH_3	CH_3 [a]	96 (0.441)	nil		
37	CH_3	n-$CH_3(CH_2)_2$ [a]	120 (0.448)	pos		55 ± 4 (0.22 ± 0.02)
22	CH_3CH_2	n-$CH_3(CH_2)_2$	22.6 (0.087)	3.2 ± 1.5	2.3 ± 1.1	33 ± 4 (0.12 ± 0.01)
			45.2 (0.174)	3.2 ± 1.1	6.3 ± 2.1	
			67.8 (0.261)	3.6 ± 0.8	11.2 ± 2.5	
23	n-$CH_3(CH_2)_2$	n-$CH_3(CH_2)_2$	23.8 (0.087)	1.8 ± 0.7	6.2 ± 2.5	16.0 ± 0.9 (0.058 ± 0.003)
			47.6 (0.174)	3.7 ± 0.6	13.9 ± 0.6	
			71.4 (0.261)	3.1 ± 0.6	21.9 ± 1.2	
38	H	n-$CH_3(CH_2)_3$ [b]	90.8 (0.348)	nil		
39	CH_3	n-$CH_3(CH_2)_3$ [b]	22.6 (0.087)	0.4 ± 0.4	3.7 ± 3.7	61 ± 7 (0.23 ± 0.03)
			45.2 (0.174)	1.3 ± 1.3	2.3 ± 2.3	
			67.8 (0.261)	3.1 ± 2.4	2.2 ± 1.7	
24	CH_3CH_2	n-$CH_3(CH_2)_3$	23.8 (0.087)	2.1 ± 1.7	4.2 ± 2.8	34 ± 3 (0.12 ± 0.01)
			47.6 (0.174)	2.3 ± 1.5	2.5 ± 1.6	
			71.5 (0.261)	5.0 ± 0.5	19.4 ± 3	
40	n-$CH_3(CH_2)_2$	n-$CH_3(CH_2)_3$ [b]	25.0 (0.087)	3.7 ± 0.3	6.4 ± 1.6	8.6 ± 0.9 (0.030 ± 0.003)
			50.0 (0.174)	3.7 ± 0.6	25.8 ± 4.2	
41	n-$CH_3(CH_2)_3$	n-$CH_3(CH_2)_3$ [b]	104.8 (0.348)	nil		
42	H	n-$CH_3(CH_2)_4$ [b]	90.8 (0.348)	nil		
43	CH_3	n-$CH_3(CH_2)_4$ [b]				46 ± 4 (0.17 ± 0.02)
44	n-$CH_3(CH_2)_2$	n-$CH_3(CH_2)_4$ [b]	34.2 (0.087)	3.7 ± 0.4	17.4 ± 2.0	8.7 ± 0.7 (0.022 ± 0.002)
			68.4 (0.174)	4.2 ± 0.5	20.6 ± 2.6	
25	n-$CH_3(CH_2)_3$	n-$CH_3(CH_2)_4$	100.5 (0.305)	nil		
45	H	$(CH_3)_2CHCH_2$ [b]		nil		
46	n-$CH_3(CH_2)_2$	$(CH_3)_2CHCH_2$	25.4 (0.087)	2.8 ± 0.2	18 ± 2	7.4 ± 0.6 (0.026 ± 0.002)
			50.8 (0.174)	2.6 ± 0.1	39 ± 5	
26	$CH_3CH_2(CH_3)CH$	$CH_3CH_2(CH_3)CH$	26.3 (0.087)	nil		
			52.6 (0.174)	nil		
			78.9 (0.261)	1.8 ± 1.8	7.0 ± 2.6	
			92.0 (0.304)	5.2 ± 1.8	7.0 ± 2.6	neg
			105.1 (0.348)	5.0 ± 1.9	10.8 ± 5.3	neg
47	H	$C_6H_5(CH_2)_2$ [b]	102.2 (0.348)	nil		
48	CH_3	$C_6H_5(CH_2)_2$ [b]	26.8 (0.087)	nil		101 ± 7 (0.31 ± 0.02)
			107.2 (0.348)	6.9 ± 1.1	21.2 ± 5.0	

29	n-$CH_3(CH_2)_2$	$C_6H_5(CH_2)_2$	29.2 (0.087)	4.4 ± 0.6	19.8 ± 2.2	7.4 ± 0.9 (0.022 ± 0.003)
			58.4 (0.174)	3.2 ± 0.6	47.4 ± 1.7	
30	n-$CH_3(CH_2)_3$	$C_6H_5(CH_2)_2$	91.2 (0.261)	nil		
31	$C_6H_5(CH_2)_2$	$C_6H_5(CH_2)_2$	51.9 (0.131)	nil		
27	n-$CH_3(CH_2)_2$	$C_6H_5CH_2$	28.0 (0.087)	5.2 ± 0.7	7.8 ± 2.2	21 ± 3 (0.065 ± 0.008)
			56.0 (0.174)	5.7 ± 1.1	26.6 ± 6.1	
28	n-$CH_3(CH_2)_2$	$C_6H_5(CH_2)_3$	30.4 (0.087)	7.6 ± 1.2	6.4 ± 1.9	9.0 ± 1.3 (0.026 ± 0.004)
			60.8 (0.174)	5.8 ± 1.2	18.2 ± 2	
32	n-$CH_3(CH_2)_2$	cyclohexylethyl	29.8 (0.087)	4.2 ± 0.4	14.1 ± 7.0	18 ± 2 (0.054 ± 0.005)
			44.6 (0.131)	toxic		
49	n-$CH_3(CH_2)_2$	n-$CH_3(CH_2)_2$	29.9 (0.087)	2.8 ± 0.4	17.0 ± 3.0	1.6 ± 0.1 (0.0046 ± 0.0004)
			59.8 (0.174)	2.0 ± 0.4	31.5 ± 5.6	
33	n-$CH_3(CH_2)_2$	n-$CH_3(CH_2)_3$	27.3 (0.087)	2.8 ± 0.4	17.0 ± 2.8	1.3 ± 0.3 (0.0038 ± 0.0008)
			41.0 (0.131)	2.0 ± 0.4	31.5 ± 5.6	
			54.6 (0.174)	toxic		
34	n-$CH_3(CH_2)_3$	n-$CH_3(CH_2)_3$	32.3 (0.087)	1.0 ± 1.0	1.6 ± 1.6	44.0 ± 5.0 (0.12 ± 0.01)
			64.6 (0.174)	5.3 ± 1.3	8.8 ± 2.3	
			96.9 (0.261)	4.1 ± 0.6	13.7 ± 1.0	

[a] See ref 3 for preparation and physical characteristics. Maximum dose used was 40% of the drug's LD_{50}. Lesioned mouse results reported as negative or positive at this dose. [b] See ref 1 for preparation and physical characteristics. Onset and duration for conjugate curvature were reported. [c] HI salt of 40 prepared and tested. [d] See ref 13 for preparation and physical characteristics.

behavioral effects, the degree of N-substitution, and the nature and the size of the N substituent.

All secondary DA analogues tested were found to be inactive when given intraperitoneally to lesioned mice (compounds **35**, **38**, **42**, **45**, and **47**, Table VI). This was also shown to be true, with the exception of epinine, when these were tested for effects on renal blood flow in the pentobarbital-anesthetized dog.[2] This appears to be consistent to some extent with the findings of others. Thus, Cannon et al.[13] have shown that *N*-Me- and *N*-*n*-Bu-5,6-ADTN and *N*-Me- and *N*-*n*-Pr-6,7-ADTN failed to induce stereotypy in mice when given subcutaneously but were active, with the exception of *N*-*n*-Bu-5,6-ADTN, when given intrastriatally. Also, McDermed et al.[14] have shown that, in contrast to *N*-*n*-Pr-5,6-ADTN, *N*-*n*-hexyl- and *N*-Bzl-5,6-ADTN were similarly inactive when given subcutaneously to mice. Their results suggest that some of our N-monosubstituted compounds may be inactive because of their inability to cross the blood–brain barrier. Of the N,N-disubstituted DA analogues, the *N*-*n*-propyl N-substituted were, in general, the most effective in inducing asymmetric postures in caudectomized mice. Thus, in ranking them in decreasing order of potency according to the molar ED_{50} values for reversal of catalepsy and within the limits of accuracy of the method, compounds **44**, **29**, **28**, and **46** were shown to be about equipotent, while **40** was slightly less potent than **44** and **29** but equipotent with **28** and **46**. In general, **27**, **32**, and **23** were about two times less potent than the aforementioned ones, while **24** and **22**, both with an *N*-ethyl substituent, were four to five times less potent than **44** and **29**. In contrast, the *N*-methyl N-substituted homologues showed little or no effect. Moreover, the symmetrically N,N-disubstituted DA analogues were found to be inactive as direct DA agonists, with the exception of **23**. Although **26** did induce an asymmetric posture in lesioned mice when given in high doses (0.348 mmol/kg, ip), it failed to reverse catalepsy in reserpinized mice, suggesting that it may be an indirect DA agonist.

Because of its two asymmetric centers, **26** is a mixture of the *d*, l, and meso forms. It is not known at this time which form is the pharmacologically active one. Compound **31** unexpectedly induced dose-dependent tremors, followed by, apparently, myoclonic seizures in lesioned as well as in intact mice. The pharmacological properties of this compound are being further investigated in mice.

In the 6,7-ADTN series, compound **33** appears to be about equipotent with compound **49**, both being homologues of N-substituted *N*-*n*-Pr-6,7-ADTN, and about 8 and 15 times more potent, respectively, than **40** and **23** of the DA analogues. On the other hand, **34**, in which the length of the *n*-propyl substituent of **33** was increased by one carbon atom, was shown to be about 30 times less active than **33**. This is consistent with our findings in the DA analogue series and parallels the findings of Kohli et al.[15a,b] in the dog. Similarly, **44**, **29**, and **40** were rendered inactive by increasing the length of the *N*-*n*-propyl substituent to yield the corresponding compounds **25**, **30**, and **41**. McDermed et al.[14] have also shown in their structure–activity studies of N-substituted 5,6-ADTN derivatives that the *N*,*N*-di-*n*-Bu-5,6-ADTN was about 130 times less potent than *N*,*N*-di-*n*-Pr-5,6-ADTN. Cannon et al.[13] have shown that compound **36** and **41** in the N,-N-disubstituted DA series were inactive when injected intrastriatally in the nucleus accumbens.

Increasing the alkyl chain of the *N*-phenethyl substituent of **29** by one carbon failed to change significantly its ED_{50}. In contrast, decreasing the alkyl chain by one carbon

(compound **27**) increased the ED_{50} by a factor of about three but also produced a striking change in the behavioral effects in lesioned as well as in intact mice in comparison with those of other DA analogues (**40** and **29**). In addition to the ipsilateral asymmetric posture, **27** induced a continuous fast and tight circular movement ipsilateral to the lesion accompanied by occasional stereotypy, such as gnawing and/or biting. A comparison under controlled conditions of locomotor activity induced by **27** in intact mice with that of **40** in Opto-Varimex activity cages has shown that animals treated with **27** displayed higher motility. A comparative study of drug-induced locomotor activity is presently being continued with other DA analogues.

The mean latency to onset of postural effects in lesioned mice varied from 3 to 7 min for all the compounds assayed, with the exception of L-Dopa with a mean latency of 25 min. The latency to onset of reversal of catalepsy in reserpinized mice ranged from 4 to 10 min for all the DA analogues tested and about 18 min for L-Dopa.

APO and L-Dopa, a drug currently used in the treatment of parkinsonism,[16] were used as reference compounds. APO was the most potent ($ED_{50} = 3.6 \times 10^{-4}$ mmol/kg) of the DA agonists in reversing reserpine-induced catalepsy. It was about 10 times more potent than **33**, while L-Dopa ($ED_{50} = 1.3$ mmol/kg) was found to be about 350 times less potent than **33**. The longer onset to latency of behavioral effects for L-Dopa and its large ED_{50} may be attributed to its dependency on L-Dopa decarboxylase for its conversion to the effective metabolite dopamine.[17] Large amounts of L-Dopa must be administered, unless a peripheral decarboxylase inhibitor is used, to overcome the metabolic attrition of the drug in the periphery.[18] Unlike DA, 2-NH_2-6,7-ADTN, and 2-NH_2-5,6-ADTN, their N,N-disubstituted derivatives cross the blood–brain barrier. As tertiary amines they are resistant to deamination by monoamine oxidase.[19]

Our results confirm and strengthen previous findings that the *N*-*n*-propyl substituent in a homologous series of DA analogues is a requirement for optimum dopaminomimetic action. Increasing the length of the propyl group by one carbon, the other N-substituent being either an alkyl group larger then *n*-propyl or a phenethyl group, abolishes dopaminergic effects or sharply reduces them as in the case of **34**. One may speculate in the light of the evidence available that the *N*-*n*-propyl group, because of its optimum size and its hydrophobic nature, contributes favorably to the binding of these agonists to the receptor.

The availability of an array of structurally related DA analogues with dopaminomimetic properties makes it possible to test the notion that there is more than one type of DA receptor[20a,b] and that stereotypy and locomotor activity may have different CNS loci.[21] Moreover, they may be of potential use in the treatment of parkinsonism, offering the following advantages over L-Dopa: (1) their action is not dependent on the presence of L-Dopa decarboxylase which may be deficient in the brains of patients with parkinsonism, particularly ones in whom the disease has progressively destroyed a large number of their nigro-striatal pathways;[22] (2) as tertiary amines they are poor substrates for MAO and, in contrast to DA, cross the blood–brain barrier.

Experimental Section

Uncorrected melting points were determined on a Thomas-Hoover apparatus. ^{1}H NMR spectra were recorded on a Varian T-60 in $CDCl_3$ with $(Me)_4Si$ as an internal standard. IR spectra were recorded on a Perkin-Elmer 267 infrared spectrophotometer. Eastman chromatogram sheets (6060 silica gel with fluorescent indicator) were used. The following TLC solvent systems were used: (A) cyclohexane–EtOAc, 1:1; (B) 1:4; (C) 4:1; (D) $CHCl_3$–MeOH–AcOH, 17:2:1; (E) *n*-BuOH–H_2O–AcOH, 4:1:1; (F) C_6H_6–EtOAc, 4:1; (G) *n*-PrOH–H_2O, 89:28. Visualization was done with UV and/or I_2 vapors. Elemental analyses were done by Galbraith Laboratories, Inc.

Dimethylformamide (DMF) was fractionally distilled under reduced pressure and under anhydrous conditions after drying over KOH pellets. After discarding the forerun, the major fraction distilling within a range of 4 °C was collected and stored over 4Å molecular sieves and under N_2 in a tightly sealed brown bottle and kept under refrigeration. Prior to use, DMF was tested for the presence of dimethylamine with 3,4-dinitrofluorobenzene.[23] Tetrahydrofuran (THF) was distilled over $LiAlH_4$ and stored over 4Å molecular sieves under refrigeration. The pyridine that was used was reagent grade and stored over 4Å molecular sieves.

^{1}H NMR spectra were obtained routinely for each of the preparations described below, and, unless otherwise stated, they were consistent with the structures of the compounds synthesized.

The following preparations are described as representative illustrations of synthetic Schemes I and II.

Carboxylic Acid Chloride 50. 3,4-Dimethoxyphenylacetyl chloride (**50**) was prepared as described elsewhere.[1] Hydrocinnamyl chloride [59–61 °C (0.26–0.28 mmHg)][24] and cyclohexylacetyl chloride [68–72 °C (13 mmHg)] used in the corresponding preparations of *N*-*n*-propylhydrocinnamide and *N*-*n*-propyl-β-cyclohexylacetamide were prepared similarly.

***N*-Phenethylbutyramide (51).** To a stirred solution of 100 mL of DMF and 21.8 g (0.18 mol) of 2-phenylethylamine was added dropwise 12.1 g (0.08 mol) of freshly distilled *n*-butyryl bromide under anhydrous conditions; the temperature was kept below 55 °C and then cooled to ice–water temperature. The reaction mixture was transferred to a separatory funnel with water, followed by extraction with Et_2O (5 × 50 mL). The Et_2O extracts were combined and washed successively with water, aqueous 1 N HCl, aqueous 1 N NaOH, and finally with water to a neutral pH. The organic layer, after drying over anhydrous $MgSO_4$, yielded upon removal of the solvent 12.7 g (93%) of an oil: TLC (solvent systems A, B, and C) showed a single spot; IR (film) showed a strong band at 1640 cm^{-1} (C=O stretch, secondary amide); the COCl stretching band was absent. The crude product was fractionated by a short-path distillation apparatus and a colorless liquid was collected at bp 129–133 °C (0.45–0.50 mmHg) [lit. 155–160 °C (0.8 mmHg);[25] 187 °C (12 mmHg)[26]].

***N*-*n*-Butyl-*N*-2-phenylethylamine (52).** To a stirred solution of 130 mL of B_2H_6–THF (1.0 M) was carefully added, at below 20 °C and under anhydrous conditions, 9.9 g of **51** (0.135 mol) dissolved in 30 mL of THF. The reaction was carried out under N_2. After refluxing for 1.5 h, the major portion of the solvent was removed under reduced pressure, and the liquid residue was refluxed with 80 mL of 6 N HCl–MeOH for 0.5 h. The solvent was removed and the acid residue was extracted with ether several times. The Et_2O extracts were combined and evaporated, and the oil residue was treated again as above with HCl–MeOH. The remaining aqueous phase was combined with aqueous NaOH, followed by extraction of the oily precipitate with Et_2O (4 × 40 mL). The combined ether extracts were washed with water to a neutral pH and dried over anhydrous $MgSO_4$, followed by the evaporation of the solvent under reduced pressure. The oily residue was dried to constant weight under high vacuum to give 8.0 g (89.9%): TLC (solvent systems A, B, and C) showed one major spot and a minor one. Because short-path fractional distillation failed to effect the desired degree of purification, the crude product was converted into its hydrochloride salt in Et_2O saturated with HCl and crystallized from absolute EtOH–Et_2O, yielding colorless crystals weighing 5.65 g (79%), mp 160–161 °C.

***N*-*n*-Butyl-*N*-phenethyl-β-(3,4-dimethoxyphenyl)acetamide (53).** To a stirred solution of 4.6 g (0.026 mol) of **52**, 2.6 g (0.033 mol) of pyridine, and 45 mL of DMF was added slowly 5.2 g (0.024 mol) of freshly distilled **50** under anhydrous conditions with temperature maintained below 50 °C. After heating the reaction mixture at 55 °C for 1 h, it was diluted with 60 mL of water, and the product was extracted with Et_2O in a manner similarly described for the extraction of **51**. The fractionation of the crude product by a short-path distillation apparatus yielded 5.7 g (67%) of a colorless liquid: bp 204–206 °C (0.20 mmHg);

TLC (solvent systems A, B, and C) showed only one spot; IR (film) 1640 cm^{-1} (C=O stretch, tertiary amide), NH and COCl stretching bands were completely absent.

***N*-*n*-Butyl-*N*-phenethyl-β-(3,4-dimethoxyphenyl)ethylamine (13).** **13** was prepared in the same manner as **52**: yield (a viscous liquid) 2.7 g (75%); TLC (solvent systems A, B, and C) showed only one spot. The HCl salt, a viscous liquid, could not be crystallized.

***N*,*N*-Bis(phenylethyl)-β-(3,4-dimethoxyphenyl)ethylamine (14).** To a stirred solution of 20.4 g (0.15 mol) of phenylacetic acid and 45 mL of dry C_6H_6 was added over a period of 25 min 1.89 g (0.05 mol) of $NaBH_4$ under anhydrous conditions; temperature was maintained at 10–15 °C. One hour after the addition of $NaBH_4$, a solution of 1.9 g (0.01 mol) of 3,4-dimethoxyphenylethylamine and 5 mL of dry benzene was added and refluxed for 19 h. The cooled reaction solution was transferred to a separatory funnel and extracted with 2 N NaOH (3 × 40 mL). The aqueous phase was discarded. The organic phase was then extracted with aqueous 1 N HCl (3 × 40 mL). The extracts and the oily precipitate were combined and made basic with aqueous NaOH and then extracted with ether (4 × 40 mL). The Et_2O extracts were combined and washed with water to a neutral pH. Removal of the Et_2O under reduced pressure, after drying over anhydrous $MgSO_4$, yielded 1.98 g (51%) of an oil which gradually crystallized as small colorless needles, mp 45–46 °C. Recrystallization from petroleum ether (bp 35.8–36.8 °C) twice, yielded 1.6 g: mp 46–47 °C; TLC (solvent systems D, F, and J) yielded one spot. Anal. ($C_{26}H_{31}NO_2$) C, H, N. The hydrochloride salt yielded material with no definite melting point. The picrate salt, mp 133–134 °C, was prepared from a saturated solution of picric acid in EtOH–Et_2O.

***N*-*n*-Butyl-2-amino-6,7-dimethoxy-1,2,3,4-tetrahydronaphthalene Hydrochloride (19).** To a solution of 1.85 g (0.009 mol) of 6,7-dimethoxy-2-tetralone in 40 mL of dry C_6H_6 was added 2 g of n-$C_4H_9NH_2$ and 2 g of anhydrous Na_2SO_4. The mixture was stirred under N_2 for 18 h and filtered, and the filtrate was concentrated under vacuum. The resulting oil was dissolved in 45 mL of absolute EtOH and shaken over 150 mg of 5% Pt/C at 50 psig of H_2 until absorption ceased (about 2 h). The reduction mixture was filtered, acidified with 5% HCl–EtOH, and concentrated. Dilution of the liquid residue with Et_2O or EtOAc afforded the crystalline HCl salt of the secondary amine: yield 77%; mp 221–222 °C.

***N*-*n*-Propyl-*N*-*n*-butyl-2-amino-6,7-dimethoxy-1,2,3,4-tetrahydronaphthalene Hydrochloride (21).** To a solution of 5.13 g (0.069 mol) of propionic acid in 100 mL of dry C_6H_6 was added, in three portions, 0.80 g (0.021 mol) of $NaBH_4$ while the temperature was kept below 20 °C. After H_2 evolution had ceased (ca. 1 h), a solution of 1.29 g (4.8 mmol) of the free base of **19** in 15 mL of dry C_6H_6 was added all at once. The mixture was refluxed under N_2 for 3 h. The reaction mixture was then cooled and the C_6H_6 solution was successively washed with 5% NaOH and saturated NaCl and dried over anhydrous Na_2SO_4. After filtration, the solvent was removed, and the oily residue was taken up into EtOH, acidified with 5% HCl–EtOH, and Et_2O was added. The solution was chilled at 5 °C overnight, and the salt was collected by filtration and dried to yield 1.32 g (80%) of the tertiary amine, mp 150 °C.

Demethylation of the *O*-Methyl Derivatives. The ether cleavage of N-substituted *O*-methyldopamine derivatives was accomplished by reflux in 57% HI and acetic anhydride[1,27] for 0.75–1.0 h and the *O*-methyl derivatives of 6,7-ADTN by reflux in 48% HBr[8] for 1.0 h.

Tests with Caudectomized Mice (Table VI). A total of 18 Swiss albino, Hale–Stoner male mice were used for each compound tested, with 5- to 6-day intervals elapsing before the same ones were retested. Animals were selected and injected intraperitoneally at random in groups of six. The mean and SE of the onset and duration of the asymmetric posture induced by each compound in a total of six animals were calculated. The maximum injected dose was 0.348 mmol/kg. All compounds tested were dissolved in normal saline (0.9%) with total volumes of injection equal to 0.4–0.6 mL. APO and L-Dopa were used as reference compounds.

Test with Reserpinized Mice. Swiss albino, Charles River (CD 1) male mice, 5 weeks old, were injected with reserpine (5 mg/kg, ip) and 17 h later with α-MTM (250 mg/kg, ip), 4 h prior to the injection of the test compound. To determine the ED_{50} value for each compound tested, a minimum of four dose levels were used, and for each dose at least eight mice were treated. For each compound tested, the percent of animals with a positive reaction was plotted against its corresponding dose on logarithmic probit graph paper.[28] Reserpine was dissolved in a minimum amount of glacial acetic acid and then diluted with water; final pH 3.0.

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