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Cerebral Dopamine Agonist Properties of Some 2-Aminotetralin Derivatives after Peripheral and Intracerebral Administration

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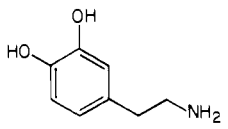
A series of variously N-substituted 2-aminotetralins having OH groups at 5 and 6 and at 6 and 7 positions, as well as nonoxygenated systems, has been evaluated for central dopaminergic effects. Stereotypical behavioral effects (sniffing, compulsive gnawing, and hyperactivity) produced by direct intracerebral administration of some of the agents were shown to differ strikingly from responses resulting from peripheral administration. The centrally mediated responses of hyperactivity and stereotypical gnawing-biting head and limb movements were shown to be separable in some test compounds. An improved route to 2-aminotetralin systems has been utilized for some of the compounds, which involves Pummerer rearrangement and cyclization of β-keto sulfoxides and reductive amination of β-tetralones with a $NaBH_4$–carboxylic acid complex.

A similarity in structure between dopamine (1) and 2-amino-5,6-dihydroxytetralins **2** prompted the synthesis



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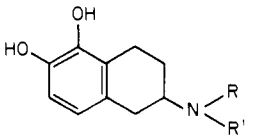

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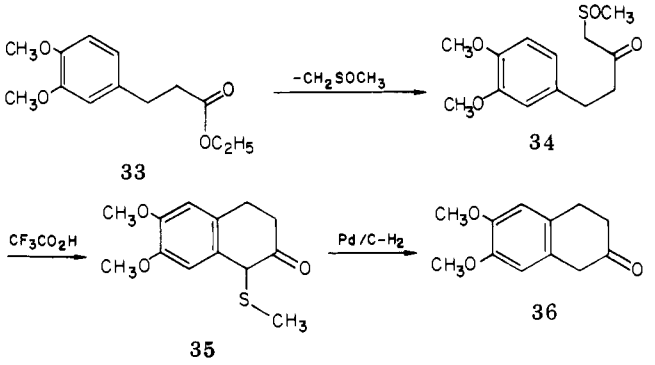
of these agents as potential dopaminergic agonists.[1,2] McDermed et al.[2] have evaluated the dopaminergic activity of a large number of 2-aminotetralins and have concluded that there are marked differences in the structural requirements for these compounds as compared to the aporphine and phenethylamine series. Thus, using stereotypy induction after peripheral administration as an index of cerebral dopamine stimulation, some compounds with an etherified catechol group were found to be active, whereas a primary amine, 2-amino-5,6-dihydroxytetralin (**2**, R = R′ = H), the compound most structurally analogous to dopamine, was inactive. It is possible that the apparent activity of the etherified compounds may result from the peripheral metabolism of the compounds and the formation of active products. The apparent inactivity of 2-amino-5,6-dihydroxytetralin may simply reflect an inability to pass the blood–brain barrier.

In an attempt further to assess the structure–activity relationships within the 2-aminotetralin series, we have extended the range of compounds used by the McDermed group to include 2-amino-6,7-dihydroxytetralin derivatives and, in order to eliminate the interpretational problems presented by differences in metabolism and cerebral penetration following peripheral administration, we have also investigated the activity of the 2-aminotetralin derivatives on intracerebral injection into the striatum of rats. Table I lists the compounds prepared and centrally originated results of peripheral administration of certain of them.

Scheme I. Preparation of 2-Tetralones



Chemistry. The methoxylated 2-aminotetralins were prepared from the appropriate 2-tetralones, which were in turn best prepared by a sequence involving a Pummerer rearrangement of a β-keto sulfoxide, as described by Oikawa and Yonemitsu.[3] This is illustrated for 6,7-dimethoxy-2-tetralone (**36**) (Scheme I).

Oikawa and Yonemitsu[4] recently cited reduction of **35** to **36** with $NaBH_4$, but they did not describe experimental conditions, nor did they report a percent yield.

In the present work, reductive amination of 2-tetralones was achieved with a variety of primary amines and $NaBH_3CN$. In some instances, the 2-tetralone was refluxed with a primary amine and the resulting imino system was hydrogenated. Some primary and secondary 2-aminotetralins were further N-alkylated by use of a $NaBH_4$–

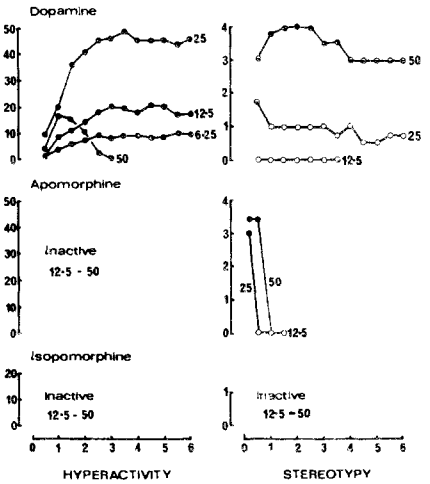


Figure 1. Hyperactivity and stereotyped behavior induced by dopamine, apomorphine, and isoapomorphine injected bilaterally into the striatum. Doses are indicated in μg administered in 1 μL. Hyperactivity is expressed in counts/5 min and stereotypy was scored according to Table I. ○ represents sniffing behavior or repetitive head and limb movements; ● represents biting, gnawing or licking; ◒ indicates that some aminals exhibited sniffing while others were biting. Hyperactivity and stereotyped behavior were each monitored for 6 h as indicated. Six to eight animals were used at each dose level of the drug. Standard errors on the means are all less than 18%. All compounds were used in a dose range of 0.39–50 μg, but results are presented for selected doses for the sake of clarity. All hyperactivity results presented are considered to reflect "true" hyperactivity and not stereotyped movements.

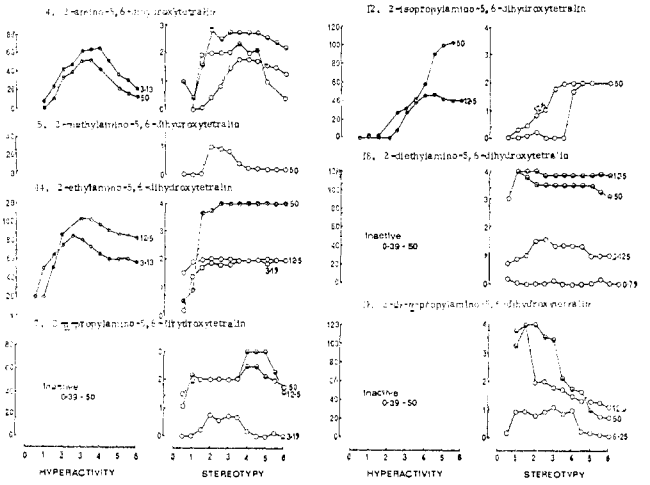


Figure 2. Hyperactivity and stereotyped behavior induced by derivatives of 2-amino-5,6-dihydroxytetralin injected bilaterally into the striatum. Symbols and experimental details are given under Figure 1. Standard errors are less than 15% of the means.

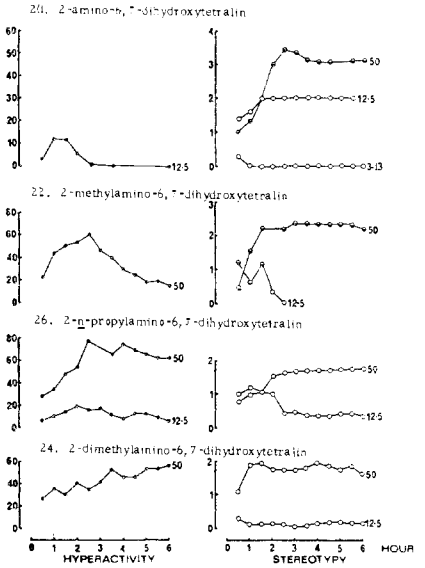


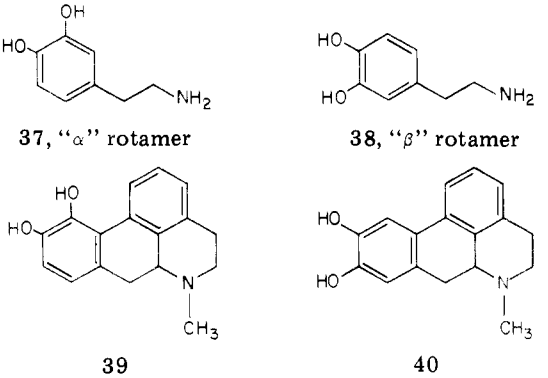
Figure 3. Hyperactivity and stereotyped behavior induced by derivatives of 2-amino-6,7-dihydroxytetralin injected bilaterally into the striatum. Symbols and experimental details are given under Figure 1. Standard errors are less than 19% of the means.

Results

The abilities of a series of 2-aminotetralins having OH groups at 5 and 6 and at 6 and 7 positions as well as nonoxygenated systems to induce stereotyped behavior on peripheral (subcutaneous) administration are indicated in Table I. Stereotyped behavior and/or hyperactivity induced by the same agents on direct bilateral injection into the striatum are indicated in Figures 2 and 3. The effects of similar injections of dopamine, apomorphine, and isoapomorphine (**40**) are indicated in Figure 1 for reference purposes. Control injections of vehicle were carried out for all intrastriatal injection studies. Except for a brief (2–8 min) period of injection artifact, characterized by hyperactivity with occasional biting, such control injections failed to modify the motor behavior of rats.

Discussion

The rationale for the synthesis and evaluation of 2-aminotetralin derivatives as potential dopaminergic agonists is based upon the similarity in the structural relationships of the nitrogen and the OH functions to those found in the extended (antiperiplanar) conformation of dopamine.[6] 2-Amino-5,6-dihydroxytetralin (**4**) and 2-amino-6,7-dihydroxytetralin (**20**) are analogous to the opposing rotameric conformations (**37** and **38**) of dopamine,[6] and from the former series (inter alia) a number of N,N-dialkylated derivatives were found to possess very potent central dopamine agonist activity.[2] However, a satisfactory analysis of structural requirements for dopamine agonist activity was made unusually difficult by the apparent inactivity of the parent primary amino compounds upon peripheral administration. The present study used both peripheral and intracerebral injection techniques and it demonstrates the considerable attendant difficulties in attempting a structure–activity study for centrally acting compounds, using only the peripheral route.



carboxylic acid complex, according to a method of Marchini et al.[5] This appears to be an exceptionally useful and convenient N-alkylation procedure (see Table I). The methyl ether groups were cleaved by treatment with 48% HBr. Spectral data (IR and NMR) on all intermediates and final products were consistent with the proposed structures.

In a series of 2-dialkylated aminotetralins unsubstituted in the aromatic ring, dopamine agonist activity (as assessed in the stereotypy test in the rat) was observed only for the *N,N*-di-*n*-propyl compound **31**; derivatives with smaller (methyl or ethyl) or larger (*n*-butyl) substituents were inactive. McDermed and co-workers[2] reported that the stereotyped behavior induced by **31** was unaffected by a combined reserpine and α-methyltyrosine pretreatment regimen, and they concluded that the compound was capable of direct stimulation of a dopamine receptor. In the present study, this pretreatment completely abolished the stereotypic responses to 2-di-*n*-propylaminotetralin **31**, although such animals developed stereotyped behavior on peripheral administration of apomorphine. However, in agreement with the McDermed studies, we found that hydroxylation of the benzene ring in the 5,6 positions markedly increased the stereotypic potency of the *N,N*-di-*n*-propyl compound and conferred stereotypic potency on the *N,N*-dimethyl and the *N,N*-diethyl derivatives **9** and **18**. The importance of the OH functions for dopamine-like activity is emphasized by the inactivity of 2-amino-5,6-dimethoxytetralin (**3**), by the greatly reduced activity of 2-di-*n*-propylamino-5,6-dimethoxytetralin (**10**),[2] 2-di-*n*-propylamino-5-methyl-6-hydroxytetralin,[2] and 2-di-*n*-propylamino-5-hydroxytetralin,[7] and by the low activity of analogous compounds from the aporphine series, 10-hydroxy-*N*-*n*-propylnoraporphine and 11-hydroxy-*N*-*n*-propylnoraporphine,[8] which would suggest that although a dihydroxy substitution pattern enhances potency, it is not essential for dopamine-like activity. The positions of the OH functions on the ring are critically important, since compounds possessing OH at the 6,7 positions were much less active than the analogous 5,6-dihydroxyaminotetralins. These results from peripheral injection studies would indicate the importance of apomorphine-like (**39**) steric disposition of the OH and nitrogen functions for optimal activity. The inactivity of "isoapomorphine" **40**, which bears an OH substitution pattern analogous to 2-amino-6,7-dihydroxytetralin (**20**), further indicates that dopamine itself may be more active in the assays considered herein in its "α" rotameric disposition **37** than in its "β" rotamer **38**. However, it is not possible to investigate this hypothesis by observing the effects of peripherally administered drugs, since the primary amines themselves lacked effect by this route.

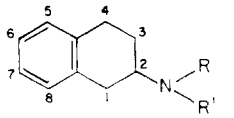
It is generally accepted that many primary amines poorly penetrate the blood–brain barrier, and this may partly explain the inactivity of the 5,6- and 6,7-dihydroxy-2-aminotetralins **4** and **20**. Observations that these agents exert some activity when administered intracerebrally, either into the nucleus accumbens[9] or into the ventricular system,[10] would favor this suggestion. We therefore administered 2-aminotetralins directly into the brain and, for this study, selected the caudate-putamen as being a dopamine area essentially involved in the control of stereotyped motor behavior.[11] In contrast to results obtained from peripheral experiments, 2-amino-5,6-dihydroxytetralin (**4**) was shown to induce stereotypy on injection into the caudate-putamen. In addition, animals became hyperactive at lower doses, although the development of stereotypy at the higher doses prevented a further increase in activity. With the exception of a monoethyl substitution (compound **14**), N-alkylation of the parent 5,6-dihydroxy-2-aminotetralin with methyl, ethyl, *n*-propyl, or *n*-butyl abolished any hyperactivity potential. The mono- or disubstitution with methyl or *n*-butyl groups similarly reduced or abolished the stereotypic activity, while ethyl or *n*-propyl substitution *increased* this effect.

Three conclusions may be drawn from these observations: (1) the caudate-putamen may normally serve as an anatomic substrate for the 2-aminotetralin derivatives to induce stereotyped behavior following their peripheral administration; (2) within the caudate-putamen, the dissociation between an ability to induce hyperactivity and stereotypy (Figures 2 and 3) suggests the presence of two distinct mechanisms for the mediation of these two behavioral effects; and (3) the specific inhibition of both hyperactivity and stereotypy by neuroleptic agents indicates an important dopaminergic involvement with both effects. There did not appear to be any relationships between the potencies of the N-alkylated 5,6-dihydroxytetralins to induce stereotypy after peripheral administration or after direct injection into the caudate-putamen. This discrepancy may reflect one or more of the following possibilities: (1) the potencies of the compounds after peripheral administration may partially reflect their ability to pass the blood–brain barrier; (2) metabolism may occur after peripheral administration, to yield products of greater or lesser effectiveness; or (3) the striatum may not be an exclusive site for the induction of stereotyped behavior. This latter possibility is supported by the observation that derivatives of 2-aminotetralin can induce hyperactivity and stereotyped behavior on injection into the nucleus accumbens.[9]

More difficult interpretational problems arise when the hyperactivity–stereotypy induced by injection of 6,7-dihydroxy compounds into the caudate-putamen is considered. If the "α" conformation **37** of dopamine is the more effective for the stimulation of striatal dopamine mechanisms, it may then be expected that the opposing "β" rotamer **38**, as exemplified in these studies by 2-amino-6,7-dihydroxytetralin (**20**), should exhibit little or no agonist activity. This was found to be the case for hyperactivity induction, but the 6,7-dihydroxy compound **20** was equally potent to its 5,6-dihydroxy isomer **4** in induction of stereotyped behavior (Figures 2 and 3). Further, while N-alkylation abolished the potential to cause hyperactivity in the 5,6-dihydroxy series, substitution with methyl or *n*-propyl groups enhanced this effect in the 6,7-dihydroxy series. Also, marked differences were observed between the abilities of N-alkylated derivatives of 5,6- and 6,7-dihydroxylated systems to induce stereotypy. In contrast to the 5,6-dihydroxy series, compounds with *N*-methyl (**22**) and *N,N*-dimethyl (**24**) substitutions in the 6,7-dihydroxy series retained modest stereotypic potency, but the *N,N*-di-*n*-propyl system **28** completely lacked any stereotypic action.

The negative correlation between analogous agents in the 5,6 and the 6,7 series strongly suggests that hydroxylation at these different positions on the aromatic ring produces compounds which act via different mechanisms to induce the observed behavioral response. The intensities of the hyperactivity and stereotypy responses produced by the various N-alkylated 6,7-dihydroxy derivatives and by the corresponding primary amine were similar and may reflect a somewhat nonspecific action on the presynaptic uptake mechanisms,[12] or even an action on the release of neurotransmitter. The necessity to pretreat with nialamide in order to demonstrate clearly the dopamine-like effects of the 6,7-dihydroxytetralins (in contrast to the effects elicited by the 5,6-dihydroxytetralins[13]) may reflect the need for raised catecholamine levels. Also, while we have suggested a primary dopaminergic involvement with the drug-induced behavioral effects, it is possible that some 2-aminotetralin derivatives may possess adrenergic agonist action[14] which may modify

Table I. 2-Aminotetralin Derivatives. Structural Modifications, Characterization Data, and Stereotypic Activity of Certain Derivatives Administered by the Peripheral Route



No.	Aromatic substitution	R	R'	Method of prepn	Yield, %	Mp, °C[a] (salt)	Dose, mg/kg sc	Stereotypy score[b]
3	5,6-$(OCH_3)_2$	H	H	A[c]	94	269-272[d,e] (HCl)	16	0
							8	0
4	5,6-$(OH)_2$	H	H	*f*		(HBr)	16	0
							8	0
5	5,6-$(OH)_2$	CH_3	H	*f*		(HBr)	16	0
							8	0
6	5,6-$(OCH_3)_2$	*n*-C_3H_7	H	A	69	237-239[d,g] (HCl)		
7	5,6-$(OH)_2$	*n*-C_3H_7	H		91	225-226[d,h] (HBr)	1.0	4
							0.5	3-4
							0.25	1
							0.125	0-1
8	5,6-$(OCH_3)_2$	CH_3	CH_3	*f*		(HCl)	16	0
							8	0
9	5,6-$(OH)_2$	CH_3	CH_3	*f*		(HBr)	2	4
							1	4
							0.5	0-1
10	5,6-$(OCH_3)_2$	*n*-C_3H_7	*n*-C_3H_7	B	61	182-183[d,i] (HCl)		
11	5,6-$(OH)_2$	*n*-C_3H_7	*n*-C_3H_7		60	222-225[h,j] (HBr)	0.1	4
							0.05	3-4
							0.025	4
							0.0125	2-4
							0.0063	0
12	5,6-$(OH)_2$	2-C_3H_7	H	*k*		(HBr)		
13	5,6-$(OCH_3)_2$	C_2H_5	H	A	42	234-236[d] (HCl)		
14	5,6-$(OH)_2$	C_2H_5	H		95	234-237[d] (HBr)	8	4
							4	3-4
							2	4
							1	3
							0.5	0-1
							0.25	0
15	5,6-$(OCH_3)_2$	*n*-C_4H_9	H	A	17	220-224[l] (HCl)		
16	5,6-$(OH)_2$	*n*-C_4H_9	H		90	235-240[d] (HBr)	4	0
							2	0
							1	0
17	5,6-$(OCH_3)_2$	C_2H_5	C_2H_5	B[m]	77	188-190[d,n] (HCl)		
18	5,6-$(OH)_2$	C_2H_5	C_2H_5		96	190-192[d,o] (HBr)	0.5	4
							0.25	3-4
							0.125	0-1
							0.063	0
19	6,7-$(OCH_3)_2$	H	H	A[c]	54	228-230[d,p] (HCl)		
20	6,7-$(OH)_2$	H	H		95	267-269[d,q] (HBr)		
21	6,7-$(OCH_3)_2$	CH_3	H	C	56	243-244[r] (HCl)		
22	6,7-$(OH)_2$	CH_3	H		89	221-223[d] (HBr)	8	0
							4	0
							1	0
23	6,7-$(OCH_3)_2$	CH_3	CH_3	D	89	251-252[d] (HCl)		
24	6,7-$(OH)_2$	CH_3	CH_3		90	110-112[s] (HBr)	8	0
							4	0
							1	0
25	6,7-$(OCH_3)_2$	*n*-C_3H_7	H	C	56	218-221[d] (HCl)		
26	6,7-$(OH)_2$	*n*-C_3H_7	H		87	240-243[d] (HBr)	8	1-2
							4	1
							2	0
27	6,7-$(OCH_3)_2$	*n*-C_3H_7	*n*-C_3H_7	B[t]	93	165-168[d] (HCl)		
28	6,7-$(OH)_2$	*n*-C_3H_7	*n*-C_3H_7		90	234-237[d] (HBr)	2	3-4
							1	2-4
							0.5	1-2
							0.125	1
							0.003	0
29		CH_3	CH_3	A	25	210-212[j,u] (HCl)	16	0
							8	0
30		C_2H_5	C_2H_5	C	8	146-148[d,v] (HCl)	16	0
							8	0
31		*n*-C_3H_7	*n*-C_3H_7	C	31	155-156[d,w] (HCl)	8	3-4
							4	3
							2	1-3
							1	0-1
32		*n*-C_4H_9	*n*-C_4H_9	C	52	102-106[x] (HCl)	16	0
							8	0

Table I (*Continued*)

	Dose, mg/kg sc	Stereotypy score[b]
Dopamine hydrochloride[y]	50	0
	100	0
Apomorphine hydrochloride[z]	0.5	2
	1.0	3
	2.0	4
Isoapomorphine hydrobromide[aa]	4	0
	8	0
	16	0

[a] All new compounds gave satisfactory analyses for C, H, and N. [b] Stereotypy intensity was assessed according to the following scoring system: 0, no stereotyped behavior; 1, periodic sniffing or repetitive head and limb movements; 2, continuous sniffing or repetitive head and limb movements; 3, periodic biting, gnawing, or licking; 4, continuous biting, gnawing, or licking. [c] Source of NH_3 was NH_4OAc. [d] From MeOH-Et_2O. [e] Lit.[21] mp 270–272 °C. [f] Prepared by method in ref 1. [g] Lit.[2] mp 227–229 °C. [h] Reference 2 reported the HCl salt. [i] Lit.[2] mp 178–179 °C. [j] From EtOH-Et_2O. [k] Prepared by method in ref 11. [l] From 2-PrOH-hexane. [m] Starting material was the primary amine 3. N,N-Diethylation was achieved by $NaBH_4$-AcOH-amine molar ratio of 0.01:0.034:0.00097. [n] Lit.[2] mp 177–179 °C. [o] Reference 2 reported the HI salt. [p] Lit.[22] mp 220–221 °C. [q] Lit.[22] mp 270–271 °C. [r] From MeOH-Me_2CO-Et_2O. [s] From 2-PrOH-Et_2O. [t] Starting material was the *N*-*n*-propyl compound 23. [u] Lit.[23] mp 216.5 °C. [v] Lit.[2] mp 145–147 °C. [w] Lit.[2] mp 154–154.5 °C. [x] From EtOAc-hexane. [y] Koch-Light. [z] Macfarlan-Smith. [aa] Prepared by method in ref 24.

any potential dopamine-like effect.[15] Further detailed biochemical examinations are required to evaluate these possibilites.

Since the two different series of dihydroxylated 2-aminotetralins used in this study may possess basic differences in their mode(s) of action, no firm conclusion may be drawn as to the preferred rotameric form ("α" or "β") of dopamine for stereotypy or hyperactivity induction in the striatum. However, it should be noted that, whereas 2-di-*n*-propylamino-5,6-dihydroxytetralin (**11**) was an effective stereotypic agent, 2-di-*n*-propylamino-6,7-dihydroxytetralin (**28**) was inactive, and while apomorphine **39** also initiates stereotyped behavior on injection into the caudate-putamen, "isoapomorphine" **40** is inactive.[16] Thus, we would suggest that the "α" conformation of dopamine may be preferred for dopamine agonist activity in this brain region.

These studies emphasize the limitations of studying the central activity of drugs by using only the peripheral route of administration. In particular, when studying the activities of dopamine agonists, one must consider not only that more than one brain region may be involved with the mediation of a certain behavioral response but also that different dopamine mechanisms within one area may modulate that response. The complexities of such mechanisms are exemplified by the differing activity spectra of the different series of 2-aminotetralins used in the present studies.

Experimental Section

Melting points were determined in open glass capillaries on a Thomas-Hoover Umimelt apparatus and are corrected. Elemental analyses were performed by Galbraith Laboratories, Knoxville, Tenn. Where analyses are indicated by the symbols of the elements, the analytical results were within ±0.4% of the theoretical values.

Pharmacology. Methods. Male Sprague–Dawley (C.F.E.) rats weighing 250–350 g were used, and studies were carried out in a sound-proofed, diffusely illuminated room maintained at 21 ± 1 °C. The 2-aminotetralin derivatives and reference drugs (Table I) were prepared for both peripheral and intracerebral injection in aqueous solution containing 0.1% $Na_2S_2O_5$. In the peripheral studies, drugs were administered subcutaneously in a volume of 1 mL/mg, and stereotypy was assessed at 5–15-min intervals throughout the drug effect. Rats were prepared for the bilateral intrastriatal injection studies as previously described.[11] All rats receiving intrastriatal injection were pretreated with 100 mg/kg ip of nialamide 2 h before use. They were used on one occasion only. Nialamide (Sigma) was prepared as a complete solution in a minimum quantity of HCl, and this solution was neutralized before use with $NaHCO_3$. The rationale of the nialamide pretreatment has been discussed previously,[16] but in this respect, particular note should be made of the work of Cotzias et al.,[17] which would suggest that nialamide may increase the accessibility of a dopaminergic drug to its receptor site.

In addition to the stereotyped behavior, any hyperactivity induced by the test drugs on intrastriatal injection was recorded. Immediately after injection, rats were placed in activity boxes fitted with photocells, and activity was recorded as the number of interruptions of the light beam occurring within 5 min. Stereotypy was recorded simultaneously (see Figures 2 and 3).

Initial studies were also carried out to determine the antagonistic effects of α-methyltyrosine–reserpine pretreatment against stereotypy induced by 2-di-*n*-propylaminotetralin (**31**). α-Methyltyrosine (250 mg/kg) and 5 mg/kg ip of reserpine were administered 6 and 12 h, respectively, prior to the test compound. The effects of 0.1 mg/kg ip of haloperidol and fluphenazine on hyperactivity and stereotypy observed after intrastriatal administrations of 2-amino-5,6-dihydroxytetralin (**4**) and 2-amino-6,7-dihydroxytetralin (**20**) were also determined. (±)-α-Methyltyrosine (Sigma) was prepared as an aqueous suspension in 2% carboxymethylcellulose; reserpine (B.D.H.), in a minimum quantity of glacial AcOH; haloperidol (Janssen) in 1% lactic acid; and fluphenazine hydrochloride (Squibb) in distilled H_2O.

2-(2,3-Dimethoxyphenyl)ethyl Methylsulfinylmethyl Ketone (41). An oil dispersion of NaH (1.20 g, 0.05 mol) under N_2 was washed twice with pentane and traces of pentane were removed in a stream of N_2. Dimethyl sulfoxide (32 mL; purified by distillation from CaH_2) was added and the resulting mixture was stirred under N_2 at room temperature for 5 h. Ethyl 3-(2,3-dimethoxyphenyl)propanoate[18] (5.96 g, 0.025 mol) in 32 mL of tetrahydrofuran (purified by distillation from $LiAlH_4$) was added dropwise with stirring over 0.5 h, maintaining the temperature at 10 °C. The reaction mixture was stirred for 2 h at room temperature, poured over 200 mL of ice, and brought to pH 3–4 with HCl. The resulting solution was repeatedly extracted with $CHCl_3$. The combined extracts were dried (Na_2SO_4) and filtered, and volatiles were removed to afford an oil which solidified upon trituration with diisopropyl ether at −10 °C. This solid was collected on a filter and washed with cold Et_2O to afford 4.15 g (61%) of white needles, mp 55.5–56.5 °C. Anal. ($C_{13}H_{18}O_4S$) C, H.

1,2,3,4-Tetrahydro-1-methylthio-5,6-dimethoxy-2(1*H*)-naphthalenone (42). Compound **41** (5.40 g, 0.02 mol) and 4.56 g (0.04 mol) of trifluoroacetic acid were refluxed in 240 mL of benzene for 1.5 h. The cooled reaction mixture was washed with 5% Na_2CO_3 and volatiles were removed under reduced pressure to leave 5.0 g (essentially quantitative yield) of an orange-red oil which was utilized in the next step without purification. A portion of this oil was chromatographed on silica gel and eluted with benzene to afford a pure (by TLC analysis) oil. Anal. ($C_{13}H_{16}O_3S$) C, H.

1,2,3,4-Tetrahydro-5,6-dimethoxy-2(1*H*)-naphthalenone (43). The crude product **42** (17 g, 0.067 mol) in 200 mL of glacial AcOH was hydrogenated in the presence of 11 g of 5% Pd/C.

Uptake of the calculated amount of H_2 was complete in 40 h. The catalyst was removed by filtration and the filtrate was evaporated at reduced pressure to leave a heavy oil which was shaken vigorously with a solution of 48.5 g of $NaHSO_3$ in 100 mL of H_2O and 30 mL of EtOH. The bisulfite addition product was collected on a filter, washed with EtOH and Et_2O, and dried. The free ketone was obtained by treating the bisulfite addition compound with excess 10% Na_2CO_3 and extracting the resulting mixture with benzene. The extract was washed with 10% HCl and then with H_2O and dried (Na_2SO_4). Volatiles were removed under reduced pressure to leave a residue which was crystallized from cyclohexane to afford 9.7 g (70%) of white needles, mp 62–64 °C (lit.[19] mp 64–65 °C). This product was unstable and could best be stored as its bisulfite addition product.

1,2,3,4-Tetrahydro-6,7-dimethoxy-2(1*H*)-naphthalenone (36). This was prepared in 60% yield from 1,2,3,4-tetrahydro-1-methylthio-6,7-dimethoxy-2(1*H*)-naphthalenone (**35**)[4] by the method described for **43**: mp (THF–petroleum ether) 85–87 °C (lit.[20] mp 87–88 °C).

Method A. Reductive Amination of 2-Tetralones with $NaBH_3CN$. This procedure is illustrated for 2-*n*-propylamino-5,6-dimethoxytetralin hydrochloride (**6**). *n*-Propylamine (1.2 g, 0.002 mol) was treated with excess methanolic HCl (5 N) to approximately pH 7 to pH paper; then 0.7 g (0.0034 mol) of **43** was added, followed by 0.25 g (0.004 mol) of $NaBH_3CN$. The resulting mixture was stirred at room temperature for 22 h. Excess concentrated HCl was added, and volatiles were removed under reduced pressure. The residue was taken up in H_2O and washed with Et_2O. The aqueous phase was basified with KOH and extracted with $CHCl_3$. The $CHCl_3$ was removed under reduced pressure, the dark green oily residue was dissolved in Et_2O, and this solution was treated with ethereal HCl. The resulting solid was recrystallized repeatedly from MeOH–Et_2O (charcoal) and then from 2-PrOH–Et_2O to afford 0.67 g (69%) of product, mp 237–239 °C. A mass spectrum of this material exhibited a peak at *m/e* 249, corresponding to $C_{15}H_{23}NO_2$ (loss of HCl).

Method B. N-Alkylation of 2-Aminotetralins with $NaBH_4$–Carboxylic Acid Complex. This procedure is illustrated for 2-di-*n*-propylamino-5,6-dimethoxytetralin hydrochloride (**10**). $NaBH_4$ (0.532 g, 0.014 mol) was added in small portions to 3.42 g (0.046 mol) of propionic acid in 60 mL of dry benzene, maintaining the temperature below 20 °C. When H_2 evolution ceased, 0.8 g (0.0028 mol) of the free base of **6** was added and the resulting mixture was refluxed for 3 h. The cooled mixture was shaken with excess 2 N NaOH. The organic layer was dried (Na_2SO_4) and evaporated. The residue was treated with ethereal HCl to afford a brown oil which crystallized from MeOH–Et_2O to yield 0.85 g (93%) of product, mp 182–183 °C (lit.[2] mp 178–179 °C).

Method C. Reductive Amination of 2-Tetralones by Catalytic Hydrogenation. This method is illustrated for 2-methylamino-6,7-dimethoxytetralin hydrochloride (**21**). Compound **36** (0.9 g, 0.0044 mol), 1.5 g (0.025 mol) of AcOH, 1.1 g (0.027 mol) of methylamine, and 0.2 g of *p*-toluenesulfonic acid monohydrate were refluxed for 18 h in 40 mL of benzene in a Dean-Stark apparatus with the trap half-filled with 3A molecular sieves to entrap H_2O. At the end of this period, the light yellow-orange reaction mixture was cooled and 30 mL of glacial AcOH and 0.5 g of PtO_2 were added, and this mixture was hydrogenated at an initial pressure of 30 psig. When the calculated uptake of H_2 was complete (approx 4 h), 25 mL of 20% HCl was added and the volatiles were removed under reduced pressure. The residue was washed three times with Et_2O and then repeatedly with $CHCl_3$. The pooled $CHCl_3$ extracts were evaporated to leave a yellow-brown solid which was crystallized from MeOH–Me_2CO to yield 0.63 g (56%) of a light yellow solid, mp 243–244 °C.

Method D. Reductive Alkylation of Secondary Amine with an Aldehyde and $NaBH_3CN$. This procedure is illustrated for 2-dimethylamino-6,7-dimethoxytetralin (**23**). Compound **21**·HCl (0.31 g, 0.0012 mol), 0.6 mL (0.006 mol) of 37% aqueous formaldehyde solution, and 0.25 g (0.004 mol) of $NaBH_3CN$ in 15 mL of MeOH were stirred at room temperature for 3 days in the presence of 2 g of 3A molecular sieves. The reaction was quenched by addition of 25 mL of 3 N HCl; then the mixture was extracted repeatedly with $CHCl_3$. The combined $CHCl_3$ extracts were dried (Na_2SO_4) and evaporated to afford an orange solid which was recrystallized from MeOH–Et_2O to yield 0.29 g (89%) of a light pink solid, mp 250.5–252 °C.

Ether Cleavage Reactions. The amine hydrochloride (0.001 mol) was heated in 30 mL of 48% HBr under N_2 at 135–145 °C for 3 h. Volatiles were removed under reduced pressure and the residue was recrystallized (see Table I).

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