5,8-Disubstituted 1-Aminotetralins. A Class of Compounds with a Novel Profile of Central Nervous System Activity

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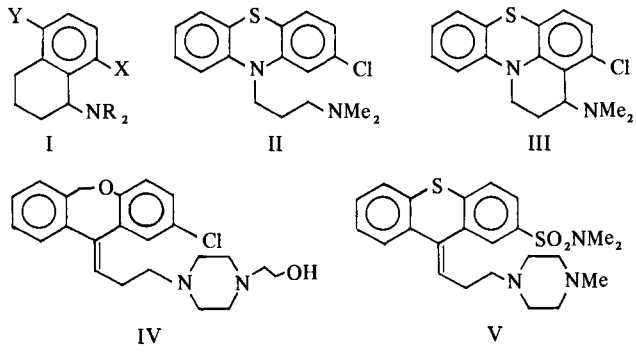
Synthesis of a series of 5,8-disubstituted 1-aminotetralins was undertaken based on electronic and conformational similarities to tricyclic neuroleptic drugs. Although none of these compounds exerted pronounced neuroleptic activity in animals, certain members of this novel series exhibited an unusual array of biological activities: suppression of a conditioned emotional response (CER) similar to that shown by benzodiazepine tranquilizers, reversal of trifluoperazine catalepsy, reversal of tetrabenazine catalepsy and depression similar to that shown by tricyclic antidepressants, and the ability to block peripheral α-adrenergic receptors. Interestingly, resolution of the racemic aminotetralins resulted in a clear-cut separation of biological activities: tetrabenazine reversal and anticataleptic effects were characteristic for *S* isomers, while suppression of CER and α-blocking properties were retained by *R* isomers. Systematic exploration of other structural parameters showed that one or two alkyl substituents on nitrogen, a methoxy group in the 5 position, and an electronegative substituent in the 8 position were necessary for CER activity, while anticataleptic activity was associated with analogs having small substituents on nitrogen.

Our interest in 5,8-disubstituted 1-aminotetralins I (Chart I) was stimulated by their electronic and configurational relationships to certain tricyclic neuroleptic agents. Although several types of structural and electronic parameters are undoubtedly associated with the activity of these drugs, an important factor was judged to be the conformation of the propylamine moiety. Structure-activity considerations led to the proposal that the biologically active conformation of neuroleptic drugs, such as chlorpromazine II, is one in which the side-chain amine function is arranged in space so as to be close to the electronegative chlorine substituent of the ring system, with both groups interacting with adjacent complementary sites on the receptor.[1] Support for this hypothesis comes from the fact that in tricyclic drugs such as pinoxepin IV and thiothixene V, where the side chain is linked through a double bond to the ring system, the cis isomer is many times more potent than the trans isomer,[2] and X-ray analysis has established such conformations in crystalline thiothixene[3a] and chlorprothixene.[3b] The tetracyclic analog III of chlorpromazine, which fixes the amine group in a position close to the chlorine atom, has been described in the literature[4] and would be an interesting test case for this hypothesis. Unfortunately, no pharmacological data have been reported for this compound. It was of interest, however, to investigate whether simple nontricyclic molecules, which afford a similarly close spatial relationship between an amine function and a highly electronegative nuclear substituent, would exert CNS effects. Substituted 1-aminotetralins of type I represent one class of such compounds.

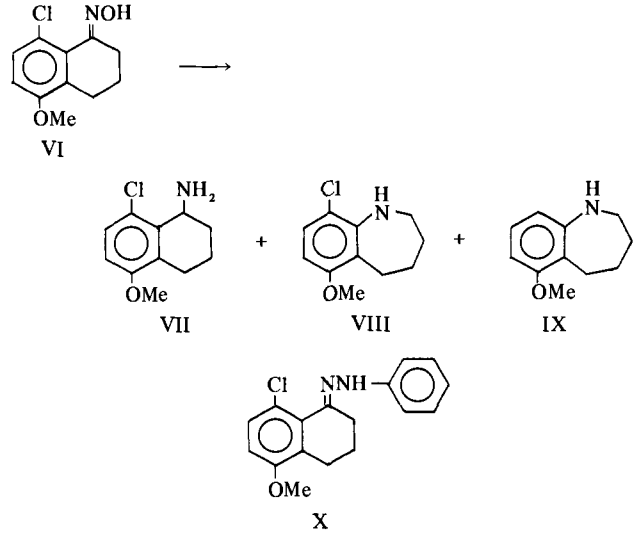
Chart I



In contrast to 2-aminotetralin derivatives, 1-aminotetralin derivatives have received little attention from medicinal chemists. *N*-Propargyl-substituted 1-aminotetralins are reported to be potent monoamine oxidase inhibitors,[5] and quarternary derivatives are claimed[6] to cause a selective blockade in the peripheral sympathetic nervous system.

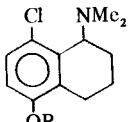
Chemistry. The 1-aminotetralin derivatives were prepared from the corresponding ketones, which are either commercially available or which were obtained according to published procedures. Primary amines were synthesized by catalytic hydrogenation of the oximes, except in the case of compounds with aromatic halogen substituents, where $LiAlH_4$ reduction was used in order to avoid the possibility of dehalogenation. However, $LiAlH_4$ reduction of oxime VI (Scheme I) gave only a modest yield of the expected product

Scheme I



VII, accompanied by two rearranged products, the benzo[*b*]azepins VIII and IX. Analogous rearrangements occurring in the reduction of oximes have been reported previously.[7] Zinc-acetic acid reduction[8] of the phenylhydrazine X ultimately gave VII in good yield. Secondary amines were obtained in excellent yield by $TiCl_4$ catalyzed conversion of the ketones to ketimines,[9] followed by reduction with $NaBH_4$ in methanol.[10] Tertiary amines were prepared by a similar $TiCl_4$ catalyzed enamine formation[11] and subsequent reduction with formic acid[12] or alternatively with $LiBH_4$ in the presence of formic acid.[13] A second route to tertiary amines

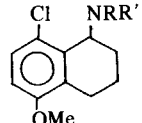
Table I



No.	R	Mp, °C	Formula[a]	Method	% yield	LD_{50} (mouse), mg/kg ip[f]	Tetrabenazine stereotypy (rat), ED_{50},[b] mg/kg ip[f]	Trifluoperazine reversal (rat), ED_{50},[b] mg/kg ip[f]	CER activity (rat), mg/kg ip[d,f]
1	Me	191–193	$C_{13}H_{18}ClNO \cdot HCl$	A	58	100–316	21.2[c]	5.3[c]	18–32+
2	Et	188–190	$C_{14}H_{20}ClNO \cdot HCl$	B	77	100–316	>32	10–32	32–
3	Pr	188–189	$C_{15}H_{22}ClNO \cdot HCl$	B	78	100–316	18–32	NT	32–
4	*i*-Pr	170–171	$C_{15}H_{22}ClNO \cdot HCl$	B	31	100–316	>32	NT	32–
5	Bu	182–183	$C_{16}H_{24}ClNO \cdot HCl$	B	90	100–316	>32	NT	32–
6	*i*-Bu	161–162	$C_{16}H_{24}ClNO \cdot HBr$	B	7	NT	NT	NT	32–
7	$(CH_2)_{11}Me$	148–149	$C_{24}H_{40}ClNO \cdot HCl$	B	18	100–316	>32	NT	32–
8	$CH_2CH{=}CH_2$	198–199	$C_{15}H_{20}ClNO \cdot HCl$	B	55	100–316	>32	>32	32–
9	$CH_2C{\equiv}CH$	189–190	$C_{15}H_{18}ClNO \cdot HCl$	B	34	100–316	10–18	18–32	32–
10	$C_6H_5CH_2$	200–201	$C_{19}H_{22}ClNO \cdot HCl$	B	59	100–316	NT	NT	NT
11	$4\text{-}CH_3C_6H_4CH_2$	214–215	$C_{20}H_{24}ClNO \cdot HCl$	B	68	316–1000	NT	NT	NT
12	$3\text{-}ClC_6H_4CH_2$	185–187	$C_{19}H_{21}Cl_2NO \cdot HBr$	B	42	100–316	>32	>32	32–
13	$4\text{-}ClC_6H_4CH_2$	227–229	$C_{19}H_{21}Cl_2NO \cdot HCl$	B	90	316–1000	>32	>32	75–
14	$3\text{-}CF_3C_6H_4CH_2$	188–191	$C_{20}H_{21}ClF_3NO \cdot HBr$	B	40	316–1000	>32	>32	75–
15	H	190–191	$C_{12}H_{16}ClNO \cdot HI$	*e*	76	100–316	>100	10–32	32–

[a] All compounds were analyzed for C, H, and N. [b] > signifies inactivity at the dose indicated; NT signifies not tested. [c] Calculated. [d] + indicates statistically reliable activity. – indicates lack of statistically reliable difference between drug and normal saline control groups; if more than one dose was used, only the highest inactive dose is reported. [e] See Experimental Section. [f] The pharmacology methods are described in detail in the Experimental Section.

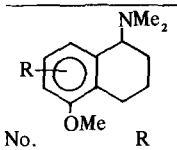
Table II



No.	R, R'	Mp, °C	Formula[a]	Method	% yield	LD_{50} (mouse), mg/kg ip	Tetrabenazine stereotypy (rat), ED_{50},[b] mg/kg ip	Trifluoperazine reversal (rat), ED_{50},[b] mg/kg ip	CER activity (rat), mg/kg ip[a]
1	Me, Me	191–193	$C_{13}H_{18}ClNO \cdot HCl$	A	58	100–316	21.2[c]	5.3[c]	18–32+
16	H, H	274–275	$C_{11}H_{14}ClNO \cdot HCl$	*f*	82	100–316	10–18	10–32	75–
17	H, Me	203–205	$C_{12}H_{16}ClNO \cdot HCl$	C	77	100–316	10–32	3.2–5.6	18–32+
18	H, Et	210–211	$C_{13}H_{18}ClNO \cdot HCl$	C	74	32–100	32–56	5.6–10	18–32+
19	Et, Et	112–114	$C_{15}H_{22}ClNO \cdot HCl \cdot H_2O$	D[g]	56	NT	>32	10–32	32+
20	$-(CH_2)_4-$	205–206	$C_{15}H_{20}ClNO \cdot HCl$	A, D[h]	59, 52	100–316	32–56	10–32	10–32+
21	$-(CH_2)_5-$	175–177	$C_{16}H_{22}ClNO \cdot HCl \cdot 0.25H_2O$	A[i]	34	100–316	>32	10–32	32+
22	$-(CH_2)_2O(CH_2)_2-$	206–208	$C_{15}H_{20}ClNO_2 \cdot HCl$	A[h]	52	316–1000	>32	>32	32–
23	$-(CH_2)_2NMe(CH_2)_2-$	235–237	$C_{16}H_{23}ClN_2O \cdot 2HCl \cdot 0.5H_2O$	A[h]	22	100–316	>32	10–32	32–
24	H, *i*-Pr	231–234	$C_{14}H_{20}ClNO \cdot HCl$	C	80	100–316	18–32	10–32	56–
25	Me, *i*-Pr	178–179	$C_{15}H_{22}ClNO \cdot HBr$	E	48	100–316	18–32	10–32	32
26	H, $(CH_2)_2C_6H_5$	269–270	$C_{19}H_{22}ClNO \cdot HCl$	C	75	316–1000	>32	>32	32–
27	Me, $(CH_2)_2C_6H_5$	194–195	$C_{20}H_{24}ClNO \cdot HBr$	E	23	100–316	NT	NT	56–
28	Me, $CH_2C{\equiv}CH$	216–217	$C_{15}H_{18}ClNO \cdot HCl$	D	73	100–316	>32[e]	NT	32–
29	Et, $CH_2C{\equiv}CH$	194–195	$C_{16}H_{20}ClNO \cdot HCl$	D	54	316–1000	>32[e]	NT	32–
30	H, CHO	168–169	$C_{12}H_{14}ClNO_2$	*f*	67	NT	>32	>32	32–

[a] All compounds were analyzed for C, H, and N. [b] > signifies inactivity at the dose indicated; NT signifies not tested. [c] Calculated. [d] + indicates statistically reliable activity. – indicates lack of statistically reliable difference between drug and normal saline control groups; if more than one dose was used, only the highest inactive dose is reported. [e] The interaction with tetrabenazine was that of a typical MAO inhibitor, *viz.* piloerection, exophthalmos, tremors, etc. [f] See Experimental Section. [g] 60 equiv of EtI was used. [h] *Cf.* R. B. Moffet, *J. Org. Chem.*, 14, 862 (1949). [i] The enamine was reduced with $LiBH_4$–HCOOH according to the method of Marshall and Johnson.[13]

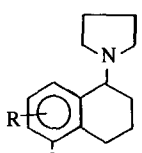
Table III



No.	R	Mp, °C	Formula[a]	Method	% yield	LD_{50} (mouse), mg/kg ip	Tetrabenazine stereotypy (rat), ED_{50},[b] mg/kg ip	Trifluoperazine reversal (rat), ED_{50},[b] mg/kg ip	CER activity (rat), mg/kg ip[d]
1	8-Cl	191–193	$C_{13}H_{18}ClNO \cdot HCl$	A	58	100–316	21.2[c]	5.3[c]	18–32+
31	H	167–168	$C_{13}H_{19}NO \cdot HCl$	A	79	100–316	>32	10–32	32–
32	8-Br	176–178	$C_{13}H_{18}NOBr \cdot HCl$	E	24	NT	10–32	10–32	56+
33	8-COMe	115–116	$C_{15}H_{21}NO_2$	F	61	32–100	>32	>32	32+
34	8-COEt	74–75	$C_{16}H_{23}NO_2$	F	42	32–100	>56	10–32	32+
35	8-COPr	72–73	$C_{17}H_{25}NO_2$	F	77	100–316	>32	NT	32–
36	8-CO-*i*-Pr	69–70	$C_{17}H_{25}NO_2$	F	55	100–316	>32	NT	32–
37	8-COBu	158–159	$C_{18}H_{27}NO_2 \cdot HCl$	F	60	100–316	>32	NT	32–
38	8-CO-*i*-Bu	153–155	$C_{18}H_{27}NO_2 \cdot HCl$	F	54	100–316	>32	NT	32–
39	8-SO_2NMe_2	156–158	$C_{15}H_{24}N_2O_3S \cdot HCl$	G	31	NT	>32	NT	32–
40	8-F	186–188	$C_{13}H_{18}FNO \cdot HCl$	A	41	100–316	>32	10–32	10–32+
41	8-NO_2	202–203	$C_{13}H_{18}N_2O_3 \cdot HCl$	*f*	31	100–316	10–18	3.2–18	32–
42	8-NHAc	198–199	$C_{15}H_{22}N_2O_2 \cdot HCl$	*f*		100–316	>32	NT	32–
43	6-Cl	186–187	$C_{13}H_{18}ClNO \cdot HCl$	*h*		32–100	>32	NT	32–[e]
44	6-NO_2	199–200	$C_{13}H_{18}N_2O_3 \cdot HCl$	*f*	31	32–100	>32	NT	32–[e]
45	6,8-Cl_2	187–188	$C_{13}H_{17}Cl_2NO \cdot HBr$	F[g]	38	100–316	18–32	>32	32–[e]
46	6,8-$(NO_2)_2$	148–149	$C_{13}H_{17}N_3O_5 \cdot HCl$	*f*		316–1000	>32	NT	32–[e]

[a] All compounds were analyzed for C, H, and N. [b] > signifies inactivity of the dose indicated; NT signifies not tested. [c] Calculated. [d] + indicates statistically reliable activity. – indicates lack of statistically reliable difference between drug and normal saline control groups; if more than one dose was used, only the highest inactive dose is reported. [e] Recovery times were longer than those of saline control groups. [f] See Experimental Section. [g] 3 equiv of Cl_2 was used in this experiment. [h] This material was isolated in small yield from a large run in which 1 had been prepared by chlorination of 31 (method F).

Table IV



No.	R	Mp, °C	Formula[a]	Method	% yield	LD_{50} (mouse), mg/kg ip	Tetrabenazine stereotypy (rat), ED_{50},[b] mg/kg ip	Trifluoperazine reversal (rat), ED_{50},[b] mg/kg ip	CER activity (rat), mg/kg ip[c]
20	8-Cl	205–206	$C_{15}H_{20}ClNO \cdot HCl$	D	59	100–316	32–56	10–32	10–32+
47	H	171–172	$C_{15}H_{21}NO \cdot HCl$	A	52	100–316	>32	18–32	32+
48	8-Br	198–199	$C_{15}H_{20}BrNO \cdot HCl$	D	25	100–316	>32	NT	32+
49	8-F	205–207	$C_{15}H_{20}FNO \cdot HCl$	A	61	100–316	>32	10–32	3.2–32+
50	8-Ac	124–125	$C_{17}H_{23}NO_2$	F	59	32–100	>32	NT	18–32+
51	8-COEt	96–97	$C_{18}H_{25}NO_2$	F	77	100–316	>32	NT	32+
52	8-COPr	68–69	$C_{19}H_{27}NO_2$	F	33	32–100	>32	NT	18+
53	8-CO-*i*-Pr	188–189	$C_{19}H_{27}NO_2 \cdot HCl$	F	13	100–316	>32	NT	32–
54	8-COBu	154–155	$C_{20}H_{29}NO_2 \cdot HCl$	F	17	100–316	>32	NT	32–
55	8-CO-*i*-Bu	177–178	$C_{20}H_{29}NO_2 \cdot HCl$	F	29	32–100	>32	NT	32+
56	8-SO_2NMe_2	184–185	$C_{17}H_{26}N_2O_3S \cdot HCl$	G	8	32–100	>32	NT	32–
57	8-SO_2NHMe	189–190	$C_{16}H_{24}N_2O_3S \cdot HCl$	G	23	32–100	>32	NT	32–
58	8-$SO_2NMeCH_2C_6H_5$	168–169	$C_{23}H_{30}N_2O_3S \cdot HCl \cdot H_2O$	G	33	100–316	>32	NT	32–
59	8-SO_2-c-NC_4H_8	180–181	$C_{19}H_{28}N_2O_3S \cdot HCl$	G	17	32–100	>32	NT	32–

[a] All compounds were analyzed for C, H, and N. [b] > signifies inactivity at the dose indicated; NT signifies not tested. [c] + indicates statistically reliable activity. – indicates lack of statistically reliable difference between drug and normal saline control groups; if more than one dose was used, only the highest inactive dose is reported.

consisted of alkylation of primary or secondary amine precursors.

Ether cleavage of **1** with HI provided the phenol **15**, which was alkylated with various halides to give the compounds listed in Table I. Compounds with varied N substituents listed in Table II were prepared according to the general methods listed above and are described in more detail in the Experimental Section. The diethyl compound **19** could only be prepared by dialkylation of **16**, since enamine formation was not observed with diethylamine even under forcing reaction conditions. Most of the 5-methoxy-substituted derivatives listed in Tables III and IV were obtained by electrophilic substitution of **31** and **47**, respectively, which in the case of chlorination, bromination, or acylation gave predominantly the 8 isomers. Trace quantities of the corresponding 6 isomers, such as **43**, were also isolated from mother liquors. In contrast, nitration of **31** led to an equimolar mixture of 6- and 8-nitro isomers. The preference for substitution in the 8 position in the former cases suggests participation by the adjacent nitrogen function, since steric considerations would be expected to favor substitution at the 6 position. Indicative of the steric crowding of the 8 position is the nmr spectrum of the hydrochloride of **1** in $CDCl_3$, in which the *N*-methyl protons appear as two doublets due to hindered rotation. However, in the case of the 1-alkyl-substituted compounds **95** and **97** steric factors are sufficient to lead to the formation of both 6- and 8-chloro isomers in nearly a 1:1 ratio. Attempts to obtain the 8-fluoro derivatives **40** and **49** by fluorination of **31** and **47** with CF_3OF[14] failed.

The resolution of the optical isomers of the primary and secondary 1-aminotetralins was carried out by treating a methanol–ether solution of the racemate with 0.5 equiv of either *N*-acetyl-L-tyrosine or L-mandelic acid, leading to a quantitative precipitation of the less soluble *S* isomer salt. The *R* isomer was then recovered from the filtrate by the addition of 1 equiv of D-mandelic acid. No more than one recrystallization was needed to achieve optical purity (constant rotation). The relative configuration of the derivatives (listed in Table VI) was established by chemical interconversions, and the absolute *S* configuration of **62** was established by X-ray crystallography of its *d*-10-camphorsulfonate.† Since tertiary amines could not be resolved by these procedures, they were prepared by dialkylation of the optically pure primary amines. Similarly, the sterically crowded *N*-isopropyl derivative **24** could not be resolved, whereas its deschloro analog **109** was resolved without difficulty to yield **76** and **77**. The deschloro compounds **70**, **71**, **72**, and **73** were obtained from the corresponding 8-chloro derivative by catalytic hydrogenation which required the presence of triethylamine.[15]

Structure–Activity Relationship. The first compound to be prepared in this series, *N,N*-dimethyl-8-chloro-5-methoxy-1,2,3,4-tetrahydro-1-naphthylamine (**1**), indeed exhibited pronounced central nervous system activity but qualitatively different from that exhibited by chlorpromazine. As indicated in Table V, **1** was similar to chlordiazepoxide in blocking a conditioned emotional response (CER)[16] in rats, a behavioral procedure in which antianxiety drugs are active and major tranquilizers generally inactive. In addition, when administered to rats, **1** resembled desmethylimipramine in reversing tetrabenazine sedation and in inducing typical hyperactivity and jumping behavior.[17,18] Unlike desmethylimipramine, however, **1** is not a norepinephrine reuptake blocker in rat heart. **1** also reversed the cataleptic symptoms induced by trifluoperazine in rats with a potency greater than that of benztropine mesylate,[19] although it lacks anticholinergic properties.

Table V

	Tetrabenazine stereotypy (rat), ED_{50}, mg/kg ip	Trifluoperazine reversal (rat), ED_{50}, mg/kg ip	CER activity (rat), mg/kg ip
Desmethylimipramine	9.3 (6.8–14.4)		
Benztropine mesylate		21.6 (13.6–30.1)	
Chlordiazepoxide			10–18+
1	21.2 (17.2–26.0)	5.3 (3.4–7.0)	18–32+

This unique psychopharmacological profile of **1** has been described in a preliminary report.[20] From the studies in anesthetized dogs and with isolated aortic strips, it was concluded that **1** competitively blocks α-adrenergic receptors. Details of this work will be reported elsewhere.‡

The novel profile of psychopharmacological action of **1** suggested exploration of the structural parameters responsible for the various behavioral activities. This led to a systemic investigation of the role of (a) the aromatic substitution pattern, (b) the nitrogen substituents, (c) the size of the alicyclic ring, and (d) the configuration of the asymmetric carbon atom.

Table I compares the chemical and pharmacological properties of the parent compound **1** with those derivatives modified at C-5. Such modifications abolished CER activity and reduced or abolished tetrabenazine and trifluoperazine reversal. The benzyloxy-substituted derivatives **10–14**, which bear some resemblance to dibenzoxepin type antipsychotic agents (IV, Chart I), showed no noteworthy activity.

Derivatives of **1** in which the substituents on nitrogen were modified are listed in Table II. CER activity was shared by several analogs, either mono- or dialkylated with sterically small substituents (*i.e.*, **17–19**, **24**) or in which the nitrogen was part of a pyrrolidine or piperidine ring (**20** and **21**). Activity in reversing trifluoperazine catalepsy did not parallel CER activity, the monomethyl derivative **17** being the most potent compound in this respect. Antitetrabenazine activity also appeared to be independent of anticataleptic and CER activity, with the most noteworthy divergence of activity shown by the pyrrolidine analog **20**. Of interest are the two propargyl-substituted derivatives **28** and **29** which have been described as monoamine oxidase inhibitors.[21] In agreement with this, **28** and **29** interacted with tetrabenazine to elicit a profusion of sympathomimetic and central effects, such as exophthalmos, piloerection, tremors, and salivation, but not the "compulsive hyperactivity" syndrome seen after desmethylimipramine[17,18] and other active aminotetralins of this series.

Further structure-activity studies were carried out using the dimethylamino and pyrrolidino compounds **1** and **20** as prototypes. Table III shows the influence of modifying the chlorine function of **1**; replacement of chlorine by fluorine (**40**) enhanced, by bromine (**32**) diminished, and by hydrogen (**31**) abolished CER activity, suggesting a correlation of this activity with the electronegativity of the 8 substituent. Several 8-acyl derivatives also retained CER activity. It is

† We are grateful to Professor John P. Schaefer for this determination.

‡ R. Sarges, W. K. McShane, and J. W. Constantine, unpublished results.

noteworthy that the 6-chloro isomer **43** and of the 6,8-dichloro analog **45** are inactive, indicating that the proper aromatic substitution pattern is necessary for biological activity in this series. Anticataleptic and antitetrabenazine activity of these derivatives was generally modest. α-Adrenergic blocking potency was greatly diminished for the 8-acyl and 8-fluoro derivatives,‡ indicating some divergence of peripheral α-adrenergic from CER activity.

The structure-activity results seen with the dimethylamino derivatives also applied to the pyrrolidine analogs listed in Table IV. Again, replacement of chlorine by fluorine (**49**) enhanced CER activity, while the corresponding bromine (**48**) and hydrogen (**47**) analogs showed diminished potency. Simple 8-acyl analogs were again active in CER testing. Antitetrabenazine activity was absent in this series.

Dramatic results were obtained by separating several biologically active 1-aminotetralin analogs into their enantiomers (Table VI). Without exception, activity in the CER test was exhibited only by compounds with the *R* configuration. Conversely, only *S* isomers exhibited antitetrabenazine activity, indicative of the rigid structural specificity involved in these actions. Anticataleptic activity was less rigorously dependent on the configuration, but *S* isomers were clearly more potent in this test. The α-adrenergic activity was again highly configuration specific, being associated with *R* isomers; the implications of this specificity will be discussed subsequently.‡

The activities of analogs in which (a) the nitrogen and the aromatic substituents as well as the substitution patterns were modified, (b) alkyl substituents in the 1 position added, and (c) the aliphatic ring contracted are listed in Table VII. With the exception of the indan analogs **90** and **91** and of the dimethoxychloro analog **103**, none of these compounds suppressed CER. Antitetrabenazine and anticataleptic activity was more widely distributed in this group and did not appear to follow any discernible pattern.

In conclusion, although the anticipated neuroleptic activity was not found in this novel series of substituted 1-aminotetralins, an intriguing profile of "antianxiety" and "antidepressant/anticataleptic" activity was observed which is highly structure specific: CER activity is dependent upon (a) the *R* configuration at C-1, (b) the presence of a strongly electronegative substituent at C-8, (c) the presence of a methoxy group in the 5 position, and (d) the presence of relatively small alkyl substituents on nitrogen, maximum activity being reached when these substituents form a pyrrolidine ring; tetrabenazine reversal and anticataleptic activity, on the other hand, are associated with (a) the *S* configuration at C-1 and (b) the presence of very small nitrogen substituents.

Experimental Section§

General Method A. Tertiary amines were synthesized from the corresponding ketones *via* the enamines[11,12] as illustrated for the preparation of *N,N*-dimethyl-5-methoxy-8-chloro-1,2,3,4-tetrahydro-1-naphthylamine (**1**). In a flame-dried three-necked flask, equipped with stirrer, internal thermometer, and dropping funnel, a solution of 4.13 ml (0.038 mol) of $TiCl_4$ in 25 ml of PhH was added dropwise under a nitrogen atmosphere to a precooled solution (0–5°) of 15.8 g (0.075 mol) of 5-methoxy-8-chloro-3,4-dihydro-1(2*H*)-naphthalenone[22] and 29.78 ml (0.45 mol) of anhydrous dimethylamine in 225 ml of PhH, keeping the temperature below 10°. The mixture was allowed to warm up and stirred at temperature until glc analysis of aliquots showed complete conversion of the ketone to the enamine (1–5 hr). The mixture was filtered; the solids were slurried twice with 100 ml of PhH and filtered. The combined filtrates were evaporated to give 18 g (100%) of oily enamine. Formic acid (14 ml, 98%) was added dropwise to the enamine, resulting in gas evolution and heat generation. The mixture was stirred 1 hr at 70°, diluted with 100 ml of H_2O, adjusted to pH 1 with 6 *N* HCl, and washed with Et_2O. The aqueous layer was adjusted with 4 *N* NaOH to pH 12 and extracted three times with Et_2O. The Et_2O layers were combined, washed with H_2O, dried, and evaporated to 14.5 g (81%) of oily amine. The amine was treated with HCl gas in Et_2O to give 16.2 g (78% of the hydrochloride, mp 186–189°). Recrystallization from MeOH-Et_2O gave a first crop of 11.96 g (58%, of 1, mp 191–193°).

N,N-Dimethyl-8-chloro-5-hydroxy-1,2,3,4-tetrahydro-1-naphthylamine (**15**). A solution of 13.2 g (0.048 mol) of **1** in 48 ml of AcOH and 59 ml of 50% HI was refluxed for 5 hr. Evaporation and recrystallization of the residue from MeOH-Et_2O gave 12.8 g (76%) of **15** as the HI salt, mp 188–189°.

General Method B. Compounds **2–14** with modified alkoxy substituents were prepared from **15** as illustrated for the synthesis of 3. A solution of 12.7 g (0.036 mol) of **15** (HI salt) in 150 ml of DMF was treated with 4.3 g (0.09 mol) of 50% NaH at 65°. After the H_2 evolution had ceased, the reaction mixture was treated at room temperature with 6.7 g (0.0395 mol) of PrI, dissolved in 10 ml of DMF. The mixture was warmed to 70° for 3.5 hr, evaporated, and worked up in the usual manner to give 8.6 g (78%) of 3 as the hydrochloride, mp 188–189°.

8-Chloro-5-methoxy-1,2,3,4-tetrahydro-1-naphthylamine (16). A mixture of 31.5 g (0.15 mol) of 8-chloro-5-methoxy-3,4-dihydro-1(2*H*)-naphthalenone[22] in 600 ml of EtOH, 30 ml of phenylhydrazine, and 120 ml of AcOH was heated on the steam bath for 30 min. After cooling, 45 g (100%) of the crystalline phenylhydrazone V was collected, mp 178–180°. An analytical sample was recrystallized from EtOAc, mp 182–183°. *Anal.* ($C_{17}H_{17}ClO_2$) C, H, N. The phenylhydrazone V (45 g, 0.015 mol) was suspended in 2000 ml of AcOH, 111 g of activated zinc dust was added in small portions over 10 min, and the stirred mixture was warmed to 70° for 3 hr and then stirred at room temperature for 20 hr. After filtration and evaporation the residue was diluted with 500 ml of H_2O, the pH of the mixture adjusted to 4.5 with 6 *N* HCl, and the aniline removed by three extractions with 200 ml of Et_2O. The aqueous layer was made strongly alkaline with 4 *N* NaOH and extracted three times with 300 ml of Et_2O. The combined Et_2O extracts were worked up in the usual manner to give 31.4 g (82%) of 16 as the HCl salt, mp 269–272°.

The alternate synthesis, conversion of 8-chloro-5-methoxy-3,4-dihydro-1(2*H*)-naphthalenone to the oxime, mp 186–187° (87% yield), followed by $LiAlH_4$ reduction gave only a 50% yield of **16**, a 30% yield of 9-chloro-6-methoxy-2,3,4,5-tetrahydro-1*H*-benzo[*b*]-azepine hydrochloride (III), mp 221–225° [*Anal.* ($C_{11}H_{14}ClNO\cdot HCl$) C, H, N], and a 10% yield of 6-methoxy-2,3,4,5-tetrahydro-1*H*-benzo[*b*]azepine hydrochloride (IV), mp 259–260° [*Anal.* ($C_{11}H_{16}ClNO$) C, H, N].

General Method C. The preparation of secondary amines is exemplified by the synthesis of *N*-methyl-8-chloro-5-methoxy-1,2,3,4-tetrahydro-1-naphthylamine (**17**). 8-Chloro-5-methoxy-3,4-dihydro-1(2*H*)-naphthalenone[22] (10.5 g, 0.05 mol) was treated with 9.3 g (0.3 mol) of $MeNH_2$ and 2.75 ml (0.025 mol) of $TiCl_4$ as described in General Method A to give 11.5 g (100%) of the Schiff base.[9] The Schiff base was dissolved in 100 ml of MeOH and 1.9 g (0.05 mol) of $NaBH_4$ was added in portions. After 0.5 hr of stirring at room temperature the mixture was evaporated and then worked up in the usual manner to give 11 g (98%) of the oily amine. Conversion to the hydrochloride gave 10.8 g (83%), mp 200–203°, after recrystallization from MeOH-Et_2O, 10.0 g (77%), mp 202–204°, of **17**.

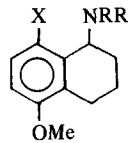
General Method D. Alkylation with Alkyl Halides. A mixture of 2.2 g (0.01 mol) of 17 as the free base, 30 ml of Me_2CO, 1.06 g (0.01 mol) of Na_2CO_3, and 0.075 ml of (0.01 mol) freshly distilled propargyl bromide was refluxed overnight. An additional 0.025 ml of propargyl bromide and 0.03 g of Na_2CO_3 were added and the mixture was refluxed for another 5 hr. The usual work-up and conversion to the hydrochloride salt gave 2.2 g (73%) of **28**, mp 216–217°.

General Method E. Methylation with HCHO-HCOOH. A mixture of 2.4 g (0.0094 mol) of **24** as the free base, 25 ml of HCOOH, and 25 ml of 37% HCHO was heated on the steam bath for 30 min. The usual work-up gave 3.28 g (48%) of **25** as the hydrobromide.

N-Formyl-8-chloro-5-methoxy-1,2,3,4-tetrahydro-1-naphthylamine (30). A solution of 3 g (0.014 mol) of **16** as the free base and 30 ml of Et_2O was added dropwise to HCOOAc, prepared from 3 ml of Ac_2O and 1.3 ml of HCO_2H, keeping the temperature below

§ Melting points were determined in a Thomas-Hoover capillary melting point apparatus and are uncorrected. Where analyses are indicated only by symbols of the elements or functions, analytical results obtained for those elements or functions were within ±0.4% of the theoretical values.

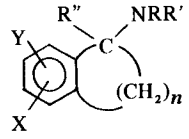
Table VI



No.	R, R'	X	Configuration at C-1	Mp, °C	Formula[a]	[α]D, deg (c 1, MeOH)	LD_{50} (mouse), mg/kg ip	Tetrabenazine stereotypy (rat), ED_{50},[b] mg/kg ip	Trifluoperazine reversal (rat), ED_{50},[b] mg/kg ip	CER activity (rat), mg/kg ip[c]
60	Me, Me	Cl	*S*	195–196	$C_{13}H_{18}ClNO \cdot HCl$	+36.6	32–100	10–18	3.2–10	18–
61	Me, Me	Cl	*R*	196–197	$C_{13}H_{18}ClNO \cdot HCl$	–36.5	100–316	>56	10–18	10–18+
62	H, H	Cl	*S*	293–293.5	$C_{11}H_{14}ClNO \cdot HCl$	–34.4	100–316	10–18	10–18	18–
63	H, H	Cl	*R*	293–293.5	$C_{11}H_{14}ClNO \cdot HCl$	+33.2	32–100	>32	>32	42–
64	H, Me	Cl	*S*	198–199	$C_{12}H_{16}ClNO \cdot HCl$	–14.9	32–100	5.6–10	5.6–10	18–
65	H, Me	Cl	*R*	198–199	$C_{12}H_{16}ClNO \cdot HCl$	+14.8	100–316	>56	18–32	18+
66	H, Et	Cl	*S*	180–181	$C_{13}H_{18}ClNO \cdot HCl$	–5.7	100–316	18–32	1–3.2	18–
67	H, Et	Cl	*R*	180–181	$C_{13}H_{18}ClNO \cdot HCl$	+5.1	100–316	>56	>32	18–32+
68	$-(CH_2)_4-$	Cl	*S*	235–236	$C_{15}H_{20}ClNO \cdot HCl$	+62.1	100–316	>56	>56	18–
69	$-(CH_2)_4-$	Cl	*R*	235–236	$C_{15}H_{20}ClNO \cdot HCl$	–61.7	100–316	>32	>32	10–32+
70	H, Et	H	*S*	186–187	$C_{13}H_{19}NO \cdot HCl$	–11.4	32–100	>32	>32	32–
71	H, Et	H	*R*	186–187	$C_{13}H_{19}NO \cdot HCl$	+10.1	32–100	>32	>32	32+
72	$-(CH_2)_4-$	H	*S*	158–159	$C_{15}H_{21}NO \cdot HCl$	+33	NT	>32	NT	18–
73	$-(CH_2)_4-$	H	*R*	158–159	$C_{15}H_{21}NO \cdot HCl$	–32	NT	>32	NT	18+
74	$-(CH_2)_4-$	$COCH_3$	*S*	136–137	$C_{17}H_{23}NO_2$	+84	NT	>32	>32	18–
75	$-(CH_2)_4-$	$COCH_3$	*R*	136–137	$C_{17}H_{23}NO_2$	–84	NT	>32	NT	10–18+
76	H, *i*-Pr	H	*S*	234–235	$C_{14}H_{21}NO \cdot HCl$	–10.7	NT	>32	NT	NT
77	H, *i*-Pr	H	*R*	234–235	$C_{14}H_{21}NO \cdot HCl$	+11.1	NT	>32	NT	NT
78	H, *i*-Pr	Cl	*S*	161–162	$C_{14}H_{20}ClNO \cdot HCl$	–3.5	100–316	5.6–10	5.6–10	NT

[a] All compounds were analyzed for C, H, and N. [b] > signifies inactivity at the dose indicated; NT signifies not tested. [c] + indicates statistically reliable activity. indicates lack of statistically reliable difference between drug and normal saline control groups; if more than one dose was used, only the highest inactive dose is recorded.

Table VII



No.	X, Y	R, R'	R"	*n*	Mp, °C	Formula[a]	Method	% yield	LD_{50} (mouse), mg/kg ip	Tetrabenazine stereotypy (rat), ED_{50},[b] mg/kg ip	Trifluoperazine reversal (rat), ED_{50},[b] mg/kg ip	CER activity (rat), mg/kg ip[c]
79	5-OMe	H, H	H	3	249–250	$C_{11}H_{15}NO \cdot HCl$	H	74	32–100	18–32	10–32	NT
80	H	Me, Me	H	3	155–157	$C_{12}H_{17}N \cdot HCl$	E	53	100–316	18–32	10–32	32–
81	H	H, Me	H	3	153–155	$C_{11}H_{15}N \cdot HCl$[d]	C	55	100–316	18–32	10–32	32
82	H	H, H	H	3	177–178	$C_{10}H_{13}N \cdot HCl$[e]	H	88	100–316	18–32	10–32	32–
83	H	$-(CH_2)_4-$	H	3	170–172	$C_{14}H_{19}N \cdot HCl$	A	29	32–100	>32	10–32	32
84	5-OMe, 8-OMe	H, H	H	3	252–253	$C_{12}H_{17}NO_2 \cdot HCl \cdot 0.5H_2O$	H[f]	95	32–100	10–18	NT	32–
85	5-OMe, 8-Br	H, H	H	3	272–273	$C_{11}H_{14}BrNO \cdot HCl$	F	89	100–316	10–32	10–32	NT
86	6-OMe	H, H	H	3	>300	$C_{11}H_{15}NO \cdot HCl$	H	67	100–316	18–32	>32	NT
87	5-Me, 7-Me	Me, Me	H	3	162–163	$C_{14}H_{21}N \cdot HCl$	E	53	32–100	10–32	18–32	32–
88	5-Me, 7-Me	H, H	H	3	247–249	$C_{12}H_{17}N \cdot HCl$	H	85	NT	10–32	1–3.2	32
89	5-OH, 6-Cl	Me, Me	H	3	244–245	$C_{12}H_{16}ClNO \cdot HI$	g		100–316	NT	NT	NT
90	7-Cl	Me, Me	H	2	123–130	$C_{11}H_{14}ClN \cdot HCl \cdot 0.5H_2O$	A	25	NT	>32	10–32	32+
91	4-OMe, 7-Cl	Me, Me	H	2	186–188	$C_{12}H_{16}ClNO \cdot HCl$	E	35	NT	18–32	NT	32+

92	5-OMe, 6-OMe	Me, Me	H	2	178–179	$C_{13}H_{19}NO_2 \cdot HCl$	A	50	32–100	NT	32–
93	5-OMe	H, H	CO_2H	3	270–271	$C_{12}H_{15}NO_3 \cdot HCl$	*h*	>1000	>32	NT	NT
94	5-OMe, 6-Cl	Me, Me	CH_2OH	3	221–222	$C_{14}H_{20}ClNO_2 \cdot HBr$	F	42	100–316	>32	32–
95	5-OMe	Me, Me	CH_2OH	3	182–183	$C_{14}H_{21}NO_2 \cdot HCl$	E	45	32–100	>32	32–
96	5-OMe	H, H	CH_2OH	3	225–226	$C_{12}H_{17}NO_2 \cdot HCl$	*h*		100–316	>32	32–
97	5-OMe	H, Me	Me	3	250–251	$C_{13}H_{19}NO \cdot HCl$	*h*		32–100	NT	32–
98	5-OMe, 6-Cl	H, Me	Me	3	235–237	$C_{13}H_{18}ClNO \cdot HCl \cdot 0.25H_2O$	F	10	NT	NT	32–
99	5-OMe, 8-Cl	H, Me	Me	3	252–253	$C_{13}H_{18}ClNO \cdot HCl$	F	12	NT	18–32	18–
100	5-OMe, 8-Cl	Me, Me	Me	3	201–202	$C_{14}H_{20}ClNO \cdot HCl \cdot 0.25H_2O$	*i*		NT	NT	32–
101	5-OMe, 8-F	H, H	H	3	230–231	$C_{11}H_{14}FNO \cdot HCl$	*h*		100–316	>32	56–
102	5-Cl, 7-OMe, 8-OMe	Me, Me	H	3	185–186	$C_{14}H_{20}ClNO_2 \cdot HCl$	*A*[j]	24	10–32	>10	18–
103	5-Cl, 7-OMe, 8-OMe	$-(CH_2)_4-$	H	3	217–218	$C_{16}H_{22}ClNO_2 \cdot HCl$	*A*[j]	69	100–316	>32	18+
104	7-OH, 8-OH	H, Me	H	3	160–162	$C_{11}H_{15}NO_2 \cdot HI$	*k*		100–316	>32	32–
105	7-OH, 8-OH	$-(CH_2)_4-$	H	3	164–166	$C_{14}H_{19}NO_2 \cdot HI$	*l*		NT	>32	NT
106	7-OMe, 8-OMe	$-(CH_2)_4-$	H	3	191–192	$C_{16}H_{23}NO_2 \cdot HCl$	*m*		32–100	>32	18–
107	5-Cl, 7-OMe, 8-OMe	H, Me	H	3	224–225	$C_{13}H_{18}ClNO_2 \cdot HCl$	*O*	86	10–32	>10	18–
108	7-OMe, 8-OMe	H, Me	H	3	169–170	$C_{13}H_{19}NO_2 \cdot HCl$	*n*		100–316	>32	NT
109	5-OMe	H, *i*-Pr	H	3	214–215	$C_{14}H_{21}NO \cdot HCl$	C	95	100–316	>32	NT
110	5-OMe	H, Et	H	3	192–194	$C_{13}H_{19}NO \cdot HCl$	C	78	32–100	>32	10–32

[a] All compounds were analyzed for C, H, and N. [b] > signifies activity at the dose indicated; NT signifies not tested. [c] + indicates statistically reliable activity. – indicates lack of statistically reliable difference between drug and normal saline control groups; if more than one dose was used, only the highest inactive dose is reported. [d] Known compound: J. Pitha, M. Horák, J. Kovář, and K. Bláha, *Collect. Czech. Chem. Commun.*, **25**, 2733 (1960). [e] Known compound: C. F. Huebner, E. M. Donoghue, A. J. Plummer, and P. A. Furness, *J. Med. Chem.*, **9**, 830 (1966). [f] The oxime, mp 217–219°, was prepared in 90% yield from the ketone: J. A. Moore and M. Rahm, *J. Org. Chem.*, **26**, 1109 (1961). [g] Obtained in 66% yield from **43** according to the method given for the preparation of 15. [h] See Experimental Section. [i] This compound was prepared in 7% yield from the enamine according to the method of P. P. Lynch and P. H. Doyle, *Gazz. Chim. Ital.*, 98, 645 (1968). [j] The starting ketone was prepared according to R. Ghosh and R. Robinson, *J. Chem. Soc.*, 508 (1944). [k] Obtained in 28% yield by HI treatment of **108**. [l] Obtained in 50% yield by HI treatment of **106**. [m] Obtained in 71% yield by hydrogenation of **103** in EtOH over 10% Pd/C in the presence of NEt_3. [n] Obtained in 94% yield by hydrogenation of 107 in EtOH over 10% Pd/C in the presence of NEt_3.

40°. After stirring at room temperature for 2 hr, the solvent was evaporated and the residue recrystallized from EtOAc–petroleum ether (bp 30–60°) to give 2.25 g (67%) of **30**, mp 168–169°.

General Method F. Electrophilic Substitution in the 8 (or 6) Position Exemplified by the Acetylation of 31. To a mixture of 4.3 g (0.018 mol) of **31** in 60 ml of $PhNO_2$ and 7.8 g (0.072 mol) of Ac_2O was added 9.6 g (0.072 mol) of $AlCl_3$ in portions, keeping the temperature at 0–5°. After stirring at room temperature overnight, the mixture was warmed to 80° for 2 hr. After pouring into ice, containing 50 ml of 6 *N* HCl, followed by the usual work-up and recrystallization from Et_2O, 2.73 g (61%) of **33** was obtained. Similarly, chlorinations and brominations were carried out at room temperature with 1 equiv of halogen in AcOH, in some cases in the presence of a Lewis acid such as $FeCl_3$.

General Method G. Preparation of Sulfonamido Derivatives. To 4.8 g (0.02 mol) of **31** was added dropwise with stirring 5.2 ml (0.08 mol) of $ClSO_3H$, keeping the temperature at 0–5°. The mixture was allowed to warm to room temperature and kept for 1 hr, followed by warming to 65° for 1.5 hr. After cooling, this mixture was dissolved in 50 ml of $CHCl_3$ and added dropwise with stirring at 0–10° into a mixture of 125 ml of 25% aqueous dimethylamine and 125 ml of $CHCl_3$. After stirring at room temperature for 1 hr, the $CHCl_3$ layer was collected and worked up in the usual manner to give after recrystallization from $CHCl_3$–Et_2O 1.27 g (31%) of **39**.

Preparation of 8-Fluoro-5-methoxy-3,4-dihydro-1(2*H*)-naphthalenone. Succinoylation of 4-fluoroanisole according to the procedure of Ghosh and Robinson[23] gave a 22% yield of 3-(5-fluoro-2-methoxybenzoyl)propionic acid, mp 128–130°, soluble in CH_2Cl_2 [*Anal.* ($C_{11}H_{11}FO_4$) C, H], and a 36% yield of 3-(5-fluoro-2 hydroxybenzoyl)propionic acid, mp 170–171°, insoluble in CH_2Cl_2 [*Anal.* ($C_{19}H_9FO_4$) C, H]. Clemmensen reduction of 3-(5-fluoro-2-methoxybenzoyl)propionic acid or of the crude mixture containing the demethylated derivative gave a mixture of 4-(5-fluoro-2-methoxyphenyl)butyric acid and 4-(5-fluoro-2-hydroxyphenyl)butyric acid. Remethylation of this crude mixture with Me_2SO_4–2 *N* NaOH gave a 46% yield of 4-(5-fluoro-2-methoxyphenyl)butyric acid, mp 68–70°. *Anal.* ($C_{11}H_{13}FO_3$) C, H. This acid was converted with $SOCl_2$ to the acid chloride and cyclized with poly(phosphoric acid) according to the procedure of Bhati, *et al.*,[24] to give a 49% yield of 8-fluoro-5-methoxy-3,4-dihydro-1(2*H*)-naphthalenone, mp 82–84°. *Anal.* ($C_{11}H_{11}FO_2$) C, H.

Preparation of the Nitro Derivatives 41, 44, and 46. A solution of 10.3 g (0.05 mol) of **31** as the free base in 50 ml of trifluoroacetic acid was treated with 3.6 ml of 70% HNO_3 below 10° according to the method of Smith, *et al.*,[25] to give a mixture of the 8 isomer (R_f 0.6 on tlc in a 95% cyclohexane–5% diethylamine system) and the 6 isomer (R_f 0.8).

After chromatography on a silica gel column using 95% cyclohexane–5% diethylamine, there was obtained 4.5 g (31%) of **41** and 4.5 g (31%) of **44** (structure assigned by nmr analysis). Treatment of 10.3 g (0.05 mol) of **31** (free base) with 35 ml of concentrated H_2SO_4 and 10.1 g (0.01 mol) of KNO_3 at 0°, followed by stirring at room temperature for 1 hr and the usual work-up, gave 3.6 g (22%) of **46**.

Preparation of 42. Hydrogenation of 2.3 g (0.008 mol) of **41** in EtOH–HCl over 0.5 g of 10% Pd/C gave a first crop of 1.1 g (47%) of 8-amino-5-methoxy-1-dimethylamino-1,2,3,4-tetrahydronaphthylamine dihydrochloride hemihydrate, mp 137–140°. An analytical sample had mp 140–141°. *Anal.* ($C_{13}H_{20}N_2O \cdot 2HCl \cdot 0.5H_2O$) C, H, N. A mixture of 1 g (0.0033 mol) of this material, 50 ml of saturated aqueous $NaHCO_3$, and 50 ml of Et_2O was treated with 0.37 ml of AcCl and stirred at room temperature for 1 hr. The usual work-up, followed by conversion to the hydrochloride and recrystallization from EtOH–Et_2O, gave 0.7 g (70%) of **42**, mp 198–199°.

Preparation of the Pure Enantiomers Listed in Table VI. Resolution of 17. A solution of 29.5 g (0.13 mol) of **17** as the free base in 100 ml of MeOH was treated with 14.8 g (0.066 mol) of *N*-acetyl-L-tyrosine, the mixture was warmed on the steam bath until dissolution occurred, 100 ml of Et_2O was added, and the mixture kept overnight in the refrigerator. The crystals (28.7 g, 97%), mp 177–180°, were filtered off and recrystallized from MeOH–Et_2O to give 27.0 g (92%) of the *N*-acetyltyrosine salt of the *S* isomer of **17**, mp 179–181°. Conversion to the hydrochloride yielded 30.7 g (80%) of **64**, mp 198–199° after recrystallization from MeOH–Et_2O. The original mother liquor containing the *R* isomer of **17** was evaporated, dissolved in 20 ml of $CHCl_3$, treated with 9.9 g (0.065 mol) of D(–)-mandelic acid, and warmed until dissolution occurred. The mixture was treated with 150 ml of Et_2O and kept in the refrigerator overnight. The crystals (23.4 g, 96%), mp 146–148°, were filtered off and recrystallized from MeOH–Et_2O (1:9) to give 17.8 g (73%) of

the D-mandelate of the *R* isomer of 17, mp 151–152°. Conversion to the hydrochloride and recrystallization from MeOH–Et_2O (1:4) gave 11.9 g (69%) of **65**, mp 198–199°.

Similarly, 16, 17, 18, 110, and 109 were resolved into **62** and **63**, **64** and **65**, 66 and 67, 70 and 71, and 76 and 77, respectively. **62** and **63** were converted by method E to 60 and 61, in 74 and 78% yield, respectively. Alkylation of **62** and **63** with 1,4-dibromobutane (method D) gave 68 and 69 in 50 and 53% yield, respectively. Hydrogenation of 68 and 69 in MeOH over Pd/C in the presence of 2 equiv of triethylamine gave quantitative yields of **72** and **73**, respectively. Acetylation of **72** and **73** (method F) gave 74 and **75** in 39 and 31% yield, respectively. Alkylation of **62** (method D) gave 78 in 51% yield.

The absolute configuration of **62** was established by an X-ray analysis† of its *d*-10-camphorsulfonate, mp 207–207.5° (MeOH–Et_2O). The configuration of the other derivatives listed in Table VI was established by the following interconversion (in addition to those listed above). Conversion of 63 to its *N*-formyl derivative (mp 168–169°), followed by $LiAlH_4$ reduction, gave **65**. Alkylation of **62** with EtI (method D) gave 66 in 47% yield. Chlorination of 76 gave 78 in 80% yield (method F).

General Method H. Preparation of Primary Amines. To a mixture of 20 g (0.113 mol) of 5-methoxy-3,4-dihydro-1(2*H*)-naphthalenone and 12.8 g of $NH_2OH \cdot HCl$ in 200 ml of EtOH was added a solution of 28 g of NaOAc in 60 ml of warm H_2O. After heating on the steam bath for 20 min, 30 ml of EtOH and 40 ml of H_2O were added, the mixture was cooled, and the oxime [20.4 g (94%), mp 157–159°[26]] was collected. A solution of 20 g (0.015 mol) of this oxime in 200 ml of AcOH was hydrogenated over 2 g of 10% Pd/C at 25° and 50 psi (4 hr). After filtration, evaporation of the filtrate, conversion of the residue to the hydrochloride, and recrystallization from MeOH, 16.5 g (74%) of 79 was obtained.

1-Amino-5-methoxy-1,2,3,4-tetrahydro-1-naphthoic Acid (93). According to method B of Goodson,[27] *et al.*, 58 g (0.33 mol) of 5-methoxy-3,4-dihydro-1(2*H*)-naphthalenone was converted to 60.2 g (74%) of the hydantoin derivative, mp 242–242.5°. *Anal.* ($C_{13}H_{14}N_2O_3$) C, H, N. Hydrolysis of 60 g (0.24 mol) of hydantoin with 1 ml of 20% NaOH in a steel reaction vessel at 165° for 20 hr gave after acidification, filtration, and recrystallization from MeOH–Et_2O 48.5 g (77%) of 93, mp 275–276° dec.

1-Hydroxymethyl-5-methoxy-1,2,3,4-tetrahydro-1-naphthylamine (96). A suspension of 38 g (0.184 mol) of 93 in 1 l. of THF was refluxed in the presence of 10 g (0.26 mol) of $LiAlH_4$ for 18 hr. After the usual work-up, 21.2 g (69%) of 96 was obtained as the free base, mp 125–127°.

***N*-Methyl-5-methoxy-1-methyl-1,2,3,4-tetrahydro-1-naphthylamine (97).** A solution of 4.4 g (0.023 mol) of 5-methoxy-1-methylimino-1,2,3,4-tetrahydronaphthalene (obtained from the ketone according to method C) in 100 ml of Et_2O was treated dropwise at room temperature with 3 ml of freshly distilled $BF_3 \cdot Et_2O$.

The reaction mixture was cooled to −50° and 12.4 ml of a 2.1 *M* solution of LiMe in Et_2O was added dropwise. After stirring at room temperature overnight the mixture was diluted with 50 ml of H_2O, basified, and extracted with Et_2O. The Et_2O extracts were evaporated and the residue was heated to 100° for 15 min with 50 ml of 1 *N* HCl in order to hydrolyze unreacted starting material. After the usual work-up and conversion to the hydrochloride, followed by recrystallization from MeOH–Me_2CO–Et_2O, 1.19 g (23%) of 97, mp 250–251°, was obtained.

8-Fluoro-5-methoxy-1,2,3,4-tetrahydro-1-naphthylamine (101). This compound was prepared in analogy to the synthesis of compound 16 described above. 8-Fluoro-5methoxy-3,4-dihydro-1(2*H*)-naphthalenone was converted in 100% yield to the phenylhydrazone, mp 132–134°. *Anal.* ($C_{17}H_{17}FN_2O$) C, H, N. Reduction with Zn in AcOH gave 101 in 23% yield.

Pharmacology Methods. LD_{50}'s in Mice. Groups of three mice were treated with doses of 32, 100, 320, and 1000 mg/kg ip. Lower entries in the tables are the highest doses at which none or one mouse died (24-hr basis); higher entries are the lowest doses at which two or three mice died.

Tetrabenazine Stereotypy in Rats. The method used was based on observations that desmethylimipramine, given prior to rapid-acting amine releasers such as tetrabenazine, causes the releasers to elicit unique "compulsive hyperactivity" and "jumping behavior" from a platform.[17,18] The so-called "jumping behavior" is characterized in rats by extension of the head and trunk further and further over the side of a platform until support by the hind feet is impossible. Groups of at least five rats were first pretreated with experimental compounds and were subsequently treated with tetrabenazine, 32 mg/kg iv, given as an HCl solution. Immediately after tetrabenazine was administered, each rat was placed on a circular platform of 26 cm in diameter elevated 23 cm above the tabletop (simply an inverted pail). Each jump from the platform onto the tabletop was recorded. Following each jump the rat was rapidly but gently returned to the center of the platform. Drugs were considered active if more than half of the tested rats jumped five or more times during the 2.5 hr following tetrabenazine. ED_{50}'s were estimated from the data.

Trifluoperazine Reversal in Rats. Apparatus consisted of four pedestals (rubber stoppers), larger circumference downward, centered on the angles of an isosceles trapezoid with bases of 9.7 and 6.5 cm and height of 8.5 cm. Each pedestal was 2.6 cm high. A catalepsy trial was conducted by placing a rat's two front paws onto the two stoppers describing the shorter base and the two hind paws onto the stoppers describing the longer base. If a rat could be made to remain in this awkward posture for 30 sec he was judged to be cataleptic; if he consistently moved his paws off the stoppers before 30 sec elapsed he was judged to be noncataleptic. Groups of at least five rats were first treated with trifluoperazine at the high dose of 32 mg/kg ip. Later (2 hr) they were treated with experimental compounds, and ED_{50}'s for reversing catalepsy 0.5 hr after treatment were estimated.

Conditioned Emotional Response (CER) Activity. A CER to a previously neutral stimulus was established by the general procedure of Tenen.[16] Rats deprived of water for 24 hr were placed in a test chamber until they accumulated 20 sec of drinking time at a drinking bottle containing a 3% sucrose solution. The rats were then divided into "CER" and "NO CER" groups. CER animals were placed into a dark shock chamber. After about 1 min, flashing lights and an intermittent tone were simultaneously presented for 10 sec; during the last 0.5 sec, current of about 1.5 mA was delivered through the grid floor. Each CER rat was given three such trials. The NO CER (control) animals were treated identically except that foot shock was not administered. On the next day, the animals were given two 20-sec drinking sessions in the test chamber. Afterward they were given access to water in their home cages for 30 min. On the third (test) day, the rats were placed into the test chamber 30 min after drug or control treatment. After a rat had accumulated 20 sec of drinking time, the intermittent tone and flashing wall lights were presented for 3 sec. Because of the dependence of testing on drinking behavior the time of drug pretreatment varied from about 30 to about 45 min before actual testing. The stimuli were not at this time followed by shock. The time that the animal required to accumulate 3 sec of drinking time following the presentation of the CER stimuli was recorded to the nearest 0.1 sec. This value was termed the recovery time. If the rat did not accumulate 3 sec of drinking time within 5 min following the presentation of the CER stimuli the test was terminated and a score of 300.0+ sec was recorded. Recovery times of "CER" and contemporary "NO CER" controls were compared by the Mann-Whitney U test, and significance was based on $p < 0.05$.

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Benzodiazepines with Psychotropic Activity. 7.[1] Synthesis and Biological Action of 4-Amino-1,5-benzodiazepines

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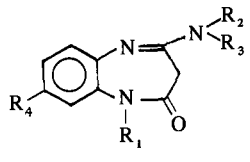
This paper gives a description of the syntheses of substituted 4-amino-1,5-benzodiazepines **1**. In addition, the possibility is discussed that due to corresponding structural features the 1,5- and 1,4-benzodiazepines (see **6**, **7**) exhibit similar effects on the central nervous system (CNS). Pharmacological data are given for **1**. The biological properties of some particularly active compounds (*e.g.*, **1c** and **1n**) are dealt with in detail.

Diazepam **2**[2] and **3a**†,[3,4] on the one hand and medazepam **4**[2] and benzodiazepines of type **5**[5] on the other hand show a partly analogous action in the animal experiment in respect to their effect on the CNS. Apparently the two structural types **6** and **7** have a similar profile of pharmacological action. Compounds of structure **1** were of interest in this



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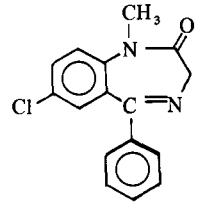

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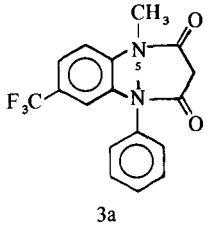
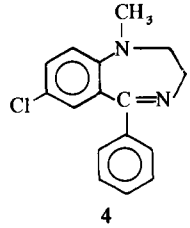


3a



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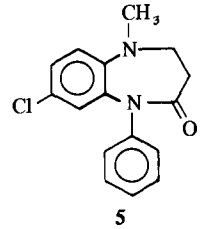

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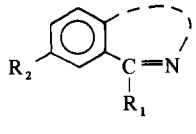

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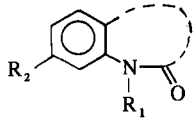

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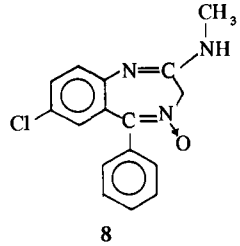

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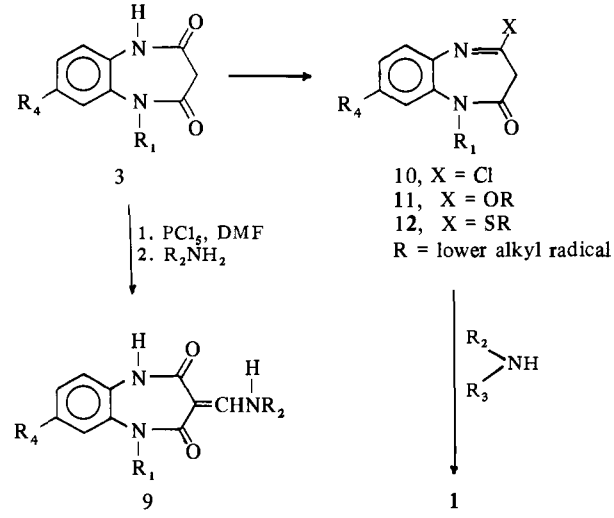
context; they exhibit a structural relationship to chlordiazepoxide[2] **8** and can be expected to have the ability to form water-soluble salts, which appears favorable for pharmacological reasons.

Chemistry. 1,5-Benzodiazepine-2,4 diones **3**[4] could be converted to 3-aminomethylidene-1,5-benzodiazepines **9**[6] by means of phosphorus pentachloride and alkylamines in DMF. A high yield of **9** was obtained only if the alkylamine was added to the reaction mixture of phosphorus pentachloride, DMF, and **3** after several hours. If the alkylamine was added after only a few minutes, the amidine **1** in a mixture of **3** and **9** was obtained. A high yield of **1** was obtained in dioxane and also to some degree in other inert solvent. The imino chloride **10**[7-9] probably occurs as an intermediate but was not isolated. The conversion of **3** to **1** could also be directed through the iminoether **11** or the imino sulfide **12**, which could relatively smoothly be converted to **1** by means of the amine as was expected.[10,11] In order to trace structure-activity relationships we have synthesized a series of these compounds[12] as shown in Scheme I. A selection is given together with pharmacological data for guidance (Table I).

Scheme 1



Compounds **3**,[4] **5**,[5] **9**,[6] **11**, and **12** have previously been described; we synthesized **3** with $R_4 = NO_2$ by way of oxi-

†Compound **3a** has been designated ORF 8063 in earlier publications. In ref 4 it appeared as 1n.