gested by the parameter values based on the class models. And according to the suggestion, the peptide with the following structure is expected to have a sweet taste: L-Asp-NH-CH_2OH.

Acknowledgment. We thank the Computer Center, Institute for Molecular Science, for affording facilities for computation and thank Hoogenstraaten for sending the STERIMOL program.

Registry No. 1, 25352-43-6; **2**, 25352-57-2; **3**, 30239-25-9; **4**, 58889-59-1; **5**, 25352-56-1; **6**, 25352-46-9; **7**, 25353-70-2; **8**, 25353-69-9; **9**, 25353-72-4; **10**, 101145-65-7; 11, 101145-66-8; **12**, 25352-48-1; **13**, 22839-89-0; 14, 59917-64-5; **15**, 101145-67-9; **16**, 74216-15-2; 17, 59917-63-4; **18**, 51871-24-0; **19**, 51871-18-2; **20**, 39614-06-7; **21**, 39613-86-0; **22**, 39613-88-2; **23**, 39613-91-7; **24**, 39613-94-0; **25**, 50833-41-5; **26**, 50833-42-6; **27**, 101145-68-0; **28**, 51871-23-9; **29**, 52945-91-2; **30**, 101145-69-1; **31**, 52946-15-3; **32**, 39613-97-3; **33**, 52945-89-8; **34**, 101145-70-4; **35**, 39614-00-1; **36**, 101145-71-5; **37**, 59917-61-2; **38**, 49558-29-4; **39**, 101145-72-6; **40**, 77096-46-9; 41, 52946-00-6; **42**, 52993-06-3; **43**, 101223-13-6; 44, 22839-47-0; **45**, 26270-66-6; **46**, 101145-73-7; **47**, 22839-51-6; **48**, 101145-74-8; **49**, 37622-39-2; **50**, 52946-01-7; **51**, 52946-02-8; **52**, 52946-03-9; **53**, 52946-04-0; **54**, 52946-05-1; **55**, 52946-06-2; **56**, 52946-07-3; **57**, 22839-92-5; **58**, 52946-08-4; **59**, 52946-10-8; **60**, 52946-11-9; **61**, 53022-01-8; **62**, 53022-03-0; **63**, 53022-04-1; **64**, 52945-94-5; **65**, 52945-95-6; **66**, 37465-92-2; **67**, 58406-52-3; **68**, 58406-53-4; **69**, 43188-74-5; **70**, 43188-75-6; 71, 25352-44-7; **72**, 25352-45-8; **73**, 101145-75-9; **74**, 101145-76-0; **75**, 25353-71-3; **76**, 52945-90-1; **77**, 5241-71-4; **78**, 72683-65-9; **79**, 72683-70-6; **80**, 72683-74-0; **81**, 72683-76-2; **82**, 101145-77-1; **83**, 22839-93-6; **84**, 22839-88-9; **85**, 72683-62-6; **86**, 22839-48-1; **87**, 22840-07-9; **88**, 101145-78-2; **89**, 30239-44-2; **90**, 30239-43-1; **91**, 22838-86-4; **92**, 22839-52-7; **93**, 59917-62-3; **94**, 22839-91-4; **95**, 50833-44-8; **96**, 22839-90-3; **97**, 101145-79-3; **98**, 13433-09-5; **99**, 15368-70-4; **100**, 22849-03-2; **101**, 22839-65-2; **102**, 101145-80-6; **103**, 52945-93-4; **104**, 22839-49-2; **105**, 22839-50-5; **106**, 22840-03-5; **107**, 22840-08-0; **108**, 22840-09-1.

Structure-Activity Relationships of Dopaminergic 5-Hydroxy-2-aminotetralin Derivatives with Functionalized *N*-Alkyl Substituents

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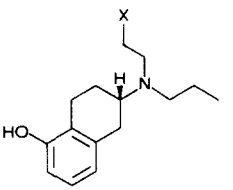
5-Hydroxy-2-aminotetralin derivatives in which one *N*-alkyl substituent carries a functional group have been prepared and their dopaminergic activities compared with those of 5-hydroxy-2-(di-*n*-propylamino)tetralin (5-OH-DPAT) and known ergolines. Several members of the series demonstrated high affinities in dopamine (DA) receptor binding and DA agonist properties in the rotational behavior model in the range of known potent ergolines. The results suggest that the accessory binding site for the larger *N*-alkyl substituent of the 5-hydroxy-2-aminotetralins can accommodate various neutral and bulky functionalities and is probably identical with the site(s) to which the 8-substituents of the ergolines bind.

Dopaminergic activity has been identified in a variety of structural types. The tetracyclic ergoline derivatives with three asymmetric centers figure certainly among the most complex ones, whereas the phenolic 2-aminotetralins seem to contain the minimal structural requirements for longer acting, metabolically stabilized dopamine (DA) analogues.[1] We have chosen the 2-aminotetralin skeleton as the starting point for the design of new clinically useful dopaminergic drugs to investigate whether these relatively simple structures could compete in in vivo tests with the prominent dopaminergic activities of the ergolines.

By comparing phenolic 2-aminotetralins with either a primary or a tertiary amino group in vitro, we have observed that on DA_1 and DA_2 receptor subtypes *N,N*-di-*n*-propylation has no influence upon the activity of 7-hydroxyaminotetralin, the most active primary amine, but leads to an increase in activity of the corresponding 5-hydroxy derivative, rendering 5-hydroxy-2-(di-*n*-propylamino)tetralin (5-OH-DPAT) the most potent member of the series. This increase in activity (and affinity in DA receptor binding) upon N,N-dialkylation has been interpreted in the sense that the *N*-propyl substituents of the 5-hydroxylated aminotetralins can reach accessory binding sites.[2,3] Earlier investigations have revealed that the DA receptor can accommodate N,N-disubstituted DA analogues with one *N*-alkyl substituent not larger than *n*-propyl, whereas the structural requirements for the second N-substituent are less stringent.[4-10] Similarly, *n*-butyl substitution at the basic nitrogen of the ergolines results in compounds with strongly reduced dopaminergic activities,[11] suggesting that this N-substituent corresponds to the DA N-substituent with reduced steric freedom. It is tempting to speculate that the larger N-substituent of the N,N-dialkylated 5-hydroxyaminotetralins I (X = alkyl) could reach at the DA receptor the site(s) of the important 8-substituent Y of the ergolines II. We have therefore



I

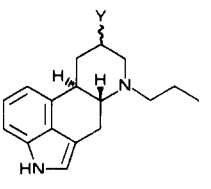


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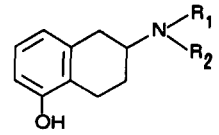
Table I. Biological Activities



no.[a]	R_1	R_2	DA receptor binding: [^{3}H]DA: IC_{50}, nM	DA receptor binding: [^{3}H]spiroperidol: IC_{50}, nm	contralateral turning in 6-OH-DA-lesioned rats[b]: dose, mg/kg ip	total turnings	max intensity, turnings/min	duration, h
1	$(CH_2)_2CH_3$	*n*-Pr	49 ± 10	1350 ± 40	1	2538 ± 346	22.7	6
2	$(CH_2)_2CN$	*n*-Pr	130 ± 15	7500 ± 1450	1	<150		
3	$(CH_2)_3CN$	*n*-Pr	35 ± 10	790 ± 117	1	1170 ± 418	10.3	3
(−)-3[c]			37 ± 10	370 ± 80	1	3265 ± 1085	12	6
(+)-3[d]			490 ± 85	3500 ± 350	1	ϕ[e]		
4	$(CH_2)_3CN$	Et	68 ± 10	920 ± 220	1	<150		
5	$(CH_2)_3CN$	Me	500 ± 60	3500 ± 500	1	<150		
6	$(CH_2)_4CN$	*n*-Pr	91 ± 35	1500 ± 230	1	1455 ± 519	10.8	4
7	$(CH_2)_2Ph$	*n*-Pr	40 ± 10	180 ± 30	1	1517 ± 715	8.7	6
8	$(CH_2)_3Ph$	*n*-Pr	48 ± 10	140 ± 30	1	656 ± 358	6.6	5
9	$(CH_2)_3CH{=}CH_2$	*n*-Pr	48 ± 3	400 ± 10	1	1735 ± 600	7.7	7
10	$(CH_2)_3N_3$	*n*-Pr	58 ± 15	530 ± 100	1	1859 ± 390	6.7	7
11	$(CH_2)_3Cl$	*n*-Pr	46 ± 5	1020 ± 10	1	2658 ± 425	12.5	7
12	$(CH_2)_3SCH_3$	*n*-Pr	43 ± 9	220 ± 12	1	1982 ± 374	9.8	7
(−)-12[c]			38 ± 8	230 ± 10	1	3590 ± 697	15.2	7
13	$(CH_2)_3SO_2CH_3$	*n*-Pr	110 ± 15	1860 ± 20	1	531 ± 211	5.7	1
14	$(CH_2)_3OCH_3$	*n*-Pr	150 ± 20	2200 ± 100	1	347 ± 172	7.4	2
15	$(CH_2)_3OH$	*n*-Pr	185 ± 65	1450 ± 350	1	721 ± 170	10.2	3
16	$(CH_2)_3NH_2$	*n*-Pr	2000 ± 500	4580 ± 940	1			
17	$(CH_2)_3NHAc$	*n*-Pr	190 ± 40	1800 ± 620	1	159 ± 115	1.6	4
18	$(CH_2)_3CONHCH_3$	*n*-Pr	38 ± 20	825 ± 250	10	413 ± 115	6.4	6
19	$(CH_2)_2NHSO_2N(Et)_2$	*n*-Pr	41 ± 9	220 ± 19	1	1015 ± 279	7.8	3
20	$(CH_2)_3NHSO_2N(CH_3)_2$	*n*-Pr	100 ± 20	370 ± 40	10	857 ± 176	7.6	4
21	$(CH_2)_3NHCON(Et)_2$	*n*-Pr	220 ± 50	1300 ± 150	10			
22	$(CH_2)_3NHCOOEt$	*n*-Pr	77 ± 8	525 ± 85	1	1216 ± 465	10.4	5
23	$(CH_2)_3COOCH_3$	*n*-Pr	140 ± 30	910 ± 50	1	<150		
ref compd								
24	CM 29-712		265 ± 15	520 ± 15	1	2607 ± 155	14.4	>7
25	CQ 32-084		120 ± 4	25 ± 5	1	3688 ± 357	11.8	>7
26	pergolide		18 ± 4	145 ± 15	1	1796 ± 60	9.7	>7

[a] Compounds are racemic except were indicated. [b] $n = 3$. [c] (2*S*) form. [d] (2*R*) form. [e] ϕ = inactive.

synthesized 5-hydroxy-2-aminotetralins I in which one of the *N*-alkyl substituents carries a functional group X. The latter could eventually further increase the affinity for the proposed accessory binding site. In addition, this functional group provides a means to modify the pharmacokinetic parameters of the compounds, e.g., to decrease or facilitate the transport to the central nervous system (CNS). We report here the results of a series of compounds tested for circling behavior that appears to represent a valid model for antiparkinson activity. In addition, DA receptor binding was performed to allow a better interpretation of the in vivo studies.

Chemistry

Compounds were prepared by the methods illustrated in Scheme I, starting from known N-monoalkylated aminotetralins III and IV.[8] Direct N-alkylation of the phenolic amines IV with alkyl halides carrying the desired functional group X was normally the preferred method. The products I thus obtained could in several cases be transformed into new products I′ by functional group interchange reactions. Compounds with aminoalkyl N-substituents were advantageously prepared by an N-acylation/reduction procedure using protected amino acids as coupling partners for the methoxylated amines III. Phenol ether cleavage was performed under acidic or nucleophilic conditions depending on the nature of the functional group X.

Enantiomers were obtained analogously to the racemates from the enantiomers of III and IV, respectively, which were prepared from the described enantiomers of 2-(benzylamino)-5-methoxytetralin.[12] The absolute configurations of the latter can be deduced from the literature.[12,13] Since configuration-preserving transformations were used, the absolute configuration of the products were determined.

Results and Discussion

Table I summarizes the dopaminergic activity of the 5-hydroxy-2-aminotetralin derivatives. 5-OH-DPAT (**1**)[4] was used as standard to study the influence of the functional group X. The three ergolines CM 29-712 (**24**),[14] CQ 32-084 (**25**),[15] and pergolide (**26**)[16] were used as reference compounds for a comparison between aminotetralin and ergoline skeletons.

5-OH-DPAT (**1**) showed a high activity in the Ungerstedt model as could be expected from its ability to induce stereotyped behavior[4] and from the results of the DA receptor binding,[2] respectively. Among the aminotetralins

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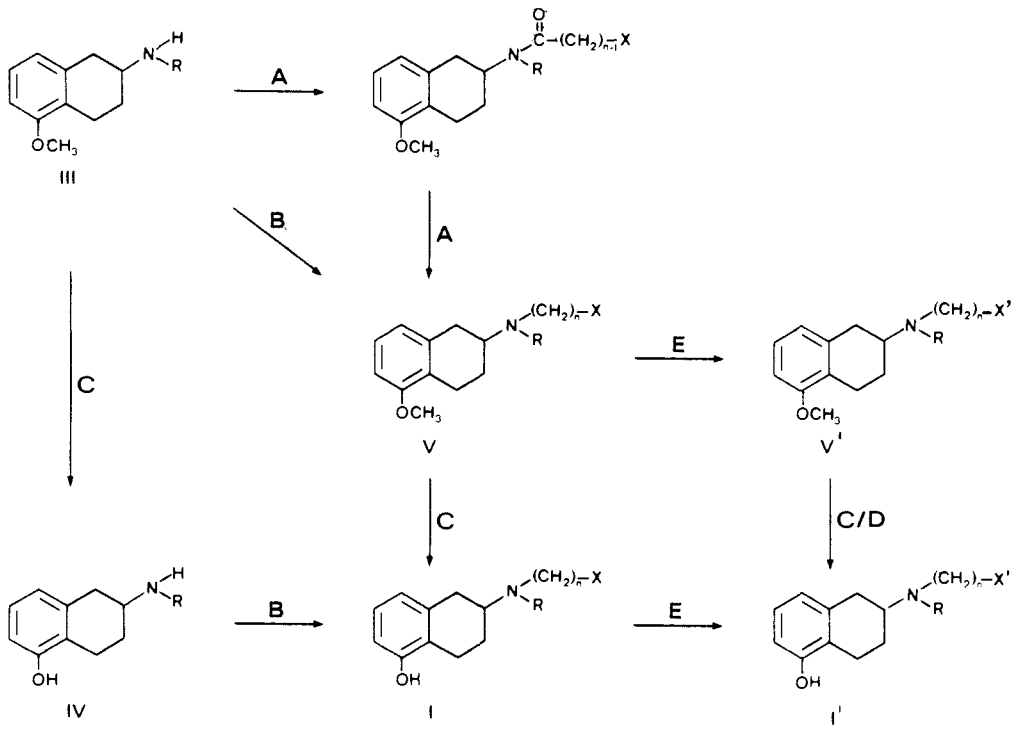
Scheme I[a]



[a] Method A: N-acetylation/reduction. Method B: N-alkylation. Method C: acidic phenol ether cleavage. Method D: nucleophilic phenol ether cleavage. Method E: functional group interchange.

with functionalized *N*-alkyl substituents, many demonstrated quite prominent in vitro and in vivo effects, depending on the nature of the functional group X and the length of the connecting polymethylene chain. In the case of the nitrile derivatives **2**, **3**, and **6**, a three- or a four-atom link gave optimal results. The phenylalkyl derivatives **7** and **8** did not differ largely, whereas among the sulfamides **19** and **20**, highest activities were found with an ethylene link. According to these results the optimal length of the connecting chain seem to depend on the incorporated functional groups X that may bind to different parts of the accessory binding site. Reduction of the size of the unsubstituted *N*-alkyl rest from *n*-propyl to ethyl and methyl in **4** and **5**, respectively, resulted in a progressive decrease in in vitro activities and, propably due to lipophilicity values below the threshold for a transport to the CNS, in compounds inactive in vivo.

The various incorporated functional groups X caused a considerable modulation of activities. Aminotetralins containing *N*-alkyl substituents with terminal π-systems, e.g., **3**, **7**, **9**, and **10**, showed, in general, excellent effects. Also terminal halogen atoms or built-in heteroatoms lead in the case of the chloropropyl and (methylthio)propyl derivatives **11** and **12** to activities similar to that of 5-OH-DPAT. The corresponding methoxypropyl and hydroxypropyl derivatives **14** and **15** were considerably weaker, however, and introduction of a basic aminopropyl substituent yielded even an inactive compound (**16**). Transformation of the primary amino group in **16** into the corresponding *N*-acetamide **17**, diethylurea **21**, or dimethylsulfamides **20** reestablished slightly the in vitro, and in **17** and **20** also the in vivo activities, phenomena that might partly be explained by different distributions. The corresponding carbamate **22** demonstrated again high potency. Among the two enantiomers of **3**, only the (-)-(2*S*) form showed in vivo activities as could be expected from a similar enantiospecificity of 5-OH-DPAT.[2,3,12,13]

These results can be interpreted with respect to the suggested accessory binding site for the larger N-substituent of the 5-hydroxy-2-aminotetralins. The finding that replacement of one *N*-alkyl group of 5-OH-DPAT by various functionalized *N*-alkyl substituents has resulted in similar but not improved activities could mean that interactions with π-systems or electron lone pairs of heteroatoms or hydrogen bonding with carbonyl or amide functions play no important role. This site, on the other hand, appears to accommodate large, bulky groups (e.g., diethylsulfamides) and very different functionalities without loss of affinity. Similar characteristics are known to exist for the binding site(s) of the 8-substituent of dopaminergic ergolines.[15,17] The 8-substituent Y of the highly active ergolines **24**, **25**, and **26**, when linked to the nitrogen of 2-(*n*-propylamino)-5-hydroxytetralin with an ethylene bridge, yield the equally potent compounds **3**, **19**, and **12**. Together, this seems to support our assumption that the larger *N*-alkyl substituent of the 5-hydroxy-2-aminotetralins and DA respectively bind to the same site as the 8-substituent of the dopaminergic ergolines. It can be expected that, in dopaminomimetic compounds such as the *trans*-7-hydroxyoctahydrobenzo[*f*]quinolines in which the *N*-alkyl substituent points toward this site,[10] similar functionalization should also preserve high dopaminergic effects. Finally, the results of the two (-)-(2*S*) enantiomers of **3** and **12** demonstrate that, with relatively simple aminotetralins containing only one asymmetric center, one can reach the activities of complex ergoline molecules such as **24–26**, i.e., the higher rigidity of the ergoline skeleton leads neither to increased affinity nor efficacy.

In summary, it has been found that the larger *N*-alkyl substituent of the dopaminergic 5-hydroxy-2-aminotetralins can be substituted by a variety of functional groups which most probably bind to the same accessory binding site(s) as the corresponding 8-substituent of the

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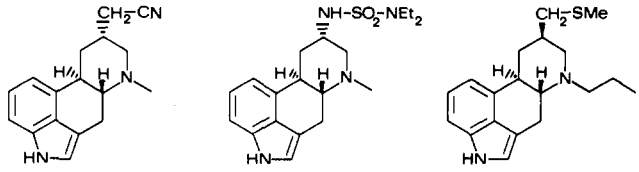

24 25 26

ergolines. Several of these derivatives show high in vitro and in vivo dopaminergic activities in the range of the corresponding ergolines and offer promise as antiparkinson agents. The (−)-(2*S*) enantiomers of **3** and **12** were therefore selected for extended pharmacological and toxicological evaluation.

Experimental Section

Chemistry. Melting points were determined on a Büchi SMP-20 instrument and are not corrected. ^{1}H NMR spectra were measured on a Bruker Spectrospin 360 MHz (WH-360) instrument or 90-MHz (HX-90) spectrometer using Me_4Si as an internal standard. IR and mass spectra were also taken of the new compounds and were consistent with the proposed structures. Elemental analyses were within 0.4% of theoretical values, except where noted. All reactions were followed by TLC carried out on Merck F254 silica gel plates. Solutions were dried over Na_2SO_4 and concentrated with a Büchi rotary evaporator at low pressure (water aspirator). Yields of crude oily products are only given if pure according to TLC and NMR. Each preparative method (Scheme I) is illustrated by a representative example; starting materials, method of synthesis, and physical properties of all new phenolic compounds are given in Table II.

General Methods (A–D). Method A. 2-[*N*-(2-Aminoethyl)-*N*-*n*-propylamino]-5-methoxytetralin (V, R = *n*-propyl, X = NH_2, *n* = 2). *N*-Hydroxysuccinimide (5.1 g, 44.3 mmol) was added to a solution of *N*-Cbz-glycine (9.3 g, 44.3 mmol) in 150 mL of CH_3CN. The stirred mixture was cooled to 0 °C, dicyclohexylcarbodiimide (9.15 g, 44.3 mmol) was added, and stirring was continued for 2 h at room temperature. The formed dicyclohexylurea was removed by filtration, and 2-(*n*-propylamino)-5-methoxytetralin[8] (III, R = *n*-propyl) (9.7 g, 44.3 mmol) in 50 mL of CH_3CN was added to the clear solution. After standing for 15 h at room temperature, the reaction mixture was concentrated in vacuo. Chromatography of the residue on silica gel using CH_2Cl_2/MeOH (9:1, CH_2Cl_2/10% saturated with NH_3) as eluant gave 15.0 g (82%) of the Cbz-glycinamide derivative as an oil.

It was subjected to Cbz group cleavage by hydrogenation in 150 mL of MeOH in the presence of 2 g of 10% Pd/C. The resulting glycinamide (9.5 g, 34.4 mmol) obtained as an oil after filtration and evaporation of the solvent was used without further purification in the following reduction reaction: after dissolution in 150 mL of THF, 1 M borane–THF complex (140 mL) was added and the resulting reaction mixture stirred during 20 h at 80 °C. After treatment with EtOH and evaporation, the residue was taken up in 2 N EtOH–HCl, refluxed during 2 h, evaporated, and distributed between CH_2Cl_2 and 1 N $NaHCO_3$. Chromatography of the CH_2Cl_2 layer on silica gel using CH_2Cl_2/MeOH (9:1, CH_2Cl_2 10% saturated with NH_3) yielded 6.8 g (75%) of the title compound. Dihydrochloride (Et_2O): mp 110–112 °C. Anal. ($C_{16}H_{26}N_2O\cdot 2HCl$) C, H; N: calcd, 8.4; found, 7.9.

2-[*N*-(3-Aminopropyl)-*N*-*n*-propylamino]-5-methoxytetralin (V, R = *n*-propyl, X = NH_2, *n* = 3) was obtained in an analogous manner. Naphthalene-1,5-disulfonate (MeOH/Et_2O) mp 280–284 °C. Anal. ($C_{17}H_{28}N_2O\cdot C_{10}H_8O_6S_2$) C, H, N.

Method B. 2-[*N*-(3-Cyanopropyl)-*N*-*n*-propylamino]-5-hydroxytetralin (3). A solution of IV (R = *n*-propyl) (3.6 g, 18 mmol), 4-bromobutyronitrile (2.6 g, 18 mmol), and *N*,*N*-diisopropylethylamine (2,3 g, 18 mmol) in 50 mL of DMF was stirred at 50 °C for 60 h. The solvent was evaporated, and the residue was taken up in water, adjusted with 2 N NaOH to pH 9, and extracted with CH_2Cl_2. The organic layer was purified by chromatography on silica gel with CH_2Cl_2/MeOH (9:1, CH_2Cl_2 10% saturated with NH_3) as eluant. The product (3.3 g, 64 %)) was obtained as a colorless oil. Hydrochloride (EtOH/Et_2O) mp 194–197 °C.

Method C. 2-[*N*-[2-[(*N*,*N*-Diethylsulfamoyl)amino]ethyl]-*N*-*n*-propylamino]-5-hydroxytetralin (19). To a stirred solution of 2-[*N*-[2-(*N*,*N*-Diethylsulfamoyl)amino]ethyl]-*N*-*n*-propylamino]-5-methoxytetralin (V, R = *n*-propyl, X = $(Et_2)NSO_2NH$, *n* = 2) (2.1 g, 5.3 mmol) in 50 mL of CH_2Cl_2 was added dropwise BBr3 (1.8 mL, 18.6 mmol) at 0 °C. The reaction mixture was allowed to reach room temperature, stirred for 2 h, poured into 2 N Na_2CO_3, and extracted with CH_2Cl_2. After drying and evaporation, the organic layer yielded 2.0 g (100%) of the product as an oil. Hydrochloride (EtOH/Et_2O) mp 220–222 °C.

Method D. 2-[*N*-[3-(Methylthio)propyl]-*N*-*n*-propylamino]-5-hydroxytetralin (12). A suspension of NaH (1.25 g, 52 mmol) in 50 mL of DMF was treated with EtSH (4.2 mL, 57 mmol) and stirred at room temperature for 15 min. Then, a solution of 2-[*N*-[3-(methylthio)propyl]-*N*-*n*-propylamino]-5-methoxytetralin (V, R = *n*-propyl, X = CH_3S, *n* = 3) (5.7 g, 18.5 mmol) in 40 mL of DMF was added and the mixture stirred for 20 h at 120 °C. After removal of the solvent, the residue was dissolved in 2 N HCl and washed with Et_2O. The aqueous phase was adjusted to pH 11 and reextracted with CH_2Cl_2. Chromatography of the content of the organic layer on silica gel with CH_2Cl_2/EtOH/NH_4OH (980:18:2) gave 3.8 g (70%) of the title compound. Hydrogen fumarate (EtOH) mp 70 °C dec.

Special Methods (E). 2-[*N*-(3-Azidopropyl)-*N*-propylamino]-5-hydroxytetralin (10). A solution of methanesulfonyl chloride (3.7 mL, 48 mmol) in 10 mL of $CHCl_3$ was slowly added at −5 °C to a solution of **15** (5.0 g, 19 mmol) and Et_3N (6.9 mL, 49 mmol) in 10 mL of $CHCl_3$. After 1 h at 0 °C the reaction mixture was quenched with 30 mL of water and the CH_2Cl_2 layer was separated, washed with water, and concentrated. The crude dimesylate, obtained as an oil, was dissolved in 50 mL of DMF and a solution of NaN_3 (13.0 g, 200 mmol) in 30 mL of water was added. The mixture was stirred at 100 °C under Ar for 15 h and finally concentrated at 40 °C in vacuo. The residue that contained the title compound in the form of its 5-mesylate was dissolved in 30 mL of *i*-PrOH and hydrolyzed by stirring with 20 mL of 30% NaOH at 90 °C for 6 h. The pH of the reaction mixture was then adjusted with HCl to 9, and the mixture was extracted with CH_2Cl_2. The content of the organic layer was chromatographed on silica gel with CH_2Cl_2/EtOH/NH_4OH (990:10:1) as eluant and gave 2.9 g (52%) of pure product. Hydrochloride (*i*-PrOH) mp 126–128 °C.

2-[*N*-[3-(Methylthio)propyl]-*N*-*n*-propylamino]-5-methoxytetralin (V, R = *n*-propyl, X = CH_3S, *n* = 3). N-Alkylation of III (R = *n*-propyl) by method B using 3-iodopropanol as reagent gave **2-[*N*-(3-hydroxypropyl)-*N*-*n*-propylamino]-5-methoxytetralin** in 86% yield [naphthalene-1,5-disulfonate (EtOH) mp 99–101 °C; anal. ($C_{17}H_{27}NO_2$) H, N, O; C: calcd, 73.6; found, 74.2]. This compound (6.2 g, 22 mmol) was dissolved in 50 mL of $CHCl_3$, and $SOCl_2$ (3.7 mL, 50 mmol) was added dropwise. The mixture was refluxed for 1 h and then evaporated. The residue was distributed between water and CH_2Cl_2, and the organic layer was washed with 2 N NaOH and water, dried, and evaporated. Crude **2-[*N*-(3-chloropropyl)-*N*-*n*-propylamino]-5-methoxytetralin** (V, R = *n*-propyl, X = Cl, *n* = 3), thus obtained, was converted in ethanolic solution to the naphthalene-1,5-disulfonate: 8.5 g (87%), mp 193–195 °C; anal. ($C_{17}H_{26}ClNO$) C, H, Cl, N, O.

The title compound was obtained from the 3-chloropropyl derivative in the following way: Na (0.67 g, 29 mequiv) was dissolved in 15 mL of EtOH, a solution of MeSH (1.56 mL, 28 mmol) in 20 mL of EtOH was added, and the mixture was stirred at 45 °C for 10 min. Then, a solution of V (R = *n*-propyl, X = Cl, *n* = 3) (5.6 g, 19 mmol) in 35 mL of EtOH was added and the mixture stirred at 50 °C for 1 h. After evaporation, the residue was distributed between Et_2O and water, and the organic layer was washed with saturated aqueous NaCl, dried, and evaporated. The oily residue (5.8 g, 100%) was directly employed in the ether cleavage reaction (method D).

2-[*N*-[3-(Methylsulfonyl)propyl]-*N*-*n*-propylamino]-5-methoxytetralin (V, R = *n*-propyl, X = CH_3SO_2, *n* = 3). Compound V (R = *n*-propyl, X = CH_3S, *n* = 3) (9.2 g, 30 mmol) in 90 mL of AcOH was stirred with 35% H_2O_2 (7.5 mL, 87 mmol) at 60 °C for 1 h. After cooling, the reaction mixture was poured on 30% NaOH/ice, extracted with CH_2Cl_2, and washed with water. The organic layer was dried and evaporated and the resulting oil chromatographed on silica gel with toluene/EtOAc (3:1) as eluant

Table II. Physical Properties

no.	R_1	R_2	starting material/ prepn method[a]	mp, °C	formula[c]	anal.
2	$(CH_2)_2CN$	*n*-Pr	IV/B	203–204	$C_{16}H_{22}N_2O$·HCl	C, H, Cl, N, O
3	$(CH_2)_3CN$	*n*-Pr	IV/B	194–197	$C_{17}H_{24}N_2O$·HCl	C, H, Cl, N, O
4	$(CH_2)_3CN$	Et	IV/B	237–239	$C_{16}H_{22}N_2O$·HCl	C[e], H, Cl, N, O
5	$(CH_2)_3CN$	Me	IV/B	230–232	$C_{15}H_{20}N_2O$·$^1/_2$nd	C, H, N, O, S
6	$(CH_2)_4CN$	*n*-Pr	IV/B	156–158	$C_{18}H_{26}N_2O$·HCl	C[f], H, Cl, N, O
7[b]	$(CH_2)_2Ph$	*n*-Pr	IV/B	178–181	$C_{21}H_{27}NO$·HCl	C, H, Cl, N, O
8	$(CH_2)_3Ph$	*n*-Pr	IV/B	161–164	$C_{22}H_{29}NO$·HCl	C, H, Cl, N, O
9	$(CH_2)_3CH{=}CH_2$	*n*-Pr	IV/B	148–151	$C_{18}H_{27}NO$·HCl	C, H, Cl, N
10	$(CH_2)_3N_3$	*n*-Pr	15/E	126–128	$C_{16}H_{24}N_4O$·HCl	C, H, Cl, N, O
11	$(CH_2)_3Cl$	*n*-Pr	15/E	218–220	$C_{16}H_{24}ClNO$·$^1/_2$nd	C, H, Cl, N, O, S
12	$(CH_2)_3SMe$	*n*-Pr	III/B, E, D	70 dec	$C_{17}H_{27}NOS$·fu	C, H, N, S
13	$(CH_2)_3SO_2Me$	*n*-Pr	III/B, E, D	196–200	$C_{17}H_{27}NO_3S$·HCl	C, H, Cl, N, S
14	$(CH_2)_3OMe$	*n*-Pr	IV/B	127–128	$C_{17}H_{27}NO_2$	C, H, N
15	$(CH_2)_3OH$	*n*-Pr	IV/B	129–130	$C_{16}H_{25}NO_2$	C, H, N, O
16	$(CH_2)_3NH_2$	*n*-Pr	III/A, C	81–83	$C_{16}H_{26}N_2O$	C, H, N, O
17	$(CH_2)_3NHAc$	*n*-Pr	16/E	117–118	$C_{18}H_{28}N_2O_2$	C, H, N, O
18	$(CH_2)_3CONHMe$	*n*-Pr	23/E	226–229	$C_{18}H_{28}N_2O_2$·$^1/_2$nd	C, H, N, O, S
19	$(CH_2)_2NHSO_2NEt_2$	*n*-Pr	III/A, E, C	220–222	$C_{19}H_{33}N_3O_3S$·HCl	C, H, N, O, S
20	$(CH_2)_3NHSO_2NMe_2$	*n*-Pr	16/E	161–163	$C_{18}H_{31}N_3O_3S$·HCl	C, H, Cl, N, O, S
21	$(CH_2)_3NHCONEt_2$	*n*-Pr	16/E	150 dec	$C_{21}H_{35}N_3O_2$·pm	C[g], H, N, O
22	$(CH_2)_3NHCOOEt$	*n*-Pr	16/E	123 dec	$C_{19}H_{30}N_2O_3$·HCl	C, H, Cl, N
23	$(CH_2)_3COOMe$	*n*-Pr	3/E	159–161	$C_{18}H_{27}NO_3$·HCl	C, H, Cl, N, O

[a] Compare Scheme I. [b] Reference 8. [c] nd = naphthalene-1,5-disulfonic acid; fu = fumaric acid; pm = pamoic acid = 2,2′-dihydroxy-1,1′-dinaphthylmethane-3,3′-dicarboxylic acid. [d] Decomposition. [e] C: calcd, 65.2; found, 64.7. [f] C: calcd, 67.0; found, 66.5. [g] C: calcd, 70.5; found, 70.0.

to obtain 3.3 g (32%) of the title compound as a resin. Anal. ($C_{18}H_{29}NO_3S$) C, H, N, S.

2-[*N*-[3-[(*N*,*N*-Dimethylsulfamoyl)amino]propyl]-*N*-propylamino]-5-hydroxytetralin (20). Compound **16** (1.3 g, 5 mmol) and Et_3N (0.77 mL, 5.5 mmol) in 20 mL of THF was treated dropwise with dimethylsulfamoyl chloride (0.6 mL, 5.5 mmol) at −10 °C. The reaction mixture was allowed to reach room temperature and stirred for 15 h. Then a new portion of dimethylsulfamoyl chloride (0.6 mL) and Et_3N (0.77 mL) was added, and stirring was continued for 24 h. After evaporation the residue was distributed between CH_2Cl_2 and 2 N tartaric acid, and the aqueous phase was adjusted with NaOH to pH 9 and reextracted with CH_2Cl_2. The organic layer was dried and evaporated, and the crude title compound was converted to its hydrochloride in EtOAc/*i*-PrOH/Et_2O: 1.55 g (77%), mp 161–163 °C. In an analogous manner compounds **17**, **19**, **21**, and **22** were synthesized.

2-[*N*-[3-(Methylcarbamoyl)propyl]-*N*-*n*-propylamino]-5-hydroxytetralin (18). Compound **23**·HCl (195 g, 4.4 mmol) was treated in an autoclave with excess $MeNH_2$ at 70 °C for 48 h. After evaporation, the residue was distributed between CH_2Cl_2 and 2 N Na_2CO_3, and the organic phase was dried, concentrated, and converted in EtOH to its naphthalene-1,5-disulfonate: 1.45 g 73%), mp 226–229 °C.

2-[*N*-[3-(Methoxycarbonyl)propyl]-*N*-*n*-propylamino]-5-hydroxytetralin (23). A solution of **3**·HCl (2.2 g, 7.1 mmol) in 50 mL of MeOH was saturated with HCl at 20 °C. The resulting mixture was stirred at 70 °C for 3 h. Water (0.15 mL, 8.3 mmol) was added and stirring continued for another hour. After evaporation, the residue was distributed between CH_2Cl_2 and NaOH (pH 10), the organic layer dried and concentrated, and the crude product converted in *i*-PrOH to its hydrochloride: 1.25 g (52%), mp 159–161 °C.

Enantiomers. (−)-(2*S*)-2-(*n*-Propylamino)-5-methoxytetralin ((−)-III, R = *n*-propyl). 1-Iodopropane (13.4 g, 74.4 mmol) was added to a stirred mixture of (−)-2-(benzylamino)-5-methoxytetralin[12] (7.0 g, 26.1 mmol) and K_2CO_3 (10.8 g, 78.3 mmol) in 70 mL of 2-butanone. The mixture was stirred during 30 h at 90 °C and then evaporated. The residue was distributed between CH_2Cl_2 and water, and the organic layer was separated, dried, and evaporated to give 8.0 g (99%) of crude (−)-(2*S*)-2-(*N*-benzyl-*N*-*n*-propylamino)-5-methoxytetralin ($[\alpha]^{20}_D$ −50.0° (*c* 1, CH_3OH)), which was pure according to TLC and NMR and was used without further purification. Debenzylation of this compound (6.2 g, 20 mmol) was accomplished by hydrogenation in 100 mL of EtOH containing AcOH (1.2 g, 20 mmol) in the presence of 10% Pd/C (0.62 g) under room temperature condition. The residue obtained after filtration and evaporation of the solvent was distilled at 120–126 °C (0.01 mmHg) and yielded 3.7 g (84%) of the product; $[\alpha]^{20}_D$ −72.7° (*c* 1, CH_3OH). The optical purity of the compound was checked by conversion with (−)-(*R*)-α-methylbenzyl isocyanate into the corresponding urea: in the NMR (C_6D_6, 360 MHz) only one doublet was observed in the CH_3 region, centered at δ 1.38, as compared to the corresponding racemate with two doublets appearing.

The corresponding (+)-(2*S*) enantiomer was synthesized in an analogous manner; $[\alpha]^{20}_D$ +70.5° (*c* 1, CH_3OH).

(−)-(2*S*)-2-(*n*-Propylamino)-5-hydroxytetralin ((−)-IV, R = *n*-propyl). Compound (−)-III (R = *n*-propyl) (11.8 g, 54 mmol) was dissolved in 80 mL of 48% HBr and stirred under Ar at 130 °C for 15 h. After the solution cooled, the hydrobromide crystallized from the aqueous solution. It was filtered, converted to the free base by treatment with 2 N NaOH (final pH = 9), and extracted with CH_2Cl_2. The dried organic layer was evaporated and yielded 6.8 g (61%) of the product as an oil; $[\alpha]^{20}_D$ −75.0° (*c* 1, CH_3OH). The corresponding (+)-(2*R*) enantiomer was synthesized in an analogous manner; $[\alpha]^{20}_D$ +73.7° (*c* 1, CH_3OH).

(−)-(2*S*)-2-[*N*-(3-Cyanopropyl)-*N*-*n*-propylamino]-5-hydroxytetralin ((−)-3). The compound was synthesized starting from (−)-IV (R = *n*-propyl) according to method B. Hydrochloride (*i*-PrOH): mp 189–190 °C; free base, $[\alpha]^{20}_D$ −45.6° (*c* 1, CH_3OH). (+)-**3** was obtained in an analogous manner; hydrochloride (*i*-PrOH): mp 189–190 °C; free base, $[\alpha]^{20}_D$ +45.0° (*c* 1, CH_3OH).

(−)-(2*S*)-2-[*N*-[3-(Methylthio)propyl]-*N*-*n*-propylamino]-5-hydroxytetralin ((−)-12). The compound was prepared with use of (−)-III (R = *n*-propyl) as the starting material according to the method described for the racemate: hydrogen fumarate mp 70 °C dec; free base, $[\alpha]^{20}_D$ −45.2° (*c* 1, CH_3OH). The intermediates showed the following optical rotations (free base): (−)-V (R = *n*-propyl), X = OH (*n* = 3), $[\alpha]^{20}_D$ −52.0° (*c* 1, CH_3OH); (−)-V (R = *n*-propyl), X = Cl (*n* = 3), $[\alpha]^{20}_D$ −46.8° (*c* 1, CH_3OH); (−)-V (R = *n*-propyl), X = SCH_3 (*n* = 3), $[\alpha]^{20}_D$ −48.4° (*c* 1, CH_3OH).

Pharmacology. Circling Behavior. Induction of contralateral turnings were determined in rats with unilateral degeneration of the nigrostriatal pathways. The technique employed was derived from that of Ungerstedt[18] as described in detail in ref 14.

DA Receptor Binding. Binding studies with [^{3}H]DA and [^{3}H]spiroperidol as radioligands in membrane fractions from calf caudate nucleus were performed according to the literature[19,20]

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with minor modifications as described in ref 21.

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Registry No. (±)-1, 69367-50-6; (±)-2, 101403-04-7; (±)-2·HCl, 78598-56-8; (±)-3, 101403-05-8; (−)-(*S*)-3, 88322-07-0; (+)-(*R*)-3, 101540-25-4; (±)-3·HCl, 78598-52-4; (±)-4, 101403-06-9; (±)-4·HCl, 78598-54-6; (±)-5, 78615-30-2; (±)-5·$^1/_2$nd, 78615-31-3; (±)-6, 78598-46-6; (±)-6·HCl, 78598-48-8; (±)-7, 99755-60-9; (±)-7·HCl, 101403-00-3; (±)-8, 101403-07-0; (±)-8·HCl, 101403-01-4; (±)-9, 101403-08-1; (±)-9·HCl, 78598-61-5; (±)-10, 101403-09-2; (±)-10 (5-mesylate), 101403-16-1; (±)-10·HCl, 78598-62-6; (±)-11, 78598-65-9; (±)-11·$^1/_2$nd, 78598-66-0; (±)-12, 78598-47-7; (−)-(*S*)-12, 78598-85-3; (±)-12·fu, 78598-51-3; (±)-13, 101403-10-5; (±)-13·HCl, 78598-63-7; (±)-14, 78598-58-0; (±)-15, 78598-59-1; (±)-15 (dimesylate), 101403-15-0; (±)-16, 101403-02-5; (±)-17, 78598-83-1; (±)-18, 78598-79-5; (±)-18·$^1/_2$nd, 78598-80-8; (±)-19, 101403-11-6; (±)-19·HCl, 78598-53-5; (±)-20, 101403-12-7; (±)-20·HCl, 78598-78-4; (±)-21, 78598-72-8; (±)-21·pm, 101403-03-6; (±)-22, 101403-13-8; (±)-22·HCl, 78598-70-6; (±)-23, 101403-14-9; (±)-23·HCl, 78598-71-7; (±)-III (R = Pr), 78598-91-1; (−)-(*S*)-III (R = $CH_2C_6H_5$), 58349-23-8; (−)-(*S*)-III (R = Pr), 101403-24-1; (+)-(*R*)-III (R = Pr), 101403-25-2; (±)-IV (R = Pr), 78598-89-7; (±)-IV (R = Et), 101403-19-4; (±)-IV (R = Me), 101403-20-7; (−)-(*S*)-IV (R = Pr), 101470-23-9; (+)-(*R*)-IV (R = Pr), 101470-24-0; (±)-V (R = Pr, X = NH_2, *n* = 2), 101403-17-2; (±)-V (R = Pr, X = NH_2, *n* = 3), 101403-18-3; (±)-V (R = Pr, X = $NHSO_2NEt_2$, *n* = 2), 101403-21-8; (±)-V (R = Pr, X = SMe, *n* = 3), 78598-90-0; (±)-V (R = Pr, X = OH, *n* = 3)·$^1/_2$nd, 78598-88-6; (±)-V (R = Pr, X = Cl, *n* = 3), 78598-49-9; (±)-V (R = Pr, X = Cl, *n* = 3)·$^1/_2$nd, 78598-50-2; (±)-V (R = Pr, X = SO_2Me, *n* = 3), 101403-22-9; (−)-(*S*)-V (R = $CH_2C_6H_5$, X = CH_3), 101403-23-0; (−)-(*S*)-V (R = Pr, X = OH, *n* = 3), 101470-25-1; (−)-(*S*)-V (R = Pr, X = Cl, *n* = 3), 101470-26-2; (−)-(*S*)-V (R = Pr, X = SMe, *n* = 3), 101470-27-3; $C_6H_5CH_2OCONHCH_2CO_2H$, 1138-80-3; $C_6H_5CH_2OCONHCH_2CONH_2$, 949-90-6; $H_2NCH_2CH_2NH_2$, 107-15-3; $Br(CH_2)_3CN$, 5332-06-9; $I(CH_2)_3OH$, 627-32-7.

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Conformational Analysis of the Dopamine-Receptor Agonist 5-Hydroxy-2-(dipropylamino)tetralin and Its C(2)-Methyl-Substituted Derivative

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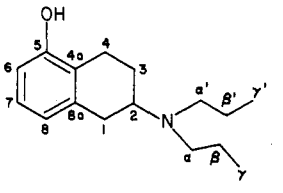
The conformational preferences of the dopamine (DA) receptor agonist 5-hydroxy-2-(di-*n*-propylamino)tetralin (1) and the DA-inactive 5-hydroxy-2-methyl-2-(di-*n*-propylamino)tetralin (2) have been studied by use of molecular mechanics (MMP2) calculations and NMR spectroscopy. A good agreement is demonstrated between the experimentally determined (by NMR) and the calculated (by MMP2) conformational distribution of 1 and 2. In addition, there is a good agreement between bond distances and bond angles in the X-ray structure of the hydrobromide of 1 and those in the corresponding MMP2 conformation. Results obtained demonstrate that the energetically preferred conformations of 1 and 2 are different: Compound 1 preferentially adopts half-chair conformations with a pseudoequatorial nitrogen substituent whereas the low-energy conformations of compound 2 have a pseudoaxial nitrogen substituent. However, the results also indicate that the difference in conformational preferences is too small to account for the dopaminergic inactivity of 2. Therefore it is suggested that the steric bulk of the C(2)-methyl group per se prevents a proper alignment of (2*S*)-2 with DA receptors.

5-Hydroxy-2-(di-*n*-propylamino)tetralin (1)[1] is a well-established dopamine (DA) receptor agonist in vivo[1a,b] and in vitro.[2] Due to its potency and selectivity for DA receptors, compound 1 has served as the lead compound in several structure–activity relationship (SAR) studies.[3] As part of an ongoing investigation of the effects of introduction of methyl substituents in the nonaromatic ring of 1,[4] we synthesized and tested racemic 5-hydroxy-2-methyl-2-(di-*n*-propylamino)tetralin (2),[5] the C(2)-methyl-substituted derivative of 1. Compound 2 exhibits a complex pharmacological profile:[5] (a) It reverses reserpine-induced akinesia, but this effect is not blocked by pretreatment with the DA-receptor antagonist haloperidol. (b) It increases the synthesis rate of 5-hydroxytryptamine but does not affect that of DA. (c) It raises the body temperature in rats. Notably, neither racemic 2 nor the enantiomers of 2[6] appear to act on DA receptors. Thus, the introduction of a C(2)-methyl substituent in 1 completely changes the pharmacological profile.



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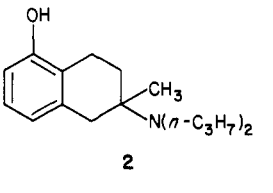

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