14 (100 mg, 0.42 mmol) in MeOH (2 mL) was added $NaBH_4$ (20 mg, 0.52 mmol), and stirring was continued for 30 min at 25 °C. The mixture was diluted with CH_2Cl_2, washed with brine, dried ($MgSO_4$), and evaporated to afford 18 as an oil: IR (CCl_4) 3635, 3480 cm^{-1}; NMR ($CDCl_3$) δ 4.20 (br s, $W_{1/2}$ = 8 Hz, 1 H, C_8 H), 2.80–2.30 (m, 2 H, C_2 H_2), 2.20 (s, 3 H, NCH_3), 2.10–1.00 (m, 19 H), 0.92 (br t, J = 6 Hz, 3 H, CH_2CH_3). Hydrochloride of 18 (77 mg, 67%): mp 239–241 °C (MeOH–Et_2O); IR (KBr) 3330 cm^{-1}; NMR ($CDCl_3$) δ 10.02 (br s, 1 H, OH), 4.26 (br s, $W_{1/2}$ = 8 Hz, 1 H, C_8 H), 3.50–2.75 (m, 2 H, C_2 H_2), 2.60 (d, J = 6 Hz, 3 H, NCH_3), 2.50–1.00 (m, 19 H), 0.92 (br t, J = 6 Hz, 3 H, CH_2CH_3); EIMS, m/e 239 (M^+ – HCl). Anal. ($C_{15}H_{29}NO$·HCl) C, H, N, Cl.

(6*R*,7*S*,8*R*)- and (6*S*,7*R*,8*S*)-7-*n*-Butyl-8-hydroxy-1,1-dimethyl-1-azoniaspiro[5.5]undecane Iodide (19). A mixture of the amino alcohol 18 (120 mg, 0.5 mmol), methyl iodide (1 mL, 16 mmol), and acetone (3 mL) was set aside at 25 °C for 5 h. The precipitate was collected by filtration and recrystallized to give 19 (119 mg, 62%): mp 165–167 °C (MeOH–Et_2O); IR (KBr) 3370, 1480, 1455 cm^{-1}; NMR (CD_3OD) δ 4.10 (br s, $W_{1/2}$ = 8 Hz, 1 H, C_8 H), 3.86–3.70 (m, 1 H), 3.35–3.20 (m, 1 H), 3.20 and 3.05 (each s, each 3 H, 2 NCH_3), 2.40–1.20 (m, 19 H), 0.94 (br t, J = 6 Hz, CH_2CH_3); CIMS (NH_3), m/e 254 (M^+ + 1 – HI). Anal. ($C_{16}H_{32}NOI$) C, N; H: calcd, 8.46; found, 8.04.

(6*R*,7*S*,8*S*)- and (6*S*,7*R*,8*R*)-8-Acetoxy-7-*n*-butyl-1,1-dimethyl-1-azoniaspiro[5.5]undecane Iodide (20). A solution of the amine 11 (140 mg, 0.5 mmol) and MeI (1 mL, 16 mmol) in acetone (2 mL) was stirred at 40 °C for 3 days. Evaporation of the mixture afforded an oil, which was washed with Et_2O. The residue was crystallized from EtOAc to give 20 (90 mg, 43%): mp 153–154 °C (EtOAc); IR (KBr) 1725, 1480, 1450 cm^{-1}; NMR (CD_3OD) δ 5.02 (br s, $W_{1/2}$ = 8 Hz, 1 H, C_8 H), 3.95–3.80 (m, 1 H, C_2 H), 3.40–3.30 (m, 1 H, C_2 H), 3.24 and 3.10 (each s, each 3 H, 2 NCH_3), 2.15 (s, 3 H, Ac), 2.50–1.20 (m, 19 H), 0.94 (br t, J = 6 Hz, 3 H, CH_2CH_3); CIMS (NH_3), m/e 296 (M^+ + 1 – HI). Anal. ($C_{18}H_{34}NO_2I$) C, H, N.

(6*R*,7*S*,8*S*)- and (6*S*,7*R*,8*R*)-7-*n*-Butyl-8-hydroxy-1,1-dimethyl-1-azoniaspiro[5.5]undecane Iodide (21). A mixture of the amino alcohol 5 (100 mg, 0.42 mmol), MeI (1 mL, 16 mmol), and acetone (10 mL) was set aside at 40–50 °C for 11 days. (The reaction can be monitored by TLC and NMR in acetone-d_6.) The mixture was evaporated, and the residue was washed with EtOAc. Recrystallization from MeOH–Et_2O gave 21 (61 mg, 38%): mp 164–165 °C; IR (KBr) 3420, 1485 cm^{-1}; NMR (CD_3OD) δ 3.75 (br s, $W_{1/2}$ = 8 Hz, 1 H, C_8 H) 3.45–2.80 (m, 2 H, C_2H_2), 3.17 and 3.04 (each s, each 3 H, 2 NCH_3), 2.40–1.00 (m, 19 H), 0.95 (br t, J = 6 Hz, 3 H, CH_2CH_3); CIMS (NH_3), m/e 254 (M^+ – HI + 1). Anal. ($C_{16}H_{32}NOI$) C, H, N.

Electrophysiological Techniques. All experiments were performed at room temperature (20–22 °C) on sciatic sartorius muscle preparations of the frog, *Rana pipiens*. The physiological solutions used had the following composition (mM): NaCl, 115.5; KCl, 2.0; $CaCl_2$, 1.8; Na_2HPO_4, 1.3; NaH_2PO_4, 0.7. The solution was bubbled with 100% O_2 and had a pH of 6.9–7.1. For twitch tension studies, the nerve was stimulated with supramaximal pulses having a duration varying from 0.05 to 0.1 ms via a Ag–AgCl salt bridge electrode connected to a wet electrode.[2a] Direct stimulation of the muscle was accomplished by applying supramaximal rectangular pulses of 1.0–2.0 ms duration at a rate of 0.05 Hz through a bipolar platinum electrode placed around the middle portion of the muscle. The muscle tension generated by both direct and indirect stimulation was recorded by attaching the muscle to a Grass FT03 force displacement transducer. The twitches were also displayed on a Grass polygraph.

The stock solution (10–500 mM) were made in 95% ethanol and stored as refrigerated stock solutions. They were diluted with physiological solution immediately before use.

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Supplementary Material Available: Tables containing atomic parameters, bond angles, and observed and calculated structure factors (3 pages). Ordering information is given on any current masthead page.

Monophenolic Octahydrobenzo[*f*]quinolines: Central Dopamine- and Serotonin-Receptor Stimulating Activity

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Eight monophenolic *cis*- and *trans*-4-*n*-propyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[*f*]quinolines have been synthesized and tested for central dopamine- and serotonin-receptor stimulating activity, using biochemical and behavioral tests in rats. The *trans*-7-, -8-, and -9-hydroxy isomers all elicited central pre- and postsynaptic dopaminergic receptor stimulation, while the *trans*-10-hydroxy isomer was devoid of dopaminergic activity but instead showed central serotoninergic activity. In all four isomeric pairs, the trans isomers were consistently much more potent than their corresponding cis analogues. The apparent presynaptic selectivity of the dopaminergic cis isomer *cis*-9-hydroxy-4-*n*-propyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[*f*]quinoline could not be confirmed due to the toxic properties of this compound. Central dopamine receptors (autoreceptors and postsynaptic receptors) can accept dopaminergic compounds with one of possibly two N-substituents being larger than *n*-propyl, if this substituent is properly oriented in relation to the rest of the molecule.

Recently, we described the unique pharmacological profile of 3-(3-hydroxyphenyl)-*N*-*n*-propylpiperidine (1, 3-PPP), indicating selective central dopamine (DA) autoreceptor stimulating activity.[1] In another study, we compared the four isomeric monohydroxylated 2-(di-*n*-propylamino)tetralins 2–5, with regard to their effects upon central monoaminergic transmission.[2] It was demon-

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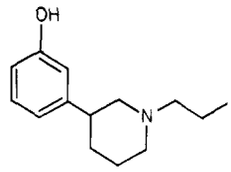

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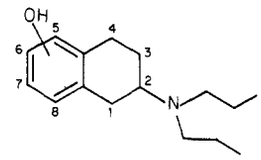
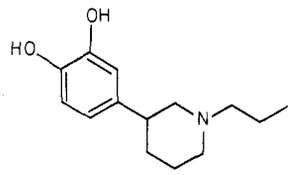


2, 5-OH
3, 6-OH
4, 7-OH
5, 8-OH



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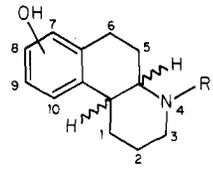
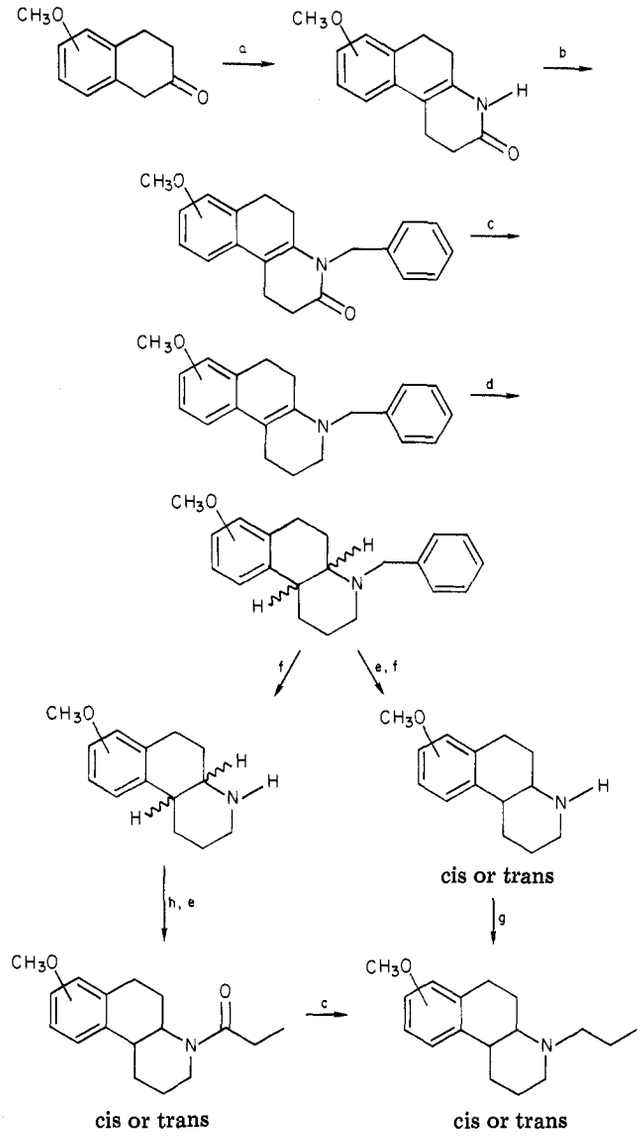


		R	confign
6	7-OH	*n*-Pr	cis
7	7-OH	*n*-Pr	trans
8	9-OH	*n*-Pr	cis
9	9-OH	*n*-Pr	trans
10	7-OH	CH_3	cis
11	7-OH	CH_3	trans
12	8-OH	CH_3	cis
13	8-OH	CH_3	trans
15	8-OH	*n*-Pr	cis
16	8-OH	*n*-Pr	trans
17	10-OH	*n*-Pr	cis
18	10-OH	*n*-Pr	trans
19	7-OH	*n*-Bu	trans

strated that compounds **2–4** possess pre- and postsynaptic DA-receptor stimulating activity with the rank order of potency **2** > **4** > **3**. In contrast, compound **5** was found to be devoid of dopaminergic activity but instead exhibited pronounced sertonin (5-HT) receptor stimulatory properties. When extending our studies on DA congeners, we became interested in combining the structural elements of the flexible compound 3-PPP (1) with the monohydroxylated 2-aminotetralin moiety, resulting in the derivatives **6/7** (cis/trans) and **8/9** of the 1,2,3,4,4a,5,6,10b-octahydrobenzo[*f*]quinoline system. Derivatives of the octahydrobenzo[*f*]quinoline system have been investigated by Cannon and co-workers.[3-5] They found that several of these compounds are potent central and peripheral dopaminergic stimulants. Most of their studies deal with dihydroxylated derivatives, but four isomeric monohydroxylated analogues of the 1,2,3,4,4a,5,6,10b-octahydrobenzo[*f*]quinoline system (**10–13**) have been synthesized and some of their biological effects have also been described.

Scheme I[a]



[a] Reagents: a = pyrrolidine, acrylamide; b = *t*-BuOK, $PhCH_2Cl$; c = $LiAlH_4$; d = $NaBH_3CN$, HOAc; e = chromatography (SiO_2); f = Pd/C, H_2; g = $NaBH_4$, CH_3CH_2COOH; h = Et_3N, CH_3CH_2COCl.

The catechol analogue of 3-PPP (1), 3-(3,4-dihydroxyphenyl)-*N*-*n*-propylpiperidine (**14**), claimed by Nedelec et al. to have potential anti-Parkinsonian utility,[6] shows dopaminergic activity but lacks the presynaptic selectivity exhibited by 3-PPP (1).[7] Similarly, N-alkylated 7,8-dihydroxy-1,2,3,4,4a,5,6,10b-octahydrobenzo[*f*]quinoline derivatives hitherto reported are nonselective, also possessing postsynaptic dopaminergic activity.[4] The four monohydroxylated derivatives **10–13** have not been tested in models that can distinguish between central pre- and postsynaptic dopaminergic stimulation.[3] Based upon the above considerations, we have focused upon monohydroxylated octahydrobenzo[*f*]quinolines in this study.

Due to the interesting pharmacological properties of the 2-aminotetralins described above, we also prepared and tested the four isomeric monohydroxy derivatives **15/16**

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Table I. Physical and Biological Data

compd [a]	yield, [b] %	mp, °C	recrystn solvent [c]	Dopa accumulation: [d] ED_{50}, [e,f] nmol/kg sc limbic	Dopa accumulation striatum	5-HTP accumulation: [d] ED_{50}, [g] nmol/kg sc limbic	5-HTP accumulation striatum	hemispheres (cortex)	motor act., [h] accumulated counts/60 min
1				3600 [i]	3600 [i]	I [j,k]	I [j,k]	I [j,k]	
2				11 [j]	9 [j]	I [j,k]	I [j,k]	I [j,k]	688 ± 63
3				180 [j]	170 [j]	I [j,k]	I [j,k]	I [j,k]	
4				27 [j]	30 [j]	I [j,k]	I [j,k]	I [j,k]	
5				I [j,k]	I [j,k]	48 [j]	45 [j]	68 [j]	
6	72	271-273	D	I [l]	I [l]	I [m]	I [m]	I [m]	17 ± 6
7	89	298-301	B	130	130	I [k]	I [k]	I [k]	327 ± 40
8	67	252-253	C	2000	3400	I [n]	I [n]	I [n]	*o*
9	73	185-187	B	8	12	I [k]	I [k]	I [k]	365 ± 32
15	65	266-267.5	B	I [p]	I [p]	I [p]	I [p]	I [p]	*o*
16	63	265-274	A	540	530	I [q]	I [q]	I [q]	179 ± 34
17	43	255-257	A	I [q]	I [q]	3400	3400	4500	NT [r]
18	40	274-276	B	*s*	*s*	230	180	160	NT
19	69	224-226	A	80	70	I [k]	I [k]	I [k]	418 ± 55
apomorphine				190 [t]	220 [t]	I [k]	I [k]	I [k]	624 ± 51 [i]

[a] Formula for compounds 6-9 and 15-18, $C_{16}H_{23}NO \cdot HBr$; for compound 19, $C_{17}H_{25}NO \cdot HBr$. [b] Yield in the demethylation step. [c] Recrystallization solvents: A, EtOH-ether; B, MeOH-ether; C, EtOH; D, MeOH. [d] For experimental details, see ref 17. [e] Dose giving a half-maximal decrease of Dopa formation in the rat brain part, estimated from a dose-response curve comprising five to seven dose levels (n = 3-5) of the compound tested. The maximal reduction of the Dopa level was empirically found to be 65% from the control level (635 ng of Dopa/g of tissue) for the limbic and 80% from the control level (1670 ng of Dopa/g of tissue) for the striatal brain portions. [f] No significant effect on Dopa accumulation was obtained in the hemispheral portions (cortex). [g] Dose giving a half-maximal decrease of 5-HTP formation in the rat brain part, estimated from a dose-response curve comprising five to seven dose levels (n = 3-5) of the compound tested. The maximal reduction of the 5-HTP level was empirically found to be 50% from control levels (120 ng of 5-HTP/g of limbic tissue, 75 ng of 5-HTP/g of striatal tissue, and 75 ng of 5-HTP/g of hemispheral tissue). [h] For experimental details, see Experimental Section. The trans derivatives were tested at 1 mg/kg (3100 nmol/kg) and the cis derivatives at 10 mg/kg (31000 nmol/kg). Shown are the means ± SEM (N = 4). The data for apomorphine come from ref 7 and the dose used was 0.61 mg/kg (2000 nmol/kg). [i] From ref 7. [j] From ref 2. [k] Inactive; no significant effect at doses approximately 40 times the ED_{50} for Dopa or 5-HTP accumulation, respectively. [l] Maximal reduction of the Dopa level could not be obtained. For the limbic brain portions, 40% reduction (at 12500 nmol/kg) from the control level was reached; for the striatal brain portions, 60% reduction (at 12500 nmol/kg) from the control level was reached. [m] Inactive; no significant reduction at 45000 nmol/kg (the highest dose tested). [n] Inactive at 11 300 nmol/kg; at 45000 nmol/kg, the animals died within 15 min. [o] All four animals died within 15 min after administration. [p] Inactive at 2800 nmol/kg; at 22500 nmol/kg, the animals died within 15 min after administration. [q] Inactive; no significant effect at doses approximately 10 times the ED_{50} for Dopa or 5-HTP accumulation, respectively. [r] Not tested. [s] Inactive at 500 nmol/kg (the highest dose tested due to shortage of substance). [t] From ref 10.

and 17/18. In most previous studies on the N-substitution pattern of dopaminergic compounds, it has been found that an *n*-propyl group is optimal for high dopaminergic activity.[8-10] However, analogues of 3-PPP (1) with N-substituents larger than *n*-propyl, i.a. *n*-butyl, were found to be more active than 3-PPP (1) itself.[7] Thus, *trans*-4-*n*-butyl-7-hydroxy-1,2,3,4,4a,5,6,10b-octahydrobenzo[*f*]-quinoline (19) was also included in this study. The compounds were tested in rats using biochemical and behavioral methods previously described.[10] The compounds synthesized and the biological data obtained are presented in Table I.

Chemistry. The compounds were prepared according to the method described by Cannon et al.[3] with only slight modifications (Scheme I). Due to difficulties in obtaining the high yields reported by these authors in the N-alkylation of the enamide, we used the base potassium *tert*-butoxide in refluxing *tert*-butyl alcohol instead of sodium hydride in dimethoxyethane.

The whole reaction sequence was followed using gas chromatography (the cis isomers had consistently shorter retention times than their trans analogues). The reduction of the 7-, 8-, and 9-methoxy enamines yielded approximately equal amounts of cis and trans isomers. In the case of the 10-methoxy isomer, however, the ratio between cis and trans isomers was 86:14. The reason for this discrepancy may be due to the steric interaction of the 10-methoxy group with the heterocyclic ring, forcing this ring into a conformation which favors formation of the cis isomer. Separation of the cis and trans isomers was accomplished by a combination of chromatography and crystallization of the 7-, 9-, and 10-methoxy isomers, whereas in the case of the 8-methoxy isomers these were separated solely by chromatography of the *N*-propionyl isomers, which were subsequently reduced to the corresponding *N*-*n*-propyl derivatives with $LiAlH_4$ in dry ether (Scheme I). The phenols presented in Table I were all prepared from the corresponding methoxy compounds via demethylation in 48% aqueous HBr.

The geometry of ring fusion was established by NMR spectroscopy of the *N*-benzylamines. The *N*-benzyl protons ($N\text{-}CH_2Ph$) of all trans isomers gave rise to AB quartets, whereas these protons in the corresponding cis isomers show up as singlets.[4] GC/MS was performed for all the eight hydroxy isomers. It was found that all compounds had M^+ at *m/e* 245 and the base peak at *m/e* 216.

Pharmacology. The in vivo biochemical test method utilizes the well-established phenomenon of receptor-mediated feedback inhibition of the presynaptic neuron.[11] Thus, the synthesis rate of the catecholamines DA and

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noradrenaline (NA) is inhibited by agonists activating dopaminergic and adrenergic receptors, respectively. Similarly the synthesis of 5-HT is inhibited by 5-HT-receptor agonists.[12,13] The Dopa accumulation, following decarboxylase inhibition by means of 3-hydroxybenzylhydrazine (NSD 1015), was thus used as an indicator of the DA synthesis rate in the DA-predominated parts (i.e., limbic system, corpus striatum) and the NA synthesis rate in the NA-dominated remaining hemispheral portions (mainly cortex). The 5-HTP accumulation was taken as an indicator of the 5-HT synthesis rate in the three brain parts. Behavioral and motor activity recordings were carried out as previously described[10] using motility meters. The data are presented in Table I.

Results and Discussion

The 7-, 8-, and 9-hydroxy isomers **7**, **16**, and **8**/**9** all exhibited central dopaminergic activity, while the 10-hydroxy isomers **17**/**18** showed central serotoninergic activity. In all four isomeric pairs, the trans isomers were consistently much more potent with respect to their actions on DA receptors (**6**/**7**, **15**/**16**, and **8**/**9**) and 5-HT receptors (**17**/**18**) than their corresponding cis analogues. This is analogous to the findings of Cannon et al. on dihydroxylated 1,2,3,4,4a,5,6,10b-octahydrobenzo[*f*]quinolines.[3-5] The reason for this difference may be that the receptors involved, due to sterical hindrance, prefer flat molecules before bulkier ones.

The doses of the compounds required to produce a half-maximal reduction (ED_{50}) of the DA synthesis rate (Dopa formation) in the different brain areas of the reserpinized rat are presented in Table I. At these doses no significant behavioral stimulation could be demonstrated (gross behavioral observations), thus paralleling our findings in the 2-aminotetralin[10] and 2-aminoindan[14] series of dopaminergic agonists. Consequently, in line with previous suggestions,[10] the ED_{50} values for Dopa formation are thought to reflect predominantly presynaptic DA-receptor (autoreceptor) activation and may thus be taken as an index of presynaptic DA-receptor potency in the reserpinized rat for the compounds studied.

The dopaminergic trans compounds (**7**, **16**, and **9**) were all able to stimulate central presynaptic DA receptors, the most potent derivative in this respect being *trans*-9-hydroxy-4-*n*-propyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[*f*]quinoline (**9**). When given in higher doses, these compounds elicited typical and marked postsynaptic DA-receptor stimulatory effects (cf. the motor activity data in Table I), i.e., stereotypies and increased locomotion. Since these effects occurred despite prior DA depletion and biosynthesis inhibition by means of reserpine and α-methyl-*p*-tyrosine, respectively, they are considered to result from direct receptor activation.[15] Thus, although being potent stimulants of central DA receptors, the monohydroxylated *trans*-octahydrobenzo[*f*]quinolines apparently lack the presynaptic selectivity exhibited by 3-PPP (**1**)[1] and other derivatives in the 3-(3-hydroxyphenyl)piperidine series.[7] However, the 9-OH isomer (**9**) may have more preference for the presynaptic DA receptor than the aminotetralins and aminoindans earlier investigated by us[10,14] (cf. below). These compounds possess similar relative potencies in stimulating pre- and postsynaptic DA receptors in the CNS.

The cis isomer **8** retains DA autoreceptor stimulatory capacity, albeit of weaker potency than its corresponding trans analogue (**9**) (no ED_{50} values could be determined for compounds **6** and **15**; see footnotes to Table I). In addition, at a dose of 10 mg/kg (31 000 nmol/kg) sc of the cis isomers **6**, **15**, and **8**, no postsynaptic DA-receptor stimulatory effects could be seen (motor activity experiments; see Table I). Instead, within 15 min after administration, some of the animals (those given compunds **15** and **8**) started exhibiting symptoms of toxicity, manifested as severe convulsions leading to death. Therefore, the apparent autoreceptor selectivity of compound **8** could indicate that the selectivity demonstrated for 3-PPP (**1**) is due to a preferred conformation of this compound, where the two rings are located in a manner similar to that of the cis derivative **8** studied here. However, due to the toxicity of **8**, this conclusion can merely be speculative.

When comparing the *trans*-octahydrobenzo[*f*]quinolines (**7**, **16**, **9**, and **18**) with their corresponding positional isomers in the 2-aminotetralin series (**2**, **3**, **4**, and **5**, respectively; included as reference compounds in Table I), it can be seen that, though exhibiting the same relative pattern of biological activities, in general the *trans*-octahydrobenzo[*f*]quinolines are less potent than their corresponding 2-aminotetralin analogues. The only notable exception from this is *trans*-9-hydroxy-4-*n*-propyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[*f*]quinoline (**9**), which is three times as potent as 7-hydroxy-2-(di-*n*-propylamino)tetralin (**4**) and equipotent to 5-hydroxy-2-(di-*n*-propylamino)tetralin (**2**) in stimulating presynaptic DA receptors. As judged from motor activity data, however, compound **9** may be less efficient in stimulating postsynaptic DA receptors than is compound **2**, possibly reflecting presynaptic preference for compound **9** as mentioned above.

Interestingly, *trans*-4-*n*-butyl-7-hydroxy-1,2,3,4,4a,5,6,10b-octahydrobenzo[*f*]quinoline (**19**) was more active than its 4-*n*-propyl analogue **7** in both the biochemical and the behavioral model. Thus, this result is in analogy with the findings in the 3-hydroxyphenylpiperidine series mentioned above, where some compounds with N-substituents larger than *n*-propyl are more potent than 3-PPP (**1**) itself.[7] On the other hand, while *N*-*n*-propylnorapomorphine and the *N*,*N*-di-*n*-propyl- and the *N*-*n*-propyl-*N*-*n*-butyl derivatives of phenethylamines and 2-aminotetralins are potent DA-receptor stimulating agents, their corresponding *N*-*n*-butyl and *N*,*N*-di-*n*-butyl derivatives consistently suffer marked losses in activity.[8-10,16,17] These observations may be reconciled with the suggestion that the carbon atoms 1–3 present in the "piperidine" ring moiety of the *trans*-1,2,3,4,4a,5,6,10b-octahydrobenzo[*f*]quinoline system constitute a structural element corresponding to that nitrogen substituent in, for example, the 2-aminotetralin series that is assumed to fit into a cavity (or bind to a part of the receptor) which can maximally accommodate an *n*-propyl group.[10]

In contrast to the other monophenolic isomers, the 10-hydroxyoctahydrobenzo[*f*]quinolines **17**/**18** are devoid of

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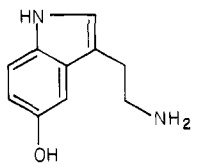
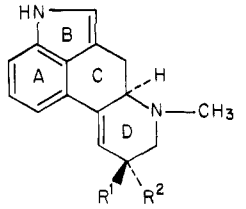
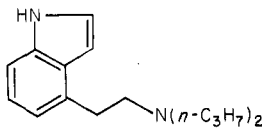


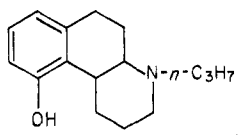
5-HT



LSD, R^1 = H; R^2 = $CON(C_2H_5)_2$
lisuride, R^1 = $NHCON(C_2H_5)_2$; R^2 = H



DPAI



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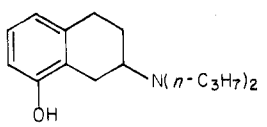

5

dopaminergic activity; instead, they appear to stimulate 5-HT receptors. This is indicated by the marked and selective decrease in brain 5-HTP formation (Table I) and the appearance of a behavioral syndrome considered characteristic for central 5-HT-receptor activation (cf. ref 18). The results are thus in agreement with the findings in the corresponding 2-aminotetralin series showing that 8-hydroxy-2-(di-*n*-propylamino)tetralin (**5**) is a potent and selective direct 5-HT-receptor agonist devoid of DA-receptor stimulatory properties,[2] whereas the 5-hydroxy- (**2**), 6-hydroxy- (**3**), and 7-hydroxy-2-(di-*n*-propylamino)tetralins (**4**), while lacking 5-HT effects, show considerable DA-receptor stimulating activity.[2] Interestingly, the structure of 5-HT can be excellently fitted on both compounds **5** and **18** with the hydroxy groups and the amino-nitrogen atoms overlapping and with the aliphatic side chain of 5-HT matching the 2-, 3-, and 4-carbon atoms of the 2-aminotetralin and the 4a-, 5-, and 6-carbon atoms of the 1,2,3,4,4a,5,6,10b-octahydrobenzo[*f*]quinoline, respectively.

The above matching of 5-HT, **5**, and **18** constructs the ergot skeleton with a hydroxy group in position 12, albeit lacking the 9,10 double bond and the substituent in position 8. The ergots LSD and Lisuride exhibit about the same serotoninergic activity (5-HTP accumulation) as compound **5** (unpublished data from this group), whereas compound **18** is approximately four times less potent. The original suggestion by Nichols in 1976[19] that the pyrroleethylamine moiety of the ergots confers dopaminergic properties to drugs of this class was experimentally substantiated by Bach et al. in 1980.[20,21] Thus, taken together, the above-mentioned data indicate that while the A ring of the ergot structure is of minor importance for the dopaminergic activity, this ring may be more important for the serotoninergic activity. It has been reported[22] that ergot derivatives can be in vivo hydroxylated in position 12, a finding that may be worth noting in this context. However, on the basis of results obtained with 4-[2-(di-*n*-propylamino)ethyl]indole (DPAI), containing the A and B rings of the ergots, Cannon et al.[23] have recently challenged the view as to which is the dopaminergic pharmacophore of drugs belonging to the ergot class. No effects of DPAI on 5-HT systems have so far been reported.

In conclusion, the position of the hydroxy group of the monohydroxylated 1,2,3,4,4a,5,6,10b-octahydrobenzo[*f*]quinolines (as well as of the monohydroxylated 2-aminotetralins) is essential for the type of biological activity (dopaminergic or serotoninergic) exhibited. None of the new dopaminergic *trans*-octahydrobenzo[*f*]quinolines presented here (**7**, **16**, and **9**) were nearly as selective as 3-PPP (**1**) in stimulating central DA autoreceptors, although compound **9** seemed to have some preference for DA autoreceptors. Central DA receptors (autoreceptors and postsynaptic receptors) can accept dopaminergic compounds with one of possibly two N-substituents being larger than *n*-propyl, if this substituent is properly oriented in relation to the rest of the molecule. However, one must consider that all compounds presented here are racemic mixtures and that resolution into the pure enantiomers must be undertaken in order to gain a more detailed knowledge of the pharmacological properties of the compounds tested.

Experimental Section

Chemistry. Melting points (uncorrected) were determined in open glass capillaries on a Thomas-Hoover apparatus. ^{1}H NMR spectra were recorded with a Varian Associates EM-360 instrument (Me_4Si). GC/MS spectra were recorded on a Finnegan MAT 44S instrument at 70 eV. All spectra recorded were in accordance with assigned structures. GLC was performed with a Hewlett-Packard 5830A instrument with a flame-ionization detector. A glass column (2 m × 5 mm i.d.) packed with 3% OV-17 or 3% OV-11 on Gas-Chrom Q (Supelko, Inc.) was used throughout. The elemental analyses (C, H, and N) for the new substances (Microanalytical Laboratory Agricultural College, Uppsala, Sweden) were within ±0.4% of the theoretical values. For purity tests, TLC was performed on fluorescent silica gel plates developed in at least two different systems. For all the compounds, only one spot (visualized by UV light and I_2 vapor) was obtained.

4-Benzyl-7-methoxy-1,4,5,6-tetrahydrobenzo[*f*]quinolin-3(2*H*)-one (20). A mixture of 7-methoxy-1,4,5,6-tetrahydrobenzo[*f*]quinolin-3(2*H*)-one[3] (31.0 g, 135 mmol) and *t*-BuOK (20.0 g, 178 mmol) in *t*-BuOH (500 mL) was refluxed for 15 min before adding benzyl chloride (15.5 mL, 135 mmol) and then refluxing for 2 h. The mixture was cooled to room temperature, H_2O (200 mL) was added, and the mixture was extracted with ether. The organic layer was separated and dried (Na_2SO_4), and the solvent was evaporated. The residue was crystallized from $EtOH/H_2O$, yielding 28.6 g (66%) of **20**, mp 101–104 °C. Anal. ($C_{21}H_{21}NO_2$) C, H, N; C: calcd, 79.0; found, 78.5.

***cis*- and *trans*-4-Benzyl-7-methoxy-1,2,3,4,4a,5,6,10b-octahydrobenzo[*f*]quinoline (21 and 22).** Compound **20** (2.60 g, 8.14 mmol) in dry THF (100 mL) was added to a slurry of $LiAlH_4$ (0.620 g, 16.3 mmol) in dry THF (50 mL). After 4 h, ether (200 mL) was added and then excess hydride was destroyed by the dropwise addition of 0.6 mL of H_2O, 0.6 mL of 15% NaOH, and 1.8 mL of H_2O. Inorganic material was filtered off, and the filtrate was washed with H_2O. The organic layer was separated and dried (Na_2SO_4), and the solvent was evaporated, yielding a crude oil (2.2 g), which was reduced in the next step without further purification. $NaBH_3CN$ (18.2 g, 131 mmol) was added in portions to the crude oil (24.6 g, 80.7 mmol) in CH_3CN (150 mL), and HOAc was added until the pH was ~5. This mixture was stirred overnight at room temperature. Excess hydride was

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destroyed by adding concentrated HCl (65 mL). This mixture was stirred for 30 min, alkalized with 10% NaOH (350 mL), and extracted with ether. The organic layer was separated and dried (Na_2SO_4), and the solvent was evaporated, yielding an oil in essentially quantitative yield with a cis/trans ratio of 53:47 according to GLC. This mixture was chromatographed on SiO_2 using CH_2Cl_2/MeOH (19:1) as eluant. Fractions containing primarily the cis and the trans isomers, respectively, were pooled separately. The amines were converted to their HCl salts and then crystallization (or refluxing with acetone) yielded separately the cis isomer (**21**·HCl; 3.7 g, 13%), mp 241–243.5 °C, and the trans isomer (**22**·HCl; 5.2 g, 19%), mp 235–238 °C. A mixture of cis and trans (4.0 g) with a cis/trans ratio of 83:17 was also recovered. Anal. ($C_{21}H_{25}NO$·HCl) C, H, N (both **21**·HCl and **22**·HCl).

***cis*-7-Methoxy-1,2,3,4,4a,5,6,10b-octahydrobenzo[*f*]quinoline (23).** The cis isomer **21**·HCl (1.00 g, 2.91 mmol) was dissolved in MeOH (250 mL) and hydrogenated over 10% Pd/C (0.50 g) at 25 psig at room temperature overnight. After filtration of the catalyst and evaporation of the solvent, 0.43 g (58%) of crystals was obtained, mp 272–274 °C (from ethanol–ether). Anal. ($C_{14}H_{19}NO$·HCl) C, H, N.

***trans*-7-Methoxy-1,2,3,4,4a,5,6,10b-octahydrobenzo[*f*]quinoline (24).** The trans isomer **22**·HCl (4.70 g, 13.7 mmol) was dissolved in MeOH (250 mL) and hydrogenated as described for **23**, yielding 3.0 g (87%) of crystals, mp 300–301 °C (from ethanol). Anal. ($C_{14}H_{19}NO$·HCl) C, H, N.

***cis*-7-Methoxy-4-*n*-propyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[*f*]quinoline (25).** To **23**·HCl (0.328 g, 1.29 mmol) in CH_2Cl_2 (25 mL) was added Et_3N (0.50 mL) and propionyl chloride (0.214 g, 2.31 mmol). The mixture was stirred at room temperature for 0.5 h, water was added, and the aqueous layer was alkalized with 10% Na_2CO_3. The organic layer was separated and dried (Na_2SO_4). Evaporation of the solvent yielded 0.24 g (67%) of an oil, which was dissolved in anhydrous ether and added dropwise to a slurry of $LiAlH_4$ (0.500 g, 10.5 mmol) in dry ether. Usual workup yielded the base as an oil. Crystals were precipitated from anhydrous ether with HCl/ether, filtered off, and recrystallized (ethanol–ether), yielding 0.16 g (64%) of crystals, mp 239–241 °C. Anal. ($C_{17}H_{25}NO$·HCl) C, H, N.

***trans*-7-Methoxy-4-*n*-propyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[*f*]quinoline (26).** Finely divided $NaBH_4$ (0.370 g, 10.0 mmol) was stirred for 6 h below 20 °C in dry benzene (50 mL), together with propionic acid (2.54 mL, 34.0 mmol), to form a complex. To this complex was then added **24** (0.400 g, 1.97 mmol) dissolved in benzene, and the mixture was refluxed for 4 h. After the mixture was cooled, excess 2 N NaOH was added, and the mixture was extracted with ether. The organic layer was dried (Na_2SO_4), and the solvent was evaporated, yielding an oil (0.34 g, 68%). A small amount was converted to the hydrochloride (HCl/ether) and recrystallized, mp 244–246 °C (acetone–ether). Anal. ($C_{17}H_{25}NO$·HCl) C, H, N.

***trans*-4-*n*-Butyl-7-methoxy-1,2,3,4,4a,5,6,10b-octahydrobenzo[*f*]quinoline (27).** Compound **24** (0.428 g, 1.97 mmol) was N-*n*-butylated with a complex of butanoic acid (3.00 mL, 34.0 mmol) and $NaBH_4$ (0.374 g, 9.89 mmol) in benzene as described for **26**, yielding an oil (0.50 g, 93%). A small amount of this oil was converted to the hydrochloride and recrystallized (acetone–ether), mp 213–214 °C. The rest of the crude oil was hydrolyzed in the subsequent step without further purification (see Table I).

4-Benzyl-8-methoxy-1,4,5,6-tetrahydrobenzo[*f*]quinolin-3(2*H*)-one (28). 8-Methoxy-1,4,5,6-tetrahydrobenzo[*f*]-quinolin-3(2*H*)-one[3] (10.0 g, 43.6 mmol) was treated with *t*-BuOK (10.0 g, 89.0 mmol) and benzyl chloride (7.00 mL, 61.0 mmol) in refluxing *t*-BuOH as described for **20**. The crude oil was chromatographed on SiO_2 with ether as eluent, yielding 8.2 g (61%) of crystals, mp 92–96 °C. Anal. ($C_{21}H_{21}NO_2$) C, H, N.

***cis*- and *trans*-8-Methoxy-1,2,3,4,4a,5,6,10b-octahydrobenzo[*f*]quinolinepropionamide (29 and 30).** A solution of **28** (6.00 g, 19.5 mmol) in anhydrous THF (100 mL) was added to a suspension of $LiAlH_4$ (2.00 g, 52.7 mmol) in THF (50 mL). Usual workup gave an oil in essentially quantitative yield, which was reduced with $NaBH_3CN$ (2.00 g, 31.8 mmol) as described for **21** and **22**. The crude product (4.5 g) had a cis/trans ratio of 50:50 according to GLC; 300 mg was chromatographed (SiO_2 MeOH) for NMR studies in order to assign the cis/trans geometry of the separated *N*-benzyl derivatives. These were separately debenzylated and propionylated as described for **23** and **25**, respectively, and compared on GLC with compounds **29** and **30**. The hydrochloride of the cis/trans mixture (1.90 g, 5.53 mmol) was dissolved in MeOH (100 mL) hydrogenolyzed in the presence of 10% Pd/C (0.80 g) as described for **23**, yielding 1.10 g (78%) of foamy crystals. To this crude material was added CH_2Cl_2 (25 mL), Et_3N (5 mL), and propionyl chloride (2.12 g, 22.9 mmol). Et_2O (100 mL) was added after 1 h at room temperature, and inorganic material was filtered off. The filtrate was shaken with 10% Na_2CO_3, and the organic layer was dried (Na_2SO_4). Evaporation of the solvent yielded an oil (2.0 g), which was chromatographed on SiO_2 (200 g) and eluted with Et_2O. Fractions of 30 mL were collected: fractions 11–13 contained the pure trans isomer **30** (0.15 g), fraction 14 contained a mixture of cis and trans isomers (0.30 g; cis/trans, 36:64), and fractions 15–17 contained the pure cis isomer **29** (0.45 g). The isomers were reduced separately in the next step without further purification.

***cis*-8-Methoxy-4-*n*-propyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[*f*]quinoline (31).** Compound **29** (0.450 g, 1.65 mmol) was dissolved in anhydrous ether (10 mL) and added dropwise to $LiAlH_4$ (0.200 g, 5.26 mmol) suspended in anhydrous ether (25 mL). Workup was made according to compound **25**, yielding **31**·HCl (0.35 g, 72%), mp 209–211 °C (acetone–ether). Anal. ($C_{17}H_{25}NO$·HCl) H, N; C: calcd, 69.0; found, 68.5.

***trans*-8-Methoxy-4-*n*-propyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[*f*]quinoline (32).** Compound **30** (0.150 g, 0.548 mmol) was reduced with $LiAlH_4$ (0.100 g, 2.63 mmol) as described for **25**, yielding 0.15 g (95%) of **32**·HCl, mp 174–176 °C (acetone–ether). Anal. ($C_{17}H_{25}NO$·HCl) H, N; C: calcd, 69.0; found, 68.5.

***cis*- and *trans*-4-Benzyl-9-methoxy-1,2,3,4,4a,5,6,10b-octahydrobenzo[*f*]quinoline (33 and 34).** 7-Methoxy-2-tetralone (10.0 g, 56.8 mmol) was converted to its pyrrolidine enamine, which was further reacted with acrylamide (9.03 g, 127 mmol) in a fashion analogous to the method described by Cannon et al.,[3] yielding 9-methoxy-1,4,5,6-tetrahydrobenzo[*f*]quinoline-3(2*H*)-one (6.5 g, 33%). This compound (6.00 g, 26.2 mmol) was *N*-alkylated without further purification as described for **20**, yielding an oil (11.3 g), which was dissolved in 50 mL of anhydrous THF and reduced with $LiAlH_4$ (2.70 g, 71.1 mmol), yielding a crystalline residue (7.7 g). The crystals were dissolved in 100 mL of acetonitrile and treated with $NaBH_3CN$ (2.54 g, 40.4 mmol) and HOAc as described for **21** and **22**. The residual oil (6.9 g) had a cis/trans ratio of 55:45 according to GLC. This crude material was chromatographed on SiO_2 (500 g) with CH_2Cl_2/MeOH (19:1) as eluent. After the first 800 mL were discarded, 10-mL fractions were collected. Fractions 16–29 were combined, and the product was converted to its hydrochloride and then crystallized out by treatment with boiling acetone, yielding 0.50 g of **33**·HCl, mp 238–239 °C. Fractions 30–80 were combined, and crystallization (acetone and ethanol–ether) gave an additional amount of **33**·HCl (1.29 g) and 1.00 g of **34**·HCl, mp 235–236 °C. Anal. ($C_{21}H_{25}NO$·HCl) C, H, N (both **33**·HCl and **34**·HCl).

***cis*-9-Methoxy-1,2,3,4,4a,5,6,10b-octahydrobenzo[*f*]quinoline (35).** This compound was obtained from **33**·HCl (1.00 g, 2.90 mmol) as described for **23**: yield 0.70 g (95%); mp 259–260 °C (from ethanol–ether). Anal. ($C_{14}H_{19}NO$·HCl) C, H, N.

***trans*-9-Methoxy-1,2,3,4,4a,5,6,10b-octahydrobenzo[*f*]quinoline (36).** This compound was obtained from **34**·HCl (0.75 g, 2.20 mmol) as described for **23**: yield 0.50 g (89%); mp 287–288 °C (from ethanol–ether). Anal. ($C_{14}H_{19}NO$·HCl) C, H, N.

***cis*-9-Methoxy-4-*n*-propyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[*f*]quinoline (37).** This compound was prepared from **35** (0.50 g, 2.30 mmol) as described for **26**, and was obtained as an oil in essentially quantitative yield. Its hydrochloride had mp 223–225 °C (from acetone). Anal. ($C_{17}H_{25}NO$·HCl) C, H, N.

***trans*-9-Methoxy-4-*n*-propyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[*f*]quinoline (38).** This compound was obtained as an oil in essentially quantitative yield from **36** (0.40 g, 1.80 mmol) as described for **26**. Its hydrochloride had mp 168–170 °C (from acetone–ether). Anal. ($C_{17}H_{25}NO$·HCl) C, H, N.

10-Methoxy-1,4,5,6-tetrahydrobenzo[*f*]quinoline-3(2*H*)-one (39). 8-Methoxy-2-tetralone (23.0 g, 131 mmol) was converted to its pyrrolidine enamine, which was further reacted with acrylamide (14.0 g, 197 mmol) in a fasion analogous to the method described by Cannon et al.,[3] yielding 9.3 g (33%) of **39**, mp 202–205

°C (from acetone–petroleum ether). Anal. ($C_{14}H_{15}NO_2$) C, H, N.

***cis*- and *trans*-4-Benzyl-10-methoxy-1,2,3,4,4a,5,6,10b-octahydrobenzo[*f*]quinoline (40 and 41).** The enamide **39** (9.30 g, 40.6 mmol) was *N*-benzylated as described for **20** to yield an oil (13.6 g), which was reduced using first $LiAlH_4$ (4.00 g, 105 mmol) and then $NaBH_3CN$ (3.38 g, 53.8 mmol) as described for **21** and **22** to leave an oil (11.5 g) with a cis/trans ratio 86:14 according to GLC. Repeated treatment of the hydrochloride of the mixture with boiling acetone gave several crops of the pure cis isomer **40**·HCl (totally 3.15 g), mp 250–253 °C. Anal. ($C_{21}H_{25}NO$·HCl) C, H, N. The mother liquors were chromatographed on SiO_2 with CH_2Cl_2/acetone (5:1) as eluent, and 0.177 g of the trans isomer **41**·HCl was isolated, mp 100–140 °C (not recrystallized due to the small amount isolated). Anal. ($C_{21}H_{25}NO$·HCl) C, H, N.

***cis*-10-Methoxy-1,2,3,4,4a,5,6,10b-octahydrobenzo[*f*]quinoline (42).** This compound was obtained from **40**·HCl (0.55 g, 1.7 mmol) as described for **23**: yield 0.40 g (95%); mp 260–262 °C (from ethanol–ether). Anal. ($C_{14}H_{19}NO$·HCl) C, H, N.

***trans*-10-Methoxy-1,2,3,4,4a,5,6,10b-octahydrobenzo[*f*]quinoline (43).** This compound was obtained from **41**·HCl (0.170 g, 0.490 mmol) as described for **23**: yield 0.050 g (40%); mp 266–269 °C (not analyzed due to the small amount isolated).

***cis*-10-Methoxy-4-*n*-propyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[*f*]quinoline (44).** This compound was prepared from **42**·HCl (0.27 g, 1.1 mmol) as described for **26**, yielding 0.22 g (68%) of the hydrochloride, mp 223.5–224.5 °C (from ethanol–ether). Anal. ($C_{17}H_{25}NO$·HCl) C, H, N.

***trans*-10-Methoxy-4-*n*-propyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[*f*]quinoline (45).** This compound was prepared from **43**·HCl (0.05 g, 0.20 mmol) as described for **27**, yielding 0.050 g (86%) of an oil, which was demethylated with 48% aqueous HBr without further purification (see Table I).

Demethylation of Methoxy Compounds. The phenols were obtained by heating the appropriate methoxy compounds in 48% aqueous HBr for 2 h at 125 °C under nitrogen. The hydrobromic acid was evaporated, and the residue was recrystallized at least twice.

Pharmacology. Animals used in the biochemical and motor activity experiments were male rats of Sprague–Dawley strain (Anticimex, Stockholm) weighing 200–300 g.

All substances to be tested were dissolved in saline immediately before use, occasionally with the addition of a few drops of glacial acetic acid and/or moderate heating in order to obtain complete dissolution. Reserpine was dissolved in a few drops of glacial acetic acid and made up to volume with 5.5% glucose. Injection volumes were 5 or 10 mL/kg and were all neutral (except for the solutions of reserpine).

Biochemistry. The biochemical experiments and the spectrophotometric determinations of Dopa and 5-HTP were performed as previously described.[10,17]

Separate dose-response curves based on four to six dose levels for each substance (sc administration) and brain area were constructed (cf. ref 14). From these curves was estimated the dose of the drug yielding a half-maximal decrease of the Dopa level, the ED_{50} value (presented in Table I).

Motor Activity. The motor activity was measured by means of photocell recordings ("M/P 40 Fc Electronic Motility Meter", Motron Products, Stockholm) as previously described.[10,17]

Six hours prior to the motility testing (carried out between 1 and 6 p.m.), the rats were intraperitoneally injected with reserpine (10 mg/kg), and 1 h before the test, DL-α-methyl-*p*-tryosine methyl ester hydrochloride (250 mg/kg) was injected intraperitoneally. The different compounds under investigation were administered subcutaneously in the neck region ($n = 4$) in a dose of 1 mg/kg (3100 nmol/kg) for the trans derivatives and 10 mg/kg (31 000 nmol/kg) for the cis derivatives.

Immediately after drug administration the rats were placed in the test cages (one rat per cage) and put into the motility meters. Motor activity was then followed and recorded for the subsequent 60 min. Each box was equipped with a semitransparent mirror that allowed gross behavior observations of the animals during the experiments. The motor activity results are shown in Table I.

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Use of (*S*)-(Trifloxymethyl)oxirane in the Synthesis of a Chiral β-Adrenoceptor Antagonist, (*R*)- and (*S*)-9-[[3-(*tert*-Butylamino)-2-hydroxypropyl]oximino]fluorene

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Two synthetic approaches were used to prepare, in chirally pure form, the β-adrenoceptor antagonist 9-[[3-(*tert*-butylamino)-2-hydroxypropyl]oximino]fluorene (**1a**). One of these employed the oxazolidine (*S*)-**6** generated from D-mannitol, while the other utilized (*S*)-[[(trifluoromethanesulfonyl)oxy]methyl]oxirane (**4**) as the chiral three-carbon fragment. This latter synthesis was designed to incorporate the amino function in the last step. In vitro, a β_2 selectivity of only 2.2 was observed for **1a**. The example, (*S*)-9-[[3-(*tert*-amylamino)-2-hydroxypropyl]oximino]fluorene (**1b**), was also prepared and found to be selective for the β_1 receptor by a factor of 2.5. In contrast to other β-adrenoceptor antagonists, the enantiomers of **1a** exhibited no chiral preference; i.e., (*S*)-**1a** and (*R*)-**1a** possessed a similar order of β-adrenoceptor antagonistic activity.

Since the β-adrenoceptor blocking agent 9-[[3-(*tert*-butylamino)-2-hydroxypropyl]oximino]fluorene [(*RS*)-**1a**] has been reported to be a selective antagonist for the β_2 receptor,[1] it was felt that the *S* enantiomer [(*S*)-**1a**] or a

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