NH_4OH and then reprecipitated by the addition of 2 N HCl to pH 4. The product was collected on a filter, washed with H_2O and $(Me)_2CO$, and dried in vacuo over P_2O_5. There was obtained 1.08 g (60%): mp >200 °C dec (lit.[27] mp 247–249 °C dec, hemihydrate); TLC; HPLC; UV λ_{max} 242 nm (ϵ 49.1 × 10^3); NMR (CF_3COOD) δ 8.04–7.24 (m, 7, aromatic), 5.33–5.00 (m, 3, NCH_2 + NCH), 3.18–2.30 (m, 4, $(CH_2)_2$). Anal. ($C_{21}H_{22}N_6O_5 \cdot 2.5H_2O$) C, H, N.

5,8-Dideazaisoamethopterin (3b). A 600-mg (1.37 mmol) sample of **3a** was added to 33 mL of 0.1 N NaOH with stirring in a N_2 atmosphere. A few drops of 1 N NaOH were added to effect complete dissolution and the pH was then adjusted to 6.3 by the addition of 1 N HCl. Next, 0.54 mL (6.85 mmol) of 38% CH_2O was added followed by slow addition of 172 mg (2.74 mmol) of $NaB(CN)H_3$. The pH was maintained at approximately 6.3 by periodic addition of 1 N HCl. After the addition was complete, the mixture was allowed to stir overnight. The solution was then basified to pH 12 with 1 N NaOH, stirred for 10 min to allow HCN gas to escape, and then neutralized to pH 4 with 1 N HCl. The precipitate was separated by filtration, washed with H_2O, and dried at 100 °C to yield 556 mg (90%) of greenish powder: mp 233–240 °C dec; TLC; HPLC (no **3a** was detected in this sample); UV λ_{max} 245 nm (ϵ 40.6 × 10^3), 285 (14.1 × 10^3); NMR (CF_3COOD) δ 8.41–7.30 (m, 7, aromatic), 4.9 (m, 3, NCH_2 + NCH), 3.51 (s, 3, NCH_3), 2.8–2.1 (m, 4, $(CH_2)_2$). Anal. ($C_{22}H_{24}N_6O_5 \cdot 2.5H_2O$) C, H, N.

10-Formyl-5,8-dideazaisoaminopterin (3c). A 480-mg (1.1 mmol) sample of **3a** was dissolved in a mixture of 5 mL of $(Ac)_2O$ and 10 mL of HCOOH (97%) and stirred for 1.5 h. The solution was added to 75 mL of Et_2O and refrigerated. The resulting solid was isolated by filtration and then washed with Et_2O and H_2O. The solid was suspended in 25 mL of H_2O and basified to pH 9 with 1 N NH_4OH. The pH was then adjusted to 4 with 0.5 N HCl. The precipitate was separated by filtration, washed with H_2O, $(Me)_2CO$, and Et_2O and then vacuum dried to yield 446 mg (87%): mp >321 °C dec; TLC; HPLC; UV λ_{max} 235 nm (ϵ 44.5 × 10^3); NMR (CF_3COOD) δ 8.73 (s, 1, NCHO), 8.10–7.25 (m, 7, aromatic), 5.4–5.03 (m, 3, NCH_2 + NCH), 3.15–2.30 (m, 4, $(CH_2)_2$). Anal. ($C_{22}H_{22}N_6O_6 \cdot 3H_2O$) C, H, N.

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Registry No. **1a**, 59-05-2; **2a**, 18921-68-1; **2b**, 27244-49-1; **2c**, 61075-41-0; **3a**, 56239-22-6; **3b**, 93502-95-5; **3c**, 93502-96-6; **4**, 18917-68-5; **5**, 88050-23-1; **6**, 76282-66-1; **7**, 93502-97-7; **8**, 87597-84-0; **9**, 88050-31-1; DHFR, 9002-03-3; 4-nitrobenozyl chloride, 122-04-3; di-*tert*-butyl-L-glutamate, 16874-06-9; 2,4,6-triaminoquinazoline, 13741-90-7.

Resolved Monophenolic 2-Aminotetralins and 1,2,3,4,4a,5,6,10b-Octahydrobenzo[*f*]quinolines: Structural and Stereochemical Considerations for Centrally Acting Pre- and Postsynaptic Dopamine-Receptor Agonists

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A detailed structure–activity relationship is revealed for resolved, centrally acting dopamine (DA) agonists acting on both pre- and postsynaptic DA receptors. The compounds resolved are 5- and 7-hydroxy-2-(di-*n*-propylamino)tetralin and *cis*- and *trans*-7-hydroxy-4-*n*-propyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[*f*]quinoline. By the superimposition of the structures of the more active enantiomers of these compounds with those of known dopaminergic agonists, apomorphine and ergolines, a new DA-receptor model is proposed as an outgrowth of current DA-receptor theories. One of the most important concepts of this receptor model is its emphasis on the possible positions taken by the N-substituents of dopaminergic compounds. One of these positions is sterically well defined while the other direction is sterically less critical. The model has been used to explain the lack of dopaminergic activity of some previously reported structures and also to predict properties of novel structures, including inherent chirality, which should be active at DA receptors. Hopefully, this heuristic DA-receptor model will lead to the discovery of more selective and potent pharmacological tools, which ultimately might lead to the development of therapeutic agents for treating diseases of dopaminergic function in the central nervous system.

In recent years much interest has focused on the stereochemical aspects of drug action.[1] In the dopaminergic field, the two well-known research tools apomorphine and LSD are both optically pure and stereochemically defined entities, i.e., apomorphine has the 6a*R* and LSD the 5*R*,8*R* configuration.

By comparison of these two molecules (Figure 1) with respect to their incorporated 2-aminotetralin structures, it is obvious that the chiral carbon atoms have opposite stereochemistry. This has led several authors to propose that the pyrroleethylamine moiety of ergots confers dopaminergic properties to this class of compound.[2-4] All available data indicate that it is the phenethylamine, or

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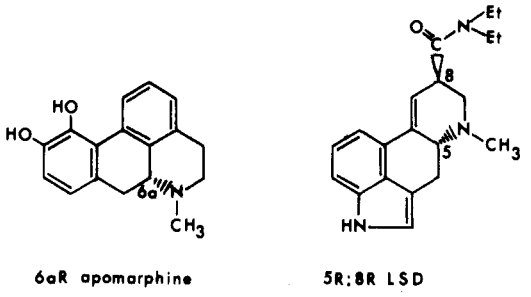

Figure 1. The absolute configurations of apomorphine and LSD.

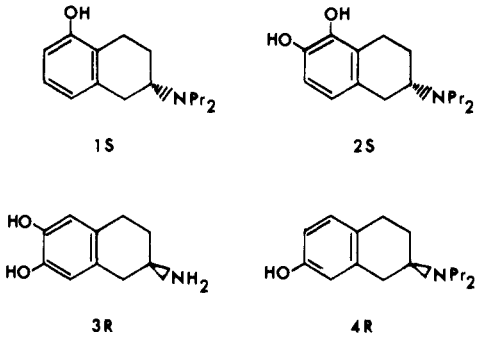

Figure 2. Resolved 2-aminotetralins.

rather the 2-aminotetralin moiety, which confers the high, central dopaminergic properties to apomorphine. Many studies have been performed on 2-aminotetralins substituted in various ways, both in the aromatic nucleus and on the 2-amino function.[5-11] Very intriguing results have been presented by McDermed et al., who studied resolved 2-aminotetralin derivatives.[5] The first compound to be resolved was 5-hydroxy-2-(di-*n*-propylamino)tetralin (1) (Figure 2).

The *S* enantiomer (1(S)) was about 10 times more potent than apomorphine in eliciting stereotopy in the rat and emesis in the dog. The *R* enantiomer (1(*R*)) was inactive at the doses tested. This work was continued with the resolution and pharmacological evaluation of 5,6-dihydroxy-2-(di-*n*-propylamino)tetralin (2), 6,7-dihydroxy-2-aminotetralin (3), and 7-hydroxy-2-(di-*n*-propylamino)-tetralin (4)[12,13] (Figure 2). It was found that the stereochemistry at carbon 2 for the more active enantiomer was

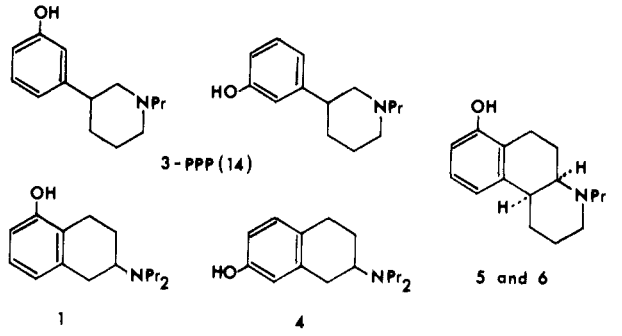

Figure 3. The fictive combination of 3-PPP and 2-aminotetralins.

S in the case of compounds 1 and 2, whereas it was the opposite for compounds 4 and 3. These results were organized within the context of a hypothetical DA-receptor model.[12]

Similar receptor models have been proposed by Grol and Rollema[14] from a very different approach using molecular orbital calculations of low-energy conformations of DA and by Seiler and Markstein[15] after the pharmacological evaluation of essentially the same compounds that McDermed studied in models claimed to measure D1-receptor activities (cAmp and [H^3]DA binding).[15] In our opinion, the above-mentioned studies comprise some of the most interesting DA structure–activity relationships (SAR) to date, and the proposed receptor models might be used in the design of new dopaminergic agonists.

Another dimension of DA SAR which can be brought into discussion at this stage is related to the concept of presynaptic DA receptors (autoreceptors).[16] When we first reported 3-(3-hydroxyphenyl)-*N*-*n*-propylpiperidine (3-PPP; 14) to be a selective DA-autoreceptor agonist, it was in its racemic form.[17] Recently we have published an extensive pharmacological study on the resolved enantiomers of 14,[18] where we present the (+)-3*R* enantiomer to be a classical DA-receptor stimulant, i.e., stimulating both DA autoreceptors (low doses) and postsynaptic DA receptors (high doses). The (−)-3*S* enantiomer likewise stimulates DA autoreceptors at low doses but unexpectedly also blocks postsynaptic DA receptors at higher doses. In the racemate, the *S* isomer blocks the postsynaptic stimulation from the *R* isomer, thus explaining the interpretation of autoreceptor selectivity of the racemic mixture. A similar antagonistic effect has been documented for the apomorphine enantiomers, where the (+)-6a*S* enantiomer antagonizes the stereotypic cage-climbing behavioral effects in mice having received the (−)-6a*R* enantiomer, which is the enantiomer commonly referred to simply as apomorphine.[19] These aspects of agonist–antagonist interactions between enantiomers have recently been discussed

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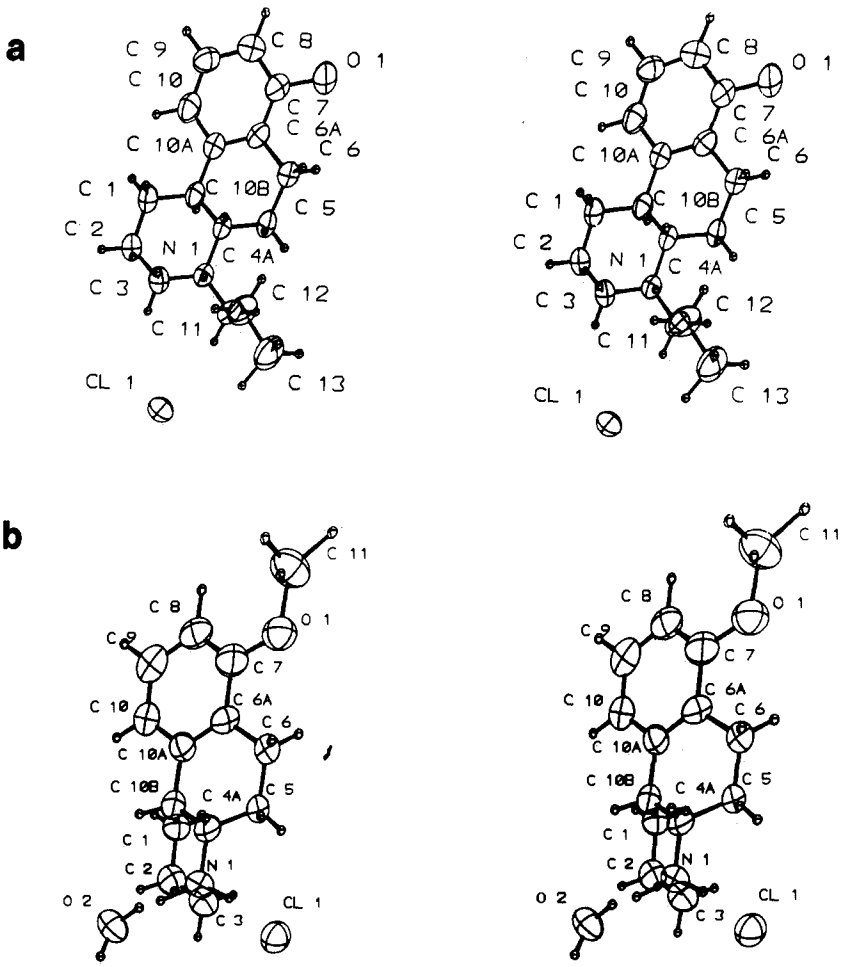

Figure 4. (a) Stereoscopic pair of compound 6(4a*S*,10b*S*). (b) Stereoscopic pair of compound 10(4a*S*,10b*R*).

for a series of resolved phenylpiperidines related to compound 14.[20] McDermed et al. have tested the possibility of such an interaction of the enantiomers of compound 1 but have found no such interaction.[5]

With these very interesting results at hand, we thought that it might be worthwhile to also investigate the enantiomers of compounds 1 and 4 from the point of view of their potential interaction with pre- and postsynaptic DA receptors. The reason for selecting OH positions 5 and 7 in the aminotetralins is obvious from Figure 3. Free rotation around the axis between the two rings of 14 gives rise to an infinite amount of rotameric forms, two of which are shown in Figure 3.

Previous studies on resolved compounds have not taken into account the potential selective effects of these compounds on central DA autoreceptors. Such effects would not have been distinguished from postsynaptic effects if solely in vitro methods were used[15] or not discovered at all if only behavioral models were used.[5] Thus, it would be interesting to find out whether those enantiomers of 1 and 4, which have been classified as less potent in the previous studies, possibly might be selective in stimulating DA autoreceptors. In order to make the SAR study even more comprehensive in this respect, we also performed the resolution and pharmacological testing of both *cis*- and *trans*-7-hydroxy-4-*n*-propyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[*f*]quinoline (**5** and **6**, respectively), with special reference to central pre- and postsynaptic DA-receptor stimulation (Figure 3).

In our paper on racemic octahydrobenzo[*f*]quinolines, the cis isomer **5** was reported to be of low potency in tests related to dopaminergic activity.[21] Theoretically, the reason for this could be that one enantiomer antagonizes the other as in the case of racemic 14. The resolution and pharmacological testing of the enantiomers of compound **5** were performed to examine such a possibility. Thus, the aim of the present study was to make use of stereochemically defined dopaminergic agonists of high potency for a detailed SAR concerning pre- and postsynaptic DA receptors and, furthermore, to examine dopaminergic agonists from this point of view.

The absolute configurations of the tricyclic compounds have been determined by X-ray chrystallography. The stereopictures are shown in Figures 4a and 4b.[22]

Chemistry. All compounds synthesized (except for compound **16**) are previously known in their racemic forms.[5,21,23] Compounds 1 and 4 have also been reported to be resolved.[5,15] These resolutions were performed by using the conventional recrystallization technique.

Another possibility for the preparative resolution of optically active amines has been presented by Helmchen

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Table I. HPLC Separation Factors for Diastereomeric Amides

acid part	amine part	α value	HPLC system hexane/EtOAc/EtOH
lactone 7	α-phenylethylamine	1.50	75:15:10
lactone 7	3-(3-methoxyphenyl)piperidine	1.10	0:100:0
lactone 7	5-methoxy-2-aminotetralin	1.00	80:15:5
O-methylmandelic acid	α-phenylethylamine	1.75	95.5:3.75:0.75
O-methylmandelic acid	3-(3-methoxyphenyl)piperidine	1.50	82:15:3
O-methylmandelic acid	5-methoxy-2-aminotetralin	1.00	82:15:3
O-methylmandelic acid	5-hydroxy-2-aminotetralin	1.26	82:15:3
O-methylmandelic acid	5-methoxy-2-(*N*-*n*-propylamino)tetralin	1.25	91:7.5:1.5
O-methylmandelic acid	5-methoxy-2-(*N*-benzylamino)tetralin	1.16	91:7.5:1.5
O-methylmandelic acid	5-hydroxy-2-(*N*-*n*-propylamino)tetralin	1.17	82:15:3
O-methylmandelic acid	7-methoxy-2-(*N*-*n*-propylamino)tetralin	1.23	82:15:3
O-methylmandelic acid	*cis*-7-OMe-OHB[*f*]Q[a]	1.31	82:15:3
O-methylmandelic acid	*trans*-7-OMe-OHB[*f*]Q	1.15	95.5:3.75:0.75

[a] 7-OMe-OHB[*f*]Q denotes 7-methoxy-1,2,3,4,4a,5,6,10b-octahydrobenzo[*f*]quinoline.

Table II. Physical Data

compd. no. and abs config	prepn method	yield,[a] %	mp,[b] °C	$[\alpha]^{22}_D$ (MeOH)	optical purity,[c] %	formula
1(*R*), *R*-5-OH-DPAT[d]	B	50	226–229[e]	+67.2 (*c* 1.0)[e]	98.9	$C_{16}H_{25}NO\cdot HCl$
1(*S*), *S*-5-OH-DPAT	B	90	229–231[f]	−63.7 (*c* 1.0)[f]	99.3	
4(*R*), *R*-7-OH-DPAT	B	89	165–168	+76.2 (*c* 0.82)[g]	98.7	$C_{16}H_{25}NO\cdot HCl$
4(*S*), *S*-7-OH-DPAT	B	56	169–171	−76.2 (*c* 0.70)[h]	99.5	
5(4a*R*,10b*S*), *cis*-7-OH-4-*n*-Pr-OHB[*f*]Q[i]	D	95	270–275	−12.8 (*c* 1.0)	99.5	$C_{16}H_{23}NO\cdot HCl$
5(4a*S*,10b*R*), *cis*-7-OH-4-*n*-Pr-OHB[*f*]Q	E	60	275–278	+9.8 (*c* 1.0)	100	
6(4a*R*,10b*R*), *trans*-7-OH-4-*n*-Pr-OHB[*f*]Q	B	35	292–295	+62.9 (*c* 0.33)	95.6	$C_{16}H_{23}NO\cdot HCl$
6(4a*S*,10b*S*), *trans*-7-OH-4-*n*-Pr-OHB[*f*]Q	C, D	86	296–299	−75.9 (*c* 0.32)	98.0	
8(*R*), *R*-5-OMe-PAT[j]	A	30	278–280	+69.7 (*c* 1.0)	98.9	$C_{14}H_{21}NO\cdot HCl$
8(*S*), *S*-5-OMe-PAT	A	31	278–280	−63.0 (*c* 1.0)	99.3	
9(*R*), *R*-7-OMe-PAT	A	43	260–262	+70.2 (*c* 1.06)	98.7	$C_{14}H_{21}NO\cdot HCl$
9(*S*), *S*-7-OMe-PAT	A	57	260–261	−72.6 (*c* 0.80)	99.5	
10(4a*R*,10b*S*), *cis*-7-OMe-OHB[*f*]Q	A	38	226–229	+2.0 (*c* 1.0)	99.5	$C_{14}H_{19}NO\cdot HCl$
10(4a*S*,10b*R*), *cis*-7-OMe-OHB[*f*]Q	A	43	228–230	−2.4 (*c* 1.0)	100	
11(4a*R*,10b*S*), *cis*-7-OMe-4-*n*-Pr-OHB[*f*]Q	C	78	258–260	−13.0 (*c* 1.0)	99.5	$C_{17}H_{25}NO\cdot HCl$
11(4a*S*,10b*R*), *cis*-7-OMe-4-*n*-Pr-OHB[*f*]Q	C	65	254–258	+12.8 (*c* 1.0)	100	
12(4a*R*,10b*R*), *trans*-7-OMe-OHB[*f*]Q	A	87	294–297	+81.1 (*c* 0.96)	95.6	$C_{14}H_{19}NO\cdot HCl$[k]
12(4a*S*,10b*S*), *trans*-7-OMe-OHB[*f*]Q	A	50	296–301	−88.2 (*c* 1.05)	98.0	
16, *trans*-4-*n*-Bu-9-OH-OHB[*f*]Q	D[l]	75	277–279	–	–	$C_{17}H_{25}NO\cdot HBr$[m]

[a] The yield notation is from the last step in the corresponding reaction sequence. [b] Recrystallization solvent was EtOH/ether for compounds (both enantiomers) 1, 5, 8, 9, 10, 11, 12, and 16; MeOH/ether for compound 6 and acetone/ether for compound 4. [c] Optical purity means the percentage of the dominating amide in the mixture, when coupling the resolved amine to (*R*)-(−)-*O*-methylmandelic acid. For the tertiary amines the results from the corresponding secondary amines are given. [d] DPAT denotes 2-(di-*n*-propylamino)tetralin. [e] Lit.[5] mp 228–229 °C dec.; $[\alpha]^{28}_D$ +70° (*c* 2.0, MeOH). [f] Lit.[5] mp 228–229.5 °C dec; $[\alpha]^{22}_D$ −71° (*c* 2.0, MeOH). [g] Lit.[15] $[\alpha]^{20}_D$ +79.6° (*c* 1.0, MeOH). [h] Lit.[15] $[\alpha]^{20}_D$ −79.7° (*c* 1.0, MeOH). [i] OHB[*f*]Q denotes octahydrobenzo[*f*]quinoline. [j] PAT denotes 2-(*n*-propylamino)tetralin. [k] Not analyzed due to the small amount isolated. TLC and GLC show no impurities and both compounds were identical on GC/MS, showing M^+ at *m/e* 217 and the base peak at *m/e* 216. [l] This compound was synthesized according to the methods used in ref 21 for the preparation of the corresponding 4-*n*-Pr compound. [m] Not analyzed due to the small amount isolated. TLC and GLC show no impurities and GC/MS show M^+ at *m/e* 259 and the base peak at *m/e* 216.

et al.[24] The method utilizes optically pure β-phenyl-γ-butyrolactone (7) for the formation of diastereomeric amides, which can be separated by conventional column chromatography on SiO_2. The amine enantiomers can be recovered from the separated amides by mild acid hydrolysis. The reason for these amides to be liable to hydrolysis under mild conditions is anchimeric assistance from the OH group in the side chain of the amides. The method is also advantageous in the respect that one easily recovers the starting lactone by simple extraction.

From the analytical work on optical purity determinations made by Helmchen et al.,[25] it is obvious that the commercially available (*R*)-(−)-*O*-methylmandelic acid (i.e., (*R*)-(−)-α-methoxyphenylacetic acid) has qualities which give its diastereomeric amides high α values in HPLC analysis. This was the reason for us to compare the separation factors for the diastereomeric amides of those amines, which also were coupled to the lactone 7 (Table I). In addition, (*R*)-(−)-*O*-methylmandeloyl chloride was coupled to some other amines, which are potential precursors to the present series of resolved compounds. Table I shows that there is a tendency for the separation factors of the *O*-methylmandelic amides to be better than those of the corresponding amides obtained from lactone 7. In addition, the chemical reactivity of *O*-methylmandeloyl chloride for amide formation is much greater than that of lactone 7.

However, *O*-methylmandelic amides suffer from the disadvantage of not being easily hydrolyzable. Thus, we have applied a method for cleaving these amides (tertiary) in THF by using the base potoassium *tert*-butoxide.[20]

The compounds synthesized and their physical data are presented in Table II.

Pharmacology. The in vivo biochemical test method utilizes the well-established phenomenon of receptor-me-

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Table III. Biochemical and Behavioral Data

no. and abs config	Dopa accumulation:[a] ED_{50},[b] nmol/kg limbic	striatum	motor activity[b] dose, nmol/kg	acc counts[c]
1(*R*)	410	650	39000	43 ± 9*
1(*S*)	3.7	3.7	310	155 ± 27*
4(*R*)	9.5	11	310	46 ± 18*[d]
4(*S*)	1900	2400	39000	33 ± 6*
5(4a*R*,10b*S*)	I[e]	I[e]	50000	31 ± 23 ns
5(4a*S*,10b*R*)	I[f]	I[f]	50000	I
6(4a*R*,10b*R*)	320	410	3100	59 ± 11*[g]
			31000	138 ± 20*[g]
6(4a*S*,10b*S*)	14	14	1300	62 ± 11*[g]
			3100	78 ± 11*[g]
16[h]	I[i]	I[i]	50000	75 ± 16*[j]
14(*R*)[k]	1000	1300	13000	78 ± 14*
14(*S*)[k]	800	1700	213000	12 ± 2*
(−)-(6a*R*)-apomorphine[l]	190	220	NT[m]	

[a] For experimental details, see the Experimental Section. [b] Dose giving a half-maximal decrease of Dopa formation in the rat brain part, estimated from a dose–response curve comprising four to six dose levels (n = 3–5) of the compound tested. [c] Statistics according to the Student's t-test; (*) p = 0.05 or less. [d] This effect was blocked by haloperidol (0.5 mg/kg ip 30 min before drug administration). [e] Inactive at 50 μmol/kg. Dopa accumulation expressed as percent of controls were limbic 86%, striatum 60%. [f] Inactive at 50 μmol/kg. Dopa accumulation expressed as percent of controls were limbic 93%, striatum 92%. [g] This result was obtained after α-methyl-*p*-tyrosine (250 mg/kg ip 60 min before drug administration). [h] Compound 16 is *trans*-4-*n*-butyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[*f*]quinoline. [i] Inactive at 50 μmol/kg. Dopa accumulation expressed as percent of controls were limbic 85%, striatum 75%. The corresponding values after haloperidol pretreatment (0.5 mg/kg ip 30 min before drug administration) were limbic 90%, striatum 79%. [j] This effect was not blocked by haloperidol (0.5 mg/kg ip 30 min before drug administration) but gave accumulated counts (54 ± 10) not significantly different from the result obtained without haloperidol pretreatment. [k] From ref 20. [l] From ref 11. [m] NT = not tested.

diated feedback inhibition of the presynaptic neuron.[26] Thus, the synthesis rate of the catecholamines DA and norepinephrine (NE) is inhibited by agonists (and activated by antagonists) at dopaminergic and α-adrenergic receptors, respectively. Similarly, the synthesis rate of 5-HT is inhibited by 5-HT-receptor agonists.[27,28] The Dopa accumulation, following decarboxylase inhibition by means of (3-hydroxybenzyl)hydrazine (NSD 1015), was thus used as an indicator of the DA-synthesis rate in the DA-predominant parts (i.e., limbic system, corpus striatum) and the NE-synthesis rate in the NE-dominant 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 with use of motility meters.[11,29] The biological data are presented in Table III.

Results and Discussion

The biochemical results (Table III) from testing the aminotetralins 1(*R*) and 1(*S*) and 4(*R*) and 4(*S*) are in agreement with the results of McDermed et al.[5] and Seiler and Markstein,[15] thus confirming that the two more active enantiomers are 1(*S*) and 4(*R*), respectively. The biochemically measured effects of the two less active enantiomers 1(*R*) and 4(*S*) can completely be explained by optical impurity (1.1% in the case of 1(*R*) and 0.5% in the case of 4(*S*)). This result does not give any obvious support for the above-proposed hypothesis that the less active enantiomers might be selective for DA autoreceptors but does not, however, exclude such a possibility, assuming a relatively low potency for such an action. Both compound 1(*S*) and compound 4(*R*) are very potent DA-autoreceptor stimulants but are nonselective, i.e., they also stimulate central postsynaptic DA receptors (Table III, motor activity). From our previous paper on racemic, monophenolic octahydrobenzo[*f*]quinolines, it is quite clear that the 7-OH-trans compound is far more active than its cis analogue.[21] This result is confirmed in the present study on the resolved analogues. The result from the X-ray crystallography[22] is in agreement with the geometrical assignments for cis and trans in our previous study (Figures 4a and 4b).

The most potent trans enantiomer is 6(4a*S*,10b*S*). According to the discussion of the less active aminotetralins above (1(*R*) and 4(*S*)), the activity of 6(4a*R*,10b*R*) might be explained by optical impurity (4.4%) from the more active enantiomer. Compound 6(4a*S*,10b*S*) nonselectively stimulates both DA autoreceptors and postsynaptic DA receptors in the central nervous system (Table III, ED_{50} and motor activity, respectively). Both cis enantiomers have weak biochemical effects. However, the tendency for activity of the racemic compound[21] seems to derive from the 5(4a*R*,10b*S*) enantiomer.

These results give further support for the hypothesis that central DA receptors (autoreceptors as well as postsynaptic receptors) prefer flat molecules (e.g., apomorphine, aminotetralins, and *trans*-1,2,3,4,4a,5,6,10b-octahydrobenzo[*f*]quinolines) before bulkier ones (e.g., the *cis*-1,2,3,4,4a,5,6,10b-octahydrobenzo[*f*]quinolines). Assuming that both the cis and the trans compounds are in their preferred conformations (which is implied from X-ray studies according to Figures 4a and 4b), both the cis and the trans isomers have their nitrogen atom approximately 0.2 Å from the plane of the aromatic ring (Dreiding models). Thus, one explanation for the differences in potency between the cis and the trans isomers could be steric interaction between the piperidine ring of the cis enantiomers and the DA receptor(s).

When drawing the structures as depicted in Figure 5, one might argue, from the result of the totally inactive cis enantiomer 5(4a*S*,10b*R*), which has its piperidine ring downwards, that the central DA receptor is very sensitive to protrusions under the plane of the aromatic ring. Protrusions above this plane might not be as detrimental, but on the other hand, the low activity of compound 5-(4a*R*,10b*S*) could be explained by improper sterical arrangement around carbon 4a. Both of the potent enantiomers in Table III (1(*S*) and 6(4a*S*,10b*S*)), which have their 5-hydroxy-2-aminotetralin moiety incorporated in their structures, have the *S* configuration at this carbon atom.

Other possible structural aspects which might be important for the low activity of the cis enantiomers (5) are the improper direction of the nitrogen lone pair of electrons or, more likely under physiological conditions, the sterically unhindered direction of the nitrogen positive charge or the direction of the nitrogen substituent.

In our previous study on racemic 1, 4, and 6 the ED_{50} values of these compounds in the limbic system were determined to be 11, 27, and 130 nmol/kg, respectively.[21]

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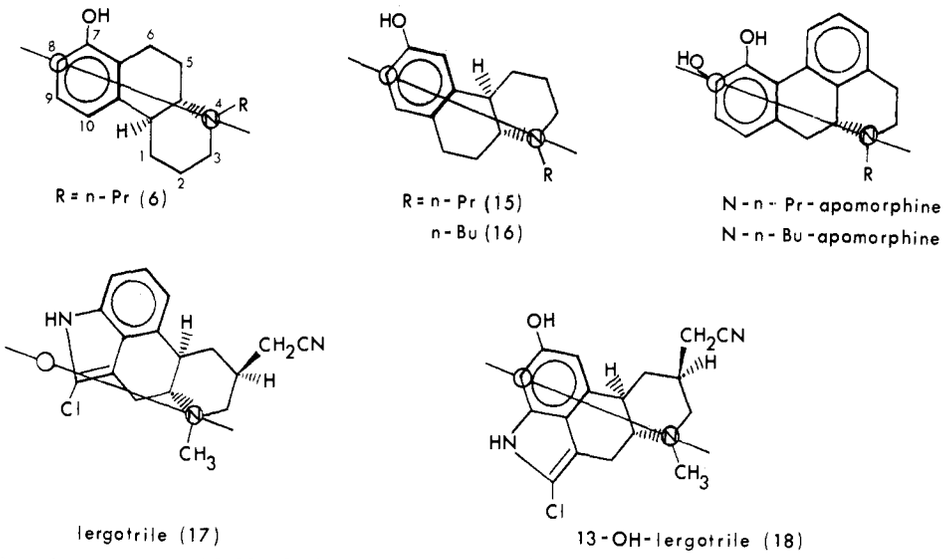

Figure 5. Dopaminergic structures with N-substituents in two main directions.

When deriving the ratios between these values and those of the more active enantiomers in the present study, one gets 3, 3, and 9, respectively. The tetralin ratios are feasible, but the ratio 9 for compound **6**(4a*S*,10b*S*) is far too high to be interpreted in terms of one enantiomer being completely inactive. There may be some antagonism or competitive inhibition between the two enantiomers of the racemic compound **6**. Further pharmacological studies are needed to clarify this possibility.

Both enantiomers of **14** have been included together with apomorphine as reference compounds in this study (Table III). The interesting feature of **14**(*S*) is not only that it stimulates DA autoreceptors but rather that it does not stimulate postsynaptic DA receptors even at very high doses (in fact, it blocks them). In a recent paper we describe the pharmacological effects of a series of resolved *N*-alkyl analogues of **14**.[20] From the *S* enantiomers of this series it is implicated that the liability of these compounds to stimulate postsynaptic DA receptors is strongly dependent on the N-substituent. Substituents being larger (or bulkier) than *n*-propyl give postsynaptically active compounds. This shows that lipophilic and/or steric factors might alter affinity and/or intrinsic activity of these compounds at the postsynaptic receptors. The balance between the agonistic and antagonistic effects at these receptors is obviously altered by the N-substitution pattern of the phenylpiperidines.

These considerations clearly demonstrate that one must be very cautious when looking for the preferred rotamer and conformation of **14**(*S*), in the search for the structural elements which confer autoreceptor selectivity to a dopaminergic compound.

The potent trans compound **6**(4a*S*,10b*S*) has the same absolute configuration at carbon 4a as has **14**(*S*) at the corresponding carbon atom, but still it shows postsynaptic DA-receptor stimulation (Table III, motor activity).

From previous studies[21] we know that racemic *trans*-9-hydroxy-4-*n*-propyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[*f*]-quinoline (**15**) is a very potent compound (ED_{50} limbic = 8 nmol/kg). The corresponding cis compound is equipotent to **14** (ED_{50} limbic = 2.000 nmol/kg). McDermed's receptor model would predict that the more active enantiomer of the 9-OH-trans analogue is 4a*R*,10b*R* (Figure 5). In preliminary studies in our laboratories, this has been confirmed. In considering the corresponding cis enantiomers, the protruding piperidine ring in these molecules presents a more complicated picture (see above). Assuming that no protrusions are accepted by the receptor downwards, one would predict 4a*S*,10b*R* to be the more active enantiomer.

An assumption which can be made from Figure 5 is that, due to the different directions in which the N-substituents of these compounds point, the space available for the N-substituent of compound **15** might be more restricted than for the corresponding 7-OH analogue **6**. Previous studies[21] show that racemic *trans*-4-*n*-butyl-7-hydroxy-1,2,3,4,4a,5,6,10b-octahydrobenzo[*f*]quinoline (**13**) is more potent than its 4-*n*-propyl analogue **6** in the assays of DA activity. However, the N-substituent of apomorphine (Figure 5) is oriented in much the same direction as is the N-substituent of compound **15**. Knowing that *N*-*n*-butylapomorphine[30] is dopaminergically inactive, one would predict the same loss of activity for the tricyclic compound *trans*-4-*n*-butyl-9-hydroxy-1,2,3,4,4a,5,6,10b-octahydrobenzo[*f*]quinoline (**16**). This was the reason that this compound was synthesized and tested.

Interestingly, compound **16** exhibits no dopaminergic effects in the central nervous system in our models (Table III). At the 50 μmol/kg dose, a behavioral effect was observed in the motility meters. However, this effect which consisted of compulsive head twitches and forepaw movements (piano playing) was not mediated by DA receptors since it was not blocked by haloperidol pretreatment (Table III, footnote *j*).

Another class of centrally acting dopaminergic compounds is the ergots. Strong evidence has been presented that the pyrrolylethylamine moiety of the ergots is crucial for dopaminergic activity.[2-4] The fitting of the ergots into the central DA receptor according to the prerequisites of McDermed et al.[12,13] and Bach et al.[3,4] is given in Figure 5.

As seen from this figure, the ergots have to be turned around an axis, through the basic nitrogen and perpendicular to the plane of the aromatic rings, to position the indole nitrogen properly for the assumed hydrogen bond interaction with a receptor subunit. This rotation places the N-substituent of the ergots downwards, i.e., in the same direction as apomorphine and compound **16**. It is known that ergolines[31] and oxaergolines[32,33] are much less active

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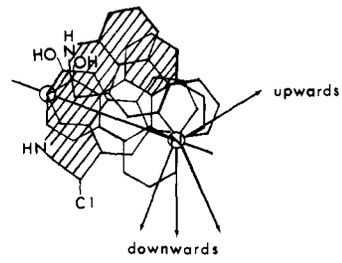

Figure 6. Dopaminergic structures superimposed.

with the N-substituent *n*-butyl than they are with the N-substituent *n*-propyl. This is in agreement with the dopaminergic inactivity of both *N*-*n*-butylapomorphine and compound **16**.

The ergoline lergotrile (**17**) is a centrally acting dopaminergic compound.[34] Moreover, lergotrile (**17**) is known to be hydroxylated in vivo in position 13 to give a molecule (**18**) which is even more potent than lergotrile itself.[35,36] By comparison of compounds **15** and **18**, it is seen that these molecules have the *trans*-9-hydroxy-1,2,3,4,4a,5,6,10b-octahydrobenzo[*f*]quinoline skeleton in common. One might speculate that the potent lergotrile metabolite **18** fits into the DA receptor in the same way as the very potent tricyclic compound **15**.[21] By superimposing the active enantiomers of compounds **1**, **4**, **6**, **15**, **17**, **18**, and apomorphine according to the prerequisites stated above, one creates a three-dimensional total volume of active structures, which might be looked upon as the complement of the DA-receptor structure volume (Figure 6). Some parts of this structure seem to be well defined by previous studies, while others are still open to discussion. The well defined portions are as follows: (1) aromatic nucleus with a *m*-OH phenolic function or a pyrrole or pyrrazole ring mimicking these two functions; (2) a proper distance (extended phenylethylamine) between the aromatic nucleus and the basic nitrogen; (3) two main positions for the N-substituent(s) (upwards or downwards in Figure 6), one of which (downwards) is sterically restricted to accommodate maximally an *n*-propyl group or a piperidine ring, but not for instance *n*-butyl, whereas the other direction (upwards) has less restricted demands (cf. also ref 11 and 20); (4) the stereochemistry of the carbon next to the basic nitrogen (carbon 2 in the 2-aminotetralins, carbon 4a in the *trans*-1,2,3,4,4a,5,6,10b-octahydrobenzo-[*f*]quinolines, carbon 6a in apomorphine and carbon 5 in the ergolines) is critically important. When drawn as in Figures 5 and 6 the active enantiomer in all structures has the direction of the carbon–nitrogen downwards, toward the plane of the paper.

Considering these new prerequisites, previously reported compounds which had been predicted to be active dopaminergic agents from previous models but which proved to be inactive can be reexamined.

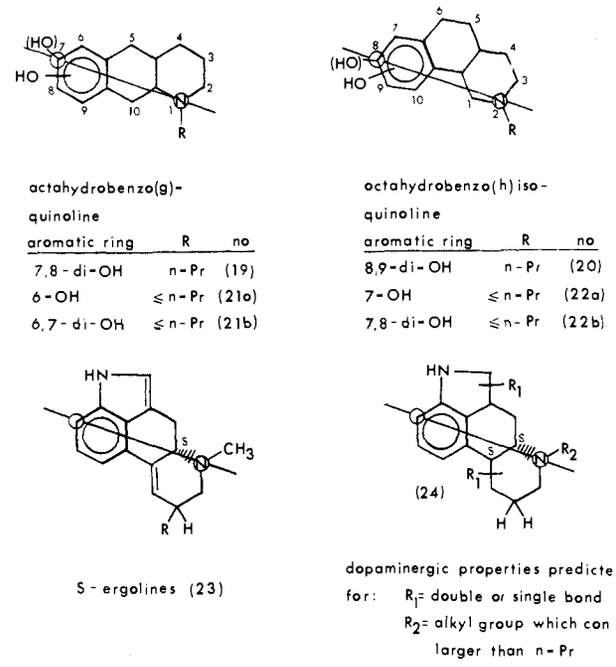

Figure 7. Miscellaneous structures.

The two tricyclic compounds 7,8-dihydroxy-1-*n*-propyl-1,2,3,4,4a,5,10,10b-octahydrobenzo[*g*]quinoline (**19**) and 8,9-dihydroxy-2-*n*-propyl-1,2,3,4,4a,5,6,10a-octahydrobenz[*h*]isoquinoline (**20**) have been reported by Cannon et al. to have no or weak dopaminergic properties (Figure 7).[37,38] The reason for this might be steric. When fitting these molecules into the proposed receptor model, both molecules should be turned around 180° (upside down) to get the hydroxyl function at carbon 8 (compound **19**) and 9 (compound **20**), respectively, into proper position for hydrogen bond interaction with the receptor. When doing so, carbon 2 (compound **19**) protrudes outside the very well-defined piperidine cavity and carbon 5 (compound **20**) possibly interacts sterically in the area where the obstacle of McDermed's receptor model is located.[12] A convenient way to visualize this (in two dimensions) is to get a copy of the structures on a transparency and put it upside down over a drawing of the proposed receptor model, with the prerequisites of this model in mind.

The model also predicts compounds 6-hydroxy(and 6,7-dihydroxy)-1,2,3,4,4a,5,10b-octahydrobenzo[*g*]quinoline (**21a** and **21b**, respectively) and 7-hydroxy(and 7,8-dihydroxy)-1,2,3,4,4a,5,6,10a-octahydrobenz[*h*]isoquinoline (**22a** and **22b**, respectively) to be dopaminergic compounds (Figure 7). As to the N-substituents of these molecules, the model predicts that both structures could have N-substituents ≤ *n*-propyl, i.e., the corresponding *n*-butyl analogues should be inactive (protrudes downwards in the piperidine cavity). Compound **21b** with the *N*-*n*-propyl substitution has been reported to have dopaminergic properties.[39]

If the model is correct, it should also predict the chirality of the more active enantiomer at the chiral carbon atom next (or closest) to the basic nitrogen. For compounds **21a** and **21b** this would be carbon 10a*R*. With the prerequisite

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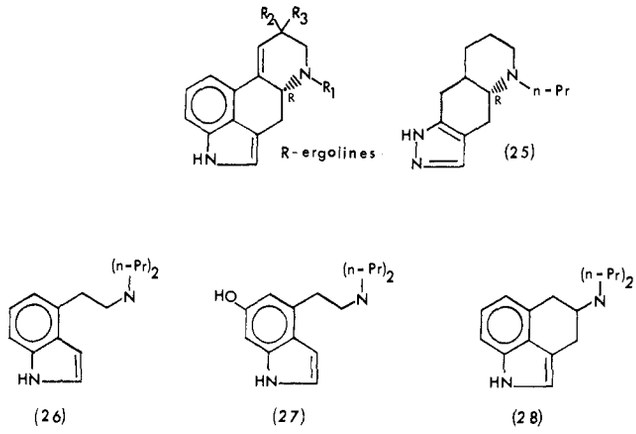

Figure 8. Dopaminergic moiety of ergolines.

of a downwards direction of the carbon–nitrogen bond and a flat molecule (trans), the prediction would be that compounds **22a** and **22b** are active in their 4a*R*, 10b*R* form (Figure 7).

The natural ergolines have the 5*R* configuration at the chiral carbon closest to the basic nitrogen.[40] The 5*S* enantiomers are known to be inactive.[41] These unnatural ergolines (**23**) should be turned around 180° (upside down) relative to the natural ones to satisfy the stereochemical demands of the receptor model. In doing so a sterically perfect fit is gained for the indole nitrogen at the hydrogen bonding site and also for the piperidine ring in the well-defined cleft. However, the 8-substituent probably constitutes a severe steric hindrance in this cleft, thus preventing the necessary fit to obtain a receptor-mediated response. One would thus predict that compounds of the general structure **24**, lacking the 8-substituent, would show dopaminergic activity.

There has been considerable interest lately as to which is the dopaminergic structural moiety of the natural ergolines.[2-4,42,43] Some groups[2-4] claim (from stereochemical and partial structure considerations) that it is the pyrrolylethylamine moiety which confers dopaminergic properties to this class of compounds, while others[42] (from partial structures only) claim that it is the phenylethylamine or rather indolylethylamine partial structure which is the important one (see Figure 8).

When considering the stereochemical aspects, which have been shown to be very critical for tetralins, aporphines, and octahydrobenzo[*f*]quinolines in this context (this paper), one sees that the pyrrolylethylamine moiety should have the 4a*R* configuration to match the natural (5*R*)-ergolines. This has been shown to be the case for a pyrrazole analogue (**25**) of the pyrrolylethylamine moiety of these ergolines.[44]

Also, the partial ergoline structure 4-[2-(di-*n*-propylamino)ethyl]indole (DPAI; **26**) in the context of the

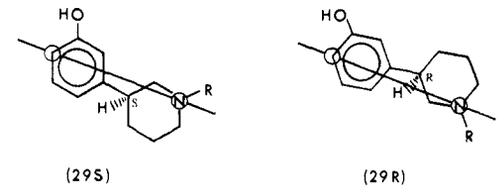

Figure 9. DA receptor fit for resolved 3-(3-hydroxyphenyl)-piperidines.

prerequisites stated above for dopaminergic compounds, it is obvious that a perfect fit of this compound, in all aspects, is gained when superimposing its structure over the 8-nonsubstituted unnatural (*S*)-ergolines (**24**). It is thus our proposal, from the hypothetical DA-receptor model stated above, that the dopaminergic activity exhibited by DPAI (**26**) emanates from this fit and/or from the metabolic activation to its tentative 6-OH metabolite **27**.[45]

The dopaminergic compound **28** of the tetrahydrobenz[*cd*]indolamine class[3,46] can fit both the (*R*)-(pyrrolylethylamine moiety) and the (*S*)-ergolines (phenethylamine moiety). This compound has yet not been resolved, but it is predicted that both enantiomers should exhibit dopaminergic properties, though the potency ratio between the enantiomers is hard to predict.

We will now attempt to apply this receptor model to explain the complicated SAR presented recently for the resolved monophenolic phenylpiperidines[20] (Figure 9). Knowing that these compounds have low rotational barriers between the aromatic ring and the piperidine ring,[47] it is possible to superimpose compound 14(*S*) completely over compound 6(4a*S*,10b*S*) with a small energy input. This explains why 14(*S*) can accommodate, without losing activity, N-substituents being larger or bulkier than *n*-propyl. On the other hand, for its enantiomer 14(*R*) the piperidine ring must be rotated around 180° (upside down) to get the proper direction of its C2–N bond, i.e., downwards. This places the N-substituent in the well-defined piperidine cleft (see above) and would mean that 14(*R*) can have only N-substituents equal to or smaller than *n*-propyl. Bulkier substituents would not be accommodated and thus induce a rotation out of this cleft. An alternative way for the *R* enantiomers with N-substituents larger than *n*-propyl to fit the DA receptor must be possible since they are still dopaminergically active, though less so than their corresponding *S* enantiomers.

The proposed model does not take into consideration all the subpopulations of DA receptors currently under discussion in the literature. It simply deals with the concept of central pre- and postsynaptic receptors according to the pharmacological models used. It seems as if the distinction between these two receptor types, apart from differences in location, is a matter of receptor sensitivity, since even analogues of 14(*S*) can exhibit postsynaptic effects, provided that the N-substituent is large enough to interact in the presumably lipophilic region (upwards). The proposition of Carlsson,[48] that the pre- and the postsynaptic receptors have a common origin and differ only in terms of receptor sensitivity, which might reflect different receptor conformations,[49] seems thus to

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be supported by the phenylpiperidine series. Compounds in the *S* series having N-substituents smaller than or equal to *n*-propyl stimulate presynaptic DA receptors at low doses; i.e., they exhibit both affinity and intrinsic activity at these receptors. At high doses they block postsynaptic DA receptors, which implies affinity but low or no intrinsic activity at these receptors. Compounds with larger N-substituents stimulate both pre- and postsynaptic DA receptors; i.e., they exhibit both affinity and intrinsic activity at both receptor types.

In light of the potent centrally acting dopaminergic compound **15**, the lack of central dopaminergic properties of a series of N-alkylated *trans*-8,9-dihydroxy-1,2,3,4,4a,5,6,10b-octahydrobenzo[*f*]quinolines related to **15** (Figure 5), even at very high doses, is unexpected.[50] In addition, these compounds were very potent in a model measuring peripheral dopaminergic effects. One possible explanation for these observations could be that the models used for monitoring central effects were all postsynaptic in nature. No experiments were performed to reveal central presynaptic effects in this study. Thus, the compounds in this series might be selective for DA autoreceptors. Since all compounds were tested in their racemic form, an alternative explanation for the lack of central effects might be antagonistic interaction of one enantiomer upon the other.

In conclusion, the intense work in the field of dopaminergic compounds of many medicinal chemistry groups throughout the world has led to a number of hypothetical receptor models, one of which is presented in this paper. Hopefully, these models will help guide chemists in the synthesis of more selective and more active pharmacological entities, which might ultimately lead to the development of better drugs to ameliorate diseases connected with disturbances in dopaminergic function in the central nervous system.

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 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 (Supelco, Inc.) was used throughout. HPLC was performed on a Waters 5 Si 10 column using hexane/EtOAc/EtOH (different compositions) as the mobile phase, working in the pressure range 1000–3000 psi and with the flow rate of 2 mL/min. Detection was made by a Waters Model 440 UV monitor. Optical purity was estimated by comparing peak areas (height times width at half-height). Optical rotation was measured with a Perkin-Elmer 141 polarimeter equipped with a thermostat (22 °C).

The elemental analyses (C, H, N) for the new substances 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.

β-Phenyl-γ-butyrolactone (7).[24] Sodium acetate (190 g, 2.3 mol) was added to EtOH (2.300 mL) and to this mixture α-chloroacetophenone (300 g, 1.6 mol) was added before refluxing for 12 h and evaporating off the solvent. Water (1000 mL) was added and the mixture was extracted with toluene (2 × 500 mL). The organic layer was dried and filtered and the solvent was removed under reduced pressure. The residue was distilled (0.5 mmHg; bp 110 °C), yielding 172 g (60%) of 2-oxo-2-phenylethyl acetate (8).

Triethyl phosphonoacetate (13 g, 60 mmol) was added dropwise to NaH (2.5 g of 55%, 57 mmol) in dry toluene (20 mL). During the preparation of the NaH–phosphonoacetate mixture hydrogen was evolved and the temperature was kept below 35 °C. This mixture was stirred for 1 h before the dropwise addition of the distilled keto ester 8 from above (10 g, 56 mmol). Temperature was kept below 30 °C and the reaction mixture was stirred in room temperature overnight before warming to reflux and then allowing to cool to 60 °C. The toluene phase was decanted and this procedure was repeated (2 × 50 mL). The toluene phases were collected, and the solvent was evaporated, giving 13 g (96%) of the desired α,β-unsaturated ester having a 17:76 ratio of cis/trans (or vice versa) according to GLC. This product was reduced in HOAc, in a Parr apparatus, using Pd/C (10%) as catalyst. Filtration and evaporation gave 11 g (87%) of the reduced product, which was hydrolyzed and lactonized in an hour in a mixture of 4 N H_2SO_4 (60 mL) and dioxane (60 mL). After cooling, extraction with toluene, evaporation of the solvent and distillation in vacuum (0.1 mmHg, bp 110–114 °C) gave 5.0 g (70%) of the desired compound **7**.

Resolution of compound **7** was performed with α-phenylethylamine as described by Helmchen et al.[24] The separation factors in Table I were determined with the racemic lactone **7**.

(*S*)-(−)-7-Methoxy-2-(*n*-propylamino)tetralin (9(*S*)) (Method A). (*R*)-(−)-*O*-methylmandelic acid (3.6 g, 22 mmol) was dissolved in CH_2Cl_2 (100 mL), and $SOCl_2$ (30 mL) was added and the mixture was refluxed for 30 min. Excess $SOCl_2$ was evaporated and the residual acid chloride was dissolved in CH_2Cl_2 (100 mL). This solution was added at 20 °C to a rigorously stirred mixture of 7-methoxy-2-(*n*-propylamino)tetralin hydrochloride (5.0 g, 20 mmol), CH_2Cl_2 (100 mL), and 5% NaOH (200 mL). After 15 min of stirring, the phases were separated, and the organic phase was washed once with water and dried (Na_2SO_4). Filtration and evaporation of the solvent gave 6.3 g (88%) of the diastereomeric amides as an oil, which was chromatographed on SiO_2 (0.040–0.063 mm), using light petroleum–ether (1:1) as eluant.

The fractions containing one of the two diastereomers, which is eluted first in at least 98% optical purity, were combined, and the solvent was evaporated, giving 1.2 g (17%) of the desired diastereomeric amide as an oil. The optical purity of this oil was determined by HPLC (hexane/EtOAc/EtOH, 91:7.5:1.5) to be 99.7%. This oil (1.1 g, 2.9 mmol) was dissolved in dry THF (100 mL) and potassium *tert*-butoxide (2.1 g, 18 mmol), and water (0.16 mL (8.8 mmol) was added with stirring at room temperature. The mixture was stirred at this temperature overnight and was then partitioned between ether and water. The organic layer was extracted with 5% HCl and the water phase was alkalinized (10% Na_2CO_3) and extracted with ether. The organic layer was separated and dried (Na_2SO_4), and the solvent was evaporated. The residual oil was converted to the hydrochloride by the addition of HCl-saturated EtOH. Evaporation of the solvent and recrystallization from EtOH–ether gave 0.23 g (32%). The acidic ether phase from above was dried (Na_2SO_4) and the solvent was evaporated, leaving an oil (0.55 g) which contained a nonbasic compound with an intermediate retention time (t_R = 5.3 min) on GLC (OV-17; 200 °C for 1 min; 320 °C; 40 mL/min) between the starting amide (t_R = 8.2 and 8.4 min) and the amine product (t_R = 2.4 min).

This compound is probably the *N*-formyl derivative, an analogue of which has previously been detected and characterized.[20] This oil was dissolved in dry THF (25 mL), and 2 equiv of MeLi (1.6 M in hexane) was added at room temperature. The reaction mixture was quenched with H_2O after 15 min and acidified with 10% HCl. The acidic water was washed with ether, alkalinized (10% Na_2CO_3), and extracted with ether. The organic layer was separated and dried (Na_2SO_4), and the solvent was evaporated. The residue was converted to its hydrochloride, evaporated, and recrystallized (EtOH–ether), giving 185 mg (25%) of the desired product, i.e., the total yield in the amide cleavage step was 57%.

(*S*)-(−)-7-Hydroxy-2-(di-*n*-propylamino)tetralin (4(*S*)) (Method B). Ten milliliters of CH_2Cl_2 and 10 mL of 5% NaOH were added to compound 9(*S*)·HCl (185 mg, 0.72 mmol). With vigorous stirring, propionic acid chloride (160 μL, 1.9 mmol) was

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added. After 30 min the organic layer was separated and dried (Na_2SO_4), and the solvent was evaporated, yielding an oil (0.20 g, 100%) which was dissolved in anhydrous ether (20 mL) and reduced with $LiAlH_4$ (0.20 g, 5.3 mmol). Workup in the usual way gave an oil (170 mg, 90%) which was dissolved in CH_2Cl_2 and chilled to −70 °C. At this temperature BBr_3 (0.30 mL, 3.1 mmol) was added with stirring. The reaction mixture was allowed to reach room temperature overnight and thereafter workup was made by the addition of H_2O, alkalinization (10% Na_2CO_3 until pH reached 10), and CH_2Cl_2 extraction. The organic layer was separated and dried (Na_2SO_4), and the solvent was removed under reduced pressure, leaving an oil which was chromatographed (SiO_2) with MeOH as eluant. The pure fractions were pooled, and the solvent was evaporated. The residue was converted to the hydrochloride by the addition of HCl-saturated EtOH and evaporation. Recrystallization (acetone–EtOAc) gave 103 mg (56%) of the desired 4(*S*)·HCl.

***cis*-(4a*S*,10b*R*)-7-Methoxy-1,2,3,4,4a,5,6,10b-octahydrobenzo[*f*]quinoline (10(4a*S*,10b*R*)) (Method A).** *cis*-7-Methoxy-1,2,3,4,4a,5,6,10b-octahydrobenzo[*f*]quinoline hydrochloride[21] (2.5 g, 9.7 mmol) was converted to its (*R*)-(−)-*O*-methylmandelic amide as described for compound 9(*S*) above, yielding 4.4 g (theoretically 3.5 g), which was chromatographed (SiO_2) with light petroleum/ether (first with 1000 mL of the composition 2:1 and then throughout with the composition 1:1). Fractions (15 mL) were collected, and isomer 1 was recovered from fractions (240–290 (1.6 g, 45%) and was 100% optically pure. Fractions 325–380 were pooled and evaporated, giving 1.3 g (36%) of isomer 2 with the optical purity 98.7%. Isomer 1 above (1.5 g, 1.4 mmol) was dissolved in dry THF (100 mL) and treated with potassium *tert*-butoxide (6.4 g, 57 mmol) and H_2O (0.52 mL, 29 mmol) as described for the preparation of 9(*S*).

Formation of the intermediate *N*-formyl derivative (t_R = 3.5 min) as well as racemization of the starting amide (t_R = 9.2 and 9.7 min) took place during amide cleavage according to GLC (OV-17, 250–300 °C, 10 °C/min, 30 mL/min) (cf. 9(*S*) above). The reaction was not complete until more potassium *tert*-butoxide (1.0 g, 8.9 mmol) had been added and the reaction mixture refluxed for 2 h. The product was isolated as the hydrochloride (0.45 g, 43%).

***cis*-(4a*S*,10b*R*)-7-Methoxy-4-*n*-propyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[*f*]quinoline (11(4a*S*,10b*R*)) (Method C).** $NaBH_4$ (0.40 g, 11 mmol) was added protionwise with stirring to a solution of propionic acid (1.7 mL, 22 mmol) in dry benzene (25 mL). The temperature was kept below 15 °C for 2 h and then optically pure 10(4a*S*,10b*R*)·HCl (0.25 g, 0.99 mmol) was added and the mixture was refluxed for 4 h. The reaction mixture was allowed to reach room temperature and excess 2 N NaOH was added. After being stirred for 30 min, the reaction mixture was extracted with ether, all the organic phases were mixed and dried (Na_2SO_4), and the solvent was evaporated, giving an oily residue, which was converted to the hydrochloride. Recrystallization from EtOH/ether gave the desired product (0.19 g, 65%).

***trans*-(4a*R*,10b*R*)-7-Methoxy-1,2,3,4,4a,5,6,10b-Octahydrobenzo[*f*]quinoline (12(4a*R*,10b*R*)) (Method A).** *trans*-7-Methoxy-1,2,3,4,4a,5,6,10b-octahydrobenzo[*f*]quinoline hydrochloride[21] (0.50 g, 2.0 mmol) was converted to its (*R*)-(−)-*O*-methylmandelic amide was described for compound 9(*S*) above, yielding 0.77 g (theoretically 0.72 g). When ether was added to this oil, crystals melting at 151–153 °C were precipitated (0.20 g, 28%). The optical purity of these crystals was found by HPLC to be 96.3%.

This crystalline amide (0.19 g, 0.52 mmol) was dissolved in dry THF (20 mL) and treated with potassium *tert*-butoxide (0.81 g, 7.1 mmol) and H_2O (64 μL, 3.6 mmol) as described for the preparation of 9(*S*). Formation of the intermediate *N*-formyl derivative (t_R = 5.1 min) was indicated from GLC (OV-17, 250 °C for 3 min, 20 °C/min, 300 °C, 34 mL/min) (cf. 9(*S*) above). This intermediate was consumed during reflux (1 h) and workup gave the desired compound 12(4a*R*,10b*R*) as its hydrochloride (120 mg, 87%).

***trans*-(4a*S*,10b*S*)-7-Methoxy-1,2,3,4,4a,5,6,10b-octahydrobenzo[*f*]quinoline (12(4a*S*,10b*S*)) (Method A).** The solvent from the collected mother liquors from the isolation of crystalline isomer 1 above was evaporated off, giving an oil (0.26 g, 0.71 mmol). This oil was dissolved in CH_2Cl_2 (2 ml) and mobil phase (4 mL of hexane/EtOAc/EtOH with the composition 95.5:3.75:0.75). One milliliter of this solution was applied to a Waters semipreparative HPLC (SiO_2, 8 mm inner diameter) column using a flow rate of 3 mL/min.

Fractions (2 mL) were collected, using UV detection to indicate the start of sample collection. Fractions 4–9 were pooled in six consecutive runs, giving after solvent removal 0.16 g (22%) of isomer 2 with the optical purity 98.2%. Amide cleavage was performed as described for compound 12 (4aR;10bR) above, yielding 55 mg (50%) of the desired product as the hydrochloride.

Demethylation of Methoxy Compounds. Method D. The phenols were obtained by heating the appropriate methoxy compound in 48% aqueous HBr for 2 h at 125 °C under nitrogen. The hydrobromic acid was evaporated and the residue was recrystallized. Alternatively, the residue was alkalized (10% Na_2CO_3) to pH 10 and extracted with ether or EtOAc. The organic layer was separated and dried. After filtration the solvent was evaporated, leaving an oil, which was converted to its hydrochloride by using ethereal HCl. Evaporation of the solvent and recrystallization gave the desired product.

Method E. The base of the appropriate methoxy compound was dissolved in CH_2Cl_2 and the solute was chilled to −70 °C. At this temperature 2 equiv of BBr_3 was added and the temperature was allowed to reach room temperature (overnight). The reaction mixture was quenched with water. The mixture was alkalized (10% Na_2CO_3) to pH 10 and the organic layer was worked up as described under method D above.

Estimation of the optical purity of the secondary amines was performed as previously described.[20]

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 all solutions had neutral pH (except for the solutions of reserpine).

Biochemistry. The biochemical experiments and the determinations of Dopa and 5-HTP by means of HPLC with electrochemical detection were performed as previously described.[20] Separate dose–response curves based on four to six dose levels for each substance (sc administration) and brain area were constructed. From these curves was estimated the dose of the drug yielding a half-maximal decrease of the Dopa level, the ED_{50} value (Table III).

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.[11,29] Eighteen hours prior to the motility testing (carried out between 9 a.m. and 1 p.m.), the rats were intraperitoneally injected with reserpine (5 mg/kg). The different compounds under investigation were administered subcutaneously in the neck region (n = 4). Immediately after drug administration, the rats were placed in the test cages (one rat/cage) and put into the motility meters. Motor activity was then followed and recorded for the subsequent 30 min. The results are presented in Table III.

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Registry No. 1(*R*), 69367-51-7; 1(*R*)·HCl, 58349-18-1; 1(*S*), 68643-08-3; 1(*S*)·HCl, 58349-19-2; 4(*R*), 82730-72-1; 4(*R*)·HCl, 93503-06-1; 4(*S*), 82730-73-2; 4(*S*)·HCl, 93503-07-2; 5(4a*R*,10b*S*), 93601-80-0; 5(4a*R*,10b*S*)·HCl, 93711-33-2; 5(4a*S*,10b*R*), 93601-81-1;

5(4aS,10bR)·HCl, 93711-34-3; 6(4aR,10bR), 93601-82-2; 6-(4aR,10bR)·HCl, 93711-35-4; 6(4a5,10bS), 93601-83-3; 6-(4aS,10bS)·HCl, 93711-36-5; 7, 93601-84-4; 8(R), 93601-85-5; 8(S), 93601-86-6; 9(R), 93503-08-3; 9(S), 93503-09-4; 10(4aR,10bS), 93601-87-7; 10(4aS,10bR), 93601-88-8; 11(4aR,10bS), 93601-89-9; 11(4aS,10bR), 93601-90-2; 12(4aR,10bR), 93601-91-3; 12(4aS,10bS), 93601-92-4; 16, 93503-11-8; 16·HBr, 93503-10-7; 2-oxo-2-phenylethyl acetate, 2243-35-8; α-chloroacetophenone, 532-27-4; triethyl phosphonoacetate, 867-13-0; (E)-4-acetoxy-3-phenyl-2-butenoic acid ethyl ester, 72335-13-8; (Z)-4-acetoxy-3-phenyl-2-butenoic acid ethyl ester, 72335-15-0; 4-acetoxy-3-phenylbutanoic acid ethyl ester, 93503-12-9; (R)-O-methylmandelic acid, 3966-32-3; (±)-7-methoxy-2-(propylamino)tetralin hydrochloride, 93601-93-5; (S)-7-methoxy-2-(propylamine)tetralin (R)-O-methylmandelamide, 93503-13-0; (R)-7-methoxy-2-(propylamine)tetralin (R)-O-methylmandelamide, 93503-14-1; (S)-N-propionyl-7-methoxy-2-(propylamine)tetralin, 93503-15-2; (S)-7-methoxy-2-dipropylamino)tetralin, 93601-94-6; *cis*-7-methoxyoctahydrobenzoquinoline hydrochloride, 93503-16-3; (4aR,10bS)-7-methoxyoctahydrobenzo[f]quinoline (R)-O-mandelamide, 93503-17-4; (4aS,10bR)-7-methoxyoctahydrobenzo[f]quinoline (R)-O-mandelamide, 93601-95-7; *trans*-7-methoxyoctalhydrobenzo[f]-quinoline hydrochloride, 93503-18-5; (4aR,10bR)-7-methoxyoctahydrobenzo[f]quinoline (R)-O-mandelamide, 93601-96-8.

Substituted 5*H*-Dibenz[*b*,*g*]-1,4-oxazocines and Related Amino Acids with Antiinflammatory Activity

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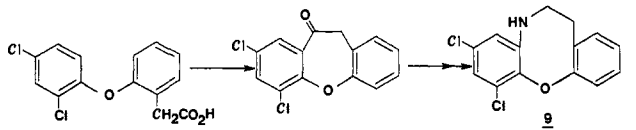
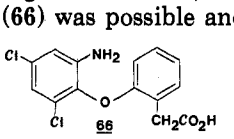
During an investigation of the antiinflammatory properties of a number of tetracyclic derivatives of 6,8-dichlorodibenz[b,f]oxepin-10(11*H*)-one, the ring-expanded 1,3-dichloro-5*H*-dibenz[b,g]-1,4-oxazocine (**9**) was prepared and found to be of considerable pharmacological interest. It was subsequently found that the corresponding ring-opened amino acid **66**, a close analogue of the antiinflammatory agent fenclofenac, also possessed significant antiinflammatory activity, superior both to the dibenzoxazocine and to fenclofenac. These findings prompted extensive synthetic programs in both areas, and a number of derivatives in the amino acid series showed potencies considerably in excess of the standard compound. These phenylacetic acids, however, were significantly more ulcerogenic than fenclofenac whereas the corresponding dibenzoxazocines showed few signs of ulcerogenicity at doses up to 1 g/kg.

In our continuing search for compounds of greater potency than fenclofenac,[1] [2-(2,4-dichlorophenoxy)phenylacetic acid], derivatives of the ring-closed compound 6,8-dichlorodibenz[b,f]oxepin-10(11*H*)-one were prepared. One of these, 1,3-dichloro-6,7-dihydro-5*H*-dibenz[b,g]-1,4-oxazocine (**9**) was found not only to be twice as potent



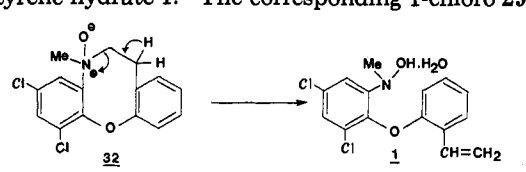
as fenclofenac in the adjuvant arthritis test but also to have no measurable ulcerogenic potential at doses up to 1 g/kg. This was considered to be a lead of considerable importance particularly as it was one of the few nonacidic compounds which showed activity in the adjuvant arthritis test. It was soon realized however that a metabolic breakdown to the corresponding 2-(6-amino-2,4-dichlorophenoxy)-phenylacetic acid (**66**) was possible and this was subsequently confirmed in metabolic studies in rats.[2] The amino acid **66** showed enhanced potency over the corresponding oxazocine **9** in the adjuvant arthritis test, and extensive synthetic programs in both the amino acid and oxazocine series were initiated. This paper describes the synthesis and testing results for these compounds.



Chemistry. The route used to prepare all the NH-substituted oxazocines was that described in Scheme I. Cyclization of the readily available phenoxyphenylacetic acids[1] using polyphosphoric acid gave the corresponding oxepinones which were then treated with sodium azide in sulfuric acid to give the highly insoluble oxazocinones. Without further purification these were reduced with lithium aluminum hydride to give the oxazocines, the majority of which were purified by crystallization of their hydrochloride salts. An alternative scheme involving the Beckman rearrangement of the oximes derived from the oxepinones failed to give satisfactory results.

N-Methyl derivatives of the oxazocines were normally prepared by simple methylation as described in Scheme I, although in one case (compound **28**), formylation and reduction was used. A potentially useful method involving the lithium aluminum hydride reduction of the corresponding *N*-methyloxazocinone gave complex mixtures of products. Other *N*-alkyl, *N*-alkenyl, *N*-acyl, and *N*-benzyl derivatives of the oxazocines were prepared by standard procedures and representative examples are described in the Experimental Section.

Oxidation of the *N*-alkyl compounds **28**, **31**, and **33** with peracid gave the corresponding *N*-oxides **29**, **32**, and **34**. After storage at room temperature for 1 month, compound **32** showed some signs of decomposition and further investigations revealed that heating the free base in ethyl acetate for 10 min resulted in complete decomposition to the styrene hydrate **1**. The corresponding 1-chloro **29** and



N-propyl **34** compounds appeared to be considerably more stable although even in these cases some degre of decomposition was noted after storage for several months.

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(2) Rance, M. J., unpublished results.

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