Monophenolic 2-(Dipropylamino)indans and Related Compounds: Central Dopamine-Receptor Stimulating Activity

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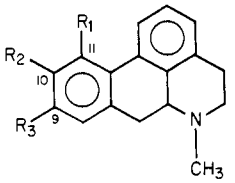
Monophenolic 2-(dipropylamino)indans and related compounds have been synthesized and tested for central dopamine-receptor stimulating activity, using biochemical and behavioral tests in rats and emesis tests in dogs. The active compounds possess similar relative potencies in eliciting the three different dopamine-receptor mediated effects measured. 4-Hydroxy-2-(dipropylamino)indan was the most potent of the new compounds. The corresponding 5-hydroxy analogue was less active. 4-Hydroxy-2-[(dipropylamino)methyl]indan is a new type of dopaminergic agent with a phenylpropylamine moiety in its framework instead of the phenylethylamine structure, common to most dopamine-receptor agonists. This compound was 10–20 times less active than apomorphine. 6,7,8,9-Tetrahydro-1-hydroxy-*N*,*N*-dipropyl-5*H*-6-benzocycloheptenylamine and 5-hydroxy-2-[(dipropylamino)methyl]tetralin were both inactive. Since the intramolecular distances between functional groups in the indans studied here are different from those in, for example, apomorphine, it is concluded that a certain variation of these distances can be accepted by the receptor. It could also be demonstrated that the position of the OH group on the aromatic ring is of importance for the activity and that emetic activity may be associated with dopaminergic agonists of the indan as well as of the tetralin type of structure.

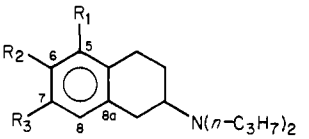
Compounds acting on central dopaminergic receptors may be used as pharmacological tools and may find clinical applications in the treatment of a variety of disorders such as Parkinson's disease, alcoholism, and schizophrenia.[1,2] These possibilities have inititated numerous investigations concerning pharmacology and structure–activity relationships of dopamine (DA) receptor agonists during the last decade. Next to DA itself, apomorphine (1) is the most



	R_1	R_2	R_3
1	OH	OH	H
2	OH	H	H
3	H	OH	H
4	H	H	OH

thoroughly examined DA-receptor agonist. Three reviews covering apomorphine and other central DA-receptor agonists have recently been published.[3-5]

Research efforts aimed at finding the pharmacophore of apomorphine have yielded various structurally simplified analogues, among which the 2-aminotetralins are the most active DA-receptor agonists known at present. McDermed et al.[6] found that the catechol **5** and the monohydroxy derivative **6** were more potent than apomorphine in inducing stereotypy in rats and emesis in dogs. The corresponding 6-hydroxy and 7-hydroxy derivatives **7** and **8** were approximately equipotent to apomorphine in provoking emesis in the dog but considerably less active in inducing stereotypy in the rat.[6] As to the N-substitution, it has recently been established, using behavioral and biochemical methods,[7,8] that *N*,*N*-dipropyl gives maximal dopaminergic activity in the 2-aminotetralin series.



	R_1	R_2	R_3
5	OH	OH	H
6	OH	H	H
7	H	OH	H
8	H	H	OH

A few indan derivatives have also been tested.[9,10] In the 2-aminoindan skeleton the ethylamine moiety has a different conformation from that in apomorphine and in the 2-aminotetralins. Nevertheless, some 2-aminoindan derivatives possess high activity as central DA-receptor agonists. Cannon et al.[9] have found that compounds **9** and **10** are comparable in potency to apomorphine as stereotypy-inducing agents in mice but much less active than apomorphine as emetics in dogs. The pharmacology of **10**

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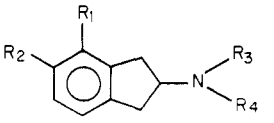


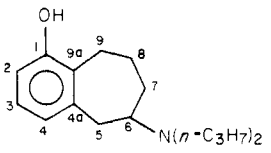
	R_1	R_2	R_3	R_4
9	OH	OH	CH_3	H
10	OH	OH	CH_3	CH_3
11	H	H	n-C_3H_7	n-C_3H_7
24	OH	H	n-C_3H_7	n-C_3H_7
25	H	OH	n-C_3H_7	n-C_3H_7

was further studied by Cheng et al.[10] They concluded that **10** was a directly acting central dopaminergic agent. The aminoindan **11** was prepared and tested by Rusterholz et al.,[11] who observed dopaminergic effects in rats (circling, inhibition of prolactin release) and in dogs (emesis). However, they did not exclude the possibility that **11** was metabolically hydroxylated before exerting its effect.

The 2-aminoindans tested so far have either been catechols or nonhydroxylated derivatives. In a catechol structure, the relative importance of each hydroxyl group cannot be determined. Such information can only be obtained from monohydroxy compounds.

In 4-hydroxy-2-(dipropylamino)indan (**24**), the position of the hydroxyl group can be described as ortho to one of the aromatic/aliphatic ring junctions and meta to one of the ethylamine moieties of the molecule. In the most active monophenolic tetralin derivative, 5-hydroxy-2-(dipropylamino)tetralin (**6**), the hydroxyl group occupies a similar relative position. The nitrogen–oxygen distance, however, is considerably shorter in **24** than in **6**. Thus, the monohydroxy indan derivatives **24** and **25** may be used in studying the importance of the N–O distance and of the position of the hydroxyl group for dopaminergic activity.

The 2-aminoindans can be considered as modified apomorphine fragments. Such compounds may give new information about the structure–activity relationships for dopaminergic agonists, in addition to what can be obtained from compounds retaining the tetralin fragment of the apomorphine skeleton. Therefore, we have also included the ring-expanded 2-aminotetralin analogue **26**, as well as the (aminomethyl)indan **27** and the (aminomethyl)tetralin **28**, in this study. The results are presented in Figure 1 and Tables I–II.



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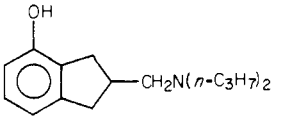

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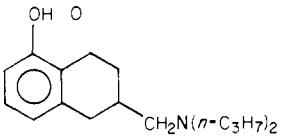

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Chemistry. The compounds studied were synthesized as depicted in Schemes I–III. Oxidation of 6-methoxy-1-indene[12] (**12**) to the trans-diol, followed by acid-catalyzed dehydration, gave 5-methoxy-2-indanone (**13**). Reduction of the enamine resulting from treatment of **13** with dipropylamine yielded 5-methoxy-2-(*N*,*N*-dipropylamino)indan (**14**) (Scheme I).

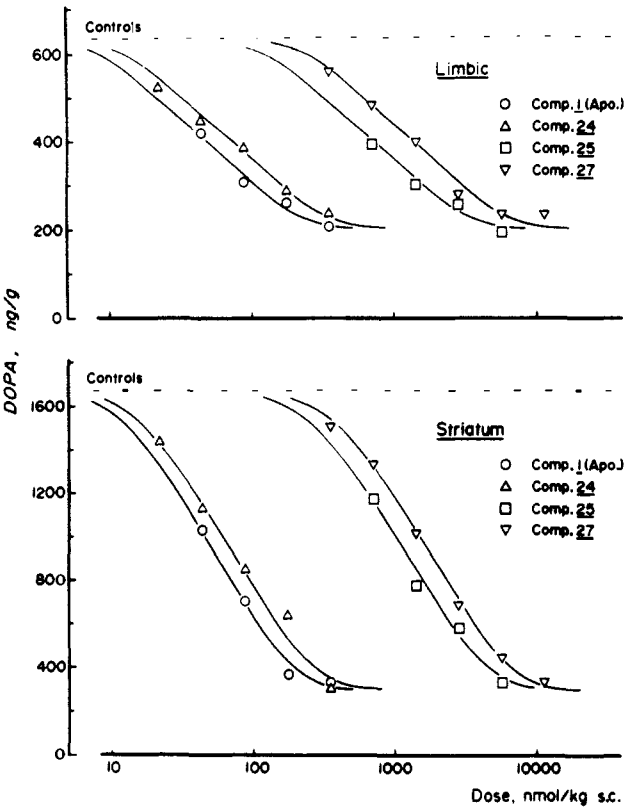
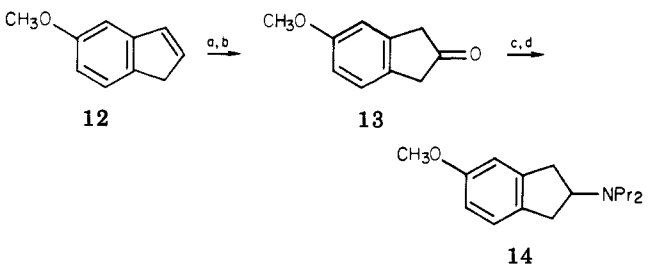


Figure 1. Dose-dependent decreases in rat brain DOPA formation in vivo induced by the active compounds. Shown are the means of two to six experiments; SEM values (not shown) were less than 15% of the means. Control values were 635 and 1670 ng/g in the limbic and the striatal brain parts, respectively. No effects were obtained in the hemispheral parts (results not shown).

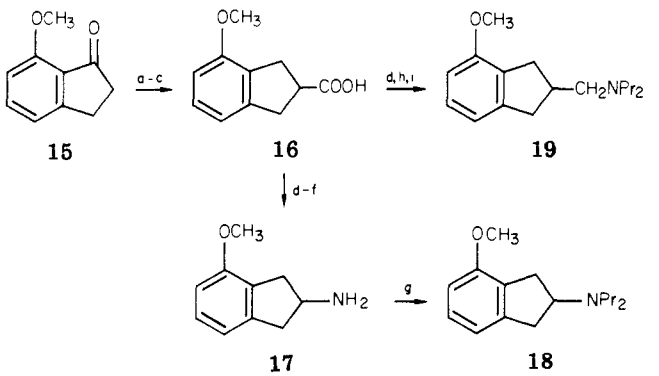
Scheme I[a]



12 **13** **14**

[a] Reagents: a = H_2O_2, HCOOH; b = H_2SO_4, Δ; c = $(C_3H_7)_2NH$, H^+; d = H_2/Pt.

Scheme II[a]



15 **16** **17** **18** **19**

[a] Reagents: a = $(CH_3O)_2CO$, NaH/THF; b = H_2/Pd, H^+; c = NaOH/H_2O/MeOH; d = $ClCOOC_2H_5$; e = NaN_3; f = H^+; g = C_2H_5COOH/$NaBH_4$; h = $(C_3H_7)_2NH$; i = $LiAlH_4$.

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Table I. Physical and Biological Data for the Compounds Studied

compd	yield,[a] %	mp,[b] °C	formula	biochem act. in rats: ED_{50},[c] nmol/kg limbic	ED_{50},[c] nmol/kg striatum	ED_{100},[d] nmol/kg	emetic act. in dogs: TED,[e] nmol/kg	rel k_0[f] (range)
1 (apomorphine)				41[g]	44[g]	230	32.3 ± 6.7	1.0
6				11[h]	9[h]	40[i]	4.7 ± 0.98	0.1 (0.09-0.16)
24	83	204-205	$C_{15}H_{23}NO\cdot HBr$	59	63	350	25.0 ± 6.8	0.9 (0.5-1.2)
25	80	206-207	$C_{15}H_{23}NO\cdot HBr$	1250	1440	6500	247 ± 53	9.9 (7.2-13.8)
26	78	237-238	$C_{17}H_{17}NO\cdot HBr$	I[j]		I		NT[k]
27	58	148.5-149.5	$C_{16}H_{25}NO\cdot HBr$	670	960	4500	292 ± 81	9.1 (6.6-11.4)
28	61	181-182	$C_{17}H_{27}NO\cdot HBr$	I		I		NT

[a] Yield in the demethylation step. [b] Recrystallized from ethanol–ether. [c] Estimated dose giving a half-maximal decrease of the DA synthesis rate in the rat brain part; see Figure 1. [d] Estimated dose giving an approximately maximal decrease of the DA synthesis rate; extrapolated from Figure 1. [e] Total dose at which the animal vomits. Shown are the means ± SEM (n = 3-4). [f] For definition of k_0 see Pharmacology section. Relative k_0 = k_0 (test compound)/k_0 (apomorphine). [g] These values are 190 and 220, respectively, if apomorphine is given 45 min before the administration of NSD 1015 (ref 8). [h] From ref 8. [i] Estimated from the dose-response curve of 6 (unpublished). [j] Inactive, i.e., >45 μmol/kg. [k] Not tested.

Table II. DA-Agonist Induced Motor Activity in Reserpinized Rats at the Biochemical ED_{50} and ED_{100} Dose Levels[a]

compd	accum counts/60 min: at a dose equal to ED_{50}[b]	at a dose equal to ED_{100}[b]
1 (apomorphine)	24 ± 7[c]	64 ± 4[e]
6	25 ± 6[c]	76 ± 15[e]
24	13 ± 5[c]	108 ± 15[e]
25	23 ± 6[c]	89 ± 13[e]
26	NT[d]	NT
27	25 ± 9[c]	89 ± 6[e]
28	NT	NT
control	15 ± 5	

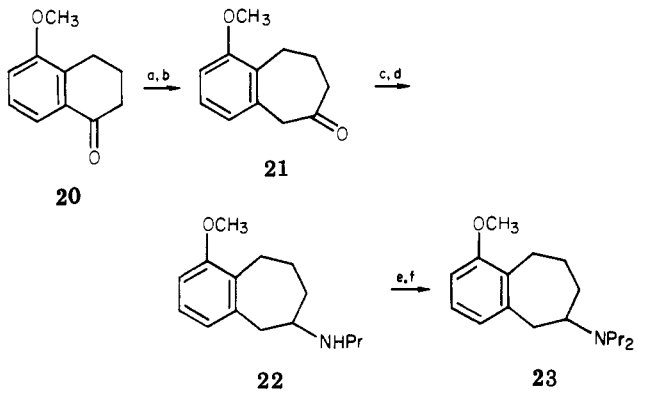
[a] Shown are the means ± SEM (n = 3-4). For statistical comparisons of the results, one-way analysis of variance (ANOVA), followed by Student's t test, was performed. [b] See Table I. [c] Not significantly different from control; $p > 0.1$ or more. [d] Not tested. [e] Significantly different from control; $p < 0.01$ or less.

Attempts to prepare 4-methoxy-2-(*N*,*N*-dipropylamino)indan (**18**) from 7-methoxy-1-indene as described for the 5-methoxy isomer failed, mainly because of the pronounced tendency of 7-methoxy-1-indene to undergo acid-catalyzed polymerization.[13] Therefore, we chose to synthesize compound **18** as depicted in Scheme II. Carboxymethylation of 7-methoxy-1-indanone[14] (**15**), followed by hydrogenolysis of the keto function and alkaline hydrolysis of the ester group, gave 4-methoxyindan-2-carboxylic acid (**16**), which was converted to 2-amino-4-methoxyindan (**17**) via a mild Curtius rearrangement. The primary amine was alkylated with a $NaBH_4$-carboxylic acid complex to give compound **18**.

4-Methoxy-2-[(*N*,*N*-dipropylamino)methyl]indan (**19**) was prepared from compound **16** via a mixed anhydride acylation followed by $LiAlH_4$ reduction of the resulting amide (Scheme II). The same procedure was used for the conversion of 5-methoxytetralin-2-carboxylic acid[15] to 5-methoxy-2-[(*N*,*N*-dipropylamino)methyl]tetralin (see Experimental Section).

Treatment of 5-methoxy-1-tetralone (**20**) with methylenetriphenylphosphorane, followed by oxidative rearrangement with $Tl(NO_3)_3$,[16] gave 6,7,8,9-tetrahydro-1-methoxy-5*H*-benzocyclohepten-6-one (**21**) in excellent yield. Reductive amination of the ketone yielded 6,7,8,9-tetrahydro-1-methoxy-*N*-propyl-5*H*-6-benzocycloheptenylamine (**22**), which was N-acylated and then reduced to give 6,7,8,9-tetrahydro-1-methoxy-*N*,*N*-dipropyl-5*H*-6-benzocycloheptenylamine (**23**) (Scheme III).

Scheme III[a]



[a] Reagents: a = $(C_6H_5)_3P{=}CH_2$/Me_2SO; b = TTN/MeOH; c = $C_3H_7NH_2$; d = H_2/Pt; e = C_2H_5COCl; f = $LiAlH_4$.

The phenols presented in Table I were all prepared from the corresponding methoxy compounds via demethylation in 48% aqueous HBr.

Pharmacology. The compounds were tested for central DA-receptor stimulating activity in reserpinized rats using biochemical and behavioral methods and for emetic activity using nonpretreated dogs.

The biochemical method has been described[8,17] previously. The concept of this method is that a DA-receptor agonist will stimulate the receptor and through regulatory feedback systems effect a decline in tyrosine hydroxylase activity and, thus, a subsequent reduction in the synthesis rate for DA in the presynaptic neuron. DOPA formation, as determined after in vivo inhibition of the aromatic L-amino acid decarboxylase by NSD 1015 (3-hydroxybenzylhydrazine hydrochloride, 100 mg/kg ip, 30 min prior to death), is taken as an indirect measure of DA synthesis rate.

In an attempt to reduce the influence of the differences in pharmacokinetic properties (preliminary experiments; cf. also ref 18) on the experimental results, apomorphine was given at a shorter time interval (chosen to 15 min

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(14) Loudon, J. D.; Razdan, R. K. *J. Chem. Soc.* **1954**, 4299.
(15) Johnson, D. W.; Mander, L. N. *Aust. J. Chem.* **1974**, *27*, 1277.
(16) Taylor, E. C.; Chiang, C.-S.; McKillop, A. *Tetrahedron Lett.* **1977**, 1827.
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instead of 45 min) before NSD 1015. The biochemical results are given in Figure 1.

The behavioral and motor activity recordings were carried out as previously described[17] using reserpinized rats (10 mg/kg ip, 6 h before the experiment) in motility meters. Test compounds were administered sc in doses equal to the half-maximal (ED_{50}) and approximately maximal (ED_{100}) decrease in brain DA-synthesis rate according to the results obtained in the biochemical test. The motor activity results are shown in Table II.

In the emesis test the drugs were administered as solutions by constant-rate intravenous infusion. The rate of administration was adjusted so that equilibrium was established between blood and receptor tissue at each moment over the infusion period. Therefore, the total dose given reflects the minimum concentration of the drug in the body at which the animal vomits. The time needed to reach this level is dependent on the rate of drug administration (k_0), the apparent volume of distribution, the overall elimination from the body, and the responsiveness of the receptors. Since k_0 was adjusted to induce vomiting about 10 min after the start of the infusion, its actual value will be proportional to the drug concentration at the receptor for the effect to appear. All drugs investigated were given in a cross-over fashion which reduces interindividual differences in drug elimination and volume of distribution, and each drug was tested and evaluated against apomorphine to minimize interindividual receptor sensitivity. The results of the emesis test are presented in Table I.

Results and Discussion

In the reserpinized rat no significant behavioral stimulation can be demonstrated when the compounds studied are given in doses equal to the ED_{50} values (Table II and gross behavioral observations), indicating, as previously suggested by us,[8] a predominant presynaptic DA-receptor (autoreceptor) stimulation at these doses. This interpretation is also supported by the demonstration that the biochemical effect can be antagonized by haloperidol in a dose-dependent manner (results not shown). Accordingly, for the tested compounds the ED_{50} values (see Table I) may be considered to represent measures of central presynaptic DA-receptor potency in the reserpinized rat.

Each compound shows similar ED_{50} values for the limbic system and for striatum analogous to our previous results from the 2-aminotetralin[8] and phenethylamine[17] series. The DOPA accumulation in the hemispheral portion and the 5-HTP accumulation in hemispheral, limbic, and striatal portions of the brain were not affected by the compounds tested. These results suggest that none of these compounds possess central noradrenaline- or serotonin-receptor stimulatory effects, respectively, at the administered doses.

At the doses eliciting an approximately maximal decrease in the DA-synthesis rate (ED_{100}; see Table I) there is a clearly significant ($p < 0.01$ or less; Table II), though not pronounced, behavioral stimulation of the reserpinized rat, i.e., sniffing and occasional locomotor activity (Table II and gross behavioral observations). Thus, these doses are probably near-threshold for postsynaptic DA-receptor activation.

When the active compounds are tested in higher doses, the behavioral stimulation gradually increases. Thus, apomorphine and compound **6** yield a total of 600–800 motor activity counts/60 min at doses approximately 10 times the ED_{100} values (data not shown). When given the compounds **24**, **25**, and **27** at high dosage, the rats initially exhibit marked stereotypies and locomotor stimulation (indistinguishable from that of apomorphine and compound **6**). These effects disappear 30–45 min later and the animals lie down on the cage floors, frequently wailing.

4-Hydroxy-2-(dipropylamino)indan (**24**) is the most potent DA-receptor agonist of the new compounds. It may be slightly less potent than apomorphine in the biochemical test and seems equipotent to apomorphine in the emesis test (Table I and Figure 1). However, in all the tests it is considerably less potent than the previously reported 5-hydroxy-2-(dipropylamino)tetralin[6,8] (**6**), which is included here as a reference. 5-Hydroxy-2-(dipropylamino)indan (**25**) is much less active than compound **24**. In **24**, the position of the OH group can be described as ortho to one of the aliphatic/aromatic ring junctions and meta to one of the ethylamine moieties of the molecule. When the OH group is meta to one aliphatic/aromatic ring junction and para to one ethylamine moiety as in **25**, the activity is considerably lower. This relationship corresponds closely to that previously reported in the tetralin series, where 5-hydroxy-2-(dipropylamino)tetralin (**6**) is much more potent in inducing stereotypy than its 6- and 7-hydroxy isomers **7** and **8**,[6] and in the aporphine series, where 11-hydroxy substitution confers higher activity than 10- or 9-hydroxy substitution[19] (**3** and **4**, respectively). Thus, the most potent monophenolic isomers in the aporphine, 2-aminotetralin, and 2-aminoindan series (**2**, **6**, and **24**, respectively) have the hydroxyl group in similar relative positions. Among these compounds, **24** has a relatively short N–O distance (5.5 Å) as compared to that of **2** (6.48 Å) and of **6** (6.47 Å). In the 2-aminoindans the distance from the nitrogen to the center of the aromatic ring (N–ArC distance) is approximately 4.8 Å as compared to 5.1–5.2 Å in the 2-aminotetralins (distances not available in the literature were measured on Dreiding models). These comparisons show that a certain variation of the N–O and the N–ArC distances can be accepted by the receptor and indicate that the position of the hydroxyl group on the aromatic ring is of primary importance for the dopaminergic activity.

The benzocycloheptene derivative **26** was found to be inactive in our tests. This result is in agreement with that reported by Rusterholz et al.,[11] who showed that 6,7,8,9-tetrahydro-*N*,*N*-dipropyl-5*H*-6-benzocycloheptenylamine failed to induce emesis in dogs and rotational behavior in unilaterally nigra-lesioned rats and to displace [^{3}H]DA from tissue homogenates. The inactivity of **26** may be due to a number of factors, since this benzocycloheptene derivative differs from known dopaminergic compounds in several respects. A seemingly stable form of the seven-membered ring is a chair conformation with a torsion angle (C_4–C_{4a}–C_5–C_6) of approximately 120° (Dreiding models), whereas the corresponding angle in **6** (C_8–C_{8a}–C_1–C_2) is 168°.[20] Superimposing the hydroxyl group, the aromatic ring, and the ethylamine chain of **26** upon the corresponding elements of **6** results in a conformation (boat form) of the seven-membered ring that is much bulkier than the aliphatic ring of **6**. Moreover, this may not be a preferred conformation of **26**, since it results in an interaction between the cis-hydrogens of C_6 and C_9.

4-Hydroxy-2-[(dipropylamino)methyl]indan (**27**) is a new type of dopaminergic agent, which, instead of the phenethylamine structure common to most DA-receptor agonists, has a phenylpropylamine moiety in its framework. Compound **27** is 10–20 times less active than apomorphine in our tests. A comparison of Dreiding models of both

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enantiomers of **27** with the *S* enantiomer of **6** by superimposing the benzene ring and the OH group upon the corresponding structural elements of **6** reveals that the nitrogen of the two enantiomers of **27** can adopt the same or almost the same spatial position as the nitrogen of **6**. This may explain the activity of compound **27**. When comparing the models, the substituents of the aliphatic rings were placed in equatorial positions, which has been demonstrated to give the most stable conformations for 2-substituted indans[21] and tetralins.[20]

If part of the propylamine chain is incorporated into a six-membered ring as in **28** rather than into a five-membered ring as in **27**, all dopaminergic activity is lost. Superimposing **28** upon **6** as described above for **27** and **6** reveals that the nitrogen of **28** cannot be superimposed upon the nitrogen of **6** and that the minimum distance between the nitrogens is approximately 1 Å. The inactivity of **28** may therefore be explained by the assumption that the nitrogen is out of position for proper binding to the receptor.

The emetic action, common to most investigated DA agonists, is thought to be dopaminergic in nature, involving direct DA-receptor stimulation. Hence, the emetic activity in dogs (see Experimental Section) was also assessed for the biochemically active compounds.

Previous reports[9,22] have suggested that it may be possible to separate emesis from other effects considered to result from DA-receptor stimulation. In particular, in the tests performed by Cannon et al.,[9] the indan derivative **10** was about 100 times less active than 5,6-dihydroxy-2-(dimethylamino)tetralin in inducing emesis in dogs in spite of similar and high potencies in inducing stereotypy in mice. In contrast, Rusterholz et al.[11] found that 2-(dipropylamino)indan (**11**) was almost as potent as 2-(dipropylamino)tetralin in inducing emesis in dogs. In our emesis test the indan derivative **24** was equipotent to apomorphine, whereas the tetralin derivative **6** was 6–10 times more potent. The 2-aminoindan **25** and the 2-(aminomethyl)indan **27** are 10 times less active than apomorphine. The results presented here, as well as by Rusterholz et al.,[11] indicate that strong emetic activity may be associated with dopaminergic agonists of the indan as well as of the tetralin type of structure.

Interestingly, the ranking order of potency for emetic activity parallels the biochemically determined ED_{50} values for the active compounds. This may be compared with previously reported results for DA-receptor agonists of the aporphine,[23] 2-aminotetralin,[6,24] and octahydrobenzo[*f*]-quinoline[25] types where the relative emetic and stereotypic potencies often correlate.

Taken together, our present results suggest that the compounds investigated possess similar relative potencies in eliciting the three different DA-receptor mediated effects measured.

Experimental Section

Chemistry. Melting points (uncorrected) were determined in open glass capillaries on a Thomas-Hoover apparatus. ^1H NMR spectra recorded on a Perkin-Elmer R 12B spectrometer, IR spectra recorded on a Perkin-Elmer 157 G spectrophotometer, and mass spectra recorded at 70 eV on a LKB 9000 spectrometer were all in accordance with the assigned structures. The elemental analyses (C, H, and N) for the new substances (Agricultural College, Uppsala, Sweden) were within ±0.4% of the theoretical values. For purity tests, TLC was performed on Fluorescent silica gel or alumina plates. For all the compounds, only one spot (visualized by UV light and I_2 vapor) was obtained.

5-Methoxy-2-indanone (13) was prepared from 6-methoxyindene[12] (**12**) according to the method described by Horan and Schiessler[26] for the synthesis of 2-indanone from indene: yield 30%; mp 79–80 °C (from 50% ethanol). Anal. ($C_{10}H_{10}O_2$) C, H.

5-Methoxy-2-(dipropylamino)indan (14). 5-Methoxy-2-indanone (**13**; 4.9 g, 30 mmol), dipropylamine (12.1 g, 120 mmol), and *p*-toluenesulfonic acid were refluxed in dry benzene (250 mL) under nitrogen for 36 h. The water formed in the reaction was collected in a Dean–Stark trap. Since the enamine prepared darkened very rapidly when in contact with air, it was hydrogenated directly. The hydrogenation was run overnight in a Parr high-pressure apparatus at 40 atm over Platinum black at room temperature. After the catalyst had been removed by filtration through Celite, the solvent was evaporated. Distillation of the residue in vacuo yielded 6.5 g (88%) of the product as a clear, viscous oil boiling at 107–108 °C (0.2 mmHg). Anal. ($C_{16}H_{25}NO$) H, N; C: calcd, 77.7; found, 77.1.

4-Methoxyindan-2-carboxylic acid (16) was prepared from 7-methoxy-1-indanone (**15**;[14] 8.1 g, 50 mmol) according to the procedure described by Johnson and Mander[15] for the synthesis of 5-methoxytetralin-2-carboxylic acid from 5-methoxy-1-tetralone: yield 7.1 g (74%); mp 122–124 °C (from benzene). Anal. ($C_{11}H_{12}O_3$) C, H.

4-Methoxyindan-2-amine (17) was synthesized from 4-methoxyindan-2-carboxylic acid (**16**; 5.8 g, 30 mmol) according to the method used by Nichols et al.[27] for the preparation of 2,3-dimethoxy-9-amino-9,10-dihydrophenanthrene from 2,3-dimethoxy-9,10-dihydrophenanthrene-9-carboxylic acid. The crude product was distilled under reduced pressure, yielding 3.9 g (80%) of the title compound, bp 105–107 °C (1 mmHg). A sample was converted to the hydrochloride, which had mp 240–241 °C (from ethanol–ether). Anal. ($C_{10}H_{13}NO\cdot HCl$) C, H, N.

4-Methoxy-2-(dipropylamino)indan (18). The N-alkylation method reported by Marchini et al.[28] was followed. 4-Methoxyindan-2-amine (**17**; 1.0 g, 6 mmol) was allowed to react with sodium borohydride (2.3 g, 60 mmol)/propionic acid (7.4 g, 100 mmol) in benzene (20 mL). The crude amine was isolated as the hydrochloride, which was placed on a silica gel column and eluted with chloroform–methanol (9:1). Evaporation of the solvents and recrystallization from ethanol–ether yielded 2.7 g (80%) of product, mp 189–190 °C. Anal. ($C_{16}H_{25}NO\cdot HCl$) C, H, N.

4-Methoxy-2-[(dipropylamino)methyl]indan (19). To a solution of 5.0 g (26 mmol) of **16** in 80 mL of dry acetone, maintained at −5 °C, were added 3.0 g (30 mmol) of triethylamine in 20 mL of dry acetone and 5.8 g (34 mmol) of ethyl chloroformate in 20 mL of dry acetone. After the reaction mixture stirred at −5 °C for 1.5 h, a solution of 4.2 g (41.5 mmol) of dipropylamine in 20 mL of dry acetone was added. The salt–ice bath was removed, and the suspension was stirred for another hour. Filtration, followed by evaporation of the volatiles under reduced pressure, afforded the crude amide. This was purified on an alumina column eluted with ether. The purified amide dissolved in 50 mL of dry tetrahydrofuran was added to a suspension of 3.0 g (70 mmol) of $LiAlH_4$ in 150 mL of dry tetrahydrofuran. The reaction mixture was stirred and refluxed for 5 h. Dropwise addition of 3 mL of water, 3 mL of 15% NaOH, and 9 mL of water, filtration of the precipitate formed, and evaporation of the volatiles in vacuo afforded the crude amine, which was chromatographed on an alumina column eluted with ether to yield 4.1 g (60%) of

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pure 19. The hydrochloride was prepared by addition of etheral hydrogen chloride to an ether solution of the base, mp 104–106 °C (from ethanol–ether). Anal. ($C_{17}H_{27}NO$·HCl) C, H, N.

5-Methoxy-2-[(dipropylamino)methyl]tetralin. This compound was prepared from 2.5 g (12 mmol) of 5-methoxytetralin-2-carboxylic acid[15] according to the procedure described above for the preparation of **19**. The pure base (1.75 g, 53%) was converted to its hydrochloride, mp 140–141 °C (from ethanol–ether). Anal. ($C_{18}H_{29}NO$·HCl) C, H, N.

6,7,8,9-Tetrahydro-1-methoxy-5*H*-benzocyclohepten-6-one (21). A slurry of 3.4 g (113 mmol) of 80% NaH in 20 mL of dry dimethyl sulfoxide under nitrogen was heated at 80 °C for 1 h. After addition of 20 mL of dry dimethyl sulfoxide, 40.0 g (113 mmol) of methyltriphenylphosphonium iodide was added in portions. Stirring for 20 min, addition of a solution of 10 g (57 mmol) of 5-methoxy-1-tetralone (**20**) in 20 mL of dry dimethyl sulfoxide, and heating the mixture at 70 °C overnight completed the reaction. The reaction mixture was poured into 100 mL of ice–water, followed by the addition of 100 mL of hexane. Filtration of precipitated triphenylphosphine oxide, washing the organic layer with water, drying ($MgSO_4$), and evaporation of the hexane in vacuo afforded 8.35 g of the crude 1-methylene-5-methoxytetralin. This was dissolved in 60 mL of methanol and added in one portion to a freshly prepared solution of 21.75 g (48 mmol) of $Tl(NO_3)_3·3H_2O$ in 200 mL of methanol. The mixture was stirred for 1 min and chloroform (200 mL) was added. Filtration, evaporation of the volatiles in vacuo, with distillation of the residue gave 9.2 g (93%) of pure **21**, bp 105–106 °C (0.3 mmHg). Anal. ($C_{12}H_{14}O_2$) C, H.

6,7,8,9-Tetrahydro-1-methoxy-*N*-propyl-5*H*-6-benzocycloheptenylamine (22). The reductive amination of **21** (6.0 g, 32 mmol) was accomplished as described for the preparation of 5-methoxy-2-(propylamino)tetralin from 5-methoxy-2-tetralone:[8] yield 6.0 g (81%). A small sample was converted into the hydrochloride, mp 202–203 °C (from ethanol–ether). Anal. ($C_{15}H_{23}NO$·HCl) C, H, N.

6,7,8,9-Tetrahydro-1-methoxy-*N,N*-dipropyl-5*H*-6-benzocycloheptenylamine (23). Acylation of 4.8 g (21 mmol) of **22** with 2.4 g (25 mmol) of propionyl chloride, followed by $LiAlH_4$ reduction of the resulting amide, was performed as described for the preparation of 2-(*N*-butyl-*N*-propylamino)-5-methoxytetralin from 2-(butylamino)-5-methoxytetralin:[8] yield 4.6 g (81%). The base was converted to its hydrochloride, mp 193–194 °C (from ethanol–ether). Anal. ($C_{18}H_{29}NO$·HCl) C, H, N.

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

Pharmacology. Animals used in the biochemical and motor activity experiments were male rats of Sprague–Dawley strain (Anticimex, Stockholm), weighing 200–350 g.

All substances to be tested were dissolved in saline immediately before use. 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 injection solutions had neutral pH.

Biochemistry. The biochemical experiments and the spectrophotometric determinations of DOPA and 5-HTP were performed as previously described.[17] The experiments were always carried out at 9–12 a.m.

Separate dose–response curves based on four to six dose levels for each substance (sc administration) and brain area were constructed (Figure 1). From these curves the doses of the drug yielding a half-maximal and an approximately maximal decrease (cf. ref 8) of the DOPA level, ED_{50} and ED_{100} values (presented in Table I), respectively, were estimated. These doses were then used in the motor activity experiments as described below (cf. Table II).

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.[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). The different compounds under investigation were administered subcutaneously in the neck region. For each compound the doses corresponding to the half-maximal (ED_{50}) and to an approximately maximal (ED_{100}) decrease in brain DA-synthesis rate were chosen, according to the results obtained in the biochemical test (cf. above). 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 II.

Emesis. Four female beagle dogs (8–15 kg) were used through the experiments. They had free access to water an food. Drugs were administered by constant-rate intravenous infusion in the cephalic vein by an infusion pump (Sage Instruments Model 355). The rate of drug administration was adjusted to give an expected vomiting about 10 min after the start of infusion. When this end point of effect was reached, the infusion was stopped and the animal was left and not used until at least 3 days had passed.

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