particularly potent.[12] The activity of 4 could be blocked by (-)-sulpiride,[13] a selective dopaminergic antagonist, with a K_B of 8.8 nM (Figure 1). This K_B value is comparable to that obtained for this antagonist against dopamine in the same series of experiments (32 nM) and is essentially identical with the value of 9.3 nM reported for (-)-sulpiride as an antagonist of 6,7-ADTN in the ear artery.[14] Therefore, the activity of 4 in the rabbit ear artery is attributed to activation of presynaptic dopamine receptors. These results indicate that the di-*n*-propylindolone 4 is one of the most potent presynaptic dopamine receptor agonists reported to date.

Acknowledgment. We are grateful to James M. Smith, Jr., and Caleb A. Jervay for their expert assistance in conducting the biological experiments.

(12) Vasoconstriction was observed in the rabbit ear artery for both compounds 3 and 4 at doses on the order of 1000 nM. This result is consistent with the previously mentioned pressor effects exhibited by 3 and 4 at higher doses (Table I).
(13) Brown, R. A.; O'Connor, S. E. *Br. J. Pharmacol.* 1981, *73*, 189P. The (-)-sulpiride was kindly supplied by Professor P. Fresia, Ravizza S.P.A., Milan, Italy.
(14) Steinsland, O. S.; Hieble, J. P. *Adv. Biosci.* 1979, *18*, 93-97.
(15) An EC_{50} value of 110 nM in the rabbit ear artery has been reported (ref 13) for this compound.

(16) Present address: Department of Pharmacology, Eli Lilly Co., Indianapolis, IN.

William F. Huffman,* Ralph F. Hall
Janet A. Grant, James W. Wilson
Department of Medicinal Chemistry

J. Paul Hieble, Richard A. Hahn[16]
Department of Pharmacology
Smith Kline & French Laboratories
Philadelphia, Pennsylvania 19101
Received February 22, 1983

Articles

Neuroleptic Activity and Dopamine-Uptake Inhibition in 1-Piperazino-3-phenylindans

Klaus P. Bøgesø

Department of Medicinal Chemistry, H. Lundbeck & Co. A/S, Ottiliavej 7-9, DK-2500 Copenhagen-Valby, Denmark.
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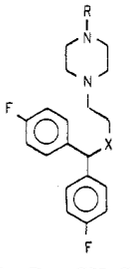
A series of 1-piperazino-3-phenylindans was synthesized and tested for neuroleptic and thymoleptic activity. Neuroleptic activity was found only in trans racemates and was associated with one of the enantiomers only. The potent and long-acting neuroleptic compound *trans*-4-[3-(4-fluorophenyl)-6-(trifluoromethyl)indan-1-yl]-1-piperazineethanol (Lu 18-012, tefludazine) was developed by systematic variation of structural components. Thymoleptic activity was optimized, especially with respect to dopamine-uptake inhibition. No geometrical stereoselectivity was found with regard to dopamine-uptake inhibition, but a high enantioselectivity could be demonstrated for both cis and trans racemates. The most potent compounds were 1-piperazino-3-(3,4-dichlorophenyl)indans with IC_{50} values of about 2 nM for inhibition of dopamine uptake.

Since the introduction of chlorpromazine as an antipsychotic drug many compounds with neuroleptic activity have been synthesized. These compounds include a diversity of chemical structures and are often categorized on the basis of a common "nucleus", i.e., phenothiazines, thioxanthenes, thiepins, butyrophenones, etc.[1] The piperazine ring is common to many of these compounds. This piperazine ring can either be part of a flexible piperazinopropyl(idene) side chain, as in perphenazine or flupentixol, or be attached directly to a tricyclic nucleus, as in clozapine or octoclothepin (4).

The butyrophenones have no polycyclic nucleus, but the related diphenylbutylamines, for example, penfluridol, have two phenyl rings that might interact with the dopamine (DA) receptor at the same site as the tricyclic nucleus.[2] The great majority of butyrophenones and diphenylbutylamines contain a 4-substituted piperidine ring as the amine part. If the diphenylbutyl part of penfluridol is combined with a piperazine base, compounds without neuroleptic activity are obtained. For example, 1 (VUFB



1, X = CH_2; R = CH_2CH_2OH
2, X = O; R = $CH_2CH{=}CH{-}C_6H_5$

10.674) is reported to have no central depressant activity.[3] We have also synthesized 1 (Lu 9-106) and also can report that we found no antistereotypic effect (methyl phenidate

(1) Kaiser, C.; Setler, P. E. "Burger's Medicinal Chemistry", Part III, 4th ed.; Wolff, M. E., Ed.; Wiley: New York, 1981; p 859.
(2) Olson, G. L.; Cheung, H.-C.; Morgan, K. D.; Blount, J. F.; Todaro, L.; Berger, L.; Davidson, A. B.; Boff, E. *J. Med. Chem.* 1981, *24*, 1026.
(3) Rajšner, M.; Kopicová, Z.; Holubek, J.; Svátek, E.; Metyš, J.; Bartošová, M.; Mikšik, F.; Protiva, M. *Collect. Czech. Chem. Comm.* 1978, *43*, 1760.

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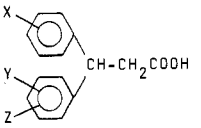
Table I. 3,3-Diphenylpropanoic Acids

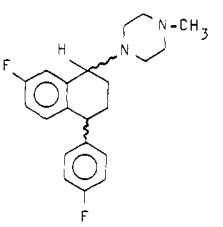


compd	X	Y	Z	mp, °C	yield,[a] %	recrystn solvent[b]	formula[c]
6	4-F	H	H	111-114[d]	81	A	$C_{15}H_{13}FO_2$
7	4-F	H	4'-F	107-108[e]	95	A	$C_{15}H_{12}F_2O_2$
8	4-F	H	3'-F	109-111	73	A	$C_{15}H_{12}F_2O_2$
9	4-F	H	4'-CH_3	137-139[f]	80	A	$C_{16}H_{15}FO_2$
10	4-F	H	4'-*i*-Pr	118-120	73	A	$C_{18}H_{19}FO_2$
11	4-F	H	4'-OCH_3	83-86	77	A	$C_{16}H_{15}FO_3$
12	4-F	H	4'-SCH_3	105-107	72	A	$C_{16}H_{15}FO_2S$
13	4-F	2'-Br	4'-CF_3	126-130	70	B	$C_{16}H_{11}BrF_4O_2$
14	H	2'-Br	4'-CF_3	153-155	69	A	$C_{16}H_{12}BrF_3O_2$
15	4-CH_3	2'-Br	4'-CF_3	111-112	73	A	$C_{17}H_{14}BrF_3O_2$
16	4-Cl	2'-Br	4'-CF_3	123-125	84	A	$C_{16}H_{11}BrClF_3O_2$
17	4-F	2'-Br	4'-Cl	120-121	55	C	$C_{15}H_{11}BrClFO_2$
18	4-Cl	H	4'-Cl	186-191[g]	80	D	$C_{15}H_{12}Cl_2O_2$
19	H	3'-Cl	4'-Cl	75-77	73	B	$C_{15}H_{12}Cl_2O_2$
20	H	2'-Cl	4'-Cl	117-119	81	A	$C_{15}H_{12}Cl_2O_2$

[a] Calculated yield based on the substituted ethyl 2-cyano-3-phenyl-2-propenoates. [b] A = ethyl ether-hexane; B = isopropyl ether-hexane; C = cyclohexane; D = not recrystallized. [c] Anal. C, H. [d] Mp 118 °C.[11] [e] Mp 108-109 °C.[11] [f] Mp 138-139 °C.[11] [g] Mp 193-195 °C.[12]

antagonism).[4] The related piperazine derivative **2** (GBR 13.069)[5] is a strong DA-uptake inhibitor, but like **1**, is not a DA antagonist.

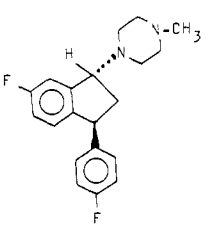
The cyclic analogues of **1**, *trans*- and *cis*-1-piperazino-4-phenyl-1,2,3,4-tetrahydronaphthalenes **3a** (Lu 13-157)



3a,b

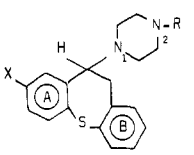
and **3b** (Lu 13-161), were found to have no antistereotypic effect (methyl phenidate antagonism, Table IV). Compound **3a** is identical with VUFB 10.587, which also is reported to have no central depressant effects.[3]

It was therefore somewhat unexpected that the 1-piperazino-3-phenylindan derivative **53** had neuroleptic



53

activity similar to chlorpromazine. Many indan and indene derivatives are pharmacologically active,[6] and certain 1-amino-3-phenylindans are reported to have analgesic,[7] coronary dilating,[8] or tranquilizing properties.[9] However, no pharmacologically active piperazine-substituted indans have yet been reported. The synthesis of a series of such compounds was therefore started in order to determine the structure–activity relationships in this class of neuroleptic agents. It was concluded from NMR studies that the neuroleptically active isomers had the trans configuration. This was later confirmed by X-ray diffraction of compound **88**.[10] This compound (Lu 18-012, tefludazine) was also the most potent derivative, since it was more than 100 times more potent than **53**. A comparison of the three-dimensional structures of **88**, **4**, and oxyprothepin (**5**) revealed, as shown below, a strong structural resemblance between the *trans*-1-piperazino-3-phenylindans and the thiepins.



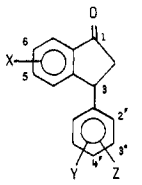
4, X = Cl; R = CH_3
5, X = SCH_3; R = $(CH_2)_3OH$

At the same time it was found that many of the compounds were potent DA-uptake inhibitors. A selective DA-uptake inhibitor would be of potential interest both in anti-Parkinson therapy and as a tool to clarify the role of DA-uptake inhibition in depression. By suitable substitution, compounds were obtained that, like **2**, had no DA-antagonistic activity but still were potent inhibitors of DA uptake.

Chemistry. The 1-piperazino-3-phenylindans were prepared as outlined in Scheme I. 1,4-Addition of a substituted phenylmagnesium bromide to ethyl 2-cyano-3-phenyl-2-propenoates (I) gave high yields of ethyl 2-cyano-3,3-diphenylpropanoates. These were either sapo-

(4) Christensen, A. V.; Hyttel, J.; Arnt, J.; Svendsen, O., H. Lundbeck & Co. A/S, unpublished results.
(5) van der Zee, P.; Koger, H. S.; Gootjes, J.; Hespe, W. *Eur. J. Med. Chem.* **1980**, *15*, 363.
(6) Ganellin, C. R. *Adv. Drug Res.* **1967**, *4*, 163.
(7) Barltrop, J. A.; Acheson, R. M.; Philpott, P. G.; MacPhee, K. E.; Hunt, J. S. *J. Chem. Soc.* **1956**, 2928.
(8) Busch, E.; Langecker, H.; Richter, H. *Arzneim.-Forsch.* **1961**, *11*, 915.
(9) Schaub, W.; Gerhards, H.; Schmitt, K. German Offen. 2339715, 1973.
(10) Jensen, B., Royal Danish School of Pharmacy, personal communication.

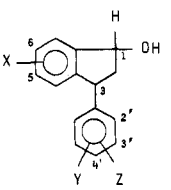
Table II. 3-Phenylindan-1-ones



compd	X	Y	Z	mp, °C	ring closure conditions	yield, %	recrystn solvent[a]	formula[b]
21	H	4'-F	H	121-122	PPA, 100 °C, 3 h	58	A	$C_{15}H_{11}FO$
22	6-F	4'-F	H	80-81	PPA, 105 °C, 2 h	71	C	$C_{15}H_{10}F_2O$
23	5-F	4'-F	H	102-104	$AlCl_3$, 25 °C, 3 h	67	A	$C_{15}H_{10}F_2O$
24	6-CH_3	4'-F	H	69-70	PPA, 95 °C, 3 h	62	A	$C_{16}H_{13}FO$
25	6-*i*-Pr	4'-F	H	52-53	PPA, 95 °C, 4.5 h	100[c]	B	$C_{18}H_{17}FO$
26	6-OCH_3	4'-F	H	88-91	PPA, 95 °C, 2 h	13[d]	A	$C_{16}H_{13}FO_2$
27	6-SCH_3	4'-F	H	72-73	PPA, 90 °C, 2 h	70	A	$C_{16}H_{13}FOS$
28	6-CF_3	4'-F	H	44-45	BuLi[e]	82	B	$C_{16}H_{10}F_4O$
29	6-CF_3	H	H	32-34	BuLi[e]	71	B	$C_{16}H_{11}F_3O$
30	6-CF_3	4'-CH_3	H	71-73	BuLi[e]	51	B	$C_{17}H_{13}F_3O$
31	6-CF_3	4'-Cl	H	60-61	BuLi[e]	38	A	$C_{16}H_{10}ClF_3O$
32	6-Cl	4'-F	H	95-96	BuLi[e]	73	A	$C_{15}H_{10}ClFO$
33	6-Cl	4'-Cl	H	114-118[f]	$AlCl_3$, 25 °C, 16 h	82	D	$C_{15}H_{10}Cl_2O$
34	H	3'-Cl	4'-Cl	113-115	PPA, 100 °C, 2 h	91	E	$C_{15}H_{10}Cl_2O$
35	H	2'-Cl	4'-Cl	132-134	PPA, 110 °C, 1 h	53	E	$C_{15}H_{10}Cl_2O$
36	6-SO_2CH_3	4'-F	H	113-115	g	70	D	$C_{16}H_{13}FO_3S$

[a] A = isopropyl ether-hexane; B = hexane; C = isopropyl ether; D = ethanol; E = cyclohexane. [b] Anal. C, H. [c] Yield of crude, not crystalline, product pure enough to be used in the next step. A crystalline sample was obtained by column chromatography. [d] Yield of crude product was 100%. Decomposition occurred during distillation at 190 °C (0.5 mm). [e] See Experimental Section. [f] Mp 117-118.5 °C.[13] [g] Made by oxidation of 27; see Experimental Section.

Table III. 3-Phenylindan-1-ols



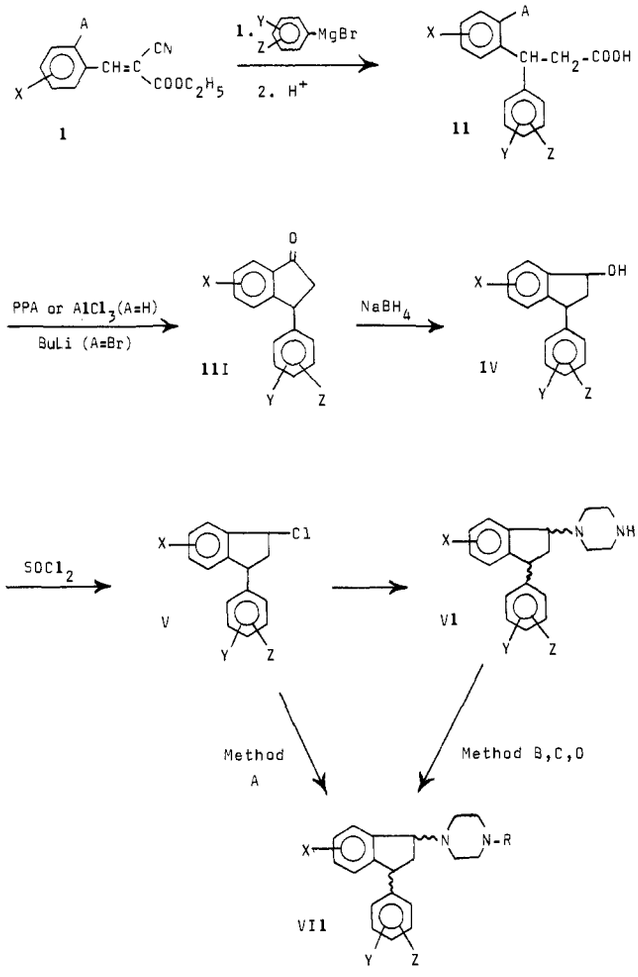
compd	X	Y	Z	mp, °C	yield, %	recrystn solvent[a]	formula[b]
37	H	4'-F	H	74-75	98	A	$C_{15}H_{13}FO$
38	6-F	4'-F	H	64-67	92	B	$C_{15}H_{12}F_2O$
39	5-F	4'-F	H	84-86	88	A	$C_{15}H_{12}F_2O$
40	6-CH_3	4'-F	H	127-129	90	A	$C_{16}H_{15}FO$
41	6-*i*-Pr	4'-F	H	102-103	66	A	$C_{18}H_{19}FO$
42	6-OCH_3	4'-F	H	97-98	88	A	$C_{16}H_{15}FO_2$
43	6-SCH_3	4'-F	H	98-99	53	C	$C_{16}H_{15}FOS$
44	6-CF_3	4'-F	H	78-80	75	B	$C_{16}H_{12}F_4O$
45	6-CF_3	H	H	55-58	80	B	$C_{16}H_{13}F_3O$
46	6-CF_3	4'-CH_3	H	80-81	78	A	$C_{17}H_{15}F_3O$
47	6-CF_3	4'-Cl	H	105-107	75	A	$C_{16}H_{12}ClF_3O$
48	6-Cl	4'-F	H	138-139	92	C	$C_{15}H_{12}ClFO$
49	6-Cl	4'-Cl	H	110-113	60	C	$C_{15}H_{12}Cl_2O$
50	H	3'-Cl	4'-Cl	90-91	76	A	$C_{15}H_{12}Cl_2O$
51	H	2'-Cl	4'-Cl	88-89	61	A	$C_{15}H_{12}Cl_2O$
52	6-SO_2CH_3	4'-F	H	162-163	89	D	$C_{16}H_{15}FO_3S$

[a,b] See corresponding footnotes to Table II.

nified, decarboxylated, and hydrolyzed to the 3,3-diphenylpropanoic acids[11] (II, see Table I) as described in the literature[12] or directly decarboxyethylated and hydrolyzed with acid to II. Depending on the substituents, two different methods were used in the cyclization of II to the 3-phenylindan-1-ones (III, see Table II). Conventional cyclization with polyphosphoric acid (PPA)[7] or with $AlCl_3$[13] could be used in all cases, except for acids with a trifluoromethyl group, because we found that PPA hydrolyzed this group to a carboxy group and $AlCl_3$ transformed it to a CCl_3 group. The trifluoromethyl-substituted indanones were obtained instead by treating 2-bromo-substituted 3,3-diphenylpropanoic acids with 2 equiv of *n*-butyllithium (BuLi). This reaction was carried out at −5 °C, in contrast to the low reaction temperature reported in the preparation of 1-indanone.[14] It was complete in 30

(11) Bergmann, F.; Welzmann, M.; Dimant, E.; Patai, J.; Szmuskowicz, J. *J. Am. Chem. Soc.* **1948**, *70*, 1612.
(12) Schorr, M.; Loewe, H.; Jürgens, E.; Weber, H.; Lämmler, G. *Arzneim.-Forsch.* **1964**, *14*, 1151.
(13) Feeman, J. F.; Amstutz, E. D. *J. Am. Chem. Soc.* **1950**, *72*, 1522.
(14) Parham, W. E.; Jones, L. D.; Sayed, Y. *J. Org. Chem.* **1975**, *40*, 2394.

Scheme I



min, even with molar quantities of reactants.

This method also was used in the case of compound **27**, because cyclization of the nonbrominated acid with PPA led to an isomeric mixture, which was difficult to separate. All other cyclizations with PPA or $AlCl_3$ resulted in products with a high content of the desired isomer (Table II). The structures of the indanones were confirmed by ^1H and ^{13}C NMR spectroscopy. In particular, ^{13}C NMR was valuable for structure determination of indanones with a 4-fluorophenyl group, because of the easily detectable double-intensity doublets (C–F coupling) originating from the carbon atoms ortho and meta to the fluorine-substituted carbon atom.

Reduction of the indanones (III) with sodium borohydride gave high yields of the 3-phenylindan-1-ols (IV, Table III). The reduction resulted in almost pure cis racemates in contrast to the sodium borohydride reduction of the corresponding 4-phenyl-1-tetralones, which gave a mixture of cis and trans racemates.[3] The cis configuration was confirmed by reduction of indanone **18** with potassium tri-*sec*-butyl borohydride (K-Selectride), a reagent reported to yield almost pure cis isomers in the reduction of cyclic ketones.[15] The resulting indanol (**33**) was shown by HPLC to be >99% pure *cis*-isomer. Reduction of **18** with sodium borohydride or lithium aluminum hydride resulted in **97** and 95% pure cis isomers, respectively.

When the indanols (IV) were treated with thionyl chloride in toluene, some degree of isomerization took place, and an isomeric mixture containing from 20 to 30% *trans*-1-chloro-3-phenylindan (V) was obtained. The crude isomeric mixture of 1-chloro-3-phenylindans was reacted directly with a substituted piperazine (method A) or piperazine to produce the 1-piperazino-3-phenylindans VII or VI, respectively. This must almost exclusively be a S_N2 reaction, since an isomeric mixture with the reverse cis–trans ratio (i.e., 20–30% cis racemate and 70–80% trans racemate) was obtained. The secondary amines VI were either alkylated (method B), acylated, and reduced with lithium aluminum hydride (method C) or allowed to react with an epoxide (method D) to give the final product VII. Separation of the cis and trans racemates was, in most cases, easily done via their oxalates, because of very different solubilities in water (oxalates of trans racemates were almost insoluble). Cis isomers could alternatively be obtained by another route. When the indanols (IV) were allowed to react with methanesulfonyl chloride in pyridine and the resulting mesylates were subsequently allowed to react with a piperazine base, almost pure cis isomers could be obtained. The racemic compounds **53**, **94**, and **97** were further separated into their (+) and (–) enantiomers.

Results and Discussion

Neuroleptic Activity. The neuroleptic activity in Tables IV–VI was assessed by the ability of the compounds to antagonize methyl phenidate induced stereotypies in mice. In this test the compounds were given intraperitoneally (ip), but most of the compounds were also tested orally (po) in rats for antagonism of stereotypies induced by amphetamine. Most compounds were likewise tested in rats (po) for their ability to induce catalepsy, an effect normally related to clinical extrapyramidal side effects.[16] Selected compounds were also tested for their ability to displace [^{3}H]haloperidol bound to rat striatal membranes, in order to measure their intrinsic affinity for the DA receptor.

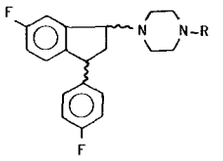
A number of 4′,6-difluoro-substituted compounds were initially synthesized to investigate the effect of variation of the piperazine N-substitution on neuroleptic activity (Table IV). Both racemic cis and trans isomers were tested, but none of the cis isomers displayed any neuroleptic activity in the doses tested, which fits nicely with the low activity found for the cis-isomers **56** and **66** in the [^{3}H]haloperidol binding test. The hydroxyethyl-substituted compound **65** was found to be more active than **53** and to have an even more favorable ratio between the doses needed to antagonize amphetamine stereotypies and to induce catalepsy. Substitution with small alkyl groups, as in **57** and **59**, gave compounds equipotent with **53**, while substitution with larger groups, as in **61** and **63**, resulted in diminished neuroleptic activity. Hydroxypropyl- or dihydroxypropyl-substituted compounds (**67**, **71**, **74**, and **76**) were more active in the methyl phenidate antagonism test than **65**. However, **67** was much more cataleptogenic than **65**, while **71**, **74**, and **76** were no better than **65** in the oral tests. The acetamido- and the cyanoethyl-substituted compounds **78** and **79** were both inactive.

By resolution of **53** into the enantiomers **54** and **55**, it was found that only the (+) enantiomer (**54**) had neuroleptic activity. However, the (–) enantiomer (**55**) was, as will be shown later (Table VIII), not a pharmacologically inactive compound. Its activity might explain why the

(15) Brown, H. C.; Krishnamurthy, S. *J. Am. Chem. Soc.* **1972**, *94*, 7159.

(16) van Rossum, J. M.; Boissier, J. R.; Janssen, P. A. J.; Julou, L.; Loew, D. M.; Møller Nielsen, I.; Munkvad, I.; Randrup, A.; Stille, G.; Tedeschi, D. H. "Pharmacology of Neuroleptic Drugs. Modern Problems of Pharmacopsychiatry (Neuroleptics)"; Bobon, J.; Janssen, P., Eds.; S. Karger: Basel, 1970; p 23.

Table IV. Influence of Stereochemistry and Piperazine N-Substitution on Neuroleptic Activity



compd	R	isomerism[a]	method	mp, °C	formula[b]	methyl phenidate antagonism, mice: ED_{50}, μmol/kg ip[c]	amphetamine antagonism, rats: ED_{50}, μmol/kg po[c]	catalepsy, rats: ED_{50}, μmol/kg po[c]	receptor binding: [^{3}H]haloperidol IC_{50}, nM[d]
53	CH_3	t	A	249-251	$C_{20}H_{22}F_2N_2 \cdot 2HCl$	11 (7-16)	37 (29-48)	202 (118-347)	57
54	CH_3	(+)t	A	249-251	$C_{20}H_{22}F_2N_2 \cdot 2HCl \cdot 0.13H_2O$	2.5 (1.7-3.6)	15 (10-23)	41 (30-55)	22
55	CH_3	(−)t	A	252-254	$C_{20}H_{22}F_2N_2 \cdot 2HCl \cdot 0.15H_2O$	42 (10-175)	>200	>790	780
56	CH_3	c	A	267-269	$C_{20}H_{22}F_2N_2 \cdot 2HCl$	>95	>95	NT	2500
57	C_2H_5	t	C	250-252	$C_{21}H_{24}F_2N_2 \cdot 2HCl \cdot 0.44H_2O$	7 (4-12)	14 (11-18)	53 (26-110)	NT
58	C_2H_5	c	C	268-270	$C_{21}H_{24}F_2N_2 \cdot 2HCl$	>96	NT	NT	NT
59	CH_2-c-C_3H_5	t	C	254-256	$C_{23}H_{26}F_2N_2 \cdot 2HCl$	11 (5-24)	36 (26-51)	53 (16-172)	NT
60	CH_2-c-C_3H_5	c	C	260-262	$C_{23}H_{26}F_2N_2 \cdot 2HCl$	>91	NT	NT	NT
61	$(CH_2)_2$-C_6H_5	t	B	80-82	$C_{27}H_{28}F_2N_2$	37 (4-314)	NT	NT	NT
62	$(CH_2)_2$-C_6H_5	c	B	75-77	$C_{27}H_{28}F_2N_2$	>95	NT	NT	NT
63	$CH_2CH{=}CH{-}C_6H_5$	t	C	263-265	$C_{28}H_{28}F_2N_2 \cdot 2HCl$	57 (22-147)	NT	NT	NT
64	$CH_2CH{=}CH{-}C_6H_5$	c	C	268-270	$C_{28}H_{28}F_2N_2 \cdot 2HCl$	>79	NT	NT	NT
65	CH_2CH_2OH	t	A	245-248	$C_{21}H_{24}F_2N_2O \cdot 2HCl$	7.0 (4.5-11)	14 (10-20)	184 (43-789)	43
66	CH_2CH_2OH	c	A	133-135	$C_{21}H_{24}F_2N_2O$	>112	>112	NT	3200
67	$(CH_2)_3OH$	~90% t	A	246-249	$C_{22}H_{26}F_2N_2O \cdot 2HCl$	3.7 (1.9-7.3)	5.2 (3.9-6.9)	8.3 (1.5-45.6)	21
68	$(CH_2)_3OH$	c	A	92-94	$C_{22}H_{26}F_2N_2O$	>90	NT	NT	190
69	$(CH_2)_4OH$	t	A	230-232	$C_{23}H_{28}F_2N_2O \cdot 2HCl$	6.5 (3.3-13)	7.7 (5.7-10)	47 (26-86)	48
70	$(CH_2)_4OH$	~94% c	A	246-248	$C_{23}H_{28}F_2N_2O \cdot 2HCl$	54 (22-129)	NT	NT	NT
71	$CH_2CHOHCH_3$	t	D	255-258	$C_{22}H_{26}F_2N_2O \cdot 2HCl$	2.8 (0.8-10)	12 (7-21)	37 (11-124)	NT
72	$CH_2CHOHCH_3$	c	D	262-265	$C_{22}H_{26}F_2N_2O \cdot 2HCl$	45	NT	NT	NT
73	$CH_2COH(CH_3)_2$	t	B	254-256	$C_{23}H_{28}F_2N_2O \cdot 2HCl$	>87	30 (20-46)	NT	NT
74	$CH_2CHOH{-}CH_2OH$	~90% t	A	243-245	$C_{22}H_{26}F_2N_2O_2 \cdot 2HCl \cdot 0.21H_2O$	2.9 (1.1-7.9)	33 (23-46)	>280	150
75	$CH_2CHOH{-}CH_2OH$	~90% c	A	114-117	$C_{22}H_{26}F_2N_2O_2 \cdot 0.25H_2O$	>51	NT	>102	NT
76	$CH(CH_2OH)_2$	t	A	245-247	$C_{22}H_{26}F_2N_2O_2 \cdot 2HCl$	4.2 (2.1-8.5)	25 (18-36)	124 (40-380)	64
77	$CH(CH_2OH)_2$	c	A	250-252	$C_{22}H_{26}F_2N_2O_2 \cdot 2HCl$	>43	NT	NT	NT
78	CH_2CONH_2	t	B	253-257	$C_{21}H_{23}F_2N_3O \cdot 2HCl \cdot 0.53H_2O$	>88	NT	NT	NT
79	CH_2CH_2CN	t		247-249	$C_{22}H_{23}F_2N_3 \cdot 2HCl$	73 (9-564)	>91	NT	NT
3a		t[f]				>117	NT	NT	NT
3b		c[f]				>96	NT	NT	NT
cis(2)-flupentixol						0.14 (0.10-0.19)	3.5 (2.5-4.7)	2.1 (1.3-3.4)	3
chlorpromazine						16 (10-25)	60 (42-86)	70 (25-194)	12
octoclothepin (4)						6.7 (2.5-18)	0.56 (0.18-1.8)	4.5 (2.2-9.5)	3

[a] t (trans) and c (cis) indicate isomers >95% pure as estimated by TLC. [b] Anal. C, H, N supplemented with Karl-Fischer titrations for compounds with a partial mole of water. [c] 95% confidence limits in parentheses. Details are given under Experimental Section. [d] All results are the mean of at least two determinations each with five concentrations of test compounds in triplicate. Details are given under Experimental Section. [e] NT = not tested. [f] See Experimental Section.

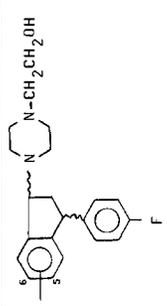
activity of **54** is more than twice that of **53**. The affinity to the DA receptor is 35 times higher for **54** than for **55**, as measured by [^{3}H]haloperidol binding. A similar stereoselectivity (measured by inhibition of [^{3}H]spiroperidol binding to calf striatal membranes) has been demonstrated for (+)- and (−)-octoclothepin (**4**).[17] In this case the affinity of the (+) enantiomer was 11 times higher than that of the (−) enantiomer.

The next step was to investigate the activity of other *N*-hydroxyethyl-substituted trans isomers (Table V). We suspected that the 6-substituent, like the 2-substituent in the thioxanthenes and the phenothiazines or the 8-substituent in the thiepins, was a "neuroleptic" substituent of crucial importance for the neuroleptic activity. Variation of the 6-substituent confirmed this theory. The unsubstituted derivative, **80**, was inactive, and the 5-fluoro-substituted compound **81** was only active intraperitoneally, but was still weaker than **65**. Compounds with 6-methyl, 6-isopropyl, or 6-methylthio substitution were equipotent with **65**, while compounds substituted with 6-methoxy or 6-methylsulfonyl were weaker than **65**. The 6-chloro-substituted compound **87**, however, was more active than **65**. A very dramatic increase in potency was seen when we succeeded in synthesizing the 6-trifluoromethyl-substituted compound **88**, which was from 60–100 times more active than **65**. The increase in activity obtained by 6-trifluoromethyl substitution compared to 6-chloro substitution is also considerably higher than the increase seen for a similar change in "neuroleptic" substituents within the thioxanthenes[18] or the thiepins.[1] The inactivity of **89**, (cis isomer of **88**) demonstrates again the highly stereospecific neuroleptic activity of the trans isomers. The greatly increased potency of **88** cannot be explained by an increased affinity for the DA receptor, since the IC_{50} values for inhibition of [^{3}H]haloperidol binding for **82**, **87**, and **88** are nearly the same. The explanation might instead be that the pharmacokinetics of **88** are different from that of the other compounds. Compound **88** was also the only long-acting compound with a duration of action in the methyl phenidate and amphetamine antagonism tests of more than 24 h.[4] In other tests for neuroleptic activity, such as inhibition of conditioned avoidance response in rats or antiemetic activity in dogs, the duration of action of compound **88** was more than 48 h.[4] The high ratio between the dose needed to induce catalepsy and the dose needed to antagonize amphetamine stereotypies that was found for some of the 6-fluoro-substituted compounds (such as **65**) was not found for compounds with other 6-substituents.

Variation of the 4′-substituent (Table VI) in **87** and **88** revealed that this position was even more sensitive for substitution than the 6-position. Potency was greatly reduced in the unsubstituted derivative **90**. 4′-Methyl- or 4′-chloro-substitution gave inactive or very weak compounds compared to the 4′-fluoro-substituted derivatives. Fluorine substitution at the 6-position in the thioxanthenes[18] or the 3-position in the thiepins[19] leads also to an increase in potency (and sometimes also to a longer duration of action), but the effect is not as pronounced as in this series of compounds.

An interesting structural resemblance between the

Table V. Variation of the 6-Substituent

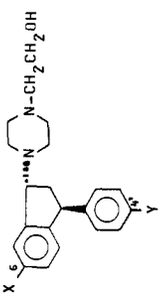


compd	X	isomerism[a]	mp, °C	formula[b]	methyl phenidate antagonism, mice: ED_{50}, μmol/kg ip[c]	amphetamine antagonism, rats: ED_{50}, μmol/kg po[c]	catalepsy, rats: ED_{50}, μmol/kg po[c]	receptor binding: [^{3}H]haloperidol IC_{50},[d] nM
80	H	t	92–95	$C_{21}H_{25}FN_2O$	>118	NT[e]	NT	NT
65	6-F	t			7.0 (4.5–11)	14 (10–20)	184 (43–789)	43
81	5-F	90% t	185–187	$C_{21}H_{24}F_2N_2O$·2HCl	14 (3.3–58)	>93	>93	NT
82	6-CH_3	t	170–174	$C_{21}H_{24}F_2N_2O$·2HCl·0.6H_2O	7.6 (3.7–16)	21 (15–30)	17 (6.6–45)	8.1
83	6-*i*-Pr	~90% t	243–245	$C_{24}H_{31}FN_2O$·2HCl	9.6 (5.1–18)	26 (19–37)	17 (9.0–33)	NT
84	6-CH_3O	t	221–224	$C_{22}H_{27}FN_2O_2$·2HCl	19 (5.1–73)	38 (27–53)	102 (53–195)	NT
85	6-CH_3S	>90% t	230–232	$C_{22}H_{27}FN_2OS$·2HCl	2.8 (0.8–9.4)	20 (14–29)	14 (7.5–25)	NT
86	6-CH_3SO_2	t	265–270	$C_{22}H_{27}FN_2O_3S$·2HCl	20 (14–31)	NT	NT	NT
87	6-Cl	t	244–247	$C_{21}H_{24}ClFN_2O$·2HCl	2.8 (1.5–5.1)	3.5 (2.7–4.5)	3.3 (1.7–6.6)	13
88	6-CF_3	t	85–86	$C_{22}H_{24}F_4N_2O$	0.07 (0.02–0.33)	0.22 (0.15–0.31)	0.27 (0.19–0.38)	8.8
89	6-CF_3	c	186–189	$C_{22}H_{24}F_4N_2O$·2HCl	>80		>166	NT

[a–e] See corresponding footnotes in Table IV. All compounds were made by method A.

(17) Seeman, P.; Westman, K.; Protiva, M.; Jilek, J.; Jain, P. C.; Saxena, A. K.; Anand, N.; Humber, L.; Philipp, A. *Eur. J. Pharmacol.* **1979**, *56*, 247.
(18) Petersen, P. V.; Nielsen, I. M.; Pedersen, V.; Jørgensen, A.; Lassen, N. In "Psychotherapeutic Drugs", Part II; Usdin, E.; Forrest, I. S., Eds.; Marcel Dekker: New York, 1977; p 827.
(19) Protiva, M. *Pharmazie* **1979**, *34*, 274.

Table VI. Variation of the 4'-Substituent



compd	X	Y	isomerism[a]	mp, °C	formula[b]	methyl phenidate antagonism, mice: ED_{50},[c] μmol/kg po	amphetamine antagonism, rats ED_{50},[c] μmol/kg po	catalepsy, rats ED_{50},[c] μmol/kg po
90	CF_3	H	t	250–253	$C_{22}H_{25}F_3N_2O \cdot 2HCl \cdot 1.1H_2O$[d]	4.7 (1.3–1.7)	10.4 (8.2–13)	5.7 (2.0–16)
91	CF_3	CH_3	90% t	246–248	$C_{23}H_{27}F_3N_2O \cdot 2HCl \cdot 1.0H_2O$	42 (14–131)	64 (48–86)	>81
92	CF_3	Cl	>90% t	235–240	$C_{22}H_{24}ClF_3N_2O \cdot 2HCl$	40 (19–84)	22 (15–32)	29 (17–50)
88	CF_3	F	t			0.07 (0.02–0.33)	0.22 (0.15–0.31)	0.27 (0.19–0.38)
93	Cl	Cl	t	246–251	$C_{21}H_{24}Cl_2N_2O \cdot 2HCl$	>86	NT[e]	>86
87	Cl	F	t			2.8 (1.5–5.1)	3.5 (2.7–4.5)	3.3 (1.7–6.6)

[a–c,e] See corresponding footnotes in Table IV. All compounds were made by method A. [d] C: calcd, 54.68; Found, 54.14.

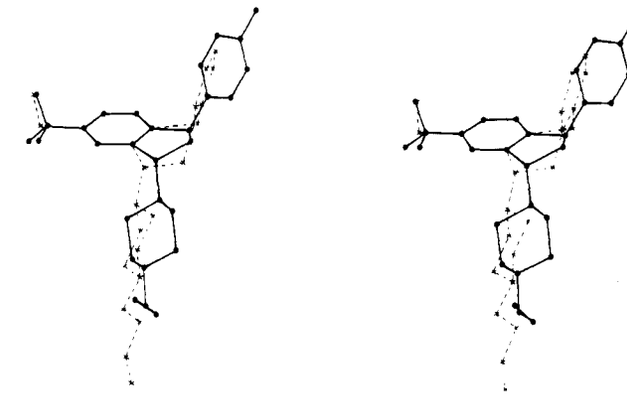


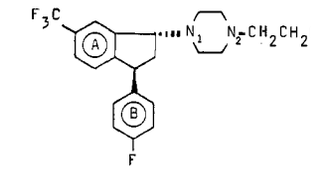
Figure 1. Superimposition of the crystal structures of 88 and 5 (oxyprothepine).

Table VII. Intramolecular Distances in Compounds 4, 5,[a] and 88[b]

compd	A-N_2[c]	B-N_2[c]	A-Z[d]
(+)-4	6.2	7.5	3.2
(±)-5	6.0	7.7	4.1
(±)-88	5.64	8.6	4.06

[a] Reference 22. [b] Reference 10. [c] Distances (in angstroms) from the centers of the phenyl rings A and B to the piperazine nitrogen N_2. [d] Distance (in angstroms) from the piperazine nitrogen N_2 to the plane of ring A.

thiepins 4 and 5 and the phenylindans, represented by 88, was revealed by comparison of 88 and 5 (oxyprothepine)



88

as found in the crystal structures (Figure 1).[10,20] The molecules shown in the stereoscopic view are those that correspond to the pharmacologically active (+)*S* enantiomer of 4.[17,21] When the indan phenyl ring of 88 and the A-phenyl ring of 5 (or 4) are superimposed, with the "neuroleptic" substituents in the same position, the position of the piperazine rings of the two molecules is approximately the same. In *cis*-1-piperazino-3-phenylindans the piperazine ring has a completely different orientation, and this difference might explain why these isomers have no neuroleptic activity. The orientation of the 3-phenyl ring in 88 roughly corresponds to that of the B-phenyl ring in 5. An even better fit between the molecules of 88 and 5 presumably could be obtained by rotation of the 3-phenyl ring in 88 or by a conformational change of the five-membered ring of indan. In the crystals of 88, the indan ring system almost is planar, with only C_2 out of plane. The piperazine ring has a pseudoaxial orientation, while the phenyl ring is found to be pseudoequatorial. This conformation of the indan ring system is, however, only marginally preferred over the one in which C_2 is found on the opposite side of the ring system (calculated difference ~1 kcal/mol[10]), and no real energy barrier hinders the conformational change. This flexibility of the phenylindans may be an important quality in explaining their

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(21) Jaunin, A.; Petcher, T. J.; Weber, H. P. *J. Chem. Soc., Perkin Trans. 2* **1977**, *186*.

interaction with different receptor sites.

A comparison (Table VII) of selected *intra*molecular distances[10,22] in **4**, **5**, and **88** further documents the structural resemblance between these compounds. A hypothetical DA receptor model has recently been proposed by Olson et al.[2] The three-dimensional structure of **88** contains all the structural elements necessary to make this compound at least qualitatively compatible with the model. If phenyl ring A in **88** occupies the binding area corresponding to the A ring in (+)-dexclamol (which is used as a model compound to illustrate the receptor model), then phenyl ring B and nitrogen N_2 will appear at locations corresponding to the second aromatic binding site and the ammonium–carboxylate binding site, respectively. The hypothetical model also includes certain geometrical relationships between the aromatic ring (A) and the nitrogen atom. The distance A–N_2 (Table VII) in **88** is within the expected range of 5–7 Å, but the angular relationships are not within the range found for the semirigid dopaminergic drugs used as examples (the values,[10] as defined by Olson et al.,[2] are $\theta_1 = 43.8°$, $\theta_2 = 59.5°$, and $\tau = \pm 82.8°$). Compound **88** is, however, a much more flexible compound, and it is possible that the angular relationships are considerably different in conformations other than the conformation found in the crystal structure.

The three-dimensional structure of **88** presumably is compatible to a certain degree with the earlier DA receptor model proposed by Humber et al.[23,24] However, this model postulates that the distance from the nitrogen atom binding site to the plane of the primary phenyl-ring binding site has a critical value of +0.9 Å. This distance (A–Z, Table VII) is 4.06 Å for **88**, very near the values found for **4** and **5** and many other DA antagonists.[22] It has been shown,[22] however, by superimposition of a number of neuroleptic drugs on (+)-dexclamol, that even when the nitrogen atoms of the neuroleptic drugs and the matching molecule are not coincident, good fits can be obtained in which the lone pairs of the nitrogen atoms point in the same direction. This suggests that the positions of the nitrogen lone pairs are more important than the above-mentioned distance A–Z. Superimposition of Dreiding models of **88** and (+)-dexclamol do not preclude a similar good fit.

Compound **88** also is a potent 5-HT_2 receptor antagonist, as measured by inhibition of [^{3}H]spiroperidol binding to rat cortical membranes (IC_{50} = 8.6 nM).[4] Methiothepin also is a potent 5-HT_2 antagonist but, in contrast to **88**, is also a potent blocker of α-adrenolytic receptors.[4] In addition, **88** has no anticholinergic activity. The detailed pharmacology of **88** will be published elsewhere. This compound has been selected for clinical trials as an antipsychotic agent.

Thymoleptic Activity. As mentioned in the beginning of this paper, it was quickly recognized that many of the compounds were potent inhibitors of DA uptake. It should be mentioned that this quality is not shared by the structurally related thiepins, since both octoclothepin (**4**) and methiothepin are very weak inhibitors of DA uptake.[4]

The most active compounds were found among the 4′,6-difluoro-substituted derivatives (Table IV). The effects of selected compounds from this series on inhibition of DA, noradrenaline (NA), and 5-hydroxytryptamine (5-HT) uptake, are shown in Table VIII. Both cis and trans isomers were active. Cis isomers were generally more potent DA-uptake inhibitors than the trans isomers, while the trans isomers were more potent NA- and 5-HT-uptake inhibitors. While the antistereotypic activity of the trans racemate **53** arose from the (+) enantiomer (**54**) only, it was found that the (−) enantiomer (**55**) was the active amine uptake inhibitor. The uptake-inhibiting activity of **55** might, as mentioned earlier, explain the relatively weak in vivo potency of **53** compared to **54**. The 3-phenyl-2-propenylpiperazine substituent of **2**[5] (compounds **63** and **64**) did not increase the DA-uptake inhibiting activity in this series, where the highest activity was found in the 4-hydroxybutyl-substituted derivative **70**. The potent neuroleptic compound **88** is included for comparison and is seen to be a three to four times weaker amine uptake inhibitor than the corresponding 6-fluoro-substituted compound (**65**).

Table VIII. Effects of Selected Compounds on DA-, NA-, and 5-HT-Uptake Inhibn

	synaptosomal uptake inhibn: IC_{50},[a] nM		
compd	DA	NA	5-HT
53	180	45	2000
54	1800	13 000	4000
55	88	32	630
56	110	97	6100
63	340	NT	160
64	210	NT	400
65	170	150	2300
66	44	140	9700
69	25	19	610
70	9	30	1900
88	520	660	7000[b]
89	93	NT	NT

[a] See footnote *d* in Table IV. [b] Data for the dihydrochloride of compound **88**.

A number of new derivatives were synthesized in the hope of obtaining a DA-uptake inhibitor even more selective and potent than **70**. We soon recognized that the 6-substituent, which was so important for neuroleptic activity, was not essential for DA-uptake inhibition. The most potent compounds in the new series were the 3′,4′-dichloro-substituted derivatives presented in Table IX. In addition to the amine-uptake inhibiting activity, thymoleptic activity was also assessed by the ability of the compounds to antagonize tetrabenazine ptosis in mice. None of the trans isomers of 3′,4′-dichloro-substituted derivatives had antistereotypic activity[4] (not shown in Table IX). Most compounds were more potent DA-uptake inhibitors than **70**, but they also were potent NA-uptake inhibitors, so a higher selectivity for DA-uptake inhibition was not obtained. The 3-phenyl-2-propenyl substituent (**104** and **105**) was also ineffective in this series, and a change from 3′,4′- to 2′,4′-dichloro substitution (**106** and **107**) resulted in loss of activity.

In this series, the cis and trans racemates were almost equipotent, demonstrating that there was no geometrical stereoselectivity at the amine uptake sites. However, a clear enantioselectivity at all three uptake sites was found for the enantiomers of **94** and **97**. As for **53**, all amine-uptake inhibiting activity was found in the (−) enantiomers (**96** and **99**). Although a selective DA-uptake inhibitor was not obtained, the most active compounds **99** and **100** were still more active and selective than the reference compounds nomifensine and **108** (LR 5182).[25] The latter

(22) Tollenaere, J. P.; Moereels, H.; Raymaekers, L. A. *Drug Des.*, **1980**, *10*, 71.
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Table IX. Influence of Stereochemistry and Piperazine N-Substitution on the Thymoleptic Activity of Selected Compounds

compd	X	Y	R	isomerism[a]	mp, °C	formula[b]	synaptosomal uptake inhibn: IC_{50},[c] nM DA	NA	5-HT	tetrabenazine ptosis, mice: ED_{50},[d] μmol/kg ip
94	3-Cl	4-Cl	CH_3	t	251–255	$C_{20}H_{22}Cl_2N_2 \cdot 2HCl$	11	32	200	48 (22–107)
95	3-Cl	4-Cl	CH_3	(+)t	237–239	$C_{20}H_{22}Cl_2N_2 \cdot 2HCl \cdot 0.19H_2O$	340	120	2500	>91
96	3-Cl	4-Cl	CH_3	(−)t	241–242	$C_{20}H_{22}Cl_2N_2 \cdot 2HCl$	10	7.8	230	26 (15–43)
97	3-Cl	4-Cl	CH_3	c	257–261	$C_{20}H_{22}Cl_2N_2 \cdot 2HCl \cdot 0.77H_2O$	4.4	7.7	630	100 (34–295)
98	3-Cl	4-Cl	CH_3	(+)c	236–240	$C_{20}H_{22}Cl_2N_2 \cdot 2HCl \cdot 0.82H_2O$	1700	910	2300	>89
99	3-Cl	4-Cl	CH_3	(−)c	236–240	$C_{20}H_{22}Cl_2N_2 \cdot 2HCl \cdot 0.88H_2O$	2.3	2.5	530	69 (35–139)
100	3-Cl	4-Cl	CH_2CH_2OH	93% t	248–253	$C_{21}H_{24}Cl_2N_2O \cdot 2HCl$	2.8	8.2	210	45 (23–85)
101	3-Cl	4-Cl	CH_2CH_2OH	c	254–259	$C_{21}H_{24}Cl_2N_2O \cdot 2HCl$	12	10	600	72 (8.7–595)
102	3-Cl	4-Cl	$(CH_2)_3OH$	t	93–94	$C_{22}H_{26}Cl_2N_2O$	15	6.8	120	12 (6.7–21)
103	3-Cl	4-Cl	$(CH_2)_3OH$	>90% c	269–272	$C_{22}H_{26}Cl_2N_2O \cdot 2HCl$	5.6	0.3	440	71 (29–176)
104	3-Cl	4-Cl	$CH_2CH{=}CH{-}C_6H_5$	85% t	259–261	$C_{28}H_{28}Cl_2N_2 \cdot 2HCl$	100	NT[e]	NT	>75
105	3-Cl	4-Cl	$CH_2CH{=}CH{-}C_6H_5$	c	250–252	$C_{28}H_{28}Cl_2N_2 \cdot 2HCl \cdot 1.0H_2O$	35	NT	NT	>73
106	2-Cl	4-Cl	CH_2CH_2OH	~90% t	260–263	$C_{21}H_{24}Cl_2N_2O \cdot 2HCl$	4500	NT	NT	>86
107	2-Cl	4-Cl	CH_2CH_2OH	90% c	255–257	$C_{21}H_{24}Cl_2N_2O \cdot 2HCl$	2000	NT	NT	>94
108 (LR 5182)[f]							9.3	5.4	51	43 (21–85)
109 (trans isomer of LR 5182)[f] nomifensine							11	NT	13	NT
							48	6.6	830	4.3 (1.8–10.1)

[a,b,e] See corresponding footnotes in Table IV. All compounds were made by method A, except 104 and 105, which were made by method C. [c] See footnote d in Table IV. [d] 95% confidence limits in parentheses. [f] These compounds were synthesized according to the procedures given in ref 27 and 28.

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compound has some structural resemblance to the phenylindans, since it has both a 3′,4′-dichloro-substituted phenyl ring and a three-carbon separation between this ring and the amine part. The stereochemical requirements at the DA-uptake site seem to be qualitatively the same for the 3-phenyl-2-(aminomethyl)bicyclo[2.2.2]octanes and the 1-piperazino-3-phenylindans. The trans isomer (**109**, see Table IX) of **108** also is a potent DA-uptake inhibitor, but it has been reported[26] that the (−) enantiomer of **108** is a three times more potent DA-uptake inhibitor than the (+) enantiomer. The 1-piperazino-3-phenylindan structure seems, however, to have structural elements that greatly enhance enantioselectivity. Further work is in progress in order to investigate the thymoleptic activity of 3-phenyl-1-indanamines.

Experimental Section

Melting points (uncorrected) were determined on a Büchi SMP-20 apparatus. ^1H NMR spectra were recorded at 80 MHz and ^{13}C NMR spectra were recorded at 20 MHz on a Brucker WP 80 DS spectrometer. Me_4Si was used as internal reference standard. All compounds were routinely checked by TLC. The isomeric purity of the cis and trans isomers was determined by TLC with Merck silica gel 60 F_{254} precoated plates and acetone–toluene–NH_4OH–2-propanol (60:40:2:2) as the developing solvent. The substances were visualized by spraying the complete dried plate with a mixture of concentrated sulfuric acid–37% formaldehyde solution (47:3), by heating the plate for 5 min at 110 °C, and then by observing it under an ultraviolet source at 365 nm. In order to obtain satisfactory sensitivity, sometimes it was necessary to spray with 5% potassium dichromate in 40% sulfuric acid and to heat at 110 °C for 20 min. The estimation of isomeric purity was based on comparison with small samples of the opposite isomer or small samples of the substance itself. Trans isomers had in all cases the lowest R_f values. HPLC analyses were performed on a DuPont 830 liquid chromatograph. Microanalyses (within ±0.4% of theoretical values except where noted) were performed by the Lundbeck Analytical Department. Some of the dihydrochloride salts retained a partial mole of H_2O despite drying in vacuo. This was confirmed by Karl–Fischer (KF) determination.

Substituted Piperazines. 1-Methylpiperazine and 1-piperazineethanol were commercial products. 1-(3-Hydroxy-1-propyl)piperazine, 1-(4-hydroxy-1-butyl)piperazine, and 1-(2,3-dihydroxy-1-propyl)piperazine were prepared by methods established in the literature.[29] 1-(1,3-Dihydroxy-2-propyl)-piperazine was prepared by alkylation of 1-benzylpiperazine with diethyl bromomalonate, followed by reduction with lithium aluminum hydride and catalytic debenzylation with H_2 and Pd/C.

Ethyl 2-Cyano-3-phenyl-2-propenoates (I). 2-Bromo-4-(trifluoromethyl)benzoic acid was prepared from 4-(trifluoromethyl)anthranilic acid by the Sandmeyer reaction: yield 84%; mp 120–122 °C. Anal. ($C_8H_4BrF_3O_2$) C, H.

The acid was treated with thionyl chloride, and the resulting 2-bromo-4-(trifluoromethyl)benzoyl chloride was purified by distillation: yield 95%; bp 98–100 °C (10 mmHg).

The acid chloride was reduced by the Rosenmund method,[30]

(26) Wong, D. T.; Bymaster, F. P.; Reid, L. R. *J. Neurochem.* **1980**, *34*, 1453.
(27) Redies, F.; Reides, B.; Türk, D.; Gille, C. German Offen. 2354931, 1972.
(28) Redies, F.; Redies, B.; Türk, D.; Gille, C. German Offen. 2619617, 1975.
(29) Barret, P. A.; Caldwell, A. G.; Walls, L. P. *J. Chem. Soc.* **1961**, 2404.

and the resulting aldehyde was purified via the bisulfite addition compound from which 69% of 2-bromo-4-(trifluoromethyl)-benzaldehyde was obtained.

To a solution of 2-bromo-4-(trifluoromethyl)benzaldehyde (306 g, 1.21 mol) and ethyl cyanoacetate (155 g, 1.37 mol) in toluene (1 L) was added piperidine (2 mL), and the mixture was refluxed for 30 min with a Dean–Stark separator to remove water. The toluene was evaporated in vacuo, and the resulting oil was crystallized from isopropyl ether–hexane (1:1) to give 345 g (82%) of ethyl 3-[2-bromo-4-(trifluoromethyl)phenyl]-2-cyano-2-propenoate, mp 104–106 °C. Anal. ($C_{13}H_9BrF_3NO_2$) C, H, N.

2-Bromo-4-chlorobenzaldehyde, mp 65–67 °C, obtained in a similar way from 2-bromo-4-chlorobenzoic acid, gave a 59% yield of ethyl 3-(2-bromo-4-chlorophenyl)-2-cyano-2-propenoate, mp 78–82 °C.

All other compounds were obtained from commercially available aldehydes and ethyl cyanoacetate.

3,3-Diphenylpropanoic Acids. General Procedure. 3-[2-Bromo-4-(trifluoromethyl)phenyl]-3-(4-fluorophenyl)-propanoic Acid (13). A Grignard solution was prepared from 1-bromo-4-fluorobenzene (350 g, 2 mol) and magnesium turnings (49 g, 2.04 g-atoms) in dry ether (1 L). A solution of ethyl 3-[2-bromo-4-(trifluoromethyl)phenyl]-2-cyano-2-propenoate (612 g, 1.76 mol) in dry, warm toluene (1 L) was added to the Grignard solution over 15 min, with simultaneous distillation of ether. The distillation was continued until an internal temperature of 80 °C was reached. The mixture was refluxed for 30 min and then poured into ice (2 kg) and concentrated H_2SO_4 (100 mL). The organic phase was separated, washed once with water, dried ($MgSO_4$), and evaporated in vacuo to give a quantitative yield of crude ethyl 3-[2-bromo-4-(trifluoromethyl)phenyl]-2-cyano-3-(4-fluorophenyl)propanoate. A sample was recrystallized from isopropyl ether–hexane, mp 133–135 °C. Anal. ($C_{19}H_{14}BrF_4NO_2$) H, N; C: calcd, 51.37; found, 51.82. A mixture of crude ester (830 g), acetic acid (1600 mL), concentrated H_2SO_4 (800 mL), and water (800 mL) was refluxed with stirring for 24 h and then poured into ice. The crystalline acid was filtered, dissolved in ether, and dried ($MgSO_4$). The ether solution was transferred to a beaker and evaporated on a steam bath with addition of hexane (1.5 L) to give 547 g (70%) of **13**, mp 126–130 °C. Anal. ($C_{16}H_{11}BrF_4O_2$) C, H.

3-Phenylindan-1-ones (III). The reaction conditions for cyclizations with PPA or $SOCl_2/AlCl_3$ are given in Table II.

Cyclization with *n*-Butyllithium. General Procedure. 3-(4-Fluorophenyl)-6-(trifluoromethyl)indan-1-one (28). *n*-Butyllithium (1 L, 20% in hexane, 2.19 mol) was added, with stirring and under a N_2 atmosphere, to a solution of **8** (391 g, 1 mol) in dry ether (1 L). The temperature was kept at −5 °C throughout the addition (15 min) by means of a CO_2–acetone bath. The mixture was stirred at 0 °C for 30 min and then poured on ice and concentrated HCl (200 mL). The organic phase was separated, washed with water, 10% aqueous Na_2CO_3 solution and water, dried ($MgSO_4$), and evaporated in vacuo. The resulting oil was distilled in vacuo to give 241 g (82%) of **28**, bp 158–162 °C (1 mmHg). A crystalline sample was obtained by chromatography on silica gel with isopropyl ether–hexane (1:1) as eluent, mp 44–45 °C. Anal. ($C_{16}H_{10}F_4O$) C, H.

Preparation of 3-(4-Fluorophenyl)-6-(methylsulfonyl)-indan-1-one (36). 3-Chloroperbenzoic acid (85%, 175 g, 0.86 mol) was added in portions to a solution of **27** (112 g, 0.41 mol) in chloroform (1 L) with cooling and stirring at 20–30 °C. After 30 min at room temperature, the mixture was filtered, and the filtrate was washed with dilute NaOH, dried ($MgSO_4$), and evaporated in vacuo. The product was recrystallized from ethyl acetate to give 90 g (72%) of **36**, mp 113–115 °C. Anal. ($C_{16}H_{13}FO_3S$) C, H.

3-Phenylindan-1-ols (IV). General Procedure (Reduction with Sodium Borohydride). 3-(4-Fluorophenyl)-6-(trifluoromethyl)indan-1-ol (44). Sodium borohydride (10 g, 0.26 mol) was added in portions with stirring at 10–15 °C to a solution of **23** (241 g, 0.82 mol) in methanol (2 L). The mixture was stirred at room temperature for 1 h and then evaporated in vacuo. The resulting oil was treated with water and ether, and the organic phase was separated, washed with water and 0.1 N HCl, dried ($MgSO_4$), and evaporated in vacuo. The resulting oil was dissolved in hexane (400 mL) and crystallized to give 182 g (75%) of **44**, mp 72–79 °C. A sample was recrystallized from hexane, mp 78–80 °C. Anal. ($C_{16}H_{12}F_4O$) C, H.

Reduction with Potassium Tri-*sec*-butyl Borohydride (K-Selectride). *cis*-6-Fluoro-3-(4-fluorophenyl)indan-1-ol (38). Under a nitrogen atmosphere, potassium tri-*sec*-butyl borohydride (K-Selectride, 0.5 M in THF, 200 mL, 0.1 mol) was added from a syringe to a stirred solution of **22** (24 g, 0.1 mol) in THF (50 mL), kept at 2–4 °C. After 40 min at 0 °C, 3 N NaOH (50 mL) was added without cooling, followed by the dropwise addition of 35% H_2O_2 (30 mL) with cooling. The phases were separated, and the organic phase was washed twice with a saturated solution of NaCl in water and once with 1 N $FeSO_4$ in water. After the solution was dried ($MgSO_4$) and evaporated in vacuo, the resulting oil was crystallized from isopropyl ether–hexane to give 18.4 g (75%) of **38**, mp 70–71 °C. Anal. ($C_{15}H_{12}F_2O$) C, H. After HPLC analysis (Spherisorp ODS, 5 μm; mobile phase methylene chloride–heptane–acetonitril, 45:45:5; UV_{254} detector), the product was found to contain less than 1% of the other isomer (trans). Similar analysis of **38** obtained by sodium borohydride (mp 64–67 °C) or lithium aluminum hydride (mp 64–67 °C) reduction of **22** showed that the content of trans isomer in these products was 3 and 5%, respectively.

1-Chloro-3-phenylindans (V). General Procedure. 1-Chloro-3-(4-fluorophenyl)-6-(trifluoromethyl)indan. Thionyl chloride (18.5 mL, 0.25 mol) was added with stirring and cooling at 15 °C to a solution of **44** (50 g, 0.17 mol) in toluene (300 mL). The mixture was stirred at room temperature for 30 min and then heated to 50–55 °C and kept at that temperature for 1 h. The mixture was cooled, washed twice with water, dried ($MgSO_4$), and evaporated in vacuo to give a quantitative yield of the title compound as an oil, which was used without further purification in the next step: NMR ($CDCl_3$) δ 2.1–3.5 (2 H, m, CH_2), 4.3 (0.75 H, br t, Ar_2CH, J = 8 Hz), 4.5–4.9 (0.25 H, m, Ar_2CH), 5.4 (0.75 H, t, $CHCl$, J = 8 Hz), 5.55 (0.25 H, dd, $CHCl$), 6.9–7.9 (7 H, m, ArH).

Method A. General Procedure. *trans*- and *cis*-4-[3-(4-Fluorophenyl)-6-(trifluoromethyl)indan-1-yl]-1-piperazineethanol (88 and 89). A mixture of crude (see example above) 1-chloro-3-(4-fluorophenyl)-6-(trifluoromethyl)indan (54 g, 0.17 mol) and 1-piperazineethanol (50 g, 0.38 mol) in ethyl methyl ketone (250 mL) was refluxed for 16 h. The mixture was cooled, extracted with water, and evaporated in vacuo. The residue was dissolved in ether, washed with water, and extracted with a 2 N solution of methanesulfonic acid in water. This extract was basified with concentrated ammonium hydroxide and extracted with ether. After the extract was dried ($MgSO_4$) and evaporated in vacuo, 57 g (82%) of an isomeric mixture of **88** and **89** was obtained. The isomeric mixture was dissolved in methanol (300 mL), and a solution of oxalic acid dihydrate (40 g, 0.32 mol) in water (500 mL) and methanol (100 mL) was added. The precipitate was filtered, boiled in methanol (1 L), cooled, and filtered again. A slurry of the oxalate in water was basified with dimethylamine (40% solution in water) and extracted with ether. After the extract was dried ($MgSO_4$) and evaporated in vacuo, the residual oil was dissolved in isopropyl ether (60 mL) and hexane (300 mL) and crystallized to give 35.4 g (51%) of **88**, mp 85–86 °C; isomeric purity >99% trans (TLC). Anal. ($C_{22}H_{24}F_4N_2O$) C, H, N. The combined filtrates from the oxalate were concentrated, basified, and extracted with ether. The ether extract was dried, concentrated in vacuo, dissolved in acetone, and acidified with a saturated solution of HCl in ether. The dihydrochloride salt was recrystallized from methanol to give 3.5 g (4%) of **89**: mp 186–189 °C; isomeric purity >99% (TLC). Anal. ($C_{22}H_{26}Cl_2F_4N_2O$) C, H, N.

1-(3-Phenylindan-1-yl)piperazines (VI). 1-[6-Fluoro-3-(4-fluorophenyl)indan-1-yl]piperazine (Isomeric Mixture, VIa). A mixture of 1-chloro-3-(4-fluorophenyl)-6-fluoroindan (60 g, 0.23 mol) and piperazine (120 g, 1.4 mol) in ethyl methyl ketone (500 mL) was refluxed with stirring for 3 h. The mixture was worked up as described above to give 67 g (94%) of an isomeric mixture (VIa) of the title compound as an oil, which was used directly in the next step.

(30) Hershberg, E. B.; Cason, J. "Organic Syntheses"; Horning, E. C., Ed.; Wiley: New York, 1955; Collect. Vol. III, p 627.

Method B. General Procedure. *trans*- and *cis*-1-[6-Fluoro-3-(4-fluorophenyl)indan-1-yl]-4-(2-phenylethyl)-piperazine (61 and 62). A mixture of the above-mentioned compound (VIa; 31 g, 0.1 mol), phenethyl bromide (25 g, 0.14 mol), and potassium carbonate (30 g, 0.21 mol) in isobutyl methyl ketone (200 mL) was refluxed with stirring for 16 h. The reaction mixture was worked up, and the isomers were separated as described above (route A). There was obtained 18 g (43%) of **61**: mp 80–82 °C (hexane); isomeric purity >99% trans (TLC). Anal. ($C_{27}H_{28}F_2N_2$) C, H, N. Of the cis-isomer **62** was obtained 4 g (9.6%): mp 75–77 °C (hexane); isomeric purity >99% (TLC). Anal. ($C_{27}H_{28}F_2N_2$) H, N; C: calcd, 77.47; found, 76.84.

Method C. General Procedure. *trans*- and *cis*-1-(Cyclopropylmethyl)-4-[6-fluoro-3-(4-fluorophenyl)indan-1-yl]piperazine (59 and 60). A mixture of VIa (31 g, 0.1 mol) and cyclopropanecarbonyl chloride (15 g, 0.14 mol) in toluene (200 mL) was stirred for 30 min at 70–80 °C. The mixture was cooled, and the crystalline hydrochloride was filtered and converted to the base to give 40 g of the amide as an oil. The amide in ether (500 mL) was reduced with lithium aluminum hydride to afford an isomeric mixture of **59** and **60**, which was separated into the pure isomers as described above. There was obtained 17 g (38%) of **59** as the dihydrochloride salt: mp 254–256 °C; isomeric purity >99% (TLC) trans. Anal. ($C_{23}H_{28}Cl_2F_2N_2$) C, H, N. Of the cis-isomer **60** was obtained 3 g (6.8%) as the dihydrochloride salt: mp 260–262 °C; isomeric purity 98% (TLC). Anal. ($C_{23}H_{28}Cl_2F_2N_2$) C, H, N.

Method D. *trans*- and *cis*-1-[6-Fluoro-3-(4-fluorophenyl)indan-1-yl]-4-(2-hydroxy-1-propyl)piperazine (71 and 72). A mixture of VIa (31 g, 0.1 mol) and propylene oxide (7 g, 0.12 mol) in methanol (100 mL) was left at room temperature for 16 h. The base obtained after evaporation in vacuo was converted to the dihydrochloride salt, and the isomers were separated by fractional crystallization from ethanol to give 13 g (29%) of **71**: mp 255–258 °C; isomeric purity 95% trans. Anal. ($C_{22}H_{18}Cl_2F_2N_2O$) C, H, N. Of the cis-isomer **72** was obtained 1.1 g (2.4%): mp 262–265 °C; isomeric purity 95%. Anal. ($C_{22}H_{18}Cl_2F_2N_2O$) C, H, N.

Alternative Procedure for Preparation of Cis Isomers. *cis*-4-[6-Fluoro-3-(4-fluorophenyl)indan-1-yl]-1-piperazinepropanol (68). A solution of methanesulfonyl chloride (22.5 g, 0.2 mol) in methylene chloride (25 mL) was added dropwise with cooling and stirring to a solution of **38** (25 g, 0.1 mol) in methylene chloride (75 mL) and pyridine (35 mL) at 20 °C. The mixture was stirred for 2.5 h at room temperature and then poured on ice–water. The organic phase was separated, washed with cold water and cold dilute hydrochloric acid, dried ($MgSO_4$), and evaporated in vacuo to give 24.6 g (76%) of the mesylate of **38** as an oil.

A mixture of this oil in ethyl methyl ketone (100 mL), 1-(3-hydroxy-1-propyl)piperazine (17 g, 0.12 mol), and potassium carbonate (14 g, 0.1 mol) was refluxed with stirring for 16 h. The mixture was cooled and extracted with water, the extract was evaporated in vacuo, and the crystalline residue was treated with isopropyl ether to give 14.5 g (39%) of **68**. After recrystallization from isopropyl ether–hexane, there was obtained 11.5 g (31%) of pure **68**: mp 92–94 °C; isomeric purity >98% (TLC). Anal. ($C_{22}H_{26}F_2N_2O$) C, H, N.

Optical Resolution of Enantiomers. (+)- and (−)-*trans*-1-[6-Fluoro-3-(4-fluorophenyl)indan-1-yl]-4-methylpiperazine (54 and 55). To a solution of **53** (base) (39 g, 0.12 mol) in ethyl acetate (300 mL) was added (+)-*O,O'*-dibenzoyl-D-tartaric acid hydrate (44.5 g, 0.12 mol), and the mixture was heated on a steam bath until a clear solution was obtained. The mixture was left in the refrigerator for 16 h, and the precipitate was filtered and recrystallized from ethyl acetate–acetone, 1:1 (400 mL), to give 24 g of the (+)-*O,O'*-dibenzoyl-D-tartaric acid salt of **54**, mp 145–146 °C. The salt was converted to the base with dilute sodium hydroxide and extracted with ether, and the extract was dried ($MgSO_4$) and evaporated in vacuo. The base was dissolved in acetone and converted to the dihydrochloride salt by addition of a saturated solution of HCl in ether to give 12 g of **54**: mp 249–251 °C: $[\alpha]^{22}_D$ +19.8° (*c* 5, MeOH); KF determination 0.57% H_2O. Anal. ($C_{20}H_{24}Cl_2F_2N_2 \cdot 0.13H_2O$) C, H, N.

The first filtrate from the isolation of the (+)-*O,O'*-dibenzoyl-D-tartaric acid salt was converted to the base. The base was dissolved in hot ethyl acetate (150 mL) and D-(−)-tartaric acid (10.5 g) was added. The mixture was cooled, and the precipitate was filtered and recrystallized from methanol (500 mL) to give 18.5 g of the D-(−)-tartrate of **55**, mp 207–209 °C. The tartrate was converted to the dihydrochloride as described above to give 10 g of **55**: mp 252–254 °C; $[\alpha]^{22}_D$ −19.8° (*c* 5, MeOH); KF determination 0.65% H_2O. Anal. ($C_{20}H_{24}Cl_2F_2N_2 \cdot 0.15H_2O$) C, H, N.

(+)- and (−)-*trans*-1-[3-(3,4-Dichlorophenyl)indan-1-yl]-4-methylpiperazine (95 and 96). Compound **94** (124 g) was separated as described above to give 31 g of the (+)-*O,O'*-dibenzoyl-D-tartaric acid salt of **96**, mp 175–176 °C (after four recrystallizations from methanol). The salt was converted to the base, $[\alpha]^{22}_D$ −23.8° (*c* 4, MeOH), to give 8.6 g of **96** as the dihydrochloride salt, mp 241–242 °C. Anal. ($C_{20}H_{24}Cl_4N_2$) C, H, N.

The D-(−)-tartaric acid salt of **95** (mp 197–198 °C after four recrystallizations from methanol) was converted to the base, $[\alpha]^{22}_D$ +20.0° (*c* 5.1, MeOH), to give 3 g of **95** as the dihydrochloride salt, mp 237–239 °C; KF determination 0.8% H_2O. Anal. ($C_{20}H_{24}Cl_4N_2 \cdot 0.19H_2O$) C, H, N.

(+)- and (−)-*cis*-1-[3-(3,4-Dichlorophenyl)indan-1-yl]-4-methylpiperazine (98 and 99). Compound **97** (70 g) was separated as described above, with the exception that (−)-*O,O'*-dibenzoyltartaric acid was used instead of D-(−)-tartaric acid. The (+)-*O,O'*-dibenzoyltartaric salt of **98** (mp 158–159 °C after three recrystallizations from ethanol) was converted to the base, $[\alpha]^{22}_D$ +48.5° (*c* 5.2, MeOH), to give 12 g of **98** as the dihydrochloride salt: mp 236–240 °C; KF determination 3.3% H_2O. Anal. ($C_{20}H_{24}Cl_4N_2 \cdot 0.82H_2O$) C, H, N.

The (−)-*O,O'*-dibenzoyltartaric acid salt of **99** (mp 152–153 °C after three recrystallizations from ethanol–methanol, 3:1) was converted to the base $[\alpha]^{22}_D$ −49.8° (*c* 1.14, MeOH), to give 7 g of **99** as the dihydrochloride salt, mp 236–240 °C; KF determination 3.5% H_2O. Anal. ($C_{22}H_{24}Cl_4N_2 \cdot 0.88H_2O$) C, H, N.

***trans*- and *cis*-1-[7-Fluoro-4-(4-fluorophenyl)-1,2,3,4-tetrahydro-1-naphthyl]-4-methylpiperazine (3a and 3b).** 4-Chloro-6-fluoro-1-(4-fluorophenyl)-1,2,3,4-tetrahydronaphthalene was obtained essentially as described in the literature.[3] The crude chloride was not crystallized but was directly mixed with excess 1-methylpiperazine and kept at 90 °C for 16 h. The reaction mixture was worked up to give **3a**: mp 119–121 °C (lit.[3] mp 120–121 °C); isomeric purity ≥95% (probably trans by analogy to the corresponding indans). Anal. ($C_{21}H_{24}F_2N_2$) C, H, N. The first mother liquor from the crystallization of **3a** was concentrated and converted to the dihydrochloride salt, which was recrystallized twice from ethanol–ether to give **3b** as the dihydrochloride salt (hygroscopic): mp 285–287 °C; KF determination 1.7% H_2O; isomeric purity ≥95% (cis). Anal. ($C_{21}H_{26}Cl_2F_2N_2 \cdot 0.42H_2O$) C, H, N.

Pharmacology. The pharmacological and biochemical screening were done in the Department of Pharmacology and Toxicology, H. Lundbeck & Co. A/S, by Drs. A. V. Christensen, J. Hyttel, and J. Arnt.

Animals. Experiments were performed on male mice (NMRI/BOM) and male rats (Mol/Wist.).

Statistics. ED_{50} values were calculated by probit analysis by using a log dose scale.

Methods. Methyl Phenidate Antagonism. The antagonism against methyl phenidate was estimated as described by Pedersen and Christensen (1972).[31] Two hours after ip injection of test substance, the mice were given a subcutaneous injection of methyl phenidate (60 mg/kg). Immediately after the injection of methyl phenidate, the mice were placed for exactly 1 h in observation cages, two mice to a cage. The cages consisted of 30-cm high perspex boxes (12 × 25 cm) without bottom or lid. During the experiments the cages were placed on corrugated cardboard, the corrugation facing upwards. For each dose level, at least five pairs of mice were used, and the number of pairs that did not bite the corrugated cardboard was registered.

Amphetamine Antagonism. The rats were placed in 30-cm high perspex boxes (12 × 25 cm) without bottom or lid. Ster-

(31) Pedersen, V.; Christensen, A. V. *Acta Pharmacol. Toxicol.* **1972**, *31*, 488.

eotypies (gnawing, licking, or head movements) were observed 1 h after amphetamine administration. The presence or absence of any kind of stereotypy was evaluated according to an all or none test situation. Test compounds were injected orally 2 h before amphetamine sulfate (13.6 mg/kg ~10 mg/kg of amphetamine base, iv).

Catalepsy. Catalepsy was measured in separate groups of rats by placing each rat on a vertical wire mesh (mesh diameter 12 mm). The rat was considered cataleptic if it remained immobile for at least 15 s. The number of cataleptic rats in each dose group was determined every hour during 6 h.

Tetrabenazine Ptosis. Mice were given test substance intraperitoneally 30 min before tetrabenazine (40 mg/kg ip). Thirty minutes after administration of tetrabenazine, the animal boxes were tilted up and down, and 30 s later, the animals were scored for the degree of ptosis. The scoring system was that of Rubin et al.,[32] and the ED_{50} values were calculated as the doses reducing the ptosis score to half of a control group (tetrabenazine alone).

Biochemistry. Inhibition of [^{3}H]Haloperidol Binding. Rat striatal membranes were obtained essentially as described by Burt et al.[33] Striatal tissue was homogenized (Ultra Turrax, 10 s) in 100 vol (w/v) of ice-cold 50 mM Tris buffer, pH 7.7 (at 25 °C). Homogenate was centrifuged at 40000*g* for 10 min at 4 °C, with rehomogenization of the pellet in fresh buffer. The final pellet was homogenized in 125 vol (w/v) of ice-cold, freshly prepared 50 mM Tris buffer containing 0.1% ascorbic acid, 10 μM pargyline, 120 mM NaCl, 5 mM KCl, 2 mM $CaCl_2$, and 1 mM $MgCl_2$, pH 7.1 (at 37 °C). The tissue suspension (8 mg/mL) was heated to 37 °C for 10 min before immersion in ice.

Incubation tubes kept on ice in triplicate received 100 μL of drugs, 100 μL of [^{3}H]haloperidol (15 Ci/mmol, New England Nuclear Corp.) (final concentration 2 nM), and 800 μL of cold tissue suspension. The tubes were incubated at 37 °C for 10 min and rapidly filtered under vacuum through Whatman GF/B filters (25 mm). The tubes were rinsed with 5 mL of Tris buffer, pH 7.7, and thereafter the filters were rinsed with 2 × 5 mL of 50 mM Tris buffer, pH 7.7 (at 25 °C). Radioactivity on the filters was determined by liquid scintillation counting after addition of Insta Gel. Specific binding was measured as the excess over blanks in the presence of 1 μM (+)-butaclamol. For determination of inhibition, five concentrations of neuroleptics were used.

Inhibition of DA, NA, and 5-HT Uptake in Vitro. The labeled compounds [^{3}H]DA (40–55 Ci/mmol), [^{3}H]NA (30–45 Ci/mmol), and [^{3}H]5-HT (10–30 Ci/mmol) were all obtained from New England Nuclear Corp.

Male rats [Mol/Wist (Syn Wistar), SPF, 200-250 g] were killed by decapitation and exsanguinated, and their brains were removed. The brain was placed on a precooled glass plate, and appropriate brain parts were dissected out and gently homogenized in 40 vol of ice-cold 0.32 M of sucrose containing 1 mM of nialamide, with a hand homogenizer with Teflon pestle (Potter-Elvehjem type, Thomas Tissue Grinder, clearange 0.004–0.006 in., ten strokes up and down). The following brain parts were used: corpus striatum ([^{3}H]DA), occipital plus temporal cortex ([^{3}H]NA), and whole brain minus pons, medulla oblongata, and cerebellum ([^{3}H]5-HT). The P_2 fraction (crude synaptosomal fraction) was obtained by centrifugation (600*g* for 10 min, 25000*g* for 55 min) and suspended in 40 (DA and 5-HT uptake) or 25 vol (NA uptake) of a modified Krebs–Ringer–phosphate buffer, pH 7.4 (122 mM NaCl, 4.8 mM KCl, 972 μM $CaCl_2$, 1.2 mM $MgSO_4$, 12.7 mM Na_2HPO_4, 3.0 mM NaH_2PO_4, 162 μM Na_2EDTA, 1.14 mM ascorbic acid, and 10.1 mM glucose, oxygenated with pure oxygen for 10 min before use). To 200 μL of the crude synaptosomal fraction on ice was added 3700 μL of modified Krebs–Ringer–phosphate buffer containing test compounds. After a preincubation at 37 °C for 5 min, 100 μL of labeled amine (final concentration [^{3}H]DA 12.5 nM; [^{3}H]NA, 10 nM; [^{3}H]5-HT, 10 nM) were added, and the samples were incubated for 5, 30, or 10 min (for DA, NA, and 5-HT, respectively) at 37 °C. The incubation was terminated by filtering the samples under vacuum through Millipore filters (HAWP 02500, 0.45 μm, composed of a mixture of cellulose acetate and cellulose nitrate) with a wash of 5 mL of buffer containing 10 μM of the unlabeled amine. After solubilizing the filters in 1 mL of cellosolve, the radioactivity was determined by liquid scintillation counting after the addition of 10 mL of scintillation fluid. The unspecific binding of labeled amine was determined by incubating control samples with 100 μM benztropin, 10 μM Lu 5-003 (1,3-dihydro-*N*,3,3-trimethyl-1-phenylbenzo[*c*]thiophene-1-propanamine hydrochloride), and 1 μM citalopram (for DA, NA, and 5-HT uptake, respectively). IC_{50} values were derived from concentrations causing 50% inhibition of the active uptake. Five concentrations each in triplicate were used for constructing the concentration–response curves. At least two determinations were performed with each substance.

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Registry No. (±) **3a**, 85663-22-5; (±) **3b**, 85663-40-7; (±)-**3b**·2HCl, 85663-23-6; (±)-**6**, 85662-72-2; **7**, 342-75-6; (±)-**8**, 85662-73-3; (±)-**9**, 85662-74-4; (±)-**10**, 85662-75-5; (±)-11, 85662-76-6; (±)-**12**, 85662-77-7; (±)-**13**, 85662-78-8; (±)-14, 85662-79-9; (±)-**15**, 85662-80-2; (±)-**16**, 85662-81-3; (±)-**17**, 85662-82-4; **18**, 2540-35-4; (±)-**19**, 85662-83-5; (±)-**20**, 85662-84-6; (±)-**21**, 85662-85-7; (±)-**22**, 85662-86-8; (±)-**23**, 85662-87-9; (±)-**24**, 85662-88-0; (±)-**25**, 85662-89-1; (±)-**26**, 85662-90-4; (±)-**27**, 85662-91-5; (±)-**28**, 85662-92-6; (±)-**29**, 85662-93-7; (±)-**30**, 85662-94-8; (±)-**31**, 85662-95-9; (±)-**32**, 85662-96-0; (±)-**33**, 85662-97-1; (±)-**34**, 85662-98-2; (±)-**35**, 85662-99-3; (±)-**36**, 85663-00-9; (±)-*cis*-**37**, 80272-55-5; (±)-*cis*-**38**, 80272-65-7; (±)-*cis*-V (X = 6-F; Y = *p*-F; Z = H), 80272-97-5; (±)-*trans*-V (X = 6-F; Y = *p*-F; Z = H), 80272-98-6; **38** mesylate, 85663-13-4; (±)-*cis*-**39**, 80272-69-1; (±)-*cis*-**40**, 80272-47-5; (±)-*cis*-41, 80272-81-7; (±)-*cis*-**42**, 80272-77-1; (±)-*cis*-**43**, 80272-79-3; (±)-*cis*-44, 80272-85-1; (±)-*cis*-**45**, 80272-83-9; (±)-*cis*-**46**, 80272-89-5; (±)-*cis*-**47**, 80272-87-3; (±)-*cis*-**48**, 80272-71-5; (±)-*cis*-**49**, 80272-73-7; (±)-*cis*-**50**, 80272-59-9; (±)-*cis*-**51**, 80272-57-7; (±)-*cis*-**52**, 85663-01-0; (±)-**53**, 85663-24-7; (±)-**53**·2HCl, 80273-01-4; (+)-**54**, 80274-49-3; (+)-**54**·2HCl, 80274-51-7; (+)-**54** D-(+)-dibenzoyltartrate, 80274-50-6; (−)-**55**, 80274-52-8; (−)-**55**·2HCl, 80274-54-0; (−)-**55** D-(−)-tartrate, 80274-53-9; (±)-**56**, 80273-00-3; (±)-**56**·2HCl, 80272-99-7; (±)-**57**, 85663-25-8; (±)-**57**·2HCl, 80274-31-3; (±)-**58**, 85663-26-9; (±)-**58**·2HCl, 80274-32-4; (±)-**59**, 85663-27-0; (±)-**59**·2HCl, 80274-29-9; (±)-**60**, 85663-28-1; (±)-**60**·2HCl, 80274-30-2; (±)-**61**, 80274-12-0; (±)-**62**, 80274-13-1; (±)-**63**, 85663-29-2; (±)-**63**·2HCl, 80274-08-4; (±)-**64**, 85663-30-5; (±)-**64**·2HCl, 80274-09-5; (±)-**65**, 80273-31-0; (±)-**65**·2HCl, 84370-97-8; (±)-**66**, 80273-32-1; (±)-**67**, 85663-31-6; (±)-**67**·2HCl, 80273-33-2; (±)-**68**, 85680-82-6; (±)-**69**, 85663-32-7; (±)-**19**·2HCl, 80273-35-4; (±)-**70**, 85663-33-8; (±)-**70**·2HCl, 80273-36-5; **71**, 85663-34-9; **71**·2HCl, 80274-06-2; (±)-**73**, 85663-35-0; (±)-**73**·2HCl, 80274-10-8; **74**, 80273-37-6; **74**·2HCl, 85663-02-1; (±)-**76**, 85663-36-1; (±)-**76**·2HCl, 80274-42-6; (±)-**77**, 85663-37-2; (±)-**77**·2HCl, 80274-43-7; (±)-**78**, 85663-38-3; (±)-**78**·2HCl, 80274-11-9; (±)-**79**, 85663-39-4; (±)-**79**·2HCl, 80287-46-3; (±)-**80**, 80273-08-1; (±)-**81**, 85663-41-8; (±)-**81**·2HCl, 80273-40-1; (±)-**82**, 85663-42-9; (±)-**82**·2HCl, 80273-59-2; (±)-**83**, 85663-43-0; (±)-**83**·2HCl, 80273-71-8; (±)-**84**, 85663-44-1; (±)-**84**·2HCl, 80273-91-2; (±)-**85**, 85663-45-2; (±)-**85**·2HCl, 80273-63-8; (±)-**86**, 85663-46-3; (±)-**86**·2HCl, 80273-68-3; (±)-**87**, 85663-47-4; (±)-**87**·2HCl, 85663-03-2; (±)-**88**, 84370-99-0; (±)-**89**, 85663-48-5; (±)-**89**·2HCl, 80273-80-9; (±)-**90**, 85663-49-6; (±)-**90**·2HCl, 80273-13-8; (±)-**91**, 85663-50-9; (±)-**91**·2HCl, 80273-89-8; (±)-**92**, 85663-51-0; (±)-**92**·2HCl, 80273-87-6; (±)-**93**, 85663-52-1; (±)-**93**·2HCl, 80273-55-8; (±)-**94**, 85663-53-2; (±)-**94**·2HCl, 80273-15-0; (+)-**95**, 85663-16-7; (+)-**95**·2HCl, 80273-15-0; (+)-**95** D-(−)-tartrate, 85663-17-8; (−)-**96**, 85663-14-5; (−)-**96**·2HCl, 85663-04-3; (−)-**96** D-(+)-dibenzoyltartrate, 85663-15-6; (±)-**97**, 85663-54-3; (±)-**97**·2HCl, 80273-16-1; (+)-**98**, 85663-18-9; (+)-**98**·2HCl, 85663-05-4; (+)-**98** (+)-dibenzoyltartrate, 85663-19-0; (−)-**99**, 85663-20-3; (−)-**99**·2HCl, 85663-06-5; (−)-**99**

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(−)-dibenzoyltartrate, 85663-21-4; (±)-**100**, 85663-55-4; (±)-**100**·2HCl, 80273-17-2; (±)-**101**, 85663-56-5; (±)-**101**·2HCl, 80273-18-3; (±)-**102**, 80273-19-4; (±)-**103**, 85663-57-6; (±)-**103**·2HCl, 80273-20-7; (±)-**104**, 85663-58-7; (±)-**104**·2HCl, 85663-07-6; (±)-**105**, 85663-59-8; (±)-**105**·2HCl, 85663-08-7; (±)-**106**, 85663-60-1; (±)-**106**·2HCl, 80273-26-3; (±)-**107**, 85663-61-2; (±)-**107**·2HCl, 80273-27-4; **108**, 62373-97-1; **109**, 52807-79-1; (±)-*cis*-V (X = 6-CF_3; Y = *p*-F; Z = H), 85663-12-3; (±)-*trans*-V (X = 6-CF_3; Y = *p*-F; Z = H), 85662-71-1; I (A = Br; X = 4-CF_3), 85118-34-9; I (A = Br; X = 4-Cl), 85663-10-1; (±)-*cis*-VIa, 80274-02-8; (±)-*trans*-VIa, 80274-59-5; dopamine, 51-61-6; 2-bromo-4-(trifluoromethyl)benzoic acid, 328-89-2; 4-(trifluoromethyl)anthranilic acid, 402-13-1; 2-bromo-4-(trifluoromethyl)benzoyl chloride, 85663-09-8; 2-bromo-4-(trifluoromethyl)benzaldehyde, 85118-24-7; ethyl cyanoacetate, 105-56-6; 2-bromo-4-chlorobenzaldehyde, 84459-33-6; 2-bromo-4-chlorobenzoic acid, 936-08-3; 1-bromo-4-fluorobenzene, 460-00-4; ethyl 3-[2-bromo-4-(trifluoromethyl)phenyl]-2-cyano-3-(4-fluorophenyl)propanoate, 85663-11-2; K-Selectride, 54575-49-4; 1-piperazineethanol, 103-76-4; piperazine, 110-85-0; phenethyl bromide, 103-63-9; cyclopropanecarbonyl chloride, 4023-34-1; propylene oxide, 75-56-9; methanesulfonyl chloride, 124-63-0; 1-(3-hydroxy-1-propyl)piperazine, 5317-32-8; 4-chloro-6-fluoro-1-(4-fluorophenyl)-1,2,3,4-tetrahydronaphthalene, 68351-24-6; 1-methylpiperazine, 109-01-3.

New Selenium-75 Labeled Radiopharmaceuticals: Selenonium Analogues of Dopamine[1]

Samy A. Sadek,* Garo P. Basmadjian, Pan M. Hsu, and Joseph A. Rieger

College of Pharmacy, University of Oklahoma, Health Sciences Center, Oklahoma City, Oklahoma 73190.
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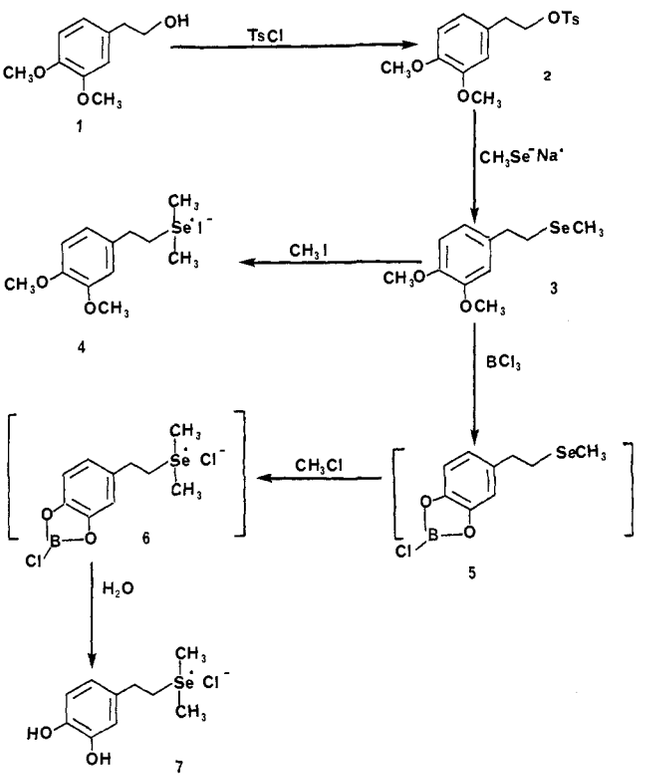
Selenium-75 labeled selenonium analogues of dopamine, [2-(3,4-dimethoxyphenyl)ethyl]dimethylselenonium iodide (4) and its dihydroxy analogue (7), were prepared by reducing [^{75}Se]selenious acid with sodium borohydride at pH 6.0 and reacting the NaSeH produced with 1-(3,4-dimethoxyphenyl)-2-(*p*-toluenesulfonyloxy)ethane. Tissue distribution studies in rats given the ^{75}Se-labeled selenonium agents intravenously demonstrated high initial heart uptake (2.38% dose/g at 5 min). Prolonged adrenal retention ($t_{1/2}$ = 10 h) and high adrenal to blood ratio of compound 4 (21/1 at 4 h after injection) were observed. The high uptake and adrenal to blood ratio suggest the potential use of compound 4 as a radiopharmaceutical for the adrenal gland.

The adrenal gland consists of two histologically and functionally distinct regions, the cortex and the medulla. Imaging the human adrenal cortex and its neoplasms has been possible for nearly a decade by using the radioiodinated cholesterol and ^{75}Se-labeled cholesterol analogues.[2-4] A comparable radiopharmaceutical is needed for imaging the adrenal medulla and its neoplasms, such as pheochromocytoma and neuroblastoma. Using guanidine derivatives, *m*-[^{123}I]iodo- and *m*-[^{131}I]iodobenzylguanidine, Wieland et al. were able to obtain scintiscans of the monkey adrenal medulla.[5] Recently, Hanson[6] has prepared another guanidine derivative, 1-carboxyimidine-4-phenylpiperazine, and demonstrated that its uptake by the adrenals was higher than that of radioiodobenzylguanidine.

It is well known that dopamine is synthesized and stored in the adrenal medulla.[7] Radiolabeled derivatives of dopamine have been proposed as potential adrenal medulla imaging agents.[8] In an attempt to develop such an agent, ^{11}C ($t_{1/2}$ = 20 min) was used as the radiolabel.[9] The short half-life of ^{11}C and the need for rapid synthesis were major drawbacks. There have been some attempts to use radiohalogen derivatives of dopamine as scanning agents for

Scheme I



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