pH 7.4. Samples were incubated for 1 h at 25 °C. Incubations were terminated by rapid filtration under reduced pressure through glass fiber filters (Whatman GF/B). The filters were rinsed three times with 10-mL aliquots of cold assay buffer. The radioactivity retained on the filters was counted on a liquid scintillation spectrophotometer in 10 mL of Beckman H-P scintillation cocktail after being mechanically shaken for 1 h. Nonspecific binding, which was defined as the binding in the presence of 100 μM oxotremorine, was subtracted from the mean of the triplicate samples to determine specific binding. The concentration of test agent needed to displace 50% of the specific binding (IC_{50}) was determined by a nonlinear computer curve fit from four or more concentrations (in triplicate) of the test agent.[12]

α_1-Adrenergic Receptor Binding.[11] The relative affinities of compounds for the α_1-adrenergic receptor were evaluated on the basis of their ability to displace [^{3}H]WB-4101 from rat frontal cortex membranes. Male Long–Evans rats were decapitated, the brains were removed, and the frontal cortex membranes were dissected. The cortex tissue was homogenized in 50 volumes of 50 mM Tris-HCl buffer at pH 7.7. The homogenate was centrifuged twice with rehomogenization of the intermediate pellet in 50 mL of fresh buffer. The final pellet was resuspended in 50 mM the buffer at pH 7.7 at a concentration of 20 mg/mL of original wet tissue. Incubation samples contained 1.0 mL (or 10 mg/mL of wet tissue weight) of brain membranes, 100 μL of various concentrations of test agents, and 0.5 nM of [^{3}H]WB-4101 in a final volume of 2 mL of 50 mM Tris-HCl buffer at pH 7.7. Samples were incubated for 30 min at 25 °C and rapidly filtered under reduced pressure through Whatman GF/B filters. The filters were rinsed three times with 5-mL aliquots of 50 mM assay buffer and shaken for 1 h in 10 mL of Beckman H-P scintillation cocktail. The radioactivity retained on the filters was counted by liquid scintillation spectrophotometry. Nonspecific binding was defined as the binding in the presence of 100 μM (-)-norepinephrine. This was subtracted from the mean of the triplicate samples to determine specific binding. The concentration of test agent needed to displace 50% of the specific binding (IC_{50}) was determined by nonlinear computer curve fit from four or more concentrations (in triplicate) of the test agent.[12]

Acknowledgment. We thank Dr. F. A. MacKeller and his associates for the microanalyses and spectral data and also Drs. F. Hershenson and T. Heffner for their timely suggestions.

Registry No. 1, 80119-31-9; 2, 97861-25-1; 2 (free base), 80119-57-9; 3, 80120-14-5; 4, 97861-00-2; 5, 97861-01-3; 6, 97861-02-4; 7, 97861-03-5; 8, 97861-04-6; 9, 80119-32-0; 10, 97861-05-7; 11, 97861-06-8; 12, 97877-59-3; 12 (free base), 97861-07-9; 13, 97861-09-1; 13 (free base), 97861-08-0; 14, 97861-10-4; 14 (free base), 97861-11-5; 15, 97861-12-6; 15 (free base), 97861-13-7; 16, 97861-14-8; 17, 97861-15-9; 18, 97861-16-0; 18 (free base), 97861-17-1; 19, 97861-19-3; 19 (free base), 97861-18-2; 20, 97861-21-7; 20 (free base), 97861-20-6; 21, 97861-22-8; 21 (free base), 97861-23-9; 22, 97861-24-0; 1-(4-fluorophenyl)-1,3,8-triazaspiro[4.5]decan-4-one, 58012-16-1; 4-piperidinone, 41661-47-6; 4-chlorobenzenamine, 106-47-8; acetone cyanohydrin, 75-86-5; 1-[3-[bis(4-fluorophenyl)amino]propyl]-4-[(4-chlorophenyl)amino]-4-piperidinecarbonitrile, 97861-26-2; 1-[3-[bis(4-fluorophenyl)amino]propyl]-4-[(4-chlorophenyl)amino]-4-piperidinecarbonitrile maleate, 97861-27-3; 1-[3-[bis(4-fluorophenyl)amino]propyl]-4-[(4-chlorophenyl)amino]-4-piperidinecarboxamide, 97861-28-4; dimethoxy-*N*,*N*-dimethylmethanamine, 4637-24-5; 8-[3-[bis(4-fluorophenyl)amino]propyl]-1-(4-chlorophenyl)-1,3,8-triazaspiro[4.5]dec-2-en-4-one, 97861-29-5; 8-[3-[bis(4-fluorophenyl)amino]propyl]-1-(4-chlorophenyl)-1,3,8-triazaspiro[4.5]dec-2-en-4-one maleate, 97861-30-8; 1-phenyl-1,3,8-triazaspiro[4.5]decan-4-one, 1021-25-6; 1-(4-methoxyphenyl)-1,3,8-triazaspiro[4.5]decan-4-one, 1027-69-6; 1-(4-methylphenyl)-1,3,8-triazaspiro[4.5]decan-4-one, 1023-87-6; 1-(4-isopropylphenyl)-1,3,8-triazaspiro[4.5]decan-4-one, 97861-31-9; 1-[3-(trifluoromethyl)phenyl]-1,3,8-triazaspiro[4.5]decan-4-one, 97861-32-0; 1-(3-fluorophenyl)-1,3,8-triazaspiro[4.5]decan-4-one, 97861-33-1; 1-(2-fluorophenyl)-1,3,8-triazaspiro[4.5]decan-4-one, 97861-34-2.

3-Phenyl-1-indanamines. Potential Antidepressant Activity and Potent Inhibition of Dopamine, Norepinephrine, and Serotonin Uptake

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A series of 3-phenyl-1-indanamines was synthesized and tested for potential antidepressant activity and for inhibition of dopamine (DA), norepinephrine (NE), and serotonin (5-HT) uptake. Trans isomers were generally potent inhibitors of DA, NE, and 5-HT uptake, while cis isomers preferentially inhibited the uptake of 5-HT. The affinity for the DA-uptake site was very dependent on the aromatic substitution pattern where highest potency was found for 3′,4′-dichloro substituted compounds (**45**). This substitution pattern also resulted in high affinity for the NE- and 5-HT-uptake sites, but potent 5-HT-uptake inhibiting activity could also be obtained with other substitution patterns. Only small amines could be accommodated at the 5-HT-uptake site while larger amines such as piperazine could be accommodated both at the DA- and NE-uptake sites. The observed structure–activity relationships were explained from the results of superimpositions of a trans (**45**) and cis (**72**) isomer with 5-HT and DA, respectively, in relation to a proposed three-point binding of the uptake inhibitors at the uptake sites. Finally, comparison of the structures of the 3-phenyl-1-indanamines with other newer bicyclic catecholamine- and/or serotonin-uptake inhibitors revealed common structural elements important for potent DA-, NE-, and/or 5-HT-uptake inhibition.

Traditionally, the mode of action of antidepressant agents has been explained as being a result of facilitation of norepinephrinergic and/or serotonergic transmission caused by inhibition of norepinephrine (NE) and/or 5-hydroxytryptamine (5-HT) uptake. However, a few years ago it was found that chronic treatment with tricyclic antidepressants such as amitriptyline or imipramine induced subsensitivity of presynaptic dopamine (DA) auto-

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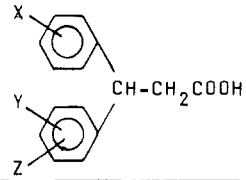
Table I. 3,3-Diphenylpropanoic Acids



compd	X	Y	Z	mp, °C	yield,[a] %	recryst solvent[b]	formula[c]
4	3-Cl	H	H	95–96	83	A	$C_{15}H_{13}ClO_2$
5	4-Cl	H	H	99–101[d]	95	C	$C_{15}H_{13}ClO_2$
6	4-Br	H	H	129–131[e]	61	C	$C_{15}H_{13}BrO_2$
7	H	3-F	4-F	101–102	73	A	$C_{15}H_{12}F_2O_2$
8	H	3-Cl	4-F	81–82	85	B	$C_{15}H_{12}ClFO_2$
9	4-F	3-Cl	4-Cl	102–103	83	A	$C_{15}H_{11}Cl_2FO_2$
10	4-CH_3O	3-Cl	4-Cl	121–123	63	B	$C_{16}H_{14}Cl_2O_3$
11	2-Br	3-CF_3	4-Cl	144–146	73	A	$C_{16}H_{11}BrClF_3O_2$
12	2-Br	4-CF_3	H	121–123	64	A	$C_{16}H_{12}BrF_3O_2$

[a] Yield of crude, crystalline product calculated from the substituted ethyl 2-cyano-3-phenyl-2-propenoates. [b] A = ethyl ether/hexane; B = isopropyl ether/hexane; C = not recrystallized. [c] Anal. C, H. [d] Mp 108 °C.[25] [e] Mp 107–108 °C.[26]

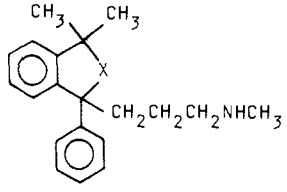


Figure 1. Compounds: 1, X = O; 2, X = S.

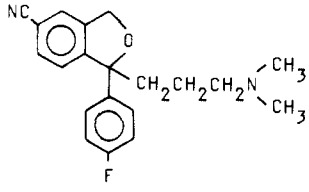


Figure 2. Compound 3.

receptors in rats.[1,2] Whether this effect is related to the clinical effect is an open question, but the idea that DA may play an important role in the etiology of affective disorders is not new. Evidence has been presented for a role of DA in depression and mania.[3,4] This has resulted in a growing interest in antidepressant agents with a stimulating effect on DA transmission.[5]

However, the large majority of antidepressant agents are much more potent NE and/or 5-HT-uptake inhibitors than DA-uptake inhibitors.[6] It seems to be difficult to design a highly selective DA-uptake inhibitor, which would be a valuable tool to test the "dopamine theory" of depression. In contrast, highly selective uptake inhibitors of NE and 5-HT are known. Compound 1 (talopram)[7] and 2 (talsupram)[8] (Figure 1) are very selective NE-uptake inhibitors (see Table IV). These compounds, did show antidepressant activity in the clinic,[9,10] especially in patients with psychomotor retardation. This was in agreement with the theory suggesting that facilitation of NE transmission was related to an increase in drive, while facilitation of 5-HT transmission was related to mood elevation.[11-13] This theory started a search for selective 5-HT-uptake inhibitors. Compound 3 (citalopram) (Figure 2)was developed by making relatively small changes in the structure of 1, which surprisingly changed the profile[3] to an extremely selective 5-HT-uptake inhibitor[6,14] (see Table IV). The clinical results with 3[6] and other selective 5-HT-uptake inhibitors seem to confirm that these agents do have antidepressant effects in man.

However, a compound with a selectivity for DA-uptake inhibition comparable to the selectivity shown by 1 (or 2) and 3 for NE- and 5-HT-uptake inhibition, respectively, is not known. Some compounds such as nomifensine (103) (see Table IV) or diclofensine[15] (104) are potent DA-uptake inhibitors but are still very strong NE and 5-HT-uptake inhibitors. A number of other reported DA-uptake inhibitors also have relatively low selectivity.[16-20]

Recently, we reported on a series of 1-piperazino-3-phenylindans.[21] This series included both potent neuroleptic compounds as well as potent DA- and NE-uptake inhibitors. The most potent uptake inhibitors were com-

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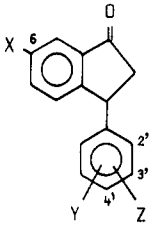
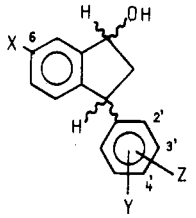
Table II. 3-Phenylindan-1-ones



compd	X	Y	Z	mp, °C	ring closure condns	yield, %	recryst solvent[a]	formula[b]
13	H	3′-Cl	H	109–110	PPA, 100 °C, 2.5 h	35	C	$C_{15}H_{11}ClO$
14	H	4′-Cl	H	75–77[c]	PPA, 110 °C, 2.5 h	61	A	$C_{15}H_{11}ClO$
15	H	4′-Br	H	59–60[d]	$AlCl_3$, 25 °C, 18 h	45	B	$C_{15}H_{11}BrO$
16	H	3′-F	4′-F	109–112	PPA, 100 °C, 2 h	71	A	$C_{15}H_{10}F_2O$
17	H	3′-Cl	4′-F	170–171	PPA, 100 °C, 2 h	72	C	$C_{15}H_{10}ClFO$
18	6-F	3′-Cl	4′-Cl	119–121	PPA, 125 °C, 2.5 h	14	D	$C_{15}H_9Cl_2FO$
19	6-CH_3O	3′-Cl	4′-Cl	67–69	$AlCl_3$, 25 °C, 2 h	59	B	$C_{16}H_{12}Cl_2O_2$
20	H	3′-CF_3	4′-Cl	93–94	BuLi, −5 °C, 1 h	27	E	$C_{16}H_{10}ClF_3O$
21	H	4′-CF_3	H	84–85	BuLi, −5 °C, 1 h	26	A	$C_{16}H_{11}F_3O$

[a] A = ethyl ether/hexane; B = isopropyl ether/hexane; C = CH_2Cl_2/hexane; D = cyclohexane; E = pentane. [b] Anal. C, H. [c] Mp 77–78 °C.[27] [d] Mp 59–60 °C.[26]

Table III. 3-Phenylindan-1-ols



compd	X	Y	Z	mp, °C	yield, %	recryst solvent[a]	formula[b]
22	H	3′-Cl	H	99–100	79	A	$C_{15}H_{13}ClO$
23	H	4′-Cl	H	96–97	87	B	$C_{15}H_{13}ClO$
24	H	4′-Br	H	100–102	90	A	$C_{15}H_{13}BrO$
25	H	3′-F	4′-F	59–63	77	D	$C_{15}H_{12}F_2O$
26	H	3′-Cl	4′-F	72–75	84	C	$C_{15}H_{12}ClFO$
27	6-F	3′-Cl	4′-Cl	80–84	84	D	$C_{15}H_{11}Cl_2FO$
28	6-CH_3O	3′-Cl	4′-Cl	104–106	65	B	$C_{16}H_{14}Cl_2O_2$
29	H	3′-CF_3	4′-Cl	101–102	89	D	$C_{16}H_{12}ClF_3O$
30	H	4′-CF_3	H	68–70	97	D	$C_{16}H_{13}F_3O$

[a] A = ethyl ether/hexane; B = isopropyl ether/hexane; C = hexane; D = not recrystallized. [b] Anal. C, H.

pounds **101** and **102** (see Table VI). In order to investigate whether or not we could further increase the selectivity for DA-uptake inhibition, we synthesized a series of 3-phenyl-1-indanamines.

Pharmacological activity has previously been reported for 3-phenyl-1-indanamines.[22] Compound **31** and some close analogues (without aromatic substitution) were reported to have analgesic activity[23] and *N,N*-diethyl-3-(4-ethoxyphenyl)-1-indanamine was reported to produce marked coronary dilation.[24]

We now report potent catecholamine- and serotonin-uptake inhibition and potential antidepressant activity in a series of aromatic substituted 3-phenyl-1-indanamines.

The different profiles for DA-, NE-, and 5-HT-uptake inhibition found for the cis and trans isomers in this series, combined with the limited conformational mobility of these compounds, make them interesting model compounds to probe the preferred conformations of the catecholamines and serotonin at the uptake sites. In addition, comparison of these compounds with the previously reported piperazinoindans[21] and compounds with related structure reveals some common structural and stereochemical elements that appear to be important for potent catecholamine- and serotonin-uptake inhibition.

Chemistry

Substituted 3,3-diphenylpropanoic acids (Table I) and 3-phenylindan-1-ones (I, Table II) were prepared by the methods described earlier.[21] The indanones **14–17** and **19** were predominantly formed as the desired isomer and were easily purified by recrystallization. Cyclization of the acids **4** and **9** gave isomeric mixtures, but in both cases the desired indanones (**13** and **18**) could be purified by several recrystallizations. The structures of the indanones were confirmed by ^1H and ^{13}C NMR spectroscopy. Reduction of the indanones with sodium borohydride gave, as previously reported,[21] almost pure *cis*-3-phenylindan-1-ols (II, Table III).

Most of the 3-phenyl-1-indanamines were prepared by method A (Scheme I) because this method directly gave both cis and trans isomers, which in most cases could be separated by fractional crystallization. Both isomers were obtained because the reaction of the *cis*-3-phenylindan-1-ols with thionyl chloride in toluene resulted in an isomeric mixture of *cis*- and *trans*-1-chloro-3-phenylindans (III) with a cis:trans ratio of about 70:30. The following reaction with excess alkylamine in an autoclave gave, as earlier reported for the similar S_N2 reaction with piperazine,[21] an isomeric mixture of *cis*- and *trans*-3-phenyl-1-indanamines (IV) with the reverse cis:trans ratio, i.e. 30:70.

In the cases where it proved difficult to obtain sufficient

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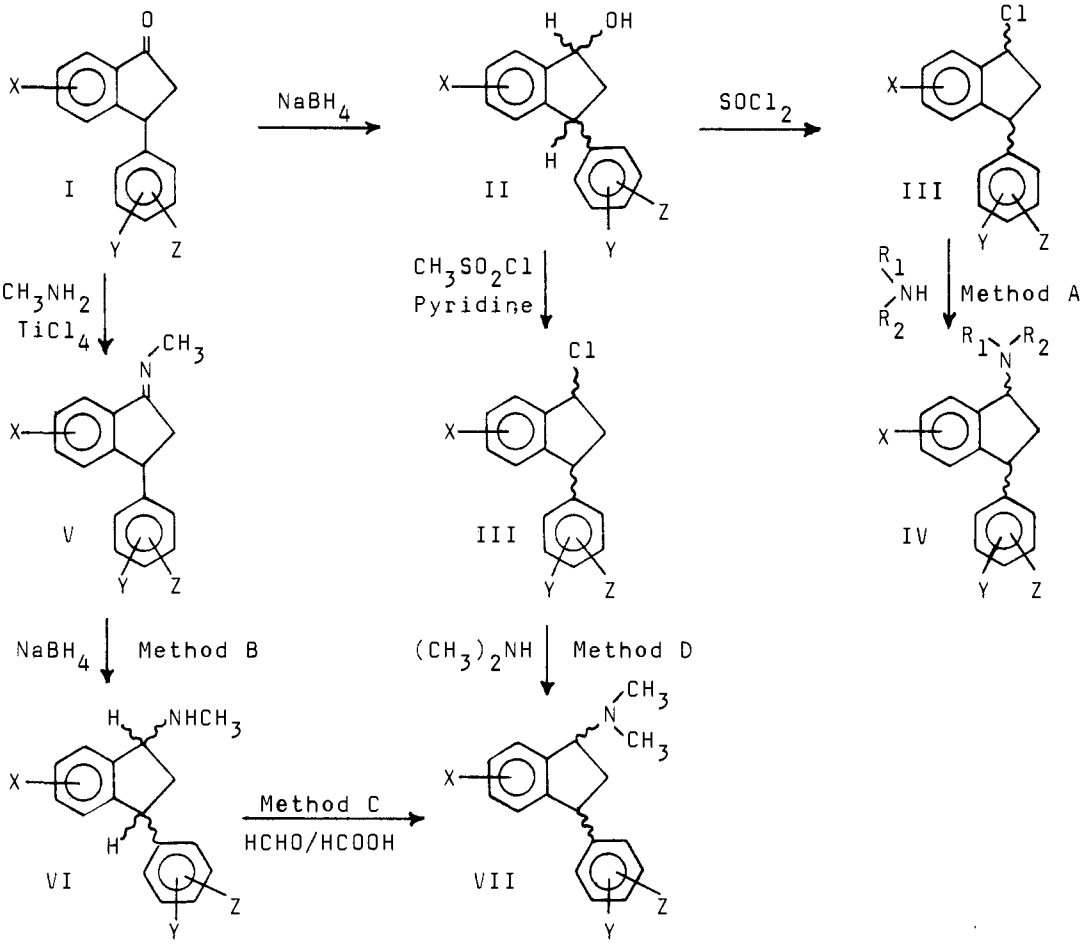
Scheme I



amounts of the cis isomer by method A, alternative methods were used. We earlier reported[21] that *cis*-1-piperazino-3-phenylindans could be obtained from the mesylate of the 3-phenylindan-1-ols (II). The mesylates were obtained by treating the 3-phenylindan-1-ols (II) with methanesulfonyl chloride in pyridine/methylene chloride. However, reinvestigation of this step showed that the product obtained was not a mesylate but a mixture of chloroindanisomers (III). It is known that pyridine hydrochloride can convert tosylates to the corresponding chlorides,[28] and obviously it is this reaction that occurs spontaneously with the mesylates of the 3-phenylindan-1-ols. The reaction proceeds partly with inversion of the configuration, resulting in a mixture of chloroindans with a cis:trans ratio of about 40:60. By the subsequent reaction with dimethylamine (method D) a product mixture with a high content of cis isomer was obtained.

Alternatively cis isomers could be obtained in high yield by method B (Scheme I). Reduction of the methylimines (V) with sodium borohydride gave as in the case of the reduction of the indan-1-ones (I) to the indan-1-ols (II) almost pure cis monomethylamines (VI). The corresponding dimethylamines (VII) could then be obtained by Eschweiler–Clarke methylation of VI (method C).

By resolution of compound **45** with L-(+)- and D-(−)-tartaric acid the neutral (2:1) enantiomeric salts were obtained. The enantiomeric purity of the corresponding bases was determined by ^{1}H NMR using (*R*)-(−)-2,2,2-trifluoro-1-(9-anthryl)ethanol as shift reagent. A difference of 0.08 ppm in the chemical shifts of the amino CH_3 singlets was observed. The purity of both enantiomers was in this way established to be greater than 95%.

The absolute configuration of the enantiomers was determined by comparing their CD spectra with the CD spectrum of a 1-piperazino-3-phenylindan derivative[37] of known absolute configuration. The configuration of (+)-**45** and (−)-**45** (Table IV) was determined to be 1*R*,3*S* and 1*S*,3*R* respectively.

Results

Antagonism of tetrabenazine-induced ptosis[21] and potentiation of 5-HTP-induced behavioral sympatomatology in mice were used to measure the potential antidepressant activity of the compounds. Inhibition of the uptake of DA, NE, and 5-HT[21] was measured for most of the compounds. The results are shown in Tables IV–VI. Also shown in Table IV are the activities of compounds **1**–**3** and nomifensine (**103**). Results for many other standard compounds have been reported elsewhere.[6]

Spearman–Rank correlation analysis of the results in the five tests revealed that a highly significant ($r = 0.74$, $p < 0.001$) correlation was found between inhibition of 5-HT uptake and potentiation of 5-HTP and also between inhibition of DA uptake and inhibition of NE uptake ($r = 0.81$, $p < 0.001$). Tetrabenzine-induced ptosis was not significantly correlated with any of the uptake inhibition tests.

The change in the amino function from a piperazine ring (as in **101** and **102**)[21] to the smaller aliphatic amines did not result in any increased selectivity toward DA-uptake inhibition. A separation of the activity on DA uptake from activity on NE uptake was not possible in this series, a fact that was confirmed by the close correlation between these tests, as mentioned above. On the other hand, many of the new compounds shown in Tables IV and V were considerably more potent than the piperazino compounds, and in contrast to these they were potent 5-HT-uptake inhib-

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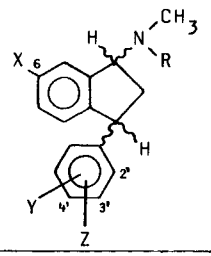
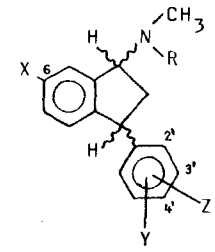
Table IV. Thymoleptic Activity of *trans*-*N*-Methyl- and *N*,*N*-Dimethyl-3-phenyl-1-indanamines[a]



compd	X	Y	Z	R	mp, °C	formula[b]	ED_{50},[c] μmol/kg ip: tetrabenazine ptosis, mice	ED_{50},[c] μmol/kg ip: 5-HTP potentiation, mice	synaptosomal uptake inhibn: IC_{50},[d] nM: DA	NE	5-HT
31	H	H	H	CH_3	186–189[e]	$C_{17}H_{19}N \cdot HCl \cdot 0.5H_2O$	17 (7–40)	>35	600	130	150
32	H	4′-F	H	H	162–163	$C_{16}H_{16}FN \cdot HCl$	19 (11–32)	>144	29	2.9	76
33	H	4′-F	H	CH_3	156–158	$C_{17}H_{18}FN \cdot HCl \cdot 0.8H_2O$	7.8 (4.2–14)	45 (26–74)	320	100	33
34	H	4′-Cl	H	H	68–69	$C_{16}H_{16}ClN$	>155	34 (17–68)	5.6	0.51	4.0
35	H	4′-Cl	H	CH_3	79–81	$C_{17}H_{18}ClN$	56 (20–157)	48 (11–28)	140	23	0.64
36	H	4′-Br	H	H	213–215	$C_{16}H_{16}BrN \cdot HCl$	47 (15–142)	8.8 (5.6–15)	2.5	0.30	0.28
37	H	4′-Br	H	CH_3	75–77	$C_{17}H_{18}BrN$	9.8 (3.6–27)	8.4 (5.4–13)	54	28	0.04
38	H	4′-CF_3	H	H	214–215	$C_{17}H_{16}F_3N \cdot HCl$	58 (28–118)	45 (32–62)	160	67	4.7
39	H	3′-Cl	H	H	159–160	$C_{16}H_{16}ClN \cdot HCl$	45 (16–125)	92 (60–141)	14	0.12	41
40	H	3′-Cl	H	CH_3	201–202	$C_{17}H_{18}ClN \cdot HCl$	10 (3.4–29)	43 (27–69)	71	15	16
41	H	3′-F	4′-F	H	170–174	$C_{16}H_{15}F_2N \cdot HCl$	58 (22–152)	22 (14–34)	21	1.6	49
42	H	3′-F	4′-F	CH_3	180–182	$C_{17}H_{17}F_2N \cdot HCl$	7.1 (1.3–40)	73 (48–112)	250	62	20
43	H	3′-Cl	4′-F	H	184–185	$C_{16}H_{15}ClFN \cdot HCl$	12 (5.1–27)	47 (29–76)	NT[f]	NT	NT
44	H	3′-Cl	4′-F	CH_3	215–216	$C_{17}H_{17}ClFN \cdot HCl$	4.5 (1.9–10)	37 (27–50)	NT	NT	NT
45	H	3′-Cl	4′-Cl	H	183–185	$C_{16}H_{15}Cl_2N \cdot HCl$	2.9 (1.5–5.5)	7.8 (5.2–12)	0.99	0.26	0.48
(+)-45	H	3′-Cl	4′-Cl	H	159–162	$C_{16}H_{15}Cl_2N \cdot 0.5C_4H_6O_6$	5.0 (1.7–14.5)	9.2 (7.1–12)	0.17	0.60	1.0
(−)-45	H	3′-Cl	4′-Cl	H	161–164	$C_{16}H_{15}Cl_2N \cdot 0.5C_4H_6O_6$	>108	64 (40–102)	8.6	5.3	5.2
46	H	3′-Cl	4′-Cl	CH_3	78–79	$C_{17}H_{17}Cl_2N$	83 (25–278)	5.0 (3.9–6.6)	28	24	0.64
47	H	3′-CF_3	4′-Cl	H	201–202	$C_{17}H_{15}ClF_3N \cdot HCl$	>110	55 (42–73)	3500	25	4.2
48	H	2′-Cl	4′-Cl	H	195–197	$C_{16}H_{15}Cl_2N \cdot HCl$	19 (7.9–46)	67 (44–103)	510	15	0.91
49	H	2′-Cl	4′-Cl	CH_3	262–264	$C_{17}H_{17}Cl_2N \cdot HCl$	23 (12–44)	19 (13–28)	2000	90	0.58
50	F	3′-Cl	4′-Cl	H	222–224	$C_{16}H_{14}Cl_2FN \cdot HCl$	33 (9.4–117)	27 (20–37)	0.12	0.71	2.3
51	F	3′-Cl	4′-Cl	CH_3	173–175	$C_{17}H_{16}Cl_2FN \cdot HCl$	>111	20 (12–34)	12	21	1.1
52	CH_3O	3′-Cl	4′-Cl	H	231–233	$C_{17}H_{17}Cl_2NO \cdot 0.5C_2H_2O_4$	7.0 (3.3–15)	14 (9.1–21)	2.5	0.67	0.62
53	CH_3O	3′-Cl	4′-Cl	CH_3	153–157	$C_{18}H_{19}Cl_2NO \cdot C_2H_2O_4$	33 (5.3–204)	14 (6.6–31)	10	16	1.6
54	HO	3′-Cl	4′-Cl	H	206–210	$C_{16}H_{15}Cl_2NO \cdot 0.3H_2O$	21 (9.5–46)	>128	0.52	0.82	2.5
55	HO	3′-Cl	4′-Cl	CH_3	217–221	$C_{17}H_{17}Cl_2NO \cdot HBr$	22 (5.9–83)	18 (12–28)	7.9	16	0.37
56	F	4′-F	H	CH_3	239–242	$C_{17}H_{17}F_2N \cdot HCl$	28 (15–53)	>129	620	350	18
57	CF_3	4′-F	H	CH_3	244–245	$C_{18}H_{17}F_4N \cdot HCl$	116 (20–681)	123 (96–157)	240	85	43
1	talopram						1.2 (0.34–4.2)	44 (14–136)	44000	2.9	1400
2	talsupram						2.3 (0.85–6.3)	>115	9300	0.79	850
3	citalopram						51 (7.8–331)	3.3 (2.8–3.9)	41000	8800	1.8
103	nomifensine						4.3 (1.8–10)	>56	48	6.6	830

[a] Racemates except compd (+)-45 and (−)-45. Isomeric purity (with respect to content of cis racemate) was in all cases > 95% except for 41 where it was 85%. All compounds were made by method A except 40 which was made by method C and 54 and 55 which were made by cleavage of compd 52 and 53 with HBr. [b] Anal. C, H, N. [c] 95% confidence limits in parentheses. [d] All results are the mean of at least two determinations each with five concentrations of test compounds in triplicate. [e] Mp 191–192 °C.[23] [f] NT = Not tested.

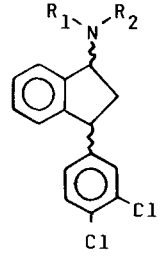
Table V. Thymoleptic activity of *cis*-*N*-Methyl- and *N*,*N*-Dimethyl-3-phenyl-1-indanamines[a]



compd	X	Y	Z	R	mp, °C	formula[b]	ED_{50},[c] μmol/kg ip: tetrabenazine ptosis, mice	ED_{50},[c] μmol/kg ip: 5-HTP potentiation, mice	synaptosomal uptake inhibn: IC_{50},[d] nM: DA	NE	5-HT
58	H	H	H	H	235–237[e]	$C_{16}H_{17}N\cdot HCl\cdot 0.2H_2O$	>154	211 (94–475)	1400	320	210
59	H	H	H	CH_3	196–197	$C_{17}H_{19}N\cdot HCl$	>143	>36	340	41	9.5
60	H	4′-F	H	H	257–258	$C_{16}H_{16}FN\cdot HCl$	79 (22–291)	72 (47–112)	330	120	21
61	H	4′-F	H	CH_3	207–209	$C_{17}H_{18}FN\cdot HCl$	24 (4.9–121)	25 (15–41)	250	24	6.2
62	H	4′-Cl	H	H	246–247	$C_{16}H_{16}ClN\cdot HCl$	376 (90–1580)	23 (16–32)	120	24	0.65
63	H	4′-Cl	H	CH_3	78–80	$C_{17}H_{18}ClN$	43 (13–142)	14 (8.6–24)	190	4.4	0.34
64	H	4′-Br	H	H	240–242	$C_{16}H_{16}BrN\cdot HCl$	29 (13–63)	6.6 (2.9–15)	67	8.8	0.16
65	H	4′-Br	H	CH_3	86–89	$C_{17}H_{18}BrN$	2.3 (0.3–20)	12 (8.7–16)	83	4.3	0.14
66	H	3′-Cl	H	H	215–216	$C_{16}H_{16}ClN\cdot HCl$	119 (43–333)	124 (73–211)	220	19	6.8
67	H	3′-Cl	H	CH_3	198–200	$C_{17}H_{18}ClN\cdot HCl$	85 (27–267)	78 (56–108)	54	0.77	2.6
68	H	3′-F	4′-F	H	240–243	$C_{16}H_{15}F_2N\cdot HCl$	23 (8–66)	63 (45–89)	150	33	4.6
69	H	3′-F	4′-F	CH_3	165–167	$C_{17}H_{17}F_2N\cdot C_2H_4O_2$	13 (3.2–48)	42 (27–65)	180	29	1.3
70	H	3′-Cl	4′-F	H	225–226	$C_{16}H_{15}ClFN\cdot HCl$	32 (9.6–106)	30 (23–41)	NT[f]	NT	NT
71	H	3′-Cl	4′-F	CH_3	189–191	$C_{17}H_{17}ClFN\cdot HCl$	13 (2.7–65)	51 (30–87)	NT	NT	NT
72	H	3′-Cl	4′-Cl	H	230–232	$C_{16}H_{15}Cl_2N\cdot HCl$	5.8 (1.7–20)	6.4 (4.9–8.3)	20	5.2	0.44
73	H	3′-Cl	4′-Cl	CH_3	180–184	$C_{17}H_{17}Cl_2N\cdot HCl\cdot 0.5H_2O$	14 (7.3–27)	10 (5.4–19)	27	2.4	0.37
74	H	2′-Cl	4′-Cl	H	247–249	$C_{16}H_{15}Cl_2N\cdot HCl$	98 (25–382)	71 (47–108)	100	6.1	21
75	H	2′-Cl	4′-Cl	CH_3	237–239	$C_{17}H_{17}Cl_2N\cdot HCl$	23 (11–50)	19 (10–36)	860	34	0.03
76	F	3′-Cl	4′-Cl	H	267–269	$C_{16}H_{14}Cl_2FN\cdot HCl$	15 (6.5–36)	15 (8.4–27)	5.0	14	0.75
77	F	3′-Cl	4′-Cl	CH_3	218–220	$C_{17}H_{16}Cl_2FN\cdot HCl$	>111	29 (15–53)	31	3.7	2.5
78	CH_3O	3′-Cl	4′-Cl	H	262–264	$C_{17}H_{17}Cl_2NO\cdot HCl$	14 (6.4–31)	2.9 (0.83–10)	19	19	0.53
79	CH_3O	3′-Cl	4′-Cl	CH_3	75–77	$C_{18}H_{19}Cl_2NO$	34 (14–80)	7.4 (3.2–18)	15	3.0	2.0
80	HO	3′-Cl	4′-Cl	H	211–213	$C_{16}H_{15}Cl_2NO$	15 (8.1–29)	59 (32–107)	4.1	6.3	0.11
81	F	4′-F	H	CH_3	77–80	$C_{17}H_{17}F_2N$	>147	21 (14–30)	440	90	1.2
82	CF_3	4′-F	H	CH_3	234–236	$C_{18}H_{17}F_4N\cdot HCl$	>111	101 (59–172)	340	350	4.3

[a] All compounds are racemates. Isomeric purity (with respect to content of trans racemate) was in all cases >95% (TLC). The following were made by methods other than A: **60**, **62**, **74**, **76**, **78** (method B); **63**, **67**, **77** (method C); **65**, **73**, **81**, **82** (method D). [b–d] See corresponding footnotes in Table IV. [e] Mp 230 °C.[23] [f] NT = not tested.

Table VI. Thymoleptic Activity of 3-(3,4-Dichlorophenyl)-1-indanamines[a]



compd	R_1	R_2	isomerism[e]	mp, °C	formula[b]	ED_{50},[c] μmol/kg ip: tetrabenazine ptosis, mice	ED_{50},[c] μmol/kg ip: 5-HTP potentiation, mice	synaptosomal uptake inhibn: IC_{50},[d] nM: DA	NE	5-HT
83	H	C_2H_5	t	227-229	$C_{17}H_{17}Cl_2N \cdot HCl$	21 (9.2-48)	26 (19-35)	1.5	0.32	2.3
84	H	C_2H_5	c	268-270	$C_{17}H_{17}Cl_2N \cdot HCl$	66 (37-117)	26 (17-38)	62	49	1.6
85	C_2H_5	C_2H_5	~94% t	157-158	$C_{19}H_{21}Cl_2N \cdot HCl$	52 (28-95)	19 (13-28)	2.1	0.56	2.8
86	C_2H_5	C_2H_5	c	226-227	$C_{19}H_{21}Cl_2N \cdot HCl$	>108	204 (129-323)	120	13	13
87	H	n-C_3H_7	t	214-215	$C_{18}H_{19}Cl_2N \cdot HCl$	68 (28-163)	87 (55-137)	6.6	0.66	150
88	H	n-C_3H_7	>90% c	268-270	$C_{18}H_{19}Cl_2N \cdot HCl$	>112	>112	NT[f]	NT	NT
89	n-C_3H_7	n-C_3H_7	t	219-222	$C_{21}H_{25}Cl_2N \cdot HCl$	~25	>100	150	73	720
90	n-C_3H_7	n-C_3H_7	c	190-193	$C_{21}H_{25}Cl_2N \cdot HCl$	>100	>100	180	NT	NT
91	H	CH_2CH_2OH	t	167-169	$C_{17}H_{17}Cl_2NO \cdot HCl$	75 (23-240)	171 (66-444)	NT	NT	NT
92	H	CH_2CH_2OH	c	235-238	$C_{17}H_{17}Cl_2NO \cdot HCl$	>111	>111	NT	NT	NT
93	H	$CH_2C_6H_5$	t	269-272	$C_{22}H_{19}Cl_2N \cdot HCl$	>50	47 (37-59)	NT	NT	NT
94	H	$CH_2C_6H_5$	c	230-233	$C_{22}H_{19}Cl_2N \cdot HCl$	>198	207 (153-280)	NT	NT	NT
95	H	$CH_2CH_2C_6H_5$	~90% t	241-243	$C_{23}H_{21}Cl_2N \cdot HCl$	33 (17-66)	142 (47-426)	NT	NT	NT
96	H	$CH_2CH_2C_6H_5$	~90% c	228-230	$C_{23}H_{21}Cl_2N \cdot C_2H_4O_2$	>85	>85	NT	NT	NT
97	$(CH_2)_4$		t	194-196	$C_{19}H_{19}Cl_2N \cdot HCl$	>108	>108	320	NT	NT
98	$(CH_2)_4$		>90% c	197-200	$C_{19}H_{19}Cl_2N \cdot HCl$	>108	161 (54-483)	32	27	3.1
99	$(CH_2)_5$		>92% t	267-270	$C_{20}H_{21}Cl_2N \cdot HCl$	>104	>209	720	NT	NT
100	$(CH_2)_5$		>90% c	245-249	$C_{20}H_{21}Cl_2N \cdot HCl$	>104	>209	79	79	420
101	$CH_2CH_2N(CH_3)CH_2CH_2$		(±) t			48 (22-107)	97 (68-138)	11	32	200
(+)-**101**	$CH_2CH_2N(CH_3)CH_2CH_2$		(+) t			>91	>91	340	120	2500
(−)-**101**	$CH_2CH_2N(CH_3)CH_2CH_2$		(−) t			26 (15-43)	>92	10	7.8	230
102	$CH_2CH_2N(CH_3)CH_2CH_2$		(±) c			100 (34-295)	>89	4.4	7.7	630
(+)-**102**	$CH_2CH_2N(CH_3)CH_2CH_2$		(+) c			>89	>89	1700	910	2300
(−)-**102**	$CH_2CH_2N(CH_3)CH_2CH_2$		(−) c			69 (35-139)	>89	2.3	2.5	530

[a] **83-100** are all racemates. All compounds were made by method A. [b-d] See corresponding footnotes in Table IV. [e] t (trans) and c (cis) indicate isomers >95% pure as estimated by TLC. [f] NT = not tested.

itors. A clearly different profile of cis vs. trans isomers, not seen for the piperazino compounds, was found: The trans isomers were potent inhibitors of both catecholamine and 5-HT uptake, while the cis isomers were more or less selective 5-HT-uptake inhibitors.

Comparison of the activities of mono- and dimethylamines in Tables IV and V reveals an interesting pattern of activity. Among tricyclic antidepressants monomethylamines are consistantly more potent NE-uptake inhibitors than the corresponding dimethylamines,[6] while the reverse is true for 5-HT-uptake inhibition. This is also found for other antidepressant agents including **1**–**3**.[6] This rule also seems to apply in the trans series (Table IV), while the reverse is true in the cis series (Table V), although the cis compounds are less potent. The monomethylamines are also the most potent DA-uptake inhibitors in the trans series, while the cis derivatives are weak DA-uptake inhibitors with no significant difference between mono- and dimethylamines.

With regard to the effect of aromatic substitution in the 3-phenyl ring, the pattern was in good agreement with the Topliss scheme for enhancing activity by benzene ring substitution.[29] The 4′-chloro derivatives (**35**, **62**, **63**) were clearly more active than the unsubstituted compounds, and this leads automatically, according to the Topliss scheme, to the 3′,4′-dichloro compounds (**45**, **46**, **72**, **73**) which were the most active compounds in both series. The 4′-chloro-3′-trifluoromethyl substituted compound (**47**), which is the next substitution pattern recommended by Topliss, had very low activity, compared with the 3′,4′-dichloro analogue (**45**).

However, as we were not only interested in high potency but also in the differential activity of the compounds in the three tests for uptake inhibition, other substitution patterns were tried as well. Compounds with 4′-bromo substitution (**36**, **37**, **64**, **65**) were nearly as active as the corresponding 3′,4′-dichloro compounds, while a 4′-trifluoromethyl-substituted compound (**38**) was weak. The bromo and the trifluoromethyl groups have largely similar hydrophobic and electronic characteristics,[29] so the difference in activity is probably due to the difference in steric effects of the two substituents. Compounds with 4′-fluoro substitution were generally weak, except for an unexplainably high activity of **33** in the tetrabenazine ptosis test. Compounds with alternative 3′,4′-disubstitution such as 3′,4′-difluoro or 3′-chloro-4′-fluoro were weaker than the 3′,4′-dichloro-substituted compounds. A change to 2′,4′-dichloro substitution (**48**, **49**, **75**) resulted in compounds that were highly selective inhibitors of 5-HT uptake. On the whole, widely different substitution patterns seem to be acceptable at the 5-HT-uptake site, while the DA- and NE-uptake sites make stricter demands.

Compounds with a 3′,4′-dichloro substitution and an additional substituent such as fluoro, methoxy, or hydroxy in the 6-position of the indane ring were nearly as active in vitro as the compounds unsubstituted in the 6-position. However, in vivo only the 6-methoxy-substituted compounds (**52**, **53**, **78**, **79**) had similar activity.

In the series of 1-piperazino-3-phenylindans[21] described earlier some of the 4′,6-difluoro-substituted cis isomers were potent uptake inhibitors. However, this substitution pattern was unsuccessful in this series, as compounds **56** and **81** were only weakly active. Compounds with 4′-fluoro-6-trifluoromethyl substitution (**57** and **82**), as found in the potent neuroleptic compound tefludazine, also had low activity in this series.

The effect of change in the N substituent was investigated in a series of compounds with the optimal 3′,4′-dichloro substitution. The results are shown in Table VI. Monoethyl, diethyl, and monopropyl N-substituted compounds all retained good activity in vitro with an activity pattern similar to the corresponding methyl compounds, but all compounds were considerably less potent in vivo. Dipropylamines and secondary amines with larger substituents such as benzyl or phenethyl were weak or inactive. Compounds with a pyrrolidine or piperidine ring (**97**, **98**, **99**, **100**) were inactive in vivo. Interestingly, the pyrrolidine derivative **98** was still a potent 5-HT-uptake inhibitor in vitro, while the piperidine derivative **100** was nearly inactive.

The pharmacological and biochemical testing of the enantiomeric salts of **45** revealed that most of the activity resided in (+)-**45** (Table IV). As the enantiomeric purity of (−)-**45** as mentioned above was determined to be greater than 95%, it is not likely that the observed activity of this enantiomer could be due to content of (+)-**45**. The enantioselectivity of these compounds was therefore not as pronounced as demonstrated previously for the enantiomers of **101** and **102**(Table VI).

Compound **45** (as the racemate) was selected for further pharmacological characterization.[30-32] The compound was shown to be a competitive inhibitor of the uptake of both the catecholamines and serotonin. In receptor binding models **45** had no affinity for DA, 5-HT, and NE receptors, and in functional in vitro tests it had no histaminergic or cholinergic inhibiting properties. Although **45** caused release of [^{3}H]-DA in rabbit striatal slices in high concentrations, accumulation was inhibited in concentrations 100 times lower, indicating that the compound must be considered as an uptake inhibitor and not as a DA-releasing compound. Furthermore, **45** attenuated both DA and NE depletion caused by 6-OHDA, an effect not expected for a DA-releasing compound.[30]

The effects of compound **45** in vivo[31] were qualitatively similar to nomifensine, but lasted longer. Stereotyped behavior was induced after parenteral and oral administration and lasted more than 24 h. In lower doses **45** induced ipsilateral circling in unilaterally 6-OHDA-lesioned rats.[31] Finally, **45** antagonized perphenazine-induced catalepsy. These effects are clearly related to DA-uptake inhibition, as indicated by the lack of activity in these tests of the selective NE-and 5-HT-uptake inhibitors **2** and **3**, respectively. In experiments with prolonged treatment of rats with **45**, downregulation of β and 5-HT receptors in cortex and D-2 receptors in striatum could be demonstrated.[32]

Discussion

As mentioned above, trans isomers in this series were in general potent inhibitors of both catecholamine and 5-HT uptake, while cis isomers more or less were selective 5-HT-uptake inhibitors. This fact led us to wonder whether superimposition of the molecules of the cis and trans isomers respectively with the catecholamines and 5-HT could explain the observed different activity pattern. It was presumed that both isomers competitively inhibited the uptake of the transmitter molecules by binding to the same active site of the carrier molecule.

Because of the great molecular similarity of DA and NE

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(30) Hyttel, J.; Larsen, J.-J. *J. Neurochem.* **1985**, *44*, 1615.

(31) Arnt, J.; Hyttel, J. *Naunyn-Schmidelberg's Arch. Pharmacol.* **1985**, *329*, 101.

(32) Nowak, G.; Arnt, J.; Hyttel, J.; Svendsen, O. *J. Neural. Transm.*, in press.

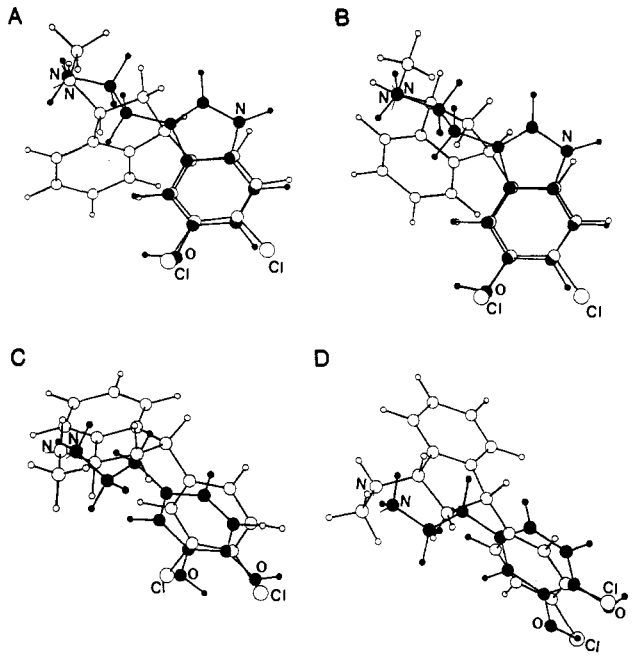

Figure 3. Superimpositions of **45** and **72** with DA and 5-HT. The following atoms were included in a least-squares fitting procedure: (1) the N atoms; (2) C–O (in DA and 5-HT) with C–Cl (in indans); (3) centers of phenyl rings (3-phenyl ring in indans). Mean distance between fitted atoms: (A) **45** and 5-HT, mean distance 0.176 Å; (B) **72** and 5-HT, mean distance 0.136 Å; (C) **45** and DA, mean distance 0.424 Å; (D) **72** and DA, mean distance 0.679 Å.

we decided it would be sufficient to make the superimpositions with DA only. Both NMR studies and molecular orbital calculations have shown that the synclinal and the antiperiplanar conformations of DA are approximately equally stable.[33] However, the results presented here are with DA in its antiperiplanar conformation, because relevant superimpositions of the synclinal conformer with the indanamines could not be obtained.

Molecular orbital calculations on serotonin[34] have shown that the preferred conformation of this compound is antiperiplanar with the side chain in a trans conformation perpendicular to the aromatic system.

The MIMIC[35] molecular modeling system was used to construct models of the trans (**45**) and cis (**72**) isomers, and minimum energy structures were calculated by using the MMP2 molecular mechanics program.[36] In the trans isomer the 3-phenyl ring has a pseudoaxial orientation and the amine group has a pseudoequatorial orientation. For the cis isomer the conformer with both substituents in a pseudoequatorial position was chosen because this conformer gave the best fit and because the steric energy was about 1 kcal/mol lower than the energy of the conformer with both substituents in pseudoaxial position.

The superimpositions shown in Figure 3 illustrate the very good fits between both trans and cis (**3A** and **3B**) isomers and 5-HT in accordance with the potent 5-HT-uptake inhibition found for both types of isomers. Note also that the position of the indan phenyl ring in the two isomers is very similar. In addition to the fact that the geometry of both cis and trans isomers fits the 5-HT-uptake site, the affinity of the compounds for this site was, as mentioned above, considerably less sensitive toward changes in the aromatic substitution pattern. For these reasons it was relatively easy to obtain highly selective 5-HT-uptake inhibitors in this series such as **37**, **49**, or **75**. The size of the amino group was considerably more critical for the affinity for the 5-HT-uptake site. Amines with small substituents such as methyl or ethyl, or in the cyclic series pyrrolidine, had significant activity while activity was completely lost with larger amines—both aliphatic and heterocyclic such as piperidine or piperazine. Derivatives of **3** with a piperidine or piperazine ring instead of a dimethylamino group were also inactive.[37] This seems to indicate that only very limited space is available at the nitrogen binding site at the 5-HT-uptake site.

Superimpositions with DA (**3C**, **3D**) gave a better fit of the trans isomer than the cis isomer, also in accordance with the biological results. Note that the position of the indan phenyl ring in this case is rather different for the two isomers. Perhaps it is a disturbance of an interaction of this ring with a third lipophilic binding site, rather than the less precise fit with DA that in the case of the cis isomer leads to the diminished affinity for the DA-uptake site. The affinity for this site was also, as mentioned earlier, very dependent on the aromatic substitution pattern. It is obvious from the structure–activity relationships discussed above that the lipophilic, electronic, and steric qualities of the 3′,4′-dichloro substitution lead to optimal affinity for the DA-uptake site. However, the fact that this particular substitution pattern in many other compounds (see below) leads to maximal DA-uptake inhibiting activity suggests that the chlorine atoms might interact directly with the same sites as the two hydroxy groups in DA (or NE). A very interesting difference between the binding sites for 5-HT and DA (or NE) is the ability of the latter to accomodate a larger amine group such as piperazine. Furthermore, in the series of piperazine-substituted compounds[21] the cis isomers are equally or more active than the trans isomers (**101**, **102**). Two possible explanations of the potent activity of the piperazino cis isomers are as follows: (1) The outer nitrogen atom might be able to reach the nitrogen binding site. (2) A change of the total orientation of the compound at the receptor induced by the piperazine ring might lead to a more favorable orientation of the indan phenyl ring in relation to the hypothetical lipophilic binding site mentioned above.

A comprehensive study of this problem and a more detailed discussion of the superimpositions shown in Figure 3 will be published later. Another effect of introducing a piperazine ring instead of a monomethyl amino group is an increased enantioselectivity found for the enantiomers of **101** and **102** (Table VI) compared to the enantiomers of **45**.

As mentioned above the absolute configuration of (+)-**45** was 1*R*,3*S*. The same relative position of the two phenyl rings "A" and "B" is also found in the structures of a number of reported (see Chart I) uptake inhibitors of DA, NE, and/or 5-HT.

Nomifensine (**103**) and the derivatives diclofensine (**104**) and compound **105**[38] have an obvious structural resemblance to the 3-phenyl-1-indanamines. Although the nitrogen atom here is incorporated in a ring system, superimpositions of Dreiding models indicate that very good fits can be obtained between antiperiplanar DA and these

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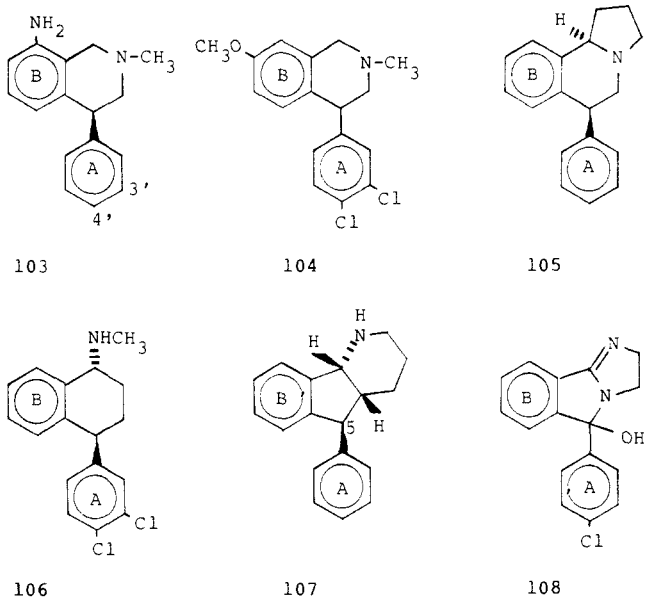
Chart I



compounds. The compounds are also potent NE-uptake inhibitors, but regarding 5-HT uptake inhibition, **104**[15,37] and **105**[38] are much more potent than nomifensine. High enantioselectivity has been reported for both *S*-(+)-nomifensine[39] and the (+)-(6*S*,10b*R*) enantiomer of **105**.[38] When we consider the correspondance between the 3′,4′-dichloro atoms in **45** and 3,4-dihydroxy groups in DA, it is interesting to note that 3′,4′-dihydroxynomifensine has been reported to be a potent DA D-1 *agonist*[40] and that it also in this case is the *S*-(+) enantiomer that is active. The exact effect of 3′,4′-dichloro substitution in nomifensine in relation to DA-uptake inhibition is not known because this derivative is only described in the patent literature[41] where an increased activity in 5-HT-uptake inhibition is claimed. However, diclofensine, which is a very close derivative, is a much more potent DA-uptake inhibitor than nomifensine.[37]

The 4-phenyl-1,2,3,4-tetrahydro-1-naphthylamine derivatives corresponding to **45** and **72** have recently been reported.[42] The profiles of both trans and cis isomers are qualitatively very similar to the indans. The trans isomer (**106**) is potent inhibitor of both catecholamine and 5-HT uptake, while the cis isomer is a selective 5-HT-uptake inhibitor. The stereoselectivity is not as pronounced as for **101–103** or **105**, but also in this case highest potency is found in compounds with 4*S* configuration.

Compound **107** belongs to a series of hexahydroindenopyridines[43] where the amino group in the 3-phenyl-1-indanamines has been connected to the 2-position in the indane ring by a three-carbon bridge. This modification results in complete loss of affinity for the 5-HT-uptake site, as also seen in the indan series with larger amines. In addition, this structural change completely abolishes the affinity for the DA- and NE-uptake sites in compounds with a cis orientation of the nitrogen atom and the 5-phenyl ring, so only compounds with trans configuration as **107** are active. The absolute configuration of the 5-phenyl ring here also is *S*.[44]

Finally, mazindole (**108**) has a structural resemblance to **45** and also a similar pharmacological profile, although the duration of action is much shorter than for **45**. Also, here the 3,4-dichloro substitution results in strongly increased DA- and 5-HT-uptake inhibiting activity.[20]

On the basis of the structures and the pharmacological activity of the compounds mentioned above, we propose a number of structural elements that seem to be important for potent catecholamine- and/or serotonin-uptake inhibition:

1. **DA-Uptake Inhibition.** All the compounds have a phenyl ring (A, Scheme II) and a nitrogen atom held by the molecular framework in a position to each other that mimics the antiperiplanar conformation of DA. Furthermore, 3,4-dichloro substitution of this phenyl ring leads generally to optimal activity, possibly by a direct interaction of the chlorine atoms with the same sites with which the 3,4-dihydroxy groups in DA interact. Finally, another phenyl ring (B, Scheme II) is held by the molecular framework in an optimal position relative to phenyl ring A and the nitrogen atom, as illustrated in Figure 3C. The same relative position of the phenyl ring A and B and the nitrogen atom is found in all active enantiomers for which the absolute configuration has been established (Chart I).

2. **NE-Uptake Inhibition.** The structural elements that are important in a potent NE-uptake inhibitor seem to be qualitatively the same as described above for DA-uptake inhibitors. As a consequence of this, all compounds with affinity for the DA-uptake site also have an equal or greater affinity for the NE-uptake site.

However, at the latter site the position of phenyl ring B seems to be less critical, because a number of the *cis*-indanamines (Table V) with weak activity as DA-uptake inhibitors still are potent NE-uptake inhibitors. As earlier proposed by Koe,[45] this could also explain why all tricyclic antidepressive compounds are very weak DA-uptake inhibitors[6] but potent NE-uptake inhibitors. The position of phenyl ring B might be unfavorable at the DA-uptake site, while it still might be accomodated at the "less restrictive" NE-uptake site. It should also be mentioned that the receptor concept presented here resembles a model earlier presented by Maxwell[46] in that both have the same three major binding sites. However, a difference is that phenyl ring A and the nitrogen atom should not be in the same plane: Instead an antiperiplanar conformation (as also recently suggested by Rutledge[33]) is suggested. Finally, the idea of a NE-uptake site structurally related to but less restrictive than the DA-uptake site offers an explanation of why it is difficult to prepare a selective DA-uptake inhibitor, but not a selective NE-uptake inhibitor such as **1** or **2**. Because of the similarities any compound with affinity for the DA-uptake site will also have affinity for the NE-uptake site, while the opposite is not necessarily true.

3. **5-HT-Uptake Inhibition.** As demonstrated by the indanamines, potent 5-HT-uptake inhibition can be obtained with the same structures that are potent DA- and NE-uptake inhibitors: a phenyl ring and a nitrogen atom held by the molecular framework in a position relative to each other corresponding to the antiperiplanar confor-

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mation of serotonin, and in addition a second phenyl-ring binding site. The aromatic substitution pattern seems to be less critical, but on the other hand there seems to be less space available near the nitrogen binding site as exemplified by the inactivity of **101**, **102**, and **107**.

In conclusion, the indanamines presented here and a number of other newer antidepressant compounds are excellent model compounds for mapping the topography of the uptake sites for catecholamines and serotonin. Resolution and determination of the absolute configuration of more compounds, including highly specific compounds such as **2** or **3**, will hopefully lead to even more precise descriptions of these sites.

Experimental Section

Melting points (uncorrected) were determined on a Buchi 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 (40:60:2:2) 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, it was sometimes 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. Microanalyses (within ±0.4% of theoretical values except where noted) were performed by the Lundbeck Analytical Department.

3,3-Diphenylpropanoic Acids. Substituted ethyl 2-cyano-3-phenyl-2-propenoates were prepared from commercially available aldehydes and ethyl cyanoacetate as earlier described.[21] Substituted bromobenzenes either were commercial products or were prepared by methods established in the literature. From these sources the substituted 3,3-diphenylpropanoic acids (see Table I) were obtained as described earlier.[21]

3-Phenylindan-1-ones (Table II) and 3-phenylindan-1-ols (Table III) were prepared by the methods described earlier.[21]

Method A. General Procedure. *cis*- and *trans*-3-(3,4-Dichlorophenyl)-*N*-methyl-1-indanamine (72 and 45). A mixture of a crude isomeric mixture of 1-chloro-3-(3,4-dichlorophenyl)indan[21] (44 g, 0.15 mol) and 120 mL of 33% methylamine in ethanol was kept at 100 °C in a steel autoclave for 16 h. The mixture was cooled 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 made basic with 10 N NaOH and extracted with ether. After the extract was dried ($MgSO_4$) and evpaorated in vacuo, 35 g (81%) of an isomeric mixture of **45** and **72** was obtained. The isomeric mixture was dissolved in methanol (350 mL) and 14 g of maleic acid was added with stirring. The resulting maleate was filtered and recrystallized from methanol (350 mL). A slurry of the maleate in water was basified with concentrated ammonium hydroxide and extracted with ether. After the extract was dried ($MgSO_4$) and evaporated in vacuo, the residual oil was dissolved in acetone and acidified with a saturated solution of HCl in ether. The hydrochloride salt was recrystallized three times from acetone/ethanol/ether to give 3.3 g (6.8%) of **72**: mp 230–232 °C; isomeric purity 97% (TLC). Anal. ($C_{16}H_{16}Cl_3N$) C, H, N. The filtrate from the maleate was concentrated, basified, and extracted with ether. The ether extract was dried, concentrated in vacuo, dissolved in acetone, and acidified with HCl in ether. The hydrochloride salt was recrystallized two times from acetone/ethanol/ether (1:1:2) to give 12.9 g (26.5%) of **45**: mp 183–185 °C; isomeric purity 99% (TLC). Anal. ($C_{16}H_{16}Cl_3N$) C, H, N.

Cis isomers were generally, as in the above mentioned example, isolated first as the least soluble salt. In some cases oxalic acid was used instead of maleic acid, and in other cases the cis isomer could be isolated directly as the hydrochloride from water or methanol.

Method B. General Procedure. *cis*-3-(3,4-Dichlorophenyl)-6-fluoro-*N*-methyl-1-indanamine (76). 3-(3,4-Dichlorophenyl)-6-fluoroindan-1-one (**18**; 12.5 g, 0.042 mol) and methylamine (9 g, 0.29 mol) were dissolved in 150 mL of dry toluene. To this solution at −5 to 0 °C was added $TiCl_4$ (4.3 g, 0.023 mol) dissolved in 20 mL of toluene. The mixture was stirred at 5 °C for 1 h and at room temperature for 16 h. The mixture was filtered and evaporated in vacuo to give 3-(3,4-dichlorophenyl)-6-fluoro-*N*-methylindanamine: 11.5 g (88%); mp 110–112 °C. Sodium borohydride (5 g, 0.13 mol) was added in portions with stirring at 10–15 °C to a solution of the imine in methanol (150 mL). The mixture was stirred at room temperature for 2 h, and the solvent was then evaporated in vacuo. The residue was treated with ether and water, and the base was purified by extraction with acid, as described above, to give crude **76** (11 g). The base was converted to the hydrochloride salt, which was recrystallized from ethyl acetate/acetone to give 9 g (62%) of **76**: mp 267–269 °C; isomeric purity >95% (TLC). Anal. ($C_{16}H_{15}Cl_3FN$) C, H, N.

Method C. General Procedure. *cis*-3-(3,4-Dichlorophenyl)-*N*,*N*-dimethyl-6-fluoro-1-indanamine (77). A mixture of **76** (5 g of hydrochloride salt, 0.014 mol), 25 mL of HCOOH, and 5 mL of 30% HCHO was refluxed for 3 h. The mixture was cooled, basified with concentrated ammonium hydroxide, and extracted with CH_2Cl_2. The CH_2Cl_2 extract was dried, concentrated in vacuo, dissolved in ethyl acetate, and acidified with HCl in ether. The resulting hydrochloride salt was recrystallized from from acetone/ethanol to give 3.9 g (75%) of **77**: mp 218–220 °C; isomeric purity >97% (TLC). Anal. ($C_{17}H_{17}Cl_3FN$) C, H, N.

Method D. General Procedure. *cis*-3-(3,4-Dichlorophenyl)-*N*,*N*-dimethyl-1-indanamine (73). 3-(3,4-Dichlorophenyl)-indan-1-ol (14 g, 0.05 mol) was treated with methanesulfonyl chloride in methylene chloride as described earlier.[21] The product was shown by NMR analysis not to be a mesylate but an isomeric mixture (2:3) of *cis*- and *trans*-3-(3,4-dichlorophenyl)-1-chloroindans. The crude isomeric mixture (10.2 g) was mixed with 33% dimethylamine in ethanol (40 mL) in a steel autoclave and kept at 90 °C for 16 h. The mixture was worked up as described above to give 6.5 g (74%) of an isomeric mixture, predominantly containing **73**. The hydrochloride salt was crystallized from ethyl acetate to give 3.2 g (33%) of **73**: mp 180–184 °C; isomeric purity 99% (TLC). Anal. ($C_{17}H_{18}Cl_3N \cdot 0.4H_2O$) C, H, N. Karl-Fischer determination: 2% H_2O.

Preparation of Hydroxy-Substituted Compounds. *cis*-3-(3,4-Dichlorophenyl)-6-hydroxy-*N*-methyl-1-indanamine (80). Compound **78** (14 g of hydrochloride salt, 0.04 mol) was refluxed in 48% HBr (320 mL) for 3.5 h. The mixture was evaporated in vacuo, dissolved in ethanol, and evaporated again. The resulting oil was dissolved in ethanol and cooled. The resulting hydrobromide salt was filtered, dried, and recrystallized from ethanol (60 mL) to give 11.6 g (74%) of **80** as the hydrobromide salt. A slurry of the salt in water was treated with triethylamine (3.7 mL) with stirring. The mixture was stirred for 1 h and filtered to give 8.2 g (67%) of **80**: mp 211–213 °C; isomeric purity 100% (TLC). Anal. ($C_{16}H_{15}Cl_2NO$) C, H, N.

Enantiomeric D-(−)- and L-(+)-Tartrates of 45. To a solution of **45** (24.5 g, 0.084 mol) in hot ethyl acetate (200 mL) was added a solution of D-(−)-tartaric acid (3.14 g, 0.021 mol) in ethanol (40 mL). The mixture was left in the refrigerator for 4 h, and the precipitate was filtered and dried to give 10 g of the crude D-(−)-tartaric acid salt of **45**, mp 155–163 °C. The salt was recrystallized from ethanol (120 mL) and acetone (250 mL) to give 9.1 g, melting point as before, and was again recrystallized from ethanol (150 mL) to give 8 g of the D-(−)-tartaric acid salt of **45** [(−)-**45**], mp 161–164 °C; $[\alpha]^{22}_D$ −35.1° (*c* 4.2, MeOH); Karl-Fischer determination 0.9% H_2O. Anal. ($C_{18}H_{18}Cl_2NO_3$) C, H, N.

To the first filtrate from the D-(−)-tartaric acid salt was added ether (one part); the supernatant was decanted, treated with aqueous ammonia, dried ($MgSO_4$), and evaporated in vacuo to give the base (15.3 g). This was dissolved in ethanol (100 mL) and treated with a solution of L-(+)-tartaric acid (6.3 g, 0.042 mol) in ethanol (40 mL). The mixture was left in the refrigerator for 65 h, and the precipitate was filtered and dried to give 19 g of the crude L-(+)-tartaric acid salt of **45** [(+)-**45**], mp 100–105 °C.

The salt was recrystallized four times from ethanol and finally from MeOH/ethyl acetate to give 3.5 g of the L-(+)-tartaric acid salt of **45**: mp 159-162 °C; $[\alpha]^{22}_D$ +33.5° (*c* 3, MeOH). Anal. ($C_{18}H_{18}Cl_2NO_3$) C, H, N.

For optical purity determinations the bases (ca. 30 mg) were mixed with an equivalent amount of (*R*)-(−)-2,2,2-trifluoro-1-(9-anthryl)ethanol in 0.5 mL of $CDCl_3$, and the ^1H NMR spectra was recorded. Under these conditions δ (CH_3NH) was 2.23 for **45** and 2.31 ppm for (+)-**45**.

Pharmacology. Inhibition of DA, NE, and 5-HT uptake in vitro, tetrabenazine ptosis, and 5-HTP potentiation was measured as earlier described.[21,47]

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Inhibition of Human Leukocyte Elastase, Porcine Pancreatic Elastase, and Chymotrypsin by Elasnin and Other 4-Hydroxy-2-pyrones[1]

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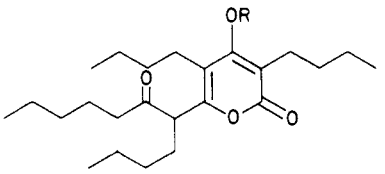
Elasnin and 15 related 4-hydroxy-2-pyrones have been assayed for in vitro inhibition of human leukocyte elastase, porcine pancreatic elastase, and bovine chymotrypsin. Inhibition constants for HL elastase range from 0.1 to 10 mM. The principal determinant of potency against the elastases is probably the substituent at position 3, which may account for the observed strong homology between the elastases in their inhibition by these compounds. Acetylation of the 4-hydroxy group has no effect on inhibition. The inhibition is noncovalent; there is no evidence of enzyme acylation by these pyrones.

Since leukocyte elastase has been implicated in a number of inflammatory and degradative disease states,[2] we have been seeking specific synthetic inhibitors of this enzyme. After Omura et al. reported the isolation and structure of elasnin (**1**),[3] J.R.P. published a synthesis of this naturally occurring compound.[4] We report here the in vitro enzyme inhibitory properties of elasnin and a number of its analogues.

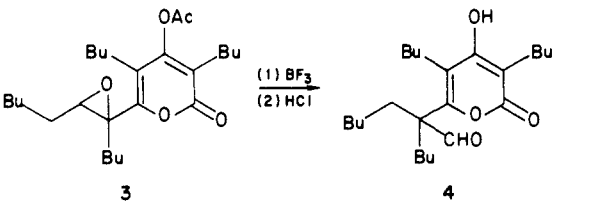


1, R = H
2, R = Ac

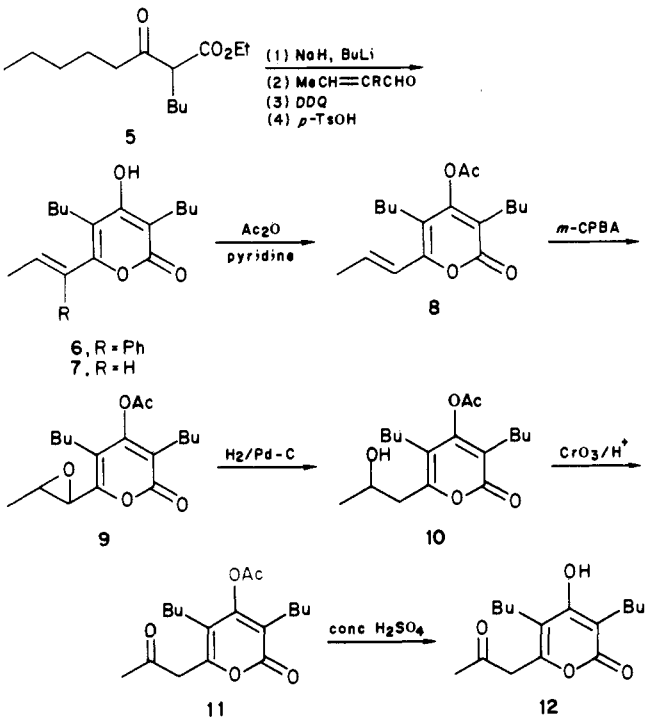
Chemistry. Boron trifluoride induced rearrangement of epoxide **3**,[4] followed by acid-catalyzed deacetylation, produced the tertiary aldehyde **4** exclusively (Scheme I). This transformation could also be achieved by employing proton acids such as concentrated H_2SO_4, HCOOH, or $HClO_4$/dioxane. The vinyl derivatives **6** and **7** were obtained as described previously[4] by reaction of the dianion of keto ester **5** with the requisite aldehyde, oxidation of the resulting δ-hydroxy keto ester to the diketo ester, and enol lactonization. Whereas the *O*-acetate derived from the phenyl compound **6** proved to be completely inert under forced epoxidation conditions,[5] the less hindered propenyl derivative **8** gave the expected epoxide **9** in good yield. The latter was transformed into the elasnin analogue **12** as described previously[4] (Scheme II).

Acylation of the dianion of **5** with methyl acetate and methyl hexanoate gave the diketo esters **13** and **14**, which were cyclized to the corresponding enol lactones **15** and **16**. The latter was again deprotonated (NaH, *n*-BuLi), and the resulting dianion was reacted with methyl benzoate to provide the benzoyl derivative **17** (Scheme III). The

Scheme I



Scheme II



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