Affinity of 10-(4-Methylpiperazino)dibenz[*b*,*f*]oxepins for Clozapine and Spiroperidol Binding Sites in Rat Brain[1]

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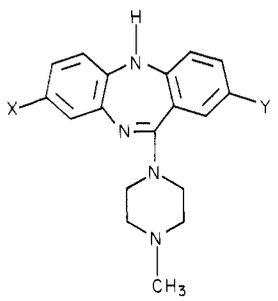
Received October 13, 1981

10-(4-Methylpiperazino)dibenz[*b*,*f*]oxepins were prepared and evaluated as potential antipsychotic agents using specific clozapine [8-chloro-11-(4-methylpiperazino)-5*H*-dibenzo[*b*,*e*][1,4]diazepine] binding sites in rat forebrain that are noncholinergic and nondopaminergic in nature and from which [^{3}H]clozapine is displaced by known antipsychotic agents. [^{3}H]Clozapine binding in the presence of atropine represents nonmuscarinic binding, while binding in the absence of atropine represents muscarinic (cholinergic) plus nonmuscarinic binding. The relative affinity for dopamine binding sites was determined by displacement of [^{3}H]spiroperidol from binding sites in rat caudate nuclei. Thus, clozapine, its 2-chloro isomer, its dechloro analogue, and their 5*H*-dibenzo[*a*,*d*]cycloheptene and dibenz[*b*,*f*]oxepin analogues have about the same relative affinity for the nonmuscarinic clozapine binding sites. At the spiroperidol (dopaminergic) sites, both the nature of the tricyclic system and the presence of a chlorine atom on the tricyclic system have a substantial effect on the binding affinity. Within each series, shift of a chlorine atom from the position distal to the piperazino group to the proximal position increases the binding affinity by a factor of about nine, but removal of the chlorine atom substantially decreases the binding affinity. Nevertheless, 10-(4-methylpiperazino)dibenz[*b*,*f*]oxepin has a threefold greater affinity for the dopaminergic binding sites than does clozapine itself.

Reports that clozapine [8-chloro-11-(4-methylpiperazino)-5*H*-dibenzo[*b*,*e*][1,4]diazepine, **1a**] is an antipsychotic drug which in clinical use produces practically no extrapyramidal effects[2] suggest that the pharmacological separation of these side effects from antipsychotic activity seems clearly feasible. Since clozapine displays agranulocytosis as a serious toxic effect,[3] we initiated an investigation of some of the pharmacological properties of analogues of **1a** in pursuit of a potential antipsychotic agent free of extrapyramidal and other toxic side effects.[4]



1a, X = Cl; Y = H
b, X = H; Y = Cl
c, X = Y = H

The problem of finding drugs with a clozapine-like profile using the classical neuroleptic testing method is well known.[5] Recently it has been shown that clozapine binds to sites in rat forebrain that appear not to be dopaminergic in nature.[6,7] The binding of [^{3}H]clozapine in the presence of atropine represents nonmuscarinic binding,[7] and binding in the absence of atropine represents muscarinic plus nonmuscarinic binding. While the identity of the nonmuscarinic binding sites and their relationship to the antipsychotic properties of clozapine are unknown, displacement of [^{3}H]clozapine from these sites by antipsychotic drugs[6,7] suggests the use of these binding sites for the evaluation of analogues of clozapine as potential antipsychotic agents.

Since the low incidence of extrapyramidal effects shown by clozapine may be related to its poor blockade of dopamine receptors,[5] analogues of clozapine were sought which not only interact strongly with the nonmuscarinic [^{3}H]-clozapine binding site in rat forebrain but are also similar to clozapine in its weak potency for displacing [^{3}H]-spiroperidol from binding sites in rat caudate nuclei.[8]

Table I. Inhibition of Muscarinic and Nonmuscarinic [^{3}H]Clozapine and [^{3}H]Spiroperidol Binding in Rat Brain in Vitro

	IC_{50} SEM,[a] nM		
	[^{3}H]clozapine binding[b]		[^{3}H]spiroperidol
no.	muscarinic	nonmuscarinic[c]	binding[d]
1a[e]	12 ± 2 (17)	13 ± 2 (19)	4 310 ± 226 (3)
1b[e]	28 ± 6 (3)	17 ± 4 (4)	758 ± 167 (3)
1c	31 ± 2 (3)	25 ± 4 (6)	>10 000 (2)
2a[e]	670 ± 170 (6)	13 ± 3 (6)	342 ± 16 (3)
2b[e]	290 ± 98 (6)	10 ± 5 (6)	39 ± 4 (3)
2c[e]	610 ± 120 (5)	3.7 ± 0.4 (5)	808 ± 222 (4)
3a	1970 ± 236 (4)	9.4 ± 2.0 (4)	357 ± 89 (3)
3b	2027 ± 189 (3)	7.3 ± 2.7 (3)	27 ± 1 (2)
3c	2290 ± 429 (3)	4.0 ± 1.3 (3)	1 500 ± 260 (4)

[a] An IC_{50} value designates the concentration of clozapine (**1a**) or an analogue that displaces specific binding of the radiolabeled ligand by 50%. SEM is the standard error of the mean for the number of displacement curves, given in parentheses, from which the IC_{50} values were determined. [b] [^{3}H]Clozapine concentration was 2.1 nM. [c] Binding in the presence of 1 μM atropine. [d] [^{3}H]Spiroperidol concentration was 2.2 nM. [e] Characterized in ref 4.

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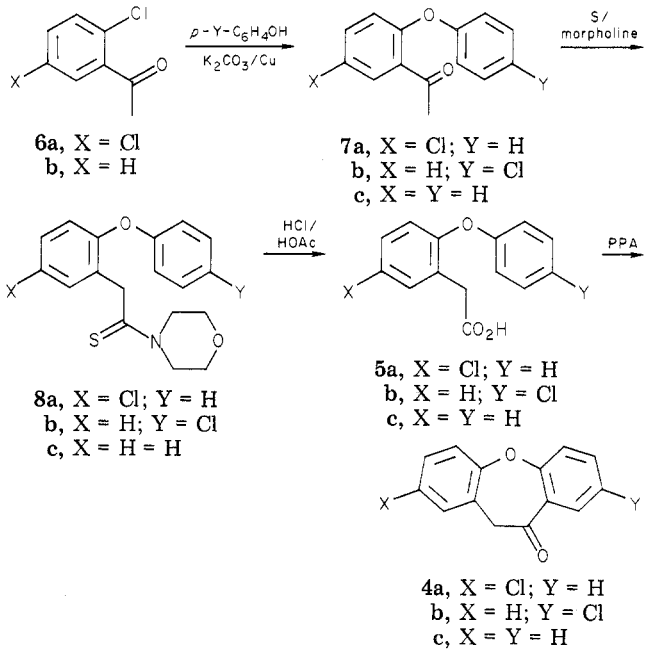
Scheme I



6a, X = Cl
b, X = H

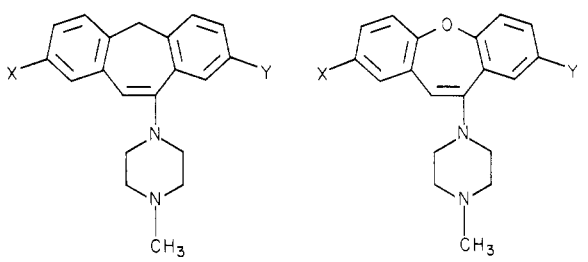
7a, X = Cl; Y = H
b, X = H; Y = Cl
c, X = Y = H

8a, X = Cl; Y = H
b, X = H; Y = Cl
c, X = H = H

5a, X = Cl; Y = H
b, X = H; Y = Cl
c, X = Y = H

4a, X = Cl; Y = H
b, X = H; Y = Cl
c, X = Y = H

In previously reported work,[4] 2-chloro-10-(4-methylpiperazino)-5*H*-dibenzo[*a*,*d*]cycloheptene (**2a**) and its



2a, X = Cl; Y = H
b, X = H; Y = Cl
c, X = Y = H

3a, X = Cl; Y = H
b, X = H; Y = Cl
c, X = Y = H

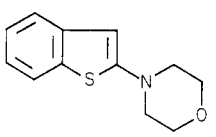
11-(4-methylpiperazino) isomer (**2b**) and dechloro analogue (**2c**) were prepared and evaluated in comparison to clozapine (**1a**) and its 2-chloro isomer[9] (**1b**) (Table I).

On the basis of these comparisons, we have now prepared a series of dibenz[*b*,*f*]oxepin analogues (**3a–c**) of clozapine (**1a**) and evaluated these analogues in comparison to **1a**, its 2-chloro isomer (**1b**), its dechloro analogue[9] (**1c**), and their 5*H*-dibenzo[*a*,*d*]cycloheptene analogues (**2a–c**).

Results and Discussion

Synthesis. For the synthesis of the dibenz[*b*,*f*]oxepin analogues of clozapine, the key intermediates were the tricyclic ketones **4a–c**, formed by cyclization of the corresponding *o*-phenoxyphenylacetic acids **5a–c** in hot polyphosphoric acid (PPA) (Scheme I).[10] The ketones **4a–c** were then condensed with *N*-methylpiperazine in boiling benzene with titanium tetrachloride as catalyst and water scavenger[10,11] to give the corresponding 10-(4-methylpiperazino)dibenz[*b*,*f*]oxepins **3a–c**. The synthesis of the *o*-phenoxyphenylacetic acids **5a–c** began with a nucleophilic substitution of chloride ion[10] from an *o*-chloroacetophenone (**6a** or **6b**) by phenoxide or *p*-chlorophenoxide ion in the presence of copper to form the corresponding *o*-phenoxyacetophenones **7a–c**. The latter were oxidized to the thioamides **8a–c** by the Kindler modification of the Willgerodt reaction using sulfur in boiling morpholine.[10,12] Without isolation, the amides **8a–c** were susequently hydrolyzed in acetic acid–hydrochloric acid to **5a–c**.

From a Willgerodt reaction with **7c**, the thioamide **8c** was obtained as a crystalline solid. The structure of **8c** was established on the basis of its proton nuclear magnetic resonance (^{1}H NMR) spectrum and its conversion in hot polyphosphoric acid to 2-morpholinobenzo[*b*]thiophene[13] (**9**) by way of a reaction in which the thione sulfur is involved in a nucleophilic displacement of phenoxide ion.[14]



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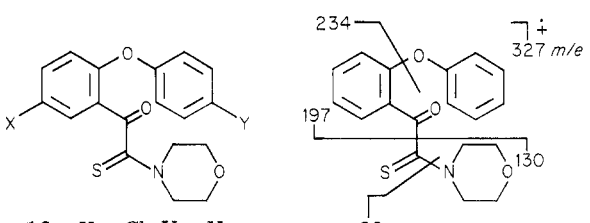
In the conversion of the acetophenones **7a–c** to the thioamides **8a–c**, the formation of the 2-morpholino-2-thioxo-1-(*o*-phenoxyphenyl)-1-ethanones **10a–c**, arising by way of a recently proposed mechanism,[15] substantially reduced the eventual yield of the *o*-phenoxyphenylacetic acids **5a–c**. The acids were easily purified, since **10a–c** are not hydrolyzed using boiling acetic acid–hydrochloric acid, and **10a–c** were separated from **5a–c** as neutral components after hydrolysis of **8a–c**.



10a, X = Cl; Y = H
b, Y = H; Y = Cl

10c

2-Morpholino-2-thioxo-1-(*o*-phenoxyphenyl)-1-ethanone (**10c**) crystallized from the neutral extract of **5c**. The structure of **10c** was established on the basis of its ^{1}H NMR and mass spectra, the fragmentation pattern (**10c**) in the latter eliminating an alternate structure for **10c** in which the sulfur and the carbonyl oxygen atoms are interchanged. The chloro analogues **10a** and **10b** of **10c** were not isolated but were identified as present in the neutral extracts of **5a** and **5b** by ^{1}H NMR spectroscopy.

Biological Activity. As seen in Table I, relative to the 5*H*-dibenzo[*b*,*e*][1,4]diazepines (**1a–c**), the binding at the muscarinic (cholinergic) binding sites is substantially decreased for the 5*H*-dibenzo[*a*,*d*]cycloheptenes (**2b–c**) and to an even greater extent for the dibenz[*b*,*f*]oxepins (**3a–c**). Within each series, the binding affinity is essentially the same, the presence or position of the chlorine atom having only a small effect.

The dibenzo[*b*,*e*][1,4]diazepines (**1a–c**), the 5*H*-dibenzo[*a*,*d*]cycloheptenes (**2b–c**), and the dibenz[*b*,*f*]oxepins (**3a–c**) all have about the same relative affinity for the nonmuscarinic binding sites. At the spiroperidol (dopaminergic) sites, however, both the nature of the tricyclic

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system and the presence of the chlorine atom on the tricyclic system have a substantial effect on the binding affinity. Within each series, shift of the chlorine atom from the position distal to the piperazino group (**1a**, **2a**, **3a**) to the proximal position (**1b**, **2b**, **3b**) increases the binding affinity by a factor of about nine, but removal of the chlorine atom substantially decreases the binding affinity.

The data in Table I show that for binding to nonmuscarinic clozapine and spiroperidol sites there is a subtle interplay between the atoms in the seven-membered ring and the substituent of the tricyclic system and that the relative affinity for each binding site type may be changed independent of the other by a change in the nature and the substitution of the tricyclic system. Thus, the ratios of the IC_{50} values for dopaminergic to nonmuscarinic clozapine binding for **1a** and **3c** are the same, but the ratio of the IC_{50} values for dopaminergic to muscarinic clozapine binding for **1a** is about 570 times greater than that for **3c**.

Experimental Section

Melting points were taken in open capillary tubes and are corrected. Boiling points are not corrected. Evaporations were done at reduced pressure using a water pump. Proton nuclear magnetic resonance (^{1}H NMR) spectra were obtained in chloroform-*d* with tetramethylsilane as an internal standard using a JEOL JNM-MH-100 spectrometer. Chemical shifts (δ) are reported in parts per million downfield from the standard. The mass spectrum was obtained using an LKB Model 9000 mass spectrometer with 70-eV ionizing potential and a direct-introduction probe. Microanalyses were done by Galbraith Laboratories, Knoxville, TN, and agreed to within 0.4% of the calculated values unless otherwise noted.

11-(4-Methylpiperazino)-5*H*-dibenzo[*b*,*e*][1,4]diazepine (1c) was a gift from Dr. Jean Schmutz, Wander, Ltd., Berne, and was a yellow solid with mp 182–184 °C (lit.[9] mp 182–184 °C).

2-Chloro-10-(4-methylpiperazino)dibenz[*b*,*f*]oxepin (3a). A solution of *N*-methylpiperazine (2.00 g, 20.0 mmol) in dry benzene (30 mL) was slowly added under nitrogen to a solution of 2-chloro-10,11-dihydrodibenz[*b*,*f*]oxepin-10-one (**4a**; 1.30 g, 5.31 mmol) and $TiCl_4$ (1.1 g, 5.8 mmol) in dry benzene (40 mL) at room temperature, and the mixture was boiled for 4 h. After the mixture was cooled, saturated Na_2CO_3 (75 mL) was added, and the mixture was stirred overnight and then filtered to remove solid TiO_2. The filter cake was washed with ether, and the filtrate and washings were combined and then separated. The aqueous layer was extracted with ether, and the ether extract was added to the benzene–ether solution. This mixture was dried (Na_2SO_4) and evaporated. Recrystallization of the solid residue from isopropyl ether gave **3a** (1.05 g, 60%): mp 122–123 °C; ^{1}H NMR δ 2.38 (s, 3, NCH_3), 2.64 (m, 4, piperazino C-3 and C-5 H), 3.08 (m, 4, piperazino C-2 and C-6 H), 5.92 (s, 1, C-11 H), 7.08–7.62 (m, 7, aromatic H). Anal. ($C_{19}H_{19}ClN_2O$) C, H, Cl, N.

2-Chloro-11-(4-methylpiperazino)dibenz[*b*,*f*]oxepin (3b) was prepared from **4b** as described for the preparation of **3a** from **4a** and was recrystallized from isopropyl ether (58%): mp 127–128 °C (lit.[16] mp 125–128 °C); ^{1}H NMR δ 2.34 (s, 3, NCH_3), 2.52 (m, 4, piperazino C-3 and C-5 H), 3.00 (m, 4, piperazino C-2 and C-6 H), 6.04 (s, 1, C-10 H), 7.00–7.56 (m, 7, aromatic H).

10-(4-Methylpiperazino)dibenz[*b*,*f*]oxepin (3c) was prepared from **4c** as described for the preparation of **3a** from **4a** and was recrystallized from isopropyl ether (70%): mp 111–112 °C (lit.[10] mp 109–110 °C); ^{1}H NMR δ 2.06 (s, 3, NCH_3), 2.50 (m, 4, piperazino C-3 and C-5 H), 3.00 (m, 4, piperazino C-2 and C-6 H), 6.00 (s, 1, C-11 H), 7.00–7.68 (m, 8, aromatic H).

2-Chloro-10,11-dihydrodibenz[*b*,*f*]oxepin-10-one (4a). 5-Chloro-2-phenoxyphenylacetic acid (**5a**; 2.20 g, 8.38 mmol) was added in small portions with stirring to polyphosphoric acid ($H_6P_4O_{15}$; 20 mL) at 100–105 °C. After the mixture was cooled, ice–water (150 mL) was slowly added, and the mixture was extracted with ether. The ether extract was washed with saturated sodium carbonate, dried (Na_2SO_4), and evaporated. Recrystallization of the solid residue from hexane gave **4a** (1.25 g, 61%): mp 78–79 °C; ^{1}H NMR δ 4.04 (s, 2, C-11 H), 7.08–7.64 (m, 6, aromatic H), 8.04 (d of d, 1, J = 2 and 8 Hz, C-9 H). Anal. ($C_{14}H_9ClO_2$) C, H, Cl.

8-Chloro-10,11-dihydrodibenz[*b*,*f*]oxepin-10-one (4b) was prepared from **5b** as described for the preparation of **4a** from **5a** and was recrystallized from hexane (85%): mp 83–84 °C (lit.[10] mp 80–81 °C); ^{1}H NMR δ 4.16 (s, 2, C-11 H), 7.20–7.68 (m, 6, aromatic H), 8.12 (d, 1, J = 2 Hz, C-9 H).

10,11-Dihydrodibenz[*b*,*f*]oxepin-10-one (4c) was prepared from **5c** as described for the preparation of **4a** from **5a** and was recrystallized from hexane (53%): mp 53–54 °C (lit.[10] mp 50 °C); ^{1}H NMR δ 4.08 (s, 2, C-11 H), 7.08–7.60 (m, 7, aromatic H), 8.08 (d of d, J = 2 and 8 Hz, C-9 H).

5-Chloro-2-phenoxyphenylacetic Acid (5a). A mixture of 5-chloro-2-phenoxyacetophenone (**7a**; 5.00 g, 20.4 mmol), morpholine (2.82 g, 32.4 mmol), and sulfur (1.0 g, 0.031 g-atom) was boiled for 12 h. After the mixture was cooled, glacial acetic acid (25 mL) and concentrated hydrochloric acid (25 mL) were added, and the mixture was boiled for 8 h. The reaction mixture was evaporated to one-third its initial volume. Water (100 mL) was added, and the mixture was extracted with ether. The ether extract was washed with sodium bicarbonate. This aqueous layer was acidified with concentrated hydrochloric acid and extracted with ether. This ether layer was dried (Na_2SO_4) and evaporated. The residual oil crystallized after the addition of water. Recrystallization of this solid from benzene–hexane gave **5a** (2.44 g, 46%): mp 124–125 °C; ^{1}H NMR δ 3.75 (s, 2, CH_2CO_2), 6.75–7.40 (m, 8, aromatic H), 10.10 (br s, 1, CO_2H). Anal. ($C_{14}H_{11}ClO_3$) H, Cl; C: calcd, 64.01; found, 64.48.

***o*-(*p*-Chlorophenoxy)phenylacetic acid (5b)** was prepared from **7b** as described for the preparation of **5a** from **7a** and was recrystallized from benzene–hexane (66%): mp 120–121 °C (lit.[10] mp 115–118 °C); ^{1}H NMR δ 3.72 (s, 2, CH_2CO_2), 6.78–7.30 (m, 8, aromatic H), 10.80 (br s, 1, CO_2H).

***o*-Phenoxyphenylacetic Acid (5c) and 2-Morpholino-2-thioxo-1-(*o*-phenoxyphenyl)-1-ethanone (10c).** *o*-Phenoxyphenylacetic acid (**5c**) was prepared from **7c** as described for the preparation of **5a** from **7a** and was recrystallized from benzene–hexane (62%): mp 90–91 °C (lit.[10] mp 89–91 °C); ^{1}H NMR δ 3.75 (s, 2, CH_2CO_2), 6.80–7.40 (m, 9, aromatic H), 9.60 (br s, 1, CO_2H).

After washing of the initial ether extract with sodium bicarbonate, the ether solution was dried (Na_2SO_4) and evaporated. On standing, the residual oil crystallized, and recrystallization of the solid from toluene gave yellow **10c** (8.1 g, 13%): mp 135–137 °C; ^{1}H NMR δ 3.70 (m, 2, morpholino C-2 H), 3.76 (s, 4, morpholino C-5 and C-6 H), 4.06 (m, 2, morpholino C-3 H), 6.76–7.50 (m, 8, aromatic H), 8.40 (d of d, 1, J = 2 and 9 Hz, CHCCO); mass spectrum, m/e (relative intensity) 327 (3), 234 (50), 197 (100), 130 (12), 86 (16). Sublimation at 135 °C (0.05 mm) gave the analytical sample, mp 136–137 °C. Anal. ($C_{18}H_{17}NO_3S$) C, H, N, S.

5-Chloro-2-phenoxyacetophenone (7a). A mixture of 2,5-dichloroacetophenone (**6a**; 30.7 g, 0.162 mol), phenol (19.3 g, 0.205 mol), and potassium carbonate (30.2 g, 0.219 mol) was boiled for 10 h in the presence of copper power (1.5 g, 0.024 g-atom). After cooling, the mixture was filtered, and the filter cake was washed with ether. The filtrate and washings were combined and extracted with 1 N sodium hydroxide. The ether solution was evaporated. Distillation of the residue gave **6a** (1.91 g, 6%), bp 56–58 °C (0.09 mm), and **7a** (25.1 g, 63%), bp 122–124 °C (0.09 mm). On standing, **7a** crystallized and was recrystallized from methanol: mp 58–59 °C; ^{1}H NMR δ 2.60 (s, 3, CH_3CO), 6.75–7.38 (m, 7, aromatic H), 7.78 (d, 1, J = 3, C-6 H). Anal. ($C_{14}H_{11}ClO_2$) C, H, Cl.

***o*-(*p*-Chlorophenoxy)acetophenone (7b)** was prepared from *o*-chloroacetophenone (**6b**) as described for the preparation of **7a** from **6a**, with the exception that *p*-chlorophenol was used instead of phenol. Distillation gave **7b** (60%): bp 140–142 °C (0.4 mm) [lit.[10] bp 135–140 °C (0.35 mm)]; ^{1}H NMR δ 2.63 (s, 3, CH_3CO), 6.78–7.38 (m, 7, aromatic H), 7.80 (d of d, 1, J = 3 and 8 Hz, CHCCO).

***o*-Phenoxyacetophenone (7c)** was prepared from *o*-chloroacetophenone (**6b**) as described for the preparation of **7a**. Distillation gave **7c** (71%): bp 120–122 °C (0.1 mm) [lit.[10] bp 132–138 °C (3 mm)]; ^{1}H NMR δ 2.62 (s, 3, CH_3CO), 6.08–7.40 (m, 8,

(16) Mastursi, M.; Lembo, S.; Viterbo, R. South African Patent 6801774, **1968**; *Chem. Abstr.* **1969**, *70*, 96823*q*.

aromatic H), 7.82 (d of d, 1, J = 3 and 8 Hz, CHCCO).

1-Morpholino-2-(*o*-phenoxyphenyl)-1-ethanethione (8c). A mixture of *o*-phenoxyacetophenone (**7c**; 17.5 g, 82.5 mmol), morpholine (14.2 g, 0.163 mol), and sulfur (3.8 g, 0.12 g-atom) was boiled for 6 h. The reaction mixture was diluted with water, and this mixture was extracted with ether. The ether solution was filtered and extracted with 1 N hydrochloric acid and dried (Na_2SO_4). Evaporation of the ether left a residual oil, which on standing partially crystallized, mp 87–93 °C. Repeated recrystallization of this solid from isopropyl ether–ethanol (2:1) gave **8c** (7.18 g, 28%): mp 105–106 °C; ^{1}H NMR δ 3.50 (m, 2, morpholino H), 3.70 (m, 2, morpholino H), 3.72 (m, 2, morpholino H), 4.32 (s, 2, C-2 H), 4.36 (m, 2, morpholino H), 6.76–7.40 (m, 8, aromatic H), 7.56 (d of d, 1, J = 2 and 7 Hz, C*H*CCH$_2$). Anal. ($C_{18}H_{19}NO_2S$) C, H, N.

2-Morpholinobenzo[*b*]thiophene (9). 1-Morpholino-2-(*o*-phenoxyphenyl)-1-ethanethione (**8c**; 0.99 g, 3.2 mmol) was added with stirring to polyphosphoric acid ($H_6P_4O_{15}$; 10 mL) at 90–100 °C, and the mixture was stirred for 2 h. After the mixture was cooled, water was added, and the mixture was extracted with ether. The ether solution was extracted with saturated sodium carbonate and dried (Na_2SO_4). After the ether was evaporated, recrystallization of the solid residue from toluene gave **9** (0.63 g, 91%): mp 177–178 °C (lit.[13] mp 175 °C); ^{1}H NMR δ 3.12 (m, 4, morpholino H), 3.75 (m, 4, morpholino H), 6.08 (s, 1, C-3 H), 6.84–7.52 (m, 4, aromatic H). Anal. ($C_{12}H_{13}NOS$) C, H, N, S.

Biological Activity. Brain tissue and other materials for biological testing were as reported earlier.[4] Displacements of [^{3}H]clozapine from specific muscarinic and nonmuscarinic binding sites in rat forebrain and [^{3}H]spiroperidol from specific binding sites in rat caudate nuclei by the clozapine analogues were determined as described previously.[4]

Acknowledgment. These studies were supported by the Tennessee Department of Mental Health and Mental Retardation and by a fellowship from Hoffmann-La Roche to P.L.M. We thank Dr. Brian C. Sweetman, Department of Pharmacology, for the mass spectrum.

2-Amino-4,7-dimethoxyindan Derivatives: Synthesis and Assessment of Dopaminergic and Cardiovascular Actions

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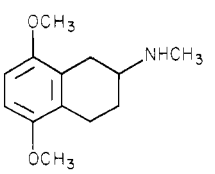
N-Alkylated derivatives of 2-amino-4,7-dimethoxyindan were prepared for evaluation of central and peripheral dopaminergic activity using biochemical and behavioral tests in the rat and cardiovascular responses in the cat. 2-(Di-*n*-propylamino)-4,7-dimethoxyindan (**4e**) demonstrated equal activity with apomorphine to activate peripheral presynaptic dopamine receptors. Central pre- and postsynaptic dopamine receptors were also activated with **4e**. In contrast to the intense long-acting sympathomimetic actions previously reported for the 2-amino-5,8-dimethoxytetralins, these compounds produced weak, transient effects in heart rate and blood pressure. The majority of 2-amino-4,7-dimethoxyindan derivatives tested are weak or inactive pre- and postsynaptic dopamine receptor agonists.

Various researchers have prepared an extensive series of 2-amino-1,2,3,4-tetrahydronaphthalenes (2-aminotetralins) as restricted conformers of compounds containing the β-phenethylamine skeleton. These efforts have been useful in studying the structure–activity relationships of substances related to lysergic acid diethylamide (LSD), the psychotomimetic phenylisopropylamines, and dopamine.[1-6] In 1976 Rusterholz and co-workers[7] reported the synthesis and pharmacological testing of several compounds as potential inhibitors of prolactin release, among them certain 2-amino-5,8-dimethoxytetralins.

Of particular interest is *N*-methyl-2-amino-5,8-dimethoxytetralin (**1**). Although compound **1** is ineffective as an



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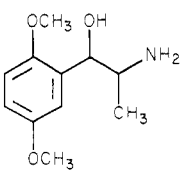

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inhibitor of prolactin release, it has the ability to inhibit several apomorphine-induced responses,[8] which suggests that it may interact with some dopamine receptor mediated responses. An interesting action of the 2-amino-5,8-dimethoxytetralins that Rusterholtz and co-workers reported is the ability of these derivatives to block apomorphine-induced emesis in dogs. Cardiovascular testing demonstrated that compound **1** also produces prolonged hypertension in dogs which is the result of postsynaptic α-receptor stimulation.[9] Inspection of the chemical structures shows that the pressor agent methoxamine (**2**) and compound **1** are structurally related. Other 2-amino-5,8-dimethoxytetralin derivatives also appear to interact with α receptors in the periphery[4] and in the CNS.[10]

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