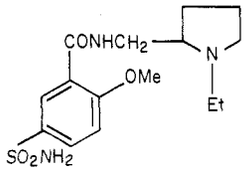
Anilides Related to Substituted Benzamides. Potential Antipsychotic Activity of *N*-(4-Amino-5-chloro-2-methoxyphenyl)-1-(phenylmethyl)-4-piperidinecarboxamide[1]

Frank E. Blaney, Michael S. G. Clark, Derek V. Gardner, Michael S. Hadley,* David Middleton, and Trevor J. White

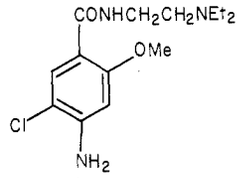
Beecham Pharmaceuticals Research Division, Medicinal Research Centre, The Pinnacles, Harlow, Essex, CM19 5AD, England.
Received December 17, 1982

The substituted benzamides are used clinically both as antipsychotics and as stimulants of gastric motility. The antipsychotic effects are considered to be a consequence of their central dopamine antagonist properties, but there is evidence that the gastric stimulatory effects may be mediated by other mechanisms. Clebopride (3) is a substituted benzamide that although marketed for its stimulatory effects on gastric motility, is also a potent central dopamine antagonist. The corresponding anilide, BRL 20596 (4a), where the amide bond has been reversed, has been synthesized and found to lack gastric stimulatory activity. However, the potent central dopamine antagonist activity is retained, suggesting that benzamides and anilides have similar affinities for central dopamine receptors. The implications of the conformations adopted by benzamides and anilides at such receptors are discussed. Evidence is also presented that there is a further lipophilic binding site on such receptors for which the *N*-benzyl group is an optimal fit.

The substituted benzamides form a class of drugs used clinically both as antipsychotics and as stimulants of gastric motility. The two most important compounds in these markets are sulpiride (1) and metoclopramide (2),



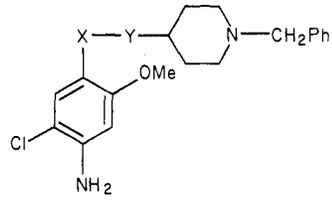
1



2

respectively. The biochemical mechanisms responsible for the observed clinical effects are not clearly understood. Sulpiride[2] is classed as an atypical neuroleptic and is thought to act by blocking a subpopulation (D-2) of dopamine receptors in mesolimbic brain areas. Metoclopramide is also a central dopamine antagonist and has been shown to have antipsychotic activity at high doses.[3] However, at the lower doses used clinically it has a stimulatory effect on gastric motility.[4] This effect could be a consequence of its ability to reverse the inhibitory effect of dopamine on the motility of the upper gastrointestinal tract.[5] However, it now seems more likely to be due to its ability to stimulate acetylcholine release from parasympathetic nerve terminals.[6] The exact mechanism of this action is currently being investigated.

Recently, clebopride (3) has been marketed for gut disorders of a psychosomatic origin.[7] However, it is also a potent central dopamine antagonist in aminal models, although no clinical antipsychotic activity has been reported. Since the antipsychotic and gastric effects of the substituted benzamides may be mediated by different neurotransmitters, it should be possible to make subtle alterations to the structure of clebopride and obtain a compound with a more selective biological profile.



3, X–Y = CONH
4a, X–Y = NHCO

The present work is concerned with the effects of reversal of the amide linkage of clebopride. This results not only in a change in the electronic distribution in the region of the amide group and within the aromatic ring but also in the probable preferred conformations of the molecule.

Chemistry. The parent anilide **4a** was initially prepared by path a (Scheme I). The substituted aniline **5** was coupled with *N*-benzyl-4-piperidinecarboxylic acid in the presence of dicyclohexylcarbodiimide to give the anilide **8a**, which was nitrated to give **11a**. Subsequent reduction of **11a** with stannous chloride gave the desired amino anilide **4a**. Since the isolation procedure in this step was tedious, other reducing agents were investigated. Either iron in acetic acid or hydrogenation over Raney nickel resulted in comparable yields and easier isolation procedures. In the latter case, no hydrogenolysis of the 5-chloro substituent was observed.

An extensive series of analogues (Table I) of **4a** was prepared where substituents (R′) were introduced into the phenyl ring of the *N*-benzyl group. The compounds **4b–d** prepared initially were isolated as hydrochlorides: however, since these crystallized with varying amounts of water, compounds prepared subsequently were isolated as free bases.

Alternative syntheses were investigated so that the R′ substituent could be more easily varied. Thus, the key intermediate **9**, prepared from **5** (path b, Scheme I) by reaction with pyridine-4-carbonyl chloride followed by catalytic hydrogenation of the intermediate pyridinecarboxamide **6**, could be alkylated to intermediate **8**. The alternative procedure (path d, Scheme I) of alkylation of **6** to the quaternary salt **7** followed by catalytic hydrogenation offered no advantage.

An even more attractive route (path c, Scheme I) used for the preparation of most analogues involved nitration of **9** to nitroanilide **10**, followed by alkylation to intermediate **11**.

The 4-nitro analogue **4f** was prepared (path e, Scheme I) by catalytic hydrogenation of **10**, followed by regiospecific alkylation of the intermediate **12**. The 4-hydroxy

(1) Presented in part at 185th National Meeting of the American Chemical Society, Seattle, Washington, March 1983; see "Abstracts of Papers"; American Chemical Society: Washington, DC, 1983; Abstr MEDI 7.
(2) Spano, P. F.; Trabucchi, M.; Corsini, G. U.; Gessa, G. L. "Sulpiride and Other Benzamides"; Italian Brain Research Foundation Press: Milan, 1979.
(3) Stanley, M.; Lautin, A.; Rotrosen, J.; Gershon, S.; Kleinberg, D. *Psychopharmacology* **1980**, *71*, 219.
(4) Pinder, R. M.; Brogden, R. N.; Sawyer, P. R.; Speight, T. M.; Avery, G. S. *Drugs* **1976**, *12*, 81.
(5) Valenzuela, J. E. *Gastroenterology* **1976**, *71*, 1019.
(6) Schulze-Delrieu, K. *Gastroenterology* **1979**, *77*, 768.
(7) Roberts, D. J. *Curr. Ther. Res.* **1982**, S1.

0022-2623/83/1826-1747$01.50/0

Scheme I

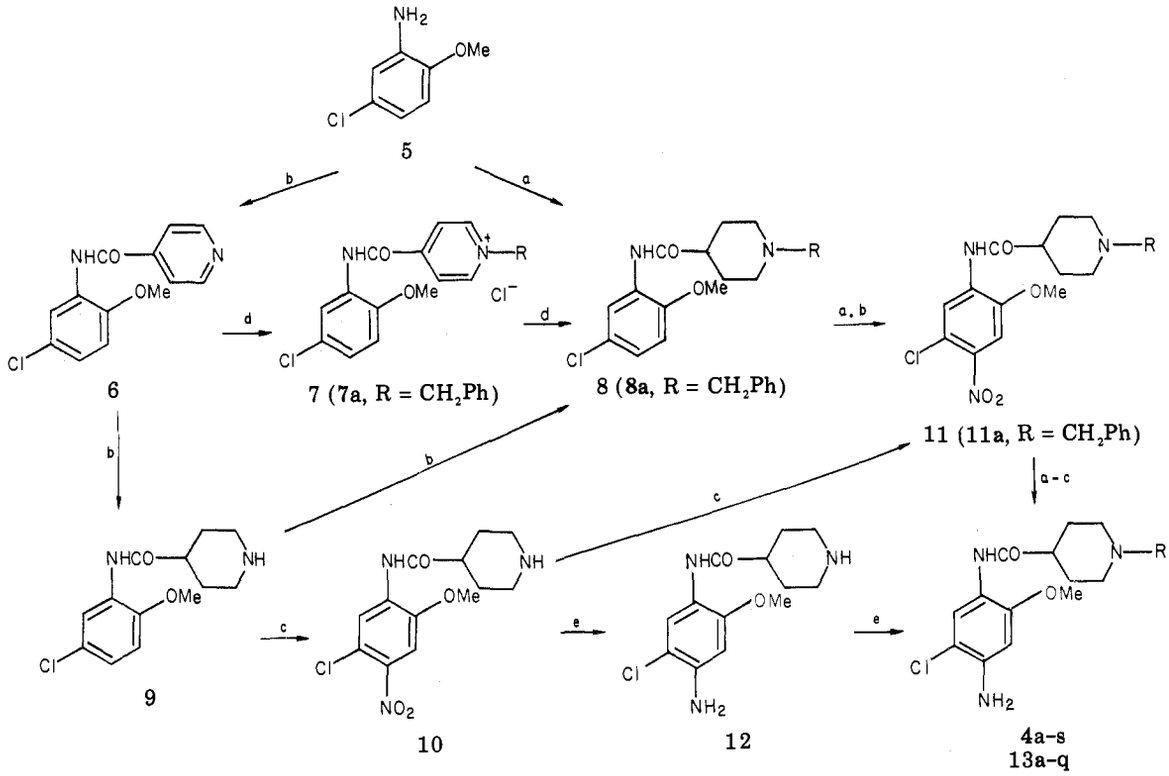
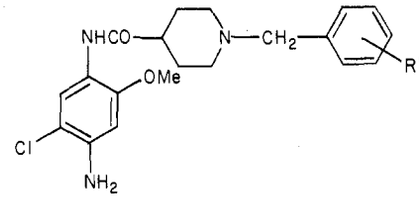


Table I. Substitution in the *N*-Benzyl Group. Physical Properties and Anti-apomorphine Climbing Activities



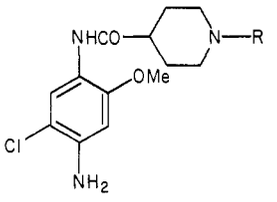
no.	R'	method[a]	yield,[b] %	mp, °C	formula	anal.	anti-apomorphine climbing: ED_{50}, mg/kg po (95% CL)
4a	H	A	26	105-106	$C_{20}H_{24}ClH_3O_2$	C, H, N, Cl	0.5 (0.37-0.83)
4b[c]	4-Cl	B	21	210 dec	$C_{20}H_{25}Cl_4N_3O_2$	H, N; C, Cl[d]	1.2 (0.89-1.88)
4c[e]	4-OMe	C	24	202-205 dec	$C_{21}H_{30}Cl_3N_3O_4$	C, H, N; Cl[f]	0.9 (0.54-1.48)
4d[g]	4-Me	C	15	210 dec	$C_{21}H_{29}Cl_2N_3O_3$	C, H, N; Cl[h]	50% at 0.5[i]
4e	4-F	C	14	112-115	$C_{20}H_{23}ClFN_3O_2$	C, H, N, Cl	0.6 (0.53-0.67)
4f	4-NO_2	D	7	163-165	$C_{20}H_{23}ClN_4O_4$	C, H, N, Cl	>4
4g	4-OCH_2Ph	G	10	143-145	$C_{27}H_{30}ClN_3O_3$	C, H, N, Cl	>4
4h	4-OH	E	9	174-176	$C_{20}H_{24}ClN_3O_3$	C, H, N, Cl	>8
4i	4-OEt	G	12	88-90	$C_{22}H_{28}ClN_3O_3$	C, H, N, Cl	6.3 (3.7-9.6)
4j	3,4-OCH_2O	G	25	127-129	$C_{21}H_{24}ClN_3O_4$	C, H, N, Cl	4.3 (1.5-11.9)
4k	3-Cl	G	18	82-86	$C_{20}H_{23}Cl_2N_3O_2$	C, H, N, Cl	>4
4l	3-F	F	26	106-109	$C_{20}H_{23}ClFN_3O_2$	C, H, N, Cl	58% at 2.0[i]
4m	3-Me	G	15	87-91	$C_{21}H_{26}ClN_3O_2$	C, H, N, Cl	2.4 (1.3-3.6)
4n	3-CN	F	15	76-80	$C_{21}H_{23}ClN_4O_2$	H, Cl; C, N[j]	>4
4o	3-OMe	G	11	68-71	$C_{21}H_{26}ClN_3O_3$	C, H, N, Cl	>4
4p	3,4-Me_2	G	19	128-129	$C_{22}H_{28}ClN_3O_2$	C, H, N, Cl	>8
4q	2-F	F	22	113-115	$C_{20}H_{23}ClFN_3O_2$	C, H, N, Cl	>4
4r	2-Cl	G	20	138-141	$C_{20}H_{23}Cl_2N_3O_2$	C, H, N, Cl	>4
4s	2-Me	G	22	103-105	$C_{21}H_{26}ClN_3O_2$	C, H, N, Cl	77% at 2.0[i]

[a] See Experimental Section. [b] Overall yield from 5-chloro-2-methoxybenzenamine. [c] Dihydrochloride. [d] C: calcd, 49.89; found, 49.11. Cl: calcd, 29.49; found, 27.48. [e] Dihydrochloride monohydrate. [f] Cl: calcd, 21.51; found, 20.59. [g] Hydrochloride monohydrate. [h] Cl: calcd, 16.04; found, 17.72. [i] Percent antagonism at dose quoted. [j] C: calcd, 63.21; found, 62.68. N: calcd, 14.05; found, 13.56.

analogue **4h** was prepared by alkylation of **10** with 4-(benzyloxy)benzyl chloride, followed by simultaneous reduction of the nitro group and hydrogenolysis of the benzyloxy group by hydrogenation over 10% palladium on charcoal. Selective reduction using Raney nickel as a catalyst gave the 4-benzyloxy analogue **4g**.

A further series of analogues (Table II) was prepared (path c, Scheme I) where the benzyl group of **4a** was replaced by other hydrocarbon groups. The cyclopentyl analogue **13m** was prepared by reductive alkylation of **10**

Table II. Replacement of the *N*-Benzyl Group. Physical Properties and Anti-apomorphine Climbing Activities



no.	R	method[a]	yield,[b] %	mp, °C	formula	anal.	anti-apomorphine climbing:[a] ED_{50}, mg/kg po (95% CL)
13a	CH_2-c-C_6H_{11}	C	24	146-148	$C_{20}H_{30}ClN_3O_2$	C, H, N, Cl	2.9 (0.9-9.0)
13b	$CH_2CH(CH_2CH_3)_2$	F	14	61-63	$C_{19}H_{30}ClN_3O_2$	C, H, N, Cl	>10
13c	CH_2-c-C_5H_9	G	7	165-167	$C_{19}H_{28}ClN_3O_2$	C, H, N, Cl	>10
13d	CH_2-c-C_4H_7	G	7	169-171	$C_{18}H_{26}ClN_3O_2$	C, H, N, Cl	>10
13e	CH_2-c-C_3H_5	F	10	147-149	$C_{17}H_{24}ClN_3O_2$	C, H, N, Cl	>10
13f	CH_2-c-C_7H_{13}	G	7	122-124	$C_{21}H_{32}ClN_3O_2$	H, N, Cl; C[c]	>10
13g	C_2H_5	F	20	157-159	$C_{15}H_{22}ClN_3O_2$	C, H, N, Cl	>10
13h	*n*-C_3H_7	F	15	181-183	$C_{16}H_{24}ClN_3O_2$	C, H, N, Cl	>10
13i	*n*-C_4H_9	F	15	136-139	$C_{17}H_{26}ClN_3O_2$	C, H, N, Cl	>10
13j	*n*-C_5H_{11}	C	14	133-135	$C_{18}H_{28}ClN_3O_2$	C, H, N, Cl	>10
13k	*n*-C_6H_{13}	C	12	128-129	$C_{19}H_{30}ClN_3O_2$	C, H, N, Cl	>10
13l	*n*-C_7H_{15}	C	7	127-128	$C_{20}H_{32}ClN_3O_2$	C, H, N, Cl	>10
13m	c-C_5H_9	H	5	210-213	$C_{18}H_{26}ClN_3O_2$	C, H, N, Cl	>10
13n[d]	CH_2CH_2Ph	C	6	210-212	$C_{21}H_{30}Cl_3N_3O_3$	C, H, N, Cl	>10
13o	CH_2CH=$CHPh$	C	9	146-149	$C_{22}H_{26}ClN_3O_2$	C, H, N, Cl	>10
13p	2-thenyl	C	12	100-102	$C_{18}H_{22}ClN_3O_2S$	C, H, N, Cl, S	77% at 10[e]
13q	3-thenyl	C	8	118-120	$C_{18}H_{22}ClN_3O_2S$	C, H, N, Cl, S	3.4 (1.1-9.8)

[a] See Experimental Section. [b] Overall yield from 5-chloro-2-methoxybenzenamine. [c] C: calcd, 64.00; found, 63.32. [d] Dihydrochloride monohydrate. [e] Percent antagonism at dose quoted.

Table III. Comparative Activities of BRL 20596 and Clebopride

test	dose,[a] mg/kg	
	4a (BRL20596)	3 (clebopride)
antagonism of apomorphine-induced climbing	0.5 po (0.37-0.83)	0.7 po (0.38-1.22)
antagonism of apomorphine-induced delay in gastric emptying	50 sc (inactive)	0.11 sc (0.08-0.13)
increase in intragastric pressure	5-50 sc (inactive)	1 sc (lowest active dose)
antagonism of amphetamine-induced stereotyped behavior	0.25 ip (0.16-0.40)	not tested
elevation of prolactin levels	0.5 sc (0.22-1.14)	0.14 sc (0.04-0.50)
elevation of HVA levels in limbic system	0.5 sc (0.33-0.77)	0.2 sc (0.12-0.37)
elevation of HVA levels in striatum	0.4 sc (0.26-0.62)	0.1 sc (0.07-0.14)

[a] Doses are ED_{50} values with 95% fiducial limits in parentheses, except where indicated.

with cyclopentanone in the presence of sodium cyanoborohydride.

Results and Discussion

Potential antipsychotic activity of these compounds was assessed by their ability to antagonize apomorphine-induced climbing in mice. This antagonism is considered to be a consequence of dopamine receptor blockade in the limbic system.[8] The parent anilide **4a** was virtually equipotent with clebopride in this test (Table III), suggesting that both compounds have similar affinities for central dopamine receptors.

Within the substituted benzamides, a methoxy substituent in the benzene ring ortho to the amide group is essential for good central dopamine antagonist activity. This methoxy substituent may stabilize a particular planar conformation (Figure 1, *a*) of the molecule by intramolecular hydrogen bonding.[9,10] If substituted benzamides

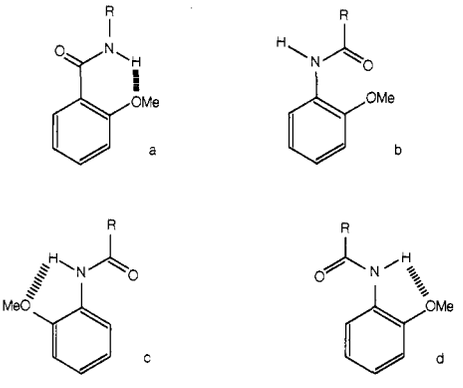


Figure 1. Possible conformations of substituted benzamides (*a*) and anilides (*b–d*) at central dopamine receptors. The side chains incorporating the tertiary nitrogen atoms are represented by R.

adopt conformation *a* at central dopamine receptors, it is important to consider whether the corresponding anilides can adopt a conformation that results in good molecular overlap with conformation *a*. Three possible planar conformations (*b–d*) of the anilides are shown in Figure 1. Of these, conformation *b* gives the best molecular overlap for the whole molecule, including the side chain with conformation *a*. However, conformation *b* can be dismissed

(8) Costall, B.; Naylor, R. J. *Life Sci.* 1981, *28*, 215.
(9) Hadley, M. S. In "Chemical Regulation of Biological Mechanisms"; Creighton, A. M.; Turner, S.; Eds.; Royal Society of Chemistry: London, 1982; p 140.
(10) Pannatier, A.; Anker, L.; Testa, B.; Carrupt, P. A. *J. Pharm. Pharmacol.* 1981, *33*, 145.

as a receptor binding conformation, since molecular orbital calculations (MNDO) show it to be of high energy, due to nonbonded interactions between the oxygen atoms of the methoxy and amide groups. Conformation *c* results in good molecular overlap with conformation *a* apart from the location of the methoxy groups. However, the polarizations of π electrons in the region of the amide groups of *a* and *c* are in opposite directions. The polarization of π electrons in conformation *d* of the anilides is closer to that in conformation *a* of the benzamides, but the molecular overlap is poor.

Thus, if the substituted benzamides do indeed adopt conformation *a* at central dopamine receptors, the substituted anilides could be considered to be binding in either conformation *c* or *d*. If it is the former conformation, the direction of polarization of π electrons in the region of the amide groups of benzamides and annilides appears to be unimportant for receptor binding. If it is the latter conformation, the aromatic rings of benzamides and anilides appear to bind to different but adjacent parts of the receptor surface. A similar explanation has been proposed to explain the equal potencies of butaclamol and isobutaclamol as central dopamine antagonists.[11]

To assess the importance of hydrogen bonding in determining the conformations of benzamides and anilides, we investigated clebopride and **4a** by infrared spectroscopy. The shifts in the frequencies of the amide NH and carbonyl I bands between Nujol and a 1%, w/v, solution in chloroform were measured. For clebopride, these shifts were +32 and −7 cm^{-1}, respectively. However, for **4a**, the shifts were much greater, +170 and +26 cm^{-1}, respectively. These results suggest that intramolecular hydrogen bonding in clebopride is strong and, consequently, is relatively unaffected by its environment. Conversely, intramolecular hydrogen bonding in **4a** is weaker, and thus **4a** appears to be free to exist in different molecular forms. These differences may be due to the greater separation of H and O atoms in **4a** (ca 2.4 Å) compared to clebopride (ca 1.8 Å).

Gastric stimulatory activities of **4a** and clebopride were assessed by their ability to antagonize the delay in gastric emptying in rats induced by apomorphine and by their ability to increase resting intragastric pressure in rats. The former test will detect compounds acting on the gut by dopaminergic mechanisms, and the latter test will detect compounds acting peripherally by other mechanisms. In both test systems, **4a** was inactive up to 50 mg/kg sc, in contrast to clebopride, which had an ED_{50} in the former test of 0.11 mg/kg sc and was active at a dose of 1 mg/kg sc in the latter test. It therefore appears that reversal of the amide bond has resulted in a compound that is unable to bind to receptors mediating gut stimulatory activity. It is unclear whether this is due to the electronic or conformational changes caused by amide reversal.

Since gastric activity was lost on amide reversal, analogues of **4a** were only screened as potential antipsychotics, their ability to antagonize apomorphine-induced climbing being determined. Analogues incorporating substituents with a wide range of electronic and lipophilic characteristics at the ortho, meta, or para position of the phenyl ring of the *N*-benzyl group of **4a** were, in general, less potent than **4a** (Table I). Only the 4-Me (**4d**) and 4-F (**4e**) analogues had potencies comparable to that of **4a**.

Potency (Table II) was reduced by replacement of the *N*-benzyl group of **4a** by *N*-cyclohexylmethyl (**13a**). However, other *N*-cycloalkylmethyl analogues with either larger (**13f**) or smaller (**13c–e**) cycloalkyl rings were inactive at the doses tested. The analogue **13b** with a cleaved *N*-cycloalkyl group, simple *N*-alkyl analogues (**13g–l**), the N-cyclopentyl analogue **13m**, the *N*-phenethyl analogue **13n**, and the vinylogue **13o** were all inactive. Reduced activity was found for the *N*-thenyl analogues (**13p,q**). These results suggest that there is a further lipophilic binding site on central dopamine receptors to accommodate a substituent on the tertiary nitrogen atom. Other workers,[11] studying structurally different dopamine antagonists, have drawn similar conclusions. The present work suggests that this binding site has a defined size for which the *N*-benzyl group is an optimal fit, since the introduction of substituents, irrespective of their nature, into the phenyl ring of the *N*-benzyl group results in reduced potency. The activity of the *N*-cyclohexylmethyl analogue shows that a delocalized π-electron system is not essential, and the lack of activity for other *N*-cycloalkylmethyl analogues supports the hypothesis that size may indeed be the key factor.

Compound **4a** (BRL 20596) was selected for further evaluation as a potential antipsychotic, and the results of these studies will be reported in detail elsewhere. Some of these data and a comparison with clebopride are shown in Table III. In general, **4a** is active in the dose range of 0.2–0.5 mg/kg, slightly less potent than clebopride. Antagonism of amphetamine-induced stereotyped behavior,[12] elevation of prolactin levels, and elevation of the levels of the dopamine metabolite, homovanillic acid (HVA), are all measures of dopamine antagonist activity. Compound **4a** also inhibits conditioned avoidance behavior at 0.25 mg/kg sc, a test considered to be predictive of antipsychotic activity.[13] It does induce catalepsy but only at higher doses, ED_{50} = 4.8 (3.1–7.7, 95% CL) mg/kg ip. Catalepsy in rodents is considered to be predictive of extrapyramidal effects in man.[14] General depressant effects, as measured by the potentiation of the effects of hexobarbitone, ED_{50} > 20 mg/kg po, or by the ability to supress spontaneous locomotor activity, ED_{50} = 7.5 (3.9–14.2, 95% CL) mg/kg po, are weak, suggesting low sedative activity at antipsychotic dose levels. It is relatively weak at displacing [^{3}H]spiroperidol from striatal sites in vitro, IC_{50} = 5×10^{-7} M.

Experimental Section

Chemistry. For most new compounds, the melting point, overall yield, method of preparation, and analyses carried out are summarized in Tables *I* and *II*; details of other new compounds are given later in this section. Each preparative method is illustrated by a representative example. The spectroscopic properties of all new compounds were considered to be consistent with their proposed structure. Melting points are uncorrected. The elemental analyses indicated were within 0.4% of the theoretical values. Light petroleum refers to the fraction boiling between 60 and 80 °C. Evaporation of solvents was conducted under reduced pressure. For column chromatography, the silica gel used was Merck Kieselgel 60, and the alumina used was basic grade II.

***N*-(5-Chloro-2-methoxyphenyl)-4-pyridinecarboxamide (6).** Thionyl chloride (14.2 mL, 0.20 mol) was added to a stirred solution of 4-pyridinecarboxylic acid (22.9 g, 0.19 mol) in HMPA (150 mL) at 5 °C. After 30 min, 5-chloro-2-methoxybenzenamine (29.4 g, 0.19 mol) in HMPA (50 mL) was added, and the mixture

(11) Humber, L. G.; Bruderlein, F. T.; Philipp, A. H.; Gotz, M.; Voith, K. *J. Med. Chem.* **1979**, *22*, 761.

(12) Niemegeers, C. J. E.; Janssen, P. A. J. *Life Sci.* **1979**, *24*, 2201.

(13) Niemegeers, C. J. E.; Verbruggen, F. J.; Janssen P. A. J. *Psychopharmacologia* **1969**, *16*, 161.

(14) Carlsson, A. In "Psychopharmacology: A Generation of Progress"; Lipton, M. A., Dimascio, A.; Killan, K. F., Eds.; Raven Press: New York, 1978; p 1071.

was stirred overnight at ambient temperature and then poured into H_2O and basified (NaOH). The precipitate was filtered, washed (H_2O), dried, and recrystallized from EtOAc–light petroleum to give **6** (38.5 g, 79%), mp 147–149 °C. Anal. ($C_{13}H_{11}ClN_2O_2$) C, H, N, Cl.

***N*-(5-Chloro-2-methoxyphenyl)-1-(phenylmethyl)-4-piperidinecarboxamide (8a). Via Path a of Scheme I.** A mixture of 5-chloro-2-methoxybenzenamine (10 g, 0.064 mol), 1-(phenylmethyl)-4-piperidinecarboxylic acid (13.9 g, 0.064 mol), and dicyclohexylcarbodiimide (13.15 g, 0.068 mol) in CH_2Cl_2 (250 mL) and THF (250 mL) was stirred for 24 h. It was then filtered, the filtrate was evaporated, and the residue was extracted with Et_2O. Evaporation of Et_2O gave an oil, which was chromatographed on silica gel. Elution with Et_2O containing progressively increasing amounts of EtOAc gave a crude product, which was recrystallized from light petroleum to give **8a** (12 g, 53%), mp 86–87 °C. Anal. ($C_{20}H_{24}ClN_2O_2$) C, H, N, Cl.

Via Path d of Scheme I. Compound **6** (25 g, 0.095 mol) and $PhCH_2Cl$ (12 mL, 0.10 mol) in DMF (250 mL) were heated at 110 °C for 4 h. Solvent was evaporated, and the residue was boiled with EtOAc. Filtration gave crude 4-[[(5-chloro-2-methoxyphenyl)amino]carbonyl]-1-(phenylmethyl)pyridinium chloride (**7a**; 30 g). Compound **7a** (26.8 g) was hydrogenated over PtO_2 (0.8 g) at 250 psi in EtOH (50 mL) at ambient temperature for 6 h. The solution was filtered, the filtrate was evaporated, and the residue was extracted with EtOAc and aqueous Na_2CO_3. The EtOAc extract was dried (Na_2SO_4) and evaporated to give an oil, which was chromatographed on silica gel. Elution with light petroleum containing progressively increasing amounts of EtOAc gave **8a** (14.2 g, 46%).

***N*-(5-Chloro-2-methoxyphenyl)-4-piperidinecarboxamide (9).** The HCl salt (10 g, 0.038 mol) of **6** was hydrogenated in EtOH at 300 psi over PtO_2 (0.25 g) at 70 °C for 6 h. The solution was filtered, the filtrate was evaporated, and the residue was partitioned between EtOAc and aqueous Na_2CO_3. The EtOAc extract was separated, dried (Na_2SO_4), and evaporated. The residue was recrystallized from EtOAc to give **9** (7.4 g, 72%), mp 124–126 °C. Anal. ($C_{13}H_{17}ClN_2O_2$) C, H, N, Cl.

***N*-(5-Chloro-2-methoxy-4-nitrophenyl)-4-piperidinecarboxamide (10).** Fuming HNO_3 (2.1 mL) was added dropwise, at 25–30 °C, to **9** (10.4 g, 0.039 mol) in HOAc (100 mL) and H_2SO_4 (5 mL). After 2 h, the solution was poured onto ice (500 mL), basified (NaOH), and extracted with EtOAc. The EtOAc extract was dried (Na_2SO_4) and evaporated. The residue was recrystallized from EtOAc–light petroleum to give **10** (9.9 g, 82%), mp 167–170 °C. Anal. ($C_{13}H_{16}ClN_3O_4$) C, H, N, Cl.

***N*-(5-Chloro-2-methoxy-4-nitrophenyl)-1-(phenylmethyl)-4-piperidinecarboxamide (11a).** Fuming HNO_3 (5 mL) was added dropwise to a stirred solution of **8a** (4 g, 0.011 mol) in HOAc (20 mL) at 30–35 °C. After 4 h, the solution was poured onto ice, basified (NaOH), and extracted with EtOAc. The EtOAc extract was dried (Na_2SO_4) and evaporated to give a residue, which was recrystallized from light petroleum to give **11a** (3.5 g, 78%), mp 122–123 °C. Anal. ($C_{20}H_{22}ClN_3O_4$) C, H, N, Cl. Et_2O–HCl gave the hydrochloride, mp 194–195 °C (recrystallized from EtOH–Et_2O).

Method A. *N*-(4-Amino-5-chloro-2-methoxyphenyl)-1-(phenylmethyl)-4-piperidinecarboxamide (4a). $SnCl_2$ (21.7 g, 0.11 mol) in concentrated HCl (50 mL) was added to **11a** (15.4 g, 0.038 mol) in HOAc (150 mL) at ambient temperature, and the solution stirred overnight. It was poured onto ice, basified (NaOH), and extracted with EtOAc. The EtOAc extract was filtered through alumina, and the filtrate was evaporated. The residue was recrystallized from Et_2O–light petroleum to give **4a** (9 g, 63%), mp 105–106 °C. Et_2O–HCl gave the dihydrochloride, mp 180 °C dec (recrystallized from *i*-PrOH).

Method B. *N*-(4-Amino-5-chloro-2-methoxyphenyl)-1-[(4-chlorophenyl)methyl]-4-piperidinecarboxamide Dihydrochloride (4b). Compound **9** (5 g, 0.019 mol), 1-chloro-4-(chloromethyl)benzene (3.6 g, 0.022 mol), and K_2CO_3 (3.1 g, 0.022 mol) in DMF (150 mL) were stirred at ambient temperature for 17 h. Solvent was evaporated, and the residue was partitioned between $CHCl_3$ and H_2O. The $CHCl_3$ extract was dried (K_2CO_3) and evaporated, and the residue was converted with Et_2O–HCl to *N*-(5-chloro-2-methoxyphenyl)-1-[(4-chlorophenyl)methyl]-4-piperidinecarboxamide hydrochloride (7.4 g, 92%), mp 239–243 °C. Subsequent nitration and reduction to **4b** were carried out as described for **11a** and **4a**.

Method C. *N*-(4-Amino-5-chloro-2-methoxyphenyl)-1-[(4-methoxyphenyl)methyl]-4-piperidinecarboxamide (4c). Compound **10** (3.14 g, 0.01 mol), 1-(chloromethyl)-4-methoxybenzene (1.57 g, 0.01 mol), and K_2CO_3 (1.4 g, 0.01 mol) in DMF (50 mL) were stirred for 16 h. Solvent was evaporated, and the residue was extracted with EtOAc (200 mL) and aqueous NaOH (10%, 200 mL). The EtOAc extract was passed through alumina and evaporated. The residue was recrystallized from EtOAc–light petroleum to give *N*-(5-chloro-2-methoxy-4-nitrophenyl)-1-[(4-methoxyphenyl)methyl]-4-piperidinecarboxamide (2.9 g, 68%), mp 139–142 °C. Subsequent reduction to **4c** was carried out as described for **4a**.

Method D. *N*-(4-Amino-5-chloro-2-methoxyphenyl)-1-[(4-nitrophenyl)methyl]-4-piperidinecarboxamide (4f). Compound **10** (2 g, 0.0064 mol) in EtOH (100 mL) and H_2O (5 mL) was adjusted to pH 3 with 5 N HCl and hydrogenated over Raney Ni at atmospheric pressure overnight. The mixture was filtered, the filtrate was evaporated, and the residue was partitioned between EtOAc and excess 5 N NaOH. The EtOAc extract was dried (K_2CO_3) and evaporated. The residue was recrystallized from EtOAc–light petroleum to give *N*-(4-amino-5-chloro-2-methoxyphenyl)-4-piperidinecarboxamide (**12**: 0.55 g, 31%), mp 145 °C. 1-(Bromomethyl)-4-nitrobenzene (0.92 g, 0.0043 mol) in Me_2CO (10 mL) was added dropwise to a stirred mixture of **12** (1.45 g, 0.0051 mol) and K_2CO_3 (0.85 g, 0.0062 mol) in Me_2CO (100 mL). The mixture was stirred overnight; then solvent was evaporated, and the residue was partitioned between EtOAc and H_2O. The EtOAc extract was separated, dried (Na_2SO_4), and evaporated to give an oil, which was chromatographed on alumina. Elution with light petroleum containing progressively increasing amounts of EtOAc gave **4f** (1.1 g, 51%).

Method E. *N*-(4-Amino-5-chloro-2-methoxyphenyl)-1-[(4-hydroxyphenyl)methyl]-4-piperidinecarboxamide (4h). *N*-(5-Chloro-2-methoxy-4-nitrophenyl)-1-[[4-(phenylmethoxy)-phenyl]methyl]-4-piperidinecarboxamide [4 g, 0.0079 mol, prepared in 54% yield from **10** by alkylation with 1-(chloromethyl)-4-(phenylmethoxy)benzene] was hydrogenated at ambient pressure and temperature in EtOH over 10% Pd/C (0.5 g). Catalyst was removed by filtration, solvent was evaporated, and the residue was chromatographed on silica gel. Elution with light petroleum containing progressively increasing amounts of EtOAc gave **4h** (1.1 g, 37%).

Method F. *N*-(4-Amino-5-chloro-2-methoxyphenyl)-1-[(3-fluorophenyl)methyl]-4-piperidinecarboxamide (4l). A mixture of *N*-(5-chloro-2-methoxy-4-nitrophenyl)-1-[(3-fluorophenyl)methyl]-4-piperidinecarboxamide [2.1 g, 0.005 mol, prepared in 72% yield from **10** by alkylation with 1-(chloromethyl)-3-fluorobenzene] and Fe powder (1 g, 0.017 mol) in HOAc (2.1 g, 0.035 mol) and EtOH (12 mL) was heated at reflux overnight under N_2. It was poured into H_2O, basified (NaOH), and extracted with EtOAc. The EtOAc extract was dried (K_2CO_3) and evaporated to give an oil, which was chromatographed on alumina. Elution with progressively light petroleum containing progressively increasing amounts of EtOAc gave **4l** (1.5 g, 77%).

Method G. *N*-(4-Amino-5-chloro-2-methoxyphenyl)-1-(cyclobutylmethyl)-4-piperidinecarboxamide (13d). *N*-(5-Chloro-2-methoxy-4-nitrophenyl)-1-(cyclobutylmethyl)-4-piperidinecarboxamide (8.5 g, 0.023 mol, prepared in 41% yield from **10** by alkylation with cyclobutylmethyl 4-methylbenzenesulfonate) in EtOH (100 mL) was hydrogenated over Raney Ni for 4 h at ambient temperature and pressure. Catalyst was removed by filtration, the filtrate was evaporated, and the residue was chromatographed on alumina. Elution with light petroleum containing progressively increasing amounts of EtOAc gave **13d** (2.9 g, 37%).

Method H. *N*-(4-Amino-5-chloro-2-methoxyphenyl)-1-cyclopentyl-4-piperidinecarboxamide (13m). A stirred solution of cyclopentanone (2.56 g, 0.03 mol), **10** (4 g, 0.0127 mol), and $NaCNBH_3$ (1.6 g, 0.025 mol) in MeOH (50 mL) and THF (20 mL) was adjusted to pH 1 with EtOH/HCl. After 10 min, the pH was adjusted to 5 with Et_3N and maintained at this pH overnight. Solvents were evaporated, and the residue was partitioned between EtOAc and 5 N HCl. The acid extract was washed with EtOAc, basified (NaOH), and extracted with EtOAc. This extract was

dried (K_2CO_3) and evaporated to give crude *N*-(5-chloro-2-methoxy-4-nitrophenyl)-1-cyclopentyl-4-piperidinecarboxamide (24 g), which was reduced to **13m** as described for **41**.

Pharmacology. Antagonism of apomorphine-induced climbing behavior was assessed by a modification of the method of Protais et al.[15] Usually, four groups of five male CD-1 mice (20–25 g) were treated orally with either a graded dose of test compound or vehicle, 30 min before administration of submaximal dose of apomorphine (1 mg/kg sc). Animals were scored 10, 20, and 30 min later for their ability to antagonize the climbing behavior.

For the antagonism of amphetamine-induced stereotyped behavior, four groups of five male CD rats (200–250 g) were treated intraperitoneally with either a graded dose of test compound or vehicle, 10 min before administration of dexamphetamine sulfate (10 mg/kg sc). Stereotypy was assessed after 1 h by a modification of the method of Costall and Naylor.[16]

A procedure modified from that of Sidman[17] was used to study conditioned avoidance behavior in a shuttle box with groups of four male Hooded Lister rats. Sessions were run 45 min before subcutaneous administration of test compound or vehicle and at various times afterwards. The same animals were used on several occasions at different dose levels and to provide controls. The Student's *t* test was used for statistical analysis.

Catalepsy was assessed in groups of five male CD rats (200–400 g) where graded doses of test drug or vehicle were given intraperitoneally, and 1 h later, the number of paws that would remain on a 4.2-cm bung for more than 15 s was counted. The ability to potentiate the 30% loss of righting reflex caused by a standard intravenous dose of hexobarbitone sodium was assessed in groups of 10 male CD-1 mice (25-35 g). A graded dose of test compound or vehicle was administered orally 1 h before challenge with hexobarbitone, and a "plus" (+) was given if the animal righted itself in 20 s, and a "minus" (−) score was given if it failed. The dose of test compound to double the number of mice reaching the 20-s criterion was determined.

Spontaneous locomotor activity in groups of three male CD-1 mice was monitored for 2 h after an oral dose using 4 Animex meters (LKB Farad) in a Latin Square design with graded doses and vehicle controls in which each dose level was tested 4 times.

Prolactin and HVA levels were estimated in the same groups of five male Hooded Lister rats (175–225 g) by the methods of Niswender et al.[18] and Earley and Leonard,[19] respectively. The methods of the latter group and of Westerink and Korf[20] were used to develop the fluorophore. Drugs and vehicle controls were given subcutaneously 1 h before decapitation and assay.

Displacement of [^{3}H]spiroperidol (0.5 nM) from striatal tissue of male Hooded Lister rats were estimated by a method based on that of Leysen et al.[21] IC_{50} values were obtained graphically.

Activity on gastric motility and emptying was determined in male Wistar rats (400–500 g) in which chronic fistulas had previously been established.[22] The rats were starved overnight. After the stomachs were lavaged, the animals were placed in restraining cages for the duration of the experiments.

Intragastric pressure changes were recorded from a fluid-filled catheter placed in the fistula and connected to a recorder. Animals showing low activity were selected, and for each, a comparison was made of the mean amplitude of pressure waves for four 10-min periods before and after subcutaneous administration of the compound. With groups of eight to ten animals, the lowest dose of compound that showed a statistical increase ($p < 0.05$, Student's *t* test) in a greater number of rats than is encountered in a control (vehicle dosed) group was ascertained.

Gastric emptying was assessed in four groups of six to eight rats by determining the percent recovery of the volume of a standard liquid test meal (5 mL of Tris buffer, pH 9, containing 0.1%, w/v, Phenol red) remaining in the stomach 10 min after instillation through the fistula. Delay in gastric emptying was induced by apomorphine hydrochloride (5 mg/kg sc) given 15 min prior to subcutaneous administration of graded doses of test compound (three groups) or vehicle, and percent recoveries of the test meal were determined after 15–25 and 45–55 min.

ED_{50} values and 95% confidence limits were calculated by the method of Litchfield and Wilcoxon[23] for apomorphine climbing, amphetamine stereotypy, catalepsy, spontaneous locomotor activity, and gastric emptying and by the method of Goldstein[24] for the biochemical experiments.

Acknowledgment. The authors thank W. Campbell, A. M. Johnson, B. McRitchie, P. L. Needham, and D. H. Turner for the biological testing, and I. R. Lynch for the infrared study.

Registry No. **4a**, 69082-47-9; **4a**·2HCl, 69082-48-0; **4b**, 69082-51-5; **4b**·2HCl, 69082-52-6; **4c**, 86956-12-9; **4c**·2HCl, 86956-13-0; **4d**, 86956-14-1; **4d**·HCl, 86956-15-2; **4e**, 86956-16-3; **4f**, 86956-17-4; **4g**, 86956-18-5; **4h**, 86956-19-6; **4i**, 86956-20-9; **4j**, 86968-55-0; **4k**, 86956-21-0; **4l**, 86956-22-1; **4m**, 86956-23-2; **4n**, 86956-24-3; **4o**, 86956-25-4; **4p**, 86956-26-5; **4q**, 86956-27-6; **4r**, 86956-28-7; **4s**, 86956-29-8; **5**, 95-03-4; **6**, 69082-72-0; **6**·HCl, 69082-74-2; **7a**, 69082-71-9; **8a**, 69082-40-2; **9**, 69082-73-1; **10**, 69082-75-3; **11a**, 69082-42-4; **11a**·HCl, 69082-43-5; **12**, 86956-30-1; **13a**, 86956-31-2; **13b**, 86956-32-3; **13c**, 86956-33-4; **13d**, 86956-34-5; **13e**, 86956-35-6; **13f**, 86956-36-7; **13g**, 86956-37-8; **13h**, 86956-38-9; **13i**, 86956-39-0; **13j**, 86956-40-3; **13k**, 86956-41-4; **13l**, 86956-42-5; **13m**, 86956-43-6; **13n**, 69082-49-1; **13n**·2HCl, 69082-50-4; **13o**, 86956-44-7; **13p**, 86956-45-8; **13q**, 86956-46-9; $PhCH_2Cl$, 100-44-7; 4-pyridinecarboxylic acid, 55-22-1; 1-(phenylmethyl)-4-piperidinecarboxylic acid, 10315-07-8; 1-chloro-4-(chloromethyl)benzene, 104-83-6; *N*-(5-chloro-2-methoxyphenyl)-1-[(4-chlorophenyl)methyl]-4-piperidinecarboxamide hydrochloride, 69082-62-8; 1-(chloromethyl)-4-methoxybenzene, 824-94-2; *N*-(5-chloro-2-methoxy-4-nitrophenyl)-1-[(4-methoxyphenyl)-methyl]-4-piperidinecarboxamide, 69082-63-9; 1-(bromomethyl)-4-nitrobenzene, 100-11-8; *N*-(5-chloro-2-methoxy-4-nitrophenyl)-1-[[4-(phenylmethoxy)phenyl]methyl]-4-piperidinecarboxamide, 86956-47-0; 1-(chloromethyl)-4-(phenylmethoxy)benzene, 836-42-0; *N*-(5-chloro-2-methoxy-4-nitrophenyl)-1-[(3-fluorophenyl)methyl]-4-piperidinecarboxamide, 86956-48-1; 1-(chloromethyl)-3-fluorobenzene, 456-42-8; *N*-(5-chloro-2-methoxy-4-nitrophenyl)-1-(cyclobutylmethyl)-4-piperidinecarboxamide, 86956-49-2; cyclobutylmethyl 4-methylbenzenesulfonate, 13295-53-9; cyclopentanone, 120-92-3; *N*-(5-chloro-2-methoxy-4-nitrophenyl)-1-cyclopentyl-4-piperidinecarboxamide, 86956-50-5.

(15) Protais, P.; Constentin, J.; Schwartz, J. C. *Psychopharmacology* **1976**, *50*, 1.
(16) Costall, B.; Naylor, R. J. *Life Sci.* **1972**, *11*, 1135.
(17) Sidman, M. *Science* **1953**, *118*, 157.
(18) Niswender, G. N.; Chem, C. L.; Midgley, A. R.; Meites, J.; Ellis, S. *Proc. Soc. Exp. Biol. Med.* **1969**, *130*, 793.
(19) Earley, C. J.; Leonard, B. E. *J. Pharmacol. Methods* **1978**, *1*, 67.
(20) Westerink, B. H. C.; Korf, J. *Biochem. Med.* **1965**, *12*, 106.
(21) Leysen, J. E.; Gommeren, W.; Laduron, P. M. *Biochem. Pharmacol.* **1978**, *27*, 307.
(22) Brodie, D. A. In "Pathophysiology of Peptic Ulcer"; Skoryna, S. C., Ed.; Lippincott: Philadelphia, 1963; p 403.
(23) Litchfield, J. T.; Wilcoxon, F. *J. Pharmacol. Exp. Ther.* **1949**, *96*, 99.
(24) Goldstein, A., "Biostatistics"; MacMillan: New York and London, 1964; p 156.