opiate agonist effects of nalorphine have been related to variations in this torsion angle,[9] but its variability may simply serve to emphasize the obvious flexibility of such a substituent; indeed, from published data, the conformation of the allyl group in the quaternary derivative is of somewhat lower energy than that found in nalorphine hydrobromide.[9] The possibility that this torsion angle is influenced by ionic interactions should not be discounted, since the iodide ion is found 5.32 and 5.34 Å, respectively, from the quaternary nitrogen atoms of two adjacent drug molecules. in addition, the iodide ion is part of the chain of hydrogen bonds, O(6)–H···O(H_2O)–H···I^-···H–O(3) linking the 6-hydroxy and 3-phenolic substituents of the same molecule. The remaining water hydrogen atom interacts with the 6-hydroxy group of a symmetry-related drug molecule, resulting in an infinite chain of hydrogen bonds extending along the a-axial direction.

Other interesting observations emerge from the pharmacological evaluation of A and B. The fact that isomer A with an axial N-substituent possesses some agonist activity whereas B with an equatorial N-substituent is a pure opiate antagonist lends support to the hypothesis of Feinberg et al.[2] relating to N-substituent conformations. It must be stressed, however, that isomer A has but a low intrinsic agonist activity and still possesses a very substantial (in comparison to its agonist activity) antagonist component. Both isomers A and B possess affinity for the μ rather than the δ receptor. Since isomer B has greater affinity at both μ and δ receptors than isomer A, it is apparent that the equatorial configuration of the N-allyl group is the favored conformation for interaction at both types of opiate receptor.

To our knowledge this is the first unequivocal experimental determination of the contribution of configuration about the N atom to antagonist effects in opiates.

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Supplementary Material Available: Atomic coordinates, anisotropic temperature factors, bond distances, and bond angles for isomer B (3 pages). Ordering information is given on any current masthead page.

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Articles

Potential Neuroleptic Agents. 2,6-Dialkoxybenzamide Derivatives with Potent Dopamine Receptor Blocking Activities

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A series of some novel N-(1-ethyl-2-pyrrolidinylmethyl)benzamides was synthesized and tested for dopamine receptor blockade in vivo by the ability to block the apomorphine syndrome in the rat. Several compounds were considerably more potent than sulpiride as dopamine receptor blockers and displayed low liability to induce extrapyramidal side effects (catalepsy) in the rat. The blockade of dopamine receptor activity in vivo was mainly confined to the levorotatory isomers having the S absolute configuration. The structure–activity relationships are discussed.

The substituted benzamides sulpiride, metoclopramide, and tiapride display pharmacological properties characteristic for neuroleptic drugs.[1-6] Sulpiride has been reported to be an effective antipsychotic agent that at therapeutic doses produces less marked extrapyramidal side effects than most antipsychotic compounds.[7,8] Animal investigations have demonstrated that many of the pharmacological effects of this compound are associated with blockade of (DA) receptors in both striatal, mesolimbic, and tuberoinfundibular DA containing neurons. Thus, sulpiride blocks some of the behavioral effects of the DA agonist apomorphine that are mediated via activation of striatal and mesolimbic DA receptors[4,10] and inhibits the binding of radiolabeled dopamine receptor antagonists,

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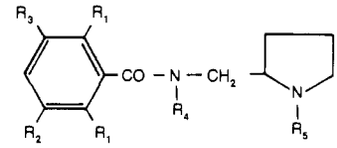
0022-2623/82/1825-1280$01.25/0

Table I. 2-[(2,6-Dialkoxybenzamido)methyl]-1-ethylpyrrolidines[a]



no.	R_1	R_2	R_3	R_4	R_5	isomer	$[\alpha]^{20}_D$ (c, solvent), deg	mp, °C	yield, %	formula	anal.
1	OCH_3	H	H	H	C_2H_5			182-184	81	$C_{16}H_{24}N_2O_3 \cdot HCl$	C, H, Cl, N
2	OCH_3	Br	H	H	C_2H_5			184-185	77	$C_{16}H_{23}BrN_2O_3 \cdot HCl$	C, H, N, O
3	OCH_3	Br	H	H	C_2H_5	$R(+)$	+10.7 (0.5, H_2O)	166-168	88	$C_{16}H_{23}BrN_2O_3 \cdot HCl$	C, H, Cl, N
4	OCH_3	Br	H	H	C_2H_5	$S(-)$	−11.1 (0.5, H_2O)	168-169	76	$C_{16}H_{23}BrN_2O_3 \cdot HCl$	C, H, Cl, N
5	OCH_3	Br	Br	H	C_2H_5			164-165[b]	69	$C_{16}H_{22}Br_2N_2O_3 \cdot HCl$	C, H, Br, Cl, N, O
6	OCH_3	Br	Br	H	C_2H_5	$R(+)$	+53.4 (1.0, acetone)	161-162	68	$C_{16}H_{22}Br_2N_2O_3$	C, H, Br, N, O
7	OCH_3	Br	Br	H	C_2H_5	$S(-)$	−56.4 (0.4, acetone)	161-162	88	$C_{16}H_{22}Br_2N_2O_3$[d]	C, H, Cl, N
8	OCH_3	Cl	H	H	C_2H_5			179-180	75	$C_{16}H_{23}ClN_2O_3 \cdot HCl$	C, H, Cl, N, O
9	OCH_3	Cl	H	H	C_2H_5	$S(-)$	−11.6 (2.0, H_2O)	164-165	76	$C_{16}H_{23}ClN_2O_3 \cdot HCl$	C, H, Cl, N, O
10	OCH_3	Cl	Cl	H	C_2H_5			120-121	53	$C_{16}H_{22}Cl_2N_2O_3$	C, H, Cl, N, O
11	OCH_3	Br	Cl	H	C_2H_5			124-125	74	$C_{16}H_{22}BrClN_2O_3$	C, H, Cl, N, O
12	OC_2H_5	H	H	H	C_2H_5			158-160	47	$C_{18}H_{28}N_2O_3 \cdot HCl$	C, H, Cl, N, O
13	OC_2H_5	Br	H	H	C_2H_5			182-183	69	$C_{18}H_{27}BrN_2O_3 \cdot HCl$	C, H, Cl, N, O
14	OC_2H_5	Br	H	H	C_2H_5	$S(-)$	−16.6 (0.5, H_2O)	163-164	68	$C_{18}H_{27}BrN_2O_3 \cdot HCl$	C, H, Cl, N, O
15	OC_2H_5	Cl	H	H	C_2H_5			187-188	75	$C_{18}H_{27}ClN_2O_3 \cdot HCl$	C, H, Cl, N, O
16	$OCH(CH_3)_2$	H	H	H	C_2H_5			~60 (sinters)	41	$C_{20}H_{32}N_2O_3 \cdot HCl$[c]	C, H, Cl, N, O
17	OCH_3	Br	Br	C_2H_5	C_2H_5			184-185	50	$C_{18}H_{26}Br_2N_2O_3 \cdot HCl$	C, H, Cl, N, O
18	Cl	H	H	H	C_2H_5			164-165	68	$C_{14}H_{18}Cl_2N_2O \cdot HCl$	C, H, N, O
19	OCH_3	Br	H	H	H	$S(-)$	−2.3 (1.0, H_2O)	174-175	47	$C_{14}H_{19}BrN_2O_3 \cdot HCl$	C, H, Cl, N, O

[a] Compounds 1-17. [b] The melting point of the base is 133-134 °C. [c] Due to hygroscopic properties, the analytical values of this salt are unreliable. C: calcd, 62.40; found, 61.3. Cl: calcd, 9.21; found, 10.1. O: calcd, 12.47; found, 13.2. [d] Analyzed as the HCl salt.

such as [^{3}H]haloperidol and [^{3}H]spiperone, to their binding sites.[9-11] The substituted benzamides display marked pharmacological differences from those of the "classical" neuroleptic drugs, e.g., haloperidol and chloropromazine.[2,4] Sulpiridie seems to act on a population of DA receptors not linked to DA-mediated adenylate cyclase activity.[12,13] Moreover, it is a weak blocker of apomorphine-induced stereotypies[2,4] and appears in vivo to act on a restricted DA receptor population preferentially in some limbic areas.[4,14]

Sulpiride has a relatively low neuroleptic potency both in animals[2,4] and in humans.[7] The low potency could be due to a combination of several factors, including low penetration into the brain[15] and low degree of biological availability and metabolic inactivation.[16] In view of the atypical neuroleptic properties of sulpiride, it was of interest to synthesize and evaluate some appropriately substituted benzamides. In the present paper we present modifications involving sterically hindered amides with high lipophilicity. The replacement of the sulfonamide residue in sulpiride with a halogen atom, coupled with a 2,6-dialkoxy substitution in the benzene nucleus, was found to result in particularly potent DA receptor blocking agents.

Both the neuroleptic and the antipsychotic properties of sulpiride have been shown to depend on the configuration about its chiral center, with the S isomer being much more active that the R isomer.[17-19] These considerations

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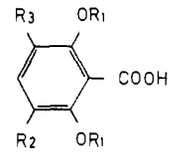
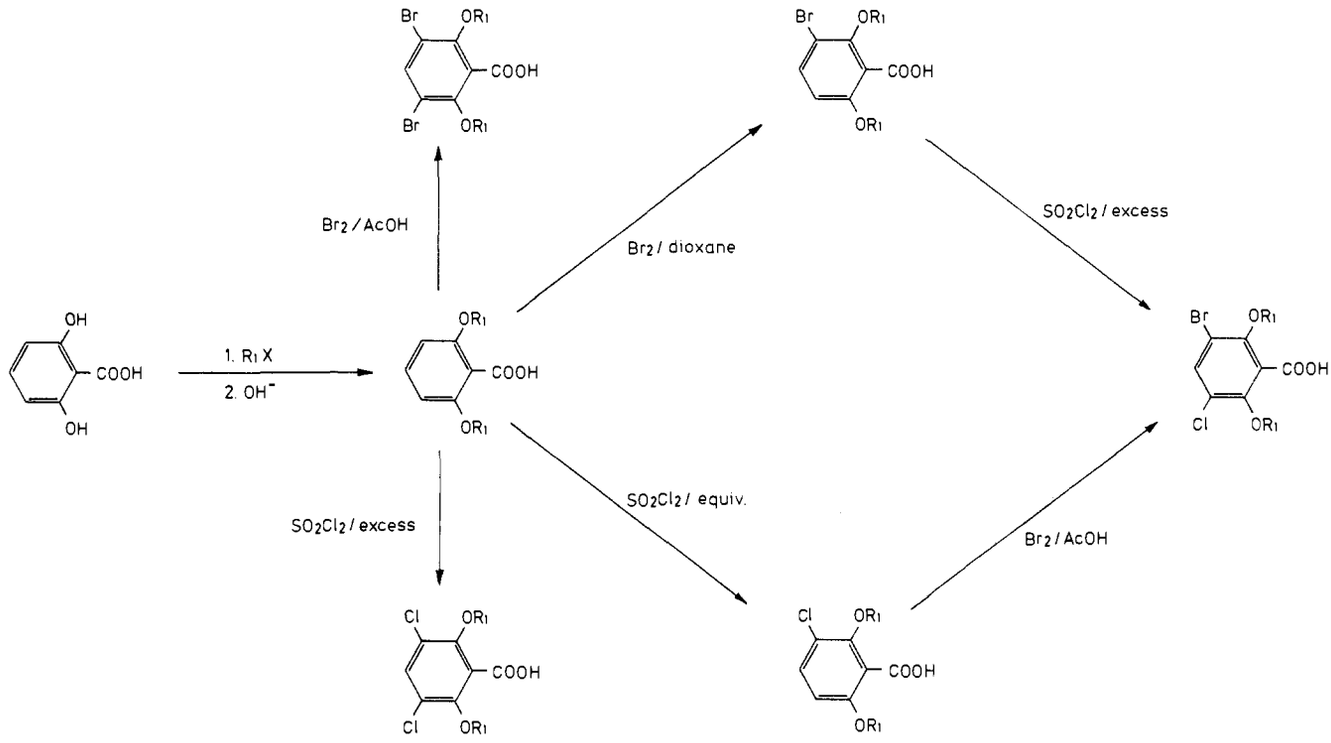
Table II. 2,6-Dialkoxybenzoic Acids



no.	R_1	R_2	R_3	mp, °C	yield, %	formula	anal.
20	CH_3	Br	H	144-145	85	$C_9H_9BrO_4$	
21	CH_3	Br	Br	108-110	41	$C_9H_8Br_2O_4$	
22	CH_3	Cl	H	130-133	78	$C_9H_9ClO_4$	
23	CH_3	Cl	Cl	102-103	60	$C_9H_8Cl_2O_4$	
24[b]	CH_3	Br	Cl	99-100	80		
24[c]	CH_3	Br	Cl	99-100	17	$C_9H_8BrClO_4$	C, H, Cl; O[a]
25	C_2H_5	H	H	131-131.5	39	$C_{11}H_{14}O_4$	
26	C_2H_5	Br	H	125-126	72	$C_{11}H_{13}BrO_4$	C, H, Br, O
27	C_2H_5	Cl	H	108-109	83	$C_{11}H_{13}ClO_4$	C, H, Cl, O
28	$CH(CH_3)_2$	H	H	106-107	35	$C_{13}H_{18}O_4$	

[a] O: calcd, 21.65; found, 21.0. [b] Prepared from 3-bromo-2,6-dimethoxybenzoic acid. [c] Prepared from 3-chloro-2,6-dimethoxybenzoic acid.

Scheme I



led us to undertake an investigation of the enantiomers of some of the prepared compounds. The structure–activity relationships of these derivatives are presented, and their neuroleptic properties are described.

Chemistry. The 2,6-dialkoxybenzamides presented in Table I were prepared from the appropriate benzoic acid chlorides and 2-(aminomethyl)pyrrolidines. The acid chlorides were obtained from thionyl chloride and the corresponding 2,6-dialkoxybenzoic acids. After excess thionyl chloride was removed, the undistilled products were directly used in the subsequent reaction. The 2,6-dichlorobenzamide **18** was prepared in a similar procedure from 2,6-dichlorobenzoic acid. The enantiomers of selected 2,6-dialkoxybenzamides were obtained from (*S*)-(−)- and (*R*)-(+)-2-(aminomethyl)-1-ethylpyrrolidine.[19,23]

The synthetic routes used for the preparation of the necessary 2,6-dialkoxybenzoic acids (Table II) are outlined in Scheme I. Compounds **21–23** have been prepared previously by methylation of the corresponding 2-hydroxy-6-methoxy- and 2,6-dihydroxybenzoic acids with dimethyl sulfate and potassium carbonate in acetone.[20] In the present work, the dibromobenzoic acid **21** was obtained by bromination of 2,6-dimethoxybenzoic acid in the presence of anhydrous sodium acetate. In addition, the monochlorination of 2,6-dimethoxybenzoic acid was effected with an equivalent amount of sulfuryl chloride, while treatment with sulfuryl chloride in excess yielded the dichloro acid **23**.

Bromination of 2,6-dimethoxybenzoic acid with bromine in dioxane gave 2,6-dimethoxy-3-bromobenzoic acid (**20**). The previously described method[20] was simplified in that the dioxane dibromide reagent was not isolated but generated in situ. 3-Bromo-5-chloro-2,6-dimethoxybenzoic acid (**24**) was obtained from 3-chloro-2,6-dimethoxybenzoic acid by treatment with bromine in the presence of an-

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Table III. Pharmacological Effects of 2-[(2,6-Dialkoxybenzamido)methyl]-1-ethylpyrrolidines

compd	block of apomorphine[b] ED_{50}, μmol/kg ip (90% CL) stereotypies	block of apomorphine[b] ED_{50}, μmol/kg ip (90% CL) hyperactivity	catalepsy:[c] ED_{50}, μmol/kg ip (95% CL)	LD_{50},[c] μmol/kg ip (95% CL)
1	100.6 (98.5-107.9)	71.1 (71.1-73)		
2	21.3 (20.4-21.8)	12.8 (11.3-13.7)	47 (27-68)	817 (712-912)
3	>196	120.2 (112-148)		~699[d]
4	6.5 (6.2-6.7)	0.86 (0.98-0.81)	24.5 (17.4-40.2)	794 (690-887)
5	4.6 (4.5-4.7)	1.15 (1.0-1.2)	8.2 (6.2-10.2)	177 (133-215)
6	>82	13.1 (12-13.8)		159 (107-211)
7	2.1 (2.0-2.2)	0.44 (0.42-0.44)	5.3 (5.3-5.8)	~164[d]
8	42.7 (42.4-44.6)	30.8 (30.2-32.2)		
9	11.7 (11.2-12.3)	5.6 (4.7-6.0)		~826[d]
10	5.4 (5.3-5.5)	3.1 (3.0-3.2)	16.8 (16.7-17.5)	224 (160-274)
11	7.3 (6.2-7.8)	3.9 (3.7-4.1)	5 (4.2-6.2)	206 (144-259)
12	>40	23.4 (22.4-26.3)		~80[d]
13	4.7 (4.5-5.0)	1.1 (1.0-1.1)	15.7 (9.5-27.4)	
14	1.9 (1.8-2.2)	0.47 (0.46-0.49)	8.9 (4.8-13.4)	206 (176-247)
15	7.2 (6.9-7.8)	2.8 (2.7-2.9)	31 (21-44)	
16	>80	>80		~160[d]
17	>80	>80		
18	>80	>80		
19	100 (90-105)	47 (44-58)		
haloperidol[a]	0.27 (0.26-0.29)	0.29 (0.27-0.35)	0.67 (0.45-0.96)	
sulpiride[a]	212 (198-238)	65.6 (62.7-68.5)	161 (114-219)	

[a] Reference compound. [b] ED_{50} was determined by Theil's method. [c] ED_{50} and LD_{50} were determined by probit analysis. [d] Approximate values based on log dose-response curves.

hydrous sodium acetate. Alternatively, compound **24** could be prepared by chlorination of 3-bromo-2,6-dimethoxybenzoic acid with sulfuryl chloride.

The 2,6-dialkoxybenzoic acids **25** and **28** were prepared essentially as described in the literature by alkylation of 2,6-dihydroxybenzoic acid with the appropriate alkyl bromide in the presence of dimethylformamide and anhydrous potassium carbonate.[21] The synthesis of the 3-bromo- and 3-chloro-2,6-diethoxybenzoic acids **26** and **27** was effected under the same conditions given for the preparation of the 2,6-dimethoxy analgoues **20** and **22**.

2-[(Ethylamino)methyl]-1-ethylpyrrolidine was prepared by acetylation of 2-(aminoethyl)-1-ethylpyrrolidine with acetic anhydride and then reducing the resulting acetyl derivative with lithium aluminum hydride. The compound was not isolated but directly transformed into amide **17**.

The preparation of the deethyl compound **19** was effected in a route using the trityl protecting group. The synthesis started from (*S*)-(−)-prolinamide, which was prepared analogously to a method given for the *R* isomer.[22] The amide was tritylated by the action of trityl chloride. The obtained compound (**29**) was then reduced with lithium aluminum hydride to the intermediate diamine, (*S*)-(−)-1-trityl-2-(aminomethyl)pyrrolidine. In the next step, the protected amine was benzoylated with 2,6-dimethoxy-3-bromobenzoyl chloride in the presence of triethylamine. The resulting benzamide was not isolated but detritylated directly to compound **19** with dilute hydrochloric acid at room temperature. The optical rotation of the obtained deethyl compound was low ($[\alpha]^{20}_D$ −2.3°) when compared with the value of $[\alpha]^{20}_D$ −11.1° found for the ethyl compound **4**. This result may indicate the introduction of some racemization during the reduction step. On the other hand, a related example shows that lithium aluminum hydride reduction of (*S*)-(−)-1-(cyclopropylcarbonyl)prolinamide to (*S*)-(−)-1-(cyclopropylmethyl)-2-(aminomethyl)pyrrolidine causes no racemization.[24] Since the specific rotation of the pure *S* enantiomer of **19** is unknown, the optical purity of the deethyl compound could not be determined at this time.

Pharmacology. The pharmacological results are summarized in Table III. The potency of compounds in the present series was dependent on substitution of alkoxy groups in the 2- and 6-position. Combining a halogen atom with methoxy groups in the 2- and 6-position in the

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benzene nucleus enhanced anti-apomorphine activity markedly. Thus, compounds **2** and **8** substituted in the 3-position with bromine and chlorine, respectively, were markedly more potent than the unsubstituted amide **1**. Compound **2** was about five times more potent than sulpiride in blocking apomorphine-induced hyperactivity. Substitution with bromine or chlorine in both the 3- and 5-position increased further the ability to block apomorphine (compounds **5** and **10**). It should be noted that bromine-substituted compounds (in the 3- and/or 5-position) were more active than the corresponding chlorine substituted compounds. Substitution with bromine in the 3-position and chlorine in the 5-position (compound **11**) gave the same activities as chlorine substitutions at both positions (compound **10**).

The introduction of ethoxy groups in the 2- and 6-position enhanced activity of the halogen-substituted compounds. Thus, compounds **13** and **15** were markedly more potent than the corresponding methoxy derivatives **2** and **8**. Bromine substitution again resulted in a higher potency than chlorine substitution (compare **13** and **15**). In contrast, the replacement of the methoxy groups in compound **1** by isopropoxy groups greatly reduced activity and led to enhanced acute toxicity (compound **16**).

The importance of the *N*-ethyl group in the pyrrolidine nucleus was demonstrated by the poor activity shown by the deethyl compound (**19**). Furthermore, replacement of the alkoxy groups in compound **1** with chlorine resulted in a compound (**18**) that virtually is devoid of activity. The incorporation of an ethyl group at the amide nitrogen of compound **5** resulted in the inactive compound **17**. It may be noted that the presence of an intramolecular hydrogen bond between the amide nitrogen atom and the methoxy oxygen is only possible in the unsubstituted amide **5**. In fact, hydrogen bonding of this type has just been shown to exist in some closely related 2-methoxybenzamides. In addition, these molecules are shown to have only limited conformational freedom due to the locking up effect of this hydrogen bonding.[25]

The optical isomers of the most potent compounds were prepared and tested. Most of the DA receptor blocking activity was found to reside in the levorotatory enantiomers of the new benzamides in accordance with previous findings with sulpiride.[17-19] Table III shows the relative potency of the optical isomers to inhibit apomorphine-induced stereotypies and hyperactivity. The activity of compounds **4**, **7**, and **14** to block apomorphine-induced hyperactivity was in the same dose range as that of haloperidol. Interestingly, the anti-dopaminergic effect of the isomers differed, depending on the type of substitution. Thus, the levorotatory isomer of the amide **2** showed the largest increase in potency in blocking apomorphine-induced hyperactivity.

Like sulpiride,[4] the bromine-substituted compounds **2**, **5**, and **13** caused a preferential blockade of apomorphine-induced hyperactivity with less potency to block stereotypies. The enantiomers **4**, **7**, and **14** showed an even greater separation between blockade of hyperactivity and stereotypies than the corresponding racemates. In addition, the most potent compounds were found to produce a weak, atypical form of catalepsia with a wide separation between ED_{50} for blockage of apomorphine-induced hyperactivity and ED_{50} for catalepsia. The very low toxicity of the most potent levorotatory diastereomers (**4**, **7**, and **14**) is notable in view of their high potency. Interestingly, the inactive dextrorotatory isomers showed a higher toxicity than the corresponding levorotatory isomers.

These results show that the pharmacological profile of the new benzamides is similar to that of sulpiride. They preferentially block apomorphine-induced hyperactivity. They cause a weak atypical form of catalepsy predictive of extrapyramidal side effects, which is clearly resembling that of clozapine and sulpiride.[2,4] In contrast to haloperidol, there is a wide separation between the dose range in which the new benzamides block apomorphine-induced hyperactivity and the dose range in which they produce catalepsy in the rat. The levorotatory forms are more potent and show higher specificity than the corresponding racemates and show an even greater specificity compared with sulpiride. The compounds differ from sulpiride by their high DA-receptor blocking potency both when given ip and po (to be published). Several factors could contribute to the high potency of these new benzamides, such as steric inhibition of metabolic degradation. In addition, the exchange of the sulfonamide function in sulpiride for a halogen atom in position 3 changes the electronic properties of the molecules and could possibly increase the penetration into brain tissue.

Recent studies indicate the possibility of different types of DA receptors in striatal and extrastriatal DA systems[12,26] and that sulpiride may be classified as a selective antagonist in the D-2 system.[9,27,28] The present data support the view that the benzamides may block a DA-receptor population that is different from the classical neuroleptics.

Experimental Section

Chemistry. The analyses were performed by the Department of Analytical Chemistry at the University of Lund, Sweden. Melting points were determined in an electrically heated metal block, with calibrated Anschütz thermometers. Where analyses in Tables I and II are indicated by symbols of the elements, analytical results obtained for those elements were within ±0.4% of the theoretical values. Optical rotations were measured with a Perkin-Elmer Model 41 polarimeter and NMR spectra were recorded with a Varian A-60A spectrometer. The absence of precursors in the prepared compounds were examined by GC with a Perkin-Elmer 3920 gas chromatograph equipped with flame-ionization detector.

2-[(2,6-Dialkoxybenzamido)methyl]-1-ethylpyrrolidines 1, 2, 5, 8, 10–13, 15, 16, and 18 in Table I were prepared by the following general procedure exemplified by the synthesis of compounds **11** and **13**. The *S* enantiomers **4**, **7**, **9**, and **14** were obtained similarly to the *R* enantiomers by the use of (*S*)-(−)-2-(aminomethyl)-1-ethylpyrrolidine.

2-[(3-Bromo-5-chloro-2,6-dimethoxybenzamido)methyl]-1-ethylpyrrolidine (**11**). $SOCl_2$ (20 mL) was added to 11.8 g (0.04 mol) of 3-bromo-5-chloro-2,6-dimethoxybenzoic acid. The mixture was heated on a steam bath for 1 h. To the solution was added 50 mL of toluene. The solvent and excess $SOCl_2$ were evaporated at reduced pressure. The residue was dissolved in 50 mL of dry methyl ethyl ketone (MEK), and the solution was added, while stirring and cooling, to a solution of 5.13 g (0.04 mol) of 2-(aminomethyl)-1-ethylpyrrolidine in 50 mL of MEK. After stirring for 30 min, 300 mL of Et_2O was added. The obtained semisolid product was separated, dissolved in 300 mL of H_2O, and acidified with 12 N HCl. NaOH was added while stirring and cooling in ice. The precipitate was collected and washed with water: yield 12.0 g.

2-[(3-Bromo-2,6-diethoxybenzamido)methyl]-1-ethylpyrrolidine Hydrochloride (**13**). A solution of 30 mL of $SOCl_2$ in 50 mL of toluene was added to 8.67 g (0.03 mol) of 3-bromo-2,6-diethoxybenzoic acid. The mixture was heated at a steam

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bath for 30 min. The solvent and excess $SOCl_2$ were evaporated at reduced pressure. To the residue was added dropwise with stirring and cooling a solution of 4.0 g (0.03 mol) of 2-(aminomethyl)-1-ethylpyrrolidine in 50 mL of dry MEK. After stirring at room temperature for 2 h, the solvent was evaporated. The semisolid residue was dissolved in water, acidified with 12 N HCl, and extracted with Et_2O. The water layer was made alkaline with 10 N NaOH and extracted with $CHCl_3$. The extract was dried with $MgSO_4$ and acidified with 3 N HCl gas in Et_2O. The solvent was evaporated, and the residue was recrystallized from EtOH–Et_2O: yield 9.0 g.

(*R*)-(+)-2-[(3,5-Dibromo-2,6-dimethoxybenzamido)methyl]-1-ethylpyrrolidine (6). $SOCl_2$ (20 mL) was added to 12.2 g (0.036 mol) of 3,5-dibromo-2,6-dimethoxybenzoic aciod. The mixture was heated on a steam bath for 30 min. Toluene was added, and the solvent and excess $SOCl_2$ were evaporated at reduced pressure. To the residue was added while stirring a chloroform extract prepared as follows: 75 mL of 10 N NaOH was added to 10.0 g (0.023 mol) of (*R*)-(+)-2-(aminomethyl)-1-ethylpyrrolidine (+)-ditartrate. The mixture was extracted with 100 mL of $CHCl_3$, and the extract was dried with $MgSO_4$.

After the addition of the extract, the obtained solution was heated on a steam bath for 10 min. The solvent was then evaporated, and the residue was dissolved in 150 mL of H_2O, acidified with 12 N HCl, and extracted with Et_2O. The water layer was made alkaline with 10 N NaOH solution, and the obtained precipitate was collected and washed with water: yield 7.0 g.

(*S*)-(−)-2-[(3,5-Dibromo-2,6-dimethoxybenzamido)methyl]-1-ethylpyrrolidine (7) was similarly obtained from 15.8 g (0.036 mol) of (*S*)-(−)-2-(aminomethyl)-1-ethylpyrrolidine (−)-ditartrate 19.8 g (0.056 mol) of 3,5-dibromo-2,6-dimethoxybenzoic acid, and 30 mL of $SOCl_2$: yield 14.3 g. The free base (13.1 g) was converted to the hydrochloride salt by adding a solution of 3 N HCl gas in Et_2O to a solution of the base in acetone: yield 13.5 g; mp 159–160 °C.

A mixture of equal amounts of the enantiomers **6** and **7** melted at 134–135 °C, which is the same as the melting point of racemate **5** (Table I).

(*R*)-(+)-2-[(3-Bromo-2,6-dimethoxybenzamido)methyl]-1-ethylpyrrolidine Hydrochloride (3). This compound was prepared analogously to the 3,5-dibromo compound (**6**) from 9.0 g (0.021 mol) of (*R*)-(+)-2-(aminomethyl)-1-ethylpyrrolidine (+)-ditartate, 8.4 g (0.032 mol) of 3-bromo-2,6-dimethoxybenzoic acid, and 20 mL of $SOCl_2$. The hydrochloride was isolated as follows: After evaporation of the chloroform, the residue was dissolved in 150 mL of H_2O and acidified with 12 N HCl, and the solution was then extracted with Et_2O. The water layer was made alkaline with 10 N NaOH and extracted with $CHCl_3$. The extract was dried with $MgSO_4$, and the solvent was evaporated. The residue was dissolved in Et_2O and acidified with 3 N HCl gas in ether. The resulting precipitate was collected by filtration: yield 7.5 g.

2-[(*N*-Ethyl-3,5-dibromo-2,6-dimethoxybenzamido)methyl]-1-ethylpyrrolidine Hydrochloride (17). Ac_2O (11.0 mL, 0.12 mol) was added to 12.8 g (0.1 mol) of 2-(aminomethyl)-1-ethylpyrrolidine in 150 mL of toluene. The solution was refluxed for 1 h, and the solvent was evaporated. To the residue was added 150 mL of H_2O. The mixture was made alkaline with 10 N NaOH and extracted with $CHCl_3$. The extract was dried with Na_2SO_4, and the solvent was evaporated. The residual oil was dissolved in 100 m of dry Et_2O, and the solution was added dropwise with stirring to 5.0 g of $LiAlH_4$ in 100 mL of Et_2O. The mixture was stirred and heated under reflux for 7 h. After the dropwise addition of 25 mL of saturated Na_2SO_4, the mixture was filtered. The filtrate was dried over Na_2SO_4, and the solvent was evaporated. The obtained crude 2-[(ethylamino)methyl]-1-ethylpyrrolidine (15.0 g of residual oil) was used in the next step.

$SOCl_2$ (20 mL) was added to 8.7 g (0.025 mol) of 3,5-dibromo-2,6-dimethoxybenzoic acid. The mixture was heated on a steam bath for 30 min. Toluene was added, and the solvent and excess $SOCl_2$ were evaporated. The residue was dissolved in 50 mL of MEK. The solution was added to a stirred solution of 3.9 g (0.025 mol) of crude 2-[(ethylamino)methyl]-1-ethylpyrrolidine in 25 mL of MEK. After the addition, the mixture was heated on a steam bath for 15 min. The hydrochloride was precipitated by the addition of 300 mL of Et_2O. The product was recrystallized from EtOH–$(i\text{-}Pr)_2O$: yield 6.4 g.

3,5-Dibromo-2,6-dimethoxybenzoic Acid (21). A solution of 12 mL (0.23 mol) of Br_2 in 50 mL of AcOH was added dropwise, while stirring, to a mixture of 18.2 g (0.1 mol) of 2,6-dimethoxybenzoic acid and 21.0 g (0.25 mol) of dry AcONa in 150 mL of AcOH. The mixture was stirred overnight at room temperature and was then poured into 1 L of ice–water. The precipitate was filtered off, washed with water, and dried. The crude compound was purified by recrystallization from light petroleum: yield 14.1 g (41%); mp 108–110 °C (lit.[20] mp 109–111 °C).

3-Chloro-2,6-dimethoxybenzoic Acid (22). A solution of 8.1 mL (0.1 mol) of SO_2Cl_2 in 50 mL of $CHCl_3$ was added dropwise, while stirring, to a solution of 18.2 g (0.1 mol) of 2,6-dimethoxybenzoic acid in 150 mL of $CHCl_3$. The solution was heated at 50 °C for 0.5 h and left overnight at room temperature. The solvent was evaporated and the residue was dissolved in 500 mL of NaOH solution. The solution was acidified with 12 N HCl while stirring and cooling in ice. The obtained precipitate was filtered off and washed with water: yield 17.0 g (78%); mp 130–133 °C (lit.[20] mp 133 °C).

3,5-Dichloro-2,6-dimethoxybenzoic Acid (23). A solution of 20 mL (0.25 mol) of SO_2Cl_2 in 50 mL of $CHCl_3$ was added dropwise to a solution of 15.0 g (0.08 mol) of 2,6-dimethoxybenzoic acid in 100 mL of $CHCl_3$. The solution was left overnight at room temperature and was then refluxed for 0.5 h. The solvent was evaporated, and the residue was recrystallized twice from light petroleum: yield 12.0 g (60%); mp 102–103 °C (lit.[20] mp 104–106 °C).

3-Bromo-2,6-dimethoxybenzoic Acid (20). A solution of 20 mL (0.4 mol) of Br_2 in 100 mL of $CHCl_3$ was added dropwise, while stirring, to a solution of 72.8 g (0.4 mol) of 2,6-dimethoxybenzoic acid in 600 mL of dioxane. The solution was stirred at room temperature for 2 h. The solvent was evaporated, and the residue was recrystallized from aqueous EtOH: yield 89.2 g (85%); mp 144–145 °C (lit.[20] mp 146–148 °C).

3-Bromo-5-chloro-2,6-dimethoxybenzoic Acid (24). A solution of 1.5 mL (0.03 mol) of Br_2 in AcOH was added to a mixture of 2.7 g (0.01 mol) of 3-chloro-2,6-dimethoxybenzoic acid and 3.0 g of anhydrous AcONa in 50 mL of AcOH. The mixture was left at room temperature overnight and was then poured into 300 mL of ice–water. The precipitate was filtered, washed with water, dried, and recrystallized from isopropyl ether–light petroleum: yield 0.5 g.

Alternatively, the compound could be prepared as follows: A solution of 40 mL (0.5 mol) of SO_2Cl_2 in 100 mL of $CHCl_3$ was added dropwise to a solution of 26.1 g (0.1 mol) of 3-bromo-2,6-dimethoxybenzoic acid in 150 mL of $CHCl_3$. After 12 h at room temperature, the solution was refluxed for 45 min. The solvent was then evaporated, and the residue was recrystallized from isopropyl ether–light petroleum: yield 23.5 g. The melting point was undepressed on admixture of samples of the two preparations.

2,6-Diisopropoxybenzoic Acid (28). A mixture of 53.9 g (0.35 mol) of 2,6-dihydroxybenzoic acid, 145 g (1.05 mol) of anhydrous K_2CO_3, 113 mL (1.2 mol) of 2-bromopropane, and 5.0 g of NaI in 200 mL of DMF was heated at reflux temperature for 72 h. The inorganic salts were removed by filtration, and most of the DMF was evaporated. To the residue was added 800 mL of H_2O, and the mixture was extracted with Et_2O. The solvent was evaporated, and the obtained crude ester (59.0 g of oil) was dissolved in a mixture of 150 mL of butanol, 50 mL of H_2O, and 50 g of KOH. The solution was refluxed for 18 h and then the solvent was evaporated. The residue was dissolved in 800 mL of H_2O, and the solution was extracted with Et_2O. The water layer was acidified with 12 N HCl, and the precipitate was filtered and recrystallized from aqueous EtOH: yield 28.8 g (35%); mp 106–107 °C (lit.[21] 107–108 °C).

Similarly prepared was **2,6-diethoxybenzoic acid (25)**, which was obtained from 53.9 g (0.35 mol) of 2,6-dihydroxybenzoic acid, 145 g (1.05 mol) of K_2CO_3, 113 mL (1.2 mol) of EtBr and 5.0 g of NaI in 200 mL of DMF. The mixture was heated at 140 °C for 24 h. The ester hydrolysis was effected by heating at reflux temperature for 4 h: yield 28.8 g (39%); mp 131–132 °C (lit.[21] 132–134 °C).

3-Bromo-2,6-diethoxybenzoic Acid (26). This compound was prepared analogously to the 2,6-dimethoxy compound from 28.8

g (0.14 mol) of 2,6-diethoxybenzoic acid and 7 mL (0.14 mol) of Br_2. The product was recrystallized from isopropyl ether–light petroleum: yield 28.7 g.

3-Chloro-2,6-diethoxybenzoic Acid (27). A solution of 4.05 mL (0.05 mol) of SO_2Cl_2 in 25 mL of $CHCl_3$ was added dropwise, while stirring, to a solution of 10.5 g (0.05 mol) of 2,6-diethoxybenzoic acid in 75 mL of $CHCl_3$. The mixture was heated at 50 °C for 30 min. The solvent was then evaporated, and the residue was recrystallized from isopropyl ether–light petroleum: yield 10.1 g.

(*S*)-(−)-1-Trityl-2-pyrrolidinecarboxamide (29). Trityl chloride (88.0 g, 0.31 mol) was added in portions to a mixture of 47.6 g (0.31 mol) of (*S*)-(−)-prolinamide hydrochloride and 88 mL (0.63 mol) of triethylamine in 350 mL of $CHCl_3$ while stirring and cooling in ice. The mixture was stirred overnight at room temperature and was then extracted with H_2O. The organic layer was separated and dried with anhydrous $MgSO_4$, and the chloroform was evaporated. The residue was recrystallized twice from EtOH–$(i\text{-Pr})_2O$: yield 59.0 g (53%); mp 198–199 °C; $[\alpha]^{20}_D$ −34.3° (*c* 1.0, $CHCl_3$). Anal. ($C_{24}H_{24}N_2O$) C, H, N.

(*S*)-(−)-2-[(3-Bromo-2,6-dimethoxybenzamido)methyl]-pyrrolidine Hydrochloride (19). A solution of 35.6 g (0.1 mol) of **29** in 200 mL of dry THF was added dropwise, while stirring and cooling in ice, to a stirred mixture of 8.0 g (0.2 mol) of $LiAlH_4$ in 150 mL of dry Et_2O. The mixture was stirred and heated under reflux for 27 h. After dropwise addition of 50 mL of a saturated Na_2SO_4 solution while stirring and cooling in ice, the mixture was filtered. The filtrate was dried over anhydrous Na_2SO_4, and the solvent was evaporated. The residue (41.0 g of oil) was dissolved in a mixture of 400 mL of $CHCl_3$ and 15 mL of triethylamine. To the solution was added dropwise, while stirring a solution prepared as follows: A mixture of 50 mL of $SOCl_2$ and 26.1 g (0.1 mol) of 2,6-dimethoxy-3-bromobenzoic acid was heated on a steam bath for 0.5 h. Toluene was added, and the solvent and excess $SOCl_2$ were evaporated at reduced pressure. The residual acid chloride was dissolved in 200 mL of $CHCl_3$.

After the addition of the chloroform solution, the mixture was left overnight at room temperature. The solvent was then evaporated, and to the residue was added 15 mL of 12 N HCl in 300 mL of EtOH. The solution was left at room temperature for 1 h. The ethanol was then evaporated, and the residue was triturated with Et_2O, stirred with 700 mL of H_2O, and extracted with Et_2O. The water layer was made alkaline with NaOH and extracted with $CHCl_3$. The extract was dried with $MgSO_4$, and the solvent was evaporated. The residue, an oil which crystallized on scratching, was washed with peteroleum ether and dried: yield 18.6 g; mp 85–90 °C.

The crude free base was converted to the hydrochloride salt by adding a solution of 3 N HCl gas in Et_2O to a solution of the base in 100 mL of EtOH. The salt was precipitated by the addition of Et_2O. The product was filtered off and recrystallized from EtOH–$(i\text{-Pr})_2O$, yielding 18.0 g of the pure compound. Three grams of the hydrochloride dissolved in 200 mL of H_2O was converted into the free base by the addition of NaOH. After the solution was extracted with $CHCl_3$, the extract was dried, and the solvent was evaporated, 2.1 g of the pure base was obtained, mp 106–107 °C.

Pharmacology. Apomorphine-Induced Behavior. Blockade of apomorphine-induced hyperactivity and sterotypies was performed as described previously.[4,10] Male Sprague–Dawley rats, weighing 250–300 g, were used. the behavior was scored 5, 20, 40, and 60 min after injection of apomorphine (1 mg/kg), given subcutaneously into the neck. The test compounds were dissolved in saline or water and injected ip 60 min prior to apomorphine. The ED_{50}'s for stereotypies are the doses that reduce the strength of apomorphine-induced stereotypies by 50% over the total observation period of 60 min. The ED_{50}'s for hyperactivity are the doses that reduce the number of animals showing hyperactivity by 50% over the observation period of 60 min. Each ED_{50} was calculated by Theil's method and corrected for ties according to Sen's procedure based on Kendell's τ.[29,30] The 90% confidence interval was calculated according to a slightly modified version of Sen's procedure.

Measurement of Catalepsy in Rats. Eight rats at each dose level were tested in open perspex cages [40 (l) × 25 (w) ×15 (h) cm] fitted with a 7-cm-high horizontal bar. Catalepsy was measured 1, 2, 4, 8, and 24 h after injection of the test compound. The fore limbs of each animal were placed on the horizontal bar. A cataleptic state was scored if the rat failed to remove itself from the bar within 60 s. Maximal catalepsy tended to occur between 2 and 8 h following the treatment. The dosage at which 50% of the animals were cataleptic (ED_{50} and the 95% confidence interval) was calculated by probit analysis on the peak cataleptic effect observed for each compound.

Acute Toxicity. The acute toxicity was assessed in rats observed for 24 h after ip injection. The LD_{50} values and the 95% confidence intervals were determined by probit analysis based on four doses, with five animals per dose level. If data were not suitable for regression analysis, the approximate LD_{50} values were determined from log dose–response curves.

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β-Adrenergic Blocking Agents. 22. 1-Phenoxy-3-[[(substituted-amido)alkyl]amino]-2-propanols

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The synthesis of a series of 1-phenoxy-3-[[(substituted-amido)alkyl]amino]-2-propanols is described. Many of the compounds are more potent than propanolol as β blockers, while having cardioselectivity comparable to that of practolol, when given intravenously to anesthetized cats. The structure–activity relationships shown by this series of compounds provide further evidence that the addition of substituents to the alkylamino moeity of a β blocker can confer cardioselectivity and that amidic substituents are remarkably effective.

Cardioselectivity has been shown to be associated with a variety of para substituents in the aryl moiety of an (aryloxy)propranolamine.[1-3] More recent work shows that the property can also be obtained by replacing the conventional isopropyl or *tert*-butyl substituent of a β-blocker

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