Synthesis and Neuroleptic Activity of Benzamides. *cis*-*N*-(1-Benzyl-2-methylpyrrolidin-3-yl)-5-chloro-2-methoxy-4-(methylamino)benzamide and Related Compounds

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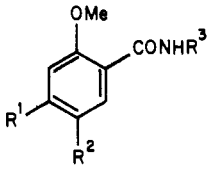
Three series of benzamides of N,N-disubstituted ethylenediamines (linear alkane-1,2-diamines), 1-substituted 2-(aminomethyl)pyrrolidines, and 1-substituted 3-aminopyrrolidines (cyclic alkane-1,2-diamines) were designed and synthesized as potential neuroleptics. All target compounds were evaluated for their inhibitory effects on apomorphine-induced stereotyped behavior in rats, and a good correlation between structure and activity was found throughout the series. In the linear series (analogues of metoclopramide), introduction of a benzyl group on the terminal nitrogen, rather than an ethyl group, and a methyl group on the *p*-amino group of metoclopramide both enhanced the activity. The resulting *N*-[2-(*N*-benzyl-*N*-methylamino)ethyl]-5-chloro-2-methoxy-4-(methylamino)benzamide (**23**) was about 15 times more active than metoclopramide. In the cyclic series, particularly among the benzamides of 1-benzyl-3-aminopyrrolidine, most of the compounds tested were more active than the corresponding linear benzamides. *cis*-*N*-(1-Benzyl-2-methylpyrrolidin-3-yl)-5-chloro-2-methoxy-4-(methylamino)benzamide (YM-09151-2, **55**) was the most active among all of the compounds tested, being 13 and 408 times more potent than haloperidol and metoclopramide, respectively. Moreover, compound **55** exhibited a fairly high ratio of antistereotypic activity to cataleptogenicity compared with haloperidol and metoclopramide. It is expected that compound **55** may be used as a potent drug with few side effects in the treatment of psychosis.

The majority of neuroleptic drugs that are useful in the clinical treatment of schizophrenia are butyrophenones (e.g., haloperidol) and phenothiazines. The correlations of structure and activity in these series of compounds have been thoroughly investigated.[1]

On the other hand, though it is well known that some benzamide derivatives of alkane-1,2-diamines, such as metoclopramide, sulpiride, and sultopride, exhibit neuroleptic activities,[2] up to the present no benzamide derivatives have been reported to be more potent than haloperidol.



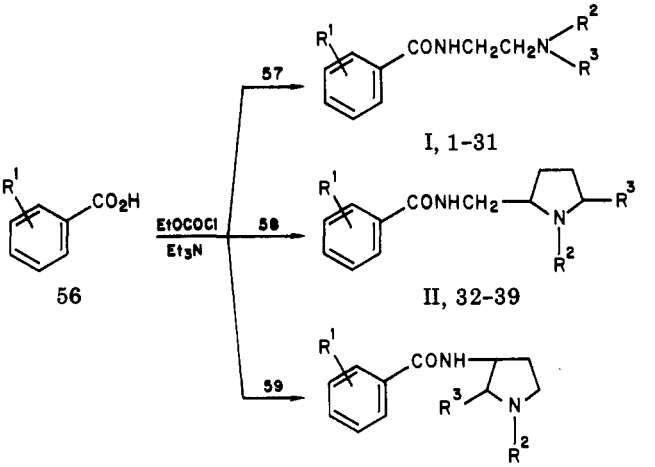
metoclopramide, $R^1 = NH_2$; $R^2 = Cl$; $R^3 = CH_2CH_2NEt_2$

sulpiride, $R^1 = H$; $R^2 = SO_2NH_2$; $R^3 =$ 

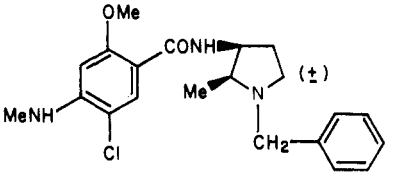
sultopride, $R^1 = H$; $R^2 = SO_2Et$; $R^3 =$ 

The object of our work was to find more potential neuroleptics in this group of compounds. We have designed and prepared a number of substituted benzamides of linear and cyclic alkane-1,2-diamines (analogues of metoclopramide and sulpiride) and subjected them to the screening tests for antiapomorphine, antimethamphetamine, and some other neuroleptic effects.[3,4] Such effects

Scheme I



are known to be well correlated with the clinical potency of neuroleptic drugs for schizophrenia.[5] From the results of the screening tests, it has been found that *cis*-*N*-(1-benzyl-2-methylpyrrolidin-3-yl)-5-chloro-2-methoxy-4-(methylamino)benzamide (YM-09151-2, **55**) demonstrates 13 times greater inhibitory effect on apomorphine-induced stereotyped behavior in rats than haloperidol.



YM-09151-2 (**55**)

This paper describes the synthesis and structure–activity relationships for the antiapomorphine effects in the three series of benzamides. In addition, compound **55** and some of the other interesting compounds were examined for their

(1) D. Bente and P. B. Bradley, Eds., "Neuropsychopharmacology", Proceedings of the Meeting of the Collegium Internationale Neuro-Psychopharmacologicum, 4th, Birmingham, England, Aug 31–Sept 3, 1964, Elsevier, Amsterdam, 1965, p 518.

(2) A. Dolphine, P. Jenner, C. D. Marsden, C. Pycock, and D. Tarsy, *Psychopharmacologia*, **41**, 133 (1975).

(3) (a) K. Takahashi, M. Murakami, Y. Hirata, M. Takashima, S. Iwanami, O. Hasegawa, and S. Usuda, Japan Kokai 52128368 (1977); U.S. Patent 4097487 (1978). (b) M. Takashima, S. Iwanami, and S. Usuda, U.S. Patent 4210660 (1980).

(4) S. Usuda, K. Sano, and H. Maeno, *Arch. Int. Pharmacodyn. Ther.*, **241**, 68 (1979).

(5) O. Vinař and M. Kršiak, "The Phenothiazines and Structurally Related Drugs", Raven Press, New York, 1974, p 675.

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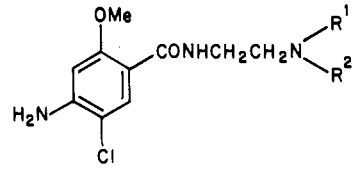
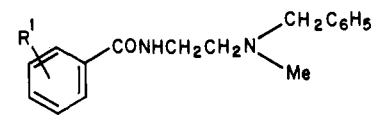
Table I. Chemical and Pharmacological Data on *N*-[2-(N-Substituted-amino)ethyl]benzamides (I, 1-31)



1-22



23-31

compd	R^1	R^2	method	yield, %	mp, °C	recrystn solvent	formula	inhibn of stereotypy: ED_{50},[a] mg/kg sc
metoclopramide	Et	Et						3.1 (1.8-5.3)
1	$C_6H_5CH_2$	Et	B	73	96-98	toluene/*n*-hexane	$C_{19}H_{24}ClN_3O_2$	0.31 (0.18-0.54)
2	furfuryl	Et	B	97	109	*i*-PrOH	$C_{17}H_{22}ClN_3O_3$	3
3	2-pyridylmethyl	Et	A	47	100-101	AcOEt	$C_{18}H_{23}ClN_4O_2 \cdot 0.25H_2O$	30
4[b]	H	Et						>30
5	$C_6H_5CH(Me)$	Me	A	72	139-140	AcOEt	$C_{19}H_{24}ClN_3O_2$[c]	1
6	$C_6H_{11}CH_2$	Me	A	28	115-118	benzene/*n*-hexane	$C_{18}H_{28}ClN_3O_2$	3
7	$2\text{-}MeOC_6H_4CH_2$	Et	A	80	119-120	toluene	$C_{20}H_{26}ClN_3O_3$	10
8	$3\text{-}MeOC_6H_4CH_2$	Et	A	77	109-110	AcOEt	$C_{20}H_{26}ClN_3O_3$	1
9	$4\text{-}MeOC_6H_4CH_2$	Et	A	84	117-119	AcOEt	$C_{20}H_{26}ClN_3O_3$	0.2
10	$2\text{-}ClC_6H_4CH_2$	Et	A	76	110-111	toluene	$C_{19}H_{23}Cl_2N_3O_2$	10
11	$3\text{-}ClC_6H_4CH_2$	Et	A	74	128-130	toluene	$C_{19}H_{23}Cl_2N_3O_2$	0.58 (0.30-1.1)
12	$4\text{-}ClC_6H_4CH_2$	Et	A	76	127-128	toluene	$C_{19}H_{23}Cl_2N_3O_2$	0.24 (0.12-0.47)
13	$2,4\text{-}Cl_2C_6H_3CH_2$	Et	B	74	95-96	MeOH/ether	$C_{19}H_{22}Cl_3N_3O_2$	10
14	$4\text{-}FC_6H_4CH_2$	Et	B	79	127-128	MeOH	$C_{19}H_{23}ClFN_3O_2$[d]	0.20 (0.12-0.37)
15	$2\text{-}MeC_6H_4CH_2$	Me	B	80	118-120	toluene/*n*-hexane	$C_{19}H_{24}ClN_3O_2$	2
16	$2\text{-}CF_3C_6H_4CH_2$	Me	B	58	149	toluene	$C_{19}H_{21}ClF_3N_3O_2$	30
17	$C_6H_5CH_2$	Me	B	64	119-120	benzene/*n*-hexane	$C_{18}H_{22}ClN_3O_2$	0.38 (0.21-0.67)
18	$4\text{-}ClC_6H_4CH_2$	*n*-Pr	B	64	108-109	*i*-PrOH	$C_{20}H_{25}Cl_2N_3O_2$	3
19	$4\text{-}ClC_6H_4CH_2$	*i*-Pr	B	78	121	*i*-PrOH	$C_{20}H_{25}Cl_2N_3O_2$	3
20	$4\text{-}ClC_6H_4CH_2$	*n*-Bu	B	85	115-116	MeOH	$C_{21}H_{27}Cl_2N_3O_2$	20
21	$C_6H_5CH_2$	*t*-Bu	A	72	134-135	*i*-PrOH	$C_{21}H_{28}ClN_3O_2 \cdot 0.25H_2O$	>30
22	$C_6H_5CH_2$	$C_6H_5CH_2$	B	65	133	toluene	$C_{27}H_{26}ClN_3O_2$	>30
23	2-MeO,4-MeNH, 5-Cl		C	58	213-214	EtOH	$C_{19}H_{24}ClN_3O_2 \cdot HCl$	0.21 (0.12-0.37)
24	2-MeO, 4-Me_2N, 5-Cl		A	65	138-139	*i*-PrOH	$C_{20}H_{26}ClN_3O_2 \cdot C_4H_4O_4$[e]	0.54
25	2-MeO, 5-Cl		C	65	158-159	*i*-PrOH	$C_{18}H_{21}ClN_2O_2 \cdot HCl$	3
26	$2,5\text{-}(MeO)_2$		C	77	130	*i*-PrOH/ether	$C_{19}H_{24}N_2O_3 \cdot HCl$	3
27	2-MeO, 5-H_2NSO_2		D	88	202-203	*i*-PrOH/MeOH	$C_{18}H_{23}N_3O_4S$	>30
28	2-MeO, 5-$EtNHSO_2$		D	64	132-133	MeOH	$C_{20}H_{27}N_3O_4S$	>30
29	2-MeO, 5-$MeSO_2$		B	89	129-130	*i*-PrOH/MeOH	$C_{19}H_{24}N_2O_4S$	3
30	4-F		C	81	182-183	*i*-PrOH	$C_{17}H_{19}FN_2O \cdot HCl$	>30
31[f]	$3,4,5\text{-}(MeO)_3$							>30

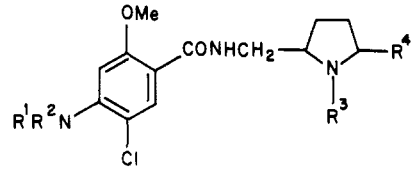
[a] ED_{50}, the dose to inhibit induction of the stereotypy in 50% of the rats, was estimated according to either the method of Litchfield and Wilcoxon[11] or the graphical method; 95% confidence limits are included in parentheses. [b] Known as a metabolite of metoclopramide: I. Inoue, O. Toyonari, Y. Yamada, and J. Tani, Japan Kokai, 75 24 240 (1975); *Chem. Abstr.*, 83, 78913*h* (1975). [c] C: calcd, 63.06; found, 63.71. [d] C; calcd, 60.08; found, 60.50. [e] Fumarate. [f] Bristol Laboratories Inc., British Patent 797 476; *Chem. Abstr.*, 53, 11417*e* (1959).

ability to inhibit a conditioned avoidance and to induce catalepsy in rats and are discussed in comparison with metoclopramide and haloperidol.

Chemistry. The benzamide derivatives discussed in this paper have the alkane-1,2-diamine part as a common structural unit and may be classified into the following three series according to the structures of their amine parts: (1) benzamides of N,N-disubstituted ethylenediamines (series I, compounds **1–31**; analogues of metoclopramide), (2) benzamides of 1-substituted 2-(aminomethyl)pyrrolidines (series II, compounds **32–39**; analogues of sulpiride), and (3) benzamides of 1-substituted 3-aminopyrrolidines (series III, compounds **40–55**).

Most of the benzamides were synthesized by the reaction of a substituted benzoic acid (**56**) with an ethylenediamine (**57**), a 2-(aminoethyl)pyrrolidine (**58**), or a 3-aminopyrrolidine (**59**) as shown in Scheme I. Some of *p*-(acylamido) derivatives (**52** and **53**) were synthesized from the benzamide **41** by acylation with an appropriate acid anhydride. The melting points and yields of the novel ben-

Table II. Chemical and Pharmacological Data on *N*-(1-Substituted-pyrrolidin-2-ylmethyl)benzamides (II, 32-39)

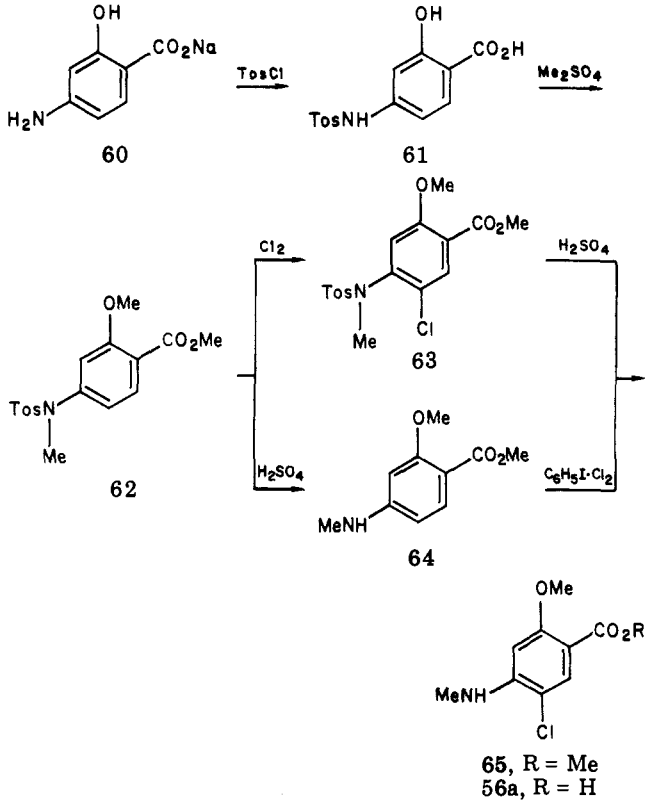


32-39

compd	R^1	R^2	R^3	R^4	method	yield, %	mp, °C	recrystn solvent	formula	inhibn of stereotypy: ED_{50},[a] mg/kg sc
32[b]	H	H	$C_6H_5CH_2$	H						1.1 (0.63-1.9)
33	H	H	$C_6H_5CH_2$	Me[c]	B	77	136-137	*i*-PrOH	$C_{21}H_{26}ClN_3O_2$	0.67 (0.41-1.1)
34	Me	H	$C_6H_5CH_2$	H	B	61	213-215 dec	*i*-PrOH	$C_{21}H_{26}ClN_3O_2 \cdot HCl$	0.94 (0.56-1.5)
35	Me	H	$C_6H_5CH_2$	Me[c]	B	62	220-225 dec	EtOH	$C_{22}H_{28}ClN_3O_2 \cdot HCl \cdot 0.25H_2O$	0.35 (0.20-0.62)
36[d]	H	H	Et	H						>30
37	Me	H	Et	C_6H_5	B	95	187-188	*i*-PrOH/MeOH	$C_{21}H_{26}ClN_3O_2 \cdot 0.25H_2O$	>30
38[e]	Me	H			A	73	185-186	*i*-PrOH	$C_{19}H_{22}ClN_3O_2$	1
39	Me	Me	C_6H_{11}	H	A	60	130-131	AcOEt/EtOH	$C_{21}H_{32}ClN_3O_2 \cdot C_2H_2O_4$[f]	>30
sulpiride										>100
sultopride										18

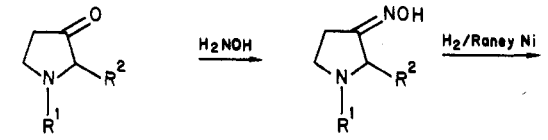
[a] See Table I, footnote *a*. [b] G. Bulteau, J. Acher, and J. C. Monier, German Offen., 2 508 045; *Chem. Abstr.*, 84, 30876*s* (1976). [c] One of the stereoisomers, and configuration of the methyl group was undetermined. [d] H. Moriyama, H. Yamamoto, H. Inaba, and S. Katayama, Japan Kokai, 75 35 126, *Chem. Abstr.*, 83, 78917*n* (1975). [e] *N*-(1-Ethyl-2-isoindolinyl)-4-amino-5-chloro-2-methoxybenzamide. [f] Oxalate.

Scheme II



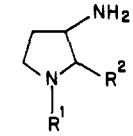
65, R = Me
56a, R = H

Scheme III



66a, $R^1 = C_6H_5CH_2$; R^2 = H
b, $R^1 = C_6H_5CH_2$; R^2 = Me
c, R^1 = Et; R^2 = H

67a, $R^1 = C_6H_5CH_2$; R^2 = H
b, $R^1 = C_6H_5CH_2$; R^2 = Me
c, R^1 = Et; R^2 = H



59a, $R^1 = C_6H_5CH_2$; R^2 = H
cis-**59b**, $R^1 = C_6H_5CH_2$; R^2 = Me (2,3-cis)
trans-**59b**, $R^1 = C_6H_5CH_2$; R^2 = Me (2,3-trans)
59c, R^1 = Et; R^2 = H

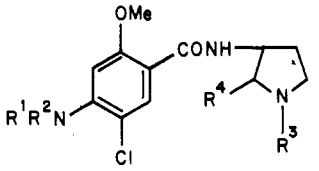
zamides prepared are shown in Tables I–III.

A number of benzoic acids were prepared by known methods. 5-Chloro-2-methoxy-4-(methylamino)benzoic acid (**56a**), a starting material of compound **55**, was prepared according to Scheme II. Monomethylation of the *p*-amino group of compound **60** was performed using the tosyl group as an amino-protecting group to afford compound **62**. Then, **62** was treated with chlorine and subsequently detosylated to give methyl 5-chloro-2-methoxy-4-(methylamino)benzoate (**65**) in high yield. In the case of detosylated derivative **64** however, the reaction with chlorine gave not only the 5-chlorinated compound **65** but also oxidized products and some other impurities, while a reaction with iodobenzene dichloride instead of chlorine afforded compound **65** exclusively. Alkaline hydrolysis of compound **65** gave the desired benzoic acid **56a**.

On the other hand, ethylenediamines (**57**) used as the starting materials were prepared from the corresponding N,N-disubstituted aminoacetonitriles by reduction with lithium aluminum hydride in ether or tetrahydrofuran. 1-Substituted 2-(aminoethyl)pyrrolidines (**58**) were prepared by catalytic hydrogenation of the corresponding 2-(nitromethylene)pyrrolidines, which were easily obtained from 1-substituted 2-pyrrolidinones as described by Meerwein et al.[6] Since the synthesis of 1-benzyl-3-

(6) H. Meerwein, W. Florian, N. Schon, and G. Stopp, *Justus Liebigs Ann. Chem.*, 641, 1 (1961).

Table III. Chemical and Pharmacological Data on *N*-(1-Substituted-pyrrolidin-3-yl)benzamides (III, **40**-55)



compd	R^1	R^2	R^3	R^4	method	yield, %	mp, °C	recrystn solvent	formula	inhibn of stereotypy: ED_{50},[a] mg/kg sc
40	H	H	$C_6H_5CH_2$	H	A	73	116-118	benzene/*n*-hexane	$C_{19}H_{22}ClN_3O_2$	0.17 (0.11-0.26)
41	Me	H	$C_6H_5CH_2$	H	B	81	100	MeOH	$C_{20}H_{24}ClN_3O_2$	0.016 (0.0092-0.026)
42	Me	Me	$C_6H_5CH_2$	H	A	62	85-86	ether	$C_{21}H_{26}ClN_3O_2$	0.12 (0.08-0.19)
43[b]	H	H	C_6H_{11}	H						1.8
44	Me	H	Et	H	B	20	109-112	AcOEt	$C_{15}H_{22}ClN_3O_2$	10
45	Me	Me	C_6H_{11}	H	B	86	158-157	*i*-PrOH/AcOEt	$C_{20}H_{30}ClN_3O_2 \cdot HCl$	1.0
46	Et	H	$C_6H_5CH_2$	H	B	69	179-180	EtOH	$C_{21}H_{26}ClN_3O_2 \cdot C_4H_4O_4$[c]	0.1
47	*n*-Pr	H	$C_6H_5CH_2$	H	B	70	192-193	*i*-PrOH	$C_{22}H_{28}ClN_3O_2 \cdot HCl$	17 (11.9-24.3)
48	$C_6H_5CH_2$	H	$C_6H_5CH_2$	H	B	80	172-173	MeOH/*i*-PrOH	$C_{26}H_{28}ClN_3O_2 \cdot C_4H_4O_4$[c]	>30
49	$-(CH_2)_4-$		$C_6H_5CH_2$	H	C	71	198-200	*i*-PrOH	$C_{23}H_{28}ClN_3O_2 \cdot HCl \cdot H_2O$	0.6
50	CHO	H	$C_6H_5CH_2$	H	B	47	100-101	ether	$C_{20}H_{22}ClN_3O_3$	0.6
51	MeCO	H	$C_6H_5CH_2$	H	B	32	117-119	EtOH	$C_{21}H_{24}ClN_3O_3 \cdot 0.5C_4H_4O_4 \cdot EtOH$[d]	1.8
52	MeCO	Me	$C_6H_5CH_2$	H	*e*	53	221-222	EtOH	$C_{22}H_{26}ClN_3O_3 \cdot HCl$	>30
53	CF_3CO	Me	$C_6H_5CH_2$	H	*e*	48	195-196	EtOH/ether	$C_{22}H_{23}ClF_3N_3O_3 \cdot HCl$	0.3
54	Me	H	$C_6H_5CH_2$	Me (trans)	B	80	232 dec	EtOH	$C_{21}H_{26}ClN_3O_2 \cdot HCl$	0.057 (0.037-0.088)
55	Me	H	$C_6H_5CH_2$	Me (cis)	B	91	150	*i*-PrOH	$C_{21}H_{26}ClN_3O_2$	0.0076 (0.0054-0.011)
metoclopramide										3.1 (1.8-5.3)
haloperidol										0.095 (0.044-0.2)

[a] See Table I, footnote *a*. [b] See ref 10. [c] Fumarate. [d] Maleate. [e] See Experimental Section.

aminopyrrolidine (**59a**) by the Gabriel method from 1-benzyl-3-hydroxypyrrolidine, which was prepared from butanetriol of 1-benzyl-3-pyrrolidinone (**66a**), was unsatisfactory in yield,[7] we have tried to synthesize compound **59a** by another method. Compound **59a** was prepared by reaction of **66a** with hydroxylamine and subsequent hydrogenation with Raney nickel in the presence of ammonia in methanol, in an overall yield of 87% (Scheme III). Moreover, 3-amino-1-benzyl-2-methylpyrrolidine (**59b**) and some of the new alkylated 3-aminopyrrolidines could also be prepared by this method in high yields.[8] The cis isomer of **59b** was isolated as the crystalline fumarate salt by the treatment of a diastereomeric mixture of **59b** with fumaric acid in water. On the other hand, the trans isomer of **59b** was isolated as the crystalline maleate salt by the treatment of a trans-rich diastereomeric mixture of **59b**, which was obtained from the mother liquor of the fumarate salt, with maleic acid in ethanol. The structures of *cis*- and *trans*-**59b** were determined by the results of an X-ray analyis as well as NMR spectroscopy with shift reagents,[9] and their purities were checked by gas chromatography.

Pharmacology. Structure–Activity Discussion. The neuroleptic activities of the benzamides were determined by their inhibitory effects on apomorphine-induced stereotyped behavior in rats. The method is described under Experimental Section.

At first, effects of the substituents on metoclopramide-like linear benzamides were investigated. As shown in Table I, the introduction of a benzyl group on the terminal nitrogen instead of an ethyl group significantly enhanced the activity. Compound 1 was found to be about 10 times as active as metoclopramide. This result suggests that the introduction of the lipophilic benzyl group has facilitated the penetration of the compound through the blood–brain barrier. Although our attempts were made to further enhance the activity of compound 1 by varying the N-substituents, we could find none of the more active compounds having a benzyl-like heterocyclic or aliphatic substituent on the terminal nitrogen (compond **2**–**6**). Since the *N*-benzyl group seemed to be one of the most potent substituents, the effects of the substituents on the benzyl group were investigated. Although the substituents on the benzyl group were not as influential as expected, *p*-chloro or *p*-fluoro substituents (compounds **12** and **14**) proved to slightly enhance the activity. On the contrary, an ortho substituent almost invariably decreased the activity (compounds **7**, **10**, **13**, and **16**). These results suggest that the antiapomorphine activity of the benzamides is closely related to the steric factor rather than the electronic factor of the substituent on the benzyl group. We investigated variation of the R^2 substituent while keeping the benzyl

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(8) (a) S. Iwanami and M. Takashima, Japan Kokai, 53 28 161; 28 163 (1978); *Chem. Abstr.*, *89*, 109065p (1978). (b) M. Takashima, S. Iwanami, and S. Usuda, Japan Kokai, 55 22 699 (1980).
(9) The X-ray analysis was performed with compounds **54** and **55**. The data of the conformational analysis of the compounds by X-ray and NMR will be published elsewhere.

Table IV. Pharmacological Data on Benzamides

compd	ED_{50}, mg/kg sc: inhibition: stereotypy[a]	inhibition: avoidance[b]	induction: catalepsy[c]	ED_{50} (catalepsy)/ ED_{50} (stereotypy)
23	0.21	0.041	16.5 (8.38-32.5)	79
35	0.35	0.11	13.5 (6.02-30.3)	39
41	0.016	0.008	1.6 (0.74-3.48)	100
55	0.0076	0.0034	0.50 (0.29-0.86)	66
metoclopramide	3.1	2.6	26.0 (12.5-54.2)	8.4
haloperidol	0.095	0.021	1.0 (0.48-2.1)	11

[a] ED_{50} was quoted from Tables I-III. [b] The inhibitory effect on the continuous avoidance was expressed as the dose to increase the number of electroshocks by 60 (1 shock/min) between 1 and 2 h after the subcutaneous administration. [c] ED_{50}, the dose to induce catalepsy in 50% of the rats, was estimated according to the method of Litchfield and Wilcoxon;[11] 95% confidence limits are included in parentheses.

substituent (R^1 = $C_6H_5CH_2$ or p-$ClC_6H_4CH_2$) on the terminal nitrogen constant, and it was found that the activity decreases in the order of Et ≥ Me > n-Pr = i-Pr > n-Bu > t-Bu, $C_6H_5CH_2$ (compounds **1**, **12**, and **17–22**). Next, effects of the substituents on the p-amino group on the benzoyl moiety were examined. It was found that monomethylation of the p-amino substituent on the benzoyl group of compound **17** increased the activity. The potency of the methylamino derivative **23** was about 15 times as great as metoclopramide. On the other hand, the dimethylamino derivative **24** exhibited less potent activity than compound **17**.

Variation of the substituents on the benzoyl group was also tried, but no improvement of the potency was achieved (compounds **25–31**). The 5-chloro-2-methoxy-4-(methylamino)benzoyl group appeared to be the most potent one among the groups examined.

Although antiemetic and neuroleptic activities of some compounds, such as **32**, sulpiride, and sultopride, in the second series [analogues of the benzamide of 2-(aminomethyl)pyrrolidine] had been reported,[2] every compound in Table II was reevaluated by our method. As in the case of the linear benzamides, the N-benzyl group also played a very important role in the inhibitory activity. N-Benzyl analogues (**32–35**) exhibited a fairly high activity, whereas N-ethyl analogues (**36**, **37**, **39**, sulpiride, and sultopride) were decidedly less active. Introduction of a methyl group into the 5 position of the pyrrolidine ring enhanced the activity of the N-benzyl analogues (**33** and **35** vs. **32** and **34**, respectively).

As regards the third series, ED_{50} values for the 4-amino-5-chloro-2-methoxybenzamides of 3-aminopyrrolidines are summarized in Table III. In this type of compound, compound **43** had already been reported to have a potent antiemetic activity.[10] In this study, compound **43** and the novel compounds synthesized were evaluated for their inhibitory effects on apomorphine-induced stereotyped behavior in rats. As expected, the N-benzyl analogues were also more active than the others (compounds **40**, **41**, and **42** vs. **43**, **44**, and **45**, respectively). Furthermore, the p-(methylamino) group on the benzoyl moiety played a more important role in this series (compound **41** vs. **40**) than in the above-mentioned two series, and compound **41** was about 200 times more active than metoclopramide. With substituents other than methyl in the p-amino group, only the ethyl group (compound **46**) slightly enhanced the activity of the mother compound **40**. As the size of the alkyl substituents became larger, the activity decreased (compounds **46–49** vs. **41**). Acylation of the p-amino group also reduced the activity (compounds **50–53**). Introduction of a methyl group into the 2 position of the pyrrolidine ring of compound **41** afforded two stereoisomers (**54** and **55**). While the trans isomer **54** was less active, the cis isomer **55** exhibited a more potent activity than the mother compound **41**. This result may be due to the differences in the conformation between the two pyrrolidine rings. In addition, the cis isomer (**55**) exhibited the most potent activity among all of the compounds tested, being 13 and 408 times more potent than haloperidol and metoclopramide, respectively.

Tests for inhibition of avoidance response and induction of catalepsy were performed with the most interesting compounds only, and the results are listed in Table IV. In general, the inhibitory activity in the avoidance response was found to be well correlative with that in stereotypy. On the other hand, there was no correlation of the potency between the induction of catalepsy, which is related to the extrapyramidal side effect, and the inhibition of stereotypy (or avoidance response). As shown in the last column of Table IV, our compounds (**23**, **35**, **41**, and **55**) exhibited fairly high ratios of the inhibitory activity to cataleptogenicity compared with metoclopramide and haloperidol and were proved to be selective for the inhibitory activities.

Of these derivatives, compound **55** is expected to be a potent drug with few side effects for the treatment of psychosis.

Experimental Section

Melting points and boiling points are uncorrected. The structures of the compounds were supported by NMR, mass spectrometry, and IR. All solid compounds were analyzed (C, H, and N), and values obtained were within ±0.4% of the theoretical values unless otherwise indicated. NMR spectra were recorded with a JEOL MH100 using Me_4Si as an internal standard. Mass spectra were obtained on a Hitachi RMU-6Mg double-focusing mass spectrometer. IR spectra were determined on a Hitachi 215 spectrometer. GC data were collected on a Hewlett Packard GC-5730A. The organic solutions were dried over $MgSO_4$, and all evaporations were carried out under reduced pressure.

General Procedure for the Preparation of Benzamides. Ethyl chloroformate (0.54 g, 5 mmol) was added to a stirred solution of the appropriate benzoic acid (5 mmol) and triethylamine (0.6 g, 5.9 mmol) in 30 mL of dry methylene chloride at −10 to −40 °C. The reaction mixture was stirred for an additional 30 min, and then the appropriate amine (5 mmol) was added to the mixture at the same temperature. The cold bath was removed and the solution was further stirred for 2 h at room temperature. Each product was isolated according to the respective method (A, B, or C) mentioned below.

Method A. The reaction mixture was washed with water and extracted with 20 mL of 0.5 N hydrochloric acid. The extract was basified with 1 N sodium hydroxide, and the product that separated was extracted three times with 20 mL each of methylene chloride. The combined extracts were washed with water, dried, and evaporated. The residue that was obtained was recrystallized to give the product. Some of the products were isolated as salts.

(10) A. D. Cale, Jr., and C. A. Leonard, U.S. Patent 3966975 (1976).

Method B. The reaction mixture was washed with water, 1 N sodium hydroxide solution, and water. The organic layer was dried and evaporated. The residue obtained was recrystallized to give the product. Some of the products were isolated as salts.

Method C. The reaction mixture was washed with water, 5 mL of 1 N sodium hydroxide solution, water, 20 mL of 0.5 N hydrochloric acid, and water. The organic layer was dried and evaporated. The residue obtained was recrystallized from 2-propanol or ethanol to give a hydrochloride salt of the corresponding benzamide.

Method D. Ethyl chloroformate (0.54 g, 5 mmol) was added to a stirred solution of the appropriate benzoic acid (5 mmol) and triethylamine (0.6 g, 5.9 mmol) in a mixture of hexamethylphosphoric triamide (10 mL) and methylene chloride (10 mL) at −10 to −40 °C. The reaction mixture was stirred for an additional 30 min, and then the appropriate amine (5 mmol) was added at the same temperature. The cold bath was removed and the solution was stirred for 2 h at room temperature. The reaction mixture was acidified with 1 N hydrochloric acid and extracted twice with 50 mL each of water. The combined aqueous extracts were basified with sodium hydroxide solution, and the crystals that precipitated were collected by filtration and recrystallized.

4-(*N*-Acetyl-*N*-methylamido)-*N*-(1-benzylpyrrolidin-3-yl)-5-chloro-2-methoxybenzamide (52). Compound 41 (1.87 g, 5.0 mmol) was refluxed in a mixture of acetic anhydride (2.0 g, 19.6 mmol) and acetic acid (10 mL) for 4 h. The solvent was evaporated and the resulting residue was extracted with 20 mL of methylene chloride. The extract was washed with 1 N sodium hydroxide and condensed. A mixture of 0.5 mL of concentrated hydrochloric acid and 5 mL of 2-propanol was added to the residue and triturated to afford crystals. Recrystallization from ethanol gave 1.2 g (53%) of the crystalline compound **52**.

***N*-(1-Benzylpyrrolidin-3-yl)-5-chloro-2-methoxy-4-[*N*-methyl-*N*-(trifluoroacetyl)amido]benzamide (53).** A solution of 1.39 mL of trifluoroacetic anhydride in 10 mL of methylene chloride was added to a solution of compound 41 (1.25 g, 3.34 mmol) and triethylamine (1.4 mL) in 50 mL of methylene chloride at −30 °C. The cold bath was removed, and the solution was stirred for 10 min, washed with water, and dried. Hydrogen chloride was then passed through the solution and the solvent was evaporated. The residue was extracted with 10 mL of ethanol, and 100 mL of ether was added to the extract. The crystals that precipitated were collected by filtration. This reprecipitation was repeated to afford 0.8 g (48%) of crystalline compound **53**.

4-(Tosylamido)salicylic Acid (61). Tosyl chloride (15.2 g, 80 mmol) was added to a solution of sodium 4-aminosalicylate dihydrate (**60**; 14.0 g, 66 mmol) and sodium carbonate (0.7 g, 6.6 mmol) in 27 mL of water at 75–80 °C. The mixture was stirred for 10 min at the same temperature, followed by the addition of aqueous sodium hydroxide (24%, 13 mL) to the mixture. After stirring for an additional 10 min, the mixture was cooled to 40 °C. To the mixture were added 14 mL of water and 22 mL of 13% hydrochloric acid with stirring. The mixture was allowed to stand for 1 h in an ice–water bath, and the precipitate was collected by filtration, washed with water, and dried overnight at 55 °C to give 18 g (88.5%) of crude compound **61**. Recrystallization from ethanol gave colorless crystals for analysis, mp 238–240 °C. Anal. ($C_{14}H_{13}NO_5S$) C, H, N.

Methyl 2-Methoxy-4-(*N*-methyl-*N*-tosylamido)benzoate (62). The crude tosylate **61** (18 g, 58.6 mmol) was stirred with potassium hydroxide (11.5 g, 288 mmol) in 140 mL of acetone at room temperature for 20 min. To the mixture was added dimethyl sulfate (23.2 g, 184 mmol) at such a rate that boiling was maintained. The mixture was heated under reflux for 2 h and cooled. After the solvent was evaporated, 115 mL of water was added to the residue, and the product was extracted with 57 mL of ethyl acetate. The extract was dried and condensed, and 18 mL of 2-propanol was added to the oily residue. The mixture was allowed to stand overnight at 4 °C. The crystals that precipitated were filtered, washed with cold 2-propanol, and dried to yield 12.8 g (62.5%) of compound **62**, mp 98–99 °C. Anal. ($C_{17}H_{19}NO_5S$) C, H, N.

Methyl 5-Chloro-2-methoxy-4-(*N*-methyl-*N*-tosylamido)benzoate (63). Chlorine was passed into a solution of compound **62** (12.8 g, 36.7 mmol) in 39 mL of chloroform at 3–10 °C until there was no further disappearance of the yellow color. The solvent was evaporated and the residue was recrystallized from 97 mL of 2-propanol to yield 13.0 g (93%) of compound **63**, mp 136–139 °C. Anal. ($C_{17}H_{18}ClNO_5S$) C, H, N.

5-Chloro-2-methoxy-4-(methylamino)benzoic Acid (56a) and Methyl Ester (65). To 15.8 mL of concentrated sulfuric acid were added the crystals of compound **63** (13 g, 56.6 mmol) with stirring at a temperature below 50 °C in an ice bath. After the crystals were dissolved, the reaction mixture was poured over crushed ice (25 g) with vigorous stirring. The precipitate was collected by filtration and washed with water. The product was recrystallized from ethyl acetate to give compound **65**, mp 129–130 °C. Anal. ($C_{10}H_{12}ClNO_3$) C, H, N.

The crude crystals of compound **65** that were obtained above were heated at 80 °C in aqueous sodium hydroxide (3.7%, 50 mL) until they were completely dissolved. To the reaction mixture were added 25 mL of water and 6 N hydrochloric acid (11.5 mL) with stirring at 10 °C. The precipitate that formed was collected by filtration, washed with cold water, and recrystallized from 125 mL of 2-propanol to yield 5.3 g (72%) of compound **56a**, mp 188–189 °C. Anal. ($C_9H_{10}ClNO_3$) C, H, N. Compound **56a** was also prepared from compound **62** by initial hydrolysis of the ester, chlorination, followed by detosylation.

Preparation of N,N-Disubstituted 1,2-Ethanediamines: *N*-(4-Chlorobenzyl)-*N*-*n*-propyl-1,2-ethanediamine (57). To a suspension of lithium aluminum hydride (4.0 g, 105 mmol) in 50 mL of dry ether was added a solution of [*N*-(4-chlorobenzyl)-*N*-*n*-propylamino]acetonitrile (10.4 g, 46.7 mmol) in 50 mL of ether at −30 °C with stirring for 10 min. After the cold bath was removed, the mixture was stirred for an additional 1 h at room temperature. An aqueous sodium hydroxide solution was then added dropwise to the mixture at a temperature below 0 °C to destroy the excess lithium aluminum hydride, and the precipitate was removed by filtration. The filtrate was evaporated and the residue was distilled to give 8.2 g (76%) of the product: bp 169–174 °C (16 mm); MS, *m/e* 226 (M^+).

1-Benzyl-3-(hydroxyimino)pyrrolidine (67a). To a solution of hydroxylamine hydrochloride (6.5 g, 93.5 mmol) and sodium carbonate (5.5 g, 51.9 mmol) in 60 mL of water was added a solution of 1-benzyl-3-pyrrolidinone (**66a**; 8.2 g, 46.9 mmol) in 40 mL of ethanol at 5–10 °C. The reaction mixture was allowed to stand overnight at 5 °C. The colorless needles that precipitated were collected by filtration, washed with ice–water, and dried to afford 6.0 g (67%) of compound **67a**. Extraction of the mother liquor with 20 mL of ether afforded another 2.8 g (31%) of compound **67a**: mp 120–125 °C dec. Anal. ($C_{11}H_{14}N_2O$) C, H, N.

3-Amino-1-benzylpyrrolidine (59a). A suspension of compound **67a** (7.0 g, 36.8 mmol) and Raney nickel (~2 g) in 100 mL of methanol containing ammonia was shaken with hydrogen until 2 equimolar amounts of hydrogen were absorbed under atmospheric or elevated pressure. The catalyst was removed by filtration and the filtrate was evaporated. The residue obtained was distilled to give a colorless liquid of **59a**: yield 5.3 g (82%); bp 76 °C (0.2 mm); MS *m/e* 176 (M^+).

1-Benzyl-3-(hydroxyimino)-2-methylpyrrolidine (67b). To a solution of hydroxylamine hydrochloride (25.7 g, 360 mmol) in a mixture of 50 mL of water and 80 mL of methanol was added a solution of 1-benzyl-2-methyl-3-pyrrolidinone (**66b**; 35 g, 185 mmol) in 20 mL of methanol at such a rate that the temperature was maintained at about 30 °C. Potassium carbonate (25.8 g, 206 mmol) was added to the mixture, and the mixture was stirred for 30 min at room temperature. To the mixture was added 72 mL of water, and the mixture was further stirred overnight at room temperature; then 200 mL of water was added to the mixture and it was stirred for an additional 1 h. The colorless crystals that precipitated were collected by filtration, washed with cold water, and dried to afford 35.0 g (88.4%) of compound **67b**: mp 97–99 °C dec. Anal. ($C_{12}H_{16}N_2O$) C, H, N.

3-Amino-1-benzyl-2-methylpyrrolidine (59b). A suspension of compound **67b** (4.0 g, 19.6 mmol) and Raney nickel (~1 g) in a mixture of methanol (12 mL) and concentrated aqueous ammonia (4 mL) was shaken with hydrogen until 2 equimolar amounts of hydrogen were absorbed. The catalyst was removed by filtration and the solvent was evaporated. The residual liquid was distilled to afford 2.7 g (72%) of compound **59b**: bp 102–103 °C (0.4 mm); GC (OV-22, 3%; 180-cm column, at 160 °C) indicated

that compound **59b** consisted of 54% *cis* isomer and 46% trans isomer; MS, *m/e* 190 (M^+).

***cis*-3-Amino-1-benzyl-2-methylpyrrolidine (*cis*-59b).** To a suspension of fumaric acid (48.8 g, 421 mmol) in 260 mL of water was added compound **59b** (80 g, cis 54%) with stirring at 20–30 °C. The suspension at once became clear, and colorless crystals precipitated. The mixture was further stirred in an ice bath for 1 h and the salt that precipitated was collected by filtration. Recrystallization of this salt from water gave 49 g (27%) of *cis*-**59b** difumarate hemihydrate, mp 185–186 °C. Anal. [$C_{12}H_{18}N_2 \cdot (C_4H_4O_4)_2 \cdot 0.5H_2O$] C, H, N. The salt was basified with aqueous sodium hydroxide, and the oil that liberated was extracted with ether. The extract was dried and condensed. The residual liquid was distilled to give 21 g of colorless liquid *cis*-**59b**: bp 102–103 °C (0.4 mm); NMR ($CDCl_3$) δ 7.3 (s, 5), 3.9 (d, 1), 3.2 (m, 1), 3.1 (d, 1), 2.8 (m, 1), 2.3 (s, 1), 2.0 (m, 2), 1.5 (m, 1), 1.4 (s, 2, NH_2), 1.1 (d, 3, CH_3); MS, *m/e* 190 (M^+).

***trans*-3-Amino-1-benzyl-2-methylpyrrolidine (*trans*-59b).** A trans-rich **59b** component (trans 75%, by GC) was obtained from the first filtrate of the *fumarate formation method* mentioned for *cis*-**59b** by basification and extraction with ether, followed by distillation, bp 102–103 °C (0.4 mm). This **59b** component (19 g, 100 mmol) was added to a solution of maleic acid (17.5 g, 150 mmol) in 190 mL of ethanol, and the mixture was allowed to stand overnight at room temperature. The crystals of the salt that separated were recrystallized at first from 50% aqueous ethanol and an additional two times from water to afford 8.4 g (20%) of *trans*-**59b** dimaleate, mp 169–170 °C. Anal. [$C_{12}H_{18}N_2(C_4H_4O_4)_2$] C, H, N. The salt was basified with aqueous sodium hydroxide. The free base liberated was extracted with ether, the extract was dried, and the solvent was evaporated. The residual liquid was distilled to give 3.4 g of a colorless liquid of *trans*-**59b**: bp 102–103 °C (0.4 mm); NMR ($CDCl_3$) δ 7.3 (s, 5), 3.9 (d, 1), 3.2 (d, 1), 2.9 (m, 2), 2.2 (m, 3), 1.4 (m, 1), 1.4 (s, 2, NH_2), 1.2 (t, 3, CH_3); MS, *m/e* 190 (M^+).

Pharmacology. Inhibition of Apomorphine-Induced Stereotyped Behavior in Rats. The method of Janssen et al.[11] was used with a slight modification. The rats were observed in individual cages (21 × 21 × 17 cm) with clear plastic walls. A dose of 1.25 mg/kg of apomorphine was injected intravenously into the rats 30 min after subcutaneous administration of test drugs. Inhibitory effects of the drugs on stereotyped behavior were judged to be positive unless both gnawing and licking behaviors were observed for the period of 20 min after apomorphine injection. ED_{50}, the dose to inhibit induction of the stereotypy in 50% of the rats, was estimated according to either the method of Litchfield and Wilcoxon[12] or the graphical method using 6 to 12 rats at each dose.

Continuous Avoidance Response in Rats. The continuous avoidance response was designed according to the Sidman avoidance schedule with a slight modification. The shock–shock and response–shock intervals were 5 and 25 s, respectively. The rats which received less than 19 shocks per hour were used for further experiments. The inhibitory effect of the test drugs was expressed as the dose to increase the number of electroshocks by 60 (1 shock/min) between 1 and 2 h after the subcutaneous administration.

Catalepsy in Rats. Two front paws of rats were placed on a horizontal wooden bar at 7 cm from the floor 30 min after subcutaneous administration of test drugs. The ED_{50}, the dose to induce catalepsy in 50% of the rats, was estimated according to the method of Litchfield and Wilcoxon[12] using six to eight rats at each dose.

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A New Nontricyclic Antidepressant Agent. Synthesis and Activity of *N*-[*trans*-2-(Dimethylamino)cyclopentyl]-*N*-(3,4-dichlorophenyl)propanamide and Related Compounds

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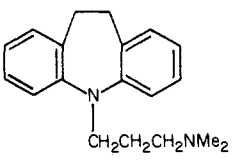
A series of new nontricyclic antidepressant compounds was synthesized. A representative of this class is compound **6**. Five structural parameters were investigated: ring size, cis/trans stereochemistry, amide substitution, aromatic substitution, and amine substitution. The pharmacological tests employed, indicative of antidepressant activity, were yohimbine potentiation test, oxotremorine antagonism test, and apomorphine potentiation test. Structure–activity relationship is discussed.

Tricyclic antidepressants, such as imipramine (**1**), are frequently used in the treatment of endogeneous depression. An induction period of several days or longer before any improvement is noted, frequent side effects, and the necessity for chronic dosing are shortcomings of this program of therapy.[1] Hence, there is a need for drugs with faster onset of action and fewer side effects. We report here some of the results of our search for new antidepressant agents.



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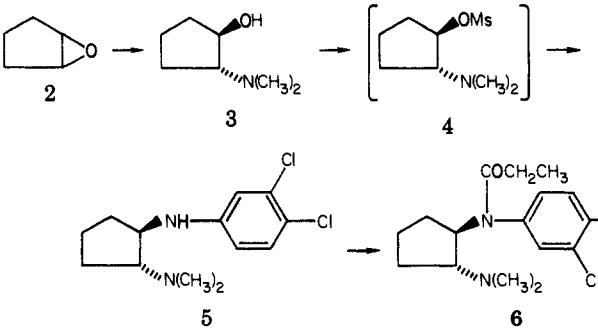
Scheme I



2 **3** **4** **5** **6**

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