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. [$C_{12}H_{18}N_2 \cdot (C_4H_4O_4)_2$] 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.

Acknowledgment. The authors express their appreciation for the X-ray analysis of T. Furuya, for the NMR analysis of H. Kaniwa, for the GC analysis of M. Shimizu, and for the excellent synthetic assistance of A. Yamazaki.

(11) P. A. J. Janssen, C. J. E. Niemegeers, and K. H. L. Schellekens, *Arzneim.-Forsch.*, **15**, 104 (1965).
(12) J. T. Litchfield and F. Wilcoxon, *J. Pharmacol. Exp. Ther.*, **96**, 99 (1945).

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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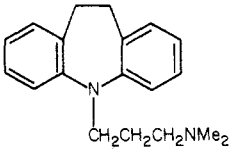
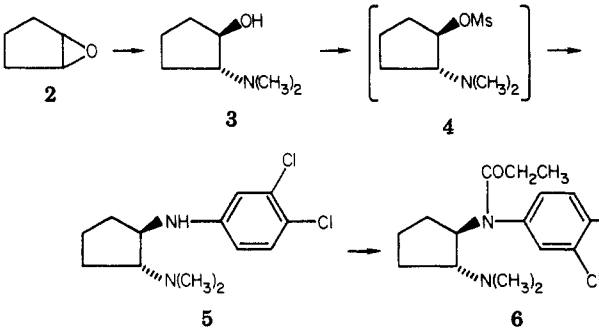
A series of new nontricyclic antidepressant compounds was synthesized. A representative of this class is compound **6**. Five structural parameters were investigated: ring size, cis/trans stereochemistry, amide substitution, aromatic substitution, and amine substitution. The pharmacological tests employed, 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.



1

Scheme I

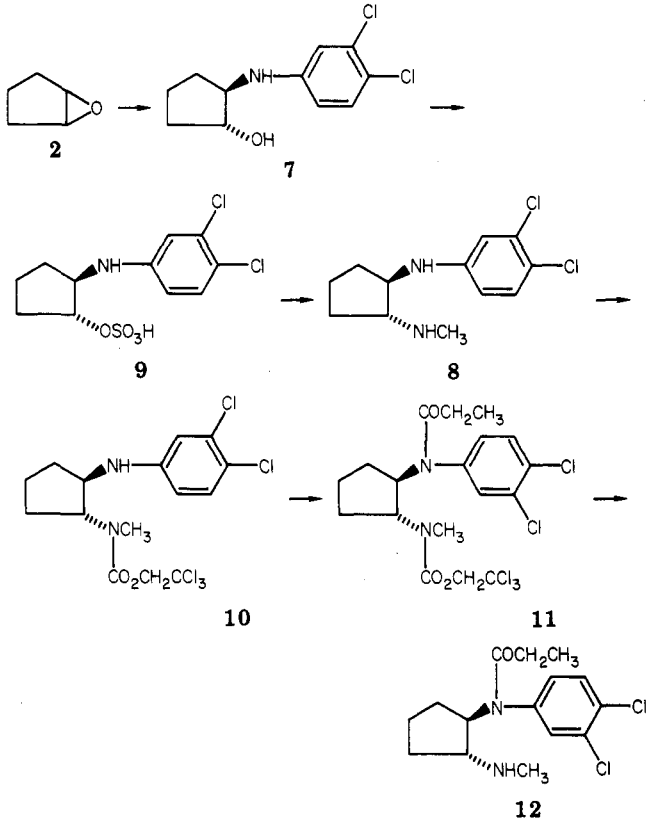


2 **3** **4** **5** **6**

(1) (a) S. Fielding and H. Lal, Eds., "Industrial Pharmacology", Vol 2, Futura, Mount Kisco, NY, 1975; (b) C. Kaiser and P. E. Setler in "Burger's Medicinal Chemistry", 4th ed, Part III, M. E. Wolff, Ed., Wiley-Interscience, New York, 1981, p 997.

0022-2623/81/1824-1230$01.25/0

Scheme II



A few years ago we became interested in the potential central nervous system (CNS) activity of compounds in the cycloalkane-1,2-diamine class. Our interest was derived, in a very broad sense, from the morphine model which has been successful in the past in the generation of CNS leads. During this research, we serendipitously discovered that some of the compounds had potent antidepressant-like activity.

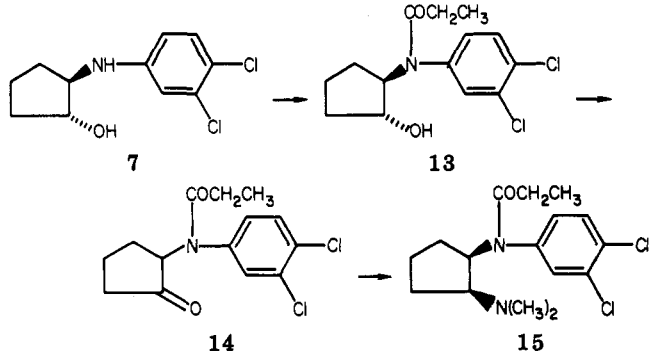
Synthesis. In the course of this investigation, a large number of analogues were prepared. Since the procedures utilized did not vary significantly, only the syntheses of a few representative entries in this series are presented.

Reaction of cyclopentene oxide (2) with aqueous dimethylamine gave the *trans*-amino alcohol 3 (Scheme I). Treatment of the anion of 3 with methanesulfonyl chloride produced the mesylate 4. Displacement with 3,4-dichloroaniline proceeded through the intermediacy of an aziridinium ion[2] to provide *trans*-diamine 5. Heating the diamine with propionic anhydride afforded *trans*-amide 6. Other representatives of this series were obtained by acylation of the diamines with the appropriate acyl halide. Formamides were produced by heating with formic acid.

The presence of a second reactive center necessitated another procedure for derivatives containing secondary amines. Reaction of cyclopentene oxide with 3,4-dichloroaniline afforded *trans*-amino alcohol 7 (Scheme II). Chlorosulfonation and subsequent displacement with aqueous methylamine gave *trans*-diamine 9. Protection with 2,2,2-trichloroethyl chloroformate led to compound 10, which was heated with propionic anhydride to give the protected amide 11. Deprotection with zinc in methanol–acetic acid produced *trans*-amide 12.

(2) (a) S. I. Kegami, K. Uoji, and S. Akaboshi, *Tetrahedron*, **30**, 2077 (1974); (b) C. F. Hammer, S. R. Leller, and J. H. Craig, *ibid.*, **28**, 239 (1972); P. F. Fanta, Aziridines, *Chem. Heterocycl. Compd.*, **19** (1), (1964).

Scheme III



A third procedure was utilized to prepare cis analogues. Heating amino alcohol 7 with propionic anhydride, followed by selective hydrolysis with ethanolic potassium hydroxide, provided hydroxy amide 13 (Scheme III). Jones oxidation, followed by reductive amination with dimethylamine and sodium cyanoborohydride, gave *cis*-amide 15.

The stereochemistry of the *cis*-amide 15 was assigned based on the fact that it was isomeric and different from the *trans*-amide 6. The stereochemistry of amide 6 was assigned based on its mode of formation.

Results and Discussion

Five parameters of the basic molecular structure were modified during this investigation: ring size, cis/trans stereochemistry, amide substitution, aromatic substitution, and amine substitution. The data in Tables I–V are arranged to show the effect on activity of changing a single parameter.

The effect of ring size on activity is demonstrated in Table I. In six cases of direct comparison, compounds with five-membered rings were more active than the corresponding six-membered analogues. In a comparison between five-, six-, seven-, and eight-membered rings, the five-membered analogue was the most active in the series, followed by the seven-, eight-, and six-membered analogues.

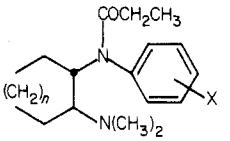
The effect of cis/trans stereochemistry on activity is shown in Table II. In both cases investigated in the five-membered ring series, the trans analogue showed better response than the cis analogue.

The results of modifying amide substitution are presented in Table III. In two series, one containing an unsubstituted benzene ring and the other containing 3,4-dichloro substitution, amide functionality was varied in the sequence of hydrogen, methyl, ethyl, and propyl. In both series, activity showed a maximum with the ethyl homologue. Further variation in the later series showed that aromatic amides were generally less active than aliphatic amides. Cyclopropyl substitution was found to be especially effective.

The parameter having the most effect on activity was found to be the pattern of aromatic substitution. These results are shown in Table IV. Meta substitution was generally found to be more effective than ortho or para substitution. In this regard, meta halo or trifluoromethyl substituents were the most effective. An additional para halo substituent was found to further enhance activity. This effect was especially noted by the 3,4-dichloro or 3,4-dibromo analogues.

Of the parameters investigated, amine substitution was the least definitive. As shown by Table V, a large variety of amines produced highly active compounds, with the diethyl analogue beng the most active. This center is

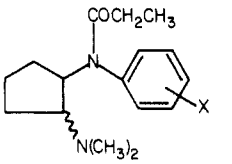
Table I. Antidepressant Agents: Effect of Ring Size on Activity



compd	*n*	X	mp, °C	recrystn solvent	formula	anal.	ED_{50},[e] mg/kg: yohimbine potentiation	ED_{50},[e] mg/kg: oxotremorine antagonism	ED_{50},[e] mg/kg: apomorphine potentiation
16	1	H	115–116	MeOH–Et_2O	$C_{16}H_{24}N_2O \cdot C_7H_8SO_2 \cdot 0.5H_2O$[a]	C, H, N, S	3	2	0.8
17	2	H	51–53	pet. ether	$C_{17}H_{26}N_2O$	C, H, N	>50	>50	>50
18	1	4-Cl	75–76	pet. ether	$C_{16}H_{23}ClN_2O$	C, H, Cl, N	3	0.2	>50
19	2	4-Cl	84–85	pet. ether	$C_{17}H_{25}ClN_2O$	C, H, Cl, N	35	17	14
20	1	4-OCH_3	146–148	MeOH–Et_2O	$C_{17}H_{26}N_2O_2 \cdot C_{10}H_8SO_3$[b]	C, H, N, S	30	20	>50
21	2	4-OCH_3	154–156	MeOH–Et_2O	$C_{18}H_{28}N_2O_2 \cdot C_7H_8SO_3$[a]	C, H, N, S	>50	>50	>50
22	1	3-CH_3	139–140	MeOH–Et_2O	$C_{17}H_{26}N_2O \cdot C_2H_2O_4$[c]	C, H, N	3	1	25
23	2	3-CH_3	120–121	MeOH–Et_2O	$C_{18}H_{28}N_2O \cdot C_4H_4O_4$[d]	C, H, N	>50	15	>50
24	1	4-CH_3	167–168	MeOH–Et_2O	$C_{17}H_{26}N_2O \cdot C_{10}H_8SO_3 \cdot 0.5H_2O$[b]	C, H, N, S	30	10	10
25	2	4-CH_3	98–100	pet. ether	$C_{18}H_{28}N_2O$	C, H, N	>50	>50	>50
6	1	3,4-Cl_2	154–155	MeOH–Et_2O	$C_{16}H_{22}Cl_2N_2O \cdot C_4H_4O_4$[d]	C, H, Cl, N	0.4	0.2	10
26	2	3,4-Cl_2	185–187	MeOH–Et_2O	$C_{17}H_{24}Cl_2N_2O \cdot C_4H_4O_4$[d]	C, H, Cl, N	30	20	20
27	3	3,4-Cl_2	165–166	MeOH–Et_2O	$C_{18}H_{22}Cl_2N_2O \cdot C_4H_4O_4$[d]	C, H, Cl, N	2	6	20
28	4	3,4-Cl_2	110–112	MeOH–Et_2O	$C_{19}H_{28}Cl_2N_2O \cdot C_4H_4O_4 \cdot 0.5H_2O$[d]	C, H, Cl, N	20	10	6
imipramine hydrochloride							4	1	1

[a] *p*-Toluenesulfonic acid salt. [b] Naphthalenesulfonic acid salt. [c] Oxalic acid salt. [d] Maleic acid salt. [e] The upper and lower 95% confidence intervals were not more than 2 and 0.5 times the ED_{50}, respectively.

Table II. Antidepressant Agents: Effect of Stereochemistry on Activity



compd	cis/trans	X	mp, °C	recrystn solvent	formula	anal.	ED_{50},[d] mg/kg: yohimbine potentiation	ED_{50},[d] mg/kg: oxotremorine antagonism	ED_{50},[d] mg/kg: apomorphine potentiation
16	trans	H	115–116	MeOH–Et_2O	$C_{16}H_{24}N_2O \cdot C_7H_8SO_3 \cdot 0.5H_2O$[a]	C, H, N, S	3	2	0.8
29	cis	H	169–170	MeOH–Et_2O	$C_{16}H_{24}N_2O \cdot HCl \cdot 0.5H_2O$	C, H, Cl, N	10	>50	>50
6	trans	3,4-Cl_2	154–155	MeOH–Et_2O	$C_{16}H_{22}Cl_2N_2O \cdot C_4H_4O_4$[b]	C, H, Cl, N	0.4	0.2	10
15	cis	3,4-Cl_2	171–173	MeOH–Et_2O	$C_{16}H_{22}Cl_2N_2O \cdot C_2H_2O_4$[c]	C, H, Cl, N	0.9	2	>50
imipramine hydrochloride							4	1	1

[a] *p*-Toluenesulfonic acid salt. [b] Maleic acid salt. [c] Oxalic acid salt. [d] The upper and lower 95% confidence intervals were not more than 2 and 0.5 times the ED_{50}, respectively.

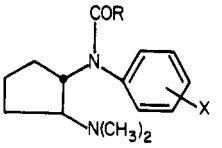
apparently the least sensitive to change. This is further demonstrated by the observation that some activity remains when the amine moiety is replaced by a hydroxyl group.

In summary, the most active compounds are those which contain a five-membered ring, have trans stereochemistry, contain an ethyl or cyclopropyl amide, and have meta halo or trifluoromethyl aromatic substitution. A variety of amine substituents are effective.

Experimental Section

Chemistry. Melting points and boiling points are uncorrected.

Table III. Antidepressant Agents: Effect of Amide Substitution on Activity



compd	R	X	mp, °C	recrystn solvent	formula	anal.	ED_{50},[g] mg/kg: yohimbine potentiation	oxotremorine antagonism	apomorphine potentiation
30	H	H	104–105	MeOH-Et_2O	$C_{14}H_{20}N_2O \cdot C_2H_2O_4$[a]	C, H, N	40	>50	
31	CH_3	H	104	Et_2O-pet. ether	$C_{15}H_{22}N_2O$	C, H, N	7	9	40
16	CH_2CH_3	H	115–116	MeOH-Et_2O	$C_{16}H_{24}N_2O \cdot C_7H_8SO_3 \cdot 0.5H_2O$[b]	C, H, N, S	3	2	0.8
32	$CH_2CH_2CH_3$	H	115–116	MeOH-Et_2O	$C_{17}H_{26}N_2O \cdot C_{10}H_8SO_3 \cdot 0.5H_2O$[b]	C, H, N, S	6	10	40
33	H	3,4-Cl_2	168–169	MeOH-Et_2O	$C_{14}H_{18}Cl_2N_2O \cdot HCl$	C, H, Cl, N	9	40	>50
34	CH_3	3,4-Cl_2	164–165	MeOH-Et_2O	$C_{15}H_{20}Cl_2N_2O \cdot C_2H_2O_4$[a]	C, H, Cl, N	9	10	20
6	CH_2CH_3	3,4-Cl_2	154–155	MeOH-Et_2O	$C_{16}H_{22}Cl_2N_2O \cdot C_4H_4O_4$[d]	C, H, Cl, N	0.4	0.2	10
35	$CH_2CH_2CH_3$	3,4-Cl_2	120–121	MeOH-Et_2O	$C_{17}H_{24}Cl_2N_2O \cdot C_4H_4O_4$[d]	C, H, Cl, N	2	7	0.9
36	c-C_3H_5	3,4-Cl_2	145–146	MeOH-Et_2O	$C_{17}H_{22}Cl_2N_2O \cdot C_2H_2O_4$[a]	C, H, Cl, N	0.2	0.3	0.4
37	c-C_4H_7	3,4-Cl_2	101–103	MeOH-Et_2O	$C_{18}H_{24}Cl_2N_2O \cdot C_2H_2O_4$[a]	C, H, Cl, N	0.8	0.6	>50
38	c-C_6H_{11}	3,4-Cl_2	118–119	pet. ether	$C_{20}H_{28}Cl_2N_2O$	C, H, Cl, N	1	2	>50
39	$CH(CH_3)_2$	3,4-Cl_2	171–174	MeOH-Et_2O	$C_{17}H_{24}Cl_2N_2O \cdot C_2H_2O_4$[a]	C, H, Cl, N	2	4	5
40	$CH=CH_2$	3,4-Cl_2	196–197	MeOH-Et_2O	$C_{16}H_{20}Cl_2N_2O \cdot C_2H_2O_4 \cdot 0.25H_2O$[a]	C, H, Cl, N	2	5	5
41		3,4-Cl_2	114–115	Et_2O-pet. ether	$C_{18}H_{20}Cl_2N_2O_2$	C, H, Cl, N	9	>50	>50
42		3,4-Cl_2	111–113	Et_2O-pet. ether	$C_{18}H_{20}Cl_2N_2SO$	C, H, Cl, N, S	20	10	>50
imipramine hydrochloride							4	1	1

[a] Oxalic acid salt. [b] *p*-Toluenesulfonic acid salt. [c] Naphthalenesulfonic acid salt. [d] Maleic acid salt. [e] Cl: calcd, 31.50; found, 32.96. [f] C: calcd, 54.77; found, 54.28. [g] The upper and lower confidence intervals were not more than 2 and 0.5 times the ED_{50}, respectively.

Melting points were obtained on a Thomas-Hoover capillary melting point apparatus. NMR spectra were determined on a Varian A-60D or XL-100 instrument. The authors are indebted to Physical and Analytical Chemistry Research of the Upjohn Co. for elemental analyses and other analytical services. The procedures described below represent general methods of synthesis employed during this investigation. Other analogues exhibited similar NMR, IR, UV, and mass spectra. Only final products are listed in Tables I–V.[3] All compounds listed, unless indicated otherwise, gave elemental analyses with ±0.4% of the calculated values. Infrared spectra (recorded in reciprocal centimeters) were determined in Nujol.

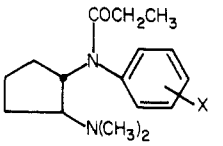
***trans*-2-(Dimethylamino)cyclopentanol (3).** A solution of cyclopentene oxide (188 g, 2.24 mol) and 40% dimethylamine (750 mL, 6.67 mol) was stirred overnight without cooling. The mixture was diluted with saturated NaCl (750 mL) and extracted several times with ether. The extract was dried over $MgSO_4$ and evaporated. The residual oil was distilled to give **3** (276 g, 90% yield): bp 98–100 °C (14 mm); NMR ($CDCl_3$) δ 2–3 (s, 1 H, OH), 3.9–4.3 (m, 1 H, CH), 2.3–2.6 (m, 1 H, CH), 2.28 (s, 6 H, CH_3), 1.2–2.0 (m, 6 H, ring CH_2); IR 3370, 3200 (OH), 2780 (*N*-alkyl), 1045 (CO) cm^{-1}; UV (EtOH) λ_{max} end absorption; mass spectrum, *m/e* 129. An analysis was determined on the fumaric acid salt, mp 149–150 °C. Anal. ($C_7H_{15}NO \cdot 0.5\ C_4H_4O_4$) C, H, N.

***trans*-*N*,*N*-Dimethyl-*N'*-(3,4-dichlorophenyl)-1,2-cyclopentanediamine (5).** A mixture of **3** (32.3 g, 0.25 mol) and 57% NaH (10.5 g, 0.25 mol) in THF (100 mL) was refluxed for 1 h. The mixture was cooled in ice, and methanesulfonyl chloride (28.6 g, 0.25 mol) was added dropwise in 30 min. When the addition was complete, 3,4-dichloroaniline (81.0 g, 0.50 mol) was added in one portion. The solvent was removed by distillation, and the residue was heated on a steam bath for 17 h. The mixture was treated with 20% NaOH (200 mL) and heating was continued for 1 h. The mixture was extracted with ether and dried over $MgSO_4$. Evaporation and distillation gave **5** (36.2 g, 53% yield): bp 160–170 °C (0.3 mm). The maleic acid salt showed mp 128–129 °C; NMR (D_2O) δ 7.1 (m, 1 H, aromatic), 6.7 (m, 1 H, aromatic), 6.5 (m, 1 H, aromatic), 6.1 (s, 2 H, vinyl), 3.8 (m, 1 H, CH), 3.35 (m, 1 H, CH), 2.75 (s, 6 H, CH_3), 1.2–2.3 (m, 6 H, ring CH_2); IR 3380 (NH), 2600, 2520, 2400 (NH^+ acid OH), 1600, 1580, 1480 (CO_2^-/C=C), 1430, 1350, 1330, 985, 870, 865 cm^{-1}; UV (EtOH) λ_{max} 210 nm (ε 45 450), 257 (19 400), 310 (2300); mass spectrum, *m/e* 272, 274, 276. Anal. ($C_{13}H_{18}Cl_2N_2 \cdot C_4H_4O_4$) C, H, Cl, N.

***N*-[*trans*-2-(Dimethylamino)cyclopentyl]-*N*-(3,4-dichlorophenyl)propanamide (6). Method A.** A solution of **5** (2.73 g, 10.0 mmol) in propionic anhydride (10 mL) was heated on a steam bath overnight. Water (100 mL) was added and heating was continued for 1 h to decompose excess anhydride.

(3) For additional experimental details, refer to J. Szmuszkovicz, U.S. Patent 4 204 003, 1980; *ibid.*, 4 148 913, 1979; *ibid.*, 4 156 014, 1979; *ibid.*, 4 156 015, 1979; *ibid.*, 4 157 398, 1979; *ibid.*, 4 159 340, 1979.

Table IV. Antidepressant Agents: Effect of Aromatic Substitution on Activity



compd	X	mp, °C	recrystn solvent	formula	anal.	ED_{50},[h] mg/kg: yohimbine potentiation	ED_{50},[h] mg/kg: oxotremorine antagonism	ED_{50},[h] mg/kg: apomorphine potentiation
16	H	115–116	MeOH Et_2O	$C_{16}H_{24}N_2O \cdot C_7H_8SO_3 \cdot 0.5H_2O$[a]	C, H, N, S	3	2	0.8
43	2-CH_3	129–130	MeOH-Et_2O	$C_{17}H_{26}N_2O \cdot C_2H_2O_4$[b]	C, H, N	7	5	>50
44	3-CH_3	139–140	MeOH-Et_2O	$C_{17}H_{26}N_2O \cdot C_2H_2O_4$[b]	C, H, N	3	1	25
45	4-CH_3	167–168	MeOH-Et_2O	$C_{17}H_{26}N_2O \cdot C_{10}H_8SO_3 \cdot 0.5H_2O$[c]	C, H, N, S	30	10	10
46	3-OCH_3	135–136	MeOH-ether	$C_{17}H_{16}N_2O_2 \cdot C_2H_2O_4 \cdot 0.5H_2O$[b]	C, H, N	0.8	4	4
47	4-OCH_3	146–148	MeOH-ether	$C_{17}H_{26}N_2O_2 \cdot C_{10}H_8SO_3$[c]	C, H, N, S	30	20	>50
48	3,4-$(OCH_3)_2$	155–156	MeOH-ether	$C_{18}H_{28}N_2O_3 \cdot C_4H_4O_4$[d]	C, H, N	9	10	10
49	3-F	85–88	EtOH-Et_2O	$C_{16}H_{23}FN_2O \cdot C_2H_2O_4$[b]	C, H, F, N	0.4	0.6	5
50	4-F	154–155	MeOH-Et_2O	$C_{16}H_{23}FN_2O \cdot C_{10}H_8SO_3$[c]	C, H, F, N, S	5	0.08	>50
51	2,3,4,5,6-F_5	152–153	MeOH-Et_2O	$C_{16}H_{19}F_5N_2O \cdot C_2H_2O_4$[b]	C, H, F, N	>50	>50	>50
52	2-Cl	156–157	MeOH-Et_2O	$C_{16}H_{23}ClN_2O \cdot C_2H_2O_4$[b]	C, H, Dl, N	6	2	>50
53	3-Cl	152–153	MeOH-Et_2O	$C_{16}H_{23}ClN_2O \cdot C_2H_2O_4$[b]	C, H, Cl, N	0.4	0.2	20
18	4-Cl	75–76	pet. ether	$C_{16}H_{23}ClN_2O$	C, H, Cl, N	3	0.2	>50
6	3,4-Cl_2	154–155	MeOH-Et_2O	$C_{16}H_{22}Cl_2N_2O \cdot C_4H_4O_4$[e]	C, H, Cl, N	0.4	0.2	10
54	3-Cl, 4-CH_3	122–123	MeOH-Et_2O	$C_{17}H_{25}ClN_2O \cdot C_2H_2O_4$[b]	C, H, Cl, N	1	0.6	2
55	4-Cl, 3-CH_3	131–132	MeOH-Et_2O	$C_{17}H_{25}ClN_2O \cdot C_2H_2O_4$[b]	C, H, Cl, N	2	2	10
56	3-Cl, 4-F	152–153	MeOH-Et_2O	$C_{16}H_{22}ClFN_2O \cdot C_2H_2O_4$[b]	C, H, Cl, F, N	0.2	2	0.7
57	3,5-Cl_2	129–130	MeOH-Et_2O	$C_{16}H_{22}Cl_2N_2O \cdot C_4H_4O_4$[e]	C, H, Cl, N	0.9	5	30
58	3,4,5-Cl_3	145–146	MeOH-Et_2O	$C_{16}H_{21}Cl_3N_2O \cdot C_4H_4O_4$	C, H, Cl, N	4	40	40
59	3-Br	167–168	MeOH-Et_2O	$C_{16}H_{23}BrN_2O \cdot C_2H_2O_4$[b]	C, H, Br, N	0.1	0.1	2
60	4-Br	78–79	pet. ether	$C_{16}H_{23}BrN_2O$	C, H, Br, N	2	3	>50
61	3,4-Br_2	146–147	MeOH-Et_2O	$C_{16}H_{22}Br_2N_2O \cdot C_2H_2O_4$[b]	C, H, Br, N	0.1	0.2	0.5
62	3-CF_3	135–136	MeOH-Et_2O	$C_{17}H_{23}F_3N_2O \cdot C_2H_2O_4$[b]	C, H, N	0.3	0.2	0.9
63	4-CF_3	184–185	MeOH-Et_2O	$C_{17}H_{23}F_3N_2O \cdot HCl$	C, H, Cl, N	10	25	10
64	4-NO_2	93–95	MeOH-Et_2O	$C_{16}H_{23}N_3O_3 \cdot C_2H_2O_4 \cdot H_2O$[b]	C, H, N	20	6	20
65	4-CO_2CH_3	139–140	MeOH-Et_2O	$C_{18}H_{22}N_2O_3 \cdot C_7H_8SO_3$[a]	C, H, N, S	>50	>50	>50
66	4-CN	146–147	MeOH-Et_2O	$C_{17}H_{23}N_3O \cdot C_4H_4O_4$[e]	C, H, N	10	40	>50
67	4-$COCH_3$	82–84	EtOH-Et_2O	$C_{18}H_{26}N_2O_2 \cdot C_2H_2O_4$[b]	C, H, N[f]	>50	40	>50
imipramine hydrochloride						4	1	1

[a] *p*-Toluenesulfonic acid salt. [b] Oxalic acid salt. [c] Naphthalenesulfonic acid salt. [d] Fumaric acid salt. [e] Maleic acid salt. [f] N: calcd, 7.14; found, 7.85. [g] N: calcd, 7.00; found, 7.85. [h] The upper and lower 95% confidence intervals were not more than 2 and 0.5 times the ED_{50}, respectively.

The solution was made basic with 20% NaOH and extracted with ether. The extract was washed with saturated NaCl, dried over $MgSO_4$, and evaporated to an oil. The crude amide was purified by formation of the maleic acid salt (3.3 g, 74% yield): mp 154–155 °C; NMR (D_2O) δ 7.6 (m, 1 H, aromatic), 7.5 (m, 1 H, aromatic), 7.3 (m, 1 H, aromatic), 6.3 (s, 2 H, vinyl), 5.1 (m, 1 H, CH), 3.8

Table V. Antidepressant Agents: Effect of Amine Substitution on Activity

compd	NRR'	mp, °C	recrystn solvent	formula	anal.	ED_{50},[g] mg/kg: yohimbine potentiation	oxotremorine antagonism	apomorphine potentiation
68	NH_2	179–180	MeOH-Et_2O	$C_{14}H_{18}Cl_2N_2O \cdot C_{10}H_8SO_3$[a]	C, H, Cl, N, S	0.02	0.8	
12	$NHCH_3$	176–177	MeOH-Et_2O	$C_{15}H_{20}Cl_2N_2O \cdot C_7H_8SO_3$[b]	C, H, Cl, N, S	0.4	0.3	
69	$NHCH_2CH_3$	162–163	MeOH-Et_2O	$C_{16}H_{22}Cl_2N_2O \cdot C_2H_2O_4$[c]	C, H, Cl, N	0.2	2	
70	$NHCH_2CH{=}CH_2$	171–172	MeOH-Et_2O	$C_{17}H_{22}Cl_2N_2O \cdot C_2H_2O_4$[c]	C, H, Cl, N	0.2	3	
6	$N(CH_3)_2$	154–155	MeOH-Et_2O	$C_{16}H_{22}Cl_2N_2O \cdot C_4H_4O_4$[d]	C, H, Cl, N	0.4	0.2	10
71	$N(CH_2CH_3)_2$	148–149	MeOH-Et_2O	$C_{18}H_{26}Cl_2N_2O \cdot CH_4SO_3$[e]	C, H, Cl, N, S	0.1	0.03	0.3
72	$N(CH_2CH_2CH_3)_2$	58–59	pet. ether	$C_{20}H_{30}Cl_2N_2O$	C, H, Cl, N	2	0.1	>50
73	c-$N(CH_2CH_2)_2$	107	MeOH-Et_2O	$C_{18}H_{24}Cl_2N_2O \cdot C_2H_2O_4 \cdot 0.5H_2O$[c]	C, H, Cl, N	0.6	2	3
74	$N(CH_3)CH_2CH{=}CH_2$	104–106	EtOH-Et_2O	$C_{18}H_{24}Cl_2N_2O \cdot C_2H_2O_4$[c]	C, H, Cl, N	0.2	0.2	6
75	$N(CH_3)CH_2Ph$	120–121	MeOH-Et_2O	$C_{22}H_{26}Cl_2N_2O \cdot C_2H_2O_4 \cdot H_2O$[c]	C, H, Cl, N	0.2	40	>50
76	$N(CH_3)CH_2CH_2Ph$	90–91	MeOH-Et_2O	$C_{23}H_{28}Cl_2N_2O \cdot C_2H_2O_4 \cdot H_2O$[c]	C, H, Cl, N	0.1	0.4	5
77	$N(CH_3)CH_2CH_2N(CH_3)_2$	165–166	MeOH-Et_2O	$C_{19}H_{29}Cl_2N_3O \cdot 2HCl \cdot H_2O$	C, H, Cl, N	0.8	5	20
78	$N(CH_3)CH_2CH_2CH_2N(CH_3)_2$	259–260	MeOH-Et_2O	$C_{20}H_{31}Cl_2N_3O \cdot 2HCl \cdot 0.25H_2O$	C, H, Cl, N	4	10	30
13	OH	105	Et_2O-pet. ether	$C_{14}H_{17}Cl_2NO_2$	C, H, Cl, N	0.4	9	20
imipramine hydrochloride						4	1	1

[a] Naphthalenesulfonic acid salt. [b] *p*-Toluenesulfonic acid salt. [c] Oxalic acid salt. [d] Maleic acid salt. [e] Methanesulfonic acid salt. [f] Cl: calcd, 13.81; found, 13.26.

(m, 1 H, CH), 2.95 (s, 6 H, CH_3), 2.0 (q, 2 H, CH_3CH_2CO), 1.1–1.9 (m, 6 H, ring CH_2), 0.9 (t, 3 H, CH_3CH_2CO); IR 2720, 2530, 2490 (NH^+/OH), 1665, 1620, 1585, 1560 (C=O/CO_2^-/C=C), 1355, 1265, 1030, 865 (other) cm^{-1}; UV (EtOH) λ_{max} end absorption, 203 nm (ϵ 61 350), 264 (828), 272 (744), 281 (592); mass spectrum, *m/e* 328, 330, 332. Anal. ($C_{16}H_{22}Cl_2N_2O \cdot C_4H_4O_4$) C, H, Cl, N.

***N*-[*trans*-2-(Dimethylamino)cyclopentyl]-*N*-[4-(trifluoromethyl)phenyl]propanamide (63). Method B.** A solution of propionyl chloride (2.11 g, 22.0 mmol) in ether (50 mL) was added dropwise with ice cooling in 30 min to a solution of *trans*-*N*,*N*-dimethyl-*N*'-[4-(trifluoromethyl)phenyl]-1,2-cyclopentanediamine (3.10 g, 11.0 mmol) and triethylamine (2.30 g, 22.0 mmol) in ether (100 mL). After the solution was stirred overnight, saturated $NaHCO_3$ (100 mL) was added. The organic layer was washed with water and saturated NaCl, dried over $MgSO_4$, and evaporated. The crude product was converted to the hydrochloride salt (3.2 g, 80% yield): mp 184–185 °C; NMR (D_2O) δ 7.9 (m, 4 H, aromatic), 2.9 (s, 6 H, CH_3), 1.4–2.3 (m, 8 H, ring CH_2 and CH_3CH_2CO), 0.9 (t, 3 H, CH_3CH_2CO); mass spectrum, *m/e* 328. Anal. ($C_{17}H_{23}F_3N_2O \cdot HCl$) C, H, Cl, F, N.

***trans*-2-(3,4-Dichloroanilino)cyclopentanol (7).** A mixture of 3,4-dichloroaniline (50.0 g, 0.31 mol), concentrated HCl (5 mL), and cyclopentene oxide (100 mL) was refluxed for 7 days. The mixture was evaporated and triturated with petroleum ether (5 × 250 mL) to remove unreacted 3,4-dichloroaniline. The residue was treated with excess ether–HCl, and the crude salt was recrystallized twice from methanol–ether (38.7 g, 44% yield): mp 167–168 °C; NMR (D_2O) δ 7.4 (m, 1 H, aromatic), 7.1 (m, 1 H, aromatic), 6.8 (m, 1 H, aromatic), 4.0 (m, 1 H, CH), 3.5 (m, 1 H, CH), 1.3–2.3 (m, 6 H, ring CH_2); IR 3420 (OH), 2740, 2660 (NH^+), 1605, 1575, 1470 (C=C/NH^+); UV (EtOH) λ_{max} end absorption, 211 nm (ϵ 26 250), 259 (17 500), 314 (2450); mass spectrum, *m/e* 245, 247, 249. Anal. ($C_{11}H_{13}Cl_2NO \cdot HCl$) C, H, N; Cl: calcd, 37.64; found, 37.20.

***trans*-2-(3,4-Dichloroanilino)cyclopentyl Hydrogen Sulfate (8).** A solution of chlorosulfonic acid (12.9 g, 0.11 mol) in methylene chloride (50 mL) was added dropwise without cooling in 15 min to a stirred suspensions of amino alcohol hydrochloride 7 (28.2 g, 0.10 mol) in methylene chloride (200 mL). After stirring overnight, the mixture was evaporated, and the precipitate was suspended in ether and filtered (29.4 g, 90% yield): mp 216–218 °C; NMR (Me_2SO) δ 7.25 (m, 1 H, aromatic), 7.05 (m, 1 H, aromatic), 6.8 (m, 1 H, aromatic), 4.45 (m, 1 H), CH), 3.8 (m, 1 H, CH), 1.4–2.4 (m, 6 H, ring CH_2); IR 2760, 2700, 2580, 2500 (NH^+), 1605 (C=C), 1265, 1210, 1035, 1020 (OSO_3H/other) cm^{-1}; UV (EtOH) λ_{max} 210 nm (ϵ 27 650), 258 (17 200), 313 (2400); mass spectrum, *m/e* 307, 309 (P – 18). Anal. ($C_{11}H_{13}Cl_2NO_4S$) C, H, Cl, N, S.

***trans*-*N*-Methyl-*N*'-(3,4-dichlorophenyl)-1,2-cyclopentanediamine (9).** A mixture of sulfate 8 (222 g, 0.17 mol) and 40% methylamine (700 mL) was heated in a rocking pressure bomb at 125 °C for 48 h. The mixture was extracted with ether, and the extract was washed with saturated NaCl, dried over $MgSO_4$, and evaporated to a brown oil. Chromatography on silica gel (1500 g), eluting first with ethyl acetate (10 mL) followed by methanol (10 L), and then evaporation of the methanol gave an orange oil (159 g). The hydrochloride salt was prepared by treatment with excess ether–HCl and recrystallization from methanol–ether (165 g, 71% yield): mp 185–187 °C; NMR (D_2O) δ 6.6–7.4 (m, 3 H, aromatic), 2.7 (s, 3 H, CH_3), 1.5–2.0 (m, 6 H, ring CH_2); IR 2760, 2680, 2600, 2480, 2420 (NH^+), 1580 (C=C), 1130, 1035, 975, 925 (other) cm^{-1}; UV (EtOH) λ_{max} 211 nm (ϵ 25 700), 256 (18 250), 310 (2300); mass spectrum, *m/e* 258, 260, 262. Anal. ($C_{12}H_{16}Cl_2N_2 \cdot 2HCl$) C, H, Cl, N.

2,2,2-Trichloroethyl *N*-[*trans*-2-(3,4-Dichloroanilino)-cyclopentyl]-*N*-methylcarbamate (10). A solution of 2,2,2-trichloroethyl chloroformate (6.36 g, 0.03 mol) in ether (50 mL) was added in 20 min with cooling to a solution of diamine 9 (7.77 g, 0.03 mol) and triethylamine (3.03 g, 0.03 mol) in ether (250 mL). After the solution was stirred for 2 h at room temperature, saturated $NaHCO_3$ (100 mL) was added. The organic layer was washed with saturated NaCl, dried over $MgSO_4$, and evaporated. The hydrochloride salt was prepared by treatment with excess ether–HCl and recrystallized from methanol–ether (11.3 g, 80% yield); mp 165–170 °C; NMR (D_2O) δ 7.1 (m, 1 H, aromatic), 6.6 (m, 1 H, aromatic), 6.4 (m, 1 H, aromatic), 4.75 (s, 2 H,

CCl_3CH_2CO), 4.3 (m, 1 H, CH), 3.65 (m, 1 H, CH), 2.95 (s, 3 H, CH_3), 1.2–2.4 (m, 6 H, ring CH_2); IR 2680, 2640, 2520, 2440 (NH^+), 1710 (C=O), 1585, 1570 (C=C) cm^{-1}; UV (EtOH) λ_{max} 211 nm (ϵ 24 100), 259 (17 250), 313 (2300); mass spectrum, *m/e* 432, 434, 436. Loss of HCl on vacuum drying prevented obtaining a satisfactory analysis.

***N*-[*trans*-2-(2,2,2-Trichloroethyl-*N'*-methylcarbamyl)cyclopentyl]-*N*-(3,4-dichlorophenyl)propanamide (11).** A mixture of carbamate **10** (21.7 g, 0.05 mol) and propionic anhydride (30 mL) was heated on a steam bath overnight. Water (150 mL) was added, and heating continued for 1 h. The mixture was made basic with 15% NaOH and extracted with ether. The extract was washed with saturated NaCl, dried over $MgSO_4$, and evaporated to an orange oil (24.5 g, 100% yield). An analytical sample was obtained by column chromatography: NMR ($CDCl_3$) δ 6.8–7.7 (m, 3 H; aromatic) 4.7 and 4.9 (AB quartet, 2 H, OCH_2CCl_3), 5.2 (m, 1 H, CH), 4.4 (m, 1 H, CH), 3.0 (s, 3 H, CH_3), 1.5–2.1 (m, 8 H, ring CH_2 and CH_3CH_2CO), 1.0 (t, 3 H, CH_3CH_2CO); IR 1710, 1765 (C=O) cm^{-1}; UV (EtOH) λ_{max} end absorption, 230 nm (ϵ 7200), 265 (653), 273 (530), 281 (412); mass spectrum, *m/e* 488, 490, 492. Anal. ($C_{18}H_{21}Cl_5N_2O_3$) C, H, Cl, N.

***N*-[*trans*-2-(Methylamino)cyclopentyl]-*N*-(3,4-dichlorophenyl)propanamide (12).** A mixture of carbamate **11** (9.8 g, 0.02 mol) and zinc dust (13.1 g, 0.20 mol) in 5% acetic acid in methanol (100 mL) was stirred without cooling for 3 h. The mixture was filtered through Celite and evaporated. The residue was treated with NH_4OH (100 mL, 5 N) and extracted with ether. The organic layer was washed with saturated NaCl, dried over $MgSO_4$, and evaporated to an oil. The *p*-toluenesulfonic acid salt was prepared and recrystallized from methanol–ether (6.8 g, 70% yield): mp 176–177 °C; NMR (D_2O) δ 7.0–7.8 (m, 7 H, aromatic), 4.8 (m, 1 H, CH), 3.3 (m, 1 H, CH), 2.6 (s, 3 H, NCH_3), 2.3 (s, 3 H, $ArCH_3$), 1.9 (m, 2 H, CH_3CH_2CO), 1.0–2.0 (m, 6 H, ring CH_2), 0.9 (t, 3 H, CH_3CH_2CO); IR 2950, 2820, 2480 (NH^+), 1676 (C=O), 1620, 1585, 1580, 1560, 1495 (C=C) cm^{-1}; UV (EtOH) λ_{max} 203 nm (ϵ 48 900), 216 (23 100), 262 (585), 268 (526), 272 (502), 281 (385); mass spectrum, *m/e* 314, 316. Anal. ($C_{15}H_{20}Cl_2N_2O \cdot C_7H_8O_3S$) C, H, Cl, N, S.

***N*-(*trans*-2-Hydroxycyclopentyl)-*N*-(3,4-dichlorophenyl)propanamide (13).** A mixture of amino alcohol **7** (61.5 g, 0.25 mol) and propionic anhydride (130 g, 1.0 mol) was heated on a steam bath for 72 h. Water (250 mL) was added and heating continued for 1 h to decompose excess anhydride. The mixture was cooled in ice, made basic with 40% NaOH, and extracted with ether. The extract was washed with saturated NaCl, dried over $MgSO_4$, and evaporated. The crude amide–ester was dissolved in a solution of KOH (17.0 g, 85%, 0.25 mol) in 95% ethanol (250 mL) and kept at room temperature for 3 h. The solution was evaporated. The residue was dissolved in ether and washed with 10% HCl and water. Evaporation and recrystallization from ether–petroleum ether gave **13** (49.5 g, 66% yield): mp 105 °C; NMR ($CDCl_3$) δ 7.5 (m, 1 H, aromatic), 7.35 (m, 1 H, aromatic), 7.1 (m, 1 H, aromatic), 4.6 (m, 1 H, CH), 4.0 (m, 1 H, CH), 3.75 (s, 1 H, OH), 2.05 (q, 2 H, CH_3CH_2CO), 1.3–2.0 (m, 6 H, ring CH_2), 1.1 (t, 3 H, CH_3CH_2CO); IR 3480, 3380 (OH), 1670, 1655 (C=O), 1585, 1560 (C=C), 1280, 1030 (other) cm^{-1}; UV (EtOH) λ_{max} end absorption, 240 nm (ϵ 4000), 264 (523), 273 (487), 281 (405); mass spectrum, *m/e* 301, 303. Anal. ($C_{14}H_{17}Cl_2NO_2$) C, H, Cl, N.

***N*-(2-Oxocyclopentyl)-*N*-(3,4-dichlorophenyl)propanamide (14).** A solution of alcohol **13** (60.4 g, 0.20 mol) in acetone (1000 mL) was cooled in ice while Jones reagent (75 mL of the following solution: 26.8 g of CrO_3, 23 mL of concentrated H_2SO_4, dilute to 100 mL with H_2O) was added dropwise in 30 min. The mixture was stirred for 30 min at room temperature, filtered to remove chromium salts, and evaporated. The residue was taken up in ether, washed with water and saturated NaCl, dried over $MgSO_4$, and evaporated to a yellow solid (59.8 g, 98% yield). Attempts to purify the crude product by recrystallization were unsuccessful, and the product was used without further purification: IR 1750, 1660 (C=O) cm^{-1}; mass spectrum, *m/e* 299, 301, 303.

***N*-[*cis*-2-(Dimethylamino)cyclopentyl]-*N*-(3,4-dichlorophenyl)propanamide (15).** A mixture of ketone **14** (18.0 g, 0.06 mol), dimethylamine (46 mL, 5.3 M in methanol, 0.24 mol), dimethylamine hydrochloride (9.8 g, 0.12 mol), and $NaCNBH_3$ (2.65 g, 0.042 mol) in methanol (250 mL) was stirred at room temperature for 8 days. The mixture was stirred with 10% HCl (200 mL) until gas evolution ceased. The mixture was evaporated to remove methanol, made basic with 40% NaOH, and extracted with ether. The extract was washed with saturated NaCl, dried over $MgSO_4$, and evaporated to an oil. The crude product was chromatographed on silica gel (150 g), eluting with 2% methanol in chloroform in 20-mL fractions. Fractions 11–33 were combined and evaporated (4.2 g). The amide was converted to the oxalic acid salt and recrystallized from methanol–ether (2.75 g, 11% yield): mp 171–173 °C; NMR (D_2O) δ 7.8 (m, 2 H, aromatic), 7.4 (m, 1 H, aromatic), 4.8 (m, 1 H, CH), 3.9 (m, 1 H, CH), 2.9 (s, 6 H, CH_3), 1.6–2.4 (m, 8 H, ring CH_2 and CH_3CH_2CO), 1.0 (t, 3 H, CH_3CH_2CO); IR 2660, 2460 (NH^+, acid OH), 1670 (C=O), 1590 (C=C) cm^{-1}; UV (EtOH) λ_{max} end absorption, 230 nm (ϵ 8250), 274 (537), 282 (453); mass spectrum, *m/e* 299, 301 (P – 29). Anal. ($C_{16}H_{22}Cl_2N_2O$) C, H, Cl, N.

Pharmacology. The procedures employed utilize drug potentiation of antagonism end points to identify compounds as antidepressant-like. In these tests, groups of four male CF-1 mice were dosed intraperitoneally with suspensions or solutions of the test compounds (50 and 25 mg/kg) in 0.25% aqueous methylcellulose at a volume of 10 mL/kg.

For the yohimbine potentiation test,[4] the mice were then injected intraperitoneally 30 min later with 20 mg/kg yohimbine hydrochloride. They were then placed in a 30 °C chamber for 1 h. Potentiation of yohimbine was evidenced by death within this period of time.

In the oxotremorine antagonism test,[5] the mice were treated subcutaneously with 1 mg/kg oxotremorine 30 min after the test compound was given. After an additional 30 min in a 19 °C chamber, their intraperitoneal temperatures were measured. Mice with temperatures more than 0.9 °C above the mean temperature of vehicle–oxotremorine treated controls are scored as displaying oxotremorine antagonism.

In the apomorphine potentiation test,[6] the mice were treated subcutaneously with 10 mg/kg apomorphine 1 h after receiving the test compound. They were then observed for 30 min for stereotyped gnawing and licking. Each animal displaying this syndrome was scored as positive.

If three or more animals were positive in any one of the tests, it was repeated at a dose 0.3 log interval lower until one or less response was observed. ED_{50} values and 95% confidence intervals were calculated by the method of Spearman and Karber.[7] The data from these tests are listed in Tables I–V.

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