

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 Wilcoxon¹² 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 Wilcoxon¹² 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).

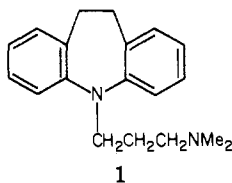
A New Nontricyclic Antidepressant Agent. Synthesis and Activity of *N*-[*trans*-2-(Dimethylamino)cyclopentyl]-*N*-(3,4-dichlorophenyl)propanamide and Related Compounds

J. Szmuszkovicz,* P. F. VonVoigtlander, and M. P. Kane

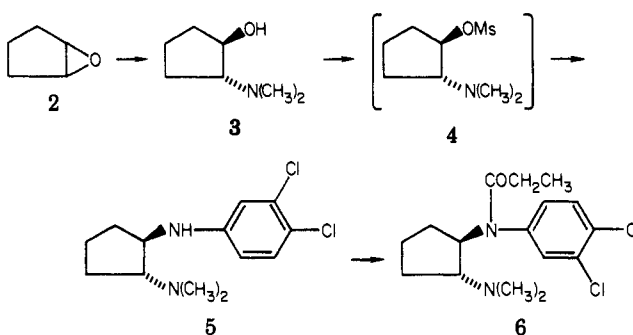
Research Laboratories, The Upjohn Company, Kalamazoo, Michigan 49001. Received May 11, 1981

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



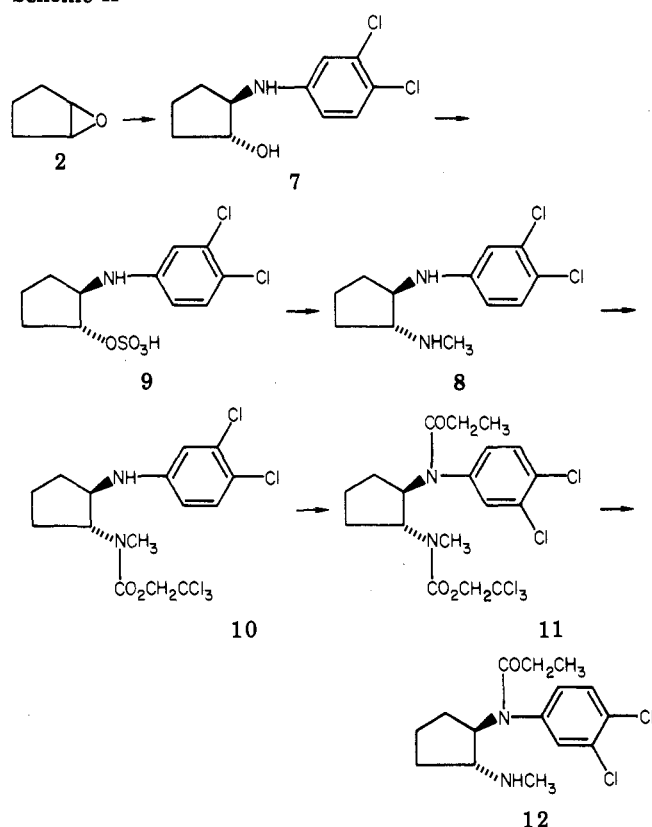
Scheme I



(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.

faster onset of action and fewer side effects. We report here some of the results of our search for new antidepressant agents.

Scheme II



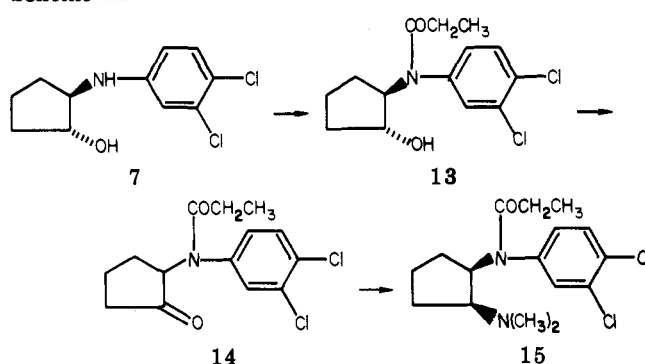
A few years ago we became interested in the potential central nervous system (CNS) activity of compounds in the cycloalkane-1,2-diamine class. Our interest was derived, in a very broad sense, from the morphine model which has been successful in the past in the generation of CNS leads. During this research, 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 ion² 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.

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.

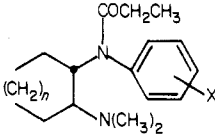
The results of modifying amide substitution are presented in Table III. In two series, one containing an unsubstituted benzene ring and the other containing 3,4-dichloro substitution, amide functionality was varied in the sequence of hydrogen, methyl, ethyl, and propyl. In both series, activity showed 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 being the most active. This center is

(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).

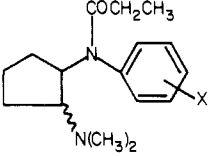
Table I. Antidepressant Agents: Effect of Ring Size on Activity



compd	n	X	mp, °C	recrystn solvent	formula	anal.	ED ₅₀ , ^e mg/kg		
							yohim-bine potentiation	oxotrem-orine antagonism	apomor-phine potentiation
16	1	H	115-116	MeOH-Et ₂ O	C ₁₆ H ₂₄ N ₂ O·C ₇ H ₈ SO ₃ ·0.5H ₂ O ^a	C, H, N, S	3	2	0.8
17	2	H	51-53	pet. ether	C ₁₇ H ₂₆ N ₂ O	C, H, N	>50	>50	>50
18	1	4-Cl	75-76	pet. ether	C ₁₆ H ₂₃ ClN ₂ O	C, H, Cl, N	3	0.2	>50
19	2	4-Cl	84-85	pet. ether	C ₁₇ H ₂₅ ClN ₂ O	C, H, Cl, N	35	17	14
20	1	4-OCH ₃	146-148	MeOH-Et ₂ O	C ₁₇ H ₂₆ N ₂ O ₂ ·C ₁₀ H ₈ SO ₃ ^b	C, H, N, S	30	20	>50
21	2	4-OCH ₃	154-156	MeOH-Et ₂ O	C ₁₈ H ₂₈ N ₂ O ₂ ·C ₇ H ₈ SO ₃ ^a	C, H, N, S	>50	>50	>50
22	1	3-CH ₃	139-140	MeOH-Et ₂ O	C ₁₇ H ₂₆ N ₂ O·C ₂ H ₂ O ₄ ^c	C, H, N	3	1	25
23	2	3-CH ₃	120-121	MeOH-Et ₂ O	C ₁₈ H ₂₈ N ₂ O·C ₄ H ₄ O ₄ ^d	C, H, N	>50	15	>50
24	1	4-CH ₃	167-168	MeOH-Et ₂ O	C ₁₇ H ₂₆ N ₂ O·C ₁₀ H ₈ SO ₃ ·0.5H ₂ O ^b	C, H, N, S	30	10	10
25	2	4-CH ₃	98-100	pet. ether	C ₁₈ H ₂₈ N ₂ O	C, H, N	>50	>50	>50
6	1	3,4-Cl ₂	154-155	MeOH-Et ₂ O	C ₁₆ H ₂₂ Cl ₂ N ₂ O·C ₄ H ₄ O ₄ ^d	C, H, Cl, N	0.4	0.2	10
26	2	3,4-Cl ₂	185-187	MeOH-Et ₂ O	C ₁₇ H ₂₄ Cl ₂ N ₂ O·C ₄ H ₄ O ₄ ^d	C, H, Cl, N	30	20	20
27	3	3,4-Cl ₂	165-166	MeOH-Et ₂ O	C ₁₈ H ₂₂ Cl ₂ N ₂ O·C ₄ H ₄ O ₄ ^d	C, H, Cl, N	2	6	20
28	4	3,4-Cl ₂	110-112	MeOH-Et ₂ O	C ₁₉ H ₂₈ Cl ₂ N ₂ O·C ₄ H ₄ O ₄ ·0.5H ₂ O ^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 ED₅₀, 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		
							yohim-bine potentiation	oxotrem-orine antagonism	apomor-phine potentiation
16	trans	H	115-116	MeOH-Et ₂ O	C ₁₆ H ₂₄ N ₂ O·C ₇ H ₈ SO ₃ ·0.5H ₂ O ^a	C, H, N, S	3	2	0.8
29	cis	H	169-170	MeOH-Et ₂ O	C ₁₆ H ₂₄ N ₂ O·HCl·0.5H ₂ O	C, H, Cl, N	10	>50	>50
6	trans	3,4-Cl ₂	154-155	MeOH-Et ₂ O	C ₁₆ H ₂₂ Cl ₂ N ₂ O·C ₄ H ₄ O ₄ ^b	C, H, Cl, N	0.4	0.2	10
15	cis	3,4-Cl ₂	171-173	MeOH-Et ₂ O	C ₁₆ H ₂₂ Cl ₂ N ₂ O·C ₂ H ₂ O 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 ED₅₀, 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			
							yohim- bine poten- tiation	oxotrem- orine antag- onism	apomor- phine poten- tiation	
30	H	H	104- 105	MeOH- Et ₂ O	C ₁₄ H ₂₆ N ₂ O· C ₂ H ₂ O ₄ ^a	C, H, N	40	>50		
31	CH ₃	H	104	Et ₂ O-pet. ether	C ₁₅ H ₂₂ N ₂ O	C, H, N	7	9	40	
16	CH ₂ CH ₃	H	115- 116	MeOH- Et ₂ O	C ₁₆ H ₂₆ N ₂ O· C ₇ H ₈ SO ₃ ·0.5H ₂ O ^b	C, H, N, S	3	2	0.8	
32	CH ₂ CH ₂ CH ₃	H	115- 116	MeOH- Et ₂ O	C ₁₇ H ₂₆ N ₂ O· C ₁₀ H ₈ SO ₃ ·0.5H ₂ O ^b	C, H, N, S	6	10	40	
33	H	3,4-Cl ₂	168- 169	MeOH- Et ₂ O	C ₁₄ H ₁₈ Cl ₂ N ₂ O·HCl	C, H, Cl, N	9	40	>50	
34	CH ₃	3,4-Cl ₂	164- 165	MeOH- Et ₂ O	C ₁₅ H ₂₀ Cl ₂ N ₂ O· C ₂ H ₂ O ₄ ^a	C, H, Cl, N	9	10	20	
6	CH ₂ CH ₃	3,4-Cl ₂	154- 155	MeOH- Et ₂ O	C ₁₆ H ₂₂ Cl ₂ N ₂ O· C ₄ H ₄ O ₄ ^d	C, H, Cl, N	0.4	0.2	10	
35	CH ₂ CH ₂ CH ₃	3,4-Cl ₂	120- 121	MeOH- Et ₂ O	C ₁₇ H ₂₂ Cl ₂ N ₂ O· C ₄ H ₄ O ₄ ^d	C, H, Cl, N	2	7	0.9	
36	c-C ₃ H ₅	3,4-Cl ₂	145- 146	MeOH- Et ₂ O	C ₁₇ H ₂₂ Cl ₂ N ₂ O· C ₂ H ₂ O ₄ ^a	C, H, Cl, N	0.2	0.3	0.4	
37	c-C ₄ H ₇	3,4-Cl ₂	101- 103	MeOH- Et ₂ O	C ₁₈ H ₂₄ Cl ₂ N ₂ O· C ₂ H ₂ O ₄ ^a	C, H, Cl, N	0.8	0.6	>50	
38	c-C ₆ H ₁₁	3,4-Cl ₂	118- 119	pet. ether	C ₂₀ H ₂₈ Cl ₂ N ₂ O	C, H, Cl, N	1	2	>50	
39	CH(CH ₃) ₂	3,4-Cl ₂	171- 174	MeOH- Et ₂ O	C ₁₇ H ₂₀ Cl ₂ N ₂ O· C ₂ H ₂ O ₄ ^a	C, H, Cl, N	2	4	5	
40	CH=CH ₂	3,4-Cl ₂	196- 197	MeOH- Et ₂ O	C ₁₆ H ₂₀ Cl ₂ N ₂ O· C ₂ H ₂ O ₄ ·0.25H ₂ O ^a	C, H, Cl, N	2	5	5	
41		3,4-Cl ₂	114- 115	Et ₂ O-pet. ether	C ₁₈ H ₂₀ Cl ₂ N ₂ O ₂	C, H, Cl, N	9	>50	>50	
42		3,4-Cl ₂	111- 113	Et ₂ O-pet. ether	C ₁₈ H ₂₀ Cl ₂ N ₂ SO	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 ED₅₀, 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 $\pm 0.4\%$ 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 MgSO₄ and evaporated. The residual oil was distilled to give 3 (276 g, 90% yield): bp 98–100 °C (14 mm); NMR (CDCl₃) 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, CH₃), 1.2–2.0 (m, 6 H, ring CH₂); 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. (C₇H₁₅NO·0.5 C₄H₄O₄) 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 MgSO₄. 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 (D₂O) 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, CH₃), 1.2–2.3 (m, 6 H, ring CH₂); IR 3380 (NH), 2600, 2520, 2400 (NH⁺ acid OH), 1600, 1580, 1480 (CO₂⁻/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. (C₁₃H₁₈Cl₂N₂·C₄H₄O₄) 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. Szmuzkovicz, U.S. Patent 4204003, 1980; *ibid.*, 4148913, 1979; *ibid.*, 4156014, 1979; *ibid.*, 4156015, 1979; *ibid.*, 4157398, 1979; *ibid.*, 4159340, 1979.

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

compd	X	mp, °C	recrystn solvent	formula	anal.	ED ₅₀ , ^h mg/kg		
						yohim- bine poten- tiation	oxotrem- orine antag- onism	apomor- phine poten- tiation
16	H	115- 116	MeOH Et ₂ O	C ₁₆ H ₂₄ N ₂ O C ₇ H ₈ SO ₃ ·0.5H ₂ O ^a	C, H, N, S	3	2	0.8
43	2-CH ₃	129- 130	MeOH- Et ₂ O	C ₁₇ H ₂₆ N ₂ O C ₂ H ₂ O ₄ ^b	C, H, N	7	5	>50
44	3-CH ₃	139- 140	MeOH- Et ₂ O	C ₁₇ H ₂₆ N ₂ O C ₂ H ₂ O ₄ ^b	C, H, N	3	1	25
45	4-CH ₃	167- 168	MeOH- Et ₂ O	C ₁₇ H ₂₆ N ₂ O C ₁₀ H ₈ SO ₃ ·0.5H ₂ O ^c	C, H, N, S	30	10	10
46	3-OCH ₃	135- 136	MeOH- ether	C ₁₇ H ₁₈ N ₂ O ₂ C ₂ H ₂ O ₄ ·0.5H ₂ O ^b	C, H, N	0.8	4	4
47	4-OCH ₃	146- 148	MeOH- ether	C ₁₇ H ₂₀ N ₂ O ₂ C ₁₀ H ₈ SO ₃ ^c	C, H, N, S	30	20	>50
48	3,4-(OCH ₃) ₂	155- 156	MeOH- ether	C ₁₈ H ₂₂ N ₂ O ₂ C ₄ H ₄ O ₄ ^d	C, H, N	9	10	10
49	3-F	85- 88	EtOH- Et ₂ O	C ₁₆ H ₁₄ FN ₂ O C ₂ H ₂ O ₄ ^b	C, H, F, N	0.4	0.6	5
50	4-F	154- 155	MeOH- Et ₂ O	C ₁₆ H ₁₄ FN ₂ O C ₁₀ H ₈ SO ₃ ^c	C, H, F, N, S	5	0.08	>50
51	2,3,4,5,6-F ₅	152- 153	MeOH- Et ₂ O	C ₁₆ H ₁₀ F ₅ N ₂ O C ₂ H ₂ O ₄ ^b	C, H, F, N	>50	>50	>50
52	2-Cl	156- 157	MeOH- Et ₂ O	C ₁₆ H ₁₄ ClN ₂ O C ₂ H ₂ O ₄ ^b	C, H, Cl, N	6	2	>50
53	3-Cl	152- 153	MeOH- Et ₂ O	C ₁₆ H ₁₄ ClN ₂ O C ₂ H ₂ O ₄ ^b	C, H, Cl, N	0.4	0.2	20
18	4-Cl	75- 76	pet. ether	C ₁₆ H ₂₃ ClN ₂ O	C, H, Cl, N	3	0.2	>50
6	3,4-Cl ₂	154- 155	MeOH- Et ₂ O	C ₁₆ H ₁₄ Cl ₂ N ₂ O C ₄ H ₄ O ₄ ^e	C, H, Cl, N	0.4	0.2	10
54	3-Cl, 4-CH ₃	122- 123	MeOH- Et ₂ O	C ₁₇ H ₁₆ ClN ₂ O C ₂ H ₂ O ₄ ^b	C, H, Cl, N	1	0.6	2
55	4-Cl, 3-CH ₃	131- 132	MeOH- Et ₂ O	C ₁₇ H ₁₆ ClN ₂ O C ₂ H ₂ O ₄ ^b	C, H, Cl, N	2	2	10
56	3-Cl, 4-F	152- 153	MeOH- Et ₂ O	C ₁₆ H ₁₂ ClFN ₂ O C ₂ H ₂ O ₄ ^b	C, H, Cl, F, N	0.2	2	0.7
57	3,5-Cl ₂	129- 130	MeOH- Et ₂ O	C ₁₆ H ₁₄ Cl ₂ N ₂ O C ₄ H ₄ O ₄ ^e	C, H, Cl, N	0.9	5	30
58	3,4,5-Cl ₃	145- 146	MeOH- Et ₂ O	C ₁₆ H ₁₂ Cl ₃ N ₂ O C ₄ H ₄ O ₄	C, H, Cl, N	4	40	40
59	3-Br	167- 168	MeOH- Et ₂ O	C ₁₆ H ₁₄ BrN ₂ O C ₂ H ₂ O ₄ ^b	C, H, Br, N	0.1	0.1	2
60	4-Br	78- 79	pet. ether	C ₁₆ H ₂₃ BrN ₂ O	C, H, Br, N	2	3	>50
61	3,4-Br ₂	146- 147	MeOH- Et ₂ O	C ₁₆ H ₁₄ Br ₂ N ₂ O C ₂ H ₂ O ₄ ^b	C, H, Br, N	0.1	0.2	0.5
62	3-CF ₃	135- 136	MeOH- Et ₂ O	C ₁₇ H ₂₃ F ₃ N ₂ O C ₂ H ₂ O ₄ ^b	C, H, N	0.3	0.2	0.9
63	4-CF ₃	184- 185	MeOH- Et ₂ O	C ₁₇ H ₂₃ F ₃ N ₂ O HCl	C, H, Cl, N	10	25	10
64	4-NO ₂	93- 95	MeOH- Et ₂ O	C ₁₆ H ₂₃ N ₃ O ₃ C ₂ H ₂ O ₄ ·H ₂ O ^b	C, H, N	20	6	20
65	4-CO ₂ CH ₃	139- 140	MeOH- Et ₂ O	C ₁₈ H ₂₂ N ₂ O ₃ C ₇ H ₈ SO ₃ ^a	C, H, N, S	>50	>50	>50
66	4-CN	146- 147	MeOH- Et ₂ O	C ₁₇ H ₁₆ N ₂ O C ₄ H ₄ O ₄ ^e	C, H, N	10	40	>50
67	4-COCH ₃	82- 84	EtOH- Et ₂ O	C ₁₈ H ₂₆ N ₂ O ₂ C ₂ H ₂ O ₄ ^b	C, H, N ^f	>50	40	>50
imipramine hydrochloride						4	1	1

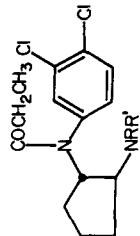
^a *p*-Toluenesulfonic acid salt. ^b Oxalic acid salt. ^c Naphthalenesulfonic acid salt. ^d Fumaric acid salt. ^e Maleic acid salt. ^f N: calcd, 7.14; found, 7.85. ^g N: calcd, 7.00; found, 7.85. ^h The upper and lower 95% confidence intervals were not more than 2 and 0.5 times the ED₅₀, respectively.

The solution was made basic with 20% NaOH and extracted with ether. The extract was washed with saturated NaCl, dried over MgSO₄, 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 (D₂O) 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.	yohim-bine poten-tiation	ED ₅₀ , ^g mg/kg	oxotrem-orine antag-onism	apomor-phine poten-tiation
68	NH ₂	179-180	MeOH-Et ₂ O	C ₁₄ H ₁₈ Cl ₂ N ₂ O·C ₁₀ H ₈ SO ₃ ^a	C, H, Cl, N, S	0.02	0.8		
12	NHCH ₃	176-177	MeOH-Et ₂ O	C ₁₅ H ₂₀ Cl ₂ N ₂ O·C ₁₀ H ₈ SO ₃ ^b	C, H, Cl, N, S	0.4	0.3		
69	NHCH ₂ CH ₃	162-163	MeOH-Et ₂ O	C ₁₆ H ₂₂ Cl ₂ N ₂ O·C ₁₀ H ₈ O ₄ ^c	C, H, Cl, N	0.2	2		
70	NHCH ₂ CH=CH ₂	171-172	MeOH-Et ₂ O	C ₁₇ H ₂₄ Cl ₂ N ₂ O·C ₁₀ H ₈ O ₄ ^c	C, H, Cl, N	0.2	3		
6	N(CH ₃) ₂	154-155	MeOH-Et ₂ O	C ₁₆ H ₂₂ Cl ₂ N ₂ O·C ₁₀ H ₈ O ₄ ^d	C, H, Cl, N	0.4	0.2		10
71	N(CH ₂ CH ₃) ₂	148-149	MeOH-Et ₂ O	C ₁₈ H ₂₆ Cl ₂ N ₂ O·C ₁₀ H ₈ O ₄ ^e	C, H, Cl, N, S	0.1	0.03		0.3
72	N(CH ₂ CH ₂ CH ₃) ₂	58-59	pet. ether	C ₂₀ H ₃₀ Cl ₂ N ₂ O	C, H, Cl, N	2	0.1		>50
73	c-N(CH ₂ CH ₂) ₂	107	MeOH-Et ₂ O	C ₁₈ H ₂₄ Cl ₂ N ₂ O·C ₁₀ H ₈ O ₄ ^c	C, H, Cl, N	0.6	2		3
74	N(CH ₂ CH ₂ CH=CH ₂)	104-106	EtOH-Et ₂ O	C ₁₈ H ₂₄ Cl ₂ N ₂ O·C ₁₀ H ₈ O ₄ ^c	C, H, Cl, N	0.2	0.2		6
75	N(CH ₂ CH ₂ CH ₂ Ph)	120-121	MeOH-Et ₂ O	C ₂₂ H ₂₆ Cl ₂ N ₂ O·C ₁₀ H ₈ O ₄ ^c	C, H, Cl, N	0.2	40		>50
76	N(CH ₂ CH ₂ CH ₂ CH ₂ Ph)	90-91	MeOH-Et ₂ O	C ₂₃ H ₂₈ Cl ₂ N ₂ O·C ₁₀ H ₈ O ₄ ^c	C, H, Cl, N	0.1	0.4		5
77	N(CH ₂ CH ₂ CH ₂ N(CH ₃) ₂)	165-166	MeOH-Et ₂ O	C ₁₉ H ₂₃ Cl ₂ N ₃ O·2HCl·H ₂ O	C, H, Cl, N	0.8	5		20
78	N(CH ₂ CH ₂ CH ₂ CH ₂ N(CH ₃) ₂)	259-260	MeOH-Et ₂ O	C ₂₀ H ₂₄ Cl ₂ N ₃ O·2HCl·0.25H ₂ O	C, H, Cl, N	4	10		30
13	OH	105	Et ₂ O-pet. ether	C ₁₄ H ₁₇ Cl ₂ N ₂ O	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, CH₃), 2.0 (q, 2 H, CH₂CH₂CO), 1.1-1.9 (m, 6 H, ring CH₂), 0.9 (t, 3 H, CH₃CH₂CO); IR 2720, 2530, 2490 (NH⁺/OH), 1665, 1620, 1585, 1560 (C=O/CO₂⁻/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. (C₁₆H₂₂Cl₂N₂O·C₄H₈O₄) 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-cyclopentanediimine (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 NaHCO₃ (100 mL) was added. The organic layer was washed with water and saturated NaCl, dried over MgSO₄, and evaporated. The crude product was converted to the hydrochloride salt (3.2 g, 80% yield): mp 184-185 °C; NMR (D₂O) δ 7.9 (m, 4 H, aromatic), 2.9 (s, 6 H, CH₃), 1.4-2.3 (m, 8 H, ring CH₂ and CH₂CH₂CO), 0.9 (t, 3 H, CH₃CH₂CO); mass spectrum, *m/e* 328. Anal. (C₁₇H₂₃F₃N₂O·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 (D₂O) 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 CH₂); 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. (C₁₁H₁₃Cl₂NO·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 suspension 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 (Me₂SO) 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 CH₂); IR 2760, 2700, 2580, 2500 (NH⁺), 1605 (C=C), 1265, 1210, 1035, 1020 (OSO₃H/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. (C₁₁H₁₃Cl₂NO₄S) C, H, Cl, N, S.

***trans*-*N*-Methyl-*N'*-(3,4-dichlorophenyl)-1,2-cyclopentanediimine (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 MgSO₄, 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 (D₂O) δ 6.6-7.4 (m, 3 H, aromatic), 2.7 (s, 3 H, CH₃), 1.5-2.0 (m, 6 H, ring CH₂); 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. (C₁₂H₁₆Cl₂N₂·2HCl) 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 NaHCO₃ (100 mL) was added. The organic layer was washed with saturated NaCl, dried over MgSO₄, 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 (D₂O) δ 7.1 (m, 1 H, aromatic), 6.6 (m, 1 H, aromatic), 6.4 (m, 1 H, aromatic), 4.75 (s, 2 H,

$\text{CCl}_3\text{CH}_2\text{CO}$), 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 ($\text{C}=\text{O}$), 1585, 1570 ($\text{C}=\text{C}$) 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 $\text{CH}_3\text{CH}_2\text{CO}$), 1.0 (t, 3 H, $\text{CH}_3\text{CH}_2\text{CO}$); IR 1710, 1765 ($\text{C}=\text{O}$) 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. ($\text{C}_{18}\text{H}_{21}\text{Cl}_5\text{N}_2\text{O}_3$) 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, $\text{CH}_3\text{CH}_2\text{CO}$), 1.0–2.0 (m, 6 H, ring CH_2), 0.9 (t, 3 H, $\text{CH}_3\text{CH}_2\text{CO}$); IR 2950, 2820, 2480 (NH^+), 1676 ($\text{C}=\text{O}$), 1620, 1585, 1580, 1560, 1495 ($\text{C}=\text{C}$) 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. ($\text{C}_{15}\text{H}_{20}\text{Cl}_2\text{N}_2\text{O}\cdot\text{C}_7\text{H}_9\text{O}_3\text{S}$) C, H, Cl, N, S.

***N*-(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, $\text{CH}_3\text{CH}_2\text{CO}$), 1.3–2.0 (m, 6 H, ring CH_2), 1.1 (t, 3 H, $\text{CH}_3\text{CH}_2\text{CO}$); IR 3480, 3380 (OH), 1670, 1655 ($\text{C}=\text{O}$), 1585, 1560 ($\text{C}=\text{C}$), 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. ($\text{C}_{14}\text{H}_{17}\text{Cl}_2\text{NO}_2$) 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 ($\text{C}=\text{O}$) 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 $\text{CH}_3\text{CH}_2\text{CO}$), 1.0 (t, 3 H, $\text{CH}_3\text{CH}_2\text{CO}$); IR 2660, 2460 (NH^+ , acid OH), 1670 ($\text{C}=\text{O}$), 1590 ($\text{C}=\text{C}$) 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. ($\text{C}_{16}\text{H}_{22}\text{Cl}_2\text{N}_2\text{O}$) 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.

(4) R. M. Quinton, *Br. J. Pharmacol.*, 21, 51 (1963).

(5) A. Ahmed and P. B. Marshall, *Br. J. Pharmacol.*, 18, 247 (1962).

(6) H. G. Menge and N. Brand, *Psychopharmacologia*, 21, 212 (1971).

(7) Spearman and Karber, D. J. Finney, "Statistical Method in Biological Assay", Hafner, New York, 1952.