For the chlorambucil peptides, the stock solutions (10 mg/mL of dimethyl sulfoxide) were diluted with normal saline immediately before the experiment in order to avoid potential undesirable interaction between chlorambucil and the buffer.[34] Preincubation experiments were carried out by mixing citrated human plasma or thrombin with the chlorambucil peptides for 15 min at 4 °C, and thrombin time for these analogues was evaluated as usual.

Thrombin amidolytic assays were carried out as described previously[35] by measuring at 405 nm (Gilford Model 240 spectrophotomer) the amount of chromophore generated by 0.5 unit of thrombin at 37 °C from the mixture of 0.25 mL of 1 mM Tos-Gly-Pro-Arg-*p*-nitroanilide acetate (Boehringer Mannheim), 0.25 mL of saline containing 2 mg/mL of peptide, and 1.5 mL of normal saline.

When preincubation was indicated, saline solutions containing the chlorambucil peptides were incubated with thrombin at 4 °C for 15 min, and the mixtures were added to the remaining buffer and chromogenic substrate solutions as usual.

Fibrin reaggregation assays were performed by diluting 25 μL of fibrin monomer solution (8.3 mg of protein/mL) derived from human fibrinogen (grade L, Kabi, Stockholm, Sweden) in 1 mL of phosphosphate buffer containing the tested peptide, and the resultant reaggregation was monitored at 350 nm (Gilford Model 240 spectrophotometer) as described by Laudano and Doolittle.[5] Different preparations of fibrin or different sets of experiments gave similar results when the concentrations of fibrin and inhibitors were held constant. Averaged values were used, and inhibitory activities were calculated on a molar basis by comparing the slopes of the linear part of the dose–response curve for the compounds with the slope of the reference.

When preincubation was indicated, 10 μL of the chlorambucil peptide (1 mg/mL of Me_2SO) and of Gly-Pro-Arg-Pro (5 mg/mL of Me_2SO) were diluted in 10 μL of 1 M NaBr/0.05 M NaOAc (pH 5.3) and mixed with 20 μL of fibrin monomers (10.6 mg of protein/mL) for 15 min at room temperature, followed by the addition of the phosphate buffer (1 mL) as usual.

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(35) G. D. Wilner, M. Danitz, M. S. Mudd, K. H. Hsieh, and J. W. Fenton II, *J. Lab. Clin. Med.*, in press.

Acknowledgment. This investigation was supported by Grant HL-22642 from the National Heart and Lung Institute, National Institutes of Health. We thank Drs. D. C. Owsley and J. J. Bloomfield for their helpful discussion, in addition to the gracious loan of the Rayonet photochemical reactor from the Monsanto Company, St. Louis, MO. Amino acid analyses performed by Dr. R. Mecham and secretarial assistance from C. Kamon and V. Newberry are gratefully acknowledged.

Salicylamide Derivatives Related to Medroxalol with α- and β-Adrenergic Antagonist and Antihypertensive Activity[1]

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Analogues of medroxalol (1) were prepared in which the carboxamide function, the phenolic hydroxy group, and the aralkylamine side chain were modified. *N*-Alkyl-substituted amide analogues of 1 showed diminishing β-blocking activity with increasing steric bulk of the alkyl group. This allowed the conclusion that deactivation of the phenolic hydroxy group of 1 by the carbonyl group of the amide function is responsible for the β-adrenergic antagonistic properties of 1. This conclusion was strengthened by the finding that the phenolic *O*-methyl analogue 5-[2-[[3-(1,3-benzodioxol-5-yl)-1-methylpropyl]amino]-1-hydroxyethyl]-2-methoxybenzamide (13) was found to have enhanced β-adrenergic blocking activity. The finding that 13 also had decreased α-blocking activity compared to 1 indicated that the phenolic hydroxy group of 1 enhances α-adrenergic antagonism. The finding that 1 and 13 showed such a large difference in relative α- to β-blocking potency while exhibiting approximately equal antihypertensive activity in spontaneously hypertensive rats was surprising. It indicated that pharmacologic properties other than α- and β-adrenergic blockade may contribute to the antihypertensive activity of medroxalol. One of the analogues in which the aralkylamine side chain of 1 was replaced by a fragment of a known α-adrenergic receptor blocker, 2-hydroxy-5-[1-hydroxy-2-[4-(2-methylphenyl)-1-piperazinyl]ethyl]benzamide (22), showed an interesting pharmacologic profile of potential therapeutic usefulness.

Adrenergic α-receptor antagonists were reported years ago to be useful in the treatment of hypertension.[2-4] However, side effects, such as postural hypertension, palpitations, and failure of sexual function, discouraged their use.[5] More recently, β-adrenergic receptor antagonists have been shown to be effective in the treatment of hypertension and they are now widely used for this indication.[6,7] Their potential to depress myocardial function or to precipitate bronchial asthma, however, limits their use.[7] Attempts to improve antihypertensive therapy by combining an α-adrenergic antagonist with a β-adrenergic antagonist have resulted in good control of blood pressure with few side effects in some studies[8,9] but with a discouraging incidence of side effects in others.[10,11] The

(1) Presented in part by T. M. Bare, J. T. Suh, J. M. Grisar, G. P. Claxton, R. C. Dage, H. C. Cheng, and J. K. Woodward at a symposium on New Advances in Cardiovascular Research, 11th Central Regional Meeting of the American Chemical Society, Columbus, Ohio, May 7–9, 1979, Abstr. MED-06.
(2) M. Moser, M. Walters, A. M. Master, R. C. Taylor, and J. Metraux, *Arch. Int. Med.*, **89**, 708 (1952).
(3) J. L. Bakke and R. H. Williams, *Am. J. Med.*, **14**, 141 (1953).
(4) S. I. Miller, R. V. Ford, J. H. Moyer, *N. Engl. J. Med.*, **248**, 576 (1953).
(5) D. G. McDevitt, *Drugs*, **17**, 267 (1979).
(6) B. N. C. Prichard and P. M. S. Gilliam, *Br. Med. J.*, **1**, 7 (1969).
(7) P. Lewis, *Am. J. Med.*, **60**, 837 (1976).
(8) P. A. Majid, M. K. Meeran, M. E. Benaim, B. Shara, and S. H. Taylor, *Br. Heart J.*, **36**, 588 (1974).
(9) N. D. Vlachakis and M. Mendlowitz, *J. Clin. Pharmacol.*, **16**, 352 (1976).
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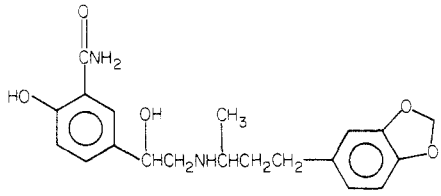
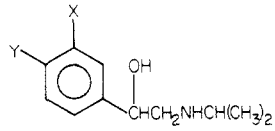
combination of both properties in a single molecule, such as labetalol, appear to offer some advantage over pure β-adrenergic receptor antagonists in the treatment of hypertension.[12,13] Medroxalol (1)[14] is another such agent;



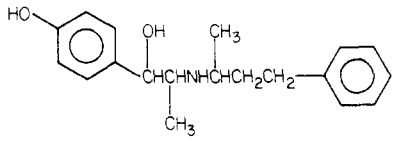
1

it blocks α- and β-adrenergic responses and lowers blood pressure in experimental hypertension.[1,15-17] We were interested in determining the effects of changes in molecular structure of medroxalol on α- and β-adrenergic antagonistic responses and on antihypertensive activity in spontaneously hypertensive (SH) rats.

A look at the structure of 1 readily reveals the portion of the molecule that corresponds to norepinephrine and isoproterenol (2). β-Adrenergic antagonists result when



2, X, Y = OH
3, X, Y = -CH=CHCH=CH-
17, X = $CONH_2$; Y = OH

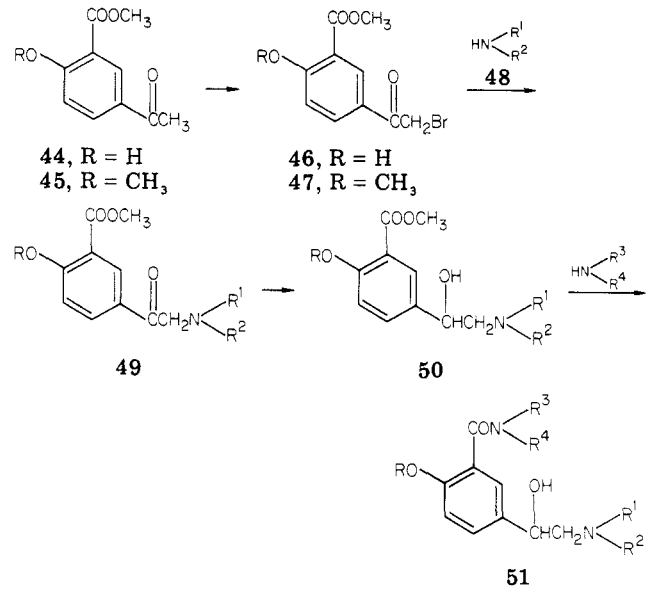


18

the phenolic hydroxy groups of isoproterenol (2) are removed or replaced by substituents, as in pronethalol (3).[18,19] To enhance β-blocking activity of 1, we decided to modify the carboxamide function and to block the phenolic hydroxy group by alkylation. Accordingly, compounds 4–13 (Table I) were synthesized. Two small variations of the aralkyl side chain of 1 that could be expected to affect β-blocking activity[18] were also synthesized (compounds 14–16).

A clue as to what produces α-adrenergic antagonism is given by the report that compound 17 is a pure β blocker devoid of α-blocking activity.[20] This would imply that the aralkyl side chain of 1 is responsible for α-blocking activity. This is corroborated by the finding reported by Ariens and co-workers,[21] and confirmed by us, that nylidrin (18), which

Scheme I



is a β-agonist, also produces α-adrenergic receptor blockade. To enhance α-adrenergic antagonistic activity we therefore considered replacing the aralkyl side chain of 1 with one of known α blockers. If a part of the structure of piperoxan (19, Chart I), a known α-adrenergic receptor blocker,[22,23] is combined with the salicylamidoethanolamine portion of 1, a molecule of structure 20 results. Another group of known α blockers, including 21,[24] is characterized by an o-tolylpiperazine moiety,[22,23] which can replace the aralkyl side chain of 1 to give 22. Droperidol (23) and related neuroleptic agents of the butyrophenone series have been reported to be potent α-adrenergic receptor blockers,[25] and one way of combining its structure with that of medroxalol is shown in 24. Lastly, prazosin (25) was recently shown to be a potent postsynaptic α blocker,[26] and its 1-furoylpiperazine moiety can replace the aralkyl side chain of medroxalol as in 26. We synthesized and evaluated compounds 20, 22, 24, and 26. Since 22 had an interesting pharmacologic profile, additional close structural analogues (27–43) were prepared. The compounds prepared and the results of their pharmacologic evaluation are listed in Table I.

Chemistry. The compounds listed in Table I were synthesized by the route shown in Scheme I, which was also used for the synthesis of 1.[15] Bromo ketone 46 (or 47) was condensed with amine 48 in THF at 25 °C in the presence of 1 equiv of Et_3N (or 100% excess amine 48). The Et_3N·HBr that precipitated was removed by filtration and 49 was recovered from the filtrate as the HCl salt. For primary amines (48, R^1 = H), prolonged reaction and/or elevated reaction temperatures led to side products (probably Schiff bases with 46 and/or 49) and, therefore, low yields. Since compounds 49 were unstable as free bases and as hydrochloride salts, purification by recrystallization was avoided. The yields in this step were only fair and

(12) B. N. C. Prichard and A. J. Boakes, *Br. J. Clin. Pharmacol.*, 3 (Suppl 3), 743 (1976).
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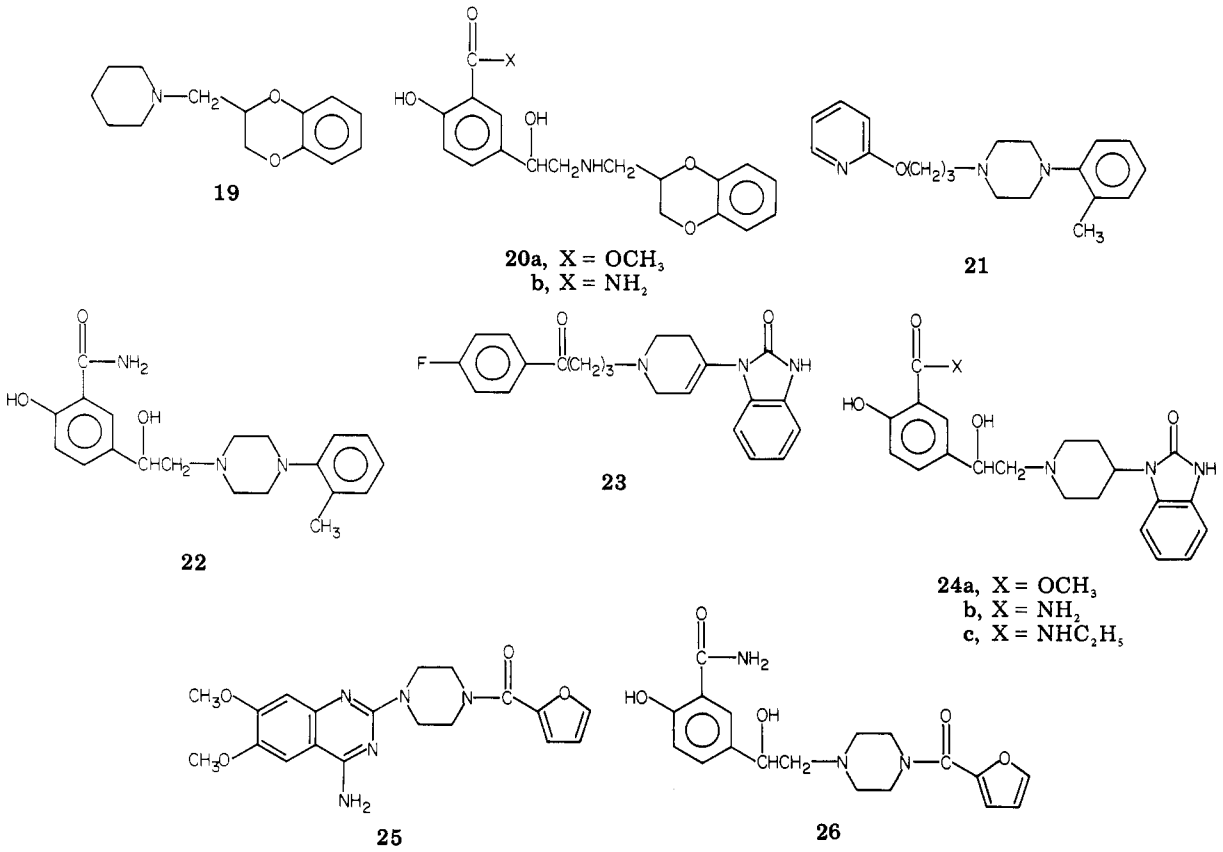
Chart I



sometimes poor. The amino ketones **49** were reduced to amino alcohols **50** by hydrogenation over Pd/C or, preferably, with $NaBH_4$ in MeOH at 0 °C. Amination of esters **50** to amides **51** proceeded slowly even in the presence of freshly prepared NaOMe as catalyst; the reaction was monitored by TLC to determine disappearance of the ester. To prepare the dimethyl amide analogue **11** the procedure of Basha et al.[27] was used, in which Me_2AlNMe_2 was generated from Me_3Al and $HNMe_2$ and allowed to react with ester **50**. Some of the amides **51** with two asymmetric centers were assayed for diastereoisomer composition by GLC of derivatives formed by treatment with excess butaneboronic acid.[28]

Results and Discussion

The results of the pharmacologic evaluation are shown in Tables I and II. Modification of the carboxamide function of **1** represented by compounds **4–11** gave the following results. The acid **4** corresponding to **1** was totally inactive, while the pharmacologic profile of the methyl ester **5** was quite similar to that of **1**. The alkyl-substituted secondary amide analogues **6–9** changed very little in α-blocking activity, but β-blocking activity decreased and a larger decrease was observed with increasing bulk of the substituent. This has some interesting implications. A competitive β-adrenergic receptor antagonist, such as pronethalol (**3**), binds to the receptor but is unable to elicit the response because it lacks the catechol hydroxy groups of isoproterenol (**2**).[18,29] The fact that medroxalol (**1**) is a β-receptor antagonist gives rise to the possibility that the amide group somehow shields or deactivates the phenolic *p*-OH group (which is present in **1**) and with it the β-adrenergic response. Three ways in which the amide group might do this are (a) by steric bulk, (b) by hydrogen bonding of an amide N proton to the OH group or its counterpart at the receptor, or (c) by deactivation of the OH group by the carbonyl function by electron withdrawal, resonance, and/or hydrogen bonding. Our data on β-blocking activity of compounds **6–9** rule out the steric bulk theory; the hydrogen-bonding theory is ruled out by the fact that the ester and dimethyl amide analogues **5** and **11** (that have no NH) are effective β blockers. The conclusion can be made, therefore, that deactivation of the phenolic OH group by inductive, resonance, and/or hydrogen bonding of the carbonyl group of the amide function is responsible for the ability of **1** to display the properties of a competitive antagonist at β-adrenergic receptors. This conclusion is consistent with reports that sulfamoyl[30] and methylsulfinyl[31] analogues are also potent β blockers, while analogues lacking a carbonyl group adjacent to the phenolic *p*-OH group are β-adrenergic agonists.[30,32]

It has been reported that N-substituted salicylamides, particularly *N*-dodecylsalicylamide, elicit papaverine-like spasmolytic activity.[33] The medroxalol analogues were therefore evaluated for antagonism to $BaCl_2$-induced

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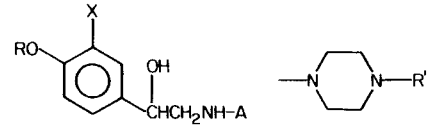
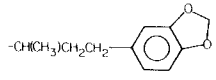
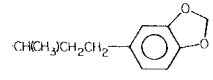
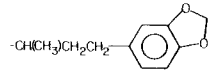
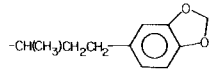
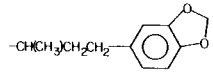
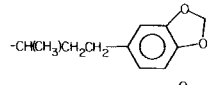
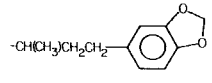
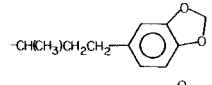
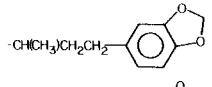
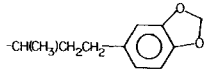
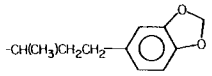
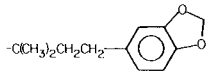
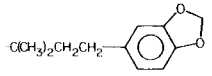
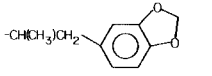
Table I. Medroxalol Analogues. In Vitro Sympatholytic and Spasmolytic Activity and Antihypertensive Activity in Spontaneously Hypertensive Rats



1-16 27-43

no.	X	R	A	mp, °C (recrystn solvent)[a]	formula	anal.	sympatholytic act.: pA_2, $-\log K_B$			spasmolytic act.: pA_2: $-\log K_B$; $BaCl_2$[e]	BP decrease, mmHg, 50 mg/kg po, SHR[f]	
							α[b]	β[c]	ratio β/α[d]		1 h	4 h
1[g]	$CONH_2$	H		211-213 dec (A)	$C_{20}H_{24}N_2O_5 \cdot HCl$	C, H, N	6.08	7.82	55	5.63	88[h]	90[h]
4	COOH	H		163-166 dec (A)	$C_{20}H_{23}NO_6 \cdot HCl$	C, H, N	5.20	5.10	0.8	<4	6[i]	5[i]
5	$COOCH_3$	H		197 dec (B)	$C_{21}H_{25}NO_6 \cdot HCl$	C, H, N	5.73	7.62	78	6.90	56[h]	53[h]
6	$CONHCH_3$	H		215-216 dec (A)	$C_{21}H_{26}N_2O_5 \cdot HCl$	C, H, N	5.90	6.69	6.2	6.42	84[h]	91[h]
7	$CONHC_2H_5$	H		182-183 dec (A)	$C_{22}H_{29}N_2O_5 \cdot HCl$	C, H, Cl, N	5.86	6.36	3.2	5.76	95[h]	108[h]
8	$CONHCH(CH_3)_2$	H		167-169 dec (A)	$C_{23}H_{30}N_2O_5 \cdot HCl$	C, H, Cl, N	5.85	5.88	1.1	6.38	48[i]	10[i]
9	$CONHCH_2C(CH_3)_3$	H		206-207 dec (A)	$C_{25}H_{34}N_2O_5 \cdot HCl$	C, H, N	6.05	5.88	0.8	6.90	55[h,j]	24[i,j]
10	$CONHC_{12}H_{25}$	H		185-187 dec (A)	$C_{32}H_{48}N_2O_5 \cdot HCl$	C, H, N	<5	4.53		>4.2[k]	16[i]	18[i]
11	$CON(CH_3)_2$	H		192-194 dec (A)	$C_{22}H_{28}N_2O_5 \cdot HCl$	C, H, N	5.46	7.21	56	5.06	24[h]	22[i]
12	$COOCH_3$	CH_3		159-162 dec (C)	$C_{22}H_{27}NO_6 \cdot HCl$	C, H, N	5.56	8.10	372	5.56[l]	44[h]	22[i]

13[m]	$CONH_2$	CH_3		147–156 dec (C)	$C_{21}H_{26}N_2O_5 \cdot HCl$	C, H, N	<5.14	8.46	>2089	4.36	76[h]	78[h]
14	$COOCH_3$	H		225–226 dec (C)	$C_{22}H_{27}NO_6 \cdot HCl \cdot 0.5H_2O$	C, H, N	<5	6.55		5.58	41[h]	39[i]
15	$CONH_2$	H		217–218 dec (D)	$C_{21}H_{26}N_2O_5 \cdot HCl$	C, H, N	5.31	7.15	69	6.17	43[h]	61[h]
16[n]	$CONH_2$	H		185–186 dec (D)	$C_{19}H_{22}N_2O_5$	C, H, N	6.04	5.97	0.9	5.34	79[h]	73[h]
20a	see structure in text			195–196 dec (A)	$C_{19}H_{21}NO_6 \cdot HCl$	C, H, N	6.21	5.92	0.5	5.39	46[h]	31[h]
20b	see structure in text			160–162 dec (E)	$C_{18}H_{20}N_2O_5$	C, H, N	6.20	5.84	0.4	4.57	24[h]	18[i]
22[o]	see structure in text			192–193 dec (C)	$C_{20}H_{25}N_3O_3 \cdot 2HCl$	C, H, N	7.57	6.70	0.1	5.73	48[h]	37[h]
24a[p]	see structure in text			229–230 dec (C)	$C_{22}H_{25}N_3O_5 \cdot HCl$	C, H, Cl, N	6.94	5.71	0.06	5.90	52[h]	37[h]
24b	see structure in text			213–215 dec (A)	$C_{21}H_{24}N_4O_4 \cdot HCl \cdot H_2O$	C, H, Cl, N[q]	6.70	5.45	0.06	<4.21	6[i]	15[i]
24c	see structure in text			222–224 dec (A)	$C_{23}H_{28}N_4O_4 \cdot HCl$	C, H, N	6.63	<5.38	<0.06	5.16	22[h]	51[h]
26	see structure in text			189–191 dec (C)	$C_{18}H_{21}N_3O_5$	C, H, N	<5	<5		<4	30[i]	28[i]
			R′									
27	$CONH_2$	H	C_6H_5	128–132 dec (D)	$C_{19}H_{23}N_3O_3 \cdot HCl \cdot 0.33H_2O$	C, H, N[q]	7.04	r		4.19	7[i]	9[i]
28	$CONH_2$	H	C_6H_4Cl-*p*	157–160 dec (C)	$C_{19}H_{22}ClN_3O_3 \cdot HCl \cdot H_2O$	C, H, N[q]	6.87	6.17	0.2	4.58	49[h]	56[h]
29	$CONH_2$	H	$C_6H_4OCH_3$-*p*	207–208 dec (C)	$C_{20}H_{25}N_3O_4 \cdot 2HCl$	C, H, N	6.13	5.84	0.5	<4.28	10[i]	7[i]
30	$CONH_2$	H	$C_6H_5OCH_3$-*o*	226–227 dec (A)	$C_{20}H_{25}N_3O_4 \cdot HCl$	C, H, N	7.42	6.44	0.1	4.87	45[h]	35[h]
31	$CONH_2$	H	$C_6H_5CF_3$-*m*	218–220 dec (C)	$C_{20}H_{22}F_3N_3O_3 \cdot HCl$	C, H, N	6.33	6.90	3.7	5.74	1[i]	18[i]
32	$CONH_2$	H	C_5H_4N-2	220–222 dec (C)	$C_{18}H_{22}N_4O_3 \cdot HCl \cdot 0.25H_2O$	C, H, N[q]	6.08	5.37	0.2	3.90	16[i]	13[i]
33	$CONH_2$	H	$CH_2C_6H_5$	172–175 dec (C)	$C_{20}H_{25}N_3O_3 \cdot 2HCl$	C, H, Cl, N	5.13	5.07	0.9	<4.13	35[i]	40[i]
34	$CONHCH_3$	H	$C_6H_4OCH_3$-*p*	188–189 dec (C)	$C_{21}H_{27}N_3O_4 \cdot HCl \cdot 0.8H_2O$	C, H, N[q]	5.47	5.17	0.2	4.82	20[i]	14[i]
35[s]	$CONHCH_3$	H	$C_6H_4OCH_3$-*o*	162–165 dec (F)	$C_{21}H_{27}N_3O_4 \cdot HCl \cdot H_2O$	C, H, N[q]	7.95	r		5.02	44[h]	52[h]
36	$CONHCH_2C(CH_3)_3$	H	$C_6H_4CH_3$-*o*	239–240 dec (C)	$C_{25}H_{35}N_3O_3 \cdot HCl$	C, H, N	7.21	6.33	0.1	6.65	41[h]	32[h]
37	$COOCH_3$	H	$C_6H_4CH_3$-*o*	226–227 dec (C)	$C_{21}H_{26}N_2O_4 \cdot HCl$	C, H, N	7.45	6.79	0.2	6.06	5[i]	6[i]
38	$COOCH_3$	H	COC_4H_3O-2	192–195 dec (C)	$C_{19}H_{22}N_2O_6 \cdot HCl$	C, H, Cl, N	<5	<5		4.76	37[i]	15[i]
39	CHN_4-5	H	$C_6H_4CH_3$-*o*	186–188 dec (C)	$C_{20}H_{24}N_6O_2 \cdot H_2O$	C, H, Cl, N[q]	7.56	6.14	0.04	<4	48[h]	47[i]
40	$CONH_2$	CH_3	C_6H_5	235–236 dec (C)	$C_{20}H_{25}N_3O_3 \cdot HCl$	C, H, N	6.54	<5		4.19	38[h]	25[h]
41	$CONH_2$	CH_3	$C_6H_4OCH_3$-*o*	247–248 dec (A)	$C_{21}H_{27}N_3O_4 \cdot HCl$	C, H, N	6.80	5.41	0.04	4.48	56[h]	46[h]
42	$COOCH_3$	CH_3	$C_6H_4OCH_3$-*o*	198–200 dec (A)	$C_{22}H_{28}N_2O_5 \cdot HCl$	C, H, Cl, N	7.00	6.41	0.3	4.46	37[h]	35[h]
43	$CONH_2$	C_2H_5	C_6H_5	208–210 dec (C)	$C_{21}H_{27}N_3O_3 \cdot HCl$	C, H, N	6.27	5.27	0.1	4.67	22[h]	19[i]
phentolamine							7.78	<5		5.70	62[h]	60[h]
propranolol							<5	8.89		5.75	28[i]	46[i]
nylidrin							6.21	r		5.37	54[h]	51[h]

[a] A = *i*-PrOH/H_2O; B = MeOH; C = MeOH/H_2O; D = MeOH/Et_2O; E = CH_2Cl_2; F = H_2O; G = MeOH/EtOAc. [b] Rabbit aortic strips; norepinephrine-induced contraction. [c] Guinea pig atria; isoproterenol-induced chronotropy. [d] Obtained by converting pA_2 values to their antilogarithms and obtaining the ratio. [e] Guinea pig ileum; $BaCl_2$-induced contraction. [f] Spontaneously hypertensive rats, 12 animals per group compared to control. [g] Medroxalol; RMI 81 968. [h] Statistically significant at $p < 0.05$. [i] Not statistically significant, $p > 0.05$. [j] 10 mg/kg ip; not active at 50 mg/kg po. [k] Compound insoluble. [l] Based on one determination only. [m] RMI 18 106. [n] RMI 81 929. [o] RMi 17 340. [p] RMI 17 352. [q] To confirm H_2O content, a neutralization equivalent was determined and was found to be within ±0.4% of theoretical values. [r] β-Adrenergic agonist. [s] RMI 17 964.

Table II. Medroxalol Analogues. In Vivo Sympatholytic Activity in Anesthetized Dogs

compd	sympatholytic act., DR_{10}, X ± SE (n), mg/kg iv		
	α[a]	β_1[b]	β_2[c]
1	3.86 ± 0.18 (3)	0.84 ± 0.12 (3)	1.17 ± 0.69 (3)
5	5.82 ± 0.60 (3)	2.19 ± 0.27 (3)	5.46 ± 1.9 (3)
6	5.44 ± 0.77 (3)	8.63 ± 1.3 (3)	3.61 ± 0.22 (3)
7	3.22 ± 1.4 (3)	11.82 + 2.9 (3)	16.8 ± 4.2 (3)
8	4.84 ± 0.36 (3)	22.52 ± 9.8 (3)	14.8 ± 1.7 (3)
9	6.60 ± 1.7 (3)	>10 (3)	>10 (3)
13	9.68 ± 4.14 (2)	0.23 ± 0.03 (2)	1.64 ± 0.98 (2)
15		2.10 ± 0.63 (3)	0.76 ± 0.04 (3)
16	16.04 ± 1.71 (2)	6.75 ± 2.79 (3)	7.13 ± 2.06 (3)
22	1.09 ± 0.14 (3)	15.3 ± 5.6 (3)	>10 (3)
phentolamine	2.64 ± 0.29 (3)		
propranolol		0.54 ± 0.01 (3)	0.26 ± 0.05 (3)

[a] Phenylphrine-induced vasopressor response. [b] Isoproterenol-induced chronotropy. [c] Isoproterenol-induced vasodepression (diastolic).

contractions in an isolated guinea pig ileum preparation (Table I, column 11). The amide *N*-alkyl analogues **6–9** showed increased potency in $BaCl_2$ antagonism compared to **1**, and activity increased with increasing bulk of the alkyl substituent. The trend is obscured in the data on antihypertensive activity, apparently due to lack of oral absorption of the more highly substituted analogues. The neopentyl analogue **9** showed antihypertensive activity after intraperitoneal, but not after oral, administration. The *N*-dodecyl analogue **10** could not be evaluated for $BaCl_2$ antagonism because of lack of solubility, and it did not lower blood pressure in SH rats.

The phenolic *O*-methyl analogue **13** showed increased β-blocking activity (by a factor of 4.5 compared to **1**) and drastically decreased α-blocking activity with an in vitro β/α ratio of over 2000. In vivo evaluation (Table II) showed **13** to have enhanced β_1-blocking (by a factor of 3.7) but somewhat greater β_2-blocking and about one-third the α-blocking activity, compared to **1**. This finding indicates that the free phenolic OH group of medroxalol enhances α-adrenergic antagonism. The side-chain modified analogues **15** and **16** showed decreased α- and β-blocking activity in vitro, as well as in vivo. Unlike medroxalol and compound **13**, the *gem*-dimethyl analogue **15** antagonized β_2-receptors to a greater extent than β_1-receptors. Compounds **13**, **15**, and **16** lowered blood pressure in SH rats. This finding is surprising, since **13** showed significantly less α-blocking and **16** less β-blocking potency, compared to medroxalol (**1**). Pharmacologic studies of medroxalol indicated that α- and β-adrenergic blockade does not fully account for its antihypertensive properties and that alternative or additional mechanisms cannot be ruled out at this time.[16,17] The present finding with medroxalol analogues **13** and **16** tends to confirm this conclusion.

Evaluation of the analogues in which the aralkyl side chain of **1** was replaced with a fragment of known α blockers gave the following results. Compound **20b**, which contains part of the piperoxan structure, had slightly increased α-blocking and a 100-fold decrease in β-blocking activity, compared to **1**. The *o*-tolylpiperazine analogue **22** showed a 25-fold increase in α-blocking and a 13-fold decrease in β-blocking activity, compared to **1**. The droperidol analogue **24b** showed a 4-fold increase in α-blocking and a 125-fold decrease in β-blocking activity. Finally, the analogue **26**, modeled after prazosin, had no α- nor β-blocking activity. Thus, with the exception of the last compound, our objective to increase the α-blocking component was achieved, although at the expense of β-blocking activity.

The marked α-adrenergic receptor blocking activity of compound **22**, combined with still significant β-adrenergic receptor blocking activity, was confirmed in vivo (Table II). Studies currently in progress suggest that the α-adrenergic antagonism of **22** is predominantly postsynaptic (α_1), as defined in ref 34 and 35. Compound **22** lowered blood pressure in SH rats at 12.5 mg/kg po, in anesthetized dogs at 1 mg/kg iv, and in normotensive, anesthetized rats at doses as low as 0.1 and 0.3 mg/kg iv.

Since compound **22** was judged to have possible therapeutic potential, its structure–activity relationship was further scrutinized. With compounds **27–32** the effect of aromatic substitution was explored. As expected from previous studies of arylpiperazine derivatives,[22-24,36,37] ortho substitution was found to enhance α-adrenergic blocking activity significantly, as seen with compounds **22** and **30**. Modification of the amide function (compounds **20a**, **24a,c**, and **34–39**) had little effect on α-adrenergic blocking activity. Analogue **39** with a 5-tetrazolyl group, which has frequently been shown to be biologically equivalent to a carboxylic acid function,[38] was active. The phenolic *O*-methyl analogue **41** had only slightly less α-blocking activity than **30**, while the corresponding modification of medroxalol decreased α-blocking activity drastically (**13** vs. **1**). This indicates that the phenolic hydroxy group contributes to the α-blocking activity of **1** but not to that of **22**. The effects of structural modification on β-adrenergic antagonism were variable; indeed, two analogues (**27** and **35**) were found to be β-adrenergic agonists. Only three compounds (**22**, **31**, and **37**), however, had $pA_2 > 6.5$. Spasmolytic activity was elevated for the *N*-neopentyl amide analogue **21** (as it was for the corresponding medroxalol analogue **9**) and this compound also had antihypertensive activity in SH rats. In general, however, no correlation of these two properties was found. Compounds **20a**, **22**, **24a**, **28**, **30**, **35**, and **39–43** also had antihypertensive activity, including some (e.g., **20a**, **28**, and **40**) with relatively low α-adrenergic blocking activity. Antihypertensive activity is therefore likely to be due to a variety of mechanisms (cf. ref 36).

In conclusion, structural modifications of the medroxalol molecule described in this paper resulted in compounds with ratios of β-/α-adrenergic blocking activity varying

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(37) R. C. Gupta, S. Mukerji, S. K. Chatterjee, S. N. Rastogi, N. Armand, M. P. Dube, R. N. Sur, Jr., K. C. Mukerji, and R. C. Srimal, *Arzneim.-Forsch.*, 28, 241 (1978).
(38) See, for instance, R. A. Parker, T. Kariya, J. M. Grisar, and V. Petrow, *J. Med. Chem.*, 20, 781 (1977).

from <0.03 to >2000. The antihypertensive activity of certain members of this series may not result solely from α- and β-adrenergic blockade. In addition to the treatment of hypertension, agents that combine α- and β-adrenergic antagonism may also prove useful in diseases involving cardiovascular dysfunctions, such as arrhythmias, congestive heart failure, and recovery from myocardial infarcts.[39-41] Compounds **22**, **24a**, and **35** are currently being studied in pharmacologic models of these disease states in our laboratories and elsewhere.

Experimental Section

Melting points were determined in open capillaries in a Thomas-Hoover apparatus and are uncorrected. IR spectra were taken on a Perkin-Elmer 521 instrument. NMR spectra were taken on a Varian Model A-60 instrument (Me_4Si as internal standard). Where analyses are indicated only by symbols of the elements, results obtained were within ±0.4% of theoretical values.

Biological Evaluations. In vitro α-adrenergic receptor blocking activity was determined by performing cumulative dose–response experiments in the isolated rabbit aortic strip preparation; norepinephrine was used as the agonist.[17] The contractile response of the preparation was expressed as percent of the maximal attainable response. Relative antagonistic potency was expressed as a pA_2 value.[42] pA_2 is defined as the negative logarithm of the concentration of the antagonist which produces a twofold increase of the EC_{50} value of the agonist. β_1-Adrenergic receptor blocking activity was determined in vitro in the isolated guinea pig atria preparation by measuring the potency in antagonizing the increase in rate of contraction in response to isoproterenol; data were expressed as pA_2 values. pA_2 values for antagonism to $BaCl_2$-induced contractions were obtained in the isolated guinea pig ileum preparation. The pA_2 values in Table I represent means of at least three determinations.

In vivo α-adrenergic receptor blocking activity was determined by performing cumulative dose–response experiments in the anesthetized dog; phenylephrine was used as the agonist.[17] The increase in diastolic blood pressure produced by phenylephrine was determined in the absence of, and again in the presence of, increasing doses of the compounds being tested. Relative antagonistic potency was expressed as DR_{10}. DR_{10} is defined as the dose of the antagonist that increased by 10 times the dose of agonist necessary to produce the same response. Antagonism at β_1-adrenergic receptors was determined by isoproterenol-induced increases in heart rate and at β_2-adrenergic receptors by isoproterenol-induced decreases in diastolic blood pressure.

Antihypertensive activity was determined in SH rats of the Okamoto-Aoki strain.[17] Systolic blood pressure of the SH rats was measured from the caudal artery by means of an indirect method in which a photocell transducer/tail cuff occluder system was used. Groups of 12 rats were treated and their means plus or minus SE response was compared to that of a concurrent vehicle-treated control group of 12 rats. Statistical significance was determined by a two-tailed grouped Student's t test.

5-[2-[[3-(1,3-Benzodioxol-5-yl)-1-methylpropyl]amino]-1-hydroxyethyl]-2-hydroxybenzamide (1). To a solution of 92.0 g of **5** (free base) in 300 mL of MeOH was added 1600 mL of cold (0 °C) MeOH that was saturated with gaseous NH_3 and a small amount of NaOMe. The mixture was allowed to warm to 25 °C in a cork-stoppered flask and was stirred for 3 days. (The time required for this reaction to go to completion is unpredictable; it is therefore best to follow the reaction by TLC and to check the crude product for the absence of ester by IR and/or NMR.) The mixture was evaporated to dryness and the residue was recrystallized from $EtOH/H_2O$ to give 72.5 g (82%) of **1**: mp 162–163 °C dec; IR (KBr) 1630, 1655 (sh) cm^{-1}; NMR (Me_2SO-d_6) δ 7.92 (d, 1, J = 2 Hz), 7.46 (dd, 1, J = 2 Hz, J' = 9 Hz), 6.9 (d, 1, J = 9 Hz), 6.00 (s, 2), 1.04 (d, 3, J = 6.5 Hz). Anal. ($C_{20}H_{24}N_2O_5$) C, H, N.

To assay for diastereoisomer composition a 5-mg sample was allowed to react with butaneboronic acid in THF with warming. An aliquot of this solution was chromatographed on a 60 × 0.2 cm column of 2% OV-17 silicone at 275 °C. The area under the peaks (7.8 min for A isomer and 9.6 min for B isomer) were obtained to calculate isomer composition. The isomer ratio in the above sample was found to be 49:51.[28]

A hydrochloride salt was prepared, mp 211–213 °C dec (Table I).

5-[2-[[3-(1,3-Benzodioxol-5-yl)-1-methylpropyl]amino]-1-hydroxyethyl]-2-hydroxybenzoic Acid (4). A suspension of 12.7 g (0.03 mol) of **5**·HCl in 45 mL (0.09 mol) of 2 N NaOH was heated on a steam bath under a stream of N_2 until homogeneous (1.3 h). The solution was cooled and acidified with 2 N HCl. The semicrystalline residue was recrystallized twice from i-$PrOH/H_2O$ to give 4.5 g of **16**·HCl, mp 163–166 °C dec; IR (KBr) 1660 cm^{-1}; NMR (Me_2SO-d_6) no OCH_3 protons. A second crop of 3.6 g (total 66%), mp 166–168 °C dec, was obtained.

Methyl 5-[2-[[3-(1,3-Benzodioxol-5-yl)-1-methylpropyl]amino]-1-hydroxyethyl]-2-hydroxybenzoate (5). A solution of 21.3 g (0.0782 mol) of **46** in 115 mL of THF was added dropwise over 20 min to a solution of 15.2 g (0.0782 mol) of α-methyl-1,3-benzodioxole-5-propanamine and 8.88 g (0.088 mol) of Et_3N in 55 mL of THF at 25 °C. The mixture was stirred at 25 °C for 2 h and then filtered to separate 12.28 g of Et_3N·HBr. The filtrate was concentrated, and the residual orange oil was dissolved in 50 mL of MeOH and acidified with ethereal HCl. After the solution was diluted with Et_2O (25 mL), the amino ketone precipitated as the HCl salt; it was collected, washed with EtOH and Et_2O, and dried to give 17.9 g (54%), mp 193 °C dec. Recrystallization of this product leads to substantial losses, probably due to decomposition, and should be avoided. A sample was recrystallized from EtOH, mp 197 °C dec. Anal. ($C_{21}H_{23}NO_6$·HCl) C, H, Cl, N.

A solution of 27.84 g (66 mmol) of the amino ketone hydrochloride in 300 mL of MeOH was hydrogenated over 3.0 g of 10% Pd/C in a Parr shaker for 11.5 h. The resulting mixture was diluted with 500 mL of MeOH, warmed to dissolve the organic solid, and filtered hot. The filtrate was concentrated and **5**·HCl crystallized: yield 20.7 g (74%); mp 194 °C dec. A sample was recrystallized from MeOH, mp 197 °C dec. Anal. ($C_{21}H_{25}NO_6$·HCl) C, H, N. A sample was converted to the free base and crystallized from CH_2Cl_2/Et_2O: mp 105–108 °C; NMR ($CDCl_3$) δ 7.85 (d, 1, J = 2 Hz), 7.49 (dd, 1, J = 2 Hz, J' = 9 Hz), 6.98 (d, 1, J = 9 Hz), 6.7 (m, 3), 5.96 (s, 2), 5.4 (m, 2), 4.6 (m, 1), 4.01 (s, 3), 3.0–2.5 (m, 5), 1.7 (m, 2), 1.17 (d, 3, J = 7 Hz). **5** was also obtained by $NaBH_4$ reduction.

***N*-Methyl, *N*-Ethyl, *N*-Isopropyl, *N*-Neopentyl, and *N*-Dodecyl Amides 6–10.** To 20 mL of dry (type 3A molecular sieve) MeOH in a pressure bottle under N_2 was added a small (~1 mm^3) piece of freshly cut Na. When the Na had reacted, 10.9 g (28.1 mmol) of **5** (free base) and a cold (−20 °C) solution of 30 g of CH_3NH_2 gas in 50 mL of dry MeOH were added. The bottle was stoppered and stirred at 25 °C for 22 h. TLC (silica gel, EtOAc, two passes) indicated that no more **5** was present. The mixture was evaporated to dryness, the residue was taken up in EtOAc, and the solution was washed with saturated $NaHCO_3$ solution, H_2O, and saturated NaCl solution, dried (Na_2SO_4), and evaporated to dryness. The residue was dissolved in i-PrOH, an equivalent of isopropanolic HCl was added, and **6**·HCl crystallized; recrystallization from i-$PrOH/H_2O$ gave 8.3 g (70%) of **6**·HCl, mp 215.5–216 °C dec. Diastereoisomer ratio was determined by GLC of the butaneboronic acid derivative to be 55:45 (A/B, where A is the isomer with shorter retention time).

The amides **7–10** were similarly obtained, and their isomer ratios were found to be 48:52 for **7**, 75:25 for **8**, and 66:34 for **9**.

5-[2-[[3-(1,3-Benzodioxol-5-yl)-1-methylpropyl]amino]-1-hydroxyethyl]-2-hydroxy-*N*,*N*-dimethylbenzamide (11). After several unsuccessful attempts to effect this amination with $HNMe_2$ in MeOH and NaOMe as catalyst, the procedure of Basha et al.[27] was used with Me_2AlNMe_2 as reagent. A solution of Me_2NH (2 mmol/mL) in CH_2Cl_2 was prepared. To 19.35 mL (0.0387 mol) of this solution in 100 mL of CH_2Cl_2 at −25 °C under Ar was added by syringe 10.9 mL (0.0258 mol) of 25% Me_3Al in

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(42) J. M. Van Rossum, *Arch. Int. Pharmacodyn.*, **143**, 299 (1963).

hexane. The solution was allowed to warm to 25 °C over 15 min and a solution of 5.0 g (0.0129 mol) of **5** (free base) in 75 mL of CH_2Cl_2 was added over 15 min. After a 3 h reflux, TLC (silica gel, 5% EtOH in $CHCl_3$) of an aliquot (treated with 2 N HCl, made basic with $NaHCO_3$, extracted into EtOAc) indicated nearly complete disappearance of **5**. The mixture was refluxed overnight, and 2 N HCl was added carefully, made basic with $NaHCO_3$, and extracted with EtOAc. The extract was washed (H_2O), dried ($MgSO_4$), and evaporated to dryness. The residue (3.9 g) was dissolved in MeOH, 1 equiv of methanolic HCl was added, and the product crystallized reluctantly. Recrystallization from *i*-PrOH/H_2O gave 0.83 g (15%) of **11**·HCl: mp 192–194 °C dec; IR (KBr) 1620 cm^{-1}.

Methyl 5-[2-[[3-(1,3-Benzodioxol-5-yl)-1-methylpropyl]amino]-1-hydroxethyl]-2-methoxybenzoate (12). A solution of 25.0 g (0.0871 mol) of **47** in 850 mL of THF was added dropwise over 4 h to a stirred solution of 16.8 g (0.0871 mol) of α-methyl-1,3-benzodiozole-5-propanamine and 8.81 g (0.0871 mol) of Et_3N in 150 mL of THF at 25 °C. The mixture was stirred for another 3 h. The resulting precipitate of Et_3N·HBr was removed by filtration, and the filtrate was evaporated to dryness. The residue was dissolved in MeOH (100 mL), 1 equiv of methanolic HCl was added, and the solution was diluted with Et_2O. The crude product, methyl 5-[2-[[3-(1,3-benzodioxol-5-yl)-1-methylpropyl]amino]-acetyl]-2-methoxybenzoate hydrochloride, crystallized in several portions: yield 15.9 g (46%); mp 185–187 °C dec.

To a cold (ice–salt bath) solution of 15.9 g (0.0365 mol) of this ketone in 400 mL of MeOH was added 6.90 g (0.182 mol) of $NaBH_4$ in portions over 45 min. The mixture was stirred for 30 min, poured on ice–water, acidified with 20% acetic acid (500 mL), made basic with $NaHCO_3$, and extracted with CH_2Cl_2. The extract was washed (H_2O) and dried ($MgSO_4$), and the solvent was evaporated to give crude **12**·HCl (12.1 g). A sample was recrystallized from MeOH/Et_2O: mp 159–162 °C; IR (KBr) 1720 cm^{-1}; NMR (Me_2SO-d_6) δ 7.68 (2 d, 1, J = 9 Hz, J' = 2 Hz), 7.20 (d, 1, J = 9 Hz), 6.01 (s, 2), 3.87 (s, 3), 3.84 (s, 3), 1.33 (d, 3, J = 7 Hz).

5-[2-[[3-(1,3-Benzodioxol-5-yl)-1-methylpropyl]amino]-1-hydroxyethyl]-2-methoxybenzamide (13). The ester **12** (free base, 6.8 g) was dissolved in MeOH to which a small piece (about 100 mg) of Na had been added, and the solution was cooled (0 °C) and saturated with gaseous NH_3. The resulting mixture was stirred at room temperature for several days. The reaction was followed by TLC. When all of the ester had been converted to the amide, the solvent was evaporated. The residue was taken up in EtOAc, and the solution was washed with $NaHCO_3$ solution, dried over $MgSO_4$, and evaporated to dryness. The residue was dissolved in methanol, 1 equiv of methanolic HCl was added, and **13**·HCl crystallized after addition of ethyl ether: yield 2.5 g; mp 147–156 °C dec; IR (KBr) 1655 cm^{-1}; NMR (Me_2SO-d_6) δ 5.99 (s, 2), 3.91 (s, 3), 1.33 (d, 3, J = 6.5 Hz). GLC assay of the butaneboronic acid derivative (cf. 1) gave two peaks with areas of 59 and 41% at retention time 10.4 and 12.6 min, respectively.

Methyl 5-[2-[[3-(1,3-Benzodioxol-5-yl)-1,1-dimethylpropyl]amino]-1-hydroxyethyl]-2-hydroxybenzoate (14). To CH_3MgI (prepared from 0.72 mol each of Mg and CH_3I) in 500 mL of Et_2O was added a solution of 100 g (0.52 mol) of 4-(1,3-benzodioxol-5-yl)butan-2-one in 500 mL of Et_2O over 2 h. After the solution was refluxed for 1 h, 2 N NH_4Cl was added dropwise, and the organic phase was separated, washed with saturated NaCl solution, dried ($MgSO_4$), and evaporated to dryness. The product, α,α-dimethyl-1,3-benzodioxole-5-propanol (100.7 g, 93% yield), was free of starting material (ketone) as indicated by IR and TLC.

To an ice-cooled, stirred suspension of this alcohol (0.484 mol) and 76.0 g (1.55 mol) of NaCN in 260 mL of AcOH was added dropwise over 1.5 h 218.7 g (2.23 mol) of concentrated H_2SO_4 [**Caution**: To prevent HCN from escaping, the reaction was run in a closed system equipped with a gas trap containing 30% NaOH solution]. The mixture was stirred at 25 °C for 18 h. The mixture was cooled and 2.5 L of 4 N NaOH was added dropwise. Product was extracted with Et_2O, and the extract was washed (H_2O), dried ($MgSO_4$), and evaporated to dryness. The residue (85.0 g) was dissolved in Et_2O and passed through a column of silica gel for purification to give, after removal of solvent, a residue of 76.0 g. It was dissolved in 250 mL of EtOH, 250 mL of 2 N NaOH was added, and the mixture was refluxed for 48 h. EtOH was evaporated, 1 L of H_2O was added, and the product was extracted into Et_2O. The extract was washed with water (5 times) and stirred, and 161 mL of 2 N HCl was added. The precipitated salt was collected and recrystallized from MeOH to give 47.8 g (40%) of α,α-dimethyl-1,3-benzodioxole-5-propanamine hydrochloride, mp 199–201 °C dec. A sample was recrystallized from *i*-PrOH/Et_2O: mp 199–201 °C dec; NMR (Me_2SO-d_6) δ 5.75 (s, 2 OCH_2O), 1.10 (s, 6, CH_3). Anal. ($C_{12}H_{17}NO_2$·HCl·0.5H_2O) C, H, N.

A solution of 13.7 g (50.2 mmol) of **46** in 75 mL of dry THF was added dropwise over 20 min to a solution of 10.4 g (50.2 mmol) of α,α-dimethyl-1,3-benzodioxole-5-propranamine (free base) and 5.77 g (56 mmol) of Et_3N in 35 mL of THF at 25 °C. The mixture was stirred at 25 °C for 2 h. Precipitated Et_3N·HBr was removed by filtration and the filtrate was evaporated to dryness. The residue was dissolved in 40 mL of MeOH and acidified with ethereal HCl; the product crystallized in two crops: yield 6.88 g (31.5%); mp 183–194 °C dec.

The amino ketone hydrochloride (7.38 g) was hydrogenated in 75 mL of MeOH over 0.75 g of 10% Pd/C in a Parr shaker. **14**·HCl crystallized from MeOH/Et_2O: yield 6.08 g (82%); mp 225–226 °C dec; NMR ($CDCl_3$/TFA) δ 7.88 (d, 1, J = 2 Hz), 7.51 (dd, 1, J = 2 Hz, J' = 9 Hz), 7.00 (d, 1, J = 9 Hz), 6.74 (s, 4), 5.96 (s, 2), 5.4 (m, 1), 4.02 (s, 3), 3.3 (m, 2), 2.7 (m, 2), 2.2 (m, 2), 1.63 (s, 6).

5-[2-[[3-(1,3-Benzodioxol-5-yl)-1,1-dimethylpropyl]amino]-1-hydroxyethyl]-2-hydroxybenzamide (15). **14**·HCl (3.1 g) was converted to the free base, which was dissolved in 250 mL of MeOH to which a piece of clean Na had been added under Ar in a stainless-steel bomb. The solution was cooled to −10 °C and saturated with gaseous NH_3; the bomb was sealed and the content was stirred magnetically at 25 °C for 25 days. The solution was evaporated to dryness, and the residue was treated with 10% HOAc, neutralized with $NaHCO_3$, and extracted with EtOAc. The extract was washed (H_2O, saturated NaCl solution) and dried ($MgSO_4$), and the solvent was evaporated. The residue was dissolved in EtOH, 1 equiv of ethereal HCl was added, and the resulting precipitate was recrystallized from EtOH/H_2O to give 1.7 g (57%) of **15**·HCl: mp 217–218 °C dec; NMR ($CDCl_3$/TFA) no OCH_3.

5-[2-[[2-(1,3-Benzodioxol-5-yl)-1-methylethyl]amino]-1-hydroxyethyl]-2-hydroxybenzamide (16). In the manner described for **5**, methyl 5-[2-[[2-(1,3-benzodioxol-5-yl)-1-methylethyl]amino]acetyl]-2-hydroxybenzoate hydrochloride was obtained in 72% yield, mp 214 °C dec. Anal. ($C_{20}H_{21}NO_6$·HCl) C, H, N. It was reduced by catalytic hydrogenation to give methyl 5-[2-[[2-(1,3-benzodioxol-5-yl)-1-methylethyl]amino]-1-hydroxyethyl]-2-hydroxybenzoate hydrochloride, mp 202 °C dec. Anal. ($C_{20}H_{23}NO_6$·HCl) C, H, N. Amination, carried out as for 1, gave **16**, mp 185–186 °C dec.

Methyl 5-[2-[[(2,3-Dihydro-1,4-benzodioxan-2-yl)methyl]amino]-1-hydroxyethyl]-2-hydroxybenzoate (20a). A solution of 27.3 g (0.1 mol) of **46** in 125 mL of THF was added dropwise over 45 min to a solution of 33.0 g (0.2 mol) of [(2,3-dihydro-1,4-benzodioxan-2-yl)methyl]amine[43] in 75 mL of THF at 25–28 °C. The mixture was stirred for 1 h at 25 °C and cooled to 5 °C; precipitated [(2,3-dihydro-1,4-benzodioxan-2-yl)-methyl]amine hydrobromide was collected and washed with small portions of THF. Et_2O (250 mL) was added to the filtrate, and additional precipitate was separated. The filtrate was evaporated to dryness, dissolved in *i*-PrOH, and acidified with 1 equiv of 2 N HCl. The product was recrystallized from *i*-PrOH/H_2O (1:1) to give 21.1 g (55%) of methyl 5-[[[(2,3-dihydro-1,4-benzodioxan-2-yl)methyl]amino]acetyl]-2-hydroxybenzoate hydrochloride: mp 206–207 °C dec; IR (KBr) 1695, 1675 cm^{-1}; NMR (Me_2SO-d_6) δ 8.43 (d, 1, J = 2 Hz), 8.18 (2 d, 1, J = 2 Hz, J' = 9 Hz), 7.30 (d, 1, J = 9 Hz), 6.96 (s, 4, arom), 4.89 (s, 2, $COCH_2N$), 3.96 (s, 3, OCH_3). Anal. ($C_{19}H_{19}NO_6$·HCl) C, H, N.

A solution of 15.2 g of this compound in 900 mL of MeOH and 100 mL of H_2O was hydrogenated over 10.0 g of 10% Pd/C in a Parr shaker for 20 h. The catalyst was removed by filtration under nitrogen and solvent was evaporated. The residue was recrystallized 3 times from *i*-PrOH/H_2O to give 6.4 g of **20a**: mp

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195–196 °C dec; IR (KBr) 1675 cm^{-1}; NMR (Me_2SO-d_6) δ 7.90 (d, 1, J = 2 Hz), 7.63 (dd, 1, J = 2 Hz, J' = 9 Hz), 7.08 (d, 1, J = 9 Hz), 6.96 (s, 4, arom), 5.1 (m, 1, HCOH, 3.96 (s, 3, OCH_3).

5-[2-[[(2,3-Dihydro-1,4-benzodioxan-2-yl)methyl]amino]-1-hydroxyethyl]-2-hydroxybenzamide (20b). Compound **20a**·HCl (5.0 g) was converted to its free base by addition of $NaHCO_3$ solution and extraction with CH_2Cl_2. The residue, after evaporation of solvent, was dissolved in 100 mL of anhydrous MeOH in a pressure bottle; the solution was saturated at 0 °C with gaseous NH_3 and stirred at room temperature for 3 days. Solvent was evaporated and the residue was crystallized and recrystallized from methylene chloride to give 2.7 g of **20b**: mp 160–162 °C dec; IR (KBr) 1650 cm^{-1}.

2-Hydroxy-5-[1-hydroxy-2-[4-(2-methylphenyl)-1-piperazinyl]ethyl]benzamide (22). Compound **37**·HCl was converted to its free base by treatment with $NaHCO_3$ solution and extraction with CH_2Cl_2. It was dissolved in anhydrous MeOH and the solution was saturated with gaseous NH_3 at 0 °C. As a catalyst, a small amount of NaOMe was added. The mixture was then allowed to warm to room temperature and was stirred for several days. The reaction was followed by TLC to determine disappearance of ester. When the reaction was completed (which is some instances required addition of more catalyst), the reaction mixture was evaporated to dryness, treated with 10% acetic acid (to destroy catalyst), and made basic with $NaHCO_3$, and the product was extracted into EtOAc. The extract was washed with H_2O and $NaHCO_3$ solution and dried ($MgSO_4$), and the solvent was evaporated. Addition of 2 equiv of methanolic HCl and recrystallization from MeOH/H_2O gave **22**·2HCl, mp 192–193 °C dec. Vacuum drying over KOH at 80 °C resulted in formation of the hydrochloride: mp 232 °C dec; IR (KBr) 1655 cm^{-1}; NMR (Me_2SO-d_6) δ 8.15 (d, 1, J = 2 Hz), 7.53 (dd, 1, J = 2 Hz, J' = 9 Hz), 6.96 (d, 1, J = 9 Hz), 6.9–7.2 (m, 4), 5.2 (m, 1), 3–3.8 (m, 10), 2.29 (s, 3). Anal. ($C_{20}H_{25}N_3O_3$·HCl) C, H, N. Compounds **27–36** were similarly prepared.

Methyl 5-[2-[4-(2,3-Dihydro-2-oxo-1*H*-benzimidazol-1-yl)-1-piperidinyl]-1-hydroxyethyl]-2-hydroxybenzoate (24a). A solution of 12.57 g (0.046 mol) of **46** in 60 mL of dry DMF was added dropwise over 60 min to a solution of 10.0 g (0.046 mol) of 4-(2,3-dihydro-2-oxo-1*H*-benzimidazol-1-yl)piperidine and 5.12 g (0.0506 mol) of Et_3N in 90 mL of DMF at 25 °C. The mixture was stirred for 60 min at 25 °C. Precipitated NEt_3·HBr was removed by filtration, and the filtrate was poured into 1 L of water. The product was extracted into CH_2Cl_2. The extract was washed with H_2O and dried (Na_2SO_4), and solvent was evaporated, leaving a residue (17.0 g) to which methanol and 1 equiv of methanolic HCl were added. The product, methyl 5-[2-[4-(2,3-dihydro-2-oxo-1*H*-benzimidazol-1-yl)-1-piperidyl]acetyl]-2-hydroxybenzoate hydrochloride, crystallized (14.6 g), mp 229–232 °C dec. This material was dissolved in 1 L of MeOH, the solution was cooled in an ice–methanol bath, and 7.44 g of $NaBH_4$ was added portionwise over 25 min. The mixture was stirred for 30 min and then was poured on 1 L of ice–water. The mixture was acidified with 500 mL of 10% AcOH, made basic by the addition of $NaHCO_3$, and extracted with CH_2Cl_2. The extract was washed with H_2O and dried ($MgSO_4$), and the solvent was evaporated, leaving a residue of 11.3 g, mp 211–213 °C dec. Addition of 1 equiv of methanolic HCl, precipitation from Et_2O, and recrystallization from MeOH gave **24a**·HCl: mp 229–230 °C dec; IR (KBr) 1665–1705 cm^{-1} (broad); NMR ($CDCl_3$/TFA) δ 7.96 (d, 1, J = 2 Hz), 7.04 (d, 1, J = 9 Hz) 7.2–7.8 (m, 5), 5.4 (m, 1), 4.0 (s, 3).

5-[2-[4-(2,3-Dihydro-2-oxo-1*H*-benzimidazol-1-yl)-1-piperidinyl]-1-hydroxyethyl]-2-hydroxybenzamide (24b). Compound **24a**·HCl (10.0 g) was converted to its free base by treatment with $NaHCO_3$ solution, extraction with CH_2Cl_2, and evaporation of solvent. The residue was dissolved in 900 mL of MeOH to which a small piece (about 100 mg) of metallic Na had been added. The mixture was cooled in an ice–methanol bath and saturated with gaseous NH_3 (27.4 g). The reaction mixture was stirred at 25 °C until all ester was converted to amide as indicated by TLC, which required addition of more catalyst ($NaOCH_3$) and ammonia. The solution, which became homogeneous, was evaporated to dryness. Ethereal HCl was added to the residue and the product was crystallized and recrystallized from 2-propanol–water to give 6.2 g (64%) of **24b**·HCl·H_2O: mp 213–215 °C dec; IR (KBr) 1645, 1680 cm^{-1}.

The *N*-ethyl amide **24c** was similarly prepared with liquid anhydrous $EtNH_2$ instead of NH_3: mp 222–224 °C dec; IR (KBr) 1640, 1700 cm^{-1}.

5-[2-[4-(2-Furanylcarbonyl)-1-piperazinyl]-1-hydroxyethyl]-2-hydroxybenzamide (26). **38**·HCl (6.95 g) was converted to the free base, 200 mL of MeOH containing NaOMe (formed by addition of a sphere of Na) was added in a stainless-steel bomb, and the mixture was cooled to below 0 °C and was saturated with gaseous NH_3. The bomb was sealed and the content was stirred magnetically at 25 °C for 31 days. The bomb was opened and the homogeneous solution was evaporated to dryness. The residue was treated with 10% AcOH (100 mL), made basic with $NaHCO_3$, and extracted with CH_2Cl_2/EtOAc. The extract was washed with H_2O and dried ($MgSO_4$), and the solvent was evaporated. The solid residue was recrystallized from MeOH to give 2.2 g of **26**: mp 189–191 °C dec; IR (KBr) 1670 cm^{-1}; NMR (Me_2SO-d_6) no OCH_3.

Methyl 2-Hydroxy-5-[1-hydroxy-2-[4-(2-methylphenyl)-1-piperazinyl]ethyl]benzoate (37). A solution of 10.9 g (0.04 mol) of **46** in 100 mL dry THF was added dropwise over 4 h to a stirred solution of 7.1 g (0.04 mol) of 1-(2-methylphenyl)piperazine and 4.0 g (0.04 mol) of triethylamine in 75 mL of THF at room temperature. Stirring was continued for 4 h. Precipitated NEt_3·HBr was removed by filtration and the filtrate was evaporated to dryness. Addition of 2 equiv of methanolic HCl and precipitation by addition of Et_2O at room temperature gave crude methyl 2-hydroxy-5-[2-[4-(2-methylphenyl)-1-piperazinyl]acetyl]benzoate dihydrochloride (9.4 g).

Attempts to purify this product by recrystallization frequently led to decomposition and were subsequently avoided.

The crude ketone was suspended in about 300 mL of MeOH, the mixture was cooled to 0 °C, and 4.8 g (0.126 mol) of $NaBH_4$ was added over 10 min. After the mixture was stirred at 0 °C for another 15–60 min, it was poured on ice, acidified with 10% AcOH, and then made basic with $NaHCO_3$. The product was extracted into EtOAc, the extract was washed with H_2O and saturated NaCl solution and dried ($MgSO_4$), and the solvent was evaporated. Addition of 2 equiv of methanolic HCl and two recrystallizations from MeOH gave 3.1 g of **37**·2HCl. Vacuum drying over KOH at 80 °C and 0.05 mmHg resulted in loss of 1 of the 2 mol of HCl and gave the monohydrochloride salt: mp 226–227 °C dec; IR (KBr) 1675 cm^{-1}; NMR ($CDCl_3$/TFA) δ 7.90 (d, 1, J = 2 Hz), 7.4–7.7 (m, 5), 7.0 (d, 1, J = 9 Hz), 5.32 (m, 1), 4.39 (m, 8), 3.98 (s, 3), 3.57 (m, 2), 2.62 (s, 3).

Methyl 5-[2-[4-(2-Furanylcarbonyl)-1-piperazinyl]-1-hydroxyethyl]-2-hydroxybenzoate (38). A solution of 23.35 g (0.0855 mol) of **46** in 140 mL of dry THF was added dropwise over 1 h to a solution of 15.4 g (0.0855 mol) of 1-(2-furanylcarbonyl)piperazine (free base)[44,45] and 9.52 g (0.0941 mol) of Et_3N in 200 mL of dry THF at 25 °C. Stirring was continued for 4 h, the precipitated Et_3N·HBr was collected by filtration and washed with little THF, and the filtrate was evaporated to dryness. The residue was dissolved in MeOH and 1 equiv of methanolic HCl was added. Crude methyl 5-[2-[4-(2-furanylcarbonyl)-1-piperazinyl]acetyl]-2-hydroxybenzoate hydrochloride was obtained: yield 28.9 g (83%); mp 225–226 °C dec; IR (KBr) 1625, 1680 cm^{-1}; NMR ($CDCl_3$/TFA) δ 4.95 (s, d, $COCH_2N$).

This material was suspended in 800 mL of MeOH, and 16.06 g (0.4242 mol) of $NaBH_4$ was added in portions while the reaction was kept below 0 °C (ice–salt bath) over 45 min. Stirring was continued for 30 min, and then the mixture (which had become homogeneous) was poured on ice, acidified with 10% AcOH (to destroy boron complex), made basic with $NaHCO_3$, and extracted with CH_2Cl_2. The extract was washed with H_2O and saturated NaCl solution, dried ($MgSO_4$), and evaporated to dryness. The residue was dissolved in MeOH, 1 equiv of methanolic HCl was added, and **38**·HCl crystallized: yield 17.2 g (59%); mp 190–192 °C dec. A portion was recrystallized from MeOH: mp 193–195 °C dec; IR (KBr) 1675 cm^{-1}; NMR ($CDCl_3$/TFA) δ 7.88 (d, 1, J = 2 Hz, 6-phenyl), 7.63 (d, 1, J = 1.5 Hz, 5-furyl), 7.52 (dd, 1, J,

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= 2 Hz, J' = 9 Hz, 4-phenyl), 7.28 (d, 1, J = 4 Hz, 3-furyl), 6.98 (d, 1, J = 9 Hz, 3-phenyl), 6.61 (q, 1,4-furyl), 5.4 (m, 1, *H*COH), 3.96 (s, 3, OCH_3).

Methyl 5-(2-Bromoacetyl)-2-hydroxybenzoate (46). To a stirred solution of 19.42 g (0.1 mol) of methyl 5-acetyl-2-hydroxybenzoate (**44**) in 65 mL of $CHCl_3$ was added dropwise a solution of 16.0 g (0.1 mol) of Br_2 in 190 mL of $CHCl_3$. The solution was evaporated to dryness and the residue was recrystallized from EtOAc/heptane to give 22.1 g (81%) of **46**, mp 89–90 °C.

Methyl 5-(2-Bromoacetyl)-2-methyoxybenzoate (47). A mixture of 66.1 g (0.341 mol) of **44**, 7.26 g (0.511 mol) of MeI, and 47.0 g (0.341 mol) of K_2CO_3 in 400 mL of DMF was stirred at room temperature for 65 h. The mixture was poured on 1.5 L of 1 N HCl and extracted 6 times with Et_2O; the extract was washed with water, $NaHCO_3$ solution, and cold 1 N NaOH and dried over Na_2SO_4, and the solvent was evaporated to give 51.3 g (72%) of **45**, mp 95–96 °C.

To a solution of 52.0 (0.25 mol) of **45** in 400 mL of $CHCl_3$ was added a solution of 40.0 g (0.25 mol) of Br_2 in 200 mL of $CHCl_3$ at such a rate that the reaction mixture decolorized (50 min after a 25-min initiation period). Solvent was evaporated and the residue was recrystallized from MeOH to give 54.1 g (75%) of **47**, mp 149–153 °C. A second crop of 10.4 g was obtained from the mother liquor.

2-Bromo-1-[4-hydroxy-3-(1*H*-tetrazol-5-yl)phenyl]-ethanone (52). 5-(2-Hydroxyphenyl)-1*H*-tetrazole (**53**) was prepared from 2-hydroxybenzonitrile and hydrazoic acid in 86% yield by the procedure of Veldstra.[46] To a cooled (0 °C) suspension of 16.2 g (0.1 mol) of **53** in 300 mL of CH_2Cl_2 was added 39.9 g (0.3 mol) of $AlCl_3$ and, dropwise, 8.1 g (0.1 mol) of CH_3COCl. The mixture was refluxed for 3.5 h, cooled, and decomposed by the addition of 200 mL of 2 N HCl. The resulting precipitate was washed with 2 N HCl and water and recrystallized twice from *i*-PrOH/H_2O to give 8.0 g (39%) of [(4-hydroxy-3-1*H*-tetrazol-5-yl)phenyl]ethanone (**54**), mp 260–261 °C dec; IR (KBr) 1680 cm^{-1}. Anal. ($C_9H_8N_4O_2$) C, H, N.

To a solution of 6.9 g (0.034 mol) of **54** in 800 mL of refluxing THF was added 15.2 g (0.068 mol) of cupric bromide in six portions over 2 h. About 600 mL of THF was removed by distillation, the cuprous bromide formed was removed by filtration, and the filtrate was concentrated and diluted with $CHCl_3$. The product **52** crystallized, 8.2 g (84%), and a sample was recrystallized from THF/$CHCl_3$: mp 177–178 °C dec; IR (KBr) 1670 cm^{-1}; NMR (Me_2SO) δ 4.93 (s, 2). Anal. ($C_9H_7BrN_4O_2$) C, H, N.

Compound **39** was prepared from **52** as described for **37**.

Methyl 5-(2-Bromoacetyl)-2-ethoxybenzoate (55). A mixture of 19.4 g (0.1 mol) of methyl 5-acetyl-2-hydroxybenzoate, 13.8 g (0.1 mol) of K_2CO_3, and 23.4 g (0.15 mol) C_2H_5I in 70 mL of dry DMF was stirred at room temperature for 45 h. The mixture was poured into ice–water and extracted with CH_2Cl_2. The extract was washed with H_2O, 2 N Na_2CO_3, and NaCl solution, dried (Na_2SO_4), and evaporated. The residue was crystallized from Et_2O/pentane to yield 16.8 g (76%) of methyl 5-acetyl-2-ethoxybenzoate (**56**), mp 47–50 °C.

To a solution of 14.4 g (0.065 mol) of **56** in 80 mL of $CHCl_3$ was added dropwise a solution of 10.4 g (0.065 mol) of Br_2 in 30 mL of $CHCl_3$. After an initiation period of 1.5 h and the addition of a few drops of HBr/AcOH, the addition was complete after 1 h. The solution was evaported to dryness and the residue was recrystallized from methanol/acetone to give 10.0 g (51%) of **55**, mp 147–149 °C; IR (KBr) 1690, 1680 cm^{-1}; NMR ($CDCl_3$) δ 4.43 (s, 2, $COCH_2Br$). Anal. ($C_{12}H_{13}BrO_4$) C, H, Br.

Compound **43** was prepared from **55** as described for **37** and **22**. Compounds **40** and **41** were similarly prepared from methyl 5-(2-bromoacetyl)-2-methoxybenzoate (**47**).

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Imine Analogues of Tricyclic Antidepressants[1a]

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Analogues of tricyclic antidepressants were synthesized in which the α-carbon of the side chain was replaced by nitrogen. The antidepressant activity of these imines, as measured by the reversal of the effects of tetrabenazine in mice, showed a structure–activity relationship similar to that of the carbon analogues. The most active imine (**19**) was six times as potent as amitriptyline. Some of the compounds differed from amitriptyline in that they produced stimulation in mice.

Since the introduction of amitriptyline for the treatment of depressive states, numerous analogues of this drug have been synthesized and some are being used clinically.[2] Although many tricyclic oxime ethers with a basic side chain have been described in the literature, there had been at the time this work was initiated no report of the syn-

(1) (a) Contribution no. 2529 from the Central Research & Development Department of E. I. du Pont de Nemours & Co. (b) Geomet Technologies Inc., Rockville, MD 20852.

(2) N. Finch in "Antidepressants", S. Fielding and H. Lal, Eds., Futura Publishing Co., Mount Kisco, NY, 1975, and references cited there.

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