Structure–Activity Studies on Antidepressant 2,2-Diarylethylamines

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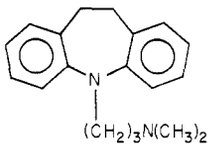
A series of 2,2-diarylethylamine derivatives has been examined for potential antidepressant activity in the tetrabenazine (TBZ) test. Diethanolamine 4 (McN-4187) was one of the more potent compounds despite its polar alcohol functionalities [ED_{50} values of 15 mg/kg (exploratory activity) and 1.5 mg/kg (ptosis)]. Structure–activity relationships are described. Minor structural modifications of 4 were sufficient to strongly attenuate activity. For example, changing one phenyl group to a 2-thienyl, cyclohexyl, or 3,4-dimethoxyphenyl group greatly reduced activity. Replacing both phenyl groups by 4-chlorophenyl groups also dissipated activity. The bisethanol functionality was not essential for activity (q.v. 17–19 in Table I). Although 17–19 compared well with 4 in the TBZ assay, only 19 (like 4) showed a satisfactory profile in the maximal electroshock seizure threshold test.

Although many clinically useful antidepressants possess a classical "tricyclic" structure, such as that of imipramine (1) and amitriptyline (2), intense interest has been directed in the last decade to "nontricyclic" antidepressants.[1] For several years, a research program to discover antidepressant compounds with a nonclassical structure, i.e., those lacking a typical tricylic format, has been underway in our Laboratories. Azepindole (3) was the first novel agent to emerge from this effort into a clinical milieu.[2] More recently, diethanolamine 4 was found to exhibit antidepressant activity by its ability to antagonize the effects of tetrabenazine on exploratory activity (EA) and ptosis (Pt) in mice. This observation led us to investigate compounds related to 4, as well as 2,2-diarylethylamines without the two ethanol groups. In this paper, we describe structure–activity studies on this series of potential antidepressants.



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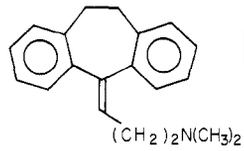

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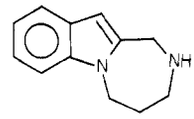


3 (McN-2453)

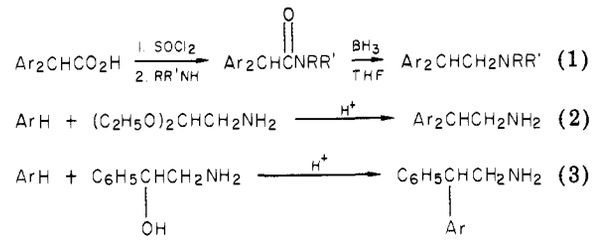
$(C_6H_5)_2CHCH_2N(CH_2CH_2OH)_2$

4 (McN-4187)

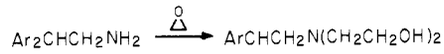
Chemistry. 2,2-Diarylethylamines (Table I) were generally prepared by the straightforward methods depicted in Scheme I.[3] Diethanol derivatives (Table I) were generally prepared from 2,2-diarylethylamines and ethylene oxide (Scheme II) or from diphenylacetaldehyde and diethanolamine (Scheme III).[4]

Structure–Activity Relationships. Potential antidepressant activity was first ascertained in the mouse tetrabenazine (TBZ) test.[2c,5] The effects of the test agents on two parameters, exploratory activity (EA) and ptosis (Pt), were recorded. ED_{50} values were determined for most of the active compounds (Table I). A listing of 95% confidence limits for the TBZ data is furnished in the supplementary material.[6,7] This discussion deals with the TBZ data in Table I.

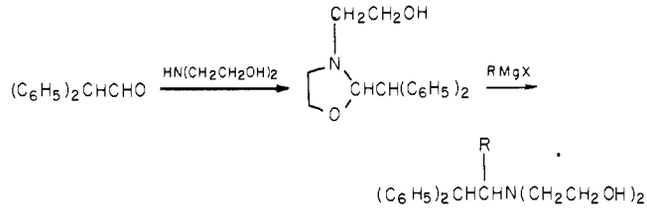
Scheme I



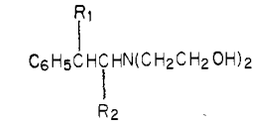
Scheme II



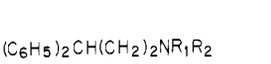
Scheme III



The central (CNS) activity of prototype 4 was surprising to us because we surmised a priori that 4 would be too polar, i.e., too hydrophilic, to cross the blood–brain barrier in sufficient amounts. Early structural modification of 4 entailed the preparation of analogue **32**, in which a phenyl is moved one carbon; **32** was devoid of activity. Diphenylpropyl homologue **34** showed reasonable activity, but it was less potent than 4. Interestingly, desphenyl analogue **33** showed respectable activity, even though it is less structurally lipophilic than 4.



32, R_1 = H; R_2 = C_6H_5
33, R_1 = R_2 = H
36, R_1 = c-C_6H_{11}; R_2 = H



34, R_1 = R_2 = CH_2CH_2OH
35, R_1 = H; R_2 = CH_2CH_3
37, R_1 = CH_2CH_2OH; R_2 = C_2H_5

(1) (a) Csaky, T. Z. "Cutting's Handbook of Pharmacology", 6th ed.; Appleton-Century-Crofts: New York, 1979; pp 630–637. (b) Kaiser, C.; Setler, P. E. In "Burger's Medicinal Chemistry", 4th ed.; Wolff, M. E., Ed.; Wiley-Interscience: New York, 1981; Part 3, Chapter 58.

(2) (a) Reynolds, B. E.; Carson, J. R. U.S. Patent 3 867 374, 1975; 3 689 503, 1972. (b) Shopsin, B. *Psychopharmacol. Bull.* **1981**, *17*, 33. (c) Gardocki, J. F. U.S. Patent 3 787 577, 1974.

(3) For chemistry related to that in eq 2 and 3 of Scheme I, see: (a) Watanabe, Y.; Kamochi, Y.; Kido, K.; Kudo, T.; Nose, A. *Chem. Abstr.* **1974**, *81*, 91256z. (b) Quelet, R.; Hoch, J.; Borgel, C.; Mansouri, M.; Pineau, R.; Tchiroukine, E.; Vinot, N. *Bull. Soc. Chem. Fr.* **1956**, 26. (c) Berney, D. *Helv. Chim. Acta* **1978**, *61*, 1110.

(4) For the reaction of oxazolidines with Grignard reagents, see: Senkus, M. *J. Am. Chem. Soc.* **1945**, *67*, 1515.

(5) Vernier, V. G.; Hanson, H. M.; Stone, C. A. In "Psychosomatic Medicine"; Nodine, J. M., Moyer, J. H., Eds.; Lea and Febiger: Philadelphia, 1962; p 683.

(6) See paragraph at end of paper regarding the supplementary material.

(7) Ninety-five percent confidence limits were calculated according to a published method. Litchfield, J. T.; Wilcoxon, F. *J. Pharmacol. Expt. Ther.* **1949**, *96*, 99.

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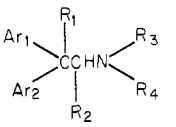
Table I. 2,2-Diarylethylamines and Their Diethanol Derivatives



compd	Ar_1[a]	Ar_2[a]	R_1	R_2	R_3[b]	R_4[b]	formula[c]	mp, °C (solv)[d]	TBZ ED_{50},[e] mg/kg EA	TBZ ED_{50},[e] mg/kg Pt
4	Ph	Ph	H	H	2-HE	2-HE	$C_{18}H_{23}NO\cdot HCl$	163.5–165 (M/EA)	15	2
5	Ph	Ph	CH_3	H	2-HE	2-HE	$C_{19}H_{25}NO_2\cdot HCl$[f]	183–184.5 (M/EA)	28	35
6	Ph	Ph	H	CH_3	2-HE	2-HE	$C_{19}H_{25}NO_2\cdot C_4H_4O_4$[g]	149–151 (M/I/EA)	13	8
7	Ph	Ph	H	C_2H_5	2-HE	2-HE	$C_{20}H_{27}NO_2\cdot C_4H_4O_4$[g,h]	155–157.5 (M/EA)	23	19
8	Ph	Ph	OH	H	2-HE	2-HE	$C_{18}H_{23}NO_2\cdot HCl$	210–215 (M/EA)	80	8
9	Ph	Ph	F	H	2-HE	2-HE	$C_{18}H_{22}FNO\cdot 2C_6H_{13}NO_3S$[g,i]	142–144 (M/EA)	40	12
10[j]	Ph	Ph	H	H	2-HP	2-HP	$C_{20}H_{27}NO_2\cdot HCl$[f]	*j* (M/EA)	18/11	7/6
11	Ph	DMP	H	H	2-HE	2-HE	$C_{20}H_{27}NO_4\cdot HCl$[f]	144–146 (M/EA)	(60)	(60)
12[k]	Ph	2-Th	H	H	2-HE	2-HE	$C_{16}H_{21}NO_2S\cdot HI$[g]	118–120 (M/EA)	~60	~60
13	DMP	DMP	H	H	2-HE	2-HE	$C_{22}H_{31}NO_6\cdot HClO_4$[f]	178–179 (98% M)	(60)	(60)
14	MPh	MPh	H	H	2-HE	2-HE	$C_{20}H_{27}NO_4$	90–92 (M/EE)	(60)	(60)
15	ClPh	ClPh	H	H	2-HE	2-HE	$C_{18}H_{21}Cl_2N_2O_2$[f]	75–76 (EA/H)	~60	~60
16	2-Th	2-Th	H	H	2-HE	2-HE	$C_{14}H_{19}NO_2S_2\cdot C_2H_2O_4$[l]	164–165.5 (M)	(30)	(30)
17[m]	Ph	Ph	H	H	H	H	$C_{14}H_{15}N\cdot HCl$	257–264 (E)	1.8[n]	1.7[n]
18[o]	Ph	Ph	H	H	H	CH_3	$C_{15}H_{17}N\cdot HCl$	173–175 (M/EA)	~5	2.3
19[p]	Ph	Ph	H	H	CH_3	CH_3	$C_{16}H_{19}N\cdot HCl$	203–205 (I)	9	2.5
20[q]	Ph	Ph	H	CH_3	H	H	$C_{15}H_{17}N\cdot HCl$	281–285 (E/EE)	3.5	3.8
21	Ph	Ph	H	H	2-AE	2-AE	$C_{22}H_{27}NO_4\cdot 2C_6H_{13}NO_3S$[g,r]	134–138 (A)	23	13
22[s]	Ph	Ph	OH	H	H	H	$C_{14}H_{15}NO\cdot HCl$	199–199.5 (M/EA)	9	6
23[t]	Ph	Ph	F	H	H	H	$C_{14}H_{14}FN\cdot HCl$	193–197 dec (M/EE)	(30)[u]	(10)[u]
24[v]	ClPh	ClPh	H	H	H	H	$C_{14}H_{13}Cl_2N\cdot HCl$	232–234 (E/EE)	(30)	(30)
25	ClPh	ClPh	H	H	H	CH_3	$C_{15}H_{15}Cl_2N\cdot C_4H_4O_4$[f]	157–158 (M/EA)	~14	~13
26	ClPh	ClPh	H	H	CH_3	CH_3	$C_{16}H_{17}ClN\cdot HCl$[f]	240–243 (M/EA)	11	16
27[w]	DMP	Ph	H	H	H	H	$C_{16}H_{19}NO_2\cdot HCl$	143–145 (M/EA)	(30)	(30)
28	DMP	Ph	H	H	H	CH_3	$C_{17}H_{21}NO_2\cdot C_2H_2O_4$	208–209 (M)	>30	11
29	DMP	Ph	H	H	CH_3	CH_3	$C_{18}H_{23}NO_2\cdot HClO_4$[f]	178–180 (98% E)	(30)	14
30[x]	DMP	DMP	H	H	H	H	$C_{18}H_{23}NO_4\cdot C_4H_4O_4$[y]	119–123 (M/EA)	(60)	(60)
31	MPh	MPh	H	H	H	H	$C_{16}H_{19}NO_2\cdot 0.5C_4H_4O_4$[aa]	160–165 (M/EA)	(60)[bb]	>10[bb]
32[cc]							$C_{18}H_{23}NO_2\cdot HCl$	168.5–170 (M/EA)	(30)	(30)
33[dd]							$C_{12}H_{19}NO_2\cdot C_7H_5NO_3S$[h]	109–111 (A)	17	12
34							$C_{19}H_{25}NO_2\cdot HCl$[f]	92.5–95 (A/EE)	24	20
35[ee]							$C_{17}H_{21}N\cdot HCl$[f,g]	156–158 (M/EE)	15	23
36							$C_{18}H_{29}NO_2\cdot C_7H_5NO_3S$[h]	174–177 (M)	~50	22
37 (PF-82)									10	1.9
imipramine									1.3	0.9
azepindole									11	9

[a] Ph = phenyl; DMP = 3,4-dimethoxyphenyl; 2-Th = 2-thienyl; MPh= methoxyphenyl; ClPh = 4-chlorophenyl. [b] 2-HE = 2-hydroxy-1-ethyl; 2-HP = 2-hydroxy-1-propyl; 2-AE = 2-acetoxy-1-ethyl. [c] All new compounds analyzed within ±0.4% for C and H, unless otherwise noted; some compounds also were analyzed for N, Cl, S, or water (within ±0.4%). For acid-addition salts: $C_4H_4O_4$ = fumaric acid, $C_6H_{12}NO_3S$ = hexamic acid, $C_2H_2O_4$ = oxalic acid, $C_7H_5NO_3S$ = saccharin. Water composition was confirmed by Karl–Fischer analysis and solvent additives were confirmed by ^1H NMR integration. [d] The recrystallization solvent is given in parentheses: M = methanol, EA = ethyl acetate, I = 2-propanol, EE = ethyl ether, H = hexane, E = ethanol, A = acetone. [e] Tetrabenazine (TBZ) antagonism test in mice: ED_{50} (unless otherwise noted) in inhibiting the effect of TBZ on exploratory activity (EA) and in prevention of TBZ-induced ptosis (see text). Compounds were administered intraperitoneally. Numbers in parentheses mean inactive at that dose. Ninety-five percent confidence ranges appear in the supplementary material. [f] Cl analysis. [g] N analysis. [h] 0.1 mol of water present. [i] 0.2 mol of water present. [j] Two diastereomers (meso and *dl*) were present. Two samples were obtained: one contained largely one isomer (70–80%), mp 146–155 °C, and one contained largely the other isomer (85–90%), mp 171–179 °C. The amount of each isomer was estimated by TLC and ^1H NMR. [k] This sample contained 10–15% 3-thienyl isomer (^1H NMR, TLC, ^{13}C NMR). [l] S analysis. [m] Lit. mp 258–260 °C (Zuccarello, W. A.; et al. *J. Med. Chem.* **1969**, *12*, 9). [n] Overt CNS stimulation. [o] Lit. mp 175 °C dec (Berti, G. *Chem. Abstr.* **1961**, *55*, 15485h). [p] Lit. mp 203–205 °C (ref 15c). [q] Lit. mp 279–280 °C (Zuccarello, W. A.; et al. *J. Med. Chem.* **1969**, *12*, 9). [r] 0.125 mol of H_2O present. [s] Lit. mp 193–195 °C (Lindner, E.; Stein, L. *Arzneim.-Forsch.* **1959**, *9*, 94). [t] Lit. mp 192–194 °C (Wade, T. N. *J. Org. Chem.* **1980**, *45*, 5328). [u] Preconvulsant at 30 mg/kg. [v] Lit. mp 227–228 °C (Skerrett, E. J.; Woodcock, D. *J. Chem. Soc.* **1952**, 3308). [w] Lit. mp 173–174 °C (Deshpande, V. N.; Nargunda, K. S. *Chem. Abstr.* **1959**, *52*, 7183f). This compound exhibits a propensity to form polymorphs. [x] Lit. mp 45 °C for the free base (ref 3b). C, H, H_2O analyses. [y] 0.60 mol of H_2O, 0.5 mol of ethyl acetate, and 0.1 mol of methanol present. [z] References to free base: Singh, G.; et al. *Chem. Abstr.* **1957**, *51*, 418e; **1958**, *52*, 7183f; Govindachari, T.; et al. **1959**, *53*, 12288f. [aa] 0.24 mol of water and 0.06 mol of ethyl acetate present. [bb] Lethal at 60 mg/kg. [cc] Lit. mp 166–167 °C (Goodsen, L. H.; Christopher, H. *J. Am. Chem. Soc.* **1950**, *72*, 358). [dd] Reference to free base: Wilson, E.; Tishley, M. *J. Am. Chem. Soc.* **1951**, *73*, 3635. [ee] Lit. mp 163–164 °C (Adamson, D. W. *J. Chem. Soc.* **1949**, 5144; *Chem. Abstr.* **1950**, *44*, 584d).

At this point the diarylethylamine–diethanol structure was held constant and structural fine-tuning was instituted. Addition of a methyl (**5**), hydroxy (**8**), or fluoro (**9**) substituent (R_1) onto the benzhydryl carbon diminished activity relative to **4**. Placement of methyl on the other phenethyl carbon (**6**) did not impair activity much, but ethyl (**7**) substitution did reduce activity. Substitution of methyl onto each ethanol group (**10**) did not significantly alter activity. Changing one phenyl group to a 3,4-dimethoxyphenyl (**11**), 2-thienyl (**12**), or cyclohexyl (**36**) group severely attenuated activity; changing both phenyl groups in **4** to 3,4-dimethoxyphenyl (**13**), 4-methoxyphenyl (**14**), 4-chlorophenyl (**15**), or 2-thienyl (**16**) groups also dissipated activity.

It was also of interest to evaluate the influence of the diethanol groups, so compounds lacking these were exam-

Table II. Biodata on Selected Compounds

compd[a]	TBZ ED_{50}[b] EA	TBZ ED_{50}[b] Pt	MEST screen[c] A	MEST screen[c] TBZ	LD_{50} range, mg/kg	gross behavior[d]
4	15	2	20.3	15.4	100–300	sl irr and startle, sl decr in MA at 30 mg/kg (ip)
19	9	2.5	7	3	30–100	sl irr at 1, 3, and 10 mg/kg (ip); sl incr in reac at 3 and 10 mg/kg
18	~5	2.3	8.2	~9	30–100	sl irr, sl decr in MA and reac at 10 mg/kg (ip)
17	1.8	1.7	10–15	>15	30–100	sl-mod incr in irr and reac 3 and 10 mg/kg (ip), mod incr in MA at 10 mg/kg
22	9	6	8.1	9.9	30–100	sl irr and reac at 3 and 10 mg/kg (ip); sl incr in MA at 1 and 3 mg/kg
33	17	12	>50	>50	300–1000	sl irr at 3, 10 and 100 mg/kg (ip), sl ataxia and decr in MA at 30 and 100 mg/kg
37	10	1.9	>25	21.4	100–300	sl irr and mod decr in MA at 30 mg/kg
IMIP	1.3	0.9	20.3	14.9	100–300	sl irr, sl decr in MA at 3, 10, and 30 mg/kg (ip)
AZEP	11	9	46	32	100–300	sl irr andd sl decr in MA at 10 and 30 mg/kg (ip); sl ataxia at 30 mg/kg

[a] AZEP = azepindole, IMIP = imipramine. [b] See Table I for details. [c] Maximal electroshock seizure threshold test; ED_{50} in TBZ-treated mice and untreated (alone = A) mice in mg/kg (ip) (see text). [d] General behavior effects observed; sl = slight, mod = moderate, irr = irritability, reac = reactivity, incr = increase, decr = decrease, MA = motor activity.

ined. The compounds included primary, secondary, and tertiary 2,2-diarylethylamines, that is compounds in which the ethanol groups are replaced by H/H, H/CH_3, or CH_3/CH_3, respectively. Primary amines **17**, **20**, and **22** exhibited potent activity, whereas primary amines **23**, **24**, **27**, **30**, and **31** were virtually inactive. Secondary amine **18** had potent activity and **25** had reasonable activity, but **28** was just weakly active. Diphenylpropyl secondary amine **35** showed moderate activity. Tertiary amines **19** and **26** were highly active, but **29** was very weak. The diacetate derivative of **4** (**21**) showed only moderate activity.

The activity of the compounds that we have studied is placed in proper perspective by a comparison with the reference agents imipramine, azepindole, and PF-82 (**37**), a compound structurally related to **4** and possessing analogous activity (Table I; also vide infra).

Pharmacology. Some of the diarylethylamine compounds from Table I were further examined. Observations on general behavioral effects of, and LD_{50} estimates for, these compounds in mice are presented in Table II. Selected compounds were also assayed in a maximal electroshock seizure threshold (MEST) test, a modification of the CS_{50} method of Chen et al.[8] (see Experimental Section).

Chen determined the change in current level required to produce tonic-extensor seizures in mice pretreated with a fixed dose of compound alone and with TBZ. Antidepressants, such as desmethylimipramine (DMI; 16 mg/kg) raised the seizure threshold (6.85 ± 0.12 mA) vs. saline (5.70 ± 0.06 mA) or saline in combination with TBZ (5.15 ± 0.05 mA), whereas DMI in combination with TBZ raised the threshold further (9.45 ± 0.32 mA). In our method, a fixed current of 8.0 mA is applied and the dose of test compound is varied. The 8.0-mA current was previously determined to be the minimal current strength required to produce hind-limb tonic-extensor seizures in approximately 100% of normal, untreated mice and to be higher than the minimal current strength (6.0 mA) required to produce seizures in mice pretreated with TBZ. Clinically effective antidepressants are usually more potent inhibitors of electrically induced seizures when given together with TBZ than when given alone. Data for **4**, and other selected compounds, in the MEST test are presented in Table II. Referral to reference agents **37**, imipramine, and azepindole reveals greater potency in the MEST test with TBZ than in the absence of TBZ (however, **37** was inactive alone). A similar enhancement of potency in TBZ-treated mice was observed with **4** and **19** but not with the other compounds studied. Since TBZ activity per se (or any single CNS screen) does not necessarily indicate, nor guarantee, clinical effectiveness for a compound, the MEST data for **4** and **19** offer encouragement for their potential clinical utility as antidepressants.

Some biochemical measurements were also performed.[9] The effects of **4** on brain levels of norepinephrine (NE), dopamine (DA), serotonin (5HT), and their metabolites (MOPEG-SO_4,[9] homovanillic acid (HVA), and 5-hydroxyindole-3-acetic acid (5-HIAA), respectively) were evaluated. Compound **4** had no significant effects at 45 mg/kg (ip) except for a slight elevation of MOPEG-SO_4. By contrast, imipramine at 45 mg/kg (ip) caused significant elevation of NE and depletion of 5-HIAA. Azepindole at 75 mg/kg (ip) mildly increased levels of NE, DA, and 5HT and strongly decreased levels of HVA and 5-HIAA.

Discussion. Many 2,2-diarylethylamine derivatives have been synthesized by Klosa,[10] and some CNS stimu-

(8) Chen, G.; Ensor, C. R.; Bohner, B. *Life Sci.* **1968**, *7*, 1063.

(9) (3-Methoxy-4-hydroxyphenyl)ethylene glycol sulfate = MOPEG-SO_4. Biochemical methodology for the biogenic amines is contained in the following references: (a) Weil-Malherre, H. *Meth. Biochem. Anal.* **1971**, Suppl., 136 (on catecholamines). (b) Lovenberg, W.; Engelman, K. *Ibid.*, 1 (on serotonin). (c) Meek, J. L.; Neff, N. H. *Br. J. Pharmacol.* **1972**, *45*, 435 (assay for MOPEG-SO_4). (d) Karasawa, T.; Nakamura, I.; Masanao, S. *Life Sci.* **1975**, *15*, 1465 (assays for HVA and 5-HIAA). Tissue preparation proceeded as follows: Male CFN rats, after dosing, were sacrificed by cervical dislocation. Brains were removed, weighed, and homogenized for 20 s. The homogenates were spun on a centrifuge at 30000*g* (16 500 rpm Sorvall SS-34) for 20 min. The supernates were then assayed after appropriate pH adjustment.

lant activity has been reported. A series of (ω-hydroxyalkyl)-2,2-diarylethylamines was found by French researchers to possess CNS stimulant and antidepressant activity.[11] (ω-Hydroxyalkyl)-3,3-diarylpropylamine derivatives have also been reported to have antidepressant activity.[12] Shimizu et al.[12b] have described in some detail the pharmacological profile for the interesting antidepressant **37**, an example from their 3,3-diarylpropylamine series. Compound **37**, structurally related to **4**, has pharmacological and biochemical properties similar to imipramine.

Compounds **4** and **19** resemble standard tricyclic antidepressants and azepindole in their CNS pharmacologic properties. They antagonize TBZ EA and ptosis parameters; they block electroshock seizures and are more potent with TBZ present. Compound **4** is also relatively nonlethal (Table II). Such preclinical characteristics suggest their potential utility as antidepressant drugs.

Experimental Section

General Chemical Procedures. UV data (Cary 14 spectrophotometer), IR spectra (Perkin-Elmer 521 spectrophotometer), and ^{1}H NMR spectra [Perkin-Elmer R-32 (90 MHz) spectrometer] were recorded on all target compounds (Table I) and were consistent with the assigned structures. ^{1}H NMR spectra had Me_4Si as an internal reference (abbreviations: s = singlet, d = doublet, t = triplet, m = multiplet, br = broadened). GLC analysis was conducted on a Perkin-Elmer 3920B instrument with a flame-ionization detector, equipped with a Hewlett-Packard 3352B data system and 18652 A/D converter, with a 3% SE-30 on Chromosorb Q (100/120 mesh) column (6 ft × $^1/_8$ in.). TLC analysis was performed on Whatman MK1F silica gel (80 Å) plates (1 × 3 in.), which were visualized with UV and I_2 vapor. Melting points are corrected; melting ranges may be preceded by softening ranges in parentheses. Mass spectra (electron impact) were determined on a Hitachi Perkin-Elmer RMU-6E instrument at 70 eV.

2,2′-[(2,2-Diphenylethyl)imino]bis[ethanol] (4). This procedure exemplifies a general method for reacting amines with ethylene oxide.[13] Sixteen grams (0.08 mol) of 2,2-diphenylethylamine was dissolved in 40 mL of methanol, and two drops of concentrated HCl were added. The mixture was cooled to 0 °C and treated with a cold (0 °C) solution of 18 mL of ethylene oxide in 10 mL of methanol. The reaction was heated at reflux for 1 h, cooled, and concentrated in vacuo to a viscous oil. About 200 mL of dry ether was added and the solution was decanted from any minor amounts of solid. It was then treated with dry HCl to give a light tan solid, which was collected by filtration (23 g). Recrystallization twice from a mixture of ethyl acetate/methanol afforded pure white **4**·HCl (14.2 g): mp 163.5–165 °C; ^{1}H NMR ($CDCl_3$/Me_2SO-d_6, 3:1) δ 3.2–3.6 (m, 4, 2 NCH_2CH_2O), 3.6–4.3 (m, 6, 2 CH_2O and CH_2N), 4.4–6.0 (m, 3, 2 OH and Ph_2CH), 7.0–7.7 (m, 10), 9.35 (br s, 1, NH^+); D_2O exchange revealed a triplet at 4.77 of 1 H for Ph_2CH; IR (KBr) ν_{max} 3200, 1457, 1448, 1388, 1179, 1084, 1075, 1038, 793, 766, 750, 714, 704 cm^{-1}.

1,1′-[(2,2-Diphenylethyl)imino]bis[2-propanol] (10). This compound, actually a mixture of two diastereomers because of the chiral centers of the propanol groups, was prepared from 2,2-diphenylethylamine and propylene oxide according to the procedure for **4**. The crude, oily product showed both diastereomers by ^{1}H NMR and TLC (ethyl acetate/95% ethanol, 5:1), in a ratio of ca. 1:1. Recrystallization of the HCl salt from ethyl acetate/methanol (6:1) resulted in a partial separation of the meso and *dl* diastereomers. The less soluble, first fraction was recrystallized again to give a higher melting mixture (A), enriched in one isomer (ca. 85%), mp 171–179 °C.[14] The mother liquor from the first recrystallization was diluted with dry ether to induce material enriched in the other isomer to separate. The more soluble, second fraction was recrystallized again to give a lower melting mixture (B), enriched in the other isomer (ca. 75%), mp 146–155 °C.[14] A: ^{1}H NMR ($CDCl_3$/Me_2SO-d_6, 8:1) δ 1.11 (d, 6, 2 CH_3, J = 6 Hz), 3.0–3.4 (m, 4, 2 NCH_2CHO), 3.9–4.4 (m, 4, 2 CHO and CH_2N), 4.78 (t, 1, Ph_2CH, J = 7 Hz), 4.9–5.7 (br s, 2, OH), 7.1–7.8 (m, 10), 8.5–8.9 (br s, 1); IR (KBr) ν_{max} 3225, 3155, 1451, 1380, 1142, 1006, 1000, 752, 711, 698 cm^{-1}. B: ^{1}H NMR ($CDCl_3$) δ 1.04 (d, 6, J = 6 Hz), 2.9–3.4 (m, 4), 3.9–4.5 (m, 4), 4.6–5.4 (m, 3; t at δ 4.84 for Ph_2CH; br s at δ 5.09 for OH), 7.1–7.8 (m, 10), 9.53 (br s, 1).

2,2′-[(1,1-Diphenyl-2-butyl)imino]bis[ethanol] (7). A mixture of 60 g (0.306 mol) of diphenylacetaldehyde and 32.4 g (0.308 mol) of diethanolamine in 60 mL of toluene was heated at reflux for 1.5 h, using a Dean–Stark trap to collect the water that was generated. The toluene was distilled in vacuo to leave a viscous oil. Part of this oil (19.9 g) in 100 mL of dry ether was added slowly to 76 mL of 3 M ethylmagnesium bromide in ether. After 2 h, 200 mL of water was added. The organic layer was separated and rinsed with brine, dried over Na_2SO_4, and concentrated to a yellow viscous oil (20.2 g). This oil was chromatographed on silica gel to give 11 g of TLC-pure material. Part of the purified material (3.0 g) was converted into a salt with fumaric acid. Recrystallization twice from ethyl acetate/methanol furnished 2.4 g of white solid: mp 155–157.5 °C; ^{1}H NMR ($CDCl_3$/Me_2SO-d_6, 1:1) δ 0.6–1.0 (m, 3, CH_3), 1.2–1.6 (m, 2, CH_2CH_3), 2.5–2.8 (m, 4, 2 CH_2N), 3.1–3.7 (m, 5, 2 CH_2O and CHN), 3.97 (d, 1, Ph_2CH), 6.66 (s, 2, vinyl H), 7.0–7.6 (m, 10), 7.7 (br s, 4, 2 OH, NH^+ and COOH); IR (KBr) ν_{max} 3250, 3100, 1615, 1445, 1070, 985, 792, 762, 747, 708, 695 cm^{-1}.

2,2′-[(2,2-Diphenylethyl)imino]bis[ethanol acetate] (21). An 8.55-g sample (0.03 mol) of amine diol **4** in 75 mL of dry ether was combined with 13.1 g (0.13 mol) of triethylamine. To this solution was added 7.8 g (0.1 mol) of acetyl chloride in 20 mL of dry ether with ice-bath cooling and stirring. The reaction was stirred for 30 min and treated with 25 mL of 15% NaOH solution with mixing. The organic layer was separated and rinsed with water, dried over Na_2SO_4, and concentrated to an oil. Residual triethylamine was removed from the oil under high vacuum (10 g of residue). A dihexamate salt was made by dissolving the oil in 50 mL of dry ether and adding a solution of 5.5 g of cyclohexylsulfamic acid in 10 mL of methanol (9.3 g). Recrystallization from acetone gave 6.0 g of **21** as colorless needles: mp 136.5–139 °C; ^{1}H NMR ($CDCl_3$/Me_2SO-d_6, 4:1) δ 1.0–2.0 (m, 22; δ 1.0–2.0, m of 16 H for $CCH_2CH_2CH_2C$ of acid and $(CH_2)_5$ of anion; δ 1.93, s of 6 H for 2 CH_3CO), 2.1–2.4 (m, 4; remaining CH_2CCH_2 for the acid), 2.79 (t, 4; 2 NCH_2CH_2OAc), 3.1–3.5 (m, 4; δ 3.19, d of 2 H for CH_2N^+; δ 3.1–3.5, m of 2 H for CHN), 3.97 and 4.14 (pair of t, 5, 2 CH_2O and Ph_2CH, respectively), 7.22 (m, 10), 6.5–8.9 (br s, 4; 2 NH + 2 SO_3H); IR (KBr) ν_{max} 3210, 2925, 2850, 2435, 1746 (CO), 1443, 1370, 1288, 1272, 1237, 1205, 1164, 1030, 704, 695, 589, 523 cm^{-1}. The monohexamate salt of **21** never crystallized.

Tetrabenazine Antagonism Assay.[5] The effect of the test compound on TBZ-induced decrease in motor activity (sedation) and ptosis was determined in mice. Nonfasted male albino mice of the Swiss Webster strain (Royal Hart Laboratories), weighing 18–24 g, were used in this assay. The test compound was administered intraperitoneally 30 min prior to the injection of 32 mg/kg ip of TBZ. Control mice were injected with saline 30 min prior to the administration of TBZ. Thirty minutes later, the mice were individually placed in the center of a 12-in. × 24-in. screen raised 6 in. above the bench top and observed for 10 s for the presence of exploratory activity and the degree of bilateral

(10) (a) Klosa, J.; Starke, H. *Chem. Abstr.* **1965**, *63*, 11426b; 11579b. (b) Klosa, J., *J. Prakt. Chem.* **1966**, *34*, 312; **1969**, *311*, 520.

(11) Schmidt, J.; Brunard, M. D. P. Fr. Patent 1 526 188, 1968; *Chem. Abstr.* **1969**, *71*, 30213e. Fr. M. 6491, *Chem. Abstr.* **1971**, *74*, 42126d.

(12) (a) Kaneko, H.; Nakamura, K.; Aritomi, J. *Chem. Abstr.* **1970**, *73*, 109469t; **1972**, *77*, 48035g. (b) Shimizu, M.; Hirooka, T.; Karasawa, T.; Masuda, Y.; Oka, M.; Kamei, C.; Sohji, Y.; Hori, M.; Yosida, K.; Kaneko, H. *Arzneim.-Forsch.* **1974**, *24*, 166. (c) Kaneko, H., Aritomi, J., Nakamura, K., U.S. Patent 3 895 057, 1975.

(13) Reactions of this type were also carried out in a pressure flask at 100 °C. These more stringent conditions were required for α-substituted amines to achieve completion of reaction within 24 h without the addition of more ethylene oxide.

(14) Diastereomer quantities were estimated (±10%) by TLC (ΔR_f = 0.10) and by integration of ^{1}H NMR spectra of the free bases **10A** and **10B** (methyl groups).

eyelid closure. The presence of normal locomotor activity or exploratory head movements and less than 50% eyelid closure indicated a block of TBZ sedation and ptosis, respectively. Ten mice were used per dosage level of the test compound and in the control group. When the response, sedation and/or ptosis, to TBZ was 90% or less in the control group, the response in the drug-treated group was corrected by using Abbott's formula.[15] Four to five dosage levels of the test compounds were used in obtaining an ED_{50} value. ED_{50} values and 95% confidence limits were calculated by probit analysis.[15]

Maximal Electroshock Threshold Seizures (MEST) Test. The effect of selected members of the series on electroshock seizures was determined in normal and in TBZ-treated mice. Nonfasted male albino mice of the Swiss Webster strain (Royal Hart Laboratories), weighing 18–24 g, were used in this procedure. The test compound or saline was injected 30 min prior to electroshock. Tetrabenazine methanesulfonate (64 mg/kg) was injected intraperitoneally 15 min after the administration of the test compound. These mice were subjected to electroshock 15 min later. Hind-limb tonic-extensor seizures were induced by the delivery of a 60-Hz current of 8-mA intensity for 0.25 s through ear-clip electrodes. The use of a current intensity of 8 mA for 0.25 s was previously determined to be the minimal current strength required to induce hind-limb tonic-extensor seizures in approximately 100% of mice used in this study (ED_{99}). The incidence of hind-limb tonic-extensor seizures in TBZ-treated mice was also 100% (ED_{99} = 6.0 mA). Abolition of the hind-limb tonic-extensor seizure indicated activity. The dose ED_{50} required to block seizures in 50% of normal and TBZ-treated mice was determined. Four to five dosage levels of the test compound were used in obtaining an ED_{50} value. ED_{50} values and 95% confidence limits were calculated by probit analysis.[15]

Gross Behavioral Effects and Lethality. The gross behavioral effects of selected compounds were observed in mice following intraperitoneal doses of 1, 3, 10, 30, 100, and 300 mg/kg. The mice were held for 4 days following administration of the test compounds. An estimated LD_{50} range based on lethality count was made on day 4. Three male albino mice of the Swiss Webster strain (Royal Hart Laboratories), weighing 18–24 g, were used per dosage level of compound administered.

(15) Finney, D. J. "Probit Analysis"; Cambridge University Press: London, 1964.

Acknowledgment. We thank Craig Schneider, Richard Shank, and Russell Taylor, Jr., for biochemical results and Linda Labinsky for experimental assistance.

Note Added in Proof: A brief examination of uptake inhibition of NE, DA, and 5HT for **4**, **19**, and **37** (according to Horn, A. S.; Snyder, S. H. *J. Pharmacol. Exp. Ther.* **1972**, *180*, 523) showed rather weak activity. For **4** (100 nM), **19** (1000 nM), and **37** (1000 nM), percent inhibition values were 24, 37, and 26 for DA; 2, 85, and 40 for NE; and 5, 56, and 7 for 5HT, respectively. K_i values for imipramine were >10 000 nM for DA, 12 nM for NE, and 42 nM for 5HT.

Registry No. **4**, 90530-62-4; **4**·HCl, 90530-63-5; **5**, 90530-97-5; **5**·HCl, 90530-64-6; **6**·fumarate, 90530-66-8; **7**, 90530-67-9; **7**·fumarate, 90530-68-0; **8**, 90552-80-0; **8**·HCl, 90552-78-6; **9**·dihexamate, 90530-70-4; *meso*-**10**, 90530-98-6; *dl*-**10**, 90552-81-1; *meso*-**10**·HCl, 90530-71-5; *dl*-**10**·HCl, 90530-72-6; **11**, 90530-99-7; **11**·HCl, 90530-73-7; **12** (2-thienyl isomer), 90531-00-3; **12** (2-thienyl isomer)·HCl, 90530-74-8; **12** (3-thienyl isomer), 90531-01-4; **12** (3-thienyl isomer)·HCl, 90530-75-9; **13**, 90530-76-0; **13**·$HClO_4$, 90530-77-1; **14**, 90530-78-2; **15**, 90552-79-7; **16**·oxalate, 90530-80-6; **17**·HCl, 7351-52-2; **18**, 80376-82-5; **18**·HCl, 80376-83-6; **19**, 7647-54-3; **19**·HCl, 13636-10-7; **20**, 3139-55-7; **20**·HCl, 3139-54-6; **21**, 90530-81-7; **21**·dihexamate, 90530-82-8; **22**, 4382-96-1; **22**·HCl, 6949-96-8; **23**, 69681-77-2; **23**·HCl, 75198-08-2; **24**, 85336-82-9; **24**·HCl, 21998-53-8; **25**·fumarate, 90530-84-0; **26**, 90531-02-5; **26**·HCl, 90530-85-1; **27**, 36756-35-1; **27**·HCl, 90530-86-2; **28**·oxalate, 90530-88-4; **29**, 90530-89-5; **29**·$HClO_4$, 90530-90-8; **30**·fumarate, 90530-91-9; **31**·hemifumarate, 90530-92-0; **32**, 90531-03-6; **32**·HCl, 6635-05-8; **33**·saccharin, 90530-93-1; **34**, 90531-04-7; **34**·HCl, 90530-94-2; **35**, 90531-05-8; **35**·HCl, 22101-74-2; **36**·saccharin, 90530-96-4; ethylene oxide, 75-21-8; propylene oxide, 75-56-9; diphenylacetaldehyde, 947-91-1; diethanolamine, 111-42-2.

Supplementary Material Available: Ninety-five percent confidence limits for the biodata presented in Tables I and II (1 page). Ordering information is given on any current masthead page.

Radiohalogen-Labeled Imaging Agents. 3. Compounds for Measurement of Brain Blood Flow by Emission Tomography

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The radioiodine-labeled amines currently available as brain-imaging agents, based on our previous work and that of others, are prepared either by exchange labeling or by direct iodination of a protected intermediate. The intrinsic slowness of these processes limits their potential for use with the positron-emitting ^{122}I, as it has a half-life of only 3.6 min. This isotope has advantages of a low dose to the patient and availability from a generator containing the parent 20-h ^{122}Xe. To develop a radiopharmaceutical in which ^{122}I could be utilized, we prepared a number of secondary and tertiary amines (maintaining the 2,5-dimethoxy substitution pattern which allows direct iodination at the 4-position) with ^{131}I. The organ distributions of these compounds were studied, and the best properties were found in the *N*,*N*-dimethyl homologue (2,5-dimethoxy-*N*,*N*-dimethyl-4-iodoamphetamine). This compound was successfully synthesized in a matter of seconds, with a chemical yield and radioactive purity both in excess of 90% and an incorporation efficiency of radioiodine of about 40%.

Paper 1 of this series[1] described an amphetamine analogue, 2-(4-[^{82}Br]bromo-2,5-dimethoxyphenyl)isopropylamine, which was the first reported radiohalogen-labeled organic compound that showed uptake and reasonably long retention in normal human brain. The second paper[2] described the synthesis of the analogous radioiodinated agent, 2-(4-[^{131}I]iodo-2,5-dimethoxyphenyl)isopropylamine (**1r**), which showed first-pass extraction in the monkey from blood to brain. Because of this property, we proposed

(1) Sargent III, T.; Kalbhen, D. A.; Shulgin, A. T.; Braun, G.; Stauffer, H.; Kusubov, N. *Neuropharmacology* **1975**, *14*, 165, to be considered paper 1 of this series.

(2) Braun, U.; Shulgin, A. T.; Braun, G.; Sargent III, T. *J. Med. Chem.* **1977**, *20*, 1543, to be considered paper 2 of this series.

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