(m, 1 H, 5β), 3.35 (m, 1 H, 5α), 3.52 (dd, 1 H, 3β), 4.02 (d, 1 H, 3α), 4.47 (br s, 1 H, 8), 5.51 (br s, 1 H, 7), 4.91 and 4.87 (AB q, 2 H, 9), 5.94 (br s, 1 H, 2), 7.36, 7.46, 7.89 (aromatic).

C-9 Mono(phenylacetate) of Retronecine (22). Compound **22** was prepared as described above for **23** and the crude reaction mixture was chromatographed on activity III alumina. The major product, C-9 monoester **22**, was eluted in $CHCl_3$–CH_3OH (97:3). For **22**: ^1H NMR ($CDCl_3$) δ 1.85 (m, 2 H, 6α and 6β), 2.66 (m, 1 H, 5β), 3.16 (dd, 1 H, 3β), 3.32 (m, 1 H, 5α), 3.83 (d, 1 H, 3α), 4.06 (br s, 2 H, 7 and 8), 4.69 (br s, 2 H, 9), 5.68 (br s, 1 H, 2), 7.26 (m, aromatic), 3.62 (s, 2 H, 2'); EIMS, *m/e* (relative intensity) 53 (13), 55 (20), 57 (12), 60 (14), 66 (16), 67 (12), 68 (21), 69 (11), 70 (17), 80 (17), 81 (27), 82 (11), 92 (16), 94 (100), 95 (48), 96 (12), 136 (10), 137 (13), 138 (23), 139 (22); CIMS, *m/e* (relative intensity) 274 (M + 1, 33), 69 (100); exact mass calcd for $C_{16}H_{19}NO_3$ 273.1366, found 273.1379. Anal. ($C_{16}H_{19}NO_3 \cdot {}^1/_4H_2O$) C-7 H. For C-7 monoester **25**: mp 83–85 °C; ^1H NMR ($CDCl_3$) δ 2.05 (m, 2 H, 6α and 6β), 2.55 (q, 1 H, 5β), 3.14 (dm, 1 H, 5β), 3.28 (m, 1 H, 3β), 3.83 (d, 1 H, 3β), 3.93 (s, 2 H, 9), 4.23 (br s, 1 H, 8), 5.27 (q, 1 H, 7), 5.38 (d, 1 H, 2), 3.54 (s, 2 H, CH_2Ph), 7.2–7.3 (aromatic); EIMS, *m/e* (relative intensity) 68 (12), 80 (95), 81 (14), 91 (42), 93 (12), 94 (34), 106 (61), 111 (100), 120 (10), 123 (34), 124 (26), 136 (25), 137 (47), 255 (23), 273 (7); exact mass calcd for $C_{16}H_{19}NO_3$ 273.1366, found 273.1326.

C-9 Ester of Retronecine and Isovaleric Acid (23). Compound **23** was prepared as described above and the crude product was chromatographed on activity III alumina, and **25**, the major product, was eluted in chloroform: ^1H NMR ($CDCl_3$), run at 60 MHz, consistent with that of other C-9 monoesters run at 300 MHz mentioned above; EIMS, *m/e* (relative intensity) 41 (16), 80 (18), 93 (100), 94 (35), 135 (15), 137 (35), 138 (37), 155 (21), 239 (1); exact mass calcd for $C_{13}H_{21}NO_3$ 239.1522, found 239.1508. Anal. ($C_{13}H_{21}NO_3 \cdot {}^1/_2H_2O$) C, H.

Acknowledgment. This investigation was supported by the National Cancer Institute, National Institutes of Health (Grant ROI CA31490). We thank James McManus for development of the procedure for preparation of the *N*-oxides.

Registry No. **7**, 480-82-0; **7** (*N*-oxide), 41708-76-3; **7** (isopropylidene), 95363-32-9; **14**, 10285-06-0; **14** (isopropylidene), 95462-10-5; **14** (*N*-oxide), 95462-14-9; **15**, 10285-07-1; **15** (isopropylidene), 95462-11-6; **15** (*N*-oxide), 95462-15-0; **16**, 95462-13-8; **16** (isopropylidene), 95462-12-7; **16** (*N*-oxide), 95462-16-1; **19**, 95363-35-2; **19** (isopropylidene), 95363-33-0; **19** (isopropylidene *N*-oxide), 95363-34-1; **19** (*N*-oxide), 95363-36-3; **20**, 95462-18-3; **20** (isopropylidene), 95462-17-2; **20** (isopropylidene *N*-oxide), 95463-25-5; **20** (*N*-oxide), 95462-19-4; **21**, 95363-37-4; **21** (*N*-oxide), 6870-33-3; **22**, 95363-38-5; **23**, 95363-39-6; *trans*-α-isopropylcrotonic acid, 94773-28-1; tiglic acid, 80-59-1; (±)-*threo*-2,3-dihydroxy-2-methylbutyric acid, 40634-99-9; (±)-*threo*-2,3-dihydroxy-2-methylbutyric acid (isopropylene), 95363-40-9; (±)-viridifloric acid, 17132-45-5; (+)-viridifloric acid·(+)-phenylethylamine, 95363-29-4; (−)-viridifloric acid·(−)-phenylethylamine, 95363-30-7; (+)-trachelanthic acid·(−)-α-phenylethylamine, 23944-49-2; (−)-trachelanthic acid·(+)-α-phenylethylamine, 95363-31-8; (−)-trachelanthic acid (isopropylidene), 95462-07-0; (+)-trachelanthic acid (isopropylidene), 95462-08-1; (+)-viridifloric acid (isopropylidene), 81816-10-6; (−)-viridifloric acid (isopropylidene), 95462-09-2; (±)-trachelanthic acid, 23944-47-0; (+)-viridifloric acid, 17233-93-1; (−)-viridifloric acid, 17132-48-8; (+)-trachelanthic acid, 23944-48-1; (−)-trachelanthic acid, 23944-50-5; retronecine, 480-85-3; phenylacetic acid, 103-82-2.

Synthesis and Antidepressant Profiles of Phenyl-Substituted 2-Amino- and 2-[(Alkoxycarbonyl)amino]-1,4,5,6-tetrahydropyrimidines[1]

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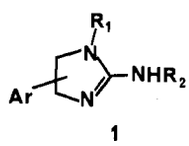
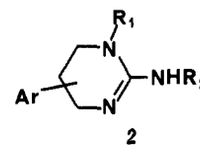
A series of 4(6)- and 5-phenyl-substituted 2-amino- and 2-[(alkoxycarbonyl)amino]-1,4,5,6-tetrahydropyrimidines **2** were prepared and evaluated for central nervous system (CNS) effects in animal models. Several 5-phenyl-substituted compounds possessed potent antidepressant activity and all compounds in this series were devoid of significant activity in any of the other CNS (anticonvulsant, muscle relaxant, and depressant) assays. The most active compound in the in vivo screen for antidepressant activity (reversal of reserpine-induced hypothermia), 2-[(methoxycarbonyl)amino]-5-phenyl-1,4,5,6-tetrahydropyrimidine (**16**), was considerably more potent than tricyclic antidepressant (TCA) standards. The 2-amino parent compound **27** on the other hand was >100-fold as effective as TCA's in in vitro inhibition of norepinephrine and dopamine uptake.

During our studies of structure–activity relationships (SAR) in a series of 2-[(alkoxycarbonyl)amino]-4(5)-phenyl-2-imidazolines **1**[2] (imidazolines) with central nervous system (CNS) activity we became interested in exploring the effect of enlarging of the imidazole moiety to give the appropriately substituted 2-amino-1,4,5,6-tetrahydropyrimidines **2** (tetrahydropyrimidines). A



1



2

R_1 = H or Me, R_2 = H or alkoxycarbonyl

number of representative compounds were prepared[3] and evaluated for their CNS activities[4] according to our previously reported procedures.[2]

Chemistry. Several methods were available for the preparation of cyclic guanidines from diamines and reactants containing the central guanidine C–N fragment. Therefore, our synthetic route was based in part on the intermediacy of 1-phenyl- and 2-phenyl-1,3-diaminopropanes (Scheme I). Cyanogen bromide was known to react with 1,2-diamines to yield 2-aminoimidazolines,[5] but it was not effective for the preparation of six- and seven-

(1) Contribution No. 680 from the Institute of Organic Chemistry.
(2) Weinhardt, K.; Beard, C. C.; Dvorak, C.; Marx, M.; Patterson, J.; Roszkowski, A.; Schuler, M.; Unger, S. H.; Wagner, P. J.; Wallach, M. B. *J. Med. Chem.* **1984**, *27*, 616–627.
(3) Weinhardt, K.; Marx, M. U.S. Patent 4 322 421, 1982.
(4) Peterson, K. E.; Hedley, L. R.; Schuler, M. E.; Wallach, M. B. *Fed. Proc., Fed. Am. Soc. Biol.* **1982**, *41*, 1066. Ohnmacht, C. J.; Malick, J. B.: Frazee, W. J. *Annu. Rep. Med. Chem.* **1983**, *18*, 42.
(5) (a) Matier, W. L.; Owens, D. A.; Comer, W. T.; Deitchmam, D.; Ferguson, H. C.; Seidehamel, R. J.; Young, J. R. *J. Med. Chem.* **1973**, *16*, 901. (b) Ishikawa, F.; Kosayama, A.; Nakamura, S.; Konno, T. *Chem. Pharm. Bull.* **1978**, *26*, 3657. (c) Rodricks, J. V.; Rapoport, H. *J. Org. Chem.* **1971**, *36*, 46 and references therein.

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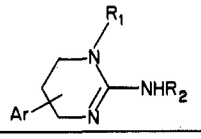
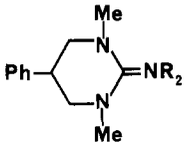
Table I. 2-[(Alkoxycarbonyl)amino]- and 2-Amino-1,4,5,6-tetrahydropyrimidines



no.	Ar	R_1	R_2	mp,[a] °C free base	mp,[a] °C HCl salt	formula (free base)	HYPO[b]
16	5-Ph	H	CO_2CH_3	329–333[c]	184–186	$C_{12}H_{15}N_3O_2$	0.0006[d]
17	5-Ph	H	$CO_2CH_2CH_3$	338–343[c]	184–186	$C_{13}H_{17}N_3O_2$	0.04[e]
18	5-Ph	H	$CO_2CH(CH_3)_2$	338–342[c]	>220 dec	$C_{14}H_{19}N_3O_2$	0.04[e]
19	5-(2-ClPh)	H	CO_2CH_3	353–357[c]	181	$C_{12}H_{14}N_3O_2Cl$	10
20	5-(3-BrPh)	H	CO_2CH_3	213–215	178–180	$C_{12}H_{14}N_3O_2Br$	1
21	5-(3-CH_3OPh)	H	CO_2CH_3	218–221	163–165	$C_{13}H_{17}N_3O_3$	(10)[f]
22	5-(4-$(CH_3)_2$CHPh)	H	CO_2CH_3	>360[c]	>200 dec	$C_{15}H_{21}N_3O_2$	1
23	5-(4-FPh)	H	CO_2CH_3	>300[c]	179–182	$C_{12}H_{14}N_3O_2F$	0.04
24	5-(2,6-Cl_2Ph)	H	CO_2CH_3	231–4	140–142[g]	$C_{12}H_{13}N_3O_2Cl_2$	0.15–0.6
25	5-(2,4-Cl_2Ph)	H	CO_2CH_3	>310[c]	209–210	$C_{12}H_{13}N_3O_2Cl_2$	(10)
26	5-Ph	CH_3	CO_2CH_3	176–177		$C_{13}H_{17}N_3O_2$	0.15–0.6
27	5-Ph	H	H		264–267[h]	$C_{10}H_{13}N_3$	0.01–0.15[i]
28	5-(3-BrPh)	H	H		223–227[j]	$C_{10}H_{12}N_3Br$	(10)
29	5-Ph	H	CH_3		145–148[g]	$C_{11}H_{15}N_3$	1
30	5-Ph	CH_3	CH_3		188–191[g,k]	$C_{12}H_{17}N_3$	10
31	4(6)-Ph	H	CO_2CH_3	186–189[g]	156–157	$C_{12}H_{15}N_3O_2$	2.5[l]
32	4(6)-Ph	H	$CO_2(CH_2)_2CH_3$	134–137[m]	163–165	$C_{14}H_{19}N_3O_2$	I
33	4(6)-(2-CF_3Ph)	H	CO_2CH_3	195–197	155–157	$C_{13}H_{14}N_3O_2F_3$	(10)
34	4(6)-(3-CH_3OPh)	H	CO_2CH_3	145–148	177–178	$C_{13}H_{17}N_3O_3$	(10)
35	4(6)-(4-CH_3Ph)	H	CO_2CH_3	198–200		$C_{13}H_{17}N_3O_2$	I
36	4(6)-(4-FPh)	H	CO_2CH_3	211–212	166–168	$C_{12}H_{14}N_3O_2F$	1
37	6-Ph	CH_3	CO_2CH_3	oil[g]		$C_{13}H_{17}N_3O_2$	10
38	4(6)-Ph	H	H		192–194[n]	$C_{10}H_{13}N_3$	10^0
39			CO_2Me	96–98		$C_{14}H_{19}N_3O_2$	10[l]
40			H		306–309[k]	$C_{12}H_{17}N_3$	10[l]
amitryptyline							0.15
imipramine							0.15

[a] Satisfactory analyses (C, H, and N; ±0.4% of the theoretical values) for all compounds, except where otherwise noted. [b] Antagonism of reserpine-induced hypothermia. Minimum oral dose (milligrams/kilogram) producing a significant reversal. I = inactive at 10 mg/kg, (10) = weak activity at 10 mg/kg, 10 = at least 40% reversal at 10 mg/kg but steep drop off. [c] Apparent phase changes at 210–230 °C. [d] LD_{50} mice, po 142 (111–182), ip 27 (25–28) mg/kg. [e] LD_{50} mice, po >1000 mg/kg. [f] LD_{50} mice, po ~700 mg/kg (estimated from mouse behavior screen). [g] An analysis was not obtained. [h] Hemisulfate salt. [i] LD_{50} mice, po 78 (50–122), ip 42 (31–53) mg/kg. [j] HBr salt; C: calcd, 35.85; found, 34.79. [k] HI salt. [l] Short acting. [m] C: calcd, 64.35; found, 63.82. [n] HBr salt. [o] Not tested at a lower dose.

membered monocyclic guanidines from the corresponding diamines.[5b] On the other hand, successful syntheses of fused 2-amino-1,4,5,6-tetrahydropyrimidines with cyanogen bromide have been reported.[6] N-Substituted *S,S*-dimethylcarbonimidodithioates have been used as reagents for the preparation of six- and seven-membered cyclic guanidines.[5b,c,7]

We found that phenyl-substituted 1,3-diaminopropanes (Table II) do react with cyanogen bromide to form 2-aminotetrahydropyrimidines **2** (R_2 = H) (Table I). The reaction of the 2-phenyl analogues **5** was slower than that of the 1-phenyl isomers **8**. The symmetrically substituted 2-amino-5-phenyltetrahydropyrimidine **27** was best prepared by fusion of diamine **43** with 2-methyl-2-thiopseudourea hemisulfate. In addition, cyclization reactions of the phenyl-1,3-diaminopropanes with bis(alkoxycarbonyl) derivatives of 2-methyl-2-thiopseudourea **15**[8] could be used to form tetrahydropyrimidines **2** (R_2 = alkoxycarbonyl) (Table I) in yields comparable to those obtained for the formation of imidazolines **1**[2] in a related reaction.

Symmetrical 3-phenylglutaronitriles **3** (Table II) were prepared by the procedure of Schiemenz and Engelhard[9] and the 2-phenyl analogues **6** (Table II) were prepared according to the method of Bertocchio and Dreux.[10] Initially, we converted the dinitriles into glutaramides **4** and **7** (Table II) by hydrolysis with sulfuric acid; however, application of these conditions to 3-(3-methoxyphenyl)-glutaronitrile (**50**) gave rise to extensive ring sulfonation. Nitrile hydrolysis with aqueous sodium carbonate and hydrogen peroxide[11] circumvented this problem and was a generally preferred method due to the improved ease of diamide isolation from the reaction mixture (see Experimental Section). The glutaramides **4** and **7** were converted into phenyl-1,3-diaminopropanes **5** and **8**, respectively, by a double Hofmann rearrangement as described by Aspinall[12] for glutaramide. Several 1-phenyl-1,3-diaminopropanes **8** were prepared by the diborane reduction of 3-amino-3-phenylacrylonitriles **9**.[13] *N*-Methyl-1,3-di-

(6) (a) Armagero, W. L. F.; Tucker, P. G. *Aust. J. Chem.* **1979**, *32*, 1805. (b) Kienzle, F.; Kaiser, A.; Chodnekar, M. S. *Eur. J. Med. Chem.-Chim. Ther.* **1982**, *17*, 547.
(7) Hougten, R. A.; Simpson, R. A.; Hanson, R. N.; Rapoport, H. *J. Org. Chem.* **1979**, *44*, 4536.
(8) Klopping, H. L. U.S. Patent 2933504, 1960; *Chem. Abstr.* **1961**, *55*, 9431f.
(9) Schiemenz, G. P.; Engelhard, H. *Chem. Ber.* **1962**, *95*, 195.
(10) Bertocchio, R.; Dreux, J. *Bull. Soc. Chim. Fr.* **1962**, 1809.
(11) Murray, J. V.; Cloke, J. B. *J. Am. Chem. Soc.* **1934**, *56*, 2749.
(12) Aspinall, S. R. *J. Am. Chem. Soc.* **1941**, *63*, 2843.
(13) Dornow, A.; Kuehlcke, I.; Baxmann, F. *Chem. Ber.* **1949**, *82*, 254.

Scheme I

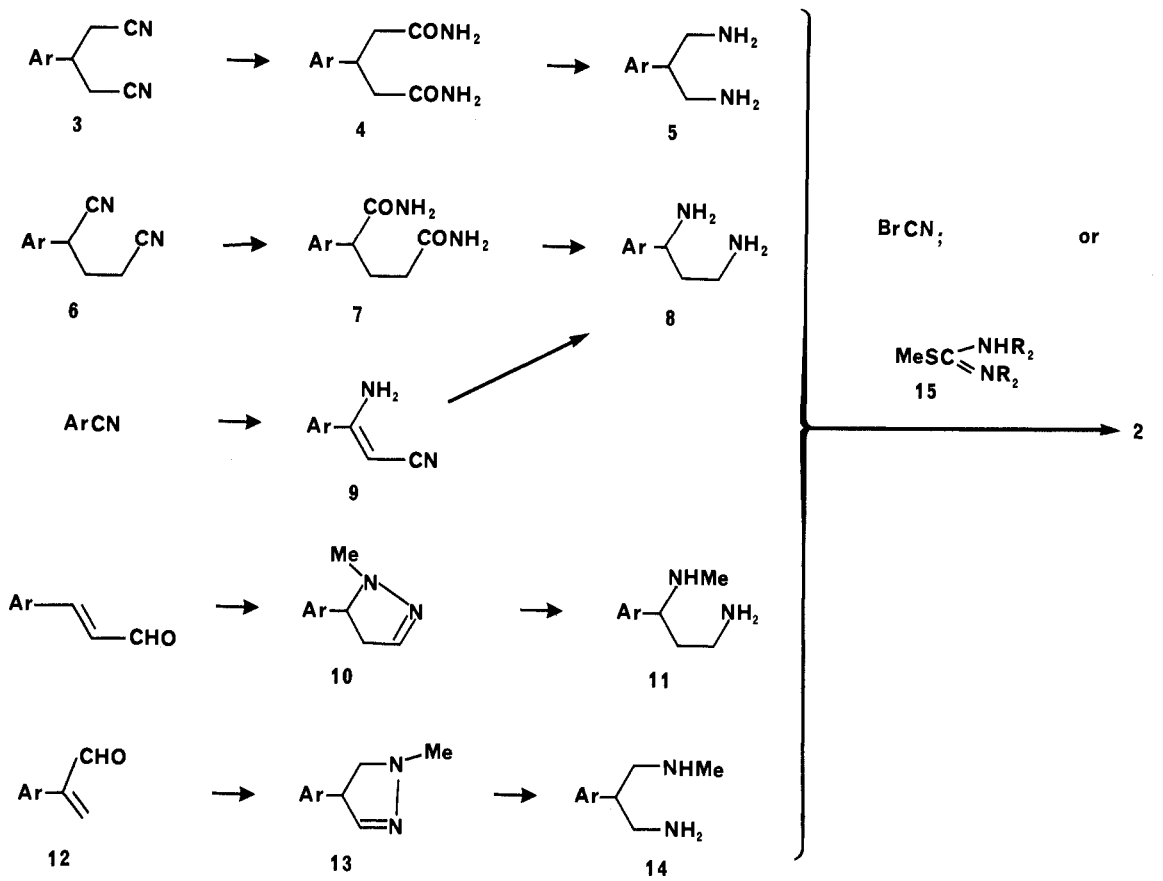


Table II. Intermediates for Tetrahydropyrimidines

Ar	phenyl-1,3-dicyanopropanes 3 and 6: formula,[a] bp, °C/mmHg or mp, °C[b]	no.	(A) 4 and 7, (B) 9, or (C) phenylmethylpyrazolines: formula,[a] mp, °C or bp, °C/mmHg	no.	Ph, NHR, NH2: formula[a] (free base), mp, °C[l]	R, no.
2-Ph	$C_{11}H_{10}N_2$, 134/0.02[c]	41	(A) $C_{11}H_{14}N_2O_2$, 180–184, E[d]	42	$C_9H_{14}N_2$, 258–262[e]	H, 43
2-(2-ClPh)	$C_{11}H_9N_2Cl$, ~150/0.02	44	(A) $C_{11}H_{13}N_2O_2Cl$, 189, B	45	$C_9H_{13}N_2Cl$, 253–257	H, 46
2-(3-BrPh)	$C_{11}H_9N_2Br$, 94–96, A	47	(A) $C_{11}H_{13}N_2O_2Br$, 168–170, C	48	$C_9H_{13}N_2Br$, 260–265	H, 49
2-(3-CH_3OPh)	$C_{12}H_{12}N_2O$, 146–153/0.01	50	(A) $C_{12}H_{16}N_2O_3$, 161–162, C	51	$C_{10}H_{16}N_2O$, 232–234	H, 52
2-(4-$(CH_3)_2$CHPh)	$C_{14}H_{16}N_2$, ~180/0.05[g]	53	(A) $C_{14}H_{20}N_2O_2$, 192–193, F[g]	54	$C_{12}H_{20}N_2$, 284–287	H, 55
2-(4-FPh)	$C_{11}H_9N_2F$, 138–140/0.01	56	(A) $C_{11}H_{13}N_2O_2F$, 184–186, B	57	$C_9H_{13}N_2F$, 292.5–295	H, 58
2-(2,4-Cl_2Ph)	$C_{11}H_8N_2Cl_2$, 76–78, A–C	59	(A) $C_{11}H_{12}N_2O_2Cl_2$, 194–196, C	60	$C_9H_{12}N_2Cl_2$, 268–270	H, 61
2-(2,6-Cl_2Ph)	$C_{11}H_8N_2Cl_2$, 104–106, C	62	(A) $C_{11}H_{12}N_2O_2Cl_2$, 224–226, B	63	$C_9H_{12}N_2Cl_2$, >300 dec[h]	H, 64
1-Ph	$C_{11}H_{10}N_2$, 144–153/1[i]	65	(A) $C_{11}H_{14}N_2O_2$, 155–156, E	66	$C_9H_{14}N_2$, 244–246	H, 67
1-(4-FPh)	$C_{11}H_9N_2F$, 118–222/0.03[g]	68	(A) $C_{11}H_{13}N_2O_2F$, 154–157, D	69	$C_9H_{13}N_2F$, 262–266[j]	H, 70
1-(2-CF_3Ph)			(B) $C_{10}H_7N_2F_3$, 101–103, A–F[j]	71	$C_{10}H_{13}N_2F_3$, 214–216	H, 72
1-(3-CH_3OPh)			(B) $C_{10}H_{10}N_2O$, 70–73, B–F	73	$C_{10}H_{16}N_2O$, 225–227	H, 74
2-Ph(diamine), 4-Ph-pyrazoline			(C) $C_{10}H_{12}N_2$, 80–90/0.01[g]	13	$C_{10}H_{16}N_2$, 265–267	CH_3, 14
1-Ph(diamine), 5-Ph-pyrazoline			(C) $C_{10}H_{12}N_2$, 51–56/0.01[g]	10	$C_{10}H_{16}N_2$, 247–250[g]	CH_3, 11

[a] Satisfactory analyses (C, H, and N) for all compounds, except where otherwise noted. [b] Crystallization solvent code: A = MeOH, B = EtOH, C = *i*-PrOH, D = $CHCl_3$, E = crude extract, F = water. [c] Lit.[9] bp 158 °C (1 mmHg). [d] Lit.[9] mp 183–185 °C. [e] Lit. mp 249–251 °C. Riemschneider, R.; Rook, A. *Monatsh. Chem.* **1961**, *92*, 1227. [f] N: calcd, 9.82; found, 10.34. [g] Satisfactory analysis was not obtained. [h] Picrate mp 253–255 °C (EtOH). [i] Lit.[10] bp 137–138 °C (0.5 mmHg). [j] C: calcd, 44.83; found, 44.39. [k] C: calcd, 56.61; found, 57.05. [l] Dihydrochloride salt.

aminopropanes **11** and **14** were obtained by catalytic hydrogenation of the corresponding *N*-methyl-2-pyrazolines (Table II). 1-Methyl-5-phenyl-2-pyrazoline (**10**)[14,15] and 1-methyl-4-phenyl-2-pyrazoline (**13**) were prepared by addition of methylhydrazine to cinnamaldehyde and atropaldehyde (**12**), respectively. Because of its instability, atropaldehyde was generated from its ethylene ketal[16] immediately prior to its reaction with methylhydrazine.

A few selected reactions were carried out with tetrahydropyrimidine **16**. A reduction of the *N*-carbamate side chain with lithium aluminum hydride furnished 2-(*N*-methylamino)tetrahydropyrimidine **29**. Direct methylation of the anion of **16**, prepared with NaH, resulted in the

(14) (a) Auwers, K.; Heimke, P. *Justus Liebigs Ann. Chem.* **1927**, *458*, 204. (b) Gibert, J.-P.; Petrus, C.; Petrus, F. *J. Heterocycl. Chem.* **1979**, *16*, 311.

(15) The mass spectrum matched that reported for the assigned structure, not that of the isomeric 1-methyl-3-phenylpyrazoline. Jaquier, R.; Ramos, M.-J. *Bull. Soc. Chim. Fr.* **1973**, *5*, 737.

(16) Elkik, E. *Bull. Soc. Chim. Fr.* **1968**, *1*, 283.

Table III. Inhibition of Uptake of Neurogenic Amines

compd	in vivo NE (mouse heart): ED_{50},[b] ip	in vitro IC_{50},[a] $\times 10^{-6}$ NE	dopamine	5-HT
16	0.038 (0.01–0.14)	4.9[c]	24	160
27	0.038 (0.01–0.15)	0.01	0.03[d]	1.6
amitryptyline	4.4 (2.8–6.9)	2.5	12	12
desipramine	1.4 (0.5–3.5)		12	12
imipramine	6.7 (3.1–14.6)	4.6	12	16

[a] Molar concentration that causes 50% inhibition of norepinephrine, dopamine, and 5-hydroxytryptamine uptake, respectively, in rat brain slices. [b] Milligrams/kilogram; 95% confidence limits in parenthesis. [c] The *N*-methyl analogue **26** was inactive. [d] The 4(6)-phenyl analogue **38** measures $\sim 1/10$.

formation of mixtures of **26**, **30**, **39**, and **40**.

Results and Discussion

Our testing of 2-aminotetrahydropyrimidines and their 2-(alkoxycarbonyl)amino derivatives **2** showed that they possessed pure antidepressant profiles. Compounds **17**, **18**, **23**, **27**, and especially **16** were much more potent than tricyclic antidepressant (TCA) standards in their ability to reverse reserpine-induced hypothermia (Table I).[17] In addition, they showed either no anticonvulsant, muscle relaxant, or depressant activity or were active only near lethal doses. By contrast, the class of imidazolines **1** had demonstrated a mixed profile of activities, with only antidepressant potency reaching the level of standards.

Compounds with phenyl groups in the symmetrical 5-position of the tetrahydropyrimidine moiety were more active than compounds with a phenyl substituent at position 4 or 6. Further substitution on the phenyl ring or N-methylation of the guanidine moiety gave less active compounds. This is in contrast to imidazolines **1**, where N-methylation and introduction of halogen into the 2- and 3-positions of the phenyl ring had produced some very active compounds.[2] Increasing the chain length of the 2-(alkoxycarbonyl)amino beyond methoxy reduced antidepressant activity.

Some of the hypotheses concerning the mechanism of antidepressant activity are based on the ability of drugs to influence the turnover of neurotransmitters.[18] Many publications have appeared that describe measurements of the inhibition of uptake of [^{3}H]norepinephrine (NE), [^{14}C]serotonin (5-HT), and [^{3}H]dopamine in vivo and in tissue cultures.[19] We measured in vivo inhibition of uptake of NE and in vitro inhibition of uptake of NE, dopamine, and 5-HT by our most active compounds (Table III). The 2-(methoxycarbonyl)amino derivative **16** was of comparable potency to TCA's in in vitro inhibition of NE and dopamine uptake. The parent amine **27** was 100-fold more active and it was also more active in 5-HT-uptake inhibition. Both compounds were equipotent and significantly more potent than TCA's in in vivo inhibition of NE uptake. It is interesting to note that for the reversal of hypothermia (orally in mice) the 2-(methoxycarbonyl)amino analogue **16** was far more active than its free 2-amino analogue **27**, which is the reverse of the in vitro uptake results.

In summary, it is clear that tetrahydropyrimidines **2** differ greatly from the analogous imidazolines **1** in terms of both potency and selectivity for antidepressant properties. The SAR with regard to phenyl substituents and *N*-methyl substitution is different in both series. In both series the 2-amino analogues were significantly more active in in vitro assays than their 2-(alkoxycarbonyl)amino counterparts. On the basis of its high in vivo potency and its in vivo activity, compound **16** was chosen for clinical development. Development of the compound was stopped after the discovery of drug-related agranular cytosis in preclinical primate toxicity studies.

Experimental Section

Pharmacology. Test procedures were followed as previously described for imidazolines.[2]

Chemistry. Melting points were determined on a Thomas-Hoover apparatus and are uncorrected. The structures of all compounds are supported by NMR spectroscopy (Varian A60 for ^{1}H and Bruker WH90 for ^{13}C). IR spectra were recorded (Perkin-Elmer 217B) for all compounds except diaminopropanes and their salts. Mass spectra of selected compounds were obtained at 70 eV with a Finnigan/MAT CH7 spectrometer.

3-Phenylglutaramide (42). A solution of 14.3 g of 3-phenylglutaronitrile (41; 139 mmol) in 100 mL of concentrated sulfuric acid and 4 mL of water was allowed to stand at 20 °C for 48 h. The reaction mixture was poured over ca. 700 g of ice and neutralized with concentrated NH_4OH. Extraction of the resulting solution in a liquid–liquid extractor with $CHCl_3$ for 2 days yielded 1.1 g of a solid, mp 173–180 °C. After an additional 14 days of extraction, 10 g (60%) of pure product [mp 180–184 °C (lit.[9] mp 183–184 °C)] was obtained. Substituted phenylglutaronitriles **45**, **48**, **54**, **60**, and **63**, prepared by this method, crystallized from their neutralized aqueous solutions and were collected by filtration.

3-(3-Methoxyphenyl)glutaramide (51). A solution of 18.7 g (93 mmol) of dinitrile **50** in 250 mL of acetone and 125 mL of water was stirred in an ice bath and treated with 40 mL of 30% H_2O_2 and 25 mL of 10% aqueous Na_2CO_3. After 16 h at 20 °C, the mixture was concentrated to ~100 mL and then cooled 4 h in an ice bath. The precipitate of fine needles was collected, washed with water, and dried under vacuum at 55 °C, yielding 17.4 g (79%) of pure **51**.

1-[2-(Trifluoromethyl)phenyl]-1,3-diaminopropane (72). A solution of 7.6 g (35 mmol) of the acrylonitrile **71** in 100 mL of ether was treated with 55 mL of a 1 M solution of borane–tetrahydrofuran complex and the mixture was allowed to stand at 20 °C for 16 h. The reaction mixture was treated with 10 mL of water and was then concentrated to a small volume. The residue was dissolved in a mixture of 2-propanol and 15% HCl, heated at reflux for 2 h, and concentrated again to a small volume. After addition of an excess of 30% NaOH, the solution was extracted with CH_2Cl_2. Concentration of the extract and distillation of the residue gave 1.7 g of crude diamine **72**, bp 73–77 °C (0.1 mmHg). The dihydrochloride was prepared by treatment of the distillate with EtOH–HCl and ether, yielding 1.3 g (17%), mp 213–217 °C. A sample was recrystallized from EtOH: mp 214–216 °C.

2-(3-Methoxyphenyl)-1,3-diaminopropane (52). A solution of 27 g of NaOH (680 mmol) in 200 mL of water was cooled to 0 °C and 23 g of Br_2 (145 mmol) was added. After the mixture was stirred for a few minutes, 16 g of the diamide **51** (68 mmol) was added in five portions and stirring was continued at 0 °C until there was a clear solution. The reaction temperature was raised to 20 °C for 1 h and finally to 70 °C for 30 min. After cooling to 20 °C, the reaction mixture was shaken with 15 separate 70-mL portions of CH_2Cl_2. The combined extracts were dried over Na_2SO_4, filtered, and concentrated. The residue was distilled, affording 5.1 g (42%) of diamine **52**, bp 140 °C (1 mmHg). A few drops of the diamine were dissolved in EtOH–HCl and the dihydrochloride was crystallized by the addition of ether.

1-Methyl-4-phenyl-2-pyrazoline (13). A sample of 15.3 g of the ethylene ketal of atropaldehyde **12** (87 mmol) was hydrolyzed in a mixture of 800 mL of EtOH and 150 mL of water containing 0.5 g of oxalic acid dihydrate (4 mmol) at 75 °C. The reaction

(17) Kaiser, C.; Setler, P. E. "Burgers Medicinal Chemistry"; 4th ed.; Wolff, M. E., Ed., Wiley-Interscience: New York, 1981; Part 3, p 1005.
(18) Reference 17, pp 1002–1004.
(19) For example: (a) Kimelberg, H. K.; Pelton, E. W., II *J. Neurochem.* **1983**, *40*, 1265 and references therein. (b) Cooper, B. R.; Hester, T. J.; Maxwell, R. A. *J. Pharmacol. Exp. Ther.* **1980**, 215.

was followed by GLC (3% SE-30) and when the ketal had been consumed (45 min), 5 g of methylhydrazine (107 mmol) was added. Solvents were removed on a rotatory evaporator and saturated $NaHCO_3$ was added to the residue. The crude product was extracted into ether and the ether was removed under vacuum. The remaining liquid was distilled to give a 10.2-g fraction: bp 80–90 °C (0.01 mmHg). GLC analysis (3% SE-30) showed the distillate to be a mixture of at least seven products with one major product accounting for about 60% (the starting ethylene ketal had been ca. 90% pure). Column chromatography (700 g of silica gel 60; gradient elution with 10–20% of EtOAc in hexane) afforded 4.4 g (32%) of pure pyrazoline **13**: ^1H NMR ($CDCl_3/Me_4Si$) δ 2.8 (t, J = 10.0 Hz, 1 H of CH_2), 2.85 (s, 3 H, NMe), 3.5 (t, J = 10.0 Hz, 1 H of CH_2), 4.18 (dt, J = 10.0, 2.0 Hz, 1 H, benzylic CH), 6.78 (d, J = 2.0, 1 H, vinyl CH), 7.28 (br s, 5 H, phenyl protons); ^{13}C NMR δ ($CDCl_3/Me_4Si$) 43.40 (NMe), 53.77 (benzylic C), 63.59 (CH_2), 127.37, 127.86, 128.93, and 139.69 (phenyl C's), 145.35 (vinyl C).

1-Amino-3-(methylamino)-2-phenylpropane (14). A solution of 3.8 g of 4-phenylpyrazoline **13** (23 mmol) in 50 mL of AcOH and 10 mL of 10% HCl was hydrogenated at atmospheric pressure over 1 g of 5% Pt/C. The calculated amount of H_2 was taken up in 6 h. The catalyst was removed by filtration and the filtrate was concentrated. The residue was treated with *i*-PrOH and toluene and concentrated again. The crude product (still containing some AcOH) was dissolved in *i*-PrOH and ether was added to precipitate an oil. Digestion of the mixture at reflux for 3 h transformed the oil into a powder. Filtration then gave 2.8 g (50%) of *N*-methyldiaminopropane **14** as the dihydrochloride, mp 238–247 °C. Recrystallization from EtOH–*i*-PrOH afforded pure product: mp 265–267 °C.

2-Amino-5-(3-bromophenyl)-1,4,5,6-tetrahydropyrimidine (28). A solution containing 1.55 g of 2-(3-bromophenyl)-1,3-diaminopropane (**49**; 6.77 mmol) and 0.72 g of cyanogen bromide (6.77 mmol) in 300 mL of MeOH was allowed to stand at 20 °C for 16 h. TLC (silica gel GF, MeOH) revealed substantial amounts of unreacted starting diamine. The reaction mixture was stored at 20 °C for 1 week and heated at reflux for 16 h. The solvent was removed under vacuum and the residual oil was dissolved in hot *i*-PrOH, which resulted in spontaneous crystallization of 0.87 g (38%) of 2-aminotetrahydropyrimidine **28**. The 4(6)-phenyl analogue **38** was formed in a similar reaction in 40% yield after a reaction time of only 6 h at 20 °C.

2-Amino-5-phenyl-1,4,5,6-tetrahydropyrimidine Hemisulfate (27). A mixture of 3.25 g of 2-phenyl-1,3-diaminopropane (**43**; 21.6 mmol) and 3.02 g of 2-methyl-2-thiopseudurea hemisulfate (10.8 mmol) in a 200-mL, round-bottom flask was immersed into a 240 °C hot oil bath. The mixture fumed and solidified. The bath temperature was raised to 265 °C and the now liquid reaction mixture was stirred for a few minutes. After the mixture cooled, the solid product was digested with 50 mL of refluxing MeOH and was then collected by filtration. Recrystallization from 20 mL of water afforded 2.24 g (46%) of pure product **27** as the hemisulfate.

5-(2,6-Dichlorophenyl)-2-[(methoxycarbonyl)amino]-1,4,5,6-tetrahydropyrimidine (24). A solution of 900 mg of diamine **64** (4.1 mmol) and 885 mg of the reagent **15** (R_2 = CO_2CH_3) (4.3 mmol) in 125 mL of MeOH was kept at reflux for 1 h. The solution was concentrated to 25 mL and the product that crystallized was collected and dried under vacuum, yielding 830 mg (67%) of pure **24**. A sample of 800 mg of **24** was dissolved in 5 mL of EtOH containing ca. 150 mg of HCl. Addition of ether caused crystallization of 660 mg of the hydrochloride of **24**.

2-[(Methoxycarbonyl)amino]-1-methyl-5-phenyl-1,4,5,6-tetrahydropyrimidine (26). A solution of 1.5 g of the dihydrochloride of the *N*-methyldiamine **14** (6.33 mmol) in 200 mL of MeOH was stirred with 0.68 g of MeONa (12.6 mmol) for 10 min and was then combined with a solution of 1.3 g of the reagent **15** (R_2 = CO_2CH_3) (6.31 mmol) in 200 mL of MeOH. The mixture was stored at 20 °C for 16 h and was then heated at reflux for 1 h. The solvent was removed under vacuum and the residue was dissolved in 50 mL of 3% HCl. This solution was washed with ether and was then neutralized with $NaHCO_3$. The precipitated product was collected by filtration, stirred with fresh water, and collected again. Drying under vacuum yielded 0.99 g (63%) of **26**: mp 177–179 °C. A small sample was recrystallized from ether: mp 176–177 °C.

2-(Methylamino)-5-phenyl-1,4,5,6-tetrahydropyrimidine (29). A mixture of 430 mg of the 2-(methoxycarbonyl)amino derivative **16** (1.9 mmol) and 270 mg of lithium aluminum hydride (7.1 mmol) in 50 mL of THF was kept at reflux for 16 h. The mixture was cooled to 20 °C and stirred with 1 mL of 10% NaOH until the precipitate appeared white. The mixture was filtered, and the insoluble materials were washed with 95% THF. The filtrate was concentrated and the residue was dissolved in 10 mL of EtOH containing 150 mg of HCl. The solvent was removed under reduced pressure and crystallization of the residue was induced by treatment with a refluxing mixture of MeCN–Et_2O, affording 310 mg (74%) of the product **29** as the hydrochloride.

Methylation of the Anion of 16. A slurry of 1.2 g of **16** (5.15 mmol) in 60 mL of THF was stirred at 20 °C for 30 min and 250 mg of ca. 50% NaH in mineral oil (5.2 mmol) was then added. Stirring was continued for 1 h after the H_2 evolution had ceased. A solution 780 mg of CH_3I (5.5 mmol) in a few milliliters of THF was added over a period of 2 h and stirring at 20 °C was continued for 16 h. Water (1 mL) was then added to the reaction mixture, which was a clear solution at this point. A TLC analysis (silica gel GF; 8% MeOH in CH_2Cl_2) revealed the presence of two new products, unreacted starting material, and polar materials. The three mobile components were separated by column chromatography (150 g of silica gel 60; gradient elution with 3–10% MeOH in CH_2Cl_2), which afforded 320 mg (25%) of **26**, 380 mg (32%) of starting material **16**, and 100 mg (7%) of **39**. When the reaction was repeated with 2 equiv each of NaH and CH_3I, 77% of **39** and 12% of **30** were isolated. Compound **39** in this case was obtained as a glassy material that seemed to contain polar impurities. Hydrolysis of **39** took place during purification attempts by recrystallization (MeCN, *i*-PrOH) and we obtained the hydroiodide of **40** instead.

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Registry No. **8** (Ar = 4-CH_3Ph), 95724-96-2; **10** (Ar = Ph), 53657-63-9; **11** (Ar = Ph), 95724-79-1; **11** (Ar = Ph)·2HCl, 95724-80-4; **13** (Ar = Ph), 95724-74-6; **14** (Ar = Ph), 95724-78-0; **14** (Ar = Ph)·2HCl, 78534-06-2; **15** (R_2 = H)·1/2H_2SO_4, 867-44-7; **15** (R_2 = CO_2CH_3), 34840-23-8; **15** (R_2 = $CO_2CH_2CH_3$), 34840-26-1; **15** (R_2 = $CO_2CH(CH_3)_2$), 58306-41-5; **16**, 78533-56-9; **16**·HCl, 95724-81-5; **17**, 78533-62-7; **17**·HCl, 95724-82-6; **18**, 78533-65-0; **18**·HCl, 95724-83-7; **19**, 78533-66-1; **19**·HCl, 95724-84-8; **20**, 78533-58-1; **20**·HCl, 95739-51-8; **21**, 78533-69-4; **21**·HCl, 95724-85-9; **22**, 78533-71-8; **22**·HCl, 95724-86-0; **23**, 78533-70-7; **23**·HCl, 78534-23-3; **24**, 78533-54-7; **24**·HCl, 95724-87-1; **25**, 78533-59-2; **25**·HCl, 78534-24-4; **26**, 78533-67-2; **27**, 78533-68-3; **27**·1/2H_2SO_4, 78534-19-7; **28**, 78533-57-0; **28**·HBr, 78534-18-6; **29**, 95724-75-7; **29**·HCl, 95724-88-2; **30**, 95724-97-3; **30**·HI, 95724-89-3; **31**, 78533-55-8; **31**·HCl, 95724-90-6; **32**, 78533-60-5; **32**·HCl, 95724-91-7; **33**, 78533-63-8; **33**·HCl, 95739-52-9; **34**, 78533-64-9; **34**·HCl, 95724-92-8; **35**, 78534-28-8; **36**, 78533-52-5; **36**·HCl, 78534-27-7; **37**, 95724-93-9; **38**, 78533-53-6; **38**·HBr, 78534-25-5; **39**, 95724-94-0; **40**, 95739-53-0; **40**·HI, 95724-95-1; **41**, 78533-73-0; **42**, 78533-83-2; **43**, 55165-09-8; **43**·2HCl, 78533-94-5; **44**, 78533-74-1; **45**, 78533-84-3; **46**, 78533-95-6; **46**·2HCl, 78533-96-7; **47**, 78533-76-3; **48**, 78533-86-5; **49**, 78533-98-9; **42**·2HCl, 78533-99-0; **50**, 78533-78-5; **51**, 78533-88-7; **52**, 78533-92-3; **52**·2HCl, 78533-93-4; **53**, 78533-81-0; **54**, 78533-91-2; **55**, 78534-04-0; **55**·2HCl, 78534-05-1; **56**, 78533-75-2; **57**, 78533-85-4; **58**, 95724-76-8; **58**·2HCl, 78533-97-8; **59**, 78533-77-4; **60**, 78533-87-6; **61**, 78534-00-6; **61**·2HCl, 78534-01-7; **62**, 78533-72-9; **63**, 78533-82-1; **64**, 78534-02-8; **64**·picrate, 95724-77-9; **65**, 91137-66-5; **66**, 74298-71-8; **67**, 4888-74-8; **67**·2HCl, 78534-09-5; **68**, 78534-07-3; **69**, 78534-08-4; **70**, 78534-14-2; **70**·2HCl, 78534-15-3; **71**, 78534-10-8; **72**, 78534-12-0; **72**·2HCl, 78534-13-1; **73**, 78534-11-9; **74**, 78534-16-4; **74**·2HCl, 78534-17-5; PhCH=CHCHO, 104-55-2; CH_3NHNH_2, 60-34-4; atropaldehyde, 4432-63-7; atropaldehyde ethylene ketal, 16486-91-2.