concentrated under reduced pressure to afford 436 mg of a colorless oil. Purification by flash chromatography using $CHCl_3$ as eluent gave 400 mg (99%) of **22** as a colorless, viscous oil: IR (neat) 3600–3100, 2930, 2870, 1680, 700 cm^{-1}; NMR ($CDCl_3$, 90 MHz) δ 1.0–2.2 (m, 12 H), 2.8–4.0 (m, 6 H), 5.12 (s, 2 H, CH_2Ph), 7.34 (s, 5 H, phenyl); MS, *m/e* calcd (M^+) 303.1834, obsd 303.1856.

(4aα,5β,8aβ)-Octahydro-1,5(2*H*)-quinolinedicarboxylic Acid 1-Phenylmethyl Ester (23). To a biphasic mixture of **22** (103 mg, 0.340 mmol) and $NaIO_4$ (255 mg, 1.190 mmol)[35] in CCl_4 (1.5 mL), CH_3CN (1.5 mL), and H_2O (2.25 mL) was added $RuCl_3 \cdot 3H_2O$ (2 mg, 2.2 mol %). After the mixture was stirred vigorously for 2 h, CH_2Cl_2 (10 mL) was added, and the solvent layers were separated. The aqueous layer was extracted (three times) with CH_2Cl_2, and the combined organic extracts were dried ($MgSO_4$) and concentrated. The residue was dissolved in Et_2O, passed through a small plug of Celite, and concentrated under reduced pressure, affording 99 mg of an oil. Purification by preparative TLC ($CHCl_3$/HOAc, 100:2) produced 77 mg of crude **23** as a viscous oil which was used directly without further purification.

Acknowledgment. FT NMR 300-MHz spectra were produced at The Ohio State University Chemical Instrumentation Center using a Bruker WM-300 spectrometer funded in part by NIH Grant No. 1-S10-RR01458-01A1. Spectra were obtained by Dr. C. E. Cottrell.

Registry No. *trans*-**3**, 98761-59-2; *trans*-**3**·HCl, 98761-61-6; *trans*-**4**, 98761-62-7; *trans*-**4**·HCl, 98761-63-8; **10**, 5057-12-5; **11**, 70075-68-2; **13**, 98761-65-0; **16**, 98761-66-1; **17**, 98761-67-2; **18**, 98761-69-4; **19**, 98761-64-9; **20**, 98761-70-7; **21**, 98761-71-8; **22**, 98761-72-9; **23**, 98761-60-5; I, 77823-89-3; II, 98819-45-5; III, 98819-46-6; IV, 98819-47-7; V, 98761-73-0; VI, 98761-74-1; $Ph_3PCHCHO$, 2136-75-6; 2-(trimethylsilyl)-1,3-dithiane, 13411-42-2; (4aα,5α,8aα)-5-(1,3-dithian-2-yl)decahydroquinoline, 98761-68-3.

Neuroleptic Activity of Chiral *trans*-Hexahydro-γ-carbolines†

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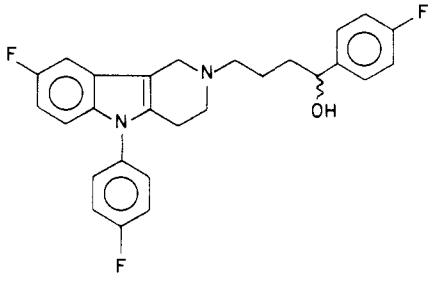
Pfizer Central Research, Pfizer Inc., Groton, Connecticut 06340, and North Carolina State University, Raleigh, North Carolina 27695. *Received March 8, 1985*

A series of *trans*-8-fluoro-5-(4-fluorophenyl)-2,3,4,4a,5,9b-hexahydro-1*H*-pyrido[4,3-*b*]indoles with various N-2 substituents has been prepared and tested for neuroleptic activity ([^{3}H]spiroperidol binding and amphetamine antagonism). Several members of this series showed exceptional in vivo potency, especially the hydantoin derivatives **27–30**. Resolution into the enantiomers showed that neuroleptic activity is associated with the 4a*S*,9b*S* absolute configuration. These rigid neuroleptics have been correlated with other rigid neuroleptics [(+)-dexclamol, Ro 22-1319] and can serve to further define the topography of the dopamine receptor.

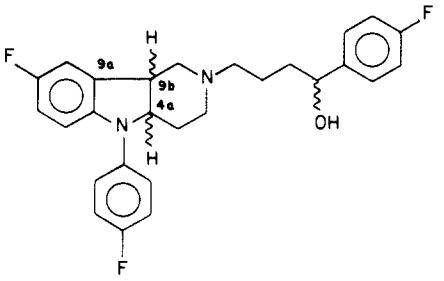
Previous work from these laboratories has shown that the tetrahydro-γ-carboline derivative flutroline (**1**; CP-36,584; 8-fluoro-5-(4-fluorophenyl)-2-[4-hydroxy-4-(4-fluorophenyl)butyl]-2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]-indole) is a potent neuroleptic agent in animal models, apparently due to blockade of dopamine receptors in the central nervous system.[1] Reduction of the 4a,9b double



1 (flutroline)

bond of flutroline with borane resulted in the formation of a 1:1 mixture of two *trans*-hexahydro-γ-carboline diastereomers. These were separated by crystallization and subsequently resolved as the L-phenylalanine esters into their respective enantiomers **2a** to **2d**.[2] Interestingly, neuroleptic activity appeared to residue exclusively in two of these isomers, **2a** and **2c**, their in vitro activity (inhibition of spiroperidol binding) approaching that of haloperidol (**3**, Table I) and their in vivo activity (amphetamine antagonism) greatly surpassing that of haloperidol, especially at later time points. These findings made it im-

Table I. Activity of Flutroline and Its Four *trans*-Hexahydro-γ-carboline Reduction Products



2a-d

no.	$[\alpha]^{20}_D$, deg	inhibn of [^{3}H]-spiroperidol binding:[a] IC_{50}, nM	antagonism of amphetamine (rat):[b] ED_{50}, mg/kg sc 1 h	5 h	24 h
2a	+3.1	25	0.21	0.05	0.02
2b	−2.7	350	>10	5.7	>10
2c	+32.2	22	0.05	0.02	0.02
2d	−33.0	1800	>10	18.1	>10
1 (flutroline)		12 ± 1 (7)	1.0	0.15	2.2
3 (haloperidol)		9	0.66	0.75	>10
4 (penfluridol)		62	~32	2.4	3.9[c]

[a] IC_{50} values were determined on rat striatal membrane using 0.5 nM radioligand. Entries are based on one to two determinations. For multiple determinations, mean IC_{50} ± SE are given with number of determinations in parentheses. [b] 5 mg/kg ip *d*-amphetamine sulfate was administered to rats at 1, 5, 24 h after test drug (N = 5). [c] The ED_{50} of **4** at 48 h was ~32 mg/kg. This time course is consistent with the one observed after po dosing of **4** by Janssen et al., *Eur. J. Pharmacol.* **1970**, *11*, 139.

† For simplicity's sake, the common name γ-carboline is used in general throughout this paper instead of 1*H*-pyrido[4,3-*b*]indole.

‡ Pfizer Inc.

§ North Carolina State University.

0022-2623/86/1829-0008$01.50/0

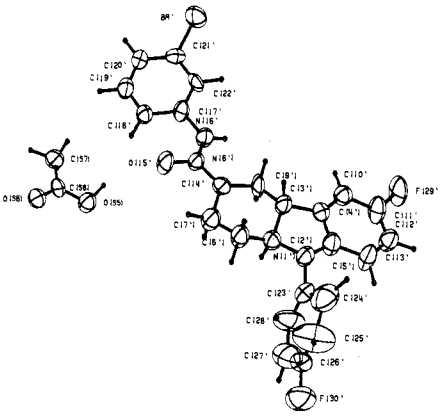
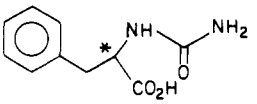


Figure 1. X-ray structure of 8.

portant to determine the absolute configuration of the active isomers and to correlate their structure with other neuroleptics.

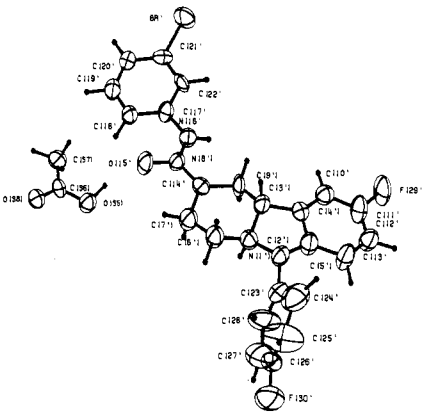
Our approach involved development of a process for resolution of the racemic *trans*-hexahydro-γ-carboline nucleus **5**. After extensive investigation of acidic resolving agents, *N*-carbamoyl-D(or L)-phenylalanine **6a**(or **6b**) were found to be the reagents of choice. They proved superior to *N*-acetyl-D(or L)-phenylalanine, which tended to racemize too readily. Thus, *N*-carbamoyl-D-phenylalanine **6a** produced in very good yield a crystalline salt which was converted to the dextrorotatory hydrochloride salt of the *trans*-hexahydro-γ-carboline nucleus **5a** ($[\alpha]^{20}_D$ +39.2°, *c* 1, MeOH) (Scheme I). Using *N*-carbamoyl-L-phenylalanine **6b** we obtained the levorotatory hydrochloride **5b** ($[\alpha]^{20}_D$ 40.9°, *c* 1, MeOH).[3]



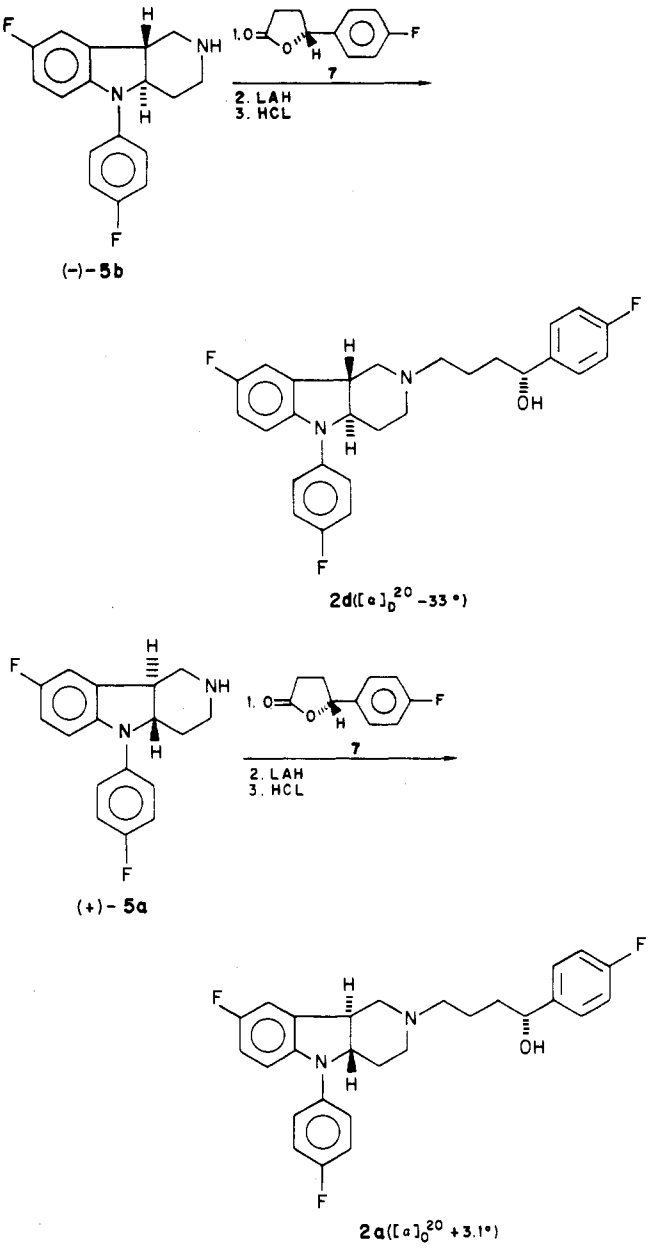
6a ($[\alpha]^{20}_D$ -40.7° (*R*))
6b ($[\alpha]^{20}_D$ +39.0° (*S*))

The determination of the absolute configuration of the active isomers **2a** and **2c** was made in the following way (Scheme I). The levorotatory nucleus **5b** was coupled with the (−)-γ-lactone **7**[4] and subsequently reduced with lithium aluminum hydride to give a compound with a rotation of $[\alpha]^{20}_D$ −33°, corresponding to **2d**, one of the inactive enantiomers from the flutroline reduction. However, when the same (−)-γ-lactone **7** was coupled with the dextrorotatory nucleus **5a** we obtained a compound ($[\alpha]^{20}_D$ 3.1°) which corresponded to the active enantiomer **2a**. This establishes that intrinsic activity is determined not by the configuration of the alcohol group in the N-2 side chain, but by the absolute configuration of the hexahydro-*trans*-γ-carboline nucleus, and that biological activity is associated with the dextrorotatory nucleus **5a**. An X-ray analysis of the N-2-[*N'*-(3-bromophenyl)carbamoyl] derivative **8** of **5a** established that the absolute configuration of **5a** is 4a*S*,9b*S* (Figure 1).

It was surprising that the dextrorotatory *trans*-hexahydro-γ-carboline nucleus **5a**, unsubstituted at N-2, displayed excellent intrinsic activity in our in vitro [^{3}H]-



Scheme I



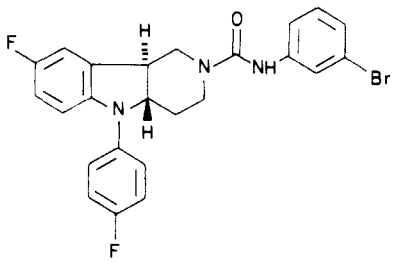
(−)-**5b**

2d ($[\alpha]^{20}_D$ −33°)

(+)-**5a**

2a ($[\alpha]^{20}_D$ +3.1°)

(1) Harbert, C. A.; Plattner, J. J.; Welch, W. M.; Weissman, A.; Koe, B. K. *Mol. Pharmacol.* **1980**, *17*, 381.
(2) Welch, W. M.; Ewing, F. E.; Harbert, C. A.; Weissman, A.; Koe, B. K. *J. Med. Chem.* **1980**, *23*, 949.
(3) Endo Laboratories, Inc. has reported a resolution of the desdifluoro analogue of **5** with di-*p*-toluoyltartaric acid in U.S. Patent 4 141 980.
(4) Presumably, this material has the *R* configuration indicated in Scheme I as suggested by an independent synthesis of **7** starting with (*S*)-(+)-*p*-fluoromandelic acid (Collet, A.; Jacques, J. *Bull. Soc. Chim. Fr.* **1973**, 3330); we are grateful to Dr. Paul Weeks of Pfizer Central Research for this determination.



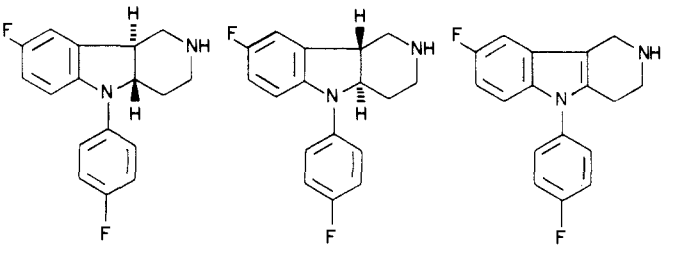
8 (4aS,9bS)

spiroperidol binding inhibition assay (IC_{50} 6.7 nM vs. >1000 nM for the levorotatory isomer **5b**), as well as antagonism of amphetamine in the rat comparable to that shown by haloperidol **3**. In marked contrast, the unsubstituted tetrahydro-γ-carboline nucleus **9** was essentially inactive in vitro and in vivo (Table II). This finding suggested that the 5-aryl-hexahydro-γ-carboline nucleus **5a** is an active pharmacophore for neuroleptic activity and that the N-2 side chain may only modulate tissue distribution and/or the duration of action. Indeed, as shown in Table III, derivatives in the hexahydro-γ-carboline series with a variety of N-2 substituents retain in vitro and in vivo activity. The corresponding tetrahydro-γ-carboline derivatives (with the exception of flutroline) have generally diminished in vitro and in vivo activity.

This apparent freedom to incorporate a variety of side chains while maintaining neuroleptic activity in the hexahydro-γ-carboline series prompted us to attempt to incorporate anticholinergic properties via appropriate side chains. Such compounds might minimize the adverse side effects (e.g., the extrapyramidal effects) associated with many neuroleptics, since the reduced incidence of extrapyramidal side effects observed with antipsychotic agents such as clozapine and thioridazine has been attributed to their intrinsic anticholinergic properties.[5] On the basis of anticholinergic structural features described in the literature,[6] we prepared a number of N-2 substituted hexahydro-γ-carbolines as shown in Table IV. The carbazole **14** and the carbinol **15** displayed loss of in vitro and in vivo neuroleptic activity, possibly as a consequence of excessive steric bulk of these groups. Several of the amides, however, were modestly active in vitro with good in vivo neuroleptic activity. A few compounds, **17–19**, were tested for anticholinergic activity (mydriasis in tetrabenazine-treated mice) but showed no significant difference from control values at doses as high as 32 or 100 mg/kg, sc (Table IV), in clear contrast to clozapine, atropine sulfate or desipramine hydrochloride, all of which exhibited significant mydriasis.

While the attempt to incorporate anticholinergic activity was unsuccessful, the neuroleptic potency of some of the analogues, particularly the amides, was encouraging. Therefore, we expanded this series to cyclic amides, the 3-alkylhydantoins **24** being the most notable. These compounds were prepared in modest yields by alkylation of potassium hydantoin, followed by coupling to the *trans*-hexahydro-γ-carboline nucleus as shown in Scheme II. These compounds all showed very potent in vitro and in vivo activity as shown in Table V, optimum activity being reached with the pentamethylene and hexamethylene side chain derivatives **28** and **29**. For comparison purposes, the hexamethylene hydantoin side chain was also coupled to the tetrahydro-γ-carboline nucleus to give **31**. In vitro activity was excellent, but the in vivo activity was clearly less than that of the hexahydro congener **29a**. Finally we

Table II. Activity of N-2 Unsubstituted Nuclei

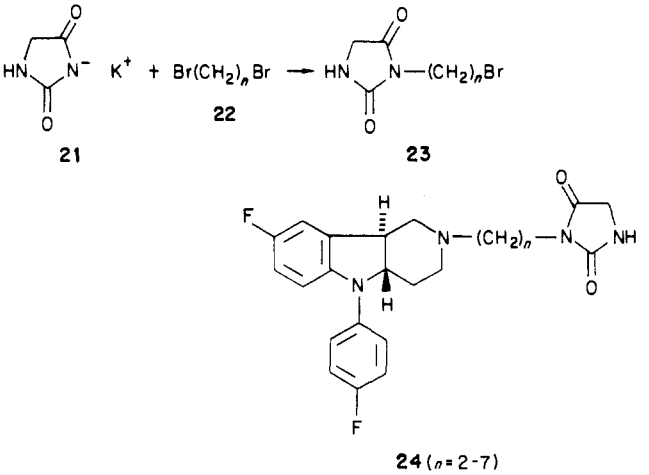


5a 5b 9

	inhibn of [^{3}H]-spiroperidol binding:[a] IC_{50}, nM	antagonism of amphetamine:[b] ED_{50}, mg/kg sc		
		1 h	5 h	24 h
5a ((+)-4a*S*,9b*S*)	6.7 ± 0.9 (3)	0.36	0.45	>10
5b ((−)-4a*R*,9b*R*)	3200	c	c	c
9	350 ± 46 (4)	>10	c	c

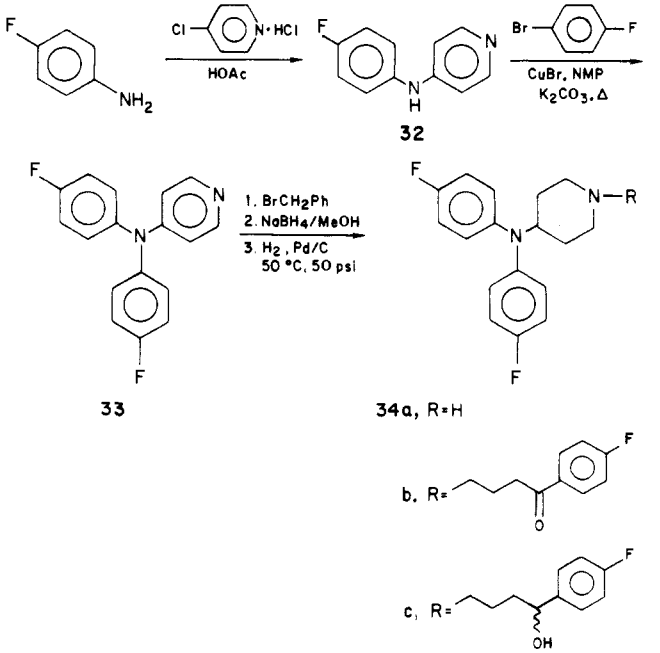
[a] See footnote *a* of Table I. [b] See footnote *b* of Table I. [c] Not determined.

Scheme II. Alkylhydantoins



21 22 23 24 (n = 2-7)

Scheme III. Synthesis of (Diphenylamino)piperidines



32 33 34a, R=H

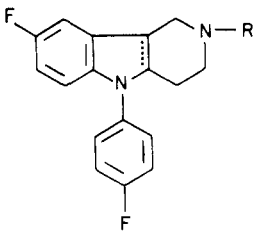
b. R=

c. R=

(5) Snyder, S.; Greenberg, D.; Yamamura, H. *Arch. Gen. Psychiat.* **1974**, *31*, 58. Miller, R.; Hiley, C. R. *Nature (London)* **1974**, *248*, 596.

(6) Sastry, R. V. R. In "Burgers Medicinal Chemistry", 3rd ed.; Wiley: New York, 1970; p 1544.

Table III. In Vitro/in Vivo Comparison of Tetra- and Hexahydro-γ-carbolines



no.	nucleus	R	method	yield, %	mp, °C	recrystn	formula[a]	inhibn of [H]spiroperidol binding:[b] IC_{50}, nM	antagonism of amphetamine (rat):[b] ED_{50}, mg/kg sc
10a	9	CH_3	*d*	60	295–297	Et_2O	$C_{18}H_{16}F_2N_2 \cdot HCl$	83 ± 10 (5)	>1.0
10b	5	CH_3	*d*		*e*		$C_{18}H_{18}F_2N_2 \cdot HCl$	7.5 ± 0.8 (3)	0.3
11a	9	$(CH_2)_3CO_2H$	E	53	250–252 dec	IPO	$C_{21}H_{20}F_2N_2O_2 \cdot HCl$	>320	
11b	5	$(CH_2)_3CO_2H$	E	58	267–268 dec	EtOH	$C_{21}H_{22}F_2N_2O_2 \cdot H_2O \cdot {}^1/_2H_2O$	140	0.36
12a	9	$(CH_2)_4NHCOCH_3$	G	49	167–169	EtOH/Hex	$C_{23}H_{25}F_2N_3O \cdot HCl$	54	>3.2
12b	5	$(CH_2)_4NHCOCH_3$	G	35	243–245	MeCN/MeOH	$C_{23}H_{27}F_2N_3O \cdot HCl \cdot {}^1/_2H_2O$	13 ± 4 (3)	0.006
13a	9	$(CH_2)_6NHCOPh$	G		194–197	Et_2O[f]	$C_{30}H_{31}F_2N_3O \cdot HCl \cdot {}^1/_2H_2O$	8.5	>10
13b	5	$(CH_2)_6NHCOPh$	G	31	227–231	EA/Et_2O	$C_{30}H_{33}F_2N_3O \cdot HCl \cdot H_2O$[g]	13	0.1–0.3

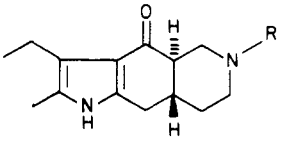
[a] All compounds gave satisfactory elemental analyses for C, H, N, except as noted. [b] See footnote *a* of Table I. [c] ED_{50} was determined 5 h after administration of test compound. [d] Harbert, C. A.; Plattner, J. J.; Welch, W. M.; Koe, B. K.; Weissman, A. *J. Med. Chem.* **1980**, *23*, 635. [e] Amorphous solid. [f] Precipitated. [g] C: calcd, 66.22; found, 65.79.

investigated the activity of a series of 4-(diphenylamino)piperidines (Table VI, **34a–c**). These "ring-opened carbolines" lack chirality at the **4a** and **9b** carbons as well as the rigid "phenethylamine moiety". They were prepared in a staightforward manner as shown in Scheme III. However, these compounds were found to be inactive in both assays (Table VI).

Discussion

It is clear from these findings that the dopamine receptor in the central nervous system, as defined by [^{3}H]-spiroperidol binding, has a highly stereoselective binding site for (4a*S*,9b*S*)-*trans*-8-fluoro-5-(4-fluorophenyl)-2,3,4,4a,5,9b-hexahydro-1*H*-pyrido[4,3-*d*]indole (**5a**) and several N-2 substituted derivatives. It is therefore of interest to compare this very rigid γ-carboline ring system to other rigid neuroleptics. Molecular mechanical energy computations[7] of **5a** suggest energy minima for a chair form and a boat form (Figure 2, Table VII). The chair form is favored by 2.50 kcal over the boat form. The chair form of **5a** has an aryl–N-2 distance of 5.24 Å (taken from the center of the aromatic ring of the carboline nucleus) and an out-of-plane elevation of N-2 relative to that of the aromatic ring of +0.38 Å (the nitrogen coming toward the viewer, when the molecule is oriented as shown in **5a**, Scheme I). Interestingly, these values are close to the corresponding values (Table VII) reported for conformer A of the rigid neuroleptic (+)-dexclamol (5.10 Å, +0.19 Å [between the A ring and the nitrogen]) but not for conformer B (5.1 Å, −0.9 Å).[8] This finding is interesting since conformers B of (+)-dexclamol and of its congener (+)-butaclamol have been judged to be the ones likely to be important for the interaction with the central dopamine receptor,[9a] although it has been proposed recently[9b] that on the basis of conformational energy calculations conformer A of (+)-butaclamol is more likely to represent the biologically active form. Our molecular mechanical energy computation[7] (Table VII) also indicates a 3.90 kcal energy advantage for conformer A of (+)-dexclamol, and an overlap between this conformer and the chair form of **5a** is shown in Figure 3. Interestingly, this overlap brings carbon 8 of **5a**, the one bearing the fluorine substituent, close to carbon 11 of dexclamol which, if substituted with chlorine, retains dopamine receptor affinity.[9c] If we presume that **5a** interacts at the same dopamine binding site as (+)-dexclamol or (+)-butaclamol, then it would be evident (Figure 3) that the C ring of the latter compounds occupies a topographical position quite different from that of the 5-aryl ring in our series, which suggests the existence of a large binding pocket or of two distinct binding sites for these rings.

Furthermore, there is a structural similarity between our carboline series and pyrroloisoquinoline neuroleptics of structure **35**.[10a] A key compound in that series is Ro

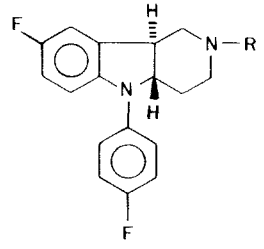


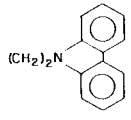
35

22-1319 (**35**, R = Me), which is a selective D-2 dopamine receptor antagonist, the active enantiomer having the 4a*R*,8a*R* configuration which is superimposable over the 4a*S*,9b*S* configuration of compound **5a**. Molecular mechanical computations[7] on compound **35** show that its chair form is favored by 5.67 kcal over its boat form (Table VII). In this chair form the out-of-plane elevation between the

(7) These energy calculations were carried out with use of the MMI program (Allinger, N. L.; et al. *QCPE* **1976**, *11*, 318.
(8) Bird, P. H.; Bruderlein, F. T.; Humber, L. G. *Can. J. Chem.* **1976**, *54*, 2715.
(9) (a) Phillip, A. H.; Humber, L. G.; Voith, K. *J. Med. Chem.* **1979**, *22*, 768. (b) Froimowitz, M.; Matthysse, S. *Mol. Pharmacol.* **1983**, *24*, 243. (c) Pugsley, T. A.; Lippmann, W. *J. Pharm. Pharmacol.* **1979**, *31*, 47.
(10) (a) Olson, G. L.; Cheung, H.-C.; Chiang, E.; Berger, L. In "Dopamine Receptors", ACS Symp. Ser.; Kaiser, C., Kebabian, J. W., Ed.; American Chemical Society: Washington, DC, 1983; p 251. (b) Olson, G. L.; Cheung, H.-C.; Morgan, K. D.; Blount, J. F.; Todaro, L.; Berger, L.; Davidson, A. B.; Boff, E. *J. Med. Chem.* **1981**, *24*, 1026. (c) Bogeso, K. P. *J. Med. Chem.* **1983**, *26*, 935. (d) Chrzanowski, F. A.; McGrogan, B. A.; Maryanoff, B. E. *J. Med. Chem.* **1985**, *28*, 399.

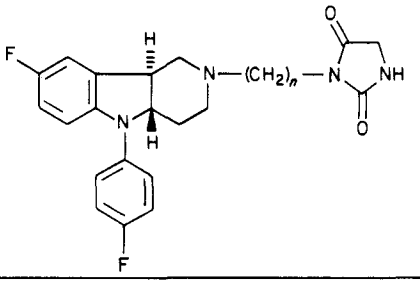
Table IV. Biological Activity of Hexahydro-γ-carboline Derivatives with "Anticholinergic" N-2 Substituents



no.	R	method	mp, °C	recrystn	yield, %	formula	anal.	inhibn of [^{3}H]-spiroperidol binding:[a] IC_{50}, nM	antagonism of amphetamine:[b] ED_{50}, mg/kg sc 1 h	5 h	24 h	dose (mg/kg, sc) and mean ± SD pupil size (mm) in tetrabenazine-treated mice
14		D	192–193 dec	$CHCl_3$/Hex	58	$C_{31}H_{27}F_2N_3$	C, H, N	c	>32	>32	*d*	
15	$(CH_2)_2COH(Ph)_2$	H	164–165	IPO	16	$C_{32}H_{30}F_2N_2$	C, H, N	220	>10	>10	*d*	
16	$(CH_2)_3C(O)N(C_6H_{11})Ph$	I	276–278 dec	EtOH	12	$C_{33}H_{37}F_2N_3O\cdot HI$	C, H, N	c	>32	1–32	<32	
17	$(CH_2)_2NHC(O)CH(Ph)CH_2OH$	J	247–249	EtOH	30	$C_{28}H_{29}F_2N_3O_2\cdot C_4H_4O_3S$	C, H, N	35	2.8	0.89	32	32: 0.23 ± 0.01 100: 0.31 ± 0.06
18	$(CH_2)_3C(O)NHPh$	I	250–252	$CHCl_3$/Hex	24	$C_{27}H_{27}F_2N_3O\cdot HCl$	C, H, N	19	0.45	0.18	1.8	32: 0.28 ± 0.05
19	$(CH_2)_3C(O)NH(C_6H_{11})$	I	139–142	$CHCl_3$/Hex	17	$C_{27}H_{33}F_2N_3O$	C, H, N	12	0.45	0.14	0.57	32: 0.23 ± 0.03
20	$(CH_2)_2OC(O)NHPh$	K	228–230 dec	$CHCl_3$/Et_2O	15	$C_{26}H_{25}F_2N_3O_2\cdot HCl\cdot 0.125H_2O$	C, H, N	45	0.57	0.45	2.3	
(clozapine)												100: 1.13 ± 0.11
(atropine sulfate)												1: 1.98 ± 0.10
(desipramine hydrochloride)												10: 0.66 ± 0.09

[a] See footnote *a* of Table I. [b] See footnote *b* of Table I. [c] Insoluble. [d] Not determined.

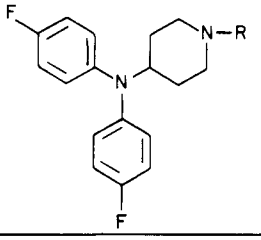
Table V. Activity of N-2 Alkylhydantoins



no.	nucleus	*n*	mp, °C	recrystn	yield,[a] %	formula	anal.	inhibn of [^{3}H]-spiroperidol binding:[b] IC_{50}, nM	antagonism of amphetamine:[c] ED_{50}, mg/kg sc 1 h	5 h	24 h
25	5	2	191–193	MeOH	54	$C_{22}H_{22}F_2N_4O_2$	C, H, N	26	0.57	0.57	>32
26	5	3	246–249 dec	EtOH	50	$C_{23}H_{24}F_2N_4O_2 \cdot CH_2O_3S \cdot 0.33H_2O$	C, H, N	14	0.11	0.05	>0.32
27	5a	4	165–168 dec	EtOH/Et_2O	16	$C_{24}H_{26}F_2N_4O_2 \cdot HCl \cdot H_2O$	C, H, N	12	0.057	0.018	0.18
28	5a	5	150–152 dec	EtOH/Et_2O	31	$C_{25}H_{28}F_2N_4O_2 \cdot HCl \cdot H_2O$	C, H, N	6	0.04	0.02	0.05
29a	5	6	168–171 dec	EtOH	22	$C_{26}H_{30}F_2N_4O_2 \cdot HCl \cdot 0.5H_2O$	C, H, N	9.4	0.18	0.033	>0.32
29b	5a	6	138–140 dec	EtOH/Et_2O	34	$C_{26}H_{30}F_2N_4O_2 \cdot HCl \cdot H_2O$	C, H, N	14	0.13	0.02	0.07
30	5a	7	239–241 dec	EtOH/Et_2O	56	$C_{27}H_{32}F_2N_4O_2 \cdot HCl \cdot 0.5H_2O$	C, H, N	19	0.18	0.018	0.18
31	9	6	187–190 dec	EtOH	34	$C_{26}H_{28}N_4O_2F_2 \cdot HCl$	C, H, N	5.8	1–3.2	0.75	>10

[a] By method D. [b] See footnote *a* of Table I. [c] See footnote *b* of Table I.

Table VI. Activity of Diphenylaminopiperidines

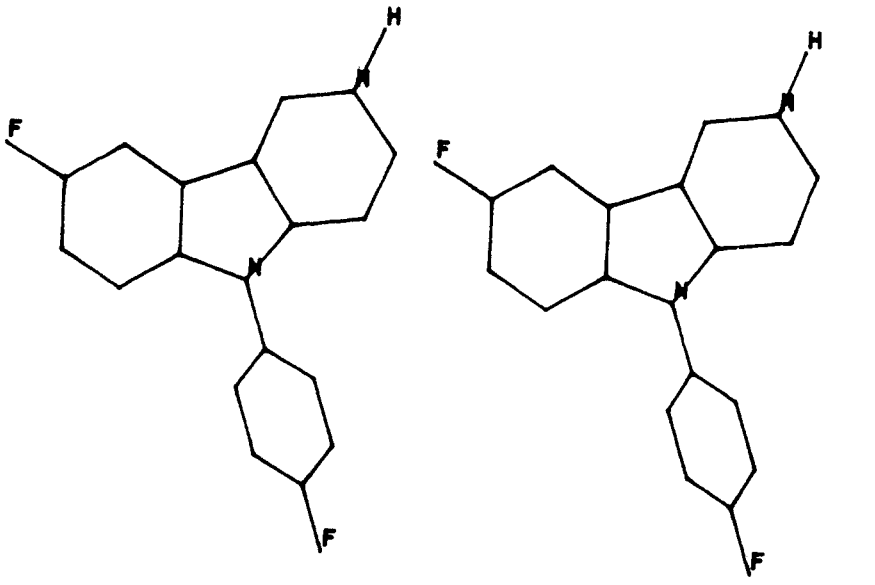


no.	R	method	mp, °C	recrystn	yield, %	formula	anal.	inhibn of [^{3}H]-spiroperidol binding:[a] IC_{50}, nm	antagonism of amphetamine:[b] ED_{50}, mg/kg sc 1 h	5 h	24 h
34a	H	M	292–295	EtOH/Et_2O	41	$C_{17}H_{18}F_2N_2 \cdot HCl$	C, H, N	>1000	c	c	c
34b	$(CH_2)_3C(O)C_6H_4$-4-F	D	116–119	Et_2O	55	$C_{27}H_{27}F_3N_2O \cdot HCl \cdot 0.5H_2O$	C, H, N	68	>32	c	>32
34c	$(CH_2)_3CH(OH)C_6H_4$-4-F	N	92–94 dec	CH_2Cl_2	48	$C_{27}H_{29}F_3N_2O \cdot HCl \cdot H_2O$	C, H, N	1000	c	c	c
2								25	0.21	0.05	0.02

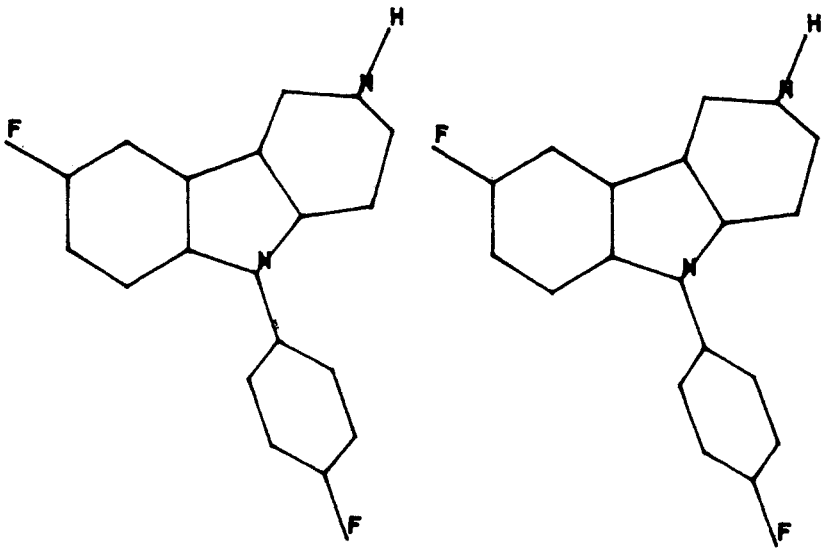
[a] See footnote *a* of Table I. [b] See footnote *b* of Table I. [c] Not determined.

pyrrole ring and the basic N is –0.15 Å and somewhat lower than that seen in **5a**. The N-aryl distance is more difficult to define but is longer than in **5a**. Nevertheless, a good overlap between Ro 22-1319 and **5a** can be obtained as shown in Figure 3. Support for this overlap comes from the fact that the SAR in the pyrroloisoquinoline series **35** is similar to that observed in our series, although the intrinsic activity of the compound unsubstituted on the piperidine nitrogen (R = H) is less than that seen in **5a**.[10a] Molecular mechanical energy calculations for a minimum energy conformer of our ring-opened compound give an out of plane N position of –2.56 Å. This latter value may be too large for an optimal receptor fit and may explain the inactivity of these compounds. Compound **34c** can be forced to assume a conformation that overlaps very well with **5a**, but that conformation is extremely high in energy since an aromatic hydrogen must assume a position very close to a methylene group of a piperidine ring.

While an excellent overlap can be obtained between the appropriate aryl ring and the basic nitrogen of our hexahydro-γ-carbolines, the A conformer of (+)-dexclamol/(+)-butaclamol and the pyrroloisoquinolines **35**, the ori-



5a, Chair Form



5a, Boat Form

Figure 2. Stereoviews of the chair and boat conformations of **5a** derived from molecular mechanical energy calculations.

Table VII. Structural Parameters Based on Molecular Mechanical Energy Calculations

compd	distance (Å) of N to aryl plane	distance (Å) of N to aryl center	strain energy	ΔE
5a chair	0.38	5.24	32.97	
				2.50
5a boat	1.08	5.17	35.47	
(+)-dexclamol X-ray	0.19	5.10		
(+)-dexclamol conformer A	0.45	5.19	42.26	
				3.90
(+)-dexclamol conformer B	−0.91	5.22	46.16	
Ro 22-1319 chair	−0.15	5.96	24.86	
				5.67
Ro 22-1319 boat	0.77	5.87	30.53	
34c	−2.56	5.99		

entation of the lone pair of electrons on nitrogen is different (by a ~90° angle) between **5a** and (+)-dexclamol. While some[9a,b,10b,c] believe that this orientation is critical for optimal receptor interactions, our findings suggest that N–H or lone-pair orientation is of minor importance for good receptor binding, as might be expected if it involves mainly a Coulombic interaction between a protonated N and an acidic function on the receptor. The Coulombic interaction is supported by the recent finding[10d] that the pK_a of butaclamol is not abnormally low, as previously reported.[9a] The alternate explanations would be that the receptor part which interacts with nitrogen is flexible enough to accommodate both orientations or that the overlap envisioned here between **5a** and (+)-dexclamol is not valid. Regardless of which interpretation is correct, the hexahydro-γ-carbolines constitute another series of rigid and potent neuroleptics which may play a useful role in further defining the topography of the central nervous system dopamine receptor.

Beyond this utility in exploring dopamine receptor topography, several potent hexahydro-γ-carbolines of this series are of interest because their prominent characteristic is prolonged in vivo activity in rats. Seventeen of the compounds reported here are more potent than haloperidol (**3**) as antagonists of amphetamine-induced stereotypy at the 5-h time point. Reminiscent of the long-acting, but

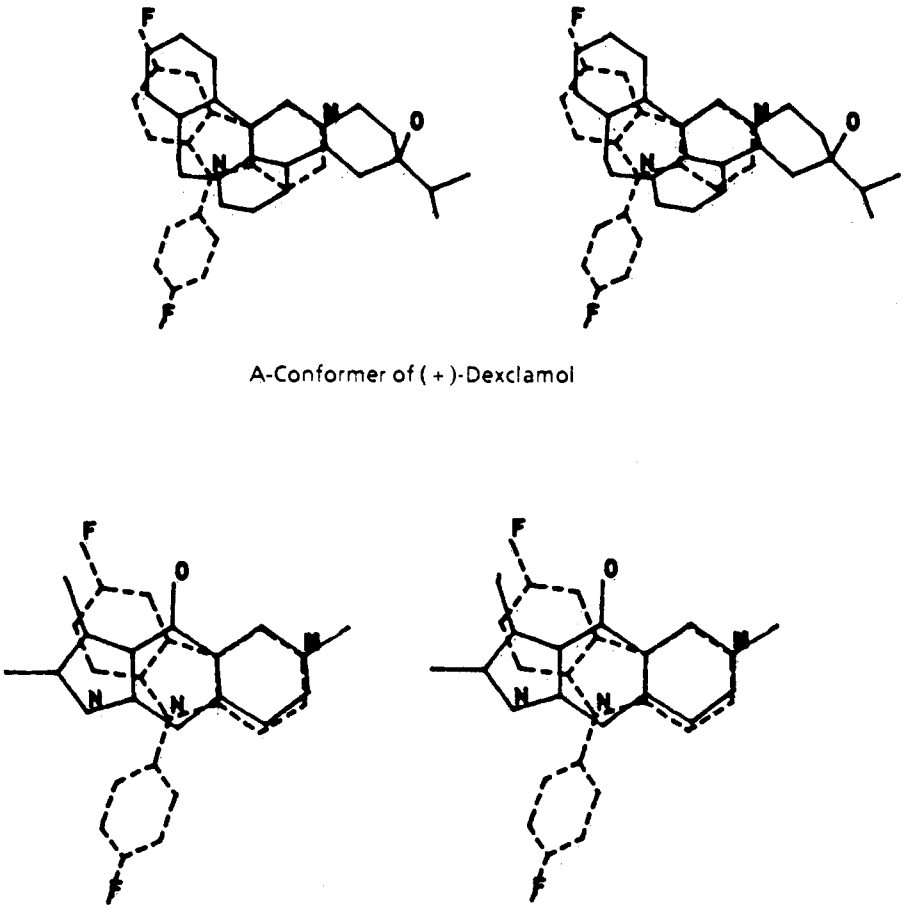


Figure 3. Overlap of **5a**-chair with rigid neuroleptics.

less potent agent penfluridol (**4**, Table I), several compounds (**2a**, **2c**, **27**, **28**, **29b**, and **30**) are still very potent antagonists to an amphetamine challenge 24 h after their administration. Since haloperidol (**3**), which is also a very potent dopamine receptor blocker in vitro, loses most of its activity by 24 h, it is likely that favorable pharmacokinetic effects play an important role in the prolonged in vivo activity of the hexahydro-γ-carbolines.

Experimental Section

Melting points were determined on a Büchi 510 melting point apparatus and are uncorrected. NMR spectra were recorded on Varian A-60, T-60, or XL-100 spectrometers with Me_4Si as an internal standard. IR spectra were recorded on a Perkin-Elmer Model 21 spectrophotometer, while mass spectra were obtained on a Perkin-Elmer RMU-6E mass spectrometer. Microanalyses were performed by the Pfizer Analytical Department and agree within ±0.4% of calculated values, unless noted otherwise.

Method A. Preparation of Resolving Agents. (*R*)-(−)-*N*-Carbamoylphenylalanine (6a). To a suspension of 16.52 g (0.10 mol) of D-(+)-phenylalanine in 75 mL of H_2O was added 12.4 g (0.10 mol) of $Na_2CO_3 \cdot H_2O$. To the resulting solution was added, with stirring, 12.17 g (0.15 mol) of potassium cyanate and the mixture was heated on the steam bath (internal temperatures 80–90 °C) for 1.5–2.0 h. After cooling in an ice bath, the reaction mixture was carefully acidified to pH 1–2 with concentrated HCl. The precipitate was collected by filtration and washed with ice water and then with Et_2O to obtain 15 g of crude product. This was recrystallized by dissolving in 250 mL of warm MeOH, diluting with 400 mL of H_2O, allowing to cool slowly to room temperature, and then refrigerating until precipitation was complete. The product was obtained as white opaque needles in 58% yield after recrystallization, mp 203–204 °C dec, $[\alpha]^{20}_D$ −40.7° (*c* 1, MeOH).

(*S*)-(+)-*N*-Carbamoylphenylalanine (6b). Employing L-(−)-phenylalanine in the above procedure in place of the D-(+) isomer afforded (*S*)-(+)-*N*-carbamoylphenylalanine in 42% yield after recrystallization, mp 205–207 °C dec, $[\alpha]^{20}_D$ +39.0° (*c* 1, MeOH).

Method B. Resolution of 4a,9b-*trans*-8-Fluoro-5-(4-fluorophenyl)-1,2,3,4,4a,9b-hexahydro-γ-carboline (5). A. Preparation of *N*-Carbamoylphenylalanine Salts. 1. To 1 equiv of 4a,9b-*trans*-8-fluoro-5-(4-fluorophenyl)-1,2,3,4,4a,9b-hexahydro-γ-carboline (**5**)[11] free base dissolved in a minimum amount of EtOH was added one equivalent of S(+)-*N*-carbamoylphenylalanine (**6b**). The mixture was heated on a steam bath while adding additional EtOH until a homogeneous solution was obtained. The solution was allowed to cool to room temperature and the precipitated white needles of the *S*(+)-*N*-carbamoylphenylalanine salt of the (−)enantiomer of the free base were collected by filtration and dried, mp 207–209 °C, $[\alpha]^{20}_D$ −5.9° (*c* 1, MeOH).

2. The mother liquor from above was evaporated to dryness, the residue partitioned between aqueous Na_2CO_3 and EtOAc, and the organic layer dried over $MgSO_4$ and evaporated in vacuo to afford a residual oil. The oil was dissolved in a small amount of EtOH and treated with 1 equiv of (*R*)-(−)-*N*-carbamoylphenylalanine (**6a**). The mixture was warmed on the steam bath while more EtOH was added until dissolution was complete. The solution was cooled and worked up as above to afford a 92% yield of crude (*R*)-(−)-*N*-carbamoylphenylalanine salt of the (+) enantiomer of the free base. This was recrystallized from EtOH (75 mL/g) in 65% overall yield, mp 209–211 °C, $[\alpha]^{20}_D$ +6.6° (*c* 1, MeOH).

B. Isolation of the Free Bases. 1. The *N*-carbamoylphenylalanine salt obtained in Part A.1. was partitioned between aqueous saturated $NaHCO_3$ and EtOAc and the organic layer dried over $MgSO_4$ and concentrated in vacuo without heating. The residual oil was dissolved in anhydrous Et_2O (50–100 mL/g) and dry HCl gas was passed over the surface of the solution with swirling to afford a white precipitate. The excess HCl and Et_2O

(11) Welch, W. M. U.S. Patent 4 224 329.

were removed by evaporation at reduced pressure and ambient temperature to give (−)-4a,9b-*trans*-8-fluoro-5-(4-fluorophenyl)-1,2,3,4,4a,9b-hexahydro-γ-carboline (**5b**) hydrochloride in about 96% yield. This was recrystallized by dissolving in a minimum amount of boiling EtOH and adding Et_2O until the solution became turbid. The product was obtained as small white crystals (75% recovery), mp 258–260 °C, $[\alpha]^{20}_D$ −40.9° (*c* 1, MeOH). Anal. ($C_{17}H_{16}F_2N_2$·HCl·0.25H_2O) C, H, N.

2. In the same manner, (+)-4a,9b-*trans*-8-fluoro-5-(4-fluorophenyl)-1,2,3,4,4a,9b-hexahydro-γ-carboline (**5a**) was obtained from the salt provided above in Part A.2, in 96% crude yield and 75% recovery upon recrystallization, mp 260–262.5 °C $[\alpha]^{20}$d +39.2° (*c* 1, MeOH). Anal. ($C_{17}H_{16}F_2N_2$·HCl·0.5H_2O) C, H, N.

Method C. Preparation of Isomer 2a and 2d. A. Preparation of *l*-(4-Fluorophenyl)-3,4-dihydrofuran-2(3*H*)-one [*l*-(4-Fluorophenyl)-γ-butyrolactone, 7].[4] 1. Resolution of *dl*-4-hydroxy-4-(4-fluorophenyl)butyric acid. Commerical γ-(*p*-fluorophenyl)-γ-butyrolactone (Aldrich; 18.0g, 0.10 mol) was added to a solution of 14.0 g (0.35 mol) of NaOH in 100 mL of H_2O and the mixture heated at reflux for 40 min. After the mixture was cooled to 0 °C, 70 mL of 6 N HCl was added and stirring was continued at 0–5 °C for 1 h. The white solid which formed was filtered, washed with pentane, and air-dried to afford racemic 4-hydroxy-4-(4-fluorophenyl)butyric acid, 18.43 g (93% yield). When heated to temperatures of about 100 °C, the hydroxy acid was converted back to the starting lactone.

The hydroxy acid obtained above (18.43 g, 0.093 mol) was dissolved in 200 mL of EtOAc with gentle warming and to the solution was added a solution of 15.04 g (0.91 mol) of *d*-ephedrine, $[\alpha]^{20}_D$ +11.4 (*c* 1, acetone), in 80 mL of EtOAc. The mixture was stirred at room temperature overnight during which time a crop of crystals formed, which was removed by filtration and air-dried to give 18.3 g, mp 97–99 °C. This material was recrystallized by dissolving it in a minimum amount of hot EtOAc and allowing it to stand at ambient temperature overnight. After three such recrystallizations, 8.9 g of the *d*-ephedrine salt of *l*-4-hydroxy-4-(4-fluorophenyl)butyric acid, mp 105.5–106.5 °C, was obtained.

This product was taken up in a mixture of ice-cold 5% HCl (300 mL) and EtOAc (150 mL), the aqueous phase was extraced five times with 100-mL portions of cold EtOAc, and the combined organic extracts were washed with saturated brine and dried ($MgSO_4$). The solvent was evaporated in vacuo to a small volume to obtain 3.8 g of the *l* enantiomer as crystals, mp 98–104 °C, $[\alpha]^{20}_D$ −32.6° (*c* 1, acetone). Upon recrystallization from CH_2Cl_2, the optical rotation was $[\alpha]^{20}_D$ −33.4° (*c* 1, acetone). An additional 0.4 g of product was obtained from the combined filtrates from the three crystallizations above.

2. (−)-γ-(4-Fluorophenyl)-γ-butyrolactone. *l*-4-Hydroxy-4-(4-fluorophenyl)butyric acid (250 mg, 1.26 mmol) was dissolved in 15 mL of EtOAc, and several crystals of *p*-toluenesulfonic acid were added. The mixture was heated at reflux for 25 min, cooled to room temperature, washed with saturated brine, and dried ($MgSO_4$). The solvent was evaporated to yield 216 mg (91%) of the *l*-lactone **7** as a white solid, mp 52–54 °C, $[\alpha]^{20}_D$ −4.0° (*c* 1, acetone).

B. 8-Fluoro-5-(4-fluorophenyl)-2-[4(*R*)-hydroxy-4-(4-fluorophenyl)butyl]-1,2,3,4,4a*R*,9b*R*-hexahydro-γ-carboline (2d). Dilute acetonitrile solutions of 289 mg (1 mmol) of the (−)-γ-carboline isomer **5b** and 226 mg (1.2 mmol) of (−)-lactone **7** were combined and concentrated in vacuo to give an oil which was heated for 4 h under N_2 at 130–150 °C (oil bath temperature). The resultant oil was chromatographed on 75 mL of silica gel (70–230 mesh), eluting with $CHCl_3$. Product fractions were combined and concentrated in vacuo to an oil, 260 mg (55%).

A solution of 100 mg of the oil (0.21 mmol) in 2 mL of THF was treated under N_2 with 49 mg of $LiAlH_4$. After 15 min at reflux, the mixture was cooled in an ice bath and treated with 200 mg of Na_2SO_4, 0.5 mL of H_2O, and 0.5 mL of THF. After 30 min, the mixture was filtered and concentrated in vacuo, and the oil was redissolved in 25 mL of $CHCl_3$, washed with saturated NaCl, and dried ($MgSO_4$). The $CHCl_3$ solution was concentrated in vacuo, and the residual oil was chromatographed on 75 mL of silica gel, eluting with EtOAc–hexane (5:1). The product (27 mg) was converted to the HCl salt in EtOH, the solvent evaporated, and the residue triturated with EtOAc and filtered, washing with acetone, to give **2d** as a white crystalline solid, 11 mg, mp 252–254 °C dec, $[\alpha]^{20}_D$ −35.3° (*c* 1, EtOH).

In a similar manner, 350 mg (1.2 mmol) of the (+)-isomer **5a** and 218 mg (1.2 mmol) of **7** gave 300 mg of the intermediate amide, which on subsequent treatment with $LiAlH_4$ in THF gave a crystalline hydrochloride salt of **2a**, mp 254–256 °C dec, $[\alpha]^{20}_D$ +1.7° (*c* 1, MeOH). Anal. ($C_{27}H_{27}F_3N_2O$·HCl) H, N; C: calcd, 66.32; found, 65.89.

Method D. N-2 Alkylation of γ-Carbolines. 4a,9b-*trans*-8-Fluoro-5-(4-fluorophenyl)-2-[2-(9-carbazolyl)ethyl]-1,2,3,4,4a,9b-hexahydro-γ-carboline (14). A suspension of 0.286 g (1 mmol) of **5**, 0.459 (2 mmol) of 9-(β-chloroethyl)carbazole,[12] 0.530 g (5.0 mmol) of anhydrous Na_2CO_3, 0.001 g of KI, and 5 mL of methyl isobutyl ketone was heated at 80–90 °C for 18 h and then at 120–130 °C for 72 h, when TLC (90% $CHCl_3$:10% CH_3OH) showed a new product spot. The mixture was cooled and filtered, the insoluble salts were washed with $CHCl_3$, and the combined filtrates were concentrated in vacuo to give an oil. Chromatography on 75 mL of silica gel (70–230 mesh), eluting with $CHCl_3$, gave a foam which was recrystallized from $CHCl_3$–cyclcohexane to give **14** as a crystalline white solid, 0.280 g (58.3%), mp 192–193 °C dec. Anal. ($C_{31}H_{27}F_2N_3$) C, H, N.

By a similar method, the following intermediates were prepared. In the hexahydro-γ-carboline series: 2-(2-hydroxyethyl), (80%, oil); 2-cyanomethyl (71%, oil), 2-(3-cyanopropyl) (72%, mp 245–249 °C), 2-(5-cyanopentyl) (76%, mp 234–238 °C), 2-(3-oxo-3-phenylpropyl) (38%, mp 225–227 °C dec), and 2-(3-carboethoxypropyl) (75%, oil). In the tetrahydro-γ-carboline series: 2-(3-cyanopropyl) (mp 234–236 °C), 2-(5-cyanopentyl) (87%, mp 90–98 °C), and 2-(o-carboethoxypropyl) (78%, oil).

Also, by the same method, the alkylhydantoins **25–31** were prepared with the corresponding nuclei **5**, **5a**, or **9** and the (bromoalkyl)hydantoins **23**.

Method E. Saponifications of Esters. 8-Fluoro-5-(4-fluorophenyl)-1,2,3,4-tetrahydro-γ-carboline-2-butyric Acid (11a). A mixture of 3.0 g (7.5 mmol) of the 2-(3-carboethoxypropyl)-γ-carboline from the preceding method and 4.2 g (75 mmol) of KOH in 45 mL of H_2O and 15 mL of EtOH was refluxed for 18 h, cooled, diluted with H_2O, and extracted with Et_2O (2×). The aqueous layer was adjusted to pH 2.0 and stirred for 30 min to give a precipitate, which was filtered. Recrystallization from 2-propanol gave 2.0 g (53%) of **11a**, mp 250–252 °C dec; MS, *m/e* 370 (M^+). Anal. ($C_{21}H_{20}F_2N_2O_2$·HCl) C, H, N.

By a similar procedure, **11b** was obtained in 58% yield, mp 267–268 °C dec.

Method F. Nitrile Reduction. 8-Fluoro-5-(4-fluorophenyl)-2-(6-aminohexyl)-1,2,3,4-tetrahydro-γ-carboline. A mixture of 11.3 g (0.03 mol) of 8-fluoro-5-(4-fluorophenyl)-2-(5-cyanopentyl)-1,2,3,4-tetrahydro-γ-carboline in 500 mL of Et_2O was treated with 3.0 g (0.079 mol) of $LiAlH_4$ portionwise under N_2 with good stirring. After 1.5 h, approximately 5 g of Glauber's salt (Na_2SO_4·10H_2O) was added portionwise and stirring was continued a further 15 min. After filtration, the filtrate was concentrated in vacuo to afford an oil, 10.7 g (94.7%).

Similarly, the following were prepared as oils, which were used without purification in the subsequent amide formations: in the tetrahydro-γ-carboline series, 2-(4-aminobutyl), and in the hexahydro-γ-carboline series, 2-(4-aminobutyl), 2-(6-aminohexyl), and 2-(2-aminoethyl).

Method G. N-Acylation of Carboline Amines. 8-Fluoro-5-(4-fluorophenyl)-2-(4-acetamidobutyl)-1,2,3,4-tetrahydro-γ-carboline (12a). The butylamine prepared as in method F (0.028 mol) was dissolved in 80 mL of CH_2Cl_2, 15.6 mL (0.112 mol) of triethylamine was added, and then 2.35 g (0.030 mol) of acetyl chloride was added dropwise, causing a slight exotherm. After 30 min, the mixture was concentrated to provide an oil, which was chromatographed on silica gel, using 1:1 MeOH–EtOAc as eluant. Product fractions were concentrated in vacuo to give a residue, which was dissolved in Et_2O and treated with HCl gas in the usual manner to give the acetamide **12a**, mp 167–169 °C. Anal. ($C_{23}H_{25}F_2N_3O$·HCl·0.5 H_2O) C, H, N.

Method H. Grignard Addition. 4a,9b-*trans*-8-Fluoro-5-(4-fluorophenyl)-2-(3,3-diphenyl-3-hydroxypropyl)-

(12) Pielichowski, J. *Rocz. Chem.* **1968**, *42*, 591; *Chem. Abstr.* 62, 14612d.

1,2,3,4,4a,9b-hexahydro-γ-carboline (15). Under N_2 in a flame-dried 150-mL round-bottomed flask, 0.750 g (1.8 mmol) of 4a,9b-*trans*-8-fluoro-5-(4-flurophenyl)-2-(3-oxo-3-phenylpropyl)-1,2,3,4,4a,9b-hexahydro-γ-carboline in 50 mL of anhydrous Et_2O was stirred and cooled in an ice bath and 0.8 mL of 3 M phenylmagnesium bromide in Et_2O (Alfa) was added dropwise. The reaction was stirred overnight, allowing it to warm to room temperature. After pouring the mixture over 100 mL of saturated NH_4Cl, the product was extracted into EtOAc, washed with H_2O and saturated aqueous NaCl, dried over $MgSO_4$, and concentrated in vacuo to an oil. After chromatography (75 mL of silica gel) eluting with Et_2O, the product was recrystallized twice from 2-propanol to give 0.140 g (16%), mp 164–165 °C; MS, *m/e* 496 (M^+). Anal. ($C_{32}H_{30}F_2N_2O$) C, H, N.

Method I. Amide Formation from γ-Carboline Acids. 4a,9b-*trans*-8-Fluoro-5-(4-fluorophenyl)-2-[3-(*N*-cyclohexyl-*N*-phenylcarbamoyl)propyl]-1,2,3,4,4a,9b-hexahydro-γ-carboline (16). To a solution of 0.408 g (1 mmol) of **11b** and 1.75 g (10 mmol) of 2-bromo-*N*-methylpyridinium iodide[13] in 20 mL of CH_2Cl_2 was added 0.360 g (2.1 mmol) of *N*-phenylcyclohexylamine. The mixture was refluxed 96 h, another 0.180 g of *N*-phenylcyclohexylamine was added, and reflux was continued another 18 h. After cooling to room temperature, the mixture was concentrated in vacuo to an oil which was triturated with EtOAc to give a white solid. Recrystallization from EtOH gave **16** in 12% yield, mp 276–278 °C dec; MS, *m/e* 529.2866 (calcd 529.2895). Anal. ($C_{33}H_{37}F_2N_3O$·HI) C, H, N.

In a similar manner the following were prepared: **18** (using **11b**, DCC, and aniline), 24% yield, mp 250–252 °C, and **19** (using **11b**, DCC, and cyclohexylamine), 16%, mp 139–142 °C.

Method J. Amide Formation from γ-Carboline Amines. 4a,9b-*trans*-8-Fluoro-5-(4-fluorophenyl)-2-[2-(3-hydroxy-2-phenylpropionamido)ethyl]-1,2,3,4,4a,9b-*trans*-hexahydro-γ-carboline (17). Under N_2 in a flame-dried 100-mL round-bottomed flask, 0.332 g (2 mmol) of tropic acid (Aldrich) in 10 mL of CH_2Cl_2 was stirred and cooled in an ice bath. A solution of 0.412 g of DCC in 5 mL of CH_2Cl_2 was added dropwise and stirred for 20 min to give a milky solution. A solution of 0.670 g (2 mmol) of the N-2 ethylamine intermediate (method F) in 10 mL of CH_2Cl_2 was added dropwise and the mixture stirred in the cold for 1 h and at room temperature overnight. TLC ($CHCl_3$–MeOH) showed no amine remaining. The reaction was filtered, washing with CH_2Cl_2, the filtrate was concentrated in vacuo to a yellow foam which was chromatographed (150 mL of 70–230-mesh silica gel, 5% MeOH–95% $CHCl_3$) to give a white foam, 0.700 g (60%). A portion (0.4 g) of this foam was dissolved in EtOH, treated with 1.1 equiv of methanesulfonic acid, and left at room temperature to give a crystalline salt, 0.240 g (29.6%), mp 247–249 °C. Anal. ($C_{28}H_{29}F_2N_3O_2$·CH_4O_3S) C, H, N, S.

Method K. Carbamate Formation. 4a,9b-*trans*-8-Fluoro-5-(4-fluorophenyl)-2-[2-[(*N*-phenylcarbamoyl)oxy]-ethyl]-1,2,3,4,4a,9b-hexahydro-γ-carboline (20). A solution of 1.0 g (3 mmol) of the N-2 ethyl alcohol (from method D), 5 mL of phenyl isocyanate, and 20 mL of pyridine was stirred at room temperature for 18 h and then concentrated in vacuo (at 70 °C). The residue was chromatographed on 50 mL of silica gel, eluting with $CHCl_3$, and the product fractions were concentrated to a yellow foam, 0.800 g. The foam was dissolved in Et_2O and treated with HCl-saturated Et_2O, and the salt was filtered and recrystallized from $CHCl_3$–Et_2O to give **20**, 0.230 g (15%), mp 228–230 °C dec; MS, *m/e* 449 (M^+). Anal. ($C_{26}H_{25}F_2N_3O_2$·HCl·0.125H_2O) C, H, N.

Method L. Preparation of (Bromoalkyl)hydantoins (23). A. Twenty-five grams (0.25 mmol) of hydantoin (2,4-imidazolidinedione) was dissolved in 1 L of 90% aqueous EtOH. Fifteen grams (0.27 mol) of KOH in 125 mL of EtOH was added, the mixture was stirred 16 h and filtered, and the salt was dried at 80 °C at reduced pressure for 24 h to give 25.2 g (80%) of **21**, mp 271–272 °C dec.

B. Five grams (36 mmol) of potassium salt **21** and 12.8 mL (91 mmol) of 1,5-dibromopentane (97%, Aldrich) were stirred in 50 mL of dry DMF under N_2 for 6 days at 25 °C. The mixture was diluted with 300 mL of $CHCl_3$, washed well with H_2O and brine, dried over $MgSO_4$, and concentrated to an oil. After the oil was layered with hexane, it was cooled at −78 °C to induce crystallization, and after 18 h at 25 °C the white crystals were filtered and washed (hexane) to give 2.35 g (26%) of **23** (n = 5), mp 76–78 °C; MS, *m/e* 250, 248 (M^+). Anal. ($C_8H_{13}BrN_2O_2$) C, H, N.

Method M. Preparation of (Diphenylamino)piperidines. A. 4-[(4-Fluorophenyl)amino]pyridine (32). To 25 g (0.167 mol) of 4-chloropyridine hydrochloride (Aldrich) in 75 mL of glacial acetic acid was added 31.6 mL (0.333 mol) of 4-fluoroaniline (slight exotherm) and the brown suspension was heated at 90–95 °C for 8 h and cooled to room temperature overnight. This was poured over 250 mL of ice water, stirred 30 min, filtered, and basified with saturated aqueous K_2CO_3 (foams!) to pH 9.0 to give a tan precipitate. Recrystallization from **2B** EtOH gave 25.3 g (81%), mp 196–198 °C;[14] MS, *m/e* 188 (M^+). Anal. ($C_{11}H_9FN_2$·0.25H_2O) C, H, N.

B. 4-[*N*,*N*-Bis(4-fluorophenyl)amino]pyridine (33). A mixture of 9.0 g (0.048 mol) of **32**, 22 mL (0.200 mol) of 4-bromo-1-fluorobenzene, 27.5 g (0.095 mmol) of cuprous bromide (Alfa), and 13.2 g (0.095 mol) of anhydrous K_2CO_3 in 100 mL of dry *N*-methyl-2-pyrrolidinone was heated at 185–190 °C for 24 h, cooled to 25 °C, filtered through a Celite (diatomaceous earth) pad, diluted with 500 mL of EtOAc, and washed several times with 100-mL portions of concentrated NH_4OH–H_2O (1:1) and finally with saturated aqueous NaCl. After drying over $MgSO_4$, treatment with decolorizing charcoal, and filtration through Celite, the organic extracts were concentrated to a tan solid, 13.4 g. Chromatography on 1 kg of silica gel using EtOAc and then adding MeOH to increase polarity to 20% MeOH–80% EtOAc gave 3.2 g of recovered **32** and 5.2 g (38.4% of the desired diphenylamine **33**, mp 105–107.5 °C; MS, *m/e* 282 (M^+). Anal. ($C_{17}H_{12}F_2N_2$) C, H, N.

C. 4-[*N*,*N*-Bis(4-fluorophenyl)amino]piperidine Hydrochloride (34a). A solution of 5 g (17.7 mmol) of **33** and 2.1 mL (17.5 mmol) of benzyl bromide in 100 mL of dry benzene was refluxed for 2 h under N_2, cooled, and filtered to give a tan solid, 6.45 g (83%), mp 292–294 °C. To 6 g (0.0132 mol) of this bromide in 200 mL of anhydrous MeOH was added 25.8 g (0.68 mol) of sodium borohydride portionwise over 30 min. After an additional 1 h of stirring, the mixture was heated 1 h on a steam bath, cooled, and diluted with 75 mL of H_2O and 300 mL of Et_2O. The Et_2O layer was removed, the aqueous layer was extracted with 2 × 150 mL of Et_2O, and the combined Et_2O layers were washed with H_2O, dried (K_2CO_3), filtered, and concentrated in vacuo to give a pale yellow oil, 4.5 g (90%); MS, *m/e* 376 (M^+).

A solution of 4.0 g of the above oil and 1.0 g of 10% Pd/C in MeOH were hydrogenated at 50 °C (initial H_2 pressure of 50 psi) for 18 h. After being cooled, the mixture was filtered through a Celite pad and concentrated in vacuo to afford a gum, 2.7 g (88%). The gum was dissolved in EtOH and treated with HCl gas and finally Et_2O to precipitate **34a** as white needles, 1.43 g (41.4%), mp 292–295 °C. Anal. ($C_{17}H_{18}F_2N_2$·HCl) C, H, N.

Method N. Reduction of Ketones. A. 4-[*N*,*N*-Bis(4-fluorophenyl)amino]-1-[4-(4-fluorophenyl)-4-oxobutyl]-piperidine (34b). In a flame-dried 50-mL flask under N_2 were combined 0.4 g (1.23 mmol) of **34a**, 0.653 g (6.16 mmol) of anhydrous Na_2CO_3, 30 mg of KI, and 0.41 mL of (2.46 mmol) γ-chloro-*p*-fluorobutyrophenone (Aldrich) in 10 mL of methyl isobutyl ketone. The reaction mixture was heated at 110–120 °C for 24 h at which time TLC (EtOAc–CH_3OH, 1:1) showed essentially one major spot at R_f 0.90. The mixture was cooled to room temperature and diluted with 150 mL of EtOAc, washed with H_2O, saturated aqueous $NaHCO_3$, and saturated aqueous NaCl, and dried over $MgSO_4$. After filtration, it was concentrated in vacuo to give an oil, ~1.0 g. Chromatography on 200 g of 70–230-mesh silica gel with EtOAc gave the pure product, 0.35 g which was converted to the HCl salt in Et_2O. Recrystallization from Et_2O gave **34b** as a white solid, 0.334 g (54.5%), mp 116–119 °C; MS, *m/e* 452 (M^+). Anal. ($C_{27}H_{27}F_3N_2O$·HCl·0.5 H_2O) C, H, N.

B. 4-[*N*,*N*-Bis(4-fluorophenyl)amino]-1-[4-(4-fluorophenyl)-4-hydroxybutyl]piperidine (34c). A solution of 0.100 g (0.2 mmol) of **34b** in 10 mL of absolute MeOH was treated cautiously with 0.80 g (2 mmol) of $NaBH_4$ and stirred 1.5 h. TLC

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Table VIII. Single-Crystal X-ray Crystallographic Analysis

A. Crystal Parameters	
formula	$C_{24}H_{20}ON_8BrF_2 \cdot C_2H_4O_2$ (544.41)
crystn medium	acetic acid/water
crystal size, mm	0.11 × 0.12 × 0.17
cell dimensions	a = 14.539 (2) Å
	b = 9.868 (1) Å
	c = 9.760 (1) Å
	α = 115.49 (1)°
	β = 91.66 (1)°
	γ = 103.18 (1)°
	V = 1217.7 (3) Å^3
space group	$P\bar{1}$
molecules/unit cell	2
d (obsd), g/cm^3	1.48
d (calcd), g/cm^3	1.485
linear abs coefft, cm^{-1}	29.7
B. Refinement Parameters	
no. of reflections	2528
nonzero reflections ($I > 3.0\sigma$)	2442
R index = $\sum\|\|F_o\| - \|F_c\|\|/\sum\|F_o\|$	0.051
GOF = $[\sum w(F_o^2 - F_c^2)^2/(m - s)]^{1/2}$	4.00
scale factor	0.846 (3)
secondary extinction coeff	2.0 (6) × 10^{-6}

(EtOAc–benzene–DEA, 10:10:1) showed a new spot at R_f 0.55 and no spot for **11a** at R_f 0.80 (all spots iodoplatinic (+)). The mixture was treated with 5 g of crushed ice and extracted with 2 × 25 mL of Et_2O. The Et_2O layers were dried over $MgSO_4$ and concentrated in vacuo to afford a gum, 0.082 g. This gum was dissolved in 30 mL of Et_2O, treated with HCl gas, and immediately concentrated in vacuo. The residue was redissolved in a minimal amount of CH_2Cl_2 and refrigerated for 24 h. The precipitated product was filtered under N_2, washed with petroleum ether, and dried in a vacuum desiccator (P_2O_5) for 2 h to give **34c** as a pale tan solid, 0.044 g (48.4%), mp 92–94 °C dec; MS, m/e 454 (M^+), 436 ($M^+ - H_2O$). Anal. ($C_{27}H_{29}F_3N_2O \cdot HCl \cdot H_2O$) C, H, N.

Single-Crystal X-ray Analysis. A representative crystal was surveyed and a 1-Å data set (maximum sin θ/λ = 0.5) was collected on a Syntex $P\bar{1}$ diffractometer. The diffractometer was equipped with a graphite monochromator and copper radiation (λ = 1.5418 Å). Atomic scattering factors were taken from the International Tables for X-ray Crystallography,[15] except hydrogen which was taken from Stewart et al.[16] and bromine which was taken from Cromer and Mann.[17] All crystallographic calculations were facilitated by the CRYM system.[18] All diffractometer data were collected at room temperature. Pertinent crystal, data collection, and refinement parameters are summarized in Table VIII.

A trial structure was obtained by conventional Patterson and Fourier techniques. This trial structure refined routinely. Hydrogen positions were calculated whenever possible. The amide hydrogens were located by difference Fourier techniques. The hydrogen parameters were added to the structure factor calculations but were not refined. The final cycles of full-matrix least-squares refinement contained the scale factor, secondary extinction coefficient, coordinates, and anisotropic temperature factors in three matrices. The shifts calculated in the final cycle were all less than 0.1 of their corresponding standard deviation. The final R index was 0.051. A final difference Fourier revealed no missing or misplaced electron density. The absolute configuration of the molecule was established by the method of Ibers and Hamilton.[19] The presence of the bromine atom made this determination a straightforward one and was correct at the 0.5% level of confidence.[20] As it was suspected from the beginning, the correct space was $P1$ and not $P\bar{1}$. The unit cell contained two molecules of the same hand and therefore could not accommodate a center of symmetry. The two molecules were different in respect to their relationship with the acetic acid of crystallization.

The refined structure was plotted by using the ORTEP computer program of Johnson[21] (Figure 1). Coordinates, anisotropic temperature factors, distances and angles are available as supplementary material.

Pharmacological Testing. [^{3}H]Spiroperidol Binding to the Dopamine Receptor. Binding of [^{3}H]spiroperidol (0.5 nM) to corpora striata membranes of Sprague–Dawley CD male rats (Charles River Breeding Laboratories Inc., Wilmington, MA) was conducted as described by Harbert et al.[1] Three to four concentrations (in triplicate) of each compound were tested for inhibition of binding; the concentration that decreased binding by 50% (IC_{50}) was estimated on semilog paper. The IC_{50} values in Tables I–VI were based on one to two determinations. For multiple determinations, the mean $IC_{50} \pm$ SE are given with the number of determinations in parentheses. For compounds of low solubility, binding assays were run in an incubation medium containing 1% ethanol.

Antagonism of (+)-Amphetamine-Induced Symptoms in Rats. Neuroleptic effects in vivo were estimated by the blockade of amphetamine-induced stereotypy. Rats were placed individually in covered plastic compartments; after a brief period of acclimation in the cages, the rats in groups of five were treated subcutaneously with compounds at doses separated by 0.5 log unit (i.e., ... 1, 3.2, 10, 32, ... mg/kg). They were subsequently treated 1, 5, and 24 h later with d-amphetamine sulfate, 5 mg/kg ip. One hour after each amphetamine challenge, each rat was assessed for its most characteristic behavior on a six-point scale, following the rating procedure described by Weissman et al.[22] and Harbert et al.[1] Approximate ED_{50}'s were either calculated by linear regression or estimated by inspection. Because only three doses were occasionally used for the estimation of ED_{50}'s and because fractions protected were often 0/5 or 5/5, fiducial limits or standard errors of the ED_{50}'s were not calculated. It should be noted, however, that Weissman et al.[22] reported that in a series of 428 consecutive control-pretreated rats exposed to the present amphetamine challenge, only 14% failed to exhibit sniffing, licking, or gnawing (collectively termed "stereotypy"). If one thereby assumes that the estimated binomial probability of "protection" in an infinite control population is 14, then the probability of observing three rats protected out of five tested is 0.02, of observing four rats protected out of five is 0.002, and of observing five rats protected out of five is 0.00005. On every occasion when an ED_{50} was estimated (and therefore presented in the data tables), on of these three fractions applied at the next higher dose tested; i.e., if the calculated ED_{50} was 0.2 mg/kg, then the protection data at the tested dose of 0.32 mg/kg were significant with $p < 0.02$, and often with $p < 0.002$.

Anticholinergic Activity. Anticholinergic activity was estimated by the presence of mydriasis in tetrabenazine-treated mice. Groups of five mice were first dosed sc with the test compounds and 1 h later with tetrabenazine (32 mg/kg ip) to reduce any conceivable indirect sympathomimetic basis for mydriasis. After a 30-min period pupil sizes were determined with a binocular microscope, and reticle readings were converted to millimeters of pupil. These data are listed in Table IV. In three control groups of five vehicle-pretreated mice exposed to tetrabenazine the pupil sizes (±SD) in millimeters were 0.23 ± 0.04, 0.29 ± 0.15, .20 ± 0.03.

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of the carboline nuclei **5** and **5a**. Additionally we appreciate the support of Dr. Gwen Chmurny for determination of 100-MHz NMR spectra, Richard Ware for mass spectral determinations and the Analytical Department of Pfizer Central Research for elemental analyses.

Registry No. **2a**, 74311-69-6; **2a** (amide), 98717-38-5; **2a**·HCl, 98675-08-2; **2b**, 74311-68-5; **2c**, 74311-70-9; **2d** (amide), 98651-75-3; **2d**·HCl, 98675-07-1; (±)-**5**, 69623-07-0; (±)-**5** ($(CH_2)_2OH$ deriv), 98634-60-7; (±)-**5** (CH_2CN deriv), 98634-61-8; (±)-**5** ($(CH_2)_3CN$ deriv), 77378-64-4; (±)-**5** ($(CH_2)_5CN$ deriv), 98634-62-9; (±)-**5** ($(CH_2)_2COPh$ deriv), 98634-63-0; (±)-**5** ($(CH_2)_3COOEt$ deriv), 98634-64-1; (±)-**5** ($(CH_2)_4NHz$ deriv), 98651-79-7; (±)-**5** ($(CH_2)_6$ NHz deriv), 98651-80-0; (±)-**5** ($(CH_2)_2NHz$ deriv), 98651-81-1; **5a**·**6a**, 76700-26-0; **5a**·HCl, 83502-36-7; **5b**·**6b**, 76700-24-8; **5b**·HCl, 98818-01-0; **6a**, 54896-72-9; **6b**, 949-45-1; (±)-**7**, 76700-29-3; **7**, 75738-79-3; **8**, 98634-89-0; **9**, 58038-68-9; **9** ($(CH_2)_3CN$ deriv), 58039-14-8; **9** ($(CH_2)_5CN$ deriv), 83535-77-7; **9** ($(CH_2)_3COOEt$ deriv), 98634-65-2; **9** ($(CH_2)_6NH_2$ deriv), 83545-87-3; **10a**·HCl, 58039-02-4; (±)-**10b**·HCl, 98634-82-3; **11a**, 98634-66-3; (±)-**11b**, 98634-67-4; **12a**, 98634-68-5; (±)-**12b**·HCl, 77378-81-5; **13g**·HCl, 98634-83-4; (±)-**13b**·HCl, 98634-84-5; (±)-**14**, 98634-59-4; (±)-**15**, 98634-70-9; (±)-**16**, 98634-71-0; **17**, 98651-78-6; (±)-**18**, 98651-76-4; (±)-**19**, 98634-72-1; (±)-**20**·HCl, 98651-82-2; **21**, 98634-73-2; **23** (n = 5), 98634-74-3; (±)-**25**, 83514-71-0; (±)-**26**, 83514-73-2; **27**, 98634-85-6; **28**, 98634-86-7; (±)-**29a**, 83514-78-7; **29b**, 98675-09-3; **30**, 98634-87-8; **31**, 98634-88-9; **32**, 72358-71-5; **33**, 98634-75-4; **33**·$PhCH_2Br$, 98634-77-6; **34a**·HCl, 98634-76-5; **34b**, 98634-79-8; **34b**·HCl, 98634-80-1; **34c**, 98634-81-2; (±)-4-$FC_6H_4CH(OH)(CH_2)_2CO_2H$, 75738-74-8; ($R$)-4-$FC_6H_4CH(OH)(CH_2)_2CO_2H$-*d*-ephedrine, 75738-76-0; (R)-4-$FC_6H_4CH(OH)(CH_2)_2CO_2H$, 75738-75-9; C_6H_5Br, 108-86-1; $C_6H_5NH_2$, 62-53-3; (±)-$C_6H_5CH(CH_2OH)CO_2H$, 552-63-6; C_6H_5NCO, 103-71-9; $Br(CH_2)_5Br$, 111-24-0; 4-$FC_6H_4NH_2$, 371-40-4; 4-BrC_6H_4F, 460-00-4; $C_6H_5CH_2Br$, 100-39-0; 4-$C(CH_2)_3COC_6H_4F$, 3874-54-2; D-(+)-phenyalanine, 673-06-3; L-(−)-phenylalanine, 63-91-2; 2-(4-aminobutyl)tetrahydro-γ-carboline, 98634-69-6; 9-(β-chloroethyl)carbazole, 1140-35-8; 2-bromo-*N*-methylpyridinium iodide, 52693-56-8; *N*-phenylcyclohexylamine, 1821-36-9; cyclohexylamine, 108-91-8; hydantoin, 461-72-3; 4-chloropyridine hydrochloride, 7379-35-3; 1-benzyl-4-[*N*,*N*-bis[(4-fluorophenyl)amino]]-2*H*-pyridine, 98634-78-7.

Synthesis and Antihypertensive Activity of a Series of 4-Amino-6,7-dimethoxyquinazoline Derivatives

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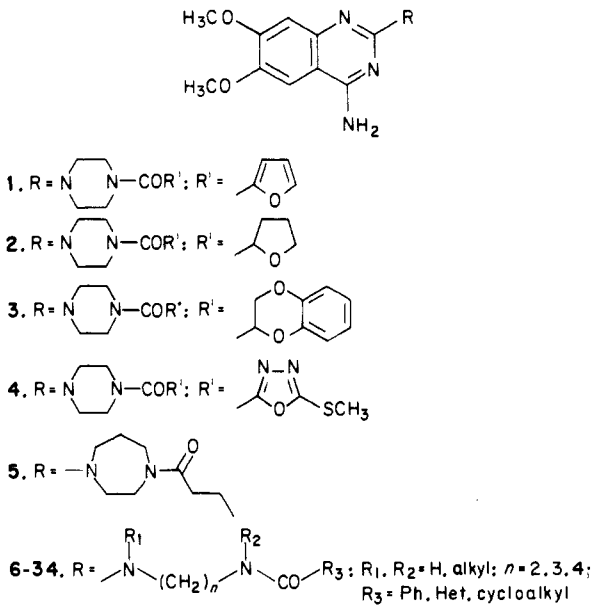
A series of N^2-[(acylamino)alkyl]-6,7-dimethoxy-2,4-qui[illegible]olinediamines was synthesized as potential α_1-adrenoceptor antagonists. When administered to spontaneously hy[illegible]ensive rats at 10 mg/kg po, a number of propanediamine derivatives showed good antihypertensive activity, wh[illegible]s the ethanediamine derivatives, albeit being structurally more closely related to prazosin, were devoid of this property. The most active derivative, *N*-[3-[(4-amino-6,7-dimethoxy-2-quinazolinyl)methylamino]propyl]tetrahydro-2-furancarboxamide hydrochloride, alfuzosin (**12**), showed high selectivity for peripheral α_1-postjunctional adrenoceptors. At equiactive antihypertensive doses, its effect on the pressor response to postural changes in conscious dog was less marked than that shown by prazosin. In the light of these results, alfuzosin was selected for clinical evaluation.

Prazosin (**1**) may be considered as the first member of a new class of antihypertensive agents for which the main mechanism of action appears to be the competitive antagonism of α_1-adrenoceptors.[1] The clinical efficacy of this agent[2] encouraged us to search, through modifications of the structure of its side chain, a new derivative in which the blockade of α_1-adrenoceptors would be associated with other desirable properties for the treatment of hypertension, such as diuresis, direct vasodilation, or the lack of serious orthostatic hypotension upon the administration of the first dose as it was reported for prazosin.[3] Although many derivatives of prazosin—terazosin[4] (**2**), doxazosin[5] (**3**), tiodazosin[6] (**4**), bunazosin (**5**)—are under clinical investigation, none, to our knowledge, appears to have a structure in which the piperazine moiety has been replaced by an alkanediamine chain. In this report, we describe the synthesis and biological activity of some N^2-[(acylamino)alkyl]-6,7-dimethoxy-2,4-quinazolinediamines (**6**–**34**).



Chemistry. The compounds listed in Table I were synthesized by the routes shown in Schemes I and II. The preparation involved the condensation, in refluxing isoamyl

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