× 50 cm) of silica gel in $CHCl_3$, washed with 200 mL of $CHCl_3$, and eluted with $CHCl_3$–CH_3OH (9:1). The appropriate fractions were combined, evaporated to dryness, and recrystallized from petroleum ether to give 4.55 g (44%) of **5**, with its ^1H NMR in $CDCl_3$–CD_3OD showing a resonance pattern identical with that of Boc-DL-Hfv regenerated from the DCHA salt **6** without any benzylic protons.

Boc-Sar-Arg-Val-Tyr-Val-His-Pro (7) was prepared by standard solid-phase procedure, with the resultant Boc-Sar-Arg(NO_2)-Val-Tyr(Bzl)-Val-His(Bzl)-Pro-resin (2.1 mmol) hydrogenated twice with palladium acetate (0.95 g, 4.2 mmol) in dimethylformamide (40 mL) at 45 °C under 60 psi of H_2 for 5 days to give 1.57 g of crude peptide.[16] Sequential purification of the peptide by countercurrent distribution in 8:1:2:9 1-butanol–pyridine–acetic acid–water for 600 transfer followed by 1000 transfers in 4:1:5 1-butanol–acetic acid–water gave 418 mg (21%) of **7**: TLC R_f (i) 0.18, (iii) 0.27. Amino acid analysis of hydrolysate gave Sar (1.02), Arg (1.04), Val (0.96), Tyr (1.00), Val (0.96), His (1.02), Pro (1.02); peptide content 89%.

Sar-Arg-Val-Tyr-Val-His-Pro-Hfv (8) and Sar-Arg-Val-Tyr-Val-His-Pro-D-Hfv (9). [Boc-Sar[1],des-Phe[8]]AII (**7**; 100 mg, 0.1 mmol), DL-Hfv-OBzl·HCl (**3**; 80 mg, 0.25 mmol), 1-hydroxybenzotriazole monohydrate (19 mg, 0.12 mmol), and dicyclohexylcarbodiimide (51 mg, 0.25 mmol) were dissolved in dimethylformamide (4 mL). The mixture was stirred at room temperature for 1 h and at 45 °C for 5 h and was evaporated to dryness. The residue was washed with chloroform and ether, followed by chromatography on a column (1 × 25 cm) of microcrystalline (carboxymethyl)cellulose (Whatman CM 52) in the upper phase of the solvent mixture of 8:1:2:9 butanol–pyridine–acetic acid–water. Elution of the column by the same solvent mixture gave 120 mg of [Boc-Sar[1],DL-Hfv-OBzl[8]]AII.

Subsequent hydrogenolysis of the peptide with 10% Pd/C (80 mg) in DMF (4 mL) under 40 psi of H_2 for 2 h, followed by treatment of the product with trifluoroacetic acid (40 mL) for 2 h, gave 111 mg of [Sar[1],DL-Hfv[8]]AII.

Separation of this diastereomeric mixture by countercurrent distribution in 8:1:2:9 1-butanol–pyridine–acetic acid–water for 800 transfers gave two fractions of K values 0.52 and 0.83. Further purification of the respective fractions by gel filtration on Sephadex G10 (2 × 96 cm) in 10% AcOH gave 24 mg (42%) of the L diastereomer (**8**: K = 0.52; TLC R_f (i) 0.17, (iii) 0.19) and 40 mg (64%) of the D diastereomer (**9**: K = 0.83; TLC R_f (i) 0.18, (iii) 0.22). The stereochemical assignments of these diastereomers were based on their susceptibilities to carboxypeptidase Y digestion, in which the L diastereomer **8** gave Val (0.59), Tyr (1.00), Val (0.59), His (0.95), Pro (0.87), Hfv (0.54), whereas the D diastereomer **9** gave only Tyr (0.16) and His (0.21) without any Hfv. FAB-MS analyses gave M + 1 of 1049 for both **8** and **9**. Amino acid analysis of a hydrolysate gave Sar (0.98), Arg (1.03), Val (0.98), Tyr (1.05), Val (0.98), His (0.98), Pro (0.95), Hfv (1.04), peptide content 91% for **8**; and Sar (1.01), Arg (1.01), Val (1.00), Tyr (1.03), Val (1.00), His (0.97), Pro (0.97), Hfv (0.96), peptide content 84% for **9**.

Acknowledgment. Support for this investigation by the National Institutes of Health (HL 32264, HL 14504, and GM 24483), the American Heart Association (73–754), and the American Heart Association, Missouri Affiliates is gratefully acknowledged. We thank Dr. George Goodloe of the Auburn University Mass Spectrometry Center for FAB-MS analyses.

Registry No. **1**, 107496-44-6; **2**, 107496-45-7; **3**, 78164-91-7; **4**, 16063-80-2; **5**, 107496-46-8; **6**, 107496-47-9; **7**, 107496-48-0; **8**, 107496-49-1; **9**, 107538-64-7; [BOC-Sar[1],DL-Hfv-OBzl[8]]AII, 107496-51-5; $BrCH_2COOCH_2Ph$, 5437-45-6; PPh_3, 603-35-0; $Ph_3P{=}CHCOOCH_2Ph$, 15097-38-8; $(CF_3)_2CO$, 684-16-2; $(BOC)_2O$, 24424-99-5; 5-L-valine angiotensin II, 58-49-1.

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Psychotropic Agents: Synthesis and Antipsychotic Activity of Substituted β-Carbolines

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A series of novel substituted β-carbolines was synthesized and tested for potential antipsychotic activity. Several compounds displayed moderate antipsychotic activity in vitro and in vivo as determined by relevant receptor binding assays and behavioral tests. The effect of substituents on antipsychotic activity was examined. The β-carbolines **10** and **19** containing 2-(2-pyridinyl)ethyl and 2-(2-quinolinyl)ethyl side chains were the most potent analogues, blocking discrete trial conditioned avoidance responding in rats with AB_{50}'s of 23 and 10 mg/kg, respectively. Both showed moderate activity at the D_2 receptor sites, but they lacked oral activity. In contrast, the β-carboline **13** containing the 4-(4-pyridinyl)butyl side chain exhibited oral activity in the discrete trial conditioned avoidance screen with an AB_{50} of 31 mg/kg. Most compounds did not antagonize apomorphine-induced stereotyped behavior, which is indicative of low potential for extrapyramidal side effect (EPS) liability.

While dopamine (DA) antagonists are used effectively in the treatment of schizophrenia,[1-3] some patients fail to respond to treatment.[4,5] Furthermore, antipsychotic therapies are known to produce extrapyramidal side effects (EPS)[5,6] such as parkinsonism, dystonia, akathisia, and tardive dyskinesia (TD).[7]

Studies have shown that neuroleptic therapy with drugs with apparent specificity for limbic as opposed to striatal regions of the brain may have a lower EPS liability.[8] Those that are potent antagonists of apomorphine-induced stereotyped behavior, on the other hand, have been asso-

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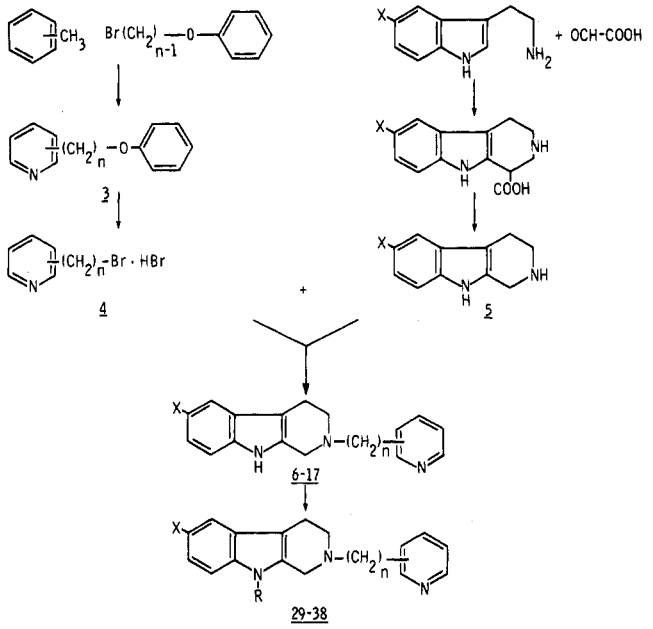
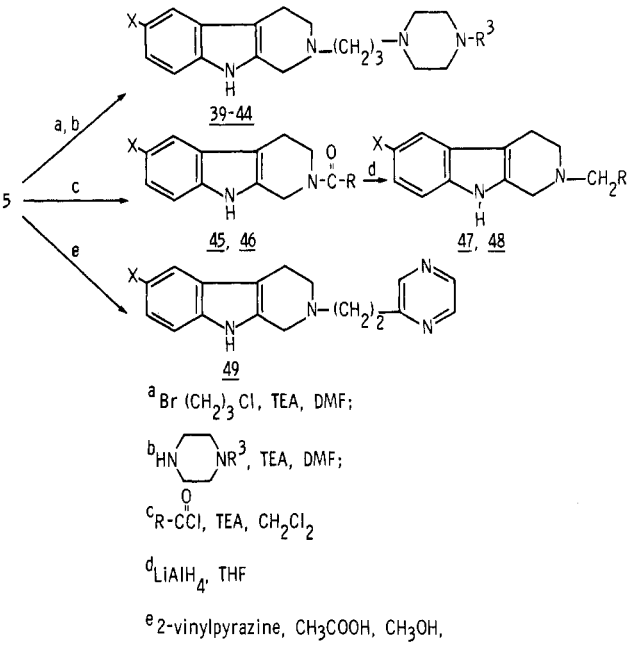
0022-2623/87/1830-1100$01.50/0

Scheme I



Scheme II



[a] $Br(CH_2)_3Cl$, TEA, DMF;

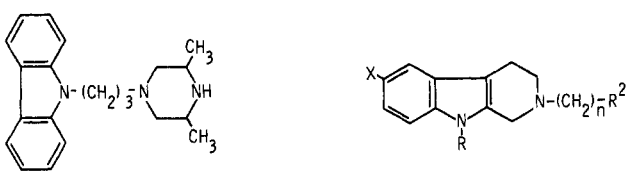
[b] HN⟨piperazine⟩NR^3, TEA, DMF;

[c] $R\text{-}CCl$, TEA, CH_2Cl_2

[d] $LiAlH_4$, THF

[e] 2-vinylpyrazine, CH_3COOH, CH_3OH,

ciated with a high incidence of EPS.[7-9] However, some atypical antipsychotic agents with a low incidence of EPS may also antagonize or weakly antagonize some apomorphine-induced behavioral effects.[10,11] In recent years, synthetic efforts have been devoted to the development of novel antipsychotic drugs that ameliorate psychosis without causing EPS.[7,11] For example, rimcazole (1), which does not antagonize apomorphine-induced stereotypy, has been reported to show efficacy as an antipsychotic agent with minimal EPS.[12,13] Our interest in 1 and our efforts to develop novel compounds that exhibit weak or moderate activity at the D_2 receptor binding sites but that do not block apomorphine-induced stereotypy and that maintain potent antipsychotic activity led to the synthesis of the series of novel β-carbolines **2**.



1 **2**

In this paper we report the synthesis and antipsychotic activity of the substituted β-carbolines.

Chemistry

Literature procedures were adapted for the preparation of unsubstituted 3,4-dihydro-β-carboline (**5**) in 90% yield.[14] Scheme I illustrates the general synthetic route for the preparation of compounds **6–17**. The reaction of phenoxyalkyl bromide with picolines in liquid ammonia in the presence of sodium amide afforded the corresponding (phenoxyalkyl)pyridines **3** as thick oils in 55–65% yield and they were used without further purification. Acid hydrolysis of **3** using 48% HBr gave the corresponding pyridinylalkyl bromide hydrobromide **4**. Substitution at the N-2 position was achieved by reacting **5** with **4** in DMF in the presence of cesium carbonate to afford target compounds **6–17**. Similarly, alkylation of **5** with the appropriately substituted quinolinylalkyl halides afforded compounds **18–25**. In addition, the reaction of **5** with 2,6-dimethoxybenzyl chloride gave compounds **26** and **27**, and reaction with 3-[bis(*p*-fluorophenyl)methyl]propyl bromide afforded **28**. Substitution at the N-9 position of the β-carboline was achieved by reacting an equimolar quantity of the 2-substituted β-carbolines **10–17** with alkyl halides in DMF in the presence of 10 equiv of sodium hydride to afford compounds **29–38**.

Scheme II describes synthetic pathways for the incorporation of piperazinylalkyl moieties into the β-carboline skeleton as in compounds **39–44**. In addition, it also illustrates synthesis of the acyl heterocyclic compounds **45** and **46** and the heteroarylmethyl compounds **47** and **48**. The reaction of **5** with 2-vinylpyrazine under the Michael conditions afforded compound **49**, which represents an alternate synthesis for compounds **7**, **9**, **10**, **14**, **16**, **22**, and **23**.

Biological Results and Discussions

All compounds were tested in vitro for their affinity for D_2 receptors of rat nucleus accumbens (unless otherwise specified) labeled with [^{3}H]spiperone. Compounds were also tested for their ability to inhibit apomorphine (APO) induced stereotypy in mice upon ip administration. Antipsychotic activity was assessed by measuring the ability of compounds to block the response of rats trained to avoid an electrical shock (inhibition of shelf-jump and/or discrete trial conditioned avoidance response (CAR)) upon ip administration. All active compounds were tested for possible oral activity in CAR. Biological results for both synthesized compounds and various standards are shown in Table I.

β-Carbolines containing pyridinylalkyl side chains at the N-2 position lacked affinity for the D_2 receptor sites but

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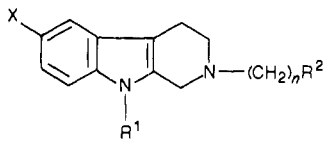
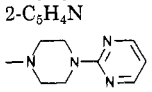
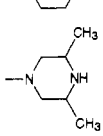
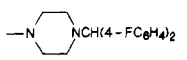
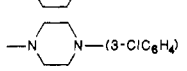
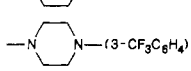
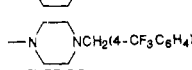
(14) Davidson, J.; Miller, R.; Wingfield, M.; Zung, W.; Dern, A. T. *Psychopharmacol. Bull.* **1982**, *18*, 173.

Table I. Substituted β-Carbolines



compd	X	R¹	n	R²	mp, °C	% yield	formula[c]	inhibn of accumbens D_2 binding (K_i or % inhibn at 1 μM)	inhibn of CAR (shelf-jump) (AB_{50}, mg/kg, ip, 95% CL)
6	H	H	1	4-C_5H_4N[a]	175–178	36	$C_{17}H_{17}N_3$[d]·2HCl	13% (27%)[r]	
7	OCH_3	H	2	2-C_5H_4N	233–236	52.5	$C_{19}H_{21}N_3O$·2HCl[e]	8%	
8	H	H	7	4-C_5H_4N	101–106	18.5	$C_{23}H_{29}N_3$·2HCl[f]	252 nM	
9	OCH_3	H	2	4-C_5H_4N	178–180	49	$C_{19}H_{21}N_3O$·2HCl[f]	53%	
10	H	H	2	2-C_5H_4N	212–215	44	$C_{18}H_{19}N_3$·2HCl[e]	38%	23 (14–49)[w]
11	H	H	3	3-C_5H_4N	257–260	92	$C_{19}H_{21}N_3$[g]·2HCl	2700 nM	21 (15–33)[w]
12	H	H	3	4-C_5H_4N	271–273	40.8	$C_{19}H_{21}N_3$·2HCl[e]	1120 nM	40[x]
13	H	H	4	4-C_5H_4N	259–261	62	$C_{20}H_{23}N_3$·2HCl	680 nM (525 nM)[s]	14 (9–24)[w] 31 (30–33) po
14	Cl	H	2	4-C_5H_4N	271–272	73	$C_{18}H_{18}ClN_3$·2HCl[e]	768 nM	>40[u]
15	F	H	4	4-C_5H_4N	165–168	56.5	$C_{20}H_{22}FN_3$·2HCl	720 nM[t]	>40
16	F	H	2	2-C_5H_4N	234–236	73.9	$C_{15}H_{16}FN_3$[h]·2HCl	75%	40[v]
17	Cl	H	4	4-C_5H_4N	270–272	78	$C_{20}H_{22}ClN_3$·2HCl[e]	51%	>40
18	H	H	1	2-C_9H_6N[b]	253–254	89	$C_{21}H_{19}N_3$·2HCl	7% (7%)[s]	48 (no CL)[w]
19	H	H	2	2-C_9H_6N	152–155	48.9	$C_{22}H_{21}N_3$·2HCl[e]	116 nM (211 nM)[s]	10 (7–18)[w]
20	H	H	4	4-C_9H_6N	180–182	49.5	$C_{24}H_{25}N_3$·2HCl[f]	172 nM	18 (15–22)[w]
21	H	H	4	2-C_9H_6N	210–215	51	$C_{24}H_{25}N_3$·2HCl[i]	83 nM (139 nM)[s]	31 (19–78)[w]
22	Cl	H	2	2-C_9H_6N	235–237	71	$C_{22}H_{20}ClN_3$·2HCl		>40
23	F	H	2	2-C_9H_6N	266–269	58.6	$C_{22}H_{20}FN_3$·2HCl[e]	216 nM	40[v]
24	F	H	4	4-C_9H_6N	195–198	61	$C_{24}H_{24}FN_3$·2HCl[e]	194 nM	>40
25	H	H	1	4-C_9H_6N	184–186	20	$C_{21}H_{19}N_3$·2HCl[f]	26%	>40
26	OCH_3	H	1	2,6-$(OCH_3)_2C_6H_3$	248–250	62	$C_{21}H_{24}N_2O_3$·HCl	15% (27%)[r]	
27	H	H	1	2,6-$(OCH_3)_2C_6H_3$	142–145	68	$C_{20}H_{22}N_2O_2$[j]·HCl	15% (27%)[r]	
28	H	H	3	$CH(4\text{-}F\text{-}C_6H_4)_2$	137–141	59	$C_{27}H_{26}F_2N_2$·HCl	145 nM	>40
29	H	$(CH_2)_3N(CH_3)_2$	3	4-C_5H_4N	153–155	72	$C_{24}H_{32}N_4$[k]·3HCl	0%	>40
30	H	$(CH_2)_3$-c-$N(CH_2)_5$	3	3-C_5H_4N	98–103	63	$C_{27}H_{36}N_4$·3HCl[l]	26%[t]	>40
31	H	$(CH_2)_3$-c-$N(CH_2)_5$	3	4-C_5H_4N	128–130	71	$C_{27}H_{36}N_4$·3HCl[l]	22%[t]	>40
32	H	$(CH_2)_3$-c-$N(CH_2)_2N(3\text{-}ClC_6H_4)$	2	2-C_5H_4N	192–194	48	$C_{31}H_{36}ClN_5$·3HCl[n]	213 nM	>40
33	H	$(CH_2)_3N(CH_3)_2$	3	3-C_5H_4N	93–95	69	$C_{24}H_{32}N_4$·3HCl[i]	17%[t]	>40
34	H	$(CH_2)_3CO(4\text{-}FC_6H_4)$	2	2-C_5H_4N	117–120	415	$C_{28}H_{28}FN_3O$·2HCl[e]	118 nM	>40
35	H	$(CH_2)_3$-c-$N(CH_2)_2C(OH)(4\text{-}ClC_6H_4)$	2	2-C_5H_4N	150–153	39	$C_{32}H_{37}ClN_4O$·3HCl[l]	91 nM	>40
36	H	$(CH_2)_3$-c-$N(CH_2)_2N(3\text{-}ClC_6H_4)$	3	3-C_5H_4N	106–108	36	$C_{32}H_{38}ClN_5$·3HCl[n]	306 nM	>40
37	H	$(CH_2)_3$-c-$N(CH_2)_5$	2	2-C_5H_4N	234–236	51	$C_{26}H_{34}N_4$·3HCl[e]	9%[t]	>40
38	H	$CH_2(C_6H_5)$	2	2-C_5H_4N	278–280	80	$C_{25}H_{25}N_3$·2HCl	185 nM	>40
39	H	H	3		121–123	63	$C_{22}H_{28}N_6$	574 nM	35 (33–37)
40	H	H	3		137–138	48.5	$C_{20}H_{30}N_4$[f]	38%	>40
41	H	H	3		218–220	59	$C_{31}H_{34}F_2N_4$[o]·3HCl[n]	143 nM	>40
42	H	H	3		268–270	63	$C_{24}H_{29}ClN_4$·2HCl[e]		>40
43	H	H	3		270–273	70	$C_{25}H_{29}F_3N_4$·2HCl[e]	407 nM	>40
44	H	H	3		243–245	73.5	$C_{26}H_{31}F_3N_4$·3HCl[f]	1200 nM	>40
45	H	H	0	4-C_9H_6N	248–250	92	$C_{21}H_{17}N_3O$·HCl	7%	>40
46	H	H	0	1-isoquinolinoyl	227–230	70	$C_{21}H_{17}N_3O$[t]·HCl	6%	>40
47	H	H	1	2-furyl	142–145		$C_{16}H_{16}N_2O$·HCl	7%	
48	H	H	1	2-(1-Me)benzimidazolyl	137–141		$C_{20}H_{20}N_4$·2HCl	6%	
49	H	H	2	2-pyrazinyl	266–269		$C_{17}H_{18}N_4$·2HCl	13%	
rimcazole (BW234U)								$>10^{-5}$ M[23]	39 (30–62)
chlorpromazine								10 nM[24]	4 (2–7), 3 (2–3) po
clozapine								34 nM	7 (6.5–7.5), 11 (8–17) po
haloperidol								4 nM	0.2 (0.12–0.33), 0.2 (0.1–3.5) po

Footnotes to Table I

[a] 4-C_5H_4N represents 4-pyridinyl. [b] 2-C_9H_6N represents 2-quinolinyl. [c] All compounds had elemental analyses (C, H, N) within ±0.4% of the theoretical values. [d] H: calcd, 12.11; found, 11.71. [e] Hemihydrate. [f] Hydrate. [g] C: calcd, 62.63; found, 62.17. [h] C: calcd,58.68; found, 58.17. [i] Sesquihydrate. [j] N: calcd, 7.81; found, 7.39. [k] C: calcd, 56.19; found, 56.60. [l] Trihydrate. [m] H: calcd, 7.76; found, 8.31. [n] Dihydrate. [o] H: calcd, 6.30; found, 5.81. [p] N: calcd, 11.55; found, 11.08. [q] C, N: calcd, C, 66.50, N, 9.70; found, C, 66.03, N, 9.10. [r] Striatum at 10 μM. [s] Striatum. [t] Accumbens at 10 μM. [u] >40 indicates insignificant activity. [v] Active at single dose. [w] Discrete trial CAR. [x] Calf striatum.

were active in the CAR screen. Compounds **10**, **11**, and **13** were the most active compounds of this series, blocking conditioned avoidance responding in rats with AB_{50}'s of 23, 21, and 14 mg/kg, respectively. Only compound **13** showed oral activity in the CAR screen with an AB_{50} of 31 mg/kg. While most compounds showed no significant antagonism of apomorphine-induced stereotyped behavior at doses up to 127 mg/kg, compounds **13** and **16** were active in that test, blocking APO-induced stereotyped behavior in mice with ED_{50}'s of 13 (9–18) and 25 (14–43) mg/kg, respectively. For comparison, haloperidol, chlorpromazine, and clozapine blocked apomorphine-induced stereotyped behavior with ED_{50}'s of 1, 9, and 30 mg/kg, respectively.

Incorporation of quinolinylalkyl moieties at the 2-position resulted in several derivatives that were active in the CAR screen. Compounds **18–21** were the most potent members of this series, blocking CAR in rats with AB_{50}'s of 48, 10, 18, and 31 mg/kg, respectively. They showed only moderate activity at the D_2 receptor sites with the exception of compound **21**, which inhibited the D_2 receptor binding with a K_i of 83 nM. These analogues were also inactive in blocking APO-stereotyped behavior except for compounds **20** and **21** (ED_{50}'s of 28 and 25 mg/kg, respectively).

Attempts to induce oral activity in these series by incorporating halogen at the C-7 or (alkylamino)alkyl substituents at the N-9 of the β-carboline were unsuccessful, resulting in several analogues such as compounds **14–17** and **29–38** that were either inactive or very weak in the CAR testings.

Compound **39**, which contains the pyrimidinylpiperazine moiety known to be present in several CNS drugs,[15] was the only active member of the piperazinylalkyl derivatives, blocking CAR in rats with an AB_{50} of 35 mg/kg. It showed weak affinity for the D_2 receptor (K_i = 574 nM) and did not block APO-stereotyped behavior at doses up to 127 mg/kg.

In summary, we have synthesized several β-carbolines that possess interesting preclinical antipsychotic activity with low extrapyrimidal side effect liabilities. Compounds **10**, **11**, **13**, and **19** are the most potent analogues in blocking CAR and lacked activity in antagonizing APO-induced stereotyped behavior.

Due to the lack of oral activity, further development is not anticipated; however, we are using information gained in this study to develop more effective, orally active compounds with a similar antipsychotic profile.

Experimental Section

Melting points were determined on a Thomas-Hoover apparatus and are uncorrected. Spectra were recorded for all compounds and were consistent with assigned structures. NMR spectra were recorded on Varian XL-300 and XL-100 instruments. Mass spectra were recorded with a Kratos MS-25 instrument. IR spectra were recorded with a Perkin-Elmer 299 infrared spectrophotometer. Elemental analyses were performed with a Perkin-Elmer Model 240 elemental analyzer by the Analytical Section of our laboratories and all analyses were within ±0.4% of theoretical values.

Typical Procedure for the Preparation of Pyridinylalkyl Halides. 4-Pyridinylbutyl Bromide Hydrobromide (4). A modified procedure of Mioque and Gautier[17] was used in which 4-picoline (19 g, 0.20 mol) was added dropwise to a solution of sodium (4.6 g, 0.20 mol) in 200 mL of liquid ammonia and stirring was continued for 1 h at −78 °C.

3-Phenoxypropyl bromide (43 g, 0.20 mol) was added dropwise and stirring was continued overnight at room temperature. Ethanol (20 mL) and water (200 mL) were added, and the solution was extracted with ether (3 × 350 mL). The ethereal solution was washed with water, dried (anhydrous Na_2SO_4), and evaporated under reduced pressure. The residue was distilled in vacuo to give 30 g (66% yield) 4-(4-phenoxybutyl)pyridine (bp 160–165 °C (0.01 mm)). 4-(4-Phenoxybutyl)pyridine (30 g, 0.13 mol) was refluxed with 48% HBr (250 mL) overnight. The solution was extracted with ether (2 × 200 mL). The ethereal layer was discarded and the aqueous layer was evaporated to dryness. The residue was recrystallized from ethanol to give 20 g (52% yield) of 4-pyridinylbutyl bromide hydrobromide as a white solid; mp 145–147 °C (lit.[16] mp 120–123 °C). Anal. ($C_9H_{12}BrN$·HBr).

General Procedure for the Preparation of Compounds of Scheme I. 2,3,4,9-Tetrahydro-2-(4-pyridinylmethyl)-1*H*-pyrido[3,4-*b*]indole (6). To a stirred suspension of 2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole (**5**)[13] (1.3 g, 0.008 mol), freshly baked anhydrous potassium carbonate (3.3 g, 0.024 mol), and cesium carbonate (0.32 g, 0.001 mol) in 70 mL of dimethylformamide was added 4-picolyl chloride hydrochloride (1.65 g, 0.001 mol). The reaction mixture was stirred for 1 h and to this mixture was added potassium iodide (0.39 g, 0.0024 mol). The reaction mixture was stirred at room temperature overnight, the solvent was removed under vacuum, and the solid cake was suspended in 100 mL of water. The aqueous suspension was extracted with chloroform (3 × 100 mL), and the chloroform layer was dried over anhydrous sodium sulfate and was concentrated under reduced pressure. The precipitated solid was separated by filtration, dissolved in ethanol, and saturated with dry hydrogen chloride. The solution was concentrated and cooled. The separated solid was filtered and recrystallized from an absolute ethanol–ether (1:1) mixture to afford 0.9 g (36% yield) of the title compound as the hydrochloride salt, mp 175–178 °C. Anal. ($C_{17}H_{17}N_3$·2HCl·0.5H_2O). Compounds **7–18** and compounds **20–28** were prepared according to the procedure described for compound **6** via the reaction of the β-carboline **5** with the appropriately substituted pyridinylalkyl halide, the appropriately substituted quinolinylalkyl halide, 2,6-methoxybenzyl chloride, or 3-[bis(*p*-fluorophenyl)-methyl]propyl bromide, respectively (Table I).

1,2,3,9-Tetrahydro-*N*,*N*-dimethyl-2-[3-(4-pyridinyl)-propyl]-1*H*-pyrido[3,4-*b*]indole-9-propanamine (29). To a stirred solution of **13** (2.90 g, 0.01 mol) in 70 mL of DMF was added 2.4 g (0.10 mol) of sodium hydride and stirring was continued for 0.5 h. To the clear solution was added (dimethylamino)propyl chloride hydrochloride (1.58 g, 0.10 mol) and stirring was continued for 16 h. DMF was evaporated in vacuo and the residue was extracted with methylene chloride (2 × 200 mL). The methylene chloride layer was evaporated and the residue was converted to the hydrochloride salt; mp 153–155 °C. Anal. ($C_{24}H_{36}N_4$·3HCl·1.5H_2O).

Compounds **30–38** were prepared in a like manner as above via the reaction of compounds **7–17** with the appropriate alkyl halide (Table I).

General Procedure for the Preparation of Compounds of Scheme II. 2,3,4,9-Tetrahydro-2-[3-[4-(2-pyrimidinyl)-1-

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piperazinyl]propyl]-1*H*-pyrido[3,4-*b*]indole (39). To a stirred solution of 2,3,4,9-tetrahydropyrido[3,4-*b*]indole (**5**) (1.72 g, 0.01 mol) in 50 mL of DMF was added 0.3 g (0.01 mol) of sodium hydride. The reaction mixture was stirred for 0.5 h and to the stirred solution was added 1-bromo-3-chloropropane (2.3 g, 0.015 mol). The reaction mixture was stirred for 24 h. DMF was removed under reduced pressure and the residue was extracted with 3 × 200 mL of methylene chloride. The methylene chloride extracts were collected, washed with water, and dried over anhydrous sodium sulfate. Evaporation of the methylene chloride afforded 2 g (83% yield) of 2,3,4,9-tetrahydro-2-(3-chloropropyl)-1*H*-pyrido[3,4-*b*]indole as a thick red oil. This chloropropyl intermediate was dissolved in 50 mL of DMF, 2 mL of triethylamine and 1.3 g (0.008 mol) of 1-(2-pyrimidyl)piperazine were added with stirring, and the reaction mixture was stirred for 48 h. DMF was removed under reduced pressure and the residue was extracted with 2 × 200 mL of methylene chloride. The methylene chloride extracts were collected and dried over anhydrous sodium sulfate, and the solvent was removed under reduced pressure. The separated oil was dissolved in ethanol and was converted to the hydrochloride salt; mp 238–240 °C. Anal. ($C_{22}H_{28}N_6 \cdot 3HCl \cdot 1.5H_2O$). Compounds **40–44** were prepared following the procedure described above for the preparation of compound **41**, via the reaction of **5** with 1-bromo-3-chloropropane and the appropriately substituted arylpiperazine (Table I).

2,3,4,9-Tetrahydro-2-[2-(2-quinolinyl)ethyl]-1*H*-pyrido[3,4-*b*]indole (19). A mixture of 2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole (**5**) (1.72 g, 0.01 mol), 2-vinylquinoline (1.5 g, 0.01 mol), and 2 mL of glacial acetic acid was refluxed in 25 mL of ethanol for 24 h. The solvent was removed in vacuo and the residue was dissolved in 4 × 200 mL of methylene chloride, washed with water, and dried over anhydrous sodium sulfate. The methylene chloride was filtered and evaporated under reduced pressure. The separated solid was recrystallized from ethanol to afford 1.6 g (48.9% yield) of the title compound, mp 169–179 °C. Anal. ($C_{22}H_{21}N_3 \cdot 2HCl \cdot 0.5H_2O$).

Compounds **7, 9, 10, 14, 16, 22, 23, and 49** were prepared following the above procedure for preparation of **19** with the exception that the appropriately substituted 2-vinylpyridine, vinylquinoline, or 2-vinylpyrazine was used.

2,3,4,9-Tetrahydro-2-(4-quinolinylcarbonyl)-1*H*-pyrido[3,4-*b*]indole (45). To a vigorously stirred solution of **5** (5.16 g, 0.003 mol) and triethylamine (9 mL, 0.008 mol) in 100 mL of acetone–methylene chloride (1:1) mixture was added dropwise 9 g (0.039 mol) of quinoline-4-carbonyl chloride in acetone–methylene chloride (1:1) mixture. The reaction mixture was stirred at room temperature for 48 h. The solvent was evaporated and the residue was extracted with methylene chloride (2 × 100 mL), washed with water, dried (anhydrous Na_2SO_4), and evaporated. It afforded 10.0 g of the crude title compound, which was purified by recrystallization from ether/methylene chloride (1:1) mixture and was converted to the hydrochloride salt, mp 248–250 °C. Anal. ($C_{21}H_{17}N_3O \cdot HCl$).

2,3,4,9-Tetrahydro-2-(4-quinolinylmethyl)-1*H*-pyrido[3,4-*b*]indole (25). To lithium aluminum hydride (3.8 g, 0.01 mol) in 250 mL of tetrahydrofuran at room temperature was added dropwise compound **45** (6 g) in THF. The mixture was then heated under reflux overnight. After workup and purification by HPLC, 0.8 g of the title compound was obtained and was converted to the hydrochloride salt, mp 184–186 °C. Anal. ($C_{21}H_{19}N_3 \cdot 2HCl$).

Antagonism of Apomorphine-Induced Stereotyped Behavior. Male mice (20–25 g, CF-1, Charles River) were prescreened 1 week prior to testing for a positive stereotyped response to apomorphine (10 mg/kg, sc). Test compounds, suspended or solubilized in 0.25% Tween 80 in water, were administered ip at several dose levels (4, 12, 40, and 127 mg/kg) to male mice (six/dose level). A control group, run simultaneously with drug groups, received equal volumes of vehicle. Thirty minutes later, drug-treated and control mice were challenged with 10 mg/kg apomorphine sc. Five minutes after the injection, the rearing–head–bobbing–licking syndrome induced by apomorphine was recorded as present or absent for each animal. Readings were repeated every 5 min during a 30-min test session. The number of positive or negative 5-min intervals during which apomorphine-induced stereotyped behavior was present or absent was recorded. ED_{50} values (with 95% confidence intervals) were calculated for inhibition of apomorphine-induced stereotyped behavior by a simple linear regression analysis with inverse prediction.

Shelf-Jump Conditioned Avoidance. Shelf-jump conditioned avoidance tests were conducted according to the methods of Herman et al.[18] Previously trained male rats (CD, Charles River), maintained at approximately 400–450 g body weight, were placed in Plexiglas experimental chambers divided into two sections; a main chamber ($10^1/_2$ in. × $6^3/_4$ in. × $11^7/_8$ in. high) and an elevated chamber or shelf ($5^7/_8$ in. × $6^7/_8$ in. × $5^3/_4$ in.). A moveable wall, controlled by a motor, determined whether the rat had access to the shelf at any time during the experiment. The experimental chamber also contained a house light and sonalert. A steel grid floor in the main chamber was wired for presentation of electric shock. Each trial consisted of a 15-s warning tone (conditioned stimulus), continuing for an additional 15 s accompanied by electric shock (unconditioned stimulus). A response (jumping onto a shelf) during the initial 15-s warning tone was considered an avoidance response, while a response occurring during shock delivery was considered an escape response. Trials were presented on a fixed interval schedule of 1 min. The session consisted of 36 trials. Animals were run twice weekly with control sessions always preceding a drug run and with at least 1 day intervening. Compounds were administered ip or po at a pretreatment time of 30 min to a minimum of five rats at a dose level of 20 or 40 mg/kg. The following experimental parameters were recorded by computer: (1) the number of avoidance responses, (2) the number of escape responses, and (3) the number of trials in which no response occurred. These data were used to calculate the percent difference from control values previously determined and were presented for visual comparison via a line graph.

Discrete Trial Conditioned Avoidance. Conditioned avoidance tests were conducted in male CD rats (Charles River) maintained at approximately 400–450 g body weight. Rats trained previously were placed in Plexiglas experimental chambers equipped with a response lever, house light, and sonalert. A steel grid floor was wired for presentation of electric shock. Each trial consisted of a 15-s warning tone (conditioned stimulus), continuing for an additional 15 s accompanied by electric shock (unconditioned stimulus). The rat could terminate a trial at any point by depressing the response lever. A response during the initial 15-s warning tone ended the trial before shock delivery and was considered an avoidance response, while a response occurring during shock delivery was an escape response. Trials were presented on a variable interval schedule of 2 min. The session consisted of 60 trials. Animals were run two to three times weekly with control sessions always preceding a drug run and with at least 1 day intervening. Compounds were administered ip at a pretreatment time of 30 min to a minimum of five rats at each dose level (20 or 40 mg/kg) or over a range of doses. The following experimental parameters were recorded by computer: (1) the number of intertrial interval responses, (2) the number of avoidance responses, (3) the number of escape responses, and 4) the number of trials in which no response occurred. These data were used to calculate the percent difference from control values previously determined. Response counts were summed over all subjects at a given dose. The number of trials in which rats failed to exhibit an avoidance response (Avoidance Block, AB) was determined at each dose. This number was expressed as a percentage of the total trials. Control performance was taken as 100% for avoidance and escape responding and the dose calculated to produce a 50% block in avoidance responding (AB_{50}) was obtained from a dose–effect regression line fitted by the method of least squares.

Measurement of Dopamine-2 Receptor Affinity in Vitro. Dopamine-2 receptor affinity was measured in limbic rat brain tissue by using a modification of the methods of Fields[19] and Bennett.[20] Several rats were decapitated and the brains were

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rapidly removed. Limbic brain tissue (nucleus accumbens, septal area, olfactory tubercle) was dissected and homogenized on ice in 9 volumes of buffer (50 mM Tris·HCl, 120 mM NaCl, 5 mM KCl, 1 mM $CaCl_2$, 0.1% L-ascorbic acid, 10 μM pargyline hydrochloride, pH 7.1) with a Polytron homogenizer. The homogenate was then diluted 4-fold with buffer and centrifuged at 30000*g* for 20 min, and the supernatant was discarded. The pellet was resuspended in the same volume of buffer and recentrifuged as before, again discarding the supernatant. This pellet was resuspended in the same volume of buffer used in the homogenization, and the protein content of the preparation was assayed by the Lowry method.[21] The homogenate was stored frozen at −70 °C until use. Thirty microliters of the homogenate (0.2–0.3 mg of protein/sample) was incubated with 0.3 nM [^{3}H]spiroperidol (New England Nuclear) and various concentrations of test drug in a final volume of 1 mL of the above buffer for 10 min in a 37 °C water bath. At the end of the incubation, 3 mL of cold 50 mM Tris·HCl, pH 7.7, were added to each tube, and the contents were rapidly vacuum-filtered through Whatman GF/B glass-fiber filters. The filters were then rapidly washed three times with 3 mL of the same buffer, placed in scintillation vials, and shaken for 15 min with 10 mL of Hydrofluor (National Diagnostics) scintillation cocktail. The vials were then counted in a Packard 460CD scintillation counter. Specific binding was defined as total binding less binding in the presence of 1 μM (+)-butaclamol. Binding in the presence of various concentrations of test drug was expressed as a percent of specific binding when no drug was added. These results were then plotted as logit percent binding vs. log concentration of test drug. Linear regression analysis yielded a straight line with 95% confidence limits from which IC_{50}'s were inversely predicted. K_i's (inhibition constant) for the test drugs were calculated by the formula (Cheng and Prusoff):[22]

$$K_i = \frac{IC_{50}}{1 + ([[^3H]\text{spiroperidol}]/K_D)}$$

where K_D = 0.3 nM for spiroperidol binding.

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Registry No. **2** (X = R = H, R^2 = Cl, *n* = 3), 107890-30-2; **3** (*n* = 4, *para*), 107890-29-9; **4** (*n* = 4, *para*), 107266-09-1; **5**, 16502-01-5; **6**, 107889-86-1; **7**, 107889-87-2; **8**, 107889-88-3; **9**, 107889-89-4; **10**, 107889-90-7; **11**, 107889-91-8; **12**, 107889-92-9; **13**, 107889-93-0; **14**, 107889-94-1; **15**, 107889-95-2; **16**, 107889-96-3; **17**, 107889-97-4; **18**, 107889-98-5; **19**, 107889-99-6; **20**, 107890-00-6; **21**, 107890-01-7; **22**, 107890-02-8; **23**, 107890-03-9; **24**, 107890-04-0; **25**, 107890-05-1; **26**, 107890-06-2; **27**, 107890-07-3; **28**, 107890-08-4; **29**, 107890-09-5; **30**, 107913-43-9; **31**, 107890-10-8; **32**, 107890-11-9; **33**, 107890-12-0; **34**, 107890-13-1; **35**, 107890-14-2; **36**, 107890-15-3; **37**, 107890-16-4; **38**, 107890-17-5; **39**, 107890-18-6; **39**·3HCl, 107890-31-3; **40**, 107890-19-7; **41**, 107890-20-0; **42**, 107890-21-1; **43**, 107890-22-2; **44**, 107890-23-3; **45**, 107890-24-4; **46**, 107890-25-5; **47**, 107890-26-6; **48**, 107890-27-7; **49**, 107890-28-8; $Br(CH_2)_3OC_6H_5$, 588-63-6; $Br(CH_2)_3CH(4\text{-}C_6H_4F)_2$, 57668-61-8; $(CH_3)_2N(CH_2)_3$-Cl·HCl, 5407-04-5; 4-picoline, 108-89-4; 4-picolyl chloride hydrochloride, 1822-51-1; 2,6-dimethoxybenzyl chloride, 71819-90-4; 1-bromo-3-chloropropane, 109-70-6; 1-(2-pyrimidyl)piperazine, 20980-22-7; 2,6-dimethylpiperazine, 108-49-6; 1-(bis(4-fluorophenyl)methyl)piperazine, 27469-60-9; 1-(chlorophenyl)piperazine, 6640-24-0; 1-(3-(trifluoromethane)phenyl)piperazine, 15532-75-9; 1-((4-(trifluoromethane)phenyl)methane)piperazine, 107890-32-4; 2-vinylquinoline, 772-03-2; quinoline-4-carbonyl chloride, 50821-72-2.

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2-Amino- and 2-Guanidino-1,2,3,4-tetrahydro-1,4-epoxynaphthalenes as Conformationally Defined Analogues of α-Adrenergic Agents

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The *exo*- and *endo*-2-amino-5,8-dimethoxy-1,2,3,4-tetrahydro-1,4-epoxynaphthalenes (**3b** and **4b**, respectively) were prepared and evaluated as conformationally defined analogues of the α_1-agonist methoxamine. Only compound **3b** exhibited significant α_1-agonist activity in the field stimulated rat vas deferens assay. Since **3b** closely approximates the antiperiplanar form of (1*R*,2*S*)-(−)-*erythro*-methoxamine, the results suggest that methoxamine interacts with the α_1-adrenoceptor in the trans extended form. The *exo*-guanidino derivative **5** was found to be a partial α_1-agonist. Among the *exo*- and *endo*-2-amino-1,2,3,4-tetrahydro-1,4-epoxynaphthalenes (**3a** and **4a**, respectively) prepared as rigid analogues of norephedrine, compound **3a** possessed agonist activity at both α_1- and α_2-adrenoceptors, whereas **4a** was inactive at either receptor.

During the past two decades a number of studies have been reported that have sought to determine the steric requirements for agonists of adrenoceptors through the pharmacological evaluation of conformationally defined analogues of adrenergic agents. Erhardt et al.[1] prepared and evaluated the cis and trans isomers of 2-(3,4-dihydroxyphenyl)cyclopropylamine in rabbit aorta and found the trans isomer to be 5 times more potent than the cis analogue. Since the trans isomer more closely approximates the fully extended antiperiplanar conformation of dopamine in which the amine and aromatic ring are at a dihedral angle of 180° to one another, the results strongly

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