Derivatives of 11-(1-Piperazinyl)-5*H*-pyrrolo[2,1-*c*][1,4]benzodiazepine as Central Nervous System Agents

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Four 11-(1-piperazinyl)-5*H*-pyrrolo[2,1-*c*][1,4]benzodiazepines were prepared and evaluated as central nervous system agents. All were active psychotropic agents as determined by animal screening tests. The most interesting compound, 11-(1-piperazinyl)-5*H*-pyrrolo[2,1-*c*][1,4]benzodiazepine, showed dual activity as an antidepressant against tetrabenazine depression and as a neuroleptic as measured by protection vs. amphetamine lethality in grouped mice.

Although tricyclic ring systems with piperazinyl side chains attached to the central ring are well-known as psychotropic agents,[1] such derivatives of the pyrrolo[2,1-*c*][1,4]benzodiazepine ring system, which has a nitrogen atom common to the five- and seven-membered rings, have not been reported.

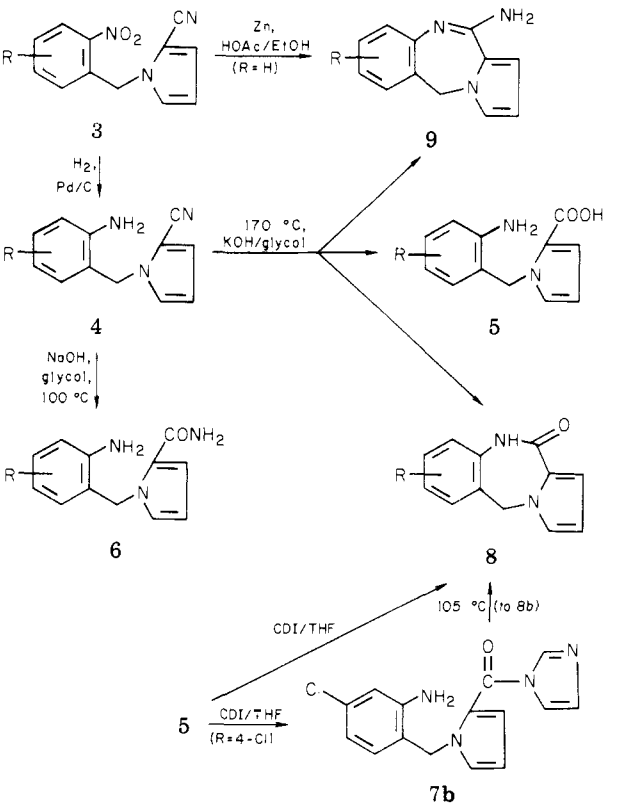
Artico[2] has described the preparation of 5,10-dihydro-5*H*-pyrrolo[2,1-*c*][1,4]benzodiazepin-11-one (**8a**) by a five-step procedure from 2-nitrobenzyl bromide and 2-pyrrolecarboxaldehyde. We have followed this procedure, with variations where desirable, to prepare **8a** and the corresponding 7-chloro (**8c**) and 8-chloro (**8b**) derivatives (Scheme I and Tables I and II). In our attempts to follow this procedure for the one-step conversion of 1-(2-aminobenzyl)-2-pyrrolecarbonitrile (**4a**) to **8a** by heating at 170 °C in KOH/glycol, we obtained 1-(2-aminobenzyl)-2-pyrrolecarboxylic acid (**5a**) as the major product, and the lactam (**8a**) and amidine (**9a**) were isolated in lower yield. **5a** could then be converted to **8a** by treatment with *N*,*N*′-carbonyldiimidazole (CDI). When this reaction was run with 1-(2-amino-4-chlorobenzyl)-2-pyrrolecarboxlic acid (**5b**), the relatively stable amide intermediate **7b** was isolated and converted to **8b** by heating at 105 °C. The amide **6a** could be isolated in good yield by heating **4a** with NaOH/glycol at 100 °C, and **6a** was converted to a mixture of **8a** and **9a** by heating in KOH/glycol at 170 °C. A direct synthesis of **9a** was accomplished from **3a** by simultaneous reduction of the nitro group and Pinner cyclization using zinc dust and ethanol (ca. 40–50%). Lactams **8** and 11-amino derivatives (**9**) were then key intermediates for introduction of the piperazinyl side chain.

The 11-(4-methyl-1-piperazinyl)-5*H*-pyrrolo[2,1-*c*][1,4]benzodiazepines (**10**) were prepared (Scheme II) from **8** by treating with $TiCl_4$ and methylpiperazine by the method of Fryer et al.[3] We were unable to prepare **13** by this method, but were successful in preparing this compound via the thiolactam (**11**) and the 11-(methylthio) derivative (**12**); **13** could also be prepared by heating **9** with piperazine, in which reaction the side chain was introduced by transamination.

Pharmacology. Basic CNS screening procedures used for these compounds include antidepressant and/or neuroleptic testing by antagonism of *d*-amphetamine lethality in grouped mice (GAL), reduction of spontaneous motor activity in rats (MDD), and antidepressant testing by inhibiting the depression produced by tetrabenazine (TBZ) (see Experimental Section). The results are summarized in Table III.

The methylpiperazinyl derivative **10a** displayed the profile of a moderately potent neuroleptic agent, which had some similarities to clozapine.[1] It did not have an antidepressant component. In subsequent secondary testing, like clozapine, it did not antagonize apomorphine-induced gnawing in rats[4a] at doses up to 50 mg/kg. However, **10a** displayed a chlorpromazine-like profile (albeit ca. one-half the potency) when measured by catalepsy in rats.[4b]

Scheme I



Chloro substitution in the 7 position (**10c**) markedly reduced the neuroleptic potency, and the 8-chloro derivative (**10b**), unlike clozapine, was somewhat less active than the 8-H counterpart (**10a**).

The demethyl derivative **13** showed neuroleptic and antidepressant activity in approximately similar dose ranges. It was approximately equipotent with imipramine as an antagonist of tetrabenazine depression.

Overall, the present piperazinylpyrrolobenzodiazepines establish another new piperazinyl tricyclic system with mixed CNS actions,[1,4b] including neuroleptic and antidepressant activities. A profile for parkinsonian effects intermediate between chlorpromazine and clozapine[4b] was also suggested for **10a** in preliminary secondary testing.

(1) J. Schmutz, *Arzneim.-Forsch.*, **25**, 712 (1975).
(2) (a) M. Artico, G. deMartino, G. Filacchioni, and R. Giuliano, *Farmaco, Ed. Sci.*, **24**, 276 (1969); (b) M. Artico, G. deMartino, R. Giuliano, S. Massa, and G. C. Pometta, *ibid.*, **24**, 980 (1969).
(3) R. I. Fryer, J. V. Earley, G. F. Field, W. Fally, and R. H. Sternbach, *J. Org. Chem.*, **34**, 1143 (1969).
(4) (a) E. N. Greenblatt, A. S. Lippa, and A. C. Osterberg, *Arch. Int. Pharmacodyn.*, **233**, 107 (1978); (b) J. B. Press, C. M. Hofmann, N. H. Eudy, W. J. Fanshawe, I. P. Day, E. N. Greenblatt, and S. R. Safir, *J. Med. Chem.*, **22**, 725 (1979).

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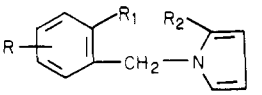
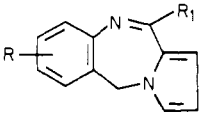
Table I. Derivatives of 1-Benzylpyrrole



no.	R	R_1	R_2	procedure	yield, %	mp, °C	formula
1a	H	NO_2	CHO	A	76	133-136[a]	$C_{12}H_{10}N_2O_3$
1b	4-Cl	NO_2	CHO	A	25	117-119[b]	$C_{12}H_9ClN_2O_3$
1c	5-Cl	NO_2	CHO	A	28	137-140	$C_{12}H_9ClN_2O_3$
2a	H	NO_2	CH=NOH	B	74	135-137[c]	$C_{12}H_{11}N_3O_3$
2b	4-Cl	NO_2	CH=NOH	B	93	113-115[d]	$C_{12}H_{10}ClN_3O_3$
2c	5-Cl	NO_2	CH=NOH	B	90	122-125	$C_{12}H_{10}ClN_3O_3$
3a	H	NO_2	CN	C	80	95-96[e]	$C_{12}H_9N_3O_2$
3b	4-Cl	NO_2	CN	C	83	93-95	$C_{12}H_8ClN_3O_2$
3c	5-Cl	NO_2	CN	C	85	134-136	$C_{12}H_8ClN_3O_2$
4a	H	NH_2	CN	D	95	60-61[f]	$C_{12}H_{11}N_3$
4b	4-Cl	NH_2	CN	D	66	77-79	$C_{12}H_{10}ClN_3$
4c	5-Cl	NH_2	CN	D	71	130-132	$C_{12}H_{10}ClN_3$
5a	H	NH_2	COOH	E	50	141-142	$C_{12}H_{12}N_2O_2$
5b	4-Cl	NH_2	COOH	E	50	136 dec	$C_{12}H_{11}ClN_2O_2$
5c	5-Cl	NH_2	COOH	E	57	142-145	$C_{12}H_{11}ClN_2O_2$[g]
6a	H	NH_2	$CONH_2$	F	49	123-125[h]	$C_{12}H_{13}N_3O$
7b	4-Cl	NH_2		G[i]		~100	$C_{15}H_{13}ClN_4O$[j]

[a] Lit. (ref 2a) mp 136–138 °C. [b] Sample from chromatography. Mixtures of polymorphs, mp 104–119 °C, were generally isolated. [c] Lit. (ref 2a) mp 130–132 °C. [d] Mixture of syn and anti forms, mp as low as 107 °C. [e] Lit. (ref 2a) mp 92–93 °C. [f] Lit. (ref 2b) mp 59–60 °C. [g] Anal. ($C_{12}H_{11}ClN_2O$) C, H, N; Cl: calcd, 14.15; found, 13.53. [h] Lit. (ref 2b) mp 116–117 °C. [i] Byproduct from the preparation of 8a. [j] Anal. ($C_{15}H_{13}ClN_4O$) H, Cl, N; C: calcd, 59.91; found, 59.40.

Table II. Pyrrolo[2,1-*c*][1,4]benzodiazepines



no.	R	R_1	procedure	yield, %	mp, °C	formula
8a	H	OH[a]	E	<20[b]	223-224[d]	$C_{12}H_{10}N_2O$
			G	68[c]		
8b	8-Cl	OH[a]	G	59	238-241	$C_{12}H_9ClN_2O$
8c	7-Cl	OH[a]	E	11[c]	233-235	$C_{12}H_9ClN_2O$
			G	53[e]		
9a	H	NH_2	E	<10[e]	179-181	$C_{12}H_{11}N_3$
			H	46		
9b	8-Cl	NH_2	E	<24[f]	245-248[g]	$C_{12}H_{10}ClN_3$
9c	7-Cl	NH_2	E	10[e]	206-208	$C_{12}H_{10}ClN_3$
10a	H	c-$N(CH_2CH_2)_2N$-CH_3	I	28, 42	138-140	$C_{17}H_{20}N_4$
10b	8-Cl	c-$N(CH_2CH_2)_2N$-CH_3	I	47[i]	177-179	$C_{17}H_{19}ClN_4$
10c	7-Cl	c-$N(CH_2CH_2)_2N$-CH_3	I	43[h]	186-188	$C_{17}H_{19}ClN_4$
11	H	SH[j]	K	65	228-231	$C_{12}H_{10}N_2S$
12	H	SCH_3	L	90	152-154	$C_{13}H_{12}N_2S$
13	H	c-$N(CH_2CH_2)_2NH$	J, M	52	148-150	$C_{16}H_{18}N_4$

[a] Actual tautomer is -NHC(=O)-. [b] Product contains a small amount of 9a, best removed by chromatography. [c] Impure yield. [d] Lit (ref 2b) mp 223–224 °C. [e] Purified by partition chromatography. [f] Contained 10–20% of 8c. [g] Recrystallized from EtOH. [h] Also 31% recovery of 8b. [i] Also 20% recovery of 8c. [j] Actual tautomer is -NHC(=S).

Experimental Section

Chemistry. All melting points were taken using a Mel-Temp apparatus with open capillaries and are uncorrected. Unless otherwise noted, microanalyses of all compounds were within ±0.4% of the theoretical values for C, H, N, Cl, and S (if present). Spectra were consistent with the assigned structures, and in particular IR, UV, and NMR data were identical with or consistent with the spectral data reported by Artico et al.[2] Selected NMR data reported herein were measured on a Varian EM 360 spectrometer, and chemical shifts are parts per million (δ) downfield from tetramethylsilane internal standard. TLC was performed on Eastman silica gel sheets developed with acetone–hexane (2:3).

The preparation of the compounds is described in the following paragraphs using general procedures where possible. Physical properties and important variations from these procedures are recorded in Tables I and II.

General Procedure A. 1-(4-Chloro-2-nitrobenzyl)-2-pyrrolecarboxaldehyde (1b). A mixture of 10.0 g of 50% NaH, 10.0 g (0.2 mol) of pyrrole-2-carboxaldehyde, and 200 mL of DMF was stirred under argon with cooling as required to keep the temperature at 20–30 °C, and 39.5 g (0.19 mol) of α,4-dichloro-2-nitrotoluene was added in portions with cooling over a 10-min period. The reaction mixture was stirred at room temperature for 2–5 h and then diluted with about 400 mL of crushed ice. The crystalline product was filtered off and washed well with H_2O and two 10-mL portions of Et_2O and air dried. The crude yield was 45 g of tan solid. The crude cake was boiled with 500 mL of Et_2O, and the insoluble orange solid was collected; this was 4,4′-dichloro-2,2′-dinitrostilbene (14):[5] yield 12.0 g, pure; mp 253–256 °C. The Et_2O mother liquor was concentrated to a low volume

(5) G. Gansser and A. Yanagida, *Bull. Soc. Chim. Fr.*, 1804 (1973).

Scheme II

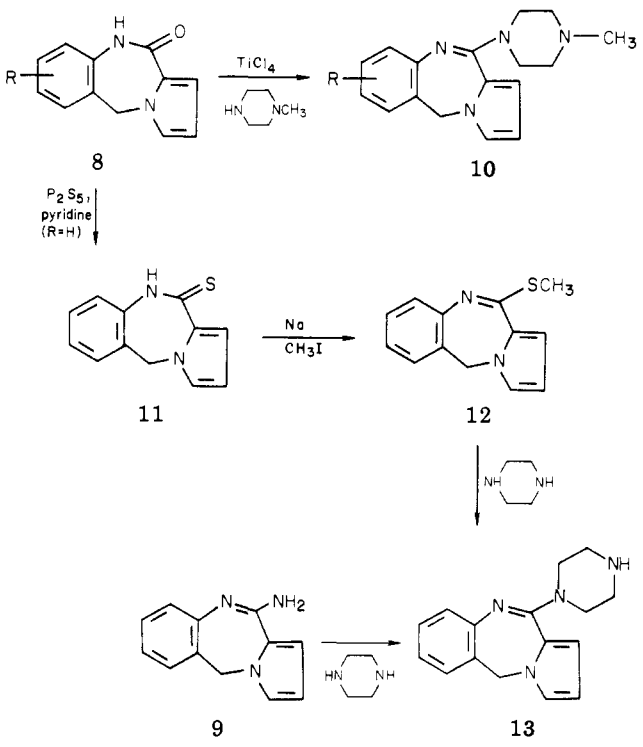


Table III. CNS Screening of 11-(1-Piperazinyl)-5*H*-pyrrolo[2,1-*c*][1,4]benzodiazepine Derivatives

compd	GAL:[a] ED_{50} (95% CL), mg/kg ip	MDD_{50},[b] mg/kg po	TBZ:[c] MED, mg/kg po
10a	1.0 (0.8-1.3)	7	inact
10b	4.0 (2.6-6.0)	12	inact
10c	16 (12-23)	50	inact
13	4.7[d] (3.7-5.9)	nt[g]	3.1
clozapine	2.2 (1.1-4.4)	21	inact
imipramine	inact[e]	>50	5[f]
chlorpromazine	0.6 (0.3-1.2)	2.4	inact

[a] Protection vs. amphetamine lethality in grouped mice. [b] Estimated dose depressing motor activity by 50% in rats. [c] Antagonism of tetrabenazine-induced depression in mice: minimum effective dose; inactive at 25 mg/kg ip. [d] Oral administration. [e] Inactive at a dose of 20 mg/kg ip; partial antagonism at 45 mg/kg ip. [f] This value in ref 4b was inadvertantly given as 12; see ref 4a. [g] Not tested.

and cooled, and **1b** was collected: yield 12.6 g; mp 104–108 °C. Recrystallization from Et_2O converts **1b** to a second polymorph, mp 117–119 °C. Mixtures were generally obtained.

In the preparation of 1-(5-chloro-2-nitrobenzyl)-2-pyrrolecarboxaldehyde (**1c**), 5,5′-dichloro-2,2′-dinitrostilbene (**15**), mp 206–210 °C, was obtained as a byproduct. No 2,2′-dinitrostilbene was observed in the preparation of the dechloro analogue (**1a**).

General Procedure B. 1-(2-Nitrobenzyl)-2-pyrrolecarboxaldehyde Oximes 2a–c. The 1-(2-nitrobenzyl)-2-pyrrolecarboxaldehyde (**1a–c**; 0.06 mol) and 150 mL of EtOH were warmed, and a solution of 18.6 g of NH_2OH·HCl and 37 g of NaOAc in 150 mL of H_2O was added. The mixture was heated for 30 min and cooled. An oil separated and then crystallized. It was collected, washed well with H_2O, and dried in a vacuum oven.

General Procedure C. 1-(2-Nitrobenzyl)-2-pyrrolecarbonitriles 3a–c. A mixture of 0.06 mol of **2a–c** and 70 mL of Ac_2O was heated in an oil bath at 140 °C for 2 h, cooled, and treated with ice, H_2O, CH_2Cl_2, and 200 g of $NaHCO_3$. When the foaming was over, the layers were filtered and separated. The CH_2Cl_2 solution was washed with H_2O, dried over $MgSO_4$, and concentrated to remove the solvent. Addition of a little Et_2O resulted in precipitation of the **3a-c**, which was collected by filtration, washed with Et_2O, and dried in a vacuum oven.

General Procedure D. 1-(2-Aminobenzyl)-2-pyrrolecarbonitriles 4a–c. A mixture of 0.02 mol of **3a–c**, 250 mL of EtOH, 2.4 mL of concentrated HCl, and 500 mg of 10% Pd/C catalyst was shaken in a Parr hydrogenator under about 3 atm of hydrogen until reduction was complete. Note: The HCl was not used with the dechloro compound. The catalyst was filtered off and the filtrate was concentrated to remove the solvent. The residue was diluted with H_2O, CH_2Cl_2, and 7.0 mL of 5 N NaOH, and the layers were separated. The CH_2Cl_2 layer was washed with H_2O, dried over $MgSO_4$, and concentrated. The residue was treated with Et_2O, and **4a–c** was collected and dried in a vacuum oven. Additional product was recovered from the Et_2O filtrate.

General Procedure E. 1-(2-Aminobenzyl)-2-pyrrolecarboxylic Acids 5a–c and Minor Yields of the Corresponding Lactams 8a–c and Amidines 9a–c. A mixture of 8.0 g of **4a–c**, 8.0 g of 86% KOH, and 50 mL of ethylene glycol in a 200-mL round-bottom flask was immersed in an oil bath regulated at 170 °C and heated for 2 h. The solution was partly cooled and diluted with 80 mL of H_2O. After cooling the solution for 1–3 h, the solid was collected and washed with H_2O. This was a mixture of the lactam (**8a–c**) and the amidine (**9a–c**), and this mixture was purified by recrystallization from 95% EtOH or by partition chromatography using a diatomaceous earth column eluted with heptane, CH_2Cl_2, methylcellosolve, and H_2O (85:15:15:6).

The glycol/H_2O mother liquor was treated with HOAc to a pH of 4–5, and **5a–c** which separated as the major product of this reaction was collected and washed with H_2O. This was further purified by dissolving in dilute alkali and reprecipitating by the addition of HOAc.

Small experiments followed by TLC indicated that under these same conditions **6a** was converted to a mixture of **8a** and **9a**.

Procedure F. 1-(2-Aminobenzyl)-2-pyrrolecarboxamide (6a). A mixture of 1.97 g (0.01 mol) of **3a**, 1.2 g of NaOH, 0.18 mL of H_2O, and 10 mL of ethylene glycol in a 50-mL round-bottom flask was immersed in an oil bath regulated at 100 °C and left for 5 h. The mixture was diluted with 20 mL of H_2O, cooled, and filtered. The yield was 1.75 g, mp 110–115 °C, which contained small amounts of the amidine (**9a**). Recrystallization from EtOH resulted in 1.1 g of analytical 1-(2-aminobenzyl)-2-pyrrolecarboxamide.

General Procedure G. 5,10-Dihydro-5*H*-pyrrolo[2,1-*c*][1,4]benzodiazepin-11-ones 8a–c. A mixture of 0.1 mol of **5a–c**, 17.0 g (0.105 mol) of *N,N′*-carbonyldiimidazole (CDI), and 180 mL of THF was allowed to stand at room temperature for 18–72 h, heated at reflux temperature for 4–8 h, diluted with a little H_2O, and concentrated to remove the THF. The gummy residue was triturated with 100 mL of 0.05 N NaOH, and the crystals which separated were collected and recrystallized from EtOH or EtOAc.

In retrospect, a 24-h period at reflux temperature would probably have resulted in higher yields, as cyclization was incomplete in most experiments. The relatively stable 1-[(2-amino-4-chlorobenzyl)-2-pyrrolecarbonyl]imidazole (**7b**) was isolated from the recrystallization mother liquors during the preparation of **8b**. When **7b** was heated at 105 °C for 1 h, **8b** was obtained in nearly quantitative yield.

Repeat preparations of **8a** frequently gave crude products which contained considerable amounts of **7a**; these were simply heated to complete the cyclization. In one experiment, 13 g of **5a** and 10 g of CDI in THF was stirred at room temperature for 2–3 h, and then the mixture was gradually heated with an oil bath (final temperature, 170 °C for 3 h); the product obtained by trituration of the residue with EtOAc and collecting the tan solid was 6 g (50%) of **8a**: mp 216–218 °C; TLC one spot; NMR ($CDCl_3$/Me_2SO-d_6) δ 10.2 (s, 1, NH), 7.6–7.0 (m, 5, H-3 and H-6, -7, -8, -9), ~6.8 (m, 1, H-1), ~6.2 (m, 1, H-2), 5.23 (s, 2, CH_2).

Procedure H. 11-Amino-5*H*-pyrrolo[2,1-*c*][1,4]benzodiazepine (9a). A mixture of 5 g (0.022 mol) of **3a**, 20 g of Zn dust, 25 mL of HOAc, and 100 mL of EtOH was stirred at room temperature for 24 h. The reaction mixture was filtered to remove unreacted Zn and the precipitate was washed with EtOH. The filtrate was cooled to 0 °C, and the precipitated Zn salts were

removed by filtration. The mother liquor was evaporated to a solid residue, which was dissolved in CH_2Cl_2 and again filtered. The solvent was removed by evaporation, and the residue was crystallized by the addition of Et_2O. Filtration yielded 4.34 g (45%) of **9a**, mp 179–181 °C, identical with an authentic sample of **9a** obtained by procedure F and purified by chromatography: NMR ($CDCl_3$/Me_2SO-d_6) δ 7.4–6.8 (m, 4, H-6, -7, -8, -9), ~6.55 (m, 1, H-3), 6.1–6.2 (m, 2, H-1 and H-2), 4.95 (s, 2, CH_2).

General Procedure I. 11-(4-Methyl-1-piperazinyl)-5*H*-pyrrolo[2,1-*c*][1,4]benzodiazepines 10a–c. A mixture of 15 mL of dry toluene, 1.5 mL of anisole, and 0.8 mL of $TiCl_4$ was cooled under argon, and a solution of 2.8 mL of *N*-methylpiperazine in 10 mL of toluene was added. In succession, 0.008 mol of **8a–c** and 1.4 mL of *N*-methylpiperazine were added. The reaction mixture was heated at reflux temperature for 5 h, cooled to 60 °C, and treated with 2.2 mL of 2-propanol, 2 mL of NH_4OH, and 1 g of diatomaceous earth. After the mixture cooled to 30 °C, 20 mL of toluene was added and the mixture was filtered and washed well with toluene. The toluene layer was washed twice with H_2O, concentrated to remove the solvent, and cooled. The solid was washed onto a filter with hexane and treated with 10 mL of 1 N NH_4OH, and the white precipitate was collected, washed with H_2O, and dried in a vacuum oven. Recrystallization from ethanol resulted in analytically pure **10a–c**.

General Procedure J. 11-(1-Piperazinyl)-5*H*-pyrrolo[2,1-*c*][1,4]benzodiazepine (13). A mixture of 4.5 g (0.023 mol) of **9a**, 20 g of piperazine, 2.0 g of NH_4Cl, and 20 mL of toluene was heated at reflux temperature for 6 h, diluted with H_2O, and evaporated to a semisolid residue. This material was triturated with H_2O and the H_2O was decanted. The crude product was dissolved in dilute HCl, the mixture was filtered, and the filtrate was made basic with concentrated NH_4OH. The solid was extracted into CH_2Cl_2, and the organic layer was dried over K_2CO_3 and evaporated. Fractional crystallization of this residue (2.55 g) from Et_2O gave a total yield of 1.5 g (25%) of pure **13** identical with an authentic sample prepared by procedure M: NMR ($CDCl_3$) δ 7.35–7.0 (m, 4, H-6, -7, -8, -9), ~6.8 (m, 1, H-3), 6.4–6.05 (m, 2, H-1 and H-2), 4.9 (s, 2, CH_2), 3.85–3.5 (m, 4, piperazine H-2's), 3.1–2.8 (m, 4, piperazine H-3's), 1.7 (s, 1, NH).

Procedure K. 5,10-Dihydro-5*H*-pyrrolo[2,1-*c*][1,4]benzodiazepine-11-thione (11). A mixture of 6.0 g (0.03 mol) of **8a**, 2.64 g (0.012 mol) of P_2S_5, and 50 mL of pyridine was stirred at reflux temperature for 4 h and concentrated to remove the pyridine. The gummy residue was treated with 75 mL of 5% Na_2CO_3 and 5 mL of MeOH and stirred for 18 h. Crystallization gradually occurred, and the solid was collected, washed with H_2O, and dried. The crude product was dissolved in CH_2Cl_2 and passed through magnesium silicate and **11** was recovered.

Procedure L. 11-(Methylthio)-5*H*-pyrrolo[2,1-*c*][1,4]benzodiazepine (12). A solution of 0.42 g (0.018 mol) of Na in 60 mL of EtOH was stirred and 3.85 g (0.018 mol) of **11** was added. After 1 h, 1.8 mL of methyl iodide was added and precipitation began almost immediately. The mixture was stirred for 4 h, and the yellow precipitate was collected and washed with a little EtOH.

Procedure M. 11-(1-Piperazinyl)-5*H*-pyrrolo[2,1-*c*][1,4]benzodiazepine (13). A mixture of 1.55 g (0.0068 mol) of **12**, 7 mL of piperazine, 4 drops of HOAc, and 15 mL of xylene was heated at reflux temperature for 48 h. The reaction mixture was concentrated to remove the xylene and most of the piperazine, and the residue was diluted with H_2O and filtered. The crystals were stirred with 50 mL of 2 N HOAc and the insoluble material was collected. The filtrate was treated with 7 mL of concentrated NH_4OH and extracted three times with CH_2Cl_2. The CH_2Cl_2 layer was washed once with H_2O, dried over $MgSO_4$, and concentrated to remove the solvent. The residue was triturated with Et_2O, and crystals of **13** separated and were collected and dried in a vacuum oven.

α,5-Dichloro-2-nitrotoluene (16). A mixture of 64 g (0.35 mol) of 5-chloro-2-nitrobenzyl alcohol and 400 mL of $CHCl_3$ was stirred while 72 g of PCl_5 was added in portions. Gas was evolved and foaming occurred. **Care: The product is a lachrymator and burns the skin!** After 30 min the reaction mixture was poured carefully into ice and stirred at intervals over the next hour. The $CHCl_3$ layer was separated, washed twice with cold H_2O, dried over $MgSO_4$, and concentrated to remove the solvent. The oil was triturated with cold H_2O and solidified. The product was dissolved in benzene and washed with H_2O, the solution was reconcentrated, and the oily residue was cooled overnight. The semicrystalline mixture was diluted with 25 mL of cold EtOH and filtered, and the precipitate was washed with 15 mL of cold EtOH and dried in a vacuum desiccator. The yield of **16**, mp 50–52 °C, was 36.0 g (52%). An additional 8 g was obtained from the mother liquor, lit.[6] mp 51.4–52.2 °C.

α,4-Dichloro-2-nitrotoluene (17). A mixture of 150 g (0.80 mol) of 4-chloro-2-nitrobenzyl alcohol and 750 mL of $CHCl_3$ was stirred and 170 g of PCl_5 was added in portions. After 1 h at room temperature, the mixture was poured into ice and stirred at intervals over 1 h. The layers were separated, and the $CHCl_3$ solution was washed twice with H_2O, dried over $MgSO_4$, and concentrated to remove the solvent. The residue was diluted with 200 mL of hexane, and the mixture was cooled in an ice/acetone bath. The solid was collected, washed with cold hexane, and dried in a vacuum desiccator. The yield was 80 g, mp 34–50 °C. The mother liquor was again concentrated, diluted with 100 mL of hexane, and left in the freezer over the weekend for additional crystalline material, yield 80 g. The crude products contained unreacted 4-chloro-2-nitrobenzyl alcohol, which is less soluble in hexane. They were boiled with about 10 parts of hexane, decanted from the insoluble oil, allowed to cool to room temperature, and filtered to remove the insoluble alcohol. The mother liquor was cooled in the freezer and **17**, mp 37–39 °C, was obtained. The purified yield was 112 g (58%).

Pharmacological Testing Procedures. The pharmacological procedures for determining antagonism of *d*-amphetamine lethality in grouped mice, reduction of motor activity in rats, and inhibition of tetrabenazine-induced depression in mice have recently been described in detail by one of us (E.N.G.) in two previous publications from our Laboratories.[5] The present procedures are exactly the same. Numbers of animals per test group varied from 5 to 10. The 95% confidence limits were calculated by the arc–sine transformation method of Finney.[7]

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