4-Nitropyridine-3-sulfonamide (13b) was prepared from **12b** by method A in 7% yield, mp 150 °C dec. Anal. ($C_5H_5N_3O_4S$) C, H, N.

6-Nitropyridine-3-sulfonamide (13c) was prepared from **12c**[8] by method A in 6% yield, mp 172–173 °C. Anal. ($C_5H_5N_3O_4S$) C, H, N.

5-Bromopyridine-3-sulfonamide (15). A mixture of **14**[15] (2.14 g, 10 mmol) and Br_2 (1.92 g, 12 mmol) was heated at 130 °C for 8 h, cooled, and added portionwise to 20% NH_4OH (30 mL) under stirring. After 1 h, the solution was saturated with NaCl and extracted with EtOAc. The extract was washed with NaCl-saturated aqueous solution, dried, and evaporated to give **15** (1.54 g, 65.0%), mp 178–179 °C on recrystallization from petroleum ether and EtOH. Anal. ($C_5H_5BrN_2O_2S$) C, H, Br, N.

5-Aminopyridine-3-sulfonamide (16). A mixture of **15** (2.4 g, 10.1 mmol) and $CuSO_4 \cdot 5H_2O$ (0.005 g) in concentrated NH_4OH (4.8 mL) was heated at 170 °C for 5 h, cooled, treated with Na_2S, and extracted with EtOAc. The extract was dried and evaporated, and the residue was recrystallized from *n*-hexane and EtOH to give **16** (1.07 g, 61.5%), mp 177–179 °C. Anal. ($C_5H_7N_3O_2S$) C, H, N, S.

5-Nitropyridine-3-sulfonamide (17). This compound was prepared from **16** in 76.5% yield by method A, mp 182–183 °C. Anal. ($C_5H_5N_3O_4S$) C, H, N, S.

5-Bromopyridine-3-sulfonic Acid (18). A mixture of **14** (12.0 g, 56.1 mmol) and Br_2 (10.8 g, 67.5 mmol) was heated at 130 °C for 8 h, cooled, diluted with H_2O (150 mL), and heated again at 80–90 °C for 1.5 h. The reaction mixture was concentrated into a small volume and diluted with acetone to give **18** (13 g, 97.4%). Recrystallization from H_2O gave analytically pure product: mp >300 °C; NMR (DMF-d_7) δ 9.0 (1 H, d, J = 1.5 Hz), 8.90 (1 H, d, J = 2.0 Hz), 8.42 (1 H, dd, J = 1.5 and 2.0 Hz). Anal. ($C_5H_4BrNO_3S$) C, H, N, Br.

5-Aminopyridine-3-sulfonic Acid (19). A suspension of **18** (75.4 g, 0.32 mol) in concentrated NH_4OH (170 mL) containing $CuSO_4 \cdot 5H_2O$ (8 g, 0.032 mol) was heated at 170 °C in a sealed tube for 20 h, cooled, and treated with Na_2S. After the CuS was separated, the filtrate was concentrated and acidified with HCl (pH 2) to give the product (47.0 g, 85.3%). Recrystallization from aqueous EtOH gave an analytically pure sample, mp >300 °C. Anal. ($C_5H_6N_2O_3S$) C, H, N, S.

***N*-Ethyl-5-nitropyridine-3-sulfonamide (21). Method C.** A solution of **19** (20 g, 0.115 mol) in concentrated H_2SO_4 (50 mL) was added dropwise below 10 °C to a mixed solution of 30% fuming H_2SO_4 (200 mL) and 30% H_2O_2 (100 mL), and stirring was continued at room temperature for 40 h. The mixture was poured into ice–water, neutralized with Na_2CO_3, and again acidified with HCl (pH 1.5). The solution was concentrated to leave a syrupy residue, which gave a powdered product by addition of acetone. The crystalline compound that separated was extracted with MeOH. The extract was concentrated to a small volume, and addition of acetone produced crude 5-nitropyridine-3-sulfonic acid (18 g, 76.9%), which was used in the next step without purification.

A mixture of the acid (2.0 g, 9.8 mmol), PCl_5 (2 g), and $POCl_3$ (60 mL) was stirred under reflux for 6 h and concentrated to dryness. The residual oil was crystallized by stirring in $CHCl_3$. The precipitate formed was filtered and added under cooling to 20% aqueous ethylamine (4.4 g, 19.6 mmol). The mixture was stirred at room temperature for 1 h, diluted with H_2O, and extracted with EtOAc. The extract was washed with H_2O, dried, and evaporated to afford an oil, which was purified by silica gel chromatography, eluting with EtOAc, and recrystallized from *n*-hexane and EtOAc to give **21** (0.23 g, 10.2%), mp 117–118 °C. Anal. ($C_7H_9N_3O_4S$) C, H, N, S.

***N*-Octanoyl-5-nitropyridine-3-sulfonamide (32). Method D.** *A mixture of* **17** *(1 g, 4.9 mmol), octanoic anhydride (3.5 mL),* and 3 drops of concentrated H_2SO_4 was stirred at 90 °C for 1 h to separate a crystalline product. After *n*-hexane was added, the precipitate that deposited was collected by filtration and recrystallized from *n*-hexane and EtOAc to give **32** (1.09 g, 67.3%), mp 103–105 °C. Anal. ($C_{13}H_{19}N_3O_5S$) C, H, N, S.

Pyridine-3-sulfonamide *N*-Oxide (35). A solution of pyridine-3-sulfonamide (0.5 g, 3.2 mmol) in 40% peracetic acid (4 mL) was stirred at 80 °C for 1.5 h. The solution was concentrated to dryness in vacuo to leave an oil, which was crystallized from EtOH to give **35** (0.37 g, 67.3%), mp 167–170 °C. Anal. ($C_5H_6N_2O_3S$) C, H, N, S.

Pyridine-4-sulfonamide *N*-Oxide (36). This compound was similarly prepared from pyridine-4-sulfonamide in 57.6% yield, mp 233 °C. Anal. ($C_5H_6N_2O_3S$) C, H, N, S.

Acknowledgment. We express our gratitude to Dr. K. Murayama, Director of these Laboratories, to Dr. N. Soma and Dr. A. Ogiso, Assistant Directors, and to Dr. I. Kawamoto for the encouragement and discussions.

7-(Aminoacyl) and 7-(Aminoalkyl) Derivatives of 1,2,6,7-Tetrahydroindolo[1,7-*ab*][1,5]benzodiazepines as Potential Antidepressant Agents[1]

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Received June 2, 1980

The synthesis of 7-(aminoacyl) and 7-(aminoalkyl) derivatives of 1,2,6,7-tetrahydroindolo[1,7-*ab*][1,5]benzodiazepines is described. These compounds were evaluated for antidepressant activity by their ability to inhibit tetrabenazine-induced ptosis in mice. Many compounds were found to be active in this animal model, and structure-activity relationships are discussed. Two analogues in particular, one from the 7-(aminoacyl) series (**13**) and one from the 7-(aminoalkyl) series (**26**), were of comparable potency to the antidepressant drugs desipramine and amitriptyline.

The benzodiazepines as a class have provided many useful psychotherapeutic agents, particularly for the treatment of anxiety and sleep disorders. Yet little has been reported on benzo- and dibenzodiazepines with antidepressant properties.[2] We recently described the

(1) Presented in part at the American Chemical Society/Chemical Society of Japan Chemical Congress. See "Abstracts of Papers", ACS/CSJ Chemical Congress, Honolulu, HI, Apr 2–6, 1979; American Chemical Society: Washington, D.C., 1979; Abstr MEDI 9.

(2) (a) Hunziker, F.; Künzle F.; Schmutz, J. *Helv. Chim. Acta* **1966**, *49*, 244, and references therein. (b) Monro, A. M.; Quinton, R. M.; Wrigley, T. I. *J. Med. Chem.* **1963**, *6*, 255. (c) Nose, T.; Kowa, Y. *Jpn. J. Pharmacol.* **1970**, *21*, 47.

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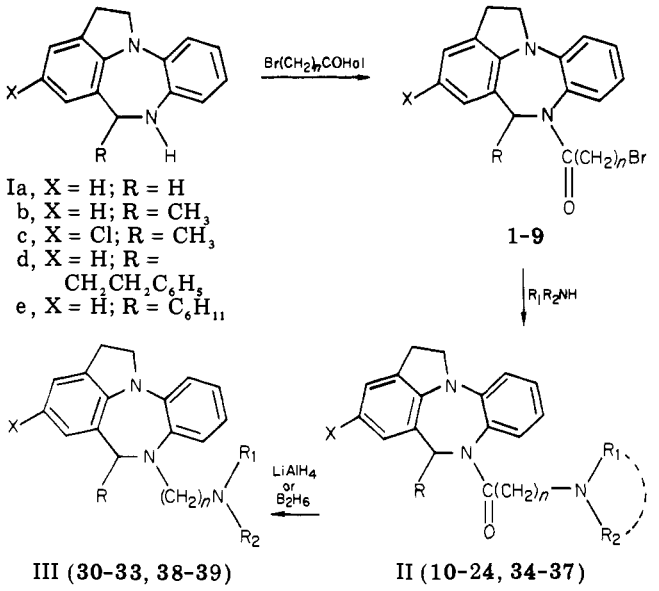
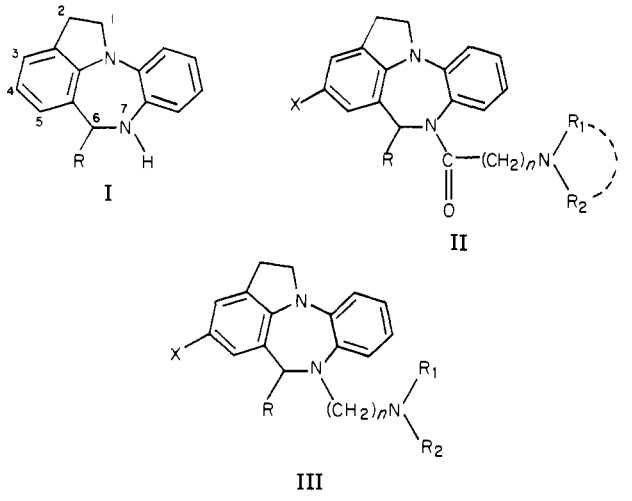
Scheme I



synthesis[3] of the novel 1,2,6,7-tetrahydroindolo[1,7-*ab*]-[1,5]benzodiazepine ring system I. We decided, therefore,

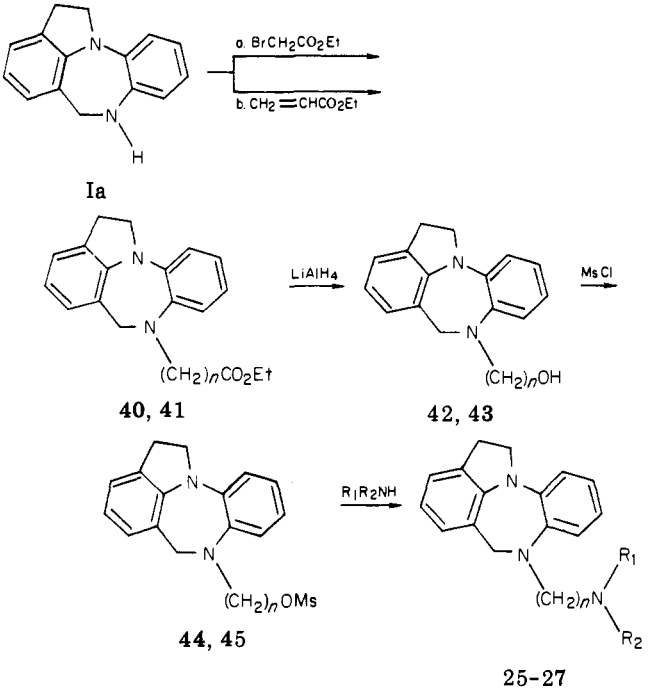


to investigate the possibility of developing potential antidepressant agents from this indolobenzodiazepine tetracycle. Construction of amine-bearing side chains at the central ring nitrogen atom afforded two series of compounds, of formula II and III, which were evaluated for antidepressant activity. These compounds represent an interesting structural departure from the classical imipramine and amitriptyline type of tricyclic antidepressants.

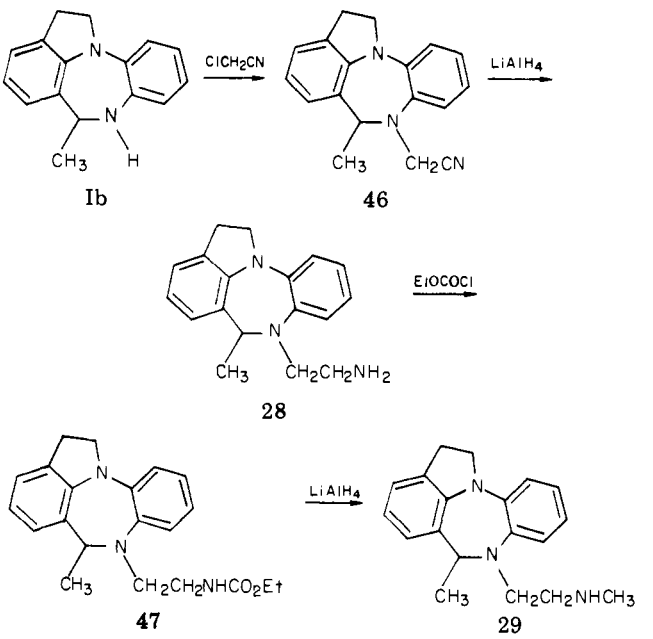
Chemistry. The synthesis of the tetrahydroindolobenzodiazepine nucleus I was described previously.[3] Scheme I illustrates how amine-containing side chains were constructed at the central ring nitrogen atom. This nitrogen was acylated, in most cases, with a bromoalkyl acid halide. An amino function was introduced at the end of the chain by nucleophilic displacement of the terminal bromine atom by the desired amine. These two steps provided the compounds of the aminoamide series of formula II. Reduction of the amide bond of II with lithium aluminum hydride or diborane completed the elaboration of an *N*-(aminoalkyl) side chain and thereby led to a second series of compounds having generic formula III.

(3) Glamkowski, E. J.; Fortunato, J. M. *J. Heterocycl. Chem.* **1979**, *16*, 865.

Scheme II

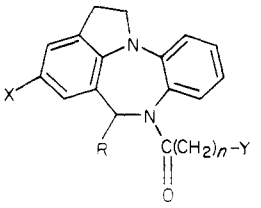


Scheme III



This sequence worked well to produce the great majority of compounds reported here. However, in those molecules where there was no pendant substituent, i.e., where R = H, reduction of the amide linkage did not proceed as expected. Instead, cleavage of the bond between the ring nitrogen atom and the side chain was the predominant reaction pathway, and the starting tetracycle Ia was the product isolated. To circumvent this problem, an alternate synthesis was devised and this approach is outlined in Scheme II. The tetracycle Ia was alkylated with ethyl bromoacetate to introduce a two-carbon chain (**40**) or condensed with ethyl acrylate to provide an intermediate (**41**) with three carbons in the side chain. In each case, the terminal ester group was then reduced to an alcohol with lithium aluminum hydride and the alcohol was converted into the mesylate ester to provide a good leaving group. Nucleophilic displacement of this group by an amine proceeded smoothly and thereby completed the

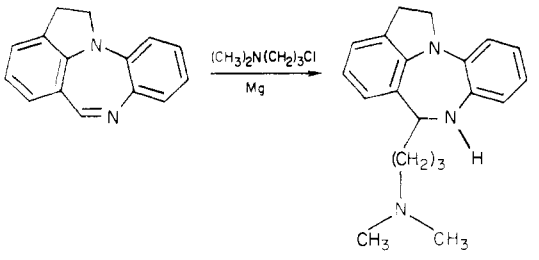
Table I. Intermediates. 7-(Haloacyl)-1,2,6,7-tetrahydroindolo[1,7-*ab*][1,5]benzodiazepines



compd	X	R	*n*	Y	yield,[a] %	mp, °C	recrystn solvent	formula[b]
1	H	H	1	Br	47	136-138	benzene	$C_{17}H_{15}BrN_2O$
2	H	H	2	Br	39	120-122	EtOH[c]	$C_{18}H_{17}BrN_2O$
3	H	CH_3	1	Br	56	123-125	EtOH	$C_{18}H_{17}BrN_2O$
4	Cl	CH_3	1	Br	75	229-233	DMF	$C_{18}H_{16}BrClN_2O$
5	H	CH_3	2	Br	64	149-151	MeOH	$C_{19}H_{19}BrN_2O$
6	Cl	CH_3	2	Br	55	163-165	toluene	$C_{19}H_{18}BrClN_2O$
7	H	CH_3	3	Cl	46	88-90	MeOH	$C_{20}H_{21}ClN_2O$
8	H	$CH_2CH_2C_6H_5$	1	Br	58	156-159	1-BuOH	$C_{25}H_{23}BrN_2O$
9	H	C_6H_{11}[d]	2	Br	50[e]			

[a] Yield of analytically pure product; no effort was made to optimize yields. [b] All compounds were analyzed for C, H, and N within ±0.40% of the calculated values. [c] Purified by dry column chromatography on silica gel using chloroform as eluant before recrystallization. [d] Cyclohexyl. [e] This intermediate could not be solidified or worked to an analytically pure state. It was of sufficient purity, however, to be used as is in subsequent reactions.

Scheme IV



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formation of the desired aminoalkyl side chain for those molecules where R = H (**25–27**).

A third synthetic approach (Scheme III) was employed to provide two other target compounds. The tetracycle Ib was alkylated with chloroacetonitrile, and then the cyano group was reduced with lithium aluminum hydride to provide an example (**28**) of a molecule with an unsubstituted terminal $-NH_2$ group. Monomethylation of this amine was achieved by acylation with ethyl chloroformate, followed by reduction of the resulting carbamate. These steps led to the formation of **29** with its methylaminoethyl side chain.

In order to make structure-activity relationships more complete, it was desirable to have at least one example in which the aminoalkyl chain was attached not to the central ring nitrogen but to the adjacent carbon atom. This was accomplished (Scheme IV) by addition of (dimethylamino)propylmagnesium chloride to the polarized imino linkage of 1,2-dihydroindolo[1,7-*ab*][1,5]benzodiazepine.[3]

Pharmacology and Structure-Activity Relationships. Table II shows the variety of target compounds prepared in the aminoamide series of formula II, X = H. They were tested for potential antidepressant activity by their ability to inhibit tetrabenazine-induced ptosis in mice. Tetrabenazine (TBZ) induces behavioral depression in mice with concomitant ptosis, in a manner similar to reserpine. The great majority of antidepressant agents are known to prevent or antagonize these effects, and the degree of inhibition correlates well with clinical efficacy.[4] The test procedure was described previously in a report from these laboratories.[5]

The results obtained in this animal model are shown in Table II. It can be seen that most of the compounds exhibited some degree of antitetrabenazine activity and that the most critical structural element for activity in this series is the nature of the pendant substituent R. When R is hydrogen, as in **10–12**, only weak activity was observed, regardless of chain length or substitution on the terminal amino group $-NR_1R_2$. Several analogues with R equal to methyl, however, were extremely active. A chain length of one or two methylene units, coupled with a single methyl substituent on the amino group, provided the most potent compounds of this series, **13** and **16**.

When the single alkyl substituent on the side-chain nitrogen was lengthened from methyl to propyl, as in **14** and **17**, antidepressant activity was greatly diminished. When the amino group bore two alkyl substituents, as in the dimethylamino compounds **15** and **18**, or when the amino group was part of a ring system as in **20** and **21**, antitetrabenazine activity was also reduced. Lengthening the carbon chain to three methylene units, as in **22**, was deleterious, as was increasing the size of the pendant group at R to cyclohexyl (**23**).

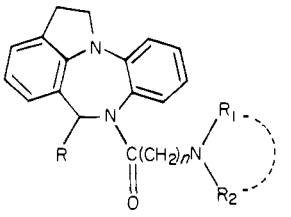
With the exception of **22–24**, compounds in this aminoamide series were of very low toxicity, with acute LD_{50} values greater than 100 mg/kg, ip, in the rat.

In summary, the most potent member of this aminoamide series is **13**, with an oral ED_{50} = 2.0. The structural features, therefore, required for maximum anti-TBZ activity, where X = H, are (1) a small alkyl substituent, methyl, at the pendant position R, (2) a short carbon side chain consisting of a carbonyl group and one methylene unit, and (3) a monomethylamino group at the end of the chain. It is interesting to note that several members of this series show very potent antidepressant activity even though the amine-bearing side chain is attached to the nuclear nitrogen atom via an amide linkage. This structural feature is apparently very rare.[6] Virtually all other

(4) Benesova, O.; Nahunek, K. *Psychopharmacologia* **1971**, *20*, 337.

(5) Bauer, V. J.; Duffy, B. J.; Hoffman, D.; Klioze, S. S.; Kosley, Jr., R. W.; Mcfadden, A. R.; Martin, L. L.; Ong, H. H.; Geyer III, H. M. *J. Med. Chem.* **1976**, *19*, 1315.

Table II. Physical and Antidepressant Properties of 7-(Aminoacyl)-1,2,6,7-tetrahydroindolo[1,7-*ab*][1,5]benzodiazepines of Formula II (X = H)



compd	R	*n*	NR_1R_2	yield,[a] %	mp, °C	recrystn solvent[b]	formula[c]	inhibition of ptosis:[d] ED_{50}, mg/kg
10	H	1	$NHCH_3$	21	128-130	A	$C_{18}H_{19}N_3O$	>20
11	H	1	$N(CH_3)_2$	52	107-109	B	$C_{19}H_{21}N_3O$	>20
12	H	2	$N(CH_3)_2$	30	91-93	C	$C_{20}H_{23}N_3O$	>20
13	CH_3	1	$NHCH_3$	49	109-111	D	$C_{19}H_{21}N_3O$	2.0 (1.7-2.3)
14	CH_3	1	$NHCH_2CH_2CH_3$	20	116-118	E	$C_{21}H_{25}N_3O$	>20
15	CH_3	1	$N(CH_3)_2$	44	106-108	B	$C_{20}H_{23}N_3O$	13.5 (11.4-16.9)
16	CH_3	2	$NHCH_3$	50	124-126	A	$C_{20}H_{23}N_3O$	4.0 (3.5-4.5)
17	CH_3	2	$NHCH_2CH_2CH_3$	19	186-190	F	$C_{22}H_{27}N_3O\cdot HCl$	>20
18	CH_3	2	$N(CH_3)_2$	45	142-144	G	$C_{21}H_{25}N_3O$	16.0 (12.5-22.2)
19	CH_3	2	$N(CH_2CH_3)_2$	57	60-62	H	$C_{23}H_{29}N_3O$	>20
20	CH_3	2	c-NC_5H_{10}	61	97-99	H	$C_{24}H_{29}N_3O$	>20
21	CH_3	2	c-$N(CH_2CH_2)_2N$-C_6H_5	46	139-141	I	$C_{29}H_{32}N_4O$	>20
22	CH_3	3	$N(CH_3)_2$	33	226-228	J	$C_{22}H_{27}N_3O\cdot HCl$	>20
23	C_6H_{11}[e]	2	$N(CH_3)_2$	30	211-214	K	$C_{26}H_{33}N_3O\cdot HCl$	>20
24	$CH_2CH_2C_6H_5$	1	$N(CH_3)_2$	28	194 dec	L	$C_{27}H_{29}N_3O\cdot C_2H_2O_4$	nd[f]
desipramine								1.5
amitriptyline								4.5

[a] Yield of analytically pure product; no effort was made to optimize yields. [b] A = EtOAc; B = benzene-hexane; C = isopropyl ether; D = EtOAc-ether; E = hexane; F = EtOH-ether; G = EtOH; H = *n*-heptane; I = MeOH; J = MeOH-ether; K = EtOH-hexane; L = 2-PrOH-$CHCl_3$. [c] All compounds were analyzed for C, H, and N within ±0.40% of the calculated values. [d] The test procedure is described in ref 5. A linear-regression analysis was used to determine the ED_{50} values and the 95% confidence intervals which are indicated in the parentheses. The designation >20 means the compound was active at the screening dose of 20 mg/kg, ip, but was not potent enough to warrant a dose-response and the determination of an ED_{50}. Specific ED_{50} values were determined upon oral administration, with the exception of the ED_{50} for compound 15, which was via the intraperitoneal route. [e] Cyclohexyl. [f] nd = not determined; this compound was toxic at the screening dose of 20 mg/kg, ip.

antidepressant agents reported in the literature have their side chain connected to a ring nitrogen by a saturated methylene ($-CH_2-$) unit.

A somewhat different and less clear-cut SAR emerges in the aminoalkyl series of generic formula III (X = H) shown in Table III. Here it can be seen that the nature of the pendant substituent R is not as critical for anti-TBZ activity as in the previous series. Several compounds with either hydrogen or methyl at position R were very potent. However, here as before, a bulkier pendant group is undesirable. For example, **33** and **31** are the same molecule except that **33** has the large phenethyl group at R and is weakly active (>20), whereas **31** with the smaller methyl at R is rather potent with an ED_{50} = 5.0.

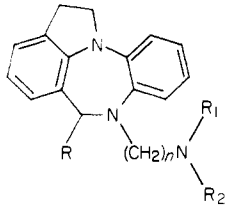
When R is hydrogen (**25–27**), the structural elements required for maximum activity are those found in **26**, namely, a three-carbon chain with a monomethylamino group at $-NR_1R_2$. For those analogues with a pendant R equal to methyl, a chain of two carbon atoms leads to the most active compounds. The multiplicity of substitution on the terminal nitrogen atom does not appear to be very crucial, in contrast to the aminoamide series. For example, compound **28** with no alkyl groups at all at $-NR_1R_2$ was very potent with an ED_{50} = 2.2, while **31** with two methyls on the terminal nitrogen was also very active with an ED_{50} = 5.0.

As a class, compounds with an aminoalkyl side chain did not show the same low toxicity as those of the aminoamide series. All active compounds inTable III had an acute LD_{50} in the rat of between 30 and 100 mg/kg, ip, with one exception: the most active compound, **26**, with a TBZ ED_{50} of 1.5 po, was also the least toxic, having an acute LD_{50} greater than 100 mg/kg, ip.

It has often been found among tricyclics with psychotropic properties that the presence of a chlorine atom at a nuclear position, such as X in formulas II and III, improves potency or alters the biological profile. This has been the case, for example, with chlorimipramine and chlorpromazine. This was not the case, however, here. In Table IV there are six pairs of molecules, the two members of each pair being identical except for the nuclear substituent X. Those compounds where X is chlorine were totally inactive at the screening dose of 20 mg/kg, whereas those same molecules but with X equal to hydrogen were rather potent in inhibiting TBZ-induced ptosis. The same effect was observed whether the pairs of molecules were in the aminoacyl or the aminoalkyl series.

(6) We are aware of only one other example, the tricyclic compound OI-77, which has a (methylamino)acetyl chain attached to a dihydrophenanthridine ring nitrogen: Itil, T. M.; Cora, R.; Hsu, W.; Cig, E.; Saletu, B. *Arzneim.-Forsch.* **1972**, *22*, 2063. van Riezen, H.; van der Burg, W. J.; Berendsen, H.; Jaspar, M. L. *Ibid.* **1973**, *23*, 1295.

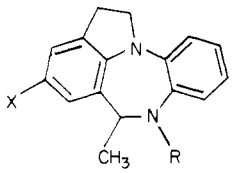
Table III. Physical and Antidepressant Properties of 7-(Aminoalkyl)-1,2,6,7-tetrahydroindolo[1,7-*ab*][1,5]benzodiazepines of Formula III (X = H)



compd	R	*n*	NR_1R_2	yield,[a] %	mp, °C	recrystn solvent[b]	formula[c]	inhibition of ptosis:[d] ED_{50}, mg/kg
25	H	2	$NHCH_3$	20	180 dec	A	$C_{18}H_{21}N_3 \cdot C_2H_2O_4$[e]	>20
26	H	3	$NHCH_3$	35	218 dec	B	$C_{19}H_{23}N_3 \cdot 2HBr$	1.5 (1.3-1.7)
27	H	3	$N(CH_3)_2$	33	199-202	C	$C_{20}H_{25}N_3 \cdot 2HCl$	16.0 (13.1-20.5)
28	CH_3	2	NH_2	40	243-245 dec	D	$C_{18}H_{21}N_3 \cdot 2HBr$	2.2 (1.9-2.5)
29	CH_3	2	$NHCH_3$	45	241-243 dec	E	$C_{19}H_{23}N_3 \cdot 2HBr$	8.0[f]
30	CH_3	2	$NHCH_2CH_2CH_3$	36	233-235 dec	F	$C_{21}H_{27}N_3 \cdot 2HBr$	>20
31	CH_3	2	$N(CH_3)_2$	20	225-227	D	$C_{20}H_{25}N_3 \cdot HBr$	5.0 (4.2-6.1)
32	CH_3	3	$NHCH_3$	48	237-239 dec	F	$C_{20}H_{25}N_3 \cdot 2HCl$	9.5 (8.3-11)
33	$CH_2CH_2C_6H_5$	2	$N(CH_3)_2$	13	208 dec	G	$C_{27}H_{31}N_3 \cdot C_2H_2O_4$[g]	>20

[a] Yield of analytically pure product; no effort was made to optimize yields. [b] A = DMF-MeCN; B = EtOH-ether; C = MeCN-EtOAc; D = EtOH; E = MeOH; F = MeOH-ether; G = Me_2CO-$CHCl_3$. [c] All compounds were analyzed for C, H, and N within ±0.40% of the calculated values except where noted. [d] See footnote *d*, Table II. [e] Anal. C: calcd, 65.03; found, 65.69. [f] Estimated ED_{50} as the dose-response determination was nonlinear. [g] Anal. C: calcd, 71.44; found, 70.87.

Table IV. Effect of a Nuclear Chlorine Substituent on the Antidepressant Properties of 1,2,6,7-Tetrahydroindolo[1,7-*ab*][1,5]benzodiazepines of Formulas II and III



compd	X	R	yield,[a] %	mp, °C	recrystn solvent[b]	formula[c]	inhibition of ptosis:[d] ED_{50}, mg/kg
34	Cl	$COCH_2NHCH_3$	43	160-162	A	$C_{19}H_{20}ClN_3O$	inact
13[e]	H	$COCH_2NHCH_3$					2.0
35	Cl	$COCH_2N(CH_3)_2$	54	149-150	A	$C_{20}H_{22}ClN_3O$	inact
15	H	$COCH_2N(CH_3)_2$					13.5
36	Cl	$COCH_2CH_2NHCH_3$	38	158-160	B	$C_{20}H_{22}ClN_3O$	inact
16	H	$COCH_2CH_2NHCH_3$					4.0
37	Cl	$COCH_2CH_2N(CH_3)_2$	49	125-127	C	$C_{21}H_{24}ClN_3O$	inact
18	H	$COCH_2CH_2N(CH_3)_2$					16.0
38	Cl	$CH_2CH_2NHCH_3$	37	245-248 dec	B	$C_{19}H_{22}ClN_3 \cdot 2HBr$	inact
29	H	$CH_2CH_2NHCH_3$					8.0
39	Cl	$CH_2CH_2CH_2NHCH_3$	24	224-227	D	$C_{20}H_{24}ClN_3 \cdot 2HBr$	inact
32	H	$CH_2CH_2CH_2NHCH_3$					9.5

[a] See footnote *a*, Table II. [b] A = EtOH; B = MeOH; C = toluene-hexane; D = MeOH-ether. [c] All compounds were analyzed for C, H, and N within ±0.40% of the calculated values. [d] See footnote *d*, Table II. An "inactive" compound is one which failed to inhibit tetrabenazine-induced ptosis at the screening dose of 20 mg/kg, ip. [e] The physical properties of compounds 13, 15, 16, and 18 are described in Table II, while 29 and 32 are described in Table III.

One more aspect to the structure-activity relationships which could not be left unexplored was the importance of the location of the side chain in the central ring. The classical (dimethylamino)propyl chain was therefore introduced at the carbon atom of the central ring by Grignard addition to the polarized imino linkage, as shown in Scheme IV. The resulting compound **48** now has the aminoalkyl chain moved over from nitrogen to the adjacent carbon atom. This structural modification led to a totally inactive compound when tested at 20 mg/kg, ip.

In conclusion, the two most potent compounds from this work are **13** from the aminoamide series and **26** from the aminoalkyl series. For comparison, the results for two well-known clinically effective antidepressant drugs are given in Table II. In inhibiting tetrabenazine-induced ptosis, **26** was essentially equipotent to desipramine: it had

an ED_{50} orally of 1.5 vs. 1.3 for desipramine, while **13** was almost as active with its ED_{50} of 2.0. Both compounds were more than twice as potent as amitriptyline, with its ED_{50} of 4.5 po in this animal model. In the rat, **13** and **26** were of equally low toxicity as the two reference drugs, which also had acute LD_{50} values greater than 100 mg/kg, ip. These 7-substituted 1,2,6,7-tetrahydroindolo[1,7-*ab*][1,5]benzodiazepines represent, therefore, a novel class of potential antidepressant agents of an interesting structural type.

Experimental Section

The structures of all novel compounds were confirmed by their IR (Perkin-Elmer 727) and NMR (JEOL C6OHL) spectra. Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Elemental analyses were performed by Micro-Tech Laboratories, Skokie, Ill. Chromatographic purifications were performed using silica gel 60 as the solid phase (70–230 mesh), from EM Laboratories, Inc., Elmsford, N.Y. The synthesis of starting materials Ia–e, shown in Scheme I, was described by us in a previous publication.[3]

General Acylation Procedure. The method used to prepare the 7-(haloacyl) tetracycle intermediates of Table I is described in the following example.

7-(Bromoacetyl)-1,2,6,7-tetrahydroindolo[1,7-*ab*][1,5]benzodiazepine (1). A stirred mixture, under N_2, of 17.8 g (0.08 mol) of Ia and 25.2 g (0.30 mol) of powdered $NaHCO_3$ in 250 mL of CH_2Cl_2 was cooled to 0 °C and then treated dropwise with a solution of 24.2 g(0.12 mol) of bromoacetyl bromide in 50 mL of CH_2Cl_2. The addition was at such a rate as to maintain the temperature below 5 °C and took 1.5 h. The reaction was stirred for 2 h more at 0–5 °C and at room temperature overnight. Water was then added to dissolve the salts. The organic phase was separated, washed with 3 N NaOH and with H_2O, dried over Na_2SO_4, and concentrated to an oily crystalline solid. This was digested on the steam bath with 20 mL of EtOH. After being stirred at room temperature for 1 h, the granular crystals were collected and found to weigh 19.5 g (71%), with mp 132–136 °C. Recrystallization from benzene (charcoal) afforded 13.3 g (47% yield) of pure **1**, mp 136–138 °C.

For intermediates **2**, **5**, **6**, and **9**, the acylating agent was 3-bromopropionyl chloride; **7** was prepared with 4-chlorobutyryl chloride.

General Synthetic Procedures for the 7-(Aminoacyl) Tetracycles of Tables II and IV. Depending on whether the amine required for halogen displacement was a gas or a liquid, two general methods were employed.

Method A. 7-[(Methylamino)acetyl]-1,2,6,7-tetrahydroindolo[1,7-*ab*][1,5]benzodiazepine (10). Into 200 mL of absolute MeOH, stirred and kept at 0–5 °C with exclusion of moisture, was passed gaseous monomethylamine until the solvent was saturated. To this was added 13.7 g (0.040 mol) of **1** in small portions. After 1 h more at low temperature and 3 h at room temperature (TLC indicated no more starting material was present), the solution was boiled with charcoal, filtered, and concentrated. The residue was partitioned between $CHCl_3$ and H_2O. The organic phase was separated, washed further with H_2O, with 3 N NaOH, and again with H_2O, dried over Na_2SO_4, and concentrated in vacuo to leave 10 g. This material could not be quickly purified by crystallization or salt formation, and so it was dissolved in 50 mL of $CHCl_3$ and adsorbed onto a chromatography column containing 600 g of silica gel packed in toluene. The column was eluted first with toluene, followed by increasing percentages (10% per step) of $CHCl_3$ in toluene, and then MeOH in $CHCl_3$ (1% per step). This brought forth 4.7 g of the pure amide using 2–3% MeOH in $CHCl_3$. Recrystallization from a small volume of EtOAc provided 2.4 g (21% overall yield) of **10**, mp 128–130 °C.

Prepared in a similar manner were **11–13**, **15**, **16**, **18**, **22–24**, and **34–37**. Compound **22** required a chromatography, followed by HCl salt formation (EtOH–ethereal HCl), in order to obtain it in a pure state. Compounds **11**, **15**, **16**, **18**, **35**, and **37** were sufficiently pure after workup that a chromatography was not necessary, and the crude products were purified directly by crystallization. The crude products of **23** and **24** were not chromatographed but were purified by conversion to the HCl and the oxalate salts, respectively.

Method B. 6-Methyl-7-[(*n*-propylamino)acetyl]-1,2,6,7-tetrahydroindolo[1,7-*ab*][1,5]benzodiazepine (14). To a stirred solution, under N_2, of 19.9 g (0.336 mol) of *n*-propylamine in 120 mL of absolute EtOH was added in portions 12.0 g (0.0336 mol) of **3**. Each successive portion was added only when the previous one had dissolved and this process took 4–5 h. When the addition was completed, the solution was treated with charcoal for 10 min, filtered, and concentrated. The residue was dissolved in 250 mL of $CHCl_3$, and this solution was extracted twice with H_2O, dried over Na_2SO_4, and concentrated in vacuo to a waxy solid (15.4 g). This was boiled and triturated with 15 mL of EtOAc and cooled, and the white crystals were collected and dried to furnish 5.2 g (46%) with mp 113–118 °C. Recrystallization from hexane afforded 2.1 g (20% overall yield) of pure **14**, mp 116–118 °C.

Similarily prepared were **17** and **19–21**.

General Procedure for Reduction with $LiAlH_4$. Compounds **14–16**, **34**, **36**, **46**, and **47** were all reduced in the same manner with $LiAlH_4$ to provide the 7-(aminoalkyl) tetracycles **28–32** and **38** and **39** of Tables III and IV. The following example illustrates the method used.

7-(2-Aminoethyl)-6-methyl-1,2,6,7-tetrahydroindolo[1,7-*ab*][1,5]benzodiazepine Dihydrobromide (28). To a stirred mixture of 4.56 g (0.12 mol) of $LiAlH_4$ in 100 mL of dry THF, kept at 0–5 °C under N_2, was added slowly a solution of 8.26 g (0.03 mol) of **46** in 90 mL of dry THF over 1 h. The reaction mixture was stirred for 1 h at room temperature, refluxed for 5 h, and then left overnight at ambient temperature. The stirred mixture was then treated slowly and cautiously with a solution of 25 mL of H_2O in 25 mL of THF while maintaining the temperature below 10 °C. After the mixture was stirred an additional 2 h, the salts were filtered, washed twice with THF, and discarded. The combined filtrates were concentrated to a residue which was taken up in CH_2Cl_2. This solution was extracted three times with H_2O, dried over Na_2SO_4, and concentrated to a thick oil (8.6 g) which crystallized. This was dissolved in 50 mL of EtOH and treated with 100 mL of ether previously saturated with gaseous HBr. The salt which separated was collected, washed with ether, and dried to afford 8.0 g (61%) of product as the dihydrobromide salt, mp 237–240 °C dec. Recrystallization from 40 mL of EtOH provided 5.3 g (40% overall yield) of pure **28** with mp 243–245 °C dec.

7-[2-(Dimethylamino)ethyl]-6-(2-phenylethyl)-1,2,6,7-tetrahydroindolo[1,7-*ab*][1,5]benzodiazepine Oxalate (33). A solution of 5.38 g (0.013 mol) of **24** (as the free base) in 40 mL of dry THF was added dropwise to a rapidly stirred, ice-cold solution of 53 mL of 1 M borane in THF, kept under N_2. The reaction was then refluxed for 2 h, cooled to 0 °C, and treated dropwise with 60 mL of 6 N HCl. The reaction was then refluxed for 15 min, cooled to 0 °C, and made alkaline by the addition of solid NaOH pellets. The resulting aqueous phase was extracted twice with 75 mL of ether. The combined ether extracts were washed with brine, dried over anhydrous K_2CO_3, and concentrated to afford 5.8 g of crude product. Attempts to purify this material by crystallization or salt formation failed. It was therefore dissolved in a small volume of $CHCl_3$ and adsorbed onto a chromatography column containing 250 g of silica gel packed in petroleum ether. The column was eluted first with petroleum ether and then with increasing percentages (20% per step) of ether in petroleum ether, followed by increasing percentages (10% per step) of methanol in ether. Those fractions containing pure product were combined, concentrated, and converted to the oxalate salt. Recrystallization from $CHCl_3$–acetone afforded 0.82 g (13% overall yield) of pure **33**, mp 208 °C dec.

Ethyl (1,2,6,7-Tetrahydroindolo[1,7-*ab*][1,5]benzodiazepin-7-yl)acetate (40). A stirred mixture, under N_2, of 11.1 g (0.050 mol) of Ia, 4.2 g (0.055 mol) of sodium bicarbonate, and 6.1 mL (0.055 mol) of ethyl bromoacetate in 100 mL of DMF was slowly heated to 94 °C. This took 1.1 h, after which TLC analysis indicated the reaction was completed. The mixture was then concentrated and the residue was partitioned between $CHCl_3$ and H_2O. The organic phase was separated, washed several times with H_2O, dried over Na_2SO_4, and concentrated in vacuo to an oil weighing 12.7 g (82% yield). This material, although virtually pure by TLC, could not be worked to an analytically pure state

and was therefore used as is in the subsequent reduction with $LiAlH_4$.

Ethyl 3-(1,2,6,7-Tetrahydroindolo[1,7-*ab*][1,5]benzodiazepin-7-yl)propionate (41). A stirred mixture of 12.9 g (0.057 mol) of Ia, 33 mL (0.31 mol) of ethyl acrylate, and 2.5 mL of acetic acid was refluxed for 18 h. The resulting solution was then concentrated. The residue was taken up in $CHCl_3$, washed with saturated $NaHCO_3$ solution and with H_2O, and dried over Na_2SO_4. After concentration in vacuo, there was obtained 17.0 g (91% yield) of **41** as an oil. This substance was virtually pure by TLC and was therefore used as is in the subsequent reduction with $LiAlH_4$.

2-(1,2,6,7-Tetrahydroindolo[1,7-*ab*][1,5]benzodiazepin-7-yl)ethanol (42). A stirred mixture of 0.98 g (0.027 mol) of $LiAlH_4$ and 100 mL of THF was cooled under N_2 to 0 °C. To this was added a solution of 10.6 g (0.034 mol) of **40** in 70 mL of THF over 1 h. When the addition was completed, the cooling bath was removed and the mixture was refluxed for 4 h. After cooling to 5 °C, the reaction was cautiously quenched by successive treatment with 1 mL of H_2O, 2 mL of 10% NaOH, and 2 mL more of H_2O. The salts were filtered and the cake washed well with 400 mL of $CHCl_3$. The combined filtrates were washed with brine, dried over Na_2SO_4, and concentrated in vacuo to afford 8.14 g (89% yield) of **42** as an oil. This oil was about 90% pure by TLC and was used as is in a subsequent reaction.

3-(1,2,6,7-Tetrahydroindolo[1,7-*ab*][1,5]benzodiazepin-7-yl)-1-propanol (43). Intermediate 41 was reduced with $LiAlH_4$ and worked up in the same manner as described above. It was, however, purified successfully by conversion to the HCl salt (ethereal HCl) and recrystallization from MeOH–ether. The pure salt had mp 193–196 °C and was obtained in 44% overall yield. Anal. ($C_{18}H_{20}N_2O$·HCl) C, H, N.

(1,2,6,7-Tetrahydroindolo[1,7-*ab*][1,5]benzodiazepin-7-yl)ethyl Methanesulfonate (44). A stirred solution of 8.1 g (0.030 mol) of **42** and 6.4 mL (0.045 mol) of triethylamine in 70 mL of CH_2Cl_2 was cooled under N_2 to 0 °C. Then 2.83 mL (0.036 mol) of methanesulfonyl chloride was added dropwise over a 15-min period. After 0.5 h, the reaction solution was extracted with H_2O, with 2.5 N HCl, and with a saturated $NaHCO_3$ solution. After drying over Na_2SO_4, the solution was concentrated in vacuo to leave 8.9 g (85% yield) of **44** as an oil which was rather pure by TLC. Due to the instability of this intermediate, an analytical sample could not be obtained and it was used as is in a subsequent reaction.

By using the same procedure as described above, there was prepared **3-(1,2,6,7-tetrahydroindolo[1,7-*ab*][1,5]benzodiazepin-7-yl)propyl methanesulfonate (45)** in 92% yield starting from **43**.

7-[2-(Methylamino)ethyl]-1,2,6,7-tetrahydroindolo[1,7-*ab*][1,5]benzodiazepine Oxalate (25). A solution of 8.8 g (0.025 mol) of **44** in 150 mL of EtOH was heated to reflux while bubbling in gaseous methylamine. After 1 h, the reaction was cooled to room temperature and the solution was decanted from a small amount of oily residue. After concentration, the product was dissolved in 150 mL of CH_2Cl_2, and this solution was extracted with 4 N NaOH and with H_2O and dried over Na_2SO_4. The solvent was removed in vacuo to leave 4.68 g (68%) of product free base an an oil. Both the HCl and HBr salts proved to be hygroscopic. The oxalate salt was prepared as follows. A solution of 2.5 g of crude base in 30 mL of warm EtOH was added in one portion to a stirred solution of 0.81 g of oxalic acid in 100 mL of ether. The resulting oxalate salt was collected and found to weigh 2.5 g. Recrystallization from DMF–acetonitrile afforded 0.97 g (20% overall yield). For the physical properties of this compound, see Table III.

7-[3-(Methylamino)propyl]-1,2,6,7-tetrahydroindolo[1,7-*ab*][1,5]benzodiazepine Dihydrobromide (26). This compound was prepared from **45** in the same manner as above. The crude amine was converted to the dihydrobromide salt (EtOH–ethereal HBr) and the salt was recrystallized from EtOH–ether in 35% overall yield. See Table III for physical properties.

7-[3-(Dimethylamino)propyl]-1,2,6,7-tetrahydroindolo[1,7-*ab*][1,5]benzodiazepine Dihydrochloride (27). This was prepared from **45** in the same way as described for the synthesis of **26**, except that gaseous dimethylamine was used. Purification was achieved by conversion of the crude base to its dihydrochloride salt (EtOH–ethereal HCl), followed by recrystallization from acetonitrile–ethyl acetate. The overall yield was 33%. See Table III for physical properties.

7-(Cyanomethyl)-6-methyl-1,2,6,7-tetrahydroindolo[1,7-*ab*][1,5]benzodiazepine (46). A stirred mixture of 23.6 g (0.10 mol) of Ib, 15.1 g (0.20 mol) of chloroacetonitrile, and 16.8 g (0.20 mol) of $NaHCO_3$ in 200 mL of DMF was heated at 75 °C under N_2 overnight. Then the mixture was cooled to room temperature and 200 mL of H_2O was added over 1 h with vigorous stirring. After the mixture was stirred for an additional hour, the crystalline product was filtered, washed five times with H_2O, and then dried to give 25.0 g (91%). Recrystallization from 700 mL of EtOH (charcoal) afforded 19.5 g (71% yield) of pure nitrile, mp 148–150 °C. Anal. ($C_{18}H_{17}N_3$) C, H.

6-Methyl-7-[2-[(ethoxycarbonyl)amino]ethyl]-1,2,6,7-tetrahydroindolo[1,7-*ab*][1,5]benzodiazepine (47). A stirred mixture of 14.0 g (0.032 mol) of **28** and 10.8 g (0.128 mol) of $NaHCO_3$ in 140 mL of CH_2Cl_2 was cooled to 0–5 °C under N_2 and then treated dropwise with a solution of 5.20 g (0.048 mol) of ethyl chloroformate in 50 mL of CH_2Cl_2. When the addition was completed (1 h), the mixture was stirred overnight at room temperature. Water was then added to dissolve the salts. The organic phase was separated, washed twice with H_2O, dried over Na_2SO_4, and concentrated in vacuo to a thick oil weighing 10.3 g (92%). This was crystallized from 10 mL of MeOH to give 8.3 g (74% yield) of pure carbamate, mp 94–96 °C. Anal. ($C_{21}H_{25}N_3O$) C, H, N.

6-[3-(Dimethylamino)propyl]-1,2,6,7-tetrahydroindolo[1,7-*ab*][1,5]benzodiazepine Dihydrochloride (48). The required Grignard reagent, 3-(dimethylamino)propylmagnesium chloride, was prepared as follows. To a stirred mixture of 1.94 g (0.08 mol) of magnesium turnings in 5 mL of THF, kept under N_2, was added dropwise a solution of 7.14 g (0.057 mol) of 3-(dimethylamino)propyl chloride and 1.61 mL (0.019 mol) of 1-bromo-2-chloroethane in 28 mL of dry THF. After 2 mL was added, the mixture became cloudy and a vigorous reaction ensued. The remaining solution was added dropwise over 75 min with periodic cooling to maintain gentle reflux. When the addition was completed, the reaction mixture was heated at reflux for 40 min and then cooled to 10–15 °C. This freshly prepared Grignard reagent was then added slowly by syringe to a stirred slurry of 5.0 g (0.019 mol) of 1,2-dihydroindolo[1,7-*ab*][1,5]benzodiazepine[3] in 76 mL of dry THF under a N_2 blanket. After 0.5 h, the reaction was poured into a stirred mixture of 200 mL of ice and 25 mL of concentrated HCl, and then enough concentrated NH_4OH was added to make the system alkaline. The product base was extracted into 400 mL of $CHCl_3$, and this was washed with H_2O and with brine, dried over Na_2SO_4, and concentrated to 5.86 g of oil. This was dissolved in 2-PrOH and treated with ethereal HCl to the turbidity point. The resulting salt was collected and found to weigh 6.58 g (91%). Recrystallization from MeOH–ether afforded 5.43 g (74% overall yield) of pure **48**·2HCl, mp 228–230 °C. Anal. ($C_{20}H_{25}N_3$·2HCl) C, H, N.

Acknowledgment. The authors express their gratitude to Marc N. Agnew and his group for spectra data, to Susan A. Bullock, Kathleen Morrison, and Jeffrey Wilker for the pharmacological assays, and to Mrs. Rose Marie Boysen for her help in the preparation of the manuscript.