boiling 10% HCl (foaming). After refluxing for 1 hr, the solution was cooled, diluted with 100 ml of H_2O, and filtered hot. The oil which separated on addition of excess 10 *N* NaOH to the cold filtrate was extracted with PhH, and the combined extracts were washed with H_2O, dried, and evaporated. Treatment of the oily residue with ethanolic HCl gave, after 2 days, 9.0 g (87%) of crystalline product: mp 217–220°. Recrystallization from 95% EtOH–Et_2O provided 5.0 g (48%): mp 225–228°. Constant melting material was obtained by two additional recrystallizations: mp 234–235°; ir 2780–2550 (NH_3^+), 2100 (NH_3^+), 1613 and 1563 (NH_3^+ and aromatic), and 1517 cm^{-1} (aromatic). Anal. ($C_{26}H_{42}Cl_2N_2O_4$) C, H, N.

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Basic Derivatives of 6,7-Dihydroindolo[1,7-*ab*][1]benzazepine and 6*H*-Indolo[7,1-*cd*][1,5]benzoxazepine as Potential Antidepressant Agents

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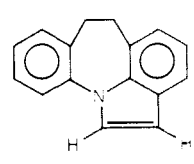
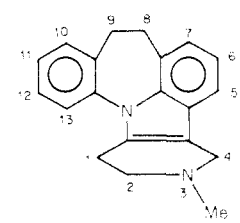
Basic derivatives of 6,7-dihydroindolo[1,7-*ab*][1]benzazepine and 6*H*-indolo[7,1-*cd*][1,5]benzoxazepine incorporating the imipramine basic side chain were synthesized and screened for antidepressant activity in mice. With few exceptions, the compounds unsubstituted at C-2 antagonized reserpine-induced ptosis and hypothermia showing negligible anticholinergic and antihistaminic properties. The compound 1-[2-(*N*-methyl-*N*-benzylamino)ethyl]-6,7-dihydroindolo[1,7-*ab*][1]benzazepine had the highest toxicity–activity ratio.

In studies of imipramine-like antidepressants, some compounds incorporating the main structural features of imipramine were investigated.[1] The imipramine basic side chain was also incorporated into 6,7-dihydroindolo[1,7-*ab*][1]benzazepine (I), but the resulting compounds all substituted at C-2 did not show imipramine-like activity in the usual pharmacological tests.[2] Continuing along this line, 3-methyl-1,2,3,4,8,9-hexahydropyrido[4',3':2,3]-indolo[1,7-*ab*][1]benzazepine (II) was also synthesized[3] and was claimed to have powerful antiserotonin activity but was devoid of antidepressant activity. It occurred to us that the alkyl substituents at C-2 could be responsible for the absence of activity, either by steric hindrance in drug–receptor interaction or by preventing the formation of some active metabolites. Therefore, novel N-substituted 1-(2-aminoethyl)-6,7-dihydroindolo[1,7-*ab*]-[1]benzazepines (Table IV, **28–31**), unsubstituted at C-2, were synthesized and evaluated for antidepressant activity. Since the initial pharmacological results were positive, we have synthesized several other compounds including some basic derivatives of 6*H*-indolo[7,1-*cd*][1,5]benzoxazepine



I



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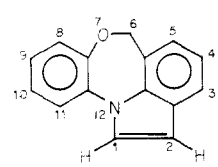
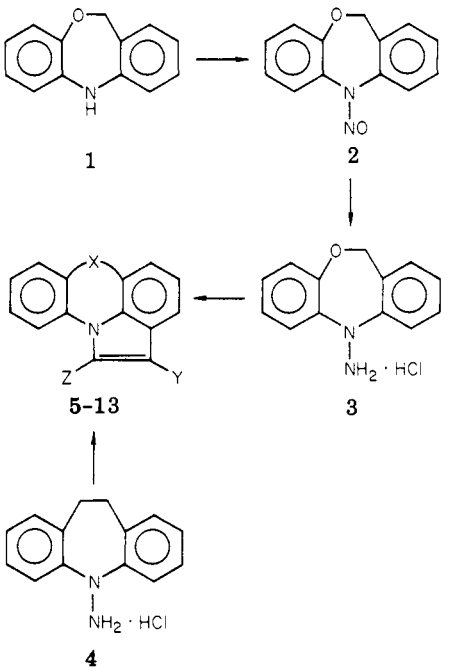


III

(III), in order to gain further insight into the structure–activity relationships.

Chemistry. The synthesis of all the compounds reported in Table IV begins with the preparation of **5–13** as

Scheme I



outlined in Scheme I. Compound **4** was prepared according to the procedure of Cattanach et al.[2] A similar synthetic approach was suitable for the preparation of 5-amino-5,11-dihydrodibenz[*b*,*e*][1,4]oxazepine (**3**). The starting material 5,11-dihydrodibenz[*b*,*e*][1,4]oxazepine[4] (**1**) was treated with powdered sodium nitrite in dimethylformamide to yield **2**.

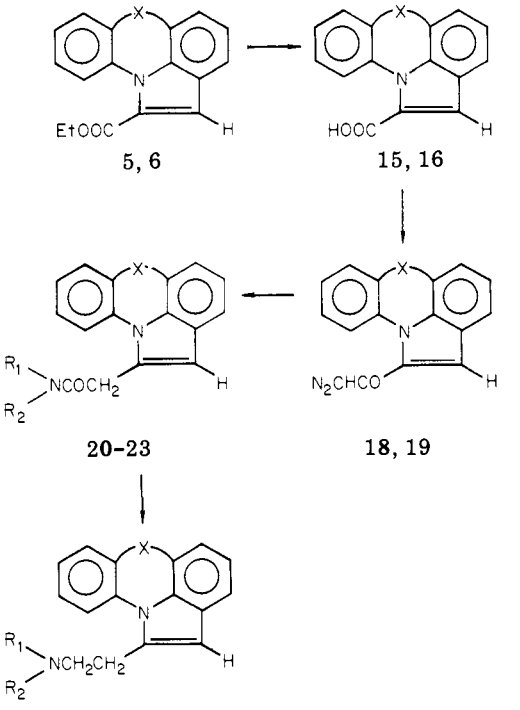
The next reduction of *N*-nitroso compound **2** with zinc dust and acetic acid[5] gave the desired hydrazine, which was converted to its hydrochloride **3**. Condensation of **3** and **4** with suitable keto compounds (Table I) gave hydrazones which without isolation cyclized (Fischer cyclization) to **5–13** in ethanolic hydrogen chloride.[2]

Compound **4** with ethyl 4-phenylacetoacetate was converted to a mixture of **11** and **12**. The two isomers were shown by NMR and GC to be present in a 1:1 ratio and separated by column chromatography on alumina. In the same manner **3** reacted with ethyl pyruvate affording a mixture of **6** and **13** isomers present in a 4:1 ratio by NMR and separated as above. In contrast reaction of **3** with 2-butanone gave only **8**.

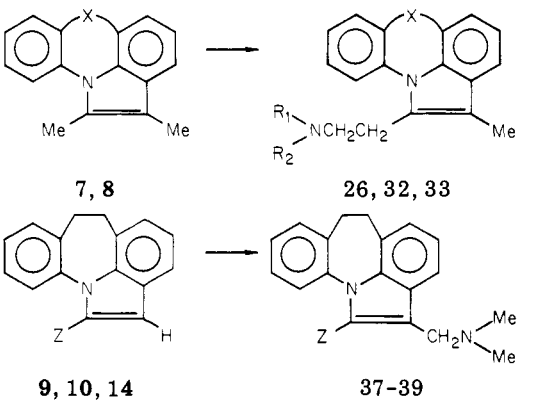
The structures of **6**, **8**, and **11–13** were assigned from their NMR spectra. Comparison of the NMR spectra of **11** and **12** showed that only in the 1-phenyl isomer the C-10 and C-11 protons were relatively shielded, as expected[6] on the basis of the structure of the isomers. When the NMR spectra of the two isomers, derived from **3** and ethyl pyruvate, were compared to the spectrum of **5**, it was found that the C-3 proton in only one isomer and in **5** showed a similar downfield one-proton quartet centered at δ 7.55 (J = 7 and 3 Hz) attributable to the deshielding influence of the indolic double bond.[7] In contrast, the C-3 proton in the other isomer shifted to higher field ($\Delta\delta$ 15 ppm) than the corresponding proton in **5**. Since it has been recognized[8] that the methoxy substituent causes significant shielding on the aromatic protons, the structure **13** was assigned to the isomer which showed the C-3 proton quartet centered at δ 7.40 (J = 7 and 3 Hz). Accordingly, the structure **8** was assigned to the single product obtained by cyclization of **3** with 2-butanone in ethanolic hydrogen chloride since its NMR spectrum presented a similar downfield C-3 proton quartet of **7**.

Hydrolysis of **5** and following decarboxylation of the acid

Scheme II



Scheme III

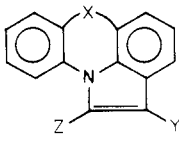


15, according to a procedure previously described,[2] resulted in the formation of the 6,7-dihydroindolo[1,7-*ab*][1]-benzazepine (**14**).

Compounds **27–30** of Table IV were prepared as shown in Scheme II. The synthesis involved formation of the acid chlorides from **5** and **6** and their reaction with diazomethane to yield the diazo ketones **18** and **19** (Table II). Photochemical Wolff rearrangement[9] of the last in the presence of an excess of secondary amines yielded the corresponding amides **20-23** (Table III) which, upon reduction with lithium aluminum hydride in refluxing ethyl ether, yielded the basic derivatives **27–30**.

In order to obtain **26**, **32**, **33**, and **37–39** of Table IV the tetracyclic compounds **7–10** and **14** were subjected to Mannich reaction[7,10] as outlined in Scheme III. Condensation of **7** and **8** with formaldehyde and dimethylamine occurred on the C-1 methyl group,[11] yielding **32** and **26**, respectively. Treatment of **8** with formaldehyde and *N*-methyl-*N*-benzylamine gave **33**. No substitution on the methyl group was observed under these conditions for **9**. Mannich condensation[2,12] of **9**, **10**, and **14** with formaldehyde and dimethylamine occurred on C-2 to give **37–39**. Compounds **31** and **34** of Table IV were obtained by catalytic debenzylation[2] of **29** and **33**.

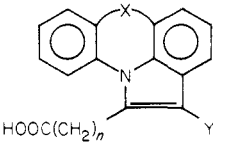
Table I. Fischer Cyclization Compounds[a]



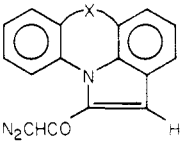
No.	X	Y	Z	Condensing keto compound	Reflux time, hr	Formula	Yield, %[b]	Mp, °C	Crystn solvent[c]	Analyses[d]
5	CH_2-CH_2	H	COOEt	MeCOCOOEt	4	$C_{19}H_{17}NO_2$	50	94-96[e,f]	P	C, H, N
6	O-CH_2	H	COOEt	MeCOCOOEt	1	$C_{18}H_{15}NO_3$	35	76-78	P	C, H, N
7	CH_2-CH_2	Me	Me	MeCOEt	1	$C_{18}H_{17}N$	42	84-86[g]	A	C, H, N
8	O-CH_2	Me	Me	MeCOEt	0.5	$C_{17}H_{15}NO$	65	135-137[h]	A	C, H, N
9	CH_2-CH_2	H	Me	MeCOMe	4	$C_{17}H_{15}N$	23	91-93[i]	M	C, H, N
10	CH_2-CH_2	H	Ph	PhCOMe	1	$C_{22}H_{17}N$	22	166-167	E	C, H, N
11	CH_2-CH_2	Ph	CH_2COOEt	$PhCH_2CO$-CH_2COOEt	5	$C_{26}H_{23}NO_2$	12[j]	*k*		
12	CH_2-CH_2	CH_2COOEt	Ph	$PhCH_2CO$-CH_2COOEt	5	$C_{26}H_{23}NO_2$	16[j]	169-170[i]	E	C, H, N
13	CH_2-O	H	COOEt	MeCOCOOEt	1	$C_{18}H_{15}NO_3$	10	125-127	P	C, H, N
14	CH_2-CH_2	H	H			$C_{16}H_{13}N$	79	99-101[m]	E	C, H, N

[a] All samples were obtained by refluxing 3 or **4** with suitable keto compounds in ethanolic HCl, except 14 which was obtained from 5 as previously described.[2] [b] No attempts were made to optimize yields. [c] P, petroleum ether; A, Me_2CO; M, MeOH; E, EtOH. [d] Analyses for elements were within ±0.4% of the theoretical values. [e] Lit.[2] mp 90-92°. [f] NMR δ 7.55 (dd, 1, *J* = 7 and 3 Hz, H-3) and 7.45 (s, 1, H-2). [g] NMR δ 7.35 (dd, 1, *J* = 7 and 3 Hz, H-3), 2.45 (s, 3, CH_3-1), and 2.30 (s, 3, CH_3-2). [h] NMR δ 7.35 (dd, 1, *J* = 7 and 3 Hz, H-3), 5.25 (s, 2, OCH_2), 2.45 (s, 3, CH_3-1), and 2.30 (s, 3, CH_3-2). [i] NMR δ 6.45 (q, 1, *J* = 1 Hz, H-2) and 2.50 (d, 3, *J* = 1 Hz, CH_3). [j] Yield given for the chromatographic isolation on alumina. [k] Sample not crystallized; NMR δ 7.70-6.95 (m, 12, Ar H) and 4.77 (s, 2, CH_2CO); ir 1740 cm^{-1} (ester C=O). [l] NMR δ 7.70-6.40 (m, 12, Ar H) and 4.72 (s, 2, $COCH_2$); ir 1740 cm^{-1} (ester C=O); $AlLiH_4$ reduction of a sample afforded 2-(2-hydroxyethyl)-6,7-dihydro-1-phenylindolo[1,7-*ab*][1]benzazepine: mp 168-170° (C_6H_6-petroleum ether); NMR δ 3.95 (t, 2, *J* = 6 Hz, CH_2CH_2O) and 3.50-2.95 (m, 6, seven-membered ring H and CH_2CH_2O) after addition of D_2O. Anal. ($C_{24}H_{21}NO$) C, H, N. [m] Lit.[2] mp 96-97°.

Table II. Acids 15-17 and Diazo Ketones 18 and 19



15-17

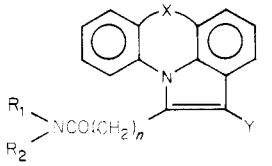


18, 19

No.	X	Y	*n*	Formula	Yield, %[a]	Mp, °C	Crystn solvent[b]	Analyses[c]
15	CH_2-CH_2	H	0	$C_{17}H_{13}NO_2$	89	218-220[d,e]	E-W	C, H, N
16	O-CH_2	H	0	$C_{16}H_{11}NO_3$	91	232-234[d,f]		
17	CH_2-CH_2	Ph	1	$C_{24}H_{19}NO_2$	66	192-194[d]	B-P	C, H, N
18	CH_2-CH_2			$C_{18}H_{13}N_3O$	88	119-121[f]		
19	O-CH_2			$C_{17}H_{11}N_3O_2$	*g*			

[a] No attempts were made to optimize yields. [b] E, EtOH; W, H_2O; B, C_6H_6; P, petroleum ether. [c] Analyses for elements were within ±0.4% of the theoretical values. [d] Decomposed. [e] Lit.[2] mp 221-223° dec. [f] Melting point was determined on the crude product. [g] Isolated in 84% yield on Florisil column and not crystallized.

Table III. Amides

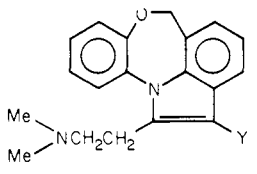


20-25

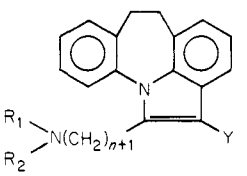
No.	X	Y	*n*	R_1	R_2	Formula	Yield, %[a]	Mp, °C	Crystn solvent[b]	Analyses[c]
20	CH_2-CH_2	H	1	Me	Me	$C_{20}H_{20}N_2O$	58[d]	*e*		
21	O-CH_2	H	1	Me	Me	$C_{19}H_{18}N_2O_2$	61[d]	*e*		
22	CH_2-CH_2	H	1	Me	$PhCH_2$	$C_{26}H_{24}N_2O$	39[d]	*e*		
23	CH_2-CH_2	H	1	$PhCH_2$	$PhCH_2$	$C_{32}H_{28}N_2O$	53[d]	*e*		
24	CH_2-CH_2	H	0	Me	Me	$C_{19}H_{18}N_2O$	96[d]	*e*		
25	CH_2-CH_2	Ph	1	Me	Me	$C_{26}H_{24}N_2O$	47	176-178	ET	C, H, N

[a] No attempts were made to optimize yields. [b] ET, Et_2O. [c] Analyses for elements were within ±0.4% of the theoretical values. [d] Yield given for the chromatographic isolation on alumina. [e] The compound was an oil.

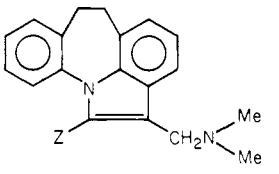
Table IV. Basic Derivatives of 6,7-Dihydroindolo[1,7-*ab*][1]benzazepine (28-39) and 6*H*-Indolo[7,1-*cd*][1,5]benzoxazepine (26, 27)



26, 27



28-36



37-39

No.	Y	Z	*n*	R_1	R_2	Formula	Yield, %[a]	Mp, °C	Crystn solvent[b]	Analyses[c]
26	Me					$C_{20}H_{22}N_2O\cdot HCl$	44	183-185[d]	M-ET	C, H, Cl, N
27	H					$C_{19}H_{20}N_2O\cdot HCl$	70	209-211	M-ET	C, H, Cl, N
28	H		1	Me	Me	$C_{20}H_{22}N_2$	92[e]	*f*		*g*
29	H		1	Me	$PhCH_2$	$C_{26}H_{26}N_2\cdot HCl$	77	201-203	M-ET	C, H, Cl, N
30	H		1	$PhCH_2$	$PhCH_2$	$C_{32}H_{30}N_2\cdot HCl$	53	197-199	E-ET	C, H, Cl, N
31	H		1	Me	H	$C_{19}H_{20}N_2\cdot HCl$	76	200-202	M-ET	C, H, Cl, N
32	Me		1	Me	Me	$C_{21}H_{24}N_2$	60[e]	*h*		*i*
33	Me		1	Me	$PhCH_2$	$C_{27}H_{28}N_2\cdot HCl$	38	199-201	M-ET	C, H, Cl, N
34	Me		1	Me	H	$C_{20}H_{22}N_2\cdot HCl$	87	204-206	M-ET	C, H, Cl, N
35	H		0	Me	Me	$C_{19}H_{20}N_2$	83	74-76	ET	*j*
36	Ph		1	Me	Me	$C_{26}H_{26}N_2$	50	156-158	ET	C, H, N
37		H				$C_{19}H_{20}N_2\cdot HCl$	67	133-135[k,l]	W	C, H, Cl, N
38		Me				$C_{20}H_{22}N_2$	51[e]	*m*		*n*
39		Ph				$C_{25}H_{24}N_2$	48	139-140	M	C, H, N

[a] No attempts were made to optimize yields. [b] M, MeOH; ET, Et_2O; E, EtOH; W, H_2O. [c] Analyses for elements were within ±0.4% of the theoretical values. [d] Free base, mp 93-95° (petroleum ether): NMR δ 2.30 (s, 1, CH_3-2). [e] Yield given for the chromatographic isolation on alumina. [f] The compound was an oil. [g] Characterized as the methiodide, mp 190-192° (ethanol). Anal. ($C_{21}H_{25}IN_2$) C, H, N. [h] The free base was an oil. [i] Characterized as the methiodide, mp 168-170° (ethanol). Anal. ($C_{22}H_{27}IN_2$) C, H, N. [j] Characterized as the methiodide, mp 265-267° (ethanol). Anal. ($C_{20}H_{23}IN_2$) C, H, N. [k] Lit.[2] mp 135-137°. [l] Free base, mp 67-69° (cyclohexane): NMR δ 7.45-6.85 (m, 8, Ar H and H-1). [m] The free base was an oil: NMR δ 2.50 (s, 3, CH_3-1). [n] Characterized as the methiodide, mp 258-260° (ethanol). Anal. ($C_{21}H_{25}IN_2$) C, H, N.

Table V. Pharmacological Data

	Reserpine antagonism		Antispasmodic activity in vitro		
No.	Ptosis prevention, MED,[a] mg/kg po	Hypothermia reversal, MED,[a] mg/kg po	Antihistaminic act., ED_{50}, μg/ml	Anticholinergic act., ED_{50}, μg/ml	Acute toxicity, LD_{50},[b] mg/kg po
26	10	>50	NT[c]	NT[c]	310 (221-434)
27	3	50	1	10	195 (156-244)
28	2	5	0.2	1	420 (258-685)
29	3.5	5	>5[d]	>5[d]	>4000
30	50	>50	>10	>10	1400 (833-2350)
31	1	2.5	0.6	4	410 (259-648)
32	7.5	>50	>10	>10	195 (129-294)
33	>50	>50	NT	NT	>4000
34	2.5	>50	5	6	390 (312-488)
35	>50	>50	NT	NT	210 (140-315)
36	>50	>50	NT	NT	1900 (1265-2850)
37	>50	>50	NT	NT	170 (94-305)
38	>50	>50	NT	NT	450 (265-765)
39	>50	>50	NT	NT	1600 (936-2730)
Imipramine	2.5	2.5	0.006	0.3	410 (284-595)

[a] MED = approximate median effective dose derived as explained in the Experimental Section. [b] 95% confidence limits of LD_{50} are reported in parentheses. [c] NT = not tested. [d] Compound insoluble at higher concentrations.

Compounds **35** and **36** of Table IV were synthesized by the procedure shown in Scheme IV. Hydrolysis of the esters **5** and **11** followed by condensation of the corresponding acid chlorides with dimethylamine,[13] afforded the amides **24** and **25**. Reduction of **24** and **25** with lithium aluminum hydride in refluxing ethyl ether gave **35** and **36**.

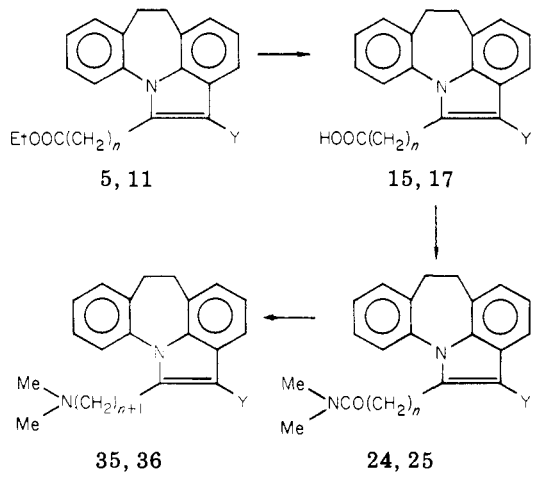
Results and Discussion

All the compounds listed in Table IV were evaluated for the antidepressant activity using the antagonism to the reserpine-induced ptosis and hypothermia tests. The results are listed in Table V wherein the antispasmodic activity in vitro and the acute toxicity are also reported.

The amino derivatives **26–29**, **31**, **32**, and **34** were able to inhibit reserpine-induced ptosis, showing various degrees of potency. Three of these compounds (**28**, **29**, and **31**) were also active in reversing reserpine-induced hypothermia. All the compounds tested for antispasmodic activity were less active than imipramine as acetylcholine and histamine antagonists. The observation of animals for gross symptomatology revealed no prominent behavioral changes indicative of CNS stimulation or depression, clonic convulsions appearing at lethal doses only.

The results of the antireserpine tests revealed some interesting aspects of the structure–activity relationships of these compounds. Mono- or disubstituted aminoalkyl groups at C-1 of 6,7-dihydroindolo[1,7-*ab*][1]benzazepine (I) are necessary for the antidepressant activity as illus-

Scheme IV



trated by the comparison of **28** and **37**. The inactivity of **35** indicates that the separation of the amino group from the nitrogen atom in structure I by three carbons is important for antireserpine activity. Substituents at C-2 resulted in reduction or elimination of activity. In particular, the substitution of a methyl group at C-2 of **29** was found to completely abolish the antidepressant activity (**33**).

As far as the amino group substituents are concerned, the monomethyl compound **31** displayed higher antireserpine activity than the corresponding dimethyl-substituted **28**. Replacement of both methyl groups of **28** by benzyl groups (**30**) completely abolished its activity, while replacement of only one methyl group of **28** with a benzyl group (**29**) reduced its acute toxicity without a corresponding decrease in antireserpine activity. Compound **29** compared favorably with imipramine in terms of the toxicity–activity ratio. The introduction of an oxygen atom into the ethylene bridge (**26** and **27**) did not improve the antidepressant activity of **32** and **28**.

Owing to these screening results, **29** and **31** showed the best activity profiles and were selected for further investigation.

Preliminary pharmacological results showed that these two compounds are devoid of anti-MAO activity as revealed by the absence of potentiation of tryptamine symptomatology in the rat.[14] The same compounds were unable to antagonize the convulsions induced by pentylenetetrazole[15] or strichnine[16] and to interfere with the motor coordination in mice as assessed by the performance on the rotating rod test.[17] Furthermore, **29** was as active as imipramine in antagonizing serotonin-induced contraction of the isolated guinea-pig ileum.[18]

Experimental Section

Synthetic Procedures. Melting points were taken in open capillary tubes using a Tottoli apparatus (N. Büchi, Flawil, Switzerland) and are uncorrected. Where analyses are indicated only by symbols of the elements, analytical results obtained for these elements were within ±0.4% of the theoretical values. All intermediates and final products were checked by ir and NMR spectroscopy (Perkin-Elmer 257 and Varian T-60A, respectively) and their spectra were found to be in agreement with the assigned structures. Ir and NMR spectra were obtained for KBr disks and for solutions in $CDCl_3$ (Me_4Si), respectively. Thin-layer chromatograms were prepared using silica gel 60F-254 plates from E. Merck, Germany. "Alumina" refers to neutral Al_2O_3 B III from E. Merck, Germany. "Florisil" refers to magnesium silicates (100–200 mesh) from Floridin Co., Pa.

5,11-Dihydro-5-nitrosodibenz[*b,e*][1,4]oxazepine (2). To a mixture of 3.94 g (0.02 mol) of **1** and 1.52 g (0.022 mol) of $NaNO_2$ in 40 ml of DMF, 20 ml of 2 *N* HCl was added slowly under stirring at 5°. The cooling bath was then removed and stirring continued for 1 hr. The mixture was poured into water; the solid was filtered off, washed, and dried to yield 4.2 g of **2** (93%), mp 96–98°. Anal. ($C_{13}H_{10}N_2O_2$) C, H, N.

5-Amino-5,11-dihydrodibenz[*b,e*][1,4]oxazepine Hydrochloride (3). A mixture of 8.43 g (0.129 g-atom) of Zn dust and 15 ml of water was stirred vigorously at 10° while a solution of 6.78 g (0.03 mol) of **2** in 6.8 ml of glacial AcOH and 200 ml of EtOH was added in a slow stream at 20°. The mixture was stirred for 10 min at room temperature. The solution was filtered from the unreacted Zn and evaporated to dryness under reduced pressure. The residue was treated with 10% NH_4OH and extracted with Et_2O. The resulting solution was dried (Na_2SO_4), cooled, and treated with 2 *N* HCl under N_2. The precipitate was filtered off, washed with Et_2O, and dried in vacuo to yield 4.6 g (62%) of **3** (green), mp 120° dec. Anal. ($C_{13}H_{13}N_2OCl$) C, H, Cl, N.

6*H*-Indolo[7,1-*cd*][1,5]benzoxazepine-1-carboxylic Acid Ethyl Ester (6) and 7*H*-Indolo[1,7-*ab*][4,1]benzoxazepine-1-carboxylic Acid Ethyl Ester (13) (Table I, 5–13). A mixture of 11.94 g (0.048 mol) of **3** and 6.15 g (0.053 mol) of MeCOCOOEt in 450 ml of EtOH was refluxed for 0.5 hr with stirring. To the hot solution 50 ml of 3 *N* ethanolic HCl was added and the whole mixture was then heated under reflux for 0.5 hr. The mixture was cooled, NH_4Cl was filtered off, the solution was evaporated to dryness, and the crude material was extracted with $CHCl_3$. The organic phase was washed neutral with water, dried (Na_2SO_4), and evaporated under reduced pressure to give 12.6 g of crude oil. NMR indicated a 4:1 mixture of isomers **6** and **13**. After column chromatography on alumina (ratio 1:50) using C_6H_6–cyclohexane (1:1) as eluent and recrystallization from petroleum ether, 5 g of **6** [mp 76–78°; NMR δ 7.55 (dd, 1, *J* = 7 and 3 Hz, H-3), 7.45 (s, 1, H-2), and 5.25 (s, 2, OCH_2)] and 1.4 g of **13** [mp 125–127°; NMR δ 7.45 (s, 1, H-2), 7.40 (dd, 1, *J* = 7 and 3 Hz, H-3), and 5.30 (s, 2, CH_2O)] were obtained.

6,7-Dihydroindolo[1,7-*ab*][1]benzazepine (Table I, 14). A mixture of 2.9 g (0.011 mol) of the acid **15**, 25 ml of quinoline, and 0.30 g (0.003 mol) of CuCl was heated at 225° for 2 hr. The mixture was cooled and poured into ice–water. The resulting mixture was made neutral with 2 *N* HCl and then extracted with $CHCl_3$. The $CHCl_3$ solution was washed with water, dried (Na_2SO_4), and evaporated under reduced pressure to dryness. The residue was purified by column chromatography on alumina (ratio 1:30) using cyclohexane–$CHCl_3$ (9:4). The first component eluted was crystallized from EtOH to give 1.9 g of **14**: mp 99–101° (lit.[2] mp 96–97°); NMR δ 7.55 (d, 1, *J* = 4 Hz, H-1) and 6.70 (d, 1, *J* = 4 Hz, H-2).

6,7-Dihydro-2-phenylindolo[1,7-*ab*][1]benzazepine-1-acetic Acid (17) (Table II, 15–17). A solution of 8.8 g (0.023 mol) of **11** in 100 ml of EtOH and 36 ml of 20% NaOH was refluxed for 2.5 hr. EtOH was removed in vacuo, and the solution was diluted with 50 ml of water and acidified with a slight excess of HCl. The precipitate was filtered, washed neutral with water, and dried in vacuo. Recrystallization from C_6H_6–petroleum ether gave 5.3 g of **17**, mp 192–194° dec.

2-Diazo-1-(6,7-dihydroindolo[1,7-*ab*][1]benzazepin-1-yl)-ethanone (18) (Table II, 18 and 19). A solution of 7.9 g (0.03 mol) of **15** and 11.9 g (0.1 mol) of $SOCl_2$ in 60 ml of dry C_6H_6 was refluxed for 3 hr. The solution was cooled and evaporated to dryness under reduced pressure. The residue was taken up in 150 ml of dry Et_2O and added to a solution of 5.9 g (0.14 mol) of CH_2N_2 in 270 ml of dry Et_2O at 5°. After 30 hr at 20–25°, the Et_2O was evaporated and the crude product was purified by column chromatography on Florisil (ratio 1:30) using C_6H_6 as eluent. The collected fractions gave 7.6 g of **18** which was used in the next step without further purification.

6,7-Dihydroindolo[1,7-*ab*][1]benzazepine-1-(*N*-benzyl-*N*-methylacetamide) (22) (Table III, 20–23). A mixture of 8.62 g (0.03 mol) of **18** and 145 g (1.2 mol) of $PhCH_2NHMe$ in 1100 ml of EtOH was photolized (lamp 3500 Å) at 10–20° for 4 hr. The solution was evaporated to dryness and purified by column chromatography on alumina (ratio 1:50) using C_6H_6 as eluent. Evaporation of the first eluted component yielded 4.5 g of **22**, homogeneous to TLC using $CHCl_3$–MeOH (98:2). It showed ir absorption (1650 cm^{-1}) characteristic of an *N*-dialkylacetamide and was used without further purification in the next step.

6,7-Dihydro-2-phenylindolo[1,7-*ab*][1]benzazepine-1-(di-

methylacetamide) (25) (Table III, 24 and 25). A solution of 14.13 g (0.04 mol) of 17 and 23.8 g (0.2 mol) of $SOCl_2$ in 350 ml of dry C_6H_6 was refluxed for 3 hr. The solvent was then evaporated to dryness under reduced pressure below 30°. The acid chloride residue was taken up in 150 ml of dry Et_2O. After filtration the resulting solution was added slowly to a solution of 9.02 g (0.2 mol) of Me_2NH in 12 ml of dry Et_2O. The reaction mixture was cooled to 5° and stirred for 30 min. The solid precipitate that formed was filtered and crystallized from Et_2O to give 7.2 g of 25, mp 176–178°.

1-[2-(Dimethylamino)ethyl]-6,7-dihydro-2-methylindolo[1,7-*ab*][1]benzazepine (32) (Table IV, 26, 32, 33, and 37–39). To 15 ml of glacial AcOH 3.7 ml of 33% aqueous Me_2NH solution (0.025 mol) was added with cooling and then 1.75 ml of 40% CH_2O solution (0.025 mol), followed by 4.2 g (0.017 mol) of 7. The mixture was stirred and refluxed for 2 hr and then poured into cold water. The aqueous portion was alkalinized and extracted with Et_2O. The Et_2O solution was washed with water, dried (Na_2SO_4), and evaporated to yield a crude product which was purified by column chromatography on alumina (ratio 1:100) using C_6H_6–petroleum ether as solvent. An amount of 3.1 g of 32 was obtained as a yellow oil [NMR δ 2.30 (s, 1, CH_3–2)], which was converted to the methiodide, mp 168–170°, according to the procedure of Snyder et al.[19]

1-[2-(*N*-Benzyl-*N*-methylamino)ethyl]-6,7-dihydroindolo[1,7-*ab*][1]benzazepine Hydrochloride (29) (Table IV, 27–30, 35, and 36). A solution of 3.42 g (0.009 mol) of 22 in 25 ml of dry Et_2O was dropped into a suspension of 1.37 g (0.036 mol) of $AlLiH_4$ in 15 ml of dry Et_2O. The mixture was refluxed under stirring for 1 hr, cooled, and decomposed with water added at a rate so as to just maintain a gentle reflux of Et_2O. When all H_2 has been evolved, a slight excess of water was added and the mixture was stirred for 30 min at room temperature. The inorganic material was removed by filtration and washed with Et_2O. The Et_2O solution was dried (Na_2SO_4) and evaporated to give a crude oil. The residue was dissolved in 3 *N* ethanolic HCl and treated with Et_2O to give 2.8 g of 29. An analytical sample of 29 from MeOH–Et_2O had mp 201–203°.

1-[2-(Methylamino)ethyl]-6,7-dihydroindolo[1,7-*ab*][1]benzazepine Hydrochloride (31) (Table IV, 31 and 34). A solution of 2.02 g (0.005 mol) of 29 in 200 ml of MeOH was hydrogenated for 23 hr over 0.700 g of 5% Pd on charcoal at 20° and 1 atm. The solution was filtered and evaporated to dryness under reduced pressure to give 1.2 g of 31. An analytical sample was obtained by recrystallization from MeOH–Et_2O, mp 200–202°.

Pharmacology. All the tests in vivo were conducted on male Swiss mice weighing 20–25 g. Five to ten animals were used at each dose level. All the compounds were administered orally, suspended or dissolved in 0.5% carboxymethylcellulose in a volume of 10 ml/kg of body weight, control animals receiving the vehicle alone. Reserpine was administered as "Serpasil" from Ciba, Switzerland.

Prevention of Reserpine-Induced Ptosis. The compounds were administered to mice at the screening dose of 50 mg/kg, 1 hr prior to reserpine (1.5 mg/kg iv). The degree of ptosis was measured by a scoring system according to Rubin et al.[20] The total score of a control group tested on the same day was expressed as 100 and the degree of antagonism by the test compounds as percentage. The compounds showing an inhibition of the control score higher than 50% at 50 mg/kg were tested at lower doses. The approximate MED (median effective dose), amount of drug in mg/kg necessary to antagonize the ptosis by 50%, was obtained by "eye-fit" linear plots on semilogarithmic paper.

Reversal of Reserpine-Induced Hypothermia. This test was carried out at room temperature of 20° according to the method of Askew[21] with minor modifications. Mice were made hypothermic by reserpine and treated orally with the compounds at the screening dose of 50 mg/kg, 18 hr after reserpine injection (5 mg/kg ip). The compounds active at the screening dose were tested at lower doses.

Cumulative temperature values were obtained for control and treated groups by summing the values taken 1, 2, 3, and 5 hr after the compounds or saline injection. The drop of normal temperature in the reserpine-treated group was considered as 100. The dose able to reverse this reserpine-induced hypothermia by 50% (MED = median effective dose) was obtained, when possible, by graphical extrapolation from "eye-fit" linear plots on semilogarithmic paper.

Antispasmodic Activity in Vitro. The test was carried out on isolated strips of ileum from male guinea pigs using 2.5×10^{-8} g/ml of acetylcholine or histamine as spasmogens. These agents were added to the Tyrode's solution maintained at 37° and oxygenated with 100% O_2, 2 min following the addition of the test compounds. The compounds were dissolved in water or in 0.1 *N* HCl. The ED_{50} of each substance was obtained by graphical extrapolation from "eye-fit" linear plots of the results from at least three different preparations.

Acute Toxicity. All the compounds were administered orally to mice at not less than three dose levels. The rate of mortality was calculated on the seventh day after administration and the LD_{50} values were determined by the method of Litchfield and Wilcoxon.[22] The animals were also observed for gross symptomatology at subtoxic doses.

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