Aminoalkylindoles with Central Nervous System Activity

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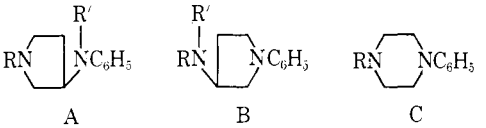
A number of novel aminoalkylindoles have been prepared and tested for central nervous system depressant activity. Many of the compounds have significant activity against the aggressive behavior of fighting mice. The tremulous syndrome produced in mice by injections of *p*-methoxyphenethylamine was effectively blocked by many of the compounds tested.

Interest in indole-containing molecules has continued to grow in recent years because of the increasing spectrum of biological activity found among this group of compounds. Within the narrower field of tryptamines, wide variations in biological activity exist even between relatively closely related compounds,[1] many of which strongly affect the central nervous system.[2] Because of our interest in compounds possessing central depressant activity, a series of novel substituted tryptamine derivatives has been prepared for pharmacological evaluation.

One of the specific objectives of this study was to prepare tryptamine analogs containing a 3-anilinopyrrolidinyl group (A) or a 1-phenyl-3-pyrrolidinylamino group (B), both of which have structural features in common with the known phenylpiperazinyl analog (C). Derivatives of C are reported to have tranquilizing properties.[3]



A B C

R = substituted 3-indolylethyl
R′ = H or alkyl

Isosters A and B have a degree of conformational freedom that C does not have and thus may fit more comfortably into the same receptor as C or possibly prefer a different one. One then might expect isosters A and B to produce a physiological response which differs either in degree or kind from each other or from C.

Chemistry.—Most of the tryptamines in this series were prepared by the general method of Speeter and Anthony[4] which involves the acylation of an appropriately substituted indole with oxalyl chloride, conversion of the resulting glyoxyl chloride to the desired glyoxamide, and lithium aluminum hydride (LAH) reduction to the corresponding tryptamine (Chart I).

The novel pyrrolidines (Table I) used in the synthetic sequence were prepared by (A) the nucleophilic displacement of the tosylate of 1-benzyl- or 1-phenyl-3-pyrrolidinol[5,6] by an amine or phenoxide ion followed by catalytic debenzylation in the case of the 1-benzyl compound, (B) displacement of the chlorine from 1-benzyl-3-chloropyrrolidine[7] followed by catalytic debenzylation, or (C) addition of an amine to N-phenylmaleimide followed by lithium aluminum hydride reduction to the desired pyrrolidine (Chart II).

Chart I

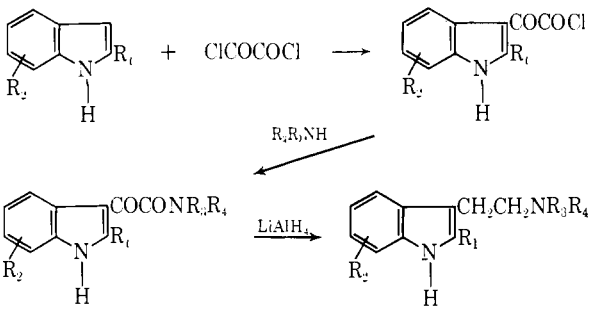
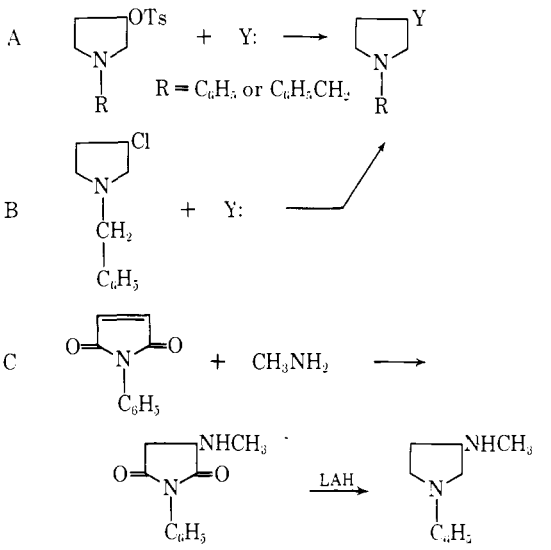


Chart II[a]



[a] See Table I for assignment of Y.

Several tryptamines produced by the lithium aluminum hydride reduction of the glyoxamides were further transformed by standard procedures into ester and carbamate derivatives as described in the Experimental Section.

In all cases but one, the styrene double bond of the tetrahydropyridine glyoxamides (**19** and **21–24**, Table II) was able to withstand lithium aluminum hydride

(1) (a) R. V. Heinzleman and J. Szmuszkovicz, *Progr. Drug. Res.*, **6**, 75 (1963); (b) V. Erspamer, *ibid.*, **3**, 151 (1961); (c) M. Gordon in "Medicinal Chemistry," A. Burger, Ed., Interscience Publishers, Inc., New York, N. Y., 1960, p 398; (d) J. F. Kerwin, C. P. Balant, and G. E. Ullyot, *ibid.*, pp 568–570.

(2) S. Archer, D. W. Wylie, L. S. Harris, T. R. Lewis, J. W. Schulenberg, M. R. Bell, R. K. Kullnig, and A. Arnold, *J. Am. Chem. Soc.*, **84**, 1306 (1962).

(3) D. W. Wylie and S. Archer, *J. Med. Pharm. Chem.*, **5**, 932 (1962).

(4) M. E. Speeter and W. C. Anthony, *J. Am. Chem. Soc.*, **76**, 6208 (1954).

(5) Yu. A. Arbuzov and Yu. A. Orchinnikov, *Dokl. Akad. Nauk SSSR*, **117**, 813 (1957); *Chem. Abstr.*, **52**, 8120 (1958).

(6) C. D. Lunsford, J. W. Ward, A. J. Pallotta, T. W. Tusing, E. K. Rose, and R. S. Murphey, *J. Med. Pharm. Chem.*, **1**, 73 (1959).

(7) C. D. Lunsford, A. D. Cale, Jr., J. W. Ward, B. V. Franko, and H. Jenkins, *J. Med. Chem.*, **7**, 302 (1964).

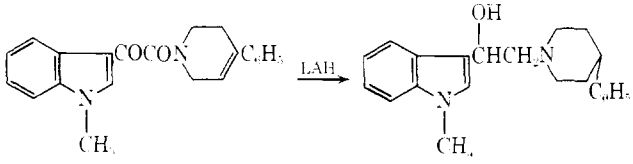
TABLE I

PYRROLIDINES

Compd	R	Y	Method of prepn[a]	Bp, °C (mm)	Recrystn solvent[b]	Mp, °C[c]	Formula	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N
1	$C_6H_5CH_2$	NHC_6H_6	A	160–164(0.01)	E	139–140.5[d]	$C_{24}H_{24}N_2O_4$[d]	68.47	6.55	7.60	68.45	6.52	7.60
2	$C_6H_5CH_2$	$N(CH_3)C_6H_5$	A	170–173(0.2)	E	120–122[e]	$C_{22}H_{26}N_2O_4$[e]	69.09	6.85	7.33	69.00	6.80	7.35
3	$C_6H_5CH_2$	$NHC_6H_4OCH_3$-*o*	A	174–175(0.02)	Ip	146–148[d]	$C_{25}H_{28}N_2O_5$[d]	66.31	6.58	7.03	66.64	6.78	7.01
4	$C_6H_5CH_2$	$OC_6H_4OCH_3$-*o*	B	150–152(0.05)	...	...	$C_{18}H_{21}NO_2$	76.29	7.47	4.94	76.41	7.47	5.00
5	H	NHC_6H_5	*f*	100–105(0.02)	...	75–78	$C_{10}H_{14}N_2$	74.03	8.70	17.27	73.86	8.51	17.07
6	H	$N(CH_3)C_6H_5$	*f*	92–94(0.02)	E	123–125[e]	$C_{18}H_{20}N_2O_4$[e]	61.61	6.90	9.59	61.26	7.02	9.63
7	H	$NHC_6H_4OCH_3$-*o*	*f*	110(0.02)	Ip-1E	100–102[g]	$C_{17}H_{20}N_2O_4S$[g]	54.96	7.87	11.31	54.76	7.76	11.71
8	H	$OC_6H_4OCH_3$-*o*	*f*	103–104(0.02)	Ip-1E	123–124.5[h]	$C_{18}H_{16}ClNO_2$[h]	57.51	7.02	6.10	57.70	7.19	6.18
9	C_6H_5	NHC_6H_9-*n*	A	120–122(0.01)	Ip-1E	145–148[h]	$C_{14}H_{21}Cl_2N_2$[h]	57.73	8.30	9.62	58.21	8.73	9.60
10	C_6H_5	$NHCH_3$	C	90–92(0.01)	E	211–213[e]	$C_{11}H_{17}ClN_2$[h]	62.11	8.03	13.17	62.23	8.17	13.05

[a] See Chart II for a description of the methods. [b] See footnote *c* of Table II for solvent abbreviations. [c] Melting points are uncorrected. [d] Fumarate salt. [e] Maleate salt. [f] Catalytic reduction of the corresponding N-benzyl compound. [g] Hexanate salt. [h] Hydrochloride salt.

reduction. The one exception was glyoxamide **20** which yielded, as the primary product, compound **56** containing a completely saturated piperidine ring, as well as a hydroxyl group on the ethyl side chain.



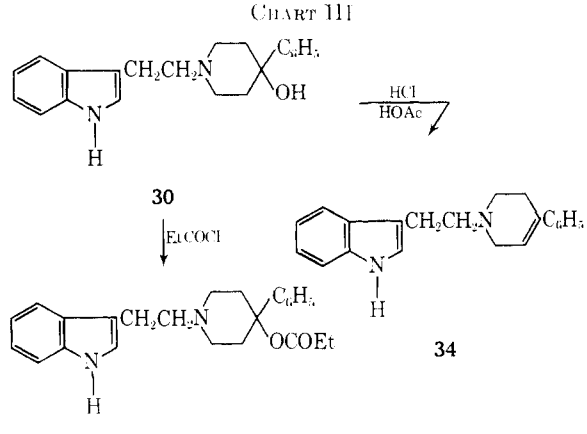
20 **56**

The formation of the aminoethanol side chain rather than the fully saturated aminoethyl group was expected in this case based on the findings of Heinzelman and Sznuszkovicz[1a] who carried out similar reductions on other 3-indolylglyoxamides methylated in the 1 position.

The nmr spectrum of **56** (Table III) showed no olefinic absorption, three additional protons in the aliphatic region (compared to the unsaturated analog), a replaceable hydroxylic proton at τ 6.0, a methyl singlet at τ 6.45, and a single proton quartet (the X portion of an ABX system) centered at τ 4.9 which corresponds to the carbinol methine.

A second method for preparing 4-phenyl-1,2,3,6-tetrahydropyridyl analogs is exemplified by the facile dehydration of the 4-phenyl-4-piperidinol derivative **30** with acid to yield **34**. Propionylation of **30** with propionyl chloride gave the ester **31** (Chart III). Alkylation of **16** with excess methyl iodide using

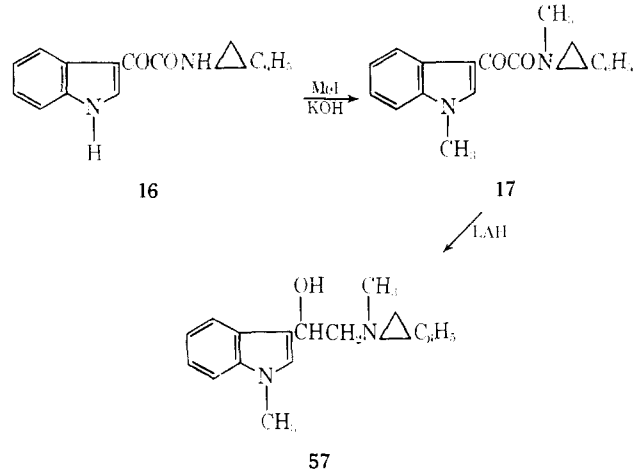
CHART III



30 **34** **31**

the slightly modified procedure of Pachter and Kloetzel[8] gave an excellent yield of the dimethylated glyoxamide **17**. Glyoxamide **19** was converted to **20** using the same method. Reduction of **17** with lithium aluminum hydride then gave the expected amino alcohol **57** (Chart IV).

CHART IV



16 **17** **57**

The structure of **57** was supported by its nmr spectrum which displayed two methyl singlets at τ 7.5 and 6.4, a replaceable hydroxyl group at τ 6.6, and the characteristic single-proton quartet of the carbinol methine centered at τ 4.9.

Pharmacology. Isolation-Induced Aggressive Behavior.—Aggressive behavior was induced in Dublin male albino mice using the method of DaVanzo, *et al.*[9] Isolated animals attack control mice introduced into the cage of the isolated animals; a well-directed attack is used as an end point in this test. Block of this attack is regarded as evidence of drug effect.

Tests were always carried out 60 min after drug administration. Compounds were dissolved or suspended in physiological saline. Groups of five mice were tested initially with a dose of 20 mg/kg ip. In those cases where a complete block was achieved with this dose, the 50% effective dose was estimated by the method of Litchfield and Wilcoxon.[10]

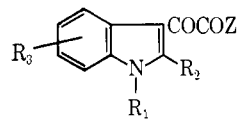
(8) T. J. Pachter and M. C. Kloetzel, *J. Am. Chem. Soc.*, **74**, 1321 (1952).

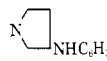
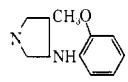
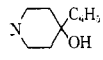
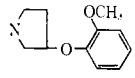
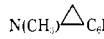
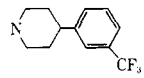
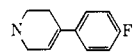
(9) J. DaVanzo, M. Daugherty, R. Ruckart, and L. Kang, *Psychopharmacologia*, **9**, 211 (1966).

(10) J. Litchfield and F. Wilcoxon, *J. Pharmacol. Exptl. Therap.*, **96**, 99 (1949).

Table II

Glyoxamides[a]



Compd	Indole substituents[b]	Z	Recrystn solvent[c]	Mp, °C[d]	Yield, %	Formula	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N
11	H		AE	216–218	70	$C_{14}H_{14}N_2O_3$	65.10	5.46	10.85	65.19	5.48	10.97
12	H		M	170–172	30	$C_{20}H_{18}N_3O_2$	72.05	6.75	12.60	71.63	5.91	13.02
13	H		Ac	200–202	48	$C_{21}H_{21}N_3O_3$	69.40	5.83	11.56	69.59	5.84	11.64
14	H		EA–I	199–201	55	$C_{21}H_{20}N_2O_3$	72.39	5.79	8.04	72.12	5.97	8.17
15	H		B–I	175–177	83	$C_{21}H_{20}N_2O_4$	69.21	5.53	7.69	69.55	5.57	7.99
16	H		AE	218–220	76	$C_{19}H_{16}N_2O_2$	74.98	5.30	9.21	74.89	5.19	9.31
17	$R_1 = CH_3$[e]		B–I	113–114	70	$C_{21}H_{20}N_2O_2$	75.88	6.07	8.43	75.82	6.29	8.41
18	H		B–I	160–162	79	$C_{22}H_{15}F_3N_2O_2$	65.99	4.78	7.00	66.05	4.94	7.08
19	H		Ac	193–195	86	$C_{21}H_{18}N_2O_2$	76.34	5.49	8.48	76.25	5.37	8.23
20	$R_1 = CH_3$[f]		A–W	173–175	92	$C_{22}H_{20}N_2O_2$	76.72	5.85	8.13	76.71	5.80	8.16
21	$R_2 = CH_3$		E	165–167	72	$C_{22}H_{20}N_2O_2$	76.72	5.85	8.13	76.75	5.89	8.14
22	R_3 = 5,6-OCH_3		Ac	236–239	65	$C_{23}H_{22}N_2O_4$	70.75	5.68	7.18	70.55	5.85	7.18
23	R_3 = 5-Cl		E–W	200–202	49	$C_{21}H_{17}ClN_2O_2$	69.13	4.70	7.68	68.83	4.57	7.71
24	H		AE	195–197	68	$C_{21}H_{17}FN_2O_3$	72.40	4.92	8.04	72.33	4.90	8.17

[a] Many of the intermediate glyoxamides were not isolated in a purified form. [b] R_1, R_2, and R_3 = hydrogen except where noted. [c] Solvent abbreviations: AE, absolute ethanol; E, 95% ethanol; A, acetone; Ac, acetonitrile; B, benzene; EA, ethyl acetate; Et, ether; I, isooctane; IE, isopropyl ether; Ip, isopropyl alcohol; M, methanol; W, water. [d] Melting points are uncorrected. [e] Prepared by methylation of **16**; see Experimental Section. [f] Prepared by methylation of **19**; see Experimental Section.

In general, the most active compounds (Table IV) which blocked the aggressive behavior of fighting mice were the 4-phenyltetrahydropyridine derivatives **34**, **35**, **51**, **52**, and **55**. It is interesting, however, that tetrahydropyridine derivatives containing 5-methyl and 5-chloro substituents on the indole ring (**53** and **54**) were completely devoid of tranquilizing activity in this test.

The aminopyrrolidine analogs (**25**, **42**, and **43**) which are structurally related to the known phenylpiperazine derivatives all had similar potencies but were not as active as the tetrahydropyridine analogs.

The most active compound in this test (**31**) was also shown to be a potent analgesic.[11] Introduction of a *m*-trifluoromethyl group, however, resulted in a compound (**33**) which demonstrated no tranquilizing action at the dose tested as well as sharply reduced analgesic potency compared to **31**.

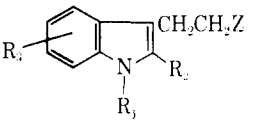
(11) Compounds **31** and **33** demonstrated analgetic activities (ED_{50} in mice) of 0.40 and 26.8 ip mg/kg, respectively, using the electric stimulation method of P. Nilsen [*Acta Pharm. Toxicol.*, **18**, 10 (1961)]. Using the same method, morphine demonstrated an analgetic ED_{50} of 1.72 mg/kg.

***p*-Methoxyphenethylamine (PMOPA)-Induced Tremors.**—It has been reported that certain methoxylated derivatives of phenethylamine produce catatonia or a hypokinetic rigid syndrome when injected into a cat, and it has been suggested that the biosynthesis of these compounds in the Parkinsonian may explain the symptoms of this disease.[12]

We have found that administration of *p*-methoxyphenethylamine (50 mg/kg ip) to mice results in a syndrome consisting of tremors, lateral head shake, straub tail, horripilation, and lacrimation. Female Dublin albino mice are given the test drugs, solubilized or suspended in saline, 60 min prior to being challenged with PMOPA. Adequate numbers of controls are given only PMOPA, when the test animals receive it. The animals are observed for 20 min or until such time as the symptoms abate in the controls. The end point used in this test is complete abolition of the syndrome. When warranted, ED_{50}'s were established by the method referred to in the previous section.[10]

(12) (a) A. M. Ernst, *Nature*, **193**, 178 (1962); (b) *Acta Physiol. Pharmacol. Neerl.*, **11**, 48 (1962); (c) *Psychopharmacologia*, **7**, 383 (1965).

TABLE III
TRYPTAMINES



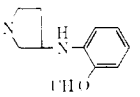
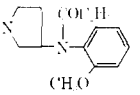
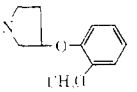
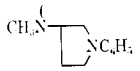
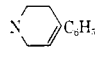
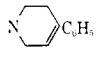
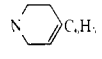
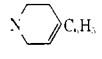
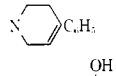
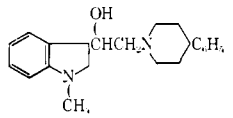
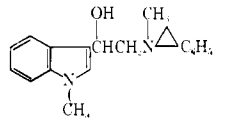
Compd	Indole substituents[a]	Z	Recrystn solvent[b]	Mp, °C[c]	Yield, %	Formula	Calcd, %			Found, %		
							C	H	N	C	H	N
25	H		Ip–IE	124–128	54	$C_{21}H_{23}N_4O_2S$[d]	65.03	7.68	11.24	65.19	7.83	11.22
26	H		e	e	75	$C_{20}H_{22}N_2$	78.65	7.59	13.76	78.42	7.50	13.81
27	H		B–I	94–96	40	$C_{20}H_{22}N_2O$	75.19	7.51	12.53	75.13	7.51	12.50
28	H		e	e	...	$C_{21}H_{24}N_2O_2$	73.63	7.15	10.73	73.11	7.33	10.76
29	H		f	50–55[g,h]	73	$C_{21}H_{25}ClN_2O_2$[i]	67.64	6.76	7.51	67.72	7.07	7.43
30	H		B	137–139	55	$C_{21}H_{24}N_2O$	78.71	7.55	8.74	78.30	7.36	8.60
31	H		B–I	142–144	64	$C_{24}H_{28}N_2O_2$	76.56	7.50	7.44	76.52	7.47	7.14
32	H		Ip–M]	244–246[h]	70	$C_{22}H_{24}ClFN_2O$[k]	62.19	5.69	6.59	62.55	6.13	6.40
33	H		Ip–IE	168–172[h]	68	$C_{24}H_{28}ClF_3N_2O_2$[k]	62.43	5.87	5.83	62.58	5.89	6.02
34	H		B–I	138–140	36	$C_{21}H_{22}N_2$	83.40	7.33	9.26	83.45	7.38	9.17
35	H		B	157–159	48	$C_{21}H_{23}FN_2$	78.72	6.60	8.74	79.04	6.71	8.60
36	H		B–I	152–154	49	$C_{22}H_{23}F_3N_2$	71.33	5.71	7.56	71.52	5.71	7.89
37	H		I	104–106	62	$C_{20}H_{23}F_3N_2$	70.95	6.23	7.52	71.20	6.50	7.22
38	H		Ac	144–146	78	$C_{14}H_{18}N_2O$	73.01	7.88	12.16	72.80	7.94	12.20
39	H		B	79–86[l]	78	$C_{26}H_{34}N_2O_4$[l]	71.69	6.82	5.57	71.46	6.77	5.94
40	H		e	e	60	$C_{22}H_{28}N_4O_2$	69.63	6.64	11.07	69.35	6.76	11.12
41	H		e	e	71	$C_{24}H_{29}N_3O_4$	65.58	6.65	9.56	65.34	6.86	9.57
42	H		E–W	104–106	72	$C_{21}H_{25}N_3$	78.96	7.80	13.16	78.73	7.90	13.05
43	H		A	113–116[h]	36	$C_{24}H_{32}ClN_3$[k]	72.13	8.10	10.56	72.01	8.17	10.77
44	$R_2 = CH_3$		E–W	131–133	65	$C_{22}H_{27}N_3$	79.21	8.18	12.60	79.59	8.22	13.04
45	$R_2 = CH_3$		Ip–Ac	208–209[h]	52	$C_{16}H_{21}ClN_2O$[k]	64.16	7.54	9.98	64.37	7.98	9.72
46	$R_2 = CH_3$		M	119–121	79	$C_{28}H_{36}N_2O_6$	68.47	6.90	6.39	68.41	7.11	6.22
47	$R_2 = CH_3$		B	142–144	17	$C_{21}H_{24}N_2O_2$	83.50	7.65	8.85	83.47	7.54	8.81
48	$R_2 = 5,6\text{-}(OCH_3)_2$		e	e	60	$C_{22}H_{26}N_2O_2$	72.79	7.70	11.07	72.18	7.78	11.20

Table III (*Continued*)

Compd	Indole substituents[a]	Z	Recrystn solvent[b]	Mp, °C[c]	Yield, %	Formula	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N
49	R_3 = 5,6-OCH$_3$		*e*	*e*	71	$C_{28}H_{29}N_3O_4$	72.79	7.70	11.07	73.00	7.59	11.17
50	R_3 = 5,6-OCH$_3$		1p-Et	95–100[j]	...	$C_{16}H_{22}ClN_2O_3$[h]	58.80	7.09	8.57	59.09	6.96	8.29
51	R_3 = 5,6-OCH$_3$		B	125–127	31	$C_{28}H_{26}N_2O_2$	76.21	7.23	7.73	75.78	7.14	7.97
52	R_3 = 5,6-OCH$_3$, R_2 = CH$_3$		B–I	116–118	51	$C_{24}H_{28}N_2O_2$	76.56	7.50	7.44	76.17	7.40	7.50
53	R_3 = 2,5-CH$_3$		B	150–152	61	$C_{28}H_{26}N_2$	83.59	7.93	8.42	83.38	7.92	8.72
54	R_3 = 5-Cl		B	168–170	53	$C_{21}H_{21}ClN_2$	74.87	6.28	8.32	75.10	6.20	8.26
55	R_1 = CH$_3$		1p	219–222[h]	...	$C_{22}H_{28}ClN_2$[h]	74.87	7.14	7.94	74.67	7.26	8.09
56			B–I	137–139	34	$C_{22}H_{26}N_2O$	79.00	7.84	8.38	79.20	7.95	8.41
57			*k*	*k*	42	$C_{21}H_{24}N_2O$	78.71	7.55	8.74	78.56	7.51	8.71

[a] R_1, R_2, and R_3 = hydrogen except where noted. [b] See footnote *c* of Table II for solvent abbreviations. [c] Melting points are uncorrected and refer to the free base except where solid derivatives are noted. [d] Hexamate. [e] Viscous oil purified by column chromatography on Florisil, eluted with benzene–acetone. [f] Precipitated from ether with ethereal HCl. [g] Ether solvate. [h] Hydrochloride salt. [i] Benzene solvate. [j] Hydrochloride monohydrate; water removed before analysis. [k] Viscous oil, purified by column chromatography on grade III neutral alumina, eluted with benzene–petroleum ether.

In general, the compounds which blocked the PMOPA syndrome most effectively (Table IV) were the same ones that most effectively blocked the aggressive behavior of fighting mice (**31**, **34**, **35**, **52**, and **55**). In addition, several glyoxamides were also effective (**16** and **17**). The most active compound in this test was the analgesic (**31**). Again, no activity was found in the *m*-trifluoromethyl analog **33**.

A number of classical anti-Parkinson agents such as trihexyphenidyl hydrochloride and scopolamine were found to be without effect in preventing or reversing the PMOPA-induced syndrome. Large doses of chlorpromazine prevented the syndrome but not without concomitant neurotoxicity.

Monamine Oxidase.—The method described by Youngdale, *et al.*,[13] was used for these determinations. Guinea pig liver was used as a source of enzyme.

Only four compounds in this series showed significant MAO-inhibitory activity in the test used. By far the most active compounds were the related pyrrolidinol analogs **38** and **45**.

Experimental Section

All melting points (uncorrected) were taken by the capillary method in a Thomas–Hoover Uni-Melt apparatus. Nmr spectra were determined with a Varian A-60 spectrometer (TMS as reference). Infrared spectra were determined on a Beckman IR-8 recording spectrophotometer. Microanalyses were conducted by the Micro-Tech Laboratories, Skokie, Ill., and Spang Microanalytical Laboratory, Ann Arbor, Mich. The following experimental procedures illustrate the general methods and modifications thereof used to synthesize the compounds listed in Tables I–III.

1-Benzyl-3-(*o*-methoxyanilino)pyrrolidine Fumarate (3).—The crude tosylate prepared from 3 moles of 1-benzyl-3-pyrrolidinol was dissolved in 500 g of *o*-anisidine (practical), and the mixture was stirred and heated slowly under nitrogen until the temperature reached 130°. At this temperature, a rapid exothermic reaction took place which raised the temperature rapidly to 160°. After cooling with ice–H_2O to 130°, the mixture was stirred for 2 hr. The temperature was raised to 160°, and the mixture was stirred an additional 2 hr. After cooling to room temperature, the mixture was dissolved in 3 *N* HCl and extracted several times with ether. The acidic layer was neutralized with 50% NaOH, and the resulting free base was extracted into $CHCl_3$. The $CHCl_3$ extracts were dried over $MgSO_4$ and evaporated under reduced pressure to an oil. The oil was fractionally distilled (Vigreux column) yielding 335.7 g (40%) of pure product.

3-(*o*-Methoxyanilino)pyrrolidine Hexamate (7).—Three 95-g batches of 1-benzyl-3-(*o*-methoxyanilino)pyrrolidine in 300 ml of ethanol were catalytically reduced in a Parr apparatus using 10% Pd-C. The bomb was heated to *ca.* 50° before reduction would take place. After the theoretical amount of hydrogen was taken up, the catalyst was filtered, and the solvent was evaporated. The product was distilled at reduced pressure; yield 149 g (77%).

1-Benzyl-3-(*o*-methoxyphenoxy)pyrrolidine (4).—A mixture of 102 g (0.70 mole) of sodium guaiacolate, 137 g (0.70 mole) of 3-chloro-3-benzylpyrrolidine, and 1 l. of dimethyl sulfoxide was heated with stirring for 16 hr at 112–115°. The mixture was cooled, diluted with 1 l. of H_2O, and treated with 80 g (1.0 mole) of 50% NaOH solution. The solution was extracted with ether, and the combined extracts were washed with H_2O and dried ($MgSO_4$). After the solvent was evaporated, the residual oil was distilled at reduced pressure; yield 92 g (47%).

3-(*o*-Methoxyphenoxy)pyrrolidine Hydrochloride (8).—A solution of 85.0 g (0.3 mole) of 1-benzyl-3-(*o*-methoxyphenoxy)-pyrrolidine in 300 ml of 95% ethanol was treated with 8 g of Raney nickel. The mixture was shaken several hours and filtered. The filtrate was placed in a Paar reduction apparatus and *ca.* 10 g of 10% Pd–C was shaken with hydrogen at 60°; absorption ceased when one-third the required amount was absorbed. More catalyst (*ca.* 15 g) was added and hydrogenation

(13) G. Youngdale, D. Anger, W. Anthony, J. DaVanzo, M. Greig, R. Heinzelman, H. Keasling, and J. Szmuszkovicz, *J. Med. Chem.*, **7**, 415 (1964).

TABLE IV

PHARMACOLOGICAL EFFECTS OF VARIOUS INDOLES

	PMOPA assay		Fighting mouse		
Compd	mg/kg ip	No. protected/no. tested	mg/kg ip	No. protected/no. tested	MAO, % inhib at 10^{-3} M
11	25	0/2	20	0/5	0
12	25	0/4	20	1/5	2
13	25	0/4	20	1/5	1
14	25	0/4	20	3/5	10
15	50	0/3	20	1/5	28
16	25	5/5	20	0/5	0
17	25	5/5	20	2/5	15
18	25	0/5	20	3/5	29
19	25	0/4	20	0/5	0
20	25	0/4	20	0/5	0
21	25	0/4	20	0/5	0
22	25	0/4	20	0/5	0
23	25	0/4	20	3/5	0
24	25	0/4	20	0/5	7
25	50	3/3	20	4/5	0
26	25	0/4	20	0/5	..
27	25	0/4	20	4/5	0
28	25	0/4	20	1/5	..
29		ED_{50} = 24	20	3/5	0
30	25	0/4	20	0/5	9
31		ED_{50} = 6		ED_{50} = 3	4
32	..			ED_{50} = 14	..
33	25	0/5	20	0/5	0
34		ED_{50} = 7		ED_{50} = 7	20
35		ED_{50} = 7		ED_{50} = 8	0
36	25	0/5	20	3/5	0
37		ED_{50} = 12	20	3/5	0
38		ED_{50} = 20	20	0/5	69
39	40	0/3	20	0/5	9
40	50	0/3	20	0/5	2
41	50	1/3	20	0/5	4
42	50	0/3	20	3/5	4
43	20	0/4		ED_{50} = 14	6
44	50	0/3	20	0/5	2
45	25	1/3	20	0/5	74
46	50	0/3	20	0/5	0
47	25	1/4		ED_{50} = 15	0
48	25	2/3	20	0/5	11
49	25	0/3	20	2/5	0
50	25	0/4	20	1/5	0
51	25	0/4		ED_{50} = 14	..
52	25	4/4		ED_{50} = 11	0
53	25	0/4	20	0/5	0
54	25	0/4	20	1/5	0
55		ED_{50} = 6.7		ED_{50} = 12	..
56	25	0/5	20	0/5	0
57	..		..		..
CPZ[a]				ED_{50} = 2.5	
CDE[b]				ED_{50} = 35	

[a] CPZ = chlorpromazine. [b] CDE = chlordiazepoxide.

continued until 1 equiv of hydrogen was absorbed. The suspension was cooled and filtered, and the solvent was evaporated at reduced pressure. The residual oil was distilled; yield 48 g (83%).

3-Methylamino-1-phenylpyrrolidine Hydrochloride (10).—A stirred solution of 70 g (0.4 mole) of N-phenylmaleimide in 600 ml of dry ether was cooled in ice while a stream of $MeNH_2$ gas was passed through until no more 3-methylamino-1-phenylsuccinimide precipitated. The crude product was recrystallized from benzene; mp 108–115°, yield 66 g (80%). Thin layer chromatography indicated some impurity.

To a stirred suspension of 71.5 g (1.9 moles) of $LiAlH_4$ in 1.5 l. of THF under nitrogen was added, over 15 min, 75 g (0.37 mole) of crude 3-methylamino-1-phenylmaleimide suspended in 250 ml of THF. After addition, the mixture was heated (reflux) for 3.5 hr, cooled, and carefully hydrolyzed with H_2O. The resulting solids were filtered, and the filter cake was washed several times with THF. Evaporation of the solvent from the combined filtrates gave crude product which was distilled at reduced pressure; yield 39 g (61%).

1-(Indol-3-ylglyoxyloyl)-3-(*o*-methoxyphenoxy)pyrrolidine (15).—To a stirred mixture of 11.5 g (0.06 mole) of 3-(*o*-methoxyphenoxy)pyrrolidine in 100 ml of $CHCl_3$ and 10 g of Na_2CO_3 in 35 ml of H_2O was added over 10 min, 11.5 g (0.06 mole) of solid indole-3-glyoxyloyl chloride. After stirring 1 hr, another 25 ml of H_2O was added, and stirring was continued an additional 2 hr. The organic layer was separated and washed successively with H_2O, 3 *N* HCl, H_2O, and 3 *N* NaOH. After drying over $MgSO_4$, the solvent was removed on a rotating evaporator yielding a viscous oil which soon solidified. The solid was suspended in hot benzene and treated with absolute alcohol until it dissolved. The volume of solvent was reduced by about one-third, then treated while hot with isooctane. After cooling, 17.0 g (83%) of product precipitated.

1-(Indol-3-ylglyoxyloyl)-4-phenyl-1,2,3,6-tetrahydropyridine (19).—A solution of 19.5 g (0.1 mole) of 4-phenyl-1,2,3,6-tetrahydropyridine hydrochloride in 100 ml of $CHCl_3$ was added to a solution of 25 g of K_2CO_3 in 100 ml of H_2O. To the stirred suspension was added, portionwise, 20 g (0.198 mole) of solid indole-3-glyoxyloyl chloride. The mixture was stirred 30 min after addition was completed; the product precipitated.

1-(Indol-3-ylglyoxyloyl)-3-pyrrolidinol (11). A solution of 1.25 g (0.014 mole) of 3-pyrrolidinol and 3 g of Na_2CO_3 in 35 ml of H_2O was treated all at once with 3 g (0.014 mole) of indole-3-glyoxyloyl chloride and stirred at room temperature for 24 hr. The product was removed by filtration.

1-[(1-Methylindol-3-yl)glyoxyloyl]-4-phenyl-1,2,3,6-tetrahydropyridine (20). A stirred solution of 20 g (0.06 mole) of 1-(indol-3-ylglyoxyloyl)-4-phenyl-1,2,3,6-tetrahydropyridine in 350 ml of refluxing methyl ethyl ketone was treated all at once with 25 g of powdered KOH followed immediately by 19.8 g (0.14 mole) of CH_3I added dropwise. After 5 min (stirring) the mixture was filtered, and the filtrate was evaporated to an oil which crystallized.

N-Methyl-N-[(1-methylindol-3-yl)glyoxyloyl]-*trans*-2-phenylcyclopropylamine (17). A stirred solution of 18 g (0.06 mole) of N-(indol-3-ylglyoxyloyl)-*trans*-2-phenylcyclopropylamine in 350 ml of dry methyl ethyl ketone was warmed nearly to reflux and treated with 25 g (0.45 mole) of powdered KOH. While stirring and gently refluxing, 40 g (0.28 mole) of CH_3I in 50 ml of methyl ethyl ketone was added dropwise. After addition, the mixture was stirred 5 min, then filtered. The solvent was removed under reduced pressure yielding an oil which crystallized from benzene–isooctane.

5,6-Dimethoxy-3-[2-(3-*N*-methylanilino-1-pyrrolidinyl)ethyl]-indole (48). A suspension of 8 g (0.02 mole) of 1-[(5,6-dimethoxyindol-3-yl)glyoxyloyl]-3-*N*-methylanilinopyrrolidine in 50 ml of THF was added dropwise to a stirred suspension of 3.8 g (0.1 mole) of $LiAlH_4$ in 100 ml of THF. After addition, the mixture was refluxed under nitrogen for 3 hr and cooled, and the excess hydride was destroyed carefully with H_2O. The inorganic precipitate was filtered and washed thoroughly with THF. The combined filtrates were then evaporated under vacuum to a glassy solid which would not crystallize. It was dissolved in benzene and chromatographed on 250 g of 60–100 mesh Florisil, eluting with benzene containing increasing amounts of acetone; yield 4.5 g (60%). A sample was molecularly distilled for analysis.

3-{2-[*N*-(1-Phenyl-3-pyrrolidinyl)-*N*-methylamino]ethyl}-indole (42). A suspension of 9 g (0.03 mole) of *N*-(indol-3-ylglyoxyloyl)-*N*-(1-phenyl-3-pyrrolidinyl)-*N*-methylamine in 50 ml of THF was added dropwise to a stirred mixture of 4.9 g (0.13 mole) of $LiAlH_4$ in 100 ml of THF. After addition, the mixture was refluxed for 3 hr under nitrogen and cooled, and the excess $LiAlH_4$ was destroyed carefully with H_2O. The mixture was filtered and the inorganic precipitate was washed thoroughly with THF. Evaporation of the combined filtrates gave an oil which was chromatographed on a Florisil column (60–100 mesh) and eluted with benzene containing increasing amounts of acetone; yield 6 g (72%). After several days, the oil crystallized.

2-Methyl-3-[2-(3-hydroxy-1-pyrrolidinyl)ethyl]indole Hydrochloride (45). A suspension of 24 g (0.09 mole) of 1-[(2-methylindol-3-yl)glyoxyloyl]-3-pyrrolidinol in 100 ml of THF was added dropwise to a stirred mixture of 15 g (0.40 mole) of $LiAlH_4$ in 200 ml of THF. After addition, the mixture was refluxed for 3 hr and cooled, and the excess $LiAlH_4$ was destroyed carefully with H_2O. The mixture was filtered, and the filter cake was washed thoroughly with THF. Evaporation of the combined

filtrates gave an oil which was converted to a hydrochloride salt.

1-(1-Methylindol-3-yl)-2-(4-phenyl-1-piperidinyl)-1-ethanol (56).—To a stirred suspension of 8.6 g (0.23 mole) of $LiAlH_4$ in 85 ml of THF was added slowly 15.5 g (0.05 mole) of 1-[(1-methylindol-3-yl)glyoxyloyl]-4-phenyl-1,2,3,6-tetrahydropyridine in 50 ml of THF. The stirred mixture was allowed to reflux under nitogen for 2 hr, then worked up in the usual manner. The crude oil was dissolved in benzene and chromatographed on 400 g of 60–100 mesh Florisil. The product was eluted with benzene containing increasing amounts of acetone. The purified product crystallized.

1-(1-Methylindol-3-yl)-2-(N-*trans*-2-phenylcyclopropyl-N-methylamino)-1-ethanol (57).—A solution of 10 g (0.03 mole) of N-methyl-N-[(1-methylindol-3-yl)glyoxyloyl]-*trans*-2-phenylcyclopropylamine in 50 ml of THF was added dropwise to a stirred suspension of 6 g of $LiAlH_4$ in 200 ml of THF under nitrogen. The mixture was refluxed for 3 hr after addition, cooled, treated with 200 ml of THF, then neutralized with a $MgSO_4$–H_2O slurry. The salt was removed by filtration, then washed well with THF. Evaporation of the filtrate gave 9 g of an oil which was chromatographed on grade III neutral alumina using benzene–petroleum ether (bp 30–60°) (50:50) to elute 4.0 g (42%) of oil. The oil (probably an isomeric mixture) was molecularly distilled for analysis.

3-{2-[4-(*m*-Trifluoromethylphenyl)-1,2,3,6-tetrahydro-1-pyridinyl]ethyl}indole (36).—A solution of 10 g (0.023 mole) of 3-{2-[4-hydroxy-4-(*m*-trifluoromethylphenyl)-1-piperidinyl]ethyl}-indole (benzene solvate) in 75 ml of glacial acetic acid–concentrated HCl (2:1) was refluxed under nitrogen for 24 hr. The mixture was cooled in ice and made alkaline with 3 *N* NaOH. The organic product was extracted with $CHCl_3$ which was then dried over $MgSO_4$. Evaporation of the solvent gave impure product (after several recrystallizations). It was dissolved in benzene and chromatographed on 300 g of 60–100 mesh Florisil using benzene containing increasing amounts of acetone to elute. The pure oil obtained solidified.

3-[2-(4-Phenyl-4-propionoxy-1-piperidinyl)ethyl]indole (31).—A mixture of 4 g (0.01 mole) of 3-[2-(4-hydroxy-4-phenyl-1-piperidinyl)ethyl]indole, 1.2 g (0.01 mole) of propionyl chloride, 7 g of K_2CO_3, and 50 ml of $CHCl_3$ was stirred for 2 hr. Then 0.4 g of additional propionyl chloride was added (stirring for another 30 min). The mixture was treated with 50 ml of H_2O and stirred 30 min. The $CHCl_3$ layer was dried ($MgSO_4$) and evaporated under reduced pressure to an oil which crystallized from benzene–isooctane.

3-[2-(3-N-Propionyl-*o*-methoxyanilino-1-pyrrolidinyl)ethyl]-indole (28).—To a stirred mixture of 4.9 g (0.15 mole) of 3-[2-(3-*o*-methoxyanilino-1-pyrrolidinyl)ethyl]indole and 7 g of K_2CO_3 in 75 ml of $CHCl_3$ was added, all at once, 1.5 g (0.02 mole) of propionyl chloride. The mixture was stirred 2.5 hr, then treated with 50 ml of H_2O and 10 ml of 3 *N* NaOH, and stirred an additional 2 hr. The $CHCl_3$ layer was dried ($MgSO_4$) and evaporated to an oil which was molecularly distilled for analysis.

2-Methyl-3-{2-[3-(3,4,5-trimethoxybenzoyloxy)pyrrolidinyl]-ethyl}indole (46).—To a suspension of 5 g (0.02 mole) of 2-methyl-3-[2-(3-hydroxypyrrolidinyl)ethyl]indole and 8 g (0.08 mole) of Na_2CO_3 in 40 ml of $CHCl_3$ was added 4.2 g (0.02 mole) of 3,4,5-trimethoxybenzoyl chloride in 30 ml of $CHCl_3$. The mixture was stirred under anhydrous conditions for 24 hr, then treated with 25 ml of H_2O, and stirred 1 additional hr. The $CHCl_3$ layer was dried ($MgSO_4$) and evaporated to a viscous oil which was chromatographed on a Florisil column (60–100 mesh) and eluted with benzene containing increasing amounts of acetone. The pure oil slowly crystallized from methanol.

3-{2-[3-(3,4,5-Trimethoxybenzoyloxy)-1-pyrrolidinyl]ethyl}-indole (39).—A mixture of 3 g (0.01 mole) of 3-[2-(3-hydroxy-1-pyrrolidinyl)ethyl]indole, 3 g (0.01 mole) of 3,4,5-trimethoxybenzoyl chloride, and 5 g (0.05 mole) of Na_2CO_3 in 40 ml of $CHCl_3$ was stirred under anhydrous conditions for 24 hr. Then, 0.3 g of acid chloride was added, and the mixture was stirred another 24 hr. The mixture was treated with 50 ml of H_2O and stirred for 1 hr, and the $CHCl_3$ was dried over $MgSO_4$. Evaporation of the $CHCl_3$ gave an oil which was chromatographed on a Florisil column (60–100 mesh) and eluted with benzene containing increasing amounts of acetone. The glassy solid was crystallized from benzene or benzene–ligroin giving a solid, mp 79–86° (gas evolution). Analysis as well as the nmr spectrum indicated benzene solvation.

3-{2-[3-(*p*-Methoxyphenylcarbamoyloxy)-1-pyrrolidinyl]-ethyl}indole (40).—A stirred suspension of 3.5 g (0.015 mole) of 3-[2-(3-hydroxy-1-pyrrolidinyl)ethyl]indole in 15 ml of dry benzene was treated dropwise with 2.3 g (0.015 mole) of *p*-methoxyphenyl isocyanate in 15 ml of dry benzene. After the addition (0.5 hr) the mixture was refluxed for 12 hr when only a small amount of solid remained suspended. It was filtered, and the filtrate was evaporated under vacuum to an orange gum. The product, in benzene, was chromatographed on 200 g of 60–100 mesh Florisil, eluting with benzene containing increasing amounts of acetone. The glassy solid would not crystallize.

3-{2-[3-(3,4,5-Trimethoxyphenylcarbamoyloxy)-1-pyrrolidinyl]-ethyl}indole (41).—A suspension of 3 g (0.01 mole) of 3-[2-(3-hydroxy-1-pyrrolidinyl)ethyl]indole and 3.05 g (0.013 mole) of 3,4,5-trimethoxybenzoyl azide in 40 ml of dry benzene was refluxed under nitrogen for 8 hr; the suspension slowly dissolved. Removal of the solvent under vacuum gave a dark, glassy solid which, in benzene, was chromatographed on 200 g of 60–100 mesh Florisil, eluting with benzene containing increasing amounts of acetone. The glassy solid did not crystallize.

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