dry ether, and reacted with lithium aluminum hydride (20 g.) in dry ether to give the pyrrolidine as a colorless oil, b.p. 130–132° (0.8 mm.), $n^{20}D$ 1.5216; yield 20 g., 29%.

Anal. Calcd. for $C_{16}H_{25}NO$: C, 77.7; H, 10.2; N, 5.7. Found: C, 77.7; H, 10.1; N, 5.8.

m-[1'-(1-Methyl-3-pyrrolidinyl)butyl]phenol.—This was prepared following method C and isolated as a hygroscopic (+)-tartrate, m.p. 70° (sealed tube).

Anal. Calcd. for $C_{19}H_{29}NO_7$: C, 59.5; H, 7.6; N, 3.7. Found: C, 59.5; H, 7.9; N, 4.0.

m-[1'-(1-Methyl-3-pyrrolidinyl)butyl]phenyl Acetate.—This was prepared from the above following method D and isolated as a colorless oil, b.p. 134–136° (0.8 mm.), $n^{20}D$ 1.5158.

Anal. Calcd. for $C_{17}N_{25}NO_2$: C, 74.1; H, 9.2; N, 5.1. Found: C, 74.3; H, 9.0; N, 5.3.

Acknowledgment.—The authors thank Dr. R. E. Bowman for helpful discussions, Mr. F. H. Oliver for the microanalyses, and Miss Sue Ketchum, Mrs. S. Stanat, and Mrs. J. Grant for help in the pharmacological work.

Synthesis and Pharmacological Activity of 3-(2-Pyrrolidinyl)indoles

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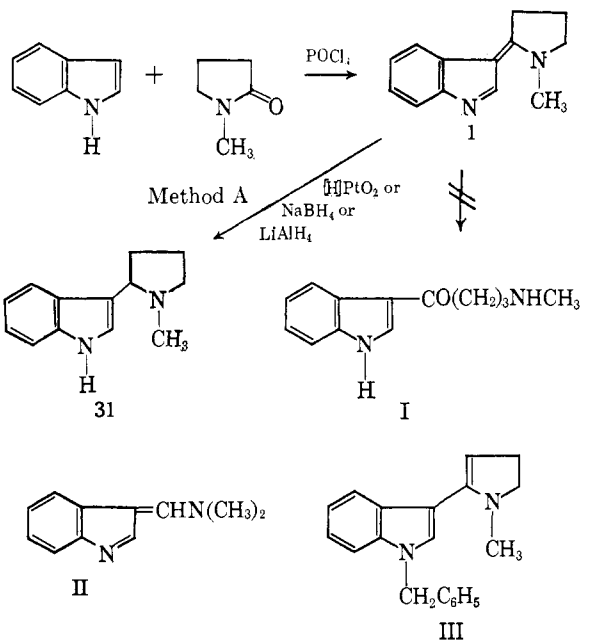
A number of 3-(2-pyrrolidinyl)indoles have been synthesized by several methods. These compounds and numerous intermediates showed various types of interesting central nervous system activity in mice and rats.

We have reported recently[1] the preparation of indole-3-C^{14}-carboxaldehyde by the method of Smith[2] involving the reaction of indole with dimethylformamide in the presence of phosphorus oxychloride. In subsequent attempts to avoid the inefficient use of excess radioactive dimethylformamide as the reaction solvent the latter was replaced by 1-methyl-2-pyrrolidinone as solvent. It was soon observed that the pyrrolidinone participated in the reaction. Consequently, indole was allowed to react with the complex formed from 1-methyl-2-pyrrolidinone and phosphorus oxychloride with the expectation that the amino ketone I would be produced.[3] Instead the product isolated had the structure **1**[4] which is reminiscent of the unstable intermediate II isolated by Smith[2] from the reaction of indole, dimethylformamide, and phosphorus oxychloride. However, whereas II was readily hydrolyzed by hot water to give indole-3-carboxaldehyde, **1** was resistant to hydrolysis to the amino ketone I. The reduction of **1** was accomplished readily by several methods to yield 3-(1-methyl-2-pyrrolidinyl)indole (**31**). The only 3-(2-pyrrolidinyl)-indole compound reported to date is the parent member of this class prepared by Fuhlhage and VanderWerf[5a,b] from indole and 1-pyrroline.



The method of preparation of **1** proved to be of general utility. A variety of substituted indoles and 2-pyrrolidinones was employed. The compounds prepared by method A are listed in Table I. Their ultraviolet spectra are similar to those reported for II[2] and other related 3H-indole derivatives,[6] and all have a band at 336–361 mμ with an extinction coefficient of 7800–20,700. Additional support for the 3H-indole over the 3-(2-pyrrolin-2-yl)indole structure is provided by the absence of an NH band in the infrared spectrum of **1** in both a Nujol mull and chloroform solution. In the case of 1-benzylindole which could not lead to the 3H-indole structure, the spectral data (see Experimental section) suggested that the product was a mixture which could contain the enamine III. Catalytic reduction of this mixture produced 1-benzyl-3-(1-methyl-2-pyrrolidinyl)indole.

The 3-(2-pyrrolidinylidene)-3H-indoles of type **1** were reduced by catalytic hydrogenation (method B), sodium borohydride (method C), or lithium aluminum hydride (method D) to the 3-(2-pyrrolidinyl)indoles listed in Tables II and III.

Another method (E) for the synthesis of 3-(2-pyrrolidinyl)indoles was developed employing Mannich bases derived from 3-acetylindoles.[7] The Mannich bases were allowed to react with a nitroalkane using a catalytic amount of sodium methoxide to produce the 3-indolyl nitro ketones (Table IV) in fair to good yield. Hydrogenation oft hese nitro ketones employing Raney nickel catalyst gave the corresponding 1-pyrrolines in

(1) J. Szmuszkovicz and R. C. Thomas, *J. Org. Chem.*, **26**, 960 (1961).

(2) G. F. Smith, *J. Chem. Soc.*, 3842 (1954).

(3) W. C. Anthony, *J. Org. Chem.*, **25**, 2049 (1960).

(4) Roman numerals refer to compounds mentioned only in the text, while Arabic numerals refer to compounds in the tables.

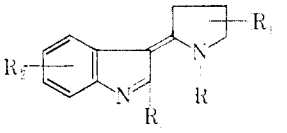
(5) (a) D. W. Fuhlhage and C. A. VanderWerf, *J. Am. Chem. Soc.*, **80**, 6249 (1958). (b) After this manuscript had been submitted for publication, the preparation of compound **43** by an alternate route was reported by F. Haglid and I. Wellings, *Acta Chem. Scand.*, **17**, 1743 (1963).

(6) E. Wenkert, J. H. Udelhofen, and N. K. Bhattacharyya, *J. Am. Chem. Soc.*, **81**, 3763 (1959).

(7) J. Szmuszkovicz, *ibid.*, **82**, 1180 (1960).

TABLE I

3-(2-PYRROLIDINYLIDENE)-3H-INDOLES

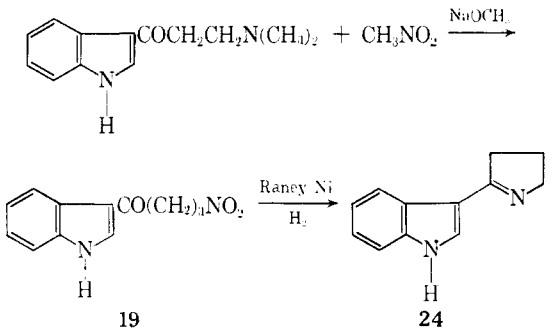


Compd. no.	R	R_1	R_2	R_3	Formula	M.p., °C.	Yield, %	Recrystn. solvents[a]	Calcd., % C	Calcd., % H	Calcd., % N	Found, % C	Found, % H	Found, % N
1	CH_3	H	H	H	$C_{13}H_{14}N_2$	229–231 dec.	89	Et-W	78.75	7.12	14.13	78.35	7.18	14.43
2	CH_3	H	5-OCH_3	H	$C_{14}H_{16}N_2O$	202–204	88	Et-W	73.65	7.06	12.27	73.66	7.40	12.46
3	CH_3	H	5-CH_3	H	$C_{14}H_{16}N_2$	209–212 dec.	93	M–W	79.21	7.60	13.20	78.87	7.64	12.94
4	CH_3	H	7-CH_3	H	$C_{14}H_{16}N_2$	210–212 dec.	93	M–W	79.21	7.60	13.20	79.37	7.54	13.01
5	CH_3	H	4-Cl	H	$C_{13}H_{13}ClN_2$	169–172 dec.	49	M–W	67.10	5.63	12.04	67.17	5.78	11.70
6	CH_3	H	5-Cl	H	$C_{13}H_{13}ClN_2$	219–221 dec.	76	M–W	67.10	6.53	12.04	67.11	5.55	11.74
7	CH_3	H	5-Br	H	$C_{13}H_{13}BrN_2$	207–210 dec.	82	M–W	56.32	4.73	10.11	56.39	4.59	9.61
8	CH_3	H	5-F	H	$C_{13}H_{13}FN_2$	211–213 dec.	69	M–W	72.19	6.06	12.95	71.92	6.14	12.66
9	CH_3	H	5-$OCH_2C_6H_5$	H	$C_{20}H_{20}N_2O$	149–152	90	A–S	78.90	6.62	9.20	78.06	6.79	9.11
10	CH_3	H	6-$OCH_2C_6H_5$	H	$C_{20}H_{20}N_2O$	180–184 dec.	88	M–W	78.90	6.62	9.20	78.72	6.82	8.80
11	CH_3	4-CH_3	H	H	$C_{14}H_{16}N_2$	175–177 dec.	53	A–S	79.21	7.60	13.20	78.94	7.65	12.93
12	CH_3	H	H	CH_3	$C_{14}H_{16}N_2 \cdot H_2O$	123–125 dec.	96	M–W	73.01	7.88	12.17	72.40	7.72	11.97
13	C_2H_5	H	H	H	$C_{14}H_{16}N_2$	160–162 dec.	95	A–S	79.21	7.60	13.20	78.91	7.35	12.90
14	n-C_4H_9	H	H	H	$C_{16}H_{20}N_2$	131–134	75	A–S	79.05	8.39	11.66	79.95	8.22	11.48
15	$CH_2C_6H_5$	H	H	H	$C_{19}H_{18}N_2$	148 dec.	50	B	83.17	6.61	10.21	82.87	6.84	10.22
16	$CH_2C_6H_5$	H	7-CH_3	H	$C_{20}H_{20}N_2 \cdot 0.5H_2O$	172–174 dec.	97	M–W	80.75	7.12	9.42	80.55	7.20	9.91
17	$CH_2C_6H_5$	H	5-Br	H	$C_{19}H_{17}BrN_2$	202 dec.	66	M–W	64.59	4.85	7.93	64.43	4.61	7.45
18	$CH_2C_6H_5$	H	5-Cl	H	$C_{19}H_{17}ClN_2$	190 dec.	79	M–W	73.90	5.55	9.07	73.60	5.59	8.57

[a] Code: A, acetone; B, benzene; Et, ethanol; M, methanol; S, Skellysolve B (a saturated hydrocarbon fraction, b.p. 60–70°); W, water.

good yield[8] (Table V). The formulation of these compounds as 1-pyrrolines rather than 3H-indoles is strongly supported by their ultraviolet spectra which

Method E

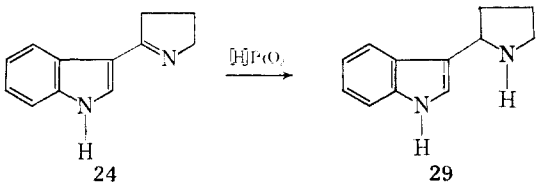


show maxima not higher than 296 mμ. On the other hand, conversion to the hydrochloride (**26**, Table V) brought about a shift to 329 mμ most likely due to formation of the 3H-indole system.

Unexpectedly the Mannich base derivative from 3-propionylindole did not react with nitromethane. To circumvent this difficulty the quaternary salt was prepared. Reaction of the latter with sodium cyanide produced 3-(2-methyl-3-cyanopropionyl)indole which upon hydrogenation employing Raney nickel as the catalyst yielded 3-(3-methyl-1-pyrrolin-2-yl)indole.[9]

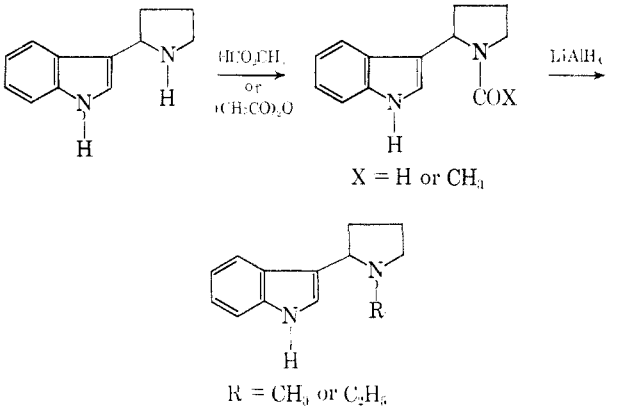
The pyrrolines were converted by several methods to the 3-(2-pyrrolidinyl)indoles listed in Table III. In some cases the intermediates were not isolated. Catalytic hydrogenation (method F) produced compounds unsubstituted on the pyrrolidine nitrogen. Treatment of the compounds with methyl formate or acetic an-

Method F



hydride gave the 1-formyl or 1-acetyl compounds, respectively, which could be reduced with lithium aluminum hydride to afford the 1-methyl or 1-ethyl product (method G). Alternatively, the pyrrolines were treated with methyl iodide to form 3-(1-methyl-

Method G



2-pyrrolidinylidene)-3H-indole hydriodides which were reduced with sodium borohydride to 3-(1-methyl-2-pyrrolidinyl)indoles (method H).

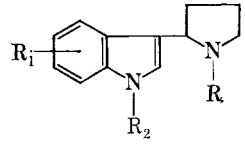
Some difficulty was encountered with the synthesis of 3-(5,5-dimethyl-2-pyrrolidinyl)indoles substituted in position 1 of the pyrrolidine moiety, presumably due to steric factors. Thus, reaction of 3-(5,5-dimethyl-1-pyrrolin-2-yl)indole (**27**) with methyl iodide (method

(8) S. Kossar and M. C. Kloetzel, *J. Org. Chem.*, **27**, 1314 (1962).

(9) A. P. Terent'ev, R. A. Gracheva, and L. M. Volkova, *J. Gen. Chem. USSR*, **31**, 2634 (1961).

TABLE II

3-(2-PYRROLIDINYL)INDOLES

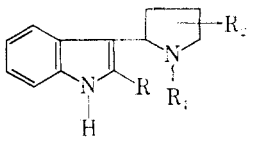


Compd. no.	Method of prepn.	R	R_1	R_2	Formula	M.p., °C.	Yield, %	Recrystn. solvents[a]	Calcd., % C	Calcd., % H	Calcd., % N	Found, % C	Found, % H	Found, % N
29	...	H	H	H	$C_{12}H_{14}N_2$	141–143	46	B–S	77.37	7.57	15.04	76.81	7.56	14.97
30	...	H	H	CH_3	$C_{13}H_{16}N_2 \cdot HCl$	215–216	73	M–E	65.95	7.24	11.83	66.45	7.18	11.35
31	D	CH_3	H	H	$C_{13}H_{16}N_2$	95–97	75	S	77.96	8.05	13.99	77.58	8.31	13.89
32	D	CH_3	5-OCH_3	H	$C_{14}H_{18}N_2O$	118–120.5	74	S	73.01	7.87	12.16	72.74	7.73	12.38
33	B	CH_3	5-CH_3	H	$C_{14}H_{18}N_2$	116.5–117.5	91	E–S	78.46	8.46	13.08	78.73	8.54	12.92
34	B	CH_3	5-$OCH_2C_6H_5$	H	$C_{20}H_{22}N_2O$	124–126	77	A–S	78.40	7.24	9.15	78.34	6.97	9.16
35	...	CH_3	5-OH	H	$C_{13}H_{16}N_2O$	161–163	60	A–S	72.19	7.46	12.95	72.17	7.63	12.47
36	C	CH_3	5-Cl	H	$C_{13}H_{15}ClN_2$	143–144.5	79	E–S	66.53	6.44	11.94	66.55	6.64	12.17
37	C	CH_3	4-Cl	H	$C_{13}H_{15}ClN_2$	157–158.5	59	A–S	66.53	6.44	11.94	66.58	6.44	11.53
38	C	CH_3	5-Br	H	$C_{13}H_{15}BrN_2$	139–141	72	A–S	55.92	5.42	10.04	56.12	5.25	9.62
39	C	CH_3	7-CH_3	H	$C_{14}H_{18}N_2$	95–97.5	72	E–S	78.46	8.46	13.08	78.69	8.58	12.89
40	C	CH_3	6-$OCH_2C_6H_5$	H	$C_{20}H_{22}N_2O$	118–119	85	A–S	78.40	7.24	9.15	78.07	7.07	9.19
41	...	CH_3	6-OH	H	$C_{13}H_{16}N_2O \cdot HCl$	193–195	15	M–I–E	61.79	6.78	11.09	61.30	6.77	10.91
42	C	CH_3	5-F	H	$C_{13}H_{15}FN_2$	142–143.5	88	A–S	71.52	6.93	12.84	71.68	7.02	12.80
43	...	CH_3	H	CH_3	$C_{14}H_{18}N_2$	45.5–47.5	49	...	78.46	8.46	13.08	77.96	8.98	13.05
44	...	CH_3	H	$CH_2C_6H_5$	$C_{20}H_{22}N_2 \cdot C_6H_{13}NO_3S$	127–129.5	38	I–E	66.48	7.51	8.95	66.48	7.31	8.91
45	...	CH_3	H	$(CH_2)_2N(C_2H_5)_2$	$C_{19}H_{29}N_3 \cdot 2HCl$	210–212	55	Et–E	61.27	8.39	11.29	61.07	8.41	11.15
46	C	C_2H_5	H	H	$C_{14}H_{18}N_2 \cdot HCl$	200–202	79	Et–E	67.04	7.64	11.18	66.77	7.20	11.07
47	C	n-C_4H_9	H	H	$C_{16}H_{22}N_2 \cdot C_6H_{13}NO_3S \cdot C_2H_5OH$	116–118	87	Et	61.63	8.83	8.98	61.69	8.41	9.36
48	D	$CH_2C_6H_5$	H	H	$C_{19}H_{20}N_2$	91.5–93	77	S	82.56	7.29	10.14	82.28	7.36	10.31
49	C	$CH_2C_6H_5$	5-Br	H	$C_{19}H_{19}BrN_2 \cdot HCl$	181–186	74	Et–E	58.25	5.15	7.15	58.55	5.08	6.79
50	C	$CH_2C_6H_5$	5-Cl	H	$C_{19}H_{19}ClN_2 \cdot HCl$	174–176	76	Et–E	65.70	5.81	8.07	65.44	5.90	7.91
51	C	$CH_2C_6H_5$	7-CH_3	H	$C_{20}H_{22}N_2$	95–98	72	E–S	82.72	7.64	9.65	82.44	7.41	9.63

[a] Code: A, acetone; B, benzene; E, ether; Et, ethanol; I, 2-propanol; M, methanol; S, Skellysolve B (a saturated hydrocarbon fraction, b.p. 60–71°).

TABLE III

3-(2-PYRROLIDINYL)INDOLES

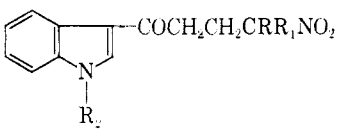


Compd. no.	Method of prepn.	R	R_1	R_2	Formula	M.p., °C.	Yield, %	Recrystn. solvents[a]	Calcd., % C	Calcd., % H	Calcd., % N	Found, % C	Found, % H	Found, % N
52	F	H	H	5-CH_3	$C_{13}H_{16}N_2 \cdot HCl$	225–226	81	M	65.95	7.24	11.84	65.94	7.10	11.70
53	F	H	H	5-C_2H_5	$C_{14}H_{18}N_2 \cdot HCl$	227–228	77	M–E	67.05	7.64	11.17	66.86	7.24	11.42
54	F	H	H	5,5-$(CH_3)_2$	$C_{14}H_{18}N_2 \cdot HCl$	220–230 dec.	97	M–E	67.05	7.64	11.17	67.20	7.78	11.14
55	G	H	CH_3	3-CH_3	$C_{14}H_{18}N_2 \cdot HCl$	211–214	23	M–I–E	67.05	7.64	11.17	67.03	7.49	10.99
56	G	H	CH_3	4-CH_3	$C_{14}H_{18}N_2 \cdot HCl$	197–200	51	M–E	67.05	7.64	11.17	66.67	7.67	11.08
57	G and H	H	CH_3	5-CH_3	$C_{13}H_{16}N_2$	151–152	17	M–E	78.46	8.47	13.07	78.36	8.45	13.07
58	G	H	CH_3	5-C_2H_5	$C_{14}H_{18}N_2$	140–141	65	E–P	78.90	8.83	12.27	78.60	8.75	12.45
59	...	H	CH_3	5,5-$(CH_3)_2$	$C_{14}H_{18}N_2$	138–140	26	E–P	78.90	8.83	12.27	78.48	8.74	12.26
60	G	H	C_2H_5	5,5-$(CH_3)_2$	$C_{16}H_{22}N_2$	82–85	80	P	79.29	9.15	11.56	79.14	9.33	11.29
61	C	CH_3	CH_3	H	$C_{14}H_{18}N_2$	122–123	68	E–S	78.46	8.46	13.08	78.80	8.30	12.97

[a] Code: E, ether; I, 2-propanol; M, methanol; P, petroleum ether (b.p. 30–60°); S, Skellysolve B (a saturated hydrocarbon fraction, b.p. 60–71°).

TABLE IV

3-INDOLYL NITRO KETONES

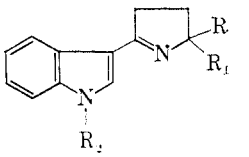


Compd. no.	R	R_1	R_2	Formula	M.p., °C.	Yield, %	Recrystn. solvents[a]	Calcd., % C	Calcd., % H	Calcd., % N	Found, % C	Found, % H	Found, % N
19	H	H	H	$C_{12}H_{12}N_2O_3$	178–180	50	M	62.06	5.21	12.06	61.91	5.05	11.84
20	H	CH_3	H	$C_{13}H_{14}N_2O_3$	155–156	47	I	63.40	5.73	11.38	63.42	5.64	10.98
21	H	C_2H_5	H	$C_{14}H_{16}N_2O_3$	172–173	71	M	64.60	6.20	10.76	64.40	6.36	10.49
22	CH_3	CH_3	H	$C_{14}H_{16}N_2O_3$	203–204	74	I	64.60	6.20	10.76	64.48	6.10	10.89
23	H	H	CH_3	$C_{13}H_{14}N_2O_3$	96–98	30	M[b]	63.40	5.73	11.38	63.48	5.48	11.04

[a] Code: I, 2-propanol; M, methanol. [b] Purified initially by column chromatography on silica.

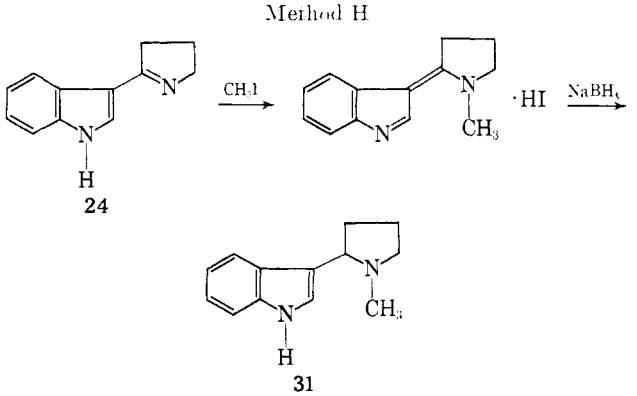
TABLE V

3-(1-PYRROLIN-2-YL)INDOLES

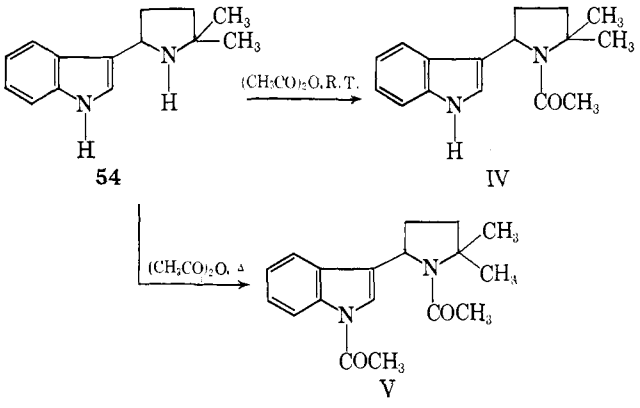


Compd. no.	R	R_1	R_2	Formula	M.p., °C.	Yield, %	Recrystn. solvents[a]	Calcd., % C	Calcd., % H	Calcd., % N	Found, % C	Found, % H	Found, % N
24	H	H	H	$C_{12}H_{12}N_2$	182.5–183.5	55	EA	78.23	6.57	15.20	77.95	6.45	14.92
25	H	CH_3	H	$C_{13}H_{14}N_2$	196–197	77	I	78.75	7.12	14.13	78.77	6.90	14.41
26	H	C_2H_5	H	$C_{14}H_{16}N_2 \cdot HCl$	218–219 dec.	86	M–E	67.59	6.89	11.26	67.78	6.61	10.98
27	CH_3	CH_3	H	$C_{14}H_{16}N_2$	197–198	84	E	79.21	7.60	13.20	79.10	7.19	13.23
28	H	H	CH_3	$C_{13}H_{14}N_2$	119–120	67	E	78.75	7.12	14.13	78.17	7.37	14.39

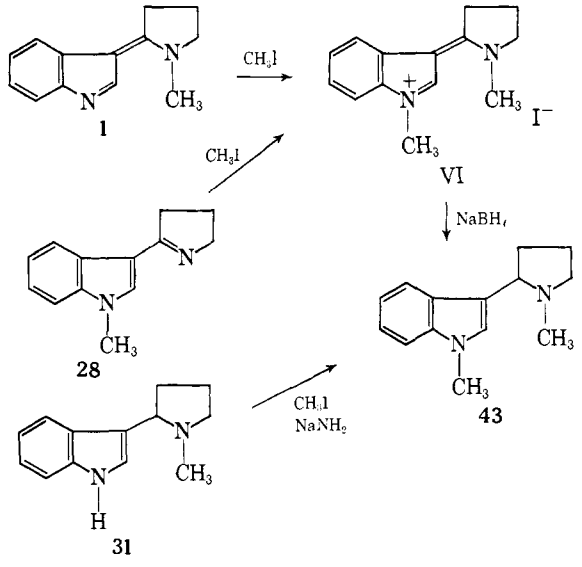
[a] Code: E, ether; EA, ethyl acetate; I, 2-propanol; M, methanol.



H) produced only the hydriodide of **27**, while no reaction occurred between the corresponding pyrrolidine (**54**) and methyl formate (method G). The desired 3-(1,5,5-trimethyl-2-pyrrolidinyl)indole (**59**) was prepared in low yield by alkylation of **54** with methyl iodide. Acetylation of **54** at room temperature with acetic anhydride afforded the monoacetyl derivative IV (infrared C=O band, 1612 cm.$^{-1}$) which led to 3-(1-ethyl-5,5-dimethyl-2-pyrrolidinyl)indole (**60**) on lithium aluminum hydride reduction (method G). Acetylation of **54** at reflux temperature gave the diacetyl derivative V which showed C=O bands in the infrared at 1640 and 1710 cm.$^{-1}$.



1-Methyl-3-(1-methyl-2-pyrrolidinyl)indole (**43**) was prepared by reaction of **31** with sodamide followed by methyl iodide, and also by treatment of **1** with methyl iodide followed by the reduction of the intermediate VI with sodium borohydride. The same intermediate (VI) resulted from the reaction of **28** with methyl iodide. The fact that the identical product **43** was obtained from these three sequences established unequivocally the position of methylation in the processes **1** to VI and **28** to VI.

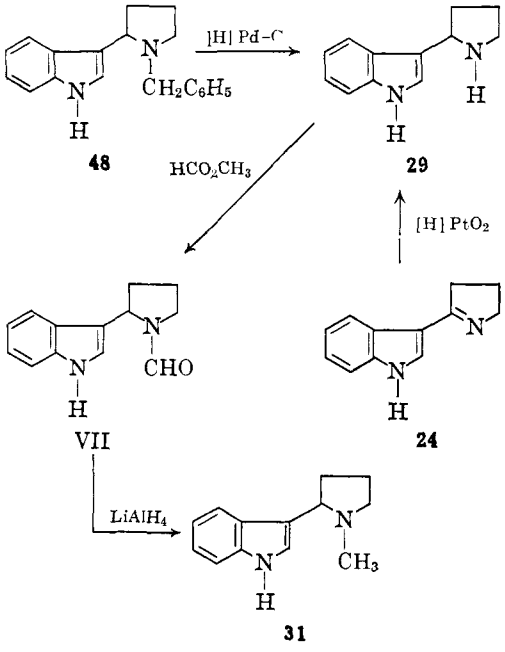


Treatment of **1** with 2-diethylaminoethyl chloride followed by sodium hydroxide, sodium borohydride, and then hydrogen chloride produced 1-(2-diethylaminoethyl)-3-(1-methyl-2-pyrrolidinyl)indole dihydrochloride (**45**).

3-(1-Methyl-2-pyrrolidinyl)indol-5-ol (**35**) and 3-(1-methyl-2-pyrrolidinyl)indol-6-ol (**41**) were prepared from **9** and **10**, respectively, by catalytic debenzylation employing palladium-on-charcoal as the catalyst. Although the reduction of **9** could be stopped before hydrogenolysis of the pyrrolidine ring occurred, it was necessary to use the hydrochloride of **10** to enable the isolation of the desired product **41**. Troxler, *et al.*,[10] previously had employed the hydrochlorides of benzyloxygramines to prevent hydrogenolysis of the dimethylamine moiety.

Proof of the structure of 3-(1-substituted 2-pyrrolidinyl)indoles produced by reduction of 3-(1-substituted 2-pyrrolidinylidene)-3H-indoles (products of method A) is based on analytical and spectral data, and on independent syntheses as shown for compounds **29** and **31**.

3-(2-Pyrrolidinyl)indole (**29**) was prepared by catalytic hydrogenolysis of 3-(1-benzyl-2-pyrrolidinyl)indole (**48**), and also by catalytic hydrogenation of 3-(1-pyrrolin-2-yl)indole (**24**). This structure (**29**) was assigned by Fuhlhage and VanderWerf[5] to the compound obtained from indole and 1-pyrroline. The melting point of our product is similar to that reported by these authors. Compound **29** was made to react with methyl formate and the resulting formyl intermediate VII



was reduced with lithium aluminum hydride to produce **31** identical with the material prepared *via* method A.

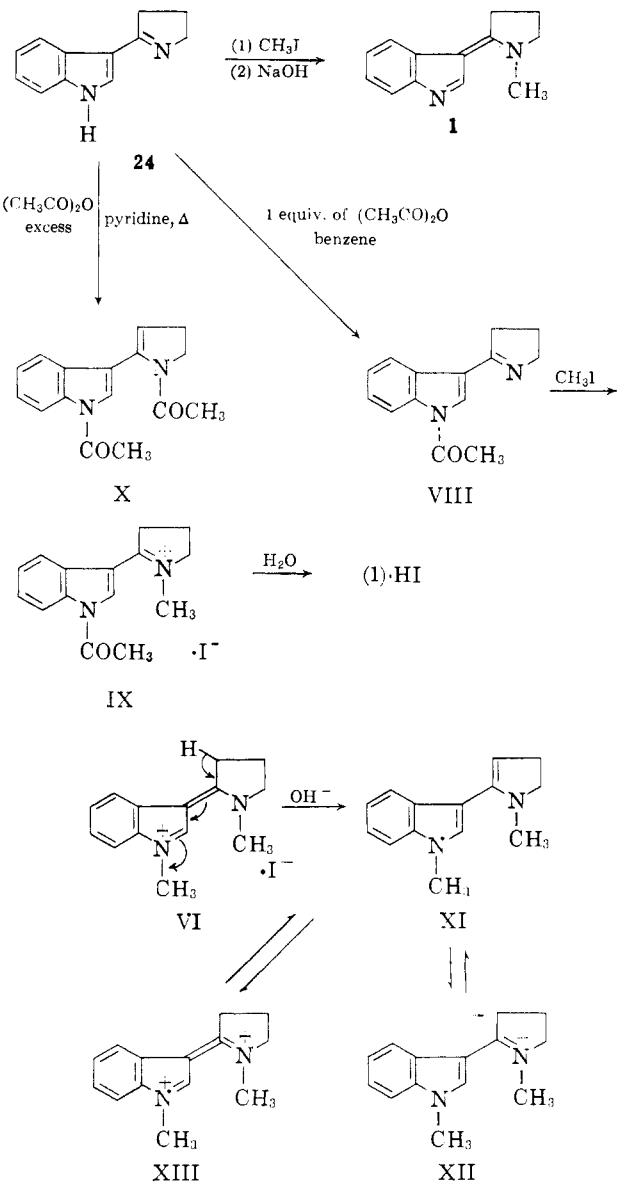
Alkylation and acetylation experiments were conducted with 3-(1-pyrrolin-2-yl)indole (**24**). Alkylation of **24** with methyl iodide led to the hydriodide of **1** which on being made basic afforded 3H-indole (**1**) identical with the compound prepared by method A. Thus, the position of methylation in the sequence **24** to **1** was established unequivocally.

Acetylation of **24** with one equivalent of acetic anhydride in benzene afforded the monoacetyl derivative VIII. It showed a C=O band at 1712 cm.$^{-1}$ and λ_{max} 305 mμ and was converted to **24** on attempted crystallization from methanol. Treatment of VIII with methyl iodide afforded methiodide IX (C=O at 1725 cm.$^{-1}$; λ_{max} 299 mμ) which on heating with water gave the hydriodide of **1**, thus confirming the assignment of the position of the acetyl group in VIII. Acetylation of **24** with excess acetic anhydride in hot pyridine[11] gave the diacetyl derivative X (C=O at 1637, 1708 cm.$^{-1}$; λ_{max} 301 mμ) which resisted alkylation upon refluxing for 21 hr. with methyl iodide.

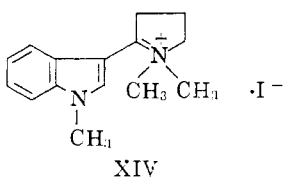
The possibility of utilizing VI as an enamine precursor was investigated. Treatment of VI with base afforded an oil which showed λ_{max} 293 mμ (ϵ 6500) in

(10) F. Troxler, F. Seeman, and A. Hofmann, *Helv. Chim. Acta*, **42**, 2073 (1959).

(11) *Cf.* A. Brossi, H. Besendorf, B. Pellmont, M. Walter, and O. Schnider, *ibid.*, **43**, 1459 (1960).



ether solution (probably due to structure XI and/or XII) and λ_{max} 335 mμ (ε 20,000) in methanol, probably due to structure XIII. Alkylation of this oil with either methyl iodide alone or in dimethylformamide afforded a mixture from which two products were isolated. The first was the iodide VI which resulted from a proton exchange equilibrium.[12] The second was a product of N-alkylation (XIV), the structure of which was supported by its nuclear magnetic resonance spectrum.[13]



XIV

Pharmacological Methods

Toxicity Experiments. A. Mice.—Groups of 4 mice (albino–Upjohn strain weighing 18–22 g.) were injected intraperitoneally with test compound dissolved or suspended in 0.25% aqueous methylcellulose. The dose was decreased in 0.5 log units from 1000 mg./kg. until completely killing and living doses were obtained. The LD_{50} was estimated by the method of Spearman and Karber.[14]

B. Rats.—Groups of 4 rats (albino–Upjohn strain weighing 260–300 g.) were injected intraperitoneally with test compound dissolved or suspended in 0.25% aqueous methylcellulose. The initial dose utilized was the mouse LD_{50} (see A) and the dose was adjusted (0.3 log intervals) to obtain completely killing and living doses. The LD_{50} was estimated by the method of Spearman and Karber.[14]

Behavioral Experiments in Mice. A. Righting Reflex. Loss of righting reflex was recorded when mice failed to right themselves within 10 sec. when placed on their back.

B. Traction (Tr).—Traction was determined as described by Boissier, *et al.*[15] Mice are allowed to grasp a horizontal wire with their forepaws; failure to place at least one hind leg on the wire in 5 sec. constitutes loss of traction.

C. Chimney (Ch).—The chimney test was carried out as described by Boissier, *et al.*[15] The animal is introduced into a glass tube 2.5 cm. in diameter and 25 cm. long. As he approaches the opposite end of the tube, it is placed vertically so that the animal is head down. Failure to back out of the tube in 30 sec. is regarded as loss of response.

D. Dish (D).—The dish test was carried out by placing treated mice in glass Petri dishes (5 × 10 cm.) partially embedded in shavings in a standard mouse box. Mice remaining in the dish longer than 4 min. are considered to evidence drug effect.

E. Pedestal (P).—Mice are placed on a pedestal (composed of two "Flex Frame" feet attached to opposite ends of a 5 cm. piece of "Flex Frame" rod) in a standard mouse box with shavings on the floor. Mice remaining on the pedestal in excess of 1 min. are considered to evidence drug effect.

F. Antagonism of Tryptamine Symptoms.—Treated mice are injected with tryptamine hydrochloride, 100 mg./kg. i.v. The mice are evaluated for the presence of the typical symptoms—head weave (HW), arch back (AB), hind leg spread (HLS), and pawing (PAW) induced by tryptamine.

G. Potentiation of Tryptamine Symptoms.—Treated mice are injected with tryptamine hydrochloride, 25 mg./kg. i.v. The mice are evaluated for the presence of the typical tryptamine symptoms (see F). This dose of tryptamine alone does not produce symptoms.

H. Antagonism of Nicotine Convulsions and Lethality. Treated mice are injected with 2 mg./kg. of nicotine salicylate i.v. Control mice exhibit running convulsions followed by tonic extensor seizures (TE) and death. The antagonism of all 3 syndromes is studied.

I. Fighting Mouse Test.—Aggressive behavior induced in mice using isolation stress (procedure similar to that of Yen, *et al.*[16]) is studied. Groups of 5 mice are tested with a maximum dose of 30 mg./kg. Isolated mice attack control mice introduced into the cage of the isolated mouse. Block of this attack is utilized as the evidence of drug effect.

In all of these experiments, groups of six Carworth Farms male mice (18–22 g.) were dosed with a maximum of 501 mg./kg. i.p. (note exceptions in procedure I.) Compounds were dissolved or suspended in 0.25% aqueous methylcellulose. Tests were carried out 60 min. after drug administration. Doses were decreased in 0.3 log intervals. The 50% effective dose was estimated by the method of Spearman and Karber.[14]

J. Behavior Experiments in Rats. Classical Avoidance. The basic procedure has been described by Verhave, *et al.*[17] Skinner boxes with a grid floor for presenting electric shock were used. A movable bar was mounted in one wall with its top 8.9 cm. above the floor and projecting 1.3 cm. into the cage. Events were programmed and recorded automatically by a system of relays, timers, etc. Discrete trials were given 40 times/hr. at variable intervals. The trials consisted of a 16-sec. period of white noise (a sound level of 76 db. above reference level) with an electric shock occurring during the last 6 sec. of this noise, provided the rat did not press the bar. A bar press during the

(12) G. Stork, R. Terrell, and J. Szmuszkovicz, *J. Am. Chem. Soc.*, **76**, 2029 (1954).

(13) N. J. Leonard, C. K. Steinhardt, and C. Lee, *J. Org. Chem.*, **27**, 4027 (1962), and references cited therein.

(14) D. J. Finney, "Statistical Method in Biological Assay," Hafner Publishing Co., New York, N. Y., 1952, p. 524.

(15) J. R. Boissier, J. Pagny, and Y. Font Du Picard, *Med. Exptl.*, **4**, 145 (1961).

(16) H. C. Y. Yen, C. A. Day, and E. B. Sigg, *Pharmacologist*, **4**, 173 (1962).

(17) T. Verhave, J. E. Owen, Jr., and E. B. Robbins, *Arch. Intern. Pharmacodyn.*, **116**, 45 (1958).

shock (an escape response) stopped both the shock and the noise immediately. A bar press during the noise before the shock (an avoidance response) stopped the noise and prevented the occurrence of any shock on that trial. The electric shock was 260 volts, 60 cycles a.c. delivered to the rat through a 150,000 ohm series resistor and through a grid scrambler (type 45 Automatic Electric stepping switch).

Animals were tested every fourth day. For drug testing, animals were required to avoid on 95% or more of the trials. Most animals developed such avoidance in four 10-hr. training periods. Subsequent test periods lasted 5.75 hr., and i.p. injections (with a blunt no. 18 needle to prevent accidental injection into the gastrointestinal tract) were given after the first 45 min. Before testing drugs, rats were tested with 5.9 or 6.9 mg./kg. of chlorpromazine hydrochloride and saline. Animals were used only when chlorpromazine produced at least 120 escape responses, *i.e.*, when on at least 120 of the 200 trials the avoidance response to noise was eliminated, but the escape response to shock occurred. Most animals showed this reaction, though a few, especially when the lower dose was used, required a second injection. This chlorpromazine control was run after every 10 test runs or less, as was a saline control where 95% avoidance was required for continuation. Data were not used if the following saline control run showed less than 90% avoidance or less than 100 escape responses with chlorpromazine. Wistar rats over 100 days old were used.

The number of escape responses that could be produced by a drug was the measure of primary interest since this measure reveals the selective action of the drug eliminating the avoidance response to the noise while allowing the escape response to the shock. The major tranquilizing drugs (such as the phenothiazines and reserpine) are distinguished by a consistent selective action which lasts for several hours and occurs over a moderate dose range. Under the conditions employed here, this effect is rarely seen outside the major tranquilizing drugs; even morphine is less consistent than chlorpromazine. The test compound was first tested at 28% of the rat LD_{50} in 2 rats. If less than 30 escape responses occurred and the animal avoided for at least 100 trials then the compound was not tested further and was recorded as negative in Table VI. If more than 30 escape responses occurred or if all behavior was eliminated for more than 100 trials, then the compound was tested further and the dose was found for each animal that produced the largest number of escape responses. The average for at least 3 rats of the escape responses at the most effective dose was represented in Table VI as follows: − = 0–30; ± = 31–60; + = 61–90; ++ = above 90. When tested in this way, chlorpromazine averages about 150 escape responses. Ordinarily testing was only carried up to 28% of the LD_{50} but a few compounds that showed some activity at 28% were tested at 40% or 56% of the LD_{50}. In those cases, if a larger selective effect was seen at either of those doses, its magnitude is indicated in Table VI in parentheses.

K. Pseudocholinesterase (Pseudo-ChE).—Inhibition of this enzyme is determined manometrically using human serum as the enzyme source and acetylcholine chloride as the substrate. Test compounds are dissolved or suspended in water. Compounds producing less than 50% inhibition at concentration of 10^{-3} *M* are considered of no interest. The I_{50} was estimated graphically using various concentrations.

L. Monamine Oxidase (MAO).—Inhibition of this enzyme is determined manometrically using guinea pig liver as the enzyme source and serotonin creatinine sulfate as the substrate. Test compounds are dissolved in water (using HCl if needed). Compounds producing less than 50% inhibition at 10^{-3} *M* are considered of no interest. The I_{50} was estimated graphically using various concentrations.

Results

The results of these test procedures are detailed in Table VI. Loss of righting reflex, antagonism of the running convulsion induced by nicotine salicylate, and tryptamine potentiation are not tabulated since no compound was active in these tests.

Structure–Activity Relations. Mouse Behavior.—In general our findings indicate that while overt depression was noted with these materials they produce little neurological deficit. Of the four end points used, the compounds were most active in dish (D) and chimney (Ch) and occasionally in pedestal (P), but little effect on traction (Tr) was noted. Indole nitrogen substitution reduced activity (**31** *vs.* **43, 44, 45**), whereas pyrrolidine nitrogen substitution with small groups enhanced it (**29** *vs.* **31, 46; 52** *vs.* **57; 53** *vs.* **58; 54** *vs.* **59**). Benzyl groups on pyrrolidine nitrogen eliminated activity (**36** *vs.* **50; 38** *vs.* **49; 39** *vs.* **51**). Benzene ring substitution in an active compound had little effect (**31** *vs.* **32–42**). Pyrrolidine ring substitution on carbon often reduced activity (**46** *vs.* **60; 31** *vs.* **55–59**). Introduction of a 2-methyl substituent into the indole ring of one of the most active compounds (**31** *vs.* **61**) eliminated mouse behavior along with tryptamine antagonism, classical avoidance, and MAO inhibition activities, while leaving fighting mouse and pseudo-ChE effects unchanged and imparting nicotine antagonism to the molecule.

Correlation with classical avoidance showed that all compounds significantly active in mouse behavior also possessed some activity in classical avoidance and further, that all but two of the 12 compounds showing any activity in classical avoidance had significant activity in mouse behavior (**31, 33, 36, 39, 42, 46, 59**), five were significantly active in inhibiting monamine oxidase (MAO), while of the 11 best MAO inhibitors seven were significantly active in mouse behavior.

Tryptamine Antagonism.—Substitution on the indole-N (**31** *vs.* **43**) and especially on a pyrrolidine ring carbon (**46** *vs.* **60; 31** *vs.* **55–59**) reduced activity while pyrrolidine-N substitution by small groups (**29** *vs.* **31, 46**) enhanced and by large groups (**36** *vs.* **50; 38** *vs* **49; 39** *vs.* **51**) eliminated activity. Benzene ring substitution in an already active molecule usually had no effect on activity (**31** *vs.* **32–39**). In the majority of cases, antagonism was considerably greater against AB and PAW than against HLS and HW. The most active compound here seems to be **39**. The antagonism of AB by these agents is in marked contrast to chlorpromazine which is not able to antagonize this effect of tryptamine. These differential antagonisms cannot be correlated clearly with clinical efficacy at this time.

Nicotine Antagonism.—This test seemed to correlate very poorly with either structure or other tests. More often than not, compounds with this activity seemed to have little activity in the mouse behavior or tryptamine antagonism tests and were the most highly substituted compounds, especially in the pyrrolidine ring (*e.g.*, **54, 56, 58, 59, 60**). If nicotine acts within the central nervous system as it does in the peripheral nervous system these data would indicate that these indoles have little central anticholinergic activity.

Fighting Mouse.—To be active in this test a compound must have a small alkyl group on one or both nitrogens (**29** *vs.* **30, 31–43, 46, 56–59, 61**). Larger groups on nitrogen either reduced or eliminated activity (**43** *vs.* **44, 45; 46** *vs.* **47, 48; 36** *vs.* **50; 38** *vs.* **49; 39** *vs.* **51**). Introduction of a benzene ring substituent retained activity except for the case of OH (**35**) where penetration into the brain may be poor. Introduction of alkyl groups on a pyrrolidine carbon enhanced (**29** *vs.* **52**) or retained activity (**31** *vs.* **55–59**) except in one case (**46** *vs.* **60**).

The most active compounds in this test were **30, 37,**

TABLE VI

PHARMACOLOGY

Compound no.	LD_{50} Mouse	LD_{50} Rat	Mouse behavior[a] TrD_{50}	DD_{50}	ChD_{50}	PD_{50}	Antagonizing dose$_{50}$[a] Tryptamine HLS	AB	PAW	HW	Nicotine TE	Death	ED_{50}[b] Fighting mouse	Classical avoidance[c]	I_{50}[c] Pseudo-ChE *in vitro*	MAO *in vitro*
29	200	171	—	50	—	—	—	—	—	—	32	36	—	−	2×10^{-4}	-
30	56	100	—	40	45	50	—	—	—	—	32	36	9	−	2×10^{-4}	—
31	65	176	32	18	16	18	56	25	28	45	—	—	14	++	1×10^{-3}	4×10^{-4}
32	65	55	—	32	28	35	45	32	28	-	- -	- -	21	−	—	—
33	65	92	35	16	14	18	—	40	45	-	—	-	21	± (+)	1×10^{-3}	—
34	100	71	—	- -	- -	—	- -	—	- -	- -	-	-	16	-	6×10^{-5}	-
35	178	282	—	—	—	- -	-	—	-	- -	23	20	- -	- -	3×10^{-5}	-
36	56	40	50	16	22	14	56	28	32	28	—	- -	11	+ (++)	1×10^{-3}	—
37	56	71	—	25	25	32	—	23	18	50	—	—	9	++	4×10^{-4}	4×10^{-4}
38	56	35	—	35	10	35	- -	32	25	—	- -	-	14	±	9×10^{-4}	—
39	178	126	—	18	22	-	—	18	18	-	32	28	8	++	1×10^{-4}	2×10^{-5}
42	42	56	—	18	20	28	—	-	—	-	—	-	9	+	—	4×10^{-4}
43	56	140	—	36	50	-	—	- -	—	- -	—	-	9	-	2×10^{-4}	
41	133	93		—	35	-	-	35	35	-	-	-	-	- -	1×10^{-5}	
45	100	280	—	—	—	- -	56	35	35	50	-	-	-	—	6×10^{-6}	
46	56	71	-	28	18	-	-	35	28	—	—	-	11	±	5×10^{-5}	5×10^{-4}
47	200	71	-	—	-	- -	—	- -	—	-	- -	-	—	- -	2×10^{-5}	- -
48	65	55	—	-	—	-	- -	- -	- -	-	45	40	28	-	6×10^{-5}	-
49	100	253	—		- -	-	—	—	- -	-	—	- -	-	-	2×10^{-5}	-
50	75	212	—	—	—	—	—	-	-	-	- -		-	-	4×10^{-5}	-
51	178	106	-	- -	- -	—	—	-	-		-		-	−	5×10^{-5}	-
52	56	42	—	—	—	- -	-	-	-		-	-	14	−	1×10^{-5}	4×10^{-4}
53	178	111	—	—	-	-	-	—	—	-	- -	- -	24	-	7×10^{-5}	1×10^{-4}
54	56	92	—	50	40	-	-			—	32	36	21	—	1×10^{-4}	2×10^{-4}
55	56	71	—	-	—	-	—	—	—	—	-	- -	21	- -	9×10^{-5}	- -
56	75	126	—	—	—	-	- -	-	-		20	20	16	± (++)	2×10^{-4}	—
57	178	125	-	40	20	-	- -	- -	-		—	-	12	++	1×10^{-4}	2×10^{-4}
58	100	140	—	—	—	—	—	- -	—	—	32	36	19	+	1×10^{-5}	1×10^{-4}
59	56	71	-	—	18	28	-	-	—	-	36	36	14	±	8×10^{-5}	3×10^{-5}
60	56	71	—	—	—	—	-	-	-	-	23	20	—	-	3×10^{-5}	1×10^{-4}
61	65	92	-	—	-	—	-	- -	-	-	32	32	11	-	1×10^{-4}	-
Chlorpromazine	142	160	6	2	3	6	>20	>20	5	3	2.3	2.3	2	++	2×10^{-5}	-

[a] Dash indicates less than 50% of treated mice responded at 50 mg./kg.; for explanation of symbols see Methods section. [b] Dash indicates less than 50% of treated mice responded at 50 mg./kg. [c] Dash indicates less than 50% inhibition at 10^{-3} *M*.

39, 42, and **43,** although several others were almost as active as these. Of the five best only two were potent in classical avoidance and two in mouse behavior. Little correlation with other tests was apparent.

Classical Avoidance.—There appears to be greater structural specificity for activity here than in any of the other tests. The most critical substituent was a small pyrrolidine-N-alkyl group. All compounds possessing a pyrrolidine-NH group (**29, 30, 52, 53, 54**) were inactive, while introduction of a small alkyl group on the pyrrolidine nitrogen resulted in active compounds (**29** *vs.* **31, 46; 52** *vs.* **57; 53** *vs.* **58; 54** *vs.* **59**). Larger groups such as butyl or benzyl, and sometimes even ethyl, gave inactive compounds (**47, 48, 60**). On the other hand, substitution on the indole nitrogen resulted in inactive compounds (**31** *vs.* **43, 44, 45**). Introduction of a benzene ring substituent into an active compound eliminated activity if it was an oxygen function (**31** *vs.* **32, 34, 35**) and either reduced or retained activity if it was an alkyl or halogen function (**31** *vs.* **33, 39; 31** *vs.* **36, 37, 38, 42**). Introduction of an alkyl group onto a pyrrolidine ring carbon of an active compound eliminated (**31** *vs.* **55; 46** *vs.* **60**), reduced (**31** *vs.* **56, 58, 59**), or retained activity (**31** *vs.* **57**).

The most active compounds in this test were **31, 37, 39,** and **57**. All of these were also very active in the fighting mouse assay and exhibited moderately good MAO inhibition. Several of these were also active in either D and Ch or AB and PAW or both. No correlation with other tests was apparent.

Pseudocholinesterase Inhibition.—The substituent which was most important for activity was that on the pyrrolidine nitrogen. Activity increased as this substituent became larger (**31** *vs.* **46, 47, 48**). In all cases, replacement of a pyrrolidine-N-methyl group by a pyrrolidine-N-benzyl group enhanced activity (**36** *vs.* **50; 38** *vs.* **49; 39** *vs.* **51**). Although an indole-N-alkyl group was desirable (**31** *vs.* **43, 44, 45**), it was not necessary for good activity (*cf.* **34, 35, 46–53, 55, 58, 59, 60**). Benzene ring substitution either had no effect (**31** *vs.* **33, 36, 37, 38; 48** *vs.* **49, 50, 51**) or enhanced activity (**31** *vs.* **34, 35**). Pyrrolidine ring substitution on carbon always enhanced activity (**29** *vs.* **52, 53, 54; 31** *vs.* **55, 56, 57, 58, 59; 46** *vs.* **60**).

The most active compounds in this test were **44, 45, 58,** and **60**. It is interesting that only one of these (**58**) had even slight activity in fighting mice or classical avoidance. Two of them (**58, 60**) possess fair nicotine antagonism. There was a notable tendency for the more active compounds to be more consistently inactive in the remaining tests (*e.g.* **34, 35, 44, 45, 47–51, 60**).

Monamine Oxidase Inhibition.—A free indole-NH (**31** *vs.* **43, 44, 45**) and a small pyrrolidine-N-alkyl group (**29** *vs.* **31, 46; 31** *vs.* **47, 48; 39** *vs.* **51**) were needed for good activity. A benzene ring substituent was not necessary and may eliminate activity (**31** *vs.* **32–36, 38**), but the best compound (**39**) contained a 7-methyl substituent. A pyrrolidine ring substituent on carbon either did not change activity significantly (**46** *vs.* **60; 31** *vs.* **55–58**) or enhanced it (**31** *vs* **59**, in which case both pseudo-ChE and MAO inhibition were increased more than tenfold by introduction of 5,5-dimethyl groups).

The two most active compounds were **39** and **59,** with I_{50} values close to 10^{-5} *M*. It is interesting that these compounds did not demonstrate overt stimulation in the mouse or rat. Compounds **31, 37, 39,** and **57,** the four most potent in classical avoidance, all possess significant MAO inhibition, but one of the most potent MAO inhibitors (**59**) had only slight activity in the classical avoidance assay.

General Comments.—The data presented show that these materials share many of the actions of chlorpromazine although they are less active on a mg. basis. In particular, they are quite active in the classical avoidance assay and protect against the isolation-induced aggressive behavior in mice. On the other hand, there are a number of other tests in which these compounds are clearly different from chlorpromazine. The significance of these similarities and differences for therapeutic effectiveness can only be assessed in man.

The compounds showing activity in the greatest number of assays are **31, 39, 58,** and **59**. Of these compound **31** has been studied in considerably more detail preparatory to clinical trial in the mental disease area. The complete pharmacology of this compound will be reported elsewhere.

Most of the intermediates described in this paper have not been screened as widely as the final products. However, representative members of the unsaturated intermediates of Tables I and V as well as their quaternary salts have consistently shown lack of classical avoidance activity, fair to poor activity in the fighting mouse test, and good to excellent inhibition of the two enzyme systems. The I_{50} values ranged from 10^{-4} to 10^{-5} *M* for MAO inhibition and 10^{-4} and 10^{-6} *M* for pseudo-ChE inhibition.

Experimental[18]

Method A. Example: 3-(1-Methyl-2-pyrrolidinylidene)-3H-indole (1).—To 40 ml. (0.4 mole) of 1-methyl-2-pyrrolidinone cooled in an ice bath was added 40.8 g. (0.26 mole) of phosphorus oxychloride with stirring during 30 min. The temperature did not exceed 15°. The mixture was stirred an additional 10 min. and then a solution of 28 g. (0.24 mole) of indole in 40 ml. (0.4 mole) of 1-methyl-2-pyrrolidinone was added slowly during 1 hr. The temperature rose to 45° and a solid separated. The mixture was heated at 80° for 2 hr. and then mixed with 1 l. of water. The clear solution was made basic by the addition of 60 g. of sodium hydroxide in 300 ml. of water causing a solid to separate. The solid was filtered and washed with water. Crystallization from ethanol–water afforded 41.6 g. (89%) of product, m.p. 229–231° dec.; ν_{max} 3020, 1600, 1560, 1500, 1315, 1300, 1208, 767, and 736 cm.$^{-1}$; λ_{max} sh 244 mμ (ϵ 7400), 251 (8850), 271 (11,700), sh 276 (9050), and 339 (15,300).

1-Benzyl-3-(1-methyl-2-pyrrolidinyl)indole Cyclohexanesulfamate (44).—Reaction of 49.7 g. of 1-benzylindole[19] according to method A produced 58.7 g. of oil isolated by ether extraction; ν_{max} 3460, 3320, 3120, 3070, 3040, 2810, 1645, 1615, 1575, 1530, 1500, 1485, 1180, 1080, 1050, 745, and 695 cm.$^{-1}$; λ_{max} 209 mμ (ϵ 8750), 252 (12,600), sh 269 (7500), and 333 (12,750). A solution of 14.5 g. of the oil in 150 ml. of ethanol containing 0.2 g. of platinum oxide was shaken on a Parr apparatus at an initial pressure of 3 atm. After 3.5 hr. 1 equiv. of hydrogen was absorbed (based on structure III). The catalyst was removed by filtration and the solvent under reduced pressure on a steam bath. The remaining material was distilled giving 7 g. of oil, b.p. 171–181° (0.03 mm). A 6.3-g. (0.0216 mole) portion of the oil was dissolved in a minimum volume of 2-propanol and added

(18) Melting points were taken in a capillary tube and are corrected. Infrared spectra were recorded on a Perkin-Elmer Model 21 spectrophotometer from Nujol mulls unless otherwise noted. Ultraviolet spectra were determined in 95% ethanolic solution unless otherwise noted, using a Cary Model 14 spectrophotometer.

(19) H. Plieninger, *Chem. Ber.*, **87**, 127 (1954).

to a solution of 3.88 g. (0.0216 mole) of cyclohexanesulfamic acid in 2-propanol. Ether was added until a solid began to separate. The solid was crystallized from 2-propanol–ether giving 6.5 g., m.p. 127–129.5, and a second crop of 2.4 g., m.p. 125–129.5. A portion of the first crop was recrystallized from 2-propanol–ether for an analytical sample, m.p. 127–129.5°; ν_{max} 3260, 2740, 2600, 1614, 1604, 1585, 1548, 1495, 1225, 1165, 1115, 1075, 1034, 1005, 765, 735, 720, and 687 cm.$^{-1}$; λ_{max} 218 mμ (ε 41,700), sh 260 (4900), sh 268 (6750), sh 273 μ (7100), 280 (7350), and sh 291 (5850).

Method B. Example: 5-Methyl-3-(1-methyl-2-pyrrolidinyl)indole (33).—A mixture of 12.7 g. of 5-methyl-3-(1-methyl-2-pyrrolidinylidene)-3H-indole, 150 ml. of methanol, and 0.2 g. of platinum oxide was shaken on a Parr apparatus at an initial pressure of 3 atm. In 10 min. 1 equiv. of hydrogen was absorbed. The catalyst was removed by filtration and the solvent under reduced pressure on the steam bath. The remaining yellow oil was crystallized from Skellysolve B giving 11.5 g. (91%) of yellow prisms, m.p. 116–117.5°. The analytical sample was recrystallized from ether–Skellysolve B affording colorless prisms: m.p. 116.5–117.5°; ν_{max} 3130, 3030, 2790, 1625, 1590, 1545, 1235, 1190, 1145, 1120, 1030, 875, and 790 cm.$^{-1}$; λ_{max} 218 mμ (ε 33,200), 277 (5700), 285 (5700), and 295 (4100).

Method C. Example: 5-Chloro-3-(1-methyl-2-pyrrolidinyl)indole (36).—A mixture of 23 g. of 5-chloro-3-(1-methyl-2-pyrrolidinylidene)-3H-indole, 12 g. of sodium borohydride, and 250 ml. of absolute ethanol was allowed to stand overnight at room temperature. The solvent was removed under reduced pressure on a steam bath. The residue was treated with 300 ml. of water and extracted with two 300-ml. portions of ether. The extracts were washed with two 100-ml. portions of water and dried over anhydrous magnesium sulfate. The ether was evaporated and the residue was crystallized from ether–Skellysolve B giving 18.3 g. (79%) of ivory prisms, m.p. 139.5–141°. The analytical sample was recrystallized twice from ether–Skellysolve B affording colorless prisms; m.p. 143–144.5°; ν_{max} 3180, 3125, 3025, 2815, 1615, 1570, 1550, 1490, 1255, 1227, 1210, 1154, 1117, 1075, and 1028 cm.$^{-1}$; λ_{max} 226 mμ (ε 35,150); sh 283 (5200), 289 (5550), and sh 297 (4250).

Method D. Example: 3-(1-Methyl-2-pyrrolidinyl)indole (31).—A 9.8-g. (0.05 mole) portion of solid 3-(1-methyl-2-pyrrolidinylidene)-3H-indole was added to a refluxing mixture of 4.5 g. (0.12 mole) of lithium aluminum hydride and 150 ml. of tetrahydrofuran. The mixture was refluxed for 6 hr., cooled, and decomposed with water followed by approximately 10 ml. of 50% sodium hydroxide. The mixture was filtered and the solid was washed with ether. The combined filtrates were dried over potassium carbonate and evaporated. The oily residue was crystallized from Skellysolve B affording 7.5 g. (75%) of product; m.p. 95–97°; ν_{max} 3100, 3020, 2780, 2760, 2690, 1620, 1587, 1550, 1505, 1235, 1215, 1135, 1130, 1118, 740, and 735 cm.$^{-1}$; λ_{max} 219 mμ (ε 36,750); sh 274 (5950), 281 (6350), and 289 (5400).

Method E. Example: 1-Indol-3-yl-4-nitro-1-butanone (19).—A mixture of 129.6 g. (0.6 mole) of 3-dimethylamino-1-indol-3-yl-1-propanone,[7] 600 ml. of nitromethane, and 3.18 g. (0.059 mole) of sodium methoxide was stirred and refluxed for 7 hr. while a slow stream of nitrogen was passed through the suspension. The reaction mixture was allowed to crystallize overnight and filtered. The solid was dissolved in 900 ml. of acetone (filtered from some insoluble material), 300 ml. of ethyl acetate was added, and the solution was evaporated to *ca.* 500 ml. Cooling produced 54 g. of solid and 14.9 g. was obtained from the filtrate giving a total of 68.9 g. (50%) of product, m.p. 178–180°. The analytical sample was recrystallized from methanol; m.p. 178–180°; ν_{max} 3180, 3060, 1625, 1585, 1565, 1530, 1500, and 1385 cm.$^{-1}$; λ_{max} 209 mμ (ε 32,100), 241.5 (13,650), sh 257 (9450), and 298 (13,200).

3-(1-Pyrrolin-2-yl)indole (24).—A solution of 12.3 g. of 1-indol-3-yl-4-nitro-1-butanone in 300 ml. of absolute ethanol containing 2 teaspoons of Raney nickel was shaken on a Parr apparatus at an initial pressure of 3 atm. Three equivalents of hydrogen were absorbed in 18 hr. Three runs were combined, filtered, and evaporated. The crude product was crystallized from ethyl acetate affording 16 g. (55%), m.p. 178–181°. The crude product from some runs was contaminated with the saturated compound. Separation was achieved readily by passing an acetone solution of the product through a column of Woelm neutral alumina whereby the impurity was retained on the column. The analytical sample was recrystallized from ethyl acetate; m.p. 182.5–183.5°; ν_{max} 3120, 3080, 3060, 3040, 3020, 2730, 2700, 2660, 2620, 1575, 1530, and 1500 cm.$^{-1}$; λ_{max} 217 mμ (ε 23,400), 255 (11,700), sh 271 (9400), 289 (11,950), and sh 332 (1200).

3-(5-Ethyl-1-pyrrolin-2-yl)indole Hydrochloride (26).—The filtrate from the hydrogenation of four runs of 13 g. each of 1-indol-3-yl-4-nitro-1-hexanone was acidified with ethereal hydrogen chloride. Ether was then added until crystallization began. Cooling produced 42.6 g. (86%), m.p. 216–217°. Recrystallization from methanol–ether afforded colorless plates; m.p. 218–219°; ν_{max} 3080, 2720, 1620, 1610, 1515, and 1495 cm.$^{-1}$; λ_{max} sh 244 mμ (ε 11,100), 249.5 (12,850), 264 (10,650), 270 (11,300), and 329 (18,850).

3-(2-Methyl-3-dimethylaminopropionyl)indole Methiodide Methanol Solvate.—To a solution of 62.8 g. (0.272 mole) of 3-(2-methyl-3-dimethylaminopropionyl)indole[7] in 300 ml. of methanol cooled in an ice bath was added 42.6 g. (0.3 mole) of methyl iodide. After 30 min. the ice bath was removed and the mixture was allowed to stand overnight at room temperature. Cooling gave 100 g. (91%) of product. Two recrystallizations from methanol and one from ethanol afforded colorless prisms; m.p. 174–177° dec.; ν_{max} 3465, 3210, 3185, 3020, 1640, 1580, 1520, 1490, 1238, 1157, 1133, 1090, 1046, 1004, 770, 755, 747, and 705 cm.$^{-1}$.

Anal. Calcd. for $C_{15}H_{21}IN_2O \cdot CH_3OH$: C, 47.53; H, 6.23; I, 31.39; N, 6.93. Found: C, 47.92; H, 6.17; I, 31.30; N, 7.02.

3-(2-Methyl-3-cyanopropionyl)indole.—A mixture of 8.9 g. (0.022 mole) of 3-(2-methyl-3-dimethylaminopropionyl)indole methiodide methanol solvate, 5 g. (0.102 mole) of sodium cyanide, and 50 ml. of dimethylformamide was heated on a steam bath for 2.5 hr. The mixture was poured into 800 ml. of water and cooled in an ice bath. The solid was filtered, washed with water, dried, and crystallized from acetone–Skellysolve B giving 3.05 g. (65%), m.p. 166–169°. Recrystallization from acetone–Skellysolve B afforded colorless prisms: m.p. 168.5–170°; ν_{max} 3220, 3120, 3050, 2245, 1611, 1585, 1524, 1498, 1242, 1162, 1118, 1094, 775, and 755 cm.$^{-1}$; λ_{max} 242.5 mμ (ε 13,300), 258 (9450), and 300 (12,950).

Anal. Calcd. for $C_{13}H_{12}N_2O$: C, 73.56; H, 5.70; N, 13.20. Found: C, 73.69; H, 6.27; N, 12.96.

3-(3-Methyl-1-pyrrolin-2-yl)indole.—A mixture of 2.5 g. of 3-(2-methyl-3-cyanopropionyl)indole, 150 ml. of ethanol, and a teaspoon of Raney nickel was shaken on a Parr apparatus at 3 atm. initial pressure. After 27 hr. the hydrogen uptake ceased. The catalyst was removed by filtration and the solvent under reduced pressure. The oily residue was crystallized from acetone–Skellysolve B giving 1.8 g. (77%) of brown crystals, m.p. 137.5–141°. Two recrystallizations from acetone–Skellysolve B afforded brown prisms; m.p. 144–146°; ν_{max} 3120, 3090, 3055, 1603, 1575, 1527, 1495, 1246, 1160, 1140, 742 cm.$^{-1}$; λ_{max} 218.5 mμ (ε 24,700), sh 250 (10,550), 256 (11,650), sh 273 (9600), sh 280 (10,450), 291 (11,650), and sh 330 (1500).

Anal. Calcd. for $C_{13}H_{14}N_2$: C, 78.75; H, 7.12; N, 14.13. Found: C, 78.67; H, 7.23; N, 13.97.

Method F. Example: 3-(5-Methyl-2-pyrrolidinyl)indole Hydrochloride (52).—A solution of 9.4 g. of 3-(5-methyl-1-pyrrolin-2-yl)indole in 300 ml. of ethanol containing 0.5 g. of platinum oxide was shaken on a Parr apparatus at 3 atm. initial pressure. In 4 hr. 1 equiv. of hydrogen was absorbed. The catalyst was removed by filtration. The filtrate was evaporated to *ca.* 25 ml. and acidified with ethereal hydrogen chloride. Ether was added until crystallization began. Cooling produced 10 g., m.p. 212–214°. Three recrystallizations from methanol afforded 9.1 g. (81%); m.p. 225–226°; ν_{max} 3260, 2720, 2620, 2520, 1620, 1595, and 1550 cm.$^{-1}$; λ_{max} 215 mμ (ε 41,650), 270 (6500), 276 (6350), 279 (6350), 286 (5600), and 326 (419).

Method G. Example: 3-(1,5-Dimethyl-2-pyrrolidinyl)indole (57).—A solution of 1 g. of 3-(5-methyl-2-pyrrolidinyl)indole (prepared from 1.2 g. of the hydrochloride) in 50 ml. of methyl formate was refluxed for 93 hr. It was evaporated to dryness to give an amorphous solid which showed a strong amide band at 1660 cm.$^{-1}$. The crude formyl compound was dissolved in benzene and added to a mixture of 1.2 g. of lithium aluminum hydride in 100 ml. of ether. After refluxing for 18 hr. it was decomposed in succession with 1.2 ml. of water, 1.2 ml. of 15% sodium hydroxide, and 3.6 ml. of water. The suspension was filtered, the solid was washed with ether, and the filtrate was evaporated to give 1.11 g. of oily crystals. Three recrystallizations from ether–Skellysolve B afforded 0.182 g. (17%),

m.p. 145–148°. This compound was identical (ultraviolet and infrared spectra) with the sample obtained by method H.

3-(1-Acetyl-5,5-dimethyl-2-pyrrolidinyl)indole (IV).—A solution of 1.05 g. of 3-(5,5-dimethyl-2-pyrrolidinyl)indole (prepared from the hydrochloride) in 10 ml. of acetic anhydride was allowed to stand overnight at room temperature. The resulting suspension was diluted with 25 ml. of water and 4.5 g. of sodium carbonate was added slowly with stirring. The solid was filtered, washed with water, dried, and crystallized from methanol to give 0.9 g. (70%) of colorless prisms; m.p. 203–204°; ν_{max} 3200, 3120, 3060, 1612, 1562, 1239, 1120, 1100, 1059, 1039, 1010, 765, 745, and 705 cm.$^{-1}$; λ_{max} 220 mμ (ε 40,950), sh 274 (5600), 281 (6000), and 289 (5300).

Anal. Calcd. for $C_{16}H_{20}N_2O$: C, 74.96; H, 7.86, N, 10.93; $COCH_3$, 16.78. Found: C, 74.86; H, 8.20; N, 10.86; $COCH_3$ (1 *N* alcoholic potassium hydroxide, 75-min. reflux), 1.09. (Note: N-acetylpyrrolidine is not hydrolyzed.)

3-(1-Ethyl-5,5-dimethyl-2-pyrrolidinyl)indole (60).—A solution of 0.6 g. of 3-(1-acetyl-5,5-dimethyl-2-pyrrolidinyl)indole in 100 ml. of benzene was added to a mixture of 0.6 g. of lithium aluminum hydride and 100 ml. of benzene. The mixture was refluxed for 12 hr. and allowed to stand for 24 hr. It was decomposed by successive addition of 1 ml. of water, 1 ml. of 15% sodium hydroxide, and 3 ml. of water. The mixture was filtered and the filtrate evaporated to dryness to give 0.5 g. of an oil. Crystallization from petroleum ether afforded 0.45 g. (80%) of colorless prisms; m.p. 82–85° unchanged on further recrystallization; ν_{max} 3160, 3100, 3030, 2750, 1620, 1586, 1540, 1227, 1185, 1153, 1131, 1115, 1050, 1028, 1012, 766, and 742 cm.$^{-1}$; λ_{max} 220 mμ (ε 33,150), sh 275 (5400), 281 (5800), and sh 288 (5000).

Method H. Example: 3-(1,5-Dimethyl-2-pyrrolidinylidene)-3H-indole Hydriodide.—A solution of 1.98 g. (0.01 mole) of 3-(5-methyl-1-pyrrolin-2-yl)indole in 15 ml. of methanol and 5 ml. of methyl iodide was refluxed for 3 hr. It was then evaporated to dryness and the resulting solid crystallized from methanol–ether to give 1.7 g. (50%), m.p. 224–227°. Two recrystallizations raised the m.p. to 237–239.5°; ν_{max} 3100, 1605, 1515, 1495, 1240, 760, and 750 cm.$^{-1}$; λ_{max} sh 246 mμ (ε 11,200), 251 (13,500), 265 (10,050), 271 (10,400), and 332 (18,700).

Anal. Calcd. for $C_{14}H_{17}IN_2$: C, 49.42; H, 5.04; I, 37.30; N, 8.24. Found: C, 49.49; H, 4.98; I, 37.11; N, 8.62.

3-(1,5-Dimethyl-2-pyrrolidinyl)indole (57).—A mixture of 1.3 g. of 3-(1,5-dimethyl-2-pyrrolidinylidene)-3H-indole hydriodide, 1.3 g. of sodium borohydride, and 100 ml. of ethanol was stirred for 4 hr. It was then evaporated to dryness and 100 ml. of water and 10 ml. of 20% sodium hydroxide were added. The mixture was extracted with ether. The extract was washed with water, dried through sodium sulfate, and evaporated to give 0.8 g. of crude product. Two crystallizations from ether–petroleum ether afforded colorless prisms, m.p. 151–152°; ν_{max} 3120, 2770, 1620, 1580, 1540, 1500, 1225, 1195, 1170, 1130, 1110, 1055, 1010, and 735 cm.$^{-1}$; λ_{max} 217 mμ (ε 37,750), sh 274 (5950), 280 (6350), and 289 (5250).

Treatment of 3-(5,5-Dimethyl-1-pyrrolin-2-yl)indole with Methyl Iodide. 3-(5,5-Dimethyl-2-pyrrolidinylidene)-3H-indole Hydriodide.—A solution of 2.1 g. of 3-(5,5-dimethyl-1-pyrrolin-2-yl)indole in 25 ml. of methanol and 5 ml. of methyl iodide was refluxed 4 hr. The resulting suspension was evaporated to dryness and the residue was crystallized from ethanol affording 1.56 g. (46%), m.p. 280° dec. Two recrystallizations raised the m.p. to 289°; ν_{max} 3140, 3080, 1630, 1615, 1595, 1525, 1235, 1150, and 740 cm.$^{-1}$; λ_{max} 250 mμ (ε 12,600); 264 (10,000), 270 (10,500), and 330 (17,700).

Anal. Calcd. for $C_{14}H_{17}IN_2$: C, 49.42; H, 5.04; I, 37.30; N, 8.24. Found: 49.65; H, 4.90; I, 36.78; N, 7.99

3-(1,5,5-Trimethyl-2-pyrrolidinyl)indole (59).—A solution of 24.8 g. of 3-(5,5-dimethyl-2-pyrrolidinyl)indole in 350 ml. of methanol and 116 ml. of methyl iodide was refluxed under nitrogen for 48 hr. It was evaporated to dryness *in vacuo* and the residue was triturated with methanol. The resulting solid was dissolved in 500 ml. of water and filtered. The filtrate was cooled, made basic with sodium hydroxide, and extracted with methylene chloride. The extract was washed with saturated salt solution, dried through sodium sulfate, and evaporated to give 18.8 g. of an oily solid. It was chromatographed on 300 g. of silica. Elution with 3150 ml. of ethyl acetate afforded 11.85 g. of product. Crystallization from ether–petroleum ether gave 6.9 g. (26%); m.p. 138–140° unchanged on further recrystallization; ν_{max} 3140, 3100, 3040, 2805, 2780, 2750, 1620, 1606, 1540, 1500, 1227, 1195, 1148, 1112, 1010, 765, and 740 cm.$^{-1}$; λ_{max} 219 mμ (ε 35,600), sh 274 (5650), 279 (5950), and sh 287 (4900). This product was recovered unchanged from attempted acetylation with acetic anhydride at room temperature overnight under which conditions 3-(5,5-dimethyl-2-pyrrolidinyl)indole undergoes monoacetylation on the pyrrolidine nitrogen.

1-Acetyl-3-(1-acetyl-5,5-dimethyl-2-pyrrolidinyl)indole (V).—A solution of 1.05 g. of 3-(5,5-dimethyl-2-pyrrolidinyl)indole in 10 ml. of acetic anhydride was refluxed overnight. It was cooled and 25 ml. of water followed by 4.5 g. of sodium carbonate were added. The solid was filtered, dried, and crystallized twice from ethyl acetate affording 0.8 g. (54%) of colorless prisms; m.p. 189–190°; ν_{max} 3120, 1710, 1640, 1250, 1220, 1145, 1040, 1020, 1000, 770, and 750 cm.$^{-1}$; λ_{max} 239 mμ (ε 17,950), 260 (8200), sh 270 (7300), 290 (6700), and 299 (7400).

Anal. Calcd. for $C_{18}H_{22}N_2O_2$: C, 72.45; H, 7.43; N, 9.39; $COCH_3$, 28.85. Found: C, 72.52; H, 7.56; N, 9.15; $COCH_3$, 15.35.

1-Methyl-3-(1-methyl-2-pyrrolidinylidene)-3H-indolium Iodide (VI). A. From 3-(1-Methyl-2-pyrrolidinylidene)-3H-indole (1) and Methyl Iodide.—A solution of 248 g. of 1 in 1875 ml. of methanol and 781 ml. of methyl iodide was refluxed for 1 hr. The product began separating 5 min. after reflux began. After cooling the solid was filtered, washed with methanol and then ether, and dried affording 372 g. (87%); m.p. 252–254°; ν_{max} 3080, 3050, 3015, 1243, 1140, 1107, 1091, 762, and 755 cm.$^{-1}$; λ_{max} 211.5 mμ (ε 37,900), 254 (14,700), sh 262, 270 (8900), and 335 (20,100).

Anal. Calcd. for $C_{14}H_{17}IN_2$: C, 49.42; H, 5.04; I, 37.30; N, 8.24. Found: C, 49.25; H, 4.63; I, 37.05; N, 8.39.

B. From 1-Methyl-3-(1-pyrrolin-2-yl)indole (28) and Methyl Iodide.—A solution of 1.98 g. of **28** in 15 ml. of methanol and 5 ml. of methyl iodide was refluxed for 1.5 hr. A suspension resulted during reflux. After cooling the solid was filtered and washed with methanol affording 2.58 g. (76%), m.p. 253–254°. This compound was identical (by mixture melting point, analyses, and ultraviolet and infrared spectra) with the sample obtained from 1 and methyl iodide.

1-Methyl-3-(1-methyl-2-pyrrolidinyl)indole (43). A. By Methylation of 3-(1-Methyl-2-pyrrolidinyl)indole (31).—A solution of 25 g. (0.125 mole) of **31** in 100 ml. of ether was added with stirring, during 20 min., to a suspension of sodamide (0.128 mole) in 475 ml. of liquid ammonia. Then 18 g. (0.128 mole) of methyl iodide was added during 30 min. and the mixture was stirred for an additional 30 min. The ammonia was allowed to evaporate, 100 ml. of water was added, and the mixture was extracted with ether. The extract was washed with saturated salt solution, dried through sodium sulfate, and evaporated to give 20 g. of oil. Distillation of 19 g. of oil afforded 12.5 g. (49%), b.p. 113° (0.01 mm.). The oil crystallized on standing in the cold for several days; m.p. 45.5–47.5°; ν_{max} 3040, 2760, 1615, 1555, 1239, 1212, 1154, 1130, 1040, 1014, and 735 cm.$^{-1}$; λ_{max} 221 mμ (ε 34,850), 287 (5950), and sh 328 (184). A solution of 0.119 g. (0.56 mmole) of the oil in 10 ml. of ethanol was treated with 7.6 ml. of saturated ethanolic picric acid solution. Crystallization commenced after a few seconds giving 0.217 g., m.p. 196–196.5°. Recrystallization from ethanol afforded yellow plates; m.p. 196.5–197°; ν_{max} 3120, 2745, 1633, 1518, and 1479 cm.$^{-1}$; λ_{max} 218 mμ (ε 59,150), sh 244 (12,400), 270 (8800), 282 (8700), sh 286, 293 (7700), 358 (16,400), and sh 400 (1000).

Anal. Calcd. for $C_{20}H_{21}N_5O_7$: C, 54.17; H, 4.77; N, 15.80. Found: C, 53.93, H, 4.41; N, 15.85.

B. By Reduction of 1-Methyl-3-(1-methyl-2-pyrrolidinylidene)-3H-indolium Iodide (VI) with Sodium Borohydride.—A warm solution of 0.76 g. of VI in 75 ml. of ethanol was treated with 1 g. of sodium borohydride. The resulting solution was stirred at room temperature for 21 hr. It was then evaporated *in vacuo*, water was added, and the mixture was extracted twice with ether. The extract was washed with water and saturated salt solution, dried through sodium sulfate, and evaporated to give 0.536 g. of an oily solid. It was dissolved in 10 ml. of acetone and chromatographed on 10 g. of silica. Elution with four 20-ml. portions of acetone followed by two 20-ml. portions of 2% methanol–acetone gave 0.336 g. of oil. One drop of the oil was diluted with 3 drops of methylene chloride and subjected to vapor phase chromatography. The column for the v.p.c. was a 2.135-m. stainless steel column, 6 mm. internal diameter, containing 2% SE-30 as the stationary liquid on 60 mesh firebrick support. Helium at 60 ml./min. was used as the carrier gas and thermistors were employed for the detection of the

sample peaks. The temperature was 170°. Retention time was 8.3 min., identical with that of the sample prepared by methylation of **31**. There was a minute amount of impurity with retention time of 1.8 min. Evaporation distillation at 115° (0.03 mm.) gave a colorless oil which showed an infrared spectrum identical with that of the authentic sample. The picrates were also identical.

1-(2-Diethylaminoethyl)-3-(1-methyl-2-pyrrolidinyl)indole Dihydrochloride (45).—A mixture of 10 g. (0.0505 mole) of 3-(1-methyl-2-pyrrolidinylidene)-3H-indole, 8.15 g. (0.06 mole) of 2-diethylaminoethyl chloride, and 300 ml. of absolute ethanol was heated under reflux for 16 hr. The solvent was evaporated and the residual oil was dissolved in 150 ml. of water. The solution was made basic with sodium hydroxide solution and extracted with two 400-ml. portions of ether. The extract, which contained some insoluble solid, was washed with four 200-ml. portions of water and dried over anhydrous magnesium sulfate. Evaporation of the ether gave 11.9 g. of brown oil. A mixture of the oil, 6 g. of sodium borohydride, and 250 ml. of absolute ethanol was allowed to stand overnight at room temperature. The solvent was evaporated and the residue was treated with 200 ml. of water. The mixture was extracted with two 400-ml. portions of ether. The extract was washed with three 200-ml. portions of water and dried over anhydrous magnesium sulfate. The ether solution was treated with ethereal hydrogen chloride. The solid was filtered and crystallized twice from ethanol–ether giving 10.3 g. (55%) of pale violet solid, m.p. 209–211°. Recrystallization from ethanol–ether afforded gray crystals: m.p. 210–212°; ν_{max} 3045, 2640, 2550, 2460, 1616, 1555, 1170, 1025, 1006, and 740 cm.$^{-1}$; λ_{max} 216 mμ (ε 40,350), 272 (6800), 280 (6650), sh 284 (6400), and 241 (5100).

3-(1-Methyl-2-pyrrolidinyl)indol-5-ol (35).—A mixture of 12.2 g. of 5-benzyloxy-3-(1-methyl-2-pyrrolidinyl)indole, 150 ml. of ethanol, and 0.5 g. of 10% palladium on charcoal was shaken on a Parr apparatus at 3 atm. initial pressure. After 4 hr. 1 equiv. of hydrogen was absorbed. The catalyst was removed and the solvent evaporated. The residual oil was shaken with 300 ml. of ether. The ether solution was decanted from a small amount of tarry material. The ether was evaporated and the residue was crystallized from acetone–Skellysolve B giving 5.2 g. (60%), m.p. 159–161°. Two recrystallizations from acetone–Skellysolve B afforded buff crystals: m.p. 161–163°; ν_{max} 3320, 3050, 2480, 1623, 1576, 1252, 1222, 1205, 1178, 1105, 1086, and 1030 cm.$^{-1}$; λ_{max} 275 mμ (ε 6150), 299 (4700), and sh 310 (3650).

3-(1-Methyl-2-pyrrolidinyl)indol-6-ol (41).—A solution of 2 g. of 6-benzyloxy-3-(1-methyl-2-pyrrolidinyl)indole in 100 ml. of ether was treated with ethereal hydrogen chloride. The solid was filtered and washed with ether giving 2.2 g. of colorless solid, m.p. 105–111°. Attempted crystallization of a portion of the hydrochloride from ethanol–ether caused decomposition. A mixture of 2 g. of the crude hydrochloride, 0.2 g. of 10% palladium on charcoal, and 50 ml. of absolute ethanol was shaken on a Parr apparatus at 3 atm. initial pressure. After 6 hr. 1 equiv. of hydrogen had been absorbed. The catalyst was removed by filtration and the solvent was evaporated. The residue was crystallized from methanol–ether giving a sticky solid. The filtrate was diluted with ether and cooled to give 0.22 g. (15%), m.p. 193–195°. Recrystallization from methanol–2-propanol–ether afforded 0.21 g. of ivory needles: m.p. 193–195°; ν_{max} 3320, 3140, 3020, 2675, 2560, 1632, 1594, 1548, 1520, 1170, 1128, and 700 cm.$^{-1}$; λ_{max} 215 mμ (ε 30,050), sh 254 (2750), sh 262 (3750), 270 (4250), 293 (4650), and sh 302 (3550).

3-(2-Pyrrolidinyl)indole (29). A. From 3-(1-Benzyl-2-pyrrolidinyl)indole (48).—A mixture of 5.5 g. of **48**, 8 g. of 10% palladium on carbon, and 100 ml. of methanol was shaken on a Parr apparatus at 3 atm. initial pressure. The hydrogen uptake stopped after 1 equiv. of hydrogen had been absorbed. The catalyst was removed by filtration and the solvent was evaporated. The residue was crystallized from benzene–Skellysolve B affording 1.7 g. (46%); m.p. 141–143°; ν_{max} 3280, 3110, 3070, 3020, 2730, 2620, 1616, 1580, 1550, 1505, 1237, 1147, 1135, 1120, 1060, 1050, 1110, 840, 827, and 735 cm.$^{-1}$; λ_{max} 216 mμ (ε 37,750), sh 274 (5700), 280 6050), and 287 (4950).

B. From 3-(1-Pyrrolin-2-yl)indole (24).—Seventy-two ml. of an ethanolic solution of crude **24** obtained by hydrogenation of 1-indol-3-yl-4-nitro-1-butanone (0.005 mole) with Raney nickel was hydrogenated further for 4.25 hr. in the presence of 0.2 g. of platinum oxide at an initial pressure of 3 atm. The mixture was nitered and the solution evaporated to dryness. The resulting 0.9 g. of yellow solid was crystallized from benzene–petroleum ether followed by ethyl acetate to give 0.3 g. (32%), m.p. 142–144°. This material was identical (mixture melting point, ultraviolet and infrared spectra) with the sample obtained from **48**.

3-(1-Methyl-2-pyrrolidinyl)indole (31). From 3-(2-Pyrrolidinyl)indole (29).—A mixture of 10 g. of **29** and 246 ml. of methyl formate was refluxed for 48 hr. The resulting solution was evaporated to dryness to give an oil which showed a strong band at 1650 cm.$^{-1}$ in the infrared spectrum. A solution of this oil in 100 ml. of benzene was added to a suspension of 10 g. of lithium aluminum hydride in 1 l. of ether. The mixture was refluxed for 18 hr. It was decomposed by the successive addition of 10 ml. of water, 10 ml. of 15% aqueous sodium hydroxide, and 30 ml. of water. The resulting suspension was filtered and the filtrate evaporated to dryness *in vacuo*. The oily residue was crystallized from ether–petroleum ether to give 5 g., m.p. 94–97°. There was no depression on mixture m.p. with **31** prepared *via* method A. The filtrate was evaporated to dryness and the 4 g. of residue was chromatographed on 120 g. of neutral alumina. Elution with nine 150-ml. portions of 0.5% methanol benzene afforded 2.98 of solid which was crystallized from ether–petroleum ether to give 1.92 g., m.p. 95–97°. The total yield was 6.92 g. (64%).

3-(1-Methyl-2-pyrrolidinylidene)-3H-indole Hydriodide.—A solution of 9.2 g. of 3-(1-pyrrolin-2-yl) indole in 75 ml. of methanol and 25 ml. of methyl iodide was refluxed for 1.5 hr. The resulting suspension was cooled in ice and filtered to give 11.3 g. (70%), m.p. 270–283°. Two crystallizations from methanol afforded long needles, m.p. 293–296° dec.; ν_{max} 3170, 3110, 3035, 1610, 1520, 1490, 1236, 1218, 1112, 1100, 1020, 760, 750, and 740 cm.$^{-1}$; λ_{max} sh 225 mμ (ε 18,600), sh 245 (11,600), 251 (13,200), 265 (9650), 271 (9900), and 331.5 (17,600).

Anal. Calcd. for $C_{13}H_{15}IN_2$: C, 47.87; H, 4.64; I, 38.91; N, 8.59. Found: C, 47.86; H, 4.48; I, 38.92; N, 8.41.

3-(1-Methyl-2-pyrrolidinylidene)-3H-indole (1). From the hydriodide. A suspension of 1.6 g. of 3-(1-methyl-2-pyrrolidinylidene)-3H-indole hydriodide in 10 ml. of water, 25 ml. of benzene, 30 ml. of 1 *N* sodium hydroxide, 25 ml. of methylene chloride, and 10 ml. of methanol was shaken until two clear layers resulted. The aqueous layer was extracted twice with methylene chloride. The extract was washed with saturated salt solution, dried through sodium sulfate, and evaporated to give 0.9 g. (91%), m.p. 195–220°. Crystallization from benzene–methanol afforded colorless plates, m.p. 220° dec. This material was identical (analyses, mixture melting point, and ultraviolet and infrared spectra) with the sample obtained by method A.

1-Acetyl-3-(1-pyrrolin-2-yl)indole (VIII).—A solution of 0.52 g. (5.1 mmoles) of acetic anhydride in 3 ml. of benzene was added dropwise during 2 min. to a hot solution of 0.92 g. (5 mmoles) of 3-(1-pyrrolin-2-yl)indole in 50 ml. of benzene. The solution was allowed to stand at room temperature for 2.5 hr. It was then evaporated to dryness *in vacuo* to give a quantitative yield of a colorless solid melting at 180–185°. On attempted crystallization from methanol only about 10% of the monoacetyl compound could be recovered; the majority was converted to the starting material. It was crystallized from benzene–petroleum ether to give colorless needles; m.p. 184.5–186°; ν_{max} 1712, 1618, 1550, and 1483 cm.$^{-1}$; λ_{max} (in dioxane) 236 mμ (ε 10,850), sh 256 (5650), 268 (4850), 276 (4950), 295 (6950), and 305 (7600).

Anal. Calcd. for $C_{14}H_{14}N_2O$: C, 74.31; H, 6.24; N, 12.38. Found: C, 73.99; H, 5.98; N, 12.73.

1-Methyl-2-(1-acetylindol-3-yl)-1-pyrrolinium Iodide (IX). A suspension of 0.833 g. of VIII in 50 ml. of methyl iodide was refluxed under nitrogen for 17.5 hr. The resulting suspension was filtered and the yellow solid washed with ether giving 1.28 g. (94%), m.p. 218–220°. Since attempted crystallization from methanol led to partial deacetylation, the product was crystallized from dimethylformamide–ether at room temperature affording yellow needles; m.p. 217–219°; ν_{max} 3220, 3100, 3085, 1725, 1614, 1574, 1530, 1243, and 1205 cm.$^{-1}$; λ_{max} (in dioxane containing 1% dimethylformamide) sh 258 mμ (ε 9800), sh 270 (8500), 291 (8600), and 299 (9050).

Anal. Calcd. for $C_{16}H_{17}IN_2O$: C, 48.92; H, 4.66; I, 34.47; N, 7.61; $COCH_3$, 11.69. Found: C, 49.19; H, 5.11; I, 34.04; N, 7.47; $COCH_3$, 12.88.

3-(1-Methyl-2-pyrrolidinylidene)-3H-indole Hydriodide. From IX.—A solution of 0.2 g. of IX in 4 ml. of water was refluxed for 5 min. and then allowed to crystallize giving 0.117

g., m.p. 302–307°. Recrystallization from water afforded colorless needles, m.p. 302–304°. This material was identical (C, H, I, and N analyses, ultraviolet and infrared spectra) with the sample prepared from 3-(1-pyrrolin-2-yl)indole and methyl iodide.

1-Acetyl-3-(1-acetyl-2-pyrrolin-2-yl)indole (X).[11]—A solution containing 5.2 ml. (0.065 mole) of pyridine and 5.2 ml. (0.051 mole) of acetic anhydride was added to 1.84 g. (0.01 mole) of 3-(1-pyrrolin-2-yl)indole. The mixture was heated on a steam bath for 2 hr. The resulting brown solution was evaporated *in vacuo*. The brown oily residue was dissolved at room temperature in 10 ml. of ethyl acetate and crystallization was induced by scratching and allowed to proceed overnight. The crystals were filtered, washed with ethyl acetate, then with petroleum ether to give 1.4 g. (52%), m.p. 130–144°. Crystallization from pyridine–petroleum ether at room temperature afforded clusters of colorless rods; m.p. 132–144°; ν_{max} 3060, 1708, 1636, 1588, and 1558 cm.$^{-1}$; λ_{max} (in dioxane) 238 mμ (ε 25,850), sh 292 (7250), and 301 (8800).

Anal. Calcd. for $C_{16}H_{16}N_2O_2$: C, 71.62; H, 6.01; N, 10.44. Found: C, 72.02; H, 6.20; N, 10.15.

1-Acetyl-3-(2-pyrrolidinyl)indoline Hydrochloride (XI).—A solution of 0.452 g. of VIII in 25 ml. of acetic acid containing 0.1 g. of platinum oxide was shaken on a Parr apparatus at 3 atm. initial pressure. After 20 min. the solution was filtered and evaporated to dryness. The residue was dissolved in water, made basic with sodium bicarbonate, and extracted with ether. The extract was washed with water and saturated salt solution, dried through sodium sulfate, and evaporated to give 0.393 g. of a pale yellow oil. The hydrochloride was prepared in 2-propanol. Two crystallizations from 2-propanol–methanol followed by methanol afforded 0.173 g. (33%); m.p. 259–261°; ν_{max} 2740, 2550, 2520, 2490, 2425, and 1655 cm.$^{-1}$; λ_{max} 252 mμ (ε 15,500), sh 278 (3100), and sh 287 (2200).

Anal. Calcd. for $C_{14}H_{18}N_2O\cdot HCl$: C, 63.03; H, 7.18; Cl, 13.29; N, 10.50. Found: C, 62.80; H, 7.58; Cl, 13.05; N, 10.35.

1-Methyl-3-(1-methyl-2-pyrrolin-2-yl)indole (XII).—A solution of 34 g. (0.1 mole) of VI in 200 ml. of methanol and 300 ml. of methylene chloride was prepared under nitrogen and 600 ml. of 1 *N* sodium hydroxide was added. The mixture was stirred for 2 hr. The organic layer was separated and the aqueous solution was extracted with two 200-ml. portions of methylene chloride. The combined organic solution was washed with saturated salt solution and dried through sodium sulfate. It was evaporated *in vacuo* below 40° to give 27 g. of yellow oil; λ_{max} (in ether) 238 mμ (ε 7450), 293 (6500), and sh 301 (5650); λ_{max} (in methanol) 253 mμ (ε 15,000), sh 270 (8900), and 335 (20,000).

1,1-Dimethyl-2-(1-methylindol-3-yl)-2-pyrrolinium Iodide (XIV and VI) by Alkylation of XII with Methyl Iodide. A. Without Solvent.—Methyl iodide (200 ml.) was added cautiously with cooling to 27 g. of XII, whereupon a suspension resulted. It was refluxed for 15 min., cooled to room temperature, and filtered to give 34.5 g., m.p. 186–206°. Two recrystallizations from methanol afforded 10.4 g. of colorless needles, m.p. 253–254°. This material was identical (mixture melting point, ultraviolet and infrared spectra) with VI. The last filtrate from the above crystallization was concentrated and afforded 9.5 g. of solid, m.p. 180–190°. Six crystallizations from methanol gave 3.16 g. of XIV; m.p. 205–207°; ν_{max} 3070, 1643, 1614, 1575, and 1531 cm.$^{-1}$; λ_{max} 212 mμ (ε 34,000), 243 (12,850), sh 260 (7050), and 303 (12,900). The structure proposed for XIV was supported by the n.m.r. spectrum which showed indole N–CH_3 at 239 c.p.s. (area 3) and pyrrolidine N–CH_3 at 206 c.p.s. (area 6),[13,20] and by the following analysis.

Anal. Calcd. for $C_{15}H_{19}IN_2$: C, 50.85; H, 5.41. Found: C, 50.74; H, 5.98.

B. In Dimethylformamide.—A solution of 27 g. of XII in 100 ml. of dry dimethylformamide was treated during 10 min. with 34 ml. (0.54 mole) of methyl iodide. The temperature was kept at 15–20° by cooling in ice. The suspension was stirred overnight at room temperature and then heated at 55° for 1 hr. It was cooled, filtered, and the solid was washed with cold dimethylformamide and then with ether to give 6 g. of VI, m.p. 254–255°. The solvent was evaporated from the filtrate under a high vacuum below 45° and the resulting oil was crystallized from methanol–ether. Another crystallization afforded 10.1 g. of XIV, m.p. 203–205°. A mixture melting point with XIV obtained previously showed no depression.

(20) The n.m.r. spectrum was run with a Varian D.P. 60 spectrometer and deuterated dimethylformamide as solvent. Frequencies are reported in c.p.s. downfield from internal tetramethylsilane. We thank Dr. G. Slomp and F. A. McKellar for the spectrum and its interpretation.

4-Aminomorpholines[1]

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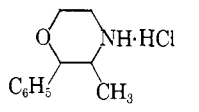
A variety of substituted 4-aminomorpholines has been prepared. The preparation of such hydrazines, in which one nitrogen is part of a cyclic structure, has been investigated and the methods used are discussed. One of these compounds, 3-methyl-4-(1-phenyl-2-propylamino)-2-phenylmorpholine, has been shown to possess very interesting central nervous system activity. The preparation of some of the optically active isomers of this compound is also discussed.

The substitution of the morpholine radical for other dialkylamine or cyclic amine radicals in biologically active substances has generally resulted in reduction or elimination of activity. A notable exception has been observed in compounds affecting the central nervous system.[2] A morpholine derivative of particular interest has been 3-methyl-2-phenylmorpholine hydrochloride (**1**) which finds use as an appetite inhibitor[3] and has also been shown to affect the central nervous system by producing mild stimulation and euphoria.[4] Such stimulant activity, coupled with the discovery that 2-hydrazino-1-phenylpropane hydrochloride (**2**) is a potent central nervous system stimulant and inhibitor of monoamine oxidase[5] led to the investigation of 4-aminomorpholines related structurally to 3-methyl-2-phenylmorpholine.



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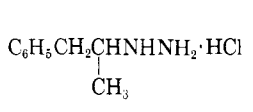

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