Antidepressant Agents. Derivatives of 2,3-Polymethyleneindoles[1]

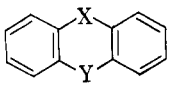
LEONARD M. RICE, ELISABETH HERTZ, AND MEIER E. FREED

Wyeth Laboratories, Inc., Research and Development Division, Philadelphia, Pennsylvania

Received June 8, 1963

A series of 1-substituted 2,3-polymethyleneindoles was prepared and examined for central nervous system activity. A number of these compounds were found to be active as antidepressants. The required 2,3-polymethyleneindoles were prepared by suitable modifications of the Fischer indole synthesis from arylhydrazines and alicyclic ketones. These were converted to N-substituted derivatives by various methods.

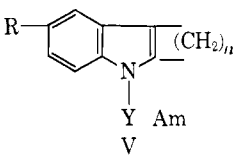
The search for compounds which would be efficacious in the treatment of mental disease has led to the discovery of such psychotropic agents as imipramine (I),[2] chlorprothixene (II),[3] and amitriptyline (III).[4] These compounds may be regarded as isosteres of the



I, X = $(CH_2)_2$; Y = $N(CH_2)_3N(CH_3)_2$
II, X = S; Y = $C{=}CH(CH_2)_2N(CH_3)_2$
III, X = $(CH_2)_2$; Y = $C{=}CH(CH_2)_2N(CH_3)_2$
IV, X = S; Y = $N{-}(CH_2)_3N(CH_3)_2$

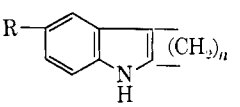
corresponding phenothiazine derivative (IV)[5] in which first the sulfur, then the nitrogen, and finally both these moieties have been replaced by an isosterically similar carbon group.

In this investigation we decided to examine compounds having the general structure V and to vary, over as wide a range as practical, the substituent in the



aromatic ring (R), the size of the cycloalkyl ring (n + 2), the alkylene unit (Y), and the amino function (Am). Homologs with n = 4 (tetrahydrocarbazole) have been reported[6] in the patent literature. The N-dimethylaminopropyltetrahydrocarbazole was prepared (Table IV, n = 4) for comparison.

TABLE I
POLYMETHYLENEINDOLES



	R	n	M.p., °C.	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
1	H[a]	5	143–145	$C_{13}H_{15}N$						
2	CH_3	5	123–127	$C_{14}H_{17}N$	84.37	84.36	8.60	8.52	7.03	6.92
3	F	5	115–116	$C_{13}H_{14}FN$	76.80	76.80	6.96	7.02	6.90	7.06
4	Cl	5	128–129	$C_{13}H_{14}ClN$	*e*	*e*			6.38	6.10
5	NO_2	5	165–166	$C_{13}H_{14}N_2O_2$	67.81	67.82	6.13	6.24	12.17	12.15
6	CH_3O	5	130–131	$C_{14}H_{17}NO$					6.53	6.42
7	H[b]	6	74.5–76	$C_{14}H_{17}N$						
8	NO_2	6	177–178	$C_{14}H_{16}N_2O_2$	68.83	68.71	6.60	6.63	11.47	11.51
9	H	7	65–66	$C_{15}H_{19}N$	84.45	83.72	8.98	8.72	6.57	6.41
10	H	8	92–93	$C_{16}H_{21}N$	84.53	84.25	9.31	9.30	6.16	6.13
11	H	9	*d*	$C_{17}H_{23}N$						
12	H	10	100–101	$C_{18}H_{25}N$	84.65	84.61	9.87	9.67	5.49	5.47
13	H[c]	11	116–117	$C_{19}H_{27}N$						
14	H[c]	13	68–69	$C_{21}H_{31}N$						

[a] W. H. Perkin, Jr., and S. G. P. Plant, *J. Chem. Soc.*, 2583 (1928). [b] B. Witkop, J. G. Patrick, and M. Rosenblum, *J. Am. Chem. Soc.*, **73**, 2641 (1951). [c] Ng. Ph. Buu-Hoi, *J. Chem. Soc.*, 2882 (1949). [d] Constant melting sample was not obtained. [e] *Anal.* Calcd.: Cl, 16.15. Found: Cl, 16.05.

The penta- and hexamethyleneindoles required (Table I) were prepared from phenylhydrazines and alicyclic ketones by the Rogers–Corson[7] modification of the Fischer indole synthesis. Higher homologs (Table I) were prepared by the method of Buu-Hoi.[8]

The *p*-nitrophenylhydrazones of cycloheptanone and cyclooctanone, which failed to cyclize under Rogers–Corson conditions, gave the corresponding 5-nitro-2,3-

(1) Presented in part before the Division of Medicinal Chemistry; see Abstracts, 143rd National Meeting, American Chemical Society, Los Angeles, Calif., April 1, 1963, p. 6L.

(2) W. Schindler and F. Haflinger, *Helv. Chim. Acta*, **37**, 474 (1954).

(3) P. V. Petersen, N. Lassen, T. Holm, R. Kopf, and I. M. Nielsen, *Arzneimittel-Forsch.*, **8**, 395 (1958).

(4) E. L. Engelhardt, M. E. Christy, H. C. Zell, C. M. Dylion, M. B. Freedman, and J. M. Sprague, Abstracts, 141st National Meeting, American Chemical Society, Washington, D. C., March, 1962, p. 4N.

(5) P. Charpentier, U. S. Patent 2,519,886 (1950).

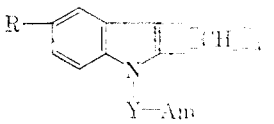
(6) J. W. Cusic and C. A. Dornfeld, U. S. Patent 2,541,211 (1951).

(7) C. U. Rogers and B. B. Corson, *J. Am. Chem. Soc.*, **69**, 2910 (1947).

(8) Ng. Ph. Buu-Hoi, *J. Chem. Soc.*, 2882 (1949).

Table II

Basic 2,3-Pentamethyleneindoles



	R	Am	Y	Salt	M.p., °C.
1	H	$(CH_3)_2N$	CH_2CH_2	Fumarate	220–221
2	H	$(CH_3CH_2)_2N$	CH_2CH_2	Fumarate	187–188
3	H	$(CH_3CH_2)_2N$	CH_2CH_2	CH_3I	187–188
4	H	$(CH_3)_2N$	$CH_2(CH_3)CH$	HCl	189–190
5	H	$(CH_3)_2N$	$CH(Ph)CH_2$	Fumarate	195–197
6	H	$(CH_2)_4N$	CH_2CH_2	Fumarate	244–245
7	H	$(CH_2)_5N$	CH_2CH_2	HCl	209–210
8	H	$O(CH_2CH_2)_2N$	CH_2CH_2	HCl	181–182
9	H	H_2N	$(CH_2)_3$	HCl	271–272
10	H	CH_3NH	$(CH_2)_3$	HCl	172–174
11	H	$(CH_3)_2N$	$(CH_2)_3$	HCl	207–208
12	H	$(CH_3CH_2CH_2)_2N$	$(CH_2)_3$	Maleate	101–102
13	H	$(CH_3CH_2CH_2)_2N$	$(CH_2)_3$	CH_3I	159–160
14	H	$HN(CH_2CH_3)_2N$	$(CH_2)_3$	Difumarate	172–174
15	H	$CH_3N(CH_2CH_2)_2N$	$(CH_2)_3$	Difumarate	218–219
16	H	$HOEtN(CH_2CH_2)_2N$	$(CH_2)_3$	Dihydrochloride	209–210
17	H	$(CH_3)_2N$	$(CH_2)_4$	HCl	164–166
18	H	$(CH_3)_2N$	$(CH_2)_6$	HCl	158.5–159.5
19	CH_3	$(CH_3)_2N$	$(CH_2)_3$	Fumarate	142–145
20	F	$(CH_3)_2N$	$(CH_2)_3$	HCl	177–178
21	Cl	$(CH_3)_2N$	$(CH_2)_3$	Fumarate	141–142
22	NH_2	$(CH_3)_2N$	$(CH_2)_3$	Dihydrochloride	260–261
23	NO_2	$(CH_3)_2N$	$(CH_2)_3$	HCl	220–223

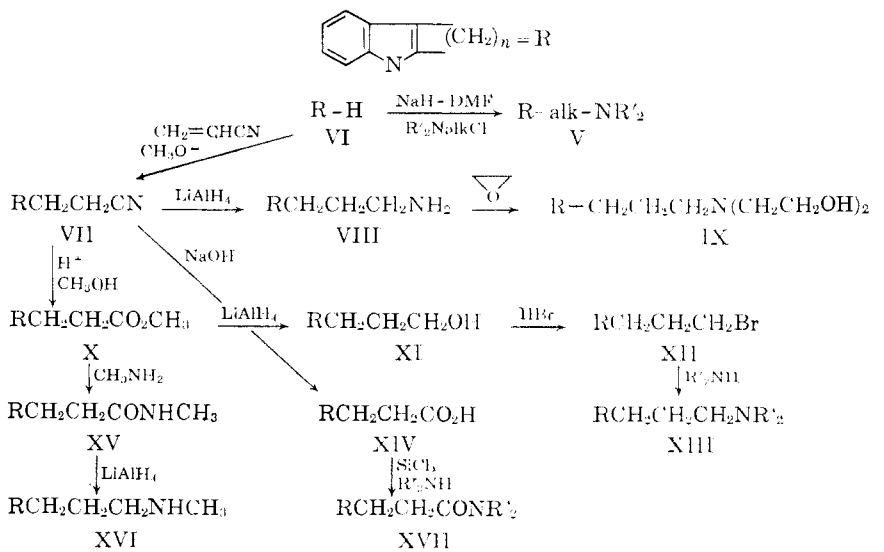
[a] Iodine.

polymethyleneindoles in good yield when heated under reflux in glacial acetic acid saturated with hydrogen chloride for an extended period (5–6 hr.).

The synthesis of compounds of type V was accomplished, for the most part, by the alkylation of the sodium derivative of the polymethyleneindoles with dialkylaminoalkyl chlorides. In addition, a variety of methods were utilized where necessary to prepare special examples. These reactions are summarized in Scheme I.

The polymethyleneindoles VI were converted into their sodium salts by treatment with a 48% dispersion of sodium hydride in mineral oil, using dimethylformamide as solvent, and the sodium salts were then treated with suitable dialkylaminoalkyl chlorides. The products V (Tables II, III, and IV) were isolated either directly as hydrochloride salts or the bases were first purified by vacuum distillation and then converted to a suitable salt, generally the hydrochloride or the fumaric acid salt.

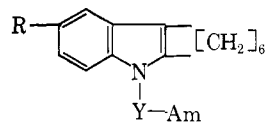
Scheme I



Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found	Chlorine, % Calcd.	Chlorine, % Found
$C_{21}H_{28}N_2O_4$	67.72	67.70	7.58	7.38	7.52	7.41		
$C_{23}H_{32}N_2O_4$	69.20	69.48	8.05	8.02	6.98	7.28		
$C_{20}H_{31}IN_2$					6.58	6.65	29.55[a]	29.07
$C_{18}H_{27}ClN_2$					9.13	9.13	11.57	11.53
$C_{27}H_{32}N_2O_4$	72.29	72.27	7.19	7.20	6.25	6.18		
$C_{23}H_{30}N_2O_4$	69.30	69.20	7.55	7.41	7.03	7.15		
$C_{20}H_{29}ClN_2$					8.44	8.43	10.38	10.42
$C_{19}H_{27}ClN_2O$					8.38	8.35	10.58	10.45
$C_{16}H_{23}ClN_2$					10.50	10.15	12.72	12.76
$C_{17}H_{25}ClN_2$	69.72	69.62	8.60	8.49	9.57	9.46	12.11	12.25
$C_{18}H_{27}ClN_2$					9.13	9.25	11.57	11.60
$C_{26}H_{38}N_2O_4$	70.60	70.74	8.62	8.68	6.33	6.44		
$C_{23}H_{37}IN_2$					6.00	5.72	26.95[a]	25.65
$C_{28}H_{37}N_3O_8$	61.86	61.73	6.86	7.10	7.73	7.98		
$C_{29}H_{39}N_3O_8$	62.46	62.41	7.05	7.33	7.54	7.47		
$C_{22}H_{35}Cl_2N_3O$					9.82	9.52	16.55	16.70
$C_{19}H_{29}ClN_2$	71.11	70.96	9.11	8.82	8.73	8.89	11.05	10.84
$C_{21}H_{33}ClN_2$	72.28	72.22	9.53	9.56	8.03	8.12	10.16	10.30
$C_{23}H_{32}N_2O_4$	68.97	68.75	8.05	8.01	7.00	6.96		
$C_{18}H_{26}ClFN_2$					8.64	8.65	10.92	10.92
$C_{22}H_{29}ClN_2O_4$	62.40	62.69	6.94	6.82	6.67	6.61		
$C_{18}H_{29}Cl_2N_3$					11.73	11.70	19.78	19.50
$C_{18}H_{25}ClN_3O_2$	61.44	61.26	7.45	7.49	11.94	12.04	10.08	10.04

TABLE III

BASIC 2,3-HEXAMETHYLENEINDOLES



R	Am	Y	Salt	M.p., °C.	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
H	$(CH_3)_2N$	CH_2CH_2	Fumarate	199–201	$C_{22}H_{30}N_2O_4$	68.36	68.32	7.82	8.04	7.25	7.28
H	$(CH_3)_2N$	$CH_2CH(CH_3)$	Fumarate	182–184	$C_{23}H_{32}N_2O_4$	68.97	68.71	8.05	8.11	7.00	6.82
H	$(CH_3CH_2)_2N$	CH_2CH_2	Fumarate	190–193	$C_{24}H_{34}N_2O_4$	69.53	69.53	8.27	8.47	6.76	6.65
H	$(CH_2)_4N$	CH_2CH_2	Fumarate	231–233	$C_{24}H_{32}N_2O_4$	69.88	69.94	7.82	7.76	6.79	6.89
H	$(CH_2)_5N$	CH_2CH_2	Fumarate	224–224.5	$C_{25}H_{34}N_2O_4$	70.39	70.30	8.03	8.16	6.57	6.44
H	$O(CH_2CH_2)_2N$	CH_2CH_2	Fumarate	174–176	$C_{24}H_{32}N_2O_5$	67.27	66.97	7.53	7.45	6.53	6.50
H	H_2N	$(CH_2)_3$	HCl	253–255	$C_{17}H_{25}ClN_2$[b]	69.72	69.88	8.60	8.59	9.57	9.41
H	CH_3NH	$(CH_2)_3$	HCl	180–181	$C_{18}H_{27}ClN_2$[c]	70.45	70.76	8.87	9.00	9.13	9.41
H	$(CH_3)_2N$	$(CH_2)_3$	HCl	146–147	$C_{19}H_{29}ClN_2$[d]					8.74	8.59
H	$(CH_3CH_2CH_2)_2N$	$(CH_2)_3$	Fumarate	164–167	$C_{27}H_{40}N_2O_4$	71.02	70.71	8.83	8.76	6.14	6.18
H	$(HOCH_2CH_2)_2N$	$(CH_2)_3$	(base)	a	$C_{21}H_{32}N_2O_2$	73.20	72.98	9.36	9.62	8.13	7.92
H	$CH_3N(CH_2CH_2)_2N$	$(CH_2)_3$	Difumarate	219–220	$C_{30}H_{41}N_3O_8$	63.03	62.66	7.23	7.26	7.35	7.24
H	$(CH_3)_2N$	$(CH_2)_3$	HCl	231–234	$C_{19}H_{28}ClN_3O_2$[e]	62.37	62.09	7.71	7.81	11.48	11.80
NH_2	$(CH_3)_2N$	$(CH_2)_3$	Dihydrochloride	264–265	$C_{19}H_{31}Cl_2N_3$[f]					11.27	11.47

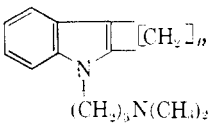
[a] B.p. 245–250° (0.01 mm.). [b] *Anal.* Calcd.: Cl, 12.11. Found: Cl, 12.10. [c] *Anal.* Calcd.: Cl, 11.56. Found: Cl, 11.28. [d] *Anal* Calcd.: Cl, 11.08. Found: Cl, 10.75. [e] *Anal.* Calcd.: Cl, 9.69. Found: Cl, 9.20. [f] *Anal.* Calcd.: Cl, 19.05. Found: Cl, 18.5

In an alternate route, VI was cyanoethylated in benzene, using trimethylbenzylammonium methoxide as a catalyst. As can be seen from Table V, the yield of cyanoethylation product of polymethyleneindoles (n = 5–11) varied from 41.2% to 92.5%. The cyanoethylpenta- and -hexamethyleneindoles (VII, n = 5,6; Table V) were reduced with lithium aluminum hydride to the corresponding primary amines (VIII). Treatment of one of these amines (VIII, n = 6) with a slight excess of ethylene oxide gave a nearly theoretical yield of the diol, IX. The treatment of IX with thionyl chloride, in an effort to obtain the corresponding "mustard," resulted in extensive resinification of the compound.

The nitriles VII (n = 5,6) were esterified directly with alcoholic hydrogen chloride. The ester X (n = 5) was reduced ($LiAlH_4$) in good yield to XI. Treatment of XI with 48% aqueous hydrobromic acid gave XII, which with hydroxyethylpiperazine gave XIII (NR_2 = 4-(2-hydroxyethyl)-1-piperazinyl).

TABLE IV

BASIC 2,3-POLYMETHYLENEINDOLES

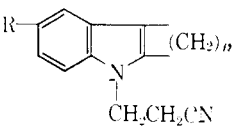


n	Salt	M.p., °C.	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
4[a]	HCl	194–195	$C_{17}H_{25}ClN_2$	[b]				9.56	9.66
5	HCl	207–208	$C_{18}H_{27}ClN_2$	[c]				9.13	9.25
6	HCl	146–147	$C_{19}H_{29}ClN_2$	[d]				8.74	8.59
7	Fumarate	172–174	$C_{24}H_{34}N_2O_4$	69.53	69.21	8.27	8.06	6.76	6.74
8	Fumarate	173–176	$C_{25}H_{36}N_2O_4$	70.06	69.81	8.47	8.20	6.54	6.58
9	Fumarate	151–152	$C_{26}H_{38}N_2O_4$	70.56	70.30	8.65	8.58	6.33	6.55
10	Fumarate	161–162	$C_{27}H_{40}N_2O_4$	71.02	71.26	8.83	8.84	6.14	6.14
11	HCl	184–185	$C_{24}H_{39}ClN_2$	73.71	73.57	10.05	9.74	7.17	7.26
13	Fumarate	147–149	$C_{30}H_{46}N_2O_4$	72.25	72.11	9.30	9.38	5.62	5.71

[a] J. W. Cusic and C. A. Dornfeld, U. S. Patent 2,541,211 (1951). [b] *Anal.* Calcd.: Cl, 12.11. Found: Cl, 12.24. [c] *Anal.* Calcd.: Cl, 11.57. Found: Cl, 11.60. [d] *Anal.* Calcd.: Cl, 11.08. Found: Cl, 10.75. [e] *Anal.* Calcd.: Cl, 9.07. Found: Cl, 9.20.

TABLE V

1-CYANOETHYL-2,3-POLYMETHYLENEINDOLES



R	n	M.p., °C.	Yield, %	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
H	5	95.5–97	87.2	$C_{16}H_{18}N_2$	80.50	80.41	7.60	7.64	11.78	11.76
CH_3	5	103–104	73.9	$C_{17}H_{20}N_2$	80.91	80.57	7.99	8.09	11.10	11.23
Cl	5	105–106	89.4	$C_{16}H_{17}ClN_2$	70.45	70.49	6.28	6.12	10.27	10.02
F	5	91.5–93	92.5	$C_{16}H_{17}FN_2$	74.87	74.96	6.69	6.61	10.93	10.75
NO_2	5	189–190	75.6	$C_{16}H_{17}N_3O_2$	67.82	67.82	6.05	5.97	14.83	14.93
H	6	94.5–96	80.6	$C_{17}H_{20}N_2$	80.91	81.02	7.99	7.80	11.10	11.30
NO_2	6	176–177	61	$C_{17}H_{19}N_3O_2$	68.67	68.57	6.44	6.59	14.13	13.89
H	7	97–98	41.2	$C_{18}H_{22}N_2$	81.16	80.95	8.33	8.13	10.52	10.27
H	8	137–138	60	$C_{19}H_{24}N_2$	81.38	81.06	8.63	8.58	9.99	10.20
H	9	92–93	48	$C_{20}H_{26}N_2$	81.58	81.22	8.90	8.70	9.52	9.41
H	10	89–92	53	$C_{21}H_{28}N_2$	81.77	81.49	9.15	8.89	9.08	8.85
H	11	117–119	57	$C_{22}H_{30}N_2$	81.94	81.68	9.38	9.11	8.69	8.59

Alkaline hydrolysis of VII readily afforded the propionic acid derivatives (Table VI). These acids were expected to be a ready source of the corresponding amides, *via* the acyl chlorides. Because of the observed behavior of IX with thionyl chloride, the acid XIV ($n = 5$) was not treated with this reagent; instead, it was converted to the acyl chloride using silicon tetrachloride.[9] Without isolation this was treated with N-(2-aminoethyl)-pyrrolidine, and the amide XVII ($n = 5$, R_2N = 1-pyrrolidinylethyl) was isolated as the hydrochloride salt.

Alternatively, X was subjected to aminolysis with methylamine. The N-methylpropionamide XV (n = 5,6), which was obtained in very high yield, was reduced in the usual manner with lithium aluminum hydride to give XVI.

Pharmacology. Methods.—The compounds under investigation were studied in three standard *in vivo* tests used to reveal central nervous system effects: (1) Decreased Motor Activity (D.M.A.).—The compound is administered orally to three mice (14–24 g.) at each of 5 doses, 400, 127, 40, 4, and 0.4 mg./kg. and the animals are observed for a minimum of 2 hr. for signs of decreased motor activity. (2) Antimorphine Activity (A.M.A.).[10] The compounds are administered orally at a number of dose levels to groups of 6 mice. One hour later the animals are challenged with morphine sulfate, 100 mg./kg., i.p. The incidence of Straub-tail and circling is noted and compared with controls. (3) Antireserpine[11] (A.R.A.).—The procedure is the same as for the antimorphine test but the animals are challenged with reserpine at a dose level of 2.5 mg./kg., i.p. The degree of ptosis for each eye is determined at 1 and 2 hr. post treatment. Prevention of ptosis, if any, is determined for each time period.

In addition, the compounds were examined by means of a recently developed[12] weight-loss test (W.L.). This test is based on the finding that amphetamine produces a weight loss in animals (rats), due in part to the increase in activity induced by this drug, which is markedly potentiated by pretreatment with an antidepressive drug. Imipramine produces up to 3 times the loss in weight obtained with amphetamine alone. The compounds are scored on an arbitrary scale (+1 to +4) with the effect caused by imipramine (5 mg./kg., i.p.) and amphetamine (0.75 mg./kg., i.p.) assigned a score of +3. In all the tests, imipramine was used as a standard.

(9) A. L. Mndzhoian, G. T. Tatevosian, and M. P. Unarian, in "Synthesis of Heterocyclic Compounds," Vol. 4, A. L. Mndzhoian, Ed., Consultants Bureau, New York, N. Y., 1960, p. 103.

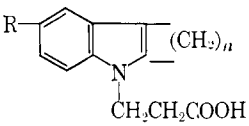
(10) C. H. Holtet, *Acta Pharmacol. Toxicol.*, **13**, 113 (1957).

(11) R. Rubio, M. H. Malone, M. H. Waugh, and J. C. Bucke, *J. Pharmacol. Exptl. Therap.*, **120**, 125 (1957).

(12) L. Stein, Private communication.

TABLE VI

1-CARBOXYETHYL-2,3-POLYMETHYLENEINDOLES



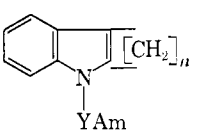
R	n	M.p., °C.	Yield, %	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
H	5	119–120	78.7	$C_{16}H_{19}NO_2$	74.80	74.55	7.45	7.14	5.45	5.52
F	5	105–107	74.9	$C_{16}H_{18}FNO_2$	69.80	70.06	6.59	6.60	5.09	5.16
Cl	5	128.5–130	80.7	$C_{16}H_{18}ClNO_2$	65.86	66.16	6.22	6.09	4.80	4.89
NO_2	5	198–199	51.4	$C_{16}H_{18}N_2O_4$	63.56	63.72	6.00	5.97	9.27	9.08
CH_3	5	123–125	63.2	$C_{17}N_{21}N_2O_2$	75.24	75.31	7.80	7.51	5.16	5.40
H	6	137–138	88.2	$C_{17}H_{21}NO_2$	75.24	75.09	7.80	7.60	5.16	5.02
NO_2	6	182.5–183.5	60.1	$C_{17}H_{20}N_2O_4$	64.54	64.45	6.37	6.18	8.86	9.13
H	7	102–104	66.2	$C_{18}H_{23}NO_2$	75.75	75.54	8.12	7.88	4.91	5.09
H	8	106–107.5	30.0	$C_{19}H_{25}NO_2$	76.22	76.29	8.42	8.44	4.68	4.41
H	9	130.5–133	43.1	$C_{20}H_{27}NO_2$	76.64	76.36	8.69	8.65	4.47	4.36
H	10	139–141	58.4	$C_{21}H_{29}NO_2$	77.02	76.95	8.93	9.06	4.28	4.15
H	11	144–145	63.9	$C_{22}H_{31}NO_2$	77.37	77.55	9.15	9.21	4.10	4.10

Results

The results obtained with a group of 1-substituted 2,3-polymethyleneindoles in four *in vivo* tests is shown in Table VII. As an indication of toxicity, the lowest dose causing death (D.) is included. These compounds were not significantly active in the standard tests (D.M.A., A.R.A., and A.M.A.). In the critical weight loss test some of the compounds had marked activity. The most active of these, 5-(3-dimethylaminopropyl)-6,7,8,9,10,11-hexahydro-5H-cyclooct[*b*]indole, is currently undergoing clinical trials. In conclusion, the N-substituted cycloalkylindoles are centrally active and seem to belong to the same psychopharmacological family as imipramine.

TABLE VII

PHARMACOLOGICAL STUDIES



n	YAm	D.M.A.	A.M.A.	A.R.A.	W.L.	D
6	$(CH_3)_2N(CH_2)_3$	100	>800	>262	÷4	1600
6	$(CH_3)_2N(CH_2)_2$	100	130	200	+3	800
5	$(CH_3)_2N(CH_2)_3$	200	400	287	+3	1600
5	$(CH_3CH_2)_2NCH_2CH_2$	200	560	478	0	1600
5	$C_5H_{10}NCH_2CH_2$	200	300	680	+2	1600
5	$NH_2(CH_2)_3$	100	200	>200	+1	1600
4	$(CH_3)_2N(CH_2)_3$	400	200	200	+1	800
(Imipramine, I)		40	160	5.6	+3	400

Experimental

Melting points were determined by the capillary tube method using the Hoover-Thomas apparatus. The melting point values are corrected.

The 2,3-polymethyleneindoles (Table I) were prepared by methods adequately described in the literature.[7,8] The 5-nitro-2,3-polymethyleneindoles required a departure from these procedures and a detailed example is given. The dialkylaminoalkyl-2,3-polymethyleneindoles (Tables II, III, and IV) were prepared for the most part by the procedure given for V. Exceptions are given in detail.

2-Nitro-6,7,8,9,10,11-hexahydro-5H-cyclooct[*b*]indole.—A solution of cyclooctanone (20.3 g., 0.16 mole) in 100 ml. of ethanol was added during 30 min. to a hot suspension of *p*-nitrophenylhydrazine in 300 ml. of the same solvent and the mixture refluxed 5 hr. Sufficient hot water (200 ml.) was added to produce turbidity. Upon cooling, cyclooctanone *p*-nitrophenylhydrazone crystallized and was filtered from the solution, washed with aqueous ethanol, and dried. The product weighed 37.2 g. (89%) and melted at 107–108°. The hydrazone (37.2 g.) was suspended in glacial acetic acid (325 ml.) saturated with dry hydrogen chloride, and the reaction mixture was heated under reflux 6 hr. After cooling to room temperature, the solution was chilled. The product was separated by filtration, washed well with water, and dried. After recrystallization from methanol it melted at 177–178°; yield, 25.3 g. (64.7%).

5-(3-Dimethylaminopropyl)-6,7,8,9,10,11-hexahydro-5H-cyclooct[*b*]indole (V).—Sodium hydride (60 g. of 48% dispersion in mineral oil) was suspended by stirring in 500 ml. of dimethylformamide (reagent grade). To this was added slowly a solution of 6,7,8,9,10,11-hexahydro-5H-cyclooct[b]indole (199 g., 1 mole) in 500 ml. of dimethylformamide. After evolution of hydrogen was no longer vigorous, the suspension was stirred an additional 2 hr. at 35° and 3-dimethylaminopropyl chloride (121 g., 1 mole) was added in portions, keeping the temperature below 60°. The reaction mixture was stirred and heated at 35° for 12 hr. after addition was complete. This was poured into 3 l. of ice–water and the mixture acidified with concentrated hydrochloric acid. The solution was extracted well with ether. The aqueous acid fraction was then made basic with 20% sodium hydroxide solution and the oil layer extracted into ether. The ether solution was washed with saline and dried over sodium sulfate. After removal of the drying agent, the solvent was distilled. The residue, an orange oil, was dissolved in absolute ethanol (600 ml.) and dry hydrogen chloride passed into the solution, with cooling, until it was strongly acidic. Sufficient anhydrous ether was added to produce cloudiness. After standing 24 hr. in the cold, the precipitate was collected, washed with ether–alcohol, and dried. The hydrochloride (204 g., 63.5%) was recrystallized from methanol–acetone, m.p. 146–147°.

5-(2-Cyanoethyl)-5,6,7,8,9,10-hexahydrocyclohept[*b*]indole (VII, *n* = 5).—A suspension of 5,6,7,8,9,10-hexahydrocyclohept[*b*]indole (185 g., 1 mole) in 500 ml. of dry benzene was placed in a 2-l. flask fitted with stirrer, thermometer, addition funnel, and condenser protected by drying tube filled with calcium chloride. After the addition of 2 ml. of 40% solution of trimethylbenzylammonium methoxide in methanol, acrylonitrile (58.4 g., 1.1 mole) was added dropwise, with stirring. The reaction was exothermic and a clear solution resulted. This was stirred for 1 hr. and finally heated to reflux on a steam bath for 1 hr. The reaction mixture was cooled and acidified with 1:1 hydrochloric acid. The solution was washed with a saline solution and the organic layer dried over sodium sulfate. This was filtered and the solvent removed under reduced pressure. The residue was crystallized from methanol–acetone and 208 g. (87.2%) of VII (*n* = 5) was obtained, m.p. 96–97°.

5-(3-Aminopropyl)-5,6,7,8,9,10-hexahydrocyclohept[*b*]indole (VIII, *n* = 5).—5-(2-Cyanoethyl)-5,6,7,8,9,10-hexahydrocyclo-

hept[*b*]indole (24.2 g., 0.1 mole) dissolved in 100 ml. of benzene was added slowly to a well-stirred suspension of lithium aluminum hydride (5.7 g., 0.15 mole) in 500 ml. of anhydrous ether. The mixture was heated under reflux and stirred 12 hr. After cooling, 30 ml. of water was added cautiously and stirring continued 1 hr. The reaction mixture was filtered and the solvent removed by distillation. The residue was distilled *in vacuo* and afforded 20 g. (81.5%) of product, b.p. 190–192° (0.5 mm.).

Anal. Calcd. for $C_{16}H_{22}N_2$: C, 79.25; H, 9.22; N, 11.58. Found: C, 78.99; H, 9.18; N, 11.61.

The hydrochloride was prepared in dry ether and recrystallized from methanol–acetone, m.p. 271–272°.

5-(2-Carboxyethyl)-5,6,7,8,9,10-hexahydrocyclohept[*b*]indole (XIV, *n* = 5).—5-(2-Cyanoethyl)-5,6,7,8,9,10-hexahydrocyclohept[*b*]indole (33 g., 0.14 mole) was dissolved in 600 ml. of 90% ethanol containing 33 g. of sodium hydroxide. After boiling under reflux for 30 hr., the solvent was removed by distillation and the remaining solid cake was dissolved in 300 ml. of cold water. The solution was filtered clear and the filtrate acidified with dilute hydrochloric acid. The product separated as a semi-solid material. After decanting the supernatant liquid, the material was stirred well with cold water (100 ml.) and allowed to settle. The liquid was decanted and the residue crystallized from aqueous methanol. The acid (28 g., 74.6%) melted at 119–120°.

5-(2-Carbethoxyethyl)-5,6,7,8,9,10-hexahydrocyclohept[*b*]indole (X, *n* = 5, R^1 = C_2H_5).—5-(2-Cyanoethyl-5,6,7,8,9,10-hexahydrocyclohept[*b*]indole (150 g., 0.63 mole) was dissolved in 1600 ml. of absolute ethanol and placed in a 3-l. flask fitted with stirrer, condenser (protected with a calcium chloride drying tube), and a gas inlet tube below the surface of the liquid. The solution was cooled (ice bath) and dry hydrogen chloride passed into the solution at a rapid rate for 4 hr. After standing at room temperature overnight, water (10 ml.) was added and the reaction heated to reflux for 2 hr. A precipitate formed rapidly. After cooling, the solution was filtered clear and the filtrate concentrated *in vacuo*. The residue was taken up in ether, washed well with water, and dried over sodium sulfate. The product (134 g., 74.6%) was purified by distillation, b.p. 182–185 (0.1 mm.).

Anal. Calcd. for $C_{18}H_{23}NO_2$: C, 75.75; H, 8.12; N, 4.92. Found: C, 75.76; H, 8.26; N, 4.79.

5-(2-Methylcarbamoylethyl)-5,6,7,8,9,10-hexahydrocyclohept[*b*]indole (XV, *n* = 5).—5-(2-Carbethoxyethyl)-5,6,7,8,9,10-hexamethylenecyclohept[*b*]indole (20 g., 0.07 mole) was dissolved in 100 ml. of absolute ethanol previously saturated with gaseous methylamine at 0°. The solution was kept in a stoppered pressure bottle at room temperature for 2 days. It was then concentrated on the steam bath and the residue was crystallized from aqueous methanol (80%), yielding 16.5 g. (86.8%) of product, m.p. 94–95°.

Anal. Calcd. for $C_{17}H_{22}N_2O$: C, 75.60; H, 8.19; N, 10.37. Found: C, 75.76; H, 8.22; N, 10.40.

5-(3-Methylaminopropyl)-5,6,7,8,9,10-hexahydrocyclohept[*b*]indole (XVI, *n* = 5).—5-(2-N-Methylcarbamoylethyl)-5,6,7,8,9,10-hexahydrocyclohept[*b*]indole (16 g., 0.06 mole) was dissolved in benzene and added slowly to a well-stirred suspension of lithium aluminum hydride (10 g., 0.26 mole) in anhydrous ether (500 ml.). The reaction mixture was stirred at room temperature for 12 hr. and then decomposed by the addition of water (30 ml.). The mixture was filtered and the filter cake washed well with ether. The combined filtrate was concentrated under reduced pressure. The residue was distilled and the fraction boiling at 165–170° (0.1 mm.) was collected (13 g., 84.8%).

Anal. Calcd for $C_{17}H_{24}N_2$: C, 79.64; H, 9.44; N, 10.93. Found: C, 79.78; H, 9.51; N, 10.93.

The hydrochloride was prepared in ether and recrystallized from ethanol–ether, m.p. 172–174°.

5-(3-Hydroxypropyl)-5,6,7,8,9,10-hexahydrocyclohept[*b*]-indole (XI, *n* = 5).—To a stirred suspension of lithium aluminum hydride (3 g., 0.05 mole) in 200 ml. of anhydrous ether was added slowly 5-(2-carbethoxyethyl)-5,6,7,8,9,10-hexahydrocyclohept[*b*]-indole (31 g., 0.11 mole) dissolved in 200 ml. of the same solvent. When the initial exothermic reaction slowed, the mixture was warmed and refluxed for about 4 hr. longer. After cooling, water (12 ml.) was added, cautiously and with stirring. To this was added 2-propanol (50 ml.), and then the whole mixture was filtered. The filter cake was washed with 2-propanol (100 ml.) and the combined filtrate was concentrated *in vacuo* to a small volume. Distillation gave the product (22 g., 82.3%) as a colorless viscous liquid, b.p. 210–215° (0.05 mm.)

Anal. Calcd. for $C_{16}H_{21}NO$: C, 78.90; H, 8.70. Found: C, 78.84; H, 8.40.

5-(3-Bromopropyl)-5,6,7,8,9,10-hexahydrocyclohept[*b*]indole (XII, *n* = 5).—5-(3-Hydroxypropyl)-5,6,7,8,9,10-hexahydrocyclohept[*b*]indole (18 g., 0.073 mole) was dissolved in a mixture of aqueous 48% hydrobromic acid (35 ml.) and concentrated sulfuric acid (7 ml.). The solution was refluxed for 1.5 hr. The reaction mixture was allowed to cool and the solution was then poured onto ice (100 g.). The organic layer was extracted into ether and the extract washed with dilute aqueous sodium bicarbonate solution, then with water, and dried over sodium sulfate. After removal of the solvent, the product was distilled *in vacuo* (8.4 g., 37.3%), b.p. 185–190° (0.05 mm.).

Anal. Calcd. for $C_{16}H_{20}BrN$: N, 4.57; Br, 26.08. Found: N, 4.49; Br, 25.92.

5-(3-[1-(Hydroxyethyl)-4-piperazinyl]propyl)-5,6,7,8,9,10-hexahydrocyclohept[*b*]indole (XIII, *n* = 5, R_2N = 1-(hydroxyethyl)-4-piperazinyl).—A solution of 5-(3-bromopropyl)-5,6,7,8,9,10-hexahydrocyclohept[*b*]indole (8 g., 0.026 mole) and 1-(2-hydroxyethyl)piperazine (3.9 g., 0.03 mole) in 100 ml. of xylene was refluxed 24 hr. After the reaction had cooled, the solution was washed with aqueous potassium carbonate, then with water. The organic layer was separated and dried over magnesium sulfate. This was filtered, the filtrate diluted with 2 volumes of ether and dry hydrogen chloride passed into the solution till acidic. The precipitate was separated and twice recrystallized from alcohol (2.4 g., 21.6%). After being dried rigorously (24 hr. in a drying pistol over P_2O_5 at 100° and 0.2 mm.) the sample melted at 209–210°.

5-[2-(1-Pyrrolidinylcarbamoyl)ethyl]-5,6,7,8,9,10-hexahydrocyclohept[*b*]indole (XVII, *n* = 5, R_2N = 2-pyrrolidinoethylamine). 5-(2-Carbethoxyethyl)-5,6,7,8,9,10-hexahydrocyclohept[*b*]indole (7.58 g., 0.03 mole) was placed in a 1-l. flask fitted with a seal-type stirrer, reflux condenser (protected by a calcium chloride drying tube), and dropping funnel. Anhydrous benzene (300 ml.) was added, and to this solution was added silicon tetrachloride (3.25 g., 0.019 mole). The mixture was warmed to 50°, stirred 12 hr., and finally refluxed for 2 hr. After cooling to room temperature, N-2-aminoethylpyrrolidine (16.5 g., 0.15 mole) was added dropwise, with stirring. The reactants were refluxed 12 hr. and the solvent was then distilled. The residue was treated with 5% aqueous sodium hydroxide and extracted with ether. The extract was washed with a saline solution and dried over sodium sulfate. After filtration, the solvent was removed and the residue taken up in a small volume of ethanol. This solution was acidified with an alcoholic solution of hydrogen chloride and then ether added to it until it became cloudy. After 2 days in a cold room, the product crystallized. The solid (3.8 g., 32%) was filtered from the solution, washed with ether, and dried, m.p. 173–174°.

Anal. Calcd. for $C_{22}H_{32}ClN_3O$: N, 10.78; Cl, 9.05. Found: N, 10.71; Cl, 8.95.

5-[2-(2-Dimethylaminoethyl)carbamoylethyl]-6,7,8,9,10,11-hexahydro-5H-cyclooct[*b*]indole (XVII, *n* = 6, R_2N = 2-dimethylaminoethyl amine).—5-(2-Carbomethoxyethyl)-6,7,8,9,10,11-hexahydro-5H-cyclooct[*b*]indole (5 g., 0.02 mole) and dimethylaminoethylamine (10 ml.) were heated together under reflux for 8 hr. The excess of dimethylaminoethylamine was removed by distillation, first at atmospheric pressure and finally at 0.2 mm. The residue was taken up in dilute hydrochloric acid and the solution extracted with ether. The aqueous layer was made basic and the thick oil extracted into benzene. The extract was washed with water and dried. Treatment with maleic acid gave a crystalline salt. This was recrystallized from 2-propanol, yielding the product (3.5 g., 38%) melting at 133–134°.

Anal. Calcd. for $C_{25}H_{34}N_2O_5$: C, 65.28; H, 7.71; N, 9.19. Found: C, 65.54; H, 7.63; N, 8.96.

5-[2-(1-[4-Methylpiperazinyl]carbamoyl)ethyl]-5,6,7,8,9,10-hexahydrocyclohept[*b*]indole (XVII, *n* = 5, R_2N = N-methylpiperazinyl).—A mixture of 5-(2-carbethoxyethyl)-5,6,7,8,9,10-hexahydrocyclohept[*b*]indole (5.2 g., 0.02 mole) and N-methylpiperazine (3 g., 0.03 mole) was heated (oil bath) in 15 ml. of ethylene glycol until ethanol distilled from the mixture. After 2 hr. at a bath temperature of 140–150°, excess N-methylpiperazine was removed *in vacuo*. The reaction mixture was poured into ice-water (100 ml.) and the oil was extracted into ether, washed well with a saline solution, and dried over sodium sulfate. The drying agent was filtered from the solution and the filtrate added to an ethereal solution of maleic acid. The precipitate

(1.3 g.) was recrystallized from a methanol–acetone mixture and finally from 2-propanol, m.p. 169–170°.

Anal. Calcd. for $C_{25}H_{33}N_3O_5$: C, 65.85; H, 7.3; N, 9.22. Found: C, 65.74; H, 7.32; N, 9.16.

5-(3-Bis[2-hydroxyethyl]aminopropyl)-6,7,8,9,10,11-5H-cyclooct[*b*]indole (IX, *n* = 6).—5-(3-Aminopropyl)-6,7,8,9,10,11-5H-cyclooct[*b*]indole (11.5 g., 0.045 mole) was dissolved in methanol (50 ml.), and ethylene oxide (4.4 g., 0.1 mole) was added slowly. The solution was allowed to stand for 2 days and the solvent then distilled. The residue was transferred to a small (25 ml.) pear-shaped flask and distilled *in vacuo*. The product (12 g., 77.5%) was an extremely viscous liquid, b.p. 245–250° (0.01 mm.), and it was necessary to apply heat to the condenser to maintain a flow.

Acknowledgments.—The authors wish to thank Drs. Melvin Gluckman and Larry Stein for the pharmacologic data supplied and Dr. Gordon Ellis and his staff for microanalyses.

Central Nervous System Depressants. VI. Polymethoxyphenyl Esters and Amides

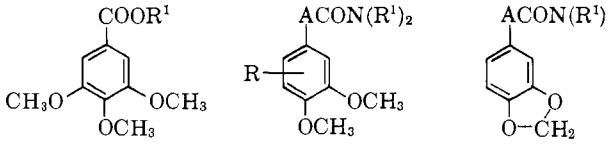
ROBERT BRUCE MOFFETT

Research Laboratories, The Upjohn Company, Kalamazoo, Michigan

Received November 16, 1963

A large number of esters and amides were prepared from 3,4,5-trimethoxy-, 3,4-dimethoxy-, and 3,4-methylenedioxybenzoic, -phenylacetic, -cinnamic, and -hydrocinnamic acids (I, II, and III). Most of these were made by reaction of the acid chlorides with the appropriate alcohol or amine, but some involved the rearrangements shown in Chart I. The compounds generally produced central nervous system (CNS) depressant effects as shown by gross observation of intact animals and confirmed by avoidance behavior and motor activity studies.

The interesting central nervous system depressant activity found for certain di- and trimethoxyacetophenones, described in paper V of this series,[1] encouraged us to continue the study. In previous, somewhat related work,[2] acids, esters, and especially amides were found to be active depressants. Therefore a considerable number of compounds of the types I, II, and III were prepared.



I II III

A = single bond, $-CH_2-$, $-CH_2CH_2-$, or $-CH{=}CH-$; R = H or 5-OCH_3

In general the esters and amides were prepared from the corresponding acid chlorides by treatment with the appropriate alcohol or amine in the presence of a proton acceptor. In the preparation of the amides an excess of the amine usually served for this purpose.

The preparation of several compounds involved rearrangement of oxazoline hydrohalides to N-(β-haloethyl)amides. These in turn rearranged during hydrolysis to β-aminoethyl esters as is shown in Chart I.

These findings confirm and extend the work of Fry[3] who carried out some similar rearrangements from N-benzoylethanolamine. It is interesting to note that whereas the oxazoline hydrochloride **18** rearranged essentially completely to the β-chloroethylamide **16** on heating, either the corresponding oxazoline hydrobromide **19** or the β-bromoethylamide **17** went to an equilibrium mixture when heated under the same conditions. This doubtless reflects the difference between the C–Cl and C–Br bond energies.

Pharmacology.—Table I lists the compounds prepared in this work with some of their central nervous system activities in mice and rats. A number of old compounds are included for comparison. Methodology details may be found in paper V of this series.[1] It may be noted that most of these compounds are depressants. This was observed in intact mice and rats during toxicity studies and confirmed by avoidance behavior studies[4] and in some cases by motor activity tests.[2]

In general, the amides are more depressive than the esters and the 3,4,5-trimethoxyphenyl compounds are more active than the corresponding dimethoxy compounds. The methoxybenzamides and cinnamides are better than the phenylacetamides or hydrocinnamides. It seems that small substituents, for example hydrogen, methyl or allyl, on the amide nitrogen are desirable. Larger radicals, especially those containing functional groups, decrease the depressant activity.

Experimental[5]

1-Methyl-4-piperidyl 3,4,5-Trimethoxybenzoate[6] [2 (base)].—A solution of 23.0 g. (0.1 mole) of 3,4,5-trimethoxybenzoyl chloride and 23.0 g. (0.2 mole) of N-methyl-4-hydroxypiperidine in 300 ml. of benzene was heated under reflux for 2 hr. A white solid separated and after cooling the mixture was extracted with cold dilute hydrochloric acid. The free base was liberated with sodium hydroxide and extracted with ether. After washing with water and saturated sodium chloride, the ether solution was dried over sodium sulfate, filtered, and evaporated. The

(1) R. B. Moffett, A. R. Hanze, and P. H. Seay, *J. Med. Chem.*, **7**, 178 (1964).

(2) R. B. Moffett, P. H. Seay, and W. B. Reid, *ibid.*, **2**, 179 (1960).

(3) E. M. Fry, *J. Org. Chem.*, **14**, 887 (1949).

(4) To be reported by Dr. D. G. Anger, The Upjohn Co., Kalamazoo, Mich.

(5) Melting points were taken in capillary tubes with a partial immersion thermometer. Calibration of the apparatus against standard compounds showed no need for correction. Infrared spectra were obtained on all pure compounds and unless otherwise noted were in accordance with the proposed structures.

(6) Prepared by Dr. R. P. Holysz in these laboratories.