interaction" in blocking conduction of the nerve impulse. In contrast, our biological data show no consistent correlation between conformation and biological activity. Rather it seems that differences in electron distribution[39] and differences in hydrophobic bonding ability may be more important than the conformations of the molecules. It should be emphasized[34] that the conformers seen in the crystal and in D_2O solution may not necessarily be the conformers predominating at the active site.

References

(1) D. Nachmansohn, "The Chemical and Molecular Basis of Nerve Activity," Academic Press, New York, N. Y., 1959.
(2) P. Rosenberg, H. B. Higman, and E. Bartels, *Biochim. Biophys. Acta*, 66, 406 (1949).
(3) E. Bartels, *ibid.*, 109, 194 (1965).
(4) E. Bartels and D. Nachmansohn, *Biochem. Z.*, 342, 359 (1965).
(5) I. Tasaki, "Nerve Excitation," Thomas, Springfield, Ill., 1968.
(6) I. Tasaki, A. Watanabe, R. Sandlin, and L. Carnay, *Proc. Nat. Acad. Sci. U. S.*, 61, 883 (1968).
(7) L. B. Cohen and R. D. Keynes, *J. Physiol.*, 194, 85 (1968).
(8) I. Tasaki, L. Carnay, and R. Sandlin, *Science*, 163, 683 (1969).
(9) W. H. H. Günther and H. G. Mautner, *J. Med. Chem.*, 7, 229 (1964).
(10) K. A. Scott and H. G. Mautner, *Biochem. Pharmacol.*, 13, 907 (1964); 16, 1903 (1967).
(11) H. G. Mautner, E. Bartels, and G. D. Webb, *ibid.*, 15, 187 (1966).
(12) G. D. Webb and H. G. Mautner, *ibid.*, 15, 2105 (1966).
(13) H. G. Mautner, *J. Gen. Physiol. Pt. 2*, 54, 2715 (1969).
(14) E. Shefter and H. G. Mautner, *Proc. Nat. Acad. Sci. U. S.*, 63, 1253 (1969).
(15) R. J. Cushley and H. G. Mautner, *Tetrahedron*, 26, 2151 (1970).
(16) P. Rosenberg, H. G. Mautner, and D. Nachmansohn, *Proc. Nat. Acad. Sci. U. S.*, 55, 835 (1966).
(17) P. Rosenberg and H. G. Mautner, *Science*, 155, 1569 (1967).
(18) R. Mayer, S. Scheithauer, and D. Kunz, *Chem. Ber.*, 99, 1393 (1966).
(19) E. J. Hedgley and H. G. Fletcher, *J. Org. Chem.*, 30, 1282 (1965).
(20) P. Rosenberg and T. R. Podleski, *J. Pharmacol. Exp. Ther.*, 137, 249 (1962).
(21) A. M. Shanes, W. H. Freygang, H. Grundfest, and E. Amatnieck, *J. Gen. Physiol.*, 42, 793 (1959).
(22) M. B. Feinstein, *ibid.*, 48, 357 (1964).
(23) M. P. Blaustein and D. E. Goldman, *ibid.*, 49, 1043 (1966).
(24) F. Brink, *Pharmacol. Rev.*, 6, 243 (1954).
(25) D. Nachmansohn, "Symposium on Membrane Proteins," Little, Brown and Co., Boston, Mass., 1969, p 190.
(26) M. Sax and J. Pletcher, *Science*, 166, 1546 (1969).
(27) S. H. Chu and H. G. Mautner, *J. Org. Chem.*, 31, 308 (1966).
(28) M. H. Krackov, C. M. Lee, and H. G. Mautner, *J. Amer. Chem. Soc.*, 87, 892 (1965).
(29) F. P. Canepa, P. Pauling, and H. Sörum, *Nature (London)*, 210, 907 (1966).
(30) D. Dexter, Abstracts of the American Crystallographic Association, Winter Meeting, March 1970, F-8.
(31) R. Beall, J. Herdklotz, and R. L. Sass, *Biochem. Biophys. Res. Commun.*, 39, 329 (1970).
(32) D. Dexter, *Acta Crystallogr.*, in press.
(33) C. C. J. Culvenor and N. S. Ham, *Chem. Commun.*, 537 (1966).
(34) R. J. Cushley and H. G. Mautner, *Tetrahedron*, 26, 2151 (1970).
(35) C. C. J. Culvenor and N. S. Ham, *J. Chem. Soc. D*, 1242 (1970).
(36) A. Makriyannis, R. Sullivan, and H. G. Mautner, *Fed. Proc., Fed. Amer. Soc. Exp. Biol.*, in press.
(37) M. Sundaralingam, *Nature (London)*, 217, 35 (1968).
(38) R. W. Baker, C. H. Chothia, P. Pauling, and T. J. Petcher, *ibid.*, 230, 439 (1971).
(39) I. Wallmark, M. H. Krackov, S. H. Chu, and H. G. Mautner, *J. Amer. Chem. Soc.*, 92, 4447 (1970).

N-Phenyl-2-indolinones and *N*-Phenylindolines. A New Class of Antidepressant Agents†

A. Cañas-Rodriguez* and P. R. Leeming

Research Division, The Pfizer Group, Sandwich, Kent, England. *Received November 22, 1971*

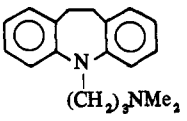
Biological activity of an adrenergic-potentiating type in animals indicative of antidepressant action in man is displayed by compounds of formula II, especially 3-methyl-3-(3-methylaminopropyl)-1-phenyl-2-indolinone (Amedalin) and 3-methyl-3-(3-methylaminopropyl)-1-phenylindoline (Daledalin). They do not possess the antihistaminic and anticholinergic side effects shown by other antidepressant drugs. The syntheses of compounds depicted by formula II (X = O or H_2; R_1 = alkyl; R_2, R_3 = H or alkyl) are described together with structure–activity relationships.

A number of 3-(ω-aminoalkyl)-1-phenyl-2-indolinones and the corresponding 1-phenylindolines have been synthesized and evaluated pharmacologically as potential antidepressant agents. These series were designed to incorporate the main structural characteristics of the established antidepressants (*e.g.*, imipramine) in a nontricyclic framework. Pharmacological evaluation of these two groups of compounds showed widespread biological activity of an adrenergic-potentiating type. The properties of the most potent compounds, indolinone **11** (Amedalin‡) and indoline **44** (Daledalin‡), are compared with those of the standard antidepressant drugs. Two side reactions which gave X and XI were encountered in the synthetic work and these are discussed briefly.

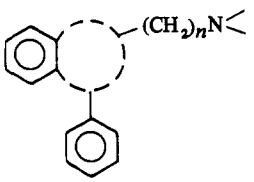
Imipramine is the prototype of a series of structurally closely related drugs usually referred to as the tricyclic antidepressants.[2] All members of the series cause varying degrees of side effects which are believed to originate from inherent anticholinergic and antihistaminic properties,[3-7] and our objective was to synthesize an antidepressant which lacked these side effects. We decided to investigate substances incorporating the main structural features of imipramine and its congeners in a nontricyclic chemical framework. This is readily achieved in phenyl-substituted bicyclic systems of general formula I. Substances derived from *N*-phenylindole seemed particularly attractive in view of the well-documented involvement of indole compounds in brain function (*e.g.*, tryptophan,[8-11] 5-HT,[12-18] and bufotenine[19]). We here report the structure–activity relationships of two series of

†A preliminary account of this work has appeared,[1a] and preparation of the compound has been described in ref 1b. After completion of this manuscript, compounds 1, 2, 6, 12, and 66 were reported in another context.[1c]

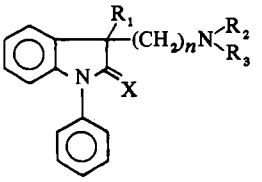
‡USAN Council approved name.



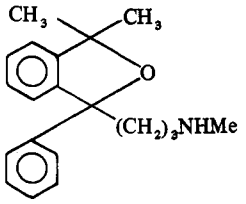
imipramine



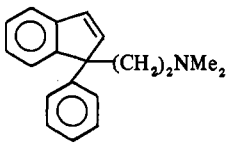
I



II; X = O or H_2



3,3-dimethyl-1-(3-methylaminopropyl)-1-phenylphthalan



indriline

such compounds, namely 3-aminoalkyl-substituted *N*-phenyl-2-indolinones and the corresponding indolines (see formula II).

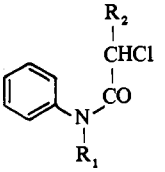
During the course of this work, descriptions of other compounds of general formula I were published and these are claimed to have antidepressant activity, notably 3,3-dimethyl-1-(3-methylaminopropyl)-1-phenylphthalan[20] and indriline.[21] The synthesis of 3-(2-dimethylaminoethyl)-1-phenyl-2-indolinone[22] was also announced, and it was claimed to have antiinflammatory activity. No effect on the central nervous system was reported.

Chemistry. The 2-indolinone series was prepared by the general route shown in Scheme I. Reaction of diphenylamine or *N*-alkylanilines (III) with 2-halogenoacyl chlorides (method A) gave the 2-halogenoalkylamides IV (see Table I). Cyclization of IV (method B[23] or C) gave the 2-indolinones V (Table II). If a diphenylamine with one substituent was used, cyclization of IV occurred at either aromatic ring, resulting in mixtures of products V which were very difficult to separate. The 5-bromo-2-indolinone **64** (Table II) was prepared by direct bromination of V (R_1 = Ph; R_2 = Me). The 5-methoxy compound **65** was made by a completely different procedure which is the subject of a separate paper.[24] 3-Benzyl-1-phenyl-2-indolinone (**61**) was prepared by reduction of the corresponding 3-benzylidene derivative.[23]

The 3-monosubstituted indolinones V were converted to the desired 3-aminoalkyl products VII (Table III) by various procedures which are detailed in the Experimental Section under methods D, E, F,[25] and G–O.

The 5-halo-substituted indolinones **18** and **19** were prepared by allowing **11** to react with SO_2Cl_2 and Br_2, respectively. That aromatic substitution took place at position 5 of the indole ring (compounds **18** and **19**) was ascertained by comparison of their nmr spectra with that

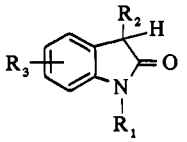
Table I



No.	R_1	R_2	Method	Cryst solvent[a]	Mp, °C	Yield, %	Formula	Analyses
52	Ph	H	A	P	119–121	97	$C_{14}H_{12}ClNO$	C, H, N
53	Ph	Me	A	P	91–94	98	$C_{15}H_{14}ClNO$	C, H, N
54	Ph	*n*-Bu	A	P	69–73	97	$C_{18}H_{20}BrNO$	C, H, N
55	Ph	Ph	A	P–B	141–144	98	$C_{20}H_{16}ClNO$	C, H, N
56	CH_2Ph	Me	A	P	74–76	97	$C_{16}H_{16}ClNO$	C, H, N
57	Cyclohexyl	Me	A	Ph	79–81	98	$C_{15}H_{20}ClNO$	C, H, N

[a] Crystallization solvents: ethyl acetate = A; chloroform = C; petr ether (bp 60–80°) = P; 2-propanol = Ip; ethanol = E; methanol = M; benzene = B; ether = Et; water = W.

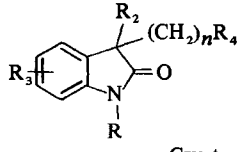
Table II



No.	R_1	R_2	R_3	Method	Cryst solvent[a]	Mp or bp (mm), °C	Yield, %	Formula	Analyses
58	Ph	Me	H	B, C	C–P	80–81	92	$C_{15}H_{13}NO$	C, H, N
59	Ph	*n*-C_4H_9	H	B		170–190 (0.5)	81	$C_{18}H_{19}NO$	C, H, N
60	Ph	Ph	H	B, C	P	111–113	79	$C_{20}H_{15}NO$	C, H, N
61	Ph	CH_2Ph	H	*b*	P	86–88	91	$C_{21}H_{17}NO$	C, H, N
62	Cyclohexyl	Me	H	B	P	84–85	70	$C_{15}H_{19}NO$	C, H, N
63	CH_2Ph	Me	H	B	P	117–118	37	$C_{16}H_{15}NO$	C, H, N
64	Ph	Me	5-Br	*b*	Ip–P	112–115	33	$C_{15}H_{12}BrNO$	C, H, Br, N
65	Ph	Me	5-MeO	*c*	A–P	100–102	33	$C_{16}H_{15}NO_2$	C, H, N

[a] See footnote *a*, Table I. [b] Refers to the individual preparative procedure described in the text. [c] Extracted from ref 22.

Table III

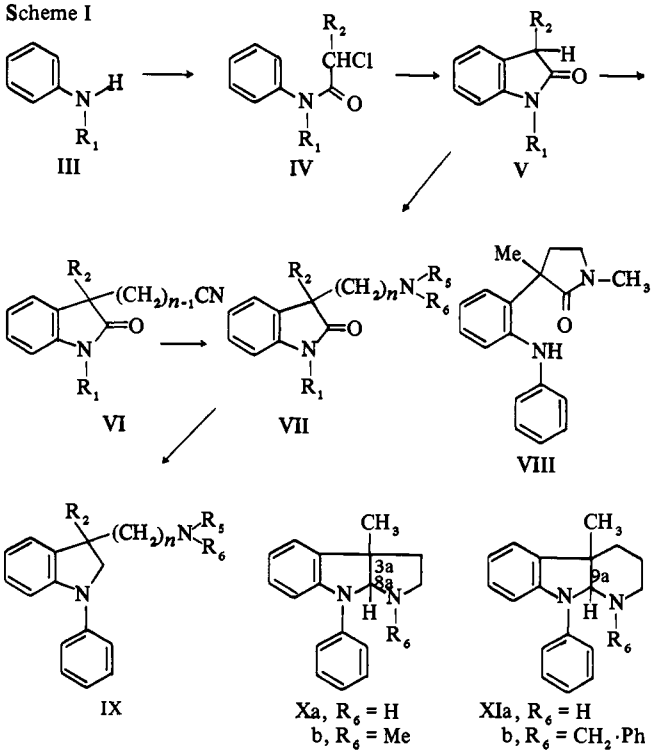


No.	R_1	R_2	R_3	R_4	n	Method	Formula	Cryst solvent[a]	Yield, %	Mp, °C	Salt[c]	Analysis	Pharmacological results[d] Amphet	TBZ	Res	Nor
1	Ph	Me	H	NMe_2	1	O	$C_{18}H_{20}N_2O \cdot HCl$	C-A	62	204–207	HCl	C, H, N	0	0	0	++
2	Ph	Me	H		1	O	$C_{21}H_{24}N_2O$	P	58	92–94		C, H, N	++	0	0	0
3	Ph	Me	H	NH_2	2	F	$C_{17}H_{18}N_2O \cdot HCl$	A	70	209.5–210.5	HCl	C, H, N	+	+	0	+++
4	Ph	Me	H	NHMe	2	G, H	$C_{18}H_{20}N_2O \cdot HCl$	Ip-A	69	194–197	HCl	C, H, N	+	0	++	+++
5	Ph	Me	H	$NHCH_2Ph$	2	K	$C_{24}H_{24}N_2O \cdot HCl$	Ip	60	213.5–215	HCl	C, H, N	++	0	0	0
6	Ph	Me	H	NMe_2	2	I, J	$C_{19}H_{22}N_2O \cdot HCl$	C-A	72	252–255	HCl	C, H, N	++	0	++	+++
7	Ph	Me	H	$N(Me)(CH_2Ph)$	2	I, J	$C_{25}H_{26}N_2O \cdot C_4H_4O_4$	A	75	165–166	Mal	C, H, N	+	0	0	++++
8	Ph	Me	H		2	M, N	$C_{22}H_{27}N_3O \cdot 2C_4H_4O_4$	E-W	77	178–179	Mal	C, H, N	++	0	0	++
9	Ph	Me	H		2	M	$C_{23}H_{29}N_3O_2 \cdot 2C_4H_4O_4$	Ip	57	148–149	Mal	C, H, N	+	0	0	0
10	Ph	Me	H	NH_2	3	F	$C_{18}H_{20}N_2O \cdot HCl$	Ip-A	80	187–188.5	HCl	C, H, N	+++	+	0	+++
11	Ph	Me	H	NHMe	3	G, H	$C_{19}H_{22}N_2O \cdot HCl$	C-A	99	168–170	HCl	C, H, N	++	++	++++	++++
12	Ph	Me	H	NMe_2	3	I, J	$C_{20}H_{24}N_2O \cdot HCl \cdot H_2O$	C-A	73	168–170	HCl	C, H, N	++	+	++	++++
13	Ph	Me	H	$NHCH_2Ph$	3	K	$C_{25}H_{26}N_2O \cdot C_4H_4O_4$	Ip-A	52	157–159	Mal	C, H, N	+++	0	0	+++
14	Ph	Me	H	$N(Me)(CH_2Ph)$	3	I, J	$C_{26}H_{28}N_2O \cdot HCl$	W	80	198–205	HCl	C, H, N	++++	++	+	++++
15	Ph	Me	H		3	M, N	$C_{23}H_{28}N_2O \cdot C_2H_2O_4$	M-E	50	219–220	Ox	C, H, N	++	0	0	+++
16	Ph	Me	H		3	M	$C_{23}H_{29}N_3O \cdot 2C_4H_4O_4$	E	43	178.5–179.5	Mal	C, H, N	+++	0	0	+++
17	Ph	Me	H		3	M	$C_{24}H_{31}N_3O_2 \cdot 2C_4H_4O_4$	Ip	45	141.5–142	Mal	C, H, N	0	0	0	+++
18	Ph	Me	5-Cl	NHMe	3	*b*	$C_{19}H_{21}ClN_2O \cdot HCl$	Ip-P	58	196–199	HCl	C, H, N, Cl	+	0	0	++++
19	Ph	Me	5-Br	NHMe	3	*b*	$C_{19}H_{21}BrN_2O \cdot HCl$	E-P	89	189–191	HCl	C, H, N, Br, Cl	+	0	0	++++
20	Ph	Me	5-Br	NMe_2	3	I	$C_{20}H_{23}BrN_2O \cdot HCl$	E-P	59	263–264	HCl	C, H, N, Br, Cl	+	0	0	+++
21	Ph	Me	5-MeO	NHMe	3	G, H	$C_{20}H_{24}N_2O_2 \cdot HCl \cdot 0.25H_2O$	Ip-A	80	211–212	HCl	C, H, N	++++	0	0	++++
22	Ph	Me	5-HO	NHMe	3	H	$C_{19}H_{22}N_2O_2 \cdot HI$	Ip	65	224–227	HI	C, H, N	+	0	++	–
23	Ph	Me	5-MeO	N(Me)(COOEt)	3	H	$C_{23}H_{28}N_2O_4$	Et-P	78	86–89		C, H, N	0	0	0	0
24	Ph	Me	5-MeO	NMe_2	3	I, J	$C_{21}H_{26}N_2O_2 \cdot HCl$	E-A	70	227–230	HCl	C, H, N	++++	0	0	+++

25	Ph	Me	H	$CH(Me)NHMe$	2	*b*	$C_{20}H_{24}N_2O \cdot HCl$	Ip–A	74	178–181	HCl	C, H, N	++	0	+	+++
26	Ph	Me	H	NH_2	4	F	$C_{19}H_{22}N_2O \cdot HCl$	C–A	75	197.5–199	HCl	C, H, N	+++	+	0	+++
27	Ph	Me	H	NHMe	4	L	$C_{20}H_{24}N_2O \cdot HCl$	C–A	53	164–167	HCl	C, H, N	+++	0	+	+++
28	Ph	*n*-Bu	H	NHMe	2	G, H	$C_{21}H_{26}N_2O \cdot C_4H_4O_4$	C–A	75	154–157	Mal	C, H, N	0	0	0	+++
29	Ph	*n*-Bu	H	NMe_2	2	I	$C_{22}H_{28}N_2O \cdot HCl$	C–A	85	157–160	HCl	C, H, N	+	0	0	++
30	Ph	*n*-Bu	H	NH_2	3	F	$C_{21}H_{26}N_2O \cdot C_4H_4O_4$	A–P	79	118–121	Mal	C, H, N	+	+	0	0
31	Ph	*n*-Bu	H	NHMe	3	L	$2(C_{22}H_{28}N_2O) \cdot C_4H_4O_4$	Ip–A	71	173–175	Fum	C, H, N	++	0	+	+++
32	Ph	*n*-Bu	H	NMe_2	3	I	$C_{23}H_{30}N_2O \cdot C_4H_4O_4$	C–A	50	144–145	Mal	C, H, N	+	0	0	++
33	Ph	$PhCH_2$	H	NHMe	3	G	$C_{25}H_{26}N_2O \cdot C_2H_2O_4$	E	40	162–165	Ox	C, H, N	+	0	0	0
34	Ph	$PhCH_2$	H	$N(Me)(CH_2 \cdot Ph)$	3	J	$C_{32}H_{32}N_2O \cdot C_2H_2O_4$	Ip	80	158–160	Ox	C, H, N	0	0	0	0
35	Ph	Ph	H	NMe_2	3	I, J	$C_{25}H_{26}N_2O \cdot HCl$	Ip–A	67	240.5–242	HCl	C, H, N	++	0	+	++
36	Cyclohexyl	Me	H	NHMe	3	H	$C_{19}H_{28}N_2O \cdot HCl$	Ip	10	192–195	HCl	C, H, N	0	0	0	0
37	Cyclohexyl	Me	H	NMe_2	3	J	$C_{20}H_{30}N_2O \cdot HCl$	Ip	80	207–208	HCl	C, H, N	0	0	+	0
38	Ph-CH_2	Me	H	NMe_2	3	J	$C_{21}H_{26}N_2O \cdot C_2H_2O_4$	Ip	10	138–141	Ox	C, H, N	+++	0	0	++
39	Me	Ph	H	NHMe	3	J	$C_{19}H_{22}N_2O \cdot C_2H_2O_4 \cdot H_2O$	Ip	25	130–132	Ox	C, H, N	++	0	0	0

[a-b] See footnotes *a*, *b*, Table I. [c] Mal = maleate; Fum = fumarate; Ox = oxalate. [d] Amphetamine = potentiation of (±) amphetamine excitation. TBZ = reversal of tetrabenazine sedation. Reserpine = antagonism of reserpine hypothermia. Norepinephrine = antagonism of norepinephrine hypothermia.

Scheme I



of **64**. The proton 7 of the indolinone ring in all cases showed ortho and para coupling (8.3 ppm, 7 H, quartet, $J_{4,7}$ = 1.5 Hz, $J_{6,7}$ = 7.5 Hz).

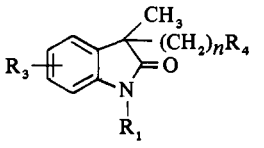
The branched-chain secondary amine **25** was prepared by Michael addition of methyl vinyl ketone to indolinone V (R_1 = Ph; R_2 = Me) to give ketone **70** (Table IV), followed by reductive amination with $MeNH_2$.

The N-demethylation procedure (method H) was that of Bickelhaupt, *et al.*,[26] *via* urethanes VII (R_5 = CO_2Et; R_6 = Me) to give VII (R_5 = H; R_6 = Me). Alkaline treatment of the urethane VII (R_5 = CO_2Et; R_6 = Me; n = 2) gave a nonbasic product which was isomeric with the expected indolinone **4** (Table III). Its ir spectra showed amide carbonyl absorption at 1665 cm^{-1} (KBr) but not the typical absorption of the 2-indolinones at 1710–1720 cm^{-1}. It gave a deep blue color similar to that shown by diphenylamines when sprayed with a mixture of HNO_3 and H_2SO_4 whereas indolinones give a yellow coloration with this reagent. On the basis of this evidence, the pyrrolidone structure VIII was assigned to this substance. Clearly, the indolinone ring had opened under basic conditions and recyclization had taken place on the side-chain nitrogen.[27-30] The fact that this reaction does not occur with alkaline hydrolysis of VIII (R_5 = CO_2Et; R_6 = Me; n = 3) when the expected secondary amine **11** was produced provides a good example of the preference for formation of 5- rather than 6-membered rings.

The indolines IX (Table V) were prepared by reduction of the corresponding tertiary aminoalkyl-2-indolinones VII (methods P, Q), followed by removal of one of the nitrogen substituents when secondary amines were required. N-Debenzylation (method G) proceeded smoothly, but in the urethane procedure (method H) for N-demethylation of indolines, it was essential to use basic conditions for the hydrolysis and decarboxylation since indolines are unstable to strong acid treatment.

Reduction of the nitriles VI and secondary amines VII (R_5 = H; R_6 = Me; n = 2 and 3) with LAH resulted in the intermediate formation of the tricyclic systems X and XI

Table IV



No.	R_1	R_3	R_4	n	Method	Cryst solvent[a]	Mp, °C	Yield, %	Formula	Analyses
66	Ph	H	CN	1	D, I	E-P	112–113.5	80	$C_{17}H_{14}N_2O$	C, H, N
67	Ph	H	CN	2	E	B-P	111.5–112.5	85	$C_{18}H_{16}N_2O$	C, H, N
68	Ph	H	CN	3	D, I	E-P	109.5–110	76	$C_{19}H_{18}N_2O$	C, H, N
69	Ph	5-MeO	CN	2	E	E-P	90–92	78	$C_{19}H_{20}N_2O_2$	C, H, N
70	Ph	H	$COCH_3$	2	E	E	110–112	95	$C_{19}H_{19}NO_2$	C, H, N

[a] See footnote *a*, Table I.

(R_6 = H and Me, respectively), which on catalytic reduction yielded indolines IX. The structures of X and XI followed from their nmr spectra which showed a strongly deshielded singlet in the region of δ 5.0, assignable to the methine proton adjacent to the two nitrogen atoms of the fused heterocyclic systems. Structures X and XI presumably arise from participation of the side-chain amino group during the reduction of the indolinone ring. Systems X and XI have the same carbon skeleton as physostigmine, but they were devoid of interesting biological activity.

Pharmacology. The pharmacological investigations were based on the premise that the clinical activity of antidepressant drugs is a consequence of the potentiation of adrenergic mechanisms. Consequently, antidepressant activity was assessed by the ability of compounds to potentiate (±)-amphetamine excitation in rats,[31] to reverse the sedative action of tetrabenazine in rats,[3a] and to antagonize reserpine- and norepinephrine-induced hypothermia in mice.[32] DMI, amitriptyline, and protriptyline were used as reference compounds. In addition, the more interesting compounds were further examined in chloralosed cats for a potentiating effect on the contraction of the nictitating membrane produced by electrical stimulation of the preganglionic sympathetic nerve trunk or by epinephrine, norepinephrine, and 5-hydroxytryptamine (5-HT). Brief descriptions of procedure and rating system are given in the Experimental Section, and the results for the first four of these biological assays on test compounds are given in Tables III and V.

Structure-Activity Relationships. The results for test compounds are shown in Tables III and V from which it can be seen that the SAR of the indolinone and indoline series run in parallel. The most active compounds were **10**, **11**, **12**, **14**, **26**, **27**, **41**, **43**, and **44** with **11** and **44** being outstanding. The optimal side-chain structure was clearly $(CH_2)_3NHMe$ or alternatives which are readily metabolized to this [*e.g.*, $(CH_2)_3NMe_2$ and $(CH_2)_3N(Me)CH_2Ph$]. Side-chain branching reduced activity (*cf.* **25** with **11**). All compounds with heterocyclic terminations to the side chain were of very low activity (*e.g.*, **15**, **16**, **17**), and these were also devoid of tranquillizing properties. Substitution of the aromatic ring of the indolinone nucleus (**18–24**, **46**, and **47**) invariably reduced potency. The second substituent at position 3 had to be small. Thus increasing the size from methyl (**11**, **44**) to butyl (**31**, **50**), benzyl (**33**, **34**), or phenyl (**35**) caused marked reductions of activity. Finally the substituent on the heterocyclic nitrogen atom had to be phenyl (*cf.* **36–39**).

The structural requirements for optimal activity strongly recall those of the established antidepressants. Compounds **11** and **44** are compared with standard antidepressants in Table VI. Compound **44** was inactive in tests for potentiation of the contractions of the nictitating membrane, but 4 hr after dosing, pronounced potentiations were seen which lasted for 18 hr. This suggests the involvement of a metabolite, but studies of the metabolism of **44** to date have not provided any confirmatory evidence. Compounds **11** and **44** clearly possess activity in all the "antidepressant" tests shown in Table VI, in most cases of comparable degree to the standard drugs. In the final two columns of Table VI, **11** and **44** are shown to have appreciably lower antihistaminic and anticholinergic activity than the tricyclic antidepressants. It is these two properties of the latter which are thought to contribute to their clinical side effects such as dry mouth, constipation, blurring of vision, and postural hypotension.[3-7] In other tests, not detailed here, neither **11** nor **44** showed any properties typical of tranquillizing agents (*e.g.*, in conditioned avoidance response and EEG arousal), and both drugs are devoid of MAO inhibitory activity.

It was considered on the basis of all this evidence that **11** and **44** achieved our original objectives as far as can be assessed in experimental animals and both drugs have been submitted for clinical evaluation in man as antidepressant agents.

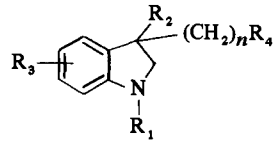
Experimental Section

Where analyses are indicated only by symbols of the elements, results obtained for those elements were within ±0.4% of the theoretical values. Boiling points and melting points (Electrothermal capillary melting point apparatus) are uncorrected. Infrared spectra were measured with a Perkin-Elmer Infracord, uv spectra with a Perkin-Elmer Ultracord, and nmr spectra with a Varian A-60 (Me_4Si as internal standard).

Method A. *N*-(2-Chloroacyl)diphenylamines (IV). To diphenylamine (1.352 kg, 8 moles) in PhH (4 l.) was added 2-chloropropionyl chloride (1.270 kg, 10 moles) over 70 min with stirring. An exothermic reaction occurred at first, the temperature rising to 56°, and diphenylamine hydrochloride separated. The mixture was heated to reflux for 4 hr, with a copious evolution of HCl in the first 2 hr. The clear reaction mixture was evaporated to dryness, and the oily residue was stirred with 60–80° petr ether (5 l.). *N*-(2-Chloropropionyl)diphenylamine (53) separated as a cream-colored cryst solid. This was washed with 60–80° petr ether (750 ml) and the dried solid, 1.9 kg, mp 90–93°, was used without further purification. A small sample was recrystd from 80–100° petr ether.

Method B. 3-Methyl-1-phenyl-2-indolinone (58) (Stolle Cyclization[23]). *N*-(2-Chloropropionyl)diphenylamine (520 g, 2 moles) and $AlCl_3$ (570 g, 4.27 moles) were mixed and gently heated with hand stirring. When the temp reached 50° a vigorous reaction started and without further heating the temp rose to 140°. The mixture foamed as HCl was evolved and when this ceased it was heated to 160–175° for a few minutes and then allowed to cool to 90°. The syrup was poured into a mixture of ice (1 kg) and concd

Table V



No.	R_1	R_2	R_3	R_4	n	Method	Formula	Cryst solvent[a]	Yield, %	Mp or bp (mm), °C	Salt[b]	Analyses	Amphet	TBZ	Res	Nor
40	Ph	Me	H	NMe_2	1	P	$C_{18}H_{22}N_2 \cdot C_4H_4O_4$	Ip	93	155–157	Mal	C, H, N	0	0	+	++
41	Ph	Me	H	NMe_2	2	P	$C_{19}H_{24}N_2 \cdot C_4H_4O_4$	Ip–W	85	140–142	Mal	C, H, N	++++	0	+++	+++
42	Ph	Me	H	N(Me)(CH_2-Ph)	2	P	$C_{25}H_{28}N_2$	P	98	75–78		C, H, N	+++	0	+	+
43	Ph	Me	H	NMe_2	3	P	$C_{20}H_{26}N_2 \cdot C_4H_4O_4$	Ip	96	124–127	Mal	C, H, N	++++	+	+	++
44	Ph	Me	H	NHMe	3	G, H_{ii}, Q	$C_{19}H_{24}N_2 \cdot C_7H_8O_3S$	B	98	122–122.5	TsOH	C, H, N, S	++++	++	++	+++
45	Ph	Me	H	N(Me)(CH_2·Ph)	3	P	$C_{26}H_{30}N_2$		85	204–206 (0.2)		C, H, N	++++	0	+++	++
46	Ph	Me	5-MeO	NHMe	3	H_{ii}, Q	$C_{20}H_{26}N_2O \cdot HCl$	Ip	33	162–164	HCl	C, H, N, Cl	+++	0	0	0
47	Ph	Me	5-MeO	NMe_2	3	P	$C_{21}H_{28}N_2O \cdot HCl$	E–Et	95	210–213	HCl	C, H, N, Cl	++++	0	0	++
48	Ph	*n*-Bu	H	NHMe	2	H_{ii}	$C_{21}H_{28}N_2 \cdot C_4H_4O_4$	C–A	50	153–156	Mal	C, H, N	+++	0	+	+
49	Ph	*n*-Bu	H	NMe_2	2	P	$C_{22}H_{30}N_2 \cdot C_4H_4O_4$	Ip–C–A	55	176–179	Fum	C, H, N	+++	0	++	+
50	Ph	*n*-Bu	H	NHMe	3	H_{ii}, Q	$C_{22}H_{30}N_2 \cdot C_2H_2O_4$	Ip–M	75	166–168	Ox	C, H, N	++++	0	+	++++
51	Ph	*n*-Bu	H	NMe_2	3	P	$C_{23}H_{32}N_2 \cdot C_2H_2O_4$	Ip–M	68	165–168	Ox	C, H, N	++++	0	++	++

[a]See footnote *a*, Table I. [b]See footnote *c*, Table III. [c]See footnote *d*, Table III.

Table VI

Test Compound	Potentiation amphetamine excitation	Reversal tetrabenazine sedation	Antagonism reserpine hypothermia	Antagonism norepinephrine hypothermia	Contraction of nictitating membrane in chloralosed cats Potentiation factors					Antihistamine	Anticholinergic (guinea pig ileum)
					Electric stimulation	Norepinephrine	Epinephrine	Tyramine	5-HT		
Imipramine	++++	+++	++++	+++	3	1	3	1	2	7.6	6.7
Desmethyl-imipramine	++++	+++	++++	++++	10	3	2	1	4	7.1	6.7
Amitriptyline	+++	+	++++	+++	7	3	1	1	1		8.4
11	++	++	++++	++++	6	4	4	10	3	5.9	5.8
44	++++	++	++	+++	1	1	1	1	1	6.3	6.0

HCl (600 ml). The sticky solid which separated was extd into CH_2Cl_2. These extracts were evapd to yield an oil which was triturated with 40–60° petr ether. The resultant solid was recrystd from 80–100° petr ether–EtOH, yield 413.5 g.

Method C. 3-Methyl-1-phenyl-2-indolinone (58). *N*-(2-Chloropropionyl)diphenylamine (161 g) was dissolved in methyl cyclohexane (400 ml) and $AlCl_3$ (176 g) was added over a few minutes. The reaction mixture was carefully heated (exothermic at 30°) under reflux for 2.5 hr, then cooled and poured into ice and concd HCl (500 ml) with stirring. The granular solid which separated was recrystd from petr ether–EtOH, yield 126 g.

3-Benzyl-1-phenyl-2-indolinone (61). 3-Benzylidene-1-phenyl-2-indolinone (17 g)[23] was dissolved in hot EtOAc (200 ml) and hydrogenated at 3 atm and 50° over 10% Pd/C (700 mg) until uptake ceased. The mixture was filtered and evaporated, whereupon 61 solidified, yield 15.5 g (91%), mp 86–88°. A small portion was recrystd from *i*-PrOH, mp 90–94°.

5-Bromo-3-methyl-1-phenyl-2-indolinone (64). A mixture of bromine (8 g, 0.05 mole), KBr (12 g), and H_2O (20 ml) was added fairly rapidly to a hot solution of 3-methyl-1-phenyl-2-indolinone (11.15 g, 0.05 mole) in 50% aqueous dioxan (150 ml). The reaction was almost instantaneous. The solvents were evaporated to give an oily solid which was twice recrystd from ethanol to give 64 as colorless plates, yield 5 g (33%), mp 112–115°.

Method D. 3-Cyanomethyl-3-methyl-1-phenyl-2-indolinone (66). To a suspension of NaH (2.64 g, 0.11 mole) in THF (100 ml) was added 3-methyl-1-phenyl-2-indolinone (58) (22.3 g, 0.1 mole) in small portions with vigorous stirring. When the effervescence had ceased, the reaction mixture was warmed to reflux for 0.5 hr, after which time the solution was cooled. Chloroacetonitrile (8.2 g, 0.11 mole) in THF (50 ml) was added with stirring, and the mixture was heated under reflux for a further 2 hr. Evaporation of the solvent left a syrupy material which was poured into water. This was neutralized with dil AcOH and extracted into Et_2O. After the usual treatment of the extracts the remaining oil slowly crystd. The solid 66 was recrystd from 40–60° petr ether, yield 21 g.

Method E. 3-(2-Cyanoethyl)-3-methyl-1-phenyl-2-indolinone (67). 3-Methyl-1-phenyl-2-indolinone (58) (22.3 g, 0.1 mole) was dissolved in dioxane (250 ml), and a few drops of 40% alcoholic solution of Triton B were added, followed by acrylonitrile (7.8 g, 0.15 mole) in small portions. The mixture was heated under reflux for 3–4 hr, the solvent removed under reduced pressure, and the resultant oil, which solidified on standing, was then dissolved in PhH. The solution was decolorized with charcoal and hot 40–60° petr ether was then added, whereupon colorless crystals of 67 separated, yield 23.3 g.

Method F. 3-(2-Aminoethyl)-3-methyl-1-phenyl-2-indolinone (3). 3-Cyanomethyl-3-methyl-1-phenyl-2-indolinone (66) (45 g, 0.17 mole), dissolved in a mixture of glacial AcOH (250 ml) and concd H_2SO_4 (5 ml), was hydrogenated at 3 atm and 50° over PtO_2 (0.5 g) until the uptake of H_2 had ceased. The catalyst was filtered and the solution was concd *in vacuo*, basified with Na_2CO_3 soln, and extracted with ether. The extracts were dried over Na_2CO_3, filtered, and treated with an ethereal solution of HCl gas. The hydrochloride of 3 precipitated and was recrystd from EtOAc and *i*-PrOH–EtOAc to give colorless crystals, yield 36.2 g.

Method G. 3-Methyl-3-(2-methylaminoethyl)-1-phenyl-2-indolinone (4). 3-[2-(*N*-Benzyl-*N*-methylamino)ethyl]-3-methyl-1-phenyl-2-indolinone (7) (164 g, 0.4 mole) was dissolved in abs EtOH (650 ml), and a solution of $PdCl_2$ (6 g) in H_2O (40 ml) containing NaCl (4 g) was added. The mixture was cautiously treated with a solution of $NaBH_4$ (6 g) in H_2O (40 ml) over a period of 10 min with stirring. Stirring was continued for a further 15 min, and the mixture was then adjusted to pH 1 with concd HCl. The mixture was hydrogenated at 3 atm and 60° for 16 hr and filtered, and the solvent was removed under reduced pressure. The residual oil was dissolved in H_2O (250 ml), basified with 5 *N* NaOH, and extracted into Et_2O (4 × 200 ml). The dried extracts ($MgSO_4$) were treated with dry HCl and the resultant gum solidified by trituration with Me_2CO. The product was filtered, washed with Me_2CO and Et_2O, and dried at room temperature *in vacuo* to give 4 (HCl) as a white solid, 95 g. It was recrystd from *i*-PrOH–EtOAc.

Method H. 3-Methyl-3-(3-methylaminopropyl)-1-phenyl-2-indolinone (11). 3-(3-Dimethylaminopropyl)-3-methyl-1-phenyl-2-indolinone (12) (10 g) was dissolved in xylene (40 ml) at 60° and ethyl chloroformate (10 ml) was added. The temperature was kept below 65° by cooling in order to control the exothermic reaction. A gas was evolved and a small amount of gum precipitated. The reaction was kept at 60–70° for 1 hr and then a further 10 ml of ethyl chloroformate was added and the reaction was maintained at 60–70° for a further 1–1.5 hr. The excess of acid chloride was boiled off, xylene being added during this process to keep the volume of the reaction mixture constant. The mixture was boiled under reflux (130°) for 4 hr, cooled, and extracted with 1 *N* HCl and water. It was then dried over $MgSO_4$ and evaporated to give 3-(*N*-ethoxycarbonyl-3-methylaminopropyl)-3-methyl-1-phenyl-2-indolinone (8.3 g) as a syrup. This derivative could be hydrolyzed under acidic or basic conditions.

(i) Acidic Hydrolysis (Used with Indolinones). The *N*-ethoxycarbonyl compound was dissolved in glacial AcOH (30 ml) and 48% aqueous HBr (20 ml) and the solution boiled under reflux for 4–5 hr. The dark solution was evaporated to dryness *in vacuo* to give a syrup which was dissolved in water and this mixture was extd with ether to remove 4.5 g of unchanged urethane. The aqueous layer was basified with 5 *N* NaOH and the oil which separated was extd into ether and converted to the hydrochloride of 11 in the usual way. It was recrystd from $CHCl_3$–EtOAc as an off-white solid, 1.6 g.

(ii) Basic Hydrolysis (Used with Indolines). The *N*-ethoxycarbonyl derivative of 44 (10 g) was dissolved in *n*-BuOH (50 ml) and 20% aqueous KOH (30 ml). The mixture was vigorously stirred and heated under reflux for 10 hr. The solvents were then evaporated *in vacuo*, the separated oil was extracted into ether, and the amine was separated from unchanged material by means of an acid–base extraction cycle. The resultant base was converted into the *p*-toluenesulfonate of 44 in ether solution. It was recrystd from PhH (11.5 g).

Method I. 3-(3-Dimethylaminopropyl)-3-methyl-1-phenyl-2-indolinone (12). 3-Methyl-1-phenyl-2-indolinone (58) (22.3 g, 0.1 mole) in dry toluene (50 ml) was added slowly to $NaNH_2$ (4.68 g, 0.12 mole) in dry toluene (200 ml). The mixture was heated under reflux for 3 hr, by which time the evolution of NH_3 had ceased. Dimethylaminopropyl chloride (21 g, 0.173 mole, from 31 g of the corresponding hydrochloride) was added to the cooled toluene solution. The mixture was then boiled under reflux for 3 hr, cooled, and poured into H_2O. The aqueous layer was extd with Et_2O, the extracts combined with the toluene layer, and the mixture subjected to an acid–base cycle. The resultant dark oil was distilled at 190–200° (1 mm) (22.5 g, 73%). The hydrochloride of 12 was a colorless solid which after two recrystn ($CHCl_3$–EtOAc and EtOAc–MeOH) had mp 168–170° and contained 1 mole of water.

Method J. 3-Benzyl-3-[3-(*N*-benzyl-*N*-methylaminopropyl)]-1-phenyl-2-indolinone (34). Indolinone 61 (15 g, 0.05 mole) was dissolved in dry DMF (60 ml) and treated carefully with NaH (1.2 g, 0.05 mole) at 60°. 3-(*N*-Benzyl-*N*-methylamino)propyl chloride (9.9 g, 0.05 mole) was added, and the mixture was heated to 60° for 4 hr. It was allowed to cool, poured into water, and ether extracted. The organic extract was washed with water, dried, and evaporated to give an oil which was treated with oxalic acid in Et_2O to yield colorless crystals of 34 hydrogen oxalate. It was recrystd three times from *i*-PrOH.

Method K. 3-(3-Benzylaminopropyl)-3-methyl-1-phenyl-2-indolinone (13). A mixture of 3-methyl-3-(3-aminopropyl)-1-phenyl-2-indolinone (10) (21 g, 0.075 mole) and benzaldehyde (8 g, 0.08 mole) in dry xylene (100 ml) was heated under reflux for 3 hr with continuous removal of the water formed during the reaction (Dean–Stark). The solvent was evaporated *in vacuo* and the residual oil was dissolved in EtOH (100 ml) and cooled to 5°. A solution of $NaBH_4$ (8 g) in H_2O (20 ml) containing 2 *N* NaOH (1 ml) was added with stirring and the mixture was allowed to stand overnight. The EtOH was removed *in vacuo* and the resultant oil was extracted into Et_2O. The extracts were subjected to an acid–base cycle and the organic base was obtained as a yellowish oil (19 g). This was treated with maleic acid, and the resultant hydrogen maleate salt of 13 was recrystd from *i*-PrOH–EtOAc to give colorless crystals (19.4 g).

Method L. 3-*n*-Butyl-3-(3-methylaminopropyl)-1-phenyl-2-indolinone (31). A mixture of 3-(3-aminopropyl)-3-*n*-butyl-1-phenyl-2-indolinone (30) (18.2 g, 0.0566 mole) and benzaldehyde (6.36 g, 0.06 mole) in dry PhH (200 ml) was heated under reflux with azeotropic removal of the water until the calculated quantity had been collected. The reaction was evaporated to a thick oil which crystallized slowly on standing. Trituration of the semicrystalline mass with 60–80° petr ether gave a colorless solid which was recrystd from 60–80° petr ether–$CHCl_3$ to yield pure 3-*n*-butyl-3-(3-benzylideniminopropyl)-1-phenyl-2-indolinone. This compound (20 g, 0.05 mole) and methyl iodide (70 ml) were heated at 100° in a pressure vessel for 5–6 hr. The reaction mixture was evaporated *in vacuo* and the residual oil was extracted into Et_2O and subjected to an acid–base cycle. The resultant oil distilled at 206–210° (1 mm)

was converted to the neutral fumarate salt of 31 and recrystd from *i*-PrOH–EtOAc to give colorless crystals, yield 10.4 g.

3-(3-Methyl-3-methylaminopropyl)-3-methyl-1-phenyl-2-indolinone (25). A mixture of 3-methyl-3-(3-oxobutyl)-1-phenyl-2-indolinone (70) (59.3 g, 0.2 mole), $MeNH_2$ (33% soln in EtOH, 94 ml, 2 moles), Raney Ni W2 (2 ml), and EtOH (250 ml) was hydrogenated at 75 atm, 100° for 40 hr. The filtered reaction mixture was evaporated and the residue worked up in the usual way. The resultant syrup was triturated with *i*-PrOH and recrystd from *i*-PrOH–EtOAc to give 25 as colorless crystals, 50.5 g.

Method M. 3-Methyl-3-(3-piperidinopropyl)-1-phenyl-2-indolinone (15). A solution of 3-methyl-1-phenyl-2-indolinone (58) (22.3 g, 0.1 mole) in toluene (100 ml) was added to a suspension of NaH (2.4 g, 0.1 mole), and the mixture was heated under reflux until the hydride had reacted. To the cooled reaction mixture 1,3-dibromopropane (40.4 g, 0.2 mole) was added. The resultant solution was heated under reflux for 4 hr, cooled, and poured into water, neutralized with a little HCl, washed with water, and concentrated *in vacuo* to a thick oil. The excess of dibromopropane was distilled off at 110° (0.1 mm). The residual oil could not be purified by fractional distillation or crystallization and it was used directly for alkylations after analysis of the active bromine. Piperidine (17 g, 0.1 mole) was added to the oil (30 g) in EtOH and the mixture was heated under reflux for 5 hr and evaporated *in vacuo* to yield an oil. This was dissolved in H_2O, acidified with HCl, and extracted with Et_2O. The aqueous phase was basified with 5 *N* NaOH and extracted with Et_2O. The extracts were washed with water, dried, and evaporated *in vacuo* to remove the excess of piperidine. The residual oil was converted to the hydrogen oxalate of 15 and recrystd twice from MeOH–EtOH, yield 20 g.

Method N. 3-Methyl-3-[3-(4-methyl-1-piperazino)propyl]-1-phenyl-2-indolinone (16). A mixture of 3-methyl-3-(3-dimethylaminopropyl)-1-phenyl-2-indolinone (12) (3.08 g, 0.01 mole), 1-methylpiperazine (2 g, 0.02 mole), and *n*-BuOH (50 ml) was heated under reflux for 5 hr. The Me_2NH formed was removed with a stream of N_2 and the reaction mixture was evaporated *in vacuo* to give an oil. After washing with water and extraction into ether, the extracts were dried and treated with an ethereal solution of maleic acid to give the dimaleate salt of 16 as a white solid which was recrystd from EtOH–H_2O, yield 3 g, 43%.

Method O. 3-Dimethylaminomethyl-3-methyl-1-phenyl-2-indolinone (1). To a cooled (10°) mixture of formalin (11.3 ml, 40%, 0.15 mole) and dimethylamine (26.7 ml, 33% in ethanol, 0.15 mole), 3-methyl-1-phenyl-2-indolinone (58) (22.3 g, 0.1 mole) in EtOH (50 ml) was added. The mixture was allowed to stand at room temperature for 24 hr, after which it was acidified with HCl and the solvents were evaporated. The residual oily material was acid–base extracted and the resultant oil was distilled *in vacuo* to give 1, bp 164–168° (0.3 mm), yield 15 g, 58%. This oil solidified overnight and was recrystd from 40–60° petr ether, mp 58–61°. The hydrochloride of 1 was recrystd from $CHCl_3$–EtOAc.

1-Methyl-3-phenyl-2-indolinone and 3-(3-Dimethylaminopropyl)-1-methyl-3-phenyl-2-indolinone. These compounds were obtained according to methods described in the literature[33,34] and were intermediates in the preparation of 39.

5-Chloro-3-methyl-3-(3-methylaminopropyl)-1-phenyl-2-indolinone (18). Sulfuryl chloride (4.1 g, 0.03 mole) in glacial AcOH (10 ml) was added to a cooled solution of the hydrochloride of 11 (10 g, 0.03 mole) in glacial AcOH (100 ml), the temperature being maintained below 20°. The mixture was stirred at room temperature for 2 hr, evaporated, basified, and extracted into ether. The dried ethereal solution was treated with HCl gas and the precipitated oil solidified by trituration with dry Et_2O. The solid was recrystd from *i*-PrOH–60–80° petr ether to give colorless crystals of 18·hydrochloride, 6.3 g, nmr ($CDCl_3$) δ 6.85 (7 H, quartet, $J_{4,7}$ = 1.5 Hz, $J_{6,7}$ = 7.5 Hz).

5-Bromo-3-methyl-3-(3-methylaminopropyl)-1-phenyl-2-indolinone (19). To a cooled and stirred solution of 11·HCl (33 g, 0.01 mole) in glacial AcOH (30 ml) was added a solution of Br_2 (1.60 g) in glacial AcOH (5 ml). The mixture was allowed to stand at room temperature for 30 min, after which it was evaporated, basified, and extracted with Et_2O. When the dry ethereal extract was treated with dry HCl gas, an oil precipitated which solidified on trituration with Et_2O. The solid was recrystd from *i*-PrOH–EtOAc to give 19 (HCl) as colorless crystals, 2.9 g, nmr ($CDCl_3$) δ 6.83 (7 H, quartet, $J_{4,7}$ = 1.5 Hz, $J_{6,7}$ = 7.5 Hz).

Method P. 3-(3-Dimethylaminopropyl)-3-methyl-1-phenylindoline (43). Indolinone 12 (25 g, 0.081 mole) in Et_2O (250 ml) was added, over 0.5 hr, to an ice-cooled suspension of LAH (5 g, 0.132 mole) in Et_2O (250 ml). The reaction mixture was heated under reflux for 9 hr, cooled in ice, and carefully treated with H_2O (5 ml) followed by 5 *N* NaOH (5 ml). The mixture was filtered, and the residue washed with Et_2O. The filtrate was dried (Na_2CO_3) and evapd. The residual oil 43 (24 g) was converted to the colorless crystalline hydrogen maleate salt, yield 31.9 g.

Method Q. 3-Methyl-3-(3-methylaminopropyl)-1-phenylindoline (44). Indolinone 11 (40 g, 0.136 mole) in THF (400 ml) was placed in a flask fitted with an inlet from a diborane generator. The B_2H_6 generator was charged with $NaBH_4$ (95 g, 2.5 moles) and dimethyl digol (600 ml). After a preliminary purge of the apparatus for 15 min with N_2, the cautious addition of boron trifluoride diethyl etherate (440 ml, 3.5 moles) to the generator was commenced with strong ice cooling. The generation of B_2H_6 took 3 hr and at the end of this period the apparatus was purged with N_2 for 0.5 hr and the THF solution in the reaction vessel was heated under reflux for 1 hr. The solution was then cooled in ice and cautiously treated with 5 *N* HCl (100 ml). The solvents were removed *in vacuo* leaving a thick, colorless oil, which was dissolved in hot water (300 ml), cooled to room temperature, basified with 5 *N* NaOH (200 ml), and extracted with Et_2O. The extracts gave on evaporation 44 as an oil (39 g). This was converted to the *p*-toluenesulfonate salt in Et_2O when it precipitated as an oil. This was dissolved in PhH (250 ml), evaporated to half-volume, and allowed to cool. 44·*p*-toluenesulfonate (56 g) crystd slowly.

1,3-Dimethyl-3-(2-phenylaminophenyl)pyrrolid-2-one (VIII). To indolinone 4 (3.18 g, 0.01 mole) in *n*-BuOH (25 ml), KOH (1 g, 0.018 mole) in water (1 ml) was added, and the mixture was heated under reflux for 5 hr. The solvents were evapd *in vacuo* and the residue was taken up in water, partially neutralized with HCl, and extracted with Et_2O. The extracts were evapd to give VIII as a white solid which was recrystd from EtOH, yield 2.9 g, mp 129–130°, ν_{max}^{KBr} (cm^{-1}) 3270 (NH), 1665 (C=O cyclic amide), nmr ($CDCl_3$, deuterated base), δ 1.56 (3, CH_3, singlet); δ 2.85 (1, *N*-Me, singlet); δ 3.33 (5, CH_2, triplet); δ 1.7–2.8 (4, CH_2, two sets of multiplets). *Anal.* ($C_{18}H_{20}N_2O$) C, H, N.

3a-Methyl-8-phenyl-2,3,3a,8a-tetrahydropyrrolo[2,3-*b*]indole (Xa) (R_6 = H). Indolinone 66 (26.23 g, 0.1 mole) in Et_2O (300 ml) was heated and stirred under reflux. To this solution was added a suspension of LAH (7.6 g, 0.2 mole) in Et_2O (200 ml) over a period of 0.5 hr. The mixture was then heated under reflux for a further 10 hr. The reaction mixture was worked up by the cautious addition of water (7.6 ml) followed by 5 *N* NaOH (7.6 ml). The filtered solution was evaporated to dryness to give a light yellow oil (25.3 g) which was dissolved in dry Et_2O. To this solution, ethereal oxalic acid was added and the precipitated oxalate was recrystd twice from EtOAc–*i*-PrOH and *i*-PrOH–EtOH to yield X (R_6 = H) as a white crystalline hydrogen oxalate, 15 g (44%), mp 175.5–177°, nmr ($CDCl_3$, deuterated base), δ 1.5 (3a, CH_3, singlet); δ 5.14 (8a, H, singlet). *Anal.* ($C_{17}H_{18}N_2 \cdot C_2H_2O_4$) C, H, N.

1,3a-Dimethyl-8-phenyl-2,3,3a,8a-tetrahydropyrrolo[2,3-*b*]indole Picrate (Xb) (R_6 = Me). To a refluxing and stirred solution of indolinone 4 (5.8 g, 0.02 mole) in Et_2O (150 ml) a suspension of LAH (1.05 g, 0.027 mole) was added over a period of 0.3 hr, after which the mixture was heated under reflux for a further 10 hr. The complex was destroyed by the careful addition of water (1 ml) followed by 5 *N* NaOH (1 ml). The filtered solution was evaporated to dryness, the residue (5.3 g) was dissolved in dry EtOH, and the picrate was precipitated by the addition of alcoholic picric acid (6 g). The crystalline picrate was recrystd from EtOH–H_2O, yield 3 g, mp 145–147°, nmr ($CDCl_3$) base, δ 5.14 (8a, H, singlet). *Anal.* ($C_{18}H_{20}N_2 \cdot C_6H_3N_3O_7$) C, H, N.

1-Benzyl-4a-methyl-9-phenyl-1,2,3,4,4a,9a-hexahydro(9*H*)pyrido[2,3-*b*]indole (XIb) (R_6 = CH_2Ph). Indolinone 10 (21 g, 0.075 mole) in dry xylene (100 ml) and benzaldehyde (8 g) were heated under reflux for 3 hr while the H_2O formed was continuously removed (Dean–Stark). The reaction mixture was then concd *in vacuo* and the residue dissolved in dry Et_2O (125 ml). This ethereal solution was added to a refluxing and stirred solution of LAH (5 g) in dry Et_2O (150 ml). The mixture was heated under reflux for a further 3 hr and the complex was destroyed by the careful addition of H_2O (5 ml) followed by 5 *N* NaOH (5 ml). The filtered solution was evapd to give an oil which was distilled at bp 200–205° (0.04 mm). The oil crystd on standing and it was recrystd from ether–40–60° petr ether, yield 10 g (31%), mp 109–112°, nmr ($CDCl_3$) δ 4.77 (9a, H, singlet); δ 3.65 (1-NCH_2Ph, singlet); δ 1.5 (4a, CH_3, singlet); δ 6.35–6.65 (8, H, multiplet). *Anal.* ($C_{25}H_{26}N_2$) C, H, N.

4a-Methyl-9-phenyl-1,2,3,4,4a,9a-hexahydro(9*H*)pyrido[2,3-*b*]indole (XIa) (R_6 = H). Indolinone 10 was reduced with LAH in the same way as described for compound Xa. The residual oil was distilled at 200–220° (0.2 mm), yield 2 g (76%). It solidified after

standing and was recrystd from petr ether, mp 65.5°, nmr δ 4.77 (9a, H, singlet), δ 1.5 (4a, CH_3, singlet). *Anal.* ($C_{18}H_{20}N_2$) C, H, N.

Pharmacological Tests. a. Potentiation of (±)-Amphetamine Excitation. Male albino rats (180–220 g) were dosed orally with the test compound (25 mg/kg) followed by (±)-amphetamine sulfate (5 mg/kg ip) 1.5 hr later. The potentiation was assessed as described elsewhere[31] and quantified by addition of the half-hourly scores for each group of four treated rats and subtracting from this the total scores of rats given amphetamine only. The results in Table III are expressed as : score of 0–25 = 0; 26–50 = +; 51–75 = ++; 76–100 = +++; >100 = ++++.

b. Reversal of Tetrabenazine Sedation. The method was based on the observations of Sulser, *et al.*[32] Male albino rats (5 groups, 3 per group) were dosed orally with the test compound at 50 mg/kg at 18 hr, and 20 mg/kg at 1.5 hr before ip injection of tetrabenazine hydrochloride (25 mg/kg). Any hyperactivity was noted on a simple presence or absence basis every hour for 5 hr. Tetrabenazine alone produced marked immobility at this dose. A maximum reversal would produce a score of 15/15 active or 100%. Results in Table III are expressed as: 0–25% = 0; 26–50% = +; 51–75% = ++; 76–100% = +++.

c. Antagonism of Reserpine Hypothermia. The method of Askew[32] was used, the oesophageal temperatures being monitored with an electric thermometer.[35] The test compounds were injected ip (10 mg/kg) and the results are expressed in Table III based on the net total increase in mean body temperature: 0–5° = 0; 6–10° = +; 11–15° = ++; 16–20° = +++; 20° and more = ++++.

d. Antagonism of Norepinephrine Hypothermia. The ability of test compounds to reverse the hypothermic response induced by injection of norepinephrine (10 μg) directly into the lateral ventricles of mice was assessed by recording the oesophageal temperature at 15, 30, and 60 min after administration.[36] Norepinephrine alone produces a hypothermia of 2–3°. The results are expressed as percentages of antagonism of this hypothermia: 0–25% = 0; 26–50% = +; 51–75% = ++; 76–100% = +++; >100% = ++++.

Acknowledgments. We thank Messrs. A. G. Davie and D. C. Mills for their able technical assistance and Dr. Emrys R. H. Jones for his interest and encouragement in the course of this work. We are grateful to Mr. P. Brown and his staff for analytical and spectral data and to our colleagues of the Pharmacological Research Department for the biological results.

References

(1) (a) A. Canas-Rodriguez and P. R. Leeming, *Nature (London)*, 223, 75 (1969); (b) Pfizer British Patent 1,154,976 (1969); application filed Feb 21, 1967; (c) S. Toyoshima, W. Hirose, K. Yamatsu, and S. Sohda, *Yakugaku Zasshi*, 90, 1524 (1970).
(2) J. H. Biel, "Drugs Affecting the Central Nervous System," Vol. 2, A. Burger, Ed., Arnold, London, 1968, p 61.
(3) (a) F. Sulser, M. H. Bickel, and B. B. Brodie, *J. Pharmacol. Exp. Ther.*, 144, 321 (1964); (b) K. D. Cairncross, S. Gershon, and I. D. Gust, *J. Neuropsychiat.*, 4, 224 (1963).
(4) D. F. Bogdanski, F. Sulser, and B. B. Brodie, *J. Pharmacol. Exp. Ther.*, 132, 176 (1961).
(5) E. Costa, S. Garratini, and L. Valzelli, *Experientia*, 16, 461 (1960).
(6) R. Domenajoz and W. Theobald, *Arch. Int. Pharmacodyn.*, 21, 450 (1959).
(7) R. C. Rathbun and I. H. Slatter, *Psychopharmacologia*, 4, 114 (1963).
(8) B. Smith and D. J. Prockop, *N. Engl. J. Med.*, 267, 1338 (1962).
(9) A. Coppen, D. M. Shaw, and J. P. Farrell, *Lancet*, 1, 79 (1963).
(10) C. M. B. Pare, *ibid.*, 2, 527 (1963).
(11) A. Coppen, D. M. Shaw, B. Berzberg, and R. Maggs, *ibid.*, 2, 1178 (1967).
(12) B. B. Brodie and P. A. Shore, *Ann. N. Y. Acad. Sci.*, 66, 631 (1957).
(13) N. J. Giarman, *Yale J. Biol. Med.*, 32, 73 (1959).
(14) M. Vogt, *J. Physiol.*, 123, 451 (1954).
(15) T. B. B. Crawford, "5-Hydroxytryptamine: Proceedings of a Symposium," G. P. Lewis, Ed., Pergamon, New York, N.Y., 1958, pp 20–25.
(16) G. G. Brune and H. E. Himwich, *Recent Advan. Biol. Psychiat.*, 5, 144 (1963).
(17) J. Crossland, *West Eur. Symp. Clin. Chem.*, 2, 175 (1962).
(18) N. A. Hillarp, K. Fuxe, and A. Dahlstrom, *Pharmacol. Rev.*, 18, 727 (1966).
(19) H. D. Fabing and J. R. Hawkins, *Science*, 123, 886 (1956).
(20) P. V. Petersen and I. Møeller-Nielsen, *Antidepressant Drugs. Pro Int. Symp. 1st, 1966*, 217 (1967).
(21) T. W. Kissel, *ibid.*, 233 (1967).
(22) G. N. Walker, R. T. Smith, and B. N. Weaver, *J. Med. Chem.*, 8, 626 (1965).
(23) R. Stolle, *Ber.*, 46, 3915 (1913); 47, 2120 (1914).
(24) A. Canas-Rodriguez and J. R. Stichbury, paper in preparation.
(25) P. L. Julian and J. Pikl, *J. Amer. Chem. Soc.*, 57, 539 (1935).
(26) F. Bickelhaupt, K. Stach, and M. Thiel, *Monatsh.*, 95, 485 (1964).
(27) James B. Hendrickson, Thesis, Harvard University, 1954.
(28) K. Freter, H. Weissbach, B. Redfield, S. Udenfriend, and B. Witkop, *J. Amer. Chem. Soc.*, 80, 983 (1958).
(29) E. Wenkert, B. S. Bernstein, and J. H. Udelhofen, *J. Amer. Chem. Soc.*, 80, 4899 (1958).
(30) P. J. Islip and A. C. White, *J. Chem. Soc.*, 120 (1964).
(31) R. M. Quinton and G. Halliwell, *Nature (London)*, 200, 178 (1963).
(32) B. Askew, *Life Sci.*, 2, 725 (1963).
(33) G. Palazzo and V. Rosnatti, *Gazz. Chim. Ital.*, 82, 584 (1952); *Chem. Abstr.*, 47, 12347 (1953).
(34) M. E. Speeter, U. S. Patent 2,759,935 (1956); *Chem. Abstr.*, 51, 2050 (1957).
(35) R. T. Brittain, *J. Pharm. Pharmacol.*, 18, 621 (1966).
(36) P. Cowell and M. J. Davey, *Brit. J. Pharmacol. Chemother.*, 34, 159 (1968).