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Structure–Activity Relationships of 1-[(3-Indolyl)alkyl]-4-arylpiperazines. A New Series of Tranquilizers

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Compounds of a new series of indolylalkylphenylpiperazines have been found active as central nervous system depressants; in general they exhibited properties similar to those of other agents used in the treatment of psychoses. Certain relationships exist between structure and activity. Although these agents possess peripheral adrenolytic activity to the same degree as the phenothiazines and benzodioxanes, no definite correlation could be found between various central activities and peripheral adrenolytic activity.

Various members of a new series of indolylalkylphenylpiperazines synthesized in our laboratories[1] have been found to possess potent central depressant activity. The pharmacological properties of individual compounds differ to some degree, but these properties place this series in the category of major tranquilizers. A large number of these agents has been tested and the relationship between structure and activity studied. Like other groups of potent tranquilizers, the compounds in this series possess some adrenergic blocking activity and the large number of agents tested has allowed a study of the relationship between this and central depressant activity.

Methods.—Potentiation of hexobarbital anesthesia was determined by the method previously described.[2] Male mice weighing 18 to 24 g. were used and at least three dose levels of each drug were tested using 10 mice per dose. The mice were pretreated with the compound orally and 40 min. later a subhypnotic dose of

(1) S. Archer, D. W. Wylie, L. S. Harris, T. R. Lewis, J. W. Schulenberg, M. R. Bell, R. K. Kullnig, and A. Arnold, *J. Am. Chem. Soc.*, in press.

(2) D. W. Wylie, *Proc. Soc. Exptl. Biol. Med.*, **98**, 716 (1958).

hexobarbital sodium (40 mg./kg.) was administered intraperitoneally. The number of mice losing their righting reflex for 1 min. or more was counted over a period of 20 min. and the ED_{50} and its standard error calculated.[3]

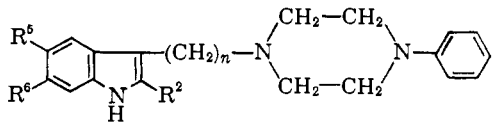
The head-withdrawal reflex resulting when the vibrissae are touched was measured as previously described.[4] The normal mouse withdraws its head instantly when the vibrissae are touched and in this measurement the reflex is considered lost when the mouse does not withdraw its head for 5 or more sec.; at least 3 doses were tested by the oral route using 10 mice per dose. The reflex was tested at half-hour intervals for 2 hr. The rhesus monkeys used in these studies were held on chains in individual observation chambers which provided adequate space for unrestricted movement and climbing. The rectal temperature was determined before medication and at hourly intervals thereafter. Reduced locomotion and closing of the eyes, accompanied by a fall in rectal temperature of at least 0.6° was considered to be sedation; if the monkey allowed approach of the observer and handling without aggressiveness it was considered to be "tamed," and catalepsy was present when the animal maintained a bizarre position for at least 4 to 5 min.

Adrenergic blocking activity was determined by the method described by Luduena, *et al.*[5] Intravenous epinephrine and norepinephrine are particularly toxic to the white rat and the potency of an agent was determined by administering it simultaneously with 200 μg./kg. of epinephrine or 400 μg./kg. norepinephrine (approx. 4.3 × LD_{50} of each amine) and counting the number protected over 24 hr. By use of at least 3 dose levels and usually 15–20 rats (80–100 g. body weight) per dose it was possible to determine the ED_{50} and its standard error.

These indolylalkylpiperazines are relatively insoluble in water so that medication was always by the oral route except in the test for adrenergic blockade where it was administered intravenously. In the latter case the compound, usually 10 mg., was dissolved in 0.2 ml. of absolute ethanol plus 0.1 ml. of glacial acetic acid, such a solution could be diluted with distilled water without precipitation, the usual dilution being 1:100 or 1:200; the solubilizing agents even at much greater concentrations had no effect on the toxicity of the catecholamines.

Results.—The compounds were tested by four procedures in which chlorpromazine shows activity. In addition to these properties, many of these agents possess antiemetic activity, are weak histamine antagonists, reduce locomotor activity in mice and antagonize caffeine-induced hyperactivity, but do not protect against convulsions induced by electroshock or pentylenetetrazole.

Basic Structural Requirements.—In general, the basic structure for central depressant activity was found to be



(3) L. C. Miller and M. L. Tainter, *Proc. Soc. Exptl. Biol. Med.*, **57**, 261 (1946).
(4) D. W. Wylie, *J. Pharmacol. Exptl. Therap.*, **127**, 276 (1959).
(5) F. P. Luduena, E. O'Malley, and I. H. Oyen, *Arch. intern. Pharmacodynamie*, **122**, 111 (1959).

and the compounds have been classified according to (a) substituents on the indole moiety (Tables I and II), (b) length of the alkyl chain (Table III), (c) substituents on the phenyl group (Table IV) and (d) substituents replacing the phenyl group (Table V). The length of the alkyl chain (*n*) may be varied from 1 to 4 carbons and activity was still present. Removal of the phenyl group or its replacement by a methyl group eliminated all central depressant and adrenergic blocking activities (compounds 58, 62 and 59, Table V); replacement of the phenyl group by a 2-pyridyl group caused little alteration (compounds 60, 61 and 63), but replacement by 2-pyrimidyl or benzyl groups altered the properties so that the agent had little more than slight activity in potentiating hexobarbital (Table V). Substituents on the indole and phenyl groups altered specific activities markedly.

Effect of Various Substituents on the Indole Moiety.—Compounds with a single methoxy substituent on positions 4, 5 or 7 of the indole moiety were little different from each other and from the parent compound (No. 1) which has no substituents on these positions (Table IA); the 6-methoxy derivative, however, was more active in the three tests for central depression, with no significant change in adrenolytic potency. The 6-ethoxy derivative was much less active than the 6-methoxy derivative as an inhibitor of the head-withdrawal reflex, but in the other tests, there were smaller differences between the two compounds. Other compounds with single substituents, such as N-methyl, 2-methyl, and 6-methyl, showed again marked reduction in potencies as inhibitors of the head-withdrawal reflex with little change in any of the other properties. The 5,6-disubstituted compounds possessed potencies similar to each other and to the 6-methoxy derivative.

In Table IB are shown similar compounds with, in addition, an *o*-methoxy substituent on the phenyl group; again the 6-methoxy and the 5,6-disubstituted compounds possessed similar potencies, but here the compound with no indole substituent (No. 14, Table I) was almost as active in contrast to the relationship in Table IA. The presence of the *o*-methoxy substituent on the terminal phenyl group, as will be discussed later, markedly increased activity, particularly as an adrenolytic, and substitution here had obviously a more predominant effect than substitution on the indole moiety.

It would appear from these results that indole substitution affected most markedly the potency in inhibiting the head-withdrawal reflex, less markedly the potency in potentiating hexobarbital anesthesia and had only slight, if any, action on adrenolytic potency.

Effect of 2-Methyl Substitution of the Indole Moiety.—The results

TABLE I

EFFECT OF VARIOUS INDOLE SUBSTITUENTS ON ACTIVITY OF COMPOUNDS[a]

Cpd.	Indole substituents	H.P.[b] ED_{50} ± SE. mg./kg. P.O.	I.H.W.R.[c] ED_{50} ± SE. mg./kg. P.O.	Adrenolytic Activity ED_{50} ± SE. μg./kg. I.V.	Monkey overt behavior — minimum effective dose mg./kg. p.o. — Sedation	Taming	Catalepsy	Fall in rectal[d] temp., °C.
			A. No Substituent on Phenyl Group					
1	None	14.4 ± 3.0	90.5 ± 23.3	103.0 ± 25.9	128	>128	>128	1.5(64)
2	4-OCH_3	15.2 ± 4.0	92.0 ± 39.3	92.0 ± 21.6	64	64	128	3.5(64)
3	5-OCH_3	26.0 ± 6.0	98.0 ± 19.9	64.0 ± 10.5	64	64	>64	1.0(64)
4	6-OCH_3	6.7 ± 0.7	9.1 ± 2.1	56.0 ± 8.1	4	4	8	1.8(8)
5	7-OCH_3	22.0 ± 3.5	58.0 ± 29.8	36.5 ± 6.1	64	>64	>64	1.1(64)
6	5-OCH_3, 6-OCH_3	8.6 ± 1.5	22.0 ± 7.6	57.0 ± 10.2	8	16	32	2.3(16)
7	5-OC_2H_5, 6-OC_2H_5	7.7 ± 1.1	14.6 ± 3.1	86.0 ± 16.2	16	16	>16	1.1(16)
8	5-OC_2H_5, 6-OCH_3	8.6 ± 1.8	11.1 ± 2.0	73.0 ± 24.5	16	16	32	2.6(32)
9	5,6-CH_2O_2	8.0 ± 1.6	40.0 ± 12.0	34.0 ± 4.8	8	8	64	1.0(8)
10	NCH_3	11.0 ± 2.0	100.0 ± 39.9	62.0 ± 13.1	64	>64	>64	1.7(64)
11	6-OC_2H_5	13.0 ± 3.8	>128	56 ± 18.1	8	16	16	1.9(16)
12	2-CH_3	5.0 ± 0.9	>128	55.0 ± 5.3	32	64	64	2.0(64)
13	6-CH_3	38.0 ± 9.2	>128	153.0 ± 33.3	64	64	64	2.8(64)
			B. *o*-CH_3O on Phenyl Group					
14	None	13.4 ± 2.8	19.5 ± 3.9	12.2 ± 2.6	8	16	16	1.8(8)
15	6-OCH_3	7.4 ± 1.3	6.4 ± 1.3	11.3 ± 3.5	4	>64	>64	1.3(4)
16	5-OCH_3, 6-OCH_3	4.9 ± 1.1	4.9 ± 0.8	6.0 ± 0.9	2	2	4	2.4(4)
17	5-OC_2H_5, 6-OC_2H_5	9.0 ± 3.3	12.4 ± 2.0	24.0 ± 9.4	4	8	8	4.9(8)
18	5,6-CH_2O_2	8.2 ± 1.4	10.0 ± 2.8	12.0 ± 1.3	2	4	4	3.2(4)

[a] All compounds have ethylene chain between indole and piperazine moieties. [b] H.P.: hexobarbital potentiation. [c] I.H.W.R.: inhibition of head withdrawal reflex. [d] Dose mg./kg. in parentheses.

in Table II show that the presence of a 2-methyl substituent on the indole moiety can markedly alter the properties of individual compounds, but it produced no alteration common to all compounds. This substituent approximately doubled the central activity and halved peripheral adrenolytic activity of compound 19 (oxypertine) over compound 6, whereas in the other pairs of compounds such substitution usually reduced both central depressant and peripheral adrenolytic activity.

Effect of Varying the Length of the Alkyl Chain.—The data for compounds with alkyl chains of different lengths are presented in Table III. Compounds with methylene bridges of 1–4 carbons showed activity but the optimal chain length was found to be 2–3 carbons. The property most affected by the chain length was that of inhibition of the head-withdrawal reflex, the compounds with two-carbon bridges usually being more active. Except where the chain consisted of only one methylene group there was little difference between the compounds in potentiating hexobarbital and there was no distinct trend in adrenolytic potency.

From the data in Table IIIB it is obvious again that the dominant substitution was *o*-methoxy on the phenyl group. In this group of compounds with alkyl chains of different lengths, the differences between the various agents as shown in Table IIIA were markedly reduced by *o*-methoxy substitution, so that even the compound with a single methylene bridge showed definite activity.

Effects of Substituents on the Phenyl Group.—Adrenolytic potency is most markedly affected by substitution on the terminal phenyl group (Tables IVA, B, and C). Irrespective of the substituents on the indole moiety, the compounds with *o*-phenyl substituents were most active and in almost all cases the compounds next in adrenolytic potency were those without substituents on the phenyl group. Generally speaking, compounds with *m* and *p* substituents were weaker.

The property of potentiating hexobarbital anesthesia was not as markedly affected by the position of the substituent on the phenyl group. In this instance, the compounds with methoxy and methyl substituents at the *o*-position and those with no substitution of the phenyl group were usually more active than the *m*- and *p*-substituted compounds, but the differences where they existed, were little more than two-fold as compared to as much as a twenty-fold in adrenolytic activity. Compare compound 18 (solypertine) with compound 9 (Table I) where *o*-methoxy substitution did not alter activity in potentiating hexobarbital, but increased adrenolytic activity three-fold.

Ethyl, ethoxy, and chloro substituents affected individual compounds in a variety of ways, but apart from the fact that *o*-substitution increased activity, no other general trend was obvious.

Effect of Replacement of Phenyl Group.—The results in Table V show that aryl substitution at the 4-position of the piperazine group was essential for activity, replacement of the phenyl group by a hydrogen atom or by an alkyl group eliminated activity in all tests; replacement by a 2-pyridyl group may reduce activity but such compounds still possessed activity in all the tests; replacement by benzyl or 2-pyrimidyl groups eliminated activity in the head-withdrawal reflex and adrenolytic tests, but these agents still showed activity in potentiating hexobarbital.

Discussion

The four properties studied in this series are, within certain limits, present in all tranquilizers used in the therapy of psychoses. Many agents such as sedatives and hypnotics are active in the test for potentiation of hexobarbital, but this is due to addition rather than potentiation as a four-fold increase in dosage of the sedative alone will cause loss of righting reflex. The agents studied here do not cause such loss of righting reflex until the dose is increased 20–30 times. Inhibition of the head-withdrawal reflex in mice is specific to this type of agent as other central depressants do not affect the reflex until anesthetic doses are used. The behavioral test in monkeys is predominantly of value for the detection of catalepsy and as a means of finding the difference between the dose causing sedation and the dose causing catalepsy.

The procedure used in this study for determination of adrenergic blocking activity measured antagonism of the lethal effects of epinephrine. Studies with some of these compounds, compounds 18 and 19 being studied in more detail, showed that they fell within the more accepted definition of adrenolytic agents as they also blocked the pressor effects of the catecholamines in the spinal cat preparation. Unfortunately, insufficient studies were done to show the relationship in potencies as determined by the two methods. For comparative purposes, the adrenolytic activity of chlorpromazine in rats was found to be 35.2 ± 5.6 μg./kg.

It seems more than coincidence that this group of indole derivatives, together with phenothiazine and benzodioxane derivatives,[6] which are all different chemically, nevertheless, possess similar central

(6) I. H. Slater and G. I. Jones, *J. Pharm. Exptl. Therap.*, **122**, 69A (1958).

TABLE II

EFFECT OF 2-CH_3-SUBSTITUTION ON THE INDOLE MOIETY

Cpd.	Indole substituents			Phenyl substituent	H.P. ED_{50} ± SE. mg./kg. P.O.	I.H.W.R. ED_{50} ± SE. mg./kg. P.O.	Adrenolytic Activity ED_{50} ± SE. μg./kg. I.V.
	R_2	R_5	R_6				
1	H	H	H	None	14.4 ± 3.0	90.0 ± 23.3	103.0 ± 25.9
12	CH_3	H	H	None	5.0 ± 0.9	225.0 ± 30.0	55.0 ± 5.3
6	H	OCH_3	OCH_3	None	8.6 ± 1.5	22.0 ± 7.6	57.0 ± 10.2
19	CH_3	OCH_3	OCH_3	None	3.7 ± 0.4	6.5 ± 2.1	106.0 ± 10.7
16	H	OCH_3	OCH_3	*o*-OCH_3	4.9 ± 1.1	4.9 ± 0.8	6.0 ± 0.9
20	CH_3	OCH_3	OCH_3	*o*-OCH_3	7.2 ± 1.1	9.4 ± 2.2	9.8 ± 3.1
21	H	OCH_3	OCH_3	*m*-OCH_3	5.2 ± 1.8	10.6 ± 1.6	160.0 ± 23.3
22	CH_3	OCH_3	OCH_3	*m*-OCH_3	9.4 ± 2.3	10.6 ± 2.3	305.0 ± 48.2
23	H	OCH_3	OCH_3	*o*-CH_3	6.0 ± 0.7	8.6 ± 1.4	38.0 ± 14.7
24	CH_3	OCH_3	OCH_3	*o*-CH_3	13.0 ± 5.5	28.0 ± 6.2	84.0 ± 13.9

TABLE III

EFFECT OF ALTERING DISTANCE BETWEEN INDOLE AND PIPERAZINE MOIETIES

Cpd.	Indole substituents	*n*	H.P. ED_{50} ± SE. mg./kg. P.O.	I.H.W.R. ED_{50} ± SE. mg./kg. P.O.	Adrenolytic activity ED_{50} ± SE. μg./kg. I.V.	Monkey overt behavior — minimal effective dose, mg./kg. p.o.			
						Sedation	Taming	Catalepsy	Fall in rectal temp. °C.
A. No Substitution on Phenyl Group									
26	None	1	>128	>128	>800	>64	>64	>64	0 (64)
1	None	2	14.4 ± 3.0	90.0 ± 23.3	103.0 ± 25.9	>64	>64	>64	1.5 (64)
27	None	3	10.8 ± 2.6	48.0 ± 8.0	45.5 ± 11.7	32	64	>64	0.6 (64)

(TABLE III *Continued*)

28	None	4	10.4 ± 3.4	>128	94.0 ± 24.6	8	8	16	2.0(16)
4	6-OCH_3	2	6.7 ± 0.7	9.1 ± 2.1	56.0 ± 8.1	4	4	8	1.8(8)
29	6-OCH_3	3	12.8 ± 2.1	67.0 ± 18.6	132.0 ± 35.1	64	>64	>64	2.0(64)
30	5-OCH_3, 6-OCH_3	1	57.6 ± 14.8	>128	164.0 ± 21.9	>128	>128	>128	0(128)
6	5-OCH_3, 6-OCH_3	2	8.6 ± 1.5	22.0 ± 7.6	57.0 ± 10.2	8	16	32	2.3(16)
31	5-OCH_3, 6-OCH_3	3	11.8 ± 2.2	90.0 ± 21.5	68.5 ± 6.9	64	>64	>64	1.0(64)
9	5,6-CH_2O_2	2	8.0 ± 1.6	40.0 ± 12.0	34.0 ± 6.2	8	8	64	1.0(8)
32	5,6-CH_2O_2	3	6.4 ± 1.3	34.5 ± 8.4	114.0 ± 29.9	16	64	64	2.2(16)
19	5-OCH_3, 6-OCH_3, 2-CH_3	2	3.7 ± 0.6	6.5 ± 2.1	106.0 ± 10.7	2	2	4	2.2(4)
33	5-OCH_3, 6-OCH_3, 2-CH_3	3	5.5 ± 1.5	21.2 ± 3.9	45.0 ± 8.1	4	8	8	2.1(8)
				B. *o*-CH_3O on Phenyl Group					
14	None	2	13.4 ± 2.8	19.5 ± 3.9	12.2 ± 2.6	8	16	16	1.8(8)
34	None	3	30.0 ± 10.2	39.0 ± 11.5	22.3 ± 6.1	2	4	8	1.5(8)
35	None	4	15.0 ± 4.0	60.0 ± 14.0	25.5 ± 4.3	8	8	8	3.5(8)
15	6-OCH_3	2	7.4 ± 1.3	6.4 ± 1.3	11.3 ± 3.5	4	>64	>64	1.3(4)
36	6-OCH_3	3	9.4 ± 2.8	10.2 ± 1.7	14.0 ± 4.3	2	4	4	2.4(4)
16	5-OCH_3, 6-OCH_3	2	4.9 ± 1.1	4.9 ± 0.8	6.0 ± 0.9	2	2	4	1.8(2)
37	5-OCH_3, 6-OCH_3	3	3.7 ± 1.1	15.5 ± 4.3	14.0 ± 2.6	2	4	4	3.0(4)

TABLE IV

EFFECT OF VARIOUS SUBSTITUENTS ON THE PHENYL GROUP

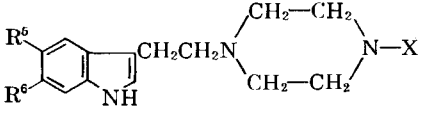
Cpd.	Substituent on phenyl group	H.P. ED_{50} ± SE. mg./kg. P.O.	I.H.W.R. ED_{50} ± SE. mg./kg. P.O.	Adrenolytic activity ED_{50} ± SE. μg./kg. I.V.	Monkey overt behavior Minimal effective dose mg./kg. P.O. Sedation	Taming	Catalepsy	Fall in rectal temp. °C.
			A. No Substituent on Indole					
1	None	14.4 ± 3.0	90.0 ± 23.3	103.0 ± 25.9	—	—	—	1.5(64)
14	*o*-OCH_3	13.4 ± 2.8	19.5 ± 3.9	12.2 ± 2.6	8	16	16	1.8(8)
38	*m*-OCH_3	42.5 ± 9.0	98.0 ± 15.6	122.0 ± 15.4	64	>64	>64	0 (64)

(TABLE IV *Continued*)

39	*p*-OCH_3	46.0 ± 12.1	>128	173.0 ± 44.1	64	>64	>64	0 (64)
40	*o*-CH_3	32.0 ± 4.2	96.0 ± 28.5	43.0 ± 14.7	8	>64	>64	1.1(8)
41	*m*-CH_3	27.0 ± 5.6	>128	195.0 ± 56.2	64	>64	>64	0 (64)
42	*p*-CH_3	14.0 ± 2.8	93.0 ± 22.2	80.5 ± 23.6	64	>64	>64	0.6(64)
			B. 6-OCH_3 Substitution on Indole					
4	None	6.7 ± 0.7	9.1 ± 2.1	56.0 ± 8.1	8	8	16	1.8(8)
15	*o*-OCH_3	7.4 ± 1.3	6.4 ± 1.3	11.3 ± 3.5	4	>64	>64	1.3(4)
43	*m*-OCH_3	19.0 ± 4.3	74.0 ± 15.7	175.0 ± 44.9	64	64	>64	2.1(32)
44	*p*-OCH_3	95.0 ± 34.5	>128	430.0 ± 133.5	>64	>64	>64	0 (64)
45	*o*-CH_3	5.9 ± 1.1	18.5 ± 2.4	28.0 ± 5.6	8	16	64	1.6(8)
46	*m*-CH_3	12.6 ± 3.0	20.5 ± 4.9	176.0 ± 25.5	8	16	32	1.7(16)
47	*p*-CH_3	16.0 ± 3.7	14.6 ± 4.3	110.0 ± 32.0	—	—	—	—
48	*o*-OC_2H_5	19.5 ± 5.0	26.5 ± 8.3	5.5 ± 2.7	8	8	32	4.0(8)
49	*o*-Cl	6.6 ± 2.1	29.0 ± 5.5	30.5 ± 5.0	8	16	16	2.4(16)
50	*m*-Cl	77.0 ± 27.6	>128	220.0 ± 84.4	32	64	64	0.8(32)
			C. 5-OCH_3, 6-OCH_3 Substitutions on Indole					
6	None	8.6 ± 1.5	22.0 ± 7.6	57.0 ± 10.2	8	16	32	1.4(8)
16	*o*-OCH_3	4.9 ± 1.1	4.9 ± 0.8	6.0 ± 0.9	2	2	4	2.4(4)
21	*m*-OCH_3	5.9 ± 1.8	10.6 ± 1.6	160.0 ± 23.3	4	8	8	2.3(4)
51	*p*-OCH_3	13.2 ± 3.7	61.0 ± 14.2	254.0 ± 30.9	>64	>64	>64	0 (64)
23	*o*-CH_3	6.6 ± 0.7	8.6 ± 1.4	38.0 ± 14.7	2	4	8	2.3(8)
52	*m*-CH_3	2.8 ± 0.6	16.5 ± 4.0	73.0 ± 20.5	4	8	>32	1.4(4)
53	*p*-CH_3	8.0 ± 2.1	64.0 ± 12.5	88.0 ± 8.1	16	32	>128	0.9(32)
54	*o*-OC_2H_5	5.8 ± 1.1	3.7 ± 0.6	6.1 ± 0.8	4	8	16	1.6(4)
55	*o*-C_2H_5	20.5 ± 3.7	30.5 ± 6.6	10.4 ± 3.2	4	8	8	3.2(8)
56	*o*-Cl	7.4 ± 2.1	12.6 ± 2.0	31.0 ± 6.5	—	—	—	—
57	*m*-Cl	8.6 ± 3.0	29.0 ± 8.4	200.0 ± 46.4	2	4	8	1.9(2)

TABLE V

EFFECT OF REPLACING PHENYL GROUP



Cpd.	Indole substituents R5	Indole substituents R6	X	HP. ED50 ± SE. mg./kg. P.O.	I.H.W.R. ED50 ± SE. mg./kg. P.O.	Adrenolytic activit ED50 ± SE μg./kg.
1	H	H	Phenyl	14.4 ± 3.0	90.0 ± 23.3	103.0 ± 25.9
58	H	H	H	>128	>128	>800
59	H	H	CH_3	>128	>128	>800
60	H	H	2-Pyridyl	69.0 ± 16.0	>128	100.0 ± 24.1
4	H	OCH_3	Phenyl	6.7 ± 0.7	9.1 ± 2.1	56.0 ± 8.1
61	H	OCH_3	2-Pyridyl	13.6 ± 2.8	69.0 ± 13.9	72.0 ± 13.2
6	OCH_3	OCH_3	Phenyl	8.6 ± 1.5	22.0 ± 7.6	57.0 ± 10.2
62	OCH_3	OCH_3	H	>128	>128	>800
63	OCH_3	OCH_3	2-Pyridyl	9.6 ± 2.6	21.0 ± 4.8	86.0 ± 9.3
64	OCH_3	OCH_3	2-Pyrimidyl	40.0 ± 13.0	>128	>800
65	OCH_3	OCH_3	Benzyl	79.0 ± 24.6	>128	>800

properties and adrenolytic activity; in addition reserpine, which also possesses many similar central properties, eliminates catecholamines from the brain. Such facts suggest that the tranquilizing properties of such agents are due to their effects on the catecholamines. Unfortunately, there is no single laboratory test which is directly related to the tranquilizing effect of these agents, nor is there a test for central adrenolytic activity and it is therefore necessary to try to correlate peripheral adrenolytic activity with the various central properties which can be measured.

Various observations can be made regarding correlations of adrenolytic activity and central depressant activity. It should first be noted that agents may be active potentiators of hexobarbital anesthesia and inactive as inhibitors of the head-withdrawal reflex, implying that although the compound was able to enter the central nervous system it may possess only one of the two properties; compounds 11 and 12 in Table I can be compared with compound 4 which is active in both central tests. In Table I there are also agents which were actively adrenolytic but did not inhibit the head-withdrawal reflex; comparison of compounds 11 and 12 with compounds 4, 6, and 8 shows that these two properties are not closely related; but it should be noted that in no instance does a compound inhibit the head-withdrawal reflex without also possessing adrenolytic activity. Finally, some compounds (Nos. 64 and 65 in Table V) were active only in potentiating hexobarbital anesthesia. Such an examination of the data suggests that there is no correlation between peripheral adrenolytic activity and central depression as determined by the test procedures used in this study. To determine whether a better correlation existed between antagonism of norepinephrine lethality and central depression, a series of compounds were tested against both epinephrine and norepinephrine. The results (Table VI) showed that the activities against both amines were very similar and that the lack of correlation would probably apply to both.

The calculated correlation factors for these compounds, omitting those inactive in all tests, were found to be 0.33 between the data for inhibition of the head-withdrawal reflex and adrenolysis and 0.36 between the data for potentiation of hexobarbital anesthesia and adrenolysis. In calculating the correlation, it was necessary to use the highest dose tested for compounds which were too weak to determine the ED_{50}, but it is easily conceivable that such a figure would be too low. The data presented in this study, therefore, do not show a correlation between adrenolytic and central depressant activities. This does not necessarily preclude a correlation between

TABLE VI
ADRENOLYTIC POTENCY AGAINST EPINEPHRINE AND NOREPINEPHRINE

	Adrenolytic activity against	
	Epinephrine $ED_{50} \pm SE$	Norepinephrine $ED_{50} \pm SE$
Cpd.	μg./kg. I.V.	μg./kg. I.V.
12	55.0 ± 5.3	67.0 ± 16.3
14	12.2 ± 2.6	10.2 ± 1.7
16	6.0 ± 0.9	8.0 ± 2.9
18	12.0 ± 1.3	11.8 ± 5.3
19	106.0 ± 10.7	105.0 ± 12.6
20	9.8 ± 3.1	10.5 ± 2.5
Phentolamine HCl	19.3 ± 5.4	14.1 ± 3.3

such properties as it may be necessary to determine adrenolytic activity within the central nervous system before any correlation could be drawn.

It has been shown recently that oxypertine (cpd. 19), like chlorpromazine, does not affect the concentration of serotonin in the heart[7] but does cause the release of norepinephrine from the heart.[8] Thus oxypertine appears to be unique in that it can both release and antagonize the action of norepinephrine. Such a dual effect on the catecholamines may also account for the lack of correlation between adrenolytic and central activities and still allow for the possibility that the mechanism of action of such agents involves the catecholamines in the central nervous system.

These compounds in general caused sedation, loss of aggressiveness, and catalepsy in the rhesus monkey in a manner similar to that of phenothiazine tranquilizers. Most of the agents effective in the other two tests for central activity produced behavioral changes in the monkey and, in general, the potency as an inhibitor of the head-withdrawal reflex in the mouse was similar to the potency as a cataleptogenic agent in the monkey; however, this latter test is crude from a quantitative point of view as it is only possible to detect gross behavioral changes. An interesting observation was that in instances of obvious behavioral change there was a fall in rectal temperature which was, in general, directly proportional to the degree of behavioral change; in this laboratory we usually consider a possible mild behavioral change to be absent unless it is accompanied by a fall of more than 0.6° in rectal temperature.

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