determined in normal, thyroxin-treated, thyroidectomized and propylthiouracil-treated rats. The results obtained were as follows:

1. Thyroxin decreased electroshock threshold for minimal seizures (increased brain excitability), whereas thyroidectomy and propylthiouracil increased this threshold (decreased brain excitability).

2. Thyroxin decreased total duration of maximal (tonic-clonic) electroshock seizures by shortening the clonic phase. Thyroidectomy increased total duration by markedly prolonging the hindleg extensor component of the tonic phase whereas propylthiouracil increased total duration by prolonging the flexor component.

3. Thyroxin slightly accelerated and thyroidectomy markedly accelerated recovery from maximal electroshock seizures. In contrast, propylthiouracil moderately prolonged postictal recovery.

4. Thyroxin increased susceptibility to Metrazol-induced seizures, whereas thyroidectomy and propylthiouracil both decreased susceptibility to such seizures.

Since certain effects of propylthiouracil unexpectedly differed from those of thyroidectomy, the possibility that propylthiouracil has a direct depressant effect on the central nervous system must be considered. All the changes in seizure properties exhibited by the propylthiouracil-treated rats are characteristic of those caused by anticonvulsant drugs. A comparison of propylthiouracil with phenobarbital and diphenylhydantion is presented (table 4).

Quantitative information has been presented which indicates the intimate relationship between brain function and level of activity of the thyroid gland.

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THE VASOPRESSOR ACTION AND TOXICITY OF CYCLOHEXYLETHYLAMINE DERIVATIVES

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Various sympathomimetic amines containing saturated rings have been described in the pharmacological publications listed below. Gunn and Gurd (1940) have described cyclohexylmethyl-, 1- and 2-cyclohexylethylamines, 2-cyclohexylisopropyl- and 2-cyclohexenylisopropylamines; Lands, Lewis and Nash (1945), N-methyl-, N-ethyl-, N,N-dimethyl- and N,N-diethyl-2-cyclohexylethylamines, N-methyl- and N,N-dimethyl-1-cyclohexylpropylamines; Lands, Nash, Granger and Dertinger (1947), the *d*-, *dl*- and *l*-isomers of N-methyl-2-cyclohexylisopropylamine; Swanson and Chen (1948), 2-cyclohexylisopropylamine, N-methyl-, N,N-dimethyl-2-cyclohexylisopropylamine, 2-(3-methylcyclohexyl)-isopropylamine, various cyclopentylethyl- and cyclopentylpropylamines; Marsh, Pelletier and Ross (1947), cyclopentylethylamine and cyclopentylpropylamine; Marsh (1948), 2-cyclohexylethylamine, N-methyl-2-cyclohexylethylamine, 2-cyclohexylpropylamine, N-methyl-2-cyclohexylpropylamine, 2-cyclohexylisopropylamine and N-methyl-2-cyclohexylisopropylamine.

Zenitz, Macks and Moore have synthesized several cyclohexylalkylamines (1947) and -alkanolamines with a hydroxyl substitution of the ring in the *para*-position. We have investigated the effects of these and related compounds on the blood pressure of anesthetized dogs. The results obtained along with acute toxicity data in mice are presented in this communication.

METHODS. Dogs were anesthetized by the intraperitoneal administration of pentobarbital sodium (35 mgm./kgm.) or by an intravenous injection of thiopental sodium (15 mgm./kgm.) followed by barbital sodium (250 to 300 mgm./kgm.). Carotid blood pressure was recorded kymographically by means of a mercury manometer. Pulse rates were determined in representative experiments. The compounds, dissolved in 0.1 per cent sodium acetone bisulfite, were injected into the exposed femoral vein. Bleeding was minimized by injecting through a 26-gauge needle. Test animals in which mean carotid blood pressure was initially below 75 mm. Hg were rejected as were animals in which there were spontaneous fluctuations in pressure or large respiratory effects. The cholinergic system was blocked by the intravenous injection of 1.0 mgm./kgm. of atropine sulfate. Subsequent fractional doses of atropine were administered when the intravenous injection of 10 micrograms/kgm. of acetylcholine caused a small vasodepressor response.

The marked myocardial stimulation observed with potent sympathomimetic amines such as epinephrine and *l*-arterenol contributes importantly to the initial rise in pressure and frequently causes a spike rise which precedes the slower but more sustained rise in pressure (Lands *et al.*, 1950). We have not been able to construct a satisfactory dose/response curve from the spike rises in blood pressure. However, when the secondary pressor response was used a linear relationship was disclosed by plotting log dose against log response (Hjort *et al.*, 1941). The mean values for the secondary responses obtained in nine experiments are shown in fig. 1. The pressor ratios reported in this investigation and shown in table 1 were obtained by using this secondary epinephrine pressor response as the basis for comparison.

Acute toxicity was determined in albino mice by intraperitoneal (Dertinger *et al.*, 1948) and intravenous (Hoppe *et al.*, 1949) injection

RESULTS. The structural formulae of the compounds used in this investigation are shown in table 1. The epinephrine pressor ratio for phenethylamine is 67 whereas that for the cyclohexyl analog is 169 (expressed as multiples of an equi-active dose of epinephrine). Compared on the basis of molecular weight, the latter has about 40 per cent of the activity of the former. N-methyl substitution (WIN 5553) decreases the pressor potency of phenethylamine but causes an

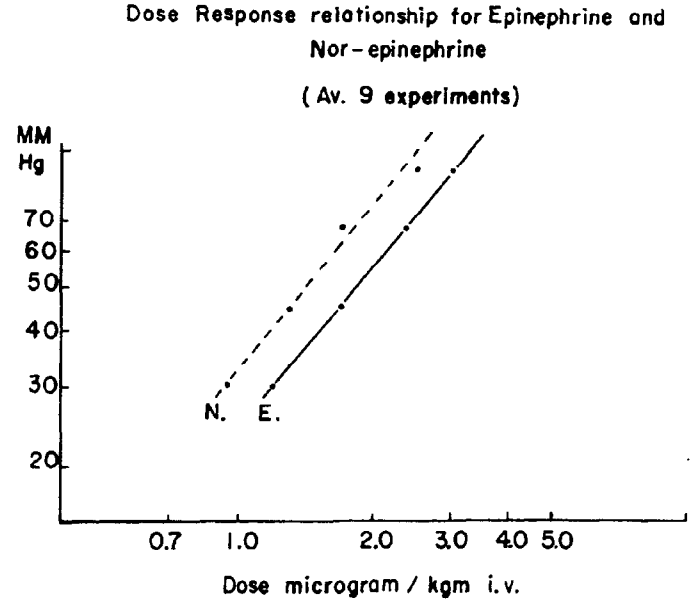


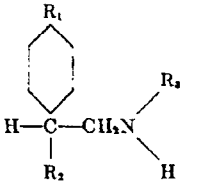
FIG. 1. Dose-response relationship for the secondary rise in blood pressure obtained in anesthetized dogs following intravenous injection of epinephrine and l-arterenol (Levophed). The latter is about 1.3 times more pressor than the former

increase in the pressor action of the cyclohexyl compound (cf. WIN 5522-2 and WIN 828). When the pressor activity of phenethylamine is compared with that of the 4-hydroxyphenyl analog (WIN 5582), the latter has about twice the pressor activity. It is interesting to note that the replacement of one hydrogen atom of the 2-carbon by a hydroxyl (WIN 5529-2 and WIN 5512) reduces pressor action. The least pressor derivative, 1-(4-hydroxyphenyl)-2-methylaminoethanol (Sympatol) differs in structure from epinephrine in that the second hydroxyl is absent from the phenyl ring. With the exception of the primary amine (WIN 5522-2) and its N-methyl analog (WIN 828), the structural

modifications described above cause similar reductions in pressor potency with the cyclohexyl derivatives They also are clearly less potent than the corresponding phenyl analogs. Tachyphylaxis was small or absent with cyclohexyl derivatives used in this investigation.

TABLE 1

A comparison of the pressor action of several cyclohexylethylamine derivatives with that of the corresponding phenyl analogs



COMPOUND	STRUCTURE ring	R_1	R_2	R_3	NO. EXP.	DOSE I.V. AMINE BASE MGM./KGM.	CHANGE IN BLOOD PRESSURE MM. Hg	APPROX. DURATION MIN.	RELATIVE POTENCY RECIPROCALS epi. pressor ratio*	RELATIVE POTENCY RECIPROCALS amine equivalent 1 molecule epi.†
WIN 5522-2	Cyclohexyl	H	H	H	9	0.44	+49	2-7	169	244
Phenethylamine.	Phenyl	H	H	H	9	0 19	+57	2-5	67	100
WIN 828	Cyclohexyl	H	H	CH_3	11	0.31	+51	2-4	122	160
WIN 5553	Phenyl	H	H	CH_3	12	0.22	+50	2-4	86	117
WIN 5581.	Cyclohexyl	H	OH	CH_3	8	1.78	+43	3-10	774	900
WIN 5529-2	Phenyl	H	OH	CH_3	16	0.41	+38	3-10	204	244
WIN 5583	Cyclohexyl	OH	H	CH_3	11	0.28	+43	3-12	122	141
WIN 5582. NMT	Phenyl	OH	H	CH_3	12	0.09	+36	2-5	46	55
WIN 5580	Cyclohexyl	OH	OH	CH_3	6	2.80	+23	3-10	±2150	±2280
Sympatol	Phenyl	OH	OH	CH_3	8	0 61	+34	5-10	285	310
WIN 5579.	Cyclohexyl	OH	OH	$CH(CH_3)_2$	10	1.85	+6	5-10		
WIN 833.	Phenyl	OH	OH	$CH(CH_3)_2$	15	0.15	−42	>10		
Tyramine	Phenyl	OH	H	H	11	0 13	+60	2-5	42	56
WIN 5512	Phenyl	OH	OH	H	9	0 17	+46	5-10	71	85

* Multiples of the dose of epinephrine producing a comparable rise in blood pressure

† Molecules of amine equivalent to 1 molecule of epinephrine

Previous publications have described the depressor potency of 1-(4-hydroxyphenyl)-2-isopropylaminoethanol (Lands *et al.*, 1947). The cyclohexyl analog

(WIN 5579) does not cause a fall in blood pressure. With large doses, there may be a small rise in blood pressure (table 1). Hydrogenation of the phenyl ring is not favorable for sympathomimetic depressor action.

The increases in pulse rate obtained with doses of drug to cause an assay rise in blood pressure were similar for all compounds except WIN 5529–2 with which the cardiac effects appeared to be less. The large dosage of WIN 5580 and Sympatol required to produce a moderate rise in pressure made comparison of their cardiac effects difficult. The depressor compound, WIN 833, caused marked cardiac stimulation (Lands *et al.*, 1947); the cyclohexyl analog had little or no cardiac stimulating action.

TABLE 2

The acute toxicity in mice of several cyclohexylethylamine derivatives and the corresponding phenyl analogs

COMPOUND	TOXICITY (MGM./KGM. SALT)	
	Approx. LD_{50} i.p.	$LD_{50} \pm$ s.e. i.v.
WIN 5522–2	140	44 ± 2
Phenethylamine		100 ± 6
WIN 828	118	43 ± 2
WIN 5553	190	90 ± 3
WIN 5581	260	32 ± 2
WIN 5529–2	500	85 ± 2
WIN 5583		610 ± 40
WIN 5582	780	275
WIN 5580	620	795 ± 46
Sympatol	>1000	270 ± 12
WIN 5579		460 ± 24
WIN 833	370	144 ± 10
Tyramine		260 ± 20
WIN 5512	600	75 ± 1.6

The acute toxicity of the 4-hydroxycyclohexyl derivatives is clearly less than that of the corresponding 4-hydroxyphenyl analogs whereas, in the case of compounds in which the ring is not substituted by a hydroxyl, the relationship is reversed (table 2). In the absence of a hydroxyl in the 4-position, neither the N-methyl group nor the alcoholic hydroxyl of the 2-carbon caused any significant change in toxicity. With both groups present in the molecule, the addition of a hydroxyl at the 4-position results in a large reduction in toxicity and activity. For example, N-methyl-2-cyclohexylethanolamine (WIN 5581) has a mouse acute intravenous LD_{50} of 32 ± 2 mgm./kgm. whereas N-methyl-2-(4-hydroxycyclohexyl)-ethanolamine (WIN 5580) has a value of 795 ± 46 mgm./kgm. In general, the effects of structural modification on toxicity appears to follow the same pattern with both the cyclohexylethylamines and the corresponding phenyl analogs.

SUMMARY

Hydrogenation of the ring of some phenethylamine derivatives reduces sympathomimetic pressor action and abolishes sympathomimetic depressor action. The cyclohexylethylamine derivative is clearly less potent than the corresponding phenyl analog. The 4-hydroxycyclohexyl compounds are less toxic than their phenyl analogs whereas the relationship is reversed in the absence of the 4-hydroxy substitution.

Potent sympathomimetic amines such as epinephrine and l-arterenol cause marked myocardial stimulation. The spike component of the pressor response is largely the result of this action and for that reason should not be used as a basis for the comparison of vasoconstrictor action. The secondary rise in pressure corresponds most exactly with vasoconstriction and was used as the basis for the estimation of epinephrine ratios in this investigation of pressor action.

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