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Autonomic Effects of a Series of Phenylalkylamine Derivatives

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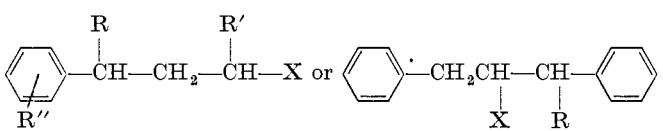
Barger and Dale[1] published one of the first structure–activity studies on a series of phenethylamine derivatives, describing their sympathomimetic activity. Since then, many reports on the autonomic activity of various types of alkylamine and aralkylamine derivatives have appeared[2-6]. In separate studies, Dutta[7] and Hebb and Konzett[8] reported that methadone depressed synaptic transmission. Larson, Van Slyke, Finnegan and Haag,[6] studying a series of aralkylamine derivatives for antinicotinic activity, found that methadone was the most active of their group. The present report describes the autonomic activity of 53 phenylalkylamine derivatives having the general structure:



where R is a hydrogen, hydroxyl, or ketone oxygen, R′ is a hydrogen, alkyl, aryl or aralkyl, and R″ is a hydrogen, alkoxy, or halogen. X represents an amino function which may be alkylated or heterocyclic; and in many instances primary, secondary, tertiary, and quaternary amines of the same basic compound were prepared for study of the amino function. All tertiary amines were prepared as hydrochlorides and the quaternaries were employed as the bromides or iodides. These compounds were synthesized by one of the authors (JDS).

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Methods

General autonomic action. Mongrel dogs anaesthetized with pentobarbital sodium (30 mg/kg i.v.) were prepared for recording arterial blood pressure *via* the cannulated carotid artery by means of a mercury manometer, and respiration by a pneumograph about the chest. Each drug was administered intravenously (femoral) to at least two animals for bio-assay of autonomic activity. Control blood pressure and respiratory responses to 0·02–0·08 mg/kg of a highly purified preparation of nicotine in a 0·4 per cent aqueous solution, 0·002–0·004 mg/kg of epinephrine, bilateral carotid occlusion (40 sec), and electrical stimulation of the peripheral stump of the sectioned right vagus nerve were recorded kymographically. Once reproducible stable responses were obtained, the test agent was administered intravenously, the drug response observed and the animal again challenged by the above procedures 5 min later and subsequently as necessary to follow recovery. The degree of inhibitory activity against any of the test procedures was measured as a percentage decrease from the control values. Numerical values from 0 to 4 were then assigned to the results, corresponding to 0 to 100 per cent inhibition of the test response. Using this scheme, a potency value of 0 indicates that no inhibition occurred, 1 signifies a 25 per cent decrease from control, 2 signifies a 50 per cent reduction, 3 a 75 per cent reduction, and 4 shows 100 per cent inhibition. The letter, P, in the tables signifies that a pressor response was obtained, either primarily, or following a fall in pressure as the case may be. If a biphasic depressor–pressor response occurred, it might be represented by 1/P or 2/P depending on the magnitude of the initial fall in blood-pressure. The symbol, Pot, indicates that potentiation of the control response occurred.

Following the introduction by Chen and Portman[9] of dimethylphenylpiperazinium iodide (DMPP) as a more reliable ganglionic stimulant than nicotine, together with the opportunity of studying both sympathetic and parasympathetic activity by using a combination of blood pressure and bladder contraction responses, the method described by these authors was adopted, juggling the DMPP dosage so that both responses could be recorded from a given dose of DMPP in the same animal. It was usually possible

to accomplish this with DMPP at doses of 10 to 20 μg/kg. Using this technique, dose response curves for individual test drugs were constructed and the SD_{50} (dose causing 50 per cent suppression of response) was calculated by the method of Weil[10] employing 3 or 4 animals per dose level.

In experiments involving electrical stimulation of the greater splanchnic nerve, the nerve was exposed on the left side through a paravertebral incision, sectioned, and the distal stump placed on shielded platinum electrodes for stimulation by an induction coil stimulator.

It was soon found that the most characteristic action of note in this series was apparent ganglionic blockade. Compounds causing apparent ganglionic blockade were further studied in anaesthetized cats (pentobarbital sodium, 35 mg/kg, i.p.) by recording responses of the nictitating membrane to electrical stimulation of pre- and post-ganglionic portions of the superior cervical nerve. A Harvard inductorium was employed as the current source, stimulation being applied at 2-min intervals. In this way it was possible to follow accurately the correlation between depressor effect and ganglionic depression. In some cases where postganglionic stimulation was omitted, the response of receptors was ascertained by eliciting membrane contractions with epinephrine.

Action in neurogenic hypertensive dogs. The most active members of the series were evaluated for hypotensive activity in anaesthetized dogs made acutely hypertensive by bilateral carotid occlusion and vagotomy. In animals where the blood pressure became stabilized at high levels (more than 166 mm/Hg in 18 prepared dogs compared with a mean of 100 mm/Hg in 13 normotensive controls) the test compounds were administered intravenously in graded doses at 20-min intervals, blood pressure being recorded continuously. At least three animals were employed for assay of each active compound. The HD_{500} dose was determined and was that dose required to produce a fall in blood pressure such that the fall in millimetres of mercury × duration in minutes = 500, e.g. a fall of 50 mm lasting 10 min, and so forth. This could also be approximated as a total area of blood pressure decrease of approximately 50 cm^2, with a drum speed of 1 cm/min.

Acute toxicity. The acute LD_{50} values for several active members of the series were determined by intravenous administration to CF–1 white mice weighing 15–30 g. At least five mice at each of four dose levels were employed for each compound with LD_{50} values determined by the method of Weil.[10]

Neuromuscular effects. The effects of some of the more active compounds were studied on the conventional frog sartorius nerve-muscle preparation.

Isometric contractions of the muscle in response to direct electrical stimulation and of stimulation of its nerve were recorded optically by means of a mirror mounted on the isometric torsion lever to which one end of the muscle was attached. The amplified image was photographed by a moving paper camera. The preparation was stimulated by a fixed tetanus of 0·3-sec duration from a Harvard inductorium and care was taken to ensure constant temperature control, optimum oxygen diffusion, optimum resting muscle-length for maximum tetanic tension, uniform adequate equilibration, and prevention of fatigue. Paired muscles were employed and where possible served as their own control as well as for comparison with *d*-tubocurarine, the reference standard. Test drugs were allowed to be in contact with the preparation for 30 min, washed and recovery followed for two hours. In most cases, eight to ten muscles were exposed to each test compound.

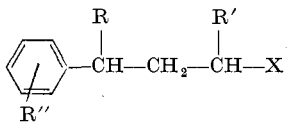
Antispasmodic activity. Antimuscarinic activity was determined by measuring the effects of the compounds on spasmogenic responses of isolated rabbit ileal segments at 37° to acetylcholine at a bath concentration of one part per million.[11] The effect of the test drugs on spontaneous tone and motility of similar paired segments was also determined.

Results

The results of the autonomic screening studies are presented in Tables I and II. The test compounds have been grouped according to their chemical similarities so that the relationship between changes in activity and changes in chemical structure can be readily seen.

Inspection of the tables reveals individual structure–activity relationships which need not be repeated in detail but certain general observations seem worthy of further comment. It seems

Table I. Comparison of autonomic effects in dogs



YS no.	R	R′	R″	X	mg/kg	BP	Nic	Epi	CO	Vag
2	H	H	—	$N(CH_3)_2$	20	P	1	2	3	4
1	H	H	—	$N(C_2H_5)_2$	20	1	2	3	2	4
14	H	H	—	$N(C_4H_9)_2$	20	1/P	3	Pot	2	2
13	H	H	—	pyrrolidino	10	P	0	0	0	0
3	H	H	—	piperidino	20	2/P	3	2	2	3
15	H	H	—	morpholino	20	2	1	1	2	0
11	—OH	H	—	piperidino	40	2/P	0	0	0	1
9	—OH	H	—	morpholino	20	1	0	0	0	0
6	=O	H	—	piperidino	20	2	1	1	3	3
5	=O	H	—	morpholino	20	2	0	1	0	0
18	H	methyl	—	NH_2	5	P	0	0	0	0
27	H	methyl	—	$N(CH_3)_2$	10	P	0	0	0	0
44	H	methyl	—	$N(C_2H_5)_2$	20	3	3	Pot	3	4
16	H	methyl	—	piperidino	20	3	2	1	3	4
19	H	methyl	—	morpholino	20	2	3	3	1	1
52	H	methyl	—	$^{+}N(C_2H_5)_2CH_3$	5	3	4	Pot	3	3
45	H	methyl	—	$^{+}N(C_2H_5)_3$	5	3	4	Pot	2	2
28	H	phenyl	—	NH_2	10	2	Pot	Pot	0	0
8	H	phenyl	—	NHC_2H_5	20	1	2	1	1	2
41	H	phenyl	—	$N(CH_3)_2$	20	2	2	Pot	1	2
43	H	phenyl	—	$N(C_2H_5)_2$	20	3	3	Pot	1	3
51	H	phenyl	—	$N(i\text{-}C_4H_9)_2$	20	2	0	0	1	2
12	H	phenyl	—	piperidino	5[a]	1/P	1	Pot	0	0
4	H	phenyl	—	piperidino	20	3	3	Pot		3
7	H	phenyl	—	morpholino	20	1	0	0	0	0
32	H	phenyl	p-OCH_3	NH_2	20	3	1	Pot	1	1
40	H	phenyl	p-OCH_3	$N(CH_3)_2$	20	1/P	0	1	0	0
22	H	phenyl	p-OCH_3	$N(C_2H_5)_2$	10	3	3	Pot	1	3
30	H	phenyl	p-OCH_3	morpholino	20	1	1	0	0	0
33	H	phenyl	o-Cl	NH_2	20	0	Pot	Pot	0	1
26	H	phenyl	o-Cl	$N(CH_3)_2$	20	2	1	1	0	1
23	H	phenyl	o-Cl	$N(C_2H_5)_2$	20	3	4	Pot	1	1
20	H	phenyl	o-Cl	piperidino	20	3	3	Pot	1	1
21	H	phenyl	o-Cl	morpholino	20	2	Pot	Pot	0	0

Table I—*continued*

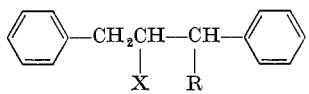
YS no.	R	R′	R″	X	mg/kg	BP	Nic	Epi	CO	Vag
22a	H	phenyl	*p*-Cl	$N(CH_3)_2$	20	2	1	1	0	1
50	H	phenyl	*p*-Cl	$N(C_2H_5)_2$	20	3	3	Pot		3
24	H	phenyl	*p*-Cl	piperidino	20	1	1	0	0	0
25	H	phenyl	*p*-Cl	morpholino	20	0	0	0	0	1
36	H	phenethyl	—	NH_2	20	3	Pot	Pot	1	2
39	H	phenethyl	—	NHC_2H_5	20	2	3	1	1	1
37	H	phenethyl	—	$N(CH_3)_2$	20	0	0	0	0	0
38	H	phenethyl	—	$N(C_2H_5)_2$	20	3	4	0	2	4
42	H	phenethyl	—	piperidino	20	2	1	Pot	2	0
46	H	phenethyl	—	$^+N(CH_3)_3$	9	3	0	Pot	1	1
53	H	phenethyl	—	$^+N(C_2H_5)_2CH_3$	5	3	4	Pot	3	1

[a] Limit of dose due to insolubility.

YS no.: compound number; mg/kg: intravenous dose of test compound; BP: effect on blood pressure; Nic.: effect on nicotine pressor response; Epi.: effect on epinephrine pressor response; CO: effect on carotid occlusion reflex pressor response; Vag.: effect on depressor response to peripheral vagal stimulation.

The figures listed under the appropriate headings refer to the degree of depression of that particular response (see text). 0: no change from control; 1: 25 per cent reduction from control; 2: 50 per cent reduction from control; 3: 75 per cent reduction from control; 4: 100 per cent reduction from control; P: pressor response obtained; Pot: potentiation of control response.

Table II. Comparison of autonomic effects in dogs



YS no.	R	X	mg/kg	BP	Nic	Epi	CO	Vag
35	H	NH_2	20	P	Pot	Pot	1	0
34	H	$N(CH_3)_2$	20	P	0	0	0	0
48	H	$N(C_2H_5)_2$	20	2	4	Pot	2	2
47	H	piperidino	15	1/P	0	0	2	2
10	=O	piperidino	20	2	0	0	0	0

YS no.: compound number; mg/kg: intravenous dose of test compound; BP: effect on blood pressure; Nic.: effect on nicotine pressor response; Epi.: effect on epinephrine pressor response; CO: effect on carotid occlusion reflex pressor response; Vag.: effect on depressor response to peripheral vagal stimulation.

The figures listed under the appropriate headings refer to the degree of depression of that particular response (see text). 0: no change from control; 1: 25 per cent reduction from control; 2: 50 per cent reduction from control; 3: 75 per cent reduction from control; 4: 100 per cent reduction from control; P: pressor response obtained; Pot: potentiation of control response.

evident that the essential type and magnitude of autonomic effect of these agents is largely determined by the amino function rather than by configurations of the arylalkyl portion of the molecules.

The major exceptions to this statement are to be found in the 3-phenyl-*n*-propylamine series and the 1-methyl substituted 3-phenylpropylamines where adrenergic blockade rather than ganglionic inhibition appear to account for the autonomic depressant effect observed in some compounds (YS–1, 2, 3, 19). As branching of the alkyl portion of the molecule increased, autonomic inhibition became more uniformly and completely ganglionic in nature.

In two instances, primary amines caused pressor responses (YS–18 and YS–35) whereas transient depressor responses occurred with the other primary amino compounds. In no instance did primary amines exert significant autonomic depressant activity, but in all but one instance they potentiated epinephrine and/or nicotine pressor responses (YS–28, 32, 36, 35). Dimethylamino tertiary amines were usually pressor, either wholly or secondarily (YS–2, 27, 40, 34), with little general effect on autonomic reactivity. On the other hand, the diethylamino derivatives were generally the most potent hypotensives and antinicotinic (ganglionic blocking) agents of the tertiary amines of each series (YS–1, 44, 43, 22, 23, 50, 38, 48). The piperidino member sometimes showed comparable activity (YS–3, 16, 4, 20).

Morpholino derivatives were usually considerably less active as autonomic agents. However, an unexpected observation was made in the case of the 1-methyl-3-phenylpropylamine series when a morpholine group was introduced. This compound (YS–19) suppressed epinephrine pressor responses as well as nicotine responses. Fig. 1 demonstrates this action of YS–19. It may be seen that the pressor responses to injected nicotine and epinephrine and to electrical stimulation of the peripheral greater splanchnic nerve were almost completely abolished by YS–19 at 20 mg/kg. The pressor responses to bilateral carotid occlusion were partially suppressed but only within 5–10 min after the injection (not shown in Fig. 1). The carotid occlusion response has recovered in this tracing. Recovery was complete for all elicited responses within two hours after administration. Comparable activity was observed in only one other compound; the

diethylamino derivative of 3-phenylpropylamine (YS–1). Substitution in the terminal phenyl ring did not appreciably alter autonomic activity of these compounds.

Quaternization with methyl–ethyl or ethyl groups resulted in marked increases in antinicotinic (ganglionic blocking YS–52, 45, and 53) activity, but quaternization solely by methyl groups did not result in enhanced activity (YS–46).

All those compounds which exhibited grade 3 (75 per cent) or grade 4 (100 per cent) inhibition of pressor responses to nicotine and epinephrine were further evaluated.

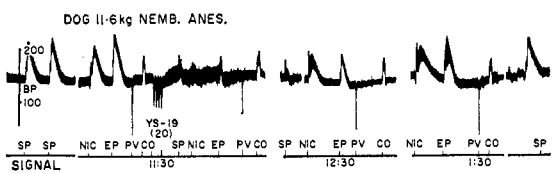


Fig. 1. Some autonomic effects of YS–19 in the dog. Demonstration of adrenergic blocking activity.

BP: blood pressure; SP: electrical stimulation of the left peripheral splanchnic nerve for 15 sec; NIC: intravenous injection of nicotine, 0·04 mg/kg; EP: intravenous injection of epinephrine, 0·003 mg/kg; PV: electrical stimulation of the right peripheral vagus nerve for 5 sec; CO: bilateral carotid occlusion for 1 min. Drum speed same as Fig. 2. Dose of test drug (mg/kg) in parentheses.

Table III presents the intravenous doses (SD_{50}) of various agents required to produce a 50 per cent suppression of the pressor response (sympathetic) and bladder contraction (parasympathetic) in response to injected dimethylphenylpiperazinium iodide (DMPP). Values for tetraethylammonium (TEA) and hexamethonium are included for comparison. The most active tertiary amine was 1-(*N*,*N*-diethylamino)-1,3-diphenylpropane (YS–43). The three quaternaries were quite active by this test, two comparing favourably with hexamethonium (YS–45, 53) and one with TEA (YS–52). There was no definite indication of any specificity towards one or the other branches of the autonomic system. In experiments where the anticholinergic and antihistaminic actions of these agents were assayed against injected acetylcholine and histamine, they were without inhibitory effect on the responses.

Table III also presents the SD_{50} doses for the more active compounds against the contraction of the cat nictitating membrane

in response to electrical excitation of the preganglionic trunk of the superior cervical nerve. Again 1-(*N*,*N*-diethylamino)-1,3-diphenylpropane (YS–43) was the most active tertiary amine tested, being about one-third as potent as TEA. The quaternaries (YS–45, 52) were as potent as TEA by this test but only one-tenth as potent as hexamethonium. YS–53 was only as potent as TEA. The response of the nicitating membrane to post-ganglionic stimulation of the superior cervical nerve was not altered

Table III. Autonomic and hypotensive effects of highly active analogues. Comparison of autonomic and hypotensive activity of active analogues based on inhibition of pressor responses and urinary bladder contractions induced by DMPP in dogs, nictitating membrane contractions in cats, and hypotensive responses in normotensive and acutely hypertensive dogs

YS no.	Autonomic activity			Hypotensive activity	
	SD_{50} (mg/kg, dog)		SD_{50} (mg/kg, cat)	HD_{500} (mg/kg, dog)	
	Sympath. (BP)	Parasympath. (bladder)	(nict. memb.)	Normo-tensive	Hyper-tensive
14	6·0	6·0			
44	3·7	4·2	6·4	10·0	2·5
45	0·5	0·5	1·1	1·0	0·3
52	1·4	1·7	1·0	2·0	1·0
43	3·2	2·7	3·2	8·0	4·4
23	5·7	3·3	7·0	10·0	6·4
20	6·9	2·5			
39	8·0	8·0			
38	13·9	6·7	15·0	15·0	5·0
53	0·3	0·2	3·5	6·4	1·0
48	6·0			> 3·2	>6·0
TEA	2·0	0·9	1·1	5·0	1·8
Hexa-methonium	0·3	0·5	0·1	0·8	0·1

SD_{50}: dose (mg/kg) required to suppress autonomic response by approximately 50 per cent.
Sympath. (BP): pressor response to dimethylphenylpiperazinium iodide (DMPP).
Parasympath. (Bladder): bladder contraction induced by DMPP.
Nict. memb.: contraction induced by electrical stimulation of preganglionic superior cervical nerve.
HD_{500}: dose (mg/kg) required to produce hypotension such that fall in BP (mm Hg) × duration in minutes = 500 (e.g. 50 mm fall lasting 10 min).

by doses which completely blocked the response to preganglionic stimulation (Fig. 2).

Table III also compares the hypotensive doses of these compounds in normotensive and neurogenically hypertensive dogs. Of the tertiary group, YS–43 and 44 were again the most active. The quaternaries were again active, YS–45 approaching hexamethonium, YS–53 comparing with TEA and YS–52 being intermediate. The dose necessary to decrease blood pressure the prescribed amount in hypertensive animals was uniformly much smaller than that required for normotensive animals.

Table IV summarizes the acute toxicity information obtained following intravenous administration in mice. Tertiary amines

Table IV. Acute intravenous toxicities of highly active analogues

YS no.	i.v. LD_{50}, mg/kg	SD	Symptoms
19	75	±12	Ataxia, flaccidity, loss of righting reflex (RA), areflexia, respiratory paralysis (RP)
44	18	± 3	Hyperexcitable, convulsions, RP
52	10	± 2	Ataxia, flaccidity, loss of RA, areflexia, RP
45	6	± 1	Ataxia, flaccidity, RP
43	22	± 4	Convulsions, tremor, RP
50	36	±12	Convulsions, urination, defecation, RP
22	26	± 7	Convulsions, cardiac death?
23	16	± 3	Gasping respirations, flaccidity
38	37	± 1	Convulsions, cardiac death?
46	6	± 1	Gasping respirations, flaccidity, RP
53	6	± 1	Brief convulsions, ataxia, RP
48	35		Convulsions, RP
TEA	36	± 7	Convulsions, RP
Hexamethonium	45	± 6	Ataxia, convulsions, RP
Methantheline	7	± 1	Convulsions, RP
d-Tubocurarine	0·2		Flaccidity, RP

generally produced severe convulsions, tremor, and death from respiratory paralysis. These symptoms were also observed following TEA, methantheline, and hexamethonium. The quaternaries of this series (YS–45, 52, and 46) did not cause convulsions

but instead brought about ataxia, flaccidity, and eventual paralysis. YS–53 produced a similar state after a brief convulsive episode.

These observations led to the study of their effect on the frog nerve muscle preparation. Surprisingly some of the tertiary amines, as well as quaternaries, produced some neuromuscular blockade. Bath concentrations of the order of 0·02–0·04 per cent of the compounds tested by this technique resulted in a 65–75 per cent depression of the contractile response. Compounds included in this study were YS–52, 45, 43, 50, 38, 53, 34, and *d*-tubocurarine chloride. It will be remembered that of this group, YS–52, 45, and 53 are quaternary ammonium compounds while the others are all tertiary amines. All of the compounds tested, except YS–52, washed out of the muscle in the 2-h period allowed, permitting recovery of the muscle tension to near the control level. YS–52 did not wash out in two hours, the tension remaining at the pre-washing level. That the effects were not caused by depression of muscle contractile elements was shown by obtaining control level responses when the muscle was stimulated directly by a second electrode imbedded in the muscle tissue itself.

Antispasmodic studies showed that none of the 53 compounds tested exerted pronounced action on the isolated ileal strips. Methantheline, at a concentration of 1 part in 50 million ($1 : 50 \times 10^6$) relaxed the acetylcholine-stimulated strip while atropine sulphate was similarly effective at $1 : 75 \times 10^6$. On the unstimulated ileum both caused relaxation at $1 : 5 \times 10^6$. TEA was active against acetylcholine at 1 : 100,000 and on the unstimulated strip at 1 : 200,000. Most of the compounds of the test series exhibited activity comparable to TEA. Of the active ganglionic blocking agents of the series, the diethylamino derivative (YS–38) of the 1-phenethyl substituted series was the most active on the ileal strips, inhibiting the acetylcholine spasm at 1 : 200,000 but relaxing the unstimulated strip at $1 : 1 \times 10^6$, indicating that a large part of its action on the strips may be musculotropic. There were several instances, notably YS–22, 33, 34 and 47, where concentrations as low as $1 : 1 \times 10^6$ caused relaxation of the unstimulated segments, but the dose effective against acetylcholine spasm was greater in all cases. In general, tertiary amines were more antimuscarinic than quaternaries.

Reference to the respiratory effects of these compounds has been made. No striking respiratory effects were observed at subtoxic doses. In most cases, moderate respiratory stimulation occurred during depressor responses following drug injection. This stimulation was of brief duration; it usually paralleled the hypotensive action, and was probably reflex in nature. It was observed in some cases, notably with the more active antinicotinic members of the series, that the respiratory stimulant effect of nicotine and DMPP was blocked or partially depressed (Fig. 2). Death from administration of most of these compounds was due to respiratory paralysis.

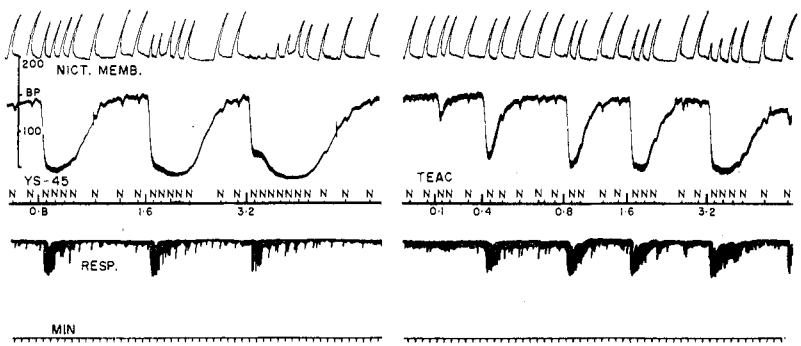


Fig. 2. Comparison of the ganglionic blocking activity of YS–45 and TEA on the superior cervical ganglion of the cat. Animal anaesthetized with sodium pentobarbital, 35 mg/kg, i.p.

BP: blood pressure; N: electrical stimulation of the preganglionic superior cervical nerve at 10 c/s with an output of 2 V for 10 sec. Time in minutes. Figures elevated above signal line indicate test drug doses (mg/kg).

Discussion

Inspection of the general chemical structure of the compounds described reveals certain similarities to a wide range of pharmacologically active agents including the sympathomimetic amines, anti-Parkinson drugs, methadone, caramiphene hydrochloride, and others. Many of these agents possess some degree of antinicotinic, synaptic depressant, or anticholinergic activity. The observation was made that primary and secondary amines in the

series generally caused little impairment of autonomic activity; indeed potentiation of pressor responses to nicotine and epinephrine often accompanied their administration. A basis for these actions is to be found in the observations of Hartung and Munch[12] who demonstrated that 3-phenylpropylamines and 2-phenethylamines exhibited pressor activity and like ephedrine were capable of potentiating pressor responses to epinephrine. It was only with the tertiary and quaternary amines that significant autonomic depressant activity became manifest. Quaternization of active tertiary amines resulted in further enhancement of synaptic depressant activity. Winbury's[2] observations on some related arylalkylamines are pertinent. He studied the effect of branching of the alkyl chain in a series which actually included YS–45 of the present series. He reported this compound to be twice as active as TEA on the superior cervical ganglion of the cat. The unbranched phenylpropylamine derivative, in his hands, was less active than the 1-methyl derivative (YS–45). Although the unbranched analogue was not prepared in the present series, it is apparent that branching of the alkyl chain enhanced gangliolytic activity somewhat. Winbury found that substitution of other aryl groups in place of the phenyl group had little effect on blocking activity. Further substitution of oxygen substituents on the alkyl chain decreased activity. This action was confirmed in the present series (see Table I). Winbury also reported that substitution on carbon number 2 of the alkyl chain decreased activity. It would therefore appear that future syntheses might logically be directed towards further alkyl substitutions in the 1-position. It might also prove fruitful to introduce a second nitrogen which could be quaternized.

The lack of nicotinolytic activity observed in the methyl quaternized 1,1-diphenethyl-*N*,*N*,*N*-trimethylaminomethane (YS–46) compound was interesting since the analogous compound quaternized with one methyl group and two ethyl groups was a highly potent blocking agent. Another study by Winbury *et al.*[3] bears on this relationship. In a series of alkylamines and *N*-methylpiperidines, quaternization with methyl groups caused ganglionic stimulation but ethyl or larger radicals resulted in blockade. No evidence of synaptic stimulation was observed with YS–46 but the lack of blocking action was evident. Wien and Mason[4]

have reported just the opposite relationship with bis-quaternary nitrogen compounds, namely that quaternization with methyl groups promotes greater ganglionic blocking potency than if ethyl groups are used. The presence of the second ammonium grouping must be responsible for this alteration in events. Wien and Mason also reported increased neuromuscular paralysant activity with ethyl quaternized bis-compounds. Winbury did not study neuromuscular effects, but in the present studies no marked neuromuscular activity resulted with either methyl or ethyl quaternaries. This action is probably related to the bis ammonium configuration specifically since it is known that most active curareform agents have two nitrogen atoms spaced approximately 14 Å apart.[13]

In the present studies the tertiary amines appeared to be as active as the quaternaries in blocking neuromuscular transmission. The synthetic compounds were much less active than *d*-tubocurarine chloride, for the latter was effective in causing a similar degree of blockade of the junction at a concentration of only 0·0001 per cent. The most active member of the test series is thus, on a dosage basis, 200 times less active than curare. It should be noted, however, that these compounds are much less toxic on intravenous administration than curare. Thus a comparison of YS–43, a tertiary amine, shows it to be 200 times less potent than curare as a blocking agent but it is about 200 times less toxic when compared on an intravenous basis. On the other hand, the quaternaries were also about 200 times less active on the neuromuscular junction but are only about 60 times less toxic.

With regard to the tertiary amines and ganglioplegic activity, most are known to be less potent than their quaternized derivatives but Phillips[14] reported that his tertiary nicotine derivatives offered better therapeutic ratios than the corresponding quaternaries. In the present series 1-(*N*,*N*-diethylamino)-1,3-diphenylpropane (YS–43) approaches this condition. By all tests employed it was one-fourth to one-half as active as quaternary derivatives but only one-fourth to one-third as toxic. Plummer *et al.*[15] found that quaternization of some tertiary amines of tris(2-diethylaminoethyl)amine derivatives caused a loss of activity. Although in this series, primary and secondary amines

were without significant autonomic depressant activity, the recent introduction by Stone *et al.*[16] of mecamylamine demonstrates that the amino function is not always the determinant of the type of autonomic activity to be found.

Many members of the series produced transient blood pressure decreases which, in many cases, correlated spatially and temporally with the degree of autonomic depression (Fig. 2). Several tertiary amines produced depressor responses which did not always correlate with peripheral autonomic depression. Since none of the compounds possessed significant smooth muscle-relaxant properties or cholinergic properties and since the hypotensive effects were not altered in bilaterally vagotomized animals, it would appear that peripheral and reflex mechanisms were not responsible for the hypotension observed, leaving the possibility of central or perhaps unrecognized cardiac effects as the mechanism of action in these instances.

Finally, Wenzel and Emick[17] studied the antispasmodic and antinicotinic actions of a series of 17 3-phenylpropylamines, most of which were substituted in both the 1- and 3-alkyl positions. None of their compounds were markedly effective against acetylcholine on rat ileal segments but three compounds exhibited antinicotinic activity manifest as blockade of nicotine tremor in rats. These three derivatives contained either an oxygen or an aryl substituent in the 3-position, however, making these compounds most closely related to trihexyphenidyl.

Although none of the present series produced prolonged hypotension in either normotensive or neurogenically hypertensive dogs, there was a definite indication that some specificity of action was present since much smaller doses were generally required in the hypertensive animals to produce comparable depressor effects. Perhaps further substitutions in this highly active phenylalkylamine moiety will prove fruitful.

Summary. A series of 53 1-substituted-3-phenylpropylamine compounds were evaluated for their effects upon autonomic function. Activity varied from sympathomimetic to sympatholytic depending primarily upon the amino portion of the molecule and to a lesser extent on substitution in the 1-position of the alkyl portion of the molecule. Quaternization of the nitrogen atom enhanced blocking activity but also increased toxicity.

The most potent members of the series were more active than TEA but less active than hexamethonium by most comparisons.

None of the compounds showed significant musculotropic, muscarinic, or antimuscarinic activity. Curareform activity was weak being, in general, about one two-hundredth as active as the reference standard. Unexplained hypotensive activity in some instances was assumed to be due to central mechanisms, cardiac effects or local actions.

Structure–activity correlations have been discussed and compared with published data on related series.

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