Journal of Medicinal and Pharmaceutical Chemistry

VOL. 3, No. 3 (1961)

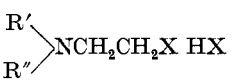
The Pharmacology of a Series of Substituted 2-Halogenoalkylamines

J. D. P. GRAHAM and G. W. L. JAMES, *Department of Pharmacology, Welsh National School of Medicine, Cardiff*

Hunt[1] included the compound *N*,*N*-dimethyl-2-chlorophenethylamine (DMEA) in a report on the antiadrenaline activity of some 2-halogenoalkylamines. According to Ferguson and Wescoe,[2] DMEA possesses muscarine-like, nicotine-like and relaxant properties, in addition to powerful but short-lasting antagonism to the pressor actions of adrenaline.

The present paper is concerned with the potency and other features of the antagonism to adrenaline, noradrenaline, 5-hydroxytryptamine and histamine, and the relaxant, muscarine-like and local anaesthetic properties of a series of compounds of the DMEA type. Some sixty of these were studied, including the alcohols related to some of the more active compounds and their methiodides. This report deals with selected members of the series. All of them (see I) differ from Dibenamine (II; R′ = R″ = $PhCH_2$) in having a phenyl group attached to the β-carbon of the alkyl chain. They resemble adrenaline in structure more closely than do molecules of the Dibenamine type. A brief notice of their

(I)



(II)

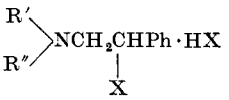
properties has appeared.[3] The structures and code numbers are shown in Table I. Compound L_1 is D-1 and L_{18} is A-6 of Nickerson and Gump.[4]

Methods

All the compounds are crystalline substances easily soluble in water, with the exception of L_{17}–L_{20} which are more readily soluble in acetone or alcohol. All are unstable in water, e.g. a

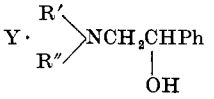
Table I. A series of 2-halogenoalkylamines related to DMEA

Type 1



Code No.	R′		R″	X
L_1	CH_3		CH_3	Cl
L_2	CH_3		CH_3	Br
L_3	CH_3		CH_3	I
L_4	C_2H_5		C_2H_5	Br
L_5	n-C_3H_7		n-C_3H_7	Br
L_6	iso-C_3H_7		iso-C_3H_7	Br
L_7	n-C_4H_9		n-C_4H_9	Br
L_8		piperidino-		Br
L_{10}		morpholino-		Br
L_{11}	CH_3		H	Br
L_{12}	C_2H_5		H	Br
L_{13}	n-C_3H_7		H	Br
L_{14}	n-C_4H_9		H	Br
L_{17}	$C_6H_5CH_2$		H	Br
L_{18}	$C_6H_5CH_2$		$C_6H_5CH_2$	Cl
L_{19}	$C_6H_5CH_2$		$C_6H_5CH_2$	Br
L_{20}	$C_6H_5CH_2$		$C_6H_5CH_2$	I
L_{21}	$CH_3CH=CH$		$CH_3CH=CH$	Br
L_{22}	C_2H_5		CH_3	Br
L_{23}		pyrrolidino-		Br
L_{24}	CH_3		$C_6H_5CH_2$	Br
L_{25}	CH_3		$C_6H_5OCH_2CH_2$	Br

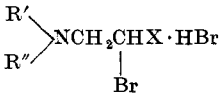
Type 2



Code No.	R′	R″	Y
L_1—OH	CH_3	CH_3	
L_4—OH	C_2H_5	C_2H_5	
L_5—OH	n-C_3H_7	n-C_3H_7	
L_7—OH	n-C_4H_9	n-C_4H_9	
L_1—3-OH-MeI	CH_3	CH_3	CH_3I
L_4—OH-MeI	C_2H_5	C_2H_5	CH_3I

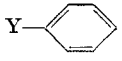
Table I—*continued*

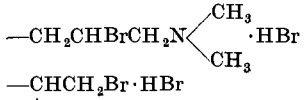
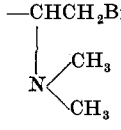
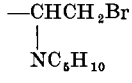
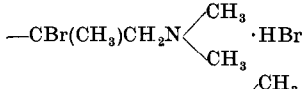
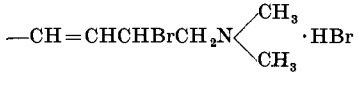
Type 3



Code No.	R′	R″	X
L_{34}	CH_3	CH_3	p·BrC_6H_4
L_{35}	CH_3	CH_3	p·$CH_3C_6H_4$
L_{39}	CH_3	CH_3	1·$C_{10}H_7$
L_{40}	CH_3	CH_3	2·$C_{10}H_7$
L_{54}	C_6H_{11}	C_6H_{11}	p·$CH_3C_6H_4$
L_{55}	piperidino·		p·$CH_3C_6H_4$

Type 4



Code No.	Y
L_{30}	
L_{31}	
L_{32}	
L_{42}	
L_{53}	

The structures of the compounds related to *N*,*N*·dimethyl·2·chlorophenethyl·amine (DMEA) which were examined are grouped into four types as follows: (1) the close analogues of DMEA; (2) some alcohols and methiodides related to them; (3) compounds in which the phenyl group has been replaced, e.g. by α·naphthyl; and (4) miscellaneous compounds.

10^{-3} solution w/v of L_1 releases halogen almost instantly to 100 per cent of the theoretically possible maximum, presumably with cyclization to ethyleneimonium ion. Fall of pH to about 4 takes place within a few minutes owing to release of combined acid. Hydrolysis to the corresponding alcohols proceeds at a variable rate. All compounds were administered using freshly made solutions in saline or water. Neutralization of acid by alkali speeds up hydrolysis.

Acute toxicities were measured by the method of Kärber[5] in white mice injected intravenously. They are expressed in mmoles/kg.

Subacute toxicity was measured in litter mate groups of Wistar rats injected daily intraperitoneally with saline or with 1 mg/kg of compound L_1 for 21 days and weighed regularly. The rats were then killed and blood and selected organs examined.

Antagonism to the pressor action of adrenaline (1 μg/kg or $5{\cdot}4 \times 10^{-9}$ moles/kg base given as HCl) and noradrenaline ($0{\cdot}5$ μg/kg or $2{\cdot}7 \times 10^{-9}$ moles/kg base given as bitartrate) was measured on groups of atropinized spinal rats pretreated with 5 mg/kg of hexamethonium bromide (C_6). Extrapolated ED_{50}'s in μmoles/kg are given for comparison of potencies in Table II. Further studies were made with selected compounds on the blood pressure of spinal cats, and of cats and dogs anaesthetized with 40 mg/kg of pentobarbitone sodium and injected intravenously with 4 μg/kg ($2{\cdot}16 \times 10^{-8}$ moles/kg) of adrenaline or 2 μg/kg ($1{\cdot}06 \times 10^{-8}$ moles/kg) of noradrenaline. The mouse protection test[6] was used in groups of 25 mice to determine the ED_{50} of compounds L_2–L_{19} against an LD_{66} of adrenaline which was injected intraperitoneally 1 h after intravenous administration of graded doses of the compounds. The ED_{50} of each, measured from a regression line, was then administered intravenously to groups of 25 mice and the LD_{66} of adrenaline injected at various time intervals. A plot of the 'loss of protection against adrenaline' against time gave an ET_{50} for each drug, i.e. the time taken by an ED_{50} dose of the drug to lose half its potency in protecting a group of mice from the lethal effect of injection of an LD_{66} of adrenaline. This index is a measure of the duration of action of the drug, and the routes of administration should be stated when quoting it. The effect of compound L_1 on the glycogenolytic action of adrenaline on slices

of rabbit liver was determined.[7] Conventional manometry was used to investigate the action of selected compounds on the amine oxidase of guinea pig liver homogenate.

Antagonism to 5-hydroxytryptamine (4 ng/ml or $2 \cdot 4 \times 10^{-8}$ M final concentration base given as creatinine sulphate) was determined on isolated rat uterus and guinea-pig ileum.[8]

Antagonism to histamine was measured by a modification of the guinea pig aerosol method[9] and confirmed for selected compounds on the blood pressure of cats anaesthetized with pentobarbitone sodium, 40 mg/kg, and injected intravenously with 4 μg/kg ($2 \cdot 7 \times 10^{-8}$ moles/kg) of histamine base given as the diphosphate. The action of compound L_2 on histaminase from hog kidney was investigated.[10] The pA_2 values of selected compounds were measured at 5 minutes contact time on isolated guinea-pig ileum stimulated with histamine (10 ng/ml or 9×10^{-8} M final concentration).

Local anaesthetic potency was measured in guinea pigs[11] and surface action tested by instillation into the conjunctival sacs of rabbits.

Acetylcholine-like activity was investigated on isolated guinea-pig and rabbit ileum and on the isolated perfused rabbit heart. Graded doses of compounds were injected intravenously in cats anaesthetized with 60 mg/kg of chloralose and the effect noted on salivary flow induced by a constant infusion of a solution of carbachol and adrenaline.[12] The actions of selected compounds on the peristaltic reflex in isolated rabbit gut were examined. The pre- and post-ganglionic cervical sympathetic nerves were stimulated with square pulses (0·5 V, 0·5 c/sec, 0·05 msec) in cats anaesthetized with 40 mg/kg of pentobarbitone sodium, so as to produce maximal contractions of the nictitating membrane, which were recorded. Compounds in solution were applied directly to the ganglion or were injected into the carotid artery or the jugular vein before and after ganglionectomy.

Neuromuscular activity was investigated (*a*) by intravenous injection into young chicks or pigeons and comparison of the effects with those of *d*-tubocurarine (*d*-TBC), decamethonium and suxamethonium; (*b*) on the isolated phrenic nerve-diaphragm of the rat and guinea pig[13] stimulated maximally by 12 square pulses per min; (*c*) by close-arterial injections to the

soleus and the anterior tibial muscles of cats anaesthetized with 60 mg/kg of chloralose and given a supramaximal nerve stimulus at a frequency of 8 per min; and (*d*) by determining the pA_2 on the isolated frog rectus muscle at 2 min contact time after acetylcholine, 10^{-7}, for a 45-sec exposure.

Cardiovascular and respiratory action. The effect of compound L_1 on the perfused vessels of the rabbit ear and on the isolated auricles and the perfused heart of the rabbit was examined. The effect on the action of adrenaline was noted in preparations of the hearts of frogs and rabbits. Dogs were anaesthetized with 40 mg/kg of pentobarbitone sodium injected intravenously and a left thoracotomy was performed, with artificial respiration of oxygen (2·5 l./min). Thoracic aortic pressure was recorded from a polythene catheter inserted retrogradely from the femoral artery. Left pulmonary arterial pressure was recorded by direct cannulation of a lobar branch. Shillingford–Muller transducers (Cambridge Instrument Co. London, 73428) and a Cambridge recording outfit (C398748) were used to measure the effect of compound L_1 injected intravenously. Electrocardiograms (lead I) were taken from subcutaneous electrodes. In other dogs similarly anaesthetized, tracheotomy was performed and the minute volume recorded by attaching a Drager volumeter, or by using a recording spirometer.

Results

Toxicity. The LD_{50}'s of the compounds tested are given in Table III in mmoles/kg. All are convulsants of rapid onset and great severity. This activity is largely central in origin but is increased by the fasciculatory action on the muscles and by the asphyxial effect of paralysis of the diaphragm in certain cases. A small number of delayed deaths occurred after 24 h. Young rats injected daily with compound L_1 lagged behind their sibs in rate of growth, and the spleen, liver, kidney and adrenals were notably small but no cellular damage was noted in tissues or blood.

Antagonism to adrenaline and noradrenaline. The ED_{50}'s for antagonism of the pressor action of adrenaline and noradrenaline in the rat are shown in Table II, and in the cat in Table III; also the ED_{50}'s and the ET_{50}'s of selected compounds for protection of mice from the lethal effects of injected adrenaline are shown.

The relative potencies in the two tests on pressor action are parallel.

The most potent compound, L_{35} or *N*,*N*′-dimethyl-2-bromo-*p*-methylphenethylamine had an ED_{50} in the rat pressor test of

Table II. The anti-adrenaline potencies of compounds related to DMEA

Code no.	ED_{50} on rat blood pressure		Code no.[a]	ED_{50} on rat blood pressure	
	adrenaline	noradrenaline		adrenaline	noradrenaline
L_1	0·046	0·1	L_{21}	0·03	0·03
L_2	0·035	0·056	L_{22}	2·8	3
L_3	0·022	0·015	L_{23}	0·05	0·08
L_1—OH	250[c]	350[c]	L_{24}	0·22	0·39
L_4	5	1·8	L_{25}	0·14	0·23
L_5	1	1·3	L_{30}	100[b]	100[b]
L_6	30	22	L_{31}	0·04	0·05
L_7	4·4	4·5	L_{32}	13	15
L_8	15	14	L_{34}	0·0006	0·0002
L_{10}	4	4·5	L_{35}	0·0003	0·0007
L_{11}	0·6	0·5	L_{39}	0·02	0·02
L_{12}	100	80	L_{40}	0·002	0·06
L_{13}	250[c]	250[c]	L_{42}	100[b]	100[b]
L_{14}	200[c]	200[c]	L_{53}	100[b]	100[b]
L_{17}	3	2·8	L_{54}	100[b]	100[b]
L_{18}	1·5	1	1	7·7	10
L_{19}	2·4	1·7	2	0·28	0·55
L_{20}	0·34	0·27			

The antagonism of the DMEA compounds to the pressor action of adrenaline (1 μg/kg or 0·005 μmoles/kg) and noradrenaline (0·5 μg/kg or 0·003 μmoles/kg) in the spinal rat, as μmoles/kg.

[a] 1 = Dibenamine, 2 = phenoxybenzamine.

[b] No activity was detected in the doses recorded.

[c] Weak activity was recorded and the figure given is an extrapolated ED_{50}.

0·14 μg/kg, whereas that of Dibenamine was 2 mg/kg or more, i.e. the former is 10–20,000 times stronger. This figure implies that one molecule of the antagonist can block the 'receptor' for approximately 1–5 molecules of adrenaline, or, alternatively, that the affinity of L_{35} is five times that of adrenaline. The compounds most effective against the pressor action of adrenaline are most active in protecting mice. As may be seen from Table III, the

Table III. Pharmacology of compounds related to DMEA

(1) Code no.	(2) Mouse protection test ED_{50}	(3) Mouse protection test ET_{50}	(4) Cat blood pressure A ED_{50}	(5) Cat blood pressure NA ED_{50}	(6) Cat blood pressure A ET_{50}	(7) Cat blood pressure NA ET_{50}	(8) 5 OH-Tryptamine uterus	(9) 5 OH-Tryptamine gut	(10) Histamine aerosol	(11) Histamine pA_2	(12) L.A.	(13) LD_{50}
L_1	—	—	0·03	0·05	135	120	0·25	—	2·1	5·8	0·4	—
L_2	1·4	105	0·03	0·04	150	60	0·35	—	0·9	5·3	0·33	1·16
L_3	—	—	0·02	0·03	180	105	0·05	—	2·1	5·3	0·33	—
L_1—OH	100[a]	100[a]	250	220	—	—	250[a]	250[a]	25[a]	0	27	100
L_4	15	250	2·7	7·6	115	100	1·9	59	7·5	5·2	0·22	7·2
L_5	6·3	60	4·3	5·5	100	100	1·9	100	13	5·1	0·5	2·0
L_6	—	—	200	240	—	—	—	—	17	4·2	—	—
L_7	11	95	7·6	10	240	240	5·3	500	23	4·1	1·4	0·21
L_8	28	65	50	50	320	370	—	24	16	4·4	0·22	0·12
L_{10}	40	—	11	17	300	325	5·7	27	25	4·0	0·1	3·5
L_{11}	13	240	5·5	2·4	150	220	8·8	24	25[a]	4·0	0·1	2·1
L_{12}	260	90	26	20	240	280	26	75	25[a]	4·2	0·1	1·0
L_{13}	160	—	210	280	210	260	31	83	25[a]	4·0	0·1	95
L_{14}	260	—	120	360	210	210	64	300	25[a]	4·0	0·5	15
L_{17}	25	370	7·6	7·7	—	—	—	—	25[a]	4·6	—	2·5
L_{19}	18	600	—	—	—	—	—	—	25[a]	5·2	0·1	5·3

The pharmacological properties of compounds related to DMEA are given. (1) The code numbers; (2) the mouse protection test with adrenaline, as an ED_{50} in μmoles/kg and (3) the duration of the protection as an ET_{50} in min; (4) the antagonism to the pressor effect of 4 μg/kg (0·02 μmoles/kg) adrenaline and (5) 2 μg/kg (0·01 μmoles/kg) noradrenaline as an ED_{50} in μmoles/kg and (6)–(7) its duration as an ET_{50} in min; (8) the antagonism to 5-hydroxytryptamine as an ED_{50} measured in μmoles/ml on the isolated rat uterus and (9) guinea-pig ileum; (10) the antagonism to histamine as an ED_{50} in μmoles/kg measured by the aerosol technique and (11) as a pA_2 on isolated guinea-pig ileum; (12) the potency as an infiltration local anaesthetic in terms of procaine as unity; and (13) the LD_{50} in mmoles/kg measured intravenously in white mice by Kärber's method. The symbol (—) means that no trial has been made. [a] No activity was detected in the doses recorded.

duration of action is relatively short if the substituent on the amino nitrogen is small (e.g. methyl, as in L_1) but longer if it is a benzyl group (L_{19}). Duration of action does not parallel potency; L_{12}, which has much less potency than L_2, has a rather shorter action, and L_{19}, which also has less potency than L_2, has a much longer action.

The onset of the action after intravenous injection is immediate, there being no need to wait for activity to develop as with phenoxybenzamine. Because large doses of adrenaline or noradrenaline do not produce a pressor response in fully treated animals, it is deduced that the nature of the antagonism is a non-competitive one. Prior administration of sodium thiosulphate (3 g/kg followed by 1 g/kg every 10 min) reduces the antagonistic activity of compound L_1 in rats to 25 per cent of its activity, as with the Dibenamine series. There is little difference in potency against adrenaline or noradrenaline on the blood pressure of the spinal rat but some in the potency and duration of antagonism to the pressor actions in anaesthetized cats and dogs. Stimulation by adrenaline of the mammalian cardiac muscle is not antagonized. Compound L_1 in a 0·65 mM solution produces a 50 per cent inhibition of the hyperglycaemic response to adrenaline in the test with liver slices.

Antagonism to 5-hydroxytryptamine. The compounds tested (see Table III) display considerable activity in antagonizing the effect of 5-hydroxytryptamine on the isolated rat uterus. Compound L_3 has almost 20 per cent of the activity of lysergic acid diethylamide on this preparation. It takes 100 times as much of compound L_3 to reduce by half the action of 5-hydroxytryptamine on the ileum as it does to reduce its action on the uterus to the same extent. Compounds L_1–L_3, which have a considerable degree of muscarinic activity, cannot be examined by this test.

Antagonism to histamine. The compounds tested are active antagonists of certain effects of histamine (see Table III). There is little correlation between this activity as tested on isolated guinea-pig ileum and the power of protection from the effects of inhaling histamine as an aerosol. This may relate to absorption from the site of subcutaneous injection since for compound L_5 there is a delay of 10–30 min after injection before peak protective activity is found and a lack of potency relative to L_1, which is

effective speedily. There is little difference in the values for pA_2 measured on isolated ileum. The alcohols (Table I, type 2) corresponding to the halogeno-amines are inactive so that the active chemical species of the latter compounds is probably the imonium ion. The action on isolated tissue is prolonged and not readily reversible, but if a low concentration is used, partial recovery takes place after repeated washing. No antagonism to the depressor action of histamine on the blood pressure of cats was observed in doses which abolished the pressor action of adrenaline. There is an approximate parallelism between anti-adrenaline and antihistamine potency, in the series as a whole.

Compound L_2 inhibits the activity of histaminase *in vitro*.

Local anaesthesia. On infiltration, the above compounds exert a powerful action but are inactive when applied to the conjunctival surface. Their potencies relative to procaine are listed in Table III. The increase in effectiveness of the alcohol (L_1-OH) relative to the parent compound is at once apparent, and the most active of the series, *N*,*N*-di-*n*-butyl-2-hydroxyphenethylamine, is some 35–40 times more powerful than procaine by this test. This substance, and the other alcohols, do not antagonize the effects of adrenaline, histamine or 5-hydroxytryptamine and have no effect on the peristaltic reflex in isolated rabbit gut. The more active among them prevent the action of acetylcholine on frog rectus muscle to a greater degree than procaine. Unlike some of the amines they have no muscarinic activity. They are tissue irritants in solutions of 0·1 per cent (w/v) concentration. The local anaesthetic effect passes off after about 45 min; inflammatory reaction is not then apparent.

Acetylcholine-like activity is found in compounds L_1–L_4 and L_{11}, particularly in compound L_3 which has an activity approximately one-tenth of that of acetylcholine on isolated gut. Hydrolysis of this compound abolishes activity. The corresponding methiodide is active. An atropine-sensitive contraction of smooth muscle by this compound was demonstrated on rabbit and guinea-pig ileum. The diethyl compound (L_4) and the monomethyl compound (L_{11}) are much less active than the dimethyl compounds (L_1–L_3). Doses of 0·05 mg/kg of compound L_1 cause a brief increase in salivation in the anaesthetized cat infused with carbachol. This action is abolished by atropine, but doses of 1

mg/kg of L_1 produce a salivation which is resistant to atropine and lasts for approximately 90 min. These compounds have no effect on the peristaltic reflex. On injection into the bloodstream, they cause contraction of the nictitating membrane in anaesthetized cats. Bilateral superior cervical ganglionectomy does not affect this action. There is no evidence of action on ganglion cells or any inhibition of the contraction of the membrane produced by continued stimulation of the sympathetic nerve.

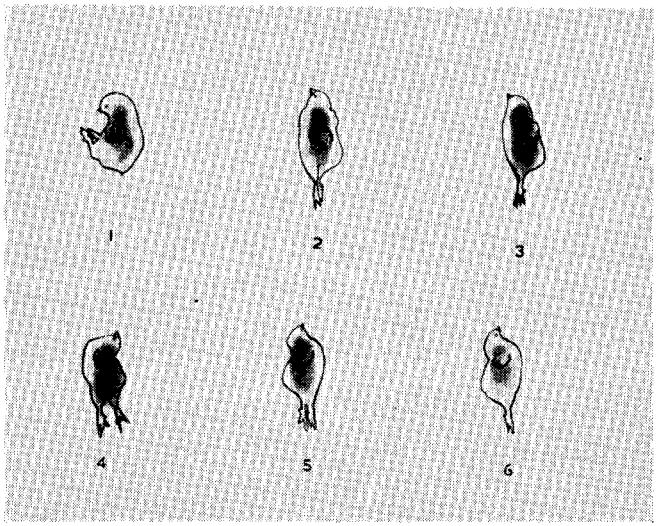


Fig. 1. The postures assumed by 2-day-old chicks killed by intravenous injection of the following drugs: (1) gallamine, (2) suxamethonium, (3) decamethonium, (4) compound L_1, (5) L_2 and (6) L_3.

Neuromuscular relaxant activity is displayed in varying degrees by compounds L_1–L_5 and L_{11} but not by the others. These are the compounds which have weak acetylcholine-like activity. Intravenous injection in young chickens (see Fig. 1) produces an extensor spasm resembling the effect of decamethonium rather than the flaccid paralysis caused by *d*-TBC. The alcohols are inactive. Concentrations of 10^{-4}–10^{-5} M in solution cause a transient increase in the force of contraction of the isolated and indirectly stimulated diaphragmatic muscle of rats or guinea

pigs. If the concentration is raised to 10^{-3} M, or if 10^{-4} M acetylcholine is added, a partial block occurs. This effect is abolished by *d*-TBC. Compounds L_1–L_4 greatly reduce contractions of the indirectly stimulated anterior tibial muscle of the cat when injected intra-arterially in doses of 1 mg/kg, while only slightly reducing the contractions of the soleus muscle. Injection of 1 mg/kg of eserine fully restores the contractile power of the soleus and abolishes that of the tibialis. These compounds show no blocking activity on the indirectly stimulated gastrocnemius of the rat but reduce contractions of this muscle in the cat by 50 per cent in doses of approximately 20 mg/kg. The alcohol derived from L_1 is inactive. Compounds L_1–L_3 cause a slow but reversible contracture of the isolated frog rectus muscle; compound L_3 causes an irreversible Lundsgaard type of contracture in the isolated gastrocnemius muscle of the frog stimulated directly. Compounds L_6, L_7, L_{13} and L_{14} exert a feeble antagonism to the action of acetylcholine on the rectus preparation. This effect is of long duration, not easily removed by washing the tissue, and is abolished by eserine. The alcohol related to L_7 also exerts this action and is more potent than is the parent compound. It is a powerful local anaesthetic.

These actions are, in the main, those of a decamethonium type of neuromuscular blocking activity.

Cardiovascular and respiratory actions. The vessels of the isolated perfused rabbit ear are dilated by compound L_1 in a concentration of 10 μg/ml. The force of the contraction of the auricles and of the perfused heart of the rabbit are reduced by a direct action which is of long duration. The voltage of the E.C.G. complex, which may be recorded by applying electrodes directly to the isolated heart, is reduced, but the rhythm remains regular and the rate is little affected. In the anaesthetized or intact rabbit the compound causes a transient bradycardia which is atropine-sensitive. The stimulant action of adrenaline on the heart is abolished in frogs but not in rabbits.

In the anaesthetized dog, intravenous injection of compound L_1 in a dose of 1 mg/kg causes an initial slowing and deepening of respiration which is followed by a doubling of respiratory rate and minute volume. This augmentation of breathing lasts for 45 min. The pulse rate is quickened and the systemic pressure

rises, largely due to a rise in peripheral resistance. The pulse pressure in the pulmonary artery is greatly increased. These effects on cardiovascular dynamics are transient; they are illustrated in Fig. 2. The pressor effect of adrenaline, but not its cardiac stimulant action, is abolished or reversed.

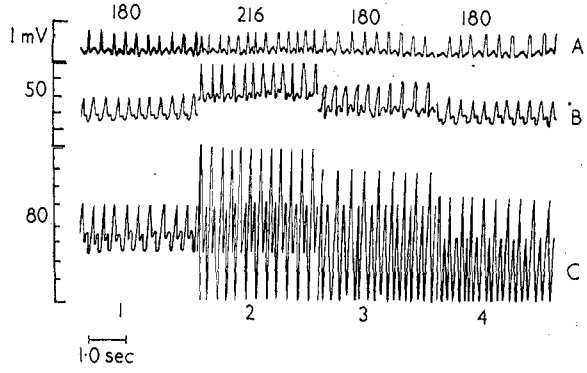


Fig. 2. Dog, male, 12·3 kg, pentobarbitone sodium, 40 mg/kg intravenously, left thoracotomy, 2·5 l. oxygen/min by pump. Record (A) of lead 1 ECG, (B) of pulmonary and (C) of systemic arterial pressures made (1) before and (2) 30 sec after intravenous injection of compound L_1, 1 mg/kg, (3) 1 min later, and (4) 2 min later. The pulse rates per minute are marked above and the pressures in intervals of 10 mm Hg on the abscissae.

Discussion

Structure–action relations. Consideration of the findings summarized in Tables II and III indicates that there are three structural needs for antiadrenaline activity in the DMEA type of compound. These are: (1) an aromatic ring structure; (2) a β-halogenoethyl group; and (3) a secondary or tertiary amino group. Optimal activity occurs when the aromatic ring is a *p*-substituted phenyl or a weighted phenyl (naphthyl) and the amine is a dimethylamino group. Replacement of any of these substituent groups abolishes activity and minor variation of the substituents diminishes activity. The closer the approximation to the structure of adrenaline itself (e.g. L_{34} and L_{35}), the greater the potency found, e.g. some 10–20,000 times that of Dibenamine. With regard to the halogen component, the same relation holds

for these compounds as for other series reported previously;[14] viz: I > Br > Cl. When the compounds are very insoluble, this order of potency may not hold (L_{18}–L_{20}). Weighting of the alkyl chain decreases activity (L_2–L_5), but if the substituent is a phenoxyethyl group, this moiety which confers other properties tending to produce high potency in 2-halogenoalkylamines (e.g. in phenoxybenzamine) may more than compensate (L_{25}). Fixing of the chain in a piperidine (L_8) or morpholino group (L_{10}) does not significantly alter activity when compared with a weighted alkyl chain (e.g. L_8 and L_{10} *cf.* L_4, L_5, L_7), but a branched chain is inactive (L_5 and L_6). These general relations hold also if there is only one substituent on the terminal N atom, although potency is reduced in each case to 10 per cent of that of the disubstituted analogue (compare L_2, L_4, L_5, L_7 with L_{11}, L_{12}, L_{13} and L_{14} respectively).

Replacement of the phenyl ring by methyl (L_{54} and L_{55}) abolishes activity, introduction of a *p*-Br (L_{34}) or a *p*-CH_3 (L_{35}) enhances activity, but replacement with the naphthylmethyl group has little effect. This latter group is a constituent of the active compound J_{11}[9] or SY_{28} (*N*-ethyl-*N*-1-naphthylmethyl bromoethylamine·HBr). Increasing the number of carbon atoms between the phenyl ring and the N atom from two to three (L_{30}) or four (L_{53}) abolishes activity, as does methylation of the β-carbon (L_{42}). The alcohols related to L_{1-3}, L_4, L_5 and L_7 were tested and found to be inactive. The small amount of activity shown for L_1—OH in Table II may be due to the presence of parent compound as an impurity in the sample tested. The active form of these halogenoalkyl amines is probably the ethyleneimonium ion. The reduction of activity by previous treatment with thiosulphate, the rapid liberation of halogen in aqueous solution of the free bases and the direct relation between consumption of thiosulphate under these circumstances and the potency of the solution as an antagonist of adrenaline imply that these compounds cyclize in solution, as does phenoxybenzamine. The isomers in this series which form the same ethyleneimonium ion have the same activity (e.g. L_2 and L_{31}; L_8 and L_{32}). The isolation, purification and direct testing of a number of alcohols demonstrates their inactivity.

The compounds tested were all extremely toxic, which is due to over-stimulation of the central nervous system. This is not

exerted by the alcohol but by the parent compound or the imonium ion. The reason for the extreme toxicity of the di-*n*-butyl and piperidino compounds L_7–L_8 may be related to their powerful activity as local anaesthetics. There appears to be a relation between increasing toxicity and increasing antiadrenaline activity, but it is spurious since the active and toxic compounds L_1–L_3 have also considerable acetylcholine-like and neuromuscular blocking activity whereas the most active antiadrenaline compound, L_{35}, is not the most toxic.

The most active antagonist of adrenaline is also the most active inhibitor of the uterine response to 5-hydroxytryptamine and this relation holds (more or less) for antagonism to histamine, where compound L_3 has about one-tenth the potency of mepyramine. Again, the alcohols are inactive as antagonists. The antagonisms to adrenaline, noradrenaline, histamine and 5-hydroxytryptamine therefore probably reside in the imonium ion and have similar features. The attachment to receptors of the catechol amines is more firm than that of the indole or the imidazole amine; the latter antagonisms are briefer and in part reversible by washing isolated preparations. The extreme potency of compound L_{35} introduces the possibility of a number of the α receptors for catecholamines being blocked by one molecule of this drug.

The potent local anaesthetic activity of the otherwise inactive alcohols dissociates this feature of the general action from the blockade of specific tissue receptors. The moderate activity which has been noted in other 2-halogenoalkylamines and in the parent compounds of the DMEA series is probably due to formation of hydrolysis products in the solutions tested.

Activity resembling that of acetylcholine is abundantly present in the compounds with methyl groups on the amino nitrogen. The most active, the methiodide of the alcohol related to L_1–L_3, exists in solution as a substituted quaternary ammonium cation and produces atropine-sensitive spasms of smooth muscle of the uterus and intestine, some contraction of the nictitating membrane, dilatation of perfused vessels, depression of the heart muscle, and salivation. The long-lasting depression of cardiac muscle and the prolonged salivation which result from higher doses than those which cause the transient atropine-sensitive effects, resemble the effects caused by nitrogen mustards. There is no evidence of

a nicotine-like action. The neuromuscular blocking action is present in compounds L_1–L_5 and L_{11} and absent in the alcohols; that displayed by compounds L_1–L_5 resembles the action of decamethonium. These compounds are methyl derivatives, with the exception of L_5 which is a *n*-propyl derivative. Chain shape in the substituent on the nitrogen atom appears to affect the characteristics of the neuromuscular blocking action.

Despite the considerable change in structure from the more familiar Dibenamine-type molecule, these compounds display most of the characteristic actions of 2-halogenoalkylamines of the dibenamine type. Some of them have in addition the property of interfering with the sites of action of acetycholine.

Summary. The antagonism to adrenaline, noradrenaline, histamine and 5-hydroxytryptamine has been investigated in a series of compounds related to *N*,*N*-dimethyl-2-chlorophenethylamine (DMEA) and the main relations of structure and activity have been determined. The alcohols derived by hydrolysis from certain of these compounds have been shown to possess none of this antagonistic action but to be local anaesthetics of some potency. Certain of the compounds display muscarine-like and neuromuscular blocking activity, the latter resembling that caused by decamethonium. All the active compounds are convulsants.

Acknowledgements. All compounds and their chemical and physical data were supplied by N. B. Chapman and his colleagues of Hull University.

References

[1] Hunt, C. C. *J. Pharmacol.*, **95**, 177 (1949)
[2] Ferguson, F. C. and Wescoe, W. C. *J. Pharmacol.*, **100**, 100 (1950)
[3] James, G. W. L. *J. Physiol.*, **147**, 60P (1959)
[4] Nickerson, M. and Gump, W. S. *J. Pharmacol.*, **97**, 25 (1949)
[5] Kärber, G. *Arch. exp. Path. Pharmak.*, **162**, 480 (1931)
[6] Loew, E. R. and Micetich, A. *Fed. Proc.*, **6**, 351 (1947)
[7] Harvey, S. C., Wang, R. A. and Nickerson, M. *J. Pharmacol.*, **104**, 3 (1952)
[8] Gaddum, J. H. and Hameed, K. A. *Brit. J. Pharmacol.*, **9**, 240 (1954)
[9] Graham, J. D. P. and Lewis, G. P. *Brit. J. Pharmacol.*, **8**, 54 (1953)
[10] Kapeller Adler, R. *Biochem. J.*, **48**, 99 (1951)
[11] Bülbring, E. and Wajda, I. *J. Pharmacol.*, **85**, 78 (1945)
[12] Bülbring, E. and Dawes, G. S. *J. Pharmacol.*, **84**, 182 (1945)
[13] Jenden, D. J. *J. Pharmacol.*, **114**, 398 (1955)
[14] Graham, J. D. P. This Journal, **2**, 499 (1960)