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# THE ANTIHISTAMINE AND ANTIADRENALINE PROPERTIES OF A SERIES OF N-NAPHTHYLMETHYL-2-HALO-ETHYLAMINE DERIVATIVES

BY

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Dibenamine (N: N-dibenzyl-2-chloroethylamine hydrochloride) was described by Nickerson and Goodman (1945, 1947) as a specific antagonist of the effects of injected adrenaline and of stimulation of the sympathetic nervous system. A relationship between chemical structure and pharmacological action was postulated (Nickerson, Nomaguchi, and Goodman, 1946). Later Nickerson and Gump (1949) examined some 200 analogues of dibenamine, among which were four compounds included in the series reported here.

The nature of the antagonism to adrenaline shown by these compounds, of the structural type R R'N.$CH_2CH_2Cl$, was reported to be different from that of any other known series of antiadrenaline compounds (Nickerson, 1949). The essential difference lay in the fact that the dibenamine type of compound exerted an absolute or non-competitive antagonism to adrenaline whereas compounds such as the ergot alkaloids, yohimbine, F883, or F933 exerted a competitive type of inhibition.

Loew and Micetich (1948a) showed that some of these haloalkylamine derivatives possess a strong antihistamine action in addition to their antagonism to adrenaline.

The object of this investigation was to examine quantitatively some of the properties of a closely related group of these compounds (Chapman, James, Graham, and Lewis, 1951), paying particular attention to the specific activity in inhibiting the actions of histamine, adrenaline, and adrenergic nerve stimulation.

## METHODS

*Acute Toxicity.*—The LD50 was estimated by Karber's method in male white mice weighing 20–25 g., mepyramine maleate being included with the compounds under examination (referred to by code numbers J5–J28, see Table I). Readings were taken at 1, 24, 48, and 72 hours. The aqueous solubility of some of these compounds was not sufficient for the tests; arachis oil or an aqueous solution of propylene glycol was then used as solvent (see Table I). Fine suspensions of a few substances had to be used. All injections were made in a volume of 1 ml./100 g. of mouse.

*Cats.*—Cats anaesthetized with chloralose (60 mg./kg.) were prepared for recording the carotid blood pressure; injections were made into the external jugular vein. To one group adrenaline (4 μg./kg.), histamine (2 μg./kg.), and acetylcholine HBr (1 μg./kg.) were administered before and five minutes after increasing doses of each compound, until the response to adrenaline was reversed, that to the other agents inhibited, or toxic symptoms were manifested. The haloethylamines are long-acting, and for this reason, when assessing the results of the test, the doses were considered as being cumulative.

In a further group of cats histamine (2 μg./kg.) was injected before and five minutes after each of three to five dose levels of compound. The doses selected were based on information obtained from the first group of experiments. The results were variable, and so a scatter diagram was made of the percentage inhibition of the fall of blood pressure due to histamine, plotted against the logarithm of each dose, and the regression line was calculated for each compound. The ED75 was read from these and compared with that of mepyramine.

In another group of cats anaesthetized with chloralose four doses of histamine (1, 2, 4, and 8 μg./kg.) and three doses of adrenaline (4, 8, and 16 μg./kg.) were regularly and repeatedly injected before and at intervals of 5, 30, 60, 120, 180, and 240 minutes after a suitable dose of each haloethylamine. In this way the course of the inhibition with time was followed.

A series of spinal cats was used to evaluate the effects of the compounds on the pressor response to adrenaline, according to the technique of Chen, Nash, and Russell (1950) and Chen and Russell (1950), either alternating a standard dose of adrenaline (4 μg./kg.) or graded doses of 2, 4, 8, and 16 μg./kg. of adrenaline with increasing doses of a haloethylamine. In most animals contractions of the nictitating membrane were also recorded. Similar experi-

ments, injecting graded doses of histamine and antagonist, were carried out on cats anaesthetized with chloralose.

*Dogs.*—In dogs anaesthetized with sodium pentobarbitone (40 mg./kg.) injected intraperitoneally, the pressor effect of 4 μg./kg. of adrenaline injected into the right femoral vein, and the pressor response to 30 seconds' carotid occlusion, were recorded from the left femoral artery. Increasing doses of haloethylamines were administered until the pressor response to adrenaline had been reversed and the pressor response to carotid occlusion inhibited.

*Guinea-pig Aerosol.*—Groups of 15 guinea-pigs of 300–400 g. weight were exposed to a 0.5% solution of histamine as a spray, of particle size 0.5–2.5 μ (mean size 1 μ). This was delivered into a box fitted with an exit tube leading to waste at a rate of 4 l./min. The time elapsing between onset of spray and collapse from asphyxia was recorded and the animal resuscitated in a stream of 5% $CO_2$ in $O_2$. Twenty-four hours later the same animals were injected subcutaneously with haloethylamines, one dose level to each group. Each animal was exposed to the aerosol one hour after injection, and the protective effect was assessed. After seven days the test was repeated, a different dose level for each compound being used. As animals developed tolerance to the effects of the histamine aerosol they were replaced. Mepyramine was included as a reference compound and assessment of potency made by comparing the ED75 obtained from a plot of percentage increase of time to asphyxia against logarithm of dose of compound.

*Guinea-pig Ileum.*—The mean response to at least four additions of histamine (1–3 μg./100 ml. Tyrode's solution, in a 10-ml. bath, *p*H 7.3, temperature 37° C., 5% $CO_2$ in $O_2$) was recorded and a dose of haloethylamines left in contact for five minutes before repetition. As these compounds have a prolonged action only one reading could be made from each piece of intestine. The ED75 was recorded by plotting the percentage inhibition against the logarithm of the dose, and was used for comparison with mepyramine.

Various preparations of isolated perfused rabbit and cat heart, isolated auricle, and isolated intestine and uterus of rabbit were made and the effect of varying doses of haloethylamines on the responses to adrenaline and histamine investigated.

*Enzymatic Oxidation.*—The effect of amine oxidase (from guinea-pig liver) on the oxidation of adrenaline was observed according to the method of Blaschko, Richter, and Schlossman (1937). Varying concentrations of haloethylamines ($10^{-7}$–$10^{-3}$) were added during separate trials.

The action of histaminase (serum of pregnant women in the third trimester) on histamine was examined according to the method of Kapeller-Adler (1949), and the effects of varying concentrations of the compounds observed.

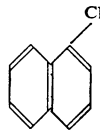
## Results

The code numbers and structure of the 19 compounds examined are listed in Table I.

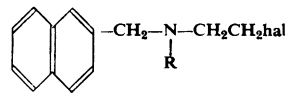
TABLE I

STRUCTURE AND ACUTE TOXICITY (I.P. MICE) OF NAPHTHYLMETHYL-2-HALOETHYLAMINE DERIVATIVES

N-1-naphthylmethyl-2-haloethylamine derivatives (J5–J19).




N-2-naphthylmethyl-2-haloethylamine derivatives (J20–J28).




| Code No. | R | Halogen | Solvent | LD50 (Karber) mg./kg. 48 hrs. | Death in |
|---|---|---|---|---|---|
| Mepyramine | | | Water | 157 | 1 hour |
| J5 | Phenyl | Cl | *Arachis oil | 2,500 | 2–3 days |
| J6 | ,, | Br | * ,, ,, | 1,000† | 2–3 ,, |
| J7 | ,, | I | * ,, ,, | 2,000 | 2–3 ,, |
| J10 | Ethyl | Cl | Water | 128 | 24 hours |
| J11 | ,, | Br | ,, | 42 | 24 ,, |
| J12 | ,, | I | ,, | 42 | 24 ,, |
| J13 | ,, | F | ‡Dil. HCl | 350 | 1 hour |
| J16 | Methyl | Cl | Water | 162 | 2 hours |
| J17 | ,, | Br | ,, | 49 | 24 ,, |
| J18 | ,, | I | ,, | 57 | 24 ,, |
| J19 | ,, | F | ,, | 200 | 2 ,, |
| J20 | Ethyl | Cl | ,, | 90 | 24 ,, |
| J21 | ,, | Br | ,, | 20 | 1–2 days |
| J22 | ,, | I | Watery soln. propylene glycol | 11 | 1–2 ,, |
| J23 | ,, | F | ‡Dil. HCl | 135 | 4 hours |
| J25 | Methyl | Cl | Watery so'n. propylene g'ycol | 138 | 1–2 days |
| J26 | ,, | Br | Water | 40 | 1–2 ,, |
| J27 | ,, | I | Watery so'n. propylene glycol | 40 | 1–2 ,, |
| J28 | ,, | F | ‡Dil. HCl | 180 | 4 hours |

All Cl derivatives were used as hydrochlorides, Br derivatives as hydrobromides, I derivatives as hydriodides. J13, J23, and J28 are bases which were disso'ved in hydrochloric acid just before injection, as the salts are very hygroscopic. J19 is a hydrochloride.

* 5–10% so'ubility in arachis oil. At higher concentrations a finely divided suspension was used.

† 540 mg./kg. at 72 hours.

‡ Before injection alkali was added until c'oudiness appeared.

*Toxicity.*—The toxic symptoms were fairly constant throughout the series, being a general depression of the central nervous system followed by cardiovascular and respiratory failure. The exceptions were the fluoroethylamines (J13, J19, J23, J28) which caused prolonged convulsions, although after a few hours a terminal phase of depression or exhaustion occurred, especially with J19, J23, and J28. Some of the chloro derivatives caused excitement of short duration at first. J5, J6, and J7 were relatively innocuous, although this may be partly due to poor solubility. The halogen derivatives showed decreasing toxicity in the order I, Br, Cl, F; this agrees with the descending order of molecular weights. The LD50s are given in Table I.

It is perhaps significant that death was generally delayed for 12–24 hours, in some instances longer. Again the exceptions were the fluoro derivatives which killed within one hour (J13), in 1–2 hours (J19), or within four hours (J23, J28). Death was due to asphyxia. J5, J6, and J7 caused some delayed deaths after 2–3 days.

*Antiacetylcholine Action.*—None of the compounds affected the depressor response to acetylcholine (Fig. 1) or the pressor response to pituitrin.

*Antiadrenaline Action.*—The majority of the compounds antagonized to a greater or less degree the pressor response to adrenaline (Fig. 1C). J5, J6, and J7 had little activity, only J6 causing any significant inhibition of the pressor response. On the other hand, J10, J11, and J12 were most active, and are about as potent as any antiadrenaline agent so far reported. The fluoro derivative of this group, J13, was inactive, as also were the other fluorides. Activity decreased gradually in the other members of the series; the chloro-compounds were noticeably less active than either the bromo- or iodo-compounds.

When graded doses of the inhibitor agent were injected alternately with the standard dose of adrenaline, the pressor response to the latter was reduced in steps until it was abolished. A linear relationship was established between the probit of the percentage inhibition and the logarithm of the dose (Bliss, 1935; Chen *et al.*, 1950).

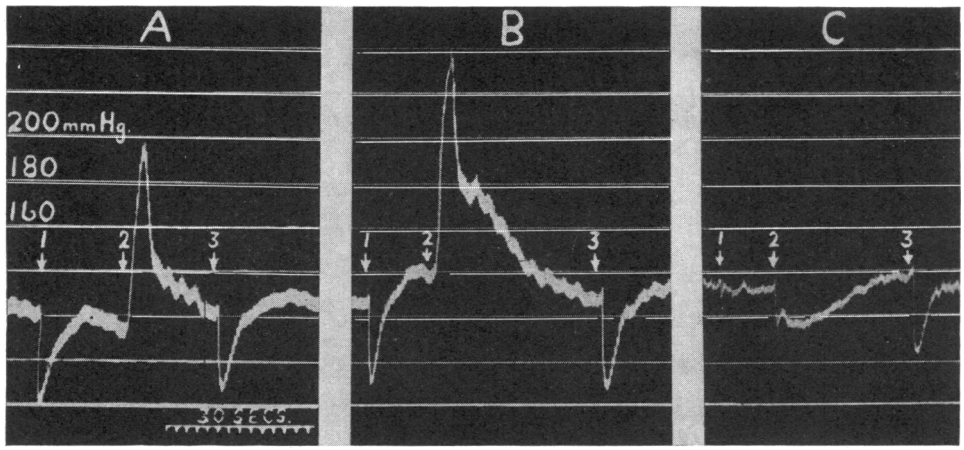



FIG. 1.—Cat, ♂, 3 kg. wt. chloralose 60 mg./kg. Carotid blood pressure. Time in 30 sec. A, Standard responses to histamine 2 μg./kg. (1), adrenaline 4 μg./kg. (2), and acetylcholine 1 μg./kg. (3). B, 5 min. after J18 100 μg./kg. C, 5 min. after J18 1.5 mg./kg. Note potentiation of response to adrenaline with the smaller dose and reversal with the larger dose, which inhibits the effect of histamine. Neither dose level affects responses to acetylcholine.

TABLE II

ADRENERGIC INHIBITION (EFFECTIVE DOSES IN MG./KG.)

| Compound | Cats | | Dogs; Sodium Pentobarbitone | |
|---|---|---|---|---|
| | Chloralose. Reversal of Pressor Response to Adrenaline | Spinal. 99% Reduction of Pressor Response to Adrenaline | Reversal of Pressor Response to to Adrenaline | Inhibition of Pressor Response to Carotid Occlusion |
| J5 | — | — | | |
| J6 | 20 | — | 20 | — |
| J7 | — | — | | |
| J10 | 0·5–1·0 | 0·17 | 0·50 | 5·50 |
| J11 | 0·5–1·0 | 0·23 | 0·20 | 3·50 |
| J12 | 0·5–1·0 | 0·57 | | |
| J13 | — | — | | |
| J16 | 8–10·0 | 21·4 | | |
| J17 | 0·5–1·0 | 0·47 | 0·25 | 2·5 |
| J18 | 1·0–1·5 | 4·17 | | |
| J19 | — | — | | |
| J20 | 5–7 | 8·90 | | |
| J21 | 1·0–2·0 | 5·30 | 1·5 | 3·50 |
| J22 | 2·0–2·5 | 4·50 | | |
| J23 | — | — | | |
| J25 | — | — | | |
| J26 | 3·0 | 6·75 | 2·5 | 3·50 |
| J27 | 3·0 | 5·37 | | |
| J28 | — | 50·0 | | |

— Indicates inactivity. Blank indicates not tested.

When graded doses of adrenaline (2, 4, 8, and 16 μg./kg.) were used in addition to graded doses of antagonist (Fig. 2) it could be shown that before the pressor response was completely inhibited in a spinal cat (or reversed in a cat anaesthetized with chloralose) the action was of a competitive nature, the response depending upon the dose of agonist and antagonist.

Gaddum's equation for competitive antagonism $K_1C_1=[1+(K_2C_2)^n]^a/1-a$ (Gaddum, 1943) was

The dose corresponding to 99% inhibition for each compound was taken as a measure of activity and is shown in column 1 of Table II. The ED99 rather than the dose bringing about reversal was chosen because the phenomena of reversal cannot be obtained regularly in spinal cats with a low blood pressure.

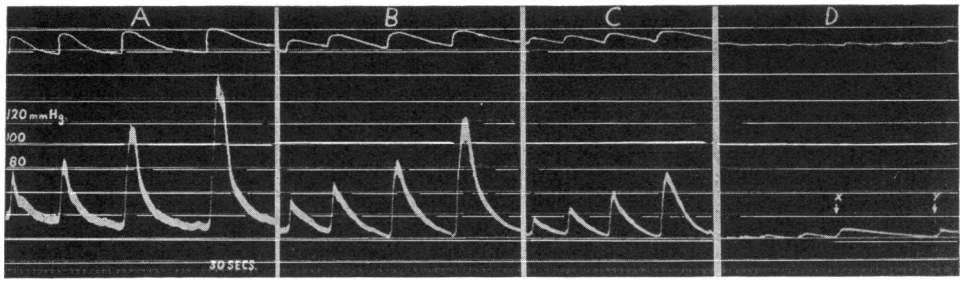



FIG. 2.—Cat, ♂, 2.8 kg. wt. Spinal preparation, nictitating membrane (above), and carotid blood pressure (below). Time in 30 sec. A, normal responses to 2, 4, 8, and 16 μg./kg. adrenaline. B, the responses to similar doses 5 min. after J17, 25 μg./kg. C, 5 min. after J17, 150 μg./kg. D, responses to the same doses of adrenaline, and also to 300 μg./kg. and 1 mg./kg. at X and Y respectively, 5 min. after J17, 300 μg./kg. Note in B and C that the inhibition is competitive in nature (the response is related to the dose of adrenaline); this is not so in D. The small residual pressor responses to the larger doses of adrenaline are probably due to cardiac stimulation which is not inhibited by the J compounds. The nictitating membrane record is similar to the blood pressure record.

employed to test the nature of this antagonism by the method described by Chen and Russell (1950). The equation was satisfied for all the active compounds. An example is shown in Fig. 3. The value of $n$ was always found, empirically, to be 2, which agrees with the observation of Chen and Russell (1950) on J11 (SY28).

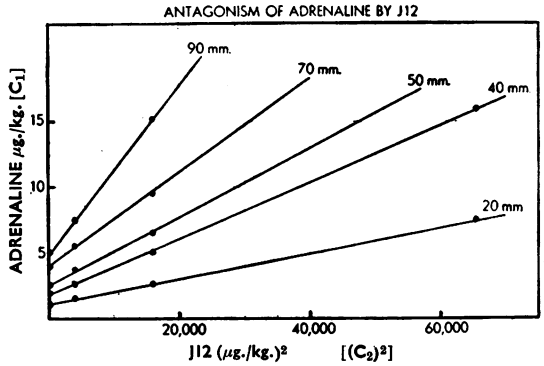



FIG. 3.—Application of Gaddum's equation for competitive antagonism $K_1C_1=[1+(K_2C_2)^n]^a/1-a$ to the effect of compound J12 in small doses (50–275 μg./kg.) on the pressor responses to adrenaline in a spinal cat. The abscissa is the square of the dose of antagonist in μg./kg., the ordinate is the amount of adrenaline injected in μg./kg. The pressor responses to several doses of adrenaline were measured and equipressor amounts of adrenaline determined after injecting various dose-levels of J12. The linearity of the relationship indicates the competitive nature of the antagonism exerted by J12 in these doses against adrenaline.

Once completely inhibited by larger doses of antagonist the dose of adrenaline can be increased to 1 mg./kg. or more and no pressor response is evident (Fig. 2). At this stage the equilibrium between adrenaline and antagonist had disappeared.

The action of the haloethylamines investigated is like that of other haloalkylamine derivatives in that they antagonize the excitatory actions of adrenaline, e.g. on cat pregnant uterus, rabbit pregnant and non-pregnant uterus, and cat nictitating membrane, but do not affect the inhibitory actions of adrenaline, e.g. on cat non-pregnant uterus, rabbit intestine, or the effect of adrenaline on the heart. It was observed that in high concentrations (250–500 μg./100 ml.) the haloethylamines depressed the tone and movement of isolated rabbit intestine and that this direct action masked the response to adrenaline.

In small doses (10 μg.) some of these compounds stimulated isolated perfused rabbit hearts. These doses inhibited the stimulant action of histamine, but not that of adrenaline, nor the inhibitory action of acetylcholine. Larger doses of these compounds (250 μg. to 1 mg.) inhibited cardiac action. Similar effects were found with the isolated auricle. The tone of the non-pregnant cat uterus *in situ* was lowered by large doses of the haloethylamines (20–30 mg./kg.) so that it no longer responded to adrenaline.

When injected *in small doses* (20–60 μg./kg.) the haloethylamines potentiated the pressor response to adrenaline (Fig. 1B). This effect was produced even by the most potent adrenaline inhibitors, J10, J11, and J12, as well as those compounds which did not antagonize adrenaline at all, such as J13 and J25. In the potent antiadrenaline compounds, however, this effect was not very great. With J13 and J25, the potentiation was considerable, reaching 100%. It is not due to atropine-like activity, occurring in spinal cats and atropinized cats.

*Adrenergic Inhibition.*—Stone and Loew (1948) and others showed that haloalkylamine derivatives (e.g. SY28—J11 in our series) not only reversed the pressor effects of adrenaline but also inhibited responses due to sympathetic nerve stimulation.

We have found, in agreement with others, that there was a considerable difference in the dose required to reverse the response to adrenaline and

that necessary to inhibit the pressor response to carotid occlusion. These doses for some of our haloethylamines are given in columns 3 and 4 of Table II.

The blood pressure is frequently lowered by the haloethylamines, usually more so in the cat than in the dog. It is likely that this effect is at least partly due to inhibition of the sympathetic tone in the peripheral vascular bed.

TABLE III
ANTIHISTAMINE ACTIVITY

| Compound | Blood Pressure Cats (Chloralose) ED75 (mg./kg.) | Guinea-pig Aerosol ED75 (mg./kg.) | Guinea-pig Ileum ED75 (μg./100 ml.) |
|---|---|---|---|
| Mepyramine maleate .. | 0·43 | 0·09 | 0·27 |
| J5 | >25·0 | 9·34 | >100·0 |
| J6 | >25·0 | 9·00 | >100·0 |
| J7 | >25·0 | 8·50 | >100·0 |
| J10 | 0·26 | 0·08 | 0·40 |
| J11 | 0·29 | 0·10 | 0·69 |
| J12 | 0·31 | 0·10 | 0·62 |
| J13 | >25·0 | >25·0 | >100·0 |
| J16 | >25·0 | 0·20 | 0·89 |
| J17 | 1·72 | 0·11 | 0·83 |
| J18 | 1·34 | 0·14 | 1·20 |
| J19 | >25·0 | >25·0 | 80·00 |
| J20 | 6·76 | 3·55 | 5·31 |
| J21 | 8·51 | 1·45 | 3·63 |
| J22 | 8·13 | 1·86 | 4·79 |
| J23 | >25·0 | 20·0 | >100·0 |
| J25 | >25·0 | 4·36 | 17·00 |
| J26 | 9·55 | 2·10 | 13·80 |
| J27 | 16·20 | 2·40 | 15·85 |
| J28 | 20·0 | 25·0 | 90·0 |

*Antihistamine Action.*—Antihistamine action was strongest in J10, J11, and J12. The fluoro-derivatives, J13, J19, J23, and J28, were inactive. The other members of the series were less active than the former group, and it was noticeable that the chloro-derivatives were less active than the bromo- or iodo-derivatives. The ED75 for each compound for three different methods of assessment of potency is shown in Table III. They are in good agreement except for the fact that the two chloro-derivatives J16 and J25 are inactive against the fall of blood pressure caused by histamine, whereas they are active against the effects of histamine on the isolated ileum or when inhaled by guinea-pigs. In dogs the depressor response to histamine was not reduced by more than 50–60% by any of the compounds. Mepyramine was used as a standard of comparison throughout the experiments, and it will be seen that J10, J11, and J12 are as active as this substance, if not more so. Application of Gaddum's equation demonstrated the competitive nature of the antagonism to the effects of histamine on the blood pressure of cats.

*Time-Action Relationship.*—The effects of both histamine and adrenaline are inhibited within five minutes of intravenous injection of a haloethylamine (Figs. 4 and 5), even if the solubility is poor as with J27. The results of the previous tests show that the two properties of the compounds (antiadrenaline and antihistamine) when present run parallel throughout this small series—e.g., J10 inhibits both agents powerfully, whereas J13 inhibits neither.

However, this latter test revealed some difference between the nature of the inhibition of adrenaline and that of histamine (Graham and Lewis, 1951). The responses to all doses of adrenaline were reversed so that there was 100% reduction in the pressor responses to adrenaline, and absolute or non-competitive antagonism was established within a few minutes. This was not so with histamine, as, although all responses were reduced, they were not abolished. The response was dependent upon the doses of antagonist and of histamine, showing that the antagonism was of a competitive nature (Figs. 4 and 5).

The time of action is another factor separating these two properties. The onset of action was the same, but the durations were different. The antagonism to histamine began to wear off quickly, whereas it was several hours before the effects of the antagonism to adrenaline began to disappear. In about 1½ hours the responses to histamine were almost normal, but it was four hours before the absolute antagonism of the pressor responses to adrenaline became competitive in nature.

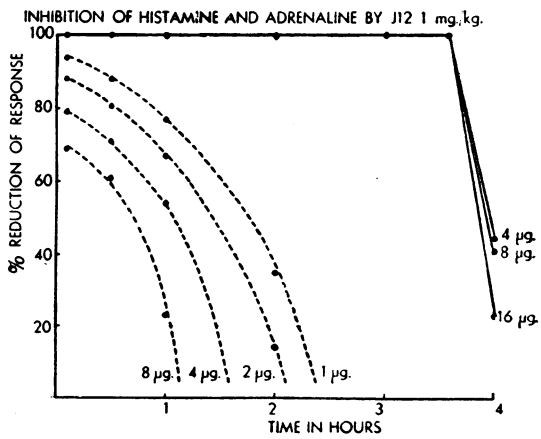



FIG. 4.—The relationship of antiadrenaline and antihistamine action in J12. Ordinate, percentage reduction of the response; abscissa, time in hours. At zero time 1 mg./kg. of J12 was injected i.v. into a cat under chloralose. Graded doses of adrenaline and histamine were injected before and at fixed intervals after J12. Reversal of the response to adrenaline is recorded as 100% reduction. Adrenaline (uninterrupted lines) was inhibited in a "non-competitive" manner for 3½ hours. Histamine (interrupted lines) was inhibited in a "competitive" manner, as shown by the fact that the response depended upon the dose of histamine.

It was observed that a dose of inhibitor producing competitive antagonism did not progress with time to produce an absolute antagonism. These remarks apply to all the compounds examined.

*Actions on Enzymes.*—One phase of the action of haloethylamines on the pressor response to adrenaline was potentiation. Several of the compounds were tested for their effect upon the enzymic oxidation of adrenaline. It was observed that they antagonized the action of amine oxidase to about the same degree—i.e., 20–80% within the range of concentration $10^{-4}$–$10^{-3}$. This holds whether the compounds are potent antiadrenaline agents or not.

The action of histaminase on histamine was studied in only a small number of experiments, as the purpose was to confirm that the antihistamine action of the haloethylamines was not due to potentiation of the enzyme. On the contrary, slight inhibition was observed. The action was not studied quantitatively.

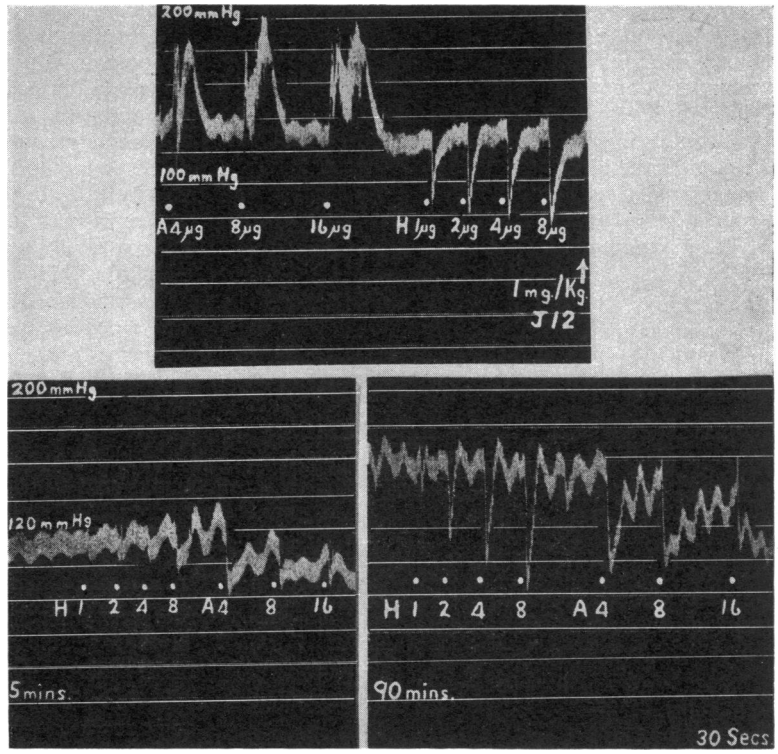



FIG. 5.—Kymograph record illustrating Fig. 4. Cat, ♂, 2.7 kg./wt. Chloralose 60 mg./kg. carotid blood pressure, time in 30 sec. Injections of adrenaline (4, 8, 16 μg./kg.) and histamine (1, 2, 4, 8 μg./kg.) before and at 5 and 90 min. interval after J12, 1 mg./kg. i.v.

## DISCUSSION

The structural features in this series of 2-haloethylamines which favour antagonism to adrenaline also favour antagonism to histamine. Parallellism between these two actions is a constant feature of the results, increasing antiadrenaline potency going with increasing antihistamine potency, and decline in one activity accompanying diminution of the other. Thus substitution in the 1-position on the naphthyl ring and the presence of an ethyl group on the N-atom favour activity, whereas the 2-naphthylmethyl moiety and the presence of phenyl or methyl groups on the N-atom produce a less active molecule. Loew and Micetich (1948a) also found a loss of activity with alteration from the 1- to the 2-position in the naphthyl ring in the mouse protection test, and Nickerson and Gump (1949) confirmed this on cat blood pressure. The halogen in the haloethyl side-chain also alters the activity (Chapman *et al.*, 1951), fluorine in the side-chain rendering the molecule inactive. The bromides and iodides having a 2-naphthyl ring and/or a methyl group show much greater activity than do the corresponding chlorides. Thus we do not regard the methyl and 2-naphthyl moieties as having such an inactivating influence as Nickerson and Gump (1949) and Loew and Micetich (1948a) did. These authors only examined the chloro-derivatives in this series. Variation in halogen is as important as other variations in the molecular structure.

Nickerson and Gump (1949) have suggested that the halogen in the side-chain of the 2-haloalkylamines splits off and the resulting carbonium ion undergoes cyclization to form a pharmacodynamically active cyclic immonium ion. Fluorine being chemically immobile, it might be supposed that cyclization would not occur in fluoro-compounds, which would be inactive. Inactivity as antiadrenaline and antihistamine agents has been found in the fluoro-compounds in this series and a marked difference in acute toxicity from the other haloalkylamines, which supports the theory of Nickerson and Gump (1949) concerning the mode of

formation of active intermediates. A noticeable feature is the relative weakness of activity in two chloro-compounds, viz., N-methyl-N-1-naphthylmethyl-2-chloroethylamine (J16) and N-methyl-N-2-naphthylmethyl-2-chloroethylamine (J25) in contrast to the considerable activity in the bromo- and iodo-analogues. Investigations at present being undertaken into the reactivity and kinetics of cyclization *in vitro* of these compounds may explain this anomaly.

One of the most potent antiadrenaline agents in the series is J11 (N-ethyl-N-1-naphthylmethyl-2-bromoethylamine HBr), also known as SY28 (Loew and Micetich, 1948b). Several reports as to the actions of this compound have appeared.

A dose of haloethylamine which is inadequate to cause inhibition usually causes potentiation, some compounds being more potent in this respect than others. Such an effect passes off with time and does not alter its nature to inhibition. A dose which is enough to cause an inhibition of the response to adrenaline may display one of two alleged types of action. The first of these is the competitive type of inhibition where the degree of the pressor response depends on the relative amounts of 2-haloethylamine and adrenaline injected. The second type as defined by Nickerson (1949) occurs when, " once an adequate block has been established, it cannot be overcome by massive adrenergic stimulation " ; thus when larger doses of the 2-haloethylamines are given no pressor responses are elicited by 10 mg./kg. of adrenaline.

The use of the pressor reflex following upon occlusion of the carotid arteries in dogs is a recognized technique for eliciting activity in the sympathetic nervous system (Heymans and Regniers, 1929). Agents which are known to inhibit the pressor response to injected adrenaline may be assumed to diminish reflex responses by peripheral action rather than by ganglionic block or inhibition of the afferent side of the reflex (Stone and Loew, 1948). In this respect the most potent compound is J17, N-methyl-N-1-naphthylmethyl-bromoethylamine HBr. The administration of 0.5 mg./kg. of J17 causes a fall in blood pressure in cats and dogs of some 40 mm. Hg and four hours' duration.

As stated, there is a general correlation between molecular structures favouring antiadrenaline activity and those favouring antihistamine activity. There are, however, certain differences between these two activities (Graham and Lewis, 1951), viz., the shorter duration of the antihistamine action of any effective dose of 2-haloethylamine ; the absence of a dose range causing potentiation of responses to histamine ; the fact that the antihistamine activity is always within the competitive range even with large doses of powerful inhibiting compounds which exhibit an extreme degree of " non-equilibrium " inhibition of adrenaline ; and the inhibition of the action of histamine but not of adrenaline on the heart. Nickerson and Harris (1949) in a short note suggest that antihistamine activity in a large series of 2-haloethylamines develops in two stages with time—firstly a competitive inhibition and then a non-competitive inhibition. The test object used was guinea-pig ileum, and no details of doses, duration of effect, etc., are available. Our results with 2-haloethylamines (0.1–1.0 $\mu$g.) in doses sufficient to abolish the response of isolated guinea-pig ileum to added histamine (0.1–0.3 $\mu$g.) do not support this. Such adequate doses left in contact with the tissue for some hours retain a competitive type of inhibition, larger amounts of histamine (10 $\mu$g.) causing a contraction. The studies on blood pressure reported confirm the competitive nature of the inhibition of histamine, in the doses used. Larger doses of these compounds " permanently " lower the blood pressure, which modifies responses to histamine. Even in toxic doses, the responses to large doses of histamine have never been abolished completely.

The antihistamine potency of some of these compounds is very high, being equal to that of mepyramine. The indices of potency compared with mepyramine differ according to the preparation and technique employed for the assay. This is usual, but the overall picture is very consistent.

The inhibitor effect on preparations of amine oxidase is of interest in relation to the potentiating action of comparable concentrations on the pressor response to adrenaline. Other agents, such as mepyramine, which potentiate adrenaline in certain doses (Graham, 1949) also inhibit amine oxidase (Tickner, 1951).

This action of our haloethylamines is not due to the reactive intermediate immonium ion, as the antihistamine and antiadrenaline properties appear to be. This is shown by the fact that compounds which do not form immonium ions, e.g., fluorides (Chapman *et al.*, unpublished), exert an equivalent degree of inhibition on the enzyme. None of the other structural rearrangements made in this series affect the inhibitory action on amine oxidase.

The antihistamine effect is obviously not due to potentiation of the activity of histaminase any more than is that of mepyramine (Kapeller-Adler, 1951). Whether or not it is due to formation of the same cyclic immonium intermediate product as effects antiadrenaline activity is not finally settled, but seems probable.

While not as potent as the phenoxy-haloethylamines (Nickerson and Nomaguchi, 1951) this series of 2-haloethylamines contains some of the most specific and most powerful antiadrenaline and antihistamine agents known, with both properties in the one molecule.

## Summary

1. We have examined a series of N-naphthylmethyl-N-(aryl or alkyl)-2-haloethylamines and reported on their antiadrenaline and antihistamine properties.

2. The structural configurations which favour antiadrenaline action also favour antihistamine action. The presence of 1-naphthylmethyl in the molecule is favourable, while the 2-naphthylmethyl moiety produces a less active molecule. When the aryl or alkyl group is ethyl, activity is usually greater than when it is methyl, while activity is minimal when it is phenyl.

3. The importance of the nature of the halogen atom in the haloethyl side-chain is stressed. Bromine is usually most favourable, whereas fluorine produces an inactive molecule.

4. These compounds do not appreciably affect the responses to acetylcholine.

5. These compounds in small doses potentiate the pressor response to adrenaline; the activity of amine oxidase is also inhibited.

6. Inhibition of adrenaline is competitive in low dosage but becomes non-competitive when a larger dose is used.

7. Inhibition of histamine is always of a competitive nature.

8. The action of histamine on the heart of rabbits is inhibited by active compounds; that of adrenaline is not.

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