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SOME PHARMACOLOGICAL PROPERTIES OF 3 : 3-DIPHENYL-PROPANOLAMINES, -ALLYLAMINES, AND -PROPYLAMINES

BY

A. C. WHITE, A. F. GREEN, AND AUDREY HUDSON

From the Wellcome Research Laboratories, Beckenham, Kent

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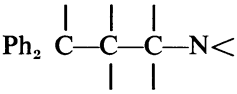
An extensive programme for the synthesis and pharmacological examination of compounds incorporating the structure (I) was initiated in these laboratories in 1946.



(I)

This programme was undertaken with the knowledge that some compounds containing this structure exhibit pharmacological activity. This is exemplified by Höchst 10116 ($Ph_2CH.CH_2CH_2N<[CH_2]_4>CH_2$), which is a component of the anti-asthmatic mixture "Aspasan," in which it increases the effectiveness of dihydroxyephedrine (Schaumann, 1942). There is little clinical literature on its use, but from the amounts manufactured "Aspasan" seems to have been used to a considerable extent in Germany during the war years (B.I.O.S., 1945). The structure (I) is also found in the series of ketones among which amidone ($Ph_2C(CO.Et)CH_2CHMe.NMe_2$) together with closely related analogues is of importance for high analgesic activity, and is now the subject of a very considerable literature. Substituted phenylpropylpiperidines show considerable spasmolytic activity (Becker *et al.*, 1946), and a diphenylpropylpiperidine carboxylic ester ($Ph_2C(CO.OEt)CH_2CH_2N<(CH_2)_4>CH_2$) has spasmolytic and slight analgesic activity (Macdonald *et al.*, 1946).

The present paper is concerned with the pharmacological properties of three series of compounds whose synthesis is described by our colleague Dr. D. W. Adamson (Adamson, 1949). These are the 3 : 3-diphenylpropan-3-olamines (II), 3 : 3-diphenylallylamines (III), and 3 : 3-diphenylpropylamines (IV), where the amino group is primary, secondary, or tertiary, and the quaternary derivatives of the latter.

$Ph_2C(OH)CH_2CH_2NRR'$ (II) $\quad Ph_2C : CH.CH_2NRR'$ (III) $\quad Ph_2CH.CH_2CH_2NRR'$ (IV)

Since our examination of these compounds, Cunningham *et al.* (1949) have found considerable spasmolytic activity in compounds of the type $PhR.C(OH)CH_2CH_2N<(CH_2)_4>CH_2$, particularly where R is phenyl or *cyclo*hexyl ("Artane")

METHODS

The examination of a large number of compounds in several pharmacological tests could only be accomplished with rapid screening methods, and it has therefore frequently been necessary to restrict the use of more precise methods of estimating activity to compounds which have shown high activity in these tests. The following screening methods have been used in compiling Tables I to VI.

Toxicity.—Approximate LD50s by intravenous injection were determined in groups of five mice with a twofold difference between the doses.

Spasmolysis.—Contractures of isolated rabbit ileum suspended in aerated Tyrode-Ringer at 38° C. were induced by carbachol or pilocarpine, the log dilutions or pD values (Miller, Becker, and Tainter, 1948) of these substances being 6.6 and 4.3 respectively. Each test compound at pD 6.0 was added after the spasm was established, and where relaxation occurred lower concentrations were tested. From the relationship between the percentage relaxation and the log dilution an estimate was made of the pD for 50 per cent reduction in spasm, hereafter referred to as the pD50 value. These estimates are subject to very considerable variations between different preparations and are only sufficient in indicate the approximate activity.

Where compounds have shown high activity against carbachol the test was repeated on at least three occasions. The mean estimates are quoted. Some compounds have been tested by direct comparison with atropine on the same pieces of gut, but we would emphasize that unless two compounds have an identical mode of action we cannot expect them to give the same relative activities in all preparations. Tests were also carried out using barium chloride (pD 4.3), but because of the extreme variability of the estimates we have not included these in the Tables.

Antihistamine activity.—This was determined similarly, but on spasm of guinea-pig ileum induced by histamine, pD 6.3. Comparative tests on the same strips of gut were carried out in some instances.

Rabbit eye tests.—The eyes of albino rabbits were used for measuring corneal anaesthetic, mydriatic, and irritant effects. Two rabbits were used for each compound, one eye of each being bathed for one minute with the test solution at 5 mg./c.c. and the other with cocaine at 5 mg./c.c. The reflex to pricking the eye with a fine bristle was tested, and the pupil diameters were measured at five-minute intervals; the illumination was kept constant during the test. The Tables show the mean duration of corneal anaesthesia with the test solutions, and symbols are used to indicate the degrees of mydriasis and irritation. For mydriasis the sign " − " indicates no effect, " ± " a slight but lesser effect than with cocaine, " + " a response equal to that of 5 mg./c.c. cocaine, and " + + " a greater response. For the irritant effect " − " signifies nil, " ± " slight, "+" a definite redness of the conjunctiva, and "+ +" more severe damage which is frequently associated with increased lacrimation and later perhaps peeling of the cornea. Where estimates of corneal anaesthetic activity have been made we have used the relationship between log dose and log duration described by Young (1951).

Mydriasis by the parenteral route was measured in groups of 10 mice 30 minutes after intraperitoneal injection. At least two doses of atropine sulphate were given on each occasion. Activity in terms of atropine sulphate was estimated by the method described by Ing, Dawes, and Wajda (1945). In general, the fiducial limits for $p=0.95$ are ±10 per cent.

Analgesia.—The effects of each compound on the pain threshold of rats were investigated by the method described by Thorp (1946). No important effects were observed, and no mention of this property is made in the Tables.

A description of other methods used in testing particular compounds is given in the text.

The limits of estimates given in parentheses are the calculated fiducial limits for p=0.95.

RESULTS

The pharmacological properties revealed by our screening tests are given in Tables I to VI, where the compounds are classified as follows:

Propanolamines (II)	Amine hydrochlorides, Table I Quaternary ammonium salts, Table II
Allylamines (III)	Amine hydrochlorides, Table III Quaternary ammonium salts, Table IV
Propylamines (IV)	Amine hydrochlorides, Table V Quaternary ammonium salts, Table VI

Propanolamines (II)

Amine hydrochlorides (Table I).—These show fairly powerful atropine-like activity in antagonizing carbachol and pilocarpine spasms of isolated rabbit ileum, and in mydriatic activity by local application in the rabbit and by intraperitoneal injection in mice. While there is no clearly defined correlation between these different aspects of atropine-like function, this does not necessarily imply a true physiological differentiation of function, as different species and modes of application have been used.

TABLE I

PROPANOLAMINE HYDROCHLORIDES

$Ph_2C(OH)CH_2CH_2NRR',HCl$

Serial No.	NRR′	LD50 mg./kg.	Log dilution for 50% antagonism of			Rabbit eye tests with 5 mg./c.c. solutions			Mydriasis (mouse) atropine sulph.=1
			Carbachol*	Pilocarpine	Histamine	Corneal anaesthesia (min.)	Mydriasis	Irritation	
1	NH_2	90	—	—	—	0	—	—	<0.002
2	NHMe	65	—	—	—	10	—	—	0.0023
3	NHEt	50	—	—	—	0	—	+	0.0044
4	$NHCH_2Ph$	15	—	—	—	35	+	+	
5	NMe_2	100	6.0	—	—	0	—	—	0.0046
6	NMeEt	75	6.5	—	6.1	25	+	—	0.008
7	NEt_2	25	6.7	—	—	20	+	±	0.01
8	NPr^{α}_2	40	—	—	—	10	—	+	0.0022(t)
9	NBu^{α}_2	25	—	—	—	25 (a)	—	++	0.002(t)
10	$NMeCHMeCH_2Ph$	15	6.0	6.0	—	30 (a)	—	±	—
11	$N<[CH_2CH:CH_2]_2$	55	—	.	—	15	—	+	.
12	$N<[CH_2]_3>CH_2$	50	6.9	—	6.2	25	+	—	0.014
13	$N<[CH_2]_4>CH_2$	60	7.6	6.3	6.0	30	+	±	0.02
14	$N<[CH_2]_4>O$	200	—	—	—	.	.	.	—

(t) Mydriasis was accompanied by toxic manifestations. (a) Tested at 2.5 mg./c.c.

* Comparative estimates on the same strips of gut (approximate standard error = ±0.05) except for that of No. 10, which was assumed from the response to one concentration only.

The most active is the piperidino compound No. 13. This, by direct comparison with atropine sulphate on the same strips of rabbit ileum, was found to be about a quarter to a half as active as atropine sulphate in relaxing spasm due to carbachol. By the mydriatic test in mice when the pupil is measured 30 minutes after intraperitoneal injection it is only a fiftieth as active as atropine sulphate.

We have also investigated the effect of this compound on bronchial tone and intestinal movements in dogs, under pentobarbitone sodium, receiving a continuous intravenous infusion of eserine at the rate of 3.2 mg. per hour. The bronchial tone was judged simply from tracings of the amplitude of pressure changes in the tracheal cannula, and movements of the duodenum and ileum recorded with the usual balloon-tambour system. Under these conditions compound No. 13 reduced the bronchoconstriction and inhibited tone and motility of the gut at a dose of 0.1 to 0.2 mg./kg., whereas atropine had a similar action for a longer duration at approximately 0.01 mg./kg. in each of two dogs. Small doses of both compounds commonly produce increased intestinal activity. The spasmolytic activity of this compound has also been examined by Cunningham *et al.* (1949), who found that it showed 36 per cent of the activity of atropine in relaxing spasm of isolated rabbit ileum due to " Furmethide " (furfuryltrimethylammonium iodide). It has a lesser effect by intravenous injection in the dog on furmethide-induced contractions of Thiry-Vella fistulae, on furmethide-induced salivation and on vagal activity, and a smaller mydriatic effect than atropine by local application in the cat.

An investigation of this compound in man (Card, personal communication) has shown that by mouth 25 mg. is ineffective, but 50 mg. reduces gastric motility induced by mecholyl to a lesser extent and for a much shorter duration than a full therapeutic dose of atropine. Card also observed that intravenous injection even of very dilute solutions caused severe thrombosis in man. We were unable to reproduce this by intravenous injection of a 0.5 per cent solution in the rabbit ear, and further when present to the extent of 1 mg./c.c. the compound had no significant effect on the clotting time of horse blood or plasma.

The morpholino analogue (No. 14) is also described by Denton *et al.* (1950), who agree that it is less active than the piperidino compound.

Three compounds of the series, Nos. 6, 12, and 13, showed some antagonism of histamine spasm, but these compounds are very weak antihistamines compared with mepyramine, the pD50 of which is commonly 8.1 to 8.6 under similar conditions.

The antihistamine activity of the propanolamines (II) is less than that of the allylamines (III) and the propylamines (IV). Antagonism of barium spasm was demonstrated with some compounds, and it is likely that such an effect would have been observed with others had higher concentrations been tested, as all members of the group at a log dilution of 4.5 caused inhibition of motility and tone of isolated rabbit ileum.

Some of the compounds (Table I) possess a local anaesthetic activity which, with a 5 mg./c.c. solution, is roughly equal in duration to that of the same concentration of cocaine. Cocaine in our type of test gives a mean duration of 24 minutes with 5.0 mg./c.c. and 70 minutes with 50 mg./c.c., the variation between rabbits being high. Since the local anaesthetic effect of these compounds was frequently accompanied by an irritant action on the conjunctiva, we have not examined this property in more detail.

Quaternary ammonium salts (Table II).—Like other workers, we have found that quaternary ammonium salts are in general more potent than the amine hydrochlorides in atropine-like activity. Several compounds (Nos. 22, 23, 27, 28, and 29) in this series approximate to atropine in activity, the most active being No. 22 (NRR′R″}X = $NMeEt_2$}I), which is described at the end of this section.

TABLE II

PROPANOLAMINE QUATERNARY AMMONIUM SALTS

$Ph_2C(OH)CH_2CH_2NRR'R''\}X$

Serial No.	NRR′R″}X	LD50 mg./kg.	Log dilution for 50% antagonism of			Rabbit eye tests with 5 mg./c.c. solutions			Mydriasis (mouse) atropine sulph. = 1
			Carbachol	Pilocarpine	Histamine	Corneal anaesthesia (min.)	Mydriasis	Irritation	
15	NMe_3}I	20	6.5	—	—	10	++	±	0.025
16	NMe_2Et}I	20	7.2	6.0	—	0	+	±	0.1
17	NMe_2Pr^{α}}Br	15	7.1	—	—	0	+	±	0.065
18	NMe_2Bu^{α}}Br	15	6.4	—	—	0	++	—	0.023
19	NMe_2Ph}I	10	6.6	—	—	5	+	±	.
20	$NMe_2.CH_2Ph$}Cl	8	—	—	—	3	—	±	.
21	$NMe_2.CHMe.CH_2Ph$}I	5	5.8*	—	—	10	—	—	.
22	$NMeEt_2$}I	20	8.1	7.0	—	0	++	±	0.75
23	NEt_3}I	20	7.8	7.2	—	0	++	±	0.45
24	$NMePr^{\alpha}_2$}I	10	6.2	—	—	0	—	±	0.01
25	$NMeBu^{\alpha}_2$}I	10	—	—	—	0 (a)	—	—	—
26	$NMe[CH_2CH:CH_2]_2$}I	10	6.0*	—	—	0	—	—	0.01
27	$NMe<[CH_2]_3>CH.$}I	20	8.2	6.6	—	3	+	—	0.35
28	$NMe<[CH_2]_4>CH.$}I	10	8.1	6.9	—	25	++	—	0.26
29	$NEt<[CH_2]_4>CH_2$}I	10	8.3	7.2	—	0	++	—	0.42
30	$NMe<[CH_2]_4>O$}I	25	7.5	6.7	—	35	+	+	0.04

(a) Tested at 2.5 mg./c.c.

* Assumed from the response to one concentration.

The other properties of this group are not of particular interest. In general the antagonism of histamine and the local anaesthetic activities are less than in the tertiary amines. Some compounds showed a fairly powerful antagonism of barium-induced spasm of isolated rabbit ileum. No analgesic action was found.

3 : 3-Diphenylpropan-3-oldiethylamine methiodide (Compound No. 22).—In many laboratory tests this compound has shown an activity between 0.5 and 1.0 times that of atropine sulphate. Estimates ranging from 0.7 to 1.0 times atropine sulphate were obtained against spasm induced by carbachol and pilocarpine in comparative tests on the same strip of isolated rabbit ileum. Similarly the mydriatic activity in mice estimated as the unweighted mean for three separate tests was 0.7 times atropine when the pupils were measured 30 minutes after the intraperitoneal injection of the drug. However, the times for onset and duration of action are shorter than with atropine. Fig. 1 shows this in a test on groups of 10 mice when the pupils were measured at several time intervals. The activity of this compound as an antagonist of the depressor effect of carbachol in two cats (under pento-

barbitone), continuously infused with carbachol and adrenaline (Bülbring and Dawes, 1945), was found to be approximately 0.7 times that of atropine. The anti-sialogogue activity was estimated by collecting the saliva from each of six rabbits after the simultaneous injection into opposite flanks of 50 mg./kg. pilocarpine and one of

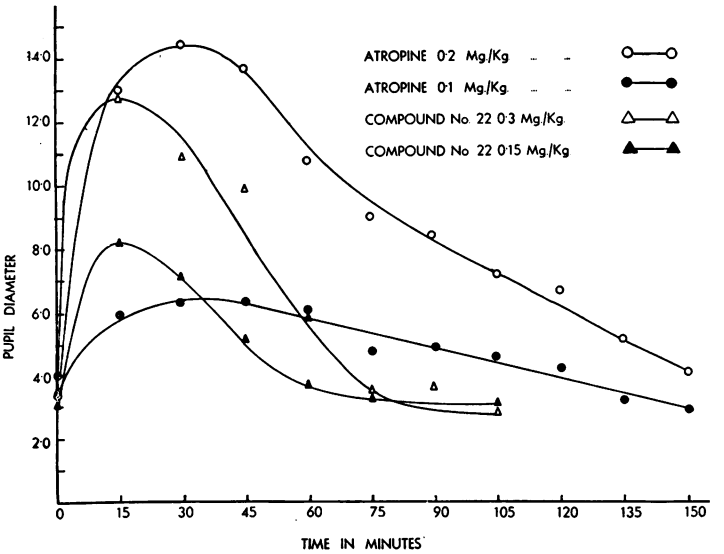


FIG. 1.—The mean pupil diameter (arbitrary units) in groups of ten mice at intervals after intraperitoneal injection of Compound No. 22 and atropine sulphate.

several doses of the antagonist or saline. Compound 22 was found to be 0.6 times as active as atropine (limits 0.23–1.75). Like atropine, and at similar doses, Compound 22 reduces the incidence and severity of the asthma in guinea-pigs produced by exposure to histamine aerosol, and it also inhibits the isolated rabbit ileum and antagonizes barium-induced spasm at pD4 to 4.5. In a dog (under pentobarbitone) 1 mg./kg. intravenously caused a slight transient rise of blood pressure of 20 mm. Hg followed by a transitory fall of 10 mm. Hg. Respiration was unaffected. There was a slight increase in the adrenaline pressor response. In a second dog 0.6 mg./kg. reduced the cardiovascular and salivary effects of 0.6 mg./kg. pilocarpine. The action of doses of between 0.1 and 2.0 mg./kg. on the blood pressure in the pithed dog was irregular. Doses of 0.5 to 2.0 mg./kg. abolished the effects of 0.3 to 1.0 mg./kg. pilocarpine on the blood pressure. The effects of arecoline were also antagonized. The tracing obtained with an intrapleural cannula (Jackson, 1939) showed no evidence of a direct effect on the bronchi in doses up to 2 mg./kg. ; this, however, does not exclude effects when the bronchi are in a state of spasm.

Against spasm of the guinea-pig ileum produced by histamine the pD50 of this compound was 5.2 and that of atropine 5.1 by direct comparison. The intravenous injection of this compound into the guinea-pig 15 minutes before the intravenous injection of histamine reduced the toxicity of the latter. In a test using groups of 10 pigs the LD50 of histamine (1.52 mg./kg. of base in the controls) was increased

1.36 times (limits 0.98 to 1.88) after 5 mg./kg. of No. 22, and 2.6 times (limits 1.7–3.9 after 10 mg./kg. Modification of the effect of histamine on the bronchial system of pithed artificially respired guinea-pigs was shown by an adaptation of the method described by Jackson (1939) for the dog. The initial sensitivity to intravenous histamine was first tested by an injection of 25 or 50 μg. histamine, and only those pigs were used in which a sharp bronchoconstriction occurred. After the histamine antagonist, which was also given intravenously, the dose of histamine required to cause an effect equal to that of the original 25 or 50 μg. was determined. The effect of a given dose of a histamine antagonist was very variable. The dose required for a fivefold decrease in sensitivity in 50 per cent of the test animals was very approximately 0.5 mg./kg. of Compound No. 22 and 0.0025 mg./kg. of mepyramine. Atropine sulphate at 1.0 mg./kg. gave a slight protection, but less than the same dose of Compound No. 22 in another series of tests.

The toxicity in mice of this compound compared with atropine varies with the route of administration.

	LD50 in mg./kg.	
	Intravenous	Intraperitoneal
Compound No. 22	20.5 (19.1–22.0)	114 (104–124)
Atropine	89.0 (83.5–94.5)	245 (220–274)

The difference in toxicity by the two routes is greater for Compound No. 22 and suggests the intervention of some cardiovascular effect on intravenous injection. By mouth, this compound is far less toxic ; 10 mice have survived 300 mg./kg. A dose of 2 mg./kg. has been given intraperitoneally to young rats daily for five days a week for two months with but slight retardation of growth and no macroscopical changes in the internal organs. Intradermally 5 mg./c.c. in the guinea-pig causes a slight transitory reddening at the site of the injection.

No local anaesthetic or analgesic effects have been found.

In man, Compound No. 22 produced atropine effects on the pupil and on salivation. Applied as a 5 mg./c.c. solution to the conjunctiva it caused a dilatation of the pupil within an hour which had disappeared after 12 hours. Its action on the vital capacity in the asthmatic subject was not sufficient for it to be of interest in the treatment of asthma (Herxheimer, personal communication).

Allylamines (III)

Amine hydrochlorides (Table III).—These compounds show less atropine-like activity than the propanolamines (II) but considerable antihistamine and local anaesthetic activity.

The most active antihistamine in this series was found to be the pyrrolidino compound No. 40, which, in a comparative test using four strips from a single guinea-pig, was found to be 0.13 times as active as mepyramine (limits, 0.07–0.23).

Several compounds gave a substantially longer duration of corneal anaesthesia than occurred with an equal concentration of cocaine in the same rabbits. Nos. 32, 37, 38, 40, and 41 showed steeper regression lines relating log dose with log duration than that of cocaine, and they cannot therefore be evaluated in terms of the latter. The following estimates have been made of the concentration for corneal anaesthesia lasting 30 minutes: cocaine 8 mg./c.c., Nos. 37 and 38 approximately

TABLE III

ALLYLAMINE HYDROCHLORIDES

Ph_2C: $CH.CH_2NRR'$,HCl

Serial No.	NRR′	LD50 mg./kg.	Log dilution for 50% antagonism of			Rabbit eye tests with 5 mg./c.c. solutions			Mydriasis (mouse) atropine sulph. = 1
			Carbachol	Pilocarpine	Histamine*	Corneal anaesthesia (min.)	Mydriasis	Irritation	
31	NH_2	45	—	—	—	15	—	++	.
32	NHEt	40	—	—	5.6	55	—	+	.
33	NMe_2	35	6.3	—	6.4	20	—	—	0.0042
34	NMeEt	40	6.5	—	6.9	90	+	+	0.0038
35	NEt_2	30	6.2	5.6	6.4	30	—	±	0.0037
36	NPr^{α}_2	35	—	—	—	30	—	+	.
37	NBu^{α}_2	40	—	—	—	275	—	++	.
38	$NMeCHMeCH_2Ph$	40	—	—	—	>60 (a)	—	+	.
39	$N[CH_2CH:CH_2]_2$	20	—	—	—	30 (a)	—	++	.
40	$N<[CH_2]_3>CH_2$	100	6.2	—	7.1	55	—	±	0.0039
41	$N<[CH_2]_4>CH_2$	50	6.5	—	6.7	90	±	±	0.0026
42	$N<[CH_2]_4O$	50	—	—	—	15	—	+	.

(a) Tested at 2.5 mg./c.c.

* Comparative estimates on the same strips of gut (approximate standard error = ± 0.05).

TABLE IV

ALLYLAMINE QUATERNARY AMMONIUM IODIDES

Ph_2C: $CH.CH_2NRR'R''$}I

Serial No.	NRR′R″	LD50 mg./kg.	Log dilution for 50% antagonism of			Rabbit eye tests with 5 mg./c.c. solutions			Mydriasis (mouse) atropine sulph. = 1
			Carbachol	Pilocarpine	Histamine	Corneal anaesthesia (min.)	Mydriasis	Irritation	
43	NMe_3	8	6.3	—	—	25	±	—	0.0026
44	$NMeEt_2$	8	7.3	—	6.1	25	+	±	0.015
45	$NMePr^{\alpha}_2$	15	6.5	—	—	25	—	+	.
46	$NMeBu^{\alpha}_2$	35	—	—	—	0	—	+	.
47	$NMe_2CHMeCH_2Ph$	40	6.0*	—	6.0*	20 (a)	—	+	.
48	$NMe[CH_2.CH:CH_2]_2$	15	6.3	—	—	0	—	±	.
49	$NMe<[CH_2]_3>CH_2$	5	7.2	—	6.1	0	—	—	0.0084
50	$NMe<[CH_2]_4>CH_2$	10	7.5	6.2	6.9	.	.	.	0.018
51	$NMe<[CH_2]_4>0$	10	6.5	—	6.0*	0	—	—	0.003

(a) Tested at 2.5 mg./c.c.

* Assumed from the response to one concentration only.

0.5 mg./c.c., and Nos. 32, 40, and 41 approximately 2.5 mg./c.c. The compounds are much less active than cinchocaine, which has a similar slope to its regression line and gives 30 minutes' anaesthesia at 0.03 mg./c.c. The irritant action and the failure on local injection of 10 mg./c.c. solutions of Nos. 37 and 38 to cause complete

sciatic nerve block in the rat also weigh heavily against any potential value of these compounds as local anaesthetics.

The compounds are not analgesics.

Quaternary ammonium salts (Table IV).—Quaternization again increases the atropine-like activity of some of the tertiary amines. None of the compounds approach the quaternary propanols in activity, but some (Nos. 44, 49, and 50) are a fiftieth to a hundredth of atropine in the mydriatic test and rather more active in antagonizing carbachol *in vitro*. Antihistamine activity in most examples is less than in the amines. It appears from Tables IV and III that the quaternary salt No. 50 is rather more active than the corresponding amine No. 41, but this was not the case in a direct comparison of the two compounds on four strips of ileum from one guinea-pig, when the pD50 of Compound No. 50 was again 6.9 but that of No. 41 was 7.2 and not 6.7. This is an example of the type of variability to which work of this kind is subject.

The compounds are more toxic by intravenous injection in mice than the amines. Local anaesthetic effects are shown to a lesser extent by some members and analgesic effects are again absent.

Propylamines (IV)

Amine hydrochlorides (Table V).—Atropine-like properties such as mydriasis and carbachol antagonism, and antihistamine activity are shown to a degree similar to that in the allylamines (III), but the local anaesthetic activities are less.

The pyrrolidino compound (No. 59) is again the most active of the series against histamine spasm in the guinea-pig. In a comparative test on four strips from one pig which was run in parallel with the test on the allylamine No. 40, Compound No. 59 gave an estimate of 0.12 × mepyramine (limits, 0.07–0.2).

TABLE V

PROPYLAMINE HYDROCHLORIDES

$Ph_2CHCH_2CH_2NRR',HCl$

Serial No.	NRR′	LD50 mg./kg.	Log dilution for 50% antagonism of			Rabbit eye tests with 5 mg./c.c. solutions			Mydriasis (mouse) atropine sulph. = 1
			Carbachol	Pilocarpine	Histamine*	Corneal anaesthesia (min.)	Mydriasis	Irritation	
52	NH_2	90	—	—	—	15	±	+	.
53	NHEt	40	—	—	5.6	5	—	+	.
54	NMe_2	65	6.7	—	6.8	30	+	—	0.0048
55	NMeEt	45	6.2	—	6.8	10	—	±	0.0088
56	NEt_2	25	6.2	—	6.3	5	—	+	0.0045
57	NPr^{α}_2	25	—	—	5.2	25	—	++	.
58	NBu^{α}_2	25	—	—	5.1	45	—	++	.
59	$N<[CH_2]_3>CH_2$	50	6.3	—	7.1	25	±	—	0.0041
60	$N<[CH_2]_4>CH_2$	70	6.8	—	6.7	20	±	+	0.0045
61	$N<[CH_2]_4>O$	80	—	—	—	15	—	±	.

* Comparative estimates on the same strips of gut (approximate standard error = 0.05).

Local anaesthetic action was moderate and frequently associated with irritation. Analgesic activity was not found.

One of these compounds, No. 60 (NRR′=piperidino) also known as "Höchst 10116," was a component of the anti-asthmatic mixture "Aspasan." Its use here was based on the observation (Schaumann, 1942) that a combination of this compound with dihydroxyephedrine gives a more complete protection of guinea-pigs against histamine asthma, and for a longer duration, than either of the two compounds alone; protection against intravenous histamine and antagonism of histamine spasm of isolated guinea-pig ileum were also demonstrated.

Quaternary ammonium salts (Table VI).—This group showed approximately the same level of atropine-like activity (mydriasis and carbachol antagonism) and

TABLE VI

PROPYLAMINE QUATERNARY AMMONIUM IODIDES

$Ph_2CHCH_2CH_2NRR'R''\}I$

Serial No.	NRR′R″	LD50 mg./kg.	Log dilution for 50% antagonism of			Rabbit eye tests with 5 mg./c.c. solutions			Mydriasis (mouse) atropine sulph.=1
			Carbachol	Pilocarpine	Histamine	Corneal anaesthesia (min.)	Mydriasis	Irritation	
62	NMe_3	12	6.9	—	—	0	+	+	0.02
63	$NMeEt_2$	8	7.3	—	—	25	+	±	0.0044
64	$NMePr^{\alpha}_2$	10	—	—	—	0	±	—	0.0025
65	$NMeBu^{\alpha}_2$	10	—	—	—	0	—	—	—
66	$NMe<[CH_2]_3>CH_2$	10	7.5	6.5	—	0	+	—	0.034
67	$NMe<[CH_2]_4>CH_2$	10	7.2	6.6	—	0 (b)	.	—	0.047
68	$NMe<[CH_2]_4>O$	25	6.7	—	—	0	—	—	0.018

(b) Tested at 1 mg./c.c.

toxicity as the quaternary allylamines (Table IV); histamine antagonism and local anaesthetic activity are less in many instances. The most active mydriatics (Nos. 63, 66, and 67) are 0.03 to 0.05 times as active as atropine.

Discussion

The series examined show several associated pharmacological activities which include the atropine-like effects of mydriasis and antagonism of spasm of isolated gut induced by carbachol or pilocarpine, antagonism of the "musculotropic" spasmogen barium chloride, antihistamine, and local anaesthetic activity. The degree to which each of these properties is shown varies between the series. It has been found that atropine-like activity is greatest in the propanols (II), antihistamine activity in the tertiary allylamines (III) and propylamines (IV), and local anaesthetic activity in the tertiary allylamines. The basic group in each series also has an important effect on activity which follows certain general trends in all three series.

Atropine-like activity as manifested by mydriasis and antagonism of carbachol and pilocarpine is frequently greater in the quaternary ammonium salts than in the

tertiary amines. Similar observations have been made in other series, and the significance of this effect has been discussed by Ing, Dawes, and Wajda (1945). These latter workers found that similar quaternary groups favoured high mydriatic activity in benzilic esters as in the three series we have examined. The relative effects of these on activity were slightly different in each series. The tertiary amines show a moderate atropine-like activity which is superior to that of the secondary and primary amines (Tables I, III, and V). Similar tertiary amino groups, namely NMe_2, NMeEt, NEt_2, pyrrolidino, and piperidino, favour activity in the three series, but again to slightly different relative degrees.

Greater differences have frequently been observed between the mydriatic and *in vitro* spasmolytic activities of the tertiary amines than between those of the quaternary ammonium salts. Such differences are frequently due to the test conditions, as with Compound No. 13, which is a fiftieth as active as atropine in the mouse mydriatic test and approximately a quarter to a half as active as atropine as a carbachol antagonist on the isolated rabbit ileum. When tested in the intact dog perfused with eserine, however, its spasmolytic activity was less than a tenth of that of atropine. A similar difference between the spasmolytic activities in isolated rabbit ileum and in the intact dog was observed by Cunningham *et al.* (1949). We wish therefore to emphasize that a true differentiation in function can only be demonstrated when the activities are determined in the same species under similar test conditions.

There is no clear-cut evidence as to the effect of the basic groups on the antagonism of barium-induced spasm in isolated rabbit ileum, but part of this may be due to the inherent variability of the test procedure.

Antihistamine activity is greatest in the tertiary allylamines and propylamines, and in particular where the basic group is NMeEt or pyrrolidino. The pyrrolidino analogues (Nos. 40 and 59) are the most active, but the relative effects of the other groups are not identical in the two series. The activity of secondary amines is not necessarily less than that of the tertiary amines; for example, greater potency occurs when NRR′ is NHEt than when it is NPr_2 or NBu_2. It is interesting that, although the quaternary ammonium salts are considerably less active than the tertiary amines in most examples, the difference is small with some allylamines (e.g., Nos. 41 and 50).

Local anaesthetic activity varies independently of the above effects, and the only general trends with modification in the basic group are a smaller incidence of active compounds among the quaternary ammonium salts than in the tertiary amines and higher activity where the alkyl substituents in the amino group are large. An example of the latter is the high activity where the basic group is NBu_2 (Nos. 9, 37, and 58) or $NMe.CHMe.CH_2Ph$ (Nos. 10 and 38).

The toxicity is also materially altered by modifications in the basic group. A general example is the high intravenous toxicity of the quaternary ammonium salts in mice, compared with the amine hydrochlorides. Different basic groups do not necessarily have the same relative effects on toxicity in the three series.

Pharmacological action varies greatly with the nature of the basic groups in these and other related series, and in any one property in a given species the optimal groups, though commonly allied, may not necessarily be the same even in closely related series. For maximal activity in a given species a compound may need a

defined physico-chemical property, such as a particular dissociation constant, and such a property will be influenced by the basic group, the rest of the molecular structure, and by the medium in which the drug is acting.

Summary

1. The hydrochlorides and quaternary ammonium salts of three closely related series of bases, namely 3 : 3-diphenyl-propanolamines, -allylamines, and -propylamines, have been examined for several pharmacological properties.

2. Atropine-like activity, as manifested by antagonism of carbachol *in vitro* and by mydriasis, is greater in the propanolamines than in the allylamines and propylamines. A very high order of activity is found in the quaternary ammonium salts, and one such compound, namely 3 : 3-diphenylpropan-3-oldiethylamine methiodide, is as active as atropine sulphate on a molecular basis.

3. Antihistamine activity is greater in the allylamines and propylamines than in the propanolamines. The pyrrolidino analogues, which are both a tenth to a fifth as active as mepyramine, are the most potent antihistamines in these series. The quaternary ammonium salts showed various degrees of antihistamine activity, but in general are less active than the tertiary amines.

4. All series showed corneal anaesthetic properties, the degree of activity being greatest in the allylamines; the most active members are a twentieth as active as cinchocaine and cause considerable irritation of the conjunctiva. The quaternary ammonium salts are in general less active than the tertiary amines.

5. No analgesic activity was found.

6. Minor changes in the basic group frequently have an important effect on pharmacological activity. The relative effects of different basic groups on any one property are not necessarily the same in all series even when the latter are closely related.

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References

Adamson, D. W. (1949). *J. chem. Soc.*, 144.

Becker, T. J., Ananenko, E., Glenwood, C., and Miller, L. C. (1946). *Fed. Proc.*, **5**, 163.

B.I.O.S. (1945). Final Report, **116**, item 24, 57.

Bülbring, E., and Dawes, G. S. (1945). *J. Pharmacol.*, **84**, 177.

Cunningham, R. W., Harned, B. K., Clark, M. C., Cosgrove, R. R., Daugherty, N. S., Hine, C. H., Vessey, R. E., and Yuda, N. N. (1949). *J. Pharmacol.*, **96**, 151.

Denton, J. J., Schedl, H. P., Lawson, V. A., and Neier, W. B. (1950). *J. Amer. chem. Soc.*, **72**, 3795.

Ing., H. R., Dawes, G. S., and Wajda, I. (1945). *J. Pharmacol.*, **85**, 85.

Jackson, D. E. (1939). *Experimental Pharmacology and Materia Medica*, p. 208. St. Louis: Mosby.

Macdonald, A. D., Woolfe, G., Bergel, F., Morrison, A. L., and Rinderknecht, H. (1946). *Brit. J. Pharmacol.*, **1**, 4.

Miller, L. C., Becker, T. J., and Tainter, M. L. (1948). *J. Pharmacol.*, **92**, 260.

Schaumann, O. (1942). *Med. u. Chem.*, **4**, 229.

Thorp, R. H. (1946). *Brit. J. Pharmacol.*, **1**, 113.

Young, P. A. (1951). *Brit. J. Pharmacol.*, **5**, 273.