to Prof. H. Sofue of Department of Applied Chemistry, Faculty of Technology, of this University, and to Dr. S. Fukuhara for the donation of the hand-made paper used in this work and for many valuable informations on this paper, and to Messrs. I. Kitagawa, M. Miyazaki, and O. Tanaka for technical help. A part of expenses for the present work was defrayed by a Grant in Aid for Scientific Research from the Ministry of Education.

Summary

Minimization of samples for infrared spectral measurement was attempted by the use of a Japanese folkcraft, hand-made paper, impregnated with liquid paraffin. By this method, it is possible to measure 0.1 mg. of a sample.

This hand-made paper was also used for paper chromatography and the developed paper was submitted directly to infrared spectral measurement. Component of *Penicillium islandicun* and inorganic sulfate ion were determined by spectral measurement of their chromatogram.

(Received November 7, 1957)

UDC 615.782 : 547.554

24. **Yutaka Kasuya**: Chemicopharmacological Studies on Antispasmodic Action. XII. Structure-Activity Relationship of Aralkylamines.

(*Pharmaceutical Institute, Medical Faculty, University of Tokyo**)

It is a matter of common knowledge that synthetic antispasmodics have atropine-like effect as well as papaverine-like effect. Many investigators have described the relationship between chemical structure and spasmolytic acivity, but they were mainly concerned with atropine-like activity.

How the papaverine-like effect is elicited, and how that effect is related to the atropine-like effect, are problems of great interest. The author already reported that some diphenylbutanolamines have considerable atropine- and papaverine-like activities.[1] A series of compounds related to the diphenylbutanolamines have been synthesised in this laboratory.

This report presents various screening data and discusses some of the relationships between structural modifications (changes of radicals attached to nitrogen, of distance between OH and N, existence of OH and optical isomer, etc.) and above two principal activities.

Method

1. *Estimation of Atropine-like Activity*: Tests were carried out with intestinal segments (20~30 mm.) isolated from white mice (male), weighing between 15 and 20 g., fasted for 12 hrs. before sacrifice.

After suspending the segment in Tyrode solution maintained at 26°(adventure of this temperature was described previously[1]), acetylcholine (ACh) was added to the bath. ACh concentration in the bath was 1.2×10^{-7} g./cc.[2]

The spasmolytic drug was added to the bath solution two mins. after ACh and the resultant reduction in contracture occurring within 5 mins. after addition of spasmolytic drug was expressed in

* Hongo, Tokyo (粕谷 豊).

1) K. Takagi, Y. Kasuya: Yakugaku Zasshi, **73**, 541(1953).

2) When assaying the atropine-like activity of compounds having both atropine-like and papaverinelike effect, it is desirable to limit the concentration of ACh as low as possible. There is a risk that high dose of preparation required for antagonism against high ACh dose will display the papaverine-like effect simultaneously with the atropine-like effect.

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per cent of the total contracture. The bath solution was removed and the segment was washed 3 times with fresh Tyrode solution. Following tests were carried out at intervals of 10 mins.

The spasmolytic effect of 4 doses, namely, 2 doses of atropine sulfate (Merck 52363) (3×10^{-9} g./cc., 4.5×10^{-9} g./cc. in bath) and 2 doses of preparation to be assayed (graded at 1.5-fold intervals) was determined for intestinal segments from at least 2 mice. Potency of preparation compared with atropine sulfate was estimated by the 4-point assay method.

2. *Estimation of Papaverine-like Activity*: Test method was similar to that used for atropine-like effect measurement, except that a high concentration (10^{-4} g./cc. in bath) of ACh was used as a stimulant, papaverine hydrochloride was used as the standard, the reduction of the contracture was determined 10 mins. after the addition of spasmolytic solution, and dose interval was 2 fold.

This method is easier and variation of the sensitivity of tissues for drugs is smaller than the usual method using $BaCl_2$ as a stimulant. Theoretical basis of this method was reported previously.[3]

Actually, the potency of a substance estimated by this method does not differ significantly from that obtained by the usual method as shown in Table I.

Table I. Inhibition Ratio (%) of Papaverine and Compound No. 33

Stimulant	Acetylcholine 10^{-4}(g./cc.)				$BaCl_2$ 3×10^{-4}(g./cc.)			
Inhibitor	Papaverine (g./cc.)		No. 33 (g./cc.)		Papaverine (g./cc.)		No. 33 (g./cc.)	
	2.5×10^{-6}	5×10^{-6}	5×10^{-6}	10^{-5}	2.5×10^{-6}	5×10^{-6}	5×10^{-6}	10^{-5}
Animal No. 1	15.6	58.8	17.6	30.0	40.0	75.0	30.6	51.6
2	14.5	88.3	29.6	44.1	55.6	92.9	31.3	50.0
3	11.1	38.7	40.0	68.9	24.0	76.5	31.8	47.4
4	23.5	43.8	34.6	72.0	25.6	53.6	36.7	80.8

Four mice were used, each mouse was assigned to each of eight treatments (4 doses after ACh stimulation and 4 doses after $BaCl_2$ stimulation) in a randomized order.

Table II. Analysis of Variance for the Data of Table I.

Nature of variance	d.f.	Sum of squares	Mean square	F
Pretreatment (Stimulants)	1	920.205	920.205	4.12
Preparations (Inhibitors)	1	49.502		
Stimulants × Inhibitors	1	486.720		
Combinations	3	1456.427		
Regression	1	8115.380		
Parallelism	3	496.247	165.416	
Treatment	7	10068.054		
Animal	3	539.164	179.721	
Error	21	4694.121	223.530	
Total	31	15301.339		

$F^{1}_{21}(0.05)=4.32$

There is no serious evidence of inequality of the regression coefficients of 4 regression lines and the stimulants component is not significant.

Potency of Compound No. 33 is 56.05% of papaverine. Fiducial limit ($P=0.05$) is 39.4~85.4% (when ACh is used).

Potency of Compound No. 33 is 39.85% of papaverine. Fiducial limit ($P=0.05$) is 24.5~56.4% (when $BaCl_2$ is used).

These analytical results support the view that this test method using high dose of ACh gives a similar estimate of papaverine-like activity to that obtained by the ordinary method using $BaCl_2$ as a stimulant.

Results[4]

1. 1,1-Diphenyl-3-aminobutanols (Table III)

A-action: Tertiary amines are more potent than secondary amines. Increase in the size of amino group leads to increased activity and the order of their potencies are as follows: -N  (No. 1) > $-NEt_2$ (No. 7) > $-NMe_2$ (No. 10).

The resolution of No. 1 into its optically active components give rise to interesting result, the

3) K. Takagi, I. Takayanagi: This Bulletin, **5**, 580(1957).

4) Hereafter following abbreviations will be used: Acetylcholine-like action=C-action; Atropine-like action=A-action; Papaverine-like action=P-action

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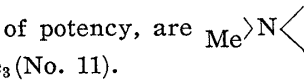
d-isomer (No. 3) being predominantly potent.

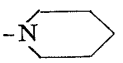
Quaternization of nitrogen causes a distinct increase in potency. The nature of N-alkyl groups, in order of potency, are  (No. 2) > $-NEt_2Me$ (No. 8) > $-NMe_2Et$ (No. 12) > $-NEt_3$ (No. 9) > $-NMe_3$ (No. 11).

P-action: In general, hydrochlorides which have stronger A-action show stronger P-action, but disparity in the P-action is not so great as that in the A-action, e.g. Compounds No. 10 vs. 14 and No. 3 vs. 5. The case of No. 13 vs. 14 is an exception.

In contrast to the A-action, P-action is decreased by quaternization (No. 1 vs. 2 and No. 10 vs. 11).

TABLE III. Spasmolytic Activity of 1,1-Diphenyl-3-aminobutanol Derivatives

$(C_6H_5)_2=C(OH)CH_2CH(NR_2)CH_3$

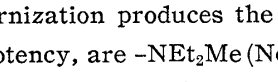
Compd. No.	NR_2	Salt	A-Action Atropine=100 molar basis (wt. basis)	No. of mice	P-Action Papaverine=100 molar basis (wt. basis)	No. of mice
1 (*dl*)		HCl	22.0 (22.1)	6	238.3 (259.1)	6
2 (*dl*)	〃	MeI	44.5 (34.3)	8	121.0 (145.3)	5
3 (*d*)	〃	HCl	50.5 (50.8)	4	333.8 (362.9)	6
4 (*d*)	〃	MeI	71.7 (55.2)	4		
5 (*l*)	〃	HCl	0.6 (0.6)	2	49.4 (53.7)	9
6 (*l*)	〃	MeI	25.8 (19.8)	3		
7	$-NEt_2$	HCl	19.6 (10.0)	3	56.8 (64.0)	4
8	〃	MeI	38.3 (31.5)	8		
9	〃	EtI	17.0 (13.0)	3		
10	$-NMe_2$	HCl	1.1 (1.2)	5	20.7 (25.4)	6
11	〃	MeI	2.8 (2.3)	9	5.0 (5.5)	3
12	〃	EtI	21.9 (16.8)	3		
13	$-NHMe$	HCl	0.2 (0.3)	4	18.6 (23.9)	5
14	$-NHCHMe_2$	HCl	0.4 (0.5)	3	10.2 (12.0)	7
15	$-NHCH_2C_6H_5$	HCl	—( )*	2	—( )**	2

* Reduced the contraction slightly at the concentration of 5×10^{-5} g./cc.

** No reduction was observed at the concentration of 10^{-4} g./cc.

2. 1,1-Diphenyl-3-aminobutenes (Table IV)

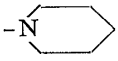
A-Action: The potencies of this group are lower than that of the corresponding 1,1-diphenyl-3-aminobutanols (No. 16 vs. 1, No. 19 vs. 7, No. 17 vs. 2, No. 20 vs. 8, No. 21 vs 9, and No. 23 vs. 12). This fact suggests that OH group exerts a favorable effect on A-action.

Quaternization produces the expected increase in potency. The nature of N-alkyl groups, in the order of potency, are $-NEt_2Me$ (No. 20) >  Me (No. 17) > Et (No. 18) > $-NEt_3$ (No. 21) $-NMe_2Et$ (No. 23) > $-NMe_3$ (No. 22).

P-Action: Because of low solubility, the P-action of some quaternary ammonium salts could not be estimated. The potency order of tertiary amines is the same as that of A-action, and potencies are lower than that of corresponding butanols.

TABLE IV. Spasmolytic Activity of 1,1-Diphenyl-3-aminobutene Derivatives

$(C_6H_5)_2=C=CHCH(NR_2)CH_3$

Compd. No.	NR_2	Salt	A-Action Atropine=100	No. of mice	P-Action Papaverine=100	No. of mice
16		HCl	9.8 (10.4)	6	126.9 (145.6)	4
17	〃	MeI	19.3 (15.5)	8	54.3 (47.1)	6
18	〃	EtI	12.4 (9.6)	3	56.1 (47.2)	8
19	$-NEt_2$	tartarate	4.6 (3.8)	5	54.1 (47.4)	6
20	〃	MeI	27.9 (23.1)	5		
21	〃	EtI	11.6 (9.3)	4		
22	$-NMe_2$	MeI	4.2 (3.8)	5		
23	〃	EtI	6.6 (5.6)	2		

3. 1,1-Diphenyl-3-aminobutanes (Table V)

The order of atropine-like potency, the same as can be seen in P-action except the quaternary ammoniums, is as follows: Quaternary ammonium > tertiary amine > secondary amine > primary amine.

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Table V. Spasmolytic Activity of 1,1-Diphenyl-3-aminobutane Derivatives

$(C_6H_5)_2=CHCH_2CH(NR_2)CH_3$

Compd. No.	NR_2	Salt	A-Action Atropine=100	No. of mice	P-Action Papaverine=100	No. of mice
24	$-NH_2$	HCl	0.1 (0.2)	2	12.3 (17.6)	2
25	-NHMe	HCl	0.4 (0.5)	3	19.0 (25.9)	7
26	$-NMe_2$	HI	0.9 (0.8)	3	36.6 (36.1)	4
27	$-NMe_2$	MeI	4.9 (5.2)	5		

4. 1-Substituted 3-Aminopropanols (Table VI)

Among the hydrochlorides, piperidino compound (No. 33) is the most potent in both A- and P-actions.

The A-action of 1,1-diphenyl-3-aminopropanols have been reported by White, Green, and Hudson[5] but the present estimates of potencies are rather lower than their's. This difference may be derived from the difference of test animal and of test method.

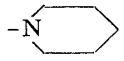
Quaternization leads to distinct increase of A-action, and methobromide is stronger than ethobromide.

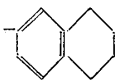
Replacement of phenyl group with 5,6,7,8-tetrahydro-2-naphthyl group induced reduction of spasmolytic activity.

The fact that the potency of No. 36 is between No. 28 and No. 41, and that No. 37 has tendency to inhibit the spasm in high concentration (2×10^{-4} g./cc.), while corresponding ketone compound (No. 38) shows a stimulant activity, supports the view that presence of OH group and quaternary carbon is important in A-action.

Table VI. Spasmolytic Activity of 1-Substituted 3-Aminopropanol Derivatives

$$\begin{matrix} R' \\ R'' \end{matrix}\!\!>\!C\!<\!\begin{matrix} OH \\ CH_2CH_2NR_2 \end{matrix}$$

Compd. No.	NR_2	R′	R″	Salt	A-Action Atropine=100	No. of mice	P-Action Papaverine=100	No. of mice
28	$-NEt_2$	C_6H_5	C_6H_5	HCl	2.5 (2.7)	3	29.3 (34.4)	4
29	〃	〃	〃	MeI	44.5 (36.4)	2		
30	〃	〃	〃	EtI	4.6 (3.6)	2		
31	〃	$C_{10}H_{11}$*	〃	HCl	0.9 (0.8)	4	24.8 (25.0)	5
32	〃	〃	〃	MeI				
33		C_6H_5	〃	HCl	15.0 (15.7)	6	44.0 (56.1)	4
34	〃	〃	〃	MeI	43.4 (34.5)	6		
35	〃	〃	〃	EtI	36.6 (28.2)	3		
36	$-NEt_2$	H	〃	HCl	0.2 (0.3)	4		
37	〃	〃	Me	HCl	—(**)	2		

* $C_{10}H_{11}=$ 

** Reduced the contraction slightly at the concentration of 2×10^{-4}.

5. β-Aminoketones (Table VII)

Compound Nos. 38, 39, and 40 show a stimulating activity. No. 40 is between 1/500~1/200 times as potent as ACh. In the phenyl diethylaminoethyl ketones, the order of A-action is $-NEt_2Me$ (No. 42)> $-NEt_3$ (No. 43) > $-NEt_2$ (No. 41). P-Action of this group is not significant.

Table VII. Spasmolytic Activity of β-Aminoketone Derivatives

$RCOCH_2CH_2NEt_2$

Compd. No.	R	Salt	A-Action Atropine=100	No. of mice	P-Action Papaverine=100	No. of mice
38	Me	HCl	Stimulant		—	
39	〃	MeI	〃		—	
40	〃	EtI	〃		—	
41	C_6H_5	HCl	0.033 (0.047)	4	1.5 (2.3)	2
42	〃	MeI	0.13 (0.13)	2		
43	〃	EtI				
44	$C_{10}H_{11}$	HCl	0.03 (0.04)	3	3.7 (4.5)	2

5) White, Green, Hudson : Brit. J. Pharmacol., **6**, 560(1951).

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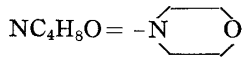
Table VIII. Spasmolytic Activity of 1,1-Diphenyl-4-aminopropanol Derivatives

$(C_6H_5)_2$=C(OH)$CH_2CH_2CH_2NR_2$·HCl

Compd. No.	Salt	A-Action Atropine=100	No. of mice	P-Action Papaverine=100	No. of mice
45	$-NMe_2$	2.6 (3.0)	2	37.7 (46.5)	4
46	$-NC_4H_8O$*	0.9 (0.9)	2	28.2 (30.4)	5

* NC_4H_8O= 

6. Diphenylmethanols (Table IX)

A-Action: In hydrochlorides piperidino compounds are slightly stronger than pyridyl compounds, and the reverse is true in quaternary ammoniums. That is to say, among the tertiary amines, piperidino compounds which have stronger basicity show stronger A-action than pyridyl compounds, but among the quaternary ammoniums, pyridyl compounds in which the charge at nitrogen is dispersed through the aromatic ring are a little better than piperidino compounds.

Potency order of quaternary pyridyl compounds are as follows: 4-Pyridyl > 2-pyridyl > 3-pyridyl.

Table IX. Spasmolytic Activity of Diphenylcarbinol Derivatives

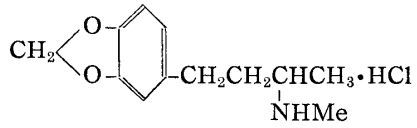
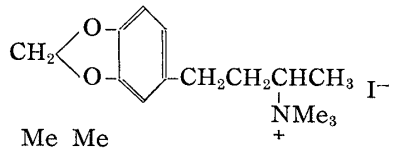
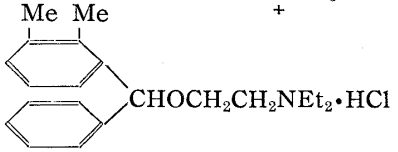
$(C_6H_5)_2C(OH)R$

Compd. No.	R	Salt	A-Action Atropine=100	No. of mice	P-Action Papaverine=100	No. of mice
47	2-pyridyl	HCl	0.03 (0.04)	5	21.7 (27.4)	6
48	〃	MeI	0.9 (0.77)	3		
49	3-pyridyl	HCl	0.02 (0.03)	5	12.6 (15.9)	6
50	〃	MeI	0.8 (0.7)	3		
51	4-pyridyl	MeI	1.2 (1.0)	3		
52	1-methyl-4-piperidyl	HCl	0.26 (0.3)	3		
53	〃	MeI	0.45 (0.38)	3		
54	1-methyl-3-piperidyl	HCl	0.22 (0.26)	3	30.7 (38.0)	3
55	〃	MeI	0.44 (0.36)	4		

7. Miscellaneous Group (Table X)

Though the A-action of Compounds No. 56 and No. 57 is feeble, the benefit of quaternization can be illustrated. The A- and P-action of No. 58 are of the same order of magnitude as that of No. 28

Table X. Spasmolytic Activity of a Miscellaneous Group

Compd. No.	Structure	A-Action Atropine=100	No. of mice	P-Action Papaverine=100	No. of mice
56		0.02 (0.03)	2		
57		0.05 (0.05)	3		
58		3.23 (3.23)	3	32.1 (34.7)	4

Discussion

One must discuss the structure-action ralationship of atropine-like substances in relation to acetylcholine-like compounds. Lands has stated that the latter would initiate the active process when they approach closely to their receptors, and that the former would be attached less readily with the receptors, so that they cannot initiate the reaction, but can block the access of ACh to the receptors.[6]

6) A. M. Lands: J. Pharmacol. Exptl. Therap., **102**, 234(1951); *ibid.*, **117**, 36(1956).

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In chemical reactions reactant molecules must approach within a limited distance and form an activated complex. Such a complex of ACh and the receptor might be supposed to exist before the initiation of the active process. On the other hand, the antagonists must be designed not only to be attracted on the receptor surface, but to place some hindrance to such a closer fit that is seen in the active compounds.

Factors concerning with the adsorbability of drug molecules on the receptors are as follows :

1. Chemical factors (a) cationic head
   (b) ester group
   (c) hydroxyl group
2. Steric factors
3. Physicochemical factors
4. Relative position of functional groups in a molecule.

1. (a) Cationic nature is necessary for adsorption on the receptor and for the initiation of the active process.

In substituted trialkylammonium compounds polarity is the greatest at trimethyl compounds, and substitution of methyl with other radicals or hydrogen atoms lowers both the polarity of cationic head and C-action. Although quaternization of tertiary amines generally potentiates A-action, increase in activity is rather insignificant in some instances and also diethylmethylammonium derivatives are more effective than trimethylammonium compounds in the present series, if the fourth substituents are the same. Thus strong electrostatic attracting force determines C-action strictly and, on the other hand, it does not seem to exert such a decisive influence upon A-action. Especially in the latter example, the magnitudes of polarity of molecules reverse the potencies of A-action, which would be controlled predominantly by other factors (cf. Tables Ⅲ and Ⅴ).

(b) The carbonyl carbon in ester might contribute to the adsorption on the receptor surface, but the effect is not discussed here, because these compounds lack ester grouping.

(c) The importance of an aliphatic hydroxyl radical, situating some distance away from N atom for A-action is also illustrated in the present series, as recognized in other compounds having A-action.

2. When methyl groups of trimethylammonium compounds are substituted successively with ethyl, A-action is the maximum at the diethylmethyl derivatives.

The low potency of triethyl compounds can be explained only by steric hindrance near the anionic site of the receptor. A larger substituent at the terminal carbon of the fourth substituent of cationic head tends to intensify A-action. This is generally attributed to steric hindrance by the substituents. It was reported that optical isomerism in the terminal carbon exerts decisive influence upon A-action.[7]

Now the optical isomers at the carbon adjacent to the amino group have been separated (No. 3, 4 and No. 5, 6) and it was found that the dextrorotatory compound surpasses the levorotatory compound in A-action. If one phenyl radical of diphenylpropanolamines was substituted with a tetrahydronaphthyl, the A-action is significantly diminished. All the facts suggest the strict stereochemical limitation of the shape of ACh-receptor.

3. In general, the effective concentration of potent atropine-like substances is much lower than that of potent ACh-like substances, that is to say, the apparent drug-receptor affinity is much larger in the former.[8]

7) A. M. Lands : J. Pharmacol. Exptl. Therap., **117**, 29(1956); W. M. Duffin, A. F. Green : Brit. J. Pharmacol., **10**, 383(1955).
8) R. P. Stephenson : Brit. J. Pharmacol., **11**, 379(1956).

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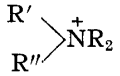
When pentyltrimethylammonium salt (PTMA), which is the most active stimulant among alkyltrimethylammonium salts, is compared with No. 27, and No. 39 with No. 42, similar conclusion is drawn. Introduction of the second phenyl group results in much higher activity (No. 36 to No. 28).

The actual attracting force between drug and receptor is produced by the above-mentioned chemical forces and by Van der Waal's force, that were already cited by some authors.[9]

The comparison of chemical structures between agonists (PTMA, No. 39) and antagonists (No. 27, 42) reveals that only an introduction of phenyl and/or methyl groups into long chain substituent results in such lowering of effective concentrations.

Table XI. Comparison of Effective Concentrations required to cause 50% Inhibition in Ileal Strips of Mice stimulated by ACh (1.2×10^{-7} g./cc. in bath)



Compd. No.	R′	NR_2	R″	Effective concn.(mole/L)
2	$(C_6H_5)_2C(OH)CH_2CHCH_3$		Me	3.1×10^{-8}
8	〃	$-NEt_2$	〃	4.6×10^{-8}
11	〃	$-NMe_2$	〃	5.1×10^{-7}
17	$(C_6H_5)_2C{=}CHCHCH_3$		〃	6.1×10^{-8}
20	〃	$-NEt_2$	〃	4.2×10^{-8}
22	〃	$-NMe_2$	〃	2.9×10^{-7}
Atropine				1.3×10^{-8}
ACh*	$CH_3COOCH_2CH_2-$	〃	Me	2.6×10^{-7}
PTMA*	$C_5H_{11}-$	〃	〃	2.3×10^{-5}
27	$(C_6H_5)_2CHCH_2CHCH_3$	〃	〃	2.0×10^{-7}
39*	$CH_3COCH_2CH_2-$	$-NEt_2$	〃	6.7×10^{-4}
42	$C_6H_5COCH_2CH_2-$	〃	〃	8.0×10^{-6}
36	$C_6H_5CH(OH)CH_2CH_2-$	〃	H	9.0×10^{-6}
28	$(C_6H_5)_2C(OH)CH_2CH_2-$	〃	〃	7.0×10^{-7}

* These compounds have C-action

Because the chemical attracting forces of the antagonists are supposed to be rather diminished from that of the corresponding agonist's only an increase of Van der Waal's force contributes to the increase of the stability of the drug-receptor complex. Moreover, it may now be assumed that some physicochemical properties of aryl or alkyl groups might reinforce the physiological activity. The effective concentration in usual experiments is given only as the concentration at the external phase·and the actual concentration in the biophase which directly surrounds the receptor is never konwn. We must be satisfied merely by the assumption of a linear relation between the concentrations at the two phases. The large radicals would increase the concentration ratio of a drug between a biophase, where lipoidal substances are abundant, and an external phase and would increase apparent affinity to the receptor.

The more potent activities of piperidylmethyl- (No. 2, 17) and diethylmethyl-ammonium salts (No. 8, 20), compared with the corresponding trimethyl compounds (No, 11. 22) reverse the Coulombic force that is the strongest at the trimethyl compounds. Here we must consider that larger radicals attached to nitrogen increase lipoid solubility and Van der Waal's force. In this respect A-action is intimately correlated to non-competitive P-action.

9) A.M. Lands: J. Pharmacol. Exptl. Therap., **117**, 29(1956); Barlow: "Introduction to Chemical Pharmacology," 163(1955).

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The compounds with P-action have too varied a structure to be arranged into a few fundamental groups of compounds. These sequences are somewhat similar to general anesthetics, which are supposed to act by some undefined physicochemical properties.[10]

In the present series of compounds activity is diminished but not completely abolished by quaternization. Such results are reverse of A-action and ionic state is considered not to be necessary for P-action. On the contrary, in the tertiary amines tested here the P-action roughly paralleled the A-action, although the discrepancy of the effect is not so significant as that in the A-action.

These facts suggest that some common procesess might exist in both actions, probably before the agents reach their site of action.

Again, we come to the conclusion that the A-action depends unexpectedly upon physicochemical properties, which are shared by large radicals like phenyl or cycloalkyl groups in addition to their well known steric effects.

4. Pfeiffer and Ing proposed the theories about spatial relationships of the functional groups required for muscarinic action.

Discussing the structure-activity relationship of antiacetylcholine drugs, many investigators illustrated the importance of this viewpoint. However there is a doubt as to the advisability of discussing the intramolecular distance in the not rigid molecule which allows extended and folded forms according to surroundings. Moreover, there is no reason to believe that receptors have a definite spatial configuration. Schueler[11] pointed this out, and tried to explain the activity discrepancy in some acetylcholine-like compounds by comparison of characteristics involving probability distribution of spatial distances in molecules and receptors.

An attempt was made to examine the effect of distance between the cationic nitrogen and a benzhydrol group which are included in many antispasmodics, and some compounds having such rigid structure as pyridine ring (No. 47 to No. 51) were prepared. Their A-action is feeble and discrepancy of potencies is not so significant as expected, though they have considerable P-action. It would be dangerous to derive some conclusions about spatial factor from this result.

The author is grateful to Prof. H. Kumagai and to Prof. K. Takagi for their guidance and encouragement. He is also indebted to Dr. Takatori, Dr. Katayanagi, Dr. Sugimura, and to Dr. Ozawa for the supply of compounds (No. 15, 41, 45, 46, 58, 59) used in this work.

Summary

1. Fifty-eight aralkylamines were tested for atropine-like activity against acetylcholine-stimulated ileal strips of mice.

2. Papaverine-like activity of the aralkylamines was tested against excess acetylcholine-stimulated ileal strips of mice.

3. The relationship between chemical structure and pharmacological activity has been discussed.

In almost all the compounds tested here, atropine-like activities change somewhat parallel with the papaverine-like activities of the compounds. The effect of quaternization of tertiary amines is the only exception, where the quaternary ammonium compounds have stronger atropine-like and weaker papaverine-like action than the corresponding tertiary amines.

It is suggested that some physicochemical properties such as lipoid solubility would influence the papaverine-like activity and also participate even in intensifying the atropine-like antiacetylcholine activity.

(Received November 14, 1957)

10) Barlow : "Introduction to Chemical Pharmacology," Methuen Press, 167(1955).
11) F. W. Schueler : Arch. inter. Pharmacodynamie, **93**, 417(1953).

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