UDC 615.782 : 545.3 : 547.554

25. Yutaka Kasuya : Chemicopharmacological Studies on Antispasmodic Action. XIII.[1] Paper Electrophoresis of Aralkylamines and their Quaternary Salts.

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

In the preceding paper,[1] the author discussed some factors concerning atropine-like (A-action), acetylcholine-like (C-action), and papaverine-like (P-action) actions and arrived at the conclusion that a cationic property in the molecule is essential to C-action, but seems not to be dicisive on A-action and other factor would be predominant for differentiating the activity among atropine-like compounds.

In the present work, cationic properties of various compounds are compared approximately by paper electrophoresis and their relations with biological activities are discussed.

Experimental

Experimental conditions.

Date : November 13, 1956, to March 6, 1957.
Apparatus : Horizontal open-strip type (plastic flame support).
Temperature : Room temp.
Filter paper : Toyo Roshi No. 51 (12.5×37.5 cm).
Current : 0.6 mA/cm.
Voltage : 150~350 V/30 cm.
Duration of development : 1.5 hrs.
Concentration of test substance : $10^{-2}M$
Color reagent : Dragendorff reagent.

Experiments were carried out in the following manner : The sheet of filter paper was placed between electrolyte vessels, then electrical potential was applied for a suitable length of time until the electric current became constant. Eleven kinds of samples were spotted by capillary at intervals of 1 cm. After 1.5 hrs. the sheet was removed, dried for 15~20 mins. at room temperature, and sprayed with the Dragendorff reagent.

Results

The pH-migration distance relationships for papaverine, atropine, and acetylcholine (ACh) are

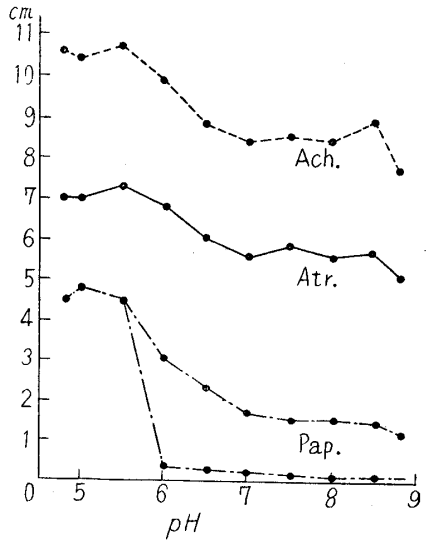


Fig. 1. Migration Distances of ACh, Atr. and Pap.

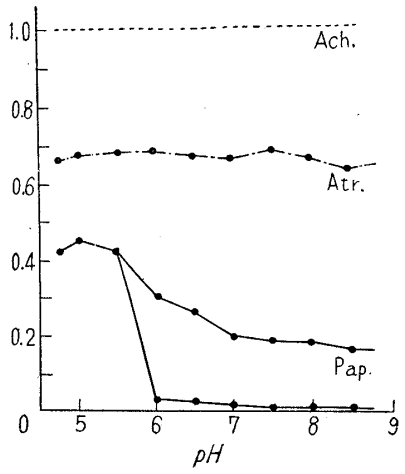


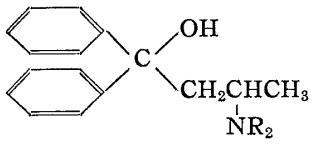
Fig. 2. Migration Ratios at Various pH

* Hongo, Tokyo (粕谷 豊).

1) Part XII : This Bulletin, **6**, 147(1958).

shown in Fig. 1. All migration distance show a tendency to decrease with the increasing pH value. Especially in region of pH 6~9, papaverine shows sudden decrease of migration distance and a greater part remains near the origin. It is difficult in paper electrophoresis to fix both the electric current and the voltage every time. In this experiment the current was fixed and migration distance was converted into migration ratio in terms of ACh. Thus, Fig. 2 corresponds to Fig. 1. All migration ratios of samples are listed in Tables I to VII.

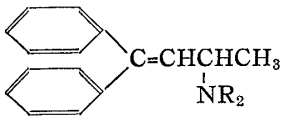
TABLE I. Migration Ratio of 1,1-Diphenyl-3-aminobutanols at Various pH



No.	NR_2	Salt	Migration ratio* ACh=1.0 pH 4.8	5.0	5.5	6.0	6.5	7.0	7.5	8.0	8.5
1	-N⟨ ⟩	HCl	0.59	0.60	0.60	0.65	0.63	0.58	0.51	0.52	0.32 (0.12)
2	〃	MeCl		0.62	0.59	0.59	0.60	0.57	0.54 (0.52)	0.35 (0.29)	0.35 (0.02)
3(*d*)	〃	HCl		0.60	0.59	0.62	0.60	0.59	0.50	0.47	0.35 (0.23)
5(*l*)	〃	*d*-tartarate	0.59	0.60	0.57	0.63	0.58	0.57	0.49	0.47	0.37 (0.34)
7	$-NEt_2$	HCl	0.58	0.58	0.64	0.64	0.65	0.65	0.58	0.64	0.58
8	〃	MeI		0.59	0.63	0.64	0.64	0.66	0.60	0.66	0.65
9	〃	EtI		0.61	0.65	0.64	0.64	0.64	0.59	0.64	0.66
10	$-NMe_2$	HCl	0.65	0.68	0.65	0.62	0.65	0.63	0.68	0.60	0.57
11	〃	MeI		0.62	0.66	0.66	0.67	0.68	0.63	0.67	0.66
12	〃	EtI	0.64	0.65	0.65	0.65	0.67	0.65	0.69	0.66	0.63
13	$-NH(CHMe_2)$	HCl		0.62	0.61	0.61	0.61	0.60	0.65	0.64	0.58
14	-NHMe	〃	0.60	0.63	0.68	0.63	0.63	0.63	0.64	0.64	0.50

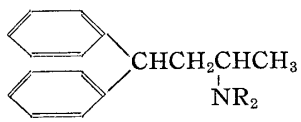
* Figures in parentheses show migration distance of smaller spot.

TABLE II. Migration Ratio of 1,1-Diphenyl-3-aminobutenes at Various pH



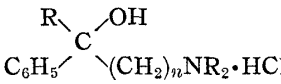
No.	NR_2	Salt	Migration ratio ACh=1.0 pH 4.8	5.0	5.5	6.0	6.5	7.0	7.5	8.0	8.5
16	-N⟨ ⟩	tartarate	0.62	0.61	0.61	0.60	0.65	0.61	0.61	0.49	0.45
17	〃	MeI	0.63	0.61	0.63	0.62	0.69	0.65	0.65	0.61	0.62
19	$-NEt_2$	tartarate		0.62	0.61	0.63	0.62	0.63	0.67	0.64	0.61
20	〃	MeI	0.61	0.62	0.61	0.66	0.65	0.64	0.64	0.67	0.64
21	〃	EtI	0.60	0.60	0.60	0.66	0.64	0.61	0.61	0.65	0.62
22	$-NMe_2$	MeI		0.64	0.66	0.67	0.70	0.72	0.66	0.67	0.67

TABLE III. Migrartion Ratio of 1,1-Diphenyl-3-aminobutanes at Various pH



No.	NR_2	Salt	Migration ratio ACh=1.0 pH 5.0	5.5	6.0	6.5	7.0	7.5	8.0	8.5
27	$-NMe_2$	MeI	0.66	0.67	0.67	0.71	0.72	0.68	0.67	0.68
25	-NHMe	HCl	0.64	0.65	0.63	0.64	0.66	0.62	0.60	0.69
24	$-NH_2$	〃	0.73	0.70	0.70	0.71	0.70	0.58	0.66	0.67

Table IV. Migration Ratio of α-Phenyl-ω-aminoalkanol Derivatives at Various pH



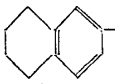
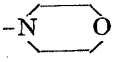
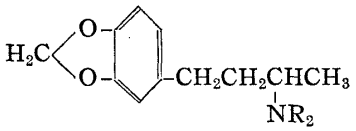
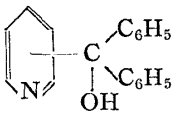
No.	R	n	NR_2	Migration ratio pH 5.0	5.5	6.0	6.5	7.0	7.5	8.0	8.5	ACh=1.0
28	C_6H_5	2	$-NEt_2$	0.65	0.60	0.68	0.59	0.62	0.63	0.61	0.60	
31		〃	〃	0.55	0.50	0.55	0.52	0.52	0.51	0.53	0.44	
45	C_6H_5	3	$-NMe_2$	0.64	0.61	0.65	0.58	0.60	0.62	0.61	0.57	
46	〃	〃		0.60	0.50	0.45	0.36	0.27	0.02	0.00	0.00	

Table V. Migration Ratio of 2-Piperonylisopropylamines at Various pH



No.	NR_2	Salt	Migration ratio pH 5.0	5.5	6.0	6.5	7.0	7.5	8.0	8.5	ACh=1.0
56	-NHMe	HCl	0.78	0.78	0.78	0.76	0.73	0.74	0.77	0.70	
57	$-NMe_2$	MeI	0.80	0.76	0.81	0.77	0.77	0.77	0.78	0.77	

Table VI. Migration Ratio of Diphenylpiperidylmethanols at Various pH



No.	Structure	Salt	Migration ratio PH 4.8	5.0	5.5	6.0	6.5	7.0	7.5	8.0	8.5	ACh=1.0
49	3-piperidyl	HCl		0.32	0.05	0.01	0.00	0.00	0.00	0.00	0.01	
50	〃	MeI	0.64	0.67	0.69	0.68	0.69	0.69	0.77	0.69	0.69	
47	2-piperidyl	HCl		0.25	0.03	0.04	0.04	0.05	0.02	0.04	0.03	
48	〃	MeI	0.67	0.67	0.69	0.68	0.68	0.69	0.75	0.69	0.69	
51	4-piperidyl	〃	0.67	0.67	0.68	0.67	0.69	0.69	0.76	0.69	0.69	

Table VII. Migration Ratio of Miscellaneous Compounds at Various pH

No.	Structure	Migration ratio PH 4.8	5.0	5.5	6.0	6.5	7.0	7.5	8.0	8.5	ACh=1.0
No. 39	$CH_3COCH_2CH_2-{}^+NEt_2MeI^-$	0.76	0.79	0.78	0.79	0.79	0.79	0.80	0.80	0.90	
BTMA	$C_4H_9-{}^+NMe_3I^-$	1.00	1.00	1.01	1.01	1.00	1.00	1.01	1.01	1.00	
	$C_4H_9-{}^+NMe_3Br^-$	1.01	1.01	1.01	1.01	0.99	1.14	1.01	1.00	1.00	
PTMA	$C_5H_{11}-{}^+NMe_3I^-$	0.94	0.95	0.96	0.96	0.97	0.96	0.98	0.94	0.94	
	Benactyzine	0.61	0.64	0.62	0.62	0.62	0.59	0.63	0.58	0.53	
	Avacan	0.63	0.63	0.62	0.60	0.66	0.60	0.67	0.58	0.55	
Atr.	Atropine sulfate	0.66	0.68	0.68	0.69	0.67	0.66	0.68	0.66	0.63	
Atr. MeBr	Atropine MeBr	0.67	0.70	0.68	0.70	0.73	0.70	0.74	0.72	0.68	
DHNS	Dihydroneuspasverine	0.60	0.62	0.61	0.60	0.59	0.52	0.48	0.24 (0.07)	0.22 (0.02)	
Pap.	Papaverine	0.42	0.45	0.42	0.30 (0.03)	0.26 (0.02)	0.20 (0.02)	0.18 (0.01)	0.18 (0.01)	0.16 (0.01)	
Ach	Acetylcholine	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	

Discussion

The main factors governing the migration of samples in this experiment may be considered to be the polarity of amine group and the size of molecule. In homologous compounds, it is expected that polarities run parallel to the migration ratios, although

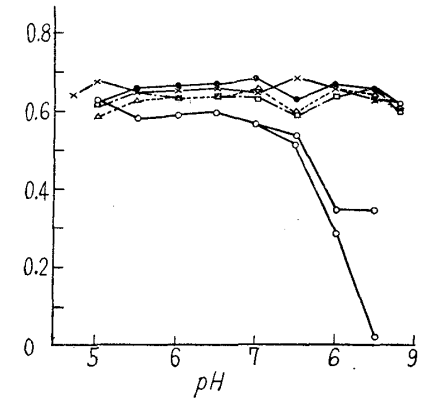
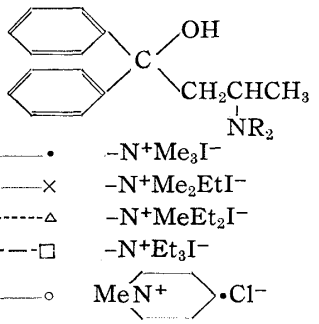


Fig. 3.
Migration Ratios of 1,1-Diphenyl-3-aminobutanols



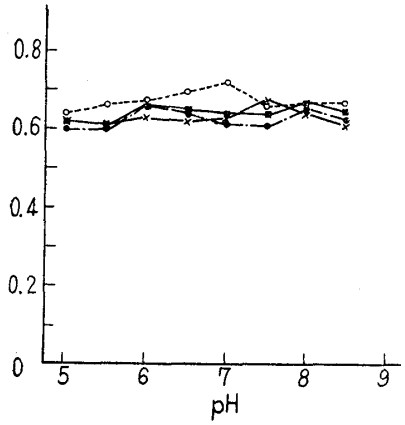
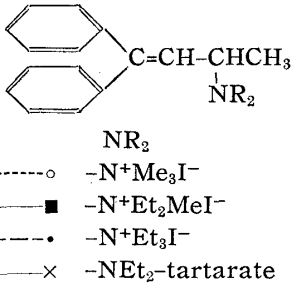


Fig. 4.
Migration Ratios of 1,1-Diphenyl-3-aminobutenes



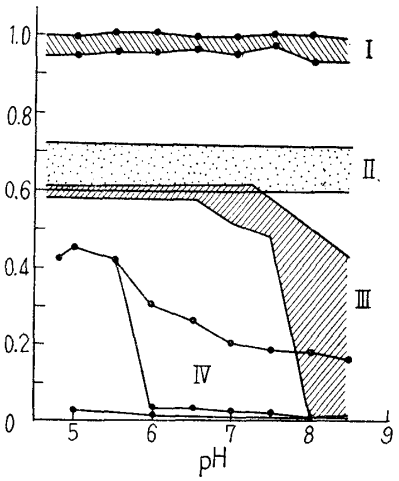


Fig. 5.
Grouping of Migration Ratios

it is dangerous to accommodate polarity with mobility in paper electrophoresis in every compound tested.

For example, $-NMe_3$ and $-NMe_2Et$ derivatives show somewhat larger migration ratios than others as shown in Figs. 3 and 4. In Tables I to VII, the increase of cationic property by quaternization of amine is shown rather well by the comparison of atropine with atropine methobromide, No. 47 with No. 48, and No. 49 with No. 50.

As a matter of course, No. 3 and 5 (optical isomers) showed identical migration ratios at various pH.

All compounds are broadly divisible into four groups on the basis of their migration ratio.

Group I consists of ACh, PTMA, and BTMA. Members of this group show migration ratio of nearly 1.0.

Group II compounds have migration ratio between 0.6 and 0.7 at every pH. Most of the compounds tested belong to this group and atropine can be considered as a representative of one.

Group III contains Compounds Nos. 1, 2, 3, 5, 16, and 46, and DHNS. Their migration ratio is similar to that of group II in the region of pH 5~7, but suddenly decreases in the region of pH 7~7.5.

Group IV consists of Compounds No. 47 and 49, and papaverine.

All members of group I are trimethylammonium compounds, and have a strong C-action. No member of other groups shows C-action. This fact supports the view that existence of a cationic head would be necessary for C-action.

Compounds of group II and III, except DHNS, show A-action, but there is a wide deviation in their activity, and there is no parallelism between the activity and the migration ratio.

From this, it is supposed that the cationic property is required to some extent for A-action, but it would not be a decisive factor. Every compound of group IV, III, and II shows P-action in greater or lesser degree. No member of group IV shows A-action.

For P-action, the existence of a cationic head seems to be of little importance, and other factors such as physicochemical properties would be essential.

Among the members of group III, Nos. 1, 2, 3, 5, and 16 are characterized by the existence of a piperidino group in the molecule and by the considerable activies in both A- and P-actions. It is interesting that they show a similar migration to that of atropine at pH below 6.5 and their migration ratio lies between atropine and papaverine in the region of pH 6.5~8.5.

The author is grateful to Prof. H. Kumagai and to Prof. K. Takagi for their guidance and encouragement. He is also indebted to Miss Reiko Terada for technical assistance in the experiment.

Summary

The cationic properties of aralkylamines were compared approximately by paper electrophoresis. These compounds were broadly divisible into four groups on the basis of their mobilities. Biological characteristics of each group were discussed.

(Received November 14, 1957)

UDC 547.734.07

26. Ryuichi Kimura, Takahiro Yabuuchi, and Yasutaka Tamura : Studies on Thiophene Derivatives. I. Syntheses of 2-Amino-1,1-di(2-thienyl)alkanols.

(*Scientific Research Institute for Practical Life, University of Kyoto**)

In 1950, Adamson and Green[1,2] synthesized 3-amino-1,1-di(2′-thienyl)alkenes (A) and reported that the compounds possessed an analgesic and antispasmodic action. Moreover, Kasé[3] reporting on the result of "Coughing Dog method" said that 3-piperidino-1,1-di(2-thienyl)butene (B) had a more potent antitussive action than

* Yoshida-Konoe-cho, Sakyo-ku, Kyoto (木村隆一, 藪内隆弘, 田村泰隆).

1) D. W. Adamson : J. Chem. Soc., **1950**, 885.
2) a) D. W. Adamson, A. F. Green : Nature, **165**, 122(1950).
b) D. W. Adamson, W. H. Duffin, A. F. Green : *Ibid.*, **167**, 153(1951).
3) Y. Kasé : This Bulletin, **3**, 394(1955).