DEPENCENCE OF TYPE OF ACTION OF BIS-QUATERNARY AMMONIUM MUSCLE RELAXANTS ON THE CONFORMATION POSSIBILITIES OF THE MOLECULE

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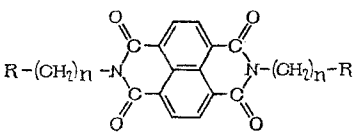
UDC 615.216.5:547.333.4].015.11

We showed previously that muscle relaxants which have an absolutely rigid structure and a distance of approximately 20 Å between the quaternary nitrogen atoms (structure C-16)possess an antidepolarizing type of action which is independent of the size of the cationic groupings [1]. The rigid structure of these compounds is caused by the presence of the polycyclic middle portion which makes the molecule unwieldy ("pachy-structure"). An opinion had appeared in the literature that unwieldy muscle relaxant molecules generally possess an antidepolarizing type of action [2]. Thus, the problem remained unresolved as to what determined the type of action in the case under consideration: the unwieldy middle portion of the molecule or its absolute rigidity.

To resolve this question, we have synthesized the muscle relaxants I-V (Table 1) of general formula



I-VIII

The middle unwieldy polycyclic portion of the molecule and the distance between the quaternary nitrogen atoms (at n=4 it is 19.2 Å) are retained in these compounds. However, owing to the presence of the tetramethylene chains, the molecule possesses considerable flexibility (Fig. 1). A pharmacological study showed that compounds I and II are highly active muscle relaxants of the depolarizing type of action in spite of the unwieldy structure of the middle portion of the molecule [3].

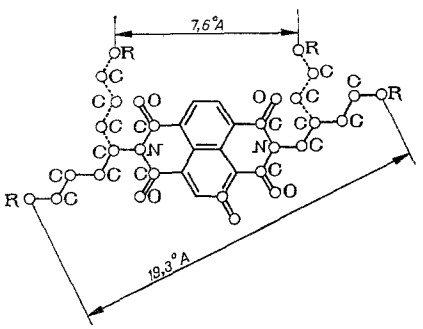


Fig. 1. Extreme conformations of compounds I and II.

With dimethylene chains present (III, IV, and V) the flexibility of the molecule is very insignificant: in the extreme conformations the distance between the quaternary nitrogen atoms differ by only 0.3 Å (Fig. 2). These compounds proved to be muscle relaxants with an antidepolarizing type of action.

Thus, a comparison of the structural parameters and pharmacological characteristics of the bis-quaternary derivatives of naphthalene-peritetracarboxylic acid being studied leads to the conclusion that the possibility of conformational transformations is a very important factor determining the type of action of muscle relaxants. The results of the pharmaco-

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TABLE 1. Bis-(Dialkylaminoalkylimides) of Naphthalene-peritetracarboxylic Acid (VI–VIII) and Their Bis-Quaternary Salts (I–V)

Compound	R	n	Yield (in %)	Melting point (in degrees)	Found (in %)				Empirical formula	Calculated (in %)			
					C	H	N	S		C	H	N	S
I	$+N(CH_3)_3C_6H_5SO_3^-$	4	97	324—325°	59,26	6,19	6,59	8,21	$C_{40}H_{46}N_4O_{10}S_2$	59,39	5,98	6,93	7,93
					59,00	5,86	6,69	8,04					
II	$+N(CH_3)_2C_2H_5C_6H_5SO_3^-$	4	92,5	275°	59,80	6,18	6,55	7,94	$C_{42}H_{52}N_4O_{10}S_2$	60,26	6,26	6,69	7,66
					60,00	6,33	6,35	7,84					
III	$+N(CH_3)_3C_6H_5SO_3^-$	2	69,5	304—306°	57,50	5,88	7,44	8,53	$C_{36}H_{40}N_4O_{10}S_2$	57,43	5,36	7,44	8,52
					57,63	5,61	7,72	8,57					
IV	$+N(C_2H_5)_2CH_3C_6H_5SO_3^-$	2	72,5	256°	59,52	6,18	6,92	8,37	$C_{40}H_{48}N_4O_{10}S_2$	59,39	5,98	6,93	7,93
					59,14	6,31	7,00	8,33					
V	$+N(C_2H_5)_3C_6H_5SO_3^-$	2	90	260° (decomp.)	57,36	6,70	6,63	7,89	$C_{42}H_{52}N_4O_{10}S_2 \cdot 2H_2O$	57,78	6,47	6,42	7,35
					57,53	6,52	6,64	7,84					
VI	$N(CH_3)_2$	2	57	220—222°	64,99	6,00	13,44	—	$C_{22}H_{24}N_4O_4$	64,69	5,92	13,72	—
					64,99	6,16	13,38						
VII	$N(C_2H_5)_2$	2	79	246—248°	66,67	6,92	11,84	—	$C_{26}H_{32}N_4O_4$	67,22	6,94	12,06	—
					66,74	6,66	11,60						
VIII	$N(CH_2)_2$	4	85	175—176° (decomp.)	66,82	7,09	11,88	—	$C_{28}H_{32}N_4O_4$	67,2	6,94	12,06	—
					66,71	7,13	11,90						

Note. Compounds I and III were crystallized from dilute alcohol, II and IV from undiluted alcohol, V from absolute alcohol, and VI, VII, and VIII from dimethylformamide.

Fig. 2. Extreme conformations of compounds III, IV, and V.

TABLE 2. Pharmacological Properties of Bis-Quaternary Derivatives of Naphthalene-peri-tetracarboxylic Acid

Compound	ED_{50} in mole/kg (cat)	HIS* in mole/kg (rabbit)
I	0,03	0,06
II	0,06	0,1
III	4,0	3,0
IV	0,5	0,3
V	0,5	0,3

*HIS – Head inclination symptom.

logical studies are given in Table 2. A description of the synthesis is given in the experimental section.

EXPERIMENTAL

Bis-(Dimethylaminobutylimide) of Naphthalene-peri-tetracarboxylic Acid (VIII). To 1.33 g of naphthalene-peri-tetracarboxylic acid was added 30 ml of glacial acetic acid, and the mixture was boiled for 2 h with stirring. Dimethylaminobutylamine dihydrochloride (2.6 g) and anhydrous sodium acetate (2.3 g) were added to the reaction mixture at room temperature. The heating was continued for a further 1.5 h. The mixture was filtered (from the precipitate of sodium chloride), the filtrate was diluted with 50 ml of water, and 30% sodium hydroxide solution was added until a pH of 10.0. The precipitate which separated was filtered off, washed with water, and dried at 80°C. The weight was 1.7 g of a dark lilac colored solid.

The purification, melting point, yield, and analytical data for the obtained compound and for all the following substances are given in Table 1.

Bis-(Dialkylaminoethylimides) of Naphthalene-peri-tetracarboxylic Acid (VI and VII). To 0.01 mole of naphthalene-

peri-tetracarboxylic acid was added 60 ml of acetic acid and the mixture was heated with stirring for 2 h. Then 0.03 mole (50% excess) of the appropriate dialkylaminoethylamine was added at room temperature and the heating continued for a further 1 h. A dark brown colored solution was formed which after cooling was diluted with water and treated with 30% sodium hydroxide solution until pH 8.0-10.0. The precipitate which separated was filtered off, washed with water and with alcohol, and dried in a desiccator.

Bis-Quaternary Ammonium Salts (I-V). To 1 g of the appropriate base was added 10 ml of the methyl or corresponding ethyl ester of benzenesulfonic acid and the mixture heated with stirring for 1 h at a temperature of 105-115° (for III 150-155°). The precipitate was filtered off, washed with absolute ether, and dried in a vacuum desiccator.

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