SYNTHESIS AND COMPARISON OF THE CURARE-LIKE ACTIVITY OF MONO- AND DIQUATERNARY AMMONIUM COMPOUNDS WITH RIGID STRUCTURES

N. V. Khromov-Borisov, M. L. Indenbom, and A. F. Danilov

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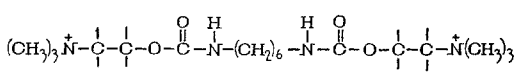
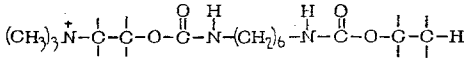
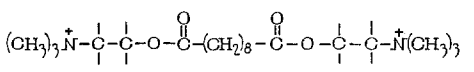
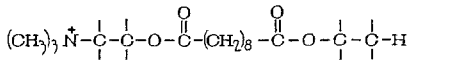
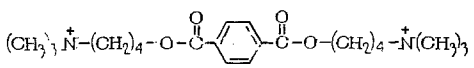
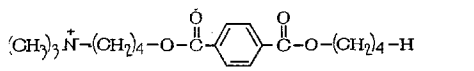
It is known that muscle relaxants in which the distance between the quaternary nitrogen atoms is 20-22 Å are capable of interacting with cholinoreceptors not only by means of their cationic ends but also by means of the dipole groupings if the latter are in the "acetylcholine position" [1,2]. The loss of one cationic group in such molecules leads to only a slight reduction in the activity (by a factor of 5-10). However, if the dipole groupings are not in the "acetylcholine position," the removal of one cationic group induces a sharp drop in the activity (by factors of tens and hundreds) (Table 1). This sort of comparison of the activity of the dications and the corresponding monocations of muscle relaxants was made only for compounds with flexible molecular structures. It seemed of interest to study this sort of dependence for compounds with rigid molecular structures and an antidepolarizing type of action.

For this, we synthesized and investigated mono- and diquaternary ammonium compounds VII-X, which have rigid molecular structures.

TABLE 1. Comparison of the Activity of Muscle Relaxants with Depolarizing Action upon Interacting with the C-16 Structure

Comp.	Structure	ED_{50} (cats)	HDS (rabbits)
		μmole/kg	
I		0,008	0,06
II		0,08	0,4
III		0,02	—
IV		0,1	—
V		0,005	0,025
VI		3,5	10,0

Note. Here and in Table 2, HDS is the head dipping symptom.

Institute of Experimental Medicine, Academy of Medical Sciences of the USSR. I. M. Sechenov Institute of Evolutionary Physiology and Biochemistry, Academy of Medical Sciences of the USSR, Leningrad.
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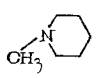
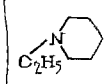
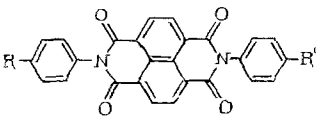
TABLE 2. Blocking Activity of Mono- and Diquaternary Ammonium Derivatives of Naphthalene-peri-tetracarboxylic Acid

Comp.	R	R'	ED_{50} (cats)	HDS (rabbits)
			μmole/kg	
VII			0,04	0,04
VIII		H	2,0	0,7
IX			0,12	0,08
X		H	12,0	1,8

Note. All of the compounds are salts of benzenesulfonic acid.

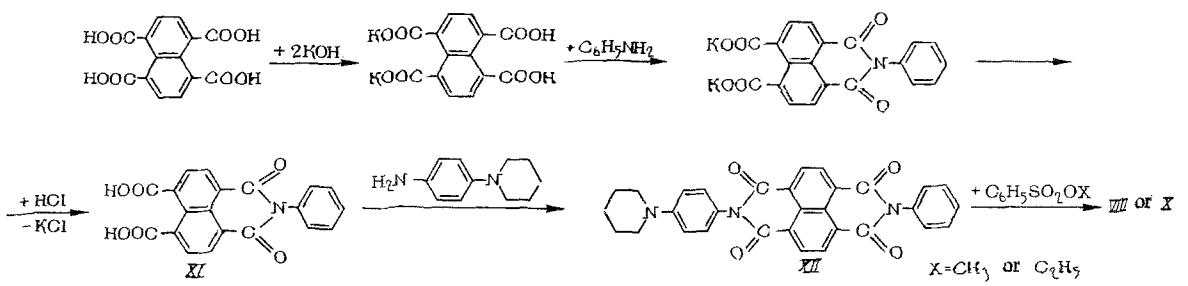


VII-X

Both the dicationic compounds (VII and IX) and the corresponding monocationic compounds (VIII and X) proved to be muscle relaxants with an antidepolarizing type of action. The results of the pharmacological investigation of VII-X are presented in Table 2.

It is seen from Table 2 that the curare-like activity of monoquaternary derivatives of naphthalene-peri-tetracarboxylic acid (VIII and X) is considerably lower (by tens of times) than that of their diquaternary analogs (VII and IX). Thus it turned out that the above-indicated dependence is characteristic not only for flexible but also for rigid muscle relaxants.

Derivatives VIII and X were synthesized via the following scheme:



We have previously described the synthesis of derivatives VII and IX [3].

EXPERIMENTAL

Naphthalene-peri-tetracarboxylic Acid Monophenylamide (XI). A mixture of 3 g of naphthalene-peri-tetracarboxylic acid, 1.2 g (10% excess) of potassium hydroxide, and 100 ml of water was heated until a solution was formed. The hot solution was filtered, 1 ml of aniline was added to the filtrate, and the mixture was refluxed for 4 h. The solution was treated with charcoal and filtered. Concentrated hydrochloric acid (about 4 ml) was added to the refluxing filtrate, and the resulting precipitate was removed by filtration, washed repeatedly with hot water (until it was neutral), and dried in a vacuum desiccator over sulfuric acid to give 2.75 g (80.17%) of product. Crystallization from acetic acid–acetic anhydride (3 : 1) gave 1.8 g of a product with mp 295-296°. Found, %: C 69.72, 70.05; H 2.78, 2.85; N 3.94, 3.71. $C_{20}H_9NO_5$. Calculated,%: C 69.96; H 2.64; N 4.07.

Naphthalene-peri-tetracarboxylic Acid N-Phenyl-N'-(p-piperidinophenyl)diimide (XII). A mixture of 4.45 g of XI and 90 ml of acetic acid was refluxed with stirring for 2 h. The suspension was cooled to room temperature, 2.5 g of freshly distilled N-(p-aminophenyl)piperidine was added, and the mixture was heated for another 6 h. The mixture was then filtered without cooling, and the solid was washed successively with acetic acid, alcohol, and ether, and dried in a vacuum desiccator to give 7.1 g of product. Crystallization from dimethylformamide gave a product with mp 310-312° (dec.). Found,%: C 74.19, 74.46; H 4.85, 4.94; N 8.20, 8.16. $C_{31}H_{23}N_3O_4$. Calculated,%: C 74.24; H 4.62; N 8.38.

Naphthalene-peri-tetracarboxylic Acid N-Phenyl-N'-(p-piperidinophenyl)diimide Methobenzenesulfonate (VIII). A mixture of 1 g of base XII and 10 ml of methyl benzenesulfonate was heated with stirring at 140-150° for 2 h. The solution was cooled, absolute ether was added, and an oil separated. The liquid was decanted, and the oil was washed two to three times with absolute ether. The oil gradually solidified

on trituration in ether to give 1.1 g (82%) of product. Crystallization from dilute alcohol (2:1) gave a product with mp 255-256° (dec.). Found,%: C 66.13, 66.20; H 5.05, 4.99; N 5.92, 6.07; S 4.49, 4.72; $C_{38}H_{31}N_3O_7S \cdot H_2O$. Calculated,%: C 65.98; H 4.81; N 6.08; S 4.63.

Naphthalene-peri-tetracarboxylic Acid N-Phenyl-N'-(p-piperidinophenyl)diimide Ethobenzenesulfonate (X). A mixture of 1.5 g of base XII and 15 ml of ethyl benzenesulfonate was heated at 140-160° for 1.5 h. The mixture was cooled, and absolute ether was added, whereupon a precipitate formed immediately. The precipitate was removed by filtration and washed repeatedly with ether to give 2 g (98.5%) of product. Crystallization from methanol gave a product with mp 262-263°. Found,%: C 65.90, 65.85; H 5.09, 5.26; N 5.76, 5.57; S 4.57, 4.57. $C_{39}H_{33}N_3O_7S \cdot H_2O$. Calculated,%: C 66.37; H 5.00; N 5.95; S 4.54.

LITERATURE CITED

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3. N. V. Khromov-Borisov, M. L. Indenbom, and A. F. Danilov, Khim.-Farmats. Zh., 5, No. 9, 3 (1971).