N-CHOLINOLYTIC ACTIVITY AND π-ELECTRONIC STRUCTURE OF THE MOLECULE

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I. V. Komissarov

Chair of Pharmacology (Head—Docent I. V. Komissarov) Pediatric and Sanitary Hygiene Faculty of Donetsk Medical Institute
(Presented by Member of the Academy of Medical Sciences, USSR, V. V. Zakusov)
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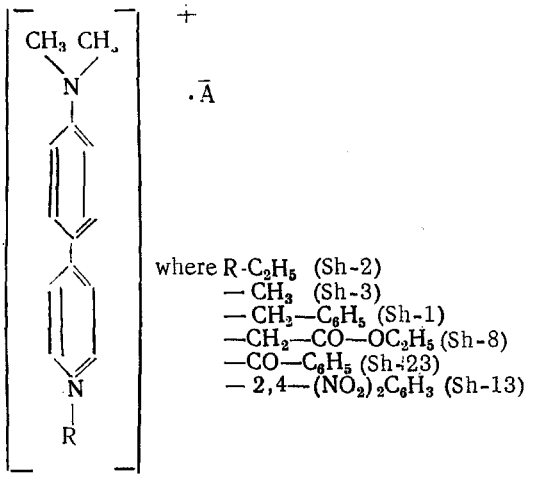
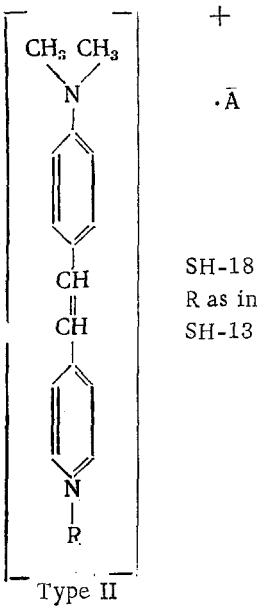
The electronic structure of the molecule in certain cases evidently determines the pharmacological activity of chemical substances. Thus, in the alkyl phosphates, the anticholinesterase activity is directly related to the degree of deformation of the electronic cloud of the phosphorus atom [4, 5]. The introduction of electrophilic substituents—dinitrophenyl or nitrobenzoyl groups—into morphine in place of the phenolic hydroxyl, is accompanied by an increase in the analgesic activity, whereas replacement by a positively inducing radical (methyl, ethyl) leads to decreasing anesthetizing properties of the preparations [2]. It was also shown that the decamethonium analog with electrophilic substituents at the four nitrogen atoms does not possess depolarizing, acholinolytic action [6]. By comparing the activity and mechanism of the action of the N-cholinoreactive structures of a number of bisquaternary derivatives of piperidine and 1, 2, 3, 4-tetrahydroquinoline with analogous derivatives of pyridine and quinoline, an attempt was made to explain the peculiarities of the latter by the presence of a π-electronic cloud in their molecules [7]. In this work the influence of the π-electronic structure of molecules on the N-cholinolytic activity was studied on sample substances with conjugated double bonds. Substances with the following structures were studied:



Type I

where R-C_2H_5 (Sh-2)
— CH_3 (Sh-3)
— CH_2—C_6H_5 (Sh-1)
—CH_2—CO—OC_2H_5 (Sh-8)
—CO—C_6H_5 (Sh-23)
— 2,4—$(NO_2)_2C_6H_3$ (Sh-13)



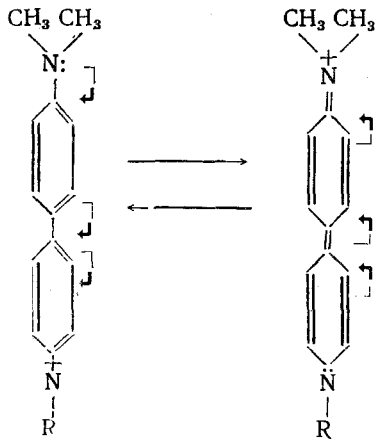
Type II

SH-18
R as in
SH-13

The preparations were synthesized in the Donetsk branch of the Institute of Organic Chemistry, Academy of Sciences, Ukr. SSSR, by A. K. Sheikman. *

*I should like to take this opportunity to express my gratitude to Docent M. L. Tarakhovskii for supplying the aforementioned preparations for the investigation.

These compounds are very convenient for resolving the problem posed, because the noncollectivized pair of p-electrons of the nitrogen of the dimethylamino group may interact with the π-electrons of the benzene ring, and due to the presence of conjugated bonds and the greater lability of the π-electrons, the latter may be displaced in the entire conjugated system as a whole. Thus, depending on the electrophilic character of the substituent (R) at the nitrogen of the pyridine, the the π-electronic cloud in the molecules of these substances may be substantially deformed within the limits of two extreme variations:



PROCEDURE

The experiments were carried out on the rectus muscle of male R. esculenta. The muscle was suspended in a 100-ml beaker in an isotonic aerated salt solution. We studied the dependence of the contraction of the rectus muscle (in % of the maximum) on the concentration of acetylcholine in the absence and presence of constant concentrations of the investigated preparations. These concentrations for the preparations SH-1, SH-3, SH-8, and SH-23 were $1 \cdot 10^{-4}$ moles/liter; for SH-13 it was $5 \cdot 10^{-5}$, and for the preparations SH-2 and SH-18 it was $0.5 \cdot 10^{-5}$ moles/liter. The average values of the contraction of the muscles at each concentration of acetylcholine was calculated on the basis of the results of four experiments. The experimental data were treated graphically [1].

RESULTS OF THE EXPERIMENTS

In the experiments on the rectus abdominis muscle of the frog, all of the investigated compounds revealed an antagonism with respect to acetylcholine.

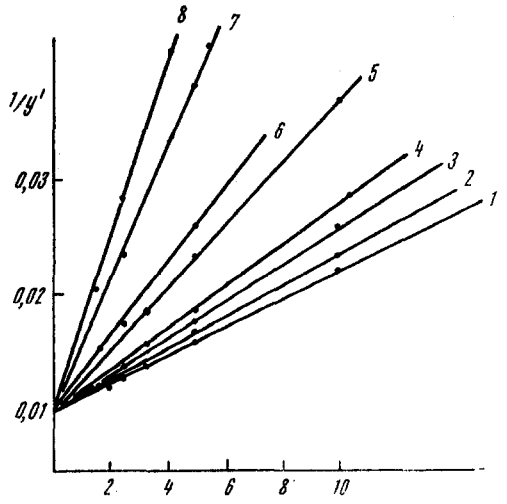
In the graph (see figure), constructed in a reciprocal scale, the dependence of the degree of contraction of the muscles on the acetylcholine concentration obtained in the presence of the compounds studied is expressed by straight lines cutting off a segment equal to 0.01 on the y-axis. Thus, [1] all of the compounds studied, independent of the electrophilic nature of the introduced substituents (R) and, consequently, independent of the π-electronic structure of the molecules, are competitive antagonists of acetylcholine.

The activity of the compounds studied may be expressed quantitatively by the affinity constant of the preparation-receptor complex (K_C^1). The values of K_C^1, determined upon analysis of the graph, are presented in the table.

It was shown that among compounds of type I, the most activity was manifested by those substances (SH-2 and SH-3) in which the substituents at the nitrogen of their pyridine are positively inducing radicals. Moreover, when the positive induction effect of the substituent is increased, an increase in the N-cholinolytic activity of the substance is observed.

Analogous relationships are also observed in a number of those compounds of type I where the substituents at the nitrogen of pyridine are negatively inducing radicals. The N-cholinolytic activity of these substances increases in the following order: SH-1 < SH-8 < SH-23 < SH-13, i.e., in proportion to the increase in the negative inducing effect of the substituent.

Thus, the greatest activity among the compounds of type 1 is found in preparation SH-2 in which the substituent at the nitrogen shows the greatest positive induction effect, and also in the preparation SH-13, in which the substituent



Acetylcholine concentration (in 10^{-5} moles/liter)

Dependence (in a reciprocal scale) of the degree of contraction of the rectus muscle on the acetylcholine concentration in the absence (1) and in the presence (2) of preparation SH-1, SH-8 (3), SH-23 (4), SH-3 (5), SH-13 (6), SH-2 (7), and SH-18 (8).

N-Cholinolytic Activity of the Preparations

Preparation	c
SH-2	$5.61 \cdot 10^5$
SH-3	$0.85 \cdot 10^4$
SH-1	$0.01 \cdot 10^4$
SH-8	$0.04 \cdot 10^4$
SH-23	$0.16 \cdot 10^4$
SH-13	$0.23 \cdot 10^5$
SH-9-18	$7.99 \cdot 10^5$

possesses the most electrophilic properties. The aforementioned circumstance is evidently a result of a firmer fixation of the positive charge on the nitrogen of pyridine in the first case and on the nitrogen of the dimethylamino group in the second case. The firmness of the fixation of the charge in turn was caused by the greatest displacement of the π-electronic cloud in the molecules of these compounds.

However, a comparison of SH-13 and SH-18, the activities of which differ 35-fold, despite the fact that their π-electronic structures are the same, indicates that the π-electronic structure of the preparations is not the only factor determining the N-cholinolytic activity. In particular, the higher activity of the preparation SH-18 in comparison with that of SH-13 is probably due to a more optimum distance between the active centers of the molecule of the substance, and also the well-known "rigidity" of the vinyl bridge [3].

Thus, the π-electronic structure of the compounds studied is only one of the factors determining the N-cholinolytic activity and to no degree determines the mechanism of their action.

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