PREPARATION OF N-(β-ACETOXYETHYL)ANABASINE, -BRUCINE, -STRYCHNINE, AND -COCAINE IODIDES AND A STUDY OF SOME OF THEIR BIOLOGICAL PROPERTIES

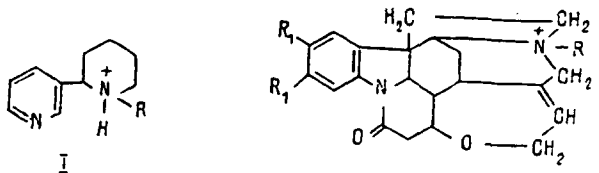
L. A. Srybnaya, Z. Tulyabaev,
A. A. Sadykov, and D. N. Dalimov

UDC 547.94:577.152:612.815.1

Many drugs are obtained by modifying the structures of alkaloids, and some of them are used for the study of the organization and topography of cholinergic structures in warm-blooded animals and arthropods [1].

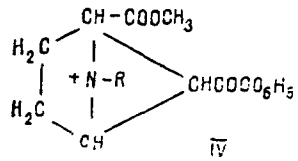
The present work is a continuation of investigations of the specific effectors of cholinesterases and GABA receptors using the modification of alkaloids. To solve the problem posed, the N-β-acetoxylethyl iodides of -anabasine (I), of -brucine (II), of -strychnine (III), and of -cocaine (IV) were synthesized.

These acetoxyethylammonium iodides were obtained by keeping alcoholic solutions of the alkaloids with the calculated amount of β-iodoethyl acetate [3] at room temperature for several days. Then the solvent was partially eliminated and the reaction product was precipitated by the addition of an excess of ethyl ether. The substances were purified by recrystallization from a mixture of absolute alcohol and ethyl ether [2]. The structures of the compounds synthesized were confirmed by their IR and PMR spectra. The IR spectrum of N-(β-acetoxyethyl)anabasine iodide had the following absorption bands (ν, cm^{-1}): 300 (C—H), 1760 (C=O), 1510 (C—N), 1460 (CH_2), 1020 (C—O—C).

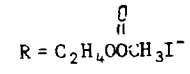


I

II. $R_1 = OCH_3$
III. $R_1 = H$



IV



The PMR spectrum of N-(β-acetoxyethyl)anabasine iodide (D_2O) was characterized by the following signals (ppm): $-\overset{\overset{O}{\|}}{C}-CH_2-$, 2.02 (t); $-\overset{\overset{O}{\|}}{C}-CH_2-$, 2.64 (t); $O-CH_2-$, 3.66 (t); $N-CH_2-$, 3.87 (t); $-CH_2-OC-$, 4.74 (m).

Analogous signals are observed in the spectra of N-(β-acyloxyethyl)amines.

As is well known [4], many narcotics lower the enzyme activity of cholinesterases in the organism, and an inhibition of the activity of cholinesterases by morphine and strychnine has been detected [5, 6].

We have investigated the influence of the acetoxyethylammonium iodines on the catalytic activities of human blood erythrocyte acetylcholinesterase (ACE) and horse blood serum butyrylcholinesterase (BuCE).

The activities of the cholinesterases investigated under the action of the acetoxyethylammonium iodides were reversibly suppressed. The brucine derivative inhibited the ac-

A. S. Sadykov Institute of Bioorganic Chemistry, Tashkent. Translated from Khimiya Prirodnykh Soedinenii, No. 3, pp. 413-415, May-June, 1990. Original article submitted July 6, 1989.

0009-3130/90/2603-0347$12.50

tivity of ACE by the mixed type of inhibition. The catalytic properties of BuCE under the action of N-(acetoxyethyl)anabasine iodide were suppressed by the competitive type of action. The other modified alkaloids interacted with ACE and BuCE noncompetitively. The overwhelming majority of the inhibitors were more effective in relation to BuCE, and this was particularly clear in the case of the strychnine derivative, which suppressed the activity of BuCE 16 times more strongly than that of ACE. The great affinity of these inhibitors for BuCE is connected with their possible hydrophobic interaction with the peripheral hydrophobic groups located close to the active center of the enzyme.

With the aim of revealing a possible action of the quaternary ammonium iodides obtained on the GABA receptor systems, we investigated the influence of these compounds on the binding of [^{3}H]fluoronitrazepan with the benzodiazepine-binding section of the GABA receptor. It was established that the cocaine, brucine, and strychnine derivatives inhibited the binding of [^{3}H]fluoronitrazepam. This showed that at least part of their physiological action is mediated through the GABA receptor complexes. The anabasine derivative did not exhibit a corresponding action on binding with the GABA receptor sections.

The information obtained confirms the possibility of regulating the biological action of modified alkaloids by acting on the cholinergic and GABA-ergic systems [sic] which opens up new possibilities in the creation of drugs with a selective action.

LITERATURE CITED

1. A. A. Abduvakhabov, A. A. Sadykov, D. N. Dalimov, and Kh. A. Aslanov, Alkaloids and Their Derivatives as Tools for Studying the Cholinergic System [in Russian], FAN, Tashkent (1984), p. 287.
2. Methods of Obtaining Chemical Reagents and Preparations [in Russian], Moscow, No. 2 (1961).
3. A. Simplan, Ann. Chem., 113, 115 (1960).
4. M. Ya. Mikhelson, The Action of Narcotics on Cholinesterase [in Russian], Izd-vo Voenno-Morskoi Meditsinskoi Akademii, Leningrad (1948), p. 61.
5. H. Kuhn, Arch. Int. Pharmacol. Ther., 58, 88 (1983).
6. D. Nachmanson, Comp. Rend. Soc. Biol., 129 (33), 410 (1938).