SYNTHESIS OF ORGANOPHOSPHORUS DERIVATIVES OF ANABASINE AND INVESTIGATION OF THEIR CHOLINERGIC ACTIVITY

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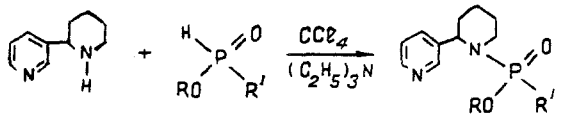
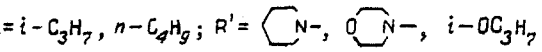
Anabasine sulfate is used in the practice of protecting the cotton plant and other plants from harmful insects, since it possesses a high toxicity for them [1, 2]. Dialkyl phosphates containing residues of various alkaloids, including anabasine, have been tested for insecticidal activity in the All-Union Institute of Plant Protection. It was found that in relation to its toxicity for the greenbug N-[β-(diethoxyphosphinylmercapto)ethyl]-anabasine is close to a widely used pesticide – rogor (dimethoate) [3]. In view of the possibility of the creation of insecticides with a directed action, we decided to intensify the biological properties of anabasine by modifying its structure through phosphorylation, since it is known that the mechanism of the toxic action of anabasine and of esters of pentavalent phosphorus is due to their interaction with cholinergic systems of insects [1, 2, 4].

Developing investigations in this direction, by means of the Atherton-Todd reaction [5] and by an electrochemical method [6] (the electrolyte being tetraethyl perchlorate, voltage 3 V), we have synthesized a number of phosphoramides containing anabasine and various groupings on the phosphorus atom. The synthesis was effected by the interaction of anabasine with the corresponding alkylphosphonic esters in the presence of CCl_4 according to the scheme given below.



$R = i\text{-}C_3H_7$, $n\text{-}C_4H_9$; R' = 

The final products of the reaction were purified on a column of type L 100/160 SiO_2 with isopropanol–chloroform (5:2) as eluent, and their structures were established on the basis of IR and PMR spectra and the results of elementary analysis. An investigation of the interactions of the phosphoramides obtained with acetylcholinesterase (ACE) and butyrylcholinesterase (BuCE) showed that they all irreversibly inhibited the hydrolysis of acetylcholine – the natural substrate of these hydrolases. Among them, pronounced antibutyrylcholinesterase activity was possessed by a compound with two isopropyl radicals and a compound where one of the isopropyl radicals had been replaced by piperidine. The efficiency of these compounds in relation to BuCE was 2-3 orders of magnitude greater than in the case of ACE. The results on anticholinesterase activity were the basis for the study of their toxicity with respect to some arthropods, since it is known [7] that the organism of a number of insects contains ACE and BuCE and a correlation exists between anticholinesterase activity and toxicity.

With respect to its toxic action on the housefly diisopropyl anabasinylphosphonate proved to be equal to chlorophos (trichlorfon), and its efficiency with respect to the rice weevil exceeded that of chlorophos by a factor of 1.7. At the same time, its aphicidal activity was 15 times greater than that of carbophos (malathion).

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Thus, by modifying the structure of anabasine, it is possible to obtain substances with a higher biological activity than the alkaloid itself.

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STRUCTURE OF THE PRODUCT OF PHOTOCHEMICAL OXIDATION OF THIOCHROME

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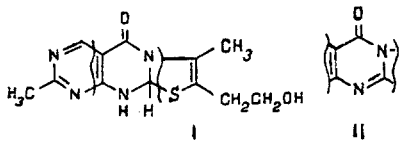
In an alkaline medium, thiamine is readily oxidized with the formation of the tricyclic compound thiochrome [1]. As is known [2], thiochrome is also formed in small amounts in the animal organism as a product of the catabolism of thiamine. On long storage, particularly in the light and in the presence of oxygen, thiochrome undergoes further transformations. We have previously [3] reported the structure of the main product of the redox disproportionation of thiochrome – oxodihydrothiochrome (I).

We have studied the photochemical oxidation of aqueous solutions of thiochrome by singlet oxygen. The reaction gave a previously unknown thiochrome transformation product (II), having a greater chromatographic mobility than thiochrome, and then oxodihydrothiochrome [R_f in the butan-1-ol–ethanol–water (2:1:1) system 0.84], $C_{12}H_{12}N_4O_2S$, M^+ 276 (mass-spectrometrically).

The singlet oxygen was generated by irradiating the dye Rose Bengal sorbed on Sephadex G-25 and present in an aqueous solution of thiochrome. Irradiation was performed with visible light, using a ZhS-17 filter. In independent experiments, singlet oxygen was obtained chemically in the reaction of bromine with H_2O_2 [4].

PMR spectrum (300 MHz, D_2O, internal standard TSP, δ, ppm): 1.96 (3H, s, CH_3-7), 2.69 (3H, s, CH_3-2), 3.18 (2H, t, J = 8 Hz, CH_2-α), 4.20 (2H, t, J = 8 Hz, CH_2-β), 8.35 (1H, s, H-4); IR spectrum ($\nu_{max}^{CHCl_3}$, cm^{-1}): 1725 (C=O), 1694 (C=N); UV spectrum ($\lambda_{max}^{H_2O}$, nm): 337 (pH 7), 355 (pH 3); fluorescence spectrum (H_2O; $\lambda_{max}^{emission}$, nm): 450 (pH 7), 475 (pH 3). From its combination of physicochemical properties, the new thiochrome transformation product was characterized as 8-(2-hydroxyethyl)-2,7-dimethyl-5-oxo-5,6-dihydrothiazolo[2,3-a]pyrimido-[4,5-d]pyrimidine (II).



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