THE SYNTHESIS OF ESTERS OF PHOSPHINIC ACIDS CONTAINING HETEROCYCLIC RADICALS

COMMUNICATION 7. ESTERS OF PHOSPHINIC ACID WITH MONO- AND DI-OXIDOQUINOXALINIC RADICALS

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In recent years the attention of chemists and microbiologists has been attracted to heterocyclic compounds which contain in their composition so-called "N-oxy" groups. These N-oxy compounds have both chemical and biological interest. As has been shown by the work of contemporary English, American, Russian and Japanese investigators, similar compounds possess to various degrees physiological and antibacterial activity. Thus, in 1941 McIlwain [1] reported that iodinin, the dye of Chromobacterium iodinum, showed considerable antibacterial activity: at a dilution of 1:1 million it is able to suppress several kinds of bacteria: streptococcus haemolyticus, corynebacterium diphtheriae etc.

The study of the chemical nature of iodinin, begun earlier by Clemo and McIlwain [2], led the authors to conclude that this antibiotic was the N,N-dioxide of 1,2-dioxyphenazine. Its formula was finally established by the Soviet chemist Kiprianov et al. [3]. The latter ascribed to iodinin the structure: N,N'-dioxide of 1,5-dioxyphenazine.

The authors were later able to synthesize iodinin itself [4]. Aspergillus acid is known in medicine as a strong antibiotic, the region of action of which is much wider than that of penicillin; it appears to be a derivative of pyrazine.

The N-oxides of pyridine and quinoline [5], the mono- and di-N-oxides of quinoxaline and their various derivatives [6] are also known. Several hydroxy- and methoxy-derivatives of quinoxaline studied by King, Clark and Davis [7] showed anti-bacterial activity close to that of iodinin. Our problem was to obtain and study the properties of phosphinic esters containing the N-oxy-quinoxalinic group, i.e., compounds with possible biological activity. In the present work we propose syntheses of compounds with mono-N and di-N-oxy-quinoxalinic radicals starting from the previously prepared esters.
which were studied earlier by us [8].

However experiments on the oxidation of these esters under conditions described by Landquist [6] for the oxidation of quinoxaline itself and some of its derivatives did not give positive results. In this case we obtained the original ester or a mixture of unknown composition (upon longer heating). The application of more concentrated solutions of acetyl hydroperoxide (23.5 and 56.5% in glacial acetic acid), and also oxidation by hydrogen peroxide in glacial acetic acid led to partial or complete tar formation. There are indications in the literature (Newbold Spring, Elina and Magidson [9-11]) that the presence of some substituents in the ortho position to the nitrogen of the quinoxaline nucleus hinder its oxidation sterically. It is possible that in our case we have also met with a similar fact.

Esters of phosphinic acids with mono-N- and di-N-oxidoquinoxalnic radicals were obtained by us in good yield by the rearrangement reaction of A. E. Arbuzov. The mono-N- and di-N-oxides of 2,3-di-(ω-bromomethyl) quinoxaline were taken as the halogen alkyls.

The reactions of the N-oxides with phosphites were carried out in benzene or toluene at the boiling point of the solvent. The ethyl and methyl esters were easily crystallized from the reaction mixture, but the propyl with great difficulty. The allyl ester could not be separated in the crystalline state.

The physical properties of the esters are given in the table.

None of the esters described above are stable to light. In light they become covered with an orange film because of decomposition. The melting points of the esters with a mono-N-oxidoquinoxalnic radical are somewhat higher than the corresponding esters with an unoxidized quinoxalnic radical (an exception is the ester with the methyl radical, see [8]). The esters which contain the di-N-oxide of the quinoxalnic radical melt considerably higher. Esters of the mono-N- and di-N-oxides of 2,3-di-(ω-phosphonemethyl)quinoxaline dissolved in the ordinary organic solvents and in water, the ethyl and methyl esters being most soluble in water and the isopropyl ester considerably less soluble. The products of the hydrolysis of the esters - the phosphinic acids with N-oxidoquinoxalnic radicals - are also crystalline substances; they decompose above 200° without melting.

All of the compounds synthesized by us were given to Prof. B. L. Mazur of the Kazan State Medical Institute for testing as antibacterials.

**EXPERIMENTAL**

The interaction of the mono-N-oxide of 2,3-di-(ω-bromomethyl)-quinoxaline with trimethyl phosphite. 1.1 g of the mono-N-oxide of 2,3-di-(ω-bromomethyl)-quinoxaline and 0.82 g of trimethyl phosphite were heated in 10 ml of dry benzene under reflux on a boiling water bath for 3.5 hr. The evolution of methyl bromide was observed; when lighted it burned with a greenish flame. Toward the end of the heating the reaction mixture changed from orange to light yellow. Half of the benzene was distilled off and 2 ml of n-hexane was added to the mixture. When the walls of the flask were rubbed with glass rod, 1.2 g of a yellow precipitate appeared (95.23% of the theoretical). The latter was twice crystallized from a mixture of benzene and n-hexane (1:1); activated charcoal was used. Slightly yellowish needles were obtained with m. p. 111-112°. The product was quite soluble in ether, methyl and ethyl alcohols, and also in water. The analysis of the product was carried out by heating it in sealed tubes with concentrated nitric acid; this same procedure was used for all of the subsequent cases. Found: P 15.68, 15.47%. C₁₄H₂₀N₂P₂O₇. Calculated: P 15.89%. According to the analytical data the product was the dimethyl ester of the mono-N-oxide of 2,3-di-(ω-phosphonemethyl)quinoxaline.