SYNTHESIS OF TRIS[(ORGANYLPYRIDINO)ETHYL]-PHOSPHORYL HALIDES AND THEIR ANTI-BACTERIAL ACTIVITY*

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In recent years research has been markedly intensified to find and synthesize medicinal preparations based on organo-phosphorus compounds (OPC), of which more than 100 have been recorded [1]. Among them OPC with nitrogen-containing heterocyclic groupings occupy a prominent place. These include, for example, the group of vitamins, such as phosphothiamine, benfotiamine, pyridoxal phosphate [1]. It should also be noted that the biological activity of OPC containing the P—C bond, including phosphine oxides, has been little studied.

The present work is devoted to the development of convenient methods of synthesis of previously unknown tris(organylpyridino)ethylphosphoryl halides III and IV and also to the study of their antibacterial activity. As starting OPC, we used the available tris-[2-(4-pyridyl)ethyl]phosphine oxide (I) and tris-(2-[5-(2-methylpyridyl)ethyl])phosphine oxide (II), which can be readily obtained from red phosphorus and 4-vinyl- or 2-methyl-5-vinylpyridines in the presence of strong bases.

Phosphine oxide (I) reacts under mild conditions with concentrated aqueous solutions of hydrogen halides or with alkyl halides to form pyridinium salts (IIIa-e).

\[
\begin{align*}
(\text{I}) & \quad (\text{II}) \\
R = \text{H}, X = \text{Cl} \quad (\text{IIIa}); & \quad R = \text{H}, X = \text{Br} \quad (\text{IIib}); & \quad R = \text{H}, X = \text{I} \quad (\text{IIIc}); & \quad R = \text{Me}, X = \text{I} \quad (\text{IIId}); & \quad R = \text{Et}, X = \text{I} \quad (\text{IIle}).
\end{align*}
\]

The synthesis of salts (IVa,b) was carried out from phosphine oxide II, methyl iodide and benzyl chloride.

\[
\begin{align*}
(\text{IV}) & \quad (\text{IVb}) \\
R = \text{Me}, X = \text{I}; & \quad (\text{IVa}); & \quad R = \text{PhCH}_2, X = \text{Cl} \quad (\text{IVb}).
\end{align*}
\]

Reactions (1, 2) proceed readily at room temperature or with slight heating (40-50°C) in an ethanol or acetonitrile medium. The yield of the end products III, IV was high in most cases (Table 1).

EXPERIMENTAL (CHEMICAL)

The \(^{31}\text{P}\) NMR spectra were run on a "Jeol FX 90Q" spectrometer (external standard — 85% \(\text{H}_3\text{PO}_4\), solvent — \(\text{D}_2\text{O}\)).

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TABLE 1. Characteristics of Tris[(organylpyridino)ethyl]-phosphoryl Halides

<table>
<thead>
<tr>
<th>Compound</th>
<th>Yield, %</th>
<th>Mp, °C</th>
<th>31P NMR, ¢P ppm</th>
<th>Empirical formula</th>
</tr>
</thead>
<tbody>
<tr>
<td>IIIa</td>
<td>70</td>
<td>260–2</td>
<td>53.03</td>
<td>C21H35Cl2N3OP</td>
</tr>
<tr>
<td>IIIb</td>
<td>82</td>
<td>282–4</td>
<td>52.93</td>
<td>C21H35Br2N3OP</td>
</tr>
<tr>
<td>IIIc</td>
<td>25</td>
<td>210–2</td>
<td>53.75</td>
<td>C21H35I2N3OP</td>
</tr>
<tr>
<td>IIId</td>
<td>98</td>
<td>289–92</td>
<td>53.08</td>
<td>C21H35I2N3OP</td>
</tr>
<tr>
<td>IIIe</td>
<td>60</td>
<td>285–7</td>
<td>53.03</td>
<td>C21H35I2N3OP</td>
</tr>
<tr>
<td>IVa</td>
<td>89</td>
<td>236–8</td>
<td>56.71</td>
<td>C27H39IaN3OP</td>
</tr>
<tr>
<td>IVb</td>
<td>25</td>
<td>158–60</td>
<td>56.03</td>
<td>C25H39I2N3OP</td>
</tr>
</tbody>
</table>

Note. The elemental analysis of the synthesized compounds corresponded to the values calculated according to the empirical formulas given.

Tris[2-(4-pyridino)ethyl]phosphoryl Trichloride (IIIa). A 0.37 ml portion of conc. HCl was added to a solution of 0.34 g (0.93 mmole) of phosphine oxide I in 10 ml of ethanol. The mixture was heated at a temperature of 40-45°C for 5 h. The white precipitate that separated out was filtered off and washed with cold ethanol. Yield 0.31 g (70%) of IIIa.

Compounds IIIb,c were synthesized in a similar way at room temperature from phosphine oxide I and HBr and HI, respectively.

Tris{2-[4-(1-methylpyridino)]ethyl}phosphoryl Triiodide (IIId). A 1.1 g portion (7.7 moles) of methyl iodide was added to a solution of 0.29 g (0.79 mmole) of phosphine oxide I in 8 ml of ethanol. After 5 h the crystals that separated out were filtered off. Yield 0.62 g (98%) of IIId.

Compound IIIe was synthesized in a similar way from phosphine oxide I and ethyl iodide at the temperature of 40-50°C.

Tris{2-[5-(1,2-dimethylpyridino)ethyl]phosphoryl Triiodide (IVa). A solution of 1.5 g (0.0037 mole) of phosphine oxide II and 1.8 g (0.0127 mole) of methyl iodide in 10 ml of acetonitrile was allowed to stand for 24 h. The precipitate that formed was filtered off, washed with diethyl ether, and dried. Yield 2.74 g (89%) of IVa.

Compound IVb was synthesized in a similar way from phosphine oxide II and benzyl chloride by heating the reaction mixture (50°C) for 5 h.

EXPERIMENTAL (PHARMACOLOGICAL)

The investigation of the acute toxicity of compounds IIIa-e was studied with intraperitoneal administration on nonpedigree white mice of both sexes, each weighing 20-22 g, according to the Kerber method.

The antimicrobial activity of the synthesized compounds II-IV was studied by the method of consecutive serial dilutions in a culture medium on 9 strains of Gram-positive and Gram-negative microorganisms: Staphylococcus aureus, two of its clinical varieties, Baccilus pyocyaneous, Escherichia coli, Baccilus subtilis, Proteus vulgaris, Salmonella typhosa, Anthracoid baccilus.

The starting concentration of the compounds (II-IV) studied was 200 µg/ml, the microbial load was 250,000 microbial cells in 1 ml [4]. The experimental results were recorded 18-20 h after the incubation in a thermostat at 37°C, and then after 2, 4, and 6 days.

The LD50 values of compounds IIIa, b, d, e and I were 446, 269, 169, 18.2, and 602.6 mg/kg, respectively, which makes it possible to relate them to moderately or slightly toxic compounds [3].

It was found (Table 2) that compounds II, IV in a dose of 12.5 µg/ml, and IIIa-b in a dose of 200 µg/ml inhibit the growth of Proteus vulgaris, while salt IIIe in a dose of 12.5 µg/ml has a bacteriostatic action on this strain.

Moreover, phosphine oxide II (dose 12.5 µg/ml) and pyridinium salts IIIa-e (dose 200 µg/ml) are bactericides with respect to Baccilus subtilis, while compound IIIe inhibits the growth of Staphylococcus aureus (in a concentration of 200 µg/ml) and two of its clinical varieties (in a concentration of 50 µg/ml). Salt IIIc in a dose of 200 µg/ml also has a bacteriostatic property with respect to one of the clinical varieties of the Staphylococcus aureus.