SUBSTITUTED AMMONIUM SALTS OF ALKOXYTRICHLOROMETHYLPHOSPHONIC AND ALKYL(ARYL)TRICHLOROMETHYLPHOSPHINIC ACIDS

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UDC 615.285.7:547.241].07

It was found earlier that the reaction of alkyl esters of trichlormetylphosphonic and alkyl(aryl)trichloromethylphosphinic acids [2, 9] with substituted amines leads to formation of the corresponding ammonium salts of alkoxytrichloromethylphosphonic and alkyl(aryl)trichloromethylphosphinic acids and the alkylated amine [3, 6-8] according to the scheme:

$$R(CCl_3)P(O)OR' + 2HNR''_2 \longrightarrow R(CCl_3)P(O)OH\cdot HNR''_2 - R'NR''_2$$

I—XVI, XX—XXXIX

R = Et (I), Pr (II), Ph (III—XII), p-tolyl (XIII, XIV) p-BrC_6H_4 (XIV—XVI);
R″ = cyclohexyl (I, II, XIV), H (III, XV), C_6H_{13} (XI), $C_6H_5CH_2$ (XII), C_2H_5 (XIII), R''_2N=CH_3NH (IV), $HO(CH_2)_3NH$ (V), $C_{16}H_{33}NH$ (VI), $(C_6H_5NH)_2C$=N (VII), N-piperidyl (VIII), $(CH_2$=$CHCH_2)_2N$ (IX), $C_6H_5CH_2N(CH_3)$ (X), $(NH_2)_2C$=N (XVI).

There is hardly any information about the biological activity of ammonium salts of trichloromethylphosphinic acids. There has only been published about the pesticidal properties of some ammonium salts of ethyl- and phenyltrichloromethylphosphinic acids [5, 10].

With the purpose of developing novel biologically active preparations based upon substituted ammonium salts of acids of phosphorus, this article deals with the synthesis and the investigation of antibacterial and antiviral activities, and also of the stimulating action on the growth of bacteria of a number of ammonium salts of alkoxytrichloromethylphosphonic and alkyl(aryl)trichloromethylphosphinic acids (compounds I-XVI and XX-XXXIX).

The synthesis of these compounds was carried out by the method that we described earlier [3, 6-8]. For their identification we devised also a direct synthesis starting from the corresponding acids and the amine. The products were obtained in good yields in a crystalline form, purified by recrystallization form a suitable solvent, and characterized by IR spectral data and elemental analyses. Some properties of the novel compounds (I-XVI) are summarized in Table 1, which also contains our investigations of the novel guanidine salts: 4-$XC_6H_4(R)P(O)OH\cdot HN$=$C(NH_2)$ (see Table 1, XVII-XIX), prepared from the guanidine carbonate and the corresponding phosphinic acids. R = H (XVIII, XIX), C_2H_5 (XVII), X = Br (XIX), H (XVII), CH_3 (XVIII).

Earlier we synthesized compounds XX-XXXIX (literature references between brackets):
R = C_2H_5O (XX, [9]), C_4H_9O (XXI, XXII, [9]), C_2H_5 (XXIII-XXV, [10]), $(C_2H_5)_2N$ (XXVI, [10]), C_6H_5 (XXVII-XXXIV, [8-10]), 4-BrC_6H_4 (XXXV, XXXVI, [8]), 4-ClC_6H_4 (XXXVII-XXXIX, [8, 9]); R″ = C_3H_7 (XX, XXIV, XXXVIII), H (XXI), C_4H_9 (XXII, XXXIX), C_2H_5 (XXIII, XXVI, XXXII, XXXV), C_3H_7 (XXIV, XXXIII), C_6H_5NH (XXV, XXIX, XXXVI), H (XXVII, XXXVII), C_4H_9NH (XXVIII), 4-$CH_3OC_6H_4NH$ (XXX), cyclohexylamino (XXXI), cyclohexyl (XXXIV).

S. M. Kirov Kazan Institute of Chemical Engineering. Translated from Khimiko-farmatsevticheskii Zhurnal, Vol. 23, No. 12, pp. 1482-1485, December, 1989. Original article submitted January 18, 1988.

 0091-150X/89/2312-1010$12.50

TABLE 1. Properties of Compounds I-XIX

Compound	mp., °C	Crystallization solvent	Empirical formula
I	198,0—199,0	Toluene–alcohol, 6:1	$C_{15}H_{29}Cl_3NO_2P$
II	193,0—199,0	Toluene–ether, 6:1	$C_{16}H_{31}Cl_3NO_2P$
III	224,0—224,5	Alcohol–amyl chloride, 1:1	$C_7H_9Cl_3NO_2P$
IV	203,5—204,5	Alcohol–amyl chloride, 1:1	$C_8H_{11}Cl_3NO_2P$
V	152,5—153,5	Isopropanol	$C_{10}H_{15}Cl_3NO_3P$
VI	129,5—130,0	Alcohol–ether	$C_{23}H_{41}Cl_3N_3O_2P$
VII	198,5—199,5	Toluene–alcohol, 10:1	$C_{20}H_{19}Cl_3N_3O_2P$
VIII	207,5—208,5	Toluene	$C_{12}H_{17}Cl_3NO_2P$
IX	212,0—213,0	Carbon tetrachloride	$C_{13}H_{17}Cl_3NO_2P$
X	152,0—152,5	Isopropanol–heptane, 1:1	$C_{14}H_{17}Cl_3NO_2P$
XI	220,0—221,0	Ether–hexane, 1:3	$C_{19}H_{31}Cl_3NO_2P$
XII	190,0—191,0	Isopropanol–heptane 1:1	$C_{21}H_{21}Cl_3NO_2P$
XIII	179,5—180,5	Acetone	$C_{12}H_{19}Cl_3NO_2P$
XIV	253,0—254,0	Alcohol–toluene, 1:1	$C_{20}H_{31}Cl_3NO_2P$
XV	242,0—243,0	Propanol–ether, 10:1	$C_7H_8BrCl_3NO_2P$
XVI	184,5—185,5	Alcohol	$C_9H_{16}N_3O_2P$
XVII	185,0—185,5	Alcohol–ether	$C_9H_{16}N_3O_2P$
XVIII	190,5—191,5	Propanol–hexane, 1:1	$C_8H_{14}N_3O_2P$
XIX	182,0—184,0	Propanol–hexane, 1:1	$C_7H_{11}BrN_3O_2P$

EXPERIMENTAL (CHEMICAL)

N-Phenylammonium Salt of Phenyltrichloromethylphosphinic Acid (XXIX). A solution of 5.8 g (0.02 mole) of ethyl phenyltrichloromethylphosphinate and 3.8 g (0.041 mole) of aniline in 50 ml of toluene was refluxed for 4 h. The precipitate was separated, crystallized from 50% aqueous alcohol, and dried in a vacuum desiccator over phosphorus pentoxide. Yield 6.1 g (87%) of the desired product, a light grey powder, mp 214.5-215.5°C (dec.). $C_{13}H_{13}Cl_3NO_2P$.

In the IR spectrum, taken from a suspension in paraffin oil, the aromatic nucleus is identified by a valence vibration band of the C—H bond in the region 3000-3100 cm^{-1} as weak peaks superimposed on the strong paraffin absorptions, and the $\nu_{C=C}$ of the nucleus between 1600 and 1440 cm^{-1}. The N-phenylammonium nature of the compound was confirmed by bands at 2150 cm^{-1}, the torsional vibrations of N^+H_3 at 480 cm^{-1}, 1535 cm^{-1} ($\delta_{N^+H_3\text{-symm}}$), and 1600 cm^{-1} ($\delta_{N^+H_3\text{-asymm}}$), and the $\nu_{P=O}$ frequency at 1205 cm^{-1}.

In much the same way the reactions of the ethyl or propyl esters of the corresponding alkyl(aryl)trichloromethylphosphinic acids with an excess of amine yielded the other compounds. Data of elemental analyses corresponded with the calculated values.

EXPERIMENTAL (BIOLOGICAL)

In the study of the antibacterial and antiviral properties of the compounds phenol was used as reference.

The antibacterial activity of the compounds was judged by their minimal inhibitory concentrations (MIC), which were determined by the method of serial dilution in culture medium 4 with regard to meningococci, staphylococci, and streptococci. When the bactericidal concentration of the compound was lower than the bactericidal concentration of the reference, the compound was considered to have antibacterial activity [1].

The following 24 compounds were tested for antibacterial activity: I, II, VI, IX, XI, XIII, XX-XXIX, XXX-XXXIV, and XXXVII-XXXIX.

Among the compounds investigated, XX, XXIV, XXV, XXII, and XXXVII were found to act selectively on Gram-negative cocci (meningococci). Their bactericidal concentrations range from 0.00025 (compounds XX, XXIV, XXXII, and XXXVII) to 0.0025 g/ml (compounds XXV and XXXI). In this case the antibacterial activity is much more characteristic of salts of alkyl- and aryltrichloromethylphosphinic acids with cyclic primary amines, aryltrichloromethylphosphinic acids with cyclic primary amines, such as N-phenyl and N-cyclohexylamines (compounds XXV and XXXI). In the whole series, the antibacterial activity of salts with secondary amines is lower than that of salts with primary amines.

The compounds investigated were not active against Gram-positive cocci (streptococci and staphylococci).

Under comparable conditions the antibacterial activity of phenol is 0.0050-0.015 g/mole.

We have also investigated the activity of the compounds that stimulate the growth of streptococci, staphylococci, meningococci, and diphtheria bacilli.

Determinations of the minimal concentration of the preparation that shows a stimulating action on the growth of the enumerated microorganisms was carried out according to Pershin [4].

We have tested 19 compounds for stimulating activity: I, II, VI, XI, XIII, XX-XXVIII, and XXVII-XXXIX.

As reference was used an extract of nutrient yeast and a culture medium without a stimulator served as control.

With four compounds, namely VI, XXXI, XXXII, and XXXIV, a slight stimulating activity with regard to staphylococci was found. However, the stimulating activity of these compounds was inferior to that of the reference.

All the compounds were tested for antiviral activity, which was performed by the arboviral and mycoviral methods of the agar-diffusion screening test on a culture of chicken fibroblasts according to the inhibition of plaque formation at the concentration of the compound of maximally transferable cells (MTC) of chicken fibroblasts.

RNA and DNA containing viruses were used in the tests.

As MIC was taken half of the concentration that did not cause visible toxic changes in the cell monolayer.

The infected tissue culture was covered with agar; after solidification of the latter a filter disk soaked with a solution of the compound to be tested was applied. The compounds were used as solutions in water, aqueous acetone, or DMSO in an amount of 10 μg per disk. The inhibitory action of the compounds was judged after keeping at 37°C for 72 h. As the criterion for the assessment of antiviral activity was used the size of the inhibition zone (IZ) of the formation of virus plaques. When the IZ of the compound was larger than that of the reference, it was assumed that the compound had antiviral properties.

The investigations have shown that in the case of maximal transferable concentrations the compounds do not have antiviral properties.

Thus, the study of the biological activities of a series of substituted ammonium slats of alkoxytrichloromethylphosphonic and alkyl(aryl)trichloromethylphosphinic acids have shown that ammonium salts of the phosphorus acids mentioned may be of interest in the search for novel compounds having antibacterial activity.

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