SYNTHESIS AND PROPERTIES OF PYRIMIDINYLALKYLPHOSPHONIC ACIDS

COMMUNICATION 5. SYNTHESIS OF β-(OXOPYRIMIDINYL-N)-ETHYLPHOSPHONIC ACIDS

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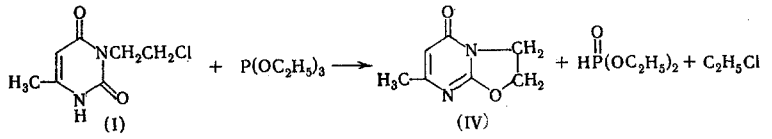
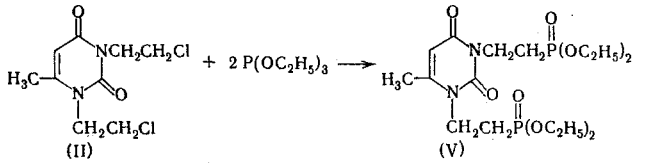
As a continuation of our research on the synthesis of pyrimidinylalkylphosphonic acids we studied some of the routes for the preparation of β-(oxopyrimidinyl-N)-ethylphosphonic acids.

Previously it was mentioned [1] that the preparation of β-(oxopyrimidinyl-N)-ethyl phosphonates from the Na salts of hydroxypyrimidines and dialkyl β-chloroethyl phosphonates is impossible due to the dehydrochlorination of the phosphorus component. For this reason we studied the reaction of 3-(β-chloroethyl)-6-methyluracil (I) and 1,3-bis-(β-chloroethyl)-6-methyluracil (II) with triethyl phosphite (III) by the Arbuzov reaction. From the reaction products of (I) and (III) were isolated 2,3,4,5-tetrahydro-5-oxo-7-methyloxazolo[3,2-*a*]pyrimidine (IV), described by us previously [2], and diethylphosphorous acid



1,3-Bis-(β-chloroethyl)-6-methyluracil (II), which lacks groups capable of tautomerism, reacts smoothly with (III) at 150-160° to give 1,3-bis-[β-(diethylphosphono)ethyl]-6-methyluracil (V)



Compound (V) is a clear reddish viscous oil that is soluble in most organic solvents, and is insoluble in the petroleum and diethyl ethers. The IR spectrum of this compound does not contradict the assigned structure.

The synthesis of alkylphosphonic acids by the reaction of the appropriate tosylates with the salts of dialkylphosphorous acids is described in the literature [3]. We tried to use this reaction for the synthesis of β-(oxopyrimidinyl-N)-ethylphosphonic acids. However, the tosylate of 3-(β-hydroxyethyl)-6-methyluracil (VI) could not be obtained. Compound (IV) is formed when (VI) is reacted with p-toluenesulfonyl chloride in basic media. 3,6-Dimethyl-1-(β-hydroxyethyl)uracil (VII) forms the tosylate in 24% yield. The reaction of the tosylate of compound (VII) with sodium dibutyl phosphite gave the dibutyl ester of β-(3,6-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidinyl-1-N)-ethylphosphonic acid (VIII) as a colorless viscous oil that is readily soluble in benzene and CCl_4. The obtained results testify to the fact that the presence in the molecules of the 3-(β-hydroxyethyl)- or 3-(β-chloroethyl)-6-methyluracils of an OH group that is capable of tautomerism in the 2 position of the pyrimidine ring facilitates closure of the five-membered oxazole ring.

In order to obtain 4-oxopyrimidinyl-N-ethylphosphonic acids that contain a group capable of tautomerism in the molecule we studied the reaction of (VI) and 2-amino-3-(β-hydroxyethyl)-4-oxo-6-methyl-3,4-dihydropyrimidine (IX) with triphenyl phosphite (X). The reaction of (VI) with (X) proceeds at 230-240°.

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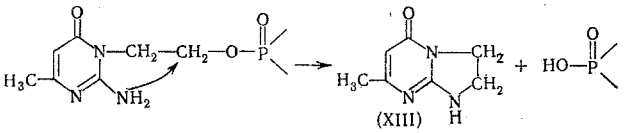
After hydrolysis of the reaction mass, together with the starting (VI), we isolated β-(2-hydroxy-4-oxo-6-methyl-3,4-dihydropyrimidinyl-3)-ethylphosphonic acid (XI) as an amorphous powder that is insoluble in alcohol and readily soluble in water. The presence in the IR spectrum of compound (XI) of intense absorption at 930-1250 cm^{-1}, is characteristic for the grouping $P(=O)(OH)$ [14]. The diffuse absorption in the 2250-3600 cm^{-1} region is caused by the superimposition of the ν_{P-OH} and ν_{N-H} of the pyrimidine ring; the $\nu_{C=O}$ appear at 1660 and 1715 cm^{-1}.

The reaction of (IX) with (X) begins at 160° and leads to β-(2-amino-4-oxo-6-methyl-3,4-dihydropyrimidinyl-3)-ethylphosphonic acid (XII) and 2,3,4,5-tetrahydro-5-oxo-7-methylimidazolo[3,2-*a*]-pyrimidine (XIII). Acid (XII) is an amorphous substance that is insoluble in alcohols and readily soluble in water. An aqueous solution of acid (XII) has a pH of 6, which suggests the inner salt character of this compound. In the IR spectrum of (XII) in the 900-1250 cm^{-1} region are present three bands at 1080, 1175 and 1230 cm^{-1}, which are characteristic for the ionic grouping $P(=O)(O^-)$ [14]. The 1000-1300 cm^{-1} region in the IR spectrum of (XII) is analogous to the same region in the IR spectrum of 2-amino-4-oxo-6-methyl-3,4-dihydropyrimidinyl-3-methylphosphonic acid, described by us previously [5]. Broad absorption at 2300-3500 cm^{-1} is present in the high-frequency region of the spectrum, the maximum of which masked by the ν_{C-H}; the ν_{P-OH} and the stretching vibrations of the NH_3 group are superimposed in this region.

The formation of imidazolo[3,2-*a*]pyrimidine (XIII) is explained by the attack of the amino group of the pyrimidine ring on the β-carbon atom, the electrophilic properties of which are enhanced due to the induction effect of the hydroxyphosphoryl group



(XIII)

Compound (XIII) is a crystalline compound that is readily soluble in water, moderately soluble in hot n-butanol, and insoluble in acetone. In harmony with the structure, the vibrations in the ν_{OH} region are absent in the IR spectrum of (XIII), while the ν_{N-H} appear at 3060-3125 cm^{-1}; the $\nu_{C=O}$ appears at 1670 cm^{-1}.

The reaction of (X) with 1,3-bis-(β-hydroxyethyl)-6-methyluracil proceeds vigorously at 160-165°, and as the main product after hydrolysis was isolated 1,3-bis-(β-phosphonoethyl)-6-methyluracil (XIV) as an amorphous powder that is insoluble in alcohol and readily soluble in water. Together with (XIV), from the reaction mass was isolated a product that, on the basis of the elemental analysis data and the IR spectrum, was identified as being 1,3-bis(β-phenoxyethyl)-6-methyluracil (XV).

The formation of ether (XV) can be depicted as being due to the alkylation of the phenol formed during the reaction process by the phosphonate. The alkylation of phenol and thiophenol by alkyl phosphates was described in [6].

Compound (XV) is a crystalline compound that is readily soluble in benzene and acetone, moderately soluble in alcohols, and insoluble in water. In harmony with the assigned structure, absorption is absent in its IR spectrum in the 3000-3600 cm^{-1} region (OH and NH); the $\nu_{C=O}$ appear at 1670 and 1710 cm^{-1}. In the region of low frequencies the spectrum has two intense bands at 690 and 760 cm^{-1}, the position of which is characteristic for the out-of-plane deformation vibrations of the C–H of monosubstituted benzenes, and a very strong band at 1255 cm^{-1}, which can be assigned to the vibrations of the ether linkage [7].

EXPERIMENTAL METHOD

The IR spectra were taken on a UR-10 spectrophotometer; the solids as Nujol mulls, while the liquids were taken between KBr plates.

Reaction of 3-(β-Chloroethyl)-6-methyluracil (I) with Triethyl Phosphite (III). A mixture of 5.6 g of (I) and 5 g of (III) was heated for 8 h at 150-155°, cooled, and dissolved in benzene. The solution was treated with active carbon and evaporated in vacuo at 30-40°. After several days the residue crystallized partially.

The crystals were filtered (filtrate "A"), washed with petroleum ether, and extracted with cold benzene (2 × 75 ml). The benzene solution was treated with active carbon, filtered, and evaporated in vacuo. The residue was recrystallized from a 2:1 benzene–diethyl ether mixture, and then from benzene. We obtained 2.9 g (63%) of (IV) as needles, mp 113-114°. Filtrate "A" was vacuum-distilled. We obtained 2.1 g (51%) of diethylphosphorous acid, bp 70-74° (10 mm); n_D^{20} 1.4093; see [8]. The IR spectrum has a band at 2400 cm^{-1} (P–H).

1,3-Bis-[β-(diethylphosphono)ethyl]-6-methyluracil (V). A mixture of 5 g of (II) and 6.7 g of (III) was heated at 160-165° for 6 h. After cooling, the mass was dissolved in benzene, treated with active carbon, then with Al_2O_3, filtered, evaporated, and dried in vacuo at 0.01 mm and 100°. We obtained 7.1 g (80%) of (V) as a viscous oil; n_D^{20} 1.5030. Infrared spectrum (ν, cm^{-1}): 1665 and 1705 (C=O); 1265 (P=O); 1035 and 976 (P–O–C). Found: C 44.71; H 7.05; N 6.22; P 13.94%. $C_{17}H_{32}O_8N_2P_2$. Calculated: C 44.89; H 7.09; N 6.16; P 13.63%.

β-(3,6-Dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidinyl-N-1)-ethyl-p-toluenesulfonate. To a suspension of 5 g of (VII) in 12 g of triethylamine was gradually added 5.5 g of p-toluenesulfonyl chloride in such a manner that the temperature of the mixture did not exceed 40°. The mixture was cooled to 20°, treated with 100 ml of water, and rubbed well. The insoluble precipitate was filtered and dried. We obtained 2.2 g (24%) of β-(3,6-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidinyl-N-1)-ethyl-p-toluenesulfonate, mp 153.5-155.5° (from benzene). Infrared spectrum (ν, cm^{-1}); 1665, 1695 (C=O), 1185, 1370 (SO_2). Found: C 53.33; H 5.32; N 8.36%. $C_{15}H_{18}N_2O_5S$. Calculated: C 53.25; H 5.33; N 8.28%.

Dibutyl Ester of β-(3,6-Dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidinyl-1-N)-ethylphosphonic Acid (VIII). To 0.36 g of Na in 200 ml of absolute benzene was added 2.5 g of dibutyl phosphite and the mixture was refluxed until all of the Na had dissolved. Then 4.5 g of β-(3,6-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidinyl-N-1)-ethyl-p-toluenesulfonate was added and the mixture was refluxed until neutral. The reaction mixture was stirred well with active carbon and filtered. The benzene was vacuum-distilled from the filtrate. The residual oily liquid was dissolved in ether, treated with active carbon, and the ether was distilled off. We obtained 1.5 g (36%) of (VIII); the latter was dissolved in absolute benzene, refluxed with Na, and the solvent was vacuum-distilled. We obtained a pale yellow undistillable oily liquid; n_D^{20} 1.4895. Infrared spectrum (ν, cm^{-1}): 1.675, 1703 (C=O), 1270 (P=O), 1000, 1025 (P–O–C). Found: N 7.09; P 8.57%. $C_{16}H_{28}N_2PO_5$. Calculated: N 7.78; P 8.61%.

β-(2-Hydroxy-4-oxo-6-methyl-3,4-dihydropyrimidinyl-3)-ethyl-phosphonic Acid (XI). A stirred mixture of 27 g of (VI) and 15.5 g of (X) was heated at 230-240° for 2 h. After cooling, 200 ml of acetone was added. The obtained precipitate was filtered, boiled in 200 ml of isopropanol, and filtered. The insoluble residue was refluxed in dilute HCl solution for 2 h, and then the solution was evaporated in vacuo. The solid residue was boiled in isopropanol, filtered, and then extracted with isopropanol in a Soxhlet apparatus until all of the (VI) impurity was removed. After extraction we obtained 4.8 g (51%) of (XI) as a pale yellow powder that decomposes slowly above 200°. Found: C 35.78; H 4.76; N 12.07; P 12.95%. $C_7H_{11}O_5N_2P$. Calculated: C 35.90; H 4.71; N 11.95; P 13.22%.

Reaction of 2-Amino-3-(β-hydroxyethyl)-4-oxo-6-methyl-3,4-dihydropyrimidine (IX) with Triphenyl Phosphite (X). A stirred mixture of 30.5 g of (IX) and 18.6 g of (X) was heated at 220-230° for 3 h (at 160° the mixture heats up spontaneously up to 230°). After cooling, the mixture was boiled twice with benzene, and the benzene solutions were decanted (solution "A"). The residue was treated with 300 ml of n-butanol, and the precipitate that separated after some time was filtered and extracted with isopropanol in a Soxhlet apparatus to remove any possible (IX). After extraction we obtained 4.5 g (42%) of (XII), which decomposes when heated above 200°. Found: C 36.42; H 4.75; N 17.86; P 12.95%. $C_7H_{12}O_4N_3P$. Calculated: C 36.0; H 5.15; N 18.0; P 13.3%. Solution "A" was evaporated in vacuo. The residue crystallized partially after a day. Acetone was added, and the obtained crystals were filtered and recrystallized three times from n-butanol. We obtained 7.4 g (36%) of (XIII) as colorless needles, mp 234-236°. Found: C 55.80; H 6.06; N 27.60%. $C_7H_9ON_3$. Calculated: C 55.60; H 5.96; N 27.8%.

Reaction of 1,3-Bis-(β-hydroxyethyl)-6-methyluracil with Triphenyl Phosphite (X). A stirred mixture of 30 g of 1,3-bis-(β-hydroxyethyl)-6-methyluracil and 21.8 g of (X) was heated at 230-240° for 2 h (at 160-165° the mixture heats up spontaneously up to 230°). After cooling, 250 ml of 20% HCl solution was added and the mixture was refluxed for 9 h. The aqueous layer (solution "A") was decanted from the separated tarry mass. The latter was stirred with 150 ml of acetone and then filtered. The substance that remained after evaporation of the acetone was washed on the filter with isopropanol, and then recrystallized twice

from isopropanol. We obtained 8 g (21%) of (XV) as colorless needles, mp 144-145.5°. Found: C 69.27; H 6.15; N 7.66%. $C_{21}H_{22}O_4N_2$. Calculated: C 69.0; H 6.02; N 7.65%.

The aqueous solution "A" was treated with active carbon, filtered, and evaporated in vacuo. The residue was rubbed with isopropanol, and the insoluble precipitate was filtered and then extracted with isopropanol in a Soxhlet apparatus to remove any (XV). After extraction we obtained 7.5 g (33%) of (XIV), which decomposes in a wide temperature range above 200°. Infrared spectrum (ν, cm^{-1}): 1655, 1715 (C=O), 940-1010, 1075, 1225, and 2100-3500 ($P(O)(OH)_2$). Found: C 31.28; H 5.20; N 7.95; P 17.88%. $C_9H_{16}O_8N_2P_2$. Calculated: C 31.6; H 4.68; N 8.2; P 18.1%.

CONCLUSIONS

1. A study was made of the reaction of 3-(β-chloroethyl)-6-methyluracil and 1,3-bis-(β-chloroethyl)-6-methyluracil with triethyl phosphite.

2. A study was made of the reaction of 3-(β-hydroxyethyl)-6-methyluracil, 1,3-bis-(β-hydroxyethyl)-6-methyluracil and 2-amino-4-oxo-3-(β-hydroxyethyl)-6-methyl-3,4-dihydropyrimidine with triphenyl phosphite.

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