SYNTHESIS AND SOME CHEMICAL TRANSFORMATIONS OF 1-N-(β-HYDROXYETHYL)-3,6-DIMETHYLURACIL

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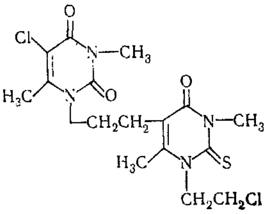
The natural nucleosides and nucleotides, including the pyrimidine series, have been assiduously studied for a long time. However, in recent years a constantly increasing amount of attention is being given to a study of the simple N-substituted hydropyrimidines, which, in their structure, are analogs of the natural compounds.

In continuation of studying the formal analogs of the pyrimidine-nucleosides and pyrimidine-nucleotides [1-4] we studied the synthesis and some of the chemical transformations of 1-N-(β-hydroxyethyl)-3,6-dimethyluracil (I). It was interesting to compare the properties of (I) with the analogous properties of the 3-N-(β-hydroxyethyl)uracils. Compound (I) was obtained by the previously described reaction [1], starting with 3,6-dimethyluracil and ethylene chlorohydrin, as a colorless crystalline substance that is soluble in alcohols and chloroform. Compound (I), the same as other N-hydroxyalkyluracils [2], is easily brominated to give the corresponding 5-bromo derivative (II), which is a crystalline substance that is soluble in alcohols.

In contrast to 3-N-(β-hydroxyethyl)-6-methyluracil [3], we were unable to isolate the β-chloroethyl derivative by reacting (I) with thionyl chloride in the presence of pyridine. A crystalline substance (A) of composition $C_{16}H_{21}N_4O_3SCl_2$ is formed in the given case, which melts at 176-178°C, is readily soluble in acetone, and is practically insoluble in water. When compared with the IR spectra of (I) and 1-N-(β-chloroethyl)-3,6-dimethyluracil, a substantial shift of the bands in the region of the vibrations of the uracil ring (1400-1700 cm^{-1}) is observed in the IR spectrum of compound (A) (Fig. 1). A similar shift of the band occurs when a halogen atom is inserted in the 5 position of (I). Thus, the IR spectrum of the 5-bromo derivative (I) in the 1400-1700 cm^{-1} region is analogous to the IR spectrum of compound (A), but is quite different from the spectrum of (I) (see Fig. 1). A similar picture of the shift is also observed when the oxygen atom in the 2 position of the uracil ring is replaced by sulfur [5]. In the IR spectrum of compound (A), the absorption of ν_{OH} is absent in the 3200-3600 cm^{-1} region, and also absorption at 3080-3090 cm^{-1}, which is associated with the vibrations of the C–H bond in the 5 position in the uracil ring. The discussed data make it possible to propose the following structure for compound (A), but due to



the absence of data on the UV spectra of the model compounds it is impossible to assign an exact structure to compound (A).

The reaction of (I) with the dichloride of phenylthiophosphonic acid in the presence of triethylamine, the same as in the case of 3-N-(β-hydroxyethyl)-6-methyluracil [4], proceeds normally and leads to the formation of the phenyl thiophosphonate (III).

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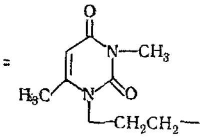
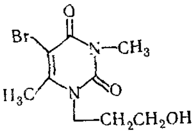
TABLE 1. Properties of Synthesized Compounds

R =


No.	Compound	Yield, %	mp, °C	Empirical formula	Found/Calculated, %				
					C	H	N	P	Cl
I	R—OH	42,6 *	134—136	$C_8H_{12}N_2O_3$	52,36 52,17	6,58 6,52	15,60 15,22	—	—
II		87,5	143—144	$C_8H_{11}N_2O_3Br$	36,34 36,5	4,32 4,18	10,63 10,65	—	—
III	$(RO)_2\underset{S}{\underset{\|}{P}}C_6H_5$	14,5	139—142	$C_{22}H_{27}N_4O_6PS$	50,98 52,2	5,43 5,34	10,16 11,05	7,07 6,13	—
IV	R—Cl	23,6	95—96	$C_8H_{11}N_2O_2Cl$	46,68 47,3	5,48 5,43	14,92 13,8	—	16,25 17,5
V	R—S—R	— *	170—171	$C_{16}H_{22}N_4O_4S$	52,67 52,5	6,17 6,02	—	—	—
VI	R—S—S—R	— *	217—218,5	$C_{16}H_{22}N_4O_4S_2$	48,20 48,2	6,02 5,54	14,01 14,05	—	—
VII	$R{-}\underset{O}{\underset{\|}{P}}(OR)_2$	60,5	276—279 (decompn.)	$C_{24}H_{33}N_6O_8P$	49,73 49,7	5,94 5,7	14,91 14,5	5,40 5,35	—

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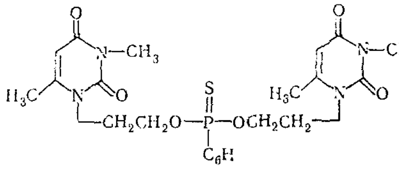
* See "Experimental" section.

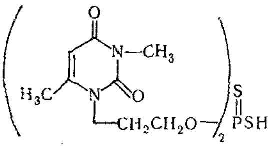


(III)

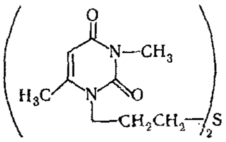
In contrast to bis-[β-(2,4-dioxo-6-methyl-1,2,3,4-tetrahydro-3-pyrimidinyl)ethyl]phenyl thiophosphonate, phenyl thiophosphonate (III) is unstable and its purification is exceedingly difficult.

The reaction of (I) with the dichloride of chloromethylphosphonic acid proceeds in an abnormal manner, and here instead of the expected phosphonate was isolated a small amount of a product that, based on the IR-spectroscopy data, is most probably 1-N-(β-chloroethyl)-3,6-dimethyluracil (IV). Absorption in the 3200-3600 cm^{-1} region, which is associated with the vibrations of the OH group of a hydroxyalkyl radical, is absent in the IR spectrum of (IV) (see Fig. 1). The absorption in the 1400-1600 cm^{-1} region is analogous to that for (I).

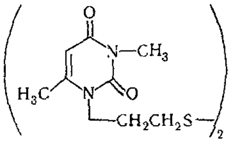
The reaction of (I) with P_2S_5 also proceeds in an abnormal manner. Instead of the expected acid with the structure:



we isolated two substances, devoid of phosphorus, which, on the basis of the elemental analysis and IR-spectroscopy data, were assigned the structures of sulfide (V) and disulfide (VI)

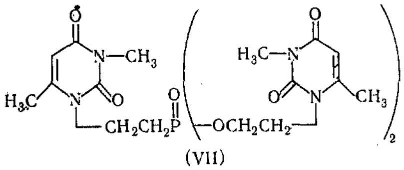


(V)



(VI)

The reaction of (I) with triphenyl phosphite at 210-220°C gave ester (VII), which has one C–P bond in the N-alkyl radical



(VII)

Ester (VII) is difficultly soluble in alcohols and is practically insoluble in benzene. In the IR spectrum of compound (VII) (see Fig. 1) the absorption of the P = O group appears at 1225 cm^{-1}, while the absorption of the P – O – C – appears at 1050 cm^{-1}. Some of the data for the synthesized compounds are given in Table 1.

EXPERIMENTAL

1-N-(β-Hydroxyethyl)–3,6-dimethyluracil (I). To a stirred suspension of 107.8 g of 3,6-dimethyluracil in 300 ml of distilled water was added a solution of 30.6 g of NaOH in 100 ml of water, followed by the addition of another 100 ml of water. The solution was heated up to 80°C, 70 ml of ethylene chlorohydrin was added, and the mass was refluxed for 1.5 h (to pH ~6). Then the reaction mass was cooled, allowed to stand overnight, and the obtained precipitate was filtered, washed in succession with water (50 ml) and acetone (30 ml), and dried. We obtained 46.7 g of 3,6-dimethyluracil with mp 259-261°C. The filtrate was evaporated in vacuo. The crystalline residue was refluxed with 250 ml of ethanol, the NaCl was filtered, and the ethanol solution was evaporated to a volume of 70-80 ml. The crystalline product was filtered, washed with acetone (~15 ml), and dried. We obtained 55.8 g of (I). From the mother liquor was isolated another 4.7 g of (I). The total yield was 60.5 g (42.6% of theory, or 75.5% when based on reacted 3,6-dimethyluracil). After one recrystallization from n-butanol and a double recrystallization from chloroform, mp 134-136°C.

1-N-(β-Hydroxyethyl)–3,6-dimethyl-5-bromouracil (II). To a solution of 2 g of (I) in 20 ml of n-butanol, heated to 80°C, was added Br_2 in drops until decolorization ceased. Then the solution was evaporated to approximately 1/3 volume and cooled. The obtained crystalline product was filtered, washed with about 5 ml of acetone, recrystallized from boiling n-butanol, washed with about 5 ml of absolute benzene, and dried in vacuo. We obtained 2.5 g (87.5% of theory) of (II) with mp 143-144°C.

Reaction of (I) with Thionyl Chloride. To a stirred suspension of 50 g of (I) in 300 ml of absolute benzene and 23.5 ml of pyridine at 20-40°C was added dropwise a solution of 30 ml of thionyl chloride in 30 ml of absolute benzene. Then the vigorously stirred mass was refluxed for 5.5 h. The solution was decanted, heated with active carbon, filtered, and evaporated in vacuo. The residual oily liquid was dissolved in 200 ml of benzene and shaken in a separatory funnel with 300 ml of distilled water. The benzene layer was separated, dried over Na_2SO_4, filtered, and the benzene was vacuum distilled. The residual oily product was treated with about 10 ml of absolute benzene and allowed to crystallize. After 20 days the obtained solid product was filtered, washed on the filter with n-butanol (4 × ~20 ml), and dried in vacuo. The entire product was dissolved in acetone, filtered, and distilled water was added to the solution until a permanent suspension appeared. Then acetone was added in small portions until the suspension disappeared. The solution became clear and soon a crystalline product began to deposit from it. It was filtered and dried. We obtained 7 g of substance with mp 176-178°C. The complete evaporation of the acetone and water gave an additional 8.6 g of this substance. The total yield was 15.6 g. The product was recrystallized twice from acetone. We obtained a substance with mp 176-178°C. Found: C 45.41, 45.22; H 5.00, 4.71; N 13.27, 13.04; Cl 17.10, 16.95; S 7.32, 7.57%. Ultraviolet spectrum (λ_{max}, nm): 297 (pH 1.2); 303-305 (methanol); 303 (pH 11.9).

bis-[β-(3,6-Dimethyl–2,4-dioxo-1,2,3,4-tetrahydro–1-pyrimidinyl)ethyl]phenyl Thiophosphonate (III). To a suspension of 5 g of (I) in 60 ml of absolute benzene and 2.8 g of triethylamine at 2-3°C was added dropwise a solution of 2.9 g of the dichloride of phenylthiophosphonic acid in 30 ml of absolute benzene. Then the mixture was refluxed for 30 min and filtered hot. The triethylamine hydrochloride was filtered. The filtrate was allowed to stand overnight and the deposited $Et_3N \cdot HCl$ was filtered, while the solution was boiled with active carbon and filtered. After 2 days the obtained $Et_3N \cdot HCl$ was filtered, the benzene was distilled from the solution in vacuo, and a small amount of oily liquid was obtained. It was dissolved in

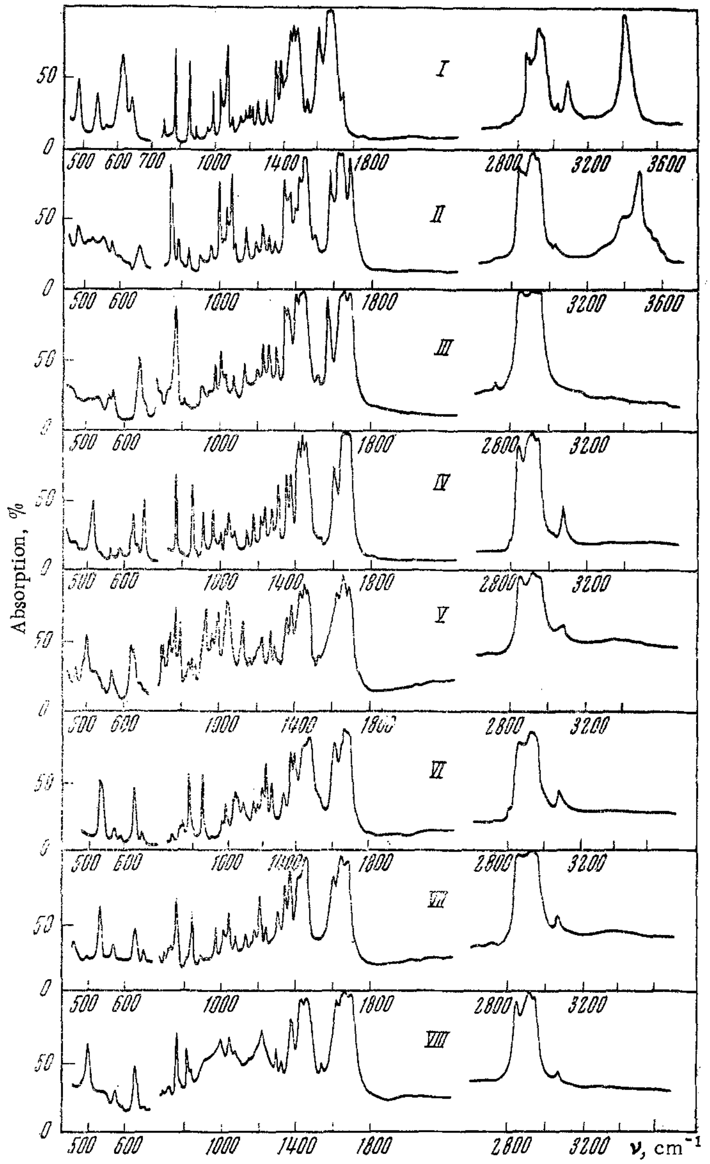


Fig. 1. Infrared spectra: I) 1-N-(β-hydroxyethyl)-3,6-dimethyluracil; II) 1-N-(β-hydroxyethyl)-3,6-dimethyl-5-bromouracil; III) reaction product of 1-N-(β-hydroxyethyl)-3,6-dimethyluracil and thionyl chloride; IV) 1-N-(β-chloroethyl)-3,6-dimethyluracil; V) bis-[β-(3,6-dimethyl-2,4-dioxo-1,2,3,4-tetrahydro-1-pyrimidinyl)-ethyl]phenyl thiophosphonate; VI) bis-[β-(3,6-dimethyl-2,4-dioxo-1,2,3,4-tetrahydro-1-pyrimidinyl)ethyl] sulfide; VII) bis-[β-(3,6-dimethyl-2,4-dioxo-1,2,3,4-tetrahydro-1-pyrimidinyl)ethyl] disulfide; VIII) bis-[β-(3,6-dimethyl-2,4-dioxo-1,2,3,4-tetrahydro-1-pyrimidinyl)ethyl] β-(3,6-dimethyl-2,4-dioxo-1,2,3,4-tetrahydro-1-pyrimidinyl)ethyl phosphonate.

80 ml of absolute benzene and shaken in a separatory funnel with 40 ml of distilled water. The benzene layer was separated, dried over Na_2SO_4, filtered, boiled with active carbon, filtered, and the solvent was distilled from the filtrate in vacuo. After 5 days the residue was treated with about 5 ml of absolute petroleum ether. After 10 days the product crystallized. The sticky crystalline product was filtered, dissolved in about 20 ml of absolute benzene, boiled with active carbon and Al_2O_3, and filtered. The filtrate was evaporated to ~2/3 volume. After 2 days the obtained crystals were filtered and washed with about 5 ml

of absolute petroleum ether. The above purification was repeated. We obtained 1 g (14.5% of theory) of (III) with mp 139-142°C.

Reaction of (I) with the Dichloride of Chloromethylphosphonic Acid. To a stirred suspension of 5 g of (I) in 60 ml of absolute benzene and 2.8 g of triethylamine at 21-25°C was slowly added dropwise a solution of 2.3 g of the dichloride of chloromethylphosphonic acid in 30 ml of absolute benzene. Then the mass was refluxed for 1.5 h and cooled. The next day the triethylamine hydrochloride was filtered, and the benzene was distilled from the solution in vacuo. The residual pale orange oily liquid was dissolved in about 50 ml of absolute benzene, boiled with active carbon, and filtered. The benzene was distilled from the solution in vacuo, and the obtained yellow oily liquid was allowed to crystallize. The crystallization proceeded very slowly. About 7 ml of petroleum ether was added and the mixture was allowed to stand. After a month the obtained product was filtered, washed with petroleum ether–acetone mixture (~10 ml, ~8: 2), and then it was dissolved in about 30 ml of hot benzene, boiled with active carbon, and filtered. The filtrate was evaporated to a volume of about 7 ml. After 3 days the obtained product was filtered and washed with about 30 ml of a petroleum ether–benzene mixture (~3: 1). We obtained 1.3 g (23.6% of theory) of a substance with mp 90.5-93°C. After three recrystallizations from boiling absolute benzene, followed by washing with petroleum ether and drying, we obtained 1-N-(β-chloroethyl)–3,6-dimethyluracil (IV) with mp 95-96°C.

Reaction of (I) with P_2S_5. A suspension of 1.5 g of P_2S_5 and 5 g of (I) in 100 ml of absolute m-xylene was refluxed for 2 h. H_2S was liberated. A small amount of a sticky dark mass deposited on the flask walls. The solution was decanted and cooled. The obtained crystals were filtered, and after a double recrystallization from m-xylene we obtained 0.5 g of (I) with mp 258-260°C. The filtrate was evaporated in vacuo to give an oily liquid. It was treated with about 3 ml of methanol and allowed to crystallize. After a month the obtained crystals were filtered and washed with absolute benzene. We obtained 0.9 g of substance with mp 146-180°C, which is readily soluble in chloroform and practically insoluble in absolute benzene. The product was triturated in about 30 ml of a benzene–chloroform mixture (~1: 2), the solid product with mp 206-211°C was filtered, while the filtrate (A) was allowed to stand for further work-up. The solid product was dissolved in about 40 ml of boiling chloroform, filtered, and the solution was evaporated to ~2/3 volume. The obtained product was filtered, mp 210-213°C. After a second recrystallization from chloroform, mp 215-218.5°C. The substance was refluxed with about 40 ml of absolute benzene, filtered, and the solid residue was again recrystallized from chloroform. We obtained bis-[β-(2,4-dioxo–3,6-dimethyl–1,2,3,4-tetrahydro–1-pyrimidinyl)ethyl] disulfide (VI) with mp 214.5-215.5°C. After drying in vacuo, mp 217-218.5°C. The filtrate (A) was evaporated to incipient crystallization. The obtained solid product was filtered and washed with about 5 ml of absolute benzene; mp 160-180°C. An additional amount of this substance was isolated from the mother liquor. After three recrystallizations from boiling absolute benzene we obtained bis-[β-(2,4-dioxo–3,6-dimethyl–1,2,3,4-tetrahydro–1-pyrimidinyl)ethyl] sulfide (V) with mp 170-171°C.

Reaction of (I) with Triphenyl Phosphite. A mixture of 30 g of (I) and 16.9 g of triphenyl phosphite was heated at 210-220°C for 5.5 h. Phenol was liberated at 200°C, and the mass began to darken. The mass turned to a glass on cooling. It was treated with about 50 ml of absolute benzene and allowed to stand. The powdery mass was triturated well in benzene. This operation was repeated many times, after which the product was filtered, washed on the filter with absolute benzene (5 × ~30 ml), and dried in vacuo. We obtained 19.2 g (60.5% of theory) of bis-[β-(2,4-dioxo–3,6-dimethyl–1,2,3,4-tetrahydro–1-pyrimidinyl)ethyl] β-(2,4-dioxo–3,6-dimethyl–1, 2, 3, 4-tetrahydro–1-pyrimidinyl)ethyl phosphonate (VII) with mp 190-245°C (decompn.). About 10 g of the product was dissolved in boiling n-propanol, boiled with active carbon, and filtered. The obtained product was filtered, washed with n-propanol and benzene, and dried, mp 264-280°C (decompn.). A second portion of the substance, with mp 267-275°C (decompn.), was obtained from the mother liquor. Recrystallization of this material from boiling n-propanol gave (VII) with mp 276-279°C (decompn.).

The IR spectra were taken on a UR-10 spectrophotometer. The samples were prepared as Nujol mulls. The UV spectra were taken on an SF-8 spectrophotometer.

CONCLUSIONS

A study was made of the synthesis and some of the chemical transformations of 1-N-(β-hydroxyethyl)–3,6-dimethyluracil.

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