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BROMO DERIVATIVES OF 1-(4-HYDROXYPHENYL)DIHYDROURACIL AND 1-(4-HYDROXYPHENYL)-5- OR -6-METHYLDIHYDROURACILS

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Bromination of 1-(4-hydroxyphenyl)dihydrouracil and its 6-methyl derivative with bromine in refluxing acetic acid gave 1-(3,5-dibromo-4-hydroxyphenyl)-5-bromo-, 1-(3,5-dibromo-4-hydroxyphenyl)-5-bromo-, and 1-(3,5-dibromo-4-hydroxyphenyl)-5-bromo-6-methyldihydrouracils and 1-(3,5-dibromo-4-hydroxyphenyl)-5-methyluracil. 5-Bromo- and 5,5-dibromodihydrouracils were dehydrobrominated, and the same compounds undergo decomposition to 3,5-dibromo-4-hydroxyphenylurea upon alkaline hydrolysis.

A number of studies has been devoted to the bromination of 1-aryldihydrouracils. It has been pointed out [1] that 1-(1-naphthyl)-5-bromodihydrouracil is formed in the bromination of 1-(1-naphthyl)dihydrouracil, but later in [2] it was demonstrated that under these conditions replacement by bromine takes place in the aromatic ring rather than in the heterocyclic ring to give 1-(4-bromonaphthyl)dihydrouracil.

In the present research we accomplished the bromination of 1-(4-hydroxyphenyl)dihydrouracil (Ia) and its derivatives (Ib,c) with bromine in refluxing acetic acid. Depending on the amount of bromine used for the bromination of dihydrouracil Ia, 1-(3,5-dibromo-4-hydroxyphenyl)-5-bromodihydrouracil (IIa) or 1-(3,5-dibromo-4-hydroxyphenyl)-5,5-dibromohydrouracil (IIIa) is formed in good yield. Bromination of the heteroring of 1-hydroxyphenyldihydrouracils takes place when 2 moles of bromine are added per mole of dihydrouracil Ia, i.e., the amount that is necessary for replacement of the hydrogen in the aromatic ring. A small amount of 5-bromodihydrouracil IIa is also formed, this is easily followed by means of NMR spectroscopy. In the synthesis of IIa 5-10% of 5,5-dibromodihydrouracil IIIa is also formed.

1-Substituted thymines were obtained by the action of bromine in refluxing glacial acetic acid on 1-substituted 5-methyldihydrouracils [3]. Consequently, replacement of the hydrogen atom in the 5 position of the heteroring by bromine is accompanied by dehydrobromination. Under the same conditions 1-(3,5-dibromo-4-hydroxyphenyl)-5-methyluracil (IVb) was obtained from Ib.

However, the bromination of 1-(4-hydroxyphenyl)-6-methyldihydrouracil (Ia) leads to the formation of 1-(3,5-dibromo-4-hydroxyphenyl)-5-bromo-6-methyl-dihydrouracil (IIc), and we were unable to detect the corresponding 5,5-dibromo derivative.

1-Substituted 5-bromodihydrouracils are converted to the corresponding uracils by the action of nucleophilic reagents [1,4] and also by heating at the melting points [5]. Dehydrobromination occurs when bromodihydrouracils IIa,c are refluxed in dimethylformamide (DMF) in the presence of lithium chloride or in solutions of alkalis. Dibromo derivative

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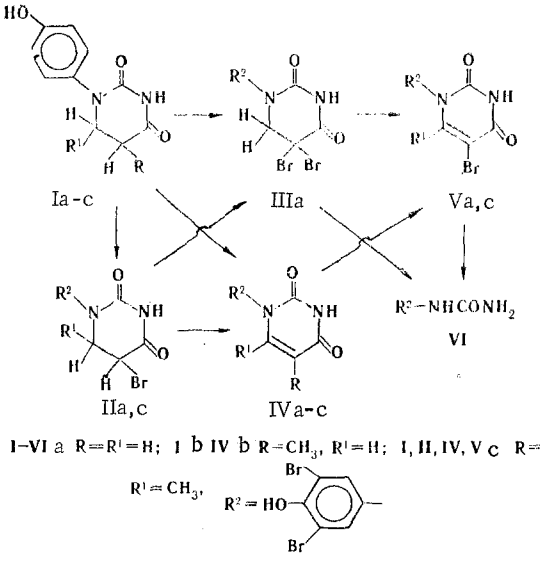
IIIa was converted to 5-bromouracil Va, which, like Vc, was obtained by bromination of IVa,c in acetic acid, by the action of lithium chloride in DMF. Dihydrouracils undergo decylization upon alkaline hydrolysis to give the corresponding β-ureido acids [2], while 5,5-dibromodihydrouracil IIIa and the 5-bromouracil derivatives (Va,c) under the same conditions undergo decomposition to 3,5-dibromo-4-hydroxyphenylurea (VI).



I–VI a $R=R^1=H$; I b IV b $R=CH_3$, $R^1=H$; I, II, IV, V c $R=H$, $R^1=CH_3$, $R^2=$

Although they are chromatographically individual substances, IIa,c and IIIa do not give distinct melting points. It follows from the results of thermal analysis* of these compounds that this phenomenon is associated with their thermal instability. Compound IIa decomposes at 232-270°C with a 17.5% loss in mass, which is in agreement with the mass of one HBr molecule. The melting of IIa [according to the results of differential thermal analysis (DTA)] is not expressed by a large endothermic effect, evidently because of exothermic decomposition, but is completely discernible and takes place at 259°C. The second melting point observed on the derivatogram of IIa is related to the 1-(3,5-dibromo-4-hydroxyphenyl)uracil (IVa) that is formed during heating and is 292°C. A similar phenomenon also occurs in the thermal analysis of IIc and IIIa:

$$\text{IIc} \xrightarrow[-\text{HBr}]{232-270^\circ} \text{IVc} \quad \text{and} \quad \text{IIIa} \xrightarrow[-\text{HBr}]{208-253^\circ} \text{Va}$$

Stretching vibrations of OH, NH, and C=O groups are observed in the IR spectra of all of the synthesized compounds. The hydroxy group of IVa-c in the long-wave region of the spectrum does not give a distinct absorption band, evidently because of strong hydrogen bonds in the crystal. The presence of bromine in the 5 position of the heteroring of IIa,c and IIIa promotes an increase of 25-30 cm^{-1} in the frequency of the stretching vibrations [6] of the carbonyl group attached to the C_4 atom with respect to dihydrouracils Ia,c. This shift of the frequencies is explained by interaction of the carbonyl gorup with the equatorial bromine atom in the α position. In the spectra of 5-bromouracils Va,c the stretching vibrations of the same carbonyl group are shifted 35-40 cm^{-1} to the higher-frequency region with respect to the vibration of the C=O group of starting Ia,c.

In the PMR spectrum of IIa the protons of the $-CH_2-CH=$ fragment form an ABX spin system. The X part of the ABX spin system is a triplet, while the signals of the AB nuclei consist of a pair of intense doublets surrounded by four less intense lines. The protons of the vinyl grouping of IVa form an AB spin system with spin-spin coupling constant (SSCC) J = 7.8 Hz, which indicates the cis orientation of the protons in this system. As a consequence of the effect of the magnetic anisotropy of the aromatic ring, the proton attached to C_6 resonates at weaker field (7.43 ppm) than the signal of the proton (5.81 ppm) attached to C_5.

*We thank E. A. Samarskis for carrying out the thermal analysis.

TABLE 1. Spectral Data for the Synthesized II-VI

Compound	IR spectrum, ν, cm^{-1}				PMR spectrum, δ, ppm, SSCC,[a] Hz
	OH	NH	2-C=O	4-C=O	
IIa	3405	3200	1705	1690	[3.83: 4,41 (2H, AB part of ABX CH_2); 5,03 (1H, X part of ABX CH); J_{AB}=14,2; J_{AX}=2,8; J_{BX}=3,3]; 7,66 (2H, s, arom)
IIc	3260	3200	1710	1690	1,15 (3H, d, J=7,5, CH_3); 3,70—4,10 (1H, m, 5-CH); 4,65 (1H, d, J=2,2, 6-CH); 7,38 (2H, s, arom); 9,82—10,35 (1H, br s, NH); 10,81 (1H, s, OH)
IIIa	3415	3190	1740	1685	4,45 (2H, s, CH_2); 7,74 (2H, s, arom); 9,93—10,25 (1H, br s, NH); 11,16 (1H, s, OH)
IVa	3400—3250	3215	1705	1680	5,81; 7,43 (2H, AB system, CH=CH, J_{AB}=7,8); 7,60 (2H, s, arom); 11,58—12,30 (2H, br s, NH and OH)
IVb	3400—3200	3170	1705	1690	1,64 (3H, s, CH_3); 7,41 (1H, s, CH); 7,52 (2H, s, arom); 11,26 (1H, s, OH)
IVc	3400—3250	3205	1705	1685	1,75 (3H, s, CH_3); 5,55 (1H, s, CH); 7,64 (2H, s, arom); 9,90—10,45 (1H, br s, NH); 11,14 (1H, s, OH)
Va	3360	3185	1715	1705	7,59 (2H, s, arom); 8,08 (1H, s, CH)
Vc	3435	3180	1715	1705	
VI	3480	3340 3290 3175	1645		5,85 (2H, s, NH_2); 7,54 (2H, s, arom); 8,48 (1H, s, NH); 9,25 (1H, s, OH)

[a]The PMR spectra of IIa and IVa in d_5-pyridine were recorded whereas the PMR spectra of the remaining compounds in d_6-DMSO were recorded.

This phenomenon is also confirmed by the data from the PMR spectra of other uracil derivatives (see Table 1).

EXPERIMENTAL

The IR spectra of KBr pellets of the compounds were recorded with a UR-20 spectrometer, while the PMR spectra were recorded with a Tesla BS-487C spectrometer (80 MHz) with hexamethyldisiloxane as the internal standard. The derivatographic studies were made with an MOM derivatograph (with the Paulik—Paulik—Erdey system): The sample mass was 100 mg, the maximum heating temperature was 600°C, and the heating rate was 6°/min. The sensitivities were as follows: 100 for thermogravimetry (TG), 1/10 for differential thermogravimetry (DTA), and 1/5 for differential thermal analysis (DTA). The inert substance (Al_2O_3) was calcined at 1200°C. The pressure was atmospheric pressure, and the environment was air. The individuality of the compounds was determined by thin-layer chromatography (TLC) on Silufol UV-254 plates in ether—hexane (4:1) and methyl ethyl ketone—hexane (1:1 and 1:2.5) systems.

1-(3,5-Dibromo-4-hydroxyphenyl)-5-bromodihyrouracil (IIa). A solution of 4.0 ml (0.078 mole) of bromine in 10 ml of glacial acetic acid was added dropwise in the course of an hour to a refluxing solution of 5.15 g (0.025 mole) of dihydrouracil Ia in 50 ml of glacial acetic acid, and refluxing was continued for another 3-3.5 h. The mixture was cooled, and the precipitated crystals of IIa were removed by filtration. The yield was 9.45 g.

1-(3,5-Dibromo-4-hydroxyphenyl)-5,5-dibromodihydrouracil (IIIa). A solution of 6.0 ml (0.12 mole) of bromine in 10 ml of glacial acetic acid was added dropwise in the course of 2.5-3 h to a refluxing solution of 5.15 g (0.025 mole) of dihydrouracil Ia in 100 ml of glacial acetic acid, and refluxing was continued for another 8-10 h. The mixture was then cooled and diluted with water (1:5) and the precipitated IIIa was removed by filtration. The yield was 12.3 g.

1-(3,5-Dibromo-4-hydroxyphenyl)-5-methyluracil (IVb). A solution of 8.0 ml (0.16 mole) of bromine in 10 ml of glacial acetic acid was added dropwise to a refluxing solution

of 11.1 g (0.05 mole) of 5-methyldihydrouracil Ic in 100 ml of glacial acetic acid, and the mixture was refluxed for another 3 h. It was then cooled, and the precipitated crystals were removed by filtration. The yield was 16.5 g.

1-(3,5-Dibromo-4-hydroxyphenyl)-5-bromo-6-methyldihydrouracil (IVc). This compound was obtained from 11.1 g (0.05 mole) of 6-methyldihydrouracil Ic and 10 ml (0.19 mole) of bromine by a method similar to that used to prepare IVb. The yield was 22.1 g.

1-(3,5-Dibromo-4-hydroxyphenyl)uracil (IVa). A) A mixture of 2.2 g (5 mmole) of 5-bromodihydrouracil IIa and 0.43 g (0.01 mole) of anhydrous LiCl was refluxed for 3 h in 20 ml of dimethylformamide, after which it was diluted with water (1:4). The precipitate was removed by filtration to give 1.7 g of IVa.

B) A 4.4-g (0.01 mole) sample of IIa was refluxed in 30 ml of 10% NaOH solution for 5 min, after which 100 ml of water was added, and the mixture was acidified to pH 6 with acetic acid. The precipitated crystals of IVa were removed by filtration. The yield was 1.8 g.

1-(3,5-Dibromo-4-hydroxyphenyl)-6-methyluracil (IVc). A) This compound was obtained from 2.3 g (0.05 mole) of dihydrouracil IIc by a method similar to method A in the experiment described above. The yield of IVc was 1.7 g.

B) This compound was obtained from 4.6 g (0.01 mole) of IIc by a method similar to method B in the experiment described above. The yield of IVc was 3.7 g.

1-(3,5-Dibromo-4-hydroxyphenyl)-5-bromouracil (Va). A mixture of 1.2 g (2.3 mmole) of IIIa, 0.2 g (4.6 mmole) of anhydrous LiCl, and 20 ml of DMF was refluxed for 2 h, after which it was diluted with water (1:4) to give 0.94 g of Va.

B) A 1.8-g (5 mmole) sample of uracil IIa was dissolved in 40 ml of refluxing acetic acid, a solution of 0.4 ml (0.078 mole) of bromine in 2 ml of glacial acetic acid was added dropwise in the course of 30 min, and the mixture was refluxed for another 1.5 h. It was then cooled, and Va was removed by filtration. The yield was 2.0 g.

1-(3,5-Dibromo-4-hydroxyphenyl)-5-bromo-6-methyluracil (Vc). This compound was obtained from 1.9 g (5 mmole) of uracil IVc and 0.4 ml (7.8 mmole) of bromine just as in the preparation of Va by method B. The yield was 2.2 g.

3,5-Dibromo-4-hydroxyphenylurea (VI). A) A 5.2-g (0.01 mole) of IIIa was dissolved in 50 ml of 10% aqueous NaOH solution, and the solution was refluxed for 5 min. It was then cooled, 50 ml of water was added, and the mixture was acidified to pH 5 with hydrochloric acid. The resulting precipitate was removed by filtration to give 2.4 g of VI.

B) The reaction of 4.6 g (0.1 mole) of Vc by a method similar to method A gave 2.6 g of VI.

TABLE 2. Characteristics of the Synthesized II-VI

Substance	mp, °C [a]	Found, %		Empirical formula	Calc., %		Yield, % (synthetic method)
		N	Br		N	Br	
II a	259 [b]	53,9	6,6	$C_{10}H_7Br_3N_2O_3$	54,1	6,3	85
II c	264 [b]	52,7	6,1	$C_{11}H_9Br_3N_2O_3$	52,5	6,1	97
III a	240 [c]	61,1	5,7	$C_{10}H_6Br_4N_2O_3$	61,2	5,4	94
IV a	291 [c]	43,9	8,0	$C_{10}H_6Br_2N_2O_3$	44,1	7,7	99 (A) 50 (B)
IV b	264 [b]	42,7	7,3	$C_{11}H_8Br_2N_2O_3$	42,5	7,4	88
IV c	294 [c]	42,3	7,6	$C_{11}H_8Br_2N_2O_3$	42,5	7,4	96 (A) 96 (B)
Va	319 c	54,2	6,3	$C_{10}H_5Br_3N_2O_3$	54,4	6,4	93 (A) 94 (B)
V c	279 c	53,2	6,5	$C_{11}H_7Br_3N_2O_3$	52,7	6,2	97
VI	196 [d]	51,4	9,2	$C_7H_6Br_2N_2O_2$	51,6	9,1	77 (A) 84 (B)

[a] The melting points were determined from the derivatograms. Compound IVb decomposed without melting. [b] DMSO–H_2O. [c] CH_3COOH. [d] Acetone–hexane.

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MASS-SPECTROMETRIC INVESTIGATION OF SOME 2,6-DIMETHYLOXAZOLO[4,5-d]-PYRIMIDINE DERIVATIVES

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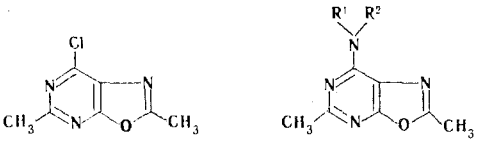
The fragmentation of the molecular ions of 4-chloro- and 4-alkylamino-2,6-dimethyloxazolo[4,5-d]pyrimidines involves splitting out or fragmentation of the substituent in the 4 position or cleavage of the oxazole ring. The compositions of the fragment ions were determined on the basis of the high-resolution mass spectra.

Oxazolo[4,5-d]pyrimidines are oxygen analogs of purines, and this is responsible for the heightened interest of pharmacologists in them. At the same time, the principles of the mass-spectrometric fragmentation of these compounds are virtually unknown.*



I

II–V

II $R^1=H$, $R^2=CH_3$; III $R^1=R^2=CH_3$; IV $R^1=R^2=C_2H_5$; V $R^1=CH_3$, $R^2=CH_2C_6H_5$

We studied the behavior of a series of substituted oxazolo[4,5-d]pyrimidines I-V under electron impact by determining the compositions of the most important ions on the basis of the high-resolution mass spectra.

An analysis of the mass spectra obtained (Table 1) and the intensities of the peaks of the characteristic ions (Table 2) makes it possible to note that an increase in the size of the substituents in the amino group decreases the stabilities of the molecular ions.

The principal processes of dissociative ionization of the molecules of I-V involve the loss by their molecular ions of one hydrogen atom (pathway A, Schemes 1 and 2) or splitting out of the substituent from the 4 position (pathway B). In the case of I the more electronegative group, viz., the chlorine atom, is split out to give the cation of the heterocycle.

*Only the partial mass spectra of six 4-monoalkylaminooxazolo[4,5-d]pyrimidines without a detailed discussion of the scheme of their fragmentation are presented in [1].

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