ANALOGS OF PYRIMIDINE NUCLEOSIDES

V. UV Spectra and Photolysis Constants of 5-Substituted N^1-(Tetrahydrofuran-2'yl)- and N^1-(2'-Oxotetrahydrofuran-3'-yl)uracils*

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The UV absorption spectra of 5-substituted N^1-(tetrahydrofuran-2'-yl)- and N^1-(2'oxotetrahydrofuran-3'-yl)uracils have been studied and their protolysis constants have been determined by the spectrophotometric method. A comparison is given with the spectra and pK_a values of the corresponding N^1-methyl derivatives and ribosides and deoxyribosides.

Recently, the attention of many workers has been attracted to the study of the UV and IR spectra, and also the NMR, of pyrimidine and purine bases, their ribosides, 2'-deoxyribosides, and 2',3'-dideoxyribosides [1-6]. In addition to this, the protolysis constants [3, 4] and the kinetics of the hydrolysis of the glycosidic bond [7, 8] have been studied.

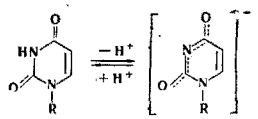
Since we have synthesized for the first time a series of N^1-(tetrahydrofuran-2'-yl)- and N^1-(2'-oxotetrahydrofuran-3'-yl) [N^1-(α-butyrolactone)] derivatives of the pyrimidine bases [9-12], it was of interest of investigate the physicochemical properties of these compounds and compare them with the properties of the nucleosides. In the present work we have studied the UV absorption spectra as a function of the pH of the medium and have also determined by a spectrophotometric method the protolysis constants of N^1-(tetrahydrofuran-2'-yl) and N^1-(2'-oxotetrahydrofuran-3'-yl) derivatives of 5-substituted uracils.

A comparison of the results obtained with literature data for the ribosides and 2'-deoxyribosides [1-4] permits some conclusions on the interrelationship between the structure and properties of these compounds. The results of a study of the kinetics of the hydrolysis of these compounds will be discussed in a subsequent communication.

As is well known, in the undissociated state at pH 1-5 the pyrimidine bases (uracil, thymine, 5-halogenouracils) have a single characteristic absorption maximum in the far UV region of the spectrum. The introduction of a CH_3 group as substituent at N^1 causes a bathochromic shift of the order of 6-9 nm and an increase in the absorption coefficient [1-3, 13, 14]. In the case of the N^1-ribosides and 2'-deoxyribosides of the pyrimidine bases, this shift is considerably less – 2-4 nm, the smallest shift being given by the 2'-deoxyribosides [3]. We have established that the N^1-tetrahydrofuranyl derivatives in the undissociated state give a bathochromic shift of the main absorption maximum of of the order of 2-4 nm and an increase in the absorption coefficient close to that for the 2'-deoxyribosides (Fig. 1).

The introduction of a halogen into N^1-(tetrahydrofuran-2'-yl)uracil causes a bathochromic shift rising in the sequence F < Cl < Br < I (Fig. 2). Simultaneously there is a decrease in the absorption coefficient amounting to 21% in the case of F, Cl, and Br, and 38% in the case of I. A similar pattern is observed for the N^1-(2'-oxotetrahydrofuran-3'-yl)-derivatives.

On passing to alkaline media, the N^1-substituted pyrimidine bases give no bathochromic shift of the main absorption maximum, which is explained by protolysis with the formation of a monoanion having, according to literature data [14], a structure with an equally-distributed electron cloud:



The analogous form of the N^1-(tetrahydrofuran-2'-yl) derivatives gives a hypsochromic shift of the absorption maximum, as compared with the undissociated form, which is small in the F, Cl, and Br derivatives, but is extremely con-

*For part IV see [11].

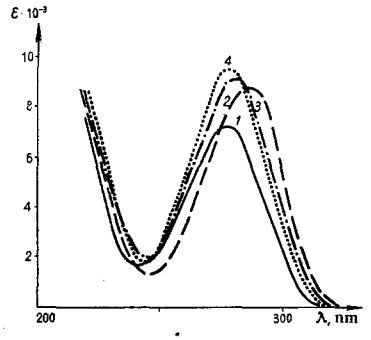


Fig. 1

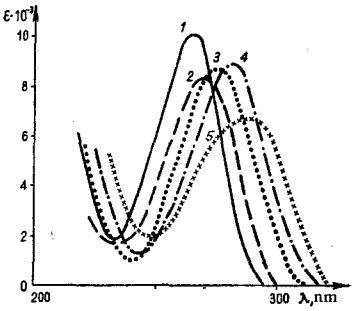


Fig. 2

Fig. 1. UV spectra of 5-bromouracil (1), 5-bromo-1-methyluracil (2), 5-bromo-1-(2'-deoxyribofuranosyl)uracil (3), and 5-bromo-1-(tetrahydrofuran-2'-yl)uracil (4) at pH 4.

Fig. 2. UV spectra of N^1-(tetrahydrofuran-2'-yl) derivatives of uracil (1), 5-fluorouracil (2), 5-chlorouracil (3), 5-bromouracil (4), and 5-iodouracil (5) at pH 4.

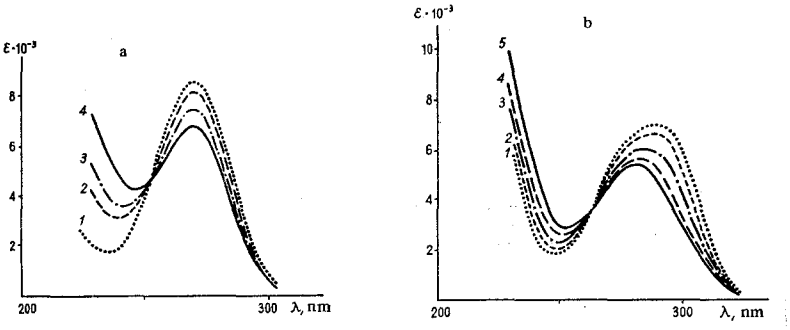


Fig. 3. Change in the UV spectra as a function of the pH of the medium: a) 5-fluoro-1-(tetrahydrofuran-2'-yl)uracil: 1) pH 1.97; 2) pH 7.44; 3) pH 7.81; 4) pH 12.48; b) 5-iodo-1-(tetrahydrofuran-2'-yl-uracil: 1) pH 2.00; 2) pH 8.18; 3) pH 9.02; 4) pH 9.67; 5) pH 12.47.

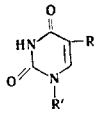
considerable in the I derivative (10 nm) Fig. 3). This also applies to the N^1-(2'-oxotetrahydrofuran-3'-yl) derivatives of the 5-substituted uracils.

The protolysis constants of the N^1-(tetrahydrofuran-2'-yl) and N^1-(2'-oxotetrahydrofuran-3'-yl) derivatives of the 5-substituted uracils which we determined spectrometrically with the introduction of corrections for the ionic strength of the solutions, are in full agreement with the expected values.

Because of the negative induction effect of a halogen, the introduction of a halogen into position 5 of the pyrimidine ring causes a fall in the electron density on the N_3H group [6] and thereby increases the acid properties both of the bases and of their N^1-derivatives. This effect falls in the sequence F > Cl > Br > I as the electronegativity of the halogen decreases. The replacement of H on N^1 by a CH_3 group causes an increase in the electron density on the nitrogen of the N_3H group and thereby decreases the acidic properties of the initial compound. In contrast to this, the N^1-ribosides and 2'-deoxyribosides are more acidic than the corresponding bases [3]. As our investigations have shown (Table 1) the N'-(tetrahydrofuran-2'-yl) derivatives of the pyrimidine bases have similar properties to those of the N^1-(2'-deoxyriboside)s (showing a tendency to an increase in acidity as compared with the latter) and differ considerably from the N^1-methyl derivatives.

So far as concerns the N^1-(2'-oxotetrahydrofuran-3'-yl) derivatives, we have established that the introduction of a C=O group into the molecule decreases the electron density on the nitrogen of the N_3H group and thereby enhances the acidity of the compounds by 0.3-0.5 pK_a units as compared with the tetrahydrofuranyl derivatives.

Table 1. Protolysis Constants of the Uracil Derivatives



R′	R					
	H	CH_3	F	Cl	Br	I
	9.54	9.59	7.80	7.87	8.00	8.17
	9.05	9.14	7.30	7.75	7.54	7.76

On the basis of the results presented, it may be assumed that the similarity of some biological properties of the N′-(tetrahydrofuran-2′-yl) derivatives and the 2′-deoxyribosides can be explained not only by similarities of spatial structure, but also by the closeness of the acidic characteristics of these compounds.

EXPERIMENTAL

The UV spectra were recorded on an SF-4 spectrophotometer, and also on an automatic recording spectrophotometer.

To determine the pK_a values, 0.01 M solutions of the following substances were used: hydrochloric acid (pH 2), formic acid (pH 3.2-2.4), acetic acid (pH 4.2-5.4), monopotassium phosphate (pH 6.5-7.7), boric acid (pH 8.6-9.8), ethylamine (pH 10.1-11.3), and caustic potash (pH 12). The required pH value was established by the addition of 1 N caustic potash or hydrochloric acid. The pH values were determined on an LPU-01 pH-meter with an accuracy of ± 0.02.

The pK_a values were determined by a published method [15]. The protolysis constants were calculated from the formula

$$pK_a = pH + \lg \frac{D - D_A}{D_M - D},$$

where D_A is the optical density of the anionic form, D_M is the optical density of the undissociated form, and D is the optical density of the mixture of the anionic and undissociated forms. A correction was introduced for the ionic strength of the buffer solutions. The final value of pK_a was determined as the arithmetic mean of several values obtained at various pH values of the buffer solutions. The scatter of the results did not exceed 0.05 pK_a unit.

The work was carried out with analytical samples of compounds obtained by us previously [9-12].

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