THE SYNTHESIS OF 1-ARYL-5,6-DIHYDROURACILS AND 1-ARYL-2-THIO-5,6-DIHYDROURACILS

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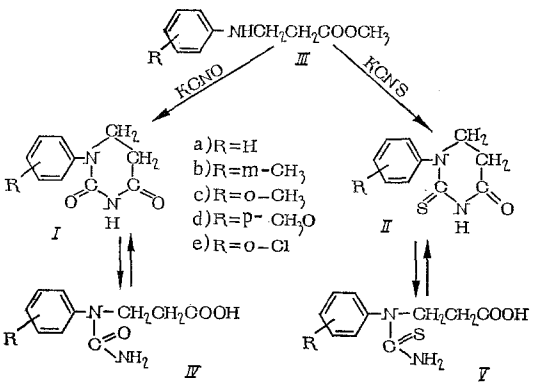
Certain derivatives of dihydrouracil and dihydrothiouracil possess significant chemotherapeutic activity [1, 2]. Furthermore, dihydrouracils and also ureido acids are important metabolites of nucleic acids [3, 4].

In continuation of our investigations [5], the synthesis of 1-aryl-5,6-dihydrouracils (I), 1-aryl-2-thio-5,6-dihydrouracils (II), ureido and thioureido acids (IV) and (V) (Tables 1 and 2) has been accomplished in the present study. Compounds (Ia-e) and (IIa-e) were obtained from the methyl esters of the respective N-aryl derivatives of β-alanine (III) by reaction with potassium cyanate or thiocyanate in acid medium, and also by heating N-aryl-β-ureido derivatives (IV) or N-aryl-β-thioureidopropionic acid (V) in hydrochloric acid. Complete fission of the dihydrouracils and thiodihydrouracils to the corresponding ureido acids was effected by the action of a 10% alkaline solution.



There is no single point of view on the problem of dihydrouracil structure for which the possible existence of tautomeric forms has been proposed. Some authors, on the basis of IR and UV spectroscopic data [3], have considered that these compounds exist in the enolic form. Later [6, 7], with the aid of an analysis of the carbonyl region of the IR spectra of dihydrouracils measured in dioxan, it was established that dihydrouracils have a di-carbonyl structure.

We have measured the UV spectra of 1-phenyl- and 1-p-methoxyphenyl-5,6-dihydrouracils (Ia, d) and also 1-phenyl-2-thio-5,6-dihydrouracil (IIa) in neutral, acidic, and alkaline media. Data are given in Table 3 for comparison of the spectra of 1-methyluracil [8], 1-methylthymidine [9], and dihydrouracil [3] taken in alcohol at various pH values. It is seen that the spectrum of (Ia) in the undissociated state is very similar to the spectrum of (Id), but differs in an appreciable increase in intensity which is connected with the influence of the methoxy group in the aromatic nucleus. The spectrum of the thio analog (IIa) was more complicated and was characterized by two maxima of significantly greater intensity compared to the spectrum

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TABLE 1. 1-Aryl-5,6-dihydrouracils and 1-Aryl-2-thio-5,6-dihydrouracils

Compound	Yield (in %)*	mp (in deg)	Found N (in %)	Empirical formula	Calculated N (in %)	R_f ‡
I b	45	159,5—160	13,66 14,04	$C_{11}H_{12}N_2O_2$	13,72	0,67
Ic	20	169—170 †	—	—	—	—
I d	50	203,5—04	12,79 12,48	$C_{11}H_{12}N_2O_3$	12,72	0,51
Ie	17	246,5—247	12,6 12,73	$C_{10}H_9ClN_2O_2$	12,47	0,66
II b	53	204,5—205 217—218 †	12,84 12,35	$C_{11}H_{12}N_2OS$	12,72	0,65
IIc	51		—	—	—	—
IId	48	255—256	11,84 11,62	$C_{11}H_{12}N_2O_2S$	11,86	0,75
II e	26	248	11,46 11,87	$C_{10}H_9ClN_2OS$	11,64	0,69

*Indicated yield is for method *a*, the yield of compound from method b was quantitative.

† See literature reference [16].

‡ Chromatography of compounds was carried out on aluminum oxide activity grade II in the system chloroform—alcohol (20:1).

TABLE 2. N-Aryl-β-(thio)ureidopropionic Acids

Compound	Yield (in %)	mp (in deg)	Found N (in %)	Empirical formula	Calculated N (in %)	R_f*
IVb	77	144	12,68 12,95	$C_{11}H_{14}N_2O_3$	12,61	0,87
IVd	80	149—149.5	11,52 11,40	$C_{11}H_{14}N_2O_4$	11,76	0,72
IVe	65	132—133	11,96 11,78	$C_{10}H_{11}ClN_2O_3$	11,54	0,85
Vb	86	126,5—127	11,96 11,82	$C_{11}H_{14}N_2O_2S$	11,76	0,88
V c	75	158—159	11,99 11,90	$C_{11}H_{14}N_2O_2S$	11,76	0,89
V d	84	166,5—167	11,00 11,20	$C_{11}H_{14}N_2O_3S$	11,02	0,82
V e	70	147—148	10,52 10,40	$C_{10}H_{11}ClN_2O_2S$	10,83	0,84

*Chromatographed on Leningrad type-B paper in the system pyridine—n-butanol—water (1:1:1).

of (Ia). Such differences were also observed on comparing the spectra of phenylureas [10] and phenylthioureas [11], fragments of which occur in the structures of (Ia) and (IIa). This difference is explained by the strong chromophoric properties of the C=S group in comparison with the C=O group [12].

On going from the undissociated form to the ionic form of compounds (Ia), (Id), and (IIa) the region of absorption was either unchanged or small hypsochromic shifts of absorption maxima were observed which were accompanied by a reduction in intensity. These peculiarities were also observed in the spectra of uracil, thymine, and dihydrouracil (see Table 3). Thus, the character of the spectra of the compounds being studied was not disrupted by the change in pH of the solution which excludes the enolization of dihydrouracils in alkaline medium.

A band in the 1690-1710 cm^{-1} region occurred in the IR spectra of compounds (Ia, IIa-d) which may be assigned to the stretching vibration of an NH—C=O entering into the composition of the heterocyclic ring [13]. A band in the 1500-1510 cm^{-1} region is typical of a secondary amide group. The stretching vibration of the pyrimidine ring corresponds to a band in the 1430-1460 cm^{-1} region [14]. Intense bands in the 1210-1240 cm^{-1} region correspond to the stretching vibration of the RC_6H_4—N= group. In the NH stretching vibra-

TABLE 3. The UV Spectra of Uracils

Compound	λ_{max} (in nm)		
Ia	pH 7,0	pH 1,05	pH 12,0
	237	235	235
Id	229	229	229
IIa	235	235	235
	280	281	282
	pH 6,86	pH 9,71	pH 12,0
1-Methyluracil	268	267	266
	pH 5,9	pH 10,15	pH 11,5
1-Methythymine	273	272	271
Dihydrouracil	263	232	

tion region for (Ib-d), two bands occurred within the range 3110-3400 cm^{-1}. In the case of compound (Ia), which does not contain a substituent in the aromatic nucleus, these bands were not resolved (ν 3300 cm^{-1}). In the thiodihydrouracils (IIa-d) a band in the 1170-1190 cm^{-1} region corresponded to the deformation vibration of the C=S group.

As was shown by testing carried out in the All-Union Pharmaceutical Chemistry Research Institute, 1-p-anisyl-5,6-dihydrouracil (Id) at a dilution of 1:1000 possessed bacteriostatic activity against acid-resistant bacteria. At the same dilution (Id) and 1-p-anisyl-2-thio-5,6-dihydrouracil (IId) displayed fungistatic activity on pathogenic fungi.

EXPERIMENTAL

IR spectra were taken on an IKS-22 instrument in Nujol and hexachlorobutadiene. UV spectra were taken on an SF-4A spectrophotometer (in alcohol: pH 1.05, 7, and 12.5). PMR spectra were taken on an RS-60 instrument with hexamethyldisiloxane as internal standard.

Methyl Esters of N-Aryl Derivatives of β-Alanine (III). These were obtained by reported methods [15].

1-Aryl-5,6-dihydrouracils (I). *a*) A mixture of 0.05 mole (III), 6 g (0.075 mole) potassium cyanate, and 7 ml concentrated sulfuric acid in 90 ml water was boiled for 5-6 h. The solid which had separated was filtered off, washed with water, and recrystallized from ethanol. Yield and constants, see Table 1.

b) A mixture of 0.003 mole (IV) and 20 ml 10% hydrochloric acid was boiled for 1 h. The solid which had separated was filtered off and recrystallized from aqueous alcohol (see Table 1). Substances obtained by methods *a* and b gave no depression of melting point.

In the PMR spectrum of (I) there were two triplets in the 3.0 and 3.93 ppm region (two methylene groups) and a singlet for the proton of the NH group in the region of 5.86 ppm.

1-Aryl-2-thio-5,6-dihydrouracils (II). *a*) A mixture of 0.06 mole (III), 9.7 g (0.1 mole) potassium thiocyanate, and 6 ml concentrated sulfuric acid in 80 ml water was boiled for 4 h. The solid which had precipitated was recrystallized from butanol (see Table 1).

b)The corresponding (II) were obtained from (V) by method b for (I) (see Table 1).

N-Aryl-β-ureidopropionic (IV) and N-Aryl-β-thioureidopropionic (V) Acids. 0.01 Mole (I) or (II) was dissolved in 20 ml 10% sodium hydroxide solution and kept for a day. The solution was neutralized with dilute hydrochloric acid, the solid which precipitated was filtered off, and recrystallized from ethanol (see Table 2).

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