SYNTHESIS AND PROPERTIES OF β-(1-URACILYL)-α-HYDROXYPROPIONIC ACID DERIVATIVES

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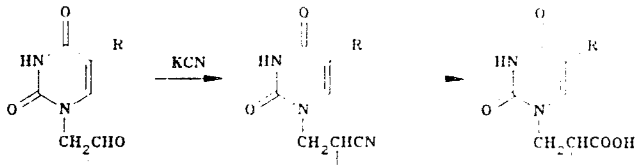
β-(1-Uracilyl)-α-substituted propionitriles were obtained by cyanohydrin synthesis from 1-uracilylacetaldehydes. Their hydrolysis, bromination, and amination were studied.

We have previously shown that, depending on the reaction conditions, either replacement of the bromine atom by an amino group or cine substitution with the formation of ω-(6-alkylamino-1-uracilyl)alkylamines or intramolecular cyclization, which leads to imidazo[1,2-c]- or pyrimido[1,2-c]pyrimidine systems occurs in the reaction of β-(5-bromo-1-uracilyl)-α-aminopropionic acid and ω-(5-bromo-1-uracilyl)ethyl(propyl)amines with primary and secondary amines [1-3]. Intramolecular $C_{(6)}$–$O_{(5')}$ cyclization is observed when 2',3'-isopropylidene-5-bromouridine is heated with sodium ethoxide in ethanol, and the corresponding 6,5'-cyclonucleoside is formed in high yield [4].

We felt it was expedient to investigate the behavior of β-(5-bromo-1-uracilyl)-α-hydroxypropionic acid under similar conditions.

The cyanohydrin method was used to obtain unknown β-(1-uracilyl)-α-hydroxypropionic acids:



Ia, b IIa, b IIIa, b

I–III a R=H; b R=CH_3

The corresponding nitriles IIa, b were isolated as a result of the reaction of 1-uracilylacetaldehydes Ia, b with potassium cyanide in an aqueous medium (pH 6.0-6.5). The IR spectra of IIa, b are characterized by the presence of absorption bands at 1675-1700 cm^{-1}, which correspond to stretching vibrations of CO groups and the C=N bond of uracil, and by absorption at 2220 cm^{-1} (C≡N). In addition to signals of protons of the uracil ring and the alkyl chain, a doublet of the proton of the C_α–OH group (6.80 ppm), which vanishes upon deuteration, is observed in the PMR spectra.

It has been noted [5] that β-(9-adeninyl)-α-hydroxypropionitrile is unstable and that its aqueous solutions are readily hydrolyzed at room temperature. Nitriles IIa, b are stable crystalline substances with high melting points; they are hydrolyzed to acids IIIa, b only on refluxing with 9 N HCl.

There are data [6, 7] that indicate that oxidation occurs in the bromination of α-hydroxy carboxylic acids; for example, acetic acid is formed from lactic acid, and benzaldehyde is formed from mandelic acid. In our case, the formation of 1-uracilylacetic acid was not observed in the reaction of acid IIIa with bromine in aqueous solution, and β-(5-bromo-1-uracilyl)-α-hydroxypropionic acid (IIIc) was isolated as the only product. Data from the UV spectra provide evidence for the presence of bromine in the 5 position of the uracil ring: A bathochromic shift of the absorption maximum from 265 nm (IIa) to 280 nm (IIIc) is observed. Retention of the α-hydroxypropionic acid fragment is confirmed by the IR spectra, which contain an intense absorption band of stretching vibrations of a carboxy carbonyl group at 1730 cm^{-1} and a broad absorption band at 3150-3475 cm^{-1} (α-OH). In the PMR spectra the positions of the signals of the protons of IIIa-c correspond to the structures assigned to them.

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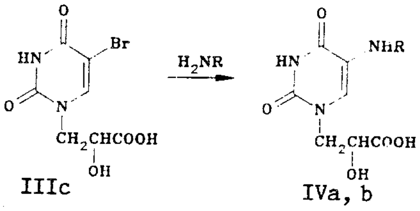
TABLE 1. Characteristics of II-X

Compound	Empirical formula	mp, °C	R_f		UV spectrum, λ_{max}, nm (log ε)	Yield, %
			A	B		
IIa	$C_7H_7N_3O_3$	164...165	0,69	0,55	264 (3,79)	83
IIb	$C_8H_9N_3O_3$	176...177	0,67	0,69	270 (3,68)	77
IIIa	$C_7H_8N_2O_5$	137...138	0,05	0,58	265 (3,71)	88
IIIb	$C_8H_{10}N_2O_5 \cdot H_2O$	103...104	0,12	0,67	269 (3,74)	85
IIIc	$C_7H_7N_2BrO_5$	218...220	0,55	—	280 (3,74)	69
IVa	$C_{10}H_{15}N_3O_5 \cdot 2H_2O$	207...208	0,05	0,68	288 (3,84)	41
IVb	$C_{11}H_{17}N_3O_5 \cdot 2H_2O$	204...205	0,05	0,48	288 (3,76)	46
Va	$C_{14}H_{14}N_4O_3$	154...155	0,82	0,90	264 (3,84)	82
Vb	$C_{12}H_{12}N_4O_3$	175...176	0,80	0,87	264 (3,78)	59
VI	$C_{14}H_{16}N_4O_3$	213	0,64	0,84	268 (3,80)	72
VII	$C_7H_9N_3O_4$	212	0,16	0,55	265 (3,75)	74
VIII	$C_9H_{10}N_3BrO_5$	224...225	0,60	0,67	280 (3,76)	56
IX	$C_7H_8N_3BrO_4$	235...237	0,40	0,67	280 (3,75)	79
X	$C_{21}H_{22}N_4O_4$	162...163	0,91	0,97	305 (3,68)	83

The reaction of 5-bromo derivative IIIc with propyl(butyl)amine was carried out using excess amine at its boiling point. Analysis of the reaction mixture by TLC showed that the reaction proceeds unambiguously, and β-(5-alkylamino-1-uracilyl)-α-hydroxypropionic acids IVa, b were isolated as the only products.



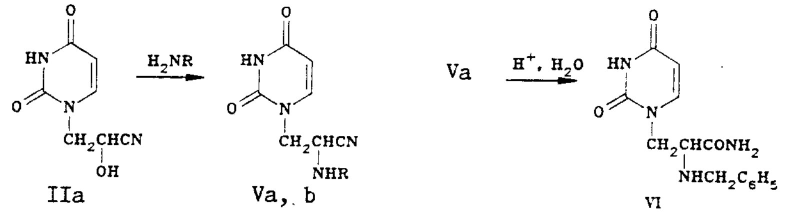
IIIc IVa, b

IVa $R=(CH_2)_2CH_3$; b $R=(CH_2)_3CH_3$

A bathochromic shift of the absorption maximum of 20 nm (from 267 nm to 289 nm) is observed in the UV spectra of IVa, b on passing from an acidic medium to an alkaline medium; this is characteristic for 1-substituted 5-alkylaminouracils [2, 8]. A singlet at 6.66 ppm from the $C_{(6)}$ proton of the uracil ring was observed in the PMR spectra. A signal of protons of a CH_2 group of the $C_{(5)}$–NH–CH_2 fragment is observed at 2.78 ppm, a multiplet of protons of methylene groups of an alkyl chain is observed at 1.35-1.46 ppm, and a triplet of a methyl group is observed at 0.78 ppm. The position of the signals of the protons of the α-hydroxypropionic acid fragment does not change substantially as compared with starting IIIc.

Since α-hydroxy nitriles of the pyrimidine series were not known, the chemical properties of β-(1-uracilyl)-α-hydroxypropionitrile (IIa) were studied in greater detail.

Replacement of the α-OH group by an amino group to give the corresponding β-(1-uracilyl)-α-benzylamino(furfurylamino)propionitriles Va, b occurs when IIa is heated with excess amine (benzylamine, furfurylamine).



IIa Va, b Va VI

Va $R=-CH_2C_6H_5$; b R=5-furfuryl

One absorption band corresponding to the stretching vibrations of the N–H bond of a secondary amine is observed at 3295-3300 cm^{-1} in the IR spectra of Va, b, while a C≡N absorption band is observed at 2220 cm^{-1}. Signals of protons of a furan ring at 7.60 ppm (β-CH) and 6.26 and 6.33 ppm (α-CH) are observed in the PMR spectrum of Vb. In the case of Va a multiplet of protons of a benzene ring at 7.22 ppm appears in the PMR spectrum.

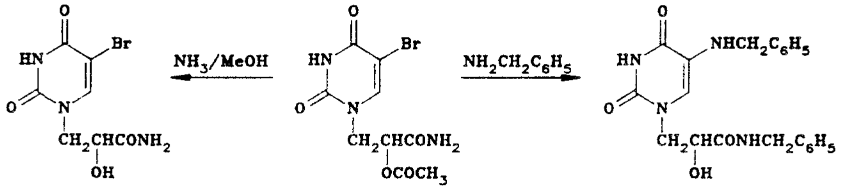
Amide VI was isolated in the hydrolysis of nitrile Va with concentrated sulfuric acid. The C≡N absorption band at 2220 cm^{-1} vanishes in its IR spectrum, and strongly expressed bands of stretching vibrations of an amide carbonyl group at 1650 cm^{-1} and of an amide N–H bond at 3410 cm^{-1} appear. The signal of protons of an amide group at 7.64 ppm is observed in the PMR spectrum.

TABLE 2. PMR Spectra of II-X

Compound	Chemical shifts, δ, ppm							
	$N_{(3)}H$, br-s	6-H	5-H, d	β-CH_2	α-CH, m	5-CH_3, s	α-OH, d	other signals
IIa	11,26	7,57 d	6,77	4,00 d	4,77	—	5,55	—
IIb	11,20	7,42 s	—	8,93 d	4,77	1,78	6,80	—
IIIa	11,15	7,47 d	5,47	4,09 m	3,58	—	—	—
IIIb	11,11	7,33 s	—	4,02 m	3,93	1,67	—	—
IIIc	11,73	8,00 s	—	4,11 m	3,73	—	—	—
IVa	11,11	6,50 s	—	4,09 m	3,72	—	—	2,78 (2H, m, N—CH_2); 1,51 (2H, m, CH_2); 0,88 (3H, t, CH_3)
IVb	11,33	6,66 s	—	4,17 m	3,78	—	—	2,78 (2H, m, N—CH_2); 1,47 ... 1,31 (4H, m, CH_2—CH_2); 0,88 (3H, t, CH_3)
Va	11,11	7,51 d	5,56	4,08 m	3,60	—	—	7,22 (5H, s, C_6H_5); 3,74 (2H, m, NCH_2)
Vb	11,24	7,55 d	5,56	4,11 m	3,58	—	—	7,60 (1H, d, β-CH); 6,16 ... 6,13 (2H, m, CH=CH); 3,75 (2H, m, NCH_2)
VI	11,37	7,55 d	5,64	4,56 m	3,78	—	—	7,37 (5H, s, C_6H_5); 3,86 (2H, m, N—CH_2); 7,64 (2H, s, $CONH_2$)
VII	11,20	6,77 d	5,58	4,06 m	3,55	—	5,88	7,28 (2H, br.s, $CONH_2$)
VIII	11,70	8,04 s	—	3,77 m	4,33	—	—	7,55 (2H, br.s, $CONH_2$); 2,04 (3H, s, $COCH_3$)
IX	11,66	8,00 s	—	4,11 m	3,55	—	5,93	7,29 (2H, br.s, $CONH_2$)
X	11,24	6,46 s	—	4,88 m	3,82	—	5,89	7,22 (10H, s, C_6H_5); 8,33 (1H, t, NHCO); 4,88 (1H, t, 5-NH); 4,36 ... 3,82 (N—CH_2, $CONCH_2$)

The hydrolysis of nitrile IIa proceeds similarly. It should be noted that the hydrolysis is a stepwise process and that, depending on the concentration of the hydrolyzing agent, one can isolate either the β-(1-uracilyl)-α-hydroxypropionamide (VII) intermediate or acid IIIa. The formation of sulfate esters of the hydroxy amide, as in the hydrolysis of α-hydroxy nitriles of alkanecarboxylic acids [9], was not observed. A broad singlet of amide protons and a signal of the proton of a hydroxy group at 5.88 ppm are clearly singled out in the PMR spectrum of amide VII.

Compound VIII was isolated in the bromination of nitrile IIa with bromine in glacial acetic acid. The UV spectrum (λ_{max} 280 nm) provides evidence for the presence of bromine in the 5 position of the uracil ring. In addition to a single of a $C_{(6)}$–H proton, a singlet signal of an acetyl group (2.04 ppm) and a signal of amide protons at 7.55 ppm are observed in the PMR spectrum. The structure of VIII is confirmed by data from the IR spectra – absorption bands of an acetyl group (ν 1740 cm^{-1}) and an unsubstituted amide (ν 3410 cm^{-1}) appear. When amide VIII is treated with a saturated solution of ammonia in methanol, the acetyl group is split out, and amide IX is formed.



IX VIII X

Heating VIII with excess benzylamine at 100°C for 1 h led to X. Data from the UV spectra recorded at pH [sic] (λ_{max} 289 nm) provide evidence for the presence of a benzylamino group in the 5 position. A multiplet signal at 7.22 ppm, which, with respect to its integral intensity, corresponds to the protons of two phenyl groups, a doublet of a hydroxy group (5.89 ppm), and signals of NH protons of amino (4.88 ppm) and amido (8.33 ppm) groups appear in the PMR spectrum. Thus, the β-(5-benzylamino-1-uracilyl)-α-hydroxypropionic acid N-benzylamide structure can be assigned with confidence to X. The transamidation reaction proceeds relatively easily. The absence of substituents attached to the amide nitrogen atom and the presence of hydrogen bromide, which is formed during the reaction [10] have a positive effect on its occurrence.

The physicochemical characteristics of II-X are presented in Tables 1 and 2.

EXPERIMENTAL

The IR spectra of suspensions of the compounds in mineral oil were recorded with a Perkin–Elmer 257 spectrometer. The UV spectra of solutions of the substances ($5 \cdot 10^{-4}$ M) in 0.1 N HCl, the Fluka aqueous buffer solution (pH 7), 0.1 N NaOH, and ethanol were recorded with an SF-26 spectrophotometer. The PMR spectra were recorded with a Bruker WM-90 spectrometer with tetramethylsilane (TMS) as the internal standard. The course of the reactions and the individuality of the compounds were monitored by means of TLC on Silufol UV-254F plates in systems A [chloroform–methanol (4:1)] and B [2-propanol–ammonia–water (7:1:2)] with development with UV light and ninhydrin. Column chromatography was carried out on Amberlite IRA-401 (OH^-) ion-exchange resin with elution with formic acid (stepwise gradient). The melting points were determined with a Kofler apparatus.

The results of elementary analysis for C, H, and N for IIa, b, IIIa-c, IVa, b, Va, b, and VI-X were in agreement with the calculated values.

1-Uracilylacetaldehyde (Ia) and 1-thyminylacetaldehyde (Ib) were obtained by the methods in [11, 12].

β-(1-Uracilyl)-α-hydroxypropionitrile (IIa, $C_7H_7N_3O_3$). A suspension of 15.4 g (0.1 mole) of 1-uracilylacetaldehyde (Ia) in 200 ml of water was added in 3-5 ml portions at 0°C to a solution of 13.0 g (0.2 mole) of potassium cyanide in 30 ml of water. The pH of the solution was brought up to 6.0-6.5 by the addition of acetic acid, and the mixture was stirred for 2 h at 10-15°C. The precipitated IIa was removed by filtration, washed with cold water, and recrystallized from water. The yield was 14.9 g (83%).

β-(1-Thyminyl)-α-hydroxypropionitrile (IIb, $C_8H_9N_3O_3$). This compound was obtained from 1-thyminylacetaldehyde in the same way as IIa.

β-(1-Uracilyl)-α-hydroxypropionic Acid (IIIa, $C_7H_8N_2O_5$). A 9.5-g (0.05 mole) sample of IIa was refluxed for 1 h in 60 ml of 9 N HCl, after which the solution was evaporated in vacuo to 2/3 of its initial volume and cooled. The precipitate was removed by filtration and recrystallized from water–isopropyl alcohol (1:1). The yield was 9.3 g (88%).

β-(1-Thyminyl)-α-hydroxypropionic Acid (IIIb, $C_8H_{10}N_2O_5$). This compound was obtained from nitrile IIb in the same way as IIIa.

β-(5-Bromo-1-uracilyl)-α-hydroxypropionic Acid (IIIc, $C_7H_7BrN_2O_5$). A 2.0-ml sample of bromine was added to a suspension of 4.0 g (0.02 mole) of acid IIIa in 30 ml of water, and the mixture was refluxed for 15 min. The solution was evaporated to dryness in vacuo, and the residue was evaporated repeatedly with 5 ml of water. The residue was stirred with 5 ml of isopropyl alcohol, the mixture was filtered, and the solid material was recrystallized from water. The yield was 3.8 g (69%).

β-(5-Propylamino-1-uracilyl)-α-hydroxypropionic Acid (IVa, $C_{10}H_{15}N_3O_5$). A 2.79-g (0.01 mole) sample of IIIc was refluxed in 15 ml of propylamine for 30 min, after which the mixture was cooled, the precipitated propylamine hydrobromide was removed by filtration, and the filtrate was evaporated to dryness in vacuo. The residue was dissolved in the minimum amount of water, and the solution was applied to a column packed with Amberlite IRA-401 (OH^-) ion-exchange resin and eluted with formic acid (stepwise gradient, 0.05-0.2 M). The fractions containing acid IVa were combined and evaporated in vacuo to a small volume, and the concentrate was maintained at 0°C for 24 h. The precipitated IVa was removed by filtration and washed on the filter with isopropyl alcohol. The yield was 1.21 g (41%).

β-(5-Butylamino-1-uracilyl)-α-hydroxypropionic Acid (IVb, $C_{11}H_{17}N_3O_5$). This compound was obtained from IIIc and butylamine in the same way as IVa.

β-(1-Uracilyl)-α-benzylaminopropionitrile (Va, $C_{14}H_{14}N_4O_3$). A 1.8-g (0.01 mole) sample of IIa was heated in 15 ml of benzylamine on a boiling water bath for 1 h, after which the solution was evaporated in vacuo to 1/3 of its initial volume, and the residue was poured into 50 ml of diethyl ether. The resulting precipitate was removed by filtration and recrystallized from ethanol. The yield was 2.1 g (82%).

β-(1-Uracilyl)-α-furfurylaminopropionitrile (Vb, $C_{12}H_{12}N_4O_3$). This compound was obtained from IIa and 2-furfurylamine in the same way as Va.

β-(1-Uracilyl)-α-benzylaminopropionamide (VI, $C_{14}H_{16}N_4O_3$). A 2.7-g (0.01 mole) sample of nitrile Va was stirred with 5 ml of sulfuric acid, and the mixture was maintained at 20°C for 3 h. The solution was then poured with stirring over ice (~10 ml), and the pH of the solution was brought up to 5 with ammonium hydroxide. The resulting precipitate was removed by filtration, washed on the filter with cold water, and recrystallized from water. The yield was 2.2 g (72%).

β-(1-Uracilyl)-α-hydroxypropionamide (VII, $C_7H_9N_3O_4$). This compound was obtained from IIa in the same way as propionamide VI.

β-(5-Bromo-1-uracilyl)-α-acetoxypropionamide (VIII, $C_9H_{10}BrN_3O_5$). A 9.6-g [4.0 ml (0.06 mole)] of bromine was added with stirring to a suspension of 9.0 g (0.05 mole) of nitrile IIa in 30 ml of glacial acetic acid, and the mixture was maintained at 20°C for 3 h. The solution was evaporated in vacuo to dryness, 5 ml of water was added to the residue, and the mixture was reevaporated. The residue was recrystallized from water. The yield was 9.0 g (56%).

β-(5-Bromo-1-uracilyl)-α-hydroxypropionamide (IX, $C_7H_8BrN_3O_4$). A 10-ml sample of methanol saturated with ammonia was added to 0.32 g (1.0 mmole) of amide VIII, and the mixture was maintained at 20°C for 4 h. The solution was evaporated in vacuo to dryness, and the residue was recrystallized from water. The yield was 0.22 g (79%).

β-(5-Benzylamino-1-uracilyl)-α-hydroxypropionic Acid Benzylamide (X, $C_{21}H_{22}N_4O_4$). A suspension of 6.4 g (0.02 mole) of VIII in 30 ml of benzylamine was heated for 1 h on a boiling-water bath. The resulting solution was evaporated to dryness in vacuo, the oily residue was washed with water (two 5-ml portions), and the residue was dissolved in methanol (15 ml) and maintained at 0°C for 24 h. Compound X was removed by filtration and recrystallized from methanol. The yield was 0.5 g (83%).

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