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ACYCLIC ANALOGS OF PYRIMIDINE NUCLEOSIDES. SYNTHESIS OF 1-(2-HYDROXYETHOXYMETHYL)- AND 1-(4-HYDROXYBUTYL)-5-AMINO DERIVATIVES OF URACIL

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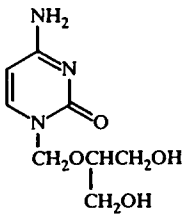
With the objective of discovering new antiviral agents based on acyclic analogs of pyrimidine nucleosides, we have synthesized 1-(2-hydroxyethoxymethyl)- and 1-(4-hydroxybutyl) derivatives of uracil having various aromatic and heterocyclic amino-containing substituents in the 5 position of the pyrimidine ring.

Acyclic analogs of nucleosides have a broad spectrum of biological activity. Among these analogs we observe highly effective antiviral agents used in clinical practice. 9-(2-Hydroxyethoxymethyl)guanine (acyclovir) remains one of the most active antiherpetic drugs today [1, 2]. Its branched analog 9-(1,3-dihydroxy-2-propoxymethyl)guanine (ganciclovir) has demonstrated high efficacy in cytomegaloviral infection [3, 4]. The corresponding carbon chain analog of ganciclovir 9-[4-hydroxy-3-(hydroxymethyl)butyl]guanine (penciclovir) exhibits a spectrum and level of antiviral action similar to that of acyclovir [5]. A series of pyrimidine acyclonucleosides is known which display pronounced antiviral activity. 1-(1,3-Dihydroxy-2-propoxymethyl)cytosine (I) has exhibited high activity with respect to the Epstein–Barr virus and cytomegaloviruses *in vitro* [6]. 1-(2-Hydroxyethoxymethyl)-6-(phenylthio)thymine (II) and its many derivatives have effectively and selectively inhibited the type I human immunodeficiency virus *in vitro* [7,8]. 5-Substituted derivatives of pyrimidine acyclonucleosides, such as 5-benzyl-1-(1,3-dihydroxy-2-propoxymethyl)uracil (III) and its analogs having additional substituents on the aromatic ring have exhibited pronounced inhibitory properties with respect to uridine phosphorylase and have enhanced the antitumor action of 2′-deoxy-5-fluorouridine [9-11]. Recently the synthesis and inhibitory properties of 1-(2-hydroxyethoxymethyl)-5-(phenylthio)- (IV) and -5-(phenylseleno)uracils (V) with respect to uridine phosphorylase have been described in [12].



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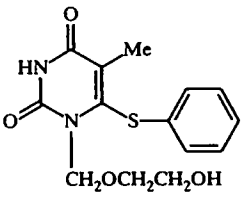

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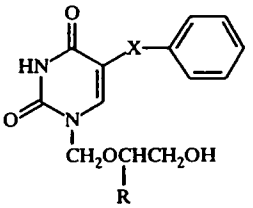

III–V

III X = CH_2, R = CH_2OH; IV, V R = H; IV X = S; V X = Se

In this paper we present the synthesis of novel acyclic analogs of uridine containing an oxygen atom in the side chain, and carbon chain analogs obtained on the basis of 5-amino-substituted derivatives of uracil which are of interest as potential inhibitors of cellular and virus-specific enzymes. The starting 5-(phenylamino)- (VI), 5-(*o*-tolylamino)- (VII), 5-(*m*-tolylamino)- (VIII), and 5-(*p*-tolylamino)uracil (IX) were obtained by the procedure we suggested earlier in [13]. 5-(N-Morpholino)- (X), 5-(N-piperidino)- (XI), and 5-(cyclohexylamino)uracil (XII) have been synthesized by boiling 5-bromouracil in an excess of the corresponding amine [14].

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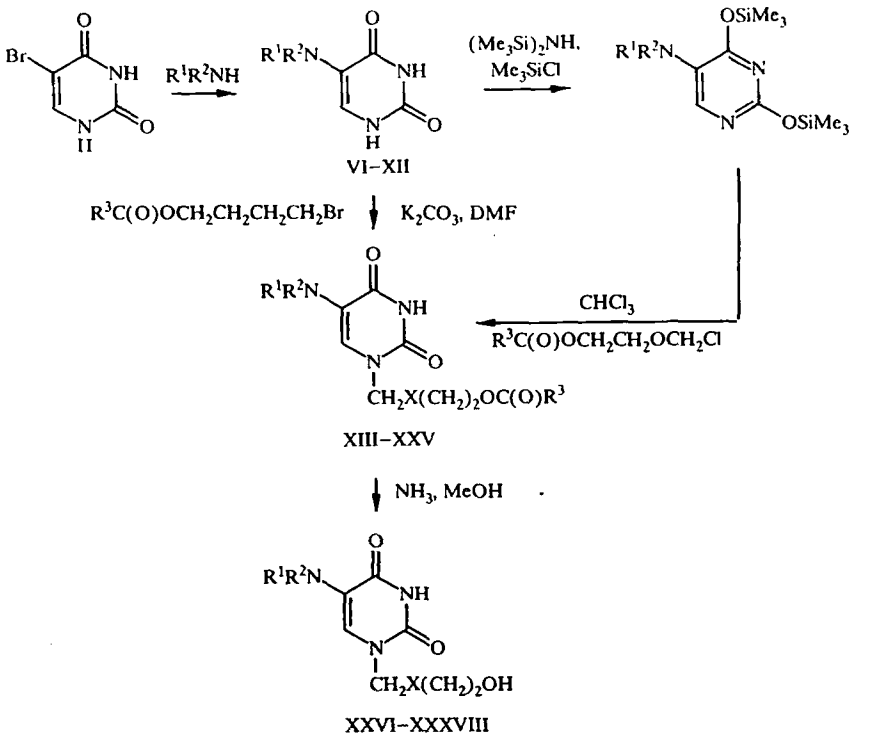

VI, XIII, XIX, XXVI, XXXII R^1 = Ph; VII, XIV, XX, XXVII, XXXIII R^1 = *o*-MeC_6H_4; VIII, XV, XXI, XXVIII, XXXIV R^1 = *m*-MeC_6H_4; IX, XVI, XXII, XXIX, XXXV R^1 = *p*-MeC_6H_4; XII, XXV, XXXVIII R^1 = C_6H_{13}; VI—IX, XII—XVI, XIX—XXII, XXV—XXIX, XXXII—XXXV, XXXVIII R^2 = H; X, XVII, XXIII, XXX, XXXVI R^1,R^2 = N-morpholino; XI, XVIII, XXIV, XXXI, XXXVII R^1,R^2 = N- piperidino ; XIII—XVIII R^3 = Me; XIX—XXV R^3 = Ph; XIII—XVIII, XXVI—XXXI X = CH_2; XIX—XXV, XXXII—XXXVIII X = O

Subsequent alkylation of 5-amino-substituted uracils VI-XI by 4-chloro- or 4-bromobutylacetate in DMF at 80-85°C in the presence of an equimolar amount of potassium carbonate led to a mixture of the corresponding N^1-mono- and N^1,N^3-disubstituted alkylation products, which were separated by preparative chromatography as described for uracil and thymine in [15]. The yield of the target 1-(4-acetoxybutyl)-substituted (XIII-XVIII) was 14-15% (Table 1); in the case of alkylation of uracil derivatives having substituents with a tertiary nitrogen atom (N-morpholino- and N-piperidino derivatives X and XI), we observe a substantial increase (by 20% on the average) in the yield of the N^1-monosubstitution products compared with phenylamino- (VI) and toluidinouracils (VII-IX). Under identical conditions, alkylation of 5-(cyclohexylamino)uracil (XII) led exclusively to tarry products.

Milder conditions for alkylation of silylated amino derivatives of uracil VI-XII by α-haloethers by the Hilbert–Johnson method results in significantly higher selectivity and yield (55% to 95%) of the N^1-monosubstitution products. As the alkylating agents, we used both 2-benzoyloxyethoxymethylchloride obtained by the Henry reaction from paraformaldehyde and ethylene glycol monobenzoate, and 2-acetoxyethoxymethylbromide obtained *in situ* as a result of reaction of 1,3-dioxolane with an equimolar amount of acetylbromide [16]. Alkylation of trimethylsilyl derivatives of 5-(N-piperidino)- (X), 5-(N-morpholino)- (XI), and 5-(cyclohexylamino)uracil (XII) at room temperature in dry chloroform occurs with yields close to quantitative. The corresponding 1-(2-benzoyloxyethoxymethyl)substituted XXIII-XXV are easily crystallized as the hydrochlorides from the reaction mass when it is treated with 95% ethanol. In contrast, upon alkylation of trimethylsilyl derivatives of 5-(phenylamino)- (VI), 5-(*o*-tolylamino)- (VII), 5-(*m*-tolylamino)- (VIII), and 5-(*p*-tolylamino)uracil (IX), we observe formation of 1-(2-benzoyloxyethoxymethyl) derivatives XIX-XXII. These compounds contain arylamino groups in the 5 position and consequently are significantly weaker bases and do not form stable hydrochlorides.

The final removal of acetyl or benzoyl groups by a methanol solution of ammonia saturated at 0°C occurs without important complications, and leads to the final 1-(4-hydroxybutyl)- (XXVI-XXXI) and 1-(2-hydroxyethoxymethyl)-substituted derivatives (XXXII-XXXVIII) (Table 2) in 52-88% yield.

TABLE 1. Characteristics of Intermediate 1-(4-Acetoxybutyl) (XIII-XVIII), 1-(2-Benzoyloxyethoxymethyl) (XIX-XXI, XXIII-XXV), and 1-(2-Acetoxyethoxymethyl) (XXII) Derivatives of 5-Amino-Substituted Uracils

Compound	Empirical formula	Found. % / Calculated %			mp, °C	R_f*	Yield, %
		C	H	N			
XIII	$C_{16}H_{19}N_3O_4$	60,93 / 60,55	6,36 / 6,04	13,00 / 13,24	125 - 127	0,63	34,8
XIV	$C_{17}H_{21}N_3O_4$	61,88 / 61,61	6,79 / 6,39	12,31 / 12,68	113 - 116	0,64	26,7
XV	$C_{17}H_{21}N_3O_4$	61,95 / 61,61	6,77 / 6,39	12,30 / 12,68	93 - 96	0,65	20,7
XVI	$C_{17}H_{21}N_3O_4$	61,96 / 61,61	5,98 / 6,39	12,34 / 12,68	114 - 119	0,61	14,2
XVII	$C_{14}H_{21}N_3O_5$	54,44 / 54,01	7,02 / 6,80	13,23 / 13,50	154 - 156	0,39	40,2
XVIII	$C_{15}H_{23}N_3O_4$	58,34 / 58,24	7,73 / 7,49	13,24 / 13,58	108 - 111	0,31	44,7
XIX	$C_{20}H_{19}N_3O_5$	62,62 / 62,99	5,32 / 5,02	10,71 / 11,02	95 - 98	0,72	80,0
XX	$C_{21}H_{21}N_3O_5$	63,57 / 63,79	5,69 / 5,35	10,38 / 10,63	126 - 128	0,77	64,0
XXI	$C_{21}H_{21}N_3O_5$	64,05 / 63,79	5,68 / 5,35	10,20 / 10,63	123 - 125	0,76	71,2
XXII	$C_{16}H_{19}N_3O_5$	57,21 / 57,65	6,04 / 5,75	12,89 / 12,61	146 - 149	0,64	55,4
XXIII*2	$C_{18}H_{22}ClN_3O_6$	52,79 / 52,50	5,71 / 5,38	10,11 / 10,20	208 - 213	0,28	93,4
XXIV*2	$C_{19}H_{24}ClN_3O_5$	56,03 / 55,68	5,60 / 5,90	10,02 / 10,25	205 - 211	0,49	95,2
XXV*2	$C_{20}H_{25}ClN_3O_5$	57,12 / 56,80	6,22 / 5,96	9,60 / 9,94	183 - 186	0,61	87,4

*In system A.

*2 Compounds XXIII, XXIV, and XXV were obtained as the hydrochlorides.

In the PMR spectra of compounds XXVI-XXXI and XXXII-XXXVIII, the H^6 proton signal appears as a single-proton singlet in the 7.23-7.49 ppm region for compounds with aromatic substituents and in the 6.58-6.99 ppm region for 5-(N-piperidino), 5-(N-morpholino), and 5-(cyclohexylamino) derivatives (Tables 3 and 4). The proton of the exocyclic amino group in the 5 position for the phenylamino and toluidino derivatives is represented by a broad singlet in the 5.90-6.56 ppm region. In the case of the *o*-toluidine derivatives, this signal is shifted upfield by 0.5 ppm on the average compared with the corresponding *meta* and *para* isomers. The chemical shifts and the integrated intensities of the signals from protons of the acyclic moieties of the synthesized compounds on the whole correspond to the analogous parameters for classical pyrimidine acyclonucleosides [17].

Analysis of the electronic structure and geometric parameters of 1-(2-hydroxyethoxymethyl)-5-(phenylamino)uracil (XXXII) *in vacuo* by quantum chemistry (MNDO) and molecular mechanics methods suggests they are close to the analogous characteristics determined both for 1-(2-hydroxyethoxymethyl)-6-phenylthiothymine) (II) and for 5-benzylacyclouridine (III), which is grounds for expecting a selective inhibiting effect of the synthesized compounds on various viral and cellular enzymes.

EXPERIMENTAL

The PMR spectra were recorded on a Tesla BS-567A spectrometer (100 MHz) in DMSO-D_6 solutions, external standard HMDS. TLC was performed on Silufol UV-254 plates, using ethylacetate (A) and a 9:1 chloroform–methanol mixture (B) as the eluents; visualization in iodine vapors. Silica gel L 40/100 was used for preparative chromatography. HPLC was performed on a Milikhrom-2. The melting points were determined in glass capillaries and were uncorrected.

Compounds VI-IX were synthesized according to the method described earlier in [13]; X-XII were synthesized by the method in [14].

TABLE 2. Characteristics of Target 1-(4-Hydroxybutyl) (XXVI-XXXI) and 1-(2-Hydroxyethoxymethyl) (XXXII-XXXVIII) Derivatives of 5-Amino-Substituted Uracils

Compound	Empirical formula	Found, % / Calculated %			mp, °C	R_f*	Yield, %
		C	H	N			
XXVI	$C_{14}H_{17}N_3O_3$	61,87 / 61,08	6,98 / 6,22	14,19 / 15,26	159 - 161	0,43	67,2
XXVII	$C_{15}H_{19}N_3O_3$	63,34 / 62,27	6,96 / 6,62	14,10 / 14,52	105 - 108	0,47	65,4
XXVIII	$C_{15}H_{19}N_3O_3$	63,21 / 62,27	7,23 / 6,62	14,02 / 14,52	156 - 158	0,40	73,6
XXIX	$C_{15}H_{19}N_3O_3$	61,88 / 62,27	7,54 / 6,62	13,78 / 14,52	146 - 150	0,42	78,7
XXX	$C_{12}H_{19}N_3O_4$	52,74 / 53,52	7,91 / 7,11	16,57 / 15,60	145 - 148	0,21	81,0
XXXI	$C_{13}H_{21}N_3O_3$	58,94 / 58,41	8,67 / 7,92	16,92 / 15,82	94 - 96	0,24	88,0
XXXII	$C_{13}H_{15}N_3O_4$	55,68 / 56,31	5,82 / 5,45	15,94 / 15,15	123 - 126	0,56	74,0
XXXIII	$C_{14}H_{17}N_3O_4$	58,36 / 57,72	6,18 / 5,88	14,01 / 14,42	165 - 167	0,56	75,8
XXXIV	$C_{14}H_{17}N_3O_4$	58,66 / 57,72	6,12 / 5,88	13,98 / 14,42	122 - 124	0,53	67,9
XXXV	$C_{14}H_{17}N_3O_4$	58,59 / 57,72	5,10 / 5,88	15,24 / 14,42	82 - 85	0,60	74,7
XXXVI	$C_{11}H_{17}N_3O_5$	47,41 / 48,70	6,78 / 6,32	16,36 / 15,49	169 - 170	0,35	70,7
XXXVII	$C_{12}H_{19}N_3O_4$	52,77 / 53,52	6,52 / 7,11	16,92 / 15,60	132 - 135	0,41	52,2
XXXVIII	$C_{13}H_{21}N_3O_4$	56,23 / 55,11	7,93 / 7,47	13,94 / 14,83	154- 157	0,30	61,6

*In system B.

1-(4-Acetoxybutyl)-5-phenylaminouracil (XIII). A suspension of 3.0 g (14.8 mmoles) 5-phenylaminouracil VI and 2.0 g (14.5 mmoles) potassium carbonate in 100 ml dry DMF was stirred for 1 h at 80-85°C. Then 2.2 ml (15.2 mmoles) 4-bromobutylacetate was added and the reaction mixture was stirred at this temperature for 8 h. Then it was cooled and filtered. The filtrate was evaporated down under vacuum and the residue was treated with 100 ml of boiling 2-propanol. The hot solution was filtered and evaporated down under vacuum. The residue was dissolved in 10 ml chloroform, transferred to a column packed with silica gel (30 × 2.5 cm), and eluted with chloroform. After evaporation of the eluate, we obtained 1.5 g (22.9%) 1,3-bis(4-acetoxybutyl)-5-phenylaminouracil in the form of a viscous yellow oil. The column was eluted with a chloroform–2-propanol system (5:1). The eluate was evaporated under vacuum and the residue was recrystallized from ethylacetate. Obtained: 1.6 g (34.8%) compound XIII. White crystals; mp 125-127°C.

Compounds XIV-XVIII were obtained similarly.

1-(2-Benzoyloxyethoxymethyl)-5-phenylaminouracil (XIX). A mixture of 2.0 g (9.84 mmoles) 5-phenylaminouracil VI, 50 ml hexamethyldisilazane, 1 ml DMF, and 0.5 ml trimethylchlorosilane was boiled (while protected from moisture in the air) for 8 h until a transparent solution was formed. The excess hexamethyldisilazane was driven off under vacuum. The residue was dissolved in 20 ml methylene chloride and 2.2 g (10.2 mmoles) 2-benzoyloxyethoxymethylchloride was added. This was stirred at room temperature for 24 h, then 10 ml 2-propanol, 20 ml H_2O, and 5 ml NH_4OH were added to the reaction mixture; the organic layer was separated, dried over $MgSO_4$, filtered, and evaporated down. The residue was recrystallized from an ethylacetate–hexane (1:1) mixture and 3.0 g (80%) XIX was obtained. Light yellow crystals; mp 95-98°C.

Compounds XX and XXI were synthesized by a method similar to that described for XIX.

1-(2-Acetyloxyethoxymethyl)-5-(*p*-tolylamino)uracil (XXII). A mixture of 2.0 g (9.21 mmoles) 5-(*p*-tolylamino)uracil IX, 50 ml hexamethyldisilazane, and 0.5 ml trimethylchlorosilane was boiled (while protected from moisture in the air) for 8 h until a transparent solution was formed. The excess hexamethyldisilazane was driven off under vacuum and the residue was

TABLE 3. Parameters of PMR Spectra for 1-(4-Acetoxybutyl) (XIII-XVIII) and 1-(4-Hydroxybutyl) (XXVI-XXXI) Derivatives of 5-Amino-Substituted Uracil

Compound	Chemical shift, d, ppm			
	R^1R^2N	H^6 s (1H)	$NCH_2CH_2CH_2CH_2O$	$OC(O)R^3$ or OH
XIII	6,34 br.s (1H); 6,49...7,15 m (5H)	7,40	1,47...1,76 m (4H); 3,70 t (6Hz, 2H); 3,95 t (6Hz, 2H)	1,87 s (3H)
XIV	2,13 s (3H); 5,71 br.s (1H); 6,55...7,10 m (4H)	7,17	1,49...1,81 m (4H); 3,69 t (6Hz, 2H); 3,93 t (6Hz, 2H)	1,85 s (3H)
XV	2,10 s (3H); 6,44...7,09 m (5H)	7,41	1,44...1,68 m (4H); 3,68 t (6Hz, 2H); 3,95 t (6Hz, 2H)	1,88 s (3H)
XVI	2,08 s (3H); 6,44 br.s (1H); 6,60...6,95 m (4H)	7,32	1,41...1,70 m (4H); 3,65 t (6Hz, 2H); 3,93 t (6Hz, 2H)	1,88 s (3H)
XVII	2,75...2,94 m (4H); 3,53...3,76 m (4H)	6,89	1,46...1,74 m (4H); 3,65 t (6Hz, 2H); 3,94 t (6Hz, 2H)	1,88 s (3H)
XVIII	1,30...1,78 m (6H); 2,62...2,92 m (4H)	6,80	1,30...1,78 m (4H); 3,65 t (6Hz, 2H); 3,93 t (6Hz, 2H)	1,87 s (3H)
XXVI	6,51...7,17 m (6H)	7,49	1,27...1,79 m (4H); 3,28...3,50 m (4H)	4,56 t (5Hz, 1H)
XXVII	2,12 s (3H); 5,90 br.s (1H); 6,50...7,06 m (4H)	7,25	1,32...1,76 m (4H); 3,32...3,54 m (4H)	4,59 t (5 Hz, 1H)
XXVIII	2,11 s (3H); 6,34...7,03 m (5H)	7,39	1,32...1,78 m (4H); 3,29...3,51 m (4H)	4,58 t (5 Hz, 1H)
XXIX	2,12 s (3H); 6,51 br.s (1H); 6,63...7,02 m (4H)	7,36	1,32...1,82 m (4H); 3,32...3,52 m (4H)	4,64 t (5 Hz, 1H)
XXX	2,69...2,90 m (4H); 3,54...3,80 m (4H)	6,94	1,28...1,71 m (4H); 3,23...3,51 m (4H)	4,51 t (5 Hz, 1H)
XXXI	1,28...1,69 m (6H); 2,62...2,84 m (4H)	6,88	1,28...1,69 m (4H); 3,26...3,52 m (4H)	4,49 t (5 Hz, 1H)

dissolved in 30 ml chloroform. A total of 0.8 g (10.82 mmoles) freshly distilled acetylbromide was added to 0.8 ml (11.45 mmoles) 1,3-dioxolane cooled down to −20°C. The mixture was held at room temperature for 1 h and then diluted with 5 ml chloroform. The solution obtained was added to a solution of the trimethylsilyl derivative IX. The reaction mixture was stirred at room temperature for 24 h. Then 10 ml 2-propanol, 20 ml H_2O, and 5 ml NH_4OH were added. The organic layer was separated and dried with $MgSO_4$, then filtered and evaporated down. The residue was dissolved in a minimal volume of chloroform, transferred to a column packed with silica gel (25 × 2.5 cm), and eluted first with chloroform and then with a chloroform−2-propanol mixture (9:1). The eluate containing the target product was evaporated down and recrystallized from 2-propanol. Obtained: 1.7 g (55.4%) XXII. Light yellow crystals; mp 146-149°C.

1-(2-Benzoyloxyethoxymethyl)-5-(N-morpholino)uracil hydrochloride (XXIII). A mixture of 2.0 g (10.1 mmoles) 5-(N-morpholino)uracil X, 50 ml hexamethyldisilazane, and 0.5 ml trimethylchlorosilane was boiled (while protected from moisture in the air) for 8 h until a transparent solution was formed. The excess hexamethyldisilazane was driven off under vacuum and the residue was dissolved in 25 ml dry chloroform. 2-Benzoyloxyethoxymethylchloride (2.2 g, 10.2 mmoles) was added and it was stirred at room temperature for 24 h. A total of 5 ml 95% ethanol was added to the reaction mixture and it was held at −5°C for 24 h. The light rose crystalline precipitate was filtered off and washed with 10 ml diethyl ether. Obtained: 3.9 g (93.4%) XXIV; mp 208-211°C (decomp.).

Compounds XXIV and XXV were synthesized by a method similar to that described for XXIII.

1-(4-Hydroxybutyl)-5-phenylaminouracil (XXVI). 1-(4-Acetoxybutyl)-5-phenylaminouracil XIII (1.0 g, 3.15 mmoles) and 25 ml of a methanol solution of ammonia saturated at 0°C were held in a hermetically sealed container at room temperature for 24 h. The solvent was driven off under vacuum. The residue was triturated twice with 15 ml diethyl ether and recrystallized from an ethylacetate−methanol mixture (1:1). Obtained: 0.6 g (67.2%) XXVI in the form of a white crystalline material; mp 159-161°C.

TABLE 4. Parameters of PMR Spectra of 1-(2-Benzoyloxyethoxymethyl) (XIX-XXI, XXIII-XXV), 1-(2-Acetoxyethoxymethyl) (XXII), and 1-(2-Hydroxyethoxymethyl) (XXXII-XXXVIII) Derivatives of 5-Amino-Substituted Uracil

Compound	Chemical shift, d, ppm				
	R^1R^2N	H^6 s (1H)	NCH_2O s (2H)	OCH_2CH_2O	$OC(O)R^3$ or OH
XIX	6,27 br.s (1H); 6,55...7,18 m (5H)	7,30	5,18	3,87 t (5 Hz, 2H); 4,36 t (5 Hz, 2H)	7,18...8,00 m (5H)
XX	2,14 s (3H); 6,20 br.s (1H); 6,68...7,11 m (4H)	7,24	5,18	3,86 t (5 Hz, 2H); 4,37 t (5 Hz, 2H)	7,30...7,97 m (5H)
XXI	2,15 s (3H); 6,40...7,00 m (5H)	7,32	5,16	3,87 t (5 Hz, 2H); 4,37 t (5 Hz, 2H)	7,38...7,98 m (5H)
XXII	2,14 s (3H); 6,55 br.s (1H); 6,73...7,03 m (4H)	7,35	5,12	3,48 t (5 Hz, 2H); 4,29 t (5 Hz, 2H)	1,91 s (3H)
XXIII	2,79...3,00 m (4H); 3,56...3,74 m (4H)	7,29	5,10	3,81 t (5 Hz, 2H); 4,33 t (5 Hz, 2H)	7,37...7,92 m (5H)
XXVI	1,63...2,00 m (6H); 3,09...3,30 m (4H)	8,03	5,12	3,76 t (5 Hz, 2H); 4,35 t (5 Hz, 2H)	7,36...7,93 m (5H)
XXV	0,99...2,11 m (10H)	8,05	5,18	3,84 t (5 Hz, 2H); 4,37 t (5 Hz, 2H)	7,34...7,95 m (5H)
XXXII	6,60...7,22 m (6H)	7,46	5,10	3,52 s (4H)	4,79 br.s (1H)
XXXIII	2,15 s (3H); 6,02 br.s (1H); 6,63...7,08 m (4H)	7,23	5,06	3,50 s (4H)	4,79 br.s (1H)
XXXIV	2,13 s (3H); 6,37...7,05 m (5H)	7,43	5,06	3,47 s (4H)	4,84 br.s (1H)
XXXV	2,12 s (3H); 6,56 br.s (1H); 6,67...7,00 m (4H)	7,35	5,08	3,50 s (4H)	4,78 br.s (1H)
XXXVI	2,74...2,99 m (4H); 3,40...3,70 m (4H)	6,96	5,06	3,51 s (4H)	4,80 br.s (1H)
XXXVII	1,40...1,74 m (6H); 2,71...2,94 m (4H)	6,99	5,10	3,55 s (4H)	4,88 br.s (1H)
XXXVIII	0,98...2,08 m (10H)	6,58	5,03	3,47 s (4H)	4,44 br.s (1H)

Compounds XXVII-XXXV were synthesized by a method similar to that described for XXVI.

1-(2-Hydroxyethoxymethyl)-5-(N-morpholino)uracil (XXXVI). A mixture of 1.5 g (3.6 mmoles) of 1-(2-benzoyloxyethoxymethyl)-5-(N-morpholino)uracil hydrochloride XXIII and 25 ml of a methanol solution of ammonia saturated at 0°C were held in a hermetically sealed container at room temperature for 24 h. The solvent was driven off under vacuum and the residue was washed with diethyl ether (2 × 15 ml) and extracted with 50 ml of boiling 2-propanol. The hot extract was filtered and held at −5°C for 24 h. The white crystalline precipitate was filtered off and washed with 10 ml diethyl ether. Obtained: 0.7 g (70.7%) XXXVI; mp 169-170°C.

Compounds XXXVII and XXVIII were synthesized by a method similar to that described for XXVI.

REFERENCES

1. G. B. Elion, P. A. Furman, J. A. Fyfe, P. de Miranda, L. Beauchamp, and H. J. Schaeffer, Proc. Nat. Acad. Sci. USA, **74**, 5716 (1977).
2. H. J. Schaeffer, L. Beauchamp, P. de Miranda, G. B. Elion, D. J. Bauer, and P. Collins, Nature, **272**, 583 (1978).
3. M. J. Tocci, T. J. Livelli, and H. C. Perry, Antimicrob. Agents Chemother., **25**, 247 (1984).
4. K. K. Biron, S. C. Stanat, J. B. Sorrell, J. A. Fyfe, P. M. Keller, C. U. Lambe, and D. J. Nelson, Proc. Nat. Acad. Sci. USA, **82**, 2473 (1985).
5. M. R. Boyd, T. H. Bacon, D. Sutton, and M. Cole, Antimicrob. Agents Chemother., **31**, 1238 (1987).
6. L. M. Beauchamp, B. L. Serling, J. E. Kelsey, K. K. Biron, P. Collins, J. Selway, J.-C. Lin, and H. J. Schaeffer, J. Med. Chem., **31**, 144 (1988).

7. T. Miyasaka, H. Tanaka, M. Baba, H. Hayakawa, R. T. Walker, J. Balzarini, and E. De Clercq, J. Med. Chem., **32**, 2507 (1989).
8. H. Tanaka, H. Takashima, M. Ubasawa, K. Sekiya, I. Nitta, M. Baba, S. Shigeta, R. T. Walker, E. De Clercq, and T. Miyasaka, J. Med. Chem., **35**, 4713 (1992).
9. M. Y. W. Chu, F. N. M. Naguib, M. H. Iltzsch, M. H. El Kouni, S. H. Chu, S. Cha, and P. Calabresi, Cancer Res., **44**, 1852 (1984).
10. K. S. Park, M. H. El Kouni, T. A. Krenitsky, S. H. Chu, and S. Cha, Biochem. Pharmacol., **35**, 3853 (1986).
11. T.-S. Lin and M.-C. Liu, J. Med. Chem., **28**, 971 (1985).
12. N. M. Goudgaon, F. N. M. Naguib, M. H. El Kouni, and R. F. Schinazi, J. Med. Chem., **36**, 4250 (1993).
13. A. A. Ozerov, M. S. Novikov, A. K. Brel', and G. N. Solodunova, Khim. Geterotsikl. Soedin., No. 5, 691 (1998).
14. A. P. Phillips, J. Am. Chem. Soc., **73**, 1061 (1951).
15. B. R. Baker, G. D. F. Jackson, and G. Chhedda, J. Pharm. Sci., **54**, 1617 (1965).
16. H. Matsumoto, C. Kaneko, K. Yamada, T. Takeuchi, T. Mori, and Y. Mizuno, Chem. Pharm. Bull., **36**, 1153 (1980).
17. H. M. Abrams, L. Ho, and S. H. Chu., J. Heterocycl. Chem., **18**, 947 (1981).