ANALOGS OF PYRIMIDINE NUCLEOSIDES

VII.* 5-SUBSTITUTED N_1-(1,4-DIHYDROXY-2-BUTYL)- AND N_1-(2,5-DIHYDROXY-1-PENTYL)URACILS

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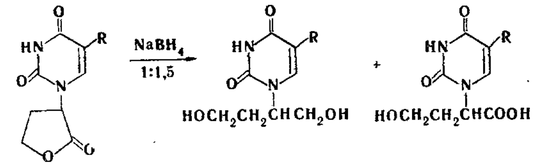
A new method for the synthesis of N_1-(dihydroxyalkyl)uracils by reduction of substituted α-(1-uracilyl)- and γ-[(1-uracilyl)methyl]-γ-butyrolactones with sodium borohydride was found.

N_1-Dihydroxyalkyl derivatives of uracil and thymine can be considered to be analogs of pyrimidine nucleosides in which the sugar residue is replaced by a polymethylene chain. The synthesis of model compounds that differ with respect to the length and configuration of the alkyl chain and thereby with respect to the spatial orientation of the hydroxyl groups (both between one another and with respect to the pyrimidine base) seems of great interest. A study of the physicochemical characteristics of model compounds and their reactions with some nucleic metabolism enzymes, in particular with nucleosidekinases, may give important information regarding the mechanism of the bonding of the enzyme with the substrate and its analogs.

Baker and co-workers [2-4] have synthesized a number of N_1-hydroxyalkyl derivatives of uracil and have studied their bonding with thymidinekinase, but they were unable to obtain N_1-dihydroxyalkyl derivatives having a greater affinity for the enzyme than the monohydroxy compounds. This is apparently explained by the fact that in the N_1-(3,5-dihydroxy-1-pentyl)uracil investigated by Baker and co-workers the spatial orientation of the hydroxyl groups differs considerably from the orientation of the 3'- and 5'-hydroxyl groups in desoxynucleosides.

N_1-Dihydroxyalkyl derivatives of 5-fluorouracil are of interest as potential inhibitors of thymidylatesynthetases [3]. It should also be noted that N_1-dihydroxyalkyluracils and their phosphate esters are starting compounds for the synthesis of model analogs of oligo- and polynucleotides [5]. We have found a convenient method for the synthesis of 5-substituted N_1-(1,4-dihydroxyalkyl)uracils (IIa-c, Table 1) by reduction of uracilyllactones Ia-c, which we have previously described [6], with sodium borohydride in aqueous solution.



I a-c II a-c III a-c

I-III a R = H; b R = CH_3; c R = F

The double bond in the pyrimidine ring is not involved in the reduction, as attested to by the absence of a change in the optical density of the solution at 260-270 nm during the reaction. In addition to reduction,

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[*] See [1] for communication VI.

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TABLE 1. Substituted Uracils

Compound	mp, °C	Empirical formula	Found, %			Calculated, %			UV spectrum						IR spectrum, cm^{-1}			Yield, %
									pH 2		pH 7		pH 11					
			C	H	N	C	H	N	λ_{max}, nm	$\varepsilon \cdot 10^{-3}$	λ_{max}, nm	$\varepsilon \cdot 10^{-3}$	λ_{max}, nm	$\varepsilon \cdot 10^{-3}$	δ_{OH}	ν_{OH}	$\nu_{C=O}$	
IIa	108–110	$C_8H_{12}N_2O_4$	48,2	6,2	14,1	48,0	6,0	14,0	266	9,6	266	9,6	265	7,1	1050	3340	1680–1720	53
IIb	178–179	$C_9H_{14}N_2O_4$	51,4	6,4	13,1	50,5	6,6	13,1	271	10,7	270	9,0	271	5,4	1050	3320, 3420	1680–1700	60
IIc	168–170	$C_8H_{11}N_2O_4$	43,8	4,8	13,5	44,0	5,1	12,8	268	10,4	268	9,6	272	6,9	1050	3300	1670–1720	35
VIa	243–245	$C_9H_{10}N_2O_4$	51,6	5,1	13,1	51,4	4,8	13,3	265	14,2	266	13,3	264	11,4	—	—	1670–1700, 1780	62
VIb	213–215	$C_{10}H_{12}N_2O_4$	53,1	5,5	12,4	53,6	5,4	12,5	272	8,6	272	8,9	270	7,1	—	—	1670–1700, 1770	30
VIc	263–265	$C_9H_9ClN_2O_4$	44,8	3,3	11.5	44,2	3,7	11,4	282	9,4	280	10,6	280	6,7	—	—	1680–1720, 1780	52
VId	256–258	$C_9H_9BrN_2O_4$	37,2	2,8	9,1	37,4	3,1	9,7	282	9,2	282	9,2	280	6,6	—	—	1670–1720, 1780	29
VIIa	123–124	$C_9H_{14}N_2O_4$	49,9	6,7	12,9	50,4	6,6	13,1	267	10,4	267	10,0	264	7,4	1050, 1100	3320	1670–1700	22
VIIb	85–87	$C_{10}H_{16}N_2O_4$	52,2	7,3	12,3	52,6	7,1	12,3	271	11,0	270	10,0	272	6,5	1050, 1100	3370	1670–1700	43

side hydrolysis of the lactone ring to give 5-substituted N_1-(1-carboxy-3-hydroxy-1-propyl)uracils (IIIa-c) occurs. Reduction by means of $LiAlH_4$ in this case is not expedient, inasmuch as neither the starting materials nor the final products are soluble in ether. In addition, the probability of saturation of the C = C double bond in the uracil increases during reduction with $LiAlH_4$ [3].

In contrast to starting Ia-c, the IR spectra of (dihydroxybutyl)uracils IIa-c do not contain a band at 1770 cm^{-1} (lactone $\nu_{C=O}$) but do have an intense ν_{OH} absorption band at 3300-3420 cm^{-1} and a band at 1050 cm^{-1}, which can be assigned to the primary hydroxyl δ_{OH} frequency, inasmuch as it is absent in starting Ia-c. The position of the ν_{NH} band (3160-3200 cm^{-1}) changes only slightly in all of the compounds under consideration.

In the PMR spectrum of N_1-(1,4-dihydroxy-2-butyl)thymine in dimethyl sulfoxide (DMSO) the CH protons in the 6 position of the uracil ring are represented by a singlet that is broadened because of spin–spin coupling with the CH_3 proton; this constitutes evidence in favor of the presence of a substituent attached to N_1 of the uracil ring [7].

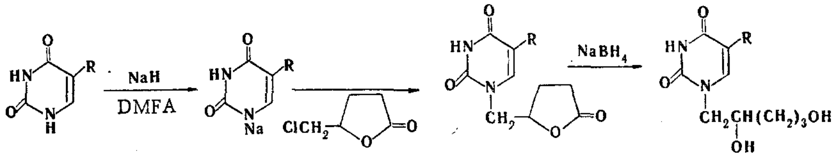
In order to obtain 5-substituted N_1-(2,5-dihydroxy-1-pentyl)-uracils, we examined the alkylation of uracil and thymine with γ-chloromethylbutyrolactone. The activity of the halogen in γ-chloromethylbutyrolactone is considerably less than that in α-bromo-substituted butyrolactones. As a consequence of this, γ-chloromethylbutyrolactone does not alkylate silyl derivatives of uracil and thymine. However, the reaction was found to be realizable with the more reactive sodium derivatives (Va, b) under more severe conditions than in the case of α-bromobutyrolactone [6]. We used this method to synthesize uracil and thymine derivatives VIa,b (Table 1). Derivatives (VIc,d, Table 1) of 5-chloro- and 5-bromouracil were obtained by direct halogenation of lactone VIa as described in [6]. (See scheme on top of following page.)

N_1-(2,5-Dihydroxy-1-pentyl) derivatives (VIIa,b, Table 1) of uracil and thymine were obtained by reduction of lactones VIa,b with sodium borohydride.

EXPERIMENTAL

The melting points were determined with a Boëtius stage. The PMR spectra of DMSO solutions were recored with a Perkin–Elmer R-12A spectrometer (60 MHz) with tert-butyl alcohol as the interal standard (δ 1.23 ppm). The IR spectra of Nujol suspensions of the compounds were recorded with a UR-20 spectrometer. The UV spectra were obtained with a Specord spectrophotomer.

N_1-(1,4-Dihydroxy-2-butyl)-5-methyluracil (IIb). A suspension of 6.47 g (0.031 mole) of α-(5-methyluracilyl)-γ-butyrolactone in 100 ml of water was added with stirring in the course of 15 min to a solution of 1.75 g (0.045 mole) of sodium borohydride in 50 ml of water, after which the mixture was stirred at room temperature for 1 h and acidified to pH 5-6 with dilute acetic acid (1 : 1). Distilled water was then added up to a volume of 300 ml, and the mixture was passed through a column containing strongly acidic Amberlite IR-120 cation-exchange resin (H^+ form). The column was eluted with water until the eluate was neutral,



IVa, b   Va, b   VIa, b   VIIa, b

IV–VII a R=H; b R=CH$_3$

and the eluate (1000 ml) was passed through a column containing weak Dowex-3 anion-exchange resin (OH$^-$ form). The product was eluted successively with water and 0.5 N NH$_4$OH.

The aqueous eluate was vacuum evaporated to dryness, the residue was dissolved in 50 ml of methanol, the solvent was again evaporated, and the residue was dissolved in 50 ml of ethanol. It was precipitated by the addition of ethyl acetate to give 4.43 g of uracil IIb as colorless crystals. The product was recrystallized from ethanol–ethyl acetate to give 3.9 g (60%) of IIb. PMR spectrum: δ 11.1 (NH), 7.47 (6-H), and 1.89 (CH$_3$). The adduct with phenyl isocyanate had mp 191-193°. Found: C 61.2; H 5.4; N 12.0%. $C_{23}H_{24}N_4O_6$. Calculated: C 61.0; H 5.4; N 12.4%.

The precipitate that formed during evaporation of the ammoniacal eluate was recrystallized from aqueous alcohol to give 1.13 g of the ammonium salt of acid IIIb with mp 257-262°. IR spectrum: 1690 ($\nu_{C=O}$) 1610 cm^{-1} (ν_{COO^-}). The salt was dissolved in water, and the solution was passed through a column containing Amberlite IR-120 cation-exchange resin. The eluate was evaporated to give 1.0 g (15%) of 1-(1-carboxy-3-hydroxy-1-propyl)-5-methyluracil (IIIb) with mp 267-269° (from acetone). IR spectrum: ν 1690 (C=O), 1230, and 1725 (COO$^-$), 3190 (NH), and 3400 cm^{-1} (OH). Found: C 47.0; H 5.6; N 11.8%. $C_9H_{12}N_2O_5$. Calculated: C 47.4; H 5.3; N 12.3%.

Compounds IIa, IIc, VIIa, and VIIb were similarly obtained (see Table 1).

γ-[(1-Uracilyl)methyl]-γ-butyrolactone (VIa). Absolute dimethylformamide (25 ml) was added to 2.1 g (0.019 mole) of the uracil, the mixture was stirred, and 0.45 g (0.019 mole) of sodium hydride was added rapidly, during which the temperature of the reaction mixture rose to 36° and then gradually fell to room temperature. The mixture was stirred at room temperature for 2 h, after which it was cooled with ice and treated with a solution of 5.2 g (0.04 mole) of γ-chloromethylbutyrolactone in 10 ml of DMFA. The mixture was stirred at room temperature for 30 min and at 150° for 1.5 h, after which the excess DMFA was removed by vacuum distillation. The residue was removed by filtration and dissolved in hot ethanol. The insoluble portion of the material was the uracil [1.4 g (67%)]. Cooling of the ethanol solution precipitated 0.8 g (21%) of lactone VIa.

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