ANALOGS OF PYRIMIDINE NUCLEOSIDES

VIII.* SYNTHESIS AND PROPERTIES OF SUBSTITUTED α-(1-URACILYL)-γ-METHYL-γ-BUTYROLACTONES AND N_1-(1,4-DIHYDROXY-2-PENTYL)URACILS

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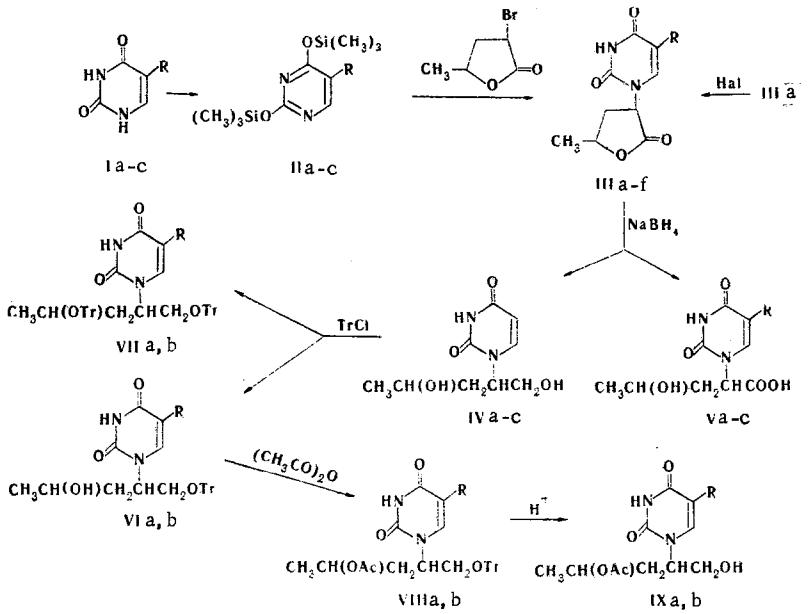
The corresponding α-(1-uracilyl)-γ-methyl-γ-butyrolactones, the reduction of which with sodium borohydride gives 5-substituted N_1-(1,4-dihydroxy-2-pentyl)uracils, were obtained by alkylation of 2,4-bis(trimethylsilyl) derivatives of uracil, thymine, and 5-fluorouracil with α-bromo-γ-methylbutyrolactone. Diol derivatives with respect to both the primary and secondary hydroxyl groups were obtained by selective protection. On the basis of an analysis of the PMR spectra, it is shown that the uracilyllactones are mixtures of the cis and trans isomers, whereas N_1-(1,4-dihydroxy-2-pentyl)uracils are mixtures of diastereomers.

In a continuation of our investigations of N_1-(dihydroxyalkyl) derivatives of pyrimidine bases as analogs of pyrimidine nucleosides [1] we have synthesized 5-substituted N_1-(1,4-dihydroxy-2-pentyl)uracils (IV) containing one primary and one secondary hydroxyl group and thereby having certain advantages as monomers for the synthesis of models of oligonucleotides as compared with the compounds we have previously described [1].



a R=H; b R=CH_3; c R=F; d R=Cl; e R=Br; f R=I; Tr=$C(C_6H_5)_3$; Ac=$COCH_3$

*See [1] for communication VII.

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TABLE 1. α-(1-Uracilyl)-γ-methyl-γ-butyrolactones (III) and N_1-(1,4-Dihydroxy-2-pentyl)- (IV) and N_1-(1-Carboxy-3-hydroxybutyl)-uracils (V)

Compound	mp, °C	Rf in systems		Empirical formula	Found, %			Calc., %			UV spectra pH 2		UV spectra pH 12		Yield, %
		A	B		C	H	N	C	H	N	λmax, nm	ε · 10⁻³	λmax, nm	ε · 10⁻³	
IIIa	235—236	0,82	0,72	$C_9H_{10}N_2O_4$	51,4	4,9	13,2	51,4	4,8	13,3	264	9,8	266	7,8	70
IIIb	258—260	0,89	0,82	$C_{10}H_{12}N_2O_4$	53,6	5,4	12,6	53,6	5,4	12,5	268	9,8	272	8,0	75
IIIc	223—225	0,79	0,78	$C_9H_9FN_2O_4$	47,5	4,0	12,3	47,4	4,0	12,3	269	10,5	275	7,0	49
IIId	280 (dec.)	0,75	0,74	$C_9H_9ClN_2O_4$	44,1	3,7	11,2	44,2	3,7	11,4	276	9,2	277	6,0	59
IIIe	300 (dec.)	0,75	0,73	$C_9H_9BrN_2O_4$	37,4	3,4	9,6	37,4	3,1	9,7	279	10,2	278	7,6	75
IIIf	310 (dec.)	0,74	0,72	$C_9H_9IN_2O_4$	32,2	2,6	8,4	32,2	2,7	8,3	282	6,0	278	5,4	55
IVa	153—154	0,89	0,40	$C_9H_{14}N_2O_4$	50,6	6,7	13,0	50,5	6,5	13,1	266	9,7	266	7,5	60
IVb	167—168	0,70	0,49	$C_{10}H_{16}N_2O_4$	52,4	7,3	12,4	52,6	7,0	12,3	273	9,2	273	7,1	72
IVc	174—176	0,70	0,53	$C_9H_{13}FN_2O_4$	46,6	5,6	11,7	46,6	5,6	12,1	276	8,7	276	6,5	46
Va	170—175	0,52	0,47	$C_9H_{15}N_3O_5$	44,1	6,3	17,0	44,1	6,2	17,1	265	9,8	267	7,4	7
Vb	230—235	0,68	0,61	$C_{10}H_{17}N_3O_5$	46,2	6,6	16,1	46,3	6,6	16,2	271	9,2	273	7,1	12
Vc	184—187	0,67	0,65	$C_9H_{14}FN_3O_5$	45,8	5,5	16,7	45,6	5,3	15,9	273	8,9	274	7,0	20

TABLE 2. Substituted N_1-(1,4-Dihydroxy-2-pentyl)uracils (VI-IX)

Compound	mp, °C	R_f*	Empirical formula	Found, %			Calc., %			UV spectrum in ethanol		IR spectrum, νOH, cm⁻¹	Yield, %
				C	H	N	C	H	N	λmax, nm	ε · 10⁻³		
VIa	195—196	0,58	$C_{28}H_{28}N_2O_4$	73,6	6,1	6,3	73,6	6,2	6,2	268	9,6	3440	54
VIb	175—176	0,64	$C_{29}H_{30}N_2O_4$	74,2	6,4	5,9	73,9	6,4	6,0	273	9,7	3440	62
VIIa	234—235	0,93	$C_{47}H_{42}N_2O_4$	80,9	5,9	4,1	80,8	6,0	4,0	268	4,0	—	1
VIIb	239—240	0,95	$C_{48}H_{44}N_2O_4$	80,9	6,3	3,9	80,7	6,2	3,9	273	3,9	—	1
VIIIa	200—203	0,80	$C_{30}H_{30}N_2O_5$	72,0	6,2	5,6	72,2	6,1	5,6	268	9,0	—	96
VIIIb	111—113	0,92	$C_{31}H_{32}N_2O_5$	72,6	6,2	5,3	72,7	6,2	5,5	273	9,4	—	93
IXa	146—147	0,13	$C_{11}H_{16}N_2O_5$	51,3	6,5	11,0	51,2	6,3	11,0	268	9,7	3380	72
IXb	205—206	0,30	$C_{12}H_{18}N_2O_5$	53,2	6,8	10,2	53,3	6,7	10,4	273	10,0	3380	70

* See the experimental section for the TLC conditions.

TABLE 3. PMR spectra of α-(1-Uracilyl)-γ-methyl-γ-butyrolactones

Compound	Chemical shift, δ, ppm							J, Hz			
	5'-CH_3	3'-H	4'-H	5'-H	6-H	5-H (6-CH_3)	NH	CH_3—5'H	3'H—4'H	4'H—5'H	6H—5H
IIIa cis-	1,43	5,16	1,9—3,0	4,4—4,9	7,58	5,60	11,30	5,8	10,9; 9,3	*	7,7
trans	1,38	5,08						6,1	10,0; 8,5		
IIIb cis-	1,42	5,23	2,0—2,9	4,5—4,9	7,50	1,76	11,30	5,8	11,5; 9,5	9,9; 5,7	1,0 (H—CH_3)
trans	1,38	5,12						6,1	11,6; 9,2		
IIIc cis-	1,44	5,21	2,0—2,9	4,4—4,9	8,08	—	11,90	5,7	11,6; 8,9	*	6,7 (H—F)
trans	1,39	5,08						6,1	10,2; 8,6		

* Not determined because of pronounced overlapping of the signals from both isomers.

The starting substituted α-(1-uracilyl)-γ-methyl-γ-butyrolactones (III) were obtained by alkylation of silyl derivatives of uracil (II) with α-bromo-γ-methylbutyrolactone with removal of the volatile products formed during the reaction by distillation. It was noted that uracil IIb is alkylated at a lower temperature (165) than IIa(180°) and IIc (200°). Considering the possibility of elimination of halogen under the reaction conditions, uracilyllactons IId-f were obtained by direct halogenation of lactone IIIa by the methods that we described in [2].

Reduction of lactones III with sodium borohydride was accomplished by a modified method [1]. 5-Substituted N_1-(1-carboxy-3-hydroxy-1-butyl)uracils (V) (Table 1) are formed as side products.

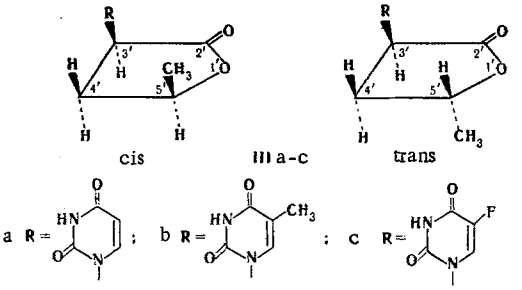
According to [3, 4], tritylation of ribonucleosides gives, depending on the conditions, mono-, di-, and tritrityl derivatives. By changing the ratio of the reacting substances, the temperature, and the time for the reaction of dihydroxy derivatives IV with triphenylchloromethane and by monitoring the course of the

reaction by thin-layer chromatography (TLC), we found conditions under which primarily monotrityl derivatives VI are formed; the small amounts of ditrityl derivatives VII are easily separated owing to their low solubility in polar solvents.

N_1-(1-O-Trityloxy-4-O-acetoxy-2-pentyl)uracils (VIII) were obtained by acetylation of VI [5], and N_1-(1-hydroxy-4-O-acetoxy-2-pentyl)uracils (IX) (Table 2) were obtained after removal of the acid-labile trityl protective group.

Thus, derivatives substituted at the primary or secondary hydroxyl groups were obtained from 5-substituted N_1-(1,4-dihydroxy-2-pentyl)uracils.

The ν_{CO} band at 1770 cm^{-1} is absent in the IR spectra of diols IVa-c, and absorption bands are observed at 3330-3450 cm^{-1} (ν_{OH}) [6]. The ν_{OH} bands are absent in the spectra of VII and VIII, in which both hydroxy groups are protected. The IR spectra of acetates VIII and IX contain the characteristic bands of an acetyl group at 1735 cm^{-1}.



The PMR spectra (Table 3) showed that the uracilyllactones (III) that we synthesized are mixtures of cis and trans isomers. The chemical shifts were assigned on the basis of a comparison of the PMR spectra of III with the spectra of cis- and trans-2-methoxy-4-methyl-γ-butyrolactone [7].

Diols IV have two asymmetric carbon atoms and are evidently mixtures of diastereomers.

EXPERIMENTAL

The purity of the substances was monitored by means of chromatography on "Leningrad medium" paper in the following systems: A) 1-butanol–morpholine–diethylene glycol–water (9 : 3 : 2 : 4) (ascending) and B) ethyl acetate–water–formic acid (60 : 35 : 5) (descending) or by TLC on Silufol UV-254 plates in ethyl acetate. The UV spectra were recorded with a Specord spectrophotometer. The IR spectra of mineral oil or hexachlorobutadiene suspensions were recorded with a UR-20 spectrometer. The PMR spectra of DMSO solutions were obtained with a Perkin–Elmer R-12A spectrometer (60 MHz) with tetramethylsilane as the internal standard.

Substituted α-(1-Uracilyl)-γ-methyl-γ-butyrolactones (IIIa-c, Table 1). A 3-ml sample of trimethylchlorosilane was added to a suspension of 0.1 mole of uracil Ia-c in 30 ml of hexamethyldisilazane [2 ml of dimethylformamide (DMFA) was added in the case of Ib to improve its solubility], and the mixture was heated on an oil bath (150-180°) for 2-4 h; the transparent solution was cooled to 80°, and 35.8 g (0.2 mole) of α-bromo-γ-methylbutyrolactone [8] was added gradually with stirring in the course of 30 min. The flask was fitted with a Dean–Stark trap, and the mixture was stirred vigorously and heated to 165-200°*, during which the excess hexamethyldisilazane and the trimethylbromosilane formed during the reaction were removed by distillation. The mixture was cooled to room temperature, 20 ml of ethanol was added gradually, and the mixture was stirred for 1 h. Precipitated lactones IIIa-c were separated and recrystallized from water.

5-Substituted N_1-(1,4-Dihydroxy-2-pentyl)- (IVa-c) and N_1-(1-Carboxy-3-hydroxy-1-butyl)uracils (Va-c, Table 1). A solution of 4.0 g (0.1 mole) of $NaBH_4$ in 175 ml of water was added with stirring in the course of 10 min to a suspension of 0.04 mole of lactones IIIa-c in 175 ml of ethanol, after which the mixture was stirred at room temperature for 4 h. The inorganic salts were removed by filtration, the filtrate was acidified to pH 5 with acetic acid, and the mixture was vacuum evaporated to 100 ml. This condensate was passed through a column containing 200 g of Amberlite IR-120 cation-exchange resin. The materials were eluted with water. The eluate (700 ml) was passed through a column containing 200 g of Dowex-3-anion-

* For Ia, 165-170°, as compared with 170-180° for Ib, and ~200° for Ic.

exchange resin. The material was eluted with water (0.05 N NH_4OH was used for IVc). The eluate (~1 liter) was vacuum evaporated to dryness, and the residue was dried by repeated evaporation with absolute ethanol and recrystallized from ethanol. Diols IVa-c were obtained. Subsequent elution of the anion-exchange resin with 0.5 N NH_4OH gave acids Va-c in the form of the ammonium salts.

5-Substituted N_1-[1-O-Trityloxy-4-hydroxy-2-pentyl]- (VIa,b) and N_1-[1-O,4-O-Di(trityloxy)-2-pentyl]uracils (VIIa,b, Table 2). A solution of 0.03 mole of diol IVa,b and 8.3 g (0.03 mole) of triphenylchloromethane in 50 ml of absolute pyridine was heated at 80-100° for 1 h, after which it was poured with stirring into 1.5 liter of a mixture of water and ice. The resulting precipitate was separated, washed with water, and dissolved in 70 ml of acetone. The insoluble residue (VIIa,b) was removed by filtration and crystallized from dioxane. The filtrate was evaporated to dryness, and the syrupy residue was dried by repeated evaporation with absolute ethanol. It was then dissolved in 30 ml of benzene-hexane (1 : 1). Workup gave VIa,b.

5-Substituted N_1-(1-O-Trityloxy-4-O-Acetoxy-2-pentyl)uracil (VIIIa,b, Table 2). Acetic anhydride (22 ml) was added to a solution of 0.017 mole of VIa, b in 70 ml of absolute pyridine, and the mixture was allowed to stand at room temperature for 24 h. It was then poured with stirring into 1 liter of water and ice, and the resulting precipitate was removed by filtration, washed with water, and recrystallized from ethanol.

5-Substituted N_1-(1-Hydroxy-4-O-acetoxy-2-pentyl)uracils (IXa,b, Table 2). A mixture of 0.016 mole of VIIIa, b and 35 ml of 80% acetic acid was heated at 100° for 40 min. It was then cooled, and the precipitated triphenylmethanol was removed by filtration. The filtrate was vacuum evaporated to dryness, and the residue was dried by repeated evaporation with absolute ethanol. The product was recrystallized from absolute ethanol–hexane (1 : 1).

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