ANALOGS OF PYRIMIDINE MONO- AND POLYNUCLEOTIDES

7.* 2-(1-URACILYL)TETRAHYDROFURAN-5-CARBOXYLIC ACIDS AND THEIR DERIVATIVES

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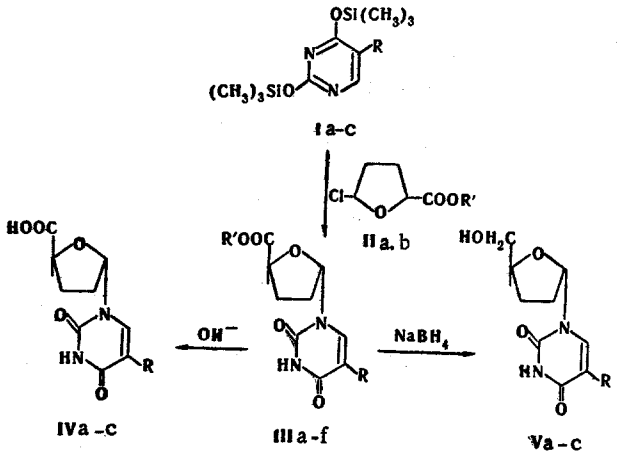
2-(5-R-1-Uracilyl)tetrahydrofuran-5-carboxylic acids can be regarded as analogs of pyrimidine nucleotides in which the hydroxyl groups at positions 2' and 3' are absent and the phosphooxymethyl group is replaced by a carboxyl. These acids are close in structure to 1-(2'-deoxy-β-D-erythropentafuranosyl-5'-uronic) acid derivatives of 5-substituted uracils ("nucleoside-5'-carboxylic acids"), which are formed during oxidation of the primary hydroxyl group in 2'-deoxyribosides of pyrimidine bases [2-5].

In order to obtain 2-(1-uracilyl)tetrahydrofuran-5-carboxylic acids (IV) we studied the alkylation of 2,4-bis(trimethylsilyl)uracils (I) by 5-chlorotetrahydrofuran-2-carboxylic esters (II) [6].



I, IV, V **a** R=H; **b** R=CH_3; **c** R=F; II **a** R′=CH_3; **b** R′=C_2H_5; III **a** R=H, R′=CH_3; **b** R=R′=CH_3; **c** R=F, R′=CH_3; **d** R=H, R′=C_2H_5; **e** R=CH_3, R′=C_2H_5; **f** R=F, R′=C_2H_5

The alkylation of pyrimidines I by the esters II occurs at 20-30°C, whereas 2-chlorotetrahydrofuran reacts at a lower temperature (−15°) [7]. The esters IIIa-f were obtained with yields of 70-80%. Alkaline hydrolysis of the esters IIIa-f leads to the corresponding acids IVa-c (Tables 1 and 2). The UV spectra of the esters IIIa-f and of the acids IVa-c are characteristic of 1-substituted uracils; a shift of the absorption maximum is not observed in the transition from an acidic to an alkaline medium. In the PMR spectra of compounds IIIa and IVa the signal for the 6-H protons is a doublet with $^3H_{6-5}$ = 8.2 Hz, and this is also characteristic of 1-substituted uracils [8]. The PMR spectra indicate that the synthesized compounds represent one of the possible isomers (cis or trans). Comparison of the constants of the ester IIIc with the constants of ethyl 3-deoxythymidinuronate [9] favors the trans configuration for IIIb. By reduction of the esters IIIa-f with sodium borohydride we obtained racemic 2',3'-dideoxynucleosides (Va-c) (Table 3). By comparison of the PMR spectrum of compound Va with the spectrum of β-D-2',3'-dideoxyuridine

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TABLE 1. 2-(5-R-1-Uracilyl)tetrahydrofuran-5-carboxylic Acids and Their Esters (III and IV)

Compound	R	R′	mp °C	R_f*	UV spectrum, λ_{max}, nm ($\varepsilon \cdot 10^{-3}$)			Yield, %
					pH 2	pH 7	pH 10	
IIIa	H	CH_3	166—168	0,79	262 (7,5)	263 (7,6)	264 (5,8)	60
IIId	H	C_2H_5	150—152	0,88	262 (10,2)	263 (11,0)	263 (8,3)	52
IVa	H	H	219—221	0,61	262 (9,9)	263 (10,5)	262 (10,0)	69†
IIIb	CH_3	CH_3	182—183	0,89	266 (9,7)	266 (9,3)	266 (7,2)	45
IIIe	CH_3	C_2H_5	187—189	0,90	270 (7,7)	270 (8,3)	270 (7,2)	65
IVb	CH_3	H	221—223	0,63	264 (9,8)	265 (9,8)	263 (7,9)	80†
IIIc	F	CH_3	218—220	0,90	267 (9,2)	266 (9,2)	270 (7,2)	40
IIIf	F	C_2H_5	160—162	0,90	271 (7,8)	270 (8,9)	272 (7,2)	32
IVc	F	H	213—215	0,69	263 (9,1)	264 (9,1)	263 (7,2)	65†

*In the 86:14 n-butanol—water system.
†The yield from alkaline hydrolysis of the respective methyl ester is given.

TABLE 2. PMR Spectra of 2-(5-R-1-Uracilyl)tetrahydrofuran-5-carboxylic Acids and Their Esters (III, IV)

Compound	R	R′	Chemical shift, δ, ppm							J, Hz	Half-width of signal	
			2′-H	5′-H	3′-H, 4′-H	NH	6-H	R	R′		2′-H	5′-H
IIIa	H	CH_3	6,08	4,60	2,4—1,8	11,2	8,03	5,66	3,72	$^3J_{6-5}$=8,2	10,9	13,6
IIId	H	C_2H_5	6,04	4,56	2,4—1,9	11,3	8,01	5,64	4,18 (CH_2) 1,21 (CH_3)			
IVa	H	H	6,06	4,50	2,4—1,9	11,2	8,12	5,63	—		10,8	14,0
IIIb	CH_3	CH_3	6,13	4,60	2,4—1,9	11,1	7,93	1,83	3,76	$^4J_{6-5}$=0,9	11,0	13,4
IIIe	CH_3	C_2H_5	6,09	4,58	2,4—1,9	11,3	7,88	1,80	4,19 (CH_2) 1,21 (CH_3)			
IVb	CH_3	H	6,10	4,31	2,4—1,9	11,2	8,10	1,81	—		11,4	14,0
IIIc	F	CH_3	6,10	4,64	2,4—1,9	11,5	8,35	—	3,79			
IIIf	F	C_2H_5	6,05	4,61	2,4—1,9	11,8	8,37	—	4,20 (CH_2) 1,22 (CH_3)	$^3J_{H-F}$=7,5	11,6 11,5	13,7 14,0
IVc	F	H	6,04	4,52	2,4—1,9	11,5	8,48	—	—			

[10] it was possible to establish the configuration of compound Va as the α-anomer of 2′,3′-dideoxyuridine. The signal of the 2′-H anomeric proton (Fig. 1) represents a quarter of 6.08 ppm with J = 3.2 and 5.9 Hz and a half-width of 10.7 Hz. In the case of the β-anomers of 2′-deoxyribosides the signal for the 2′-H proton represents a pseudotriplet with $J_{1',2'}$ = 7 Hz and a half-width of 14 Hz [11-14].

The alkylation of 2,4-bis(trimethylsilyl)-5-fluorouracil by the ester IIa at 100°C with distillation of the trimethylchlorosilane formed in the reaction leads to the formation of a small amount of the cis isomer in addition to the trans isomer of IIIc. In the synthesis of certain 2′-deoxyribosides an increase in the yield of the β-anomers was observed when the trimethylchlorosilane was removed from the reaction medium [14], but this effect may also be due to other differences in the reaction conditions [15].

EXPERIMENTAL

The purity of the compounds was monitored by ascending chromatography on FN-1 paper in the 86:14 n-butanol—water system. The UV spectra were recorded on a Specord UV-vis spectrophotometer. The PMR spectra of the 2-(5-R-1-uracil)tetrahydrofuran-5-carboxylic acids and their esters were obtained on a Perkin-Elmer R-12A instrument at 60 MHz in DMSO-d_6 with TMS as internal standard. The PMR spectra of the 2′,3′-dideoxynucleosides were recorded on a Bruker WH-90 instrument in heavy water with DSS as internal standard.

The melting points were determined on Boetius bench.

Methyl trans-D,L-2-(1-Uracilyl)tetrahydrofuran-5-carboxylate (IIIa) (Tables 1 and 2). A mixture of 2.24 g (0.02 mole) of uracil, 10 ml of hexamethyldisilazane, and 0.5 ml of

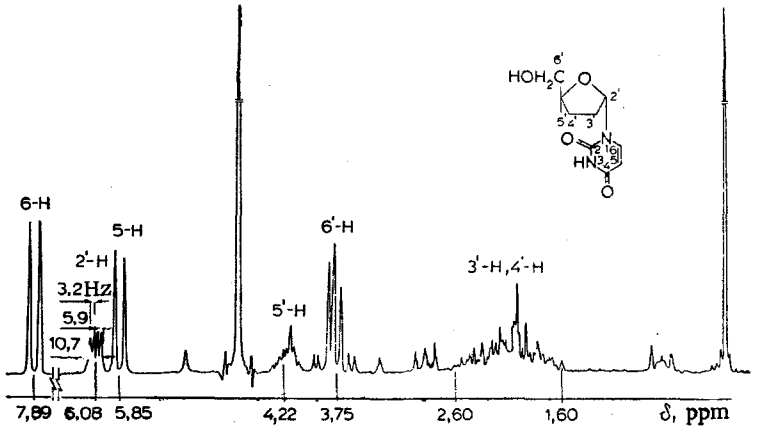

Fig. 1. PMR spectrum of 1-(trans-D,L-5-hydroxymethyl-tetrahydro-2-furyl)uracil.

TABLE 3. 5-Substituted 1-(trans-D,L-5-Hydroxymethyltetrahydro-2-furyl)uracils (Va-c)

Compound	R	mp, °C	R_f*	Chemical shift, δ, ppm in PMR spectrum						Half-width of signal, 2'-H, Hz	Yield, %
				2'-H	3'-H, 4'-H	5'-H	6'-H	5-H	6-H		
Va	H	173—174	0,46	6,08	1,6—2,6	4,22	3,75	5,85	7,89	10,7	72
Vb	CH_3	184—187	0,67	6,13	1,9—2,4	4,60	3,76	1,83	7,93	11,1	65
Vc	F	141—143	0,55	6,10	1,8—2,6	4,15	3,70—3,76	—	7,93	12,0	50

*In the 8:2 chloroform–methanol system, Silufol UV-254.

trimethylchlorosilane was heated at 150-170°C until the uracil had completely dissolved and then for a further 2 h. The excess of hexamethyldisilazane was distilled under vacuum. To the obtained 2,4-bis(trimethylsilyl)uracil we added 3.3 g (0.02 mole) of the ester IIa [6]. The mixture was kept at room temperature for 2 h, and 10 ml of ethanol was added in such a way that the temperature did not rise above 40°C. The mixture was stirred at room temperature for 1 h, and the precipitate was filtered off by suction and recrystallized from ethanol. We obtained 2.08 g of the ester IIIa (60%).

The esters IIIb-f were obtained similarly (Tables 1 and 2).

Methyl 2-(5-Fluoro-1-uracilyl)tetrahydrofuran-5-carboxylate (IIIc) (mixture of cis and trans isomers). To 5.5 g (0.02 mole) of freshly distilled 2,4-bis(trimethylsilyl)-5-fluorouracil at 0-2°C we added 3.3 g (0.02 mole) of the ester IIa. Condensation was realized at reduced pressure (25-30 mm) in an atmosphere of nitrogen, while the temperature was gradually raised to 100°C. After the reaction the mixture was cooled, 10 ml of ethanol was added, and the mixture was stirred at room temperature for 1 h. The precipitate was filtered off by suction, washed with a small amount of ethanol, extracted with chloroform, and the chloroform was evaporated. We obtained 1.4 g (40%) of the ester IIIc; mp 198-303°C, R_f = 0.90. PMR spectrum (DMSO-d_6), δ: 8.35 (d, 6-H) (84% of the trans isomer), 8.05 (d, 6-H) (16% of the cis isomer), 6.15; 6.06 (m, 2'-H), 5.01; 4.67 (m, 5'-H), 3.76, 3.70 (s, CH_3), 2.4-1.9 ppm (m, 3'-H, 4'-H).

trans-D,L-2-(1-Uracilyl)tetrahydrofuran-5-carboxylic Acid (IVa) (Tables 1 and 2). A 0.5-g sample (2 mmole) of the ester IIIa was added to 10 ml of a 5% aqueous solution of sodium hydroxide. The mixture was stirred at 60-60°C for 7 h, cooled, and acidified to pH 2 with hydrochloric acid. The precipitate was filtered off by suction and recrystallized from water and then from ethyl acetate. A 0.33-g yield (70%) of the acid IVa was obtained. The acids IVb, c were obtained similarly.

1-(trans-D,L-5-Hydroxymethyltetrahydro-2-furyl)-uracil (Va) (Table 3). A 0.48-g sample (2 mmole) of the ester IIIa was suspended in 10 ml of water, 0.11 g (3 mmole) of sodium

borohydride was added, and the mixture was stirred at room temperature. The reaction was monitored by thin-layer chromatography on Silufol UV-254 plates in the 8:2 chloroform—methanol system. At the end of the reaction (4 h) the mixture was neutralized to pH 6 with acetic acid and evaporated to dryness. The residue was dissolved in 7 ml of water and extracted with ethyl acetate (6 × 5 ml). The ethyl acetate solution was dried over magnesium sulfate and evaporated. The residue was recrystallized from a 1:1 mixture of methanol and ethyl acetate. We obtained 0.32 g (72%) of compound Va.

Compounds Vb, c were obtained similarly (Table 3).

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HETEROCYCLIC NITRO COMPOUNDS.

24.* NITRATION OF 5-AMINO-1,2,4-TRIAZOLE AND 5-ACETAMIDO-1,2,4-TRIAZOLE WITH ACETYL NITRATE AND NITRONIUM SALTS

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The reaction of 5-amino-1,2,4-triazole and its derivatives with electrophilic reagents can occur at the hetero atoms of the ring (protonation [2-4], methylation [5, 6]), at the exocyclic nitrogen atom of the amino group (nitration with nitric acid and nitrating mixtures [7, 8]), or at both centers (acylation [9, 10]), depending on the conditions and on the nature of the reagent. The nitration of 1,2,4-triazole and its derivatives by nitronium salts leads to N-nitrotriazoles [11], and they undergo subsequent rearrangement to the C-nitro compounds. In order to investigate the direction of the reaction with an additional reaction center (amino group) in the molecule we undertook an investigation into the nitration of 5-amino-1,2,4-triazole (I) and 5-acetamido-1,2,4-triazole (II) by nonacidic nitrating agents (acetyl nitrate and nitronium salts).

*For Communication 23, see [1].

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