SYNTHESIS OF 6-METHYLURACIL NUCLEOSIDES FROM PENTAFURANOSE AMINOOXAZOLINES AND DIKETENE

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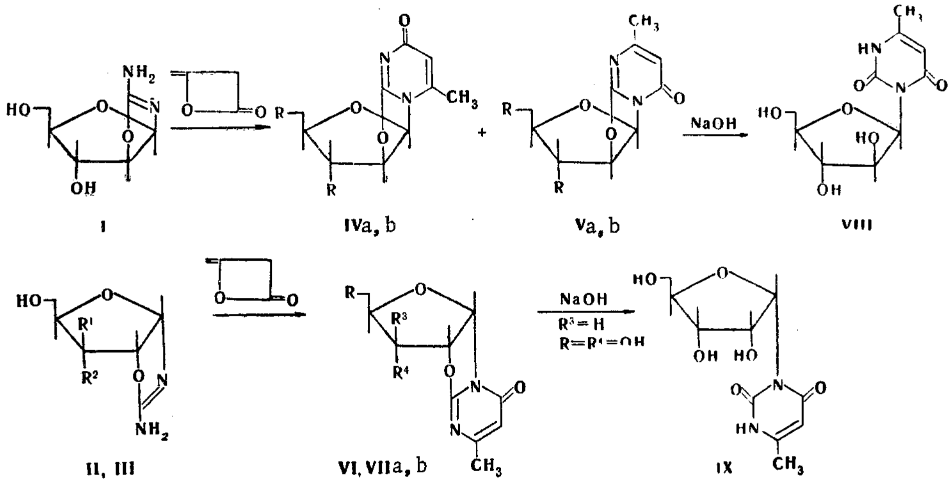
The corresponding acetoacetylated 2,2'-anhydro-N^3-nucleosides were obtained from diketene and arabinose, xylose, and ribose aminooxazolines. The protective groups were removed, and the anhydro bond was cleaved. The structures and reactivities of the intermediate – 2,2'-anhydro-3-β-D-arabinofuranosyl-6-methyl-5,6-dihydrouracil – were studied.

The reaction of aminooxazolines of sugars with compounds containing a triple [1, 2] or activated double bond [3, 4] is a new and convenient method for the stereospecific synthesis of nucleosides.

In order to extend the range of application of this reaction we investigated the reaction of pentafuranose aminooxazolines I-III with diketene, which is known to react with amidines and urea to give pyrimidine derivatives [5].

The principal reaction products are acetoacetylated N^3-anhydronucleosides V-VIIa (λ_{max} 270 nm; $\delta_{H_1'}$ 6.44, $\delta_{H_2'}$ 5.42 ppm [7]). Thus, as in the overwhelming majority of the reactions of aminooxazolines [6] and aminooxazolines of sugars [1-4], the most nucleophilic ring nitrogen atom is the primary center of attack. However, in the case of 2-amino-β-D-arabinofurano[1',2':4,5]oxazoline (I), acetoacetylated N^1-anhydronucleoside IVa (λ_{max} 255 nm; $\delta_{H_1'}$ 6.56, $\delta_{H_2'}$ 5.45 ppm [2]) was isolated in small amounts.



II R¹=H, R²=OH; III R¹=OH, R²=H; IVa, Va R=OCOCH₂COCH₃; b R=OH; VIa R=R⁴=OCOCH₂COCH₃, R³=H; b R=R⁴=OH, R³=H; VIIa R=R³=OCOCH₂COCH₃, R⁴=H; b R=R³=OH, R⁴=H

The acetoacetyl groups of IVa-VIIa are removed by methanolysis with retention of the 2,2'-anhydronucleoside structure. The 2,2'-anhydronucleoside bond is cleaved by 1 N NaOH to give nucleosides VIII and IX. The UV spectra of the nucleosides (with a characteristic bathochromic shift in alkaline media [8]) confirm the presence of a glycoside bond at 3-N and the $J_{H_1',H_2'}$ spin–spin coupling constant (SSCC) of 6.7-6.8 Hz confirms retention of the arabino configuration [6] (Tables 1 and 2).

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TABLE 1. 6-Methyluracil Nucleosides

Compound	mp, °C (crystallization solvent)	Found, %			Empirical formula	Calc., %			$[\alpha]_D^{20}$ (solvent)	UV spectra, λ_{max}, nm (log ε)		Yield, %
		C	H	N		C	H	N		H_2O	0,1 N NaOH	
Va	Syrup	53,0	4,8	6,4	$C_{18}H_{20}N_2O_9$	52,9	4,9	6,8	−132°(methanol 1,0)	217 (3,79), 270 (3,79)	276 (4,54)	55
IVa	55—60 (ethanol)	52,9	5,3	6,4	$C_{18}H_{20}N_2O_9$	52,9	4,9	6,8	−43,3°(methanol 0,8)	224 (3,87), 255 (3,92)	—	10
VIa	Syrup	53,1	5,3	6,9	$C_{18}H_{20}N_2O_9$	52,9	4,9	6,8	+208° (DMF 1,0)	218 (3,85), 272 (3,85)	276 (4,64)	60
VIIa	Syrup	52,4	5,4	6,3	$C_{18}H_{20}N_2O_9$	52,9	4,9	6,8	+67° (DMF 1,0)	215 (3,83), 272 (3,83)	276 (4,60)	50
Vb	164—165 (isopropyl alcohol)	50,0	5,0	11,4	$C_{10}H_{12}N_2O_5$	50,0	5,0	11,6	−163° (DMF 1,5)	218 (3,75), 272 (3,80)	—	75
VIb	314—315 (80% ethanol)	49,8	5,2	11,3	$C_{10}H_{12}N_2O_5$	50,0	5,0	11,6	+242° (DMF 0,8)	218 (3,85), 272 (3,88)	—	95
VIIb	244—245 (ethanol)	49,9	5,0	11,6	$C_{10}H_{12}N_2O_5$	50,0	5,0	11,6	+131° (DMF 1,0)	215 (4,0), 272 (3,95)	—	83
VIII	222—223 (ethanol)	46,6	5,2	10,8	$C_{10}H_{14}N_2O_6$	46,5	5,5	10,9	−5,2 (DMF 0,5)	208 (3,90), 262 (3,96)	286 (4,0)	60
IX	187—188 (80% ethanol)	46,2	5,5	10,4	$C_{10}H_{14}N_2O_6$	46,5	5,5	10,9	+16° (H_2O, 0,1)	205 (4,00), 265 (3,97)	292 (4,04)	70
X	111—113	46,3	5,4	10,9	$C_{10}H_{14}N_2O_6$	46,5	5,5	10,9	—*	210 (3,5)	—	52

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*Not determined because of the low solubility in aprotic solvents.

TABLE 2. Parameters of the PMR Spectra of 6-Methyluracil Nucleosides (in d_6-DMSO)

Compound	Chemical shifts, δ, ppm								SSCC, J, Hz		
	H_1'	H_2'	H_3'	H_4'	H_5'	H_5	CH_2	CH_3	1′,2′	2′,3′	3′,4′
Va	6,44	5,42	5,37	4,5	4,0—4,4	5,89	3,70 (3′), 3,48 (5′)	2,21 (3′) 2,15 (5′ and 6)	5,6	0	0,6
IVa	6,56	5,45	5,40	4,6	3,9—4,3	5,75	3,72 (3′), 3,52 (5′)	2,23 (3′ and 6) 2,18 (5′)	5,3	0	0,8
VIa	6,46	5,56	5,20	4,1	4,1—4,6	5,98	3,79 (3′), 3,69 (5′)	2,20 (6) 2,23 (5′) 2,28 (3′)	5,3	5,3	7,7
VIIa	6,48	5,37	5,50	4,3	4,1—4,5	5,98	3,78 (3′), 3,65 (5′)	2,21 (5′ and 6) 2,27 (3′)	5,3	0	1,8
Vb	6,40	5,21	4,41	4,07	3,2—3,4	5,92	—	2,13	5,7	0	1,0
IVb	6,51	5,21	4,42	4,12	3,32	5,75	—	2,32	5,8	0	0,6
VIb	6,30	5,20	4,12	3,4—3,7	3,4—3,7	5,90	—	2,18	5,1	5,1	8,0
VIIb	6,42	5,16	4,33	3,4—3,7	3,4—3,7	5,96	—	2,16	5,3	0	1,6
VIII	6,43	4,2	4,2	3,6	3,6	5,40	—	2,05	6,7	—*	—*
IX	6,60	4,36	4,0	4,0	3,5	5,52	—	2,8	6,8	6,6	—*
X	6,08	4,85	4,23	3,95	3,3	—	2,5	1,34	5,4	0	0,5
X†	6,12	4,85	4,32	4,03	3,42	—	2,59 and 2,44‡	1,39	5,0	0	1,0
XI	6,03	4,84	4,23	3,95	3,3	—	2,5	1,21	5,4	0	0,5
XI†	6,12	4,85	4,32	4,03	3,37	—	2,53	1,28	5,0	0	1,0

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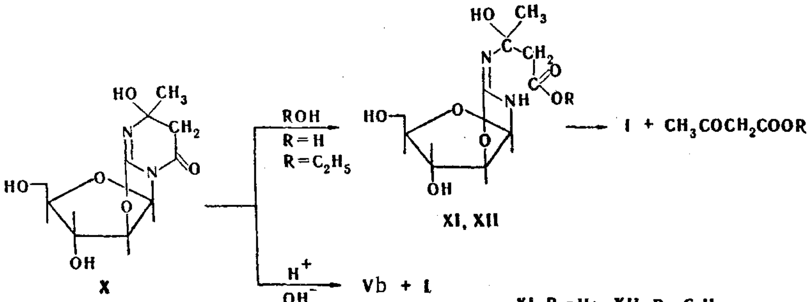
*Not determined because of overlapping with other signals.

†In CD_3CN.

‡J = 16.0 Hz.

The reaction sequence was studied in greater detail in the case of aminooxazoline I. In the reactions of urea with diketene [9] and acetoacetic ester [5] the intermediates have the open form of ureides; however, we isolated a cyclic intermediate — 2,2'-anhydro-3-β-D-arabinofuranosyl-6-hydroxy-6-methyl-5,6-dihydrouracil (X).



XI R=H; XII R=C_2H_5

The presence in the PMR spectrum of X of a singlet of an OH group at 5.78 ppm, the shielding of the CH_3 group (1.34 ppm), the corresponding chemical shift in the case of sp^3 hybridization of the carbon atom, and the characteristic (for a cyclic structure) splitting of the CH_2 group into an AB quartet constitute evidence in favor of this structure. The chemical shift of the CH_2 group (2.5 ppm) and the SSCC (J = 16 Hz) correspond to a CH_2 group adjacent to one C=O group. This demonstrated that a pyrimidine structure is formed initially and that the carbohydrate residue is acetoacetylated only subsequently.

During a study of the spectra and the chromatographic behavior of product X we observed that it is unusually easily hydrolyzed in proton-containing solvents (ethanol and water). It is stable in aprotic solvents (chloroform, dioxane, acetonitrile, and acetone) but is only very slightly soluble.

The sequence of hydrolysis of the bonds of X was followed by means of PMR spectroscopy. The signal of a second CH_3 group attached to an sp^3-hybridized carbon atom (1.21 ppm) appears rapidly in the presence of water, and the CH_2 group appears as a singlet (2.5 ppm), i.e., despite our expectations, the ring C_4—N_3 amide bond is initially hydrolyzed to give acid XI.

The presence of a COOH group was confirmed by means of an indicator (Methyl Red). Hydrolysis of the C_6—N_1 bond to give starting aminooxazoline I is observed immediately after hydrolysis of the amide bond, and we were therefore unable to isolate acid XI in solid form. In the hydrolysis of X with ethanol, in addition to oxazoline I, the presence of a second hydrolysis product — acetoacetic ester — was proved chromatographically with a reference compound.

The peculiarities of the structure of X promote facile splitting out of water to give unprotected nucleoside Vb. However, in the presence of acids and alkalis the formation of Vb is accompanied by competitive hydrolysis of intermediate X to starting oxazoline I.

Blank experiments showed that under the conditions of the reaction of aminooxazolines with diketene in acetone splitting out of water from intermediate X is due to the action of diketene rather than to the basic properties of aminooxazoline (pK_a 6.52 [1]).

EXPERIMENTAL

The individuality of the compounds obtained was confirmed by thin-layer chromatography (TLC) on Silufol plates in chloroform—methanol systems (9:1 and 7:3). The plates were developed in UV light or with iodine vapors. The melting points were determined with a Boëtius apparatus and were not corrected. The PMR spectra of the compounds were recorded with Perkin—Elmer 12A (60 MHz) and Brukker WH-90 (90 MHz) spectrometers with tetramethylsilane as the internal standard. The UV spectra were recorded with a Specord spectrophotometer. The $[\alpha]_D^{20}$ values were determined with a Perkin—Elmer 141 polarimeter. The constants of the compounds obtained are presented in Tables 1 and 2. Column chromatography was monitored by means of a CSAV flow absorptiometer. Woelm silica gel was used for the column chromatography.

<u>2,2'-Anhydro-3-β-D-(3',5'-di-O-acetoacetylarabinofuranosyl)-6-methyluracil (Va)</u>. Diketene (8 ml) was added to a solution of 3.48 g (20 mmole) of aminooxazoline I in 40 ml of

acetone, and the mixture was stirred at room temperature for 2 days. The mixture was then evaporated, and the oily residue was dissolved in 8 ml of chloroform. The chloroform solution was applied to a column filled with 300 ml of silica gel and eluted successively with 1.5 liters of chloroform and a mixture of chloroform and methanol (95:5). The eluate was evaporated to give the product in the form of a yellow syrup. Compounds VI and VIIa were similarly synthesized.

2,2'-Anhydro-1-β-D-(3',5'-di-O-acetoacetylarabinofuranosyl)-6-methyluracil (IVa). The separation of the mixture of products obtained in the preparation of Va was continued by elution with chloroform–methanol (4:1). The eluate was evaporated to give an oily residue that crystallized when it was evaporated repeatedly with ethanol and methanol.

2,2'-Anhydro-3-β-D-arabinofuranosyl-6-methyluracil (Vb). A solution of 0.85 g (2 mmole) of nucleoside Va in 25 ml of 0.1 M methanolic CH_3ONa was allowed to stand at room temperature overnight, after which it was neutralized with Dowex in the H^+ form and filtered. The filtrate was evaporated to dryness, and the residual oil was crystallized by repeated evaporation with ethyl acetate and recrystallized from isopropyl alcohol. Compounds IVb,* VIb, and VIIb were similarly obtained.

3-β-D-Arabinofuranosyl-6-methyluracil (VIII). A 0.63-g (2.6 mmole) sample of nucleoside Vb was dissolved in 3 ml of 1 N NaOH, and the solution was allowed to stand at room temperature for 4 h. It was then neutralized with Dowex in the H^+ form and filtered, and the filtrate was evaporated. The product was crystallized from ethanol. Compound IX was similarly obtained.

2,2'-Anhydro-3-β-D-arabinofuranosyl-6-hydroxy-6-methyl-5,6-dihydrouracil (X). A 0.35-g (2 mmole) sample of aminooxazoline I was suspended in 10 ml of acetone, and 0.8 ml of diketene was added. After 2 h, the precipitate was removed by filtration and washed with acetone and ether.

Reaction of X with H_2O. A 0.2-g sample of X was dissolved in water, and the solution was chromatographed on a Silufol plate after 30 min. The chromatogram indicated a mixture of X, XI, and I. The structure of the XI eluted from the plate was confirmed by the UV ($\lambda_{max}^{C_2H_5OH}$ 205 nm) and PMR spectra (Table 2). The COOH group was revealed on a MERCK silica gel plate with Methyl Red indicator (XI was red).

Reaction of X with Ethanol. A 0.2-g sample of X was dissolved in ethanol, and the solution was chromatographed on a Silufol plate after 30 min. The chromatogram indicated a mixture of X, XII, I, and acetoacetic ester. The UV spectrum ($\lambda_{max}^{C_2H_5OH}$ 205 nm), the absence of coloration with Methyl Red, and the presence of acetoacetic ester constituted evidence in favor of hypothetical structure XII. The determination of the ester group of XII in the PMR spectrum was hindered by the presence of acetoacetic ester.

Reaction of X with CH_3COOH. A 0.7-g (2.8 mmole) sample of X was dissolved in 2 ml of glacial CH_3COOH. After 2 h, the solution was evaporated, and the residue was applied to a column filled with 100 ml of silica gel and eluted with chloroform–ethanol (9:1). Compound Vb was subsequently eluted with chloroform–ethanol (4:1) to give 0.1 g (14%) of Vb. Subsequent elution with ethanol gave 0.5 g of aminooxazoline I.

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*Compound IVb was also obtained by reaction of aminooxazoline I with ethyl 2-butynoate [2].