# SYNTHESIS OF ANALOGS OF URIDYLIC AND 6-AZAURIDYLIC ACIDS CONTAINING A PHOSPHORAMIDE BOND

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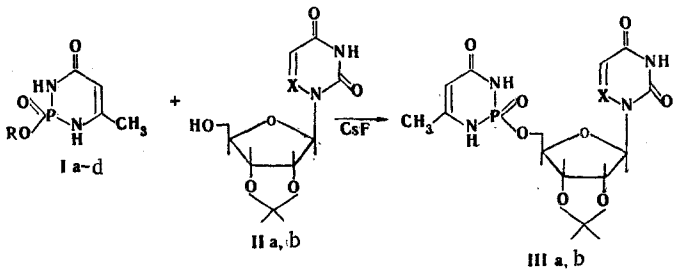
Nucleotides and their analogs, having a $PO(OH)_2$ group able to ionize, are not usually able to ionize, are not usually able to pass through cell membranes. This limits the search for biologically active substances among nucleotide analogs. In this connection it seemed of interest to study nucleotide derivatives which are not so strongly acidic and which might be able to be converted under definite conditions *in vivo* into the corresponding nucleotides.




I a-d

II a, b

III a, b

I a R=H; b R=$CH_3$; c R=$C_2H_5$; d R=$C_6H_5$; II, III a X=CH; II, III b X=N

Derivatives of 1-hydroxy-5-methyl-1,2,3,6-tetrahydro-1,2,6-phosphadiazine-1,3-dione (Ia) were selected by us as an analog or a phosphate derivative. For the transition to nucleotide derivatives we used the method of ester exchange in the presence of CsF, proposed by Ogilvie and co-workers [1]. The transition from compound (Id) to ester (Ib) or (Ic) was effected by us under analogous conditions [2]. Protected nucleosides used as the alcohol component in the present work were 2',3'-O-isopropylidenuridine (IIa) and 2',3'-O-isopropylidenazauridine (IIb). On interacting (IIa, b) with compound (Id) in pyridine in the presence of CsF 2',3'-O-isopropylidene-5'-O-(5-methyl-1,2,3,6-tetrahydro-1,2,6-phosphadiazine-1,3-dion-1-yl)uridine (IIIa) or -6-azauridine (IIIb) were formed in 43 or 37% yield, respectively. It should be mentioned that in the case of simple alcohols the yield of transesterified compound was significantly greater since these compounds serve simultaneously as solvents and are used in large excess.

In the PMR spectrum of compound (IIIa) the signals of the 5H and 6H protons of the uracil nucleus in the 6.22 and 8.70 ppm regions respectively were a doublet of doublets with spin–spin interaction constants $^3J_{5,6}$ = 8.1, $^4J_{5,NH}$ = 2.4, and $^4J_{6',1'}$ = 1.6 Hz. The signal for the anomeric proton was located at 6.46 ppm ($J_{1',2'} < 0.5$ Hz). Signals for the protons of the ribose ring 2'H, 3'H, 4'H, and 5',5"H had the form of complex multiplets at 5.48, 5.20, 4.54, and 4.16-4.40 ppm, respectively. The 4H proton of the phosphadiazine ring appeared as a singlet at 5.38 ppm but the signal of the methyl group protons was a doublet at 1.82 ppm with $J_{HP}$ = 5.2 Hz. Signals for the methyl group protons of the isopropylidene protection had the form of two singlets at 1.28 and 1.04 ppm. In the spectrum of compound (IIIb) signals of the 5H and 1'H protons were observed in the region of 7.45 and 6.12 ppm ($J_{1',2'} < 1$ Hz). Signals of the 2H and 3H protons at 4.70-5.12 ppm overlapped. The signal of the 4H proton of the phosphadiazine ring was observed in the same region. Multiplets of signals of the 4'H and 5',5"H protons of the ribose ring also overlapped in the 2.80-4.40 region. Signals of methyl group protons of the phosphadiazine ring and isopropylidene protection were observed as singlets at 1.93, 1.48, and 1.29 ppm, respectively.

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Intense peaks were contained in the mass spectra of compounds (IIIa) and (IIIb) for the molecular ions of m/e 428 and 429, respectively. In the spectrum of the uridine derivative (IIIa) there were also intense peaks for fragment ions corresponding to splitting away of the uracil ring (m/e 317) and the phosphadiazine ring (m/e 267). In the spectrum of compound (IIIb) there was also a peak for a fragment ion corresponding to splitting away of the phosphadiazine ring (m/e 268).

The obtained substances (IIIa) and (IIIb) proved to be rather labile and on attempting to remove the protection in acid medium they were converted into the initial nucleoside and acid (Ia).

## EXPERIMENTAL

PMR spectra were obtained on a Brucker WH-360 instrument with a frequency of 360 MHz (for IIIa) and a Jeol JNM-MH-100 with a frequency of 100 MHz (for IIIb) in $d_6$-DMSO, internal standard was tetramethylsilane. UV spectra were drawn on a Unicam SP-80 spectrophotometer in ethanol. Mass spectra were measured on an LKB-9000 spectrometer at an energy of ionizing electrons of 70 eV and a temperature of the ionization chamber of 130-160°C. Specific rotations were determined on a Perkin-Elmer 241 instrument. Preparative thin-layer chromatography (TLC) was carried out on glass plates (20 × 20 cm) in a binder-free layer of silica gel LSL-254 5/40 μm (Chemapol, Czechoslovakia) of layer thickness 1.5 mm. Silufol UV-254 was used for TLC.

2',3'-O-Isopropylidene-5'-O-(5-methyl-1,2,3,6-tetrahydro-1,2,6-phosphadiazine-1,3-dion-1-yl)uridine (IIIa). CsF (1.52 g; 10 mmole) was added to a solution of phenyl ester (Id) (119 mg; 0.5 mmole) and (IIa) (285 mg; 1 mmole) in dry pyridine (10 ml). The mixture was stirred for 10 days at 100°C. The solution was then filtered, the precipitate of CsF washed with pyridine, and the filtrate evaporated. The obtained bright yellow oil was chromatographed in the system chloroform–methanol (5:1) and the substance was eluted from the silica gel with ethanol. The yield of compound (IIIa) was 92 mg (43.%) in form of an amorphous powder. UV spectrum $\lambda_{max}$ (log ε): 259 nm (4.23). $[\alpha]_D^{25}$ − 4.7° (s 1.0, ethanol). Found: C 44.5; H 5.4; N 12.7; P 7.2%. $C_{16}H_{21}N_4O_8P \times 0.25\ C_2H_5OH$. Calculated: C 45.1; H 5.2; N 12.7; P 7.0%.

2',3'-O-Isopropylidene-5'-O-(5-methyl-1,2,3,6-tetrahydro-1,2,6-phosphadiazine-1,3-dion-1-yl)-6-azauridine (IIIb). Compounds (Id) (1.19 g; 5 mmole) and (IIb) (2.85 g; 10 mmole) were dissolved in dry pyridine (30 ml). CsF (3.79 g; 25 mmole) was added to the solution and the reaction mixture was stored at room temperature for 25 days. The precipitated solid was filtered off, separated from CsF, and dried. The filtrate was evaporated to dryness and chromatographed on a column in the system chloroform–methanol (4:1) then (2:1). A substance (0.92 g) was isolated which was further purified on plates in the system chloroform–methanol (6:1) and eluted with ethanol. Compound (IIIb) (788 mg; 37%) was obtained as an amorphous powder. UV spectrum, $\lambda_{max}$ (log ε): 259 nm (4.20). $[\alpha]_D^{25}$ − 41.7° (s 1.0, ethanol). Found: N 14.6%. $C_{15}H_{20}N_5O_8P \cdot C_2H_5OH$. Calculated. N 14.8%.

## LITERATURE CITED


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