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A SYNTHESIS OF 6-METHYL-2′-DEOXYURIDINE

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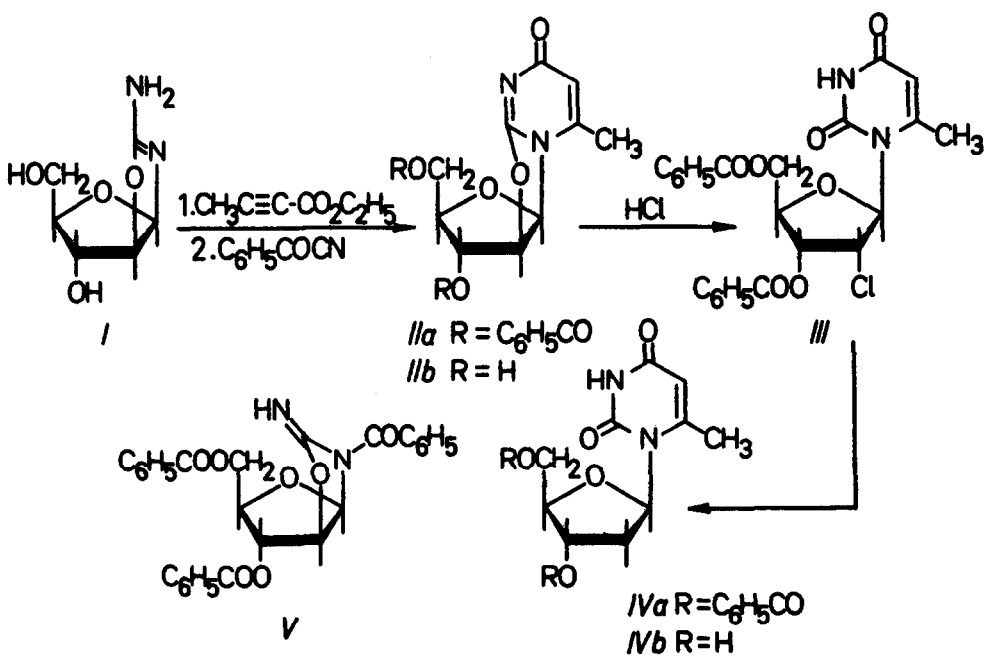
In connection with our investigation of pyrimidine 2′-deoxyribonucleoside analogues[1-3], the title compound aroused our interest from several reasons : (a) the physico-chemical study of pyrimidine base conformation which was shown to be syn in 6-methyluridine and 6-methyl-2′-deoxycytidine, (b) the investigation of 6-methyl-2′-deoxyuridine nucleotides affinity towards the enzymes of nucleic acid metabolism[4] and, finally, (c) the examination of the possible biological activity of this 2′-deoxythymidine analogue. The formation of 6-methyl-2′-deoxyuridine (IVb) as a by-product of 5-bromo-2′-deoxyuridine C-alkylation was reported in the literature[5]; however, this reaction cannot be applied as an effective synthetic approach. The same complications are to be expected in the direct glycosylation procedure[6], as 6-methyluracil is known to afford rather the 3-glycosylated derivatives than the 1-glycosides[6,7]. It was therefore felt desirable to devise an unequivocal synthetic procedure eliminating both the difficulties mentioned, and the necessity of α- and β-anomer separation which would arise on application of the latter method[7].

Such a procedure was encountered in the route applied successfully for the preparation of pyrimidine 2′-deoxyribonucleosides[1], 2′-deoxy-α-ribonucleosides[2] and 2′-deoxy-α-lyxofuranosides[3] the crucial step of which consists in the $O^{2,2'}$-anhydronucleoside formation from sugar 2-amino-1′,2′-oxazolines described originally by Sanchez and Orgel[8]. In contrast to propiolic acid esters[1-3], the ethyl 2-butynoate does not react with 2-amino-β-D-arabinofuro[1′,2′:4,5]oxazoline (I) either in aqueous ethanol or dimethylformamide solutions. However, the reaction does proceed smoothly at room temperature in dimethylformamide in the presence of triethylamine, affording 6-methyl-$O^{2,2'}$-anhydrouridine (II).

This compound was benzoylated in situ by the action of benzoyl cyanide[9] anc the 3′,5′-dibenzoyl derivative IIb was easily separated from the $N^1,O^{3'},5'$-tribenzoyl derivative V formed from the unreacted compound 1. In a typical experiment, compound I (5.2 g, 30 mmol) and ethyl 2-butynoate (10 ml) was stirred in dimethylformamide (25 ml) in the presence of triethylamine (3 ml) at room temperature for three days, evaporated at 40°C/0.1 Torr to dryness and treated in acetonitrile (100 ml) with benzoyl cyanide (13 g, 0.1 mol) and triethylamine (5 ml) for 30 min under stirring at room temperature. The mixture was taken up to dryness and applied to a column (400 g) of silica in chloroform. The elution with chloroform (2 l) afforded the compound V (3.5 g, 24%, after crystallization from ethanol), m.p. 146-147°C, $[\alpha]_D^{25}$-113.3 (c=1, dimethylformamide). For $C_{27}H_{22}N_2O_7$ (486.5) calc. (found) C 66.65% (66.55%), H 4.56% (4.53%), N 5.76% (5.87%). The additional elution of the column with chloroform-ethanol (95:5) mixture afforded 3′,5′-di-O-benzoyl-6-methyl-$O^{2,2'}$-anhydrouridine (IIa) (7.4 g, 55%), m.p. 223-224°C (ethanol), $[\alpha]_D^{25}$-47.9 (c=1, dimethylformamide). For $C_{24}H_{20}N_2O_7$ (448.4) calc. (found) C 64.28% (64.52%), H 4.49% (4.56%), N 6.25% (6.40%). NMR-Spectrum (d_3-chloroform): 2.28 ppm, (s,3H) 6-CH_3, 4.40 (m,2H) 2 $H_{5'}$,



4.64 (m,1H) $H_{4'}$, 5.67 (s,1H) H_5, 6.64 (d,1H) $H_{1'}$ ($J_{1',2'}$=5.7), 5.60-5.80 (m,2H) $H_{2'}$+$H_{3'}$, 7.20-8.10 (m,10H) 2 C_6H_5CO.

On treatment of compound IIa (3.5 g, 7.8 mmol) with 3 M hydrogen chloride in dimethylformamide (35 ml) at 100°C for 2 hours, dilution with water (500 ml), filtration of the product with suction, washing with water, drying and crystallization from ethanol, compound III (2.2 g, 58%) was obtained. M.p. 178-179°C, $[\alpha]_D^{25}$-52.6 (c=1, dimethylformamide). For $C_{24}H_{21}ClN_2O_7$ (484.9) calc. (found) C 59.44% (59.65%), H 4.36% (4.28%), Cl 7.31% (7.54%), N 5.77% (5.81%). NMR-Spectrum (d_3-chloroform): 2.27 (s,3H) 6-CH_3, 4.35-4.80 (m,3H) $H_{4'}$+$2H_{5'}$, 5.49 (dd,1H) $H_{2'}$ ($J_{1',2'}$=3.5, $J_{2',3'}$=6.5), 5.58 (s,1H) H_5, 5.88 (d,1H) $H_{1'}$ ($J_{1',2'}$= 3.5), 5.90 (t,1H) $H_{3'}$, 9.80 (br s,1H) NH, 7.20-8.10 (m,10H) 2 C_6H_5CO. The chloro derivative III (1.8 g, 3.7 mmol) and tri-n-butyltin hydride (3.5 g) in benzene (35 ml) were refluxed in the presence of 2,2′-azo-bis-isobutyronitrile (20 mg) for 20 min, the mixture concentrated in vacuo, diluted with petroleum ether (200 ml), the precipitate filtered off, washed with petroleum ether (200 ml) and crystallized from ethanol. Yield, 1.5 g (90%) IVa, m.p. 151-152°C, $[\alpha]_D^{25}$-24.1 (c=1, dimethylformamide). For $C_{24}H_{22}N_2O_7$ (450.4) calc. (found) C 64.00% (64.12%), H 4.92% (5.05%), N 6.22% (6.55%). NMR-Spectrum (d_3-chloroform): 2.33 (s,3H)6-CH_3, 2.45 (m,1H) $H_{2'}$, 3.30 (m,1H) $H_{2''}$, 4.49 (m,1H) $H_{4'}$, 4.72 (m,2H) $2H_{5'}$, 5.57 (s,1H) H_5, 5.84 (m,1H) $H_{3'}$, 6.15 (dd,1H) $H_{1'}$ ($J_{1',2'}$=4.5, $J_{1',2''}$=7.7).

The methanolysis of compound IVa afforded the required 6-methyl-2′-deoxyuridine IVb) (yield, 90%), m.p. 168-169°C (ethanol-acetonitril). For $C_{10}H_{14}N_2O_5$ (242.2) calc. (found) C 49.58% (49.35%), H 5.82% (6.02%), N 11.56% (11.56%). NMR-Spectrum (dimethyl sulfoxide-d_6): 2.25 (s,3H) 6-CH_3, 1.85-2.30 (m,2H) $2H_{2'}$, 3.62 (m,2H) $2H_{5'}$, 4.10-4.50 (m,2H) $H_{3'}$+$H_{4'}$, 5.49 (s,1H) H_5, 6.02 (t,1H) $H_{1'}$ ($J_{1',2'}$=6.8), 11.08 (br s,1H) NH. UV-Spectrum (H_2O): λ_{max} 261 nm (ε_{max} 12000), λ_{min} 232 nm (ε_{min} 3000). CD-Spectrum (H_2O): 261.5 nm (+4750), sh 246 (+3750), 229 (0), 209.5 (-5600), ! 200 (-1350). $[\alpha]_D^{25}$+24.7 (c=1, H_2O) (cf.[5], +22.0).

On removal of benzoyl groups from compound IIa by methanolysis, 6-methyl-$O^{2,2'}$-anhydrouridine (IIb), m.p. 230-231°C (ethanol-acetonitril) was obtained in 70% yield. For $C_{10}H_{12}N_2O_5$ (240.2) calc. (found) C 50.00% (50.21%), H 5.03% (4.95%), N 11.66% (11.80%). UV-Spectrum (H_2O): λ_{max} 250 nm (ε_{max} 10000), λ_{min} 230 nm (ε_{min} 7100). CD-Spectrum (H_2O): 241.5 nm (+14700), 224 (0), 215.5

(-5200), ! 200 (-4200); $[\alpha]_D^{25}$-39.4 (c=1, H_2O).

The positive Cotton effect displayed by the cyclonucleoside IIb corresponds to the data described for the $O^{2,2'}$-anhydrouridine derivatives[10]. The same sign of Cotton effect observed for 6-methyl-2'-deoxyuridine (IVb) speaks rather in favour of an anti conformation of the uracil base, or, a diminished restriction of its free rotation, if compared with the riboside[6,7]. This fact is not in agreement with the data published for the anomers of 6-methyl-2'-deoxycytidine[11] which are claimed to follow the rules accepted for 6-methylpyrimidine ribosides (negative Cotton effect and a syn-conformation for the β-anomer). On the other hand, the assignment of the β-configuration to 6-methyl-2'-deoxyuridine prepared by the present method follows unequivocally (a) from the synthetic route used which starts from a preformed fragment of the arabo configuration and proceeds through the cyclonucleoside II without any possible anomerisation, (b) from the NMR-spectra of compound IVa (the interaction constants $J_{1',2'}$ and $J_{1',2''}$ resemble the values for 3',5'-di-O-benzoyl-2'-deoxythymidine[1]) and IVb (the occurence of a pseudotriplet of H_1 with $J_{1',2'}$=6.8 is in agreement with the data for 2'-deoxy-β-ribonucleosides[1-3,11]) and (c) the $[\alpha]_D^{25}$ value is nearly identical with that described for the compound prepared by a different route.

The present method constitutes a simple approach to 6-methyluracil and 6-methylcytosine 2'-deoxyribonucleosides. Its application for the preparation of other 6-alkylsubstituted pyrimidine nucleosides will be described elsewhere.

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