CONVENIENT SYNTHESIS OF 5'-METHYL-2'-DESOXYURIDINES

S. N. Mikhailov, N. Sh. Padyukova, and K. I. Panov

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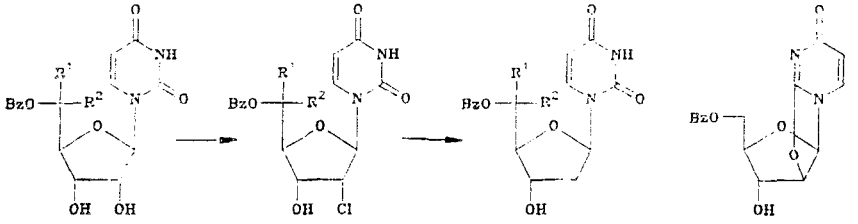
A convenient method has been developed for the synthesis of 5'-methyl-2'-desoxyuridines. Chlorination of 5'-O-benzoyl-5'-methyluridines with a mixture of Ph_3P and CCl_4 in DMF affords the 2'-desoxy-2'-chloro-derivatives, which are then reduced with tributyltin hydride. The crystalline 5'-O-benzoyl-5'-methyl-2'-desoxyuridines were obtained in overall yields of 40-60%. In a similar way, 5'-O-benzoyluridine has given 5'-O-benzoyl-2'-desoxyuridine.

The synthesis of D-allo- and L-talo-5'-methyluridines has been reported [1]. It was shown that the corresponding 5'-triphosphates are substrates for E. coli RNA polymerase [2]. The present report describes the development of methods for the synthesis of differentially-protected 5'-methyl-2'-desoxyuridines. A general method developed for the synthesis of 2'-desoxynucleosides from ribonucleosides using the 3',5'-O-(1,1,3,3-tetraisopropyldisiloxan)-1,3-diyl derivatives [3] is unsuitable for 5'-methylnucleosides [4]. We here describe a synthesis of 2'-desoxyuridines from the accessible 5'-O-benzoates (Ia-c) [1, 5], using standard methods of chlorination [6] and reduction [7].

According to TLC, chlorination of the benzoates (Ia-c) with a mixture of P_3Ph and CCl_4 in DMF gives, in addition to the required compounds (IIa-c), by-products which could not be completely removed by column chromatography on silica gel. Purification of the chlorides (IIa-c) was achieved by repeated chromatography, as in the case of the chloro-compound (IIa). The formation of 2'-deoxy-2'-chlororibonucleosides may be rationalized as occurring via the intermediate 2,2'-O-anhydro-compounds, as reported previously in the chlorination of uridine [6]. Further confirmation of the structure of (IIa) was provided by its conversion into the 2,2'-anhydronucleoside (III) by treatment with 1,8-diazabicyclo[5.4.0]undec-7-ene in methylene chloride [8]. This reaction results in a characteristic shift to lower field of the signal for the 2'-proton in the PMR spectra.



Ia-c IIa-c IVa-c III

I, II, IVa $R^1=R^2=H$; b $R^1=Me$, $R^2=H$; c $R^1=H$, $R^2=Me$

Reduction of the chloro-compounds (IIa-c) with tributyltin hydride afforded the crystalline 2'-desoxynucleosides (IVa-c) in overall yields of 40-60%. It is desirable to use partially purified chloro-compounds (IIa-c) for reduction, in view of the losses incurred on further purification.

The PMR spectra of the nucleosides (IVa-c) in DMSO-D_6 showed a D_2O-exchangeable signal doublet signal for the 3'-OH group proton, and signals for the protons of the benzoyl group, the heterocyclic base, and the carbohydrate residue, the signals for the 2'-H protons being seen as a multiplet at 2.2 ppm, which is characteristic of 2'-deoxynucleosides.

The differentially protected compounds obtained (IVa-c) are convenient starting materials for the preparation of nucleotides. The appearance of a simple method for the synthesis of 5'-O-acylnucleosides from fully acylated nucleosides [5] makes this method for the preparation

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of 2'-desoxynucleosides competitive with standard methods (see citations in [3]), and hence the entire synthetic route: monosaccharide → protected ribonucleoside → 2'-desoxynucleoside → 2'-desoxynucleotide, in which all the stages are stereo- and regiospecific.

EXPERIMENTAL

PMR spectra were recorded on a Varian XL-100 spectrometer in $CDCl_3$ and DMSO-D_6, internal standard TMS. Preparative chromatography was carried out on silica gel L 40/100 (Czech SSR), and TLC on Silufol UV-254 plates in the systems chloroform (A), chloroform–ethanol, 95:5 (B), and chloroform–ethanol, 9:1 (C). Melting points were measured on a TP instrument (USSR), and are uncorrected. The elemental analyses for C, H, and N were in agreement with the calculated values.

5'-O-Benzoyl-2'-desoxy-β-D-ribofuranosyluracil (IVa, $C_{16}H_{16}N_2O_6$). To a solution of 1 mmole of the nucleoside (Ia) [5] in 5 ml of dry DMF was added 524 mg (2 mmole) of Ph_3P and 1 ml of CCl_4. The solution was kept for 48 h at 20°C, then evaporated under reduced pressure to dryness, and the residue chromatographed on a column of silica gel (30 g). System A was used first to elute Ph_3PO, then system B to obtain the nucleoside (IIa). The fractions containing the latter were evaporated to dryness under reduced pressure, and the residue treated with 5 ml of dioxane, 5 ml of toluene, 0.5 ml (1.9 mmole) of tributyltin hydride, and 10 mg of α,α'-azobisisobutyronitrile, and the mixture boiled for 3 h. The solution was evaporated to dryness under reduced pressure, and the residue chromatographed on a column of silica gel (20 g). The column was washed with system A, and eluted with system B to give 210 mg (63%) of product, mp 160-162°C (from alcohol), R_f 0.36 (B). PMR spectrum (DMSO-D_6): 11.12 (1H, br. s, NH, exchanged on addition of D_2O); 8.00-7.38 (5H, m. C_6H_5); 7.58 (1H, d, J = 8.0 Hz,6-H); 6.14 (1H, t, J = 6.7, 1'-H); 5.48 (1H, d.d, J = 8.0 and J = 1.0 Hz, converted into a doublet with J = 8.0 Hz on addition of D_2O); 5.42 (1H, d, J = 4.0 Hz, 3'-OH, exchanged on addition of D_2O); 4.60-4.00 (4H, m, 3'...5'-H); 2.22 ppm (2H, m, 2'-H).

5'-O-Benzoyl-2', 6'-didesoxy-α-allo-furanosylurcil (IVb, $C_{17}H_{18}N_2O_6$). Obtained as for (IVa), from the nucleoside (Ib) [1]. Yield 56%, mp 192-194°C, R_f 0.40 (system B). PMR spectrum (DMSO-D_6): 11.20 (1H, br. s, NH, exchanged on addition of D_2O); 8.00-7.44 (5H, m, C_6H_5); 7.36 (1H, d, J = 8.0 Hz, 6-H); 6.11 (1H, t, J = 7.0 Hz, 1'-H); 5.43 (1H, d, J = 4.5 Hz, 3'-OH), exchanged on addition of D_2O); 5.27 (1H, d.d, J = 8.0 and J = 2.0 Hz, 5-H, converted into a doublet with J = 8.0 Hz on addition of D_2O); 5.23 (1H, m, 5'-H); 4.43 (1H, m, 3'-H); 3.88 (1H, t, J = 4.0 Hz, 4'-H); 2.17 (2H, 2'-H); 1.35 ppm (3H, d, J = 6.5 Hz, Me).

5'-O-Benzoyl-2',6'-didesoxy-α-L-talo-furanosyluracil (IVc). Obtained similarly, from the nucleoside (Ic) [1]. Yield 43%, mp 158-159°C, R_f 0.40 (B). PMR spectrum (DMSO-D_6); 11.22 (br. s, NH, exchanged on treatment with D_2O); 7.96-7.48 (5H, m, C_6H_5); 7.61 (1H, d, J = 8.0 Hz, 6-H); 6.11 (1H, t, J = 6.5 Hz, 1'-H); 5.61 (1H, d.d, J = 8.0 and J = 2.0 Hz, 5-H, converted into a doublet with J = 8.0 Hz on treatment with D_2O); 5.41 (1H, d, J = 4.5 Hz, 3'-OH, exchanged on addition of D_2O); 5.26 (1H, d.t, J = 5.0 and J = 6.5 Hz, 5'-H); 4.25 (1H, m, 3'-H); 3.87 (1H, d.d, J = 4.0 and J = 5.0 Hz, 4'-H); 2.16 (2H, m, 2'-H); 1.39 ppm (3H, d, J = 6.5 Hz, Me).

5'-O-Benzoyl-2'-desoxy-2'-chloro-β-D-ribofuranosyluracil (IIa). The chloro-compound (IIa) was further purified by repeated chromatography on a column with 30 g of silica gel and system B. Yield 200 mg (55%) (syrup), R_f 0.50 (B). PMR spectrum ($CDCl_3$): 8.46 (1H, br. s, NH); 8.00-7.30 (5H, m, C_6H_5); 7.39 (1H, d, J = 8.0 Hz, 6-H); 5.99 (1H, d, J = 3.5 Hz, 1'-H); 5.50 (1H, d.d, J = 8.0 and J = 1.5 Hz, 5-H); 4.68-4.30 (5H, m, 2'–5'-H).

2,2'-O-Anhydro-5'-O-benzoyl-β-D-arabinofuranosyluracil (III). To a solution of 300 mg (0.82 mmole) of the nucleoside (IIa) in 10 ml of methylene chloride was added 0.15 ml (1 mmole) of 1,8-diazabicyclo[5.4.0]undec-7-ene, and the solution kept for 16 h at 20°C. Column chromatography with 20 g of silica gel and system C gave 200 mg (73%) of product, mp 194-196°C, R_f 0.09 (C). PMR spectrum (DMSO-D_6): 7.89-7.34 (5H, m, C_6H_5); 7.81 (1H, d, J = 7.5 Hz, 6-H); 6.31 (1H, d, J = 5.5 Hz, 1'-H); 6.09 (1H, d, J = 4.5 Hz, 3'-OH, exchanged on adding D_2O); 5.81 (1H, d, J = 7.5 Hz, 5-H); 5.27 (1H, d.d, J = 5.5 and J = 1.0 Hz, 2'-H); 4.51-4.11 ppm (4H, m, 3'... 5'-H).

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NOVEL SYNTHESIS OF 5-HALOURACILS FROM 5-MERCURI-2,4-DIMETHOXYPYRIMIDINES

L. Skul'ski, A. Kuyava, and P. Vrochin'ski

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Direct C-mercuration of 2,4-dimethoxypyrimidine with mercury (II) acetate has been shown to give the 5-mercuri-derivative, which is readily converted, either directly or via 5,5'-mercuribis (2,4-dimethoxypyrimidine), into the 5-halo derivatives. Hydrolysis of the latter with hydrochloric acid affords the 5-halouracils.

Conversion of 5-halouracils into their mercuri-derivatives is hindered by the formation, on treatment of uracil with solutions of mercury(II) salts, of difficultly soluble 1:1 mercury complexes, which do not undergo further rections [1]. It has, however, recently been reported that micro-amounts of radioactive 5-halouracils may be obtained without isolation of the intermediate 5-chloromercuriuracil [2]*. Unlike uracil itself, 1-methyluracil [3], 1,3-dimethyluracil [3-5], uridine [6], and 2-desoxyuridine [7] are readily C-mercurated in high yields with mercury(II) acetate solution.

We have previously reported [8] the direct C-mercuration of 1-acetyluracil with mercury (II) trifluoroacetate in anhydrous acetonitrile. Symmetrization of the resulting 5-trifluoroacetozymercuriuracil with potassium iodide, and hydrolytic removal of the acyl protection affords 5,5'-mercuribisuracil, which is readily converted into 5-iodo- and 5-chlorouracil [8].

We here report the use of this method for the preparation in high yields of 5-bromouracil (VIb), by treatment of 1-acetyl-5-trifluoroacetoxy-mercuriuracil or 5,5'-mercuribisuracil with KBr_3 solution. A drawback of this method, which has also been used for the preparation of 8-halotheophyllins and theobromines [9], is the great ease of hydrolysis of the N-acyl protection and the consequent reduction of the electron density at the 5-position in the uracil, requiring the use of a more powerful mercurating agent such as the expensive trifluoromercuriacetate, the use of the more readily available mercury(II) and chloride being unsatisfactory in this instance [8, 9].

In the present investigation, we therefore developed a novel, general approach to 5-halouracils (VI) via the intermediate 5-mercuri-2,4-dimethoxy-pyrimidines:

*The use of this method for large quantities will form the subject of a further communication.

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