Synthesis of 5-Iodo-1-(sodium 2-deoxy-β-D-ribofuranosyluronate)uracil and 5-Iodo-1-(sodium β-D-ribofuranosyluronate)uracil

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5-Iodo-1-(sodium 2-deoxy-β-D-ribofuranosyluronate)uracil and 5-Iodo-1-(sodium β-D-ribofuranosyluronate)uracil were synthesized through a sequence of steps involving two key transformations, \textit{i.e.}, iodination in the 5-position of the uracil moiety, using iodine monochloride and triethylamine, and oxidation of the 5'-position of the ribose moiety to give the corresponding t-butyl ribofuranosyluronates in a single reaction step using pyridinium dichromate-acetic anhydride (PDCA) as oxidant in the presence of t-butyl alcohol. After removal of the protective groups the title compounds were obtained.

5-Iodo-2'-deoxyuridine (IDU) is a structural analogue to thymidine. This apparent similarity induces phosphorylation of the 5'-hydroxyl by a herpes virus induced enzyme, thymidine kinase. The resulting 5'-monophosphate is further enzymatically phosphorylated yielding the triphosphate which subsequently is incorporated into herpes virus DNA as well as cellular DNA of infected cells leading to miscoding and the synthesis of defective proteins.

IDU is today a clinically used antiherpes drug even though its use is somewhat restricted due to its high general cell toxicity.

In this paper we report the synthesis of two structural analogues to 5-iodo-5'-monophosphate-2'-deoxyuridine namely 5-iodo-1-(sodium 2-deoxy-β-D-ribofuranosyluronate)uracil (II) and 5-iido-1-(sodium β-D-ribofuranosyluronate)uracil (4).

Iodination at C-5 of 2',3'-O-isopropylideneuridine\textsuperscript{1} (I) and 2'-deoxyuridine (5) was performed using a modification of the method of Robins.\textsuperscript{2} Addition of iodine monochloride to these substrates produced intermediates detected by TLC, presumably the corresponding 6-chloro-5-iodo derivatives. Subsequent addition of triethylamine resulted in elimination of hydrogen chloride to give 5-iido-2'-3'-O-isopropylideneuridine (2) and 5-iido-2'-deoxyuridine (6) isolated in 73 % and 85 % yields, respectively.

Conversion of the hydroxymethyl group of 2 and 8 into a t-butyloxycarbonyl group was attained in a one pot reaction according to the procedure of Corey and Samuelsson.\textsuperscript{3} The oxidation step was slightly modified in that pyridinium dichromate-acetic anhydride (PDCA)\textsuperscript{4} was used in the place of chromium(VI) oxide-pyridine-acetic anhydride.

Reacting 5-iido-2',3'-O-isopropylideneuridine (2) and 3'-O-acetyl-5-iido-2'-deoxyuridine (8) with pyridinium dichromate (2.2 equiv.), acetic anhydride (10 equiv.) and t-butyl
alcohol (20 equiv.) in dichloromethane for 30 min afforded after work up 1-(t-butyl 2,3-O-isopropylidene-β-D-ribofuranosyluronate)-5-iodouracil (3) and 1-(t-butyl-3-O-acetyl-2-deoxy-β-D-ribofuranosyluronate)-5-iodouracil (9) in 77 % and 76 % yields, respectively.

Conventional deblocking of the protective groups afforded the title compounds 5-iodo-1-(sodium β-D-ribofuranosyluronate)uracil (4) (59 % from 3) and 5-iodo-1-(sodium β-D-ribofuranosyluronate)uracil (11) (65 % from 9).

The products 4 and 11 were tested for activity against herpes virus, influenza virus and RNA polymerase but were found to be essentially inactive.

EXPERIMENTAL

General methods were the same as those previously reported.  

5-Iodo-2'-3'-O-isopropylidene-uridine 2. Iodine monochloride, warmed to liquefy, (0.450 ml, 8.59 mmol) was added to a cooled (ice-bath) and stirred solution of 2',3'-O-isopropylidene-uridine (I) (1.0 g, 3.52 mmol) in methanol (20 ml) containing molecular sieves 3Å. After 30 minutes TLC (chloroform—methanol 9:1) indicated complete reaction and the formation of a faster moving component. Triethylamine (10 ml) was added during 30 min and the mixture was stirred for an additional 4 h at 0 °C and filtered through a short pad of silica gel using chloroform—methanol 1:1. The filtrate was concentrated to dryness and the residue subjected to silica gel column chromatography using chloroform—methanol (9:1) as eluent yielding 1.05 g (73%) of 2, m.p. 225–227 °C (from methanol) lit. 9 m.p. 225–227 °C.

1-(Butyl 2,3-O-isopropylidene-β-D-ribofuranosyluronate)-5-iodouracil 3. Pyridinium dichromate (935 mg, 2.49 mmol), acetic anhydride (1.25 g, 12.2 mmol) and t-butyl alcohol (2.30 ml, 24.4 mmol) were added to a stirred solution of 2 (500 mg, 1.22 mmol) in dichloromethane (10 ml) at ambient temperature. After 1 h the reaction mixture was transferred to a silica gel column (3x3 cm) with ethyl acetate (15 ml) on the top. After standing for 15 min the product was eluted with ethyl acetate (3x15 ml). Concentration of the filtrate and silica gel column chromatography using toluene—ethyl acetate (3:1) yielded the title compound 3, 450 mg (77%) as a colourless syrup.

5-Iodo-1-(sodium β-D-ribofuranosyluronate)uracil 4. A solution of 3 (400 mg, 0.83 mmol) in aqueous trifluoroacetic acid (80%, 3 ml) was stirred at room temperature for 3 h, concentrated to dryness and co-evaporated to dryness twice from water (3 ml). Water (3 ml) was added to the resulting residue followed by the dropwise addition of triethylamine until dissolution was complete. The solution was concentrated to dryness, dissolved in a minimum amount of water and passed through a short column of Dowex 50 (sodium form) using water as eluent. Lyophilisation of the eluate, followed by recrystallisation from water, yielded the title compound 4, 300 mg (59%), m.p. 237 °C. Anal: C₂₅H₂₅N₃O₉: C, H, N.

5-Iodo-2'-deoxyuridine 6. Iodine monochloride (1.1 ml, 21 mmol), warmed to liquefy, was added to a stirred and cooled (ice-bath) solution of 2'-deoxyuridine 5 (2.5 g, 11 mmol) in methanol (25 ml). After 30 min triethylamine (25 ml) was added under 30 min. After 1 h the mixture was filtered and evaporated to a thick syrup which was crystallised from methanol-ether 1:1 yielding 2.4 g of 6. The mother liquid was submitted to silica gel column chromatography using chloroform/methanol (9:1) as eluent to yield a second crop 0.9 g. Total yield 3.3 g (85%), m.p. 195 °C (dec) lit. 10 m.p. 160 °C (dec) (from H₂O).

3'-O-Acetyl-5'-O-dimethoxytrityl-5-ido-deoxyuridine 7. Dimethoxytrityl chloride (2.9 g, 8.6 mmol) in pyridine (30 ml) was added to a cooled (ice-bath) and stirred solution of 6 (2.8 g, 7.9 mmol) in pyridine (30 ml) with molecular sieves 3Å. After 4 h acetic anhydride (5 ml) was added. After being stirred for an additional 3 h the mixture was diluted with chloroform (100 ml). The organic layer was washed with water (100 ml), dried (MgSO₄), filtered and concentrated. The crude product was submitted to silica gel column chromatography using toluene—ethyl acetate (3:1) as eluent to yield 3.4 g (62%), of 7 m.p. 195 °C (ether—hexane). Anal: C₉₂H₅₂N₂O₈: C, H, N.

3'-O-Acetyl-5-ido-2'-deoxyuridine 8. 7 (1.1 g, 1.6 mmol) dissolved in 80% trifluoroacetic acid was heated at 50 °C for 30 min. The solvent was evaporated to dryness and diethyl ether (40 ml) was added, which initiated a momentaneous crystallisation. Recrystallisation from ethanol yielded 440 mg (69%) m.p. 189–190 °C. Anal: C₂₁H₁₉N₂O₇: C, H, N, l.

1-(Butyl 3-O-acetyl-2-deoxy-β-D-ribofuranosyluronate)-5-iodouracil 9. Pyridinium dichromate (965 mg, 2.57 mmol), t-butyl alcohol (2.38 ml, 25.2 mmol) and acetic anhydride (1.29 g, 12.6 mmol) were added to a stirred solution of 8 (500 mg, 1.26 mmol) in dichloromethane (10 ml). The mixture was stirred for 30 min at r.t. and then transferred to a silica gel column (3x3 cm) with ethyl acetate (15 ml) on the top. After 15 min the product was eluted with ethyl acetate (3x25 ml) and concentrated to dryness. The residue was dissolved in chloroform (5 ml) and filtered through silica gel (2 cm), using chloroform—ethyl acetate 1:1 as eluent. Recrystallisation from diethyl ether yielded 450 mg (76%) of 9, m.p. 152 °C. Anal: C₁₉H₁₅N₂O₇: C, H, N.

5-Iodo-1-(sodium 2-deoxy-β-D-ribofuranosyluronate)uracil 11. Compound 9 (400 mg,
Table 1. $^{13}$C NMR shifts are given in ppm-values with the respective solvents used as references: DMSO-$d_6$ 39.6 ppm and CDCl$_3$ 77.17 ppm.

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* Were run in DMSO-$d_6$ at 50 °C.  
* Were run in CDCl$_3$ at ambient temperature.

0.86 mol) dissolved in aqueous trifluoroacetic acid (80 %, 3 ml), was stirred at ambient temperature for 30 min. After concentration to dryness water (10 ml) was added, followed by dropwise addition of triethylamine until the product dissolved. After evaporation of the solvent and drying in a vacuum, the product was dissolved in a minimum amount of water and added to a column of Dowex 50 (sodium form). Elution with water and lyophilisation yielded 5-iodo-(sodium 3-O-acetyl-2-deoxy-β-D-ribofuranosyluronate)uracil 10 in a quantitative yield (according to $^{13}$C NMR). The crude product was dissolved in methanol (5 ml) containing sodium methoxide (1.2 mmol) and kept at room temperature overnight. Water (1 ml) was added and the solution was concentrated to approximately 1.5 ml and left at 0 °C to crystallise. Recrystallisation from methanol-water yielded 205 mg (65 %) m.p. approx. 250 °C (dec). Anal: C$_9$H$_8$N$_2$NaO$_6$×6H$_2$O: C, H, N, I.

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REFERENCES


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