Acta Chemica Scandinavica B 39 (1985) 501–504

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, *i.e.*, iodonation 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 (*11*) and 5-iodo-1-(sodium β-D-ribofuranosyluronate)uracil (*4*).

Iodination at C-5 of 2′,3′-*O*-isopropylideneuridine[1] (*1*) and 2′-deoxyuridine (*5*) was performed using a modification of the method of Robins.[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-iodo-2′-3′-*O*-isopropylideneuridine (*2*) and 5-iodo-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.[3] The oxidation step was slightly modified in that pyridinium dichromate-acetic anhydride (PDCA)[4] was used in the place of chromium(VI) oxide-pyridine-acetic anhydride.

Reacting 5-iodo-2′,3′-*O*-isopropylideneuridine (*2*) and 3′-*O*-acetyl-5-iodo-2′-deoxyuridine (*8*) with pyridinium dichromate (2.2 equiv.), acetic anhydride (10 equiv.) and *t*-butyl

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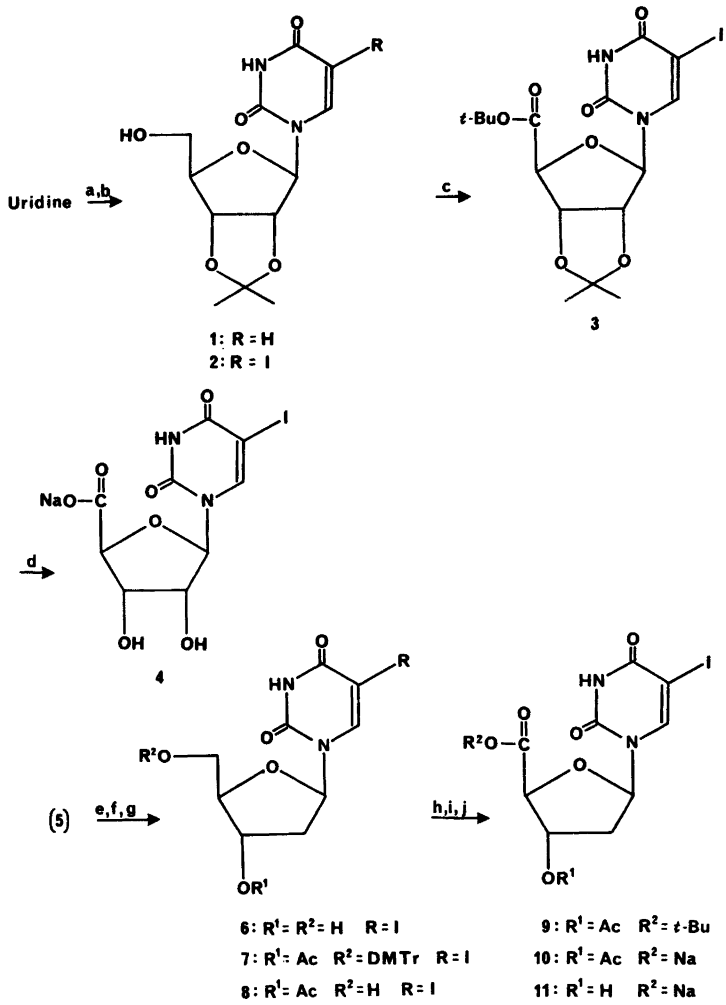

Scheme 1. a: $HC(OMe)_3$, TsOH; b: ICI, Et_3N; c: PDC, Ac_2O, *t*-BuOH; d: TFA, Et_3N, Dowex 50 (Na^+); e: ICI, Et_3N; f: DmTrCl, Pyridine, then Ac_2O; g: HOAc; h: PDCA, Ac_2O; *t*-BuOH; i: TFA; j: NaOMe.

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,[5] influenza virus[6] and RNA polymerase[7] but were found to be essentially inactive.

EXPERIMENTAL

General methods were the same as those previously reported.[8]

*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 (*1*) (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-(t-*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 transfered to a silica gel column (3×3 cm) with ethyl acetate (15 ml) on the top. After standing for 15 min the product was eluated with ethyl acetate (3×15 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: $C_9H_8IN_2NaO_7$: 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 cromatography using chloroformmethanol (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 H_2O).

*3'-*O*-Acetyl-5'-*O*-dimethoxytrityl-5-iodo-deoxyuridine 7.* Dimethoxytritylchloride (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 ($MgSO_4$), 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: $C_{32}H_{31}N_2IO_8$: C, H, N.

*3'-*O*-Acetyl-5-iodo-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 momentanious crystallisation. Recrystallisation from ethanol yielded 440 mg (69 %) m.p. 189–190 °C. Anal: $C_{11}H_{13}N_2IO_6$: C, H, N, I.

1-(t-*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 (3×3 cm) with ethyl acetate (15 ml) on the top. After 15 min the product was eluted with ethyl acetate (3×25 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: $C_{15}H_{19}N_2IO_7$: 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.

	C-1′	C-2′	C-3′	C-4′	C-5′	C-2	C-4	C-5	C-6
1[a]	91.2	83.8	80.6	86.6	61.3	150.4	163.2	101.8	141.9
2[a]	91.4	84.0	80.3	87.0	61.2	150.1	160.6	69.5	146.2
3[b]	97.4	84.4	84.4	88.1	168.5	150.4	160.9	68.7	148.3
4[a]	88.3	74.8	74.0	85.8	174.2	151.4	161.2	68.7	147.3
6[a]	87.4	39.9	69.9	84.7	60.8	149.7	159.9	68.4	144.7
7[b]	85.3	38.7	75.2	84.6	63.6	150.3	160.1	69.3	144.3
8[a]	84.6	37.1	74.2	84.9	60.9	149.8	159.9	68.8	144.5
9[b]	86.9	37.2	76.0	82.9	169.0	150.4	160.1	68.9	145.0
10[a]	86.0	37.2	78.0	85.3	172.6	150.9	161.0	68.4	147.0
11[a]	87.8	39.9	74.5	86.1	174.7	157.7	169.6	72.6	145.0

[a] Were run in DMSO-d_6 at 50 °C. [b] 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: $C_9H_8N_2INaO_6 \times 6H_2O$: C, H, N, I.

Acknowledgements. We are indebted to Professors Bengt Lindberg and Per J. Garegg for their interest, to the Swedish Board for Technical Development and to the Swedish Science Research Council for financial support and to Dr Birgitta Gotthammar at Astra Pharmaceuticals, Södertälje, for the biological evaluation.

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Received October 8, 1984.