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Synthesis of some 2-methylthiouracil nucleosides and its 5-halo analogues of 2-acetamido-2-deoxy-D-glucose

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This paper describes the regiospecific synthesis of 5-halo-2-methylthiouracil nucleosides by direct glycosylation followed by halogenation by an electrophilic halogen reagent and sodium azide under mild conditions. The compounds were suggested to be effective as antiviral agents.

1. Introduction

Many nucleoside analogues have been designed and synthesized by modifying the carbohydrate moiety [1] and/or the base unit [2]. These compounds have been used as broad spectrum antiviral, antibacterial or antitumor agents [3]. Several 5-halouracil nucleosides of chemical and biochemical interest [4–11] have been investigated extensively as antineoplastic and antiviral agents [12–16]. Among these, 5-chlorouracil nucleosides, which are less cytotoxic, exhibit selective anti-HIV activity [17]. 5-Fluoro-2′-deoxyuridine exhibits antileukemic activity, while its 5′-phosphate (FDUMP) is a potent inhibitor of the enzyme thymidylate synthase, and an active antitumor and antifungal agent [18–20]. On the other hand, 5-fluoro-2-thio-2′-deoxyuridine (S^2FDUMP) and its 2-thiocytosine analogue [21] have been proved to be effective inhibitors of the proliferation of several mammalian tumor cell lines [22]. 5-Iodo-2′-deoxyuridine (IDDU) [23] and the new promising antiherpetic agent (2S′)-2′-methyl-5-iodouridine (SMIU) [24] have been proved to be effective against viral infections. In addition, halogenated nucleosides have also been used as synthons for the synthesis of many biologically active nucleosides [25–30]. In this direction, we were successful in synthesizing a series of S^2-alkylated 2-thiouracil nucleosides [31–37] in order to find new antiviral agents. We envisaged that the introduction of 5-fluorouracil moiety, which itself possesses antileukemic properties [38], into a D-glucosamine unit would furnish potential analogues. We report herein the synthesis of new type of 5-halo-2-methylthiouracil nucleosides carrying a 2-acetamido-2-deoxy-D-glucosyl moiety at N-1 as promising antiviral agents.

2. Investigations, results and discussion

In recent years, the chemical synthesis, physical properties and antitumor activity of 1-(2-acetamido-2-deoxy-β-D-glucopyranosyl)uracil (**A**) [39] and 5-halouracil derivatives (**B**) [40] have been described.

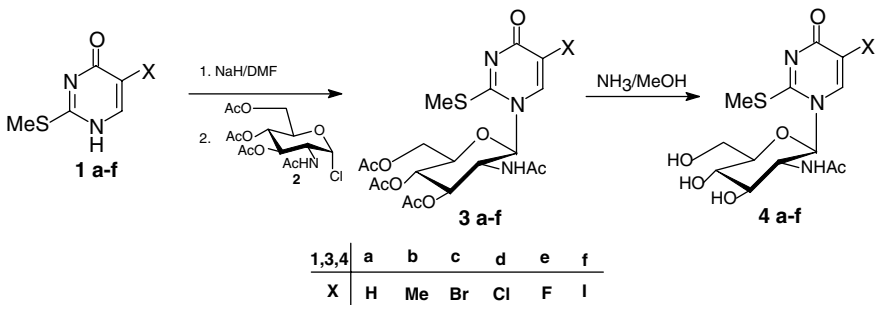
The ease of accessibility and the biological significance of 2-acetamido-2-deoxy-D-glucose [41–43] have prompted us to use this aminosugar as a starting material in glycosylation reactions according to the protocol of Sasaki et al. [44]. Thus, the sodium salt of the 2-methylthiouracils **1a**, **b** [45] and their halo analogues **1c–f** [46, 47] were condensed with 2-acetamido-1-chloro-3,4,6-tri-*O*-acetyl-2-deoxy-D-glucose (**2**) [48] in dry DMF. The reaction was proceeded at 90 °C to give the desired 1-(2-acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-β-D-glucopyranosyl)-2-methylthiouracils **3a**, **b** and their 5-halo analogues **3c–f** in 67–81% yield. Deacetylation of **3a–f** in a mixture of methanol and ammonium hydroxide (25%) (1:1) at room temperature afforded the free nucleosides **4a–f** in 85–93% yield, respectively (Scheme 1).

An attempt to synthesize the free 5-halonucleosides from the parent 2-methylthiouracil derivative **4a**, using the method of Knaus et al. [49] has been examined. The reaction of **4a** with *N*-bromosuccinimide or iodine monochloride, in the presence of sodium azide at 35 °C, gave 5-bromo- and 5-iodo-2-methylthiouracil nucleosides **4c** and **4f** in 68 and 70% yield, respectively. The formation of these products was assumed to occur via a 5-halo-6-azido-5,6-dihydro intermediate, followed by elimination of HN_3 (Scheme 2).

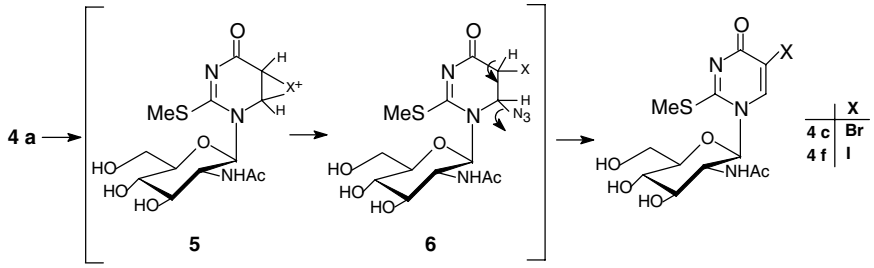
The structures of the nucleosides **3** and **4** were determined on the basis of their respective ^{1}H NMR and mass spectra which were found to be consistent with the assigned structures by comparison with the structures of glycopyranoside analogues [40, 50].

The ^{1}H NMR spectra of **3a–f** showed the anomeric protons as doublets at δ 5.61, 5.65, 5.75, 5.72, 5.73 and 5.43 with J coupling of 9.5, 9.5, 9.5, 9.2, 9.3 and 10.1 Hz, respectively, corresponding to a diaxial orientation of H-1′ and H-2′ protons which are indicative of the β-configu-

Scheme 1



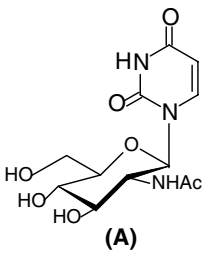
Scheme 2

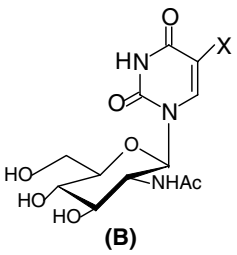


ration. The large coupling constants $J_{2,3}$, $J_{3,4}$, and $J_{4,5}$, (9.0–10.0) Hz confirmed the $^4C_1$ conformation of the sugar moiety. Similarly, the free nucleosides **4a–f** showed, in their ^{1}H NMR spectra, the signals corresponding to anomeric protons as doublets at δ 5.57, 5.35, 5.39, 5.38, 5.39 and 5.57 with large $J_{1',2'}$, coupling constants (10.0, 9.7, 9.5, 9.6, 9.5 and 9.5 Hz, respectively) clearly indicating that these compounds have also the β-configuration. The assignments of the hydroxy groups in these compounds were determined by D_2O exchange.

In conclusion, we have achieved a regiospecific synthesis of 5-halo-2-methylthiouracil nucleosides by the direct glycosylation of 5-halo-2-methylthiouracil with 2-acetamido sugar derivative followed by the halogenation of 2-methylthiouracil nucleoside by an electrophilic halogen reagent and sodium azide under mild conditions.

Preliminary viral screening against HBV indicated that compound **4b** showed moderate viral replication inhibition and low cytotoxicity, while compounds **4c–f** showed high inhibition with moderate cytotoxicity.





3. Experimental

All m.p.'s are uncorrected. Solvents were purified in the usual way. Analytical silica gel TLC plates 60 F_{254} and silica gel (230–400 mesh) were purchased from Merck. The ^{1}H NMR spectra were recorded on a Bruker AC 250 MHz spectrophotometer. Chemical shifts were reported in δ scale (ppm) relative to TMS as internal, and described as s (singlet), d (doublet), t (triplet), q (quartet), or m (multiplet). EI and FAB MS spectra were recorded on MAT 312 mass spectrometer. The microanalyses were performed at the microanalytical unit, Universität Konstanz, Germany, and the values were within ± 0.2% of the theoretical data. Concentrations were performed on a rotary evaporator at a temperature below 40 °C.

3.1. 2-Methylthiouracil nucleosides and its 5-halo analogues of 2-acetamido-3,4,6-tri-O-acetyl-2-deoxy-β-D-glucose (3a–f)

A mixture of 2-methylthiouracils **1a–f** (10 mmol) and 50% oil-immersed sodium hydride (0.48 g, 10 mmol) in DMF (30 ml) was stirred at 70–80 °C for 1 h and then cooled to room temperature. α-Chloroacetamido sugar **2** (3.65 g, 10 mmol) was added to the mixture, and stirred at 90 °C for 2–5 h. The mixture was evaporated to dryness under reduced pressure and chromatographed on a silica gel column with $CHCl_3/CH_3OH$ (97:3) to give **3a–f** in 67–81% yield (Table).

3.1.1. 1-(2-Acetamido-3,4,6-tri-O-acetyl-2-deoxy-β-D-glucopyranosyl)-2methylthiopyrimidin-4(1 H)-one (**3a**)

FAB MS, m/z 472 $(MH)^+$. ^{1}H NMR ($CDCl_3$), (δ ppm): 1.75 (s, 3 H, NHAc), 1.94, 1.99, 2.01 (3 s, 9 H, 3 OAc); 2.50 (s, 3 H, SCH_3); 3.86–4.10 (m, 3 H, H-5′, H-6′); 4.50 (q, 1 H, J = 9.8 Hz, H-2′); 5.11 (dd, 1 H, J = 9.0 Hz, H-4′); 5.25 (t, 1 H, J = 9.8 Hz, H-3′); 5.61 (d, 1 H, J = 9.5 Hz, H-1′); 6.71 (d, 1 H, J = 5.6 Hz, 5-H); 7.80 (d, 1 H, J = 7.7 Hz, NHAc, D_2O exchangeable); 8.48 (d, 1 H, J = 5.5 Hz, 6-H).

Table: Characteristics of compounds 3 and 4

Compd.	Time (h)	Yield (%)	m.p. (°C) (solvent)	Molecular formula (mol. wt.)
3a	3	70	oil	$C_{19}H_{25}N_3O_9S$ (471.5)
3b	2	81	oil	$C_{20}H_{27}N_3O_9S$ (485.5)
3c	4	78	foam	$C_{19}H_{24}BrN_3O_9S$ (550.4)
3d	4	67	oil	$C_{19}H_{24}ClN_3O_9S$ (505.9)
3e	5	69	oil	$C_{19}H_{24}FN_3O_9S$ (489.5)
3f	4	80	foam	$C_{19}H_{24}IN_3O_9S$ (597.4)
4a	2	90	foam	$C_{13}H_{19}N_3O_6S$ (345.4)
4b	2	92	foam	$C_{14}H_{21}N_3O_6S$ (359.4)
4c	2	86	100–101 (EtOH)	$C_{13}H_{18}BrN_3O_6S$ (424.2)
4d	2	85	150–152 (EtOH)	$C_{13}H_{18}ClN_3O_6S$ (379.8)
4e	2	88	foam	$C_{13}H_{18}FN_3O_6S$ (363.3)
4f	2	93	198–199 (EtOH)	$C_{13}H_{18}IN_3O_6S$ (471.2)

3.1.2. 1-(2-Acetamido-3,4,6-tri-O-acetyl-2-deoxy-β-D-glucopyranosyl)-5-methyl-2-methylthiopyrimidin-4(1 H)-one (**3b**)

FAB MS, m/z 486 $(MH)^+$. ^{1}H NMR ($CDCl_3$), (δ ppm): 1.44 (s, 3 H, CH_3); 1.71 (s, 3 H, NHAc); 1.91, 1.98, 2.00 (3 s, 9 H, 3 OAc); 2.49 (s, 3 H, SCH_3); 3.89–4.00 (m, 3 H, H-5′, H-6′); 4.54 (q, 1 H, J = 9.7 Hz, H-2′); 5.15 (dd, 1 H, J = 9.1 Hz, H-4′); 5.23 (t, 1 H, J = 9.8 Hz, H-3′); 5.65 (d, 1 H, J = 9.5 Hz, H-1′); 7.78 (d, 1 H, J = 7.7 Hz, NHAc, D_2O exchangeable); 8.28 (s, 1 H, 6-H).

3.1.3. 1-(2-Acetamido-3,4,6-tri-O-acetyl-2-deoxy-β-D-glucopyranosyl)-5-bromo-2-methylthiopyrimidin-4(1 H)-one (**3c**)

EI MS, m/z 549/551 (bromine isotopes) $(M)^+$. ^{1}H NMR ($CDCl_3$), (δ ppm): 1.79 (s, 3 H, NHAc); 1.94, 1.97, 2.04 (3 s, 9 H, 3 OAc); 2.51 (s, 3 H, SCH_3); 3.91–4.18 (m, 3 H, H-5′, H-6′); 4.47 (q, 1 H, J = 9.7 Hz, H-2′); 5.21 (dd, 1 H, J = 9.1 Hz, H-4′); 5.28 (t, 1 H, J = 9.7 Hz, H-3′); 5.75 (d, 1 H, J = 9.5 Hz, H-1′); 7.75 (d, 1 H, J = 7.7 Hz, NHAc, D_2O exchangeable); 7.98 (s, 1 H, 6-H).

3.1.4. 1-(2-Acetamido-3,4,6-tri-O-acetyl-2-deoxy-β-D-glucopyranosyl)-5-chloro-2-methylthiopyrimidin-4(1 H)-one (**3d**)

FAB MS, m/z 528/530 (chlorine isotopes) $(M + Na)^+$. ^{1}H NMR ($CDCl_3$), (δ ppm): 1.72 (s, 3 H, NHAc); 1.89, 1.98, 2.03 (3 s, 9 H, 3 OAc); 2.50 (s, 3 H, SCH_3); 3.90–4.20 (m, 3 H, H-5′, H-6′); 4.55 (q, 1 H, J = 9.7 Hz, H-2′); 5.32 (dd, 1 H, J = 9.2 Hz, H-4′); 5.31 (t, 1 H, J = 9.7 Hz, H-3′); 5.72 (d, 1 H, J = 9.2 Hz, H-1′); 7.79 (d, 1 H, J = 7.7 Hz, NHAc, D_2O exchangeable); 8.01 (s, 1 H, 6-H).

3.1.5. 1-(2-Acetamido-3,4,6-tri-O-acetyl-2-deoxy-β-D-glucopyranosyl)-5-fluoro-2-methylthiopyrimidin-4(1H)-one (**3e**)

FAB MS, m/z 490 $(MH)^+$. ^{1}H NMR ($CDCl_3$), (δ ppm): 1.80 (s, 3H, NHAc); 1.90, 1.97, 2.00 (3 s, 9H, 3 OAc); 2.50 (s, 3H, SCH_3); 3.90–4.16 (m, 3H, H-5′, H-6′); 4.39 (q, 1H, J = 9.7 Hz, H-2′); 5.20 (dd, 1H, J = 9.0 Hz, H-4′); 5.28 (t, 1H, J = 9.8 Hz, H-3′); 5.73 (d, 1H, J = 9.3 Hz, H-1′); 7.48 (d, 1H, J = 5.5 Hz, 6-H); 7.78 (d, 1H, J = 7.7 Hz, NHAc, D_2O exchangeable).

3.1.6. 1-(2-Acetamido-3,4,6-tri-O-acetyl-2-deoxy-β-D-glucopyranosyl)-5-iodo-2-methylthiopyrimidin-4(1H)-one (**3f**)

FAB MS, m/z 620 $(M + Na)^+$. ^{1}H NMR ($CDCl_3$), (δ ppm): 1.75 (s, 3H, NHAc); 1.91, 1.97, 2.01 (3 s, 9H, 3 OAc); 2.50 (s, 3H, SCH_3); 3.91–4.21 (m, 3H, H-5′, H-6′); 4.45 (q, 1H, J = 9.7 Hz, H-2′); 5.24 (dd, 1H, J = 9.1 Hz, H-4′); 5.29 (t, 1H, J = 9.7 Hz, H-3′); 5.43 (d, 1H, J = 10.1 Hz, H-1′); 7.77 (d, 1H, J = 7.7 Hz, NHAc, D_2O exchangeable); 7.94 (s, 1H, 6-H).

3.2. Free nucleosides of 2-acetamido-2-deoxy-D-glucose (**4a–f**)

A solution of **3a–f** (1 mmol) in a 1 : 1 mixture (50 ml) of CH_3OH and conc. NH_3 was stirred at room temperature for 2 h. The reaction mixtures were concentrated under reduced pressure. The residue were chromatographed on silica gel column using $CHCl_3/CH_3OH$ (93 : 7) to give **4a–f** in 85–93% yield (Table).

3.2.1. 1-(2-Acetamido-2-deoxy-β-D-glucopyranosyl)-2-methylthiopyrimidin-4(1H)-one (**4a**)

FAB MS, m/z 346 $(MH)^+$. ^{1}H NMR ($CDCl_3$), (δ ppm): 1.69 (s, 3H, NHAc); 2.50 (s, 3H, SCH_3); 3.06–3.28 (m, 2H, H-6′); 3.39–3.48 (m, 2H, H-4′, H-5′); 3.65 (dd, 1H, J = 9.0 Hz, H-3′); 3.84 (q, 1H, J = 10.0 Hz, H-2′); 5.11–5.29 (m, 3H, 3 OH, D_2O exchangeable); 5.57 (d, 1H, J = 10.0 Hz, H-1′); 6.68 (d, 1H, J = 5.5 Hz, 5-H); 7.92 (d, 1H, J = 8.5 Hz, NHAc, D_2O exchangeable); 8.41 (d, 1H, J = 5.5 Hz, 6-H).

3.2.2. 1-(2-Acetamido-2-deoxy-β-D-glucopyranosyl)-5-methyl-2-methylthiopyrimidin-4(1H)-one (**4b**)

FAB MS, m/z 360 $(MH)^+$. ^{1}H NMR ($CDCl_3$), (δ ppm): 1.43 (s, 3H, CH_3); 1.68 (s, 3H, NHAc); 2.49 (s, 3H, SCH_3); 3.11–3.30 (m, 2H, H-6′); 3.40–3.50 (m, 2H, H-4′, H-5′); 3.63 (dd, 1H, J = 9.1 Hz, H-3′); 3.86 (q, 1H, J = 10.0 Hz, H-2′); 5.09–5.24 (m, 3H, 3 OH, D_2O exchangeable); 5.35 (d, 1H, J = 9.7 Hz, H-1′); 7.98 (d, 1H, J = 8.6 Hz, NHAc, D_2O exchangeable); 8.40 (s, 1H, 6-H).

3.2.3. 1-(2-Acetamido-2-deoxy-β-D-glucopyranosyl)-5-bromo-2-methylthiopyrimidin-4(1H)-one (**4c**)

(a) From deprotection experiment: EI MS, m/z 423/425 (bromine isotopes) $(M)^+$. ^{1}H NMR ($CDCl_3$), (δ ppm): 1.73 (s, 3H, NHAc); 2.51 (s, 3H, SCH_3); 3.01–3.27 (m, 2H, H-6′); 3.36–3.47 (m, 2H, H-4′, H-5′); 3.79 (t, 1H, J = 9.9 Hz, H-3′); 3.84 (q, 1H, J = 9.8 Hz, H-2′); 4.50–4.64 (m, 3H, 3 OH, D_2O exchangeable); 5.39 (d, 1H, J = 9.5 Hz, H-1′); 7.78 (d, 1H, J = 8.7 Hz, NHAc, D_2O exchangeable); 8.00 (s, 1H, 6-H).
(b) From reaction of **4a** with N-bromosuccinimide: N-Bromosuccinimide (NBS) (0.20 g, 1.1 mmol) was added at 35 °C to a suspension of **4a** (0.34 g, 1 mmol) in 1,2-dimethoxyethane (25 ml) and DMF (5 ml) with a solution of sodium azide (0.26 g, 4 mmol) in H_2O (2 ml). The reaction mixture was stirred for 3 h, the solvent was removed under reduced pressure and the residue was purified by silica gel column using $CHCl_3/CH_3OH$ (93 : 7) to give **4c** in 68% yield. The ^{1}H NMR, m.p. and mixed m.p. were identical with those for the compound prepared according to method (a).

3.2.4. 1-(2-Acetamido-2-deoxy-β-D-glucopyranosyl)-5-chloro-2-methylthiopyrimidin-4(1H)-one (**4d**)

FAB MS, m/z 380/382 (chlorine isotopes) $(MH)^+$. ^{1}H NMR ($CDCl_3$), (δ ppm): 1.71 (s, 3H, NHAc); 2.50 (s, 3H, SCH_3); 3.09–3.25 (m, 2H, H-6′); 3.31–3.47 (m, 2H, H-4′, H-5′); 3.86 (m, 2H, H-2′, H-3′); 4.54–4.70 (m, 3H, 3 OH, D_2O exchangeable); 5.38 (d, 1H, J = 9.6 Hz, H-1′); 7.75 (d, 1H, J = 8.7 Hz, NHAc, D_2O exchangeable); 8.04 (s, 1H, 6-H).

3.2.5. 1-(2-Acetamido-2-deoxy-β-D-glucopyranosyl)-5-fluoro-2-methylthiopyrimidin-4(1H)-one (**4e**)

FAB MS, m/z 364 $(MH)^+$. ^{1}H NMR ($CDCl_3$), (δ ppm): 1.75 (s, 3H, NHAc); 2.50 (s, 3H, SCH_3); 3.25–3.45 (m, 4H, H-4′, H-5′, H-6′); 3.61–3.73 (m, 2H, H-2′, H-3′); 4.54–4.62 (m, 3H, 3 OH, D_2O exchangeable); 5.39 (d, 1H, J = 9.5 Hz, H-1′); 7.56 (d, 1H, J = 5.5 Hz, 6-H); 7.96 (d, 1H, J = 8.6 Hz, NHAc, D_2O exchangeable).

3.2.6. 1-(2-Acetamido-2-deoxy-β-D-glucopyranosyl)-5-iodo-2-methylthiopyrimidin-4(1H)-one (**4f**)

(a) From deprotection experiment: FAB MS, m/z 472 $(MH)^+$. ^{1}H NMR ($CDCl_3$), (δ ppm): 1.72 (s, 3H, NHAc); 2.50 (s, 3H, SCH_3); 3.29–3.75 (m, 8H, H-3′, H-4′, H-5′, H-6′, 3 OH); 3.89 (m, 1H, H-2′); 5.57 (d, 1H, J = 9.5 Hz, H-1′); 7.95–7 (m, 2H, NHAc, 6-H).
(b) From reaction of **4a** with iodine monochloride: Iodine monochloride (ICl, 0.40 g, 2.5 mmol) was added slowly over a 10 min. period to a suspension of sodium azide (0.26 g, 4.0 mmol) in CH_3CN (30 ml) at ice-bath temperature and the stirring was continued for another 5 min. A solution of **4a** (0.34 g, 1 mmol) in CH_3CN (30 ml) and DMF (5 ml) was added to the reaction mixture. The reaction mixture was stirred for overnight at room temperature and the solvent was evaporated off. The residue was chromatographed on silica gel column using $CHCl_3/CH_3OH$ (93 : 7) to give **4f** in 70% yield. The ^{1}H NMR, m.p. and mixed m.p. were identical with those for the compound prepared according to method (a).

3.3. Biological activity studies

Maintenance media were added to the cell culture (Hep G2 2.2.15) together with the tested compounds (final concentration = 10 μM). The supernatant liquid was collected after one, two and/or three weeks. The DNA replication was estimated by the polymerase chain reaction technique. The percentage inhibition could be calculated by the relation between the blanc experiment (containing maintenance media without the tested compounds) and the results obtained after the mentioned periods. The percentage cytotoxicity could be estimated by the relation between the number of the living and dead cells after three weeks counted by the Haemocytometer.

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