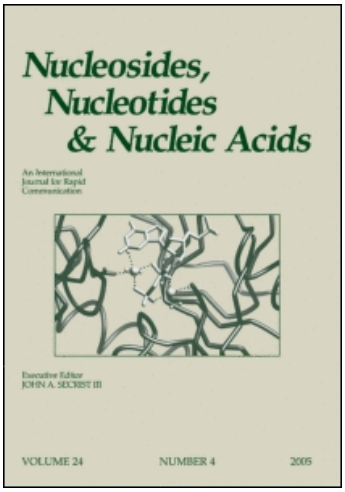

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Haruo Ogura[a]; Hiroshi Takahashi[a]; Kikuko Ohokubo[a]
[a] School of Pharmaceutical Sciences, Kitasato University 5-9-1 Shirokane, Minato-ku, Tokyo, Japan

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STUDIES ON NUCLEOSIDE ANALOGS. XXV.[1)]

SYNTHESIS OF 5,7-DIOXOPYRIMIDO[5,4-e]-AS-TRIAZINE GLYCOSIDES

Haruo Ogura*, Hiroshi Takahashi, and Kikuko Ohokubo

School of Pharmaceutical Sciences, Kitasato University
5-9-1 Shirokane, Minato-ku, Tokyo 108, Japan

Abstract

The reaction of glycosyl isothiocyanates (1a, b, c, d, e) with 5,6-diamino-1,3-dimethyluracil gave the respective 1-glycosyl-3-(6-amino-1,3-dimethyl-2,4-dioxopyrimidine-5-yl)thioureas (2a, b, c, d, e) in excellent yields. Treatment of these thioureas with NBS afforded the respective 5,7-dioxopyrimido-[5,4-e]-as-triazine glycosides (4a, b, c, d, e) in good yields.

Fervenulin, which has some biological activities, was isolated in 1960[2)] and its structure was confirmed by Robins et al.[3)] as 6,8-dimethyl-5,7-dioxo-5,6,7,8-tetrahydro-pyrimido[5,4-e]-as-triazine, which is isomeric with toxoflavin.

Previously, we have reported a synthetic method for sulfur containing nucleoside analogs utilizing glycosyl isothiocyanates[4)] as starting materials, e. g., 1,2,4-triazole glycosides,[5)] 1,2,4,6-thiatriazine-S-glycosides,[6)] glycosylaminoisothiazolo[3,4-d]pyrimidines,[7)] and 1,3,5-triazine glycosides.[8)]

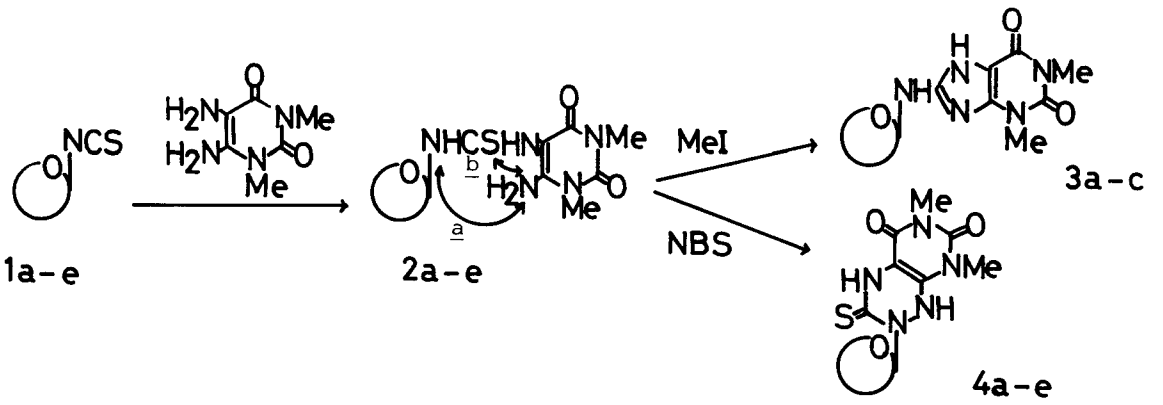
We have also reported a synthetic method for glycosylaminopyrimido[4,5-e]-1,3,4-thiadiazines,[9] polyhydroxyalkyl theophyllines,[10] and 1,2,4-triazole glycosides[11] by the NBS (N-bromosuccinimide) oxidation of glycosyl thiocarboxamides and Schiff bases.

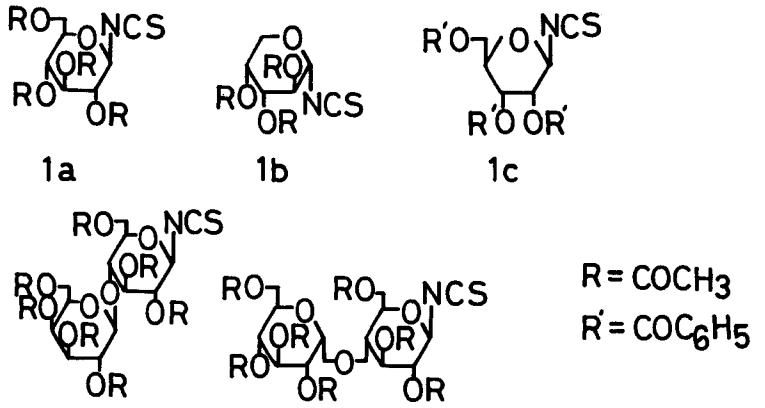
In this paper, we wish to report a convenient method for synthesizing nucleoside analogs possessing the pyrimido[5,4-e]-as-triazine ring system.

Treatment of 2,3,4,6-tetra-O-acetyl-β-D-glucoypranosyl- (1a), 2,3,4-tri-O-acetyl-α-D-arabinopyranosyl- (1b) or 2,3,5-tri-O-benzoyl-β-D-ribofuranosyl isothiocyanate (1c) with 5,6-diamino-1,3-dimethyluracil gave the respective 1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)- (2a), 1-(2,3,4-tri-O-acetyl-α-D-arabinopyranosyl)- (2b), or 1-(2,3,5-tri-O-benzoyl-β-D-ribofuranosyl)-3-(6-amino-1,3-dimethyl-2,4-dioxopyrimidin-5-yl)thiourea (2c) in 94-97% yields. Treatment of 2a-2c with methyl iodide gave the respective glycosylaminotheophyllines (3a, b, c) through a cyclodesulfurization reaction.[12] Similar treatment of hepta-O-acetyl-β-D-lactosyl- (1d) or hepta-O-acetyl-β-D-maltosyl isothiocyanate (1e) with 5,6-diamino-1,3-dimethyluracil in dry acetonitrile under reflux afforded the respective thioureas (2d and e) in 87-95% yields.

The nuclear magnetic resonance (NMR) spectra of 2d and e showed a broad singlet at δ 6.55-6.56 due to the amino group at the 6-position of the pyrimidine ring. Signals of N-CH_3 group appeared at δ 3.06-3.08 and δ 3.28 as singlets, respectively. A doublet peak at δ 7.68 and δ 7.76 (J=8.0 Hz) due to the NH group was attributed to the anomeric position. Another NH proton was observed at δ 8.36-8.40 as a broad singlet, and both NH signals disappeared on addition of D_2O.

The oxidative cyclization reaction of these thioureas was observed with NBS. When 1-glucopyranosyl-3-(6-amino-1,3-dimethyl-





CHART

2,4-dioxopyrimidin-5-yl)thiourea (2a) was treated with NBS at 0-5°C for 30 min, the cyclized product (4a) was obtained in 92% yield after chromatography. In this cyclization reaction, route a is probable. Similarly, ring closure of these thioureas (2b, c; 2d, e) was successful with NBS in chloroform to obtain the respective pyrimido[5,4-e]-as-triazine glycosides (4b, c, d, e) in good yields. The thione structure of the product was established by comparison of the UV spectrum of 4b with the previous values from a report.[13]

In the mass spectrum of thiourea (2b), the molecular ion was observed at m/z 487 (4.2%) and the cleavage of the glycosidic bond produced m/z 259 (100%) (sugar moiety). However, in glycoside 4b, the molecular ion was observed at m/z 485 (2.3%) and the loss of the sulfur atom produced m/z 353 (86%).

In conclusion, the syntheses of the titled glycosides were conveniently accomplished by using NBS as an oxidative cyclization reagent.

EXPERIMENTAL

All melting points are uncorrected. Infrared (IR) spectra were measured with a JASCO A-2 spectrometer and NMR spectra with a Varian T-60 spectrometer. Tetramethyl silane was used as an internal standard. Mass spectra (MS) were determined with a JMS-D-100 spectrometer using a direct inlet system at 75 eV. Optical rotations were measured in $CHCl_3$ or MeOH solution in a 50 mm cell with a JASCO DIP-181 automatic polarimeter. Thin-layer chromatography was performed on pre-coated plates (layer thickness 0.2 mm) of Silica gel F 254 (E. Merck, Darmstadt, Germany).

1-Glycosyl-3-(6-amino-1,3-dimethyl-2,4-dioxopyrimidin-5-yl)thioureas (2a, b, c) ----- These thioureas (2a, b, c) were prepared by our reported method.[12]

1-[O-(2,3,4,6-Tetra-O-acetyl-β-D-galactopyranosyl)-(1→4)-(2,3,6-tri-O-acetyl-β-D-glucopyranosyl)]-3-(6-amino-1,3-dimethyl-2,4-dioxopyrimidin-5-yl)thiourea (2d) ----- A mixture of hepta-O-acetyl-β-D-lactosyl isothiocyanate[14] (1d, 680 mg, 0.001 mol) and 5,6-diamino-1,3-dimethyluracil (170 mg, 0.001 mol) in dry MeCN (10 ml) was refluxed for 6 hr on a water bath, then evaporated to dryness under reduced pressure. The residue was chromatographed on silica gel with $CHCl_3$-acetone (97:3) to give 2d as a syrup in 92% yield. Crystallization from EtOH-Et_2O (1:2) gave 2d as an yellow powder (737 mg, 87%), mp 164-169°C, $[\alpha]_D^{27}$ +22.0° (c=1.0, $CHCl_3$), Rf 0.44 in 9:1 $CHCl_3$-MeOH, NMR (δ, DMSO-d_6): 3.06 (s, 3H, NMe), 3.28 (s, 3H, NMe), 6.55 (bs, 2H, NH_2), 7.68 (bs, 1H, NH), and 8.36 (bs, 1H, NH). MS: m/z 846 (M^+). Anal. Calcd for $C_{33}H_{45}O_{19}N_5S$: C, 46.74; H, 5.35; N, 8.26. Found: C, 46.80; H, 5.38; N, 8.25.

1-[O-(2,3,4,6-Tetra-O-acetyl-β-D-glucopyranosyl)-(1→4)-(2,3,4-tri-O-acetyl-β-D-glucopyranosyl)]-3-(6-amino-1,3-dimethyl-2,4-dioxopyrimidin-5-yl)thiourea (2e) ----- A mixture of hepta-O-acetyl-β-D-maltosyl isothiocyanate[14] (1e, 677 mg, 0.001 mol) and 5,6-diamino-1,3-dimethyluracil (170 mg, 0.001 mol) in dry MeCN (15 ml) was refluxed for 8 hr and treated by a similar manner described above for 2d. Crystallization from EtOH-Et_2O (1:2) afforded 2e as fine colorless needles (805 mg, 95%), mp 157-162°C, $[\alpha]_D^{27}$ +59.0° (c=1.0, $CHCl_3$), Rf 0.57 in 9:1 $CHCl_3$-MeOH, NMR (δ, DMSO-d_6): 3.08 (s, 3H, NMe), 3.28 (s, 3H, NMe), 6.56 (bs, 2H, NH_2), 7.76 (bs, 1H, NH), and 8.40 (bs, 1H, NH). MS: m/z 847 (M^+). Anal. Calcd for $C_{33}H_{45}O_{19}N_5S$: C, 46.74; H, 5.35; N, 8.26. Found: C, 46.72; H, 5.38; N, 8.30.

2-Glycosyl-6,8-dimethyl-5,7-dioxopyrimido[5,4-e]-as-triazine-3-thiones (4a, b, and c) (Table I) ----- NBS (177 mg, 0.001 mol) was added to an ice-cooled solution of 2a, b, or c (0.001 mol) in $CHCl_3$ (10-15 ml) under stirring. After stirring at 0-5°C for

TABLE I. 2-Glycosyl-6,8-dimethyl-5,7-dioxopyrimido[5,4-e]-as-triazine-3-thiones (4a, b, c, d, and e)

Compound	Yield (%)	mp (°c)	NMR (δ, $CDCl_3$) NMe	NH	$[\alpha]_D^{27}$ (c 1.0, MeOH)	MS (m/z)
4a	92	182-185	3.43, 3.52	6.35	-25.0	557 (M^+)
b	86	157-159	3.45, 3.54	6.30	-37.2	485 (M^+)
c	90	syrup[a]	3.12, 3.47	7.42	+4.0	
d	95	150-153	3.24, 3.40	6.60, 8.40[b]	-50.3[c]	
e	88	134-137	3.25, 3.35	7.45[b]		

a: Rf 0.63 t. l. c. [silica gel, benzene-acetone (3:2)]

b: in DMSO-d_6

c: in $CHCl_3$

0.5-1.5 hr, the reaction solution was washed with sat. $NaHCO_3$ solution and H_2O. The organic layer was dried over $MgSO_4$, and evaporated to leave a slight brownish residue. The residue was chromatographed on silica gel with $CHCl_3$-acetone (9:1) to give 4a, b, or c, respectively. 4a: Anal. Calcd for $C_{21}H_{27}O_{11}N_5S$: C, 45.22; H, 4.88; N, 12.57. Found: C, 45.27; H, 4.94; N, 12.51. 4b: Anal. Calcd for $C_{18}H_{23}O_9N_5S$: C, 44.53; H, 4.78; N, 14.43. Found: C, 44.58; H, 4.82; N, 14.43. 4c: Anal. Calcd for $C_{33}H_{29}O_9N_5S$: C, 59.01; H, 4.35; N, 10.43. Found: C, 59.05; H, 4.38; N, 10.40.

2-[O-(2,3,4,6-Tetra-O-acetyl-β-D-galactopyranosyl)-(1→4)-O-2,3,6-tri-O-acetyl-β-D-glucopyranosyl)]-6,8-dimethyl-5,7-dioxopyrimido-[5,4-e]-as-triazine-3-thione (4d) and 2-[O-(2,3,4,6-Tetra-O-acetyl-α-D-glucopyranosyl)-(1→4)-O-(2,3,6-tri-O-acetyl-β-D-glucopyranosyl)]-6,8-dimethyl-5,7-dioxopyrimido[5,4-e]-as-triazine-3-one (4e) ----- To a solution of 2d or e (0.001 mol) in $CHCl_3$ (20-25 ml), NBS (180 mg, 0.001 mol) was added with stirring. After 1-1.5 hr, the reaction solution was treated as described above for 4a. The residue was chromatographed on silica gel, and elution with $CHCl_3$-acetone (97:3) gave the cyclized product as a syrup. Crystallization from EtOH-Et_2O (1:1) or EtOH-iso-Pr_2O (1:1) afforded 4d (800 mg, 95%) as yellow needles, or 4e (740 mg, 88%) as colorless fine needles, respectively. 4d: Rf 0.52 in 9:1 $CHCl_3$-MeOH, IR ν_{max}^{KBr} cm^{-1}: 3250 (NH) and 1740 ($OCOCH_3$). Anal. Calcd for $C_{33}H_{43}O_{19}N_5S$: C, 46.86; H, 5.12; N, 8.28. Found: C, 46.91; H, 5.10; N, 8.32. 4e: Rf 0.62 in 9:1 $CHCl_3$-MeOH, IR ν_{max}^{KBr} cm^{-1}: 3250 (NH) and 1740 ($OCOCH_3$). MS: m/z 813 (M^+-32). Anal. Calcd for $C_{33}H_{43}O_{19}N_5S$: C, 46.86; H, 5.12; N, 8.28. Found: C, 46.80; H, 5.16; N, 8.30.

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