A RECONFIRMATION OF THE REACTION OF GLUCOSYL ISOTHIOCYANATE WITH 2-CHLOROETHYLAMINE

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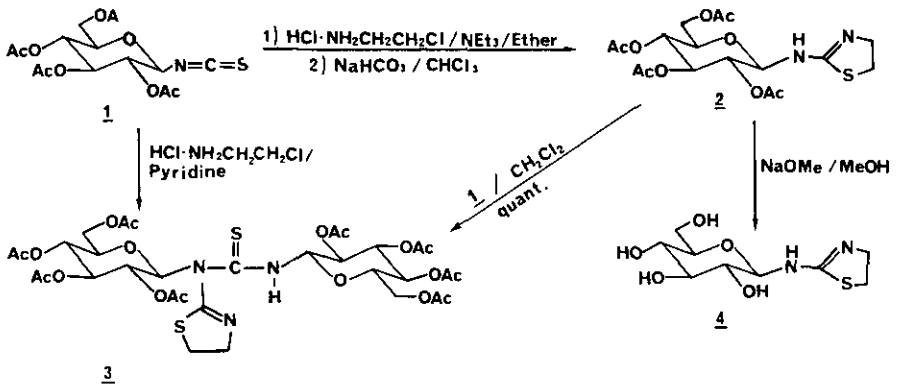
Abstract —— The reaction of tetra-O-acetylglucosyl isothiocyanate (1) with 2-chloroethylamine under basic conditions in aprotic solvent afforded 2-(2',3',4',6'-tetra-O-acetyl-β-D-glucopyranosylamino)-2-thiazoline (2). On the other hand, in pyridine solution this reaction proceeded to form N,N'-bis(2',3',4',6'-tetra-O-acetyl-β-D-glucopyranosyl)-N-(2-thiazolin-2-yl)thiourea (3).
Alkaline hydrolysis of 2 afforded 2-(β-D-glucopyranosylamino)-2-thiazoline (4) as colorless plates, which was confirmed by means of X-ray analysis.

Previously, we have reported a facile synthesis of nucleoside analogs containing thioureylene group from glycosyl isothiocyanates with ω-chloroalkylamine or ethanol amine to yield glycosyl imidazolidine-2-thione derivatives.[1] On the other hand, Gonzalez et al.[2] reported the products formed in the same reaction to be glycosyl-aminoheterocycles in stead of the N-nucleosides.

On the process of the revaluation of this reaction, we found some mistakes in the previous report.[1] In this paper, we reconfirmed a product of the same reaction by means of X-ray analysis.

2,3,4,6-Tetra-O-acetyl-β-D-glucopyranosyl isothiocyanate (1) was treated with 2-chloroethylamine hydrochloride-triethylamine in dry ether. After evaporation of reaction solvent, sodium hydrogen carbonate solution was added and the mixture was extracted with chloroform to yield 2-(2',3',4',6'-tetra-O-acetyl-β-D-glucopyranosyl amino)-2-thiazoline (2) in 63% yield as a syrup.

On the other hand, treatment of 1 with 2-chloroethylamine hydrochloride in pyridine afforded N,N'-bis(2',3',4',6'-tetra-O-acetyl-β-D-glucopyranosyl)-N-(2-thiazolin-2-



yl)thiourea (3) in low yield as a syrup. Structure of this compound was confirmed by means of nmr and mass spectra as shown in experimental part.

This compound (3) was obtained from equimolar of 1 and 2 in dichloromethane immediately. Sodium methoxide treatment of 2 at room temperature gave rise to 2-(β-D-glucopyranosylamino)-2-thiazoline (4) in quantitative yield as colorless plates, mp 179-184℃. The structure of this compound was confirmed by means of X-ray analysis.

EXPERIMENTAL

Melting points were determined with Yamato melting point apparatus, and are uncorrected. Field desorption mass spectra (FD-ms) and fast atom bombardment mass spectra (FAB-ms) were measured with JEOL JMS DX-300 and JEOL JMA-3100 instruments. Infrared (ir) spectra were measured with JASCO ir-A 2 instrument. Nuclear magnetic resonance (nmr) spectra were obtained with Varian 300 and 400 instruments in the FT mode. Chemical shifts (δ) were expressed in part per million (ppm) from internal tetramethylsilane in deuteriochloroform ($CDCl_3$).

2-(2',3',4',6'-Tetra-O-acetyl-β-D-glucopyranoxylamino)-2-thiazoline (2)

A suspension of 2-chloroethylamine hydrochloride (58 mg, 0.5 mmol) and triethylamine (51 mg, 0.5 mmol) in dry ether (10 ml) was stirred for 5 h at room temperature. 2,3-4,6-Tetra-O-acetyl-β-D-glucopyranosyl isothiocyanate (1) (180 mg, 0.5 mmol) was added to the suspension, which was stirred at room temperature for 24 h. After evaporation of ether, chloroform (10 ml) and 4% $NaHCO_3$ solution (10 ml) were added

to the residue. The resulted mixture was stirred for 1 h at room temperature, which was extracted with chloroform (X 3), and the chloroform solution was washed with water and brine solution successively, dried over $MgSO_4$ and concentrated. The residual syrup was purified by preparative tlc on silica gel (benzene: acetone = 5 : 1) to yield 2 (135 mg, 63%) as a syrup. Mass: Calcd for $C_{17}H_{24}O_9N_2S$: 432.120. Found *m/z*: M^+ 432.118. Ir ν_{max}^{film} cm^{-1}: 3350, 2950, 1750, 1640. ^{1}H-Nmr (300 MHz) δ: 1.96, 1.98, 2.00, 2.03 (12H, s x 4, $(OAc)_4$), 3.27 (2H, t, J=7.5 Hz, SCH_2), 3.73-3.80 (1H, m, H-5'), 3.80-3.95 (2H, m, NCH_2), 4.06 (1H, dd, J=2.0, 12.1 Hz, H-6'a), 4.24 (1H, dd, J=4.5, 12.1 Hz, H-6'b), 4.84 (1H, d, J=9.0 Hz, H-1'), 4.90 (1H, t, J=9.0 Hz, H-2'), 5.04 (1H, t, J=10.0 Hz, H-4'), 4.95-5.10 (1 H, NH), 5.23 (1H, t, J=9.0 Hz, H-3').

N,N'-Bis(2',3',4',6'-tetra-O-acetyl-β-D-glucopyranosyl)-N-(2-thiazolin-2-yl)thiourea (3)

To a solution of 2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl isothiocyanate (1) (180 mg, 0.5 mmol) in pyridine (3 ml), 2-chloroethylamine hydrochloride (58 mg, 0.5 mmol) was added at room temperature under stirring. After 24 h, reaction mixture was quenched with water, and the solution was extracted with ethyl acetate (x 3) and the organic layer was washed with 0.5 N HCl, water, and brine solution successively. Evaporation of the dried organic layer left a syrup, which was purified by preparative tlc on silica gel (benzene : acetone = 5 : 1) to yield 3 (113.2 mg, 28%) as a colorless syrup. This compound (3) was obtained quantitatively from equimolar of 1 and 2 in benzene. Mass (FAB) *m/z*: 822 (M^++1). Ir ν_{max}^{film} cm^{-1}: 2960, 1760, 1603. Anal. Calcd for $C_{32}H_{43}O_{18}N_3S_2.\frac{1}{2}H_2O$: C, 46.26; H, 5.33; N, 5.05. Found: C, 46.38; H, 5.22; N, 4.79. ^{1}H-Nmr (300 MHz) δ: 1.98, 1.99, 2.00, 2.01, 2.02, 2.03, 2.04 (24 H, s × 7, $(OAc)_8$), 3.14 (2H, m, CH_2S), 3.77 (2H, m, H_2-5'), 4.08 (1H, m, H-6"a), 4.10 (1H, m, H-6"b), 4.21 (2H, m, H_2-6'), 4.36 (1H, m, CH_xCH_yN=), 4.37 (1H, d, J=8.6 Hz, H-1'a), 5.02 (1H, m, CH_xCH_yN=), 5.08 (1H, t, J=10.0 Hz, H-4'a), 5.09 (1H, t, J=10.0 Hz, H-4'b), 5.26 (2H, t, J=9.5 Hz, H-3'a, H-3'b), 5.42 (1H, dd, J=8.5, 9.5 Hz, H-2'a), 5.48 (1H, t, J=9.5 Hz, H-2'b), 5.75 (1H, dd, J=8.3, 9.5 Hz, H-1'a), 12.50 (1H, d, J=8.3 Hz, NH).

2-(β-D-Glucopyranosylamino)-2-thiazoline (4)

A one drop of 28% sodium methoxide in methanol was added to 2 (50 mg) in dry methanol (0.5 ml) at room temperature. After 30 min, the solution was subjected by preparative tlc on silica gel (MeOH : $CHCl_3$=1 : 1) to yield 4 (30.5 mg) quantitatively,

as colorless crystals. Recrystallization from EtOH-MeOH gave colorless plates, mp 179-184℃. Mass *m/z*: 265 (M^++1). Ir ν_{max}^{film} cm^{-1}: 3350, 3260, 2900, 1630. Anal. Calcd for $C_9H_{16}O_5N_2S$: C, 40.90; H, 6.10; N, 10.59. Found: C, 40.85; H, 6.11; N, 10.29.

X-Ray Analysis

Crystal Data: $C_9H_{16}O_5N_2S$, M 264.36, orthorhombic, space group $P2_12_12_1$, a=8.742 (3), b=17.886(4), c=7.814(3) Å, V=1221.8 Å^3, Dc=1.437 g/cm^3 for Z=4. μ(Cu-$K\alpha$ = 2.644 cm^{-1}). F(000)=2240.

A colorless platelet crystal with approximate dimensions of 0.25 X 0.20 X 0.20 mm^3 was used. X-ray experiments were carried out on a Rigaku automated four-circle diffractometer (AFC-4) using graphite-monochromated Cu-$K\alpha$ radiation (λ=1.5418 Å). Crystal density was measured by a flotation method using carbon tetrachloride-hexane mixture. Intensity data of the crystal were collected by the ω-2θ scan technique at a 2θ rate of 8° /min. Backgrounds were counted for 5 sec at both ends of a scan. Three standard reflections were measured after every 100 reflections to monitor the stability and orientation of the crystal, which showed no significant decay throughout the data collection. Total of 1064 reflections out of 1241 were observed ($|Fo| > 3\sigma(Fo)$), where $\sigma(Fo)$ is the standard deviation obtained by the counting statistics of intensities. Usual Lorentz and polarization corrections were applied but no absorption and extinction corrections were made.

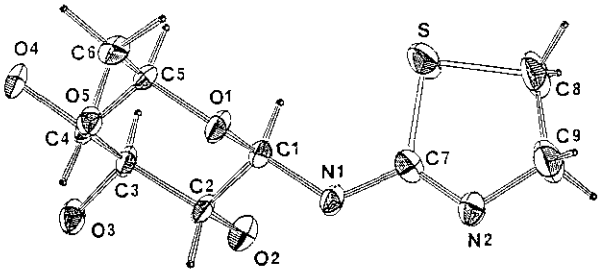


Fig. 1. Perspective drawing of the molecule with the atomic numbering

Structure Solution and Refinement

The structure of each crystal was established by the direct method (MULTAN 78)[3] and refined anisotropically by the block-diagonal least-squares procedure. Hydrogen

atoms (except for the hydrogen atoms attached to C6, C8, and C9) could be located on the difference Fourier map, including the refinement with isotropic temperature factors. In the final cycle of the refinement, all the parameter shifts were less than one-third of the corresponding standard deviations. The scattering factors were taken from Tables.[4] The function minimized was $\Sigma w(|Fo|-|Fc|)^2$. The weighting scheme used was w=1.0. The final $R(=\Sigma||Fo|-|Fc||/\Sigma|Fo|)$ was 0.096 for observed reflections.

Results and Discussion

The positional parameters of nonhydrogen atoms with their isotropic equivalent temperature factors are shown in Table I.[5] Atomic distances and bond angles are shown in Tables II and III. The perspective drawing[6] of the compound and the numbering scheme of the atoms are shown in Fig. 1.

Table I. The Positional Parameters and Equivalent Isotropic Thermal Parameters with Their Estimated Standard Deviation in Parentheses

Atom	x (×10⁴)	y (×10⁴)	z (×10⁴)	Beq/Å²
S 1	9076(4)	5278(2)	6602(8)	6.9
O 1	11262(8)	3592(5)	5313(10)	3.4
O 2	10797(9)	3414(5)	9990(10)	3.5
O 3	13532(9)	2601(5)	9389(10)	3.9
O 4	15227(8)	3051(5)	6392(11)	3.5
O 5	12774(9)	2697(4)	2862(9)	3.0
N 1	9051(9)	3768(5)	6911(13)	3.1
N 2	6739(10)	4376(6)	6826(15)	4.0
C 1	10709(11)	3782(6)	7036(15)	2.7
C 2	11274(11)	3208(6)	8267(15)	2.9
C 3	13028(11)	3189(6)	8298(15)	2.9
C 4	13587(11)	3019(6)	6475(16)	2.9
C 5	12916(12)	3593(6)	5184(18)	3.5
C 6	13263(12)	3414(7)	3295(15)	3.3
C 7	8216(13)	4398(6)	6809(16)	3.2
C 8	7258(18)	5750(7)	6843(25)	6.4
C 9	6069(16)	5125(8)	6689(27)	6.5

Table II. Bond Lengths (l/Å)

(Standard deviations are in parentheses.)

S 1	—	C 7	1.752(11)
S 1	—	C 8	1.809(15)
O 1	—	C 1	1.470(13)
O 1	—	C 5	1.450(12)
O 2	—	C 2	1.458(13)
O 3	—	C 3	1.424(14)
O 4	—	C 4	1.436(11)
O 5	—	C 6	1.393(13)
N 1	—	C 1	1.453(12)
N 1	—	C 7	1.346(13)
N 2	—	C 7	1.292(14)
N 2	—	C 9	1.464(16)
C 1	—	C 2	1.491(15)
C 2	—	C 3	1.533(13)
C 3	—	C 4	1.537(16)
C 4	—	C 5	1.554(16)
C 5	—	C 6	1.541(18)
C 8	—	C 9	1.531(20)
C 9	—	C 8	1.531(20)

Table III. Bond Angles (ϕ/°)

(Standard deviations are in parentheses.)

C 7	—	S 1	—	C 8	91.8(6)
C 1	—	O 1	—	C 5	113.1(8)
C 1	—	N 1	—	C 7	122.1(8)
C 7	—	N 2	—	C 9	111.8(9)
O 1	—	C 1	—	N 1	105.2(8)
O 1	—	C 1	—	C 2	108.8(8)
N 1	—	C 1	—	C 2	111.2(8)
O 2	—	C 2	—	C 1	109.1(8)
O 2	—	C 2	—	C 3	106.1(8)
C 1	—	C 2	—	C 3	110.9(8)
O 3	—	C 3	—	C 2	109.6(8)
O 3	—	C 3	—	C 4	108.1(8)
C 2	—	C 3	—	C 4	107.9(8)
O 4	—	C 4	—	C 3	110.6(8)
O 4	—	C 4	—	C 5	108.7(8)
C 3	—	C 4	—	C 5	110.5(8)
O 1	—	C 5	—	C 4	109.3(8)
O 1	—	C 5	—	C 6	105.2(9)
C 4	—	C 5	—	C 6	114.2(9)
O 5	—	C 6	—	C 5	111.3(8)
S 1	—	C 7	—	N 1	121.7(8)
S 1	—	C 7	—	N 2	117.2(8)
N 1	—	C 7	—	N 2	121.1(9)
S 1	—	C 8	—	C 9	104.4(9)
N 2	—	C 9	—	C 8	113.0(11)

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