The Structure of the Oxazolidine-2-thione Derivative of D-Glucose[*1]

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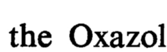
Some reducing sugars[1-3] have been reported to give crystalline condensation products having an oxazolidine-2-thione ring by reaction with thiocyanic acid. The structural studies on the mode of condensation between oxazolidine-2-thione ring and sugar ring in these compounds have been mainly performed for the corresponding glucose derivative (I).

A



B

Zemplen *et al.*[1] gave the formula A for I, however, the formula B has generally been accepted from the following facts. Edward and Martlew[4] showed by paper chromatography the presence of 1-aminoglucose and diglucosylamine in the hydrolysate of I, but no glucosamine was demonstrated which was expected from the formula A. Wickström and Wold[5] also supported the formula B by comparison of the pK_a value of I with those of simple oxazolidine-2-thiones. As for the ring size of the sugar moiety in I, Schwarz[6] concluded the presence of a furanose ring from the facts that one mole of formaldehyde was liberated by periodate oxidation and orthoformate was formed by treatment with ethyl orthoformate.

Recently Jochims *et al.*[7] reported on the synthesis and the structure of I and its homologues in which I was proved to be D-glucofurano[1′, 2′: 4, 5]-oxazolidine-2-thione (formula B) from the NMR data in dimethylsulfoxide-d_6. H_1 (the proton attached to the C-1 of the sugar moiety) was found to be weakly coupled to NH and H_4 not to any hydroxyl protons. The authors have also obtained the same results by NMR studies of some derivatives of I.

It will be rationally expected that the *N*-acetylation of I should affect most strongly the chemical

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[*1] This paper was presented at the 20th Annual Meeting of The Chemical Society of Japan, April, 1967.

1) G. Zemplen, A. Gerecs and M. Rados, *Ber.*, **69**, 748 (1936).

2) G. Zemplen, A. Gerecs and E. Illes, *ibid.*, **71**, 590 (1938).

3) N. H. Bromund and R. M. Herbst, *J. Org. Chem.*, **10**, 2267 (1945).

4) J. T. Edward and E. F. Martlew, *Chem. Ind. (London)*, **1952**, 1034.

5) A. Wickström and J. K. Wold, *Acta. Chem. Scand.*, **13**, 1129 (1959).

6) J. P. C. Schwarz, *J. Chem. Soc.*, **1954**, 2644.

7) J. C. Jochims, A. Seeliger and G. Taigel, *Chem. Ber.*, **100**, 845 (1967).

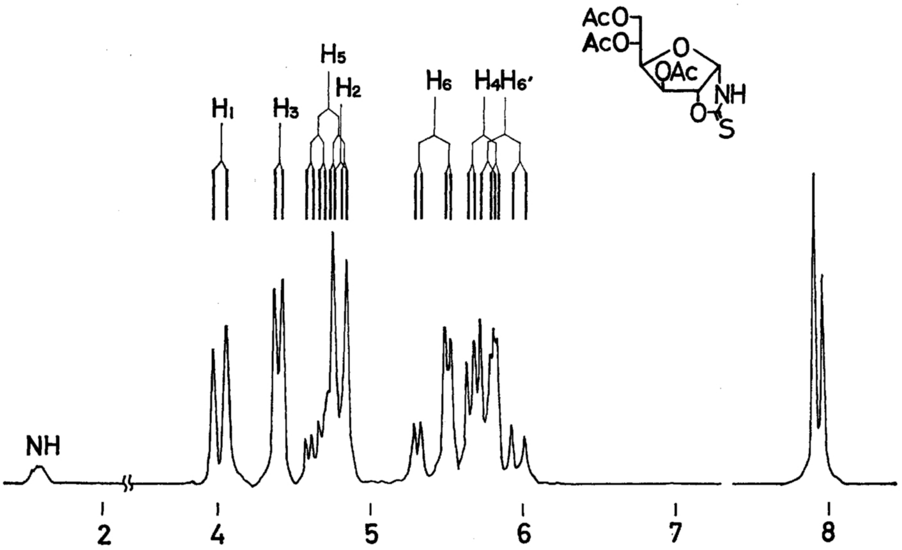

Fig. 1. NMR spectrum of II in $CDCl_3$ at 60 Mc.

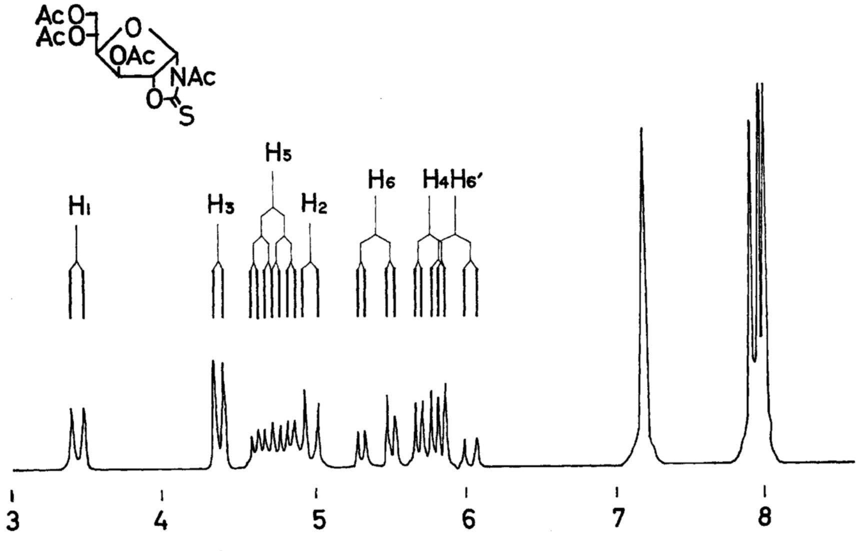

Fig. 2. NMR spectrum of III in $CDCl_3$ at 60Mc.

shift of the proton on the carbon attached to the nitrogen atom. In comparison of the NMR spectra of the tri-*O*-acetate (II) and tetra-*N*, *O*-acetate (III) of I[1] (Figs. 1 and 2), it was observed that the chemical shift of H_1 was shifted far to the lower field, but that of H_2 was slightly to the higher field although those of other ring protons were almost identical (Table 1). This fact indicates that the nitrogen is attached to C-1 of the sugar ring. The unexpected shift of H_2 will be explained by the prevention of the contribution from the en-thiol structure in the *N*-acetyl derivative.

The dihedral angles in compounds II and III calculated from observed coupling constants by the modified Karplus equation of Abraham and coworkers[8] were 40° and 42° between H_1 and H_2, 80° and 80° between H_2 and H_3, and 53° and 53° between H_3 and H_4 respectively. These values imply that the furanose ring in these compounds has a "twist" conformation in which C-2 and C-3 are out of the plane containing the other ring members as shown in the case of 1, 2-*O*-isopropylidene-D-glucofuranose and its derivatives.[8]

The presence of the furanose ring in I was also ascertained by chemical methods. It is known

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[8] R. J. Abraham, L. D. Hall, L. Hough and K. A. McLauchlan, *J. Chem. Soc.*, **1962**, 3699.

Table 1. The NMR spectral data of D-glucofurano[1′, 2′:4, 5]oxazolidine-2-thione derivatives

Chemical shifts (τ values)

Compound	H_1	H_2	H_3	H_4	H_5	H_6	$H_{6'}$	OH
II	4.03 d	4.82 d	4.41 d	5.75 q	4.73 m	5.42 q	5.89 q	—
III	3.50 d	5.02 d	4.43 d	5.81 q	4.78 m	5.46 q	5.98 q	—
IV	4.12 d	4.92 d	5.80 d	6.37 q	5.68 m	6.10 q	6.18 q	4.28 d
V	4.00 d	4.75 d	5.18 d	···	···	···	···	4.84 t
VI	4.05 d	4.90 d	5.65 b	6.12 q	5.60 m	5.90 q	6.05 q	4.20 d

Coupling constants (cps)

Compound	$J_{1,2}$	$J_{2,3}$	$J_{3,4}$	$J_{4,5}$	$J_{5,6}$	$J_{5,6'}$	$J_{6,6'}$	$J_{H,OH}$
II	5.1	<0.5	3.0	9.0	2.6	5.4	12.3	—
III	4.8	<0.5	3.0	9.0	2.7	5.7	12.3	—
IV	5.4	<0.5	2.5	6.0	6.0	6.0	6.5	5.0
V	6.0	<0.5	2.0	···	···	···	···	*ca.* 5.0
VI	5.4	<0.5	2.5	5.0	6.0	6.0	6.0	*ca.* 5.0

d : doublet, t : triplet, q : quartet, m: multiplet, b : broad.
--- These peaks were not resolved.

that the glucopyranose ring can not be isopropylidenated,[9] however, I gave a mono-isopropylidene derivative (IV), whose NMR spectrum measured in dimethyl sulfoxide-d_6 showed the hydroxyl signal at 4.28 (τ value) in doublet, indicating the presence of the secondary hydroxyl group. Therefore, IV should be 5′, 6′-*O*-isopropylidene-D-glucofurano[1′, 2′:4, 5]oxazolidine-2-thione, but not the corresponding 3′, 5′-*O*-isopropylidene derivative.

When I was benzylidenated with benzaldehyde and zinc chloride, two isomers which showed mp 232—233°C (V) and 186—188°C (VI) respectively were obtained. In the NMR spectra of these compounds also measured in dimethyl sulfoxide-d_6, each hydroxyl proton appears at 4.83 in triplet and at 4.20 in doublet, indicating the presence of a primary and a secondary hydroxyl group respectively. So V and VI were proved to be 3′, 5′-*O*-benzylidene- and 5′, 6′-*O*-benzylidene-D-glucofurano[1′, 2′: 4, 5]oxazolidine-2-thione respectively.

Experimental

NMR spectra were measured on JNM-3H-60 spectrometer at 60 Mc in deuterochloroform for II and III, and in dimethyl sulfoxide-d_6 for IV, V and VI respectively. Tetramethylsilane was used as an internal reference in each case.

5′, 6′-*O*-Isopropylidene-D-glucofurano[1′,2′ : 4,5]-oxazolidine-2-thione (IV). To a suspension of I (2.4 g) in dry acetone (60 m*l*) concentrated sulfuric acid (0.8 m*l*) was added dropwise with stirring in an ice-water bath, and the stirring was continued for a few hours. The reaction mixture was poured into ice-water containing sodium bicarbonate (5 g), and extracted with methylene chloride (100 m*l*). Methylene chloride layer was washed with water and dried over anhydrous sodium sulfate. Evaporation of methylene chloride gave white residue, which was recrystallized from ethanol, mp 220—221°C, $[\alpha]_D^{22}$ +33.0° (*c* 1.8, pyridine), yield 1.7 g.

Found: C, 46.05; H, 5.74; N, 5.48%. Calcd for $C_{10}H_{15}O_5NS$: C, 45.97; H, 5.79; N, 5.36%.

3′, 5′-*O*-Benzylidene- and 5′, 6′-*O*-Benzylidene-D-glucofurano[1′, 2′ : 4, 5]oxazolidine-2-thione (V and VI). A suspension of I (2.5 g) and anhydrous zinc chloride (3.0 g) in benzaldehyde (20 m*l*) was shaken for 1 hr to give a clear solution. The reaction mixture was poured into ice-water, stirred with petroleum ether, and the petroleum ether layer was decanted. It was repeated twice more to give a mixture of crystals and hard sirup. When this mixture was dissolved in hot ethanol (*ca.* 30 m*l*), a small amount of crystals was remained undissolved, which was filtered and recrystallized from a little larger amount of ethanol to give V as white crystals, mp 232—233°C, $[\alpha]_D^{22}$ +66.5° (*c* 1.0, pyridine), yield 0.2 g.

Found: C, 54.27; H, 4.84; N, 4.57%. Calcd for $C_{14}H_{15}O_5NS$: C, 54.36; H, 4.89; N, 4.53%.

From the filtrate, another crystals were separated and recrystallized from ethanol to give VI, mp 186—188°C, $[\alpha]_D^{22}$ +68.1° (*c* 1.0, pyridine), yield 0.6 g.

Found: C, 54.43; H, 4.92; N, 4.68%. Calcd for $C_{14}H_{15}O_5NS$: C, 54.36; H, 4.89; N, 4.53%.

The authors thank Mr. T. Tanaka of Science University of Tokyo for the oxazolidine-2-thione derivative of D-glucose.

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[9] J. A. Mills, "Advances in Carbohydrate Chemistry," Vol. 10, ed. by C. S. Hudson and S. M. Cantor, Academic Press Inc., Publishers, New York, N. Y. (1955), p. 1.