Synthesis of Acetyl Derivatives of 2-Amino-2-deoxy-1,6-dithio-D-glucose

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From 2-anisylideneamino-1,3,4-tri-O-acetyl-2,6-dideoxy-6-S-acetyl-6-thio-β-D-glucopyranose, three derivatives of 2-amino-2-deoxy-1,6-dithio-n-glucose were prepared, i.e., 2-anisylideneamino-3,4-di-O-acetyl-1,2,6-trideoxy-1,6-di-S-acetyl-1,6-dithio-β-D-glucopyranose, 2-amino-3,4-di-O-acetyl-1,2,6-trideoxy-1,6-di-S-acetyl-1,6-dithio-β-n-glucopyranose hydrochloride and 2-acetamido-3,4-di-O-acetyl-1,2,6-trideoxy-1-mercapto-6-S-acetyl-1,6-thio-β-n-glucopyranose; and some of their properties were described.

Amino sugars containing sulfhydryl group have attracted attention in the last few years, because some of the aminothiol compounds have been reported to protect animal cells from damage by ionizing radiation1). The syntheses of the derivatives of 3-amino-3-deoxy-2-thio-D-allose and 3-amino-3-deoxy-2-thio-D-altrose were reported by J.E. Christensen and L. Goodman2). W. Meyer Zu Reckendorf and W. A. Bonner3) published a series of papers dealing with the synthesis of sulfur substitution compounds of amino sugar. The synthetic methods of 2-acetamido-2-deoxy-1-thio-D-glucose and its derivatives were described by M. Akagi, S. Tejima and M. Haga4); and very recently, D. Horton and M. L. Wolfrom5) reported the synthesis of the derivatives of 2-amino-2-deoxy-1-thio-n-glucose. In our laboratory, 2-amino-6-mercapto-2,6-dideoxy-D-glucose hydrochloride6) was prepared in the crystalline form.

The present work is concerned with the synthesis of acetyl derivatives of 2-amino-2-deoxy-1,6-dithio-n-glucose. The starting material was 2-anisylideneamino-1,3,4-tri-O-acetyl-2,6-dideoxy-6-S-acetyl-6-thio-β-D-glucopyranose (I)6,3d).

Treatment of compound I with hydrogen bromide7) in acetic acid solution afforded 2-anisylideneamino-3,4,6-tri-O-acetyl-2-deoxy-β-D-glucopyranosyl bromide (II), which was unstable and was used without further purification. Compound II condensed readily with potassium thiolacetate8) and 2-anisylideneamino-3,4-di-O-acetyl-1,2,6-trideoxy-1,6-di-S-acetyl-1,6-dithio-β-n-glucopyranose (III) crystallized from the solution. The structure of III was confirmed by the comparison of its infrared absorption spectrum with those of 2-anisylideneamino-1,3,4-tri-O-acetyl-2,6-dideoxy-6-S-acetyl-6-thio-β-D-glucopyranose (VI) and 2-anisylideneamino-3,4,6-tri-O-acetyl-1,2-dideoxy-1-thio-β-D-glucopyranosyl bromide described by L. Zervas and S. Korotas: Chem. Ber., 93, 435 (1960). The condensation of potassium thiolacetate with halogeno compounds of glucosamine was reported by W. Meyer Zu Reckendorf and W.A. Bonner8b), and D. Horton and M.L. Wolfrom9a).
Compound III showed the absorption bands of O-acetate carbonyl at 1740 cm\(^{-1}\) and S-acetate carbonyl at 1690 cm\(^{-1}\) (with a shoulder at 170 cm\(^{-1}\)) (in Nujol) and the intensities of these two bands were almost identical, while the absorption peaks of S-acetate carbonyl in compound VI and VII have weaker intensities than their peaks of O-acetate carbonyl groups. The \(\beta\)-anomeric configuration was assigned to compound III on the basis of the similarity of its molecular rotation ([\(\alpha\)]\(_D\)^23 +85° in CHCl\(_3\)) with those of compound VI\(^6\) ([\(\alpha\)]\(_D\)^20 +84° in CHCl\(_3\)) and VII\(^{3a}\) ([\(\alpha\)]\(_D\)^25 +125° in CHCl\(_3\)).

Hydrolysis of anisylidene group of compound III with hydrogen chloride in acetone gave hydrochloride of 2-amino-3,4-di-O-acetyl-1,2,6-trideoxy-1,6-di-S-acetyl-1,6-dithio-\(\beta\)-D-glucopyranose (IV), in good yield. The anomeric center of compound IV is assumed.

**FIG. 1. Infrared Spectrum of 2-Acetamido-3,4-di-O-acetyl-1,2,6-trideoxy-1-mercaptopo-6-S-acetyl-6-thio-\(\beta\)-D-glucopyranose (in KBr pellet).**
to be β-configuration from its negative optical rotation in water.

On treatment of compound IV with sodium acetate in water, 2-acetamido-3,4-di-O-acetyl-1,2,6-trideoxy-1-mercapto-6-S-acetyl-6-thio-β-D-glucopyranose (V) was obtained. Similar conversion of 2-amino-3,4,6-tri-O-acetyl-1,2-di-deoxy-1-S-acetyl-1-thio-β-D-glucopyranose hydrochloride to 2-acetamido-3,4,6-tri-O-acetyl-1,2-dideoxy-1-mercapto-β-D-glucopyranose was reported by W. Meyer Zu Reckendorf and W. A. Bonner. The infrared spectrum (in KBr) (Fig. 1) of compound V showed bands of SH (2560 cm⁻¹), acetamido (1668 and 1538 cm⁻¹), O-acetate (1760 cm⁻¹) and S-acetate (1700 cm⁻¹) groups. The negative optical rotation suggested an anomeric β-configuration.

The compounds III, IV and V may be the first examples of trideoxy trisubstituted glucopyranose.

**EXPERIMENTAL**

Melting points are uncorrected. Infrared spectra were determined by Nippon Bunko DS 401 infrared spectrophotometer.

2-Anisylideneamino-3,4-di-O-acetyl-1,2,6-trideoxy-1,6-di-S-acetyl-1,6-dithio-β-D-glucopyranose (III).

Glacial acetic acid (5 ml), which had been saturated with hydrogen bromide at 0°C, and dry chloroform (3 ml) was added to 2-anisylideneamino-1,3,4-tri-O-acetyl-2,6-dideoxy-6-S-acetyl-6-thio-β-D-glucopyranose (I) (5 g). After dissolving, the mixture was allowed to stand for 2 hours at room temperature, then was poured into 200 ml of dry ether. The gummy precipitate was washed with ether and petroleum ether, and was dried in a desiccator over sodium hydroxide. This crude 2-anisylideneamino-3,4-di-O-acetyl-2,6-dideoxy-6-S-acetyl-6-thio-β-D-glucopyranosyl bromide (II) (4.9 g) was dissolved in 25 ml of dry acetone and was mixed with the ethanolic solution (16 ml) of potassium thiolacetate (2 g). The precipitated potassium bromide was filtered off and the solution was allowed to stand at room temperature. After about three hours, the separated needle crystals of compound III were filtered off and washed with ether. The yield was 2.1 g (40% from compound I). This was recrystallized from acetone, m.p. 210-211°C, [α]₂⁰_D+85° (c, 1.2 in chloroform).

Anal. Found: C, 53.2; H, 5.4; N, 2.4; S, 13.2. Calcd. for C₂₂H₂₇NO₈S₂: C, 53.1; H, 5.5; N, 2.8; S, 12.9%.

2-Amino-3,4-di-O-acetyl-1,2,6-trideoxy-1,6-di-S-acetyl-1,6-dithio-β-D-glucopyranose Hydrochloride (IV).

The above compound III (250 mg) was dissolved in hot acetone (50 ml), and to this solution concd. hydrochloric acid (0.06 ml) was added. After 3 hours standing in a refrigerator, the needle crystals were filtered off.

The yield, 200 mg (95%). This was recrystallized from a mixture of methanol and ether, m.p. 191°C, [α]₂⁰_D+27° (c, 1 in dimethyl sulfoxide), [α]₁⁰_D+45° (c, 1.5 in water). Anal. Found: C, 40.7; H, 5.6; N, 3.0. Calcd. for C₁₄H₂₁O₇NS₂.HCl: C, 40.4; H, 5.3; N, 3.4%.

2-Amino-1,3,4-tri-O-acetyl-2,6-dideoxy-6-S-acetyl-6-thio-β-D-glucopyranosyl hydrochloride reported to have [α]₂⁰_D+3.8° (in water) and [α]₁⁰_D+38.2° (in dimethyl sulfoxide). 2-Amino-1,3,4,6-tri-O-acetyl-1,2-dideoxy-1-S-acetyl-1-thio-β-D-glucopyranose hydrochloride was reported to have [α]₂⁰_D−2.4° (in water).

2-Acetamido-3,4-di-O-acetyl-1,2,6-trideoxy-1-mercapto-6-S-acetyl-6-thio-β-D-glucopyranose (V).

A solution of compound IV (110 mg) and sodium acetate trihydroxide (80 mg) in water (5 ml) was extracted four times with chloroform. After the extract was evaporated in vacuo to dryness, the crystalline residue was recrystallized from a mixture of ethylacetate and petroleum ether, 60 mg (50%), m.p. 165-168°C, [α]₁⁰_D−4° (c, 1.8 in CHCl₃). Anal. Found: C, 44.6; H, 5.9; N, 3.6; S, 17.4. Calcd. for C₁₄H₂₁O₇NS₂: C, 44.3; H, 5.6; N, 3.9; S, 16.9%.

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