hydrochloric acid was added. The mixture was warmed on the steam bath for 15 min., allowed to cool, and extracted with ether. The extract was washed with water, dried over anhydrous magnesium sulfate, filtered, and evaporated to leave a solid residue of 0.916 g., which was purified by chromatography on 100 g. of silica gel. From the benzene-ether (1:1) eluates a total of 0.186 g. of crude lactone VII was obtained. The compound was recrystallized from acetone to give 0.098 g., m.p. 214–216°; admixture of this compound with a reference sample of VII did not depress the melting point.

The eluates with ether and ether-acetone (95:5) gave, after the evaporation of the solvent, 0.747 g. of impure 17β-hydroxy-3-oxo-4-estren-16β-ylacetic acid lactone (IX). The compound was recrystallized from acetone–petroleum ether (b.p. 90–95°) to yield 0.573 g. of the desired lactone IX, m.p. 212–213°.

An analytical sample had a m.p. of 212–213°; $[\alpha]_D^{25}$ +76° (*c*, 1.07 chloroform); $\lambda_{max}^{CH_3OH}$ 239 mμ (ε 18,200); $\lambda_{max}^{CHCl_3}$ 5.66 μ, 6.00 μ, 6.17 μ, 8.53 μ.

Anal. Calcd. for $C_{20}H_{28}O_3$: C, 76.40; H, 8.34. Found: C, 76.32; H, 8.46.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, STANFORD UNIVERSITY]

Sulfur Substitution Compounds of Amino Sugars. I 1-Thio-D-glucosamine[1]

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We have attempted to devise synthetic methods for the preparation of a new class of carbohydrates, the 2-amino-2-deoxy-1-thioaldoses, of which 1-thio-D-glucosamine hydrochloride (XI) is a prototype. Various preliminary attempts to prepare XI, unsuccessful, but leading to crystalline derivatives of XI, as well as a successful preparation of XI, are described.

Besides a small number of alkyl thioglycosides and thioacetals of D-glucosamine (2-amino-2-deoxy-D-glucose)[2] no sulfur-containing substitution products of aminosugars seem to be known. Only very recently Christensen and Goodman[3] described a potential starting material for the synthesis of 2,3-, and 3,2-thioamino sugars. On the other hand thio- derivatives of nitrogen-free carbohydrates are well known and readily available. About fifty years ago Schneider and co-workers[4] published a series of papers dealing with the synthesis and reactions of 1-thio-D-glucose, the most accessible of the various thioglucose isomers. However, crystalline unsubstituted thioglucose derivatives have yet to be described, despite continued interest in these substances.[4,5] Our own interest in this field has directed our studies toward the synthesis of 1-thio-D-glucosamine and its disulfide, prototypical of two new classes of *S,N*-containing carbohydrates, making use of several of the polyacetyl-α-D-glucosaminyl halide derivatives already described in the literature. Of the methods known for introducing a mercapto group we have chosen the reaction of such halogeno compounds with potassium thioacetate, with the hope of obtaining easily hydrolyzable *S*-acetyl derivatives[6] as precursors.

Reaction of 3,4,6-tri-*O*-acetyl-*N*-acetyl-α-D-glucosaminyl chloride[7] with potassium thioacetate gave the expected 3,4,6-tri-*O*-acetyl-*N*-acetyl-*S*-acetyl-1-thio-β-D-glucosamine (I) in 80% yield. Hydrolysis of the latter with ammonia in methanol without exclusion of air led, with simultaneous autooxidation, to di(*N*-acetyl-β-D-glucosaminyl) disulfide (II). Attempts to hydrolyze I by the Zemplen method failed to give an *O*-acetyl-free product. Reacetylation of II gave the corresponding acetate, di(3,4,6-tri-*O*-acetyl-*N*-acetyl-β-D-glucosaminyl) disulfide (III). Reduction of III under acetylating conditions[8] regenerated the starting material I. The course of these reactions was readily followed with infrared spectra, which showed the presence or absence of *O*-, *S*-, and *N*-acetyl groups unambiguously.

As it has proved impossible to hydrolyze the *N*-acetyl group in I, II, and III without affecting the glycosidic center of these compounds, it became obvious that a more readily removable nitrogen substituent would be required before unsubstituted 1-thio-D-glucosamine could be obtained. A compound promising in this connection appeared to us to be the recently described[9] 3,4,6-tri-*O*-acetyl-*N*-

(1) The authors are indebted to the U.S. Army Medical Research and Development Command (Contract DA-49-193-MD-2070) for its generous support of this investigation.

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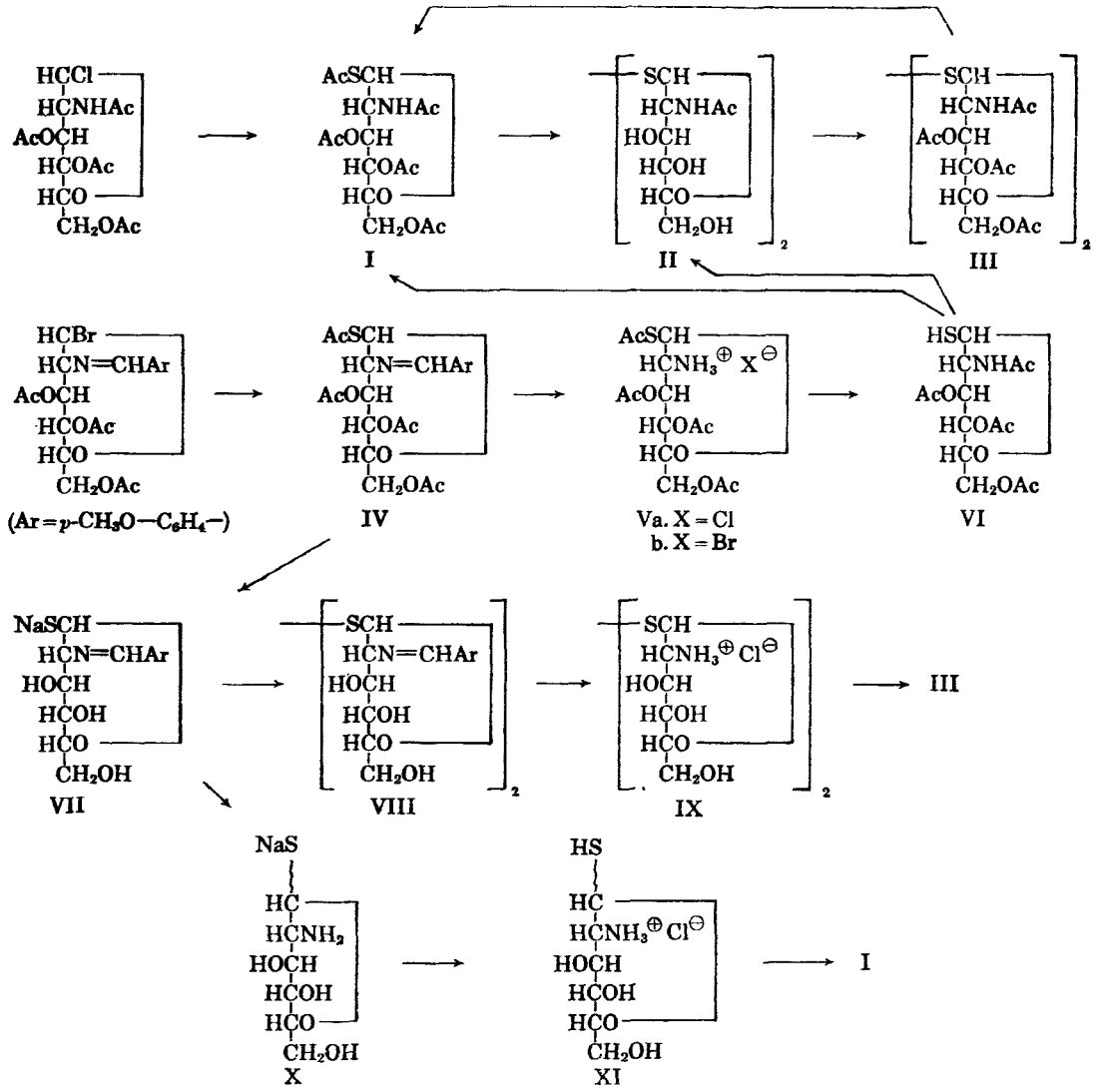

p-methoxybenzylidene-α-D-glucosaminyl bromide. Reaction of this substance with potassium thioacetate readily yielded the expected 3,4,6-tri-*O*-acetyl-*S*-acetyl-*p*-methoxybenzylidene-1-thio-β-D-glucosamine (IV). Hydrolysis of the latter Schiff base with hydrogen chloride and hydrogen bromide in acetone, according to the method of Bergmann and Zervas,[10] afforded in good yield both the hydrochloride (Va) and hydrobromide (Vb) of 3,4,6-tri-*O*-acetyl-*S*-acetyl-1-thio-β-D-glucosamine. Attempts, however, to convert the hydrohalides Va and Vb to the corresponding free base either by sodium acetate in water[10] or by rapid passage of their methanolic solution through an anion exchange resin (Amberlite IRA-400 in the OH-form) failed, 3,4,6-tri-*O*-acetyl-*N*-acetyl-1-thio-β-D-glucosamine (VI) being obtained in good yield instead. Thus a facile acetyl migration from sulfur at C-1 to nitrogen at C-2 apparently occurs as soon as the amino group in Va or Vb becomes freed. Acetylation of VI readily yielded the above mentioned 3,4,6-tri-*O*-acetyl-*N*-acetyl-*S*-acetyl-1-thio-β-D-glucosamine (I). The product obtained by hydrolysis of VI with ammonia in methanol was identical with the above described di(*N*-acetyl-β-D-glucosaminyl) disulfide (II).

This route to the synthesis of a nitrogen-unsubstituted derivative having failed, we next attempted to remove the acetyl groups of IV *prior* to removal of the Schiff base function. The Zemplen method, using a catalytic trace of sodium methylate, again failed probably because of the formation of the sodium salt of the resulting mercaptan. Treatment with ammonia in methanol also proved unsuccessful in that the desired product, obtained under a variety of conditions, was invariably contaminated with *N*-acetyl byproducts. Reaction of IV, however, with a large *excess* of sodium methylate proved successful, resulting in the theoretical quantity of the sodium salt of *N*-*p*-methoxybenzylidene-1-thio-β-D-glucosamine (VII), which crystallized as an analytically pure monohydrate. Oxidation of the sodium salt VII with iodine led to the formation of di(*N*-*p*-methoxybenzylidene-β-D-glucosaminyl) disulfide (VIII) which, on hydrolysis with dilute hy-

(10) M. Bergmann and L. Zervas, *Ber.*, 64, 975 (1931).

drochloric acid, gave the desired di(β-D-glucosaminyl) disulfide dihydrochloride (IX) as a crystalline white powder. The product obtained by acetylation of the latter substance was identical with the above described di-(3,4,6-tri-*O*-acetyl-*N*-acetyl-β-D-glucosaminyl) disulfide (III), showing the identity of configurations at their respective anomeric carbon atoms. Following the general rules of substitution for poly-*O*-acetyl-α-D-glycosyl halides, the anomeric centers in the above described compounds are assumed to be of the β-configuration, an assumption given tentative support by their low or negative optical rotations.

The conversion of the Schiff base VII to its primary amine analog X was next undertaken by direct acid- and base-catalyzed hydrolyses. Treatment of VII with dilute ammonium hydroxide engendered the immediate liberation of anisaldehyde and yielded the anticipated sodium salt of 1-thioglucosamine (X), a stable, white powder. The latter was readily convertible into the desired 1-thio-D-glucosamine hydrochloride (XI) by absorption on Amberlite IRA-400, followed by washing and elution with dilute hydrochloric acid. Similar conversion of VII to XI could be conveniently conducted without the intermediate isolation of the sodium salt X. Acidic hydrolysis of VII also led to X, but in inferior yield and purity.

The lability of the hydrochloride XI, due apparently to its ready autooxidation, anomerization, and hydrolysis, led to difficulties in its purification and characterization. Its recrystallization (from mixtures of methanol and 2-propanol) invariably led to several fractions of differing optical rotation, the highest noted of which was $[\alpha]_D^{25}$ +167° (water), a value tentatively suggestive of an anomeric α-configuration. Both the optical rotation and the oxidizable sulfur content of XI dropped markedly after several days, even when the sample was kept in a dry atmosphere. Aqueous solutions of XI, colorless when fresh, became yellow and evolved hydrogen sulfide within less than twenty-four hours, apparently because of the spontaneous hydrolysis of XI to D-glucosamine, which could be subsequently detected by paper chromatography. Despite its lability, however, the structure of XI was readily demonstrable by its facile, almost quantitative acetylation to the above described 3,4,6-tri-*O*-acetyl-*N*-acetyl-*S*-acetyl-1-thio-β-D-glucosamine (I).

EXPERIMENTAL[11]

3,4,6-Tri-O-acetyl-N-acetyl-S-acetyl-1-thio-β-D-glucosamine (I).[12] To a solution of 3,4,6-tri-*O*-acetyl-*N*-acetyl-α-D-glucosaminyl chloride[7] (3.65 g.; 0.01 mole) in acetone (50 ml.) was added a solution of thioacetic acid (1.5 g.; 0.02 mole) and potassium hydroxide (1.0 g.; 0.018 mole) in dilute ethanol (50 ml.). After precipitation of potassium chloride and standing for 1 hr. the mixture was poured into water and extracted with chloroform. The chloroform layer was washed with sodium bicarbonate solution and water, then dried and evaporated *in vacuo* to give the product (3.3 g.; 80%). This was recrystallized from 2-propanol, m.p. 196–197°, $[\alpha]_D^{25}$ + 14.1° (chloroform, *c* 2.16).

Anal. Calcd. for $C_{16}H_{23}O_9NS$: C, 47.40; H, 5.72; N, 3.46; S, 7.91. Found: C, 47.11, 47.25; H, 5.92, 5.79; N, 3.25; S, 7.96.

Di-(N-acetyl-β-D-glucosaminyl) disulfide (II). The above compound I (810 mg., 2 mmoles) was dissolved in absolute methanol saturated with dry ammonia (60 ml.) and the solution was allowed to stand overnight at room temperature. After evaporation *in vacuo* the resulting syrup was dissolved in absolute ethanol and precipitated as a white solid by addition of absolute ether. The latter was recrystallized from a small amount of ethanol yielding 400 mg. (83%) of product, m.p. 207–208° dec. Several recrystallizations from a mixture of dilute ethanol and ethyl acetate raised the m.p. to 226–227° dec., $[\alpha]_D^{25}$ −224° (water, *c* 1.0).

Anal. Calcd. for $C_{16}H_{28}O_{10}N_2S_2 \cdot {}^1/_2\ H_2O$: C, 39.91; H, 6.07; N, 5.82; S, 13.32. Found: C, 39.74, 39.83; H, 5.97, 6.01; N, 5.77; S, 13.54.

Di(3,4,6-tri-O-acetyl-N-acetyl-β-D-glucosaminyl) disulfide (III). The above disulfide II (50 mg.) was warmed with a mixture of acetic anhydride (0.3 ml.) and pyridine (0.5 ml.) until solution was complete, then left at room temperature overnight and evaporated *in vacuo*. The solid residue was recrystallized three times from 2-propanol to give 30 mg. (40%) of product, m.p. 240–241° dec., $[\alpha]_D^{25}$ −98° (pyridine, *c* 0.9).

Anal. Calcd. for $C_{28}H_{40}O_{16}N_2S_2$: C, 46.40; H, 5.56; N, 3.87; S, 8.85. Found: C, 46.41; H, 5.74; N, 3.82; S, 8.90.

Reduction of III *to* I. The disulfide III (50 mg.) and anhydrous sodium acetate (10 mg.) in acetic anhydride (0.6 ml.) were boiled for 10 min. after adding 100 mg. of zinc dust. The undissolved material was centrifuged and the solution was diluted with water and extracted with chloroform. After drying and evaporation of the chloroform layer the solid residue was recrystallized from 2-propanol yielding 45 mg. (80%) of colorless needles, m.p. and mixed m.p. with I, 195–196°, infrared spectrum identical to that of I.

3,4,6-Tri-O-acetyl-S-acetyl-N-p-methoxybenzylidene-1-thio-β-D-glucosamine (IV). To 490 mg. (1 mmole) of 3,4,6-tri-*O*-acetyl-*N*-*p*-methoxybenzylidene-α-D-glucosaminyl bromide[9] in acetone (5 ml.) was added a solution of thioacetic acid (150 mg.) and potassium hydroxide (100 mg.) in dilute ethanol (5 ml.). After precipitation of potassium bromide the product crystallized, and was completely precipitated by pouring the mixture into water (50 ml.). The crystals were filtered, washed with water, dried over potassium hydroxide and recrystallized thrice from ethanol to give 280 mg. (58%) of product, m.p. 199–200° dec., $[\alpha]_D^{25}$ +125° (chloroform, *c* 0.87).

Anal. Calcd. for $C_{22}H_{27}O_9NS$: C, 54.87; H, 5.65; N, 2.91; S, 6.66. Found: C, 54.60, 54.54; H, 5.45, 5.37; N, 2.88; S, 6.64.

3,4,6-Tri-O-acetyl-S-acetyl-1-thio-β-D-glucosamine hydrochloride (Va). A solution of the above product IV (480 mg.; 1 mmole) in acetone (15 ml.) was heated to boiling and concd. hydrochloric acid (0.1 ml.) was added. After cooling and addition of ether the product crystallized and was recrystallized from glacial acetic acid to give 360 mg. (90%) of colorless crystals, m.p. 202–203° dec. $[\alpha]_D^{25}$ −2.4° (water, *c* 1.68).

Anal. Calcd. for $C_{14}H_{22}O_8NSCl$: C, 42.05; H, 5.55; N, 3.50; S, 8.02; Cl, 8.87. Found: C, 42.16, 42.07; H, 5.55, 5.53; N, 3.51; S, 7.90; Cl, 8.76.

3,4,6-Tri-O-acetyl-S-acetyl-1-thio-β-D-glucosamine hydrobromide (Vb). This material was prepared in a manner analogous to that of Va above. Yield, 400 mg. (90%), m.p. 218–219° dec., $[\alpha]_D^{25}$ −4.4° (water, *c* 2.04).

Anal. Calcd. for $C_{14}H_{22}O_8NSBr$: C, 37.85; H, 4.99; N, 3.15; S, 7.22; Br, 17.99. Found: C, 37.69, 37.75; H, 4.89, 4.97; N, 3.15; S, 7.21; Br, 18.15.

3,4,6-Tri-O-acetyl-N-acetyl-1-thio-β-D-glucosamine (VI). (a) *With sodium acetate.* A solution of the above product Vb

(11) Melting points are corrected.

(12) Synthesized by Mr. Philip I. McNamee.

(440 mg.; 1 mmole) and anhydrous sodium acetate (160 mg.) in water (10 ml.) was extracted three times with chloroform. The extract was evaporated to yield a crystalline product which was recrystallized from a mixture of ethyl acetate and petroleum ether (b.p. 35–55°), 290 mg. (80%), m.p. 167–168°, $[\alpha]_D^{25}$ −14.5° (chloroform, *c* 0.9).

Anal. Calcd. for $C_{14}H_{21}O_8NS$: C, 46.27; H, 5.83; N, 3.86; S, 8.82. Found: C, 46.15, 46.27; H, 5.73, 5.74; N, 3.98; S, 8.77.

(b) *With Amberlite IRA 400.* The above Vb (220 mg., 0.5 mmole) dissolved in methanol (15 mg.) was passed rapidly within 5 min. through a column of Amberlite IRA 400 (10 g., OH-form) wet with methanol. After elution with methanol (50 ml.) the solution was evaporated to a syrup which rapidly crystallized and proved to be completely identical with the preceding product.

Hydrolysis of VI. A solution of the above product VI (50 mg.) in absolute methanol (3 ml.) saturated with ammonia was left at room temperature overnight, then evaporated. The residue was dissolved in absolute ethanol and the product was precipitated by addition of absolute ether. After recrystallization from a mixture of ethanol and ethyl acetate the pure product, 20 mg. (61%) was obtained. Its identity with the above described di(*N*-acetyl-β-D-glucosaminyl) disulfide (II) was established by m.p. and mixed m.p., 207–208° dec., and infrared spectral comparison.

Acetylation of VI. The above compound VI (50 mg.) was left at room temperature overnight in a mixture of pyridine (0.2 ml.) and acetic anhydride (0.1 ml.). The solution was then evaporated *in vacuo* to give a crystalline residue which, after recrystallization from 2-propanol had a m.p. of 196–197° and showed no mixed melting point depression with and no infrared spectral differences from the above described 3,4,6-tri-*O*-acetyl-*N*-acetyl-*S*-acetyl-1-thio-β-D-glucosamine (I).

Sodium salt of N-p-methoxybenzylidene-1-thio-β-D-glucosamine (VII). Six milliliters of a solution of sodium (3 g.) in absolute methanol (100 ml.) was added with vigorous stirring to a suspension of the above compound IV (2 g.) under nitrogen. The suspension at once became a thin slurry from which the product crystallized immediately. After standing for 30 min. at room temperature the sodium salt was filtered, washed with methanol and dried to give 1.4 g. (95%), m.p. 163–164° dec., $[\alpha]_D^{22}$ − 33.4° (water, *c* 1.32). It analyzed as a monohydrate.

Anal. Calcd. for $C_{14}H_{18}O_5NSNa \cdot H_2O$: C, 47.58; H, 5.71; N, 3.96; S, 9.07. Found: C, 47.0; H, 5.7, 5.8; N, 3.9; S, 9.0.

Di(N-p-methoxybenzylidene-β-D-glucosaminyl) disulfide (VIII). The above sodium salt VII (1.4 g.) in water (28 ml.) was oxidized with a solution of potassium triiodide in water until the uptake of iodine ceased. The disulfide crystallized as colorless needles during the reaction, was filtered, carefully washed with water, and recrystallized from hot water. The yield was 850 mg. (65%) of a product which softened at about 135° and had $[\alpha]_D^{25}$ −336° (ethanol, *c* 0.81).

Anal. Calcd. for $C_{28}H_{36}O_{10}N_2S_2$: C, 53.83; H, 5.81; N, 4.49; S, 10.27. Found: C, 53.0, 53.1; H, 5.8, 5.9; N, 4.4; S, 9.8.

Di(β-D-glucosaminyl) disulfide dihydrochloride (IX). The above compound VIII (850 mg.) in dilute hydrochloric acid (1 ml. of concd. hydrochloric acid and 19 ml. of water) was left overnight at room temperature. The solution was then extracted three times with ether to remove the anisaldehyde and finally evaporated *in vacuo* to dryness. The crystalline residue was recrystallized from a mixture of methanol and 2-propanol to give 510 mg. (83%) of a white, crystalline, hygroscopic powder which began to swell at about 180° and decomposed at about 200° and showed $[\alpha]_D^{25}$ −87° (water, *c* 1.2) without mutarotation.

Anal. Calcd. for $C_{12}H_{26}O_8N_2S_2Cl_2 \cdot H_2O$: C, 30.07; H, 5.89; N, 5.84; S, 13.38; Cl, 14.80. Found: C, 30.6; H, 6.1; N, 6.1; S, 13.4; Cl, 14.6.

Acetylation of IX. A solution of the above compound IX (50 mg.) in acetic anhydride (0.3 ml.) and pyridine (0.5 ml.) was allowed to stand at room temperature overnight, then evaporated *in vacuo* to a sirup which was dissolved in chloroform. The solution was washed with water, evaporated *in vacuo*, and the residue was freed of water by addition of absolute ethanol and evaporation. The crystalline product was recrystallized from 2-propanol, 56 mg. (75%), m.p. 240–241°, and was shown by infrared spectra and mixed melting point to be the above di(3,4,6-tri-*O*-acetyl-*N*-acetyl-β-D-glucosaminyl) disulfide (III).

Sodium salt of 1-thio-D-glucosamine (X). The sodium salt of *N-p*-methoxybenzylidene-1-thio-β-D-glucosamine (VII), (1.4 g.) was dissolved in dilute ammonia (10 ml. of concd. ammonium hydroxide and 40 ml. of water) and the solution allowed to stand overnight, then extracted three times with ether. After evaporation of the aqueous layer *in vacuo* with the aid of absolute ethanol and 2-propanol the crystalline residue was recrystallized from a mixture of dilute methanol and 2-propanol to give 870 mg. (93%) of a crystalline, white, hygroscopic powder, which swelled and decomposed between 130 and 140° and showed no optical rotation (water, *c* 0.9). The hygroscopic nature and ready decomposition of this product precluded a satisfactory analysis. Its oxidizable sulfur content was found to be about 75% of the theoretical value on titration with iodine solution.

1-Thio-D-glucosamine hydrochloride (XI). The above sodium salt of *N-p*-methoxybenzylidene-1-thio-β-D-glucosamine (VII), (2.8 g.) was dissolved in dilute ammonia (10 ml. of concd. ammonium hydroxide and 40 ml. of water) and the solution allowed to stand for 2 hr. at room temperature under nitrogen. The anisaldehyde was extracted with ether and the water phase was freed from ether by brief evaporation, then percolated through a column of Amberlite IRA-400 (30 g.; OH-form). The column was washed with water until neutral and the product eluted therefrom with dilute hydrochloric acid (60 ml. of concd. hydrochloric acid and 340 ml. of water). The eluate was evaporated *in vacuo*, the temperature of the water bath not exceeding 40°. The residue was freed of moisture by evaporating from it several portions of absolute ethanol, yielding the product as a colorless, dry powder. This was dissolved in absolute methanol and gradually crystallized by addition of 2-propanol, affording the following fractions: I: 479 mg.; $[\alpha]_D^{25}$ + 44.7° (water, *c* 0.89); II: 576 mg.; $[\alpha]_D^{25}$ +167° (water, *c* 0.24); III: 300 mg.; $[\alpha]_D^{25}$ +100° (water, *c* 0.23). Fractions I and III were very hygroscopic and analyzed for about 80% of free thiol while fraction II analyzed for about 100% on titration with iodine. A sample of particularly large, non-hygroscopic crystals separated from a different preparation, were collected by decantation and showed the same optical rotation as fraction II. Solutions of the latter compound in water showed a yellow color after 24 hr., smelled strongly of hydrogen sulfide and displayed a marked decrease in the optical rotation, the values of which, however, never became identical. Paper chromatography (pyridine–ethyl acetate–water–acetic acid 5:5:3:1,[13] sprayed with ammoniacal silver nitrate) proved the uniformity of fraction II in fresh solutions. On standing for 24 hr., however, considerable quantities of D-glucosamine were noted in the paper chromatograms. (It was, of course, not possible to distinguish between the free thiol and its disulfide by such techniques due to the autooxidation of the former under the chromatographic conditions.) The analysis of the product was not satisfactory apparently because of its instability and ease of oxidation.

Anal. Calcd. for $C_6H_{14}O_4NSCl$: C, 31.10; H, 6.09; N, 6.05; S, 13.84; Cl, 15.30. Found: C, 33.0; H, 6.4; N, 5.5; S, 12.0; Cl, 13.7.

Acetylation of XI. This was conducted in a manner analogous to the acetylation of IX. Twenty-five milligrams of XI gave 40 mg. (100%) of crude acetate, which after recrystallization from 2-propanol, had a m.p. and mixed m.p. (with I) of 196–197° and showed an identical infrared spectrum with that of I.

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