Ethyl 3,4,6-Tri-*O*-acetyl-2-amino-2-deoxy-1-thio-β-D-glucopyranoside[1]

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Conditions were established for preparation of the title compound (II) or its hydrochloride (VI) from 3,4,6-tri-*O*-acetyl-2-amino-2-deoxy-α-D-glucopyranosyl bromide hydrobromide (I), thereby furnishing a route to *O*-acetylated thioglycosides of 2-amino-2-deoxy-D-glucose with the amino group unsubstituted. An alternative synthesis utilized the Schiff base derivative V. Chlorination of the salt VI of the title compound (II) gave 3,4,6-tri-*O*-acetyl-2-amino-2-deoxy-α-D-glucopyranosyl chloride hydrochloride (III), characterized by conversion into the derivatives IV and VIII.

The condensation of a poly-*O*-acylglycosyl halide with the sodium or potassium salt of a thiol in a polar solvent medium is a standard preparative route for acylated 1-thioglycosides, such as alkyl and aryl 1-thio-β-D-glucopyranoside tetraacetates.[2] As part of a program directed toward synthesis of compounds having potential radiation-protective ability in biological systems,[3] we were interested in a convenient preparative route to *O*-acetylated 1-thioglycosides of amino sugars, with the amino group unsubstituted. The conventional route, employing an alkali metal salt of a thiol in alcoholic solution, cannot be used with poly-*O*-acetylglycosyl halides of amino sugar salts, since $O \rightarrow N$ acyl group migration[4] is very probable under the reaction conditions, and subsequent *N*-deacylation cannot conveniently be achieved. This difficulty has been noted by Weidmann and co-workers,[5] who suggest that liberation of the free base of the *O*-acetylated amino sugar halide, by the action of mercaptide ion, would permit a facile polycondensation side reaction. These workers[5] prepared *O*-benzoylated thioglycoside derivatives, starting from the stable 2-amino-3,4,6-tri-*O*-benzoyl-2-deoxy-α-D-gluco-pyranosyl bromide.

This report describes the synthesis of ethyl 3,4,6-tri-*O*-acetyl-2-amino-2-deoxy-1-thio-β-D-glucopyranoside (II) or its hydrochloride salt VI, by three different methods (see Scheme I), from either 3,4,6-tri-*O*-acetyl-2-deoxy-2-*p*-methoxybenzylideneamino-α-D-glucopyranosyl bromide[6] (V) or 3,4,6-tri-*O*-acetyl-2-amino-2-deoxy-α-D-glucopyranosyl bromide hydrobromide[7,8] (I); the structure of II is established by its conversion into the known ethyl 2-acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-1-thio-β-D-glucopyranoside[9] (VII).

Attempted condensation of the bromo sugar I with the sodium salt of ethanethiol in alcohol or acetone media gave sirups which were revealed by thin layer chromatography to be complex mixtures. It was found that the condensation proceeded satisfactorily when a solution of the bromo sugar I and an excess of ethanethiol in dry methylene chloride was treated with a slight excess of metallic sodium, and isolation of the product was conducted with the exclusion of polar solvents. The procedure gave the crystalline free base II of the desired thioglycoside in 67% yield, and was considered to be the most satisfactory preparative route for II. A satisfactory alternative procedure, giving II in 55% yield, involved condensation of the bromo sugar I and ethanethiol in methylene chloride solution, in the presence of zinc chloride as an acidic catalyst. If the work-up procedure was modified, with omission of an aqueous sodium bicarbonate washing stage, the product could be isolated in 50% yield as the crystalline hydrochloride salt VI. The salt VI could be converted into the free base II by action of aqueous sodium bicarbonate, and the free base II could be converted, by action of ethereal hydrogen chloride, into the salt VI. The thioglycoside free base II could also be obtained by the zinc chloride catalyzed condensation of 3,4,6-tri-*O*-acetyl-2-deoxy-2-*p*-methoxybenzylideneamino-α-D-glucopyranosyl bromide[6] (V) with an excess of ethanethiol in chloroform; the *N*-substituent undergoes cleavage, probably during the work-up procedure. This route was the least satisfactory since the yield is only moderate and the synthesis of the bromo sugar V involves several steps.

Acetylation of the thioglycoside II with pyridine–acetic anhydride gave a product, m.p. 190–192°, $[\alpha]^{22}D$ −52.5° (chloroform), which was identical with an authentic sample of ethyl 2-acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-1-thio-β-D-glucopyranoside (VII) synthesized by the procedure of Hough and Taha[9]; this establishes that the thioglycoside II and its salt VI have the β-D anomeric configuration.

Treatment of ethyl 3,4,6-tri-*O*-acetyl-2-amino-2-deoxy-1-thio-β-D-glucopyranoside hydrochloride (VI) in methylene chloride with an excess of chlorine in chloroform solution gave a high yield of the crystalline 3,4,6-tri-*O*-acetyl-2-amino-2-deoxy-α-D-glucopyranosyl chloride hydrochloride (III), identical with material prepared by a different route.[10] The reactions of this compound were sluggish compared with those of the bromo analog I, but it could be converted, by conventional procedures, into the known derivatives 3,4,6-tri-*O*-acetyl-2-amino-2-deoxy-β-D-glucopyranosyl ethylxanthate hydrochloride[11] (IV) and methyl 3,4,6-

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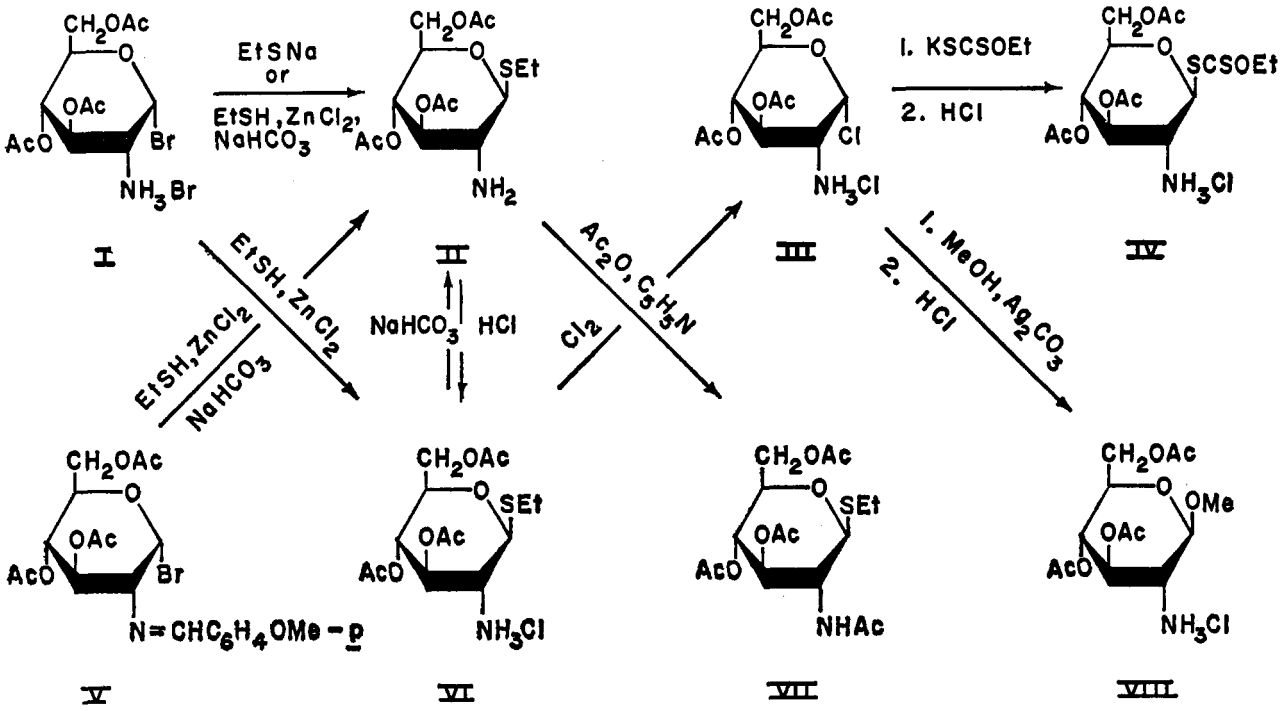
SCHEME I



tri-O-acetyl-2-amino-2-deoxy-β-D-glucopyranoside hydrochloride[12] (VIII).

Experimental[13]

Ethyl 3,4,6-Tri-O-acetyl-2-amino-2-deoxy-1-thio-β-D-glucopyranoside (II). A.—To a solution of 3,4,6-tri-O-acetyl-2-amino-2-deoxy-α-D-glucopyranosyl bromide hydrobromide[7,8] (I, 5.0 g.) in methylene chloride (150 ml.) was added ethanethiol (5 ml.), the solution was cooled to 0°, and sodium (0.56 g., 1.1 equiv.) was added in small pieces. The mixture was stirred vigorously with exclusion of moisture, and after 4 hr. the sodium was all dissolved. After 24 hr. the solution was filtered from salts, and the filtrate was evaporated to give a crystalline residue. The product was recrystallized as small needles from methylene chloride–ether: yield 2.6 g. (67%); m.p. 140–142°; $[\alpha]^{24}D$ +5.5 ± 1° (*c* 1, chloroform); λ_{max}^{KBr} 3.08, 6.24 (NH_2), 5.72 μ (OAc); X-ray powder diffraction data,[13] 13.27 (s), 11.99 (vs, 2) 10.17 (vs, 3,3), 7.49 (m), 6.60 (m), 6.15 (s), 5.04 (m), 4.70 (vs, 1), 4.35 (m), 4.11 (s), 3.80 (vs, 3,3); ninhydrin test positive; Fehling test negative.

Anal. Calcd. for $C_{14}H_{23}NO_7S$: C, 48.11; H, 6.63; N, 4.0; S, 9.18. Found: C, 48.33; H, 6.61; N, 4.14; S, 9.14.

B.—Anhydrous zinc chloride (2.5 g.) was added rapidly to a solution of 3,4,6-tri-O-acetyl-2-amino-2-deoxy-α-D-glucopyranosyl bromide hydrobromide[7,8] (I, 5.0 g.) in methylene chloride (150 ml.) and ethanethiol (10 ml.) at 5–10°. The mixture was shaken at 10° until homogeneous, and was then left overnight at room temperature. The solution was evaporated, the residue was extracted with a mixture of chloroform (100 ml.) and saturated sodium bicarbonate solution (50 ml.), the mixture was filtered, and the chloroform layer was separated. The aqueous phase was extracted with a further 100 ml. of chloroform; the combined chloroform extracts were washed with water, dried (magnesium sulfate), and evaporated to a sirup which crystallized on standing. The product was recrystallized from methylene chloride–ether: yield 2.1 g. (55%); m.p. 138–139° undepressed in admixture with material prepared by the first method; $[\alpha]^{23}D$ +5.7 ± 1° (*c* 1.25, chloroform); infrared spectrum and microanalytical data almost identical with those obtained in the first procedure.

C.—A mixture of 3,4,6-tri-O-acetyl-2-deoxy-2-*p*-methoxybenzylideneamino-2-deoxy-α-D-glucopyranosyl bromide[6] (V, 1.5 g.), chloroform (25 ml.), and ethanethiol (5 ml.) was shaken at 0° with zinc chloride (0.5 g.) until the salt had dissolved, and the solution was stored overnight at 0°. The solution was concentrated, water (10 ml.) and acetone (3 ml.) were added, and after 1 hr. the product was extracted with three 50-ml. portions of chloroform. The combined extract was washed with sodium bicarbonate solution, dried (magnesium sulfate), and evaporated to a sirup which was crystallized from methylene chloride–ether: yield 0.5 g. (46%); m.p. 140–142°; $[\alpha]^{22}D$ +5.4 ± 1° (*c* 1, chloroform); identical by infrared spectrum, X-ray powder diffraction pattern, and microanalysis with II prepared by the other routes.

Ethyl 3,4,6-Tri-O-acetyl-2-amino-2-deoxy-1-thio-β-D-glucopyranoside Hydrochloride (VI).—Anhydrous zinc chloride (2.5 g.) was added rapidly to a solution of 3,4,6-tri-O-acetyl-2-amino-2-deoxy-α-D-glucopyranosyl bromide hydrobromide[7,8] (5.0 g.) in methylene chloride (150 ml.) containing ethanethiol (10 ml.), the mixture was shaken at 10° until homogeneous, then left at room temperature overnight. The solution was evaporated, and the residue was partitioned between chloroform (100 ml.) and saturated aqueous sodium chloride (50 ml.). The organic layer was separated and the aqueous phase was extracted with a further two 50-ml. portions of chloroform. The combined extracts were dried (magnesium sulfate) and evaporated, and the residue was crystallized from chloroform: yield 1.8 g. (50%); m.p. 207–209° dec.; $[\alpha]^{22}D$ +45 ± 2° (*c* 0.6, chloroform); X-ray powder diffraction data,[13] 12.88 (w), 11.30 (vs, 1), 8.27 (m), 5.34 (s), 4.84 (s), 4.55 (w), 4.21 (w), 4.06 (vs, 2), 3.95 (m), 3.74 (s), 3.52 (w), 3.35 (w), 3.19 (m); Fehling test negative.

Anal. Calcd. for $C_{14}H_{24}ClNO_7S$: C, 43.57; H, 6.27; N, 3.62; S, 8.31. Found: C, 43.52; H, 6.32; N, 3.66; S, 8.10.

The product could be converted into the free base II by shaking a chloroform solution of the hydrochloride with an excess of aqueous sodium bicarbonate. Conversion of the free base II to the hydrochloride could be effected by adding an excess of ethereal hydrogen chloride to a solution of II in methylene chloride.

Ethyl 2-Acetamido-3,4,6-tri-O-acetyl-2-deoxy-1-thio-β-D-glucopyranoside (VII).—A mixture of ethyl 3,4,6-tri-O-acetyl-2-

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(13) Melting points were determined with a Hershberg-type apparatus [A. Thompson and M. L. Wolfrom, *Methods Carbohydrate Chem.*, **1**, 517 (1962)]. Specific rotations were determined in a 2-dm. polarimeter tube. Infrared spectra were measured with a Perkin-Elmer Infracord infrared spectrometer. Microanalytical determinations were made by W. N. Rond. X-Ray powder diffraction data give interplanar spacings, in Å., for Cu Kα radiation. Relative intensities were estimated visually: s, strong; m, moderate; w, weak; v, very. The strongest lines are numbered (1, strongest), double numbers indicate approximately equal intensities. Thin layer chromatography was carried out with Desaga equipment, using silica gel G (E. Merck, Darmstadt, Germany) activated at 100°, with indication by sulfuric acid.

amino-2-deoxy-1-thio-β-D-glucopyranoside (II, 0.5 g.), pyridine (8 ml.), and acetic anhydride (2.5 ml.) was left 18 hr. at room temperature, then poured onto ice (100 g.). A part of the product separated in crystalline form and was filtered, the remainder was extracted from the filtrate with two 100-ml. portions of chloroform, and the extract was washed with sodium bicarbonate solution, dried (magnesium sulfate), evaporated, and crystallized from methanol–ether. The two fractions had identical infrared spectra and were combined, yield 0.35 g. (64%), m.p. 188–189°. Further recrystallization gave pure product: m.p. 190–192°; $[\alpha]^{22}D$ −52 ± 2° (*c* 1, chloroform); λ_{max}^{KBr} 5.72 (OAc), 6.01, 6.45 μ (NHAc); X-ray powder diffraction data,[13] 11.10 (vs, 1), 7.69 (m), 6.81 (m), 5.98 (s), 4.72 (vs, 3,3), 4.40 (s), 4.17 (vs, 2), 3.82 (m), 3.69 (vs, 3,3), 3.56 (s), 3.41 (s), 3.30 (s), 3.05 (m).

Anal. Calcd. for $C_{16}H_{25}NO_8S$: C, 49.07; H, 6.44; N, 3.58; S, 8.19. Found: C, 49.18; H, 6.46; N, 3.71; S, 8.15.

For this compound, Hough and Taha report[9] m.p. 181°, $[\alpha]D$ −35.4° (*c* 1.4, chloroform). A sample prepared essentially by the procedure of Hough and Taha was recrystallized to constant melting point, when it showed m.p. 190–192°, $[\alpha]^{22}D$ −49 ± 2° (*c* 1.2, chloroform), and was identical with the above product by mixture melting point, infrared spectrum, X-ray powder diffraction pattern, and microanalysis.

3,4,6-Tri-*O*-acetyl-2-amino-2-deoxy-α-D-glucopyranosyl Chloride Hydrochloride (III).—A chilled solution of ethyl 3,4,6-tri-*O*-acetyl-2-amino-2-deoxy-1-thio-β-D-glucopyranoside hydrochloride (VI, 0.40 g.) in methylene chloride (25 ml.) was treated with a solution of chlorine (0.1 g.) in chloroform (0.8 ml.). The solution was maintained for 30 min. at 0°; then the solvent was evaporated and the residue was crystallized from methylene chloride as fine needles, yield 0.31 g. (82%), m.p. 155–157°, which on further recrystallization had m.p. 161–163°, $[\alpha]^{22}D$ +158 ± 2° (*c* 1, chloroform). The compound was identical by mixture melting point, infrared spectrum, and X-ray powder diffraction pattern, with a sample prepared by a different route.[10]

Anal. Calcd. for $C_{12}H_{19}Cl_2NO_7$: C, 40.00; H, 5.27; Cl, 19.72; N, 3.88. Found: C, 39.87; H, 5.21; Cl, 19.77; N, 3.96.

3,4,6-Tri-*O*-acetyl-2-amino-2-deoxy-β-D-glucopyranosyl Ethylxanthate Hydrochloride (IV).—A solution of 3,4,6-tri-*O*-acetyl-2-amino-2-deoxy-α-D-glucopyranosyl chloride hydrochloride (III, 150 mg.) in dry acetone (5 ml.) was mixed with a solution of potassium ethylxanthate (110 mg.) in ethanol (10 ml.). After 1 hr. the inorganic precipitate was filtered, the filtrate was concentrated to 5 ml., and methanolic hydrogen chloride (2.5%, 2 ml.) was added, followed by ether to incipient crystallization. After 3 hr. at 0° the product was filtered and recrystallized from ethanol–ether. The pure product had m.p. 174–176°, $[\alpha]^{22}D$ +25 ± 3° (*c* 0.3, ethanol). This compound, prepared by a different route, has been reported[11] to have m.p. 177–179° dec., $[\alpha]^{20}D$ +23 ± 1.5° (*c* 0.2, ethanol).

Methyl 3,4,6-Tri-*O*-acetyl-2-amino-2-deoxy-β-D-glucopyranoside Hydrochloride (VIII).—A solution of 3,4,6-tri-*O*-acetyl-2-amino-2-deoxy-α-D-glucopyranosyl chloride hydrochloride (III, 0.50 g.) in dry methanol (5 ml.) was shaken overnight with Drierite (3 g.) and an excess of silver carbonate. The solution was filtered, and 1% methanolic hydrogen chloride was added dropwise until the solution was just acid. The solution was decolorized with activated carbon, then concentrated and treated with ether to give upon refrigeration a crystalline product, yield 0.30 g. (60%), m.p. 225–230° dec., $[\alpha]^{22}D$ +17 ± 2° (*c* 0.7, methanol).

The following constants have been reported[12] for this compound, prepared by a different route: m.p. 233° dec., $[\alpha]D$ +17° (methanol).

Benzylsulfonyl as *N*-Blocking Group in Amino Sugar Nucleoside Synthesis

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3,4,6-Tri-*O*-acetyl-2-benzylsulfonylamino-2-deoxy-α-D-glucopyranosyl chloride (II), prepared from 1,3,4,6-tetra-*O*-acetyl-2-benzylsulfonylamino-2-deoxy-β-D-glucopyranose (I), was condensed with 6-benzamido-9-chloromercuripurine to give the substituted nucleoside III (amorphous) and this on *N*-debenzoylation yielded 9-(3,4,6-tri-*O*-acetyl-2-benzylsulfonylamino-2-deoxy-β-D-glucopyranosyl)adenine (IV, dimorphous) which was converted to 9-(2-acetamido-2-deoxy-β-D-glucopyranosyl)adenine (VI).

The synthesis of nucleosides of 2-amino-2-deoxy sugars is normally accomplished by the coupling of a properly blocked amino sugar halide with a purine or pyrimidine derivative according to the Fischer–Helferich[2a] method, in the modification of Davoll and Lowy,[2b,3] or the Hilbert–Johnson procedure.[4] *N*-Blocking groups, so far used for the synthesis of nucleosides of 2-amino-2-deoxy-D-glucose, are the acetyl,[5–7] benzyloxycarbonyl,[8] methoxycarbonyl,[8] and, in a recent publication, the 2,4-dinitrophenyl group.[9] The *N*-acetyl group can only be removed from derivatives of 2-amino-2-deoxy-D-glucose by acid hydrolysis, conditions under which the *N*-glucosyl linkages of purine nucleosides are unstable.[10] The benzyloxycarbonyl group could be eliminated by hydrogenolysis to give pyrimidine nucleosides of 2-amino-2-deoxy-D-glucose.[8] The 2,4-dinitrophenyl group serves excellently and gives both anomeric forms of the nucleoside[9] since it shows no tendency to participate at C-1.

In an effort to introduce other *N*-blocking groups into 2-amino-2-deoxy-D-glucose which might stabilize the halide derivative and be removed with reagents not attacking the *N*-glucosyl linkage of the nucleoside, we have used the benzylsulfonyl group in the synthesis of 9-(2-acetamido-2-deoxy-β-D-glucopyranosyl)-adenine.[11] This group was originally used in the amino acid field and is reported to be removed easily by re-

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(11) This compound is described in French Patent 1,324,011 (1963).[7] However, no melting point, optical rotation, or analytical values are given for the product.