A New Route to 2-Amino-2-deoxy-β-D-glucosides

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Received August 17, 1965

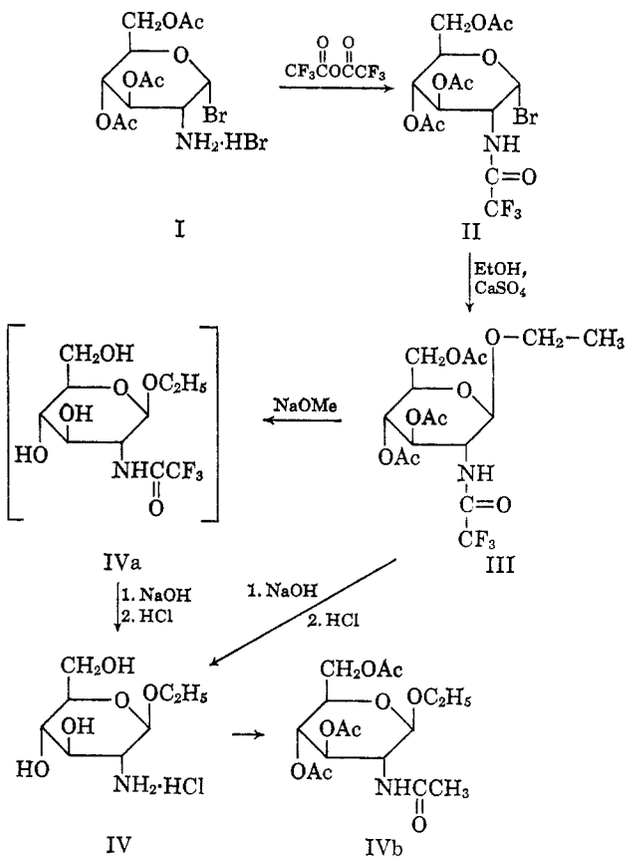
The synthesis of 3,4,6-tri-*O*-acetyl-2-deoxy-2-trifluoroacetamido-α-D-glucopyranosyl bromide is described. This compound is far less prone to undergo rearrangement reactions than the corresponding 2-acetamido sugar. It is useful in Koenigs–Knorr reactions. Ease of hydrolysis of the amide linkage in the resulting glycosides affords a convenient route to 2-amino-2-deoxy-β-D-glucosides. The new reagent was successfully employed in the synthesis of the 2-amino-2-deoxy-β-D-glucopyranosides of ethanol and of salicylic acid. Attempts to prepare the latter by alternate routes were unavailing.

The condensation of fully acetylated glycosyl halides with alcohols and phenols has been of great value in the synthesis of glycosides.[1] It has been recognized, however, that the synthesis of 3,4,6-tri-*O*-acyl-2-acylamido-2-deoxy-β-D-glucopyranosides and of the corresponding 2-amino-2-deoxyglycosides pose unique problems. Thus, 3,4,6-tri-*O*-acetyl-2-acetamido-2-deoxy-α-D-glucopyranosyl bromide readily undergoes rearrangement to 1,3,4,6-tetra-*O*-acetyl-2-amino-2-deoxy-α-D-glucopyranose hydrobromide[2] in the presence of water. Other 2-acylamido-2-deoxyglucosyl halides rearrange to oxazolines[3] and to oxazolidines.[4] 2-Acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-α-D-glucopyranosyl chloride[4,5] is less prone to undergo rearrangement than the bromo analog, but in our hands the chloro sugar required elevated temperatures for the synthesis of a steroidal glycoside.[6] Most *N*-acylglycosyl halides which have been described suffer from the additional disadvantage that they afford *N*-acylated glycosides which cannot be converted into amino sugars under mild conditions.[7] The use of glycosyl halides with an unprotected amino group has been described, but the method has not been used extensively.[8,9]

We have prepared 3,4,6-tri-*O*-acetyl-2-deoxy-2-trifluoroacetamido-α-D-glucopyranosyl bromide (II). We hoped that the inductive effect of the fluorine atoms would prevent oxazoline formation and that it would also permit hydrolysis[10] of the amide linkage under mild conditions after glycoside synthesis.

Treatment of I[8] with trifluoroacetic anhydride gave II in 75% yield (Scheme I). The infrared spectrum of this halo sugar in chloroform solution revealed only a single carbonyl peak at 5.71 μ. Compound II was converted into the fully acylated ethyl glycoside III. To relate the latter to a known compound, III was deacetylated with sodium methoxide, and the trifluoroacetamido group was then hydrolyzed with sodium hydroxide at room temperature to give IV. It was also possible to convert III directly into IV with aqueous sodium hydroxide. The physical constants of IV agreed with those given in the literature. Compound IV was further characterized by conversion into IVb[11] with acetic anhydride.

SCHEME I



The new derivative (II), was also applied successfully to the synthesis of a 2-amino-2-deoxy-β-D-glucoside of a phenol, (*o*-carboxyphenyl)-2-amino-2-deoxy-β-D-glucopyranoside (Vc). The sodium phenolate of methyl salicylate, prepared *in situ*, was allowed to react with II in toluene to furnish the blocked glycoside Va. Treatment of the latter with sodium methoxide removed only the *O*-acetyl groups. The resulting compound, Vb, was allowed to react with 1 *N* sodium hydroxide to effect hydrolysis of both the *N*-trifluoroacetyl and methyl ester groups to give the 2-amino-2-deoxy-β-D-glucoside of salicylic acid, Vc.

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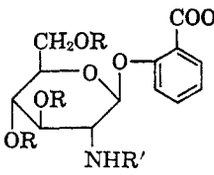

Va, R = CH_3CO; R′ = CF_3CO; R″ = CH_3
b, R = H; R′ = CF_3CO; R″ = CH_3
c, R = R′ = R″ = H
d, R = R′ = CH_3CO; R″ = CH_3
e, R = H; R′ = CH_3CO; R″ = CH_3
f, R = R″ = H; R′ = CH_3CO
g, R = R′ = CH_3CO; R″ = H

Alternative preparative methods for Vc had been investigated briefly. Selective hydrolysis of the *N*-acetyl group of Vf (see below) was not achieved in a practical sense. Under acidic conditions[12] cleavage of the glycosidic bond appeared to occur as rapidly as that of the amide linkage. The *N*-acetyl group in Vf was quite resistant to alkaline hydrolysis, and the use of vigorous alkaline conditions led to extensive degradation. Attempts to condense methyl salicylate with 3,4,6-tri-*O*-acetyl-2-[(benzyloxycarbonyl)amino]-α-D-glucopyranosyl bromide[13] were unsuccessful.

In order to relate Vc to the corresponding 3,4,6-tri-*O*-acetyl-2-acetamido-2-deoxy-β-D-glucopyranoside (Vd), the latter was prepared in a conventional manner.[1] Methyl salicylate was allowed to react with 2-acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-α-D-glucopyranosyl chloride[4,5] in acetone in the presence of potassium carbonate. The resulting compound (Vd) was *O*-deacetylated and saponified to furnish the 2-acetamido-2-deoxy-β-D-glucopyranoside Vf. Both Vf and Vc were acetylated to give (*o*-carboxyphenyl)-2-acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-β-D-glucopyranoside (Vg).

Experimental Section

3,4,6-Tri-*O*-acetyl-2-deoxy-2-trifluoroacetamido-α-D-glucopyranosyl Bromide (II).—To 15 ml. of trifluoroacetic anhydride was added 2 g. (4.45 mmoles) of I[8] in a 100-ml. round-bottomed flask. The flask was protected from moisture with Drierite and the solution was kept at room temperature overnight. The solution was concentrated *in vacuo* to a viscous brown oil, which was dissolved in methylene chloride and extracted three times with 200-ml. portions of a saturated solution of sodium chloride. The organic layer was dried over magnesium sulfate and the solvent was evaporated. The white foam (1.77 g.) was crystallized from about 250 ml. of hot *n*-hexane to give 1.53 g. of II (74% yield), m.p. 95–97°, showing $\lambda_{max}^{CHCl_3}$ 5.71 (ester and amide I), 6.60 (amide II), 8.15–8.30 (ester), and 8.60 μ (C–F).

Anal. Calcd. for $C_{14}H_{17}BrF_3NO_8$: C, 36.22; H, 3.69; Br, 17.22; F, 12.28; N, 3.02. Found: C, 36.45; H, 3.92; Br, 16.92; F, 12.40; N, 2.94.

Ethyl 3,4,6-Tri-*O*-acetyl-2-deoxy-2-trifluoroacetamido-β-D-glucopyranoside (III).—To 125 ml. of anhydrous ethanol was added 5 g. of silver carbonate and 5 g. of calcium sulfate, and the resultant slurry was stirred vigorously for 30 min. II (6.4 g., 13.8 mmoles) was added, and the mixture was stirred overnight in the dark. Inorganic products were removed by filtration, and the mother liquor was concentrated to dryness to yield a colorless oil, which was dissolved in chloroform and extracted with a cold 2% solution of aqueous ammonia and then with water until the washings were neutral. The chloroform layer was dried and concentrated *in vacuo* to yield an oil, which was crystallized from ethanol to yield 3.46 g. (58% yield) of III: m.p. 177.5–178°; $[\alpha]^{25}D$ −26° (*c* 1, MeOH); $\lambda_{max}^{CHCl_3}$ 5.71 (ester and amide I), 6.45 (amide II), 8.20 (ester), 8.60 μ (C–F).

Anal. Calcd. for $C_{16}H_{22}F_3NO_9$: C, 44.76; H, 5.16. F, 13.27; N, 3.26. Found: C, 44.57; H, 4.96; F, 13.05; N, 2.91.

Ethyl 2-Amino-2-deoxy-β-D-glucoside Hydrochloride (IV).—To 200 mg. (0.466 mmole) of III in 7 ml. of methanol was added 4.8 ml. of a solution of 0.1 *N* sodium methoxide. The mixture was stirred at room temperature in an atmosphere of nitrogen for 15 min. The pH of an aliquot of this solution when diluted with water was 10. The clear solution was taken to dryness. The resultant oil showed greatly diminished absorption at 5.70 μ ($CHCl_3$), and no absorption maximum between 8.00 and 8.30 μ (ester), but retained some absorption at 5.70 μ (amide I) and showed strong maxima at 6.55 (amide II) and 8.60 μ (C–F). The crude product was dissolved in 95% alcohol and hydrolyzed with 10 ml. of an aqueous solution of sodium hydroxide (10%) for 16 hr. at room temperature. The product was isolated as the amine hydrochloride IV: dec. pt. 211.5–213°; $[\alpha]^{25}D$ +26° (*c* 2, water) [lit.[14] dec. pt. 213–214°, $[\alpha]^{25}D$ +27.75° (*c* 2.68, water)].

It was possible to effect simultaneous deacylation of ester and amide functions. To 200 mg. (0.466 mmole) of III, dissolved in 95% ethanol, was added 10 ml. of a 10% aqueous solution of sodium hydroxide. The solution was kept at room temperature for 16 hr. and it was then neutralized with a dilute solution of hydrochloric acid. The solution was concentrated to dryness and extracted three times with a small volume of anhydrous ethanol. The product was isolated as the amine hydrochloride IV, dec. pt. 212–213.5°, $[\alpha]^{25}D$ +26° (*c* 2, water).

Acetylation of 100 mg. of IV with 1 ml. of acetic anhydride and 1 ml. of pyridine gave the known **ethyl 2-acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-β-D-glucopyranoside (IVb)**, m.p. 167–168.5°, (lit.[11] m.p. 167°). A mixture melting point with IVb prepared as described by Leaback and Walker[11] was undepressed and the infrared spectra in Nujol of the two specimens were superimposable.

(*o*-Methoxycarbonylphenyl) 3,4,6-Tri-*O*-acetyl-2-deoxy-2-trifluoroacetamido-β-D-glucoside (Va).—To a suspension of 0.92 g. of sodium hydride (1.8 g. of a 51% dispersion in mineral oil,[15] 38.3 mmoles) in 250 ml. of dry toluene was added dropwise 10 g. (65.8 mmoles) of methyl salicylate. After the mixture had been stirred at room temperature for 10 min., a solution of 14.8 g. (33.4 mmoles) of II in 50 ml. of toluene was added, and the resulting mixture was refluxed with stirring for 15 min. After cooling, the mixture was treated with charcoal and filtered, and the solvent was removed *in vacuo*. The residue was triturated with hexane to afford 11.0 g. of an amorphous solid. Recrystallization from ethanol–hexane yielded 6.4 g. (36%) of Va, m.p. 184–186°. Further recrystallization did not alter the melting point.

Anal. Calcd. for $C_{22}H_{24}F_3NO_{11}$: C, 49.35; H, 4.52; F, 10.65; N, 2.62. Found: C, 49.38; H, 4.34; F, 10.4; N, 2.35.

(*o*-Methoxycarbonylphenyl) 2-Deoxy-2-trifluoroacetamido-β-D-glucoside (Vb).—To a suspension of 6.4 g. (12 mmoles) of Va in 50 ml. of methanol was added 10 ml. of 1.25 *N* solution of sodium methoxide in methanol. After stirring at room temperature for 15 min., approximately 4 g. of Dry Ice was added to the solution, followed by 200 ml. of water. The crystalline product was filtered, washed, and dried: yield 4.45 g. (91%), m.p. 260–265° (subl.). The analytical sample was obtained by recrystallization from aqueous methanol.

Anal. Calcd. for $C_{16}H_{18}F_3NO_8$: C, 46.91; H, 4.43; N, 3.43. Found: C, 47.11; H, 4.73; N, 3.77.

(*o*-Carboxyphenyl) 2-Amino-2-deoxy-β-D-glucoside (Vc).—A mixture of 4.25 g. (10.4 mmoles) of Vb, 40 ml. of water, and 30 ml. of 1 *N* sodium hydroxide was stirred at room temperature for 2.5 hr. After cooling the clear solution in ice, the pH was brought to 3.5 by the addition of about 25 ml. of 1 *N* hydrochloric acid. The solution was concentrated to dryness *in vacuo* below 30°. The residue was dissolved in 15–20 ml. of water and applied to a column of 50 ml. of IR-120 (H^+) resin. The column was eluted with water until a negative test for chloride ion was obtained (150 ml.), and then with 1% ammonium hydroxide until no more product was removed (375 ml.).

The ammonia eluates were concentrated to dryness *in vacuo*, and the residue was recrystallized from aqueous acetone. The yield was 1.45 g. (47%). The compound darkened on heating

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(14) J. C. Irvine and A. Hynd, *J. Chem. Soc.*, **103**, 41 (1913).
(15) Metal Hydrides, Inc., Beverly, Mass.

to 210°, but did not melt below 300°: $[\alpha]^{25}D$ −5.0° (*c* 0.747, water).

Anal. Calcd. for $C_{13}H_{17}NO_7$: C, 52.17; H, 5.73; N, 4.68. Found: C, 52.10; H, 6.02; N, 4.66.

(*o*-**Methoxycarbonylphenyl**) **2-acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-β-D-glucopyranoside** (**Vd**).—To a mixture of 62.3 g. (450 mmoles) of anhydrous potassium carbonate, 34.7 ml. (41 g., 270 mmoles) of methyl salicylate, and 1380 ml. of acetone was added 57 g. (156 mmoles) of 2-acetamido-3,4,6-*O*-acetyl-2-deoxy-α-D-glucopyranosyl chloride.[4,5] The mixture was stirred at room temperature for 21 hr., and the inorganic salts were removed by filtration. The filtrate was subjected to vacuum distillation to remove the acetone, and the residual oil was triturated with ether. The yield of crystalline Vd was 52 g. (69.5%), m.p. 202–203°.

An analytical sample was prepared by recrystallization from ethanol: m.p. 202–204°.

Anal. Calcd. for $C_{22}H_{27}NO_{11}$: C, 54.87; H, 5.65; N, 2.91. Found: C, 54.75; H, 5.76; N, 2.91.

(*o*-**Methoxycarbonylphenyl**) **2-Acetamido-2-deoxy-β-D-glucopyranoside** (**Ve**).—A solution of 52 g. (108 mmoles) of Vd in 780 ml. of methanol was warmed to 35°. A solution from 2.0 g. (87 mg.-atoms) of sodium metal and 85 ml. of methanol was added, and the mixture was stirred at 35–40° for 5 min. The product began to crystallize promptly. After cooling to 10° in an ice bath, the product was filtered, washed with cold methanol and with ether, and dried *in vacuo* to give 30.1 g. (78%), m.p. 205–207° dec.

Anal. Calcd. for $C_{16}H_{21}NO_8$: C, 54.08; H, 5.96; N, 3.94. Found: C, 53.93; H, 5.79; N, 3.68.

(*o*-**Carboxyphenyl**) **2-Acetamido-2-deoxy-β-D-glucopyranoside** (**Vf**).—To a suspension of 30.1 g. (84 mmoles) of Ve in 1 l. of water was added 87 ml. of 1 *N* sodium hydroxide solution. After stirring at room temperature for 3 hr., *ca.* 5 g. of Dry Ice was added to the clear solution. After the Dry Ice had dissolved, the solution was freeze dried to give 31 g. (quantitative yield) of an amorphous solid. The sodium salt may be crystallized from 98–99% ethanol, or from methanol–2-propanol mixtures to give a product which is still contaminated with sodium bicarbonate (4%) and with water (5–10%), on the basis of analytical results.

The sodium salt was converted to the acid by acidifying a cold concentrated aqueous solution of the salt, filtering quickly, and washing with a small amount of cold water. Recrystallization from methanol–acetone gave an analytical sample, m.p. 151–152° dec., $[\alpha]^{25}D$ −54° (*c* 0.84, water).

Anal. Calcd. for $C_{15}H_9NO_8$: C, 52.78; H, 5.61; N, 4.10. Found: C, 52.28; H, 5.78; N, 4.09.

(*o*-**Carboxyphenyl**) **2-Acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-β-D-glucopyranoside** (**Vg**).—A mixture of 3.5 g. of the sodium salt of (*o*-carboxyphenyl)-2-acetamido-2-deoxy-β-D-glucopyranoside (Vf), 15 ml. of acetic anhydride, and 15 ml. of pyridine was heated on the steam bath for 40 min. The cooled reaction mixture was poured into 300 ml. of ice–water containing 15 ml. of concentrated hydrochloric acid. The mixture was extracted five times with 40-ml. portions of methylene chloride. After drying with magnesium sulfate, the solvent was removed *in vacuo*, and the residue was crystallized from glacial acetic acid, affording needles, 3.7 g., m.p. 139–140°.

Anal. Calcd. for $C_{21}H_{25}NO_{11}\cdot C_2H_4O_2$: C, 52.37; H, 5.54; N, 2.72. Found: C, 52.88; H, 5.73; N, 2.82.

An unsolvated sample was prepared by recrystallization from ethyl acetate–ether: m.p. 139–140°.

Anal. Calcd. for $C_{21}H_{25}NO_{11}$: C, 53.96; H, 5.39. Found: C, 53.83; H, 5.79.

A sample of Vc, acetylated by the foregoing procedure, furnished Vg which was identical (melting point, mixture melting point, infrared absorption spectrum) with the specimen reported above.

Acknowledgment.—The authors are indebted to Mr. R. Boos and his colleagues for the elemental analyses reported herein. R. H. is pleased to acknowledge stimulating discussions with Dr. D. Taub of these laboratories and with Dr. D. Horton of The Ohio State University.

Photochemistry of Carbohydrate Derivatives. Photolysis of D-Galactose Diethyl Dithioacetal[1]

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Received September 10, 1965

Irradiation of a methanolic solution of D-galactose diethyl dithioacetal (I) with ultraviolet light gives 1-*S*-ethyl-1-thio-D-galactitol (II), isolable in 60% yield. Further irradiation converts this substance into L-fucitol (III), together with two minor products. One of the later is shown to be 1-deoxy-1-ethylsulfinyl-D-galactitol (IV), and the other, formed in lesser proportion, was identified as galactitol (V). Irradiation of IV gives V. Nmr data for the products are presented and discussed. Ultraviolet absorption data for a range of aldose dithioacetal derivatives are tabulated.

Simple dithioacetals exhibit ultraviolet absorption in the 230–250-mμ region, with absorptivities generally in the range[2-4] ε 300–850. Similar absorption is observed with dithioacetals of sugars (Table I), whereas the unsubstituted sugars possess no chromophores in this spectral region. It was of interest to study the photolytic cleavage of carbon–sulfur bonds in carbohydrate dithioacetals, as part of a general study of photochemical transformations in carbohydrate systems. This paper describes the transformations observed when a methanolic solution of D-galactose diethyl dithioacetal (I) was irradiated with ultraviolet light.

A high-pressure mercury lamp mounted in a quartz immersion well was used to irradiate a methanolic solution of the dithioacetal I, and no special precautions were taken to exclude air. The progress of the reaction was monitored by cellulose thin layer chromatography on aliquot samples. It was observed that the starting dithioacetal (I), R_f 0.76, was transformed into a product having R_f 0.63, together with small proportions of slower moving components, R_f 0.35 and 0.28. The major product, R_f 0.63, could be isolated crystalline in 55–60% yield, and it was shown to be 1-*S*-ethyl-1-thio-D-galactitol

(1) (a) Supported in part by the Agricultural Research Service, U. S. Department of Agriculture, Grant No. 12-14-100-7208 (71) (The Ohio State University Research Foundation Project 1827), administered by the Northern Utilization Research and Development Division, Peoria, Ill. Funds for purchase of the nmr spectrometer were provided by the National Science Foundation. (b) Preliminary report: Abstracts, 151st National Meeting of the American Chemical Society, Phoenix, Ariz., Jan 1966, p 4c.

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