which 186 mg. of pure XIV, m.p. 209–211°, was obtained after recrystallization from a mixture of methanol and ether.

Further elution of the silica gel column with pure acetone, and with a mixture of acetone and methanol, 19:1, gave 593 mg. of a pale yellow sirup which could not be crystallized; $[\alpha]^{28}D$ −175° (*c* 1.08 in methanol). The elemental analysis corresponded to that of a **monoacetamido-1,6-anhydro-monodeoxy-β-D-hexopyranose** with one mole of methanol added.

Anal. Calcd. for $C_8H_{13}O_5N \cdot CH_3OH$: C, 45.95; H, 7.28; N, 5.96. Found: C, 46.12; H, 7.38; N, 6.01.

On paper chromatography (Whatman No. 54) this product moved with an $R_{2\text{-amino-2-deoxyglucose}}$ 2.07 and reacted weakly with the alkaline silver reagent.

A solution of 80 mg. of this sirup in 3.5 ml. of 0.5 *N* hydrochloric acid was heated for 15 hr. at 100° in a sealed tube. The solution was then evaporated to dryness, the last traces of acid being removed by codistillation with ethanol and toluene. This residue was crystallized from a mixture of water, ethanol, and ether to give 34 mg. (51%) of elongated prisms, decomposing at 215–225° without melting. This compound had $[\alpha]^{26}D$ −169° (*c* 1.10 in water), and no mutarotation was observed. The elemental analysis corresponded to a **monoamino-1,6-anhydro-monodeoxy-β-D-hexopyranose hydrochloride.**

Anal. Calcd. for $C_6H_{12}O_4NCl$: C, 36.46; H, 6.12; Cl, 17.94. Found: C, 36.34; H, 6.15; Cl, 18.05.

This hydrochloride gave a positive ninhydrin reaction, but no color in either the Elson–Morgan or the Morgan–Elson test. By paper chromatography (Whatman No. 1 and 54) a single spot was obtained with R_f 0.32 and $R_{2\text{ amino-2 deoxyglucose}}$ 1.10.

Several attempts were made to obtain the free sugar by opening the 1,6-anhydro ring by hydrolysis with 2 *N*, 3 *N*, or 6 *N* hydrochloric acid, but this was always accompanied by much decomposition, as evidenced on paper chromatograms by trailing and multiple spots, and no pure material could be obtained. Attempts to obtain other crystalline derivatives by acetylation, tosylation, or acetolysis were also unsuccessful.

1,6;3,4-Dianhydro-2-O-p-tolylsulfonyl-β-D-galactopyranose (I).[21]—A solution of 300 mg. of II[20] in 10 ml. of methanol and 5.8 ml. of a solution of 0.43 *N* sodium methylate (3.7 moles) was refluxed for 24 hr. After concentration to 3 ml., the sirup was diluted with 30 ml. of water and 76 mg. of crystals were filtered. The filtrate was deionized by passage through columns of Amberlite IR 400 (OH^- form) and Dowex 50 (H^+ form) and evaporated to dryness. The residue was crystallized from methanol to give an additional yield of 9 mg. (total yield, 70%). Recrystallization from a mixture of methanol and pentane raised the melting point to 149–150°; $[\alpha]^{28}D$ −37° (*c* 0.56 in chloroform).[24]

Anal. Calcd. for $C_{13}H_{14}O_6S$: C, 52.34; H, 4.73; S, 10.75. Found: C, 52.42; H, 4.80; S, 10.59.

Acknowledgment.—The authors wish to thank Dr. R. B. Baker for providing before publication the experimental conditions for the replacement of a mesyloxy group with an azide group, and Dr. H. H. Baer for a sample of 3-acetamido-3-deoxy-D-glucose.

(24) Černý, Gut, and Pacák[25] reported m.p. 148–150°; $[\alpha]D$ −40° (*c* 1.4 in chloroform); Hann and Richtmyer[5] observed 149–149.5°; $[\alpha]^{20}D$ −41.7° (*c* 1 in chloroform).

(25) M. Černý, V. Gut, and J. Pacák, *Collection Czech. Chem. Commun.*, **26**, 2542 (1961).

The Synthesis of 2-Acetamido-3-*O*-(D-1-carboxyethyl)-2-deoxy-α-D-glucose (*N*-Acetylmuramic Acid) and of Benzyl Glycoside Derivatives of 2-Amino-3-*O*-(D-1-carboxyethyl)-2-deoxy-D-glucose (Muramic Acid)[1]

HAROLD M. FLOWERS[2] AND ROGER W. JEANLOZ

Laboratory for Carbohydrate Research, Departments of Biological Chemistry and Medicine, Harvard Medical School and the Massachusetts General Hospital, Boston, Massachusetts

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The synthesis of various derivatives of the benzyl α-D-glycoside of 2-amino-3-*O*-(D-1-carboxyethyl)-2-deoxy-D-glucose (muramic acid) and of the disaccharide benzyl 6-*O*-(2-acetamido-2-deoxy-β-D-glucopyranosyl)-2-acetamido-3-*O*-(D-1-carboxyethyl)-2-deoxy-α-D-glucopyranoside is described. In addition, crystalline 2-acetamido-3-*O*-(D-1-carboxyethyl)-2-deoxy-α-D-glucose (*N*-acetylmuramic acid) has been obtained.

In a previous paper,[3] the synthesis of the acetylated methyl α-glycoside of the disaccharide 2-acetamido-2-deoxy-D-glucopyranosyl-(1 → 6)-*N*-acetylmuramic acid has been described. This disaccharide has been postulated as one of the repeating units of the 2-amino-2-deoxyglucan, which constitutes the backbone of the cell wall of numerous Gram-positive and Gram-negative bacteria.[4–6] Since removal of the protective methyl α-glycosidic group cannot be accomplished without considerable degradation of the disaccharide linkage, the synthesis of the disaccharide was repeated using the protective benzyl α-glycoside group, which can be removed by catalytic hydrogenolysis. Starting from benzyl 2-acetamido-4,6-*O*-benzylidene-2-deoxy-α-D-glucopyranoside (I),[7] the synthesis proceeded along a route similar to the one described for the methyl α-glycoside derivative.[3] The various crystalline muramic acid derivatives II to VIII were obtained in yields quite similar to those obtained for the methyl α-glycoside derivatives. The condensation of benzyl 2-acetamido-4-*O*-acetyl-2-deoxy-3-*O*-[D-1-(methyl carboxylate)ethyl] - α - D - glucopyranoside (VI) with 2-acetamido - 3,4,6 - tri - *O* - acetyl - 2 - deoxy - α - D - glucopyranosyl bromide (XI) proceeded, however, in very low yield, and only 3 to 4% of the desired disaccharide (XII) was obtained. Removal of the benzyl glycoside group of the deacetylated product XII by catalytic hydrogenation gave an amorphous disaccharide; its properties, compared to those of the disaccharide isolated from *Micrococcus lysodeikticus* cell wall, will be described in a forthcoming publication.

Removal of the benzyl glycoside group of benzyl 2-acetamido - 3 - *O* - (D - 1 - carboxyethyl) - 2 - deoxy-

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(2) On leave of absence from the Weizmann Institute of Science, Rehovoth, Israel.

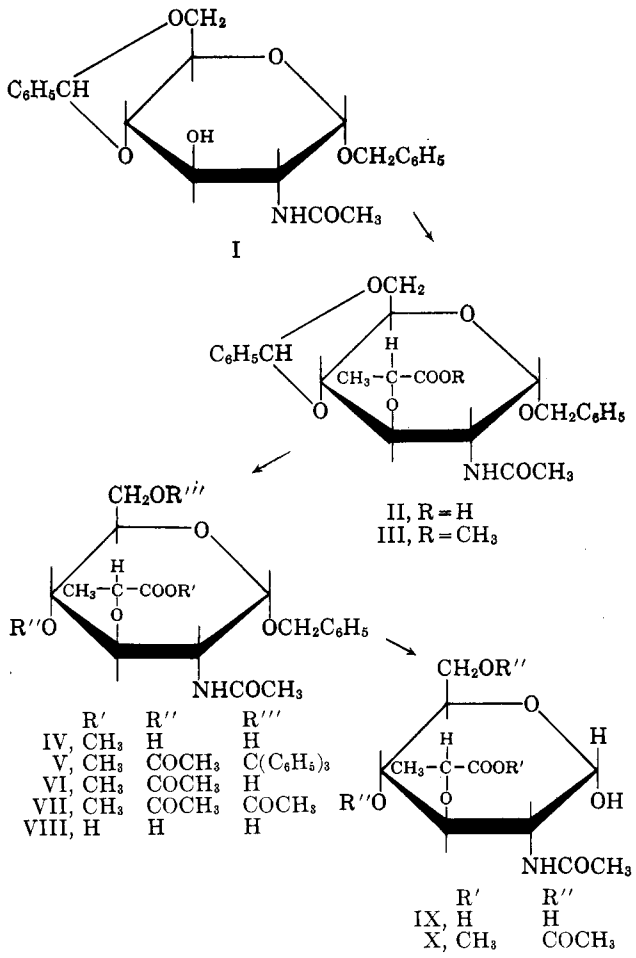
(3) H. M. Flowers and R. W. Jeanloz, *J. Org. Chem.*, **28**, 1564 (1963).

(4) M. R. J. Salton and J. M. Ghuysen, *Biochim. Biophys. Acta*, **36**, 552 (1959).

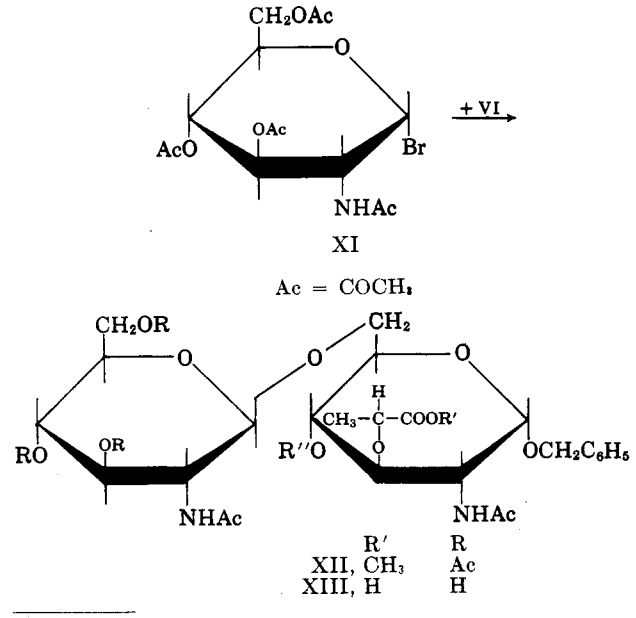
(5) M. R. J. Salton and J. M. Ghuysen, *ibid.*, **45**, 355 (1960).

(6) H. R. Perkins, *Biochem. J.*, **74**, 182 (1960).

(7) R. Kuhn, H. H. Baer, and A. Seeliger, *Ann.*, **611**, 236 (1958).



α - D - glucopyranoside (VIII) gave crystalline 2-acetamido - 3 - *O* - (D - 1 - carboxyethyl) - 2 - deoxy-α - D - glucose or *N* - acetylmuramic acid (IX). The preparation of a compound with a similar structure, but obtained in an amorphous form, recently has been reported.[8] The preparation of VIII in a pure state allows the determination of its physical and chemical properties, especially its reactions with the Morgan and Elson reagent[9] and with the periodate ion. These tests have been extensively used in the determination of the structure of the glucosaminyl–muramic acid derivative isolated from bacterial cell wall,[4-6] but no comparison of the results with those obtained with pure *N*-acetylmuramic acid has been reported.



Experimental

Melting points were taken on a hot stage, equipped with a microscope, and correspond to "corrected melting point." Rotations were determined in semimicro- or micro- (for amounts smaller than 3 mg.) tubes with lengths of 100 or 200 mm., using a Rudolph photoelectric polarimeter attachment, Model 200; the chloroform used was A.R. grade and contained approximately 0.75% of ethanol. Infrared spectra were determined on a Perkin-Elmer spectrophotometer, Model 237. Chromatograms were made with the flowing method on "Silica Gel Davison," from the Davison Co., Baltimore 3, Md. (grade 950, 60–200 mesh), which was used without pretreatment. When deactivation by contact with moist air occurred, reactivation was obtained by heating to 170–200° (manufacturer's instructions). The sequence of eluents was hexane, benzene or ethylene dichloride, ether, ethyl acetate, acetone, and methanol individually or in binary mixtures. The proportion of weight of substance to be adsorbed to weight of adsorbent was 1 to 50–100. The proportion of weight of substance in grams to volume of fraction of eluent in milliliters was 1 to 100. The ratio of diameter to length of the column was 1 to 20. Evaporations were carried out *in vacuo*, with an outside bath temperature kept below 45°. Amounts of volatile solvent smaller than 20 ml. were evaporated under a stream of dry nitrogen. The microanalyses were done by Dr. M. Manser, Zürich, Switzerland.

Benzyl 2-Acetamido-4,6-*O*-benzylidene-3-*O*-(D-1-carboxyethyl)-2-deoxy-α-D-glucopyranoside (II).—A solution of 8 g. of benzyl 2-acetamido-4,6-*O*-benzylidene-2-deoxy-α-D-glucopyranoside (I) dissolved in 500 ml. of dry dioxane was treated with sodium hydride and L-α-chloropropionic acid as described previously for the preparation of the corresponding methyl α-glycoside derivative,[3] except that the stirred mixture was maintained at 60° overnight to complete the reaction. After addition of 20 ml. of ice–water, the clear solution was cooled and acidified with cold 6 *N* hydrochloric acid. Addition of 1 l. of ice–water precipitated a white solid which was separated by filtration, washed thoroughly with water and dried, giving 8.9 g. melting at 227–230°. Recrystallization from methanol gave 7.2 g. (77%) of needles, m.p. 237–239°, $[\alpha]^{18}D$ +115° (*c* 1.28, in methanol); the melting point was unaffected by a second recrystallization.

Anal. Calcd. for $C_{25}H_{29}NO_8$: C, 63.68; H, 6.20; N, 2.97. Found: C, 63.64; H, 6.29; N, 3.00.

Benzyl 2-Acetamido-4,6-*O*-benzylidene-2-deoxy-3-*O*-[D-1-(methyl carboxylate)ethyl]-α-D-glucopyranoside (III).—A solution of 140 mg. of II in the minimum of methanol was esterified by the addition of a slight excess of diazomethane in ether. Evaporation of the solution and recrystallization of the residue from methanol gave 115 mg. (80%) of needles, m.p. 212–213°, $[\alpha]^{21}D$ +94° (*c* 0.70, in chloroform). The melting point was unchanged on recrystallization from ethyl acetate.

Anal. Calcd. for $C_{26}H_{31}NO_8$: C, 64.31; H, 6.44; N, 2.89. Found: C, 64.26; H, 6.49; N, 2.89.

Benzyl 2-Acetamido-2-deoxy-3-*O*-[D-1-(methyl carboxylate) ethyl]-α-D-glucopyranoside (IV).—A mixture of 90 mg. of III and 1 ml. of 60% acetic acid was heated for 30 min. on a boiling water bath. Evaporation gave a glassy residue which was freed from benzaldehyde by codistillation with water. It was recrystallized from a mixture of acetone, ether, and pentane, giving needles, m.p. 120–122°, $[\alpha]^{28}D$ +137° (*c* 0.94, in chloroform).

Anal. Calcd. for $C_{19}H_{27}NO_8$: C, 57.42; H, 6.85; N, 3.52. Found: C, 57.40; H, 6.89; N, 3.52.

Compound IV also could be prepared conveniently directly from II: the benzylidene group was first removed with 60% acetic acid, then the crude product was esterified with diazomethane, and the resulting ester was recrystallized as described. In this way, 7.0 g. of II gave 3.0 g. of IV (50% over-all yield), m.p. 120–122°.

(8) P. M. Carroll, *Nature*, **197**, 694 (1963).

(9) W. T. J. Morgan and L. A. Elson, *Biochem. J.*, **28**, 988 (1934).

Benzyl 2-Acetamido-4-*O*-acetyl-2-deoxy-3-*O*-[D-1-(methyl carboxylate)ethyl]-6-*O*-triphenylmethyl-α-D-glucopyranoside (V).—To a solution of 110 mg. of IV in 0.5 ml. of pyridine was added 100 mg. of triphenylchloromethane. The solution was heated to 100°, and 0.3 ml. of acetic anhydride was immediately added to the hot solution, which was allowed to cool to room temperature and left overnight. The solution was then poured into ice–water and the gummy precipitate obtained was separated, washed thoroughly with water and dried. It was dissolved in benzene and the solution was chromatographed on silica gel. Elution with a mixture of benzene and ether 4:1 gave 153 mg. (81%) of crystalline material. It was recrystallized from a mixture of ethyl acetate and hexane, to give colorless prisms, m.p. 149–151°, $[\alpha]^{25}D$ +101° (*c* 0.88, in chloroform).

Anal. Calcd. for $C_{40}H_{43}NO_9$: C, 70.47; H, 6.36. Found: C, 70.44; H, 6.40.

Benzyl 2-Acetamido-4-*O*-acetyl-2-deoxy-3-*O*-[D-1-(methyl carboxylate)ethyl]-α-D-glucopyranoside (VI). From V.—Forty milligrams of V was detritylated by heating at 100° for 30 min. with 0.5 ml. of 60% acetic acid. The acetic acid was removed by evaporation, and the residue was dissolved in benzene and chromatographed on silica gel. A mixture of ether and ethyl acetate, 1:1, eluted 18.5 mg. (72%) of crystalline fractions, which were recrystallized from a mixture of acetone and ether, giving needles, m.p. 152–153° after sintering at 144° and resolidifying; $[\alpha]^{25}D$ +127° (*c* 1.49, in chloroform).

Anal. Calcd. for $C_{21}H_{29}NO_9$: C, 57.39; H, 6.65; N, 3.19. Found: C, 57.51; H, 6.79; N, 3.28.

From IV.—A solution of 2.0 g. of IV in 6 ml. of dry pyridine was allowed to react with 1.6 g. of triphenylchloromethane overnight at room temperature. The solution was then heated to 100°, 5 ml. of acetic anhydride was immediately added, and the reaction was allowed to proceed for an additional 7 hr. at room temperature. After pouring into water, the gummy precipitate was separated, then hydrolyzed with dilute acetic acid, and purified by chromatography as described in the previous section. Recrystallization from a mixture of acetone and ether gave 1.22 g. (55% over-all yield from IV), m.p. 152–153° (after sintering at 144°), identical with the product described previously.

Benzyl 2-Acetamido-4,6-di-*O*-acetyl-2-deoxy-3-*O*-[D-1-methyl carboxylate)ethyl]-α-D-glucopyranoside (VII).—Incomplete tritylation of the primary hydroxyl group occurred if insufficient time was allowed for the reaction between IV and triphenylchloromethane. A preparation of VI, obtained directly from IV, in which the addition of acetic anhydride to the mixture of IV and triphenylchloromethane in pyridine had been made without leaving the mixture overnight at room temperature, contained a second product. During the chromatography on silica gel this product was separated by elution with a mixture of ether and ethyl acetate, 9:1. Recrystallization from a mixture of acetone and ether gave needles, m.p. 128–129°, $[\alpha]^{27}D$ +118° (*c* 2.63, in chloroform). The product showed no hydroxyl group absorption in the infrared spectra. From 4.3 g. of IV, 0.6 g. (12%) of VII was thus obtained.

Anal. Calcd. for $C_{23}H_{31}NO_{10}$: C, 57.37; H, 6.49; N, 2.91. Found: C, 57.32; H, 6.50; N, 2.96.

An identical product was obtained by direct acetylation of IV in pyridine solution with acetic anhydride.

Benzyl 2-Acetamido-3-*O*-(D-1-carboxyethyl)-2-deoxy-α-D-glucopyranoside (VIII).—To a solution of 300 mg. of IV in 9 ml. of methanol was added 1 ml. of 2 *N* sodium hydroxide, and the clear solution obtained was left overnight at room temperature. The solution was acidified with dilute acetic acid and evaporated. The residue was dissolved in a few milliliters of water and passed through a column of Dowex 50W-X8 (H^+ form). Evaporation of the solution gave a residue (275 mg.), which was recrystallized from a mixture of methanol and ethyl acetate, giving 250 mg. (86%) of needles, m.p. 160–161°, $[\alpha]^{26}D$ +168° (*c* 1.25, in methanol).

Anal. Calcd. for $C_{18}H_{25}NO_8$: C, 56.39; H, 6.57; N, 3.65. Found: C, 56.34; H, 6.70; N, 3.70.

2-Acetamido-3-*O*-(D-1-carboxyethyl)-2-deoxy-α-D-glucose (*N*-acetylmuramic Acid) (IX).—A solution of 100 mg. of VIII in 10 ml. of 90% ethanol was hydrogenolyzed at room temperature and normal pressure in the presence of 10% palladium on charcoal as catalyst. The filtrate was concentrated by evaporation, and the residue was recrystallized from a mixture of ethyl acetate and methanol, giving 67 mg. (87%), m.p. 120–122°. A second crystallization gave 40 mg. of prisms, m.p. 122–124°. The product had a mutarotation from $[\alpha]^{22}D$ +59° (after 8 min.) to +39° (at equilibrium, after 6 hr., (*c* 1.58, in water).

Anal. Calcd. for $C_{11}H_{19}NO_8$: C, 45.04; H, 6.53; N, 4.77. Found: C, 44.77; H, 7.07; N, 4.71.

The substance was homogeneous in descending chromatography, using Whatman No. 1 paper. In a mixture of butanol, pyridine, and water, 6:4:3, the $R_{2\text{-amino-2-deoxyglucose}}$ was 1.0; and, in a mixture of butanol, acetic acid, and water, 4:1:5 (upper phase), the $R_{2\text{-acetamido-2-deoxyglucose}}$ was 2.0. The spot obtained with the silver nitrate reagent[10] was the pale-centered spot typical for muramic acid derivatives; a strong color was produced with a modified Morgan–Elson spray reagent.[11] Using the Reissig, *et al.*, modification[12] of the Morgan–Elson test, the molar extinction value, after a heating time of 3 min., was 17,300, very similar to that obtained for 2-acetamido-2-deoxyglucose under the same conditions; after 35 min., it was 14,500. In the Aminoff, *et al.*, modification[13] of this test, the molar extinction was 18,625 using filter no. 56 of the Klett–Sumerson spectrophotometer.

2-Acetamido-4,6-di-*O*-acetyl-2-deoxy-3-*O*-[D-1-(methyl carboxylate)ethyl]-α-D-glucose (X).—A solution of 200 mg. of VII in 10 ml. of 90% ethanol was hydrogenated at room temperature and normal pressure for 18 hr. in the presence of 10% palladium on charcoal as catalyst. After filtration, the solution was evaporated and the residue was dissolved in ethylene dichloride and chromatographed on silica gel. Elution with ethyl acetate gave 142 mg. (87%) of material, which was crystallized from a mixture of acetone and ether into needles, m.p. 181–183°. A recrystallization from the same solvents gave m.p. 182–183°, $[\alpha]^{25}D$ +66° (*c* 1.44, in 90% ethanol). The product had no apparent mutarotation and the α-anomer was assumed on the basis of the positive rotation.

Anal. Calcd. for $C_{16}H_{25}NO_{10}$: C, 49.10; H, 6.44; N, 3.58. Found: C, 48.95; H, 6.47; N, 3.72.

Benzyl 6-*O*-(2-Acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-β-D-glucopyranosyl)-2-acetamido-4-*O*-acetyl-2-deoxy-3-*O*-[D-1-(methyl carboxylate)ethyl]-α-D-glucopyranoside (XII).—Ten milliliters of a dry chloroform solution containing 1.0 g. of 2-acetamido-3,4,6-tri-*O*-acetyl-deoxy-α-D-glucopyranosyl bromide (XI), that was prepared *in situ* according to Inouye, *et al.*,[14] was added in two equal portions to a stirred mixture of 0.55 g. of VI and 0.70 g. of mercuric cyanide in 10 ml. of nitromethane at room temperature. The second portion was added after 20 hr., and the reaction was allowed to proceed an additional 24 hr. The reaction mixture was then diluted with chloroform, and the organic layer was washed several times with a saturated sodium bicarbonate solution, then with water, and dried. After evaporation, the residue (1.2 g.) was dissolved in benzene and purified by chromatography on silica gel. A mixture of ether and ethyl acetate, 4:1, eluted a fraction which, on recrystallization from a mixture of acetone and ether, gave 0.42 g. of colorless needles, m.p. 152–153° (after previously sintering at 145°), identical with the starting material V. Ethyl acetate eluted a colorless product which crystallized from a mixture of acetone and ethanol in needles, weighing 0.035 g. (3.5%), m.p. 253–254°. A second crystallization from this solvent mixture gave m.p. 252–253° with resolidification on further standing and final melting at 260°; $[\alpha]^{26}D$ +58° (*c* 1.02, in chloroform).

Anal. Calcd. for $C_{35}H_{48}N_2O_{17}$: C, 54.68; H, 6.43; N, 3.67. Found: C, 54.60; H, 6.37; N, 3.73.

Benzyl 6-*O*-(2-Acetamido-2-deoxy-β-D-glucopyranosyl)-2-acetamido-3-*O*-(D-1-carboxyethyl)-2-deoxy-α-D-glucopyranoside (XIII).—To a solution of 80 mg. of XII in 2 ml. of methanol was added 0.03 ml. of aqueous 2 *N* sodium hydroxide solution. The clear solution was left overnight at room temperature and then passed through a column of Dowex 50W-X8 (H^+ form). The column was washed with water and evaporation of the aqueous eluates gave 70 mg. of residue. Crystallization from methanol gave 35 mg. (60%) of needles, m.p. 227–228°, $[\alpha]D$ +87° (*c* 1.21, in methanol). The melting point was unchanged

(10) P. J. Stoffyn and R. W. Jeanloz, *Arch. Biochem. Biophys.*, **52**, 373 (1954); N. Sharon and R. W. Jeanloz, *J. Biol. Chem.*, **235**, 1 (1960).

(11) C. E. Cardini and L. F. Leloir, *ibid.*, **225**, 317 (1957).

(12) J. L. Reissig, J. L. Strominger, and L. F. Leloir, *ibid.*, **217**, 959 (1955).

(13) D. Aminoff, W. T. J. Morgan, and W. M. Watkins, *Biochem. J.*, **51**, 379 (1952).

(14) Y. Inouye, K. Onodera, S. Kitaoka, and H. Ochiai, *J. Am. Chem. Soc.*, **79**, 4218 (1957).

on further crystallization from methanol, and the infrared spectrum showed no ester band (potassium bromide disk).

Anal. Calcd. for $C_{26}H_{38}N_2O_{13}$: C, 53.23; H, 6.53; N, 4.77. Found: C, 53.07; H, 6.55; N, 4.70.

Acknowledgment.—The authors wish to thank Chas. Pfizer and Company for a kind gift of 2-acetamido-2-deoxy-D-glucose.

Tetra-*O*-acylglycosyl Chlorides from 1-Thioglycosides and Their Conversion to Penta-*O*-acyl Esters

M. L. WOLFROM AND WOLFGANG GROEBKE[1]

Department of Chemistry, The Ohio State University, Columbus 10, Ohio

Received May 10, 1963

The ethyl tetra-*O*-acetyl-1-thioglycosides of α(or β)-D-glucopyranose, β-D-galactopyranose, and β-D-galactofuranose reacted with chlorine to produce the tetra-*O*-acetyl-β-D-glycosyl chloride. The corresponding derivative of D-mannose yielded an anomeric mixture of tetra-*O*-acetyl-D-mannopyranosyl chlorides. All of the tetra-*O*-acetyl-β-D-glycopyranosyl chlorides reacted with mercuric acetate in acetic acid to form the β-D-glycopyranose pentaacetate; tetra-*O*-acetyl-β-D-galactofuranosyl chloride reacted similarly to form β-D-galactofuranose pentaacetate. The latter reaction gives a new route to β-D-galactofuranose pentaacetate, since the halide was made through the 1-thiofuranoside. Ethyl 1-thio-α-D-glucofuranoside was benzoylated to the tetrabenzoate, m.p. 108–109°, $[\alpha]^{24}D$ +62.5° ($CHCl_3$), which was chlorinated to its sirupy tetra-*O*-benzoyl-D-glucofuranosyl chloride, and this with mercuric acetate yielded tetra-*O*-benzoyl-β-D-glucofuranosyl acetate, m.p. 130.5°, $[\alpha]^{23}D$ −34° ($CHCl_3$). This route likewise provides a new entry to the glucofuranose series. An interpretation of the course of these reactions is given.

The reaction of alkylthio compounds with bromine was established by Bonner.[2] The reaction takes the course shown below, wherein, in the sugar series, the alkylthio group is part of a dithioacetal function or is the thioacetal group of a 1-thioglycoside.

$$-SR' + Br_2 \longrightarrow -Br + BrSR'$$

In a fully acetylated aldose dithioacetal the reaction product is an *aldehydo*-acetate formed probably through the 1,1-dibromo derivative; in a 1-thioglycoside the product is a poly-*O*-acylglycosyl bromide. Weygand and associates[3] especially developed the application of this reaction in the sugar series. We have employed this reaction for the synthesis of acyclic analogs of nucleosides[4] and of nucleohexofuranosides.[5]

Herein we wish to report on the action of chlorine on 1-thioglycosides. In all cases studied save that of ethyl 1-thio-β-D-mannopyranoside (V) wherein an anomeric mixture (VII + VIII) was obtained, the ordinarily unstable tetra-*O*-acetyl-β-D-glycosyl chloride was formed regardless of the anomeric nature of the 1-thioglycoside. This statement is based upon isolated crystalline substances and does not necessarily establish these as the only reaction products. The mother liquors were investigated by thin-layer chromatographic techniques and were found to be rather complex. Chlorides of the β-D-form were produced from the acetylated ethyl 1-thioglycosides of α(or β)-D-glucopyranose (I and II), β-D-galactopyranose, and β-D-galactofuranose.

Following Bonner,[2] the chlorine reacts with the 1-ethylthio group to form the chlorosulfonium chloride I (illustrated in the D-glucose structure), which on heterolysis of the C-1 to S bond, could lead to two types of carbonium ions: III (D-glucose) or VI (illustrated for the D-mannose derivative). It would appear that the postulated bicyclic ion III, stabilized by resonance, is the favored form. Attack of chloride ion upon III would be hindered from the bottom side (as illustrated) and would lead exclusively to the β-D-glycosyl chloride. On the other hand, attack of a chloride ion upon VI could occur from either side and would lead to an approximately equal mixture of glycosyl chlorides, as was found for the D-mannose structure. With a few modern refinements, this explanation is essentially that given by Pacsu[6] in 1945 to explain the products formed in certain Koenigs–Knorr reactions and by Bonner[2] in 1948 to interpret the action of bromine on 1-thioglycosides.

It was then our endeavor to utilize the tetra-*O*-acylglycosyl chlorides so formed as an entry to the fully esterified sugar ester series. To this end the chlorides were replaced by acetoxy groups through reaction with mercuric acetate in acetic acid.[7] This reaction had been utilized for the formation of β-D-acetates from the acylated α-D-glycosyl halides. We were, therefore, surprised to find that all the tetra-*O*-acetyl-β-D-glycosyl chlorides employed likewise gave the β-D-form of the pentaacetate. This finding could be explained by the steric course of the reaction being completely dominated by the ortho ester effect, the 1,2-*trans*-acetates being formed regardless of the anomeric nature of the glycosyl halide. This reaction series provides another source for β-D-galactofuranose pentaacetate. When applied to the sirupy tetra-*O*-benzoyl-D-glucofuranosyl chloride (XI), herein formed from the known ethyl 1-thio-α-D-glucofuranoside (IX), a crystalline tetra-*O*-benzoyl-D-glucoforanosyl acetate (XII) was obtained which was likewise of the β-D-type. First crystals of

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(2) W. A. Bonner, *J. Am. Chem. Soc.*, **70**, 770, 3491 (1948).

(3)(a) F. Weygand, H. J. Bestmann, and H. Ziemann, *Ber.*, **91**, 1040 (1958); F. Weygand, H. Ziemann, and H. J. Bestmann, *ibid.*, **91**, 2534 (1958); (b) F. Weygand and H. Ziemann, *Ann.*, **657**, 179 (1962).

(4) M. L. Wolfrom, A. B. Foster, P. McWain, W. von Bebenburg, and A. Thompson, *J. Org. Chem.*, **26**, 3095 (1961); M. L. Wolfrom, P. McWain, and A. Thompson, *ibid.*, **27**, 3549 (1962).

(5) M. L. Wolfrom and P. McWain, Abstracts, 142nd National Meeting of the American Chemical Society, Atlantic City, N. J., September, 1962, p. 70.

(6) E. Pacsu, *Advan. Carbohydrate Chem.*, **1**, 118 (1945).

(7) B. Lindberg, *Acta Chem. Scand.*, **3**, 1355 (1949); L. Asp and B. Lindberg, *ibid.*, **5**, 665 (1951); **6**, 941 (1952); M. L. Wolfrom, A. Thompson, and M. Inatome, *J. Am. Chem. Soc.*, **77**, 3160 (1955); **79**, 3868 (1957); M. L. Wolfrom and D. L. Fields, *Tappi*, **40**, 335 (1957).