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

(1) Postdoctoral Fellow under Grant G14629 of the National Science Foundation (The Ohio State University Research Foundation Project 1178). Acknowledgment is made to a Fulbright travel grant.

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

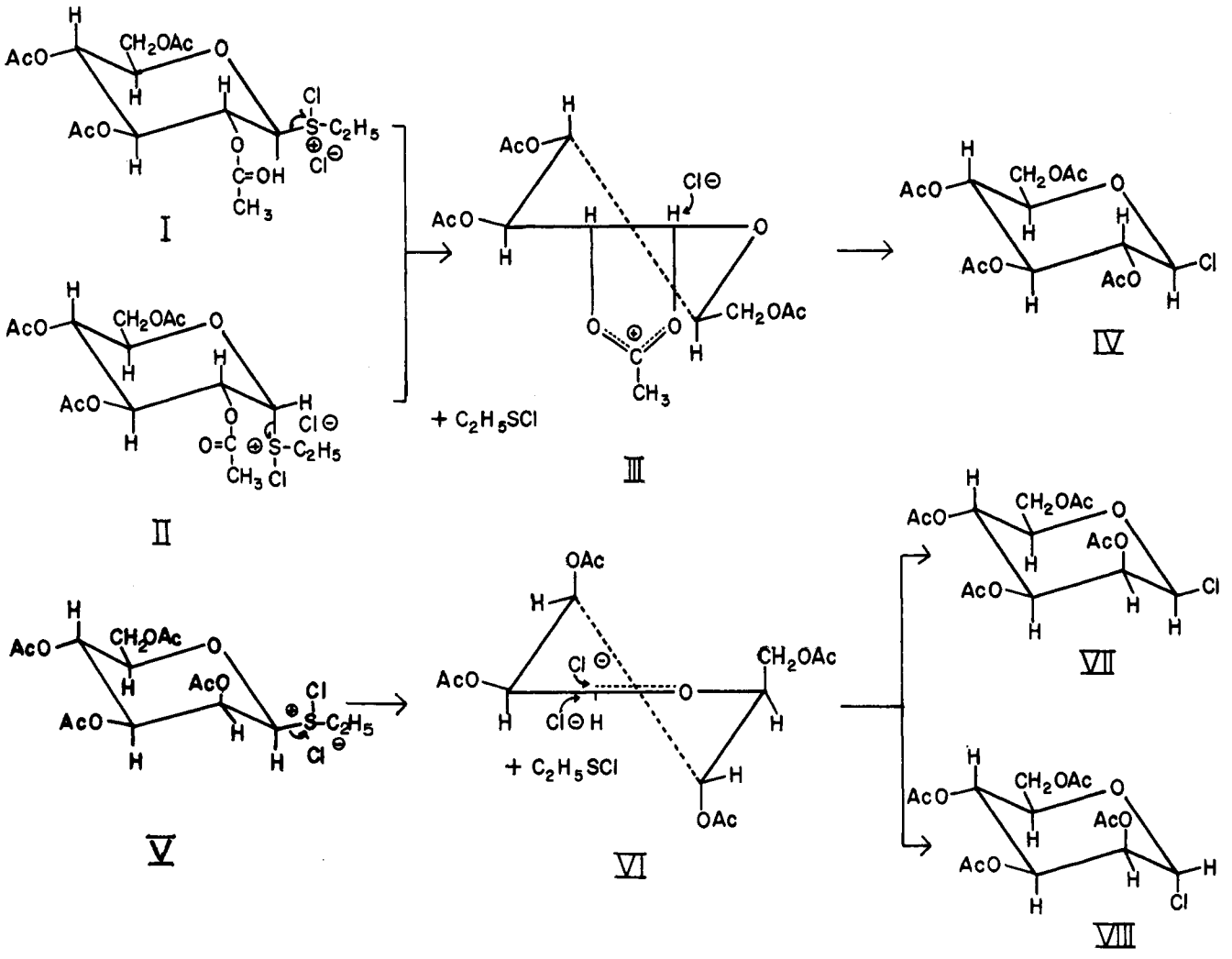
(3)(a) F. Weygand, H. J. Bestmann, and H. Ziemann, *Ber.*, **91**, 1040 (1958); F. Weygand, H. Ziemann, and H. J. Bestmann, *ibid.*, **91**, 2534 (1958); (b) F. Weygand and H. Ziemann, *Ann.*, **657**, 179 (1962).

(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).

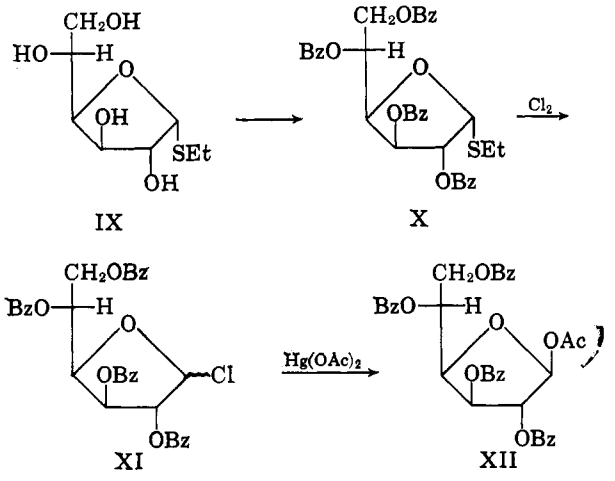
(5) M. L. Wolfrom and P. McWain, Abstracts, 142nd National Meeting of the American Chemical Society, Atlantic City, N. J., September, 1962, p. 70.

(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).



compound X were obtained by thin-layer chromatographic techniques, illustrating the further value of this method.



Experimental

Preparation of Tetra-O-acetyl-β-D-galactofuranosyl Chloride from Ethyl Tetra-O-acetyl-1-thio-α-D-galactofuranoside.—Ethyl tetra-O-acetyl-1-thio-α-D-galactofuranoside (4.0 g.) was dissolved in carbon tetrachloride (40 ml.) and to this was added 6 ml. of a solution of chlorine gas in dry chloroform (0.127 g. of chlorine per ml. of chloroform). After stirring for 0.5 hr., the solution was evaporated under reduced pressure to a colorless solid which, after removal of volatile by-products (repeated solution in ether and evaporation of solvent), was crystallized from absolute ether; yield, 3.1 g. (83%); m.p. 73°; $[\alpha]^{24}D$ −80° (*c* 0.9, chloroform). These constants identify the substance as tetra-O-acetyl-β-D-galactofuranosyl chloride.[8] The product was compared with that prepared by the method of Ness, Fletcher, and Hudson[8] and was found to be identical with it.

β-D-Galactofuranose Pentaacetate from Ethyl Tetra-O-acetyl-1-thio-β-D-galactofuranoside.—Tetra-O-acetyl-β-D-galactofuranosyl chloride (1.032 g., 2.82 mmoles), prepared from ethyl tetra-O-acetyl-1-thio-β-D-galactofuranoside as described in the preceding section, and 470 mg. (1.47 mmoles) of mercuric acetate were dissolved in 15 ml. of anhydrous acetic acid and allowed to stand overnight at room temperature. The residue obtained on solvent removal was taken up in chloroform, leaving a residue of mercuric chloride; yield of mercuric chloride, 360 mg. (93%). The chloroform solution was concentrated to a sirup which was crystallized by solution in 1 ml. of ethanol and nucleation. Recrystallization was effected from ethanol (2 ml.); yield, 645 mg. (58.5%); m.p. 98°, unchanged on admixture with authentic β-D-galactofuranose pentaacetate[8] of like melting point.

Tetra-O-acetyl-β-D-galactopyranosyl Chloride from Ethyl Tetra-O-acetyl-1-thio-β-D-galactopyranoside.—An amount of 1.00 g. (2.55 mmoles) of ethyl tetra-O-acetyl-1-thio-β-D-galactopyranoside[9,10] was dissolved in 8 ml. of carbon tetrachloride and to this was added 3 ml. of a solution of 0.45 g. of chlorine in carbon tetrachloride. The solution was maintained at room temperature for 30 min. after which the solvent was removed under reduced pressure. The residual sirup was obtained crystalline by solution in absolute ether and solvent removal (six times) and was recrystallized twice from 3 ml. of absolute ether; yield, 0.52 g. (55.5%); m.p. 93–95°; $[\alpha]^{20}D$ +12° (*c* 1, chloroform). For tetra-O-acetyl-

(8) C. S. Hudson and J. M. Johnson, *J. Am. Chem. Soc.*, **38**, 1223 (1916); H. H. Schlubach and V. Prochownick, *Ber.*, **63**, 2298 (1930); R. K. Ness, H. G. Fletcher, Jr., and C. S. Hudson, *J. Am. Chem. Soc.*, **73**, 3742 (1951).

(9) J. Fried and D. E. Walz, *ibid.*, **71**, 140 (1949).

(10) R. U. Lemieux, *Can. J. Chem.*, **29**, 1079 (1951).

β-D-galactopyranosyl chloride, Schlubach and Gilbert[11] report 93–94° and +6° while Korytnyk and Mills[12] report 93° and +15° for the constants.

The chlorination reaction also can be carried out in absolute chloroform solution. All solvents must be pure and dry. A slight excess of chlorine has no noticeable effect. For larger amounts of material, cooling with iced water is recommended. Codistillation with ether on the crude product is essential to remove the readily volatile secondary product ethanesulfenyl chloride. All of these mother liquors were investigated by thin-layer chromatography but no other crystalline products were isolated. The reaction mixtures were found to be rather complex with any anomeric forms, if present, being difficult to separate.

Penta-*O*-acetyl-β-D-galactopyranose from Tetra-*O*-acetyl-β-D-galactopyranosyl Chloride.—An amount of 247 mg. (0.67 mmole) of tetra-*O*-acetyl-β-D-galactopyranosyl chloride and 125 mg. (0.39 mmole) of mercuric acetate were dissolved in 3 ml. of acetic acid and maintained overnight at room temperature. To this solution was then added 30 ml. of chloroform and the whole was washed successively with water, 4% aqueous sodium bicarbonate, and again with water. The sirup obtained on solvent removal was crystallized from 95% ethanol and was recrystallized from this solvent; yield, 190 mg. (72%); m.p. 141°, undepressed on admixture with authentic β-D-galactopyranose pentaacetate[13] of like melting point.

Replacement of the acetic acid with dioxane, acetonitrile, or benzene led to much lower yields of product.

Tetra-*O*-acetyl-β-D-glucopyranosyl Chloride (IV) from Ethyl Tetra-*O*-acetyl-1-thio-α-D-glucopyranoside (II).—An amount of 483 mg. (1.23 mmoles) of ethyl tetra-*O*-acetyl-1-thio-α-D-glucopyranoside[14] (II) was converted to tetra-*O*-acety -β-D-glucopyranosyl chloride (IV) as described for the conversion of ethyl tetra-*O*-acetyl-1-thio-β-D-galactopyranoside to tetra-*O*-acetyl-β-D-galactopyranosyl chloride with chlorine in carbon tetrachloride, and the crystalline product was purified in the same manner; yield, 330 mg. (73%); m.p. 99°; $[\alpha]^{20}D$ −14° (*c* 1, chloroform). Schlubach[15] records 99–100° and −13° for the corresponding constants.

Tetra-*O*-acetyl-β-D-glucopyranosyl chloride also was obtained by similar treatment of 520 mg. of ethyl tetra-*O*-acetyl-1-thio-β-D-glucopyranoside[16] (I); yield, 295 mg. (61%); m.p. 97–98°, undepressed on admixture with authentic material.

Penta-*O*-acetyl-β-D-glucopyranose from Tetra-*O*-acetyl-β-D-glucopyranosyl Chloride.—Tetra-*O*-acetyl-β-D-glucopyranosyl chloride (290 mg., 0.79 mmole) was treated with mercuric acetate as described for the corresponding D-galactose compound, and the product was isolated in the same manner. Recrystallization from ethanol yielded pure penta-*O*-acetyl-β-D-glucopyranose; yield, 66 mg. (21%); m.p. 131°, undepressed on admixture with an authentic sample of like melting point.

Anomeric Mixture of Tetra-*O*-acetyl-D-mannopyranosyl Chlorides from Ethyl Tetra-*O*-acetyl-1-thio-α-D-mannopyranoside (V).—An amount of 700 mg. (1.78 mmoles) of ethyl tetra-*O*-acetyl-1-thio-α-D-mannopyranoside[3b,9] (V) was treated with chlorine in carbon tetrachloride as described previously, and the product was isolated in the same manner and recrystallized from ether; yield, 330 mg. (50.5%); m.p. 95–96°; $[\alpha]^{20}D$ +7° (*c* 1, chloroform). The rotation indicated an approximately equal anomeric mixture. Separation was effected by slow evaporation from 10 ml. of ether. The first crop separated as stout, square crystals, m.p. 79°. The α-D anomer VIII is reported[17] to melt at 81°. The second crop consisted of long needles, m.p. 159°. The β-D-anomer VII is reported[12] to melt at 165°.

Ethyl Tetra-*O*-benzoyl-1-thio-α-D-glucofuranoside (X).—A solution of 7.5 ml. of chloroform and 5 ml. of dry pyridine and another of 4.6 ml. (40 mmoles) of benzoyl chloride in 7.5 ml. of dry pyridine were mixed after precooling to −5°. To the stirred solution was added 2.92 g. (10 mmoles) of ethyl 1-thio-α-D-glucofuranoside[5,18] (IX) at such a rate as to maintain the temperature below 0°. The solution was then maintained overnight at 0°, diluted with 30 ml. of chloroform, and washed successively with cold solutions of 5% sulfuric acid, 4% aqueous sodium carbonate, and finally cold water. A sirup was obtained on solvent removal from the dried (decolorizing carbon) solution. First seed of the desired product was obtained by thin-layer chromatography. An amount of 100 mg. of the sirup was applied to a 1-mm. layer of silica gel G (Stahl) on an 8 × 8 in. plate. Development was effected with ethyl acetate–chloroform (1:9 v./v.). The zone material at R_f 0.95 was removed and eluted with acetone. The sirup obtained on solvent removal crystallized after standing 3 weeks. The remaining sirup was dissolved in a few milliliters of ether and seeded. Crystalline material was obtained on standing overnight. Recrystallization was effected from 20 ml. of ethanol; yield, 3.02 g. (47.5%); m.p. 108–109°; $[\alpha]^{24}D$ +62.5° (*c* 1.5, chloroform).

Anal. Calcd. for $C_{36}H_{32}O_9S$: C, 67.49; H, 5.39; S, 5.30. Found: C, 67.61; H, 5.03; S, 5.00.

Tetra-*O*-benzoyl-β-D-glucofuranosyl Acetate (XII).—An amount of 1.28 g. (2 mmoles) of ethyl tetra-*O*-benzoyl-1-thio-α-D-glucofuranoside (X) was dissolved in 20 ml. of carbon tetrachloride to which was added 3.5 ml. of a solution of chlorine in carbon tetrachloride (0.15 g. per ml.). After stirring 30 min. the excess chlorine and solvent were removed under reduced pressure, and ether was added (several times) to the resultant sirup and removed by distillation. The resultant sirup resisted crystallization; $[\alpha]^{20}D$ −10.5° (*c* 1, chloroform). A similar value, indicating a probable anomeric mixture, was found by Schlubach and co-workers[19] for this sirupy substance prepared from D-glucofuranose pentabenzoate. An amount of 1.10 g. (1.79 mmoles) of the sirupy tetra-*O*-benzoyl-D-glucofuranosyl chloride was dissolved in 10 ml. of acetic acid to which was added 300 mg. (0.94 mmole) of mercuric acetate, and the whole was allowed to stand overnight at room temperature. The residue obtained on solvent removal was taken up in chloroform and filtered from mercury salts. The sirup obtained on chloroform removal was crystallized from ethanol and recrystallized from the same solvent; yield, 600 mg. (52.5%); m.p. 130°. Pure material XII was obtained on further recrystallization from ethanol; m.p. 130.5°; $[\alpha]^{23}D$ −34° (*c* 2, chloroform).

Anal. Calcd. for $C_{36}H_{30}O_{11}$: C, 67.71; H, 4.73. Found: C, 67.78; H, 4.61.

(11) H. H. Schlubach and R. Gilbert, *Ber.*, **63**, 2296 (1930).
(12) W. Korytnyk and J. A. Mills, *J. Chem. Soc.*, 636 (1959).
(13) E. Erwig and W. Koenigs, *Ber.*, **22**, 2207 (1889).
(14) P. Brigl, K. Gronemeier, and A. Schulz, *ibid.*, **72**, 1052 (1939); E. Pacsu and E. J. Wilson, Jr., *J. Am. Chem. Soc.*, **61**, 1930 (1939).
(15) H. H. Schlubach, *Ber.*, **59**, 844 (1926).
(16) W. Schneider, J. Sepp, and O. Stiehler, *ibid.*, **51**, 220 (1918).
(17) E. Pacsu, *ibid.*, **61**, 1508 (1928).
(18) J. W. Green and E. Pacsu, *J. Am. Chem. Soc.*, **59**, 1205 (1937).
(19) H. H. Schlubach, F. Trefz, and W. Rauchenberger, *Ber.*, **61**, 2368 (1928).