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THIOCARBONATES AS BLOCKING GROUPS FOR THE SYNTHESIS OF PARTIAL ESTERS OF CARBOHYDRATES

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ABSTRACT

It has been found that the thiocarbonate, or (alkylthio)carbonyl derivative, serves as a versatile blocking group for the synthesis of partial ester derivatives of carbohydrates. The (alkylthio)carbonyl group is readily substituted in pyridine solution, is stable to mild acid conditions, but is decomposed by mild oxidation. Crystalline methyl 4,6-di-*O*-benzoyl-α-D-glucopyranoside has been synthesized and its structure proved by an independent synthesis of its 2,3-di-*O*-phenylcarbamate derivative. Methyl 4,6-di-*O*-benzoyl-β-D-glucopyranoside was also synthesized and its structure proved by acetylation to the known 2,3-di-*O*-acetyl derivative.

INTRODUCTION

During a study of the kinetics of acetylation of methyl glucosides in our laboratories, certain unknown di- and tri-acetate derivatives of the methyl glucosides became of interest. Many of the possible mono-, di-, and tri-acetates of the methyl glucosides are not known, as is true also for the benzoate derivatives (1), and the general methods for their synthesis have been limited. Apart from the few acetates and benzoates which can be synthesized by the specific substitution reactions or those which depend on the controlled migration of an ester group from one hydroxyl to another, the only derivatives known are those which have utilized acid-sensitive blocking groups such as 4,6-benzylidene (giving 2,3-diesters) or the triphenylmethyl ether (giving 2,3,4-triesters) for their preparation.

The (alkylthio)carbonyl[2] group, R—S—C(=O)—, has been utilized as a protective radical for amino groups in peptide synthesis (2). The (benzylthio)carbonyl derivative of methyl-α-D-glucopyranoside was encountered (3) as an intermediate during the two-step removal of the xanthate group from methyl 2,3,4-tri-*O*-benzoyl-6-*O*-(benzylthio)thiocarbonyl-α-D-glucopyranoside, and was shown to be readily decomposed by mild oxidation, the parent alcohol being liberated. Because it was proved that the benzoyl groups did not migrate during the reaction, the (benzylthio)carbonyl group was suggested as a promising blocking group for the synthesis of partial esters of carbohydrates. This paper describes the synthesis and proofs of structure of methyl 4,6-di-*O*-benzoyl-α-D-glucopyranoside and its β-anomer, demonstrating this principle.

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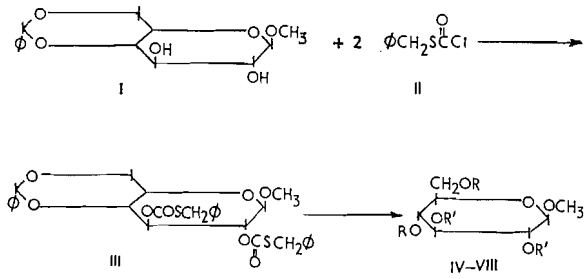
[2]*The nomenclature for thiocarbonates recommended by L. Hough, J. E. Priddle, and R. S. Theobald, Advances in Carbohydrate Chem.,* ***15****, 91 (1960), is used in this communication.*

Methyl 4,6-di-*O*-benzoyl-β-D-glucopyranoside (VI) was synthesized in 21% overall yield, as seen from Fig. 1. Methyl 4,6-*O*-benzylidene-β-D-glucopyranoside (I) was treated



WHERE:

IV R = −H; R′ = $-\overset{O}{\overset{\|}{C}}SCH_2\phi$ VII R = $-\overset{O}{\overset{\|}{C}}\phi$; R′ = $-\overset{O}{\overset{\|}{C}}CH_3$

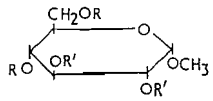
V R = $-\overset{O}{\overset{\|}{C}}\phi$; R′ = $-\overset{O}{\overset{\|}{C}}SCH_2\phi$ VIII R = $-\overset{O}{\overset{\|}{C}}CH_3$; R′ = $-\overset{O}{\overset{\|}{C}}SCH_2\phi$

VI R = $-\overset{O}{\overset{\|}{C}}\phi$; R′ = −H ϕ = $-C_6H_5$

FIG. 1.

in pyridine solution with a small excess of (benzylthio)carbonyl chloride (II), giving a crystalline 2,3-di-*O*-(benzylthio)carbonyl derivative (III). Removal of the benzylidene group by mild acid hydrolysis afforded methyl 2,3-di-*O*-(benzylthio)carbonyl-β-D-glucopyranoside (IV), which failed to crystallize. However, benzoylation gave a crystalline 4,6-di-*O*-benzoyl derivative (V) and acetylation, the crystalline diacetate (VIII). Oxidation of V with hydrogen peroxide in acetic acid – chloroform solution gave methyl 4,6-di-*O*-benzoyl-β-D-glucopyranoside (VI), the structure of which was proved by acetylation of VI to known (4) methyl 2,3-di-*O*-acetyl-4,6-di-*O*-benzoyl-β-D-glucopyranoside (VII).

Crystalline methyl 4,6-di-*O*-benzoyl-α-D-glucopyranoside (IX), Fig. 2, was synthe-



IX R = $-\overset{O}{\overset{\|}{C}}\phi$; R′ = −H

X R = $-\overset{O}{\overset{\|}{C}}\phi$; R′ = $-\overset{O}{\overset{\|}{C}}NH\phi$

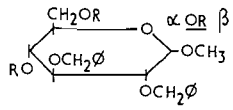
XI R = −H; R′ = $-\overset{O}{\overset{\|}{C}}NH\phi$

FIG. 2.

sized in 36% yield in the same manner from methyl 4,6-*O*-benzylidene-α-D-glucopyranoside. It gave a crystalline 2,3-di-*O*-phenylcarbamate derivative (X). Its structure was proved by benzoylation of known (5) methyl 2,3-di-*O*-phenylcarbamyl-α-D-glucopyranoside (XI), giving a product identical with that prepared from the dibenzoate derivative (IX).

DISCUSSION

During the first attempts to synthesize methyl 4,6-di-*O*-benzoyl-α- and -β-D-glucopyranosides use was made of the known (6, 7) 2,3-di-*O*-benzyl ether derivatives (XII). Methyl 2,3-di-*O*-benzyl-α- and -β-D-glucopyranosides were benzoylated to the new crystalline 4,6-di-*O*-benzoyl derivatives (XIII) seen in Fig. 3. Repeated attempts to



XII R = —H

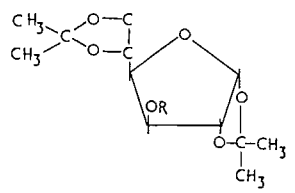
XIII R = —C(=O)Ø

XIV R = —CH3

FIG. 3.

remove the benzyl ether groups by catalytic hydrogenolysis were not successful. This was surprising in view of the experience in this laboratory that methyl 4,6-di-*O*-methyl-β-D-glucopyranoside is readily obtained by catalytic reduction (Pd) of its 2,3-di-*O*-benzyl ether derivative (XIV), a reaction described by Freudenberg and Plankenhorn (8). No reports have been found, in the literature, in which benzyl ether groups were removed by catalytic reduction from a carbohydrate also carrying ester groups. Since no other method is available for removal of benzyl ethers without loss of ester groups, the benzyl ether does not appear to be a useful blocking group in the synthesis of partial esters of the methyl glucosides.

The use of (alkylthio)carbonyl derivatives can be combined with that of any acid-sensitive blocking groups, e.g., condensed aldehydes and ketones, or triphenylmethyl ethers. The action of (benzylthio)carbonyl chloride on 1,2-5,6-di-*O*-isopropylidene-D-glucofuranose (XV), Fig. 4, gave a crystalline (benzylthio)carbonyl derivative, 1,2-5,6-



XV R = —H

XVI R = —C(=O)SCH2Ø

FIG. 4.

di-*O*-isopropylidene-3-*O*-(benzylthio)carbonyl-D-glucofuranose (XVI).

The properties of the thiocarbonate group which contribute to its value as a blocking agent are the following: (1) (benzylthio)carbonyl chloride, prepared by the action of 1 mole of phosgene on benzyl mercaptan in aqueous alkali (3, 9), can be purified by distillation and is stable during storage; (2) thiocarbonates are introduced conveniently

and in high yield in pyridine solution; (3) (benzylthio)carbonyl derivatives are generally crystalline; (4) they are stable under mild acid conditions; and (5) they can be removed by oxidative cleavage or by alkaline hydrolysis.

Although (alkylthio)carbonyl derivatives other than the benzyl analogue are prepared with equal ease, use has been confined chiefly to the (benzylthio)carbonyl ester in this laboratory.

It has been found that treatment of methyl 4,6-*O*-benzylidene-α-D-glucopyranoside with 1 mole of (benzylthio)carbonyl chloride gave a good yield of a crystalline monosubstituted (benzylthio)carbonyl derivative. This derivative increases even further the utility of the thiocarbonate as a precursor to partially esterified methyl glucosides. Investigations of this product will be reported in a later communication.

EXPERIMENTAL[3]

Methyl 2,3-Di-O-benzyl-4,6-di-O-benzoyl-α- and -β-D-glucopyranoside (XIII)

Methyl 4,6-*O*-benzylidene-β-D-glucopyranoside (I) was prepared according to the procedure of Freudenberg (10). It had m.p. 197–199°. This derivative was benzylated directly by the Zemplen procedure (11), the 2,3-di-*O*-benzyl derivative having m.p. 115–117°. The benzylidene group was removed by mild acid hydrolysis according to Bell and Lorber (12), furnishing methyl 2,3-di-*O*-benzyl-β-D-glucopyranoside (XII), m.p. 122–123°.

To 2.0 g XII in 10 ml anhydrous pyridine was added 2.5 ml benzoyl chloride, with cooling in ice bath. After standing overnight at room temperature, the product was isolated by pouring the solution into ice water, extracting the water with chloroform, and extracting the chloroform layer successively with excess 1 *N* hydrochloric acid, sodium bicarbonate solution, and finally with water. The chloroform layer was dried 0.5 hour over magnesium sulphate, filtered, and the chloroform evaporated *in vacuo*. As crystallized from ethanol, the product had m.p. 115–118°. After recrystallization it had m.p. 120–121° and $[\alpha]_D^{23}$ −7.5° (c = 1, $CHCl_3$). Anal. Calc. for $C_{35}H_{34}O_8$: C, 72.2; H, 5.84. Found: C, 70.8; H, 6.04.

The α-anomer was synthesized in the same manner and had m.p. 95–97° and $[\alpha]_D^{22}$ +20.5° (c = 1, $CHCl_3$). The product crystallized as long needles from methanol. Anal. Calc. for $C_{35}H_{34}O_8$: C, 72.4; H, 5.84. Found: C, 72.4; H, 6.04.

Repeated attempts to remove the benzyl ether groups from XIII by catalytic reduction using palladium, palladium on carbon, and platinum catalysts in various solvents resulted only in the recovery of starting materials.

1,2-5,6-Diisopropylidene-3-O-(benzylthio)carbonyl-D-glucofuranose (XVI)

To 2.0 g XV, m.p. 108–109°, in 5 ml anhydrous pyridine 1.2 ml II was added slowly with cooling in an ice bath. After standing several hours at room temperature, the product was worked up as usual. It crystallized from ligroin (unreacted diacetone glucose crystallizing out first from that solvent) after long standing in the refrigerator. The product had m.p. 66–67° and $[\alpha]_D^{22}$ −23.8° (c = 3, $CHCl_3$). Anal. Calc. for $C_{20}H_{26}O_7S$: C, 58.5; H, 6.34; S, 7.81. Found: C, 57.5; H, 6.46; S, 7.39.

(Benzylthio)carbonyl Chloride (II)

Compound II was prepared as described previously (3, 9), and had the following additional properties: $n_D^{22.5}$ 1.5748 and specific gravity 1.235.

Methyl 2,3-Di-O-(benzylthio)carbonyl-4,6-O-benzylidene-α-D-glucopyranoside (XVII)

To 6.0 g methyl 4,6-*O*-benzylidene-α-D-glucopyranoside in anhydrous pyridine was added 7.1 cc of II during 0.5 hour, with cooling in ice bath. It is essential that the pyridine be dry since II reacts preferentially with water in the presence of pyridine. The reaction can also be carried out entirely at room temperature with equivalent yields. The use of a larger excess of II resulted in increased yields.

The mixture was then allowed to come to room temperature during an additional 0.5 hour, after which it was poured into ice water. The product was extracted successively with dilute hydrochloric acid, twice with 0.5 *N* sodium hydroxide, and with water. The chloroform layer was dried over magnesium sulphate. Evaporation of the chloroform gave a sirup which crystallized as long needles from absolute ethanol, giving 10.0 g product with m.p. 130–133°. Two recrystallizations from ethanol gave 8.2 g (66%) having m.p. 133–134°. The product showed $[\alpha]_D^{22}$ +31.7° (c = 2, $CHCl_3$). Its melting point was not changed after recrystallization from methanol. Anal. Calc. for $C_{30}H_{30}O_8S_2$: C, 61.8; H, 5.16; S, 11.0. Found: C, 60.1; H, 5.44; S, 10.7.

[3]*All melting points are uncorrected. Solvents were removed in vacuo at 50°.*

Methyl 2,3-Di-O-(benzylthio)carbonyl-α-D-glucopyranoside (XVIII)

To 0.5 g of XVII in 20.0 cc of pure, dry acetone was added 6.0 cc of 0.20 *N* hydrochloric acid. The solution was refluxed and the optical rotation observed at 0.5-hour intervals. Although the material was not entirely soluble at room temperature initially, after 0.5 hour of refluxing it showed $[\alpha]_D$ +51°. A plot of the data log $(\alpha_{final}-\alpha)$ against time fits a final $[\alpha]_D$ of 87°. The solution was neutralized with barium carbonate after 3.5 hours' refluxing, the $[\alpha]_D$ being then +85.6°. The solution was filtered, evaporated to dryness, the sirup was taken up in anhydrous ether and filtered to remove additional insoluble salts. The product could not be obtained in crystalline form. It showed $[\alpha]_D^{22}$ +85.7° (c = 2, $CHCl_3$).

Methyl 2,3-Di-O-(benzylthio)carbonyl-4,6-di-O-benzoyl-α-D-glucopyranoside (XIX)

To 3.0 g of XVIII in 10 cc anhydrous pyridine was added 2.8 cc benzoyl chloride, with cooling in ice bath. The solution stood for 20 hours at room temperature. The reaction mixture was poured into ice water and isolated in the usual way. Evaporation of the chloroform solvent gave a sirup which failed to crystallize. It showed $[\alpha]_D^{22}$ +34.5° (c = 2, $CHCl_3$).

Methyl 4,6-Di-O-benzoyl-α-D-glucopyranoside (IX)

The product XIX from the previous experiment was dissolved in 15 cc glacial acetic acid. One gram of potassium acetate and 5.7 cc of 30% hydrogen peroxide solution were added. The reaction mixture stood at room temperature for 4 days, after which it was poured into water containing sufficient sodium bicarbonate to neutralize the acetic acid. The product was extracted into chloroform and the chloroform layer dried over magnesium sulphate. Evaporation of the chloroform gave a sirup which readily crystallized as fine needles from ether on the addition of petroleum ether. It showed m.p. 131–132°. Recrystallization from ethyl acetate – petroleum ether gave 1.35 g (55%) showing m.p. 133–133.5° and $[\alpha]_D^{22}$ +145.7° (c = 2, $CHCl_3$). Anal. Calc. for $C_{21}H_{22}O_8$: C, 62.8; H, 5.47. Found: C, 62.8; H, 5.44.

Methyl 2,3-Di-O-phenylcarbamyl-4,6-di-O-benzoyl-α-D-glucopyranoside (X)

To ½ g of IX dissolved in 10 cc anhydrous pyridine was added 1 cc of phenylisocyanate, and the mixture was warmed for 1 hour on the steam bath. After cooling, the reaction mixture was poured into ice water and isolated by the usual procedure. The product crystallized as needles from ethanol–water and had m.p. 154–155°. Recrystallization from ether – petroleum ether gave 0.71 g (90%) with m.p. 154–156°. The product showed $[\alpha]_D^{22}$ +56.5° (c = 2, $CHCl_3$). Anal. Calc. for $C_{35}H_{32}O_{10}N_2$: C, 65.7; H, 5.00; N, 4.38. Found: C, 66.6; H, 5.38; N, 4.10.

X from Methyl 2,3-Di-O-phenylcarbamyl-α-D-glucopyranoside

Methyl 2,3-di-*O*-phenylcarbamyl-4,6-*O*-benzylidene-α-D-glucopyranoside was prepared as described by Hearon, Hiatt, and Fordyce and had m.p. 216–217°. Reported (5) 216–217°. The benzylidene group was removed from 0.35 g by refluxing 5 hours in 20 cc acetone containing 6.0 cc 0.20 *N* hydrochloric acid. The product was recovered by the usual procedure, furnishing a sirup which was benzoylated directly, giving 0.13 g, crystallizing first from ethanol–water then from ether – petroleum ether. The product had m.p. 155–156° and $[\alpha]_D^{22}$ +56.7°. A mixed melting point with X from the previous experiment was not depressed.

Methyl 2,3-Di-O-(benzylthio)carbonyl-4,6-O-benzylidene-β-D-glucopyranoside (III)

This compound was prepared in 71% yield in the same manner as its alpha anomer, XVII, from methyl 4,6-*O*-benzylidene-β-D-glucopyranoside. The product was crystallized from a large quantity of ethanol and had m.p. 159–160° and $[\alpha]_D^{22}$ −54.75° (c = 2, $CHCl_3$). It was recrystallized from acetone – ether – petroleum ether and showed the same melting point. Anal. Calc. for $C_{30}H_{30}O_8S_2$: C, 61.8; H, 5.16; S, 11.0. Found: C, 61.8; H, 5.22; S, 10.87.

Methyl 2,3-Di-O-(benzylthio)carbonyl-β-D-glucopyranoside (IV)

One-half gram of III was treated with hydrochloric acid in acetone exactly as described for the alpha anomer while the reaction was observed polarimetrically. Five hours of reflux was required before the optical rotation was constant, its $[\alpha]_D$ then being +1.53°. The product, isolated as before, was obtained as a sirup with $[\alpha]_D^{22}$ +1.55° (c = 2, $CHCl_3$).

Methyl 2,3-Di-O-(benzylthio)carbonyl-4,6-di-O-benzoyl-β-D-glucopyranoside (V)

The product IV obtained from 4.0 g of III was benzoylated as described before for the alpha anomer. Evaporation of the chloroform gave a solid residue, which was triturated with a small amount of 95% ethanol and crystallized from 150 cc absolute ethanol, yielding 3.3 g (69%) of V, m.p. 115–116°. After recrystallization from methanol the product had m.p. 119–120° and $[\alpha]_D^{22}$ −10.7° (c = 2, $CHCl_3$). Anal. Calc. for $C_{37}H_{34}O_{10}S_2$: C, 63.3; H, 4.84; S, 9.13. Found: C, 63.1; H, 4.88; S, 9.23.

Methyl 4,6-Di-O-benzoyl-β-D-glucopyranoside (VI)

To 1.8 g of V dissolved in 20 cc glacial acetic acid containing 5 cc chloroform was added 4.2 cc 30% hydrogen peroxide and 0.6 g potassium acetate. After standing for 4 days at room temperature, the product was isolated as with the alpha anomer IX. The addition of water to an ethanol solution of the product gave 0.3 g of an unidentified product having m.p. 85° after recrystallization from ether – petroleum ether.

After the addition of more water to the filtrate and long standing, more crystalline material (needles) was obtained, giving 0.49 g (48%) with m.p. 135–137°. Recrystallization of the latter from ether – petroleum ether raised the melting point to 137–138°. The product had $[\alpha]_D^{22}$ +20.7° (c = 2, $CHCl_3$). Anal. Calc. for $C_{21}H_{22}O_8$: C, 62.8; H, 5.47. Found: C, 63.3; H, 5.50.

Methyl 2,3-Di-O-acetyl-4,6-di-O-benzoyl-β-D-glucopyranoside (VII)

To 0.30 g of VI in 5 cc anhydrous pyridine was added 1 cc of acetic anhydride. The solution was warmed 2 hours on the steam bath and cooled. On pouring the solution into ice water, a white solid was obtained which was recovered by filtration and washed with water. After crystallization twice from anhydrous ether there was obtained as prisms 0.26 g (72%) of VII, m.p. 165.5–166° and $[\alpha]_D^{22}$ −12.2° (c = 2, $CHCl_3$). Reported (4) for VII: m.p. 164–165° and $[\alpha]_D^{20}$ −5.8° (c = 2, $CHCl_3$).

Methyl 2,3-Di-O-(benzylthio)carbonyl-4,6-di-O-acetyl-β-D-glucopyranoside (VIII)

The benzylidene group was removed from 0.80 g of III as described before. The product was dissolved in 5 cc anhydrous pyridine and 2 cc acetic anhydride. After standing 24 hours at room temperature and warming 1 hour on the steam bath, the product was isolated in the usual manner. It crystallized as needles on standing in the presence of petroleum ether and was recrystallized twice from ether – petroleum ether, giving 0.60 g (75%) having m.p. 96–97° and $[\alpha]_D^{22}$ −3.0 (c = 2, $CHCl_3$). Anal. Calc. for $C_{27}H_{30}O_{10}S_2$: C, 56.0; H, 5.18; S, 11.1. Found: C, 55.6; H, 4.94; S, 11.3.

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