Unsaturated Carbohydrates. Part 20.[1] Direct Conversion of Phenyl 1-Thiohexoside Esters into Phenyl 1-Thiohex-1-enopyranosid-3-ulose Esters

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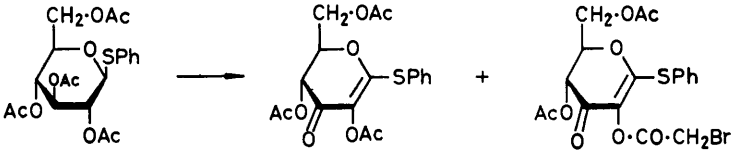
Treatment of phenyl 1-thiohexoside esters with an excess of *N*-bromosuccinimide in refluxing carbon tetrachloride and under bright visible light caused them to be converted directly into the corresponding phenyl 1-thiohex-1-enopyranosid-3-ulose esters. Whereas the reactions with benzoates proceeded smoothly and in high yield, acetates gave mixtures of products which contained minor proportions of 2-monobromoacetyl analogues of the main enones. Glycosides with equatorial phenylthio-groups reacted appreciably faster than did their anomers.

DURING attempts to prepare *N*-(glycosylthio)succinimides by treatment of bis(tetra-*O*-acetyl-β-D-glucopyranosyl) disulphide with equimolar amounts of *N*-bromosuccinimide [2] it was noted that the reagent was converted into succinimide while large proportions of the disulphide remained unchanged. In an attempt to elucidate this phenomenon the behaviour of some phenyl 1-thiohexopyranoside esters with *N*-bromosuccinimide was studied.

The main use to which *N*-bromosuccinimide has been put in carbohydrate chemistry is for the conversion of cyclic benzylidene acetals into bromodeoxymonobenzoates,[3] a reaction which often proceeds with high selectivity and offers a useful means of deoxygenation,[4] especially at primary centres.[5] Otherwise, it has been used in conjunction with triphenylphosphine to prepare bromodeoxy-compounds from corresponding alcohols,[6] to effect allylic [7] and benzylic [8] bromination, and in the synthesis of brominated nucleoside derivatives from unsaturated precursors.[9] More novel applications involve the oxidative dimerisation of tributylstannyl derivatives of compounds with primary alcohol groups to the corresponding esters, and the development of new esterification and oxidation procedures.[10]

Initially, treatment of phenyl tetra-*O*-acetyl-1-thio-β-D-glucopyranoside (1) with *N*-bromosuccinimide in refluxing carbon tetrachloride led to two products (t.l.c.), but this observation was not reproducible until it was recognised that light played a critical role in the reaction. Subsequent experiments carried out under artificial white light resulted in consistent conversion of the glycoside into the same products, isolated as a crystalline mixture (*ca.* 45% yield) and separated by chromatography. The products proved to be phenyl 2,4,6-tri-*O*-acetyl-1-thio-D-*erythro*-hex-1-enopyranosid-3-ulose (2) and its 2-bromoacetyl analogue (3), present in the ratio 3 : 1. The reaction did not proceed in the dark, and in diffuse light the main products were tetra-*O*-acetyl-α-D-glucopyranosyl bromide and *N*-(phenylthio)succinimide. Added benzoyl peroxide catalysed the formation of the



enones but less effectively than did light; thus, in keeping with many *N*-bromosuccinimide reactions,[11] this reaction is established as being initiated by free radicals.

Molecular weight and molecular formula determinations showed that compound (2) had been produced by loss of an acetyl group and three hydrogen atoms from its precursor, and the simple ^{1}H n.m.r. spectrum (Table) concurred with this finding. Phenyl resonances showed that the aromatic group remained, and the acetyl resonances revealed three such groups, one of which resonated at δ 2.20 (C:C·OAc).[12] The remaining resonances indicated that the C-4—6 portion of compound (1) had survived the reaction, H-4 resonating as a doublet ($J_{4.5}$ 12 Hz). This evidence is consistent with structure (2), and the coupling constant indicates that the compound adopts the $^4H_5$ conformation (4), as do related enones,[13] which also exhibit large $J_{4.5}$ values. Compound (2) showed $\lambda_{max.}$ 301 nm (ε 20 500), *ca.* 35 nm

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[11] C. Djerassi, *Chem. Rev.*, 1948, **43**, 271.
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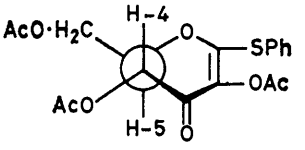
bathochromically shifted relative to analogous 2-acetoxyglycal enones [13b,14] which lack a substituent at C-1. Such a shift is in keeping with the bonding of a sulphur substituent to the enone.[15] Compound (2) showed i.r. absorptions at 1 680 and 1 570 cm^{-1}, absent from the spectrum of its precursor (1). The former band is typical of the carbonyl stretching absorption of closely related enones; [13,14,16] the latter is *ca.* 30 cm^{-1} to lower wavenumber than expected for the C:C stretching absorption of such compounds. In the mass spectrometer compound (2) gave a molecular ion (*m/e* 394), and fragment ions formed by loss of keten, acetic acid, phenylthio-radical, and carbon monoxide were most significant; a weak peak at *m/e* 279 formed by loss of keten (to give the base peak at *m/e* 352) and then the acetoxymethyl radical from C-5 was also seen.

Compound (3) gave an n.m.r. spectrum identical with that of the unbrominated enone (2) except that the low-field acetyl resonance (δ 2.20) was replaced by a two-proton singlet at δ 3.95, consistent with the vinylic acetate group having undergone monobromination.[17] On this basis the 2-bromoacetyl structure is assigned.

^1H N.m.r. data for the phenyl 1-thiohex-1-enopyranosid-3-ulose esters

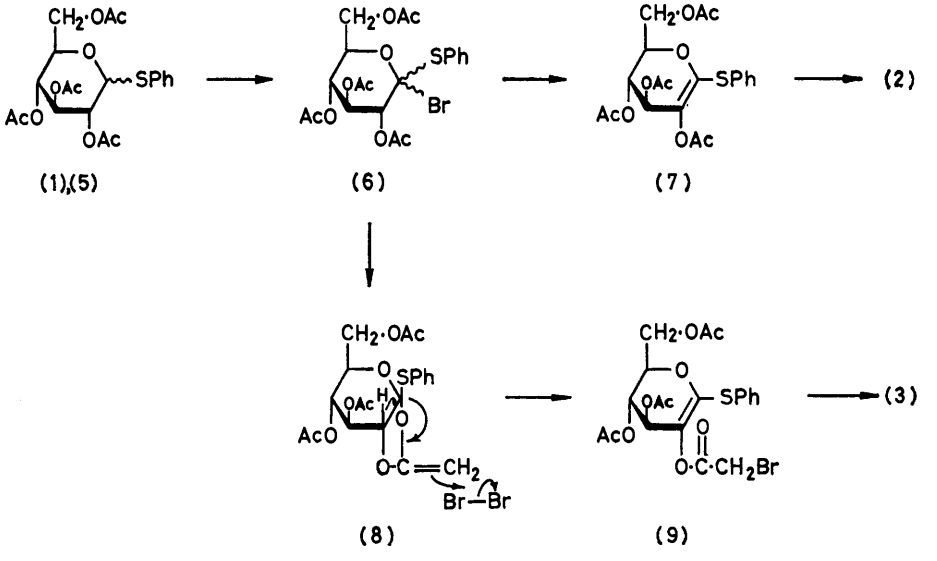
	δ($CDCl_3$)						*J*/Hz			
Compound	Aromatic	H-4	H-5	H-6	H-6′	Ac	4,5	5,6	5,6′	6,6′
(2)	7.2—7.6	5.55	4.74	4.04	4.30	1.92, 2.11, 2.20	12.0	2.7	4.8	12.0
(10)	7.1—7.5	5.45	4.67	4.3—4.0		1.83, 2.09, 2.21	3.5	5.5	6.0	
(12)	7.0—8.2	5.95	5.00	4.7—4.3			12.0	4.3	4.7	
(13)	6.9—8.2	5.89	5.06	4.43	4.70		3.5	4.5	6.5	12.0



(4)

Mass spectrometry confirmed the presence of a bromoacetate group: the base peak (*m/e* 352) was formed from the abundant molecular ion [*m/e* 478 (^{81}Br)] by loss of bromoketen. A weak peak at *m/e* 279 is consistent with a further loss of acetoxymethyl radical from C-5, but with the evidence available this does not confirm the site of bromination since it could also have arisen by successive loss of keten and the bromoacetoxymethyl radical.

Since compounds (2) and (3) are achiral at C-1, it was anticipated that they would also be obtainable from the α-anomer (5) of the glycoside (1). In practice this was achieved, but the reaction was appreciably slower, consistent with the finding that photochemically induced



SCHEME

abstraction of H-2 from 2-methoxytetrahydropyrans is faster when the hydrogen–carbon bond is axial.[18] It is envisaged, therefore, that conversion of the glycoside (1)

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[15] J. C. D. Brand and A. I. Scott in 'Techniques of Organic Chemistry,' ed. A. Weissberger, vol. XI, Interscience, New York, 1963, p. 75.

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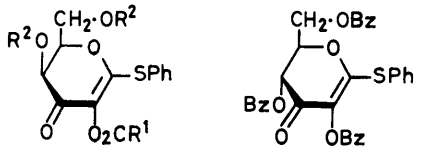
and its anomer into the enones (2) and (3) proceeds by initial abstraction of H-1 followed by radical bromination at that site to give the species (6), from which hydrogen bromide could readily be lost (conceivably by a heterolytic process) to give the substituted glycal (7). Otherwise, if bromide ion were lost with participation of the acetoxy group at C-2, deprotonation could lead to the species (8), which could undergo bromination as shown in the Scheme and give the bromoacetate (9). A related mechanism has been proposed [19] to account for the specific chlorination at the 2-acetoxy-group of penta-*O*-acetyl-β-D-glucopyranose when treated with phosphorus pentachloride.[20] Alternatively, related homolytic processes could lead to the intermediates (7) and (9) from the C-1 radical produced by the initial hydrogen abstraction step. This step, it is suggested, is facilitated in the case of the phenyl thioglycosides by the enhanced radical-stabilising characteristics of the sulphur atom,[21] and may account for the failure to detect related reactions on the several occasions [3,8] on which *O*-glycoside derivatives have been treated with *N*-bromosuccinimide. The oxidation of the intermediates (7) and (9) presumably proceeds by allylic bromination at C-3 followed by loss of acetyl bromide; to check this possibility we are currently studying the reaction of glycals with *N*-bromosuccinimide.

Similar reaction occurred on treatment of phenyl tetra-*O*-acetyl-1-thio-β-D-galactopyranoside with *N*-bromosuccinimide, and a crystalline product comprising the *threo*-enone (10) and its bromoacetyl analogue (11)



(12)

(10) R^1 = Me, R^2 = Ac
(11) R^1 = CH_2Br, R^2 = Ac
(13) R^1 = Ph, R^2 = Bz

(3 : 1) was isolated in *ca.* 40% yield. The former was obtained pure directly by recrystallisation and had spectral characteristics in accord with the assigned structure, the $J_{4,5}$ value being 3.5 Hz (Table).

The benzoates phenyl tetra-*O*-benzoyl-1-thio-D-glucopyranoside and -galactopyranoside do not undergo the side reaction which led to the bromoacetates; they reacted smoothly to give the tribenzoyl analogues (12) and (13) of the enones (2) and (10). From the β-*gluco*- and β-*galacto*-glycosides and with 3 mol. equiv. of *N*-bromosuccinimide the enones were formed within 15 min. and were isolated in 76 and 83% yield, respectively; the α-glucoside required 2.5 h for reaction when treated with 5 mol. equiv. of reagent and gave the enone (12) in 71% yield.

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Compound (2), its *threo*-isomer (10), and the tribenzoates (12) and (13) all gave positive c.d. maxima within the range 315—335 nm. The configuration at C-4 of compounds of this series therefore cannot be determined on this basis.

EXPERIMENTAL

Optical rotations were measured for solutions in chloroform in the concentration range 0.8—2%. I.r. data given are absorptions additional to those of the starting materials.

Phenyl tetra-*O*-acetyl-1-thio-α- and β-D-glucopyranoside, phenyl tetra-*O*-benzoyl-1-thio-β-D-glucopyranoside, and phenyl tetra-*O*-acetyl-β-D-galactopyranoside were prepared by standard methods.

Phenyl Tetra-O-*benzoyl*-1-*thio*-α-D-*glucopyranoside*.—Phenyl 1-thio-α-D-glucopyranoside (0.44 g) was benzoylated with benzoyl chloride (3 ml) in pyridine (3 ml) to give the crystalline *tetrabenzoate* (1.05 g, 95%). Recrystallised (× 2) from acetic acid–ethanol it had m.p. 130—132°, $[\alpha]_D$ +109° (Found: C, 69.5; H, 4.7; S, 4.8. $C_{40}H_{32}O_9S$ requires C, 69.8; H, 4.7; S, 4.7%).

Phenyl Tetra-O-*benzoyl*-1-*thio*-β-D-*galactopyranoside*.—Phenyl 1-thio-β-D-galactopyranoside (2.6 g) similarly gave the *tetrabenzoate* (4.5 g, 69%), m.p. 117—118° [from ethanol (× 3)], $[\alpha]_D$ +91° (Found: C, 70.1; H, 4.7; S, 4.7%).

Phenyl 2,4,6-*Tri*-O-*acetyl*-1-*thio*-D-erythro-*hex*-1-*enopyranosid*-3-*ulose* (2).—(a) *From phenyl* 2,3,4,6-*tetra*-O-*acetyl*-1-*thio*-β-D-*glucopyranoside* The β-glycoside (5.0 g) was heated under reflux and under a 250 W i.r. heat lamp 10 cm from the glass flask, with *N*-bromosuccinimide (6.2 g, 3.0 mol. equiv.) in carbon tetrachloride (350 ml) for 20 min. The two products had slightly lower mobilities on t.l.c. After cooling, the solids were removed and the solvent was distilled off under vacuum to leave a syrup which was dissolved in chloroform. The solution was washed with water and dried and the solvent was again removed to leave a light yellow syrup, which yielded a crystalline product (2.1 g) from ethanol. This was a mixture of the products (2) and (3) in the ratio 3 : 1 (n.m.r. analysis); this ratio was not altered by repeated recrystallisation from methanol or ethanol. On preparative t.l.c., the less mobile fraction gave the *pyranosidulose triacetate* (2), m.p. 117—118° (from ethanol), $[\alpha]_D$ +293° (Found: C, 55.0; H, 4.6; S, 8.0%, M^+, 394.072 9. $C_{18}H_{18}O_8S$ requires C, 54.8; H, 4.6; S, 8.1%; *M*, 394.0722), $\lambda_{max.}$ 301 nm (ε 20 500), $\nu_{max.}$ 1 680 and 1 570 cm^{-1}. The more mobile fraction yielded the 2-*bromoacetate* (3), m.p. 109—112° (from ethanol), $[\alpha]_D$ +258° [Found: C, 46.0; H, 3.6; S, 6.7; Br, 16.5%; M^+ (^{79}Br), 471.981 6. $C_{18}H_{17}BrO_8S$ requires C, 45.7; H, 3.6; S, 6.8; Br, 16.9%; *M* (^{79}Br), 471.982 8].

(b) *From phenyl tetra*-O-*acetyl*-1-*thio*-α-D-*glucopyranoside*. The α-glycoside (1.0 g) was heated in refluxing carbon tetrachloride (70 ml) under the lamp with *N*-bromosuccinimide (2.0 g, 5.0 mol. equiv.) for 2.5 h. Processing as in (a) gave a white crystalline product (0.24 g), shown by n.m.r. to be a 3 : 2 mixture of the triacetate and the bromoacetate.

Reaction of Phenyl Tetra-O-*acetyl*-1-*thio*-β-D-*glucopyranoside with* N-*Bromosuccinimide in Diffuse Light*.—The glycoside (1.6 g) and *N*-bromosuccinimide (2.6 g, 4.0 mol. equiv.) were heated under reflux in carbon tetrachloride

[20] P. Brigl, *Z. physiol. Chem.*, 1921, **116**, 1.

[21] P. S. Dewar, A. R. Forrester, and R. H. Thomson, *J.C.S. Perkin I*, 1972, 2857.

(30 ml) and in winter day light. After 1.5 h a carbohydrate product with higher t.l.c. mobility than starting material had been formed, and the mixture was processed as before to leave a yellow syrup, a portion of which was separated into two fractions by chromatography on a column of silica gel. The first was characterised as tetra-*O*-acetyl-α-D-glucopyranosyl bromide (t.l.c. and n.m.r. and i.r. spectra), and the second as *N*-(phenylthio)succinimide, identical with an authentic sample [m.p. 113—116° (lit.,[2] 116°), t.l.c., and n.m.r. spectrum].

Phenyl 2,4,6-*Tri*-O-*acetyl*-1-*thio*-D-threo-*hex*-1-*enopyranosid*-3-*ulose* (10). Phenyl tetra-*O*-acetyl-1-thio-β-D-galactopyranoside (8.5 g) and *N*-bromosuccinimide (10.3 g, 3.0 mol. equiv.) were heated under the lamp and under reflux in carbon tetrachloride (350 ml) for 15 min. Processing as before gave a syrup, and treatment with ethanol afforded a crystalline product (2.9 g). N.m.r. analysis indicated that this contained about 25% of a bromoacetate. Recrystallisation from ethanol, then methanol, gave the bromine-free threo-*enopyranosidulose* (1.4 g, 18%), m.p. 119—120°, $[\alpha]_D$ +51° (Found: C, 54.6; H, 4.5; S, 7.9%; M^+, 394), $\lambda_{max.}$ 306 nm (ε 21 500), $\nu_{max.}$ 1 675 and 1 580 cm^{-1}.

Phenyl 2,4,6-*Tri*-O-*benzoyl*-1-*thio*-D-erythro-*hex*-1-*enopyranosid*-3-*ulose* (12).—(a) *From phenyl tetra*-O-*benzoyl*-1-*thio*-β-D-*glucopyranoside*. The β-glycoside (5.0 g) and *N*-bromosuccinimide (3.9 g, 3.0 mol. equiv.) were heated under the lamp and under reflux in carbon tetrachloride (200 ml) for 15 min; conversion into a product of lower mobility on t.l.c. was then complete. Processing as before gave a syrup from which the crystalline erythro-*tribenzoate* (3.2 g, 76%) was obtained. Recrystallised from ethanol containing a little acetic acid and then glacial acetic acid it had m.p. 165—166°, $[\alpha]_D$ +336° (Found: C, 68.5; H, 4.3; S, 5.5. $C_{33}H_{24}O_8S$ requires C, 68.3; H, 4.2; S, 5.5%), $\lambda_{max.}$ 303 nm (ε 17 000), $\nu_{max.}$ 1 690 and 1 580 cm^{-1}.

(b) *From phenyl tetra*-O-*benzoyl*-1-*thio*-α-D-*glucopyranoside*. The α-glycoside (0.4 g) and *N*-bromosuccinimide (0.52 g, 5.0 mol. equiv.) heated under the lamp and under reflux for 2.5 h in carbon tetrachloride (30 ml) gave, after the usual processing, the tribenzoate (0.24 g, 71%), m.p. 162—164°, $[\alpha]_D$ +330°. It gave an n.m.r. spectrum identical with that obtained from the first sample.

Phenyl 2,4,6-*Tri*-O-*benzoyl*-1-*thio*-D-threo-*hex*-1-*enopyranosid*-3-*ulose* (13).—Phenyl tetra-*O*-benzoyl-1-thio-β-D-galactopyranoside (1.7 g) and *N*-bromosuccinimide (1.3 g, 3.0 mol. equiv.) were heated under the lamp and under reflux in carbon tetrachloride (70 ml) for 15 min; a product with lower mobility on t.l.c. had then been formed. The usual processing gave the crystalline threo-*tribenzoate* (1.2 g, 83%), m.p. 160—161° (from ethanol), $[\alpha]_D$ +37° (Found: C, 68.4; H, 4.3; S, 5.7%), $\lambda_{max.}$ 312 nm (ε 20 800), $\nu_{max.}$ 1 717, 1 694, 1 675, and 1 595 cm^{-1}.

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