Thio-sugars. Part V.¹ Rates of the Nucleophilic Substitution Reactions of Some 1,2:5,6-Di-O-isopropylidene-3-O-tosyl-a-p-hexoses with Potassium Thiobenzoate

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The rates of these reactions in dimethylformamide, monitored by ¹H n.m.r. spectroscopy, have been measured for derivatives of gulose, allose, glucose, and galactose, and found to decrease in that order. From the reactions with the derivatives of gulose, allose, and glucose, 3-S-benzoyl-1,2:5,6-di-O-isopropylidene-3-thio-a-D-galactose, -glucose, and -allose, respectively, were isolated, and their ¹H n.m.r. spectra are recorded.

KINETIC measurements on the substitution reactions of carbohydrate sulphonyl esters are almost non-existent, though qualitative observations indicate that there are enormous differences in the rates. The use of polar aprotic solvents has made it possible to displace many secondary sulphonyloxy-groups which otherwise are unreactive towards intermolecular attack, but a particularly resistant group is encountered in 1,2:5,6-di-O-isopropylidene-3-O-tosyl- α -D-glucose (1). Although this compound undergoes $S_N 2$ substitution with hydrazine, ammonia, and dimethylamine,^{2,3} attempts to effect displacement with charged nucleophiles such as benzoate,⁴ azide,⁵ toluene- ω -thiolate,⁶ or fluoride ⁷ ions have all failed, even under forcing conditions. This extreme inertness has been attributed ⁵ to the exo-orientation of the toluene-p-sulphonyloxy-group with respect to the bicyclo[3,3,0]fused-ring system, the approach of the anionic nucleophile from the crowded endo-side being greatly hindered by repulsive forces from the ring oxygen and from the oxygen atoms in the 1,2-isopropylidenedioxy-group. In contrast, the isomeric D-allose compound (4), having the opposite configuration at C-3, reacts fairly readily with benzoate,8 azide,8,9 and fluoride; ⁷ smooth displacement, by benzoate, ¹⁰ azide, ¹⁰ and fluoride,¹¹ also occurs with the analogous D-gulose derivative (6).

In spite of the reported unreactivity of the glucose compound (1) our interest in thio-sugars prompted us to attempt a displacement upon it with potassium thio-

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⁸ B. Coxon and L. Hough, J. Chem. Soc., 1961, 1643. ⁴ B. R. Baker and A. H. Haines, J. Org. Chem., 1963, 28,

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⁵ M. L. Wolfrom, J. Bernsmann, and D. Horton, J. Org. Chem., 1962, 27, 4505.
⁶ N. K. Jamieson and R. K. Brown, Canad. J. Chem., 1961,

benzoate in boiling dimethylformamide. Reaction did indeed occur and was largely complete in 4 hr., to give the



thiobenzoate (5), the configuration of which was confirmed by the n.m.r. spectrum; the signal for the 2-proton was a triplet (see Table 1) in agreement 1 with coupling

- 7 A. B. Foster, R. Hems, and J. M. Webber, Carbohydrate Res., 1967, 5, 292. ⁸ D. T. Williams and J. K. N. Jones, Canad. J. Chem., 1967,
- J. S. Brimacombe, J. G. H. Bryan, A. Husain, M. Stacey, and M. S. Tolley, Carbohydrate Res., 1967, 8, 318. ¹⁰ J. S. Brimacombe, P. A. Gent, and M. Stacey, J. Chem.
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 ¹¹ J. S. Brimacombe, A. B. Foster, R. Hems, and L. D. Hall,
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between the 2- and the 3-proton being allowed in the allose but not in the glucose series. Little reaction occurred when potassium thioacetate was used, under similar conditions, in place of potassium thiobenzoate, the greater nucleophilicity of the latter reagent thereby being demonstrated.

As expected, displacement occurred readily when the allose analogue (4) was treated with potassium thiobenzoate in dimethylformamide, and the resulting thiobenzoate (2) was identical with that obtained by benzoylation of 1,2:5,6-di-O-isopropylidene-3-thio-a-D-glucose

TABLE	1
A. +	

Com-	Chemical shifts in $CDCl_3$ (τ values)		Coupling constants (Hz)			
(2) (5) (6)	1-H 4·15(d) 4·12(d) 4·21(d)	2-H 5·36(d) 5·23(t)	3-H	J _{1.2} 3·8 3·5 4·0	∫ _{2.3} 0·0 3·4	J 3, 4
(8) (9)	$4.08(d) \\ 4.25(d)$	5·35(q) 5·88(q)	5• 4 7(q	$3.9 \\ 4.1$	1∙4 6∙6	2.7

(3); ¹ in the n.m.r. spectrum of this thiobenzoate, no coupling was observable between the 2- and the 3-proton, the signal for the former being a doublet.

1,2:5,6-Di-O-isopropylidene-3-O-tosyl- α -D-gulose was similarly converted into the 3-thio-D-galactose derivative (8). Although this differs from the glucose isomer (2) only in the configuration at C-4, the n.m.r. signal for the 2-proton was now a quartet, indicating a more nearly planar conformation of the sugar ring in the galactose compound, attributable to the crowding produced when both isopropylidene groups are on the same side of the ring.

1,2:5,6-Di-O-isopropylidene-3-O-tosyl- α -D-galactose (7) reacted more slowly than any of the other isomers, much decomposition occurred, and no 3-thio-D-gulose derivative was isolated.

The rates of these displacement reactions were quantitatively determined for each of the four 3-O-toluene-p-sulphonates (1), (4), (6), and (7), under pseudounimolecular conditions, a ten-fold excess of potassium thiobenzoate being used. Because the formation of some dibenzoyl disulphide cannot easily be avoided, any spectroscopic method relying on the estimation of thiobenzoate in the water-insoluble crude product would be liable to serious errors. For this reason the criterion used was the disappearance of the aryl methyl resonance in the n.m.r. spectrum; the integrated intensity of this signal was compared with that for the twelve protons in the isopropylidene groups. Great accuracy cannot be claimed for such measurements, but reasonably good straight-line logarithmic plots were nevertheless obtained for the glucose, the allose, and the gulose compounds. With the galactose derivative, on the contrary, the rate diminished sharply after the reaction had proceeded to the extent of about 25%; this abnormal kinetic be-

haviour, and the failure to isolate any substitution product from this compound, require further investigation.

A possible objection to the above method is that the rate of disappearance of the toluene-p-sulphonate group may not correspond to the rate of formation of the thiobenzoate; side reactions may also be occurring. However, when the reactions on the three toluene-psulphonates (1), (4), and (6) were virtually complete, the n.m.r. spectra of the crude products were (apart from additional signals attributable to dibenzoyl disulphide and traces of dimethylformamide) similar to those of the pure thiobenzoates.

The pseudo first-order rate constants were converted into the second-order constants summarised in Table 2.

TABLE 2

1,2:5,6-di-O-isopropylidene-3-O-tosyl-a-D-Reaction of hexoses with potassium thiobenzoate in dimethylformamide

10^4k_2 (mole ⁻¹ sec. ⁻¹ l.)							
Galactose	Glucose	Allose	Gulose				
0·37 * (156°)	1·11 (155°)	5·65 (157°)	21·9 (156°)				
	$0.35~(137^{\circ})$	1·72 (140°)					
	$0.20 (125^{\circ})$	0·80 (126°)					
	0.19 (138.)						

* First 25% of reaction only. † In hexamethylphosphoric triamide.

The relative reactivities of all four compounds follow the order which would be expected from simple considerations of the steric restrictions imposed by the isopropylidene groups on the rearward approach of the nucleophile towards C-3.

Nucleophilic displacement reactions are sometimes facilitated to a greater extent by the use of hexamethylphosphoric triamide,¹² rather than dimethylformamide, as solvent. This is now exemplified by the observation that the rate of reaction of the glucose derivative (1) with potassium thiobenzoate is about twice as great in the former solvent than in the latter (see Table 2).

As a pyranose analogue of the isopropylidene compounds 4,6-O-ethylidene-1,2-O-isopropylidene-3-O-tosyl- α -D-galactose (9)¹³ was also studied. The reactivity towards potassium thiobenzoate in dimethylformamide was surprisingly low, the values for $10^4 k_2$ being only 0.33 at 161° and 0.26 at 140° . The n.m.r. spectrum (Table 1) of this toluene-p-sulphonate shows coupling constants which, on the basis of Conroy's modified form ¹⁴ of the Karplus equation, cannot be satisfactorily explained by a chair conformation, even if distorted, and are best accommodated by a slightly flattened boat conformation with C-1 and C-4 above the plane of the other four ring-atoms. The toluene-p-sulphonyloxy-group is then in an equatorial position, pointing away from the ring oxygen atom, and the approach of the thiobenzoate

14 H. Conroy, Adv. Org. Chem., 1960, 2, 311; cf. L. D. Hall, Adv. Carbohydrate Chem., 1964, 19, 51.

H. Normant, Angew. Chem. Internat. Edn., 1967, 6, 1046.
 D. H. Ball and J. K. N. Jones, J. Chem. Soc., 1958, 905.

ion would thus be subject to polar repulsions in addition to steric hindrance by the isopropylidene group.

Although 1,2:5,6-di-O-isopropylidene-3-O-methane sulphonyl- α -D-glucose reacts smoothly with azide ion in boiling dimethylformamide,¹⁵ an attempt to effect replacement with potassium thiobenzoate resulted in the formation of an intractable product, and consequently the intention to measure the reactivities of various methanesulphonates towards thiobenzoate ion was not pursued.

EXPERIMENTAL

Spectroscopic and chromatographic techniques were as indicated in the preceding paper.

1,2:5,6-Di-O-isopropylidene-3-O-tosyl- α -D-galactose (7).— A mixture of 1,2:5,6-di-O-isopropylidene- α -D-galactose ¹⁶ (1.06 g.), toluene-*p*-sulphonyl chloride (1.17 g.), and pyridine (7 c.c.) was stirred for 24 hr. and then diluted with water to precipitate a solid. Crystallisation from ethanol gave the 3-O-toluene-p-sulphonate (1.14 g.), m.p. 95°, $[\alpha]_{p}^{25} - 14^{\circ}$ (c 0.5 in CHCl₃) (Found: C, 55·1; H, 6·6; S, 7.7. C₁₉H₂₆O₈S requires C, 55·05; H, 6·3; S, 7·7%).

3-S-Benzoyl-1,2:5,6-di-O-isopropylidene-3-thio- α -D-allose (5).—A mixture of 1,2:5,6-di-O-isopropylidene-3-O-tosyl- α -D-glucose ¹⁷ (8.0 g.), potassium thiobenzoate (17.0 g.), and dimethylformamide (100 c.c.) was boiled under reflux for 4 hr. under nitrogen, and then concentrated under reduced pressure, diluted with water, and extracted with chloroform to yield a crude product which, after an unsuccessful attempt to distil it, was purified by chromatography (chloroform) and by crystallisation from petroleum (b.p. 60—80°) to give the thiobenzoate (0.5 g.), m.p. 80—81°, [α]_D²⁵ +113° (c 0.5 in CHCl₃), λ_{max} . 239 (ε 10,800) and 267 (ε 8800) nm., ν_{max} . (CCl₄) 1670 cm.⁻¹ (SBz) (Found: C, 59.9; H, 6.1; S, 8.4. C₁₉H₂₄O₆S requires C, 60.0; H, 6.4; S, 8.4%).

3-S-Benzoyl-1,2:5,6-di-O-isopropylidene-3-thio- α -D-glucose (2).—(i) Similar treatment of 1,2:5,6-di-O-isopropylidene-3-O-tosyl- α -D-allose ⁹ (3.8 g.) with potassium thiobenzoate (8.1 g.) in boiling dimethylformamide (48 c.c.) for 4 hr. gave, after chromatography [ether-petroleum (b.p. 40— 60°); 1:4], distillation (b.p. 143—147°/10⁻⁴ mm.) and crystallisation from petroleum (b.p. 60—80°), the thiobenzoate (212 mg.), m.p. 108°, [z]_p²⁴ - 37° (c 1 in CHCl₃), (ii) A solution of 1,2:5,6-di-O-isopropylidene-3-thio- α -D-glucose¹ (0.73 g.) and benzoyl chloride (0.6 g.) in pyridine (8 c.c.) was set aside for 20 hr., and then diluted with water and extracted with ether. Evaporation of the washed and dried extract gave, after crystallisation from petroleum (b.p. 60-80°), the same thiobenzoate (0.55 g.), m.p. 108°.

3-S-Benzoyl-1,2:5,6-di-O-isopropylidene-3-thio- α -D-galactose (8).—The residual solution from a kinetics experiment (see later), in which 1,2:5,6-di-O-isopropylidene-3-O-tosyl- α -D-gulose ¹⁰ had been treated for 1 hr. with potassium thiobenzoate at 156°, was worked up as described for the glucose isomer. The product gave needles of the *thiobenzoate*, m.p. 122—123° [from petroleum (b.p. 40—60°)], [α]_D²⁵ +12° (c 0.5 in CHCl₃), ν_{max} (CCl₄) 1665 cm.⁻¹ (SBz) (Found: C, 60·1; H, 6·3; S, 8·2. C₁₉H₂₄O₆S requires C, 60·0; H, 6·4; S, 8·4%).

Rate Measurements .- These reactions were carried out in a flask (fitted with a reflux condenser and a thermometer) immersed in a thermostatically controlled oil-bath, an atmosphere of dry nitrogen being maintained throughout. Potassium thiobenzoate (8.75 g.) and dry dimethylformamide (50 c.c.) were introduced into the flask and preheated to within 5° of the reaction temperature. The toluene-psulphonate (2.0 g.) was then quickly added, with swirling. (In some experiments, smaller quantities were used, but the proportions were the same). Samples (ca. 2-3 c.c.), were withdrawn at intervals and poured into chloroform (ca. 80 c.c.); this solution was then washed with water $(2 \times 100 \text{ c.c.})$, dried, and evaporated. The crude product was kept at 10^{-4} mm. pressure for at least 30 min. and then analysed by n.m.r. spectroscopy (in CDCl₃) to determine the toluene-p-sulphonyl: di-isopropylidene ratio and hence the extent of reaction as expressed by the percentage (α) of toluene-p-sulphonate remaining. First-order rate constants were obtained from the slope of the straight-line plots of $\log_{10} \alpha$ against t and converted into second-order constants by the expression $k_2 = k_1/[\text{KSBz}]$. The temperatures indicated in Table 2 are those of the actual reaction mixtures; those of the bath were always higher, particularly for those runs conducted near the b.p. of the solvent.

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¹⁷ K. Freudenberg and H. Ivers, Ber., 1925, **55**, 929; cf. H. Zinner, G. Wulf, and R. Heinatz, Chem. Ber., 1964, **97**, 3536.

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¹⁶ H. Paulsen and H. Behre, Carbohydrate Res., 1966, 2, 80.