398. *Benzoate Displacements on 3-O-Toluene-*p*-sulphonyl-D-glucose Derivatives; a New Synthesis of D-Allose*

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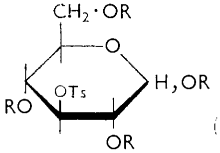
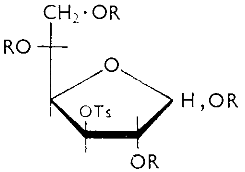
The two 1,2,4,6-tetra-*O*-benzoyl-3-*O*-toluene-*p*-sulphonyl-α- and -β-D-glucopyranoses (IIIa) and (IIIb) and a mixture of the two 1,2,5,6-tetra-*O*-benzoyl-3-*O*-toluene-*p*-sulphonyl-α- and -β-D-glucofuranoses (IVa) and (IVb) have been prepared, and their reaction with benzoate ions has been studied. Only the β-pyranose (IIIb) undergoes exchange to give 1,2,3,4,6-penta-*O*-benzoyl-β-D-allopyranose. This and other results of displacement reactions on pyranose rings are rationalised in terms of steric effects.

SEVERAL unsuccessful attempts to synthesise D-allose from 1,2:5,6-di-*O*-isopropylidene-3-*O*-toluene-*p*-sulphonyl-D-glucofuranose (I) and sodium benzoate in dimethylformamide by a nucleophilic displacement reaction have been made.[1] The successful replacement of the sulphonyloxy-group in the ester (I) by hydrazine but not by azide ion suggested that the electrostatic or steric nature of the ketal groups hindered the approach of attacking nucleophiles but hydrazine was able to overcome this resistance by hydrogen bonding.[2] Replacement of the ketal groups by ester groups may facilitate the reaction by neighbouring group participation. Two approaches along these lines have already been made. Solvolysis of methyl 2,4,6-tri-*O*-benzoyl-3-*O*-methanesulphonyl-α-D-glucopyranoside (II) in wet Cellosolve containing sodium acetate gave no product.[3] A short report on the solvolyses of some methyl 5,6-di-*O*-benzoyl-3-*O*-toluene-*p*-sulphonyl-β-D-glucofuranosides, variously acylated at the 2-hydroxyl group, in acetic acid–acetic anhydride indicated limited success in obtaining allose derivatives.[4] We have studied the reaction of the two 1,2,4,6-tetra-*O*-benzoyl-3-*O*-toluene-*p*-sulphonyl-α- and -β-D-glucopyranoses (IIIa) and (IIIb) and a mixture of the two 1,2,5,6-tetra-*O*-benzoyl-3-*O*-toluene-*p*-sulphonyl-α- and -β-D-glucofuranoses (IVa) and (IVb) with benzoate ions.

(IIIa: α - anomer)
(IIIb: β - anomer)



(R = PhCO)



(IVa: α - anomer)
(IVb: β - anomer)

Acid hydrolysis of the di-isopropylidene derivative (I) gave syrupy 3-*O*-toluene-*p*-sulphonyl-D-glucose which on benzoylation gave a mixture of the benzoates (IIIa) and (IIIb), readily separated by fractional crystallisation. Configurations were assigned from considerations of optical rotation. Acid hydrolysis of 5,6-di-*O*-benzoyl-1,2-*O*-isopropylidene-3-*O*-toluene-*p*-sulphonyl-D-glucofuranose [5] gave 5,6-di-*O*-benzoyl-3-*O*-toluene-*p*-sulphonyl-D-glucofuranose which was not isolated but was benzoylated to give a mixture of the benzoates (IVa) and (IVb). The mixture refused to crystallise and it could not be resolved by column chromatography though examination by thin-layer chromatography indicated it to be composed of only two components in approximately equal proportions.

Reaction of the β-anomer (IIIb) with sodium benzoate in dimethylformamide gave a

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[1] (*a*) B. R. Baker and A. H. Haines, *J. Org. Chem.*, 1963, **28**, 438; (*b*) K. J. Ryan, H. Arzoumanian, E. M. Acton, and L. Goodman, *J. Amer. Chem. Soc.*, 1964, **86**, 2497; (*c*) N. A. Hughes and P. R. H. Speakman, unpublished observations.

[2] M. L. Wolfrom, J. Bernsmann, and D. Horton, *J. Org. Chem.*, 1962, **27**, 4505.

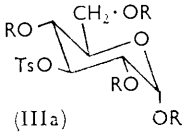
[3] R. W. Jeanloz and D. A. Jeanloz, *J. Amer. Chem. Soc.* 1958, **80**, 5692.

[4] W. A. Short, *Diss. Abs.*, 1962, **22**, 2202.

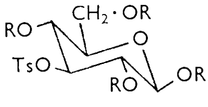
[5] H. Ohle and E. Dickhauser, *Ber.*, 1925, **58**, 2593.

single crystalline product, presumably 1,2,3,4,6-penta-*O*-benzoyl-β-D-allopyranose (V). On debenzoylation the pentabenzoate (V) gave D-allose identified by comparison with an authentic sample. The isolation of a single pentabenzoate (V) suggests a straightforward S_N2 displacement without neighbouring group assistance.[1b]

By contrast the α-anomer (IIIa) failed to undergo the displacement reaction. The axial benzoate group at position 1 in the α-anomer probably hinders the approach of benzoate ions to position 3; a similar reason may account for the lack of reaction of the α-glucoside (II). Considerations of this kind are probably of more importance than whether the sulphonyloxy-group to be displaced is axial or equatorial. It is interesting to consider the previous cases of successful displacements, all of which appear to be S_N2 reactions, by benzoate ions on pyranose rings. The sulphonyloxy-groups in methyl 2,3,6-tri-*O*-benzoyl-4-*O*-methanesulphonyl-α-D-galactopyranoside (VI)[6] and methyl 2,3,6-tri-*O*-benzoyl-4-*O*-methanesulphonyl-α-D-glucopyranoside (VII),[7] axial and equatorial, respectively, are almost equally unhindered with respect to attack by a displacing anion. In methyl 2-*O*-benzoyl-3,4-di-*O*-toluene-*p*-sulphonyl-β-D-arabinoside (VIII) only the 4-sulphonyloxy-group is replaced.[8] The axial methoxy-group in the product, methyl 2,4-di-*O*-benzoyl-3-*O*-toluene-*p*-sulphonyl-α-L-xyloside (IX), hinders attack at the remaining sulphonyloxy-group. It is significant that further displacement does not occur with the ester (IX) since anchimeric assistance from either of the neighbouring benzoate groups is possible. It appears then that displacement will not occur when the transition state for the reaction would contain a 1,3-diaxial pair of substituents.



(IIIa)



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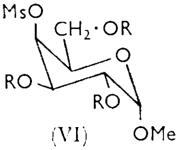
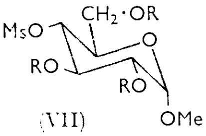
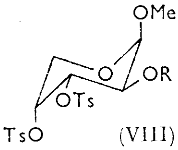


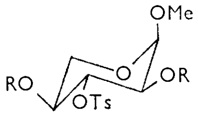
(VI)



(VII)



(VIII)



(IX)

[R = PhCO]

When the furanose mixture (IVa) and (IVb) was treated with benzoate ions under a variety of conditions no displacement occurred. This is surprising in view of a recent report of the successful synthesis of a 5-deoxy-D-allose derivative by displacement of the methanesulphonyloxy-group from methyl 2,6-di-*O*-benzoyl-5-deoxy-3-*O*-methanesulphonyl-αβ-D-glucofuranoside.[9] The presence of a hydroxyl group in the product suggested that the reaction was proceeding with anchimeric assistance from the neighbouring benzoate group.[1b]

Sodium benzoate is not freely soluble in dimethylformamide and in an effort to improve yields the more soluble tetra-n-butylammonium benzoate was used in *N*-methylpyrrolidone. Tetra-alkylammonium salts have been used successfully for displacement reactions in the steroid field,[10] and it is suggested that they are more effective than metal salts in these reactions.[11] This proved to be the case and the yield of pentabenzoate (V) from the β-anomer (IIIb) was almost doubled.

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[6] E. J. Reist, R. R. Spencer, and B. R. Baker, *J. Org. Chem.*, 1959, **24**, 1618.

[7] J. Hill, L. Hough, and A. C. Richardson, *Proc. Chem. Soc.*, 1963, 346.

[8] E. J. Reist, L. Goodman, R. R. Spencer, and D. E. Gueffroy, 19th I.U.P.A.C. Congress, London, 1963, Abstract A3—45.

[9] K. J. Ryan, H. Arzoumanian, E. M. Acton, and L. Goodman, *J. Amer. Chem. Soc.*, 1964, **86**, 2503.

[10] H. B. Henbest and W. R. Jackson, *J.*, 1962, 954.

[11] W. M. Weaver and J. D. Hutchinson, *J. Amer. Chem. Soc.*, 1964, **86**, 261, and references therein.

EXPERIMENTAL

Silica gel (Hopkin and Williams, M.F.C. grade) and alumina (Savory and Moore) were used for chromatography.

1,2,4,6-*Tetra*-O-*benzoyl*-3-O-*toluene*-p-*sulphonyl*-α- *and* -β-D-*glucopyranoses* (IIIa) and (IIIb).—A solution of 1,2:5,6-di-*O*-isopropylidene-3-*O*-toluene-*p*-sulphonyl-D-glucofuranose (I) (5·0 g.) in dioxan (50 ml.) and 0·5N-sulphuric acid (12·5 ml.) was heated under reflux for 4 hr. After neutralisation with solid barium carbonate and filtration through a bed of " Hyflo " silica the solution was evaporated to yield 3-*O*-toluene-*p*-sulphonyl-D-glucose (4·0 g.) as a pale yellow syrup. A solution of the syrup in pyridine (30 ml.) was cooled to 0° and treated with benzoyl chloride (11 ml.) in pyridine (20 ml.) during 30 min. The solution was then allowed to come to room temperature and was left for 48 hr. Addition of water (2 ml.) decomposed excess of benzoyl chloride and precipitated the β-anomer. After 30 min. chloroform (25 ml.) and ethanol (25 ml.) were added and the solid was filtered off. When crystallised from chloroform–ethanol the β-*anomer* (2·2 g., 25%) had m. p. 187—188°, $[\alpha]_D^{20}$ +14° (*c* 0·5 in $CHCl_3$) (Found: C, 65·8; H, 4·7; S, 4·5. $C_{41}H_{34}O_{12}S$ requires C, 65·6; H, 4·5; S, 4·3%). The filtrate was diluted with chloroform (100 ml.) and washed successively with 2N-sulphuric acid and dilute sodium hydrogen carbonate. After drying and evaporation the solution yielded a syrup which was triturated with hot ethanol (50 ml.) and filtration of the hot mixture gave a further crop of the β-anomer (0·1 g.). On cooling the filtrate deposited the α-*anomer* (3·1 g., 35%), m. p. 122—124°, $[\alpha]_D^{20}$ +104° (*c* 0·5 in $CHCl_3$) (Found: C, 66·0; H, 4·8; S, 4·3. $C_{41}H_{34}O_{12}S$ requires C, 65·6; H, 4·5; S, 4·3%).

In one case the yield of β-anomer was 34% though this could not be repeated.

1,2,5,6-*Tetra*-O-*benzoyl*-3-O-*toluene*-p-*sulphonyl*-αβ-D-*glucofuranose* (IV).—A solution of 5,6-di-*O*-benzoyl-1,2-*O*-isopropylidene-3-*O*-toluene-*p*-sulphonyl-D-glucofuranose (0·66 g.) in dioxan (15 ml.) and 12N-sulphuric acid (3 ml.) was heated under reflux for 90 min. The solution was neutralised with solid barium carbonate, filtered, and evaporated. The residue in benzene (5 ml.) was transferred to a column of silica gel (30 g.). Elution with benzene–ether (9 : 1) gave starting material (0·05 g.), and 5,6-di-*O*-benzoyl-3-*O*-toluene-*p*-sulphonyl-D-glucofuranose (0·40 g.) was eluted with benzene–ether (1 : 1). The latter was benzoylated with benzoyl chloride (1 ml.) in pyridine (5 ml.) for one day at room temperature to yield a syrupy product (0·55 g.). This was dissolved in benzene (5 ml.) and transferred to a column of silica gel (30 g.). The syrupy mixture of αβ-*tetrabenzoates* (0·57 g., 67%) was eluted with benzene–ether (9 : 1) (Found: C, 66·0; H, 4·9; S, 4·0. $C_{41}H_{34}O_{12}S$ requires C, 65·6; H, 4·5; S, 4·3%).

1,2,3,4,6-*Penta*-O-*benzoyl*-β-D-*allopyranose* (V).—(*a*) *By using sodium benzoate in dimethylformamide.* A solution of the sulphonate (IIIb) (150 mg.) in dimethylformamide (8 ml.) containing sodium benzoate (250 mg.) was heated under reflux for 6 hr. The mixture was diluted with ether (20 ml.) and passed through alumina (50 g.) to remove sodium benzoate, some charred material, and most of the dimethylformamide. After evaporation of the ether, residual dimethylformamide was removed by co-distillation with n-butanol and the solid residue was crystallised from chloroform–methanol to give the *pentabenzoate* (62 mg., 38%), m. p. 217—218°, $[\alpha]_D^{20}$ +12° (*c* 0·8 in $CHCl_3$) (Found: C, 70·3; H, 4·55. $C_{41}H_{32}O_{11}$ requires C, 70·3; H, 4·6%).

(*b*) *By using tetra-n-butylammonium benzoate in* N-*methylpyrrolidone.* A solution of the sulphonate (IIIb) (4·6 g.) in *N*-methylpyrrolidone (130 ml.) containing tetra-n-butylammonium benzoate (11·1 g.) was kept at 100° for 16 hr. A large proportion of the *N*-methylpyrrolidone was removed by distillation under reduced pressure (0·5 mm.). The residue was diluted with ether and passed through silica gel (600 g.) which was further eluted with ether (1·5 l.). The eluate was concentrated to 20 ml. and passed through alumina (50 g.); further elution with ether yielded the pentabenzoate (2·8 g., 65%), m. p. 217—218°, from chloroform–methanol.

Attempted Synthesis of 1,2,3,4,6-*Penta*-O-*benzoyl*-α-D-*allopyranose.*—A solution of the α-sulphonate (IIIa) (300 mg.) in *N*-methylpyrrolidone (5 ml.) containing tetra-n-butylammonium benzoate (700 mg.) was kept at 100° for 10 days. Extensive charring occurred and starting material (60 mg.) only was isolated from the reaction.

Attempted Synthesis of 1,2,3,5,6-*Penta*-O-*benzoyl*-αβ-D-*allofuranose.*—A solution of the sulphonate (IV) (70 mg.) in *N*-methylpyrrolidone (3 ml.) containing tetra-n-butylammonium benzoate (140 mg.) was kept at 100°. Thin-layer chromatographic examination of the reaction mixture showed the gradual disappearance of the sulphonate. After 10 days the reaction mixture was diluted with ether and after passage through silica and alumina columns yielded a syrup (12 mg.). Paper chromatographic examination of the product after debenzoylation revealed the absence of any free sugar.

β-D-*Allose*.—The pentabenzoate (V) (2·0 g.) was debenzoylated by stirring with methanol (50 ml.) and adding 0·5N-sodium methoxide (2 ml.) followed by sufficient dry chloroform to achieve complete solution. After 16 hr. at room temperature the solution was de-ionised by passage through Dowex-50 (ammonium form) ion exchange resin (10 ml.). After evaporation to dryness and removal of methyl benzoate by ether extraction, crystallisation from ethanol gave β-D-allose (0·40 g., 76%), m. p. 128—129°, $[\alpha]_D^{20}$ +0·7 ⟶ +12·5° (*c* 1·1 in H_2O) (lit.,[12] m. p. 128—128·5° or 140—141°, $[\alpha]_D$ +0·6° ⟶ +14·4°). When a sample of the synthetic β-D-allose was ground with a crystal of an authentic sample and left for a few days the melting point rose to 140—141°; this behaviour has been observed previously with β-D-allose.[12]

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[12] M. L. Wolfrom, J. N. Schumacher, H. S. Isbell, and F. L. Humoller, *J. Amer. Chem. Soc.*, 1954, **76**, 5816.