180. *Studies of Trifluoroacetic Acid. Part IV. The Use of* 4 : 6-*Benzylidene Trifluoroacetyl Methyl-*α-D-*glucopyranoside in the Synthesis of* 2- *and* 3-*Substituted Glucoses.*

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Controlled methanolysis of 4 : 6-benzylidene 2 : 3-bistrifluoroacetyl α-methylglucoside (II) gives a 4 : 6-benzylidene trifluoroacetyl α-methylglucoside (III). From this compound both 2- and 3-substituted 4 : 6-benzylidene α-methylglucosides have been prepared. Whereas toluenesulphonation in pyridine gives the 2-tosyl 3-trifluoroacetyl derivative (V), acetylation in pyridine affords the 3-acetyl 2-trifluoroacetyl compound (VIII). However, by treatment with an acetic acid–trifluoroacetic anhydride mixture, the 2-acetyl 3-trifluoroacetyl derivative (XV) is obtained. Proof of the structures of these mixed esters is given and the migration of the trifluoroacetyl group is discussed.

In Part II of this series (Bourne, Tatlow, and Tatlow, *J.*, 1950, 1367), the preparation and properties of certain trifluoroacetyl esters were described. These esters, which were prepared by treating the corresponding alcohols with trifluoroacetic anhydride in the presence of sodium trifluoroacetate, were shown to be very susceptible to hydrolysis and to methanolysis. Among the esters studied was 4 : 6-benzylidene 2 : 3-bistrifluoroacetyl α-methylglucoside (II), and it was found that this compound could be converted, in 98% yield, into 4 : 6-benzylidene α-methyl-

glucoside (I) simply by keeping it in methyl alcoholic solution (concentration *ca.* 1·2 g./100 c.c.) for 18 hours at room temperature. A further examination of this reaction has revealed that a crystalline intermediate compound, 4 : 6-benzylidene trifluoroacetyl α-methylglucoside (III), can be isolated when the reaction conditions are such that the compound separates from solution as it is formed. The requisite conditions may be attained either by using a concentrated solution (*ca.* 40 g./100 c.c.) of the bistrifluoroacetate in methyl alcohol, or by employing a methyl alcohol–carbon tetrachloride mixture, the mono-ester being only slightly soluble in carbon tetrachloride. The overall yield of 4 : 6-benzylidene trifluoroacetyl α-methylglucoside from 4 : 6-benzylidene α-methylglucoside can be improved three-fold if the unstable bistrifluoroacetate is not isolated.

A detailed examination of the mono-ester (III) was undertaken in order to locate the trifluoroacetoxy-group and to assess the value of the compound as a possible intermediate in the synthesis of either 2- or 3-substituted glucoses. This revealed the interesting fact that the mono-ester can give both 2- and 3-derivatives, depending on the reaction conditions. Further, the trifluoroacetyl residue has potential value as a readily removable blocking group suitable for general application in syntheses in the carbohydrate series.

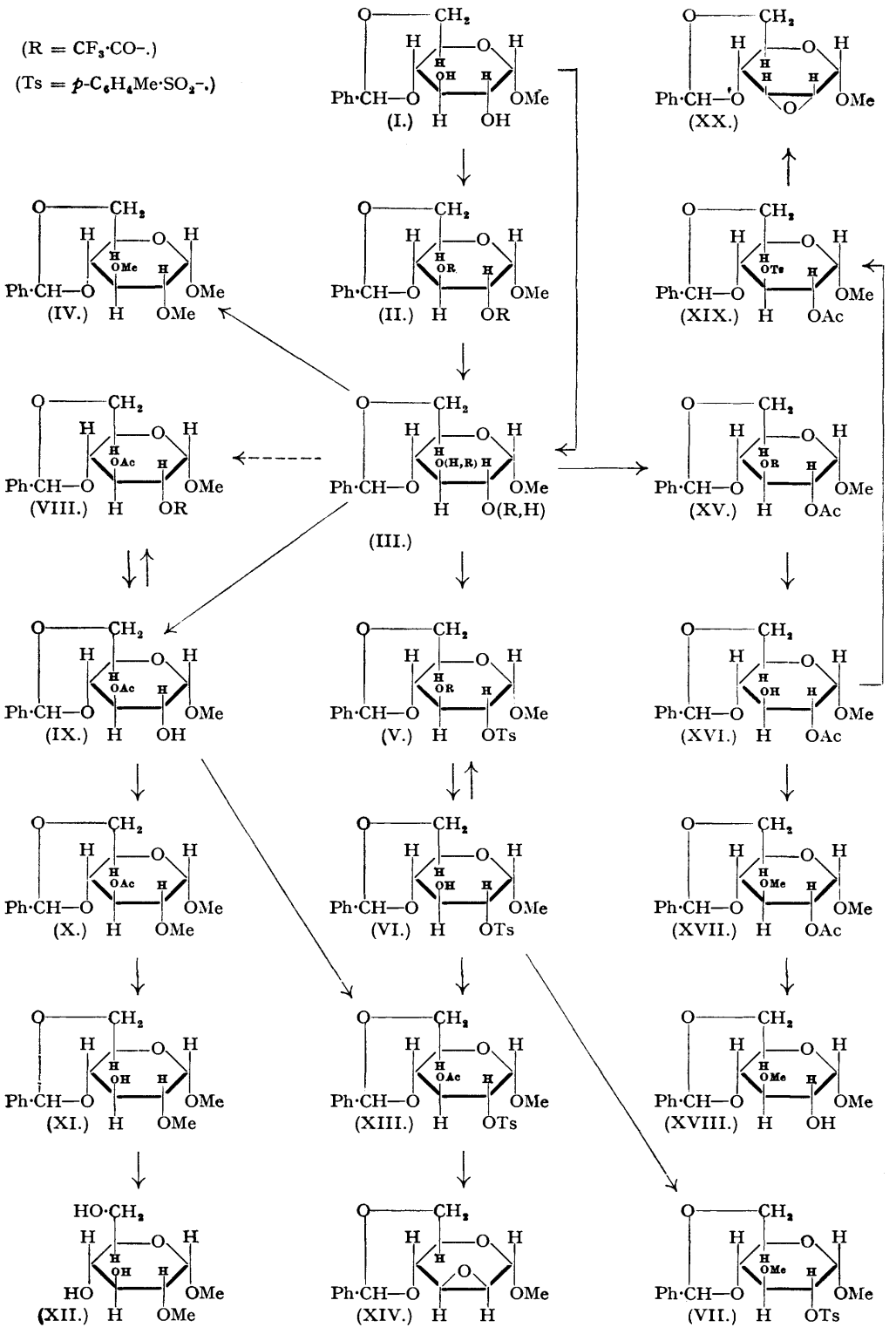
When 4 : 6-benzylidene trifluoroacetyl α-methylglucoside (III) was treated with methyl iodide and silver oxide for 3¾ hours in an attempt to prepare the corresponding 4 : 6-benzylidene methyl trifluoroacetyl α-methylglucoside, methylation was incomplete. After a longer reaction time (40 hours), 4 : 6-benzylidene 2 : 3-dimethyl α-methylglucoside (IV) was recovered in 74% yield. This replacement of trifluoroacetyl groups by methyl groups during methylation has been observed with other trifluoroacetates, but the rate of the exchange is variable and seems to depend on the particular ester concerned and on the purity of the methylating reagents.

In contrast to the above exchange, the trifluoroacetyl group was not removed when 4 : 6-benzylidene trifluoroacetyl α-methylglucoside was toluenesulphonated in pyridine solution. The crystalline di-ester (V) thus produced was identical with that obtained by trifluoroacetylation of 4 : 6-benzylidene 2-tosyl α-methylglucoside (VI); the structure of (VI) has been established beyond doubt by Robertson and Griffith (*J.*, 1935, 1193) and by Bolliger and Prins (*Helv. Chim. Acta*, 1945, **28**, 465). Furthermore, hydrolysis of each sample of the mixed ester (V) yielded 4 : 6-benzylidene 2-tosyl α-methylglucoside, which was converted by methylation into 4 : 6-benzylidene 3-methyl 2-tosyl α-methylglucoside (VII) (Bolliger and Prins, *loc. cit.*). Despite the fact that a sharp melting point could not be obtained for the toluenesulphonation product of the trifluoroacetate, there is no doubt that this product was 4 : 6-benzylidene 2-tosyl 3-trifluoroacetyl α-methylglucoside (V).

Acetylation of 4 : 6-benzylidene trifluoroacetyl α-methylglucoside, by means of acetic anhydride in pyridine, gave a product which appeared to be an acetate-trifluoroacetate but was difficult to purify. However, on alcoholysis this product afforded a pure crystalline monoacetate, later shown to be 3-acetyl 4 :6-benzylidene α-methylglucoside (IX). A pure sample of the elusive 3-acetyl 4 : 6-benzylidene 2-trifluoroacetyl α-methylglucoside (VIII) was obtained by treatment of the 3-acetyl derivative (IX) with trifluoroacetic anhydride and sodium trifluoroacetate; on methanolysis of the mixed ester the 3-acetate was regenerated. The difficulties inherent in the removal of pyridine under anhydrous conditions from this relatively unstable acetate-trifluoroacetate undoubtedly explain why the pure di-ester could not be isolated when it was prepared by the acetylation of 4 : 6-benzylidene trifluoroacetyl α-methylglucoside.

The acetyl group of the acetyl 4 : 6-benzylidene α-methylglucoside (IX) was allocated to position 3 on the basis of the behaviour of the compound during both methylation and toluenesulphonation. Treatment with methyl iodide and silver oxide gave a product which was identical with a specimen of 3-acetyl 4 : 6-benzylidene 2-methyl α-methylglucoside (X) prepared by Dr. D. J. Bell (unpublished method). This methylation product was obtained in dimorphic forms having m. p. 128·5° and 145°. The lower-melting form was obtained first, but subsequent experiments yielded the more stable higher-melting form, which was the one synthesised by Dr. Bell. The material having m. p. 128·5° ultimately changed into the higher-melting form. Both forms were converted by deacetylation into the same crystalline 4 : 6-benzylidene methyl α-methylglucoside (XI), identical with a specimen of 4 : 6-benzylidene 2-methyl α-methylglucoside prepared by Dr. D. J. Bell (method unpublished). Furthermore, graded acidic hydrolysis of the 4 : 6-benzylidene methyl α-methylglucoside (XI) afforded the well-characterised 2-methyl α-methylglucoside (XII) (Haworth, Hirst, and Teece, *J.*, 1931, 2858).

Toluenesulphonation of the above acetyl 4 : 6-benzylidene α-methylglucoside in pyridine gave 3-acetyl 4 : 6-benzylidene 2-tosyl α-methylglucoside (XIII), which was obtained also by acetylation of 4 : 6-benzylidene 2-tosyl α-methylglucoside (VI) and on treatment with sodium methoxide afforded the known 4 : 6-benzylidene 2 : 3-anhydro-α-methylmannoside (XIV)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(Robertson and Griffith, *loc. cit.*). Thus, unless migration of the acetyl group had occurred during both the methylation and the toluenesulphonation reactions, a possibility which we consider to be quite unlikely when these results are studied in conjunction with those reported later for the 2-acetate series, acetic anhydride in pyridine had introduced an acetyl group at position 3 of 4 : 6-benzylidene trifluoroacetyl α-methylglucoside.

When 4 : 6-benzylidene trifluoroacetyl α-methylglucoside was acetylated by an alternative procedure, *viz.*, by treatment with a mixture of acetic acid and trifluoroacetic anhydride (cf. Bourne, Stacey, Tatlow, and Tedder, *J.*, 1949, 2976), there was obtained a new crystalline acetate-trifluoroacetate, designated as 2-acetyl 4 : 6-benzylidene 3-trifluoroacetyl α-methylglucoside (XV). By methanolysis this yielded a second acetyl 4 : 6-benzylidene α-methylglucoside (XVI), which was characterised as the 2-acetate by methylation and by toluenesulphonation.

The acetyl methyl compound (XVII), which was obtained when the new acetate (XVI) was treated with silver oxide and methyl iodide, was hydrolysed to 4 : 6-benzylidene 3-methyl α-methylglucoside (XVIII), the structure of which has been established by Bolliger and Prins (*loc. cit.*). Toluenesulphonation of the acetyl 4 : 6-benzylidene α-methylglucoside (XVI) gave 2-acetyl 4 : 6-benzylidene 3-tosyl α-methylglucoside (XIX), as was shown by its subsequent conversion into 4 : 6-benzylidene 2 : 3-anhydro-α-methylalloside (XX) (cf. Robertson and Griffith, *loc. cit.*).

Thus it can be seen that 4 : 6-benzylidene trifluoroacetyl α-methylglucoside can be converted into (i) 4 : 6-benzylidene 2-tosyl 3-trifluoroacetyl α-methylglucoside by treatment with toluene-*p*-sulphonyl chloride in pyridine, (ii) 3-acetyl 4 : 6-benzylidene 2-trifluoroacetyl α-methylglucoside by treatment with acetic anhydride in pyridine, and (iii) 2-acetyl 4 : 6-benzylidene 3-trifluoroacetyl α-methylglucoside by treatment with acetic acid–trifluoroacetic anhydride. These striking observations may be explained in three ways: first, that the monotrifluoroacetate was a mixture of the isomeric 2- and 3-esters; secondly, that it possessed an ortho-ester structure; and thirdly, that migration of the trifluoroacetyl group occurred during one or more of the esterification reactions. The first possibility can be eliminated as the sole explanation, since the yields of the purified products of the reactions (i), (ii), and (iii) were 78%, at least 64% (based upon the yield of 3-acetyl 4 : 6-benzylidene α-methylglucoside), and 64%, respectively. Although the second possibility appeared unlikely in view of the *trans*-orientation of the 2- and 3-hydroxy-groups of the glucose molecule, evidence concerning the structure of the trifluoroacetate (III) was sought from measurements of its infra-red absorption spectrum. These measurements (see figure), carried out in collaboration with Dr. D. H. Whiffen, afforded strong evidence of the presence of a carbonyl group, and, therefore, of the probable absence of an ortho-ester structure. Hence the explanation of the experimental facts surely must lie in the migration of the trifluoroacetyl group.

Since it is known that the migration of acyl groups is favoured by alkaline conditions (for a summary see Pacsu, *Adv. Carbohydrate Chem.*, 1945, **1**, 77), it is probable that migration did not occur during the acetic acid–trifluoroacetic anhydride acetylation process, and thus that the 4 : 6-benzylidene trifluoroacetyl α-methylglucoside carried its ester group on position 3. It would appear therefore that migration of the trifluoroacetyl group occurred during the acetylation reaction in pyridine, but not during toluenesulphonation in the same medium. The behaviour of trifluoroacetate esters during methanolysis (Bourne, Tatlow, and Tatlow, *loc. cit.*) suggests their ready participation in acyl migration reactions, since both reactions involve an exchange of alkoxy-groups on a single trifluoroacetyl group. If this be so, then the trifluoroacetyl group may well be displaced, when necessary, to enable the incoming group to take up its more favoured position. This hypothesis explains the apparent anomaly that two series of products are obtained from the esterifications conducted in pyridine. It is an established fact that toluenesulphonation of 4 : 6-benzylidene α-methylglucoside proceeds preferentially at position 2 (Robertson and Griffith, *loc. cit.*; Bolliger and Prins, *loc. cit.*), whereas, if the usual migrations of acetyl groups (*i.e.*, away from the potential reducing group) be any guide (cf. Hirst and Peat, *Ann. Reports*, 1934, **31**, 172; Brown, Hough, and Jones, *J.*, 1950, 1125), the 3-acetate should be more stable than its 2-isomer. The greater lability, during methanolysis, of the acetate group of 2-acetyl 4 : 6-benzylidene 3-trifluoroacetyl α-methylglucoside (XV) compared with that of 3-acetyl 4 : 6-benzylidene 2-trifluoroacetyl α-methylglucoside (VIII) furnished some confirmation of this view.

Two main conclusions may be drawn from this work : first, that 4 : 6-benzylidene trifluoroacetyl α-methylglucoside is a new and useful intermediate for the synthesis of both 2- and 3-substituted glucoses, and, secondly, that the use of a carboxylic acid–trifluoroacetic anhydride

acylating medium possesses advantages over the more common pyridine process in cases where alkali-sensitive groupings are already present in the carbohydrate molecule. The extension of this study of acylation, using the carboxylic acid–trifluoroacetic anhydride process and other methods, to other partly trifluoroacetylated carbohydrates may well lead to the preparation of hitherto inaccessible derivatives, and this possibility is now being examined.

Experimental.

Precautions.—Unless otherwise stated, all operations involving trifluoroacetates were conducted with dry reagents under anhydrous conditions.

Preparation of 4 : 6-*Benzylidene* α-*Methylglucoside.*—Prepared by the method of Freudenberg, Toepffer, and Andersen (*Ber.*, 1928, **61**, 1750), this compound had m. p. 164° and $[\alpha]_D^{19}$ +114° (*c*, 0·55 in chloroform).

Preparation of 4 : 6-*Benzylidene* 2 : 3-*Bistrifluoroacetyl* α-*Methylglucoside.*—This bistrifluoroacetate was obtained from 4 : 6-benzylidene α-methylglucoside by the method of Bourne, Tatlow, and Tatlow (*loc. cit.*); it had m. p. 88—89°, $[\alpha]_D^{18}$ +77·6° (*c*, 0·80 in carbon tetrachloride).

Partial Methanolysis of 4 : 6-*Benzylidene* 2 : 3-*Bistrifluoroacetyl* α-*Methylglucoside.*—Methyl alcohol (2·0 c.c.), dried with magnesium and iodine as described by Vogel (" A Text-book of Practical Organic Chemistry," Longmans, Green & Co., 1948, 168), was added to a solution of the bistrifluoroacetate (0·900 g.) in carbon tetrachloride (4·0 c.c.). On being kept at room temperature, the solution gradually precipitated a solid, which was removed by filtration and proved to be 4 : 6-*benzylidene trifluoroacetyl* α-*methylglucoside* (0·503 g., 70%), m. p. 211° (unchanged by recrystallisation from carbon tetrachloride), $[\alpha]_D^{19}$ +119° (*c*, 1·60 in chloroform) (Found : C, 50·4; H, 4·5; F, 15·0; OMe, 8·5; CF_3·CO, 26·1%; *M*, 355. $C_{16}H_{17}O_7F_3$ requires C, 50·8; H, 4·5; F, 15·1; OMe, 8·2; CF_3·CO, 25·65%; *M*, 378).

Direct Preparation of 4 : 6-*Benzylidene Trifluoroacetyl* α-*Methylglucoside.*—4 : 6-Benzylidene α-methylglucoside (10·0 g.) was added to a mixture of trifluoroacetic anhydride (20·0 c.c.) and sodium trifluoroacetate (1·078 g.). When the initial vigour of the reaction had abated, the mixture was distilled under diminished pressure with several portions of carbon tetrachloride, and the residue was exhaustively extracted with the same solvent. The filtered extracts were distilled under diminished pressure and, before crystallisation commenced, the residual syrupy bistrifluoroacetate was dissolved in warm magnesium-dried methyl alcohol (35 c.c.). A crystalline precipitate soon separated from the solution. After 15 minutes, carbon tetrachloride (100 c.c.) was added and the solid removed by filtration. A further quantity of the product was recovered by concentrating the mother-liquors. The combined solids were recrystallised from carbon tetrachloride giving 4 : 6-benzylidene trifluoroacetyl α-methylglucoside (8·57 g., 64%), m. p. 211° (alone and on admixture with the specimen mentioned above), $[\alpha]_D^{21}$ +119° (*c*, 1·46 in chloroform). In three similar experiments yields of 51, 53, and 64% were obtained. Only under controlled conditions can reproducible values be obtained for the m. p. of this compound, because (*a*) the compound tends to sublime and (*b*) the m. p. depends on the time of heating.

Methylation of 4 : 6-*Benzylidene Trifluoroacetyl* α-*Methylglucoside.*—Silver oxide (0·260 g.) was added to a solution of the monotrifluoroacetate (0·350 g.) in methyl iodide (15·0 c.c.), and the mixture was refluxed for 20 hours. The methyl iodide was removed by distillation, and the residue exhaustively extracted with carbon tetrachloride. The filtered extracts were evaporated and the residual glucoside was remethylated as before. Recrystallisation of the product from light petroleum (b. p. 100—120°) afforded 4 : 6-benzylidene 2 : 3-dimethyl α-methylglucoside (0·211 g., 74%), m. p. and mixed m. p. 122°, $[\alpha]_D^{18}$ +98° (*c*, 0·43 in acetone) (Found : C, 62·0; H, 7·1; OMe, 29·95. Calc. for $C_{16}H_{22}O_6$: C, 61·9; H, 7·1; OMe, 30·0%). Irvine and Scott (*J.*, 1913, **103**, 575) give m. p. 122—123° and $[\alpha]_D^{20}$ +97° (*c*, 1·64 in acetone) for this compound.

From a second experiment, in which the methylation reaction was allowed to proceed for only 3¾ hours, a mixture was obtained. A portion of this material, after acidic hydrolysis, was submitted to filter-paper chromatography with a butanol solvent, as described by Hirst, Hough, and Jones (*J.*, 1949, 928). An aniline hydrogen phthalate spray (Partridge, *Nature*, 1949, **164**, 443) revealed two spots, having R_F values corresponding to those of glucose and a monomethyl glucose, respectively.

4 : 6-*Benzylidene* 2-*Tosyl* 3-*Trifluoroacetyl* α-*Methylglucoside from* 4 : 6-*Benzylidene* 2-*Tosyl* α-*Methylglucoside.*—4 : 6-Benzylidene 2-tosyl α-methylglucoside (0·938 g.), prepared according to Robertson and Griffith's method (*loc. cit.*), was added to a mixture of sodium trifluoroacetate (0·264 g.), trifluoroacetic anhydride (5·50 c.c.), and carbon tetrachloride (25·0 c.c.). After being refluxed for 75 minutes, by which time complete dissolution had been achieved, the mixture was distilled under diminished pressure with four portions (15 c.c. each) of carbon tetrachloride. The residue was extracted exhaustively with boiling carbon tetrachloride and the filtered extracts were distilled, leaving a residue, which, after recrystallisation from light petroleum (b. p. 100—120°), afforded 4 : 6-*benzylidene* 2-*tosyl* 3-*trifluoroacetyl* α-*methylglucoside* (0·724 g., 64%), m. p. 180—185° (unchanged by further crystallisation), $[\alpha]_D^{20}$ +44·0° (*c*, 5·0 in chloroform) (Found : OMe, 5·9; CF_3·CO, 18·0. $C_{23}H_{23}O_9SF_3$ requires OMe, 5·8; CF_3·CO, 18·2%).

4 : 6-*Benzylidene* 2-*Tosyl* 3-*Trifluoroacetyl* α-*Methylglucoside from* 4 : 6-*Benzylidene Trifluoroacetyl* α-*Methylglucoside.*—Toluene-*p*-sulphonyl chloride (0·302 g.) was added to a solution of 4 : 6-benzylidene trifluoroacetyl α-methylglucoside (0·502 g.) in pyridine (2·0 c.c.). After 2 days at room temperature, the reaction mixture was distilled under diminished pressure with three portions (15·0 c.c. each) of trichloroethylene. The residue was exhaustively extracted with boiling trichloroethylene, and the filtered extracts were distilled under diminished pressure. The residue, recrystallised from light petroleum (b. p. 100—120°), gave 4 : 6-benzylidene 2-tosyl 3-trifluoroacetyl α-methylglucoside (0·550 g., 78%), m. p. 176—182° (not depressed on admixture with the specimen previously obtained), $[\alpha]_D^{21}$ +46·7° (*c*, 1·46 in chloroform) (Found : OMe, 6·1; CF_3·CO, 18·1. $C_{23}H_{23}O_9SF_3$ requires OMe, 5·8; CF_3·CO, 18·2%).

Hydrolysis of 4 : 6-*Benzylidene* 2-*Tosyl* 3-*Trifluoroacetyl* α-*Methylglucoside.*—The titration-liquors from the trifluoroacetyl estimation on the sample of 4 : 6-benzylidene 2-tosyl 3-trifluoroacetyl α-methylglucoside, which had been prepared by toluenesulphonation of 4 : 6-benzylidene trifluoroacetyl α-methylglucoside, were made slightly alkaline to phenolphthalein and the acetone was removed under diminished pressure. The solid thus precipitated was recrystallised from aqueous alcohol containing a trace of ammonia. The product, obtained in 97% yield, had m. p. 155° [alone and on admixture with authentic 4 : 6-benzylidene 2-tosyl α-methylglucoside (Robertson and Griffith, *loc. cit.*)], $[\alpha]_D^{18}$ +59·5° (*c*, 1·21 in chloroform) (Found : C, 57·95; H, 5·7. Calc. for $C_{21}H_{24}O_8S$: C, 57·8; H, 5·5%). Methylation with silver oxide and methyl iodide gave a product (yield, 50%) having m. p. 155—156°, not depressed on admixture with authentic 4 : 6-benzylidene 3-methyl 2-tosyl α-methylglucoside supplied by Dr. J. Dewar. Bolliger and Prins (*loc. cit.*) give m. p. 156—157° for this compound.

In a similar fashion, the other sample of 4 : 6-benzylidene 2-tosyl 3-trifluoroacetyl α-methylglucoside afforded 4 : 6-benzylidene 2-tosyl α-methylglucoside in 86% yield.

Preparation of 3-*Acetyl* 4 : 6-*Benzylidene* α-*Methylglucoside.*—Acetic anhydride (0·80 c.c.) was added to a solution of 4 : 6-benzylidene trifluoroacetyl α-methylglucoside (2·014 g.) in pyridine (4·50 c.c.). After 36 hours at room temperature, the reaction mixture was distilled under diminished pressure with several portions of chloroform and carbon tetrachloride. The residual syrup was dissolved in warm ethyl alcohol, which was removed immediately by distillation at 60° (bath-temp.)/12 mm., leaving a white solid. Recrystallisation from light petroleum (b. p. 100—120°) gave 3-*acetyl* 4 : 6-*benzylidene* α-*methylglucoside* (1·086 g., 64%), m. p. 174°, $[\alpha]_D^{14}$ +110° (*c*, 0·85 in chloroform) (Found : C, 59·3; H, 6·3; OMe, 9·7; Ac, 12·9. $C_{16}H_{20}O_7$ requires C, 59·3; H, 6·2; OMe, 9·6; Ac, 13·3%). In two similar experiments the same product was isolated in yields of 56 and 60%, severally.

3-*Acetyl* 4 : 6-*Benzylidene* 2-*Trifluoroacetyl* α-*Methylglucoside from* 3-*Acetyl* 4 : 6-*Benzylidene* α-*Methylglucoside.*—The 3-acetate (0·507 g.) was heated at 50° for 10 minutes with a mixture of sodium trifluoroacetate (0·052 g.) and trifluoroacetic anhydride (3·5 c.c.). The reaction mixture was distilled under diminished pressure with four portions of carbon tetrachloride (15 c.c. each), and the residue was extracted with light petroleum (20 c.c.; b. p. 40—60°). When cooled, the filtered extract deposited long needles of 3-*acetyl* 4 : 6-*benzylidene* 2-*trifluoroacetyl* α-*methylglucoside* (0·372 g., 57%), m. p. 107—109° (unchanged by recrystallisation), $[\alpha]_D^{20}$ +125·0° (*c*, 0·61 in carbon tetrachloride) (Found : C, 51·4; H, 4·6%; N-alkali uptake, 4·84 c.c./g. $C_{18}H_{19}O_8F_3$ requires C, 51·45; H, 4·6%; N-alkali uptake, 4·76 c.c./g.). The low yield may be attributed, in some measure, to the relative instability of the compound and also to its high solubility in organic solvents. By concentration of the titration-liquors from the acyl estimation 4 : 6-benzylidene α-methylglucoside, m. p. 165°, $[\alpha]_D^{20}$ +114° (*c*, 0·56 in chloroform), was isolated in 83% yield.

Methanolysis of 3-*Acetyl* 4 : 6-*Benzylidene* 2-*Trifluoroacetyl* α-*Methylglucoside.*—A solution of 3-acetyl 4 : 6-benzylidene 2-trifluoroacetyl α-methylglucoside (0·070 g.), prepared as above, in magnesium-dried methyl alcohol (10·0 c.c.), was refluxed for 35 minutes before the solvent was removed at 12 mm. pressure. The residue (0·054 g., 100%) had m. p. 174°, alone and on admixture with the sample of 3-acetyl 4 : 6-benzylidene α-methylglucoside already obtained.

Attempted Preparation of 3-*Acetyl* 4 : 6-*Benzylidene* 2-*Trifluoroacetyl* α-*Methylglucoside from* 4 : 6-*Benzylidene Trifluoroacetyl* α-*Methylglucoside.*—Acetic anhydride (0·55 c.c.) was added to a solution of 4 : 6-benzylidene trifluoroacetyl α-methylglucoside (2·090 g.) in pyridine (7·0 c.c.), and the mixture was kept at room temperature for 36 hours. The volatile material was removed by distillation under diminished pressure with light petroleum (b. p. 100—120°), and the residue recrystallised from light petroleum (b. p. 40—60°). The product (1·798 g.), m. p. 80—95°, was recrystallised again from light petroleum (b. p. 40—60°) and then had m. p. 88—92°. This material could not be purified further by repeated crystallisation (Found : F, 12·9. $C_{18}H_{19}O_8F_3$ requires F, 13·6%).

Preparation of 3-*Acetyl* 4 : 6-*Benzylidene* 2-*Methyl* α-*Methylglucoside.*—Silver oxide (1·25 g.) was added to a solution of 3-acetyl 4 : 6-benzylidene α-methylglucoside (0·670 g.) in methyl iodide (25·0 c.c.), and the mixture was refluxed for 18 hours. The methyl iodide was removed by distillation, and the residue extracted exhaustively with boiling chloroform. Distillation of the filtered extracts left a crystalline solid, which, when recrystallised from light petroleum (b. p. 60—80°), afforded 3-acetyl 4 : 6-benzylidene 2-methyl α-methylglucoside (0·487 g., 70%), m. p. 128·5°, $[\alpha]_D^{14}$ +81·9° (*c*, 0·92 in chloroform) (Found : C, 60·1; H, 6·5; OMe, 18·4; Ac, 13·1. Calc. for $C_{17}H_{22}O_7$: C, 60·3; H, 6·6; OMe, 18·3; Ac, 12·7%). Two similar experiments gave the same compound, m. p. 128°.

From a fourth experiment, the product, isolated in 70% yield, had m. p. 145° [alone and on admixture with a specimen of 3-acetyl 4 : 6-benzylidene 2-methyl α-methylglucoside (m. p. 145°) supplied by Dr. D. J. Bell], $[\alpha]_D^{18}$ +82·5° (*c*, 0·61 in chloroform) (Found : C, 60·6; H, 6·7; OMe, 18·2%). Subsequent experiments invariably yielded the higher-melting material.

The two products isolated from these experiments appeared to be polymorphic forms of the same compound, the higher-melting form being the more stable. A mixture of the two had m. p. 145°. All the material having m. p. 128·5° ultimately changed into the higher-melting form.

Preparation of 4 : 6-*Benzylidene* 2-*Methyl* α-*Methylglucoside.*—A small piece of sodium was added to a solution of 3-acetyl 4 : 6-benzylidene 2-methyl α-methylglucoside (m. p. 128·5°; 0·102 g.) in magnesium-dried methyl alcohol (10·0 c.c.), and the solution was kept for 18 hours at room temperature. The solvent was distilled off under diminished pressure and water was added to the residue. The aqueous suspension was extracted with chloroform. The washed extracts were dried ($MgSO_4$), filtered, and distilled, leaving a residue, which, after recrystallisation from light petroleum (b. p. 60—80°), had m. p. 168° (alone and on admixture with an authentic specimen of 4 : 6-benzylidene 2-methyl α-methylglucoside supplied by Dr. D. J. Bell), $[\alpha]_D^{17}$ +78·9° (*c*, 1·19 in ethyl alcohol) (Found : C, 60·7; H, 6·8; OMe, 21·15. Calc. for $C_{15}H_{20}O_6$: C, 60·8; H, 6·8; OMe, 20·95%). Yield, 0·051 g. (57%).

In a similar fashion, the other polymorphic form (m. p. 145°) of 3-acetyl 4 : 6-benzylidene 2-methyl

α-methylglucoside gave 4 : 6-benzylidene 2-methyl α-methylglucoside in 79% yield, m. p. 167° (Found : C, 60·5; H, 7·0; OMe, 20·9%). This compound did not depress the m. p. of the specimen already prepared or of Bell's authentic compound, but it did depress the m. p. of a specimen of 4 : 6-benzylidene 3-methyl α-methylglucoside (m. p. 147°) supplied by Dr. H. R. Bolliger.

Preparation of 2-Methyl α-Methylglucoside.—4 : 6-Benzylidene 2-methyl α-methylglucoside (0·552 g.) was refluxed for 30 minutes with a mixture of ethyl alcohol (55 c.c.) and 0·1N-sulphuric acid (5·0 c.c.). The solution was neutralised with barium carbonate, and the barium salts were separated on the centrifuge. The supernatant liquid was steam-distilled under reduced pressure and then concentrated to dryness. Recrystallised twice from ethyl acetate, the product (0·114 g., 29%) had m. p. 146—148° (alone and on admixture with an authentic specimen of 2-methyl α-methylglucoside supplied by Dr. D. J. Bell), $[\alpha]_D^{20}$ +153° (*c*, 0·46 in water) (Found : C, 46·35; H, 7·9; OMe, 29·8. Calc. for $C_8H_{16}O_6$: C, 46·15; H, 7·75; OMe, 29·8%). Haworth, Hirst, and Teece (*loc. cit.*) give m. p. 147—148° and $[\alpha]_D^{19}$ +155° (in water) for this compound.

3-Acetyl 4 : 6-Benzylidene 2-Tosyl α-Methylglucoside from 4 : 6-Benzylidene 2-Tosyl α-Methylglucoside.—Acetic anhydride (0·30 c.c.) was added to a solution of 4 : 6-benzylidene 2-tosyl α-methylglucoside (0·104 g.) in pyridine (5·0 c.c.). After being kept at room temperature for 36 hours, the reaction mixture was poured into water, and the solid thus precipitated was recrystallised from ethyl alcohol. The product, *3-acetyl 4 : 6-benzylidene 2-tosyl α-methylglucoside* (0·078 g., 69%), had m. p. 160—162°, $[\alpha]_D^{18}$ +51·2° (*c*, 0·76 in chloroform) (Found : C, 57·9; H, 5·6; S, 6·3; OMe, 6·4. $C_{23}H_{26}O_9S$ requires C, 57·7; H, 5·5; S, 6·7; OMe, 6·5%).

3-Acetyl 4 : 6-Benzylidene 2-Tosyl α-Methylglucoside from 3-Acetyl 4 : 6-Benzylidene α-Methylglucoside.—Toluene-*p*-sulphonyl chloride (0·473 g.) was added to 3-acetyl 4 : 6-benzylidene α-methylglucoside (0·515 g.) in pyridine (7·0 c.c.), and the solution was kept at room temperature for 4 days, before being poured into ice-water containing hydrochloric acid. The precipitated solid (0·774 g.) was crystallised from alcohol, giving 3-acetyl 4 : 6-benzylidene 2-tosyl α-methylglucoside (0·618 g., 81%), m. p. 160—162° (alone and on admixture with the specimen already obtained), $[\alpha]_D^{18}$ +49·1° (*c*, 2·90 in chloroform) (Found : C, 57·6; H, 5·5; S, 6·5; OMe, 6·5. $C_{23}H_{26}O_9S$ requires C, 57·7; H, 5·5; S, 6·7; OMe, 6·5%).

Preparation of 4 : 6-Benzylidene 2 : 3-Anhydro-α-methylmannoside.—3-Acetyl 4 : 6-benzylidene 2-tosyl α-methylglucoside (0·228 g.), prepared from the 3-acetate, was refluxed for 2 hours with a solution of sodium (0·166 g.) in magnesium-dried methyl alcohol (8·5 c.c.) and then water (10·0 c.c.) was added. When cooled, the solution deposited crystalline 4 : 6-benzylidene 2 : 3-anhydro-α-methylmannoside (0·093 g., 74%), m. p. and mixed m. p. 146°, $[\alpha]_D^{17}$ +103·0° (*c*, 0·81 in chloroform) (Found : C, 63·3; H, 6·1. Calc. for $C_{14}H_{16}O_5$: C, 63·6; H, 6·1%). Robertson and Griffith (*loc. cit.*) cite m. p. 146—147° and $[\alpha]_D^{15}$ +107·4° (*c*, 1·61 in chloroform) for this compound.

Preparation of 2-Acetyl 4 : 6-Benzylidene 3-Trifluoroacetyl α-Methylglucoside.—A mixture of glacial acetic acid (0·160 c.c.) and trifluoroacetic anhydride (0·60 c.c.) was added to 4 : 6-benzylidene trifluoroacetyl α-methylglucoside (0·730 g.) in benzene (7·0 c.c.). After 20 minutes at 60°, carbon tetrachloride (20 c.c.) was added and the solution was evaporated under reduced pressure. The residue was re-acetylated as before for 15 minutes, and the reaction mixture was distilled under diminished pressure with four portions (20 c.c. each) of carbon tetrachloride. Recrystallised twice from light petroleum (b. p. 40—60°), *2-acetyl 4 : 6-benzylidene 3-trifluoroacetyl α-methylglucoside* (0·515 g., 64%) had m. p. 134—135°, $[\alpha]_D^{27}$ +94·5° (*c*, 1·00 in carbon tetrachloride) (Found : C, 51·55; H, 4·8%; N-alkali uptake, 4·78 c.c./g. $C_{18}H_{19}O_8F_3$ requires C, 51·45; H, 4·6%; N-alkali uptake, 4·76 c.c./g.). By concentration of the titration-liquors from the acyl estimation, 4 : 6-benzylidene α-methylglucoside, m. p. 164—165°, $[\alpha]_D^{19}$ +114° (*c*, 0·59 in chloroform), was isolated in 74% yield.

Preparation of 2-Acetyl 4 : 6-Benzylidene α-Methylglucoside.—A solution of 2-acetyl 4 : 6-benzylidene 3-trifluoroacetyl α-methylglucoside (0·410 g.) in magnesium-dried methyl alcohol (20 c.c.) was kept at 50° for 2 minutes before the alcohol was removed by distillation [50° (bath-temp.)/12 mm.]. Recrystallisation of the product from light petroleum (b. p. 60—80°) gave *2-acetyl 4 : 6-benzylidene α-methylglucoside* (0·263 g., 83%), m. p. 133—134°, $[\alpha]_D^{19}$ +112° (*c*, 0·86 in chloroform) (Found : C, 59·2; H, 6·4; Ac, 12·9. $C_{16}H_{20}O_7$ requires C, 59·3; H, 6·2; Ac, 13·3%). A mixture with 2-acetyl 4 : 6-benzylidene 3-trifluoroacetyl α-methylglucoside had m. p. 105—115°. From the titration-liquors of the acetyl estimation, 4 : 6-benzylidene α-methylglucoside, m. p. and mixed m. p. 165—166°, $[\alpha]_D^{21}$ +113° (*c*, 0·78 in chloroform), was isolated in 57% yield.

This methanolysis was repeated several times with approximately the same quantities of the reagents, and similar results were obtained. Attempts to carry out the conversion on a larger scale (three-fold or greater) invariably gave an impure product which could not be purified.

Preparation of 2-Acetyl 4 : 6-Benzylidene 3-Methyl α-Methylglucoside.—A solution of 2-acetyl 4 : 6-benzylidene α-methylglucoside (0·352 g.) in methyl iodide (15·0 c.c.) was refluxed for 19 hours with silver oxide (0·261 g.). The methyl iodide was removed by distillation and the residue was extracted with boiling chloroform. Evaporation of the extract left a residue, which was re-treated with methyl iodide and silver oxide. The product was isolated as before and twice recrystallised from light petroleum (b. p. 60—80°), giving *2-acetyl 4 : 6-benzylidene 3-methyl α-methylglucoside* (0·159 g., 43%), m. p. 121°, $[\alpha]_D^{23}$ +101·0° (*c*, 0·80 in chloroform) (Found : C, 60·2; H, 6·5; Ac, 12·9. $C_{17}H_{22}O_7$ requires C, 60·3; H, 6·6; Ac, 12·7%).

Preparation of 4 : 6-Benzylidene 3-Methyl α-Methylglucoside.—The titration-liquors from the acetyl estimation on 2-acetyl 4 : 6-benzylidene 3-methyl α-methylglucoside were made just alkaline to phenolphthalein and concentrated under diminished pressure, before being extracted with chloroform. The extracts were dried ($MgSO_4$), filtered, and evaporated. The residue was crystallised from light petroleum (b. p. 60—80°), giving 4 : 6-benzylidene 3-methyl α-methylglucoside in 65% yield, m. p. 147° [alone and on admixture with an authentic specimen (m. p. 147°; cf. Bolliger and Prins, *loc. cit.*) supplied by Dr. H. R. Bolliger], $[\alpha]_D^{22}$ +123·0° (*c*, 0·45 in tetrachloroethane) (Found : C, 60·9; H, 6·75. Calc. for

$C_{15}H_{20}O_6$: C, 60·8; H, 6·8%). The m. p. of this compound was depressed by the specimen of 4 : 6-benzylidene 2-methyl α-methylglucoside already obtained.

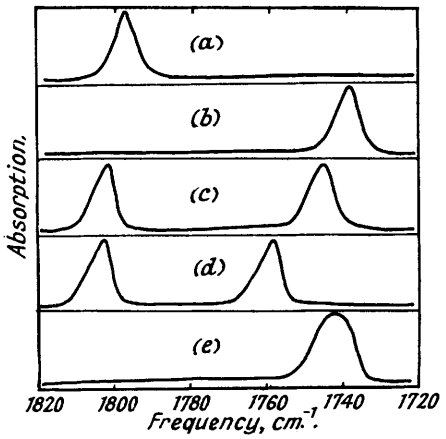
Preparation of 2-Acetyl 4 : 6-Benzylidene 3-Tosyl α-Methylglucoside.—Toluene-*p*-sulphonyl chloride (0·296 g.) was added to a solution of 2-acetyl 4 : 6-benzylidene α-methylglucoside (0·487 g.) in pyridine (4·0 c.c.), and the mixture kept at room temperature for 4 days. The solution was poured into a water–chloroform mixture, the chloroform layer was separated, and the aqueous phase was extracted with three further portions of chloroform. The combined chloroform extracts were washed with water, very dilute hydrochloric acid, aqueous sodium hydrogen carbonate, and water again, before being dried ($MgSO_4$ and $NaHCO_3$), filtered, and distilled. The residual syrup was recrystallised from aqueous alcohol and gave *2-acetyl 4 : 6-benzylidene 3-tosyl α-methylglucoside* (0·347 g., 49%), m. p. 120—121°, $[\alpha]_D^{23}$ +28·1° (*c*, 0·78 in chloroform) (Found : C, 57·8; H, 5·5; S, 6·8%; N-sodium methoxide uptake, 3·92 c.c./g. $C_{23}H_{26}O_9S$ requires C, 57·7; H, 5·5; S, 6·7%; N-sodium methoxide uptake, 4·18 c.c./g.).

Preparation of 4 : 6-Benzylidene 2 : 3-Anhydro-α-methylalloside.—A solution of 2-acetyl 4 : 6-benzylidene 3-tosyl α-methylglucoside (0·0276 g.) in methanolic sodium methoxide (1·00 c.c.; 0·20N.) was refluxed for 45 minutes. Addition of water (5·0 c.c.) caused precipitation of 4 : 6-benzylidene 2 : 3-anhydro-α-methylalloside (0·0120 g., 79%), m. p. and mixed m. p. 199—200°, $[\alpha]_D^{25}$ +144·0° (*c*, 0·23 in chloroform) (Found : C, 63·75; H, 5·9. Calc. for $C_{14}H_{16}O_5$: C, 63·6; H, 6·1%). Robertson and Griffith (*loc. cit.*) cite m. p. 199—200° and $[\alpha]_D^{15}$ +140·4° (*c*, 2·21 in chloroform) for this compound.

Analytical Methods.—(a) *Trifluoroacetyl and acetyl determinations.* These determinations were carried out by the method described by Bourne, Tatlow, and Tatlow (*loc. cit.*).

(b) *Fluorine determination.* The method, which involved fusion with sodium in a bomb of special design and determination of the resultant fluoride ion as lead chlorofluoride, was that of Belcher and Tatlow (J. C.) (unpublished).

(c) *Carbon and hydrogen determination in the presence of fluorine.* The usual combustion was modified by the inclusion of a sodium fluoride packing to absorb any silicon tetrafluoride formed (Belcher and Goulden, unpublished).



Infra-red Absorption Spectra (*with* D. H. Whiffen).—Infra-red absorption spectra of the following compounds were determined in chloroform solution (*c*, 2—3) : (*a*) 4 : 6-benzylidene trifluoroacetyl α-methylglucoside, (*b*) 3-acetyl 4 : 6-benzylidene α-methylglucoside, (*c*) 2-acetyl 4 : 6-benzylidene 3-trifluoroacetyl α-methylglucoside, (*d*) 3-acetyl 4 : 6-benzylidene 2-trifluoroacetyl α-methylglucoside, (*e*) 2 : 3-diacetyl 4 : 6-benzylidene α-methylglucoside. The results are shown graphically in the accompanying figure with the corresponding lettering.

Very strong evidence of the presence of carbonyl groups is given in each case, since only the carbonyl stretching frequency commonly gives rise to a strong infra-red band between 1700 and 1800 $cm.^{-1}$. Each acetate-trifluoroacetate shows two absorption peaks, at about 1750 and 1800 $cm.^{-1}$, respectively, and thus the different strengths of the two carbonyl groups in each of these compounds are demonstrated. The frequencies of the absorption peaks accord with those of the mono-esters (*a* and *b*) and with those reported by Hartwell, Richards, and Thompson (*J.*, 1948, 1436) for the carbonyl groups in methyl acetate (1742 $cm.^{-1}$, in chloroform) and ethyl trichloroacetate (1768 $cm.^{-1}$, as a liquid).

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