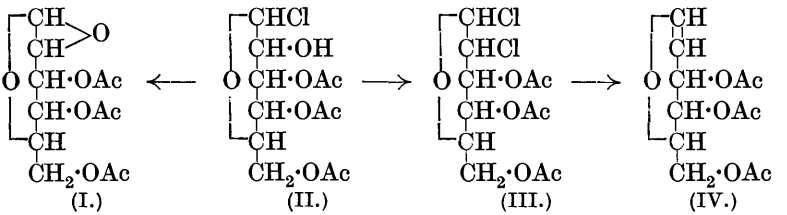
CCCCXV.—*Glucosides. Part I. The Formation of Glucosides from 3 : 4 : 6-Triacetyl Glucose 1 : 2-Anhydride.*

By WILFRED JOHN HICKINBOTTOM.

A TRIACETYL glucose anhydride has been prepared by Brigl (*Z. physiol. Chem.*, 1922, **122**, 257), who described it as a crystalline solid which reacted with methyl alcohol to yield a triacetyl β-methyl-glucoside. This anhydride may therefore prove to be a valuable general reagent for the preparation of glucosides, and more particularly of glucosides which are not obtained conveniently by the usual standard methods. Its reactions with a number of substances have been investigated; those with phenol and with alcohols are here recorded.

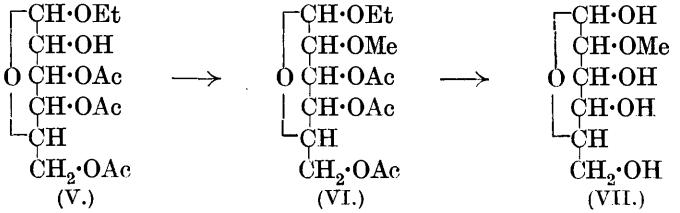
Brigl assigned to the triacetyl glucose anhydride the formula (I) on the basis of its formation from triacetyl glucosyl chloride (II), the structure of which has been determined by its conversion into a triacetyl dichloroglucose (III) and subsequent reduction to triacetyl glucal (IV).



(I.) (II.) (III.) (IV.)

This formulation of the triacetyl glucose anhydride has been confirmed by an independent method. The anhydride was converted, by the interaction of ethyl alcohol and the ethylene oxide group, into 3 : 4 : 6-*triacetyl* β-*ethylglucoside* (V), which, by methylation with methyl iodide in presence of silver oxide, yielded a *triacetyl methyl* β-*ethylglucoside* (VI). Deacetylation by means of alcoholic ammonia, followed by hydrolysis, gave a monomethyl glucose. This sugar was characterised by its *phenylhydrazone*. No phenylosazone could be obtained from it. It must be therefore

2-methyl glucose (VII), as the methyl group can only replace the hydrogen of the remaining hydroxyl group in triacetyl β-ethyl-glucoside.



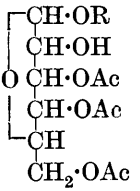
3 : 4 : 6-Triacetyl glucose anhydride reacts similarly with other primary and with secondary alcohols at room temperature to yield β-glucosides : methyl alcohol gives a product consisting principally of 3 : 4 : 6-triacetyl β-methylglucoside (compare Brigl, *loc. cit.*), *iso*propyl alcohol furnishes 3 : 4 : 6-triacetyl β-*iso*propylglucoside, and menthol gives 3 : 4 : 6-triacetyl β-menthylglucoside. The last glucoside appears to be identical with the product obtained by Fischer and Bergmann (*Ber.*, 1917, **50**, 711) from the reaction of menthol with tetra-acetyl glucosyl bromide in presence of quinoline. If it is, there must be in Fischer and Bergmann's product a free hydroxyl in position 2. This conclusion is supported by other observations which show that in the tetra-acyl glucosyl halides an acyl group is more readily removed from position 2 than from position 3, 4, or 6. For instance, in 2 : 3 : 4 : 6-tetra-acetyl glucosyl bromide the acetyl group in position 2 is eliminated on reduction to triacetyl glucal. Also 2-trichloroacetyl-3 : 4 : 6-triacetyl glucosyl chloride yields 3 : 4 : 6-triacetyl glucose by combined reduction and regulated hydrolysis (Hickinbottom, unpublished observation) and 3 : 4 : 6-triacetyl glucosyl chloride by carefully controlled deacylation (Brigl, *loc. cit.*).

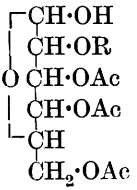
The combination of 3 : 4 : 6-triacetyl glucose anhydride with phenols proceeds less readily than with primary and secondary alcohols. The anhydride and phenol at 80—100° yield a triacetyl phenylglucoside. This was identified as an α-glucoside by conversion into α-phenylglucoside and into tetra-acetyl α-phenylglucoside and comparison of these substances with authentic specimens. This method of preparing α-phenylglucoside is more convenient than that described by Fischer and Mechel (*Ber.*, 1916, **49**, 2813), *viz.*, the condensation of phenol with tetra-acetyl glucosyl bromide in the presence of quinoline, which yields also a considerable proportion of acetylated β-phenylglucosides.

In all the cases so far examined, the products of the combination of 3 : 4 : 6-triacetyl glucose anhydride (I) with hydroxy-compounds

are glucosides of the type (VIII), no derivative of a 2-alkyl glucose (IX) having yet been isolated.

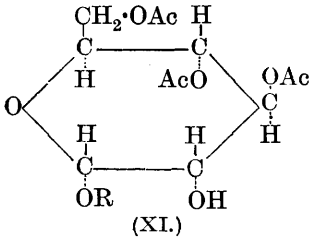
(VIII.)



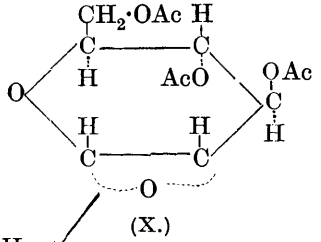


(IX.)

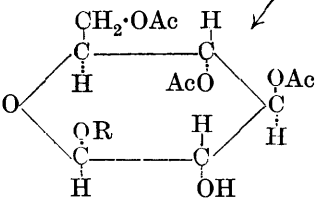
To show the relative dispositions of the groups in space, 3 : 4 : 6-triacetyl glucose anhydride may be formulated as in (X).



(XI.)



(X.)



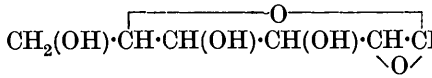
(XII.)

Then (XI) will represent its α-glucosides, and (XII) the corresponding β-glucosides (compare Drew and Haworth, J., 1926, 2305). It is seen that the formation of β-glucosides by the additive union with alcohols involves the opening of the ethylene oxide ring so that the added groups occupy the *trans*-position. Kuhn and Ebel (*Ber.*, 1925, **58**, 919) also have demonstrated the *trans*-fission of the ethylene oxide ring in *cis*-oxidoethylene-αβ-dicarboxylic acid to yield *r*-tartaric acid. If it be a general behaviour of ethylene oxide rings to yield compounds having *trans*-configurations on fission, it is difficult to explain the formation of 3 : 4 : 6-triacetyl α-phenylglucoside from 3 : 4 : 6-triacetyl glucose anhydride by the action of phenol, unless the α-configuration attributed to the phenylglucoside had been wrongly assigned. The spatial distribution of the glucosidic residue with respect to the rest of the molecule may, however, be deduced from other considerations, *e.g.*, the behaviour towards enzymes, the optical rotatory power, and the formation from glucosyl halides. The evidence from these sources indicates clearly

that the configuration of α-phenylglucoside is not similar to that of β-glucosides.

3 : 4 : 6-Triacetyl glucose anhydride, then, may yield either *cis*- or *trans*-fission products according as it reacts with phenol or alcohols. It appears, therefore, that the configuration of the product resulting from the opening of an ethylene oxide ring cannot be predicted without reference to the nature of the reactants, and probably also to the conditions during the reaction.

α-Glucosan, according to the structure assigned to it by Pictet and Castan (*Helv. Chim. Acta*, 1920, **3**, 645),



should be the parent substance of 3 : 4 : 6-triacetyl glucose anhydride. The reactions of the two substances differ so widely, however, as to shed doubt on the accuracy of the above structure.

The ethylene oxide ring in α-glucosan is surprisingly stable to reagents in comparison with that in triacetyl glucose anhydride. For instance, α-glucosan may be benzoylated or methylated by means of benzoyl chloride or methyl sulphate in presence of aqueous sodium hydroxide, and it combines additively with methyl iodide in methyl-alcoholic solution at 120° (Cramer and Cox, *Helv. Chim. Acta*, 1922, **5**, 884). Pictet and Castan isolated α-glucosan in a crystalline state by solution in cold methyl alcohol, followed by evaporation at room temperature. Under similar conditions, the ethylene oxide ring in 3 : 4 : 6-triacetyl glucose anhydride, possibly rendered more reactive by the presence of the acyl groups, is opened with the formation of 3 : 4 : 6-triacetyl β-methylglucoside.

The anhydride reacts rapidly with methyl alcohol at room temperature, the formation of the glucoside being complete in about 2 hours for a 5% solution. The rate of reaction with ethyl alcohol is slower, but is sufficiently rapid to prevent the anhydride being purified by crystallisation from this solvent. The graphs in Fig. 1 record the change of optical rotation with time for solutions of 3 : 4 : 6-triacetyl glucose anhydride in methyl and ethyl alcohols.

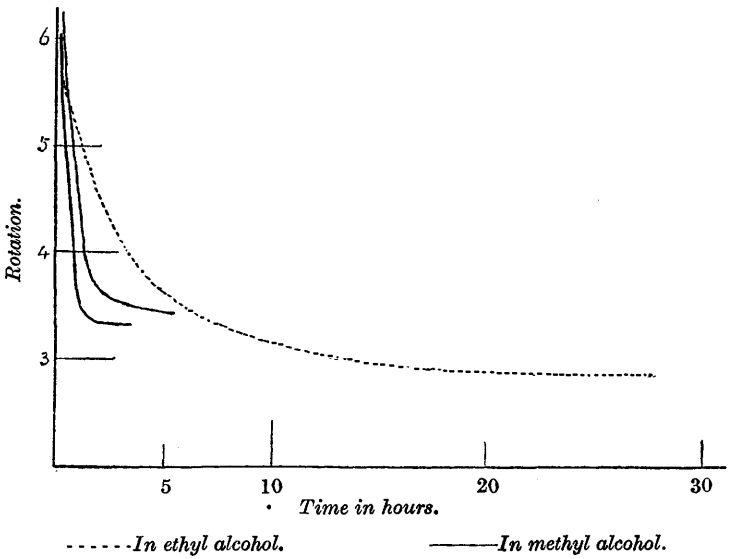
Experimental.

Preparation of 3 : 4 : 6-*Triacetyl Glucose* 1 : 2-*Anhydride* (I) (compare Brigl, *loc. cit.*).—A current of dry ammonia was slowly passed through a suspension of dry, finely powdered 3 : 4 : 6-triacetyl glucosyl chloride in 8—10 times its weight of dry benzene for 3 hours; the mixture was then kept and occasionally shaken in a sealed flask for 15 hours. The ammonium chloride having been removed, and washed with benzene, the filtrate and the washings

were freed from ammonia in a partial vacuum over concentrated sulphuric acid, and the benzene was evaporated under diminished pressure at 40°; addition of light petroleum (b. p. 40—60°) then yielded a crystalline cake of 3 : 4 : 6-triacetyl glucose 1 : 2-anhydride. It separated from a mixture of benzene and light petroleum or from the latter solvent alone in platelets, m. p. 57—58° after sintering at 56°.

The anhydride may also be obtained by shaking with silver oxide a suspension of 3 : 4 : 6-triacetyl glucosyl chloride in dry chloroform for 20 hours. The product, however, is coloured and impure.

FIG. 1.



Reaction of 3 : 4 : 6-*Triacetyl Glucose* 1 : 2-*Anhydride with Hydroxy-compounds.*

With Methyl Alcohol. Formation of 3 : 4 : 6-*Triacetyl* β-*Methyl-glucoside.*—The reaction, which took place readily in the cold, was followed polarimetrically ($l = 2$; $c = 4{\cdot}89$).

t (mins.)	7	15	20	25	30	40	60	120	180
α_D.....	+6·11°	5·18°	4·88°	4·60°	4·37°	4·02°	3·67°	3·34°	3·32° (const.)

Similar results were obtained when methyl alcohol containing a trace of methylamine was used as solvent.

Evaporation of the solvent yielded a viscid residue, from which, by crystallisation from absolute alcohol, pure 3 : 4 : 6-triacetyl

β-methylglucoside was obtained in prisms, m. p. 95—97°, $[\alpha]_D$ + 19° (Brigl, *loc. cit.*, gives m. p. 96—98°, $[\alpha]_D$ + 9·4°).

Acetylation in pyridine yielded tetra-acetyl β-methylglucoside which, alone or mixed with a genuine specimen, melted at 101—103°.

With Ethyl Alcohol. Formation of 3 : 4 : 6-*Triacetyl* β-*Ethylglucoside* (V).—A solution of 3 : 4 : 6-triacetyl glucose anhydride in ethyl alcohol deposited on spontaneous evaporation 3 : 4 : 6-*triacetyl* β-*ethylglucoside* in prisms, m. p. 121°, $[\alpha]_D$ + 14·4° in ethyl alcohol (c = 2·57) (Found : C, 50·1; H, 6·7. $C_{14}H_{22}O_9$ requires C, 50·3; H, 6·6%). By slow crystallisation from ethyl alcohol, massive prisms may be obtained having bevelled ends and hexagonal cross-section.

The following rotations were observed for a solution of the anhydride in ethyl alcohol (c = 4·81, l = 2) at 22° :

t (hrs.)	0·13	0·20	0·33	0·55	0·88	1·00	1·67
a_D	+5·90°	5·87°	5·74°	5·57°	5·32°	5·23°	4·75°
t (hrs.)	3·07	3·83	4·85	22·20	26·70		
a_D	4·15°	3·82°	3·63°	2·84°	2·89° (const.)		

The end-point may be reached more rapidly by heating the solution.

The observed constant rotation gives $[\alpha]_D$ + 25·9°, calculated as for triacetyl ethylglucoside. This value is greater than the specific rotation for pure triacetyl β-ethylglucoside in ethyl alcohol. In other experiments also, both with methyl and with ethyl alcohol, the specific rotation of the final solution was greater than that of the pure β-glucoside. It is evident that a small quantity of another substance having a relatively high specific rotation is formed.

Acetylation of the triacetyl β-ethylglucoside with acetic anhydride in pyridine solution gave 2 : 3 : 4 : 6-tetra-acetyl β-ethylglucoside, m. p. 105—106°, which was identified by comparison with a genuine specimen (Found : C, 51·6; H, 6·4. Calc. : C, 51·15; H, 6·6%).

Methylation of 3 : 4 : 6-*triacetyl* β-*ethylglucoside. Formation of* 3 : 4 : 6-*triacetyl*-2-*methyl* β-*ethylglucoside.* Pure triacetyl β-ethylglucoside (0·76 g.) dissolved in an excess of methyl iodide (18 g.) was heated under reflux, with the addition of pure dry silver oxide at intervals during a period of 30 hours. A further 10 g. of methyl iodide was then added, and the heating continued for 10 hours. Dilution with ether, filtration, washing with ether, and evaporation of the filtrate and washings under diminished pressure gave a syrup which rapidly solidified. Crystallisation from ethyl alcohol furnished pure 3 : 4 : 6-*triacetyl*-2-*methyl* β-*ethylglucoside* in needles, m. p. 95—96° (Found : C, 51·9; H, 6·95; OMe + OEt, 21·55. $C_{15}H_{24}O_9$ requires C, 52·05; H, 6·7; OMe + OEt, 21·9%). $[\alpha]_D$ + 5·0° in

ethyl alcohol ($c = 1{\cdot}01$). This glucoside is soluble in benzene, acetone, carbon tetrachloride, and chloroform and moderately easily soluble in cold ethyl alcohol; it is less readily soluble in light petroleum (b. p. 40—60°), from which it crystallises in slender needles.

2-Methyl β-ethylglucoside was obtained as a syrup by removal of the solvent from the product of the action of alcoholic ammonia on triacetyl-2-methyl β-ethylglucoside.

Hydrolysis of 2-methyl β-ethylglucoside with 0·7*N*-hydrochloric acid at 95° for 25 hours, followed by evaporation under diminished pressure after removal of the hydrochloric acid by addition of silver carbonate, gave 2-methyl glucose as a gum containing α- and β-forms. It was characterised by its *phenylhydrazone*, m. p. 175—176° (Found : N, 9·4. $C_{13}H_{20}O_5N_2$ requires N, 9·9%).

2-Methyl glucose was also prepared from β-methyl 3 : 4 : 6-triacetyl glucose by methylation with methyl iodide and silver oxide, followed by deacetylation and hydrolysis. A detailed description of this sugar and its derivatives will be given in a later communication.

With iso*Propyl Alcohol. Formation of* 3 : 4 : 6-*Triacetyl* β-iso-*Propylglucoside.*—Evaporation of a solution of the anhydride in *iso*propyl alcohol which had been kept for several hours gave 3 : 4 : 6-triacetyl β-*iso*propylglucoside. It crystallised only slowly and on acetylation with acetic anhydride in pyridine solution yielded 2 : 3 : 4 : 6-*tetra-acetyl* β-iso*propylglucoside*, which separated from alcohol in needles, m. p. 134—135° (Found : C, 52·3; H, 6·8. $C_{17}H_{26}O_{10}$ requires C, 52·3; H, 6·7%). $[\alpha]_D$ − 23·4° in alcohol. The tetra-acetyl glucoside is sparingly soluble in water and only moderately easily soluble in cold ethyl alcohol.

With Benzyl Alcohol. Formation of 3 : 4 : 6-*Triacetyl* β-*Benzyl-glucoside.*—3 : 4 : 6-Triacetyl glucose 1 : 2-anhydride was heated at 100° with benzyl alcohol. After 2 hours, the excess of alcohol was removed under diminished pressure at 100°. The residual 3 : 4 : 6-triacetyl benzylglucoside, after being washed with light petroleum, was converted into β-benzylglucoside, m. p. 119°, $[\alpha]_D$ − 49°, by the action of alcoholic ammonia.

Acetylation of the benzylglucoside yielded 2 : 3 : 4 : 6-tetra-acetyl β-benzylglucoside, m. p. 98—99°, $[\alpha]_D$ − 44° in alcohol (Found : C, 57·5; H, 6·0. Calc. : C, 57·7; H, 6·0%). Fischer and Helferich (*Annalen*, 1911, **383**, 68) give m. p. 96—101° (corr.), $[\alpha]_D$ − 48°.

With Menthol. Formation of 3 : 4 : 6-*Triacetyl* β-*Menthylglucoside.*—The anhydro-compound was heated with an equal weight of benzene and three times its weight of menthol at 90—100° for 30 hours. The excess of menthol was removed under diminished pressure at 100°, leaving a residue of 3 : 4 : 6-triacetyl menthylglucoside. A

filtered solution in ether, on treatment with light petroleum, gave triacetyl menthylglucoside, which was crystallised from carbon tetrachloride or alcohol; m. p. 144° after sintering at 141°, $[\alpha]_D$ − 10·6° in benzene. β-Menthylglucoside was obtained conveniently from the triacetyl glucoside by the action of aqueous-alcoholic potassium hydroxide. Fischer and Bergmann (*Ber.*, 1917, **50**, 711) describe a triacetyl β-menthylglucoside having m. p. 143—146°, and $[\alpha]_D$ − 12·6° in benzene.

With Phenol. Formation of **3 : 4 : 6**-*Triacetyl α-Phenylglucoside.*— As phenol and the anhydro-compound in benzene reacted only slowly at room temperature, a mixture of phenol with approximately one-third of its weight of 3 : 4 : 6-triacetyl glucose anhydride was maintained at 100° for about 20 hours. After removal of unused phenol at 100° under diminished pressure, the residue of triacetyl phenylglucoside was acetylated in pyridine solution. Crude 2 : 3 : 4 : 6-tetra-acetyl α-phenylglucoside, m. p. 109—110°, resulted, and by one crystallisation from alcohol, the melting point was raised to 112°. This value was not altered by further recrystallisation or by admixture with a genuine specimen of tetra-acetyl α-phenylglucoside. $[\alpha]_D$ + 162° in alcohol (c = 1·0). Fischer and Mechel (*loc. cit.*) give m. p. 115° (corr.), $[\alpha]_D$ + 164·9° in benzene.

A solution of tetra-acetyl phenylglucoside in twenty times its weight of dry alcohol was saturated with dry ammonia at room temperature and then kept for 15 hours. After removal of the alcohol at 30° in a partial vacuum, and thorough washing with dry ether to remove acetamide, the residue solidified, m. p. 168—169°. Crystallisation from ethyl acetate gave *α-phenylglucoside hydrate*, m. p. 155—160°, $[\alpha]_D$ + 157° in alcohol (Found : C, 52·8; H, 6·7. $C_{12}H_{16}O_6,H_2O$ requires C, 52·5; H, 6·6%).

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