Carbohydrate Research
Elsevier Publishing Company, Amsterdam
Printed in Belgium

Note

Treatment of 1,3,4,6-tetra-*O*-acetyl-α-D-galactopyranose and -α-D-glucopyranose with methyl sulphoxide–acetic anhydride; formation of kojic acid diacetate

G. J. F. CHITTENDEN

Microbiological Chemistry Research Laboratory, Department of Organic Chemistry, The University, Newcastle upon Tyne NE1 7RU (Great Britain)

(Received April 18th, 1969)

During the oxidation of some D-galactopyranose derivatives with methyl sulphoxide–acetic anhydride[1,2], an attempt was made to prepare 1,3,4,6-tetra-*O*-acetyl-D-*lyxo*-hexopyranosulose (**1**) from 1,3,4,6-tetra-*O*-acetyl-α-D-galactopyranose (**2**). The required product was not formed, instead a high yield of 5-hydroxy-2-(hydroxymethyl)pyran-4-one diacetate (kojic acid diacetate) (**3**) was given. The same product was formed by similar treatment of 1,3,4,6-tetra-*O*-acetyl-α-D-glucopyranose (**4**). The formation of kojic acid dibenzoate (**5**) from 1-*O*-acetyl-3,4,6-tri-*O*-benzoyl-D-*arabino*-hexopyranosulose (**6**) was also investigated, in an attempt to clarify the mechanism of formation of kojic acid derivatives from monosaccharides.

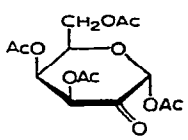
Although the true biochemical significance of kojic acid (**7**) has not been fully elucidated, its formation represents the simplest conversion of sugars into γ-pyrones. These are of interest, since many complex pyrones *e.g.*, flavones, flavanols, and furochromones, are widely distributed in the plant kingdom. The chemical synthesis of kojic acid derivatives from sugars has been described a number of times[3]. Since the γ-pyrone structure does not contain any asymmetric carbon atoms, its formation is independent of the configuration of the original sugar. This is demonstrated below, and had earlier been shown by chemical synthesis from D-glucose[4] and D-galactose[5].

Treatment of the tetra-acetate **2** with methyl sulphoxide–acetic anhydride at room temperature gave kojic acid diacetate (**3**) in 84% yield. The infrared spectrum of the product exhibited three carbonyl bands, and that occurring at 1666 cm^{-1} (pyrone carbonyl group) is characteristic of α,β,α′,β′ unsaturated, six-membered, ring ketones[6]. Those at 1752 and 1772 cm^{-1} are attributed to a normal saturated ester group and to a vinylic ester, respectively. It is known that vinylic esters show a marked enhancement of the carbonyl frequency, regardless of whether the double bond is normal or part of an aromatic ring system[7]. Definite phenolic character has been attributed to the C-5 hydroxyl group in kojic acid [8].

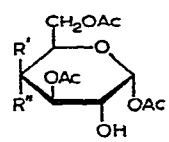
Deacetylation of compound **3** in methanolic ammonia at 0° gave kojic acid (**7**), further characterized as the known[10] phenylosazone.

Treatment of 1,3,4,6-tetra-*O*-acetyl-α-D-glucopyranose (**4**) under the same

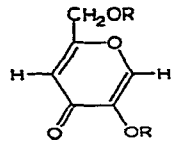
conditions described for the galactose compound **2** gave kojic acid diacetate (**3**) in 81% yield.



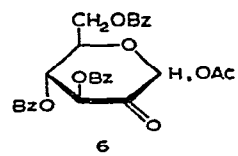
1



2 R′=OAc, R″=H
4 R′=H, R″=OAc



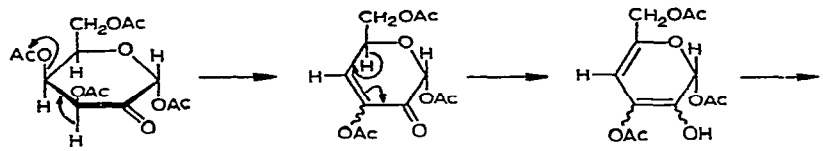
3 R = Ac
5 R = Bz
7 R = H



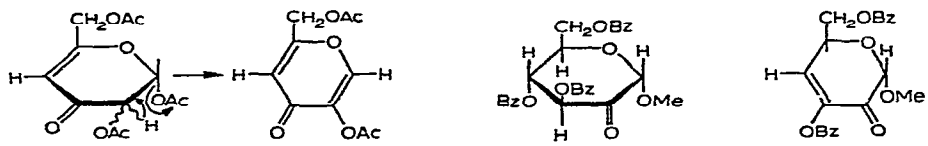
6

Assuming that the ketone **1** is initially produced by oxidation of the C-2 hydroxyl group in the acetate **2**, the formation of kojic acid diacetate (**3**) may be explained as follows. β-Elimination of the acetate group on C-4 would lead to the enone **8**, which can enolise to give the conjugated diene-diol monoacetate **9**. Intramolecular migration of an acetyl group from C-3 to C-2, to give the isomer **10**, would then facilitate a second β-elimination, giving rise to the product **3**, stabilized by resonance. The migration of acyl groups in partially acylated sugars[11–13] and similar compounds[14] is well established. The formation of diacetate **3** from the tetra-acetate **4** would proceed in the same way.

It has also been noted[15] that certain glycopyranosiduloses undergo facile eliminations to give stable enones. Attempted purification of the hexopyranosidulose **11** (obtained by the oxidation of the corresponding glycoside with ruthenium tetroxide) on silica gel led to the enone **12**, which is structurally very similar to the proposed enone intermediate **8**, and was considered to be formed from the ketone **11** by an elimination reaction.



1 **8** **9**



10 **3** **11** **12**

The above route agrees with an earlier suggestion[16]. It can also explain an alternative mechanism[9] which assumed that a proton acceptor is the essential factor in the conversion of osone hydrates into kojic acid derivatives. The formation[16,17] of tetra-acetoxybenzene from inosone pentacetates could be explained in an analogous manner.

Previously[18], it had been shown that treatment of 1-*O*-acetyl-3,4,6-tri-*O*-benzoyl-D-*arabino*-hexopyranosulose (**6**) with pyridine failed to yield kojic acid dibenzoate (**5**). Treatment of **6** with methyl sulphoxide–acetic anhydride has now given the dibenzoate **5** in 64% yield. Its formation under these conditions, with the appearance of a benzoyl group at C-5 in the γ-pyrone ring, adds support for the intramolecular migration step in the proposed mechanism. The same dibenzoate **5** was formed when the ketone **6** was treated with acetic anhydride in pyridine. It is thought probable that acetate ions may be effective in promoting the eliminations described above. The formation of acetate ions has been proposed from the reaction of methyl sulphoxide with acetic anhydride[1,2].

The reactions described provide an easy route to kojic acid derivatives from hexoses. Since free tautomeric equilibrium between the groups on C-2 and C-3 is possible in ketone **1**, the results indicate that methyl sulphoxide–acetic anhydride may be unsuitable for the preparation of hexopyranos-3-uloses from 1,2,4,6-tetra-*O*-acylhexopyranoses.

EXPERIMENTAL

Methyl sulphoxide was redistilled from calcium hydride under diminished pressure. T.l.c. was performed on silica gel (Kieselgel G); detection was by iodine vapour. I.r. spectra were determined for KBr discs.

*Treatment of 1,3,4,6-tetra-*O*-acetyl-α-*D*-galactopyranose* (**2**) *with methyl sulphoxide–acetic anhydride.* — The tetra-acetate[19] (6.96 g) in methyl sulphoxide (60 ml) was treated with acetic anhydride (40 ml) and kept for 48 h at 20°. Removal of excess reagents and by-products at 70–75°/0.5 mm gave an oil, which crystallized spontaneously on cooling. Recrystallization from isopropyl ether–dichloromethane gave 5-hydroxy-2-(hydroxymethyl)pyran-4-one diacetate (**3**, 3.8 g, 84%), m.p. 101–102°; lit.[9] m.p. 103°; λ_{max}^{MeOH} 255 μm, ε_{max} 11,000 (*cf.* data in ref. 9) [Found: mol. wt. m/e (M^+) 226·0481. $C_{10}H_{10}O_6$ calc.: 226·0478]. The m.p. was not depressed on admixture with the diacetate described below, and the i.r. spectra of the compounds were identical.

*Treatment of 1,3,4,6-tetra-*O*-acetyl-α-*D*-glucopyranose with methyl sulphoxide–acetic anhydride.* — Treatment of the tetra-acetate[19] (6.96 g) in the same way as described above gave the diacetate **3** (3.66 g, 81%), m.p. 100–102°.

Acetylation of kojic acid (**7**). Kojic acid (2 g) suspended in dry pyridine (5 ml) was treated with acetic anhydride (6 ml) and kept for 2 days at room temperature. Diisopropyl ether (25 ml) was added to give a crystalline precipitate which was kept at 0° overnight. The product was collected by filtration, washed well with ice-cold ether, and recrystallized from diisopropyl ether–dichloromethane to give kojic acid diacetate (**3**, 2.3 g, 73%), m.p. 101–103°.

Deacetylation of kojic acid diacetate (**3**). — The diacetate **3** (2 g, prepared from **2**) was treated for 18 h at 0° with methanol (15 ml) previously saturated with anhydrous ammonia. The excess ammonia was removed by aeration, and the solution was concentrated. Recrystallization of the residue from ethyl acetate–methanol gave kojic acid (**7**) as needles (61%), m.p. 150–152°; lit.[20] m.p. 152–153°.

Treatment of a portion of the product with phenylhydrazine in aqueous acetic acid gave the known phenylosazone, m.p. 169–170° (from aqueous ethanol); lit.[10] m.p. 169.5–171°.

Treatment of 1-O-acetyl-3,4,6-tri-O-benzoyl-D-arabino-hexopyranosulose[18] (6). — (*a*) *With methyl sulphoxide–acetic anhydride.* Compound **6** (1.5 g) in methyl sulphoxide (10 ml) was treated with acetic anhydride (7 ml) as described above. Recrystallization of the product from diisopropyl ether–dichloromethane gave kojic acid dibenzoate (**5**, 0.63 g, 64%), m.p. 134–136°; lit.[4] m.p. 136°.

(*b*) *With acetic anhydride–pyridine.* Compound **6** (1 g) in acetic anhydride (10 ml) and pyridine (10 ml) was kept for 14 h at 60°. Evaporation *in vacuo* at 45° gave the dibenzoate (**5**, 0.7 g, 61%), m.p. 135–136°.

ACKNOWLEDGMENTS

The author thanks Drs. J. G. Buchanan and N. A. Hughes for helpful discussion.

REFERENCES

1 J. D. Albright and L. Goldman, *J. Amer. Chem. Soc.*, 87 (1965) 4214.
2 J. D. Albright and L. Goldman, *J. Amer. Chem. Soc.*, 89 (1967) 2416.
3 A. Beélik, *Advan. Carbohyd. Chem.*, 11 (1956) 145, for complete review.
4 K. Maurer, *Ber.*, 63 (1930) 25.
5 K. Maurer and A. Müller, *Ber.*, 63 (1930) 2069.
6 R. N. Jones, P. Humphries, and K. Dobriner, *J. Amer. Chem. Soc.*, 72 (1950) 956.
7 E. J. Hartwell, R. E. Richards, and H. W. Thompson, *J. Chem. Soc.*, (1948) 1436.
8 T. Soda, T. Katura, and O. Yoda, *J. Chem. Soc. Japan*, 61 (1940) 1227.
9 M. Stacey and L. M. Turton, *J. Chem. Soc.*, (1946) 661.
10 W. M. Corbett, *J. Chem. Soc.*, (1959) 3213.
11 E. Fischer, *Ber.*, 53 (1920) 1621.
12 J. M. Sugihara, *Advan. Carbohyd. Chem.*, 8 (1953) 1.
13 E. J. Bourne, A. J. Huggard, and J. C. Tatlow, *J. Chem. Soc.*, (1953) 735.
14 S. J. Angyal, P. T. Gilham, and G. J. H. Melrose, *J. Chem. Soc.*, (1965) 5252.
15 P. J. Beynon, P. M. Collins, P. T. Doganges, and W. G. Overend, *J. Chem. Soc.* (*C*), (1966) 1131.
16 H. S. Isbell, *J. Res. Nat. Bur. Stand.*, 32 (1944) 45; *cf.* A. J. Fatiadi, *Chem. Commun.* (1967) 441.
17 T. Posternak, *Helv. Chim. Acta*, 24 (1941) 1045.
18 K. Maurer and W. Petsch, *Ber.*, 66 (1933) 995.
19 B. Helferich and J. Zirner, *Ber.*, 95 (1962) 2604.
20 D. Barnard and F. Challenger, *J. Chem. Soc.*, (1949) 110.