Note

Oxidation of alkyl glycosides

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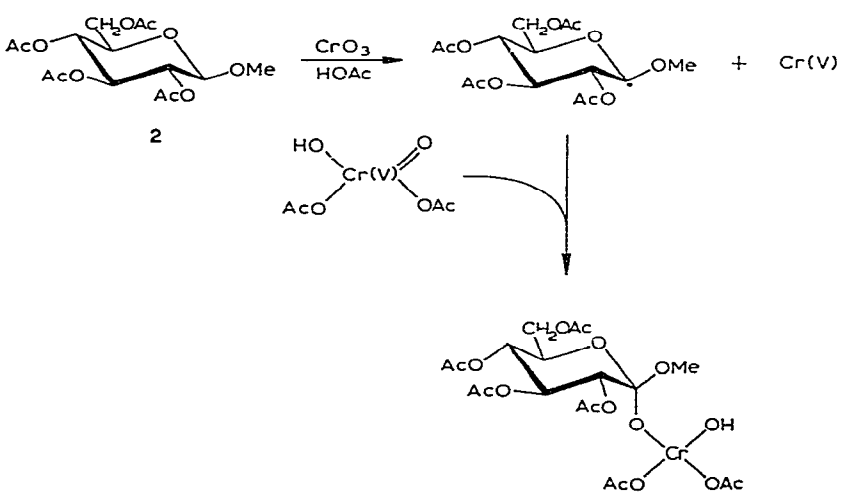
(Received August 8th, 1970; accepted August 21st, 1970)

Because of the observation that methyl ethers can be oxidized to formic esters by chromium trioxide[1], Angyal and James[2] applied this procedure to the oxidation of methyl ethers of carbohydrates, and we have used the method for the preparation of 1-*O*-acylhexoses[3]. The aforementioned authors[4] showed that methyl tetra-*O*-acetyl-α-D-glucopyranoside (**1**) and methyl tetra-*O*-acetyl-β-D-glucopyranoside (**2**) behave differently when oxidized with chromium trioxide in glacial acetic acid: compound **1** reacts slowly to give tetra-*O*-acetyl-α-D-glucopyranosyl formate (**3**), whereas **2** reacts rapidly to yield methyl tetra-*O*-acetyl-D-*xylo*-5-hexulosonate (**4**). Publication of these results prompts us to report some of our own observations.

Oxidations of this type probably take place by a free-radical mechanism[5], the initial step most likely being hydrogen abstraction from the alkyl group next to an oxygen atom, as the resulting radical is stabilized by orbital overlap with that oxygen atom. It is not unreasonable to assume that chromium trioxide would seek out C-1–H as that point in the molecule where hydrogen abstraction would be most facile. The resulting radical, which may not be completely free, should rapidly react with Cr(V) to yield an intermediate ester[6]:



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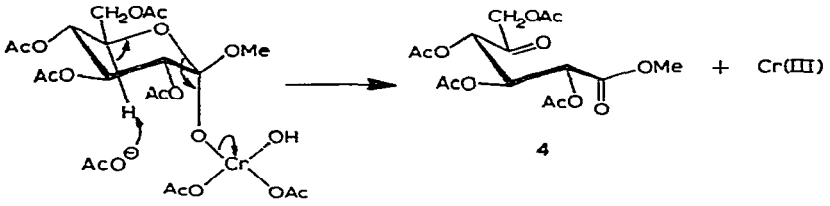
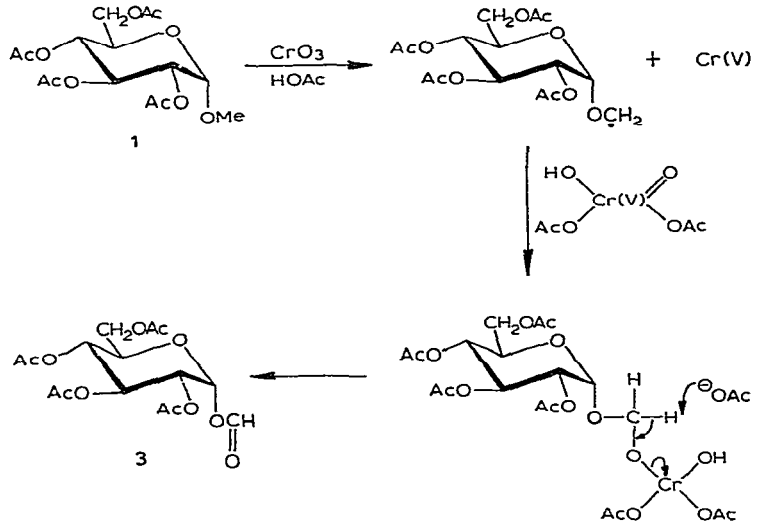
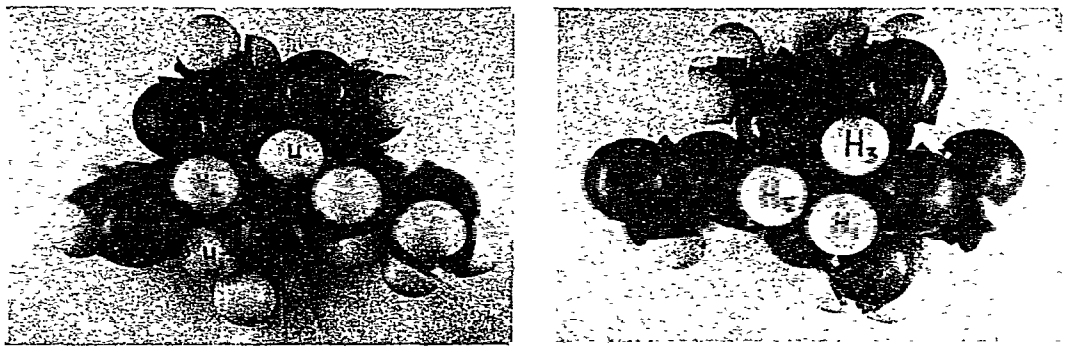
This intermediate could then dissociate by cleavage of the chromium–oxygen bond[7]:



This mechanism would readily explain the formation of **4** from **2**. However, in **1**, abstraction of H-1 seems not to occur, as this, too, would lead to the formation of **4**, which is not in accord with the experimental facts[4]. Inspection of models of **1** and **2** revealed that, in **1**, H-1 is not so sterically accessible as H-1 in **2** (see Fig. 1), and this difference could possibly account for the behavior of **2** towards chromium trioxide. The 1-*O*-methyl group is, of course, available for oxidation, albeit to a lesser degree than H-1 were not the latter sterically hindered. A possible pathway for the formation of **3** from **1** can be envisaged as follows:



All alkyl β-D-glucopyranosides studied do not, however, yield a D-*xylo*-5-hexulosonate upon oxidation. We have found that oxidation of benzyl tetra-*O*-acetyl-β-D-glucopyranoside (**5**) with chromium trioxide–acetic acid does *not* lead to benzyl tetra-*O*-acetyl-D-*xylo*-5-hexulosonate. Instead, we readily obtained tetra-*O*-acetyl-β-D-glucopyranosyl benzoate in 52% yield. It appears that the pathway mainly followed depends on the difference in the rate of hydrogen abstraction, either from C-1, or from the aglycon carbon atom adjacent to the glycosidic oxygen atom. The benzylic C–H bond is very susceptible to oxidation, because the C_6H_5CH– radical initially formed is stabilized by resonance. Thus, attack at the benzyl group of **5** is much faster than the homolysis of the C-1–H bond in the D-glucosyl group, a reaction which is,



1 2

Fig. 1. Models of methyl tetra-*O*-acetyl-α-D-glucopyranoside (**1**) and methyl tetra-*O*-acetyl-β-D-glucopyranoside (**2**).

undoubtedly, competing. The *O*-benzylic C–H bond would also have to be much more susceptible to homolysis than the C–H bond of an *O*-methyl group in order to compete favorably with the axially attached hydrogen atom on C-1, as, otherwise, oxidation of **5** would have yielded benzyl tetra-*O*-acetyl-D-*xylo*-5-hexulosonate, just as oxidation of **2** yields the *xylo*-5-hexulosonate **4**.

In order to test this hypothesis, we oxidized benzyl methyl ether with chromic anhydride in acetic acid. The two possible products, namely, methyl benzoate and benzyl formate, have boiling points lying close together (200 and 203°, respectively, at 760 torr). The reaction mixture was distilled, a single fraction being collected from 165° to the end of distillation. Analysis of the distillate by mass spectroscopy showed the ratio of methyl benzoate to benzyl formate to be 47:3.

EXPERIMENTAL

2,3,4,6-Tetra-O-acetyl-β-D-glucosyl benzoate. — To a solution of benzyl 2,3,4,6-tetra-*O*-acetyl-β-D-glucoside (1.0 g) in glacial acetic acid was added dried chromium trioxide (2.3 g), and the solution was stirred for 40 min at room temperature. Cold chloroform (300 ml) was added, and the solution was successively washed with ice–water (twice), and saturated aqueous sodium hydrogen carbonate solution. The organic layer was dried (magnesium sulfate), decolorized (charcoal), and evaporated *in vacuo* to a syrup; this was dissolved in ether, and hexane was added, affording crystalline 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl benzoate (530 mg, 52%); m.p. 140–141° (uncorrected) either alone or in admixture with authentic material; $[\alpha]_D^{20}$ −26.1° (*c* 2.0, chloroform). The authentic compound[8] had $[\alpha]_D^{20}$ −26.2°. The i.r. spectrum of the product was identical with that of the authentic compound.

Methyl benzoate. — Predried and distilled benzyl methyl ether (3 ml) was added in three 1-ml portions to a stirred suspension of chromium trioxide (6 g) in glacial

acetic acid (35 ml) at room temperature. Stirring was continued overnight, and the mixture was processed as in the previous experiment. The resulting oil showed an absorption band in the i.r. spectrum at 1710 cm^{-1} (C = O stretching vibration), and a band at 1260 cm^{-1} suggesting the presence of the benzoic ester rather than the formic ester. No band characteristic of acyl anhydrides (1740–1850 cm^{-1}) was observed. Part of the oil was dissolved in methanol and treated with 1M aqueous lithium hydroxide (3 ml). The solution was boiled for 1 h under reflux, cooled, and deionized with Amberlite IR-120 (H^+) cation-exchange resin. From this solution was isolated crystalline benzoic acid, m.p. and mixed m.p. 119–120°. Part of the syrup was distilled, and the single fraction collected was analyzed by mass spectroscopy. The spectrum showed a peak at *m/e* 105 (benzoate) accounting for 94%, and one at *m/e* 107 (formate) accounting for 6%, of the mixture.

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