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THE CONVERSION OF D-GLUCONO-1,5-LACTONE INTO AN α-PYRONE DERIVATIVE

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ABSTRACT

Treatment of D-glucono-1,5-lactone (**3**) with excess of acetic anhydride in anhydrous pyridine at room temperature afforded the tetra-acetate and 2,4,6-tri-*O*-acetyl-3-deoxy-D-*erythro*-hex-2-enono-1,5-lactone (**1**). On prolonged reaction or at 80°, 3-acetoxy-6-acetoxymethylpyran-2-one (**5**) was the unexpected main product. The mechanistic implications of the conversion of **1** → **5** are discussed.

INTRODUCTION

In connection with studies of the physical and chemical properties of polyhydroxylactone ring systems, we sought to prepare 2,4,6-tri-*O*-acetyl-3-deoxy-D-*erythro*-hex-2-enono-1,5-lactone (**1**). Generation of **1** (81%) from 2,3,4,6-tetra-*O*-acetyl-D-glucopyranose (**2**) has been accomplished by the oxidation of **2** with methyl sulfoxide–sulfur trioxide–pyridine–triethylamine[1,2]. However, it appeared that the conversion of D-glucono-1,5-lactone (**3**) into **1** might be effected directly under acetylating conditions since, under benzoylating conditions, **3** affords[3] 2,4,6-tri-*O*-benzoyl-3-deoxy-D-*erythro*-hex-2-enono-1,5-lactone (**4**, 97%). Under acetylating conditions, **3** was converted into **1** in moderate yield, but a significant amount of an unexpected, diunsaturated product **5** was also produced, on which we now report.

RESULTS AND DISCUSSION

Treatment (room temperature, 30 h) of D-glucono-1,5-lactone (**3**) with a large excess of acetic anhydride in anhydrous pyridine afforded a mixture of **1** and **5** in the ratio of 5.5:26 (determined by p.m.r. spectroscopy), from which the pure compounds (**1**, 16%; **5**, 75%) were isolated by column chromatography on silica gel as colorless and yellow syrups, respectively. Treatment of **3** with a large excess of acetic anhydride in anhydrous pyridine at 80° for 1 h afforded only **5** (92%).

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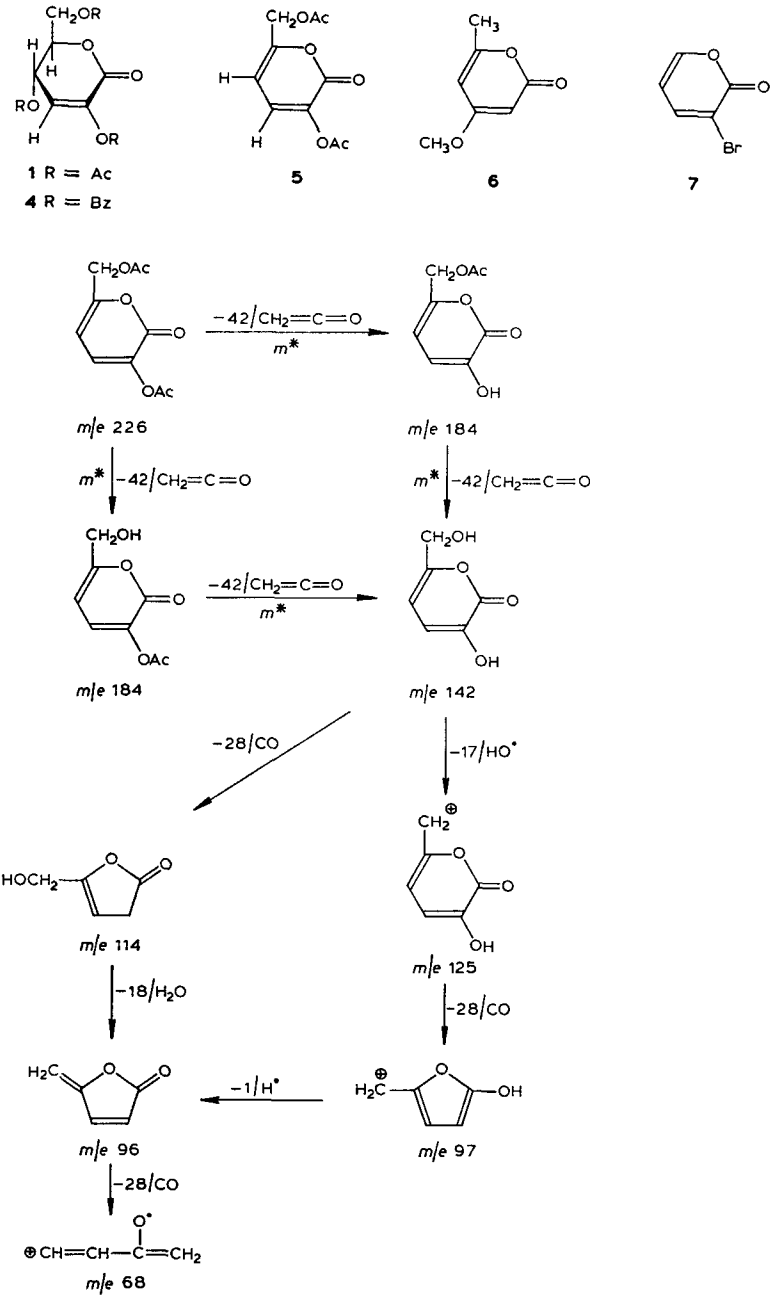


Scheme 1. Mass-spectral fragmentation pattern of 3-acetoxy-6-acetoxymethylpyran-2-one (5)

On the basis of elemental analysis, **5** was assigned the molecular formula $C_{10}H_{10}O_6$, and on the basis of i.r., u.v., and p.m.r. spectral data, the structure 3-

acetoxy-6-acetoxymethylpyran-2-one (**5**). The u.v. spectrum of **5** exhibited an absorption maximum (292 nm, ε 5761) consistent with that expected[4,5] (λ_{max} 300, ε 5450) for the α-pyrone chromophore, and similar to those of the authentic α-pyrones **6** (λ_{max} 280, ε 5879)[6,7] and **7** (λ_{max} 300, ε 5750)[8]. The i.r. spectrum of **5** showed bands at 1780 and 1760 cm^{-1}, attributed to enol acetate and saturated acetate carbonyl groups, respectively, and at 1755 and 1670 cm^{-1}, indicative of the highly conjugated carbonyl system of α-pyrones[6,8].

The 100-MHz p.m.r. spectrum ($CDCl_3$) of **5** integrated for 10 protons and contained the following signals: τ 7.92 (s, 3 H, Ac), 7.75 (s, 3 H, Ac), 5.72 (s, 2 H, CH_2), and 3.75 and 2.91 (2 d, 2 H, *J* 7.3 Hz, 2 C=CH) characteristic of 3,6-disubstituted α-pyrone derivatives[9,10].

The mass spectrum of **5** (Scheme 1) contains a base peak at *m/e* 43 (100%, Ac^+), and peaks involving sequential elimination of ketene from the molecular ion at *m/e* 226 (7%) to produce the ions at *m/e* 184 [32%, metastable at *m/e* 149.8 (calc. 149.8)] and 142 [40%, metastable at *m/e* 109.6 (calc. 109.6)]. Thus, the enol acetate and allylic acetate groups of **5** tend to be eliminated as ketene during fragmentation in the mass spectrometer[11].

The ion at *m/e* 114 (3%) corresponds to the loss of carbon monoxide from the ion at *m/e* 142, and the prominent ion at *m/e* 96 (15%) corresponds to the further elimination of water from the ion at *m/e* 114. Alternatively, the fragmentation sequence *m/e* 142 (40%) → 125 (4%) → 97 (6%) → 96 (15%) could also occur, as shown in Scheme 1. Elimination of carbon monoxide from the ion at *m/e* 96 gives the ion at *m/e* 68 (9%). Similar mass-spectral results have been reported for 2-pyrone[12] and 2-furanone[13] structures.

Table I shows some effects of time and reaction conditions upon the products formed from the acetylation of D-glucono-1,5-lactone (**3**) at room temperature. The products involved the consecutive reactions: **3** → 2,3,4,6-tetra-*O*-acetyl-D-glucono-1,5-lactone (**8**) → **1** → **5**. The conversions **8** → **1** → **5** could be conveniently monitored by p.m.r. spectroscopy (see Experimental), and the results in Table I indicate clearly that the entire process is accelerated by the presence of acid.

The formation of **5** from **1** takes place very slowly at room temperature in the presence of anhydrous pyridine, and does not occur in the presence of acid only. In anhydrous pyridine, **5** was formed much faster from **8** than from **1**. Presumably, the acetic acid liberated in the conversion **8** → **1** catalyzed the conversion **1** → **5**. Thus, the requirement of both an acid and a base is mechanistically significant in the transformation of **1** → **5**.

The mechanism of the elimination of acetic acid from **1** is best rationalized as a concerted process, involving the formation of carbonium-ion character at C-4 in the transition state. The alkyl–oxygen cleavage of AcO-4 should be facilitated by an acid catalyst, since protonation, as shown in Scheme 2, would result in the formation of carbonium-ion character at C-4 which would be stabilized by allylic resonance. Simultaneous elimination of H-5 results in the stable α-pyrone structure **5**.

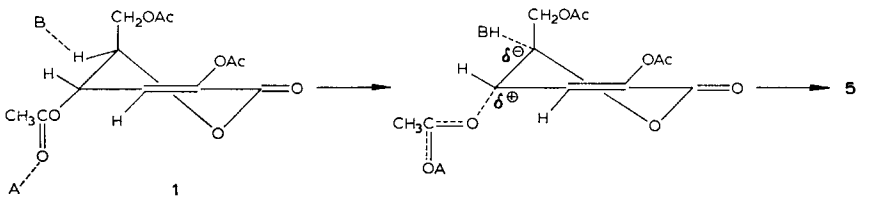
Further confirmation of the mechanism was obtained by conducting the reaction

TABLE I

COMPOSITION OF THE REACTION PRODUCTS FROM THE TREATMENT OF CARBOHYDRATE LACTONES WITH VARIOUS REAGENTS

Starting material	*Reaction conditions*[b]	*Reaction time (h)*	*Products (%)*[a]		
			2,3,4,6-Tetra-O-acetyl-D-glucono-1,5-lactone (**8**)	*2,4,6-Tri-O-acetyl-3-deoxy-D-erythro-hex-2-enono-1,5-lactone* (**1**)	*3-Acetoxy-6-(acetoxymethyl)pyran-2-one* (**5**)
3	Acetic anhydride–pyridine (1 : 1)	0.1	100		
		1.0	70.6	29.4	
		1.0	70.4	29.6	
		3.0	73.7	26.3	
		3.0	70.0	30.0	
		16.0	22.7	49.3	28.0
		16.0	33.8	47.9	18.3
		24.0		27.3	72.7
		30.0		17.5	82.5
8	Anhydrous pyridine	16.0	66.7	28.2	5.1
		30.5		81.8	18.2
1		29.0		90.2	9.8
8	Glacial acetic acid	29.0	100		
1		29.0		100	
8	Acetic anhydride–pyridine–D_2O	20.0		31.3	68.7

[a]Expressed as % of the weight of the reaction product. [b]The reactions were conducted at room temperature. For determination of reaction progress, see Experimental.



Scheme 2. Mechanism for the conversion of 2,4,6-tri-O-acetyl-3-deoxy-D-*erythro*-hex-2-enono-1,5-lactone (**1**) into 3-acetoxy-6-acetoxymethylpyran-2-one (**5**)

in the presence of deuterium oxide. When **8** was treated with acetic anhydride–pyridine–deuterium oxide, **1** and **5** were obtained after 20 h at room temperature, but contained no deuterium (see Table I). Evidently, H-4 of **1** is not abstracted by base, so that there is no deuterium incorporation. The absence of deuterium incorporation in **5** indicates that epimerization of the AcO-4 group did not occur prior to its elimination from **1**. Thus, the transformation **1** → **5** involves a *syn*-elimination of acetic acid.

It is of interest to contrast the reactions reported here with elimination reactions reported for other D-aldono-1,5-lactones. Treatment of 4-*O*-benzyl-D-*glycero*-D-*gulo*-heptono-1,5-lactone (**9**) with acetic anhydride in pyridine gave[14] only the corresponding α,β-unsaturated 1,5-lactone derivative (**10**). The non-formation of a di-unsaturated by-product is undoubtedly due to the presence of a poor leaving group at C-4. Similarly, the α,β-unsaturated lactone derivative **4** obtained (97%) from D-glucono-1,5-lactone (**3**) under benzoylating conditions[3] may be attributed to the fact that the benzoyloxy function is a poor leaving group. On the other hand, treatment of 2-amino-2-deoxy-D-gluconic acid with acetic anhydride and sodium acetate gave an optically inactive product[15] reported to be 3-acetamido-6-acetoxymethylpyran-2-one[16]. Thus, the facile formation of **5** from **3** under acetylating conditions may be attributed to the greater ease of displacement of AcO-4 in **1**, as compared to BzO-4 in **4** or BzlO-4 in **10**.

The fortuitous observation that D-glucono-1,5-lactone (**3**) could be efficiently converted into 3-acetoxy-6-acetoxymethylpyran-2-one (**5**) could simplify the task of planning synthetic strategems for preparing α-pyrone compounds.

EXPERIMENTAL

General methods. — U.v. spectra were recorded on a Cary 15 spectrophotometer, and i.r. spectra were recorded with a Beckman IR-20A-X spectrophotometer. P.m.r. spectra were recorded for 10% solutions (internal Me_4Si) with a Varian HA 100 spectrometer; chemical shifts are reported on the τ scale and coupling constants (*J*) in Hz. Assignments were substantiated by double-irradiation experiments. Mass spectra were obtained on an AEI MS-1201 spectrometer with direct sample introduction; data are in the form *m/e* (percent base-peak intensity).

Column chromatography was performed with silica gel (Merck, 0.063–0.200 mm, 70–230 mesh, ASTM) with ethyl acetate–light petroleum (b.p. 60–71°) (4:1).

Organic solvents were dried over anhydrous magnesium sulfate, and solutions were concentrated at reduced pressure on a rotary evaporator at <60° (bath). Anhydrous pyridine was prepared by distillation of reagent-grade pyridine from phosphorus pentoxide followed by storage over molecular sieves.

Reaction of D-*glucono-1,5-lactone* (**3**) *with excess of acetic anhydride in anhydrous pyridine.* — D-Glucono-1,5-lactone (**3**, 3 g) was added to a stirred solution of acetic anhydride (10 ml) and anhydrous pyridine (10 ml). Stirring was then continued in a stoppered flask at room temperature for 30 h. The mixture was poured onto crushed ice (200 ml), and extracted with chloroform (2 × 100 ml), and the combined organic layers were washed with ice-cold water (2 × 50 ml), dried, and concentrated. Toluene (2 × 5 ml) was evaporated from the syrup to remove the last traces of pyridine. A solution of the crude product in benzene was treated with activated carbon, filtered, and concentrated to give a light-yellow syrup (3.6 g) which p.m.r. spectroscopy indicated to be a mixture of **1** and **5** in the ratio of 5.5:26. Elution of the mixture from silica gel (125 g) with ethyl acetate–light petroleum (4:1), followed by concen-

tration of the fractions containing the faster-moving component, gave 2,4,6-tri-*O*-acetyl-3-deoxy-D-*erythro*-hex-2-enono-1,5-lactone (**1**) as a colorless syrup (0.76 g, 16%), $[\alpha]_D$ +108.9° (*c* 2, chloroform); lit.[2] $[\alpha]_D$ + 108°. P.m.r. data ($CDCl_3$): τ 3.56 (d, 1 H, $J_{3,4}$ 4.6 Hz, H-3), 4.39 (t, 1 H, $J_{3,4}$ 4.6, $J_{4,5}$ 5.2 Hz, H-4), 5.25 (m, 1 H, H-5), 5.62 (dd, 1 H, $J_{5,6}$ 4.4, $J_{6,6'}$ 12.5 Hz, H-6), 5.70 (dd, 1 H, $J_{5,6'}$ 4.7, $J_{6,6'}$ 12.5 Hz, H-6'), and 7.91–7.94 (9 H, 3 AcO). Mass spectrum: *m/e* 286 (M^+, 0.5%), 244 (20), 226 (13), 202 (16), 201 (11), 184 (63), 145 (5), 142 (100), 125 (55), 103 (21), 97 (87), 96 (26), 78 (81), and 43 (100).

Fractions containing the slower-moving component were combined and concentrated to give 3-acetoxy-6-acetoxymethylpyran-2-one (**5**) as a yellow syrup (2.84 g, 75%), $[\alpha]_D$ 0°, λ_{max}^{MeOH} 292 nm (ε 5761), $\nu_{max}^{CCl_4}$ 1780, 1760, 1755, and 1670 cm^{-1}. P.m.r. data ($CDCl_3$): τ 2.91 (d, 1 H, $J_{3,4}$ 7.3 Hz, H-3), 3.75 (d, 1 H, $J_{3,4}$ 7.3 Hz, H-4), 5.17 (s, 2 H, H-6), 7.75 (s, 3 H, enol AcO), and 7.92 (s, 3 H, AcO). Mass spectrum: *m/e* 226 (M^+, 7%), 184 (32), 142 (40), 125 (4), 114 (3), 113 (4), 97 (6), 96 (15), 68 (9), and 43 (100).

Anal. Calc. for $C_{10}H_{10}O_6$: C, 53.09; H, 4.43. Found: C, 52.84; H, 4.61.

When D-glucono-1,5-lactone (**3**, 3 g) was stirred with acetic anhydride (10 ml) and anhydrous pyridine (10 ml) at 80° for 1 h, and the mixture worked up as described above, **5** was obtained as a yellow syrup (3.52 g, 92%).

Determination of reaction progress. — Monitoring of the reaction on treatment of **1**, **3**, and **8** with various reagents was performed by p.m.r. spectroscopy. The products **1**, **5**, and **8** were readily distinguished and quantified on the basis of the doublets for H-2 in **8**, H-3 in **1**, and H-4 in **5**, which are well separated from other resonances. A solution of **1**, **3**, or **8** in the reaction solution (see Table I) was kept in a stoppered flask at room temperature for the required time, and then partitioned between ice-cold water and chloroform. The organic layer was washed with ice-cold water, dried, and concentrated with codistillation of toluene, and a solution of the residue in benzene was treated with activated carbon, filtered, and concentrated. A 10% solution of the residue in $CDCl_3$ was then analyzed by p.m.r. spectroscopy.

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