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PREPARATION AND SOME REACTIONS OF BENZOYLATED 4-DEOXY-D-*glycero*-HEX-3-ENOS-2-ULOSES*

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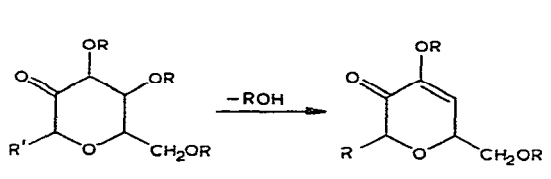
ABSTRACT

Starting from 1,3,6-tri-*O*-benzoyl-4-deoxy-α-D-*glycero*-hex-3-enos-2-ulose (**6**), for which an efficient preparation (65%) from 2,3,4,6-tetra-*O*-benzoyl-2-hydroxy-glucal (**1**) has been elaborated, a study of preparatively useful reactions is reported (*i*) synthesis of the α-haloenolones **7** and **8** by treatment with hydrogen halide–acetic acid, and their conversion, by solvolysis with various alcohols, into β-D-glycenosid-uloses (**9**, **10**, and **13**), (*ii*) formation of acetals, phenylhydrazones (at room temperature), and osazones, and (*iii*) transformation into the γ-pyrone system with loss of the anomeric substituent (giving kojic acid dibenzoate) or with its preservation (giving 6-alkoxy-allomaltol derivatives **29** and **30**) The structural and configurational assignments were based on the mode of preparation and from spectroscopic data, most conveniently from p m r spectra and chiroptical properties The sign of the long-wave Cotton effect (the enone R-band) showed a distinct dependence on the anomeric configuration

INTRODUCTION

4-Deoxy-hex-3-enos-2-uloses of type II, which may be referred to as hexos-3-enol-2-ones as they are derived formally from a mono-enol form of hexopyranose-2,3-diuloses, have been repeatedly encountered during the past 10 years[1–13], although unintentionally in most instances owing to the high propensity of hexopyranos-2-



I II

R = acyl alkyl R'= OR , NR_2

*Part V of a series on "Sugar enolones" For parts I-IV, see refs 2, 4, 9, and 12, respectively

glycosuloses to eliminate ROH from the 3,4-position (I → II) With acylated glycosuloses, this elimination takes place even on silica-gel chromatography[1], under the conditions of acylation[3 7 12], or of oxidation with methyl sulfoxide[2,4], or thermally during g l c [6] For preparative purposes, brief refluxing with moist sodium hydrogencarbonate has proved most effective[8–10] *O*-Alkylated glycosuloses, however, require more stringent conditions, such as strong alkali, to effect this conversion[5 11]

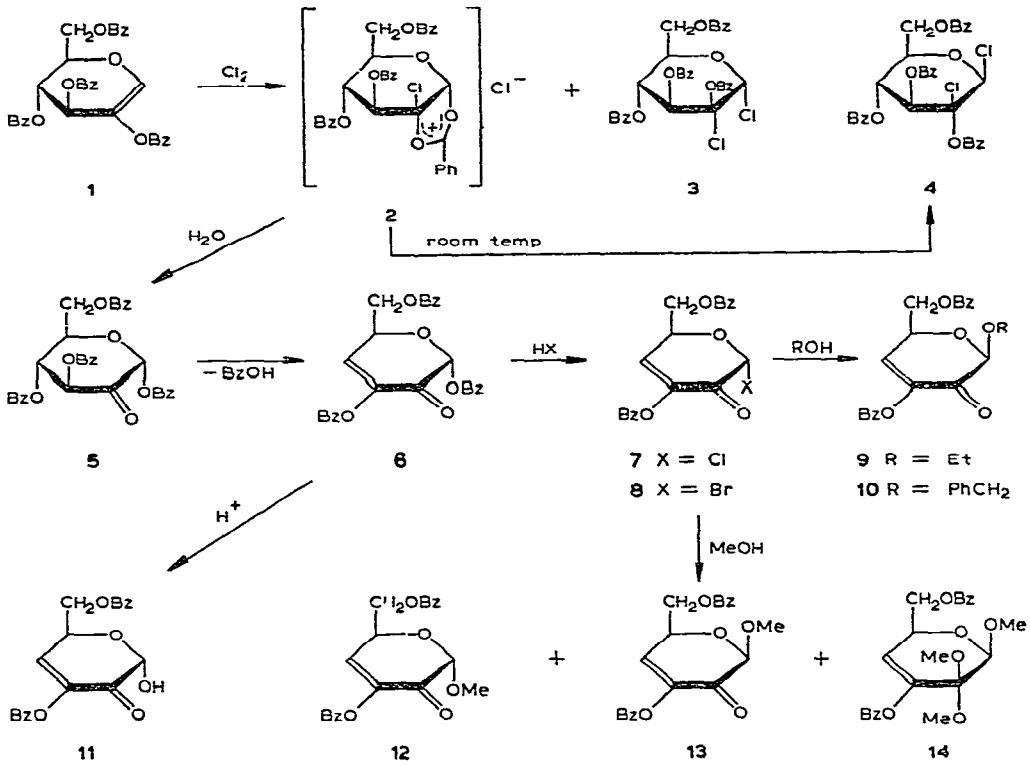
The synthetic potential of these enolones, as for the preparation of 4-deoxy-hexoses functionalized via the carbonyl groups at C-2 and/or C-3 has not thus far been explored We were therefore prompted to examine those reactions of preparative utility that may be performed on such enolones, in consideration of their pronounced tendency[2 8 12] for conversion into the more stable γ-pyrone system Although reactions involving sequential saturation of the alkenic and/or carbonyl double-bonds are currently being studied[14], we describe here a series of conversions that retain the enolone structure, these comprise in part a repetition and detailed revision of earlier studies by Maurer *et al* [15 16]

RESULTS AND DISCUSSION

The synthetic method utilized to prepare 1,3,6-tri-*O*-benzoyl-4-deoxy-α-D-*glycero*-hex-3-enos-2-ulose (**6**), the key enolone for all ensuing conversions described herein, developed from a detailed study of the solvent- and temperature-dependence of the addition of chlorine to 1,5-anhydro-2,3,4,6-tetra-*O*-benzoyl-hex-1-enitol (**1**). At room temperature, the α-D-*manno* dichloride **3** and its β-D-*gluco* isomer **4** are formed exclusively, in about 1 2 proportion when tetrachloromethane is the solvent[10], whereas in benzene or toluene a ratio of about 1 4 is observed[13] At low temperature, however, the chlorination product consists of the *manno* dichloride **3** and the benzoxonium salt **2***, (namely, the ionic precursor of **4**) which, unlike **3** and **4**, is readily hydrolyzed to the glycosulose **5** by addition of water[10 13] Thus, when low-temperature chlorination of **1** is followed by hydrolysis with water, mixtures of the glycosulose **5** and the *manno* dichloride **3** (<20% in toluene, ~30% in tetrachloromethane) are invariably obtained, complete separation requires column chromatography However, the highly crystalline enolone **6**, which is readily formed from **5** by elimination of benzoic acid, is conveniently separated from **3** by fractional recrystallization Thus, for a high-yielding route to **6**, the most favorable procedure involved chlorination of **1** in toluene for 5 min at −30°, followed directly by hydrolysis (addition of water) and elimination (refluxing with moist sodium hydrogencarbonate in toluene), all steps being performed in one continuous operation In this way, the hex-3-enos-2-ulose **6** was readily obtained in 65% yield (based on **1**) Given the ready availability[17] of **1**, compound **6**, is thus the most accessible hexose-3-enol-2-one**

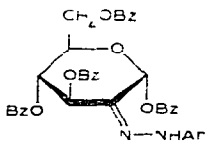
*Apart from **3**, only **2** was detectable by p m r spectroscopy at −30° in the mixture obtained by low-temperature chlorination of **1** in toluene-d_8 Consequently, an ionic precursor of **3**, analogous to the intermediate **2** must have a very high tendency to give **3**, if it is formed at all

The large-scale preparation of **6 from D-glucose has been succesfully used as an introductory excercise for laboratory courses in advanced organic chemistry



The enolone system in **6** is remarkably insensitive towards acid, and debenzoylation at C-1 could be effected by treatment with trifluoroacetic acid at 60°, to give the 1-hydroxy analog **11** Similarly, the anomeric substituent in **6** may readily be replaced by halogen by treatment with hydrogen chloride in acetyl chloride or hydrogen bromide in acetic acid The corresponding halides **7** and **8**, readily isolable in yields of >60%, proved to be versatile intermediates, as for the preparation of the hydroxyenolone **11** by hydrolysis with silver carbonate in aqueous acetone and, in particular, for the synthesis of enolone glycosides by alcoholysis Methanolysis was studied in detail On stirring in methanol at 30°, **7** or **8** were readily converted into approximately 8 1 mixtures (p m r) of the β-glycoside **13** and its α-anomer **12**, both isolable by fractional recrystallization in yields of 67 and 3%, respectively Under somewhat more forcing conditions, however, as by refluxing **8** in methanol, the mixture of glycosides formed contained substantial proportions of the 2,2-dimethyl acetal **14**, isolable by column chromatography on silica gel in 7% yield This conversion was accompanied by the loss of enolones **12** and **13**, which decomposed during extended exposure to silica gel to form γ-pyrones and other, highly-polar products (see later) Thus, for preparation of other glycosides of the enolones, such as the ethyl-β-D (**9**) and benzyl-β-D derivative (**10**), treatment of **8** with ethanol and benzyl alcohol at 30° was the procedure of choice, affording the products in yields of 78 and 69%, respectively

At room temperature, the aldosulose **5**, the enolone **6** and also its glycosides **10** and **13**, readily gave the corresponding (2,4-dinitrophenyl)hydrazones, characterized by p m r spectroscopy and by their high specific rotations However, on brief heating with, for instance, phenylhydrazine in acetic acid, formation of the phenylhydrazone was accompanied by loss of the anomeric substituent and a phenylosazone **19** was obtained from any of the enolones **6–13** as well as from the glycosulose **5**, which also eliminated benzoic acid under these conditions



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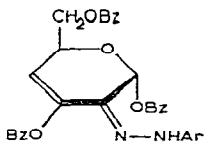

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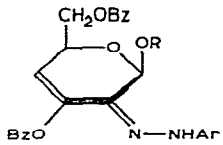
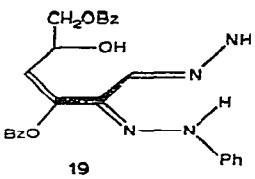


17 R = Me
18 R = $PhCH_2$



19

Ar = 2,4-dinitrophenyl

The relevant ^{1}H-n m r -spectral parameters for all of the enolones prepared (**6–13**) and also for their (2,4-dinitrophenyl)hydrazones (**16–18**) are recorded in Table I and are consistent with the structures assigned The salient features comprise a singlet for H-1, a generally well resolved sextet for H-5, and, most characteristically, a doublet for the alkenic proton (H-4) The open-chain structure for **19** was similarly deduced from its p m r spectrum which, in accord with those of other osazones[18], showed presence of singlets for a chelated and a non-chelated imino proton at δ 12 73

TABLE I

P M R [a] AND OPTICAL-ROTATION DATA FOR HEX-3-ENOPYRANOS-2-ULOSES AND RELATED COMPOUNDS

Compound	*H-1* (*s*)	*H-4* (*d*)	$J_{4,5}$	*H-5* (*sx*)	*6-CH*$_2$[b]	*OMe*	$[\alpha]_D$ (*chloroform*) (*degrees*)	(c, *degrees*)
6	6 69	7 03	1 8	5 33	4 62	—	+2 5	(1, 25)
7	6 21	6 93	2 0	5 37	4 66	—	+61	(0 8, 20)
8	6 64	6 97	2 0	5 23	4 67	—	+104	(0 8, 23)
9	5 12	6 92	3 0	5 09	4 70	—	−108	(1, 23)
10	5 17	6 93	3 0	5 10	4 65	—	−98	(0 7, 24)
11	5 49	6 91	2 0	5 35	4 61	—	−18	(1, 20)
13	5 02	6 91	3 5	5 10	4 67	3 59	−110	(0 6, 25)
14	4 80	6 02	2 0	4 86	4 48	3 57, 3 42, 3 39	−94	(1, 20)
16[c]	>7 3[d]	6 45	2 0	5 40	4 65	—	+452	(0 1, 20)
17[c]	5 64	6 35	3 5	5 04	4 64	3 80	−334	(0 1, 20)
18[c]	5 68	6 46	3 5	5 07	4 65	—	−343	(0 1, 25)

[a] In $CDCl_3$, unless otherwise indicated, δ-scale, coupling constants in Hz [b] The expected octets for H-6 and H-6′ were usually only partially resolved [c] In Me_2SO-d_6, (2,4-dinitrophenyl)hydrazone residues gave signals at ~11 6 (s, 1 H NH), 10 9 (d, 1 H, *J* 2–3 Hz, H-3), 8 2 (dd, 1 H, H-5) and 7 4 (dd, 1 H, H-6), the latter two overlapped with the benzoyl protons [d] The signal was hidden by those of the aromatic protons

and 10 81 in methyl sulfoxide-d_6, together with an OH-doublet at δ 5 56, all of these signals disappearing on deuteration or on addition of trifluoroacetic acid

Reevaluation of Maurer's findings — When comparing the results described here, on the chlorination of **1** and subsequent hydrolysis, with those reported by Maurer[15 16], the discrepancies, particularly with respect to the structures assigned, are rather serious Hence, it seems appropriate to reevaluate Maurer's experimental data and to rationalize his *a priori* assumptions and, in fact, erroneous conclusions, the latter are understandable, considering the techniques available 40 years ago It appears peculiar, however, that these rather obvious inconsistencies eluded the evaluation of Maurer's work by several competent reviewers[19–21], despite the fact that Isbell[22] in 1944 had provided the mechanistic framework for understanding the reactions involved

The highly crystalline product arising from chlorination of **1** and subsequent heating with moist sodium hydrogencarbonate in benzene, shown here to be tri-*O*-benzoyl-enolone **6**, was assumed by Maurer to be a tetrabenzoyl derivative ("Tetrabenzoyl-glucoson") on the basis of elemental analysis He assigned to it the 1,2-epoxide structure **20**, mainly on account of its conversion into dibenzoylkojic acid with pyridine and into an osazone with phenylhydrazine[15]

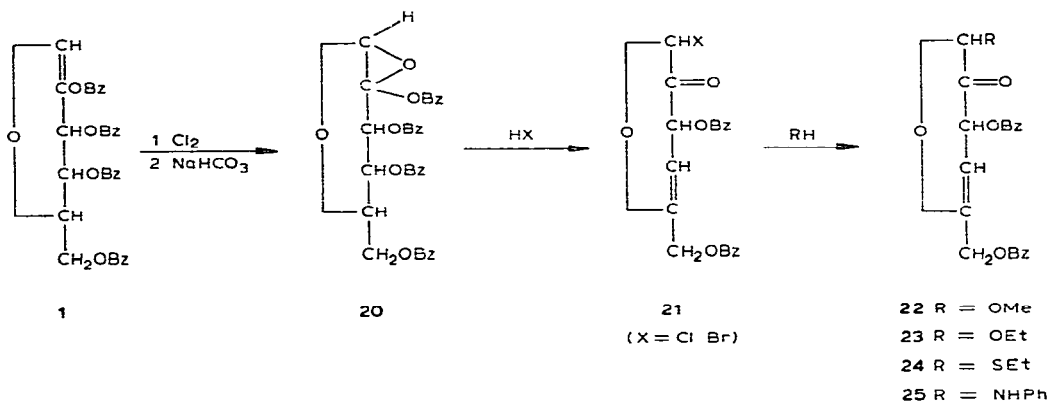


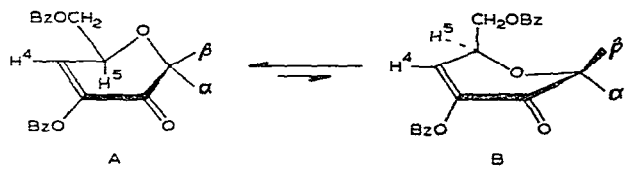
Fig 1 Structures assigned by Maurer[15 16] to the product (**20** now shown to be **6**) arising from the chlorination of **1** and subsequent hydrolysis, and products of subsequent transformations

However, neither of these chemical conversions are conclusive, nor are the analytical data, as, fortuitously, the carbon and hydrogen values for the tetrabenzoate **20** (or its isomer **5**) and the tribenzoate **6** are so close as to be within experimental error Undoubtedly, Maurer retained some reservations as to the validity of structure **20**, as he noted the unusual stability of the epoxide ring towards acetic anhydride, a solvent from which the product may be recrystallized[16] Nevertheless, all ensuing conversions were thought to occur from a product of structure **20**, the reaction with hydrogen halides, for example, being accompanied by elimination of benzoic acid

from the 4,5-position to yield the 1-halo-enolones **21**, which in turn gave the corresponding glycosides **22** and **23** on treatment with alcohols

These structural assignments must all be revised, and the alleged compounds **20–23** in fact possess the structures **6–9**, and **13**, respectively For the same reasons, the enolone structure **9** (SEt and NHPh instead of OR) needs to be assigned to the products of supposed structures **24** and **25**, which were obtained[16] by treatment of the 1-haloenolone with ethanethiol and aniline, respectively

Configurational and conformational characteristics — The anomeric configurations of the enolones **6–13** may be deduced from p m r data, but not from the chemical shifts of H-1, as these are practically identical for both anomers (for example δ 4 98 for the α-glycoside[12] **12** in comparison with δ 5 02 for the β anomer **13**) However, the $J_{4,5}$ coupling constant showed a characteristic dependence on the configuration at C-1, being ~2 0 Hz for the α anomers and 3 0–3 5 Hz for tne β anomers (see Table I) A similar result has been observed for other 3-enol-2-ones[8,12] and strongly indicates a sofa conformation having H-5 perpendicular to the ring (*A*) for the α as well as for the β anomers The latter, however, display some deviation from *A* towards the alternative conformation (*B*), as judged from the larger $J_{4,5}$-values and, thus, smaller H-4–H-5 dihedral angles



Aside from the $J_{4,5}$ coupling constants, information as to the configuration at the anomeric carbon atom may be derived from the specific rotations of the respective (2,4-dinitrophenyl)hydrazones, which exhibit large positive rotations for the α compounds (**15**, **16**) and equally high levorotations for the β-glycosides (**17** and **18**) (compare Table I), in accord with previous findings on analogous products[12]

The anomeric configurations of the 3-enol-2-ones may also be determined from the sign of the long-wavelength Cotton effect, namely the enone *R* band in the 335-nm region resulting from an $n \rightarrow \pi^*$ transition. As illustrated, for example, by the circular-dichroism curves of the anomeric methyl enolones **12** and **13** (Fig 2), the exciton-split, Cotton effects in the 210–250 nm region, arising from enone $\pi \rightarrow \pi^*$ and benzoate charge-transfer transitions, are very similar in sign, shape, and intensity, whereas their enone *R*-bands show a distinct difference in sign, being positive for the β anomers, and negative for the α compounds This correlation is also borne out by analogous effects with the ethyl β-glycoside **9** ($\Delta\varepsilon_{337}$ +0 84), the benzoyl-α-D derivative **6** ($\Delta\varepsilon_{334}$ −1.29 in methanol), and the halo-α-D derivatives **7** and **8** (−0.66 and −0 3, respectively, in 1,4-dioxane)

When trying to rationalize these data in terms of the octant rule[23], the chiroptical behavior is not consistent with an octant-diagram projection as in Fig 3,

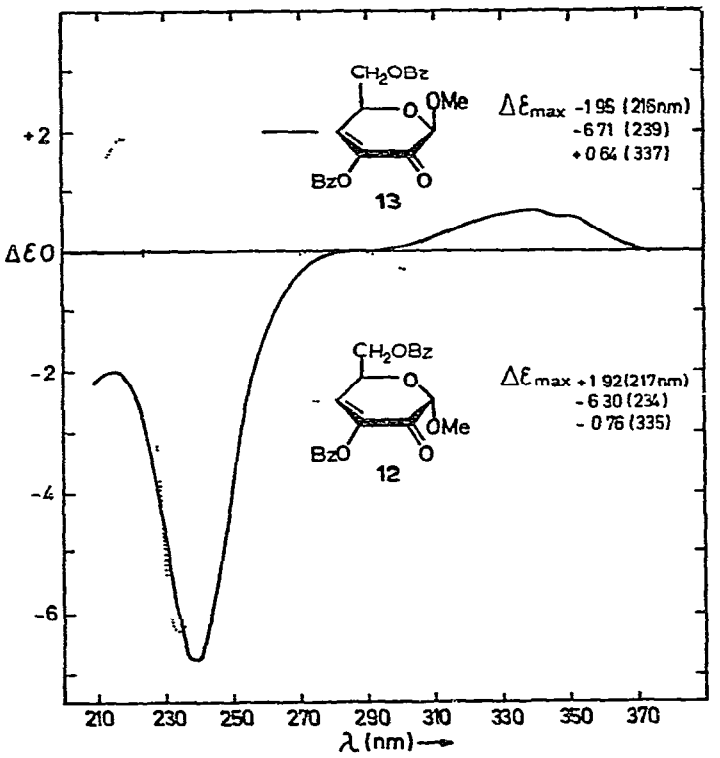


Fig 2 Circular-dichroism spectra (methanol solution) of methyl 3,6-di-*O*-benzoyl-4-deoxy-α-D-*glycero*-hex-3-enopyranosid-2-ulose (**12**, dotted line) and its β anomer (**13**, solid line)

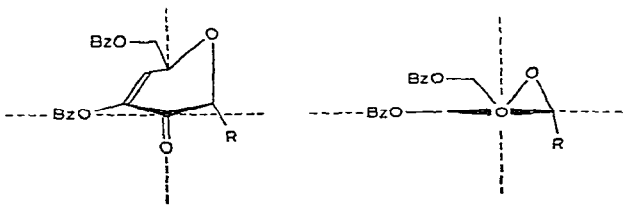


Fig 3 Octant-rule projections of 3 6-di-*O*-benzoyl-4-deoxy-α-D-hex-3-enos-2-ulose derivatives **6–8** (R = OBz, Cl, and Br)

because, for the α-compounds, the quasi-axial, anomeric substituent is placed in the lower-right, rear octant and, consequently, should give a positive sign for the enone *R* band This is the more surprising as axial substituents vicinal to the carbonyl group usually outweigh the contributions of all other atoms[24] and therefore dominate the sign of the long-wave Cotton effect The observed "inverse" enone *R* bands are thus obviously governed by other, less-tangible steric factors, a possibility being the 3-*O*-benzoyl group, which may adopt different spatial arrangements for the α and β

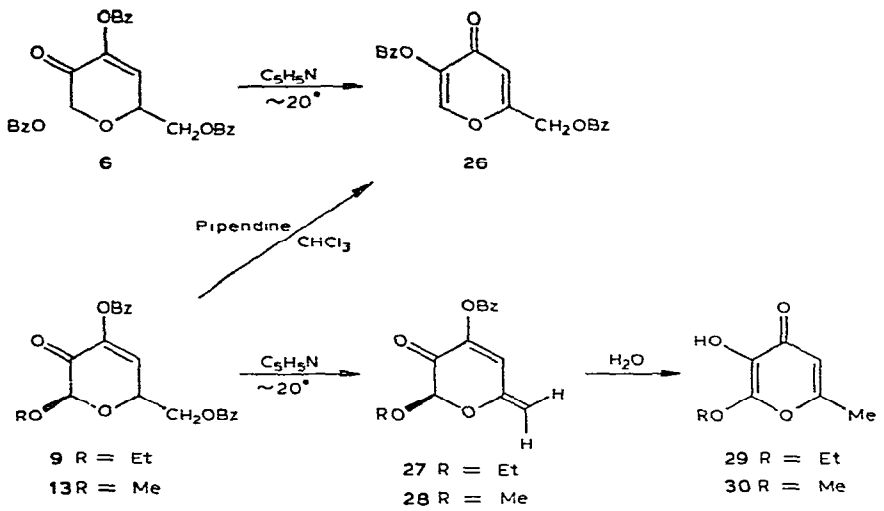
anomers and, respectively, reach into the upper-left and lower-left front octants, irrespective of whether a planar[23] or a convex[25] shape is adopted for the surface dividing the rear and front octants

Formation of γ-pyrones — All compounds described, including the 1,2-dichlorides **3** and **4**, may be converted into γ-pyrone derivatives but the conditions required vary considerably and the substitution pattern in the resultant γ-pyrone is to some extent dependent on these conditions and on the nature of the anomeric substituent

In the case of the glycosulose **5** and the enolones **6–8**, dibenzoylkojic acid (**26**) is obtained by keeping them for 20 h at ~20° in pyridine, whereas the dichlorides (**3** or **4**) required more-severe conditions to effect this conversion, as by heating in pyridine (30 min at 100° for ~50% conversion, 3 h at 100° for 100% conversion) Similarly, heating either of these products with sodium acetate in acetic acid (1 h of boiling under reflux for **3** or **4**), quantitatively converts them into **26**

These results have some relevance with respect to the "1-acetyl-3,4,6-tribenzoyl-glucosone" (1-*O*-acetyl-3,4,6-tri-*O*-benzoyl-D-*arabino*-hexopyranos-2-ulose), which Maurer and Petsch[15] claimed was formed by heating their "dichlorotetrabenzoyl-oxyglucal" (shown here to be the α-D-*manno* dichloride **3**) with sodium acetate in acetic acid over an open flame Other findings by the same authors already gave reason for questioning the structure attributed to the product, for instance, its stability towards hydrogen bromide in acetic acid, and the reisolation of unreacted dichloride from a solution in pyridine, and these inconsistencies may now be explained As brief heating of the dichloride **3** with sodium acetate in acetic acid (15 min at 90°) produced an approximately 2 1 mixture (t l c) of unreacted **3** and dibenzoylkojic acid (**26**), the alleged "1-acetyl-3,4,6-tribenzoyl-glucosone" of m p 131–132° and $[\alpha]_D$ +29 5° in pyridine[15], is in fact comprised of a mixture of unreacted dichloride **3** (m p 156–158°, $[\alpha]_D^{25}$ +44° in pyridine) and dibenzoylkojic acid **26** (m p 136°) From this it may also be concluded that the 1-*O*-acetyl-3,4,6-tri-*O*-benzoyl-D-*arabino*-hexopyranos-2-ulose, which Chittenden[26] believed he had obtained according to Maurer's[15] procedure and which he allegedly converted into dibenzoylkojic acid by treatment with methyl sulfoxide–acetic anhydride or acetic anhydride–pyridine, actually consisted of a similar mixture of **3** and **26**

The enolone glycosides **9** and **13** are similarly converted into dibenzoylkojic acid (**26**) on heating with sodium acetate–acetic acid However, on keeping in pyridine at room temperature an entirely different pathway (not unexpected in view of the behaviour of the methyl α-D-glucoside **12** under these conditions[12]) is operative, namely elimination of the terminal benzoyloxy group to give the dienones **27** and **28**, respectively Although attempts to isolate these in substantial amounts have thus far been unsuccessful, they are stable in pyridine and may be detected by p m r spectroscopy (2-Hz doublets at δ 5 2 and 5 0 for the exocyclic methylene protons) and by t l c , together with other, more-polar components, that probably result from ring opening On addition of water, these 3,5-dienones are readily converted into the



alkoxyallomaltols **29** and **30**, respectively, isolable in yields of up to 40% In this conversion, protonation occurs at the exocyclic methylene group, as was readily shown by performing the reaction **28**→**30** in deuterium oxide, which afforded a methoxy-allomaltol (**30**) specifically monodeuterated in the *C*-methyl group, thus sustaining the previous[1,2] mechanistic rationalizations for this conversion

EXPERIMENTAL

General methods — Melting points were determined on a Bock Monoskop and are uncorrected Spectral measurements were effected with Perkin–Elmer 125 (i r), Perkin–Elmer 141 (rotations), Jasco J-20 (c d), Varian A-60A and XL-100 (p m r), and Varian MAT 311 A (m s) instruments T l c was performed on Kieselgel 60 F_{254} plastic sheets (Merck, Darmstadt) and was used to monitor the reactions and to ascertain the purity of the products Developers employed were A, 10 1 tetrachloromethane–ethyl acetate, B, 1 1 chloroform–dichloromethane, and C, 19 1 dichloromethane–ethyl acetate The spots were made visible by u v light or by spraying with 80% aqueous sulfuric acid and charring for 5 min at 110° Column chromatography was performed on Kieselgel 60 (70–230 mesh, Merck)

1,3,4,6-Tetra-O-*benzoyl*-α-D-arabino-*hexopyranos-2-ulose* (**5**) — Chlorine gas was passed through a cooled (−30°) solution of 1,5-anhydro-2,3,4,6-tetra-*O*-benzoyl-D-*arabino*-hex-1-enitol (**1**, 1 45 g, 2 5 mmol) in toluene (50 ml) until a greenish color persisted (~5 min) After stirring for another 10 min, the excess of chlorine was removed by bubbling nitrogen through the solution Water (2 ml) and sodium hydrogencarbonate (300 mg) was then added with vigorous stirring and the mixture was allowed to warm to room temperature Filtration, drying (sodium sulfate), and evaporation to dryness *in vacuo* left a residue, which was applied to a column

(2 × 20 cm) of silica gel that was rapidly eluted with 2 l cyclohexane–ethyl acetate The fast-moving fraction, on concentration and filtration of the resultant crystals and washing with ethanol, afforded 190 mg (12%) of the *manno* dichloride **3**, m p 156–158° (lit [13] 156–158°) Evaporation of the fractions containing **5** (R_F 0 03 in A, 0 14 in B) afforded an amorphous solid, which was dried *in vacuo* over phosphorus pentaoxide, yield 0 95 g (63%) of **5**, identical with respect to specific rotation, and i r - and p m r -spectral data with the product described previously[10,13]

1,3,4,6-Tetra-O-*benzoyl*-α-D-arabino-*hexopyranos-2-ulose* (*2,4-dinitrophenyl*)-*hydrazone* (**15**) — An ethanolic solution of the glyculose **5** (600 mg in 30 ml) was mixed with 8 ml of 0 1M (2,4-dinitrophenyl)hydrazine in phosphoric acid–ethanol[27] The precipitate formed was recrystallized twice from ethanol, yield 360 mg (46%) of **6** as yellow needles, m p 167–169°, $[\alpha]_D^{20}$ +139° (*c* 0 2, chloroform), p m r data (Me_2SO-d_6 + 2 drops of CF_3CO_2H) δ 8 55 (d, 1 H, *J* 2 5 Hz, H-3'), 8 2–7 3 (m, 23 H, 3 Ph, H-1, H-5', H-6'), 6 40 (d, 1 H, $J_{3,4}$ 9 Hz, H-3), 5 91 (t, 1 H, $J_{3,4} = J_{4,5}$ = 9 Hz, H-4), 5 05 (m, 1 H, H-5), and 4 66 (m, 2 H, 6-CH_2)

Anal Calc for $C_{40}H_{30}N_4O_{13}$ (774 7) C, 62 01, H, 3 90, N, 7 23 Found C, 61 94, H, 3 84, N, 7 25

1,3,6-Tri-O-*benzoyl-4-deoxy*-α-D-glycero-*hex-3-enopyranos-2-ulose* (**6**) — Dry chlorine gas was passed through a cooled (−30°) solution of the glycal **1** (6 2 g, 10 7 mmol) in toluene (200 ml) for about 5 min, whereupon water (1 5 ml) was added with vigorous stirring followed by portionwise addition of solid sodium hydrogencarbonate (15 g) The mixture was allowed to warm to room temperature and was subsequently heated for 2 h at 70° The brownish salts were filtered off and the filtrate was dried (sodium sulfate) and evaporated to dryness *in vacuo* Benzene, and finally ether, were evaporated several times from the residue The crystalline residue, containing 15–20% of the *manno* dichloride **3** (R_F 0 68 in C, versus 0 60 for **6**), was usually free from **3** after two recrystallizations from ethanol, yield 3 1 g (65%) of **6** as felted needles, m p. 128–130°, $[\alpha]_D^{25}$ +3 6° (*c* 1, chloroform) and +9 4° (*c* 1, acetone), c d data (methanol) $\Delta\varepsilon$ −1 29 (334 nm)

Anal Calc for $C_{27}H_{20}O_8$ (472 4) C, 68 64, H, 4 27 Found· C, 68 74. H, 4 24

For a product ("Tetrabenzoyl-glucoson" of alleged structure **20**) prepared similarly, Maurer and Petsch[15] reported m p 132° and $[\alpha]_D^{20}$ +7 05° (*c* 0 32, acetone)

1,3,6-Tri-O-*benzoyl-4-deoxy*-α-D-glycero-*hex-3-enopyranos-2-ulose* (*2,4-dinitrophenyl*)*hydrazone* (**16**) — An ethanolic solution of the enolone **6** (500 mg in 50 ml after slight warming) was mixed with 10 ml of 0 1M (2,4-dinitrophenyl)hydrazine in phosphoric acid–ethanol[27] The yellow crystals, which soon started to precipitate, were filtered off after 3 h and recrystallized from ethyl acetate–ethanol to give 510 mg (72%) of **16**, m p 149–150°, $[\alpha]_D^{20}$ +452° (*c* 0 12, chloroform)

Anal Calc for $C_{33}H_{24}N_4O_{11}$ (652 6)· C, 60 74, H, 3 71, N, 8 58 Found C, 60 66, H, 3 63, N, 8 48

3,6-Di-O-*benzoyl-4-deoxy*-D-glycero-*hex-3-enos-2-ulose 1,2-bis*(*phenylhydrazone*) (**19**) — A suspension of the enolone **6** (250 mg, 0 5 mmol) in 75% aqueous acetic acid

(20 ml) was heated on a steam bath until a clear solution was obtained, whereupon phenylhydrazine (0 25 ml) was added gradually The yellow precipitate that separated on cooling was filtered off after 18 h and was recrystallized from ethanol, yield 200 mg (67%) of yellow crystals, m p 189–190°, $[\alpha]_D^{20}$ −44 7° (*c* 0 1, pyridine), p m r data (Me_2SO-d_6) δ 12 73 and 10 81 (two s, 1 H each, NH), 8 15 (m, 4 H, ortho-H of PhCO), 6 9–7 9 (m, 17 H, 2 Ph, *m*- and *p*-H of 2 PhCO, H-1), 5 72 (d, 1 H, $J_{4,5}$ 9 Hz, H-4), 5 56 (d, 1 H, $J_{5,OH}$ 5 Hz, OH), 5 20 (m, 1 H, H-5), and 4 50 (m, 2 H, 6-CH_2), addition of trifluoroacetic acid or deuteration removed the OH-doublet at δ 5 56 and the low field NH-singlets

Anal Calc for $C_{32}H_{28}N_4O_5$ (548 6) C, 70 06, H, 5 14, N, 10 21 Found C, 70 05, H, 5 13, N, 10 09

The same product (**19**) was also obtained from the tetra-*O*-benzoyl-hexos-2-ulose **5**, from the halo-enolones **7** and **8**, and also from the glycenosidulose **13**, when they were subjected to the foregoing treatment

*3,6-Di-O-benzoyl-4-deoxy-α-*D-glycero-*hex-3-enopyranos-2-ulose* (**11**). — *A Acid hydrolysis of the enolone* **6** A solution of **6** (300 mg, 0 64 mmol) in trifluoroacetic acid (3 ml) was kept for 3 h at 70°, and then evaporated to dryness *in vacuo*, and toluene was evaporated several times from the residue The latter was crystallized by trituration with ethyl acetate–hexane to give 105 mg (45%) of **11**, m p 117–118°, $[\alpha]_D^{20}$ −18° (*c* 1, chloroform), −4 (3 min) → −12° (24 h) in 9 1 1,4-dioxane–water (*c* 1), c d data (CH_3CN) $\Delta\varepsilon$ −1 15 (333 nm), R_F 0 13 (C, as compared with 0 60 for **6**), ν_{max}^{KBr} 3400 cm^{-1} (OH), p m r data, see Table I, *m/e* 368 (M^+), 367 (M−H), and 350 ($M-H_2O$)

The well-formed crystals of **11** contained varying amounts of ethyl acetate or of benzene, when recrystallized from these solvents, and were not entirely freed from solvent by drying *in vacuo* The relatively sharp m p appears to be unaffected by this solvation

Anal Calc for $C_{20}H_{16}O_7$ O 3 EtOAc C, 64 50, H, 4 70 Found C, 64 37, H, 4 57

B Hydrolysis of the chloro derivative **7** *with silver carbonate* To a solution of **7** (2 0 g, 5 2 mmol) in acetone (100 ml) and water (8 0 ml) was added silver carbonate (1.4 g) and the mixture was stirred for 24 h at room temperature in the dark The mixture was filtered and the filtrate was processed as just described (*A*), yielding 1 2 g (60%) of **11**, identical in all respects with the product already described

*3,6-Di-O-benzoyl-1-chloro-1,4-dideoxy-α-*D-glycero-*hex-3-enopyranos-2-ulose* (**7**) — A solution of 1 0 g (2 1 mmol) of the enolone **6** in 5 ml of acetyl chloride saturated with dry hydrogen chloride gas was kept for 12 h at room temperature, and then evaporated to dryness *in vacuo* Trituration of the residue with chloroform–hexane induced crystallization, to afford, after recrystallization from the same solvents, 440 mg (54%) of **7** as fine needles, m p 130–131°, $[\alpha]_D^{20}$ +61 3° (*c* 0 8, chloroform), +77° (*c* 0 8, acetone), c d data (1,4-dioxane) $\Delta\varepsilon$ −0 66 (333 nm), p m r data, see Table I

Anal Calc for $C_{20}H_{15}O_6Cl$ (386 8) C, 62 10, H, 3 91, Cl, 9 17 Found C, 62 01, H, 3 93, Cl, 9 02

For a similarly prepared product ("Chlor-zucker III" of alleged structure **21** having X = Cl) Maurer and Bohme[16] reported m p 131° and $[\alpha]_D^{20}$ +78° (*c* 1 4, acetone)

*3,6-Di-O-benzoyl-1-bromo-1,4-dideoxy-α-*D-glycero-*hex-3-enopyranos-2-ulose* (**8**) — To a cooled (~5°) and stirred suspension of 10 0 g (21 mmol) of **6** in ether (200 ml) was gradually added 30 ml of 40% hydrogen bromide in acetic acid After completion of the addition (~10 min), a clear solution was obtained, from which needles started to separate within a few min After 1 h at 5°, the crystals were filtered off to afford 3 8 g (42%) of essentially pure **8**, m p 150–151° The mother liquor was diluted with chloroform (300 ml) and washed with water until free of acid Drying (sodium sulfate) and removal of the solvents *in vacuo* left a syrup that crystallized on trituration with ether Recrystallization from chloroform–hexane afforded another 2 1 g of **8** (total yield 65%), m p 151–152°, $[\alpha]_D^{23}$ +104° (*c* 0 8, chloroform), +112° (*c* 1, acetone), c d data (1,4-dioxane) $\Delta\varepsilon$ −0 26 (328 nm), +0 13 (368), p m r data, see Table I

Anal Calc for $C_{20}H_{15}BrO_6$ (431 2) C, 55 71, H, 3 51, Br, 18 53 Found C, 55 80, H, 3 59, Br, 18 41

The 'Brom-zucker" obtained by Maurer and Bohme[16] on treatment of their "Benzoyl-oson' of alleged structure **20** (revised structure **6**) with hydrogen bromide in acetic acid at room temperature appears to be **8** on the basis of the reported m p 151° and $[\alpha]_D^{20}$ +112 8° (*c* 1 9, acetone)

*Methyl 3,6-di-O-benzoyl-4-deoxy-β-*D-glycero-*hex-3-enopyranosid-2-ulose* (**13**) — A suspension of the bromo derivative **8** in abs methanol (2 2 g in 50 ml) was stirred for 3 h at 30° Although a clear solution was not obtained, methanolysis had occurred (t l c in C) The colorless crystals formed were collected by filtration (for treatment of the mother liquor, see later) and washed with a little cold methanol, yield 1 3 g (67%) of **13**, m p 114–115°, $[\alpha]_D^{25}$ −110° (*c* 0 6, chloroform), c d data see Fig 1, p m r data see Table I

Anal Calc for $C_{21}H_{18}O_7$ (382 4) C, 65 96, H, 4 74 Found C, 65 94, H, 4 70

The methanolic mother liquor remaining after removal of crystalline **13** (R_F 0 54 in C) contained some of the α anomer **12** (R_F 0 57) as well as **13** After being refrigerated overnight, fiber-like crystals had separated, that consisted mostly of the α anomer **12** (t l c) Two recrystallizations from methanol gave chromatographically homogeneous *methyl 3,6-di-O-benzoyl-4-deoxy-α-*D-glycero-*hex-3-enopyranosid-2-ulose* (**12** 65 mg, 3 4%) having m p 126 5–127° (undepressed on admixture with an authentic[12] sample), $[\alpha]_D^{25}$ +21 6° (*c* 0 6, chloroform), c d data (methanol) see Fig 1

*Methyl 3,6-di-O-benzoyl-4-deoxy-β-*D-glycero-*hex-3-enopyranosid-2-ulose (2,4-dinitrophenyl)hydrazone* (**17**) — An ethanolic solution of compound **13** (200 mg in 10 ml) was mixed with 5 ml of 0 1M (2,4-dinitrophenyl)hydrazine in phosphoric acid–ethanol[27] After 3 h at ~20° the precipitate was filtered off and recrystallized

from ethanol, yield 170 mg (68%) of yellow crystals, m p 209–211°, $[\alpha]_D^{20}$ −334° (*c* 0 16, chloroform)

Anal Calc for $C_{27}H_{22}N_4O_{10}$ (562 5) C, 57 65, H, 3 94, N, 9 96 Found C, 57 46, H, 4 06, N, 9 82

*Methyl 3,6-di-*O*-benzoyl-4-deoxy-β-*D*-glycero-hex-3-enopyranosid-2-ulose 2,2-dimethyl acetal* (**14**) — A suspension of the bromide **8** (2 0 g, 5 mmol) in abs methanol (25 ml) was boiled under reflux for 20 min and subsequently refrigerated overnight The crystalline product (0 8 g) was filtered off, and the filtrate was neutralized by addition of solid sodium hydrogencarbonate and then evaporated to dryness The residue was dissolved in chloroform, washed with water, dried (sodium sulfate), and again the solution was evaporated to dryness The syrup obtained crystallized on trituration with little methanol to afford another 0 75 g of product Both crops comprised an approximately 10 1 mixture of the methyl glycoside **13** (R_F 0 54 in C) and the dimethyl acetal **14** (R_F 0 41) On elution of the combined crops from a column (3 × 25 cm) of silica gel with 50 1 dichloromethane–ethyl acetate, only **14** was obtained because of decomposition of the methyl glycoside **13** upon contact with silica gel The fractions containing **14**, contaminated by some of the decomposition products from **13**, were combined and evaporated to dryness, yielding a crystalline residue Recrystallization from methanol afforded 130 mg (6 5%) of **14** as prisms having m p 124°, $[\alpha]_D^{22}$ −94° (*c* 1, chloroform), *m/e* 396 (M − MeOH), 369 ($M-HCO_2CH_2^+$), 368 ($M-HCO_2CH_3$), 323 (M − PhCO), 263 ($M-HCO_2CH_3$ and PhCO), and 105 (PhCO, base peak), p m r data see Table I

Anal Calc for $C_{23}H_{24}O_8$ (428 1) C, 64 48, H, 5 65 Found C, 64 42, H 5 70

*Ethyl 3,6-di-*O*-benzoyl-4-deoxy-β-*D*-glycero-hex-3-enopyranosid-2-ulose* (**9**) — A suspension of the bromide **8** (4 3 g, 10 mmol) in dry ethanol (90 ml) was stirred for 5 h at 25–30°, to afford a clear solution after about 3–4 h, from which crystals slowly separated After refrigeration overnight, the suspension was filtered and the product recrystallized from ethanol, yield 3 0 g (78%) of **9** as fine needles having m p 106 , $[\alpha]_D^{22}$ −108 2° (*c* 1, chloroform), −99° (*c* 1, acetone) c d data (methanol) $\Delta\varepsilon$ +0 84 (337 nm), p m r data, see Table I

Anal Calc for $C_{22}H_{20}O_7$ (396 3) C, 66 66, H, 5 09 Found C, 66 67, H, 4 96

The "Athyl-Produkt" obtained by Maurer and Bohme[16] on refluxing their "Brom-zucker" of alleged structure **21** (X = Br, revised structure **8**) in ethanol (10 min) appears to be **9** on the basis of the reported m p 106° and $[\alpha]_D^{20}$ −97 7° (*c* 1 1, acetone) A product prepared under these conditions contained a minor component (R_F 0 42 in C versus 0 55 for **9**), conceivably the 2,2-diethyl acetal of **9**, which was only incompletely removed by two recrystallizations from ethanol

*Benzyl 3,6-di-*O*-benzoyl-4-deoxy-β-*D*-glycero-hex-3-enopyranosid-2-ulose* (**10**) — The bromide **8** (1 2 g) was stirred in benzyl alcohol (15 ml) for 5 h at 30–35° and, after refrigeration for 3 h the precipitate was filtered off and recrystallized from ethanol to afford 0 85 g (69%) of **10** as needles having m p 115–116°, $[\alpha]_D^{25}$ −98 3° (*c* 0 7, chloroform); p m r data, see Table I

Anal Calc for $C_{27}H_{22}O_6$ (442 4) C, 73 29, H, 5 01 Found C, 73 19, H, 4 90

On treatment with (2,4-dinitrophenyl)hydrazine in phosphoric acid–ethanol[27], compound **10** afforded the highly crystalline (2,4-dinitrophenyl)hydrazone **18** in 86% yield, m p 197° (after recrystallization from ethyl acetate–ethanol), $[\alpha]_D^{25}$ −343° (*c* 0 1, chloroform)

Anal Calc for $C_{33}H_{26}N_4O_{10}$ (638 6) C, 62 07, H, 4 10, N, 8 77 Found C, 61 92, H, 4 06, N, 8 73

2-Ethoxy-3-hydroxy-6-methyl-4 H-pyran-4-one (6-ethoxyallomaltol) (**29**) — A solution of **9** (1 0 g, 2 5 mmol) in pyridine (40 ml), to which 0 4 ml of piperidine had been added, was kept for 12 h at ~20°, whereupon t l c (C) indicated almost complete conversion of **9** into a mixture of **29** (R_F ~0 3) and more-polar, as yet unidentified products (R_F 0 02) Toluene (3 × 30 ml) was evaporated from the product to give a crystalline residue that was recrystallized from ethanol, yield 145 mg (34%) of **29** as fine needles having m p 174°, p m r data ($CDCl_3$)· δ 6 17 (s, 1 H, H-5), 4 44 (q, 2 H, Et-CH_2), 2 26 (s, 3 H, 6-Me), and 1 45 (t, 3 H, ethyl-Me), *m/e* 170 (M^+), 142 (M − CH_2=CH_2), 114 (M − CO), 86 (M − 2CO), 71 (M − CH_3 − 2CO), 68 (86 − H_2O), and 43 (86 − CH_3CO)

Anal Calc for $C_8H_{10}O_4$ (170 2) C, 56 46, H, 5 88 Found C, 56 45, H, 5 75

2-Methoxy-3-hydroxy-6-methyl-4 H-pyran-4-one (6-methoxy-allomaltol) (**30**) — Treatment of the β-glycoside **13** with pyridine–piperidine as already described for **29** afforded **30** in 27% yield, identical by m p (169°), mixed m p , and spectral data with the product obtained from the α anomer[12] **12**, *m/e* 156 (M^+), 127 (M − CHO), 113 (M − MeCO), and 43 (CH_3CO)

When performing the conversion **13** → **30** in pyridine (24 h at 25°) with subsequent addition of deuterium oxide, a methoxy-allomaltol specifically monodeuterated in the *C*-methyl group is obtained, as indicated by its mass spectrum *m/e* 157 (M^+), 128 (M − CHO), 114 (M − MeCO), and 44 (CH_2DCO)

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