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ESTERS OF 1,4-ANHYDRO-L-*erythro*-PENT-1-ENITOL (A FURANOID 2-HYDROXYGLYCAL)*

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ABSTRACT

Reaction of four esters of α-L-arabinofuranosyl bromide with 1,5-diazabicyclo-[5.4.0]undec-5-ene causes elimination of hydrogen bromide. In the case of the tris-(*p*-nitrobenzoate), only degradation products were observed, but from the other three esters, 1,4-anhydro-L-*erythro*-pent-1-enitol compounds were isolated. These compounds isomerise readily on standing in non-hydroxylic solvents to give 3-deoxypent-2-enofuranoses, and simultaneously lose benzoic acid to give furans. In ethanolic solution, both the 1,4-anhydropent-1-enitol esters and their 3-deoxy-2-enofuranose isomers react at room temperature to give anomeric mixtures of ethyl 3-deoxypent-2-enofuranosides. Compounds in this series are judged to be too reactive to serve generally as satisfactory glycosylating agents.

INTRODUCTION

Recent developments in the understanding of pyranosyl 2-hydroxyglycal esters have shown that they can be caused to isomerise stereospecifically to the corresponding 3-deoxyglyc-2-enopyranose esters, and from either the glycals or 2-enoses, 2,3-unsaturated pyranosides[2] or pyranosyl nucleosides[2,3] can be obtained. Hydrogenation of the products gives saturated 3-deoxy compounds, the overall sequence of reactions having recently been exemplified by the synthesis[4] of the disaccharide derivative methyl 3-*O*-(3,6-dideoxy-α-D-*ribo*-hexopyranosyl)-α-D-manno-pyranoside, as shown in Scheme 1.

Utilisation of unsaturated furanosyl glycal analogues could provide methods for obtaining specific furanosides and furanosyl nucleosides, particularly such compounds as the antibiotic cordycepin (3′-deoxyadenosine)[5], and the objective of this work was to assess the value, in this respect, of such starting materials. Apparently, furanoid 2-hydroxyglycals have not been synthesised specifically before,

*Unsaturated Carbohydrates: Part XVIII[1].

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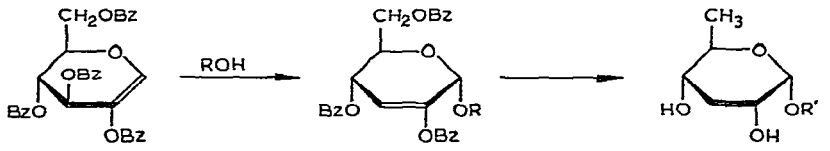


R, R' = appropriately substituted D-mannopyranosyl derivatives.
Scheme 1

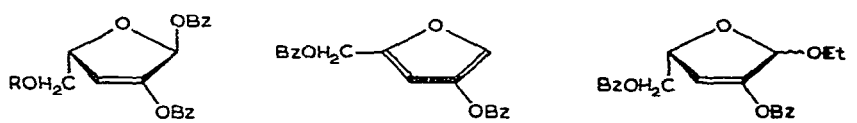
although 1,4-anhydro-2,3,5-tri-*O*-benzoyl-D-*erythro*-[6] and -D-*threo*[7]-pent-1-enitol have been reported as by-products of planned nucleoside syntheses. The physical constants of the former are not, however, in accord with its being the enantiomer of the tribenzoate **5** produced during this work.

RESULTS AND DISCUSSION

2,3,5-Tri-*O*-benzoyl-α-L-arabinofuranosyl bromide (**1**) was prepared from the corresponding methyl furanoside, as described by Ness and Fletcher[8]; by analogous procedures, the corresponding 2,3-di-*O*-benzoyl-5-*O*-(*p*-nitrobenzoyl)-, 2,3-di-*O*-benzoyl-5-*O*-(toluene-*p*-sulphonyl)-, and tri-*O*-(*p*-nitrobenzoyl)-L-arabinofuranosyl bromides (**2**, **3**, and **4**[9]) were synthesised. Each was separately treated in benzene with 1,5-diazabicyclo[5.4.0]undec-5-ene, a reagent which has previously been utilised in analogous work with pyranosyl halides to remove hydrogen halide and provide 2-hydroxyglycal esters[10]. The bromides **1** and **2** gave, respectively, the 1-enes **5** and **6** which possessed spectral characteristics in accord with their proposed structures. These compounds could not be crystallised and slowly decomposed on standing at room temperature; they were, however, stable for appreciable times when kept at 0°. From bromide **3**, a product, determined by n.m.r. methods to be 80% pure olefin, was obtained, but it decomposed on the silica gel used for its attempted purification;

1 R = R' = Bz
2 R = Bz; R' = OC·C6H4·NO2
3 R = Bz; R' = Ts
4 R = R' = OC·C6H4·NO2

5 R = Bz
6 R = OC·C6H4·NO2
7 R = Ts



8 R = Bz
9 R = OC·C6H4·NO2

10

11 α anomer
12 β anomer

from bromide **4**, only decomposition products were detectable. The n.m.r. data for **5**–**7**, given in Table I, are consistent with the assigned structures. Hydrogenation of **5** over a palladium–charcoal catalyst gave two saturated adducts having n.m.r. spectra and physical properties consistent with their being 1,4-anhydro-2,3,5-tri-*O*-benzoyl-L-arabinitol and -L-ribitol, respectively.

TABLE I

N.M.R. DATA[a] FOR COMPOUNDS **5**–**9**, **11**, AND **12**

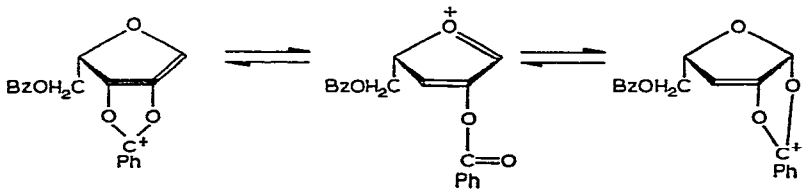
Compound	*Chemical shifts* (δ)					
	Aromatic	*H-1*	*H-3*	*H-4*	*H-5,5'*	*Me*
5	7.0–8.3 (15 H)	7.26	6.36	4.5—5.1		
6	7.0–8.3 (14 H)	7.26	6.36	4.4—5.0		
7	7.0–8.3 (14 H)	7.15	6.09	4.3—4.9		2.42
8[b]	7.1–8.3 (15 H)	7.22	6.43	5.43	4.2–4.7	
9	7.1–8.4 (14 H)	7.28	6.43	5.55	4.2–4.8	
11	7.1–8.3 (10 H)	5.98	6.23	5.28	4.3–4.6	
12	7.2–8.3 (10 H)	5.86	6.22	5.10	4.2–4.8	

Compound	*Coupling constants* (*Hz*)				
	$J_{1,3}$	$J_{1,4}$	$J_{3,4}$	$J_{4,5}$	$J_{4,5'}$
5	<1		2.5		
6	<1		2.5		
7	<1		2		
8[b]	<0.5	4	1.5	5.5	5.5
9	<1	4	2		
11	<1	4	1.5	4.5	4.5
12	<1	<1	2	5	5

[a]Measured in $CDCl_3$. [b]Measured in CCl_4.

Whereas tetra-*O*-benzoyl-2-hydroxy-D-glucal requires heating in boiling nitrobenzene for 15 min for it to isomerise to 1,2,4,6-tetra-*O*-benzoyl-3-deoxy-β-D-*erythro*-hex-2-enopyranose[11], the tribenzoate **5** underwent the analogous rearrangement to give **8** on standing at room temperature in solution in dichloromethane–ethyl acetate over silica gel, and concurrently benzoic acid was lost and the furan **10** produced. Similarly, the 5-(*p*-nitrobenzoate) **6** gave 46% of the corresponding, crystalline 2-enofuranose **9**, which was stable when stored at 0°. It is evident, therefore, that the allylic rearrangements by which compounds **8** and **9** are produced occur appreciably more readily than do the corresponding reactions of pyranosyl derivatives, which is in accord with the known, relative ease of allylic displacements from cyclopentene derivatives[12].

Consistent with observations made with 1,4-anhydro-3,5-di-*O*-benzoyl-2-deoxy-D-*erythro*-pent-1-enitol[13], both the hydroxyglycal derivative **5** and its isomer **8**,



13 15 14

when left in ethanol at room temperature, reacted to give the ethyl glycosides **11** and **12**; in addition, the furan **10** was again produced from **5**. Analogous glycoside formation is known in the pyranoid series but, as with the above isomerisation, the reaction occurs very much less readily. Significantly, both glycosides **11** and **12** were formed from both tribenzoates **5** and **8**, and ions **13** and **14**, which can interconvert *via* ion **15**, can be invoked to account for this, with ion **13** giving the β-L glycoside by *cis*-allylic displacement[14], and ion **14** affording the α-L compound by direct solvent attack at C-1. The furan **10** is readily obtainable by deprotonation at C-4 of ion **13**, analogous furan formation having been reported when 3,5-di-*O*-benzoyl-2-*O*-(*p*-nitrobenzenesulphonyl)-β-D-ribose was heated with molten benzoic acid[15]. In this work, the tribenzoate **5** likewise gave the furan **10**, quantitatively, when heated in the presence of acid. It was also formed in the mass spectrometer from the hydroxyglycal **5**, both compounds giving the same spectrum with the ion of highest mass having *m/e* 322 (molecular ion of the furan **10**), and the first fragment ion having *m/e* 201 (322—BzO). The same ions were observed in the spectrum of the glycoside **11** (loss of EtOH), but, in addition, ions formed by loss of benzoyloxy (*m/e* 247), benzoyloxymethyl (*m/e* 233), and ethyl benzoate (*m/e* 218) were observed in this case.

The anomeric configurations of the 3-deoxypent-2-enose derivatives were readily determined from the observed $J_{1,4}$ values, since in such systems H-1–H-4 coupling is large (*ca.* 4 Hz) when the protons are *trans*-related and small (*ca.* 1 Hz) when the relationship is *cis*[16].

Preliminary studies with cholesterol as a representative complex alcohol suggested that furanoid glycosides could be obtained by use of the unsaturated compounds here discussed, but the appreciable difficulties associated with isolation and storage of these precursors do not commend them for this purpose.

The mild conditions under which compound **5** isomerised persuade us that the substance previously believed[6] to be the enantiomer of **5**, and which had been subjected to boiling acetonitrile, was incorrectly assigned. With m.p. 120–122° and $[\alpha]_D$ +14.4° (chloroform), it corresponds to the enantiomer of neither of our compounds **5** or **8**.

EXPERIMENTAL

2,3,5-Tri-*O*-benzoyl-α-L-arabinosyl bromide[8] (**1**) and 2,3,5-tri-*O*-(*p*-nitrobenzoyl)-α-L-arabinosyl bromide[9] (**4**) were prepared by previously reported methods.

Methyl 5-O-(p-nitrobenzoyl)-α-L-arabinofuranoside. — A solution of *p*-nitrobenzoyl chloride (23.4 g, 1.2 mol. equiv.) in pyridine (40 ml) was added to methyl α-L-arabinofuranoside[9] (20.5 g) in pyridine (80 ml) at −5°. After 2 h at −5° and 18 h at 0°, the mixture was poured on to ice, and the precipitated oil was extracted into ethyl acetate. After drying of the extract and removal of the solvent, the residue gave a crystalline product (7.1 g, 18%) on trituration with acetone–ether. Recrystallisation from ethanol–ethyl acetate gave the title compound, m.p. 113–114°, $[\alpha]_D$ −51° (*c* 1, chloroform).

Anal. Calc. for $C_{13}H_{15}NO_8$: C, 49.8; H, 4.8; N, 4.5. Found: C, 49.7; H, 4.8; N, 4.4.

Methyl 2,3-di-O-benzoyl-5-O-(p-nitrobenzoyl)-α-L-arabinofuranoside. — The foregoing mono-ester was benzoylated, using standard procedures, to give the crude dibenzoate (5.1 g, 75%) which, when recrystallised from ethanol, had m.p. 113°, $[\alpha]_D$ +17° (*c* 1, dichloromethane).

Anal. Calc. for $C_{27}H_{23}NO_{10}$: C, 62.2; H, 4.4; N, 2.7. Found: C, 61.9; H, 4.4; N, 2.6.

2,3-Di-O-benzoyl-5-O-(p-nitrobenzoyl)-α-L-arabinofuranosyl bromide (**2**). — A solution of the foregoing triester (4 g) in acetic acid (20 ml) was treated with hydrogen bromide in acetic acid (20 ml; 50% w/v) for 15 min. Standard work-up procedures then afforded a crystalline product (3.0 g, 70%) (from anhydrous ethyl ether) which, on recrystallisation from isopropyl ether, gave the bromide **2** as pale-yellow needles, m.p. 111–112°, $[\alpha]_D$ −72° (*c* 1.9, dichloromethane), $J_{1,2}$ <0.5 Hz (therefore α-D configuration).

Anal. Calc. for $C_{26}H_{20}BrNO_9$: C, 54.7; H, 3.51; Br, 14.0; N, 2.5. Found: C, 54.4; H, 4.0; Br, 13.6; N, 2.4.

Methyl 2,3-di-O-benzoyl-5-O-toluene-p-sulphonyl-α-L-arabinofuranoside. — A solution of methyl α-L-arabinofuranoside (5.1 g) in pyridine (30 ml) was treated with toluene-*p*-sulphonyl chloride (6.0 g, 1.0 mol. equiv.) for 24 h at 5° and 24 h at 20°. Benzoyl chloride (10 ml) was then added and the solution was warmed at 50° for 30 min. The product, isolated as a glass (15 g) by standard procedures, afforded white needles (11.5 g) on trituration with ethanol (100 ml). Recrystallisation (×2) from acetone–ethanol gave the pure product (6.5 g, 40%), m.p. 120–122°, $[\alpha]_D$ +22° (*c* 2, chloroform).

Anal. Calc. for $C_{27}H_{26}O_9S$: C, 61.6; H, 5.0; S, 6.1. Found: C, 61.9; H, 5.1; S, 6.1.

2,3-Di-O-benzoyl-5-O-toluene-p-sulphonyl-α-L-arabinofuranosyl bromide (**3**). — The foregoing triester (4.0 g), when treated with hydrogen bromide in acetic acid as described above, gave a crystalline product (2.3 g, 52%; from dry ether) which was a mixture of anomers. The pure α-L compound was obtained by two recrystallisations from acetone–ether and had m.p. 138°, $[\alpha]_D$ −65° (*c* 2, dichloromethane), $J_{1,2}$ <0.5 Hz.

Anal. Calc. for $C_{26}H_{23}BrO_8S$: C, 54.2; H, 4.0; Br, 13.9. Found: C, 54.4; H, 3.9; Br, 14.2.

Synthesis of 1,4-anhydro-D-erythro-*pent-1-enitol triesters.* — (*a*) *The tribenzoate* (**5**). The tribenzoylglycosyl bromide **1** (2 g) in dry benzene (12 ml) was treated with 1,5-diazabicyclo[5.4.0]undec-5-ene (DBU) (0.8 ml, 1.2 mol. equiv.) with stirring at room temperature for 1.5 h. The crystalline base hydrobromide (0.83 g, 85%) was removed and the solution was diluted with dichloromethane (30 ml), washed with M sulphuric acid, aqueous sodium hydrogen carbonate, and water, and dried. Removal of the solvents gave a yellow gum (1.6 g, 90%) which was purified by preparative t.l.c. to give **5** as a thick, colourless oil (0.8 g, 47%), $[\alpha]_D$ −73° (*c* 2, chloroform); ν_{max} 1650 cm^{-1} (C=C); for n.m.r. data, see Table I.

(*b*) *The nitrobenzoate* (**6**). The 5-*p*-nitrobenzoate **2** (2.0 g) gave, by the method in (*a*), the corresponding, crude hydroxyglycal triester as a yellow glass which was purified by column chromatography to afford **6** as a pale-yellow gum (0.8 g, 53%), $[\alpha]_D$ −68° (*c* 1.8, chloroform); ν_{max} 1650 cm^{-1} (C=C); for n.m.r. data, see Table I.

(*c*) *The toluene*-p-*sulphonate* (**7**). Elimination was effected from the sulphonate **3**, as described above, and the desired olefin **7** was shown to be present (80%) in the crude products by n.m.r. spectroscopy. On attempted purification by chromatography on silica gel, the compound decomposed.

When trinitrobenzoylglycosyl bromide **4** was treated with DBU, only decomposition products could be detected.

Hydrogenation of the tribenzoate **5**. — The purified olefin **5** (0.8 g) was hydrogenated in ethyl acetate (15 ml) over palladium-on-charcoal (1 g, 10%). Removal of the catalyst and solvent gave a colourless syrup (0.77 g), a portion (0.4 g) of which was resolved by preparative t.l.c. to give 1,4-anhydro-2,3,5-tri-*O*-benzoyl-L-arabinitol (0.27 g, 67%), $[\alpha]_D$ −78° (*c* 1, chloroform) (lit.[17] $[\alpha]_D$ +77° for the D enantiomer), and 1,4-anhydro-2,3,5-tri-*O*-benzoyl-L-ribitol (0.07 g, 18%), $[\alpha]_D$ −103° (*c* 1, chloroform) (lit.[17] $[\alpha]_D$ +107° for the D enantiomer). The n.m.r. characteristics were consistent with the assigned structures.

1,2,5-Tri-O-*benzoyl-3-deoxy-α*-L-glycero-*pent-2-enose* (**8**). — A solution of the hydroxyglycal tribenzoate **5** (1 g) in dichloromethane–ethyl acetate (10 ml, 9:1) was stood over silica gel (Merck Kieselgel G, 3 g) for 18 h. Removal of the silica gel and the solvent left a yellow syrup (0.9 g) which was resolved by preparative t.l.c. to give **8** (0.3 g, 30%), $[\alpha]_D$ +45° (*c* 2.5, chloroform); ν_{max} 1650 cm^{-1}; for n.m.r. spectrum, see Table I. In addition, the furan **10** (0.08 g, 12%), m.p. 75°, $[\alpha]_D$ 0°, was obtained from the plate.

1,2-Di-O-*benzoyl-5*-O-(p-*nitrobenzoyl*)-*3-deoxy-α*-L-glycero-*pent-2-enose* (**9**). — A solution of the triester **6** (0.5 g) in dichloromethane–ethyl acetate (5 ml, 9:1) was stood over silica gel (1.5 g) for 18 h. Removal of the silica gel and solvents gave a yellow glass (0.44 g) which afforded yellow crystals (0.23 g, 46%) of the rearranged product. Two recrystallisations from dry ether gave **9** (0.12 g), m.p. 125–125.5°, $[\alpha]_D$ +40° (*c* 1, dichloromethane); ν_{max} 1650 cm^{-1}; for n.m.r. data, see Table I.

Anal. Calc. for $C_{26}H_{29}NO_9$: C, 63.8; H, 3.9; N, 2.9. Found: C, 63.6; H, 4.1; N, 2.5.

Reaction of tribenzoate **5** *with ethanol.* — A solution of the hydroxyglycal

tribenzoate **5** (0.6 g) in ethanol was kept at 20° for 24 h. Three products were observed (t.l.c.) to have been formed in this time. The ethanol was removed to leave a syrup which was resolved by preparative t.l.c. to give (*a*) ethyl 2,5-di-*O*-benzoyl-3-deoxy-α-L-*glycero*-pent-2-enofuranoside (**11**; 0.19 g, 38%), $[\alpha]_D$ +15° (*c* 2.5, chloroform); (*b*) ethyl 2,5-di-*O*-benzoyl-3-deoxy-β-L-*glycero*-pent-2-enofuranoside (**12**; 0.17 g, 34%), $[\alpha]_D$ +68° (*c* 2, chloroform); (*c*) 4-benzoyloxy-2-(benzoyloxymethyl)furan (**10**; 0.06 g, 14%), m.p. 75° (from methanol), $[\alpha]_D$ 0° (*c* 2, chloroform). The n.m.r. data for compounds **11** and **12** are given in Table I.

Reaction of tribenzoate **8** *with ethanol.* — The 1-*O*-benzoyl-2-enofuranose **8** (0.1 g), when dissolved in ethanol, underwent reaction which was complete in 30 min. N.m.r. spectroscopy of a solution of the dried residue in deuteriochloroform revealed that the ethyl glycosides **11** and **12** had been formed in the ratio ~1:2.

4-Benzoyloxy-2-(benzoyloxymethyl)furan (**10**). — A solution of the hydroxyglycal tribenzoate **5** (0.2 g) in benzene (5 ml) was treated with toluene-*p*-sulphonic acid (0.01 g) at 60° for 1 h. The solution was washed with aqueous sodium hydrogen carbonate and dried, and the solvent was removed to give **10** (0.15 g, 100%). Recrystallised from methanol, **10** had m.p. 75°, $[\alpha]_D$ 0°; n.m.r. data ($CDCl_3$): δ 7.1–8.3 (m, 10H, Ph), 7.86 (s, H-5), 6.62 (s, H-3), 5.27 (s, 2H, CH_2).

Anal. Calc. for $C_{19}H_{14}O_5$: C, 70.8; H, 4.4. Found: C, 71.0; H, 4.3.

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