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CATION-EXCHANGE RESIN-CATALYZED ADDITION OF METHANOL TO BENZOYLATED 1,5-ANHYDRO-2-DEOXY-D-HEX-1-ENITOLS

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ABSTRACT

1,5-Anhydro-3,4,6-tri-*O*-benzoyl-2-deoxy-D-*arabino*-hex-1-enitol (**1**) was boiled under reflux with methanol and AG 50W-X8 cation-exchange resin. A two-product mixture of glycosides (**2** and **3**) was obtained in 38% yield, together with 19% of unreacted material. 1,5-Anhydro-3,6-di-*O*-benzoyl-2-deoxy-D-*arabino*-hex-1-enitol (**7**) was prepared from 1,5-anhydro-2-deoxy-D-*arabino*-hex-1-enitol by selective benzoylation, from which the corresponding 4-methanesulfonate **8** was obtained. Treatment of **8** with sodium benzoate in hexamethylphosphoric triamide for 72 h at 100° afforded 1,5-anhydro-3,4,6-tri-*O*-benzoyl-2-deoxy-D-*lyxo*-hex-1-enitol (**9**) in 52% yield. An unknown byproduct (*B*), tentatively shown to be a tri-*O*-benzoyl-D-hex-2-enopyranose analog, was also isolated in 14% yield. The 270-MHz n.m.r. spectrum of *B* was analyzed in terms of its $J_{1,3}$, $J_{2,4}$, and $J_{4,5}$ coupling constants in relation to the various configurational and conformational possibilities for hex-2-enopyranoses, and was identified as 1,4,6-tri-*O*-benzoyl-2,3-dideoxy-α-D-*threo*-hex-2-enopyranose having the $^{\circ}H_5$ conformation. The analysis presented should also be applicable to pent-2-enopyranose systems. When **9** was treated with methanol in the presence of AG 50W-X8 cation-exchange resin, a mixture of glycosides **4** and **5** was obtained in 47% yield. The low yields were attributed to methanolysis of the benzoyl groups during the reaction.

INTRODUCTION

Unsaturated sugars, in particular the 1,5-anhydro-2-deoxy-D-hex-1-enitols[1,2], have been the subject of intensive study, in part because of their versatility as synthetic intermediates. For example, such functionalities as chloro[3], fluoro[4], difluoro[5], amino[6], and thio[7], may be introduced into the 2-position of sugars by either direct or indirect addition of suitable agents across the double bond. 1,5-Anhydro-2-deoxy-D-hex-1-enitols may also be converted into the corresponding 2,3-unsaturated glycosides by treatment with alcohols at either high temperatures[8,9] or in the presence of the catalyst boron trifluoride[10,11], a reaction that has led to the synthesis of 2′,3′-unsaturated pyranosyl nucleosides of biological interest[12]. Furthermore, their sensi-

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trait to the reaction conditions is underlined by the formation of 2,3-unsaturated glycosyl fluorides when 1,5-anhydro-2-deoxy-D-hex-1-enitols are treated with hydrogen fluoride[13-15], a reaction which contrasts with the formation of 2-deoxy glycosyl halides obtained by the use of either hydrogen chloride or hydrogen bromide[16].

The synthesis of methyl 2-deoxy-D-glycosides, by treating 1,5-anhydro-2-deoxy-D-hex-1-enitols with methanolic hydrogen chloride, was reviewed by Ferrier[1]. In their initial experiments with 1,5-anhydro-2-deoxy-D-*lyxo*-hex-1-enitol[17] and 1,5-anhydro-2-deoxy-D-*arabino*-hex-1-enitol[18], Stacey and coworkers reported good yields for the formation of methyl 2-deoxy-α-D-glycosides. A reexamination of the 1,5-anhydro-2-deoxy-D-*arabino*-hex-1-enitol reaction[19], however, indicated a very low yield of methyl 2-deoxy-α-D-*arabino*-hexopyranoside. This reaction has now been studied in more detail and the various byproducts characterized[20]. Similarly, the reactions of 1,5-anhydro-2-deoxy-L-*erythro*-pent-1-enitol[21] and 1,5-anhydro-2-deoxy-D-*threo*-pent-1-enitol[22] were also reported to give low yields of methyl 2-deoxyglycosides in favor of other byproducts. An alternative approach to the synthesis of methyl 2-deoxy-D-glycosides involving the methoxymercuration of 1,5-anhydro-2-deoxy-D-hex-1-enitols has also appeared[23,24].

The addition of methanol to 1,5-anhydro-2,6-dideoxy-L-*arabino*-hex-1-enitol and to its 3,4-di-*O*-acetyl and 3,4-di-*O*-benzoyl derivatives in the presence of AG 50W-X8 cation-exchange resin, has recently been described[25]. While 1,5-anhydro-2,6-dideoxy-L-*arabino*-hex-1-enitol and its 3,4-di-*O*-acetyl derivative appear to give several products, treatment of the corresponding dibenzoate under similar conditions afforded a mixture of the methyl 2-deoxy-α- and methyl 2-deoxy-β-D-glycosides in 70% yield. We now extend these observations and herein report on the addition of methanol to the 3,4,6-tri-*O*-benzoyl derivatives of 1,5-anhydro-2-deoxy-D-*arabino*-hex-1-enitol and 1,5-anhydro-2-deoxy-D-*lyxo*-hex-1-enitol.

RESULTS AND DISCUSSION

1,5-Anhydro-3,4,6-tri-*O*-benzoyl-2-deoxy-D-*arabino*-hex-1-enitol[14] (**1**) was treated with methanol and AG 50W-X8 cation-exchange resin, under conditions identical to those previously reported for the 1,5-anhydro-2,6-dideoxy-L-*arabino*-hex-1-enitol derivatives[25]. The reaction, however, afforded only 38% of a major two-product mixture, together with 19% of unreacted material. Other compounds of lower R_F value, as indicated by t.l.c. analysis of the mixture, were thought to be methanolysis byproducts and were not investigated further. The derivatives, subsequently separated, were shown from their 270-MHz ^{1}H-n.m.r. spectra (Table I) to be methyl 3,4,6-tri-*O*-benzoyl-2-deoxy-α-D-*arabino*-hexopyranoside (**2**, $J_{1,2a}$ 3.3 and $J_{1,2e}$ 1.1 Hz) and the corresponding methyl 2-deoxy-β-D-*arabino*-hexopyranoside (**3**, $J_{1,2a}$ 9.5 and $J_{1,2e}$ 2.2 Hz).

The second part of our study required the preparation of 1,5-anhydro-3,4,6-tri-*O*-benzoyl-2-deoxy-D-*lyxo*-hex-1-enitol (**9**). The synthesis of 1,5-anhydro-3,6-di-*O*-benzoyl-2-deoxy-D-*arabino*-hex-1-enitol (**7**) from 1,5-anhydro-2-deoxy-D-*arabino*-

TABLE I

FIRST-ORDER ^{1}H-N.M.R. DATA OF **2–9** AND **11**[a,b]

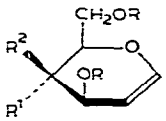
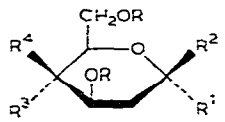
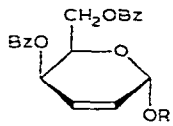
Compound	*Chemical shifts (δ values)*[c]							
	H-1	*H-2a*	*H-2e*	*H-3*	*H-4*	*H-5*	*H-6*	*H-6'*
2	4.95	2.00	2.52	5.72	5.57	4.34	4.59	4.47
3	4.68	1.93	2.59	5.44	5.55	4.00	4.62	4.49
4	5.08	2.36	2.17	5.68	5.84	4.89	4.58	4.37
5	4.67	2.22	2.29	5.40	5.80	4.15	4.67	4.46
6	4.91	2.08	1.87	5.28	5.33		← 4.0–4.11 →	
		H-2						
7[e]	6.53	4.89		5.59	4.09	4.23	4.83	4.68
8[f]	6.55	5.00		5.72	5.32	4.56[d]	4.75[d]	4.66[d]
9	6.63	4.99		5.93	5.93	4.70[d]	4.80[d]	4.56
10	6.72	6.25		6.50	5.47	4.73	4.63	4.54

	Coupling constants (Hz)										
	$J_{1,2a}$	$J_{1,2e}$	$J_{2a,2e}$	$J_{2a,3}$	$J_{2e,3}$	$J_{3,4}$	$J_{4,5}$	$J_{5,6}$	$J_{5,6'}$	$J_{6,6'}$	*OMe*
2	3.3	1.1	−12.8	11.4	5.1	9.9	9.9	2.9	5.5	−12.6	3.44
3	9.5	2.2	−12.5	9.5	5.1	9.5	9.5	3.3	5.5	−11.7	3.55
4	3.6	0.5	−12.5	12.5	5.1	2.9	1.0	7.0	5.5	−10.6	3.44
5	9.2	2.5	−12.5	12.1	5.5	3.3	1.0	6.6	6.6	−11.4	3.61
6	3.6	1.1	−12.5	12.5	5.1	2.9					3.36

	$J_{1,2}$	$J_{1,3}$	$J_{1,4}$	$J_{2,3}$	$J_{2,4}$	$J_{3,4}$	$J_{4,5}$	$J_{5,6}$	$J_{5,6'}$	$J_{6,6'}$
7	6.3	−1.5		2.6		6.6	9.5	4.4	2.5	−12.1
8	6.2	−1.5		3.3		5.8	7.7	3.6	5.1	−12.1
9	6.2	−1.1		2.9	1.5			7.3	4.4	−11.0
10	3.3	−1.1	0.3	10.2	0.3	5.5	2.6	6.9	5.5	−11.3

[a]Determined for solutions in chloroform-*d* at 270 MHz. [b]The proton on C-6 giving the higher-field signal is designated H-6'. [c]The mean points of the resonances were taken as their chemical shifts, even where second-order features were observed. [d]Second-order features were present in the splitting pattern. [e]OH δ 3.80, J_{OH} 3.2 Hz. [f]OMs δ 3.07.

hex-1-enitol, an essential intermediate of the sequence reported herein, was originally described by Blackburne *et al.*[26]. Its preparation follows from studies on the selective benzoylation of methyl 6-deoxy-α-D-glucopyranoside by Kondo and coworkers[27], who clearly indicated that the reactivities of the secondary hydroxyl groups were in the order OH-2>OH-3>OH-4. We now report complete n.m.r.-spectral data for **7** at 270 MHz (Table I). Although the product we isolated migrated as a single spot on t.l.c. and its structure was confirmed by elemental and n.m.r. analyses, its m.p. (133–134°) contrasts with that published earlier (118–119°)[26]. Mesylation of **7** then gave crystalline 1,5-anhydro-3,6-di-*O*-benzoyl-2-deoxy-4-*O*-mesyl-D-*arabino*-hex-1-enitol (**8**) in 88% yield.

1 R = Bz ; R^1 = OBz ; R^2 = H
7 R = Bz ; R^1 = OH ; R^2 = H
8 R = Bz ; R^1 = OMs ; R^2 = H
9 R = Bz ; R^2 = OBz ; R^1 = H

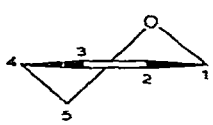
2 R^1 = OMe ; R = Bz ; R^3 = OBz ; R^2 = R^4 = H
3 R^2 = OMe ; R = Bz ; R^3 = OBz ; R^1 = R^4 = H
4 R^1 = OMe ; R = Bz ; R^4 = OBz ; R^2 = R^3 = H
5 R^2 = OMe ; R = Bz ; R^4 = OBz ; R^1 = R^3 = H
6 R^1 = OMe ; R = Ac(d_3) ; R^4 = OAc(d_3) ; R^2 = R^3 = H

10 R = Bz
11 R = Me

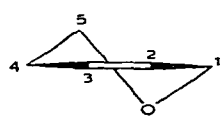
Treatment of **8** with sodium benzoate in hexamethylphosphoric triamide for 72 h at 100° afforded an apparent single product by t.l.c. analysis of the mixture. Column-chromatographic purification on silica gel, however, gave a syrupy *A* in 52% yield, from which a second product *B* partially crystallized in 14% yield. The 270-MHz ^{1}H-n.m.r. spectrum of compound *A* was similar in appearance to that of **8**, except for the overlapping H-3 and H-4 signals, and showed H-1 coupling constants ($J_{1,2}$ 6.2 and $J_{1,3}$ 1.1 Hz) in accordance with those expected for 1,5-anhydro-2-deoxy-D-hex-1-enitols[28]. A long-range $J_{2,4}$ coupling (1.5 Hz) was also visible in the H-2 resonance, which appeared as a sharply defined, eight-peak multiplet. Based on the foregoing data (Table I), compound *A* was assigned the 1,5-anhydro-3,4,6-tri-*O*-benzoyl-2-deoxy-D-*lyxo*-hex-1-enitol (**9**) structure.

Compound *B* was tentatively identified from its n.m.r. spectrum as a 2,3-unsaturated sugar, because of the characteristic $J_{2,3}$ (10 Hz) coupling-constant[29,30]. Elemental analysis, however, indicated a structure similar to that of *A*; this was further supported by integration of the spectrum, which revealed the presence of 15 aromatic and 7 ring protons. Accordingly, the foregoing data are consistent with compound *B* having the empirical structure of a tri-*O*-benzoyl-D-hex-2-enopyranose.

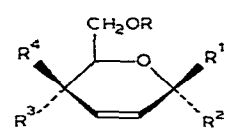
D-Hex-2-enopyranosides are represented by four configurations involving different orientations of the groupings at C-1 and C-4 namely, *α-erythro*, *β-erythro*, *α-threo*, and *β-threo*, for which there exist two major half-chair conformations $^{\circ}H_5$(D) and ^5H_o(D)*, as indicated in Fig. 1. In order to determine the configuration



$^{\circ}H_5$



^5H_o



R^1 = R^4 = H α-*erythro*
R^1 = R^3 = H α-*threo*
R^2 = R^4 = H β-*erythro*
R^2 = R^3 = H β-*threo*

Fig. 1. Hex-2-enopyranose configurations and half-chair conformations.

TABLE II

COMPLEMENTARY CONFIGURATIONAL/CONFORMATIONAL $J_{1,3}$, $J_{2,4}$, AND $J_{4,5}$ COUPLING CONSTANTS FOR HEX-2-ENOPYRANOSES[a]

$^0H_5$	$J_{1,3}$[b]	$J_{2,4}$[b]	$J_{4,5}$
α-erythro	*S*	*L*	*L*
α-threo	*S*	*S*	*S*
β-erythro	*L*	*L*	*L*
β-threo	*L*	*S*	*S*
$^5H_0$			
β-erythro	*S*	*S*	*S*
β-threo	*S*	*L*	*S*

[a] $J_{4a,5a}$ (*L*) ~9 Hz (refs. 32, 34, 36); $J_{4e,5a}$ (*S*) ~2 Hz (refs. 29, 31); $J_{4a,5e}$ (*S*) ~5 Hz (ref. 37); $J_{4e,5e}$ (*S*) 2–5 Hz (ref. 36); $J_{1,3}$ ($\phi \sim 30°$) (*S*) 0–1.0 Hz (refs. 29, 30, 38, 39); $J_{1,3}$ ($\phi \sim 90°$) (*L*) 0.8–2.0 Hz (refs. 29, 30, 38); $J_{2,4}$ ($\phi \sim 30°$) (*S*) ~0 Hz (ref. 29); $J_{2,4}$ ($\phi \sim 90°$) (*L*) ~1.6–2.5 Hz (refs. 29, 34, 38). [b] The ranges quoted for the respective $J_{1,3}$ and $J_{2,4}$ coupling constants appear, in general, to be in accordance with those found in a wide variety of non-carbohydrate systems[40]. The notations *L* and *S* have been applied independently to each of the couplings between H-4 and H-5, H-1 and H-3, and H-2 and H-4. In each of these groups, the notation *L* refers to the larger, and *S* to the smaller coupling constant(s).

and conformation of any unknown, consideration must be given to those coupling constants that collectively allow maximal distinction between the various structures.

Of the four configurations, compounds having the *α-erythro* and *α-threo* structures appear to adopt the energetically more favorable $^0H_5$ conformation, as Ferrier and Sankey[31] pointed out that the corresponding $^5H_0$ conformation would involve not only the anomeric [32] and allylic[31] effects, but also a bulky axial group at C-5 as well. An interesting exception to this rule appears in the case of 9-(4-*O*-acetyl-2,3-dideoxy-α-D-*glycero*-pent-2-enosyl)-6-chloropurine, which was reported[33] to exist as an equilibrium mixture of the $^0H_5$ and $^5H_0$ conformations, in which the $^0H_5$ form predominates. The absence of a bulky group at C-5 and the ability of the base[12,34] to bring about a reverse-anomeric effect[35] contribute significantly to the enhanced stability of the $^5H_0$ form.

The remaining configurational/conformational combinations may adequately be defined by comparison of their respective $J_{1,3}$, $J_{2,4}$, and $J_{4,5}$ coupling constants as shown in Table II. In the case of compounds possessing either the *α-threo* ($^0H_5$) or *β-erythro* ($^5H_0$) structures, absolute assignment cannot be based solely on their n.m.r. data since, as indicated in Table II, they would be expected to have essentially identical coupling-constants. Classification, therefore, requires prior knowledge of either the configuration at C-1 or C-4.

The favored conformation of the *β-erythro* and *β-threo* structures has also been predicted by Ferrier and Sankey[31]. From a consideration of the anomeric, allylic,

*The analysis presented in this article pertains only to the major half-chair forms ($^0H_5$ and $^5H_0$), although other conformations have been documented[47].

and bulky axial-group effects, *β-erythro* configurations should favor the $^5H_0$ conformation, whereas *β-threo* configurations favor the $^0H_5$ conformation. An example of a *β-threo* structure adopting the $^5H_0$ conformation appears to be lacking in the literature, however, a corresponding 1,6-anhydro analog[37] gives coupling constants in keeping with predicted values (Table II). D-*erythro*-Hex-2-enopyranosylpurine analogs[12,34] were shown to adopt the less favorable $^0H_5$ conformation, because of the reverse-anomeric effect[35]. A further interesting example also appears in the case of 4,6-di-*O*-acetyl-2,3-dideoxy-*β*-D-*erythro*-hex-2-enopyranosyl azide[41].

The n.m.r. spectrum of compound *B* was shown to have $J_{1,3}$, $J_{2,4}$, and $J_{4,5}$ coupling constants of 1.1, <0.3, and 2.6 Hz, respectively. It follows from Table II that the $J_{2,4}$ and $J_{4,5}$ couplings would give *S* and *S* notations, respectively, whereas the $J_{1,3}$ coupling constant indicates either *S* or *L*. Accordingly, the structure of compound *B* could be either *β-erythro* ($^5H_0$), *β-threo* ($^0H_5$), or *α-threo* ($^0H_5$). Consideration of the homoallylic $J_{1,4}$ coupling-constants should be a good supplement to the analysis presented in Table II, where ambiguities arise in the correct assignment of any pair of coupling constants. Angular alignment of H-1 and H-4 can take three orientations, namely, quasiequatorial/quasiequatorial; quasiaxial/quasiequatorial, quasiequatorial/quasiaxial; and quasiaxial/quasiaxial. Experimental data indicate these orientations should give rise to coupling constants on the order of 0–0.8 (refs. 29, 30, 33), 1.2–2.0 (refs. 29, 30, 34, 42), and 2.2–2.6 (refs. 29 and 34) Hz, respectively. The $J_{1,4}$ coupling constant of compound *B* was <0.3 Hz, indicating a quasiequatorial/quasiequatorial relationship between H-1 and H-4. The structure of *B*, therefore, is either *β-erythro* ($^5H_0$) or *α-threo* ($^0H_5$), as a $J_{1,4}$ coupling constant of approximately 1.2–2.0 Hz should be expected for a *β-threo* ($^0H_5$) structure. It was, however, previously concluded from Table II (and also from molecular models), that an absolute assignment for compounds having either the *β-erythro* ($^5H_0$) or *α-threo* ($^0H_5$) structures could not be based solely on their n.m.r. parameters, as the various H,H bond-angle combinations are essentially identical. As compound *B* was formed from **8** upon treatment with sodium benzoate in hexamethylphosphoric triamide and has been identified as a tribenzoate, it is natural to conclude that inversion took place at C-4. Accordingly, compound *B* was assigned the structure 1,4,6-tri-*O*-benzoyl-2,3-dideoxy-*α*-D-*threo*-hex-2-enopyranose (**10**), having the $^0H_5$ conformation. It is believed that the aforementioned analysis provides a basis for the assignment of any hex-2-enopyranose derivative, and should be extendable to pent-2-enopyranose systems as well.

The formation of 1,4,6-tri-*O*-benzoyl-2,3-dideoxy-*α*-D-*threo*-hex-2-enopyranose (**10**) from 1,5-anhydro-3,6-di-*O*-benzoyl-2-deoxy-4-*O*-mesyl-D-*arabino*-hex-1-enitol (**8**) under the conditions employed appears to be consistent with literature expectations. The peracetylated analogs of 1,5-anhydro-2-deoxy-D-*arabino*-hex-1-enitol[8] and 1,5-anhydro-2-deoxy-D-*lyxo*-hex-1-enitol[9], were shown to undergo allylic displacement of the 3-acetoxy group, with the formation of alkyl 2,3-unsaturated sugars when heated together with alcohols at high temperature. The use of boron trifluoride etherate as catalyst, however, subsequently facilitated the reaction at room tempera-

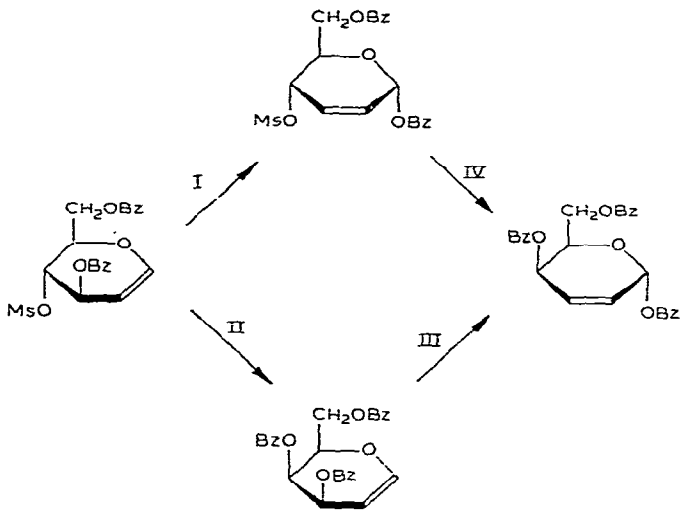


Fig. 2. Allylic rearrangement; II, nucleophilic displacement of mesyloxy group with inversion of configuration; III, allylic rearrangement; and IV, nucleophilic displacement of allylic mesyloxy group.

ture, requiring only stoichiometric amounts of alcohol[10,11,43]. Similar allylic rearrangements have also been reported for the reaction of 1,5-anhydro-2-deoxy-D-hex-1-enitols with hydrogen fluoride in benzene[15,16,39], and with purines in the presence of acid catalysts[12,33,34].

The formation of compound **10** from **8** is a two-stage process that can take place by one of two alternative pathways as shown in Fig. 2, involving nucleophilic displacement of the 4-mesyloxy group and allylic displacement of the 3-*O*-benzoyl group. Although the displacement of allylic mesyloxy groups by nucleophiles is known to occur at a much greater rate than the displacement of corresponding secondary mesyloxy groups (type II)[44], and reactions of type I are known to take place more readily than those of type III[9], the relatively higher yield of **9** compared to **10** indicates that the formation of **10** probably takes place by both pathways simultaneously.

1,5-Anhydro-3,4,6-tri-*O*-benzoyl-2-deoxy-D-*lyxo*-hex-1-enitol (**9**) containing 10% of compound **10** as an impurity (as indicated by its n.m.r. spectrum) was heated under reflux in methanol for 20 h in the presence of AG 50W-X8 cation-exchange resin. T.l.c. examination of the mixture indicated the formation of three major products, *A*, *B*, and *C*, which were separated by column chromatography on silica gel. Compounds of lower R_F value also detected were thought to be methanolysis by-products and were not investigated further. The 270-MHz ^{1}H-n.m.r. spectrum (Table I) of product *A* indicated the presence of 10 aromatic protons and a 3-proton singlet at δ 3.47. The spectrum was similar to that of compound **10**, indicating that *A* was methyl 4,6-di-*O*-benzoyl-2,3-dideoxy-α-D-*threo*-hex-2-enopyranoside (**11**, 74%). The product was obviously formed from the impurity **10** in the mixture. Compound *B* (**34**%) had an n.m.r. spectrum (Table I) essentially identical to that of methyl 3,4-

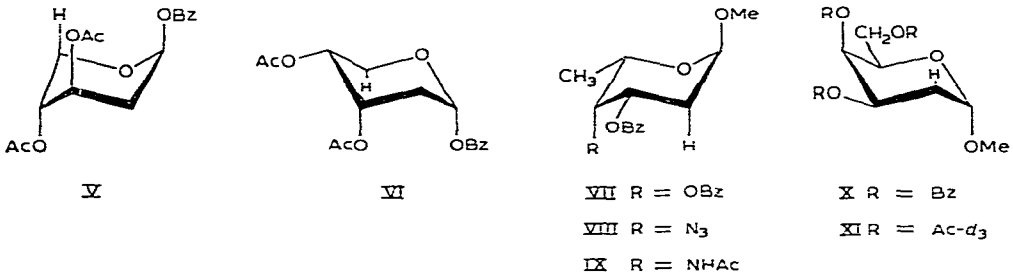


Fig. 3. Deshielding of axial proton by *syn*-axial group.

di-*O*-benzoyl-2,6-dideoxy-α-L-*lyxo*-hexopyranoside reported previously[25], and was characterized as the methyl 2-deoxy-α-D-*lyxo*-hexopyranoside (**4**). Compound *C* (13%) was identified from its n.m.r. spectrum (Table I) as the corresponding methyl 2-deoxy-β-D-*lyxo*-hexopyranoside (**5**).

Exceptions to the rule that an equatorial proton resonates at a field lower than that of a chemically similar but axially oriented proton have been documented[25]. Both methyl 3,4-di-*O*-benzoyl-2,6-dideoxy-α-L-*lyxo*- (VII) and methyl 4-azido-3-*O*-benzoyl-2,4,6-trideoxy-α-L-*lyxo*-hexopyranoside (VIII) but, interestingly, not the corresponding 4-acetamido (IX) derivative (Fig. 3) exhibit this phenomenon. Similar data were also reported for H-5a of di-*O*-acetyl-2-deoxy-α-D-*erythro* ($^4C_1$) (VI) and β-D-*threo*-$^1C_4$ (V) pentopyranoses[45]. These examples underline the presence of a *syn*-axial relationship between a group capable of exerting an anisotropic deshielding effect on a neighboring axial proton. It was accordingly anticipated and subsequently confirmed (Table I) that compound **4** (X) also elicited similar properties.

As acetyl resonances usually overlap that of the H-2e/H-2a proton signals, we have extended our previous studies by the preparation of methyl 3,4,6-tri-*O*-(acetyl-d_3)-2-deoxy-α-D-*lyxo*-hexopyranoside (**6**) (XI, Fig. 3). This compound was prepared from **4** after *O*-debenzoylation and subsequent d_3-acetylation. The n.m.r. spectrum (Table I) indicated that an acetyl group in juxtaposition to an axial proton may also cause it to resonate at lower field than the corresponding equatorial proton.

Reaction of the tribenzoates **1** and **9** with boiling methanol in the presence of AG 50-X8 cation-exchange resin afforded lower yields of methyl α,β-D-glycosides than with 1,5-anhydro-3,4-di-*O*-benzoyl-2,6-dideoxy-L-*arabino*-hex-1-enitol[25] under similar conditions. This result may be due to enhanced methanolysis of the benzoyl groups during the reaction of **1** and **9**. It was noted that the 1,5-anhydro-2-deoxy-D-*lyxo*-hex-1-enitol derivative **9** was more reactive than the corresponding 1,5-anhydro-2-deoxy-D-*arabino*-hex-1-enitol analog **1**. This observation may be rationalized in terms of the orientational inductive effect of the 4-benzoyl group on the electron density at C-2, as both compounds essentially adopt the $^4H_5$(D) conformation[28], assuming that protonation is the rate-limiting step in this reaction. This hypothesis is also supported by the lower-field chemical shift of H-2 in compound **1** (δ 5.18)[14] as compared with compound **9** (δ 4.99)[16].

EXPERIMENTAL

General methods. — All evaporations were performed under diminished pressure. Melting points were determined on a Thomas–Hoover apparatus and are uncorrected. Hexamethylphosphoric triamide was dried over calcium hydride and then distilled under diminished pressure. Column chromatography was performed on silica gel, Merck 7734 (70–235 mesh), and all reactions were monitored by t.l.c. on silica gel G (E. Merck A.G., Darmstadt, Germany). Petroleum ether refers to a fraction having b.p. 35–60°. Elemental analyses and optical rotations were performed by Baron Consulting Company, Orange, CT (U.S.A.).

Reaction of **1** *with methanol and AG 50W-X8 cation-exchange resin.* — To a solution of **1** (ref. 14) (1.26 g) in methanol (63 mL) was added AG 50W-X8 cation-exchange resin (6.3 g). The mixture was boiled for 20 h under reflux whereupon t.l.c. (10:1, v/v, petroleum ether–ethyl acetate) indicated two major products and some unreacted starting material. The suspension was filtered, the filtrate evaporated, and the residue applied to a column of silica gel. Elution with petroleum ether containing 3% (v/v) of ethyl acetate afforded unreacted starting material (0.238 g, 18.9%); further elution with 6:1 (v/v) petroleum ether–ethyl acetate afforded a mixture of the α- and β-glycosides **2** and **3** (0.516 g, 38.3%). This mixture was subsequently reapplied to a column of silica gel and eluted with petroleum ether containing 3% (v/v) ethyl acetate. The first product isolated from the column was identified by its 270-MHz ^{1}H-n.m.r. spectrum (Table I) as methyl 2-deoxy-α-D-*arabino*-hexopyranoside (**2**, 0.272 g, 20.2%), m.p. 106–107° (from petroleum ether–ethyl acetate), $[\alpha]_D^{23}$ +58° (*c* 1, chloroform); lit.[3] m.p. 110.5–111°, $[\alpha]_D^{24}$ +50.9 (*c* 0.59, 1,2-dichloromethane).

The corresponding methyl 2-deoxy-β-D-*arabino*-hexopyranoside **3** (0.181 g, 13.4%) was isolated as the second component upon further elution, m.p. 93.5–95.5° (from petroleum ether–ethyl acetate), $[\alpha]_D^{23}$ −57° (*c* 1, chloroform); lit.[3] m.p. 96.0–97.5°, $[\alpha]_D^{24}$ −51.1° (*c* 1.04, 1,2-dichloroethane).

*1,5-Anhydro-3,6-di-*O*-benzoyl-2-deoxy-*D-arabino-*hex-1-enitol* (**7**). — A solution of 1,5-anhydro-2-deoxy-D-*arabino*-hex-1-enitol (0.9 g) in pyridine (50 mL) was maintained below 0° while aliquots of benzoyl chloride were slowly added. The reaction was monitored by t.l.c. (10:1, v/v, petroleum ether–ethyl acetate) until optimal conversion into a di-*O*-benzoyl derivative was indicated; the excess of reagent was then decomposed by the addition of water. The solution, further diluted with water (50 mL) and chloroform (50 mL), was treated with an aqueous solution of sodium hydroxide until the aqueous layer remained basic. Water was then distilled from the chloroform phase to remove pyridine. The residue was chromatographed on a column of silica gel with 10:1 (v/v) petroleum ether–ethyl acetate as eluent to give **7** (1.23 g, 56%), m.p. 133–134° (from petroleum ether–ethyl acetate), $[\alpha]_D^{23}$ −24° (*c* 1, chloroform); lit.[26] m.p. 118–119°, $[M]_D^{21}$ −96° (*c* 1, chloroform).

*1,5-Anhydro-3,6-di-*O*-benzoyl-2-deoxy-4-*O*-mesyl-*D-arabino-*hex-1-enitol* (**8**). — To a solution of **7** (2.1 g) in pyridine (50 mL) cooled below 0° was added chloroform

(8 mL) containing methanesulfonyl chloride (0.96 g). The mixture was maintained for 24 h at room temperature whereupon t.l.c. (6:1, v/v, petroleum ether–ethyl acetate) showed one major product. The solution, diluted with chloroform (50 mL), was extracted with water (100 mL). The chloroform layer was evaporated and the product eluted from a column of silica gel with 6:1 (v/v) petroleum ether–ethyl acetate to give **8** (2.25 g, 88%), m.p. 99–100° (from petroleum ether–ethyl acetate), $[\alpha]_D^{23}$ −68° (*c* 1, chloroform).

Anal. Calc. for $C_{21}H_{20}O_8S$: C, 58.33; H, 4.63; S, 7.41. Found: C, 58.48; H, 4.90; S, 7.22.

*1,5-Anhydro-3,4,6-tri-*O*-benzoyl-2-deoxy-*D-lyxo*-hex-1-enitol* (**9**). — To a solution of **8** (6 g) in hexamethylphosphoric triamide (60 mL) was added sodium benzoate (3 g). The mixture was heated for 72 h at 100° when t.l.c. (6:1, v/v, petroleum ether–ethyl acetate) indicated that the reaction was virtually complete. The mixture was cooled, diluted with ethyl acetate (150 mL), and extracted with water (2 × 100 mL). The combined aqueous layers were re-extracted with ethyl acetate (75 mL) and the combined organic extracts were evaporated. Fractionation of the product on a column of silica gel with petroleum ether containing 3% (v/v) ethyl acetate as eluent afforded a syrup. Crystallization of the latter thereupon gave **10** (0.88 g, 13.9%), which was identified from its 270-MHz n.m.r. spectrum as 1,4,6-tri-*O*-benzoyl-2,3-dideoxy-α-D-*threo*-hex-2-enopyranose having m.p. 150–151° (from petroleum ether–ethyl acetate), $[\alpha]_D^{23}$ −228° (*c* 1, chloroform).

Anal. Calc. for $C_{27}H_{22}O_7$: C, 70.74; H, 4.80. Found: C, 70.46; H, 5.12.

The remaining syrupy product (still contaminated by ~10% of **10**, as indicated by its n.m.r. spectrum) was identified as **9** (3.3 g, 51.9%), $[\alpha]_D^{23}$ −92° (*c* 1, chloroform); lit.[16] $[\alpha]_D^{23}$ −106° (*c* 0.8, chloroform).

Reaction of **9** *with methanol and AG 50W-X8 cation-exchange resin.* — To a solution of **9** (1.52 g) in methanol (75 mL) was added AG 50W-X8 cation-exchange resin (7.5 g). The mixture was boiled for 20 h under reflux, at which time t.l.c. (10:1, v/v, petroleum ether–ethyl acetate) indicated three major products. The suspension was filtered, the filtrate evaporated, and the residue applied to a column of silica gel and eluted with petroleum ether containing 3% (v/v) ethyl acetate. The first product isolated was shown to be methyl 4,6-di-*O*-benzoyl-2,3-dideoxy-α-D-*threo*-hex-2-enopyranoside (**11**). This product, formed from the impurity **10** in the mixture, had m.p. 101–102°, $[\alpha]_D^{23}$ −197° (*c* 1, chloroform); lit.[16] m.p. 99–100°, $[\alpha]_D^{23}$ −186° (*c* 1, chloroform), lit.[44] m.p. 101.5–102°, $[\alpha]_D^{23}$ −197° (*c* 1, chloroform), lit.[46] m.p. 101–102°, $[\alpha]_D^{23}$ −191° (*c* 0.2, chloroform).

Further elution then gave the syrupy methyl 2-deoxy-α-D-*lyxo*-hexopyranoside **4** (0.5 g, 34.2%), $[\alpha]_D^{23}$ +55° (*c* 1, chloroform); lit.[16] $[\alpha]_D^{23}$ +68.8° (*c* 2.8, chloroform), and the syrupy methyl 2-deoxy-β-D-*lyxo*-hexopyranoside **5** (0.19 g, 13%), $[\alpha]_D^{23}$ −35° (*c* 1, chloroform); lit.[16] $[\alpha]_D^{23}$ −38° (*c* 0.8, chloroform).

*Methyl 3,4,6-tri-*O*-(acetyl-d_3)-2-deoxy-α-D-lyxo-hexopyranoside* (**6**). — A solution of **4** (0.55 g) in methanol (10 mL) saturated with anhydrous ammonia was maintained for 48 h at room temperature whereupon t.l.c. (10:1, v/v, chloroform–metha-

nol) indicated completion. The mixture was evaporated and the product eluted from a column of silica gel with chloroform containing 5% (v/v) of methanol. Evaporation of the eluate afforded a crystalline material, which was further treated with pyridine (3 mL) and acetic anhydride-d_6 (0.27 g). The solution was maintained at room temperature for 18 h, whereupon t.l.c. (4:1, v/v, petroleum ether–ethyl acetate) showed the reaction to be complete. Water was distilled from the mixture to remove the excess of reactants, and the product was applied to a column of silica gel. Elution with 10:1 (v/v) petroleum ether–ethyl acetate afforded **6** (0.11 g, 32%) as a syrup, $[\alpha]_D^{23}$ +147° (*c* 1, chloroform).

Anal. Calc. for $C_{13}H_{11}D_9O_8$: C, 49.84; H, 3.51; D, 5.75. Found: C, 50.12; H, 3.78; D, 6.18.

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