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O-ETHYLIDENE-D-ALLOPYRANOSES: 1,2-*O*-, 1,2:4,6-, AND 2,3:4,6-DI-*O*-ETHYLIDENE DERIVATIVES*

WILLIAM E. DICK, JR., DAVID WEISLEDER, AND JOHN E. HODGE
Northern Regional Research Laboratory†, *Peoria, Illinois 61604 (U. S. A.)*
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ABSTRACT

Solutions of 1,2-*O*-acetoxonium chlorides derived from *O*-acetylated D-allopyranose derivatives were treated with sodium borohydride to give three pairs of previously unknown 1,2-*O*-ethylidene-α-D-allopyranose diastereoisomers: 3,4,6-tri-*O*-acetyl-1,2-*O*-ethylidene-α-D-allopyranoses; 4,6-di-*O*-acetyl-3-*O*-benzyl-1,2-*O*-ethylidene-α-D-allopyranoses; and 3-*O*-benzyl-1,2:4,6-di-*O*-ethylidene-α-D-allopyranoses. Examples of a second class of novel *O*-ethylidene-D-allopyranoses, the diastereoisomeric methyl 2,3:4,6-di-*O*-ethylidene-α-D-allopyranosides, were prepared by treating methyl 4,6-*O*-benzylidene-α-D-alloside with acetaldehyde–sulfuric acid. Assignments of dioxolane ring configurations and pyranose conformations were made by n.m.r. analyses.

INTRODUCTION

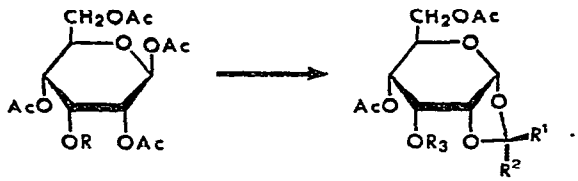
With the exception of 3-*O*-benzyl-4,6-*O*-ethylidene-β-D-allose[1], examples of 4,6-substituted acetals of D-allose have been limited to derivatives that can be obtained by transformations performed on preexisting 4,6-*O*-alkylidene-D-hexose analogs, such as methyl 4,6-*O*-benzylidene-α-D-alloside[2]. Furthermore, representatives are unknown for two other classes of *O*-alkylidene-D-allopyranoses having potential value as models for conformational studies or as intermediates for further syntheses, namely, the 1,2-*O*- and 2,3-*O*-alkylidene D-allopyranoses.

Two methods were employed to prepare examples of the previously unavailable acetals of D-allopyranose: (*1*) conversion of derived acetoxonium chloride intermediates of D-allopyranose into the corresponding 1,2-ethylidene acetals by the action of sodium borohydride, and (*2*) reaction of methyl 4,6-*O*-benzylidene-α-D-alloside with acetaldehyde under conditions of acetal hydrolysis and exchange.

*Part III of a series on D-allose acetals. For Part II, see preceding paper.
†Agricultural Research Service, U. S. Department of Agriculture. Mention of firm names or trade products does not imply that they are endorsed or recommended by the U. S. Department of Agriculture over other firms or similar products not mentioned.

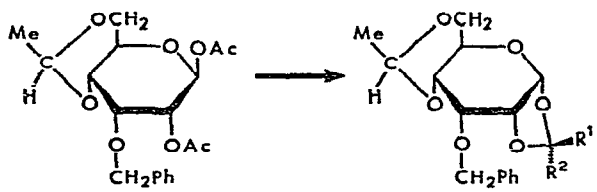
DISCUSSION

In the presence of sodium borohydride, solutions of 2-*O*-acetyl-*β*-D-glucopyranosyl chlorides rapidly generate intermediate acetoxonium chloride ions that immediately undergo further reaction to form 1,2-*O*-ethylidene-*α*-D-glucopyranose derivatives[3]. Additionally, the *O*-ethylidene isomer having an *R* configuration (*exo*-proton at C-2') is favored in the D-*gluco* series, although the solvent can modify the extent to which the *R* isomer is favored.



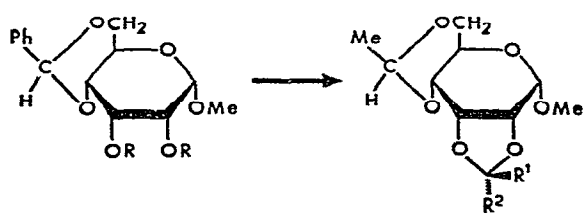
1, R = Ac
2, R = CH_2Ph

3, R^1 = H, R^2 = Me, R^3 = Ac
4, R^1 = Me, R^2 = H, R^3 = Ac
5, R^1 = H, R^2 = Me, R^3 = CH_2Ph
6, R^1 = Me, R^2 = H, R^3 = CH_2Ph



7

8, R^1 = H, R^2 = Me
9, R^1 = Me, R^2 = H



10, R = H
11, R = Ac

12, R^1 = H, R^2 = Me
13, R^1 = Me, R^2 = H

SCHEME 1

To apply the technique to derivatives of D-allose, samples of **1**, **2**, and **7** were treated first with anhydrous aluminum chloride, under conditions that give *O*-acetylated *β*-D-glycopyranosyl chlorides[4], and then with sodium borohydride. Samples of the presumed *β*-D-allopyranosyl chlorides derived from **2** and **7** reacted smoothly with borohydride in 1,2-dimethoxyethane to form the expected pairs of diastereoisomers, **5**, **6** and **8**, **9**. Chloride samples derived from **1**, however, formed a

complex mixture when the reaction was conducted in 1,2-dimethoxyethane, but they gave the desired mixture of **3** and **4** when borohydride in *N*,*N*-dimethylformamide was used.

Application of n.m.r. correlations[5–9] that relate chemical-shift differences of C-2′ substituents on the *O*-ethylidene ring to *exo* or *endo* orientations showed *R*:*S* ratios of approximately 9:1 for **3**:**4** and **5**:**6** and 92:8 for **8**:**9**. Samples of each major isomer were isolated by preparative t.l.c. for further examination.

For D-glucose derivatives, the ability of a 4,6-*O*-alkylidene ring to stabilize a $^4C_1$ pyranose conformation and to counteract most of the distortional effects imposed by the simultaneous presence of a 1,2-*O*-alkylidene ring is well known[10]. Analyses of vicinal proton coupling-constants have shown that such compounds adopt a slightly flattened $^4C_1$ chair conformation, and equivalent results were found for **8**.

As shown in Table I, the vicinal proton coupling-constants match closely the range of values predicted from models: $J_{2,3} = 5$–6.5 Hz, $J_{3,4} = 2$–4.5 Hz, and $J_{4,5} = 8$–9.5 Hz. Further comparisons to values measured for **1**, **2**, **7**, and **11** suggest that decreases in the acute dihedral angles H-2–H-3 and H-3–H-4, and increases in the corresponding coupling constants caused by flattening, are small and that the greatest change is in H-2–H-3. The absence of long-range (^4J) coupling of H-2 to H-4 is consistent with a slightly flattened $^4C_1$ chair conformation for **8**, as the two protons cannot achieve the necessary spatial relationship for coupling in such a conformation.

As dihedral angles cannot be assigned as acute or obtuse by measurement of the corresponding vicinal proton coupling-constants, the problem of whether the pyranose ring of 1,2-*O*-alkylidene-α-D-glucopyranose derivatives exists as a half-chair or flexible (skew-boat) form has been at issue for some time[11–13]. Such is not the situation for the D-allopyranose analogs, **3**, **4**, **5**, and **6**, however.

For each of the three forms suggested by inspection of models—flexible, half-chair, or slightly flattened chair—the dihedral angles H-2–H-3 and H-3–H-4 will always be acute and H-4–H-5 will remain obtuse. Furthermore, in a true half-chair, the acute dihedral angles will be small, with correspondingly large coupling-constants $J_{2,3}$ and $J_{3,4}$. If, however, the pyranose ring exists either as a flexible form, or as a slightly flattened chair, the relevant dihedral angles will be significantly larger than in the half-chair, with a marked decrease in the values of $J_{2,3}$ and $J_{3,4}$. The presence or absence of long-range coupling between H-2 and H-4 allows a judgment to be made as to whether the flattened $^4C_1$ chair or flexible form exists, as ^4J coupling of H-2 to H-4 is to be expected only in the latter conformer.

Such coupling was observed in **3** and **5**, and found to be positive for **3** by the selective irradiation technique of Hall and Manville[14]. Furthermore, the vicinal proton coupling-constants for **3** and **5** support a skewed pyranose ring conformation (flexible) for each, where the dihedral angle H-2–H-3 is approximately twice as large as that of H-3–H-4 and where H-4 has a *trans* and nearly coplanar relationship with H-5.

In this flexible conformation, H-2 and H-4 assume a spatial relationship that is nearly equivalent to those of diequatorial protons shown by Hall and Manville[14] to

TABLE I

N.M.R. DATA FOR *O*-ALKYLIDENE D-ALLOPYRANOSES AND RELATED DERIVATIVES[a]

Compound	*Chemical shift*				*Dioxolane*		*Dioxane*				*Coupling constants*					
	H-1	*H-2*	*H-3*	*H-4*	*2'-H*	*2'-CH₃*	*2'-H*	*2'-CH₃*	*Ph-CH₂*	*O-CH₃*	$J_{1,2}$	$J_{2,3}$	$J_{3,4}$	$J_{4,5}$	$J_{2,4}$	J_{CH_3-CH}
1	3.70d	4.78dd	4.01t	4.85dd							8.6	3	3	10		
2[b]	3.57d	4.94dd	5.65t	5.00dd					5.55s		8.5	2.8	2.8	10		
3	4.68d	6.15dd	4.81dd	4.53td	5.22q	8.61d					5.3	2.7	6.4	7.3	+1.0	4.8
4	4.58d				4.35q	8.88d					5	3			1	5
5	4.85d	6.22qd	6.61dd	4.51qd	5.23q	8.62d			5.55q		5.5	2.5	6.5	7	1.1	4.9
6						8.68d			5.55q							
7[b]	3.64d	5.10dd	5.84t	6.98dd			5.73q	8.75d	5.32q		8.5	3	2.3	9.2		5
8	4.92d	6.47t	6.37dd	7.13dd	4.97q	8.66d	5.63q	8.76d	5.22s		5	5	2.3	9.2		5, 5
9					4.45q		5.63q		5.25s							
11	5.32d	5.02t	4.11t	6.74t			4.65s			6.88s	4.3	3.7	2.5	9.1		
12	5.55d	5.83–6.06m	5.85–6.06m	6.68dd	4.79q	8.50d	5.44q	8.66d		6.87s	4.9		3.8	9.3		5, 5
13	5.52d	5.80–6.05m	5.80–6.05m	6.79dd	4.22q	8.73d	5.47q	8.63d		6.92s	5		4	9		5, 5

[a]100 MHz in hexadeuterobenzene, d = doublet, dd = doublet of doublets, m = multiplet, q = quartet, qd = quartet of doublets, s = singlet, t = triplet, td = triplet of doublets. [b]From Ref. 1.

exhibit positive ^4J coupling. A later report by Heitmann and Richards[15] supports our assertion that, even though H-2 and H-4 exist in a series of all possible flexible forms, the average conformation in solution places them in a relationship equivalent to diequatorial protons attached to a conformationally stable ring. Their X-ray analysis established that a D-glucopyranose orthoester analog of **3** and **5** known to display positive ^4J coupling of H-2 to H-4 in solution[3] assumes in the crystalline state a skew conformation that is almost equal to the one we propose as the solution average for **3** and **5**. In this conformation, H-2 and H-4 meet the steric requirements of Hall and Manville[14] for ^4J coupling.

The ease with which 1,2-*O*-ethylidene-α-D-allopyranoses can be prepared and defined conformationally makes them an interesting and potentially useful class of compounds. Whether they are also conformational models, as a class, for the D-*gluco* analogs of undefined conformation is an open question.

The reaction of methyl 4,6-*O*-benzylidene-α-D-alloside (**10**) with acetaldehyde–sulfuric acid, chosen as a method of preparing examples of the previously unknown 2,3-*O*-ethylidene-D-allopyranoses, proceeds in two steps: (*1*) immediate hydrolysis of the dioxane ring, followed by (*2*) condensation with 2 moles of acetaldehyde to form two pairs of compounds separable by t.l.c.

The major products were identified as the diastereoisomeric methyl 2,3:4,6-di-*O*-ethylidene-α-D-allosides (**12, 13**) by n.m.r. spectroscopy. The 2,3-*O*-ethylidene ring was assigned as *R* in **12** and *S* in **13**, as described for **3–6** and compound **8**. As no evidence for isomerism of the 4,6-*O*-ethylidene ring was found, an equatorial orientation was assumed for the C-2′ methyl group.

As seen previously for **8**, the 4,6-*O*-ethylidene group also counteracts most of the distortional effects imposed on the pyranose ring by the 2,3-*O*-ethylidene ring. The values for $J_{1,2}$, $J_{3,4}$, and $J_{4,5}$ are consistent with a slightly flattened $^4C_1$ chair conformation for the pyranose rings of **12** and **13**, the dihedral angle H-3–H-4 having been decreased somewhat from that found in an unstrained molecule such as **11**. The overlap of resonances for H-2 and H-3 prevents any evaluation of changes in the angle H-2–H-3, but a decrease would be expected, and it probably causes the small increase in the value of $J_{1,2}$ noted for each when compared to **11**.

The pair of byproducts, each of which had an R_F value greater than that of **12** or **13**, had lost the aglycon as well as the benzylidene ring, before or after condensation with acetaldehyde; they were not structurally identified. Prolonged reaction times favored the formation of these products.

Although compounds **12** and **13** are of interest primarily as examples of a previously unknown class of compounds, as they are too highly substituted for use as reaction intermediates, preparation of useful compounds can be envisaged by use of an aglycon sensitive to hydrogenation, or by insertion of temporary protecting groups at either O-4 or O-6.

EXPERIMENTAL

General methods. — N.m.r. spectra were recorded at 100 MHz on a Varian HA-100 spectrometer with tetramethylsilane ($\tau = 10.0$) as the internal standard. Solute concentrations were approximately 20% (w/v or v/v). Chemical shifts and coupling constants are first-order, measured directly from spectral spacings. A Hewlett–Packard research chromatograph, Model 5750 equipped with an electronic integrator, was used for g.l.c. The column was 1/8- in (o.d.) × 8-ft stainless-steel tubing packed with 3% HI-EFF 8BP (cyclohexanedimethanol succinate, Applied Science Labs, Inc.) on Chromosorb W (80–100 mesh). Column programming was isothermal, with helium as the carrier gas and with flame-ionization detection.

Melting points were determined in capillary tubes. Optical rotations were measured at 546.1 nm in a 0.2-dm cell with a Bendix recording polarimeter, Model 1169, or in a 1-dm tube at the D-line (doublet) of sodium. Multiplication of the specific rotations measured at 546.1 nm by 0.85 allows comparison with values reported at the D-line of a sodium lamp. Solutions were evaporated under diminished pressure. Precoated plates of Silica Gel F-254 (E. Merck, Darmstadt, Germany) were used for t.l.c. Layer thickness was 0.25 mm for analytical separations and 2.0 mm for preparative. For column chromatography, Baker Analyzed Silica Gel No. 3405 (J. T. Baker Chemical Co.) was used without pretreatment. All chromatographic solvents were proportioned on a v/v basis. Calcium hydride was used to dry 1,2-dimethoxyethane and *N,N*-dimethylformamide.

Starting materials. — Samples of **1**, **2**, **7**, **10**, and **11** were prepared by methods described elsewhere[1,2,16].

*3,4,6-Tri-*O*-acetyl-1,2-*O*-ethylidene-α-*D*-alloses* (**3**, **4**). — Crude **1** (7 g) was dissolved in dichloromethane (35 ml), anhydrous aluminum chloride (1.5 g) was added, the flask was stoppered, and the mixture was stirred magnetically for 45 min at 25°. The mixture was taken up in chloroform (100 ml), washed three times with a slurry of ice and water, and dried over anhydrous calcium chloride. Solvents were evaporated, and immediately the residue was dissolved in *N,N*-dimethylformamide (75 ml), chilled to +5°, and then treated with sodium borohydride (1.5 g). This mixture was chilled for 1 h longer and then stored for 18 h at 25° before rechilling to +5°. Excess borohydride was decomposed by serial additions of methanol and acetic acid, as previously described[3], and the final solution was then evaporated to remove volatiles. Little deacetylation was noted by t.l.c. (4:1 methylcyclopentane–acetone, 2 ascents). The mixture (5.4 g) was fractionated by preparative t.l.c. (7:3 toluene–ether, 3 ascents with subsequent refractionation in 7:3 methylcyclopentane–acetone, 2 ascents). Crystallization from 2-propanol gave **3**; m.p. 111–112°, $[\alpha]_D^{20}$ +34.7° (*c* 1.1, chloroform).

Anal. Calc. for $C_{14}H_{20}O_9$: C, 50.60; H, 6.07. Found: C, 50.75; H, 6.13.

A mixed t.l.c. fraction (**3**:**4**, 7:13) was examined by n.m.r. to determine chemical shifts for the *O*-ethylidene ring substituents at C-2′. Purification of **4** was not complete.

*4,6-Di-*O*-acetyl-3-*O*-benzyl-1,2-*O*-ethylidene-α-*D*-alloses* (**5**, **6**). — A 10-g sample of **2** in dichloromethane (50 ml) was stirred for 40 min at 25° with anhydrous aluminum chloride (2.6 g), and a yellow syrup (8.5 g) was isolated essentially as described for **1**. The syrup was dissolved in 1,2-dimethoxyethane (50 ml) without further examination, chilled to +5°, and treated with sodium borohydride (2 g) as already described. The partially deacetylated product-mixture (t.l.c., 9:1 chloroform–acetone) was reacetylated in 1:1 acetic anhydride–pyridine (50 ml) for 4 days at 25°. The final mixture weighed 8.8 g after evaporation, and contained only traces of materials other than **5** and **6**. Pure **5** was obtained by preparative t.l.c. (4:1 benzene–ether, 1 ascent) and then distilled (225°/0.1 mtorr) to yield a syrup; $[\alpha]_{546}^{25}$ −11.6° (*c* 1.1, chloroform). The ratio of **5**:**6** was 22:3 before purification.

Anal. Calc. for $C_{19}H_{24}O_8$: C, 59.99; H, 6.36. Found: C, 59.59; H, 6.51.

*3-*O*-Benzyl-1,2:4,6-di-*O*-ethylidene-α-*D*-alloses* (**8**, **9**). — Anhydrous aluminum chloride (0.5 g), dichloromethane (15 ml), and **7** (3 g) were stirred for 0.5 h at 25°, then taken up in chloroform (100 ml), and washed twice with an ice–water slurry. The washings were combined, re-extracted with fresh chloroform (15 ml), and discarded. The combined extracts were evaporated to yield a syrup that was dissolved in 1,2-dimethoxyethane (40 ml) immediately and treated with sodium borohydride (0.5 g) as already described. This mixture was diluted with ethyl acetate (200 ml), washed once with water, and then dried. N.m.r.-spectral examination of the product established that **8** and **9** were formed in the ratio of 49:4. Crude **8** (2.1 g) was recrystallized from 2-propanol and then heptane; m.p. 108–110°, $[\alpha]_{546}^{25}$ +119.4° (*c* 1, chloroform).

Anal. Calc. for $C_{17}H_{22}O_6$: C, 63.34; H, 6.88. Found: C, 63.20; H, 6.96.

*Methyl 2,3:4,6-di-*O*-ethylidene-α-*D*-allosides* (**12**, **13**). — A mixture of **10** (4 g), paraldehyde–acetaldehyde diethyl acetal (1:1, 12 ml), and *p*-toluenesulfonic acid monohydrate (0.3 g) was kept at 30° with occasional swirling and monitored periodically by t.l.c. (ethyl acetate). The sample dissolved within 2 h, with initial loss of the *O*-benzylidene group and rapid formation of **12** and **13** (*R*:*S*, 9:1). Reaction was complete after 5 h, with partial conversion of preformed **12** and **13** into byproducts by 18 h. The yield of **12** and **13** was 67% (g.l.c., 125°) after neutralization with 0.5M barium methoxide in methanol and evaporation of volatiles. The mixture was chromatographed on a column of silica gel (chloroform) and refractionated by preparative t.l.c. (7:3 benzene–ether, 2 ascents). Pure **12** was distilled (180°/0.1 mtorr) and crystallized from a mixture of 2-propanol and heptane; m.p. 74–76.5°, $[\alpha]_{546}^{27}$ +121° (*c* 0.67, chloroform).

Anal. Calc. for $C_{11}H_{18}O_6$: C, 53.65; H, 7.37. Found: C, 53.30; H, 7.67. The isolated compound **13** (85% pure) was satisfactory for n.m.r.-spectral examination.

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