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ISOMERISATION DURING DEHYDRATION OF PENTITOLS IN ACID MEDIA*

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ABSTRACT

The products of dehydration of pentitols in aqueous sulfuric acid have been studied by g.l.c.–m.s. Four isomeric 1,4-anhydropentitols were formed from D-arabinitol, but only two from xylitol and ribitol. The number of products could only be explained by assuming inversion of configuration at C-2 or C-4 during 1,4- or 2,5-cyclisation reactions. No product which involved inversion of configuration at C-3 was observed. Various mechanisms of isomerisation are considered.

INTRODUCTION

The products of dehydration of alditols[1–3] in aqueous hydrochloric acid or sulfuric acid depend on the structure of the reactants and on the conditions. Thus, in 50% sulfuric acid, L-threitol gave 1,4-anhydro-L-threitol[4], and erythritol afforded 1,4-anhydroerythritol[4] and *trans*-2,5-bis(1,2-dihydroxyethyl)-1,4-dioxane[5] due to intra- and inter-molecular elimination of water, respectively. In 2M hydrochloric acid[6,7] or 1% sulfuric acid[8], pentitols gave 1,4- and 2,5-anhydropentitols. Heating hexitols in concentrated sulfuric acid[9,10] gave 1,4- and 3,6-anhydro and 1,4:3,6-dianhydro derivatives; in concentrated hydrochloric acid, 1,5-anhydro[11], 1,4- and 2,5-anhydro, and 1,4:3,6-dianhydro derivatives[12] were formed.

The dehydration of alditols in acid media has been considered to involve S_N2 displacement of a protonated hydroxyl group from C-1 by a suitable hydroxyl group in the same molecule[13,14]. The rate of the process[14] was influenced by the environment of the leaving and entering group as well as the orientation of hydroxyl groups not directly involved in the reaction.

Although Hudson and Barker[14] reported isomerised cyclic products only from D-arabinitol, we have found diastereomeric cyclic products to be formed from all pentitols.

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TABLE I

PRODUCTS OBTAINED BY TREATMENT OF PENTITOLS WITH AQUEOUS 5% SULFURIC ACID AT 160°

Acetates	*Yields[a] (%) of products from* D-*Arabinitol*			*Xylitol*			*Ribitol*		
	Reaction times (h)								
	0.5	*1*	*2*	*0.5*	*1*	*2*	*0.5*	*1*	*2*
1,5-Anhydroxylitol	—	—	—	—	trace	trace	—	—	—
1,5-Anhydroribitol	—	—	—	—	—	—	1	4	5.5
1,5-Anhydroarabinitol	1	2	3	—	—	—	—	—	—
1,4-Anhydroarabinitol (peak *a*)	26.5	37	49	1.5	4.5	5.5	—	—	—
1,4-Anhydroxylitol (peak *b*)	4.5	6.5	9	30.5	79.5	94.5	—	—	—
1,4-Anhydroribitol (peak *c*)	3	3.5	4.5	—	—	—	55	72	90
1,4-Anhydrolyxitol (peak *d*)	6	7.5	9	—	—	—	2.5	3.5	4.5
Ribitol	—	—	—	—	—	—	41.5	20.5	—
Arabinitol	59	43	25.5	—	—	—	—	—	—
Xylitol	—	—	—	68	16	—	—	—	—

[a]Calculated from peak areas.

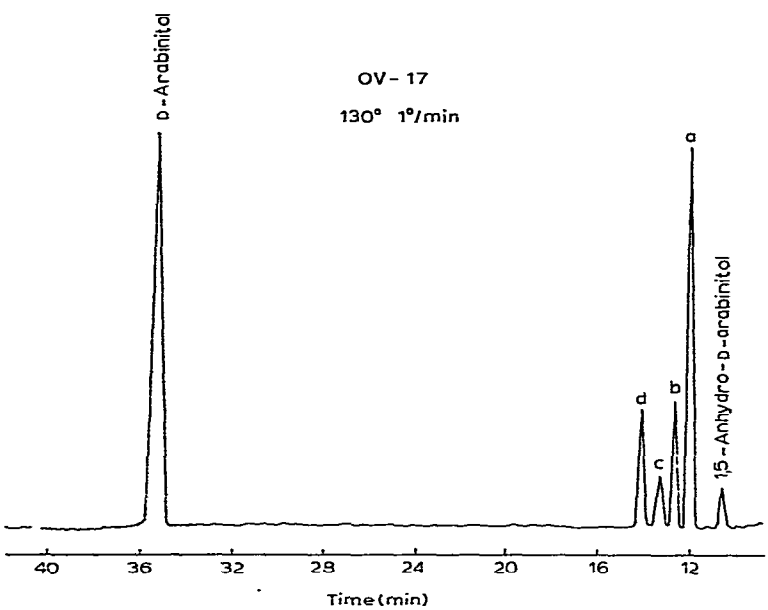


Fig. 1. Gas chromatogram of dehydration products of D-arabinitol (reaction time 1 h, see Table I): *a*, 1,4-anhydroarabinitol; *b*, 1,4-anhydroxylitol; *c*, 1,4-anhydroribitol; *d*, 1,4-anhydrolyxitol.

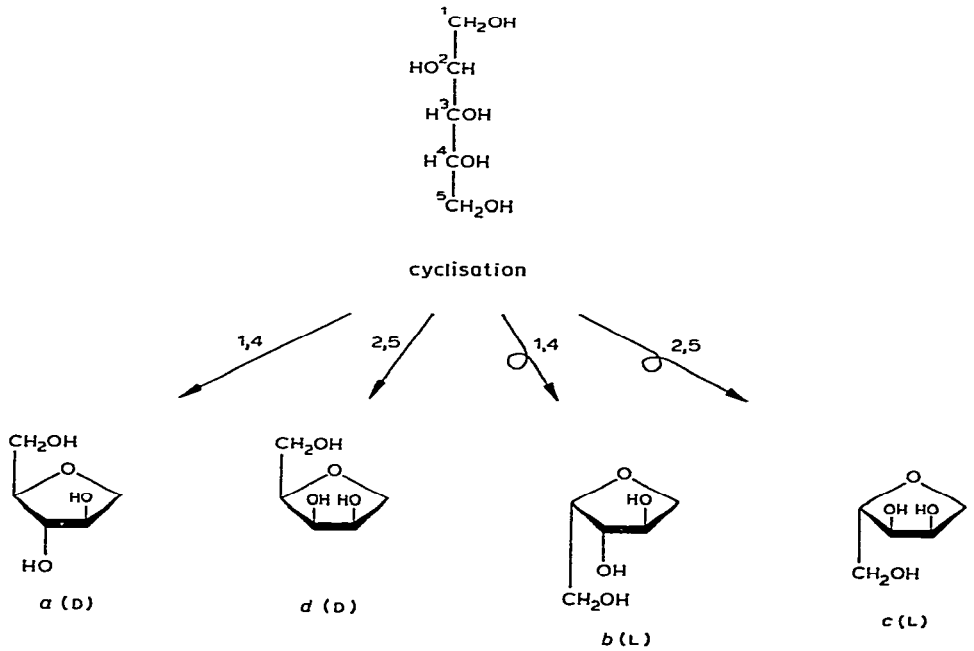
RESULTS AND DISCUSSION

Dehydration of D-arabinitol (≡ lyxitol), xylitol, and ribitol in aqueous 5% sulfuric acid at 160° followed by acetylation gave the products listed in Table I. A gas chromatogram of the D-arabinitol product-mixture after acetylation is shown in Fig. 1.

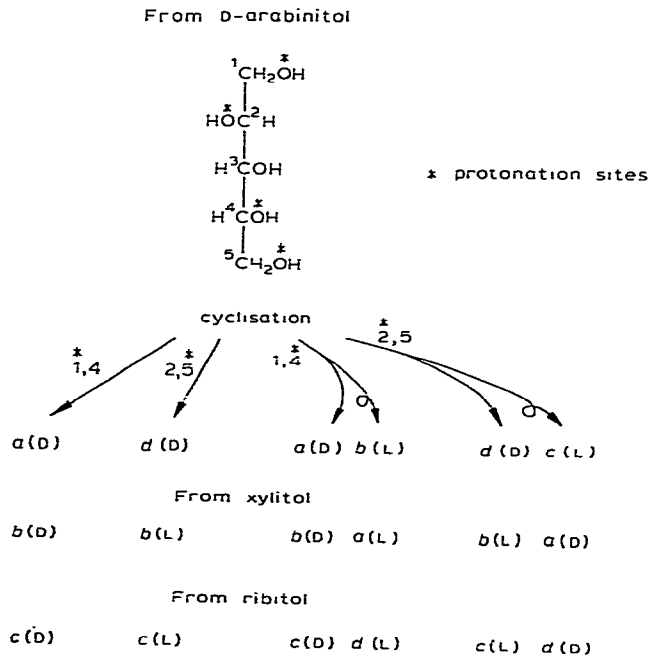
The products obtained from D-arabinitol, xylitol, and ribitol that, in each case, had the shortest retention time, yielded mass spectra indicating 1,5-anhydropentitol structures. Two of the products had retention times identical with those of authentic 1,5-anhydro-D-arabinitol and 1,5-anhydroxylitol. The third product, which had a spectrum identical with those of the above products but a different retention time, was 1,5-anhydroribitol.

The mass spectra of the products in peaks *a–d* (Table I) indicated 1,4-anhydropentitol structures[15]. The g.l.c. conditions used did not separate enantiomers. The products in peaks *a–c* had retention times identical with those of 1,4-anhydro-D-arabinitol, 1,4-anhydro-DL-xylitol, and 1,4-anhydro-D-ribitol, respectively. The product in peak *d* should correspond, therefore, to 1,4-anhydrolyxitol.

The number of dehydration products, namely, *a–d* from D-arabinitol, *a* and *b* from xylitol, and *c* and *d* from ribitol (Table I) may be explained on the basis of retention and inversion of configuration at C-2 or C-4 during cyclisation, as illustrated in Scheme 1 for D-arabinitol. The products predicted for 1,4- and 2,5-dehydration of the pentitols are shown in Scheme 2.



Scheme 1. The 1,4- and 2,5-dehydration products of D-arabinitol.



Scheme 2. The products obtained from pentitols due to nucleophilic substitution of different protonated hydroxyl groups.

Hudson and Barker[14] found the dehydration of arabinitol to be more complex than that of ribitol and xylitol. Using a complex, indirect method, they separated and identified the isomers arising by isomerisation at C-2 and C-4, and stated that the requirements of the transition state for formation of a tetrahydrofuran ring allowed the formation of more products from arabinitol than from the other pentitols. The isomerisation of arabinitol was explained as occurring most probably *via* 1,2-epoxide intermediates[14].

The results obtained herein can be accounted for in terms of a dehydration process related to intramolecular S_N2 reactions[13,14]. Dehydration–cyclisation of a pentitol which leads to furanoid products must involve HO-1,4 or HO-2,5. Protonation of any of these hydroxyl groups will allow nucleophilic attack at the corresponding carbon atom by another hydroxyl group. This process involves an active cation complex, and product formation is accompanied by inversion or retention of configuration at C-2 or C-4. Protonation of HO-1 will lead to cyclisation with retention of pentitol configuration, but protonation of HO-4 can lead to cyclisation with retention or inversion of configuration at C-4 (Scheme 2). Thus, the ratio of protonated primary and secondary hydroxyl groups and the relative rates of the various reactions control the pattern of products.

The proportion of 1,4-anhydro derivatives (Table I) having D-*arabino* and D-*lyxo* configurations in the mixture of products formed from D-arabinitol was ~5:1 (*cf.* 10:1 found by Hudson and Barker[14]).

Cyclisation of pentitols *via* vicinal 1,2- or 4,5-epoxides[14], as well as 2,3- or 3,4-epoxides, would not yield more products than predicted on the basis of the nucleophilic substitution mechanism (Scheme 2). Epoxide intermediates would be expected to react with water, giving isomers of the original alditol. Such products were not found in our studies.

The furanoid products obtained from ribitol and xylitol indicate that simultaneous inversion of configuration at C-2 and C-4 or inversion at C-3 did not occur and suggest that carbonium ion intermediates were not involved in the dehydration–cyclisation[14] and isomerisation of alditols.

Dehydration of the oxonium ions formed from secondary hydroxyl groups of the pentitols or their anhydro derivatives followed by rehydration would be expected to lead to at least a partial inversion of configuration and a larger number of products than actually observed. That such a process did not occur was demonstrated by treating xylitol with deuterated sulfuric acid and deuterium oxide. Mass spectrometry of the acetates of the resulting 1,4-anhydro derivatives of arabinitol and xylitol revealed insignificant incorporation of deuterium.

An alternative mechanism of isomerisation, namely, dehydration to give unsaturated intermediates followed by cyclisation, would also furnish more products than actually observed.

Thus, the isomerisation which occurs during the dehydration of pentitols in acidic solutions occurs only *via* intramolecular, nucleophilic substitution reactions.

EXPERIMENTAL

Dehydration of the pentitols. — A mixture of pentitol (20 mg) and aqueous 5% sulfuric acid (100 μl) was heated at 160° in sealed glass ampoules for 0.5, 1, or 2 h, and then neutralised with barium carbonate. A portion (10 μl) of each clear solution was concentrated under nitrogen and the residue was treated conventionally with acetic anhydride–sodium acetate at 100° for 1 h.

Each product mixture was subjected to g.l.c., using a Varian Aerograph 1400 instrument fitted with a capillary (20 m × 0.27 mm i.d.) of borosilicate glass coated with OV-17 containing Silanox particles. A suspension of Silanox in a chloroform solution of Carbowax 20M was forced through the column, which was then dried and heated at 300° for 0.5 h. The column was washed with chloroform (6 ml), dried, and coated by using a 10% solution of OV-17 in dichloromethane and a dynamic method[18].

The column was dried and conditioned from 50→250° at 0.5°/min, and then had 34,000 theoretical plates for 2,3,5,6-tetra-*O*-acetyl-1,4-anhydro-D-mannitol at 200°. Argon was used as the carrier gas.

Mass spectra (70 eV) were obtained with an LKB 2091 instrument linked with a PDP 11 minicomputer. The mass spectrometer was interfaced by a Ryhage molecular separator to a gas chromatograph equipped with a capillary column coated with

Carbowax 20M. The temperature of the ion sources and the molecular separator was 280°.

The standard compounds, 1,4-anhydro-D-arabinitol[15,17], 1,4-anhydro-DL-xylitol[8], 1,4-anhydro-D-ribitol[16,17], 1,5-anhydroxylitol[17], and 1,5-anhydro-D-arabinitol[17], were conventionally acetylated by using acetic anhydride–sodium acetate prior to g.l.c.

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