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## Journal of Carbohydrate Chemistry

Publication details, including instructions for authors and subscription information:

<http://www.informaworld.com/smpp/title~content=t713617200>

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**To cite this Article** Wisniewski, Andrzej , Sokolowski, Janusz and Szafranek, Janusz(1983) 'Products from the Action of Hydrochloric Acid on Pentitols', *Journal of Carbohydrate Chemistry*, 2: 3, 293 – 304

**To link to this Article:** DOI: 10.1080/07328308308057875

**URL:** <http://dx.doi.org/10.1080/07328308308057875>

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PRODUCTS FROM THE ACTION OF HYDROCHLORIC ACID ON PENTITOLS.

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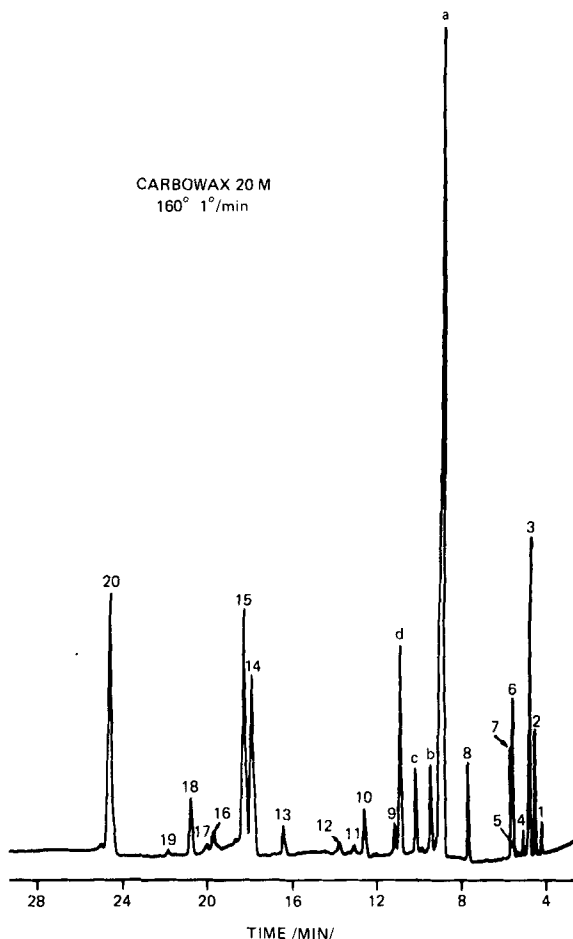
Received March 21, 1983

ABSTRACT

The treatment of pentitols in concentrated hydrochloric acid causes 1,4 (or 2,5) intramolecular dehydration with either retention or change of configuration, 1,5-dehydration and chlorine for hydroxyl substitution. These mono- and dichloroalditol derivatives mostly with the configuration of arising anhydro compounds, are formed from the alditols themselves or 1,4-anhydro-pentitols.

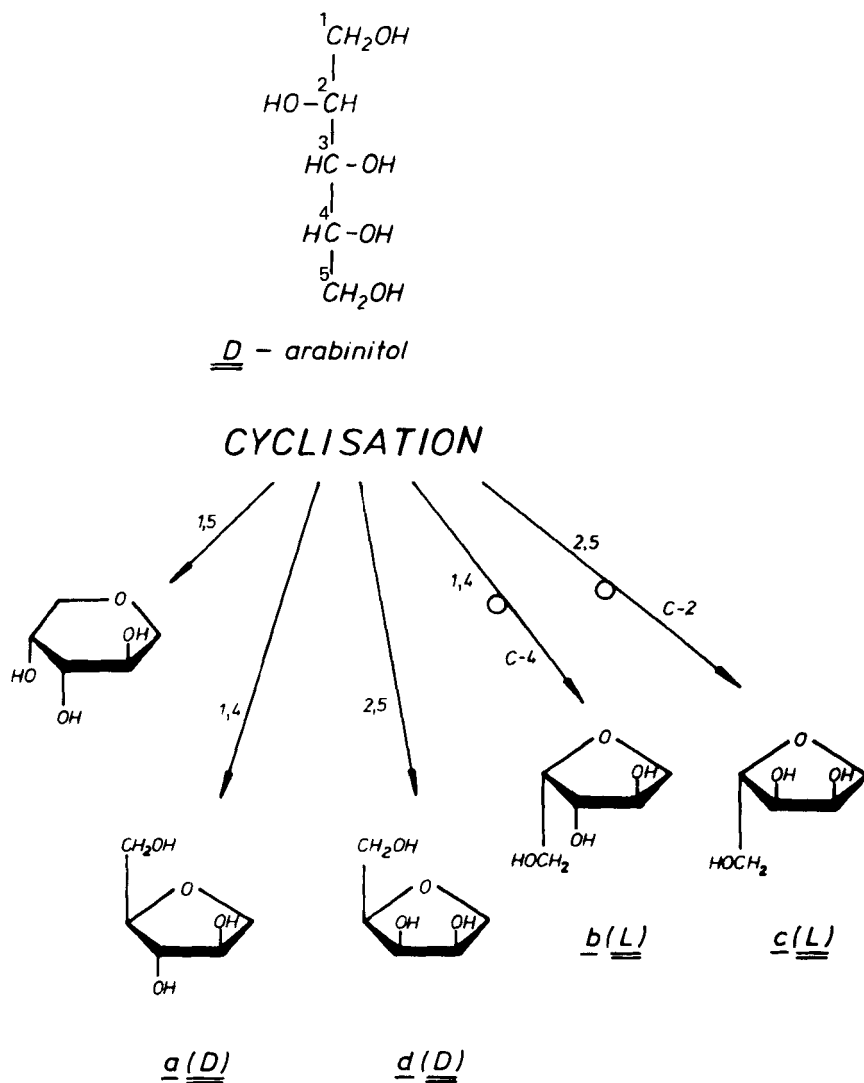
INTRODUCTION

1,6-Dihalogeno-1,6-dideoxyhexitol derivatives are clinically employed as antitumour agents.<sup>1,2</sup> A number of methods for the synthesis of these derivatives have been developed<sup>3,4</sup> some of which involve the action of a hydrohalic acid on alditol.<sup>5,6</sup>

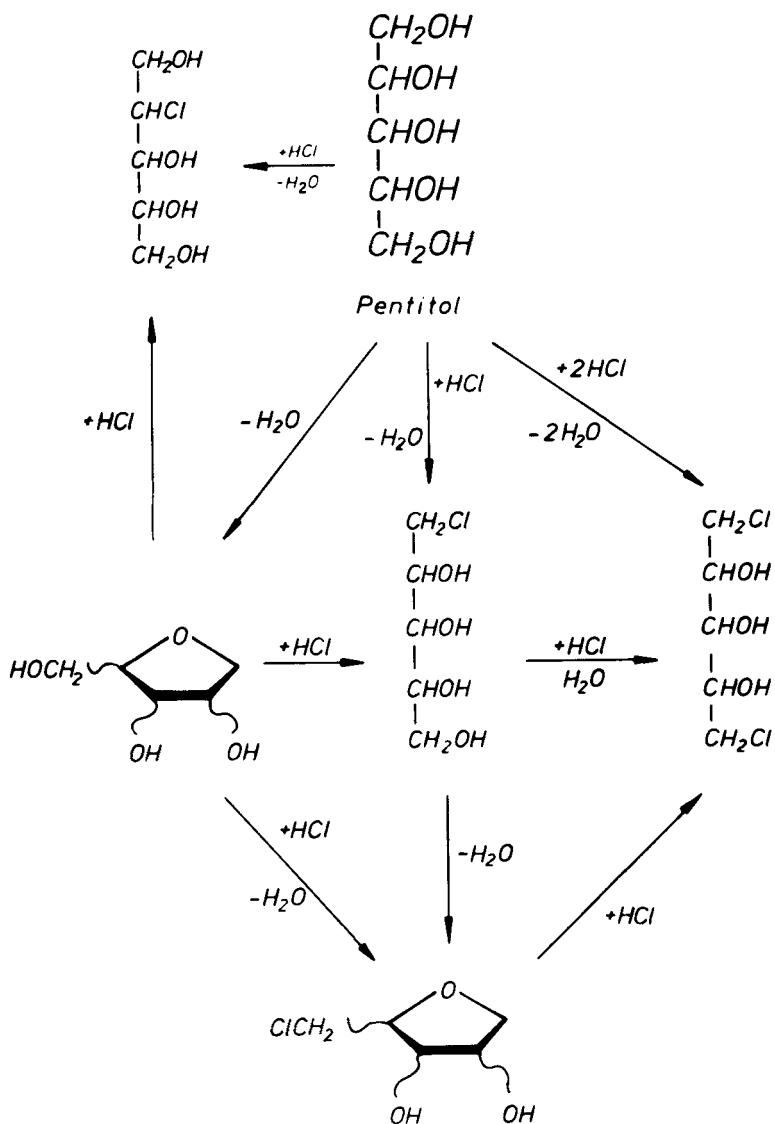


**Fig. 1:** Gas chromatogram of the fully acetylated products produced by the reaction of D-arabinitol in concentrated hydrochloric acid at 100° for 4 h.

1: unknown; 2: unknown; 3: 5-chloro-5-deoxy-1,4-anhydro-arabinitol and -xylitol; 4: unknown; 5: unknown; 6: 5-chloro-5-deoxy-1,4-anhydroarabinitol; 7: 5-chloro-5-deoxy-1,4-anhydrolyxitol; 8: 1,5-anhydroarabinitol; a: 1,4-anhydroarabinitol; b: 1,4-anhydroxylitol; c: 1,4-anhydroribitol; d: 1,4-anhydrolyxitol; 9: 1,5-dichloro-1,5-dideoxyribitol; 10: 1,5-dichloro-1,5-dideoxyarabinitol; 11: unknown; 12: 1,5-dichloro-1,5-dideoxyxylitol; 13: 1-chloro-1-deoxyribitol; 14: 1-chloro-1-deoxyarabinitol; 15: 1-chloro-1-deoxylyxitol; 16: 2-chloro-2-deoxypentitol; 17: 1-chloro-1-deoxyxylitol; 18: 2-chloro-2-deoxypentitol; 19: unknown; 20: arabinitol.



SCHEME 1



SCHEME 2

-1-deoxy-ribitol (peak 13, Fig. 1), -D-arabinitol (peak 14), -D-lyxitol (peak 15) and -xylitol (peak 17), from xylitol 1-chloro-1-deoxyxylitol and -arabinitol and from ribitol 1-chloro-1-deoxy-ribitol. The presence of ion  $m/e$  265/267, 193/195 and 163/165 in their mass spectra (Table 1, I) and the retention times indicate one chlorine atom in these molecules. In turn, the ion  $m/e$  289 strongly supports the position of chlorine at C-1. Coinjection of mixtures derived from each pentitol gave the configurational identification of isomeric compounds.

Moreover, the chromatogram (peaks 16 and 18 in Fig. 1) show other monochloro-tetra-O-acetylpentitols (Scheme 2). The presence of ions  $m/e$  265/267 and 217 and the absence of ions  $m/e$  289 and 187 (Table 1, II) indicates only possible positions of chlorine at C-2 or C-1. Because all four C-1 chloro isomers were identified before (peak 13, 14, 15 and 17), they must have chlorine atom at C-2.

Dichlorodideoxypentitols appear in reaction mixtures also in connection with previous formation of specific 1,4-anhydro-pentitols and their 5-chloro-5-deoxy derivatives (Scheme 2). In the case of D-arabinitol (Fig. 1), we identified among the reaction products all three isomers 1,5-dichloro-1,5-dideoxypentitols, 1,5-dichloro-1,5-dideoxyribitol (peak 9), -arabinitol (peak 10) and -xylitol (peak 12). Xylitol gave rise to 1,5-dichloro-1,5-dideoxyxylitol and -arabinitol. From ribitol we obtained mostly 1,5-dichloro-1,5-dideoxyribitol, owing to the absence previously observed of 1,4-anhydrolyxitol, and only

**TABLE 1:** Partial electron impact mass spectra of per-O-acetylated derivatives of 1-chloro-1-deoxy-/I, GC peaks 13, 14, 15 and 17, 2-chloro-2-deoxy-/II, GC peaks 16 and 18 and 1,5-dichloro-1,5-dideoxypentitols /III, GC peaks 9, 10 and 12.

m/e	relative intensities %/			The structure of ion
	I	II	III	
289	1.5	-	-	$\begin{array}{cccc} \text{CH}_2 & -\text{CH} & -\text{CH} & -\text{CH} \\   &   &   &    \\ \text{OAc} & \text{OAc} & \text{OAc} & \text{OAc} \end{array}$
265/267	14/4	12/3	6/2	$\begin{array}{cccc} \text{CH}_2 & -\text{CH} & -\text{CH} & -\text{CH} \\   &   &   &    \\ \text{Cl} & \text{OAc} & \text{OAc} & \text{OAc} \end{array}$
217	29	23	-	$\begin{array}{ccc} \text{CH}_2 & -\text{CH} & -\text{CH} \\   &   &    \\ \text{OAc} & \text{OAc} & \text{OAc} \end{array}$
193/195	9/3	12/4	38/13	$\begin{array}{cccc} \text{CH}_2 & -\text{CH} & -\text{CH} & \text{or} & \text{CH}_2 & -\text{CH} & -\text{CH} \\   &   &    & &   &   &    \\ \text{Cl} & \text{OAc} & \text{OAc} & & \text{OAc} & \text{Cl} & \text{OAc} \end{array}$
187	10	-	-	$\begin{array}{c} \text{O} \\ \diagup \quad \diagdown \\ \text{AcOHC} - \text{CHOAc} \end{array}$
163/165	40/13	32/11	22/7	$\begin{array}{cccc} \text{CH}_2 & -\text{C} & =\text{CH} & -\text{CH} \\   &   &   &    \\ \text{Cl} & \text{OH} & & \text{OAc} \end{array}$
73	14	12	-	$\text{CH}_2 = \overset{\oplus}{\text{O}}\text{Ac}$

a trace of 5-chloro-5-deoxyxylitol in the reaction products.

Their retention times in relation to the anhydrides and to the monochloromonodeoxyderivatives of pentitols or to the substrates and their mass spectra (Table 1, III) indicate two atoms of chlorine in the molecule of pentitol. The presence of ions m/e 265/267, 193/195 and 163/165 and the absence of ions m/e 217 and 73 in their mass spectra<sup>13</sup> (Table 1, III) indicates the positions of chlorines at C-1 and C-5.

It is striking that the products of the action of hydrochloric acid on any given pentitol contain neither isomeric epimerized pentitol nor any chloro derivatives of 1,5-anhydropentitols. Not even trace amounts of 3-chloro-3-deoxypentitols have been found among the products of these reactions. Experimental results of reaction of alditol with hydrohalic acid or sulfuric acid permit us to rule out dehydrations that lead to olefinic double bonds followed by hydration, since we have never found any products with a change of the configuration at C-3. Dehydration performed under drastic conditions (5% aq  $\text{H}_2\text{SO}_4$ , 7 days,  $180^\circ$ ) does not lead to the formation of dianhydropentitols or of any other dehydration products similar to the products of acid pentose degradation.

### CONCLUSIONS

Gas chromatography and GC-MS analysis of the products of hydrochloric action on pentitols revealed the main features of reactions consisting of dehydration to anhydrides and substitution of hydroxyl group in open-chain and anhydrides by chlorine atoms, with the last products as the most abundant for longer treatment (7 days). The primary structures of the products have been determined by GC-MS with configurations being assigned by comparing the GC retention times of compounds obtained from individual pentitols. Generally, the reactions studied were found to be very complicated and their use for preparative purposes is probably not practical.



## EXPERIMENTAL

### Gas chromatography.

The studies were performed with a Varian Aerograph 1400 gas chromatograph equipped with a capillary column coated with Carbowax 20 M.<sup>14</sup> The efficiency of a column, as determined for hexadecan at 120° was of  $n = 80,000$  theoretical plates ( $k' = 4$ ).

Acetylated 5-chloro-5-deoxy-1,4-anhydropentitols were separated on a capillary column (40 m x 0.03 cm) coated with SP-2340 liquid phase. The column was prepared according to Grob procedure.<sup>15</sup>

### Mass spectrometry.

Mass spectra of per-0-acetyl derivatives were recorded on an LKB 2091 mass spectrometer linked with a PDP e/11 minicomputer. The mass spectrometer was interfaced by a Ryhage molecular separator to a gas-chromatograph equipped with a capillary column coated with Carbowax 20 M liquid phase. The temperature of the ion source and the molecular separator was 280°. An electron beam of 70 eV energy was used for ionization. The scan from  $m/e$  10 to  $m/e$  680 was in 2 sec.

### Dehydration of pentitols in concentrated hydrochloric acid.

200 mg of the pentitol (D-arabinitol, xylitol or ribitol, 1.32 mM) and 1 mL of concentrated hydrochloric acid was heated at 100° in a sealed glass ampoule (1.5 mL) for 4 h or 7 days. Ten  $\mu$ L of the solution was evaporated to dryness under a nitrogen stream, then acetylated at 100° for 1 h with an acetic anhydride

and sodium acetate mixture.<sup>13</sup> Per-0-acetyl derivatives of the products obtained were analysed by gas chromatography (column 20 m x 0.025 cm, Carbowax 20 M, 160<sup>o</sup>, 1<sup>o</sup>/min).

Pentitol reactions with 5% aqueous sulfuric acid solution.

200 mg of the pentitol (D-arabinitol, xylitol or ribitol, 1.32 mM) and 0.8 mL of 5% aqueous sulfuric acid solution were placed in a sealed glass ampoule and heated for 7 days at 180<sup>o</sup>. The resulting mixture was then extracted three times with 30 mL of ethyl ether. The organic layer was washed with saturated sodium bicarbonate solution, then with water, and dried with calcium sulphate. The solution was concentrated to ca. 1 mL under atmospheric pressure and analyzed by capillary gas-chromatography. No products with short retention times were detected.

Preparative synthesis of 5-chloro-5-deoxy-1,4-anhydro-pentitols.<sup>12</sup>

200 mg of a pentitol (D-arabinitol, xylitol or ribitol, 1.32 mM) and 1 mL of concentrated hydrochloric acid (36%) was heated at 100<sup>o</sup> in a sealed glass ampoule for 7 days. Upon completion of the reaction, water and hydrogen chloride were removed in vacuo at 50<sup>o</sup>. The reaction product was distilled off under reduced pressure (0.1 - 0.2 Torr) on an oil bath at 145-150<sup>o</sup>. Isomeric 5-chloro-5-deoxy-1,4-anhydropentitol mixtures were obtained in each case in the following yields:

- . 140 mg of oil from D-arabinitol: yield = 70% of a mixture of 5-chloro-5-deoxy-1,4-anhydroarabinitol, -xylitol, -ribitol and -lyxitol (70:8:11:10 respectively)\*
- . 140 mg of oil from xylitol: yield = 70% of a mixture of 5-chloro-5-deoxy-1,4-anhydroarabinitol and -xylitol (1:25 respectively)\*
- . 160 mg of oil from ribitol: yield = 80% of a mixture of 5-chloro-5-deoxy-1,4-anhydroribitol and -lyxitol (50:1 respectively)\*

The mass spectra of all the 5-chloro-5-deoxy 1,4-anhydropentitols obtained were identical to those of 5-chloro-5-deoxy-1,4-anhydroxylitol whose structure had previously been determined.<sup>13</sup>

#### ACKNOWLEDGEMENT

We are grateful to our French friend Prof. Dr. G. Descotes for advice and fruitful discussions.

The financial support of the Polish Academy of Science is gratefully acknowledged.

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