Reactions Between Formaldehyde and Polyhydric Alcohols. I. 
Five-, Six-, Seven-, and Twelve-membered Cyclic Acetals 
from meso-Erythritol and Formaldehyde

R. B. JENSEN,a,* O. BUCHARTD,a S. E. JØRGENSEN,a J. U. R. NIELSEN,a G. SCHROLL,a and C. ALTONAb

a Department of General and Organic Chemistry, The H. C. Ørsted Institute, University of Copenhagen, 
Universitetsparken 5, DK-2100 Copenhagen, Denmark and b Department of Organic Chemistry, P.O. 
Box 75, University of Leiden, The Netherlands

The reaction between meso-erythritol and form- 
aldehyde has been studied. By using aqueous formaldehyde as reagent and hydrochloric acid as 
catalyst, all the possible bicyclic acetals composed of one molecule of meso-erythritol and 
two molecules of formaldehyde (II, VI, VII) were generated, as well as E-4-hydroxyethyl-
1,3-dioxane-5-ol (V).

If the reaction takes place in benzene, with paraformaldehyde as reagent and p-toluenesul- 
fonic acid as catalyst compounds II, VI, VII and one additional compound (VIII) are 
generated. This compound is composed of two 
molecules of meso-erythritol and four molecules of formaldehyde. Furthermore, it is shown that 
compound V is the precursor of compounds VI and VIII.

INTRODUCTION AND RESULTS

It is known that some polyvalent alcohols react with formaldehyde under acidic conditions 
to give cyclic acetals of varying ring size.¹ This is interesting from a mechanistic as well as a 
stereochemical point of view, and it was decided to study some of the reactions, using the little 
examined butanetetrols as substrates. These substrates appeared to present all the basic 
intriguing possibilities for reactions, but due to their simplicity, they also appeared to offer 
excellent possibilities for the understanding of the complex reaction sequences involved.

A search of the literature revealed that little attention had been paid to these substrates. In

¹ To whom the correspondence should be addressed.


1896 it was published that the reaction between erythritol (I) and aqueous formaldehyde, with 
hydrochloric acid as catalyst, led to a compound called "erythritol diformal", which according to 
Beilstein's "Handbuch der Organischen Chemie" was meso-4,4'-bi[1,3]dioxolane (II) (System 
number 3008).

More recently the formation of 1,3-dioxano-
[Z-5,4-d]-1,3-dioxane (IV) from threitol (III) was reported.²

We therefore decided to examine in details the 
reactions between butane-1,2,3,4-tetrols and 
formaldehyde, and the present paper describes the reaction between erythritol and formalde-
hyde under various conditions.
By repeating the reactions under conditions similar to those previously employed, i.e., 40% aqueous formaldehyde and concentrated hydrochloric acid, we obtained a complex reaction mixture, from which three compounds were isolated in the pure state. Their structures have been determined as shown below (formulas V, VI and VII).

Furthermore, a fourth component was observed, but it could not be isolated in the pure state from the above reaction mixture. However, it was later shown to have the structure corresponding to the original suggestion for the so-called "erythritol diformal", i.e., structure II, whereas compound VI has the same m.p. as that of the originally reported "diformal". Consequently we assume that "erythritol diformal" has structure VI.

The reaction between erythritol (I) and paraformaldehyde in benzene with p-toluenesulfonic acid as the catalyst led to a mixture of products, from which compounds II, VI and VII were isolated, as well as a new compound in low yield, which has been assigned structure VIII.

It should be noted that the detailed stereochemistry of VIII has not yet been determined, and that compounds VI and VIII can also be formed by the reaction of V with paraformaldehyde in benzene.

STRUCTURE DETERMINATION

The structure of compound V is in agreement with IR, NMR, and mass spectral data, as well as with elemental analysis. Furthermore, unambiguous evidence for the assignment was found by means of chemical reactions, as shown in Scheme I.

From this scheme it is seen that α-D-glucose in a known series of reactions can be converted to a compound, IXb, with the indicated absolute configuration. For comparison racemic V was treated with methanesulfonyl chloride to give a racemic mixture, which exhibited IR, NMR and mass spectra identical with those of compound IXb. This constitutes the basis for our structural assignment. It should be noted that the IR spectra are only identical when recorded in solution, and that the melting points of IXb and the product from V are different. However, this is what can be expected since compound V leads to a racemic mixture of IXa.
and IXb, whereas the sample prepared from glucose consists of only one stereoisomer.

\[
\text{HOC}_2\text{O} + \text{CD}_2\text{O} \xrightarrow{\text{D. Pt/FEOH}} \text{HOC}_2\text{O} \xrightarrow{\text{CH}_2\text{O}}
\]

\[
\text{HOCH}_2\text{C}\equiv\text{CCH}_2\text{OH} \xrightarrow{\text{D. Pt/FEOH}} \text{HOCH}_2\text{C}\equiv\text{CCH}_2\text{OH}
\]

\[
\text{OCH}_2\text{H}_2 \xrightarrow{\text{D. Pt/FEOH}} \text{HOCH}_2\text{C}\equiv\text{CCH}_2\text{OH}
\]

**Scheme 2.** (a) Preparation of 1,3-dioxano-\([E-5,4-d]\)-1,3-dioxane-2,2-\(d_2\) (VIa); (b) Preparation of 1,3-dioxano\([E-5,4-d]\)-1,3-dioxane-4a,8a-\(d_4\) (VIIb).

The assignment of structure to compound VI is based on the following observations: (a) Compound VI can be prepared in a high yield from compound V and paraformaldehyde. (b) After reaction between perdeuterioparaformaldehyde and compound V, the resulting compound VI contained only one \(-\text{CD}_2\)-group. This shows that compound V does not undergo ring-opening during the reaction. (c) The NMR-spectra of VI and of two different deuterated derivatives (VIa and VIIb) are in agreement with the proposed structures, as seen from Fig. 1. (d) That \(J_{1,3} = -6.2\) Hz indicates that the O-CH\(_2\)-O groups are part of six-membered rings (not five-membered) in chair conformations.\(^4\) (e) The centro-symmetrical character of VI was indicated by \(^1\text{H}\) magnetic resonance studies, which showed only three lines (proton decoupling). (f) Furthermore, the value of the dipole moment in benzene is found to be 0.97 D.

The structures of compounds II and VII are based on their NMR and mass spectra. A detailed study of their configuration and conformational equilibria is in progress and will be published later.

The gross structure of compound VIII follows from its synthesis from compound V and paraformaldehyde, which strongly indicates the presence of two 1,3-dioxane rings. However, this independent synthesis does not permit any conclusions to be drawn about the detailed structure. \textit{A priori}, two structural isomers, A and B, would be envisaged, each of which could exist in several diastereoisomeric forms.

---

**Fig. 1.** The \(^1\text{H}\) NMR spectra of (a) 1,3-dioxano-\([E-5,4-d]\)-dioxane; (b) 1,3-dioxano-\([E-5,4-d]\)-1,3-dioxane-2,2-\(d_2\); (c) 1,3-dioxano-\([E-5,4-d]\)-1,3-dioxane-4a,8a-\(d_4\). The figures in parentheses refer to the number of protons.

---

**Table 1.** \(^1\text{C}\) chemical shifts (ppm) of VI and VIII.

<table>
<thead>
<tr>
<th></th>
<th>C-2=C-6</th>
<th>C-4=C-8</th>
<th>C-4a=C-8a</th>
</tr>
</thead>
<tbody>
<tr>
<td>VI</td>
<td>93.73</td>
<td>68.22</td>
<td>73.79</td>
</tr>
<tr>
<td>VIII</td>
<td>78.19</td>
<td>93.08</td>
<td>64.47</td>
</tr>
</tbody>
</table>

---

*Acta Chem. Scand. B 29 (1975) No. 3*
The $^{13}$C and $^1$H NMR spectra of VIII (Table 1 and Fig. 2) strongly suggest that only one pair of enantiomers is formed, and since the $^{13}$C spectrum contains six lines, we assign structure A to this compound. Similarly the $^1$H NMR spectrum of VIII and the $^1$H NMR spectra of the two deuterated derivatives VIIIa and VIIIb are in agreement with this assignment. From these spectra it can be seen that there are only two different $O-\text{CH}_2-O$ groups in compound VIII. $J_{2,3}=J_{18,19} = -6.1$ Hz again indicates a six-membered ring in a chair form and $J_{7,8}=J_{17,18} = -7.5$ Hz points to a slightly different geometry of $O-\text{CH}_2-O$ in the twelve-membered ring. If the other pair of enantiomers B had been present, there would have been three different $O-\text{CH}_2-O$ groups. The deuterated derivatives of compound VIII were prepared as depicted below.

![Chemical structures and diagrams]

**Scheme 3.** (a) Preparation of 2,4,7,9,12,14,17,19-octaoxa-tricyclo[4.14.0.0^{14}.14]eicosane; (b) 2,4,7,9,12,14,17,19-octaoxa-tricyclo[4.14.0.0^{14}.14]eicosane-8,8,18,-18-d_4; (c) 2,4,7,9,12,14,17,19-octaoxa-tricyclo[4.14.0.0^{14}.14]eicosane-5,5,10,-10,15,15,20,20-d_8.

**EXPERIMENTAL**

$^1$H NMR spectra were obtained at 60 MHz in deuteriochloroform using a Varian A-60 spectrometer at ambient temperature (40 °C). The shift reference was internal TMS. Noise-decoupled $^{13}$C NMR spectra were determined with a Bruker WH-90 system (22.63 MHz) operating in the Fourier transform mode. The samples were examined at ambient temperature (40 °C) as saturated solutions in CDCl$_3$ and shieldings were measured relative to internal TMS. The IR spectra were recorded on a Perkin-Elmer 337 Grating Infrared Spectrophotometer using chloroform as solvent. The mass spectra were recorded on an AEI MS-902 mass spectrometer at 70 eV. The sample was introduced through a direct inlet system. The analytical GLC was made on a Perkin-Elmer F 11 instrument at 95 °C. Column: Silicone gum rubber (10% on Gaschrom Q, 100/120 mesh), 3 mm x 2.0 m, flow 30 ml/min, injection temp. 130 °C. The gas chromatographic separations were made on a Perkin-Elmerâ€™sâ€”Preparative Gas Chromatographâ€”F 21, using a silicone rubber gum column at 95 °C (20% on PE Chromosorb W NAV 60/80 mesh, 6 mm x 1.0 m, flow 400 ml N$_2$/min, injection temp. 130 °C). Retention times: Chloroform 1.1 min, VI 10.3 min and VII 12.9 min. In each cycle 2.5 µl of the mixture was injected. The dipole moment of VI was determined by measuring dielectric constants and densities of five solutions in benzene (molar fraction range 0.00 to 0.04) at 25 °C. The dielectric measurements were carried out by means of a low frequency Schering-bridge.

Formaldehyde and Polyhydric Alcohols 377

CH₄(OH)₂ + CH₂(OH)₃CH₂(OH)₃ + CH₂O

Scheme IV.

The various reaction paths for the reaction between meso-erythritol (I) or DL-E-4-hydroxymethyl-1,3-dioxane-5-ol (V) and formaldehyde:

Method a. (I) + 35% aq. CH₄O + conc. HCl.

Method b. (I) + paraformaldehyde + p-toluene-sulfonic acid in benzene.

Method c. (V) + paraformaldehyde + p-toluene-sulfonic acid in benzene.

Method a

Procedure 1. DL-E-4-Hydroxyethyl-1,3-dioxane-5-ol (V) and 1,3-dioxane[E-5,4-d]-1,3-dioxane (VI). A solution of meso-erythritol (I) (50 g, 0.41 mol) in 35% aqueous formaldehyde (75 ml, 0.95 mol) and concentrated hydrochloric acid (50 ml, 0.60 mol) was heated under reflux for 2 h. The water was removed from the reaction mixture by distillation under reduced pressure (14 mmHg), through a 15 cm fractionating column. On standing 24 h at room temperature, white crystals of VI precipitated from the distillate. The same material was also found deposited in the column. 10 ml of absolute ethanol was added to the residue from the distillation, and after 24 h at room temperature white needles of VI separated. These crystals were collected, and the solvent was removed by distillation in the same way as mentioned above. The residue from this distillation was re-distilled at 130–140 °C/0.04 mmHg, and 19 g of VI (35%) was obtained as a viscous liquid, which was brought to crystallize by cooling in a dry ice-acetone mixture, and after recrystallization from ether, the m.p. was 53–54 °C. VI was recrystallized from absolute ethanol, m.p. 100–101 °C. The combined yields of VI were 8.4 g (0.057 mol, 14%).

Procedure 2. V, VI, I,3-Dioxolano[E-5,4-e]-1,3-dioxepane (VII) and meso-4,4'-bi[1,3]-dioxolane (II). A solution of meso-erythritol (I) (100 g, 0.82 mol) in 35% aqueous formaldehyde (150 ml, 1.9 mol) and concentrated hydrochloric acid (100 ml, 1.2 mol) was treated in the same way as described in procedure 1. The distillate was extracted continuously with ether for 24 h (ether phase 1). The residue from the distillation was extracted with 4×50 ml portions of ether (ether phase 2). The residue from this extraction was concentrated to dryness on a Rotavapor (100 °C/14 mmHg) and distilled at 130–140 °C/0.05 mmHg to give 35 g of solid, which after recrystallization from ether gave 26 g (24%) of VII. The mother liquor was saved (ether phase 3). Ether phase 1 was cooled to −80 °C, filtered and concentrated to 10 ml. GLC on the concentrate showed the presence of three components. By means of PGLC on the concentrate 60 mg (0.05%) of VII was isolated in the pure state. The compounds VI and II could not be separated in this way. The ether was removed from the combined ether phases 2 and 3 to give a crystalline solid. Recrystallization from absolute ethanol gave 25 g of VI (21%).

Method b

VI, VII, II and 2,4,7,9,12,14,17,19-Octaoxatriacyclo[4.14.0.1⁴,01¹][κ⁺]-icosane (VIII). A suspension of meso-erythritol (15 g, 0.12 mol), paraformaldehyde (15 g, 0.5 mol) and p-toluene-sulfonic acid (0.2 g, 0.0012 mol) in 200 ml of benzene was stirred and gently refluxed for 20 h. In order to neutralize the acidic catalyst, Na₂CO₃ (3 g, 0.03 mol) was added to the reaction mixture, which was then stirred for 2 h. The solid material was filtered off and washed several times with acetone. The washings were added to the filtrate, and the solvents (benzene and acetone) were removed by distil-

<table>
<thead>
<tr>
<th>Compound</th>
<th>Formula</th>
<th>M</th>
<th>m.p. °C</th>
<th>Yield (%)</th>
<th>Number of units</th>
<th>CH₄O</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>meso-erythritol</td>
<td></td>
</tr>
<tr>
<td>V</td>
<td>C₆H₁₄O₂</td>
<td>134</td>
<td>53–54</td>
<td>35,⁴ 24 b</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>VI</td>
<td>C₆H₁₄O₂</td>
<td>146</td>
<td>100–101</td>
<td>14,⁴ 21 b</td>
<td>33</td>
<td>1</td>
</tr>
<tr>
<td>VI</td>
<td>C₆H₁₄O₂</td>
<td>146</td>
<td>100–101</td>
<td></td>
<td>86</td>
<td>1</td>
</tr>
<tr>
<td>VII</td>
<td>C₆H₁₄O₂</td>
<td>146</td>
<td>84–85</td>
<td>17 c</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>II</td>
<td>C₆H₁₄O₂</td>
<td>146</td>
<td>unknown</td>
<td>50 c</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>VIII</td>
<td>C₁₂H₂₀O₄</td>
<td>292</td>
<td>232–233</td>
<td>4.5</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>VIII</td>
<td>C₁₂H₂₀O₄</td>
<td>292</td>
<td>232–233</td>
<td>11</td>
<td>2</td>
<td>2</td>
</tr>
</tbody>
</table>

⁴ Procedure 1. ⁵ Procedure 2. ⁶ Yields estimated from ¹H NMR.

lation through a short column. The residue from the distillation partly crystallized on standing. The crystals were collected by filtration and recrystallized from absolute ethanol, this gave VIII (0.8 g, 4.5 %) m.p. 232 – 233 °C. The ethanolic solution from the recrystallization was concentrated to dryness, and recrystallization of this from acetone gave VI (6 g, 33 %). The mother liquor from above was shown to contain mainly II and VII by 1H NMR spectroscopy, corresponding to a yield of about 50 % and 17 %, respectively. However, until now, all efforts to isolate II in the pure state have been unsuccessful.

Method c

VI and VIII. A suspension of DL-E-4-hydroxymethyl-1,3-dioxane-5-ol (3 g, 0.022 mol), paraformaldehyde (4 g, 0.13 mol) and p-toluenesulfonic acid (0.1 g, 0.0006 mol) in 25 ml benzene was stirred and gently refluxed for 20 h. During the reaction formaldehyde sublimed into the reflux condensor, and at the end of the reaction the reaction mixture became clear. On cooling in an ice-water mixture a crystalline material separated. This was recrystallized twice from 98 % ethanol to give VIII (0.35 g, 11 %). The mother liquor was concentrated to dryness and recrystallized from 50 % ethanol to give VI (2.8 g, 86 %), m.p. 100 – 101 °C.

Racemic E-4-hydroxymethyl-1,3-dioxane-5-ol di-O-methanesulfonate (IXa-b). DL-E-4-Hydroxymethyl-1,3-dioxane-5-ol (Va+b) prepared by the above described procedures 1 and 2, was converted by conventional methods (see Ref. 4) into the di-O-methanesulfonate. Recrystallization from ethyl acetate gave m.p. 112 – 113 °C.

Optically active E-4-hydroxymethyl-1,3-dioxane-5-ol di-O-methanesulfonate (IXb) (=1,3-O-methylene-2,4-di-O-methanesulfonate-1-erythritol). This compound was prepared according to Barker et al. The melting point 97 – 98 °C was in, spite of careful purification, constantly 20 °C below that reported. 1,3-O-ethylidene-1-erythritol used was prepared according to a method given by Barker and MacDonald. 1,3-Dioxano[ E-5,4-d]-1,3-dioxane-2,2-d4 (VIIa) was prepared from DL-E-4-hydroxymethyl-1,3-dioxane-5-ol (Va+b) and perdeuterioparafomaldehyde using method c.

2,4,7,9,12,14,17,19-Octaoxa-tricyclo-
[4.14.0.04,11]esecane-3.8.15.18.18.18-d6 (VIIa) was prepared from DL-E-4-hydroxymethyl-1,3-dioxane-5-ol (Va+b) and perdeuterioparafomaldehyde using method c.

2,4,7,9,12,14,17,19-Octaoxa-tricyclo-
[4.14.0.04,11]esecane-5.5.10.15.15.20.20-d6 (VIIb) was prepared through the following reactions: Diethyl-2,3-d-isopropylidene mesotartrate was reduced with lithium aluminium deuteride analogously to the procedure of Feit to give 4,5-(dihydroxyperdeuteriomyethyl)-2,2-dimethyl-1,3-dioxolane. This compound was then hydrolyzed with 1 M hydrochloric acid, and the reaction mixture was evaporated to dryness. Recrystallization from absolute ethanol gave meso-1,2,3,4-butanetetrol-1,1,4,4-d4 (Ib). Treatment of Ib with paraformaldehyde in accordance with method b gave VIIIb.

cis-2-Butene-1,4-diol-2,3-d4. This compound was prepared from 2-butyn-1,4-diol by deuteration, adopting the method given by Feit for the analogous hydrogenation. The Lindlar catalyst was in this case replaced with 5 % palladium on barium sulfate. meso-1,2,3,4-Butanetetrol-2,3-d4 (Ia) was prepared from cis-2-butene-1,4-diol-2,3-d4 by hydroxylation with hydrogen peroxide and osmium tetroxide according to Reppe.

Acknowledgements. The authors wish to thank Professor K. A. Jensen for valuable discussions especially with respect to nomenclature problems.

REFERENCES

1. For review, see Barker, S. A. and Bourbe, E. J. Adean. Carboxyhd. Chem. 7 (1952) 137; Mills, J. A. Ibid. 10 (1955) 1.

Received September 27, 1974.