Separation and NMR Spectra of meso- and DL-Forms of Pentanediols

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meso- and DL-2,4-Pentanediols and their 3-methyl derivatives were separated after converting them into cyclic formaldehyde or acetaldehyde acetals. The structures of these diastereomeric diols were elucidated by means of their NMR spectra. The ABX₃ spectrum given by meso-2,4-pentanediol is fully analyzed by an abX subspectrum.

Pritchard and Vollmer¹ have reported the separation of the isomeric 2,4-pentanediols via their cyclic sulfite esters. They recorded the NMR spectra of these diols in deuterium oxide. The diastereomeric 3-methyl-2,4-pentanediols have not been resolved earlier. 3-Methyl-2,4-pentanediol has two meso forms and one DL form, the cyclic acetals of which have been prepared earlier.² meso-2,4,5,6-Tetramethyl-1,3-dioxanes cannot be separated,³ but they can easily be separated from the DL-2,4,5,6-tetramethyl-1,3-dioxanes.

GENERAL

The following direct stereoselective route to the diastereomeric 2,4-pentanediols was used:

\[
\begin{align*}
\text{CH}_2\text{COCH}_2\text{COCH}_2 & \xrightarrow{\text{H}_3} \xrightarrow{\text{EtOH}} \xrightarrow{\text{Raney Ni}} \text{CH}_2\text{CHOHCH}_2\text{CHOHCH}_2 \\
\text{I} & \text{about 1:1 mixture of meso (II)} & \text{and DL-2,4-pentanediols (III)}
\end{align*}
\]

\[
\begin{align*}
\text{II (III)} + \text{CH}_3\text{O} & \xrightarrow{\text{H}^+} \xrightarrow{\text{cis (meso)}} \xrightarrow{\text{trans (DL)}} \\
\text{IV} & \text{V}
\end{align*}
\]
IV (or V) + CH₃OH $\xrightarrow{H^+}$ CH₂(OCH₃)₂ + CH₃C-C-CCH₃

$\text{II (Fig. 1)}$

$\text{or + CH₃C-C-CCH₃}$

$\text{III}$

The diastereomeric 3-methyl-2,4-pentanediols were synthesized via their cyclic acetaldehyde acetics:

Diol mixture + CH₃CHO $\xrightarrow{H^+}$

VI

$\text{cis,cis,trans,cis, VII (meso 1)}$

$\text{cis,cis,cis,cis, VIII (meso 2)}$

$\text{cis,cis,trans,trans, IX (DL)}$

$\text{cis,cis,cis,trans, X (DL)}$

VII + VIII + CH₃OH $\xrightarrow{H^+}$ CH₃CH(OCH₃)₂ +

$\text{OH H OH}$

$\text{HC- C- CH}$

$\text{CH₃CH₂CH₃}$

$\text{meso 1, XI (Fig. 3)}$

$\text{CH₃ H CH₃}$

$\text{HC- C- CH}$

$\text{OH CH₃ OH}$

$\text{meso 2, XII (Fig. 3)}$

IX + X + CH₃OH $\xrightarrow{H^+}$ CH₂CH(OCH₃)₂ + H-C-CH

$\text{OH CH₃ CH₃}$

$\text{DL, XIII (Fig. 2)}$

SEPARATION OF ISOMERIC PENTANEDIOLS

EXPERIMENTAL

The approximately equimolar mixture of diastereomeric 2,4-pentanediols was prepared from 2,4-pentanediol by catalytic reduction in the presence of Raney nickel (100 atm, 125°C, EtOH).\(^1\)\(^2\) B.p. 106°/7 mm Hg, \(n_D^{20} 1.4330\). The yield was 80%.

The mixture of diastereomeric 3-methyl-2,4-pentanediols was obtained from Fluka AG.

The isomeric 4,6-dimethyl-1,3-dioxanes and 2,4,5,6-tetramethyl-1,3-dioxanes were prepared from the diol mixture as described elsewhere.\(^2\)

_meso_-2,4-Pentanediol (II) was prepared from cis-4,6-dimethyl-1,3-dioxane (IV) by methanolyis. IV (0.895 mole) and methanol (8.95 moles) were added to a flask which contained 6.1 g of p-toluenesulfonic acid. The flask was equipped with an efficient column. The mixture was boiled gently so that the dimethoxyxymethane formed (b.p. 42°C) was slowly distilled off. After the evolution of dimethoxyxymethane had ceased, the reaction mixture was neutralized with diethylamine and the excess methanol was evaporated off. On fractionation, the remaining syrup yielded 53.4 g (57.3%) of II. B.p. 109 – 111°C/18 mm Hg, \(n_D^{20} 1.4332\), \(d_4^{20} 0.9542\). Pritchard and Vollmer\(^1\) reported b.p. 73°/3 mm Hg, \(n_D^{20} 1.4327\). The over-all yield from 2,4-pentanediol was about 18% (Ref. 1; 30%).

Re-running the reaction with the recovered IV improves the yield.

_DL_-2,4-Pentanediol was prepared similarly from trans-4,6-dimethyl-1,3-dioxane (V, 0.68 mole). The yield was 68.8 g (97%). B.p. 110°/18 mm Hg, m.p. 47.5 – 48.5°C. Pritchard and Vollmer\(^1\) reported b.p. 74°/3 mm Hg, m.p. 48 – 49°C. The over-all yield from 2,4-pentanediol was about 27% (Ref. 1; 17%).

_meso_-3-Methyl-2,4-pentanediols (XI+XII) were prepared from an unresolvable mixture\(^2\) of cis-2, cis-4, trans-5, cis-6- (VII) and cis-2, cis-4, cis-5, cis-6-tetramethyl-1,3-dioxanes (VIII) by methanolyis. The method differed from the above procedure in that the boiling point of the formed 1,1-dimethoxyxymethane is only a few degrees lower than that of methanol and thus the preliminary fractionation was carried out more slowly. The yield was 48%. B.p. 121 – 122°/30 mm Hg, \(n_D^{20} 1.4431\), \(d_4^{20} 0.9571\). The proportion of XI was about 30% according to the NMR spectrum.

_DL_-3-Methyl-2,4-pentanediol (XIII) was prepared similarly from a mixture of cis-2, cis-4, trans-5, trans-6- (IX) and cis-2, cis-4, cis-5, trans-6-tetramethyl-1,3-dioxanes (X). The yield was 91%. B.p. 112°/15 mm Hg, \(n_D^{20} 1.4421\), \(d_4^{20} 0.9557\).

The NMR spectra were recorded on a 60 MHz Perkin-Elmer NMR spectroscopy M.R. 10 at 33.5°C. The solvents were carbon tetrachloride, benzene and pyridine (80 v.%) and tetramethylsilane as used as internal standard.

RESULTS AND DISCUSSION

Separation of the isomeric diols (except the two _meso_ forms of 3-methyl-2,4-pentanediol) by fractional distillation of their cyclic formaldehyde or acetaldehyde acetalts followed by methanolyis was successful. The conversion of the diol mixtures to cyclic acetal mixtures requires only a simple water-entainment unit.\(^2\) The _meso_ and racemic cyclic acetals can be separated easily (b.p. difference ≥10°C) in a Todd precise fractionation assembly. The conversion of these acetals to the isomeric diols by methanolyis is known to occur without change in configuration.\(^1,2\) The over-all yield of pure _meso_- and _DL_-2,4-pentanediols were 18 and 27% (30 and 17% in Ref. 1), respectively.

Pritchard and Vollmer\(^1\) recorded the NMR spectra of isomeric 2,4-pentanediols at 60 MHz in deuterium oxide. Their spectrum for the racemic diol is consistent with our spectrum (Table 1) although we recorded the spectrum using a mixture of benzene and pyridine as solvent. Our spectrum for II differs appreciably from that reported by Pritchard and Vollmer\(^1\) since the _meso_ diol gives a fully resolvable ABX\(_2\)-type spectrum in pyridine.\(^4\)

We have analyzed this spectrum as an (ABX)\(_2\) system and then calculated

Table 1. The chemical shifts and coupling constants (cps) of DL-2,4-pentanediol (III) and DL-3-methyl-2,4-pentanediol (XIII, Fig. 2).

<table>
<thead>
<tr>
<th></th>
<th>νOH</th>
<th>νsMe</th>
<th>νtMe</th>
<th>νA</th>
<th>νY</th>
<th>νX</th>
<th>JXMe</th>
<th>JYMe</th>
<th>JAX</th>
<th>JAY</th>
<th>Solvent</th>
</tr>
</thead>
<tbody>
<tr>
<td>IIIa</td>
<td>274.8</td>
<td>78.3</td>
<td>—</td>
<td>78.3</td>
<td>100.1</td>
<td>261.2</td>
<td>261.2</td>
<td>6.4</td>
<td>6.4</td>
<td>6.1</td>
<td>C₆H₅⁺</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>C₂H₄N</td>
</tr>
<tr>
<td>XIXb</td>
<td>343.1</td>
<td>77.2</td>
<td>58.4</td>
<td>78.2</td>
<td>83.0</td>
<td>245.6</td>
<td>260.5</td>
<td>6.4</td>
<td>6.2</td>
<td>3.0</td>
<td>7.6 C₂H₄N</td>
</tr>
<tr>
<td>XIX</td>
<td>—</td>
<td>69.7</td>
<td>50.0</td>
<td>67.7</td>
<td>99.7</td>
<td>224.0</td>
<td>241.5</td>
<td>6.3</td>
<td>6.1</td>
<td>2.8</td>
<td>7.6 CCl₄</td>
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</table>

*a Averaged spectrum of two pairs of equivalent conformations.

*b Average coupling constants due to two rapidly interconverting conformations. νTMS = 0.

Fig. 1. The calculated and found AB part of the NMR spectrum of meso-2,4-pentanediol (II). Also the X₂ part shown before (X₄Me) and after decoupling (X₄).

the theoretical ABX₃ spectrum which is in close agreement with the observed spectrum (Fig. 1 and Table 2). The decoupling of the X₄ or AB part of this spectrum revealed that the coupling constants did not remain constant after and before decoupling (Fig. 1) in accordance with a similar conclusion of Anet et al.⁵

The racemic 2,4-pentanediol exists in two pairs of equivalent conformations and consequently its NMR spectrum is an average one (Table 1, and Fig. 1 in Ref. 1). The spectrum of DL-3-methyl-2,4-pentanediol can be fully analyzed although this isomer is also a mixture of two conformations (ab. 1:2) and thus the coupling constants are also averaged (Fig. 2 and Table 1).
Table 2. Chemical shifts and coupling constants (cps) of meso-2,4-pentanediol (II) and the calculated and observed frequencies in the AB part of its NMR spectrum. Solvent 80 vol. % C$_2$H$_4$N (+some drops of D$_2$O). See also Fig. 1.

\[ \nu_A = 111.4, \nu_B = 96.2, \nu_X = 256.6, \nu_{Me} = 77.9. \]

\[ J_{XMe} = 6.2, J_{AB} = -13.8, J_{AX} = 8.77, J_{BX} = 3.83. \]

<table>
<thead>
<tr>
<th>Band No.</th>
<th>H</th>
<th>( \nu_H, \text{ calc.} )</th>
<th>( \nu_H, \text{ found} )</th>
<th>Relative intensity</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>B</td>
<td>82.6</td>
<td>— $^a$</td>
<td>1.0</td>
</tr>
<tr>
<td>2</td>
<td>B</td>
<td>96.2</td>
<td>96.2</td>
<td>10.1</td>
</tr>
<tr>
<td>3</td>
<td>B</td>
<td>87.3</td>
<td>87.2</td>
<td>3.6</td>
</tr>
<tr>
<td>4</td>
<td>B</td>
<td>100.9</td>
<td>100.9</td>
<td>18.7</td>
</tr>
<tr>
<td>5</td>
<td>B</td>
<td>91.85</td>
<td>91.8</td>
<td>2.4</td>
</tr>
<tr>
<td>6</td>
<td>B</td>
<td>105.25</td>
<td>105.4</td>
<td>7.9</td>
</tr>
<tr>
<td>7</td>
<td>A</td>
<td>99.3</td>
<td>99.3</td>
<td>10.1</td>
</tr>
<tr>
<td>8</td>
<td>A</td>
<td>112.9</td>
<td>113.0</td>
<td>1.0</td>
</tr>
<tr>
<td>9</td>
<td>A</td>
<td>107.2</td>
<td>107.3</td>
<td>18.7</td>
</tr>
<tr>
<td>10</td>
<td>A</td>
<td>120.8</td>
<td>120.8</td>
<td>3.6</td>
</tr>
<tr>
<td>11</td>
<td>A</td>
<td>115.45</td>
<td>115.5</td>
<td>7.9</td>
</tr>
<tr>
<td>12</td>
<td>A</td>
<td>128.9</td>
<td>128.9</td>
<td>2.4</td>
</tr>
</tbody>
</table>

$^a$ Obscured by alkyl peaks. \( \nu_{TMS} = 0 \).

Table 3. Chemical shifts and coupling constants of meso-3-methyl-2,4-pentanediols (XI and XII, Fig. 3).

<table>
<thead>
<tr>
<th>( \nu_A )</th>
<th>( \nu_X )</th>
<th>( \nu_M )</th>
<th>( \nu_{B_3} )</th>
<th>( \nu_{OH} )</th>
<th>( J_{XB} )</th>
<th>( J_{AM} )</th>
<th>( J_{AX} )</th>
<th>Solvent (80 vol. %)</th>
</tr>
</thead>
<tbody>
<tr>
<td>XI 221.3</td>
<td>80</td>
<td>67.5 45.2</td>
<td>292.2</td>
<td>6.7</td>
<td>6.2</td>
<td>7.8 ± 0.2</td>
<td>CCl$_4$</td>
<td></td>
</tr>
<tr>
<td>XI 244.0</td>
<td>90</td>
<td>75.7 53.5</td>
<td>—</td>
<td>6.7</td>
<td>6.2</td>
<td>7.8 ± 0.2</td>
<td>C$_2$H$_4$N</td>
<td></td>
</tr>
<tr>
<td>XI 227.4</td>
<td>80</td>
<td>72.2 41.4</td>
<td>—</td>
<td>6.7</td>
<td>6.2</td>
<td>7.8 ± 0.2</td>
<td>C$_2$H$_4$N</td>
<td></td>
</tr>
<tr>
<td>XII 238.7</td>
<td>65</td>
<td>67.5 50</td>
<td>292.2</td>
<td>6.7</td>
<td>6.2</td>
<td>2.6 ± 0.2</td>
<td>CCl$_4$</td>
<td></td>
</tr>
<tr>
<td>XII 253.2</td>
<td>85</td>
<td>75.7 65</td>
<td>—</td>
<td>6.7</td>
<td>6.2</td>
<td>2.6 ± 0.2</td>
<td>C$_2$H$_4$N</td>
<td></td>
</tr>
<tr>
<td>XII 241.5</td>
<td>70</td>
<td>70.7 55</td>
<td>—</td>
<td>6.7</td>
<td>6.2</td>
<td>2.6 ± 0.2</td>
<td>C$_2$H$_6$</td>
<td></td>
</tr>
</tbody>
</table>

$^a$ M means the end methyl groups. $^b$ B$_3$ means the 3-methyl group. All values in cps. \( \nu_{TMS} = 0 \).

The spectrum of the approximately 3:7 mixture of XI and XII is shown in Fig. 3. The spectrum of XI is easily analyzed, but that of XII contains an “AB$_3$” part which is due to the coupling of the protons of the 3-methyl group (B$_3$) and 3-hydrogen atom (X), since the chemical shifts of the X proton and the B$_3$ protons differ only about 2J$_{XB}$.$^4$ However, the part A of this spectrum (Fig. 3) can be analyzed by first-order analysis since J$_{AB} = 0$ (Table 3).

Fig. 2. The NMR spectrum of 3,5-dimethyl-2,4-pentanediol in CCl₄ (1:4, v/v).

Fig. 3. The NMR spectrum of the approximately 3:7 mixture of meso-3,5-dimethyl-2,4-pentanediols (XI and XII) in CCl₄ (1:4, v/v).

The recorded spectra are fully consistent with the known configurations of the studied diastereomers and we consider this analysis to provide adequate identification of the isomeric diols.

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REFERENCES

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