Solvent Effect on the Selective $N$-Acetylation of DL-$erythro$-$C_{14}$-dihydrosphingosine by Oxidation-Reduction Condensation Reaction

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The oxidation-reduction condensation reaction of DL-$erythro$-$C_{14}$-dihydrosphingosine [DL-$erythro$-(1)] with acetic acid to give N-acetyl-DL-$erythro$-$C_{14}$-dihydrosphingosine [DL-$erythro$-(3)] has been studied in the presence of triphenylphosphine and 2,2'-dipyridyl disulfide by using fourteen solvents. A variety of solvents except protic ones could be used for the condensation reaction. Separation of DL-$erythro$-(1) from 2-amino-1,3-tetradecanediol (1) is also described.

Introduction

$N$-Acetylation of long chain bases has been carried out by several methods which have been applied to the synthesis of ceramides$^{3-6}$. Some procedures for the peptide synthesis may be used for the preparation of ceramides$^{3-6}$. Mukaiyama et al$^{9}$ prepared peptides by an oxidation-reduction condensation with triphenylphosphine and 2,2'-dipyridyl disulfide. Kishimoto$^{6}$ applied this method to the synthesis of a ceramide. In this paper, the authors have studied the $N$-acetylation of DL-$erythro$-$C_{14}$-dihydrosphingosine [DL-$erythro$-(1)] as a substrate to clarify the effect of solvent on the oxidation-reduction condensation in the presence of triphenylphosphine and 2,2'-dipyridyl disulfide as condensation reagents.

Experimental

Materials.

Solvants were purified by the ordinary method$^{10}$. 2-Amino-1,3-tetradecanediol (a racemic mixture of threo- and erythro-$C_{14}$-dihydrosphingosines) (1) was prepared by the method described in a previous paper$^{11}$. DL-$erythro$-$C_{14}$-Dihydrosphingosine [DL-$erythro$-(1)]

A mixture of (1) (40 mmol), pyridine (250 ml), and acetic anhydride (100 ml) was kept at room temperature for 18 h. Then, the mixture was concentrated under reduced pressure. The residue was dissolved in chloroform (600 ml). The solution was washed with 5% HCl (300 ml, twice), water (350 ml, twice), 0.5 M sodium carbonate (300 ml, twice), and water (350 ml three times), and dried over anhydrous sodium sulfate. Removal of the solvent and recrystallization of the resulting triacetate from hexane (200 ml, twice) gave N,0,0-triacetyl-DL-$erythro$-$C_{14}$-dihydrosphingosine [DL-$erythro$-(2)]. Yield 48~54%, mp 81~82°C, $erythro$ : threo = 97.0 : 3.0 (determined as 0,0-his (trimethylsilyl)- N-acetyl derivative by GLC) (purity : 99.8%). IR ($\nu_{max}$) : 3290 (amide I), 1545 (amide III), 1650 (-NHCO-) and 1735~1745 (ester carbonyl group) cm$^{-1}$.

A mixture of (2) (8 mmol), 2M NaOH (30 ml), and methanol (270 ml) was kept at room temperature for 18 h. Then, the mixture was dissolved with chloroform (700 ml). The solution was washed with water (250 ml, twice), and dried over anhydrous sodium sulfate. Removal of the solvent and recrystallization of the resulting $N$-acetyl derivative from hexane and ethanol (10 : 1 vol/vol, 330 ml, twice) gave N-acetyl-DL-$erythro$-$C_{14}$-dihydrosphingosine [DL-$erythro$-(3)]. Yield 75~80%, and $erythro$ content was 99.9~100% (purity : 100% by GLC).
A mixture of DL-erythro-(3) (3.5 mmol) and potassium hydroxide (5 g) in MeOH+H₂O (9 : 1 vol/vol, 100 ml) was f efluxed for 10 h. Then, the mixture was dissolved with chloroform (700 ml). The solution was washed with water (250 ml, three times), and dried over anhydrous sodium sulfate. Removal of the solvent gave the desired DL-erythro-C₁₄-dihydro sphingosine [DL-erythro-(1)]. Yield 93~96%, mp 71~73°C, IR(νmax) : 3350, 3285 and 1588 cm⁻¹ ascribed to an amino group. MS(m/e) : 446(M-CH3), 358(M-CH₂OTMS), 257(M-204) and 204 (base ion peak, TMSNHCHCH₂OTMS) for N, O, O-tris(trimethylsilyl) derivative; 374 (M-CH₃), 286 (M-CH₂OTMS), 257 (M-123) and 132 (base ion peak, NH₂CHCH₂OTMS) for O, O-bis(trimethylsilyl) derivative.

Oxidation-reduction condensation of DL-erythro-(1).

A mixture of acetic acid (2 mmol), triphenylphosphine (2 mmol) and 2,2'-dipyridyl disulfide (2 mmol) in a solvent (6.1 ml) was stirred until the materials were completely dissolved. Then, DL-erythro-(1) (2 mmol) was added, and the stirring was continued for further 10 h. The crystalline DL-erythro-(1) was dissolved within three minutes in the solvents except carbon tetrachloride and cyclohexane. The reaction mixture was (participated with) a mixture of chloroform, methanol and 5% HCl (200+100+75 ml). The lower layer was washed with a mixture of methanol and water (50+50 ml, twice) and then water (50 ml), and dried over anhydrous sodium sulfate and evaporated. The residue was charged on a silica gel column (100 g) with a small amount of chloroform, and eluted with mixtures of chloroform and methanol (400+20, 200+20, 300+30 and 200+40 ml, gradiently). The combined fractions with Rᵣ = 0.40 (in CHCl₃+MeOH 9 : 1 vol/vol) were collected and evaporated to dryness. mp 122~123°C. IR(νmax) : 3290(amide I), 1545(amide II) and 1640(-NHCO-) cm⁻¹. MS(m/e) : 416 (M-CH₃), 328 (M-CH₃OTMS), 257 (M-CH₃= CONHCH₂OTMS), 247 [TMSOCH₂CH(NHTMS)COCH₃], 157 (247-TMSOH), 129 (TMSOCH₂-CH₃), 85 (CH₃CONHCH=CH₂) and 73 (base ion peak, TMS) for O, O-bis(trimethylsilyl) derivative.

Results and Discussion

Acetylation of 2-amino-1,3-tetradecanediol (1) with acetic anhydride in pyridine at room temperature and recrystallization of the resulting triacetate from hexane gave N, O, O-triacyl-DL-erythro-C₁₄-dihydrosphingosine [DL-erythro-(2)]. Mild alkaline hydrolysis of DL-erythro-(2) in the presence of sodium hydroxide in MeOH+H₂O (9 : 1 vol/vol) at room temperature and recrystallization of the resulting N-acetyl derivative from hexane+ ethanol gave pure N-acetyl-DL-erythro-C₁₄-dihydrosphingosine [DL-erythro-(3)]. The desired DL-erythro-C₁₄-dihydrosphingosine [DL-erythro-(1)] was prepared by refluxing DL-erythro-(3) in the presence of potassium hydroxide in MeOH.

\[
\begin{align*}
\text{C}_{11}\text{H}_{23} - \text{CH} - \text{CH} - \text{CH}_2\text{OH} & \quad \text{1) Ac₂O/Pyridine, R.T.} \\
\text{OH} & \quad \text{2) Recrystallization from hexane} \\
(1) & \quad (\text{erythro : 69.7%}) \\
\text{C}_{11}\text{H}_{23} - \text{CH} - \text{CH} - \text{CH}_2\text{OH}_2 & \quad \text{Ac} = \text{CH}_3\text{CO-} \\
\text{OAc NHAc OAc} & \quad \text{DL-erythro-(2)} \\
(\text{erythro : 97.0%}) \\
\text{C}_{11}\text{H}_{23} - \text{CH} - \text{CH} - \text{CH}_2 & \quad \text{1) 0.1M NaOH/MeOH+H}_2\text{O (9:1 vol/vol), R.T.} \\
\text{OH} & \quad \text{2) Recrystallization from hexane+Ethon} \\
(10:1 \text{vol/vol}) & \quad \text{DL-erythro-(3)} \\
(\text{erythro : 100%}) \\
\text{KOH/MeOH+H}_2\text{O (9:1 vol/vol)} & \quad \text{Reflux} \\
\text{DL-erythro-(1)} \\
(\text{erythro : 100%})
\end{align*}
\]
H₂O (9:1 vol/vol). Erythro content of DL-erythro-(1) was 100%. The structure of DL-erythro-(1) was confirmed by IR and MS and GLC. Purity and erythro content were determined by GLC.

The reaction of DL-erythro-(1) with acetic acid in the presence of triphenylphosphine and 2,2'-dipyridyl disulfide gave N-acetyl-DL-erythro-C₁₄-dihydrosphingosine [DL-erythro-(3)], whose structure was determined by IR, MS, and GLC. Virtually, no by-products were detected on TLC.

The solvent effect on the oxidation-reduction condensation is shown in Table-1. In carbon tetrachloride and cyclohexane, the starting material, DL-erythro-(1), was not completely dissolved. The product, DL-erythro-(3), was isolated by column chromatography. Table-1 suggests that a variety of aprotic solvents can be used for the selective N-acetylation of long chain bases, and furthermore for the synthesis of ceramides and peptides.

Table-1 Reaction of DL-erythro-C₁₄-dihydrosphingosine [DL-erythro-(1)] with acetic acid in the presence of triphenylphosphine and 2,2'-dipyridyl disulfide in various solvents at room temperature to give N-acetyl-DL-erythro-C₁₄-dihydrosphingosine [DL-erythro-(3)].

<table>
<thead>
<tr>
<th>Solvent</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dichloromethane</td>
<td>76.1</td>
</tr>
<tr>
<td>1,2-Dichloroethane</td>
<td>74.8</td>
</tr>
<tr>
<td>Acetonitrile</td>
<td>70.9</td>
</tr>
<tr>
<td>Chlorobenzene</td>
<td>69.4</td>
</tr>
<tr>
<td>Toluene</td>
<td>69.1</td>
</tr>
<tr>
<td>Benzene</td>
<td>68.4</td>
</tr>
<tr>
<td>Carbon tetrachloride</td>
<td>67.7</td>
</tr>
<tr>
<td>Tetrahydrofuran</td>
<td>65.4</td>
</tr>
<tr>
<td>Dioxane</td>
<td>63.8</td>
</tr>
<tr>
<td>Cyclohexane</td>
<td>63.2</td>
</tr>
<tr>
<td>Acetone</td>
<td>63.2</td>
</tr>
<tr>
<td>N,N-Dimethylformamide</td>
<td>53.6</td>
</tr>
<tr>
<td>Ethanol</td>
<td>5.5</td>
</tr>
<tr>
<td>Methanol</td>
<td>2.1</td>
</tr>
</tbody>
</table>

**Isolated. Reaction time = 10 h.**

Mukaiyama et al. speculated the transition state (4). In this study, the amino nitrogen atom of DL-erythro-(1) attacks on the active acetyl carbonyl group to produce DL-erythro-(3). In protic solvents, consumption of the active acetyl group of (4) by the nucleophilic attack of the oxygen atom of alcohols results in low yields as shown in Table-1.

A part of this work has been reported at the 17th meeting of Japan Oil Chemists Society (1978) Nagoya.

(Received August 7, 1980)

References
8) S. Hammerström, *J. Lipid Res.*, 12, 760 (1971)