Preparation of Desmosterol from Fucosterol\textsuperscript{1)}

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(Received December 20, 1975)

Desmosteryl acetate, a useful key intermediate for synthesis of the metabolites of vitamin D\(_3\), was synthesized from fucosterol by two routes; (1) 24, 28-epoxyfucosteryl acetate was treated with solid acids such as zeolite, silica-alumina and alumina-boria to give desmosteryl acetate in a yield of 16\%—40\%, (2) dehydration of 24-hydroxycholesterol acetate, which was obtained by ozonolysis of fucosterol acetate followed by reduction with sodium borohydride, with \( \text{P}_2\text{O}_5 \) in benzene afforded desmosteryl acetate in a yield of 85\%.

Desmosterol (4) has proved to be a useful key intermediate of the metabolites of vitamin D\(_3\), such as 25-hydroxyvitamin D\(_3\),\textsuperscript{3)} 24, 25-, 25, 26-,\textsuperscript{4)} and 1\( \alpha \),25-dihydroxyvitamin D\(_3\),\textsuperscript{5)} and 1\( \alpha \),24, 25-trihydroxyvitamin D\(_3\).\textsuperscript{6)} In the earlier synthesis of desmosterol, the 24,25-double bond was introduced by a Wittig reaction\textsuperscript{7)} on a C24-aldehyde or by dehydration of 25-hydroxycholesterol.\textsuperscript{8)} Recently Dasgupta, \textit{et al.}\textsuperscript{9)} reported new methods for the synthesis of desmosterol from 3\( \beta \)-hydroxybisnorcholesterol acid and 3\( \beta \)-hydroxynorcholnorcholic acid.

We have reported previously\textsuperscript{10)} that brief treatment of 24,28-epoxyfucosterol acetate (2) which was easily led from fucosterol, an abundant sterol in brown marine algae, with Lewis acids such as \( \text{BF}_3 \)-etherate, \( \text{SnCl}_4 \) and \( \text{AlCl}_3 \) gave desmosteryl acetate (3) by a fragmentation reaction in about 20—35\% yield. In an attempt to increase the yield of 3, the fragmentation reaction of the epoxide with solid acids was investigated (section A). An effective synthetic route for 3 from fucosteroyl acetate (1) \textit{via} 24-hydroxycholesterol acetate (6) is also described (section B).

\textbf{(A) Application of Solid Acids for the Fragmentation Reaction of Epoxide 2}

We found that 24,28-epoxyfucosterol acetate (2) was effectively converted to desmosteryl acetate (4) by solid acid such as zeolite,\textsuperscript{11)} alumina-boria, silica-gel and silica-alumina in anhydrous benzene with a simple technique. The reaction conditions and the yield of 3 are summarized in Table I. The highest yield (40\%) was obtained by use of Mn-zeolite (Y).

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1) This is Part 35 in the series of “Studies on Steroids”. For Part 34 see N. Ikekawa and N. Koizumi, \textit{J. Chromatog.}, 119, 227 (1976).
2) Location: a) Hino-shi, Tokyo; b) Ookayama, Meguro-ku, Tokyo.
Table I. Reaction of Epoxide 2 with Solid Acids

<table>
<thead>
<tr>
<th>Solid acids</th>
<th>Weights of catalyst (mg)</th>
<th>Reaction time (hr)</th>
<th>Yield of 3 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Silica-Alumina</td>
<td>300</td>
<td>1.5</td>
<td>24</td>
</tr>
<tr>
<td>Silica-gel</td>
<td>450</td>
<td>4.0</td>
<td>16</td>
</tr>
<tr>
<td>γ-Alumina-Boria</td>
<td>700</td>
<td>6.0</td>
<td>27</td>
</tr>
<tr>
<td>Mn-Zeolite (X)</td>
<td>600</td>
<td>1.5</td>
<td>34</td>
</tr>
<tr>
<td>Mn-Zeolite (Y)</td>
<td>400</td>
<td>2.0</td>
<td>40</td>
</tr>
<tr>
<td>Co-Zeolite (X)</td>
<td>700</td>
<td>3.5</td>
<td>28</td>
</tr>
<tr>
<td>Co-Zeolite (Y)</td>
<td>400</td>
<td>3.0</td>
<td>34</td>
</tr>
<tr>
<td>Zn-Zeolite (Y)</td>
<td>450</td>
<td>1.5</td>
<td>30</td>
</tr>
<tr>
<td>Ca-Zeolite (Y)</td>
<td>300</td>
<td>1.0</td>
<td>31</td>
</tr>
<tr>
<td>Mg-Zeolite (Y)</td>
<td>600</td>
<td>2.5</td>
<td>37</td>
</tr>
<tr>
<td>Ba-Zeolite (X)</td>
<td>700</td>
<td>5.0</td>
<td>28</td>
</tr>
<tr>
<td>Cu-Zeolite (X)</td>
<td>800</td>
<td>3.0</td>
<td>21</td>
</tr>
</tbody>
</table>

a) Sixty mg of the epoxide in 2 ml of benzene was used in each reaction. Reaction temperature was 18°C except for Silica-gel, 50°C.
b) Reactions were followed by GLC and TLC.
c) Product of Nikkagaku Co., Ltd., N-681-H.
d) Product of Nittokei Co., Ltd.
e) Content of boria is 15% by weight.
f) Various types of metal zeolite were prepared by treating Na-zeolite (X) or Na-zeolite (Y) with aqueous 1% metal chloride solutions. X-Type of zeolite was activated at 350°C and Y-type was activated at 280—300°C.
g) Zeolite (X) is a product of Tetsukosha, F-9.
h) Zeolite (Y) is a product of Union Carbide, SK-40.

The same by-products, as in the Lewis acid treatment,10) 24-acetylcholesterol acetate (7) (37%) and 24-formyl-24-methylcholesterol acetate (8) (13%) were obtained. The yield of 3 may be depend upon the factors such as the acid strength and the activity of the surface of the catalysts.

(B) Synthesis of Desmosterol Acetate via Ozonolysis of Fucosterol Acetate

The ozonolysis of fucosterol or its derivatives has been reported by several research groups.12) In their methods the yields of 24-oxo compounds are not satisfactory for synthetic purpose.13) We have searched for the reaction conditions of ozonolysis of 1, so that 24,28-double bond of 1 was selectively ozonized. The best yield was obtained when 1 was treated with ozone-oxygen stream of 11.8—17.2 g (O₃/m₃O₂) in CH₂Cl₂ at -78°C. The ketone 5 thus obtained was directly converted to 6 by treatment with NaBH₄ in methanol in a yield of 73% from 1. Dehydration of 6 with P₂O₅ in benzene preferentially afforded 3 in 85% yield with negligible amounts of 23-dehydrocholesterol acetate (10).

Table II. Dehydration Reaction of 24-Hydroxycholesterol Acetate (6)12)

<table>
<thead>
<tr>
<th>Catalyst (mg)</th>
<th>Solvent (ml)</th>
<th>Temp. (°C)</th>
<th>Time</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>P₂O₅ (160)</td>
<td>benzene (10)</td>
<td>5—10</td>
<td>20 min</td>
<td>85</td>
</tr>
<tr>
<td>P₂O₅ (200)</td>
<td>CH₂Cl₂ (10)</td>
<td>5—10</td>
<td>20 min</td>
<td>74</td>
</tr>
<tr>
<td>POCl₃ (0.5 ml)</td>
<td>pyridine (5)</td>
<td>20</td>
<td>3.5 hr</td>
<td>57</td>
</tr>
<tr>
<td>SOCl₂ (0.5 ml)</td>
<td>pyridine (5)</td>
<td>20</td>
<td>3.0 hr</td>
<td>58</td>
</tr>
</tbody>
</table>

a) Two hundred mg of 6 was used in each reaction.

13) Recently an improved method of ozonolysis to 24-oxo compound was reported by Y.M. Sheikh and C. Djerassi, Tetrahedron, 30, 4095 (1974).
Other dehydrating reagents such as SOCl₂ and POCl₃ gave inferior results obtaining 3 in a yield of 55—60% with a concomitant formation of 24-chlorocholesterol acetate (9). The results of the dehydration reactions are summarized in Table II. Thus, ozonolysis of fucostereryl acetate followed by NaBH₄ reduction and P₂O₅ dehydration may be a most practical route to desmostereryl acetate.

![Chart 1](image)

**Experimental**

Melting points were determined on a hot stage microscope and are uncorrected. Nuclear magnetic resonance (NMR) spectra were determined by a Varian EM360 or a JEOL SP/PFT-100 spectrometer in deuteriochloroform with tetramethylsilane as an internal standard. Mass spectra were recorded on a Shimadzu LKB-9000 GC-MS system. Optical rotation were determined with a JEOL DIP-SL model. Gas-liquid chromatography (GLC) analysis were performed on a Shimadzu GC-5AF gas chromatograph with a flame ionization detector. Column chromatography was effected with silica gel (Wakogel C-200).

**Reaction of 24,28-Epoxyfucostereryl Acetate (2) with Solid Acid**—To a solution of 24,28-epoxyfucostereryl acetate (60 mg) in 2 ml of dry benzene was added Mn-zeolite (Y) (400 mg) and the mixture was stirred at 18° for 2 hr. Mn-zeolite was filtered off and the filtrate was evaporated to dryness. The residue was applied on a column of silica gel (1 g). The fraction eluted with benzene–hexane (1:4) gave 21.8 mg of desmostereryl acetate (3), mp 83—94°, [α]D° -42.7° (c=0.45, CHCl₃). It was identical in respect to NMR and mass spectra with an authentic specimen. The fraction eluted with benzene–hexane (1:1) gave 7.8 mg of 24-formyl-24-methylcholesterol acetate (8), mp 128—130° (from acetone), identical by comparison with the authentic sample. The fraction eluted with benzene–hexane (3:1) gave 22.2 mg of 24-acetylcholesterol acetate (7), mp 130—135° (from acetone).

A similar product ratio of 3, 7, and 8 was obtained with other solid acids (Table I).

**24-Oxocholesterol Acetate (5)**—A stream of ozone (concentration of ozone, 11.8 g/m³ (O₃)) was gently passed through a solution of fucostereryl acetate (10 g) in methylenechloride (300 ml) at -78° for 80 min. After ozonization, acetic acid (500 ml) and zinc dust (25 g) were added to the solution and the mixture was stirred vigorously for 1 hr at 45°. Zinc dust and zinc acetate were removed by filtration. The filtrate was then diluted with water and extracted with methylene chloride. The methylene chloride layer was washed with 6% NaHCO₃ and then with water and dried over Na₂SO₄. The solvent was evaporated and the crude product was chromatographed on silica gel. The fraction eluted with benzene–hexane (2:1) gave 7.4 g of 24-oxocholesterol acetate (5), mp 130—132°.

**24-Hydroxycholesterol Acetate (6)**—24-Oxocholesterol acetate (6 g) was treated with NaBH₄ (5.5 g) in MeOH (1.6 liter) at room temperature for 1 hr. Acetic acid (50 ml) was added and the mixture was extracted with ether, washed with brine and dried over Na₂SO₄. Evaporation of the solvent gave a white amorphous
powder, which was purified by silica gel column using benzene as an elution solvent to afford 5.8 g of 24-hydroxycholestereryl acetate (6),\(^{10}\) mp 124—125\(^{\circ}\), identified by comparison with the authentic sample.

**Reaction of 24-Hydroxycholestereryl Acetate (6) with \(\text{POCl}_3\)**—To a stirred suspension of \(\text{POCl}_3\) (160 mg) in 10 ml of dry benzene, 6 (200 mg) was added dropwise under ice-cooling. After stirring for 20 min at 7\(^{\circ}\), the reaction mixture was extracted with ether, washed with saturated \(\text{NaHCO}_3\) solution and then with brine. Evaporation of the solvent afforded a yellow amorphous powder (198 mg), which was purified by column chromatography on silica gel. The fraction eluted with benzene–hexane (1: 4) gave 163 mg of desmosteryl acetate (3), mp 93—94.5.

The GLC analysis of the crude product using 1.5% OV-1 on Chromosorb WHP, 150 cm x 3 mm i.d. at 270\(^{\circ}\), demonstrated that 23-dehydrocholesterol acetate (10) (3%) and 6 (4%) were contained in the reaction product. The retention times of 10, 3 and 6 were 3.2, 3.6 and 6.0 min, respectively. 23-Dehydrocholestereryl acetate was identified in respect to the retention time of GLC and mass spectrum obtained by GC-MS system with an authentic sample.\(^{10}\)

**Reaction of 24-Hydroxycholestereryl Acetate (6) with \(\text{POCl}_3\)**—In a solution of 6 (200 mg) in pyridine (5 ml), phosphorus oxychloride (0.5 ml) was added and the mixture was stirred for 3.5 hr at 20\(^{\circ}\). The solution was poured into ice-water and extracted with ether. The ether solution was washed with 1N HCl and then with brine. Evaporation of the solvent afforded a slight yellow amorphous powder (200 mg) which was purified by column chromatography. The fraction eluted with benzene–hexane (1: 4) gave desmosteryl acetate (109 mg) and the fraction eluted with benzene–hexane (1.5: 4) gave 24-chlorocholestereryl acetate (9) (69 mg), Mass Spectrum \(m/e: 404\) (M+AcOH), 402, 351, 255, 253, 213; NMR \(\delta\) 0.88 (3H, s, 18-Me), 1.02 (3H, s, 19-Me), 2.02 (3H, s, Ac), 3.75 (1H, m, 24-H), 4.60 (1H, m, 3-H), 5.37 (1H, m, 6-H).

The GLC analysis of the crude product indicated that a small amount (2%) of 23-dehydrocholestereryl acetate (10) was contained in the reaction product. The yield of 3 and 9 in Table II were calculated from the chromatogram. The column conditions were same as above description. The retention time of 9 was 7.0 min.

**Acknowledgement** The authors are grateful to Drs. T. Noguchi, S. Tsunoda and S. Sakajiri of Teijin Limited, for their encouragements and advices through the course of this work.

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**Halogenation Reaction of Bis(acetylacetonato)nickel(II) and -cobalt(II) Chelate**

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(Received December 20, 1975)

Introduction of chlorine, bromine, and iodine atom into the ring of labile bivalent metal acetylacetonates, bis(acetylacetonato)nickel (II) and -cobalt(II) chelates, is effected by halosuccinimide in carbon tetrachloride. Infrared and ultraviolet spectra of halogenated metal(II)-acetylacetonate chelate derivatives were measured. The masses of substituent at the central carbon atom of these metal(II)-acetylacetonates affected the frequencies of C=O and C=C stretching bands.

The introduction of substituents at the central carbon atom of the trivalent metal-acetylacetone ring, such as cobalt(III), chromium(III), and rhodium(III), etc., by electrophilic

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1) Location: Ichigaya-funagawara-machi, Shinjuku-ku, Tokyo, 162, Japan.