41. The Synthesis of Homocholane and Bisnorsterocholane Derivatives from Desoxycholic Acid

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For the purpose of certifying the chemical constitution of natural stero-bile acid, the various stero-bile acids,1) and polyhydroxysterols3) have been already synthesized. Trihydroxyhomocholane,5) which has coprostan nucleus and cholic acid nucleus, is synthesized from potassium cholate and potassium propionate by the Kolbe reaction and by the method using diazomethane. This sterol is identical with natural sterol4) isolated from the bull frog bile, but this natural sterol is quite different from the trihydroxybisnorsterocholane,5) which is obtained from cholestane and ethylmagnesium bromide by the Grignard reaction, as well as from potassium cholate and potassium butyrate by the Kolbe reaction. In bile will be found different kinds of sterols, which may have two or three hydroxyl groups in coprostan nucleus, just like the bile acids, whose nucleus has one, two, or three hydroxyl groups at the position of C3, C7, and C12. In this respect various derivatives of homocholane and bisnorsterocholane were synthesized, such as 3.12-dihydroxyhomocholane with m.p. 218–219°, 3.12-dihydroxybisnorsterocholane with m.p. 97° with foaming, and 3.7.24-trihydroxybisnorsterocholane with m.p. 79–80° with foaming. At first by heating at about 200° in an oil bath, from different bile acid and formylamide various kinds of amides have been synthesized, as shown in Table I.

These amides are not soluble in all organic solvents. So desoxycholylamide was mixed with pyridine and acetic acid anhydride and heated for 30 hours, and the obtained acetate (I in the figure) was converted into the desoxycholylmethylketone (II in the figure) under the action of Grignard reagent. Semicarbazone was made from this ketone and then reduced by the method of Wolff-Kischner. Thus was obtained 3.12-dihydroxyhomocholane (III in the figure) which crystallizes in plate and melts at 218–219°. The ketone by action of sodium and alcohol will be reduced into an oily 3.12.24-trihydroxyhomocholane (IV in the figure), which will be oxidized into crystallized 3.12.24-triketohomocholane with m.p. 125–126°, and this ketone will thus form trioxime with m.p. 148–149°. On the other side, by the action of Grignard reagent from ethylmagnesiumjodid upon acetate of desoxycholic acid amide, there may be obtained 3.12-dihydroxy-
cholylethylketone (V in the figure) and its semicarbazone, but these
are not crystallized. This semicarbazone will be reduced into 3.12-
dihydroxybisnorsterocholane (VI in the figure) with m.p. 97° with
foaming by the method of Wolff-Kischner. Desoxycholylethylketone
will be reduced by the method of Wolf-Kischner into 3.12.24-tri-
hydroxybisnorsterocholane (VII in the figure) with m.p. 79–80° with
foaming.

**Experimental**

1. Desoxycholic acid amide

8 g of acetic acid choleic acid with m.p. 145° was dissolved in
10 dl of formic acid amide, and kept for five hours in an oil bath
at a temperature of 170–200°. The mixture formed by this reaction
was poured into water. The precipitate produced was recrystallized
from ethyl acetate. A crystal with m.p. 180° was obtained, but it
sinters at 105° and melts with foaming. This crystal was dried on
xylolbad for five hours and then analyzed.

   **Analysis:** C_{24}H_{41}O_{3}N, Caled. C 73.60% H 10.56% N 3.57%
   Found. C 73.38, 73.60% H 10.42, 10.24% N 3.57, 3.49%

By the same method various amides of different bile acids were
synthesized (Table I) and analyzed.

2. 3.12-Dihydroxyhomocholane

5 g of desoxycholic acid amide was dissolved in 30 dl of pyridine
and mixed with 25 dl of anhydrous acetic acid and refluxed in a
water bath for 28 hours. The mixture formed by this reaction was
poured into a large amount of water, and the precipitate produced
from ethyl acetate. A crystal of desoxycholic acid amide
acetate with m.p. 179° was obtained. This acetate is soluble in
benzol. 2 g of dried amide acetate was dissolved in 50 dl of benzol
and mixed with Grignard reagent and refluxed for five hours in a
water bath, which was made up from 1.7 g magnesium, 10 g jod-
methyl, and 30 dl ether. The solvent was distilled off under the
reduced pressure, then the residue was decomposed in ice water and
acidified with dilute sulfuric acid and the precipitate produced was
extracted with ether. The ether solution was at first washed with

<table>
<thead>
<tr>
<th>Bile acid</th>
<th>M.p. of amide</th>
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<tbody>
<tr>
<td>Cholic acid</td>
<td>165° (110° sintered)</td>
</tr>
<tr>
<td>Desoxycholic acid</td>
<td>187° (foaming)</td>
</tr>
<tr>
<td>Hyodesoxycholic acid</td>
<td>266–268°</td>
</tr>
<tr>
<td>Ursodesoxycholic acid</td>
<td>125° (foaming)</td>
</tr>
<tr>
<td>Chenodesoxycholic acid</td>
<td>205°</td>
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</tbody>
</table>

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Table I
sodium hyposulfite solution and then washed with water and dried. Then the ether was distilled off, and then the residue was dissolved in a 10% alcoholic solution of potassium hydroxide and was hydrolyzed in a water bath for two hours, and the mixture was poured into a large amount of water and with ether extracted. From this ether solution an oily substance was obtained. The oily desoxycholylmethylketone was made into a semicarbazone by the usual method. This semicarbazone was recrystallized from alcohol and melts at 214–215°. Yields 1.5 g.

Analysis: C_{26}H_{46}O_{3}N_{3}·2H_{2}O Caled. C 69.90% H 10.16% N 9.41% Found. C 70.05, 70.01% H 10.31, 10.20% N 9.68, 9.51% 1.5 g of this semicarbazone was dissolved in 30 dl of alcohol and re-
duced by the method of Wolff-Kischner. The reaction mixture was poured into a large amount of water, and the precipitate produced was extracted with ether. The ether extract was evaporated and the produced crystals repeatedly recrystallized from ethyl acetate and a plate crystal with m.p. 218-219° was formed:

Analysis: \( \text{C}_{25}\text{H}_{44}\text{O}_2 \cdot \text{H}_2\text{O} \) Calcd. C 76.08% H 11.76%
Found. C 75.90% H 11.50%

3.12-Diketohomocholane:
3.12-Dihydroxyhomocholane was dissolved in glacial acetic acid. Chromic acid was added, and the mixture oxidized into 3.12-diketohomocholane.

3. 3.12.24-Trihydroxyhomocholane
6 g of desoxycholylmethylketone semicarbazone was suspended in 50 dl of aceton and mixed with 5 dl of 1% hydrochloride solution and heated in a water bath. The mixture was poured into water and extracted with ether. After evaporation of the ether, an oily desoxycholylmethylketone was obtained. The ketone was dried completely and dissolved in 60 dl of anhydrous alcohol. To this solution were added several portions of sodium totaling of 5 g and the solution was heated in an oil bath at 160-180°. After the disappearance of sodium, the mixture was poured into one litre of water, and the precipitate was extracted with ether. The ether extract was washed with water, dried with potash and evaporated into thickness, but no crystal appeared. So it is considered that the obtained 3.12.24-tri hydroxyhomocholane is an oil. The oily substance was dissolved in 30 dl of glacial acetic acid and mixed with 10 dl of 20% glacial acetic acid solution of chromic acid anhydride; it oxidized into 3.12.24-triketohomocholane. The oxidized substance was recrystallized by using alcohol and water, and the obtained crystal melts at 125-126°. Yields 0.25 g.

Analysis: \( \text{C}_{25}\text{H}_{38}\text{O}_3 \) Calcd. C 77.66% H 9.91%
Found. C 78.02, 77.86% H 10.40, 10.66%

3.12.24-Triketohomocholanetioxime was obtained in the usual way, and was recrystallized by using alcohol and water; it melts at 148-149°.

Analysis: \( \text{C}_{25}\text{H}_{41}\text{O}_3\text{N}_3 \cdot \text{H}_2\text{O} \) Calcd. N 9.34%
Found. N 9.21%

4. 3.12-Dihydroxybisnorsterocholane
4 g of desoxycholylamide acetate was dissolved in 50 dl of benzol, mixed with Grignard reagent prepared from 3.5 g of magnesium, 22 g of jodethyl and 50 dl of anhydrous ether, and refluxed in a water bath for five hours. After evaporation of the benzol under reduced pressure, the residue was poured into ice water and the mixture
was acidified with dilute sulfuric acid solution and extracted with ether. The ether extract was washed at first with hyposulphate solution, then with water, and dried with potash. After evaporation of the ether, the residue was dissolved in 100 dl of 10% alcoholic potassium hydroxide solution and heated for two hours in a water bath and extracted with ether. From the ether solution 3.12-dihydroxyethylketone was obtained, but this does not crystallize from all organic solvents. So this ketone was converted into its semicarbazone in the usual way. The semicarbazone does not also crystallize, but stays as an oil, though it has been many times recrystallized.

1.7 g of the semicarbazone was dissolved in 30 dl of absolute alcohol, mixed with 1.5 g of sodium, which was divided into several portions and sealed in glass tubes and heated in an autoclave at 160-180° for six hours. The mixture was poured into a large amount of water and extracted with ether. From the ether extract a crystal with m.p. 97° with foaming was obtained.

Analysis: C_{26}H_{46}O_{2.22}H_{2}O  Calcd. C 71.67% H 11.81% 
Found. C 71.40, 71.61% H 11.23, 11.32%

3.12.24-Trihydroxybisnorsterocholane

Desoxycholylethylketone-semicarbazone was decomposed into free desoxycholylethylketone in the usual way. This ketone was reduced by the usual method of Wolff-Kischner with sodium and alcohol into 3.12.24-trihydroxybisnorsterocholane. The obtained crystal was recrystallized by using ether, and this crystal melts at 79-80° with foaming.

Analysis: C_{26}H_{46}O_{3.12}H_{2}O  Calcd. C 72.09% H 11.39% 
Found. C 72.08% H 11.51%

References