Basic Bile Acids. IV. On the Syntheses of 7β-Amino-, 12α-Amino-, and 3α-Hydroxy-12α-aminocholanic Acid and Their Derivatives*1

By Yasuo SATOH

(Received November 5, 1964)

In the previous papers of this series,[1] the syntheses and properties of 3α-, 3β-, 7α-, and 12α-aminocholanic acid and their derivatives have been reported. The present paper will describe the syntheses of 7β-amino-, 12α-amino-,*2 and 3α-hydroxy-12α-aminocholanic acid and their derivatives.

Derivatives of 7β- and 12α-aminocholanic acid were synthesized from the oximes of each ketone by reduction with sodium and *n*-propanol. Moreover, as a basic bile acid containing a hydroxyl group, 3α-hydroxy-12α-aminocholanic acid was synthesized. For the synthesis of this basic bile acid, deoxycholic acid was chosen as the starting material, and the reduction of the oxime was carried out according to the methods described for the cases of the 3-, 7-, and 12-positions.[1]

Experimental*3,*4

7β-Aminocholanic Acid Hydrochloride (II).*5—Into a boiling solution of 3.5 g. of 7-hydroxyiminocholanic acid (I) in 105 ml. of dried *n*-propanol, 10.5 g. of sodium cut into small pieces was gradually stirred. When all the sodium had been added, 15 ml. of ethanol was slowly added to the reaction mixture through the reflux condenser until the few remaining pieces of sodium had completely reacted. After the reaction mixture had then stood for 14 hr. at room temperature, 90 ml. of water was added, the separated lower layer was taken off, and 220 ml. of water was added to the upper layer. The solution, now consisting of two layers, was acidified with hydrochloric acid (1 : 1) and concentrated to half-volume under reduced pressure, and then this solution was cooled. The resultant crystals were collected, washed with water, and dried. The yield of a slightly brownish amorphous substance was 3.17 g. Attempts to crystallize the hydrochloride were unsuccessful, and so it was used for the next step without purification. IR (KBr disk): 3440, 1721, 1602 and 1508 cm^{-1}.

Methyl 7β-Aminocholanate Hydrochloride (III).—This substance was prepared according to the procedure described earlier for the synthesis of the 7α-isomer.[1] The crystallization of the resultant solid from methanol - petroleum ether gave 1.92 g. of the methyl ester from 2.7 g. of II; colorless plates, m. p. 248.5—249.5°C (which changed to needles at about 204°C), and $[\alpha]_D^{25}$ +28.5° (*c* 2.01, methanol). IR (KBr disk): 3250, 1742, 1604, 1508, and 1170 cm^{-1}.

Methyl 7β-Acetamidocholanate (IV).—The synthesis of this substance was carried out using the technique described for the synthesis of the 7α-isomer.[1] Attempts to crystallize the acetamido derivative from the ether extracts were unsuccessful. IR (KBr disk): 3264, 1732, 1636, 1559, and 1164 cm^{-1}.

When the syrupy material was submitted to thin-layer chromatography on Wako-gel B-5 (thickness, 0.5 mm.) with benzene-ether (1 : 2), a spot at 0.3 in R_f value and another weak spot at the original point were observed. Therefore, the above-described syrupy substance was subjected to separation using a large-area layer (20×20 cm^2; thickness, 0.5 mm.). A separated band, which was detected with concentrated sulfuric acid, was scraped off and extracted with warm methanol. The methanolic solution was filtered, and the filtrate was evaporated under reduced pressure. Crystallization of the residue from benzene - petroleum ether afforded a crude acetamido derivative, m. p. 115—117°C; yield 165 mg. Two crystallizations of this substance from the same solvent raised the melting point to 120—121°C; $[\alpha]_D^{20}$ +22.0° (*c* 1.01, chloroform). IR (KBr disk): 3260, 1745, 1638, 1557, and 1165 cm^{-1}.

Found: C, 75.05; H, 10.48; N, 3.20. Calcd. for $C_{27}H_{45}O_3N$: C, 75.12; H, 10.51; N, 3.26%.

12α-Aminocholanic Acid Hydrochloride (VIm).—This substance was prepared according the procedure described above for the synthesis of the 7β-isomer (II). The crystallization of the resultant solid from methanol gave 2.86 g. of the amino acid hydrochloride from 3.3 g. of the oxime (V) of 12-ketocholanic acid; m. p. 285.5—287°C, $[\alpha]_D^{25}$ +42.9° (*c* 1.89, ethanol). IR (KBr disk): 3432, 1702, 1611, and 1521 cm^{-1}.

The melting point of this derivative was not depressed by admixture with a sample VIc prepared by the catalytic reduction of the oxime,[1] and this derivative was identical in infrared spectrum with a sample of VIc.

When the oxime was reduced with sodium and ethanol, the amino derivative formed was identical with a specimen of VIm.

---

*1 Presented at the Local Meeting of the Chemical Society of Japan, Morioka, September, 1964.

*2 The method of the synthesis of this derivative used here differs from that of the previous work.

1) Y. Satoh and A. Hagitani, *J. Chem. Soc. Japan, Pure Chem. Sec.* (*Nippon Kagaku Zasshi*), **80**, 1310 (1959); Y. Satoh, ibid., **84**, 829 (1963); **85**, 54 (1964).

*3 All melting points are uncorrected.

*4 The infrared absorption spectra were measured with a Shimadzu model IR-27B infrared spectrophotometer.

*5 This compound is an epimer of the 7-amino derivative described in our previous paper.[1]

Methyl 12α-Aminocholanate Hydrochloride (VII).—This substance was prepared according to the procedure described earlier for the synthesis of the 7α-isomer.[1] The crystallization of the resultant solid from methanol gave 810 mg. of the methyl ester from 1 g. of VIm; m. p. 205.5—207°C, $[\alpha]_D^{25}$ +40.1° (*c* 1.00, ethanol). IR (KBr disk): 3220, 1730, 1605, and 1521 cm^{-1}. No depression in melting point was observed upon its admixture with a sample prepared by the catalytic reduction of the oxime.[1]

Methyl 12α-Acetamidocholanate (VIII).—The synthesis of this substance was carried out using the technique described for the synthesis of the 7α-isomer.[1] Two-hundred and forty-four milligrams of this substance (octagonal crystals; m. p. 231—232°C, $[\alpha]_D^{28}$ +29.1° (*c* 2.00, chloroform) was obtained from 500 mg. of VII. The melting point of this substance was not depressed by admixture with methyl 12α-acetamidocholanate derived from the oxime by catalytic reduction.[1] IR (KBr disk): 3272, 1735, 1636 and 1554 cm^{-1}.

Found: C, 75.09; H, 10.29; N, 3.20. Calcd. for $C_{27}H_{45}O_3N$: C, 75.12; H, 10.51; N, 3.26%.

3α-Hydroxy-12-hydroxyiminocholanic Acid (X).—This preparation followed the general method used for the synthesis of the steroidal ketoxime from 3α-hydroxy-12-ketocholanic acid (IX): m. p. 131—132°C, $[\alpha]_D^{20}$ +149.7° (*c* 0.35, chloroform). IR (KBr disk): 3310, 1704, 1644, and 938 cm^{-1}.

The Synthesis of 3α-Hydroxy-12α-aminocholanic Acid Hydrochloride (XI) from the Oxime.—*i) Catalytic Reduction.*—The method used here was identical with that described for the 7α-isomer.[1] The crystallization of the residue from methanol yielded 751 mg. of the amino acid from 1 g. of the oxime; m. p. 279—281°C, $[\alpha]_D^{25}$ +51.5° (*c* 0.91, ethanol). IR (KBr disk): 3344, 1708, 1608, and 1518 cm^{-1}.

Found: C, 68.01; H, 9.91; N, 3.20; Cl, 8.20. Calcd. for $C_{24}H_{43}O_3NCl$: C, 67.37; H, 9.82; N, 3.27; Cl, 8.30%.

ii) Reduction with Sodium and n-Propanol.—This reaction was carried out according to the procedure described above for the synthesis of the 7β-isomer (II). The crystallization of the resultant solid from methanol gave 0.96 g. of the amino acid hydrochloride from 1.6 g. of the oxime; m. p. 280.5—282.5°C, $[\alpha]_D^{25}$ +52.7° (*c* 0.68, ethanol). IR (KBr disk): 3340, 1708, 1609, and 1518 cm^{-1}.

Found: C, 67.54; H, 9.82; N, 3.32; Cl, 8.23. Calcd. for $C_{24}H_{42}O_3NCl$: C, 67.37; H, 9.82; N, 3.27; Cl, 8.30%.

The melting point of this derivative was not depressed by its admixture with a sample prepared by method i.

Moreover, when the oxime was reduced with sodium and ethanol, it was found that the product was identical with the samples XIc and XIm*6.

Methyl 3α-Hydroxy-12α-aminocholanate Hydrochloride (XII).—This substance, m. p. 255—256°C, $[\alpha]_D^{22}$ +42.7° (*c* 0.35, chloroform), was prepared from XIc and XIm with absolute methanol and dry hydrogen chloride gas. IR (KBr disk): 3344, 1723, 1613, and 1529 cm^{-1}. The mixed melting point of the two esters was 254—256°C.

Found: C, 68.20; H, 9.83; N, 3.26; Cl, 7.95 (XIIc) and C, 68.06; H, 9.87; N, 3.19; Cl, 7.91 (XIIm). Calcd. for $C_{25}H_{44}O_3NCl$: C, 67.95; H, 9.97; N; 3.17; Cl, 8.04%.

Methyl 3α-Acetoxy-12α-acetamidocholanate (XIII).—This derivative, m. p. 248—249°C, $[\alpha]_D^{25}$ +111.9° (*c* 2.10, chloroform), was prepared from XIIc and XIIm with acetic anhydride and absolute pyridine by heating it for 4 hr. at 100°C. The mixed melting point of XIIIc and XIIIm was 247.5—249°C. IR (KBr disk): 3260, 1723, 1632, 1550, and 1250 cm^{-1} (XIIIc); 3263, 1722, 1632, 1551, and 1251 cm^{-1} (XIIIm).

Found: C, 71.39; H, 9.51; N, 2.86 (XIIIc) and C, 71.37; H, 9.56; N, 2.88 (XIIIm). Calcd. for $C_{29}H_{47}O_5N$: C, 71.17; H, 9.61; N, 2.86%.

The author is grateful to Professor Akira Hagitani of St. Paul's University for many helpful discussions and suggestions during this work; thanks are to be given to Miss Itsuko Sano and Mr. Akira Satomura for their assistance in the experimental work.

Department of Chemistry
Faculty of Science
St. Paul's University (Rikkyo Daigaku)
Toshima-ku, Tokyo

*6 XIc and XIm are samples prepared by the methods i and ii respectively.