[CONTRIBUTION FROM THE INSTITUTE OF APPLIED MICROBIOLOGY, UNIVERSITY OF TOKYO]

Cholesterol and Related Compounds. V. Synthesis of Aza-D-homosteroids

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Chromic acid oxidation of Δ^{14}-cholesten-3β-ol-benzoate (II) gave 16-keto-Δ^{14}-cholesten-3β-ol-benzoate (III) and the ketocarboxylic acid IV, both of which were used as starting materials for the synthesis of aza-D-homosteroids. The dihydro compound V of III gave two stereoisomeric oximes (VIa and VIb) which upon Beckmann rearrangement yielded 17-aza-16-keto- (VII) and 16-aza-17-keto-D-homocholestan-3β-ol-benzoate (VIII), respectively. VII was also synthesized by two other routes from III. 15-Aza-16-keto-D-homocholestan-3β-ol-benzoate (XVIII) was prepared from the ketocarboxylic acid IV. The catalytic hydrogenation of 15-keto-$\Delta^{8(14)}$-cholesten-3β-ol-benzoate (XXb) in an acidic medium yielded a new stereoisomer of cholestanyl benzoate (XXV) and 15-keto-cholestan-3β-ol-benzoate (XXIV).

D-Ring lactams have been obtained[2] by Beckmann rearrangement of oximes of estrone benzoate, dehydroisoandrosterone acetate and Δ^4-androstene-3,17-dione. Other lactams of steroids have been reported by Heusser,[3] Clemo,[4] Reichstein[5] and Hara.[6] In a recent paper Regan and Hayes[7] have reported the synthesis of 17- and 17a-aza-D-homosteroids from 17-ketosteroid.

The present paper describes the synthesis from cholesterol of steroid D-ring lactams and their azasteroids. The chromic acid oxidation of Δ^{14}-cholesten-3β-ol-benzoate (II) yielded 16-keto-Δ^{14}-cholesten-3β-ol-benzoate (III), a ketocarboxylic acid IV and several by-products which are described in the Experimental section.

Compound III was used as a starting material for the synthesis of azasteroids as follows: catalytic hydrogenation gave cholestanyl benzoate and the dihydro compound of III, 16-ketocholestan-3β-ol-benzoate (V), m.p. 122–123°. Since Wolff–Kishner reduction of V afforded cholestanol, the C_{14}-hydrogen of V is assumed to be in the α-configuration. The oxime formed by the reaction of V with hydroxylamine hydrochloride was separated into two stereoisomeric oximes by chromatography. The ratio of yields of the α-oxime VIa, to the β-oxime VIb, was 7:1.

Treatment of the pyridine solution of VIa with *p*-toluenesulfonyl chloride gave lactam VII; VIb afforded the ether-insoluble lactam VIII, and the ether-soluble oxime tosylate VIIIa. Since VIIIa, which is an intermediate of the Beckmann rearrangement, of VIb is stable, the yield of VIII was poor.

Lactam VII was also obtained by two other routes from III. (a) Treatment of III with hydroxylamine yielded oxime XI, which upon Beckmann rearrangement gave lactam XII. Hydrogenation of XII yielded the dihydro lactam, which is identical with VII. (b) Oxidation of V followed by treatment of the resulting ketocarboxylic acid XIII, m.p. 146–152°, with alcoholic ammonia gave lactam XIV; VII was obtained by the hydrogenation of XIV.

The catalytic hydrogenations of XII and XIV were conducted in a neutral medium under conditions which favor *trans*-orientation of hydrogen at C_{14}, C_{17} and C_{20}.[8] Therefore, it can be concluded that lactam VII has the structure 17-aza-16-keto-D-homocholestan-3β-ol-benzoate, and that lactam VIII is 16-aza-17-keto-D-homocholestan-3β-ol-benzoate.

On the other hand, a 15-aza-D-homosteroid was synthesized from the ketocarboxylic acid IV; treatment of IV[9] with alcoholic ammonia gave 15-aza-16-keto-$\Delta^{8(14)}$-D-homocholesten-3β-ol-benzoate (XVI). The 8,14-double bond of lactam XVI migrated to the 14,15-position upon treatment with dry hydrogen chloride to give the Δ^{14}-lactam XVII.

Catalytic hydrogenation of XVII with platinum oxide in a neutral medium gave a dihydro substance. This lactam should have the structure 15-aza-16-keto-D-homocholestan-3β-ol-benzoate (XVIII); in order to establish this structure, we synthesized the intermediate XVI by the following route: 15-keto-$\Delta^{8(14)}$-cholesten-3β-ol acetate (XXa) was obtained from $\Delta^{8(14)}$-cholesten-3β-ol-acetate by chromic acid oxidation according to the method of Wintersteiner, *et al.*[10]; its oxime XXI gave 15-aza-16-keto-$\Delta^{8(14)}$-D-homocholesten-3β-ol-acetate (XXII) by Beckmann rearrangement. The lactam XXII was converted to 15-aza-16-keto-$\Delta^{8(14)}$-D-homocholesten-3β-ol (XXIII) with dilute alkali under mild conditions. XXIII was found to be identical with the saponification product of 15-aza-16-keto-$\Delta^{8(14)}$-D-homocholesten-3β-ol-benzoate (XVI).

Lactams VII, VIII and XVIII were converted to 17-aza-D-homocholestanol (IX), m.p. 196–198.5°, 16-aza-D-homocholestanol (X), m.p. 157–158°, and 15-aza-D-homocholestanol (XIX), m.p. 139–142°, respectively, with lithium aluminum hydride.

Wintersteiner[10] reported that the hydrogenation of 15-keto-$\Delta^{8(14)}$-cholestenyl acetate (XXa) with palladium as the catalyst in an acidic medium gives Δ^{14}-cholestenyl acetate, and that when this hydrogenation was carried out in a neutral medium, the absorption of hydrogen does not occur. When we hydrogenated 15-keto-$\Delta^{8(14)}$-cholesten-3β-ol-benzoate(XXb) with platinum oxide as the catalyst, with the addition of two or three drops of 10% hydrochloric acid, we obtained as hydrogenation products 15-ketocholestanyl benzoate (XXIV), m.p.

(1) Takamine Research Laboratory, Sankyo Co., Ltd., Tokyo.

(2) S. T. Kaufmann, THIS JOURNAL, **73**, 1779 (1951).

(3) H. Heusser, J. Wohlfohrt, M. Müller and R. Anliker, *Helv. Chim. Acta*, **38**, 1399 (1955); R. Anliker, M. Müller, J. W. Wohlfohrt and H. Heusser, *ibid.*, **38**, 1404 (1955).

(4) G. R. Clemo and L. K. Mishrs, *J. Chem. Soc.*, 192 (1953).

(5) J. Barnett and T. Reichstein, *Helv. Chim. Acta*, **21**, 926 (1938).

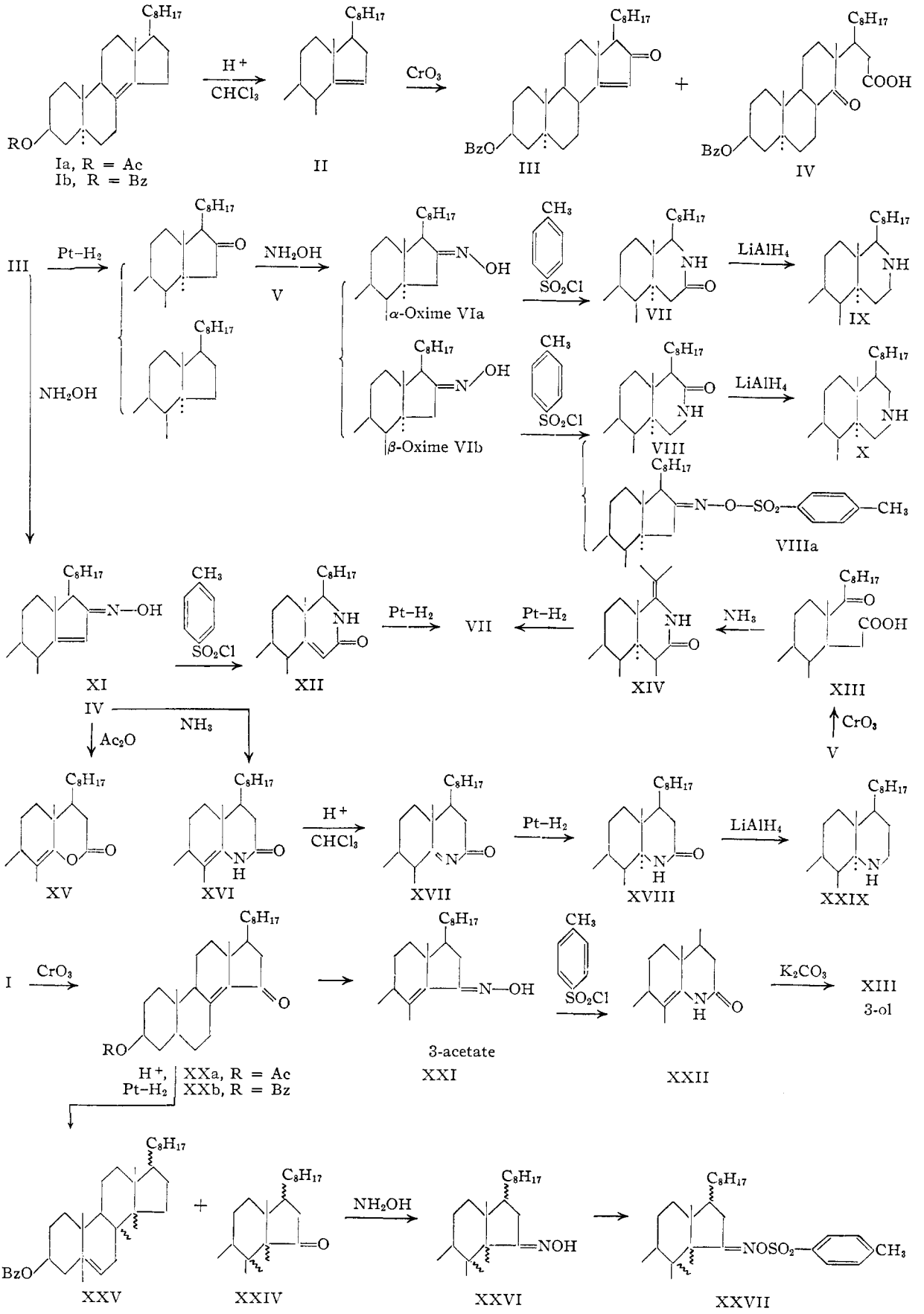
(6) S. Hara, *Pharm. Bull. (Japan)*, **3**, 209 (1955).

(7) B. M. Regan and F. N. Hayes, THIS JOURNAL, **78**, 639 (1956).

(8) L. F. Fieser and Mary Fieser, "Natural Products Related to Phenanthrene," Reinhold Publ. Corp., New York, N. Y., 1949.

(9) When IV was heated with acetic anhydride the enol lactone XV was obtained.

(10) O. Wintersteiner and M. Moore, THIS JOURNAL, **65**, 1513 (1943).


Ia, R = Ac
Ib, R = Bz
II
III
IV
V
α-Oxime VIa
β-Oxime VIb
VII
VIII
IX
X
VIIIa
XI
XII
XIII
XIV
XV
XVI
XVII
XVIII
XXIX
XXI
XXII
XXa, R = Ac
XXb, R = Bz
3-acetate
3-ol
XXIV
XXV
XXVI
XXVII

151–152°, and a stereoisomer of cholestanol benzoate (XXV). Saponification of XXV gave an isomer of cholestanol, m.p. 144–146°, α_D +35.0.[11] Beckmann rearrangement of the oxime XXVI gave the oxime tosylate XXVII; as in the case of VIb, the lactam was not obtained.

Experimental[12a,12b]

Oxidation of Δ^{14}-Cholesten-3β-ol-benzoate (II).—To a solution of 12 g. of Δ^{14}-cholesten-3β-ol-benzoate (II) in 1.2 l. of glacial acetic acid was added 9 g. of chromic acid with stirring at 50–55°; stirring was continued for 3.5 hours and then 5 ml. of ethyl alcohol was added. The acetic acid solution was distilled under reduced pressure, and the residual oil extracted with ether. The ether solution was washed with 10% potassium hydroxide twice and with water and dried; the solvent was removed under reduced pressure.

The pale yellow oil (neutral fraction 9.2 g.), fractionated by chromatography, afforded the following products in crystalline form:

Unidentified substance, m.p. 188–189.5°, yield 350 mg., no ultraviolet absorption above 228 mμ; ν_{max} 1742 and 1712 cm.$^{-1}$ in Nujol.

Anal. Calcd. for $C_{34}H_{48}O_3$: C, 80.96; H, 9.52. Found: C, 81.22; H, 9.78.

16-Keto-Δ^{14}-cholesten-3β-ol-benzoate (III), m.p. 142–143°, yield 720 mg., λ_{max}^{alc} 230 and 233 mμ (E 16180 and 15350); ν_{max} 1726, 1710 and 1612 cm.$^{-1}$ in Nujol, $[\alpha]_D^{18}$ +103.3 (c 1.20, chloroform). *Anal.* Calcd. for $C_{34}H_{48}O_3$: C, 80, 95, H, 9.52. Found: C, 81.02; H, 9.96.

16-Keto-cholesten-3β-ol-benzoate-14,15-oxide, m.p. 152–154° (clear 185°), yield 380 mg., no ultraviolet absorption above 230 mμ, ν_{max} 1742 and 1712 cm.$^{-1}$ in Nujol. *Anal.* Calcd. for $C_{34}H_{48}O_4$: C, 78.46; H, 9.23. Found: C, 78.75; H, 9.78.

Δ^{14}-Cholesten-16-one-15-ol-3β-ol-benzoate, m.p. 207–209°, yield 290 mg., λ_{max}^{alc} 228 and 231 mμ (E 15710 and 15780); ν_{max} 3465, 1725, 1692, and 1615 cm.$^{-1}$ in Nujol.

Anal. Calcd. for $C_{34}H_{48}O_4$: C, 78.46; H, 9.23. Found: C, 78.20; H, 9.49.

The alkali-soluble portion from the above oxidation was concentrated to a minimum amount under reduced pressure and allowed to stand overnight. The precipitated crystals were recrystallized from methanol-water (1:1) to give colorless prisms, m.p. 245–249°; ν_{max} 3300, 1692, 1659 and 1572 cm.$^{-1}$ in Nujol.

Anal. Calcd. for $C_{27}H_{45}O_4K$: C, 68.64; H, 9.53. Found: C, 68.12; H, 9.20.

This substance was dissolved in water and acidified with 10% hydrochloric acid. The resulting white solid was collected and crystallized from methyl alcohol (m.p. 160–180°); purification was difficult.

Anal. Calcd. for $C_{27}H_{46}O_4$: C, 74.65; H, 10.59. Found: C, 74.22; H, 10.60.

Benzoylation of this substance by the usual manner gave colorless needles of the ketocarboxylic acid IV, m.p. 159–163°.

Anal. Calcd. for $C_{34}H_{50}O_5$: C, 75.83; H, 9.92. Found: C, 75.44; H, 9.63.

Hydrogenation of 16-Keto-Δ^{14}-cholesten-3β-ol-benzoate (III).—A solution of 3 g. of III in 50 ml. of ethyl acetate was shaken with 150 mg. of platinum oxide and hydrogen; 1.3 moles of hydrogen was absorbed in 18 hours. After filtration, the filtrate was distilled under reduced pressure and the solid residue was purified by chromatography to yield the following products: **cholestanyl benzoate**, m.p. 138–141.5°, yield 70 mg., identified by a mixed melting point determination; **16-keto-cholestan-3β-ol-benzoate (V)**, m.p. 122–123°, yield 1.4 g., ν_{max} 1746 and 1712 cm.$^{-1}$ in Nujol.

Anal. Calcd. for $C_{34}H_{50}O_3$: C, 80.58; H, 9.95. Found: C, 80.26; H, 9.87.

Wolff-Kishner Reduction of V.—A mixture of 300 mg. of 16-keto-cholestan-3β-ol-benzoate (V), 700 mg. of potassium hydroxide, 0.7 ml. of 80% hydrazine hydrate and 25 ml. of triethylene glycol was refluxed for 0.5 hour; the temperature was raised to 190° in 1 hour, and kept there for 1.5 hours. The reaction mixture was poured into dilute hydrochloric acid and the separated oil was extracted with ether; the ether was washed with water and dried.

Distillation of the solvent *in vacuo* yielded a brownish oil which was chromatographed. Cholestanol was obtained, m.p. 142–143°, yield 70 mg., identified by a mixed melting point determination.

Oxime of 16-Keto-cholestan-3β-ol-benzoate (V).—A mixture of 1.5 g. of V, 700 mg. of hydroxylamine hydrochloride, 1.5 g. of potassium acetate and 150 ml. of alcohol was refluxed for 3 hours. The reaction mixture was poured into water and extracted with ether; the ether layer was washed with water and dried. The solvent was distilled *in vacuo* and the white solid residue was chromatographed.

α-Oxime (VIa), m.p. 242–244°, yield 480 mg., ν_{max} 3500, 1708 and 1668 cm.$^{-1}$ in Nujol. *Anal.* Calcd. for $C_{34}H_{51}O_3N$: C, 78.26; H, 9.85; N, 2.68. Found: C, 77.88; H, 9.92; N, 2.26.

β-Oxime (VIb), m.p. 189–191°, yield 65 mg., ν_{max} 3285, 1725 and 1670 cm.$^{-1}$ in Nujol. *Anal.* Calcd. for $C_{34}H_{51}O_3N$: C, 78.26; H, 9.85; N, 2.68. Found: C, 78.40; H, 10.13; N, 2.43.

Beckmann Rearrangement of Oximes VIa and VIb.—To a solution of 700 mg. of VIa in 20 ml. of pyridine was added 700 mg. of *p*-toluenesulfonyl chloride dissolved in 10 ml. of pyridine. The reaction mixture was kept at room temperature for 3 hours; then it was poured into water and neutralized with dilute hydrochloric acid. The separated solid was extracted with chloroform, and the solution was washed with water and dried. After distillation of the solvent the residue was crystallized from alcohol to give colorless plates of **17-aza-16-keto-D-homocholesten-3β-ol-benzoate (VII)**, m. p. 248–251°, yield 380 mg.; ν_{max} 3415, 1708, 1695 and 1670 cm.$^{-1}$ in Nujol.

Anal. Calcd. for $C_{34}H_{51}O_3N$: C, 78.26; H, 9.85; N, 2.68. Found: C, 78.44; H, 9.60; N, 2.57. Oxime VIb (300 mg.) was treated as described above and the residue from the rearrangement dissolved in ether. The ether-insoluble portion was crystallized three times from methanol to give **16-aza-17-keto-D-homocholestan-3β-ol-benzoate (VIII)**, m.p. 223–225°, yield 70 mg., ν_{max} 3230, 1712 and 1673 cm.$^{-1}$ in Nujol.

Anal. Calcd. for $C_{34}H_{51}O_3N$: C, 78.26; H, 9.85; N, 2.68. Found: C, 78.02; H, 9.38; N, 2.29.

The ethereal solution was evaporated under reduced pressure to give a yellow oil which crystallized. Recrystallization from acetone gave the oxime tosylate VIIIa, m.p. 152–153.5° dec., yield 120 mg., ν_{max} 1712 and 1602 cm.$^{-1}$ in Nujol.

Anal. Calcd. for $C_{44}H_{57}O_5NS$: C, 74.25; H, 8.01; N, 1.96. Found: C, 73.98; H, 7.76; N, 1.92.

Reduction of Lactams VII, VIII and XVIII by Lithium Aluminum Hydride.—A mixture of 300 mg. of VII, 300 mg. of lithium aluminum hydride and 40-ml. of dry ether was refluxed with exclusion of moisture for 5 hours. When the reaction mixture was poured into hydrous ether the excess lithium aluminum hydride decomposed. The ether solution was washed with water and dried. The ether was distilled under reduced pressure to give 130 mg. of pale yellow oil which crystallized from acetone–alcohol as colorless silky needles of 17-aza-D-homocholestanol (IX), m.p. 196–198.5°, $[\alpha]_D^{29}$ +20.8° (c 1.32, $CHCl_3$), ν_{max} 3480 and 3275 cm.$^{-1}$ in Nujol.

Anal. Calcd. for $C_{27}H_{49}O_3N$: C, 80.33; H, 12.24; N, 3.47; Found: C, 80.67; H, 12.60; N, 3.20.

The picrate was crystallized from benzene–alcohol as yellow needles, m.p. 221–223°.

Anal. Calcd. for $C_{33}H_{52}O_8N_4$: C, 62.63; H, 8.28; N, 8.85. Found: C, 62.33; H, 7.96; N, 8.92.

Similar treatment of lactam VIII and XVIII yielded X and XIX, respectively.

16-Aza-D-homocholestanol (X), m.p. 157–158°, $[\alpha]_D^{29}$ +26.5° (c 1.09 $CHCl_3$), ν_{max} 3410 and 3210 cm.$^{-1}$ in Nujol.

Anal. Calcd. for $C_{27}H_{49}O_3N$: C, 80.33; H, 12.24; N, 3.47. Found: C, 80.21; H, 12.50; N, 3.39.

(11) In regard to compounds XXIV and XXV, further work is necessary to establish the configurations of the hydrogens at C-17, 8 and 14.

(12) (a) All melting points are corrected; (b) Products, as indicated, were chromatographed on alumina (Brockmann Grade III) with petroleum ether–benzene (1:1).

The picrate was crystallized from benzene–alcohol, m.p. 188.5–190°.

Anal. Calcd. for $C_{33}H_{52}O_8N_4$: C, 62.63; H, 8.28; N, 8.85. Found: C, 62.70; H, 8.49; N, 8.39.

15-Aza-D-homocholestanol (XIX), m.p. 139–142, $[\alpha]_D^{29}$ +34.0° (*c* 1.21, $CHCl_3$), ν_{max} 3400 and 3208 cm.$^{-1}$ in Nujol.

Anal. Calcd. for $C_{27}H_{49}ON$: C, 80.33; H, 12.24; N, 3.47. Found: C, 80.55; H, 12.39; N, 3.60.

The picrate was obtained as yellow needles, m.p. 176–177°. *Anal.* Calcd. for $C_{33}H_{52}O_8N_4$: C, 62.63; H, 8.28; N, 8.85. Found: C, 62.26; H, 8.40; N, 8.92.

Oxime of 16-Keto-Δ^{14}-cholestenyl Benzoate (III).—To 1 g. of III dissolved in 100 ml. of alcohol, 450 mg. of hydroxylamine hydrochloride in 20 ml. of alcohol was added and the reaction mixture was kept at room temperature for 3 days. The solution was poured into water, and the precipitate was extracted with ether; the solution was washed with dilute hydrochloric acid, dilute alkali and water, and dried. The residue, obtained by evaporation of the solvent, was chromatographed to yield a colorless solid which crystallized from acetone–alcohol; recrystallization gave colorless needles of XI, m.p. 249–251°, yield 420 mg.; ν_{max} 3420, 1703, 1669 and 1635 cm.$^{-1}$ in Nujol.

Anal. Calcd. for $C_{34}H_{49}O_3N$: C, 80.12; H, 7.71; N, 2.75. Found: C, 79.86; H, 7.50; N, 2.69.

17-Aza-16-keto-Δ^{14}-D-homocholesten-3β-ol-benzoate (XII) was prepared from oxime XI (350 mg.) as previously described[13]; lactam XII, m.p. 272–273°, yield 55 mg.; ν_{max} 3380, 1710 and 1632 cm.$^{-1}$ in Nujol.

Anal. Calcd. for $C_{34}H_{49}O_3N$: C, 80.12; H, 7.71; N, 2.75. Found: C, 79.90; H, 7.88; N, 2.59.

Preparation of VII from Lactam XII.—A solution of 130 mg. of XII in 20 ml. of ethyl acetate–alcohol (1:1) was hydrogenated and treated as described. The plates obtained by four recrystallizations from alcohol were identified as VII (yield 65 mg.) from the infrared spectrum and melting point.

Oxidation of 16-Keto-cholestan-3β-ol-benzoate (V).—To a solution of 1.5 g. of V in 100 ml. of glacial acetic acid and 30 ml. of benzene, stirred at 40–45°, was added a solution of 0.9 g. of CrO_3 in 30 ml. of 90% glacial acetic acid. Stirring was continued for 2 hours and after that the reaction mixture was kept at room temperature for 4 more hours. Then the reaction mixture was treated essentially as described for the oxidation of III. The alkali solution was acidified with dilute hydrochloric acid, and the resulting white solid was collected and recrystallized from methanol to give colorless plates of XIII, m.p. 146–152°, yield 240 mg.

Anal. Calcd. for $C_{34}H_{50}O_5$: C, 75.83; H, 9.29. Found: C, 75.39; H, 9.73.

As it was difficult to purify this acid and its methyl ester because of the poor yield, the impure acid XIII was submitted directly to the following lactamization.

Lactam of Ketocarboxylic Acid XIII.—Through an ice-cooled solution of 230 mg. of ketocarboxylic acid XIII in 20 ml. of alcohol, ammonia gas was passed for 1 hour; then the solution was sealed in a tube and heated for 10 hours at 100°. Distillation under reduced pressure yielded an oil which was chromatographed. Lactam XIV was obtained, m.p. 189–191°, yield 38 mg.; ν_{max} 3320, 1718, 1670 and 1646 cm.$^{-1}$ in Nujol.

Anal. Calcd. for $C_{34}H_{49}O_3N$: C, 78.57; H, 9.50; N, 2.70. Found: C, 78.90; H, 9.92; N, 2.81.

Hydrogenation of Lactam XIV to Yield VII.—VII (17 mg.) was obtained by the hydrogenation of 30 mg. of XIV in 10 ml. of alcohol and the subsequent recrystallization of the product from alcohol; m.p. 248–251°.

Enolization of Ketocarboxylic Acid IV.—IV (200 mg.) was refluxed with 20 ml. of acetic acid anhydride for 4 hours in the presence of a small amount of sodium acetate. After standing at room temperature overnight, the reaction mixture was poured into ice-water. The solution was made alkaline with sodium bicarbonate and extracted with ether. The ethereal solution was washed with water, dried (Na_2SO_4) and distilled under diminished pressure. The resulting yellow oil, which soon solidified, as crystallized from methyl alcohol giving colorless needles of the enol lactone XV, m.p. 146–148°, yield 140 mg., ν_{max} 1745, 1724 and 1680 cm.$^{-1}$ in Nujol.

Anal. Calcd. for $C_{34}H_{48}O_4$: C, 78.46; H, 9.23. Found: C, 78.05; H, 9.13.

Synthesis of Lactam XVI from IV.—Ammonia gas was passed for 1 hour through an ice-cooled solution of 3 g. of ketocarboxylic acid IV in 60 ml. of alcohol. Then the solution was sealed in a tube and heated at 100° for 10 hours. Distillation *in vacuo* followed by chromatography yielded colorless plates of XVI which were recrystallized from methanol: m.p. 215–218°; yield 620 mg., ν_{max} 3380, 1709, 1670 and 1635 cm.$^{-1}$ in Nujol.

Anal. Calcd. for $C_{34}H_{49}O_3N$: C, 78.57; N, 2.70. Found: C, 78.35; H, 9.86; N, 2.63.

Isomerization of XVI.—Dry hydrogen chloride was passed for 3 hours through an ice-cold solution of 500 mg. of XVI in 15 ml. of dry chloroform. The solvent was evaporated to dryness under reduced pressure, and the residue dissolved in acetone. Crystals of **15-aza-16-keto-Δ^{14}-D-homocholesten-3β-ol-benzoate (XVII)** separated, m.p. 218–221°. The melting point was depressed on mixture with a starting material; yield 23 mg.; ν_{max} 1712, 1672 and 1669 cm.$^{-1}$ in Nujol.

Anal. Calcd. for $C_{34}H_{49}O_3N$: C, 78.57; H, 9.50; N, 2.70. Found: C, 78.44; H, 9.21; N, 2.72.

Hydrogenation of XVII.—XVII (150 mg.) in 40 ml. of ethyl acetate–alcohol (1:1) was hydrogenated and the product worked up as previously described. **15-Aza-16-keto-D-homocholestan-3β-ol-benzoate (XVIII)** was obtained, m.p. 258–262°, yield 90 mg.; ν_{max} 3220, 1712 and 1670 cm.$^{-1}$ in Nujol.

Anal. Calcd. for $C_{34}H_{51}O_3N$: C, 78.26; H, 9.85; N, 2.68. Found: C, 78.55; H, 10.12; N, 2.70.

Oxime of XXa.—To 800 mg. of 15-keto-$\Delta^{8(14)}$-cholesten-3β-ol-acetate (XXa) in 40 ml. of alcohol was added 200 mg. of hydroxylamine hydrochloride and the mixture was allowed to stand for 3 days. The alcohol was distilled under diminished pressure and the dried residue was chromatographed. Early fractions afforded a colorless solid which crystallized from acetone–alcohol as needles of XXI, m.p. 244–246°, yield 320 mg.; ν_{max} 3400, 1722, 1658 and 1623 cm.$^{-1}$ in Nujol.

Anal. Calcd. for $C_{29}H_{47}O_3N$: C, 76.10; H, 10.35; N, 3.06. Found: C, 75.90; H, 10.62; N, 3.32.

Beckmann Rearrangement of Oxime XXI.—The rearrangement, carried out as previously described,[13] yielded 15-aza-16-keto-$\Delta^{8(14)}$-D-homocholesten-3β-ol-acetate (XXII), m.p. 255–258°, yield 35 mg. (from 250 mg. of XXI).

Anal. Calcd. for $C_{29}H_{47}O_3N$: C, 76.10; H, 10.35; N, 3.06. Found: C, 76.29; H, 10.67; N, 3.28.

Preparation and Identification of Lactam XXIII.—To a solution of 80 mg. of XXII in 10 ml. of alcohol was added a dilute alcoholic potassium carbonate solution; the mixture was allowed to stand for 10 hours distilled *in vacuo* and the residue extracted with chloroform. The extract was washed with water and dried. After the removal of the solvent under reduced pressure the residue was crystallized from methyl alcohol as colorless plates of 15-aza-16-keto-$\Delta^{8(14)}$-D-homocholesten-3β-ol (XXIII), m.p. 296–302°, yield 25 mg.; ν_{max} 3270, 1669 and 1630 cm.$^{-1}$ in Nujol.

Anal. Calcd. for $C_{27}H_{45}O_2N$: C, 78.02; H, 10.91; N, 3.37; Found: C, 77.76; H, 10.62; N, 3.41.

The infrared spectrum and melting point showed this sample to be identical with the substance obtained by saponification of XVI.

Hydrogenation of 15-Keto-$\Delta^{8(14)}$-cholesten-3β-ol-benzoate (XXb).—A solution of 1 g. of XXb in 60 ml. of ethyl acetate containing 2 ml. of 10% hydrochloric acid was hydrogenated with platinum oxide and the product chromatographed. An early fraction afforded a colorless oil which crystallized from benzene–acetone; three recrystallizations gave colorless prisms of XXV, m.p. 142–143.5° (not clear even above 230°), yield 130 mg.

Anal. Calcd. for $C_{34}H_{52}O_2$: C, 82.44; H, 10.90. Found: C, 82.69; H, 11.22.

This substance, which was not identical with cholestanyl benzoate, may be assumed to be an isomer of cholestanyl benzoate. The 3-ol was obtained by saponification with 5%

(13) The reaction mixture was heated for 1 hour at 50° and then allowed to stand for 3 hours at room temperature.

potassium hydroxide and crystallization from acetone-alcohol; m.p. 144–146° (not clear above 230°); $[\alpha]_D^{18}$ +35.0° (*c* 0.9 $CHCl_3$), ν_{max} 3380 cm.$^{-1}$ in Nujol. This is a C_8-, C_{14}- or C_{17}-isomer of cholestanol.

Anal. Calcd. for $C_{27}H_{48}O$: C, 83.50; H, 12.37. Found: C, 83.49; G, 12.20.

A later fraction afforded a colorless oil which solidified; crystallization from acetone–alcohol gave silky needles of 15-ketocholestanyl benzoate (XXIV); m.p. 151–152°, yield 190 mg., no ultraviolet spectrum above 230 mμ, ν_{max} 1749 and 1709 cm.$^{-1}$ in Nujol.

Anal. Calcd. for $C_{34}H_{50}O_3$: C, 80.58; H, 9.95. Found: C, 80.12; H, 9.63.

Oxime of XXIV (XXVI).—To a solution of 150 mg. of XXIV in 10 ml. of alcohol–pyridine (1:1) was added 70 mg. of hydroxylamine hydrochloride in 5 ml. of alcohol. The reaction mixture was refluxed for 3 hours and the solution poured into hydrochloric acid. Then the solution was treated as previously described. The residue, obtained by removal of the solvent, was crystallized twice from methanol to yield XXVI, m.p. 236–240°, yield 100 mg., ν_{max} 3360, 1712 and 1669 cm.$^{-1}$ in Nujol.

Anal. Calcd. for $C_{34}H_{51}O_3N$: C, 78.26; H, 9.85; N, 2.68. Found: C, 78.52; H, 10.12; N, 2.79.

Beckmann Rearrangement of XXVI.—The rearrangement was carried out as previously described except that the product was extracted with ether. The oxime tosylate XXVII was obtained, m.p. 172–175°, yield 40 mg. (from 80 mg. of XXVI).

Anal. Calcd. for $C_{41}H_{57}O_5NS$: C, 74.25; H, 8.01; N, 1.96. Found: C, 74.55; H, 8.39; N, 2.06.

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[CONTRIBUTION FROM THE ORGANIC CHEMICALS DIVISION, ST. LOUIS RESEARCH DEPARTMENT, MONSANTO CHEMICAL CO.]

Studies in Steroid Total Synthesis. IV. A Stereoselective Ring A Synthesis[1]

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In the Woodward steroid total synthesis, the formation of the quaternary center at C-10 from the blocked tricyclic ketone I invariably gives unfavorable stereochemistry (I → II + III). By methylating a keto acid such as XIIIb and thus reversing the order in which the groups forming the quaternary center are attached, a favorable stereochemical result has been obtained. Moreover, it has been found that contraction of ring D prior to the formation of the quaternary center enhances reactivity at the methinyl position so that a blocking group is no longer necessary in the ring A synthesis.

The unfavorable stereochemistry observed in the conversion of the blocked tricyclic system I to the keto acid II marks the weakest point in the Woodward[2] steroid total synthesis approach. Our work[3] and that of others[2,4] has shown that variation of ring D substituents does not improve the existing 2:1 ratio of unnatural to natural isomers.

Since the final group forming the quaternary center preferentially assumes the axial position, introduction of the methyl group last could be expected to give predominantly the natural isomer. The successful achievement of this result forms the subject of this paper.

Our initial approach involved preparation of the tricyclic keto acid VIb by condensation of our basic bicyclic system (−)-*trans*-1,2,4a,5,8,8a-hexahydro-4a-methyl-2-oxo-1-naphthaldehyde (IV) with methyl 5-oxo-6-heptenoate[5] in the presence of benzyltrimethylammonium butoxide.[6]

This adduct V was then cyclized with aqueous base[2,3] to give VIb. The ring C double bond of the keto acid VIb was reduced to give VII and the 3-position was blocked with the methylanilinomethylene group[2,3] to give a non-crystalline derivative which could be methylated in low yield to give some of the desired keto acid II. The stereochemical result was obscured by the low yields of methylated products and by the multiplicity of acidic materials, both methylated and unmethylated, present in the acid fraction. Because of these unpromising results, methylation of a blocked keto acid was abandoned, and it was not until some observations were made in another tricyclic system in which ring D had been contracted to a five-membered ring that a successful stereoselective methylation was accomplished.

At approximately this time, work was begun to ascertain the effect of contracting ring D before construction of ring A. The *dl*-tricyclic ketone VIa[2] was hydroxylated in ring D with silver acetate and iodine in wet acetic acid.[3,7] Reduction of the double bond in ring C to give XIa followed by cleavage of the glycol with lead tetraacetate and ring closure of the dialdehyde by standard methods[2,3] gave the tricyclic system XIIa. The aldehyde group was protected by first reducing the double bond in ring D and then preparing the ethylene glycol acetal XIIIa.[8] Attempts to put the methylanilinomethylene blocking group on XIIIa by con-

(1) The material in this paper was first announced at the Gordon Research Conference A.A.A.S., New Hampton, N. H., August 2–6, 1954.

(2) *Cf.* R. B. Woodward, F. Sondheimer, D. Taub, K. Heusler and W. M. McLamore, THIS JOURNAL, **74**, 4223 (1952).

(3) *Cf.* L. B. Barkley, M. W. Farrar, W. S. Knowles, H. Raffelson and Q. E. Thompson, *ibid.*, **76**, 5014 (1954).

(4) P. Wieland, H. Ueberwasser, G. Anner and K. Miescher, *Helv. Chim. Acta*, **36**, 1231 (1953).

(5) (a) P. Wieland, H. Ueberwasser, G. Anner and K. Miescher [*Helv. Chim. Acta*, **36**, 376 (1953)] have prepared ethyl 7-chloro-5-oxoheptanoate and have used the crude β-chloroketone for a condensation similar to that described here. For our purposes the use of the pure vinyl ketone proved more satisfactory. (b) N. Nazarov and S. I. Savyalov [*J. Gen. Chem.* (*USSR*), **23**, 1703 (1953)] made methyl 5-oxo-6-heptenoate (n^{25}D 1.4490, b.p. 102–105° at 15 mm.) by a different route.

(6) This reagent was shown by Dr. M. W. Farrar in this Laboratory to give about 5% better yields than potassium *t*-butoxide in a similar condensation using ethyl vinyl ketone. It is prepared from 35% benzyltrimethylammonium hydroxide in methanol (obtained from Chemical Development Corp., Danvers, Mass.) by adding *n*-butyl alcohol and distilling out the methanol and water.

(7) *Cf.* D. Ginsburg, THIS JOURNAL, **75**, 5746 (1953).

(8) A number of these tricyclic intermediates with a five-membered ring D were first prepared by R. B. Woodward and A. J. Bose in connection with their study on ring contraction methods; *cf.* footnote 45 in ref. 2. Compound XIIIa was also made from *dl anti-trans*-3a,7,8,9,-9a,9b - hexahydro - 3a,6 - dimethyl - 7 - oxo - (1H)benz[e]indene - 3-carboxaldehyde[2] (m.p. 131–133°), but the one-step reduction of the double bonds in ring C and D proceeded only in low yields since base could not be used because of the sensitive aldehyde group.