Steroids. III.[1] New Synthesis of Ring-D Seco Steroids

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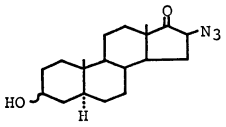
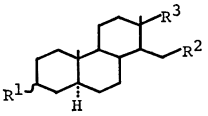
Synopsis. 16β-Azido-5α-androstan-17-one derivatives were cleaved with bromine in acetic acid at room temperature, to furnish 16-cyano and 16-carbamoyl-16,17-seco-5α-androstan-17-oic acids. 17-Aza-D-homo-5α-androstan-16,17a-dione derivatives were also synthesized.

Recently, we described a novel single step C–C bond cleavage of various α-azido steroidal ketones.[1,2] Our preliminary studies concerning the cleavage of a cyclopentane ring having an α-azido ketone group and the fact that certain ring D seco derivatives show hypocholesterolemic activity[3] prompted us to investigate the cleavage reaction in ring D of a steroid.

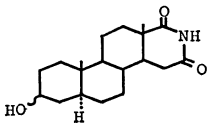
Treatment of α-azido steroidal ketones **1a** and **1b** with bromine (1 equiv.) in acetic acid for 10 h gave seco-carboxylic acids **2a** and **2b**, respectively. The IR spectra of **2a** and **2b** confirmed the presence of the cyano and carboxyl groups. The ^{1}H NMR spectra displayed a three-proton singlet at δ 2.00 (**2a**), 1.95 (**2b**) assigned to the 3-CH_3CO, and a broad one-proton peak at δ 10.19 (**2a**), 9.23 (**2b**) assigned to the carboxylic proton. 18-Angular methyl group appeared as a singlet at lower field, δ 1.25, suggesting that ring D was no longer intact but had undergone a cleavage with formation of a carboxyl group.



1a: 3α-OH
1b: 3β-OH



	R^1	R^2	R^3
2a:	α-OAc	CN	COOH
2b:	β-OAc	CN	COOH
3a:	α-OAc	$CONH_2$	COOH
3b:	β-OAc	$CONH_2$	COOH
4a:	α-OAc	$CONH_2$	$COOCH_3$
4b:	β-OAc	$CONH_2$	$COOCH_3$



5a: 3α-OH
5b: 3β-OH

When **1a** and **1b** were allowed to react under the above conditions for a long period of time, the seco-amides **3a**[1] and **3b** were formed by hydrolysis. The IR spectra showed absorption bands at 2600—2700 cm^{-1} and 1706 cm^{-1} indicative of a carboxyl group. The ^{1}H NMR spectra of **3b** showed two peaks for the amide protons at δ 6.54 and δ 6.98, which disappeared on addition of deuterium oxide.

The cleavage reaction was also useful for introduction of a nitrogen atom into the steroid D ring. Treatment of the seco-amides **3a** and **3b** with diazomethane in ether gave the methyl esters **4a** and **4b**. The ^{1}H NMR spectra showed a characteristic three-proton singlet for the methyl ester at δ 3.66, and the broad peaks centered at δ 6.63 and 7.18 (**4a**), and 6.30 (**4b**), assigned to the amide protons.

The esters were cyclized with sodium methoxide in methanol to give the imides **5a** and **5b**. The imides were characterized by their IR spectra which showed the signals for the carbonyl groups at 1690, 1726 (**5a**) and at 1690, 1721 cm^{-1} (**5b**).

Experimental

General. All the melting points are uncorrected. The IR spectra were measured with a Hitachi model 215 infrared spectrophotometer. The ^{1}H NMR spectra were obtained in a CCl_4 solution, with TMS as the internal standard, using a Hitachi-Perkin Elmer R-20A. The MS spectra were measured by means of a Hitachi M-80 instrument with direct inlet at 70 eV.

*16β-Azido-3β-hydroxy-5α-androstan-17-one (**1b**).* This compound was synthesized from 3β-hydroxy-16α-bromo-5α-androstan-17-one[4] by Ponsold's method[5] as prisms, mp 113—116 °C; Found: C, 68.85; H, 8.6; N, 12.8%. Calcd for $C_{19}H_{29}N_3O_2$: C, 68.85; H, 8.82; N, 12.68%; IR (KBr): 3300, 2100 (N_3), and 1749 cm^{-1}; ^{1}H NMR (CCl_4) δ=3.67 (2H, m, 3α-H and 16-H).

*3α-Acetoxy-16-cyano-16,17-seco-5α-androstan-17-oic Acid (**2a**) and 3β-Acetoxy-16-cyano-16,17-seco-5α-androstan-17-oic Acid (**2b**).* To a solution of **1a**[1] (200 mg) in acetic acid (10 ml) was added bromine (97 mg) in acetic acid (5 ml) with stirring for 10 h at room temperature. After the usual work-up, the resulting oil was chromatographed on a silica-gel column. Elution with 20% ether in benzene afforded an oil (**2a**) (152 mg, 70%), which resisted crystallization from various solvents. IR (NaCl): 3150, 2700—2600 (bonded COOH), 2250 (CN), 1730, and 1698 cm^{-1}; ^{1}H NMR (CCl_4) δ=1.25 (3H, s, 18-CH_3), 2.00 (3H, s, MeCO), 2.27 (2H, m, 15-CH_2), 4.92 (1H, m, 3β-H), and 10.19 (1H, br, COOH).

A similar cleavage reaction of **1b** (200 mg) gave **2b** (144 mg, 66%) as a colorless oil. IR (NaCl): 3100, 2700—2600 (bonded COOH), 2250 (CN), 1730, and 1697 cm^{-1}; ^{1}H NMR (CCl_4) δ=1.25 (3H, s, 18-CH_3), 1.95 (3H, s, MeCO), 2.25 (2H, m, 15-CH_2), 4.56 (1H, m, 3α-H), and 9.23 (1H, br, COOH).

*3β-Acetoxy-16-carbamoyl-16,17-seco-5α-androstan-17-oic Acid (**3b**).* To a solution of the α-azido ketone (**1b**) (2 g) in acetic acid (100 ml) saturated with hydrogen chloride gas was added bromine (1 g) in acetic acid (50 ml), and the reaction mixture was stirred for one week at room temperature. After work-up, crystallization of the resulting oil from hexane–ether gave compound **3b** (1.261 g, 55%), mp 185—192 °C; Found: *m/e* 379.2372. Calcd for $C_{21}H_{33}NO_5$: M, 379.2359; IR (KBr): 3450, 3350, 3200, 2700—2600 (bonded COOH), 1728, 1706, 1694, 1655 (sh), 1592, and 1241 cm^{-1}; ^{1}H NMR (DMSO) δ=1.97 (3H, s, MeCO), 4.53 (1H, br, 3α-H), 6.54 (1H, br, NH), and 6.98 (1H, br, NH); MS (70 eV), *m/e* (rel intensity), 379 (100%, M^+), 301 (66), 216 (75), and 201 (93).

Methyl 3α-Acetoxy-16-carbamoyl-16,17-seco-5α-androstan-17-oate

(4a) and Methyl 3β-Acetoxy-16-carbamoyl-16,17-seco-5α-androstan-17-oate (4b). An excess of diazomethane in ether was added dropwise to a stirred solution of the amido-acid (**3a**) (500 mg) in ether (50 ml) at room temperature until the yellow color persisted. Evaporation and crystallization of the residue from carbon tetrachloride gave compound **4a** (320 mg, 62%), mp 149—151 °C; Found: *m/e* 393.2521. Calcd for $C_{22}H_{35}NO_5$: M, 393.2515; IR (KBr): 3425, 3350, 3200, 1724, 1713, 1660, 1608, and 1247 cm^{-1}; ^1H NMR (CCl_4) δ=1.98 (3H, s, MeCO), 3.66 (3H, s, MeO), 4.93 (1H, br, 3β-H), 6.63 (1H, br, NH), and 7.18 (1H, br, NH); MS (70 eV), *m/e* (rel intensity), 393 (100%, M^+), 376 (10), 361 (20), 348 (16), 333 (25), and 274 (40).

The compound **4b** was obtained in a similar way. After the usual work-up, the resulting oil was chromatographed on silica-gel column. Elution with 40% benzene in ethyl acetate afforded compound **4b** (40%), mp 75—82 °C; Found: *m/e* 393.2572. Calcd for $C_{22}H_{35}NO_5$: M, 393.2515; IR (KBr): 3430, 3350, 3200, 1723, 1608, and 1239 cm^{-1}; ^1H NMR (CCl_4) δ=1.93 (3H, s, MeCO), 3.66 (3H, s, MeO), and 6.30 (2H, br, NH_2); MS (70 eV), *m/e* (rel intensity), 393 (100%, M^+), 376 (9), 361 (15), 348 (22), 333 (17), and 274 (25).

3α-Hydroxy-17-aza-D-homo-5α-androstan-16,17a-dione (5a) and 3β-Hydroxy-17-aza-D-homo-5α-androstan-16,17a-dione (5b). The synthesis was carried out following the procedure of Meakins.[6] The amic-ester (**4a**) (500 mg) was dissolved in a solution of sodium (35 mg) in methanol (7 ml), and the solution was refluxed for 10 min. After the usual work-up, crystallization of the resulting oil from ether–methanol gave **5a** (170 mg, 42%), mp 223—226 °C; Found: *m/e* 319.2149. Calcd for $C_{19}H_{29}NO_3$: M, 319.2147; IR (KBr): 3420, 3260, 3100, 1726, 1690, 1675, and 1275 cm^{-1}; ^1H NMR ($CDCl_3$) δ=4.03 (1H, br, 3β-H) and 8.16 (1H, br, NH); MS (70 eV), *m/e* (rel intensity), 319 (27%, M^+), 304 (51), 301 (100), 286 (100), and (12).

Compound **5b** was obtained in a similar way. The reaction mixture was refluxed for 20 min. After the usual work-up, crystallization of the resulting oil from ethyl acetate gave **5b** (46%), mp 216—219 °C; Found: *m/e* 319.2152. Calcd for $C_{19}H_{29}NO_3$: M, 319.2147; IR (KBr): 3370, 3200, 3070, 1721 (sh), 1705 (sh), 1690, and 1270 cm^{-1}; ^1H NMR ($CDCl_3$) δ=3.60 (1H, br, 3α-H), and 8.50 (1H, br, NH); MS (70 eV), *m/e* (rel intensity), 319 (54%, M^+), 304 (35), 301 (100), 286 (52), and 261 (24).

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