Steroids. Part 2.[1] C–C Bond Cleavage of α-Azido-steroidal Ketones

By **Thomas T. Takahashi**,* Department of Chemistry, The Jikei University School of Medicine, Kokuryo, Chofu, Tokyo, 182, Japan
James Y. Satoh, Department of Chemistry, Rikkyo University, Nishi-Ikebukuro, Tokyo, 171, Japan

α-Azido-steroidal ketones were cleaved with bromine in acetic acid at room temperature, to furnish cyano-carboxylic acids. The structures, reactions, and spectral characteristics of these products are discussed.

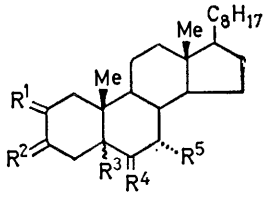
OUR interest in new synthetic approaches to biologically active steroidal alkaloids led us to investigate C–C bond-cleavage of α-azido-steroidal ketones. Recently we described a novel single-step C–C bond-cleavage of various α-azido steroidal ketones.[2] In the present paper, we report in full the details of this cleavage reaction.

RESULTS AND DISCUSSION

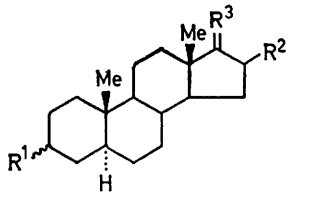
Treatment of α-azido-steroidal ketones (1)—(3) with bromine (1 equiv.) in acetic acid led to evolution of N_2 and HBr, and isolation of cyano-carboxylic acid derivatives to which the structures (7)—(9) are assigned. However, when (4) was subjected to the same reaction conditions, the corresponding amido-carboxylic acid (10) was obtained. This amide was formed by acetylation of the 3α-hydroxy-group and then hydrolysis of the cyano-group.

This cleavage reaction was also applicable to the straight-chain α-azido-ketone (5), which gave 3β-acetoxy-5α-androstane-17β-carboxylic acid (11) [with C(20)–C(21) bond cleavage] in good yield.

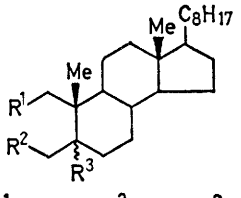
In the case of (6) the reaction gave the cyano-carboxylic acid (12) and an unidentified product of m.p. 126—129 °C in a *ca.* 1 : 1 ratio. However, the reaction of the other azido-ketones (1)—(5) gave C–C bond-cleavage products only in high yield.



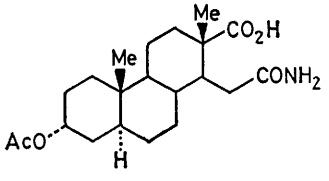
	R^1	R^2	R^3	R^4	R^5
(1)	α-N_3, β-H	O	α-H	H_2	H
(2)	O	α-H, β-N_3	α-H	H_2	H
(3)	α-H, β-N_3	O	β-H	H_2	H
(6)	H_2	α-H, β-OAc	α-H	O	N_3



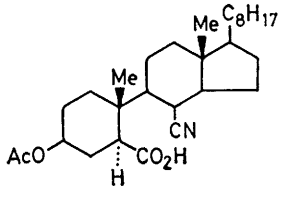
	R^1	R^2	R^3
(4)	α-OH	N_3	O
(5)	β-OAc	H	α-H, β-$COCH_2N_3$
(11)	β-OAc	H	α-H, β-CO_2H



	R^1	R^2	R^3
(7)	CN	CO_2H	α-H
(8)	CO_2H	CN	α-H
(9)	CN	CO_2H	β-H
(13)	CN	CO_2Me	α-H
(14)	$CONH_2$	CO_2H	α-H
(15)	CN	CO_2Et	α-H
(16)	$CONH_2$	CO_2Me	α-H



(10)



(12)

The n.m.r. spectra of compounds (7)—(9) displayed a four-proton multiplet at δ 2.25—2.50 assigned to the 1- and 4-methylene groups, and a broad one-proton peak at δ 8.84—10.00 assigned to the carboxylic acid proton,

which disappeared on addition of deuterium oxide without any change in the rest of the spectrum. The i.r. spectra confirmed the presence of the nitrile groups ($\nu_{max.}$ 2 240 cm^{-1}) and carboxylic acid groups ($\nu_{max.}$ 3 450—3 100 cm^{-1}). The mass spectrum of (7) had peaks at *m/e* 415 (M^+) and 375 (base peak, fission of the C-1,10 bond), 356 (fission of the C-4,5 bond), and 275 (loss of $C_4H_7CO_2H$) from the base peak; ring B fission at the C-5,10 and C-7,8 bonds). The loss of CH_2CN by fission at the C-1,10 bond is confirmed by the presence of the metastable ion at *m** 339 ($375^2/415 = 339$). The presence of the carboxylic acid group at C-3 was indicated by the mass spectrum, which showed a peak at *m/e* 275, corresponding to the loss of $HO_2C{-}C(4)H_2{-}C(5)H{-}C(6)H_2{-}C(7)H_2$ from the base peak at *m/e* 375.

Esterification of (7) with HCl–MeOH gave the methyl ester (13) in quantitative yield. The n.m.r. spectrum showed a characteristic singlet for the methyl group at δ 3.62 and a four-proton multiplet centred at δ 2.30, assigned to the 1- and 4-methylene groups. Structure (13) was further substantiated by the mass spectrum, which had peaks at *m/e* 429 (M^+) (base peak), 414 (M^+ — Me), 389 (fission of the C-1,10 bond), and 275 (loss of $C_4H_7CO_2Me$ from the peak at *m/e* 389; ring B fission at the C-5,10 and C-7,8 bonds).

Treatment of (7) with 48% hydrobromic acid in acetic acid gave the seco-amide (14). The n.m.r. spectrum showed two broad peaks for the amide protons at δ 7.08 and 7.63, and the mass spectrum had peaks at *m/e* 389 ($M^+ - CONH_2$) and 374 (base peak, $M^+ - 59$, β-cleavage of amide with transfer of a γ-hydrogen). However, the molecular-ion peak was not detectable.

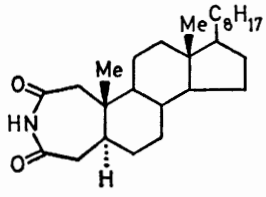
3β-Azido-5α-cholestan-2-one (2) was cleaved with bromine in acetic acid to furnish the cyano-carboxylic acid (8) which was isomeric with compound (7). The presence of nitrile and carboxylic acid groups in the seco-acid (8) was indicated by its i.r. spectrum. The mass spectrum displayed peaks at *m/e* 415 (M^+), 355 (base peak, fission of the C-1,10 bond), and 315 (loss of CH_2CN from the peak at *m/e* 355). The sequence $M^+ \rightarrow m/e$ 355 $\rightarrow m/e$ 315, was confirmed by the presence of metastable ions at *m** 304 ($355^2/415 = 304$) and 280 ($315^2/355 = 280$). The most intense peak (at *m/e* 355) was associated with α-cleavage of the most highly substituted bond. The principal mass peaks suggested that the carboxylic acid group was attached to C-1.

The reaction of 3β-acetoxy-7α-azido-5α-cholestan-6-one (6) with bromine gave (12) in 29% yield. The n.m.r. spectrum showed a double doublet at δ 2.80 which was assigned to 5-H and a broad peak at δ 10.10 due to the carboxylic acid proton, which disappeared on addition of deuterium oxide. The i.r. spectrum confirmed the presence of the nitrile group ($\nu_{max.}$ 2 240 cm^{-1}) and the carboxylic acid group ($\nu_{max.}$ 3 450 cm^{-1}). The mass spectrum displayed peaks at *m/e* 274 and 199 due to fragments arising from fission of the C-9,10 bond. These spectral data clearly support the structure (12).

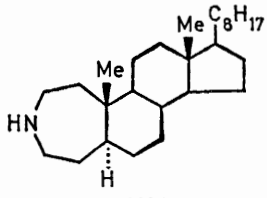
This method was also found to be applicable to an α-azido-five-membered ring-ketone and to a straight-chain α-azido-ketone. Thus 16β-azido-3α-hydroxy-5α-androstan-17-one (4), when allowed to react under the same conditions, gave the seco-amido-acid (10). The n.m.r. spectrum showed signals for the two amide protons at δ 6.94 and 6.54, and the mass spectrum showed a peak at *m/e* 379 (M^+). In the case of the 3β-acetoxy-21-azido-5α-pregnan-20-one (5), we found that it underwent the expected C-20,21 bond-cleavage with formation of 3β-acetoxy-5α-androstane-17β-carboxylic acid (11), identified by comparing its m.p. and i.r. spectrum with those of an authentic sample.

It was also found that this method was applicable to a one-step synthesis of a seco-ester nitrile. Thus the reaction of 2α-azido-5α-cholestan-3-one (1) with bromine (1 equiv.) and an excess of alcohol in ether gave the ester-nitriles (13) and (15).

In still another application, the method was also useful for introduction of a nitrogen atom into the steroid nucleus. Treatment of the seco-acid amide (14) with diazomethane in ether gave the methyl ester (16). The ester was cyclized with sodium methoxide in methanol to give the imide (17). The imide was charac-



(17)



(18)

terized by its n.m.r. spectrum, which showed characteristic signals for the methylene protons at δ 2.28—2.93, and the imide proton at δ 7.86. This spectrum agreed very closely with that obtained by Meakins for 3-aza-A-homo-5α-androstane-2,4-dione.[3] When the imide was reacted with lithium aluminium hydride, it gave the cyclic amine (18) which was identical to that prepared by Shoppee by a different route.[4]

EXPERIMENTAL

2α-Azido-5α-cholestan-3-one (1) and 3β-acetoxy-7α-azido-5α-cholestan-6-one (6) were synthesized according to the procedure of Zbiral.[5] 3β-Azido-5α-cholestan-2-one (2) was synthesized from 3β-bromo-5α-cholestan-2-one [6] by Zbiral's method [5] as needles, m.p. 97—100 °C, from methanol–ether (lit.,[7] m.p. 102—105 °C).

16β-*Azido*-3α-*hydroxy*-5α-*androstan*-17-*one* (4).—This was synthesized from 3α-hydroxy-16α-bromo-5α-androstan-17-one by Ponsold's method [8] as *needles*, m.p. 150—155 °C (from methanol) (Found: C, 68.8; H, 8.75; N, 12.6. $C_{19}H_{29}N_3O_2$ requires C, 68.85; H, 8.82; N, 12.68%); $\nu_{max.}$ (KBr) 3 550, 3 320, 2 100 ($-N_3$), and 1 730 cm^{-1}; δ (CCl_4) 3.95 (br s, 1 H, CHN_3).

3β-*Acetoxy*-21-*azido*-5α-*pregnan*-20-*one* (5).—This was synthesized from 3β-acetoxy-21-bromo-5α-pregnan-20-one by Zbiral's method [6] as *needles*, m.p. 132—135 °C (from ethanol) (Found: C, 69.0; H, 8.85; N, 10.55. $C_{23}H_{35}N_3O_3$ requires C, 68.80; H, 8.79; N, 10.46%); $\nu_{max.}$ (KBr) 2 095 ($-N_3$), 1 726, 1 715, and 1 245 cm^{-1}; δ (CCl_4) 3.90 (br m, 2 H, CH_2N_3).

2β-*Azido*-5β-*cholestan*-3-*one* (3).—This was synthesized from 2β-bromo-5β-cholestan-3-one by Zbiral's method as *needles*, m.p. 92—94 °C (from ethanol) (Found: C, 76.0; H, 10.7. $C_{27}H_{45}N_3O$ requires C, 75.83; H, 10.61%); $\nu_{max.}$ (KBr) 2 075 (−N_3) and 1 724 cm^{-1}; δ (CCl_4) 3.82 (q, *J* 5.6 and 13.6 Hz, 1 H, CHN_3).

2-*Nitrilo*-2,3-*seco*-5α-*cholestan*-3-*oic Acid* (7).—To a solution of 2α-azido-5α-cholestan-3-one (1) (400 mg) in acetic acid (20 ml) was added bromine (150 mg) in acetic acid (10 ml) with stirring for 40 min at room temperature. After work-up, crystallization of the resulting oil from hexane–ether (9 : 1) gave *compound* (7) (310 mg, 70%), m.p. 171—174 °C (Found: C, 77.8; H, 10.75; N, 3.5. $C_{27}H_{45}NO_2$ requires C, 78.02; H, 10.91; N, 3.37%); $\nu_{max.}$ (KBr) 3 350, 3 150, 2 240 (−CN), and 1 720 cm^{-1}; δ (CCl_4) 2.50 (m, 4 H, 1- and 4-H_2) and 8.84 (1 H, br, CO_2H); *m/e* 415 (M^+, 89%), 375 (100%), 356 (7%), and 275 (17%).

Methyl 2-*Nitrilo*-2,3-*seco*-5α-*cholestan*-3-*oate* (13).—(*a*) A solution of (6) (175 mg) in absolute methanol (25 ml) was saturated with dry hydrogen chloride gas, and the mixture was left for 1 h. After work-up, crystallization of the resulting oil from aqueous methanol gave *compound* (13) (142 mg, 78%), m.p. 88—89 °C (Found: C, 77.9; H, 11.15; N, 3.15. $C_{28}H_{47}NO_2$ requires C, 78.27; H, 11.02; N, 3.26%); $\nu_{max.}$ (KBr) 2 240 (−CN) and 1 728 cm^{-1}; δ (CCl_4) 2.30 (m, 4 H, 1- and 4-H_2) and 3.62 (s, 3 H, CO_2Me); *m/e* 429 (M^+, 100%), 414 (12%), 389 (89%), 356 (9%), and 275 (33%).

(*b*) To a solution of 2α-azido-5α-cholestan-3-one (1) (100 mg) in ether (15 ml) and methanol (5 ml) was added bromine (38 mg) in ether (10 ml) at room temperature, and the mixture was stirred for 4 h. After work-up, the resulting oil was chromatographed on a silica gel column (benzene as eluant) to give the methyl ester (13) (55 mg, 55%).

Ethyl 2-*Nitrilo*-2,3-*seco*-5α-*cholestan*-3-*oate* (15).—To a solution of 2α-azido-5α-cholestan-3-one (1) (100 mg) in ether (15 ml) and ethanol (5 ml) was added bromine (38 mg) in ether (10 ml) at room temperature, and the mixture was stirred for 5 h. After work-up, the resulting oil was chromatographed on a silica gel column (benzene as eluant) to give the ethyl ester (15), which crystallized from hexane as *needles* (65 mg, 63%), m.p. 82—83 °C (Found: C, 78.45; H, 10.95; N, 3.25. $C_{29}H_{49}NO_2$ requires C, 78.50; H, 11.13; N, 3.16%); $\nu_{max.}$ (KBr) 2 240 (−CN) and 1 727 cm^{-1}; δ (CCl_4) 1.25 (t, *J* 7.0 Hz, 3 H), 2.28 (m, 4 H, 1- and 4-H_2), and 4.08 (q, *J* 7.0 Hz, 2 H).

2-*Carbamoyl*-2,3-*seco*-5α-*cholestan*-3-*oic Acid* (14).—2-Nitrilo-2,3-seco-5α-cholestan-3-oic acid (7) (100 mg) was dissolved in a 20% solution of potassium hydroxide in glycerol (10 ml) and heated at 160 °C for 24 h. To the resulting mixture was added water, and the mixture was extracted with ethyl acetate and then acidified. After work-up, crystallization of the resulting oil from methanol gave *compound* (14) (65 mg, 62%), m.p. 197—200 °C (Found: C, 75.15; H, 10.6; N, 2.9. $C_{27}H_{47}NO_3$ requires C, 74.78; H, 10.92; N, 3.23%); $\nu_{max.}$ (KBr) 3 500, 3 350, 3 200, 2 600, 1 720, 1 653 ($CONH_2$) and 1 590 cm^{-1}; δ ($CDCl_3$) 2.20 (br m, 4 H, 1- and 4-H_2), 7.08 (br, 1 H, NH), and 7.63 (br, 1 H, NH); *m/e* 389 (19%), 374 (100%), and 274 (14%).

3-*Nitrilo*-2,3-*seco*-5α-*cholestan*-2-*oic Acid* (8).—The cleavage reaction of (2) (62 mg) was carried out using the technique for the synthesis of (7). After the usual work-up, crystallization of the resulting oil from hexane gave *compound* (8) (43 mg, 71%), m.p. 162—164 °C (Found: M^+, 415.348 6. $C_{27}H_{45}NO_2$ requires *M*, 415.345 2); $\nu_{max.}$ (KBr) 3 300, 3 100, 2 240 (CN), and 1 711 cm^{-1}; δ (CCl_4) 2.40 (m, 4 H, 1- and 4-H_2) and 9.30 (br, 1 H, CO_2H); *m/e* 415 (M^+, 30%), 355 (100%), and 315 (16%).

3β-*Acetoxy*-7-*nitrilo*-6,7-*seco*-5α-*cholestan*-6-*oic Acid* (12).—The cleavage reaction of (6) (884 mg) was carried out using the technique for the synthesis of (7). After the usual work-up, the resulting oil was chromatographed on silica gel. From the first elution with benzene–light petroleum (7 : 3) an unidentified product was obtained from methanol as needles, m.p. 126—129 °C. The next fraction, eluted with benzene–ether (19 : 1), on crystallization from hexane gave *needles* of (12) (250 mg, 29%), m.p. 221—223 °C (Found: C, 73.2; H, 10.0; N, 2.65. $C_{29}H_{47}NO_4$ requires C, 73.53; H, 10.00; N, 2.96%); $\nu_{max.}$ (KBr) 3 450, 2 240 (CN), 1 730, 1 700, and 1 236 cm^{-1}; δ (CCl_4) 2.02 (s, 3 H, MeCO), 2.80 (q, *J* 11.60 and 4.40 Hz, 1 H, 5-H), and 10.10 br (1 H, CO_2H); *m/e* 473 (M^+, 50%), 413 (100%), 274 (25%), and 199 (63%).

3α-*Acetoxy*-16-*carbamoyl*-16,17-*seco*-5α-*androstan*-17-*oic Acid* (10).—To a solution of 16β-azido-3α-hydroxy-5α-androstan-17-one (4) (200 mg) in acetic acid (10 ml) was added bromine (97 mg) in acetic acid (5 ml), and the reaction was stirred overnight at room temperature. After work-up, crystallization of the resulting oil from hexane–ethyl acetate gave *compound* (10) (130 mg, 57%), m.p. 168—171 °C (Found: C, 66.3; H, 8.5; N, 3.25. $C_{21}H_{33}NO_5$ requires C, 66.46; H, 8.76; N, 3.69%); $\nu_{max.}$ (KBr) 3 350, 3 200, 1 728 and 1 675 cm^{-1}; δ (DMSO) 2.00 (s, 3 H, MeCO), 6.54 (br, 1 H, NH), and 6.94 (br, 1 H, NH); *m/e* 379 (M^+).

2-*Nitrilo*-2,3-*seco*-5β-*cholestan*-3-*oic Acid* (9).—The cleavage reaction of (3) (200 mg) was carried out using the technique for the synthesis of (7). After the usual work-up, evaporation of the ether solution under reduced pressure gave (9) (150 mg, 77%) as a colourless oil, which resisted crystallization from various solvents; $\nu_{max.}$ (NaCl) 3 450, 1 370, 2 240 (CN), and 1 715 cm^{-1}; δ (CCl_4) 2.25 (m, 4 H, 1- and 4-H_2) and 10.00 (br, 1 H, CO_2H).

3β-*Acetoxy*-5α-*androstane*-17β-*carboxylic Acid* (11).—The cleavage reaction of (5) (50 mg) was carried out using the same technique as for the synthesis of (7). After the usual work-up, crystallization of the resulting oil from ether gave (11) (32 mg, 70%), which was identified by comparison with an authentic sample.

Methyl 2-*Carbamoyl*-2,3-*seco*-5α-*cholestan*-3-*oate* (16).—An excess of diazomethane in ether was added dropwise to a stirred solution of the amido-acid (14) (100 mg) in ether (20 ml) at room temperature until the yellow colour persisted. Evaporation and crystallization from hexane gave *compound* (16) (88 mg, 85%), m.p. 143—144 °C (Found: M^+, 447.372 5. $C_{28}H_{49}NO_3$ requires *M*, 447.371 5); $\nu_{max.}$ (KBr) 3 450, 3 340, 3 190, 1 738, 1 718, 1 664, and 1 614 cm^{-1}; δ ($CDCl_3$) 3.64 (s, 3 H, OMe), 6.68 (br, 1 H, NH), and 6.94 (br, 1 H, NH); *m/e* 447 (M^+, 1%), 388 (100%), and 373 (25%).

3-*Aza*-A-*homo*-5α-*cholestane*-2,4-*dione* (17).—The synthesis was carried out following the procedure of Meakins.[3] The amido-ester (16) (399 mg) was dissolved in a solution of sodium (27 mg) in methanol (5 ml), and the solution was refluxed for 10 min. After the usual work-up, crystallization of the resulting oil from ether gave *compound* (17) (262 mg, 71%), m.p. 277—230 °C (Found: C, 78.15; H, 10.6. $C_{27}H_{45}NO_2$ requires C, 78.02; H, 10.91%); $\nu_{max.}$ (KBr) 3 200, 3 095, 1 697, and 1 659 cm^{-1}; δ ($CDCl_3$) 0.91

(s, 3 H, 19-Me), 2.28—2.93 (4 H, 1- and 4a-H_2), and 7.89 (br, 1 H, NH).

3-*Aza*-A-*homo*-5α-*cholestane* (18).—The synthesis was carried out following the procedure of Shoppee.[4] The imide (17) (188 mg) was refluxed with lithium aluminium hydride (1 g) in ether (30 ml) for 48 h. After the usual work-up, evaporation of the extracts gave crude crystals, m.p. 95—101 °C; $\nu_{max.}$ (KBr) 3 300 cm^{-1} (no peaks at 1 697 and 1 659 cm^{-1}); δ ($CDCl_3$) 2.77—3.67 [5 H, 1- and 4-H_2, and NH (3.00)]; *m/e* 387 (M^+, 34%) and 372 (100%).

We thank Professors Jisaku Kuroda, Machiko Tozawa, and Tsunetaka Kushimoto of the Jikei University School of Medicine for their interest and encouragement.

[9/1420 *Received*, 6*th September*, 1979]

REFERENCES

[1] Part 1, T. T. Takahashi and J. Y. Satoh, *Bull. Chem. Soc. Japan*, 1976, **49**, 1089.
[2] T. T. Takahashi and J. Y. Satoh, *J.C.S. Chem. Comm.*, 1978, 409.
[3] R. T. Aplin, G. D. Meakins, K. T. Tuba, and P. D. Woodgate, *J. Chem. Soc.* (*C*), 1969, 1602.
[4] C. W. Shoppee, R. E. Lack, and S. K. Roy, *J. Chem. Soc.*, 1963, 3767.
[5] A. Wolloch and E. Zbiral, *Tetrahedron*, 1976, **32**, 1289.
[6] T. Nakano, M. Hasegawa, and C. Djerassi, *Chem. Pharm. Bull.* (*Tokyo*), 1962, **11**, 465.
[7] E. Zbiral and G. Nestler, *Tetrahedron*, 1971, **27**, 2293.
[8] Von B. Schonecker and K. Ponsold, *J. prakt. Chem.*, 1971. **313**, 817.