Photo-induced Transformations. Part 50.[1a] The Photo-Beckmann Rearrangement of 3α,5-Cyclo-5α-cholestan-7-one Oxime, a βγ-Cyclopropyl Ketone Oxime

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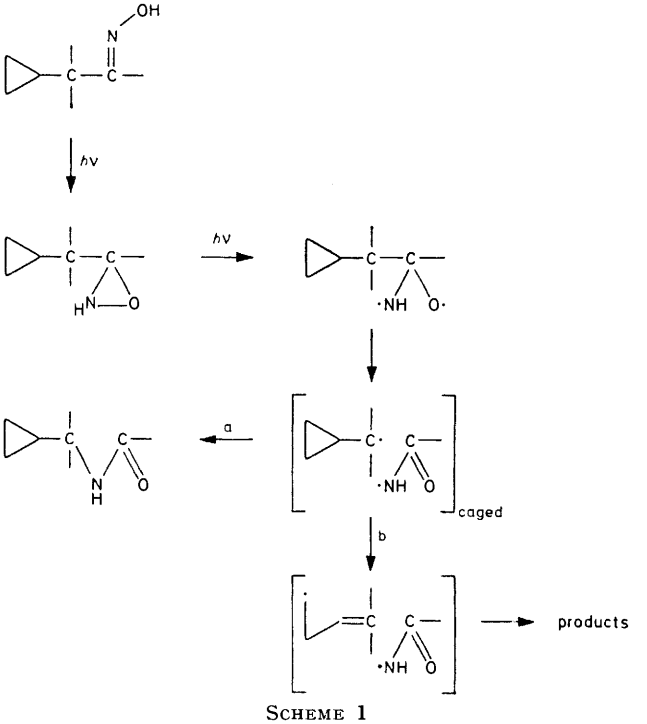
Photolysis of the title βγ-cyclopropyl ketone oxime in methanol gave 7-aza-3α,5-cyclo-B-homo-5α-cholestan-7a-one (3), 7a-aza-3α,5-cyclo-B-homo-5α-cholestan-7-one (4), and 3α,5-cyclo-7,8-seco-5α-cholestan-7-amide (5), together with the parent ketone (2), with no olefinic products resulting from cleavage of the cyclopropane ring. The results entirely parallel those obtained in the photolysis of cyclic ketone oximes and are compatible with the suggested mechanism that the *normal* photo-Beckmann rearrangement of cyclic ketone oximes does not involve any intimate radical pair or diradical species resulting from α-fission. The seco-amide (5) was identified by its synthesis from methyl 3α,5-cyclo-7,8-seco-5α-cholestan-7-oate (7) prepared by the photolysis of 3α,5-cyclo-5α-cholestan-7-one in methanol.

PREVIOUS studies [2,3] on the stereochemistry of the photo-Beckmann rearrangement of several cholestanone oximes with the chiral centre adjacent to the hydroxyimino-group showed that the chirality of the migrating group centre is retained in the product lactams and that yields of lactam resulting from migration of carbon centres substituted more heavily with alkyl groups are not significantly different from those from the migration of less substituted carbon centres. These results suggested that the migrating group centre does not become free from the migration terminus in the course of the *normal* photo-rearrangement.[2,3] On the other hand, there are a few exceptions to this rule, where the lactams are considered to be formed by ring closure of species resulting from α-fission.[1b,4] Thus, it seemed necessary to obtain more information, by a different approach, on the possibility of lactam formation occurring *via* coupling of radical pair or biradical species (path a in Scheme 1), as has been suggested for lactam formation from some fused bicyclic oxaziridines.[5]

The extremely ready isomerization of the cyclopropylcarbinyl radical to the allylcarbinyl radical is well-known,[6] and the isomerization of the primary alkyl radical was shown to be fast (k 1.3 × 10^8 l mol^{-1} s^{-1} at 25 °C) and to compete with radical recombination or molecular diffusion processes.[7] The rate of isomerization of a rigid steroidal cyclopropylcarbinyl radical generated from 6β-chloro-3α,5-cyclo-5α-cholestane with triphenyltin hydride has also been estimated to be of the same order (k 1.25 × 10^8 l mol^{-1} s^{-1} at 30 °C).[8] Thus, if the photo-Beckmann rearrangement of βγ-cyclopropyl ketone oximes involves radical pair or biradical species resulting from α-fission, the isomerization of the cyclopropylcarbinyl radical may well compete with a combination of the biradical intermediate to lactams and will give products arising from opening of the cyclopropane ring (path b in Scheme 1).

In this paper, (*E*)-3α,5-cyclo-5α-cholestan-7-one oxime (1), obtained from 3α,5-cyclo-5α-cholestan-7-one [9] by the standard method, was chosen as the substrate since the isomerization of cyclopropyl carbinyl radical from the substrate (1) should be as fast as that of the radical from 6β-chloro-3α,5-cyclo-5α-cholestane. The geometry of the hydroxyimino-group was determined by ^{1}H n.m.r. and chemical evidence as follows. The ^{1}H n.m.r. spectrum of the parent ketone (2) showed an AB quartet centred at τ 7.12 and 8.40 (J 12.0 Hz). Assuming ring B to exist in a chair conformation, 6α-H should be shielded by the cyclopropane ring and the unusually shielded doublet at τ 8.40 is therefore assigned to 6α-H.

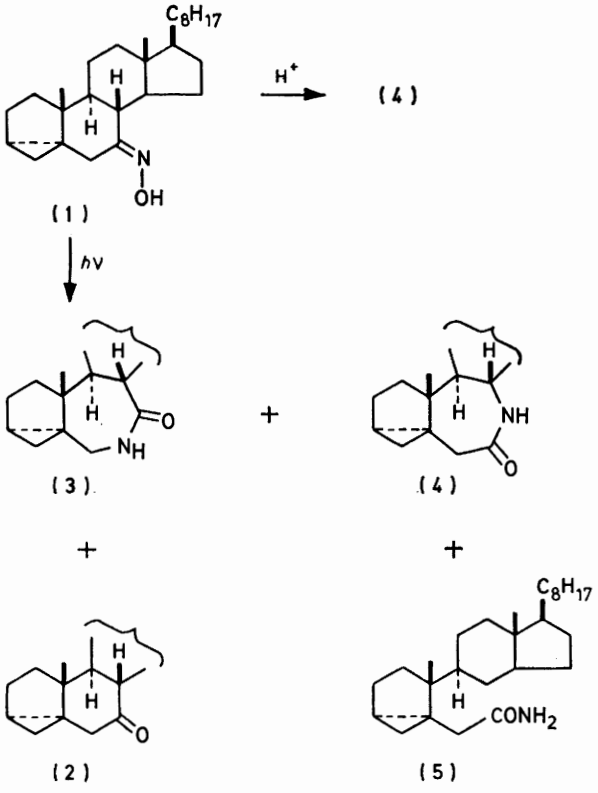


SCHEME 1

On the other hand, the corresponding protons of the oxime (1) absorbed at τ 7.22 and 7.86 (J 13.2 Hz). Assuming a chair conformation for ring B, a signal at τ 7.22 was assigned to 6β-H and one at τ 7.86 to 6α-H. the latter being shielded by the cyclopropane ring. Chemical shifts of methylene protons adjacent to an R–C=N–OR group do not generally differ significantly from those adjacent to an R–C(=O)–C=O group.[10] Therefore

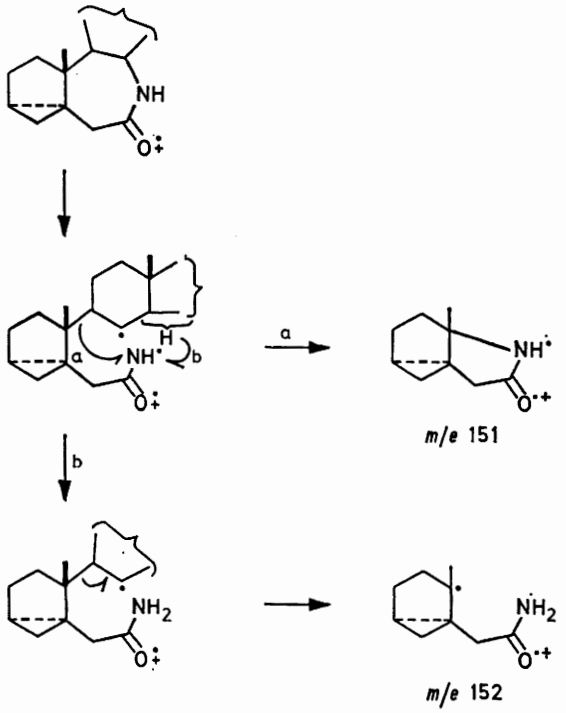
a considerable shift (0.54 p.p.m.) of the signal due to 6α-H of the oxime to lower field, when compared with the signal due to 6α-H of the ketone (2), is attributable to deshielding by the hydroxyimino-OH, the C=N bond of which is nearly eclipsed by the 6α-H, as shown by Dreiding models. On the basis of these results, the hydroxyimino-OH was concluded to be in the *E*-configuration in accordance with the result of the Beckmann rearrangement (*see later*).

Irradiation of the oxime (1) in methanol (2×10^{-4}M) with a Rayonet photochemical reactor under nitrogen gave a mixture from which 3α,5-cyclo-5α-cholestan-7-one (2) (18%) and three new rearrangement products, (3), m.p. 121—123 °C (25%), (4), m.p. 118—120 °C (16%), and (5), amorphous (3%), were isolated in order of decreasing mobility on careful preparative t.l.c. (Scheme 2). Product (3) was found to be 7-aza-3α,5-cyclo-B-homo-5α-cholestan-7a-one on the basis of spectral analysis. Its mass spectrum and elemental analysis were in agreement with the molecular formula $C_{27}H_{45}NO$. Its i.r. spectrum showed bands due to an amide group, and the ^{1}H n.m.r. spectrum showed a signal arising from one of its cyclopropane protons (4-H) at τ 9.83 as a double doublet (*J* 5 and 9 Hz), two double doublets centred at τ 7.71 and 6.02 assigned to the C-6 methylene protons, and a 1 H triplet at τ 3.33 (*J* 7.2 Hz) arising from the NH. On addition of D_2O, each double doublet collapsed to a doublet (*J* 16.4 Hz) and the signal due to NH vanished; a broad triplet at τ 7.47 after D_2O exchange was assigned to the 9β-H. A Dreiding model indicated that, assuming ring B to exist in a chair conformation, the 6α-proton should be shielded by the cyclopropane ring. Hence the signal at τ 7.71 was assigned to 6α-H and that at τ 6.02 to 6β-H. The protons at C-18 and -19 appeared at τ 9.31 and 8.84 as singlets.



SCHEME 2

Product (4) was identical with a lactam obtained as sole product from the Beckmann rearrangement of the oxime in dioxan with thionyl chloride, and was identified as 7a-aza-3α,5-cyclo-B-homo-5α-cholestan-7-one by analysis of its mass, i.r., and ^{1}H n.m.r. spectra. Scheme 3 shows the genesis and structure of the prominent ion

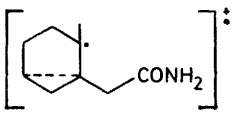


SCHEME 3

at *m/e* 151 and the base peak at *m/e* 152. Its n.m.r. spectrum exhibited a double doublet (1 H) at τ 9.83 (*J* 5 and 8 Hz), assigned to one of the cyclopropane protons (4-H), and a AB quartet centred at τ 8.33 and 6.80 (*J* 14.9 Hz) assigned to the C-6 methylene protons. The spectrum also exhibited a broad signal (1 H), partly superimposed on the doublet at τ 6.80, and a broad singlet (1 H) at 4.60 ($W_{\frac{1}{2}}$ 10 Hz). On addition of D_2O, the former signal changed to a broad triplet (*J* 9 Hz) and the latter vanished, enabling them to be assigned to the 9β-H and the NH respectively. In spin-decoupling experiments irradiation at τ 8.33 caused the doublet at τ 6.80 to collapse to a singlet. It is notable that, of the C-6 methylene protons adjacent to the carbonyl group, one appeared at an unusually low and the other at an unusually high field. As for the lactam (3), a Dreiding model indicates that if we assume ring B to exist in a chair conformation, the 6α-proton should be shielded by the cyclopropane ring;

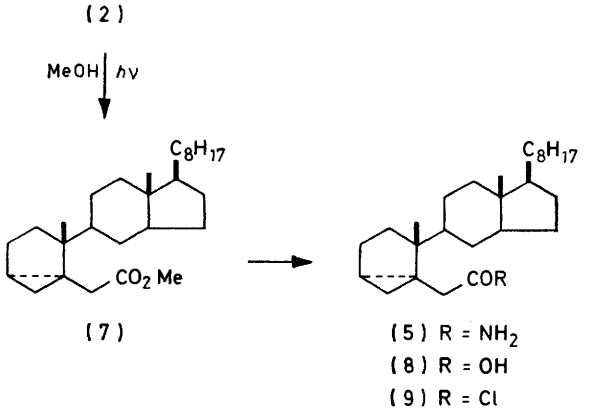
the doublet at τ 8.33 is therefore assigned to the 6α-H and the other to the 6β-H.

The structure of product (5) was ascertained as 3α,5-cyclo-7,8-seco-5α-cholestan-7-amide on the basis of its spectra. High resolution mass spectrometry indicated the molecular formula to be $C_{27}H_{47}NO$, a base peak occurring at *m/e* 152. The i.r. spectrum showed bands due to an amide group, and the ^{1}H n.m.r. spectrum showed a doublet due to one of the cyclopropane ring protons (4-H) at τ 9.62 (*J* 5 and 9 Hz), two singlets (each 3 H) arising from the 18- and the 19-H at τ 9.35 and 9.01, an AB quartet centred at τ 8.07 and 7.30 (*J* 15.0 Hz) arising from the C-6 methylene protons, and a D_2O-exchangeable broad singlet (1 H) at τ 4.36 arising from the amide NH. The base peak may have



(6) *m/e* 152

structure (6). Structure (5) was further confirmed by synthesis (Scheme 4). Irradiation of 3α,5-cyclo-5α-cholestan-7-one in methanol with a 400-W high-pressure mercury arc gave crystalline methyl 3α,5-cyclo-7,8-seco-5α-cholestan-7-oate (7) in 32% yield. Basic hydrolysis of the ester afforded the corresponding



SCHEME 4

crystalline acid (8) which was transformed into an acid chloride (9) on treatment with thionyl chloride. Reaction of the acid chloride (9) with ammonia gave an amide which was identical with the amide (5) obtained in the photo-reaction.

Some minor fractions were also obtained in the photolysis of the oxime and these fractions were examined carefully by ^{1}H n.m.r. However no olefinic signals were detected.

The present results parallel those obtained in the photolysis of saturated ketone oximes with no cyclopropane ring at the βγ-position; a pair of structurally isomeric lactams are produced in comparable amounts accompanied by a small amount of amide. The ring-opened amide is known to be a predominant product in the photo-reaction of saturated cyclic ketone oximes in isopropyl alcohol [11] and is believed to be produced by a different path to that followed during lactam formation.[2,3]

The lack of any olefinic products in the present photo-reaction, together with the entirely parallel results to the reactions of cholestanone oximes, considerably strengthens the previous conclusion that *normal* photo-Beckmann rearrangement of saturated cyclic ketone oximes does not involve any intimate radical pair or diradical species as the intermediate resulting from α-fission,[2,3] although a rigorous exclusion of the possibility that the results arise from radical combination faster that cyclopropyl–carbinyl rearrangement is still necessary..

Thus, we believe that the exceptional stereochemical results in the photo-Beckmann rearrangement of steroid-17-one oximes[4] and D-norsteroid-16-one oximes[1b] can be explained by the existence of another discrete path to lactams involving species resulting from α-fission,[5] as suggested by one of the present authors.[4]

EXPERIMENTAL

General procedures and details of instruments used are given in ref. 2. I.r. spectra were determined for Nujol mulls with a Hitachi model 260-10 spectrometer. Low resolution mass spectra were determined with a Hitachi JMS-D 300 spectrometer (ion source temperature 180 °C; ionizing voltage 70 eV unless stated otherwise) by the staff of the Faculty of Pharmaceutical Sciences of this University. High resolution mass spectra were recorded with a Hitachi RMU 7MF double-focusing mass spectrometer (ionizing voltage 70 eV) in the Coal Research Institute, Faculty of Engineering of this University. Optical rotations were measured with a JASCO DIP-SL automatic polarimeter.

3α,5-*Cyclo*-5α-*cholestan*-7-*one* (2).—This ketone was prepared from 3α,5-cyclo-5α-cholestan-6-one as previously described.[9] Some physical and spectral properties of the intermediates are recorded below.

7-Methylene-3α,5-cyclo-5α-cholestan-6-one had m.p. 56—57 °C (lit.,[9] oil); τ 9.21 (3 H, s, 18-H), 8.93 (3 H, s, 19-H), and 4.18 and 4.79 (each br s, $W_{\frac{1}{2}}$ 4.8 Hz, C-7 methylene protons); *m/e* 396 (M^+, 100%), 381 ($M^+ - CH_3$, 16), 368 (14), 367 (14), 189 (21), 188 (21), 95 (24), 55 (31), and 43 (36). 7-*Methylene*-3α,5-*cyclo*-5α-*cholestane* was amorphous, τ 9.29 (3 H, s, 18-H), 8.97 (3 H, s, 19-H), and 5.42 (2 H, br s, $W_{\frac{1}{2}}$ 5.4 Hz, C-7 methylene protons). 3α,5-Cyclo-5α-cholestan-7-one (2) had m.p. 87—88 °C (lit.,[9] 89—90 °C); τ 9.33 (3 H, s, 18-H), 8.87 (3 H, s, 19-H), and 7.12 and 8.40 (each 1 H, d, *J* 12.0 Hz, 6β-H and 6α-H).

3α,5-*Cyclo*-5α-*cholestan*-7-*one Oxime* (1).—Ketone (2) (550 mg), sodium acetate trihydrate (230 mg), and hydroxylamine hydrochloride (257 mg) in ethanol (20 ml) and water (2.5 ml) were stirred for 1 h at room temperature. After removal of the solvent, the residue was extracted with dichloromethane and the organic layer worked up as usual. The oxime (1) was amorphous and had τ 9.30 (3 H, s, 18-H), 8.95 (3 H, s, 19-H), and 7.86 and 7.22 (each 1 H, d, *J* 13.2 Hz, 6β- and 6α-H); $\nu_{max.}$ 3 400br cm^{-1} (OH); *m/e* (ion source temperature 175 °C, 70 eV), 399 (M^+, 100%), 383 ($M^+ - O$, 35.5), 382 ($M^+ - OH$, 86.7), and 286 (19.3).

Beckmann Rearrangement of 3α,5-*Cyclo*-5α-*cholestan*-7-*one Oxime* (1).—To the oxime (50 mg) in dioxan (1 ml) was added thionyl chloride (0.01 ml) at room temperature. The solution was stirred for 10 min and then poured into water. The mixture was extracted with dichloromethane. The organic layer was washed with 5% sodium hydrogen carbonate solution and then with water. The residue (56 mg) was subjected to preparative t.l.c. with a 5 : 1 mixture of dichloromethane and diethyl ether to give two major fractions A (12 mg) and B (33 mg). The less mobile fraction (33 mg) was the lactam (4) which was recrystallized from acetone–water to afford a specimen, m.p. 118—120°, for analysis (Found: C, 81.2; H, 11.5; N, 3.5: $C_{27}H_{45}NO$ requires C, 81.1; H, 11.4; N, 3.5%); $\nu_{max.}$ 3 229 (NH), 1 682 (lactam carbonyl), 1 161, 1 021, 808, 796, and 733 cm^{-1}; *m/e* (ion source temperature 175 °C, 70 eV), 339 (M^+, 74.8%), 384 ($M^+ - CH_3$, 18.8), 151 (83.1), and 152 (100); for ^1H n.m.r. spectrum see text.

Photo-Beckmann Rearrangement of 3α,5-*Cyclo*-5α-*cholestan*-7-*one Oxime*.—The oxime (350 mg) in methanol (240 ml, special grade, Wako), through which was bubbled commercial nitrogen previously passed through Fiesers solution, was irradiated with a low-pressure Hg arc (Rayonet RPR-208 preparative photochemical reactor) for 26 h. Evaporation left a pale yellow residue which was dissolved in dichloromethane. The solution was washed with water, dried, and evaporated to give a residue (353 mg). The product was subjected to preparative t.l.c. (Merck, silica gel 60 F_{254} with concentration zone) with dichloromethane–diethyl ether (4 : 1 v/v) to give seven fractions, A (112 mg), B (8 mg), C (88 mg), D (56 mg), E (11 mg), F (5 mg), and G (12 mg) in order of decreasing mobility. Fraction A was subjected again to preparative t.l.c. [benzene–diethyl ether (99 : 1 v/v)] to give the parent ketone (59 mg) which was recrystallized from ethanol. Some minor fractions (total 8 mg) were examined carefully by ^1H n.m.r. spectroscopy but no signals due to olefinic protons were detected, all fractions exhibiting signals arising from the cyclopropane protons. Fraction C (88 mg) was 7-*aza*-3α,5-*cyclo*-B-*homo*-5α-*cholestan*-7a-*one* (3), m.p. 121—123 °C (from acetone–water (Found: C, 80.3; H, 11.3; N, 3.4. $C_{27}H_{45}NO$ requires, C, 81.1; H, 11.4; N, 3.5%); $\nu_{max.}$ 3 350 (NH), 1 677—1 633 (lactam carbonyl), 1 341, 1 207, 1 024, and 710 cm^{-1}; *m/e* 399 (M^+, 100%), 384 (44.9), 286 (65.1), 107 (48.0), 93 (57.2), 79 (45.0), 55 (47.8), and 43 (76.4); for ^1H n.m.r. spectrum see text.

Fraction D (56 mg) was the lactam (4) and was recrystallized from acetone–water to give a specimen identical with the lactam obtained *via* Beckmann rearrangement. Fraction E was passed through a silica gel column (Wako gel C-200) to afford the amide (5), identical with a specimen synthesized from 3α,5-cyclo-5α-cholestan-7-one. Fractions F and G were examined by ^1H n.m.r. but no olefinic signals were detected.

Photolysis of 3α,5-*Cyclo*-5α-*cholestan*-7-*one* (2).—The ketone (2) (200 mg) in methanol (200 ml) under argon was irradiated through a Pyrex filter with a Hanovia 450-W high-pressure Hg arc for 72 h. After removal of the solvent, the residue (220 mg) was subjected to preparative t.l.c. [hexane–benzene (9 : 1 v/v)]. The most mobile major fraction (700 mg) was recrystallized from diethyl ether–methanol to give *methyl* 3α,5-*cyclo*-7,8-*seco*-5α-*cholestan*-7-*oate* (7) (56 mg), m.p. 72.0—73.0 °C $[\alpha]_D^{25}$ +1.7° (*c* 0.4 in $CHCl_3$) (Found: *m/e* 416.363 7. $C_{28}H_{48}O_2$ requires *M*, 416.365 1); *m/e* (70 eV) 417 ($M^+ + 1$, 2.9%), 401 ($M^+ - CH_3$, 1.1), 303 (2.8), 167 (100), 107 (26.4), and 93 (19.5); $\nu_{max.}$ 1 743 (ester carbonyl), 1 261, and 1 163 cm^{-1}; τ 9.67 (1 H, t, *J* 4.5 Hz, cyclopropane proton), 9.47 (1 H, dd, *J* 4.8 and 7.8 Hz, cyclopropane proton), 9.34 (3 H, s, 19-H), 9.08 (3 H, s, 18-H), 7.98 and 7.23 (each 1 H, d, *J* 13.5 Hz, C-6 methylene protons), and 6.36 (3 H, s, methoxycarbonyl protons). From less mobile fractions, the parent ketone (28 mg) was recovered unchanged.

Conversion of the Ester (7) *into* 3α,5-*Cyclo*-7,8-*seco*-5α-*cholestan*-7-*oic Acid* (8).—The ester (50 mg) in ethanol (2 ml) containing potassium hydroxide (133 mg) was heated under reflux for ½ h. After removal of the solvent, the residue was worked up as usual to give the crude oily acid (8) as an oil (51 mg), which was recrystallized from methanol–diethyl ether to give the pure *acid* (8), m.p. 110.5—111.5 °C (Found: C, 80.3; H, 11.6. $C_{27}H_{46}O_2$ requires C, 80.5; H, 11.5%); $\nu_{max.}$ 3 300, 1 736 and 1 703 (carboxy), and 1 157 cm^{-1}; τ 9.65 (1 H, t, *J* 4.5 Hz, cyclopropane proton), 9.34 (3 H, s, 19-H), 9.04 (3 H, s, 18-H), and 7.97 and 7.26 (each 1 H, d, *J* 13.5 Hz, C-6-methylene protons); *m/e* 402 (M^+, 2.8%), 153 (M^+ — c/D ring, 100), and 93 (64.4).

3α,5-*Cyclo*-7,8-*seco*-5α-*cholestan*-7-*amide* (5).—The crude acid (8) (51 mg) was treated with thionyl chloride (1 ml) at −2 °C for 2 h. The excess of thionyl chloride was removed with added benzene and the crude oily acid chloride (9) obtained was dissolved in tetrahydrofuran (2 ml). Dried ammonia was bubbled through the solution until ammonium chloride appeared (10 min). After removal of the solvent, the residue was extracted into dichloromethane, washed with water, and dried (Na_2SO_4). The residue obtained after evaporation of the solution was subjected to column chromatography (Wako gel C-200). Elution with dichloromethane–diethyl ether (4 : 1 v/v) gave the amide (15 mg) which was recrystallized from acetone to afford the pure *amide* (5), m.p. 158—159 °C (Found: *m/e* 401.365 6. $C_{27}H_{47}NO$ requires *M*, 401.365 6); for i.r., n.m.r., and mass spectra see text. Further elutions gave the recovered acid (8) (22 mg).

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