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Reactions of 4-Azacholest-5-en-3-one, 6-Azacholest-4-en-7-one, and their N-Methyl Derivatives with Electrophilic Reagents

Jacek W. Morzycki* and Agnieszka Z. Wilczewska

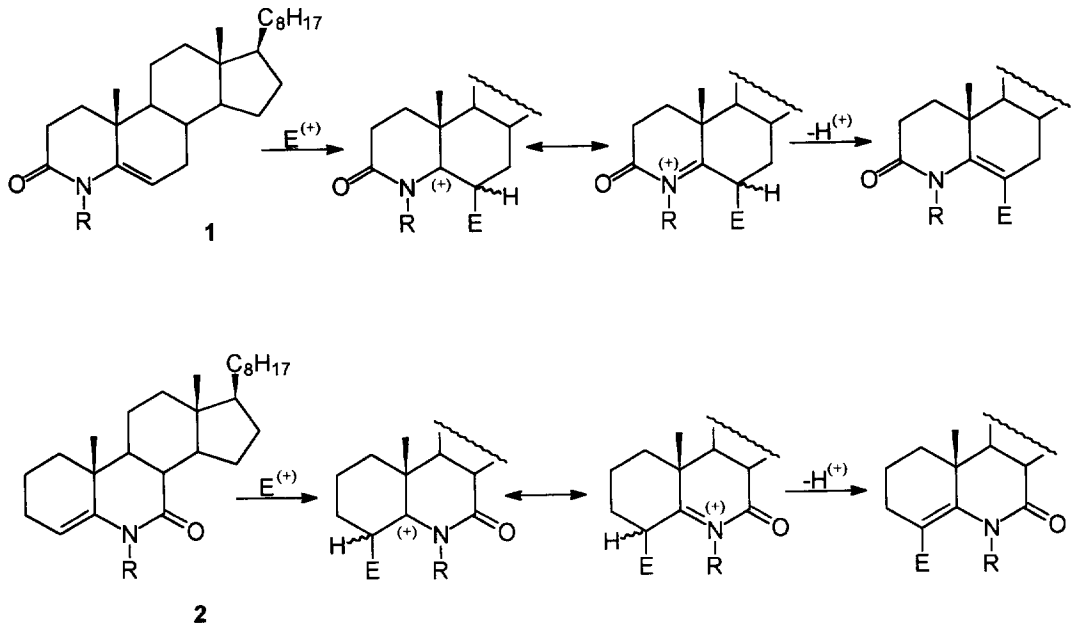
Institute of Chemistry, University of Warsaw, Bialystok Branch, Al. Pilsudskiego 11/4,15-443 Bialystok, Poland

Abstract: The reactions of four steroidal ene-lactams with electrophilic reagents, such as bromine, acetyl nitrate or CrO_3, were studied. The initial electrophilic attack took place on the terminal carbon atom of the enamide system. In some cases further reactions at the allylic position were observed. There were no reactions at the nitrogen atom or in the α position to the lactam carbonyl group. Copyright © 1996 Elsevier Science Ltd

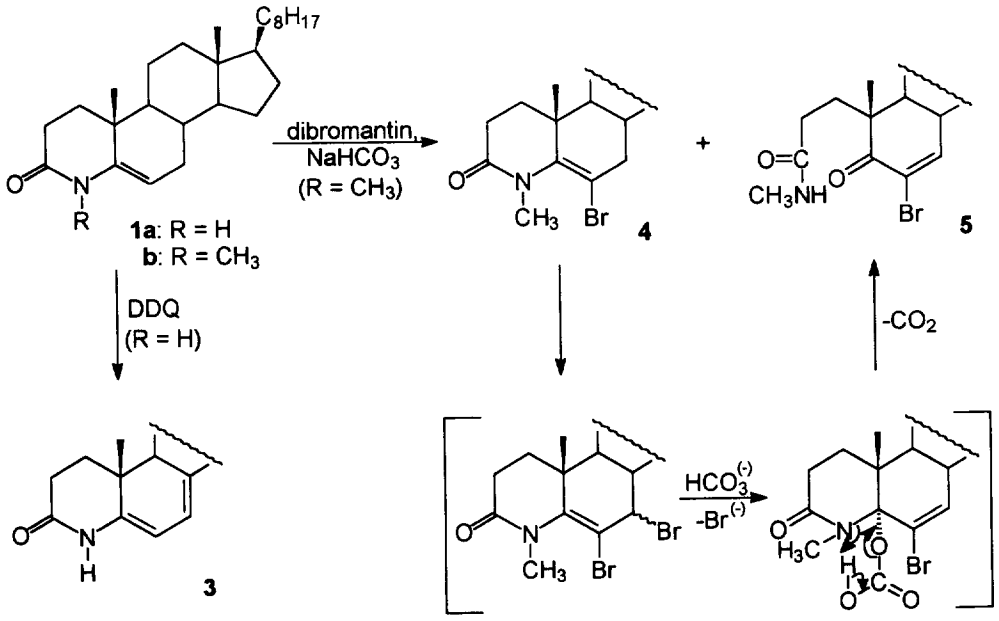
Many 4-aza and 6-azasteroids have been synthesized and some display interesting biological activity.[1] Among them are the most potent 5α-reductase inhibitors.[2-5] The enzyme 5α-reductase, present in many androgen-sensitive tumours, catalyses conversion of the major circulating androgen, testosterone, in adult males to more active metabolite 5α-dihydrotestosterone.[6] The latter is implicated in the pathogenesis of certain androgen-dependent conditions such as benign prostatic hypertrophy, acne and male pattern baldness.[7] Some 4-azasteroids also show high antimicrobial activity against Gram-positive bacteria, yeasts, and molds.[8]

We have recently described the reduction of Δ^5-3-oxo-4-azasteroids with complex borohydrides.[9] The reaction proceeds smoothly in the presence of strong acids which protonate the enamide system at the terminal carbon atom. There are three potential sites of protonation in 4-azacholest-5-en-3-one (**1a**): both heteroatoms and carbon atom C-6. The protonation preferentially takes place at the latter position since it leads to the stable carbocation (Scheme 1). The same is true for reactions with electrophilic reagents.[10] The analogous Δ^4-7-oxo-6-azasteroid system (such as **2**) is selectively attacked by electrophiles at the terminal carbon atom C-4 yielding the stabilized carbocation.

The halogenation reactions of both systems are described in the literature. For example, bromination of 6-azacholest-4-en-7-one (**2a**) with NBS affords the 4-bromo derivative.[11] Similarly, C-chlorination is favoured over N-chlorination in the case of 4-azacholest-5-en-3-one (**1a**) reaction with trichloroisocyanuric acid.[12]



Scheme 1 (**a**: R = H, **b**: R = CH_3)

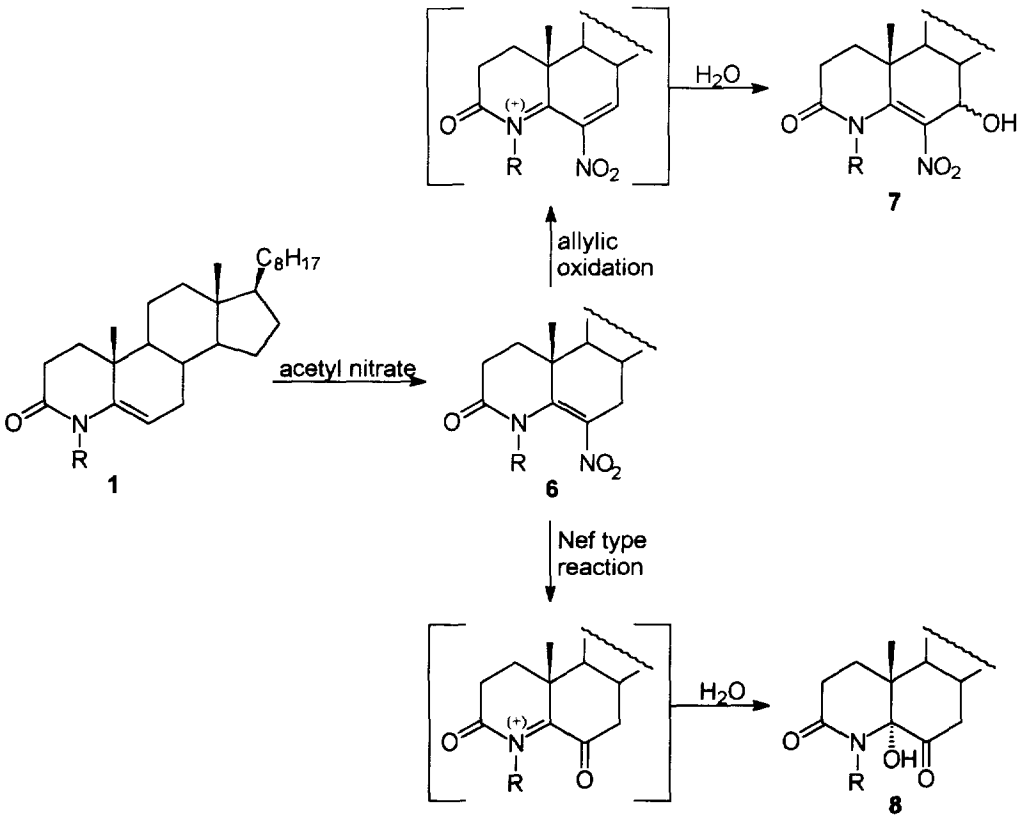


Scheme 2

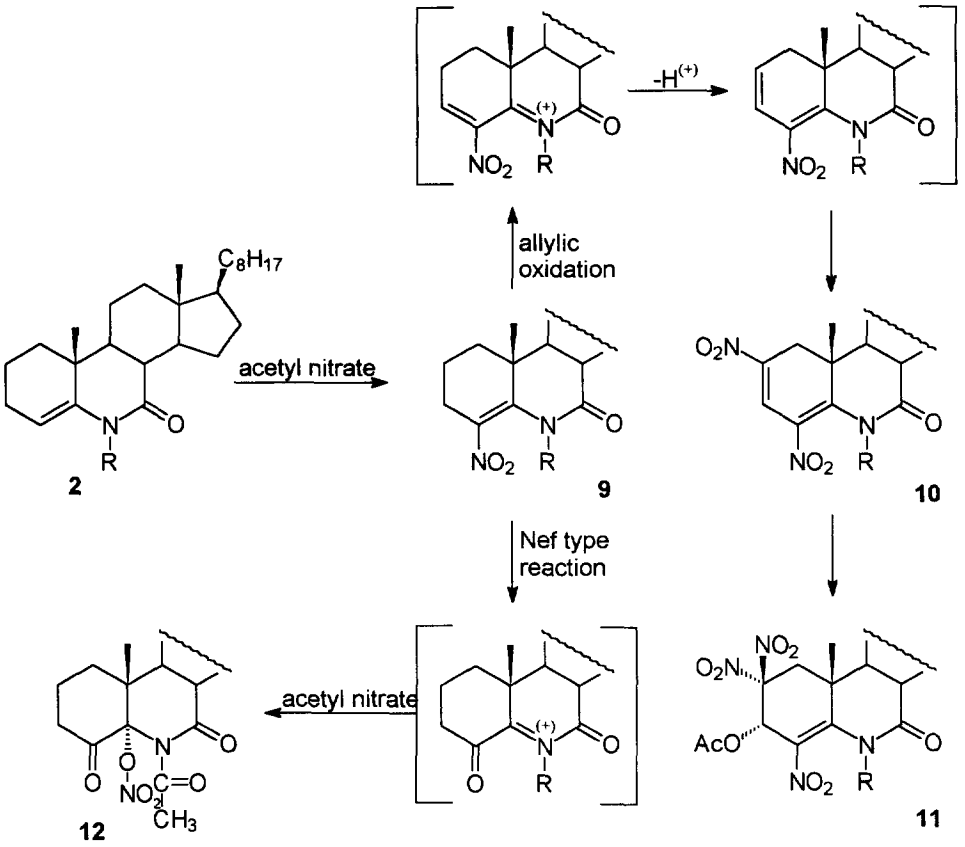
In our earlier studies a different reactivity of enamides and their N-methyl derivatives was observed.[9,13] Therefore 4-methyl-4-azacholest-5-en-3-one (**1b**) was subjected to bromination (Scheme 2) with dibromantin under the conditions frequently used for preparation of ring B dienes *via* the allylic bromination-dehydrobromination procedure.[14] The major product of the reaction appeared to be again the product of bromination at C-6 (compound **4**). Only further bromination proceeded at the allylic position. However the intermediate 7ξ-bromo compound underwent the S_N2' type substitution by bicarbonate. Finally, the A-seco amide **5** was isolated from the reaction mixture as a minor reaction product.

The ring B diene, 4-azacholesta-5,7-dien-3-one (**3**), was eventually obtained by dehydrogenation of enamide **1a** with DDQ according to the recently described procedure.[15]

Both azasteroids **1a** and **2a**, along with their N-methyl derivatives (**1b** and **2b**), were subjected to nitration with acetyl nitrate (Schemes 3 and 4).[13] The corresponding nitro derivatives (**6** or **9**) were the major reaction products but only when the starting ene-lactams were unsubstituted. In all cases electrophilic substitution by the



Scheme 3 (**a**: R = H, **b**: R = CH_3)

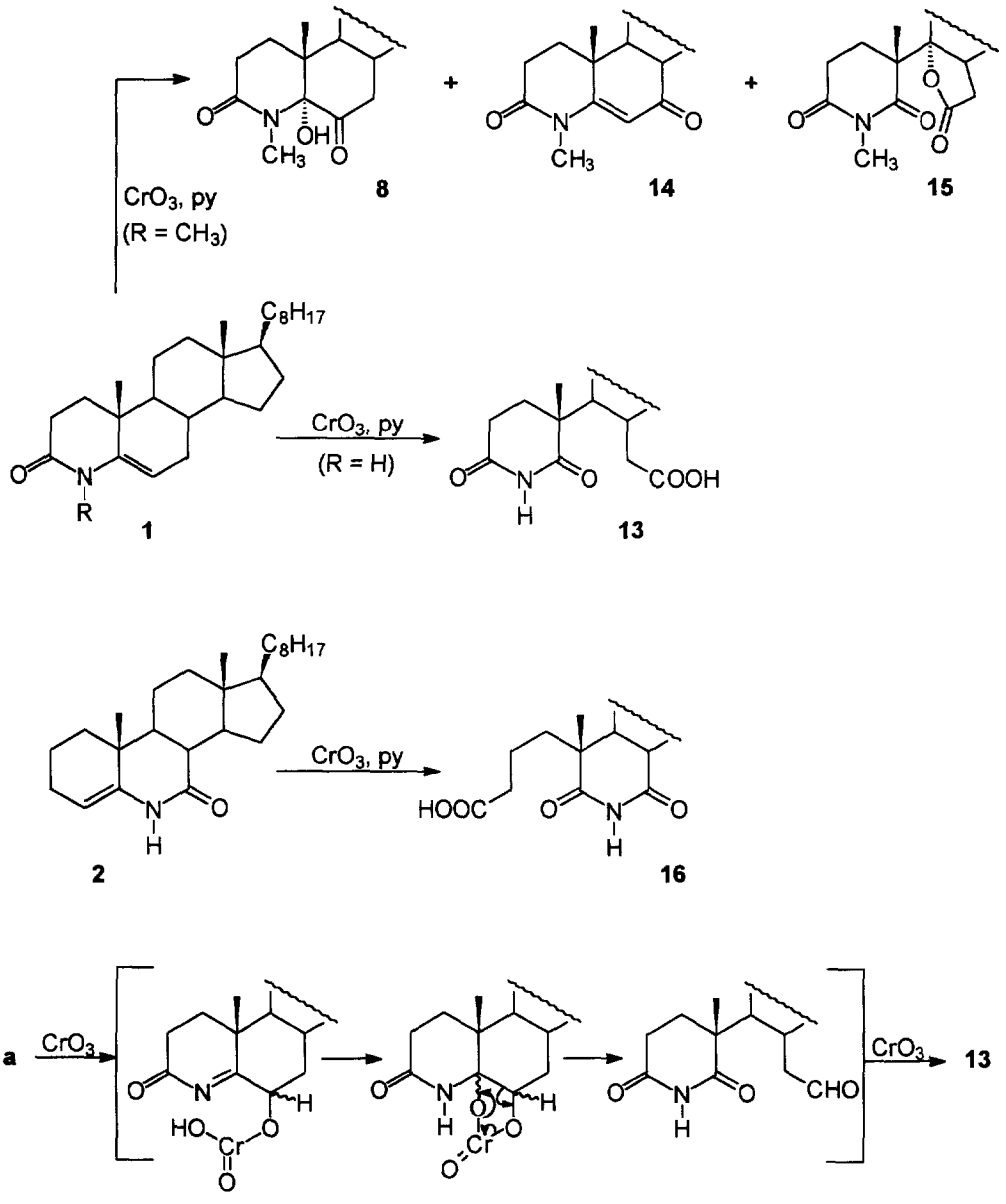


Scheme 4 (**a**: R = H, **b**: R = CH_3)

nitro group was followed by consecutive reactions, such as allylic oxidation or Nef type reaction. The allylic oxidation products were the corresponding 7-hydroxy compounds 7 (both epimers)[16] in the 4-aza series, whereas the 6-azasteroids underwent allylic dehydration followed by further nitration to dinitro **10** or even (in the case of N-methyl derivative) trinitro **11** compounds. The allylic alcohols were presumably produced from the N-acyliminium salt by its 1,4-hydration on aqueous workup. The primary nitration products may also undergo a Nef type reaction followed by hydration of the reactive N-acylimine intermediate to afford the hydroxy ketones **8**. The addition of acetyl nitrate to this intermediate is also possible (see compound **12**).

The oxidation reactions of 4-azacholest-5-en-3-one (**1a**) and its N-methyl derivative **1b** with chromic anhydride - pyridine complex were also studied (Scheme 5). This reagent is usually used for oxidation at the allylic position.[17] However in both reactions an attack on the $C_{(5)}$-$C_{(6)}$ double bond took place rather than on the allylic carbon atom C-7 (even in the case of the N-methyl derivative oxidation, the 7-oxo compound **14** was only the minor product of reaction). The apparent difference between these two reactions lies in that

the N-unsubstituted ene-lactam underwent oxidative cleavage of the double bond (to yield the B-seco acid **13**) whereas the reaction of its N-methyl derivative afforded only negligible amounts of acid fraction. This may be



Scheme 5 (**a**: R = H, **b**: R = CH_3)

explained by assuming that the formation of a cyclic chromate ester from the former compound is more likely. In the case of N-methyl derivative **1b** the allylic oxidation product **14** was accompanied by the hydroxy ketone **8**

and the B-seco lactone **15**. The latter product was obtained in low yield, probably by an intramolecular radical mechanism.

The similar oxidation of 6-azacholest-4-en-7-one (**2a**) also resulted in the double bond cleavage to afford 4,5-seco-5,7-dioxo-6-azacholestan-4-oic acid (**16**).

In conclusion, the studies performed confirm that the site for electrophilic attack on the enamide moiety is the terminal carbon atom. The reactions at the allylic position were also observed but they were less extensive and, in most cases, proceeded only after the initial electrophilic substitution at the double bond. Unsubstituted ene-lactams were proved less reactive compared with their N-methyl derivatives. The reactions at the heteroatom or in the α position to the lactam carbonyl group were not observed.

EXPERIMENTAL

Melting points were determined on a Köffler apparatus of the Boetius type and were uncorrected. NMR spectra were taken with a Bruker AC 200F spectrometer using $CDCl_3$ solutions with TMS as the internal standard. Infrared spectra were recorded on a Specord 75 IR spectrophotometer as chloroform solutions unless otherwise stated. UV spectra were taken in absolute ethanol on a Hewlett Packard 8452A Diode Array spectrometer. Mass spectra were obtained at 70 eV with an AMD-604 spectrometer. The reaction products were isolated by column chromatography performed on 70-230 or 230-400 mesh silica gel (Merck). Thin-layer chromatograms were developed on aluminum TLC sheets precoated with silica gel F_{254} and visualized with 50% sulfuric acid after heating. All solvents were dried and freshly distilled prior to use. Ene-lactams **1** and **2** were prepared according to the known procedures.[11, 18]

*Bromination of 4-methyl-4-azacholest-5-en-3-one (**1b**) with dibromantin*

Compound **1b** (0.5 g; 1.25 mmol) and 1,3-dibromo-5,5-dimethylhydantoin (0.27 g; 0.94 mmol) were dissolved in hexane (12.5 mL). The reaction mixture was stirred with sodium bicarbonate (0.57 g; 7.9 mmol) under argon and refluxed 1 h. After cooling the precipitate was removed by filtration, tetrabutylammonium bromide (0.038 g; 0.12 mmol) was added and stirring was continued for 30 min under argon at room temperature. Then 1M solution of tetrabuthylammonium fluoride in THF (11 mL) and *s*-collidine (0.7 mL) were portionwise added during 4 h. The reaction mixture was quenched by pouring into diluted hydrochloric acid and extracted with chloroform. The extract was washed with water, dried ($MgSO_4$) and evaporated *in vacuo*. The residue was subjected to silica gel column chromatography. With benzene - ethyl acetate (95:5) mixture the 6-bromo derivative **4** (240 mg; 48%) was eluted. Elution with benzene - ethyl acetate (75:25) mixture afforded the A-seco amide **5** (152 mg; 30%).

Compound **4**: mp 97-99°C (hexane); IR, ν_{max} 1738(w), 1675, 1649, 1378 cm^{-1}; UV, λ_{max} 224 nm (ε = 10900); ^1H NMR, δ 3.20 (s, 3H, N-CH_3), 2.56 (dd, J = 17.7 Hz, 5.5 Hz, 1H), 1.04 (s, 3H, 19-H), 0.92 (d, J = 6.4Hz, 3H, 21-H), 0.87 (d, J = 6.7 Hz, 6H, 26-H, 27-H), 0.69 (s, 3H, 18-H); ^{13}C NMR, δ 172.1 (C), 143.8 (C), 113.5

(C), 56.0 (CH), 55.9 (CH), 47.9 (CH), 43.5 (C), 42.5 (C), 42.1 (CH_2), 39.5 (CH_2), 39.3 (CH_2), 36.14 (CH_3), 36.08 (CH_2), 35.7 (CH), 34.4 (CH), 32.9 (CH_2), 30.9 (CH_2), 28.1 (CH_2), 27.9 (CH), 24.0 (CH_2), 23.8 (CH_2), 22.8 (CH_3), 22.5 (CH_3), 22.3 (CH_3), 21.9 (CH_2), 18.7 (CH_3), 11.8 (CH_3); MS, m/z 479 (M^+, 100), 477 (98), 398 (60), 382 (5), 370 (10).

Compound **5**: an oil; IR, ν_{max} 3365, 3492, 1675, 1670 cm^{-1}; UV, λ_{max} 256 nm (ε = 6500); ^1H NMR, δ 7.26 (d, J = 1.7 Hz, 1H, 7-H), 5.91 (bs, 1H, NH), 2.79 (d, J = 4.8 Hz, 3H, N-CH_3), 1.07 (s, 3H, 19-H), 0.92 (d, J = 6.5 Hz, 3H, 21-H), 0.87 (d, J = 6.6 Hz, 6H, 26-H, 27-H), 0.75 (s, 3H, 18-H); ^{13}C NMR, δ 196.6 (C), 173.5 (C), 153.1 (CH), 123.0 (C), 55.8 (CH), 52.6 (CH), 49.5 (C), 45.2 (CH), 43.4 (C), 40.1 (CH), 39.4 (CH_2), 38.9 (CH_2), 36.0 (CH_2), 35.6 (CH), 31.4 (CH_2), 31.2 (CH_2), 27.9 (CH), 27.8 (CH_2), 26.3 (CH_3), 23.7 (CH_2), 23.6 (CH_2), 22.7 (CH_3), 22.5 (CH_3), 20.7 (CH_2), 18.8 (CH_3), 18.5 (CH_3), 11.6 (CH_3); MS, m/z 495 (M^+, 18), 493 (18), 478 (18), 414 (96), 408 (24), 383 (21), 87 (100).

*Dehydrogenation of 4-azacholest-5-en-3-one (**1a**) with DDQ*

A stirred solution of compound **1a** (200 mg; 0.5 mmol) in methylene chloride (20 mL) was cooled to -40°C, and then a solution of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (130 mg; 0.5 mmol) in 3 mL of acetonitrile was dropwise added. The reaction mixture was allowed to reach room temperature and maintained at this temperature for 18 h. The solvents were evaporated under reduced pressure and the residue was chromatographed on a silica gel column. Diene **3** (64 mg; 32%) was eluted with benzene - ether (70:30) mixture, mp 166-170°C (hexane - methylene chloride); IR, ν_{max} 3365, 3230, 1698 (shoulder), 1671 cm^{-1}; UV, λ_{max} 304 nm (ε = 12700); ^1H NMR, δ 8.40 (bs, 1H, NH), 5.44 (m, 1H, olefinic H), 5.17 (d, J = 6.0 Hz, 1H, olefinic H), 1.07 (s, 3H, 19-H), 0.95 (d, J = 6.2 Hz, 3H, 21-H), 0.88 (d, J = 6.5 Hz, 6H, 26-H, 27-H), 0.63 (s, 3H, 18-H); ^{13}C NMR, δ 170.1 (C), 139.0 (C), 138.0 (C), 115.9 (CH), 101.3 (CH), 55.8 (CH), 54.4 (CH), 45.1 (CH), 42.8 (C), 39.5 (CH_2), 38.7 (CH_2), 36.11 (CH), 36.07 (CH_2), 34.6 (C), 31.7 (CH_2), 28.4 (CH_2), 28.1 (CH_2), 28.0 (CH), 23.8 (CH_2), 23.0 (CH_2), 22.8 (CH_3), 22.5 (CH_3), 20.7 (CH_2), 18.8 (CH_3), 15.9 (CH_3), 11.8 (CH_3); MS, m/z 383 (M^+, 100), 368 (15); exact mass calcd for $C_{26}H_{41}NO$: 383.3188; found: 383.3187.

Nitration with acetyl nitrate

To a reagent prepared from 5 mL of acetic anhydride and 1 mL of nitric acid the steroidal ene-lactam (**1a**, **1b**, **2a** or **2b**; 0.5 mmol) was added. The reaction mixtures were magnetically stirred 40 min at room temperature, quenched with water, and extracted with chloroform. The extracts were washed with sodium bicarbonate solution, water, dried ($MgSO_4$), and evaporated *in vacuo*. The products were separated by silica gel column chromatography.

The nitration of 4-azacholest-5-en-3-one (**1a**) afforded the 6-nitro derivative **6a** (eluted with benzene - ethyl acetate (98:2) mixture; 55%), the allylic alcohol **7a**[16] (eluted with benzene - ethyl acetate (95:5) mixture; 13%), and the 5α-hydroxy-6-ketone **8a** (eluted with benzene - ethyl acetate (75:25) mixture; 20%).

Compound **6a**: mp 81-83°C (hexane); IR, ν_{max} 3255, 1691, 1611, 1499, 1379, 1182, 1105 cm^{-1}; UV, λ_{max} 344 nm (ε = 8600), 212 nm (ε = 8700); ^1H NMR, δ 11.31 (bs, 1H, NH), 2.6-2.9 (m, 4H, 2-H, 7-H), 1.29 (s, 3H, 19-H), 0.92 (d, J = 6.4 Hz, 3H, 21-H), 0.87 (d, J = 6.6 Hz, 6H, 26-H, 27-H), 0.71 (s, 3H, 18-H); ^{13}C NMR, δ 169.5 (C), 150.9 (C), 123.8 (C), 56.1 (CH), 55.9 (CH), 46.5 (CH), 42.3 (C), 39.4 (CH_2), 38.9 (CH_2), 36.7 (C), 36.0 (CH_2), 35.7 (CH), 31.0 (CH_2), 30.8 (CH), 30.6 (CH_2), 28.1 (CH_2), 27.9 (CH), 27.9 (CH_2), 24.0 (CH_2), 23.8 (CH_2), 22.8 (CH_3), 22.5(CH_3), 20.9 (CH_2), 19.5 (CH_3), 18.6 (CH_3), 11.9 (CH_3); MS, m/z 430 (M^+, 42), 413 (28), 398 (38), 395 (100), 383 (21); exact mass calcd for $C_{26}H_{42}N_2O_3$: 430.3195; found: 430.3199.

Compound **7a** (7α-OH): mp 164-167°C (hexane - methylene chloride); IR, ν_{max} 3578, 3260, 1705, 1602, 1375, 1180, 1107 cm^{-1}; UV, λ_{max} 336 nm (ε = 9600), 210 nm (ε = 11500); ^1H NMR, δ 11.18 (bs, 1H, NH), 4.72 (s, 1H, 7-H), 2.68 (m, 2H, 2-H), 1.30 (s, 3H, 19-H), 0.93 (d, J = 6.3 Hz, 3H, 21-H), 0.87 (d, J = 6.3 Hz, 6H, 26-H, 27-H), 0.71 (s, 3H, 18-H); ^{13}C NMR, δ 169.8 (C), 154.4 (C), 127.1 (C), 64.5 (CH), 55.7 (CH), 48.4 (CH), 41.9 (C), 39.4 (CH_2), 38.9 (CH), 38.4 (CH_2), 37.6 (C), 36.4 (CH), 36.0 (CH_2), 35.7 (CH), 30.1 (CH_2), 28.1 (CH_2), 28.01 (CH_2), 27.97 (CH), 23.9 (CH_2), 23.7 (CH_2), 22.8 (CH_3), 22.5 (CH_3), 20.6 (CH_2), 19.3 (CH_3), 18.7 (CH_3), 11.5 (CH_3); MS, m/z 446 (M^+, 21), 428 (100), 414 (14), 411 (21), 398 (16).

Compound **8a**: mp 195-197°C (hexane - methylene chloride); IR, ν_{max} 3275, 1718, 1660, 1035 cm^{-1}; ^1H NMR, δ 7.10 (bs, 1H, NH), 4.75 (bs, 1H, OH), 2.68 (m, 1H), 0.91 (d, J = 6.6 Hz, 3H, 21-H), 0.86 (d, J = 6.7 Hz, 6H, 26-H, 27-H), 0.76 (s, 3H, 19-H), 0.66 (s, 3H, 18-H); ^{13}C NMR, δ 205.4 (C), 173.0 (C), 85.1 (C), 56.0 (2 x CH), 44.7 (CH), 43.1 (C), 42.3 (C), 41.0 (CH_2), 39.5 (CH_2), 39.3 (CH_2), 36.5 (CH), 36.1 (CH_2), 35.7 (CH), 28.1 (CH_2), 28.0 (CH), 27.9 (CH_2), 25.8 (CH_2), 23.9 (CH_2), 23.8 (CH_2), 22.8 (CH_2), 22.5 (CH_3), 21.5 (CH_2), 18.6 (CH_3), 13.6 (CH_3), 12.0 (CH_3); MS, m/z 417 (M^+, 1), 399 (29), 384 (13), 345 (13), 262 (63), 127 (100).

The nitration of 4-methyl-4-azacholest-5-en-3-one (**1b**) afforded the allylic alcohol **7b**[16] (eluted with benzene - ethyl acetate (95:5) mixture; 15%) and the 5α-hydroxy-6-ketone **8b** (eluted with benzene - ethyl acetate (93:7) mixture; 20%).

Compound **7b** (7α-OH): mp 230-234°C (hexane - methylene chloride); IR, ν_{max} 3640, 3418, 1691, 1635, 1351, 1295 cm^{-1}; UV, λ_{max} 299 nm (ε = 3500), 218 nm (ε = 13700); ^1H NMR, δ 4.91 (s, 1H, 7-H), 2.97 (s, 3H, N-CH_3), 2.55-2.70 (m, 2H, 2-H), 1.12 (s, 3H, 19-H), 0.94 (d, J = 6.3 Hz, 3H, 21-H), 0.87 (d, J = 6.5 Hz, 6H, 26-H, 27-H), 0.72 (s, 3H. 18-H); ^{13}C NMR, δ 195.5 (C), 149.9 (C), 135.6 (C), 66.7 (CH), 55.6 (CH), 48.4 (CH), 42.0 (C), 40.2 (CH), 40.1 (C), 39.5 (CH_2), 38.4 (CH_2), 37.1 (CH), 36.2 (CH_3), 36.1 (CH_2), 35.7 (CH), 31.2 (CH_2), 28.4 (CH_2), 28.1 (CH_2), 28.0 (CH), 24.3 (CH), 23.7 (CH_2), 22.8 (CH_3), 22.5 (CH_3), 20.7 (CH_2), 18.7 (CH_3), 17.3 (CH_3), 11.6 (CH_3); MS, m/z 460 (M^+, 28), 443 (30), 414 (100), 141 (29).

Compound **8b**: mp 168-171°C (hexane); IR, ν_{max} 3499, 1712, 1645 cm^{-1}; ^1H NMR, δ 2.66 (s, 3H, N-CH_3), 2.49 (m, 2H, 2-H), 0.91 (d, J = 6.6 Hz, 3H, 21-H), 0.86 (d, J = 6.7 Hz, 6H, 26-H, 27-H), 0.79 (s, 3H, 19-H), 0.66 (s, 3H, 18-H); ^{13}C NMR, δ 208.2 (C), 171.2 (C), 91.5 (C), 56.4 (CH), 56.0 (CH), 44.8 (C), 43.0 (C), 42.5 (CH_2),42.3 (CH), 39.4 (CH_2), 39.1 (CH_2), 38.2 (CH), 36.0 (CH_2), 35.7 (CH), 29.3 (CH_3), 28.4 (CH_2), 28.0

(CH), 27.9 (CH_2), 26.5 (CH_2), 23.9 (CH_2), 23.8 (CH_2), 22.8 (CH_3), 22.6 (CH_3), 21.9 (CH_2), 18.5 (CH_3), 16.2 (CH_3), 11.8 (CH_3); MS, m/z 431 (M^+, < 1), 262 (4), 141 (100).

The nitration of 6-azacholest-4-en-7-one (**2a**) afforded the 4-nitro derivative **9a** (40%), the dinitro compound **10a** (19%), and the 4-ketone **12** (17%). All products were consecutively eluted with benzene - hexane (85:15) mixture.

Compound **9a**: mp 149-152°C (hexane - methylene chloride); IR, ν_{max} 3258, 1695, 1604, 1380, 1176, 1122 cm^{-1}; UV, λ_{max} 346 nm (ε = 18200), 216 nm (ε = 13000); ^1H NMR, δ 11.21 (bs, 1H, NH), 1.27 (s, 3H, 19-H), 0.92 (d, J = 6.5 Hz, 3H, 21-H), 0.86 (d, J = 6.6 Hz, 6H, 26-H, 27-H), 0.75 (s, 3H, 18-H); ^{13}C NMR, δ 171.9 (C), 152.0 (C), 123.2 (C), 55.0 (CH), 51.4 (CH), 47.1 (CH), 43.9 (C), 41.7 (CH), 39.4 (CH_2), 38.8 (CH_2), 36.7 (C), 36.1 (CH_2), 35.7 (CH), 33.3 (CH_2), 28.4 (CH_2), 28.0 (CH), 25.9 (CH_2), 25.0 (CH_2), 23.8 (CH_2), 22.8 (CH_3), 22.5 (CH_3), 21.1 (CH_2), 18.8 (CH_3), 18.7 (CH_3), 17.1 (CH_2), 12.0 (CH_3); MS, m/z 430 (M^+, 91), 413 (100), 398 (15), 384 (46); exact mass calcd for $C_{26}H_{42}N_2O_3$: 430.3195; found: 430.3191.

Compound **10a**: mp 217-221°C (hexane - methylene chloride); IR, ν_{max} 3248, 1731, 1652(w), 1564, 1382, 1319, 1181, 1071 cm^{-1}; UV, λ_{max} 368 nm (ε = 7800), 210 nm (ε = 5900); ^1H NMR, δ 11.35 (bs, 1H, NH), 8.31 (d, J = 2.9 Hz, 1H, 3-H), 3.2 (d, J = 17.5 Hz, 1H, 1α-H), 2.6 (m, 2H, 1β-H, 8β-H), 1.30 (s, 3H, 19-H), 0.94 (d, J = 6.4 Hz, 3H, 21-H), 0.87 (d, J = 6.5 Hz, 6H, 26-H, 27-H), 0.76 (s, 3H, 18-H); ^{13}C NMR, δ 170.6 (C), 157.6 (C), 139.1 (C), 124.2 (CH), 118.7 (C), 54.9 (CH), 50.7 (CH), 45.7 (CH), 43.6 (C), 41.3 (CH), 39.5 (C), 39.4 (CH_2), 38.2 (CH_2), 36.0 (CH_2), 35.6 (CH), 33.7 (CH_2), 28.2 (CH_2), 28.0 (CH), 25.9 (CH_2), 23.8 (CH_2), 22.8 (CH_3), 22.5 (CH_3), 20.9 (CH_2), 18.8 (CH_3); MS, m/z 473 (M^+, 100), 458 (5), 443 (7), 427 (6); exact mass calcd for $C_{26}H_{39}N_3O_5$: 473.2890; found: 473.2897.

Compound **12a**: an oil; IR, ν_{max} 1750, 1613, 1147, 1009 cm^{-1}; UV, λ_{max} 214 nm (ε = 2500); ^1H NMR, δ 3.02 (m, 1H, 8β-H), 2.50 (m, 2H, 3-H), 2.20 (s, 3H, CH_3CO), 1.06 (s, 3H, 19-H), 0.91 (d, J = 6.5Hz, 3H, 21-H), 0.86 (d, J = 6.5 Hz, 6H, 26-H, 27-H), 0.70 (s, 3H, 18-H); ^{13}C NMR, δ 189.3 (C), 169.5 (C), 168.5 (C), 97.9 (C), 54.8 (CH), 50.6 (CH), 44.7 (C), 44.3 (CH), 44.2 (C), 43.9 (CH), 39.4 (CH_2), 38.8 (CH_2), 36.4 (CH_2), 36.0 (CH_2), 35.6 (CH), 29.7 (CH_2), 28.4 (CH_2), 28.0 (CH), 25.7 (CH_2), 23.7 (CH_2), 22.8 (CH_3), 22.5 (CH_3), 22,3 (CH_3), 21.6 (CH_2), 21.0 (CH_2), 18.8 (CH_3), 13.7 (CH_3), 12.1 (CH_3); MS, m/z 461 (10), 399 (100), 372 (99), 416 (29).

The nitration of 6-methyl-6-azacholest-4-en-7-one (**2b**) afforded the trinitro compound **11b** (eluted with benzene; 20%), mp 76-80°C (methanol - acetone); IR, ν_{max} 1779, 1700, 1628, 1576, 1178, 1019 cm^{-1}; UV, λ_{max} 322 nm (ε = 5200), 218 nm (ε = 18500); ^1H NMR, δ 7.38 (d, J = 2.2 Hz, 1H, 3β-H), 2.97 (s, 3H, N-CH_3), 2.88 (dd, J = 14.7 Hz, 2.2 Hz, 1H, 1β-H), 2.74 (d, J = 14.7 Hz, 1H, 1α-H), 2.44 (t, J = 10.6 Hz, 1H, 8β-H), 2.02 (s, 3H, CH_3CO), 1.00 (s, 3H, 19-H), 0.93 (d, J = 6.4 Hz, 3H, 21-H), 0.87 (d, J = 6.5 Hz, 6H, 26-H, 27-H), 0.78 (s, 3H, 18-H); ^{13}C NMR, δ 169.6 (C), 166.8 (C), 149.9 (C), 125.9 (C), 113.8 (C), 65.4 (CH), 55.2 (CH), 52.7 (CH), 50.6 (CH), 44.5 (C), 42.1 (CH), 39.4 (CH_2), 39.0 (CH_2), 37.7 (C), 37.3 (CH_2), 36.3 (CH_3), 36.0 (CH_2),

35.7 (CH), 28.3 (CH_2), 27.9 (CH), 25.1 (CH_2), 23.8 (CH_2), 22.8 (CH_3), 22.5 (CH_3), 21.9 (CH_2), 20.0 (CH_3), 18.7 (CH_3), 15.8 (CH_3), 12.3 (CH_3); MS, m/z 577 (1), 545 (1.5), 503 (23), 500 (28), 487 (100), 458 (36).

Oxidation with CrO_3 - pyridine complex

A stirred solution of pyridine (2.6 g; 0.032 mol) in 30 mL of methylene chloride was treated with P_2O_5 (3.3 g; 0.024 mol) and cooled to -4°C. Then anhydrous CrO_3 (1.6 g; 0.016 mol) was portionwise added. The reagent was stirred until complete dissolution of CrO_3 (about 1h), and then a solution of ene-lactam (0.5 mmol) in 3 mL of methylene chloride was added. The reaction mixture was heated under reflux 1h, quenched by pouring into water, and extracted with chloroform. Solvent was removed *in vacuo* from the dried ($MgSO_4$) extract and the products were separated by silica gel column chromatography.

The oxidation of 4-azacholest-5-en-3-one (**1a**) afforded B-seco acid **13** (eluted with benzene - ethyl acetate (50:50) mixture; 18%), mp 213-216°C (methanol - acetone); IR, ν_{max} 3390, 3215, 2800-3300, 1700, 1190 cm^{-1}; UV, λ_{max} 216 nm (ε = 3700); ^1H NMR, δ 9.96 (bs, 1H, NH), 3.07 (m, 1H, 7ξ-H), 1.22 (s, 3H, 19-H), 0.92 (d, J = 6.4 Hz, 3H, 21-H), 0.87 (d, J = 6.7 Hz, 6H, 26-H, 27-H), 0.68 (s, 3H, 18-H); ^{13}C NMR, δ 181.7 (C), 178.5 (C), 173.7 (C), 56.1 (CH), 52.8 (CH), 44.1 (C), 42.3 (C), 40.6 (CH), 39.5 (CH_2), 35.9 (CH_2), 35.7 (CH), 34.9 (CH), 32.5 (CH_2), 30.5 (CH_2), 28.4 (CH_2), 28.0 (CH), 27.7 (CH_2), 24.8 (CH_2), 23.7(CH_2), 23.4 (CH_2), 22.8 (CH_3), 22.5 (CH_3), 18.5 (CH_3), 17.4 (CH_3), 11.5 (CH_3); MS, m/z 433 (M^+, 1), 387 (18), 374 (18), 306 (14), 247 (16), 127 (100).

The oxidation of 4-methyl-4-azacholest-5-en-3-one (**1b**) afforded the 7-oxo compound **14** (eluted with benzene - ethyl acetate (94:6); 11%), the B-seco lactone **15** (eluted with benzene - ethyl acetate (93:7); 9%), and the hydroxy-ketone **8** (eluted with benzene - ethyl acetate (75:25); 17%), identical in all respects with the previously described product of reaction with acetyl nitrate.

Compound **14**: mp 162-164°C (hexane); IR, ν_{max} 1674, 1644, 1583, 1125 cm^{-1}; UV, λ_{max} 278 nm (ε = 29500); ^1H NMR, δ 5.46 (s, 1H, 6-H), 3.17 (s, 3H, N-CH_3), 2.70 (m, 2H, 2-H), 1.26 (s, 3H, 19-H), 0.93 (d, J = 6.4 Hz, 3H, 21-H), 0.86 (d, J = 6.5 Hz, 6H, 26-H, 27-H), 0.72 (s, 3H, 18-H); ^{13}C NMR, δ 200.7 (C), 169.1 (C), 165.7 (C), 108.1 (CH), 54.8 (CH), 50.5 (CH), 48.9 (CH), 44.4 (CH), 43.4 (C), 39.4 (CH_2), 38.7 (CH_2), 36.5 (C), 36.1 (CH_2), 35.7 (CH), 30.6 (CH_3), 30.2 (CH_2), 28.8 (CH_2), 28.6 (CH_2), 28.0 (CH), 26.3 (CH_2), 23.8 (CH_2), 22.8 (CH_3), 22.5 (CH_3), 21.1 (CH_2), 18.8 (CH_3), 17.1 (CH_3), 12.0 (CH_3); MS, m/z 413 (M^+, 100), 398 (28), 328 (10), 300 (22), 218 (67); exact mass calcd for $C_{27}H_{43}NO_2$: 413.3294; found: 413.3298.

Compound **15**: mp 194-196°C (hexane); IR, ν_{max} 1770, 1718, 1676, 1114 cm^{-1}; UV, λ_{max} 218 nm (ε = 9400); ^1H NMR, δ 3.13 (s, 3H, N-CH_3), 2.4-2.8 (m, 4H, 2-H, 7-H), 1.29 (s, 3H, 19-H), 0.92 (d, J = 6.4 Hz, 3H, 21-H), 0.86 (d, J = 6.6 Hz, 6H, 26-H, 27-H), 0.83 (s, 3H, 18-H); ^{13}C NMR, δ 177.5 (C), 176.1 (C), 171.6 (C), 100.4 (C), 50.2 (CH), 44.3 (C), 43.6 (C), 40.3 (CH_2), 30.6 (CH), 39.4 (CH_2), 36.4 (CH), 36.0 (CH_2), 35.5 (CH), 28.5 (CH_2), 28.0 (CH), 27.3 (CH_2), 27.0 (CH_3), 26.4 (CH_2), 23.9 (CH_2), 22.8 (CH_3), 22.5 (CH_3), 20.5 (CH_3), 20.0 (CH_3), 18.8 (CH_3), 15.8 (CH_3); MS, m/z 445 (M^+, 1.5), 386 (2), 332 (2), 305 (8), 191 (13), 141 (100).

The oxidation of 6-azacholest-4-en-7-one (**2a**) afforded A-seco acid **16** (eluted with ethyl acetate; 29%), mp 201-203°C (acetone); IR, ν_{max} (nujol) 3365, 2800-3350, 1709, 1462, 1376 cm^{-1}; UV, λ_{max} 214 nm (ε = 3000); ^1H NMR, δ 7.78 (bs, 1H, NH), 1.21 (s, 3H, 19-H), 0.93 (d, J = 6.4 Hz, 3H, 21-H), 0.87 (d, J = 6.4 Hz, 6H, 26-H, 27-H), 0.71 (s, 3H, 18-H); ^{13}C NMR, δ 177.8 (C), 177.0 (C), 174.1 (C), 54.9 (CH), 50.6 (CH), 45.4 (C), 43.6 (C), 41.5 (CH), 39.6 (CH), 39.4 (CH_2), 38.3 (CH_2), 36.1 (CH_2), 35.7 (CH), 34.8 (CH_2), 33.7 (CH_2), 28.4 (CH_2), 28.0 (CH), 26.1 (CH_2), 23.8 (CH_2), 22.8 (CH_3), 22.5 (CH_3), 20.5 (CH_2), 20.1 (CH_3), 19.2 (CH), 18.8 (CH_3), 11.9 (CH_3); Ms, m/z 433 (M^+, 4), 418 (2), 415 (2), 347 (100); exact mass calcd for $C_{26}H_{43}NO_4$: 433.3192; found: 433.3190.

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