REDUCTION OF 2-NITRO-5α-CHOLESTAN-3-ONE, ITS ENOL TAUTOMER AND 2-NITRO-5α-CHOLEST-2-EN-3-AMINE DERIVATIVES. SYNTHESIS OF BIS-STEROIDAL PYRAZINES

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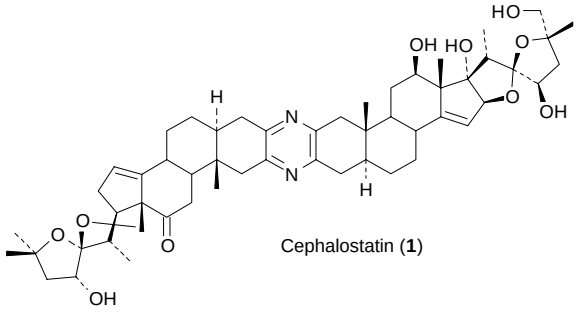
Dedicated to Dr Jan Fajkos on the occasion of his 75th birthday.

Reduction of 2α-nitro-5α-cholestan-3-one (**4**), its enol tautomer (**3a**) and 3-acetylamino-2-nitro-5α-cholest-2-ene (**2**) was studied. The latter compound was reduced with zinc in acetic acid to 3β-acetylamino-5α-cholestan-2-one (**8**). The similar reaction of **3a** or **4** led to 2α-amino-5α-cholestan-3-one (**11a**), that may be trapped as *N*-formyl derivative. When crude **11a** was subjected to air oxidation, pyrazino[2′,3′:2,3;5′,6′:2,3]bis(5α-cholestane) (**9**) was obtained.

Key words: α-Nitro ketones; α-Amino ketones; Zinc reduction; Bis-steroidal pyrazines; Steroids; Alkaloids; Cephalostatin.

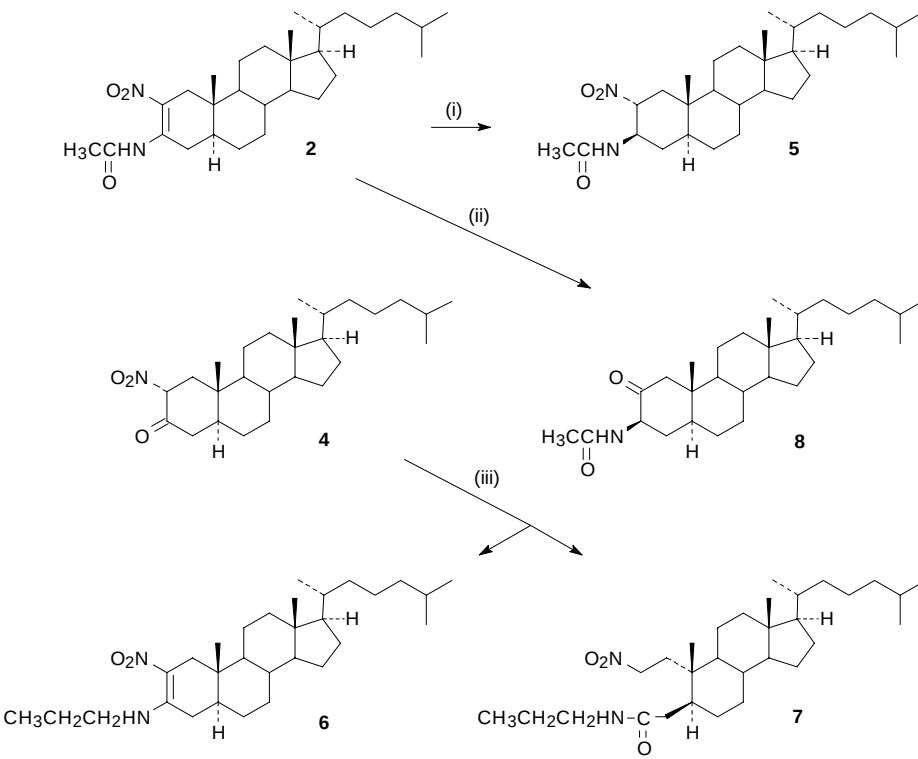
We have recently described nitration of *N*-acetyl enamines, including 3-acetylamino-5α-cholest-2-ene, with acetyl nitrate[1]. Nitration of steroidal 3-ketones or their enol derivatives with alkyl (or acyl) nitrates gives[2–4] the nitro enol compounds (such as **3**).



Cephalostatin (**1**)

A few years ago, a very mild method of nitration with trifluoroacetyl nitrate leading to 2α-nitro-5α-cholestan-3-one (**4**) was described[5]. The easy access to the nitro com-

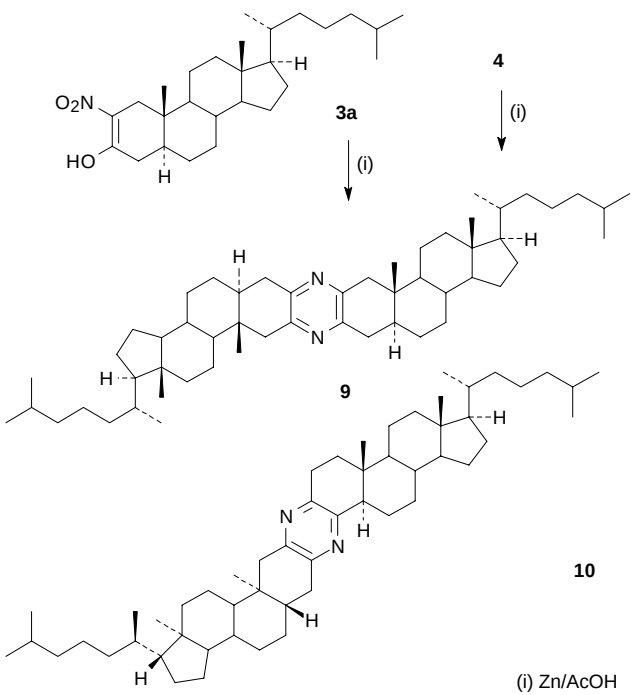
pounds prompted us to investigate their reduction in hope that it will result in a new method of synthesis of the bis-steroidal pyrazines. The family of bis-steroidal pyrazine alkaloids was isolated from the marine tube worm *Cephalodiscus gilchristi*[6] and from the tunicate *Ritterella tokioka*[7]. Cephalostatin **1** is a member of the family and with its ED_{50} of 10^{-9} μg/ml against the murine lymphocytic leukaemia cell line ranks among the most potent compounds ever recorded in the antitumour screening programmes[8]. The symmetrical bis-steroidal pyrazines have been prepared by the classical condensation of α-amino ketones[9]. The mixture of dihydropyrazines initially formed is spontaneously oxidized by air. The steroidal α-amino ketones themselves are usually synthesized by reduction of 3-ketones with a nitrogen substituent at C-2, such as azido or hydroxyimino group[10,11]. However, there has been no report on the synthesis of a pyrazine system from α-nitro ketones. 2-Nitro-5α-cholestan-3-one exists in two relatively stable tautomeric forms. The preferred form is highly hydrogen-bonded enol **3a**, which is formed under basic or acid conditions. For example, acid hydrolysis of 2-nitro-*N*-acetyl enamine **2** afforded the enol form **3a**. However, steroidal 2α-nitro 3-ketones (*e.g.* **4**) are



(i) $NaBH_4$/MeOH; (ii) Zn/AcOH; (iii) Li/$CH_3CH_2CH_2NH_2$

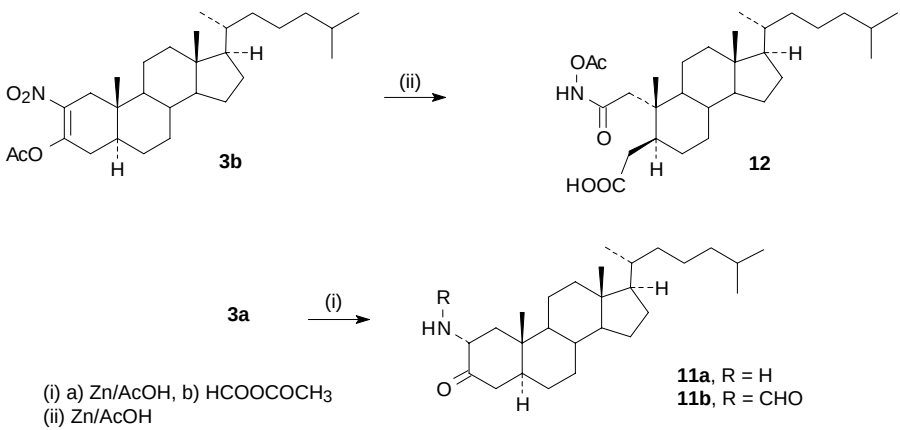
SCHEME 1

also known and can be obtained in high yields[5]. All the 2-nitro compounds, *i.e.* 2-nitro-*N*-acetyl enamine **2**, 2-nitro enol **3a**, its 3-acetyl derivative **3b**, and 2α-nitro-3-ketone **4**, were subjected to reduction under various conditions (Scheme 1–3). At first, the compounds were hydrogenated using platinum catalyst but the reactions led to complex mixtures of products. In the reduction of compound **2**, cis-hydrogenation of a double bond predominated. This reaction appeared to be faster than reduction of a nitro group. Similarly, hydrogenation of nitro enol **3a** or nitro ketone **4** (which isomerized to **3a** under the reaction conditions) gave a mixture of 2-nitro, 2-hydroxyimino, and 2-amino 3-alcohols. This proved that hydrogenation of a 3-carbonyl group (or rather of a double bond in the enol form) took place prior to reduction of a nitro group. The failure of catalytic hydrogenation prompted us to study hydride reduction (Scheme 1). The reaction of compound **2** with sodium borohydride afforded 3β-acetylamino-2α-nitro-5α-cholestane (**5**). Borohydride reduction of nitro enol **3a** yielded, as described earlier[2], 2α-nitro-5α-cholestan-3β-ol and 2-nitro-5α-cholest-2-ene. The nitro group proved resistant to borohydride. The reduction with other hydrides was also studied briefly but without success. Further attempt was a series of the dissolving metal reductions. However, a nucleophilic attack at C-3 took place instead of reduction, *e.g.*, the reaction of nitro ketone **4** with lithium in propylamine afforded products of nucleophilic ring cleavage (compound **7**) and addition to the 3-carbonyl group (compound **6**). There was



SCHEME 2

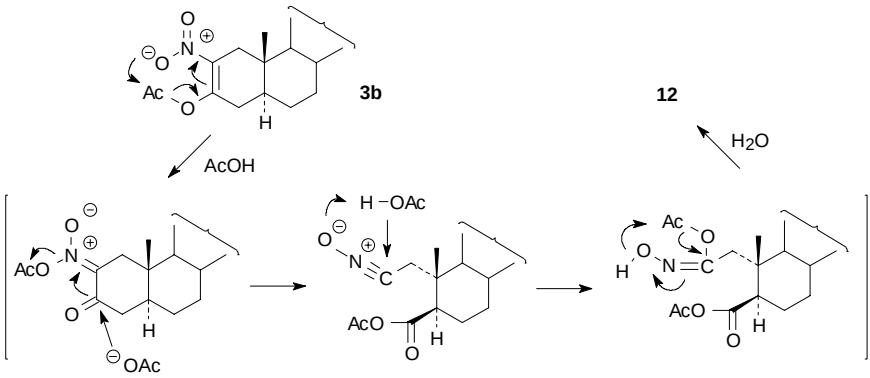
no noticeable difference in reactivity between nitro enol **3a** and nitro ketone **4** in all reactions studied so far. Next to try was reduction with zinc in acetic acid. It was reported that the reduction of 2-nitro-5α-cholest-2-ene gave 5α-cholestan-2-one[2]. Similarly, compound **2** when reduced with zinc, afforded 2-oxo derivative **8**. The reduction of nitro enol **3a** unexpectedly resulted in the formation of dimer **9** in 51% yield (Scheme 2). In further experiments zinc was replaced by iron but the yield of dimer **9** dropped down to 11%. The reduction of nitro ketone **4** with zinc proceeded in a similar way. However, when crude **4** was used (containing about 10% of its 4α-nitro isomer) in addition to **9**, an isomeric dimer **10** was obtained. The isomeric dimer **10** was formed by cross-condensation of 2-amino and 4-amino 3-ketones. The above two-step method for the synthesis of symmetrical bis-steroidal pyrazines from steroidal 3-ketones (*via* 2-nitro enols) seems to be superior to the known procedures. A preliminary study was undertaken to adjust the method to the synthesis of unsymmetrical bis-steroidal pyrazines (most of natural bis-steroidal pyrazines fit this category). The condensation of intermediate α-amino ketones takes place during the work-up of the reaction mixtures. When the reduction of nitro enol **3a** with zinc was directly followed by formylation, the product was **11b**. This compound seems to be the interesting candidate for the unsymmetrical couplings with suitable 2-amino partners containing protected 3-oxo group. Nitro enol acetate **3b** was also subjected to zinc reduction (Scheme 3). Unexpectedly,



SCHEME 3

the product appeared to be 2,3-seco derivative **12**. It was checked that the same product was obtained upon dissolving **3b** in acetic acid without addition of zinc. A tentative reaction mechanism is shown in the Scheme 4. The nucleophilic cleavage of ring A led to the nitrile oxide formation. 1,3-Dipolar addition of acetic acid to this reactive intermediate followed by Chapman rearrangement afforded *O*-acetylhydroxamic acid **12**. Similar reactions of nitrile oxides with carboxylic acids were reported earlier[12].

Although the synthesis of cephalostatin and some other natural bis-steroidal pyrazine dimers has already been accomplished[13], further synthetic studies in this field are required to improve the yields and to obtain analogues of higher cytotoxicity.



SCHEME 4

EXPERIMENTAL

Melting points were determined on a Kofler apparatus of the Boëtius type and were uncorrected. NMR spectra were taken with a Bruker AC 200F spectrometer (200 MHz for ^{1}H and 50.3 MHz for ^{13}C) using $CDCl_3$ solutions with TMS as an internal standard. Chemical shifts are given in ppm (δ-scale), coupling constants (*J*) and half-width of multiplets (*w*/2) in Hz. Infrared spectra (wavenumbers in cm^{-1}), were recorded on a Nicolet series II Magna-IR 550 FT-IR spectrometer for chloroform solutions unless stated otherwise. Electron impacts mass spectra were obtained at 70 eV with an AMD-604 spectrometer. The reaction products were isolated by column chromatography performed on 70–230 mesh silica gel (J. T. Baker). 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.

3β-Acetylamino-2α-nitro-5α-cholestane (**5**)

To a solution of 3-acetylamino-2-nitro-5α-cholest-2-ene (**2**; 100 mg; 0.4 mmol) in methanol (15 ml) sodium borohydride (30 mg; 0.8 mmol) was added. The reaction mixture was stirred at room temperature for 4 h, poured into water and extracted with chloroform. The extract was dried over magnesium sulfate and evaporated *in vacuo*. The crude product was purified by column chromatography on silica gel. The title compound (71.4 mg; 70%) was eluted with hexane–ethyl acetate (80 : 20), m.p. 190–193 °C (hexane). IR spectrum: 3 450, 3 331, 1 679, 1 555, 1 511, 1 373. ^{1}H NMR spectrum: 6.06 broad d, *J* = 8.4, 1 H (NH); 4.76 td, *J* = 12.1, 4.1, 1 H (2β-H); 4.23 m, *w*/2 = 31, 1 H (3α-H); 2.27 dd, *J* = 12.3, 4.1, 1 H (1β-H); 1.93 s, 3 H (Ac); 0.88 s, 3 H (3 × 19-H); 0.64 s, 3 H (3 × 18-H). ^{13}C NMR spectrum: 169.8 (C), 86.4 (CH), 56.2 (CH), 53.7 (CH), 52.1(CH), 44.8 (CH), 42.8 (CH_2), 42.5 (C), 39.6 (CH_2), 39.5 (CH_2), 36.9 (C), 36.1 (CH_2), 35.7 (CH), 35.0 (CH), 33.4 (CH_2), 31.5 (CH_2), 28.2 (CH_2), 28.0 (CH), 27.6 (CH_2), 24.1 (CH_2), 23.8 (CH_2), 23.4 (CH_3), 22.8 (CH_3), 22.5

(CH_3), 21.2 (CH_2), 18.6 (CH_3), 12.8 (CH_3), 12.0 (CH_3). EI-MS, *m/z* (%): 474 (M^+, 16), 459 (2.5), 426 (69), 415 (12), 367 (100). For $C_{29}H_{50}N_2O_3$: calculated: 474.3821; found: 474.3840.

2-Nitro-3-propylamino-5α-cholest-2-ene (**6**) and *N*-Propyl-2-nitro-2,3-seco-5α-cholestan-3-oic acid amide (**7**)

To the solution of 2α-nitro-5α-cholestan-3-one (**4**; 80 mg; 0.19 mmol) in propylamine (15 ml), lithium (2 mg; 0.29 mmol) was added. The reaction mixture was stirred at room temperature for 3 h, quenched by pouring into water and extracted with chloroform. The solvent was removed *in vacuo* from dried ($MgSO_4$) extract and the crude product was chromatographed on silica gel column. Hexane–ethyl acetate (88 : 12) mixture eluted compound **6** (6.2 mg; 7%). Further elution with hexane–ethyl acetate (80 : 20) afforded compound **7** (55.6 mg, 62%).

Compound **6**, m.p. 127–131 °C (hexane). IR spectrum: 3 300, 1 655, 1 597, 1 364, 1 125. ^{1}H NMR spectrum: 11.26 broad t, *J* = 5.1, 1 H (NH); 3.34 m, 2 H (CH_2NH); 2.89 d, *J* = 16.2, 1 H (1β-H); 2.43 dd, *J* = 4.9, 18.1, 1 H (4α-H); 2.12 d, *J* = 16.2, 1 H (1α-H); 1.03 t, *J* = 7.7, 3 H (propyl CH_3); 0.74 s, 3 H (3 × 19-H); 0.67 s, 3 H (18-H). ^{13}C NMR spectrum: 158.2 (C), 118.0 (C), 56.2 (2 × CH), 53.6 (CH), 44.9 (CH_2), 42.5 (C), 40.2 (CH), 40.0 (CH_2), 39.7 (2 × CH_2), 39.5 (CH_2), 36.2 (CH_2), 35.8 (CH), 35.2 (CH), 34.5 (C), 31.3 (CH_2), 31.2 (CH_2), 28.2 (CH_2), 28.0 (CH), 24.2 (CH_2), 23.8 (CH_2), 22.9 (CH_2), 22.8 (CH_3), 22.5 (CH_3), 21.1 (CH_2), 18.7 (CH_3), 12.0 (CH_3), 11.9 (CH_3), 11.4 (CH_3). EI-MS, *m/z* (%): 472 (M^+, 46), 456 (8), 437 (32), 426 (19), 412 (9).

Compound **7**, m.p. 150–152 °C (hexane–dichloromethane). IR spectrum: 3 449, 3 350, 1 662, 1 552, 1 515. ^{1}H NMR spectrum: 5.72 broad t, *J* = 5.25, 1 H (NH); 4.59 m, 1 H (2-H); 4.31 m, 1 H (2-H); 3.21 m, 2 H (C**H**$_2$NH); 0.82 s, 3 H (3 × 19-H); 0.64 s, 3 H (3 × 18-H). ^{13}C NMR spectrum: 172.3 (C), 71.2 (CH_2), 56.4 (CH), 56.1 (CH), 48.0 (CH), 42.2 (C), 41.3 (CH_2), 40.0 (CH), 39.7 (CH_2), 39.5 (CH_2), 38.3 (C), 38.2 (CH_2), 36.1 (CH_2), 35.7 (CH), 35.1 (CH), 33.8 (CH_2), 31.3 (CH_2), 28.1 (CH_2), 28.0 (CH and CH_2), 24.1 (CH_2), 23.8 (CH_2), 22.80 (CH_2), 22.77 (CH_3), 22.5 (CH_3), 21.4 (CH_2), 18.6 (CH_3), 16.1 (CH_3), 11.9 (CH_3), 11.3 (CH_3). EI-MS, *m/z* (%): 456 (M, 4), 279 (13), 167 (34), 149 (100). For $C_{30}H_{54}N_2O_3$ (490.8) calculated: 73.42% C, 11.09% H, 5.71% N; found: 73.19% C, 11.30% H, 5.76% N.

3β-Acetylamino-5α-cholestan-2-one (**8**)

To the solution of 3-acetylamino-2-nitro-5α-cholest-2-ene (**2**; 130 mg; 0.28 mmol) in acetic acid (15 ml), zinc powder (250 mg) was added. The reaction mixture was stirred at room temperature for 16 h, poured into water, neutralized with aqueous sodium hydroxide to pH 5–6 and extracted with chloroform. The solvent was removed *in vacuo* from the dried ($MgSO_4$) extract. The crude product was purified on silica gel column. Compound **8** (66.3 mg; 54%) was eluted with hexane–ethyl acetate (65 : 35), m.p. 147–150 °C (hexane–dichloromethane). IR spectrum: 3 414, 1 713, 1 664, 1 506. ^{1}H NMR spectrum: 6.5 broad d, *J* = 6.1, 1 H (NH); 4.47 m, *w*/2 = 24, 1 H (3α-H); 2.49 d, *J* = 12.5, 1 H (1β-H); 2.09 d, *J* = 12.5, 1 H (1α-H); 2.00 s, 3 H (Ac); 0.72 s, 3 H (3 × 18-H); 0.63 s, 3 H (3 × 19-H). ^{13}C NMR spectrum: 207.9 (C), 169.8 (C), 57.9 (CH), 56.1(CH), 53.9 (CH), 52.8 (CH_2), 44.3 (CH), 42.5 (C), 42.2 (C), 39.6 (CH_2), 39.5 (CH_2), 37.3 (CH_2), 36.1 (CH_2), 35.7 (CH), 34.8 (CH), 31.5 (CH_2), 28.2 (CH_2), 27.9 (2 × CH), 27.2 (CH_2), 24.1 (CH_2), 23.8 (CH_2), 23.2 (CH_3), 22.8 (CH_3), 22.5 (CH_3), 21.2 (CH_2), 18.6 (CH_3), 12.5 (CH_3), 12.0 (CH_3). EI-MS, *m/z*: 443 (M^+, 100), 428 (26), 425 (36), 401 (57), 384 (42), 371 (22). For $C_{29}H_{49}NO_2$ calculated: 443.3763; found: 443.3750.

Pyrazino[2′,3′:2,3;5′,6′:2,3]bis(5α-cholestane) (**9**) and Pyrazino[2′,3′:2,3;5′,6′:4,3]bis(5α-cholestane) (**10**)

a) To a solution of 2-nitro-5α-cholest-2-en-3-ol (**3a**; 153 mg; 0.35 mmol) in acetic acid (15 ml), zinc powder (250 mg) was added. The reaction mixture was stirred at room temperature for 16 h,

poured into water, neutralized with aqueous sodium hydroxide to pH 5–6, chloroform (several ml) was then added and the mixture was stirred vigorously for 15 min. The product was extracted with chloroform, the extract was dried ($MgSO_4$) and evaporated under reduced pressure. Pure **9** (68 mg; 51%) was obtained by silica gel column chromatography, elution with benzene–ethyl acetate (96 : 4), m.p. 335–338 °C (toluene). IR spectrum (KBr): 1 466, 1 443, 1 396, 1 385. ^{1}H NMR spectrum: 2.96–2.47 m, 8 H (2 × 1-H, 2 × 4 H, 2 × 1′-H, 2 × 4′-H); 2.04 dm, J = 12.4, 2 H (5-H and 5′-H); 0.80 s, 6 H (3 × 19-H and 3 × 19′-H); 0.69 s, 6 H (3 × 18-H and 3 × 18′-H). ^{13}C NMR spectrum: 149.0 (C), 148.5 (C), 56.4 (CH), 56.3 (CH), 53.7 (CH), 46.0 (CH_2), 42.5 (C), 41.8 (CH), 40.0 (CH_2), 39.5 (CH_2), 36.2 (CH_2), 35.8 (CH), 35.61 (CH_2), 35.57 (C), 35.4 (CH), 31.6 (CH_2), 28.5 (CH_2), 28.2 (CH_2), 28.0 (CH), 24.3 (CH_2), 23.9 (CH_2), 22.8 (CH_3), 22.6 (CH_3), 21.3 (CH_2), 18.7 (CH_3), 12.0 (2 × CH_3). EI-MS, *m/z* (%): 764 (M^+, 4), 609 (1.3), 149 (26), 37 (100).

The reduction of 2α-nitro-5α-cholestan-3-one proceeded in a similar way.

b) The above reaction was also carried out using the crude 2α-nitro-5α-cholestan-3-one (**4**) prepared according to Rank procedure[5]. However, careful spectral analysis of this material proved that it contained up to 14% of 4α-nitro isomer. Among the zinc reduction products of impure nitro ketone, in addition to the compound **9**, the less polar isomer **10** was isolated in 7% yield, elution with benzene–ethyl acetate (98 : 2), m.p. 310–313 °C (toluene). IR spectrum (KBr): 1 467, 1 444, 1 396, 1 382. ^{1}H NMR spectrum: 2.94–2.42 m, 8 H (2 × 1-H, 2 × 4-H, 2 × 1′-H, 2 × 2′-H); 0.79 and 0.76 2 × s, 2 × 3 H (3 × 19-H and 3 × 19′-H); 0.70 and 0.69 2 × s, 2 × 3 H (3 × 18-H and 3 × 18′-H). ^{13}C NMR spectrum: 151.2 (C), 148.3 (C), 148.1 (C), 148.0 (C), 56.4 (CH), 56.3 (CH), 56.3 (CH), 53.7 (CH), 53.4 (CH), 50.4 (CH), 45.9 (CH_2), 42.6 (C), 42.5(C), 41.8 (CH), 40.1 (CH_2), 40.0 (CH_2), 39.5 (2 × CH_2), 36.2 (2 × CH_2), 35.8 (2 × C), 35.7 (CH), 35.6 (CH_2), 35.4 (CH), 35.2 (CH), 34.1 (CH_2), 31.7 (CH_2), 31.5 (CH_2), 28.5 (CH_2), 28.3 (CH_2), 28.2 (CH_2), 28.1 (CH_2), 28.0 (4 × CH), 24.2 (CH_2), 24.2 (CH_2), 23.8 (2 × CH_2), 22.8 (CH_2), 22.8 (2 × CH_3), 22.5 (2 × CH_3), 21.4 (CH_2), 21.2 (CH_2), 18.7 (2 × CH_3), 12.6 (CH_3), 12.2 (CH_3), 12.0 (CH_3), 11.9 (CH_3). EI-MS, *m/z* (%): 530 (13), 515 (6), 279 (12), 149 (76). FD-MS, *m/z*: 764 (M^+). LSI-MS, 765 (MH^+).

2α-Formylamino-5α-cholestan-3-one (**11b**)

To a solution of 2-nitro-5α-cholest-2-en-3-ol (**3a**; 90 mg; 0.21 mmol) in 15 ml of acetic acid, zinc powder (250 mg) was added. After reduction (16 h), excess zinc and its salt was filtered off and formic–acetic anhydride (20 ml, prepared from 15 ml of acetic anhydride and 7.6 ml of 86% formic acid) was added. The reaction mixture was stirred at room temperature for 45 min. Then the reaction mixture was carefully poured to an aqueous solution of sodium hydroxide and stirred for about 15 min. The product was extracted with chloroform, dried over magnesium sulfate and the solvent was evaporated. Crystallization from hexane afforded **11b** (30 mg; 34%), m.p. 164–167 °C (hexane). IR spectrum: 3 404, 2 868, 1 718, 1 682. ^{1}H NMR spectrum: 8.20 s, 1 H, (HC=O); 6.47 bd, J = 6.0, 1 H (NH); 4.68 m, 1 H (2β-H); 2.66 dd, J = 12.5, 6.3, 1 H (1β-H); 2.47 t, J = 13.6, 1 H (4β-H); 2.24 dd, J = 13.6, 3.5, 1 H (4α-H); 1.18 s, 3 H (3 × 19-H); 0.67 s, 3 H (3 × 18-H). ^{13}C NMR spectrum: 207.0 (C), 160.5 (CH), 56.2 (CH), 56.1 (CH), 54.0 (CH), 53.8 (CH), 48.9 (CH), 47.2 (CH_2), 43.8 (CH_2), 42.6 (C), 39.8 (CH_2), 39.5 (CH_2), 37.0 (C), 36.1 (CH_2), 35.7 (CH), 34.8 (CH), 31.7 (CH_2), 28.7 (CH_2), 28.2 (CH_2), 28.0 (CH), 24.2 (CH_2), 23.8 (CH_2), 22.8 (CH_3), 22.5 (CH_3), 21.7 (CH_2), 18.6 (CH_3), 12.5 (CH_3), 12.0 (CH_3). EI-MS, *m/z* (%): 429 (M^+, 100), 414 (85), 401 (29), 384 (21), 274 (34).

N-Acetoxy-2,3-seco-5α-cholestane-2,3-dioic acid 2-amide (**12**)

2-Nitro-5α-cholest-2-en-3-yl acetate (**3b**; 66 mg; 0.14 mmol) was dissolved in 10 ml of acetic acid, stirred with zinc (16 h) and worked up as described above. The crude product was chromatographed on silica gel column. The title compound **12** (41.1 mg; 66%) was eluted with hexane–ethyl acetate

(50 : 50), m.p. 132–133 °C (ethyl acetate–hexane). IR spectrum (KBr): 3 197, 1 788, 1 698, 1 184. ^{1}H NMR spectrum: 9.50 s, 2 H (OH and NH); 2.63 d, J = 13.6, 1 H (1β-H); 2.02 s, 3 H (Ac); 0.82 s, 3 H (3 × 19-H); 0.66 s, 3 H (3 × 18-H). ^{13}C NMR spectrum: 178.9 (C), 169.0 (C), 168.6 (C), 56.2 (CH), 56.1 (CH), 48.1 (CH), 42.2 (C), 40.5 (CH), 40.2 (C), 39.6 (CH_2), 39.4 (2 × CH_2), 36.9 (CH_2), 36.1 (CH_2), 35.7 (CH), 35.5 (CH), 30.9 (CH_2), 28.7 (CH_2), 28.2 (CH_2), 27.9 (CH), 24.1 (CH_2), 23.8 (CH_2), 22.7 (CH_3), 22.5 (CH_3), 22.2 (CH_2), 18.6 (CH_3), 18.1 (CH_3), 15.4 (CH_3), 12.0 (CH_3). EI-MS, *m/z* (%): 473 (8), 431 (8), 414 (35), 387 (100), 232 (92). LSI-MS, *m/z*: 492 (MH^+). For $C_{29}H_{49}NO_5$ (491.7) calculated: 70.84% C, 10.04% H, 2.85% N; found: 70.58% C, 10.09% H, 2.76% N.

Compound **12** was also formed in the reaction when no zinc was added.

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