Oxidation of Azasteroid Lactams and Alcohols with Benzeneseleninic Anhydride[1]

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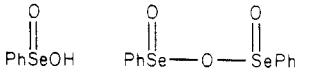
Reaction of 4-azasteroid δ-lactams **6**, **9**, **10** and **12** with benzeneseleninic anhydride (**2**) in diglyme at 120 °C smoothly effects dehydrogenation to the corresponding Δ^1 derivatives **13–16**. Oxidation of 3-aza-*A*-homo-4a-cholesten-4-one (**17**) or its saturated analogue **18** with **2** proceeds readily in refluxing benzene and affords the corresponding imides **19** and **21** and α-phenylseleno imides **20** and **22**. Treatment of 2-aza-5α-cholestan-3-one (**29a**), prepared by a new efficient route, with **2** results in both dehydrogenation and imide formation and requires forcing conditions. The different relative propensities of the substrates toward reaction via these two pathways are attributed to conformational effects in a seleninamide intermediate. Azasteroid alcohols **7** and **8** are cleanly converted to the corresponding ketones **37** and **38** with **2** under mild conditions.

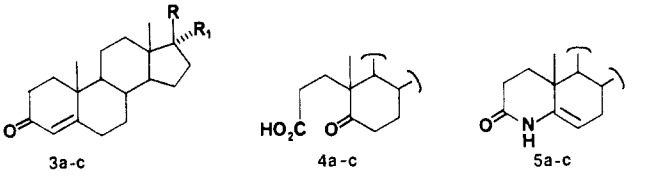
The chemical and biological properties of heterocyclic steroids have made them the subjects of much scrutiny and the targets of numerous synthetic efforts.[2] Among such compounds, the azasteroids have been the most widely studied as their diverse physiological activity makes their preparation and modification of special relevance.[2,3] These considerations, as well as the continuing interest in this laboratory in the reactions of nitrogenous substrates with benzeneseleninic acid (**1**) and anhydride (**2**),[4] prompted the present investigation of the oxidation of a number of azasteroid lactams with **2**.



1 **2**

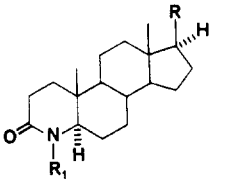
The preparation of several required 4-azasteroid lactams was accomplished according to literature methods. Thus, 4-cholesten-3-one (**3a**), progesterone (**3b**), and 4-androstene-3,17-dione (**3c**) were converted to the corresponding enamidic azasteroids **5a–c**[3c,5] (Chart I) via seco acids **4a–c**.[3c,6] Formic acid reduction of **5a** then afforded 4-aza-5α-cholestan-3-one (**6**)[7] while catalytic hydrogenation of **5b** and **5c** furnished 4-aza-20-hydroxy-5α-pregnan-3-one (**7**) and 4-aza-17-hydroxy-5α-androstan-3-one (**8**), respectively.[8] Acetylation of the latter azasteroid with acetic anhydride–pyridine provided acetate **9** while similar treatment of compound **7** gave acetate **10** or a mixture of **10** and its *N*-acetyl derivative **11**. Finally, N-benzoylation of **6** with benzoyl chloride and 4-(dimethylamino)pyridine (DMAP) produced **12**.

Chart I



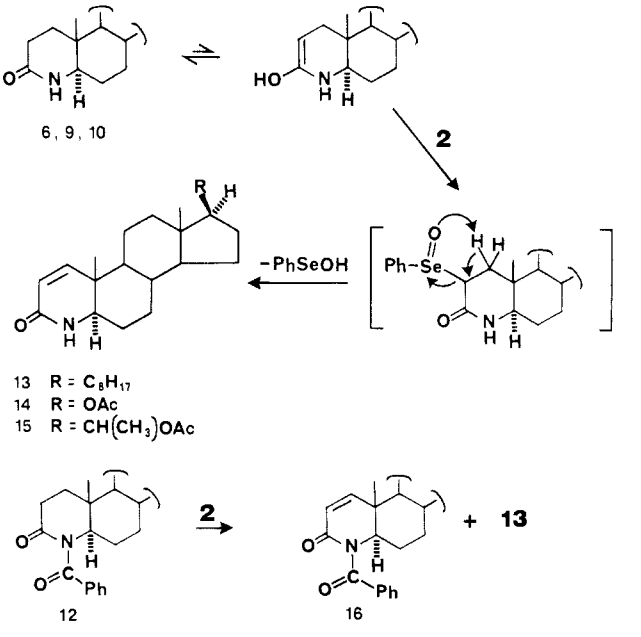
3a-c 4a-c 5a-c

a R = C_8H_{17}, R_1 = H
b R = Ac, R_1 = H
c R, R_1 = O



6 R = C_8H_{17}, R_1 = H
7 R = $CH(CH_3)OH$, R_1 = H
8 R = OH, R_1 = H
9 R = OAc, R_1 = H
10 R = $CH(CH_3)OAc$, R_1 = H
11 R = $CH(CH_3)OAc$, R_1 = Ac
12 R = C_8H_{17}, R_1 = COC_6H_5

Scheme I



6, 9, 10 2 -PhSeOH

13 R = C_8H_{17}
14 R = OAc
15 R = $CH(CH_3)OAc$

12 2 16 + 13

Azasteroids **6**, **9**, and **10** were oxidized with anhydride **2** in diglyme at 120°. Smooth dehydrogenation to afford the novel Δ^1-azasteroids[9] **13–15** in yields of 88%, 64% and

(1) Financial support from the Natural Sciences and Engineering Research Council is gratefully acknowledged.

(2) (a) H. O. Huisman in "MTP International Review of Science: Organic Chemistry, Series 1", Vol. 8, D. H. Hey and W. F. Johns, Eds., Butterworths, London, 1973, Chapter 9; (b) H. O. Huisman and W. N. Speckamp, *ibid.*, Series 2, Vol. 8, 1976, Chapter 8.

(3) See inter alia: (a) H. Singh, T. R. Bhardwaj, N. K. Ahuja, and D. Paul, *J. Chem. Soc., Perkin Trans. 1*, 305 (1979). (b) V. A. Rulin, V. F. Shner, L. I. Lisitsa, A. I. Terekhina, and N. N. Suvorov, *Zh. Org. Khim.*, **11**, 1763 (1975); (c) W. E. Solomons and N. J. Doorenbos, *J. Pharm. Sci.*, **63**, 19 (1974); (d) N. J. Doorenbos and W. E. Solomons, *ibid.*, **62**, 638 (1973); (e) N. J. Doorenbos, J. Scott, and S. S. Vaidya, *ibid.*, **60**, 1236 (1971).

(4) (a) T. G. Back and S. Collins, *Tetrahedron Lett.*, 2213 (1980); (b) *ibid.*, 2661 (1979); (c) T. G. Back and N. Ibrahim, *ibid.*, 4931 (1979); (d) T. G. Back, *J. Chem. Soc., Chem. Commun.*, 278 (1978).

(5) N. J. Doorenbos, C. L. Huang, C. R. Tamorria, and M. T. Wu, *J. Org. Chem.*, **26**, 2546 (1961).

(6) J. T. Edward, D. Holder, W. H. Lunn, and I. Puskas, *Can. J. Chem.*, **39**, 599 (1961).

(7) N. J. Doorenbos and W. E. Solomons, *Chem. Ind. (London)*, 1322 (1970).

(8) Catalytic hydrogenation of **5a** also gives chiefly the 5α isomer **6**.[3c] The same stereochemistry is assumed in **7** and **8** by analogy.

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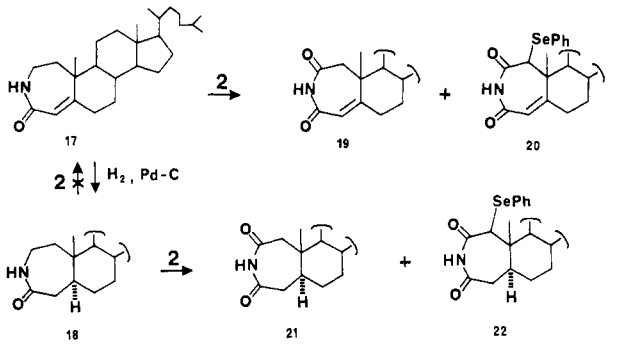
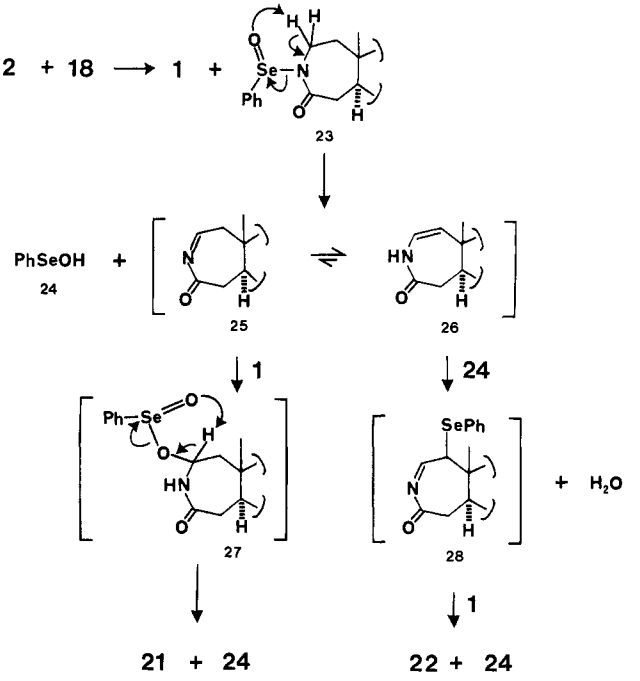
Scheme II



Scheme III



56%, respectively, was observed (Scheme I). Less forcing conditions gave recovered starting material. A lower yield of 50% of 4-aza-5α-cholest-1-en-3-one (13) was obtained with benzeneseleninic acid (1) as oxidant. Similarly, *N*-benzoyl-4-aza-5α-cholestan-3-one (12) reacted with 2 to give the corresponding Δ^1-azasteroid 16 (35%) as well as its debenzoylated derivative 13 (29%).

A plausible mechanism for the dehydrogenation is shown in Scheme I and involves seleninylation of the enolized lactam with 2, followed by a selenoxide elimination.[10] The enolization of azasteroid 6 under such conditions is confirmed by the observation that it incorporates deuterium into the 2-position when heated in diglyme containing deuterium oxide and benzoic acid as catalyst. The role of the catalyst may be played by benzeneseleninic acid (1) or anhydride (2) in the dehydrogenation process itself. Related dehydrogenations of steroidal ketones[11] and of a steroidal lactone[12] have also been reported recently.

It was reasonable to assume that dehydrogenation of acyclic amides could also be performed with 2. Thus, hydrocinnamamide and its *N*-methyl and *N,N*-dimethyl derivatives were oxidized in the usual manner. Surprisingly, the corresponding cinnamamides were not formed despite the conjugation of the expected double bond with the aromatic ring. Only starting material or complex mixtures of unidentified products were obtained. These results suggested that the conformational environment in the vicinity of the lactam moiety in azasteroids might be critical in determining the course of the reaction. For a test of this hypothesis, the oxidations of several different normal and homo-A-ring azasteroids were investigated.

Beckmann rearrangement of 4-cholesten-3-one tosyloxime afforded 3-aza-*A*-homo-4a-cholesten-4-one (17),[13] in turn reduced to 3-aza-*A*-homo-5α-cholestan-4-one (18) by catalytic hydrogenation.[14] Azasteroids 17 and 18 reacted with 2 under considerably milder conditions than those required for the oxidation of δ-lactams 6, 9, and 10. When 17 was refluxed 1.5 h with anhydride 2 in benzene solution, imide 19 and its α-phenylseleno derivative 20 were obtained in yields of 58% and 36%, respectively. Addition of triethylamine to the reaction mixture provided an enhanced yield of 19 (80%). Similarly, oxidation of the saturated azasteroid 18 with 2 afforded the analogous imide 21 and α-phenylseleno imide 22 in 65% and 24% yield. Dehydrogenation of 18 was not observed. These transformations are shown in Scheme II.

The striking difference in the behavior of δ-lactams 6, 9, 10, and 12, and ε-lactams 17 and 18 requires explanation. Scheme III displays a proposed mechanism for the oxidation of 18. The 1,2-elimination of seleninamide 23 generates N-acyl imine 25 and benzeneselenenic acid (24).[15] Reaction of intermediate 25 with seleninic acid 1 (or its conjugate base) produces seleninic ester 27 which fragments via a second elimination to form imide 21 and a second mole of selenenic acid 24. The latter process is analogous to the oxidation of certain alcohols with 2 (vide infra). Furthermore, formation of the enamide tautomer 26 from *N*-acyl imine 25 should be facile because of resonance stabilization derived from delocalization of the nitrogen lone pair in the former species. Selenenylation of 26 with selenenic acid 24 (or by a related intermediate derived from its disproportionation)[16] then leads to *N*-acyl imine 28, which is converted to the product α-phenylseleno imide 22 by a process analogous to the transformation of 25 to imide 21. Similar considerations apply to the oxidation of azasteroid 17.

It is evident that product formation via Scheme III depends on the successful five-center elimination in seleninamide 23. If, as is likely, this process resembles the syn elimination of selenoxides,[10] then it will proceed most readily when the molecule is capable of adopting a conformation which brings one of the hydrogens at C-2 into close proximity with the seleninamide oxygen and which permits coplanarity of the five participating centers in the transition state. A further constraint stems from the loss of stabilization if the required conformation disrupts the amide resonance through torsion of the amide linkage. Examination of models reveals that a suitable conformation can be achieved without difficulty in seleninamides derived from 3-aza-*A*-homo steroids such as 17 and 18. On

(9) The transformation of 6 to 13 was reported in a preliminary communication.[4d]

(10) Selenoxide eliminations have been reviewed: (a) H. J. Reich, *Acc. Chem. Res.*, 12, 22 (1979); (b) D. L. J. Clive, *Tetrahedron*, 34, 1049 (1978); (c) K. B. Sharpless, K. M. Gordon, R. F. Lauer, D. W. Patrick, S. P. Singer, and M. W. Young, *Chem. Scr.*, 8A, 9 (1975).

(11) D. H. R. Barton, D. J. Lester, and S. V. Ley, *J. Chem. Soc., Chem. Commun.*, 130 (1978).

(12) D. H. R. Barton, R. A. H. F. Hui, D. J. Lester, and S. V. Ley, *Tetrahedron Lett.*, 3331 (1979).

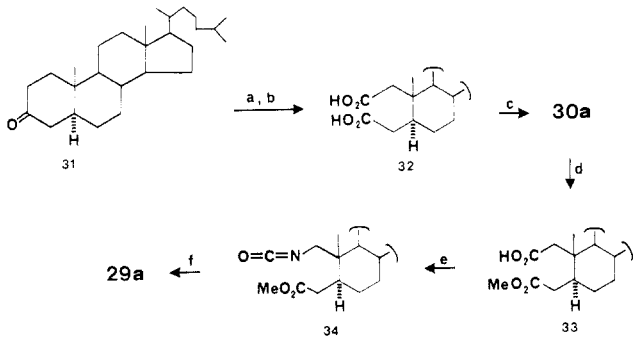
(13) K. Oka and S. Hara, *J. Org. Chem.*, 43, 3790 (1978).

(14) C. W. Shoppee, G. Krüger, and R. N. Mirrington, *J. Chem. Soc.*, 1050 (1962).

(15) A similar process presumably accounts for the oxidation of amines to imines by 2. M. R. Czarny, *J. Chem. Soc., Chem. Commun.*, 81 (1976).

(16) (a) H. J. Reich, S. Wollowitz, J. E. Trend, F. Chow, and D. F. Wendelborn, *J. Org. Chem.*, 43, 1697 (1978); (b) T. Hori and K. B. Sharpless, *ibid.*, 43, 1689 (1978).

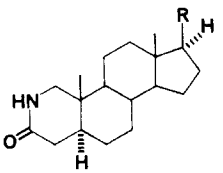
Scheme IV[a]



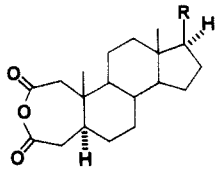
[a] (a) PhCHO-KOH, (b) $KMnO_4$-$NaIO_4$, (c) DCC, (d) MeONa-MeOH, (e) DPPA-Et_3N, (f) H_2O-DMF.

the other hand, seleninamide formation from 4-azasteroids **6**, **9**, and **10** is expected to be nonproductive as the 5α-hydrogen can only be brought into the required position for elimination at the expense of disrupted amide resonance and the introduction of severe strain and steric interactions. Thus, *N*-acyl imine formation is blocked[17] and such substrates must react *via* the alternate pathway leading to dehydrogenation. Seleninamides of 4-azasteroids are expected to be hydrolytically labile, and so it is not surprising that they were not isolated (after workup) when the oxidations were attempted at lower temperatures.

It was also of interest to study the oxidation of a δ-lactam azasteroid in which imide formation and dehydrogenation could compete. A new synthesis of 2-aza-5α-cholestan-3-one (**29a**) was developed for this purpose



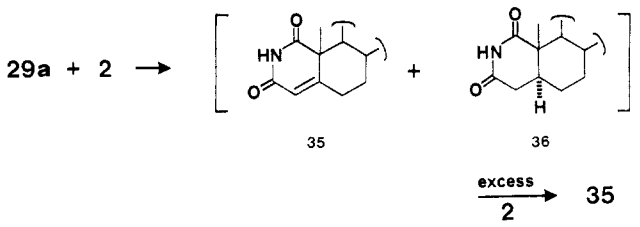
29a R = C_8H_{17}
29b R = H



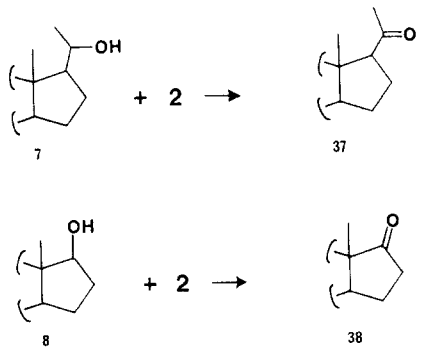
30a R = C_8H_{17}
30b R = H

and is shown in Scheme IV. This compound has been reported in the patent literature[18] and as a component in the inseparable mixture of isomers formed by Schmidt or Beckmann rearrangements of *A*-nor-5α-cholestan-2-one.[19] The related 2-azaandrostane derivative **29b** has been prepared by Jones and co-workers[20] from the cyclic anhydride **30b** in 40% overall yield *via* a six-step sequence. Their synthesis employed a regiospecific ring-opening of anhydride **30b** at C-4 by ammonia as the key step. In the present synthesis, anhydride **30a** was procured through a variation of a literature procedure[20] and was converted to the desired azasteroid **29a** in a new three-step sequence in 73% overall yield. Methanolysis of anhydride **30a** occurred regiospecifically at C-4. The ring-opened product **33** was treated with diphenylphosphoryl azide (DPPA)–triethylamine in refluxing toluene to effect a Curtius rearrangement.[21] Finally, the resulting isocyanate **34** was converted without purification to azasteroid **29a** by refluxing in wet *N*,*N*-dimethylformamide (DMF).

Scheme V



Scheme VI



The oxidation of azasteroid **29a** with **2** (Scheme V) required heating in diglyme at 120 °C. When excess oxidant and long reaction times were employed, the dehydrogenated imide **35** was obtained in 53% yield. Shorter reaction times and less oxidant provided an inseparable mixture of **35** and, presumably, the saturated imide **36**. Starting material was also detected. It is therefore evident that imide formation is more sluggish in the relatively rigid δ-lactam **29a** than in ε-lactams **17** and **18** and so cannot be performed without accompanying dehydrogenation.

Two azasteroid alcohols were also oxidized with anhydride **2**; 4-aza-20-hydroxy-5α-pregnan-3-one (**7**) and 4-aza-17-hydroxy-5α-androstan-3-one (**8**) reacted smoothly with **2** in refluxing tetrahydrofuran (THF) to afford the corresponding ketones **37** and **38** in excellent yields of 94% and 86%, respectively (Scheme VI). These results indicate that anhydride **2** is a useful oxidant for the important transformation of alcohols to ketones under exceptionally mild conditions.[22]

Experimental Section

Melting points were determined on an A. H. Thomas hot-stage apparatus or in sealed capillaries on a Gallenkamp block. IR and UV spectra were recorded on Perkin-Elmer 467 and Cary 15 spectrometers, respectively. NMR spectra were obtained on a Hitachi Perkin-Elmer R24B instrument (^1H, 60 MHz) or on a Varian XL-200 spectrometer (^1H, 200 MHz). Carbon-13 NMR spectra were recorded on the latter instrument; only those signals further downfield than $CDCl_3$ are reported. All NMR spectra were taken in $CDCl_3$ solution and are reported in parts per million downfield from tetramethylsilane as internal standard. Mass spectra were obtained on a Varian MAT CH5 spectrometer. Optical rotations were measured on a Perkin-Elmer 241 automatic polarimeter in a 10-cm cell or on a JASCO ORD-UV5 apparatus in a 1-cm cell. Elemental analyses were performed by Mr. H. Séguin (National Research Council of Canada) or by Guelph Chemical Laboratories. Preparative TLC employed Analtech 20

(17) If *N*-acyl imine formation did occur, products other than imides would form, as the ring-fusion position at C-5 cannot be the site for carbonyl formation. Products could arise from oxidation of the corresponding enamide tautomer.[4c]

(18) Z. Tuba and M. Bor, German Offen. 2130280, Dec. 23, 1971; *Chem. Abstr.*, **76**, 72717 (1972).

(19) N. J. Doorenbos and R. E. Havranek, *J. Org. Chem.*, **30**, 2474 (1965).

(20) E. R. H. Jones, G. D. Meakins, and K. Z. Tuba, *J. Chem. Soc. C.*, 1597 (1969).

(21) M. Fieser and L. F. Fieser in "Reagents for Organic Synthesis", Vol. 5, Wiley-Interscience, New York, 1975, p 280.

(22) The oxidation of a number of other alcohols with **2** was observed independently by D. H. R. Barton and co-workers. The results of the Imperial College group and those described herein were reported jointly in a preliminary communication: D. H. R. Barton, A. G. Brewster, R. A. H. F. Hui, D. J. Lester, S. V. Ley, and T. G. Back, *J. Chem. Soc., Chem. Commun.*, 952 (1978).

× 20 cm glass plates (silica gel GF, 1000 μm). Solvents were reagent grade; benzene and toluene were dried over molecular sieves, and THF and diglyme were freshly distilled from $LiAlH_4$, the latter under reduced pressure. Progesterone and 4-cholesten-3-one were obtained from the Aldrich Chemical Co. while 5α-cholestan-3-one and 4-androstene-3,17-dione were purchased from Sigma Biochemicals and Steraloids Inc., respectively. Benzeneseleninic acid and anhydride were obtained from the Aldrich Chemical Co. or prepared by a literature procedure.[23] All other reagents were commercially available or obtained by standard methods and purified as necessary. **Caution**: Selenium compounds are toxic and should be handled with care.

5-Oxo-3,5-seco-4-norcholestan-3-oic Acid (4a). The title compound was prepared by the method of Edward et al.[6]

5,20-Dioxo-3,5-seco-4-norpregnan-3-oic Acid (4b). The title compound was prepared from progesterone (**3b**) in 60% yield [mp 171–174 °C (lit.[24] mp 174.5–176.5 °C)] by the preceding procedure.

4-Aza-5-cholesten-3-one (5a) and 4-Aza-5-pregnene-3,20-dione (5b). The title compounds were prepared from seco acids **4a** and **4b** by the method of Doorenbos et al.[5]

4-Aza-5-androstene-3,17-dione (5c). The title compound was prepared from **3c** by the method of Solomons and Doorenbos.[3c]

4-Aza-5α-cholestan-3-one (6). Reduction of **5a** to **6** was accomplished by the method of Doorenbos and Solomons.[7]

4-Aza-20-hydroxy-5α-pregnan-3-one (7). Enamide **5b** (0.50 g, 1.59 mmol) was hydrogenated 5 days at 1 atm in 100 mL of 10% acetic acid–methanol containing 200 mg of PtO. The solution was filtered through Celite, evaporated, and recrystallized (methanol–ether) to give 0.38 g (75%) of compound **7**: mp 323–325 °C dec (sealed capillary); $[\alpha]_D$ +25° (*c* 0.5, $CHCl_3$); IR (Nujol) 3360, 3280, 3220, 1660 cm^{-1}. Anal. Calcd for $C_{20}H_{33}NO_2$: C, 75.17; H, 10.42; N, 4.39. Found: C, 75.03; H, 10.28; N, 4.29.

4-Aza-17-hydroxy-5α-androstan-3-one (8). Enamide **5c** was hydrogenated as in the preceding procedure to afford **8** in 63% yield (mp 251–255 °C) which was characterized as the acetate derivative **9**.

17-Acetoxy-4-aza-5α-androstan-3-one (9). Compound **8** (70 mg, 0.24 mmol) was stirred 13 h in 1 mL of pyridine and 0.5 mL of acetic anhydride. Volatile material was removed under vacuum, and the residue was recrystallized (dichloromethane–ether) to afford 71 mg (89%) of **9**: mp 265–266 °C; $[\alpha]_D$ +20° (*c* 0.5, $CHCl_3$); IR ($CHCl_3$) 3390, 1722, 1655 cm^{-1}. Anal. Calcd for $C_{20}H_{31}NO_3$: C, 72.02; H, 9.38; N, 4.20. Found: C, 72.01; H, 9.53; N, 4.39.

20-Acetoxy-4-aza-5α-pregnan-3-one (10) and *N*-Acetyl-20-acetoxy-4-aza-5α-pregnan-3-one (11). Compound **7** (143 mg, 0.45 mmol) was heated 9 h at 60 °C in 2 mL of 10% acetic anhydride–pyridine. Removal of volatile material in vacuo, preparative TLC of the residue in 5% methanol–chloroform, and recrystallization from dichloromethane–hexane provided 134 mg (83%) of **10**: mp 293–294 °C (sealed capillary); $[\alpha]_D$ +50° (*c* 0.5, $CHCl_3$); IR ($CHCl_3$) 3400, 1721, 1655 cm^{-1}. Anal. Calcd for $C_{22}H_{35}NO_3$: C, 73.07; H, 9.76; N, 3.88. Found: C, 72.87; H, 9.58; N, 3.79.

The procedure was repeated with 49 mg (0.16 mmol) of **7** for 20 h at 60 °C in 13% acetic anhydride–pyridine to afford 20 mg (36%) of **10** and 31 mg (50%) of **11**: mp 137–139 °C; $[\alpha]_D$ −40° (*c* 0.4, $CHCl_3$); IR ($CHCl_3$) 1720, 1675 cm^{-1}. Anal. Calcd for $C_{24}H_{37}NO_4$: C, 71.41; H, 9.25; N, 3.47. Found: C, 71.53; H, 9.35; N, 3.49.

***N*-Benzoyl-4-aza-5α-cholestan-3-one (12).** Azasteroid **6** (89 mg, 0.23 mmol), benzoyl chloride (42 mg, 0.30 mmol), and DMAP (37 mg, 0.30 mmol) were refluxed 9 h in 1 mL of toluene. The solution was diluted with 10 mL of chloroform, washed with water (2 × 5 mL), dried over anhydrous $MgSO_4$, and crystallized from methanol to give 99 mg (88%) of **12**: mp 167–169 °C; $[\alpha]_D$ +16° (*c* 1.4, $CHCl_3$); IR (Nujol) 1690 cm^{-1}. Anal. Calcd for $C_{33}H_{49}NO_2$: C, 80.59; H, 10.05; N, 2.85. Found: C, 80.66; H, 10.20; N, 2.98.

4-Aza-5α-cholest-1-en-3-one (13). Azasteroid **6** (41 mg, 0.11 mmol) and **2** (50 mg, 0.14 mmol) were heated 14 h in 5 mL of diglyme at 120 °C. The solvent was removed in vacuo and the residue separated by preparative TLC in 5% methanol–chloroform to furnish 36 mg (88%) of **13**: mp 234–235 °C (from dichloromethane–hexane); $[\alpha]_D$ −5° (*c* 0.8, $CHCl_3$); IR ($CHCl_3$) 3390, 1667, 1600 cm^{-1}; λ_{max} (MeOH) 242 nm (ε 1500); ^1H NMR (60 MHz) 6.82 (d, *J* = 10 Hz, 1 H), 5.82 (br s, exchanged, superimposed on d, *J* = 10 Hz, 2 H total), 3.3 (m, 1 H), 2.3–0.6 (complex, s at 0.97, 0.90, 0.80, and 0.68, 39 H total); ^{13}C NMR 166.6, 151.2, 122.9; mass spectrum, *m/e* 385 (M^+). Anal. Calcd for $C_{26}H_{43}NO$: C, 80.98; H, 11.24; N, 3.63. Found: C, 80.78; H, 11.07; N, 3.49.

The reaction was repeated with 40 mg (0.103 mmol) of **6** and 40 mg (0.21 mmol) of seleninic acid **1** to give 20 mg (50%) of **13** and 9 mg (23%) of recovered **6**.

17-Acetoxy-4-aza-5α-androst-1-en-3-one (14). Azasteroid **9** (33 mg, 0.10 mmol) and **2** (50 mg, 0.14 mmol) were heated 23 h at 120 °C in 2 mL of diglyme. Workup as for **13** afforded 21 mg (64%) of **14**: mp 232–234 °C (from dichloromethane–ether); $[\alpha]_D$ −27° (*c* 0.5, $CHCl_3$); IR ($CHCl_3$) 3410, 1722, 1670, 1600 cm^{-1}; λ_{max} (MeOH) 243 nm (ε 1020); ^1H NMR (60 MHz) 6.82 (d, *J* = 10 Hz, 1 H), 5.87 (br s, exchanged, superimposed on d, *J* = 10 Hz, 2 H total), 4.7 (m, 1 H), 3.4 (m, 1 H), 2.6–0.6 (complex, s at 2.07, 0.98, and 0.80, 24 H total); mass spectrum, *m/e* 331 (M^+). Anal. Calcd for $C_{20}H_{29}NO_3$: C, 72.45; H, 8.82; N, 4.23. Found: C, 72.25; H, 8.92; N, 4.17.

20-Acetoxy-4-aza-5α-pregn-1-en-3-one (15). Azasteroid **10** (36 mg, 0.10 mmol) and **2** (45 mg, 0.125 mmol) were heated 16 h at 120 °C in 1 mL of diglyme. Workup as for **13** afforded 20 mg (56%) of **15**: mp 274–276 °C (from dichloromethane–ether); $[\alpha]_D$ +13° (*c* 0.8, $CHCl_3$); IR ($CHCl_3$) 3410, 1720, 1669, 1599 cm^{-1}; λ_{max} (MeOH) 240 nm (ε 1100); ^1H NMR (60 MHz) 6.82 (d, *J* = 9 Hz, 1 H), 5.82 (br s, exchanged, superimposed on d, *J* = 9 Hz, 2 H total), 4.85 (m, 1 H), 2.6–0.6 (complex, s at 2.07, 1.21, 1.11, 0.98, and 0.67, 28 H total); mass spectrum, *m/e* 359 (M^+). Anal. Calcd for $C_{22}H_{33}NO_3$: C, 73.48; H, 9.26; N, 3.90. Found: C, 73.18; H, 9.14; N, 3.79.

***N*-Benzoyl-4-aza-5α-cholest-1-en-3-one (16).** Azasteroid **12** (49 mg, 0.10 mmol) and **2** (50 mg, 0.14 mmol) were heated 3 h at 120 °C in 2 mL of diglyme. After removal of the solvent under reduced pressure, preparative TLC of the residue in 10% methanol–benzene gave 11 mg (29%) of **13** and 17 mg (35%) of **16**: mp 123–125 °C (from methanol); $[\alpha]_D$ +36° (*c* 1.0, $CHCl_3$); IR (Nujol) 1690, 1628, 1600, 1581 cm^{-1}; ^1H NMR (60 MHz) 8.0–7.3 (complex, 5 H), 7.02 (d, *J* = 10 Hz, 1 H), 5.82 (d, *J* = 10 Hz, 1 H), 3.8 (m, 1 H), 2.4–0.7 (complex, s at 1.26, 0.93, 0.84, and 0.72, 39 H total); mass spectrum, *m/e* 489 (M^+). Anal. Calcd for $C_{33}H_{47}NO_2$: C, 80.92; H, 9.68; N, 2.86. Found: C, 81.11; H, 9.47; N, 3.05.

D_2O Exchange at C-2 of Azasteroid 6. Azasteroid **6** (13 mg) and benzoic acid (6 mg) in 0.5 mL of diglyme and 0.2 mL of D_2O were heated 28 h in a sealed glass tube at 120 °C. The solution was cooled and diluted with water, and the precipitated solid was filtered. After the solid was thoroughly washed with 5% $NaHCO_3$ solution followed by water and drying under vacuum, 13 mg (100% recovery) of product was obtained. Mass spectral and NMR analyses indicated that D exchange at C-2 was almost complete. When benzoic acid was omitted in a separate experiment, exchange did not take place.

3-Aza-*A*-homo-4a-cholesten-4-one (17). The title compound was prepared from **3a** by the method of Oka and Hara.[13]

3-Aza-*A*-homo-5α-cholestan-4-one (18). The title compound was prepared from **17** by the method of Shoppee et al.[14]

Oxidation of Azasteroid 17 with 2. Azasteroid **17** (121 mg, 0.30 mmol) and **2** (115 mg, 0.32 mmol) were refluxed 1.5 h in 10 mL of benzene. The solvent was evaporated in vacuo, and preparative TLC of the resulting residue in 40% ethyl acetate–hexane furnished 72 mg (58%) of 3-aza-*A*-homo-4a-cholestene-2,4-dione (**19**): mp 180–182 °C (from dichloromethane–methanol); $[\alpha]_D$ +107° (*c* 2, $CHCl_3$); IR ($CHCl_3$) 3375, 1700 (sh), 1665, 1610 cm^{-1}; ^1H NMR (200 MHz) 8.34 (br s, exchanged, 1 H), 5.91 (s, 1 H), 2.92 (d, *J* = 13 Hz, 1 H), 2.67 (d, *J* = 13 Hz, 1 H), 2.4 (m, 2 H), 2.1–0.7 (complex, s at 1.17, 0.92, 0.88, 0.85, and 0.71, 37 H total); ^{13}C NMR 171.1, 168.0, 165.5, 119.6; mass spectrum, *m/e* 413 (M^+). Anal. Calcd for $C_{27}H_{43}NO_2$: C, 78.38; H, 10.49; N, 3.39. Found: C, 78.55; H, 10.75; N, 3.32.

A more mobile band gave 62 mg (36%) of 1-(phenylseleno)-3-aza-*A*-homo-4a-cholestene-2,4-dione (**20**): mp 167–168 °C (from dichloromethane–methanol); $[\alpha]_D$ +157° (*c* 3.4, $CHCl_3$); IR ($CHCl_3$) 3375, 1665, 1607, 1580 cm^{-1}; ^1H NMR (200 MHz) 7.85 (br s, exchanged, 1 H), 7.6 (m, 2 H), 7.3 (m, 3 H), 5.95 (s, 1 H), 3.86

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(s, 1 H), 2.45 (m, 2 H), 2.2–0.7 (complex, s at 1.29, 0.92, 0.89, 0.86, and 0.70, 37 H total); ^{13}C NMR 171.5, 164.3, 163.6, 134.8 (2 C), 129.5 (2 C), 129.2, 128.7, 120.7; mass spectrum, m/e 569 (M^+,^{80}Se), 567 (M^+,^{78}Se). Anal. Calcd for $C_{33}H_{47}NO_2Se$: C, 69.68; H, 8.34; N, 2.47. Found: C, 70.18; H, 8.66; N, 2.58.

Azasteroid **17** (57 mg, 0.14 mmol), **2** (54 mg, 0.15 mmol), and triethylamine (50 mg, 0.50 mmol) were refluxed 1 h in 5 mL of benzene. Workup as before gave 47 mg (80%) of **19** and 13 mg (16%) of **20**.

Oxidation of Azasteroid 18 with 2. Azasteroid **18** (100 mg, 0.25 mmol) and **2** (90 mg, 0.25 mmol) were refluxed 2 h in 5 mL of benzene and worked up as in the preceding experiment to afford 68 mg (65%) of 3-aza-*A*-homo-5α-cholestane-2,4-dione (**21**):[25] mp 236–240 °C (from chloroform–methanol); $[\alpha]_D$ +137° (*c* 1.7, $CHCl_3$); IR (Nujol) 3210, 3100, 1698, 1660 cm^{-1}; ^1H NMR (200 MHz) 7.65 (br s, exchanged, 1 H), 2.8 (m, 2 H), 2.4 (m, 2 H), 2.1–0.6 (complex, s at 0.91, 0.905, 0.88, 0.85, and 0.66, 40 H total); ^{13}C NMR 175.8, 172.5; mass spectrum, m/e 415 (M^+). Anal. Calcd for $C_{27}H_{45}NO_2$: C, 78.00; H, 10.92; N, 3.37. Found: C, 78.13; H, 11.22; N, 3.45.

A more mobile band gave 34 mg (24%) of 1-(phenylseleno)-3-aza-*A*-homo-5α-cholestane-2,4-dione (**22**): mp 147–148 °C (from chloroform–methanol); $[\alpha]_D$ +53° (*c* 1.7, $CHCl_3$); IR ($CHCl_3$) 3365, 1685 cm^{-1}; ^1H NMR (200 MHz) 7.6 (m, 2 H), 7.55 (br s, exchanged, 1 H), 7.3 (m, 3 H), 4.18 (s, 1 H), 2.7 (m, 2 H), 2.2–0.6 (complex, s at 1.11, 0.91, 0.88, 0.85, and 0.64, 40 H total); ^{13}C NMR 172.5, 172.2, 135.5 (2 C), 129.4 (2 C), 129.0, 128.0; mass spectrum, m/e 571 (M^+, ^{80}Se), 569 (M^+, ^{78}Se). Anal. Calcd for $C_{33}H_{49}NO_2Se$: C, 69.43; H, 8.66; N, 2.46. Found: C, 69.02; H, 8.93; N, 2.33.

3-Oxa-*A*-homo-5α-cholestane-2,4-dione (30a). The title compound was obtained by a variation of the procedure of Jones et al.[20] 5α-Cholestan-3-one (**31**; 5.00 g, 12.9 mmol), KOH (1.00 g, 18.0 mmol), and 10 mL of freshly distilled benzaldehyde were refluxed 2 h in 100 mL of methanol under nitrogen. Cooling crystallized 5.90 g (96%) of 2-benzylidene-5α-cholestan-3-one, mp 145–147 °C (lit.[20] mp 146–147 °C).

The above benzylidene derivative (5.61 g, 11.8 mmol) was oxidized with potassium permanganate–sodium metaperiodate via the general procedure described by Edward et al.[6] to afford 3.85 g (75%) of diacid **32**, mp 195–198 °C (from ether–hexane) (lit.[20] mp 197–198 °C).

Diacid **31** was converted to **30a** by the method of Jones et al.[20]

2-Aza-5α-cholestan-3-one (29a). Anhydride **30a** (617 mg, 1.48 mmol) and sodium methoxide (162 mg, 3.00 mmol) were dissolved in 5 mL of methanol. After 22 h, the solvent was removed in vacuo, and the residue was triturated with 10 mL of water, acidified with concentrated HCl, and extracted with chloroform (4 × 5 mL). The organic extracts were combined, dried over anhydrous $MgSO_4$, and evaporated to dryness to afford the crude methyl ester **33**, used directly without further purification.

Ester **33**, prepared above, DPPA (454 mg, 1.65 mmol), and triethylamine (167 mg, 1.65 mmol) were refluxed 1 h in 15 mL of toluene. An aliquot was evaporated in vacuo and showed a new IR band at 2275 cm^{-1} (N=C=O). The toluene solution was washed with 5% Na_2CO_3 solution (2 × 5 mL) and evaporated to dryness, and the residue was refluxed 21 h in 15 mL of 5% water–DMF. Water (5 mL) was added, and **29a** crystallized upon cooling of the mixture. Recrystallization from acetone and then methanol gave 420 mg (73%) of product: mp 210–213 °C; $[\alpha]_D$ +45° (*c* 1.9, $CHCl_3$); IR ($CHCl_3$) 3410, 1650 cm^{-1}; ^1H NMR (200 MHz) 5.90 (br s, exchanged, 1 H), 3.13 (d, J = 12 Hz, 1 H), 2.95 (d, J = 12 Hz, 1 H), 2.4–0.6 (complex, s at 0.93, 0.92, 0.88, 0.85, and 0.67, 42 H total); mass spectrum, m/e 387 (M^+). Anal. Calcd for $C_{26}H_{45}NO$: C, 80.54; H, 11.71; N, 3.62. Found: C, 80.06; H, 11.87; N, 3.43.

2-Aza-4-cholestene-1,3-dione (35). Azasteroid **29a** (45 mg, 0.12 mmol) and **2** (100 mg, 0.28 mmol) were heated 21 h in 0.7 mL of diglyme at 120 °C. The solvent was removed in vacuo, and the residue was separated by preparative TLC in 10% methanol–benzene to provide 24 mg (53%) of **35**: mp 245–248 °C (from chloroform–ethanol); $[\alpha]_D$ −125° (*c* 1.2, $CHCl_3$); IR ($CHCl_3$) 3375, 1695, 1633 cm^{-1}; ^1H NMR (200 MHz) 8.00 (br s, exchanged, 1 H), 5.90 (s, 1 H), 2.4 (m, 2 H), 2.1–0.7 (complex, s at 1.45, 0.91, 0.88, 0.84, and 0.72, 37 H total); ^{13}C NMR 175.7, 167.7, 164.3, 114.0; mass spectrum, m/e 399 (M^+). Anal. Calcd for $C_{26}H_{41}NO_2$: C, 78.13; H, 10.35; N, 3.51. Found: C, 77.79; H, 10.42; N, 3.67.

The oxidation was repeated with 72 mg (0.19 mmol) of **29a** and 90 mg (0.25 mmol) of **2** at 120 °C in 1.5 mL of diglyme. After 12 h, TLC still detected starting material **29a**; the product was isolated as before, giving 28 mg of a mixture of **35** and a component with NMR signals at 7.76 (br s, exchanged) and 0.69 (s) ppm, formed in a ratio of ca. 1:2 (NMR integration). A mixture of both compounds also resulted when a stoichiometric amount of **2** was employed.

4-Aza-5α-pregnane-3,20-dione (37). Azasteroid **7** (32 mg, 0.10 mmol) and **2** (40 mg, 0.11 mmol) were refluxed 16 h in 3 mL of THF. After removal of the solvent, preparative TLC in 5% methanol–chloroform afforded 30 mg (94%) of **37**: mp 263–266 °C (from acetone–ether); $[\alpha]_D$ +98° (*c* 0.1, $CHCl_3$); IR ($CHCl_3$) 3390, 1700, 1655 cm^{-1}; ^1H NMR (60 MHz) 5.93 (br s, exchanged, 1 H), 3.1 (m, 1 H), 2.9–0.6 (complex, s at 2.15, 0.90, and 0.61, 29 H total); mass spectrum, m/e 317 (M^+). Anal. Calcd for $C_{20}H_{31}NO_2$: C, 75.65; H, 9.85; N, 4.42. Found: C, 75.36; H, 10.11; N, 4.60.

4-Aza-5α-androstane-3,17-dione (38). Azasteroid **8** (29 mg, 0.10 mmol) was oxidized as for **7**, giving 25 mg (86%) of **38**, mp 296–298 °C dec (sealed capillary; from acetone–ether); $[\alpha]_D$ +103° (*c* 0.4, $CHCl_3$); IR ($CHCl_3$) 3400, 1732, 1657 cm^{-1}; ^1H NMR (60 MHz) 6.30 (br s, exchanged, 1 H), 3.1 (m, 1 H), 2.7–0.6 (complex, s at 0.93 and 0.86, 25 H total); mass spectrum, m/e 289 (M^+). Anal. Calcd for $C_{18}H_{27}NO_2$: C, 74.68; H, 9.41; N, 4.84. Found: C, 74.73; H, 9.46; N, 4.78.

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