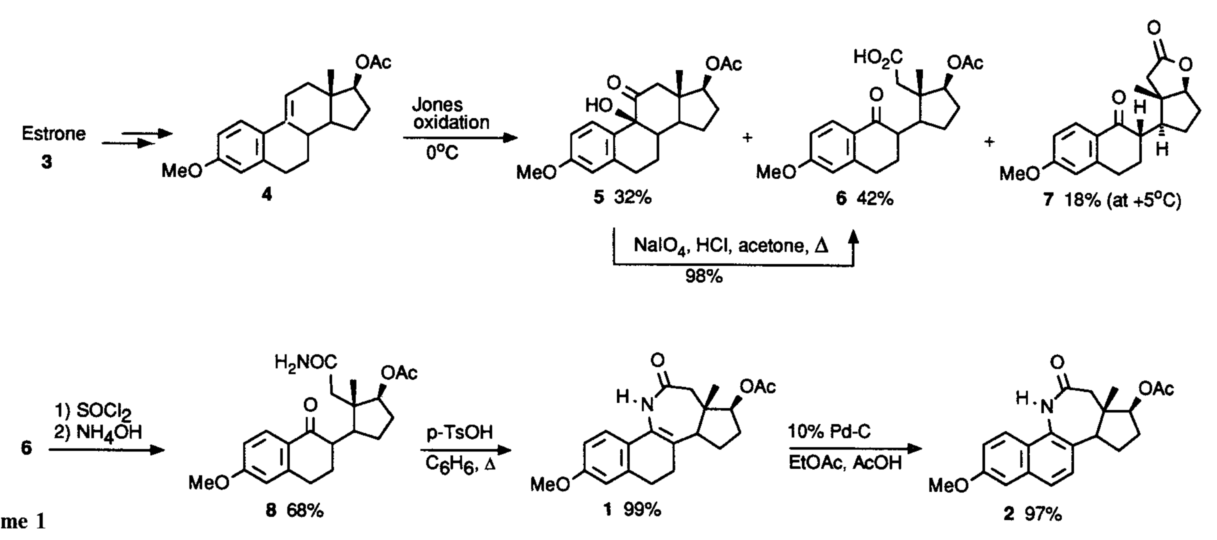
A Convenient Synthesis of 11-Aza-C-homoestranes

Thomas G. Back,* Joseph H.-L. Chau, Masood Parvez
Department of Chemistry, University of Calgary, Calgary, Alberta, Canada, T2N 1N4

Received 21 June 1994

17β-Acetoxy-3-methoxy-11-aza-C-homoestra-1,3,5(10),8(9)-tetraen-12-one (**1**) and 17β-acetoxy-3-methoxy-11-aza-C-homoestra-1,3,5(10),6,8(9)-pentaen-12-one (**2**) were prepared from estrone.

Azasteroids are of substantial current interest because of their biological and medicinal properties.[1] As part of our ongoing work in this area,[2] we required a convenient source of 11-aza-C-homoestranes **1** and **2**. While several types of 11-azasteroids are known,[3] only a few 11-azaestranes have been reported to date,[4,5] including a recent synthesis of **1** via a Schmidt rearrangement.[5] We now report a convenient preparation of lactams **1** and **2** (Scheme 1), and note that the properties of **1** obtained by this route differ substantially from those reported previously for this compound.[5] In view of these discrepancies, the structure of **1** prepared via Scheme 1 was confirmed unequivocally by both spectroscopic methods and X-ray crystallography (Figure 1).



Scheme 1

Estrone (**3**) was converted into the 9 (11) dehydrogenated derivative **4** by literature procedures.[6,7] The product was subjected to a Jones oxidation[7] to afford the 9β-ol **5** and the seco acid **6** as the principal products. Further oxidation of **5** with sodium metaperiodate produced **6** nearly quantitatively, thereby permitting the conversion of **4** into **6** in a total yield of 73 %. When the temperature was permitted to rise above 0 °C during the Jones oxidation, the lactone **7** was also produced at the expense of **6**. The amide **8** was obtained from seco acid **6** by ammoniolysis of its acyl chloride, and cyclized under acid-catalyzed conditions to afford **1**. Dehydrogenation of the latter with palladium–charcoal[8] provided the equilenin analogue **2**. This route therefore provides simple and convenient access, with unambiguous regiochemistry, to the title compounds.

Melting points were obtained on an A. H. Thomas hot-stage apparatus and are uncorrected. IR spectra were recorded on a Mattson 4030 instrument. ^{1}H NMR spectra were obtained with either a Bruker ACE 200 or an AM 400 spectrometer, and ^{13}C NMR spectra were recorded on the latter instrument. Mass spectra were obtained on a Kratos MS 80 or VG 7070 instrument with the assistance of Drs. R. Yamdagni and Q. Wu, and Ms. D. Fox. Elemental analyses were carried out by Ms. D. Fox, and satisfactory results were obtained for all compounds: C ± 0.26; H ± 0.13; N (**1** and **8** only) ± 0.08. Compound **2** was not analyzed. Chromatography was performed with silica gel as the adsorbent. Estrone was purchased from the Sigma Co. All reagents were commercially available and were used without further purification.

The X-ray crystal structure of **1** ($C_{21}H_{25}NO_4$) was determined at 23 °C on a Rigaku AFC6S diffractometer with graphite monochromated Mo–Kα radiation, using the ω-2Θ scan technique to a maximum 2Θ value of 70.2°. A total of 3495 unique reflections were collected on a crystal with dimensions of 0.30 × 0.40 × 0.50 mm, with space group $P2_12_12$(#18), and cell constants corresponding to a primitive orthorhombic cell with dimensions: $a = 12.784(1)$ Å, $b = 17.745(3)$ Å, $c = 8.040(1)$ Å, $V = 1823.9(3)$ Å^3, and a calculated density of 1.29 g/cm^3. The structure was solved by direct methods

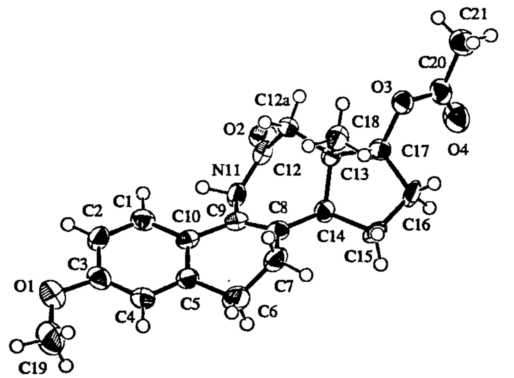


Figure 1: ORTEP Diagram of **1** with selected bond lengths (Å) and bond angles: N(11)-C(9) 1.444(7); N(11)-C(12) 1.376(7); O(2)-C(12) 1.219(7); C(8)-C(9) 1.334(8); C(8)-C(14) 1.492(8); C(7)-C(8) 1.486(8); C(9)-C(10) 1.470(9); N(11)-C(9)-C(8) 121.3(7)°; N(11)-C(9)-C(10) 116.0(6)°; C(8)-C(9)-C(10) 122.6(7)°; N(11)-C(12)-C(12a) 117.4(6)°; O(2)-C(12)-N(11) 119.5(7)°; O(2)-C(12)-C(12a) 123.0(7)°.

and refined by full-matrix least-squares calculations with non-hydrogen atoms anisotropic thermal parameters to conventional $R = 0.058$, $wR = 0.030$ for 1283 observed reflections ($I > 2.0\sigma I$). The ORTEP diagram of **1** is shown in Figure 1, along with selected bond lengths and bond angles.[9]

17β-Acetoxy-3-methoxy-9-oxo-9,11-seco-1,3,5(10)-estratrien-11-oic Acid (6):
Compound **4** was subjected to Jones oxidation by the method of Cambie[7] to afford **5** (32 %) and **6** (42 %) with properties as reported. The 9-ol **5** (477 mg, 1.33 mmol) was oxidized with sodium metaperiodate (1 mL of a sat. aq solution) in acetone (10 mL) containing 10 % HCl (0.25 mL) at reflux for 8 h. The mixture was then poured into EtOAc (25 mL) and washed several times with 25 mL portions of 10 % HCl, aq $NaHCO_3$, and NaCl, dried ($MgSO_4$) and evaporated to give 486 mg (98 %) of **6**, which was identical to the previous sample. When the temperature was allowed to rise to ca. 5 °C during the early stages of the Jones oxidation of **4**, the lactone **7** was obtained in 18 % yield by flash chromatography of the crude reaction mixture (elution with $CHCl_3$), followed by **5** (44 %) and **6** (23 %) with more polar solvents.

Compound **7**: mp 146–147 °C (from Et_2O).

IR (Nujol): $\nu = 1772, 1672, 1599, 1494, 1259\ cm^{-1}$.

^{1}H NMR (200 MHz): δ = 7.95 (d, $J = 8.8$ Hz, 1 H), 6.84 (dd, $J = 2.6, 8.8$ Hz, 1 H), 6.69 (d, $J = 2.6$ Hz, 1 H), 4.50 (dd, $J = 2.9, 7.2$ Hz, 1 H), 3.87 (s, 3 H), 1.20 (s, 3 H).

MS: m/z (%) = 314 (M$^+$, 10), 286 (6), 255 (5), 176 (100).

17β-Acetoxy-3-methoxy-9-oxo-9,11-seco-1,3,5(10)-estratrien-11-carboxamide (8):
A solution of seco acid **6** (1.50 g, 4.01 mmol) and thionyl chloride (1 mL) in CH_2Cl_2 (60 mL) was stirred for 30 min. Conc. ammonium hydroxide (20 mL) in THF (60 mL) was added and stirring was continued for an additional 30 min. The mixture was concentrated, poured into EtOAc (50 mL) and washed several times with 25 mL portions of 10 % HCl, sat. $NaHCO_3$ and NaCl, dried ($MgSO_4$) and evaporated. The residue was flash chromatographed (elution with 10 % MeOH–EtOAc) to afford 1.01 g (68 %) of **8**; mp 146–148 °C (from $CHCl_3$–MeOH).

IR (Nujol): $\nu = 3427, 1741, 1667, 1599\ cm^{-1}$.

^{1}H NMR (200 MHz): δ = 7.95 (d, $J = 8.7$ Hz, 1 H), 6.81 (dd, $J = 2.5, 8.7$ Hz, 1 H), 6.67 (d, $J = 2.5$ Hz, 1 H), 6.11 (br s, 1 H exchanged with D_2O, NH), 5.32 (br s, 1 H, exchanged with D_2O, NH), 5.15 (dd, $J = 7.2, 8.7$ Hz, 1 H), 3.85 (s, 3 H), 2.97 (m, 2 H), 2.69 (m, 2 H), 2.21 (m, 2 H), 2.06 (s, 3 H), 1.08 (s, 3 H).

MS: m/z (%) = 373 (M$^+$, 14), 356 (4), 313 (10), 255 (56), 176 (100).

17β-Acetoxy-3-methoxy-11-aza-C-homoestra-1,3,5(10),8(9)-tetraen-12-one (1):
Keto amide **8** (557 mg, 1.49 mmol) and *p*-toluenesulfonic acid monohydrate (70 mg, 0.37 mmol) were refluxed in benzene (35 mL) for 4 d, with azeotropic removal of water. The mixture was concentrated, poured into EtOAc (50 mL) and washed several times with 25 mL portions of 10 % HCl, sat. $NaHCO_3$ and NaCl, dried ($MgSO_4$) and evaporated. The residue was flash chromatographed (elution with 50 % EtOAc–hexanes) to afford 430 mg (81 %; 99 % after correction for recovered starting material) of **1**; mp 204–205 °C (from MeOH).

IR (Nujol): $\nu = 3316, 1721, 1660\ cm^{-1}$.

^{1}H NMR (400 MHz; assignments were confirmed by NOE and COSY; correlations with other ^{1}H NMR signals are indicated): δ = 7.15 (m, 1 H, H-1, corr. δ 6.78–6.72), 6.78–6.72 (m, 2 H, H-2 and H-4, corr. δ 7.15), 6.69 (br s, 1 H, exchanged with D_2O, NH), 5.00 (dd, $J = 7.3, 9.3$ Hz, 1 H, H-17, corr. δ 2.54–2.34 and 1.58–1.47), 3.82 (s, 3 H, OMe), 2.98 (dd, $J = 7.1, 12.7$ Hz, 1 H, H-14, corr. δ 1.97–1.83), 2.82–2.73 (m, 2 H, H-6 or H-7, corr. δ 2.54–2.34), 2.59 (dd, $J = 1.9, 13.9$ Hz, collapsed to d, $J = 13.9$ Hz, with D_2O, 1 H, H-12aα, corr. δ 2.21), 2.54–2.34 (m, 3 H, H-16, H-7 and H-6, corr. δ 5.00, 2.82–2.73, 1.82–1.69 and 1.58–1.47), 2.21 (d, $J = 13.9$ Hz, 1 H, enhancement was observed when the peak at δ 0.90 was irradiated in an NOE experiment, H-12aβ, corr. δ 2.59), 2.05 (s, 3 H, OAc), 1.97–1.83 (m, 1 H, H-15, corr. δ 2.98 and 1.58–1.47), 1.82–1.69 (m, 1 H, H-15, corr. δ 2.54–2.34), 1.58–1.47 (m, 1 H, H-16, corr. δ 5.00, 2.54–2.34 and 1.97–1.83), 0.90 (s, 3 H, enhancement was observed when the peak at δ 2.21 was irradiated in an NOE experiment, H-18).

^{13}C NMR (HETCOR with ^{1}H NMR signals are indicated): δ = 174.1 (C=O, lactam), 170.7 (C=O, ester), 159.2 (C-3), 137.6 (C-9), 128.8 (C-5, C-8 or C-10), 125.1 (C-5, C-8 or C-10), 124.4 (C-5, C-8 or C-10), 122.5 (C-1, corr. δ 7.15), 114.2 and 111.1 (C-2 and C-4, corr. δ 6.78–6.72), 78.9 (C-17, corr. δ 5.00), 55.3 (OMe, corr. δ 3.82), 54.5 (C-13), 46.6 (C-14, corr. δ 2.98), 43.7 (C-12a, corr. δ 2.59 and 2.21), 28.1 and 27.9 (C-6 or C-7, and C-16, corr. δ 2.82–2.73, 2.54–2.34 and 1.58–1.47), 25.1 (C-6 or C-7, corr. δ 2.54–2.34), 22.1 (C-15, corr. δ 1.97–1.83 and 1.82–1.69), 21.0 (Ac, corr. δ 2.05), 16.6 (C-18, corr. δ 0.90).

MS: m/z (%) = 355 (M$^+$, 100), 312 (11), 296 (23), 227 (38).

Exact mass calcd for $C_{21}H_{25}NO_4$: 355.1784. Found: 355.1763.

17β-Acetoxy-3-methoxy-11-aza-C-homoestra-1,3,5(10),6,8(9)-pentaen-12-one (2):
The enamide **1** (50.0 mg, 0.141 mmol) and 10 % Pd–C (52.7 mg) were stirred in acetic acid (5 mL) for 4 d. The mixture was filtered through Celite and evaporated. The residue was purified by preparative TLC (EtOAc) to give 48.3 mg (97 %) of **2**: R_f 0.60; mp 253–254 °C (from MeOH).

IR ($CHCl_3$): $\nu = 3315, 1738, 1659, 1238\ cm^{-1}$.

^{1}H NMR (200 MHz): δ = 7.84 (d, $J = 9.2$ Hz, 1 H), 7.66 (d, $J = 8.5$ Hz, 1 H), 7.46 (br s, 1 H, exchanged with D_2O, NH), 7.35 (d, $J = 8.5$ Hz, 1 H), 7.27–7.18 (m, 2 H), 5.15 (dd, $J = 7.4, 9.5$ Hz, 1 H), 3.95 (s, 3 H), 3.32 (dd, $J = 6.8, 12.7$ H, collapsed to d, $J = 12.7$ Hz, with D_2O, 1 H, H-12α), 2.08 (s, 3 H), 0.76 (s, 3 H).

^{13}C NMR: δ = 173.6 (C=O), 170.7 (C=O), 157.8 (C, Ar), 134.3 (C, Ar), 131.8 (C, Ar), 127.0 (C, Ar), 124.7 (CH, Ar), 124.6 (CH, Ar), 122.9 (CH, Ar), 119.7 (CH, Ar), 110.6 (C, Ar), 106.5 (CH, Ar), 80.0 (CH), 55.4 (OMe), 53.2 (C), 45.8 (CH), 42.8 (CH_2), 28.0 (CH_2), 21.8 (CH_2), 21.0 (CH_3), 15.6 (CH_3).

MS m/z (%) = 353 (M$^+$, 100), 310 (24), 212 (37), 199 (43).

Exact mass calc for $C_{21}H_{23}NO_4$: 353.1627. Found: 353.1638.

We would like to thank the Natural Sciences and Engineering Research Council of Canada and Merck Frosst Canada Inc. for financial support.

(1) For examples of biologically active azasteroids, see:
Antibiotic A25822 B: Back, T.G.; Hu, N.-X. *Tetrahedron* **1993**, *49*, 337.
Dolle, R.E.; Allaudeen, H.S.; Kruse, L.I. *J. Med. Chem.* **1990**, *33*, 877.
Chamberlin, J.W.; Chaney, M.O.; Chen, S.; Demarco, P.V.; Jones, N.D.; Occolowitz, J.L. *J. Antibiot.* **1974**, *27*, 992.
5α-Reductase inhibitors: Rasmusson, G.H.; Reynolds, G.F.; Steinberg, N.G.; Walton, E.; Patel, G.F.; Liang, T.; Cascieri, M.A.; Cheung, A.H.; Brooks, J.R.; Berman, C. *J. Med. Chem.* **1986**, *29*, 2298.
Liang, T.; Heiss, C.E.; Cheung, A.H.; Reynolds, G.F.; Rasmusson, G.H. *J. Biol. Chem.* **1984**, *259*, 734.
Frye, S.V.; Haffner, C.D.; Maloney, P.R.; Mook, R.A.; Jr.; Dorsey, G.F., Jr.; Hiner, R.N.; Batchelor, K.W.; Bramson, H.N.; Stuart, J.D.; Schweiker, S.L.; van Arnold, J.; Bickett, D.M.; Moss, M.L.; Tian, G.; Unwalla, R.J.; Lee, F.W.; Tippin, T.K.; James, M.K.; Grizzle, M.K.; Long, J.E.; Schuster, S.V. *J. Med. Chem.* **1993**, *36*, 4313.
Inhibitors of 3β-hydroxy-Δ^5-steroid dehydrogenase/3-keto-Δ^5-steroid isomerase: Brandt, M.; Levy, M.A. *Biochemistry* **1989**, *28*, 140.
Neuromuscular blocking agents: Singh, H.; Bhardwaj, T.R.; Ahuja, N.K.; Paul, D. *J. Chem. Soc., Perkin Trans. 1* **1979**, 305.

Antibacterial agents: Chesnut, R.W.; Durham, N.N.; Brown, R.A.; Mawdsley, E.A.; Berlin, K.D. *Steroids* **1976**, *27*, 525.
Solomons, W.E.; Doorenbos, N.J. *J. Pharm. Sci.* **1974**, *63*, 19.

(2) For lead references, see:
Back, T.G.; Baron, D.L.; Morzycki, J.W. *Heterocycles* **1994**, *38*, 1053.
Back, T.G.; Chau, J.H.-L. *Heterocycles* **1994**, *38*, 159.
Back, T.G.; Chau, J.H.-L.; Codding, P.W.; Gladstone, P.L.; Jones, D.H.; Morzycki, J.W.; Roszak, A.W. *J. Org. Chem.* **1992**, *57*, 4110.
Back, T.G.; Chau, J.H.-L.; Dyck, B.P.; Gladstone, P.L. *Can. J. Chem.* **1991**, *69*, 1482.
Back, T.G.; Brunner, K. *J. Org. Chem.* **1989**, *54*, 1904.

(3) Edwards, O.E.; Douglas, J.L.; Horwell, D.C.; Rank, W.; Sano, T. *Can. J. Chem.* **1992**, *70*, 2405.
Gregoire, P.J.; Mellor, J.M.; Merriman, G.D. *Tetrahedron Lett.* **1991**, *32*, 7099.
Gumulka, M.; Ibrahim, I.H.; Boncza-Tomaszewski, Z.; Engel, C.R. *Can. J. Chem.* **1985**, *63*, 766.
Rastogi, R.C.; Chowdhury, M.N.R.; Engel, C.R. *Steroids* **1973**, *21*, 147.
Engel, C.H.; Rakhit, S. *Can. J. Chem.* **1962**, *40*, 2153.
Kutney, J.P.; Vlattas, I.J. *Steroids* **1964**, *4*, 595.

(4) Nasipuri, D.; Ghosh, S.K. *J. Chem. Soc., Perkin Trans. 1* **1976**, 1889.
Badzanova, Y.P.; Pivnitskii, K.K. *Zh. Obshch. Khim.* **1975**, *45*, 2546; *Chem. Abstr.* **1976**, *84*, 90397.
Ibid. **1971**, *41*, 242; *Chem. Abstr.* **1971**, *75*, 36455.

(5) Dwivedy, I.; Singh, A.K.; Singh, M.M.; Ray, S. *Steroids* **1993**, *58*, 69.

(6) Collins, D.J.; Sjövall, J. *Aust. J. Chem.* **1983**, *36*, 339.

(7) Cambie, R.C.; Carlisle, V.F. *J. Chem. Soc (C)* **1970**, 1706.
Cambie, R.C.; Manning, T.D.R. *J. Chem. Soc (C)* **1968**, 2603.

(8) Rylander, P.N. *Organic Syntheses with Noble Metal Catalysts*; Academic: New York, 1973, pp 1–59.

(9) Complete X-ray data for **1** have been deposited in the Cambridge Crystallographic Data Centre.