A CONVENIENT NEW SYNTHESIS OF 6- AND 7-AZAESTRANE LACTAMS AND THEIR *N*-CHLORO DERIVATIVES

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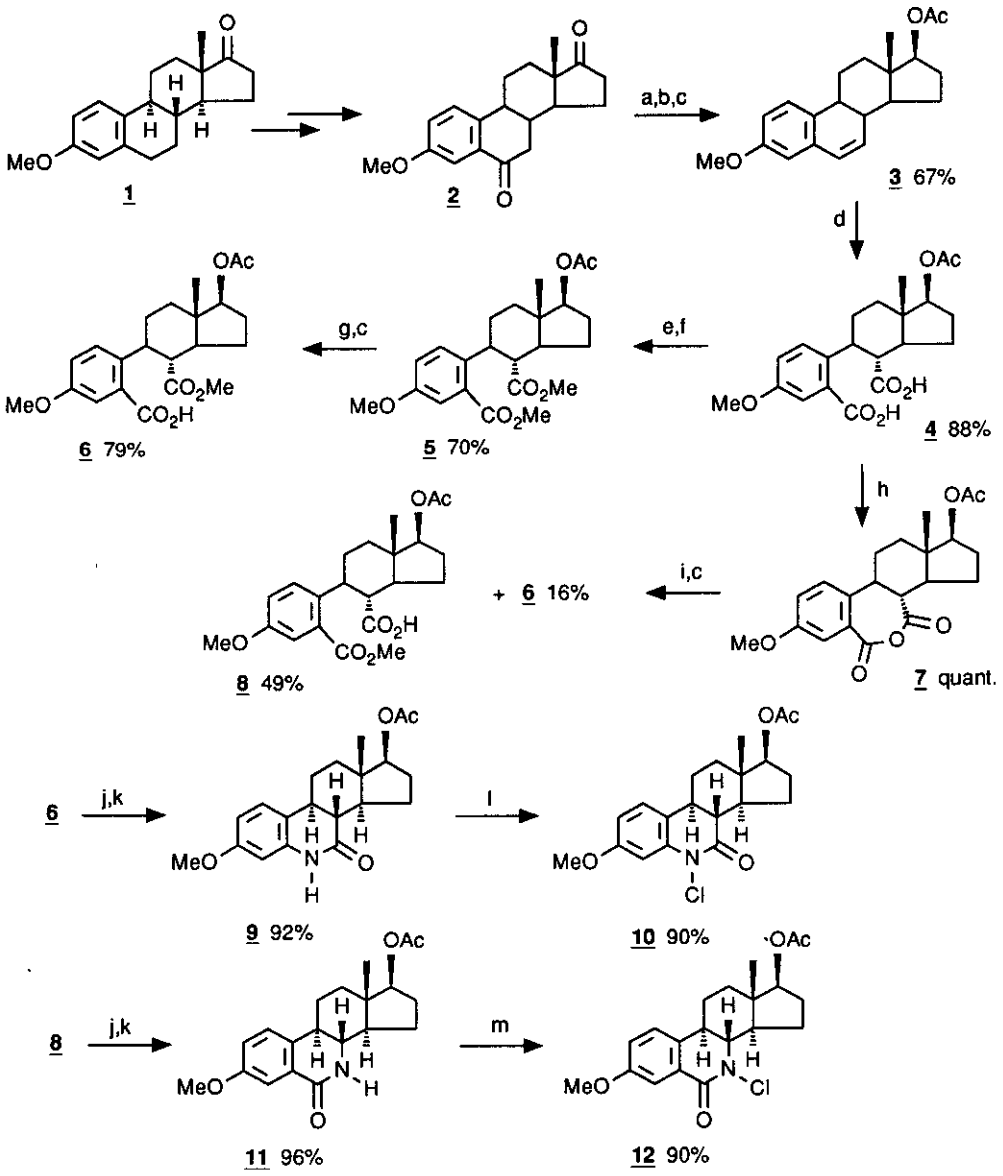
Abstract - 17β-Acetoxy-3-methoxy-6-azaestra-1,3,5(10)-trien-7-one and 17β-acetoxy-3-methoxy-7-azaestra-1,3,5(10)-trien-6-one, and their *N*-chloro derivatives were prepared from 3-methoxyestrone.

Azasteroids display diverse and often useful biological properties[1] that continue to stimulate interest in their preparation. Although many types of azasteroids are known,[2] only a few examples of 6-azaestranes, generally prepared by total synthesis,[3] have been reported to date. Furthermore, we are unaware of any existing 7-azaestranes. As part of our ongoing studies of azasteroids,[4] we now report a facile preparation of both the 6- and 7-azaestrane lactams (9) and (11), respectively, from the key intermediate 6,7-seco-dioic acid (4), in turn readily available from 3-methoxyestrone (1). Moreover, *N*-chloroazasteroids form covalent S-N bonds with free thiol groups,[5] making them of interest as thiophilic affinity labels of receptor proteins and enzymes. We *therefore also report the conversion of lactams (9) and (11) into their corresponding N-chloro derivatives (10)* and (12), respectively.

The results are shown in Scheme 1. 3-Methoxyestrone (1) was first oxidized to the 6-keto derivative (2) by the method of Pearson and Han,[6] followed by reduction to the 6,17-diol with sodium borohydride. The resulting mixture of C-6 epimers underwent selective dehydration to the Δ^6-17β-ol, acetylation of which afforded 3. Oxidative cleavage of the latter with sodium *m*-periodate and potassium permanganate provided the key intermediate 6,7-seco-dioic acid (4), which was then converted into each of the half esters (6) and (8). Selective saponification of the dimethyl ester (5) resulted in preferential cleavage of the 6-methyl ester and

Scheme 1



a) $NaBH_4$, EtOH; b) *p*-TsOH, toluene, Δ; c) Ac_2O, Py; d) $NaIO_4$, $KMnO_4$, acetone; e) $SOCl_2$, $CHCl_3$, Py; f) MeOH; g) NaOH, H_2O, dioxane; h) DCC, ether; i) NaOMe, MeOH; j) DPPA, Et_3N, toluene, Δ; k) Py, H_2O, Δ; l) KO*t*-Bu, NCS, THF; m) TCIA, $CHCl_3$, Δ.

the 17-acetate to afford the 7-methyl ester (6) in good yield after reacetylation of the 17-hydroxyl moiety.[7] On the other hand, methanolysis of the corresponding cyclic anhydride (7) produced chiefly the 6-methyl ester (8).[7] When half ester (6) was subjected to a Curtius rearrangement by treatment with diphenylphosphorylazide (DPPA) and triethylamine,[8] the desired 6-azaestrane (9) was obtained in excellent yield after hydrolysis of the intermediate isocyanate and cyclization. The similar treatment of half ester (8) produced the isomeric 7-aza derivative (11). Lactam (11) was smoothly *N*-chlorinated with trichloroisocyanuric acid (TCIA)[4c] to give 12. Unfortunately, this procedure resulted in competing chlorination of the more electron-rich aromatic ring when applied to lactam (9). However, the *N*-chloro derivative (10) was readily obtained by the use of potassium *t*-butoxide and *N*-chlorosuccinimide (NCS)[4d] instead of TCIA. The method outlined in Scheme 1 therefore provides convenient access to both 6- and 7-azaestrane lactams, as well as their *N*-chloro derivatives.

EXPERIMENTAL SECTION

Melting points were determined on an A. H. Thomas hot-stage apparatus and are uncorrected. Ir spectra were recorded on a Mattson 4030 spectrophotometer, and nmr spectra were obtained on a Bruker ACE 200 or a Bruker AM 400 spectrometer, at 200 and 400 MHz, respectively, in $CDCl_3$ solution with either $CHCl_3$ or TMS as the internal standard. Mass spectra were recorded on a Kratos MS80 or a VG 7070 spectrometer and are reported as: m/z (relative intensity, %). Elemental analyses were performed by Ms. D. Fox at the University of Calgary.

17β-Acetoxy-3-methoxyestra-1,3,5(10),6-tetraene (3)

Diketone (2) (830 mg, 2.78 mmol) and $NaBH_4$ (512 mg, 13.5 mmol) were stirred in 20 ml of ethanol for 20 h, followed by the addition of 10% HCl. The mixture was diluted with ethyl acetate, washed with 10% HCl, saturated $NaHCO_3$ and saturated NaCl solution. The organic phase was dried ($MgSO_4$) and evaporated in vacuo. The crude product was then refluxed in toluene with 103 mg of *p*-TsOH for 5 h with azeotropic removal of water. The cooled mixture was poured into ethyl acetate and washed with saturated $NaHCO_3$ solution, dried ($MgSO_4$) and evaporated. The product was treated with acetic anhydride (2 ml, 20 mmol) and pyridine (8 ml, 100 mmol) for 18 h. The mixture was concentrated in vacuo, diluted with ethyl acetate, washed repeatedly with 10% HCl, then with saturated $NaHCO_3$ and saturated NaCl solution. The organic phase was dried ($MgSO_4$), evaporated and flash chromatographed over silica gel (elution with 10% ethyl

acetate-hexane) to afford 605 mg (67%) of 3,[9] mp 92.5-93°C (from methanol).

17β-Acetoxy-3-methoxy-6,7-secoestra-1,3,5 (10)-triene-6,7-dioic acid (4)

A mixture containing compound (3) (1.076 g, 3.302 mmol) in 75 ml of acetone, 4 ml of 2.5% aqueous $KMnO_4$, and 1.21 g (5.66 mmol) of $NaIO_4$ in 10 ml of water, was stirred vigorously for 4 days. The salmon pink solution was treated with 25% aqueous $NaHSO_3$ (slowly) until it became clear yellow, and was acidified with concentrated HCl. The acidic solution was concentrated, diluted with water and extracted with chloroform. The combined organic phases were washed 25% aqueous $NaHSO_3$, dried ($MgSO_4$) and evaporated in vacuo to afford 1.137 g (88%) of the crude diacid (4) as a solid foam, ir (Nujol) 3600-2200, 1730, 1715 cm^{-1}; ^{1}H-nmr δ 7.32 (m, 2 H), 7.01 (dd, J= 8.6, 2.8 Hz, 1 H), 4.75 (t, J= 7.7 Hz, 1 H), 3.80 (s, 3 H), 2.70 (t, J= 11.1 Hz, 1 H), 2.07 (s, 3 H), 0.97 (s, 3 H); mass spectrum 390 (M^+, 19), 372 (15), 356 (14), 284 (41), 178 (42), 43 (100). Exact mass calcd for $C_{21}H_{26}O_7$: 390.1679. Found: 390.1674.

17β-Acetoxy-3-methoxy-6,7-secoestra-1,3,5(10)-triene-6,7-dioic acid dimethyl ester (5)

Diacid (4) (802 mg, 2.06 mmol) was dissolved in 60 ml of chloroform and 5 ml (60 mmol) of pyridine, and 3 ml (40 mmol) of thionyl chloride were added over 15 min. After an additional 15 min, 6 ml of methanol were added dropwise and the solution was stirred for 30 min. The mixture was diluted with ethyl acetate and washed several times with 10% HCl, aqueous saturated $NaHCO_3$ and saturated NaCl solution. The organic layer was dried ($MgSO_4$), evaporated and flash chromatographed over silica gel (elution with 50% ethyl acetate-hexane) to give 603 mg (70%) of dimethyl ester 5 as an oil, ir ($CHCl_3$) 1730, 1609 cm^{-1}; ^{1}H-nmr δ 7.29 (d, J= 8.7 Hz, 1 H), 7.21 (d, J= 2.8 Hz,1 H), 7.00 (dd, J= 8.7, 2.8 Hz, 1 H), 4.70 (t, J= 9.0 Hz, 1 H), 3.91 (s, 3 H), 3.81 (s, 3 H), 3.41 (s, 3 H), 2.74 (t, J= 11.2 Hz, 1 H), 2.06 (s, 3 H), 0.97 (s, 3 H); mass spectrum 418 (M^+, 1), 376 (4), 344 (5), 285 (8), 284 (8), 83 (25), 43 (100). Exact mass calcd for $C_{23}H_{30}O_7$: 418.1992. Found: 418.1951.

17β-Acetoxy-3-methoxy-6,7-secoestra-1,3,5(10)-triene-6,7-dioic acid 7-methyl ester (6)

Dimethyl ester (5) (554 mg, 1.32 mmol) was stirred vigorously in 25 ml of dioxane and 10 ml of 2 N aqueous NaOH for 4 days. The mixture was diluted with ethyl acetate, acidified with concentrated HCl, washed with saturated NaCl solution, dried ($MgSO_4$) and evaporated in vacuo. The residue was flash chromatographed over silica gel (elution with 10% methanol-ethyl acetate) to afford 460 mg (96%) of the crude mono ester

17β-ol, which was treated with 3 ml (30 mmol) of acetic anhydride and 12 ml (150 mmol) of pyridine for 18 h. The mixture was worked up as in the preparation of 3 and flash chromatographed over silica gel (elution with 50% ethyl acetate-hexane) to afford 421 mg (82%; 79% overall from 5) of half ester (6), with ir and ^{1}H-nmr spectra and tlc identical to those of the sample obtained as a byproduct in the preparation of half ester (8) (*vide infra*).

17β-Acetoxy-3-methoxy-6,7-secoestra-1,3,5(10)-triene-6,7-dioic acid 6-methyl ester (8)

Diacid (4) (1.137 g, 2.915 mmol) and DCC (2.137 g, 10.37 mmol) were stirred in 30 ml of ether and 10 ml of chloroform for 6 h. The solvent was evaporated, the residue was triturated with cold ethyl acetate and filtered through Celite. Evaporation of the filtrate afforded 1.14 g of the crude anhydride (7), which was dissolved in 20 ml of 0.6 N NaOMe in methanol. After 2 h, the mixture was diluted with ethyl acetate, washed with 10% HCl, extracted several times with 2 N aqueous NaOH, and the latter was acidified with concentrated HCl. The acidic solution was extracted with chloroform, dried ($MgSO_4$), evaporated in vacuo, and stirred for 22 h in 2 ml (20 mmol) of acetic anhydride and 5 ml (60 mmol) of pyridine. The mixture was worked up as in the preparation of 3 and the crude mixture of diesters (6) and (8) was separated by flash chromatography over silica gel (elution with 30% ethyl acetate-hexane) to give 574 mg (49%) of 8 as an oil, ir ($CHCl_3$) 3500-2800, 1730, 1611 cm^{-1}; ^{1}H-nmr δ 7.29 (d, J= 8.7 Hz, 1 H), 7.21 (d, J= 2.8 Hz, 1 H), 7.00 (dd, J= 8.7, 2.8 Hz, 1 H), 4.70 (t, J= 7.8 Hz, 1 H), 3.85 (s, 3 H), 3.80 (s, 3 H), 3.60 (m, 1 H), 2.72 (t, J= 11.0 Hz, 1 H), 2.06 (s, 3 H), 0.97 (s, 3 H); mass spectrum 404 (M^+, 22), 372 (12), 298 (21), 192 (39), 149 (31), 43 (100). Exact mass calcd for $C_{22}H_{28}O_7$: 404.1835. Found: 404.1827. Further elution with 50% ethyl acetate-hexane afforded 184.5 mg (16%) of 6 as an oil, ir ($CHCl_3$) 3500-2500, 1730, 1609 cm^{-1}; ^{1}H-nmr δ 7.37 (s, 1 H), 7.26 (overlaps with $CHCl_3$), 7.03 (dd, J= 8.6, 2.7 Hz, 1 H), 4.70 (t, J= 8.2 Hz, 1 H), 3.82 (s, 3 H), 3.51 (s, 3 H), 2.82 (t, J= 10.7 Hz, 1 H), 2.07 (s, 3 H), 1.00 (s, 3 H); mass spectrum 404 (M^+, 12), 386 (10), 327 (22), 284 (27), 178 (27), 43 (100). Exact mass calcd for $C_{22}H_{28}O_7$: 404.1835. Found: 404.1836.

17β-Acetoxy-3-methoxy-6-azaestra-1,3,5(10)-trien-7-one (9)

Half ester (6) (321 mg, 0.794 mmol), DPPA (643 mg, 2.34 mmol) and triethylamine (0.25 ml, 1.8 mmol) were refluxed for 5 h under argon in 30 ml of toluene. The mixture was concentrated, diluted with ethyl acetate, washed with saturated K_2CO_3 solution, dried ($MgSO_4$) and evaporated in vacuo. The resulting crude isocyanate (ir 2230 cm^{-1}) was refluxed in 5 ml of pyridine and 5 ml of water for 40 h. The mixture was

concentrated in vacuo and chromatographed over silica gel (elution with 30% ethyl acetate-hexane) to afford 252 mg (92%) of lactam (9), mp 242-243°C (from methanol); ir ($CHCl_3$) 3333, 1736, 1680, 1618 cm^{-1}; ^{1}H-nmr δ 7.56 (br s, 1 H, exchanged), 7.13 (d, J= 8.4 Hz, 1 H), 6.58 (dd, J= 8.5, 2.5 Hz, 1 H), 6.32 (d, J= 2.5 Hz, 1 H), 4.74 (dd, J= 9.1, 7.3 Hz, 1 H), 3.80 (s, 3 H), 2.58 (m, 1 H), 2.07 (s, 3 H), 0.84 (s, 3 H); ^{13}C-nmr δ 173.2 (C=O), 171.1 (C=O), 159.1 (C-3), 137.7 (C-5), 125.4 (C-1), 121.0 (C-10), 107.7 (C-2), 101.3 (C-4), 81.8 (C-17); mass spectrum 343 (M^+, 100), 244 (20), 176 (86). Anal. calcd for $C_{20}H_{25}NO_4$: C, 69.95; H, 7.34; N, 4.08. Found: C, 69.73; H, 7.59; N, 3.96.

N-Chloro-17β-acetoxy-3-methoxy-6-azaestra-1,3,5(10)-trien-7-one (10)

Lactam (9) (50.1 mg, 0.146 mmol) was dissolved in 5 ml of dry THF, followed by the addition of potassium *t*-butoxide (50.3 mg, 0.449 mmol). After 30 min, NCS (62.5 mg, 0.467 mmol) was added and stirring was continued for 3 h. The mixture was diluted with ethyl acetate, washed with aqueous saturated $NaHCO_3$, dried ($MgSO_4$) and evaporated in vacuo. The residue was separated by preparative tlc (20% ethyl acetate-hexanes) to afford 49.3 mg (90%) of the *N*-chloro derivative (10), (R_f 0.55); mp ca. 90-98°C (decomp.) (from chloroform-hexanes); ir (film) 1734, 1707, 1682, 1614 cm^{-1}; ^{1}H-nmr δ 7.12 (d, J= 8.5 Hz, 1 H), 7.03 (d, J= 2.5 Hz, 1 H), 6.65 (dd, J= 8.5, 2.5 Hz, 1 H), 4.74 (dd, J= 9.1, 7.4 Hz, 1 H), 3.84 (s, 3 H), 2.07 (s, 3 H), 0.82 (s, 3 H); mass spectrum 377 (M^+, 32), 343 (100), 176 (54). Anal. calcd for $C_{20}H_{24}NO_4Cl$: C, 63.57; H, 6.40; N, 3.71. Found: C, 63.71; H, 6.57; N, 3.83.

17β-Acetoxy-3-methoxy-7-azaestra-1,3,5(10)-triene-6-one (11)

Half ester (8) (210 mg, 0.519 mmol) was treated in a similar manner to 6 to afford 172 mg (96%)of lactam (11), mp 256-257°C (from methanol); ir (film from $CHCl_3$) 3206, 1736, 1666, 1615 cm^{-1}; ^{1}H-nmr δ 7.61 (d, J= 2.6 Hz, 1 H), 7.20 (d, J= 8.5 Hz, 1 H), 7.06 (dd, J= 8.5, 2.6 Hz, 1 H), 6.06 (br s, 1 H, exchanged), 4.75 (t, J= 8.4 Hz, 1 H), 3.85 (s, 3 H), 3.40 (t, J= 11.3 Hz, 1 H), 2.65 (m, 1 H), 2.07 (s, 3 H), 0.87 (s, 3 H); ^{13}C-nmr δ 170.9 (C=O), 166.4 (C=O), 158.6 (C-3), 134.1 (C-5), 130.0 (C-10), 124.7 (C-1), 119.4 (C-2), 111.7 (C-4), 81.5 (C-17); mass spectrum 343 (M^+, 100), 244 (7), 201 (20), 188 (60), 176 (28). Anal. calcd for $C_{20}H_{25}NO_4$: C, 69.95; H, 7.34; N, 4.08. Found: C, 69.93; H, 7.23; N, 4.08.

N-Chloro-17β-acetoxy-3-methoxy-7-azaestra-1,3,5(10)-triene-6-one (12)

Lactam (11) (30.3 mg, 0.0882 mmol) and TCIA (47.3 mg, 0.204 mmol) were refluxed in 10 ml of chloroform

for 2 h. The solution was concentrated and the product was isolated by preparative tlc (20% ethyl acetate-hexanes) to afford 30.1 mg (90%) of the *N*-chloro derivative (12), (R_f 0.50); mp 125-128°C (decomp.) (from chloroform-hexanes); ir (film) 1734, 1676, 1610 cm^{-1}; ^{1}H-nmr δ 7.64 (d, J= 2.7 Hz, 1 H), 7.24 (d, J= 8.4 Hz, 1 H), 7.07 (dd, J= 8.6, 2.7 Hz, 1 H), 4.75 (t, J= 8.7 Hz, 1 H), 3.85 (s superimposed on t, J= 10.6 Hz, total 4 H), 2.99 (m, 1 H), 2.08 (s, 3 H), 0.88 (s, 3 H); mass spectrum 377 (M^+, 5), 343 (100), 188 (89). Anal. calcd for $C_{20}H_{24}NO_4Cl$: C, 63.57; H, 6.40; N, 3.71. Found: C, 63.67; H, 6.61; N, 3.94.

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7. The preferential conversion of 5 into 6 and 7 into 8 indicates that the C(6) carbonyl group is more reactive than that at C(7) of 5 or C(7a) of 7, respectively. Molecular modeling studies (MacroModel^{R} Version 3.5a) of 5 and 7 reveal that the dihedral angles C(4)-C(5)-C(6)-O(carbonyl) are 131.4° and 46.1°, respectively, implying that conjugation of the C(6) carbonyl group and the aromatic A-ring is significantly impaired in these compounds. Moreover, the C(7) and C(7a) carbonyl groups are partly hindered by the hydrogen atoms at C(15) and by the aromatic ring. The weak resonance stabilization of the C(6) carbonyl group and the greater congestion around C(7) and C(7a) thus account for the observed regioselectivity.
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