A CONVENIENT NEW SYNTHESIS OF 17-AZASTEROIDS. PREPARATION OF SOME NOVEL *N*-CHLORO-17-AZA- AND *N*-CHLORO-17A-AZA-17A-HOMOSTEROIDS AS POTENTIAL AFFINITY LABELS AND ENZYME INHIBITORS

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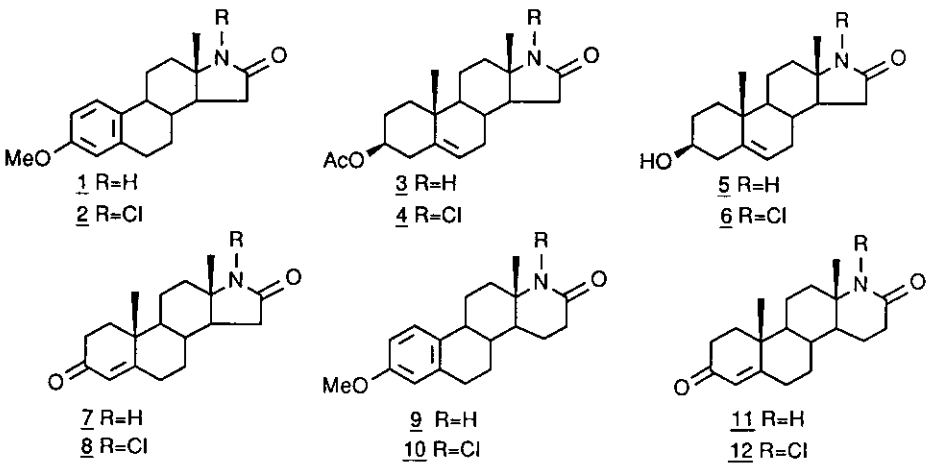
Abstract - An efficient new synthesis of 17-azasteroids in the estrane and androstane series was developed from readily available 16,17-seco 17-carboxylic acid precursors by means of a diphenylphosphoryl azide-mediated Curtius rearrangement as the key step. Several novel *N*-chloro-17-aza- and *N*-chloro-17a-aza-17a-homosteroids were prepared from the corresponding lactams with *N*-chlorosuccinimide.

Azasteroids frequently exhibit interesting biological activity and many such compounds are known.[1] The synthesis of new derivatives and the development of improved methods for their preparation is therefore of interest. We recently reported[2] the synthesis of several *N*-chloro derivatives of azasteroid lactams, which have potential utility as thiophilic affinity labels and enzyme inhibitors. Since the 17-position of steroid hormones is particularly important in both receptor recognition and as the site of key biosynthetic transformations, we wished to prepare a series of *N*-chloro derivatives of 17-aza- and 17a-aza-17a-homosteroid analogues. We now report the synthesis of the novel *N*-chloro-17-azasteroids (2), (4), (6) and (8), and the 17a-homo analogues (10) and (12), from the lactams (1), (3), (5), (7), (9) and (11), respectively (Chart 1). The required 17a-homo lactams (9) and (11) are well known compounds[3] that are easily available from the corresponding 17-keto analogues by the Beckmann rearrangement of their oximes. However, the preparation of 17-aza lactams with normal-sized D-rings, such as 1, 3, 5 and 7, is more difficult by existing methods.[4] We report an efficient new route to the latter compounds, using readily available 16,17-seco 17-carboxylic acids as precursors and a Curtius rearrangement as the key step.

Azaestrone (1) was prepared according to Scheme 1. The seco diacid (13),[5] was easily obtained from estrone methyl ether, and was dehydrated to the corresponding cyclic anhydride (14). Regioselective methanolysis of

14 at the less hindered carbonyl group afforded the half ester (15). The latter was treated with diphenylphosphoryl azide[6] (DPPA), and the intermediate acyl azide was subjected to an *in situ* Curtius rearrangement. The resulting isocyanate was hydrolyzed and cyclized without isolation to afford 1 in 83% overall yield from 15.

Chart 1



1 R=H
2 R=Cl

3 R=H
4 R=Cl

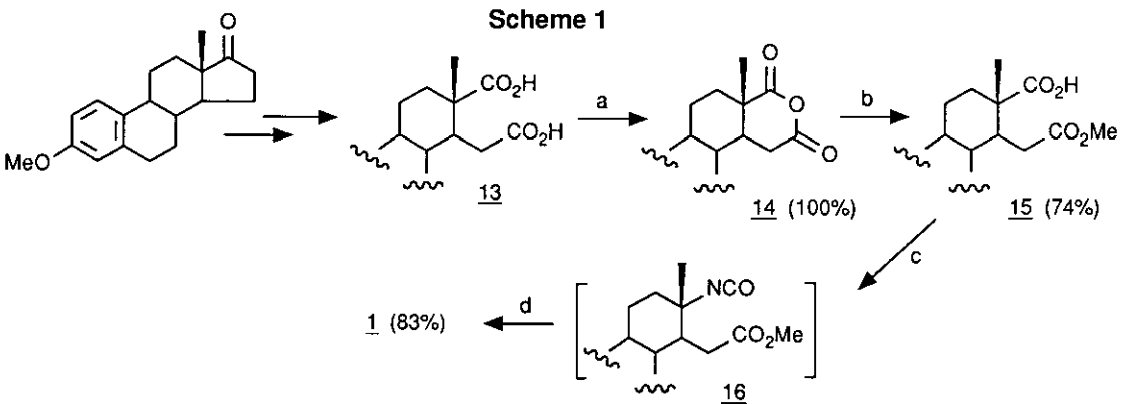
5 R=H
6 R=Cl

7 R=H
8 R=Cl

9 R=H
10 R=Cl

11 R=H
12 R=Cl

Scheme 1



13

14 (100%)

15 (74%)

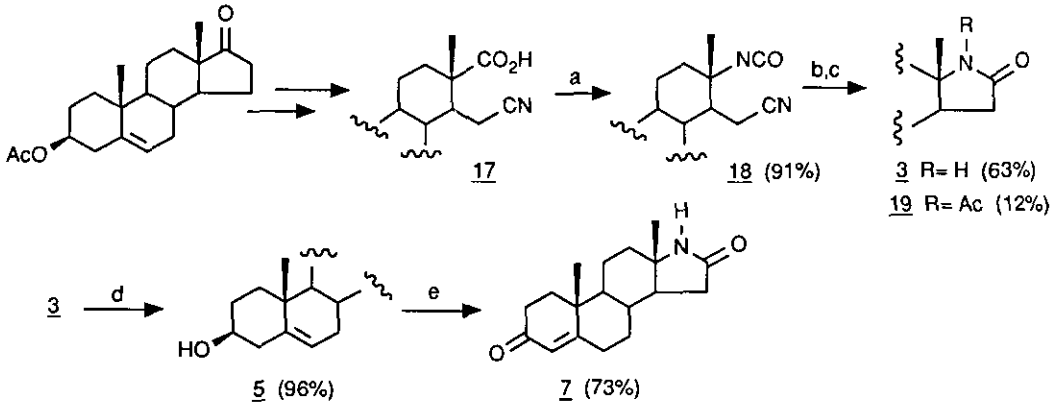
1 (83%)

16

(a) TsOH, toluene, Δ (b) NaOMe, MeOH (c) DPPA, Et_3N, toluene, Δ (d) Pyridine, H_2O, Δ

The preparation of azasteroids (3), (5) and (7) is shown in Scheme 2. The seco cyano acid (17), obtained by a known procedure[7] from dehydroisoandrosterone acetate, was similarly subjected to a Curtius rearrangement. The cyano isocyanate (18) was hydrolyzed and the intermediate amino carboxylic acid was cyclized with acetic anhydride in pyridine to afford the desired lactam (3) and a small amount of its *N*-acetyl derivative (19) in yields of 63% and 19%, respectively. The conversion of 3 to lactams (5) and (7) was accomplished by routine saponification and Oppenauer oxidation.

Scheme 2



(a) DPPA, Et_3N, toluene, Δ (b) KOH, n-BuOH, H_2O (c) Ac_2O, Pyridine (d) KOH, EtOH
(e) $(i\text{-}PrO)_3Al$, cyclohexanone

The preparation of the corresponding novel *N*-chloro derivatives from lactams (1), (3), (5), (7), (9) and (11) was achieved by either refluxing the latter with *N*-chlorosuccinimide (NCS) in chloroform, or by their reaction with potassium t-butoxide followed by NCS. The results are summarized in Table 1. These procedures therefore provide improved access to 17-azasteroids, and permit their facile conversion, as well as that of their 17a-aza-17a-homo analogues, to the corresponding *N*-chloro derivatives.

Table 1. Preparation of N-Chloroazasteroids

Azasteroid	N-Chloro Derivative	Method	Yield (%)
1	2	B	76
3	4	A	50
5	6	B	65
7	8	B	62
9	10	B	63
11	12	A	61

Method A: excess NCS, $CHCl_3$, Δ
Method B: 1. KOt-Bu,THF; 2. NCS, room temperature

EXPERIMENTAL SECTION

Melting points were determined on an A. H. Thomas hot-stage apparatus and are uncorrected. Ir spectra were recorded on a Nicolet 5DX spectrophotometer, and nmr spectra were recorded 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. Elemental analyses were obtained by Ms. D. Fox and Dr. R. Yamdagni at the University of Calgary.

3-Methoxy-16,17-secoestra-1,3,5(10)-triene-16,17-dioic acid 16-methyl ester (15)

Diacid (13)[5] (1.50 g, 4.51 mmol) and p-toluenesulfonic acid monohydrate (43 mg, 0.23 mmol) were refluxed in 35 ml of toluene for 8 h in an apparatus fitted with a Dean-Stark trap for the azeotropic removal of water. The mixture was washed with aqueous NaCl, dried with $MgSO_4$ and evaporated in vacuo to afford 1.43 g (100%) of anhydride (14), which was used in the next step without further purification. A recrystallized sample had mp 175-179°C (from ethyl acetate-hexane), ir (KBr) 1809, 1747 cm^{-1}; ^{1}H-nmr δ 7.21 (d, J= 8.3 Hz, 1 H), 6.75 (dd, J= 8.3, 2.8 Hz, 1 H), 6.64 (d, J= 2.8 Hz, 1 H), 3.78 (s, 3 H), 3.12 (dd, J= 19.0, 5.7 Hz, 1 H), 2.88 (m, 2 H), 1.25 (s, 3 H); mass spectrum, m/z (relative intensity, %) 314 (M^+, 100), 228 (42), 186 (47), 160 (40). Exact mass calcd for $C_{19}H_{22}O_4$: 314.1518. Found: 314.1535. The crude anhydride was dissolved in a solution of sodium methoxide (5.5 mmol) in 25 ml of methanol. After 14 h, the mixture was evaporated, dissolved in 20 ml of water and acidified with concentrated HCl. The product was extracted with chloroform, dried with $MgSO_4$ and evaporated in vacuo. The residue was recrystallized from ethyl acetate-hexane to afford 1.17 g (74%) of the title compound: mp 141-145°C; ir (KBr) 3500-2200 (broad), 1736, 1701 cm^{-1}; ^{1}H-nmr δ 7.20 (d, J= 8.6 Hz, 1 H), 6.72 (dd, J= 8.6, 2.7 Hz, 1 H), 6.62 (d, J= 2.7 Hz, 1 H), 3.78 (s, 3 H), 3.70 (s, 3 H), 2.82 (m, 2 H), 1.17 (s, 3 H); mass spectrum, m/z (relative intensity, %) 346 (M^+, 10), 314 (65), 237 (100), 220 (70), 152 (70). Anal. Calcd for $C_{20}H_{26}O_5$: C, 69.34; H, 7.57. Found: C, 69.57; H, 7.75.

3-Methoxy-17-azaestra-1,3,5(10)-trien-16-one (1)

The half ester (15) (306 mg, 0.884 mmol), DPPA (261 mg, 1.00 mmol) and triethylamine (0.139 ml, 1.00 mmol) were refluxed 3.5 h in 8 ml of toluene. The presence of isocyanate (16) was then evident from an ir absorption at 2251 cm^{-1}. The mixture was washed with aqueous K_2CO_3 solution, dried over $MgSO_4$ and evaporated to dryness. The residue was refluxed for three days in 8 ml of pyridine and 2 ml of water and volatile material was removed in vacuo. Preparative tlc (silica gel; benzene-methanol, 9:1) then afforded 209 mg (83%) of azasteroid (1), mp 217-219°C (from ethyl acetate), ir (Nujol) 3276, 1693, 1659, 1039 cm^{-1}; ^{1}H-nmr δ 7.16 (d, J= 8.7 Hz, 1 H), 6.72 (dd, J= 8.7, 2.7 Hz, 1 H), 6.65 (d, J=2.7 Hz, 1 H), 5.67 (broad s, 1 H), 3.78 (s, 3 H), 2.89 (m, 2 H), 1.15 (s, 3 H); mass spectrum, m/z (relative intensity, %) 285 (M^+, 90), 270 (100), 242 (10).[8] Anal. Calcd for $C_{18}H_{23}NO_2$: C, 75.75; H, 8.12; N, 4.91. Found: C, 75.56; H, 7.91; N, 4.87.

3β-Acetoxy-17-azaandrost-5-en-16-one (3)

The cyano acid (17)[7] (4.20 g, 11.7 mmol), DPPA (3.05 ml, 14.1 mmol) and triethylamine (2.00 ml, 14.3 mmol) were refluxed for 3.5 h in 140 ml of toluene. The reaction mixture was diluted with benzene, washed with aqueous K_2CO_3, dried over $MgSO_4$ and filtered through silica gel. Evaporation in vacuo afforded 3.80 g (91%) of the isocyanate (18), which was used without further purification in the next step. A recrystallized sample had mp 124-126°C (from ethanol); ir (Nujol) 2253, 1715, 1269 cm^{-1}; ^{1}H-nmr δ 5.38 (m, 1 H), 4.60 (m, 1 H), 2.61 (m, 2 H), 2.04 (s, 3 H), 1.40 (s, 3 H), 1.02 (s, 3 H); mass spectrum, m/z (relative intensity, %) 296 (M^+- HOAc, 30), 253 (19), 213 (37), 158 (60), 145 (93), 43 (100). Exact mass calcd for $C_{19}H_{24}N_2O$: 296.1888. Found: 296.1892. The crude isocyanate and KOH (6.0 g, 43 mmol) were refluxed for 16 h in 250 ml of n-butanol and 40 ml of water. Volatile material was then removed in vacuo and the resulting solid was triturated with 150 ml of pyridine and 100 ml of acetic anhydride. After 16 h, the mixture was poured into excess ice-cold 5% HCl and extracted with chloroform. The latter was dried with $MgSO_4$ and evaporated to dryness. Column chromatography over silica gel (elution with benzene-ether 85:15) afforded 0.47 g (12%) of the *N*-acetyl derivative (19), mp 224-225°C (from ethanol); ir (Nujol) 1745, 1727, 1688, 1251, 1034 cm^{-1}; ^{1}H-nmr δ 5.38 (m, 1 H), 4.60 (m, 1 H), 2.84 (m, 1 H), 2.44 (s, 3 H), 2.04 (s, 3 H), 1.29 (s, 3 H), 1.05 (s, 3 H); mass spectrum, m/z (relative intensity, %) 330 (M^+-Ac, <0.5), 313 (M^+-HOAc, 98), 256 (95), 43 (100). Anal. Calcd for $C_{22}H_{31}NO_4$: C, 70.75; H, 8.37; N, 3.75. Found: C, 70.81; H, 8.21; N, 3.78. Further elution with chloroform-methanol (99:1) afforded 2.21 g (63%) of the title compound 3, mp 278-279°C from ethanol (lit.,[4d] mp 185-187°C; lit.,[4e] mp 285-287°C); ir (Nujol) 3143, 1732, 1651, 1248, 1038 cm^{-1}; ^{1}H-nmr δ 5.77 (broad s, 1 H), 5.39 (m, 1 H), 4.60 (m, 1 H), 2.04 (s, 3 H), 1.14 (s, 3 H), 1.05 (s, 3 H); mass spectrum, m/z (relative intensity, %) 316 (M^+- CH_3, 4), 271 (M^+-HOAc, 87), 256 (100).

17-Azaandrost-4-ene-3,16-dione (7)

The 3β-acetoxy lactam (3) (300 mg, 0.90 mmol) was stirred for 12 h in 15 ml of ethanol containing 500 mg of KOH and 1.5 ml of water. The mixture was then concentrated under reduced pressure, acidified with dilute HCl and extracted with chloroform. The latter was dried with $MgSO_4$ and evaporated in vacuo to afford 251 mg (96%) of compound (5), mp 292-295°C (from ethanol); ir (Nujol) 3379, 3320, 1682, 1063 cm^{-1}; ^{1}H-nmr δ 5.93 (broad s, 1 H), 5.37 (m, 1 H), 3.53 (m, 1 H), 1.14 (s, 3 H), 1.04 (s, 3 H); mass spectrum, m/z (relative intensity, %) 289 (M^+, 12), 274 (M^+- CH_3, 100), 256 (27). Exact mass calcd for $C_{18}H_{27}NO_2$: 289.2041. Found: 289.2033. Lactam 5 (420 mg, 1.70 mmol) was dissolved in a mixture of 20 ml of dioxane, 20 ml of toluene and 5 ml of cyclohexanone. The mixture was distilled slowly while a solution of 440 mg (2.20 mmol)

of aluminum i-propoxide in 5 ml of toluene was added in portions. Distillation was continued for 2 h during which 15 ml of additional toluene was added. The mixture was refluxed for 2 h, cooled and treated with saturated potassium sodium tartrate. It was then steam distilled to remove organic solvents and extracted with chloroform. The latter was dried (Na_2SO_4) and evaporated in vacuo. The residue was recrystallized from ethyl acetate to afford 305 mg (73%) of the title compound, mp 200-202°C; ir (film) 3236, 1682, 1616, 1232 cm^{-1}; uv λ_{max} (EtOH) 240 nm (ϵ= 16,000); ^{1}H-nmr δ 5.81 (broad s, 1 H), 5,76 (s, 1 H), 1.21 (s, 3 H), 1.18 (s, 3 H); mass spectrum, m/z (relative intensity, %) 287 (M^+, 2), 272 (M^+- CH_3, 100). Anal. Calcd for $C_{18}H_{25}NO_2$: C, 75.22; H, 8.77; N, 4.87. Found: C, 75.45; H, 8.77; N, 4.93.

Preparation of N-Chloroazasteroids by Method A (Typical procedure)

Azasteroid (3) (110 mg, 0.33 mmol) and NCS (267 mg, 2.00 mmol) were refluxed 18 h in 12 ml of chloroform. Concentration of the reaction mixture in vacuo and chromatography over silica gel eluted excess NCS with benzene-ether (95:5). Further elution with benzene-ether (92:8) afforded 61 mg (50%) of *N*-chloro-3β-acetoxy-17-azaandrost-5-en-16-one (4), mp 185-188°C (from ether); ir (film) 1731, 1715, 1248, 1034 cm^{-1}; ^{1}H-nmr δ 5.39 (m, 1 H), 4.60 (m, 1 H), 2.04 (s, 3 H), 1.13 (s, 3 H), 1.06 (s, 3 H); mass spectrum, m/z (relative intensity, %) 350 (M^+-CH_3, 2), 305 (M^+-HOAc, 44), 290 (52), 271 (72), 256 (88), 43 (100). Anal. Calcd for $C_{20}H_{28}NO_3Cl$: C, 65.65; H, 7.71; N, 3.83. Found: C, 65.50; H, 7.52; N, 3.78.

Similarly was prepared: *N*-chloro-17a-aza-17a-homoandrost-4-en-3,17-dione (12), mp 228-230°C (from ethyl acetate-hexane); ir (Nujol) 1674, 1617, 1230 cm^{-1}; ^{1}H-nmr δ 5.76 (s, 1 H), 2.70 (m, 2 H), 1.32 (s, 3 H), 1.18 (s, 3 H); mass spectrum, m/z (relative intensity, %) 335 (M^+, 2), 320 (M^+-CH_3, 21), 286 (100); Anal. Calcd for $C_{19}H_{26}NO_2Cl$: C, 67.94; H, 7.80; N, 4.17. Found: C, 67.96; H, 7.73; N, 4.25.

Preparation of *N*-Chloroazasteroids by Method B (Typical procedure)

Azasteroid (1) (143 mg, 0.50 mmol) and potassium t-butoxide (56 mg, 0.50 mmol) were stirred 10 min in 6 ml of THF. NCS (73 mg, 0.55 mmol) was then added and stirring was continued for 30 min. The mixture was diluted with ether, washed with aqueous $NaHCO_3$, dried with Na_2SO_4 and evaporated in vacuo. The residue was separated by preparative tlc (silica gel; benzene-methanol, 9:1) to afford 122 mg (76%) of *N*-chloro-3-methoxy-17-azaestra-1,3,5(10)-trien-16-one (2), mp 135-138°C (from chloroform-hexane); ir (Nujol) 1724, 1608, 1240, 1229 cm^{-1}; ^{1}H-nmr δ 7.16 (d, J= 8.6 Hz, 1 H), 6.73 (dd, J= 8.6, 2.8 Hz, 1 H), 6.65 (d, J= 2.8 Hz, 1 H), 3.78 (s, 3 H), 2.90 (m, 2 H), 1.14 (s, 3 H); mass spectrum, m/z (relative intensity, %) 319

(M^+, 59), 304 (M^+- CH_3, 62), 285 (20), 270 (22), 50 (82), 36 (100). Anal. Calcd for $C_{18}H_{22}NO_2Cl$: C, 67.59; H, 6.93; N, 4.38. Found: C, 67.59; H, 6.80; N, 4.39.

Similarly were prepared:

N-Chloro-17-azaandrost-5-en-3β-ol-16-one (6), solid foam; ir (film) 3435, 1731, 1715, 1234, 1045 cm^{-1}; ^{1}H-nmr δ 5.37 (m, 1 H), 3.54 (m, 1 H), 1.13 (s, 3 H), 1.04 (s, 3 H); mass spectrum, m/z (relative intensity, %) 323 (M^+, 3), 308 (M^+- CH_3, 23), 274 (82), 36 (100). Exact mass calcd for $C_{18}H_{26}NO_2Cl$: 323.1652. Found: 323.1632.

N-Chloro-17-azaandrost-4-ene-3,16-dione (8), mp 159-161°C (from ethyl acetate-hexane); ir (film) 1732, 1716, 1674, 1616, 1230 cm^{-1}; ^{1}H-nmr δ 5.76 (s, 1 H), 1.21 (s, 3 H), 1.16 (s, 3 H); mass spectrum, m/z (relative intensity, %) 321 (M^+, 14), 306 (M^+- CH_3, 100), 272 (87). Exact mass calcd for $C_{18}H_{24}NO_2Cl$: 321.1495. Found: 321.1466. Anal. Calcd for $C_{18}H_{24}NO_2Cl$: C, 67.17; H, 7.52; N, 4.35. Found: C, 66.83; H, 7.57; N, 4.34.

N-Chloro-3-methoxy-17a-aza-17a-homoestra-1,3,5(10)-trien-17-one (10), mp 132-134°C (from ethyl acetate-hexane); ir (film) 1679, 1611, 1577, 1503, 1257, 1035 cm^{-1}; ^{1}H-nmr δ 7.21 (d, J= 8.6 Hz, 1 H), 6.75 (dd, J=8.6, 2.6 Hz, 1 H), 6.65 (d, J= 2.6 Hz, 1 H), 3.79 (s, 3 H), 2.89 (m, 2 H), 1.31 (s, 3 H); mass spectrum, m/z (relative intensity, %) 333 (M^+, 20), 318 (M^+-CH_3, 29), 299 (82), 284 (100). Anal. Calcd for $C_{19}H_{24}NO_2Cl$: C, 68.36; H, 7.25; N, 4.20. Found: C, 67.96; H, 6.85; N, 4.13.

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