PREPARATION OF 6-AZAANDROST-4-ENE-3,7,17-TRIONE AND SOME RELATED 3-OXYGENATED 6-AZAANDROSTANES

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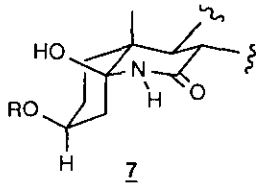
Abstract - The synthesis of 6-azaandrost-4-ene-3,7,17-trione and of several related 3-oxygenated 6-azaandrostanes was achieved from 3β-hydroxyandrost-5-en-17-one.

A variety of azasteroids has been reported and many such compounds display interesting and useful biological properties.[1] As part of our ongoing work on azasteroids,[2] we required an azaandrostane in which the A-ring enone moiety of testosterone and related compounds is conjugated to an enamidic nitrogen atom at C-6, as in the case of the title compound (1). While several early preparations of 6-azaandrostanes have been reported,[3] the products generally lacked an oxygen function at C-3, which is important for biological activity. We now describe the preparation of the novel 3-ketoenamide (1), as well as some related 3-oxygenated 6-azaandrostanes.

The synthesis of azasteroid (1) is shown in Scheme 1. The conversion of 3β-hydroxyandrost-5-en-17-one (2) into the 7,17-dione (3) was effected by silylation[4] and oxidation with chromium trioxide.[5] Although ozonolysis of a 3β-acetoxycholestane analogue of 3, followed by workup with ammonia at -78°C, was reported[6] to afford the corresponding 6-azasteroid enamide directly, this procedure proved ineffective in the androstane series, affording only complex mixtures of products under similar and other conditions. Better and more consistent results were obtained with ruthenium tetroxide-catalyzed oxidation in the presence of sodium metaperiodate, producing esters (4b) and (5b) after treatment with diazomethane. Previous attempts to cyclize B-ring seco esters in the cholestane series with ammonia[6] or benzylamine[7] resulted in elimination of the C-3

oxygen function. Similarly, the reaction of 4b with ammonia at 140°C gave diene (6) as the major product. However, under milder conditions, the two carbinol amides (7) and (8) were isolated nearly quantitatively. The assignment of the 5β- and 5α-hydroxy structures to 7 and 8, respectively, is based upon the halfwidths (w/2) of the ^{1}H-nmr signals of their 3α-protons, which are 9.5 Hz and 24 Hz, respectively. The A/B *cis*-fused carbinol amide (7) possesses an equatorial 3α-proton, while the *trans*-fused isomer (8) contains an axial one. Since only the latter is subjected to relatively large vicinal diaxial coupling, it is expected to display the greater w/2. The further downfield shift of equatorial protons relative to axial ones at C-3 in steroidal systems is also consistent with this assignment (δ 4.19 for 7 vs. δ 4.10 for 8).[8] The mixture of products (7) and (8) underwent selective dehydration of the carbinol amide moiety in dilute acetic acid, along with partial or complete desilylation of the C-3 alcohol, depending on the precise conditions, to afford enamides (9) and (10), respectively. More strongly acidic conditions resulted in desilylation and double dehydration to the diene (6).



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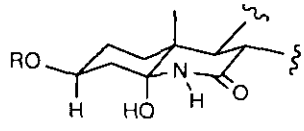

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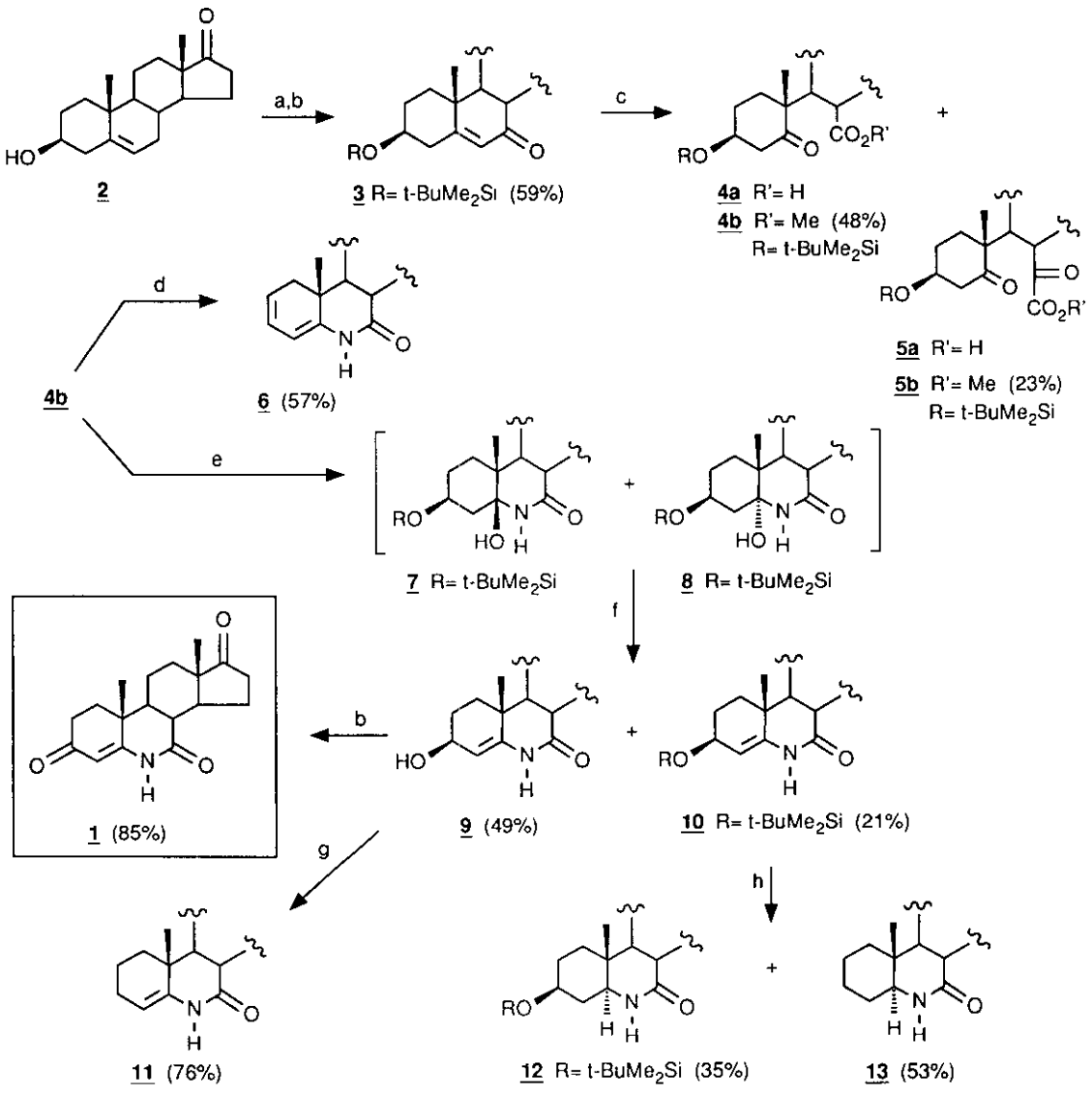
Hydrogenation of 9 with Pd/C at 1 atm in ethyl acetate resulted in selective allylic C-O cleavage to form 11,[9] while the similar reaction of the silyl ether (10) in methanol reduced both the C(3)-O bond and the C(4)-C(5) olefin to produce 13. Olefin hydrogenation proved more competitive with hydrogenolysis at higher pressures, and a modest yield of the saturated silyl ether (12) was obtained. Although hydrogenation of Δ^4-steroidal olefins can produce either 5α or 5β products, depending on the conditions,[10] nmr evidence is consistent with the 5α-configuration for 12, and for 13 by analogy. The large halfwidth of 22 Hz of the ^{1}H-nmr signal at δ 3.64, assigned to the 3α-proton of 12, indicates that the latter is axial. This in turn requires an A/B trans ring junction and the 5α-configuration.

Finally, oxidation of 9 with chromium trioxide in pyridine provided the desired 3-keto derivative (1). The above method therefore provides a convenient entry to 1 and related 6-azasteroid lactams bearing oxygen functions at C(3).

Scheme 1



(a) *t*-$BuMe_2SiCl$, imidazole; (b) CrO_3, py; (c) RuO_2, $NaIO_4$; then CH_2N_2; (d) NH_3, MeOH, 140°C; (e) NH_3, MeOH, 55°C; (f) AcOH, $CHCl_3$; (g) H_2 (1 atm), Pd-C, EtOAc, (h) H_2 (60 atm), Pd-C, EtOAc or MeOH.

EXPERIMENTAL SECTION

Melting points were obtained 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 either a Bruker AC-E 200

or AM 400 instrument, using deuteriochloroform as the solvent and residual chloroform as the internal standard unless otherwise indicated. Mass spectra were obtained on either a Kratos MS80 or a VG 7070 instrument with the assistance of Dr. R Yamdagni, Dr. Q. Wu and Ms. D. Fox, and elemental analyses were performed by Ms. D. Fox. Chromatography was carried out with silica gel as the adsorbent. 3β-Hydroxyandrost-5-en-17-one (2) was purchased from the Sigma Chemical Co.

3β-(*t*-Butyldimethylsilyloxy)androst-5-ene-7,17-dione (3)

Sterol (2) was silylated by a literature procedure[4] and the resulting silyl ether (5.69 g, 14.1 mmol) was dissolved in 200 ml of dichloromethane and 20 ml of pyridine. Phosphorus pentoxide (6 g, 4 mmol) and chromium trioxide (20 g, 5 mmol) were then added in portions. The mixture was refluxed for 16 h, filtered through silica gel and washed several times with 10% HCl, then with aqueous 10% $NaHCO_3$ and dried ($MgSO_4$). The solution was concentrated and flash chromatographed (elution with 10% ethyl acetate-dichloromethane) to afford 3.48 g (59%) of dione (3), mp 132-133°C (from hexane), which was used directly without further purification in the next step.

Ruthenium tetroxide oxidation of (3)

Sodium metaperiodate (17.8 g, 8.32 mmol) and ruthenium(IV) oxide dihydrate (63 mg, 0.47 mmol) were dissolved in 200 ml of water and added to a separatory funnel containing 200 ml of carbon tetrachloride and 200 ml of acetone. This was shaken until the mixture formed a light yellow-green solution. Enone (3) (3.47 g, 8.33 mmol) in 100 ml of acetone was added in portions over 1 h with frequent shaking. The aqueous layer was then extracted three times with chloroform and the combined organic layers were washed twice with water, dried ($MgSO_4$) and evaporated in vacuo. The residue was flash chromatographed (elution with 30% ethyl acetate-hexane) to afford 882 mg (23%) of the α-keto acid (5a), mp 192-194°C (from ethyl acetate-hexane), which was treated with excess ethereal diazomethane to produce the methyl ester (5b) quantitatively. Further elution with 30% methanol-ethyl acetate gave the crude acid (4a), mp 208-210°C (from ethyl acetate-hexane), which was similarly converted into its methyl ester and rechromatographed (elution with 30% ethyl acetate-hexane) to afford 1.80 g (48%) of (4b). Compound (4b): mp 148-150°C (from hexane); ir ($CHCl_3$) 1737, 1703, 1059, 838 cm^{-1}; ^{1}H-nmr δ 4.36 (m, 1 H), 3.60 (s, 3 H), 3.05 (dd, J= 14.4, 3.6 Hz, 1 H), 1.03 (s, 3 H), 0.88 (s, 3 H), 0.84 (s, 9 H), 0.04 (s, 3 H), 0.02 (s, 3 H); mass spectrum 419 (1.5), 393 (27), 301 (28), 110 (81), 75 (100). Anal. Calcd for $C_{25}H_{42}O_5Si$: C, 66.63; H, 9.39. Found: C, 66.47; H, 9.59.

Compound (5b): mp 150-153°C (from hexane); ir ($CHCl_3$) 1737, 1698, 1059, 838 cm^{-1}; ^{1}H-nmr δ 4.33 (m, 1 H), 3.92 (s, 3 H), 2.66 (dd, J= 15.1, 3.7 Hz, 1 H), 1.05 (s, 3 H), 0.94 (s, 3 H), 0.81 (s, 9 H), 0.00 (s, 6 H); mass spectrum 421 (32), 388 (14), 329 (54) 81 (98), 75 (100). Anal. Calcd for $C_{26}H_{42}O_6Si$: C, 65.24; H, 8.84. Found: C, 65.54; H, 9.05.

Cyclization of keto ester (4b) with ammonia at 140°C

Keto ester (4b) (50 mg, 0.11 mmol) in 35 ml of methanol and 35 ml of liquid ammonia was heated for 18 h at 140°C under pressure. Volatile material was then evaporated and the residue was flash chromatographed (elution with 20% ether-benzene) to afford 18 mg (57%) of 6-azaandrosta-2,4-diene-7,17-dione (6), mp 152-155°C (from dichloromethane-hexane); ir ($CHCl_3$) 3375, 1735, 1698, 1666 cm^{-1}; ^{1}H-nmr δ 8.22 (br s, NH, 1 H), 5.90 (m, 1 H), 5.53 (m, 1 H), 5.14 (d, J= 5.6 Hz, 1 H), 1.06 (s, 3 H), 0.93 (s, 3 H); mass spectrum 285 (M^+, 25), 270 (15), 44 (100). Exact mass calcd for $C_{18}H_{23}NO_2$: 285.1729. Found: 285.1722.

Cyclization of keto ester (4b) with ammonia at 55°C

Keto ester (4b) (208.5 mg, 0.463 mmol) in 20 ml of methanol and 5 ml of liquid ammonia was heated for 39 h at 55°C under pressure. Volatile material was then evaporated and remaining traces of ammonia were removed under vacuum. The residue was dissolved in 40 ml of chloroform and 100 µl of acetic acid. After 20 h, the mixture was washed with 10% $NaHCO_3$ solution, dried (K_2CO_3) and separated by preparative tlc on silica gel (50% ethyl acetate-hexane) to afford 68 9 mg (49%) of 3β-hydroxy-6-azaandrost-4-ene-7,17-dione (9), R_f 0.18; mp 189-191°C (from chloroform-hexane); ir (nujol) 3500-3200, 1730, 1661 cm^{-1}; ^{1}H-nmr δ 7.45 (br s, NH, 1 H), 4.85 (dd, J= 2.4, 1 1 Hz, 1 H), 4.35 (m, 1 H), 1.19 (s, 3 H), 0.94 (s, 3 H); ^{13}C-nmr δ 220.0 (C=O), 171.0 (C=O), 142.7 (C), 107.0 (CH), 66.8 (CH), 48.8 (C), 48.1 (CH), 47.3 (CH), 41.0 (CH), 35.7 (CH_2), 34.5 (C), 33.0 (CH_2), 30.8 (CH_2), 28.9 (CH_2), 24.1 (CH_2), 19.9 (CH_2), 17.4 (CH_3), 13.9 (CH_3); mass spectrum 303 (M^+, 1), 285 (68), 270 (39), 83 (100). Exact mass calcd for $C_{18}H_{25}NO_3$: 303.1834. Found:[11] 303.1787. Exact mass calcd for $C_{18}H_{23}NO_2$ (M^+- H_2O): 285.1729. Found: 285.1707. A less polar band gave 39.8 mg (21%) of 3β-(*t*-butyldimethylsilyloxy)-6-azaandrost-4-ene-7,17-dione (10), R_f 0.80; mp 203-205°C (decomp.)(from dichloromethane-hexane); ir ($CHCl_3$) 3386, 1735, 1666 cm^{-1}; ^{1}H-nmr δ 7.79 (br s, NH, 1 H), 4.79 (m, 1 H), 4.33 (m, 1 H), 1.17 (s, 3 H), 0.93 (s, 3 H), 0.90 (s, 9 H), 0.08 (s, 6 H); mass spectrum 417 (M^+, 0.1), 360 (1), 285 (54), 270 (24), 75 (100). Anal. Calcd for $C_{24}H_{39}NO_3Si$: C, 69.02; H, 9.41; N, 3.35. Found. C, 69.15; H, 9.25; N, 3.16. When the reaction of 4b with ammonia at 55°C was repeated without subsequent

treatment with acetic acid, the crude carbinol amides (7) and (8) were formed almost quantitatively in the ratio of 56:44 by nmr integration.[12] Flash chromatography (elution with 50% ether-benzene) afforded 3β-(*t*-butyldimethylsilyloxy)-5β-hydroxy-6-azaandrostane-7,17-dione (7), followed by the 5α-isomer (8) (elution with 80% ether-benzene). Compound (7): mp 198-201°C(decomp.)(from dichloromethane-hexane); ir (CCl_4) 3455, 3395, 1742, 1672 cm^{-1}; ^{1}H-nmr δ 5.70 (br s, NH, 1 H), 4.85 (br s, OH, 1 H), 4.19 (m, w/2 = 9.5 Hz, 1 H), 1.05 (s, 3 H), 0.91 (two superimposed s, total 12 H), 0.11 (s, 3 H), 0.10 (s, 3 H); mass spectrum 360 (2), 285 (29), 270 (15), 75 (100). Anal. Calcd for $C_{24}H_{41}NO_4Si$: C, 66.16; H, 9.49; N, 3.21. Found:[11] C, 65.55; H, 9.07; N, 3.10. Compound (8): mp 193-196°C(decomp.)(from dichloromethane-hexane); ir (CCl_4) 3462, 3391, 1742, 1669 cm^{-1}; ^{1}H-nmr (acetone-d_6) δ 6.71 (br s, NH, 1 H), 4.67 (br s, OH, 1 H), 4.10 (m, w/2 = 24 Hz, 1 H), 1.10 (s, 3 H), 0.89 (two superimposed s, total 12 H), 0.06 (s, 6 H); mass spectrum 378 (0.5), 360 (2), 285 (31), 270 (17), 75 (100). Anal. Calcd for $C_{24}H_{41}NO_4Si$. C, 66 16; H, 9.49; N, 3.21. Found: C, 65.99; H, 9.15; N, 3.15.

6-Azaandrost-4-ene-7,17-dione (11)

Allylic alcohol (9) (58.7 mg, 0.193 mmol) and 30 mg of 10% Pd/C were stirred in 5 ml of ethyl acetate under positive pressure of hydrogen (from a balloon) for 8 h. The catalyst was then removed by filtration through Celite and the filtrate was separated by preparative tlc (ethyl acetate), to afford 42.0 mg (76%) of 11 as a gummy solid, R_f 0.59; ir ($CHCl_3$) 3366, 1734, 1701, 1676 cm^{-1}; ^{1}H-nmr δ 7.51 (br s, NH, 1 H), 4.82 (t, J= 3.7 Hz, 1 H), 1.11 (s, 3 H), 0.94 (s, 3 H); mass spectrum 287 (M^+, 8), 83 (100). Exact mass calcd for $C_{18}H_{25}NO_2$: 287.1885. Found: 287.1865.

3β-(*t*-Butyldimethylsilyloxy)-6-aza-5α-androstane-7,17-dione (12) and 6-aza-5α-androstane-7,17-dione (13)

Silyl ether (10) (53 mg, 0.13 mmol) in 30 ml of ethyl acetate was hydrogenated for 18 h in a high pressure apparatus at 60 atm in the presence of 26 mg of 10% Pd/C. The catalyst was then removed by filtration through Celite and the filtrate was separated by flash chromatography (elution with 50% ether-benzene) to afford 18.5 mg (35%) of silyl ether (12), mp 255-256°C (from dichloromethane-hexane); ir ($CHCl_3$) 3391, 1734, 1655 cm^{-1}; ^{1}H-nmr δ 5.84 (br s, NH, 1 H), 3.64 (m, w/2 = 22 Hz, 1 H), 3.08 (dd, J= 12.3, 3.9 Hz, 1 H), 0.93 (s, 3 H), 0.92 (s, 3 H), 0.88 (s, 9 H), 0.06 (s, 6 H); mass spectrum 419 (M^+, 5), 404 (5), 362 (100), 287 (8), 75 (63). Anal. Calcd for $C_{24}H_{41}NO_3Si$· C, 68.69; H, 9.85; N, 3.34. Found: C, 68.82; H, 9.45; N, 3.73. Further elution with ethyl acetate afforded 19.3 mg (53%) of 13, mp 237-238°C (from dichloromethane-hex-

ane); ir ($CHCl_3$) 3389, 1734, 1651 cm^{-1}; ^{1}H-nmr δ 5.61 (br s, NH, 1 H), 3.04 (dd, J= 9.1, 6.2 Hz, 1 H), 0.92 (s, 3 H), 0.90 (s, 3 H); mass spectrum 289 (M^+, 33), 261 (88), 246 (100). Exact mass calcd for $C_{18}H_{27}NO_2$: 289.2042. Found: 289.2049. When the reaction was repeated using methanol as the solvent, 13 was formed quantitatively.

6-Azaandrost-4-ene-3,7,17-trione (1)

Chromium trioxide (55 mg, 0.55 mmol) was added slowly to 0.44 ml of dry pyridine at 0°C. Allylic alcohol (9) (55.7 mg, 0.184 mmol) in 0.40 ml of pyridine was then added and the mixture was stirred at room temperature for 16 h. The pyridine was removed in vacuo and the residue was separated by flash chromatography (elution with 50% acetone-benzene) to afford 47.0 mg (85%) of enone (1), mp 291-292°C (from chloroform-hexane); ir (nujol) 3273, 1724, 1692, 1643, 1605 cm^{-1}; ^{1}H-nmr δ 8.70 (br s, NH, 1 H), 5.37 (s, 1 H), 1.33 (s, 3H), 0.96 (s, 3H); ^{13}C-nmr δ 219 1 (C=O), 197.1 (C=O), 171 6 (C=O), 162.4 (C), 106.0 (CH), 48.5 (C), 46 7 (CH), 46.6 (CH), 40.8 (CH), 35.5 (CH_2), 35.2 (C), 33.5 (CH_2), 33.1 (CH_2), 30.6 (CH_2), 24.0 (CH_2), 20.0 (CH_2), 16.3 (CH_3), 13.8 (CH_3); mass spectrum 301 (M^+, 100), 273 (26), 258 (24). Exact mass calcd for $C_{18}H_{23}NO_3$: 301.1678. Found:[11] 301.1673

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11. Further recrystallization of 7 resulted in partial decomposition and a less satisfactory elemental analysis. Compounds (9) and (1) were stable and homogeneous (^{1}H-nmr and ^{13}C-nmr spectra, tlc), but gave consistently low analyses for carbon, possibly due to retention of moisture, even after prolonged drying under vacuum.
12. The $CDCl_3$ should be pretreated with K_2CO_3 to observe 7 and 8 Otherwise substantial elimination to 10 occurs, presumably because of traces of acidic impurities present in the $CDCl_3$ (e.g. HCl).

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