Highly efficient synthesis of steroid-17-spiro-5′-oxazolidine-2′,4′-diones from 17-keto steroids

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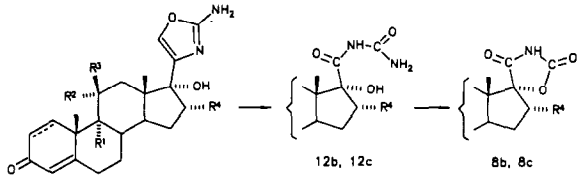
Spiro[androst-4-en-17α,5′-oxazolidine]-2′,3,4′-trione ***8a*** *and spiro[androst-4-en-17α,5′-oxazolidine]-2′,3,4′,11-tetraone* ***8b****, two potentially bioactive spiranes, were prepared from the parent 17-ketones in four steps (64% and 49.5% yield, respectively). The key intermediates were the hydroxyimidates* ***5a*** *and* ***5b****, which easily underwent cyclization to the corresponding spirooxazolinone 4′-enol ethers when treated with alkylchlorocarbonates. The respective N-amyl derivatives of the spiranes* ***8a*** *and* ***8b*** *were obtained with* n*-pentyl bromide in the presence of KF. A new method for the synthesis of steroid 17α-hydroxy-17-carboxyesters and 17α-hydroxy-17-carboxamides is described. Attempts to synthesize the title compounds from these products were unsuccessful. (Steroids* **55:**501–506, 1990)

Keywords: spirocyclization; steroid 17-spiro-5′-oxazolidinediones; androst-4-ene-3,11-dione-17-carboxy derivatives; androst-4-en-3-one-17-carboxy derivatives

Introduction

During our research directed at synthesizing small, biologically active molecules bonded to the steroidal skeleton, we prepared several anti-inflammatory 17β-(2-aminooxazol-4-yl) steroids.[1] To investigate their pharmacologic behavior, we recently subjected some of these substances to the oxidative action of hydrogen peroxide.[2] Among the reaction products isolated from compounds **13b** and **13c,** we found small amounts (5% to 10% yield) of spiro-17α,5′-oxazolidine-2′,4′-dione steroids **8b** and **8c** (SODS) (Scheme 1).



13b (R^1 = R^4 = H; R^2,R^3 = O)

13c (Δ^1; R^1 = F; R^2 = H; R^3 = OH; R^4 = Me)

Scheme 1

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Simple oxazolidine-2,4-diones are known to have various biologic and pharmacologic properties.[3–7] Preliminary experiments of lipoperoxidation on rat brain homogenates, carried out in the presence of SODS, prompted us to devise a new synthetic pathway for obtaining SODS in high yields, in order to widely test these new products in vitro and in vivo.

Experimental

General methods

Androst-4-ene-3,17-dione **1a** and androst-4-ene-3,11,17-trione **1b** were purchased from Fluka (Buchs, Switzerland). Melting points (uncorrected) were determined with a Büchi 510 (Büchi, Flawil, Switzerland) apparatus. Elemental analyses were performed on a Perkin-Elmer 240C Elemental Analyser (Perkin-Elmer Ltd., Beaconsfield, Buckinghamshire, England, UK) apparatus. Infrared (IR) spectra were recorded for KBr disks with a Perkin-Elmer 283 spectrophotometer.

Proton nuclear magnetic resonance (NMR) spectra, taken in $CDCl_3$ unless noted otherwise, were recorded on a Varian VXR-300 (Varian Associates, Inc., Palo Alto, CA, USA) apparatus; signals of protons directly bonded to nitrogen or oxygen atoms disappeared on

deuterization. ^{13}C NMR spectra were registered in the same solvent at 20 MHz with a Varian FT-80A instrument, or at 75 MHz with a Varian VXR-300 apparatus. Chemical shifts are reported in parts per million relative to tetramethylsilane. The ^{13}C resonance assignments were based on chemical shift considerations[2,8] and on the multiplicities determined by SEFT or APT experiments.[9]

Optical rotation values were measured at 20 or 25 C on a Perkin-Elmer 141 polarimeter.

Analytic thin-layer chromatographies (TLCs) were developed on Merck (Darmstadt, West Germany) precoated plastic sheets (silica gel 60 F_{254}, 0.2 mm thick); preparative flash chromatographies (PFCs)[10] were performed with suitable glass columns on 240 to 400 mesh Merck silica gel and under nitrogen pressure.

Dimethylformamide (DMF) was dried on 4 Å molecular sieves and distilled under reduced pressure. The Δ^4-3-keto steroid derivatives reported here could be used for the next steps just as isolated from the reaction mixtures, because TLC checks of these compounds showed a purity grade of at least 90%. Samples of these substances were purified, when necessary, for analytic purposes as described below.

17α-Hydroxy-3-oxoandrost-4-ene-17-carbonitrile ***(2a)***

This compound was obtained (84% yield) from androst-4-ene-3,17-dione **1a** and KCN (1 : 2 M ratio), following the reported conditions[11]: mp 169 to 170 C (dec), lit.[7] 169 to 172 C (dec); ^{13}C NMR, δ 77.49 (C-17), 120.82 (CN), 123.78 (C-4), 171.09 (C-5), 199.82 (C-3). The other analytic and spectroscopic data are in accordance.

17α-Hydroxy-3-oxoandrost-4-ene-17-carboxamide ***(4a)***

Cyanohydrin **2a** (1.27 g, 4 mmol) was suspended in anhydrous MeOH (20 ml) at −20 C, with stirring, and saturated with anhydrous HCl, keeping the temperature between −5 and 0 C. The solution was then left to stand overnight at −10 C. After 2 hours at room temperature, the solution was evaporated to dryness under reduced pressure and nitrogen flushing. The crystalline product obtained was powdered and heated at 80 C for 1.5 hours under nitrogen, affording the carboxamide **4a** (1.22 g, 91% yield). The product was purified by PFC with 1,1,1-trichloroethane/MeOH (100 : 12) and dried under reduced pressure at 40 C for 2 hours: mp 274 to 277 C (dec), lit.[12] 271 to 273.5 C; $[\alpha]_D$ + 74.4 (*c* 0.32, acetone); IR, ν_{max} 3,460 (OH), 3,360 and 3,280sh (NH_2), 1,680 [C(3)O], 1,650 to 1,640 (amide I), 1,610 cm^{-1} (C = C); ^1H NMR (hexadeuteriodimethylsulfoxide [DMSO]), δ 0.65 (s, 3H, 13-Me), 1.12 (s, 3H, 10-Me), 5.02 (s, 1H, OH), 5.63 (s, 1H, 4-H), 6.85 and 6.98 (d and d, *J* = 2.1 Hz, NH_2); ^{13}C NMR (DMSO), 84.82 (C-17), 123.10 (C-4), 170.94 (C-5), 175.70 ($CONH_2$), 197.92 (C-3).

Analysis calculated for $C_{20}H_{29}NO_3$: C,72.47; H, 8.82; N, 4.23. Found: C, 72.12; H, 8.92; N, 4.14.

Methyl 17α-hydroxy-3-oxoandrost-4-ene-17-carboximidate ***(5a)***

Compound **2a** (1.52 g, 4.8 mmol) was treated with anhydrous HCl, as described above. The solution was then concentrated under reduced pressure and cooled at 0 C. The pH value was adjusted up to 8 with concentrated aqueous NaOH and aqueous ammonia, affording the product (1.57 g, 94% yield) as a colorless precipitate. Purification was performed by PFC (1,1,1-trichloroethane/MeOH [10 : 1.5]) or by crystallization from acetone: mp 212 C (premelting point), 217 to 218 C (dec); $[\alpha]_D^{25}$ + 70 (*c* 0.108, MeOH); IR, ν_{max} 3,530 (OH), 3,280 (NH), 1,670 [C(3)O], 1,640 (C = NH), 1,620 cm^{-1} (C = C); ^1H NMR, δ 0.69 (s, 3H, 13-Me), 1.18 (s, 3H, 10-Me), 3.73 (s, 3H, OMe), 5.73 (s, 1H, 4-H), ca 7.51 (br, 1H, NH); ^{13}C NMR (DMSO), δ 53.29 (OMe), 83.32 (C-17), 123.06 (C-4), 170.73 (C-5), 173.78 (C = NH), 197.71 (C-3).

Analysis calculated for $C_{21}H_{31}NO_3$: C, 73.01; H,9.04; N, 4.05. Found: C, 73.06; H, 9.11; N, 3.88.

Methyl 17α-hydroxy-3-oxoandrost-4-ene-17-carboxylate ***(6a)***

Compound **2a** (1.56 g, 5 mmol) was treated with anhydrous HCl, as above. After 2 hours at room temperature, the reddish solution was poured in ice/water mixture (200 ml) under vigorous stirring. After 3 hours, the colorless precipitate (1.36 g, 79% yield) was collected and recrystallized from EtOAc: mp 210–211 C (became brown at 170 C); $[\alpha]_D$ + 110 (*c* 0.28, 95% EtOH); IR, ν_{max} 3,530 (OH), 1,715 (COOMe), 1,670 [C(3)O], 1,620 cm^{-1} (C = C); ^1H NMR, δ 0.71 (s, 3H, 13-Me), 1.17 (s, 3H, 10-Me), 2.86 (s, 1H, OH), 3.75 (s, 3H, COOMe), 5.71 (s, 1H, 4-H); ^{13}C NMR, δ 52.31 ($COOCH_3$), 85.93 (C-17), 123.92 (C-4), 170.92 (C-5), 174.63 (*C*OOMe), 199.34 (C-3).

Analysis calculated for $C_{21}H_{30}O_4$: C, 72.80; H, 8.73. Found: C, 72.49; H, 8.77.

Methyl 3-ethylenedioxy-17α-hydroxyandrost-5-ene-17-carboxylate ***(6a')***

Trimethyl orthoformate (0.5 ml, 4.56 mmol) and *p*-toluensulfonic acid monohydrate (6 mg) were added to the carboxylate **6a** (0.25 g, 0.7 mmol) suspended in ethylene glycol (1.5 ml). The solution was then heated at 40 C under stirring. After 40 minutes, the precipitate was collected and recrystallized from MeOH (0.203 g, 72% yield): mp 197 to 200 C (dec); $[\alpha]_D^{25}$ − 21 (*c*) 0.124, 95% EtOH); IR, ν_{max} 3,490 (OH), 1,725 (COOMe), 1,100 cm^{-1} (ethylenedioxy group); ^1H NMR, δ 0.70 (s, 3H, 13-Me), 1.03 (s, 3H, 10-Me), 2.78 (s, 1H, OH), 3.75 (s, 3H, COOMe), 3.94 (m, 4H, OCH_2CH_2O), 5.35 (m, 1H, 6-H); ^{13}C NMR, δ 52.21 ($COOCH_3$), 64.3 and 64.51 (OCH_2CH_2O), 86.20 (C-17), 109.38 (C-3), 121.94 (C-6), 140.0 (C-5), 174.76 (*C*OOMe).

Analysis calculated for $C_{23}H_{34}O_5$: C, 70.74; H, 8.78. Found: C, 70.52; H, 8.72.

*Spiro[androst-4-en-17α,5'(2'H)-oxazoline]-4'-methoxy-2',3-dione (**7a**)*

N-Methylmorpholine (NMM, 0.67 ml, 6 mmol) was added dropwise at 0 C to a solution of the methyl carboximidate **5a** (0.36 g, 1 mmol) and methyl chloroformate (0.46 ml, 6 mmol) in CH_2Cl_2 (4 ml), and the resulting suspension was left overnight at 0 C. The solid was filtered off and washed with CH_2Cl_2. The filtrates were evaporated to dryness under reduced pressure. The residue, treated with cold MeOH, afforded the product (0.27 g); a second crop (0.08 g) was obtained by the addition of a small amount of water to the methanolic solution (overall yield 90%). The compound was recrystallized from MeOH: mp 154 to 155 C; $[\alpha]_D$ + 63 (*c* 0.266, 95% EtOH); ν_{max} 1,794 [C(2')O], 1,670 [C(3)O], 1,620 cm^{-1} (C = N and C = C); ^1H NMR, δ 0.97 (s, 3H, 13-Me), 1.19 (s, 3H, 10-Me), 4.16 (s, 3H, OMe), 5.74 (s, 1H, 4-H); ^{13}C NMR, δ 59.21 (OMe), 95.37 (C-17), 124.14 (C-4), 163.26 (C-2'), 170.17 (C-5), 191.47 (C-4'), 199.08 (C-3).

Analysis calculated for $C_{22}H_{29}NO_4$: C, 71.13; H, 7.87; N, 3.77. Found: C, 70.82; H, 7.89; N, 3.74.

*Spiro[androst-4-en-17α,5'-oxazolidine]-2',3,4'-trione (**8a**)*

Aqueous 0.1 M HCl (0.6 ml) was added to a suspension of the spirane **7a** (0.2 g, 0.54 mmol) in MeOH (24 ml) at room temperature. After 15 hours, the solution was neutralized with dilute methanolic ammonia and concentrated under reduced pressure. After the addition of water and cooling with ice, the pure spirane **8a** (0.174 g, 90% yield) precipitated. The product was dried under reduced pressure at 60 C: mp 263 to 265 (dec); $[\alpha]_D$ + 115 (*c* 0.323, MeOH); IR, ν_{max} 3,200 to 2,700 (NH), 1,825 [C(2')O], 1,755 [C(4')O], 1,660 [C(3)O], 1,620 cm^{-1} (C = C); ^1H NMR (DMSO), 0.93 (s, 3H, 13-Me), 1.16 (s, 3H, 10-Me), 5.64 (s, 1H, 4-H), 11.76 (br s, 1H, NH); ^{13}C NMR (DMSO), 95.33 (C-17), 123.17 (C-4), 154.33 (C-2'), 170.31 (C-5), 174.7 (C-4'), 197.71 (C-3).

Analysis calculated for $C_{21}H_{27}NO_4$: C, 70.56; H, 7.61; N, 3.92. Found: C, 70.76; H, 7.87; N, 4.02.

*Spiro[androst-4-en-17α,5'-oxazolidine]-3'-pentyl-2',3,4'-trione (**9a**)*

Spirane **8a** (0.1 g, 0.28 mmol) was dissolved in anhydrous DMF (2.5 ml). KF (40 mg, 0.69 mmol) and, after 10 minutes, *n*-pentyl bromide (40 μl, 0.32 mmol) were added to the solution, with stirring. The mixture, left 48 hours at room temperature, gave a precipitate that was filtered off. The filtrate was concentrated under reduced pressure. Pure *n*-pentyl derivative **9a** (0.105 g, 88% yield) precipitated by adding a small amount of water. The product was dried at 60 C under vacuum: mp 160 C (wrinkled gradually from 156 C); $[\alpha]_D^{25}$ + 121 (*c* 0.138, 95% EtOH); IR, ν_{max} 1,808 [C(2')O], 1,736 [C(4')O], 1,670 [C(3)O], 1,618 cm^{-1} (C = C); ^1H NMR, δ 0.88 (t, 3H, *J* = 6.9 Hz, CH_2CH_3), 1.01 (s, 3H, 13-Me), 1.86 (s, 3H, 10-Me), 3.50 [AB m (δ_A 3.48, δ_B 3.52), 2H, J_{AB} = 13.6 Hz, NCH_2], 5.74 (s, 1H, 4-H); ^{13}C NMR, δ 95.0 (C-17), 124.18 (C-4), 154.80 (C-2'), 170.06 (C-5), 173.50 (C-4'),199.12 (C-3).

Analysis calculated for $C_{26}H_{37}NO_4$: C, 73.03; H, 8.72; N, 3.28. Found: C, 72.77; H, 8.93; N, 2.98.

*17α-Ethoxycarbonyloxy-3-oxoandrost-4-ene-17-carbonitrile (**10a**)*

Ethyl chloroformate (1.2 ml, 12.5 mmol) and 2 M aqueous Na_2CO_3 (6.4 ml, 12.8 mmol) were added to cyanohydrin **2a** (1 g, 3.2 mmol), suspended in CH_2Cl_2 (50 ml) at 0 C, together with a catalytic amount of tetrabuthylammonium chloride. The mixture was stirred at 0 C for 30 days. During this period, ethyl chloroformate (9 ml) was added and the pH was kept at 8 by adding aqueous 3 M Na_2CO_3. When compound **2a** disappeared on control TLC (CH_2Cl_2/ethyl acetate [30 : 1]), CH_2Cl_2 (5 ml) and water were added. The organic layer was collected, dried, and evaporated, affording the product (0.6 g, 49% yield). The compound was purified by PFC, with the same eluent of TLC; mp 173 C (premelting point), 178 to 180 C (dec); $[\alpha]_D$ + 76 (*c* 0.328, MeOH); IR, ν_{max} 1,770 (OCOEt), 1,680 [C(3)O], 1,620 cm^{-1} (C = C); ^1H NMR, δ 1.07 (s, 3H, 13-Me), 1.2 (s, 3H, 10-Me), 1.33 (t, 3H, CH_3CH_2), 4.24 (m, 2H, $MeCH_2$), 5.73 (s, 1H,4-H); ^{13}C NMR, δ 83.16 (C-17), 117.30 (CN), 124.10 (C-4), 152.80 (OCOEt), 170.03 (C-5), 199.13 (C-3).

Analysis calculated for $C_{23}H_{31}NO_4$: C, 71.66; H, 8.10; N, 3.63. Found: C, 71.81; H, 8.27; N, 3.55.

*3,11-Dioxo-17α-hydroxyandrost-4-ene-17-carbonitrile (**2b**)*

Glacial acetic acid (AcOH) (0.55 ml, 9.6 mmol) was added dropwise, at room temperature and under vigorous stirring, to a suspension of androst-4-ene-3,11,17-trione **1b** (2 g, 6.7 mmol) and KCN (0.8 g, 12.3 mmol) in MeOH (10 ml). After 45 minutes, the cyanohydrin **2b** began to precipitate from the solution. The suspension was left at 15 C for 5 hours and at 0 C for 30 minutes. The colorless precipitate was collected and washed with cold MeOH and water, affording the product (1.57 g, 72% yield), which was recrystallized from a saturated solution in MeOH at 40 to 50 C and cooled at −10 C; it decomposed at 185 C without melting: $[\alpha]_D^{25}$ + 248 (*c* 0.103, MeOH); IR, ν_{max} 3,340 (OH), 2,232 (CN), 1,713 [C(11)O], 1,665 [C(3)O], 1,613 cm^{-1} (C = C); ^1H NMR, δ 0.95 (s, 3H, 13-Me), 1.42 (s, 3H, 10-Me), 5.74 (s, 1H, 4-H), 6.7 (s, 1H, OH; detectable in DMSO); ^{13}C NMR, δ 77.25 (C-17), 119.84 (CN), 124.62 (C-4), 169.02 (C-5), 200.38 (C-3), 208.44 (C-11).

Analysis calculated for $C_{20}H_{25}NO_3$: C, 73.37; H, 7.70; N, 4.28. Found: C, 73.38; H, 7.83; N, 4.14.

*Methyl 3,11-dioxo-17α-hydroxyandrost-4-ene-17-carboximidate (**5b**)*

Cyanohydrin **2b** (0.5 g, 1.53 mmol) was dissolved in MeOH (20 ml) and treated as compound **2a**, giving the product (0.5 g, 91% yield). The product was recrystallized from warm (60 C) anhydrous EtOH, by cooling

to 0 C: mp 205 to 206 C (dec); $[\alpha]_D^{25}$ + 164 (*c* 0.08, MeOH); IR, ν_{max} 3,300 (OH), 3,150 (NH), 1,700 [C(11)O], 1,674 [C(3)O], 1,645 (C = N), 1,618 cm^{-1} (C = C); ^1H NMR, δ 0.65 (s, 3H, 13-Me), 1.41 (s, 3H, 10-Me), 3.74 (s, 3H, OMe), 5.73 (s, 1H,4-H), 7.58 (br s, 1H, NH); ^{13}C NMR, δ 53.0 (OMe), 84.23 (C-17), 124.6 (C-4), 168.72 (C-5), 171.71 (C = NH), 199.8 (C-3), 209.96 (C-11).

Analysis calculated for $C_{21}H_{29}NO_4$: C, 70.17; H, 8.13; N, 3.90. Found: C, 69.93; H, 8.19; N, 3.68.

Methyl 3,11-dioxo-17α-hydroxyandrost-4-ene-17-carboxylate **(6b)**

This product (0.08 g) was obtained by PFC (ethyl acetate) or crude compound **5b** (0.44 g) and recrystallized from MeOH: mp 224 to 226 C (dec); $[\alpha]_D^{25}$ + 179 (*c* 0.142, 95% EtOH); IR, ν_{max} 3,320 (OH), 1,738 (COOMe), 1,708 [C(11)O], 1,670 [C(3)O], 1,614 cm^{-1} (C = C); ^1H NMR (DMSO), 0.53 (s, 3H, 13-Me), 1.32 (s, 3H, 10-Me), 3.64 (s, 3H, OMe), 5.54 (s, 1H, OH), 5.64 (s, 1H, 4-H); ^{13}C NMR, δ 53.0 (OMe), 84.96 (C-17), 124.63 (C-4), 168.5 (C-5), 173.86 (COOMe), 199.67 (C-3), 209.53 (C-11).

Analysis calculated for $C_{21}H_{28}O_5$: C, 69.97; H, 7.83. Found: C, 69.92; H, 7.89.

Spiro[androst-4-en-17α,5'(2'H)-oxazoline]-4'-methoxy-2',3,11-trione **(7b)**

Methyl carboximidate **5b** (0.36 g, 1 mmol), treated as compound **5a**, afforded the product **7b** (0.35 g, 91% yield). The crude product was recrystallized from MeOH and dried at 50 C, under reduced pressure: mp 154 C (premelting point), 170 to 172 C; $[\alpha]_D^{25}$ + 111 (*c* 0.083, MeOH); IR (CH_2Cl_2), ν_{max} 1,791 [C(2')O], 1,712 [C(11)O], 1,670 [C(3)O], 1,608 cm^{-1}(C = N and C = C); ^1H NMR, δ 0.93 (s, 3H, 13-Me), 1.41 (s, 3H, 10-Me), 4.18 (s, 3H, OMe), 5.74 (s, 1H, 4-H); ^{13}C NMR, δ 59.62 (OMe), 94.0 (C-17), 124.84 (C-4), 162.65 (C-2'), 167.70 (C-5), 190.50 (C-4'), 199.40 (C-3), 207.35 (C-11).

Analysis calculated for $C_{22}H_{27}NO_5$: C, 68.55; H, 7.06; N, 3.63. Found: C, 68.08; H, 7.17; N, 3.91.

Spiro[androst-4-en-17α,5'-oxazolidine]-2',3,4',11-tetraone **(8b)**

Spirane **7b** (0.2 g, 0.52 mmol), was dissolved in MeOH (12 ml) and treated as described for preparing compound **8a**. On standing, a precipitate was formed. The solution was concentrated, cooled to 0 C, and filtered, affording the pure spirane **8b** (0.16 g, 83% yield). Analytic, spectroscopic, and chromatographic data are the same as the compound obtained from the aminooxazole **13b**.[2]

Spiro[androst-4-en-17α,5'-oxazolidine]-3'-pentyl-2',3,4',11-tetraone **(9b)**

Spirane **8b** (0.1 g, 0.27 mmol) was treated as compound **8a**, affording the pure derivative **9b** (0.098 g, 82% yield): mp 165 C (wrinkled gradually from 151 C); $[\alpha]_D^{25}$ + 166 (*c* 0.108, 95% EtOH); IR, ν_{max} 1,811 [C(2')O, 1,740 [C(4')O], 1,710 [C(11)O], 1,670 [C(3)O], 1,618 cm^{-1} (C = C); ^1H NMR, δ 0.89 (t, 3H, *J* = 6.9 Hz, CH_2CH_3), 0.97 (s, 3H, 13-Me), 1.41 (s, 3H, 10-Me), 3.50 [AB m (δ_A 3.48, δ_B 3.52), 2H, J_{AB} = 13.6 Hz, NCH_2], 5.74 (s, 1H, 4-H); ^{13}C NMR, δ 93.56 (C-17), 124.85 (C-4), 154.20 (C-2'), 167.58 (C-5),172.24 (C-4'), 199.30 (C-3), 207.03 (C-11).

Analysis calculated for $C_{26}H_{35}NO_5$: C, 70.72; H, 7.99; N, 3.17. Found: C, 70.78; H, 8.19; N, 2.85.

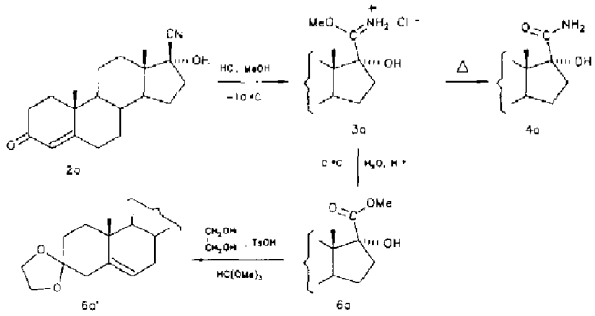
3,11,17-Trioxoandrostane-5ξ-carbonitrile **(1d)**

KCN (1.3 g, 20 mmol) and AcOH (0.9 ml, 15.7 mmol) were added to a suspension of compound **1b** (3 g, 10 mmol) in MeOH (20 ml). The precipitate formed during the reaction slowly redissolved and the solution was left overnight at room temperature. Water was then added, which gave a reddish, sticky precipitate that was redissolved in MeOH. After 48 hours at room temperature and 12 hours at 0 C, the colorless product obtained was recrystallized from 95% EtOH (0.74 g, 23% yield): mp 250 C (premelting point), 260 C (dec); $[\alpha]_D^{25}$ + 157 (*c* 0.127, 95% EtOH); IR, ν_{max} 2,220 (CN), 1,741 [C(17)O], 1,714 [C(11)O], 1,696 (1,713 cm^{-1} in CH_2Cl_2) [C(3)O]; ^1H NMR, δ 0.85 (s, 3H, 13-Me), 1.36 (s, 3H, 10-Me); ^{13}C NMR, δ 46.54 (C-4), 47.24 (C-5), 121.31 (CN), 205.25 and 207.25 (C-3 and C-11), 216.04 (C-17).

Analysis calculated for $C_{20}H_{25}NO_3$: C, 73.37; H, 7.70; N, 4.28. Found: C, 73.28; H, 7.77; N, 4.33.

Results and discussion

Oxazolidine-2,4-diones are commonly synthesized by reaction of α-hydroxyesters or α-hydroxyamides with urea and KOCN or with dialkylcarbonates and alkylchlorocarbonates.[3,5–7,13] Thus, we first prepared the known cyanohydrin **2a** from androst-4-ene-3,17-dione **1a**.[11] The 17β-cyano group was then converted both to the 17β-carboxamide **4a** and the 17β-methylcarboxylate **6a**, through a common intermediate (the methyl 17β-carboximidate hydrochloride **3a**), characterized by spectroscopic data (Scheme 2).



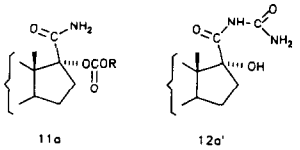
Scheme 2

The hydrolysis of the carboximidate hydrochloride, carried out according to the original method recently reported by Chatterjee and co-workers as a general way for the hydrolysis of α-tertiary and quaternary

nitriles to esters and amides,[14] gave the amide **4a** in a poor yield. Therefore, we prepared this compound in higher yield by heating the dry imidoester salt at 80 C (Pinner's method[15]). A different synthesis of amide **4a** has been previously reported without analytic and spectroscopic data.[12]

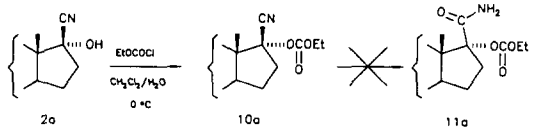
The 3-ethylenedioxy derivative **6a'** of the ester **6a** and the amide **4a** were then cyclized in the standard conditions.[3,5–7,13] Moreover, for the amide **4a,** we also used different alkylchlorocarbonate substitutions in homogeneous solution, or with a phase transfer reaction, in the presence of different bases. Surprisingly, the expected spirooxazolidinediones were not formed and, in all of the experiments, we primarily recovered the starting compounds.

Attempts to prepare the spirane from the amide **4a** and phosgene were ineffective at low temperatures. At higher temperature, the cyanohydrin **2a** was reformed. We could not detect active intermediates similar to those represented by the structures **11a** and **12a'**



Scheme 3

(Scheme 3), which were expected to afford the oxazolidine ring.[2,3,7] An attempt to obtain the 17α-ethoxycarbonyloxy-17-carboxamide **11a** by a different method, i.e., from the O-substituted 17-carbonitrile (Scheme 4),

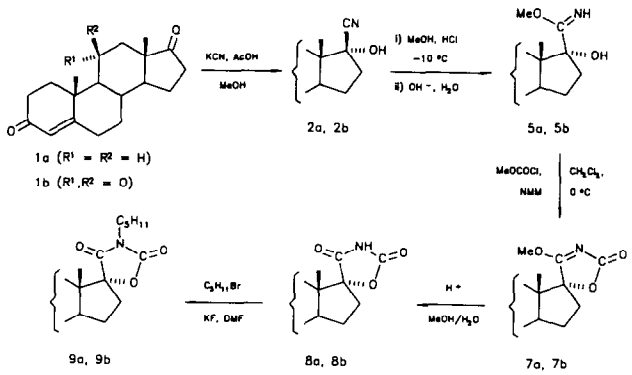


Scheme 4

failed too. We ascertained the absence of the intermediate imidoester hydrochloride in the reaction solution.

By comparing molecular models, the free imidate base seemed to offer a better access to the reagents; on the other hand, imidoesters were reported as good nucleophiles toward alkylchlorocarbonates.[16] On this basis, we devised the following synthetic pathway to SODS starting from androst-4-ene-3,17-dione and androst-4-ene-3,11,17-trione (Scheme 5).

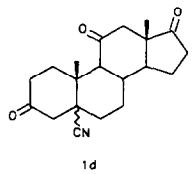
The cyanohydrin **2b** was obtained by modifying the conditions used for the cyanohydrin **2a**[11] and only the β-cyano isomer crystallized out.* The correct stereochemistry at C-17 was suggested by the proton resonance of 13-Me group at δ 0.95 (δ 0.96 for **2a** in the



Scheme 5

same solvent). This structure was then confirmed by the identity of **8b** with the compound obtained by the peroxidic oxidation of 17α-hydroxy-17-(2-aminooxazol-4-yl)-androsta-3,11-dione.[2]

On treatment of the parent androstenetrione **1b** with KCN in the conditions used for androstenedione **1a** and dissolving the crude product in MeOH, a substance, identified as the androsta-3,10,17-trioxo-5ξ-carbon-



Scheme 6

itrile **1d,** slowly crystallized (Scheme 6). In the IR spectra, the absorption of the CN group appeared at 2,220 cm^{-1} while the α-saturated C(3)O was found at 1,713 cm^{-1} (CH_2Cl_2). Proton NMR data confirmed the absence of olefinic protons. The positon of the CN group in C-5 was indicated by the number of quaternary carbons in the ^{13}C NMR spectrum; we assigned the signals at δ 46.54 and 47.24 to the C-4 and C-5 resonances, respectively. The stereochemistry of the hydrocyanation was not further investigated.

A slightly alkaline medium (approximately pH 8) favored the crystallization of the imidates **5a** and **5b** from the reaction solutions. TLC inspection revealed the presence of the corresponding methyl carboxylates as the unique impurity; their amount was rapidly increased by retention on silica gel. This feature was used to obtain and characterize the methyl 3,11-dioxo-17α-hydroxyandrost-4-ene-17-carboxylate **6b**. The IR spectra of derivatives **5a** and **5b** showed the C = N stretching at 1,640 and 1,645 cm^{-1}, respectively; NH proton resonances occurred at δ 7.5 and 7.6 in $CDCl_3$.

The free imidates **5a** and **5b** easily underwent cyclization to the spirooxazolinone 4-enol ethers **7a** and **7b** with methyl, ethyl, or benzyl chlorocarbonates at 0 C. The intermediate N-alkyloxycarbonyl imidates were not isolated: with the hindered isobutyl chlorocarbon-

* Recently, Van Rheenen claimed to have obtained the cyanohydrin **2b** from the parent steroid and acetone cyanohydrin[17]; however, no account of the reaction or of analytic and spectroscopic data was reported.

ate, at 0 C, the reaction did not take place; at higher temperatures, only the derivatives **7a** and **7b** were slowly formed. The O-methoxy spirooxazolinones were also obtained in phase transfer conditions; however, the yield was lower and the reaction times longer. In their ^{13}C NMR spectra, the C-4′ resonances were shifted downfield by approximately 18 ppm with respect to the open imidate carbon, because of the conjugation with the carbonyl group in C-2′. Our assignment of the heterocylic ring carbons is in accordance with that reported for the 4-dimethylamino-5-methyl-5-phenyl-3-oxazolin-2-one.[18]

The spiranes **8a** and **8b** were obtained by mild hydrolysis of the corresponding enol ethers in acidic medium and were isolated directly as analytically pure compounds. In their IR spectra, two strong carbonyl absorptions were detected: the band above 1,800 cm^{-1} could be related to the C(2′)O stretching.[19] ^1H NMR and ^{13}C NMR assignments are in accordance with our previous findings on these substances.[2]

To increase the liposolubility of these molecules, we prepared the N-amyl derivatives **9a** and **9b.** Although N-alkylated oxazolidine-2,4-diones may be traditionally prepared from their sodium or potassium salts and alkyl halogenides,[3,20] we avoided strong alkaline media by using a solution of KF in anhydrous DMF. This method provided an efficient route to phenacyl esters[21] and, on Celite support, to some N-alkyl amines.[22] In our case, the strong H-bond between the fluoride anion and the 3′-NH group made the nitrogen a good nucleophile toward the pentyl bromide, in spite of the two conjugated carbonyl groups. Thus, from spirooxazolidinediones **8a** and **8b,** we smoothly obtained the N-alkylated derivatives **9a** and **9b** as pure compounds from the reaction solutions; no O-alkylated oxazolines were formed in this reaction.

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