RADICAL OXIDATION OF 17-FUNCTIONALIZED 14α-HYDROXY STEROIDS

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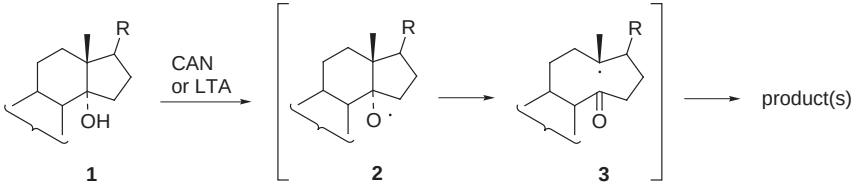
The radical oxidation of 14α-hydroxy steroids with various functional groups at C-17 was studied. Lead tetraacetate and ceric ammonium nitrate were used as oxidizing agents. It was shown that reactions of this type afforded complex mixtures of compounds. However, the radical oxidation of 14α-hydroxy-17-oxo steroid (lead tetraacetate version of the hypoiodite reaction) proceeded smoothly with formation of the 13,14-secosteroid in up to 85% yield. The structure and conformation of the formed 13α-iodo-3α,5-cyclo-13,14-seco-5α-androst-5-ene-14,17-dione was determined by X-ray analysis.

Keywords: Steroids; Secosteroids; Radical oxidations; Lead tetraacetate; Ceric ammonium nitrate; Fragmentation; Conformation analysis.

Radical oxidation of steroids with hydroxy group at C-5 has been extensively studied for the preparation of various steroidal compounds with a modified AB rings. The reaction can be effected by treatment of 5α/5β-alcohols with lead tetraacetate[1] (LTA) or 5α-alcohols with ceric ammonium nitrate[2] (CAN) and leads mainly to 5,10-secosteroids. It was assumed that these compounds would differ significantly from normal steroids by conformation of the basic carbon skeleton[3,4] and that a new set of biological properties might be expected. This was the case in acetylenic 5,10-seco-

steroids which were found[5–7] to be irreversible inhibitors of Δ^5-3-ketosteroid isomerase.

We were interested in studying similar transformations of 14α-alcohols as possible precursors of steroids with an unusual CD cyclic part. The 13,14-secosteroidal moiety is also characteristic of some natural compounds like carolinoside[8] or withaphysalins[9]. It was assumed that treatment of 14α-hydroxy derivatives **1** with CAN or LTA would result in the formation of radical **2** (Scheme 1). β-Fission of the latter should lead to radical **3**, which can produce a number of products with modified carbon skeletons depending on the substituent R.



SCHEME 1

Investigations using this approach have thus far been conducted for derivatives containing oxo group[10] or a cholestane side chain[11] at C-17. In the first case the formation of 13-iodo-13,14-secosteroids was observed using LTA/I_2; however, the stereochemistry at C-13 remained to be undetermined. Oxidation with LTA of 14α-hydroxy steroids with a cholestane side chain under thermal or photolytic conditions resulted also in fragmentation of the C_{13}–C_{14} bond to give the corresponding Δ^{12}- and $\Delta^{13(18)}$-13,14-seco derivatives[11]. In addition, formation of compounds with a pyran cycle and other cyclization products was observed. Another result of radical oxidation of 14α-alcohols with HgO/I_2 was dehydration to the Δ^{14}-alkenes.

We decided to extend the number of 14α-hydroxy steroids as substrates for the radical oxidation and to pay more attention to the stereochemistry and conformation of the formed products.

EXPERIMENTAL

Melting points were taken on a Boetius melting point microapparatus and are uncorrected. IR spectra (wavenumbers in cm^{-1}) were recorded on a UR-20 spectrophotometer. ^1H and ^{13}C NMR spectra were, unless otherwise stated, taken on a Bruker AC-200 (200 MHz for ^1H, 50 MHz for ^{13}C) spectrometer using TMS as an internal standard. Chemical shifts are given in δ (ppm), coupling constants (*J*) in Hz. MS and HRMS data were obtained with a Finnigan MAT95 spectrometer. X-Ray data collection (Nicolet R3m diffractometer) was performed *via* the ω/2θ scan mode. The structure was solved by direct methods (SIR97)[12] and refined by

full-matrix least squares (SHELXL97)[13]. Positions of hydrogen atoms were calculated, and refined by using the riding model. All chemicals were of analytical grade. 3β-Acetoxy-14α-hydroxyandrost-5-en-17-one was obtained from Organon N.V. (Akzo Nobel, Netherlands). Reactions were monitored by TLC using aluminium or plastic sheets with silica gel 60 F_{254} precoated (Merck Art. 5715). Column chromatography was carried out on Kieselgel 60 (Merck Art. 7734). Usual work-up includes washing of the organic layer with water followed by drying (anhydrous Na_2SO_4) and evaporation *in vacuo*.

Oxidation of **4** with CAN

To a stirred solution of hydroxy ketone **4** (200 mg, 0.58 mmol) in CH_3CN (3 ml), a solution of CAN (1.112 g, 2.03 mmol) in water (0.5 ml) was added at 75 °C. The solution became colorless in 0.5 min. After the usual work-up, the residue was chromatographed on SiO_2 to give:

a) *(13S)-3β-Acetoxy-13-hydroxy-13,14-secoandrost-5-ene-14,17-dione 13-nitrate* (**5**) (50 mg, 40% based on used **4**). MS, *m/z* (rel.%): 347 (12), 301 (54), 159 (71), 158 (31), 157 (64), 145 (85), 105 (41), 81 (39). HRMS: calculated for $C_{19}H_{25}NO_5$: 347.1733 (M^+ – AcOH), found: 347.1735; calculated for $C_{19}H_{25}O_3$: 301.1804 (M^+ – AcOH – NO_2), found: 301.1804.

b) Starting ketol **4** (75 mg).

Androst-5-ene-3β,14α-diol (**6**)

A solution of ketol **4** (200 mg, 0.58 mmol), KOH (325 mg, 5.8 mmol), and $N_2H_4 \cdot H_2O$ (0.5 ml, 11.6 mmol) in diethylene glycol (3 ml) was heated at 185 °C for 2 h. The reaction mixture was cooled, diluted with water, and extracted with EtOAc and toluene. The combined extracts were evaporated to give diol **6** (160 mg, 95%) as white crystals, m.p. 172–174 °C (hexane). ^{1}H NMR: 0.90 s, 3 H (3 × 18-H), 1.04 s, 3 H (3 × 19-H); 3.52 m, 1 H (3-H); 5.40 m, 1 H (6-H). ^{13}C NMR: 19.2, 19.3, 19.8, 21.9, 26.1, 30.6, 31.6, 33.7, 34.5, 36.4, 36.6, 37.3, 42.2, 43.8, 44.8, 71.6, 83.5, 121.7, 140.2.

3β-Acetoxyandrost-5-en-14α-ol (**7**)

To a solution of diol **6** (150 mg, 0.52 mmol) in pyridine (2 ml), acetic anhydride (0.5 ml, 5.2 mmol) was added. The reaction mixture was left at room temperature for 16 h, then diluted with water, and extracted with EtOAc. The extract was dried (anhydrous Na_2SO_4) and the solvent was evaporated. The residue was crystallized from hexane to give the acetate **7** (2.6 g, 76%) as white crystals, m.p. 109–110 °C. ^{1}H NMR: 0.90 s, 3 H (3 × 18-H); 1.06 s, 3 H (3 × 19-H); 2.04 s, 3 H (OAc); 4.60 m, 1 H (3-H); 5.44 brs, 1 H (6-H). IR (KBr): 1 730, 1 470, 1 440, 1 385, 1 260,1 040.

Oxidation of **7** with CAN

To a stirred solution of **7** (200 mg, 0.60 mmol) in CH_3CN (3 ml) at 55 °C, a solution of CAN (825 mg, 1.5 mmol) in water (0.4 ml) was added. The solution became dark-brown and then in 30 s colorless. The reaction mixture was diluted with ether and washed with water. The organic layer was dried (anhydrous Na_2SO_4) and evaporated. The residue was chromatographed on SiO_2 to give 3β-acetoxyandrosta-5,14-diene (**8**) (28 mg, 15%), m.p.

105–107 °C (hexane). ^{1}H NMR: 0.98 s, 3 H (3 × 18-H); 1.02 s, 3 H (3 × 19-H); 2.02 s, 3 H (OAc); 4.60 m, 1 H (3-H); 5.14 brs, 1 H (15-H); 5.44 brs, 1 H (6-H).

3β-Acetoxyandrost-5-ene-14α,17β-diol (**9**)

To a solution of ketol **4** (2.0 g, 5.7 mmol) in EtOAc (30 ml) and MeOH (7.5 ml), $NaBH_4$ (430 mg, 11 mmol) was added portionwise during 0.5 h. The mixture was stirred for 1 h and then dilute AcOH was added. The solvent was evaporated, the residue was dissolved in $CHCl_3$ and water was added. The organic layer was separated, washed with brine, dried (anhydrous Na_2SO_4) and evaporated. The residue was chromatographed on silica gel (toluene–EtOAc 5 : 1 and 1 : 1) to give diol **9** (1.8 g, 89%), m.p. 147–150 °C (hexane–EtOAc). ^{1}H NMR: 0.90 s, 3 H (3 × 18-H); 1.06 s, 3 H (3 × 19-H); 2.04 s, 3 H (OAc); 4.30 dd, 1 H, J_1 = 11, J_2 = 7 (17-H); 4.58 m, 1 H (3-H); 5.40 brs, 1 H (6-H).

Oxidation of **9** with CAN

To a solution of diol **9** (100 mg, 0.28 mmol) in CH_3CN (1.5 ml), CAN (798 mg, 1.42 mmol) dissolved in water (0.4 ml) was added at room temperature. The solution became dark-brown, and then in 30 s its color changed to yellow. The reaction mixture was diluted with ether and the organic layer was washed with brine, dried (anhydrous Na_2SO_4), and evaporated. The residue was chromatographed on silica gel (hexane–EtOAc 3 : 1 and 1 : 1) to give:

a) *3β-Acetoxy-13,14-dioxo-13,14:13,17-disecoandrost-5-en-17-al* (**10**) (35 mg, 38%) as a colorless oil. ^{1}H NMR: 1.04 s, 3 H (3 × 19-H); 2.04 s, 3 H (OAc); 2.10 s, 3 H (3 × 18-H); 4.60 m, 3 H (3-H); 5.40 brs, 1 H (6-H); 9.80 s, 1 H (-CHO). ^{13}C NMR: 18.6, 21.4, 22.8, 27.4, 30.0, 30.4, 36.0, 36.7, 37.2, 37.7, 38.2, 44.8, 46.7, 49.0, 75.4, 120.9, 139.7, 170.5, 200.1, 208.8, 213.1. IR (KBr): 1 730, 1 710, 1 440, 1 370, 1 250, 1 040.

b) *3β-Acetoxy-14-oxo-des-D-androst-5-ene 13-carbaldehyde* (**11**) (12 mg, 14%) as a colorless oil. ^{1}H NMR: 1.00 s, 3 H (3 × 19-H); 1.20 s, 3 H (3 × 18-H); 2.04 s, 3 H (OAc); 4.58 m, 1 H (3-H); 5.40 d, 1 H, J = 6 (6-H); 9.86 s, 1 H (-CHO). ^{13}C NMR: 18.4, 21.4, 23.7, 25.2, 27.4, 27.8, 33.6, 36.9, 37.4, 37.5, 48.9, 52.8, 55.7, 73.8, 122.5, 140.5, 170.4, 200.9, 213.8. IR (KBr): 1 740, 1 705, 1 625, 1 470, 1 445, 1 370, 1 250, 1 040.

c) Starting diol **9** (20 mg).

3β,17β-Diacetoxyandrost-5-en-14α-ol (**12**)

To a solution of diol **9** (2.0 g, 5.7 mmol) in Py (5 ml), Ac_2O (2 ml, 21 mmol) was added. The reaction mixture was left at room temperature for 16 h, then diluted with water and extracted with EtOAc. The extract was dried (anhydrous Na_2SO_4) and the solvent was evaporated. The residue was crystallized from hexane–EtOAc to give 17β-acetate **12** (1.92 g, 86%) as white crystals, m.p. 174–177 °C. ^{1}H NMR: 0.94 s, 3 H (3 × 18-H); 1.06 s, 3 H (3 × 19-H); 2.06 s, 3 H (OAc); 2.08 s, 3 H (OAc); 4.60 m, 1 H (3-H); 5.20 dd, 1 H, J_1 = 16, J_2 = 4 (17-H); 5.42 brs, 1 H (6-H). ^{13}C NMR: 15.7, 19.2, 19.4, 21.2, 21.4, 25.0, 27.0, 27.7, 28.9, 32.3, 34.8, 36.7, 37.0, 38.0, 43.5, 46.8, 73.8, 81.3, 82.5, 122.2, 139.2, 170.5, 171.2. IR (KBr): 1 740, 1 470, 1 450, 1 380, 1 250, 1 040.

3β,17β-Diacetoxyandrosta-5,14-diene (**13**)

To a solution of 17β-acetate **12** (160 mg, 0.41 mmol) in CH_3CN (1.0 ml), CAN (562 mg, 1.03 mmol) in water (0.2 ml) was added at 80 °C. The solution became dark-brown and then its color changed to pale-yellow in 30 s. The reaction mixture was cooled and diluted with ether. The organic layer was washed with brine, dried (Na_2SO_4), and evaporated. The residue was chromatographed on silica gel (hexane–EtOAc 3 : 1) to give diene **13** (100 mg, 65%), m.p. 150–152 °C (hexane–EtOAc). ^{1}H NMR: 1.00 s, 3 H (3 × 18-H); 1.06 s, 3 H (3 × 19-H); 2.04 s, 3 H (OAc); 2.08 s, 3 H (OAc); 2.58–2.66 m, 1 H (16-H); 4.60 m, 1 H (3-H); 4.88 t, 1 H, J = 8 (17-H); 5.16 brs, 1 H (15-H); 5.46 brs, 1 H (6-H). ^{13}C NMR: 16.7, 19.0, 21.2, 21.4, 27.6, 29.3, 31.2, 35.3, 36.7, 37.0, 38.0, 39.1, 47.2, 50.0, 73.7, 83.4, 116.0, 122.1, 138.9, 151.5, 170.4, 171.

14α-Hydroxy-6β-methoxy-3α,5-cyclo-5α-androstan-17-one (**16**)

To a suspension of 3β-acetoxy-14α-hydroxyandrost-5-en-17-one **4** (17 g) in MeOH (200 ml), a solution of MeONa (prepared from 1.5 g of Na and 50 ml of MeOH) was added. The mixture was stirred for 30 min and the solvent was partly evaporated. The mixture was diluted with water and the precipitated white crystals were filtered off, washed with water, and dried in air to give 3β,14α-dihydroxyandrost-5-en-17-one **14** (14 g, 94%).

To a suspension of ketone **14** (14 g) in pyridine (200 ml), tosyl chloride (21 g) was added. The mixture was stirred for 1 h until it became homogeneous and left at room temperature for 20 h. Then it was diluted with water, the precipitated crystals were filtered off and dried in air to give 14α-hydroxy-3β-tosyloxyandrost-5-en-17-one **15** (19.4 g, 92%).

A suspension of tosylate **15** (19.4 g) in MeOH (300 ml) and pyridine (20 ml) was refluxed for 3 h. The reaction mixture was cooled and the solvent was evaporated. The residue was dissolved in EtOAc–hexane (1 : 2) and left for crystallization. The precipitated crystals were washed with hexane and dried to give 7.5 g of ether **16**. The mother liquor was evaporated and subjected to column chromatography (hexane–EtOAc 1 : 1) to give an additional 3 g of ether **16**. Total yield was 10.5 g (78%). ^{1}H NMR: 1.06 s, 3 H (3 × 18-H); 1.07 s, 3 H (3 × 19-H); 2.90 m, 1 H (6-H); 3.37 s, 3 H (OMe). ^{13}C NMR: 13.3, 18.2, 19.3, 20.6, 21.3, 24.9, 25.1, 29.4, 30.1, 32.9, 33.3, 33.4, 34.9, 41.1, 43.7, 53.0, 56.7, 81.6, 82.1, 218.9. MS, *m/z* (rel.%): 318 (73), 303 (32), 300 (18), 286 (100), 268 (40), 263 (69), 245 (63), 243 (20), 227 (50), 213 (46), 94 (66). HRMS: calculated for $C_{20}H_{30}O_3$: 318.2195 (M^+); found: 318.2193.

6β-Methoxy-3α,5-cyclo-5α-androstane-14α,17β-diol (**17**)

To a suspension of ketol **16** (500 mg, 1.57 mmol) and $CaCl_2$ (200 mg, 2 mmol) in ethanol (5 ml), a solution of $NaBH_4$ (90 mg, 2.36 mmol) in water (0.2 ml) was added. The mixture was stirred for 30 min and then excess of $NaBH_4$ was destroyed with dilute AcOH. The usual work-up and column chromatography gave diol **17** (400 mg, 80%), m.p. 176–178 °C (hexane–EtOAc). ^{1}H NMR: 0.94 s, 3 H (3 × 18-H); 1.06 s, 3 H (3 × 19-H); 2.85 t, 1 H, J = 3 (6-H); 3.34 s, 3 H (OMe); 4.31 dd, 1 H, J_1 = 8, J_2 = 4 (17-H). IR (KBr): 1 460, 1 380, 1 100, 1 040, 920.

14α-Hydroxy-6β-methoxy-3α,5-cyclo-5α-androstan-17-one *O*-Methyloxime (**20**)

To a solution of ketol **16** (200 mg, 0.63 mmol) in pyridine (5 ml), $NH_2OMe{\cdot}HCl$ (105 mg, 1.26 mmol) was added. The reaction mixture was heated at 50 °C for 8 h. Then it was di-

luted with water and extracted with EtOAc. The extract was dried and evaporated. The residue was chromatographed on SiO_2 to give oxime **20** (240 mg, 73%), m.p. 75–78 °C (hexane–EtOAc). ^{1}H NMR: 1.04 s, 3 H (3 × 18-H); 1.08 s, 3 H (3 × 19-H); 2.85 t, 1 H, *J* = 3 (6-H); 3.33 s, 3 H (6-OMe); 3.81 s, 3 H (=NOMe). ^{13}C NMR: 13.3, 19.2, 20.9, 21.3, 21.8, 23.8, 24.9, 27.3, 30.3, 31.4, 33.4, 35.0, 40.9, 43.7, 49.1, 56.6, 61.2, 82.3, 82.9, 169.1. IR (KBr): 1 470, 1 385, 1 100, 1 060, 950.

Oxidation of **20** with LTA

A suspension of oxime **20** (1.3 g, 3.75 mmol), LTA (2.87 g, 6.62 mmol), and $CaCO_3$ (562 mg, 5.62 mmol) was refluxed for a short time. Upon cooling, iodine (714 mg, 5.62 mmol) was added and the mixture was refluxed for 15 min. The usual work-up and column chromatography on SiO_2 gave 700 mg of **21** and **22** as white crystals. Crystallization of this mixture from ethanol afforded pure *(13S)-13-acetoxy-6*β*-methoxy-3*α*,5-cyclo-13,14-seco-5*α*-androstane-13,17-dione 17-(O-methyloxime)* (**21**) (150 mg, 11%), m.p. 199–202 °C. MS, *m/z* (rel.%): 405 (9.8), 390 (1.7), 375 (23), 374 (100), 346 (10), 345 (10), 314 (33), 105 (20), 43 (59). HRMS: calculated for $C_{23}H_{35}NO_5$: 405.2515 (M^+); found: 405.2510. The mother liquor was treated with $Ca(BH_4)_2$ to decompose the rest of **21** and to allow chromatographic separation of **22**.

To a suspension of $NaBH_4$ (49 mg, 1.3 mmol) in dry EtOH (2 ml), $CaCl_2$ (71 mg, 0.64 mmol, dried at 250 °C for 2 h) was added at –10 °C. The suspension was stirred for 20 min and the mixture of **21** and **22** (130 mg, 0.32 mmol, from mother liquor) was added dropwise at the same temperature. The reaction mixture was stirred for 15 min, and then several drops of acetone were added and the mixture was worked up in a usual way. Chromatography on SiO_2 gave *14-acetoxy-13,14-epoxy-6*β*-methoxy-3*α*,5-cyclo-13,14-seco-5*α*-androstan-17-one O-methyloxime* (**22**) (38 mg, 32%). IR (KBr): 1 760, 1 470, 1 450, 1 370, 1 255, 1 220, 1 095, 1 060. MS, *m/z* (rel.%): 405 (6.9), 374 (15), 346 (27), 345 (100), 314 (37), 313 (42), 300 (20), 282 (31), 137 (32), 105 (26). HRMS: calculated for $C_{23}H_{35}NO_5$: 405.2515 (M^+), found: 405.2517; calculated for $C_{21}H_{31}NO_3$: 345.2303 (M^+ – AcOH), found: 345.2303.

Oxidation of **4** with LTA and I_2

A suspension of ketol **4** (400 mg, 1.2 mmol), LTA (786 mg, 1.54 mmol), and $CaCO_3$ (154 mg, 1.65 mmol) was shortly heated under reflux. Upon cooling, iodine (196 mg, 1.54 mmol) was added and the suspension was heated under reflux with stirring for 20 min. The reaction mixture was cooled and filtered. The filtrate was washed with a solution of $Na_2S_2O_3$ and with H_2O, dried (anhydrous Na_2SO_4), and evaporated. The residue was chromatographed on SiO_2 to give *(13S)-3*β*-acetoxy-13-iodo-13,14-secoandrost-5-ene-14,17-dione* (**24**) (85 mg, 16%), m.p. 128–131 °C (hexane–EtOAc). IR (KBr): 1 730, 1 705, 1 480, 1 445, 1 375, 1 250, 1 040.

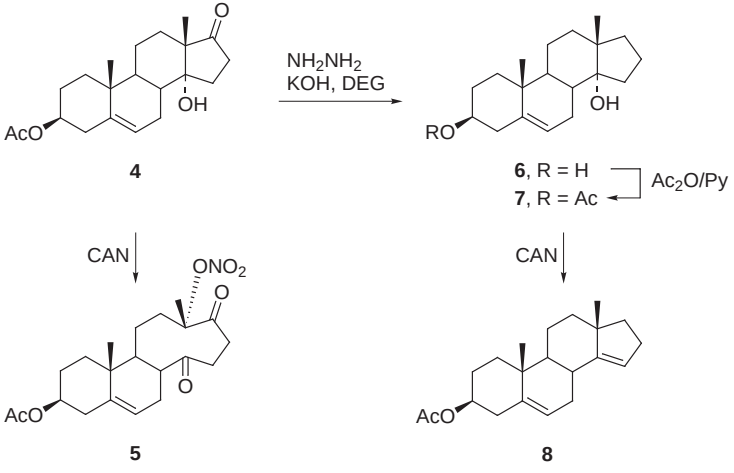
Oxidation of **16** with LTA and I_2

A suspension of ketol **16** (200 mg, 0.63 mmol), LTA (482 mg, 0.94 mmol), and $CaCO_3$ (94 mg, 0.94 mmol) was refluxed for a short time. Upon cooling, iodine (119 mg, 0.94 mmol) was added and the suspension was refluxed for 15 min. The mixture was cooled and filtered. The filtrate was washed with a solution of $Na_2S_2O_3$, and with H_2O, dried (anhydrous Na_2SO_4), and evaporated. The residue was chromatographed on SiO_2 to give *(13S)-13-iodo-6*β*-methoxy-3*α*,5-cyclo-13,14-seco-5*α*-androstane-14,17-dione* (**25**) (237 mg, 85%), m.p. 161–163 °C (ethanol). ^{1}H NMR: 0.99 s, 3 H (3 × 19-H); 1.95 s, 3 H (3 × 18-H); 3.32 s, 3 H (OMe); 3.86 t,

1 H, *J* = 11 (16α-H). ^{13}C NMR: 13.0, 18.1, 21.1, 24.5, 27.6, 27.8, 32.6, 32.8, 34.2, 34.3, 41.8, 42.2, 45.5, 48.1, 48.7, 49.5, 56.8, 81.1, 206.8, 218.1. IR (KBr): 1 705, 1 475, 1 450, 1 385, 1 280, 1 185, 1 110, 1 085. MS, *m/z* (rel.%): 444 (0.8), 429 (3), 389 (14), 318 (23), 317 (100), 299 (12), 191 (9), 137 (9), 125 (15), 105 (10). HRMS: calculated for $C_{20}H_{29}IO_3$: 444.1161 (M^+); found: 444.1156.

RESULTS AND DISCUSSION

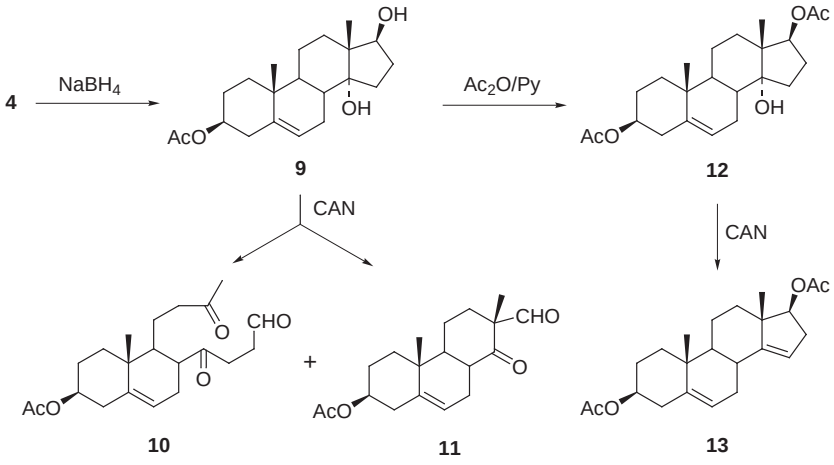
First experiments were carried out on compounds with a 3β-acetoxy-5-ene system in rings A and B (Scheme 2). The reaction of 17-oxo steroid **4** with CAN produced the 13,14-secosteroid **5** in a moderate 40% yield. Similar transformation of 17-unsubstituted 14α-hydroxy steroid **7** was studied as well. This compound was obtained by Wolf–Kishner reduction[14] of hydroxy ketone **4** followed by reacetylation. However, formation of a rather complex mixture of compounds was observed again, and only one product has been identified as the 14-ene steroid **8**.



SCHEME 2

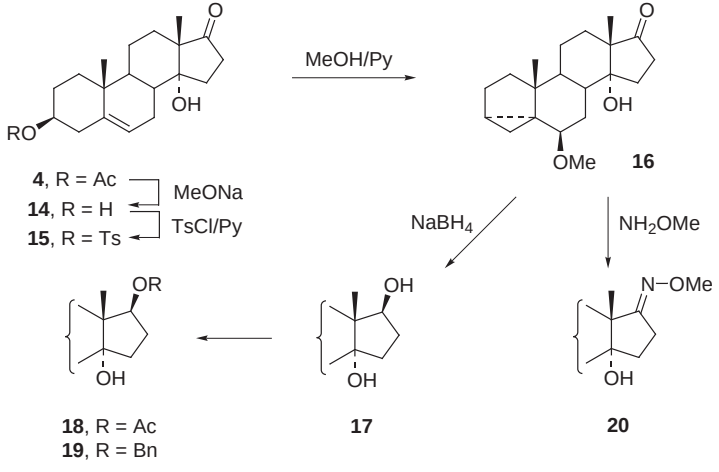
Next, the oxidation of the 17β-hydroxy derivative **9** and its corresponding acetate **12** with CAN was studied (Scheme 3). In the case of diol **9**, oxidative fragmentation of the C and D rings took place with the formation of two main products **10** and **11**. Under similar conditions, 17β-acetate **12** underwent dehydration to the 14-ene **13**.

Similar to the reaction with CAN, practically all experiments with LTA led to formation of rather complex mixtures. Thus, treatment of **6** with LTA in the presence of iodine gave 13-iodo-14,17-dioxo steroid **24** in 16% yield only. At least partly these mixtures resulted from decomposition in A and B



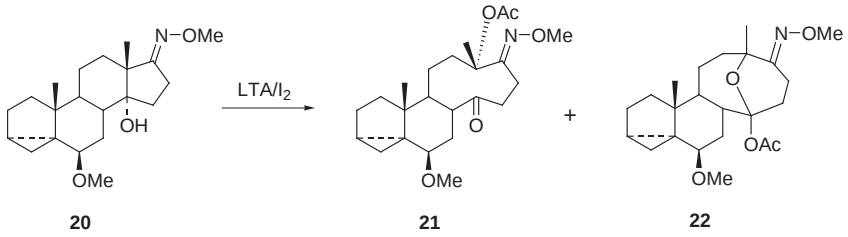
SCHEME 3

rings, and therefore the more stable 6β-methoxy-3α,5-cyclo derivatives **16**–**20** were investigated. These compounds were prepared as indicated in Scheme 4. The ketone **16** was obtained from the starting material **4** *via* deacetylation, tosylation, and *i*-steroidal rearrangement. The hydride reduction of **16** gave the 17β-alcohol **17**. Ester **18** and ether **19** were prepared from **17** using standard methods. Treatment of **16** with NH_2OMe furnished oxime **20**.



SCHEME 4

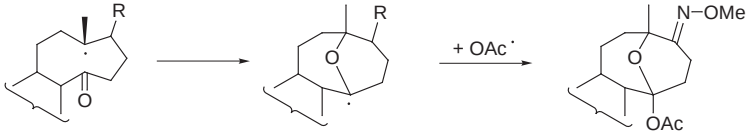
The radical oxidation of the methoxyimine **20** with LTA led to formation of a mixture of two compounds, which could not be separated by column chromatography. Crystallization of the mixture gave the secosteroid **21** (Scheme 5). Treatment of the mother liquor with $NaBH_4$ gave two products, one with the same mobility as the starting mixture and a more polar product. The less polar product separated by column chromatography was identified as compound **22**.



20 **21** **22**

SCHEME 5

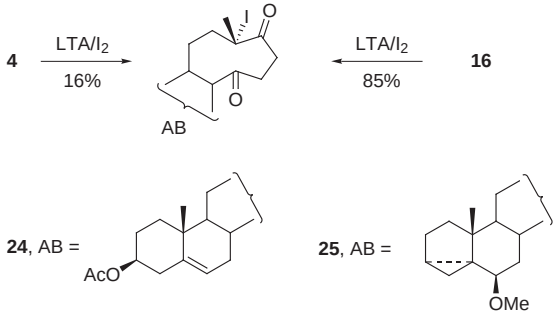
It is evident that formation of compound **22** containing a transannular epoxy bridge involves the transformation of radical **3** into **23** (Scheme 6). The subsequent reaction with acetoxy radical may produce product **22**. A similar transformation has been described for 5-hydroxy-7-norsteroids[15].



3 **23** **22**

SCHEME 6

The most promising results with respect to the synthesis of 13,14-secosteroids were obtained with LTA/I_2 oxidation of the 14α-hydroxy-17-oxo compounds (Scheme 7). Thus, the radical oxidation of compound **16** led to



SCHEME 7

the desired product **25** in 85% yield. In the case of the 17-unsubstituted 14α-alcohol, diol **17** and its derivatives **18** and **19**, all attempts to get an individual compound failed.

The stereochemical assignment of the methyl group and iodine at C-13 was done by X-ray analysis of compound **25** (Fig. 1). The ^{1}H and ^{13}C chemical shifts of secosteroids **5**, **21**, **22**, and **24** were established using standard COSY techniques (Table I), and a comparative conformational study of

TABLE I
^{13}C and ^{1}H NMR shifts (ppm) of compounds **5**, **21**, **22**, and **24** at 150 and 600 MHz, respectively

Position	**5**		**21**		**22**		**24**	
	^{13}C	^{1}H	^{13}C	^{1}H	^{13}C	^{1}H	^{13}C	^{1}H
1	35.6	1.07/1.9	33.4	0.91/1.44	34.0	0.93/1.64	35.6	1.05/1.9
2	27.7	1.9/1.6	25.0	1.80/1.59	25.3	1.75/1.57	27.7	1.9/1.58
3	73.3	4.58	21.7	0.97	23.0	0.97	74	4.59
4	37.9	2.37/2.24	13.4	0.49/0.65	13.2	0.46/0.63	38.0	2.36/2.23
5	138.7		34.7		36.7		138.6	
6	121.5	5.41	81.5	2.80	82.1	2.80	122	5.42
7	29.0	2.41/1.87	33.4	1.77/1.80	30.4	1.20/2.06	28.3	2.5/1.86
8	51	2.77	49.3	3.08	41.4	2.94	50.1	2.73
9	52	1.31	48.6	1.23	48.1	1.03	50.9	
10	38.7		45.7		45.9		38.9	
11	21.1	1.6/0.87	23.4	1.45/1.03	24.4	1.67/1.6	26.6	1.87/0.7
12	31.1	1.6/1.77	36.5	1.45/1.97	41.2	1.6/1.9	41.3	2.3/2.3
13	93.5		84.2		75.1			
14	218.3		221.1		107.5		217.5	
15	43.1	3.38/2.27	41.5	2.42/3.02	25.4	1.90/2.06	42.5	2.82/2.63
16	33.1	2.62/3.01	22.2	2.3/2.8	19.0	2.84/2.71	34.7	2.53/3.94
17	207.6		160.1		161.0		207.4	
18	17.2	1.52	20	1.54	25.6	1.40	18.6	1.95
19	18.1	0.97	18.9	1.02	19.7	1.05	18.0	0.97
AcO	20.6/ 170.9	2.03	22.3/ 170	1.96	23/ 168.8	2.02	21.3/ 170.9	2.03
–OMe			57.1	3.32	56.4			
=NOMe			62.4	3.95	61.9	3.86		

compounds **5** and **24** was done using nuclear Overhauser effect experiments (Fig. 2). It is interesting that the conformation of the nine-membered ring of **5** differs very strongly from that of compound **24**. Among possible reasons for conformational differences, steric factors (iodine being larger than nitrate prefers to be in equatorial position) and dipole interaction of nitrate and C-17 carbonyl groups can be considered.

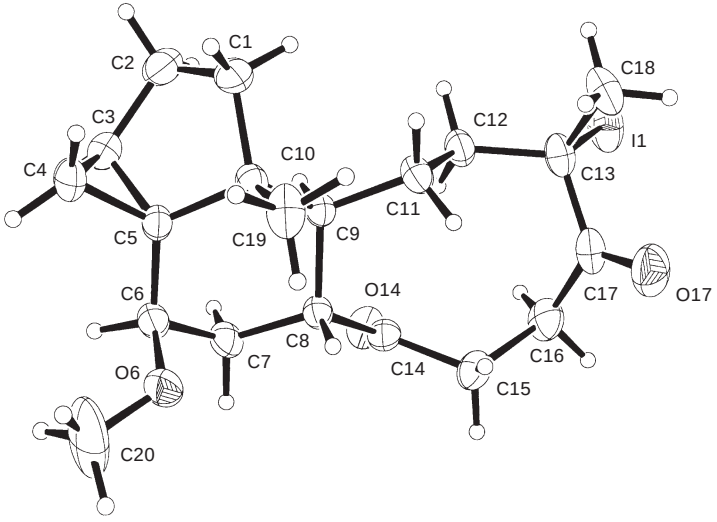


FIG. 1
ORTEP view of (13*S*)-13-iodo-6β-methoxy-3α,5-cyclo-13,14-seco-5α-androst-5-ene-14,17-dione (**25**) (displacement ellipsoids are drawn at the 30% probability level)

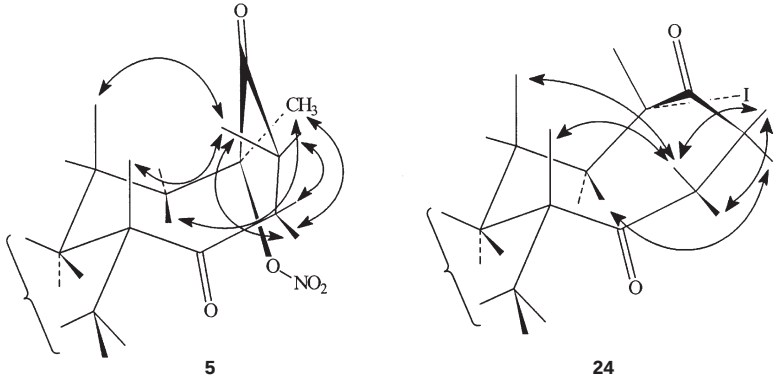


FIG. 2
CD-Rings conformation of secosteroids **5** and **24** on NMR data

Comparison of the data obtained from the X-ray (Table II) and NMR studies show that the conformation of the nine-membered ring iodides **24** and **25** in the solid state corresponds with that in solution.

TABLE II
Crystal data and structure refinement for (13*S*)-13-iodo-6β-methoxy-3α,5-cyclo-13,14-seco-5α-androst-5-ene-14,17-dione (**25**)

Empirical formula	$C_{20}H_{29}IO_3$
Formula weight	444.33
Temperature, K	293(2)
Wavelength, Å	0.71069
Crystal system	Monoclinic
Space group	$P2_1$
Unit cell dimensions, Å and °	a = 10.969(2); α = 90 b = 7.680(2); β = 96.960(10) c = 11.9430(10); γ = 90
Volume, Å^3	998.7(3)
Z	2
Density (calculated), Mg m^{-3}	1.478
Absorption coefficient, mm^{-1}	1.617
F(000)	452
Crystal size, mm^3	0.32 × 0.22 × 0.16
θ range for data collection, °	1.87 to 27.56
Index ranges	$-10 \le h \le 14$, $-9 \le k \le 9$, $-15 \le l \le 15$
Reflections collected	4 293
Independent reflections	4 039 [R_{int} = 0.0139]
Completeness to θ = 27.56°	99.9%
Refinement method	Full-matrix least-squares on F^2
Data/restraints/parameters	4 039/1/220
Goodness-of-fit on F^2	1.055
Final R indices [$I > 2\sigma(I)$]	R_1 = 0.0425, wR_2 = 0.1159
R indices (all data)	R_1 = 0.0526, wR_2 = 0.1271
Absolute structure parameter	–0.04(3)
Largest diff. peak and hole, e Å^{-3}	0.895 and –1.081

Crystallographic data for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC-171299. Copies of the data can be obtained free of charge on application to CCDC, e-mail: deposit@ccdc.cam.ac.uk.

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