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Synthesis of Steroid 5α and 5β 4-Ketones from the 4-en-3-one:1,2-Carbonyl Transposition

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Abstract. An efficient procedure for the conversion of the steroid 4-en-3-one to the 5α and 5β 4-ketones is described. Structures are established by NMR analysis.

Keywords: steroids, reduction, zinc

Introduction

Transposition of a carbonyl group to the adjacent carbon is a useful synthetic procedure. Many examples of this transposition occur in steroids and the conversion of the 3-ketone to the 4-ketone has been carried out to give the 5α and 5β derivatives.[1] In this case, as a result of the adjoining C-5 ring junction, two epimeric products are possible. The scheme described yields the thermodynamically less stable *cis* ring junction as the major product.[2] This ring junction can be readily converted to the more stable *trans* junction making it a convenient synthesis of both epimers.

Conversion of the steroid 4-en-3-one to the enolic 4-hydroxy-4-en-3-one is well established. Thus the 4-en-3-one can be converted to the 4,5–epoxides which on treatment under acidic conditions yields the diosphenol structure.[3] Metal reduction of the 4-en-3-one on treatment with Zn-HOAc yields mainly an epimeric mixture of the 5α- and 5β-3-enes in approximately equal amounts.[4] A similar reaction occurs with the 4-chloro-4-en-3-one and methyl androst-4-ene-3,17-dion-19-oate which also yield dimeric byproducts.[5,6]

NOTE: This paper is dedicated in memory of Professor Sir Derek H. R. Barton.

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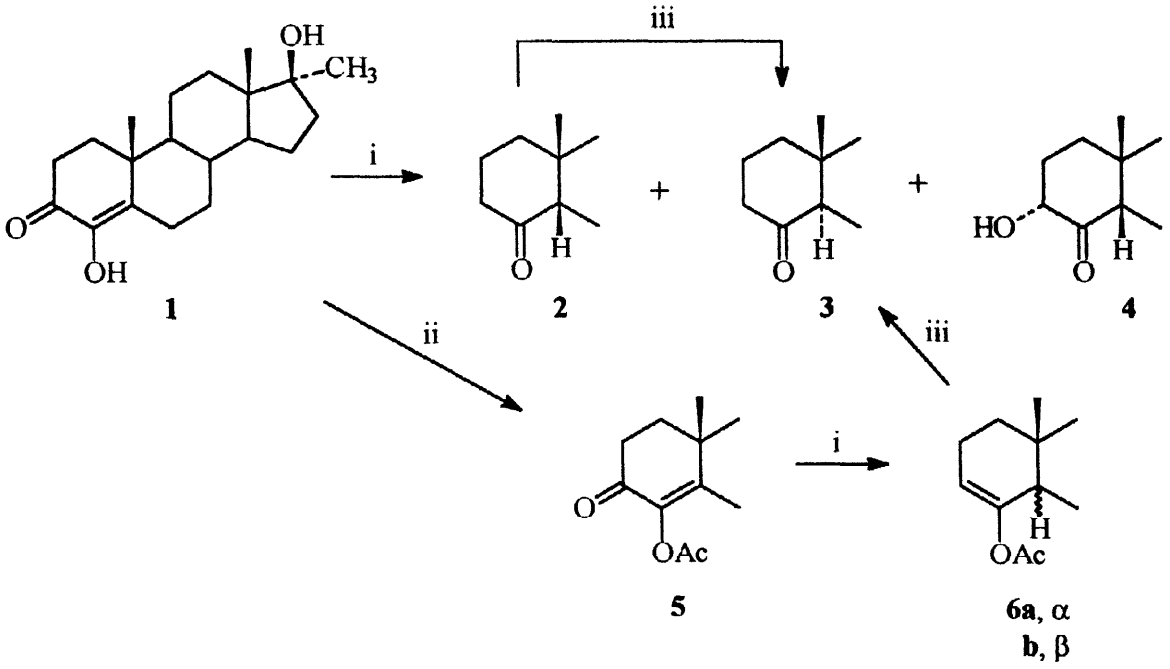


Scheme 1 i, Zn-HOAc-H_2O; ii, Ac_2O-DMAP-CH_2Cl_2; iii, KOH-MeOH

Results

Zn-HOAc reduction of the diosphenol **1** gave the 5β-4-one **2** as the major product and the 5α-4-one **3** as a minor product together with 4α-hydroxy-5β-4-one **4** based on the ^{1}H NMR of the crude reaction product (Scheme 1). Comparison of the ^{1}H NMR signals for the 10-methyl protons indicates about 10% reduction to the 5α product. Epimerization of the 5β-4-one **2** with KOH-MeOH gave the 5α-4-one **3**. Similar reduction of the 4-acetoxy-4-en-3-one **5**, prepared by acetylation of the diosphenol **1**, gave a mixture (α:β, 1:0.85 by ^{1}H NMR comparison of the H-3 protons) of the enol acetates **6a** and **6b**. From the mixture the 5α isomer **6a** was crystallized in low yield and the NMR spectra of **6b** obtained by difference. Alkaline hydrolysis of the enol acetate mixture, accompanied by epimerization at C-5, gave the 5α-4-one **3**.

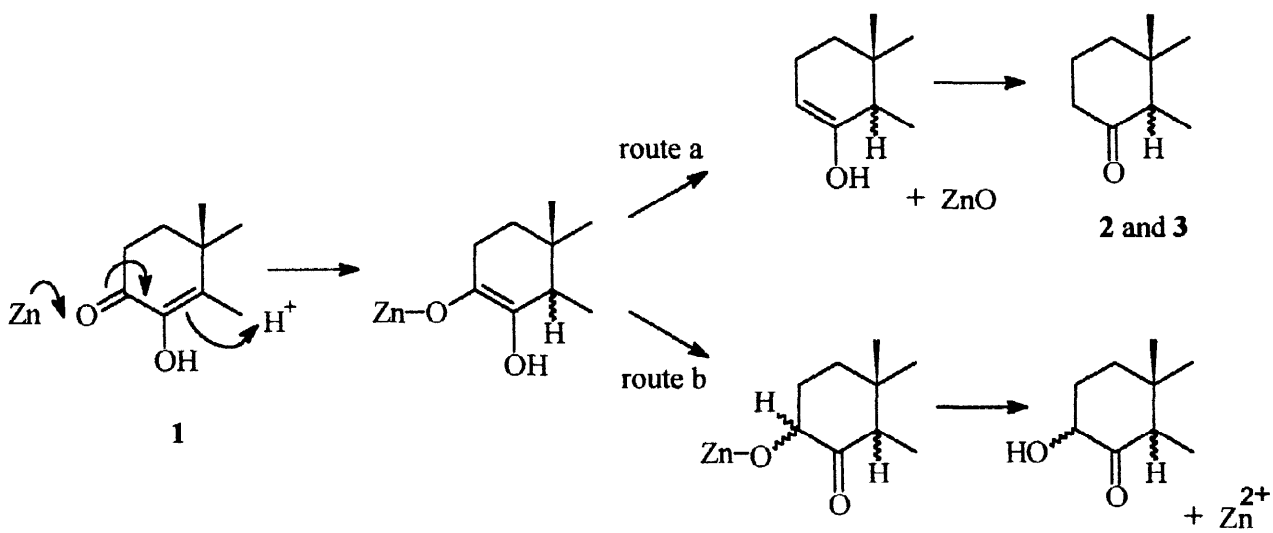
Nuclear magnetic resonance

The C and D ring structures of compounds **2-6a/b** are based upon the complete assignment of ^{1}H and ^{13}C NMR spectra of 17α-methyltestosterone (17α-methyl-17β-hydroxyandrost-4-en-3-one).[7] The A and B ring assignments of the 4-ketones **2** and **3** are consistent with the ^{1}H and ^{13}C NMR spectra of analogous compounds reported previously.[8,9] Comparison of the spectrum of the 4-ketone **2** with the hydroxy ketone **4** established its structure and 5β-H stereochemistry. The

equatorial 3α-hydroxy stereochemistry was consistent with axial H-3 coupling (J 1.6, 7.6, 10.0) and an intramolecular hydrogen bond. The 3α-hydroxy and 5β-H stereochemistry was confirmed by NOE measurements. Thus irradiation of H-3β in the hydroxyketone **4** shows an NOE with H-1β (2.6%), H-2β (2.65%) and H-5β (3.85%) establishing their *cis* relationship. H-5 also showed no axial coupling to H-6β consistent with the 5β stereochemistry.

Discussion

Zinc reduction of the 4-en-3-one to the 3-ene, in an analogous manner to other 4-en-3-one steroids, yields the enol which, on loss of ZnO, tautomerizes to the 4-ketone **2** or **3** (Scheme 2, route a).[4,5] Alternatively, tautomerism before loss of ZnO results in formation of the 3-hydroxy derivative giving the more stable equatorial 3α-hydroxy group in the 5β structure either directly or after epimerization (Scheme 2, route b). Zn reduction of the C-4 unsubstituted 4-en-3-one,[4] the enol acetate **5**, and the steroid 4-chloro-4-en-3-one,[5] also give mixtures of 5α and 5β 3-enes. The approximately equal amount of 5β product generally observed on zinc reduction of the 4-en-3-one may reflect the greater stability of the 3-enol formed in steroid 5β-3-one derivatives. The greater proportion of the 5β product obtained from the diosphenol may result from an interaction of the acidic 4-enol in **1** with the Zn surface, not possible with other C-4 substituents, favouring approach to the β face of the molecule. The synthetic procedure described provides an efficient conversion of the steroid 4-en-3-one to both the 5α- and 5β-4-ones.



Scheme 2 Reduction of the steroid 4-hydroxy-4-en-3-one by Zn-HOAc.

Experimental

NMR spectra were recorded on a Bruker AM300 instrument in $CDCl_3$. General experimental techniques and NMR methods employed are given in ref. 10. Assignments for compound **4** are based on COSY and HSQC analysis obtained on a Bruker AMX500 instrument in $CDCl_3$. TLC were run in 20% acetone-light petroleum bp 35-60°C (LP). Mps are uncorrected.

17β-Hydroxy-17α-methyl-5β-androstan-4-one **2** *and 3α,17β-Dihydroxy-17α-methyl-5β-androstan-4-one* **4**

The diosphenol **1** (1.03 g, 3.23 mmol) was stirred with Zn dust, HOAc (27 ml) and water (8 ml) for 4 h at room temperature when no starting material was detected by TLC. The mixture was filtered through a pad of silica and the filtrate extracted with CH_2Cl_2 which was washed with water, aqueous $NaHCO_3$ and dried over Na_2SO_4 to give a crude product which on flash column chromatography (FCC) in 17% acetone-LP gave (i) fractions (790 mg) which yielded the 4-ketone **2** (750 mg, 76%) mp 205-208°C (from CH_2Cl_2-EtOAc) (Found: C, 79.19; H, 10.76. $C_{20}H_{32}O_2$ requires C, 78.90; H, 10.59%); δ_H 0.83 (s, 13-Me), 1.12 (s, 10-Me), 1.18 (s, 17α-Me); δ_C 36.59 (1), 20.38 (2), 41.62 (3), 212.60 (4), 57.17 (5), 20.05 (6), 27.34 (7), 36.14 (8), 45.44 (9), 40.78 (10), 20.56 (11), 31.63 (12), 45.44 (13), 50.52 (14), 23.24 (15), 39.05 (16), 81.68 (17), 13.91 (18), 23.18 (19), 25.79 (17α) and (ii) fractions (190 mg) which gave the 3α-hydroxy-4-one **4** (52 mg, 5%) mp 156-158°C (from CH_2Cl_2-EtOAc) (Found: C, 74.95; H,.10.30; $C_{20}H_{32}O_3$ requires C, 74.96; H 10.06%); δ_H 0.82 (s, 13-Me), 1.14 (s, 10-Me), 1.18 (s, 17α-Me), 2.28 (br s, 5β-H), 4.02 (ddd, J 1.6, 7.6, 10.0, 3β-H); δ_C 33.32 (1), 29.67 (2), 74.85 (3), 212.15 (4), 54.64 (5), 20.09 (6), 27.23 (7), 35.90 (8), 43.84 (9), 41.95 (10), 20.32 (11), 31.42 (12), 45.34 (13), 50.38 (14), 23.15 (15), 38.91 (16), 81.61 (17), 13.83 (18), 22.95 (19), 25.75 (17α). The ^1H NMR of the crude product also indicated the presence of the 5α isomer **3** (δ 0.74, s, 10-Me) and the product proportions **2**:**3**:**4** (8.8:1:1.3).

17β-Hydroxy-17α-methyl-5α-androstan-4-one **3**

From **2**: A solution of the 5β-4-one **2** (530 mg, 1.74 mmol) in 0.5 M KOH-MeOH (20 ml) under N_2 was heated to reflux for 24 h to give the 5α-4-one **3** (200 mg, 38%) mp 152-155°C (from CH_2Cl_2-EtOAc); δ_H 0.88 (s, 13-Me), 0.76 (s, 10-Me), 1.21 (s, 17α-Me); δ_C 37.04 (1), 22.73 (2), 41.25 (3), 213.50 (4), 59.29 (5), 20.46 (6), 30.21 (7), 35.94 (8), 54.47 (9), 42.66 (10), 21.35 (11), 31.70 (12), 45.52 (13), 50.54 (14), 23.22 (15), 39.04 (16), 81.68 (17), 13.87 (18), 14.05 (19), 25.86 (17α); (Found: C, 79.20; H, 10.78. $C_{20}H_{32}O_2$ requires C, 78.90; H, 10.59%);

From **6a/6b**: A mixture of the enol acetates **6a** and **6b** (100 mg, 0.29 mmol) in 0.5 M KOH (10 ml) under N_2 was heated to reflux for 24 h to give the 5α-4-one **3** (70 mg, 79%), mp 153-156°C (from CH_2Cl_2-EtOAc); δ_H 0.88 (s, 13-Me), 0.76 (s, 10-Me), 1.21 (s, 17α-Me).

4-Acetoxy-17β-hydroxy-17α-methylandrost-4-en-3-one **5**

The diosphenol **1** (503 mg, 1.58 mmol) was added to a solution of CH_2Cl_2 (10 ml), Ac_2O (0.75 ml, 8 mmol) and dimethylaminopyridine (DMAP) (22 mg). After 18 h MeOH (0.5ml) was added and after a further 0.5 h water was added and the mixture extracted with CH_2Cl_2 which was washed with aqueous $NaHCO_3$ to give the acetate **5** (489 mg, 86%) mp 135-137°C (from acetone-LP) (lit.[11] mp 138-140°C, from Et_2O-LP); (Found: C, 73.36; H,.9.15; $C_{20}H_{32}O_4$ requires C, 73.30; H 8.95%); δ_H 0.89 (s, 13-Me), 1.19 (s, 10-Me), 1.25 (s, 17-Me), 2.22 (s, MeCOO); δ_C 34.68 (1), 33.44 (2), 190.63 (3), 139.12 (4), 155.92 (5), 24.20 (6), 30.75 (7), 36.06 (8), 53.83 (9), 39.22 (10), 20.71 (11), 31.44 (12), 45.39 (13), 50.11 (14), 23.23 (15), 38.91 (16), 81.46 (17), 13.95 (18), 17.77 (19), 25.88 (17α), 20.39 (MeCOO), 168.65 (MeCOO). When a sample was recrystallized from CH_2Cl_2-MeOH, mp 84-86°C was obtained. The ^1H and ^{13}C NMR of this product showed the same signals as the sample with mp 135-137°C together with a MeOH signal.

4-Acetoxy-17β-hydroxy-17α-methyl-5α- **6a** *and 5β-* **6b** *androst-3-ene*

A mixture of the acetate **5** (480 mg, 1.33 mmol) and Zn dust (12 g) in 60% aqueous HOAc (14 ml) was vigorously stirred for 16 h. The solution was filtered through a pad of silica and washed with CH_2Cl_2. The organic layer was washed with water and aqueous $NaHCO_3$ to give a mixture of the 5-enol acetates **6a** and **6b** (**6a**:**6b**, 1.0:0.86, based on their H-3 NMR signals) which on recrystallization gave the enol acetate **6a** (30 mg, 6.5%), mp 162-164.5°C (from CH_2Cl_2-EtOAc); (Found: C, 76.03; H, 10.17. $C_{22}H_{34}O_3$ requires C, 76.26; H, 9.89%); δ_H 0.86, 0.88 (2s, 10- and 13-Me), 1.22 (s, 17-Me), 2.11 (MeCOO), 5.24 (dd, 3.3, 6.5, H-3); δ_C 33.54 (1), 21.72 (2), 112.43 (3), 149.09 (4), 47.17 (5), 21.11 (6), 31.07 (7), 36.05 (8), 53.62 (9), 36.55 (10), 21.11 (11), 31.73 (12), 45.65 (13), 53.09 (14), 23.24 (15), 39.02 (16), 81.71 (17), 14.14 (18), 12.50 (19), 25.89 (17α), 20.66 (MeCOO), 169.70 (MeCOO).

The NMR spectrum of the enol acetate **6b** was obtained by subtraction of the spectrum of **6a** from that of the mother liquor: δ_H 0.84, 0.86 (2s, 10- and 13-Me), 1.21 (s, 17-Me), 2.09 (MeCOO), 5.38 (dd, 2, 5, H-3); δ_C 33.52 (1), 21.22 (2), 115.03 (3), 149.11 (4), 41.78 (5), 22.17 (6), 27.64 (7), 36.43 (8), 44.55 (9), 36.46 (10), 20.65 (11), 31.94 (12), 45.63 (13), 50.43 (14), 23.31 (15), 39.07 (16), 81.73 (17), 13.94 (18), 12.50 (19), 25.89 (17α), 21.21 (MeCOO), 169.47 (MeCOO).

Acknowledgements

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