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Synthesis and Isomerization of 19-Hydroxy-5β,19-cyclosteroids

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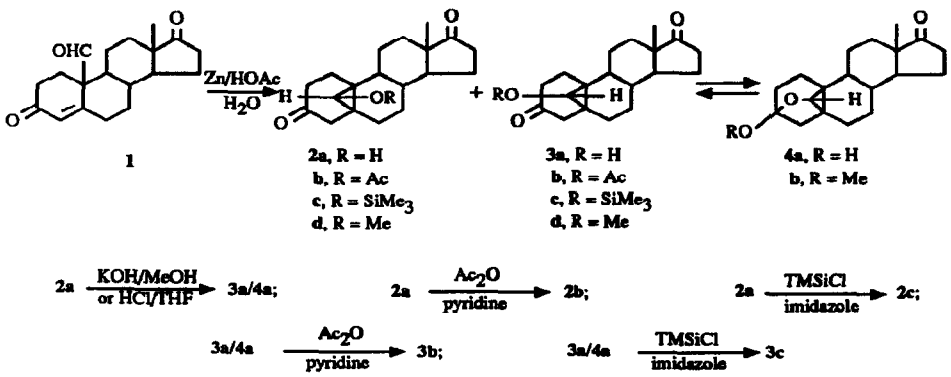
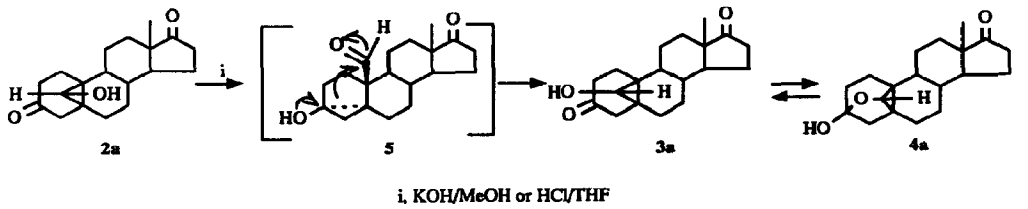
Abstract: Synthesis of 19(R/S)-hydroxy-5β,19-cycloandrostane-3,17-dione by reductive cyclization of the steroid 4-en-3-one 19-aldehyde with zinc in aqueous acetic acid is reported. On either acid or base treatment the R-isomer is converted to the S-isomer through an intermediate 3-hydroxy-3,5-cyclosteroid.

During our studies on the synthesis of potential steroid enzyme inhibitors we discovered a route to 19(R/S)-hydroxy-5β,19-cycloandrostanes. This synthesis gives access, for the first time, to C-19 oxygen substituted 5β,19-cyclosteroid derivatives. C-19 unsubstituted 5β,19-cycloandrostanes have been prepared by addition of the Simmons-Smith reagent[1] to the steroid 5(10)-double bond or by reductive elimination of a C-19 sulfonate or halogen with Li or Na/NH_3 or zinc and aqueous acetic acid in the steroid 4-en-3-one.[2] Recently we reported the preparation of 19-mono- and di-halogeno substituted 5β,19-cycloandrostane derivatives by addition of dichlorocarbene to 5(10)-unsaturated steroids.[3] Here we report a novel synthesis and isomerization of 19(R/S)-hydroxy-5β,19-cycloandrostane-3,17-dione from the 4-en-3-one 19-aldehyde through reductive cyclization with zinc and aqueous acetic acid (Scheme 1).



Scheme 1. Zinc/aqueous acetic acid treatment of androst-4-ene-3,17-dion-19-al

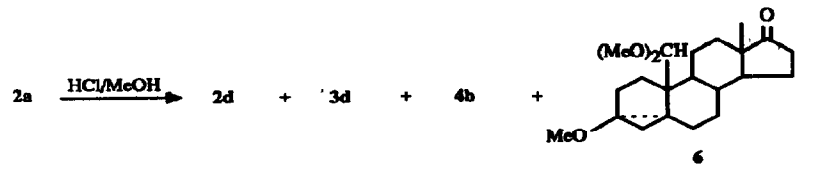
Oxidization of 19-hydroxyandrost-4-ene-3,17-dione with pyridinium dichromate gave the 19-aldehyde **1**[4] which on stirring with excess zinc and aqueous acetic acid at 20°C for 1.5 h gave the R-isomer **2a** (m.p. 160-167°C from CH_2Cl_2/Et_2O)[5] as the major product (67%) and, after chromatographic separation on silica gel, the S-isomer **3a** as a minor product (1.7%). The latter alcohol **3a** was obtained in equilibrium with the intramolecular hemiketal **4a** (m.p. 160-165°C from CH_2Cl_2/Et_2O). The 19-hydroxyl group in the S-isomer is located in a favourable position for intramolecular ring closure at C-3 to form the hemiketal **4a**, a reaction not possible with the R-isomer. Acetylation (Ac_2O/pyridine/1 h/20°C) or silylation (Me_3SiCl/imidazole/2 h/20°C) of the **3a/4a** mixture gave the non-crystalline acetate **3b** or the silyl ether **3c** (m.p. 122-125°C from Et_2O/hexane) of the S-isomer **3a**, respectively. The R-isomer **2a**, on similar acetylation or silylation gave the corresponding acetate **2b** (m.p. 180-183°C from CH_2Cl_2/Et_2O) or silyl ether **2c** (m.p. 96-98°C from Et_2O/hexane).



Scheme 2. Isomerization of the R-isomer to the S-isomer

Treatment of the R-isomer **2a** with KOH/MeOH at 20°C gave the S-isomer/hemiketal mixture **3a/4a** (70%), identical (m.p., ^1H NMR) with the minor product obtained from the initial zinc and acetic acid reaction. Conversion of the R-isomer **2a** to the more stable S-isomer **3a** can take place through the cyclopropanol **5** formed by ring opening of **2a** followed by reclosure to **3a** (Scheme 2). Similar equilibrating cyclopropyl alkoxide ions have been studied in detail by Reusch and coworkers.[6] Treatment of the R-isomer **2a** with concentrated HCl/THF (0.2 M) at 20°C also gave the S-isomer **3a/4a** hemiketal mixture (40%). Isolation of the cyclopropanol methyl ethers (**2d, 3d, 4b, 6**) on treatment of the R-isomer **2a** with concentrated HCl/MeOH (0.2 M) demonstrates that the 3β,5β-cyclopropanol is formed under conditions in which the rearrangement occurs (Scheme 3). Under acidic or basic reflux conditions the cyclopropanols **2a** and **3a** undergo conversion to A-norandrostane derivatives consistent with the ring open products described previously.[6]

The 4-en-3-one 19-aldehyde is a vinylogous β-ketoaldehyde and reductive cyclization to the cyclopropanol is comparable to the formation of a cyclopropane-1,2-diol which has been shown to be an intermediate in the abnormal Clemmensen reduction of β-diketones.[7,8] This stereoselective cyclization



Scheme 3. Concentrated HCl/MeOH (0.2 M) treatment of the cyclopropanol **2a**

of the aldehyde **1** to the R-isomer **2a** as the major product may result from the π-orbitals at C-3 to C-5 orienting the carbonyl oxygen away from ring A favouring formation of the R-isomer, or result from stereoelectronic requirements at the zinc surface. Relief of steric strain, especially from H-8β, and hemiketal formation can account for isomerization of the R-isomer to the S-isomer.

All structures were established by ^{1}H and ^{13}C NMR measurements.[9] Carbon spectra were classified as to multiplicity with the DEPT technique.[10] NOE and COSY measurements were carried out on compounds **2a, 2b, 3b** and **6**. The alcohol **2a** and acetate **2b** show NOE enhancement between H-19 and H-1β, H-2β and H-4β whereas the acetate **3b** shows NOE enhancement between H-19 and H-6β and H-8. These NOE enhancements establish that the cyclopropyl ring is located on the steroid β-face and the stereochemistry of the C-19 substituent. The 3β,5β-cyclosteroid stereochemistry of ring A in the cyclopropyl methyl ether **6** was determined by a clear NOE enhancement between H-19 and H-4β (*endo* H) while H-4α (*exo* H) shows an NOE enhancement with the C-3 methoxy group. Irradiation of H-19 shows a NOE enhancement with H-4β with little NOE to the C-3 methoxy group whereas the C-3 methoxy group shows an NOE to H-4α. Indirectly an NOE was observed between H-4β and H-1β upon irradiation of H-4α (3 spin effect). Direct irradiation of H-4β was not possible because of overlap with H-9.

19-Substituted 1β,19-cyclosteroid derivatives have been obtained by similar treatment of androst-1-ene-3,17-dion-19-al with zinc in aqueous acetic acid. The reactions of these derivatives are under investigation.

Acknowledgments

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5. Reactions were monitored by thin-layer chromatography on silica gel (Merck type 60H) in acetone, diethyl ether or ethyl acetate/petroleum ether (35-60°C) mixtures. Melting points were determined on a Kofler-type hot stage apparatus and are uncorrected. All new compounds (**2a-d**, **3a**, **3c-d**, **4a-b**, **6**) gave satisfactory elemental analysis (C,H).
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