# On the Synthesis of D-Homoandrostanes

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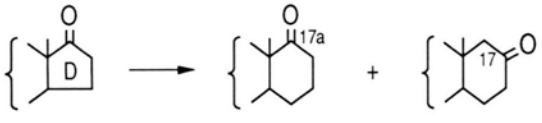
Z. Naturforsch. **48b,** 1305–1306 (1993); received April 2, 1993

D-Homoandrostanes, Epiandrosterone, Wittig Reaction, Cyanogen Azide, D-Ring Expansion

The D-ring expansion of 3β-hydroxy-5α-androstan-17-one (epiandrosterone) by the cyanogen azide ring-expansion reaction is described. Epiandrosterone was first converted to 17-methylene-3β-hydroxy-5α-androstane by a modification of the Wittig reaction employing methylsulfinyl carbanion-dimethyl sulfoxide. Treatment of the 17-methyleno derivative with cyanogen azide followed by hydrolysis led to 3β-hydroxy-D-homo-5α-androstan-17 a-one with migrational selectivity.

Preparation of D-homologs of androstan-17-ones has been traditionally carried out through intermediate formation of cyanohydrins [1] or through addition of carbene to enol ether and enol acetate derivatives [2] or, more efficiently, *via* C(17)-spirooxiranes and hydroxy azides [3]. The D-ring expansion of 17-keto steroids is often complicated by the presence of multiple reaction steps, the low overall yield, and the formation of both isomeric 17- and 17α-ketones.




We would like to report the stereoselective D-ring enlargement of 3β-hydroxy-5α-androstan-17-one (epiandrosterone (**1**) by the cyanogen azide ring expansion reaction [4] to yield 3β-hydroxy-D-homo-5α-androstan-17 a-one (**3**) (Scheme 1). Specifically, **1** was first transformed to the corresponding olefin **2** by the modification of the Wittig reaction employing methylsulfinyl carbanion/dimethyl sulfoxide [5] which proceeds with high yield (88%).

Treatment of **2** with cyanogen azide, followed by hydrolysis led to 3β-hydroxy-D-homo-5α-androstan-17 a-one (**3**) in 32% yield. Other minor products that were isolated did not amount to more than 4%.

Even though the yield of the expansion reaction is low, the observed migrational selectivity (secondary *vs.* tertiary D-ring bond) makes the above reaction scheme a useful way to D-homo-epiandrosterone. It should be noted that a great number of unsymmetrical ketones that have been subjected to the cyanogen azide ring-expansion reaction do not display any significant migrational selectivity [4].

## Experimental

Melting points were determined on a Fisher Johns melting point apparatus and are uncorrected. IR spectra were recorded on a Perkin-Elmer 521 spectrometer. NMR data were obtained in $CDCl_3$ with a Bruker AC 200 E spectrometer equipped with an Aspect 3000 computer. The solvent peak served as the internal standard. Mass spectra were obtained at the Laboratory of Pharmaceutical Chemistry, University of Salonica, Greece.

### *17-Methylene-3β-hydroxy-5α-androstane* (**2**)

Sodium hydride (0.03 mole as a 80% dispersion in parafin oil) in a 125 ml three-necked flask was repeatedly washed with hexane (4×20 ml) to remove the parafin oil. The flask was then equipped with a magnetic stirrer, rubber stoppers, and set under nitrogen atmosphere. Dimethyl sulfoxide (12 ml) was introduced *via* syringe and the mixture was stirred for 15 min. To the resulting solution of methylsulfinyl carbanion was added, *via* syringe, a solution of dry methyltriphenylphosphonium bromide (9 g, $2.5\times10^{-2}$ moles) dissolved in warm dimethyl sulfoxide (25 ml) and the mixture was stirred at room temperature for 30 min. A solution of **1** (1.45 g, $5\times10^{-3}$ moles) in warm dimethylsulfoxide (6 ml) was subsequently added to the flask *via* syringe and the solution was let stand under constant stirring and nitrogen atmosphere for 48 h. The reaction flask was then opened and ice was slowly added to it until a white precipitate appeared. Precipitation was allowed to proceed overnight and the solution was subsequently filtered. The precipitate was washed with $H_2O$ and was dried at 90 °C overnight. It was subsequently subjected to column chromatography with silica gel and EtOAc as eluent solvent. The product (88%) was recrystallized from $CH_3OH$ to yield white crystals, m.p. 140–142 °C (lit. [6] 144–145 °C), IR (KBr) 3320 (broad), 2935, 2850, 1658, 1450, 1370, 1040, 877 $cm^{-1}$.

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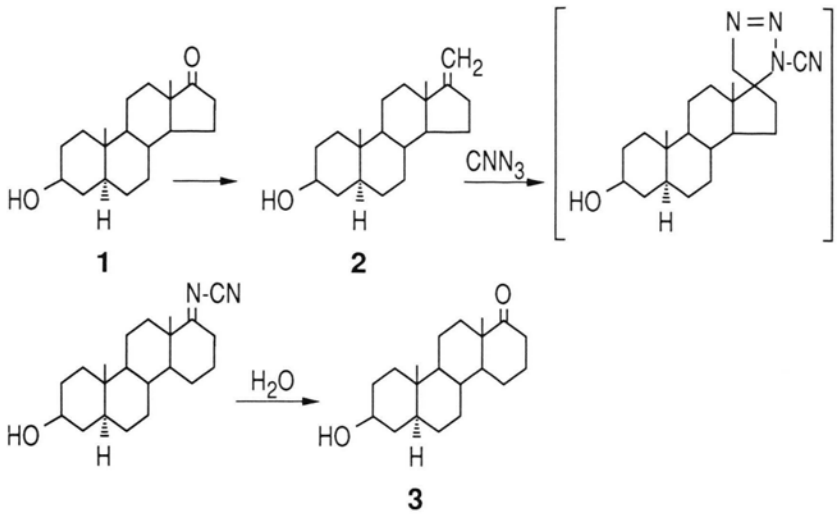
Verlag der Zeitschrift für Naturforschung, D-00000 Tübingen
0932–0776/93/0900–1305 $ 01.30/0




Scheme 1. Reaction scheme to 3 $\beta$-hydroxy-D-homo-5 $\alpha$-androstan-17 a-one (**3**).

*3 $\beta$-Hydroxy-D-homo-5 $\alpha$-androstane-17 a-one* (**3**)

Preparation of 2 M cyanogen azide solution in acetonitrile: To a stirred solution of cyanogen bromide (2.65 g, 25 mmole) (use hood!) in $CH_3CN$ (12.5 ml) in an ice bath was added finely powdered sodium azide (1.63 g, 25 mmole). The solution was stoppered and, after 4 h of stirring at ice-bath temperature, the supernatant was withdrawn by syringe. *Caution! Cyanogen azide is a dangerous explosive which should only be generated and used in solution* [4]!

17-Methylene-3 $\beta$-hydroxy-5 $\alpha$-androstane (**2**) (500 mg, 1.74 moles) was dissolved in the minimum amount of EtOAc (3 ml) and freshly prepared 2 M $CNN_3$ solution (5 ml) was added to it. The reaction mixture was capped with a rubber septum incorporating a syringe needle vent for nitrogen evolution and let stand at room temperature for 10 days. The solvent was subsequently evaporated and replaced by $CH_3OH$. The reaction mixture was treated with 6 N aqueous hydrochloric acid and warmed to 40 °C for 3 h. The mixture was poured into water and extracted with ether, washed with brine, dried over $Na_2SO_4$, percolated through a mat of basic alumina topped with celite, and the solvents evaporated. The residue was subjected to column chromatography on silica gel with $CHCl_3$ as eluent solvent. The product isolated (32%) was recrystallized from $CH_3OH$: m. p. 157 – 159 °C; MS 304 ($M^+$); IR (KBr) 3380 (broad), 2925, 2855, 1700, 1445, 1058, 1035 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta = 0.78$ (19-$CH_3$), 1.08 (18-$CH_3$), 3.59 (m, 3-H); $^{13}C$ NMR ($CDCl_3$) $\delta = 12.3$ (19-$CH_3$), 16.9 (18-$CH_3$), 71.1 (C-3), 216.8 (C=O). NMR data are in agreement with published results [3 b, 7].

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Satz und Druck: Allgäuer Zeitungsverlag GmbH, Kempten