SYNTHESIS OF 17α-AMINO-5α-ANDROST-2-ENE FROM EPIANDROSTERONE

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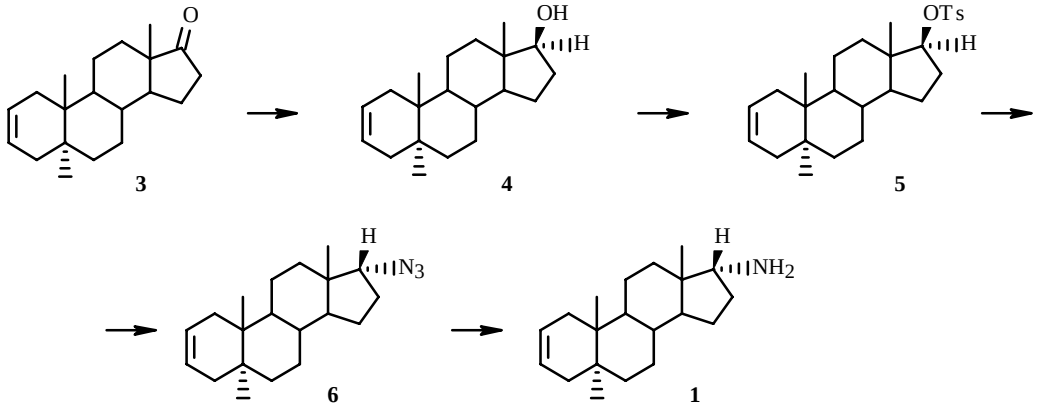
17α-Amino-5α-androst-2-ene was synthesized from epiandrosterone via formation of the tosylate followed by nucleophilic substitution by azide and reduction with $LiAlH_4$. The structures of the products were proved by NMR and IR spectroscopy and mass spectrometry.

Key words: aminosteroids, synthesis.

Steroidal compounds with NH_2-, *N*-alkyl-, *N*-alkyloxy-, and *N*,*N*′-dialkyl-substituents in the C-17 position exhhibit a broad spectrum of biological activity [1-5]. Among these compounds, amines of the 5α-androstane series are also encountered. However, the biological activity of 17-amino-5α-androst-2-ene and its derivatives has not been reported.

We have previously reported the preparation of a mixture of epimers of 17β- and 17α-amino-5α-androst-2-ene as intermediates in the synthesis of 17β-amino-5α-androstane, a compound known to have anti-inflammatory and fungicidal activity [1]. Because crystallization of the mixture of epimers formed upon reduction of 17-hydroxyimino-5α-androst-2-ene or 17β-formamido-5α-androst-2-ene could isolate only the 17β-epimer in 60% yield, we developed a scheme for preparing 17α-amino-5α-androst-2-ene (**1**) using epiandrosterone that provides for the stereoselective synthesis of this epimer (Scheme 1).



Scheme 1. Synthesis of 17α-amino-5α-androst-2-ene from epiandrosterone.

Epiandrosterone (**2**) was transformed to 5α-androst-2-ene-17-one (**3**) by the previously described method [6]. Ketone (**3**) was reduced using $NaBH_4$ in CH_3OH to give stereospecifically 17β-hydroxy-5α-androst-2-ene (**4**), reaction of which with *p*-toluenesulfonyl chloride in anhydrous pyridine gave 17β-(4-methylphenylsulfonyloxy)-5α-androst-2-ene (**5**). We used the Streitweiser—Shaeffer method, which provides for nucleophilic substitution of the 17β-tosyloxy group by azide through an S_N2

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mechanism, to invert the configuration at C-17 [7]. This method was modified by carrying out the substitution reaction using NaN_3 in DMF containing water (10%) at 105-110°C instead of *N*-methyl-2-pyrrolidone at 150°C. This formed over 48 h an oily mixture, chromatography of which over a silica-gel column isolated 17α-azido-5α-androst-2-ene (**6**) in 80% yield. Then reduction of azide (**6**) by an excess of $LiAlH_4$ in THF led to the target 17α-amino-5α-androst-2-ene (**1**) in 80% yield. Using $LiAlH_4$ to reduce the azide gives selective reduction that does not involve the C2–C3 double bond.

Thus, we performed a stereoselective transformation of **2** into **1** using a modified Streitweiser—Schaeffer method.

The structures of the synthesized compounds were confirmed by NMR and IR spectroscopy and mass spectrometry. The IR spectra exhibit characteristic absorption bands for the functional groups. Strong absorptions at 1372 and 1182 cm^{-1} in **5** were assigned to tosyl SO_2 stretching vibrations; at 2098 cm^{-1}, to the azide of **6**. The NH_2 stretches of **1** appeared near 3459 cm^{-1}.

The PMR spectra of **1**, **5**, and **6** contained signals for C-10 and C-13 methyls as singlets with chemical shifts in the range δ 0.74-0.88 ppm. A doublet at δ 3.33-3.55 ppm with SSCC J = 6.2 Hz corresponds to the 17β-proton in **6** and **1**. Signals for vicinal protons of the C2–C3 double bond of **1**, **5**, and **6** appeared as a distorted triplet at δ 5.59 ppm with SSCC J = 6.8 Hz.

The ^{13}C NMR spectra of **1**, **5**, and **6** had signals for C-18 and C-19 at δ 11.67-11.89 and 14.07-20.28 ppm, respectively; for the C=C bond of **1**, **5**, and **6**, at δ 125.8 ppm; for tosylate C–O of **5**, at δ 90.04 ppm; for C–N_3 of **6**, at δ 71.64 ppm; and for C–NH_2 of **1**, at δ 60.11 ppm.

The mass spectra of **1**, **5**, and **6** exhibited peaks for the molecular ions corresponding to the molecular weights of these compounds at 274 $[M + 1]^+$, 428 $[M]^+$, and 300 $[M + 1]^+$, respectively.

The biological activity of **1** and its 17β-epimer is being studied.

EXPERIMENTAL

Melting points were determined on a Gallenkamp block and are uncorrected. IR spectra were recorded on a Magna-IR spectrometer 550 in KBr disks. Mass spectra were recorded in a Finnigan AQA Navigator instrument (EI, 70 eV). NMR spectra were obtained on a Bruker AC 500 instrument (500 MHz working frequency for ^1H and 125 MHz for ^{13}C). Chemical shifts of protons are given on the δ (ppm) scale with TMS internal standard and DMSO-d_6 and $CDCl_3$ solvents. Elemental analyses were found on a Perkin—Elmer CHN 2004. Analyses of all compounds corresponded with those calculated. The course of reactions and purity of products were monitored by TLC on Silufol 254 plates (Kavalier, Czech Rep.) using $CHCl_3$:CH_3OH (15:1). Spots were developed by spraying with phosphomolybdic acid (10%) in ethanol and subsequent heating.

17β-Hydroxy-5α-androst-2-ene (4). A solution of **3** (2 g, 7.3 mmol) in CH_3OH (20 mL) at 0°C was treated in portions with $NaBH_4$ (0.4 g, 10.5 mmol), stirred at 20°C for 1 h, treated with acetic acid (2 mL), and poured into water (100 mL). The precipitate was filtered off and washed with water. Recrystallization from CH_3OH afforded **4** (1.81 g, 90%), mp 161-162°C (lit. [8] mp 163°C), IR spectrum (ν, cm^{-1}): 3455 (OH).

17β-(4-Methylphenylsulfonyloxy)-5α-androst-2-ene (5). A solution of **4** (1 g, 3.64 mmol) in freshly distilled pyridine (20 mL) at 0°C was treated in portions with *p*-toluenesulfonyl chloride (1.4 g, 7.28 mmol), held at 0°C for 48 h, and poured into icewater (100 mL). The precipitate was filtered off and washed with water. Recrystallization from benzene:hexane (1:4) afforded **5** (1.42 g, 85%), mp 96-98°C. IR spectrum (ν, cm^{-1}): 1372 and 1182 (SO_2). Mass spectrum (*m*/*z*, I_{rel}, %): 482 (5) $[M]^+$, 257 (100).

PMR spectrum (δ, ppm, J/Hz): 0.74 (3H, s, CH_3-18), 0.81 (3H, s, CH_3-19), 2.46 (3H, s, CH_3-OTs), 4.30 (1H, dd, J = 9.0, 7.7, H-17α), 5.59 (2H, dist. t, J = 6.8, H-2, H-3), 7.33 (2H, d, J = 8.2, OTs-17), 7.80 (2H, d, J = 8.2, OTs-17).

^{13}C NMR spectrum (δ, ppm): 11.89 (C-18), 20.28 (C-19), 23.21 (CH_3-OTs), 90.04 (C-17), 125.8 (C-2, C-3), 127.80, 129.60, 134.54, and 144.55 (C-arom.).

17α-Azido-5α-androst-2-ene (6). A mixture of **5** (1.5 g, 3.49 mmol), NaN_3 (1.5 g, 23.8 mmol), DMF (30 mL), and water (3 mL) was heated at 105-110°C for 48 h, cooled to 20°C, and poured into icewater (100 mL). The resulting oily product was chromatographed over a column (silica gel L 100/160, eluent petroleum ether:ethylacetate, 50:1) to isolate **6**, (0.83 g, 80%), mp 58-60°C. IR spectrum (ν, cm^{-1}): 2098 (N_3). Mass spectrum (*m*/*z*, I_{rel}, %): 300 (5) $[M + 1]^+$, 272 (100).

PMR spectrum (δ, ppm, J/Hz): 0.76 (3H, s, CH_3-18), 0.87 (3H, s, CH_3-19), 3.55 (1H, d, J = 6.87, H-17β), 5.59 (2H, dist. t, J = 6.8, H-2, H-3). ^{13}C NMR spectrum (δ, ppm): 11.67 (C-18), 17.71 (C-19), 71.64 (C-17), 125.8 (C-2, C-3).

17α-Amino-5α-androst-2-ene (1). A suspension of $LiAlH_4$ (1.5 g, 39.47 mmol) in THF (100 mL) at 20°C was treated

with **6** (1.5 g, 5.0 mmol) in THF (20 mL) and boiled for 6 h. The excess of $LiAlH_4$ was destroyed by adding water (1.5 mL), aqueous NaOH (1.5 mL, 15%), and water again (4.5 mL). The reaction mixture was filtered. The precipitate was washed with THF (3 × 30 mL). The mother liquor was acidified with HCl until the pH was 2. The solvent was removed in vacuo. The solid dissolved with heating in water (200 mL). The solution was filtered. The precipitate that formed when the mother liquor was made basic (NaOH to pH 8) was separated by filtration. Crystallization from benzene:hexane (1:2) afforded **1** (1.09 g, 80%), mp 138-140°C. IR spectrum (ν, cm^{-1}): 3459 (NH). Mass spectrum (*m*/*z*, I_{rel}, %): 274 (15) $[M + 1]^+$, 257 (100).

PMR spectrum (δ, ppm, J/Hz): 0.84 (3H, s, CH_3-18), 0.88 (3H, s, CH_3-19), 3.33 (1H, br.d, J = 6.2, H-17*β*), 5.59 (2H, dist. t, J = 6.8, H-2, H-3). ^{13}C NMR spectrum (δ, ppm): 11.73 (C-18), 14.07 (C-19), 60.11 (C-17), 125.83 (C-2, C-3).

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