CONVERSION OF EPIANDROSTERONE INTO 17β-AMINO-5α-ANDROSTANE

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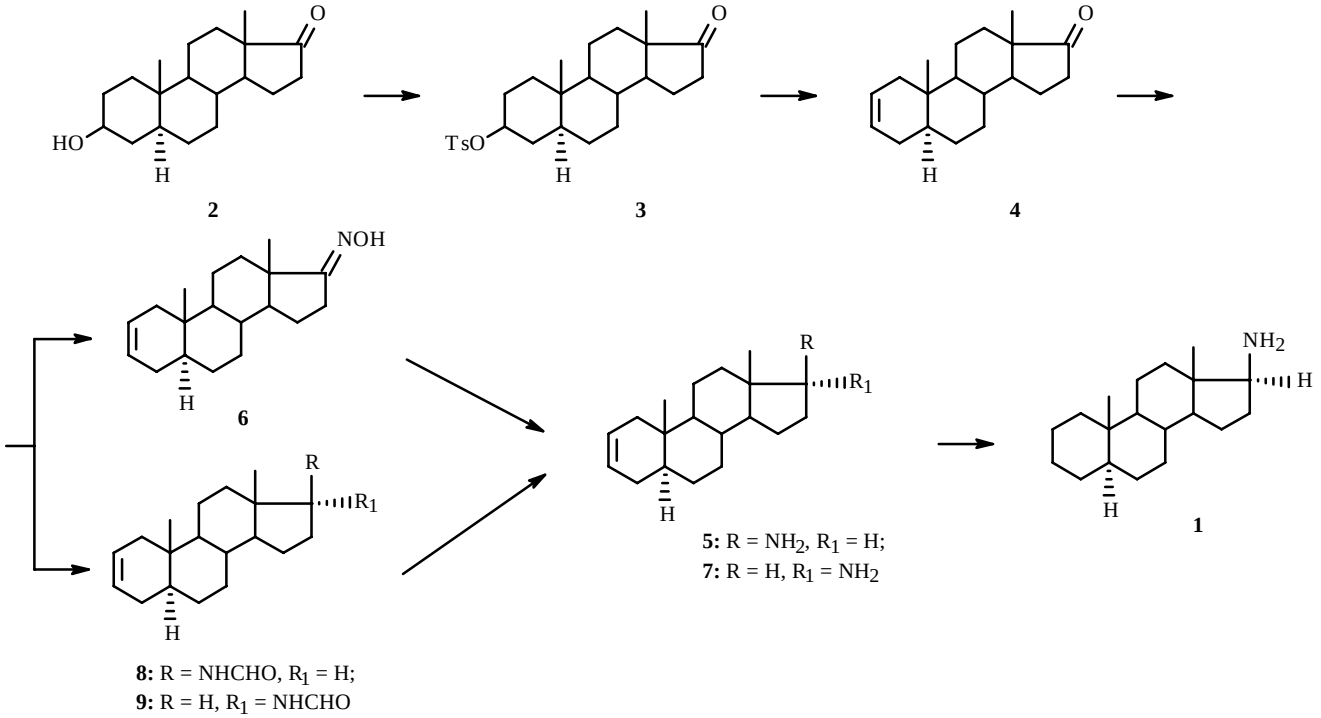
A new method for synthesizing 17β-amino-5α-androstane was developed based on tigogenin. The configuration at C-17 was proved by PMR.

Key words: aminosteroids, synthesis, 5α-androstane.

Aminosteroids of the 5α-androstane series typically have a broad spectrum of pharmacologic action, in particular, antiarhythmic, hypotensive, anti-inflammatory, and fungicidal activity [1-3].

17β-Amino-5α-androstane (**1**) was first synthesized as the hydrochloride from cholesterol [4]. Amine **1** is usually prepared by reduction of 17-hydroxyimino-5α-androstane by various reductants [5, 6]. Spectral proof of the configuration at C-17 in compound **1** has not been reported.

We developed a new scheme for synthesizing 17β-amino-5α-androstane (**1**) from epiandrosterone (**2**) (Scheme 1). Epiandrosterone was prepared from pregn-16-en-3β-ol-20-one acetate, a conversion product of tigogenin, which has been proposed as an available steroidal raw material by the I. G. Kutateladze Institute of Pharmaceutical Chemistry of the Academy of Sciences of Georgia [7].



2 **3** **4** **6**

5: R = NH_2, R_1 = H;
7: R = H, R_1 = NH_2

1

8: R = NHCHO, R_1 = H;
9: R = H, R_1 = NHCHO

Scheme 1.

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In the first step, C-3 of epiandrosterone (**2**) was defunctionalized using the literature method [8, 9] for synthesizing O-sulfonyl derivative **3** from *p*-toluenesulfonyl chloride in anhydrous pyridine followed by dehydrotosylation of **3** by LiBr in DMF. The yield of 5α-androst-2-en-17-one (**4**) was 65%.

In the second step, stereoselective addition of a N-containing substituent to the C-17 position of ketone **4** was studied. For this, amine **5** was synthesized by two methods: a known one consisting of formation of the oxime from the ketone followed by reduction of the oxime to the amine and reductive amination by the Leuckart—Wallach reaction that was used previously for epiandrosterone [10].

Formation of the oxime of **4** using hydroxylamine hydrochloride in pyridine gives 17-hydroximino-5α-androst-2-ene (**6**). Reduction of oxime **6** by metallic sodium in anhydrous propan-1-ol forms a mixture of the 17β- (**5**) and 17α-amino-5α-androst-2-ene (**7**) (in ~10:1 ratio according to PMR spectroscopy). Subsequent crystallization from benzene:hexane (1:2) isolates the pure 17β-epimer (**5**) in 60% yield. Amination of ketone **4** by a mixture of ammonium sulfate, formamide, and formic acid at 180°C gives a mixture of formyl derivatives **8** and **9**. The raw product is suitable for further transformation without additional purification. The mixture of **8** and **9** was hydrolyzed by boiling in HCl (20%) in CH_3OH into a mixture of **5** and **7** in ~10:1 ratio according to PMR. The 17β-amine was isolated in 59% yield by crystallization from benzene:hexane (1:2). Hydrogenation of **5** over Pd/C in EtOH gives saturated aminosteroid **1** in 75% yield. The yields of amine **1** calculated based on starting ketone **2** by the Leuckart—Wallach reaction and through formation of oxime **6** are 22 and 25%, respectively.

Thus, **2** can be stereoselectively converted to **1** through formation of **6** or the Leuckart—Wallach reaction.

The structures of the synthesized compounds were confirmed by NMR, IR, and mass spectrometry. Mass spectra exhibit peaks for molecular ions corresponding to the molecular weights of the studied compounds. IR spectra contain characteristic absorption bands of the functional groups. A strong absorption in **6** at 1651 cm^{-1} belongs to C=N stretching vibrations; a weak one at 1634 cm^{-1}, to the C=C bond. The presence of a hydroxyl (CN–OH) was confirmed by an absorption band at 3283 cm^{-1}. Stretching vibrations of the primary amino in **1** and **5** are found at 3439-3459 cm^{-1}.

PMR spectra of **1**, **5**, and **6** have signals for the C-18 angular methyls as singlets with chemical shifts in the range δ 0.61-0.73 ppm; for C-19 methyls, δ 0.77-0.86 ppm. A triplet at δ 2.64 ppm with SSCC J = 8.8 and 8.5 Hz corresponds to the 17α-proton of **1** and **5**. Signals from vicinal protons of the C-2=C-3 double bond in **6** and **5** appear as a distorted triplet at δ 5.54 and 5.59 ppm, respectively. The signal with chemical shift δ 8.01 ppm corresponds to the hydroxyl H of **6**. Geminal protons on C-16 of **6** are observed as two doublets with chemical shifts δ 2.45 and 2.47 ppm.

^{13}C NMR spectra of **1**, **5**, and **6** have signals from C-18 and C-19 at δ 11.66-12.18 and 17.01-20.5 ppm, respectively; the oxime C=N of **6**, at δ 171.5 ppm; the C=C of **6** and **5**, at δ 125.86 and 126.8 ppm; and the C–NH_2 of **5** and **1**, at δ 62.0 and 62.89 ppm, respectively.

EXPERIMENTAL

Melting points were determined on a Kofler block. IR spectra were recorded on a Magna-IR Spectrometer 550 instrument in KBr disks. Mass spectra were recorded in a Micromass Platform II instrument (EI, 70 eV). NMR spectra were obtained on an AC 250 instrument (Bruker, working frequency 250 MHz for ^1H and 62.5 MHz for ^{13}C). Chemical shifts of protons are given on the δ scale with TMS internal standard and $CDCl_3$ solvent. The course of the reactions and the purity of the products were monitored by TLC on Silufol 254 plates (Kavalier, Czech Rep.) using benzene:acetone (10:1) or butanol:acetic acid:water (4:1:1). Spots were detected by spraying with phosphomolybdic acid solution in EtOH (10%) and subsequent heating.

3β-(4-Methylphenylsulfonyloxy)-5α-androstan-17-one (3). A solution of **2** (2.5 g, 8.60 mmol) in freshly distilled pyridine (25 mL) at 0°C was treated with *p*-toluenesulfonylchloride (3.2 g, 16.9 mmol), held at 20°C for 20 h, and poured into icewater (100 mL). The precipitate was filtered off and washed with water to isolate the product (3.5 g). Crystallization from benzene:hexane (1:4) afforded **3** (3.36 g, 88%), mp 163-164°C, which corresponds to the literature value [8].

5α-Androst-2-en-17-one (4). A solution of **3** (2.9 g, 6.58 mmol) in DMF (10 mL) was treated with LiBr (1.4 g, 16.09 mmol), boiled for 3 h, cooled, and treated with water. The precipitate was filtered off, washed with water, and dried. Chromatography over a column (silica gel L 100/160, eluent benzene:acetone, 10:1) isolated **4** (1.15 g, 65%), mp 100-102°C, lit. [8] mp 103-105°C.

17-Hydroximino-5α-androst-2-ene (6). A mixture of **4** (2 g, 7.34 mmol) and hydroxylamine hydrochloride (0.5 g, 7.35 mmol) in pyridine (15 mL) was heated to 65-67°C for 3 h, cooled to room temperature, and poured into icewater (50 mL).

The precipitate was filtered off, washed with water, and dried. Crystallization from CH_3OH afforded **6** (2.0 g, 95%), mp 141-143°C. IR spectrum (ν, cm^{-1}): 3283 (OH), 1651 (C=N), 1634 (C=C). Mass spectrum (*m*/*z*): 287 $[M]^+$, 270 $[M - OH]^+$, 256 $[M - N - OH]^+$.

PMR spectrum (δ, ppm, J/Hz): 0.73 (3H, s, CH_3-18), 0.86 (3H, s, CH_3-19), 2.45 (1H, d, *syn*-H-16, J = 3.17), 2.47 (1H, d, *anti*-H-16, J = 8.6), 5.54 (2H, distorted t, H-2, H-3, J = 6.8), 8.01 (1H, s, C=NOH). ^{13}C NMR spectrum (δ, ppm): 11.66 (C-18), 17.09 (C-19), 34.96 (C-16), 126.8 (C-2, C-3), 171.5 (C-17).

17β-Formamido-5α-androst-2-ene (8). A mixture of **4** (0.37 g, 1.4 mmol), anhydrous ammonium sulfate (0.04 g, 0.3 mmol), and formic acid (0.14 mL, 3.7 mmol, 99.7%), and formamide (1.3 mL, 38.4 mmol) was heated at 150-160°C for 1 h and at 180-190°C for 3.5 h, cooled to 20°C, and treated with water (10 mL). After 12 h the precipitate was filtered off, washed with water, and dried to isolate the product (0.39 g). Chromatography over a column (silica gel L 100/160, eluent benzene:acetone, 20:1 and 10:1) isolated **8** (0.35 g, 85%), mp 149-151°C. IR spectrum (ν, cm^{-1}): 3250 (NH), 1655, 1560 (CONH), 1635 (C=C).

17β-Amino-5α-androst-2-ene (5). a) A boiling solution of **6** (3 g, 10.43 mmol) in propan-1-ol (100 mL) was treated with portions of metallic sodium (3 g) over 3 h, boiled for 1 h, cooled, and treated with saturated NaCl solution. The organic layer was evaporated in vacuum to dryness. The solid was dissolved in ether and washed with water until the pH was 7. The ether extracts were dried ($MgSO_4$). The solvent was evaporated to give the product (2 g). Crystallization from benzene:hexane (1:2) afforded **5** (1.73 g, 60%), mp 145-147°C.

b) A mixture of crude reaction product containing **8** and **9** (0.35 g, 1.2 mmol), aqueous HCl (0.9 mL, 20%), and CH_3OH (20 mL) was boiled for 10 h and evaporated in vacuum. The CH_3OH and solid were heated to dissolve them in water (150 mL). The insoluble precipitate was filtered off. The filtrate was made basic with NaOH until the pH was 8. The resulting precipitate was filtered off, washed with water, and dried to isolate the product (0.22 g). Crystallization from benzene:hexane (1:2) gave **5** (0.19 g, 59%).

IR spectrum (ν, cm^{-1}): 3439 (NH_2), 1634 (C=C). Mass spectrum (*m*/*z*): 273 $[M]^+$, 258 $[M - NH]^+$.

PMR spectrum (δ, ppm, J/Hz): 0.64 (3H, s, CH_3-18), 0.77 (3H, s, CH_3-19), 2.64 (1H, t, H-17α, $J_{17a'/16e'}$ = 8.5, $J_{17a'/16a'}$ = 8.8), 5.59 (2H, distorted t, H-2, H-3, J = 6.8). ^{13}C NMR spectrum (δ, ppm): 17.2 (C-18), 20.57 (C-19), 47.9 (C-16), 62.0 (C-17), 125.86 (C-2, C-3).

17β-Amino-5α-androstane (1). A solution of **5** (2 g, 7.31 mmol) in absolute EtOH (100 mL) was treated with a suspension of Pd/C (0.5 g) in EtOH (100 mL) and stirred on a magnetic stirrer under a H_2 atmosphere at 20-25°C until H_2 absorption stopped. The catalyst was filtered off and washed with hot EtOH. The filtrate was evaporated to dryness. The resulting oil was triturated in ether and filtered off. Crystallization from benzene:hexane (1:2) isolated **1** (1.51 g, 75%), mp 89-91°C, lit. [3] mp 86-90°C.

IR spectrum (ν, cm^{-1}): 3439 (NH_2). Mass spectrum (*m*/*z*): 275 $[M]^+$, 260 $[M - NH]^+$.

PMR spectrum (δ, ppm, J/Hz): 0.61 (3H, s, CH_3-18), 0.77 (3H, s, CH_3-19), 2.64 (1H, t, H-17α, $J_{17a'/16e'}$ = 8.5, $J_{17a'/16a'}$ = 8.8).

^{13}C NMR spectrum (δ, ppm): 12.18 (C-18), 20.40 (C-19), 47.08 (C-16), 62.89 (C-17).

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