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Papers

Ionic hydrogenation of 3-methoxy-14α,15α-methylenestra-1,3,5(10),8-tetraen-17α-ol: A correction

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3-Methoxy-14α,15α-methylenestra-1,3,5(10),8-tetraen-17α-ol on hydrogenation with triethylsilane/trifluoroacetic acid yielded 3-methoxy-14β,15β-methylenestra-1,3,5(10)-trien-17α-ol, not the 14α,15α-methylene-9β product as previously described. (*Steroids* **61**:48–49, 1996)

Keywords: 14α,15α-methylene estradiol; ionic hydrogenation; 14α,15α-methylene group isomerization

Introduction

Very recently, we published a novel approach to the synthesis of 14α,15α-methylene estradiol (**1**, J 824).[1] One key aspect of the described route included the hydrogenation of the title compound **2** to give the 8β,9α-derivative **3**. Ionic hydrogenation[2] of **2** was reported to afford 3-methoxy-14α,15α-methylen-9β-estra-1,3,5(10)-trien-17β-ol. In the present short paper, we will correct the structural assignment of this reduction product.

Experimental

General methods

^{1}H NMR spectra were recorded on a Varian Gemini 300 (300 MHz). Unless otherwise stated, deuteriochloroform was used as solvent, chemical shifts are reported as δ values in ppm downfield from tetramethylsilane as internal standard, *J* values are given in Hz. Melting points were measured with Boetius equipment. UV spectra were taken with a Zeiss Specord M 40 in methanolic solutions, λ_{max} in nm (log ε). Optical rotations were measured with the Polamat A (Carl Zeiss Jena), solvent chloroform (unless otherwise provided), c = 1 g per 100 mL, temperature = 20°C. Chromatography means flash chromatography, which was performed on silica (Kieselgel 60, Merck A. G. Darmstadt, 0.04–0.063 mm).

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Received July 10, 1995; accepted September 12, 1995.

All reactions were run under a nitrogen or argon atmosphere. Usual workup of the extract included the following steps: the organic phase was washed with saturated aqueous sodium hydrogen carbonate solution and water, dried over anhydrous sodium sulfate or magnesium sulfate, and rotary evaporated to dryness.

3-Methoxy-14β,15β-methylenestra-1,3,5(10)-trien-17α-ol (4)

Triethylsilane (12.8 mL; 80.3 mmol) was added to a solution of **2** (10 g; 33 mmol) in dichloromethane (50 mL) with stirring at +20°C to +25°C. Into this mixture trifluoroacetic acid (30 mL; 0.39 mol) was dropped while keeping the temperature in the same range. After having stirred for 16 h, aqueous sodium carbonate solution (20%) was added to neutralize the reaction mixture. The organic phase was separated and worked up as usual. The residue was crystallized from methanol to give 3-methoxy-14β,15β-methylenestra-1,3,5(10)-trien-17β-yl trifluoroacetate (10.04 g; 75%): m.p. 102–105°C; $[\alpha]_D$ +95°; UV 278 (3.31), 287 (3.29); ^{1}H NMR 0.25 (dd, *J* = 6.2, 3.7, 1 H, 14β,15β-CH_2), 0.69 (dd, *J* = 8.0, 6.2, 1 H, 14β,15β-CH_2), 1.11 (s, 3 H, 18-H), 3.78 (s, 3 H, 3-OCH_3), 4.72 (dd, *J* = 9.2, 7.7, 1 H, 17β-H), 6.62 (d, *J* = 2.8, 1 H, 4-H), 6.74 (dd, *J* = 8.7, 2.8, 1 H, 2-H), 7.25 (d, *J* = 8.7, 1 H, 1-H); $C_{22}H_{25}F_3O_3$ (394.43) calculated C 66.99 H 6.39, found C 66.91 H 6.41. A solution of the trifluoroacetate (8.0 g; 20.2 mmol) in methanol (300 mL) was mixed with aqueous potassium hydroxide solution (2N; 57 mL) and the mixture was allowed to react for 2 h at room temperature. Water was then added and the precipitated crystals filtered off. Recrystallization from methanol provided **4** (5.44 g; 90%): m.p 118–122°C (lit.[3] 119–121°C); $[\alpha]_D$ +102° (lit.[3] +104°C); UV 278 (3.33), 287 (3.27); ^{1}H NMR 0.17

Steroids 61:48–49, 1996

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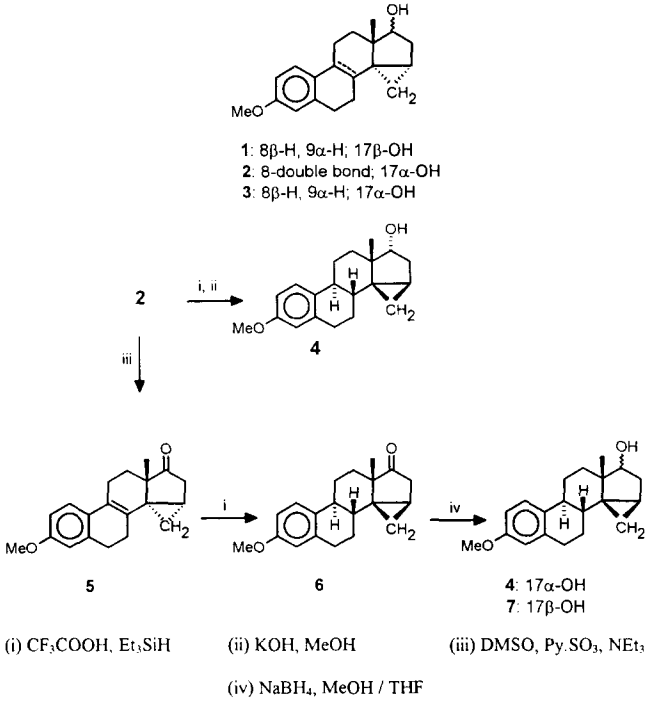
0039-128X/96/$15.00
SSDI 0039-128X(95)00175-1



Scheme 1 Ionic hydrogenation of 3-methoxy-14α,15α-methylenestra-1,3,5(10),8-tetraen-17α-ol **(2)**.

(dd, J = 5.8, 3.9, 1 H, 14β,15β-CH_2), 0.56 (dd, J = 8.4, 5.8, 1 H, 14β,15β-CH_2), 1.07 (s, 3 H, 18-H), 3.55 (dd, J = 9.1, 6.9, 1 H, 17β-H), 3.78 (s, 3 H, 3-OCH_3), 6.62 (d, J = 2.8, 1 H, 4-H), 6.73 (dd, J = 8.5, 2.8, 1 H, 2-H), 7.26 (d, J = 8.5, 1 H, 1-H); $C_{20}H_{26}O_2$ (298.43) calculated C 80.50 H 8.78, found C 80.55 H 8.75.

3-Methoxy-14β,15β-methylenestra-1,3,5(10)-trien-17-one (6)

To a solution of **5** (3.5 g; 11.8 mmol) in dichloromethane (20 mL) and triethylsilane (4.5 mL; 28.2 mmol) was added trifluoroacetic acid (8.7 mL; 0.113 mol) at +20°C to +25°C with stirring. Stirring was continued for another 16 h followed by neutralization of the reaction mixture with aqueous sodium carbonate solution (20%). The organic phase was separated and worked up as usual to give a residue which was purified by chromatography (eluent: cyclohexane/ethyl acetate 7:3 v/v). Crystallization from methanol afforded **6** (2.64 g; 75%): m.p. 166–167°C (lit.[3] 160–162°C); $[\alpha]_D$ +263° (lit.[3] +256.7°); UV 278 (3.32), 287 (3.30); ^{1}H NMR –0.25 (dd, J = 6.0, 3.8, 2 H, 14β,15β-CH_2), 1.08 s, 3 H, 18-H), 3.78 (s, 3 H, 3-OCH_3), 6.63 (d, J = 2.9, 1 H, 4-H), 6.74 (dd, J = 8.8, 2.9, 1 H, 2-H), 7.24 (d, J = 8.8, 1 H, 1-H); $C_{20}H_{24}O_2$ (296.41) calculated C 81.04 H 8.16, found C 81.00 H 8.05.

3-Methoxy-14β,15β-methylenestra-1,3,5(10)-trien-17α-ol (4) and 3-methoxy-14β,15β-methylenestra-1,3,5(10)-trien-17β-ol (7)

Sodium borohydride (2.19 g; 55.32 mmol) was added to a solution of **6** (8.2 g, 27.66 mmol) in a mixture of methanol and THF (250 mL each) within 15 min with stirring. Stirring was continued for another 45 min. The solution was then acidified with acetic acid and concentrated in vacuo to a volume of 100 mL. Dilution with water and extraction with dichloromethane gave an extract which was worked up as usual. The product was subjected to chromatography (eluent: cyclohexane/ethyl acetate 7:3 v/v) to give **7** and **4** in that order. **7** (1.22 g; 14.8%): m.p. 139–143°C (methanol; lit.[3] 140–142°C); $[\alpha]_D$ +118° (lit.[3] + 116.8°); UV 278 (3.31), 287 (3.29); ^{1}H NMR 0.68 (m, 2 H, 14β,15β-CH_2), 1.08 (s, 3 H, 18-H), 3.68 (dd, J = 6.0, 1.8, 1 H, 17α-H), 3.78 (s, 3 H, 3-OCH_3), 6.62 (d, J = 2.6, 1 H, 4-H), 6.73 (dd, J = 8.8, 2.6, 1 H, 2-H), 7.24 (d, J = 8.8, 1 H, 1-H); $C_{20}H_{26}O_2$ (298.43) calculated C 80.50 H 8.78, found C 80.68 H 8.75. **4** (5 g; 60.6%): The compound was identical in all respects with **4** prepared from **2.**

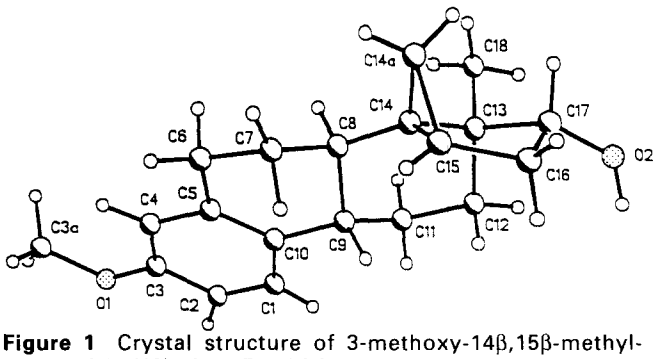


Figure 1 Crystal structure of 3-methoxy-14β,15β-methylenestra-1,3,5(10)-trien-17α-ol **(4)**.

Results and discussion

A reinvestigation into the ionic hydrogenation of compound **2** with triethylsilane/trifluoroacetic acid in dichloromethane followed by trifluoroacetate hydrolysis showed that the product, in fact, was 3-methoxy-14β,15β-methylenestra-1,3,5(10)-trien-17α-ol **(4).** Accordingly, Birch reduction[1] and also ionic hydrogenation of the 8-double bond of **2** predominantly yielded an 8β,9α-dihydro product. However, ionic hydrogenation was accompanied by an additional inversion of the 14α,15α-methylene bridge (Scheme 1). Compound **4** was alternatively synthesized from 14,15-didehydroestradiol 3-methylether via Simmons-Smith methylenation.[3] The structure of **4** was definitively established by X-ray diffraction analysis (Figure 1). The involved isomerization of the 14α,15α-methylene bridge[4] was suggested to take place in the initial stage of the reaction by influence of trifluoroacetic acid on **2** before hydrogenation of the 8-double bond had occurred. Ionic hydrogenation of the 17-oxo steroid **5** led analogously to compound **6,**[3] sodium borohydride reduction of which afforded **4** and **7.**[3]

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