Chemistry of Heterocyclic Compounds, Vol. 45, No. 9, 2009

LETTERS TO THE EDITOR

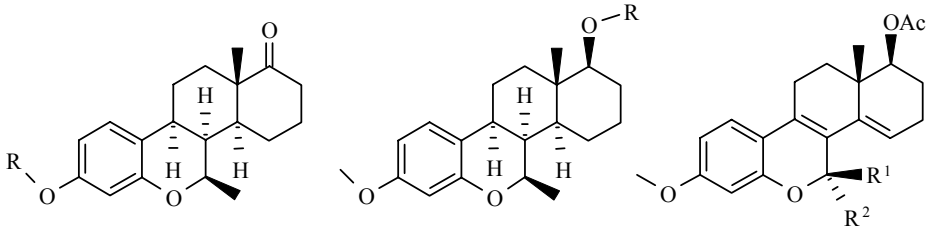
NEW VARIANT OF THE SYNTHESIS OF D-HOMO-6-OXA-8α-ANALOGS OF STEROID ESTROGENS CONTAINING A β-METHYL GROUP AT C-7

S. N. Morozkina[1], A. S. Chentsova[1], T. Yu. Hasan[1], S. I. Selivanov[1], A. L. Shavarda[1], and A. G. Shavva[1]*

Keywords: estrone sulfatase inhibitors, steroid estrogen sulfamates, complete steroid synthesis.

Estrone sulfatase inhibitors hold promise for use in the development of drugs for treating breast cancer [1-3]. One such inhibitor is 7β-methyl-D-homo-6-oxa-8α-estrone (**1a**). [4]. Such compounds irreversibly deactivate estrone sulfatase, leading to steroids with a free hydroxyl group at C-3 [5], which should lack estrogen activity [6]. Steroid **1b** conforms to this condition. Thus, improvement of the method for preparation of this compound holds considerable interest.

17aβ-Acetoxy-3-methoxy-7β-methyl-D-homo-6-oxa-8α-estra-1,3,5(10)-triene (**2a**) serves as an intermediate in the synthesis of inhibitor **1a** and its analog **1b**. Previously, trienes **2** were obtained by the catalytic hydrogenation of a mixture of epimers **3a** and **3b** at high temperature and pressure [7] but the yield of the desired steroid **2** did not exceed 25%.



1 a R = NH_2SO_2, **b** R = H, **c** R = Me; **2 a** R = Ac, **b** R = H; **3 a** R^1 = Me, R^2 = H; **b** R^1 = H, R^2 = Me

* To whom correspondence should be addressed, e-mail: Alexander.Shavva@gmail.com.

[1]St. Petersburg State University Faculty of Chemistry, Natural Products Chemistry Department, St. Petersburg 198504, Russia.

Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 9, pp. 1427-1429, September, 2009. Original article submitted July 21, 2009.

An X-ray structural analysis of acetate **3a** showed that the β-region of the molecule is sterically shielded by the methyl groups at C-7 and C-13 atoms [8]. This suggests that the predominant approach of the catalyst to the conjugated double bond system in the catalytic hydrogenation of steroid **3a** will occur from the α-side of the molecule, which opens possibilities for the reduction of the double bonds under mild conditions. We confirmed this hypothesis experimentally by carrying out the catalytic hydrogenation of estrapentaene **3a** in THF–methanol in the presence of Pd/C at room temperature and atmospheric pressure. The yield of the desired steroid **2a** was 61%. Hydrolysis of this compound with subsequent oxidation of the resultant alcohol **2b** using the Sarett reagent permitted us to synthesize methyl ether **1c** in 64% yield relative to acetate **2a**.

These results hold interest not only relative to the extensive study of the biological properties of estrone sulfatase inhibitors such as **1a** but also inhibitors of other enzymes responsible for the metabolism of steroid hormones.

The ^{1}H and ^{13}C NMR spectra were taken at 295K on a Bruker DPX-300 spectrometer at 300 and 75 MHz, respectively. Solutions of 5-7 mg of compound in 0.6 ml $CDCl_3$ were used for the ^{1}H NMR spectra, while 30-50 mg of compound in 0.6 ml $CDCl_3$ were used for the ^{13}C NMR spectra. The chemical shifts were measured relative to TMS by relation to the solvent signals ($CDCl_3/CHCl_3$ = 99.9/0.1) at 7.26 ppm for ^{1}H and 76.90 ppm for ^{13}C. The compounds were analyzed on an HP 6890 gas chromatograph with an HP 5973 mass-selective detector (GC/MS). A 30-m×0.25-mm HP-5MS capillary column (0.25 μm thickness) from Agilent, Palo Alto, CA, USA was used with helium as the gas carrier. The flow rate was 1.3 ml/min. The ionization energy was 70 eV.

All the products were racemic.

17aβ-Acetoxy-3-methoxy-7β-methyl-D-homo-6-oxa-8α-estra-1,3,5(10)-triene (2a). (5%) Pd/C (150 mg) was added to a solution of estrapentaene **3a** (500 mg) [9] in 1:1 THF–methanol (15 ml). A hydrogen stream was passed through the solution with stirring at atmospheric pressure and room temperature for 12 h. The desired product was purified by crystallization from methanol to give 0.311 mg (61%) triene **2a**, mp 201-203.5°C (mp 201-203°C [7]). The ^{1}H and ^{13}C NMR spectra of the prepared steroid corresponded to our previous data [7]. A mixed sample of the product prepared and an authentic sample did not give a depressed melting point. Found, %: C 73.35; 73.34; H 8.63; 8.63. $C_{22}H_{30}O_4$. Calculated, %: C 73.71; H 8.43.

3-Methyl Ether of 7β-Methyl-D-homo-6-oxa-8α-estradiol (2b). Hydrolysis of acetate **2a** (200 mg) under the usual conditions [7] leads to the formation of alcohol **2b**. The yield of compound **2b** after crystallization from methanol was 145 mg (82%), mp 152-153.5°C. ^{1}H NMR spectrum, δ, ppm: 7.07 (1H, H-1); 6.49 (1H, H-2); 6.35 (1H, H-4); 4.41 (1H, H-7α); 2.59 (1H, H-8α); 2.65 (1H, H-9α); 1.97 (1H, H-11α); 1.64 (1H, H-11β); 1.19 (1H, H-12α); 1.92 (1H, H-12β); 1.61 (1H, H-14α); 1.43 (1H, H-15α); 1.43 (1H, H-15β); 1.43 (1H, H-16α); 1.83 (1H, H-16β); 1.68 (1H, H-17α); 1.47 (1H, H-17β); 3.22 (1H, H-17aα); 0.93 (2H, 18-CH_3); 3.75 (3H, CH_3O); 1.42 (3H, CH_3-7β); 1.62 (1H, OH). ^{13}C NMR spectrum, δ, ppm: 129.01 (C-1); 107.16 (C-2); 158.68 (C-3); 102.27 (C-4); 153.04 (C-5); 71.55 (C-7); 40.56 (C-8); 34.91 (C-9); 118.85 (C-10); 27.14 (C-11); 36.24 (C-12); 37.73 (C-13); 43.96 (C-14); 24.67 (C-15); 24.67 (C-16); 30.13 (C-17); 80.55 (C-17a); 12.81 (C-18); 55.04 (CH_3O); 18.58 (C-7α). Mass spectrum, *m/z* (I_{rel}, %): 316 (100), 301 (19), 287 (28), 283 (11), 269 (10), 215 (8), 201 (8), 189 (15), 175 (34), 163 (30), 161 (75), 150 (37), 137 (49), 128 (5), 121 (10). Found, %: C 76.28; H 8.58. $C_{20}H_{28}O_3$. Calculated, %: C 75.91; H 8.92.

Methyl Ether of 7β-Methyl-D-homo-6-oxa-8α-estrone (1c). Sarett reagent prepared from chromium(VI) oxide (80 mg) and pyridine (2 ml) was added to a solution of ether **2b** (100 mg) in pyridine (3 ml). After 24 h, the excess oxidizing agent was decomposed by adding ethanol (2 ml). After the usual treatment [10], the yield of estrone **1c** isolated after crystallization from methanol was 78 mg (78.5%), mp 149-151°C. ^{1}H NMR spectrum, δ, ppm: 7.08 (1H, H-1); 6.50 (1H, H-2); 6.35 (1H, H-4); 4.48 (1H, H-7α); 2.65 (1H, H-8α); 2.62 (1H, H-9α); 2.05 (1H, H-11α); 1.64 (1H, H-11β); 1.74 (1H, H-12α); 1.72 (1H, H-12β); 1.94 (1H, H-14α); 1.73 (1H, H-15α); 1.84 (1H, H-15β); 1.73 (1H, H-16α); 2.13 (1H, H-16β); 2.26 (1H, H-17α); 2.60 (1H, H-17β); 1.17 (3H, 18-CH_3); 3.75 (3H, CH_3O). ^{13}C NMR spectrum, δ, ppm: 129.1 (C-1); 107.40 (C-2);

158.9 (C-3); 102.4 (C-4); 152.9 (C-5); 71.0 (C-7); 40.8 (C-8); 34.5 (C-9); 118.4 (C-10); 27.0 (C-11); 32.0 (C-12); 47.1 (C-13); 44.8 (C-14); 24.5 (C-15); 26.5 (C-16); 37.3 (C-17); 214.9 (C-17a); 19.5 (C-18); 55.1 (CH_3O); 18.7 (C-7β). Mass spectrum, *m/z* (I_{rel}, %): 314 (100), 299 (9); 285 (6), 271 (5), 257 (5), 343 (7), 229 (5), 215 (23), 189 (11), 176 (17), 175 (22), 161 (45), 150 (22), 137 (21). Found, %: C 76.16; 76.09; H 8.58; 8.66. $C_{20}H_{26}O_3$. Calculated, %: C 76.40; H 8.33.

REFERENCES

1. M. J. Reed, A. Purohit, L. W. Woo, S. P. Newman, and B. V. L. Potter, *Endocr. Rev.*, **26**, 171 (2005).
2. P. A. Foster, M. J. Reed, and A. Purohit, *Anticancer Agents Med. Chem.*, **8**, 732 (2008).
3. J. M. Day, A. Purohit, H. J. Tutill, P. A. Foster, L. W. Woo, B. V. Potter, and M. J. Reed, *Ann. N. Y. Acad. Sci.*, **1155**, 80 (2009).
4. I. A. Gluzdikov, A. Purohit, M. J. Reed, and A. G. Shavva, *Abstracts of the XVIII Mendeleev Congress on General and Applied Chemistry, Moscow, September 23-28, 2007* [in Russian], Moscow (2007); p. 2056.
5. L. W. L. Woo, M. Lightowler, A. Purohit, M. J. Reed, and B. V. L. Potter, *J. Steroid Biochem. Mol. Biol.*, **57**, 79 (1996).
6. B. Raobaikady, A. Purohit, S. K. Chandler, L. W. L. Woo, M. P. Leese, B. V. L. Potter, and M. J. Reed, *J. Steroid Biochem. Mol. Biol.*, **84**, 351 (2003).
7. A. G. Shavva, S. N. Morozkina, I. V. Ishchenko, I. I. Eliseev, G. L. Starova, and S. I. Selivanov, *Bioorg. Khim.*, **33**, 310 (2007).
8. G. L. Starova, S. K. Nikol'skaya, and A. G. Shavva, *Abstracts of the VI National Conference on the Application of X-Ray, Synchrotron Radiation, Neutrons and Electrons for the Study of Materials, Moscow, November 12-17, 2007* [in Russian], Moscow (2007), p. 166.
9. A. S. Chentsova, S. N. Morozkina, S. I. Selivanov, F. E. Putilina, L. I. Zakharova, and A. G. Shavva, *Abstracts of the International Conference on Organic Chemistry for Young Scientists (InterYCOS-2009); June 21-25, 2009*, St. Petersburg, Russia (2009), p. 75.
10. A. G. Shavva, S. I. Selivanov, G. L. Starova, T. R. Boronoeva, I. V. Ishchenko, I. A. Gluzdikov, A. N. Sharetskii, V. G. Isaeva, and B. P. Surinov, *Bioorg. Khim.*, **28**, 242 (2002).