Pergamon

Tetrahedron Vol. 51, No. 48, pp. 13379-13384, 1995
Elsevier Science Ltd
Printed in Great Britain
0040-4020/95 $9.50+0.00

0040-4020(95)00871-3

Synthesis and Unusual Beckmann Fragmentation Reaction of *syn*-3-Methoxy-6α,17β-Dihydroxyestra-1,3,5(10)-trien-7-one Oxime

Vjera M. Pejanović[✱], Julijana A. Petrović[*], János J. Csanádi[*], Slobodanka M. Stanković[*], and Dušan A. Miljković[*]

[✱] ICN Galenika Institute. 29. Novembra 111. 11000 Belgrade, Yugoslavia

[*] Department of Chemistry. Faculty of Sciences. University of Novi Sad, Yugoslavia

Abstract: Sodium borohydride reduction of *anti*-3-methoxy-17β-hydroxyestra-1,3,5(10)-trien-6,7-dione 7-oxime (**4a**) afforded *syn*-3-methoxy-6α,17β-dihydroxyestra-1,3,5(10)-trien-7-one oxime (**5**), which in thionyl chloride at -18°C underwent Beckmann fragmentation reaction to the unexpected 3-methoxy-6-oxo-17β-hydroxy-6,7-secoestra-1,3,5(10)-trien-7-nitrile (**6**). A mechanism of this fragmentation process was proposed.

INTRODUCTION

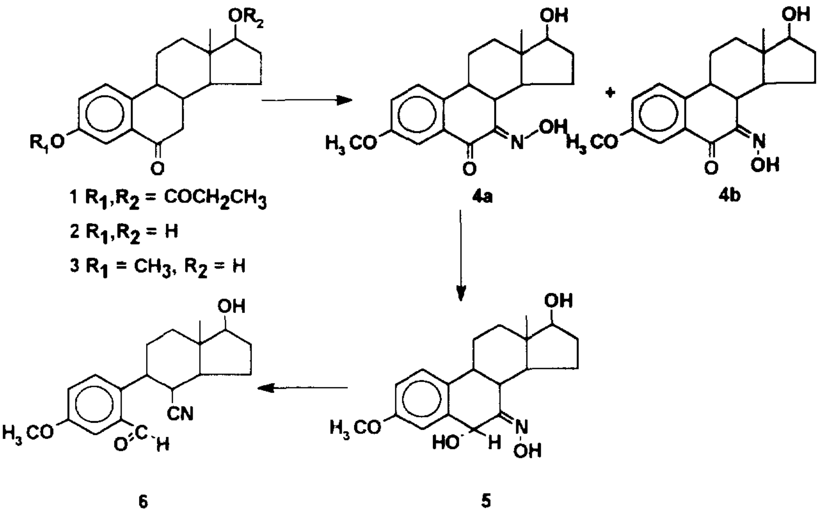
We showed in our previous work that a cleavage of some C-C bonds in estrone skeleton caused a complete loss of estrogenic activity, while at the same time newly formed D-seco compounds showed an antiestrogenic action[1]. Consequently, we directed our new research towards a synthesis of B-seco estrone derivatives, assuming that these compounds, due to a free rotation around the C_9-C_{10} bond might express different biological activity from the starting estrogens.

So far, B-seco-estrone derivatives have been exclusively obtained by total synthesis. This class of compounds have been biologically screened[2-5], or have served as intermediates in total syntheses of different estrone derivatives[6]. The main aim of this work was developing a new method for a partial synthesis of B-seco estradiol system from estradiol derivatives, based on our earlier results in D-seco-steroid field[7,8].

RESULTS AND DISCUSSION

We selected 3,17β-dipropionoxyestra-1,3,5(10)-trien-6-one[9] (**1**) as starting material. Compound **1** was obtained by oxidation of estradiol dipropionate with chromium(VI)oxide in presence of dimethylpyrazole[10,11].

Standard oximination of compound **1** (AmONO, K-O-t-Bu) did not afford the desired 7-oximino derivative, most probably due to a hydrolysis of C-3 ester function followed by a rapid deprotonation of C-3 phenolic group. Therefore, the electrophylic attack of amyl nitrite was not regioselective (at C-7).

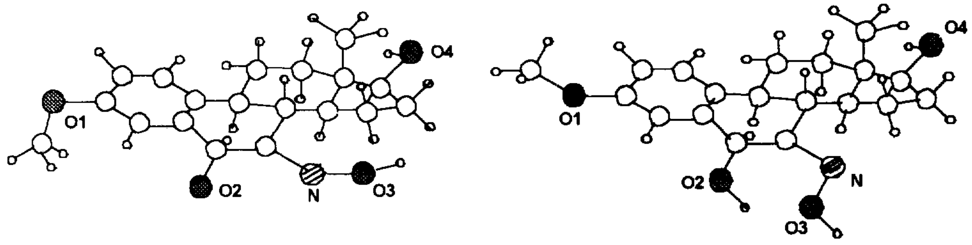


Scheme 1

In order to overcome the above mentioned difficulties, 3-propionoxy function was replaced by 3-methoxy group (Scheme 1). This time, treating compound **3** with amyl nitrite in presence of potassium-t-butoxide gave a mixture of wonted isomeric oximino ketones **4a** and **4b** in a ratio 9:1 (according to NMR- spectrum). The main product **4a** was isolated by crystallization, while the by-product **4b** was obtained from the mother liquor by chromatography. Exposing the isomer **4b** to light afforded **4a**. Ascribing the *syn*- or *anti*-geometry to **4a** (or **4b**) was not feasable on the basis of their IR-spectra (in solution). Therefore, the absolute stereochemistry of the main product **4a** was determined by X-ray structural analysis, which undoubtedly proved its *anti*-geometry 7- (see Figure 1.)[12].

Sodium borohydride reduction of **4a** stereospecifically afforded a single product **5**, in spite of the fact that approach of the reducing agent to C-6 carbonyl function seems equally probable from both sides of the main molecular plain. Our attempts to carry out Beckmann fragmentation reaction of α-hydroxy oxime **5**, similarly to our previous work[7,8] (using TsCl in pyridine), failed. Surprisingly, X-ray structural analysis revealed that the oximino function in **5** corresponded to *syn*-geometry (see Figure 1.)[13].

To the best of our knowledge, this represents a first example of *syn-anti* isomerization under the mild conditions of sodium borohydride reduction. Even quite opposite, we showed in our earlier work[7] that similar system did not undergo *syn-anti* isomerization under mentioned conditions.

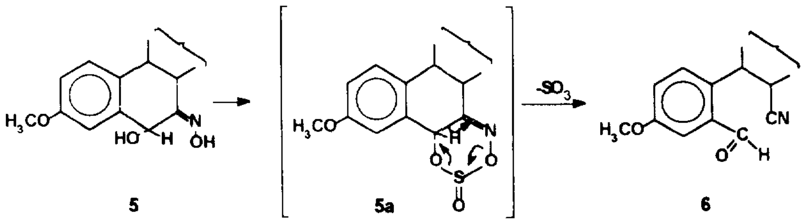


4a **5**

Figure 1. Perspective view of the molecular structure of compound 4a and 5

Having found the geometry of α-hydroxy oxime **5** was unfavourable for a concerted fragmentation process[14] (similar to one with TsCl in pyridine), we carefully examined some other reagents (or alternative pathways), which might lead to fragmentation reaction. To our initial surprise an action of thionyl chloride at -18° upon **5** brought about a rather clean fragmentation reaction, whereupon the unexpected seco-cyanoaldehyde **6** was isolated as the main reaction product. Namely, the generally accepted concept states that *syn*-α-hydroxy oximes, under Beckmann fragmentation reaction conditions, solely afford aldehydes (or ketones) and *iso-nitriles*, whereas the corresponding *anti*-isomers are cleaved to aldehydes (ketones) and *nitriles*[15]. Since in our case the *syn*-geometry of the starting oximino alcohol was firmly established, seco-*iso-nitrile* was expected *a priori*. However, a detailed ^{13}C-NMR spectroscopic analysis of compound **6** indisputably confirmed the presence of a *nitrile* function at C-8. Namely, the chemical shift of the C-atom in *iso-cyanides*, appears in the interval of 156-158 ppm, whereas C-atom in *cyanides* appears in the region of 112-126 ppm[16]. In the ^{13}C-NMR spectrum of **6** the corresponding signal appears at 120.23 ppm (CN, DEPT experiment), while, in addition, there is a signal at 35.02 ppm, corresponding to C-CN. Finally, in the IR-spectrum of **6**, there is a band at 2240 cm^{-1}, corresponding to nitrile function (unlike to iso-nitriles which appear at 2120-2185[17]).

A possible mechanism for the seco-cyano-aldehyde **6** formation from syn-α-hydroxy-oxime **5**, by an action of thionyl chloride, involves an intermediary formation of the six-membered cyclic N-O-sulfite **5a** (Scheme 2),



5 **5a** **6**

Scheme 2.

followed by its concerted fragmentation *via* a favorable six-membered transition state. This fact becomes even more clear from the X-ray structural analysis of **5**, where the most stable conformation (found in the asymmetrical unit) corresponds to B-ring being in a half-chair conformation. This means that the C_6-OH, C_6-C_7 and C_7=NOH are nearly coplanar, enabling a smooth formation of the postulated cyclic intermediate **5a**.

Further chemical modifications of compound **6** are under progress in order to obtain a series of B-seco estrone derivatives with various funcional groups at C-6 and C-7. Biological testing of these compounds will be undertaken in the nearest future.

EXPERIMENTAL

Melting points were determined in capillary tubes using Büchi SMP-instrument and are uncorrected. IR spectra were recorded with a Perkin-Elmer 457 spectrometer (in KBr or i film for oily substances); ^{1}H and ^{13}C NMR spectra were recorded on a Bruker WP 200 SY spectrometer with TMS as internal standard; Low- and high resolution data were obtained on a Finnigan MAT-8230 (EI 70 eV) instrument.

3-Methoxy-17β-hydroxyestra-1,3,5(10)-trien-6-one (3). 3,17β-Dipropionoxyestra-1,3,5(10)-trien-6-one[9] (**1**, 1 g, 2.5 mmol) was dissolved in ethanolic solution of KOH (10%, 20 ml) and refluxed for 90 minutes. After cooling the reaction mixture, pH of solution was adjusted to 7 and mixture was poured into ice cold water (150 ml). The precipitate was filtered off, washed with water and dried, affording 0.705 g (98%) of almost pure 3,17β-dihydroxyestra-1,3,5(10)-trien-6-one (**2**), m.p. 278-280°C (lit.[18] m.p. 281-283°C). Dried sample of compound **2** (705 mg, 2.46 mmol) was dissolved in acetone-methanol (1:1) mixture and methyl iodide (2 ml, 32 mmol) and potassium carbonate (1 g) ware added. The mixture was refluxed for 3 hrs, then poured into cold water. The solid was filtered off, washed with water and dried; yield of compound **3** was 726 mg (99%), m.p. 127-128°C (lit.[19] m.p. 129-130°C).

3-Methoxy-17β-hydroxyestra-1,3,5(10)-trien-6,7-dione 7-oxime (4). Potassium (1 g, 25.6 mmol) was dissolved in *tert*-butyl alcohol (22 ml), 3-methoxy-17β-hydroxyestra-1,3,5(10)-trien-6-one (**3**, 1 g, 3.33 mmol) was added, and the reaction mixture stirred for 30 min. at room temperature; n-amyl nitrite (1.1 ml, 9.69 mmol) was then introduced and stirring continued for 2.5 hrs. Reaction mixture was then diluted with 1% aqueous KOH (150 ml) and extracted with $CHCl_3$. After drying over anh. Na_2SO_4 and removal of solvent, crude 3-methoxy-17β-hydroxyestra-1,3,5(10)-trien-6,7-dione 7-oxime (**4**, 820 mg, 74.8%) was obtained. Double crystallization from methanol afforded 670 mg (61.1%) of pure **4**, m.p. 194.5-195°C. IR ν_{max} (KBr) cm^{-1}: 3410, 1670, 1600, 1490, 1030, 988; ^{1}H NMR (DMSO-d_6): 0.67 (3 H, s, 18-CH_3), 3.54 (1 H, m, with D_2O m → t, J=8.5 Hz, H-17), 3.80 (3H, s, OCH_3), 4.58 (1H, d, J=4.8 Hz, OH-17), 7.21 (1H, dd, J_1=8.5 Hz, H-1), 11.65 (1H, s, disappears with D_2O, NOH); ^{13}C-NMR (DMSO-d_6): 183.50 (C=O, C-6), 158.35 (C-OCH_3, C-3), 153.18 (C=N-OH, C-7), 139.12 (C, arom.), 134.07 (C, arom.), 127.86 (CH, arom.), 121.69 (CH, arom.), 109.84 (CH, arom.), 79.50 (C-OH, C-17), 55.53 (O-CH_3); CIMS *m/z* (rel. int.): 329 (M^+ - OH), 269 (M^+ - NOH-CH_3). Anal. Calcd. for $C_{19}H_{23}NO_4$: C, 69.28; H, 7.04; N, 4.25; found: C, 69.24; H, 7.10; N, 4.75.

The mother liquors were evaporated to dryness and oily residue (135 mg), was chromatographed on preparative silica plate (1 mm silica gel, benzene - ethyl acetate, 3:2), affording 45 mg of **4a** and 42 mg of an oily *syn*-oximino ketone **4b**. IR ν_{max} (KBr) cm^{-1}: 3380, 1685, 1605, 1495 1035, 945; ^{1}H NMR (DMSO-d_6): 0.63 (3 H, s, 18-CH_3), 3.60 (1 H, m, with D_2O m → t, J=8.5 Hz, H-17), 3.80 (3H, s, OCH_3), 4.53 (1H, d, J=4.8 Hz, OH-17), 7.03-7.66 (3H, group of signals, arom. prot.), 11.75 (1H, s, disappears with D_2O, NOH).

3-Methoxy-6α,17β-dihydroxyestra-1,3,5(10)-trien-7-one oxime **(5)**. To a methanolic solution (120 ml) of 3-methoxy-17β-hydroxyestra-1,3,5(10)-trien-6,7-dione 7-oxime (**4**, 1 g, 3,04 mmol), $NaBH_4$ (1.2 g, 32 mmol) was added portionwise at room temperature. Reaction mixture was stirred for 30 min. at room temperature and further refluxed for 5 min. After cooling, the mixture was diluted with water (100 ml), acidified to pH 3 with 2M HCl and extracted with ether. After drying and evaporation of ether, 800 mg (79.5%) of crude **5** was obtained. Crystallization from methanol afforded 640 mg (63.6%) of pure 3-methoxy-6α,17β-dihydroxyestra-1,3,5(10)-trien-7-one oxime (**5**) m.p. 195°C. IR ν_{max} (KBr) cm^{-1}: 3600-3000, 1610, 1500, 1250, 1035; ^1H NMR (DMSO-d_6): 0.70 (3 H, s, 18-CH_3), 3.55 (1 H, m, H-17), 3.75 (3H, s, OCH_3), 4.56 (1H, d, J=6 Hz, OH-17), 5.35 (1H, d, J=4 Hz, OH-6), 5.70 (1H, d, J=4 Hz, H-6), 6.75 - 7.2 (3H, group of signals, arom.prot.), 10.8 (1H, s, disappears with D_2O, NOH); ^{13}C-NMR (DMSO-d_6): 159.22 (C-OCH_3, C-3), 157.75 (C=N-OH, C-7), 138.82 (C, arom.), 134.84 (C, arom.), 124.74 (CH, arom.), 114.57 (CH, arom.), 113.25 (CH, arom.), 79.78 (C-OH, C-17), 63.42 (C-OH, C-6), 55.31 (O-CH_3); CIMS *m/z* (rel. int.): 331 (M^+), 313 (M^+ - H_2O). Anal. Calcd. for $C_{19}H_{25}NO_4$: C, 68.85; H, 7.60; N, 4.23; found: C, 68.36; H, 7.41, N, 4.94.

3-Methoxy-6-oxo-17β-hydroxy-6,7-secoestra-1,3,5(10)-triene-7-nitrile **(6)**. 3-Methoxy-6α,17β-dihydroxyestra-1,3,5(10)-trien-7-one oxime (**5**, 1 g, 3.02 mmol) was dissolved in thionyl chloride (22 ml, 301 mmol) and cooled at -18°C. The reaction mixture was kept at -18°C for 10 min., and then poured in ice-cold water (500 ml). The precipitate was collected, washed with water and dried. Purification of the crude reaction product (750 mg) on silica gel column (70 g silica, benzene - ethyl acetate, 9:1) afforded 225 mg (23.8%) of 3-methoxy-6-oxo-17β-hydroxy-6,7-secoestra-1,3,5(10)-triene-7-nitrile (**6**) in a foamy form. IR ν_{max} (film) cm^{-1}: 3460, 2240, 1690, 1500, 1260; ^1H NMR ($CDCl_3$): 0.89 (3 H, s, 18-CH_3), 3.77 (1 H, t, J=8 Hz, H-17), 3.86 (3H, s, OCH_3), 7.12 - 7.36 (3H, group of signals, arom.prot.), 10.8 (1H, s, CHO); ^{13}C-NMR ($CDCl_3$): 192.24 (CHO, C-6), 158.70 (C-OCH_3, C-3), 136.30 (C-CHO, C-5), 134.81 (C, arom.), 128.45 (CH, arom.), 120.40 (CH, arom.), 120.23(CN, C-7), 117.91 (CH, arom.), 80.48 (C-OH, C-17), 55.44 (O-CH_3); CIMS *m/z* (rel. int.): 313 (M^+), 295 (M^+ - H_2O), 278 (M^+ - H_2O - OH^-), 229, 175, 161, 149, 134; FABMS: calcd. for $C_{19}H_{23}NO_3$, 313.4000, found 313.4664.

Acknowledgments: The authors are grateful to the Scientific Fund of Republic Serbia for financial support.

REFERENCES

1. Petrović, J.A., Pejanović, V.M., Miljković D.A., Hranisavljević J.T. *Steroids* **1990**, 50, 276-278
2. Bindray, J.S.; Neyyarapally, A.T.; Gupta, R.C.; Kamboj, V.P.; Anand, N. *J. Med. Chem.* **1975**, 18, 921-925
3. Jhingran, A.G.; Gupta, R.C.; Ray, S.; Agarwal, A.K.; Singht, M.M.; Anand, N. *Steroids* **1983**, 42, 627-634
4. Jhingran, A.G.; Gupta, R.C.; Ray, S.; Agarwal, A.K.; Singht, M.M.; Anand, N. *Indian J. Chem.* **1986**, 25B, 661-662
5. Durani, S.; Agarwal, A.K.; Saxena, R.; Setty, B.S.; Gupta, R.C.; Kole, P.L. Ray, S.; Anand, N. *J. Steroid Biochem.* **1979**, 11, 67-77
6. Eder, U. *J. Steroid Biochem.* **1979**, 11(1A), 55-60
7. Miljković, D.; Petrović, J. *J. Org. Chem.* **1977**, 42, 2101-2102
8. Miljković, D.; Petrović, J.; Hadžić, P. *Tetrahedron* **1978**, 34, 3575-3577
9. Pejanović, V.; Petrović, J.; Djoković, D.; Miljković, D. *Proceedings of Faculty of Sciences, Novi Sad,* **1991**, 21, 31-36
10. Garza, G.A,; Roa, P.N. *Steroids* **1983**, 42, 469-474
11. Weber, G.; Schaumann, J.; Carl C,, Schwarz, S. *J. prakt. Chem.* **1989**, 331, 223-230

12. Stanković, S.; Lazar, D.; Petrović, J.; Miljković, D.; Pejanović, V. *Acta Cryst.* **1995**, C51, 0000-0000
13. Ribár, B.; Stanković, S.; Mészáros, Cs.; Miljković, D.; Pejanović, V.; Petrović, J. *Acta Cryst.* **1993**, C49, 270-273
14. Grob, C.A.; Schiess, P.W. *Angew. Chem.* **1967**, 79, 1-14
15. Shoppee, C.W.; Roy, S.K. *J. Chem. Soc.* **1963**, 3774-3777
16. Levy, G.C.; Nelson, G.L. *Carbon-13 Nuclear Magnetic Resonance for Organic Chemists,* Wiley-Interscience, New York, 1972; pp. 129
17. Silversten, R.M.; Bassler, G.C. *Spectrometric Identification of Organic Compounds,* J. Wiley and Sons, Inc., New York, 1964, pp 47-48
18. Longwell, B.; Wintersteiner, O. *J. Biol. Chem.* **1940**, 133, 219-229
19. Crabbé, P.; Casas-Canpillo, C. *J. Org. Chem.* **1964**, 29, 2731-2734

(*Received in UK* 26 *June* 1995; *revised* 9 *October* 1995; *accepted* 12 *October* 1995)