Beckmann Fragmentation Reaction of 3-Methoxy-17β-hydroxyestra-1,3,5(10)-trien-16-one Oxime

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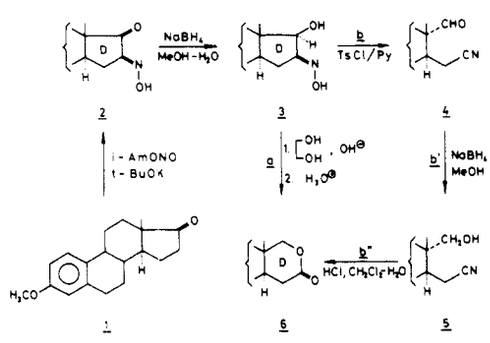
The Beckmann fragmentation reaction of 3-methoxy-17β-hydroxyestra-1,3,5(10)-trien-16-one oxime (3), achieved with *p*-toluenesulfonyl chloride in pyridine at room temperature, gave 3-methoxy-17-oxo-16,17-secoestra-1,3,5(10)-triene-16-nitrile (4) in a high yield. The structure of the fragmentation product 4 was proved on the basis of spectral data and by its conversion into the corresponding lactone 6. The same lactone 6 was prepared by a simple and novel synthetic procedure, directly from the 17β-hydroxy-16-one oxime (3) and potassium hydroxide in boiling ethylene glycol. The first step of this transformation was assumed to be the formation of 4 by the Beckmann fragmentation reaction of 3 under basic conditions, followed by a reduction of the aldehyde group of 4 with ethylene glycol catalyzed by potassium hydroxide.

The Beckmann fragmentation reaction of steroidal α-hydroxy oximes has not been extensively studied. A few characteristic examples of this reaction were given in our previous paper.[1] A recent example of the same reaction was described by Paisley and Weiler,[2] who converted 2β-hydroxy-17β-acetoxy-5β-androstan-3-one oxime into the corresponding 2,3-seco-2-oxo-3-nitrile. Our preliminary studies in estrone series and the fact that certain ring D seco derivatives of estrone show a hypocholesterolemic activity[3] prompted us to investigate the Beckmann fragmentation reaction in the estrone series.

We selected as a starting material 3-methoxyestra-1,3,5(10)-triene-16,17-dione 16-oxime (2), prepared according to the procedure of Litvan and Robinson.[4] We noticed a significant difference in melting points for the compound 2 (Litvan and Robinson claimed mp 161–162 °C; in our case mp was 212–214 °C), which was attributed to the presence of a certain amount of the syn isomer in Litvan and Robinson's case.[5] Further chemical transformations of 2 are given in Scheme I.

Scheme I



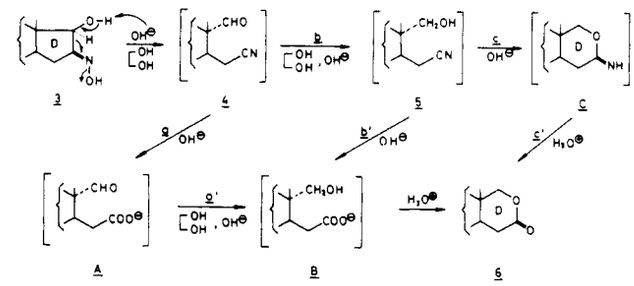
The reduction of the hydroxyimino ketone 2 with $NaBH_4$ in aqueous methanol afforded 3-methoxy-17β-hydroxyestra-1,3,5(10)-trien-16-one oxime (3) in a high yield. The anti configurations of oximes 2 and 3 were assumed for the reasons cited in our previous paper.[1]

The Beckmann cleveage of 3 (pathway b) was carried out under similar reaction conditions as earlier,[1] but in this case, the primary fragmentation product 4, mp 158–160 °C, was easily isolated and purified by direct crystallization from methylene chloride–hexane. The spectral data proved the proposed structure of 4.

Seco cyanoaldehyde 4 has been converted, in a high yield, by $NaBH_4$ reduction into the corresponding seco cyano alcohol 5 (b′), whose structure was also proved by spectral data. By the action of gaseous hydrogen chloride on the solution of 5 in methylene chloride, saturated with water, 3-methoxy-17-oxa-*D*-homoestra-1,3,5(10)-trien-16-one (6) was obtained[7] (b″). The intermediary formation of the six-membered iminolactone C (see Scheme II) has been assumed. The hydrochloride of the intermediate C was isolated, when the reaction was carried out under anhydrous conditions, but we did not succeed in getting an analytically pure sample, since the compound C·HCl hydrolyzed very readily in air to the corresponding lactone 6.

The lactone 6 has been independently prepared by a simple procedure directly from the α-hydroxy oxime 3 and potassium hydroxide in boiling ethylene glycol, in a stream of nitrogen. The assumed mechanism of this interesting transformation is given in Scheme II.

Scheme II



In the first step the Beckmann fragmentation reaction, catalyzed by OH^-, is supposed, followed by two equally possible reaction pathways: aa′ and bb′, in which, regardless of sequence, reduction of the aldehyde into the alcohol and the hydrolysis of the nitrile into the carboxylic acid take place. There exists another possibility, cc′, including an intermediary formation of the iminolactone C, which in turn, by hydrolysis, gives the lactone 6. This transformation (3 → 6) presents a novel and simple procedure for a direct preparation of steroidal lactones of the type 6 from the easily accessible compounds of the type 3.

The Beckmann fragmentation reaction under basic conditions is quite unusual and we could not find any similar example in the chemical literature. The assumed reduction of an aldehyde into an alcohol, by means of ethylene glycol in the presence of OH^-, presents an interesting case which should be studied further.

Experimental Section

The melting points are uncorrected. The IR spectra were recorded in KBr pellets with a Perkin-Elmer infrared spectrophotometer, Model 457, and NMR spectra with a Varian 60A spectrometer with tetramethylsilane as the internal standard. Chemical shifts (δ) are expressed in parts per million. Mass spectra were recorded with a Varian CH-5 spectrometer.

3-Methoxyestra-1,3,5(10)-triene-16,17-dione 16-Oxime (2). Metallic potassium (1 g, 25.5 mmol) was dissolved in *tert*-butyl alcohol (40 mL), 3-methoxyestra-1,3,5(10)-trien-17-one (**1**, 2 g, 7.0 mmol) was added, and the mixture stirred for 1 h at room temperature. Isoamyl nitrite (2 mL, 14.9 mmol) was then introduced and the stirring continued for 3 h, and for another 2 h at 50 °C. The mixture was left overnight, and then diluted with 1% aqueous KOH (200 mL) and extracted with $CHCl_3$. The aqueous layer was acidified with 2 N HCl to pH 5, and the pale yellow crystals of 3-methoxyestra-1,3,5(10)-triene-16,17-dione 16-oxime (**2**) were collected, washed with water, and dried (1.29 g, 59% yield, mp 176–180 °C dec). The crude **2** was recrystallized from ethyl acetate, giving white crystals: 0.60 g; 27% yield; mp 212–214 °C dec; IR 3500–3300, 1740, 1630, 1605, 1500, 1260, and 945 cm^{-1}; mass spectrum *m/e* 313 (71, M^+), 297 (63), 268 (71), 257 (100), 147 (52), and 121 (54).

Anal. Calcd for $C_{19}H_{23}NO_3$: C, 72.82; H, 7.40; N, 4.47. Found: C, 72.98; H, 7.41; N, 4.36.

3-Methoxy-17β-hydroxyestra-1,3,5(10)-trien-16-one Oxime (3). To an aqueous methanolic solution (30 mL of H_2O and 130 mL of methanol) of 3-methoxyestra-1,3,5(10)-triene-16,17-dione 16-oxime (**2**, 1 g, 3.19 mmol), $NaBH_4$ (1 g, 26.4 mmol) was added portionwise at room temperature. The solution was then refluxed for 5 min, cooled, and diluted with water (100 mL). The separated crystals were collected, washed thoroughly with 50% aqueous methanol, and dried (0.93 g, 93% yield, mp 203–206 °C dec). Recrystallization from methanol (100 mL) afforded analytically pure 3-methoxy-17β-hydroxyestra-1,3,5(10)-trien-16-one oxime (**3**): 0.77 g; 77% yield; mp 215 °C dec; IR 3500–3260, 1610, 1500, 1260, and 950 cm^{-1}; NMR (Py-d_5) 1.05 (18 methyl), 3.80 (C-3 methoxy), 4.55 (17α proton, d, J = 2 Hz), 5.50 (two OH groups, m), 6.80 (C-4 proton, d, $J_{2,4}$ = 3 Hz), 6.95 (C-2 proton, quartet, $J_{1,2}$ = 10, $J_{2,4}$ = 3 Hz), and 7.50 (C-1 proton, d, $J_{1,2}$ = 10 Hz); mass spectrum *m/e* 315 (90, M^+), 297 (60), 257 (85), 227 (100), 121 (84), 91 (51), and 29 (55).

Anal. Calcd for $C_{19}H_{25}NO_3$: C, 72.35; H, 7.99; N, 4.44. Found: C, 72.23; H, 8.02; N, 4.45.

3-Methoxy-17-oxo-16,17-secoestra-1,3,5(10)-triene-16-nitrile (4). α-Hydroxy oxime **3** (1 g, 3.17 mmol, finely ground and dried for 3 h at 120 °C) and *p*-toluenesulfonyl chloride (1 g, 5.25 mmol) were dissolved in absolute pyridine (20 mL). The reaction mixture was kept at room temperature for 3 h, and then poured in an excess of cold diluted HCl. The separated precipitate of the crude 3-methoxy-17-oxo-16,17-secoestra-1,3,5(10)-triene-16-nitrile (**4**) was collected, washed with water, and dried (0.94 g; 98% yield, mp 142 °C). Recrystallization from methylene chloride–hexane afforded pure **4**: 0.78 g; 82% yield; mp 158–160 °C; IR 2240, 1715, 1605, 1500, 1260, 1030, and 860 cm^{-1}; NMR ($CDCl_3$) 1.20 (18 methyl), 2.80 (C-15 protons, m), 3.65 (C-3 methoxy), 6.45 (C-4 proton, d, $J_{2,4}$ = 3 Hz), 6.90 (C-2 proton, quartet, $J_{1,2}$ = 10, $J_{2,4}$ = 3 Hz), 7.20 (C-1 proton, d, $J_{1,2}$ = 10 Hz), and 9.40 (C-17 aldehydic proton, s); mass spectrum *m/e* 297 (75, M^+), 257 (100), 121 (68), and 29 (41).

Anal. Calcd for $C_{19}H_{23}NO_2$: C, 76.73; H, 7.80; N, 4.71. Found: C, 77.10; H, 7.72; N, 4.52.

3-Methoxy-17-hydroxy-16,17-secoestra-1,3,5(10)-triene-16-nitrile (5). 3-Methoxy-17-oxo-16,17-secoestra-1,3,5(10)-triene-16-nitrile (**4**, 1 g, 3.37 mmol) was dissolved in methanol (60 mL). $NaBH_4$ (1 g, 26.4 mmol) was added portionwise to this solution at room temperature, and after 30 min the reaction mixture was diluted with water (60 mL). The white precipitate was filtered off, washed with water, and dried (0.91 g, 90% yield, mp 90 °C). Recrystallization from methylene chloride–hexane afforded analytically pure **5**: 0.86 g; 86% yield; mp 95 °C; IR 3480, 2255, 1605, 1500, 1260, and 865 cm^{-1}; NMR ($CDCl_3$) 0.92 (18 methyl), 2.80 (C-15 protons, m), 3.35 (C-17 protons, AB system, J_{AB} = 6 Hz), 3.68 (C-3 methoxy), 6.45 (C-4 proton, d, $J_{2,4}$ = 3 Hz), 6.60 (C-2 proton, quartet, $J_{1,2}$ = 10, $J_{2,4}$ = 3 Hz), and 7.08 (C-1 proton, d, $J_{1,2}$ = 10 Hz);[8] mass spectrum *m/e* 299 (58, M^+), 241 (52), 91 (51), 57 (89), 43 (83), 31 (88), and 29 (100).

Anal. Calcd for $C_{19}H_{25}NO_2$: C, 76.22; H, 8.42; N, 4.68. Found: C, 76.19; H, 8.49; N, 4.74.

3-Methoxy-17-oxa-*D*-homoestra-1,3,5(10)-trien-16-one (6) from 5. Through a solution of 3-methoxy-17-hydroxy-16,17-secoestra-1,3,5(10)-triene-16-nitrile (**5**, 1 g, 3.34 mmol) in methylene chloride (50 mL), saturated with water, an excess of gaseous HCl was bubbled. The reaction mixture was left overnight at room temperature, and then washed with water (3 × 100 mL) in a separatory funnel. The organic layer was dried and the solvent evaporated in vacuo, affording 0.93 g (93% yield) of the crude **6**, mp 161–162 °C. Recrystallization from methylene chloride–hexane gave analytically pure **6**: 0.70 g; 70% yield; mp 189 °C dec; IR 1720, 1610, 1500, 1260, 1240, 1195, and 1030 cm^{-1}; NMR ($CDCl_3$) 1.02 (18 methyl), 2.80 (C-15 protons, m), 3.85 (C-3 methoxy), 3.95 (C-17 protons, s), 6.55 (C-4 proton, d, $J_{2,4}$ = 3 Hz), 6.75 (C-2 proton, quartet, $J_{1,2}$ = 10, $J_{2,4}$ = 3 Hz), and 7.20 (C-1 proton, d, $J_{1,2}$ = 10 Hz); mass spectrum *m/e* 300 (100, M^+), and 186 (66).

Anal. Calcd for $C_{19}H_{24}O_3$: C, 75.97; H, 8.05. Found: C, 75.85; H, 8.01.

3-Methoxy-17-oxa-*D*-homoestra-1,3,5(10)-trien-16-one (6) from 3. To a solution of 3-methoxy-17β-hydroxyestra-1,3,5(10)-trien-16-one oxime (**3**, 1 g, 3.17 mmol) in ethylene glycol (50 mL), KOH (1 g, 17.8 mmol) was added. The reaction mixture was refluxed for 10 h in a stream of nitrogen; after cooling, the solution was acidified with 2 N HCl and extracted with $CHCl_3$. After drying the extract, $CHCl_3$ was removed in vacuo, affording an oily product, which was further purified by column chromatography on silica gel (100 g, benzene–ethyl acetate, 4:1); the yield of the pure **6** was 0.60 g (63%), mp 185–187 °C dec.

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References and Notes

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(2) J. K. Paisley and L. Weiler, *Tetrahedron Lett.*, 261 (1972).
(3) J. S. Baran, *J. Med. Chem.*, **10**, 1039 (1967).
(4) F. Litvan and R. Robinson, *J. Chem. Soc.*, 1997 (1938).
(5) In the mass spectrum of **2** there was a noticeable M − 16 peak, characteristic for α-hydroxyimino ketone function; see D. Goldsmith, D. Becher, S. Sample, and C. Djerassi, *Tetrahedron, Suppl.*, **7**, 145 (1966).
(6) We noticed a characteristic fragmentation pattern of **3** under the conditions of mass spectrometry, which includes an intensive M − 18 peak, showing that under given conditions a Beckmann fission takes place readily, similar to our previous findings.[1]
(7) The lactone **6** has been prepared by Huffman et al., starting from 3-methoxy-17α-hydroxyestra-1,3,5(10)-trien-16-one in two distinct steps; mp of their sample was 176–177 °C. See M. N. Huffman, M. H. Lott, and J. Ashmore *J. Am. Chem. Soc.*, **70**, 4268 (1948).
(8) The appearance of the AB quartet in the NMR spectrum at about 3.35 ppm (2 H), corresponding to C_{17} protons, indicates a probable intramolecular hydrogen bond between the C_{17} hydroxyl group and the C_{16} nitrile function, i.e., a prevented rotation about the C_{13}–C_{17} bond; the same conclusion could be made from a shifted position of –C≡N stretching vibration at 2255 cm^{-1}, in contrast to the position of the cyano group (2240 cm^{-1}) in the IR spectrum of **4**.