Reactivity of Some Unsaturated 17-Oxo Steroids under Conditions of Diimide Reduction[†]

J. Chem. Research (S), 1998, 102–103[†]

Ljubinka Lorenc,^a Lidija Bondarenko-Gheorghiu^b and Mihailo Lj. Mihailović^{*a}

^aFaculty of Chemistry, University of Belgrade, Studentski trg 12–16, P.O. Box 158, YU-11001, Belgrade, Yugoslavia ^bCenter for Chemistry, ICTM, P.O. Box 815, YU-11001, Belgrade, Yugoslavia

The olefinic double bond in 17-oxo steroids **1**, **5** and **7** is either reduced with diimide very slowly (compound **1**) or it cannot be reduced at all (compounds **5** and **7**), thus enabling hydrazine (accumulated by disproportionation of the diimide) to react with their respective 17-oxo groups to give hydrazones **3**, **6** and **8**.

It is known that the diimide reduction of a carbon-carbon multiple bond can be selectively carried out in the presence of a variety of reactive functional groups,¹ including allylic halides,^{2,3} ethers,² amines,² disulfides,⁴ unsaturated ketones,^{2,5} peroxides^{6,7} and some other functions.¹ A limitation of the use of diimide as a reducing agent is the competition between hydrogenation of the carbon-carbon multiple bond and disproportionation,^{1,8} *i.e.*, hydrogenation of the diimide nitrogen-nitrogen double bond by another diimide molecule to form nitrogen and hydrazine (Scheme 1). Which of these processes will prevail depends on the relative rate at which diimide reacts with the unsaturated substrate. If the rate of reduction is sufficiently slower than the rate of disproportionation of diimide, the latter reaction will dominate and no reduction will be accomplished. For these particular cases it was anticipated¹ that if the substrate contains any other functional group capable of reacting with hydrazine, reaction at that function with hydrazine formed by diimide disproportionation would occur.



In this paper we report on the diimide reactions of some unsaturated 17-oxo steroids, *i.e.*, 17-oxo-5,8 α -epidioxy-5 α -androst-6-en-3 β -yl acetate (1), 17-oxoandrost-5-en-3 β -yl acetate (5) and 17-oxo-7-norandrost-5-en-3 β -yl acetate (7) (Schemes 2 and 3), which illustrate the reactivity of such substrates.

When the 17-oxo epidioxide 1 was treated with an excess of diimide, generated *in situ* from dipotassium azodicarboxylate and acetic acid (for details see Experimental section), it gave, after column chromatography on SiO₂ (Scheme 2), the expected saturated 17-oxo epidioxide 2 in only 16% yield, the major reaction product being a Z–E mixture of the corresponding hydrazone 3 (isolated in 58% yield). The 17-oxo compound 2 was identified by comparison with an authentic sample,⁷ while the structure 3 was deduced as follows. In product 3 the original olefinic Δ^6 -double bond (¹H NMR: AB quartet centred at δ 6.42) and the five-membered-ring 17-oxo group (IR: absorption at 1748 cm⁻¹) were missing, indicating that both these functions had participated in the diimide reaction. In accordance with the proposed structure, the IR spectrum of 3 contained new absorptions at 3450 and 1661 cm⁻¹ assignable to the hydrazone NH₂ group and C=N bond, respectively, while its ¹H NMR spectrum, containing parts of two singlets for the CH₃-18 group (at δ 0.92 and 0.98), indicated that this product consisted of the Z and E stereoisomers.



In an attempt to purify the hydrazone **3** by recrystallization from an acetone-methanol mixture, it was spontaneously transformed to the corresponding isopropylidenehydrazono derivative **4**. This compound was obtained in only one, Z or E, stereoisomeric form, and its identification based on elemental microanalysis ($C_{24}H_{36}N_2O_4$) and spectral characteristics (see Experimental section) confirmed the hydrazone structure **3**.

On the other hand, when the Δ^5 -unsaturated androstene and B-norandrostene derivatives **5** and **7**, respectively, were subjected to the diimide reaction as above, they gave (Scheme 3) the Δ^5 -unsaturated hydrazones **6** and **8**, respectively, in quantitative yield. Signals for the olefinic HC(6) protons in the ¹H NMR spectra of **6** and **8** (at δ 5.39 for the former and at δ 5.44 for the latter compound) clearly indicated that the Δ^5 -double bond in both substrates remained unattacked by the diimide molecule.⁹ Other spectral data were also in full agreement with the structures **6** and **8**, respectively.

These results have unequivocally confirmed the validity of the above mentioned assumption. Since the olefinic double bond in the investigated 17-oxo steroids is either reduced with diimide very slowly (compound 1) or it cannot be reduced at all (compounds 5 and 7), reaction of their

^{*}To receive any correspondence.

[†]This is a **Short Paper** as defined in the Instructions for Authors, Section 5.0 [see *J. Chem. Research* (*S*), 1998, Issue 1]; there is therefore no corresponding material in *J. Chem. Research* (M).



respective 17-oxo groups with hydrazine (accumulated by diimide disproportionation) is the main process.

Experimental

Mps are uncorrected. IR spectra were recorded on a Perkin-Elmer 337 spectrometer and NMR spectra on a Varian Gemini 2000 spectrometer (¹H at 200 MHz, ¹³C at 50 MHz) in CDCl₃ solution at room temperature, using SiMe₄ as internal standard (δ in ppm, J in Hz). Mass spectra were measured on a Finnigan-MAT 8230 spectrometer at 70 eV. Column chromatography was carried out on silica gel 0.063–0.200 mm. TLC (control of reactions and separation of products) was performed on silica gel G (Stahl) (detection with 50% aqueous H₂SO₄).

17-*Oxo*-5,8α-*epidioxy*-5α-*androst*-6-*en*-3β-yl Acetate (1)¹¹.—Mp 239–240 °C (from acetone–methanol); $[\alpha]_{\rm D}$ = + 66.0 (*c*, 0.50 in CHCl₃); $\nu_{\rm max}/{\rm cm}^{-1}$ (KBr) 1748, 1735, 1248; $\delta_{\rm H}$ 0.93 (3 H, s, H-18), 1.00 (3 H, s, H-19), 2.03 (3 H, s, OCOCH₃), 5.00 (1 H, m, H-3), 6.32, 6.52 (2 H, AB, *J* 8.6 Hz, H-6, H-7) (Found: C, 69.75: H, 7.79. C₂₁H₂₈O₅ requires C, 69.98; H, 7.83%).

Diimide Reduction of 17-Oxo-5,8 α -epidioxy-5 α -androst-6-en-3 β -yl Acetate (1).—To a stirred solution of 1 (1.08 g, 3 mmol) in CH₂Cl₂ (50 ml) and absolute MeOH (70 ml) dipotassium azodicarboxylate (5g, 13.5 mmol) was added and the suspension cooled in an icebath. To this mixture was added dropwise a solution of AcOH (3 ml) in absolute MeOH (30 ml) within *ca*. 1h. Stirring was continued at room temperature for an additional 20 h, when the yellow colour disappeared. The mixture was taken up in water (250 ml) and extracted twice with CH₂Cl₂, the combined organic extract was washed with saturated aq. NaHCO₃ solution and water, dried (Na₂SO₄) and evaporated and the residue (~1.2 g) was chromatographed on SiO₂ (50 g). Elution with toluene–EtOAc 9:1 and 8:2 afforded 5,8 α -epidioxy-17-oxo-5 α -androstan-3 β -yl acetate (2) (182 mg, 16.1%), mp (141 °C), IR and ¹H NMR identical with those of an authentic sample.⁷

Toluene–EtOAc 2:8 and EtOAc eluted a mixture of (*Z*)- and (*E*)-hydrazone **3** (655 mg, 58.1%): ν_{max}/cm^{-1} (KBr) 3450, 1733, 1661, 1252; $\delta_{\rm H}$ 0.92, 0.98 (3 H, parts of two s, H-18 of *Z* and *E* isomers), 1.03 (3 H, s, H-19), 2.00 (3 H, s, OCOCH₃), 4.81 (1 H, m, H-3). Upon recrystallization from acetone–methanol, hydrazone **3** afforded 5,8*x*-epidioxy-17-isopropylidenehydrazono-5*x*-androstan-3*β*-yl acetate **4** (384 mg), mp 205 °C; ν_{max}/cm^{-1} (KBr) 1742, 1670, 1254; $\delta_{\rm H}$ 0.98 (3 H, s, H-18), 1.04 (3 H, s, H-19), 1.81, 1.99 [6 H, 2s, N=C(CH₃)_2], 2.00 (3 H, s, OCOCH₃), 4.82 (1 H, m, H-3); $\delta_{\rm C}$ 17.3 (q, C-18), 17.5 (q, C-19), 18.0 (q, CH₃C=N), 19.3 (t, C-11), 20.9 (t, C-2), 21.0 (q, OCOCH₃), 21.5 (t, C-15), 24.7 (q, CH₃C=N), 25.7 (t, C-1), 26.4 (t, C-6), 27.9 (t, C-16), 33.5 (t, C-4) 35.4 (t, C-7), 35.5 (s, C-10), 36.0 (t, C-12), 44.8 (s, C-13), 51.7 (s, C-9), 15.9 (d, C-14), 69.4 (d, C-3), 78.5 (s, C-8), 80.4 (s, C-5), 159.3 [s, N=C(CH₃)_2], 169.7 (s, OCOCH₃), 173.2 (s, C-17); *m/z* 416 (M⁺) (Found: C, 68.83; H, 8.50; N, 7.11. C₂₄H₃₆N₂O₄ requires C, 69.20; H, 8.71; N, 7.44%).

J. CHEM. RESEARCH (S), 1998 103

Diimide Reaction of 17-Oxoandrost-5-en-3β-yl Acetate (5).-To a stirred solution of 5 (200 mg, 0.6 mmol) in CH2Cl2 (10 ml) and absolute MeOH (15 ml) dipotassium azodicarboxylate (1.0 g, 2.7 mmol) was added and the suspension cooled in an ice-bath. To this mixture was added dropwise a solution of AcOH (0.6 ml) in MeOH (6 ml) within ca. 30 min and stirring was continued overnight at room temperature. Work-up as above afforded a crystalline solid (220 mg) which was chromatographed on SiO2 (12g). Elution with EtOAc gave a mixture of (Z)- and (E)hydrazones 6 (167 mg, 80.1%), mp 275–276 °C (decomp.); v_{max}/ cm⁻¹ (KBr) 3344, 1733, 1669, 1250; $\delta_{\rm H}$ 0.87, 0.92 (3 H, parts of two s, H-18 of Z and E isomers), 1.05 (3 H, s, H-19), 2.04 (3 H, s, OCOCH₃), 4.61 (1 H, m, H-3), 5.39 (1 H, d, J 5.0 Hz, H-6); δ_C 16.4, 16.6 (q, C-18), 19.2 (q, C-19), 20.5 (t, C-11), 21.3 (q, OCOCH₃), 23.2, 23.3 (t, C-15), 24.3 (t, C-2) 27.6 (t, C-7), 31.2 (d, C-8), 31.2 (t, C-12), 33.7, 33.9 (t, C-16), 36.6 (t, C-1), 36.8 (s, C-10), 38.0 (t, C-4), 43.7, 43.9 (s, C-13), 50.2 (d, C-9), 53.5, 53.8 (d, C-14), 73.7 (d, C-3), 122.0 (d, C-6), 139.8 (s, C-5), 170.5 (s, OCOCH₃), 165.9 173.6 (s, C-17); m/z 344 $(M^{+}).$

Diimide Reaction of 17-Oxo-7-norandrost-5-en-3 β -yl Acetate (7).— A stirred ice-cooled suspension of 7 (200 mg, 0.63 mmol) and potassium azodicarboxylate (1.0 g, 2.7 mmol) in CH₂Cl₂ (10 ml) and MeOH (15 ml) was treated with a solution of AcOH (0.6 ml) and MeOH (15 ml) as above. The mixture was left overnight at room temperature and worked up as above. The residue (210 mg) was purified by column chromatography on SiO₂ (12 g). Toluene– EtOAc (6:4 and 1:1) eluted the hydrazone **8** (201 mg, 96.2%), mp 224–225 °C (decomp.); ν_{max}/cm^{-1} 3445, 1733, 1662, 1245; $\delta_{\rm H}$ 0.92 (3 H, s, H-18), 0.93 (3 H, s, H-19), 2.04 (3 H, s, OCOCH₃), 4.64 (1 H, m, H-3), 5.44 (1 H, br, s, H-6); $\delta_{\rm C}$ 14.4 (q, C-18), 17.1 (q, C-19), 20.5 (t, C-11), 21.3 (q, OCOCH₃), 23.5 (t, C-15), 27.8 (t, C-2), 29.6 (t, C-12), 32.7 (t, C-4), 34.1 (t, C-16), 36.7 (t, C-1), 44.7 (d, C-14), 45.6 (s, C-10), 45.7 (s, C-13), 51.3 (d, C-8), 62.5 (d, C-9), 73.5 (d, C-3), 125.1 (d, C-6), 148.5 (s, C-5), 170.4 (s, OCOCH₃), 173.1 (s, C-17); m/z 330 (M⁺).

We thank the Serbian Academy of Sciences and Arts and the Ministry of Sciences and Technology of Serbia for financial support.

Received, 9th September 1997; Accepted, 31st October 1997 Paper E/7/06570A

References

- D. J. Pasto, Reduction of C=C and C≡C by Noncatalytic Chemical Methods in Comprehensive Organic Synthesis, ed. B. M. Trost and I. Fleming, Pergamon, Oxford, 1991, vol. 8, p. 471.
- 2 E. E. van Tamelen, M. Davis and M. F. Deem, Chem. Commun., 1965, 71.
- 3 S. Uemura, A. Onoe, H. Okazaki, M. Okano and K. Ichikawa, *Bull. Chem. Soc. Jpn.*, 1976, **49**, 1437.
- 4 E. E. van Tamelen, R. S. Dewey, M. F. Lease and W. H. Pirkle, *J. Am. Chem. Soc.*, 1961, **83**, 4302.
- 5 G. Dauben and C. H. Schallhorn, J. Am. Chem. Soc., 1971, 93, 2254.
- 6 W. Adam and H. J. Eggelte, J. Org. Chem., 1977, 42, 3987.
- 7 Lj. Lorenc, L. Bondarenko, V. Pavlović, H. Fuhrer, G. Rihs, J. Kalvoda and M. Lj. Mihailović, *Helv. Chim. Acta*, 1989, 72, 608.
- 8 R. Tang, M. L. McKee and D. M. Stanbury, J. Am. Chem. Soc., 1995, 117, 8967.
- 9 A successful diimide reduction of the olefinic double bond in some Δ^5 -B-nor-steroids has been recently reported,¹⁰ using toluene-*p*-sulfonyl hydrazide in collidine at 150 °C.
- 10 A. Kasal, H. Chodounska and W. J. Szczepek, *Tetrahedron Lett.*, 1996, 37, 6221.
- L. Bondarenko-Gheorghiu, Ph.D. Thesis, University of Belgrade, 1986.