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

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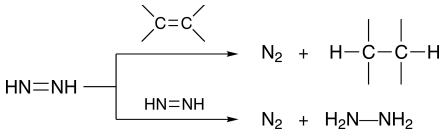
The olefinic double bond in 17-oxo steroids **1**, **5** and **7** is either reduced with diimide very slowly (compound **1**) or it cannot be reduced at all (compounds **5** and **7**), thus enabling hydrazine (accumulated by disproportionation of the diimide) to react with their respective 17-oxo groups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

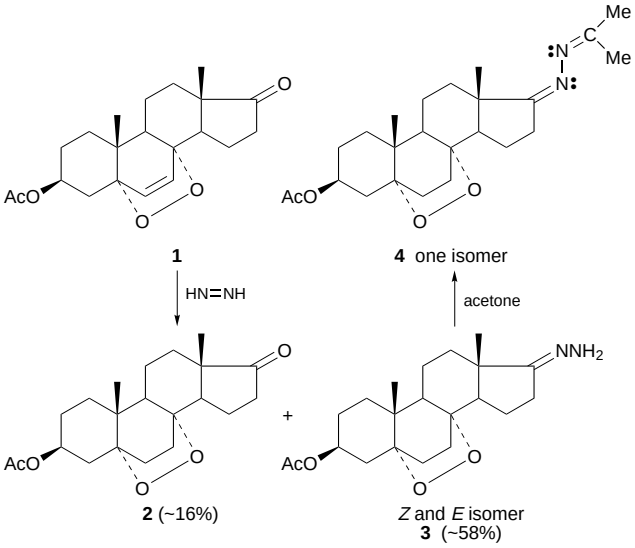
It is known that the diimide reduction of a carbon–carbon multiple bond can be selectively carried out in the presence of a variety of reactive functional groups,[1] including allylic halides,[2,3] ethers,[2] amines,[2] disulfides,[4] unsaturated ketones,[2,5] peroxides[6,7] and some other functions.[1] 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 anticipated[1] 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.




**Scheme 1**

In this paper we report on the diimide reactions of some unsaturated 17-oxo steroids, *i.e.*, 17-oxo-5,8α-epidioxy-5α-androst-6-en-3β-yl acetate (**1**), 17-oxoandrost-5-en-3β-yl acetate (**5**) and 17-oxo-7-norandrost-5-en-3β-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 $SiO_2$ (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 $\Delta^6$-double bond ($^1$H NMR: AB quartet centred at $\delta$ 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 $NH_2$ group and C=N bond, respectively, while its $^1$H NMR spectrum, containing parts of two singlets for the $CH_3$-18 group (at $\delta$ 0.92 and 0.98), indicated that this product consisted of the *Z* and *E* stereoisomers.




**Scheme 2**

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 $\Delta^5$-unsaturated androstene and B-norandrostene derivatives **5** and **7**, respectively, were subjected to the diimide reaction as above, they gave (Scheme 3) the $\Delta^5$-unsaturated hydrazones **6** and **8**, respectively, in quantitative yield. Signals for the olefinic HC(6) protons in the $^1$H NMR spectra of **6** and **8** (at $\delta$ 5.39 for the former and at $\delta$ 5.44 for the latter compound) clearly indicated that the $\Delta^5$-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

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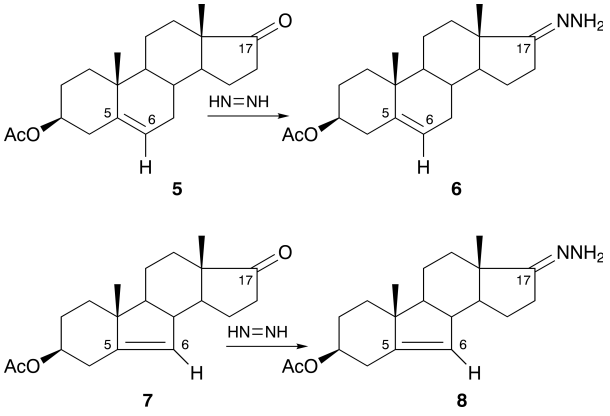


**Scheme 3**

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 ($^1$H at 200 MHz, $^{13}$C at 50 MHz) in $CDCl_3$ solution at room temperature, using $SiMe_4$ as internal standard ($\delta$ 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 $H_2SO_4$).

17-*Oxo*-5,8α-*epidioxy*-5α-*androst*-6-*en*-3β-*yl Acetate* (**1**)[11].—Mp 239–240 °C (from acetone–methanol); $[\alpha]_D$ = + 66.0 (*c*, 0.50 in $CHCl_3$); $\nu_{max}$/cm$^{-1}$ (KBr) 1748, 1735, 1248; $\delta_H$ 0.93 (3 H, s, H-18), 1.00 (3 H, s, H-19), 2.03 (3 H, s, $OCOCH_3$), 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. $C_{21}H_{28}O_5$ requires C, 69.98; H, 7.83%).

*Diimide Reduction of* 17-*Oxo*-5,8α-*epidioxy*-5α-*androst*-6-*en*-3β-*yl Acetate* (**1**).—To a stirred solution of **1** (1.08 g, 3 mmol) in $CH_2Cl_2$ (50 ml) and absolute MeOH (70 ml) dipotassium azodicarboxylate (5 g, 13.5 mmol) was added and the suspension cooled in an ice-bath. To this mixture was added dropwise a solution of AcOH (3 ml) in absolute MeOH (30 ml) within *ca.* 1 h. 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 $CH_2Cl_2$, the combined organic extract was washed with saturated aq. $NaHCO_3$ solution and water, dried ($Na_2SO_4$) and evaporated and the residue (~1.2 g) was chromatographed on $SiO_2$ (50 g). Elution with toluene–EtOAc 9:1 and 8:2 afforded 5,8α-epidioxy-17-oxo-5α-androstan-3β-yl acetate (**2**) (182 mg, 16.1%), mp (141 °C), IR and $^1$H 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%): $\nu_{max}$/cm$^{-1}$ (KBr) 3450, 1733, 1661, 1252; $\delta_H$ 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, $OCOCH_3$), 4.81 (1 H, m, H-3). Upon recrystallization from acetone–methanol, hydrazone **3** afforded 5,8α-*epidioxy*-17-*isopropylidenehydrazono*-5α-*androstan*-3β-*yl acetate* **4** (384 mg), mp 205 °C; $\nu_{max}$/cm$^{-1}$ (KBr) 1742, 1670, 1254; $\delta_H$ 0.98 (3 H, s, H-18), 1.04 (3 H, s, H-19), 1.81, 1.99 [6 H, 2 s, $N{=}C(CH_3)_2$],, 2.00 (3 H, s, $OCOCH_3$), 4.82 (1 H, m, H-3); $\delta_C$ 17.3 (q, C-18), 17.5 (q, C-19), 18.0 (q, $CH_3C{=}N$), 19.3 (t, C-11), 20.9 (t, C-2), 21.0 (q, $OCOCH_3$), 21.5 (t, C-15), 24.7 (q, $CH_3C{=}N$), 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), 51.9 (d, C-14), 69.4 (d, C-3), 78.5 (s, C-8), 80.4 (s, C-5), 159.3 [s, $N{=}C(CH_3)_2$], 169.7 (s, $OCOCH_3$), 173.2 (s, C-17); *m*/*z* 416 ($M^+$) (Found: C, 68.83; H, 8.50; N, 7.11. $C_{24}H_{36}N_2O_4$ requires C, 69.20; H, 8.71; N, 7.44%).

*Diimide Reaction of* 17-*Oxoandrost*-5-*en*-3β-*yl Acetate* (**5**).—To a stirred solution of **5** (200 mg, 0.6 mmol) in $CH_2Cl_2$ (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 $SiO_2$ (12 g). Elution with EtOAc gave a mixture of (*Z*)- and (*E*)-hydrazones **6** (167 mg, 80.1%), mp 275–276 °C (decomp.); $\nu_{max}$/cm$^{-1}$ (KBr) 3344, 1733, 1669, 1250; $\delta_H$ 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, $OCOCH_3$), 4.61 (1 H, m, H-3), 5.39 (1 H, d, $J$ 5.0 Hz, H-6); $\delta_C$ 16.4, 16.6 (q, C-18), 19.2 (q, C-19), 20.5 (t, C-11), 21.3 (q, $OCOCH_3$), 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, $OCOCH_3$), 165.9 173.6 (s, C-17); *m*/*z* 344 ($M^+$).

*Diimide Reaction of* 17-*Oxo*-7-*norandrost*-5-en-3β-*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 $CH_2Cl_2$ (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 $SiO_2$ (12 g). Toluene–EtOAc (6:4 and 1:1) eluted the hydrazone **8** (201 mg, 96.2%), mp 224–225 °C (decomp.); $\nu_{max}$/cm$^{-1}$ 3445, 1733, 1662, 1245; $\delta_H$ 0.92 (3 H, s, H-18), 0.93 (3 H, s, H-19), 2.04 (3 H, s, $OCOCH_3$), 4.64 (1 H, m, H-3), 5.44 (1 H, br, s, H-6); $\delta_C$ 14.4 (q, C-18), 17.1 (q, C-19), 20.5 (t, C-11), 21.3 (q, $OCOCH_3$), 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, $OCOCH_3$), 173.1 (s, C-17); *m*/*z* 330 ($M^+$).

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