Photooxygenation of α,β- and β,γ-Unsaturated Enamines in 17-(1-Formylethyl)etiojervanes[1]

Akio MURAI, Chizuko SATO, Hiroshi SASAMORI, and Tadashi MASAMUNE

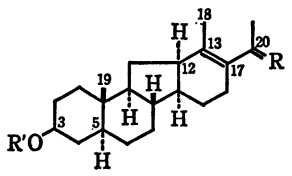
Department of Chemistry, Faculty of Science, Hokkaido University, Sapporo 060

(Received July 11, 1975)

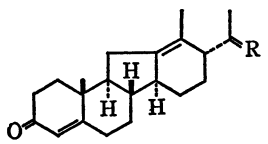
Photooxygenation of α,β(13,17)- and β,γ(12,13)-unsaturated morpholine enamines (I and II) in 17-(1-formylethyl)etiojervanes by singlet oxygen was carried out under irradiation with fluorescent bulbs. Oxidation of the former (I) afforded the corresponding α,β-unsaturated ketone (III) as the only product which could be isolated, while that of the latter gave two products, one (IV) being a normally oxidized β,γ-unsaturated ketone and the other (VIII) an α,β-unsaturated ketone with the D-ring contracted. Compound (VIII) was not obtained by treatment of IV under the same photooxygenation conditions as for II, indicating that the formation of VIII would not involve IV as an intermediate.

The photooxygenation of enamines by singlet oxygen has been demonstrated to be useful for synthesis.[2] We describe further examples which involve transformation of the enamines (I) and (II) into the corresponding unsaturated ketones. These α,β-[3] and β,γ-unsaturated ketones[4] (III and IV) are not readily obtainable by the standard chemical procedures.[5]

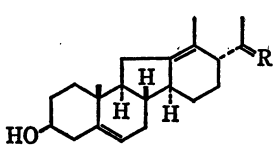
The enamines (I) and (II) were prepared as follows. 17-(1-Formylethyl)-5α,12α-etiojerv-13(17)-en-3β-ol[3] (V) was converted into the acetate (Va), oil, which was treated with morpholine[6] to give the α,β-unsaturated morpholine enamine (I), oil, in good yield; NMR, δ 1.68 and 1.74 (each 3H, s, 21- and 18-C$_3$H or *vice versa*). On the other hand, 17α-(1-formylethyl)etiojerva-5,12-dien-3β-ol[4] (VI) was transformed *via* a three-step process (acetalization of the formyl group, the Oppenauer oxidation and deacetalization) into the corresponding Δ^4-3-ketone (VII), oil, in good yield; UV, λ_{max} 238 nm (ε 10500), which smoothly formed the morpholine 20-enamine (II), oil, in the same manner as Va; NMR, δ 1.46 and 1.50 (each 3H, s, 18- and 21-C$\underline{H}_3$ or *vice versa*).



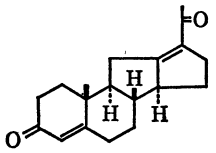
I R=CH(NC$_4$H$_8$O), R'=Ac
III R=O, R'=Ac
V R=H, CHO, R'=H
Va R=H, CHO, R'=Ac



II R=CH(NC$_4$H$_8$O)
IV R=O
VII R=H, CHO



VI R=H, CHO
IX R=O



VIII

Photooxygenation of the α,β-unsaturated enamine (I) in benzene with Rose Bengal as a sensitizer was carried out in a Pyrex tube irradiated externally with four 15-watt fluorescent bulbs at room temperature for 7.5 h, when all the starting enamine had been brought to reaction. The resulting tarry product was purified by preparative tlc to give 13, 17-unsaturated 20-ketone (III), oil, in 40% yield as the only main product which could be isolated; Mass, 358 (M$^+$) and 255; UV, λ_{max} 249 nm (ε 13000); IR, ν_{max} 1730, 1674, 1612, 1255, and 1210 cm^{-1}; NMR, δ 0.78, 1.89, 2.04, and 2.25 (each 3H, s, 19-, 18-, acetoxy, and 21-C$\underline{H}_3$), and 4.71 (1H, br W_H=21 Hz, $\underline{H}$ at C$_3$). Since α,β-unsaturated enamines have been reported to undergo autooxidation and form the cooresponding 1,4-diones,[7] photooxygenation is practicable, since ketone (III) had not been obtained by hydrolysis of the corresponding oxime[3] even under mild conditions. The α,β-(13,17)-unsaturated 20-ketone (III) was found to be very unstable as compared with the other α,β-(16,17)-unsaturated 20-ketone.[6] Double bond migration[4,8] followed by hydrooxygenation probably takes place under the conditions.

Photooxygenation of β,γ-unsaturated enamine (II) under the comparable conditions (22 h) afforded a tarry mixture, from which two products (IV) and (VIII) were isolated by preparative tlc in 11 and 22% yields, respectively. (IV), mp 131—133 °C and $[\alpha]_D$ +198°, showed the following spectra: Mass, *m/e* 312 (M$^+$) and 269; UV, λ_{max} 238 nm (ε 11500); IR, ν_{max} 1700, 1655, and 1603 cm^{-1}; NMR, δ 1.18, 1.57, and 2.14 (each 3H, s, 19-, 18-, and 21-C$\underline{H}_3$) and 5.78 (1H, s, $\underline{H}$ at C$_4$). The assigned structure of (IV) was consistent with these spectra and confirmed by the Oppenauer oxidation of the corresponding etiojerv-5-en-3β-ol[4] (IX) to IV. On the other hand, (VIII), mp 196—198 °C and $[\alpha]_D$ +110°, was identified on the basis of the spectral data to be α,β-unsaturated ketone with the D-ring contracted: Mass, *m/e* 284 (M$^+$), 269(M$^+$–CH$_3$), 241 (M$^+$–COCH$_3$), and 161 (base); UV, λ_{max} 247 nm (ε 20000); IR, ν_{max} 1654 and 1614 cm^{-1}; NMR, δ 1.22 and 2.28 (each 3H, s, 19-C$\underline{H}_3$ and COC$\underline{H}_3$) and 5.79 (1H, s, $\underline{H}$ at C$_4$). This ring-contracted product (VIII) was not obtained by treatment of IV under the same oxygenation conditions, most of the starting material being recovered unchanged. Its formation might involve initial oxygenation of the isolated 12,13-double bond[9] followed by the usual oxidation of the enamine double bond[10] and subsequent deacetylation (Norrish Type I and/or II). The same reaction of II in methanol resulted in the predominant formation of IV. Compounds IV and VIII were isolated in 24 and 3% yields. This result was in good accord with the solvent dependency

with respect to product formation in the photooxygenation of enamines.[11]

Experimental

All the mps were uncorrected. The homogenity of each compound was always checked by tlc on silica gel (Wakogel B-5), various solvent systems being used, and the spots were developed with ceric sulfate in dil sulfuric acid and/or iodine. The optical rotations and UV, IR and NMR spectra were measured in chloroform, ethanol, chloroform, and deuteriochloroform, respectively. The abbreviations "s, d, br, and m" in the NMR spectra denote "singlet, doublet, broad, and multiplet," respectively.

α,β-Unsaturated Enamine (I). 17-(1-Formylethyl)-5α, 12α-etiojerv-13(17)-en-3β-ol[3a] (V, 240 mg) was treated with acetic anhydride (5 ml) and pyridine (5 ml) at room temperature overnight. The mixture was diluted with chloroform, washed with 1 M hydrochloric acid and 5% aqueous sodium bicarbonate, dried, and evaporated to leave an oily residue (255 mg), which was purified by column chromatography (cc) over silica gel to give the 3β-acetate (Va, 180 mg), oil; Mass *m/e* 372 (M^+) and 343 (M^+—CHO); IR, ν_{max} 1728, 1252, and 1208 cm^{-1}; NMR, δ 0.76, 1.72, and 2.05 (each 3H, s, 19-, 18-, and acetoxy-C$\underline{H}_3$), 1.14 (3H, d J= 7 Hz, 21-C$\underline{H}_3$), and 3.44 (1H, br W_H=21 Hz, $\underline{H}$ at C_3), and 9.52 (1H, s, C$\underline{H}$O). This was used for the next reaction without further purification.

A solution of Va (108 mg) in a mixture of benzene (20 ml) and morpholine (0.1 ml) containing *p*-toluenesulfonic acid (PTS, 1 mg) was refluxed under nitrogen for 6 h, water being removed by means of a Dean-Stark apparatus. After removal of the solvents below 30 °C, the residue was worked up as usual to give α,β-unsaturated enamine (I, 119 mg), oil; Mass, *m/e* 441 (M^+), 426 (M^+–CH_3), and 398 (M^+—$COCH_3$); IR, ν_{max} 1720, 1644, 1256, and 1115 cm^{-1}; NMR, δ 0.81 (3H, s, 19-C$\underline{H}_3$), 2.05 (3H, s, OCOC$\underline{H}_3$), and 2.84 and 3.70 (each 4H, m W_H=13 Hz, $NC_2\underline{H}_4C_2\underline{H}_4O$), and 4.70 (1H, br W_H=21 Hz, $\underline{H}$ at C_3).

Oxygenation of I. A solution of I (108 mg) in benzene (15 ml) containing Rose Bengal (5 mg) in a Pyrex tube was bubbled with oxygen at room temperature under external irradiation with four 15-watt fluorescent bulbs (standard desk lamps) for 7.5 hr, when the starting material had disappeared on tlc. After removal of benzene, the residue was treated with water and chloroform. The chloroform extracts were worked up as usual to leave tarry material (100 mg), which was purified by preparative tlc over silica gel (Wakogel B-5) with a 1 : 1 mixture of benzene and ether to give α,β-unsaturated ketone (III, 40 mg), oil, showing a single spot; Mass, UV, IR and NMR are given in the text.

β,γ-Unsaturated Enamine (II). To a methanol solution (54 ml) of 17α-(1-formylethyl)etiojerva-5,12-dien-3β-ol[4] (VI, 605 mg) was added boron trifluoride etherate (2.0 ml) under cooling with ice, and the mixture was stirred at room temperature for 62 h under nitrogen. The solution was neutralized with 5% aqueous sodium bicarbonate and evaporated to leave an oily residue, which was worked up as usual to give the 20-aldehyde dimethyl acetal (585 mg), oil; Mass, *m/e* 342 (M^+—CH_3OH), 310 (M^+—$2CH_3OH$), and 270 [base, M^+—$CH(CH_3)CH(OCH_3)_2$]; NMR, δ 0.68 (3H, d J=7 Hz, 21-C$\underline{H}_3$) 0.98 and 1.53 (each 3H, s, 19- and 18-C$\underline{H}_3$), 3.34 (6H, s, OC$\underline{H}_3$), 4.24 (1H, d J=8 Hz, $\underline{H}$ at C_{22}), and 5.40 (1H, br W_H=9 Hz, $\underline{H}$ at C_6).

The acetal (575 mg) was dissolved in a mixture of toluene (72 ml) and cyclohexanone (3.9 ml); 30 ml of the toluene was then distilled off to remove water. Aluminium isopropoxide (530 mg) was added and, after removal of 10 ml of the toluene by distillation, the mixture was refluxed for 2.5 h and then distilled with steam to remove the organic solvents. The residue was extracted with chloroform, and the chloroform solution was washed with water, dried, and evaporated to give the corresponding Δ^4-3-ketone (569 mg), oil; UV, λ_{max} 238 nm (ε 10500); IR, ν_{max} 1666 and 1616 cm^{-1}; NMR, δ 0.69 (3H, d J=7 Hz, 21-C$\underline{H}_3$), 1.16, 1.54 (each 3H, s, 19- and 18-C$\underline{H}_3$), 3.35 (6H, s, 2OC$\underline{H}_3$), 4.22 (1H, d J= 8 Hz, $\underline{H}$ at C_{22}), and 5.80 (1H, s, $\underline{H}$ at C_4).

A solution of the α,β-unsaturated ketone (569 mg) in a mixture of acetone (170 ml) and water (30 ml) was refluxed with PTS (117 mg) for 4 h under stirring. After removal of most of the acetone, the residue was extracted with chloroform, washed with water, dried and evaporated to give 20-formyl-Δ^4-3-ketone (500 mg), oil; IR, ν_{max} 1721, 1656, and 1609 cm^{-1}; NMR, δ 0.90 (3H, d J=7 Hz, 21-C$\underline{H}_3$) 1.16 and 1.60 (3H, s, 19- and 18-C$\underline{H}_3$), 5.78 (1H, s, $\underline{H}$ at C_4), 9.68 and 9.73 (total 1H, each s, C$\underline{H}$O).

The 20-formyl-Δ^{12}-3-ketone (84 mg) in benzene (10 ml) and morpholine (0.1 ml) was treated with PTS (1 mg) in the same manner as for Va to give the 20-morpholine enamine (II, 99 mg), oil; Mass, *m/e* 395 (M^+), 380 (M^+—CH_3), 268 [M^+—(H+17-side chain)], and 127 [base, (H+17-side chain)]; IR, ν_{max} 1660, 1616, and 1116 cm^{-1}; NMR, δ 1.16 (3H, s, 19-C$\underline{H}_3$), 2.66 and 3.76 (each 4H, m, W_H=12 Hz, $NC_2\underline{H}_4C_2\underline{H}_4O$), and 5.49 and 5.82 (each 1H, s, 2$\underline{H}$ at C_{22} and C_4).

Oxygenation of II. A solution of II (337 mg) in benzene (20 ml) was oxygenated in the same manner (60 watt, 22 h, and room temperature) as for I. The reaction mixture was worked up as usual to leave an oily residue (250 mg), showing two main spots on tlc, which was separated by cc over silica gel with a 1 : 1 mixture of benzene and ether to give two crystalline compounds (IV and VIII). The former (IV, 27 mg), mp 131—133 °C on recrystallization from acetone-isopropyl ether, showed the spectra as described. The compound (IV) was also obtained by treatment of the corresponding etiojerv-5-en-3β-ol[4] (IX) under the same Oppenauer conditions as the acetal of VI. Found: C, 80.90; H, 9.15%. Calcd for $C_{21}H_{28}O_2$: C, 80.73; H, 9.03%. The latter (VIII, 52 mg) had mp 196—198 °C (acetone-isopropyl ether); Mass, UV, IR, and NMR in the text. Found: C, 80.36; H, 8.52%. Calcd for $C_{19}H_{24}O_2$: C, 80.24; H, 8.51%.

Compound II (330 mg) was oxygenated in methanol (20 ml) under almost the same conditions (60 watt, 3.5 h, and room temperature) as for benzene and gave IV (63 mg), mp 129—131 °C, and VIII (15 mg), mp 189—191 °C.

References

1) Part XXII of "C-Nor-D-homosteroids and Related Alkaloids;" Part XXI, M. Takasugi, V. H. Castro-Araya, T. Masamune, A. Furusaki, and T. Matsumoto, *Chem. Lett.*, **1974**, 1477.

2) For examples, K. Miyano, Y. Ohfune, S. Azuma, and T. Matsumoto, *Tetrahedron Lett.*, **1974**, 1545; J. E. Huber, *ibid.*, **1968**, 3271; C. S. Foote and J. Wei-Ping Lin, *ibid.*, **1968**, 3267.

3) a) T. Masamune, K. Orito, and A. Murai, This Bulletin, **39**, 2503 (1966). b) S. M. Kupchan, T. Masamune, and G. W. A. Milne, *J. Org. Chem.*, **29**, 755 (1964).

4) A. Murai, K. Arita, and T. Masamune, This Bulletin, **46**, 3536 (1973).

5) a) R. W. Franck, G. P. Rizzi, and W. S. Johnson, *Steroids*, **4**, 463 (1964). b) S. H. Pines, J. M. Chemerda,

and M. A. Kozlowski, *J. Org. Chem.*, **31**, 3446 (1966).

6) T. Masamune, A. Murai, K. Orito, H. Ono, S. Numata, and H. Suginome, *Tetrahedron*, **25**, 4853 (1969); H. Suginome, N. Sato, and T. Masamune, *Tetrahedron Lett.*, **1969**, 3353; S. M. Kupchan and M. J. A. El-Haj, *J. Org. Chem.*, **33**, 647 (1968); W. F. Johns and I. Laos, *ibid.*, **30**, 123 (1965); W. F. Johns, *ibid.*, **29**, 2545 (1964).

7) S. K. Malhotra, J. J. Hostynek, and A. F. Lundin, *J. Amer. Chem. Soc.*, **90**, 6565 (1968).

8) *Cf.*, T. Masamune, H. Matsue, and M. Fujii, This Bulletin, **45**, 1812 (1972); K. G. Lewis and G. J. Williams, *Tetrahedron Lett.*, **1965**, 4573.

9) S. Mazur and C. S. Foote, *J. Amer. Chem. Soc.*, **92**, 3225 (1970); P. D. Bartlett and A. P. Schaap, *ibid.*, **92**, 3223 (1970); A. Nickon and J. F. Bagli, *ibid.*, **83**, 1498 (1961).

10) *Cf.*, H. H. Wasserman and S. Terao, *Tetrahedron Lett.*, **1975**, 1735; I. Saito, M. Imuta, and T. Matsuura, *Chem. Lett.*, **1972**, 1173; A. Jerusei, *J. Org. Chem.*, **34**, 3648 (1969); V. V. Rheenen, *Chem. Commun.*, **1969**, 314.

11) C. S. Foote, A. A. Dzakpasn, and J. W. -P. Lin, *Tetrahedron Lett.*, **1975**, 1247. *Cf.*, A. G. Schultz and R. H. Schlessinger, *ibid.*, **1970**, 2731.