

Photo-induced Transformations. Part 63.¹ Photorearrangement of 17 β -Acetoxy-4,4-dimethylestr-5-en-3 β -yl Nitrite with Monochromatic Light

By Hiroshi Suginome * and Atsushi Osada, Department of Chemistry, Faculty of Science, Hokkaido University, Sapporo 060, Japan

Photolysis of 17 β -acetoxy-4,4-dimethylestr-5-en-3 β -yl nitrite (4) with 377 nm monochromatic light gave (*E*)-17 β -acetoxy-4,4-dimethyl-6-oxo-3,4-secoestr-4-en-3-yl 6-oxime (9), its (*Z*)-isomer (10), and 17 β -acetoxy-4-hydroxy-4a,4a-dimethyl-4-aza-A-homoeestr-5-en-3-one (8). Nitric oxide generated from the nitrite (4) thus combines predominantly with the C-6 terminus of an allyl radical intermediate formed by a β -scission of the corresponding oxyl radical. The reverse regioselectivities observed in the radical combinations between the allyl radical (B) and nitric oxide, generated from the nitrite (4) and from 4,4-dimethylcholest-5-en-3 β -yl nitrite (2), are discussed.

In a previous paper² we reported the results of the photolysis of cholesteryl nitrite (1) and 4,4-dimethylcholesteryl nitrite (2) in benzene with monochromatic light. It was found that cholesteryl nitrite (1) gave a nitroso-dimer arising from β -scission of the corresponding 3 β -oxyl radical (A). The nitrosodimer was cyclized to give a seven-membered *N*-hydroxy-lactam (6) on heating in isopropyl alcohol. On the other hand, photolysis of 4,4-dimethylcholesteryl nitrite (2) in benzene directly gave the seven-membered *N*-hydroxy-lactam (7). The nitrosodimer and the *N*-hydroxy-lactam (7) in these photoreactions are formed by dimerization or thermal cyclization [*via* intermediate (E)], respectively, of the corresponding nitroso-aldehyde intermediate [(D) R² = H or Me, R³ = Me] which arises from the combination of nitric oxide generated from the nitrite and the allyl radical [(B); R² = H or Me, R³ = Me] generated by β -scission of the corresponding oxyl radicals [(A) R² = H or Me, R³ = Me].²

An interesting feature of this photorearrangement was its regioselectivity in the radical combination involved in the reaction. The products in the photorearrangement of the nitrites (1) and (2) were exclusively those arising from the combination of nitric oxide and the C-4 terminus of the allyl radical and no products resulting from the combination of nitric oxide with the C-6 terminus were formed. It is by no means obvious that the nitric oxide shifts to the more substituted carbon centre of the intermediary allyl radical in the photolysis of the nitrite (2)³ with the formation of the product which appeared to be a less stable product; in all other nitrite photolyses where the combination of the allyl radical and nitric oxide is involved, the products were exclusively the more highly substituted olefins derived from *C*-nitroso-compounds formed by the combination of nitric oxide and the less substituted carbon centre of the allyl radical intermediates,⁴ and it has been shown that odd-electron distribution in the allyl radicals is not an important factor in directing the site of the combination of chlorine atoms with acyclic allyl radicals.⁵

In order to gain more insight into these regioselectivities in the radical combination of nitric oxide and the allyl radicals generated by the photolysis of these cyclic homoallyl nitrites, we investigated the photoreaction of

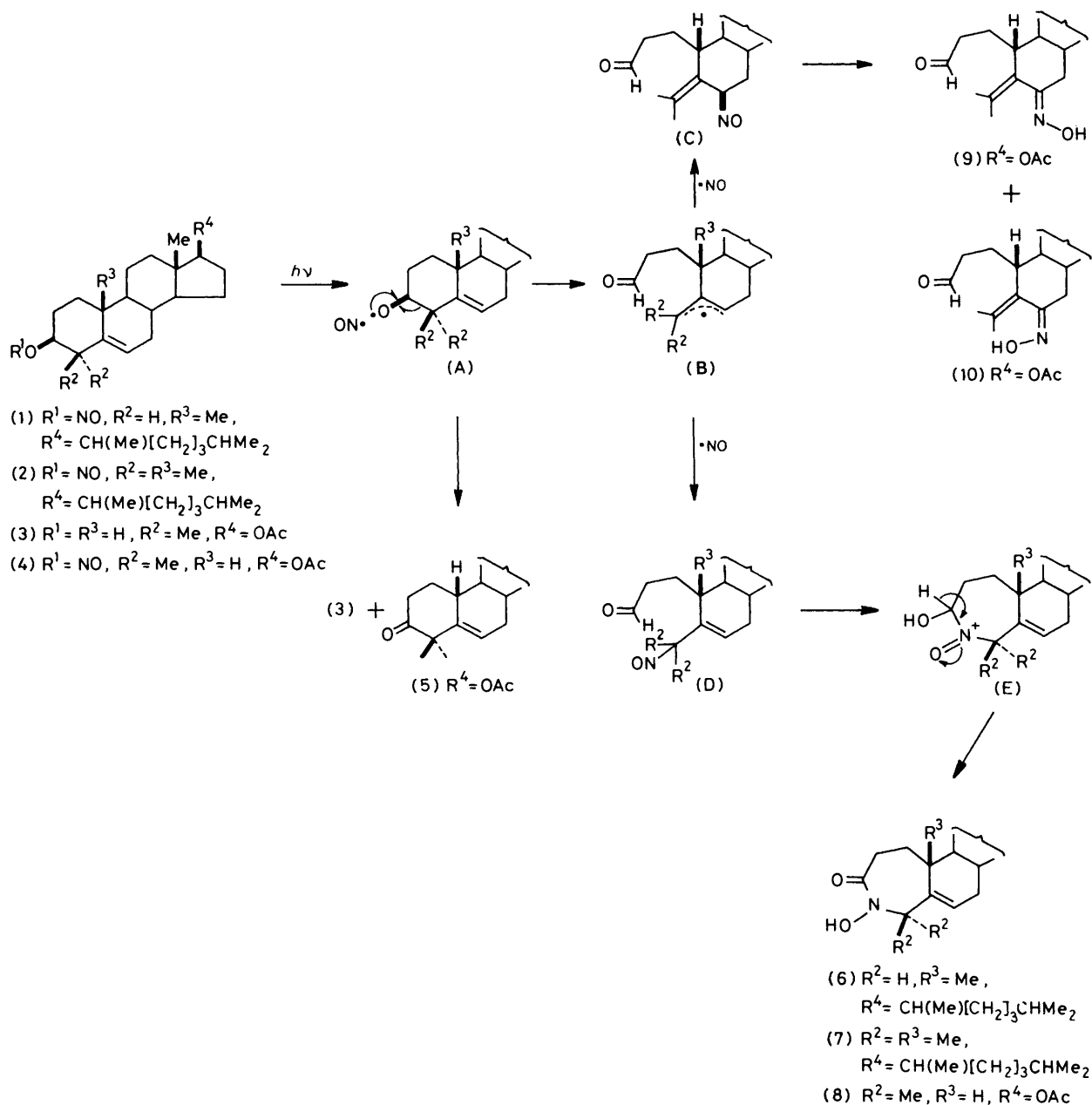
the title steroidal nitrite (4) which does not have a 10 β -methyl group. The photolysis was performed by irradiation with monochromatic light to avoid secondary photodecompositions of the products.

RESULTS AND DISCUSSION

The title nitrite (4) was readily prepared by nitrosation of 17 β -acetoxy-4,4-dimethylestr-5-en-3 β -ol (3), itself prepared by acetylation of 4,4-dimethyl-17 β -hydroxyestr-5-en-3-one⁶ followed by reduction of the keto-acetate (5) with sodium borohydride.

Irradiation of the nitrite (4) in dry benzene with 377 \pm 13 nm monochromatic light generated by JASCO CRM-FA grating spectro-irradiator for 24 h resulted in complete decomposition of the nitrite and gave a mixture of products. Separation of the products by preparative t.l.c. afforded three new compounds, (8), (9), and (10), all of them arising from rearrangement, together with the corresponding ketone (5) (3%) and the parent alcohol (3) (31%). The molecular formulae of all three rearrangement products [(8), (9), and (10)] were found to be C₂₂H₃₃NO₄ by high-resolution mass spectrometry. Compound (8) was obtained in 10% yield in an amorphous form and its i.r., ¹H n.m.r., and mass spectra showed that it was an *N*-hydroxy-lactam, 17 β -acetoxy-4-hydroxy-4a,4a-dimethyl-4-aza-A-homoeestr-5-en-3-one (8).

The crystalline compound (9) and the amorphous compound (10) were obtained in 17 and 6% yield, respectively, and both compounds were shown to be aldehydes by their ¹H n.m.r. spectra. ¹H N.m.r., i.r., and mass spectra of compounds (9) and (10) indicated that they were isomeric 17 β -acetoxy-6-hydroxyimino-4,4-dimethyl-3,4-secoestr-4-en-3-als. Although no spectroscopic evidence on the configurations of the hydroxyimino-groups was available, the (*E*)-configuration was assigned to the oxime (9) which is formed more abundantly. The ¹³C n.m.r. spectrum of compound (9), along with the off-resonance spectrum, showed signals arising from the formyl carbon, the isopropylidene carbons, C-6, and C-17 at 200.3, 138.8, and 135.3, 171.0, and 82.1 p.p.m., respectively. The (*Z*)-oxime (10) showed the corresponding signals at δ 202.7, 133.6, and 128.3, 171.1, and 82.5 p.p.m., respectively.



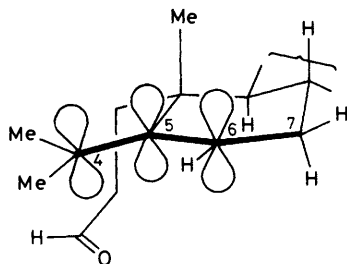
SCHEME

The pathways leading to all three rearrangement products, (8), (9), and (10), are shown in the Scheme. The hydroxy-lactam (8) and the two aldehydic oximes, (9) and (10), are clearly formed *via* β -scission of the corresponding 3β -oxyl radical (A) generated by photolysis. The total yield of products arising from the β -scission is $\geq ca. 33\%$ and this indicates that the extent of β -scission of the 3β -oxyl radical derived from a Δ^5 -steroid- 3β -ol is not appreciably influenced by the presence or absence of the 10β -methyl groups since photolysis of 4,4-dimethylcholest-5-en- 3β -yl nitrite (2) gave products due to β -scission to about the same extent.² The mechanism of formation of *N*-hydroxy-lactams, *via* the nitroso-

aldehyde (D), from acyclic nitrites has been discussed by Barton and his colleagues⁷ and by us.⁸

The aldehydic oximes (9) and (10) are formed by a thermal isomerization of an isomeric nitroso-aldehyde (C) which arises from bonding between the C-6 terminus of the allyl radical (B) and nitric oxide. It is noteworthy that the nitric oxide combined predominantly at the C-6 terminus of the allyl radical intermediate (B) in the present experiment. This selectivity in the combination of the allyl radical (B) and nitric oxide is in contrast to the result of the photolysis of 4,4-dimethylcholest-5-en- 3β -yl nitrite (2) where the nitric oxide combined exclusively at the C-4 terminus of the allyl

radical. It is thus clear that the site of combination of nitric oxide and the allyl radical is partly directed by the 10β -methyl group. In the photolysis of the nitrite (2), the 10β -methyl group hinders the attack of nitric oxide on the C-6 terminus from the β -face of the allyl radical and instead directs the nitric oxide onto the C-4 terminus. Moreover, it may also be inferred from the present results that the C-nitroso-compound formed in this radical combination may be the less stable 17β -acetoxy-4,4-dimethyl-6 β -nitroso-3,4-secoestr-4-en-3-al, formed by an approach of nitric oxide from the β -face of the allyl radical intermediate (B), and not its 6 α -isomer since no aldehydic oximes corresponding to oximes (9) and (10) were formed in the photoreaction of the nitrite (2). Although no direct spectroscopic evidence on the structure of the allyl radical (B) is available, the resonance-stabilized ⁹ allyl radical (B), which can be compared with an allyl radical generated from (*Z*)-but-2-ene,¹⁰ should have a planar structure (Figure).^{11,*} Thus it is very unlikely that the C-6 terminus of the allyl radical reacts with nitric oxide as a pyramidal sp^3 -hybridized carbon, and that the nitric oxide can combine at C-6 from only the β -face which is shielded by the 10β -methyl group. The approach of the nitric oxide to C-6 from the α -face should thus be considered to be hindered by the quasi-axial 7α -H in the half-chair conformation of ring B.



FIGURE

Regioselectivity in the combination of chlorine atoms and acyclic allyl radicals asymmetrically substituted with alkyl groups has been discussed by Walling and Thaller.⁵

With regard to the allyl radical [*e.g.* (B)], part or whole of which is within a ring system, the foregoing results appear to indicate that the shielding by an alkyl group or hydrogen present in the immediate vicinity in the ring may play a significant role in determining the site of the attachment of nitric oxide to the allyl radical.

EXPERIMENTAL

M.p.s were determined with a Yanagimoto micro m.p. apparatus. I.r. spectra were determined for Nujol mulls with a Hitachi 260-10 spectrophotometer unless stated otherwise. U.v. spectra were determined with a Hitachi

* A twist angle of *ca.* 10° was found for the sterically hindered 1,3-di-*t*-butyl-1,3-dimethylallyl radical by e.s.r. spectroscopy: H. Regenstein, W. Ahrens, and A. Berndt, *Tetrahedron*, 1975, **31**, 2873. Only very crowded allyl radicals, such as those generated by the reaction of tetramethylallene with thiyil, silyl, and stannyl radicals, were shown to have non-planar structures: W. H. Davis, Jr., and J. K. Kochi, *Tetrahedron Lett.*, 1976, 1961.

124 double-beam spectrophotometer. 100 MHz ¹H N.m.r. spectra were determined with a JEOL PS100 high-resolution spectrometer (solvent CDCl₃; SiMe₄ as internal reference). The ¹³C n.m.r. spectrum of compound (9) was recorded with a Bruker SXD pulsed FT n.m.r. spectrometer (CDCl₃; 22.63 MHz; δ in p.p.m. from SiMe₄), and the ¹³C n.m.r. spectrum of compound (10) was recorded with a JNM-FX-100 (25 MHz) high-resolution spectrometer (CDCl₃; SiMe₄ as an internal reference). T.l.c. was carried out on Wako silica gel B-5. Low-resolution mass spectra of compounds (3) and (5) were recorded with a JEOL JMS-D 300 spectrometer (70 eV) by the staff of the Faculty of Pharmaceutical Sciences of this University, and those of compounds (8), (9), and (10), and all the high-resolution mass spectra, were recorded by Miss Y. Chiba of the Faculty of Agriculture of this University.

17 β -Acetoxy-4,4-dimethylestr-5-en-3-one (5).—Acetylation of 4,4-dimethyl-17 β -hydroxyestr-5-en-3-one, prepared by the procedure of Bowers and Ringold,⁶ with pyridine-acetic anhydride gave the 17-acetate (5), m.p. 138–139 °C; ν_{\max} 1 743 (acetate), 1 714 (ketone), 1 274 (ester C–O), and 1 047 cm⁻¹; τ 4.73 (1 H, d, 6-H), 5.37 (1 H, t, *J* 9 Hz, 17 α -H), 7.96 (3 H, s, OAc), 8.75 and 8.80 (both 3 H, s, 4-Me), and 9.16 (3 H, s, 18-H₃); *m/z* 344 (*M*⁺, 100), 301 [(*M* – Ac)⁺, 17.3], 299 (40.3), and 43 (78.7%).

17 β -Acetoxy-4,4-dimethylestr-5-en-3 β -ol (3).—A solution of the ketone (5) (200 mg) in ethanol (20 ml) containing sodium borohydride (180 mg) was stirred for 30 min. After the addition of water (35 ml) and acetone (15 ml), the solution was washed with brine and with water and was then dried (Na₂SO₄). Evaporation of the solvent gave the crude alcohol (3) (216 mg) which was recrystallized from methanol to give the pure 3 β -alcohol in three crops (total 156 mg, 78%) m.p. 178–180 °C (Found: C, 76.25; H, 9.9. C₂₂H₃₄O₃ requires C, 76.00; H, 9.86%); ν_{\max} 3 441 (OH), 1 733 (acetate), 1 255 (C–O), and 955 cm⁻¹; τ (D₂O exchange) 4.57 (1 H, d, 6-H), 5.38 (1 H, t, 17 α -H), 6.75 (1 H, dd, *J* 4.5 and 11.3 Hz, 3 α -H), 7.97 (3 H, s, OAc), 8.88 and 9.07 (both 3 H, s, 4-Me), and 9.19 (3 H, s, 18-H₃); *m/z* (rel. intensity) 346 (*M*⁺, 2.7), 328 [(*M* – H₂O)⁺, 100], 268 [(*M* – H₂O – CH₃CO₂H)⁺ 37.0], and 43 (74.5%).

17 β -Acetoxy-4,4-dimethylestr-5-en-3 β -yl Nitrite (4).—To a solution of the alcohol (3) (1 g) in pyridine (10 ml), cooled by solid CO₂-acetone, was added a solution of nitrosyl chloride in pyridine. The mixture was stirred for 30 min and was then poured into ice-water. The crystals of the nitrite (4) (1.051 g, 97%) were filtered off, m.p. 146–149 °C; ν_{\max} 1 732 (acetate), 1 623 (N=O), 1 248 (ester C–O), 1 023, 912, 811, 773, and 748 cm⁻¹; τ 4.25 (1 H, d, 6-H), 4.89 (1 H, dd, *J* 7.5 and 9.0 Hz, 3 α -H), 5.30 (1 H, t, *J* 7.5 Hz, 17 α -H), 7.90 (3 H, s, OAc), 8.90 and 8.95 (both 3 H, s, 4-Me), and 9.08 (3 H, s, 18-H₃); λ_{\max} (benzene) 334 (ϵ 34), 345 (46), 358 (61), 372 (63), and 386 nm (39).

Photolysis of the Nitrite (4) with 377 nm Monochromatic Light.—A solution of the nitrite (4) (250 mg) in dry benzene (6 ml) in a quartz cell was placed in a chamber of a JASCO CRM-FA grating spectro-irradiator equipped with a 2 kW xenon arc lamp and was irradiated with 377 ± 13 nm light for 24 h; complete decomposition of the nitrite had occurred after this time. Three more irradiations on the same scale were carried out under identical conditions. The solvent from the combined solutions from the four experiments was removed under reduced pressure. The photolysate was subjected to preparative t.l.c. with benzene-acetone (9 : 1) as developer to give six fractions A to F in order of increasing

mobility. The least mobile fraction A (168 mg, 17%) was the *oxime-aldehyde* (9), and a crystalline specimen for analysis was obtained by recrystallization from methanol, m.p. 153–155 °C (Found: M^+ , 375.2391. $[C_{22}H_{33}NO_4]^+$ requires M , 375.2407); ν_{\max} , 3 500 (OH), 1 723 (formyl and OAc), 1 248 (ester C=O), and 1 028 cm^{-1} ; τ 0.21br (1 H, s, CHO), 5.34 (1 H, t, J 7.5 Hz, 17 α -H), 7.96 (3 H, s, OAc), 8.41 and 8.45 (both 3 H, s, 4-Me), and 9.14 (3 H, s, 18-H₃); m/z (rel. intensity) 375 (M^+ , 0.1), 360 [$(M^+ - CH_3)^+$, 4.9], 358 [$(M - OH)^+$, 5.3], 316 (24.8), and 43 (100%).

Fraction B (61 mg, 6%) was the isomeric *oxime-aldehyde* (10) which could not be induced to crystallize (Found: M^+ , 375.2409. $[C_{22}H_{33}NO_4]^+$ requires M , 375.2407); ν_{\max} , 3 440 (OH), 1 727 (formyl and OAc), 1 239 (ester C=O), and 1 026 cm^{-1} ; τ 0.33br (1 H, s, $W_{\frac{1}{2}}$ 7 Hz, CHO), 5.39 (1 H, t, J 7.5 Hz, 17 α -H), 7.96 (3 H, s, OAc), 8.18 and 8.27 (both 3 H, s, 4-Me), and 9.18 (3 H, s, 18-H₃); m/z (rel. intensity) 375 (M^+ , 4.9), 360 [$(M - CH_3)^+$, 10.7], 358 [$(M - OH)^+$, 10.7], 332 (14.9), 318 (14.9), and 43 (100%).

Fraction C (101 mg, 10%) was the amorphous *N-hydroxy-lactam* (8) (Found: M^+ , 375.2379. $[C_{22}H_{33}NO_4]^+$ requires M^+ , 375.2407); ν_{\max} , 3 430 (OH), 1 738 (OAc), 1 625 (lactam C=O), 1 257, 1 018, 788, and 713 cm^{-1} ; τ 9.15 (3 H, s, 18-H₃), 8.51 and 8.41 (both 3 H, s, 4a-Me), 7.96 (3 H, s, OAc), 5.38 (1 H, t, J 7.5 Hz, 17 α -H), and 3.80br (1 H, d, 6-H); m/z 375 (M^+ , 3.8), 360 (3.7), 358 (4.1), 318 (9.3), and 43 (100%).

The n.m.r. spectra of fractions D (72 mg) and E (73 mg) proved that they were impure. However, the major portions of these fractions were aldehydes and fraction D showed a signal for the formyl proton at τ 0.23 (broad singlet), and fraction E a signal at τ 0.27 (broad singlet). In the spectrum of fraction D there was no olefinic proton signal, whereas that of the fraction E showed a triplet signal (1 H) at τ 4.0, assignable to the C-6 olefinic proton. Both spectra showed a series of signals arising from the 18-H₃, *gem*-dimethyl, 17 α -H, and OAc protons. Thus, these compounds might be nitrosodimers arising from the isomeric

nitroso-aldehydes formed by the combination at either the C-4 or C-6 end of the allyl radical. No further elaboration of the structures of these compounds was attempted.

Fraction F (313 mg, 31%) was the alcohol (3). The least polar fraction (25 mg, 3%) was identified as the ketone (5) by comparison with an authentic specimen.

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