A New Photoinduced Rearrangement of Steroidal α,β-Unsaturated Cyclic Ketone Oximes into the β,γ-Unsaturated Isomer involving an Intramolecular Stereospecific Hydrogen Transfer[1]

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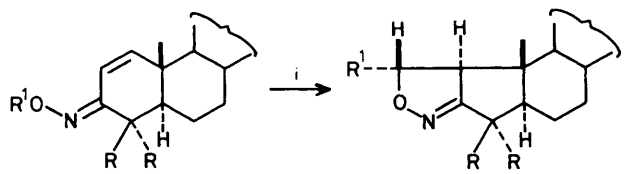
Irradiation of (*E*)-1,4,4-trimethyl-5α-cholest-1-en-3-one oxime in a protic or an aprotic solvent gave rise to 4,4-dimethyl-1-methylene-5α-cholestan-3-one oxime in 69—75% yield; mechanism for this photo-isomerization which involves an intramolecular stereospecific transfer of a hydroxyimino hydrogen is proposed on the basis of deuterium labelling studies.

We have recently reported[2] a new stereospecific rearrangement of an excited steroidal α,β-unsaturated cyclic ketone oxime; irradiation of (*E*)-5α-cholest-1-en-3-one oxime (**1**) in a protic or an aprotic solvent with a low pressure mercury arc gave 4α′,5′-dihydro-*A*-nor-5α-cholestano[2,1-*c*]isoxazole (**2**) (Scheme 1). On the basis of deuterium labelling studies, we advanced the hypothesis that the pathway involves an unusual stereospecific intramolecular transfer of the hydroxyimino hydrogen to the C-2 of oxime (**1**).[2]



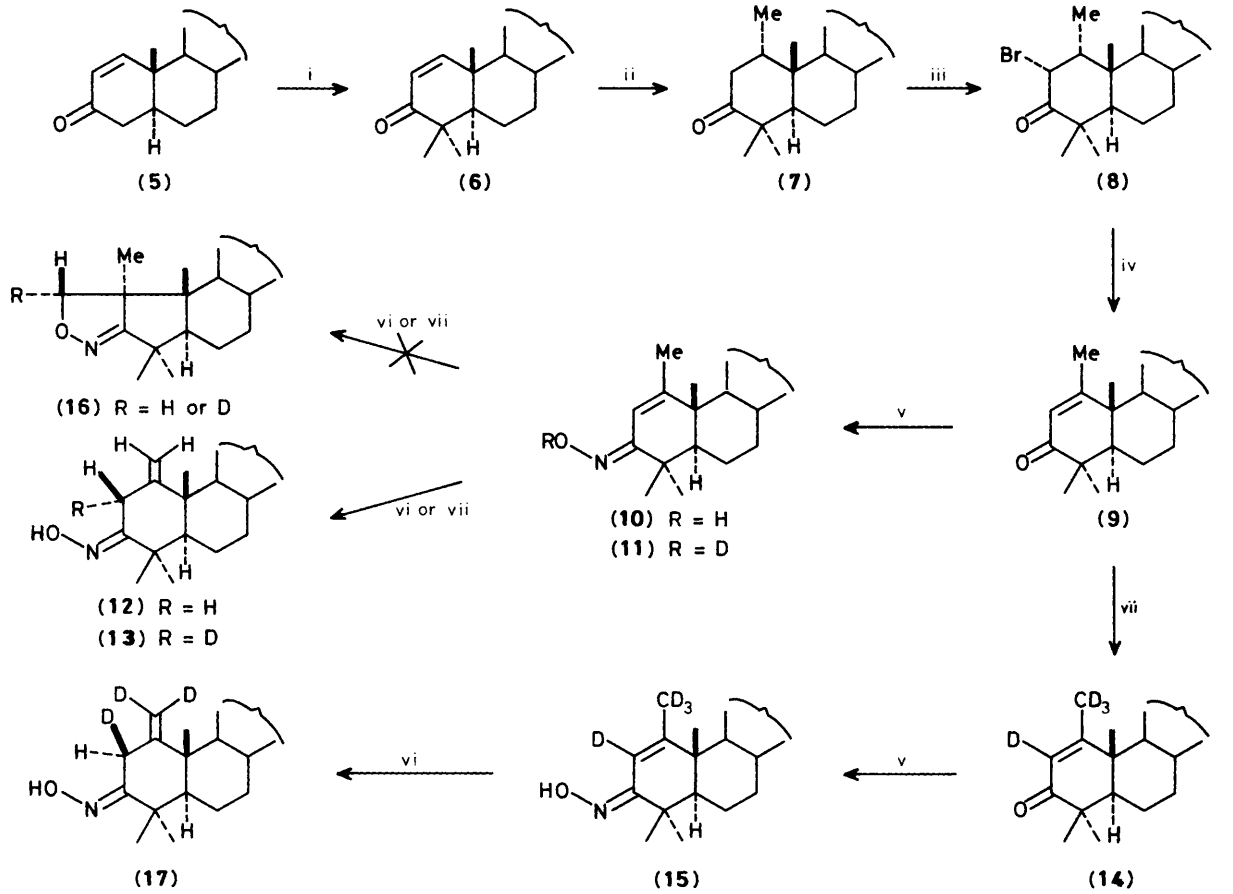
(**1**) R = H, R^1 = D
(**3**) R = Me, R^1 = H
(**2**) R = H, R^1 = D
(**4**) R = Me, R^1 = H

Scheme 1. *Reagents and conditions:* i, CD_3OD or C_6D_6–*hν*.

We have now carried out extensive investigations on the effects of the substitution by methyl groups of the hydrogens attached to the α- or β-carbon of the α,β-unsaturated hydroxyimino chromophore.

We now report that the effects of the alkyl group attached to the C–C double bond are profound and irradiation of (*E*)-β-methyl-α,β-unsaturated oxime (**10**) in protic or aprotic solvent resulted in an unprecedented isomerization involving an intramolecular stereospecific transfer of the hydroxyimino proton.

The substrates (*E*)-4,4-dimethylcholest-1-en-3-one oxime (**3**) and (*E*)-1,4,4-trimethylcholest-1-en-3-one oxime (**10**) were synthesised as follows (Scheme 2); dimethylation of cholest-1-en-3-one (**5**) gave 4,4-dimethylcholest-1-en-3-one



Scheme 2. *Reagents and conditions:* i, MeI–Bu^{t}OK–THF (tetrahydrofuran); ii, Me_2CuLi–Et_2O at 0 °C; iii, C_5H_5N·HBr·Br_2–AcOH at 60 °C; iv, $CaCO_3$–DMA (dimethylacetamide) reflux; v, NH_2OH·HCl–AcONa–EtOH, reflux; vi, *hν*–MeOH or C_6H_6 or C_6D_6; vii, *hν*–MeOD; viii, EtOD–Na.

(**6**)† (88%). Conjugate addition of a methyl group to 4,4-dimethylcholest-1-en-3-one (**6**) gave 1α,4,4-trimethyl-5α-cholestan-3-one (**7**)† (93%). Monobromination of trimethyl-

† (**6**), M.p. 90—91 °C. (**7**), M.p. 116—117 °C. (**8**), M.p. 48—50 °C. $\nu_{max.}$ 1672 cm^{-1} (C=O); δ 0.71 (3H, s, 18-H), 1.08 (6H, s, 4-Me_2), 2.05 (3H, d, *J* 1.3 Hz, 1-Me) and 5.76 (1H, d, *J* 1.1 Hz, 2-H); *m/z* 426 (M^+, 48.2).

(**10**), M.p. 180—181 °C; $\nu_{max.}$ 3236 cm^{-1} (OH); δ 0.69 (3H, s, 19-H), 1.14 (6H, s, 4-Me_2), 2.02 (3H, d, *J* 1.1 Hz, 1-Me), 6.43 (1H, d, *J* 1.1 Hz, 2-H); *m/z* (%) 441 (M^+, 65.3) and 424 [$(M-OH)^+$ 50.7].

(**3**), M.p. 196—197 °C. (**4**), M.p. 156—157 °C; $\nu_{max.}$ 1620 cm^{-1} (C=N); δ 0.64 (3H, s, 18-H), 0.90 (3H, s, 19-H), 1.16, 1.21 (each 3H, each s, 3-Me_2), 3.44 (1H, dd, 4α′-H), 3.84 (1H, dd, 5β′-H) and 4.38 (1H, dd, 5α′-H).

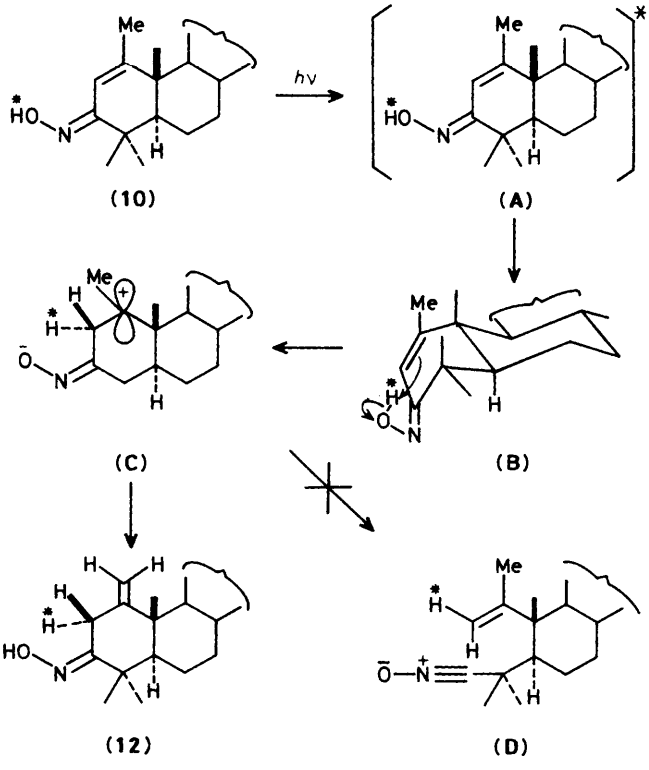
(**12**), M.p. 172—174 °C; $\nu_{max.}$ 3262 cm^{-1} (OH); δ 0.69 (3H, s, 18-H), 1.03 (3H, s, 19-H), 1.14 (6H, s, 4-Me_2), 3.27 (1H, d, *J* 17.6 Hz, 2-H), 3.34 (1H, d, *J* 17.6 Hz, 2-H), 4.67 and 4.92 (each 1H, each br. s, –C–CH_2); *m/z* 441 (M^+, 100%), 426 [$(M-Me)^+$, 89.1] and 424 [(M^+-OH), 44.8].

(**13**), M.p. 169—172 °C; $\nu_{max.}$ 3260 cm^{-1} (OH); δ 0.69 (3H, s, 18-H), 1.03 (3H, s, 19-H), 1.14 (6H, s, 4-Me_2), 3.39 (1H, s, 2β-H), 4.67 and 4.92 (each, 1H, each s, –C=CH_2); *m/z* 422 (M^+, 50.7%) and 425 [$(M-OH)^+$, 42.1].

(**15**), M.p. 184—187 °C; $\nu_{max.}$ 3278 cm^{-1} (OH); δ 0.69 (3H, s, 18-H), 1.01 (3H, s, 19-H) and 1.14 (6H, s, 4-Me_2); *m/z* 445 (M^+, 80.9%) and 428 [$(M-OH)^+$, 53.7].

(**14**), δ 0.71 (3H, s, 18-H), 1.08 (6H, s, 4-Me_2) and 1.10 (3H, s, 19-H); *m/z* 430 (M^+, 39.8%).

(**17**), M.p. 160—163 °C; $\nu_{max.}$ 3278 cm^{-1} (OH); δ 0.69 (3H, s, 18-H), 1.03 (3H, s, 19-H), 1.13 (6H, s, 4-Me_2) and 3.24 (1H, s, 2α-H); *m/z* 444 (M^+, 67.6) and 427 [$(M-OH)^+$, 68.5].



Scheme 3

5α-cholestan-3-one (**7**) afforded 2α-bromo-1α,4,4-trimethyl-5α-cholestan-3-one (**8**)† (91%) which was dehydrobrominated to give 1,4,4-trimethyl-5α-cholest-1-en-3-one (**9**)¶ (91%).

Oximation of the enones (**9**) and (**6**) gave the oxime (**10**)† and (**3**).†

Irradiation of oxime (**3**) (118 mg) in methanol (60 ml) with a low pressure Hg arc in a Rayonet photochemical reactor for 5 h under nitrogen resulted in the formation of isoxazoline (**4**)† (24%) together with (*Z*)-4,4-dimethyl-1β-methoxy-5α-cholestan-3-one oxime (23%), its (*E*)-isomer (12%) and the parent ketone (6%). These results almost parallel those obtained in the photolysis of 5α-cholest-1-en-3-one oxime (**1**).[2]

In sharp contrast to these results, when oxime (**7**) (140 mg) in methanol (70 ml) was irradiated under the above conditions for 4 h, only the product (**12**) was obtained (Scheme 2). Neither the expected isoxazole derivative (**16**) nor the unsaturated lactam that arises from the photo-Beckmann rearrangement was found. An identical product was obtained when a benzene solution of oxime (**10**) was irradiated for 7 h (17%) or a hexadeuteriobenzene solution of oxime (**10**) was irradiated for 8 h (75%). The structure of the product (**12**) was assigned on the basis of the i.r., ^{1}H n.m.r., and mass spectra.†

The following deuterium labelling studies proved that the 2α-H of photo-products (**12**) are stereospecifically derived from the hydroxyimino proton of oxime (**10**) and therefore the transfer is likely to be intramolecular.

Thus, when the hydroxyimino proton of oxime (**10**) is exchanged by deuterium by dissolution in MeOD and the resulting MeOD solution is irradiated under the above-mentioned conditions, a *single* monodeuteriated product (**13**)† is obtained. The ^{1}H n.m.r. spectrum exhibited a singlet at 3.39 assignable to 2-H. This indicated that the deuterium is stereospecifically incorporated into C-2. On the other hand, when tetradeuteriated oxime (**15**)†, prepared by oximation of the tetradeuteriated enone (**14**), obtained *via* deuteriation of enone (**9**) with EtOD and Na, was photolysed in methanol, the single trideuteriated photoproduct (**17**)† was obtained. The ^{1}H n.m.r. spectrum of product (**17**) exhibited a singlet at δ 3.24 assignable to 2-H. This again shows that the transfer of the proton is stereospecific.

The configurations of the incorporated 2-H in products (**13**) and (**17**) were assigned to be β and α respectively on the basis of our previously proposed mechanism[2] and the assignments were independently confirmed by means of nuclear Overhauser enhancement (n.O.e.) measurements. Thus, while irradiation of the 19-H of product (**14**) resulted in the enhancement of the signal area of the 2-H, no enhancement of the 2-H was observed when the 19-H of product (**17**) was irradiated. Similarly, while irradiation of the 2-H of product (**14**) caused the enhancement of the signal area of the 19-H, no enhancement of the 19-H was observed when the 2-H of product (**17**) was irradiated.

On the basis of these labelling results, we consider that the path of the present photoinduced isomerization of oxime (**10**) into oxime (**12**) takes place as outlined in Scheme 3. Irradiation of the oxime (**10**) generates excited oxime (A) and the hydroxyimino proton is transferred to the C-2 of the twisted C=C bond of the relaxed unstable species (B) from the α-face to give carbocation (C). A loss of a proton from the species (C) affords the isomeric oximes (**12**). In contrast to the photochemical behaviour of (*E*)-5α-cholest-1-en-3-one oxime (**1**)[2] and the 4,4-dimethyl derivative (**3**), no product that might arise from a competing fragmentation of carbocation (C) to give a nitrile oxide (D) was formed in the present photo reaction.

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References

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