Photoinduced Molecular Transformations. Part 130.[1] Novel Stereospecific Photorearrangement and Stereospecific Addition of Methanol in Steroidal α,β-Unsaturated Cyclic Ketone Oximes[2]

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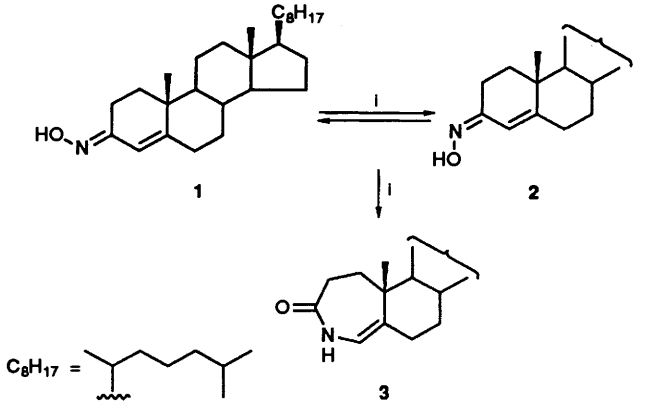
Irradiation of 5α-cholest-1-en-3-one oxime or its 4,4-dimethyl derivative in a protic or an aprotic solvent gave 4'α,5'-dihydro-4-nor-5α-cholest-1-eno[2,1-*c*]isoxazole or the corresponding 3,3-dimethyl derivative arising from an unprecedented photorearrangement. The molecular structure of the former was established by X-ray crystallographic analysis. 1β-Methoxy-5α-cholestan-3-one oximes or their 4,4-dimethyl derivatives, arising from an unprecedented photoaddition of methanol to the double bond of the enone oximes, were the accompanying products in both of these photoreactions and no lactams were formed. Deuterium-labelling studies on the photoreactions of 5α-cholest-1-en-3-one oxime and its trideuteriated derivative established that a deuteron or a proton is stereospecifically introduced at the 2α-position of the steroidal oxime in this photorearrangement. A pathway which involves an unprecedented stereospecific addition of a proton or a deuteron to the photogenerated, twisted double bond of the oximes from the rear side, followed by fragmentation of the resulting carbocation and an intramolecular 1,3-dipolar addition of the nitrile oxide intermediate, is proposed regarding the formation of the isoxazole from the excited oximes. Deuterium-labelling studies also established that the addition of methanol to the double bond of the oximes is stereospecific too. On the basis of the labelling study it is concluded that the mechanism for the photoaddition of the methanol involves a stereospecific *syn* addition of the methanol to the photogenerated, twisted, ground-state double bond of the oximes from the rear side.

Although the photoreactions of the oximes of saturated ketones have been investigated rather extensively,[3,4] only a limited number of studies have been carried out on the behaviour of excited α,β-unsaturated ketone oximes.[5]

In a previous paper[6] we reported that the photoreaction of oximes of cholest-4-en-3-one, 2,2-dimethylcholest-4-en-3-one, and cholest-5-en-7-one in protic solvents results in the formation of the corresponding enamine-type lactams arising from a regiospecific photorearrangement; the photoreaction of (*E*)- and (*Z*)-cholest-4-en-3-one oximes **1** and **2** in methanol gave 4a-homo-4-azacholest-4a-en-3-one **3** as an exclusive lactam product (Scheme 1).



Scheme 1 *Reagents and conditions:* i, MeOH, *hv*.

Since these photochemical transformations, which can be achieved solely upon irradiation with photons in the presence of a solvent, have great potential utility in organic synthesis, we decided to investigate more thoroughly the structure–product correlation in the photoreaction of the α,β-unsaturated cyclic ketone oximes by making use of several more steroidal substrates. A steroidal substrate is an excellent probe for clarifying the stereochemical aspects of organic photoreactions.

In this paper we report details concerning an investigation of the photoreaction of (*Z*)- and (*E*)-5α-cholest-1-en-3-one oximes **7** and **8**[7] and (*E*)-4,4-dimethyl-5α-cholest-1-en-3-one oxime **13**. The photoreaction of oximes **7**, **8** and **13**, to our surprise, took a course different from that of oximes **1** and **2**, resulting in the formation of products arising from unprecedented stereospecific skeletal photorearrangements[2] as well as from an unprecedented stereospecific addition of methanol to the α,β-double bond of the oximes. No lactams were formed in this photoreaction.

The results of investigations concerning the photoreactions of a number of other steroidal α,β-unsaturated cyclic ketone oximes will be reported in forthcoming publications.

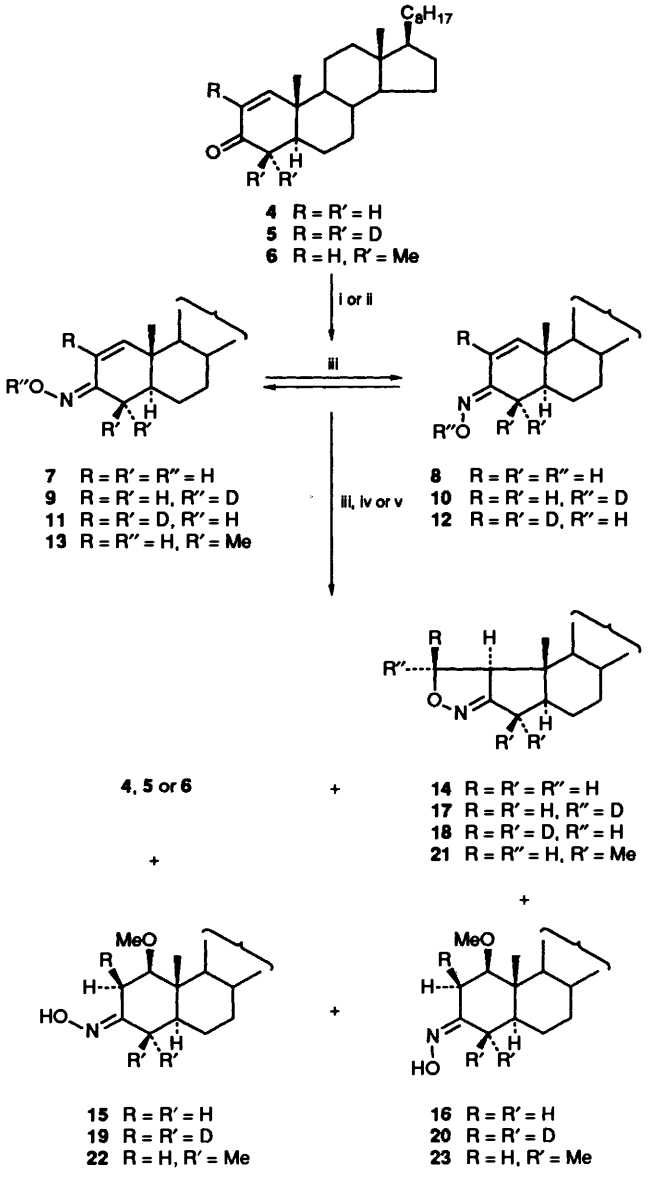
Results

Preparation of α,β-Unsaturated Cyclic Ketone Oximes **7**, **8**, **11**, **12** *and* **13** *for the Photoreactions.*—The oximation of cholest-1-en-3-one **4** by the standard method gave a 14:86 mixture of the (*Z*)- and (*E*)-oximes **7** and **8**. The *Z*/*E* ratio was determined by ^{1}H NMR spectroscopy. Recrystallization from acetone–methanol gave pure (*E*)-oxime (89%). The two protons attached to C-4 of oxime **8** appeared at δ 2.73 and 2.93, each as a doublet. The observed downfield shift of one of the doublets indicated this compound to be an (*E*)-isomer. Irradiation of the (*E*)-isomer in methanol gave a 23:77 mixture of the (*Z*)- and (*E*)-oxime **7** and **8**. We were unable to isolate pure (*Z*)-isomer, owing to its very ready isomerization to (*E*)-isomer on silica gel. [2,4,4-$^2H_3$]Cholest-1-en-3-one oximes **11** and **12** for a deuter-

ium-labelling study were also prepared by the oximation of [2,4,4-$^2H_3$]cholest-1-en-3-one **5**,[8] obtainable by the deuteration of cholest-1-en-3-one **4**.

4,4-Dimethylcholest-1-en-3-one oxime **13** was similarly prepared by the oximation of 4,4-dimethylcholest-1-en-3-one **6**[9] in order to examine the effect of the alkyl groups attached to C-4. The ^{1}H NMR spectrum showed that the hydroxyimino group was oriented *anti* to the C-4 carrying *gem* dimethyl groups, since the 2-H appeared at δ 6.45, 0.46 ppm downfield of the 2-H signal of oxime **8**.

Photoreactions of Oximes **7** *and* **8** (*Scheme 2*).—The photoreactions of oximes **7** and **8** in methanol or benzene containing a small amount of acetic acid were carried out with a low-pressure mercury arc generated by a Rayonet RPR photochemical chamber reactor. Thus, a solution of a mixture of oximes (173 mg) in methanol contained in a quartz vessel was irradiated at 20–25 °C under nitrogen for 10 h. Cholest-1-en-3-one **4** (26%) and three other products [**14** (20%), **15** (5%) and **16** (8%)] were obtained after separation by preparative TLC (Scheme 2).



Scheme 2 *Reagents and conditions:* i, NH_2OH·HCl, AcONa·$3H_2O$, EtOH, room temp.; ii, NH_2OH·HCl, AcONa·$3H_2O$, EtOH, reflux; iii, MeOH, *hν*; iv, CD_3OD, *hν*; v, C_6D_6, *hν*.

Spectroscopic analysis immediately indicated that these products were not the expected lactams that arise from a photo-Beckmann rearrangement.

The molecular formula of product **14**, $C_{27}H_{45}NO$, established by elemental analysis and high-resolution mass spectrometry, indicated that the product arose from a photorearrangement. Its IR spectrum indicated the absence of carbonyl and hydroxy groups, and its ^{1}H NMR spectrum showed the absence of olefinic protons. The molecular structure of product **14** was then established as being 4′α,5′-dihydro-4-nor-5α-cholest-1-eno[2,1-*c*]isoxazole **14** by X-ray crystallography. An ORTEP stereodrawing of the molecular structure was presented in a preliminary communication.[2]

High-resolution mass spectrometry indicated that products **15** and **16** were isomers having the molecular formula $C_{28}H_{49}NO$. The structures of these isomeric products were then established to be (*Z*)-1β-methoxy-5α-cholestan-3-one oxime **15** and its (*E*)-isomer **16** on the basis of their ^{1}H NMR spectra. Details concerning an analysis of the spectra are described in the Experimental section.

Careful TLC examination of the crude product of the photolysis indicated that none of the expected unsaturated lactams that arise from a photo-Beckmann-type rearrangement was formed. We then found that a protic solvent is not essential for the formation of the isoxazole **14**; the isoxazole **14** was formed in 18% yield together with the parent ketone **4** when oximes **7** and **8** were irradiated in hexadeuteriobenzene. The 5′α-H of isoxazole **14** should thus be supplied by the hydroxyimino group of the oxime **14** in this photoreaction in an aprotic solvent. It was also found that no isoxazole **14** was formed when oxime **2** was irradiated in methanol in the presence of oxygen.

Deuterium-labelling Experiments involving Photorearrangements of Oximes **7** *and* **8** (*Scheme 2*).—In order to establish the stereochemical course of the photorearrangement, deuterium-labelling experiments were undertaken. An exchange of the hydroxyimino proton of the oxime **7** by deuterium by dissolution of substrates **7** and **8** in CD_3OD, followed by photolysis of the deuterio oximes **9** and **10**, gave the isoxazole **17** in 12% yield. Mass spectrometric analysis indicated that one deuterium is incorporated in the isoxazole **17**. Comparison of the ^{1}H NMR spectra of the isoxazole **14** and the monodeuterioisoxazole **17** indicated that the deuterium is incorporated in the 5′α position of compound **17**; the ^{1}H NMR spectrum of the isoxazole **14** exhibited one-proton signals each at δ 3.35 (ddd, *J* 10.38, 12.82 and < 1 Hz), 3.84 (dd, *J* 8.24 and 12.82 Hz) and 4.33 (dd, *J* 8.24 and 10.38 Hz). The coupling constants and the results of NOE measurements showed that these signals are assignable to the 1α-H, 5′β-H and 5′α-H. Irradiation of the signal at δ 3.35 resulted in an enhancement of the signal area at δ 4.33 (6.0%), and *vice versa* (6.4%). There was no enhancement of the area of the signal at δ 3.84 when the signal at δ 3.35 was irradiated. These NOE results indicated that the protons due to the signals at δ 3.35 and 4.33 are *cis* oriented, and that therefore these signals are due to the 1α and 5′α protons. ^{1}H NMR spectroscopy of monodeuterioisoxazole **17** showed an absence of the signal due to the 5′α-H, and exhibited two one-proton doublets, at δ 3.34 and 3.83 (each *J* 12.8 Hz), due to the 1α-H and 5′β-H, indicating an incorporation of the deuterium at 5α′-H. No trace of the 5′β-deuterioisoxazole was detected in the crude product mixture. Hence, the photorearrangement is stereospecific.

In order to establish more firmly the stereoselectivity of the proton transfer in this photorearrangement, the photorearrangement of [2,4,4-$^2H_3$]cholest-1-en-3-one oximes **11** and **12** to the trideuterioisoxazole **18** was then investigated. Irradiation of trideuterio oximes **11** and **12** in methanol under the above

mentioned conditions resulted in formation of the trideuterioisoxazole **18** (17%), a mixture of a 1:1.2 mixture of isomers of methanol adducts, **19** and **20** (8%), and the parent enone **5** (16%). The ^{1}H NMR spectrum of the trideuterioisoxazole **18** exhibited only two doublets, at δ 3.35 and 4.33 (each J 10.3 Hz), due to the 4′α-H and 5′α-H. The signal due to 5′β-H was absent in the spectrum. This experiment firmly established that the two vicinal protons attached to C-4′ and -5′ in the trideuterioisoxazole **18** are oriented *cis*. Separation of the (*Z*)- and (*E*)-isomer **19** and **20**, by means of PLC was unsuccessful, due to their ready isomerization on silica gel. Analysis of the 400 MHz ^{1}H NMR spectrum of the mixture, however, clearly indicated that a proton incorporated at C-2 of both isomers **19** and **20** occupied their 2α-position ($J_{1\text{-H},2\text{-H}}$ 5.4 Hz). Details concerning the analysis are described in the Experimental section.

Photorearrangement of (E)-4,4-*Dimethyl*-5α-*cholest*-1-*en*-3-*one Oxime* **13**.—The photoreaction of the 4,4-dimethyl derivative **13** of oxime 7 in methanol under the conditions described above similarly gave the isoxazole **21** (24%), (*E*) and (*Z*) isomers of methoxylated oximes **22** (23%) and **23** (12%), and the parent enone (6%). The molecular formula of product **21** was established to be $C_{29}H_{49}NO$ by means of elemental analysis and high-resolution mass spectrometry. Its ^{1}H NMR spectrum indicated three double doublets, at δ 3.44 (J 11.7 and 10.6 Hz), 3.84 (J 8.2 and 11.7 Hz) and 4.38 (J 8.2 and 10.6 Hz), assignable to 1α-H, 5′β-H and 5′α-H, respectively. High-resolution mass spectrometry indicated that products **22** and **23** were isomers and that both had the molecular formula $C_{29}H_{49}NO$. The IR spectra of the two products exhibited bands assignable to their hydroxyimino group. The ^{1}H NMR spectra of products **22** and **23** exhibited a 3 H singlet at δ 3.31 and δ 3.08, respectively, assignable to the methoxy group. These spectroscopic results indicated that compounds **22** and **23** are the (*E*) and (*Z*) isomers of 1β-methoxy-4,4-dimethyl-5α-cholestan-3-one oxime. The *E* configuration was then assigned to oxime **22**, since the double doublet signal due to the 2α-H (δ 3.15) appeared considerably downfield of the corresponding signal of isomer **23**, owing to the deshielding by the hydroxyimino group.

An examination of the product mixture by TLC indicated that no lactams arising from a photo-Beckmann-type rearrangement were formed in this photoreaction.

Beckmann Rearrangement of a Mixture of (E)- *and* (Z)-*Cholest*-1-*en*-3-*one Oxime* (*Scheme 3*).—In a previous paper[6] we reported that the Beckmann rearrangement of a mixture of (*E*)- and (*Z*)-cholest-4-ene-3-one oximes **1** and **2** gave only the enone-type lactam, as had already been reported by Shoppee and colleagues.[7] A ground-state Beckmann rearrangement of cholest-1-en-3-one oximes has also been reported by Shoppee to produce an enone-type lactam, 4a-homo-4-aza-5α-cholest-1-en-3-one, **24**, exclusively.[7] In the present work we repeated the Beckmann rearrangement of cholest-1-en-3-one oximes by using a mixture of the (*E*)- and (*Z*)-isomer in order to confirm the regioselectivity of the ground-state rearrangement and to obtain lactam samples for product analysis in the photoreactions. Therefore, treatment of the 23:77 mixture of the (*E*)- and (*Z*)-oxime with thionyl dichloride in 1,4-dioxane at room temperature gave only 4a-homo-4-aza-5α-cholest-1-en-3-one **24** in poor yield, together with the recovered (*E*)-isomer, without any accompanying formation of an isomeric lactam, as indicated by TLC, and in accord with the results reported by Shoppee.[7]

7 + **8** —(i)→ **24**

Scheme 3 *Reagents and conditions:* i, $SOCl_2$, 1,4-dioxane, room temp.

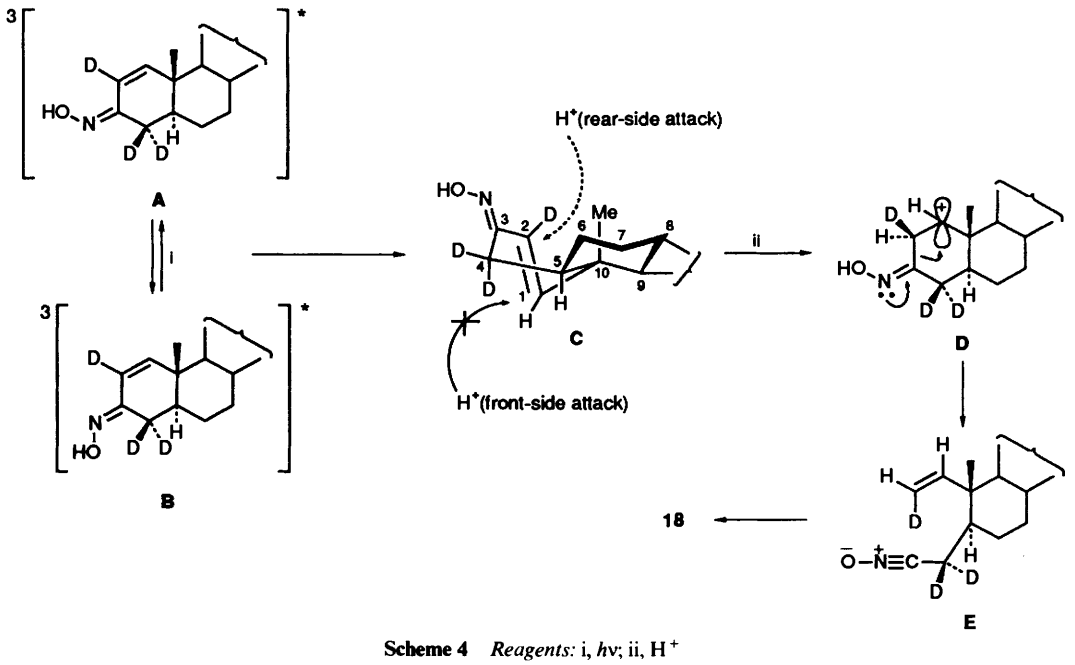
Pathways leading to Isoxazoles **14**, **17**, **18** *and* **21** *in the Photoreactions of Enone Oximes* **7**, **11** *and* **13** *in Methanol or Deuteriomethanol* (*Scheme 4*).—The pathways leading to isoxazoles, such as **14**, **17**, **18** and **21**, from the excited enone oximes **7**, **11** and **13**, are outlined in Scheme 4. Irradiation of the *A*-type oxime, such as **11**, in methanol generates singlet or triplet excited (*Z*) and (*E*) oximes **A** and **B** to give a *twisted ground-state intermediate* **C*** in which the C=C bond is twisted by more than 90°. The stereospecific protonation or deuteriation with either the hydroxyimino proton or with the protic solvent then takes place at C-2 of the reactive twisted intermediate **C** from the *rear side* to give carbocation **D**, since the front side is blocked by the ring. The source of the proton which is bonded to C-2 cannot be specified. It is, however, very likely that an intramolecular transfer of the hydroxyimino proton to C-2 will be a significant portion of the process as shown by the formation of the isoxazoline **14** in dry hexadeuteriobenzene (*vide supra*). A carbocation **D** in which the nitrogen lone pair on the C-2–C-3 bond is oriented in an appropriate geometry[11] for fragmentation may immediately give a nitrile oxide **E** by cleavage of the C-2–C-3 bond. An intramolecular stereospecific 1,3-dipolar addition[12] of nitrile oxide **E** may give the isoxazoline **18**. The carbocation **D** should be a very short-lived species since no methanol adduct **25** (*vide infra*, Scheme 5), expected to be derived from intermediate **D**, was formed.

As described previously in this paper, the isoxazoline **14** is formed even in aprotic solvents such as dry hexadeuteriobenzene. In a photorearrangement in dry hexadeuteriobenzene, the major portion of the protons which are bonded to C-2 of the twisted intermediate **C** should be supplied intramolecularly from the neighbouring hydroxyimino group in a stereospecific manner from the *rear side* of the twisted intermediate although some of the protons may also be supplied intermolecularly. No nitrile oxide intermediate **E** could be isolated in the present photorearrangement. We believe that the intramolecular 1,3-dipolar addition leading to isoxazoles such as **14** should be very easy, probably due to an appropriate geometry between the olefinic group and the nitrile oxide group in intermediate **E** for the intramolecular addition.

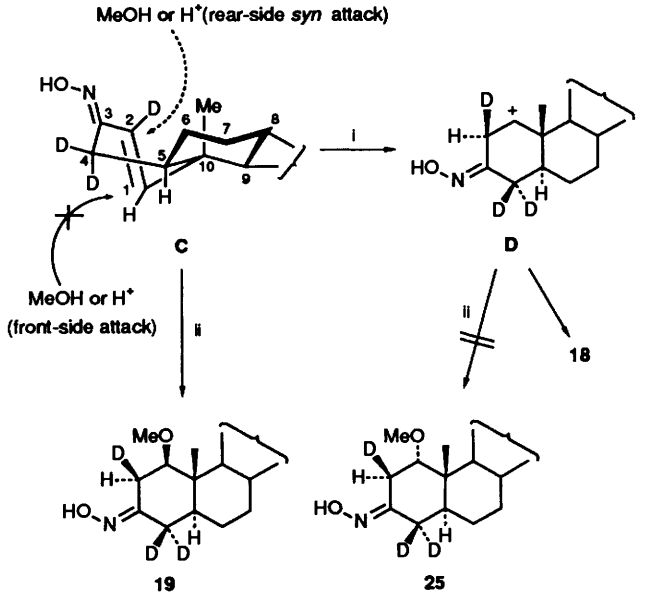
Pathways leading to Methanol Adducts **15**, **16**, **19** *and* **20** *in the Photoreactions of Enone Oximes* **7**, **9**, **11** *and* **13** *in Methanol or in Deuteriomethanol* (*Scheme 5*).—The foregoing deuterium-labelling experiments indicated that the addition of methanol is stereospecific; the proton and the methoxy group are attached to the α-position of C-2 and the β-position of C-1 of adducts **19** and **20**, respectively.

Although the formation of photoadducts between cycloalkenones and alcohols has been well documented,[13] to our knowledge the stereospecific formation of such photoadducts as

* This 'twisted intermediate' does not necessarily imply a *trans*-cyclohexene inferred from the results of flash photolysis[10] since a calculation indicated that the '*trans*-cyclohexene' in fused systems such as steroids possesses considerable strain to the extent that it is difficult to assume its existence. We, therefore, cannot exclude the possibility that intermediate **C** might be a twisted intermediate in the excited state.



Scheme 4 *Reagents:* i, *hν*; ii, H^+



Scheme 5 *Reagents:* i, H^+; ii, MeOH

15, **16**, **19** and **20** from excited cycloalkenone oximes and an alcohol is unprecedented.

There are two possible mechanisms for the formation of these methanol adducts (Scheme 5): (a) an addition of methanol to the carbocation **D** formed by protonation of the double bond in a highly strained, twisted, ground-state intermediate **C**, and (b) a nucleophilic addition of methanol to the reactive twisted double bond of a ground state intermediate **C**.* The formation of 1β-methoxysteroids indicates that the methanol adducts are formed through the latter path, since the addition by the former route may lead to more stable 1α-methoxysteroids, **25**, instead of the 1β-methoxysteroids **19** found in the present experiments. Hence, the stereochemistry of the present photoaddition of methanol to the cycloalkenone oximes, as disclosed by deuterium labelling, indicates that adducts such as **19** and **20** are formed by a *syn* addition to the twisted double bond of the ground-state intermediate **C** from the *rear side* as outlined in Scheme 5, since the front side is sterically shielded by the ring. A similar stereospecific photoaddition of alcohols to fused cyclohexenones has been reported by Hart and colleagues.[13b] The protonation leading to the carbocation **D** and the addition of methanol leading to adduct **19** take place competitively. It seems very likely that carbocation **D** rapidly fragments to give nitrile oxide **E** before it is trapped by methanol to give adduct **25**.

Finally, the foregoing results show that the dimethyl substituents attached to C-4 of enone oximes **7** and **8** had little effect on the products, their yields, or the stereochemistry of the reaction.

Experimental

M.p.s were determined with a Yanagimoto m.p. apparatus and are uncorrected. IR spectra were determined for Nujol mulls (unless stated otherwise) with either an Hitachi 285 grating infrared spectrophotometer or a JASCO IR 810 infrared spectrophotometer. ^{1}H NMR spectra were determined with either a JEOL PS100 high-resolution spectrometer operating at 100 MHz or a JEOL JNM-GX 270 FT high-resolution spectrometer operating at 270 MHz (δ_H) (solvent $CDCl_3$; $SiMe_4$ as internal reference) unless stated otherwise. *J* Values are given in Hz. Mass spectra were determined either with a JEOL JMS-D 300 or JMS-O1SG-2 spectrometer (70 eV). Elemental analyses were performed by the Faculty of Pharmaceutical Sciences of this University. PLC was carried out on a Merck silica gel 60 PF_{254} unless otherwise stated. Column chromatography was carried out with silica gel 60.

(E)-*Cholest*-1-*en*-3-*one Oxime* **8**.—Cholest-1-en-3-one **4** (2.7 g), hydroxylamine hydrochloride (3.2 g) and sodium acetate trihydrate (3.2 g) were stirred in ethanol (200 cm^3) for 15 h. The usual work-up of the solution gave a crude 14:86 mixture of (*Z*) and (*E*) oximes **7** and **8**. The mixture was recrystallized from acetone–methanol to give pure (*E*)-oxime **8** (2.5 g), m.p. 139–141 °C (lit.,[7] 149–150 °C); ν_{max}/cm^{-1} 3246 (OH), 1714 (C=N), 967 and 762; λ_{max}(MeOH)/nm 241 (ε 26 600); δ_H(400 MHz) 0.68 (3 H, s, 18-H_3), 0.87 (3 H, s, 19-H_3), 2.73 (1 H, d, *J* 10.3, 4-H), 2.93 (1 H, d, *J* 10.3, 4-H), 5.99 (1 H, d, *J* 10.2, 2-H) and 6.39 (1 H, d, *J* 10.2, 1-H); *m/z* (rel. int.) 399 (M^+, 31.7%), 384 [$(M - CH_3)^+$, 15.6], 382 [$(M - OH)^+$, 100] and 301 (20.9).

* See footnote on preceding page.

Photochemical Isomerization of (E)-*Cholest-1-en-3-one Oxime* **8** *to the* (Z)-*Isomer* **7**.—(*E*)-Oxime **8** (560 mg) in methanol (400 cm^3) was irradiated for 1 h under nitrogen. The solvent was removed, and the product subjected to PLC (Merck silica gel 60 PF_{254} containing gypsum) with benzene–diethyl ether (6:1) to give a 23:77 mixture of the (*Z*)- and (*E*)-oxime. This ratio does not imply the ratio in the photostationary state. The mixture was subjected to Beckmann rearrangement.

Beckmann Rearrangement of the Mixture of (Z)- *and* (E)-*Cholest-1-en-3-one Oximes* **7** *and* **8**.—The above mentioned mixture (388 mg) was dissolved in 1,4-dioxane (10 cm^3). To this solution was added thionyl dichloride (0.2 mg). The solution was stirred for 20 min at room temperature and then worked up in the usual manner. The product was subjected to PLC (Merck silica gel 60 PF_{254} containing gypsum) with benzene–diethyl ether (6:1) to give two fractions. The more mobile fraction was the recovered (*E*)-oxime **8** (240 mg). The less mobile fraction (26 mg) was recrystallized from acetone to yield 4a-homo-4-azacholest-1-en-3-one **24**, m.p. 219–222 °C [lit.,[7] double m.p. 253–255 °C and 276–278 °C (decomp.)]; ν_{max}/cm^{-1} 3170 (NH), 1665, 1640, 1594 (CH=CHCONH) and 828; λ_{max}(MeOH)/nm 212 (2900); δ 0.67 (3 H, s, 18-H_3), 0.99 3 H, s, 19-H_3), 2.65 (1 H, dd, *J* 13.6 and 17, 4a-H), 3.11–3.49 (1 H, m, 4a-H) and 6.65 (1 H, br s, NH); *m/z* (rel. int.) 399 (M^+, 100%), 384 [$(M - CH_3)^+$, 14.3], 370 (31.4), 137 (45.1) and 124 (54.0).

Photoreaction of Cholest-1-en-3-one Oximes **7** *and* **8**.—(a) *In methanol.* A mixture of (*Z*)- and (*E*)-cholest-1-en-3-one oximes, **7** and **8** (110 mg, 0.28 mmol), in methanol (60 cm^3) was placed in a quartz tube. The solution was flushed with nitrogen and then irradiated with a low-pressure Hg arc in a Rayonet RPR photochemical reactor for 10 h under nitrogen at 20–25 °C. After removal of the solvent under reduced pressure, the product was subjected to PLC [silica gel; (4:1) benzene–diethyl ether] to give four products (**A**, **B**, **C** and **D**, in order of their mobility on TLC).* Product **A** (28 mg, 26%) was parent enone **4**. Product **B** was *isoxazole derivative* **14** (22 mg, 20%), m.p. 111–112 °C (from MeOH–acetone); ν_{max}/cm^{-1} 1710 (C=N) and 802; δ_H(500 MHz) 0.652 (3 H, s, 18-H_3), 0.746 (3 H, s, 19-H_3), 3.34 (1 H, ddd, *J* 10.38, 12.82 and < 1, 1α-H), 3.833 (1 H, dd, *J* 8.24 and 12.82, 5'β-H) and 4.335 (1 H, dd, *J* 8.24 and 10.38, 5'α-H); *m/z* 399 (M^+, 100%), 384 [$(M - Me)^+$, 27.6], 371 (41.2), 370 (21.2), 150 (35.0), 137 (53.4) and 111 (50.4) (Found: C, 81.0; H, 11.3; N, 3.3. $C_{27}H_{45}NO$ requires C, 81.14; H, 11.35; N, 3.51%).

Product **C** was (Z)-1β-*methoxy-5α-cholestan-3-one oxime* **15** (6 mg, 5%), m.p. 155–157 °C (from MeOH–acetone); ν_{max}/cm^{-1} 3210 (OH), 1656, 1212, 1095 and 957; δ_H(270 MHz) 0.66 (3 H, s, 18-H_3), 0.80 (3 H, s, 19-H_3), 2.93 (1 H, dd, *J* 5.5 and 10.63, 1α-H), 3.31 (3 H, s, OMe) and 3.66 (1 H, dd, *J* 5.5 and 14.7, 2α-H); *m/z* 431 (M^+, 7%), 399 [$(M - MeOH)^+$, 27], 382 (49), 84 (92) and 70 (100) (Found: M^+, 431.3734. $C_{28}H_{49}NO_2$ requires *M*, 431.3763).

Product **D** was (E)-1β-*methoxy-5α-cholestan-3-one oxime* **16** (9 mg, 8%), m.p. 154–156 °C (from MeOH–acetone); ν_{max}/cm^{-1} 3220 (OH), 1650, 1212, 1095 and 970; δ_H(270 MHz) 0.66 (3 H, s, 18-H_3), 0.90 (3 H, s, 19-H_3), 2.13 (1 H, dd, *J* 9.53 and 14.7, 2β-H) 2.65 (1 H, dd, *J* 5.5 and 14.7, 2α-H), 2.80 (1 H, dd, *J* 3.8 and 15.4, 4α-H), 2.98 (1 H, dd, *J* 5.5 and 9.53, 1α-H) and 3.27 (3 H, s, OMe); *m/z* 431 (M^+, 6.5%), 399 [$(M - MeOH)^+$, 28], 382 (47), 84 (95) and 70 (100) (Found: M^+, 431.3783).

(b) *In* CD_3OD.—A mixture of (*Z*) and (*E*) oximes **7** and **8** (40 mg, 0.10 mmol) in CD_3OD (11 cm^3) in a quartz tube was irradiated for 12 h under nitrogen as mentioned above. After removal of the solvent under reduced pressure, the product was subjected to PLC, as described above, to give the parent ketone **4** (12 mg, 38% based on the consumed oximes), the monodeuterioisoxazole **17** (4 mg, 12%), and the starting oximes **7** and **8** (7 mg recovery).

Monodeuterioisoxazole **17** had δ_H(270 MHz) 3.82 (1 H, d, *J* 12.7, 4'α-H) and 3.34 (1 H, d, *J* 12.7, 5'β-H); *m/z* 400 (M^+, 100%), 383 (29) and 368 (19) (Found: M^+, 400.3577. $C_{27}H_{44}DNO$ requires *M*, 400.3564).

(c) *In hexadeuteriobenzene.* Oximes **7** and **8** (50 mg, 0.125 mmol) in hexadeuteriobenzene (Merck, art. 1789; 99.5%; 10 cm^3) contained in a quartz tube were irradiated for 20 h under nitrogen as mentioned above. The usual work-up of the photolysed solution and purification of the products gave the parent enone **4** (11 mg, 23%) and the isoxazole **14** (9 mg, 18%).

(d) *In methanol saturated with oxygen.* A solution of oximes **7** and **8** (50 mg, 0.125 mmol) in methanol (15 cm^3) was bubbled with oxygen and irradiated for 9 h as mentioned above. Work-up of the photolysed solution and purification of the products gave the parent enone **4** (19 mg, 39%). No isoxazole **14** was obtained.

[2,4,4-$^2H_3$]*Cholest-1-en-3-one* **5**.[8]—Sodium (41 mg) was dissolved in [^2H]ethanol (EtOD) (10 cm^3) under nitrogen. To this solution was added dropwise a solution of cholest-1-en-3-one **4** (390 mg) in dry diethyl ether (4 cm^3). The solution was stirred at room temperature for 50 h, and then neutralized with glacial acetic acid (0.2 cm^3). After removal of precipitates by filtration, the solvent was evaporated off to give crystals, which were dissolved in dichloromethane. After filtration of the solution, the solvent was removed under reduced pressure to give trideuteriocholest-1-en-3-one **5**;[8] ν_{max}/cm^{-1} 1713 and 1680 (CH=CDC=O); δ_H(100 MHz) 0.69 (3 H, s, 18-H_3), 1.00 (3 H, s, 19-H_3) and 7.14 (1 H, s, 1-H); *m/z* 387 (M^+, 46.1%), 343 [$(M - CD_2{=}C{=}O)^+$, 25.2] and 300 (27.6).

[2,4,4-$^2H_3$]*Cholest-1-en-3-one Oximes* **11** *and* **12**.—To a solution of [2,4,4-$^2H_3$]cholest-1-en-3-one **5** (250 mg) in ethanol (20 cm^3) were added solutions of hydroxylamine hydrochloride (230 mg) in ethanol (1 cm^3) and sodium acetate (230 mg) in ethanol (1 cm^3) as well as water (1 cm^3). The reaction solution was stirred for 20 h at room temperature, and then poured into water (200 cm^3). The resultant crystals were collected by filtration (246 mg, 82%). Recrystallization from methanol–acetone gave an analytical specimen; ν_{max}/cm^{-1} 3200 (OH) and 950; δ_H(100 MHz) 0.68 (3 H, s, 18-H_3), 0.87 (3 H, s, 19-H_3) and 6.42 (1 H, s, 1-H); *m/z* 402 (M^+, 33.1%) and 385 [$(M - OH)^+$, 100].

Photoreaction of [2,4,4-$^2H_3$]*Cholest-1-en-3-one Oxime* **11**.—Photolysis of trideuterio oxime **11** (298 mg) in methanol (180 cm^3) was carried out as described for cholest-1-en-3-one oximes **7** and **8**. The solution was irradiated for 10 h. Work-up of the solution and separation of the products were as described for oximes **7** and **8**, giving [2,4,4-$^2H_3$]cholest-1-en-3-one **5** (47 mg, 16%), trideuterioisoxazole derivative **18** (50 mg, 17%) and a 1:1.2 mixture of (*Z*)-1β-methoxy-[2β,4,4-$^2H_3$]cholestan-3-one oxime **19** and its (*E*)-isomer **20** (26 mg, 8%). Product **18**; δ_H(200 MHz) 0.65 (3 H, s, 18-H_3), 0.74 (3 H, s, 19-H_3), 3.35 (1 H, d, *J* 10.25, 1α-H) and 4.33 (1 H, d, *J* 10.25, 5'α-H).

The mixture of products **19** and **20** had δ_H(400 MHz) 0.66 (3 H, s, 18-H_3 of **19** and **20**), 0.90 (3 H, br s, 19-H_3 of **19** and **20**), 2.63 (d, *J* 5.4, 2α-H of **20**), 2.92 (d, *J* 5.4, 1α-H of **19**), 2.97 (d, *J* 5.4, 1α-H of **20**), 3.64 (d, *J* 5.4, 2α-H of **19**), 3.26 (s, 1β-OMe of **19**) and 3.31 (s, 1β-OMe of **20**).

4,4-*Dimethyl-5α-cholest-1-en-3-one* **6**.[9]—This ketone was prepared according to the reported procedure. M.p. 90–91 °C

* Note that these products do *not* correspond to the intermediate species shown in Schemes 4 and 5.

(from MeOH–acetone) (lit.,[9a] 85–86 °C; lit.,[9b] 90–91 °C); δ_H(270 MHz) 0.69 (3 H, s, 18-H_3), 1.07 (3 H, s, 4-Me), 1.08 (3 H, s, 4-Me), 1.13 (3 H, s, 19-H_3), 5.86 (1 H, d, *J* 10.3, 2-H) and 7.09 (1 H, d, *J* 10.3, 1-H); *m/z* 412 (M^+, 100%), 397 [(Me − Me)$^+$, 18] and 299 (26.0).

(E)-4,4-*Dimethyl*-5α-*cholest*-1-*en*-3-*one Oxime* **13**.—A mixture of enone **6** (380 mg, 0.92 mmol), hydroxylamine hydrochloride (330 mg, 4.8 mmol), and sodium acetate (227 mg, 2.8 mmol) in ethanol (15 cm^3) was heated under reflux for 2 h. The solution was then worked up in the usual way to give a crude oxime, which was subjected to PLC [silica gel; (10:1) benzene–diethyl ether] to give pure oxime **13** (326 mg, 83%), m.p. 196–197 °C (from acetone); ν_{max}/cm^{-1} 3198 (OH); δ_H 0.67 (3 H, s, 18-H_3), 1.01 (3 H, s, 19-H_3), 1.13 (3 H, s, 4-Me), 1.20 (3 H, s, 4-Me), 6.45 (1 H, d, *J* 10.6, 2-H) and 6.71 (1 H, d, *J* 10.6, 1-H); *m/z* 427 (M^+, 100%), 412 [(M − Me)$^+$, 45], 315 (12), 247 (8) and 113 (54); λ_{max}(MeOH)/nm 263 (13 600) (Found: C, 81.2; H, 11.6; N, 3.2. $C_{29}H_{49}NO$ requires C, 81.44; H, 11.55; N, 3.28%).

Photoreaction of (E)-4,4-*Dimethyl*-5α-*cholest*-1-*en*-3-*one Oxime* **13**.—A solution of oxime **13** (118 mg, 0.275 mmol) in methanol (60 cm^3) in a quartz vessel was flushed with nitrogen. The solution was then irradiated with a low-pressure Hg arc in a Rayonet photochemical reactor for 5 h under nitrogen. Evaporation of the solvent with the aid of a rotary evaporator gave a residue. The product was subjected to PLC [(4:1) benzene–diethyl ether] to give fractions **A**–**E** * in order of their mobilities on a TLC plate. The most mobile fraction, **A** (R_f 0.73) (27 mg, 24%), was the *isoxazole* **21**, m.p. 156–157 °C (from acetone); ν_{max}/cm^{-1} 1620 (C=N); δ_H(270 MHz) 0.64 (3 H, s, 18-H_3), 0.90 (3 H, s, 19-H_3), 1.16 (3 H, s, 3-Me), 1.21 (3 H, s, 3-Me), 3.44 (1 H, dd, *J* 11.7 and 10.6, 4′α-H), 3.84 (1 H, dd, *J* 8.2 and 11.7, 5′β-H) and 4.38 (1 H, dd, *J* 8.2 and 10.6, 5′α-H); *m/z* 427 (M^+, 29.4%), 410 (30.0), 301 (16.4), 109 (46.4), 95 (65.8), 55 (78.3) and 43 (100) (Found: C, 81.3; H, 11.4; N, 3.1. $C_{29}H_{49}NO$ requires C, 81.44; H, 11.55; N, 3.28%).

The next mobile fraction, **B** (28 mg, 23%) (R_f 0.67), was (E)-1β-*methoxy*-4,4-*dimethyl*-5α-*cholestan*-3-*one oxime* **22**, m.p. 169–170 °C (from acetone); ν_{max}/cm^{-1} 3275 (OH), 1081 and 920; δ_H(270 MHz) 0.65 (3 H, s, 18-H_3), 0.96 (3 H, s, 19-H_3), 1.09 (3 H, s, 4-Me), 1.07 (3 H, s, 4-Me), 2.42 (1 H, dd, *J* 13.9 and 8.1, 2β-H), 2.98 (1 H, dd, *J* 8.1 and 5.5, 1α-H), 3.15 (1 H, dd, *J* 13.9 and 5.5, 2α-H) and 3.31 (3 H, s, OMe); *m/z* 459 (M^+, 41.1%), 442 [(M − OH)$^+$, 7.5], 427 [(M − MeOH)$^+$, 58.8], 410 [(M − MeOH − OH)$^+$, 48.8], 127 (47.3), 55 (84.6) and 43 (100) (Found: M^+, 459.4064. $C_{30}H_{53}NO_2$ requires *M*, 459.4076).

The third mobile fraction, **C** (R_f 0.67) (15 mg, 12%), was (Z)-*oxime* **23**, m.p. 164–166 °C (from acetone); ν_{max}/cm^{-1} 3275 (OH), 1080 and 940; δ_H(270 MHz) 0.72 (3 H, s, 18-H_3), 1.02 (3 H, s, 19-H_3), 1.12 and 1.15 (each 3 H, each s, 4,4-dimethyl), 2.74 (3 H, m, 1α-, 2α- and 2β-H) and 3.08 (3 H, s, OMe); *m/z* 459 (M^+, 22.6%), 443 (29.9), 427 [(M − MeOH)$^+$, 30.5], 410 [(M − MeOH − OH)$^+$, 36.3], 305 (70.2), 247 (32.3), 122 (61.3), 85 (85.8), 59 (100) and 43 (82.5) (Found: M^+, 459.4055).

Fraction **D** (R_f 0.3) (6.1 mg, 6%) was the parent enone. The most polar fraction (6 mg) was the recovered oxime.

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* See footnote on preceding page.