Photochemistry of 3ζ,5ζ-Epoxycholestan-6-ones

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The photolysis of α-oxo-oxetanes appears to be controlled in part by stereoelectronic factors which require coplanarity of the α-cleaved oxetane bond with the singly or doubly occupied carbon p-orbital of the n,π* carbonyl group and the zwitterionic character of the initial bond cleaved species may be important.

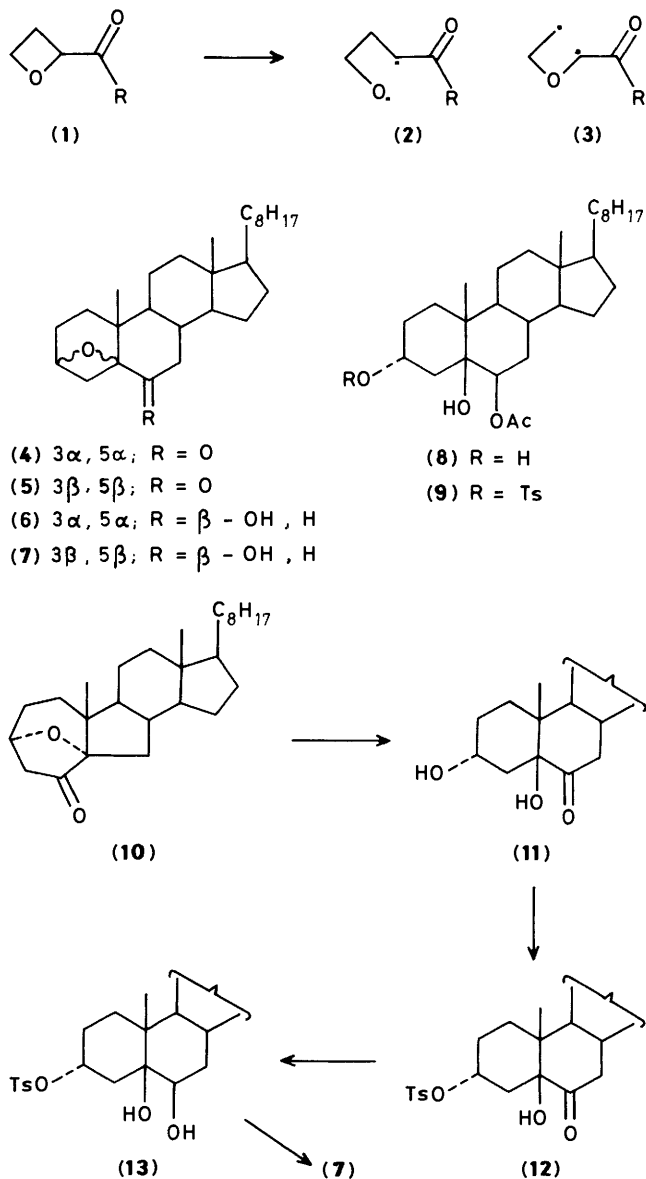Although the photorearrangement of α,β-epoxy ketones to β-dioxo compounds is well known,[1,2] there has been little investigation of the photochemistry of α-oxo-oxetanes (1).[2,3] In general, the products obtained appear to be derived from the biradicals (2) or (3) arising from oxetane C–O or C–C bond cleavage respectively. We report here the photochemistry of 3ξ,5ξ-epoxycholestan-6-ones (4) and (5), which demonstrates the importance of stereoelectronic effects in these cleavages in common with those observed in the photochemistry of β,γ-epoxy ketones.[4]

The 3α,5α-epoxy 6-ketone (4)[5] and its 3β,5β-isomer (5) were prepared respectively by oxidation of the 3α,5α-epoxy-6β-hydroxy compound (6)[6] and the 3β,5β-isomer (7). The 3β,5β-epoxy-6β-hydroxy compound (7) was prepared from the 6β-acetoxy 3α,5β-diol (8)[5] *via* the tosylate (9) or from the 3α,5α-epoxy-A-homo-B-nor 4a-ketone (10)[5,7] *via* the 3α,5β-dihydroxy 6-ketone (11)[7] as shown in Scheme 1. Photolysis of the 3α,5α-epoxy 6-ketone (4) in benzene gave one major and a number of minor products. The major product was assigned structure (14) on the basis of its spectroscopic data. In particular, the i.r. spectrum confirmed the presence of the aldehyde ($v_{max.}$ 2725 and 1 726 cm^{-1}) and the α,β-unsaturated ketone ($v_{max.}$ 1 694 and 1 604 cm^{-1}). The ^{1}H n.m.r. spectrum also indicated the presence of an aldehyde (δ 9.71), and a methylenecyclohexanone (δ 5.81 and 5.04). Compound (14), which was relatively unstable, was transformed immediately by successive NaBH$_4$ reduction and acetylation into the acetoxy ketone (16). The reduction of the double bond of (14) is unremarkable but the failure of the intermediate hydroxy ketone (15) to be reduced was somewhat surprising. That the ketone carbonyl group was intact in the end product (16) was evident from the i.r. spectrum ($v_{max.}$ 1 717 and 1 746 cm^{-1}) and the mass spectrum which showed the molecular ion at m/z 446. The loss of the fragment CH$_3$CO$_2$(CH$_2$)$_3$ giving rise to an important peak at m/z 345 further confirmed the assigned structure.

Photolysis of the 3β,5β-epoxy 6-ketone (5) over an extended period (up to 26 h) gave no significant decomposition or rearrangement products, and the starting material was largely recovered.
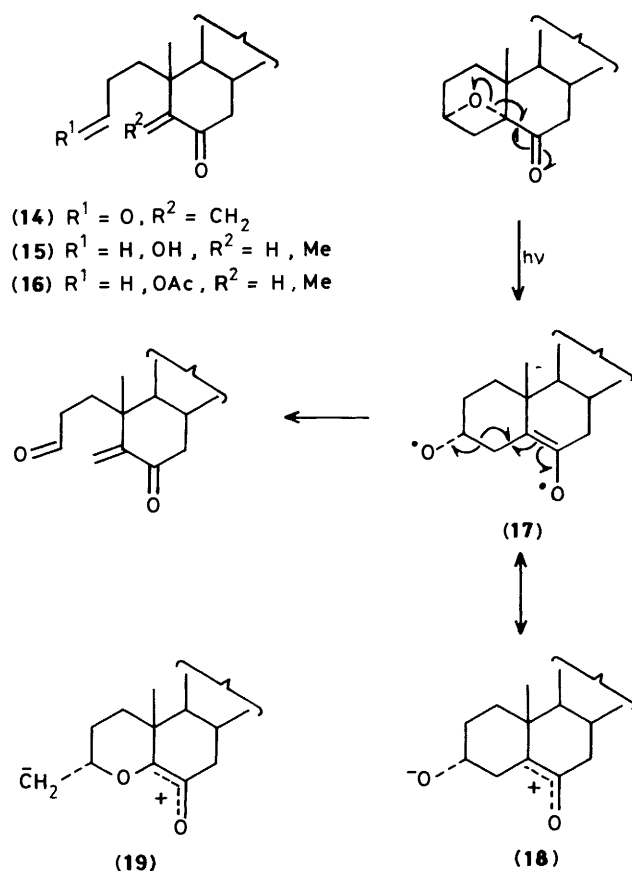
Discussion

The Paterno-Büchi photoaddition of carbonyl compounds with alkenes is well known[8] and in those cases where α-oxo-oxetanes are the primary products these may undergo secondary transformations.[2] The secondary transformations are generally thought to involve radicals formed by oxetane C–O or C–C bond cleavage [cf. (2) and (3)]. The formation of compound (14) may be rationalised through the biradical (17) as indicated in Scheme 2. The failure of the 3β,5β-epoxy 6-ketone (5) to react in a similar manner suggests that stereoelectronic effects may be important. It is assumed that n,π* excitation of the carbonyl group occurs and that the excited state will have a planar

(1) → (2) (3)
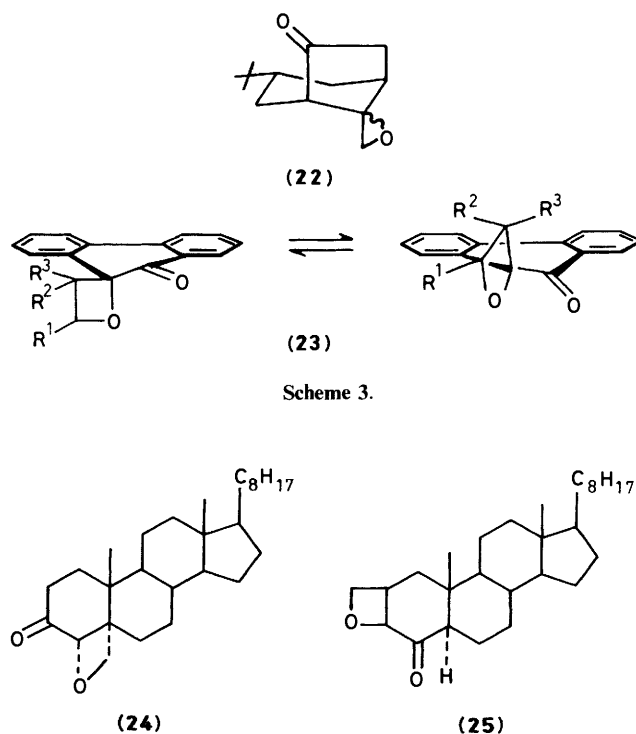

(4) 3α, 5α; R = O
(5) 3β, 5β; R = O
(6) 3α, 5α; R = β - OH , H
(7) 3β, 5β; R = β - OH , H

(8) R = H
(9) R = Ts

(10) (11)

(13) (7) (12)

Scheme 1.

structure with radical or anionic character at the carbonyl carbon atom.[9] Models show that in the 3α,5α-epoxy 6-ketone (4) the oxetane C(5)–O bond is in the same plane as the singly or doubly occupied p-orbital at C-6 whereas in the 3β,5β-epoxy 6-ketone (5) the C(5)–C(4) bond is similarly arranged [see (20) and (21)]. In radical β-scission, the requirement of coplanarity

(14) R^1 = O, R^2 = CH_2
(15) R^1 = H, OH, R^2 = H, Me
(16) R^1 = H, OAc, R^2 = H, Me

(17)

(19)

(18)

Scheme 2.

(20)

(21)

(22)

(23)

Scheme 3.

(24)

(25)

(25)[3b] the C(3)–O bond and the p-orbital at C-4 may be satisfactorily aligned for cleavage given the flexibility of the A ring.

of the singly occupied p-orbital with the bond to be broken is well established[10] and we conclude that there is a similar requirement for oxetane C–O bond cleavage in the n,π* excited state of the α-oxo-oxetanes. The absence of cleavage of the stereoelectronically aligned C(5)–C(4) bond in the 3β,6β-epoxy 6-ketone (5) may reflect the partial anionic character of the carbonyl carbon in the excited state thereby suggesting that the initially cleaved species has a contribution from a zwitterionic form (18). Stabilisation of this species would be expected to be greater than in the carbanionic equivalent (19). A similar zwitterionic species to (18) has been proposed as being significant in the photolysis of the β,γ-epoxy ketone (22) although no stereoelectronic effect was observed.[11] In the photolysis of the oxo-oxetanes (23) both oxetane C–C and C–O bond cleavage are observed.[2] Conceivably benzylic stabilisation facilitates the C–C bond cleavage presuming the required stereoelectronic factors can be accommodated. Models suggest that this is so owing to the flexibility of the non-aromatic six-membered ring (Scheme 3). The observed [3a] loss of formaldehyde during the photolysis of the 3-oxo-oxetane (24) is consistent with the suggested stereoelectronic control since the C(4)–O bond of the oxetane may readily achieve coplanarity with the p-orbital at C-3 in the n,π* excited state. Similarly, in the 3-oxo-oxetane

Experimental

Solutions were dried over anhydrous magnesium sulphate and solvents were removed under reduced pressure on a rotary evaporator. Plates (0.75 mm) of Kieselgel PF254 (Merck) were used for p.t.l.c. I.r. spectra were determined with a Perkin-Elmer 177 spectrophotometer and ¹H n.m.r. spectra were determined at 90 MHz, for solutions in deuteriochloroform, using a Perkin-Elmer R32 spectrometer. Mass spectra were determined using a Kratos MS80 spectrometer. Rotations were determined for solutions in chloroform with a Bendix polarimeter 143C. Photolyses were carried out in degassed solutions under nitrogen using a 125 W medium-pressure mercury lamp in a Hanovia water-cooled photoreactor. Light petroleum refers to the fraction b.p. 40—60 °C.

3β,5-Epoxy-5β-cholestan-6β-ol (7).—(a) The 6β-acetoxy 3α,5β-diol (8) (2.3 g) was dissolved in pyridine (20 ml) and toluene-p-sulphonyl chloride (5 g) was added. The solution was allowed to stand at room temperature for 48 h after which ice was added and the resultant mixture was allowed to stand until the ice melted; it was then extracted with ether (×3). The combined ether extracts were washed with dilute HCl and water and then dried and evaporated. Recrystallisation of the resultant solid from light petroleum–ether gave the tosylate (9) (2.06 g, 67%), m.p. 133—135 °C; δ 7.5 (m, MeC₆H₄SO₃), 4.73 and 4.59 (m, 3β-H and 6α-H), 2.53 (s, MeC₆H₄SO₃), 2.06 (s, MeCO₂), 0.93 (s, 10β-Me), and 0.65 (s, 13β-Me). A solution of the tosylate (9) (100 mg) in dry DMF (3 ml) containing sodium hydride (4 mg) was stirred under an atmosphere of nitrogen at 70 °C for 4 h. The reaction mixture was poured into water, acidified with dilute HCl and extracted with ether (×2). The combined ether extracts were washed with water, dried, and evaporated. The crude product was purified by p.t.l.c., eluting with ether–light petroleum (6:4) to afford the oxetanol (7) (50

mg, 77%) m.p. 145—150 °C (from methanol); $[\alpha]_D$ +26.8° (*c* 4.2); $\nu_{max.}$ 3 440 cm^{-1} (OH); δ 4.45 (d, *J* 6 Hz, 3α-H), 3.85 (m, $W_{\frac{1}{2}}$ 4 Hz, 6α-H), 1.24 (s, 10β-Me), and 0.68 (s, 13β-Me) (Found: C, 80.6; H, 11.3. $C_{27}H_{46}O_2$ requires C, 80.55; H, 11.5%).

(*b*) The 3α,5β-dihydroxy 6-ketone (**11**) (475 mg) was converted into the tosylate (**12**)[12] as above. A solution of the tosylate (**12**) (330 mg) in THF (10 ml) at room temperature was treated with NaBH$_4$ (20 mg) and after 2 days the reaction mixture was diluted with water and extracted with ether ($\times$ 2). The combined ether extracts were washed with water, dried, and evaporated. The crude product was purified by p.t.l.c. eluting with ether–light petroleum (1:1) to afford the dihydroxy tosylate (**13**) (164 mg, 50%); δ 7.49 (m, MeC$_6$H$_4$SO$_3$), 4.7 (m, $W_{\frac{1}{2}}$ 16 Hz, 3β-H), 3.45 (m, $W_{\frac{1}{2}}$ 7 Hz, 6α-H), 2.42 (*Me*C$_6$H$_4$SO$_3$), 0.97 (s, 10β-Me), and 0.65 (s, 13β-Me). The dihydroxy tosylate (**13**) (82 mg) was converted as above into the hydroxy oxetane (**7**) (28 mg, 52%) which was isolated after p.t.l.c.

3β,5-*Epoxy*-5β-*cholestan*-6-*one* (**5**).—A solution of the oxetanol (**7**) (50 mg) in acetone (10 ml) at 0 °C was treated with Jones reagent (5 drops) over 5 min and then diluted with water and extracted with ether. The latter was worked up and the product crystallised from methanol to give the *oxo-oxetane* (**5**) (28 mg, 56%), m.p. 167—172 °C; $\nu_{max.}$ 1 715 cm^{-1} (C=O); δ 4.41 (d, *J* 7 Hz, 3α-H), 2.8 (t, *J* 7 Hz, 4β-H), 0.98 (s, 10β-Me), and 0.66 (s, 13β-Me) (Found: C, 80.8; H, 10.9. $C_{27}H_{44}O_2$ requires C, 80.95; H, 11.1%).

Photolysis of 3α,5-*Epoxy*-5α-*cholestan*-6-*one* (**4**).—A solution of the 3α,5α-epoxy 6-ketone (**4**) (50 mg) in dry benzene (130 ml) was irradiated for 2 h. Removal of the solvent gave the crude unsaturated oxo aldehyde (**14**); $\nu_{max.}$ 2 725 (CHO), 1 726 (CHO), 1 694 (α,β-unsaturated C=O), and 1 604 cm^{-1} (C=C); δ 9.71 (m, $W_{\frac{1}{2}}$ 3 Hz, CHO), 5.81 (m, $W_{\frac{1}{2}}$ 3 Hz, H$_2$C=C–C=O, H *cis* to C=O), and 5.04 (m, $W_{\frac{1}{2}}$ 3 Hz, H$_2$C=C–C=O, H *trans* to C=O) which was dissolved in dry THF (2 ml) and treated with a solution of NaBH$_4$ (5 mg) in ethanol (0.5 ml). After 45 min the solution was diluted with water and acidified with dilute acetic acid to pH 5. The resultant mixture was extracted with ether ($\times$ 2) and the combined ether extracts were

washed with saturated aqueous sodium hydrogen carbonate and water, dried, and evaporated to give the crude hydroxy ketone (**15**); $\nu_{max.}$ 3 400 (OH) and 1 704 cm^{-1} (C=O); δ 3.6 (m, C*H*$_2$OH), 0.65 and 0.68 (s, 10β-Me and 13β-Me), and 0.91 (d, *J* 7 Hz, 5-Me). Acetylation of the hydroxy ketone (**15**) with acetic anhydride and pyridine under the usual conditions and p.t.l.c., eluting with ether–light petroleum (4:6), gave 3-*acetoxy*-3,4-*seco*-5-*cholestan*-6-*one* (**16**) (21 mg, 38%); $\nu_{max.}$ 1 746 (AcO) and 1 717 cm^{-1} (ketone C=O); δ 4.04 (m, $W_{\frac{1}{2}}$ 10 Hz, C*H*$_2$OAc), 2.05 (s, MeCO$_2$), 0.91 (d, *J* 7 Hz, 5-Me), and 0.67 and 0.69 (s, 10β-Me and 13β-Me) [Found: $M^{+\cdot}$, 446.3760 and $(M - C_5H_9O_2)^+$, 345.3165 $C_{29}H_{50}O_3$ requires M, 446.3760 and $(M - C_5H_9O_2)$, 345.3157.]

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