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A STRIKING DIFFERENCE BETWEEN THE STEREOCHEMICAL COURSE OF THE PHOTOLYSIS OF 5-HYDROXY 6-OXO STEROIDS AND THEIR BICYCLIC ANALOGUES

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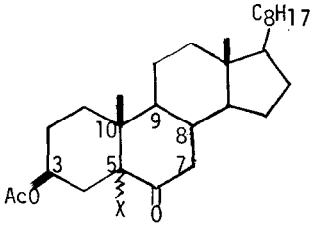
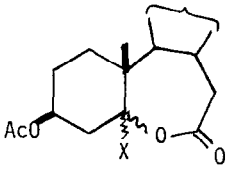
Abstract: While 5α- and 5β-hydroxy 6-oxo steroids undergo stereospecific photoisomerization, their bicyclic analogues give identical product mixtures on photolysis. This is attributed to equilibration of the intermediate acyl alkyl diradicals in the bicyclic case, which does not occur in the steroid case because of slowing of rotation about the C-9 - C-10 bond.

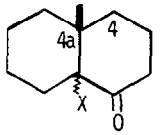
We have recently discussed the stereospecific photoisomerization of the steroidal α-ketols **1** and **2** to the lactones **3** and **4**, respectively, in benzene or ethanol.[1] We then reported that the bicyclic α-ketols **5** and **6** do not show this stereospecificity and now discuss the difference between the photochemistry of these and the steroidal α-ketols.



1 X = α-OH
2 X = β-OH

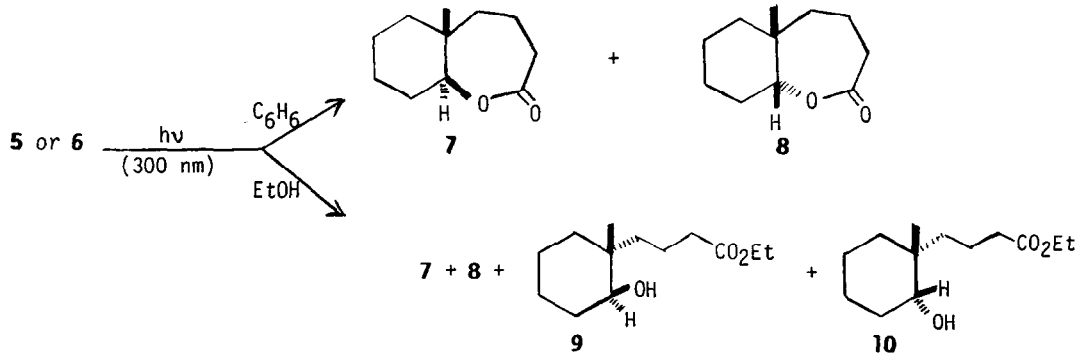


3 X = β-H
4 X = α-H



5 X = α-OH **11** X = α-H
6 X = β-OH **12** X = β-H

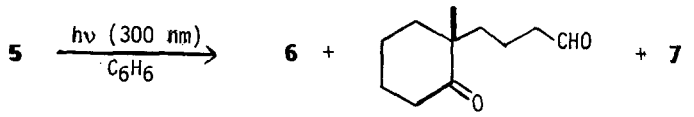
Compounds **5** and **6** in benzene both gave the lactones **7** and **8** in a 96:4 ratio (Scheme 1). In ethanol they gave **7** and **8** in essentially this ratio and the esters **9** and **10** also in this ra-



Scheme 1

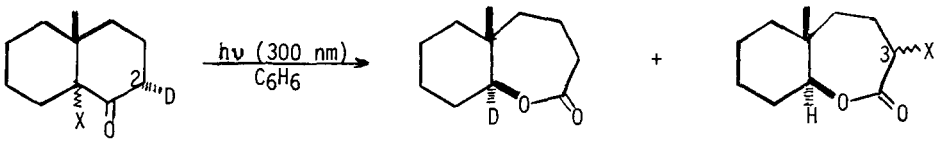
tio. The lactone/ester ratio was 43:57 in each case. The structures of the major products **7** and **9** were established by their elemental composition and ^{1}H and ^{13}C nmr spectra and by comparison with authentic samples obtained by Baeyer-Villiger oxidation of **11** and **12** and treatment of the resulting lactones with ethanol and Amberlite. The minor products **8** and **10** were identified by gc comparison with authentic samples. The product ratios were measured by gc.

That the ester **9** is a primary photochemical product and does not arise by ethanolysis of **7** was indicated by gc, which showed that **9** is formed early in the reaction and that the lactone/ester ratio remains constant throughout the photolysis and after further prolonged irradiation in ethanol. Irradiation of **5** in benzene for 0.5 hour (~10% of the time required for complete consumption) gave a photolysate whose ^{1}H nmr spectrum showed the presence of **6** and the keto aldehyde **13** in addition to **7** and unconsumed **5**. Gc monitoring showed that **6** and **13** each reached a maximum of ~20% of the volatile components of the photolysate in the early stages of the reaction.



13

Irradiation of the 2α-deutero ketols **14** and **15**[2] in benzene gave in each case a 27:60:13 mixture of deuterated lactones **16-18** as determined by ^{1}H nmr spectroscopy.

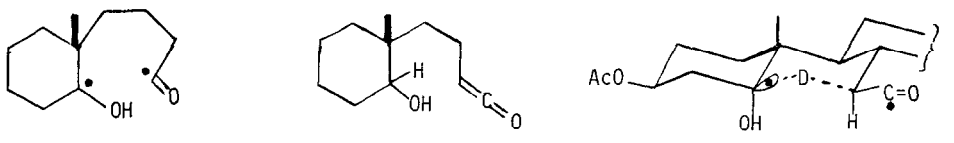


14 X = α-OH
15 X = β-OH

16

17 X = α-D
18 X = β-D

As for **1** and **2** the formation of the photoproducts isolated from **5** and **6** can be interpreted in terms of the intermediacy of acyl alkyl diradicals and ketenes of types **19** and **20**; the conversion of **5** to **6** and **13** can also occur via **19**.[3] Thus the lack of stereospecificity implies that the alkyl radical centre in **19**, unlike that in its steroidal analogue, does not retain its configuration in the course of hydrogen transfer to give **20**.[4]

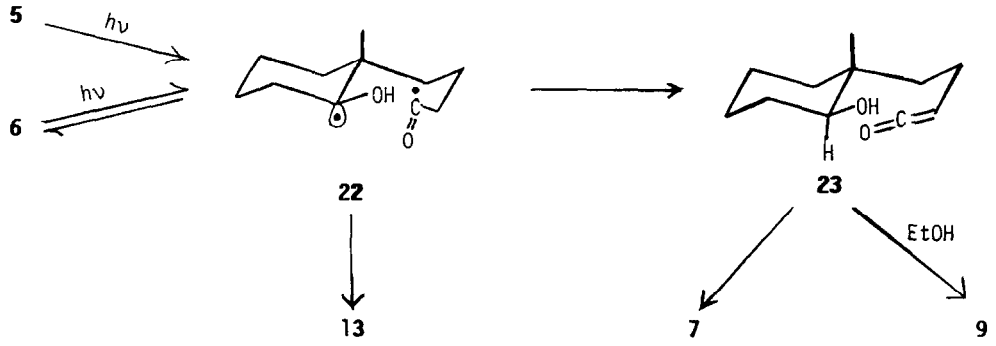


19 **20** **21**

A factor favouring the retention of configuration in the steroids is the non-planarity of the 1-hydroxycyclohexyl radical moiety.[5] This holds the electron-deficient alkyl radical orbital in an intermediate of type **19** in a favourable orientation for hydrogen abstraction to give a ketene of type **20**. A planar radical would not be so oriented and, further, should give a keto aldehyde via abstraction of the hydroxyl hydrogen by the acyl radical - a product not observed in the steroid series. However, this cannot be the critical factor since a diradical of type **19** formed from the bicyclic ketols would also have a non-planar 1-hydroxycyclohexyl radical moiety.

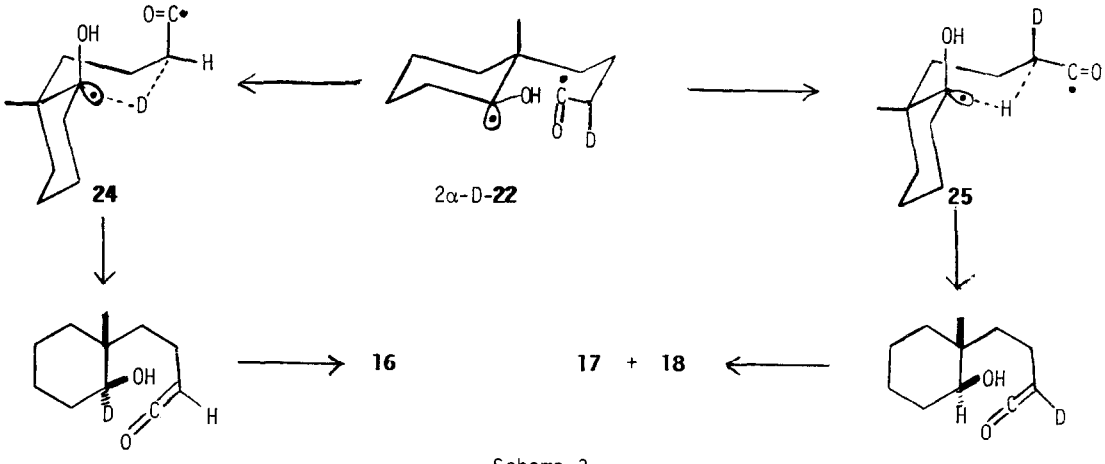
We postulate that the critical factor is the rate of hydrogen abstraction by this radical relative to ring[6] and radical centre inversion. For the steroidal ketols it is considered that hydrogen abstraction is faster because the CD ring system restricts rotational motion about the C-9 - C-10 bond in intermediates of type **19** and the C-5 radical centre and the acyl radical are held in close proximity. Clockwise rotation about the C-7 - C-8 bond of the incipient acyl radical would minimize eclipsing interactions[7] and to result in the approach of the 7α-hydrogen atom to the alkyl radical and thus account for the observed[1] exclusive transfer of the deuterium atom in the 7α-deutero steroidal ketols via transition states of type **21**. For the bicyclic ketols we consider that the rate of hydrogen abstraction leading to ketene formation is slower because of the greater flexibility of the acyl side chain in intermediates of type **19**. This results from a lower activation barrier to rotation about the C-4 - C-4a bond analogous to the C-9 - C-10 bond in the steroids. Hence equilibration of the 1-hydroxycyclohexyl radical moiety occurs prior to hydrogen abstraction and both ketols give the same products. Evidence supporting the postulate that the acyl side chains of the diradical intermediates in the bicyclic series have greater flexibility than those of the steroidal diradical intermediates comes from T_1 relaxation correlation times. Ester **9** and an analogous steroidal ester were used as models. The smaller NT_1 values for the carbons (N = no. of protons on the carbon) of the acyl side chain of the steroid relative to those of **9** confirm that its molecular motion is more hindered.[8]

The preponderant diradical is postulated to be **22**, giving the ketene **23**, which accounts for the high yield of lactone **7** relative to **8** (Scheme 2). Its preponderance is attributed to the equatorial placement of both the hydroxyl group and the acyl radical side chain. This proposal is in accord with the formation of **6** from **5** at an early stage and of **13**.[9] It is also concordant with the fact that the 2α-deutero ketols **14** and **15** give an identical mixture of the deuterated



Scheme 2

lactones **16-18**; the formation of these lactones can occur via transition states **24** and **25** derived from 2α-deutero-**22**.[10] The relative energies of these are expected to be similar since the acyl radical group is axial in **24** and equatorial in **25**, but the former is stabilized by hydrogen bonding. Thus reaction can proceed via both transition states to give a mixture of ketenes **26** and **27**, which give a mixture of **16** and **17/18**, respectively (Scheme 3).[11]



Scheme 3

The ratio of the 3-deutero lactones **17** and **18** (72:18) can be interpreted as involving steric approach control in a concerted reaction of the hydroxyl and ketene groups via a four-membered ring transition state. This is in contrast to the steroid ketols where hydroxyl labelling with deuterium gives results[1] that suggest product-development control in such a transition state. This can again be attributed to difference in the flexibility of the side chain - here the ketene side chain. This difference also accounts for the formation of hydroxy esters from **5** and **6**, but not **1** and **2**, on photolysis in ethanol.

Acknowledgements. We thank the Natural Sciences and Engineering Research Council of Canada for support and Imperial Oil Limited for the award of a Graduate Research Fellowship to S.S.

References and Notes

1. S. Stiver and P. Yates, Tetrahedron Lett., **25**, 3289 (1984).
2. Prepared by zinc and acetic acid-d reduction of a 2α-bromo-**5** and 2β-bromo-**6**, respectively. The stereochemistry of the deuterium introduced was established by ^{1}H nmr spectroscopy.
3. Cf., for example, P. Yates and R. O. Loutfy, Acc. Chem. Res., **8**, 209 (1975).
4. The stereospecifity for **1** and **2** is not dependent on the 3-acetoxy substituent.[1]
5. R. V. Lloyd, J. G. Causey, and F. A. Momany, J. Am. Chem. Soc., **102**, 2260 (1980); R. V. Lloyd and J. G. Causey, J. Chem. Soc., Perkin Trans. 2, 1143 (1981).
6. Cf. W. C. Agosta and S. Wolff, J. Am Chem. Soc., **99**, 3855 (1977); P. J. Wagner, Acc. Chem. Res., **16**, 461 (1983).
7. The direction of ring opening in α-cleavage reactions of cycloalkanones has been previously invoked to rationalize stereoselective hydrogen abstractions: J. Meinwald, R. A. Schneider, and A. F. Thomas, J. Am. Chem. Soc., **89**, 70 (1967); R. O. Duthaler and C. Ganter, Helv. Chim. Acta **59**, 415 (1976); P. J. Wagner and T. J. Stratton, Tetrahedron, **37**, 3317 (1981).
8. D. A. Wright, D. E. Axelson, and G. C. Levy, Topics C-13 NMR Spectros., **4**, 104 (1979).
9. Compound **13** is considered to undergo further reaction to give non-volatile products.
10. Transition states analogous to **24** and **25** are not possible in the steroidal systems.
11. The **26/27** ratio will also be affected by the deuterium isotope effect.

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