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SYNTHESIS AND PHOTOCHEMISTRY OF 5-HYDROXY-5β-CHOLEST-3-EN-6-ONE

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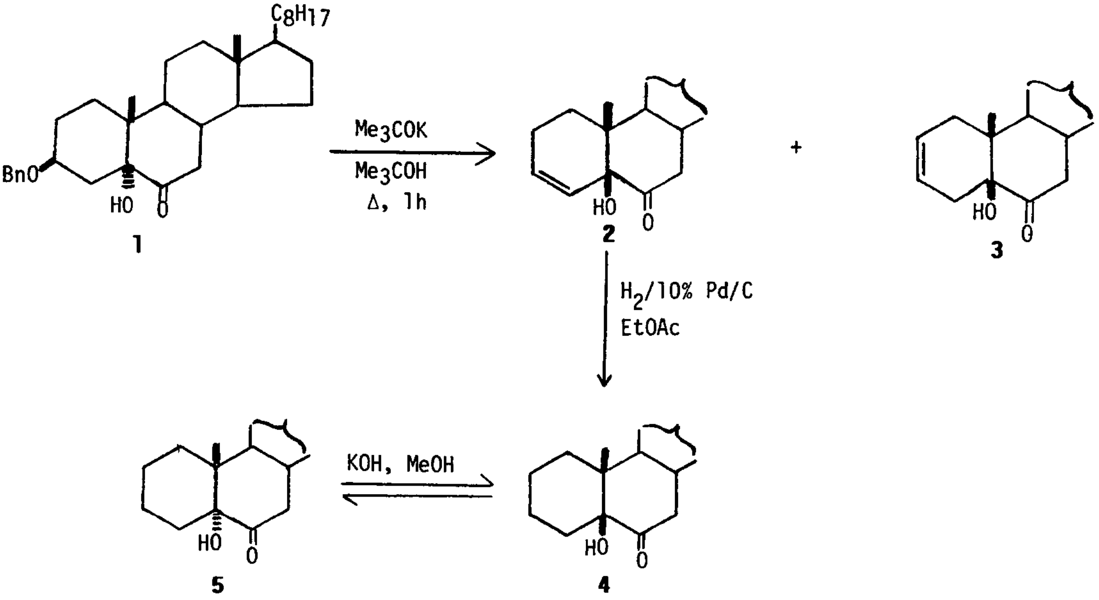
Abstract: Reaction of 3β-benzyloxy-5-hydroxy-5α-cholestan-6-one (**1**) with potassium t-butoxide in t-butyl alcohol gives 5-hydroxy-5β-cholest-3-en-6-one (**2**), which on direct irradiation (300 nm) in hexanes gives the B-seco steroid **9** and the indenacetaldehyde derivative **10**.

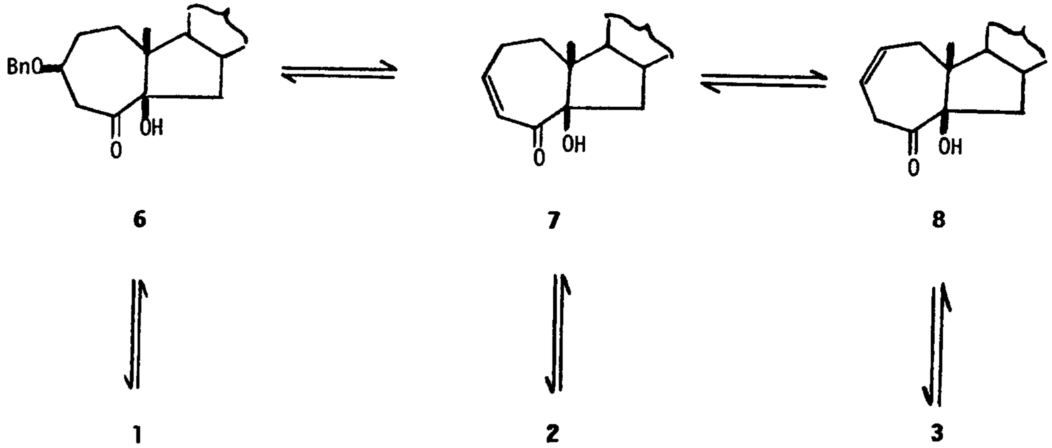
The photochemistry of β,γ-unsaturated ketones has been investigated extensively,[1] that of β,γ-unsaturated α-ketols less so,[2] presumably because of their greater rarity. Product formation on direct irradiation of β,γ-unsaturated ketones can be interpreted as involving α-cleavage and/or a concerted 1,3 acyl shift. The latter is considered to be the usual pathway for simple β,γ-unsaturated ketones, although stepwise processes involving α-cleavage have also been postulated.[1]

We have discovered that 5-hydroxy-5β-cholest-3-en-6-one (**2**) can readily be synthesized by treatment of 3β-benzyloxy-5-hydroxy-5α-cholestan-6-one (**1**) with potassium t-butoxide in t-butyl alcohol. It was isolated in 60% yield; a minor product (3%) was the Δ^2 isomer **3**. The structure of **2** was assigned on the basis of its spectra and its conversion on hydrogenation to 5-hydroxy-5β-cholestan-6-one (**4**), itself obtained by epimerization of its 5α isomer **5** with methnolic potassium hydroxide (Scheme 1).



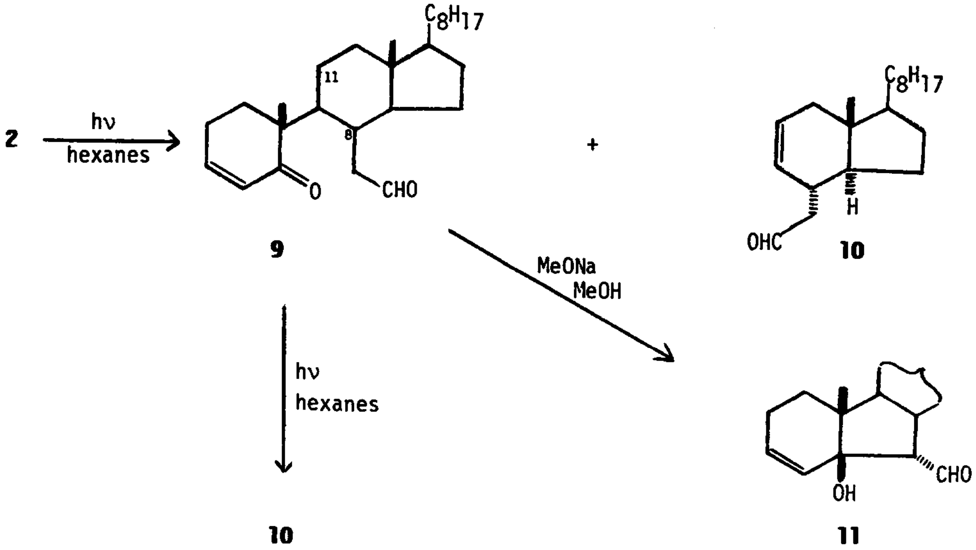
Scheme 1

5α-Hydroxy-6-keto steroids have long been recognized to equilibrate under basic conditions with their 5β counterparts.[3] Preference for the 5β epimers in these equilibria has been attributed to intramolecular hydrogen bonding in the latter. Consideration of the mechanism postulated[3] for such reactions leads to an interpretation of the origin of **2** and **3**. Base-catalyzed elimination of benzyl alcohol from the putative A-homo B-nor intermediate **6** would give **7**, which could then rearrange to **2**; **3** could also arise from **7** via equilibration with **8** (Scheme 2).



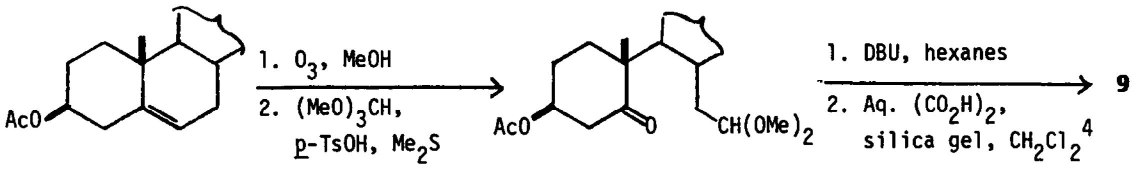
Scheme 2

Irradiation (300 nm) of **2** in hexanes gave the B-seco keto aldehyde **9** (40%) and the indenacetaldehyde derivative **10** (10%). Compound **10** was shown to be a secondary photoproduct by its formation on irradiation of **9** together with the B-nor aldehyde **11**. The latter was also formed



Scheme 3

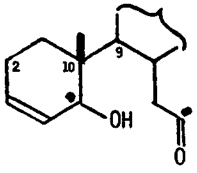
on treatment of **9** with methanolic sodium methoxide (Scheme 3). The structural assignments **9** - **11** are based on spectroscopic data and the independent synthesis of **9** from cholesteryl acetate (**12**) *via* **13** shown in Scheme 4.



12 **13**

Scheme 4

The formation of **9** from **2** can be interpreted in terms of initial α-cleavage to give the acyl alkyl diradical **14** followed by intramolecular hydrogen transfer.[5] Such transfer could occur from the hydroxyl group or C-2 in **14** or from C-4 in **15**, formed by ketonization of **14**; each of these processes involves an eight-membered ring transition state and we have demonstrated that the hydrogen transfer occurs exclusively from the hydroxyl group by the observation that irradiation of **2**-O-*d* gives **9** with deuterium incorporated only in the aldehyde group as in **16**.



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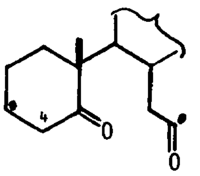

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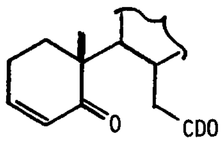

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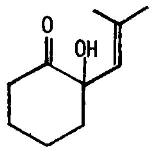
The formation of the α,β-unsaturated keto aldehyde **18** as the major product from the photolysis of the β,γ-unsaturated α-ketol **17** has been reported.[2b] However, it was postulated that this occurs by transfer of a C-5 hydrogen atom via a six-membered transition state in the acyl alkyl diradical **19** - a type of process that cannot occur in **14**. The transfer of hydrogen in an acyl alkyl diradical *via* an eight-membered ring has not, as far as we are aware, been demonstrated previously. We attribute its occurrence in the present case to restriction of rotation about



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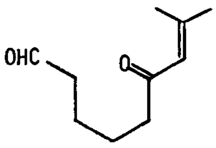

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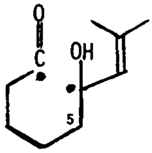

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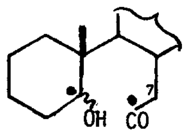

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the C-9 - C-10 bond in **14**, which holds the hydroxyl group and acyl radical in close proximity.[6] The fact that the corresponding diradicals **20** formed from the 5α and 5β saturated analogues of **2** undergo C-H abstraction from C-7 engendering ketenes is considered to be associated with a non-planar geometry of the hydroxyalkyl radical centre in **20**[6] in contrast to the planar geometry imposed in **14** by the allylic system. The planar geometry in **14** positions the hydroxyl group in the immediate vicinity of the acyl radical.

The formation of **10** from **2** and **9** is postulated to involve a Norrish II reaction of **9** following excitation of the α,β-unsaturated keto chromophore; the transfer of a C-11 rather than a C-8 hydrogen to the carbonyl group can be interpreted in conformational terms. As expected the indenacetaldehyde derivative formed on irradiation of **2**-O-d shows deuterium incorporation only in the aldehyde group. The formation of **11** during the irradiation of **9** is attributed to a "dark" aldol reaction catalyzed by an acidic species, which was observed to be formed upon irradiation of **9**.

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References and Notes

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2. Cf., for example, (a) K. G. Hancock, J. T. Lau, and P. L. Wylie, Tetrahedron Lett., 4149 (1974); J. Am. Chem. Soc., **99**, 1149 (1977) (b) R. G. Carlson and A. V. Prabhu, J. Org. Chem., **39**, 1753 (1974).
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