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Phototransformation of 16α,17α-epoxy-3β-hydroxypregn-5-ene-20-one to 3β-hydroxypregn-5-ene-16,20-dione

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UV irradiation of 16α,17α-epoxy-3β-hydroxypregn-5-ene-20-one **5** in a variety of solvents (benzene, acetonitrile, methanol), as such and in the presence of triethylamine, in a pyrex glass reactor leads to the formation of 3β-hydroxypregn-5-ene-16,20-dione **6** as the major product.

Keywords: Steroids, photochemistry, α-epoxyketone, phototransformation, β-diketone

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Photochemistry of α-epoxy-ketone chromophores has been investigated in a variety of molecular environments and has been reported to yield 1,3-diketones as the predominant photoproduct[1-3]. The phototransformation has been reported to involve cleavage of Cα-O epoxide bond leading to intermediate **A** (**Scheme I**).

In case of steroidal epoxide **3**, Jeger *et al.*[4], were first to report a unique phototransformation leading to A-nor-B-homo-1,3-diketone **4** (**Scheme II**).

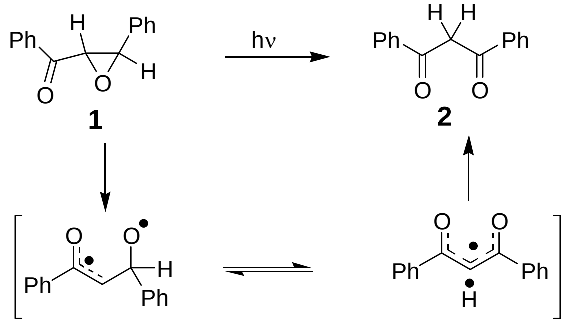
Subsequently, photo-transformations of a number of steroidal ring A and ring B α-epoxyketones have been investigated by Pete and Viriot-Villaume[5,6], who have reported isolation of a number of products under varied conditions of irradiation, derived from a similar generalized mechanistic pattern involving intermediates corresponding to **A**. However, through investigations on well-designed steroidal-epoxide system Schaffner[7] has shown that the temperature of phototransformation influences the product and stereochemical outcome. Interestingly, to the best of the present knowledge, photochemical transformation of steroidal-ring-D epoxides has not been explored. As a part of the ongoing investigations on transformations of 16α,17α-epoxy-3β-hydroxy-Δ^5-pregnen-20-one **5** (Ref. 8,9), its phototransformation has been investigated under varied conditions.

A solution of epoxide **5** in dry acetonitrile was irradiated in a pyrex glass reactor with a 125 W medium pressure Hg arc for 11 hr. The photolysate was concentrated by distilling out the solvent under reduced pressure. Resolution of the crude product by column chromatography over silica gel (60-120 mesh) afforded a gummy, light yellow, homogenous material (TLC) characterized as diketone **6** (**Scheme III**).

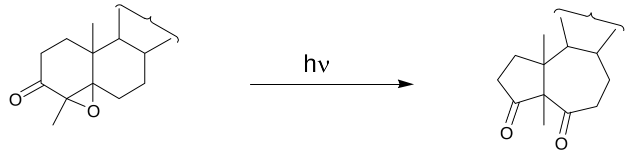
Compound **6** has been characterized on the basis of detailed analysis of its spectroscopic data. It revealed M$^+$ at *m/z* 330 indicating no loss or gain of mass during phototransformations. Its IR spectrum revealed two carbonyl bands at 1707 and 1740 cm^{-1}; the latter band was characteristic of a cyclopentanone. Its ^{1}H NMR revealed, besides resonances attributable to C6-H (broad doublet at δ 5.37) and C3-H (m at δ 3.54), a 1H singlet at δ 4.40 (C17-H). The upfield part of the spectrum revealed, amidst characteristic steroidal proton envelope, methyl resonances at δ 2.03, 1.04 and 0.94. Though the compound was homogeneous on TLC, its ^{1}H NMR showed additional sharp singlets (methyl) at δ 1.98 and 0.98 as well as additional resonances (minor) in the ^{13}C NMR spectrum. Of particular significance, in its ^{13}C NMR, besides carbonyl carbons (C20, C16) and olefinic carbons (C5, C6) resonances, were the downfield shifted olefinic resonances at δ 177.0, 166.5 and upfield shifted olefinic resonances at δ 110.0 and 100.56; the latter were indicative of existence of tautomeric structures such as **6a** and **6b**. Existence of tautomeric structures is also corroborated by additional resonances (minor) in the ^{13}C NMR spectrum and additional singlets (methyl) in the upfield part of the ^{1}H NMR spectrum.

Irradiation of epoxy-ketone was also carried out in different solvents and in the presence of triethylamine; the results are summarized in **Table I**. It may be mentioned here that irradiation of **6** in methanol furnished a complex mixture and ^{1}H NMR screening of various column chromatography fractions indicated the formation of some methanol addition products. However, these could not be resolved sufficiently for characterization. Presence of triethylamine was anticipated to influence the mode of phototransformation through electron transfer[10-13]and also by stabilizing incipient ketyl radical[14]. However, no such effect of triethylamine on phototransformation has been observed, except, when irradiation is carried out in acetonitrile wherein there is observed considerable reduction in irradiation time along with slightly improved yield of the product **6**; acetonitrile as solvent is anticipated to facilitate photoelectron transfer.

Mechanistically, the phototransformation of epoxy-ketones to β-diketone is well investigated[1-3] and existence of tautomeric structures has been established earlier. The plausible mechanism of present phototransformation is described in **Scheme IV**.



Scheme I



Scheme II

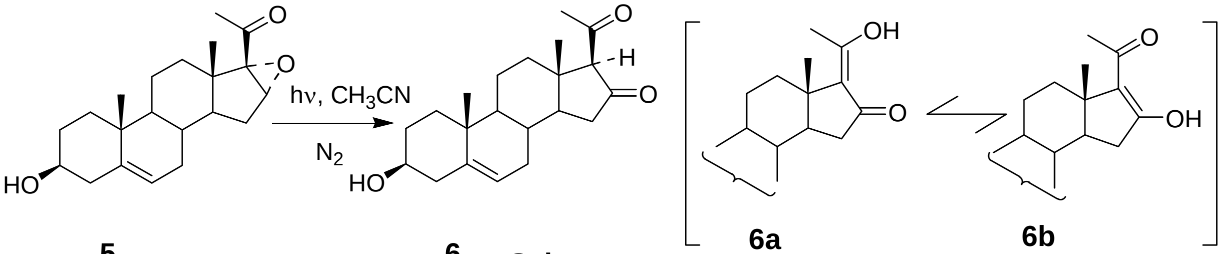
Thus, phototransformation of **5** under a variety of irradiation conditions (solvent, presence of triethylamine, *etc*.) leads to β-diketone **6** as the major product and no deviation is observed from known preferred mode of phototransformation of α-epoxy ketones. However, highest yield of **6** is obtained in acetonitrile as solvent in the presence of triethylamine.

Experimental Section

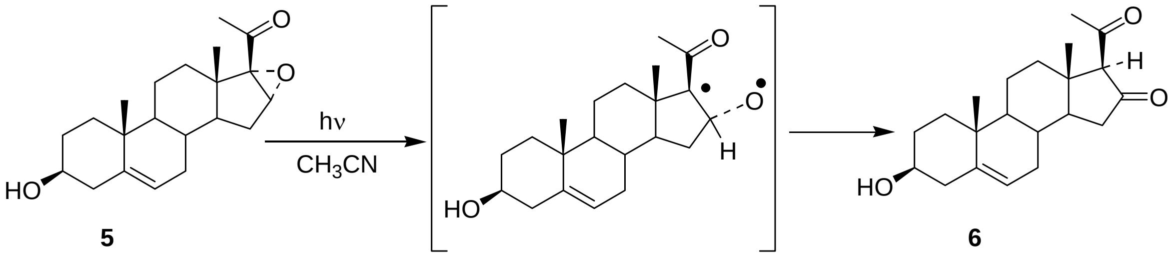
^{1}H and ^{13}C NMR spectra were recorded on Bruker AC-200 FT NMR spectrometer, using TMS as internal standard and $CDCl_3$/acetone-d_6 as solvent. Chemical shift values are expressed as δ (ppm) downfield from TMS and J values are in Hz. IR spectra ware recorded on Shimadzu DR 2001 FT-IR spectrometer in $CHCl_3$, and mass spectra were recorded on Shimadzu GCMS-QP-2000A spectrometer. Column chromatography was conducted using Silica Gel 60-120 mesh. The elemental analyses were performed on Perkin-Elmer 240C Elemental Analyzer. Products were resolved by column chromatography over silica gel (60-120 or 100-200 mesh). All solvents were purified and dried prior to use. 16α,17α-Epoxy-3β-hydroxy/acetoxypregn-5-en-20-ones **5** was prepared by the literature method and characterized spectroscopically[15].

General procedure for irradiation of 16α,17α-epoxy-3β-hydroxy-pregn-5-ene-20-one, 5

Epoxide (**5**, 200 mg) was dissolved in a dry solvent (acetonitrile/benzene/methanol, 200 mL) and the solution was taken in an immersion well type water-cooled Pyrex glass reactor; for irradiations carried out in the presence of triethylamine (acetonitrile/methanol solvents), 0.5 mL of the same was added to the solution. The solutions were purged with dry oxygen free nitrogen gas for 15 min prior to irradiation and it was continuously bubbled through the solution during



Scheme III



Scheme IV

Table I — Reaction conditions and product yields for irradiation of **5** in different solvents

S. No.	Reaction Conditions	Reaction Time hr	% Yield of **6**
1	Benzene	16	44
2	CH_3CN	11	56
3	CH_3CN/TEA	3	60
4	MeOH	12	42
5	MeOH/TEA	8	47

irradiation. The irradiation was carried out with a 125 W medium mercury arc placed coaxially and the progress of the reaction was monitored by TLC. After completion of reaction the solvent(s) from the photolysate(s) were removed under reduced pressure and the crude products were subjected to column chromatography over silica gel (60-120 mesh, column packed in hexane) employing hexane-ethyl acetate gradient as eluent. Compound **6** was obtained as colorless intractable gummy material with hexane-ethyl acetate 5:1 eluent: some mixture fractions obtained from columns in certain cases could not be resolved further.

6: Colorless gummy material; IR (KBr): 3300, 3000, 1740, 1720, 1600, 1520, 1420, 1390, 1370, 1200, 1040, 920 cm^{-1}; ^1H NMR (acetone-d_6): δ 5.37(br d, 1H), 4.40(s, 1H), 3.54(m, 1H), 2.80-0.86 (complex, 26H, with singlets at δ 2.25, 2.22, 1.04, 0.96 and 0.90); ^{13}C NMR (acetone-d_6): δ 205.1, 201.4, 177.0, 165.5, 148.3, 146.2, 125.8, 125.6, 110.0, 100.6, 76.1, 75.8, 58.8, 56.2, 53.9, 52.7, 50.5, 47.4, 47.1, 41.9, 41.7, 41.6, 41.2, 39.8, 39.0, 37.0, 36.5, 36.1, 35.6, 35.3-34.4 (solvent), 31.3, 30.9, 30.5, 29.4, 27.3, 25.9, 25.2, 24.4, 17.33, 16.6, 14.3, 12.9; MS: *m/z* (%) 332(M^++2, 2.5), 331(M^++1), 330 (M^+ 15), 329 (M^+-1, 35); Anal. Calcd. for $C_{21}H_{30}O_3$: C, 76.33; H, 9.15. Found: C, 76.19; H, 9.02%.

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