

PART – II

**(Preparation and Molecular Rearrangement of
2 α , 3 α -Epoxy Lupan-1-one Catalysed by Boron
Trifluoride and by Ultraviolet Irradiation)**

CHAPTER - I

(A Short Review on the Molecular Rearrangement of α,β -Epoxy ketones Induced by (1) the Lewis Acid, Boron Trifluoride and (2) by Ultra-violet Irradiation)

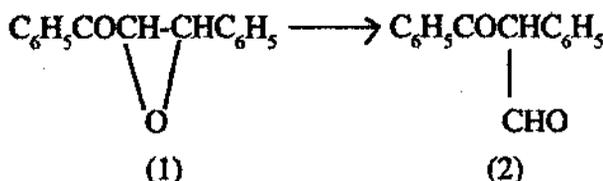
Introduction :

For several decades, ring contracted reactions involving molecular rearrangements have attracted the attention of organic chemists. These provide convenient and expedient methods for the preparation of many naturally occurring and novel synthetic compounds. Of several techniques adopted for ring contraction, molecular rearrangement of α,β -epoxy ketones induced by the Lewis acid, borontrifluoride - etherate is a unique one and has successfully been utilised by many groups. This is because of easy availability and pronounced reactivity of boron trifluoride. Interestingly, this same molecular rearrangement, in many cases, of α,β -epoxy ketones has also been effected by ultraviolet irradiation. Consequently, we have divided this review into two sections, SECTION - A, induced by BF_3 -etherate and SECTION-B, induced by ultra-violet irradiation.

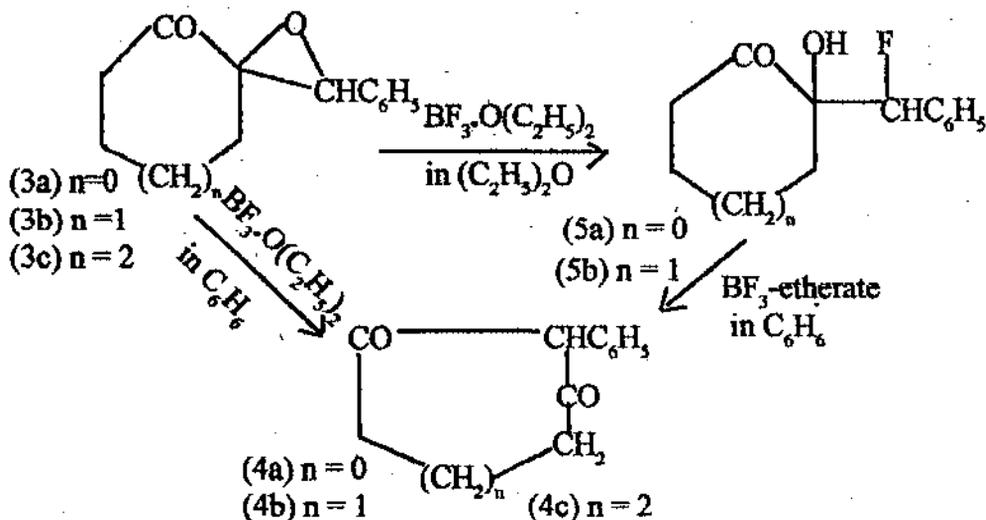
SECTION A

(Induced by BF_3 -Etherate)

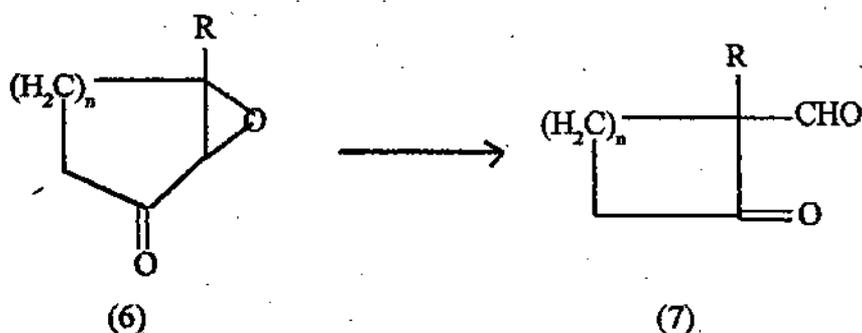
House¹ initially noticed that acid-catalysed isomerisation of *trans*-benzalacetophenone oxide (1) yielded α -formyldeoxybenzoin (2) involving a intramolecular migration of the benzoyl group.



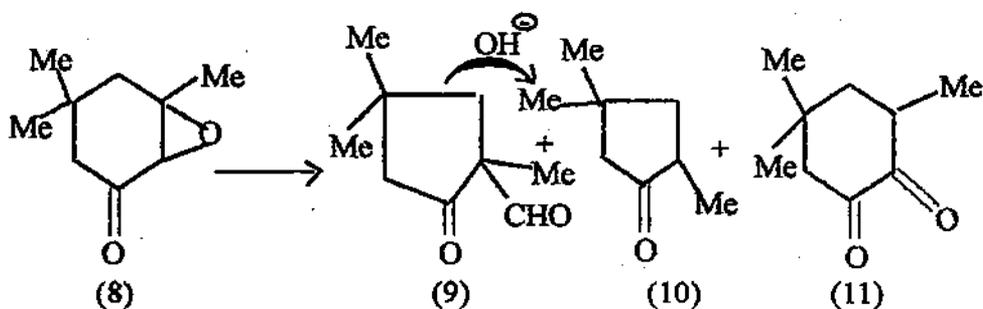
House and Wasson² then observed that 2-benzalicyclopentanone oxide (3a), 2-benzalicyclohexanone oxide (3b) and 2-benzalicycloheptanone oxide (3c) have undergone isomerisation to 2-phenyl-1,3-cyclohexanedione (4a), 2-phenyl-1,3-cycloheptanedione (4b) and 2-phenyl-1,3-cyclooctanedione (4c) respectively, on treatment with $\text{BF}_3 \cdot \text{Et}_2\text{O}$ in benzene solution. When the same cyclohexanone and cycloheptanone derivatives were treated with BF_3 in ether solvent, the products were fluorohydrins (5a-b) which ultimately produced (4a-b) on treatment with benzene. The products in these cases resulted from ring expansion.



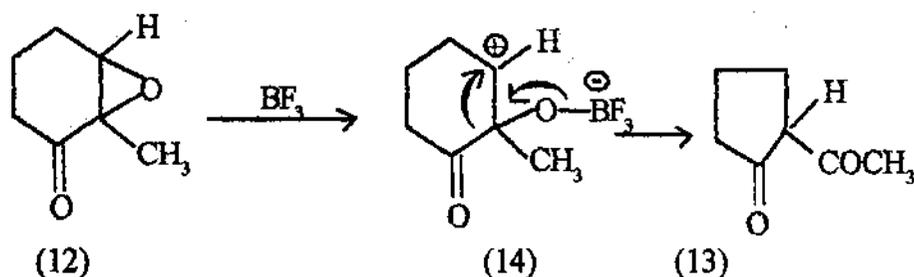
House and Wasson³ have further extended their study and have observed that cyclic epoxy ketones of the type (6, $n > 1$) in the presence of BF_3 -etherate undergo molecular rearrangement with reduction in ring size of ketones to produce the ketoaldehyde (7). This reaction is fairly general and provides a convenient method for the conversion of α,β -epoxy cyclohexanone derivatives to the corresponding ring contracted α -formyl or α -acyl cyclopentanone accompanied in certain instances by 1,2-cyclohexane diones.



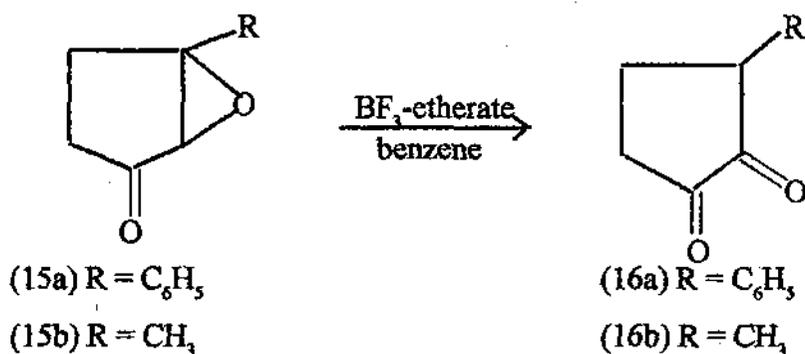
Isophorone oxide (8) gave the ring contracted ketoaldehyde (9) as the major product along with some deformed product (10) and 1,2-diketone (11). Amount of (10) increased considerably on alkali treatment of (9).



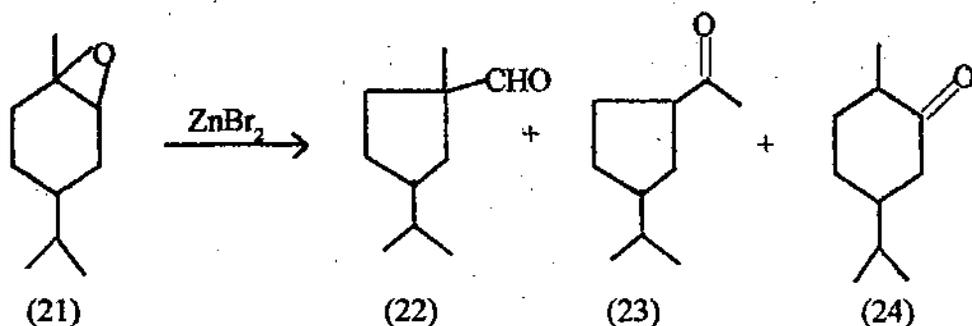
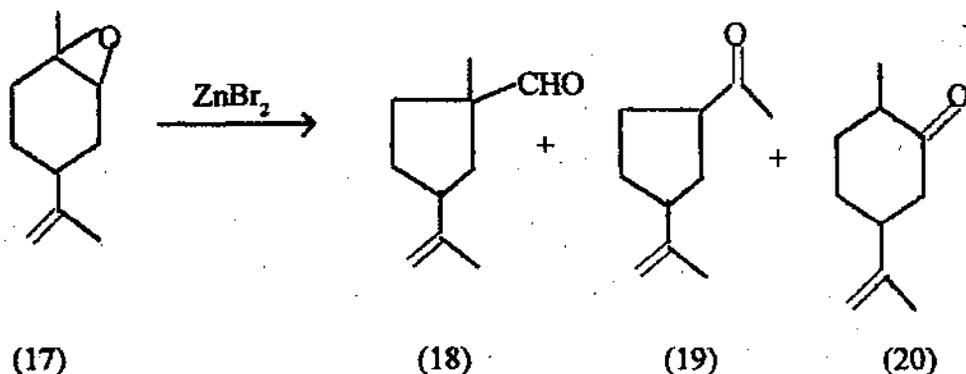
On the other hand, 2,3-epoxy-2-methyl cyclohexanone (12) afforded the ring-contracted β -diketone (13) as the sole product. They invoked the intermediate (14) which subsequently on ring contraction formed (13).



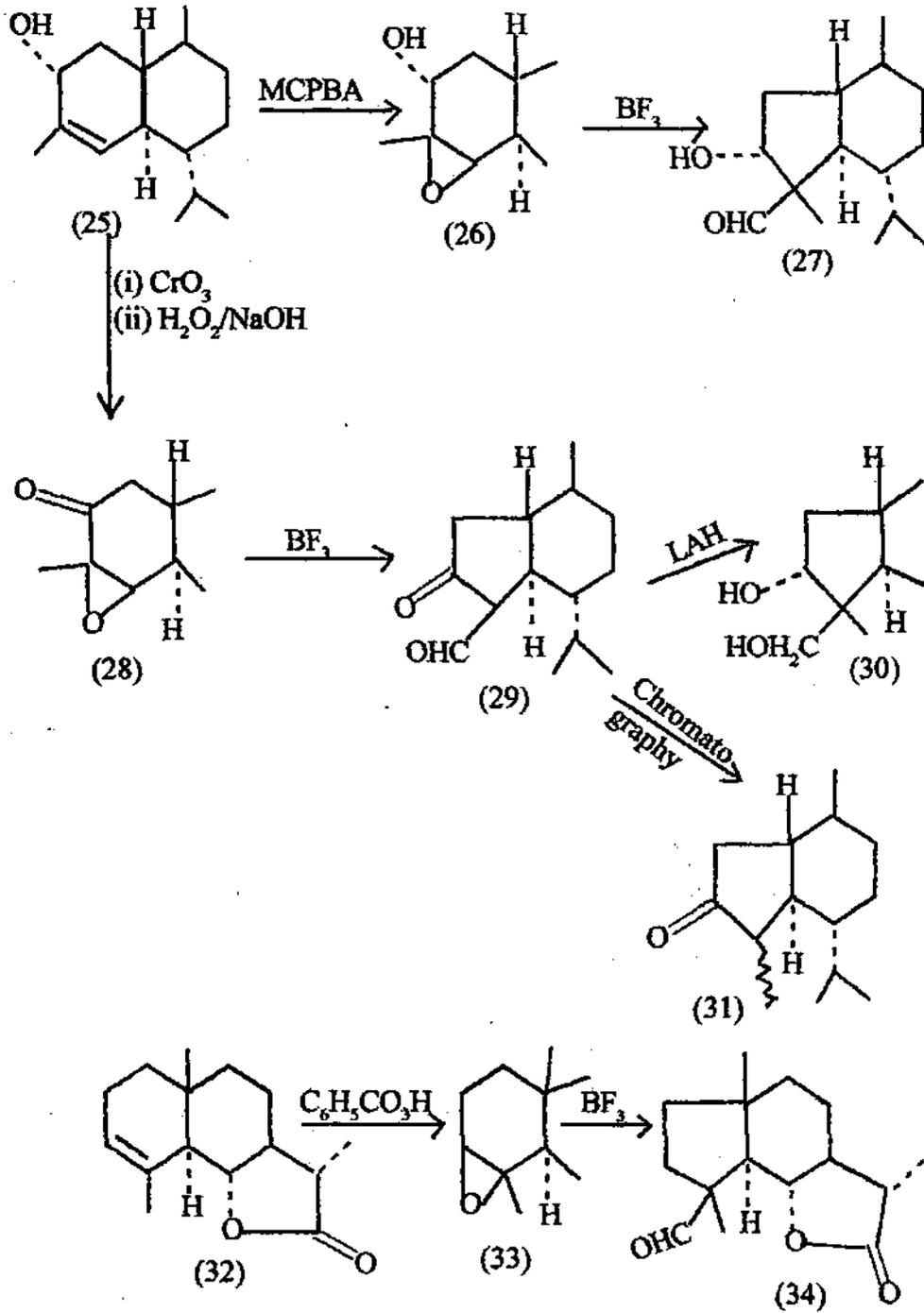
This reaction did not produce ring-contracted cyclobutanone derivatives from corresponding cyclopentanone e.g. from the rearrangement of (15a, b), (16a, b) were the only products isolated as the enol form of α -diketone.



This rearrangement is not monopoly of epoxyketones. Suitable epoxides also can undergo this reaction. Setting and coworkers⁴ carried out molecular rearrangement of monoterpenoid, limonene oxide (17) induced by ZnBr_2 and obtained a ring contracted aldehyde (18), a ring-contracted ketone (19) and a uncontracted ketone, dihydrocarvone (20) in 30%, 10% and 59% yield, respectively. They also applied this reaction on carvomentheneoxide (21) and obtained similar type of products (22), (23) and (24).

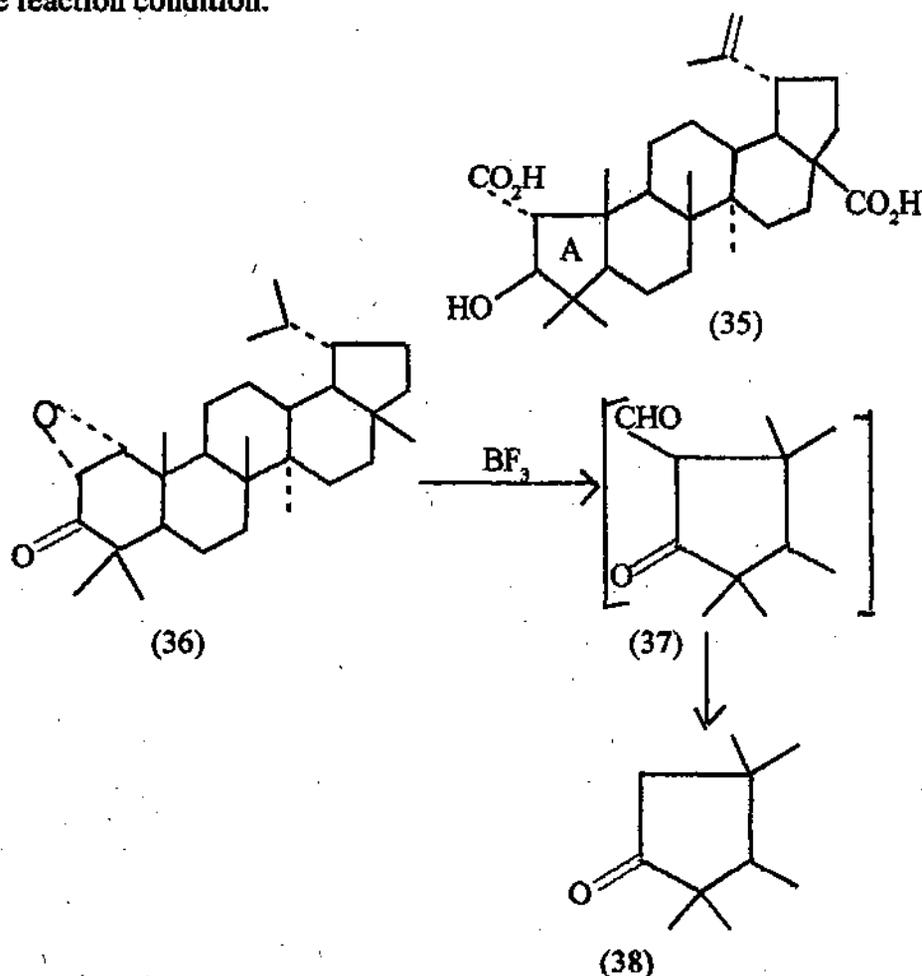


Kartha and Chakrabarti³ studied the action of BF_3 -etherate on epoxides and epoxy-ketones. They noted that BF_3 not only induced molecular rearrangement of epoxyketones but also of epoxides. The success depends on the nature and position of the double bond from which epoxides are prepared. Several cadinenic and selenic epoxides derived from sesquiterpenoids, on treatment with BF_3 have been found to undergo ring-contraction resulting in the formation of fully substituted aldehydes. The epoxide (26) derived from dihydrokhusinol (25) by MCPBA on BF_3 treatment afforded ring-contracted crystalline hydroxy aldehyde (27) possessing characteristic IR bands at 2703 and 1712 cm^{-1} . The epoxyketone (28) derived from (25) by CrO_3 oxidation followed by epoxidation by alkaline H_2O_2 , on BF_3 treatment gave the ring-contracted ketoaldehyde (29) showing IR bands at 2725, 1709 (CHO) and 1742 (cyclopentanone). The ketoaldehyde (29) on LAH treatment afforded the crystalline diol (30), and chromatography through slightly alkaline alumina gave the deformylated product, the cyclopentanone (31), the structure of which was supported by NMR analysis which displayed a peak at τ 7.8 (3H) due to three protons α to the carbonyl group.

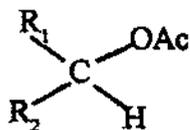


The epoxide (33) derived from α -santenolide (32) on BF_3 -etherate treatment gave fully substituted ring-contracted aldehyde (34) which exhibited IR bands at 2703, 1724 (aldehyde), 1767 cm^{-1} (γ -lactone). The NMR spectrum is in conformity with its assigned structure.

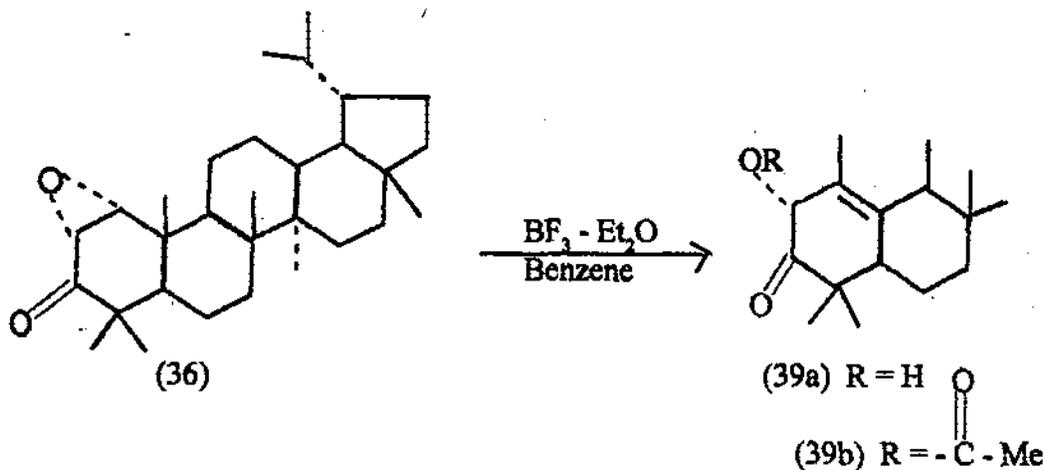
With a view to developing a method for partial synthesis of the A-ring-contracted triterpene acid, cianothic acid (35), Chatterjee and colleagues⁶ took up the study of BF_3 -etherate catalysed rearrangement of the model triterpene, $1\alpha, 2\alpha$ -epoxylupan-3-one (36) following the same procedure prescribed by House et al.⁵. However, in this reaction, they could not isolate the ketoaldehyde (37), but obtained only the ketone, A-norlupan-2-one (38) in good yield. Most probably, the intermediate ketoaldehyde (37) that was formed initially underwent easy loss of the formyl group under the reaction condition.



Ganguly et al.⁷ carried out BF_3 -catalysed rearrangement of $1\alpha, 2\alpha$ -epoxy lupan-3-one (36) and obtained a crystalline unsaturated α ketol which showed ν_{max} 3500(OH), 1712 (cyclohexanone) cm^{-1} , λ_{max} end absorption at 208 nm; on acetylation it gave a crystalline acetate ν_{max} 1740, 1220 (acetate), 1725 cm^{-1} (cyclohexanone). The NMR spectrum of the acetate showed signals at δ 2.21 ($-\text{COCH}_3$) and a sharp singlet at 85.45



which prior to acetylation appeared at δ 4.5. Finally, olefinic Me signal of the rearrangement product appeared as a singlet at δ 1.3. Based on the above observation, the rearrangement product was assigned structure 1-methyl-2 α -hydroxylup-1(10) α -3-one (39a) and the corresponding acetate (39b). Here, most probably due to the presence of a neopentyl system adjacent to the epoxy ketone system, methyl migration occurred instead of ring contraction.

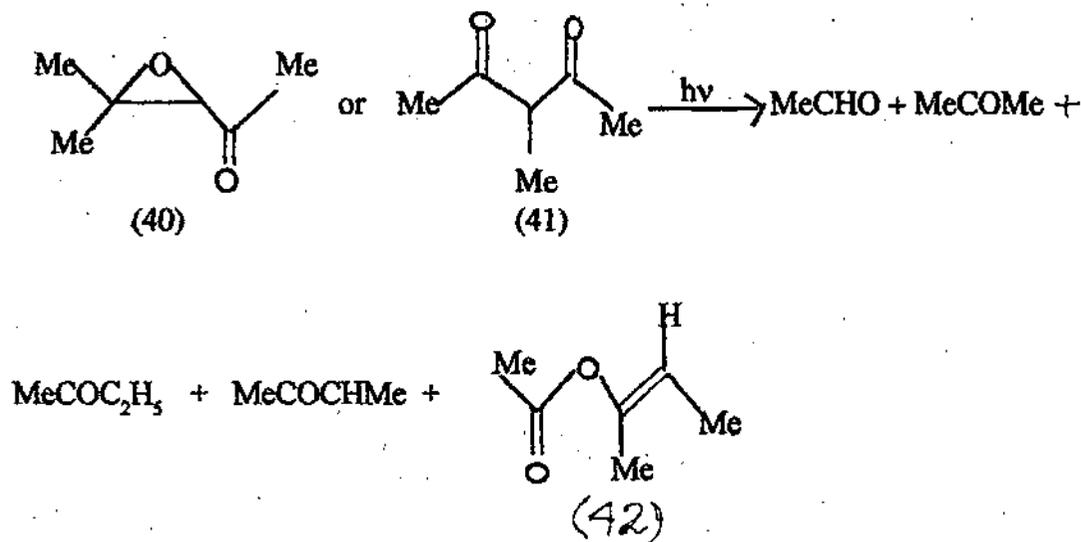


SECTION - B

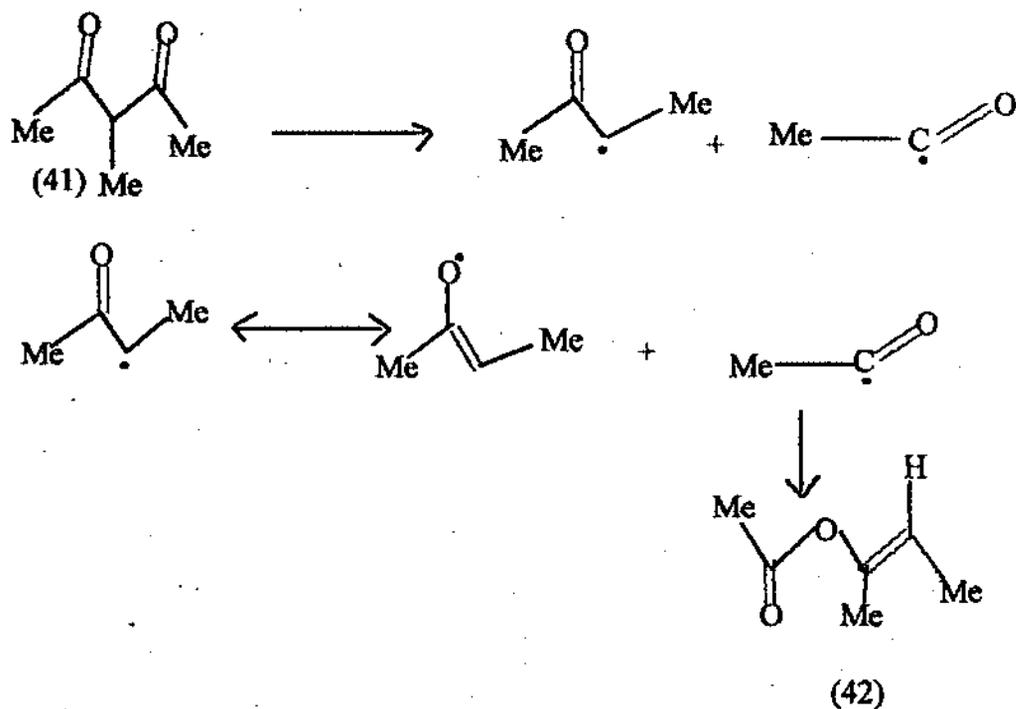
(Induced by UV Irradiation)

When atoms with π -bonding electrons such as carbonyl group, are attached to the carbon atom of adjacent three membered cyclopropyl or α,β -epoxyketone group having bent bondings, some overlapping and interaction between the bent bonds and the π -orbitals occur giving rise to delocalisation. This delocalisation has been studied by UV,^{8,9} IR⁸, NMR¹⁰ and theoretical^{11,12} considerations. The interaction becomes maximum when the three-membered ring lie parallel to the π orbital of the carbonyl group. The delocalised orbitals of the three-membered ring in this geometric position overlap with the non bonding π electrons of the carbonyl oxygen. This small amount of admixed π character makes the n,π^* somewhat comparable to the allowed π,π^* transition. As a result, the electric-dipole-transition moment of the n,π^* transition which is symmetry-forbidden in simple ketones, is no longer forbidden in these systems^{13,14}.

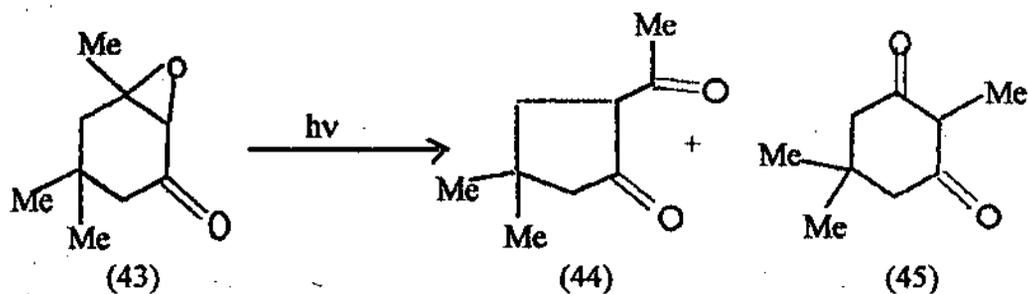
Simple acyclic α,β -epoxyketones e.g. 3,4-epoxy-4-methyl-2-pentanone (40) on photolysis using wavelength above 250 nm gave 3-methyl-pentane-2,4-dione (41) in yields of 2 to 12 per cent¹⁵. Since the photoproduct 1,3-diketone (41) is also photolabile, its yield is low and on further irradiation (40) and (41) gave acetaldehyde, acetone, methyl ethyl ketone, methyl isopropyl ketone, 2-butenyl acetate (42) and other high-boiling components. These host of products are obtained as secondary processes particularly in the absence of any radical or ion-stabilizing groups.



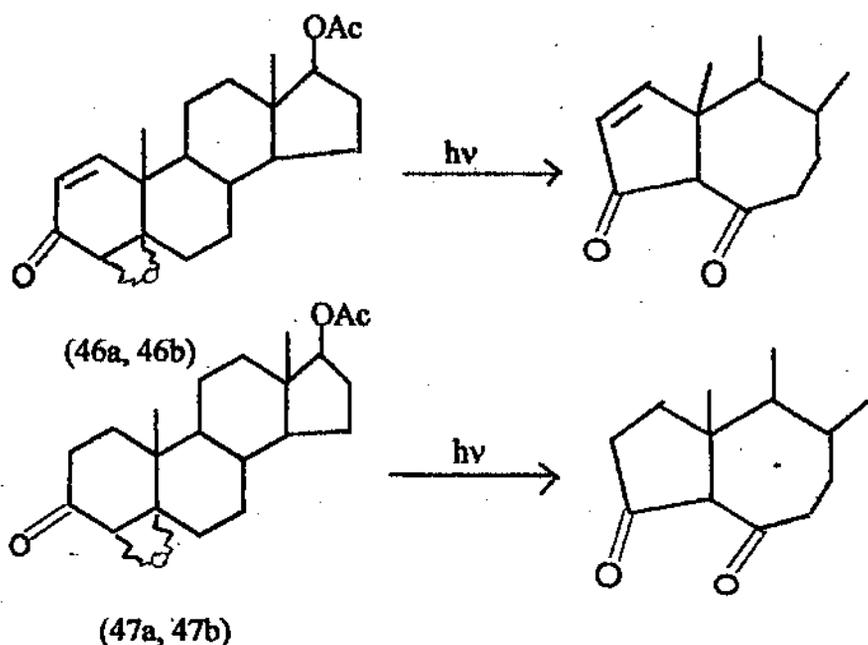
Formation of (42) is accounted for in the following way :



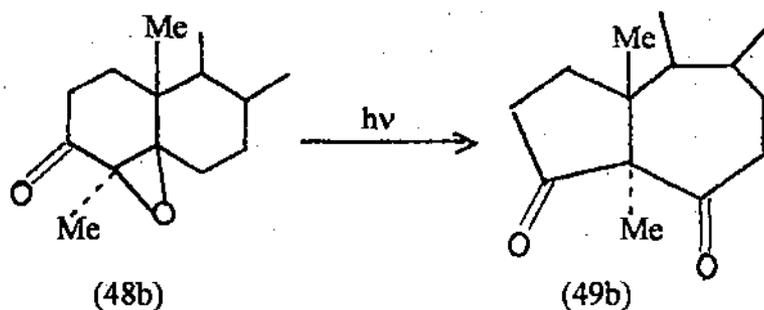
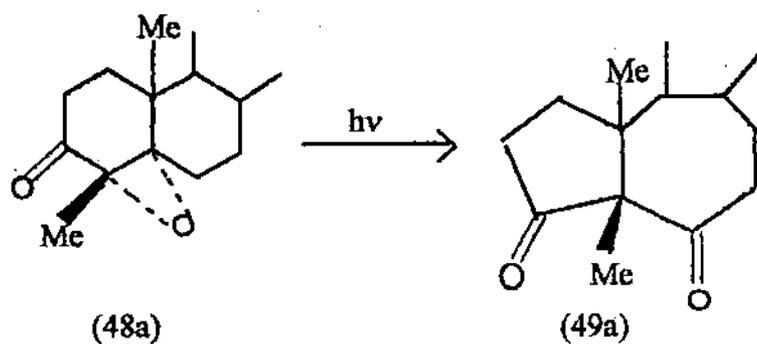
The photolysis of monocyclic isophorone oxide (43) in a variety of solvents gave a mixture of 1,3 diketones 2-acetyl-4,4-dimethylcyclohexanone (44) and 2,5,5-trimethylcyclohexanone - 1,3-dione (45) in 9 : 1 ratio.



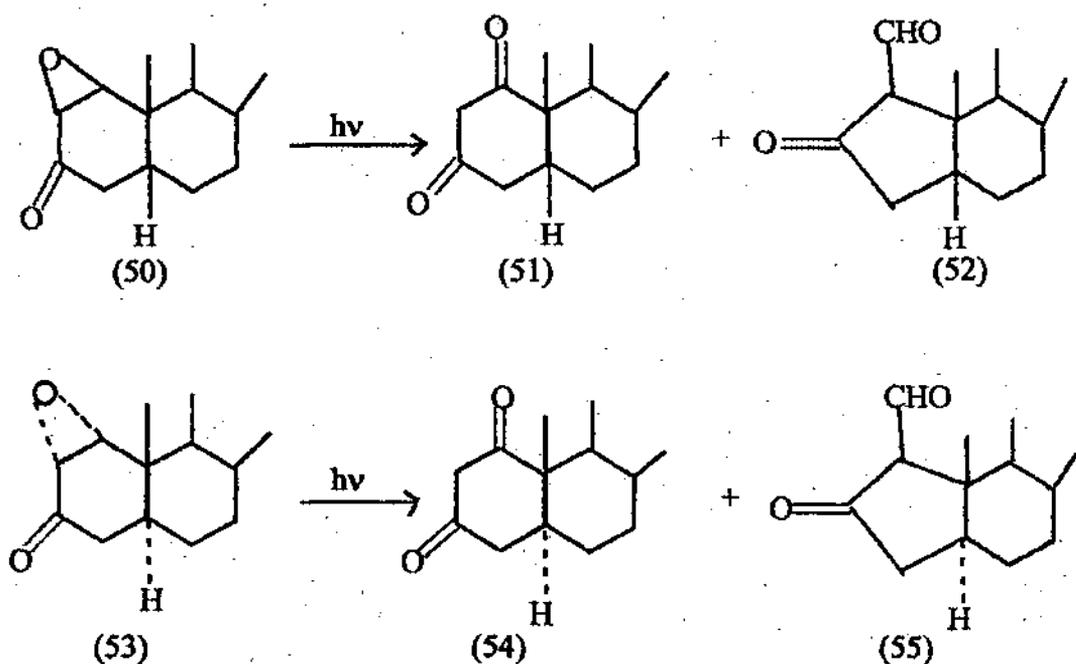
An analogous finding was reported in the polycyclic α,β -epoxy ketone derivative of steroid¹⁶. On irradiation, the oxides (46) and (47) produced the β -diketones as a result of an alkyl group shift from the β to the α carbon. Irrespective of the relative configuration of the oxide ring, two stereoisomeric pairs (46a, 46b) and (47a, 47b) yielded a single 1,3-diketone. It has been demonstrated by Wehrli and coworkers¹⁷ that the photochemical transformations occurring in the 3-oxo-4,5-oxidosteroids systems are stereospecific.



Photolysis of stereoisomeric 4-methyltestosterone oxides (48a, 48b) afforded the β -diketones (49a) and (49b) which are stereospecific, differing only in their configuration at C-4. The stereospecificity has been accounted for by assuming that the cyclodecane system of the transition state retains the relative spatial arrangements of the reaction centres in the starting epoxy ketone which makes the observed stereospecificity of this rearrangement possible.

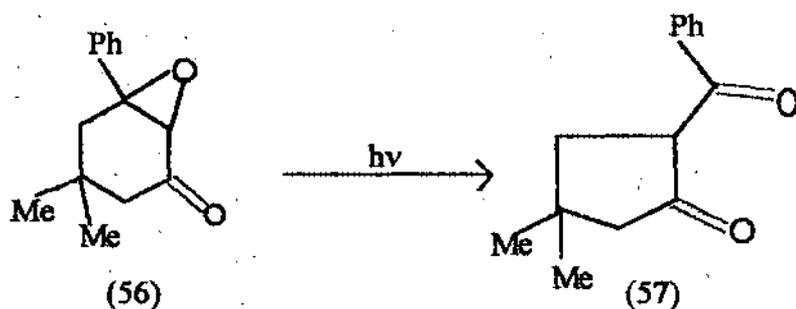


Jeger et al.¹⁸ carried out studies on the stereochemical requirement of the β -alkyl-group migration in some detail. From irradiation of a dioxane solution of 1 β , 2 β -oxido-17 β -acetoxy-5 β -androstan-3-one (50) a mixture of the 1,3-diketone (51) and ketoaldehyde (52) were obtained. Similarly, the 5 α -isomer (53) gave the related 1,3-diketone (54) and keto aldehyde (55).

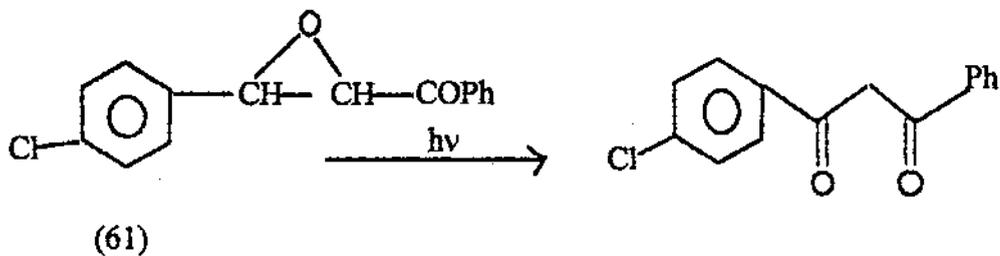
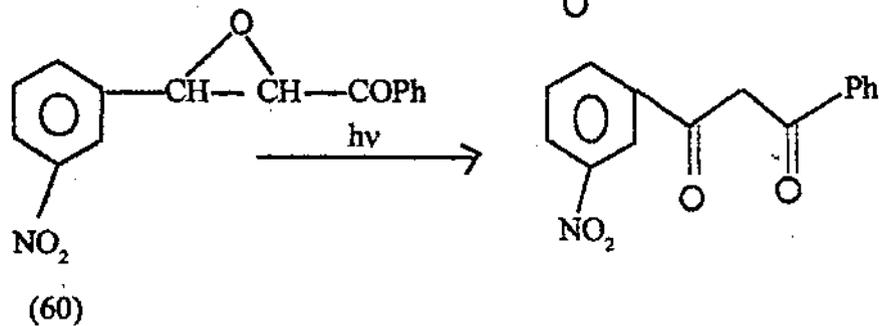
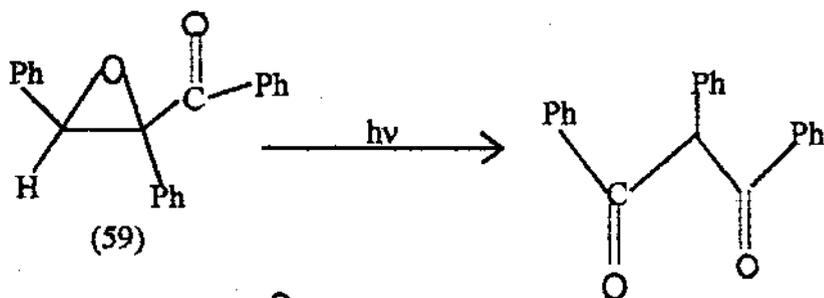
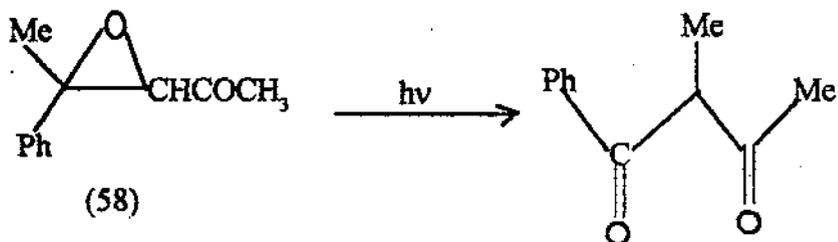


It has been envisaged that these products are formed as a result of migration of carbon atom 10 and of a competing 1,2 hydrogen shift. In order to explain the observed stereospecificity Jeger¹⁸ has proposed that the hydrogen shift or the 1,10-bond migration is concerted with the formation of carbonyl at C-1.

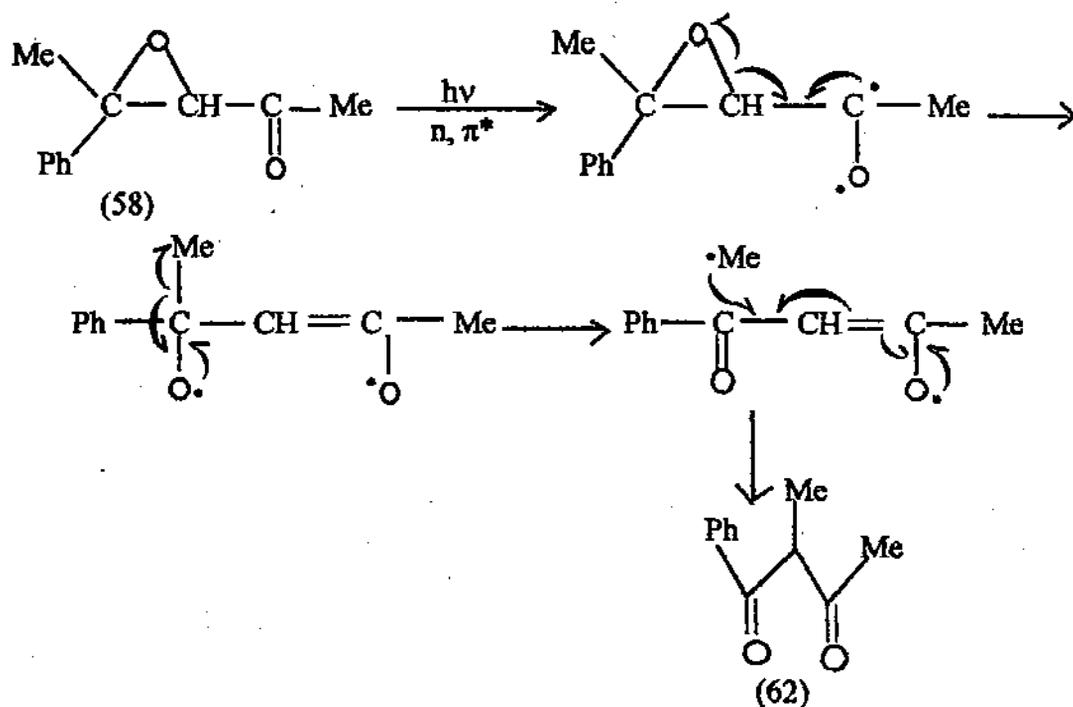
Johnson and coworkers¹⁵ carried out irradiation of 3-phenyl-5,5-dimethyl-2,3-epoxycyclohexanone (56) and obtained 2-benzoyl-4,4-dimethylcyclopentanone (57) and surprisingly, no detectable quantity of the isomeric cyclohexadienone. This preferential shift of alkyl rather than aryl group - an unusual order of migratory aptitude for the photochemical rearrangement of α,β -epoxyketones to β -diketones seems to be a fundamental characteristic of the reaction.



The absence of phenyl migration and the same preferential order of migration has been observed too in many open-chain epoxyketones (58)¹⁹, (59)²⁰ and (61)²¹. This appears to be not due to steric factors but rather suggestive of considerable bond-breaking in the transition state of this phototransformation.

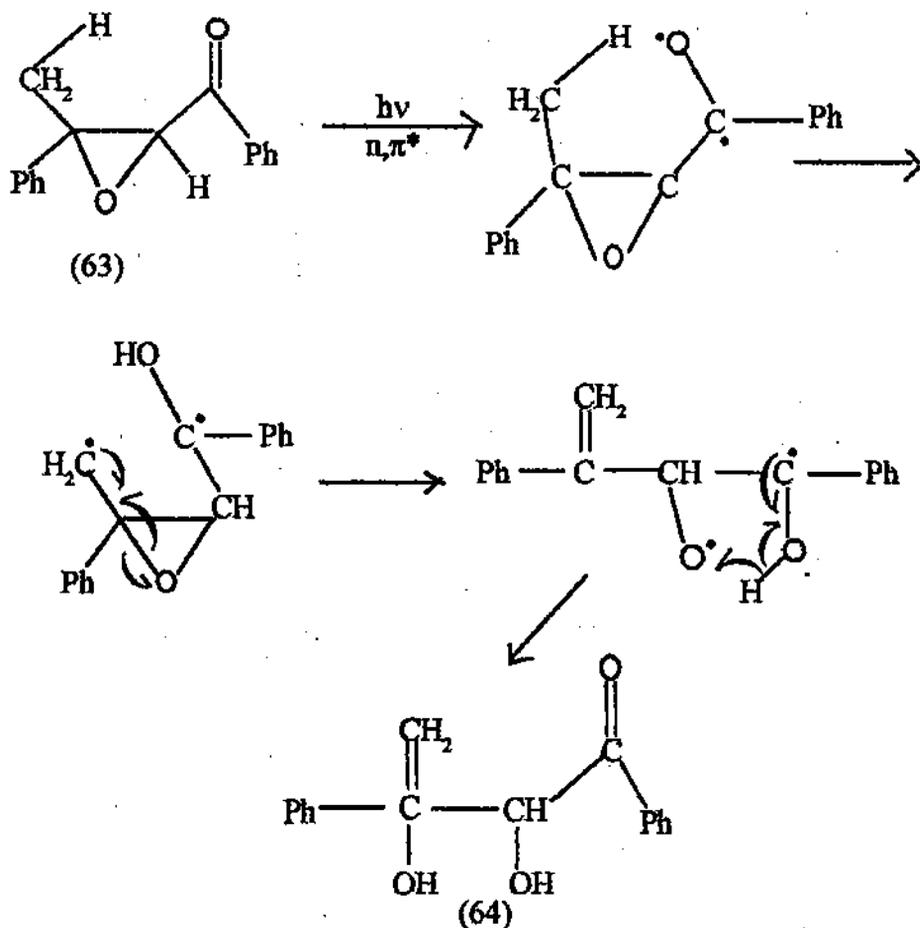


Zimmerman et al.²² proposed a mechanism for the photochemical conversion of α,β -epoxyketones to β -di-ketone. This reaction occurs from n,π^* excited state in which the electron density at the carbonyl carbon is enhanced relative to that in the ground state. Substituents alpha to the carbonyl group would readily be expelled by elimination either as anion or as odd electron species from the n,π^* excited manifold. Whether the excited state expels an anion or a radical is related to the ability of the environment to stabilize the ionic species by solvation. The unusual migratory aptitude behaviour in this system has been explained by Zimmerman by homolytic carbon oxygen fission as shown in the scheme :



The preferred expulsion of the methyl radical as opposed to the phenyl radical in the case of epoxyketone is analogous to the direction of radical fragmentation noticed in the decomposition of cumyl peroxide¹⁸ and phenyldimethylcarbinyl hypochlorite²³. Upon direct irradiation in solution (63) undergoes n,π^* excitation to form an excited state which rearranges and produces 1,3-diphenyl-3-buten-2-ol-1-one (64). After the n,π^* promotion one remaining $2p$ electron is still localised on oxygen which shows behaviour characteristic of reactive alkoxy radicals, one property of which is hydrogen abstraction. Abstraction of the γ -hydrogen gives rise to a species in which the odd electron is conjugated with the oxirane group. Homolytic

ring cleavage followed by intramolecular disproportionation rationalises nicely the observed product as depicted below :

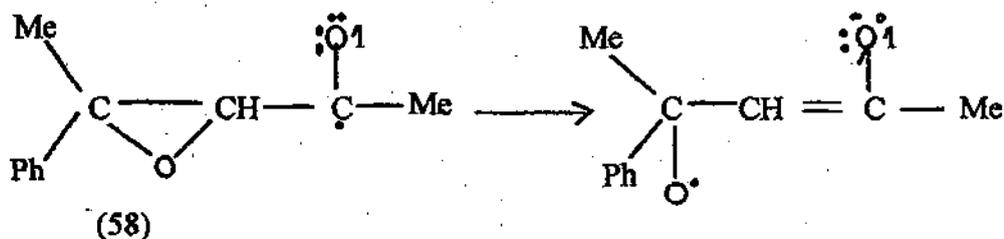


This mechanism requires proximity of the benzoyl and methyl groups for effective hydrogen transfer to occur. That cis-dynpnone oxide fails to give this reaction supports this proposition²².

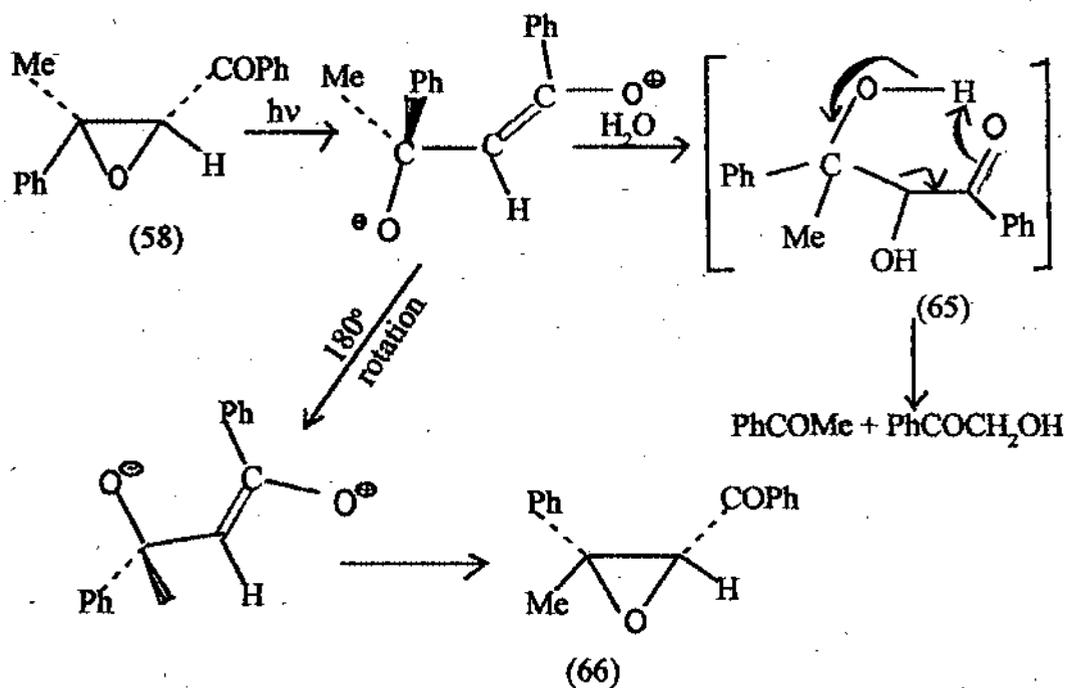
Markos and Reusch²⁴ observed that epoxy ketone photorearrangements are not sensitive to the presence of oxygen or changes in the solvents. Furthermore, the known triplet quenchers such as piperylene and 2,5-dimethyl-2,4-hexadiene used in concentration ranging from 0.1 to 9.0 M, did not affect the rate and course of rearrangement, led to the proposition that this phototransformation is derived from singlet manifold. Besides, acetophenone (0.5 M), a triplet state sensitizer, did not function as a sensitizer for the rearrangement in acetonitrile solution. The low quantum

yield observed for some of these rearrangements has been attributed to poor efficiency for the $[S_1]$ \rightarrow 1,3 diradical formation or an unfavourable competition between rearrangement and oxirane ring formation from the diradical. A report²⁵ concerning the thermal decomposition of β -methyl- β -phenyl- β -peroxypropiolactone noted a fivefold preference for methyl migration vs. phenyl and suggested a 1,3-diradical intermediate similar to the photoreaction. This unusual migrational aptitudes suggest that migrating group must have radical character.

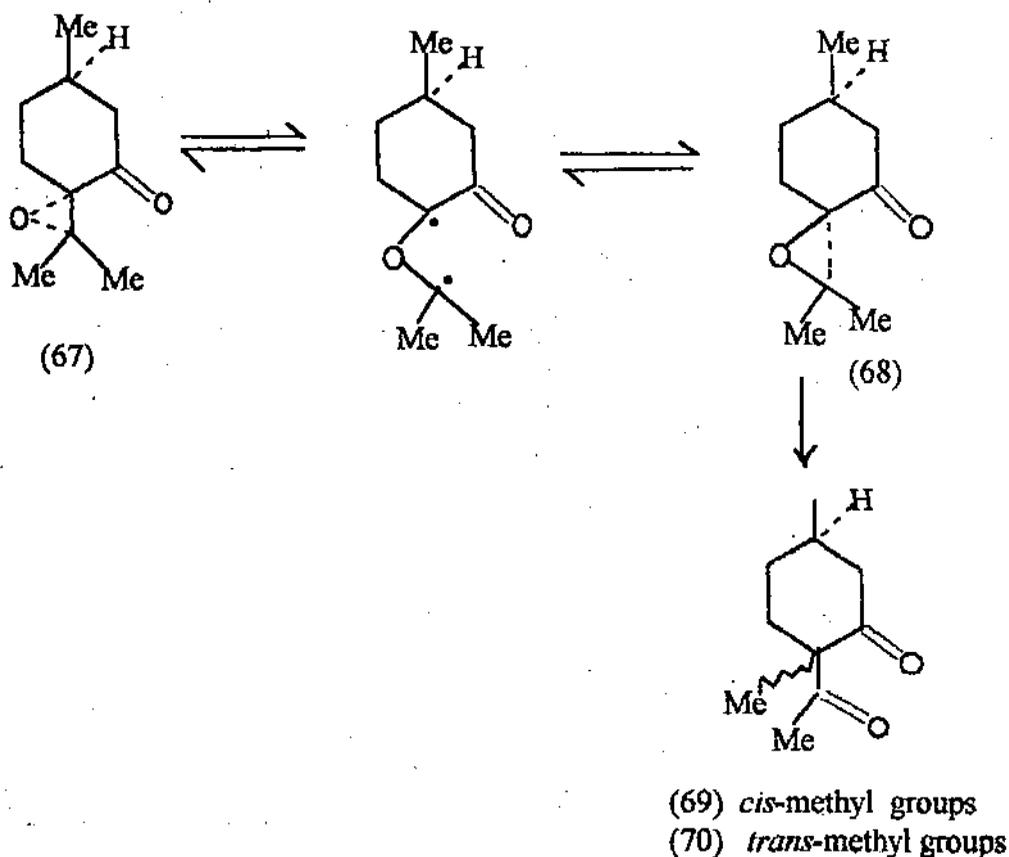
An interesting case of photo-reaction of α,β -epoxy ketone on the nature of the carbonyl group has been noted. In contrast to 3,4-epoxy-4-phenyl-2-pentanone (58) which rearranges to β -diketone (62), the structurally related *trans*-dypnone oxide (63) exhibits an entirely different photochemical sequence²². The striking difference in the photochemical behaviour of (63) and (58) is due to the greater delocalisation of the electron in the benzoyl group which decreases the possibility of ring scission in (63). On the other hand, the excited acetyl group in (58) has the electron in the π^* orbital localised on the carbon and consequently, more available for β -elimination.



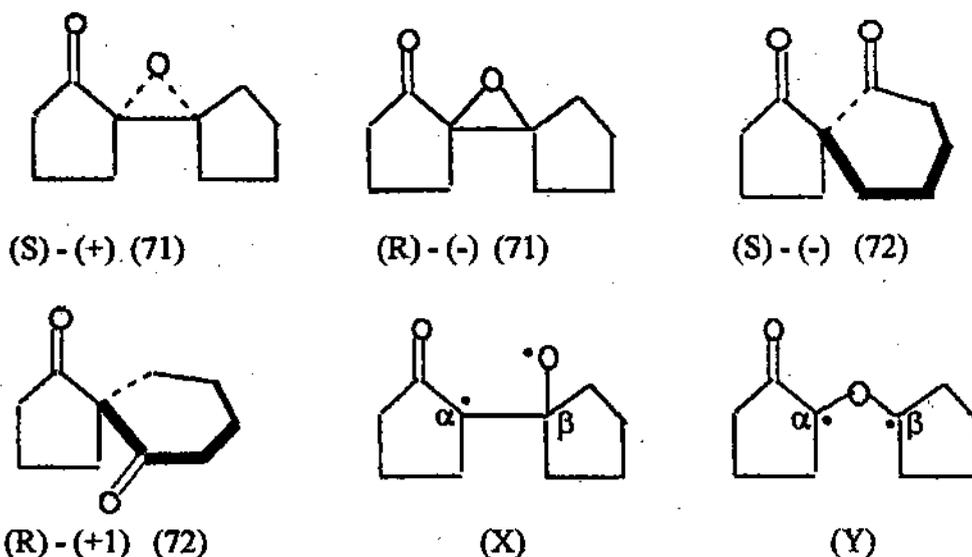
Irradiation of *trans*-dypnone oxide (58) in aqueous ethanol is interesting²⁰. Under this condition (58) isomerised to the diastereoisomer *cis* isomer (66). In addition, acetophenone and α -hydroxyacetophenone were obtained. Formation of these products has been explained by zwitterion type of intermediate. It has been postulated that the zwitterionic species can rotate about the central C—C single bond, resulting in the formation of the diastereoisomer after collapse. It can also react with a molecule of water to form an intermediate glycol (65), which subsequently undergoes photochemical dealdolisation to furnish acetophenone and α -hydroxyacetophenone.



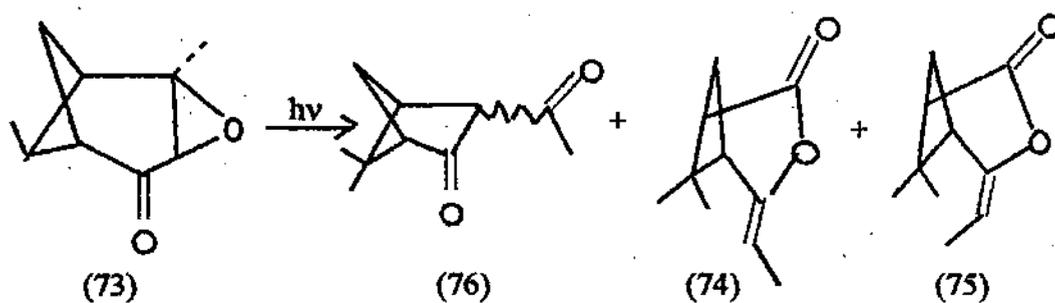
α,β -epoxy ketones in several cases undergo *cis-trans* isomerisation under photolytic conditions. It would imply the reversible formation of a reactive intermediate. Homolytic C—C bond fission and rotation prior to collapse would also account for this *cis-trans* isomerisation. When an ether solution of α - and β -pulegone oxides (67) and (68) were irradiated¹⁵ rearrangement to the stereoisomeric 2-acetyl-2,5-dimethylcyclohexanones (69) and (70) as well as isomerisation to (67) and (68) were both observed. The rate of isomerisation appears to be slightly greater than the rate of rearrangement. The steady state concentration of (69) and (70) is roughly 7% with (69) predominating.



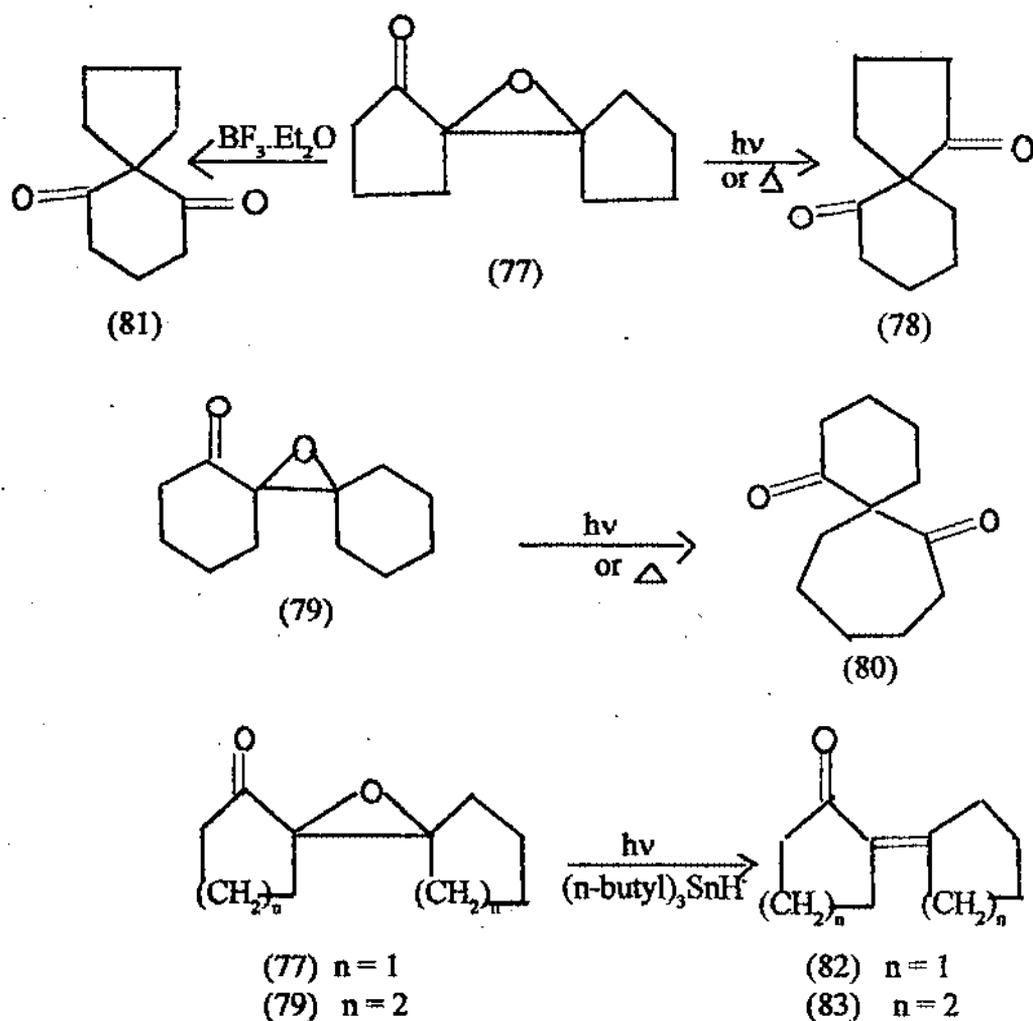
Wuthrich and coworkers²⁶ carried out studies on rearrangement and racemisation of spirocyclic α,β -epoxy ketones induced by direct UV irradiation as well as triplet sensitized by acetophenone. Spirocyclic α,β -epoxy ketone (R)-(-)(71) has undergone racemisation and rearrangement to the enantiomeric spiro- β -di ketones (R)-(+)(72) and (S)-(-)(72). They have applied spectral techniques including ORD/CD measurement for structure elucidation as well as racemisation studies. They have postulated the intermediate diradical type (X), produced by C_α -O epoxide cleavage, for rearrangement requires that the rate of rearrangement is greater than the rate of rotation around the $C_\alpha - C_\beta$ in (X) and the rate difference is greater in singlet-generated (X) than in the triplet analogue. The reclosure of diradical (X) and/or photolytic $C_\alpha - C_\beta$ cleavage to diradical (Y) and reclosure can account for the racemisation of (71).



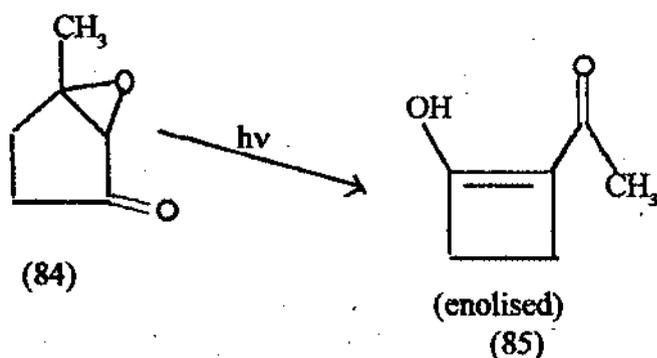
Gibson²⁷ conducted photolysis of the epoxide (73) derived from epoxidation of (-) trans-vervenone. Upon irradiation with a medium-pressure mercury arc lamp for 12 hr pentane or benzene solution of (73) produced a complex reaction mixture analysis of which by gas chromatography showed that starting material (73) comprised 56% of the mixture. Isolation of the products by preparative GLC and analysis by spectroscopic methods allowed the identification of the enol lactone (74) (30%), its isomer (75) (2%) and an inseparable 3:1 mixture of the ring-contracted diketone (76) (12%). When irradiation was performed with lamps emitting at 300 nm, only the ring-contracted diketone (76) was formed although at a slow rate.



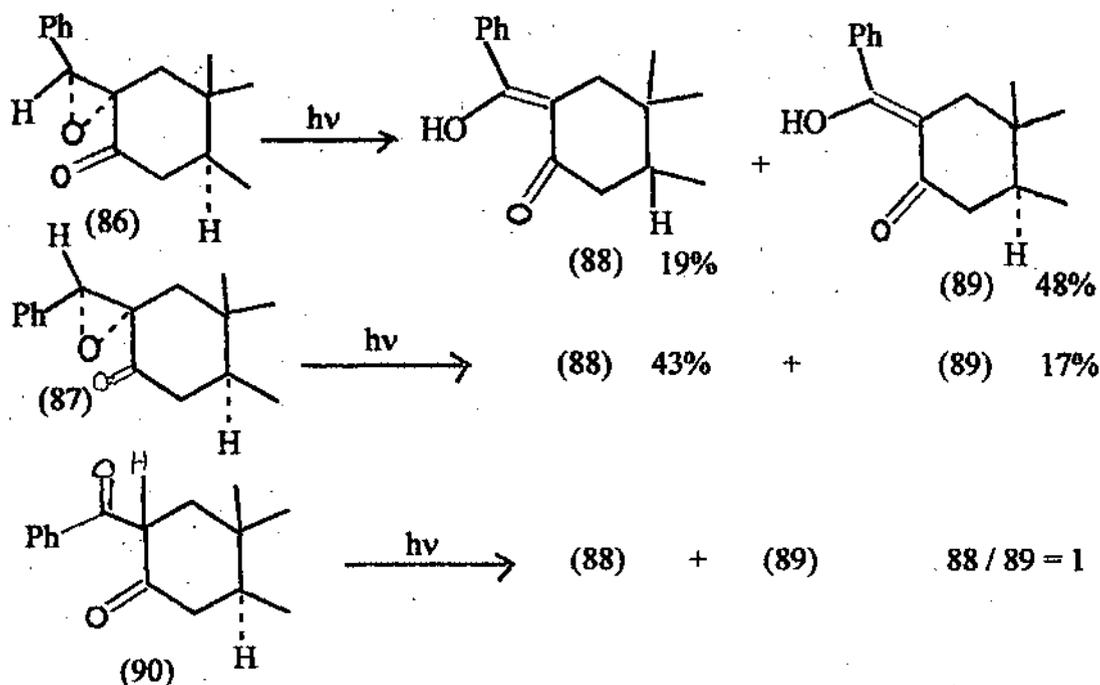
In order to synthesise spiro β -diketones, Williams et al.²⁸ subjected α,β -epoxy ketones to photochemical, thermal and acid-catalysed rearrangements. 2-cyclopentenyldene-cyclopentan-1-one oxide (77) and 2-cyclohexyldene-cyclohexan-1-one oxide (79) have been isomerised photochemically and thermally via 1,2-alkyl shift to spiro [4.5] decane - 1,6-dione (78) and spiro [5.6] dodecane - 1,7-dione (80), respectively. On the other hand, acid-catalysed isomerisation of (77) occurs via 1,2-acyl shift to yield spiro [4.5] decane - 6,10-dione (81). Interestingly, in the presence of tri-*n*-butyl stannane isomerisation does not take place and the reaction provides conjugated ketone with the elimination of epoxy oxygen, 2-cyclopentenyldene-cyclopentan-1-one (82) and 2-cyclohexyldene-cyclohexan-1-one (83) were formed respectively from the epoxy ketones (77) and (79).



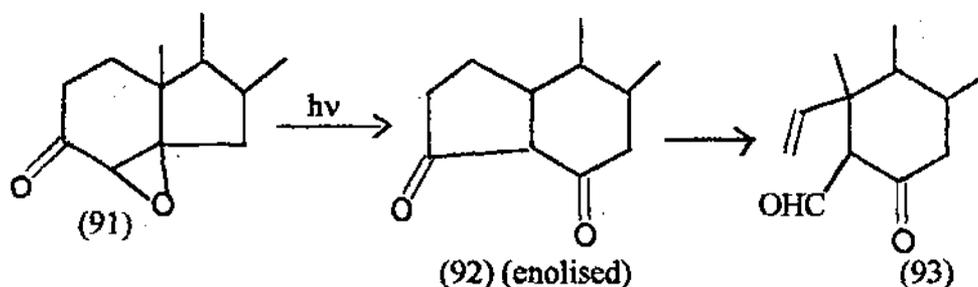
Wehrli et al.²⁹ reported the formation of a strained four-membered ring (85) from the photolysis of (84) a cyclopentane epoxy ketone. This constitutes the first example of rearrangement to a cyclobutanone derivative. The formation of this strained four-membered ring led them to prefer a single step or synchronous route for rearrangement from 1,3-diradical.



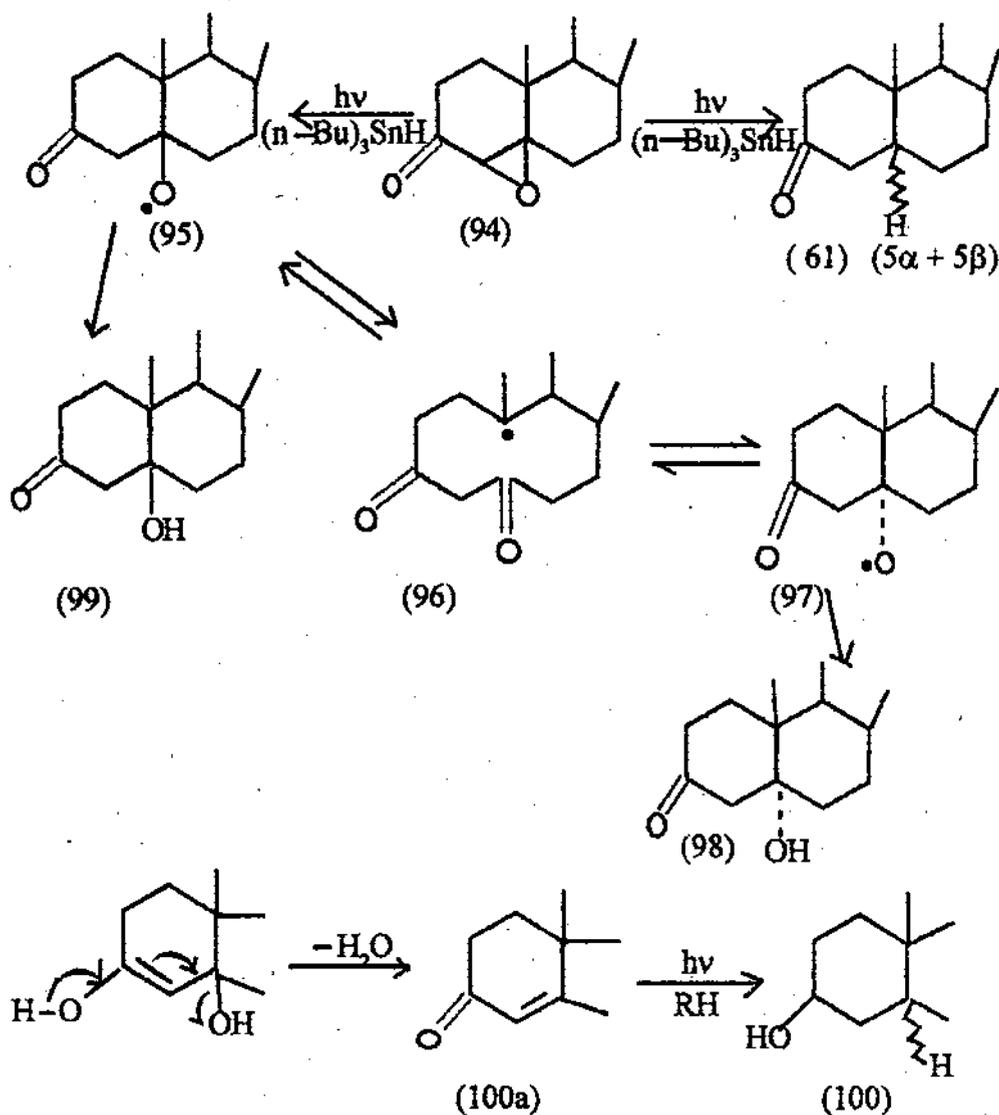
Muzart and Pete³⁰ prepared epoxides derived from 2-benzylidene-5 α -cholestan-3-one. The photochemical behaviour of these compounds depends considerably on stereochemistry. No photoepimerisation has been noticed. Expected β -diketones are formed. A δ hydrogen abstraction by the benzoyl group is involved in the photolysis of these diketones.



The initially formed β -dicarbonyl compounds are themselves photolabile and prolonged irradiation lead to further phototransformation, for example, the epoxy ketone (91) first gives rise to β -diketone (92) which undergoes partly α -cleavage and acyl-alkyl diradical disproportionation to the enolised unsaturated aldehyde-ketone (93)³¹.



In the presence of tri-*n*-butylstannane, a very good hydrogen donor, the photolytic reaction of epoxy ketones takes a different course^{32,33}. The steroidal epoxy ketone (94) on irradiation at > 310 nm in benzene solution is rapidly converted to a mixture of compounds (98) and (99) (74%, combined yield) and (100) (26%). It is proposed that the intermediate keto-oxy radical (95) which is in equilibrium with the isomer (97) through the diketo-alkyl radical (96) on addition of a stannane hydrogen produce (99) and (98), respectively. The formation of saturated ketones (100, 5α and 5β) has been postulated to involve the intermediacy of testosterone acetate (100a) resulting from the addition of a second hydrogen to the enol forms of (95) and (97) and subsequent elimination of water.



A discussion on the photochemistry of steroid with Δ^1 -4,5-epoxy-3-ketone system (101) is of much interest³⁴. The corresponding rearranged 3,5-diketone (102) is obtained in excellent yield upon excitation with light of wavelength 2537\AA to its π, π^* absorption band. This photolytic rearrangement does not occur on excitation with light of wavelength 3300\AA to its n, π^* absorption band. This wavelength dependence photoreaction of α', β' -unsaturated α, β -epoxy ketones has been attributed to the π^* -assisted cleavage and occurs selectively in the presence of additional nonconjugated keto groups which absorb in the longer wavelength only.

Here too, the rearrangement is stereospecific indicated by the reaction of the 4 β -methyl homologue (103) which give the 4 β -methyl diketone (104).

