

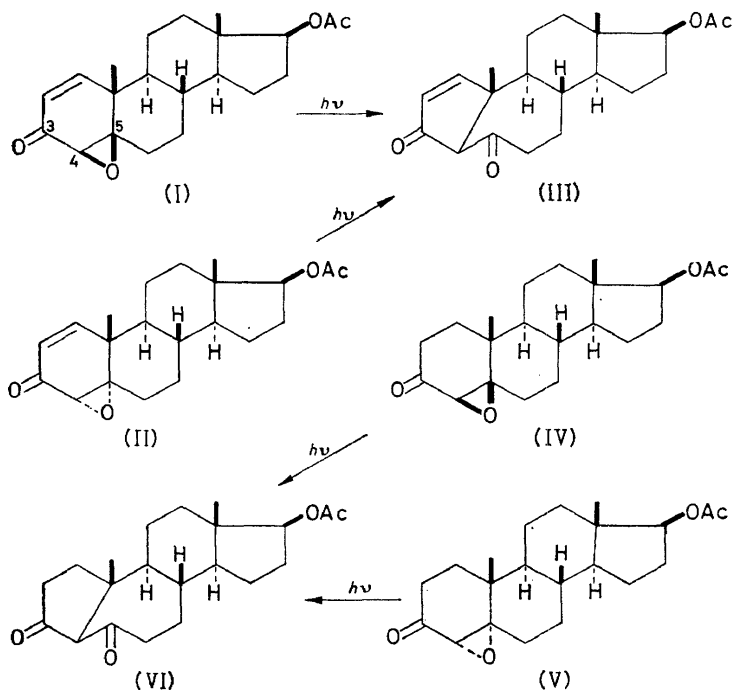
# PHOTOCHEMICAL TRANSFORMATION OF $\alpha,\beta$ -EPOXYKETONES AND RELATED CARBONYL SYSTEMS

O. JEGER, K. SCHAFFNER and H. WEHRLI

*Organisch-chemisches Laboratorium, ETH Zürich, Switzerland*

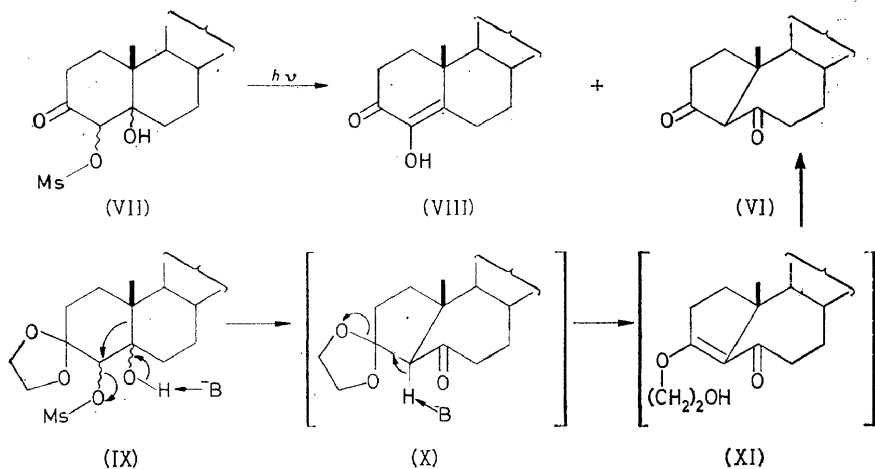
During recent years the photochemical transformations in solution of a number of alicyclic carbonyl systems have been systematically investigated in our laboratory. The main variations of this class of compounds with which our studies have until now been chiefly concerned, include non-conjugated ketones and aldehydes, homoallylic conjugated aldehydes,  $\alpha,\beta$ -unsaturated ketones, linear- and cross-conjugated dienones<sup>1</sup>. In the majority of cases, steroid derivatives have been used, as these compounds are readily available and moreover, a wide range of structural and steric variations is accessible by means of simple preparative methods.

Some three years ago, as part of this programme, the stereoisomeric 3-*exo*-4,5-oxido steroids (I) and (II), and (IV)<sup>2</sup> and (V)<sup>2</sup> respectively, were irradiated with ultraviolet light in solvents such as dioxan and ethanol<sup>3</sup>. Isomerization with opening of the oxide ring and 1,2-rearrangement of the



carbon skeleton took place in high yields. Irrespective of the relative configuration of the oxide ring, each of these two stereoisomeric pairs (I/II and IV/V) gave a single 1,3-diketone, the 10(5→4)-*abeo* steroids (III) and (VI)† respectively.

It should be mentioned here that two further methods have been found for the preparation in high yield of compounds of type (VI). For example, irradiation of the mesylate (VII) in benzene gave the 1,3-diketone (VI) as the major product, together with the 1,2-diketone (VIII)<sup>2</sup>. The nature of these light-induced conversions into (VI) and (VIII) is as yet unknown, and further work is necessary in this connection. It is, however, conceivable that the mesyloxy group is photolytically removed in a primary step. Subsequent epoxide formation (→ IV, V) should then lead to (VI) by a photorearrangement of the type already mentioned, and opening of the intermediately formed epoxide ring, catalysed by methane sulphonic acid, could yield compound (VIII). In a second—non-photochemical—method, the mesylate (IX) was treated with potassium *t*-butoxide to give compound (VI) directly, a process apparently brought about by 1,2-rearrangement (*cf.* IX)‡. The resulting 1,3-keto-ketal (X), which is unstable under the reaction conditions employed, collapses to (VI) *via*  $\beta$ -elimination of the ketal oxygen and subsequent hydrolysis of the resulting enol-ether (XI).



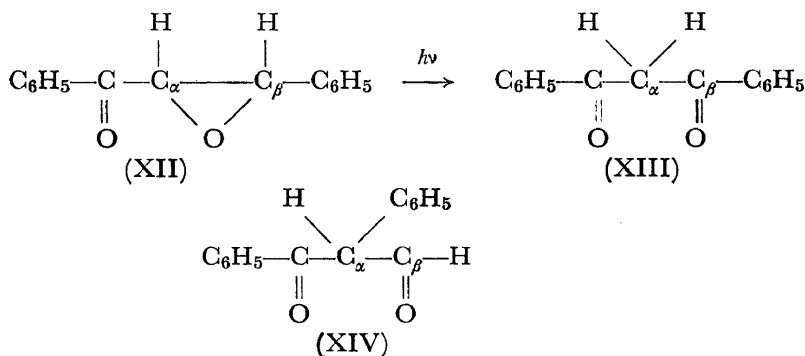
The investigations into the light-induced reaction of  $\alpha,\beta$ -epoxyketones, as illustrated by these few examples, constitute an elaboration of the earlier work of Bodfors.

As early as 1918, this author had described the rearrangement of benzalacetophenone epoxide (chalcone oxide XII) under the influence of ultraviolet light, to the corresponding 1,3-diketone (XIII)<sup>5</sup>. The photoisomerization of (XII) may be provisionally described by two consecutive

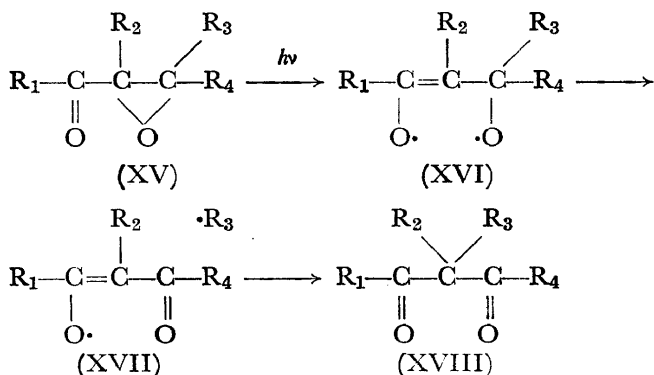
† The 1,3-dicarbonyl compounds discussed here are in most cases extensively enolized, so far that this is possible on structural grounds. For the sake of simplicity, they are represented in the formulas by their non-enolized forms.

‡ *Cf.* analogous rearrangements of compounds not possessing an oxygen function in position 3<sup>4</sup>.

steps: a fission of the  $C_\alpha$ -O bond of the oxide ring, followed by a 1,2-shift of the  $\beta$ -hydrogen to the  $\alpha$ -position. Contrary to the first step in the photo-reaction, thermal<sup>†</sup>, and acid or base-catalysed isomerizations of  $\alpha,\beta$ -epoxyketones proceed in general *via* fission of the  $C_\beta$ -O bond of the oxide ring. The formal first step of the photoreaction is reminiscent of light-induced fission processes which, in a like manner, result in the loss of electronegative substituents from the position  $\alpha$  (or in the vinylogous  $\alpha$ -position) to the keto group. Numerous examples are to be found in the literature, such as the gas-phase photolysis of chloroacetone<sup>7</sup>, and irradiation experiments in solution of carbonyl compounds possessing  $\alpha$ -substituents (*e.g.* amino<sup>8</sup>, halogen<sup>9</sup> or acyloxy<sup>10</sup>) or substituents (acetoxy<sup>11</sup> or hydroxy<sup>12</sup>) in the vinylogous  $\alpha$ -position. As Zimmerman<sup>13</sup> recently noted during a discussion on the reactivities of the  $n \rightarrow \pi^*$  excited states of carbonyl groups, such fissions may be traced back to the tendency of this excited chromophore to eliminate  $\alpha$ -substituents as odd electron or anionic species according to the reaction medium.

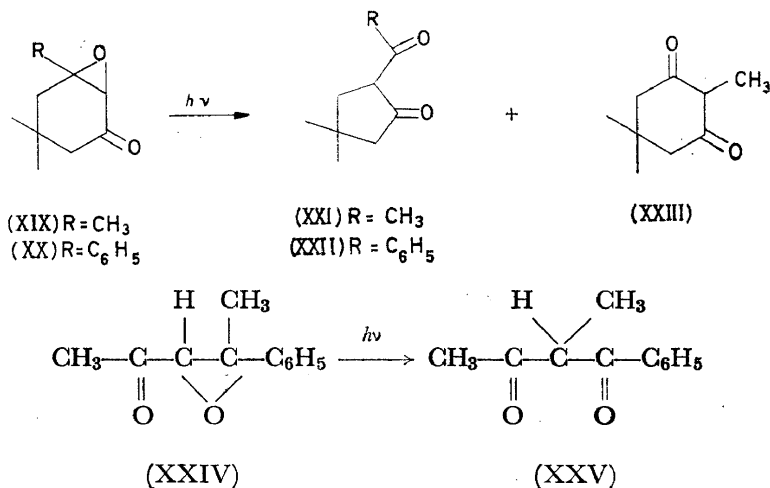


The not unexpected occurrence in the second formal step of a 1,2-migration of  $\beta$ -alkyl groups, as well as of hydrogen, was experimentally verified by the work of Reusch<sup>6</sup> and Zimmerman<sup>14</sup>, independent from, and



<sup>†</sup> The only known exception appears to be that provided by the stereoisomeric pulegone epoxides (LVII) and (LVIII), which yield a mixture of the two 1,3-diketones (LIXa) and (LIXb) by a thermal dark-process<sup>6</sup>.

at the same time as our work in this field<sup>8</sup>. The scheme (XV–XVIII)<sup>14</sup> presented in this connection does not define the exact nature of the 1,2-shift of R<sub>3</sub> (XVI–XVIII). In the case of aliphatic substrates, possibilities such as intramolecular transfer inside a solvent cage, intermolecular transfer, or concerted migration and ketone formation in the transition state (XVI), are left open. The ultraviolet irradiation of the epoxyketones (XIX), (XX) and (XXIV) did, however, lead to the significant conclusion that on isomerization to 1,3-diketones, the β → α shift of alkyl groups (methylene > methyl) dominates over the corresponding phenyl migration. This finding is in good agreement with a radical nature of the migrating group (*cf.* XVII)<sup>14</sup>. Thus on irradiation, isophorone epoxide (XIX) gave a 9 : 1 mixture of the 1,3-diketones (XXI) and (XXIII)<sup>6</sup>, whereas the phenyl analogue (XX) yielded solely the isomer (XXII)<sup>6</sup>, and only (XXV) was obtained from (XXIV)<sup>14</sup>. A similar relationship was observed on re-investigation of the irradiation of (XII) in our laboratory, when no aldehyde (*cf.* XIV) formation was detected. The opposite must be the case if phenyl migration were competitive.

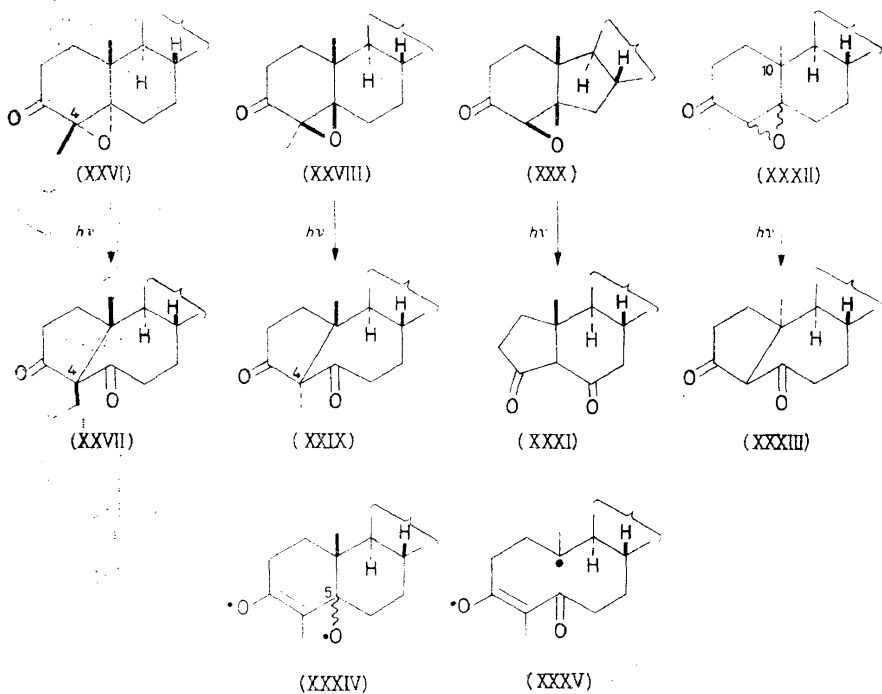


The previously mentioned skeletal rearrangements of 3-oxo-4,5-oxido-steroids, together with the following steroid transformations, provide an interesting contribution to the stereochemical aspects of this reaction. Irradiation in dioxan solution of the stereoisomeric methyl homologues (XXVI) and (XXVIII) (4-methyl-4,5-oxido-17β-acetoxy-androstan-3-ones) gave, in each case, specifically one product (XXVII) and (XXIX) respectively† (irradiation was discontinued after 66 per cent and 26 per cent, respectively, of starting material had been consumed)<sup>15</sup>. The two products are stereoisomers differing only in their configuration at C-4. This result can only be accommodated into the proposed reaction scheme (XV–XVIII),

† The stereochemistry at position 4, as shown in formulas (XXVII) and (XXIX), has not yet been experimentally proved. It corresponds to that arrangement which is to be expected from the proposed steric courses of the photochemical rearrangement. It is provisionally given here in order to clearly differentiate between the two stereoisomeric products.

if it is assumed that the cyclodecane system of the transition state (XXXV) (corresponding to XVII) as a consequence of its rigid conformation, retains the relative spatial arrangements of the reaction centres in the starting epoxyketone, thus making possible the observed stereospecificity of the rearrangement†.

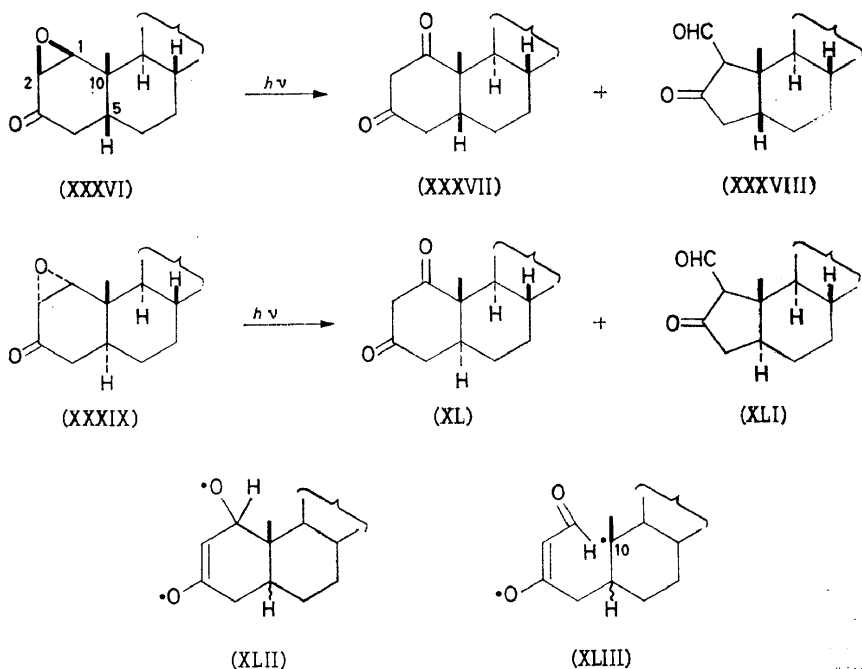
A second explanation of this rearrangement should also be considered, in which the shift of the 5,10-bond is concerted with the carbonyl formation at C<sub>(5)</sub> (cf. XXXIV  $\rightarrow$  products). Consequently, the radical centre at C<sub>(10)</sub> cannot assume a planar configuration, and hence the rearrangement is stereospecific. In this case, interaction between the radical position C<sub>(10)</sub> and the  $\pi$ -system in transition state (XXXV) (corresponding to XVII) has to be assumed. The same criteria may hold for the already mentioned steroid rearrangements (I, II  $\rightarrow$  III; IV, V  $\rightarrow$  VI) as well as for the similarly stereospecific rearrangements of  $\beta$ -nortestosterone acetate epoxide (XXX) to the diketone (XXXI), and of  $10\alpha$ -testosterone acetate epoxide (XXXII) to the diketone (XXXIII)<sup>15</sup>.



The extension of our researches to include the photochemistry of various other steroidal  $\alpha,\beta$ -epoxyketones, revealed not only the scope of this method of isomerization to 1,3-dicarbonyl compounds, but also produced additional information on the stereochemical requirements of  $\beta$ -alkyl group migration in alicyclic systems, as encompassed by the general reaction scheme (steps

† For transannular reactions in the cyclodecane series, see, for example, the reviews by Prelog<sup>16</sup>.

XVI–XVIII). Thus on irradiation in dioxan solution,  $1\beta,2$ -oxido- $17\beta$ -acetoxy- $5\beta$ -androst-3-one (XXXVI) underwent conversion into a mixture consisting of the 1,3-diketone (XXXVII) and the keto-aldehyde (XXXVIII). In a like manner, the  $5\alpha$ -isomer (XXXIX) gave a mixture of the 1,3-diketone (XL) and the keto-aldehyde (XLI)<sup>17</sup>. This formation of 1,3-diketones and keto-aldehydes may be envisaged as being the result of a 1,2-shift of hydrogen, and of a competing migration of carbon atom 10, respectively. The selectivity of the rearrangements (XXXVI  $\rightarrow$  XXXVII) and (XXXIX  $\rightarrow$  XLI) can only be explained by assuming that in the transformation of an intermediary species of type (XLII) (corresponding to XVI) to a keto-aldehydic end-product, no further intermediate of type (XLIII) (corresponding to XVII) can exist long enough to allow epimerization at C<sub>(10)</sub> to occur. In other words, these rearrangements may be considered as being of a synchronous nature. Such an interpretation, which was one of the explanations already given for the transformations of (XXVI) and (XXVIII), is also of use in connection with the conversions of (XLIV), (XLV) and (L), to be discussed later. Although the given concept of a “synchronous” rearrangement explains the overall steric course of these reactions, a more precise definition of the factors responsible for the “synchronization” of opening, migration, and ketone formation, is required. To this end a firmer experimental basis would seem desirable before entering into further discussion on this subject.

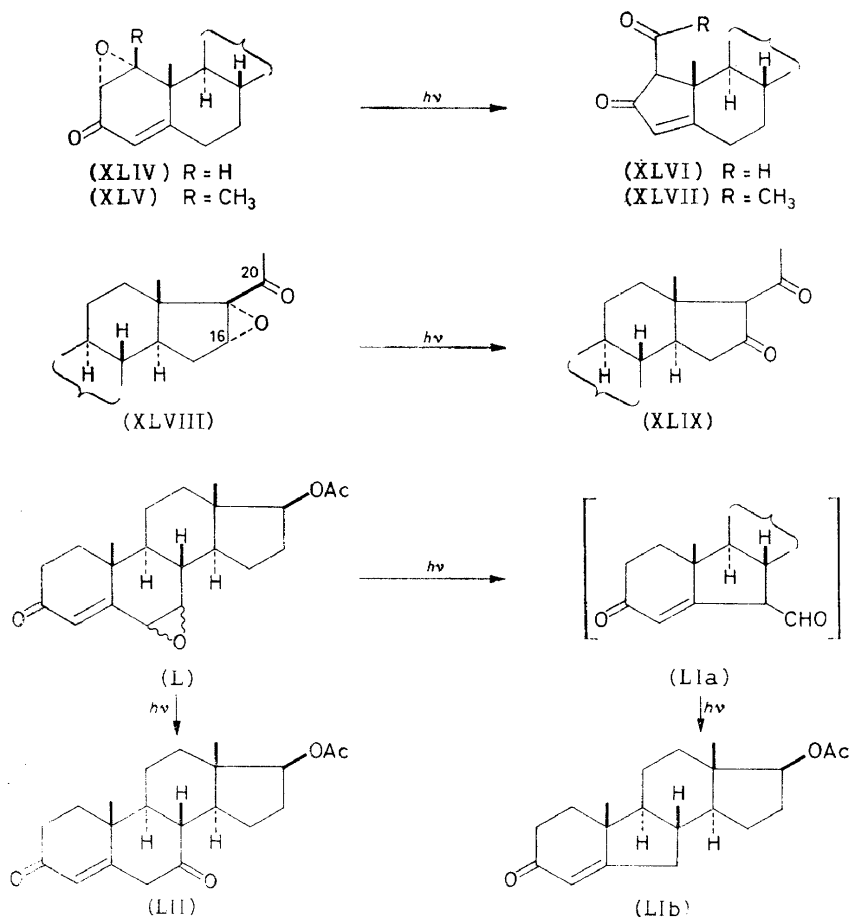


On irradiation of  $1\alpha,2$ -oxido- $17\beta$ -acetoxy-androst-4-en-3-one (XLIV) and its  $1\beta$ -methyl homologue (XLV) in dioxan, solely the  $\Delta$ -norcompounds (XLVI) and (XLVII) respectively, were isolated. When  $3\beta$ -acetoxy- $16\alpha$ ,

$\alpha,\beta$ -EPOXYKETONES AND RELATED CARBONYL SYSTEMS

17-oxido-pregn-5-en-20-one (XLVIII)<sup>18</sup> was irradiated, isomerization to the 16,20-diketone (XLIX) took place exclusively<sup>17</sup>. Here, migration of hydrogen instead of a 15(16  $\rightarrow$  17)-alkyl migration occurs, as the latter would lead to the highly strained *trans*-bicyclo[4,2,0]octane system of a D-norsteroid.

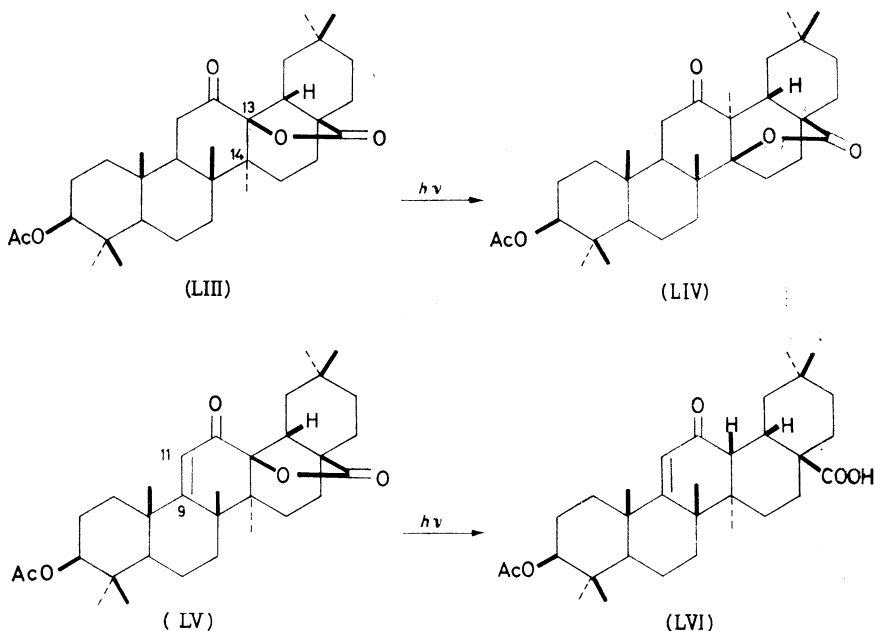
The light-induced epoxyketone rearrangement is also applicable to  $\alpha,\beta$ -unsaturated  $\gamma,\delta$ -epoxyketones. Thus compound (L) gave products (LIb) and (LII)<sup>19</sup>. (LIb) is obviously formed through ring contraction caused by a 1,2-alkyl shift, and subsequent photocarbonylation<sup>†</sup> of the intermediate



vinyllogous  $\beta$ -ketoaldehyde (LIa). (LII) arises from (L) by the competing 1,2-hydrogen shift. The reaction sequence (L  $\rightarrow$  LIb) offers a new and short approach to B-norsteroids.

<sup>†</sup> For the photodecarbonylation of a  $\beta,\gamma$ -unsaturated aldehyde in solution cf. Iriarte *et al.*<sup>20</sup>.

The rôle of the epoxide oxygen can be taken over by other oxygen functions in the  $\alpha$ - or, vinylogous  $\alpha$ -position, to a keto group. This is demonstrated by the photoisomerization of the saturated  $\gamma$ -lactone (LIII) of the oleanolic acid series to a  $\delta$ -lactone (probably LIV), in which the positions of attachment of the lactone ether oxygen at C<sub>(13)</sub>, and of the methyl group at C<sub>(14)</sub>, are interchanged. A different picture is provided by the 9,11-unsaturated  $\gamma$ -lactone (LV), which, under the same conditions (irradiation in a mixture of dioxane and ethanol), underwent reductive fission of the lactone ring and formation of the known acid (LVI)<sup>21</sup>.

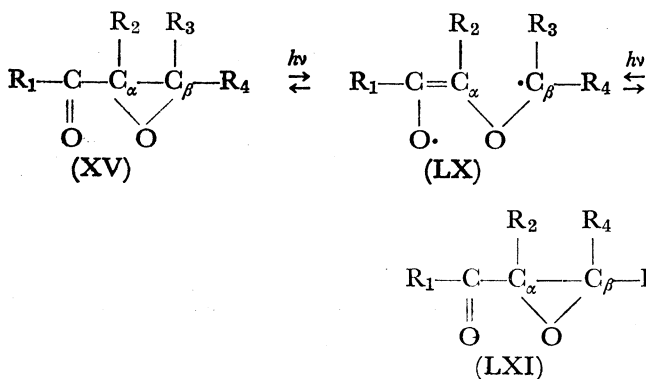
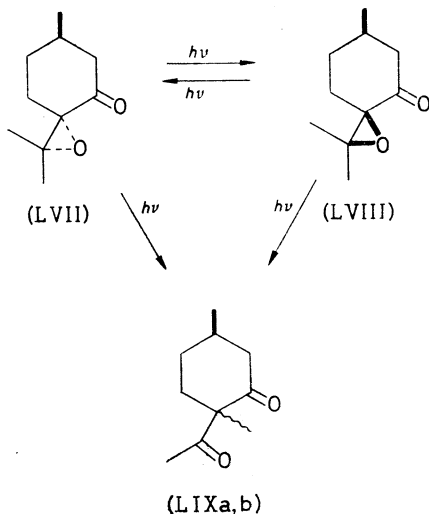


Isomerization to 1,3-dicarbonyl compounds is not the only photoreaction available to  $\alpha,\beta$ -epoxyketones. Reusch and co-workers<sup>6</sup> observed that the two stereoisomeric pulegone oxides (LVII) and (LVIII) were photochemically interconverted, rearrangement to the diketones (LIXa) and (LIXb) taking place at a slightly lower rate. In this case inversion of the stereochemistry of the oxide ring (LVII  $\rightleftharpoons$  LVIII) could be explained as being a reversible opening of the oxide ring involving C $_{\alpha}$ -O bond fission (corresponding to steps XV  $\rightleftharpoons$  XVI). Alternatively, the reaction may be envisaged as proceeding *via* fission of the C $_{\alpha}$ -C $_{\beta}$  bond (*cf.* the general scheme XV  $\rightleftharpoons$  LX  $\rightleftharpoons$  LXI). This second bond-fission process has already been observed elsewhere<sup>22</sup>.

Photolytic C—C bond fission has been firmly established in the case of *O*-acetyljerwine (LXII), which possesses an ether oxygen in the vinylogous

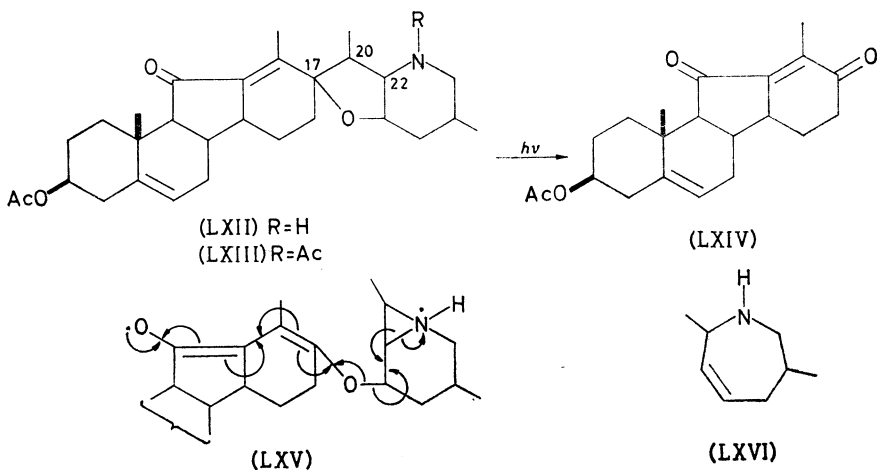


$\alpha,\beta$ -EPOXYKETONES AND RELATED CARBONYL SYSTEMS



$\alpha$ -position to a keto group. Thus on irradiation in dioxane, in the absence of oxygen, *O*-acetyljerine (LXII) underwent fragmentation, yielding the known compound (LXIV)<sup>23</sup> and a basic compound. Such a C—C bond fission can be reconciled with a suitable modified version of step (XV  $\rightarrow$  LX) in the scheme just mentioned. An important observation regarding this fragmentation is that when *N,O*-diacetyljerine (LXIII) was irradiated under the same conditions, no conversion into (LXIV) took place. This finding is indicative of an assistance by the basic nitrogen atom in the conversion (LXII  $\rightarrow$  LXIV). The diradical which can be assumed to result from fission of the 17,20 bond of (LXII), could be stabilized by the formation of an intermediate aziridinium radical (*cf.* LXV). Electron redistribution in the hypothetical intermediate (LXV) would then lead to the photoproduct (LXIV). In this case the second, basic, fragment should have the structure shown in formula (LXVI). The actual structure of this compound has not yet been verified. The photofragmentation of *O*-acetyljerine (LXII) is somewhat reminiscent of the hydramine fission

of this compound, catalysed by zinc chloride. In the latter reaction, however, the  $C_{(20)}-C_{(22)}$  and  $C_{(17)}-O$  bonds are cleaved<sup>23</sup>.



We are greatly indebted to our colleagues, namely, Dr J. Bollini, J. J. Bonet, G. Bozzato, Dr E. Cavalieri, J. Dual, G. Hüppi, P. Keller, Dr C. Lehmann, J. Saboz and Dr A. Siewinski, whose persistent efforts have played a major part in the successful pursuance of this work. We also thank Dr J. Hill for his generous assistance in translating the original German manuscript. Financial support by CIBA Aktiengesellschaft, Basel, is gratefully acknowledged.

## References

- <sup>1</sup> Cf. "Photochemical reactions", Part 29. *Helv. Chim. Acta* **47**, 1336 (1964), and earlier papers of this series;  
O. Jeger and K. Schaffner. *Chem. Weekblad* **60**, 329 (1964).
- <sup>2</sup> B. Camerino, B. Patelli, and A. Vercellone. *J. Am. Chem. Soc.* **78**, 3540 (1956).
- <sup>3</sup> C. Lehmann, K. Schaffner, and O. Jeger. *Helv. Chim. Acta.* **45**, 1031 (1962).
- <sup>4</sup> Y. Mazur and M. Nussim. *J. Am. Chem. Soc.* **83**, 3911 (1961).
- <sup>5</sup> S. Bodfors. *Chem. Ber.* **51**, 214 (1918).
- <sup>6</sup> C. K. Johnson, B. Dominy, and W. Reusch. *J. Am. Chem. Soc.* **85**, 3894 (1963).
- <sup>7</sup> A. N. Strachan and F. E. Blacet. *J. Am. Chem. Soc.* **77**, 5254 (1954).
- <sup>8</sup> C. Weizmann, Y. Hirsberg and E. Bergmann. *J. Am. Chem. Soc.* **58**, 1675 (1936); **60**, 1799 (1938);  
I. Mandel and A. D. McLaren. *J. Am. Chem. Soc.* **73**, 1826 (1951).
- <sup>9</sup> L. Farkas. *Z. Physik. Chem. (Leipzig)* **23**, 89 (1933);  
J. C. Anderson and C. B. Reese. *Tetrahedron Letters* **1962**, 1;  
J. J. Hlavka and H. M. Krazinski. *J. Org. Chem.* **28**, 1422 (1963).
- <sup>10</sup> H. Wehrli, M. Cereghetti, K. Schaffner and O. Jeger. *Helv. Chim. Acta* **43**, 367 (1960);  
H. G. Ferguson, P. de Mayo, F. L. M. Pattison, and T. Tabata. *Can. J. Chem.* **41**, 2099 (1963).
- <sup>11</sup> R. Warszawski, K. Schaffner, and O. Jeger. *Helv. Chim. Acta* **43**, 500 (1960).
- <sup>12</sup> C. Ganter, R. Warszawski, H. Wehrli, K. Schaffner, and O. Jeger. *Helv. Chim. Acta* **46**, 320 (1963).
- <sup>13</sup> H. E. Zimmerman. *Tetrahedron Suppl.* **2** **19**, 393 (1963).
- <sup>14</sup> H. E. Zimmerman, B. R. Cowley, C.-Y. Tseng, and J. W. Wilson. *J. Am. Chem. Soc.* **86**, 947 (1964).
- <sup>15</sup> H. Wehrli, C. Lehmann, K. Schaffner, and O. Jeger. *Helv. Chim. Acta* **47**, 1336 (1964).
- <sup>16</sup> V. Prelog and J. G. Traynham. In: P. de Mayo, *Molecular Rearrangements*, p. 603, Interscience Publ. New York (1963);  
V. Prelog. *Pure Appl. Chem.* **6**, 545 (1963).

$\alpha$ ,  $\beta$ -EPOXYKETONES AND RELATED CARBONYL SYSTEMS

- <sup>17</sup> K. Schaffner, H. Wehrli, and C. Lehmann. *Suppl. Abstracts*, 2nd I.U.P.A.C. Symposium on the Chemistry of Natural Products, Prague, Aug. 27th-Sept. 2nd (1962).
- <sup>18</sup> B. Löken, S. Kaufmann, G. Rosenkranz, and F. Sondheimer. *J. Am. Chem. Soc.* **78**, 1738 (1956).
- <sup>19</sup> J. Joska, J. Fajkoš, and F. Šorm. *Collection Czech. Chem. Commun.* **25**, 1086 (1960).
- <sup>20</sup> J. Iriarte, J. Hill, K. Schaffner, and O. Jeger. *Proc. Chem. Soc. (London)* **1963**, 114.
- <sup>21</sup> Cf. L. C. McKean, W. Manson, and F. S. Spring. *J. Chem. Soc. (London)* **1952**, 432.
- <sup>22</sup> E. F. Ullman. *J. Am. Chem. Soc.* **85**, 3529 (1963);  
J. M. Dunston and P. Yates. *Tetrahedron Letters* **1964**, 505;  
A. Padwa, *Tetrahedron Letters* **1964**, 813;  
H. E. Zimmerman and R. D. Simkin. *Tetrahedron Letters* **1964**, 1847.
- <sup>23</sup> J. Fried and A. Klingsberg. *J. Am. Chem. Soc.* **75**, 4929 (1953).