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REVIEW ARTICLE

Photochemistry of Steroids

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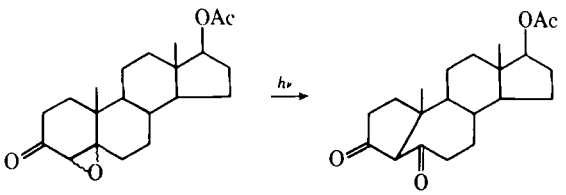
Research in the field of photochemistry has developed rapidly during the past decade and has now become sufficiently sophisticated to enable the chemist to use this method for synthetic preparative purposes. The steroid nucleus often serves as an excellent model for the study of photoreactions, and the products derived from these reactions are often unique and unattainable by the more classic organic pathways. The reactions described in this review should be of special interest to the organic medicinal chemist who seeks new approaches to compounds for pharmacological evaluation, and they often are applicable to other molecules besides steroids. Four of the more active areas of steroid photochemistry, which have been described in the literature since 1960, are discussed.

Commensurate with the growth of this field, a number of excellent reviews and surveys (1–4) and a series of monographs (5, 6) covering the general area of organic photochemistry were published recently and should be referred to if knowledge of the theoretical aspects of the various photoexcitation processes is required. Comprehensive texts on the organic chemistry of steroids serve as the basic sources of information in the field (7–9).

PHOTOREARRANGEMENTS

Photochemical rearrangements represent the largest single class of reactions in this review. The steroid nucleus in these photoproducts is usually altered to a greater degree than in linear compounds obtained from comparable photoreactions. Both free-radical and ionic intermediates have been postulated to account for the various transformations.

Photorearrangement ($n \rightarrow \pi^*$) of the saturated 3-keto-4,5-epoxy steroid (I*a* or I*b*) in dioxane gave the

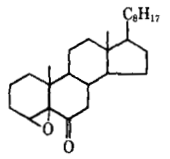
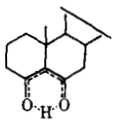
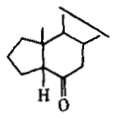
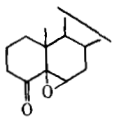
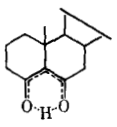
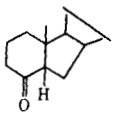
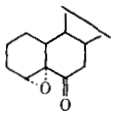
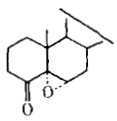
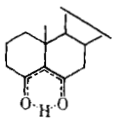
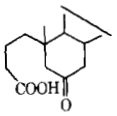


I*a*: 4β,5β
I*b*: 4α,5α

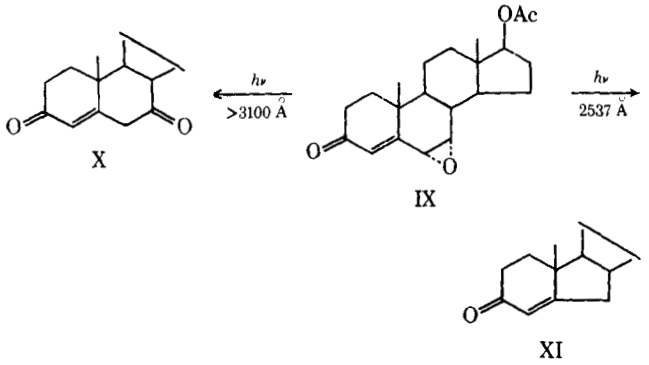
II

Scheme I

Table I—Photoreactions of Epoxyketones

Starting Material	Photoproducts	
 III	 25%	 22%
 IV	 45%	 3%
 V		
 VI	 30%	 35%

novel 3,5-diketo-10(5 → 4)-*abeo* derivative (II) (10) (Scheme I). The yields are sufficiently high so that the reaction may serve as a useful synthetic method. The

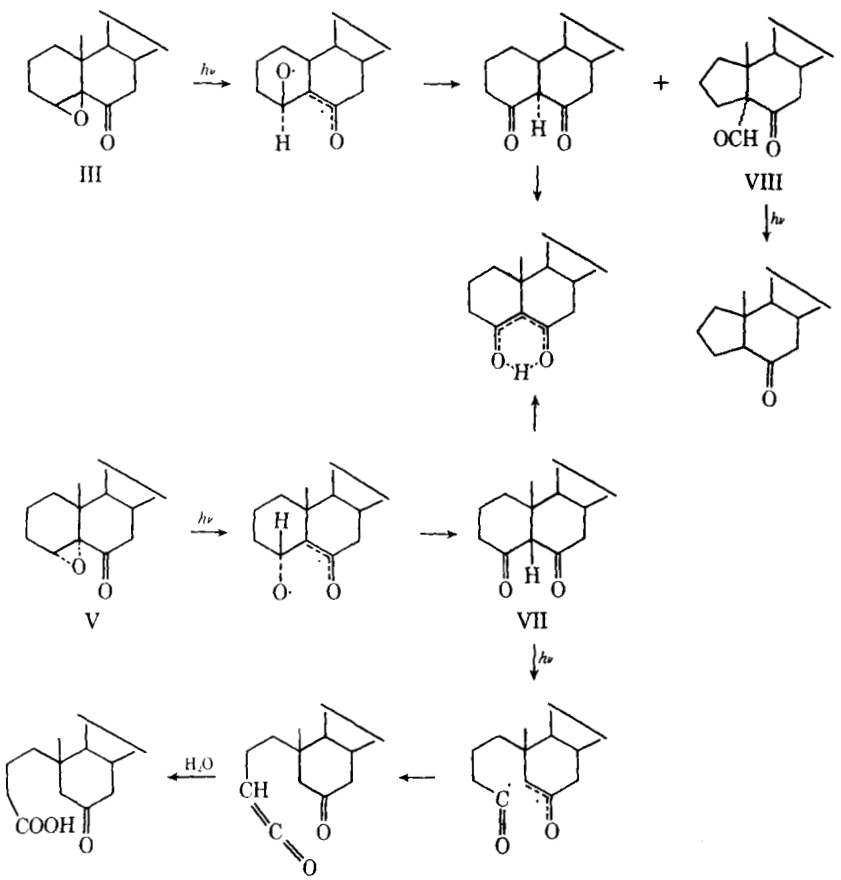


Scheme III

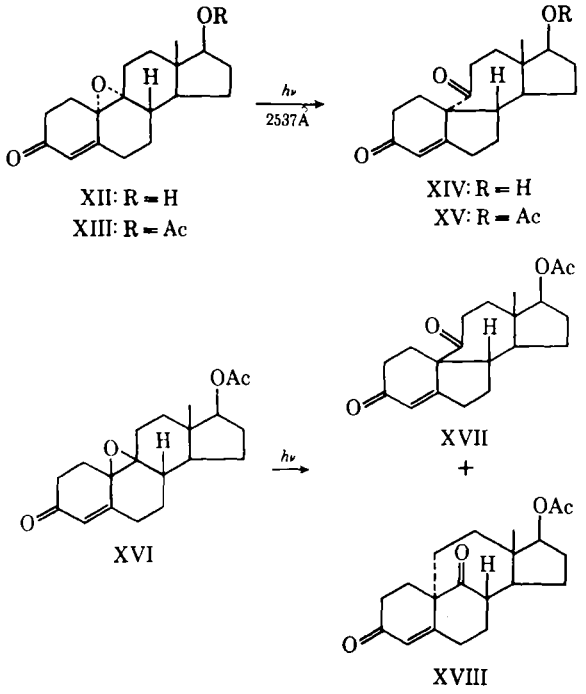
Δ^1-unsaturated and 4-methyl analogs of I*a* or I*b* on selective excitation ($\pi \rightarrow \pi^*$) undergo similar rearrangements to the corresponding unsaturated β-diketones. In later studies of the mechanism of this reaction, a biradical 1,2-alkyl shift without epimerization at C-4 or C-10 was postulated (11, 12).

In contrast to these reactions, irradiation of epoxyketones III, IV, V, and VI, in which the epoxy and/or keto groups are in different positions, gave 1,3-diketones, ring-contracted compounds, and a carboxylic acid (13) (Table I). Scheme II illustrates the formation of these three different types of compounds *via* a biradical species. Intermediates of types VII and VIII can then undergo further photolysis to yield the carboxylic acid and ring-contracted ketone, respectively.

The vinylogous epoxyketone—*viz.*, the α,β-unsaturated-γ,δ-epoxyketone (IX), on irradiation above 3100



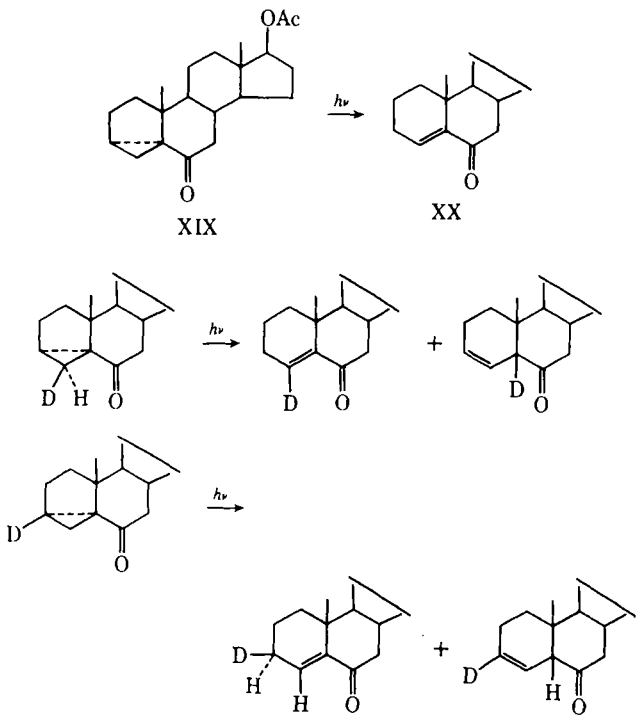
Scheme II



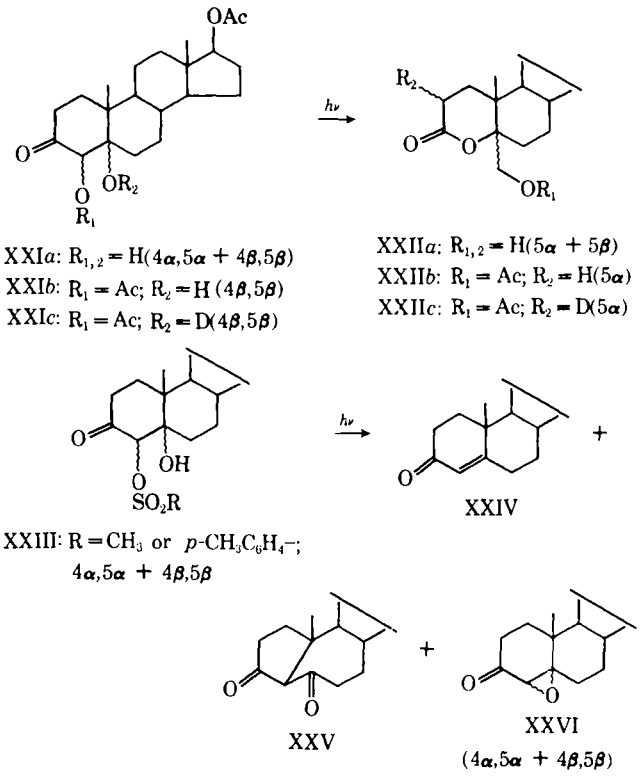
Scheme IV

Å, or on triplet-state sensitization with acetophenone, afforded the δ-diketone (X) in high yield (14). The reaction is initiated by cleavage of the γ-oxide bond with concomitant shift of the δ-hydrogen. However, $\pi \rightarrow \pi^*$ excitation at 2537 Å in anhydrous dioxane led to the formation of the B-nor-α,β-unsaturated ketone (XI) (Scheme III).

A similar class of compounds, in which the epoxy group is situated at the 9,10-position, was also studied (Scheme IV). Irradiation of 9α,10α-epoxy-17β-hydroxy-



Scheme V



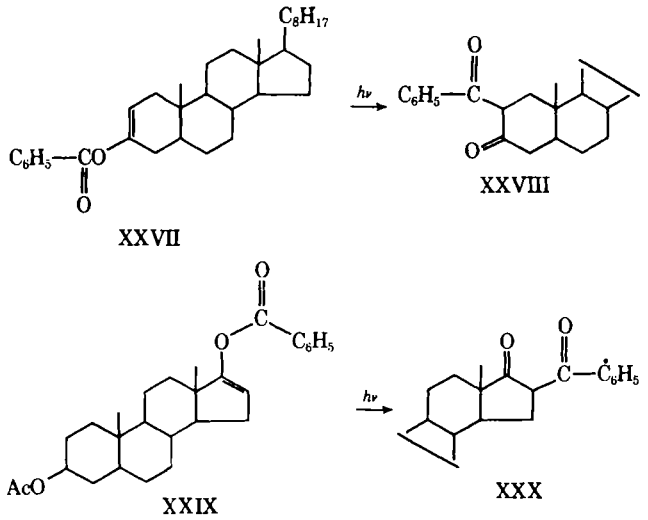
Scheme VI

4-en-3-one (XII) and of its acetate (XIII) at 2537 Å gave 17β-hydroxy-8(9 → 10)-*abeo*-3-ene-3,9-dione (XIV) and acetate (XV), respectively, whereas photolysis of the corresponding epimer (XVI) resulted in a 3:1 mixture of two isomers, namely, 8(9 → 10)-*abeo* (XVII) and 11(9 → 10)-*abeo*-10α (XVIII) steroids (15).

The photochemistry of the cyclopropane ring in conjugation with a keto group was studied in aliphatic and alicyclic systems (16) and recently applied to steroids. Photolysis of the 3α,5α-cyclo-6-ketone (XIX) in dioxane or ethanol gave the Δ^4-6-keto compound (XX) as the major product (13 and 20%, respectively) (17). A minor compound (0.5%) from the irradiation in dioxane was postulated to be a photodimer of XX, linked at position C-3. In a related study, the Δ^4-6-ketone (60–75%) analogous to XX and the nonconjugated Δ^3-6-keto compound (10–15%) were obtained by irradiation of 3α,5α-cyclo-6-ketoandrostane (18). With the aid of compounds labeled with deuterium at C-3 and C-4, it was shown that a stereospecific 1,2-shift of the 4β-hydrogen to C-5 gave the 6-keto-3-ene, while a 1,2-shift of the 4α-hydrogen to C-3 gave rise to the 6-keto-4-ene (Scheme V).

Direct $n \rightarrow \pi^*$ excitation or benzene sensitization of the α-hydroxy (or acetoxy) 3-keto steroids (XXI*a*, XXI*b*, and XXI*c*) resulted in α-fission of the bond between the keto and hydroxy (or acetoxy) groups to give the isomeric lactones (XXII*a*, XXII*b*, and XXII*c*, respectively) (19) (Scheme VI). In the structurally related α-sulfonyloxy ketones (XXIII), the substituent is eliminated to give Compounds XXIV–XXVI (19, 20).

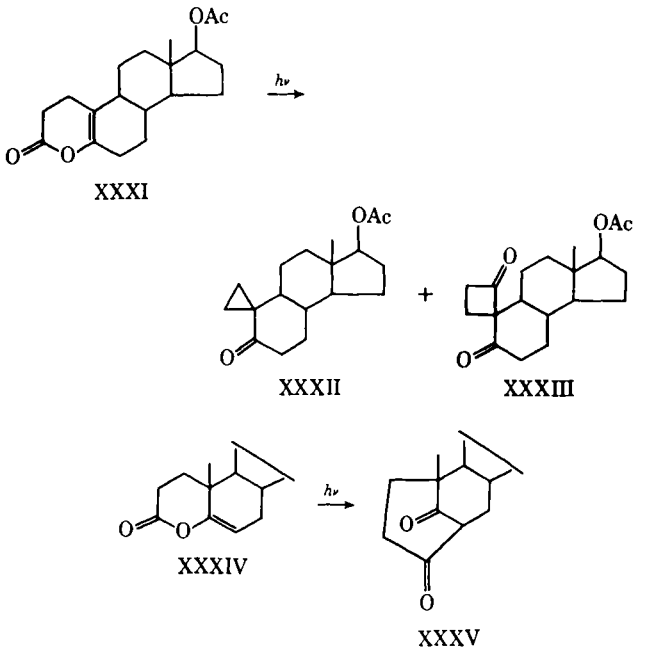
In a study of steroidal enol benzoates, irradiation of cholest-2-en-3-ol benzoate (XXVII) in cyclohexane with a low pressure mercury lamp yielded 2-benzoylcholestan-3-one (XXVIII) (21). In the androstane series, pho-



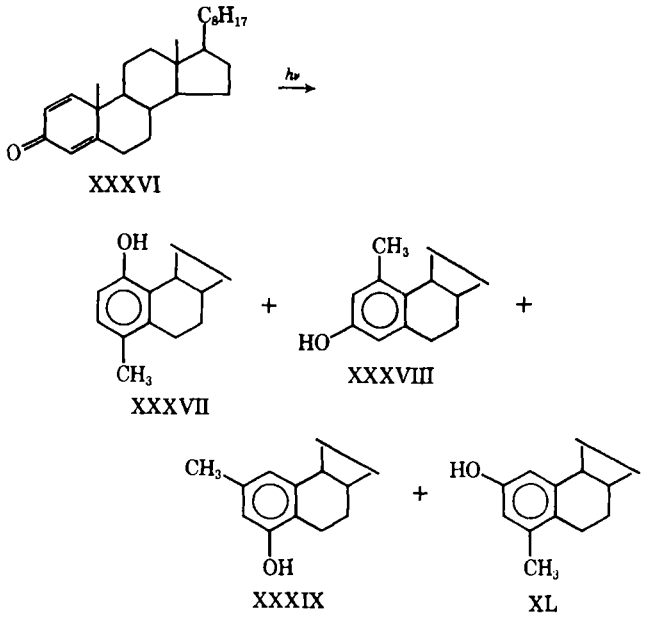
Scheme VII

tolysis of XXIX (22) afforded 16-benzoyl-5α-androstan-3β-ol-17-one acetate (XXX) in 22% yield (Scheme VII). Apparently, these products are formed by homolysis to the benzoyl and olefinic radicals and recombination to the α-benzoyl ketones. Similarly, irradiation of 2-en-3-ol and 16-en-17-ol acetates (23) results in the migration of the 3- and 17-acetyl groups to positions 2 and 16, respectively. Irradiation of a mixture of two different enol acetates, one deuterated in the acetyl group and the other nondeuterated, established the absence of exchange and the fact that acetyl migration was an *intramolecular* and not an *intermolecular* process. These experiments indicate that the acetyl radicals are not free but are trapped in a solvent cage. Studies with 2-methyl-3,17β-diacetoxy-5α-androst-2-ene gave a mixture consisting of a dimer, an acetyl-migration compound, and two other compounds (23).

Conjugated dienol acetates derived from testosterone and 4-methyltestosterone undergo acetyl rearrangement



Scheme VIII



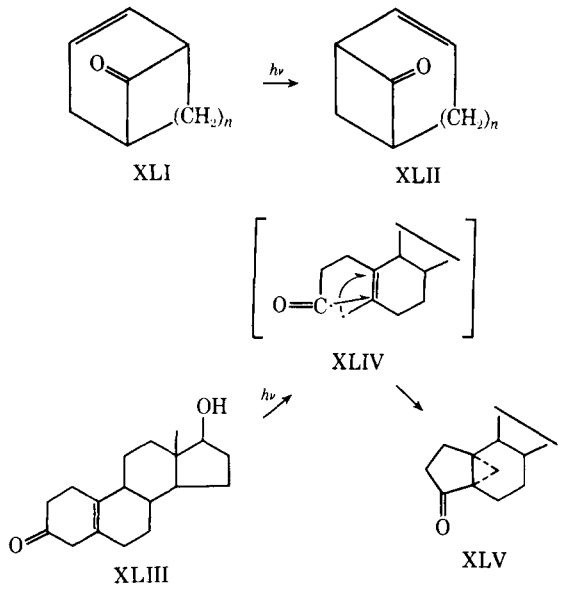
Scheme IX

from oxygen at C-3 to the C-4 and C-6 positions (24). Recently, photolysis of steroidal enol and dienol trichloroacetates was investigated. As a result of competitive fission of the carbon–chlorine and carbon–carbon bonds, some novel rearrangement products are obtained as well as the usual acyl-migration products (25). In a study of the irradiation of enol ethers, benzyl group migration was observed with benzyl-enol ethers of 4-cholesten-3-one (26).

An interesting rearrangement occurs upon irradiation of the steroidal lactone XXXI, in which a 50% conversion of XXXI takes place (Scheme VIII). The principal product was the cyclopropyl ketone XXXII (40%), in addition to the cyclobutanone XXXIII and a dimeric ketone (2%) (27). In contrast, irradiation of the Δ^5-lactone XXXIV with a low pressure mercury lamp (principal line at 2537 Å) afforded the diketone XXXV in 15% yield and starting material (85%). These results are best explained by a primary cleavage of the carbonyl oxygen bond to form a biradical, with subsequent recombination to diketone or loss of carbon monoxide with formation of the cyclopropyl compound.

In extensive studies of cross-conjugated 1,4-dien-3-ones (28), photorearrangement of *O*-acetyl-1-dehydrotestosterone and its 4-methyl analog in neutral media to a complex mixture of ketonic and phenolic isomers was described (29, 30) and subsequently summarized (31). Related studies of dienones in acidic media also were reported (32).

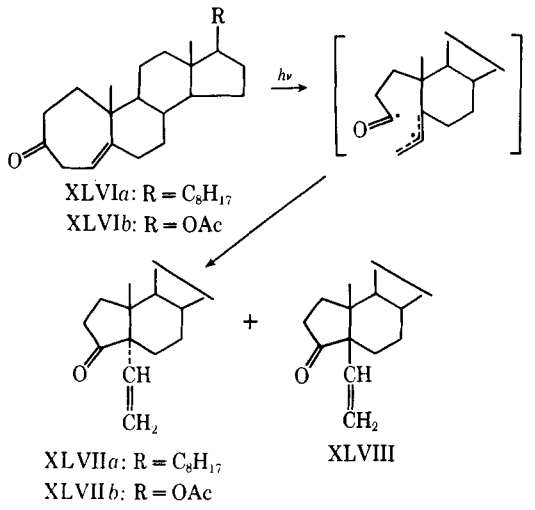
Irradiation of 1,4-cholestadien-3-one (XXXVI) in *tert*-butyl alcohol gave four phenols (XXXVII–XL) (33) analogous to those obtained from 1-dehydrotestosterone. Irradiation of the dienone XXXVI in the presence of sodium borohydride, which conceivably could attack zwitterionic species or bicyclohexenone intermediates, did not alter the reaction appreciably and again gave phenols XXXVII–XL (Scheme IX). The formation of phenols in lieu of sodium borohydride-reduced compounds in this photoreduction is in



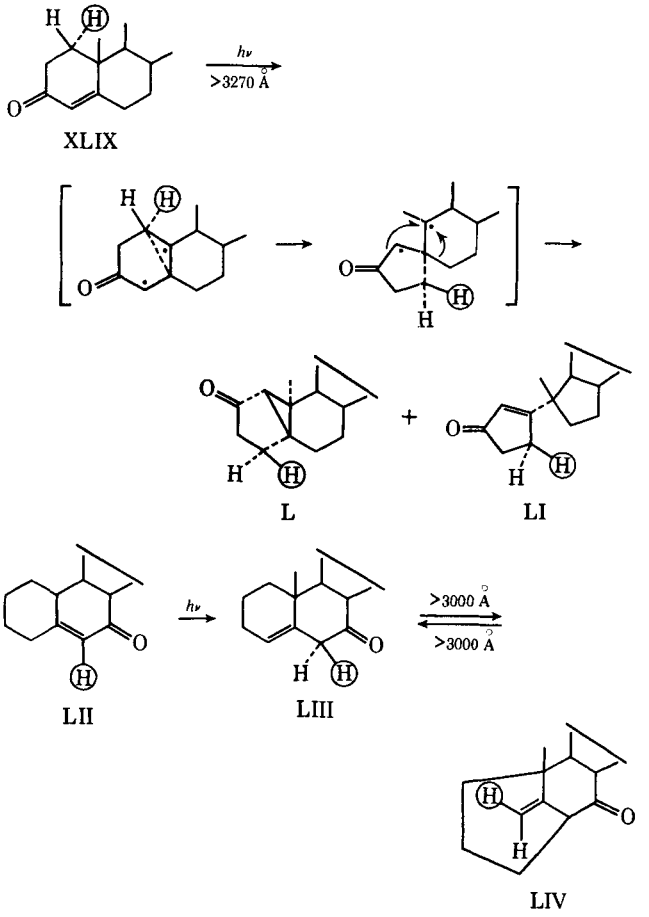
Scheme X

direct contrast to the photoreduction of 4-cholesten-3-one (discussed later), in which photo- and ground-state reduction products were essentially identical. Apparently this is because of the higher rate and quantum efficiency of triplet rearrangement in dienones in comparison with enones (34–36), coupled with the fact that the borohydride reduction of XXXVI in the ground state is extremely slow.

Whereas β,γ-unsaturated bicyclic ketones of type XLI undergo allylic rearrangement into cyclobutanones of type XLII (37) (Scheme X), irradiation of the more geometrically rigid 17β-hydroxyestr-5(10)-en-3-one (XLIII) in *tert*-butyl alcohol gave the ring-contracted cyclopropyl ketone XLV in 55% yield (38). The elucidation of the stereochemistry of the cyclopropane ring was based on optical rotatory dispersion measurements. Rearrangement of XLIII *via* a biradical species (XLIV) produced by α-cleavage at C-3,4 was postulated (38, 39). The rate of the reaction was reduced by piperylene, a triplet-state quencher. Also, photorearrangement of β,γ-unsaturated 3-ketones substituted in the 4-position was described recently (40, 41).



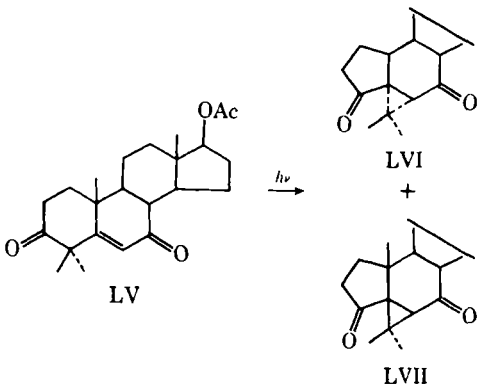
Scheme XI



Scheme XII

Studies of β,γ-unsaturated ketones of larger ring systems have provided some interesting A-nor steroids. Photolysis of the seven-membered ring A-homo-4*a*(5)-cholesten-3-one (XLVI*a*) afforded a mixture of 5α-(XLVII*a*) and 5β-vinyl-A-norcholestan-3-one (XLVIII) (42) (Scheme XI). Interestingly, irradiation of an analog, namely, A-homoandrostenone (XLVI*b*), gave XLVII*b* as the sole product in high yield (74%). The formation of the *cis*- and *trans*-isomers was rationalized as proceeding *via* the allyl radical intermediate.

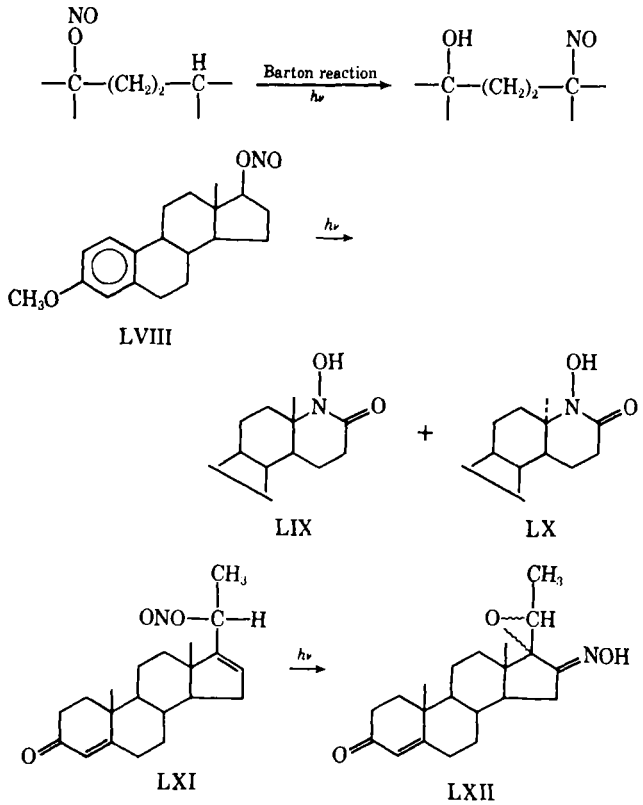
Conjugated enones in their photorearrangements resemble cross-conjugated dienones. For example, 4-cholesten-3-one (XLIX) (43, 44) or 17-acetyltestosterone (45–47), when photolyzed with a high pressure lamp in *tert*-butyl alcohol, gave the cyclopropyl ketone L and the cyclopentenone LI. The course of the reaction depends upon the solvent. Sensitization and quenching experiments provided evidence for the occurrence of a triplet-state intermediate. By contrast, irradiation of 5-en-7-one systems, *e.g.*, 5-cholesten-7-one (LII) (48), at wavelengths greater than 3000 Å afforded the deconjugated enone LIII, which is subsequently converted to the rearranged ketone LIV *via* $n \rightarrow \pi^*$ singlet excitation (Scheme XII). A photostationary state between LIII and LIV was observed. When LII was irradiated with a low pressure lamp, enone LIII and two dimeric compounds were obtained (49). Other photodimerizations of steroidal 4-en-3-ones and 4,6-dien-3-ones were reported (46, 50).



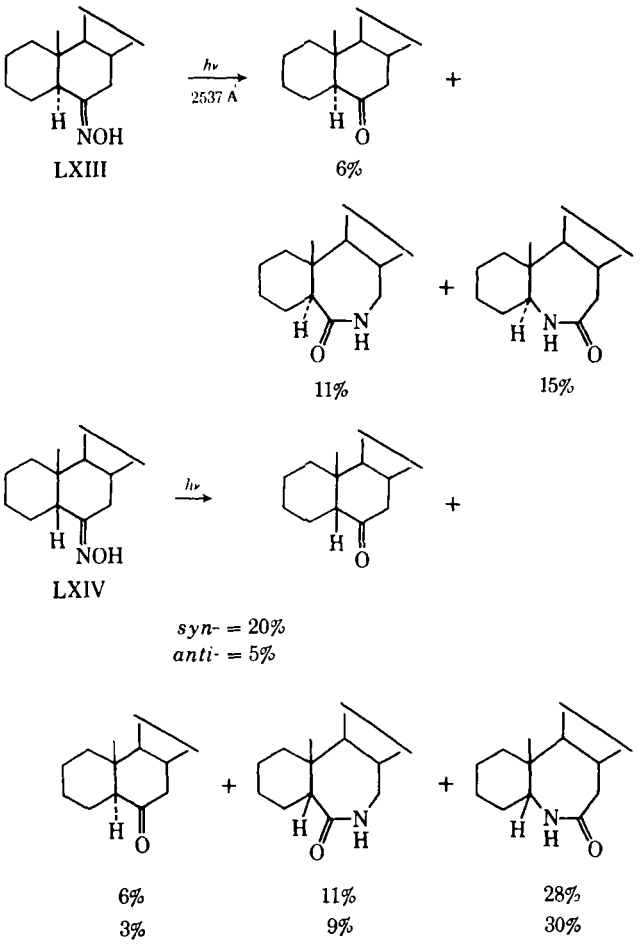
Scheme XIII

Enediones, where one of the keto groups is in conjugation with the olefin, such as 4,4-dimethyl-17β-acetoxy-5-androsten-3,17-dione (LV), rearranged to the two diastereoisomeric 3(4 → 5)-*abeo*-4,6-cyclo-androstanes (LVI and LVII) upon irradiation at 2537 Å or above 3400 Å (Scheme XIII) (51). The mechanism was elucidated using C-4-methyl deuterium-labeled analogs (52). The photorearrangement of 1,5-dien-3-ones in the androstane series (46, 53, 54) was recently studied. Mechanistically, these reactions resemble those of the conjugated enone rearrangements.

In 1960, the photolysis of nitrites (the Barton reaction), proceeding *via* a free-radical mechanism (six-membered ring transition state), was described (55) and subsequently reviewed (56). The general reaction is illustrated in Scheme XIV. Later, a study of the steroidal 17-nitrite system was prompted by the possibility of a photoinduced five-membered transition



Scheme XIV



Scheme XV

state. Photolysis of estradiol 3-methyl ether 17β-nitrite (LVIII) in benzene (200-w. Hanovia mercury lamp, Pyrex filter) gave the two isomeric hydroxamic acids LIX and LX (57). Isolation of both hydroxamic acids lends support to carbon–carbon fission at C-13 and C-17 of the intermediate alkoxy radicals derived from LVIII. Application of this photoreaction to the pregnane series, *e.g.*, 4,16-pregnadien-3-one-20β-nitrite (LXI), afforded the 16-hydroxyimino-17ξ,20ξ-epoxy derivative (LXII). An interesting conversion of triterpenoids into 14-methyl or 4α,14-dimethyl steroids using the Barton photoreaction in one of the synthetic steps was recently reported (58). Several side reactions accompanying this reaction were demonstrated (59–61).

The nature of the photochemistry of oximes varies considerably, depending on the location of the oxime on the steroid nucleus. Oximes of cholestan-3-one, 4-cholesten-3-one, 2-cholesten-3-one, and 2,4-cholestadien-3-one are photolyzed to the parent ketones (62), while the acetate and benzoate esters of oximes yield the corresponding ketones and oximes (63). By contrast, the oximes of ring B ketones, 5α-cholestan-6-one and 5β-cholestan-6-one (LXIII and LXIV), undergo photo-Beckmann rearrangement to some extent as shown in Scheme XV (64). Oxaziridines are intermediates in these rearrangements (64, 65).

Photolysis of 6-nitrocholesteryl acetate (LXV) in hexane or dioxane by a high pressure mercury lamp

equipped with a Pyrex filter gave the unconjugated nitroolefin (LXVI) (30%), isoxazole (LXVII) (10%), and by-products LXVIII and LXIX (66) (Scheme XVI). Interestingly, irradiation of LXV in ethanol (medium pressure lamp, no filter) (67) gave LXX (38%), LXVIII (2.5%), and LXIX (6.9%), while irradiation in acetone (68) gave products LXX (22%), LXIX (3%), and LXXI (52%, 1:1 mixture of 6α- and 6β-isomers). Compound LXVIII, on irradiation in acetone, gave predominantly LXX (68); hence, LXVIII is most likely an intermediate in the reaction to the oxime LXX (66–68). An $n \rightarrow \pi^*$ excitation of LXV followed by intramolecular rearrangement is favored instead of a dissociation–recombination mechanism.

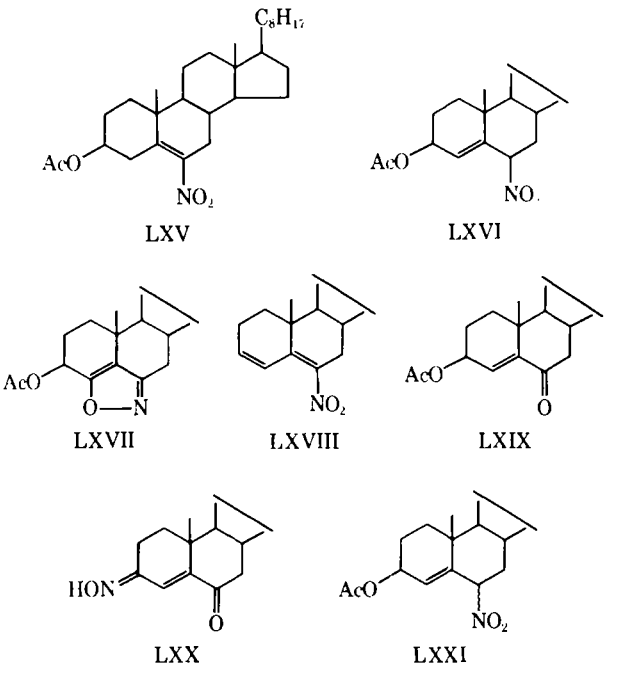
In 1962, the photolysis of azides into pyrrolidine derivatives was described and then subsequently utilized in an attempted partial synthesis of conessine (69). Irradiation of the unstable 6β-azido-5α-cholestane (LXXII) did not give the expected 6β,19-cyclic imino derivative (LXXIII); instead, ring expansion to the aza-B-homocholestene (LXXIV) (70) was observed (Scheme XVII). Another example of such a ring expansion was also described (71). In the pregnane series, irradiation of the 20α-azido LXXV with a high pressure lamp equipped with a Vycor filter afforded the dimeric Schiff base LXXVI. The structure of LXXVI was established by acid hydrolysis to 5α-pregnan-20-one and 17β-aminoandrostane (72, 73).

Other unusual photorearrangements of nitrogen-containing steroids include the formation of an A-norestrene by photolysis of a diazo derivative (74) and oxaziranes from steroidal nitrones (75).

PHOTOADDITIONS

Photoadditions of steroids usually occur by addition of solvent molecules, such as alcohols or water, to the excited state of the steroid, or by cycloaddition of low molecular weight olefins to the photoexcited molecule. These additions make accessible steroids of biochemical importance, having new polar groups or ring substituents, and may be used to study enzyme–substrate interactions.

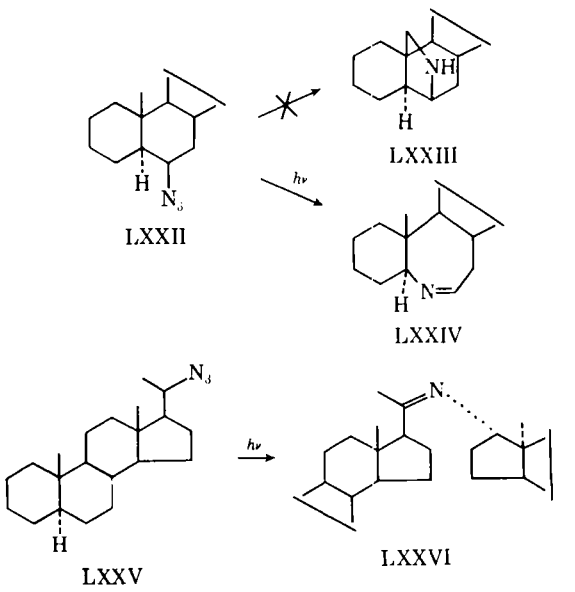
Cycloalkenes, such as (+)-3-carene and l-menthene, undergo photosensitized addition of water and alcohols to form saturated alcohols and ethers (76). Analogous photoadditions to steroidal olefins and olefinic alcohols have now been demonstrated. Irradiation of cholesterol (LXXVII) or 4-cholesten-3β-ol (LXXVIII) in the ternary solvent system of *tert*-butyl alcohol, xylene (the photosensitizer), and water gave 5β-cholestan-3β,5-diol (LXXIX) (54%), illustrative of stereospecific addition of water to the double bond, and 3β,5-oxidomethylene-5β-A-norcholestane (21%) (LXXX) (77) (Scheme XVIII). When the irradiation was carried out in an aprotic solvent, the oxetane LXXX, the ether adduct LXXXI, and the *seco* olefin-aldehyde LXXXII were obtained (78). Isolation of the olefinic aldehyde, formed *via* the intermediate carbonium ion, and subsequent irradiation showed the aldehyde LXXXII to be an intermediate on the way to the oxetane (79, 80). A detailed study of the mechanism is forthcoming (79).



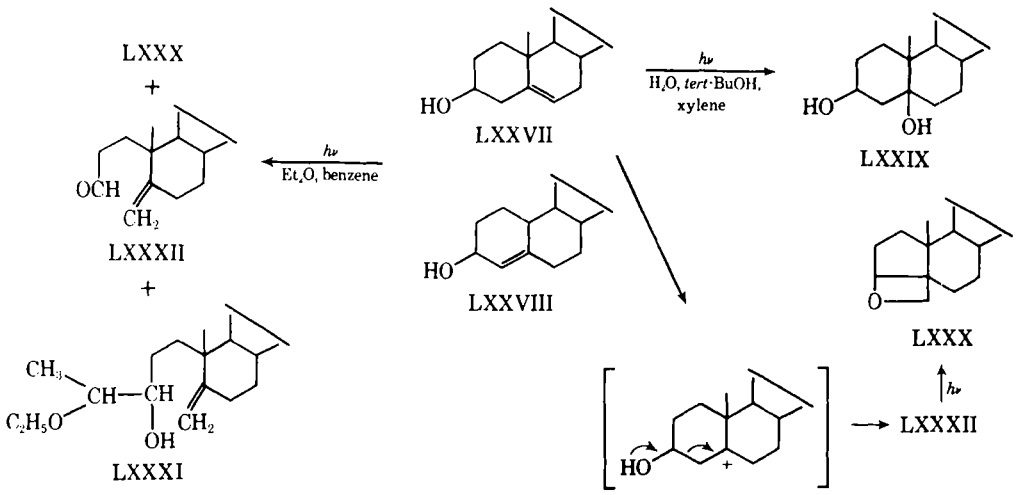
Scheme XVI

Photoaddition of alcohols to steroidal olefins (with no other substituents) was also observed (81).

The photochemistry of conjugated dienes has been studied extensively (82). Some interesting applications to steroidal dienes have been reported. Photolysis of 3,5-cholestadiene (LXXXIII) in ethanol afforded the isomeric ethyl ethers LXXXV and LXXXVI *via* the bicyclobutane intermediate LXXXIV shown in Scheme XIX (83). The homologous 3-methylcholesta-3,5-diene (LXXXVII), when irradiated in ethanol–pentane with a high pressure mercury lamp, gave 3-methylene-cholest-5-ene (LXXXVIII), 6β-ethoxy-3α-methyl-3β,5-cyclo-5β-cholestane (LXXXIX), 3β-ethoxy-3α-methyl-cholest-5-ene (XC), and 3α-methylcholesterol (XCI). When the photolysis was carried out in pentane, a unique 3β,5:4α,6α-bicyclo derivative (XCII) was obtained (84).



Scheme XVII



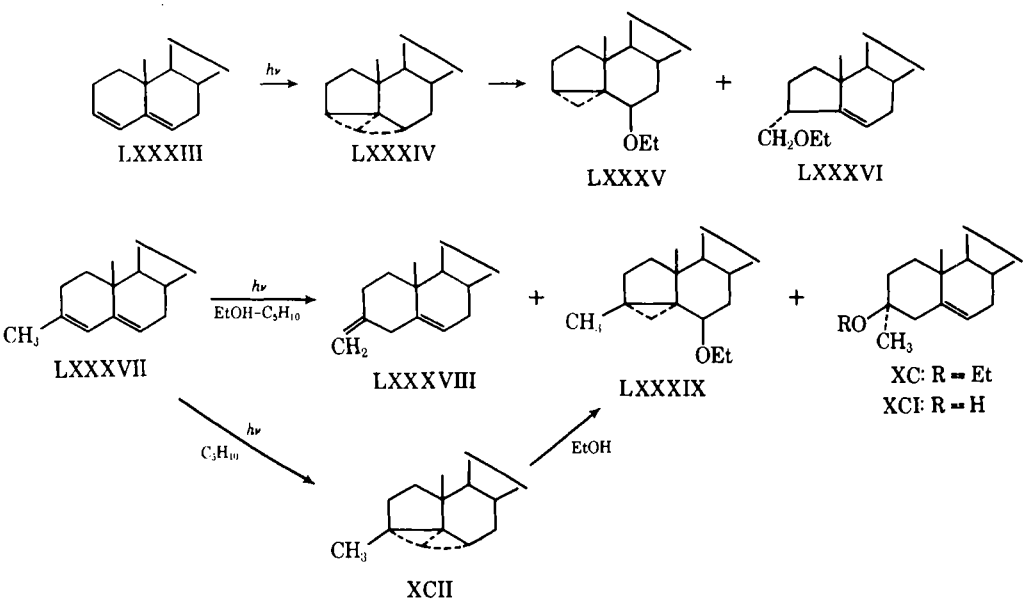
Scheme XVIII

Photosensitized irradiation of the diene XCIII in methanol containing benzene as a sensitizer was shown to give ethers XCIV (10%), XCV (5%), and XCVI (30%) (85). Further studies (86) of ethers showed that the enol ether XCVI is apparently the primary photoproduct, which subsequently undergoes photoallylic rearrangement (Scheme XX). Ethyl alcohol adds to 6-methylcholesta-3,5-diene (87) and cholesta-4,6-diene (88). Photoaddition of methanol to 3-alkoxy-3,5-dienes (XCVII) affords ketals of type XCVIII in good yields (89). The photoinduced reactions of numerous 3,6-substituted cholesta-3,5-dienes in a variety of solvent systems were studied (90). Irradiation (maximum output at 2537 Å) of the 7-formyl-diene (XCIX) in methanol gave the novel tetramethoxy Compound C in high yield. The 3-ketal is formed before the acetal, as shown by appropriate irradiation experiments of CI to yield C (91) (Scheme XX).

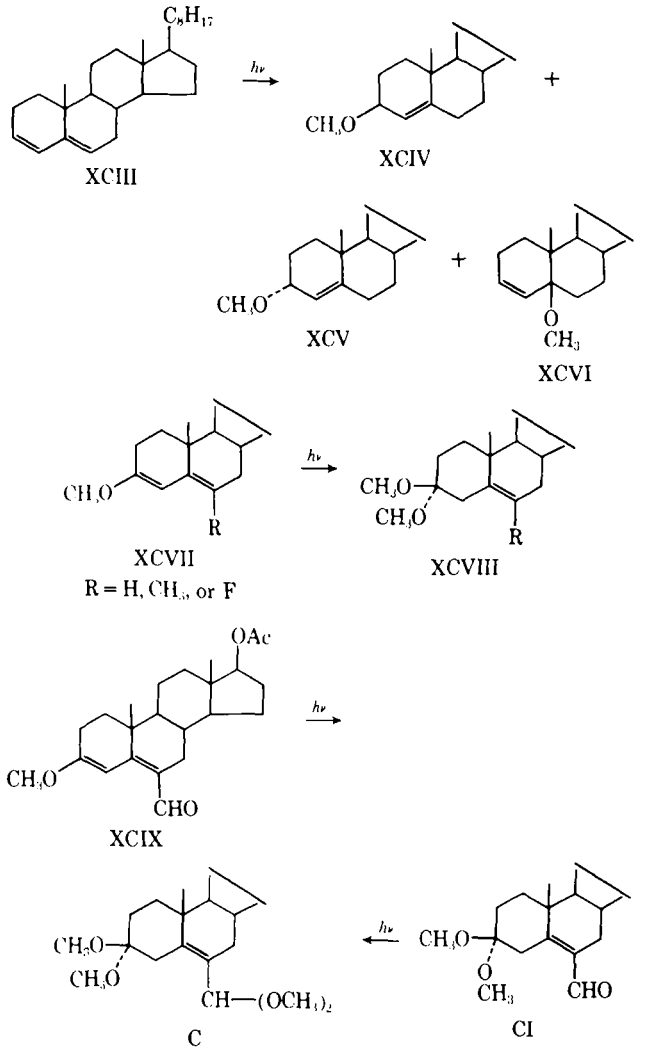
In an interesting extension of this work, irradiation of the *syn*-semicarbazone enol ether CII in methanol with 2537 Å light gives a mixture of *syn*-ketal CIII, *anti*-ketal CIV, and *anti*-semicarbazone enol ether CV (92) (Scheme XXI). However, upon irradiation of CII with 3500 Å light, an almost quantitative conversion into CV was demonstrated. Apparently the excitation of the long wavelength band (3130 Å) produces a *syn* $\rightleftarrows$ *anti* isomerization, and the short wavelength band (2280 Å) is responsible for ketalization. Irradiation of *syn*-oxime analogous to CII gave, among others, two nitrile compounds. Apparently, this is the first recorded example of photodehydration of oximes.

An example of the photoaddition of alcohols to an olefin, not occurring with saturation of the double bond to form ethers but rather 1-hydroxyalkyl olefins, was observed on irradiation of Δ^{16}-20-oxo compounds in primary and secondary alcohols (93). Partial reduction of the double bond was also noted.

Cyclobutanes in the progestational and corticoid series are now accessible by photocycloaddition of ethylene, tetrafluoroethylene (94, 95), allene, *cis*- and *trans*-dichloroethylene, acetylene, and hexafluoroacetone (95, 96). To illustrate this reaction, irradiation of 3β-



Scheme XIX



Scheme XX

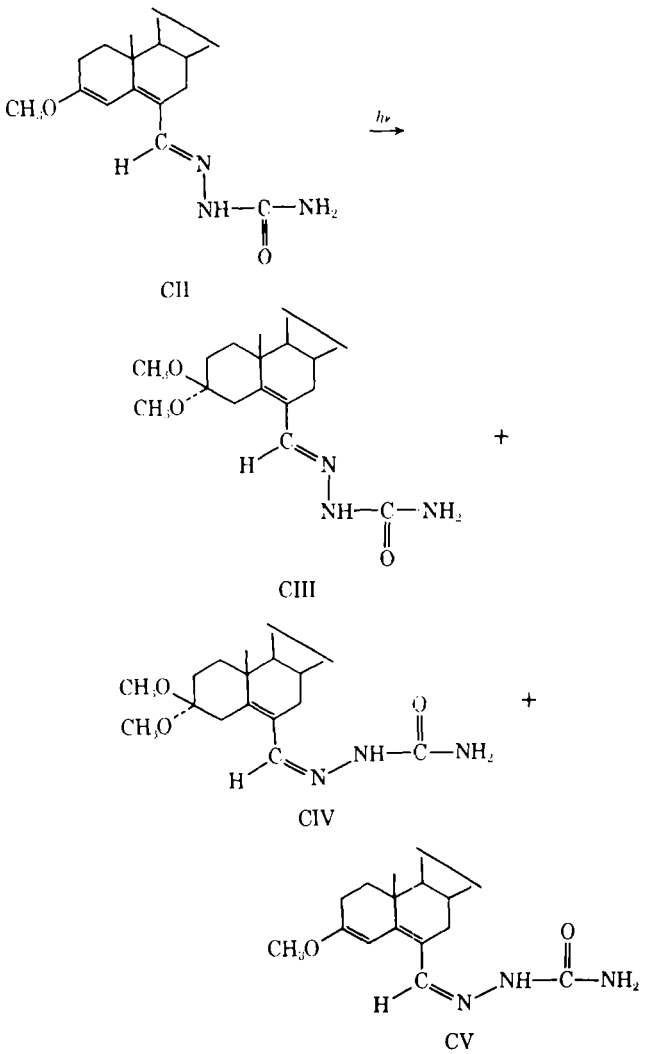
acetoxypregna-5,16-dien-20-one (CVI) in benzene saturated with ethylene gave the *cis*-fused cycloadducts CVII (52%) and CVIII (7%) (Scheme XXII). Other olefins add to the 16,17-position in a similar fashion. The stereochemistry of the adducts was deduced from NMR data. The photoaddition of CVI to another α,β-unsaturated ketone, namely, 1-acetoxybut-1-en-3-one, gave *cis*-fused adducts (97). The stereoselectivity of this reaction suggests a polar ground-state complex of the two unsaturated ketones. Subsequent photoexcitation of the complex with concerted bond formation then produces the adducts.

The photoreaction of 17β-acetoxyandrosta-4,6-dien-3-one (CIX) in the presence of ethylene gave equal amounts of the *trans*-fused adduct CX, the *cis*-fused adduct CXI, and the 6,7-adduct as a by-product (CXII) (98). 17β-Propionylandrosta-4,6-dien-3-one in the presence of cyclopentene gave preferentially the *trans*-adduct (99). Numerous novel steroidal hormones have been prepared by the photochemical cycloaddition method. In direct contrast to the aforementioned reactions, 1-en-3-ones are only partially reactive toward this reaction under sensitized and nonsensitized conditions with olefins (100). For example, 1,1-dichloroethylene added predominantly to 17β-acetoxy-5α-androst-1-en-3-one (CXIII) to give the *trans*-fused head-to-tail adduct CXIV in 16% yield (Scheme XXII).

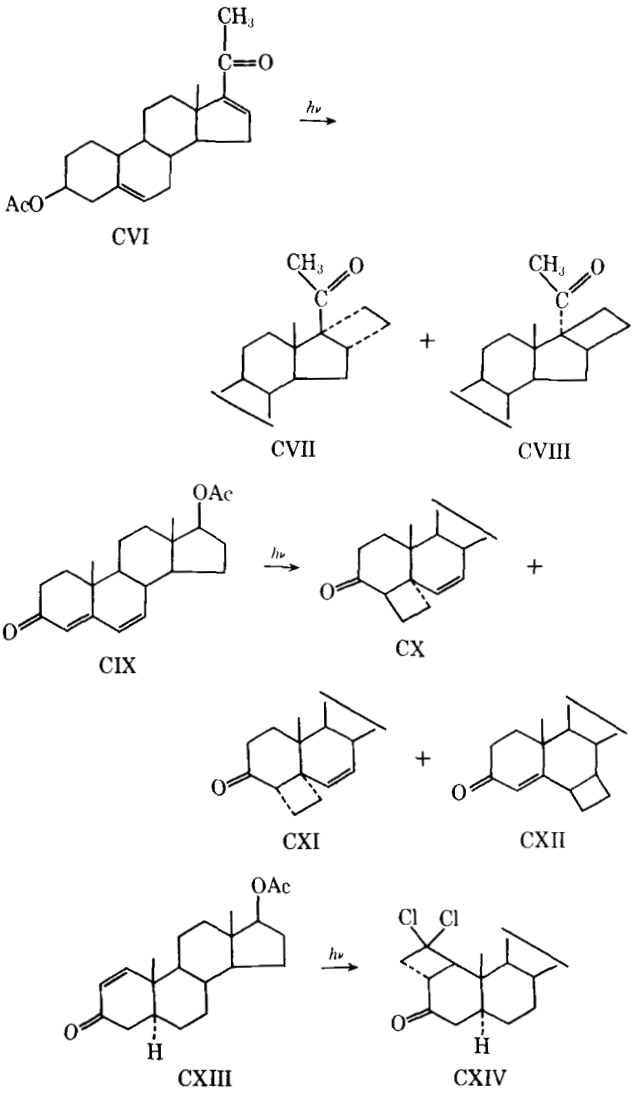
PHOTOREDUCTIONS

In connection with new routes to 19-norsteroidal hormones, normally obtained by Birch reduction, photoreductions of the aromatic ring of estradiol have been explored. The solvent-dependent photoreduction of 3,17β-estradiol (CXV) (101) in ethanol with sodium borohydride gave the estrene CXVI, the A/B *cis*-fused 5β,10β-estrane CXVII, and polymeric material (Scheme XXIII). By contrast, irradiation of CXV with sodium sulfite afforded the A/B *trans*-fused 3β,17β-dihydroxy-5α,10β-estrane CXVIII as the main product in addition to polymeric material. The reduction of CXV with sodium borohydride may result from an alternating series of hydride and proton (from solvent) additions to the nucleus, although reduction *via* radical intermediates has not been excluded. Sulfite reduction of estradiol *via* hydrolysis of sulfinate intermediates was postulated.

4-Cholesten-3-one is photorearranged to *lumicholestenone* (1β,5-cyclo-5β,10β-cholestan-2-one) (43). In a study of the UV irradiation of 4-cholesten-3-one

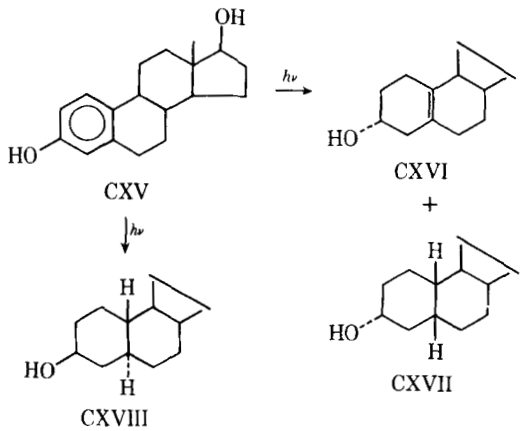


Scheme XXI



Scheme XXII

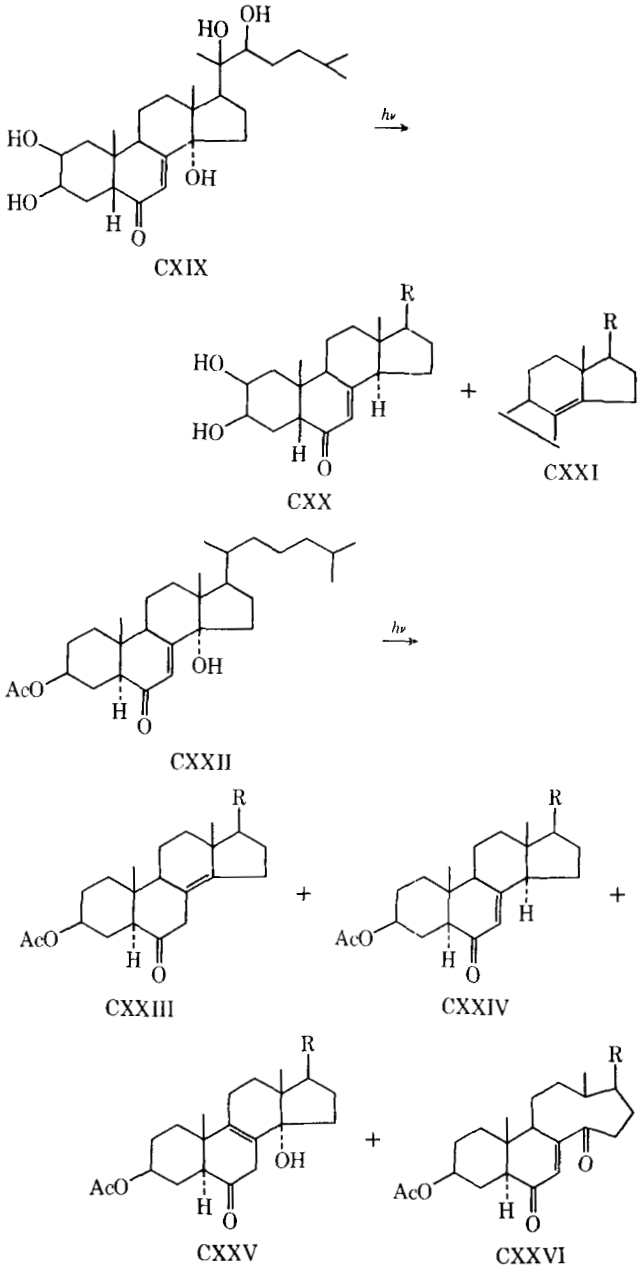
in the presence of sodium borohydride (102), 4-cholesten-3β-ol (34%), 5α-cholestan-3β-ol (16%), 5α-cholestan-3α-ol (8%), cholestan-3β,5α-diol (6%), cholestan-3α,5β-diol (6%), and unidentified products were obtained. The ground-state reduction of 4-cholesten-3-one gave mainly the three monohydroxy compounds already described. However, the rate of the photoreduction was enhanced by a factor of 22.5 in comparison with the ground-state reduction. The $NaBH_4$ reduction of cholestan-3-one in 2-propanol was not accelerated by UV light. In similar irradiation studies of 1,4-cholestadien-3-one in the presence of sodium borohydride, phenols rather than borohydride-reduced products were obtained (33).



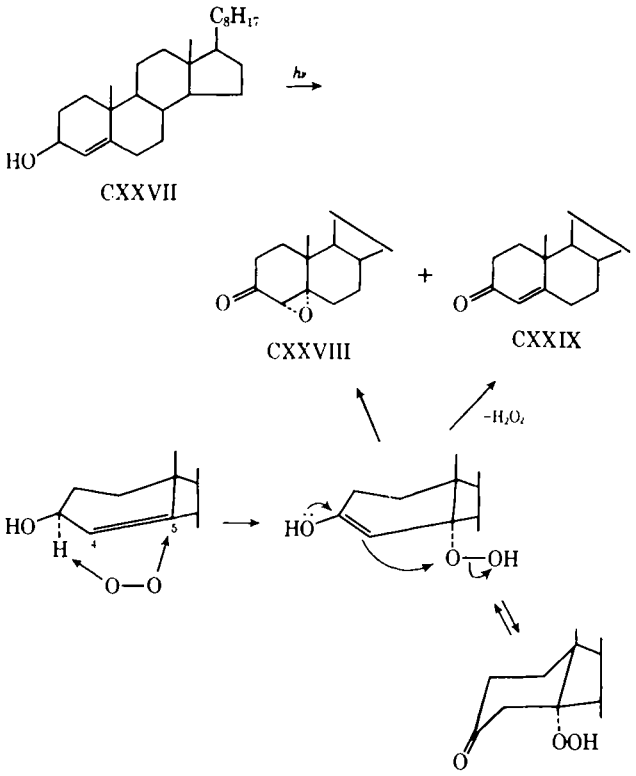
Scheme XXIII

Irradiation of 4-cholestene in cyclohexane–methanol gave coprostane in 10% yield in addition to other photoadducts. In benzene-2-propanol, coprostane was formed in 20% yield (81).

The 14-hydroxyl group in the natural product panasterone A (CXIX) was reductively removed on irradiation in methanol. The dehydroxylated Compound CXX and the homoallylic double-bond-migration product CXXI were obtained (103). Compound CXXII, possessing the same chromophore, was analogously



Scheme XXIV



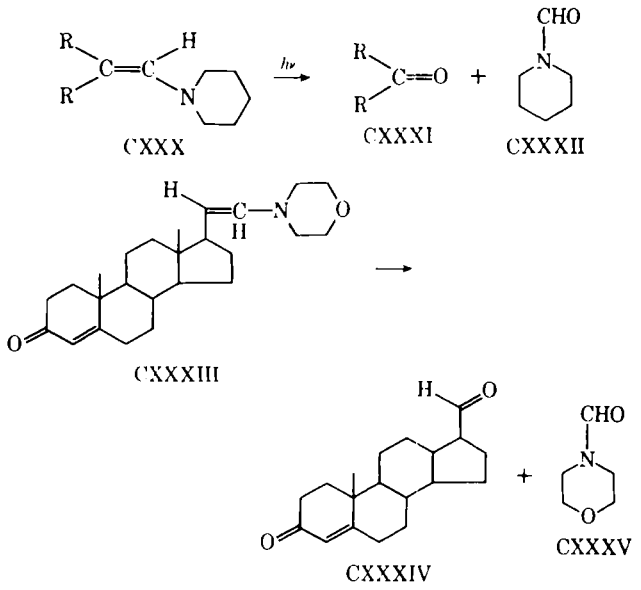
Scheme XXV

photolyzed to CXXIII and CXXIV and trace amounts of CXXV and CXXVI (104) (Scheme XXIV).

PHOTOOXIDATIONS

Photosensitized oxygenation of olefins and other unsaturated compounds has been studied extensively (105–109). By this method, oxygen is often introduced into compounds in a stereospecific manner. The basic steroid skeletons and the additional stereochemical features imposed on the nucleus by functional groups make steroidal olefins the models of choice for photosensitized oxygenations.

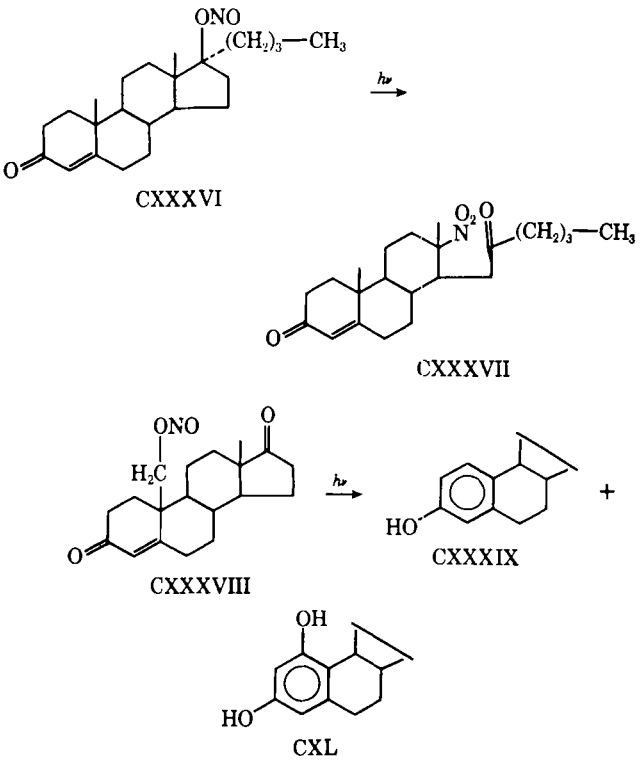
Previous photooxygenation studies with steroids showed that an allylic oxygen function is introduced with rearrangement of the double bond *via* a cyclic abstraction mechanism (109, 110). In the photosensitized oxygenation of cholest-4-ene, oxygen attacks both half-chair conformations of ring A, with abstraction of a *quasi*-axial allylic hydrogen atom (111, 112). Formation of cholest-5-en-4β-ol arises from the removal of the β-hydrogen at C-6. Photosensitized oxygenation of 4-cholesten-3β-ol (CXXVII) in pyridine in the presence of hematoporphyrin as a sensitizer gave 4α,5-epoxy-5α-cholestan-3-one (CXXVIII) (65%) and 4-cholesten-3-one (CXXIX) (113) (Scheme XXV). The 3-hydroxyl group deactivates the oxygenation, since the parent olefin, cholest-4-ene, undergoes reaction at a rate faster by a factor of about 4. This retarding effect is due in part to electron withdrawal and in part to steric hindrance by the hydroxyl group. The stereospecificity of this reaction is shown in Scheme XXV. With ring A in a half-chair conformation, oxygen, after addition at C-5, abstracts the C-3 *quasi*-axial hydrogen in a cyclic



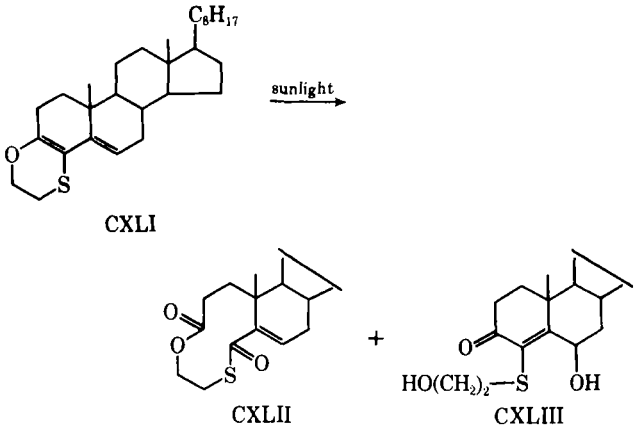
Scheme XXVI

process. Finally, the enol hydroperoxide equilibrates with the keto form. Collapse of the enol hydroperoxide by displacement on oxygen at C-5 gives the epoxide CXXVIII with competitive elimination of hydrogen peroxide to the ketone CXXIX. The participation of excited singlet-state oxygen is now generally accepted (114).

Photosensitized oxygenations of β,γ-unsaturated keto steroids were carried out by several groups (103, 115–117). A concerted cycloaddition mechanism was proposed on the basis of irradiation of deuterated derivatives (103). In the lanosterol series, photosensitized oxygenation of 3β-acetoxylanost-8-ene was de-



Scheme XXVII



Scheme XXVIII

scribed (118). A Δ^7-9α-hydroperoxide intermediate leading to a novel compound with an ether bridge between carbons 8 and 9 was postulated. Two stereoisomeric C-7,8 epoxides were also isolated.

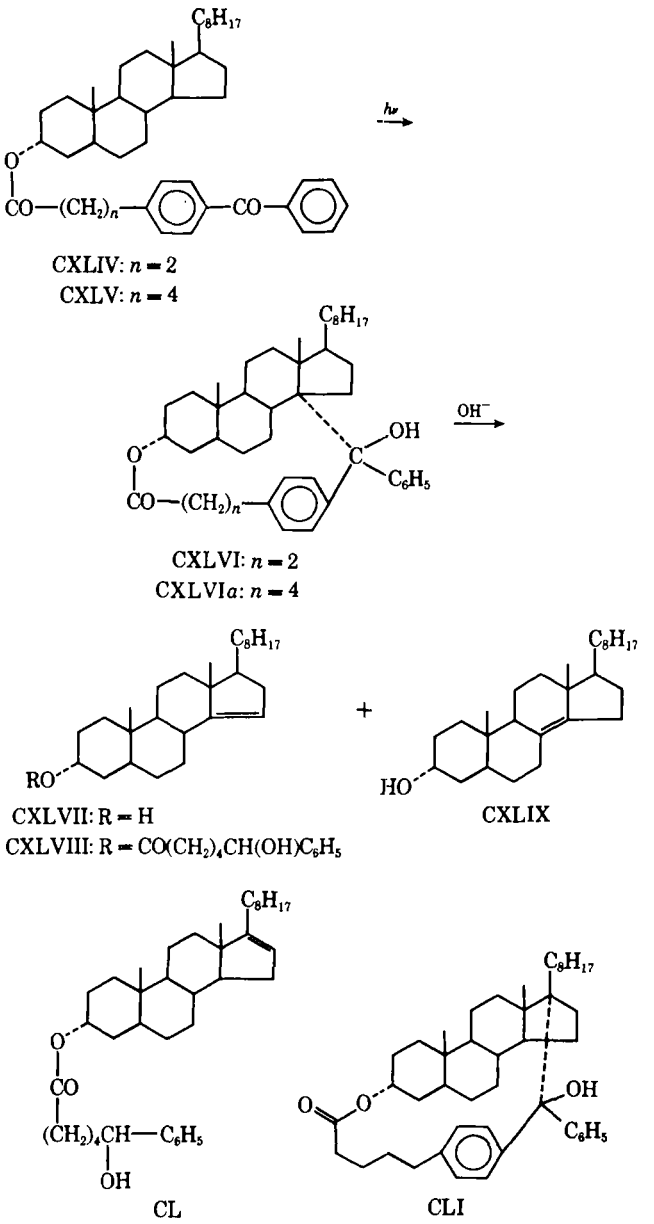
Enamines have been oxidized under photosensitizing conditions (119, 120). Irradiation of enamines CXXX in the presence of zinc tetraphenylporphine gave ketones CXXXI and the *N*-formylpiperidine CXXXII (Scheme XXVI) (119). Similarly, the photoreaction of 3-ketobisnor-4-cholen-22-al 22-morpholine enamine (CXXXIII) in dimethylformamide containing Rose Bengal yielded 3-ketobisnor-4-cholen-22-al (CXXXIV) and *N*-formylmorpholine (CXXXV) (120).

Photolysis of 17α-*n*-butyltestosterone nitrite (CXXXVI) in toluene under nitrogen followed by exposure to air gave 13-nitro-17-*n*-butyl-13,17-*seco*-4-androsten-3,17-dione (CXXXVII). Under the same conditions, 19-hydroxy-4-androsten-3,17-dione nitrite (CXXXVIII) gave the estrone CXXXIX and the 1-hydroxy-estrone CXL (121) (Scheme XXVII).

When the sulfur-containing steroid, cholesta-3,5-dieno[3,4-*b*]-1,4-oxathian (CXLI), in acetone–ether was exposed to sunlight in the presence of oxygen, it gave the 3,4-*seco*-3,4-dioxo compound (CXLII) in 37% yield and a trace of CXLIII (122) (Scheme XXVIII).

Photochemical oxidations which occur in the absence of photosensitizers have been observed. Irradiation of steroidal alcohol acetates in the presence of hexamethylphosphotriamide gave hydrocarbons (123), while ketones were formed in the presence of ethyl azidoformate (124). Nonphotosensitized oxidation of 3β-chloro-5-cholestene to chlorohydroxy and chloroepoxy derivatives was observed upon irradiation in *n*-hexane solution with a low pressure mercury lamp (125). Irradiation of a mixture of 3-oximinoandrostan-17β-ol and *N*-bromosuccinimide (126) under an air stream and subsequent sodium borohydride reduction gave 3β-nitro-5α-androstan-17β-ol (27%) and 3β,17β-dihydroxy-5α-androstane (40%).

Long-range oxidation effects in the steroid nucleus were reported by two groups (127, 128). 3α-Cholestanol *p*-benzoyl-β-phenylpropionic acid ester (CXLIV), in which the link between the two rigid systems is flexible enough to permit ring closure after the hydrogen-transfer step, was irradiated in acetonitrile and followed by hydrolysis with alkali to afford 14-cholesten-3α-ol



Scheme XXIX

(CXLVII) (27%) and 8(14)-cholesten-3α-ol (CXLIX) (8%). Apparently, both CXLVII and CXLIX arose from the initial photoproduct CXLVI as shown in Scheme XXIX. In support of this, CXLVI is obtained by direct hydrolysis of the photoproduct. The yield of CXLVII was increased to 20 and 35% when CXLIV was photolyzed in acetone and benzene, respectively (127). On the other hand, irradiation of 3α-cholestanol *p*-benzoyl-δ-phenylvaleric acid ester (CXLV) with a high pressure mercury lamp (Pyrex filter) in benzene solution afforded CXLVIII in 44% yield, CL (9%), and CXLVI*a* and CLI (combined yield of 25%), as well as 22% of the corresponding carbinol compound (128). Long-range photooxidations provide synthetic routes comparable to selective enzymatic transformation of steroids.

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