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Photochemical Methods for the Construction of an Additional Four-membered Carbocycle in Steroids

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The photochemical methods for the synthesis of pentacyclic steroids with an additional four-membered carbocycle are considered. A systematic account is given of the available literature data on the [2 + 2] photocycloaddition of steroid enones and dienones to various alkenes and alkynes and also on the dimerisation of dienones and intramolecular cyclisation of steroid ketones.
The mechanism of the photolytic reactions is discussed and the stereo- and regio-specificity of the photocycloaddition are considered as a function of the structure of both the steroid and the alkene. It is shown that the pentacyclic steroids obtained are convenient intermediates for further modifications.
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I. INTRODUCTION

In the chemistry of steroid hormones, the modification of the skeleton of natural steroids is used to obtain compounds having a narrower and specific spectrum of biological activity, which gives rise to the possibility of their practical application. Among the numerous types of such transformed steroids, compounds containing an additional carbocycle are of great interest. The methods of their synthesis are fairly varied.

This review is devoted to the photochemical method of synthesis of steroids condensed with an additional four-membered carbocycle. Such pentaranes† exhibit an enhanced hormonal activity in many instances[2-15] and are also convenient intermediates for further modifications of the steroid skeleton.[16-22] Only the photochemical methods of synthesis of pentaranes are considered, because these methods frequently constitute almost the only possibility of the construction of a four-membered ring and the contribution of other methods of synthesis of similar structures (such as, for example, the cycloaddition of dichloroketen to steroid alkenes[23-26] or the intramolecular cyclisation of tosylates[27-29]) is small.

Photochemical [2 + 2]cycloaddition is a general method for the construction of pentacyclic steroids and, in contrast to the dark reactions, makes it possible to introduce the cyclobutane fragment into any site in the steroid molecule.

The main aim of the review is to demonstrate the synthetic possibilities of photochemical cyclisation to pentaranes and its stereo- and regio-specificity as a function of the structure of the steroid and alkene; special factors associated with the mechanism of the photoexcitation of the reacting molecules, their electronic state, etc. will not be discussed in detail. These questions have been dealt with quite fully in other publications.[30-34] The review contains data mainly referring to the last 18 years. Some information about the synthesis of cyclobutanosteroids up to 1970 can be found in a monograph.[35]

II. PHOTOCYCLOADDITION OF ALKENES TO STEROID ENONES

The interaction of photochemically excited enones and dienones with alkenes or alkynes usually leads to the formation of a four-membered carbocycle and frequently constitutes the most convenient or even the only available method of synthesis of such structures. In the steroid chemistry, the photocyclo-addition of various alkenes to αβ-unsaturated ketones# is a well-developed and convenient method for the introduction into the steroid molecule of an additional four-membered carbocycle, which is widely used at the present time.[36] Here it has been shown that this reaction leads to the formation of both *cis*-αα- and *trans*-αβ-cyclobutanes; insignificant amounts of the *cis*-ββ-isomers arising simultaneously are attributed to the epimerisation of *trans*-αβ-cyclobutanes under the reaction conditions.[37] The stereochemistry of the photoannelation can be explained on the basis of the general features of the interaction of an excited enone with an alkene in the ground electronic state: the attack by the latter takes place from the sterically less hindered α-region of the enone; (2) the *trans*-cyclobutane is formed as a result of the conformational inversion of the intermediate 1,4-biradical.[37-42]

The photocycloaddition of various alkenes to derivatives of testosterone (I) has been investigated[37] (Scheme 1); the yields of the isomeric cyclobutanosteroids (II)–(IV) obtained are listed in Table 1.

†The name "pentaranes"[1] is used for pentacyclic steroids containing an additional carbocycle.

#Here and henceforth we shall use the term "addition of alkenes (or olefins) to the more bulky steroid molecule".

Scheme 1

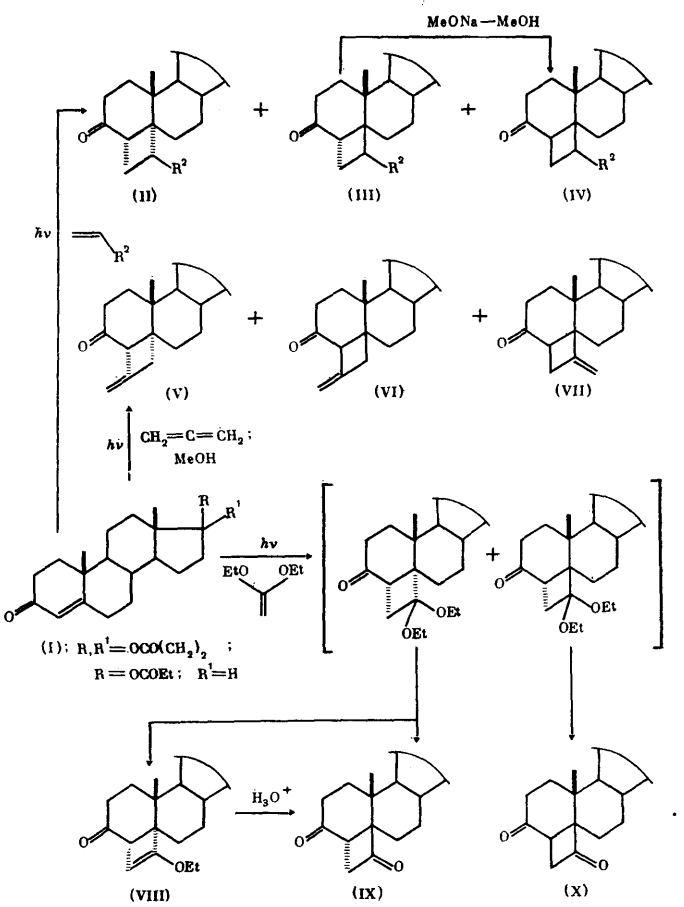


Table 1. The yields of the cyclobutanosteroids (II)–(IV).[37]

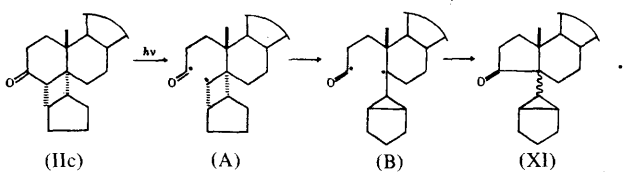
Olefin	Cyclic adduct, %		
	4α, 5α-(II)	4α, 5β-(III)	4β, 5β-(IV)
Ethylene	57	24—30	traces
Isobutene	76	12	traces
Cyclopentene	43	35	9
1-Acetoxycyclopentene	30	35	traces
Cyclohexene	40	25	12

It follows from the Table that ethylene adds to the steroid enone (I) affording the cyclic adducts (IIa) and (IIIa) with a high overall yield (81–87%), 4α,5α-cyclobutane (IIa) predominating in the mixture. Irradiation of a methanolic or ethyl acetate solution of testosterone propionate and ethylene also affords a mixture of compounds (IIa) and (IIIa) together with a small amount of the 4β,5β-epimer (IVa).[38,43] The high yields of the products of the reaction of the enone (I) with ethylene, which is a relatively unreactive alkene, can be explained by the fact that the steroid enone gives rise to a long-lived triplet state on irradiation.[44] In the reaction with a more electron-enriched alkene—isobutene—higher yields of 4α,5α-cyclobutane (IIb) were obtained. It was noted that the reactions with geminally substituted alkenes give rise only to cyclic adducts of the "head to tail" type (HT), while the reaction with cyclic alkenes affords only the *anti*-adducts,[37] although there are data[43] indicating the isolation of both the *syn*- and *anti*-isomers of the cyclic adduct of compound (I) with cyclopentene. The addition of allene to the enone (I) gives rise to a 5 : 1 mixture of compounds (V) and (VI); the reduction of the reaction temperature to −70 °C results in the exclusive formation of compound (V).[43]

In order to account for the high structural specificity of the given reaction, the empirical "Corey rule"[45] that the "enone-unsaturated substrate" exciplex plays a decisive role, which has been developed for the series of aliphatic and monocyclic αβ-unsaturated ketones, has been successfully resorted to.[37]

The addition of 1,1-diethoxyethylene to compound (I) leads to a mixture of labile primary cyclic *cis*-4α,5α- and *trans*-4α,5β-adducts, which have been characterised as the cyclobutene (VIII) and the ketones (IX) and (X) (Scheme 1).[37]

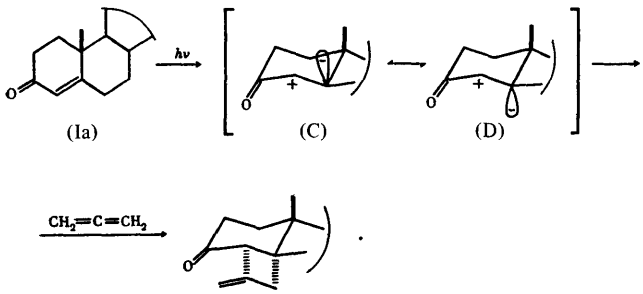
It is of interest to note that 5-cyclopropyl-A-norsteroid (XI) has been isolated as a side product from the mixture of products of reaction of compound (I) with cyclopentene. The appearance of this steroid has been explained by the Norrish type (I) cleavage of *cis*-4α,5α-cyclobutane (IIc) with formation of the acylcyclobutyl biradical (A), which then rearranges to the cyclopropyl-substituted biradical (B) with subsequent stabilisation by conversion to the final compound (XI):[37]



Extremely interesting results concerning the inversion of the stereospecificity of the photocycloaddition of alkenes to αβ-unsaturated ketones have been recently obtained by de Mayo.[43,46] It was found that irradiation of alkenes and testosterone or its propionate (I, R = OH or OCOEt), adsorbed on SiO_2 or Al_2O_3, leads to the preferential approach by the alkene to the β-region of the steroid molecule because the α-region is to a large extent blocked by the adsorbent molecules as a result of the preliminary adsorption of the steroid enone. It was shown that under these conditions the overall yield of the cycloaddition products increases. Thus, in the case of ethylene (R^2 = H, Scheme 1), the (IIa) : (IVa) = 42 : 58 mixture of cyclobutanes was obtained in a quantitative yield. *trans*-4α,5β-Cyclobutane (IIIa) was isolated only in trace amounts. Analogous results were obtained at a low temperature (−70 °C). The reaction of the testosterone propionate (I) adsorbed on SiO_2 with allene leads to a mixture of cyclic *cis*-4α,5α- and *cis*-4β,5β-adducts in the proportions (V) : (VI) = 1 : 1; the second regioisomer (VII) of the HT type was also isolated in an insignificant amount.[43] Thus the adsorption of the steroid enone on SiO_2 or Al_2O_3 prevents the conformational inversion of the intermediate biradical required for the formation of the *trans*-joined cyclobutanosteroids.

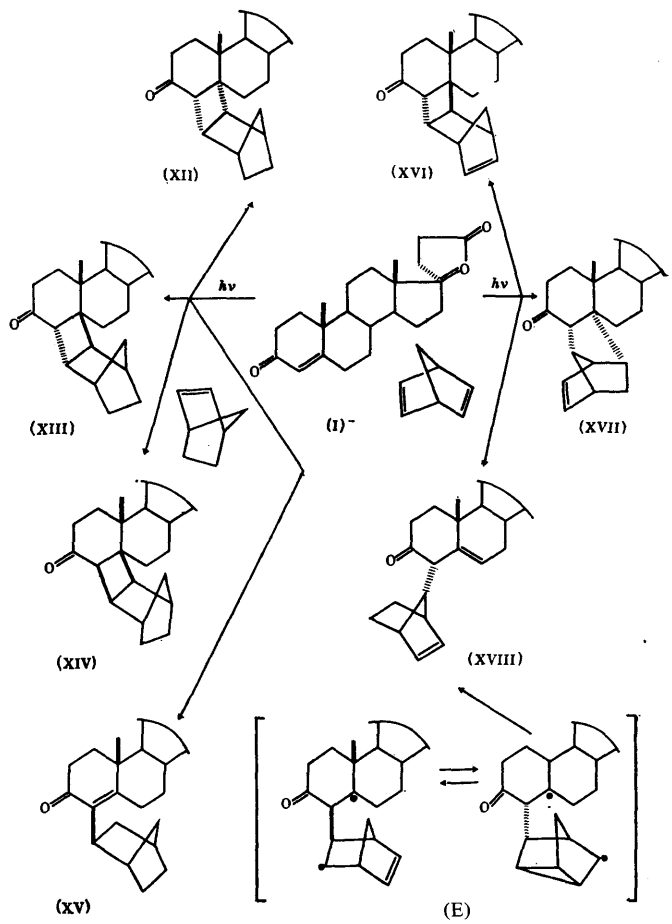
It is noteworthy that the structural specificity of the photocycloaddition of alkenes to αβ-enones is determined in the first place by the conformation of the enone reacting in the triplet state.[47] It has been shown in relation to cholest-4-en-3-one (Ia) that, of the two possible conformations (C) and (D) of the excited enone, the conformation (D) with the *trans*-disposition of the 19-CH_3 group and of the unpaired electron in the *p* orbital at C(5) is preferred. Accordingly, the cyclic adduct of the enone with allene should have a structure of the "head to head" type (HH), and the approach

of allene to the excited enone (Ia) from the α-region becomes preferred:



The addition of norbornene to the steroid enone (I) leads to a mixture of *cis*-4α,5α-cyclobutane (XII) (41%), the *trans*-4α,5β-epimer (XIII) (27%), the *cis*-4β,5β-adduct (XIV) (2%), and the adduct (XV) (17%)[48] (Scheme 2):

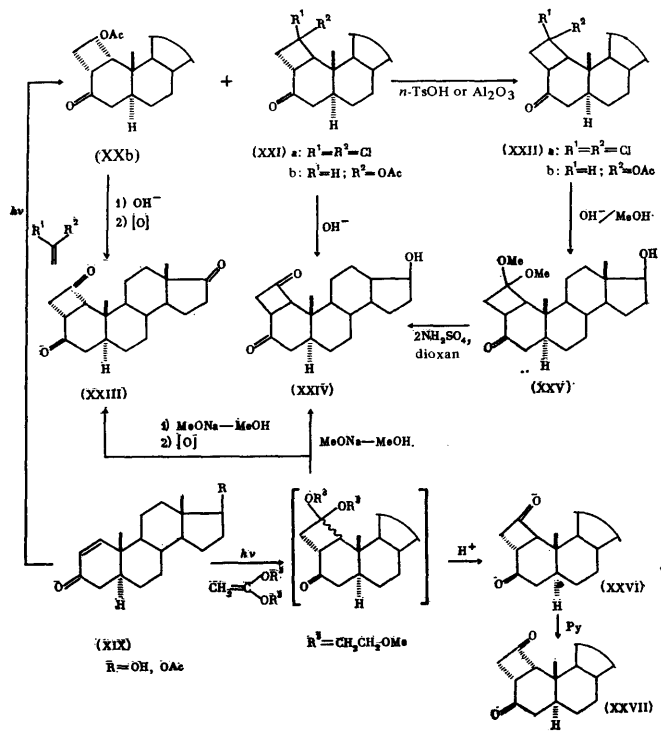
Scheme 2



The last adduct arises as a result of the 1,3-hydride shifts with formation of 4-norbornyl-3-keto-Δ[5]-steroid, which then isomerises to the Δ[4]-3-ketone (XV) in the course of the reaction. The appreciable stability of the *trans*-isomer (XIII) as regards epimerisation has been noted, which has been explained by the character of its conformation (the A ring is in the chair and not the boat form characteristic of the majority of 4α,5β-cyclobutanes,[31] which hinders the approach of the nucleophile to the 3-carbonyl group). The reaction of compound (I) with norbornadiene is fairly complex (cf. McCullough et al.[49]). *trans*-4α,5β-Cyclobutane (XVI) (10%) and two other products—(XVIII) (16%) and (XVIII) (53%)—were isolated from the mixture of substances (see Scheme 2). The formation of the last product has been explained by the steric hindrance to the rotation about the C(4)–C bond in the intermediate biradical (E).[48]

The cyclobutanosteroids condensed with the A ring in the 1- and 2-positions can be obtained by the photocycloaddition of olefins to Δ[1]-3-ketosteroids. Literature data indicate a low reactivity of these enones compared with the Δ[4]-3-ketones. Thus it has been shown that ethylene, malic anhydride, and 1,1-difluoroethylene do not add to the series of androstane and pregnane Δ[1]-3-ketones investigated.[50] However, irradiation of the Δ[1]-3-ketone (XIX) in benzene solution containing 1,1-dichloroethylene led to a 16% yield of the substituted *trans*-1β,2α-cyclobutane (XXIa), which readily undergoes epimerisation at the C(2) centre, affording compound (XXIIa)[50] (Scheme 3). The stereochemistry of compound (XXIa) has been deduced from X-ray diffraction data. The hydrolysis of *trans*-1β,2α-cyclobutane (XXIa) and of its *cis*-1β,2β-isomer (XXIIa) yielded the same *cis*-1β,2β-cyclobutan-1′-one (XXIV). The reaction of the steroid enone (XIX) with vinyl acetate under analogous conditions led to a complex mixture of substances; after chromatographic separation, two products were isolated: *trans*-1β,2α-cyclobutane (XXIb) (21%) and *cis*-1α,2α-cyclobutane (XXb) (2%). Hydrolysis of the latter and subsequent Jones oxidation yielded 1α,2α-cyclobutan-1′-one (XXIII):

Scheme 3



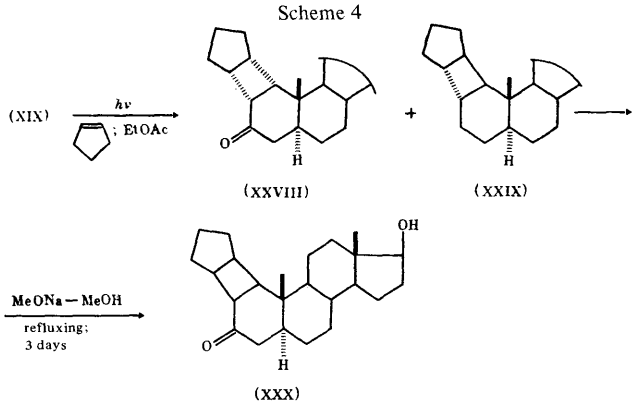
Thus the addition of substituted alkenes to Δ[1]-3-keto-steroids leads to the formation of *trans*-cyclobuane adducts of the HT type with high regio- and stereo-specificity.

These adducts readily epimerise at the C(2) centre to form the more stable *cis*-1β,2β-cyclobutanosteroids.

The addition of cyclopentene to compound (XIX) led to the preferential formation of *cis*-1α,2α-cyclobutane (XXVIII) (56%) together with the usual *trans*-isomer (XXIX) (30%)[51]

(Scheme 4):

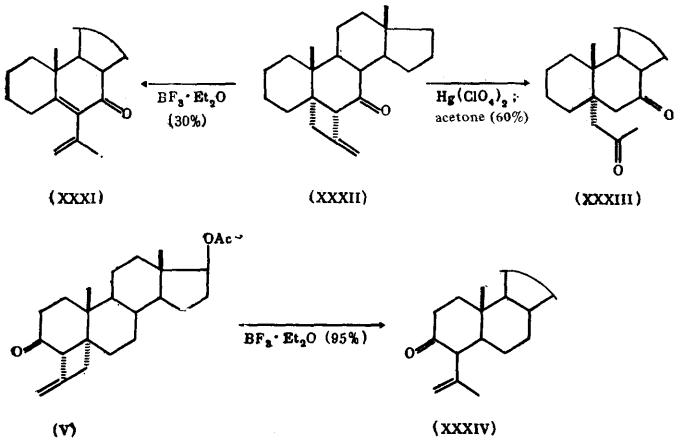
Scheme 4



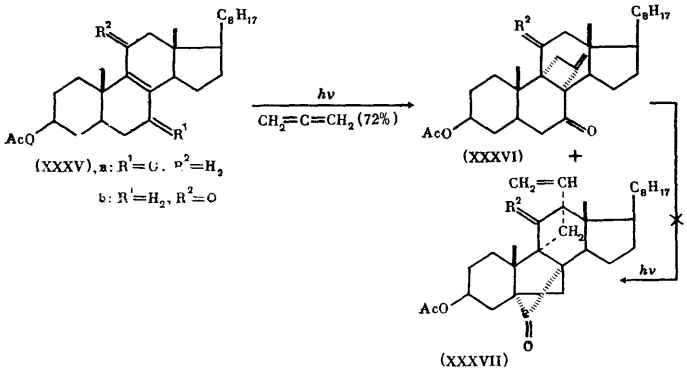
The unusual stability of the last compound as regards epimerisation was noted here: the corresponding *cis*-1β,2β-isomer (XXX) was obtained only after prolonged refluxing of compound (XXIX) with MeONa in methanol. The isomeric 1β,2α-, 1α,2α-, and 1β,2β-cyclobutanones (XXVI), (XXVII), and (XXIV) were also obtained by adding ketene bis(2-methoxyethyl)acetal to compound (XIX) [51,52] (see Scheme 3). It is of interest to note that, whereas the acid-catalysed epimerisation of the *trans*-diketone (XXVI) leads to an equimolar mixture of compounds (XXIV) and (XXVII), heating of compound (XXVI) in pyridine affords only the *cis*-1α,2α-cyclobutanone (XXVII). [51]

Steroid enones substituted in the Δ^1-bond, for example the acetate of 17β-hydroxy-2-methyl-5α-androst-3-one, do not form cyclic photoadducts by reaction with alkenes at all, [50] which agrees with Corey's observation that such photochemical reactions are difficult for C(2)-substituted enones. [45]

6'-Methylene-5α,6α-cyclobutano-7-ketosteroid (XXXII) has also been described and its cleavage under various conditions has been investigated. [53,54] For example, when compound (XXXII) is refluxed in benzene in the presence of an excess of BF_3 etherate, the 6-isopropenyl-substituted 7-ketone (XXXI) is formed. Under analogous conditions, 4'-methylene-4α,5α-cyclobutane (V) gives rise to a high yield of the 4-isopropenyl-substituted 3-ketone (XXXIV). These products are apparently formed as a result of the electrophilic attack by the BF_3 etherate on the exocyclic methylene bond with subsequent opening of the cyclobutane ring. [53] The cleavage of methylenecyclobutane (XXXII) with mercury perchlorate in acetone leads to the diketone (XXXIII) in 60% yield. [54] These examples clearly demonstrate the possibility of using cyclobutanosteroids as intermediates for the transformation of steroids.



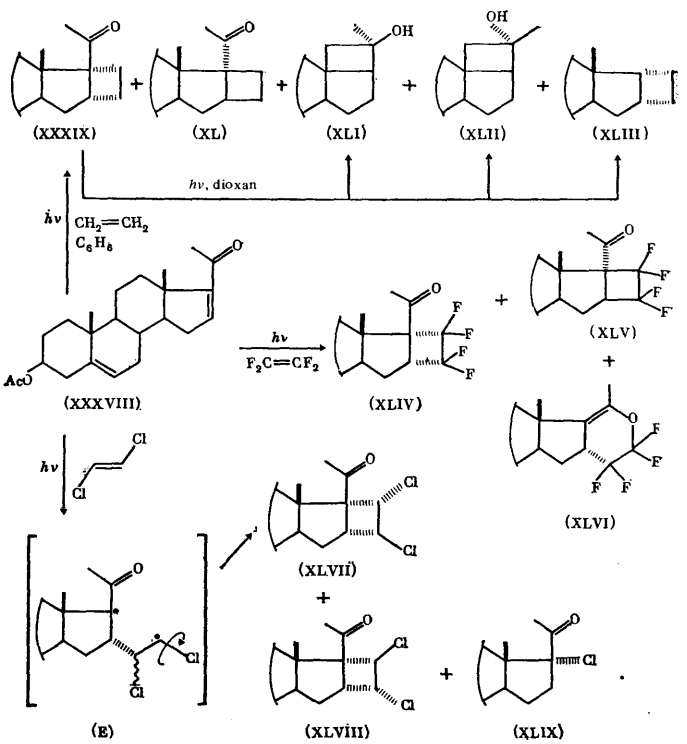
The 8α,9α-cyclobutanosteroid (XXXVI) has been obtained by the photoaddition of allene to 7-keto-$\Delta^{8(9)}$cholestene (XXXVa). The structure of the ketone (XXXVII) was attributed to the second compound arising under these conditions in ~20% yield:



Under analogous conditions, 11-keto-$\Delta^{8(9)}$-cholestene (XXXVb) does not react with allene. [55]

The 16-dehydro-20-keto-group in pregnanes is fairly reactive in photocycloaddition to various alkenes, which makes it possible to obtain the corresponding 16,17-cyclobutanosteroids. The first studies on their synthesis with participation of ethylene and its derivatives were published as early as the 1960's [56] and the formation of only *cis*-joined products with a significant predominance of the 16α,17α-isomers was demonstrated. [39,56] Thus, when ethylene is passed into an irradiated benzene solution of 16-dehydropregnenolene acetate (DPA) (XXXVIII), a mixture of 16α,17α- and 16β,17β-cyclobutanes (XXXIX) and (XL) is formed in proportions of ~7:1 (Scheme 5).

Scheme 5

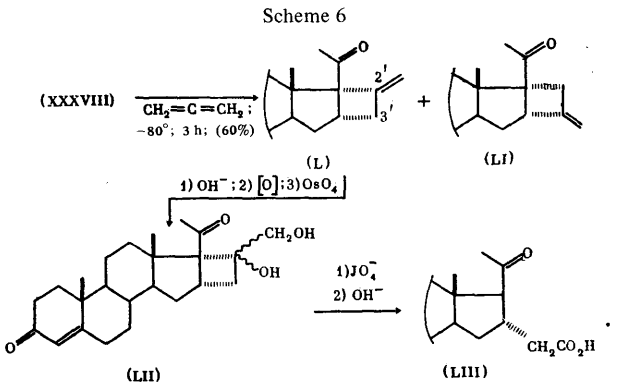


After prolonged irradiation, the cyclobutanols (XLI) and (XLII) and the desacyl compound (XLIII) were detected as additional products in the reaction mixture. They were also obtained by the photolysis of the principal product (XXXIX) in dioxan. Under these conditions, the isomeric 16β,17β-cyclobutane (XL) is stable. The formation of compounds (XLI) and (XLII) was explained by the intramolecular attack on the 20-carbonyl group in an excited state by the vicinal 18-methyl group in the molecule of compound (XXXIX) and the formation of compound (XLIII) was accounted for by the abstraction of the acyl group. When the reaction is carried out in methanol, the yield and fraction of the main cyclic adduct (XXXIX) increased to 90%. When ethylene is passed through DPA absorbed on anhydrous SiO_2 at −70 °C, the overall yield of cyclic adducts rises to 70–85% with the simultaneous change in their stereochemistry in favour of an increase in the amount of the ββ-isomer: (XXXIX)/(XL) ≅ 1:1.[43]

A high stereoselectivity of the cycloaddition has been observed also for the reaction of DPA with substituted alkenes,[2,39,57] which leads, for example, in the case of tetrafluoroethylene,[39] to a mixture of cyclic αα- and ββ-adducts (XLIV) and (XLV) in proportions of ~2:1 together with the formation of very small amounts of the dihydropyran (XLVI). The addition of *cis*- or *trans*-dichloroethylene to compound (XXXVIII) yields a mixture of substances of identical composition, from which *trans*-16α,17α-dichloro-compounds (XLVII) and (XLVIII) were isolated in proportions of ~1:1, differing in the configuration of the chlorine atoms. The 17α-chloropregnenolene (XLIX), detected in a very small amount, is apparently formed as a result of the direct addition of HCl to the initial enone (XXXVIII).[39] The fact that the *cis*- and *trans*-dichloroethylenes give rise to the same cyclic adduct agrees with the two-stage reaction mechanism via a biradical (F) (see Scheme 5); the rate of formation of the C(17)–CCl bond is evidently comparable to the rate of inversion of the C(2′)–Cl bond.

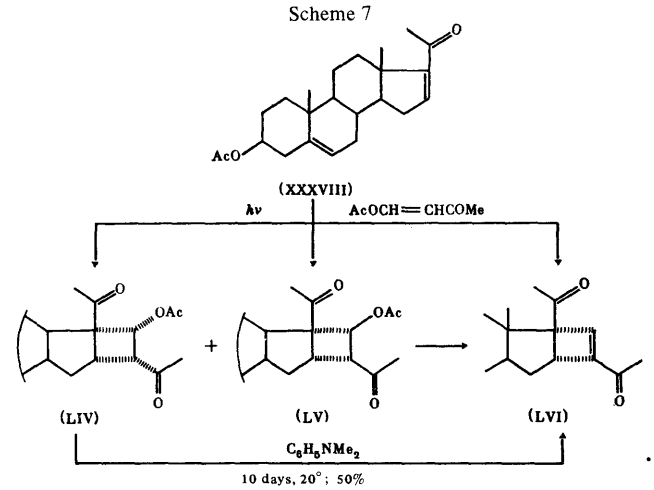
The photochemical reaction of DPA with allene is stereospecific and involves the formation of the 16α,17α-regioisomers (L) and (LI) in proportions of ~5:1 and an overall yield of ~60%[39] (Scheme 6):

Scheme 6



The structures of these compounds have been established with the aid of CD spectra in addition to certain chemical reactions with the main product (L). Thus its hydrolysis with subsequent Oppenauer oxidation afforded the corresponding Δ^4-3-ketone, whose hydroxylation with OsO_4 led to a mixture of diols (LII); successive treatment of these diols with OsO_4 and alkali yielded the familiar acid (LIII), which is formed via an intermediate stage involving the unstable cyclobutanone.[39] The photocycloaddition of 1-acetoxybut-1-en-one to DPA is of interest because both reactants can be in an excited state under the conditions of the photolysis. The cyclic 16α,17α-adducts (LIV) and (LV) in proportions of ~2:1 were then obtained together with a small amount of the cyclobutene (LVI). The latter was obtained after compound (LIV) had been kept for a long time together with dimethylaniline in solution in the $CHCl_3$–methanol mixture, although its diastereoisomer (LV) is stable under these conditions[58] (Scheme 7).

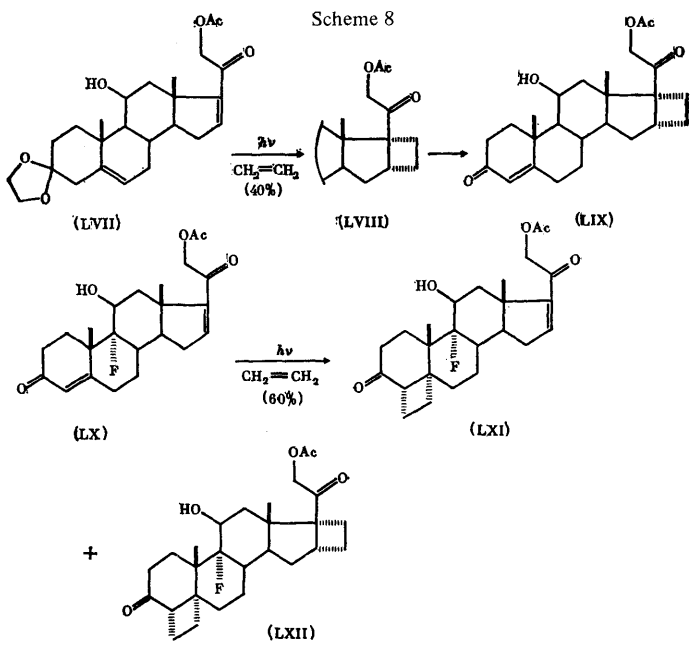
Scheme 7



The observed regiospecificity of the photochemical reaction conflicts with "Corey's rule",[45] because the preferential formation of cyclic adducts of the (EE) type should follow from an examination of the structures of the exciplexes. In order to account for this contradiction, one can postulate that the first reaction stage is the ordered orientation of the initial enones, which are in the ground state, after which the above coordinated complex undergoes photoexcitation with formation of the cyclic adducts (LIV) and (LV).[58]

The presence of substituents in the steroid skeleton of the molecule of compound (XXXVIII) does not reduce its reactivity in the photochemical reaction, but, when the Δ^4-3-keto-group is present together with the Δ^{16}-20-keto-

Scheme 8



group, cycloaddition takes place preferentially with participation of the former group. Thus it has been shown that the interaction of compound (LVII) with ethylene leads to a 40% yield of the 16α,17α-cyclobutane (LVIII), which is converted further into the Δ^4-3-ketone (LIX). On the other hand, the 4α,5α-cyclobutane (LXI) was obtained in 60% yield from the unsaturated 3,20-diketone (LX); the corresponding bis-adduct (LXII) was observed only in trace amounts in the mixture[56] (See Scheme 8).

It is of interest to note that in the monocyclic series cyclopent-2-enones exhibit a greater reactivity than cyclohex-2-enones.[59]

Thus, when account is taken of the data considered above, αβ-unsaturated ketosteroids can be arranged in the following sequence in terms of their reactivity: Δ^4-3-keto- > Δ^{16}-20-keto- > Δ^1-3-keto-. It must be emphasised that this series has been set up on the basis of a fairly limited set of steroid enones and one cannot therefore rule out the possibility that corrections will be introduced in connection with the appearance of new experimental data.

III. PHOTOCYCLOADDITION OF ALKYNES TO αβ-UNSATURATED KETOSTEROIDS

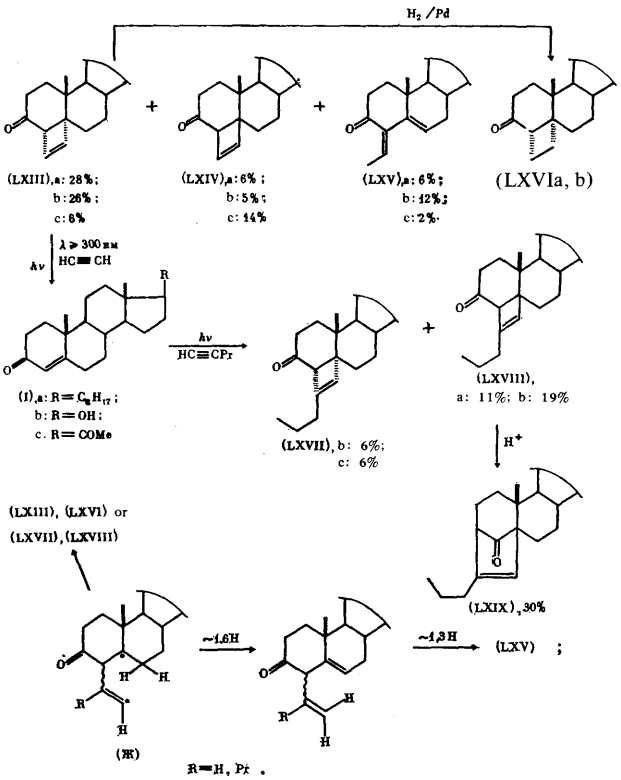
The photocycloaddition of alkynes to steroid enones gives rise to cyhclobutenosteroids with interesting synthetic possibilities. In view of their high strain, such structures undergo various transformations already under the conditions of the photolysis, which, when combined with certain dark reactions, leads to new ways of transforming steroids. Owing to the reduced nucleophilicity of the triple bond, alkynes are less reactive than alkenes in reactions involving addition to the excited enone. For example, it is known that the interaction of 2-cyclohexanone with vinylacetylene involves exclusively the double bond of the latter.[60]

When the steroid enones (Ia, b) are irradiated in ethyl acetate saturated with acetylene, mixtures of the diastereoisomers (LXIIIa, b) and (LXIVa, b) are formed in proportions of ~5 : 1 and in an overall yield of ~30%;[61] the reaction proved to be less stereoselective than the corresponding reaction with ethylene. On catalytic hydrogenation, the cyclobutenes (LXIIIa, b) afford the corresponding cyclobutanes (LXVIa, b) (Scheme 9).

Together with the cyclic adducts (LXIIIa, b) and (LXIVa, b), the ethylidene derivatives (LXVa, b) were obtained in a yield of ~6–12%. The study of the cycloaddition of acetylene to compounds (Ia, b) under the influence of light with λ ≥ 320 nm, which is absorbed solely by the initial αβ-enone, the intramolecular inversion in the cyclic adduct being ruled out, showed that all three products (LXIII)–(LXV) are also formed under these conditions, from which the authors concluded that the reaction leads immediately to both diastereoisomers.[61] Analogous results were achieved in the photolysis of compound (Ib) together with pent-1-yne, which leads to stereoisomers of the type (LXVIIb) and (LXVIIIb).[62] The mechanism proposed for their formation, via the intermediate biradical (G) stabilised as a result of its closure to form cyclobutene or by disproportionation to 1,4-diene (H), also explains the appearance of the ethylidene-substituted compounds (LXV) (see Scheme 9).[61,63] The structures of the adducts (LXIIIa, b), (LXIVa, b), (LXVIIb), and (LXVIIIb) were established spectroscopically (NMR, CD), and also on the basis of X-ray diffraction data.[64]

The appreciable decrease in the overall yield of the cyclic photoadducts (LXIIIc) and (LXIVc), observed in the reaction of progesterone (Ic) with acetylene and pent-1-yne, and the inversion, compared with the cases examined above, of the stereospecificity of the addition, consisting in the preferential formation of ββ-isomers (LXIVc) and (LXVIIIc), are very remarkable.[62] The compounds discussed are interconverted under the influence of light λ ≥ 300 nm but are stable on irradiation with light having λ ≥ 320 nm. Since the photoaddition of both alkynes to compound (Ic) affords predominantly the 4β,5β-cyclobutenosteroids (LXIVc) and (LXVIIIc), the observed stereoselectivity is not a result of secondary reactions, but is caused, according to the authors,[62] by the influence of the acetyl group at C(17) via the mechanism of the long distance stereoelectronic effect.[65] This effect was noted for the first observation of this effect in the photochemistry of steroids.

Scheme 9

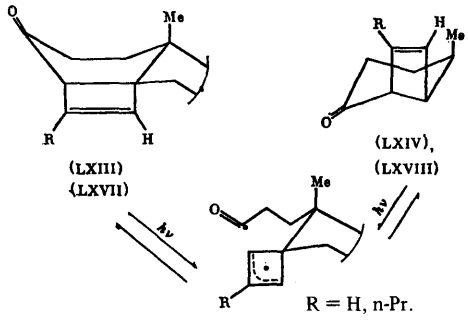


It follows from the data described that the empirical "Wiesner's rule", predicting the stereospecific course of the photoaddition of polycyclic–enones,[47] does not hold for alkynes, like "Corey's rule",[45] which predicts the structural specificity of this reaction.

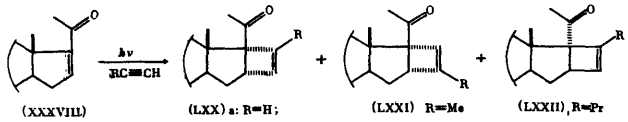
The cyclobutenosteroids (LXIIIb), (LXIVb), (LXVIIb), and (LXVIIIb) are extremely reactive compounds because of the presence of a strained double bond and the keto-group in their conformationally rigid structure. As noted above, on irradiation with light at λ ≥ 300 nm, they are interconverted via the 1,3-acyl shift mechanism, together with rapid polymerisation.[62,63]

The photoadducts considered can be converted into other steroids modified in the *A* ring. Thus, on treatment with TsOH, compound (LXVIIIb) gives rise to the bridged βγ-unsaturated ketone (LXIX) (see Scheme 9). Under analogous conditions, compound (LXIVb) does not undergo an isomerisation of this type.[62]

There exist data on the interaction of Δ^4-3-keto- and Δ^{16}-20-ketosteroids of the pregnane and corticoid series with different mono- and di-substituted actylenes.[4,66,106]



The cyclobutenosteroids (LXXa, b) and (LXXI) have been obtained by irradiating DPA [compound (XXXVIII)] in the presence of methylacetylene or acetylene.[33,103] The reaction proceeds stereospecifically from the region of the steroid molecule[67,68] and in the case of methylacetylene both regioisomers, (LXXb) and (LXXI), have been described. The interaction of DPA with pent-1-yne leads to a mixture of the stereoisomeric cyclic HH αα- and ββ-adducts (LXXc) and (LXXII) in proportions of ~10 : 1:[69,70]



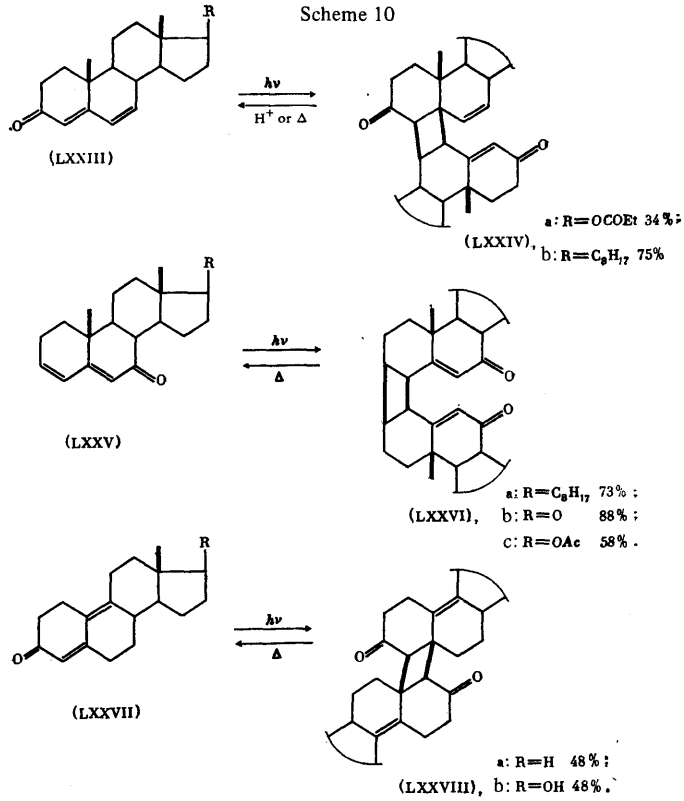
The catalytic hydrogenation of the cyclobutenosteroids (LXXa–c) leads to the corresponding cyclobutane analogues.[13,69]

IV. PHOTODIMERISATION OF STEROID DIENONES

The photodimerisation of conjugated ketones can be regarded as one of the variants of the formation of a cyclobutane ring which has found an interesting application to the steroid series. Such photodimers were first obtained and characterised by two groups of workers at the beginning of the 1960's. Thus, after irradiating the androstadienone (LXXIIIa) derivative with UV light, Rubin et al.[71] isolated as the only reaction product a dimer to which the structure of the adduct (LXXIVa) of HT type was attributed on the basis of spectroscopic data and was subsequently confirmed[72] (Scheme 10).

Analogous dimerisation has been described[73] for cholestadienone: when compound (LXXIIIb) was irradiated, the photodimer (LXXIVb) was isolated in 75% yield. Thus the dimerisation proceeds in this case via the addition of the αβ-double bond (Δ^4) in one molecule of the dienone (LXXIII) to the γδ-bond (Δ^6) of the scond monomer. The dimerisation pathway is determined by the characteristic environment of the chromophore and steric factors play a decisive role here. For example, the dimerisation of the steroid $\Delta^{3,5}$-7-ketones (LXXVa–c) afforded in all cases high yields of only one regioisomer, namely (LXXVIa–c) of the HH type,[74] i.e. the product of the addition of the γδ-double bonds of both monomeric molecules of compound (LXXV). Apparently steric hindrance prevents the approach by the second bulky molecule of compound (LXXV) to the αβ-double bond of the first monomer, whereas on irradiation of compound (LXXVa) in cyclopentene the corresponding cyclic 5,6-adduct was isolated.[74] The rate of dimerisation of compound (LXXV) is much lower than the rate of dimerisation of compound (LXXIII). The photoirradiation of the dienone (LXXVII), in the molecule of which the γδ-double bond is sterically hindered, has also been investigated. This dienone affords a lower yield of the unstable dimer (LXXVIII), than the reaction involving the Δ^4-bonds alone.[5,75] In contrast to the 17β-hydroxy- $\Delta^{4,9}$-ketone (LXXVIIb), the 17β-acetoxy-derivative forms a dimer via a reaction of the HH type.[105] On heating in the crystalline state or in solution, the dimers (LXXIV), (LXXVI), and (LXXVIII) decompose with formation of the corresponding monomeric molecules.

Scheme 10



The nature of the excited state of the steroid βγ-hexadienone systems, including their triplet π,π* state, has been investigated quantum-chemically; the results of this study do not conflict with purely chemical conclusions concerning the structure of the dimers (LXXIV) and (LXXVI).[71, 73,76] It was shown in this connection that, whereas the positive charge is concentrated on the C(3) atom of the diene component of the steroid dienone, which is in the ground state, in the π,π* state the greatest positive charge is on the C(4) atom. In view of these considerations, the formation of a bond between the C(3) atom of one molecule and the C(4) atom of a second steroid dienone appears unlikely.[76]

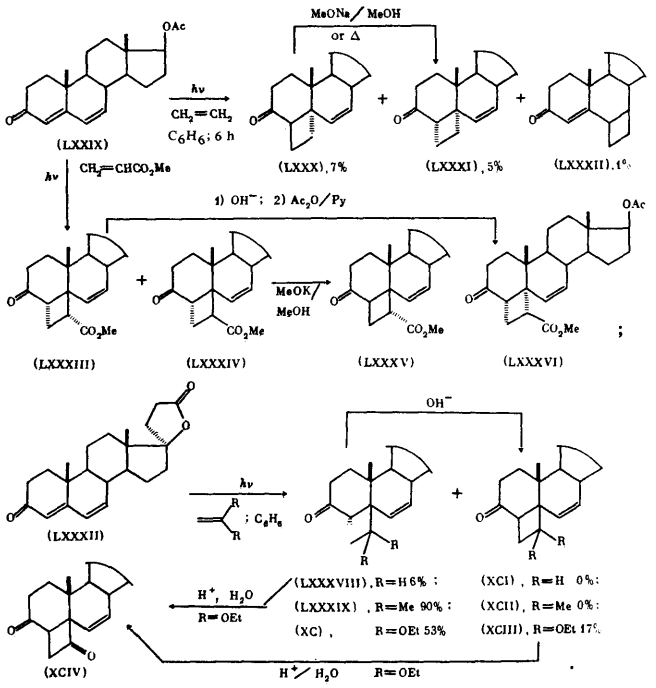
V. PHOTOCYCLOADDITION OF ALKENES TO STEROID DIENONES

The photocycloaddition of various alkenes to steroid dienones proceeds in a more complex manner than for αβ-unsaturated ketosteroids and frequently leads to a complex mixture of adducts produced via both αβ- and γδ-double bonds of the initial dienone and differing in their structures

and stereochemistry depending on the mode of addition of the alkene.

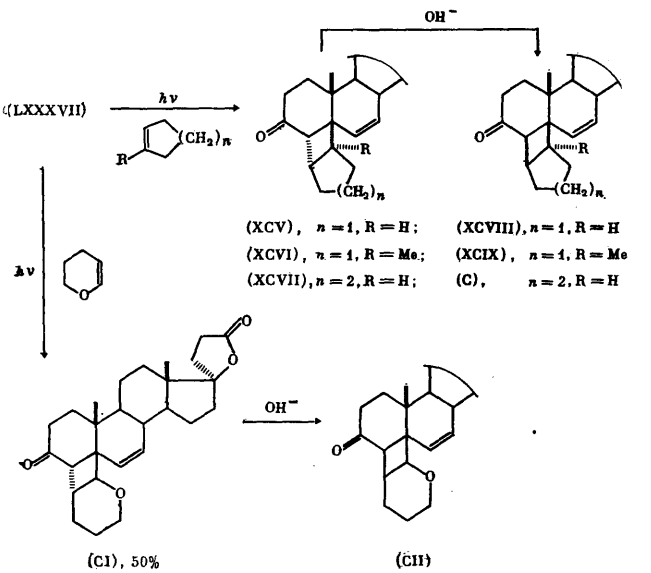
Ethylene is a relatively unreactive component of the [2 + 2]-photocycloaddition reaction. Irradiation of a benzene solution of the acetate (LXXIX) in an atmosphere of ethylene affords a low yield of *trans*-4β,5α- and *cis*-4α,5α-cyclobutanosteroids (LXXX) and (LXXXI) and also a 1% yield of the cyclic 6β,7β-adduct (LXXXII) [77] (Scheme 11):

Scheme 11



The structures attributed to compounds (LXXX)–(LXXII) are based on spectroscopic and certain chemical data. Thus *trans*-(LXXX) is known to isomerise readily to the *cis*-4*a*,5α-adduct (LXXXI) on treatment with sodium methoxide in methanol or thermally. The addition of ethylene to the $\Delta^{4,6}$-3-ketone (LXXXVII) has been achieved; [78] in this case the only product isolated (in 6%) yield was *trans*-4α-5β-cyclobutane (LXXXVIII), whose structure has been confirmed by data obtained by chiro-optical methods and also by the ready isomerisation to 4β,5β-cyclobutane (XCI). The photocycloaddition of a number of cyclic and acyclic alkenes to the ketone (LXXXVII) has also been investigated (see Scheme 11). The introduction of electron-donating substituents into the alkene molecule entails a sharp increase in the reaction rate and in the yield of cyclic adducts. [78] Thus isobutene adds to compound (LXXXVII) 20 times faster than ethylene and only *trans*-4α,5β-cyclobutane (LXXXIX) has been obtained in 90% yield. The addition of diethoxyethylene affords a 70% yield of a mixture of the adducts (XC) and (XCIII) in proportions of 3 : 1. The ready conversion of the *trans*-adducts into 4β,5β-isomers (XCI)–(XCIII) has been noted in all cases. The 4β,5β-cyclobutanone (XCIV) has been obtained by hydrolysing a mixture of cyclic adducts (XC) a and (XCIII). Cyclic alkenes also react with the photo-excited dienone (LXXXVII) (Scheme 12); for example, cyclopentene gives rise to only the one *trans*-adduct (XCV) in 50% yield, [38,78] while methylcyclopentene and methylcyclohexene react to form a mixture of the cyclic adducts (XCVI) and (XCIX), on the one hand, and (XCVII) and (C), on the other, respectively:

Scheme 12



The addition of dihydropyran to compound (LXXXVII) leads only to the *trans*-4α,5β-adduct (CI). All the *trans*-4α,5β-adducts (XCV)–(XCVII) and (CI) obtained readily isomerise to the *cis*-4β,5β-adducts (XCVIII)–(C) and (CII). [78]

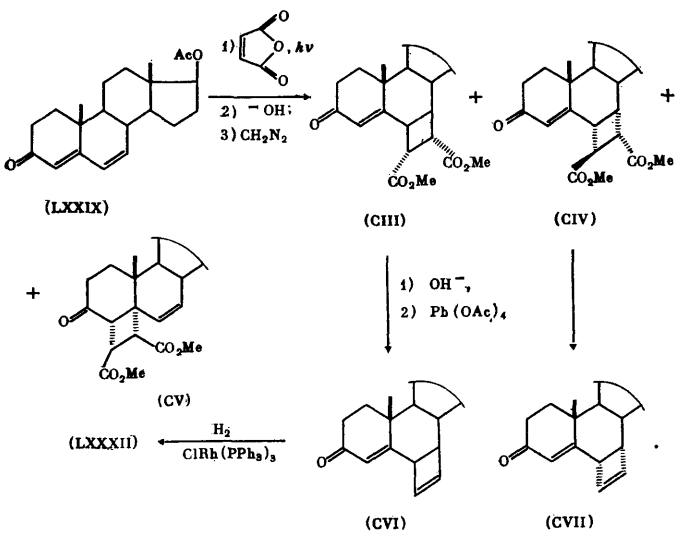
Thus the specificity of the photocycloaddition of alkenes to steroid $\Delta^{4,6}$-3-ketones, leading exclusively to *trans*-4α,5β-derivatives, has been noted in all cases.

The formation of the 4β,5β-epimer has been explained by the isomerisation of the *trans*-adduct during the photochemical reaction. Here it is assumed that, if the *cis*-adduct had in fact arisen as a result of cycloaddition, it should have had to possess the αα-structure. The stereochemical and orientational selectivity of the given reaction is explained by the fact that the dienone interacts in the excited singlet state, in contrast to the excited triplet state usually observed in photochemical cycloaddition reactions. [78]

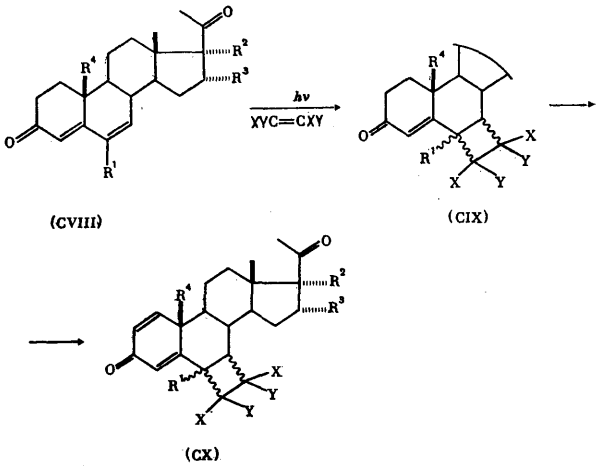
The photoaddition of methyl acrylate to Δ^6-testosterone acetate (LXXIX) (Scheme 11), which proceeds in accordance with the [2*s* + 2*a*] scheme, leads to the *trans*-substituted cyclobutane (LXXXIII); the epimer (LXXXIV) was also isolated in the chromatographic separation. The hydrolysis and isomerisation of compound (LXXXIV) (MeOK–MeOH) with subsequent reacetylation leads to *cis*-4β,5β-cyclobutane (LXXXV). Under analogous conditions, *trans*-(LXXXIII) was converted into the diester (LXXXVI) (the given stereochemistry was attributed on the basis of some of its chemical and chiro-optical properties). [79] The photocycloaddition of cyclopentene to the dienone (LXXIX) adsorbed on silica gel has been investigated. [43] Apart from cyclic *trans*-4α,5β-adduct of the type of (LXXXVIII), which is the sole product of the reactions carried out in methanol, the corresponding cyclic 6,7-adduct is also formed in 30% yield in this instance. We may recall the photoaddition of maleic anhydride, reacting in the excited state, to Δ^6-testosterone acetate (LXXIX) in the ground state [77] (Scheme 13). Here the main product is that resulting from the addition to the γγ-bond of the steroid dienone—the diester (CIII) (55%) (obtained after the methanolysis of the primary cyclic adduct) and its 6α,7α-isomer (CIV) (19%). The yield of the photoadduct (XV), formed as a result of the addition to the αβ-bond, does not exceed 15%. The *exo*-disposition of the methoxycarbonyl groups has been attributed to compounds (CIII)–(CV).

The oxidation of compounds (CIII) and (CIV) by $Pb(OAc)_4$ leads smoothly to the cyclobutenes (CVI) and (CVII). The homogeneous hydrogenation of the former in the presence of Wilkinson's complex afforded the familiar[77] cyclobutane (LXXXII):

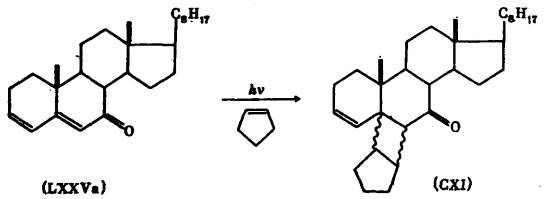
Scheme 13



A series of 6α,7α- and 6β,7β-cyclobutanopregnanes (CIX) and their 19-nor- and 17-, 16-, and 6-substituted analogues have been obtained by irradiating $\Delta^{4,6}$-3-ketopregnanes having the general formula (CVIII) in benzene in the presence of various alkenes; 4α,5α-,4β,5β-, and 4α,5β-cyclobutanes have also been mentioned as other products. The $\Delta^{1,4}$- derivatives (CX) have been obtained by chemical reactions of the cyclic adducts (CIX):[6]



The analogous 6,7-cyclobutanes of the androstane series have also been obtained.[7] The cyclic 4,5-adduct (CXI), whose stereochemistry has not been established, has been obtained by the cycloaddition of cyclopentene to cholesta-3,5-dien-7-one (LXXVa):[74]



Thus a characteristic feature of the photocyclisation considered is the ability of the steroid Δ^4- and $\Delta^{4,6}$-3-ketones in the π,π* state to form the *trans*-joined 4,5-cyclobutanosteroids, which differ significantly from the familiar results of the dark [2 + 2]cycloaddition; apparently it can be explained by the conformational flexibility of the *A* ring in the steroid systems considered (only the *cis*-adducts have been obtained for the *C* and *D* rings).

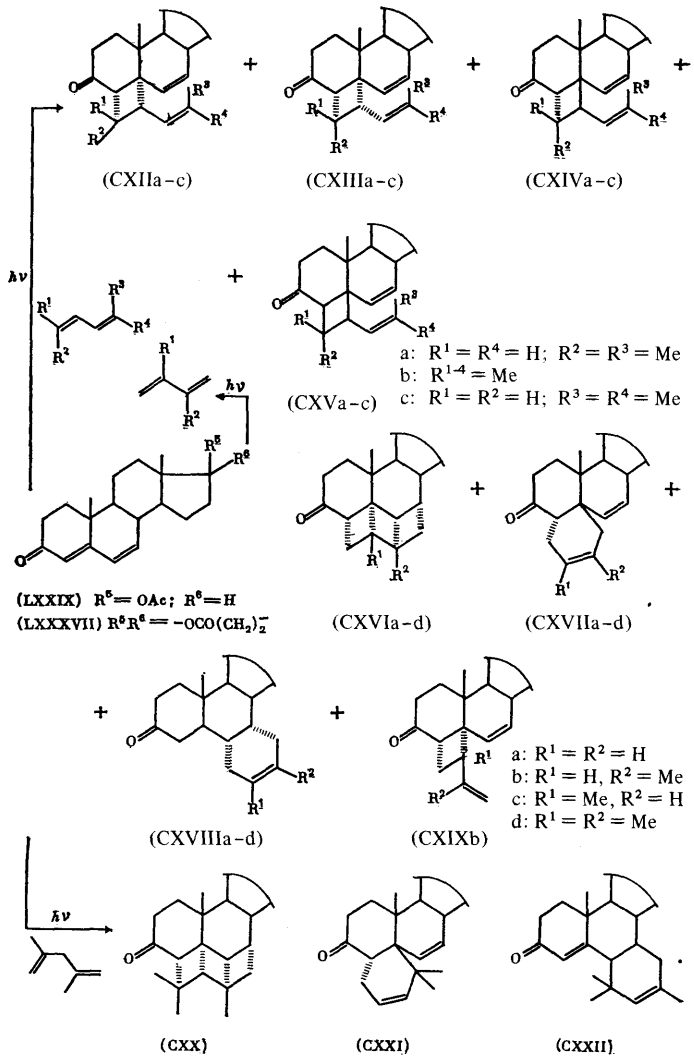
VI. PHOTOCYCLOADDITION OF DIENES TO STEROID DIENONES

It is well known that, when 1,3-dienes enter into a dark reaction with compounds containing an activated double bond, they give rise to the *cis*-products of the [2 + 2]- and [2 + 4]-cycloaddition.[80] On the other hand, the photoinduced addition of dienes leads to both *cis*- and *trans*-joined cyclic adducts. In the steroid series, this reaction has been investigated in detail by Lenz,[48,81-85] who showed that the 4,6-dien-3-ones (LXXIX) and (LXXXVII) interact with cyclic and ancyclic dienes (Table 2, Schemes 14 and 15), producing complex mixtures of substances, whose structures and stereochemistry and also composition depend on the structure of the diene and certain other factors. The results presented indicate that the isomeric cyclobutanosteroids are formed exclusively via the αβ-double bond (Δ^4-bond) of the initial steroid, which may be accounted for by its steric accessibility compared with the γδ-double bond. As can be seen from the data in Table 2, the ratio of the [2 + 2]- and [2 + 4]-adducts and the yield of the 4,5-cyclobutanosteroids depend in a definite manner on the conformation of the diene. Thus, in the reactions with transoid dienes (Table 2, compounds Nos.4–6), the yield of the isomeric cyclic 4,5-butanes (CXII)–(CXIV) is very considerable.[81,82] The 4α,5β-cyclobutanosteroids (CXIV) are converted into the 4β-epimers (CXV) in solution. On the other hand, butadiene and its 2-methyl and 2,3-dimethyl derivatives (Table 2, compound Nos.1–3) as well as *s-cis*-2,4-dimethylpenta-1,3-diene (Table 2, compound No.7) altogether fail to form cyclobutanes on reaction with steroid dienones [if one disregards the formation of compound (CXIXb) in 5% yield from isoprene]. In such cases the main reaction products are cyclic [2 + 4] adducts—the *trans*-4,5-cyclohexenosteroids (CXVII) and (CXXI) and the *cis*-6α,7α- and 6β,7β-cyclohexenosteroids (CXVIII) and (CXXII)[81-85] (Scheme 14).

Table 2. The yields of the cyclic adducts (%) in the photolysis of the dienones (LXXIX)* and (LXXVII)** in the presence of dienes.

No.	Diene	IP, eV	Yield of cyclic adducts, %					Refs.
			4α, 5α, 6α, 7α, [2+2+2+2]	*cis*-4,5 [2 + 2]	*trans*-4α, 5β [2 + 2]	*trans*-4α, 5β [2 + 4]	*cis*-6α, 7α, 6β, 7β [2 + 4]	
1	Butadiene*	9.03	25—27	—	—	33—50	8(α, β)	[81—84]
2	Isoprene*	8.76	20	5	—	40	11(α, β)	[82, 85]
3	2,3-Dimethylbutadiene*	8.89	12	—	—	48	32(α, β)	[82,84,85]
4	*trans,trans*-hexa-2,4-diene	8.19	—	45	55	—	—	[82]
5	*s-trans*-2,5-Dimethylhexa-2,4-diene**	—	—	30	25	—	—	[81]
6	4-Methylpenta-1,3-diene**	—	—	17(α, α); 44(β, β)	4.5	—	—	[81]
7	*s-cis*-2,4-Dimethylpenta-1,3-diene**	—	13	—	—	24	22(α, β)	[82—85]
8	1-Vinylcyclohexa-diene**	—	—	31	—	52	12(α, α)	[82]
9	Cyclohexa-1,3-diene*	8.25	—	31(α, α)	—	14(β, α)	—	[82]

Scheme 14

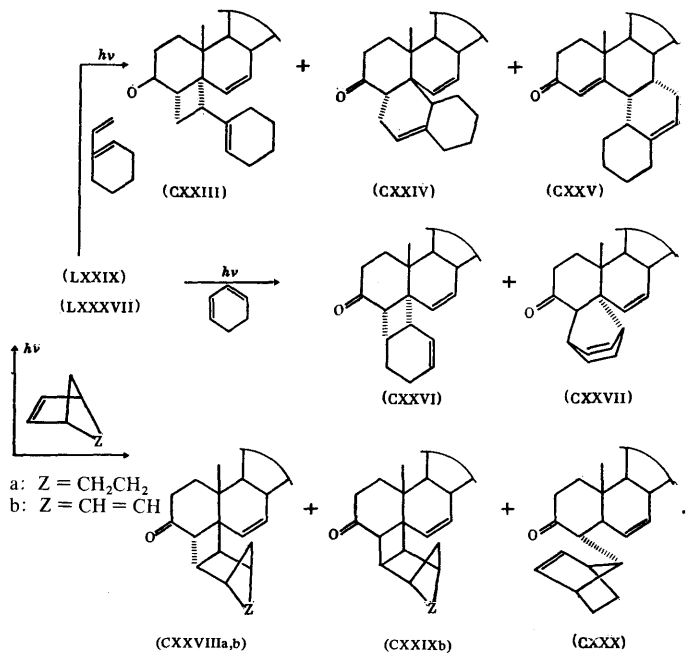


Vinylcyclohexene (Table 2, compound No.8) affords a mixture of cyclic adducts involving the Δ^4-bond: the 4α,5α-cyclobutane (CXXIII), the 4α,5β-cyclohexene derivative (CXXIV), and the product of the addition to the Δ^6-bond of the steroid dienone—compound (CXXV).[82] The interaction of the dienone with cyclohexadiene (No.9) leads exclusively to a mixture of the *cis*-4α,5α-cyclobutane (CXXVI) and the cyclic *trans*-4β,5α-adduct (CXXVII) [82] (Scheme 15).

The photocycloaddition of norbornene to the dienone (LXXXVII) leads to a 60% yield (Scheme 15) of the *trans*-4α,5β-cyclobutane derivative (CXXVIIIa), which is an exo-adduct according to X-ray diffraction data.[48] In contrast to the majority of *trans*-4α,5β-cyclobutanes, compound (CXXVIIIa) is converted into the corresponding 4β-epimer (CXXIXa) only after prolonged refluxing in methanol in the presence of sodium methoxide. Irradiation of compound (LXXXVII) in the presence of norbornadiene yielded three products: the 4α,5β- and 4β,5β-cyclobutanes (CXXVIIIb) and (CXXIXb) and the 4α-derivative (CXXX).

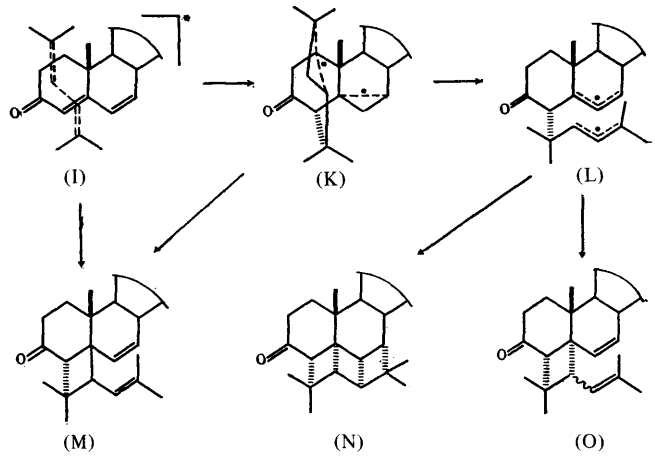
The most surprising result of the photocycloaddition of conjugated dienes to steroid dienones is the formation of "stepwise" cyclic [2 + 2 + 2 + 2]adducts (CXVI) and (CXX).[81-85] These compounds arise with a high regio- and stereo-selectivity. Thus the diene approaches exclusively the α-region of the steroid molecules, affording only a type HH adduct. Lenz[82] suggested that the possibility of the formation of the stepwise adduct depends on the ionisation potential (IP) of the diene. For IP smaller than 8.4 eV (Table 2, compound Nos.4 and 9), a product of this kind does not arise; furthermore, with increase of IP (Table 2, compound Nos.1 and 2), the yield of compound (CXVI) increases. Dienes with terminal substituents give rise to adducts of the HH type, for example, compound (CXX), while dienes with substituents at the centre of the molecule lead to a mixture of compounds (CXVIb, c).[81,82] One should also state that all the attempts to convert 4α,5α-cyclobutano-steroids (CXII) into the corresponding "stepwise" adducts were unsuccessful.[81]

Scheme 15



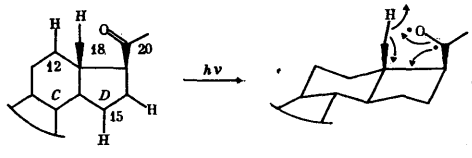
Since both the *cis*- and *trans*-cyclobutanes are formed as a result of the approach by the diene to the excited dienone in the α-region of the latter, the following reaction scheme has been proposed:[81] the photoexcited dienone interacts with the diene, to form an exciplex, in which a highly coordinating disposition of the reacting molecules obtains as a result of the adequately fixed chair conformation of the *A* ring and the presence of a pseudoequatorial current at C(4). In the complex (I), one of the double bonds of the diene is disposed orthogonally in relation to the Δ^4-bond of the dienone. Next there is a possibility of the direct formation of the *trans*-4α,5β-cyclobutanone (M), while the biradical intermediate (K) can generate, via a disrotatory transformation around the C(4α)–C bond, the allylic biradical (L), which is capable of forming the C(5)–C bond and this leads to both the *cis*-4α,5α-cyclobutane (O) and to synchronous

interaction of two allylic radicals with formation of the "stepwise" adduct (N):



VII. INTRAMOLECULAR PHOTOCYCLISATION OF STEROID KETONES

Yet another variant of the synthesis of pentaranes with an additional cyclobutane ring uses the familiar ability of carbonyl compounds to undergo intramolecular photochemical reactions with the sterically close γ-hydrogen atom (Norrish type II reactions).[86] In the series of 2-keto-steroids, such interaction is possible, in principle, with the C(12), C(15), and C(18) centres. However, the 20-carbonyl and 18-methyl groups are most favourably disposed on purely steric grounds:

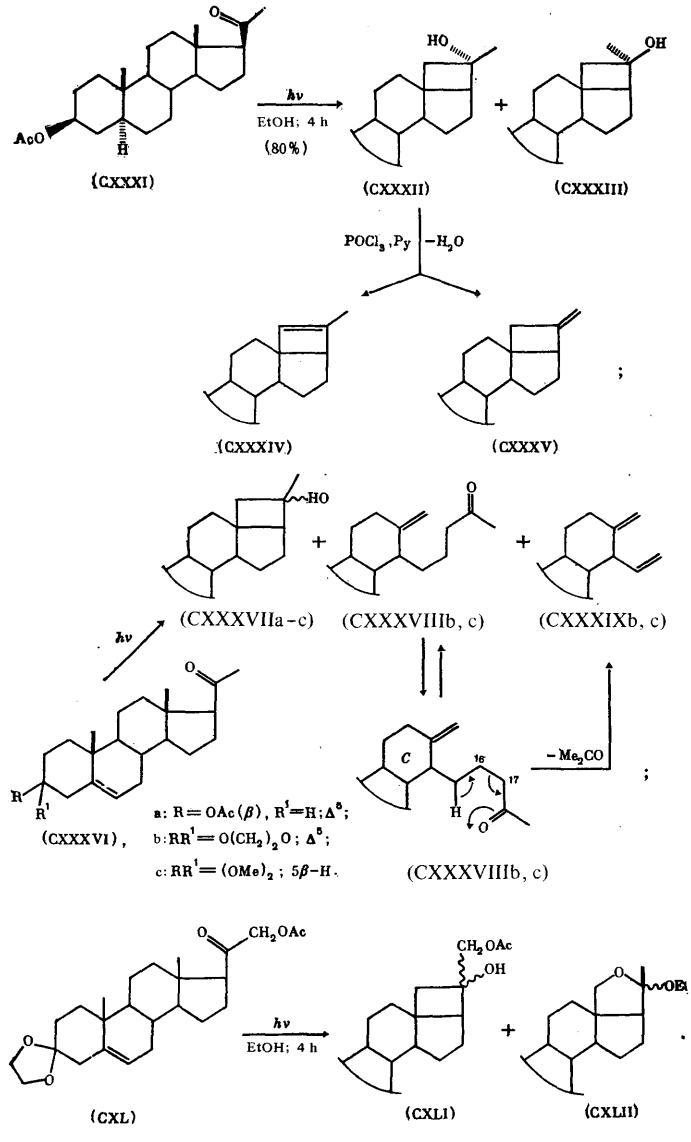


It has been shown that, when the 20-ketone (CXXXI) is irradiated in ethanol, a mixture of epimeric 13β,17β-cyclobutanols (CXXXII) and (CXXXIII) is formed in 80% yield in proportions of 3 : 1. A mixture of the alkanes (CXXXIV) and (CXXXV) was obtained by the dehydration of the 20α-epimer (CXXXII).[16,17] The structures of all these substances have been confirmed spectroscopically.[17]

The replacement of ethanol by non-polar solvents leads to the retardation of the photocyclisation and a decrease in the yield of the reaction products.[17] Thus, irradiation of compound (CXXXVIa) in hexane afforded a 33% yield of a mixture of (CXXXVIIa) epimers; compounds (CXXVIIIb, c) were obtained analogously from compounds (CXXXVIb, c) together with appreciable amounts of the D-secosteroids (CXXXVIIIb, c) and (CXXXIXb, c).[17,87] Compounds (CXXXVIII) and (CXXXIX) evidently arise as a consequence of the occurrence of two competing and consecutive photo-retro-reactions (Norrish type II), leading to the dissociation of the C(13)–C(17) bond and then the C_{16}–C_{17} bond.[17,87]

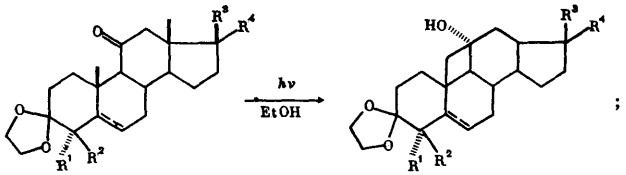
The cyclosteroids (CXXXVII) have been used as intermediates in the introduction of functional groups at the C(18) centre in the synthesis of aldosterone and its analogues.[88,89] Isolated information about such hydroxycyclobutanosteroids is available in patents.[90,91]

Substituents in the α-position relative to the 20-carbonyl group affect the course of the intramolecular photocyclisation. Thus the acetoxyketone (CXL) proved to be less active than the ketone (CXXXVIb); its irradiation leads to an equimolar mixture of the isomeric cyclobutanols (CXLI) and the tetrahydrofuran derivative (CXLII). The formation of the latter can be explained by the interaction of the excited carbonyl moiety of the 21-acetoxy-group with the 18-methyl group.



The extension of the reaction considered to the 11-keto-derivatives of steroids led to the synthesis of 11,19-cyclosteroids containing an additional four-membered ring condensed with the *B* and *C* rings.[92–96] Thus irradiation of the 11-ketones (CXLIII) in ethanol afforded 10β,11β-cyclobutanosteroids (CXLIV).[94,97,98] The yield of the latter depends to a definite extent on the presence of a substituent at C(4) and on the character of the junction of the *A* and *B* rings and is a maximum for the 4,4-disubstituted *A*–*B*-*cis*-compounds, because cyclisation in such steroids eliminates the steric interaction between the 4β-CH_3 and the 19-CH_3

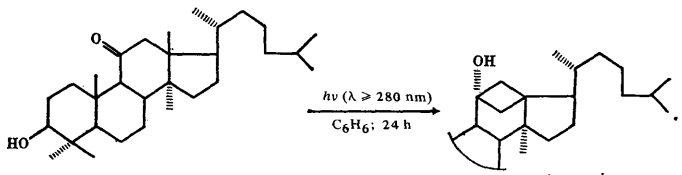
groups in compound (CXLIII):



(CXLIII) (CXLIV)

R^1 and R^2=H, Me; R^3, R^4=$O(CH_2)_2O$ or R^3=C_6H_{17}; R^4=H.

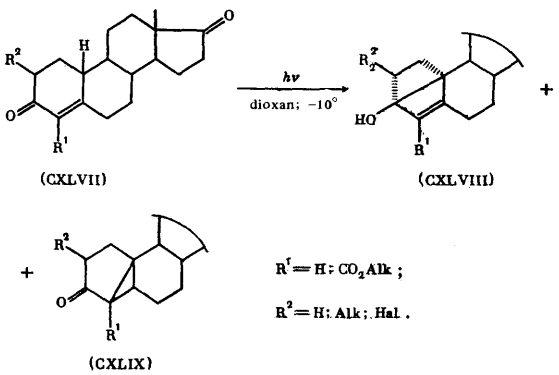
The character of the junction of the *C* and *D* rings and also the presence of the 14α-CH_3 group in the initial 11-ketosteroid affects the photocyclisation under consideration. Thus the Δ^{14}-11-ketosteroids form on irradiation the 11,8-cyclopropane derivatives;[99] the 11-ketone of the lanostane series (CXLV) is converted in ~20 yield into the 11β,13β-cyclobutanol (CXLVI):[100,101]



(CXLV) (CXLVI)

The cyclic 11,19-photoproducts in the series of triterpenoids have also been described.[92,93,102] It is noteworthy that the 11-keto-C-norsteroids do not undergo intramolecular cyclisation.[95]

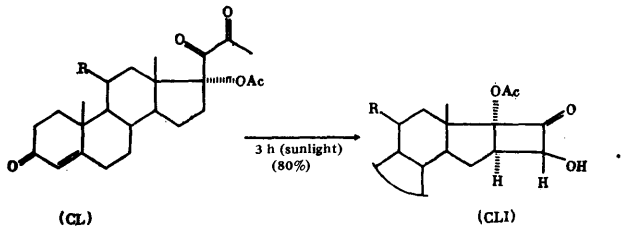
The 19-nor-Δ^4-3-ketosteroids substituted in the *A* ring produce on irradiation a low yield of the 3,10-cyclobutanol compounds (CXLVIII) together with the 4,10-cyclopropane derivatives (CXLIX):[104]



(CXLVII) (CXLVIII)

(CXLIX)

The 16,17-cyclobutanosteroid (CLI), obtained in a high yield on irradiation of compound (CL) with sunlight, has also been described:[19]



(CL) (CLI)

---oOo---

Thus the review of the literature data on the synthesis of cyclobutanosteroids (pentaranes) by photochemical methods shows that the main process in the photochemical [2 + 2]addition of unsaturated substrates to the active double bonds in the steroid molecule is sometimes accompanied by the simultaneous reactions involving both the initial steroid and the primary cyclic adducts.

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