Summary

The ultraviolet irradiation of hecogenin acetate has been shown to give two products. Lumihecogenin acetate, 3β-acetoxy-12, 13-seco-5α, 25D-spirost-13-en-12-one, which is the initial product, is converted by oxidative cyclisation into "14α-hydroxyhecogenin 3β-acetate", 3β-acetoxy-14α-hydroxy-5α, 25D-spirostan-12-one.

Prolonged irradiation of hecogenin acetate, or of lumihecogenin acetate, gives a second isomeric product, "photohecogenin acetate", 3β-acetoxy-12α,14α-epoxy-5α,25D-spirostan. Treatment of lumihecogenin acetate or photohecogenin acetate with boron trifluoride-ether complex gives a mixture of products, one product being 3β-acetoxy-12α-hydroxy-5α,25D-spirost-14-en. The other product from this reaction is believed to be a C-homo-oxasteroid.

Epoxidation of the Δ^{14}-12α-ol gives a 14α,15α-epoxide which on reduction with lithium aluminium hydride affords the same triol as is obtained on similar reduction of 14α-hydroxy-hecogenin.

Ultraviolet irradiation of 14α-hydroxyhecogenin 3β-acetate gives a compound containing a six-membered lactone ring.

Degradation of the spirostan side-chain in the 14α-hydroxy-compounds by standard methods gives very poor results. Accordingly attempts were made to prepare 14α-hydroxy-and Δ^{14}-steroids in the pregnan series. Although the ultraviolet irradation of 3β, 20ξ -diacetoxy-5α-pregnan-12-one gave good yields of the corresponding Δ^{13}-12, 13-seco-12-aldehyde and 12α,14α-epoxide, it was not found possible to prepare

14α-hydroxy- or Δ^{14}- steroids from these compounds.

The ultraviolet irradiation of Δ^{16}-20 ketones has been undertaken in a variety of solvents, and in many cases it has been found that reduction of the Δ^{16}- double bond occurs. Ultraviolet irradiation of 3β-acetoxypregna-5,16-dien-20-one ("pregnadienolone acetate") in certain alcohols (methanol, ethanol, isopropanol and cyclohexanol) causes reduction to 3β-acetoxypregn-5-en-20-one in about 40% yield, and also the addition of the alcohol across the double bond to give a 16α-hydroxyalkyl-steroid. The latter is obtained in about 40% yield in the case of ethanol, isopropanol and cyclohexanol.

The irradiation of 3β-acetoxy-16-methylpregna-5,16-dien-20-one in ethanol and in isopropanol gives good yields of 3β-acetoxy-16β-methylpregn-5-en-20-one, which is the only crystalline product.

T H E S I S

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Chemistry Department,
University of Strathclyde

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P H O T O C H E M I C A L   S T U D I E S

I N   T H E

S T E R O I D   S E R I E S .

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N O T E

Part of this work has been published already.

The photochemistry of hecogenin acetate is described in:

Bladen, McMeekin and Williams, *Proc. Chem. Soc.* 1962, 225; *J.C.S.*, 1963, 5727.

The photoaddition and photoreduction reactions of Δ^{16}-20 ketones have been described in:

Williams and Bladen, *Tetrahedron Letters*, 1964, 257.

The photoaddition reaction forms the basis of British Patent Application No. 36770/63 of September 18th, 1963.

C O N T E N T S

I N T R O D U C T I O N.

INTRODUCTION

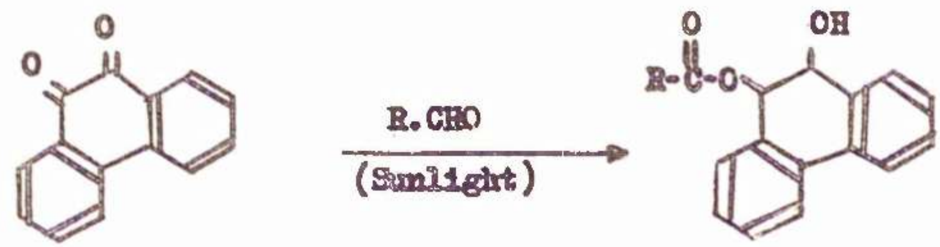
All chemical changes are associated with energy changes, and the use of radiant energy of a suitable frequency can often provide the energy necessary to effect a particular chemical reaction. In accordance with the Stark-Einstein Law[1], it is found that the frequencies which cause photochemical changes correspond to the frequencies at which the substances in question absorb radiation.

Aldehydes and ketones absorb weakly[2, 19], in the ultraviolet region between 290 and 320 mμ – depending upon the nature of the compound – with a low extinction coefficient, usually between 10 and 100 for simple saturated aldehydes and ketones. Such absorption is associated[3] with an $n \longrightarrow \pi^*$ transition, that is, the transition of an electron associated with the oxygen atom of the carbonyl group from a non-bonding to an anti-bonding orbital of higher energy. This absorption, with the formation of the energised state, seems to be responsible for most of the photochemical reactions known for simple aldehydes and ketones. The energy acquired by the molecule by the absorption of radiation can be lost by re-emission (with regeneration of the original molecule) or may result in a variety of photochemical reactions, intramolecular or intermolecular[4]. The course of photochemical reactions of aldehydes and ketones is usually explained by the transformation of the initial activated species into a diradical, which subsequently undergoes one of the reactions mentioned above. The nature of the initial activated species is, however, not fully understood.

The Ultraviolet Irradiation of Carbonyl Compounds

Some of the earliest work on the irradiation of carbonyl compounds was performed by Klinger and by Ciamician and Silber. Their experiments were carried out by exposing the reactants to sunlight for periods varying from a few minutes to several months.

Klinger[5] observed that phenanthraquinone (I) on irradiation with aldehydes, gave adducts represented by (II).



(I) (II)

He also observed[6] that a solution of phenanthraquinone in ether darkens rapidly when exposed to strong sunlight, the corresponding hydroquinone being formed.

Ciamician and Silber, working in Bologna, studied the action of sunlight on solutions of quinones in alcohols, which they showed[7] to result in the formation of hydroquinones plus the aldehyde or ketone corresponding to the alcohol used as a solvent. Attempts to reverse the reaction photochemically - by irradiating a mixture of acetone and hydroquinone "all summer" - were without success[8]. The same authors showed, too, that simple aldehydes are reduced by the action of sunlight[8] on an alcoholic solution, or, indeed, on a solution in a variety of organic solvents including formic acid, ether, benzene and even paraffin hydrocarbons.

Saturated Carbonyl Compounds

In papers published in 1907 and 1909, Ciamician and Silber described the irradiation of a cyclic ketone, menthone (III) in aqueous ethanol[9], giving the unsaturated aldehyde (IV).

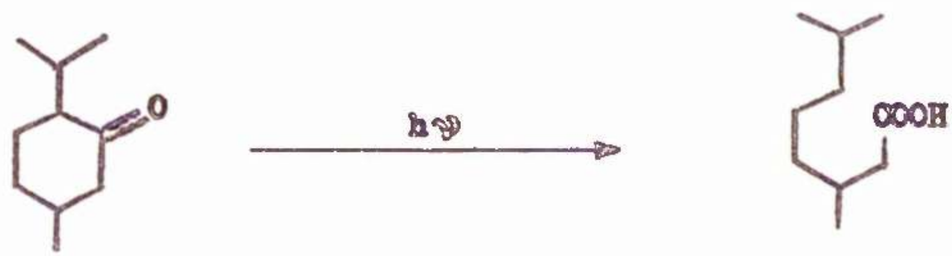
(III) (IV)

Ciamician and Silber also described[10] the photolysis of cyclohexanone (V) to give hex-5-enal (VI), of camphor (VII) to give campholenaldehyde (VIII), and of cyclohexanone, methylcyclohexanones and

(V) (VI)

(VII) (VIII)

menthone in aqueous solutions[11] to give carboxylic acids. Menthone, for example, after irradiation in aqueous ethanol by sunlight "for the duration of the summer and autumn months" gives the acid (IX)



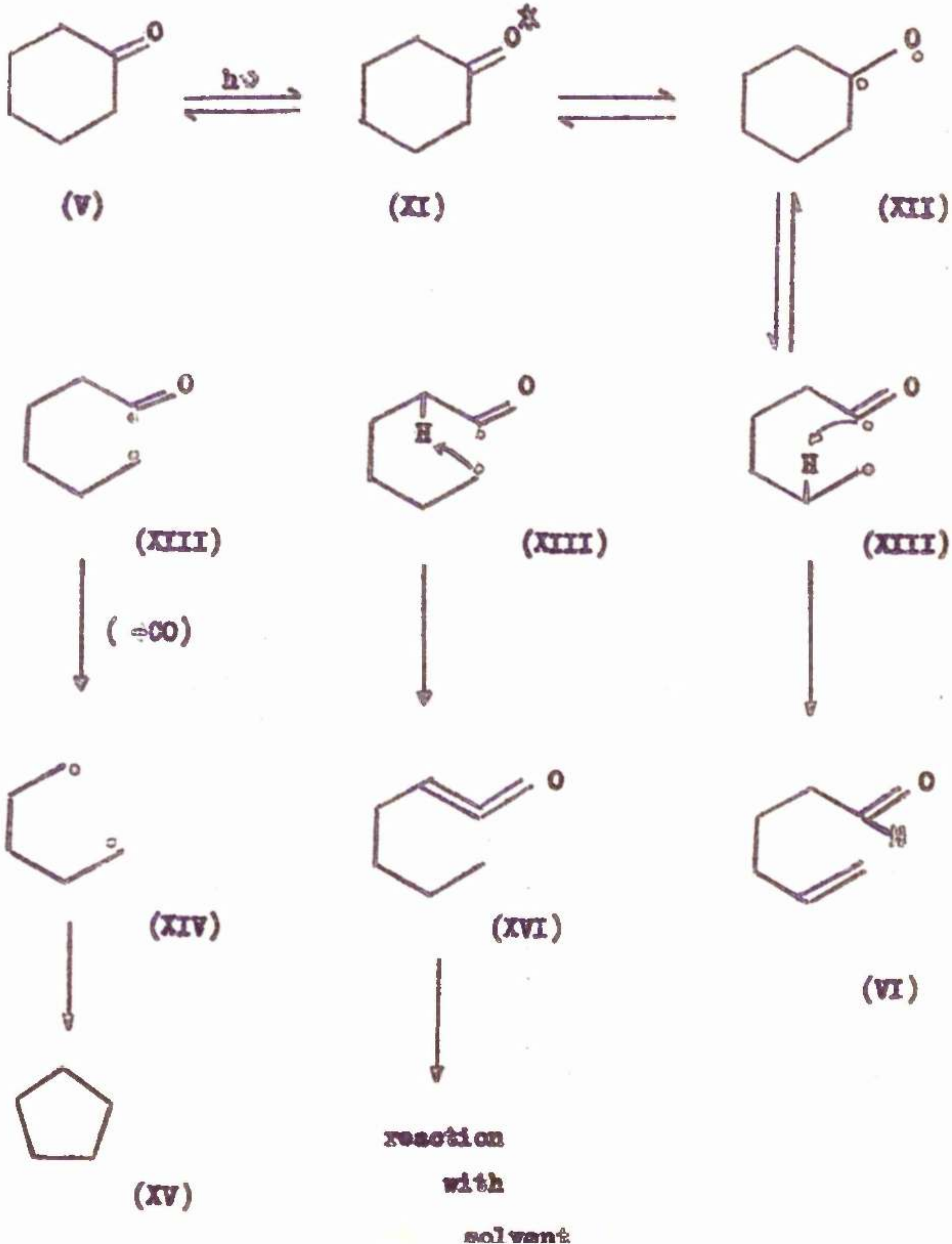
(III) (IX)

Irradiation of camphor in non-aqueous solvents has also been studied by Srinivasan who has proposed[12] the structure (X) for an isomeric ketone obtained in addition to the aldehyde (IV). He concluded that the formation of this compound can be explained on the basis of intramolecular hydrogen-abstraction by the carbonyl oxygen, "probably before ring-splitting occurs".

(X)

The formation of the unsaturated aldehydes and of the carboxylic acids mentioned above can be rationalised on the basis of the transformati of the initial activated species into a diradical. For example, in the case of cyclohexanone (V) the initial activated species (XI) can be envisaged[13] as reacting as shown in the Chart (1) below:

CHART I.



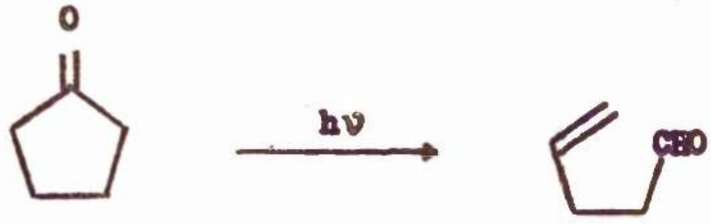
The activated species (inadequately represented by (XI)) gives rise to the diradical (XII) which is interconvertible with the diradical (XIII). The latter, in the vapour phase at least, can lose CO to give the diradical (XIV) which can cyclise to give cyclopentane (XV).

Alternatively, intramolecular hydrogen abstraction can occur, either to give the keten (XVI) which can react with the solvent or other reactan or else an alternative hydrogen abstraction can occur to give the unsaturated aldehyde (VI).

It is found[4] that whenever a photochemical reaction of a cyclic ketone gives a seco-product in which a bond is broken between the carbonyl group and an α -carbon atom, the radical which reacts to give the keten or aldehyde is always the more stable one. (That is, when a carbonyl group is located between, say, a methylene group and a tetrasubstituted carbon atom, the radical which reacts is the tertiary radical formed by cleavage of the bond between the carbonyl group and the tetrasubstituted carbon).

The diradical (XII) above, and similar radicals derived from other carbonyl compounds, can react with a solvent - or perhaps intramolecularly as suggested by Srinivasan[12] - to give a hydroxyl group, which may rearrange or remain as a hydroxyl, depending upon whether another hydrogen atom can be abstracted by the radical. There is also the possibility of pinacol formation or some other form of dimerisation.

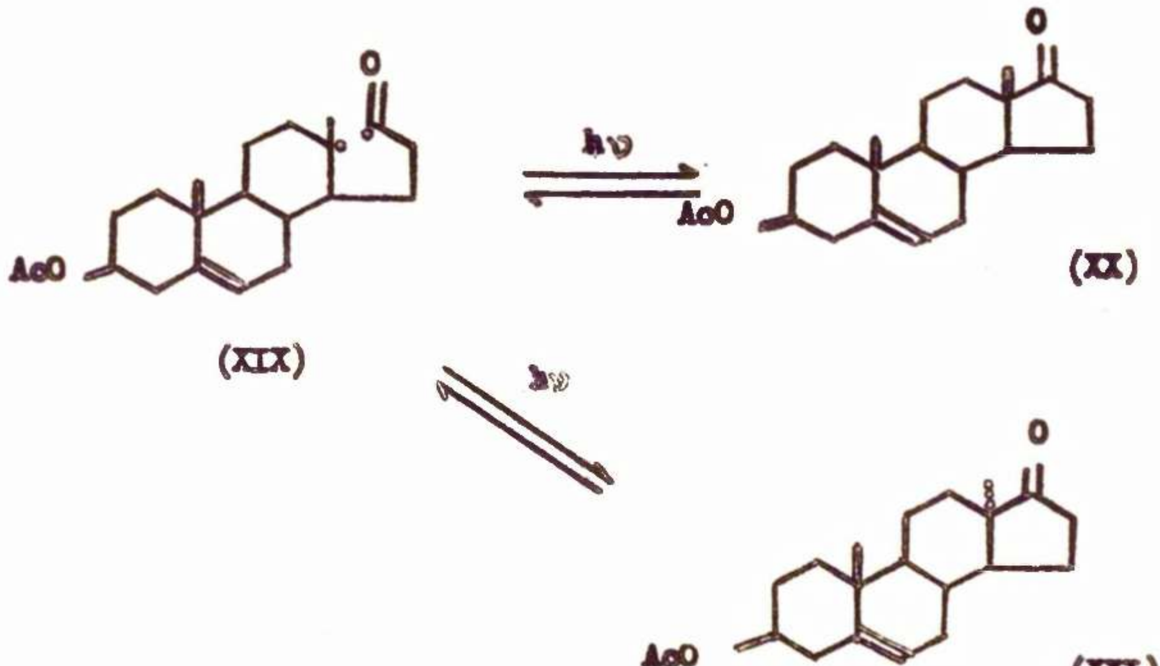
Srinivasan[14] described also the ultraviolet irradiation of cyclopentanone (XVII), both in the vapour phase and in the liquid phase, to give pent - 4 - enal (XVIII).



(XVII) (XVIII)

Now in the work of Butenandt and his co-workers[15] and of Quinkert <u>et al</u>[1] the ultraviolet irradiation of steroidal C_5-ring ketones has not been observed to give aldehydes of this type.

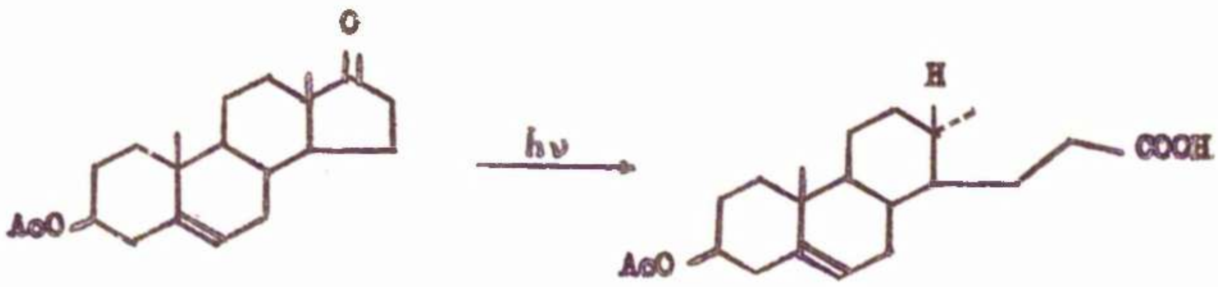
The irradiation of 17-ketosteroids such as androstenolone 3β-acetat (XX) causes epimerisation at C-13, which has been shown[17] to be a reversible reaction



(XIX) (XX) (XXI)

Clearly a diradical such as (XIX) is formed when either the ketone (XX) or its epimer (XXI) is irradiated, the diradical being capable of re-combining to give either of the epimeric ketones.

The irradiation of androstenolone acetate in aqueous dioxan has been shown by Quinkert et al[16] to give the seco-acid (XXII).



(XX) (XXII)

It would be an attractive hypothesis to suggest that the reason for non-formation of unsaturated aldehydes in the case of the irradiatic of 17-ketosteroids is that there is no hydrogen atom sterically availabl for abstraction without severe deformation of the bond angles. (This is supported by a study of Dreiding models). However, the fact that cyclopentanone does give an unsaturated aldehyde on irradiation[14] appear to rule this out, especially since the reaction occurs in the vapour pha (where intermolecular abstraction would be unlikely) as well as in the liquid. Srinivasan suggests that here, as in the case of the formation of the ketone (X) from camphor, intramolecular transfer of hydrogen may occur before the ring is split. Even so, it seems remarkable that there is such a difference between 17-ketosteroids and cyclopentanone in this respect. It is possible that the comparativ stability of the tertiary radical (XIX) which may be formed in the former case has some connection with the difference, or perhaps some more subtle effect is responsible for it.

An interesting reaction which presumably occurs by intramolecula hydrogen abstraction without cleavage of a carbon-carbon bond is the photolysis[18] of cyclodecanone (XXIII) to give cis -9- decalol (XXIV)

(XXIII) (XXIV)

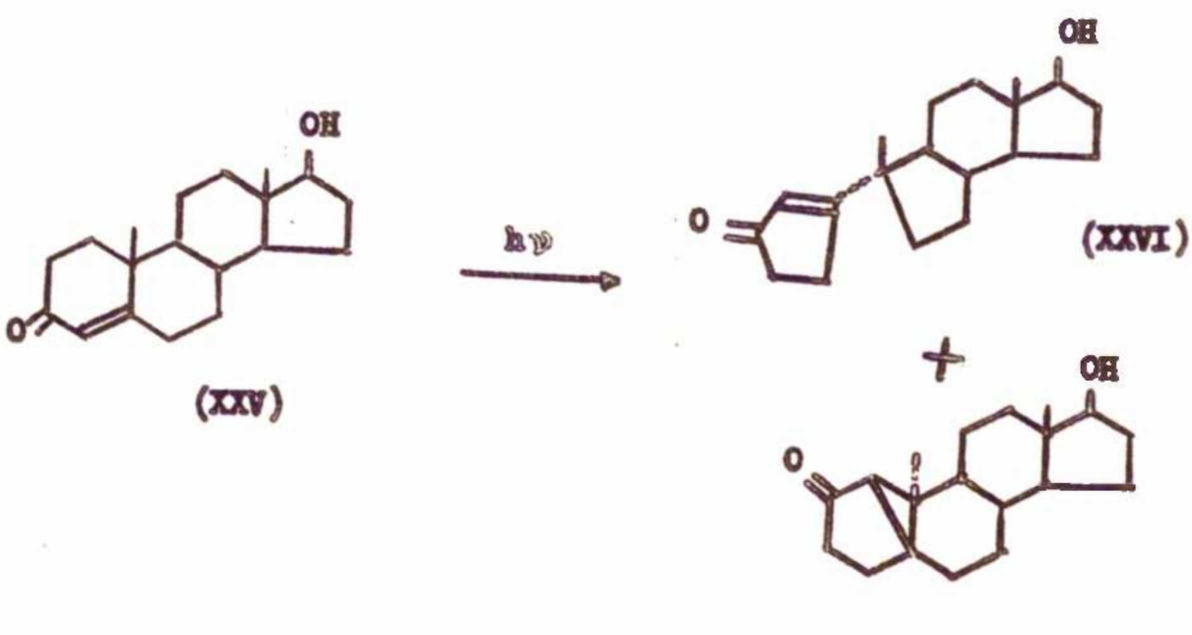
Unsaturated Carbonyl Compounds

The photolysis of conjugated carbonyl compounds has been undertal by several groups of workers. Ketones which are α,β- unsatura show a peak in the ultraviolet spectrum[19] at 240-250 mμ with an exti :tion coefficient of about 10,000. This is due to a $\pi \rightarrow \pi^*$ transition; however the absorption due to the $n \rightarrow \pi^*$ transiti at 290-320 mμ with an extinction coefficient of the order of 100, is us ually responsible for the photochemical reactions of conjugated ketones. (It should, perhaps, be pointed out that although β,γ- unsaturated carbonyl compounds show a similar - or greater - ultraviol absorption intensity at 290 mμ , for all practical purposes they behave as saturated ketones do when irradiated).

With α,β -unsaturated ketones, the products of photolysis are rarely similar to those which would be expected from a corresponding saturated ketone, as in most cases the presence of the double bond provides alternative routes for the reaction of the diradical formed from the initial activated species.

Little work appears to have been done on really simple α,β - unsaturated ketones, and in most cases where work has been done, and products isolated and identified, on more complex molecules, the mechanisms whereby the products are formed remain to be conclusively established.

The ultraviolet irradiation of testosterone (XXV) in tertiary butanol has been shown by the Swiss workers, Nann, Gravel, Schorta, Wehrli, Schaffner and Jeger[20], to give a mixture of products, formulated as (XXVI) and (XXVII)

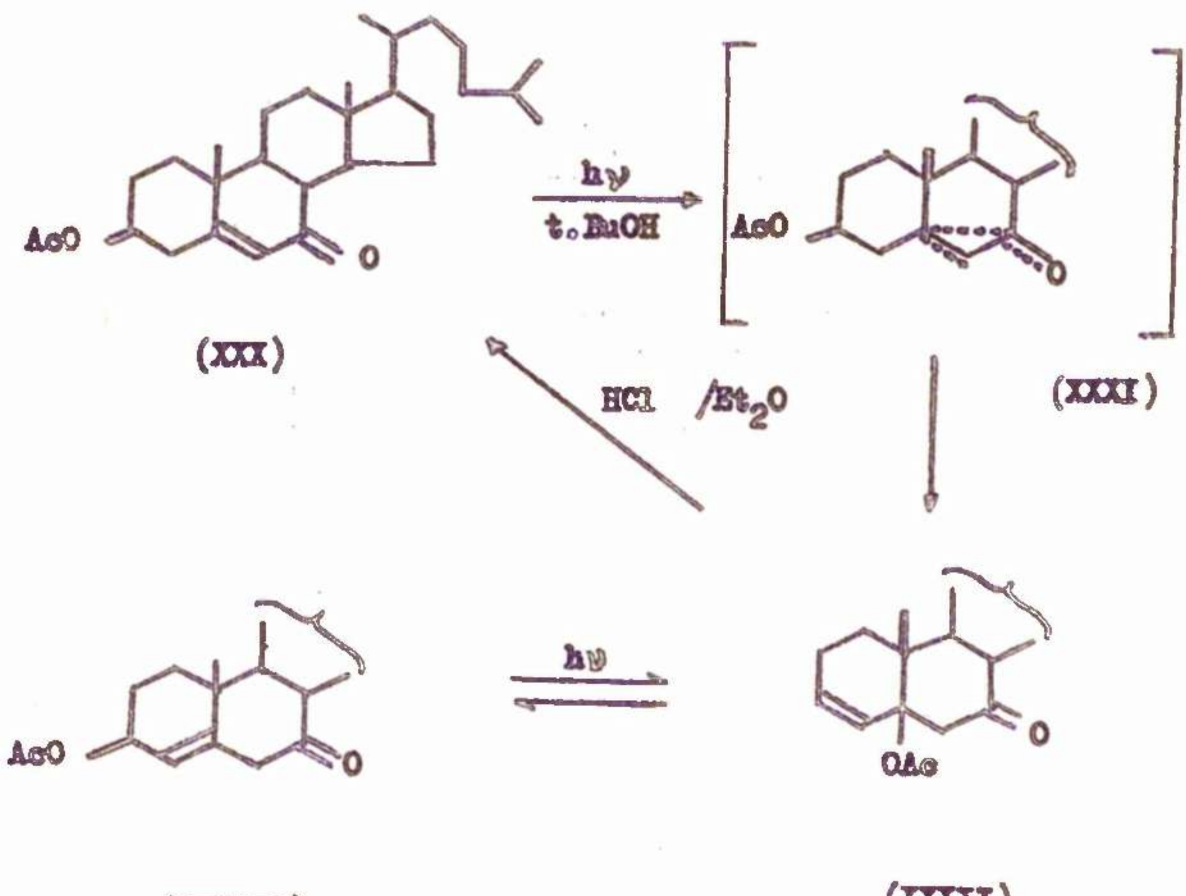


(XXV) (XXVI) (XXVII)

Similar irradiation of the 10α-epimer of testosterone (XXVIII), however, has been shown by workers from the same group[21] to cause migration of the double bond to give a Δ^5-isomer (XXIX) as the only crystalline product.

(XXVIII) (XXIX)

Gardner and Hamil[22] have studied the ultraviolet irradiation of 7-ketocholesteryl 3β-acetate (XXX)

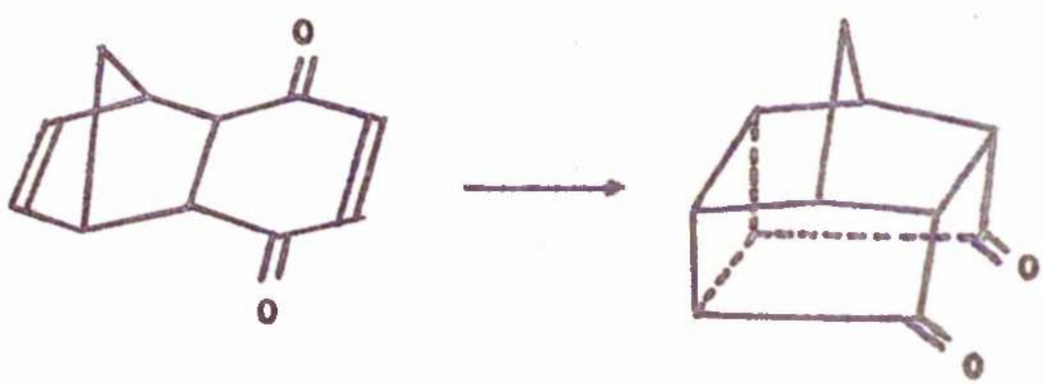


and described the isolation from the reaction mixture of the Δ^4-isomer (XXXIII) and the 5-acetoxy-Δ^3-steroid (XXXII). They have suggested the formation of an intermediate (XXXI) from the initial activated species, and it is possible that the formation of the compound (XXIX) from 10α-testosterone (XXVIII) may be explained by the initial formation of a similar intermediate.

Irradiation of verbenone (XXXIV) gives[23] the isomeric chrysanthenone (XXXV)

(XXXIV) (XXXV)

In molecules where steric factors are favourable, some rather unusual ring systems may be formed on irradiation of unsaturated ketones. For example, irradiation[24] of the compound (XXXVI) (which results from addition of cyclopentadiene to p-benzoquinone) gives the isomeric fully saturated diketone (XXXVII)

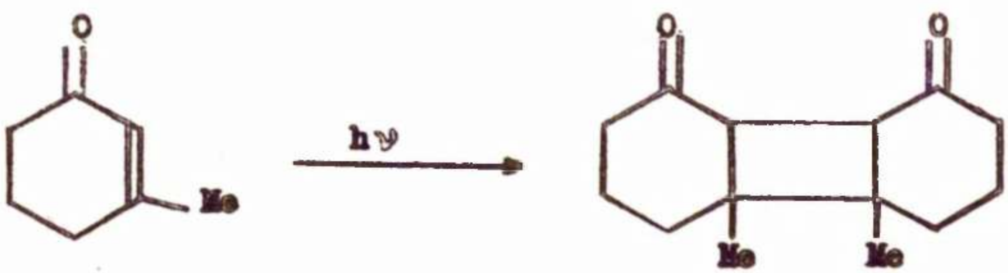


(XXXVI) (XXXVII)

A similar type of reaction[25] occurs on the irradiation of carvone (XXXVIII), the product being "carvone camphor" (XXXIX).

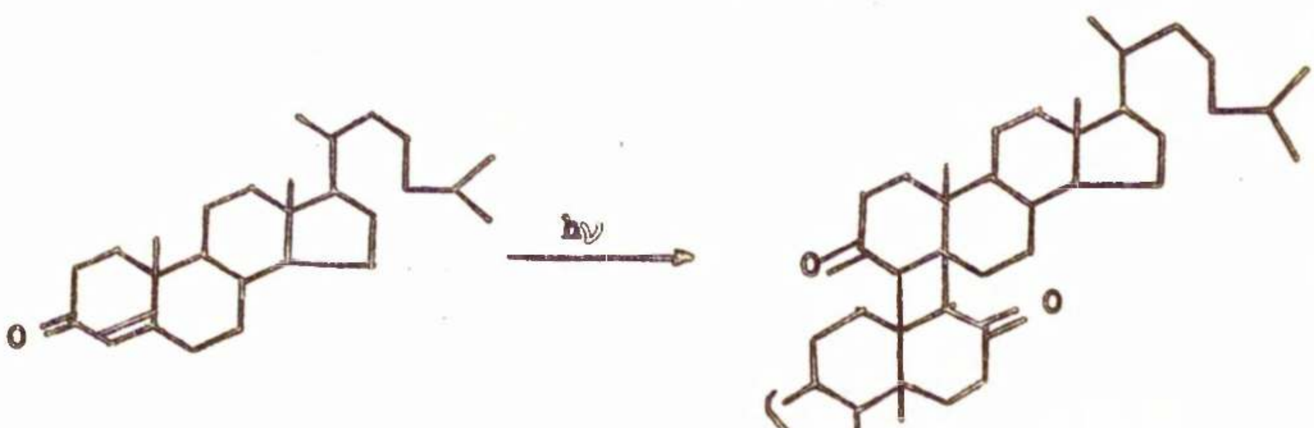
(XXXVIII) (XXXIX)

Dimerisation of α,β-unsaturated ketones on irradiation is a well-known reaction. 3-Methyl cyclohex -2-enone[26] (XL) on irradiation gives the cyclobutane derivative (XLI).

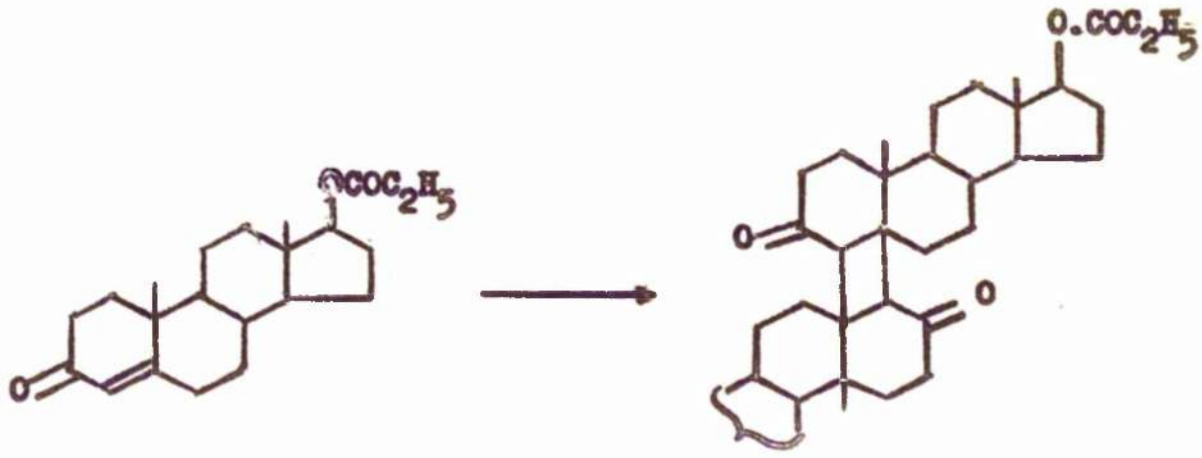


(XL) (XLI)

and similar reactions have been described in the case of Δ^4-cholestenone[27] (XLII), which gives the dimer (XLIII)



(XLII) (XLIII)



(XLIV) (XLV)

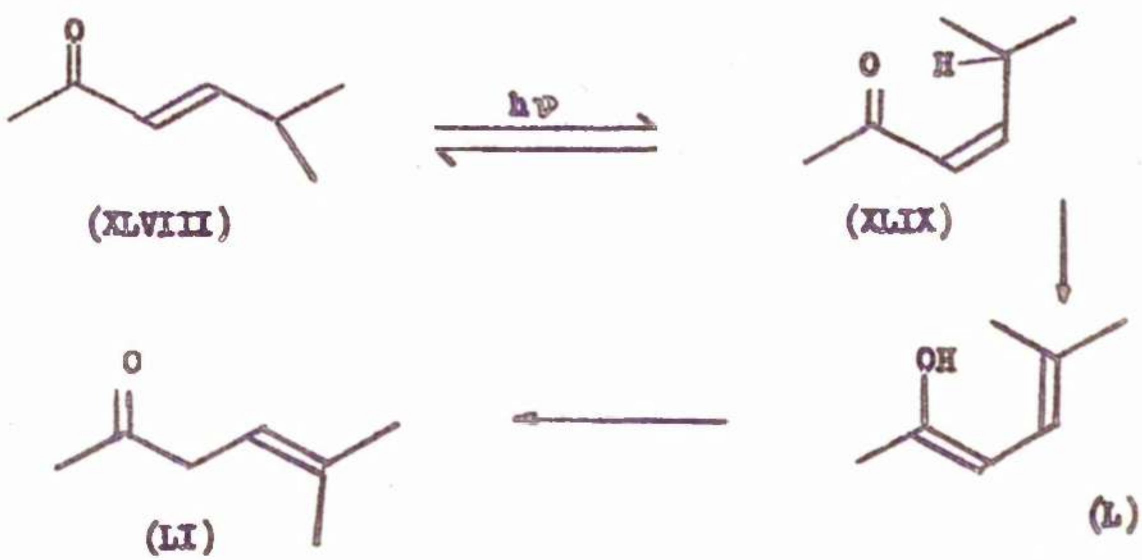
and testosterone propionate[28] (XLIV) which gives a similar cyclobutane (XLV)

(XLVI) (XLVII)

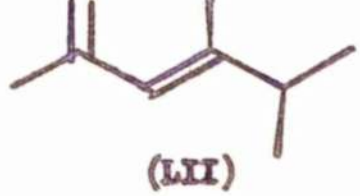
Numerous other examples of this type of dimerisation have been describe[d]
Presumably the reaction is initiated by an n ⟶ π^* transition t[o]
give an activated species which in turn forms a diradical. By redi[s]tribution of the electrons in the system, a diradical such as that represented

by (XLVI) could give rise to an alternative diradical, such as (XLVII), which could dimerise. Dimerisation would appear to occur most readily in fairly concentrated solutions, or else where no other facile reaction is possible.

A recently reported reaction[29] is the rearrangement of 5-methylhex-3-en-2-one (XLVIII) to give the β,γ-unsaturated isomer (LI)



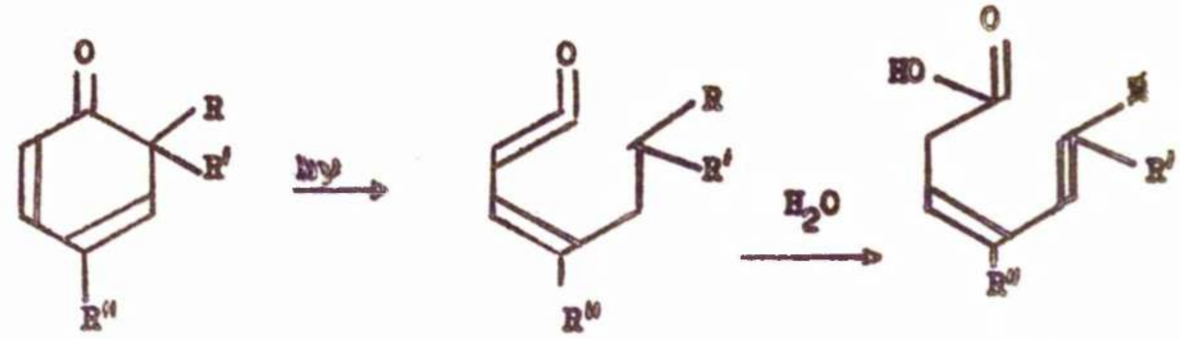
The reaction is thought to proceed as illustrated, via the cis-isomer (XLIX) which forms the usual diradical, the latter abstracting a hydrogen atom to give the enol (L) which ketonises to give the final product (LI). It is surprising, therefore, that in the case of 4,5-dimethylhex-3-en-2-on (LII) no rearrangement occurs .



(LII)

Carbonyl Compounds with Extended Conjugation

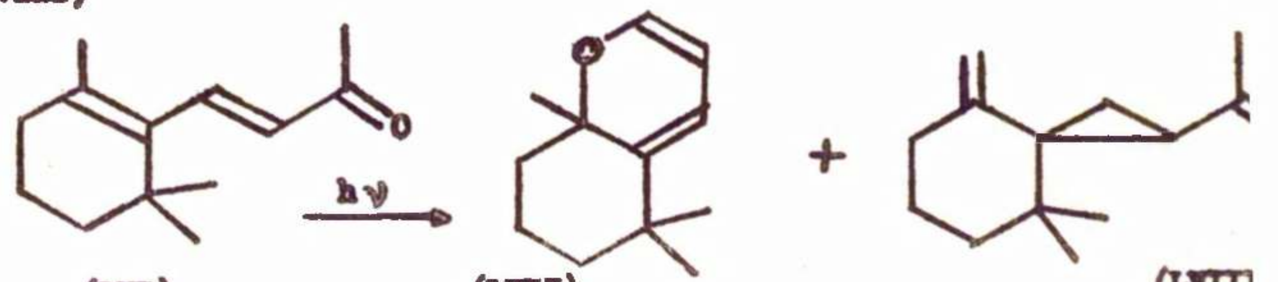
The irradiation of homoannular dienones in aqueous solvents has been used[30] as a relatively simple way of making certain open-chain acids which are difficult to obtain otherwise. The general reaction scheme is as follows:-



(LIII) (LIV) (LV)

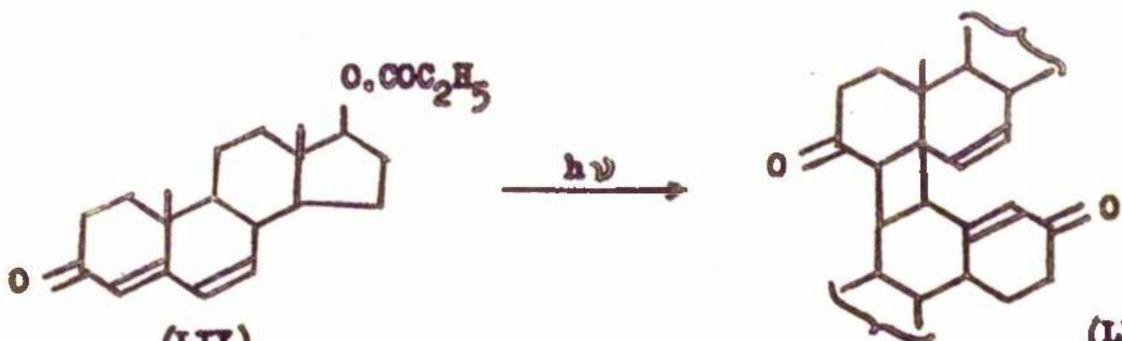
The initial dienone (LIII) which may have ($R = R^1 = Me$; $R^{11} = H$) or ($R = R^1 =$ O Ac; $R^{11} = Me$) or one of several other structures which have been described, is transformed into the ketene (LIV) which is hydrated by water to the acid (LV). It is possible to prepare amides by using an amine instead of water in this reaction. (It is likely, however, that the product will consist of a mixture of acids or amides as cis-trans isomerisation can occur under the conditions of the reaction). The presence of additional double bonds in conjugatio with a carbonyl group which is being activated photochemically not unnaturally complicates the picture when we wish to consider possible reaction pathways open to an activated species or radicals initially derived from it.

Trans -β- ionone (LVI) on ultraviolet irradiation has been shown to give the pyran (LVII) and, probably, the cyclopropane derivative (LVIII)



(LVI) (LVII) (LVIII)

(Presumably trans -β- ionone is first converted into its cis-isomer). Other dienone systems, notably steroidal 4, 6-dien-3-ones, have been irradiated, with dimerisation occurring. Rubin, Hipps and Glover[32] have recently described the irradiation of $\Delta^{4,6}$-androsta-dien-3-one-17β-propionate (LIX) to give the dimer (LX).



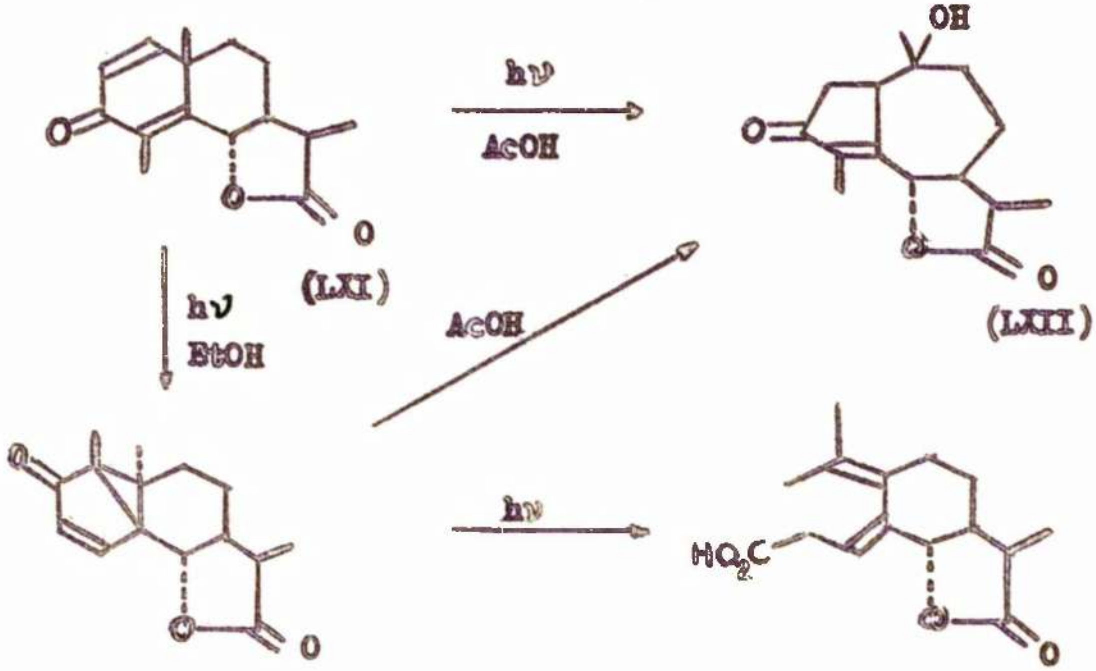
(LIX) (LX)

(Similar reactions have, however, been described before[33]).

<u>Cross-conjugated dienones</u>

The system which has attracted the greatest amount of attention recently is the cross-conjugated dienone.

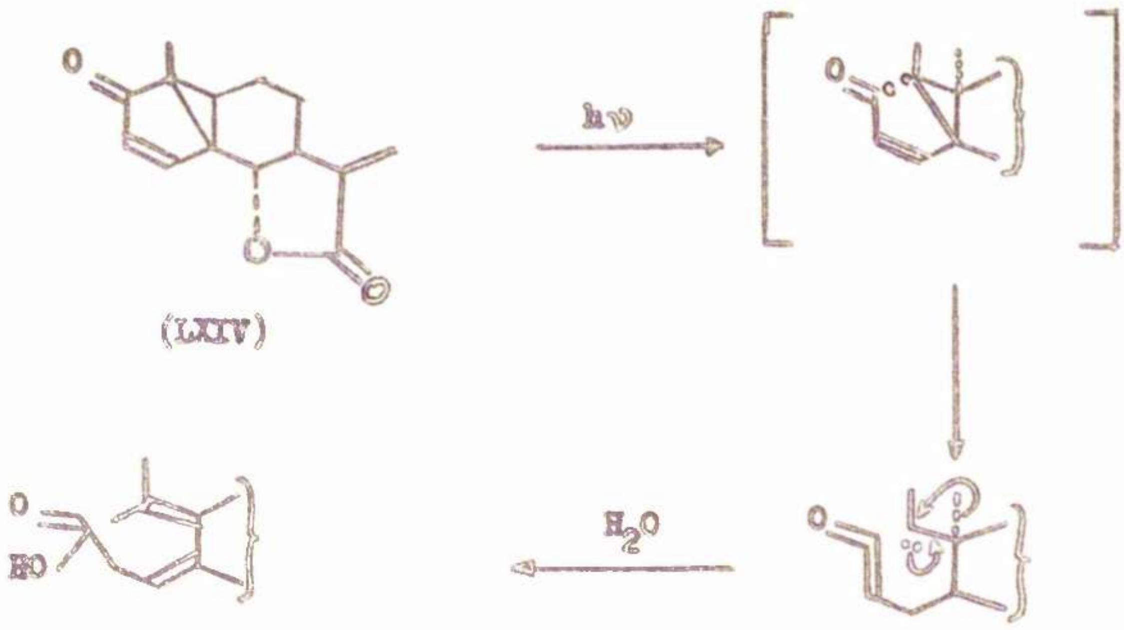
The photochemistry of santonin (LXI) was studied by Cannizzaro and Fabris[34], who isolated isophotosantonic lactone (LXII) and photosantonic acid (LXIII) although the structures shown have only recently been established[35].



(LXIV) (LXIII)

When santonin is irradiated in aqueous acetic acid, isophotosantonic lactone and photosantonic acid are obtained. Several groups of workers have repeated the early workers' experiments, and another irradiation product, lumisantonin (LXIV) has been identified. This compound is produced when santonin is irradiated in ethanol or dioxan, and when it is treated with aqueous acetic acid, in the absence of light, it gives isophotosantonic lactone. Irradiation of lumisantonin in aqueous acetic acid gives photosantonic acid.

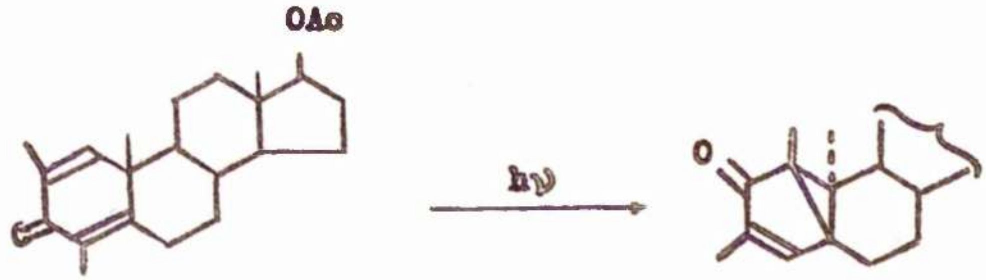
The conversion of lumisantonin into photosantonic acid is envisaged as proceeding via a ketene-carbene intermediate[36] (LXV).



(LXIV) (LXIII) (LXV)

In the steroid series, the ultraviolet irradiation of $\Delta^{1,4}$-3-ketones has attracted a good deal of attention. Irradiation of 1,2-dehydrotestosterone acetate[37] (LXVI) and of its 2,4-dimethyl derivative[38] (LXVII) has been shown to give products (LXVIII) and (LXIX) which correspond to the formation of lumisantonin from santonin.

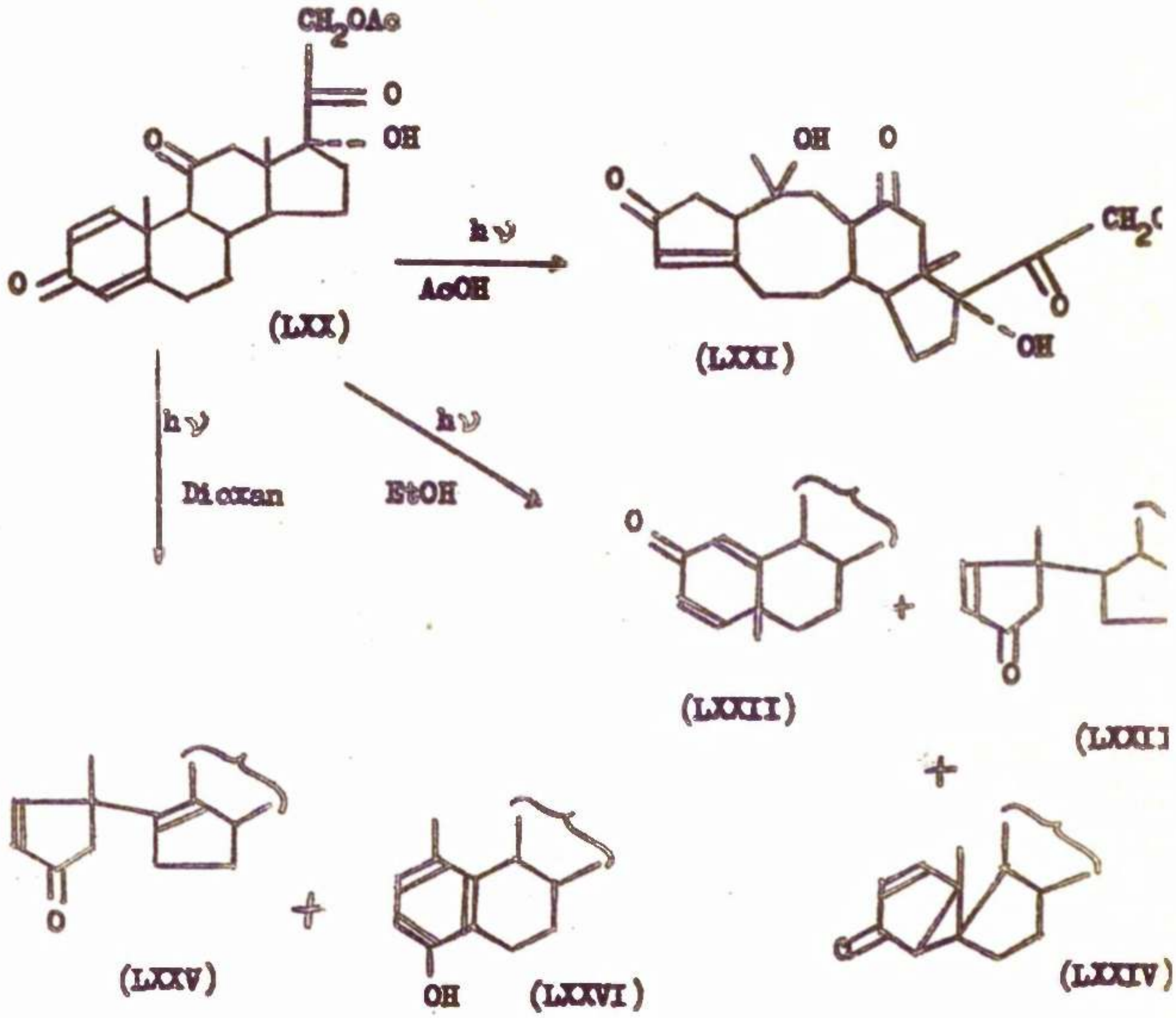
(LXVI) (LXVIII)



(LXVII) (LXIX) cf. (XXVII)

These reactions are described as proceeding quite well and in fairly good yield in dioxan. However, irradiation of 1,2-dehydrotestosterone acetate in other solvents[39] gives an amazing variety of products. This illustrates the complexity of the problem involved in deducing reaction mechanisms in this particular type of irradiation - not to mention the problems besetting anyone who is interested in predicting the nature of products. For an outline of the products obtained on irradiation of 1,2-dehydrotestosterone acetate, and references, see the chapter by Erikson and Forbess[40] in "Steroid Reactions".

Prednisone acetate (LXX) has been irradiated in a variety of solvents[41] and among the reactions reported are the following:-



(1) Irradiation in aqueous acetic acid gives the A-nor-B-homosteroid (LXXI).

(2) Irradiation in ethanol gives three products, (LXXII), (LXXIII), and (LXXIV).

(3) Irradiation in dioxan gives two isolable products (LXXV) and (LXXVI).

Here again it is observed that the cross-conjugated dienone system in this case still further complicated by the presence of an 11-keto-group which is said to weaken the C-9-C-10 bond - can give rise to a considerable variety of products. Clearly the number of factors which could influence the course of a photochemical reaction involving such a system (such as steric factors, the nature of the solvent, temperature, the precise wavelength or spectrum of the radiation used, the type and thickness of the vessel, concentration and many other variables) is such that much more detailed work will have to be undertaken before the transformations are even fairly well understood.

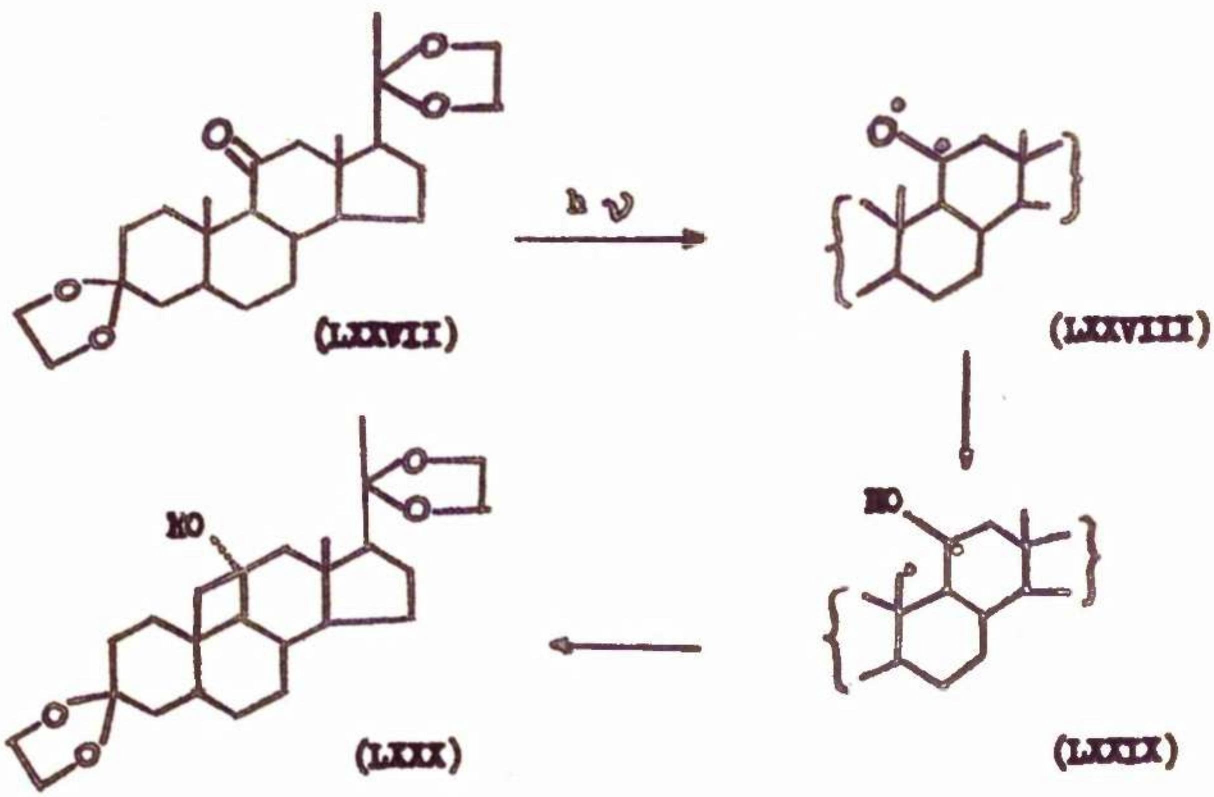
Ultraviolet Irradiation of Steroids

The preceding section describes some of the main types of reactions associated with the ultraviolet irradiation of carbonyl compounds. Som reference has been made to the ultraviolet irradiation of steroidal ketones, especially unsaturated ketones[20,21,22,27,28,32,33,37-41] and 17-ketones[15,16], but it is considered worth-while to describe in one section the ultraviolet irradiation of saturated steroidal ketones where the keto-group is located in a six-membered ring or at C-20 in a pregnane side-chain. Some reactions of substances other than ketones which give products on irradiation which are similar to those obtained from corresponding ketones, or which are formed from radicals similar to those obtained on the photolysis of ketones are also considered.

Interest in the ultraviolet irradiation of steroids began with the work of Windaus and his school on the nature of vitamin D. (A most readable account of their work is given by Fieser and Fieser[42], and it is not proposed to discuss the work on the D-vitamins, nor work on photo-oxygenation of conjugated systems, here).

Steroidal Carbonyl Compounds - Cyclobutanol formation

In the field of saturated ketones, the Swiss workers of the E.T.H., Zürich, have described the ultraviolet irradiation of 11- and 20-keto-steroids, which interact with the angular methyl groups at C-19 and C-18 respectively. In the case of 11-ketones, they have shown[43] that the formation of a cyclobutanol proceeds best when the configuratio is 5α. Yields are slightly lower when there is a Δ^5-double bond, and much lower when there is a 5β-hydrogen atom.



The formation of a cyclobutanol (e.g. LXXX) is thought to proceed from the 11-ketone (e.g. LXXVII) via a diradical (LXXVIII) in which intramolecular hydrogen-transfer can occur to give a diradical (LXXIX) in which the formation of a C-11 - C-19 bond gives the cyclobutanol. The ease with which the reaction occurs in the case of a 5α-11-ketone as compared with the corresponding Δ^5- or 5β - 11-ketone is readily accounted for on the basis of such a mechanism. Examination of Dreiding models shows that in the case of the 5α-11-ketone, the angular methyl group is subject to repulsion from the axial hydrogen atoms at C-2, C-4, C-6 and C-8 (figure LXXXI), the net

(LXXXI)

result being that it is forced closer to the oxygen atom at C-11 than is the case when a 5β-11-ketone is considered (LXXXII)

(LXXXII)

In this case, the effect due to the axial hydrogen atoms at C-2 and C-4 in the 5α-11-ketone (LXXXI) has been removed, and the resultant force is such as to force the angular methyl group further away from the oxygen atom at C-11, than in the case of the 5α-11-ketone.

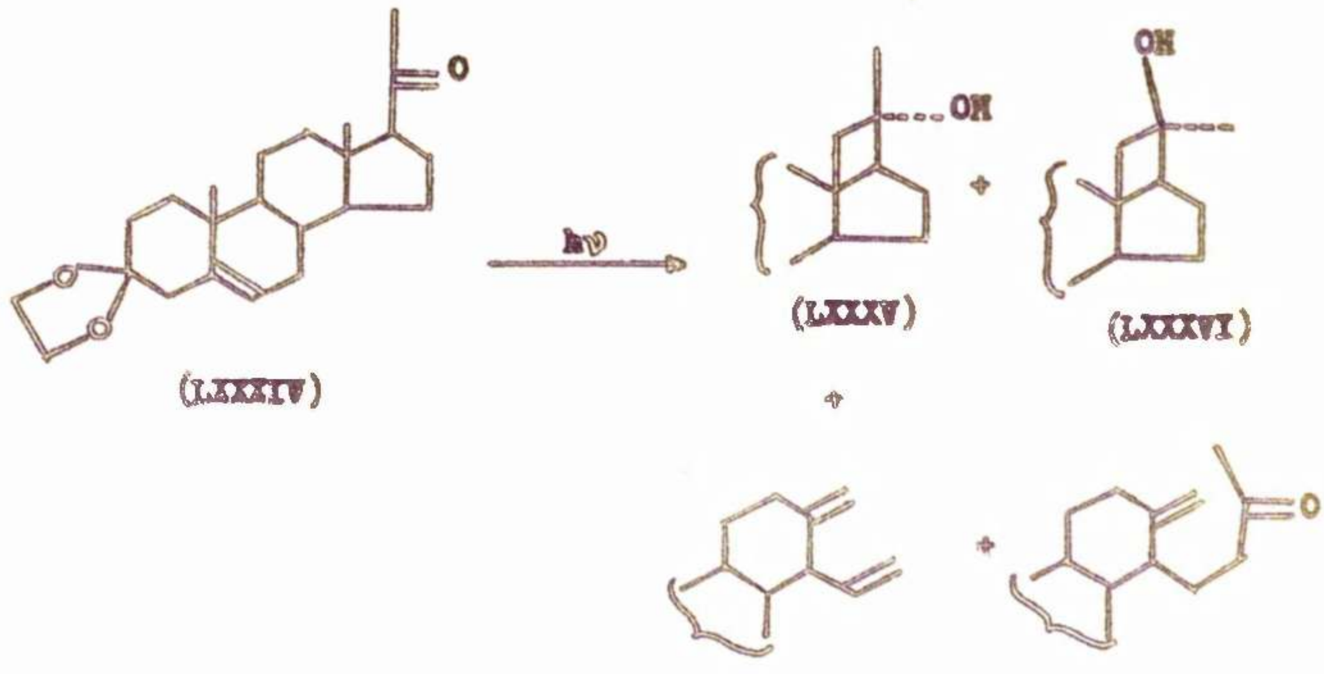
In the case of the corresponding Δ^5-11-ketone (LXXXIII) the effect of removing the hydrogen atom at C-6 from the reckoning is not so great, although it is still appreciable.

(LXXXIII)

(The deformation of rings A and B produced by the presence of the Δ^5-double bond obviously causes changes in the magnitude of the repulsive forces between the methyl group and the axial hydrogen atoms at C-2, C-4 and C-8, also).

It has been found that the presence of a gem-dimethyl group at C-4 in 11-ketosteroids improves the yield of cyclobutanol formed on irradiation. This effect is obviously due to methyl-methyl repulsion, forcing the methyl group at C-19 closer to the oxygen atom at C-11.

The Swiss workers have also studied the ultraviolet irradiation of 20-ketosteroids[44], and find that a cyclobutanol derivative may be formed here, too, by interaction of the keto-group with the 18-methyl group.



(LXXXIV) (LXXXV) (LXXXVI) (LXXXVII) (LXXXVIII)

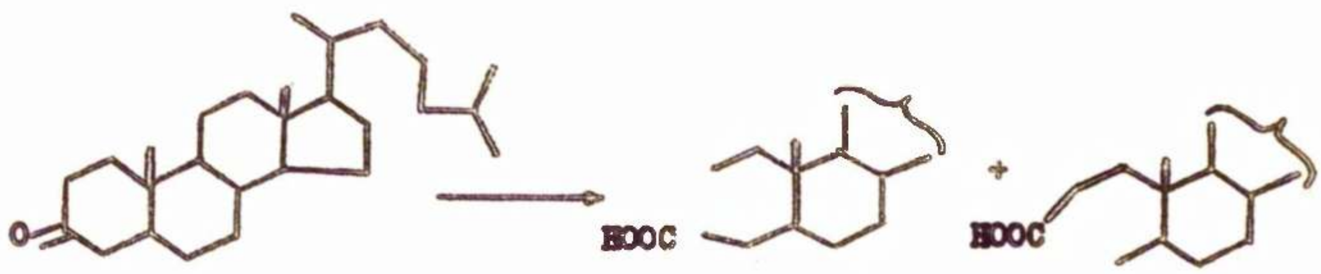
Irradiation of the 20-ketone (LXXXIV) in ethanol at room temperature gives as its major products the cyclobutanol (LXXXV) and the D-secosteroid (LXXXVIII), together with small amounts of the cyclobutanol (LXXXVI) and the diene (LXXXVII), the latter being derived from the compound (LXXXVIII) by loss of acetone. The mode of formation of the cyclobutanols is presumably similar to the reaction which occurs in the case of 11-ketosteroids, but the way in which the D-secosteroids could be formed is a matter for speculation.

Secosteroid Formation

In addition to their work on the irradiation of 17-ketosteroids (briefly described above, P.8), Quinkert and his co-workers in

Brunswick have described[16] the ultraviolet irradiation of 3,-6-, and 7-ketones in aqueous and non-aqueous solvents, and also of hecogenin acetate in aqueous dioxan (vide infra, p. 72). In all these cases, secosteroids are formed.

In the case of 5α-cholestan-3-one (LXXXIX) irradiation in aqueous acetic acid gives a mixture of the seco-acids (XC) and (XCI)



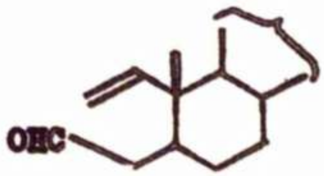
(LXXXIX) (XC) (XCI)

in approximately equal amounts. It appears in this case that the diradicals (XCII) and

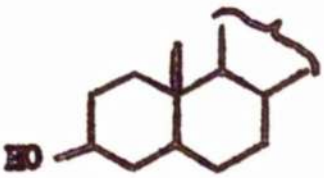
(XCII) (XCIII)

(XCIII) which could be formed from the activated ketone are equally stable, both being hydrated to the corresponding acid.

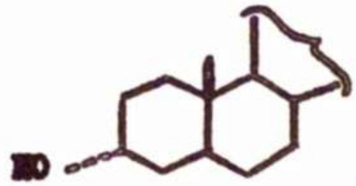
When 5α-cholestan-3-one is irradiated in acetonitrile, three products are isolated, the unsaturated aldehyde (XCIV) and the epimeric sterols (XCV) and (XCVI)



(XCIV)



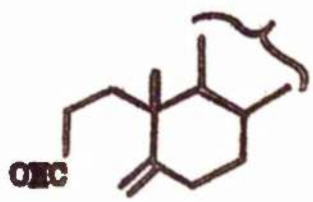
(XCV)



(XCVI)

The sterols are formed by reduction of the ketone, a well-known photochemical reaction mentioned above (p.   ).

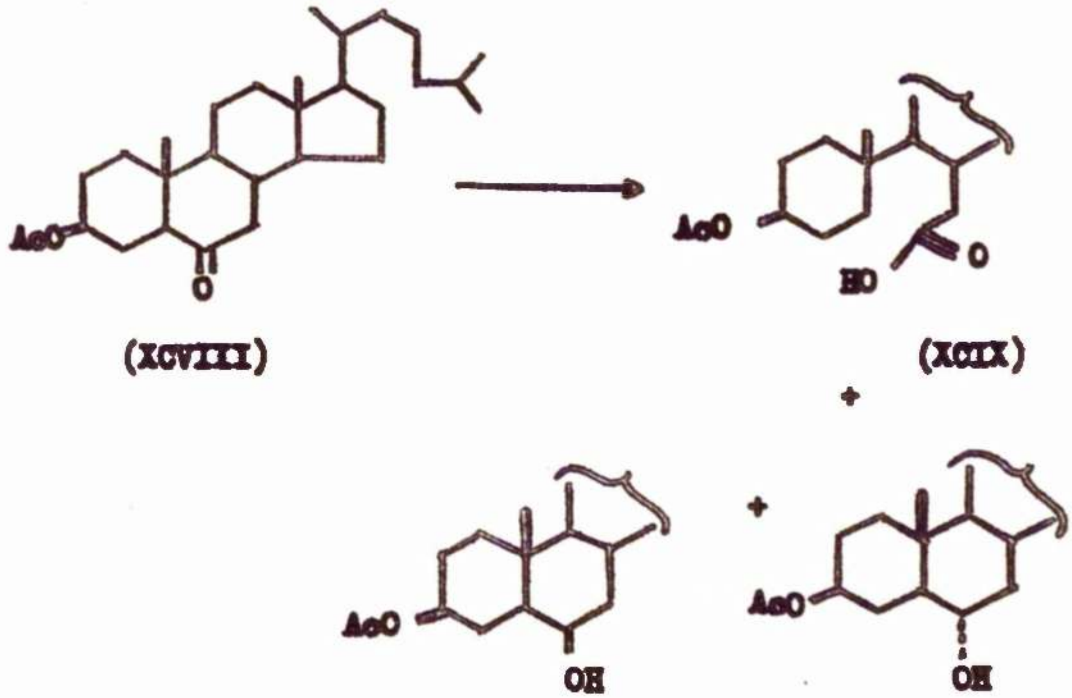
The unsaturated aldehyde is formed by intramolecular abstraction of hydrogen. It is not clear why the alternative unsaturated aldehyde (XCVII) is not formed, as a



(XCVII)

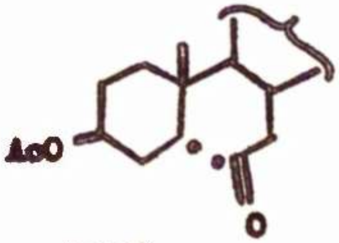
study of Dreiding models seems to indicate that hydrogen abstraction would be possible either in the case of the diradical (XCII) - abstraction occurring at C-5 - or the diradical (XCIII) with a hydrogen atom being abstracted from C-1.

Irradiation of 6-ketosteroids has also been described by Quinkert. When 6-ketocholestanyl 3β-acetate (XCVIII) is irradiated in aqueous dioxan, the acid (XCIX) is obtained, together with the epimeric sterols (C) and (CI)

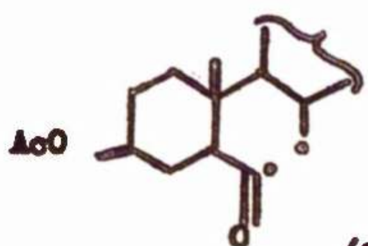


(XCVIII) (XCIX) (C) (CI)

The alcohols (C) and (CI) are products of reduction of the 6-ketone (XCVIII), and the acid (XCIX) - the sole acidic product - arises from the hydration of the diradical (CII). In this



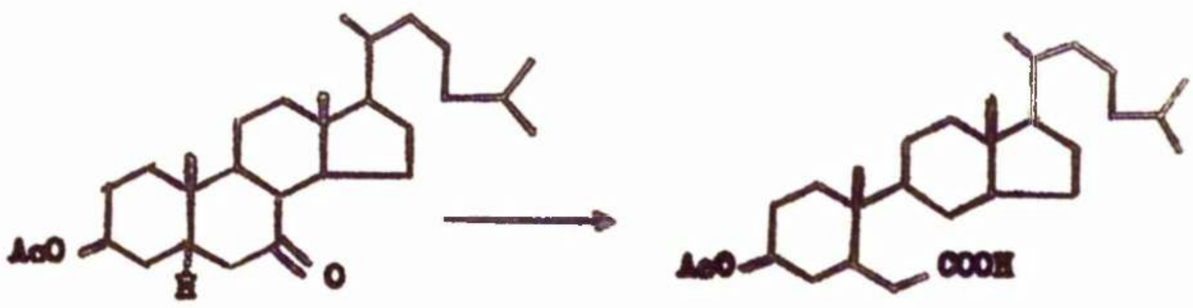
(CII)



(CIII)

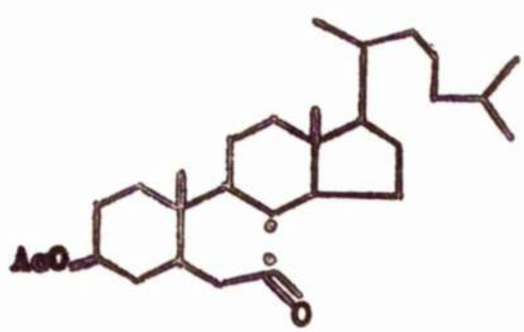
case the diradical (CII) is more stable than the alternative diradical (CIII) because one of the centres of unpaired electron spin is located at C-5, and the radical is secondary, whereas in the diradical (CIII) there would be a centre of unpaired electron spin at C-7, which would be a primary radical.

Similarly, the irradiation of 7-ketocholestanyl 3β-acetate (CIV) in aqueous dioxan gives the acid (CV) as the only acidic product.



(CIV) (CV)

In this case the more stable diradical is the one (CVI) in which the bond between C-7 and C-8 is broken, giving a secondary



(CVI)

radical at C-8. Fission of the bond between C-6 and C-7 would give a primary radical at C-6, which would be less stable than the secondary radical at C-8 in structure (CVI).

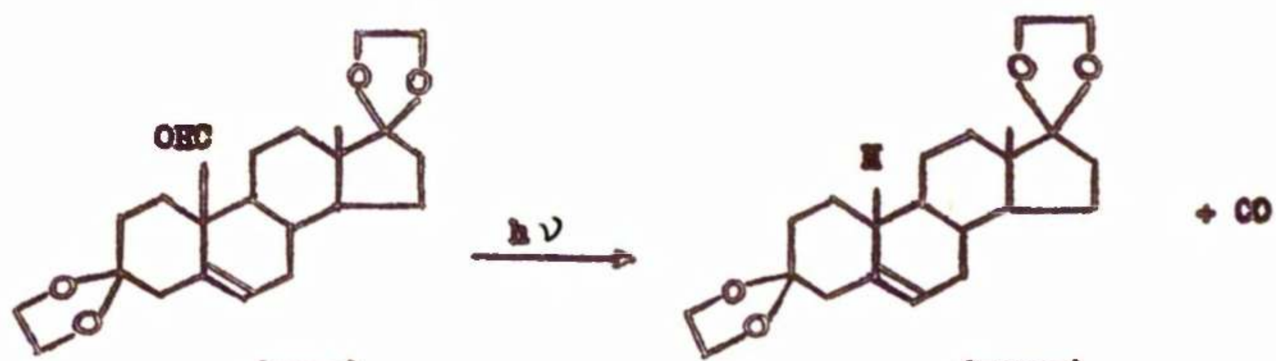
To sum up: Saturated steroidal ketones in which the keto group is located at C-3, C-6, C-7 or C-12 (vide infra) give rise to seco-steroids, via the more stable diradical, on irradiation;

11- and 20-ketones give 11-19- and 18-20- cyclosteroids respectively; C-17 ketones give seco-acids on irradiation in aqueous solvents, but epimerise in non-aqueous solvents.

As yet, no irradiations appear to have been performed on 1-, 2-, 4-, 15- or 16- ketosteroids. It would be interesting, too, to carry out irradiation experiments on A-, B- and C- norsteroid ketones, with the keto-group situated in the five-membered ring, to see whether unsaturated aldehydes can be obtained.

Aldehydes

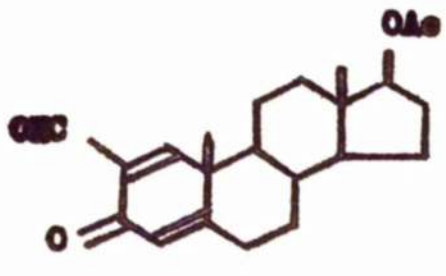
Very few steroidal aldehydes have been irradiated. The Swiss workers at the E.T.H., Zürich, have reported[45] the decarbonylation of the β,γ -unsaturated 19-aldehyde (CVII)



(CVII) (CVIII)

to the compound (CVIII). They have shown that the 10β -hydrogen atom in (CVIII) is that which was originally attached to C-19 in the aldehyde (CVII) by irradiating the deuterated aldehyde (19-CDO) and showing that the photoproduct contains the theoretical amount of deuterium.

The same group have described [46] the irradiation of 1-dehydro-2-formyltestosterone acetate (CIX)



(CIX)

to give a complex mixture of products. (In this case, with two α,β-unsaturated carbonyl groups, it is not surprising that a variety of products is obtained).

Irradiations of Steroids other than Carbonyl Compounds

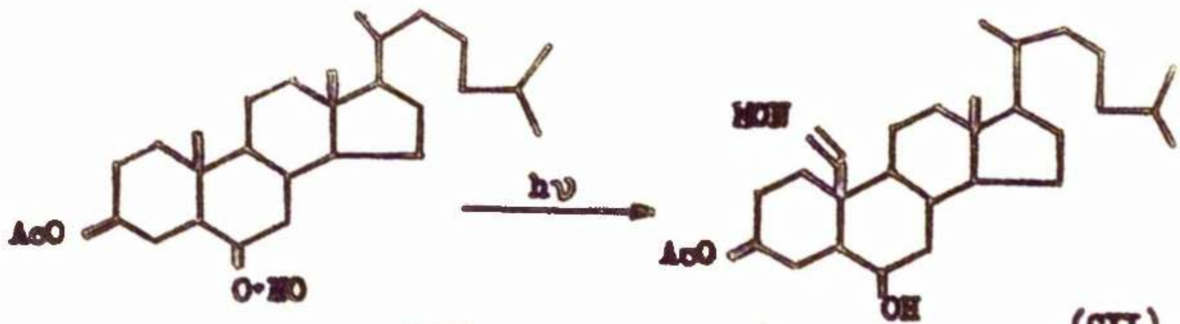
Apart from ketones and aldehydes, other functional groups exhibit ultraviolet absorption[47] associated with an $n \rightarrow \pi^*$ transition. Examples are the nitrite group[47a] (λ max = 370 mμ, ε 50), nitrate group[47a] (λ max. = 270 mμ, ε 15), nitroso group[47b] (λ max.=300 mμ, ε 100), nitro group[47a] (λ max. = 280 mμ, ε 20), azide group[47b] (λ max. = 287 mμ, ε 20) and diazo group[47b] (λ max. = 400 mμ, ε 5).

Thiones and other sulphur compounds, e.g. xanthates[47b] also exhibit weak absorption due to $n \rightarrow \pi^*$ transitions. Hypochlorites[47c] exhibit weak absorption at about 310 mμ, ε 30-50.

Some examples of reactions in the steroid series associated with $n \rightarrow \pi^*$ transitions in such groups are briefly described here.

Nitrites

The most interesting and useful photochemical reaction of steroidal nitrites is the Barton Reaction, in which a nitrite is converted into an oxime.

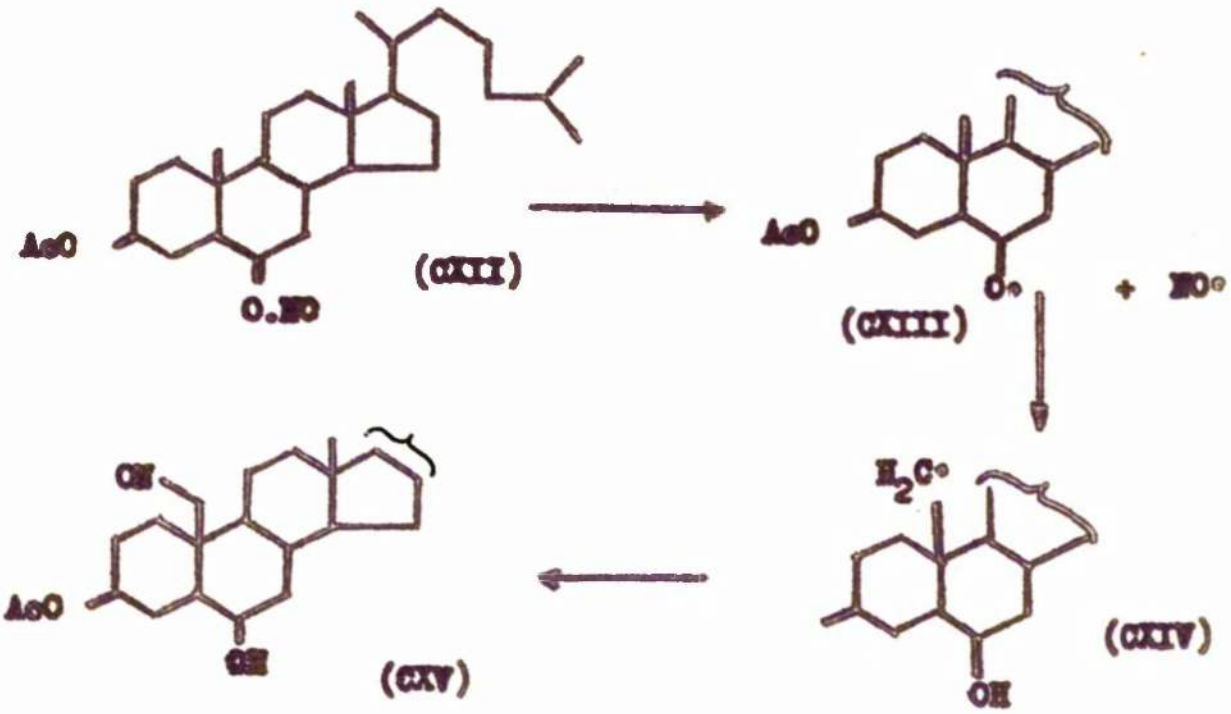


(CX) (CXI)

Irradiation of the nitrite of 6β-hydroxycholestanyl 3β-acetate (CX), for example[48], gives the 6β-hydroxy-19-oxime (CXI).

2β-Nitrites on similar treatment[49] give 2β-hydroxy-19-oximes, and 20-nitrites[50] give 20-hydroxy-18-oximes. Irradiation of 11β-nitrites[51] is said to give a mixture of 11β-hydroxy-18-oximes and 11β-hydroxy-19-oximes.

The mechanism of this type of reaction would appear to be the initial formation of an activated species, e.g. (CXII) by an $n \rightarrow \pi^*$ transition, this species then giving an alkoxy radical (CXIII) and a nitroso radical[52]

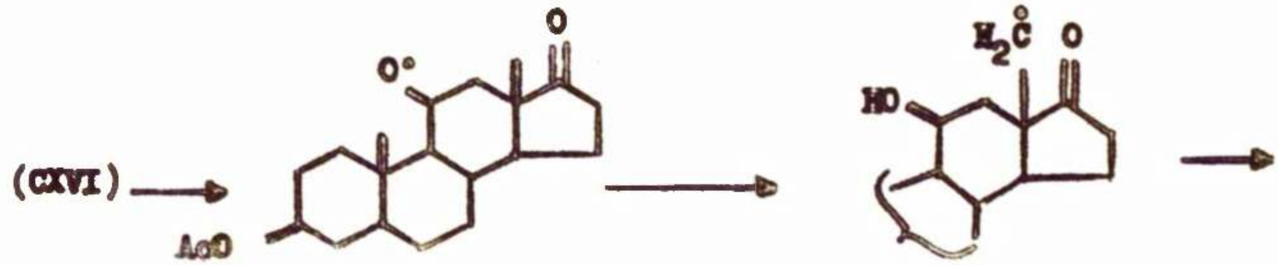


The alkoxy radical (CXIII) is able to abstract a hydrogen atom from the angular methyl group to give the radical (CXIV) which then reacts with the nitroso radical to give the nitroso compound (CXV). This is tautomeric with the oxime (CXI).

When a 17-keto 11β-nitrite, such as (CXVI) is irradiated[53], an 18-nor-D-homo-steroid (CXVII) is obtained.

(CXVI) (CXVII)

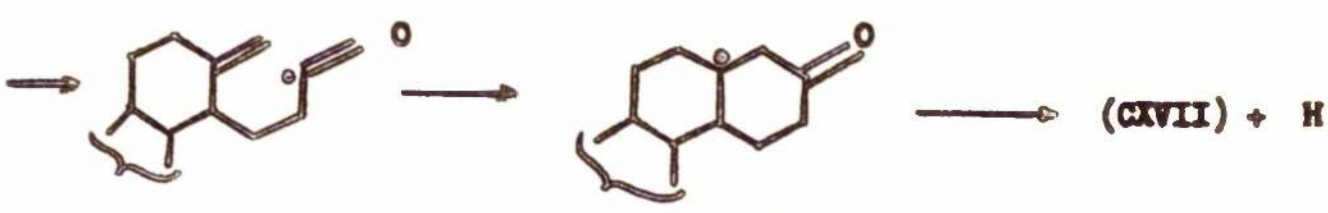
The authors suggest that the reaction proceeds via an alkoxy radical (CXVIII) (as in the cases already mentioned) which abstracts a



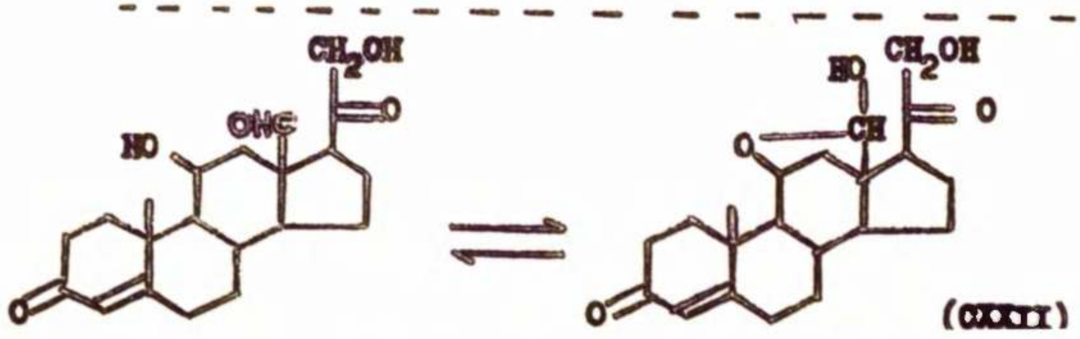
(CXVIII) (CXIX)

hydrogen atom from the angular methyl group to give the radical (CXIX). The latter rearranges to give the radical (CXX) which cyclises to give the tertiary radical (CXXI). The tertiary radical is thought to lose a hydrogen atom to a radical species in the solution to give the product, (CXVII).

Although other photochemical reactions of nitrites have been described, the formation of steroids substituted at C-18 and C-19 is the most important, as it makes possible the synthesis of compounds related to aldosterone (CXXII)



(CXX) (CXXI)

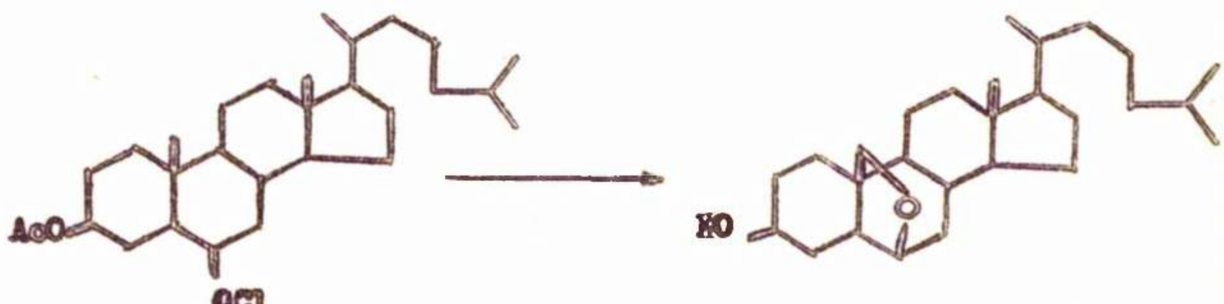


(CXXII)

(For a review of reactions of this type, see the article by Windholz and Windholz[54]. See also Reference 52).

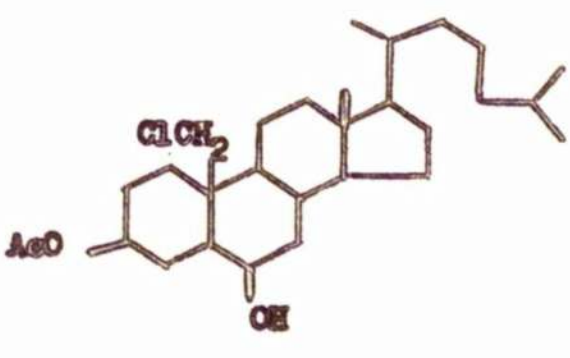
<u>Hypochlorites</u>

Attack at the angular methyl group has been shown to occur when suitable hypochlorites are photolysed[55]. Irradiation of the hypo: :chlorite (CXXIII) followed by treatment with base, gives the 6, 19-oxide (CXXIV).



(CXXIII) (CXXIV)

Here the initial activated species dissociates to give an alkoxy radical (identical in this case with (CXIII)) and a chlorine atom, the subsequent steps being similar to those outlined in the case of the irradiation of nitrites. The photoproduct is presumably the 19-chloro-compound (CXXV) which on treatment with



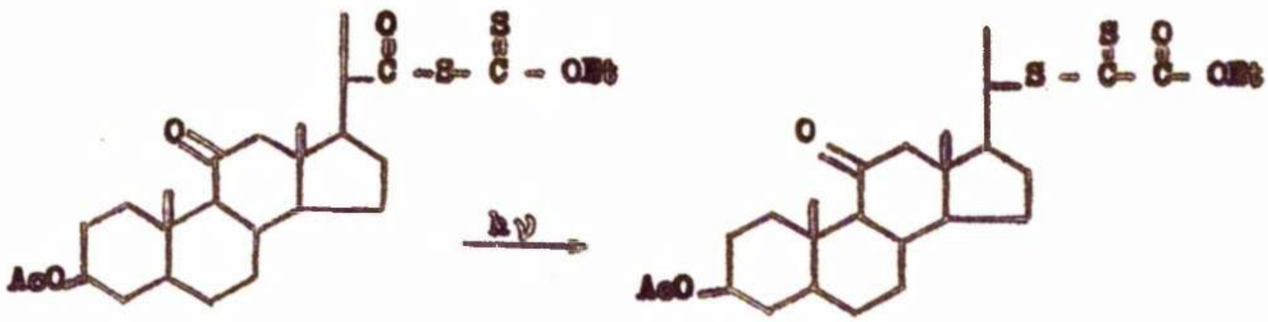
(CXXV)

alkali gives the 6, 19-oxide (CXXIV).

The irradiation of 20-hypochlorites, followed by alkali treatment, gives 18, 20 oxides by a similar mechanism[55].

Sulphur Compounds

Barton and his co-workers have described the irradiation of xanthates[56], among them the compound (CXXVI) which on irradiation



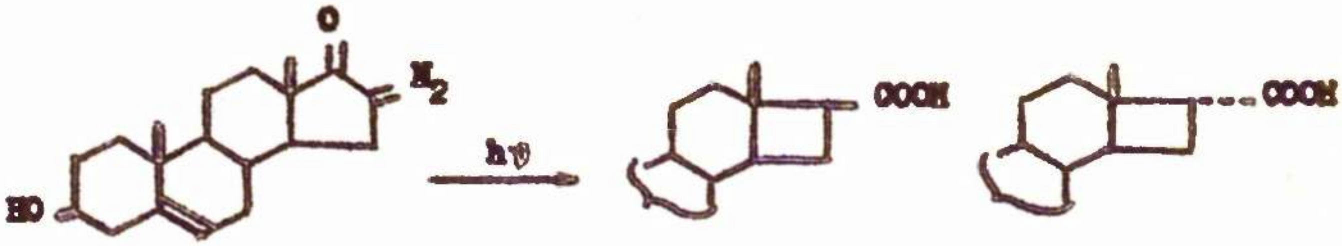
(CXXVI) (CXXVII)

gives the isomer (CXXVII). Xanthates absorb radiation at about 400 mμ, and the photo-reaction proceeds when a tungsten lamp is used, although in this case the yield of the isomer is only 10%.

Other Nitrogen Compounds

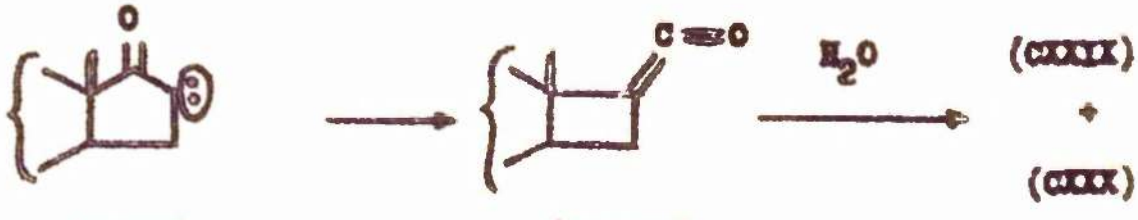
Other steroidal compounds which have been photolysed include diazo compounds, azides and pyrazolines.

The irradiation of a 16-diazo-17-ketosteroid in an aqueous solvent is reported to give a mixture of epimeric acids[57]. For example, the compound (CXXVIII) on irradiation in wet ether gives the acids (CXXIX) and (CXXX)



(CXXVIII) (CXXIX) (CXXX)

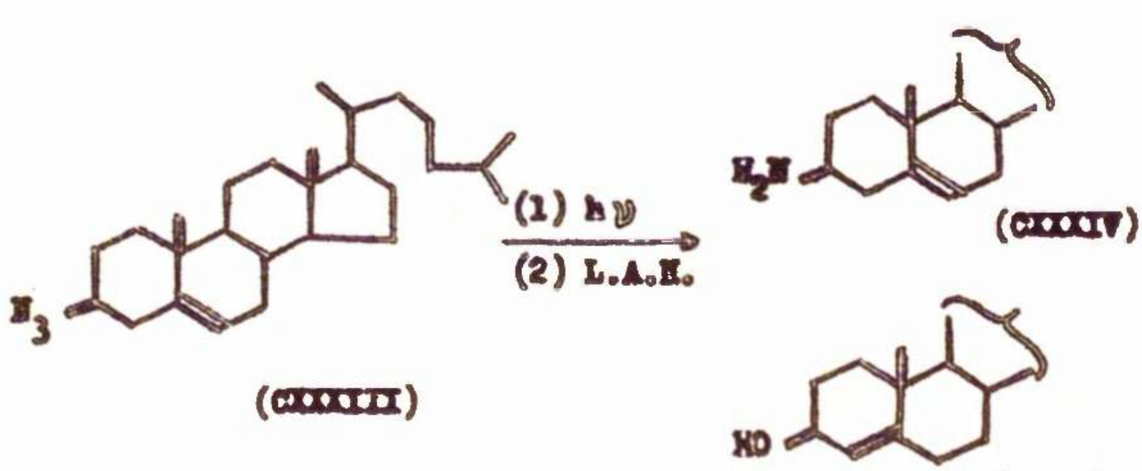
Loss of nitrogen from the activated species is thought to give a carbene (CXXXI)



(CXXXI) (CXXXII)

which rearranges to give the ketene (CXXXII). The ketene can then be hydrated to give either of the acids (CXXIX) or (CXXX).

Barton and Morgan[58] have described the photolysis of azides, among them the azide of cholesterol (CXXXIII)



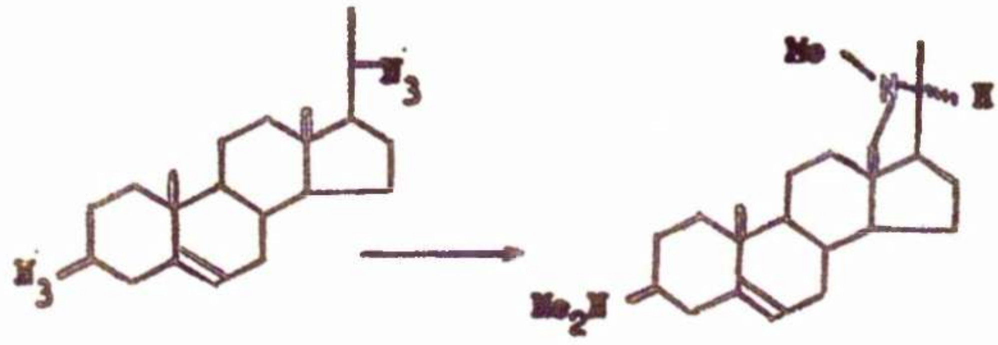
(CXXXIII) (CXXXIV) (CXXXV)

Photolysis of the azide in cyclohexane, followed by reduction of the crude product with lithium aluminium hydride, gives a mixture of products from which the amine (CXXXIV) and cholest-4-en-3β-ol (CXXXV) can be isolated. The authors consider that the reaction proceeds via an activated nitrene (CXXXVI)

(CXXXVI) (CXXXVII)

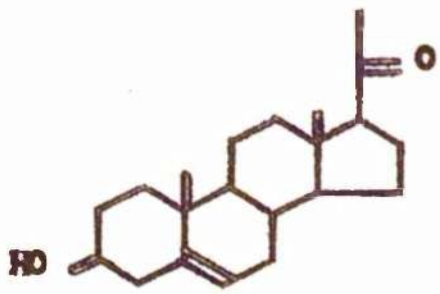
which can either abstract hydrogen atoms from the solvent to give the amine (CXXXIV) or else rearrange to give the imine (CXXXVII) - the imine presumably being reduced by lithium aluminium hydride and not by a photochemical reaction. They account for the formation of the alcohol (CXXXV) by assuming that a trace of moisture in the solvent hydrolyses the imine to the corresponding ketone, and that the double bond moves into conjugation to give Δ^4-cholestenone, which is then reduced with lithium aluminium hydride in the second stage of the preparation to give the alcohol.

In the same paper is described the synthesis of conessine (CXXXIX) by photolysis of the 3, 20-diazide (CXXXVIII).



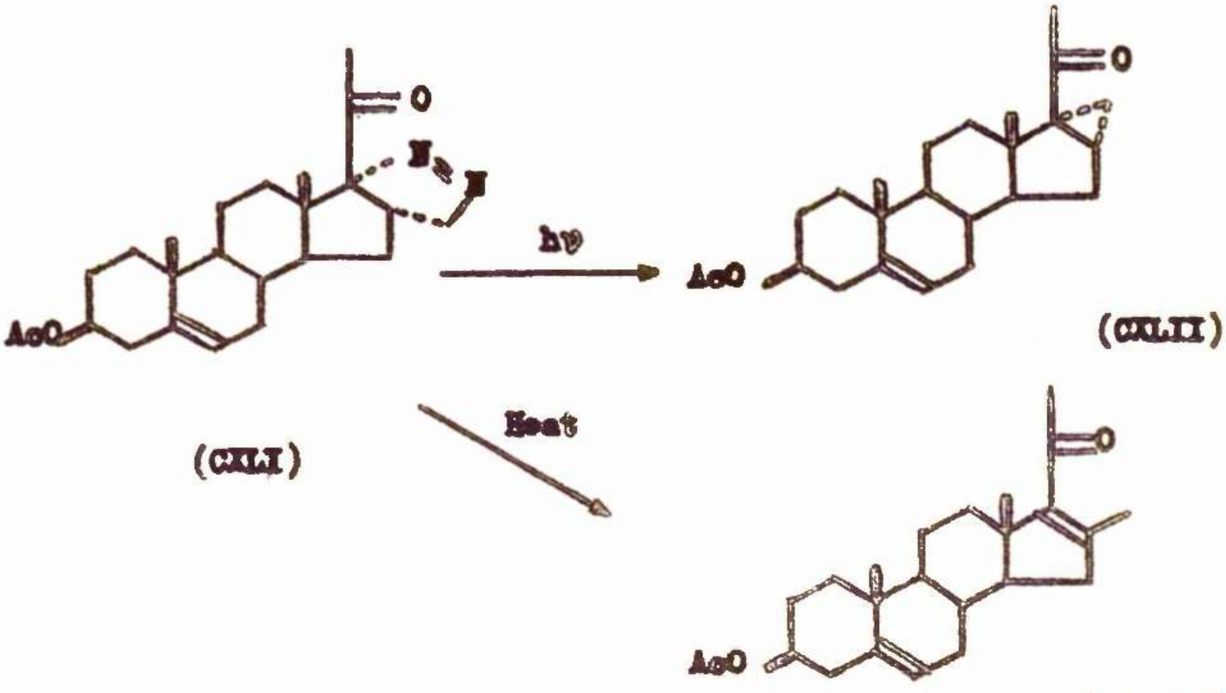
(CXXXVIII) (CXXXIX)

The crude product of photolysis is reduced by lithium aluminium hydride and then N-methylated with formic acid and formaldehyde. Pregnenolone (CXL) is also obtained, although its mode of formation is not understood



(CXL)

The irradiation of pyrazolines - the compounds formed by the addition of diazomethane to olefins - has been shown, in the case of 4α, 5α - and 16α, 17α -pyrazolino-steroids to give the corresponding 4α, 5α - and 16α, 17α - methylene compounds[59].



(CXLI)

(CXLII)

(CXLIII)

16α, 17α-Pyrazolino-pregnenolone 3β-acetate (CXLI), for example, gives the cyclopropane derivative (CXLII) on photolysis. Pyrolysis of the same pyrazoline, on the other hand[60], gives the 16-methyl-Δ^{16}-20 - ketone (CXLIII).

Two other interesting reactions which have been reported in the steroid series are the Hofmann-Löffler-Freytag Reaction and the reaction of alcohols with lead tetra-acetate and iodine or calcium carbonate. Both these reactions may be initiated photochemically, but both have been reported as taking place without the aid of light. This being so, they will not be discussed here. For references to these reactions, see the review by Wolff[61] and the chapter by Erikson and Forbess[40] in "Steroid Reactions".

The thread running through the whole series of photochemical reactions involving n ⟶ π^* transitions is that in all cases the initial activated species - of unknown nature - is transformed into a diradical, of which the subsequent reactions are determined primarily by the stereochemistry of the system. The diradical may in fact be two separate radicals - as in the case of the photolysis of nitrites or hypochlorites - or the two centres of unpaired electron spin may be located in one molecule, as in the case of the irradiation of ketones.

It is usually possible to suggest mechanisms for the formation of products in a photochemical reaction once the products have been identified. However, it is still a hazardous business to attempt to predict the course of a photochemical reaction - especially for a relatively complicated system.

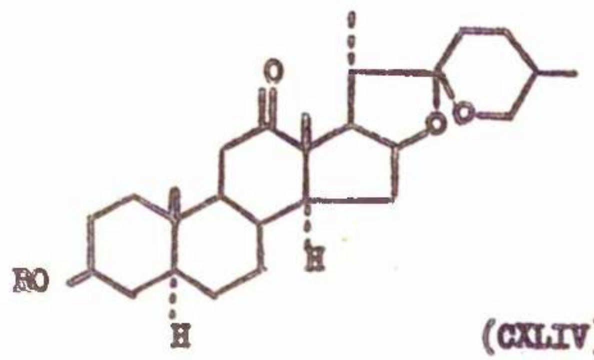
T H E O R E T I C A L

A N D

D I S C U S S I O N .

The Photochemistry of Hecogenin Acetate

Hecogenin, 3β-hydroxy-5α, 25D-spirostan-12-one (CXLIV; R = H) is a steroidal sapogenin isolated from a variety of plant sources (e.g. Hechtia Texensis, Agave Sisalana). It was first isolated by Marker and his co-workers who deduced[62] the structure shown.

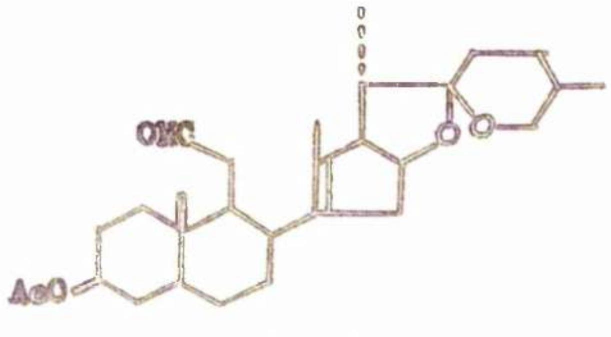


(CXLIV)

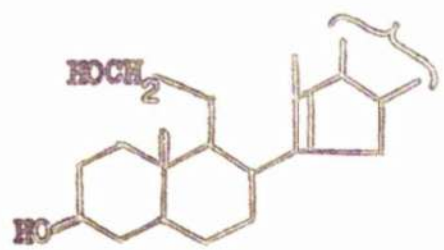
Like most of the related sapogenins, hecogenin occurs naturally as a saponin, that is a compound of the sapogenin with sugar units attached to the C-3 oxygen function. The 3β-hydroxy compound is liberated by acid hydrolysis.

As hecogenin is produced on a large scale for hormone synthesis, it is a readily available and relatively cheap starting material.

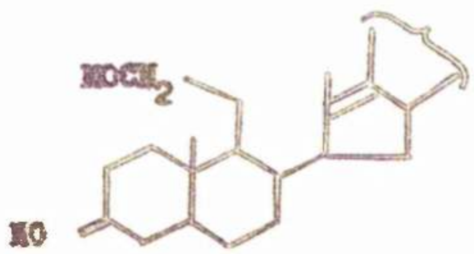
The ultra violet irradiation of hecogenin acetate was first described by McMeekin[63], who showed that on irradiation in dioxan solution - either in vacuo or under reflux in an atmosphere of nitrogen - hecogenin acetate is converted into an isomeric unsaturated aldehyde "lumihecogenin acetate", which he stated, correctly, to be 3β-acetoxy-12,13-seco-5α, 25D-spirost-13-en-12-one (CXLV). Reduction of this compound with lithium aluminium hydride gave "anhydrohecolyl alcohol" which had been shewn by Rothman, Wall and Eddy[64] to be either 3β 12-dihydroxy-12,13-seco-5α,25D-spirost-13(14)-en, (CXLVI) or 3β,12-dihydroxy-12,13-seco-5α,25D-spirost-13(17)-en, (CXLVII)



(CXLV)

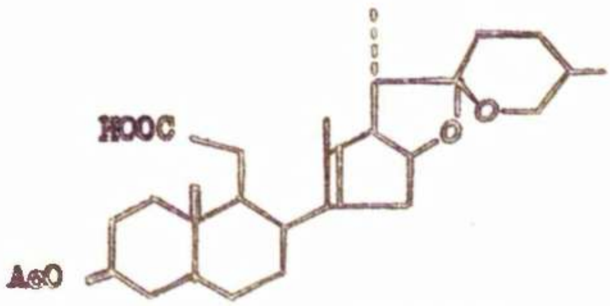


(CXLVI)

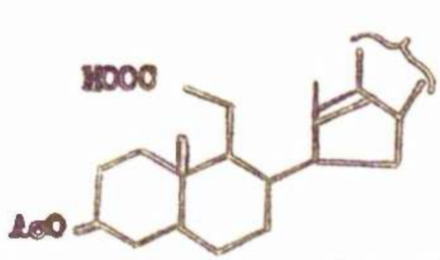


(CXLVI)

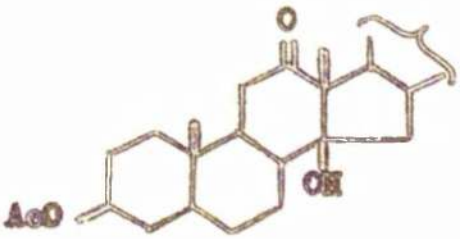
Oxidation of the aldehyde gave a small yield of the expected acid (CXLVIII) or (CXLIX). The main product was a ketone similar to hecogenin acetate but having an additional tertiary hydroxyl group. This compound McMeekin thought to be 3β-acetoxy-14β-hydroxy-5α, 25D-spirostan-12-one (CL)



(CXLVIII)



(CXLIX)



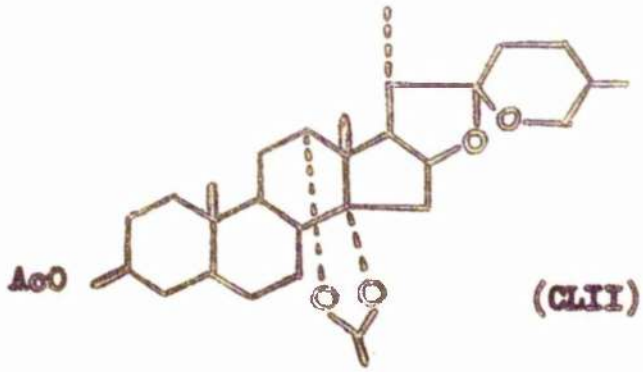
(CL)

on account of the position of the infra-red absorption maximum due to the hydroxyl group, which indicated the presence of hydrogen-bonding - "presumably to the oxygen atom in ring E".

Irradiation of hecogenin acetate for a longer period of time, or irradiation of purified lumihecogenin acetate, was shown by McMeekin to give a second product, "photohecogenin acetate". The assignment of a structure to this compound proved rather troublesome.

On the basis of the data available on photohecogenin acetate and its saponification product, photohecogenin, McMeekin tentatively suggested that the second irradiation product might consist of a molecule of hecogenin acetate or lumihecogenin acetate to which had been added C_2H_4O. This could be explained by the addition of half a molecule of dioxan, or of the molecule of an impurity known to be present in it, 2-methyldioxolane (CLI) to the steroid molecule.

(CLI)



(CLII)

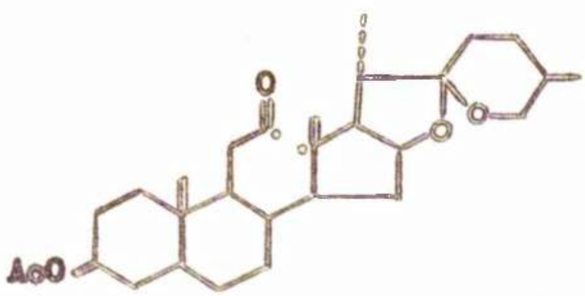
McMeekin's suggested structure for photohecogenin acetate was (CLII) in which the moiety C_2H_4O has been added across the steroid molecule between C-12 and C-14.

The presently described work was concerned with repeating McMeekin's work and attempting to establish the structures of the irradiation products.

When a solution of hecogenin acetate (CXLIV; R = Ac) in dioxan is irradiated by means of a 500 watt medium-pressure mercury vapour ultra-violet lamp (either in vacuo at room temperature, under reflux in an atmosphere of nitrogen or at room temperature under nitrogen), a decrease in the value of the specific rotation (initially $\pm 0^{\circ}$) is observed. The value decreases rapidly at first, and then levels out to a value of about -40°. By interrupting the irradiation as soon as this value is reached, it is possible to isolate lumihecogenin acetate in 80% yield. The compound prepared in this way was identical with a sample prepared by McMeekin.

The presence of an aldehyde group is confirmed by the presence of peaks at 2740, 1709 and 1408 cm.$^{-1}$ in the infra-red spectrum, and by the peak at τ 0.50 in the nuclear magnetic resonance spectrum. The compound gave a positive tetranitromethane test and also showed a peak at 204 mμ (ϵ 4,800) in the ultraviolet spectrum, indicating the presence of a double bond. However, there were no olefinic proton signals in the n.m.r. spectrum, and no $C = C^{-H}$ stretching peaks in the infra-red, which indicates that the double bond is tetrasubstituted.

It has been established that anhydrohecolyl alcohol - the product obtained on reduction of lumihecogenin acetate with lithium aluminium hydride - is a 12,13-seco compound[64]. Making the reasonable assumption - by analogy with similar reactions described above - that the formation of lumihecogenin acetate takes place via the diradical (CLIII),



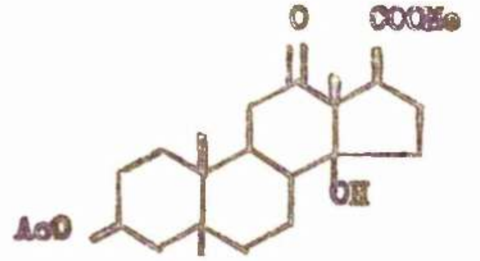
(CLIII)

followed by intramolecular abstraction of a hydrogen atom by C-12, it is observed on examination of a Dreiding model that of the two hydrogen atoms which it might be considered possible to abstract (i.e. those at C-14 and C-17), only that at C-14 is sufficiently close to C-12 to be transferred. Thus it seems almost certain that in lumihecogenin acetate, anhydrohecolyl alcohol and related acids, the double bond is located at position 13(14).

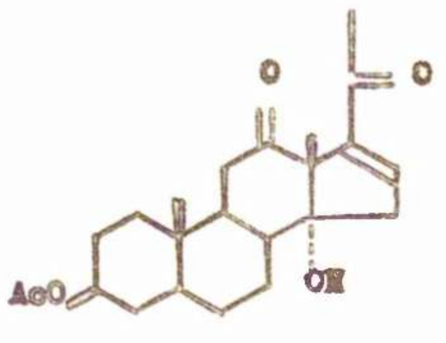
When lumihecogenin acetate is oxidised with 8-N chromic acid in acetone, two products are obtained. One, the minor product (20-40%), is the acid (CXLVIII) which has been described previously[64], though its structure had not been definitely settled. The major product (60-80%) is neutral, and is identical with the compound described by McMeekin. Its infra-red spectrum (in $C\ Cl_4$ solution) shows peaks at 3550 (weakly hydrogen-bonded OH), 1739 (O Ac), 1706 ($>C = O$) and 1250 (O Ac) cm^{-1}. The optical rotatory dispersion curve was similar to that of hecogenin acetate, the amplitude of the Cotton-effect curve being rather higher (+160 as against +70). This indicates that the immediate environment of the carbonyl group - especially the configuration of the angular methyl group - is the same as it is in the case of hecogenin acetate. (In the case of methyl 3β-acetoxy-14-hydroxy-12-oxo-5β, 14β-etianate[65] (CLIV) the sign and amplitude of the Cotton-effect curve are also similar to those of hecogenin acetate, the amplitude being (+130)). That the tertiary hydroxyl group in the oxidation product is in position (14) rather than (17) is proved by the degradation of the sapogenin by standard methods[66] to a Δ^{16}-20-ketone (λmax 228.5 mμ, ε 7320) which shows a peak at 3620 cm^{-1} in its infra-red spectrum due to a non hydrogen-bonded hydroxyl group.

Examination of Dreiding models shows that in the case of 14α-hydroxyhecogenin 3β-acetate, weak intramolecular hydrogen-bonding is just possible between the hydroxyl group at C-14 and the carbonyl group at C-12.

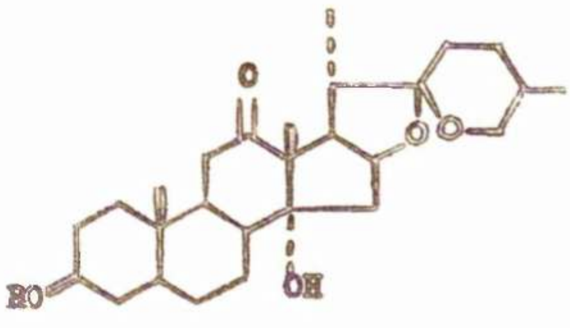
However, if the oxidation product is 14β-hydroxyhecogenin-3β-acetate, hydrogen-bonding is still possible between the hydroxyl group and the oxygen atom in ring E.



(CLIV)



(CLV)

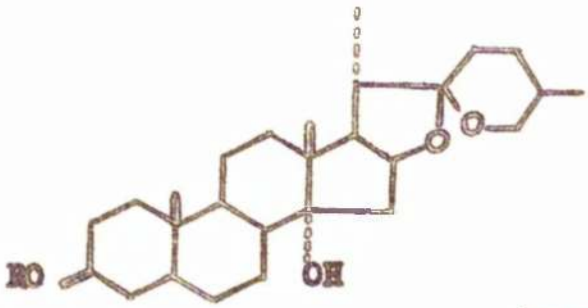


(CLVI)

Evidence for the 14α-configuration of the hydroxyl group in this series was provided when the ketone (CLVI; R = Ac) was reduced by the Huang Minlon method[67] to 3β, 14α-dihydroxy-5α, 25D-spirostan

(CLVII; R = H) which on acetylation gives 3β-acetoxy-14α-hydroxy-5α, 25D-spirostan (CLVII; R = Ac). The latter compound shows a peak at 3590 cm^{-1} in the infra-red, indicating an absence of hydrogen-bonding, which is compatible with the presence of a 14α-hydroxyl group but not a 14β-hydroxyl.

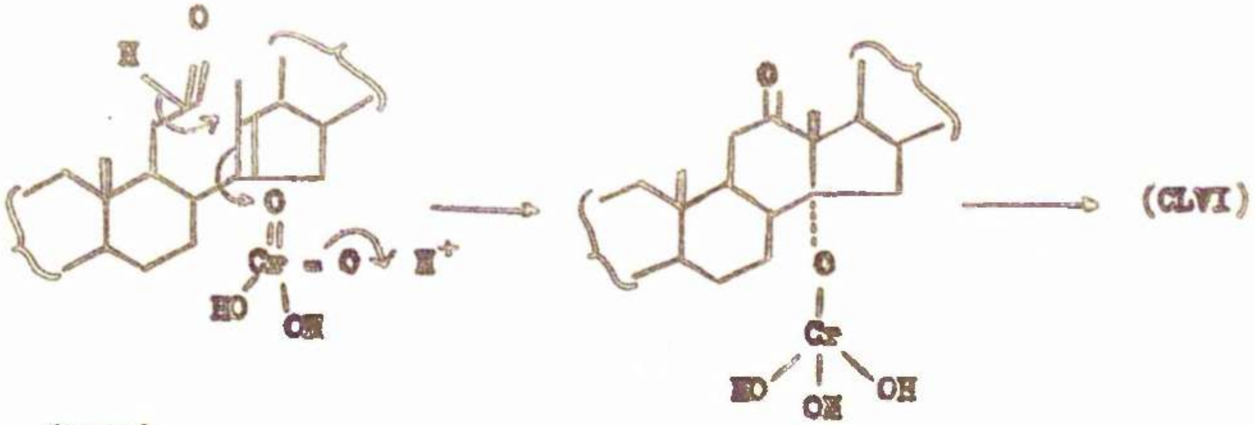
Still more evidence for the 14α configuration will be mentioned later when the reactions of photohecogenin acetate are discussed.



(CLVII)

When anhydrohecolyl alcohol (CXLVI) is treated with 8-N chromic acid in acetone[68], two products are again obtained. The major product is a diketone with a tertiary hydroxyl group and the minor product is a keto-acid. The major product is formulated as 14α-hydroxy-5α, 25D-spirostan-3, 12-dione (CLVIII). This compound may also be obtained by chromic acid oxidation of 14α-hydroxyhecogenin (CLVI; R = H), the product of saponification of 14α-hydroxyhecogenin 3β-acetate (CLVI; R = Ac).

The formation of the 14α-hydroxy compounds from the Δ^{13}-12, 13-seco compounds is envisaged as proceeding thus[69] :-



(CXLV)

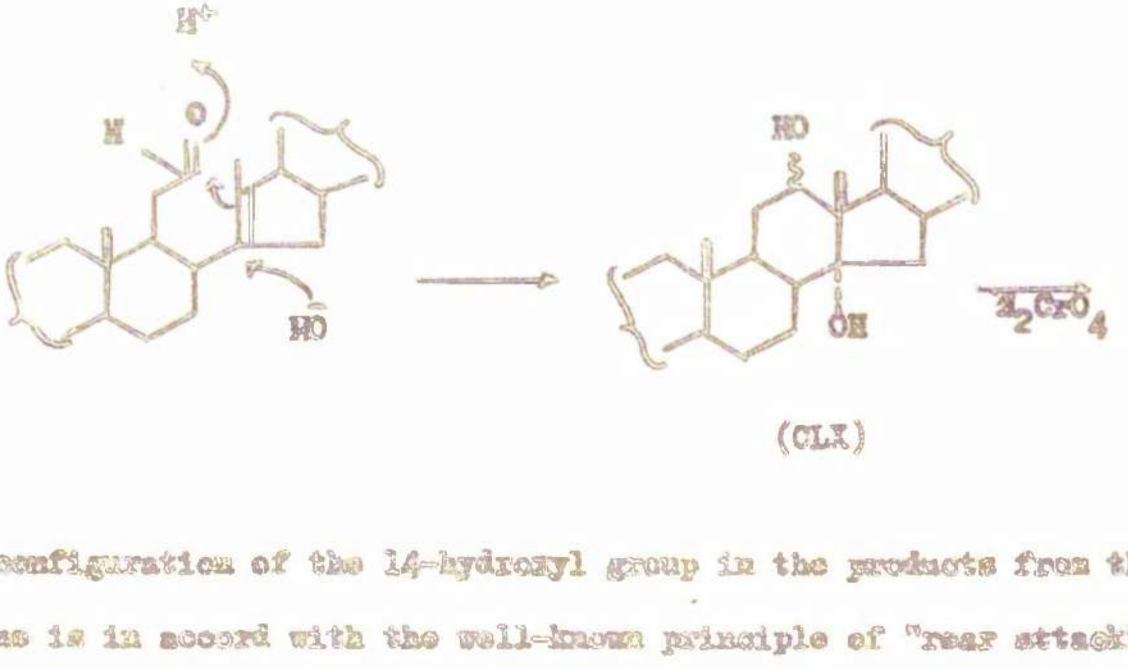
(In the case of anhydrohecolyl alcohol, oxidation at C-3 occurs also).

Another mechanism considered possible was the initial oxidation of the 12-aldehyde or 12-hydroxymethyl group to the carboxylic acid followed by cyclisation of the acylonium ion (CLIX) derived from it. However,

(CLIX)

anhydrohecolic acid 3β-acetate (CXLVIII) was recovered unchanged when subjected to treatment with chromic acid in acetone, no neutral product being obtained.

A third possible mechanism, the cyclisation to give a 12-hydroxylated intermediate (CLX) subsequently oxidised to a ketone, was also considered. It would be expected, if this mechanism operated, that the treatment of lumihecogenin acetate with 2-N sulphuric acid in acetone would result in the rapid disappearance of the aldehyde carbonyl band in the infra-red spectrum. However, when lumihecogenin acetate was thus treated - under more vigorous conditions and for three times the time usually allowed for the oxidative cyclisation reaction, the product showed no diminution of the aldehyde carbonyl peak, although the material recovered was not pure lumihecogenin acetate. Nevertheless, this mechanism would seem to be ruled out.



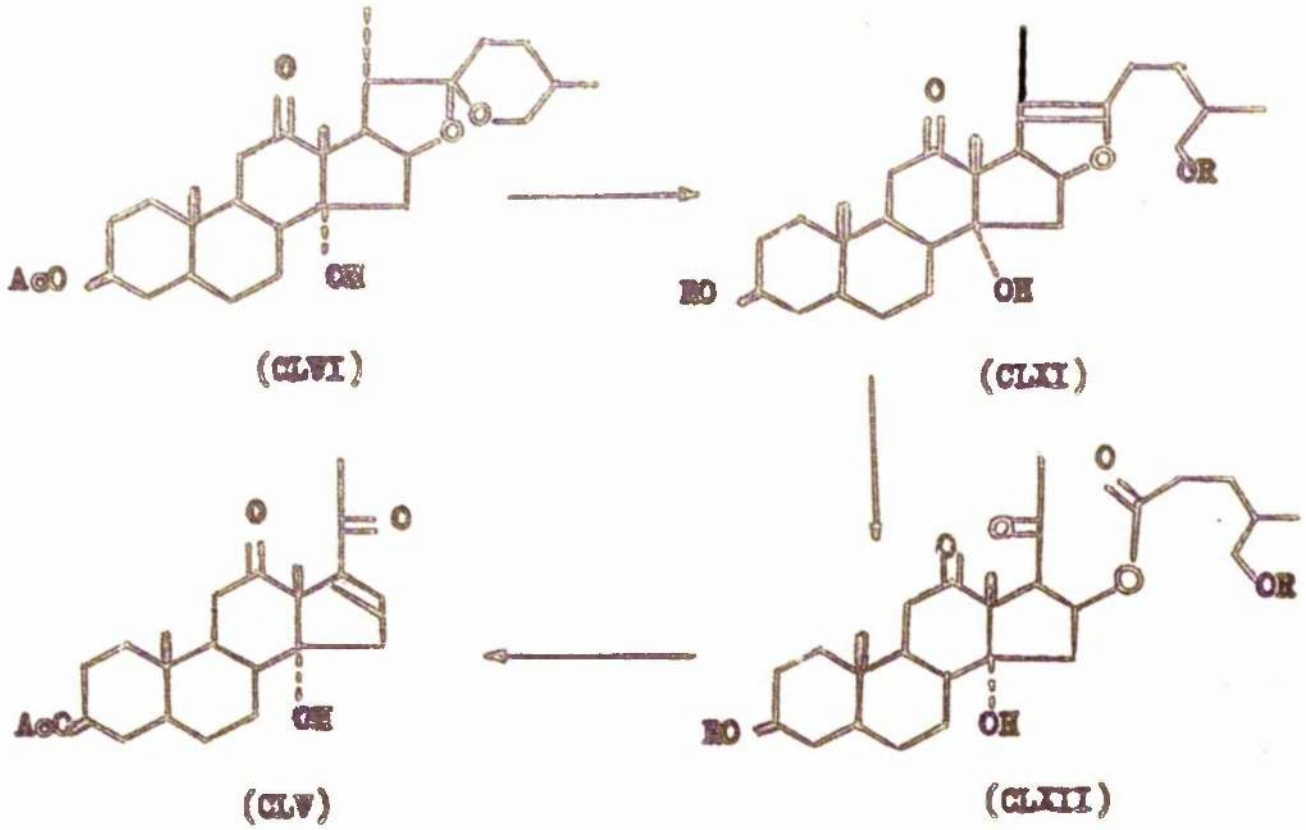
(CLX)

The α-configuration of the 14-hydroxyl group in the products from these reactions is in accord with the well-known principle of "rear attack" in the steroid series[70].

The degradation of the spirostan side-chain[66] to give a Δ^{16}-20 ketone gave a poor yield in the case of 14 α-hydroxyhecogenin.

Several variations of the basic method were tried, the only one which proved at all successful being the octoic acid-octoic anhydride method. This involves the heating of 14α-hydroxyhecogenin 3β-acetate

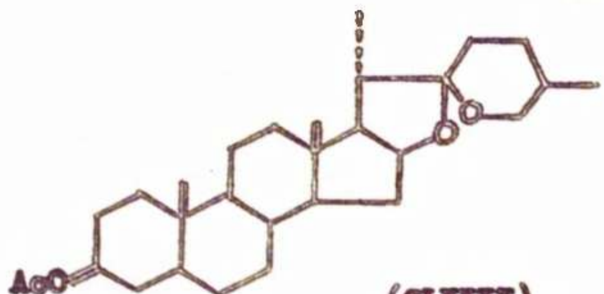
(CLVI; R = Ac) with n-octoic acid and n-octoic anhydride to give the furosten (CLXI; R = Octanoyl)



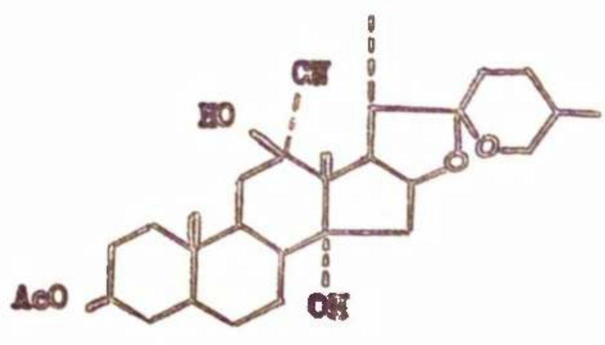
which is saponified and acetylated to give the furosten (CLXI; R = Ac). Treatment of this compound with chromium trioxide in acetic acid at steam-bath temperature cleaves the double bond to give the 20-ketone with an ester grouping at C-16 (CLXII). A solution of the latter in light petroleum/benzene left overnight with active alumina gives 3β-acetoxy-14α-hydroxy-5α-pregn-16-en-12, 20-dione (CLV). The overall yield is poor. Degradation of 14α-hydroxytigogenin 3β-acetate (CLVII; R = Ac) by the same method gave none of the expected Δ^{16}-20-ketone. Degradation of hecogenin acetate (CXLIV: R = Ac) and of tigogenin acetate (CLXIII: R = Ac) by the same method gave satisfactory results, and it is assumed that the presence of the 14α-hydroxyl group influences the reaction.

(Possibly dehydration occurs to some extent in the first stage of the reaction to give a Δ^{14} steroid[71], the Δ^{14} double bond being cleaved at the oxidation stage together with the $\Delta^{20(22)}$ double bond).

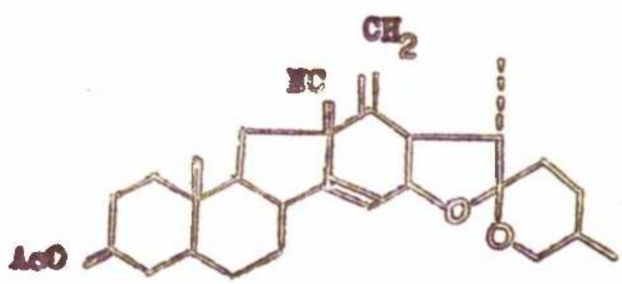
14α-Hydroxyhecogenin 3β-acetate resembles hecogenin 3β-acetate in many of its reactions. Its reduction to 14α-hydroxytigogenin (CLVII) by the Huang-Minlon method[67] has already been described. It forms an oxime and also a cyanhydrin (CLXIV) which is readily converted by thionyl chloride in pyridine into a C-nor-D-homo derivative (CLXV), both hydroxyl groups being lost in the process.



(CLXIII)



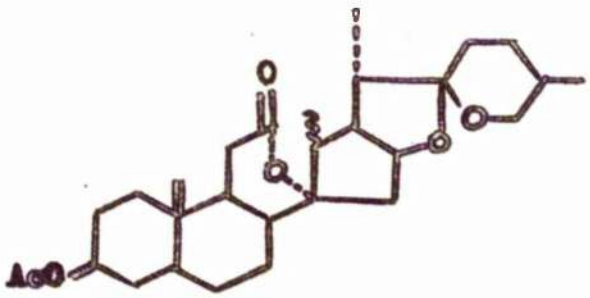
(CLXIV)



(CLXV)

This indicates that the cyanhydrin has the 12β-hydroxy-12α-cyano configuration[72]. (The Wagner-Meerwein type of reaction leading to a C-nor-D-homo-steroid requires coplanarity of the 12β-bond, C-13 and C-14).

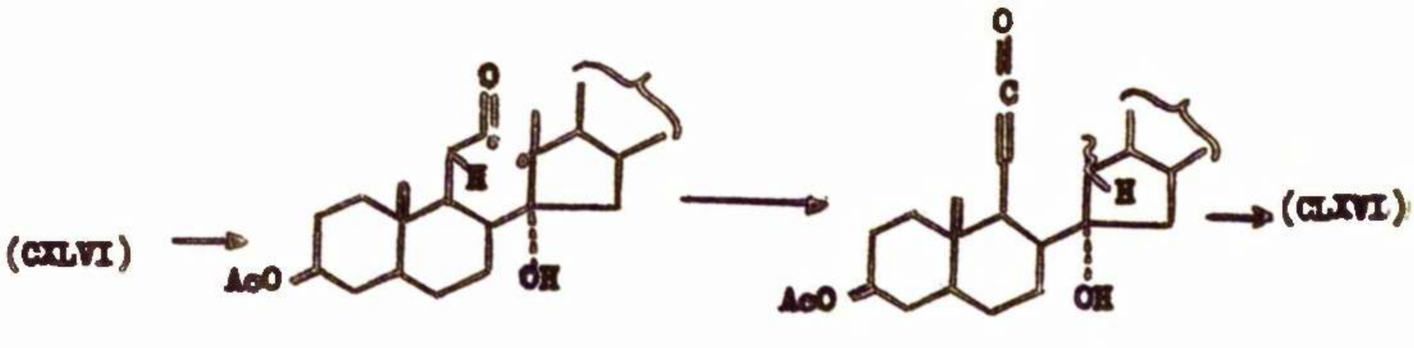
The ultraviolet irradiation of 14α-hydroxyhecogenin 3β-acetate (CLVI; R = Ac) in dioxan solution, under reflux in an atmosphere of purified nitrogen, produced a rapid decrease in the value of the specific rotation. After 5 hr. the value remained constant, and from the solution there was obtained by distilling off the solvent a good yield of the spirolactone (CLXVI: R = Ac). Analysis showed this compound to be an isomer of 14α-hydroxyhecogenin acetate, and the infra-red spectrum indicated the absence of hydroxyl and ketonic-carbonyl groups.



(CLXVI)

Saponification of the compound merely removed the 3β-acetate group to give the 3β-ol (CLXVI; R = H) which on re-acetylation gave back the original 3β-acetate. Treatment with lithium aluminium hydride, followed by treatment of the amorphous product with a solution of perchloric acid in methanol, afforded anhydrohecolyl alcohol (CXLVI) identical with an authentic sample. This establishes that the product of irradiation of 14α-hydroxyhecogenin 3β-acetate is 3β-acetoxy-14α-hydroxy-12,13-seco-5α, 25D-spirostan-12-oic acid 12 → 14 lactone (CLXVI; R = Ac).

Its formation from 14α-hydroxyhecogenin 3β-acetate is explained thus; on irradiation, a diradical (CLXVII) is formed, similar to that formed by hecogenin 3β-acetate.

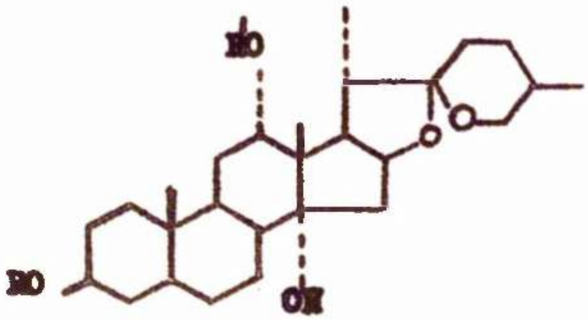


(CLXVII) (CLXVIII)

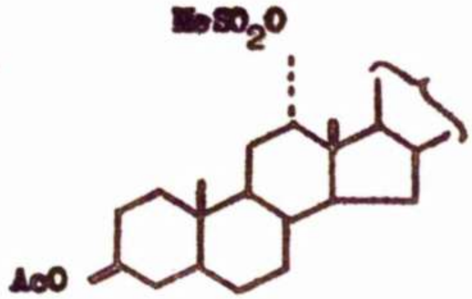
In this case, however, there is no abstraction of a hydrogen atom by C-12; rather the radical located at C-13 abstracts a hydrogen atom from C-11 to give the ketene (CLXVIII) which reacts intramolecularly to give the lactone (CLXVI).

Reduction of 14α-hydroxyhecogenin 3β-acetate with lithium aluminium hydride in tetrahydrofuran gave a mixture of triols from which only one, 3β, 12α, 14α-trihydroxy-5α, 25D-spirostan (CLXIX; $R = R^1 = H$) was obtained crystalline. It yielded a crystalline 3β-acetate (CLXIX; $R = Ac$, $R^1 = H$) and a 3β, 12α-diacetate (CLXIX; $R = R^1 = Ac$).

Oxidation of the triol with 8-N chromic acid in acetone afforded 14α-hydroxyhecogenone (CLVIII); similar treatment of the 3β-monoacetate gave 14α-hydroxyhecogenin 3β- acetate (CLVI; R = Ac).



(CLXIX)



(CLXX)

The existence of hydrogen-bonding in the 12, 14-diol (CLXIX; R = Ac, R^1 = H) and in the 3, 12-diacetate (CLXIX; R = R^1 = Ac) shows that the configuration of the oxygen function at C-12 is the same as it is at C-14.

When the 12, 14-diol (CLXIX; R = Ac, R^1 = H) was treated with methanesulphonyl chloride and the amorphous product was boiled under reflux with a solution of potassium t-butoxide in tertiary butanol, no C-nor-D-homo-compound was obtained. This agrees with the observation of Elks and co-workers concerning epi-rockogenin 3β-acetate-12α-methanesulphonate (CLXX), which gives no C-nor-D-homo compound in contrast to its 12β-epimer which does[72].

The assignment of a structure to photohecogenin acetate caused a certain amount of difficulty. The structure (CLII) assigned by McMeekin was in accord with all the evidence available to him, both for the acetate and for its hydrolysis product. Attempts were made to verify this structure, firstly by trying to show that "C_2H_4O" - either as ethylene oxide or as acetaldehyde - was generated during the irradiation of hecogenin acetate in dioxan and in 2-methyldioxolane. Although photohecogenin acetate was obtained, no trace of ethylene oxide or of acetaldehyde could be detected either by vapour-phase chromatography or by treatment of the recovered solvent with Brady's reagent.

Next, lumihecogenin acetate (CXLV) was heated with paraldehyde in an attempt to prepare photohecogenin acetate by the addition of $CH_3.CHO$ across the molecule of lumihecogenin acetate. This experiment, too, was without success.

Drastic treatment of photohecogenin acetate with lithium aluminium hydride for periods of up to 60 hr. gave only photohecogenin. Treatment of photohecogenin acetate with mineral acids gave no crystalline product.

A re-examination of McMeekin's analytical figures was next carried out. These were:-

Photohecogenin Acetate	C, 72.1; H, 9.15	$C_{31}H_{48}O_6$ requires C, 72.05; H, 9.35%
Photohecogenin	C, 73.2; H, 9.5	$C_{29}H_{46}O_5$ requires C, 73.4; H, 9.8%

A new series of analyses were undertaken on samples of photohecogenin and photohecogenin acetate, both of which were crystallised five times from methanol

Photohecogenin	C.	72.26	74.74	74.81	74.63	74.87
	H.	9.67	8.30	9.85	10.04	9.62
Photohecogenin Acetate	C.	72.75	72.41			
	H.	9.04	9.16			

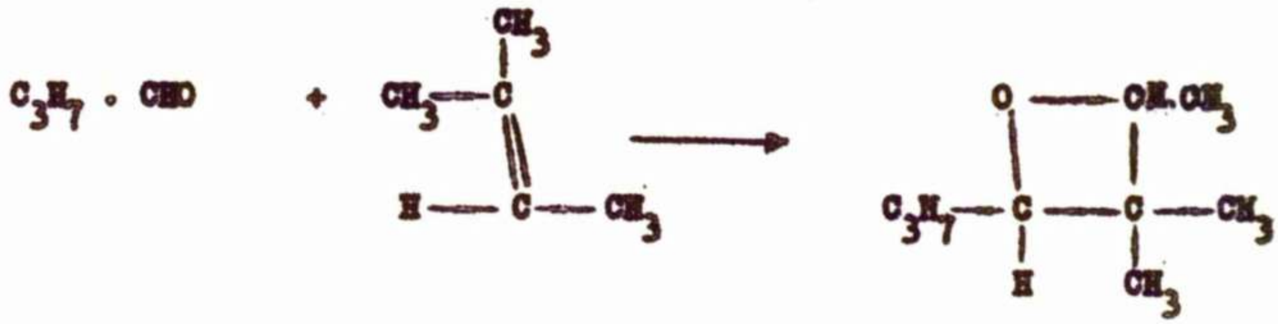
It seemed possible that these results could be explained on the basis of photohecogenin being an isomer of hecogenin, both photohecogenin and its acetate crystallising in solvated forms. If this is so, and if both molecules have 0.5 molecule of methanol of crystallisation the figures required are:-

Photohecogenin	$(C_{27}H_{42}O_4 \cdot 0.5CH_3OH)$:	C, 74.5; H, 9.9%
Photohecogenin Acetate	$(C_{29}H_{44}O_5 \cdot 0.5CH_3OH)$:	C, 72.55; H, 9.4%

A sample of photohecogenin acetate which had been rigorously dried in vacuo at 100° for several days analysed correctly for an isomer of hecogenin acetate.

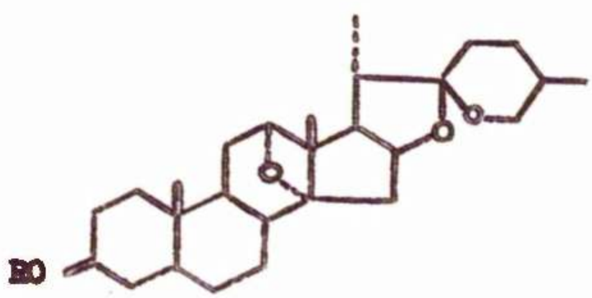
Having established the possibility that photohecogenin might be an isomer of hecogenin, the next problem was to find out the fate of the oxygen atom at C-12 in hecogenin and lumihecogenin when the acetates are photolysed. From its ultraviolet spectrum (no selective absorption) and its infra-red spectrum (acetate-carbonyl peak only) it would appear that photohecogenin acetate, unlike lumihecogenin acetate has neither unsaturation nor any carbonyl group except the 3β-acetate. It gives no colour with tetranitromethane.

Now Büchi, Inman and Lipinsky[73] have described the ultraviolet irradiation of butyraldehyde (CLXXI) in the presence of 2-methylbut-2-ene (CLXXII) which they show to give the 1,3-oxide (CLXXIII)



(CLXXI) (CLXXII) (CLXXIII)

(See also the recent paper by Arnold, Hinman and Glick[74]).
It seemed reasonable to suppose that, under ultraviolet irradiation, lumihecogenin acetate (CXLV), which has an aldehyde group and a double bond in close proximity, might undergo a reaction of this type intra-molecularly - in which case photohecogenin acetate would have the structure (CLXXIV: R = Ac)

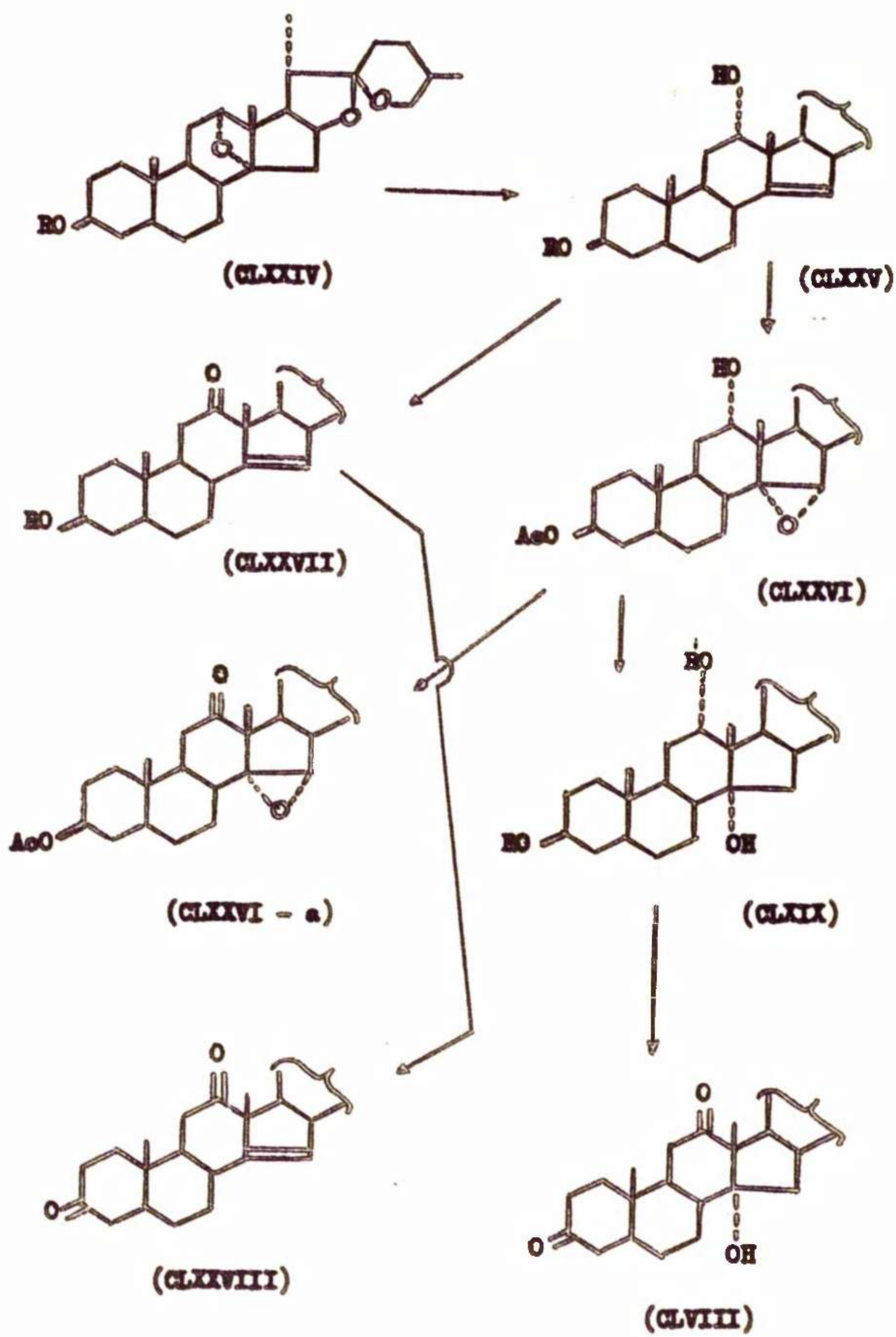


(CLXXIV)

In order to test this hypothesis, photohecogenin acetate was treated for a few minutes at room temperature with boron trifluoride-ether complex in dry benzene. The product obtained by pouring into water and extraction with ether, consisted of a mixture of two compounds which were readily separated by chromatography on alumina. The less polar product ("Compound A") was eluted by benzene. The structure of this compound will be discussed later. The more polar product ("Compound B") was eluted by ether and its infrared spectrum showed the presence of a hydroxyl group (peaks at 3620, 3560 cm^{-1}) and of a double bond (peaks at 3060, 1645 cm^{-1}).

Oxidation of "compound B" with 8-N chromic acid in acetone in the usual way gave a ketone, which showed the enhanced ultraviolet absorption intensity associated with β,γ-unsaturated ketones (λ max 294, ε 252)[75]. Its O.R.D. curve had an amplitude (a + 40).

Treatment of "compound B" with perbenzoic acid, followed by reduction of the resulting epoxide with lithium aluminium hydride, gave an amorphous solid which on oxidation with 8-N chromic acid in acetone gave 14α-hydroxy-5α,25D-spirostan-3, 12-dione (14α-hydroxyhecogenone), (CLVIII) identical in all respects with a sample prepared from anhydrohecolyl alcohol (CXLVI) by oxidative cyclisation.


RO
(CLXXIV)
HO
RO
(CLXXV)
O
RO
(CLXXVII)
HO
AcO
(CLXXVI)
O
AcO
(CLXXVI - a)
HO
RO
OH
(CLXIX)
O
O
(CLXXVIII)
O
O
OH
(CLVIII)

Treatment of the lithium aluminium hydride reduction product from the epoxide with acetic anhydride in pyridine gives the same diol monoacetate (CLXIX; R = Ac, R^1 = H) as was obtained on similar treatment of the reduction product from 14α-hydroxyhecogenin 3β-acetate - namely 3β-acetoxy-12α, 14α-dihydroxy-5α,25D-spirostan.

Oxidation of the diol monoacetate gave 14α-hydroxyhecogenin 3β-acetate (CLVI). Oxidation of the triol gave 14α-hydroxy-hecogenone (CLVIII).

It is thus established that the hydroxyl group in "compound B" is a 12α-hydroxyl. (It must be either a 12α- or a 14α- hydroxyl group, and it is capable of being oxidised to a ketone, which rules out the tertiary 14α- hydroxyl).

The ketone derived from "compound B" is β,γ-unsaturated. Since the keto group is at C-12, the possibilities for the position of the double-bond are: $\Delta^{8(9)}$, $\Delta^{8(14)}$, and $\Delta^{14(15)}$. The former is ruled out immediately, as it could hardly give rise to a 14α-hydroxyl group by epoxidation followed by lithium aluminium hydride reduction. A $\Delta^{8(14)}$ double bond is tetrasubstituted, and would not be expected to show any peaks in the infrared spectrum in the (C = C) stretching region. Neither would it exhibit any olefinic proton peaks in its nuclear magnetic resonance spectrum. Since both "compound B" and its oxidation product show (C = C) stretching frequencies in the infrared, and the ketone also shows olefinic proton peaks in the n.m.r. spectrum, it is evident that the position of the double bond in these compounds is $\Delta^{14(15)}$.

Thus, compound "B" is 3β-acetoxy-12α-hydroxy-5α,25D-spirost-14-en (CLXXV: R = Ac). Its oxidation product is thus 3β-acetoxy-5α, 25D-spirost-14-en-12-one (CLXXVII; R = Ac).

The epoxide derived from "compound "B" is 3β-acetoxy-12α-hydroxy-14α,15α-epoxy-5α, 25D-spirostan (CLXXVI). Its formation from "compound B" is in accordance with the work of Hofer, Linde and Mayer[76]. On reduction it would be expected to give a 14α-hydroxy compound, and the fact that the compound thus obtained is identical with a compound to which a 14α-hydroxy configuration had been assigned for other reasons is additional evidence for the correctness of this configuration.

Photohecogenin must therefore have a 12, 14-oxide linkage, which is split by treatment with BF_3[77]. Since one product of this reaction has a 12α-hydroxyl group, and a double bond at C-14, it must be that in photohecogenin there is a 12α, 14α-oxide linkage. Hence photohecogenin acetate is 3β-acetoxy - 12α, 14α-epoxy - 5α, 25D-spirostan (CLXXIV; R = Ac).

The ketone (CLXXVII; R = Ac) on saponification gives 14-dehydrohecogenin (CLXXVII; R = H) which on oxidation with 8-N chromic acid in acetone gives the diketone (CLXXVIII).

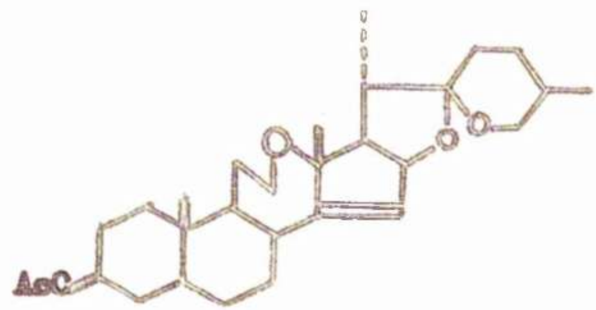
Oxidation of the epoxide (CLXXVI) with 8-N chromic acid gives the 14α, 15α-epoxy- 12 - ketone (CLXXVI-a).

Saponification of "compound B" gives 3β, 12α-dihydroxy-5α, 25D-spirost -14-en (CLXXV; R = H).

The nature of "Compound A" was something of a mystery. Its infrared absorption spectrum shows that there is no hydroxyl group present and no carbonyl group except the 3β-acetate. The compound is unsaturated (positive tetranitromethane test, peak at 1650 cm^{-1} in the infrared and olefinic proton peak in the n.m.r., τ 4.6, equivalent to one proton).

The compound contains no boron or fluorine and analysis indicates that it is an isomer of hecogenin acetate. The infrared spectrum shows that the spirostan side chain is intact[78]. Saponification of the compound gave a product which was difficult to obtain sharp-melting, but which on re-acetylation gave back "compound A". The nuclear magnetic resonance spectrum of "compound A" has a peak at τ 4.6, as mentioned above, which has an area equivalent to one proton. Hence the double bond is trisubstituted. There is also a broad band at τ 6.5 which has an area equivalent to four protons. As the spirostan side-chain is intact, two of these protons should be accounted for by the hydrogen atoms attached to C-26. (The band is in the region associated with the resonance of protons bonded to a carbon atom joined by a single bond to an oxygen atom). In "compound A", then, there are two more hydrogen atoms attached to a carbon atom (or atoms) bonded to an oxygen atom (or atoms), besides the two already accounted for and the hydrogen atoms at C-3 and C-16 which are accounted for by a broad band at τ 5.25.

Taking all these facts into consideration, we arrive at the conclusion that there is only one oxygen atom with which the two hydrogen atoms can be associated, namely the one derived (ultimately) from the 12-oxo group in hecogenin. It thus appears that there must be a $-CH_2-O-$ group in the molecule of "compound A". It is difficult to conceive of a structure which would satisfy all these observations other than the structure (CLXXIX) or perhaps a C-13 epimer, without



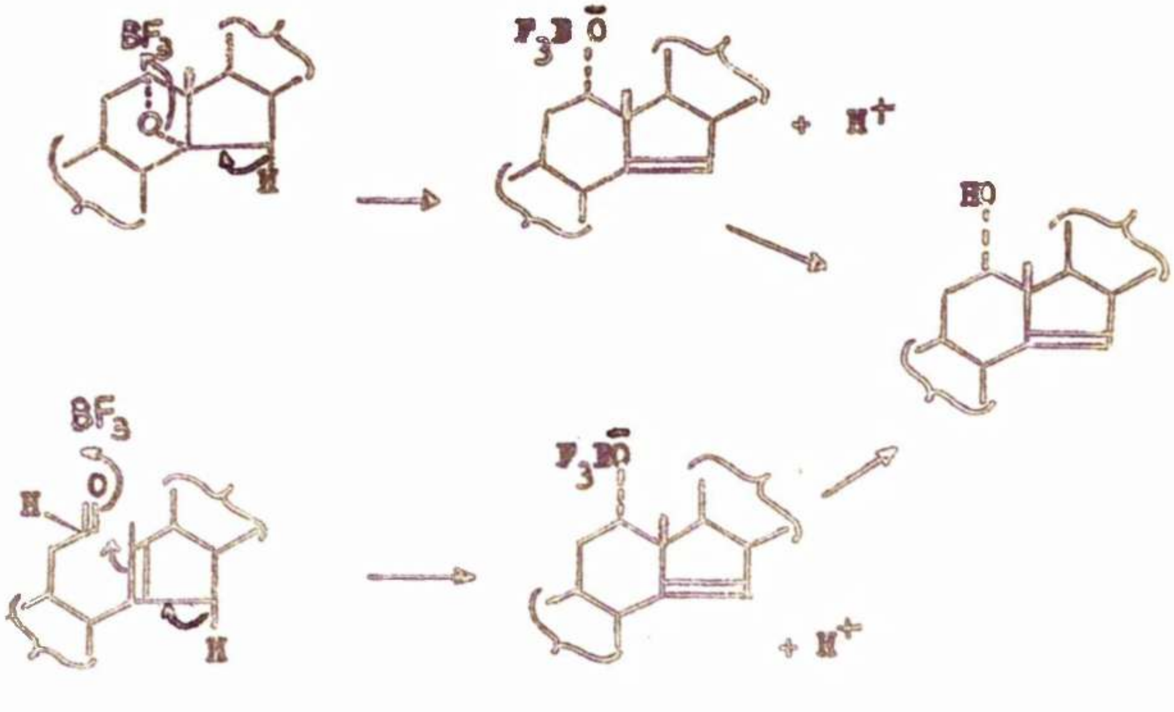
(CLXXIX)

postulating some deep-seated change elsewhere in the molecule. Therefore "compound A" is formulated, albeit tentatively, as 3β-acetoxy-12a-oxa-C-homo-5α,25D-spirost-14-en (CLXXIX).

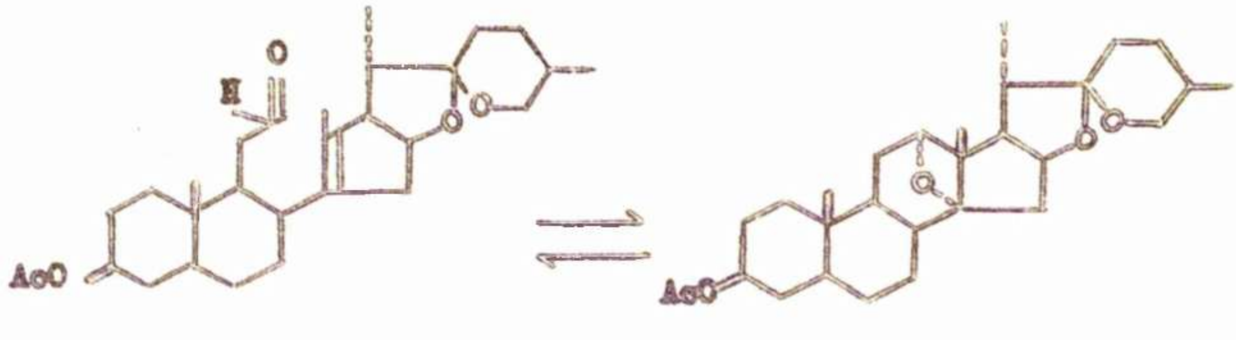
In one experiment in which photohecogenin 3β-acetate (CLXXIV; R = Ac) was treated with BF_3 - ether complex, a small amount of lumihecogenin acetate (CXLV) was isolated among the products. This observation prompted another series of experiments involving the treatment of lumihecogenin acetate with BF_3 -ether complex under the same conditions. It was found that under these conditions lumihecogenin acetate gave the same products as photohecogenin acetate, and in approximately the same proportions. The Δ^{14}-12-ol can be obtained pure by this method, but the

12a -oxa -C- homo steroid is always contaminated by hecogenin acetate from which it is difficult to separate it. (Hecogenin acetate is present in all but the most carefully purified samples of lumihecogenin acetate).

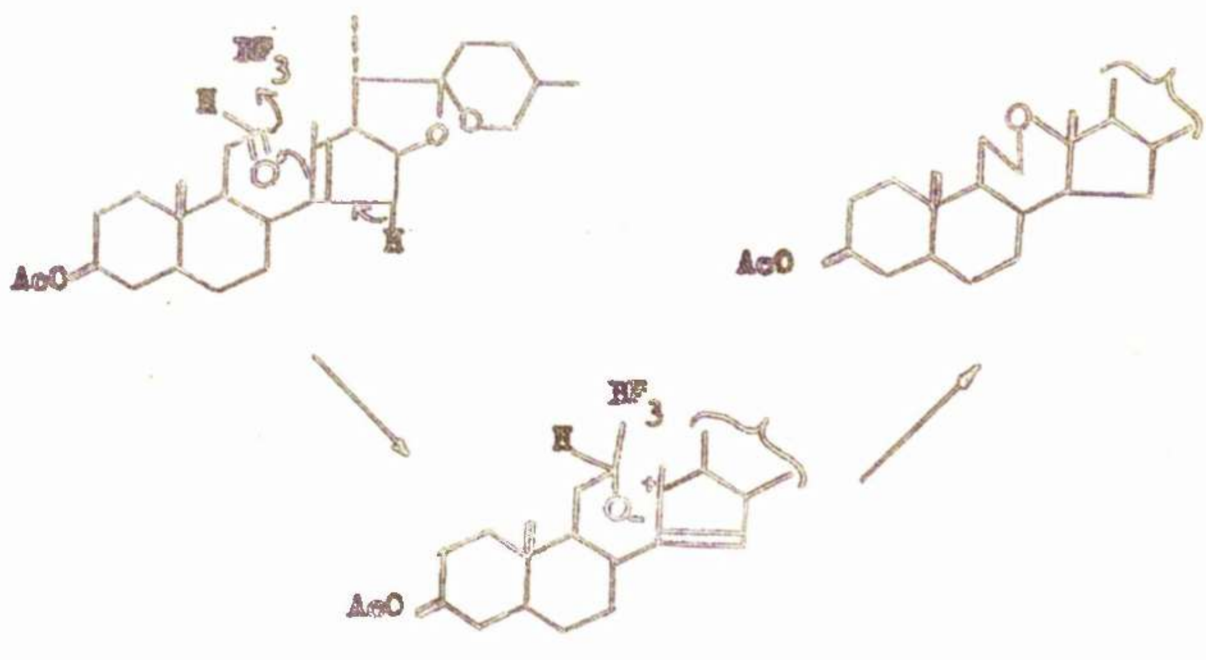
The formation of the Δ^{14} -12- ol from lumihecogenin acetate and from photohecogenin acetate can readily be explained by the following mechanisms:



The mechanism of the formation of "compound A", if indeed it is 3β-acetoxy-12a -oxa -C-homo-5α,25D - spirost-14-en , poses certain difficulties. It is possible, in view of the formation of lumi-:hecogenin acetate from photohecogenin acetate described above during one experiment, that an equilibrium is set up when either photohecogenin acetate or lumihecogenin acetate is treated with BF_3 etherate.



It is tentatively suggested that "compound A" is formed from lumihecogenin acetate by the following mechanism:



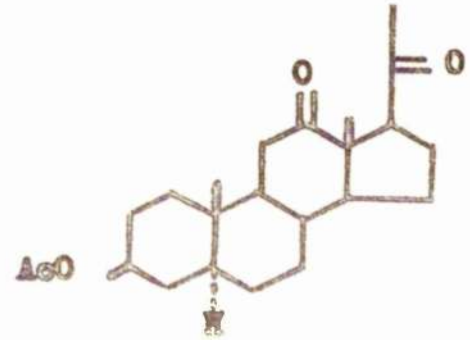
This mechanism is, of course, open to objection, involving as it does the attack of boron trifluoride at what would normally be expected to be an electropositive centre.

Photolysis of 14-dehydrohecogenin 3β- acetate (CLXXVII; R = Ac) gave no crystalline product other than recovered starting material. The specific rotation changed during the course of the irradiation, and it might be expected, (by analogy with the photolysis of 17-ketosteroids[15, 16] where, as is the case with a Δ^{14}-12-ketone no hydrogen atom is sterically available for abstraction by the radical at C-12) that epimerisation at C-13 might occur. However, no such product was isolated. Irradiation of the Δ^{14}-12-ketone in aqueous dioxan for a prolonged period gave only a trace of acidic material.

Attempts to hydrogenate the Δ^{14}-steroids were unsuccessful.

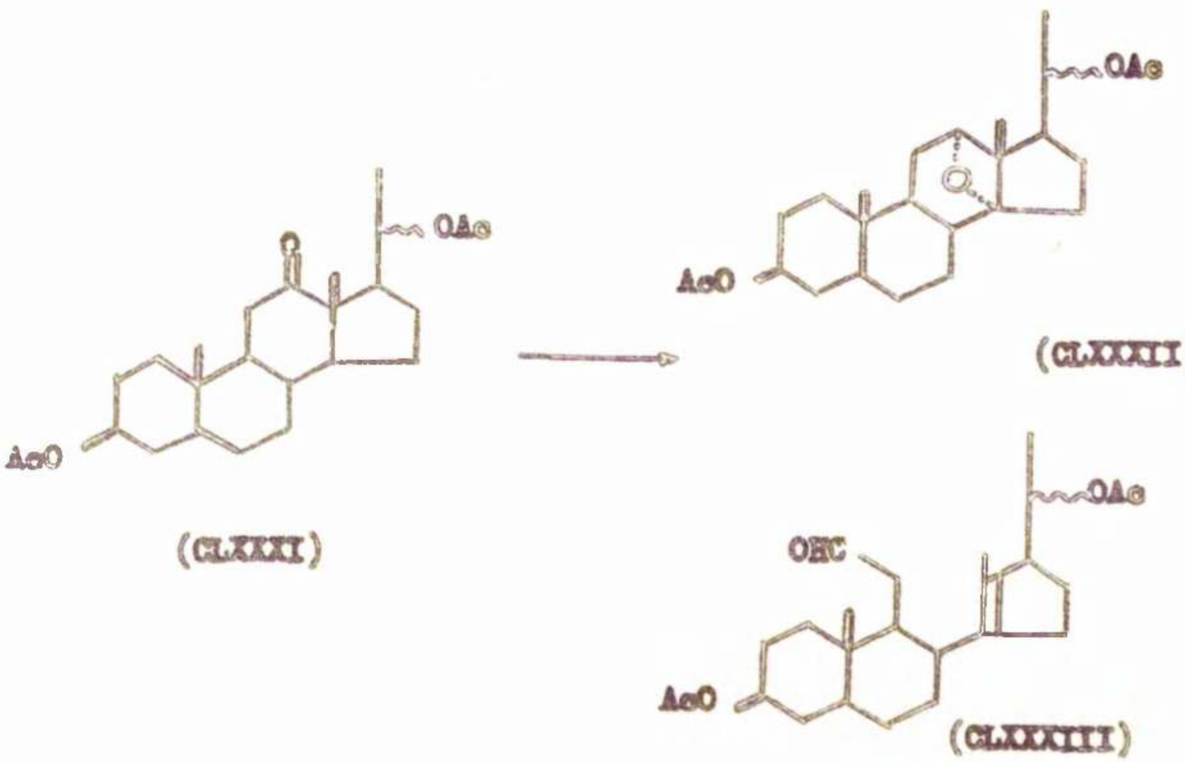
The methods described above for the introduction of 14α -hydroxyl groups and Δ^{14}- double bonds into steroid molecules are potentially valuable in hormone synthesis. (14β -Hydroxyl groups could be introducted, too, by treatment of Δ^{14}-steroids with N-bromoacetamide in acetone[76]). Since side-chain degradation of 14α- hydroxyspirostan gave such poor results, it was decided to repeat the experiments using steroids in which the spirostan side-chain is not present.

Irradiation in dioxan of 3β -acetoxy-5α- pregnan- 12, 20 - dione (CLXXX) gave no



(CLXXX)

crystalline product. Presumably the reaction is complicated in this case by reactions of both the 12- and 20-keto-groups simultaneously. (c.f. Wehrli _et_. _al_.[79]). A suitable compound was found in 3β, 20ξ-diacetoxy-5α-pregnan-12-one (CLXXXI) which is prepared from the diketone (CLXXX) by the method of Petrow _et_ _al_.[80]



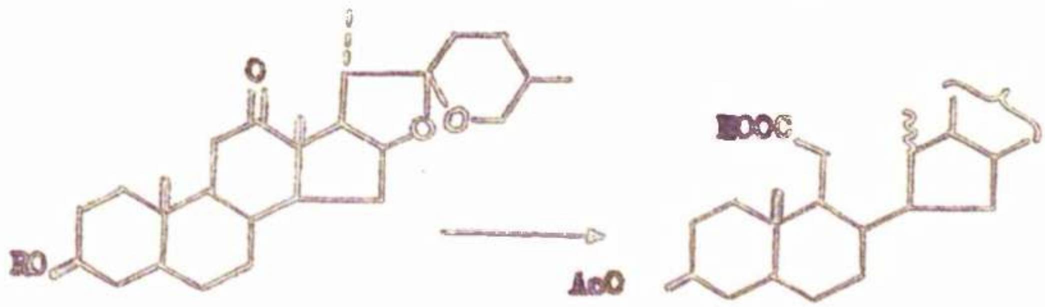
(CLXXXI)

(CLXXXII)

(CLXXXIII)

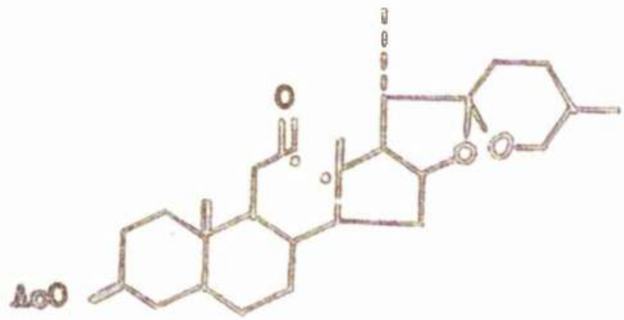
Irradiation of the ketone (CLXXXI) in dioxan caused a drop in the value of the specific rotation from + 94.2° to + 7.9° in 9.5 hr. Chromatography of the product afforded 3β,20ξ-diacetoxy-5α-pregnan-12α,14α-epoxide (CLXXXII) and 3β, 20ξ-diacetoxy-12,13-seco-5α-pregn-13-en-12-one (CLXXXIII). So far, attempts to prepare Δ^{14}- and 14α- hydroxy-steroids from these compounds have been unsuccessful. Oxidation of the aldehyde (CLXXXIII) with 8-N chromic acid in acetone gives no neutral product, and treatment of the 12α, 14α-oxide (CLXXXII) with boron trifluoride - ether complex gives no crystalline material on chromatography of the reaction product.

Since this work was performed, Quinkert, Wegemund, Homburg and Cimbollek[16] have described the ultraviolet irradiation of many non-conjugated ketones in solutions containing water. (See also Introduction, p. 27). They describe the irradiation of hecogenin acetate (CXLIV: R = Ac) in aqueous dioxan, to give the acid (CLXXXIV).



(CXLIV) (CLXXXIV)

which is in accord with the mechanism proposed above for the forma:
:tion of lumihecogenin acetate (CXLV) from hecogenin acetate on photolysis. In the case of irradiation of hecogenin acetate in aqueous dioxan, the diradical (CLIII) reacts with water to give the acid (CLXXXIV).



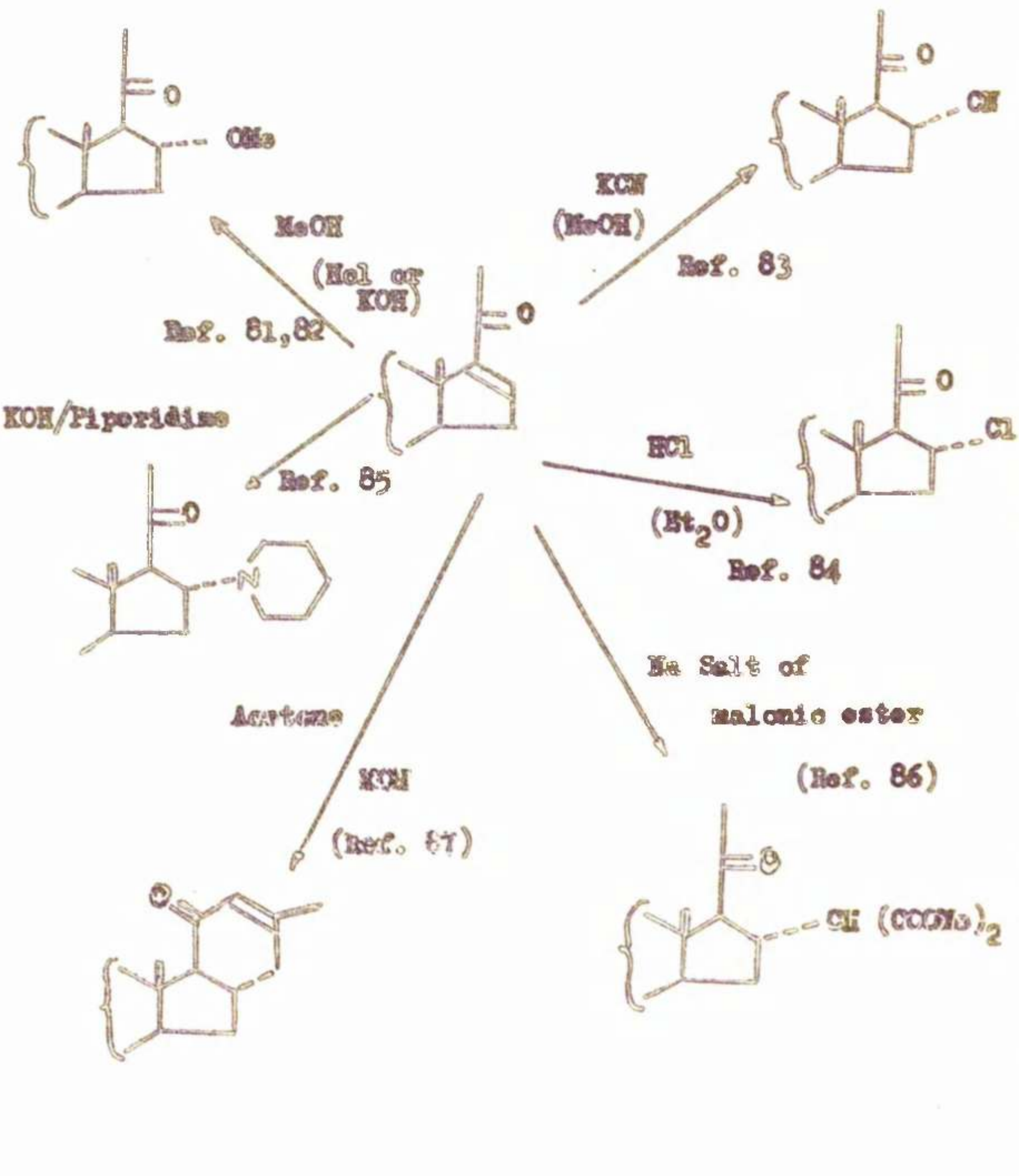
(CLIII)

Nucleophilic Addition to Δ^{16}-20-ketones

In view of the discussion to follow on the photoaddition of alcohols to Δ^{16}-20-ketones, it is interesting to consider some addition reactions which have already been described for such ketones.

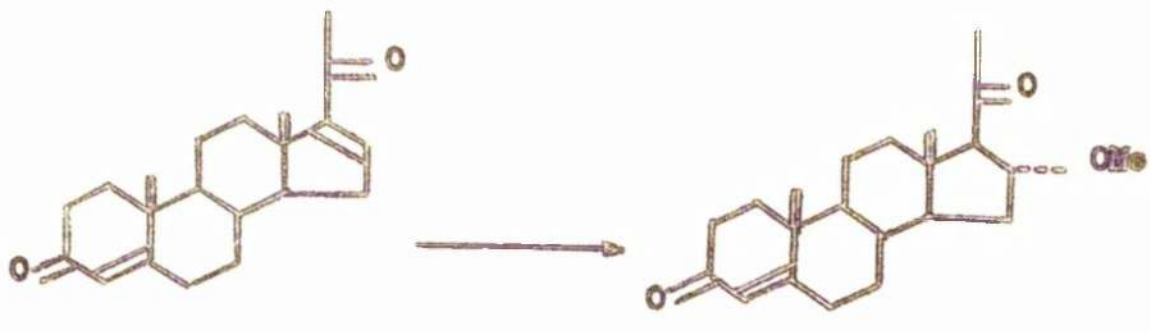
Some examples of addition to Δ^{16}-20-ketones are shown in the Chart (2) below.

Chart (2)



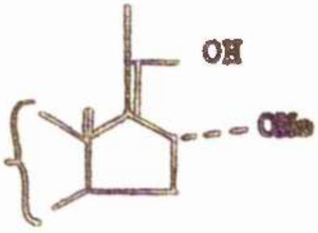
The base-catalysed addition of methanol to a Δ^{16}-20-ketone was first reported by Marker[81] - who thought, however, that the product was a 17-hydroxysteroid.

This was corrected by Fukushima and Gallagher[82], who describe the addition of methanol to pregnadienolone and Δ^{16}-progesterone (CLXXXV). In the latter case addition occurs only across the Δ^{16}-double bond, the α,β-unsaturated ketone in ring A being unaffected.



(CLXXXV)

Fukushima and Gallagher suggest that the addition occurs via an intermediate (CLXXXVI)



(CLXXXVI)

formed as a result of the addition of a methoxide ion at C-16.

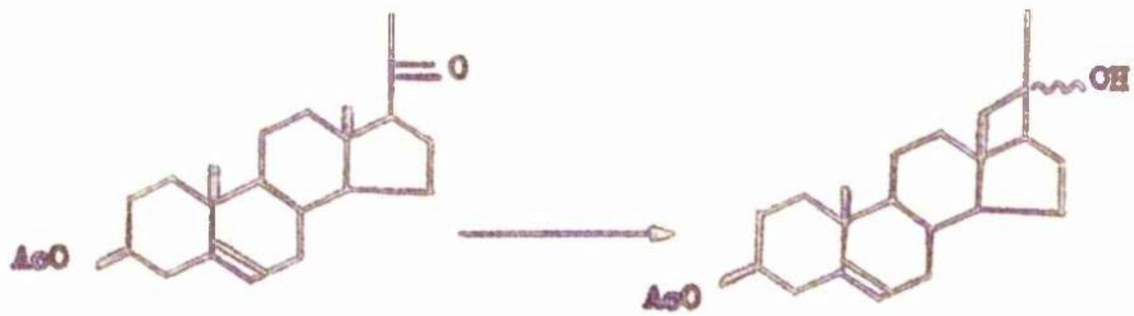
It is reasonable to suppose that in the other cases mentioned the mechanism of the addition is similar to that operating in the case of methanol and KOH. In the case of the addition of methanol yields are poor, due to the fact that the reaction is an equilibrium and that the methanol will be only slightly dissociated. However, in the case of, say, the sodium salt of malonic ester [86], the dissoci--ation is more nearly complete and yields in the addition reaction are higher.

The configuration of the product, 16α, 17β-, can be explained by invoking the principle of rear attack [70] on the steroid nucleus to give a 16α-substituted system, in which case the ketonisation of the enol, e.g. (CLXXXVI) proceeds so as to give the 17β- rather thanthe 17α-pregnan derivat--ive.

The photoaddition reactions of alcohols to Δ^{16}-20-ketones to be described below give different products from the acid- or base- catalysed additions mentioned above, and the radical mechanisms postulated account for this difference.

The Ultraviolet Irradiation of Δ^{16}-20-ketones

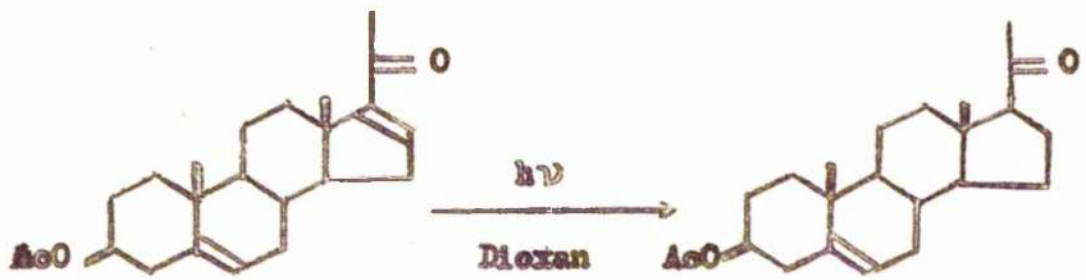
In view of the results obtained by Buchschacher, Cereghetti, Wehrli, Schaffner and Jeger[44] on irradiation of 3β-acetoxypregn-5-en-20-one (CLXXXVII), which they showed to give the 18,20 cyclosteroid (CLXXXVIII)



(CLXXXVII) (CLXXXVIII)

it seemed of interest to examine the reaction of a Δ^{16}-20 ketone on irradiation under similar conditions.

When 3β-acetoxypregna-5, 16-dien-20-one (CLXXXIX) ("pregnadienolone acetate"; "dehydropregnenolone acetate") was irradiated in dioxan solution by ultraviolet light, either in vacuo at room temperature or under reflux in a stream of nitrogen, a decrease in the intensity of the ultraviolet absorption maximum in the 240 mμ region was observed. In four hours the intensity of the absorption decreased from ε 10,000 almost to zero. The reaction mixture, on chromatography, afforded two crystalline products. One, obtained in about 40% yield, was shown to be



(CLXXXIX) (CXC) ≡ (CLXXXVII)

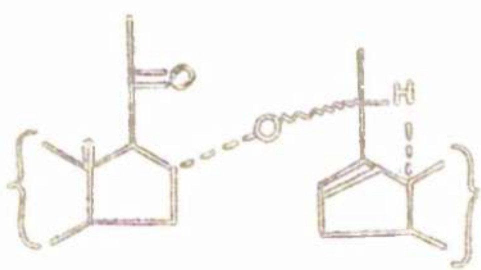
3β-acetoxypregn-5-en-20-one (CXC) ("pregnenolone acetate"), which must arise from reduction of the Δ^{16}-double bond of pregnadienolone acetate.

The second crystalline product, obtained in about 20% yield, is a dimer (molecular weight = 688). From the evidence afforded by its infrared spectrum it has no hydroxyl group; it has, apparently, two acetate groups and one saturated ketone group in the bi-steroid molecule. (The acetate peak at 1730 cm^{-1} is twice as intense as the peak at 1708 cm^{-1}). There is also a peak at 1660 cm^{-1} which suggests a double bond. (This may or may not be due to the Δ^5-double bonds which do not show absorption in this region in, for example, pregnenolone acetate).

The n.m.r. spectrum of the compound shows that the angular methyl groups are all intact, and the peak at τ 7.95 indicates the presence of the two acetate groups (six protons). The peak at τ 7.90, however, (assigned to CH_3 - CO) has an area corresponding to only three protons. It would appear, then, that in the bi-steroid molecule (assuming no really drastic changes have occurred) we have two molecules of pregnadienolone acetate joined together in such a way that the $CH_3.CO$ - side chain is intact in one of them but not in the other. The broad peak in the n.m.r. at τ 5.5 is assigned to the protons at C-3 in the steroid molecules, the peak at τ 4.6 to the protons at C-6. It is difficult to assign the peak at τ 6.35, which has an area corresponding to four protons and which would be expected to be due to protons on carbon atoms singly bonded to oxygen.

Since one of the 17-acetyl groups has changed in some way (since its methyl group does not show up sharply in the n.m.r.) and it is probable that the "ketone-oxygen" is no longer doubly bonded to one carbon in this case (the intensity of the carbonyl frequency peak in the infrared at 1706 cm^{-1} corresponding to only one $>C=O$) it would seem possible that the linkage between the two steroid mole-cules is via an oxygen atom.

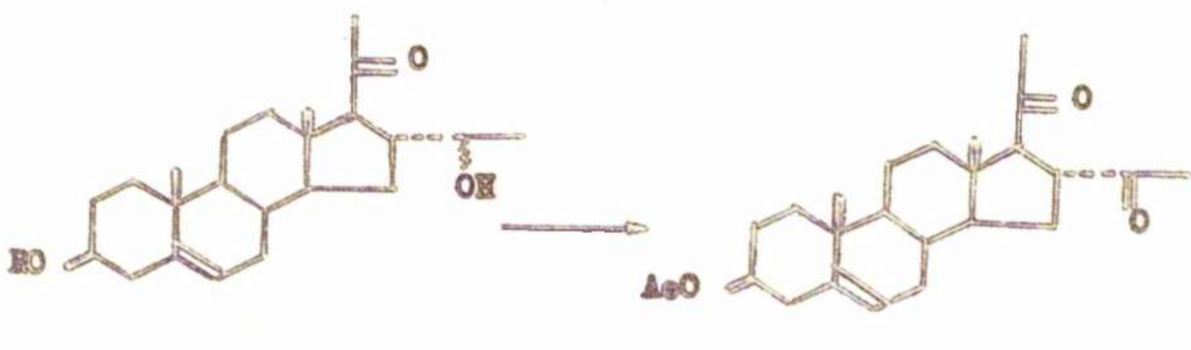
One possibility would be the structure (CXCI) below, though this does not account for all the n.m.r. evidence mentioned above.



(CXCI)

In order to gather more information about the mechanism of the reaction - and to try to identify, if possible, the dimer, it was decided to carry out irradiations of pregnadienolone acetate in hydroxylic solvents which would, it was thought, be likely to add on to the radicals formed from the steroidal ketone on irradiation.

When pregnadienolone acetate (CLXXXIX) was irradiated in ethanolic solution, either under reflux in a stream of nitrogen or in vacuo at room temperature, a rapid reaction occurred, the extinctio coefficient of the ultraviolet absorption maximum at about 240 mμ decreasing from ε 10,000 to zero in 1.5 hr. Chromatography of the crude reaction product gave two crystalline compounds, the first being pregnenolone acetate, (CXC), in ~ 40% yield, as in the case of irradiation in dioxan. The second crystalline compound, also obtained in ~ 40% yield, is formulated as 3β-acetoxy-16 α-(1′ -hydroxyethyl)-pregn-5-en-20-one (CXCII: R = Ac) for the following reasons:



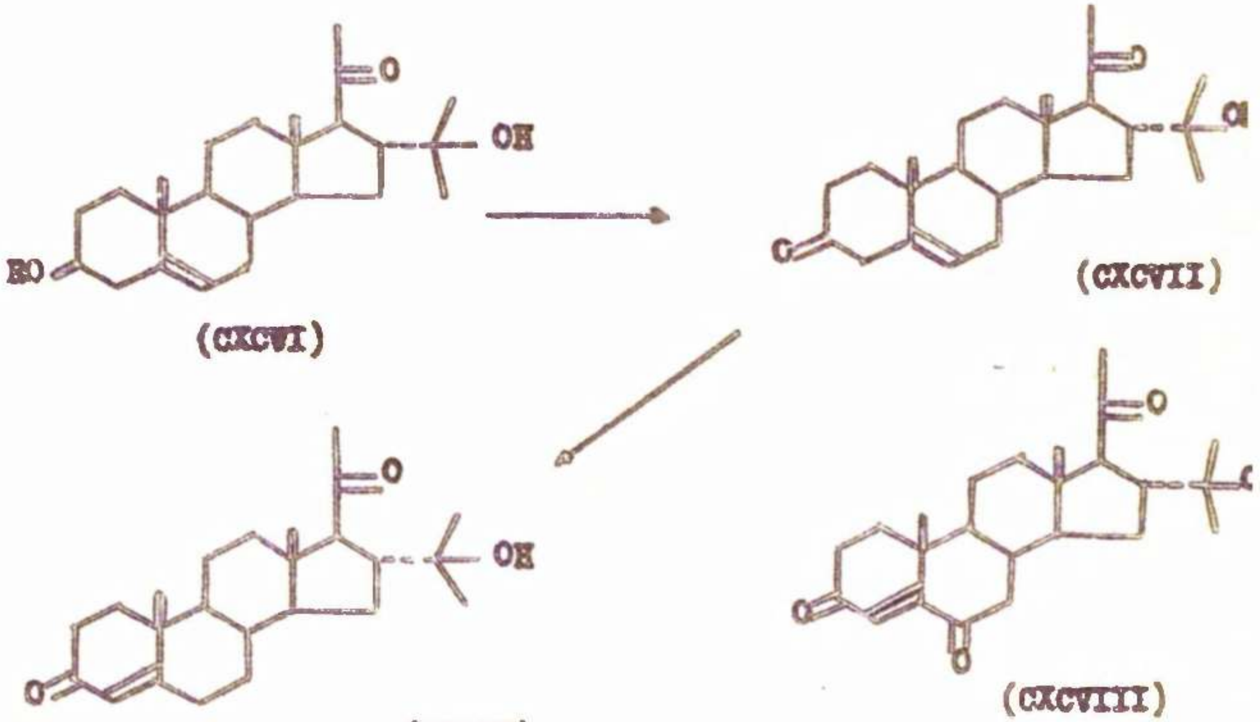
(CXCII) (CXCIII)

It shows peaks in the infrared spectrum at 3630 and 3595 cm^{-1}, indicating the presence of a hydroxyl group, and on oxidation with 8-N chromic acid in acetone gives a diketone, formulated as (CXCIII), which has a peak at τ 7.86 in its n.m.r. spectrum, equivalent in area to six protons (2 x $C\underline{H}_3CO$) in addition to the peak at τ 7.99 (equivalent in area to three protons) assigned to the 3β-acetate group. The product of saponification of the photo-addition product, the diol (CXCII; R = H), on oxidation with 8-N chromic acid in acetone gave the triketone (CXCIV) which was not isolated but was isomerised by dilute sulphuric acid in methanol to the known compound, 16α-acetylprogesterone (CXCV). The substance was identical in every respect with an authentic sample[88] kindly provided by Dr. Pierre Crabbé of Syntex S.A., Mexico.

(CXCIV) (CXCV)

This establishes that in the irradiation reaction, the compound (CXCII; R = Ac) is formed by the addition of the elements of ethanol to the molecule of pregnadienolone acetate. The photo-adduct is presumably a mixture of two compounds which are stereoisomeric at position 1′. Thin layer chromatography of the substance showed a very slight "waist" in the single spot due, presumably, to the presence of these two stereoisomers.

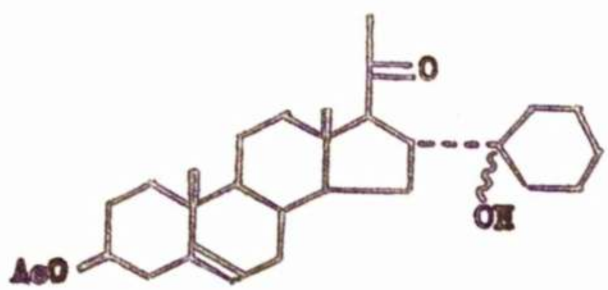
Next, pregnadienolone acetate was irradiated in solution in isopropanol, and again pregnenolone acetate was obtained in about 40% yield. An addition product was also formed, in about 30% yield. This is 3β-acetoxy-16α-(1′-hydroxyisopropyl)-pregn-5-en-20-one (CXCVI; R = Ac)



(CXCVI) (CXCVII) (CXCVIII) (CXCIX)

which shows a peak in its infrared spectrum at 3450 cm^{-1} (hydroxyl group) and which has in its n.m.r. spectrum a peak at τ 8.88, with an area corresponding to six protons, assigned to the gem-dimethyl group at position 1′ . The 3β-alcohol, (CXCVI; R = H) obtained by saponification of the photo-adduct, gives on oxidation with 8-N chromic acid a product which is principally the diketone (CXCVII), but which must also contain some of the corresponding progesterone (CXCIX) - and which also contains some of the triketone (CXCVIII). Treatment of the crude oxidation product with dilute sulphuric acid in methanol gave a mixture from which 16α-(1′-hydroxyisopropyl)-progesterone (CXCIX) and also 16α-(1′-hydroxyisopropyl)-pregn-4-en-3, 6, 20-trione (CXCVIII) were obtained pure on chromatography.

The reaction was extended to a variety of alcohols - cyclohexanol, for example, gives a photo-adduct (CC) and also pregnenolone acetate in about 45% yield.

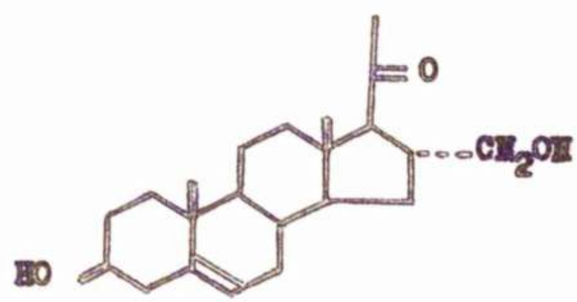


(CC)

It was found that photochemical reactions of this type proceed equally well in quartz or in pyrex flasks, which seems to indicate that the $n \rightarrow \pi^*$ transition of a non-bonding electron is responsible for the reaction, since light below 290 mμ is effectively filtered out by pyrex. The photoaddition of ethanol to pregnadienolone acetate takes place when the solvent is a mixture of equal volumes of ethanol and cyclohexane, although the yield of the adduct (CXCII; R = Ac) is rather lower in this case. Pregnenolone acetate (CXC) is again formed in about 40% yield. In all these reactions, in addition to the photo-addition product and the reduction product, there is obtained a quantity of intract:able gum, a mixture of several compounds, which becomes dark green or blue when kept in contact with methanol or chloroform. It is suggested that these may consist of a mixture of dimers and products of irradiation of pregnenolone acetate and of the photo-addition products. It is quite possible, of course, that alternative photo-reactions of pregnadienolone acetate may occur also.

When pregnadienolone acetate (CLXXXIX) is irradiated in solution in methanol, the reaction is slightly slower (i.e. the ultraviolet absorption maximum at 240 mμ takes slightly longer to disappear than in the reactions already mentioned, where the disappearance may be complete in 1 - 1.5 hr.) and a crystalline precipitate is formed. The nature of this substance, which is a single compound, is still being investigated. It contains a hydroxyl group and a saturated keto-group, and may possibly be a dimer. It is difficult to characterise fully due to its insolubility in many solvents. It was not possible to run an n.m.r. spectrum, even in deuterochloroform or deuteropyridine, and the compound was recrystallised from a large volume of hot chloroform by the addition of methanol.

The other products of the photo-reaction were chromatographed as usual and include pregnenolone acetate in about 40% yield. More polar fractions, where, by analogy with the reactions mentioned above, the adduct would be expected to be found, consisted of a mixture of several compounds. Repeated re-chromatography of these fractions gave no clear separation. However, acetylation of the material with acetic anhydride in pyridine, followed by chromatography, gave a slightly impure compound which on saponification and recrystallisation of the product afforded 3β-hydroxy-16α-hydroxymethylpregn-5-en-20-one (CCI) identical in every respect with an authentic sample[89] (kindly provided by Dr. S. Bernstein, Lederlé Laboratories, Pearl River, N.Y.).



(CCI)

This establishes that the expected photo-addition does in fact occur, although the yield is very poor.

Numerous other solvents were used in experiments with pregnadienolone acetate, with mixed success. Trifluoroethanol, benzyl alcohol, 2-methoxyethanol, ethylene glycol monoacetate, propargyl alcohol, thioacetic acid and N, N-dimethyl-2-aminoethanol gave no reduction product and no isolable addition products. In some cases some reaction apparently takes place, as chromatography of the crude reaction mixture gives a series of dark gums, in addition to unchanged pregnadienolone acetate. In the case of benzyl alcohol, starting material is recovered unchanged (quantitatively) after irradiation for three hours.

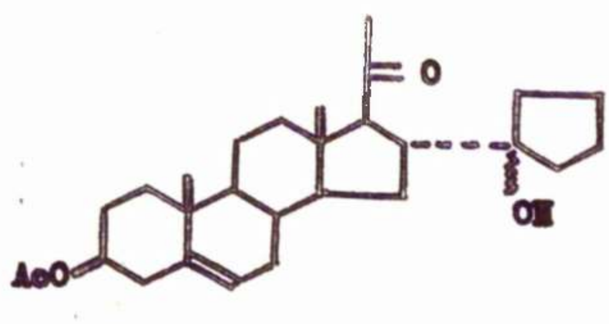
Irradiation of pregnadienolone acetate in allyl alcohol caused a diminution of the ultraviolet absorption maximum at 240 mμ in 3 hr. to 10% of its original intensity. Chromatography of the reaction product gave a mixture of unchanged starting material and pregnenolone acetate. Elution with more polar solvents gave some gum followed by a gummy crystalline material eluted by 99 : 1 ether : methanol. The latter was shown by thin layer chromatography to be a mixture, and re-chromatography, followed by re-crystallisation did not give a sharp-melting product. (This experiment was repeated several times and it was not found possible to isolate a pure compound from this fraction. However, on one occasion another crystalline compound was isolated, in very poor yield from an earlier fraction, which apparently had no keto-group and no hydroxyl group. It melted sharply (195 - 199°) and had $[\alpha]_D$ - 46.7°. Unfortunately the yield was small and the compound could not be isolated in other irradiation experiments. The identity of this compound is, therefore, obscure). The polar material gave, on oxidation, a carboxylic acid of which the structure is not known.

Irradiation of pregnadienolone acetate in ethyl acetate for 4 hr.

caused almost complete disappearance of the ultraviolet absorption maximum at 240 mμ, and chromatography of the product gave pregnenolone acetate as the only crystalline product, in about 20% yield. Irradia:tion in tertiary butanol likewise caused a relatively slow change in the ultraviolet absorption maximum, the intensity of the peak falling to 30% of its original value in 5.5 hr. The only crystalline product was a mixture of starting material with pregnenolone acetate. Irradia:tion in cyclohexane gave, after 7 hr., a 28% yield of pregnenolone acetate as the only crystalline product.

Irradiation in acetic acid for 4 hr. causes little change in the ultraviolet spectrum. From the reaction mixture the starting material can be recovered in more than 70% yield, together with a gum which consists of at least eight compounds.

Irradiation of pregnadienolone acetate in a mixture of cyclo:pentanol and cyclohexane gives pregnenolone acetate, and gives a small yield of what is probably the adduct (CCII)



(CCII)

although there was insufficient material to characterise it fully.

Irradiation of 3β-acetoxy-16-methylpregn-5, 16-dien-20-one ("16-methylpregnadienolone acetate") (CCIII) in ethanol or in

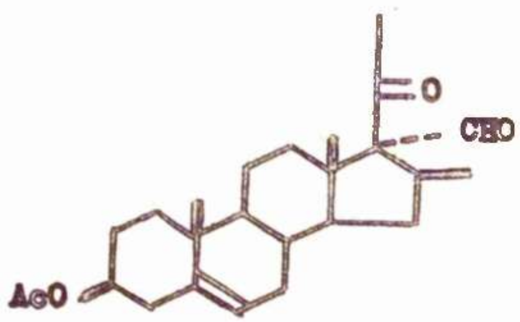
(CCIII) (CCIV)

isopropanol, under similar conditions to those described above for pregnadienolone acetate, caused a similar rapid decrease in the intensity of the ultraviolet absorption maximum at 252 mμ. After 1.5 hr., the value of the extinction coefficient had decreased from about 10,000 almost to zero.

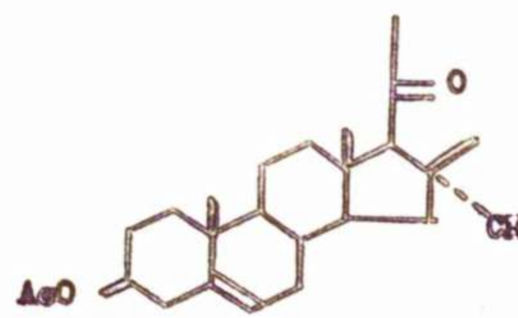
Evaporation of the solvent gave, in both cases, a crystalline product which was shown by thin layer chromatography to be almost homogeneous. Recrystallisation from methanol gave, in both cases, pure 3β-acetoxy-16β-methylpregn-5-en-20-one (CCIV) ("16β-methyl-pregnenolone acetate"), identical with an authentic sample (kindly provided by Dr. C. L. Hewett of Organon Laboratories Ltd.). This was the only crystalline product.

Irradiation of 16-methylpregnadienolone acetate in methanol gave a rather more complex reaction. After 8 hr., the ultraviolet absorption maximum at 250 mμ had disappeared, and chromatography of the crude reaction mixture on alumina gave 16β-methylpregnenolone acetate, identical with an authentic sample, in about 40% yield. More polar fractions gave a crystalline solid (in about 35% yield) which melted at 197 - 202° but which was shown by thin layer chromatography to consist of two compounds. Repeated chromatography of the mixture did not effect any clear separation, and recrystallisation did not improve matters.

However, oxidation of the mixture with 8-N chromic acid in acetone gave a neutral component and an acidic component. The neutral product was shown by thin layer chromatography to be a mixture of two compounds, and the nuclear magnetic resonance spectrum indicates that it is a mixture of two aldehydes (peaks at τ 0.09 and τ 0.21 corresponding to C<u>H</u>O). It is suggested that the two aldehydes may be (CCV) and (CCVI)

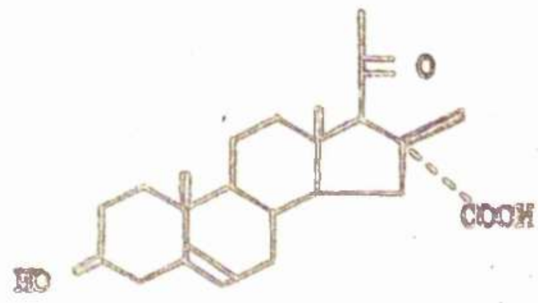


(CCV)



(CCVI)

The acidic fraction from the oxidation reaction seems to be a pure compound, namely 3β-hydroxy-16β-methylpregn-5-en-20-one-16α-carboxylic acid (CCVII). (The acetate group has been removed



(CCVII)

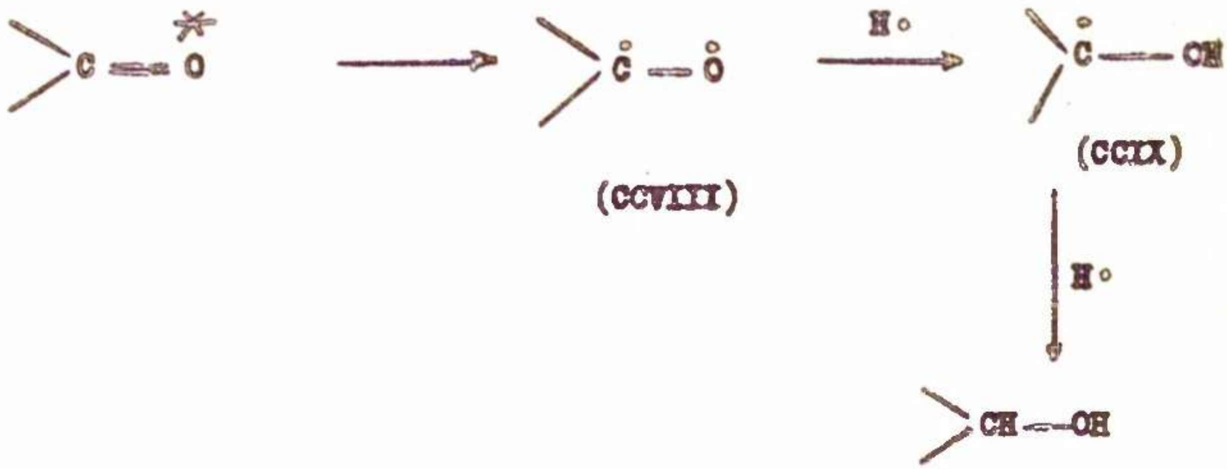
by the alkali used to extract the carboxylic acid).

The acid itself is not sufficiently soluble for the running of an n.m.r. spectrum, but the methyl ester was prepared on a small scale by treating the n.m.r. sample of the acid with an excess of diazomethane, followed by evaporation of the excess of the reagent under reduced pressure. The n.m.r. spectrum of the methyl ester shows peaks at τ 6.25 (methyl ester), 7.87 (17-acetyl group), 8.61 (16β-$C\underline{H}_3$), 8.97 (19-$C\underline{H}_3$) and 9.03 (18-$C\underline{H}_3$). The peak at τ 8.61 is sharp, indicating that there is no 16-hydrogen atom.

It is believed, on the basis of the evidence mentioned above, that in the irradiation of 16-methylpregnadienolone acetate in methanol, addition of $-CH_2OH$ occurs at positions -16 and -17 in the steroid nucleus. Possibly similar addition at C-17 occurs in the case of the irradiation of pregnadienolone acetate in methanol, which would account for the difficulty encountered in obtaining a pure sample of the adduct.

The net result in most of the irradiation reactions described in this section is reduction of the Δ^{16}-double bond in the steroid molecule, together with addition of the elements of an alcohol, in many cases, across the double bond, the reactions being stereospecific. Now the addition of alcohols to double bonds by photochemical means is rare, but Urry, Stacey, Huyser and Juveland[90] have reported the addition of ethanol to hex- 1 -ene and of isopropanol to oct - 1 -ene to give octan -2- ol and 2-methyldecan -2- ol respectively. These reactions proceed slowly and in poor yield, whereas the photochemical additions and reductions described here proceed rapidly and in fairly good yield. Since the reactions proceed as well in pyrex as in quartz, it seems likely that the $n \longrightarrow \pi^*$ transition associated with the keto-group is responsible for the formation of the initial activated species, and of the diradicals which react to give the products.

Photoreduction of saturated carbonyl compounds by alcohols has, of course, been described in the literature many times[91], and it is thought that in this type of reaction the diradical represented by (CCVIII) abstracts a hydrogen atom from the solvent

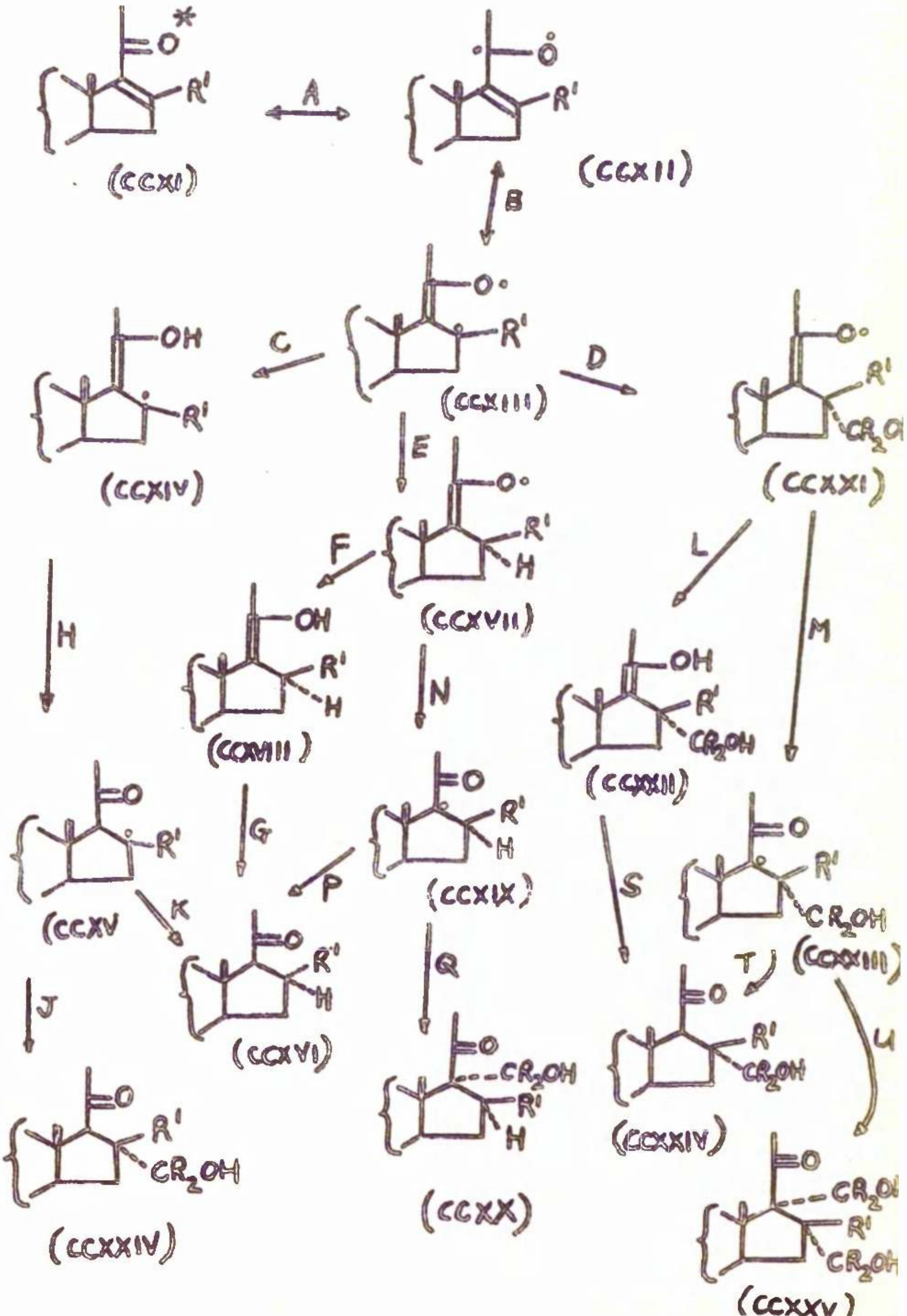


(CCVIII) (CCIX) (CCX)

to give the radical (CCIX) which can then abstract a further hydrogen atom to give the alcohol (CCX). (It is possible, of course, that the radical produced by the abstraction of a hydrogen atom from the solvent may enter into the reaction).

It is worthwhile to consider some of the possible mechanisms which could occur when a Δ^{16}-20-ketone is irradiated in an alcoholic solvent. (See Chart (3)).

Chart 3.



Initially the ketone absorbs radiation and is transformed into an activated species, inadequately represented by (CCXI). This can give the diradical (CCXII) which can rearrange by pathway (B) to give a diradical (CCXIII) in which the centres of unpaired electron-spin are further separated than in (CCXII) and which would be expected to be correspondingly more stable. The diradical (CCXIII) can be envisaged as reacting in three possible ways, viz:

(1) Abstraction of a hydrogen atom from the solvent to give (CCXIV), and the radical $\cdot CR_2OH$ (pathway (C)). Ketonisation of the enol (CCXIV) (pathway (H)) gives the radical (CCXV) which can either react with the radical $\cdot CR_2OH$ (pathway J) or else by further abstraction of a hydrogen atom from a solvent molecule to give the reduction product (CCXVI) (pathway K).

(2) Abstraction of a hydrogen atom by the alternative pathway (E) could give the radical (CCXVII) which can either abstract another hydrogen atom by pathway (F) to givethe enol (CCXVIII) which ketonises to give the reduction product (CCXVI), or else (CCXVII) can rearrange by pathway (N) to give the radical (CCXIX) which could abstract a hydrogen atom from the solvent (pathway (P)) to give the reduction product (CCXVI), or, less probably, could react with the radical $\cdot CR_2OH$ to give the 17-addition product (CCXX) by pathway (Q).

(3) The diradical (CCXIII) could react with a $\cdot CR_2OH$ radical by pathway (D) to give the radical (CCXXI) which could react by

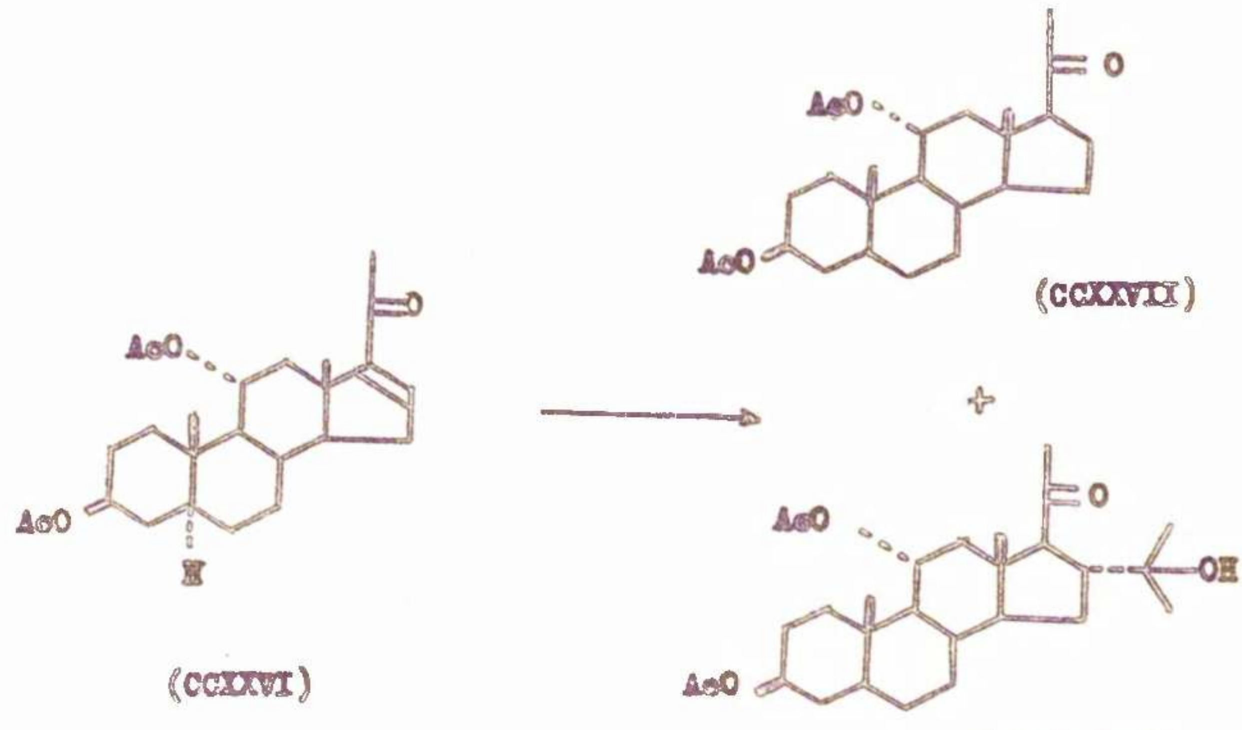
pathway (L) to give the enol (CCXXII) by hydrogen abstraction, or by pathway (M) to give the radical (CCXXIII). Both these latter radicals could give rise to the addition product (CCXXIV) by pathways (S) and (T) - namely ketonisation in the case of (CCXXII) and hydrogen abstraction in the case of (CCXXIII). It is remotely possible that the radical (CCXXIII) could react with a $\cdot CR_2OH$ radical (pathway (U)) to give the 16, 17 di-addition product. (CCXXV).

It will be observed that the addition product (CCXXIV) could be formed by four of the sequences outlined above, and the reduction product (CCXVI) by three. The principal reaction products isolated in the reactions described in this section can be considered as being formed by the sequences (C, H, J) and (C, H, K). Where (R^1 = Me), that is in 16-methylpregnadienolone acetate, (CCIII), it is considered that steric factors prevent the addition of $\cdot CR_2OH$, (K) except where (R = H) in the case of the radical derived from methanol.

The sequence (E, F, G) may occur, as may (E, N, P), in all cases. The sequence (E, N, Q) could account for substitution at C -17 such as is believed to occur in the case of irradiation of the Δ^{16}-20-ketones in methanol, but is considered to be difficult on account of steric factors. Similarly, the pathway (D) will be less likely to be followed where (R^1 = Me) in the case of 16-methylpregnadienolone acetate, even when the solvent is methanol, and pathway (U) even less likely, though it may be possible for a product such as (CCXXV) to be formed.

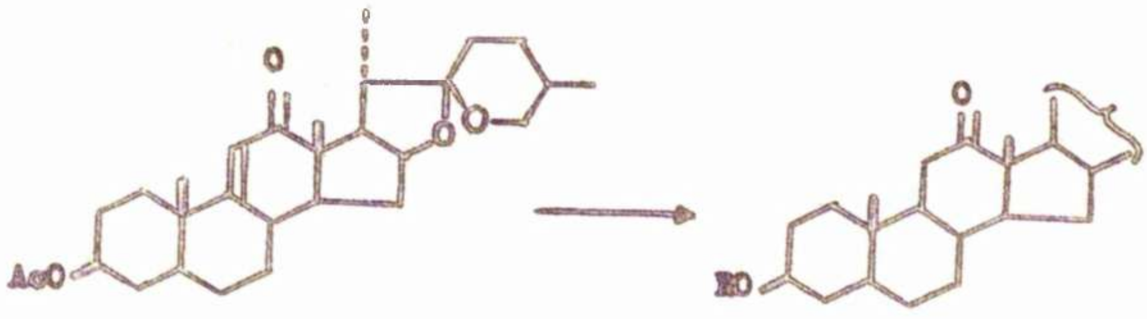
The scheme of reactions outlined here is not intended to be an exhaustive account of all the reactions and rearrangements possible when a Δ^{16}-20-ketone is irradiated. It is quite possible for dimerisation to occur at many of the stages postulated above, and other side-reactions may also occur. However, the sequences outlined here seem to account satisfactorily for the products isolated from the irradiations of Δ^{16}-20-ketones.

Other α,β-unsaturated ketones were also irradiated - 3β, 11α-diacetoxy-5α-pregn-16-en-20-one (CCXXVI) on irradiation in isopropanol, for example, gave the reduction product (CCXXVII) and the photo-addition product (CCXXVIII) expected by analogy with the irradiation of pregnadienolone acetate in the same solvent.



(CCXXVI) (CCXXVII) (CCXXVIII)

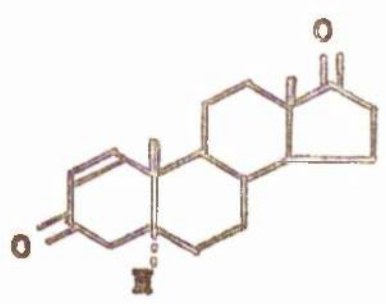
It was found, too, that when 9(11)-dehydrohecogenin 3β-acetate (CCXXIX) was irradiated under reflux either in dioxan or in ethanol, a rapid reaction occurred and the known compound hecogenin acetate (CXLIV; R = Ac) was isolated as the only crystalline product.



(CCXXXX) (CXLIV)

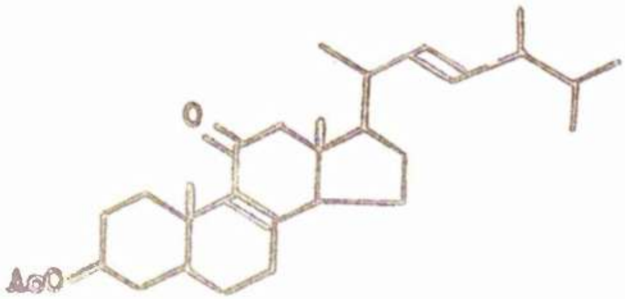
(Hecogenin is known to have a 9α-hydrogen, and the reduction of the $\Delta^{9(11)}$-12-ketone to hecogenin acetate is consistent with "rear-attack" by a solvent molecule on a radical at C-9 (c.f. Chart 3 above). No addition of solvent has been detected, and an absence of such addition in the case of irradiation in ethanol could be explained by steric hindrance.

Ultraviolet irradiation of 5α-androst-1-en-3,20-dione (CCXXX) in methanol, ethanol or isopropanol for periods of 1.5 - 2 hr. caused no appreciable change either in the ultraviolet spectrum or the thin-layer chromatogram of the reaction solution.

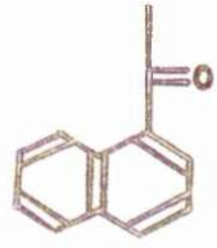


(CCXXX)

Similarly, 3β-acetoxyergosta - 8(9), 22-dien-11-one (CCXXXI) was recovered unchanged after irradiation for 3 hr. in ethanol.



(CCXXXI)

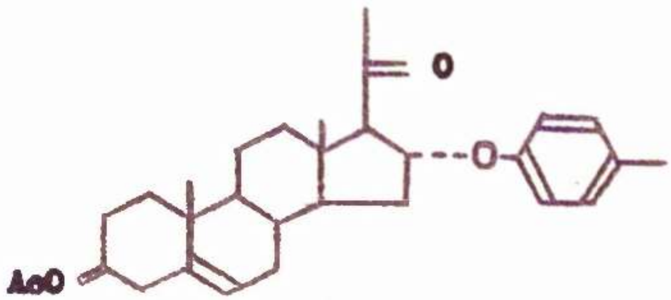


(CCXXXII)

A solution of α-acetylnaphthalene (CCXXXII) in ethanol was unchanged on irradiation, also, the starting material being recovered.

It is interesting to note that the Δ^{16}-20-ketones are capable of removing hydrogen atoms from such a great variety of solvents - even cyclohexane - when subjected to ultraviolet irradiation. (Such reactivity has been remarked by Ciamician and Silber[8] in the case of quinones).

It seemed of interest to examine the products of irradiation of pregnadienolone acetate (CLXXXIX) in a solution containing a phenol, to see if any addition of the phenolic molecule to the double bond in the Δ^{16}-20-ketone could be detected. When such an irradiation was carried out (a solution of the steroid and para cresol in cyclohexane being used), chromatography of the residual gum obtained from the reaction mixture after removal of the remaining cresol and solvent gave, on one occasion, a small yield (about 3%) of a substance which, from its infrared spectrum, could be the compound (CCXXXIII).

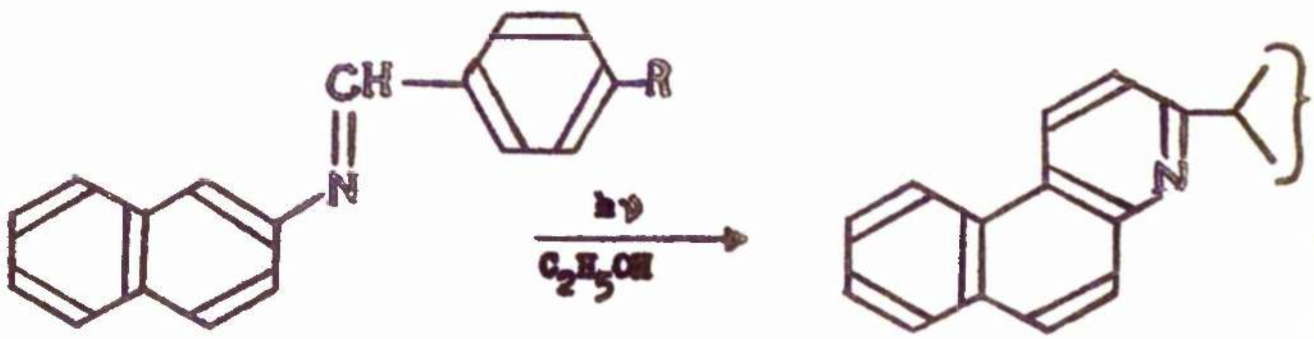


(CCXXXIII)

The compound was neutral, and showed a strong peak in the infrared spectrum at 817 cm^{-1} which could be due to a 1, 4-disubstituted benzene ring. The spectrum showed the presence of a saturated ketone (peak at 1715 cm^{-1}) and the absence of a hydroxyl group. Unfortunately, this result could not be repeated, and there was insufficient material for further studies.

In view of the known addition of negatively charged species (e.g. cyanide ions) at C -16 in Δ^{16}-20-ketones (vide supra, p. 74) an attempt was made to synthesise compound (CCXXXIII) by treatment of pregnadienolone acetate with the potassium salt of para cresol. This, too, was unsuccessful.

In view of the addition reactions described here, it is interesting to note the reaction recently reported by Shannon, Silberman and Sternhell[92] involving the addition of a C_2-fragment to a Schiff's base (CCXXXIV) on irradiation in ethanol to give the fully aromatic system (CCXXXV).



(CCXXXIV) (CCXXXV)

The nature of this reaction is not immediately apparent, although it may bear some relationship to the photoaddition reactions described above.

In the photoaddition and reduction reactions described above, no products have yet been obtained which correspond to simple oxidation or dimerisation of the solvent. Since the concentration of the steroid is usually of the order of 1 - 2%, and since the solvent does not itself absorb radiation in most cases, the concentration of any such products in the reaction solution would be low, and they would be difficult to detect.

E X P E R I M E N T A L.

EXPERIMENTAL

Unless otherwise stated, optical rotations were determined for chloroform solutions, ultraviolet spectra were obtained with ethanolic solutions and infrared spectra with potassium chloride discs on a Grubb Parsons S 4 instrument fitted with sodium chloride optics. M.ps. were determined on a Kofler block.

The alumina used for chromatography was neutralised and deactivated with 10% aqueous acetic acid (5 ml. per 100 g.).

Extracts were dried over anhydrous sodium sulphate before evaporation unless stated otherwise.

Nuclear magnetic resonance spectra were, unless otherwise stated, obtained on carbon tetrachloride solutions using a Perkin Elmer instrument operating at 40 Mc./s. Tetramethyl silane was used as an internal standard and peak positions are recorded on the τ scale[93].

Ultraviolet Irradiation of Hecogenin Acetate

In preliminary experiments on a small scale, solutions of hecogenin acetate in dry dioxan (5 g. per 100 ml.) were irradiated in quartz flasks by means of a 500 w. Hanovia medium pressure mercury lamp (Type U.V.S.500). Absence of air was found to be essential and was ensured by one of two procedures; (a) either the reaction mixture was allowed to reflux by placing the flask over the lamp, and passing a slow stream of purified oxygen-free nitrogen over the surface of the liquid, or (b) the reaction was conducted in a closed flask, from which the air had been removed by several evacuations and refillings with purified nitrogen; in this case the flask was placed alongside the lamp and was cooled by a stream of cold water.

On a large scale (procedure (c)) a Hanovia photo-chemical reaction apparatus was used. In this, the 500 w. medium pressure mercury lamp was placed in a double walled quartz thimble which fits inside the reaction flask and through which cold water circulates. The reaction mixture was stirred, and purified oxygen-free nitrogen was slowly bubbled through it. When hecogenin acetate (250 g.) in dioxan (9 l.) was treated thus, the solution showed a change in $(\alpha)_D$ from $\pm 0^\circ$ to -39.4° during 8 hr., thereafter remaining constant. After 9.25 hr. irradiation the dioxan solution was evaporated, and the solid product crystallised from methanol containing a little pyridine to give 3β-acetoxy-12,13-seco-12-oxo-5α, 25D-spirost-13-en (lumihecogenin acetate)

(CXLV), in three crops, m.p. 140-144°. Total yield 201 g. (80%). A sample recrystallised from methanol had m.p. 143-147°, $(\alpha)_D$ - 46° (c. 1.0) $\lambda_{max.}$ 204 mμ (ε ,4800), $\nu_{max.}$ 2740 (CHO), 1739 (OAc), 1709 (CHO), 1412 (CHO), 1240 cm.$^{-1}$ (OAc) τ 0.50 (CHO), 5.45 (3α-H + 16α - H), 6.40 and 6.75 (26 - H_2), 8.00 (CH_3.CO + 18 - CH_3), 9.18 (19 - CH_3). It was identical with a sample prepared by McMeekin.

In a similar experiment using hecogenin acetate (100 g.) and dioxan (7 l.) the same change of specific rotation was noted in the first 8 hr. irradiation. Thereafter the course of the reaction was followed by removing a portion of the solution, evaporating it and observing the infrared spectrum of the residue in carbon tetrachloride. The peak at 1709 cm.$^{-1}$ decreased in intensity and disappeared completely in 36 hr. The dioxan solution was passed through a column of alumina (not deactivated) to remove traces of peroxides, and evaporated. Crystallisation of the residue from methanol gave 3β-acetoxy-12α, 14α-epoxy-5α, 25D-spirostan, (photohecogenin acetate) (CLXXIV, R = Ac) (30 g.). A sample recrystallised from methanol had m.p. 205-206°, $(\alpha)_D$ - 38.7° (c.1.61) (Found: C, 73.7; H, 9.4. $C_{29}H_{44}O_5$ requires C, 73.7; H, 9.3%). $\nu_{max.}$ 1739, 1242 cm.$^{-1}$ R.D. (in MeOH) negative plain curve. Identical material was obtained by irradiation of lumihecogenin acetate in dioxan by method (a) for 39 hr. or by method (b) for 20 hr.

<u>Oxidation of Lamihecogenin Acetate.</u> Lamihecogenin acetate (10.5 g.) in acetone (700 ml.) was treated with 8N-chromium trioxide in aqueous sulphuric acid (15 ml.) at room temperature for 5 min. Aqueous sodium hydrogen sulphite and dilute hydrochloric acid were added, and the solution extracted three times with ether (100 ml. portions). The extracts were washed with water, dilute aqueous potassium hydroxide (three times), water, and dried. Evaporation of the extracts gave 14α-hydroxyhecogenin acetate (CLVI; R = Ac), as rods from acetone, m.p. 225-229° or as needles from methanol, m.p. 231-235°, $(\alpha)_D - 6°$ (c, 0.74). (Found: C, 70.0; H, 9.3. $C_{29}H_{44}O_6 \cdot 0.5\ CH_3OH$ requires C, 70.2; H, 9.1%). $\nu_{max.}$ (dried sample) (in CCl_4) 3540 (bonded OH), 1739 (OAc), 1706 (12 >C = O) and 1250 $cm.^{-1}$ (OAc). τ 5.65b (3α-H + 16α-H), 8.04 ($CH_3 \cdot CO$), 9.0 and 9.18 (19 - CH_3 and 18 - CH_3). R.D. (in MeOH); $10^{-2}\ (\phi)_{312.5}$ + 62° (peak); $10^{-2}\ (\phi)_{270}$ - 96° (trough); a + 158°.

Acidification of the alkaline washings and extraction with ether afforded a syrup, which was boiled with methanol (100 ml.) containing potassium hydroxide (2 g.) and water (10 ml.) for 1 hr. Dilution with water, acidification, and extraction with ether gave a syrup (960 mg.). Crystallisation from aqueous acetone gave anhydro-hecolic acid (CXLVIII), m.p. and mixed m.p. with an authentic sample 223-226°, having an infrared spectrum identical with that of an authentic sample.

3β. 14α-Dihydroxy-5α, 25D-spirostan-12-one (CLVI; R = H) prepared by saponification of 14α-hydroxyhecogenin acetate formed prisms from acetone-isopentane, m.p. 270-272°, $(\alpha)_D$ + 16.4° (c, 0.94). $\nu_{max.}$ 3520 (OH) 1708 cm.$^{-1}$ (12 > C = O). The infrared spectrum was identical with that of a sample prepared by McMeekin.

Reduction of Lumihecogenin Acetate with Lithium Aluminium Hydride. Lumihecogenin acetate (280 mg.) was refluxed with lithium aluminium hydride (220 mg.) in dry ether for 5 min. Excess of reagent was destroyed by addition of wet ether. Addition of dilute acid and extraction of the product in the usual way, gave a clear syrup, which on trituration with acetone-isopentane gave anhydrohecolyl alcohol (CXLVI), m.p. 180-182°, undepressed by admixture of an authentic sample, $(\alpha)_D$ - 53° (c, 0.83) having an infrared spectrum identical with that of an authentic specimen. Rothman, Wall, and Eddy[64] report m.p. 174-176°.

14α-Hydroxy-5α, 25D-spirostan-3, 12-dione (CLVIII). -
(a) Anhydrohecolyl alcohol (CXLVI) (130 mg.) in acetone (10 ml.) was oxidised with 8N chromium trioxide in aqueous sulphuric acid (2 ml.) as described above. The diketone, crystallised from acetone isopentane, had m.p. 259-261°, $(\alpha)_D$ + 31.5° (c, 1.08). The infrared spectrum was identical with that of a sample prepared by McMeekin.

(b) 14α-Hydroxyhecogenin (CLVI; R = H) (240 mg.) in acetone (50 ml.) treated with 8N chromic acid reagent (0.5 ml.) for 5 min. gave the diketone (221 mg.), m.p. 256-259°, identical in all respects with material prepared by method (a), and showing no m.p. depression on admixture.

14α-Hydroxyhecogenin Acetate Oxime. - 14α-Hydroxyhecogenin acetate (1.0 g.) and hydroxylamine hydrochloride (1.0 g.) in pyridine (16 ml.) were warmed on a steam bath for 3 hr. Addition of water and extractio with ether afforded the oxime, crystals from chloroform-methanol, m.p. 287-291° (change of crystalline form at 230°) $(\alpha)_D \pm 0°$ (c,0.49) (Found: C,69.5; H,9.05; N, 3.2. $C_{29}H_{45}NO_6$ requires C,69.2; H, 9.0; N,2.8%). $\nu_{max.}$ 3400 (OH), 1724 (OAc), 1638 (>C = NOH) and 1240 cm.$^{-1}$ (OAc). Saponification afforded the oxime of 14α-hydroxy-hecogenin, crystals from methanol, m.p. 232-236°, $(\alpha)_D$ - 0.8° (c, 0.51) (Found: C,69.5; H,9.6; N, 3.3. $C_{27}H_{43}NO_5$ 0.5CH_3OH requires C,69.2; H, 9.5; N, 2.9%). $\nu_{max.}$ 3425 (OH), 1638 cm.$^{-1}$ (>C = NOH).

3β, 14α-Dihydroxy-5α, 25D-spirostan (CLXIII: R = H) - 14α-Hydroxyhecogenin acetate (5.73 g.) in ethylene glycol (100 ml.) containing hydrazine hydrate (100%; 5 ml.) was boiled for 45 min. After the mixture had been cooled, potassium hydroxide (20 g.) in water (20 ml.) was added and the mixture boiled under reflux for 20 min. The water and excess of hydrazine were distilled off and the residue was refluxed for 4 hr. After the mixture had cooled, water was added, and the mixture was made acid with dilute hydrochloric acid. The product isolated by chloroform extraction in the usual way was a solid (5.13 g.). Crystallisation from acetone gave the diol (CLXIII; R = H) m.p. 211-212°, $(\alpha)_D$ - 58.8° (c, 0.47). (Found: C, 75.2; H, 10.1; $C_{27}H_{44}O_4$ requires C, 75.0; H, 10.25%). $\nu_{max.}$ 3440 (OH). Acetylation in the normal way gave the 3β-acetate (CLXIII; R = Ac), crystallising from methanol, m.p. 187-189°, $(\alpha)_D$ - 60.8 (c, 0.56) (Found: C, 73.4; H, 9.4. $C_{29}H_{46}O_5$ requires C, 73.4; H, 9.7%). $\nu_{max.}$ (in CCl_4) 3590 (OH), 1754 (OAc) 1242 cm.$^{-1}$ (OAc).

The 3β-benzoate (CLXIII; R = Bz) crystallised from chloroform acetone, m.p. 219-224°, $(\alpha)_D$ - 59.5° (c, 0.49) (Found: C, 76.0; H, 9.1. $C_{34}H_{48}O_5$ requires C, 76.1; H, 9.1%). $\nu_{max.}$ 1710, 1600, 1579, 1277 cm.$^{-1}$.

3β-Acetoxy-14α-hydroxy-5α-pregn-16-en-12,20-dione (CLV) - 14α-Hydroxyhecogenin acetate (2.1 g.) was refluxed with acetic acid (4 ml.) and acetic anhydride (2.2 ml.) for 2 hr. Water was added, and the mixture extracted with ether. The extracts were washed with aqueous alkali, dried and evaporated. The product (2.62 g.) was refluxed with 10% methanolic potassium hydroxide (100 ml. for 2 hr. The product (1.65 g.) isolated by ether extraction was acetylated by treatment with acetic anhydride (4 ml.) and pyridine (25 ml.) at room temperature overnight. The acetylated material (1.66 g.) isolated in the usual way was dissolved in acetic acid (16 ml.) and treated with a solution of chromium trioxide (436 mg.) and sodium acetate (1 g.) in 90% aq. acetic acid (28 ml.). The mixture was kept at room temperature for 2 hr. Excess of oxidant was removed by adding dilute mineral acid and aqueous sodium hydrogen sulphite. Isolation by ether extraction afforded a brown syrup (1.51 g.). This was dissolved in 1 : 1-light petroleum-benzene (40 ml.) and treated with active alumina (10 g.) at room temperature overnight. The alumina was filtered off and washed with ether. The filtrates were evaporated to give a yellow syrup (1.30 g.). This was dissolved in benzene and chromatographed on alumina (60 g.). Elution with benzene gave unchanged 14α-hydroxyhecogenin acetate (187 mg.) followed by oily material (812 mg.). Ether eluted 3β-acetoxy-14α-hydroxy -5α-pregn-16-en -12,20-dione (CLV), (181 mg.) which crystallised from methanol as rods, m.p. 255-256° (change of crystalline form at 210° to needles), $(\alpha)_D$ + 50.8° (c, 0.58) (Found: C,71.7; H,8.3; $C_{23}H_{32}O_5$ requires C,71.1; H, 8.3%). $\lambda_{max.}$ 228.5 mμ (ε, 7320), $\nu_{max.}$ 3620 (OH), 1740 (OAc) 1693 (12 > C = O), 1670 (20 > C = O), 1609 (C = C), 1235 $cm.^{-1}$ (OAc).

3β-Acetoxy-14α-hydroxy-12,13-seco-5α, 25D-spirostan-12-oic acid 12 → 14-lactone (CLXVI; R = Ac). - 14α-Hydroxyhecogenin acetate (CLVI; R = Ac) (2.0 g.) was dissolved in dioxan (100 ml.) and irradiated in a quartz flask at reflux temperature using a 500W. mercury lamp (method (a) above). The specific rotation changed from -5° to -20° during 5 hr. and thereafter remained constant. After 7 hr. the dioxan was removed *in vacuo* and the residue crystallised from methanol-acetone to yield the spirolactone. (CLXVI; R = Ac), m.p. 247-252°, $(\alpha)_D$ - 22.3° (c, 1.26), -21.0° (c, 0.33 in dioxan) (Found: C, 71.3; H, 9.3. $C_{29}H_{46}O_6$ requires C, 71.3; H, 9.1%). $\nu_{max.}$ (in CCl_4) 1738, 1239 cm.$^{-1}$.

Saponification in the usual way in refluxing methanol gave 3β, 14α-dihydroxy-12,13-seco-5α,25D-spirostan-12-oic acid 12 ⟶ 14 lactone (CLXVI; R = H) crystallising from chloroform acetone, m.p. 195-200°, $(\alpha)_D$ - 19.3° (c, 0.59) (Found: C, 71.4; H, 9.5. $C_{27}H_{44}O_5 \cdot C_3H_6O$ requires C, 71.4; H, 9.6%). $\nu_{max.}$ 3390 (OH), 1724 cm.$^{-1}$ (6-membered ring lactone).

Conversion of the Spirolactone into anhydrohecolyl alcohol. - The spirolactone acetate (CLXVI; R = Ac) (1.55 g.) in tetrahydrofuran (100 ml.) was treated with lithium aluminium hydride (700 mg.) and the solution refluxed for 3.5 hr. After destroying the excess of reagent with wet tetrahydrofuran, the product was isolated with ether in the usual way. It formed an amorphous mass (1.36 g.). A portion of this (990 mg.) was dissolved in methanol (50 ml.) and 70% aqueous perchloric acid (1 ml.) was added, and the solution was allowed to stand overnight. The product (650 mg.), isolated in the usual way by addition of water and extraction with ether, crystallised from acetone to give anhydrohecolyl alcohol (CXLVI) m.p. 173-177°, undepressed on admixture with authentic material and having an infrared spectrum identical with that of authentic material.

14α-Hydroxyhecogenin Acetate Cyanohydrin (CLXIV) - To a solution of 14α-hydroxyhecogenin acetate (CLVI; R = Ac) (6.0 g.) in chloroform (45 ml.) and glacial acetic acid (17 ml.) cooled to 0° was added a suspension of potassium cyanide (20 g.) in methanol (72 ml.) and the mixture was stirred for 2.5 hr. Water was added and the chloroform (which still contained some acetic acid) gave 3β-acetoxy-12β, 14α-dihydroxy-12α-cyano-5α,25D-spirostan (CLXIV), as crystals from methanol (4.6 g.), m.p. 245-267° dec. (change of crystalline form at 238°), $(\alpha)_D$ - 11.5° (c, 0.61) (Found: C,69.5; H, 9.1; N, 2.7%. $C_{30}H_{45}NO_6$ requires C, 69.9; H, 8.8; N, 2.7%). $\nu_{max.}$ 3575 and 3370 (OH), 2250 (C≡N), 1710 (OAc), 1242 cm.$^{-1}$ (OAc).

Action of Thionyl Chloride in Pyridine on 14α-Hydroxyhecogenin Acetate Cyanohydrin. - The cyanohydrin (CLXIV) (1.2 g.) in dry pyridine (20 ml.) was cooled to 0° and treated with pure thionyl chloride (0.8 ml.). The mixture was allowed to stand overnight at room temperature, and was poured on to crushed ice. The precipitated solid was filtered off, and dissolved in chloroform. The chloroform solution was washed with dilute hydrochloric acid, water, and aqueous potassium hydrogen carbonate, and finally water. It was dried and evaporated. The residue crystallised from chloroform-methanol gave 3β-acetoxy-13β-cyano-17a-methylene-C-nor-D-homo-5α, 25D-spirost-14-en (CLXV) (0.564 g.) as crystals from chloroform-methanol, m.p. 244-248° (change of crystalline form at 230-236°), $(\alpha)_D$ + 2.9° (c, 0.56) (Found: C,75.0; H, 8.0;

N, 2.7. $C_{30}H_{41}NO_4$ requires C, 75.1; H, 8.6; N. 2.9%).

$\nu_{max.}$ 3090 (>C = CH_2), 2240 (C ≡ N), 1739 (OAc) 1665 and 1620 (C = C) and 1240 cm.$^{-1}$ (OAc).

Reduction of 14α-Hydroxyhecogenin Acetate with Lithium Aluminium Hydride. - 14α-Hydroxyhecogenin acetate (CLVI; R = Ac) (5 g.) and lithium aluminium hydride (2.5 g.) in dry tetrahydrofuran (150 ml.) were refluxed for 3 hr. The excess of the hydride was destroyed by addition of wet tetrahydrofuran, and the product (4.53 g.) was isolated from the acidified solution by ether extraction. The amorphous solid was dissolved in pyridine (35 ml.) and treated with acetic anhydride (8 ml.). The solution was kept at room temperature for 6 hr. and was then poured into water. The amorphous product (4.7 g.) isolated in the usual way was dissolved in benzene and absorbed on to a column of alumina (250 g.). Elution with benzene gave tigogenin acetate (191 mg.), m.p. 208-212°, $(\alpha)_D$ - 72° (c, 0.64), a known impurity in the hecogenin acetate used as starting material. Elution with benzene ether mixture gave material which failed to crystallise (2.93 g.) and which was not investigated further. Elution with ether gave 3β-acetoxy-12α, 14α,-dihydroxy-5α,25D-spirostan (CLXIX) (R = Ac, R' = H), as crystals from methanol (1.35 g.) m.p. 219-222.5° (change of crystalline form at 199°), $(\alpha)_D$ - 17.4° (c, 0.98) (Found: C, 70.7; H, 9.3; $C_{29}H_{46}O_6$ requires C, 71.0; H, 9.45%) $\nu_{max.}$ (in CCl_4) 3620, 3510 (OH), 1735 (OAc) and 1239 cm.$^{-1}$ (OAc).

Acetylation of the above monoacetate (CLXIX; R = Ac, R' = H) (1.09 g.) with pyridine (10 ml.) and acetic anhydride (3 ml.) at steam bath temperature for 3 hr. gave 3β, 12α-diacetoxy-14α--hydroxy-5α, 25D-spirostan, (CLXIX; R = R' = Ac) (1.1 g.), m.p. 223-225.5° (from methanol), $(\alpha)_D$ - 12.2° (c, 0.49) (Found: C,70.05; H, 9.0. $C_{31}H_{48}O_7$ requires C, 69.9; H, 9.0%). $\nu_{max.}$ (in CCl_4) 3545 (OH), 1739 (OAc) and 1238 cm.$^{-1}$ (OAc). A Mixture of the mono-and diacetates melted at 193-222°.

Saponification of the above monoacetate (CLXIX; R = Ac, R' = H) gave 5α,25D-spirostan-3β, 12α, 14α-triol (CLXIX; R = R' = H), m.p. 180-184° (from methanol), $(\alpha)_D$ - 48.0° (c, 0.635) (Found: C, 72.6; H,10.4. $C_{27}H_{44}O_5$ requires C, 72.3; H, 9.9%) $\nu_{max.}$ 3420 cm.$^{-1}$ (OH).

Oxidation of 3β-acetoxy-12α,14α-dihydroxy-5α, 25D-spirostan - The diol (CLXIX; R = Ac, R' = H) (49.5 mg.) in acetone (2 ml.) was treated with 8N chromium trioxide in aqueous sulphuric acid. After 5 min. standing at room temperature, the excess of reagent was removed by addition of sodium hydrogen sulphite and hydrochloric acid. The product isolated by ether extraction when crystallised from methanol gave 14α-hydroxyhecogenin acetate (CXLVI; R = Ac) (36 mg.) m.p. 231-235°, undepressed on admixture with authentic material and having an infrared spectrum identical with that of authentic material.

12α, 14α-Epoxy-5α, 25D-spirostan-3β-ol. - Photohecogenin acetate was saponified in the usual way to yield 12α, 14α-epoxy-5α, 25D-spirostan-3β-ol (CLXXIV; R = H) as diamond shaped crystals from methanol, m.p. 166-170°, $(\alpha)_D$ - 41° (c, 1.4) (Found: C, 74.6; H, 10.0. $C_{27}H_{42}O_4 \cdot 0.5\ CH_3OH$ requires C, 74.5; H, 9.9%) $\nu_{max.}$ 3410. cm.$^{-1}$

Reduction of photohecogenin acetate with lithium aluminium hydride in ether gave photohecogenin identical with material prepared by saponification.

Acetylation of photohecogenin gave photohecogenin acetate, m.p. 203-206°.

Action of Boron Trifluoride-Ether Complex on Photohecogenin Acetate. - A solution of photohecogenin acetate (CLXXIV: R = Ac) (5.0 g.) in dry benzene (60 ml.) was treated with boron trifluoride ether complex (0.4 ml., freshly redistilled) and kept at room tempera: :ture for 5 min. Water was added and the benzene layer diluted with ether was washed with aqueous potassium hydrogen carbonate, dried and evaporated. The amorphous residue (5.0 g.) was dissolved in benzene and absorbed on a column of alumina (200 g.). Elution with benzene gave, first oily material (0.793 g.) and then 12a -oxa-C-homo- -5α, 25D-spirost-14-en-3β-yl acetate. (Compound A) (CLXXIX) (1.97 g.) crystallising from methanol, m.p. 313-314°, $(\alpha)_D$ + 33.2° (c, 0.71) (Found: C, 73.7; H, 9.2. $C_{29}H_{44}O_5$ requires C, 73.7; H, 9.3%) $\nu_{max.}$ (in CS_2) 1734 (OAc), 1650 (C = C), and 1240 cm.$^{-1}$ (OAc). τ 4.60 (15-H), 5.25 (complex; 16α H + 3α-H), 6.50 (broad, 12-H_2 + 26 - H_2), 8.00 (CH_3CO) 8.98 and 9.23 (19 - CH_3 and 18 - CH_3). Elution with 19:1 benzene-ether gave unchanged photohecogenin acetate (0.533 g.). On one occasion lumihecogenin acetate was isolated here.

Elution with ether gave 3β-acetoxy-12α-hydroxy-5α, 25D-spirost-14-en (CLXXV; R = Ac) (2.574 g.) recrystallising from methanol, m.p. 235° (change of crystalline form at 230-233°), $(\alpha)_D$ + 47.6° (c, 0.63) (Found: C, 72.8; H, 9.3. $C_{29}H_{44}O_5 \cdot 0.5CH_3OH$ requires C, 72.55; H, 9.4%) $\nu_{max.}$ (in CS_2) 3545 (OH), 3060 (C = CH-), 1735 (OAc), 1645 (C = C) and 1240 cm.$^{-1}$ (OAc).

Saponification of the acetate (307 mg.) in methanol in the usual way gave a crystalline diol (273 mg.) 3β, 12α-dihydroxy-5α, 25D-spirost-14-ene (CLXXV; R = H) m.p. 133-137° . A sample recrystallised from methanol had m.p. 133-137°, $(\alpha)_D$ + 66.5° (c 0.53) $\nu_{max.}$ 3400 (OH) and 1645 (C = C) cm.$^{-1}$ (Found: C, 75.0; H, 9.8. $C_{27}H_{42}O_4$ requires C, 75.3; H, 9.8%).

Saponification of 12a-oxa-C-homo-5α, 25D-spirost-14-en-3β-yl acetate gave material, m.p. 270-290° which could not be recrystallised. Reacetylation gave back pure 3β-acetate however.

Action of Boron Trifluoride-Ether Complex on Lumihecogenin Acetate. - Lumihecogenin Acetate (CXLV) (4.93 g.) in anhydrous benzene (60 ml.) was treated with boron trifluoride ether complex (0.4 ml. freshly redistilled) at room temperature for 5 min. By isolation of the product followed by chromatography as described in the preceding experiment, there were isolated: (a) 12a-oxa-C-homo-5α,25D-spirost-14-en-3β-yl acetate (CLXXIX) (1.61 g.) m.p. 280-282° (different crystalline form from that previously described: The infrared spectra were identical however), (b) hecogenin acetate (0.72 g.) (a known impurity in the lumihecogenin acetate used), and (c) 3β-acetoxy-12α-hydroxy-5α, 25D-spirost-14-en (CLXXV; R = Ac) (2.63 g.) identical with that previously described .

<u>Oxidation of 3β-Acetoxy-12α-hydroxy-5α, 25D-spirost-14-en</u> . - 3β-Acetoxy-12α-hydroxy-5α,25D-spirost-14-en (CLXXV; R = Ac) (2.0 g.) in acetone (80 ml.) was treated with 8N chromic acid in aqueous sulphuric acid (2 ml.) and the mixture was kept at room temperature for 5 min. Addition of water, aqueous sodium hydrogen sulphite, and dilute hydrochloric acid, followed by ether extraction in the usual way gave 3β-<u>acetoxy</u>-12-<u>oxo</u>-5α,25D-<u>spirost</u>-14-<u>en</u> (CLXXVII; R = Ac) (1.82 g.) m.p. 213-215° (from chloroform-methanol), $(\alpha)_D$ + 65.4° (c, 0.69) (Found: C, 74.3; H, 9.0. $C_{29}H_{42}O_5$ requires C, 74.0; H, 9.0%), $\lambda_{max.}$ 294 mμ (ε,252) $\nu_{max.}$ 3030 (C = CH-), 1735 (OAc), 1708 (>C = O), 1635 (C = C) and 1238 cm.$^{-1}$ (OAc)

4.55 (15-<u>H</u>), 5.25 (complex-16α<u>H</u> + 3α<u>H</u>) 8.00 (C<u>H</u>$_3$.CO) R.D. (in MeOH): 10^{-2} $(\phi)_{305}$ + 63° (peak) 10^{-2} $(\phi)_{282}$ + 23° (trough); a + 40°.

This compound in dioxan solution was irradiated by ultraviolet light in the usual way. Although $(\alpha)_D$ changed from +68.5° to +7.7° in 5 hr. isolation of the product and chromatography gave only amorphous material having $(\alpha)_D$ - 17.5°.

Saponification of the foregoing acetate (1.001 g.) in methanol in the usual way gave 3β-<u>hydroxy</u>-12-<u>oxo</u>-5α, 25D-<u>spirost</u>-14-<u>en</u> (CLXXV: R = H) (930 mg.) m.p. 221-222° with prior softening.

A pure sample (recrystallised from methanol) had m.p. 221-223° (change of crystalline form above 210°) $(\alpha)_D$ + 76.2° (c 0.82). $\lambda_{max.}$ 294 mμ (ε, 210) $\nu_{max.}$ 3430, 3310 (OH) 1700 (>C = O) and 1645 (C = C) $cm.^{-1}$. (Found: C, 75.2; H, 9.5. $C_{27}H_{40}O_4$ requires C, 75.7; H, 9.4%)

3, 12-Dioxo-5α,25D-spirost-14-en, (CLXXVIII). The foregoing alcohol (506 mg.) in acetone (100 ml.) was treated with 8N Chromic acid (1 ml.) and the mixture was kept at room temperature for 5 min. Addition of water, sodium hydrogen sulphite and dilute hydrochloric acid, followed by ether extraction in the usual way, afforded 3, 12-dioxo-5α,25D-spirost-14-en (CLXXVIII) (441 mg.) m.p. 208-212°. A pure sample (recrystallised from acetone) had m.p. 210-214°, $(\alpha)_D$ + 97.2° (c 0.51) $\lambda_{max.}$ 294 mμ (ε, 239). $\nu_{max.}$ 1702 (>C = O) and 1645 (C = C) $cm.^{-1}$. (Found: C, 75.2; H, 9.25. $C_{27}H_{38}O_4$ requires C, 76.0; H, 9.0%).

Action of Perbenzoic Acid on 3β-Acetoxy-12α-hydroxy-5α,25D-spirost-14-en. - The steroid (313 mg.) was dissolved in benzene (8 ml.) and treated with a solution of perbenzoic acid in benzene (6 ml. 0.508N). After 24 hr. at room temperature the solution was diluted with ether and washed with aqueous potassium hydroxide, then water, and dried. Evaporation afforded 3β-acetoxy-12α-hydroxy-14α,15α-epoxy-5α, 25D-spirostan (CLXXVI; R = Ac) m.p. 270-274° (change of crystalline form at 255°) (from methanol), $(\alpha)_D$ - 35.6° (c, 0.52) (Found: C, 70.9;

H, 9.1. $C_{29}H_{44}O_6$ requires C, 71.3; H, 9.1%). $\nu_{max.}$ 3450 (OH), 1725 (OAc) and 1242 cm.$^{-1}$ (OAc).

Reduction of 3β-Acetoxy-12α-hydroxy-14α, 15α-epoxy-5α, 25D-spirostan with Lithium Aluminium Hydride. - The foregoing epoxide (1.69 g.) and lithium aluminium hydride (1.61 g.) in tetrahydrofuran were refluxed for 2.25 hr. Isolation by the usual procedure afforded the crude 3β, 12α, 14α-triol (1.59 g.). A portion of this (50 mg.) in acetone (5 ml.) oxidised by 8N chromic acid in aq. sulphuric acid (0.5 ml.) gave 14β-hydroxy-3, 12-dioxo-5α, 25D-spirostan (CLXXIII) (26 mg.) m.p. and mixed m.p. 252-257°, having an infrared spectrum identical with that of authentic material.

The remaining crude triol was dissolved in pyridine (20 ml.) and acetic anhydride (2 ml.) added.

The solution was kept overnight at room temperature. Isolation of the product gave 3β-acetoxy-12α, 14α-dihydroxy-5α, 25D-spirostan (CLXIX; R = Ac, R = H), m.p. 225-229° (from methanol). This material was a different crystalline form from that already recorded above. The mixture showed no m.p. depression however and the infrared spectra were identical.

3β-Acetoxy-12-oxo-14α, 15α-epoxy-5α, 25D-spirostan (CLXXVII). - A solution of 3β-acetoxy-12α-hydroxy-14α, 15α-epoxy-5α, 25D-spirostan (CLXXVI) (375 mg.) in acetone (50 ml.) was treated with 8N chromic acid (1.0 ml.) and the mixture was kept at room temperature for 5 min. Addition of water, sodium hydrogen sulphite and dilute hydrochloric acid, followed by extraction with ether in the usual way, afforded 3β-acetoxy-12-oxo-14α, 15α-epoxy-5α, 25D-spirostan (CLXXVI - a) (325 mg.)

m.p. 246-249°. A sample recrystallised from methanol for analysis had m.p. 247-249.5° (α)$_D$ + 10.4° (c 0.815). $\nu_{max.}$ 1730 (OAc), 1702 (>C = O) and 1239 (OAc) cm.$^{-1}$. (Found): C, 72.3; H, 8.95; $C_{29}H_{42}O_6$ requires C, 71.6; H, 8.7%).

Attempted Hydrogenation of 3β-Acetoxy-12α-hydroxy-5α, 25D-spirost-14-en. - Subjection of the olefine to hydrogenation using platinum oxide catalyst in ethyl acetate solution, or Raney nickel in dioxan solution resulted in no uptake of hydrogen and quantitative recovery of starting material. With platinum oxide in acetic acid solution only part of the starting material was recovered and some polar product, eluted from an alumina column by 99:1 ether-methanol, was obtained as an amorphous solid.

Ultraviolet Irradiation of 3β, 20ξ-Diacetoxy-5α-pregnan-12-one. - The procedure described by Petrow and co-workers[80] was used for the conversion of 3β-acetoxy-5α-pregnan-12, 20-dione (CLXXX) into 3β, 20ξ-diacetoxy-5α-pregnan-12-one (CLXXXI). It had m.p. 136-139° (α)$_D$ + 94.2° (dioxan). A solution of the diacetate (1.766 g.) in dioxan (180 ml.) was irradiated by method (b). During 9.5 hr., (α)$_D$ changed from (α)$_D$ + 94.2° to + 7.9°. Removal of the solvent left a oleg gum. This was dissolved in benzene and chromatographed on alumina (100 g.). Elution with benzene gave first, 3β, 20ξ-diacetoxy-C-seco-5α-pregn-13-en-12-al (CLXXXIII), (511 mg.), m.p. 124-126.5° (from di-isopropyl ether) (α)$_D$ + 5.65° (c, 0.64) (Found: C, 71.8; H, 9.4. $C_{25}H_{38}O_5$ requires C, 71.7; H, 9.15%). $\nu_{max.}$ 2720 (CHO), 1725 (>C = O), 1412 (CHO), and 1239 cm.$^{-1}$ (OAc) τ 0.5 (CHO), 5.20 (complex 3α-H + 20H) 8.05 (CH_3.CO + 13 - CH_3), 9.15 (10 - CH_3).

Subsequent benzene fractions eluted 3β, 20ξ-diacetoxy-12α. 14α-epoxy-5α-pregnan (CLXXXII) (727 mg.), m.p. 162-167.5° (from di-isopropyl ether), $(\alpha)_D$ - 1.8° (c, 0.54) (Found: C, 71.8; H, 9.3. $C_{25}H_{38}O_5$ requires C, 71.7; H, 9.15%). $\nu_{max.}$ 1730 (OAc) and 1240 cm.$^{-1}$ (OAc).

Ultraviolet irradiation of 3β-acetoxypregna-5, 16-dien-20-one. (CLXXXIX) ("Pregnadienolone acetate") in dioxan. - A solution of pregnadienolone acetate (5.0 g.) in dioxan) 200 ml.) was irradiated in a quartz flask by method (b) described above for hecogenin acetate. In 4 hr. the intensity of the peak at 240 mμ in the ultraviolet spectrum had decreased from ε 10,000 almost to zero. Irradiation was stopped and the solvent was distilled off. Chromatography of the residual gum on deactivated alumina (200 g.) gave the following fractions:

(a) 6:4 Petrol: benzene eluted material (2.20 g.) which on crystal:lisation from methanol gave 3β-Acetoxypregn-5-en-20-one ("pregnenolone acetate") (CXC) m.p. and mixed m.p. 148-152°, $(\alpha)_D$ + 14° (c 1.0). The infrared spectrum was identical with that of an authentic sample.

(b) 4:6 Petrol:benzene eluted a crystalline solid (1.10 g.) which on recrystallisation from di-isopropyl ether had m.p. 237-240°, $(\alpha)_D$ - 65.6° (c 0.58). $\nu_{max.}$ (CCl_4) 1730 (OAc), 1708 (>C = O), 1660 (C = C) and 1238 (OAc) cm.$^{-1}$. (Found: C, 72.4; 72.9% H, 10.0; 9.3%). Molecular weight: 688. τ 4.6 (C6 - $\underline{H}$) 5.3 (3α - H) 6.35 (≡ 4 protons), 7.90 ($C\underline{H}_3$.CO; ≡ 3 protons), 7.95 ($C\underline{H}_3$.COO; ≡ 6 protons).

(c) Elution with more polar solvents gave a succession of gums (total weight 1.50 g.) which defied repeated attempts at crystallisation.

<u>Ultraviolet irradiation of pregnadienolone acetate in ethanol</u> - A solution of pregnadienolone acetate (10.2 g.) in ethanol (800 ml.) was irradiated under reflux for 1.5 hr. by method (a) described above. (Two batches, 400 ml. each). The extinction coefficient of the ultraviolet absorption peak at 240 mμ had decreased during this time from ε 10,000 to zero. The solvent was distilled off and the residual gum was dissolved in benzene and chromatographed on a column of deactivated alumina (400 g.). Elution with benzene gave pregnenolone acetate (4.133 g.) which had m.p. 143-148° (from methanol), infrared spectrum identical with that of an authentic sample. Further elution with benzene gave a total of 950 mg. crystalline material which was shown to be a mixture of pregnenolone acetate and unchanged pregnadienolone acetate.

1:1 Benzene: Ether eluted a gum (1.48 g.) which did not crystallise. On standing with methanol for some days, it turned green.

99:1 Ether: Methanol eluted 3β-<u>acetoxy</u>-16α-(1'-<u>hydroxy ethyl</u>)-<u>pregn</u>-5-<u>en</u>-20-<u>one</u> (CXCII) (4.139 g.). Recrystallised from methanol it had m.p. 199-203°, $(\alpha)_D$ - 59° (<u>c</u>, 0.57) $\nu_{max.}$ (CCl_4) 3630 and

3595 (OH), 1734 (OAc), 1705 (>C = O) and 1240 (OAc) cm.$^{-1}$.
τ 7.82 ($COC\underline{H}_3$), 7.98 ($O.COC\underline{H}_3$) , 8.80 (side-chain $C\underline{H}_3$), 8.99 (19 $C\underline{H}_3$) and 9.34 (18 $C\underline{H}_3$) (Run in $CDCl_3$)
(Found: C, 74.7; H, 9.5. $C_{25}H_{38}O_4$ requires C, 74.6; H, 9.5%).

Saponification of 3β-Acetoxy-16α-(1'-hydroxyethyl)-pregn-5-en-20-one. - The steroid (347 mg.) was heated under reflux with KOH (350 mg.), methanol (25 ml.) and water (3 ml.) for 2 hr. The product was a gum which could not be crystallised.

Acetylation of 3β-acetoxy-16α-(1'-hydroxyethyl)-pregn-5-en-20-one (CXCII). - A solution of the steroid (205 mg.) in pyridine (5 ml.) and acetic anhydride (2 ml.) was warmed on the steam bath for 3 hr. It was poured into water, extracted with ether and worked up in the usual way to give a gum (181 mg.) which crystallised from di-isopropyl ether. The melting-point of the substance (141-150°) was improved by recrystallisation from methanol (143-149°) but further recrystallisation did not give a sharp-melting substance. The substance had $(\alpha)_D$ - 5.9° (c 0.68) .

3β-Acetoxy-16α-acetyl pregn-5-en-20-one (CXCIII) - A solution of 3β-acetoxy-16α-(1'-hydroxyethyl)-preg-5-en-20-one (CXCII) (252 mg.) in acetone (20 ml.) was treated with 8N chromic acid (0.25 ml.) and kept at room temperature for 5 min. After the addition of sodium bisulphite and dilute hydrochloric acid, the mixture was extracted with ether and worked up in the usual way. Evaporation of the ether extract gave 3β-acetoxy-16α-acetyl pregn-5-en-20-one (CXCIII) (210 mg.) m.p. 178-181°. A pure sample (recrystallised from methanol) had m.p. 181.5 -184°, $(\alpha)_D$ + 7.2° (c, 0.55) $\nu_{max.}$ 1734 (OAc), 1702 (>C = O) and 1235 (OAc) cm.$^{-1}$ τ 7.86 (2($COCH_3$)), 8.00 ($O.COCH_3$), 9.00 ($19.CH_3$) and 9.35 ($18.CH_3$) (Run in $CDCl_3$). (Found: C, 74.7; H, 9.2. $C_{25}H_{36}O_4$ requires C, 75.0; H, 9.1%) .

16α-Acetylprogesterone (CXCV). - A solution of 3β-acetoxy-16α- (1'-hydroxyethyl)-pregn-5-en-20-one (CXCII) (520 mg.) in methanol (40 ml.) and water (2 ml.) was heated under reflux with KOH (500 mg. for 1.5 hr. The solution was poured into water and extracted with ether in the usual way. The product was a clear gum (353 mg.). This gum was dissolved in acetone (100 ml.), was treated with 8N chromic acid (0.75 ml.) and kept at room temperature for 5 min. Methanol was then added, followed by water, and the product was isolated by extraction with ether in the usual way. It was a clear gum (303 mg.), which was dissolved in methanol (100 ml.) and warmed on the steam bath with 2-N H_2SO_4 (3 ml.) for 10 min. Isolation of the product with ether afforded a clear gum (301 mg.), which was dissolved in benzene and chromatographed on deactivated alumina (30 g.). Elution with ether-benzene (1:99) afforded 16α-acetyl-progesterone (CXCV) (172 mg.) m.p. 171-175° $(\alpha)_D$ + 158.2° (c 0.61) after recrystallisation from acetone.

A mixed melting point (m.p. 172-176°) and comparison of the infrared spectra confirmed its identity with an authentic sample[88].

Elution of the column with more polar solvents gave only a succession of gums, none of which crystallised.

Ultraviolet irradiation of pregnadienolone acetate in isopropanol. - A solution of pregnadienolone acetate (5.0 g.) in isopropanol (350 ml.) was irradiated under reflux by method (a) described above. After 1.5 hr. the extinction coefficient of the absorption maximum at 240 mμ had decreased from ε 10,000 almost to zero. Irradiation was suspended and the solvent was distilled off. The residual gum was dissolved in benzene and chromatographed on deactivated alumina (200 g.). Elution with benzene gave pregnenolone acetate (2.48 g.) m.p. 142-146° (infrared spectrum identical with that of an authentic sample).

Elution with benzene-ether (99:1 to 1:1) gave gums, totalling 652 mg., which did not crystallise.

Elution with benzene-ether (1:1) gave 3β-acetoxy-16α-(1′-hydroxyisopropyl)-pregn-5-en-20-one (CXCVI; R = Ac) (1.70 g.) m.p. 185-188°. A pure sample, recrystallised from methanol, had m.p. 186-189°, $(\alpha)_D$ + 7.25° (c, 1.21). $\nu_{max.}$ 3540 (OH), 1730 (OAc), 1705 (>C = O) and 1242 (OAc) $cm.^{-1}$. τ 7.83 ($COCH_3$), 7.97 ($OCOCH_3$), 8.88 ($C.(CH_3)_2$), 8.98 ($19.CH_3$) and 9.35 ($18.CH_3$) (Run in $CDCl_3$) (Found: C, 75.0; H, 9.9. $C_{26}H_{40}O_4$ requires C, 75.0; H. 9.7%).

3β-Hydroxy-16α-(1′-hydroxyisopropyl)-pregn-5-en-20-one (CXCVI; R = Ac). - A solution of 3β-acetoxy-16α-(1′-hydroxyisopropyl)-pregn-5-en-20-one (CXCVI; R = Ac) (1.01 g.) in methanol (30 ml.) and water (2 ml.) was heated under reflux with KOH (1 g.)

for 1.5 hr. Isolation of the product with ether in the usual way gave 3β-hydroxy-16α-(1'-hydroxyisopropyl)-pregn-5-en-20-one (CXCVI; R = Ac) (843 mg.) m.p. 227-230°. A pure sample had m.p. 229-231.5° (change of crystalline form between 220° and 228°) $(\alpha)_D$ + 18.9° (c, 0.88). $\nu_{max.}$ 3560 (OH), 1705 (>C = O) cm.$^{-1}$. (Found: C, 77.3; H, 10.45. $C_{23}H_{38}O_3$ requires C, 77.0; H, 10.2%).

16α-(1'-Hydroxyisopropyl)-progesterone (CXCIX). - A solution of 3β-acetoxy-16α-(1'-hydroxyisopropyl)-pregn-5-en-20-one (CXCVI; R = Ac) (4.1 g.) in methanol (120 ml.) and water (5 ml.) was saponified as related above by refluxing with KOH (4.0 g.) for 1.5 hr. The yield of the diol (CXCVI; R = H) was 3.54 g. The diol was dissolved in acetone (800 ml.) and treated with 8-N chromic acid (2.8 ml.) at room temperature for 5 min. Methanol and water were added and the product (principally the diketone (CXCVII)) was isolated by extraction with ether in the usual way. The yield was 3.5 g. (crude). A small sample of the product, recrystallised from petrol-benzene had m.p. 187-190° (traces up to 202°) $(\alpha)_D$ + 40.5°. $\nu_{max.}$ 3510 (OH), 1710 and 1700 (>C = O) cm.$^{-1}$. (This substance cannot be pure 16α-(1' -hydroxyisopropyl)-pregn-5-en-3,20-dione, due to its mode of preparation which will inevitably result in the formation of the progesterone by double-bond migration).

The crude product (3.4 g.) in methanol (300 ml.) was warmed on the steam-bath with 2-N H_2SO_4 (28 ml.) for 10 min. The product was isolated with ether in the usual way. It was a clear gum which crystallised from acetone giving a yield of 2.98 g., m.p. 157-220°. Of this material. 1.2 g. was dissolved in benzene and chromatographed on deactivated alumina (100 g.).

Elution with benzene-ether (4:1) gave 16α-(1'-hydroxyisopropyl)-progesterone (CXCIX) (989 mg.), m.p. 161-164°. A pure sample, recrystallised from acetone, had m.p. 168-172° $(\alpha)_D$ + 123.5° (c, 0.64 $\lambda_{max.}$ 242 mμ (ε 13,100) $\nu_{max.}$ 3450 (OH), 1705 (saturated >C = O), 1670 (unsaturated >C = O) and 1612 (C = C) cm.$^{-1}$. τ 7.81 (COCH_3) , 8.88 (C. (CH_3)$_2$), 8.98 (19.CH_3) and 9.32 (18.CH_3) (Run in $CDCl_3$). (Found: C, 77.0; H, 9.7. $C_{23}H_{36}O_3$ requires C, 77.4; H, 9.7%).

Elution with ether gave 16α-(1'-Hydroxyisopropyl)-pregn-4-en-3, 6, 20-trione. (CXCVIII) (200 mg.) m.p. 198.5 - 200° . A pure sample, recrystallised from acetone, had m.p. 199-200°, $(\alpha)_D$ + 19.8° (c, 1.075), $\lambda_{max.}$ 252 mμ, (ε 9.850.) $\nu_{max.}$ 3495 (OH), 1710 (saturated >C = O), 1680 (unsaturated >C = O), and 1610 (C = C) cm.$^{-1}$. τ 3.79 (4 - H) , 7.81 (COCH_3), 8.82, 8.85 (19-CH_3 + C (CH_3)$_2$) and 9.30 (18-CH_3) . (Found: C, 75.0; H.8.9. $C_{24}H_{34}O_4$ requires C, 74.6; H, 8.9%).

Ultraviolet irradiation of pregnadienolone acetate in methanol. - A solution of pregnadienolone acetate (5.0 g.) in methanol (350 ml.) was irradiated under reflux by method (a) described above for hecogenin acetate. After 1.5 hr. the absorption maximum at 239 mμ in the ultraviolet spectrum had disappeared, and irradiation was stopped.

The crystalline precipitate (see below) was filtered off (375 mg.), and the solvent was distilled off. The residual gum was dissolved in benzene and chromatographed on deactivated alumina (200 g.).

Elution with benzene gave pregnenolone acetate (1.76 g.) m.p. 144-148°, infrared spectrum identical with that of an authentic sample.

Elution with ether-benzene (1:4) gave a gum (1.1 g.) which did not crystallise, and which turned green on standing with methanol.

Elution with ether gave a crystalline product (0.85 g.) whose infrared spectrum was identical with that of the material crystal: :lising during the course of the reaction. It had m.p. 162-171°. A sample recrystallised from hot chloroform-methanol had m.p. 226-230°, $(\alpha)_D$ - 60.3° (c, 0.575) $\nu_{max.}$ 3540 (OH), 1734 (OAc), 1705 (>C = O), 1660 (C = C) and 1242 (OAc) $cm.^{-1}$. (Found: C, 73.06; H, 9.01%).

Elution with ether-methanol (99:1) gave a crystalline product (550 mg.) which had m.p. 197-199.5°. A sample recrystallised from methanol had m.p. 197-201.5° $(\alpha)_D$ - 44° (c, 0.58) . Thin layer chromatography, however, showed that the substance consisted of at least three different compounds. The experiment was repeated and a total of 4.05 g. of the mixture eluted by ether-methanol (99:1) was acetylated by treatment with acetic anhydride in pyridine on the steam bath. The product (4.0 g.) was isolated in the usual way, by extraction with ether, and was chromatographed on deactivated alumina (160 g.).

Benzene eluted 694 mg. gum.

Benzene-ether (99:1) eluted a crystalline solid (525 mg.).

More polar solvents merely eluted a series of dark gums (Total 2.09 g.).

The crystalline solid was recrystallised twice from methanol, and although it melted over a range of only four degrees (165-169°) it was shown by thin layer chromatography to consist of three compound at least. This material (143 mg.) was dissolved in methanol (10 ml and water (0.2 ml.) and refluxed with KOH (200 mg.) for 2 hr. Isolation of the product by extracting with ether in the usual way gave a crystalline solid (94 mg.) which had m.p. 205-225°. A sample recrystallised from methanol had m.p. 225-227° (change of crystalline form at 205°), $(\alpha)_D$ + 19.9° (c, 0.5). This was identical with an authentic sample of 16α-hydroxymethylpregnenolone (CCl). (The infrared spectra were identical and the mixed melting-point showed no depression). Heller, Stolar and Bernstein[89] give m.p. 226-228° $(\alpha)_D$ + 17° (MeOH).

<u>Ultraviolet irradiation of pregnadienolone acetate in cyclohexanol</u>. - A solution of pregnadienolone acetate (5.0 g.) in cyclohexanol (300 ml.) was irradiated under reflux by method (a) described above. After 1 hr. the absorption maximum at 240 mμ in the ultraviolet spectrum had disappeared, and irradiation was stopped. The solvent was distilled off in vacuo and the residual gum was dissolved in benzene and chromatographed on deactivated alumina (200 g.).

Elution with benzene gave pregnenolone acetate (3.04 g.) m.p. 148-152°, with an infrared spectrum identical with that of an authentic specimen.

Elution with ether-benzene (1:99) gave a gum (1.02 g.) which did not crystallise.

Elution with ether-benzene (1:19) gave a crystalline product, 3β-<u>acetoxy</u>-16α-(1'-<u>hydroxycyclohexyl</u>)-<u>pregn</u>-5-<u>en</u>-20-<u>one</u> (CC) (1.23 g.) m.p. 200 - 204°. A pure sample had m.p. 206 - 209.5° (recrystallised from methanol) $(\alpha)_D$ + 0.8° (<u>c</u>, 0.62). $\nu_{max.}$ 3480 (OH), 1735 (OAc), 1705 (> C = O) and 1245 (OAc) $cm.^{-1}$. τ 7.90 ($COC\underline{H}_3$), 8.03 ($O.COC\underline{H}_3$), 9.00 ($19-C\underline{H}_3$) and 9.38 ($18-C\underline{H}_3$) (Run in $CDCl_3$). (Found: C, 76.4; H, 9.6. $C_{29}H_{44}O_4$ requires C, 76.3; H, 9.7%).

<u>Ultraviolet irradiation of pregnadienolone acetate in tert-butanol.</u> - A solution of pregnadienolone acetate (5.0 g.) in tertiary butanol (250 ml.) was irradiated under reflux according to method (a) described above. After 5.5 hr. the intensity of the absorption maximum in the ultraviolet spectrum had fallen to 30% of its original value, and did not decrease appreciably thereafter. Irradiation was stopped and the solvent was distilled off under reduced pressure. Chromatography of the residual gum on deactivated alumina (200 g.) gave only one crystalline product, a mixture of pregnenolone acetate and unchanged starting material (2.22 g. in all) eluted by benzene. Elution with more polar solvents gave only a dark, intractable gum (total weight 2.70 g.).

<u>Ultraviolet irradiation of pregnadienolone acetate in cyclohexane/ethanol</u>. - A solution of pregnadienolone acetate (1.21 g.) in cyclohexane (50 ml.) + ethanol (50 ml.) was irradiated under reflux as described above. After 1.5 hr. the absorption maximum in the ultraviolet spectrum at 240 mμ had disappeared. Irradiation was stopped and the solvent was distilled off. The residual gum was chromatographed on deactivated alumina (50 g.). Elution with benzene gave pregnenolone acetate (666 mg.) m.p. 142-146° with infrared spectrum identical with that of an authentic sample.

Elution with ether-benzene (1:19) gave a gum (451 mg.) which did not crystallise.

Elution with ether afforded 3β-acetoxy-16α-(1′-hydroxyethyl)-pregn-5-en-20-one (232 mg.) which on recrystallisation from methanol had m.p. 191-195°. The infrared spectrum was identical with that of a sample prepared previously.

<u>Ultraviolet irradiation of pregnadienolone acetate in cyclohexane</u>. - A solution of pregnadienolone acetate (1.004 g.) in cyclohexane (100 ml.) was irradiated under reflux according to method (a) above. After 7 hr. irradiation was stopped and the solvent was distilled off. The residual gum was dissolved in petrol and chromatographed on deactivated alumina (50 g.).

Petrol eluted a clear gum (413 mg.) which did not crystallise.

Petrol-benzene (1:1) eluted pregnenolone acetate (281 mg.)

m.p. 144-148° (crystallised from ether) having an infrared spectrum identical with that of an authentic specimen.

Benzene eluted a gum (270 mg.) which did not crystallise.

Ultraviolet irradiation of pregnadienolone acetate in ethyl acetate. - A solution of pregnadienolone acetate (1.05 g.) in ethyl acetate (100 ml.) was irradiated under reflux according to method (a) above. After 4.5 hr. the absorption maximum at 240 mμ in the ultraviolet spectrum had virtually disappeared. The solvent was distilled off and the residual gum was dissolved in benzene-petrol (4:6) and chromatographed on deactivated alumina (40 g.).

Benzene-petrol (4:6) eluted pregnenolone acetate (208 mg.) m.p. 142-146° (crystallised from methanol). The infrared spectrum was identical with that of an authentic sample.

More polar solvents eluted a series of gums, which did not crystallise (Total weight 985 mg.).

Ultraviolet irradiation of 3β-acetoxy-16-methyl pregna-5,16-dien-20-one ("16-Methylpregnadienolone acetate")

In ethanol - A solution of 16-methylpregnadienolone acetate (CCIII) (994 mg.) in ethanol (50 ml.) was irradiated under reflux by method (a) above. After 1.5 hr. the ultraviolet absorption maximum at 252 mμ had disappeared, and the solvent was distilled off to give a crystalline product. The product was dissolved in benzene and chromatographed on deactivated alumina (40 g.).

Benzene eluted 3β-acetoxy-16β-methylpregn-5-en-20-one (CCIV) (701 mg.) m.p. 136-142.5°. A sample recrystallised from methanol had m.p. 147-148°, $(\alpha)_D$ - 22.5° (c, 0.6) was identical with an authentic sample (kindly provided by Dr. C. L. Hewett, Organon Laboratories). The infrared spectra were superimposable.

Benzene-ether (19:1) eluted unchanged starting material (89 mg.).

In isopropanol.

A solution of 16-methylpregnadienolone acetate (1.058 g.) in isopropanol (50 ml.) was irradiated under reflux by method (a) above. After 1.5 hr. the ultraviolet absorption maximum at 252 mμ had dis:appeared, and the solvent was distilled off to give a crystalline product. Recrystallisation from methanol gave 3β-acetoxy-16β-methylpregn-5-en-20-one (661 mg.) m.p. 147-148° having an infrared spectrum identical with that of an authentic sample.

In methanol.

A solution of 16-methylpregnadienolone acetate (5.0 g.) in methanol (200 ml.) was irradiated under reflux by method (a) above. After 8 hr. the ultraviolet absorption maximum at 250 mμ had almost disappeared and the solvent was distilled off to give a gum. The gum was dissolved in benzene and chromatographed on deactivated alumina (200 g.).

Benzene eluted 3β-acetoxy-16β-methylpregn-5-en-20-one (2.128 g.) which after recrystallisation from methanol had m.p. 146-148°. The infrared spectrum was identical with that of an authentic sample.

Mixtures of benzene and ether eluted only gum which did not crystallise (total weight 1.7 g.). Ether eluted a crystalline material (1.789 g.) which, after recrystallisation from methanol, had m.p. 197-202°. $\nu_{max.}$ 3470 (OH), 1730 (OAc), 1700 ($>C=O$) and 1245 (OAc) cm.$^{-1}$. (This substance was shown by thin-layer chroma-:tography to consist of two compounds with very similar R_F values for a variety of eluants).

<u>Chromic acid oxidation of the ether eluate.</u> - The material eluted by ether in the preceding experiment was recrystallised from methanol once again. (Yield 720 mg., m.p. 197-202°). The product was dis-:solved in acetone (80 ml.) and treated with 8-N chromic acid (2 ml.) at room temperature for 5 min. Sodium bisulphite was added, followed by dilute HCl. and the mixture was extracted with ether.

The ether extract was washed with KOH solution, then with water and was dried over Na_2SO_4. Evaporation of the ether gave a crystalline solid (268 mg.) which on recrystallisation from methanol had m.p. 152-158° (traces melting up to 167°). Thin layer chromato-:graphy shows that this is a mixture of two compounds whose R_F values are very similar for all eluants tried.

$\nu_{max.}$ 1728 (OAc), 1695 ($>C=O$) and 1240 (OAc) cm.$^{-1}$.

τ 0.09 and 0.21 (C<u>H</u>O).

The alkali washings were rendered acid by the addition of dilute hydrochloric acid and then extracted with ether. Evaporation of the ether extract gave a clear gum (260 mg.) which was crystallised from acetone to give 3β-hydroxy-16β-methylpregn-5-en-20-one-16α-carboxylic acid (CCVII) m.p. 222-244. A sample recrystallised for analysis (from acetone) had m.p. 254-258° (change of crystalline form from 228°), $(\alpha)_D - 44°$ (c, 0.50). $\nu_{max.}$ 3390 (OH), 1712 (shoulder) and 1690 (>C = 0 + $-CO_2H$) $cm.^{-1}$. (Found: C, 73.4; H, 9.0. $C_{23}H_{34}O_4$ requires C, 73.8; H, 9.15%).

The compound was insufficiently soluble in deuterochloroform for the purpose of running an n.m.r. spectrum. However, its methyl ester was prepared by the addition of an excess of diazomethane to the sample, the excess of diazomethane being evaporated in vacuo. τ 6.27 ($COOC\underline{H}_3$), 7.89 ($COC\underline{H}_3$), 8.64 (16β-$C\underline{H}_3$), 8.99 (19-$C\underline{H}_3$) and 9.04 (18-$C\underline{H}_3$). (Run in $CDCl_3$).

Ultraviolet irradiation of 3β,11α-diacetoxy-5α-pregn-16-en-20-one (CCXXVI) in isopropanol.

A solution of the steroid (5.0 g.) in isopropanol (200 ml.) was irradiated under reflux according to method (a) above.

After 1.5 hr. the ultraviolet absorption maximum at 240 mμ had disappeared, and irradiation was stopped. The solution was concentrated and cooled, and the crystalline precipitate was filtered off (total yield 1.083 g.). This material had m.p. 214-217°, $(\alpha)_D - 39.6°$ (c, 0.91) after recrystallisation, but thin layer chromatography indicated that it consisted of two major components and several minor components.

The residue obtained from concentration of the mother liquor (totalling 4.16 g.) was dissolved in benzene and chromatographed on deactivated alumina. Benzene eluted 3β,11α-diacetoxy-5α-pregnan-20-one (CCXXVII) (1.70 g.) m.p. 168-172°. A sample recrystallised from methanol had m.p. 171-173° $(\alpha)_D$ + 27.2° (c, 0.75). (Djerassi, Batres, Romo and Rosenkranz[94] give m.p. 171-173°, $(\alpha)_D$ + 44°).

Ether-benzene (1:1) eluted a gum (1.24 g.). One fraction of this gum crystallised from ether to give a substance identical with the material which crystallised directly from the reaction mixture. The remainder of the gum, however, did not crystallise.

Ether eluted 3β, 11α-diacetoxy-16α-(1'-hydroxyisopropyl)-5α-pregnan-20-one (CCXXVIII) (1.225 g.) m.p. 174-178°. A sample recrystallised from ether for analysis had m.p. 180-184° $(\alpha)_D$ + 24.3° (c, 0.70). $\nu_{max.}$ 3470 (OH), 1728 (OAc), 1700 (>C = O) and 1243 (OAc)cm.$^{-1}$. τ 7.88 ($COC\underline{H}_3$), 8.00 (2 x ($O.COC\underline{H}_3$)), 8.90 ($C(C\underline{H}_3)_2$), 9.09 (19-$C\underline{H}_3$) and 9.33 (18-$C\underline{H}_3$). (Run in $CDCl_3$). (Found: C, 70.55; H, 9.6. $C_{28}H_{44}O_6$ requires C, 70.55; H, 9.3%). (The two pure compounds described here did not form part of the mixture which crystallised directly from the reaction solution).

Irradiation of Pregnadienolone Acetate in allyl alcohol.

A solution of pregnadienolone acetate (5.0 g.) in allyl alcohol (270 ml.) was irradiated under reflux by method (b) described above. After 3 hr. the ultraviolet absorption maximum at 239 mμ had decreased to approximately 10% of its original intensity. Irradiation was stopped and the solvent was distilled off. The residue was dissolved in benzene and chromatographed on deactivated alumina (200 g.). Benzene eluted a crystalline solid (2.395 g.) which was mainly unchanged starting material. (From the infrared spectrum it appeared to contain some pregnenolone acetate).

Benzene/Ether (4:1) eluted a gum (240 mg.) from which a small quantity of crystalline material was obtained. This had (after recrystallisation from methanol) m.p. 195-199°, $(\alpha)_D$ - 46.7° (c, 0.65) $\nu_{max.}$ 1724, 1242 cm.$^{-1}$ (OAc). It had no hydroxyl or ketonic absorption bands.

(The identity of this compound could not be established. It was not obtained in subsequent irradiations of pregnadienolone acetate in allyl alcohol).

Elution with Ether/Methanol (99:1) gave a gum (3.18 g.) which was crystallised from di-isopropyl ether. The crystals obtained (1.02 g.) were contaminated with gum. Re-chromatography of this latter material on alumina gave crystals m.p. 140-150° (traces melting up to 170°). $\nu_{max.}$ 3330 (OH) 1740, 1720, 1690 (carbonyl), 1640 (C = C) and 1243 (OAc) cm.$^{-1}$.

This substance was clearly not a pure compound, and thin layer chromatography revealed that it consisted of one major and two minor components which had similar R_F values. (Several solvent systems were tried, but none was found which would have made preparative-scale thin layer chromatography a really practical proposition).

Repeated recrystallisation did not improve the melting-point.

Oxidation of the substance with 8-N chromic acid in acetone gave a carboxylic acid, m.p. 186-190° $(\alpha)_D$ - 44.7° (c, 0.47). $\nu_{max.}$ 3440 (OH), 1726 (OAc), 1700 (>C = O) and 1240 (OAc) cm.$^{-1}$. The structure of the acid - apparently a pure compound - is not known.

Ultraviolet irradiation of Pregnadienolone Acetate in cyclopentanol/cyclohexane.

A solution of pregnadienolone acetate (1.01 g.) in cyclohexane (25 ml.) and cyclopentanol (25 ml.) was irradiated under reflux by method (a) described above. After 1.5 hr. the ultraviolet absorption maximum at 240 mμ had disappeared and the solvent was distilled off. The residue was chromatographed on deactivated alumina (40 g.). Benzene eluted a gum (762 mg.) which was crystallised from methanol to give pregnenolone acetate, m.p. 140-144°, with an infrared spectrum identical with that of an authentic sample.

Benzene/Ether (99:1) eluted an intractable gum (158 mg.).

Benzene/Ether (19:1) eluted a gum (69 mg.) from which was obtained, by crystallisation from methanol, a substance having m.p. 168-187°, $\nu_{max.}$ 3510 (OH), 1730 (OAc), 1700 (>C = 0) and 1239 (OAc) cm.$^{-1}$.

More polar eluants gave only a gum (58 mg.)

Ultraviolet irradiation of 9(11)-dehydrohecogenin 3β-acetate (CCXXI

(a) In ethanol.

A solution of 9(11)-dehydrohecogenin 3β-acetate (CCXXIX) (683 mg.) in ethanol (34 ml.) was irradiated under reflux according to method (b) described above. After 1.5 hr. the ultraviolet absorption maximum at 238 mμ had disappeared. The reaction was stopped and the solvent was distilled off. The product was a gum, which, on trituration with methanol, gave a crystalline solid, m.p. 237-242° (148 mg.) which had an infrared spectrum identical with that of an authentic sample of hecogenin 3β-acetate (CXLIV; R = Ac). The melting-point was undepressed on admixture with the authentic sample.

(b) In dioxan.

Irradiation of a solution of 9(11)-dehydrohecogenin-3β-acetate (1.01 g.) in dioxan (50 ml.) gave results similar to those observed in ethanol. The peak at 238 mμ in the ultraviolet spectrum disappeared in 1.5 hr. and evaporation of the solvent, followed by trituration of the residual gum with methanol gave crystalline hecogenin 3β-acetate (137 mg.) identical with an authentic sample.

Other Irradiation Experiments.

(All these experiments were carried out according to method (a) described above for Hecogenin Acetate).

Products were subjected to chromatography on alumina.

Substrate	Solvent	Time	Products
Pregnadienolone Acetate (1.52 g.)	2,2,2-Trifluoroethanol (100 ml.)	2 hr.	Starting material recovered unchanged (830 mg.) plus intractable gums.
Pregnadienolone Acetate (5.0 g.)	2,Methoxyethanol (250 ml.)	2 hr.	Starting material (2.37 g.) Succession of red gums.
Pregnadienolone Acetate (5.0 g.)	Benzyl Alcohol (300 ml.)	2.5 hr.	Starting material unchanged (Quantitative)
Pregnadienolone Acetate (5.0 g.)	Ethyleneglycol Monoacetate (250 ml.)	1.5 hr.	Dark gums. Traces of starting material obtained from less polar fractions. Elution with 1% MeOH/ether gave 30 mg. crystals (I.R. shows presence of hydroxyl group. Not sharp melting).
Pregnadienolone Acetate (1.18 g.)	Propargyl Alcohol (50 ml.)	3 hr.	Starting material (460 mg.) Followed by a series of dark gums. (There was no appreciable change in the U.V. spectrum).
Pregnadienolone Acetate (2.04 g.)	Acetic Acid (204 ml.)	4 hr.	Starting material (1.42 g.) Gums, shown by thin layer chromatography to consist of at least 8 compounds.

Substrate	Solvent	Time	Products
Pregnadienolone Acetate (1.01 g.)	Thioacetic Acid (50 ml.)	1 hr.	Starting material unchanged. (Not isolated; thin layer chromatography shows only one spot).
Pregnadienolone Acetate (2.1 g.)	N,N Dimethyl 2-aminoethanol (98 ml.)	1.5 hr.	Starting material (0.99 g.) Dark gums (1.0 g.)
Pregnadienolone Acetate (1.06 g.)	Cyclohexane (100 ml.) + p.Cresol (1.5 g.)	16 hr.	520 mg. eluted by benzene, gave 35 mg. crystalline product, m.p. 243-272°. More polar solvents eluted gum (268 mg.). (Could not be repeated).
Pregnadienolone Acetate Oxime (1.04 g.)	Ethanol (50 ml.)	10.5 hr.	Unchanged starting material (403 mg.). Later chromatographic fractions merely intractable gum.
16 ,17 -Epoxy pregnenolone Acetate (200 mg.)	Petrol (60-80) (20 ml.)	10 hr.	Gums. Thin layer chromatography showed the product to consist of at least eight compounds.
α-Acetyl Naphthalene (1.0 g.)	Isopropanol (50 ml.)	3 hr.	Unchanged starting material.
5α-Androst-1-en-3, 20 dione (1% solution)	(a) Methanol (b) Ethanol (c) Isopropanol	(a) 1.5 hr. (b) 4.5 hr. (c) 3 hr.	Unchanged starting material
3β-Acetoxyergosta-8(9), 22-dien-11-one (1.08 g.)	Ethanol (50 ml.)	3 hr.	Unchanged starting material

APPENDIX I

APPENDIX I

Since this thesis was written, the Chemistry Department of the University of Strathclyde has acquired a Perkin-Elmer 237 Grating Infrared Spectrophotometer. This has made possible some more accurate studies on the hydroxyl stretching frequencies in the compounds described in the thesis.

The figures given below, with one or two exceptions, are in fairly good agreement with figures obtained in studies using the Grubb Parsons S 2 instrument. However, the figures obtained with the Perkin-Elmer instrument for 3β,12α-diacetoxy-14α-hydroxy-5α,25D-spirostan and for 3β-acetoxy-12α-hydroxy-14α,15α-epoxy-5α,25D-spirostan indicate an absence of intramolecular hydrogen bonding, although such hydrogen-bonding occurs in 3β-acetoxy-12α,14α-dihydroxy-5α,25D-spirostan.

The results given below were all obtained from spectra run in carbon tetrachloride solution, the concentration being 5 mg. of the steroid in 3.0 ml. CCl_4.

Steroid	$\nu_{max.}$ (cm.$^{-1}$)
3β-acetoxy-14α-hydroxy-5α,25D-spirostan (CLVII; R = Ac)	3560
3β-acetoxy-14α-hydroxy-5α,25D-spirostan-12-one (CLVI; R = Ac)	3525
3β,12α-diacetoxy-14α-hydroxy-5α,25D-spirostan (CLXIX, R = R' = Ac)	3560
3β-acetoxy-12α,14α-dihydroxy-5α,25D-spirostan (CLXIX; R = Ac, R' = H)	3640, 3540
3β-acetoxy-12α-hydroxy-14α,15α-epoxy-5α,25D-spirostan (CLXXVI)	3640

3β-acetoxy-16α-(1'-hydroxyethyl)-pregn-5-en-20-one (CXCII; R = Ac)	3630 3595
3β-acetoxy-16α-(1'-hydroxyisopropyl)-pregn-5-en-20-one (CXCVI; R = Ac)	3620, 3590
3β,11α-diacetoxy-16α-(1'-hydroxyisopropyl)-5α-pregnan-20-one (CCXXVIII)	3620, 3590
3β-acetoxy-16α-(1'-hydroxycyclohexyl)-pregn-5-en-20-one (CC)	3620, 3590

The spectra of three other compounds related to the 16α-hydroxyalkyl steroids mentioned above were run for comparison, the concentrations bein the same as in the spectra mentioned above. These compounds were:-

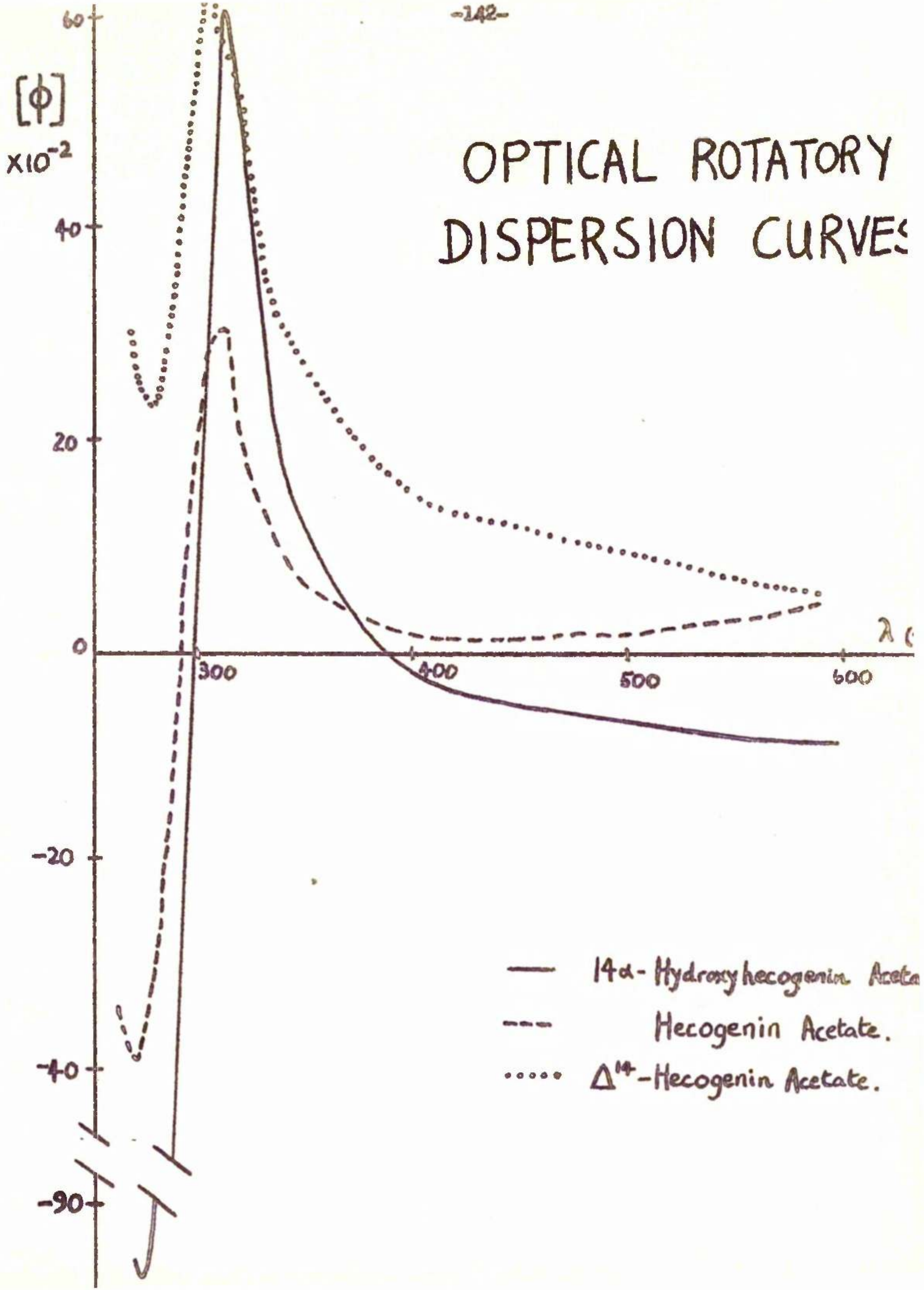
(1) 16α-Hydroxymethylprogesterone (kindly provided by Abbott Laboratories North Chicago, Ill.) which had peaks at 3650, 3620 $cm.^{-1}$;

(2) 3β, 20ξ-Dihydroxy-16α-acetylpregn-5-en which had a peak at 3620 $cm.^{-1}$; and

(3) 3β-Acetoxy-16β-(1'-hydroxyisopropyl)-17α-pregn-5-en-20-one which had a peak at 3620 $cm.^{-1}$

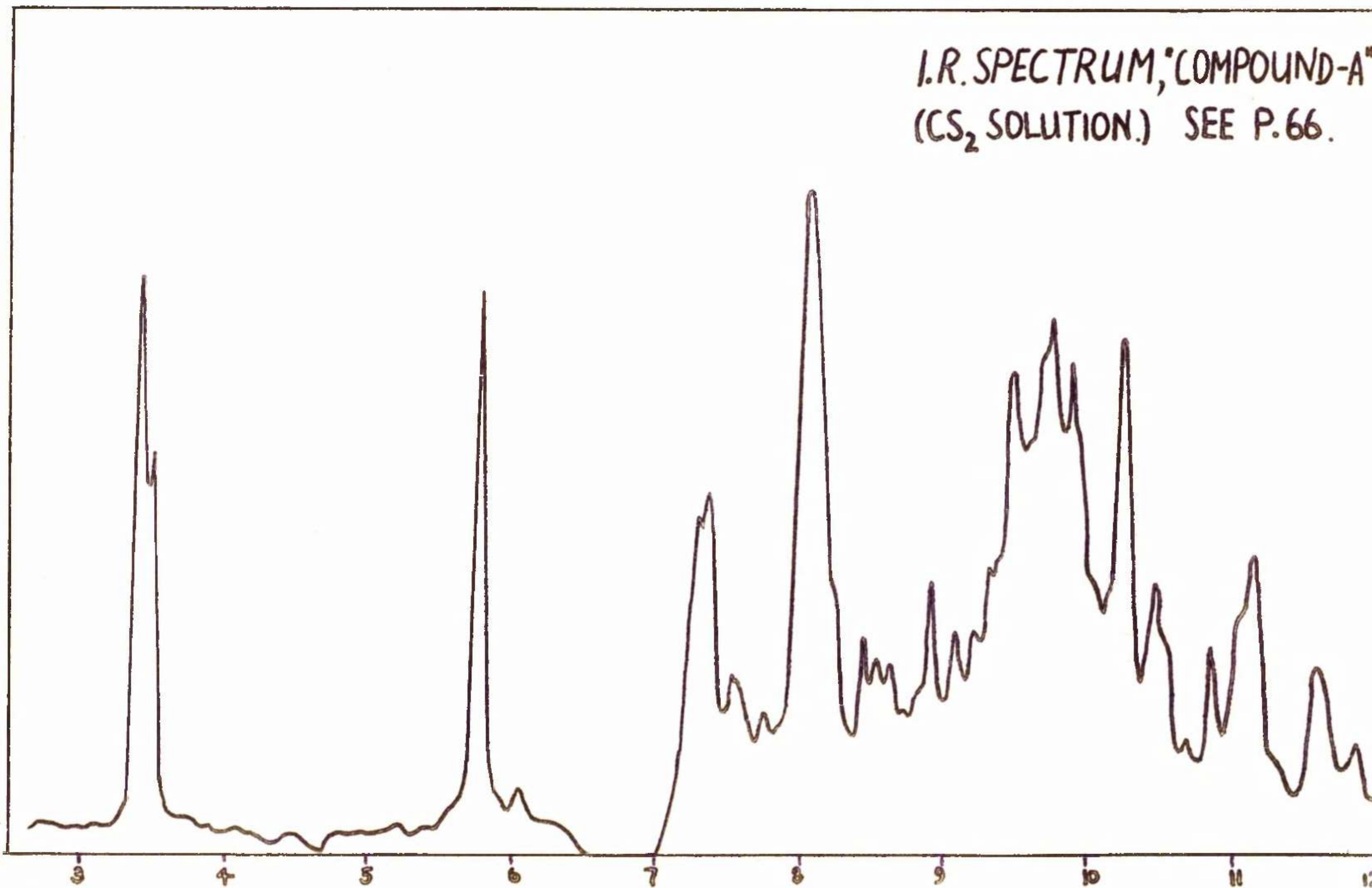
(both kindly provided by Dr. R.T. Logan, Organon Laboratories).

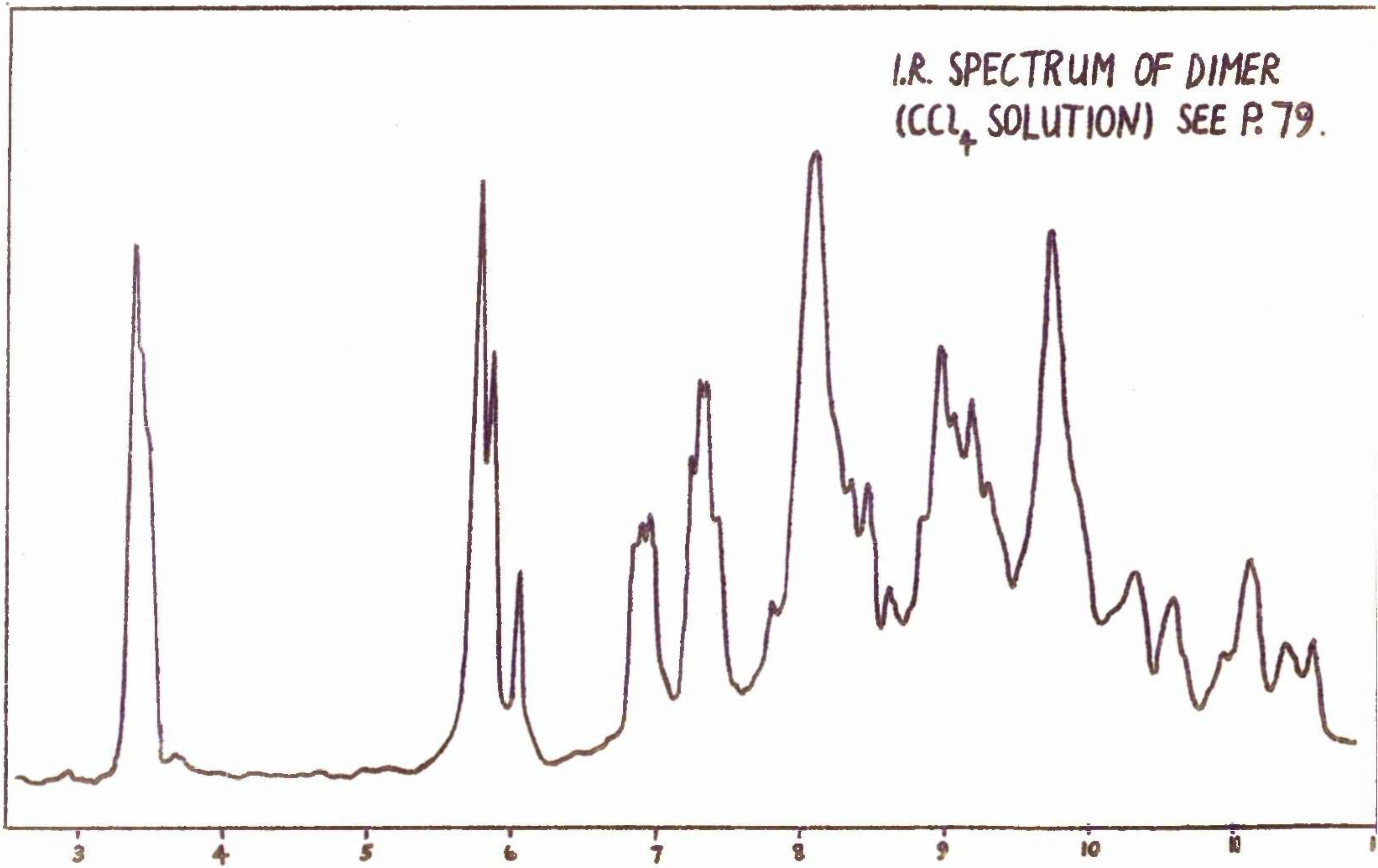
A P P E N D I X I I

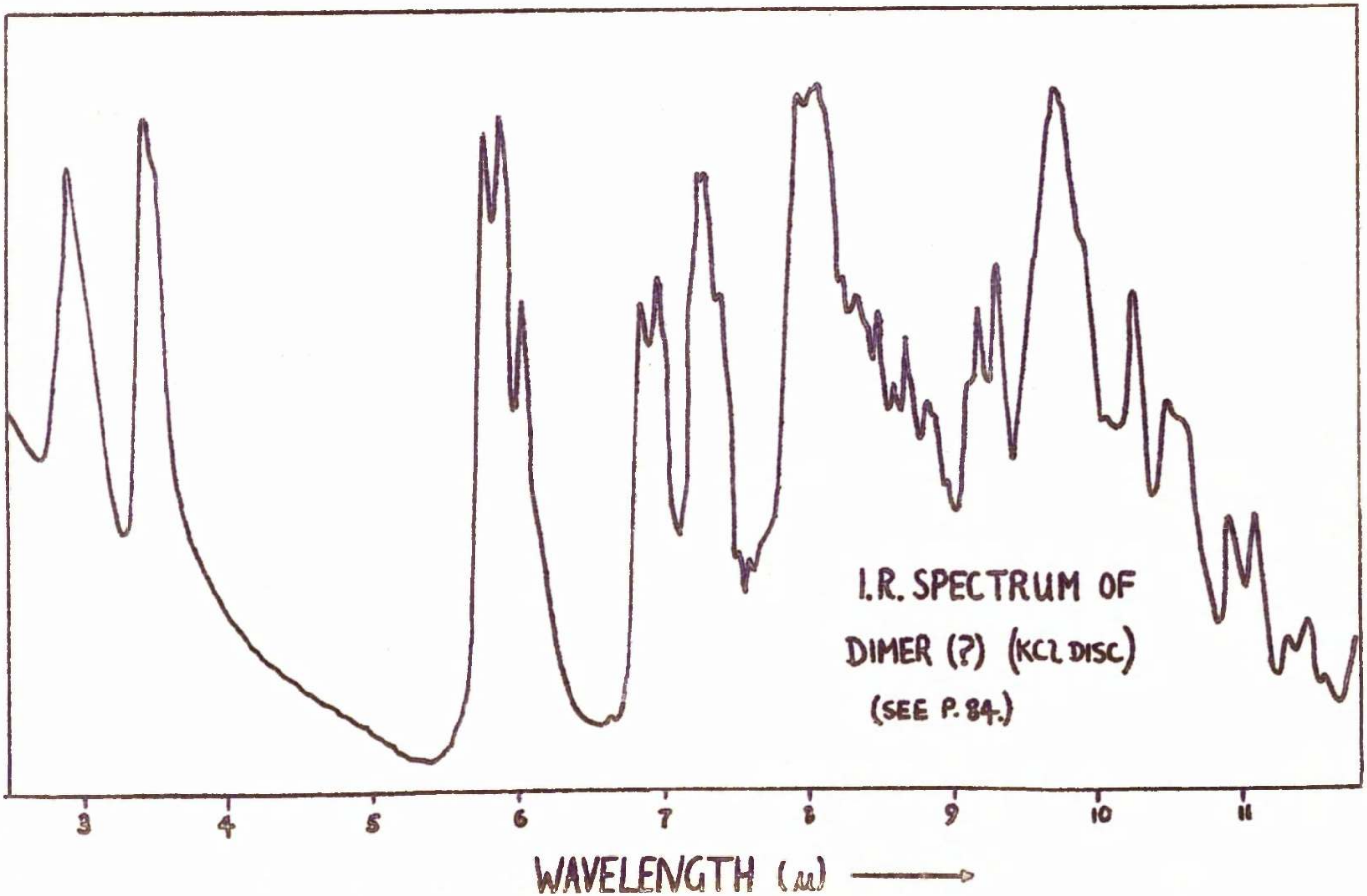


[φ]
x10^-2
60
40
20
0
-20
-40
-90
300
400
500
600
λ
OPTICAL ROTATORY
DISPERSION CURVES
14α-Hydroxyhecogenin Aceta
Hecogenin Acetate.
Δ14-Hecogenin Acetate.

I.R. SPECTRUM, "COMPOUND-A"
(CS_2 SOLUTION.) SEE P. 66.

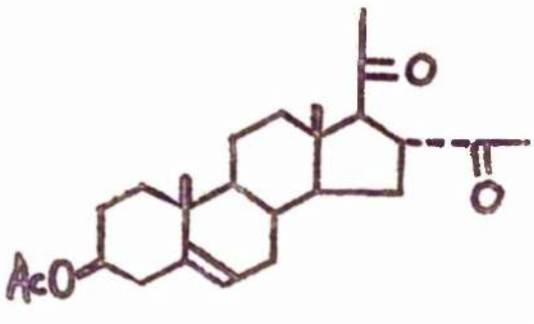



I.R. SPECTRUM OF DIMER
(CCl_4 SOLUTION) SEE P. 79.
3
4
5
6
7
8
9
10
11

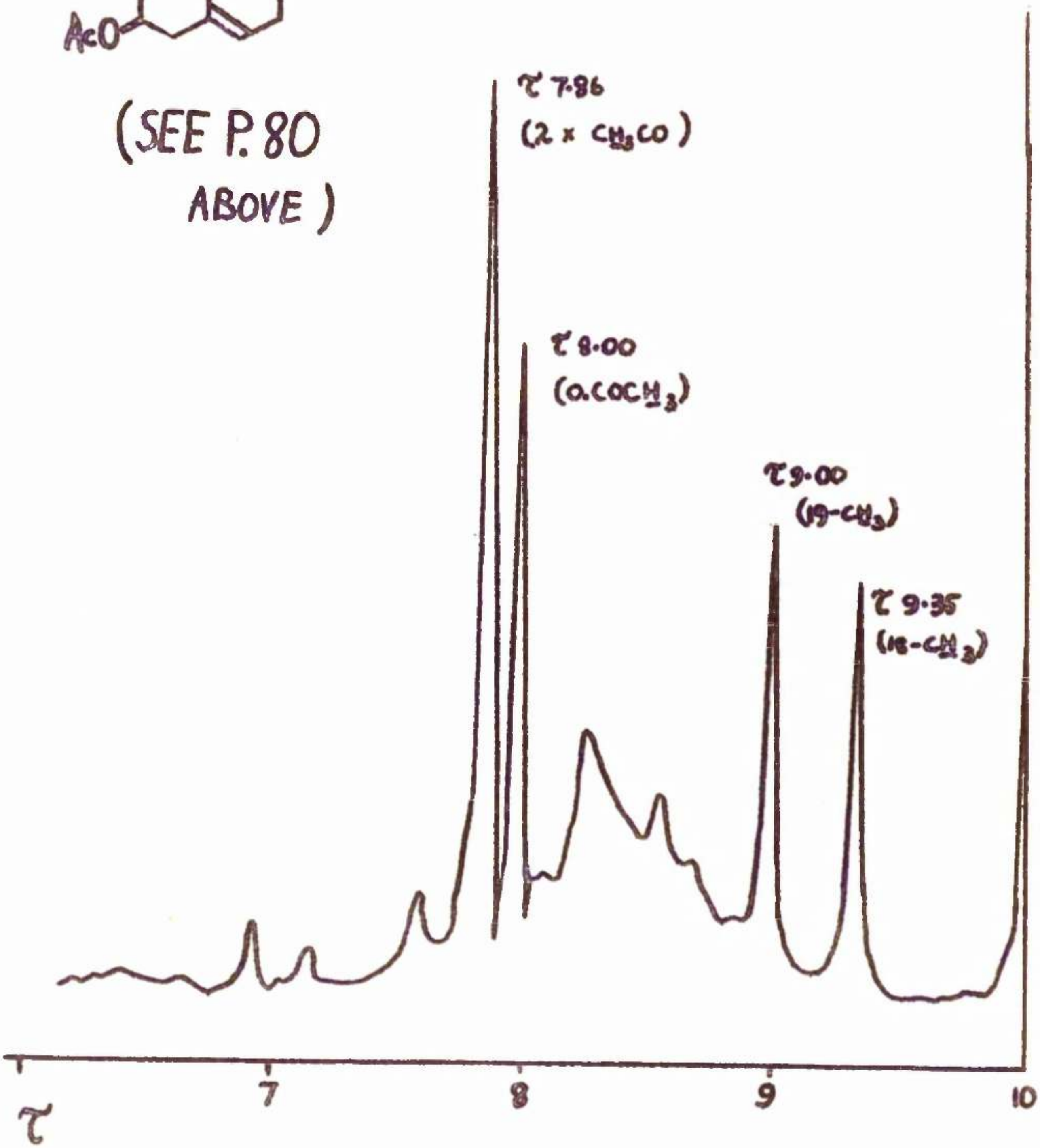

I.R. SPECTRUM OF
DIMER (?) (KCl DISC)
(SEE P. 84.)
3
4
5
6
7
8
9
10
11
WAVELENGTH (μ)

N.M.R. SPECTRUM

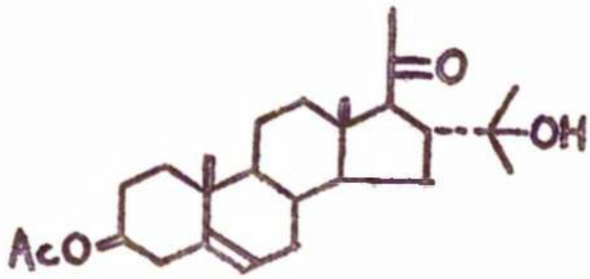
OF



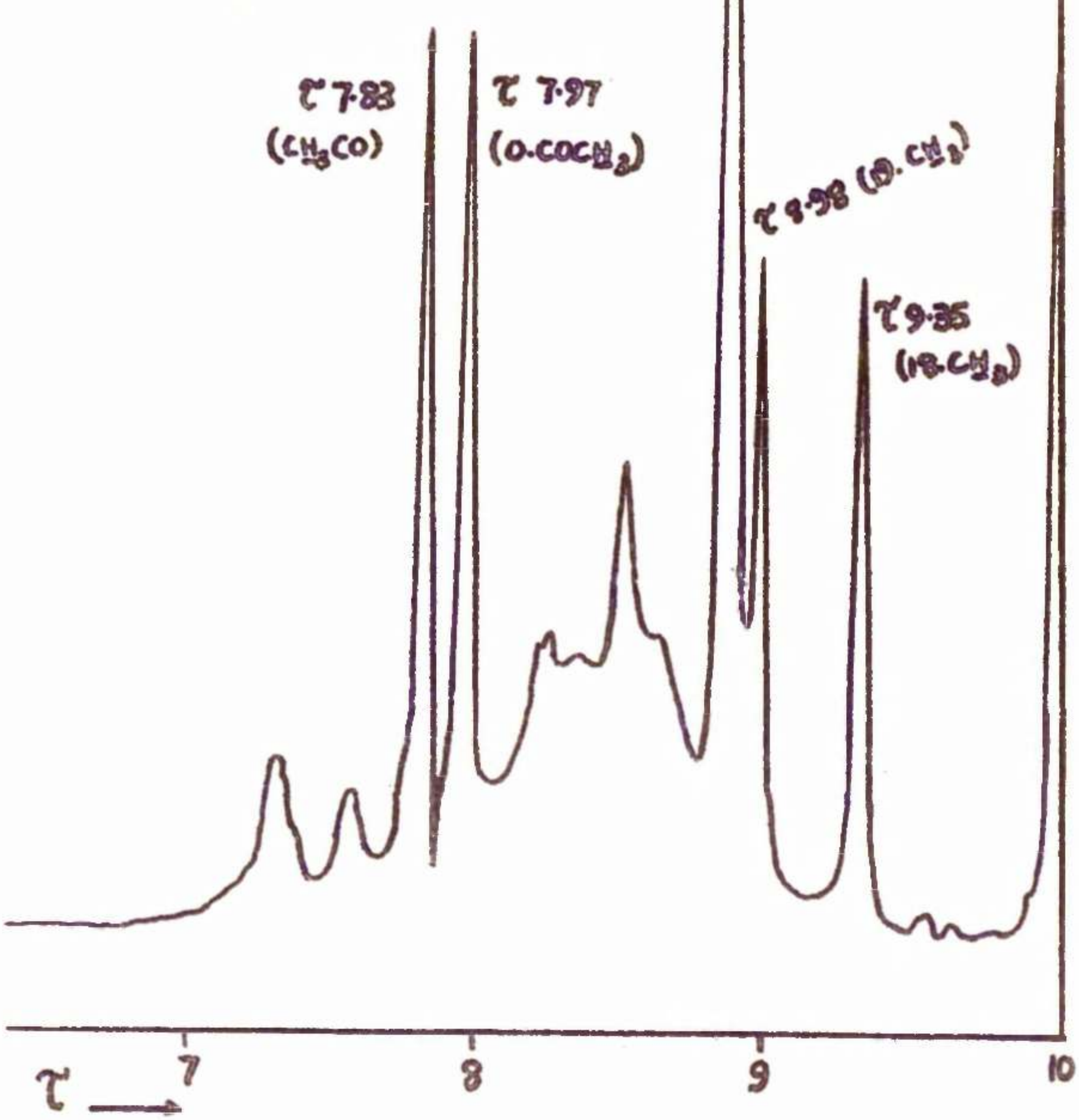
(SEE P. 80 ABOVE)

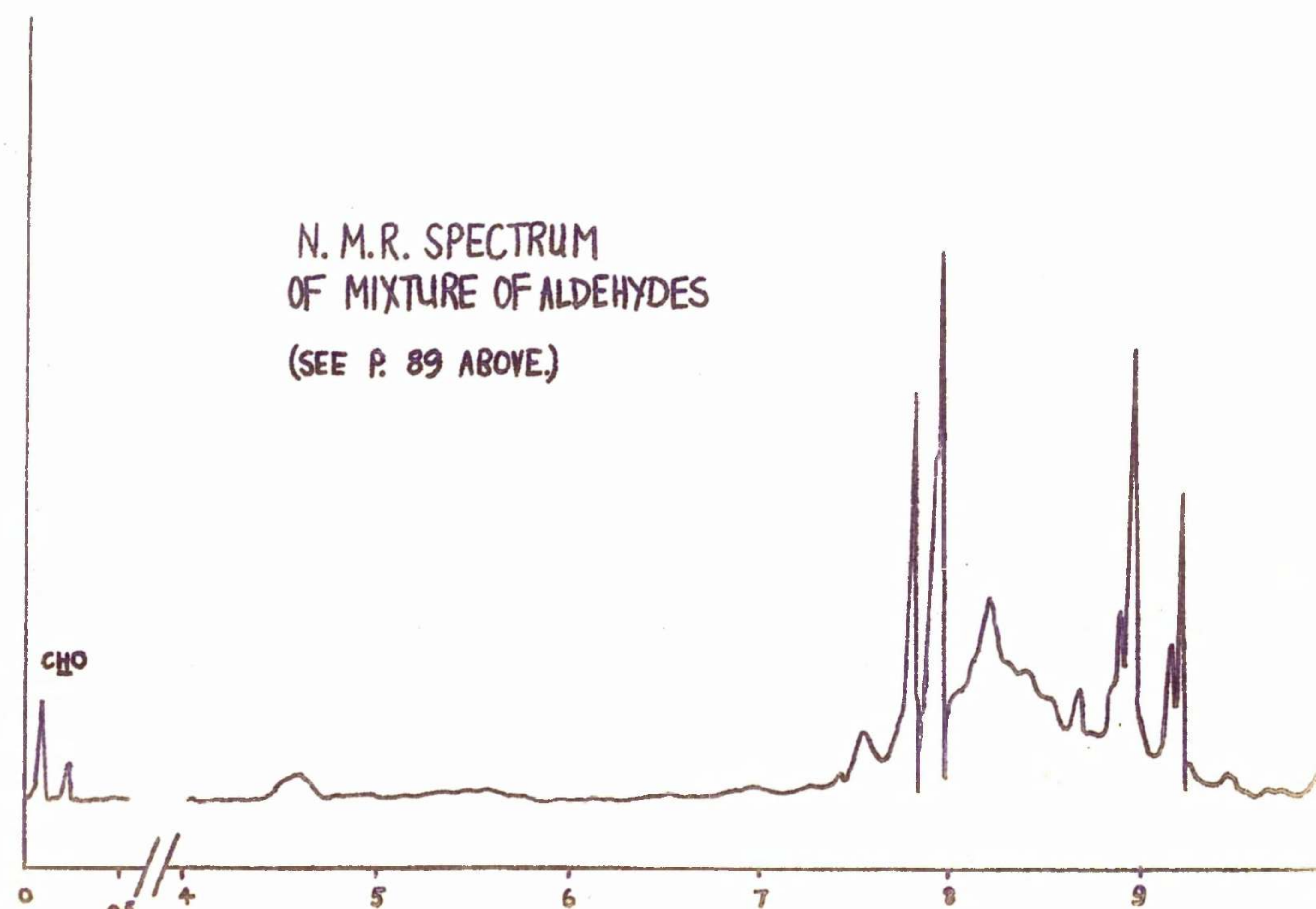


N.M.R. SPECTRUM OF



(SEE P.82 ABOVE)




N. M.R. SPECTRUM
OF MIXTURE OF ALDEHYDES
(SEE P. 89 ABOVE.)
CHO
0
4
5
6
7
8
9

B I B L I O G R A P H Y .

BIBLIOGRAPHY

1. Stark, Physik Z., 1908, 9, 898.
Einstein, Ann. Physik, 1912, 37, 832; 1913, 38, 881.
2. Bielecki and Henri, Ber., 1913, 46, 3627.
3. Mulliken, J. Chem. Phys., 1935, 3, 564.
4. (a) De Mayo and Reid, Quart. Rev., 1961, 15, 393.
(b) De Mayo, in "Advances in Organic Chemistry", Vol. II p. 369 ff. (Interscience, New York, 1960).
5. Klinger, Ann., 1884, 249, 137.
6. Klinger, Ber., 1886, 19, 1862.
7. Ciamician and Silber, Ber., 1900, 33, 2911.
8. Ciamician and Silber, Ber., 1901, 34, 1530.
9. Ciamician and Silber, Ber., 1907, 40, 2415.
Ciamician and Silber, Ber., 1909, 42, 1510.
10. Ciamician and Silber, Ber., 1910, 43, 1340.
Ciamician and Silber, Ber., 1908, 41, 1071.
11. Ciamician and Silber, Ber., 1913, 46, 3077.
12. Srinivasan, J. Amer. C.S., 1959, 81, 2604.
13. De Mayo, Reference 4(a).
Quinkert, Wegemund and Blanke, Tetrahedron Letters, 1962, 221.
14. Srinivasan, J. Amer. C.S. 1959, 81, 1546.
15. Butenandt and Wolff, Ber., 1939, 72, 1121.
Butenandt, Wolff and Karlson, Ber., 1941, 74, 1308.
Butenandt, Friedrich and Poschmann, Ber., 1942, 75, 1931.
Butenandt and Poschmann, Ber., 1944, 77, 392
16. Quinkert, Wegemund, Homburg and Cimbollek, Ber., 1964, 97, 958.
17. Wehrli and Schaffner, Helv. Chim. Acta, 1962, 42, 385.
18. Barnard and Yang, Proc. Chem. Soc., 1958, 302.
19. Dorfman, Chem. Rev., 1953, 53, 47.
20. Nann, Gravel, Schorta, Wehrli, Schaffner and Jeger, Helv. Chim. Acta, 1963, 46, 2473.

21. Wehrli, Wenger, Schaffner and Jeger, Helv. Chim. Acta, 1963, 46, 678.

22. Gardner and Hamil, J. Amer. C.S., 1961, 83, 3531.

23. Hurst and Whitham, J.C.S., 1960, 2864.

24. Cookson, Crundwell and Hudec, Chem. and Ind., 1958, 1003.

25. Büchi and Goldman, J. Amer. C.S., 1957, 79, 4741.
See also Ciamician and Silber, Ber. 1908, 41, 1928.

26. Treibs, J. prakt. Chem., 1933, 138, 299.

27. (a) Butenandt and Poschmann, Ber., 1940, 73, 893.
(b) Butenandt, Poschmann, Failer, Scheidt and Biekert, Ann., 1951, 575, 123.

28. Butenandt and Poschmann, Reference 27(a).

29. Yang and Jorgensen, Tetrahedron Letters, 1964, 1203.

30. Barton, Helv. Chim. Acta , 1959, 42, 2604.
Barton and Quinkert, J.C.S., 1960, 1.

31. Büchi and Yang, J. Amer. C.S., 1957, 79, 2318.

32. Rubin, Hipps and Glover, J. Org. Chem., 1964, 29, 68.

33. Ushakov and Kosheleva, Zhur obshchei Khim., 1944, 14, 1138.

34. Cannizzaro and Fabris, Ber., 1886, 19, 2260.
See also: Villavecchia, Ber., 1885, 18, 2859.

35. Barton, Mayo and Shafiq., J.C.S., 1957, 929.
Barton, Mayo and Shafiq., J.C.S., 1958, 140.
Barton, Mayo and Shafiq., J.C.S., 1958, 3314.
Arigoni, Bosshard, Bruderer, Büchi, Jeger and Krebaum, Helv. Chim. Acta , 1957, 40, 1732.
Cocker, Crowley, Edward, McMurry and Stuart, J.C.S., 1957, 3416.

36. Van Tamelen, Levin, Brenner, Wolinsky and Aldrich, J. Amer. C.S., 1958, 80, 501.

37. Dutler, Ganter, Ryf, Utzinger, Weinberg, Schaffner, Arigoni and Jeger, Helv. Chim. Acta , 1962, 45, 2346.

38. Weinberg, Utzinger, Arigoni and Jeger, Helv. Chim. Acta , 1960, 43, 236.

39. Ganter, Utzinger, Schaffner, Arigoni and Jeger, Helv. Chim. Acta , 1962, 45, 2403.
(See also reference 37).

40. Eriksen and Forbess, in "Steroid Reactions" (Ed. Djerassi), Chapter 8, p. 327 ff. (Holden-Day, San Francisco, 1963).

41. Barton and Taylor, J.C.S., 1958, 2500.
Barton, Proc. Chem. Soc., 1958, 61.

42. Fieser and Fieser, "Steroids" pp. 90-168 (Reinhold, New York 1959).

43. (a) Wehrli, Heller, Schaffner and Jeger, Helv. Chim. Acta , 1961, 44, 2162.
(b) Iriarte, Schaffner and Jeger, Helv. Chim. Acta , 1963, 46, 1599.
(c) Meystre, Heusler, Kalvoda, Wieland, Anner and Wettstein, Experientia, 1961, 17, 475.
See also: Orban, Schaffner and Jeger, J. Amer. C.S., 1963, 85, 3033.

44. (a) Cereghetti, Wehrli, Schaffner and Jeger, Helv. Chim. Acta , 1960, 43, 354.
(b) Buchschacher, Cereghetti, Wehrli, Schaffner and Jeger, Helv. Chim. Acta , 1959, 42, 2122.
See also reference 43(c) above.

45. Iriarte, Hill, Schaffner and Jeger, Proc. Chem. Soc., 1963, 114.
See also: Jeger, Angew. Chem., 1964, 76, 275.

46. Altenburger, Wehrli and Schaffner, Helv. Chim. Acta , 1963, 46, 2753.

47. (a) Haszeldine, J.C.S., 1953, 2525
(b) Bladon, in "Physical Methods in Organic Chemistry" (Ed. Schwarz), Chapter 4, p. 144 (Oliver and Boyd, Edinburgh, 1964).
(c) Anbar and Dostrovsky, J.C.S., 1954, 1105.

48. Barton, Beaton, Geller and Pechet, J. Amer. C.S., 1961, 83, 4076.

49. Kwok and Wolff, Chem. and Ind., 1962, 1194.

50. Barton, Beaton, Geller and Pechet, J. Amer. C.S., 1960, 82, 2640.
Nussbaum, Carlon, Oliveto, Townley, Kabasakalian and Barton, J. Amer. C.S., 1960, 83, 2973.

51. Barton and Beaton, J. Amer. C.S., 1962, 84, 199.

52. Nussbaum and Robinson, Tetrahedron, 1962, 17, 35.

53. Barton, Reimann, Capomaggi, Strauss and Oliveto, J. Amer. C.S., 1961, 83, 4481.

54. Windholz and Windholz, Angew. Chem. Internat. Edit., 1964, 3, 353.

55. Barton and Akhtar, J. Amer. C.S., 1961, 83, 2213.

56. Barton, George and Tomoeda, J.C.S. 1962, 1967.

57. Muller, Huynh and Mathieu, Bull. Soc. Chim. France, 1962, 296.
See also: Mateos and Pozas, Steroids, 1963, 2, 527.

58. Barton and Morgan, J.C.S., 1962, 622.

59. Kocsis, Ferrini, Arigoni and Jeger, Helv. Chim. Acta 1960, 43, 2178.

60. Batres, Cardenas, Edwards, Monroy, Mancera, Djerassi and Ringold, J. Org. Chem., 1961, 26, 871.

61. Wolff, Chem. Revs., 1963, 63, 55.

62. Marker, Wagner, Ulshafer, Wittbecker, Goldsmith and Ruof, J. Amer. C.S., 1947, 69, 2167.

63. McMeekin, Ph.D. Thesis, Glasgow Univ., 1961.

64. (a) Rothman, Wall and Eddy, J. Amer. C.S. 1954, 76, 527.
(b) Rothman and Wall, J. Amer. C.S., 1955, 77, 2228.

65. Djerassi, Halpern, Halpern, Schindler and Tamm, Helv. Chim. Acta, 1958, 41, 250.

66. Cameron, Evans, Hamlet, Hunt, Jones and Long, J.C.S., 1955, 2807.

67. Huang-Minlon, J. Amer. C.S., 1946, 68, 2487.

68. Bladon, Fabian, Henbest, Koch and Wood, J.C.S., 1951, 2402.

69. Waters, Quart. Rev., 1958, 12, 277.

70. Fieser, Experientia, 1950, 6, 312.

71. c.f. Steiger and Reichstein, Helv. Chim. Acta, 1938, 21, 828.

72. Elke, Phillips, Taylor and Wyman, J.C.S., 1954, 1739.
Hirschmann, Sneddy, Hiskey and Wendler, J. Amer. C.S., 1954, 76, 4013.

73. Buchi, Inman and Lipinsky, J. Amer. C.S., 1954, 76, 4327.

74. Arnold, Hinman and Glick, Tetrahedron Letters, 1964, 1425.

75. Cooksen and Wariyar, J.C.S., 1956, 2302.

76. Hofer, Linde and Mayer, Helv. Chim. Acta , 1962, 45, 1041.

77. Clayton, Henbest and Smith, J.C.S., 1957, 1982.

78. Jones, Katzenellenbogen and Dobriner, J. Amer. C.S., 1953, 75, 158.

79. Wehrli, Cereghetti, Schaffner, Urech and Vischer, Helv. Chim. Acta , 1961, 44, 1927.

80. Kirk, Patel and Petrow, J.C.S., 1957, 1046.

81. Marker , J. Amer. C.S., 1949, 71, 4149.

82. Fukushima and Gallagher, J. Amer. C.S., 1950, 72, 2306; J. Amer. C.S., 1951, 73, 196.

83. Reme, Tetrahedron, 1958, 3, 37.

84. Nakanishi, J. Med. Chem., 1963, 6, 798.

85. Gould, Shapiro and Herschberg, J. Amer. C.S., 1954, 76, 5567.

86. Bladen, J.C.S., 1958, 3723.

87. Wall, Carroll and Abernethy, J. Org. Chem., 1964, 29, 604.

88. Crabbé, Guerrero, Reme and Sanchez-Viesca, Tetrahedron, 1963, 19, 25.

89. Heller, Stolar and Bernstein, J. Org. Chem., 1962, 27, 2673.

90. Urry, Stacey, Huyser and Juveland, J. Amer. C.S., 1954, 76, 450.

91. See, for example, references 7, 8 and 16 above.

92. Shannon, Silberman and Sternhell, Tetrahedron Letters, 1964, 659.

93. Tiers, J. Phys. Chem., 1958, 62, 1151.

94. Djerassi, Batres, Reme and Rosenkranz, J. Amer. C.S., 1952, 74, 3634.