PHOTOCHEMISTRY OF KETO-PREGNANE DERIVATIVES

by

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A Dissertation Submitted to the

Graduate Faculty in Partial Fulfillment of

The Requirements for the Degree of

DOCTOR OF PHILOSOPHY

Major Subject: Organic Chemistry

Approved:

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Ames, Iowa

1966

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VITA

The author was born in Caldwell, Kansas on February, 18, 1940 to Mr. and Mrs. Raymond C. Sander. He was graduated in May, 1958 from Caldwell Public High School. In September, 1958, he enrolled at the University of Notre Dame and received the Bachelor of Science in Chemistry degree in June, 1962.

In July of 1962, he enrolled at Iowa State University of Science and Technology and began an investigation of the photochemistry of steroidal ketones under the direction of Dr. O. L. Chapman. The author was a graduate teaching assistant for the period of July, 1962 to February, 1964 and a graduate research assistant for the period of March to June of 1964. The author received a National Science Foundation Co-operative Graduate Fellowship for the period of June, 1964 to June, 1966. He was a Procter and Gamble fellow for the period of June to September, 1966. In November, 1966, he was granted the degree, Doctor of Philosophy from Iowa State University of Science and Technology.

INTRODUCTION

Research interest in organic photochemistry has been much in evidence during the last fifteen years, and the area has been the subject of many reviews (1-12). Part of this intense interest derives from the fact that as a synthetic tool, photochemistry permits structural entry into systems which are difficult or impossible to obtain by other methods. Another factor is the interest in the mechanistic paths of electronically excited molecules. A large body of information is now being collected in this area and some photochemical processes can now be understood on a sound theoretical basis. However, there is much to be done before the area of organic photochemistry can even approach the level of knowledge existing for ground state processes.

The subject of this thesis is the photochemistry of steroidal ketones. This work encompasses the photochemistry of both 2-cyclohexenones and saturated ketones. Use of the Δ^4-3-keto steroid skeleton provides a convenient source of the 3,4,4-trialkyl substituted cyclohexenone system. The inherent rigidity of the steroid skeleton also prevents excessive fragmentation reactions via the excited electronic state. The steroid system also functions well as a source of saturated ketones by way of the 20-keto function.

The main absorption of an α,β-unsaturated ketone is in the 2300-2500 Å ($\varepsilon \simeq$ 10-20,000) region corresponding to 124-114 kcal./mole which is assigned to a $\pi \rightarrow \pi^*$ transition. A less intense absorption is found

at 3100-3300 Å ($\varepsilon \approx 100$) with an energy of 92-87 kcal./mole which is assigned to a $n \rightarrow \pi^*$ transition. A saturated ketone absorbs in the 2700-2900 Å ($\varepsilon \approx 10$-60) region corresponding to an energy of 106-99 kcal./mole which is assigned to an $n \rightarrow \pi^*$ transition. It can be seen that it should be possible to use various wavelengths of light as a type of selective reagent which might be employed to selectively excite one ketone moiety in the presence of others. This type of study is one part of this work. The second part attempts to shed some mechanistic light on a novel photocyclization process of saturated ketones.

It is hoped that the results of these studies will prove useful to those attempting to use photochemistry as a selective synthetic tool and also to those who are endeavoring to construct a meaningful picture of mechanistic photochemistry.

HISTORICAL

Photochemical Reactions of α,β-Unsaturated Ketones

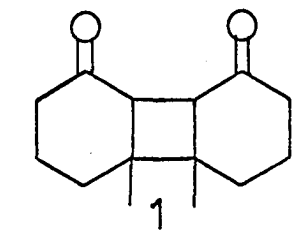
Most of the photochemistry of cyclic α,β-unsaturated ketones in the condensed phase can be described by three general types of reactions. The first is dimerization or cycloaddition to give substituted cyclobutanes, the second is the addition of solvent molecules or hydrogen resulting in 1:1 adducts of solvent and substrate or reduced substrate, and the third is skeletal rearrangement leading to various types of new and interesting structures.

Dimerization and cycloaddition

Photodimerization reactions were the first photochemical reactions discovered (1). Treibs (13) studied the dimerization of piperitone and found that it gave three crystalline dimers. However, a structural assignment was not possible. In 1933 Treibs (14) reported the isolation of a dimer from the irradiation of 3-methyl-2-cyclohexenone and assigned it the partial structure 1. From the irradiation of 3,5-dimethyl-2-cyclohexenone he isolated two dimers with the partial structures 2 and 3.

Recently Griswold (15) reported that the irradiation of isophorone (4) gave two dimers 5 and 6. Recently it has been shown that two head-to-tail dimers are formed and that the ratio of head-to-head to head-to-tail dimers varies with solvent (16). More polar solvents favor formation of the head-to-head dimer 6 while non-polar solvents favor the isomeric head-to-tail dimers. This is interpreted as being due to the

existence of two different triplet intermediates with one favored in polar media and one in non-polar media.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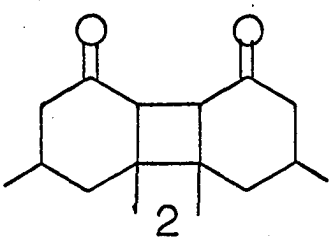
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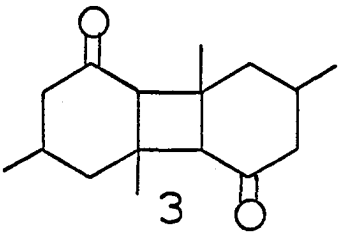
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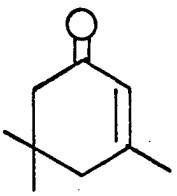
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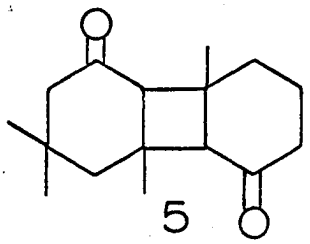
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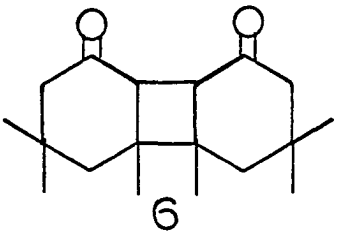
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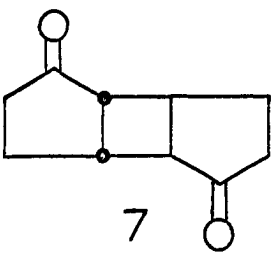
Eaton (17) has studied the dimerization of 2-cyclopentenone both as a neat liquid and in solution. He found that the two dimers 7 and 8 were formed in approximately equal amounts in all cases.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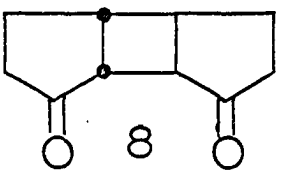
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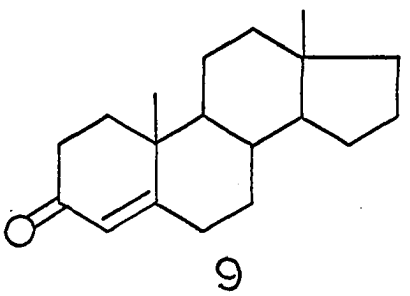
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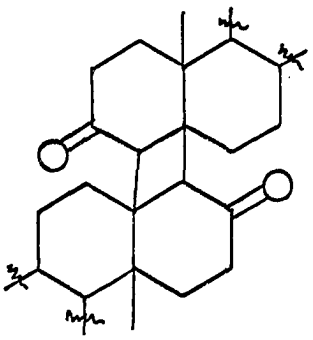
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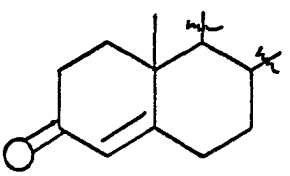
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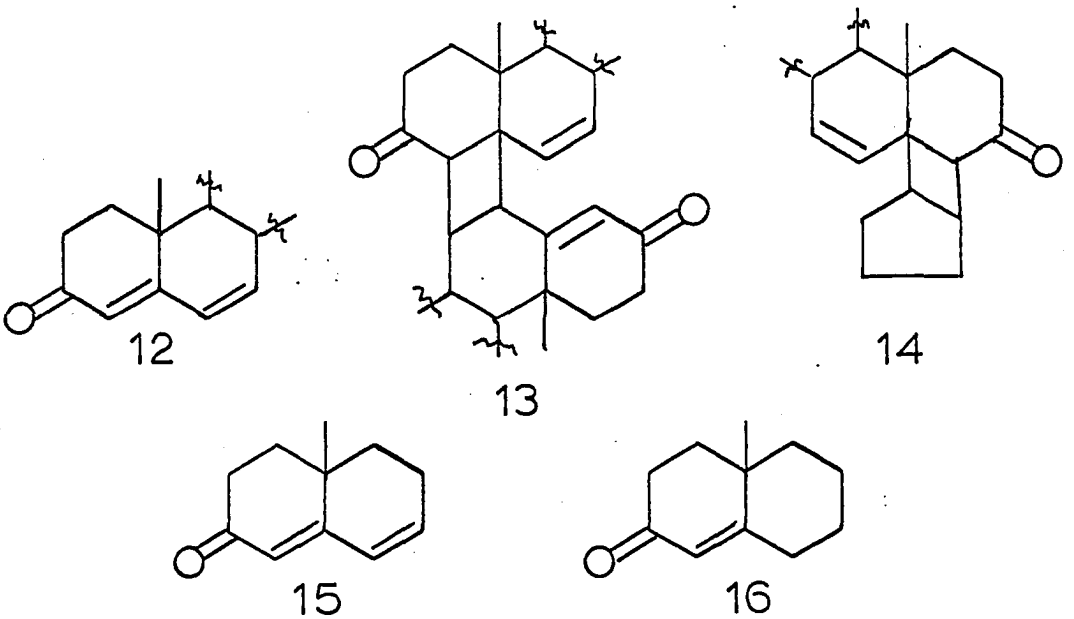
Photodimerization is not confined only to molecules of low molecular weight. Steroids can be made to undergo quite specific dimerization reactions by the proper choice of conditions. Butenandt et al. (18) isolated a dimer from the irradiation of Δ^4-androsten-3-one (9) which he assumed to have the head-to-tail type of structure represented by 10. In 1963 Jeger (Nann et al., 19) reported that the irradiation of concentrated solutions of a steroid with the partial structure 11 also gave a dimer with the structure represented by 10.

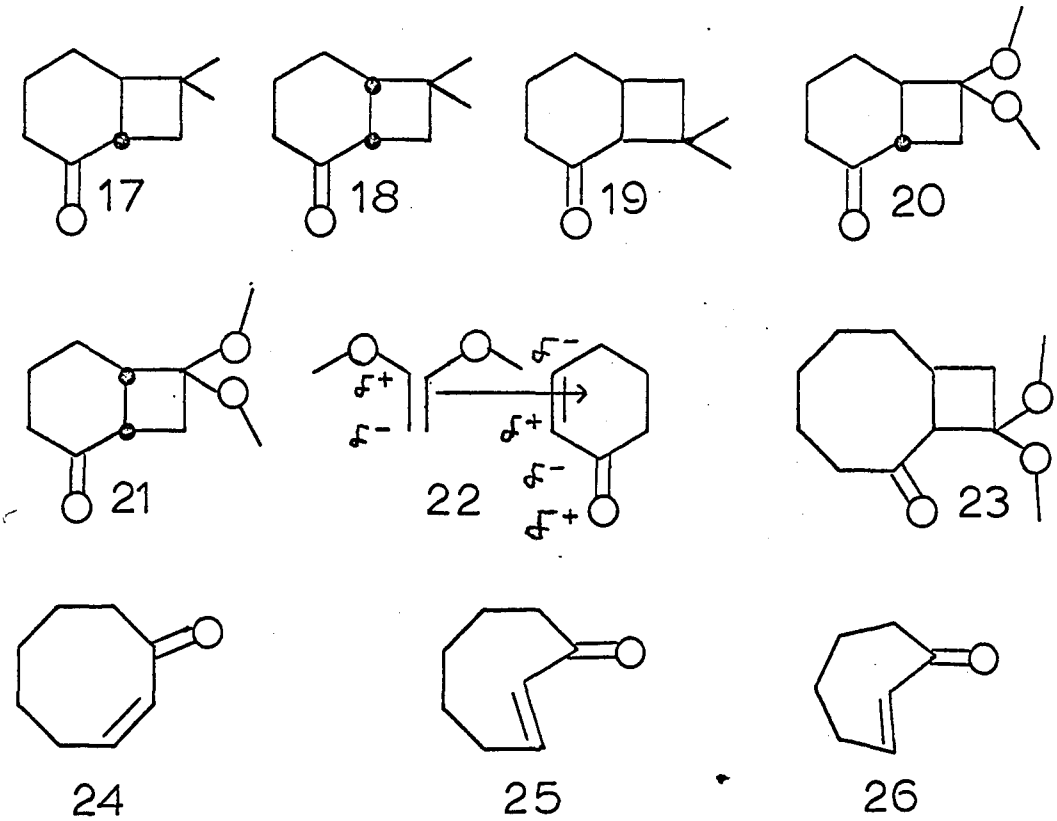
The irradiation of $\Delta^{4,6}$-diene-3-keto steroids (12) also provides dimers with the general structure 13 (20,21). Rubin et al. (21) reported that the irradiation of steroids of the general structure 12 in the presence of cyclopentene gave a 1:1 adduct assigned the structure 14. This result indicated that the course of dimerization involved the addition of an electronically excited molecule to the ground state of another to yield the dimeric product. In contrast to the behavior of steroids, compounds such as 15 and 16 gave no dimeric products upon irradiation under conditions which led to steroid dimers.

Cyclic α,β-unsaturated ketones will also yield cycloadducts with olefinic compounds. Corey et al. (22) used the addition of isobutylene to 2-cyclohexenone as the starting point for his synthesis of d,l-isocaryophyllene. Subsequent work indicated the above reaction gave several modes of addition (23). However, the dominant mode of addition gave the compounds 17 and 18 in yields of 26 and 6 per cent respectively with only 6 per cent of the isomer 19. The reaction is even more



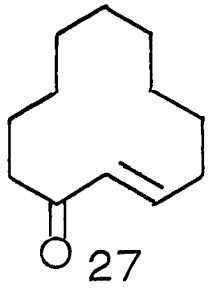
selective with 1,1-dimethoxyethylene where only the two adducts 20 and 21 are formed in 49 and 21 per cent respectively. Corey postulates that the addition is a two step reaction with the intermediate formation of a biradical species. He ascribes the unusual specificity of the reaction to the formation of a donor-acceptor complex with the ketone serving as the acceptor. In this postulate one assumes that the $n \rightarrow \pi^*$ excitation of the ketone produces an electron rich β-carbon atom and that this will lead to the orientation of the donor-acceptor complex as in 22. This orientation will lead to the observed major products.

In contrast to the formation of adducts such as 20 and 21 with 1,1-dimethoxyethylene, 2-cyclooctenone gave a head-to-head adduct 23 under similar conditions (23). Eaton and Lin (24) postulated that the different mode of addition observed for 2-cyclootenone might be the result of a different reaction path for this molecule. Mulliken and



Roothaan (25) have shown that the triplet state of ethylene has the lowest energy when the planes of the two methylenes are mutually orthogonal which gives a dihedral angle of 90°. An examination of molecular models shows that for 2-cyclopentenone a dihedral angle of 20° is about maximum and for 2-cyclohexenone about 60°. Larger dihedral angles for these molecules result in very highly strained ring systems. However, for 2-cyclooctenone a dihedral angle approximating 180° is possible and this would make a cis-trans isomerization possible like those observed in acyclic systems. Eaton and Lin (24) found that irradiation of cis-2-cyclooctenone (24) gave trans-2-cyclooctenone (25) which was characterized as a very reactive species which will dimerize

or give 1:1 adducts with olefins under suitable conditions. Corey et al. (26) and Eaton and Lin (27) both have recently prepared trans-2-cycloheptenone (26) by irradiation of cis-2-cycloheptenone. The trans-2-cycloheptenone was found to be a most reactive species and is stable only at very low temperatures. Thus the abnormal adducts of 2-cyclooctenone with 1:1-dimethoxyethylene could be explained as an addition to the very reactive trans-2-cyclooctenone ground state. Equivalent experiments with 2-cyclohexenone failed to give any adducts (26). It would appear that the feasibility of cis-trans ring isomerizations are a function of ring size, becoming more facile with increasing ring size. In accord with this observation, Zozaki et al. (28) has recently reported the facile trans-cis photoequilibrium of trans-2-cyclododecenone (27) and cis-2-cyclododecenone (28). It is found that the isomerization is a rapid photo-equilibrium. The cis-isomer is also capable of a further reaction via intramolecular γ-hydrogen abstraction to yield the β,γ-unsaturated ketone (29).



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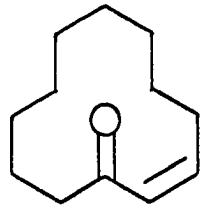

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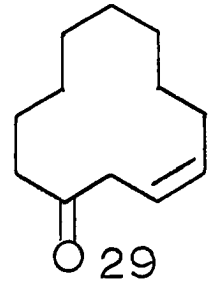

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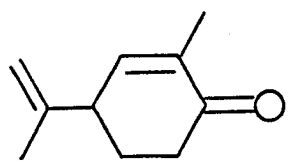
One of the more unusual cycloadducts is that formed by the irradiation of carvone (30) to give carvonecamphor (31). Ciamician and Silber (29) prepared 31 in 1908, but it was not until 1957 that Büchi and Goldman (30) unambiguously proved the structure. Structure 31 is

different than that predicted by the theory of Corey. However, the molecule is a 2-methyl-2-cyclohexenone and such compounds were shown to be very unreactive toward cyclization by Corey et al. (23) and Rettig (31). Thus an intramolecular cyclization of the type 30 to 31 may be the end result of a combination of directive factors.



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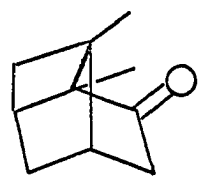

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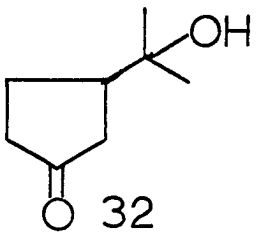
Solvent addition or reduction

One of the initial reports of solvent addition was by Pfau et al. (32) in 1962. They reported that the benzophenone sensitized irradiation of 2-cyclopentenone in isopropyl alcohol gave the adduct 32. In contrast to this result, a similar irradiation of 3,5,5-trimethyl-2-cyclohexenone gave an adduct with benzophenone assigned the structure 33, presumably by addition of the radical species 34.

In 1964 Williams and Blandon (33) carried out a systematic study of solvent addition using as a model 3β-acetoxy-pregna-5,16-diene-2-one (35). Irradiation of 35 was carried out in a variety of solvents. Solvents such as methanol, ethanol, isopropanol and cyclohexanol gave 36 by addition of the α-carbon of the solvent to 35 and the reduced product 37. As the steric bulk of the solvent increased the amount of the addition product 36 decreased and more 37 was produced. However, the overall rate

of the reaction was considerably slower. With tertiary butyl alcohol, only 37 was formed and the reaction rate was very slow. Irradiation of the 16-methyl homologue of 35 gave as the sole product the reduced compound 38 regardless of solvent. This was interpreted as the result of a steric effect.



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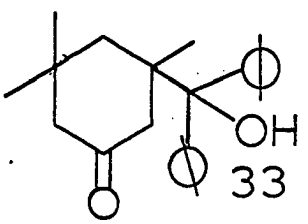

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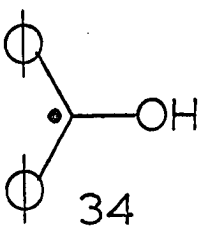

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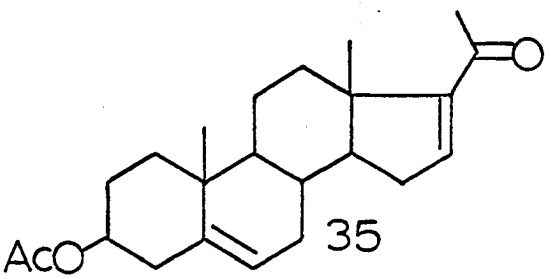

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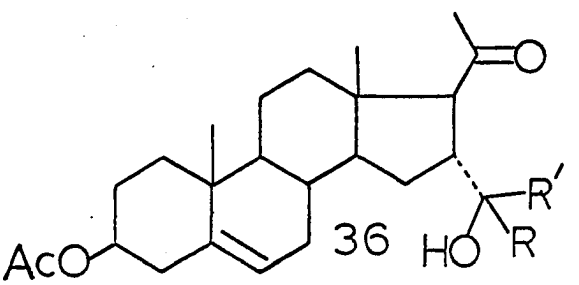

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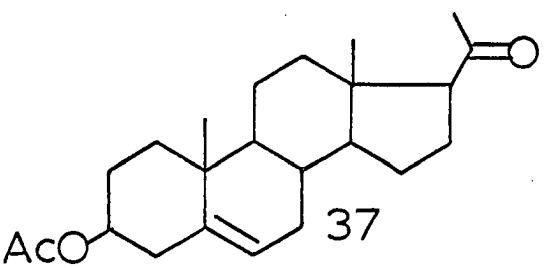

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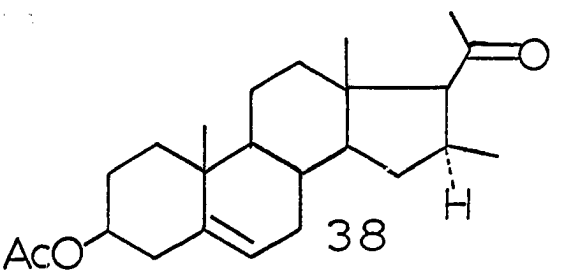

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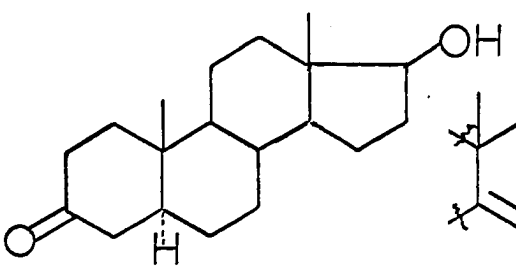

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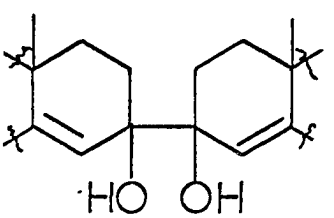

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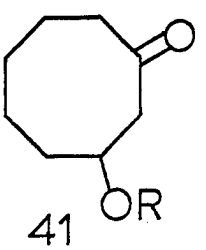

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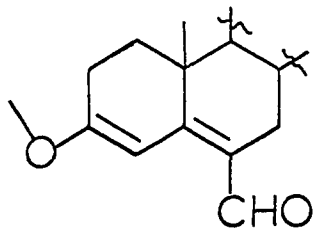
Jeger (Nann et al., 19) also observed this reduction. Irradiation of tesosterone in ethanol gave 5α-androstan-17β-hydroxy-3-one (39) as the major isolated product. Dimeric pinacols have also been reported as products of the irradiation of Δ^4-3-keto steroids in alcoholic or non-polar media (18,19,34). These adducts have the general structure 40. So far these additions have all resulted in products where the α-carbon of the alcohol adds to the β-carbon of the enone system.

Hall (35) reported the irradiation of 2-cyclooctenone in acetic acid, methanol, ethanol, isopropanol and tertiary butyl alcohol. The products of these irradiations were of the general structure 41 where R represents CH_3CO-, CH_3-, C_2H_5-, $(CH_3)_2CH$- and $(CH_3)_3C$- respectively. These additions of the alcoholic solvents constitute one of the first known examples of the photochemical addition of species which could be formally characterized as alkoxy radicals or alkoxides. Just and Pace-Asciak (36) have reported the addition of methanol to 6-formyltestosterone methyl enol ether acetate (42) upon irradiation to give the adduct 43. Chapman et al. (37) has shown that the minor products formed on irradiation of 4a-methyl-4,4a-9,10-tetrahydro-2(3H)-phenanthrone (44) in aqueous acetic acid are the water adducts 45 and 46. Matsuura and Ogura (38) have recently reported another example of solvent addition via solvent oxygen. Irradiation of Pummer's ketone (47) gave rise to a solvent addition product 48 and a rearranged product 49. Irradiation in methanol gave 79 per cent of 48 (R = CH_3). Irradiation in isopropanol



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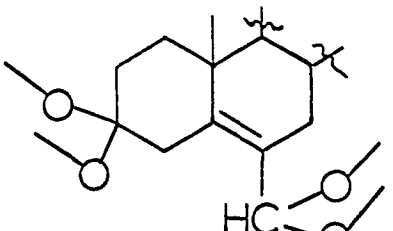

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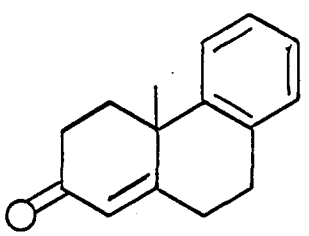

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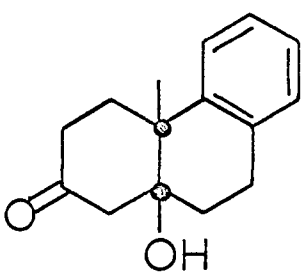

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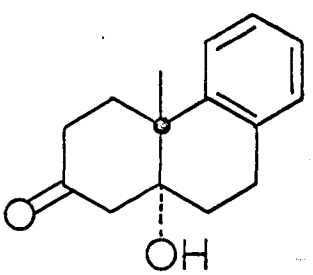

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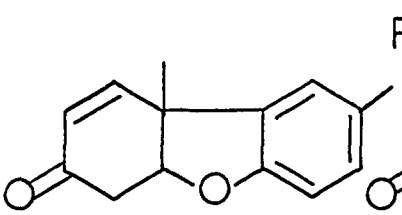

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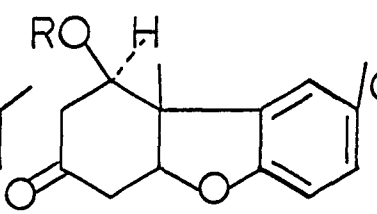

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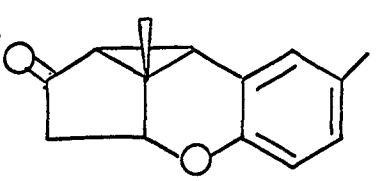


49

gave 37 per cent of 48 (R = $(CH_3)_2CH$-) and 22 per cent of 49. Irradiation in tertiary butyl alcohol, dioxane or benzene gave 43, 31 and 72 per cent of 49 respectively. No 48 was detected in these solvents. It would appear that the addition of solvent can compete with rearrangement in this case for solvents of low steric bulk, but that rearrangement is favored with a bulky solvent such as tertiary butyl alcohol and with those for which hydrogen abstraction is not a facile process such as dioxane and benzene.

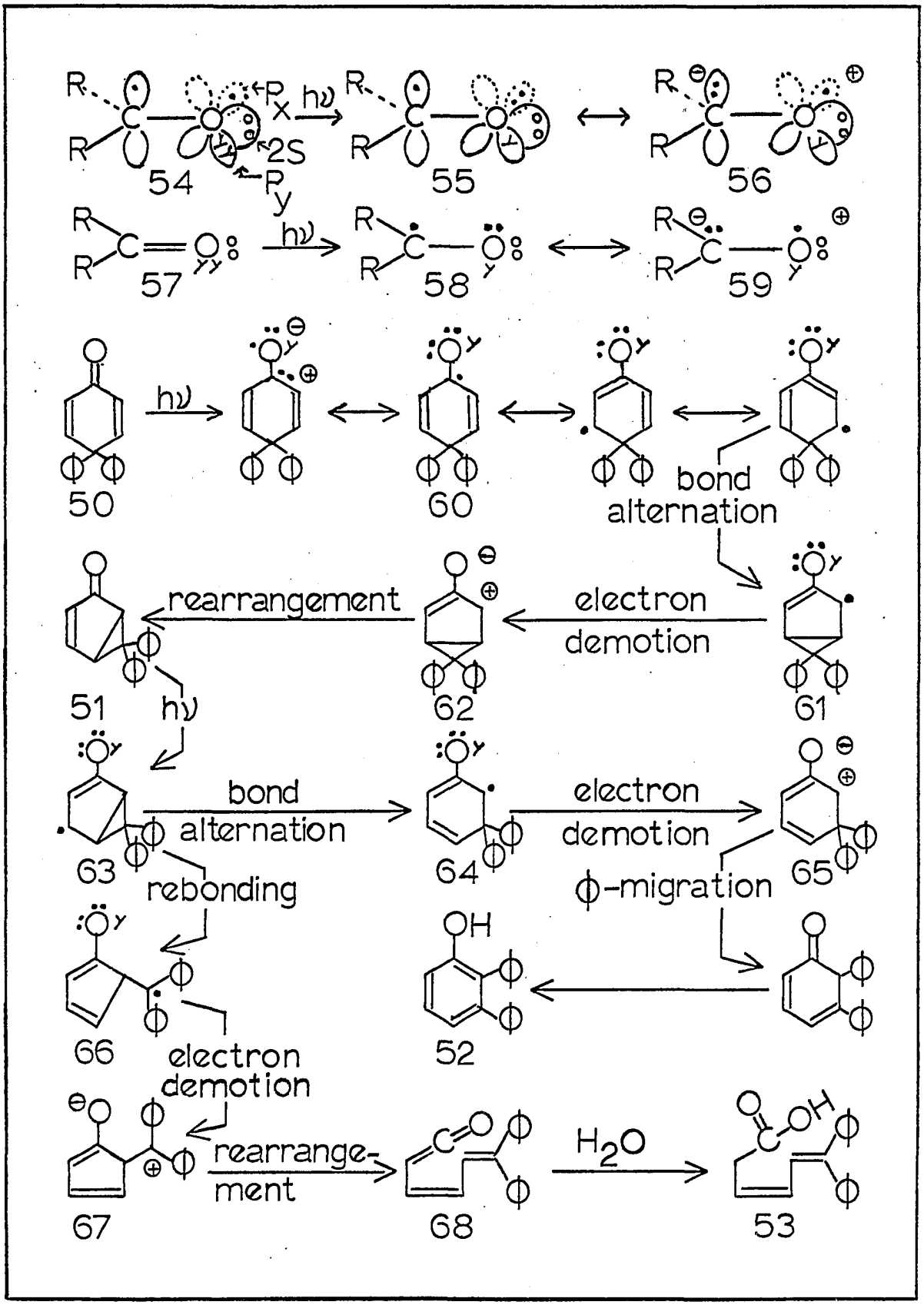
Skeletal rearrangement

The photochemistry of cross-conjugated cyclohexadienones has been one of the most explored areas of skeletal rearrangements. These studies have also furnished most of the data used in structure-reactivity correlations for cyclic α,β-unsaturated ketones.

Zimmerman and Schuster (39) initiated the study of 4,4-diphenylcyclohexadienone (50). The products of the irradiation were characterized as an isomeric ketone (51), a phenol (52) and an acid (53). Subsequent work by Zimmerman and Schuster (40) and by Zimmerman (41) established the structures of the products and led to the proposed mechanistic scheme shown in Chart 1 on page 15. The initial excitation process for a ketone such as 54 would promote a non-bonding electron on oxygen into a π* antibonding orbital. Schematically this is pictured using atomic orbitals in the resonance species 55 and 56. A simpler notation which conveys the same information is shown for the excited state of 57 pictured as 58 and 59. Note that the net effect of an n → π* transition is to make the carbonyl oxygen electron deficient in the excited state.

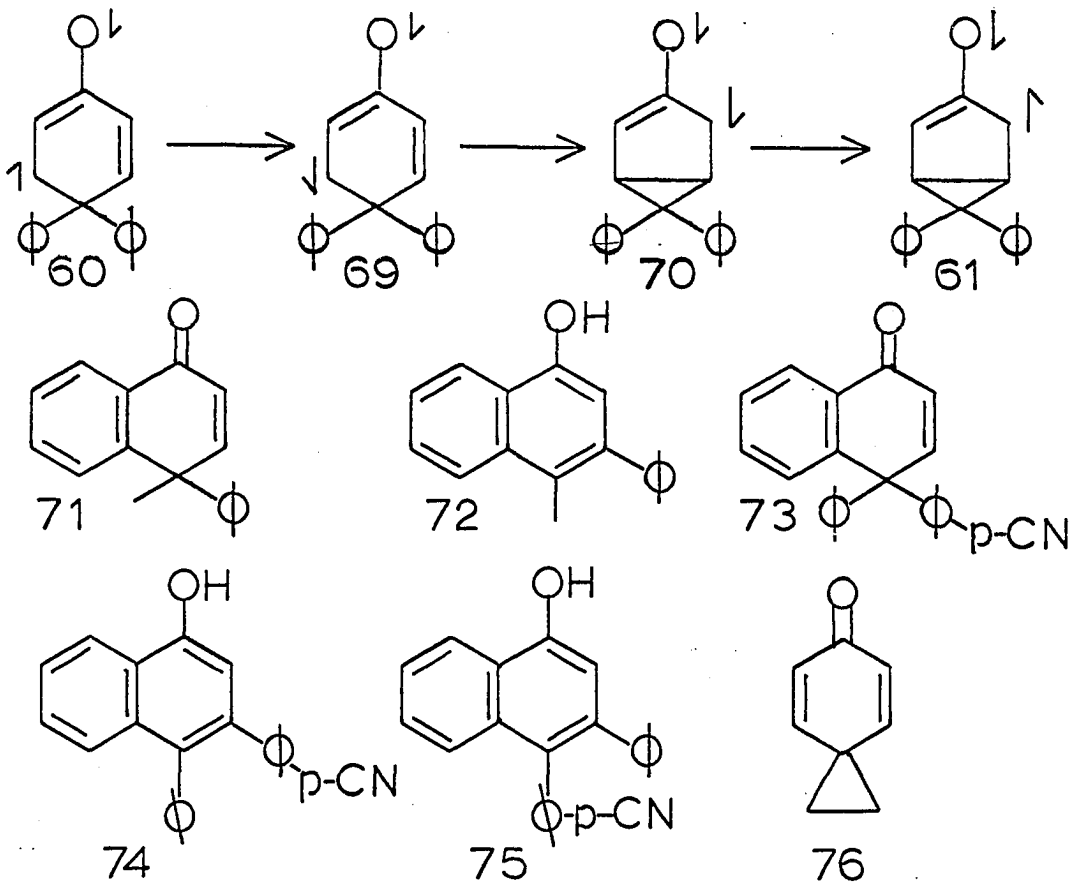
To account for the products of 4,4-diphenylcyclohexadienone, an initial n → π* excitation was proposed to give the excited species 60. Species 60 then undergoes bond alternation to 61 which gives the polar intermediate 62 by electron demotion. Intermediate 62 gives rise to the bicyclic ketone 51 by a series of bond shifts. To account for the formation of the phenol and acid products, the route from 51 was proposed. Initial excitation of 51 gave the intermediate 63. By bond alternation 63

Chart 1. Mechanistic scheme for 4,4-diphenylcyclohexadienone (50)


54
55
56
57
58
59
50
60
bond
alternation
rearrangement
electron
demotion
51
62
61
hν
bond
alternation
electron
demotion
63
64
65
rebonding
ϕ-migration
66
52
electron
demotion
rearrange-
ment
67
68
53
H2O

gives rise to 64 which undergoes electron demotion to 65. Phenyl migration occurs from the polar species 65 to yield the phenol 52. Intermediate 63 may undergo rebonding to give 66. Species 66 is subject to electron demotion to give 67 which undergoes rearrangement to the ketene 68. The acid 53 then arises by addition of water to the ketene intermediate. The intermediacy of the charge separated ionic intermediates 62, 65 and 67 is not specified as electronically excited species or as ground state species possessing high vibrational energy. This type of polar species has also been suggested by Chapman and Smith (42) to account for observed photochemical rearrangements.

Studies by Zimmerman and Swenton (43) on the nature of the rearrangement of 4,4-diphenylcyclohexadienone have led to the conclusion that the $n \rightarrow \pi^*$ triplet state is the reacting species. This was deduced from the fact that the reaction of 50 could be sensitized by known triplet sensitizers and yet was fast enough to avoid quenching via a diffusion controlled process. In terms of a pictoral representation this would simply result in an insertion of a series of intersystem crossing steps between the species 60 and 61, 63 and 64 and 63 and 66 in Chart 1 on page 15. For the route 60 to 61, this could be represented by the triplet species 69 and 70. These intermediates simply represent the triplet species involved in the rearrangement. These steps are included because the electron spins must be paired for the rebonding process.

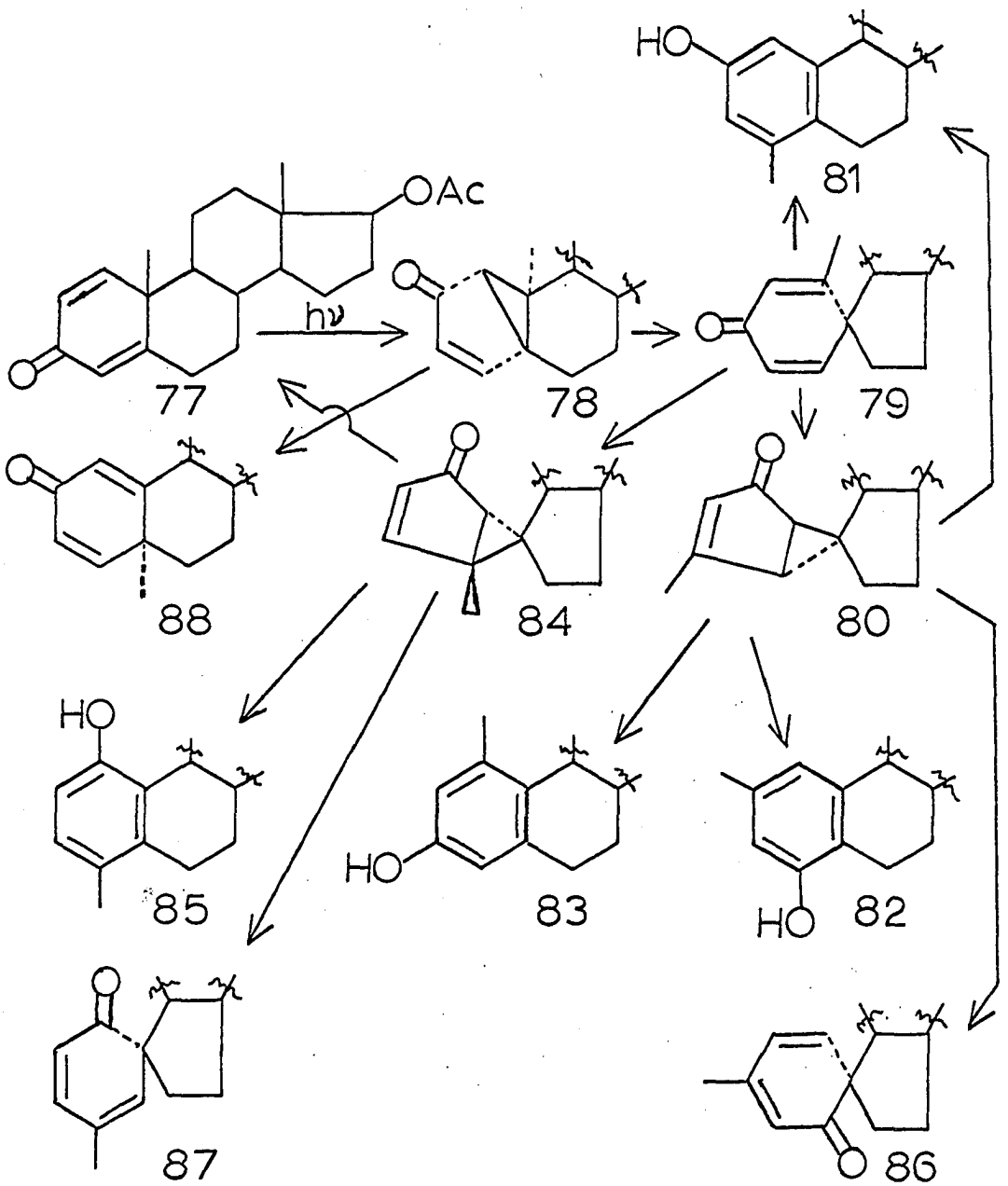


Recent work by Zimmerman et al. (44) involving the irradiation of 71 has given some information about the nature of the β-carbon atom in the excited state. Irradiation of 71 in methanol yields 72 showing that phenyl migration occurs versus skeletal rearrangement. Similarly irradiation of 73 gives 74 and 75 with the isomer 74 predominating. The preference of p-cyano-phenyl over phenyl migration is taken to indicate that the β-carbon atom of system 73 is electron rich in the excited state. Some recent experiments by Schuster and Polowczyk (45) and Schuster and Krull (46) with spiro [2.5]octa-4,7-diene-6-one (76) have shown that this highly strained dienone apparently reacts via a path that is best explained by a diradical and showing little or no

polar character. However, the excited state nature of 76 may be profoundly influenced by its severe ring strain.

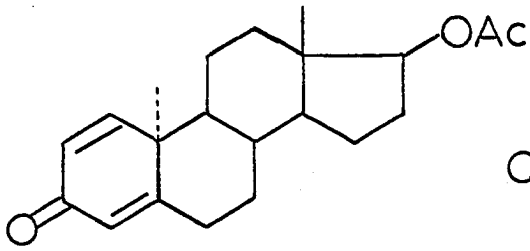
The above studies of 4,4-substituted cyclohexadienones constitutes one of the most intensive mechanistic studies to date of dienone photochemistry. Studies on further substituted cross-conjugated cyclohexadienones are also instructive. In 1957 Jeger (Dutler et al., 47) reported that the irradiation of 1-dehydro-testosterone acetate (77) gave a complex reaction mixture consisting of four ketones and four phenols from irradiation in dioxane. Subsequent study revealed that the reaction mixture was even more complex than orginally thought (48, 49). Many of the products were the result of complex interconversions with the isolated products strongly dependent on the time of irradiation. In 1966 Jeger (Frei et al., elucidated many of the structural interconversions for the irradiation of 77. The principal reaction of 77 is to yield the bicyclic ketone 78. This compound is photo-labile and reacts further to give 79 and 88. The reaction paths of these compounds and subsequent products were established by separate irradiation of the various products. It should be noted that compound 88 is a cross-conjugated dienone and is capable of a sequence of photochemical conversions similar to those of 77. A similar pathway has also been observed for 10α-methyl-1-dehydro-testosterone acetate (89).

In 1965 Hoigne et al. (50) reported that γ-irradiation of dilute solutions of 1-dehydro-testosterone acetate (77) in benzene gave the compounds 78, 79, 80, 83, 84 and 85 in about the same yield as the



ultraviolet irradiation. This remarkable observation was explained by the transfer of energy from the excited benzene used as the solvent.

In contrast to the varied reactions of 77 in dioxane, the irradiation in acetic acid and water gave only two products characterized



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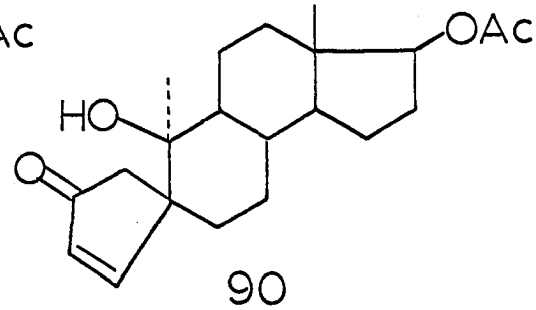
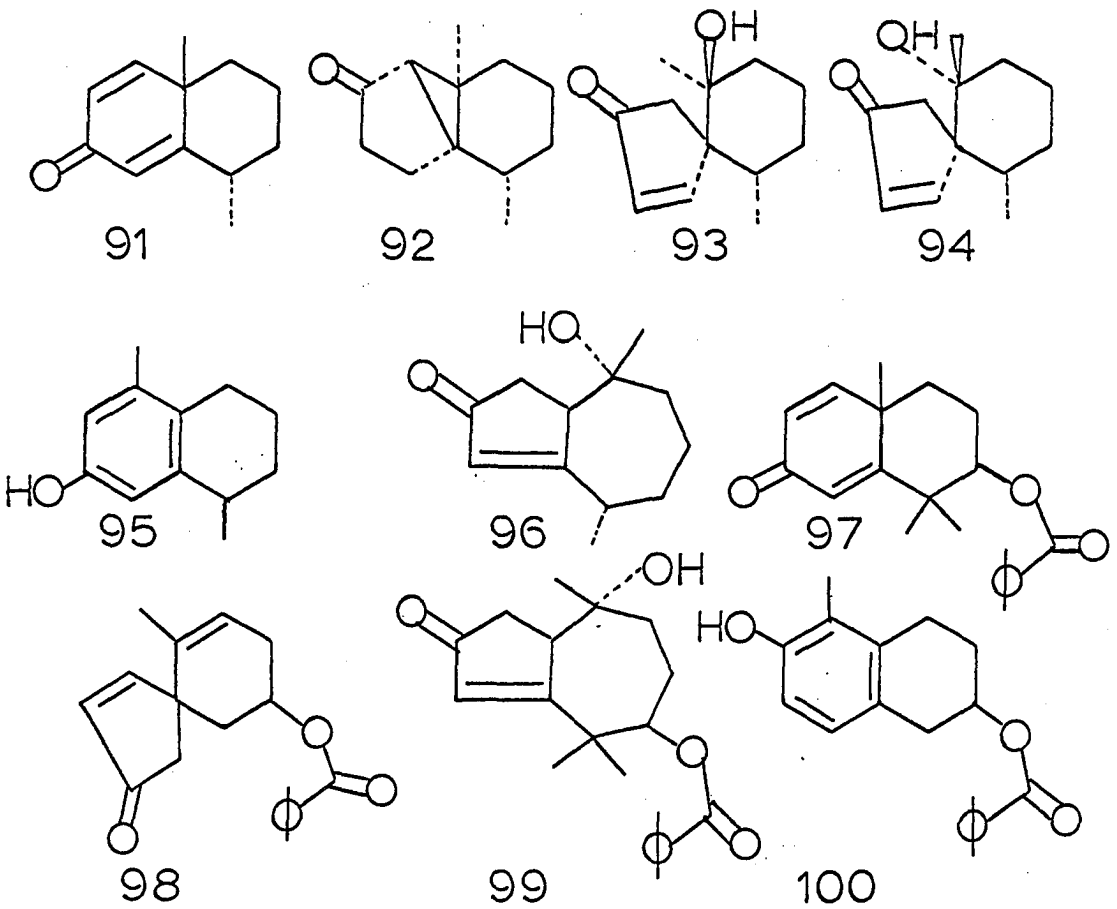


90

as 81 and the spiro compound 90 (51). Compound 90 could also be produced by treatment of 78 with acetic-sulfuric acid mixtures. Irradiation in methanol gave only the phenols 81 and 82 while in glacial acetic acid essentially the same compounds were isolated as in dioxane plus 90 and its two isomeric dehydration products. The complexity of these reactions suggests a strong solvent dependance as well as a length of irradiation factor.

Kropp and Erman (52,53) studied the photochemistry of the cross-conjugated system 91 in aqueous acetic acid. They found that short periods of irradiation gave large amounts of 92 which decreased as the time of irradiation increased. Compound 92 was also responsible for the formation of the phenolic product 95 by a photochemical process. It was found that 92 cleaved to give 93 and 94 in refluxing acetic acid but not at room temperature. Irradiation of 91 at room temperature produced 93, 95 and 96, but no 94. The ratio of 93 to 96 was about one under the conditions of the experiment. It was concluded that 93 and 96 were formed from the same type of intermediate and that 94 was a product of the thermal cleavage of 92. Irradiation of 1-dehydro-

testosterone acetate gave about equal amounts of 90 and the steroidal product analogous to 96. This result is in contrast to that of Jeger (Ganter et al., 51).



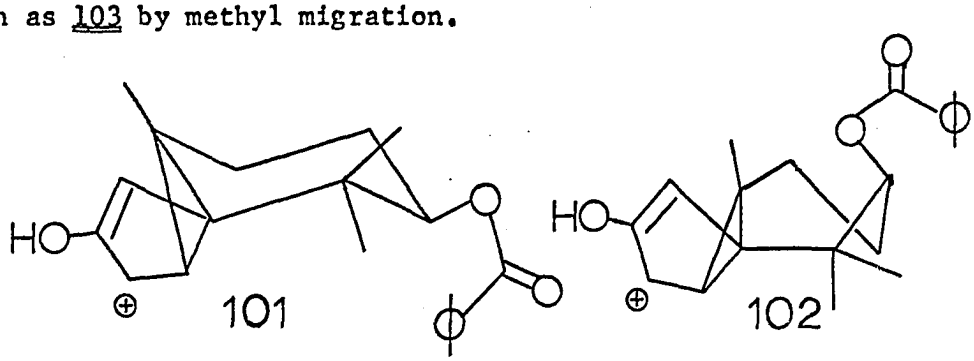
91 92 93 94

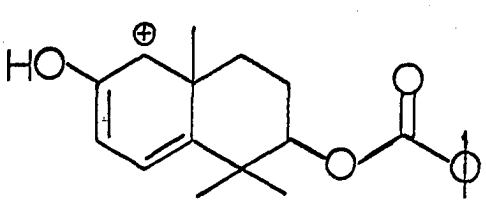
95 96 97

98 99 100

To see if the ratios of products like 93 and 96 could be influenced by steric factors, Kropp (54) irradiated the dienone 97. Irradiation in acetic acid and water mixtures gave 98, 99, and 100 with only traces of the spiro alcohol analogous to 93. The formation of the phenolic product 100 was shown to occur via a species similar to 92. The ratio of 99:98 is about 2.5:1 in 45 per cent formic acid and 3:1 in 45 per cent acetic acid. This is in contrast to the equal

formation of the two alcohols 93 and 96 from the irradiation of 91. Product formation may be viewed as resulting from a charge separated species such as 101 which has previously been proposed (51,52). It can be seen that there is another conformation of 101 designated as 102. Conformation 101 should be preferred over that of 102. Attack of a nucleophilic species such as water at C-10 would be favored from the back side of 101 rather than from the front side. This would lead to 99 rather than an alcohol similar to 93. The dehydration product 98 is formed by loss of a proton from the charge separated species with the conformation 102. The effect of the 6β-methyl is quite striking and this leads to the conclusion that steric effects can be felt even in the highly excited electronic states of organic compounds. The phenolic product 100 could be formed from a species such as 103 by methyl migration.

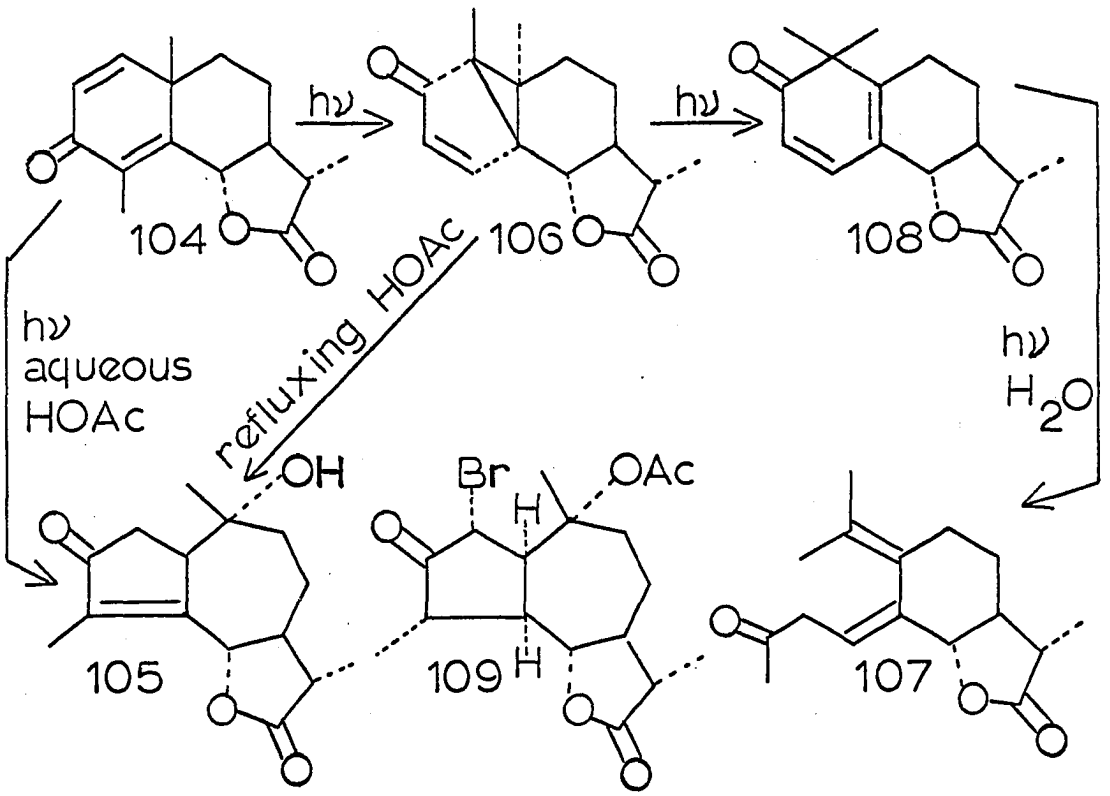




The photochemistry of C-4 substituted cross-conjugated cyclohexadienones is somewhat less complex than that of those lacking a C-4 substituent. One of the most studied cases of C-4 substitution is that of santonin. In 1957 Barton et al. (55) isolated isophotosantonic lactone (105) from the irradiation of santonin (104) in aqueous acetic acid. In the same year Jeger (Arigoni et al., 56) reported the isolation of lumi-santonin (106). In 1958 Barton et al. (57) announced the isolation of lumi-santonin (106) and photosantonic acid (107) from the irradiation of santonin. Irradiation of lumi-santonin in aqueous acetic acid gave isophotosantonic lactone (105). A route to isophotosantonic lactone directly from santonin by irradiation at or below room temperature and a thermal route from lumi-santonin in refluxing acetic acid was postulated to explain the products formed under various conditions (58). Van Tamelen et al. (59) concluded that photosantonic acid (107) results from the irradiation of lumi-santonin. In 1963 Chapman and Englert (60) and Fisch and Richards (61) isolated the intermediate 108 and showed that on further irradiation it was converted to photosantonic acid.

The absolute stereochemistry of isophotosantonic lactone was determined by Asher and Sim (62) by use of the derivative 109. This also permitted the assignment of the absolute stereochemistry of lumi-santonin.

Fisch and Richards (61) determined that the rearrangement of santonin to lumi-santonin proceeds via the triplet excited state.

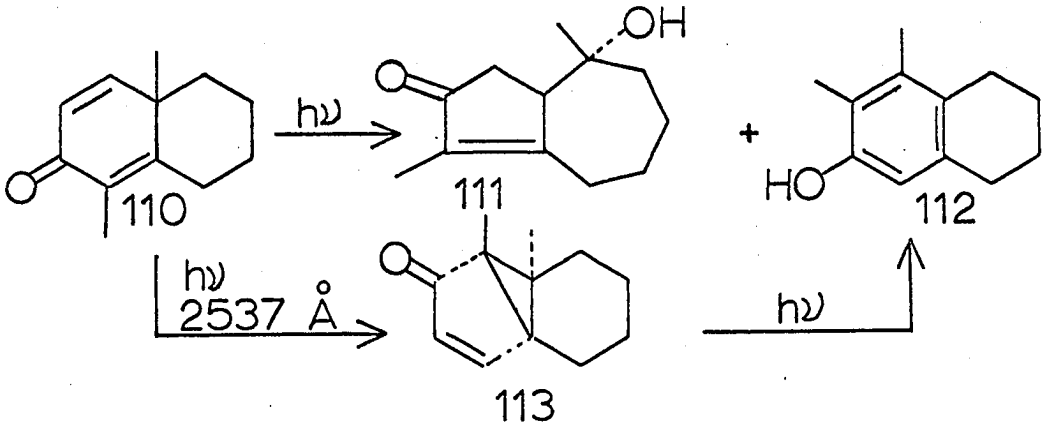


They showed that the reaction could be sensitized by triplet sensitizers, quenched by triplet quenchers and that its quantum yield was nearly unity. They also observed phosphorescence which was assigned to the $\pi \rightarrow \pi^*$ triplet. This conclusion proposes a different excited state than that suggested by Zimmerman and Swenton (43) for the rearrangement of 4,4-diphenylcyclohexadienone.

It might be noted that the route to photosantonic acid (107) via the intermediate 108 is similar to the formation of the phenol 100 from 103.

Other examples of C-4 substituted cross-conjugated cyclohexadienones have been studied. Caine and Dawson (63) irradiated 110 and isolated only 111. Kropp (64) irradiated 110 in aqueous acetic acid and isolated

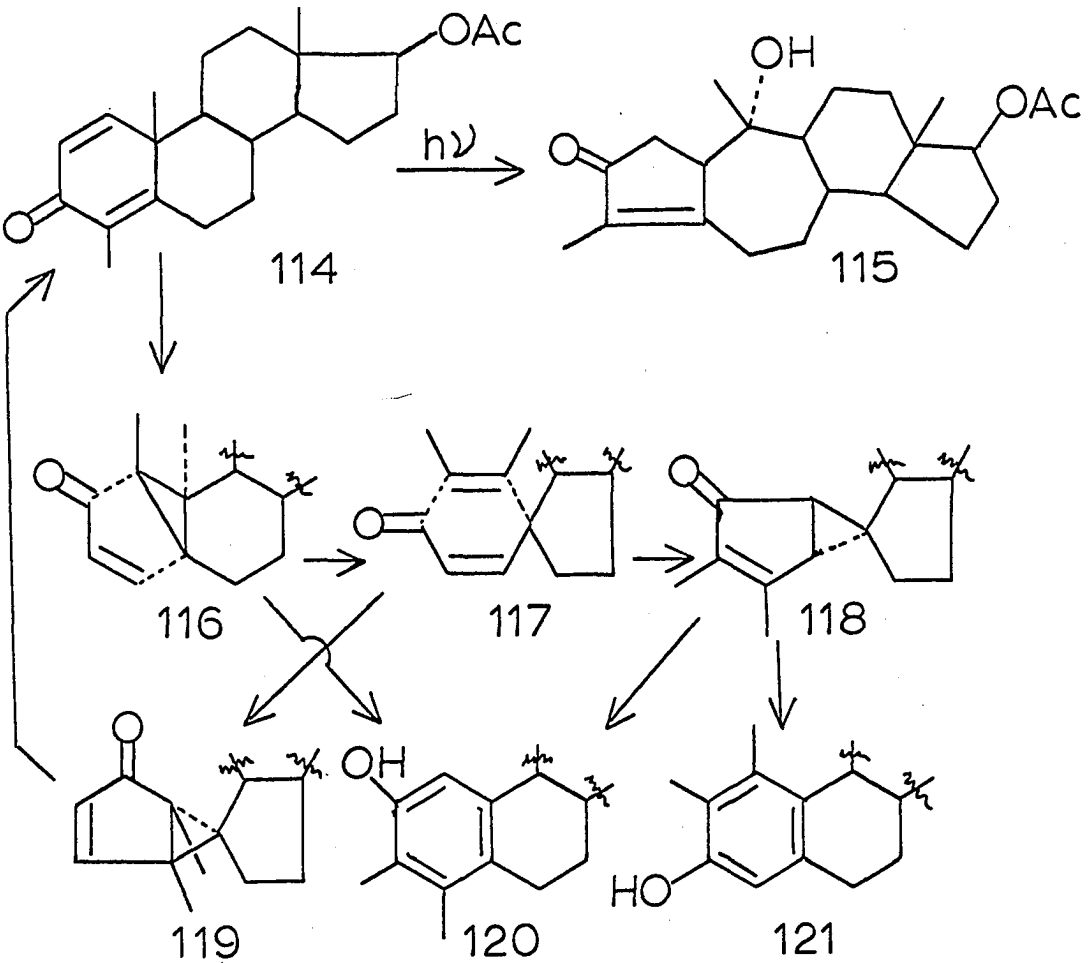
111 and the phenol 112 in 70 and 7 per cent respectively. He found that irradiation at 2537 Å gave the lumi-product 103 which on further



irradiation gave 112. The fact that 111 was formed to the total exclusion of a compound similar to 93 or 98 led to the conclusion that the effect of the C-4 methyl substituent was more electronic than steric. This is based on the observation that the product composition from 110 is markedly different than that from 97 where the effect is known to be steric.

Jeger (Weinberg et al., 65) reported that the irradiation of 4-methyl-1-dehydro-testosterone acetate (114) gave the 5/7 fused ring system 115 and two phenols in refluxing aqueous acetic acid. The formation of 115 was analogous to the rearrangement of santonin to isophotosantonic lactone. In 1966 Jeger (Frei et al., 49) reported the elucidation of the photochemistry of 114 in dioxane.

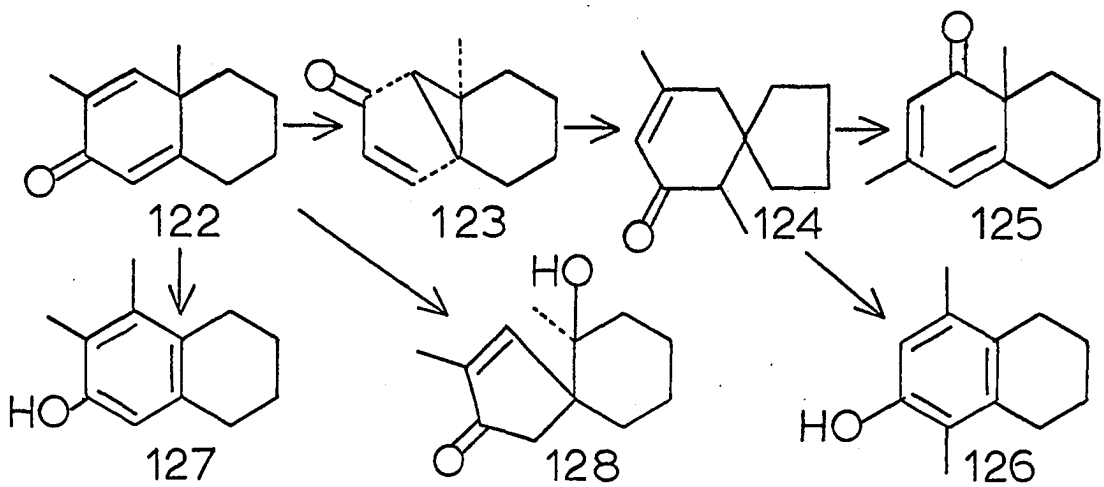
The route to photoproducts from 114 involves the initial formation of the lumi-product 116. It is this species which then gives rise to further photoproducts via its own excited state photochemistry. Compound



117 is a photo-labile species produced from 116 which gives a variety of products on further irradiation.

Kropp (66) studied the light induced rearrangements of a 2-methyl-1,3-cyclohexadienone (122). The dienone 122 gave as a primary product the lumi-isomer 123 in dioxane solution at 2537 Å. Continued irradiation in dioxane gave the products 124 to 127. The route from 123 to 124 and from 124 to 125 and 126 was confirmed by independent irradiation of the photo-products involved. In aqueous acetic acid the spiro-cyclopentenone 128 is also formed and is the major product in this

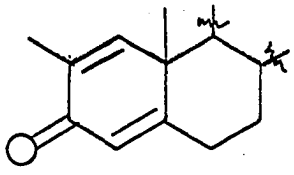
medium. Kropp (67) has shown that the cyclopentenone 128 does not come from an acid catalyzed reaction of 123 under the irradiation conditions. The phenol 127 is the result of a direct rearrangement of the starting material. Phenol 126 can also be prepared by an acid catalyzed rearrangement of 125 as well as by irradiation of 124.



Schaffner (Altenberger et al., 68) and Jeger (Ganter et al., 69, Frei et al., 49) have studied the photochemical rearrangements of 2-methyl-1-dehydro-testosterone acetate (129). The primary rearrangement product in dioxane solution is the lumi-product 130 which is analogous to 123. These workers also isolated products analogous to those found by Kropp. Two new products were also isolated. They were assigned the structures 131 and 132. These products were assumed to be formed from further rearrangements of the lumi-product 130.

Jeger (Frei et al., 49) has also studied the irradiation of 1-methyl-1-dehydro-testosterone acetate (133) in dioxane solution. The primary product was found to be the lumi-isomer 134. Compound 134 is

then capable of further transformations closely resembling those of 1-dehydro-testosterone acetate (77).



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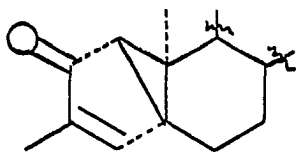

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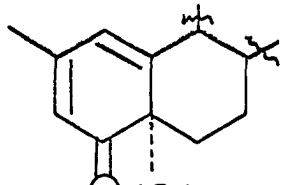

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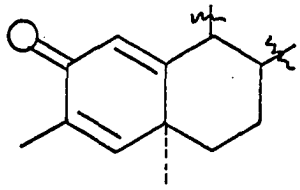

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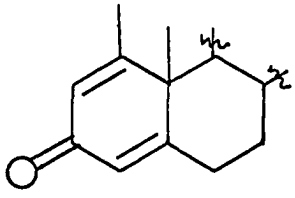

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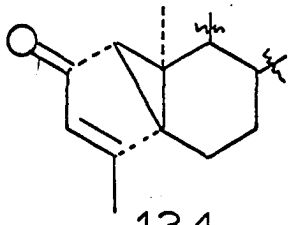
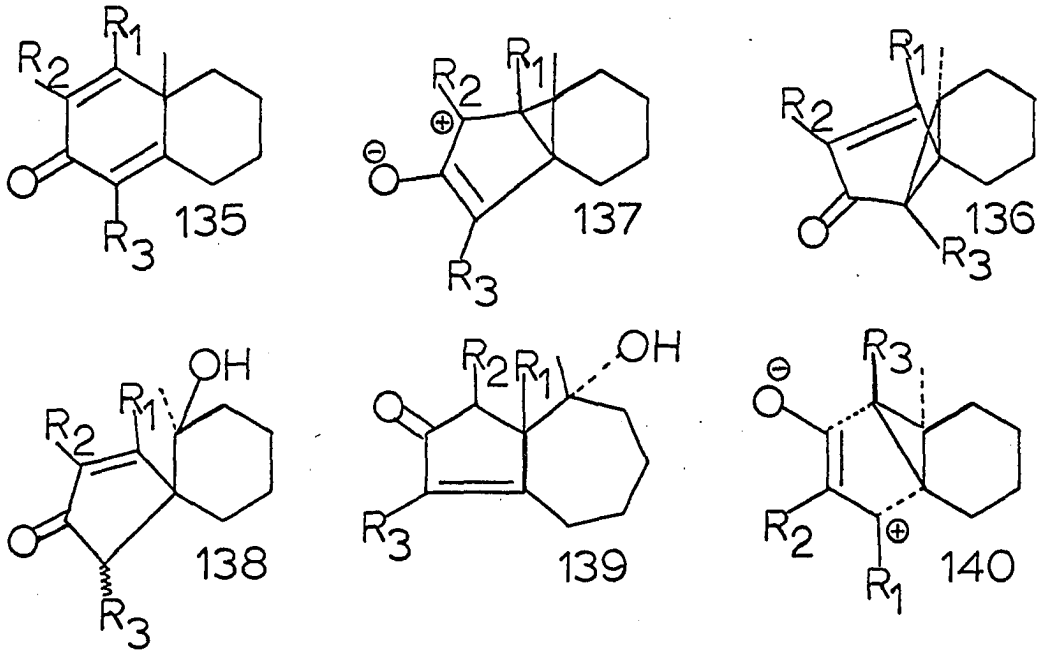


134

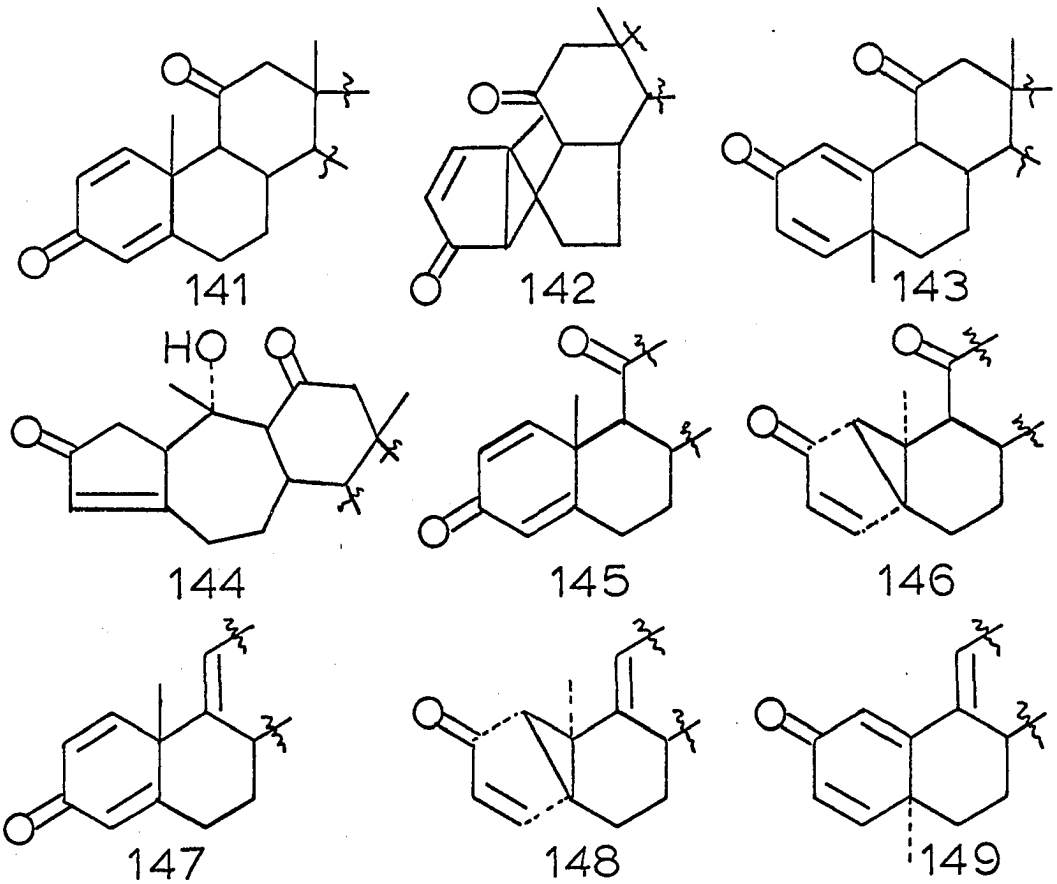
The photochemistry of the cross-conjugated dienones of the type just discussed can be seen to have four reactions paths open to them in non-polar solvents: 1) conversion of 2,5-cyclohexadienones into bicyclo[3.1.0]hexen-3-ones-2, 2) conversion of the bicyclo [3.1.0]hexen-3-ones-2 into new 2,5-cyclohexadienones, 2,4-cyclo-hexadienones or phenolic isomers depending on alkyl substituents, 3) conversions of spirocyclic bicyclo[3.1.0]hexen-3-ones-2 into spirocyclic 2,4-cyclohexadienones and 4) conversions of 2,4-cyclohexadienones into phenolic isomers. The route from a hypothetical starting material such as 135 to the lumi-product 136 can be rationalized via an intermediate like 137. Rearrangements of the lumi-product 136 can be rationalized by the excitation of 136 to give a zwitterionic species such as 140. This type of species may result from the electron demotion scheme discussed



earlier. Cleavage to products such as 138 and 139 may result from nucleophilic attack on the initial species 137. Here the stabilizing ability of the various substituents, the ability of the solvent to stabilize such an intermediate and the steric requirements of the substituents will ultimately determine the products which are formed.

In 1958 Barton and Taylor (70) studied the photochemistry of prednisone acetate (141) and found the major product in ethanol was 142 and in refluxing ethanol 143. In aqueous acetic acid the product formed was the 5/7 fused system 144. The formation of 142 can be rationalized as a preference for migration of the C-9,10 carbon-carbon bond due to activation by the 11-keto function rather than C-1,10 migration as is observed when the 11-keto function is absent.

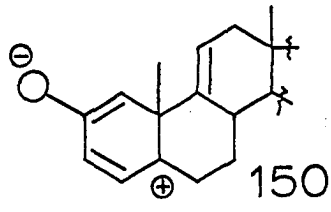
Recently Jeger (Lorenc et al., 71) has examined the photochemistry of $\Delta^{1,4}$-androstadiene-17β-acetoxy-3,11-dione (145) and found that the



main product at 2537 Å in dioxane is the usual lumi-isomer 146. This rearrangement is in contrast to that reported earlier by Barton and Taylor. It is possible that a product similar to 146 was overlooked in the earlier work or possibly the solvent effect would favor migration in ethanol to give 142 rather than a product like 146.

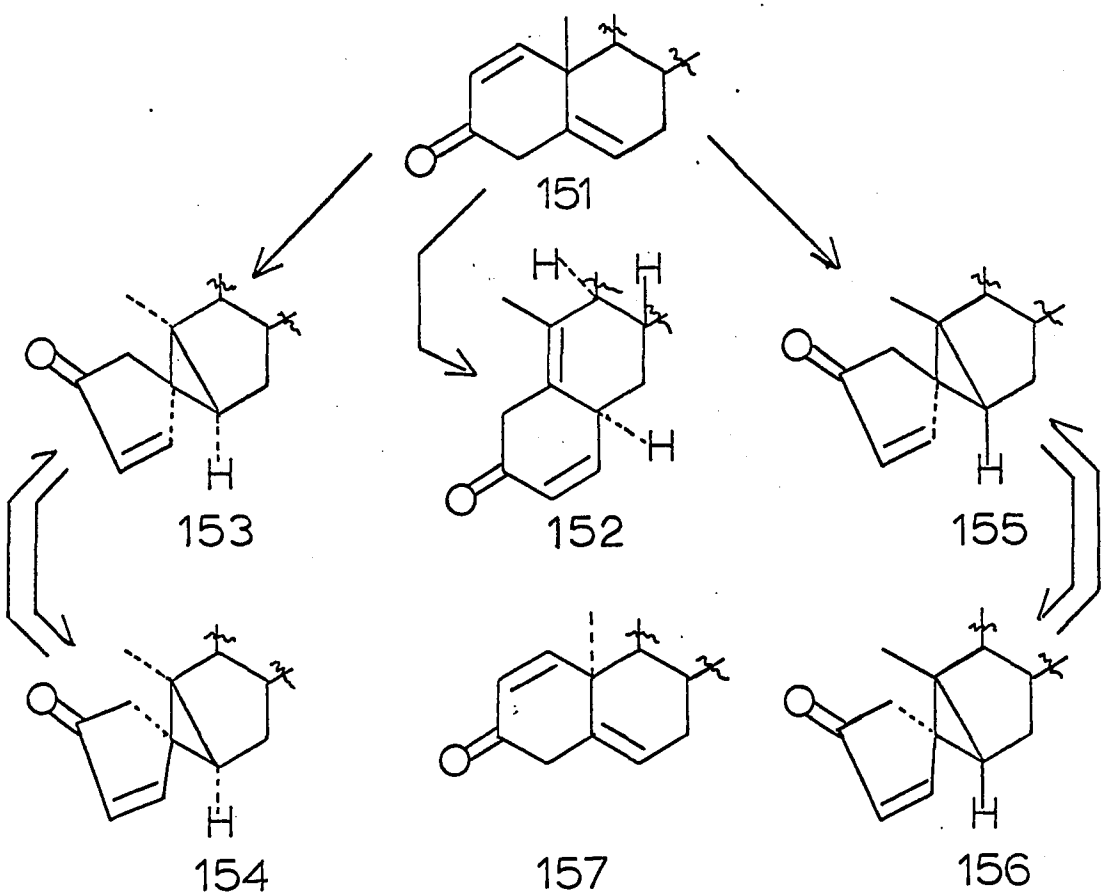
Jeger (Lorenc et al., 71) has also studied the photochemistry of $\Delta^{1,4;9(11)}$-androstatrien-17β-acetoxy-3-one (147) and found that in dioxane at 2537 Å the isomeric compounds 148 and 149 were formed. It was also shown that 148 was converted to 149 on further irradiation. The formation of 149 from 148 can be visualized as a case of C-19 methyl migration rather than a C-9,10 bond migration in the intermediate

150. Migration of the C-9,10 bond in this case would involve a vinylic type of migratory species and would not be favored. If a partial positive charge is developed at C-10, it will be allylic due to the presence of the $\Delta^{9(11)}$-double bond and this may enhance methyl migration.



150

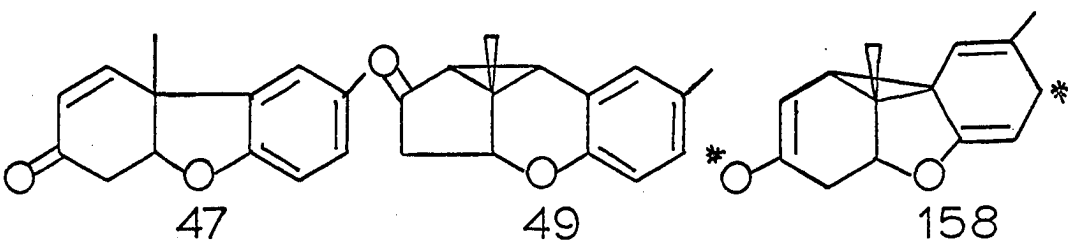
The photochemistry of $\Delta^{1,5}$-androstadiene-17β-acetoxy-3-one (151) is instructive since it is one of the few examples of a non-conjugated diene where double bond participation is possible upon irradiation. Initial work with this system was reported by Jeger (Nann et al., 19) in 1963. In 1966 Jeger (Nann et al., 72) reported the complete photochemical sequence for 151. Irradiation of 151 results in a number of photoproducts which are interconvertable. Short periods of irradiation favor the formation of 152 and longer periods favor the formation of 153, 154, 155 and 156. A similar irradiation mixture results from the irradiation of 157 which is the 10β-methyl epimer of 151. The species 153 and 154 are photochemically interconvertable as are 155 and 156. The interconversion probably occurs by a reversible cleavage of the C-5,10 or C-5,6 bonds in the compounds 153, 154, 155 and 156 followed by a rotation and recombination. The ultraviolet spectrum of 151 does not show a significant enhancement due to overlap of the enone chromophore with the $\Delta^{5,6}$-double bond, so it is assumed that the interaction must develop at a later stage in the rearrangement process.

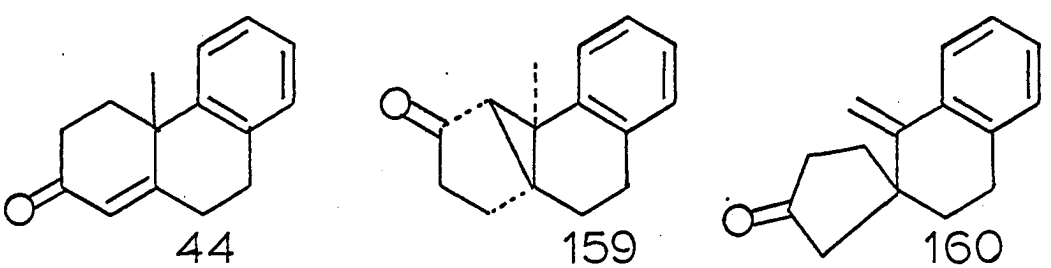


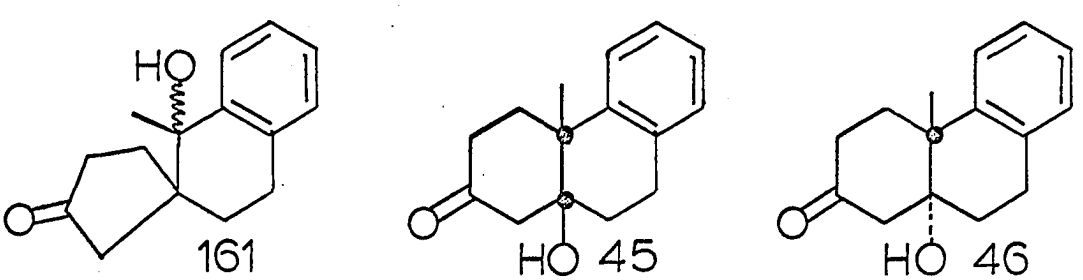
The formation of 49 from Pummer's ketone (47) reported by Matsuura and Ogura (38) in tertiary butyl alcohol, dioxane and benzene may also be an example of the participation of an electron rich moiety in a photochemical rearrangement. In this case it would involve the participation of the phenyl system. The ketone 47 has an exalted ultraviolet spectrum and this may make the participation more probable via an intermediate such as 158.

Another possible source of such an interaction is the photochemistry of 4a-methyl-4,4a-9,10-tetahydro-2(3H)-phenanthrone (44) which has been studied by Zimmerman et al. (34, 73) and by Chapman et al. (37). The phenanthrone 44 like 151 did not exhibit an enhanced ultraviolet spectrum.

It was found that irradiation of resolved 44 gave 159 with a minimum optical purity of 95 per cent. This indicated that the rearrangement proceeded in a highly stereospecific manner. Irradiation of 44 in tertiary butyl alcohol gave 159 (70%) and 160 (1.5%). Irradiation in aqueous acetic acid gave 159 (2%), 160 (5%), 161 (30%) and the epimeric alcohols 45 (1%) and 46 (3%) (37). Control experiments showed

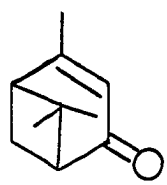






that 160 and 161 were produced via a dark reaction by cleavage of 159 in aqueous acetic acid. Chapman found that the formation of 159 was sensitized by dibenzothiophene and quenched by the addition of piperylene. Zimmerman et al. (73) showed that the conversion of 44 to the lumi-product 159 was sensitized by acetophenone in tertiary butyl alcohol and quenched by naphthalene, biphenyl and di-tertiary butyl nitroxyl. All three

quenchers are triplet quenchers. The quantum yield for the conversion of 44 to 159 is 8.40×10^{-3} which is very low compared with that of 4,4-diphenylcyclohexadienone which has a quantum yield of about 0.8. It was concluded that the triplet state was involved in the reaction but a definite distinction could not be made between an $n \rightarrow \pi^*$ and a $\pi \rightarrow \pi^*$ triplet. Possibly compounds such as 44, 47 and 151 are intermediate in reactivity between cross-conjugated cyclohexadienones and cyclic six membered α,β-unsaturated ketones.



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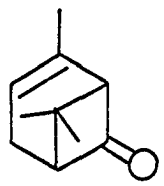

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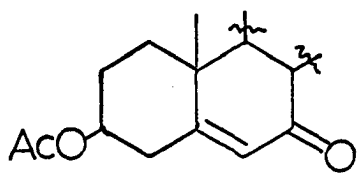

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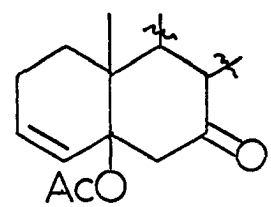

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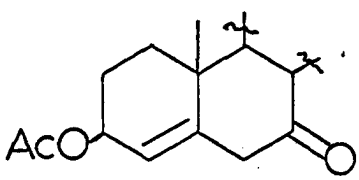

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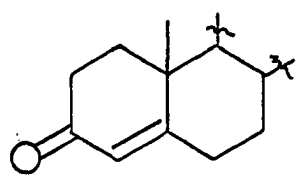

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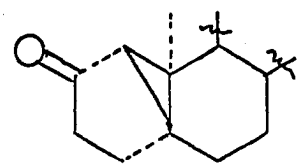

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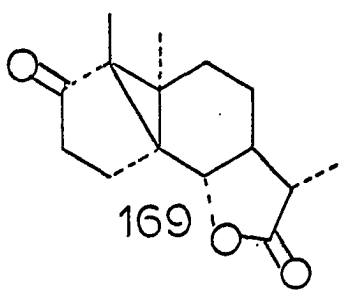

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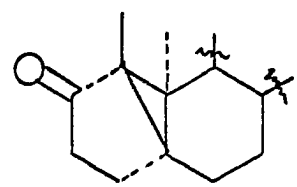

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The photochemical isomerization of verbone (162) to cyhrysanthenone (163) was studied by Hurst and Whitham (74,75). This isomerization was one of the earliest examples of the photochemistry of α,β-unsaturated

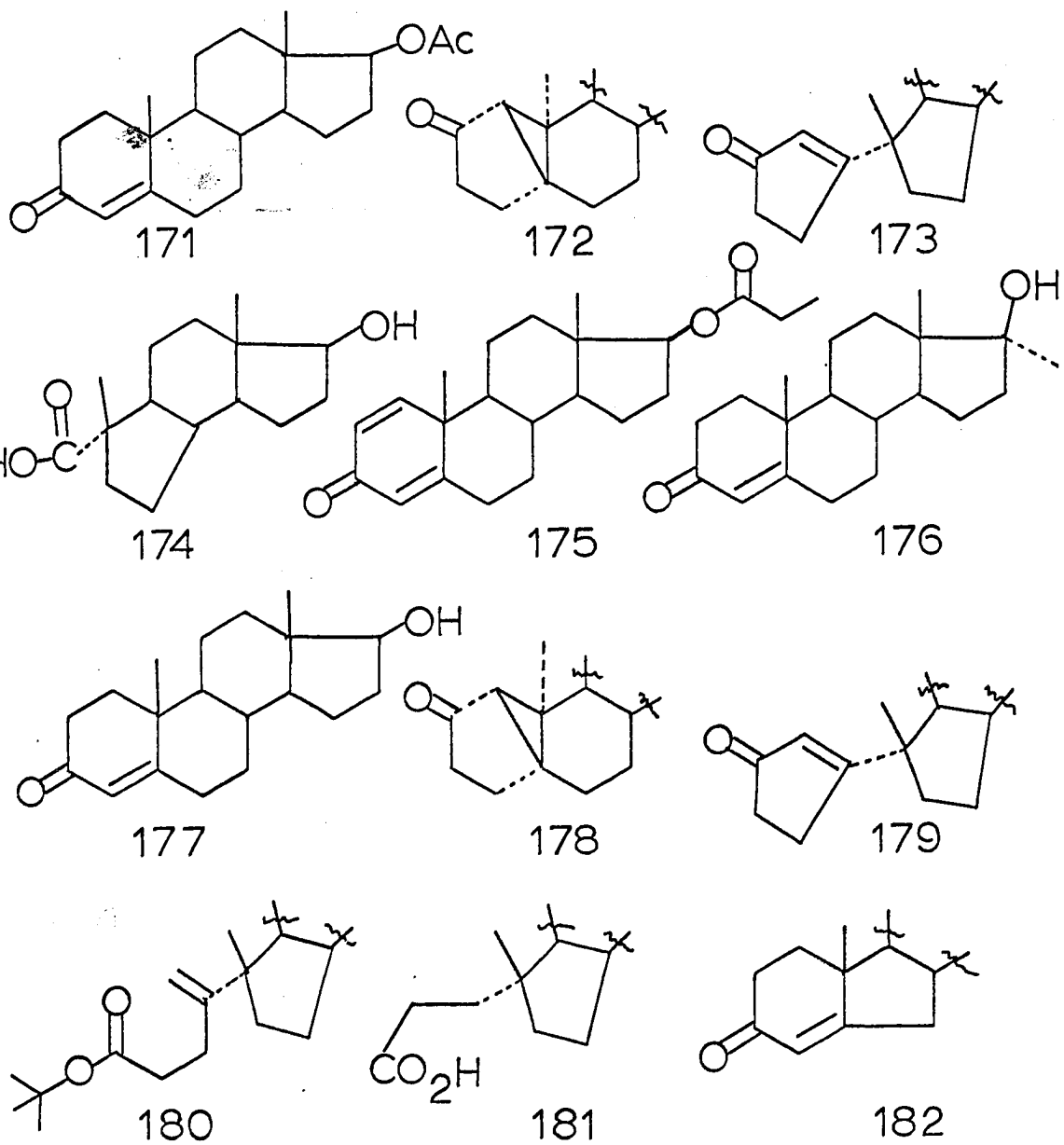
cyclohexenones. A somewhat similar migration was observed by Gardner and Hamil (76) in 1961. They found that irradiation of 7-ketocholesteryl acetate (164) gave two isomers 165 and 166 which were photochemically interconvertable. The two types of rearrangements presented here are suggestive of a positively charged β-carbon atom in the species undergoing rearrangement.

The first reported example of a lumi-product from an α,β-unsaturated cyclohexenone was reported by Gardner (Kwie et al., 77) in 1962. The irradiation of Δ^4-chlosten-3-one (167) in tertiary butyl alcohol gave the lumi-isomer 168 in 25 per cent yield plus some dimeric material which was not characterized. The assignment of the stereochemistry of 168 was made on the basis of the similarity of its optical rotatory dispersion curve with that of dihydrolumisantonin (169) and dihydro-lumi-1-dehydro-4-methyl testosterone (170). This type of assignment has been shown to be valid by Schaffner and Snatzke (78). These workers have examined a series of lumi-type products of varying stereochemistry and structure.

In 1963 Chapman et al. (79) reported the isolation of the lumi-product 172 and the β-substituted cyclopentenone 173 in 32 and 25 per cent yield respectively from the irradiation of testosterone acetate (171). The stereochemistry at C-10 of 173 was assigned on the basis of the ozonolysis of the dibenzylidene derivative of 173 followed by hydrolysis to the acid 174. Caspi et al. (80) prepared the acid 174 by

exhaustive ozonolysis of 175 followed by hydrolysis. Samples of the acids prepared by these two routes were identical.

Chapman et al. (79) also reported that the irradiation of 17α-methyl-testosterone (176) tertiary butyl alcohol gave products with structures analogous to 172 and 173.



171 172 173

174 175 176

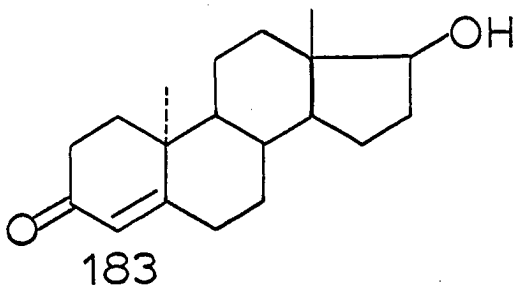
177 178 179

180 181 182

Also in 1963 Jeger (Nann et al., 19) reported the products isolated from the irradiation of testosterone (177). Irradiation of 177 in tertiary butyl alcohol gave 178 (9%), 179 (23%) and 180 (2%). The route to the ester 180 was shown to be via the cyclopentenone 179. Jeger prepared the acid 174 from 179 and also from 1-dehydro-testosterone acetate (77). He converted the acid 174 to the acid 181 by a series of steps which did not involve the asymmetric center at C-10. The acid 181 was also prepared from 182. This series of conversions unambigously confirmed the stereochemical assignments of 179 and 173.

In contrast to the photochemistry of testosterone (177) and testosterone acetate (171), Jeger (Wehrli et al., 81) reported that 10α-testosterone (183) gave only the β,γ-isomer 184 on irradiation in tertiary butyl alcohol. This transformation could be reversed by the addition of potassium carbonate. This result is opposed to the behavior of the phenanthrone 44 which would have the 10α-configuration in one of its enantiomers and also to the behavior of 1-dehydro-10α-testosterone (89) which shows the usual rearrangements of cross-conjugated dienones.

The photochemistry of $\Delta^{1,9}$-10-methyl-2-octalone (16) has been investigated by Zimmerman et al. (73). Irradiation of 16 in methanol or tertiary butyl alcohol yields only the lumi-isomer 185. No other significant products were found. The disappearance of 16 could be sensitized by acetophenone in tertiary butyl alcohol and methanol solutions. Quenching was effective in methanol and benzene solutions.



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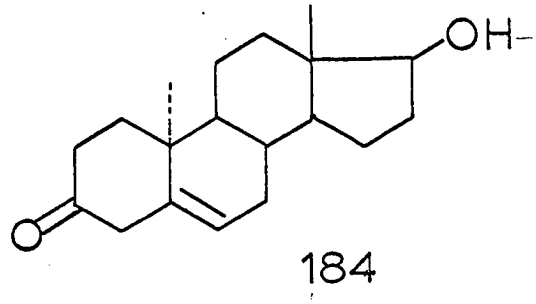

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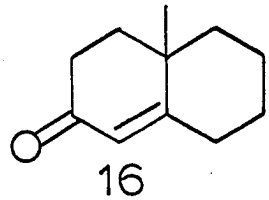

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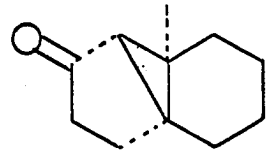

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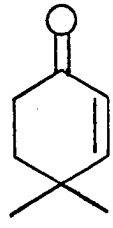

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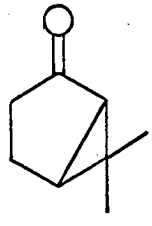

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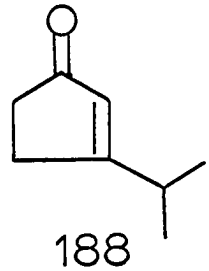

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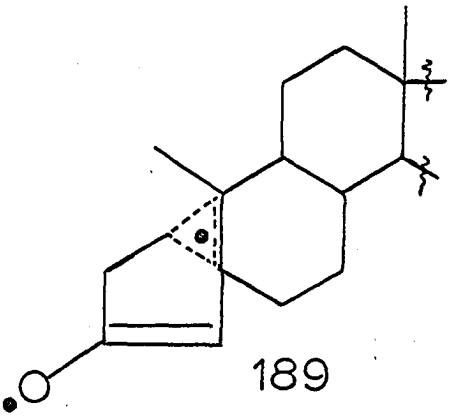
However, a variety of quenchers gave no significant quenching in tertiary butyl alcohol. The quantum yield for the disappearance of 16 was of the order of 4×10^{-3} which is about a factor of two lower than that for 44. The triplet state was proposed as the reactive species for 16. It is rather unusual that ring B contraction which is favored for the steroidal enones is not observed in the case of 44 and 16. Even in compound 47 which was studied by Matsuura and Ogura (38) the product 49 can be visualized as the result of an alkyl migration of the adjacent ring system.

The case of 4,4-dimethylcyclohexenone (186) is also instructive. Chapman et al. (79) found that irradiation of 186 in tertiary butyl

alcohol gave 187 (60%) and 188 (5%). It was also observed that β-isopropyl cyclopentenone (188) was the product of irradiation of 187 under the same conditions as were used for 186. It is not readily apparent why the migration to yield 188 occurs in the simple system 186 and in the steroidal enone systems and yet not in the octalone system 16.

The rearrangements in these compounds can be rationalized by considering a species such as 189 or 190 resulting from the excitation of the enone moiety. Intermediate 189 has a diradical character and may be formalized as a partial formation of the C-1,5 bond before the C-1,10 bond becomes completely cleaved. A bond formation between carbons C-4 and C-10 via electron return with the simultaneous formation of the C-1,5 bond would account for the stereospecific formation of lumi-products such as 178. Bonding between C-1 and C-5 followed by the formation of a carbon-carbon double bond between C-4 and C-5 would result in the migration of C-6 or the C-5,6 bond to the front side of C-10 resulting in the cyclopentenone type of product like 179 with the observed stereochemistry.

An intermediate such as 190 may be formalized as the polar species resulting after rebonding and electron demotion. The charge distribution resembles a $\pi \rightarrow \pi^*$ excited state. In 190 simultaneous migration from C-3 to C-10 of the C-3,4 electron pair of the C-3,4 double bond results in the formation of a C-4,10 bond and gives the



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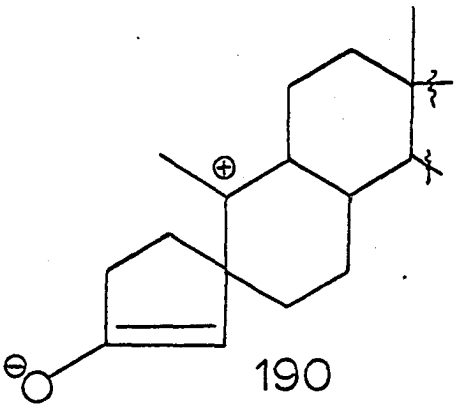

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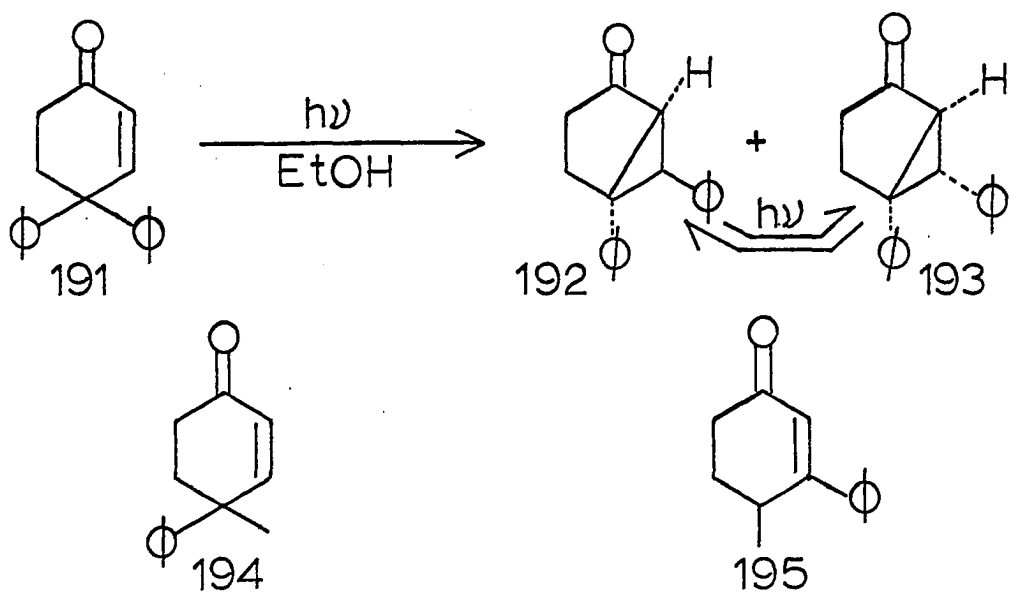
lumi-products such as 178 with the observed stereochemistry. The geometry of the intermediate 190 will only allow attack at C-10 from the front side. If the electron pair at C-3,4 returns to C-5, then the C-5,6 bond is subject to an S_N^i type of displacement resulting in migration to C-10 and bond formation. A synchronous process of this type results in the formation of cyclopentenone type products such as 179 with the correct stereochemistry at C-10. Either 189 or 190 would be subject to steric and solvent effects.

The photochemistry of cyclohexenones discussed thus far indicates that the cyclohexenones are subject to much less efficient rearrangement paths than the cross-conjugated dienones. The products formed are usually stable and not subject to further light-induced rearrangements. However, the remarkable stereo-specificity of the rearrangements is still a distinguishing feature of their photochemistry.

Zimmerman and Wilson (82) studied the photochemistry of 4,4-diphenylcyclohexenone (191) and reported the isolation of two isomeric compounds 192 and 193 which were photochemically interconvertable. The

interconversion of 192 and 193 is analogous to the photochemical interconversions observed in the case of $\Delta^{1,5}$-androstadien-17β-acetoxy-3-one (151) (19,72). The observed products in both systems result from a cleavage followed by rotation and rebonding. The preference for phenyl migration in 191 versus a path of molecular rearrangement as observed for 4,4-dimethylcyclohexenone (186) led to the postulation that the order of decreasing efficiency of photochemical processes was C-4 migration in dienones is more facile than phenyl migration in enones and that phenyl migration in enones is more efficient than C-4 migration in these systems.



Investigation of the photochemistry of 4-methyl-4-phenylcyclohexenone (194) by Rettig (31) led to the isolation of 195 (43%) as the major product. Two minor products were also reported but not characterized. The hydrogen migration in 194 from C-3 to C-4 in the formation of 195 was shown to be intramolecular. This was also shown

to be true in the conversion of 186 to 187. These experiments confirmed the order of activity proposed earlier since here phenyl migration was in direct competition with C-4 migration and with possible methyl migration.

In contrast to the facile rearrangements of 4,4-dimethylcyclohexenone (186), 2,4,4-trimethyl-2-cyclohexenone was remarkably light stable (31). It was also found that 2-cyclohexenone and 4-methyl-2-cyclohexenone gave only dimer and polymer on irradiation and no rearranged products.

The examples presented above are intended to show the diversity of photochemical routes open to α,β-unsaturated cyclic enones. The course of product formation appears to be affected by solvent, degree and type of substitution probably involving both electronic and steric effects and degree and nature of other unsaturated centers present.

Photochemical Reactions of Saturated Ketones

Type I processes

The photochemistry of saturated ketones is usually somewhat less complex but no less useful than that of the α,β-unsaturated ketones. One of the chief differences is the fact that saturated ketones possess the $n \rightarrow \pi^*$ excited state as the only easily reached electronically excited state. Under suitable conditions α,β-unsaturated ketones may have available pathways to both the $n \rightarrow \pi^*$ and the $\pi \rightarrow \pi^*$ excited states.

The primary reaction path for saturated ketones in the vapor phase is the cleavage to carbon monoxide and an olefin. The reaction was first

studied by Bamford and Norrish (83) in 1935. The type I cleavage is completely suppressed in the condensed phase (84). The yields of carbon monoxide were found to be suppressed by the addition of oxygen and iodine leading to the conclusion that this type of process involved a triplet to singlet conversion (85). The suppression of the type I cleavage in solution photochemistry allows the use of this medium to perform some interesting transformations.

Type II processes and cyclobutanol formation

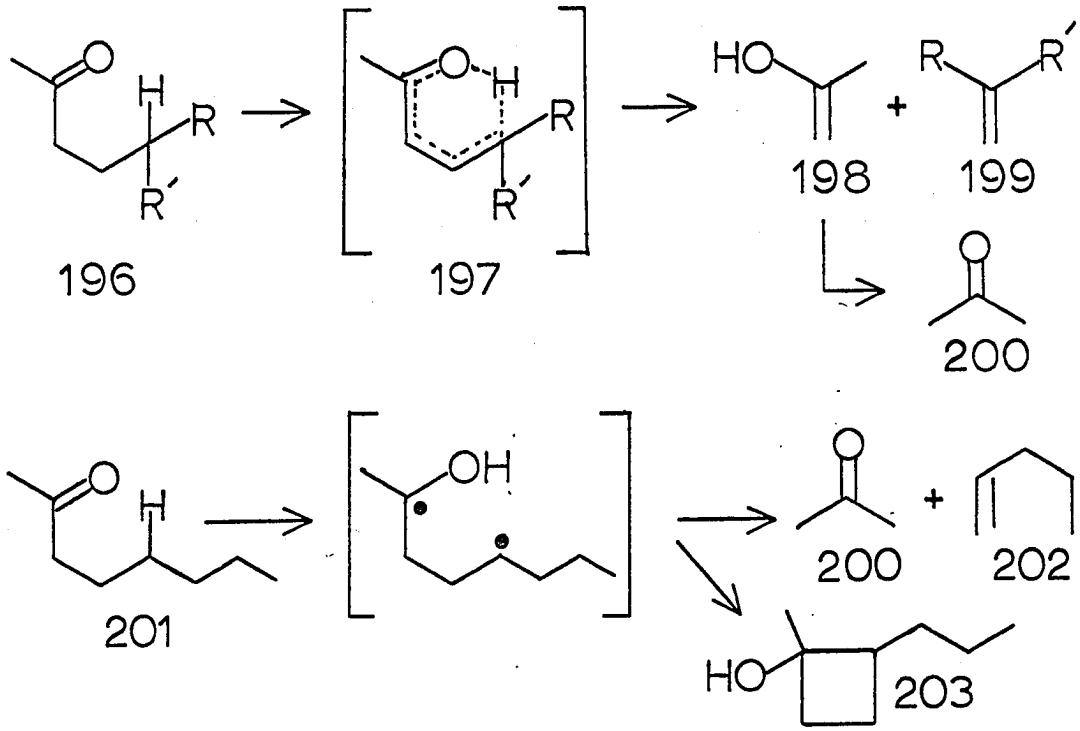
The type II process is characterized as cleavage between the α- and β-carbon atom of a methyl ketone to yield acetone and an olefin. The process has been observed in the vapor phase and in solution (83, 84). Martin and Pitts (86) studied the cleavage of methyl neopentyl ketone and isolated as the major products acetone and isobutylene. They formulated the process as involving a cyclic hydrogen bonded structure of the photoactivated ketone. The quantum yields of acetone and isobutylene are independent of temperature. This supports the cyclic intramolecular nature of the process.

The nature of the oxygen in the $n \rightarrow \pi^*$ excited ketone has been postulated to be electron deficient with a p_y electron localized on oxygen giving a reactive species which should be a good hydrogen abstractor (87,88). Srinivasan (89) irradiated 2-hexanone-5,5-d_2 in the vapor phase and found acetone which was 45% deuterium labeled. A similar irradiation of 2-hexanone in a solvent containing D_2O gave acetone which was 25% deuterium labeled. Acetone itself would not

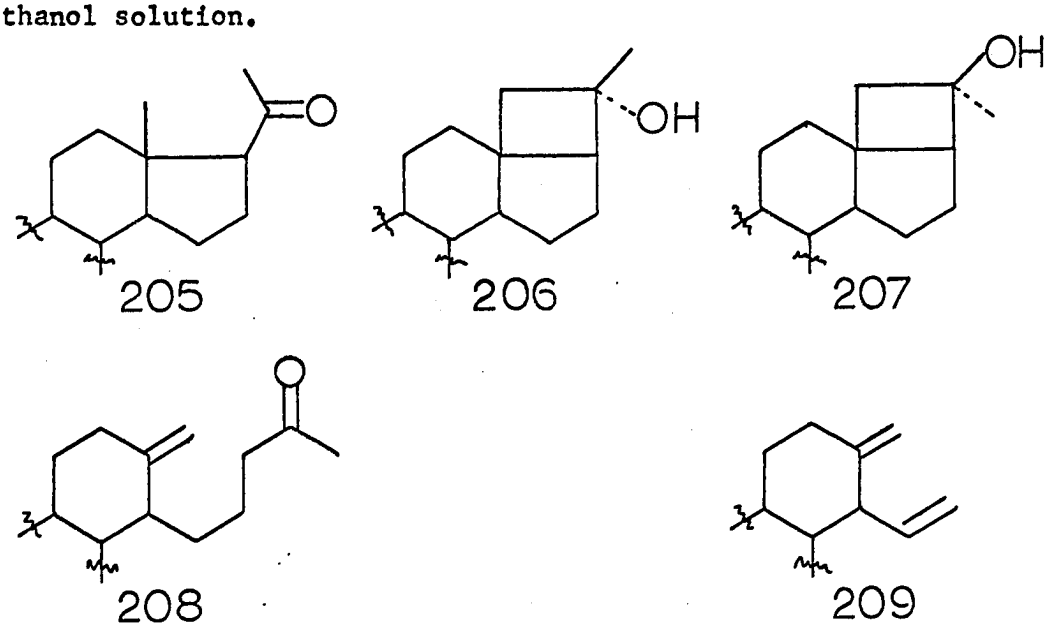
exchange under the conditions of the experiment. These results were explained by the initial production of the enolic form of acetone and olefin followed by the subsequent exchange of the enolic hydrogen with the solvent. This data supports the intramolecular hydrogen abstraction process. In 1964 Pitts (McMillian et al., 90) observed the production of the enolic form of acetone by infrared spectroscopy during the photolysis of 2-pentanone in the vapor phase. These results are accommodated by the formation of an excited species such as 197 from the ketone 196. Cleavage can then occur to yield the enol form of acetone (198) and the olefin 199. The enol form of acetone can then give rise to the observed acetone (200) formation. This scheme does not specify whether the hydrogen abstracting species is singlet or triplet in nature. Recent work by Wagner and Hammond (91,92) and by Dougherty (93) indicate that both the singlet and triplet states of the excited ketone are involved in the hydrogen abstraction process.

In 1960 Yang and Yang (94) reported that the irradiation of 2-octanone (201) gave acetone, pentene-1 and the cyclobutanol 203. A two step type of mechanism giving the intermediate 204 which then undergoes cleavage or cyclization to yield the observed products was proposed.

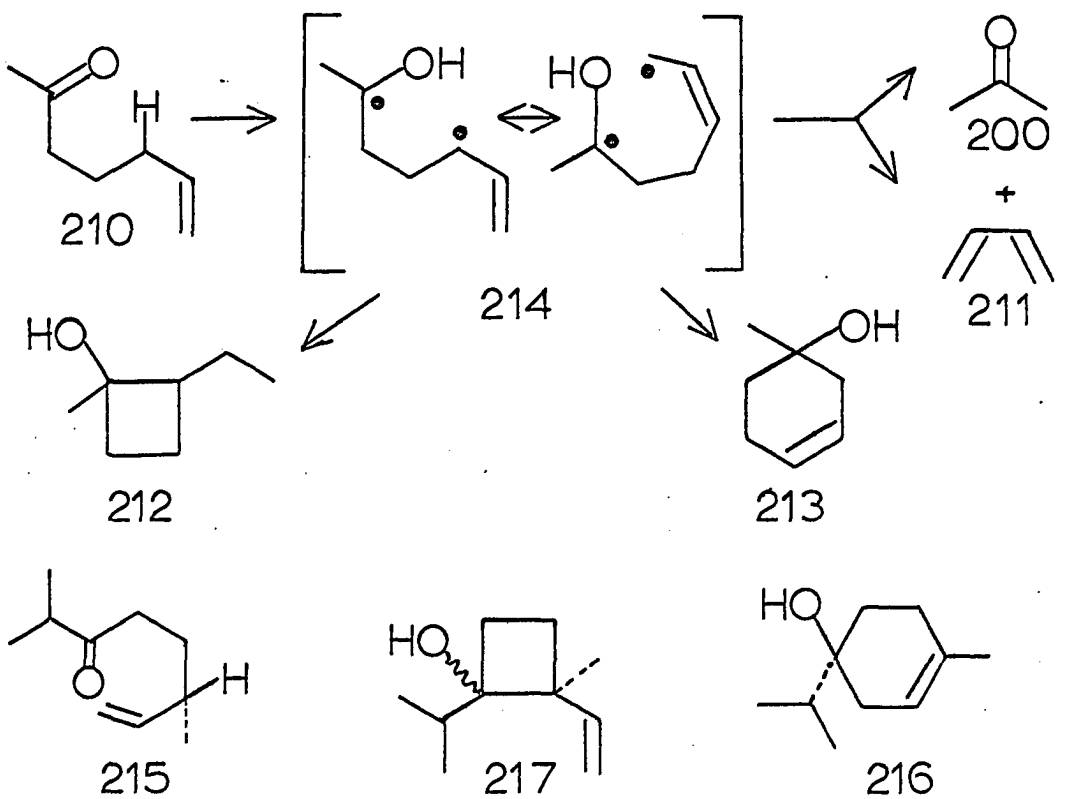
In 1959 Jeger (Buchschacher et al., 95) reported that the irradiation of 20-keto steroids (205) in n-hexane gave a single cyclobutanol isomer. Subsequent work by Yang and Yang (96) and Jeger (Cereghetti et al., 97) on the irradiation of 20-keto steroids in ethanol showed that two isomeric cyclobutanols were produced with 206 the major product and 207 the minor



one. Both groups also isolated the keto-olefin 208 and the diene 209. The diene 209 arises from the type II cleavage of the keto-olefin 208 (97). The ratio of 206:207 was found to be about 3:1 in either ethanol or methanol solution.



Yang et al. (98) reported that the irradiation of 6-hepten-2-one (210) gave acetone, butadiene (211), 1-methyl-2-vinyl cyclobutanol (212) and 1-methyl-3-cyclohexenol (213). These results were interpreted on the basis of an intermediate such as 214 which could yield either type of product. This interpretation is consistent with a two step mechanism and indicated that the reactive state may be a triplet since the intermediate radical was free to delocalize over the allylic system.



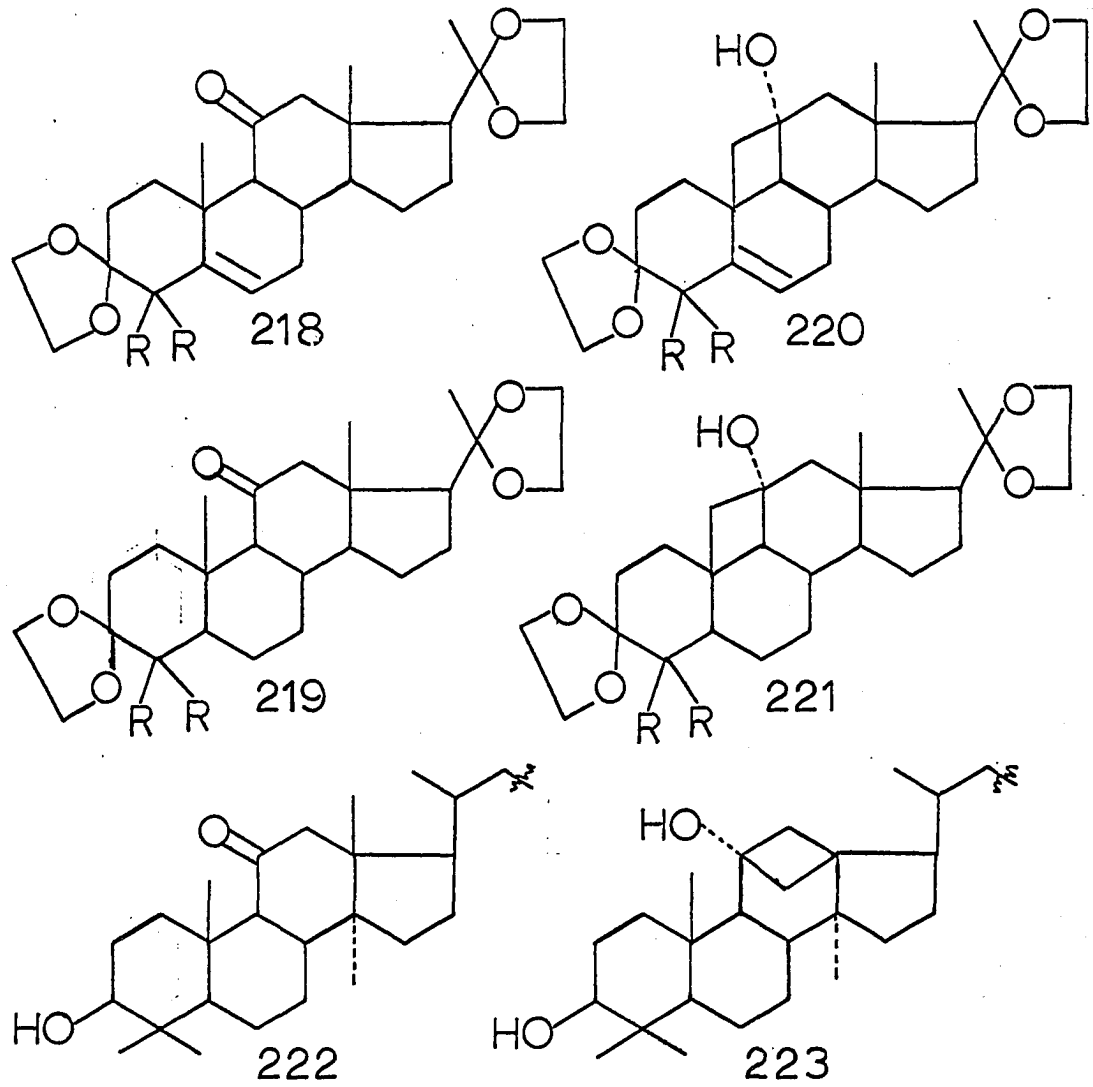
Jeger (Orbar et al., 99) irradiated (5R)-5,9-dimethyldecan-2-one in pentane solution and obtained two optically active cyclobutanols. The net retention of optical activity was 25 per cent. This observation is consistent with the production of a short lived intermediate whose rates of racemization and cyclization are of the same order of magnitude.

In 1964 Schulte-Elte and Ohloff (100) reported the isolation of the optically active terpenoid 216 and the cyclobutanol 217 from the irradiation of 205. Only one isomeric cyclobutanol was isolated and the terpene 216 was isolated in only 2.5 per cent yield. The results were interpreted on the basis of a one step concerted process. However, the low yields of the products obtained make a definite distinction subject to some doubt.

Wagner and Hammond (91) and Dougherty (93) have shown that both the singlet and triplet states of the excited ketone are involved in the type II process and cyclobutanol formation as discussed earlier.

Recently Wagner and Hammond (92) have studied the process in greater detail. They observed both the type II process and cyclobutanol formation using 2-pentanone and 2-hexanone. They found that both acetone formation and cyclobutanol formation were quenched by piperylene in solution but could not be completely quenched. Thus it was concluded the triplet state provides most of the solution photochemistry with some residual singlet reaction. The results indicate that ring closure, inversion of the γ-carbon atom, fragmentation and return of the abstracted hydrogen atom are closely competitive processes.

Jeger (Iriarte *et al.*, 101) studied examples of geminal dimethyl substitution on the photochemical transformations of 218 and 219 to give the cyclobutanols 220 and 221 respectively. It was found that the yield of cyclobutanol formation increased with substitution of geminal dimethyl groups at C-4. The yields were 31 and 51 per cent respectively for 220



where R = H and R = methyl and 47 and 83 per cent respectively for 221 where R = H and R = methyl. An examination of molecular models shows that geminal substitution forces the C-19 methyl into closer proximity with the 11-keto group. This effect is the greatest for the compound 219 and the data support this observation. The exclusive preference for the methyl group at C-19 over that at C-18 is also the result of a proximity effect resulting from the conformation of the steroid skeleton.

A striking example of the reversal of this situation is the 14α-methyl-substituted system of 3β-hydroxy-11-oxo-lanostane (222). Irradiation of 222 in ethanol gives as the sole product in 40 per cent yield the C-11,19 closure product 223 (102). The rationale for the formation of 223 is that the 14α-methyl group alters the conformation of the steroidal system to a degree where the C-19 methyl is preferred over the C-18 methyl.

The facility with which saturated ketones undergo the type II cleavage process and cyclobutanol formation offers unique synthetic advantages. The reaction may be used to prepare cyclobutanols which are difficult to obtain by other methods. The stereospecificity of the reaction and its subtle dependance on steric factors may become even more useful with the development of more inclusive structure-reactivity correlations.

RESULTS AND DISCUSSION

Photochemistry of Testosterone

The rearrangements of Δ^4-3-keto steroids on ultraviolet irradiation which yield cyclopropyl cyclopentanones and 3-substituted 2-cyclopentenones appear to be quite general (See Historical Section). However, one problem which faces any investigator in this area is the proof of structure of the resulting photoproducts. The use of infrared, ultraviolet and nuclear magnetic resonance spectroscopy does not result in an entirely unambiguous structural assignment. If an instrumental method for assignment of structure could be developed this might lead to the wider use of photochemistry to produce intermediates for synthesis.

The advent of organic mass spectroscopy has made the structural assignment of many complex molecules possible with a minimum of time and effort. At the time this investigation was initiated no data was available on the mass spectra of the type of structures usually encountered in the solution photochemistry of Δ^4-3-keto steroids.

Testosterone (177) was chosen for study since its photoproducts and those of its acetate (171) had rigorously proven structures (15,19,79). Also there was some ambiguity in the yield relationships among the various isomers isolated from the irradiation of testosterone and its acetate (19, 79).

The solvent chosen for the irradiation was tertiary butyl alcohol since it had been shown to be an excellent solvent for the photochemical rearrangements desired (15). Irradiation of testosterone in tertiary

butyl alcohol gave two photoproducts. A combination of column chromatography on alumina and Florisil and fractional recrystallization gave testosterone (22%), lumi-testosterone (178) in 31% yield and 28% of photo-testosterone (179). The isolated yields here agree closely with those obtained by Griswold (15) for the irradiation of testosterone acetate.

Lumi-testosterone (178) gave a m.p. of 204-5 °C and the infrared spectrum shown in Figure 1 on page 54 indicated the presence of an alcohol (2.86-2.90 μ) and a ketone (5.88 μ). The melting point and infrared spectrum of 178 were identical to that of the sample prepared by Griswold (15).

Acetylation of lumi-testosterone gave lumi-testosterone acetate (172) with m.p. 167-9 °C. The infrared spectrum of lumi-testosterone acetate given in Figure 1 on page 54 showed the presence of an acetate (5.82 and 7.9-8.1 μ) and a ketone (5.88 μ). The melting point and infrared spectrum of the lumi-testosterone acetate (172) prepared above was identical to that prepared by Griswold (15).

Photo-testosterone (179) gave m.p. 149-50 °C and the infrared spectrum shown in Figure 1 on page 54 indicated that an alcohol (2.86-2.90 μ) and an α,β-unsaturated ketone (5.86, 5.95 and 6.25 μ) were present. The infrared spectrum and melting point of the sample prepared above are identical to those of the photo-testosterone prepared by Griswold (15).

Acetylation of photo-testosterone gave photo-testosterone acetate (173) with m.p. 109-9.5 °C. The infrared spectrum showed the presence of an acetate (5.84 and 7.9-8.1 μ) and an α,β-unsaturated ketone (5.86, 5.95 and 6.25 μ). The spectrum is reproduced in Figure 2 on page 56. The data given above for photo-testosterone acetate are identical to those of an authentic sample previously prepared (15).

With the identity of the photoproducts thus established an investigation of their mass spectra was initiated.

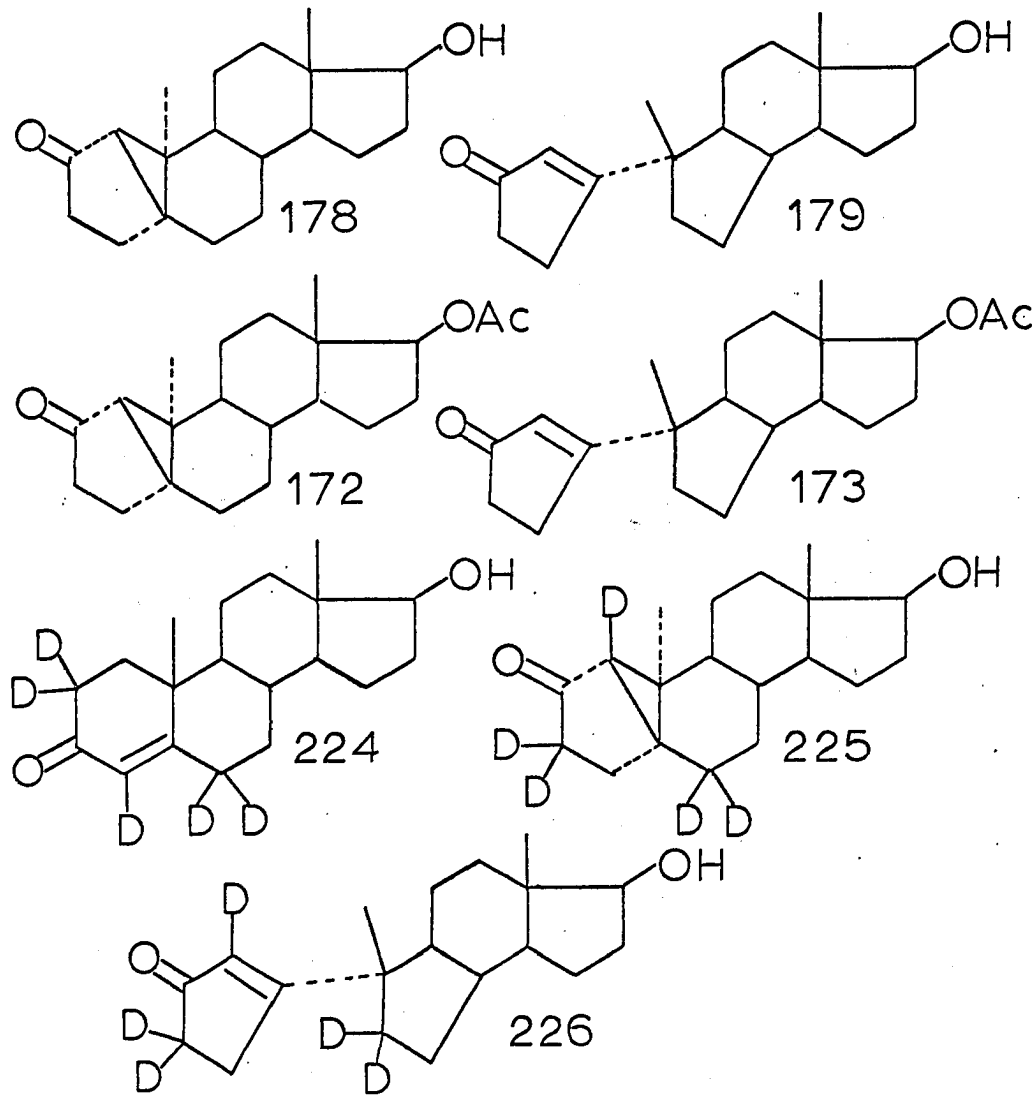
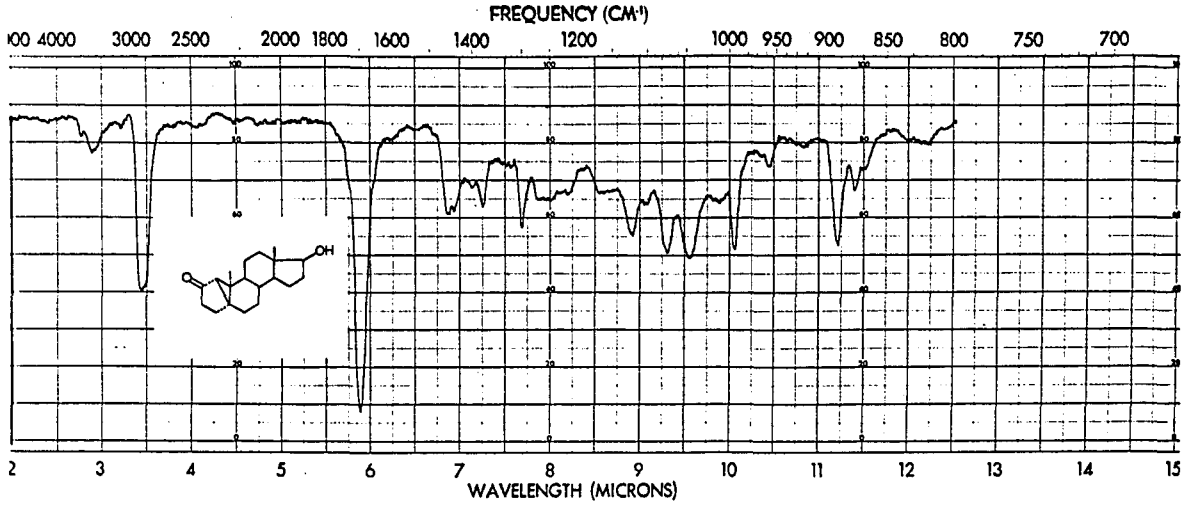


Figure 1. Infrared spectra

Top - Lumi-testosterone (178) ($CHCl_3$)

Middle - Lumi-testosterone acetate (172) ($CHCl_3$)

Bottom - Photo-testosterone (179) ($CHCl_3$)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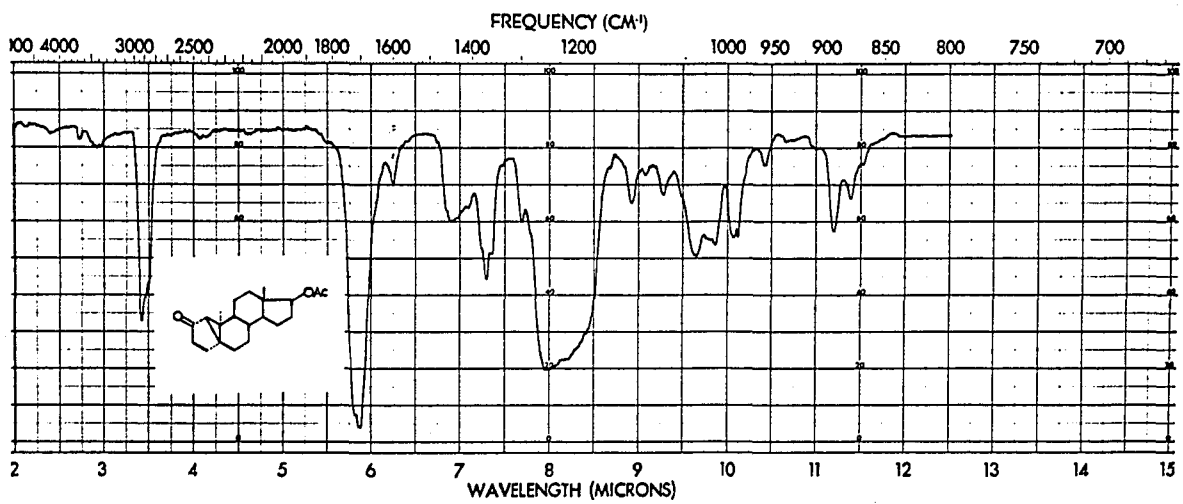
WAVELENGTH (MICRONS)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OAc
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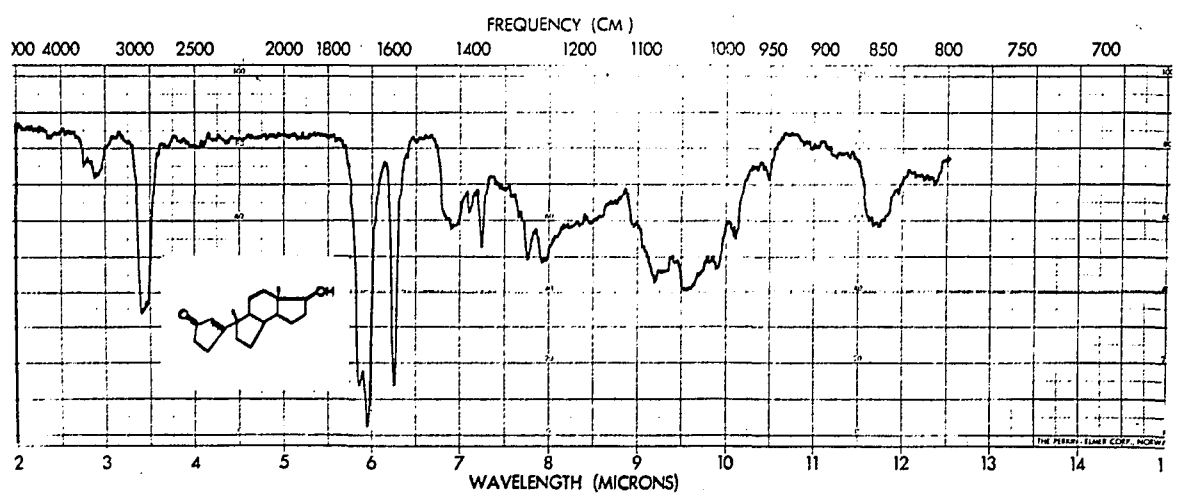
WAVELENGTH (MICRONS)


FREQUENCY (CM)
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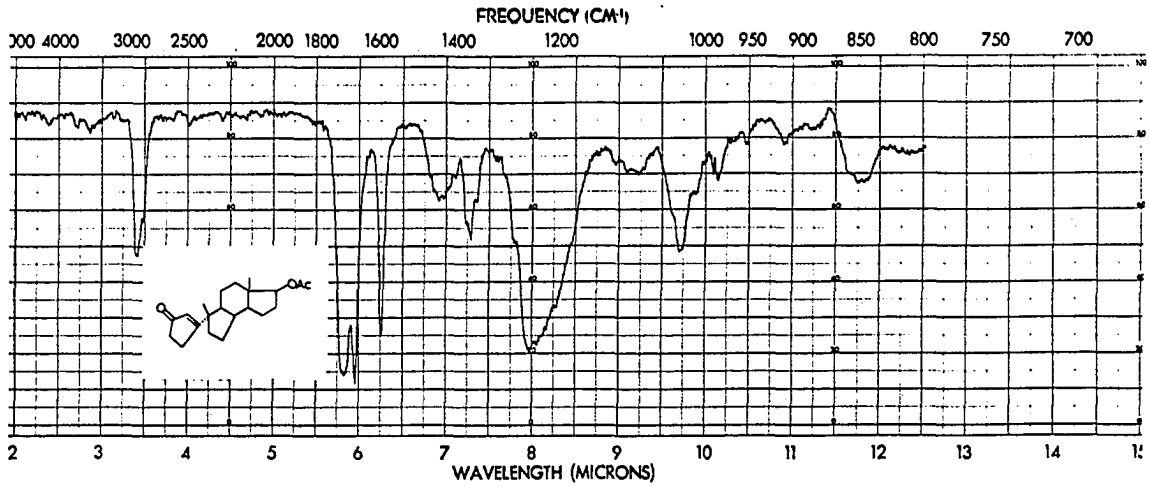
OH
2 3 4 5 6 7 8 9 10 11 12 13 14
WAVELENGTH (MICRONS)

Figure 2. Infrared spectra

Top - Photo-testosterone acetate (173) ($CHCl_3$)

Middle - Testosterone-2,2,4,6,6-d_5 (224) ($CHCl_3$)

Bottom - Lumi-testosterone-d_5 (225) ($CHCl_3$)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OAc
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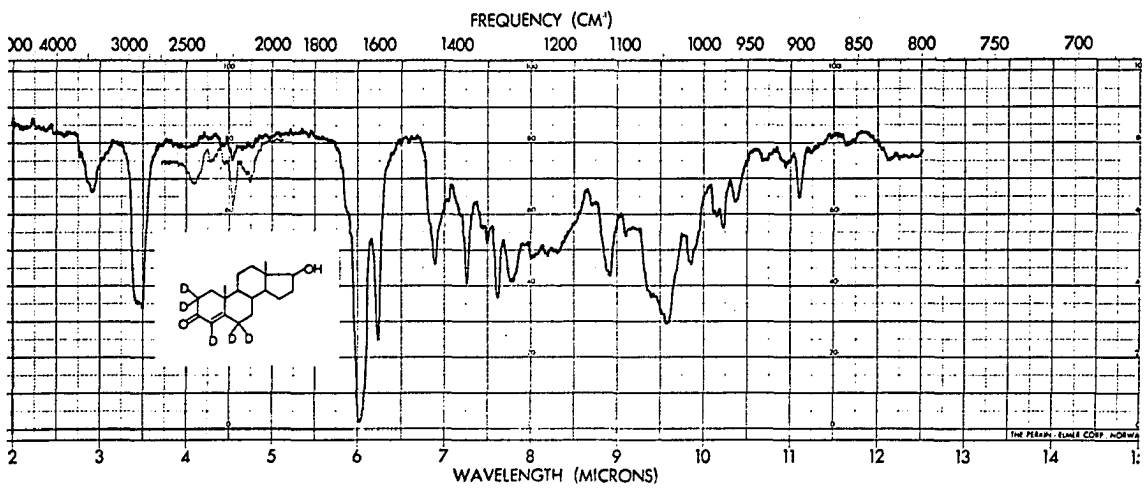
WAVELENGTH (MICRONS)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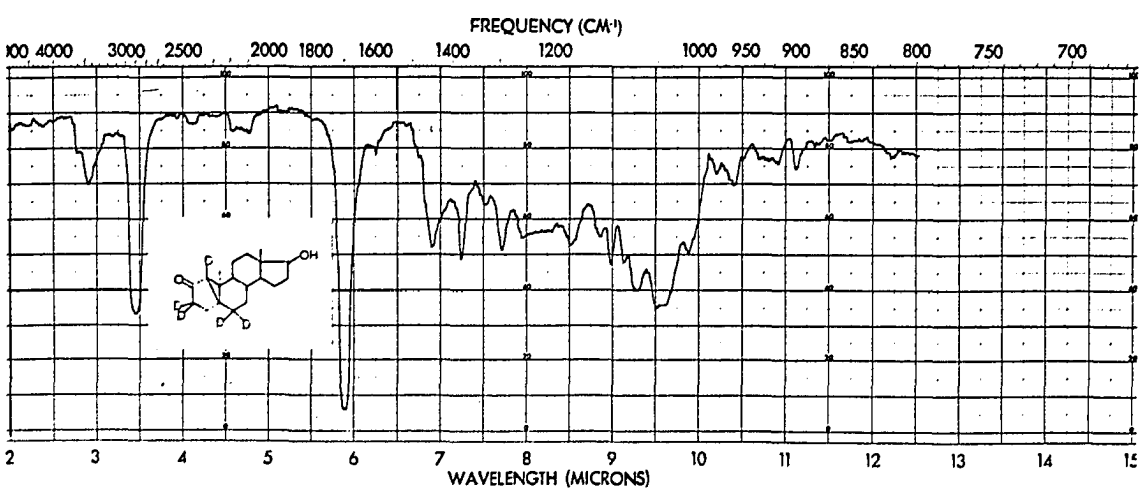
WAVELENGTH (MICRONS)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OH
2 3 4 5 6 7 8 9 10 11 12 13 14 15
WAVELENGTH (MICRONS)

Lumi-testosterone (178) showed a relatively simple mass spectrum with m/e values of 228 (90%, P^+), 123 (58%) and 109 (100%) as the only significant peaks in the spectrum at 70 e.v. When the electron voltage was lowered to 18 e.v. only m/e 109 and 288 remained significant.

Lumi-testosterone acetate (172) gave m/e values of 330 (69%, P^+), 287 (21%), 269 (20%), 123 (47%) and 109 (100%) at 70 e.v. The peak at m/e 287 is due to the loss of CH_3CO from 178 and that at m/e 269 corresponds to P^+-61 and is due to loss of CH_3CO followed by H_2O. At reduced electron voltage only m/e 330 and 109 remain significant.

The mass spectrum of photo-testosterone (179) at 70 e.v. gave peaks at m/e 288 (46%, P^+), 128 (100%) and 109 (54%). At 18 e.v. only m/e 109 and 288 remain significant.

Photo-testosterone acetate (173) gave m/e peaks at 330 (57%, P^+), 287 (22%), 269 (18%), 123 (100%) and 109 (24%) at 70 e.v. The peak at 287 corresponds to P^+-43 and is assigned to loss of CH_3CO from 173 and that at 269 corresponds to P^+-61 and is due to loss of CH_3CO followed by loss of H_2O. At 18 e.v. and below only 109 and 330 remain in the mass spectrum.

Encouraged by the differences in the fragmentation patterns of the two types of compounds, an attempt was made to locate the source of the m/e 109 and 123 fragments.

Testosterone-2,2,4,6,6-d_5 (224) was prepared by refluxing testosterone in the presence of deuteriomethanol and sodium methoxide. Initially testosterone-d_6 was formed, but recrystallization from methanol-water exchanged the C-17 hydroxyl proton and gave the d_5 compound 224 with a

m.p. of 153-4 °C. A mixed m.p. with an authentic sample of testosterone gave a mixed m.p. 153-4 °C. The infrared spectrum of testosterone-d_5 is given in Figure 2 on page 56 and indicated the presence of an alcohol (2.80-2.90 μ) and a Δ^4-3-keto function (6.02 and 6.18 μ). The n.m.r. spectrum of 224 is shown in Figure 3 on page 61. The two three proton singlets at 9.19 and 8.78 τ were assigned to the C-18 and C-19 methyl groups respectively. The hydroxyl proton appears at 8.14 τ. The poorly resolved one proton multiplet centered at 6.37 τ was due to the C-17 proton and the blip at 4.29 τ corresponds to incomplete exchange of the C-4 olefinic hydrogen. The integral gave a value of 23.5 protons versus 23 protons for complete exchange. This gives an extent of deuterium incorporation of 90%. Analysis of the mass spectrum by known methods gave d_3 = 4.2%, d_4 = 25.6% and d_5 = 70.2% (103).

Testosterone-2,2,4,6,6-d_5 was irradiated in sodium dried tertiary butyl alcohol to give lumi-testosterone-d_5 (225) and photo-testosterone-d_5 (226). It was found that 224 exchanged deuterium on column chromatography so fractional recrystallization was used to separate the mixture of photoproducts. A v.p.c. analysis showed that 225 and 226 were formed in the same ratios as was observed in the irradiation of testosterone itself.

Lumi-testosterone-d_5 (225) was obtained in 30% yield with a m.p. of 202-4 °C by fractional recrystallization. The infrared spectrum is reproduced in Figure 2 on page 56 and indicated the presence of an alcohol (2.85-2.90 μ) and a ketone (5.90 μ). The n.m.r. spectrum is shown in

Figure 3 on page 61. The two singlets of three protons each at 9.27 and 8.83 τ are assigned to the C-18 and C-19 methyl groups respectively. The hydroxyl proton appears at 8.27 τ and the C-17 methine at 6.38 τ. The absence of a broad singlet in the region 8.30-8.60 τ was taken to indicate that the assignment of this peak in previous cases to the C-1 cyclopropyl methine had been correct (15). A mixed m.p. with an authentic sample of lumi-testosterone (178) melting at 202-4 °C gave a mixed m.p. of 202-4 °C. The structure of lumi-testosterone-d_5 was regarded as secure on the basis of this data.

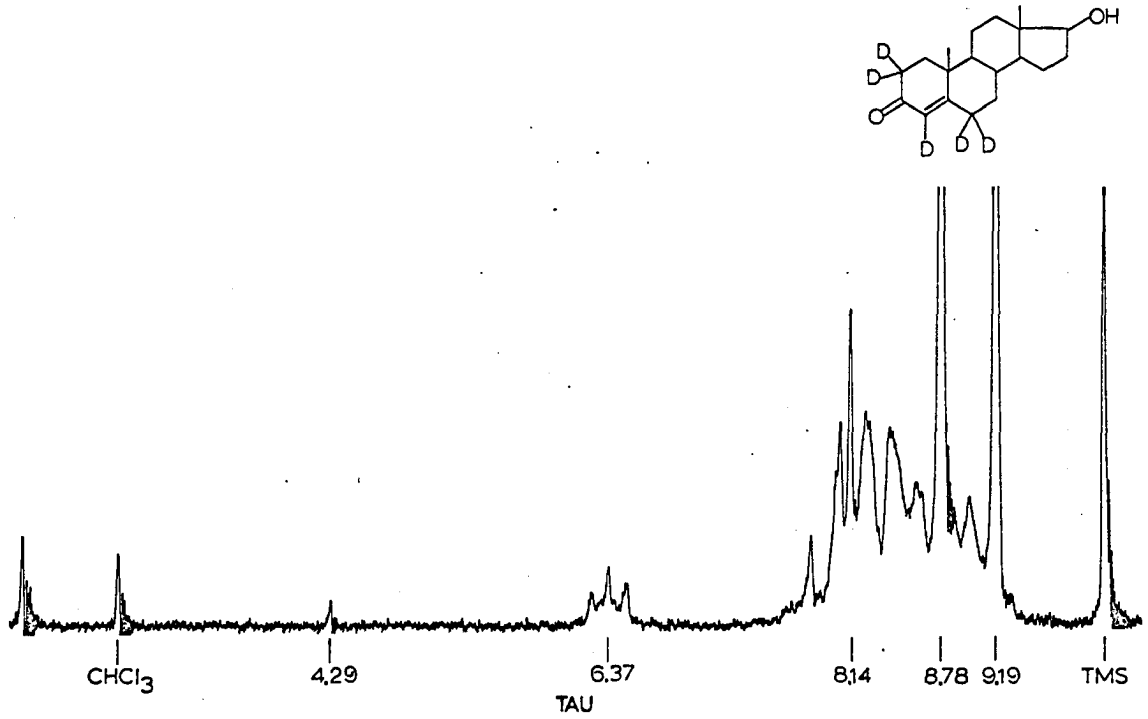
The mass spectrum of lumi-testosterone-d_5 (225) gave peaks at m/e 293 (72%, P^+), 292 (28%), 291 (5.5%), 290 (0.5%), 128 (57%), 127 (38%), 113 (100%) and 112 (48%). The extent of deuterium incorporation was calculated to be d_3 = 4.9%, d_4 = 27.6% and d_5 = 67.5%. At 20 e.v. only the peaks at m/e 113, 112, 293 and 212 remain significant.

Photo-testosterone-d_5 (226) with m.p. 148.5-50 °C was obtained in 10% yield by fractional recrystallization from the reaction mixture. The infrared spectrum is shown in Figure 4 on page 63 and indicated the presence of an alcohol (2.85-2.90 μ) and an α,β-unsaturated ketone (5.95 and 6.30 μ). The n.m.r. spectrum is shown in Figure 5 on page 65. The three proton singlets at 9.24 and 8.86 τ were assigned to the C-18 and C-19 methyl groups respectively. The hydroxyl proton appears at 8.25 τ as shown by deuterium exchange. The two proton singlet at 7.38 τ is assigned to the two protons at C-4 of the 2-cyclopentenone ring. The broad multiplet at 6.30 τ is due to the C-17 methine. A mixed m.p. with an authentic

Figure 3. Nuclear magnetic resonance spectra

Top - Testosterone-2,2,4,6,6-d_5 (224) ($CDCl_3$)

Bottom - Lumi-testosterone-d_5 (225) ($CDCl_3$)


OH
D
D
O
D
D
D
CHCl3
4.29
6.37
8.14
8.78
9.19
TMS
TAU

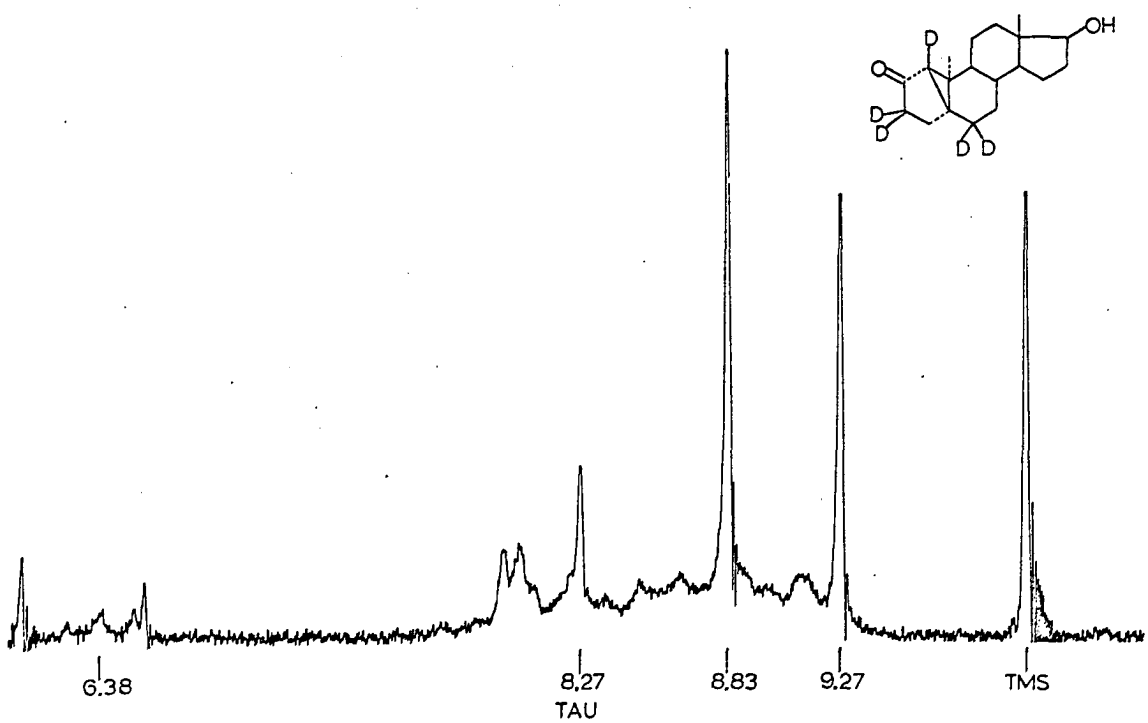
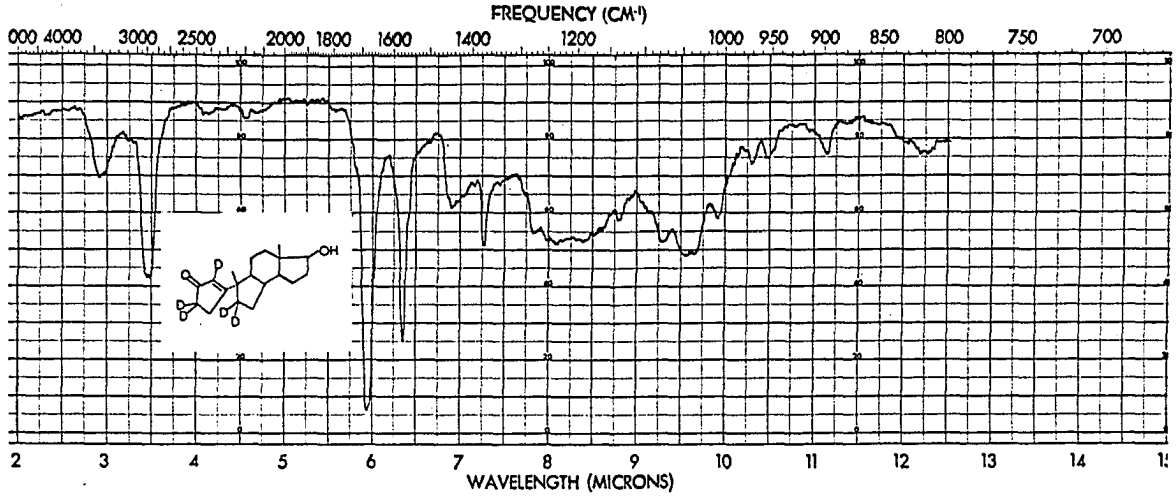

OH
D
O
D
D
D
D
6.38
8.27
8.83
9.27
TMS
TAU

Figure 4. Infrared spectra

Top - Photo-testosterone-d_5 (226) ($CHCl_3$)

Middle - Photo #1 (228) of progesterone (KBr Pellet)

Bottom - Photo #2 (229) of progesterone ($CHCl_3$)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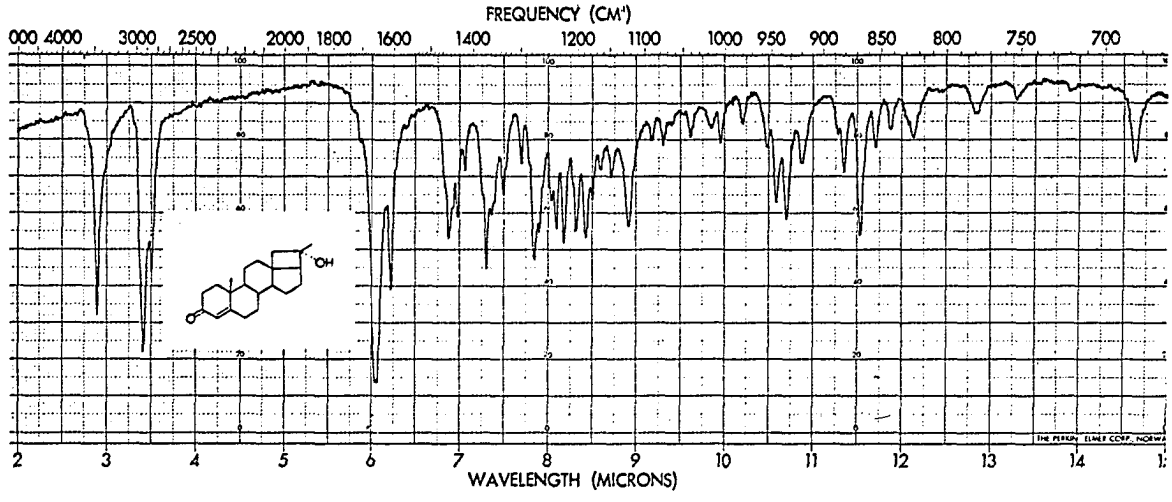
WAVELENGTH (MICRONS)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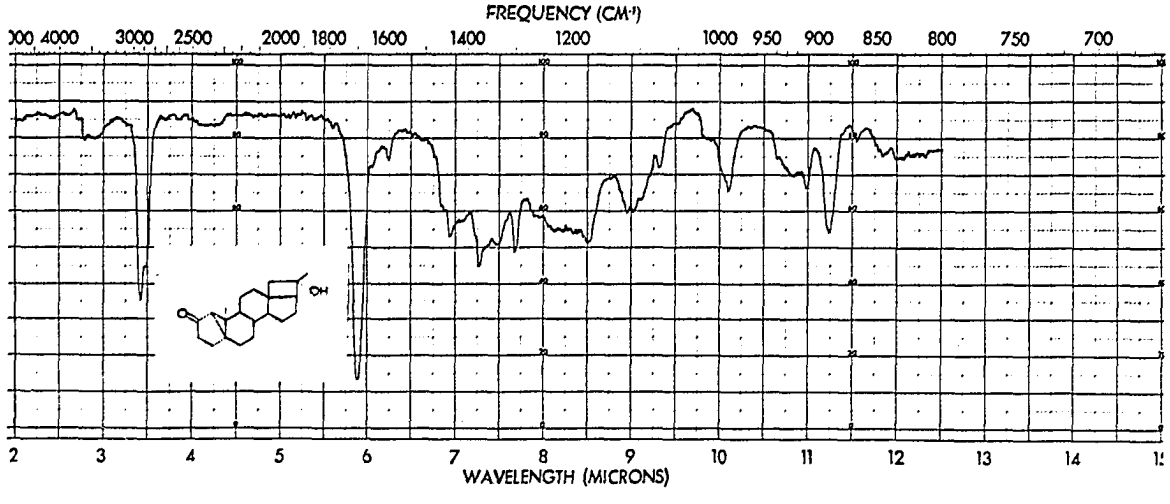
OH
2 3 4 5 6 7 8 9 10 11 12 13 14
WAVELENGTH (MICRONS)


FREQUENCY (CM-1)
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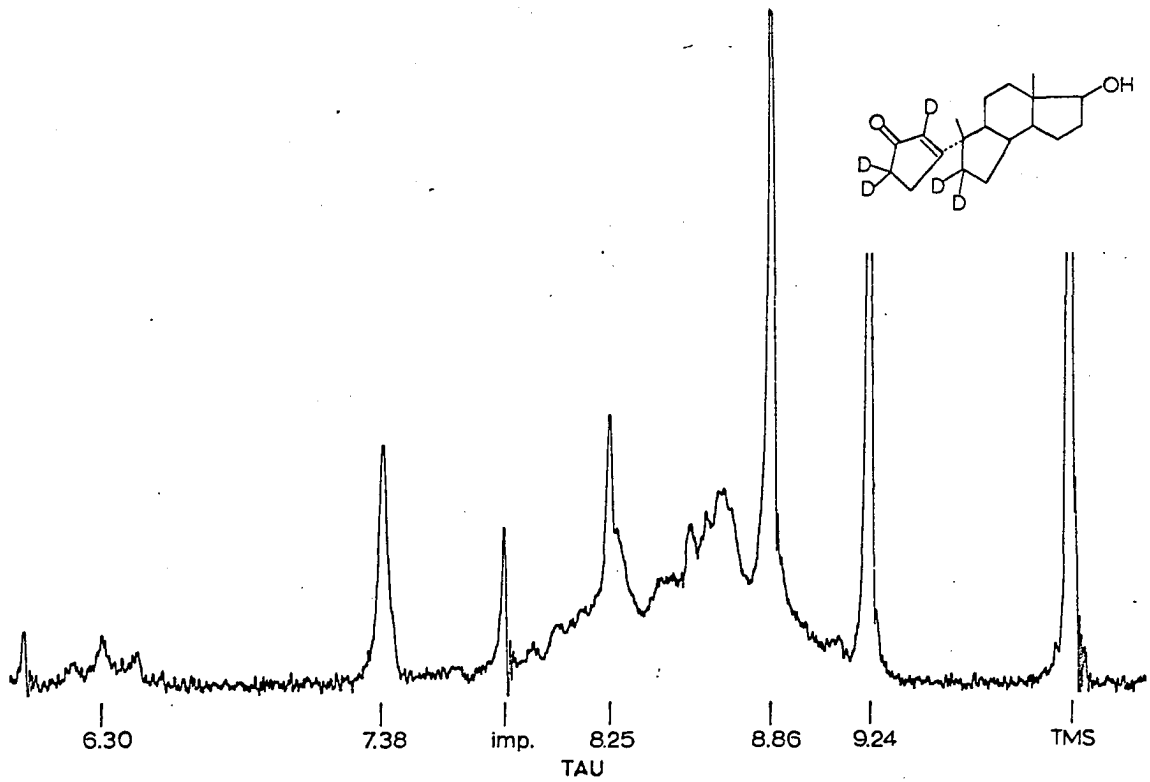
OH
2 3 4 5 6 7 8 9 10 11 12 13 14
WAVELENGTH (MICRONS)

Figure 5. Nuclear magnetic resonance spectra

Top - Photo-testosterone-d_5 (226) ($CDCl_3$)

Bottom - Photo #1 (228) of progesterone ($CDCl_3$)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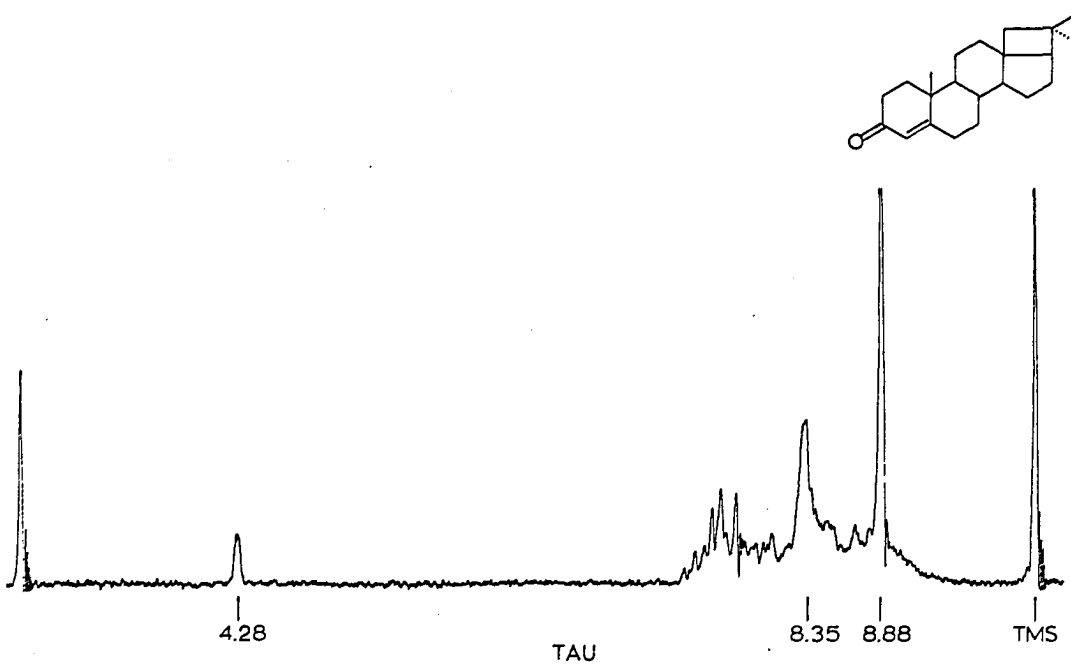
D
D
D
D
D
6.30
7.38
imp.
8.25
8.86
9.24
TMS
TAU

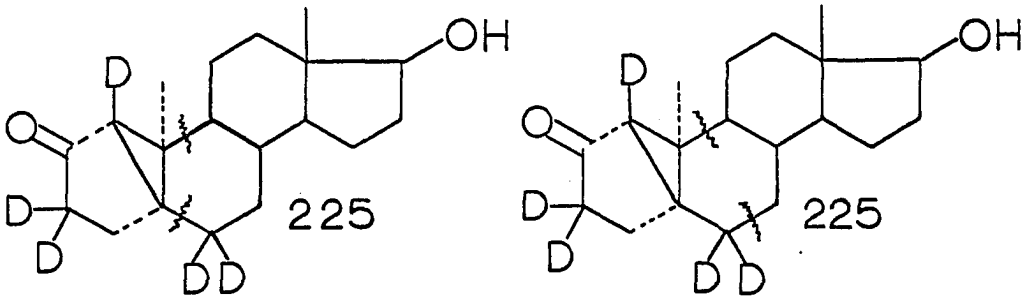

OH
4.28
8.35
8.88
TMS
TAU

sample of photo-testosterone (179) melting at 148.5-50 °C gave a mixed m.p. 148.5-50 °C.

The mass spectrum of photo-testosterone-d_5 (226) gave peaks at m/e 293 (53%, P^+), 292 (22%), 219 (4.6%), 290 (0.5%), 128 (100%), 127 (48%), 113 (65%) and 112 (30%). Calculation of the deuterium content gave d_3 = 6.1%, d_4 = 28.5% and d_5 = 65.4%. At 20 e.v. only m/e 113, 112, 292 and 293 remained significant.

The structure of lumi-testosterone-d_5 (225) is considered secure on the basis of its spectral similarity to the known lumi-testosterone and the fact that a mixed m.p. of the two samples gave no depression. All the differences in the infrared and n.m.r. spectra of lumi-testosterone-d_5 versus lumi-testosterone can be accounted for by the position of the deuterium labels. The absence of a broad one proton singlet in the n.m.r. spectrum of 225 in the 8.3-8.6 τ region confirms the assignment of this proton to the C-1 cyclopropyl methine in the undeuterated systems. This correlation will find further use in this work.

The similarity of the mass spectra of lumi-testosterone (178), lumi-testosterone acetate (172) and lumi-testosterone-d_5 (225) indicate that the source of the m/e 109 and 123 fragments for 178 and 172 and the 112, 113, 127 and 128 fragments for 225 is the A and B rings of the photo-product. The predominance of the m/e 109 fragment at low ionizing voltage suggests that this pathway is the most favored cleavage mode. The source of the fragments is pictured below.



m/e 109 D=H m/e 112,113 D=D m/e 123 D=H m/e 127,128 D=D

Cleavage in the undeuterated molecule between C-5-C-6 and C-9-C-10 would produce the m/e 109 fragment and in the deuterated molecule it would give the m/e 112 and 113 fragments. The predominance of m/e 113 over 112 indicates that the leaving fragment prefers to abstract a hydrogen or deuterium located at C-6 in preference to any others in the molecule by a factor of at least 2:1.

The production of fragment m/e 123 can be viewed as the result of a cleavage between C-9-C-10 and C-6-C-7. The ratio of 128 to 127 in the deuterated molecule is less than the ratio of d_5 to d_4 and suggests that there is some scrambling of the deuterium label during the fragmantation process. The most reasonable position for this type of process is at C-6 of lumi-testosterone-d_5 (225).

The structure of photo-testosterone-d_5 (226) is considered secure on the basis of its spectral similarity to the known photo-testosterone (179) and the fact that a mixed m.p. of the two samples gave no depression. All differences in the infrared and n.m.r. spectra of photo-testosterone-d_5

and photo-testosterone can be accounted for by the position of the deuterium labels.

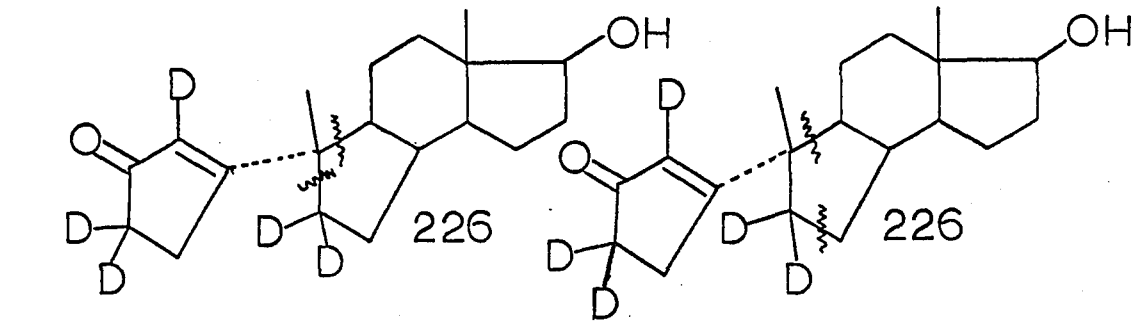
The absence of a doublet carbonyl in the infrared spectrum of photo-testosterone-d_5 (226) is also instructive. This band is present in all other known examples of undeuterated photoproducts of similar structure. Yates and Williams (104) found the phenomenon of the doublet carbonyl to be fairly general property of α,β-unsaturated cyclopentenones. They postulated that it was the result of Fermi resonance between the carbonyl and a close lying overtone and appeared to be exhibited whenever a band at 11.6-.7 μ was present. The band at 11.6-.7 μ was assigned to the out-of-plane bending vibration of the ethylenic C-H. It was found that replacement of the ethylenic C-H with deuterium removed the doublet carbonyl band. This was found to be the case with photo-testosterone-d_5 (226) and supports the assignment of the doublet carbonyl band in compounds such as 173 and 179 as due to Fermi resonance.

The n.m.r. spectra of compounds such as photo-testosterone (179) and photo-testosterone acetate (173) exhibit a highly split olefinic proton in the region of 4.28 τ which is assigned as the X portion of an ABCDX pattern resulting from cross-ring coupling with the methylenes at C-4 and C-5 of the 2-cyclopentenone ring. The ABCD portion of the spectrum is usually centered at about 7.5 τ. The pattern exhibits a high degree of symmetry in all known cases. The geometry of the 2-cyclopentenone ring is such that the AB protons at C-4 are nearly chemically equivalent. Likewise, the CD protons at C-5 are also nearly chemically equivalent.

These conditions allow the ABCD portion of the spectrum to be viewed more simply as an A_2B_2 pattern. A two proton portion of this pattern is found at lower field and another two proton portion at higher field. The low field portion had previously been assigned to the C-4 methylenes and the part at higher field to the C-5 methylenes of the 2-cyclopentenone ring (15). The n.m.r. spectrum of photo-testosterone-d_5 (226) gave a low field slightly broadened singlet at 7.38 τ which integrated for two protons. This singlet was assigned to the protons at C-4 of the 2-cyclopentenone ring in photo-testosterone-d_5. This observation confirms the assignment of the protons at lower field to those at C-4 of the 2-cyclopentenone system in the undeuterated compounds. The observation that the two protons at C-4 in photo-testosterone-d_5 appear as a slightly broadened singlet indicates that these two protons are nearly chemically equivalent. This indicated that the assumptions made in interpreting the ABCD portion of the spectrum as an A_2B_2 pattern were fundamentally correct. Use will be made of this correlation in further structural determinations.

The similarity of the mass spectral fragmantation paths of photo-testosterone, photo-testosterone acetate and photo-testosterone-d_5 (226) indicated that the source of the major fragments from these molecules was the A and B rings of the steroid system. The mode of cleavage is shown below.

The predominance of the m/e 123 fragment in 173 and 179 and the 127 and 128 fragments in 226 can be visualized as the result of cleavage of



m/e 109 m/e 112, 113 m/e 123 m/e 127, 128

D = H D = D D = H D = D

the C-9-C-10 and C-6-C-7 bonds in the photoproducts. The ratio of m/e 128 to 127 is 2.1:2 for photo-testosterone-d_5 and is only slightly less than the d_5 to d_4 ratio of 2.3 for this compound. The ratio of m/e 128: 127 for photo-testosterone-d_5 (226) is identical to that of 113:112 observed in lumi-testosterone-d_5 (225) where these peaks are the major peaks in their respective spectra. It appears that the major fragmentation patterns in both compounds reflect the ratio of d_4 to d_5 in the compound. Thus scrambling of the deuterium label is not involved in these processes.

The observation that the m/e 123 peak in compounds such as photo-testosterone (179) and the 127 and 128 m/e peaks in the deuterated compound 226 predominate at 70 e.v. indicate that these paths are energetically more favorable at higher electron voltage. At lower electron voltage, the m/e 123 peak and the corresponding peaks in the deuterated sample decrease in intensity very rapidly and the m/e 109 peak in the undeuterated sample and the m/e 112 and 113 peaks in the deuterated

compound 226 become the most favored routes of fragmentation. The most plausible explanation for this observation is that there is a definite energy level necessary for the type of fragmentation observed with compounds of structure similar to photo-testosterone (179). Once this level is exceeded the m/e 123 fragment becomes most favored. At lower electron voltage the fragmentation decreases and m/e 109 becomes significant.

The source of the m/e 109 fragment for compounds such as photo-testosterone (179) and for m/e 112 and 113 for photo-testosterone-d_5 (226) may be viewed as resulting from cleavage of the C-10-C-11 and C-10-C-6 bonds in species similar to 226. The predominance of m/e 113 over 112 for photo-testosterone-d_5 is again proposed to indicate that it is the protons or deuterium atoms at C-6 which are abstracted in the formation of the fragment. The ratio of m/e 113:112 in the case of photo-testosterone-d_5 reflects the d_5:d_4 ratio in the compound. Thus some scrambling of the deuterium label may also occur in this case but is not required to explain the observed ratio.

These mass spectral correlations will be used later in this work to establish the structure of previously unknown compounds with structures similar to lumi-testosterone and photo-testosterone.

It was reported in the literature that testosterone was inert to irradiation at 2537 Å in contrast to its cross-conjugated analogue (10). It seemed improbable that this should be the case since testosterone had

an ultraviolet absorption maximum in the neighborhood of 2537 Å and thus was capable of excitation at this wave length.

Irradiation of testosterone (177) at 2537 Å in quartz in tertiary butyl alcohol gave lumi-testosterone (178) in 32% yield and photo-testosterone (179) in 26% yield and 14% of recovered starting material. The yields compare favorably with those obtained for the irradiation of testosterone above 3000 Å. Some polymeric material was also formed but it was not studied further. The structures of lumi-testosterone and photo-testosterone were established by comparison with known samples.

A subsequent irradiation of testosterone with 2537 Å light in Pyrex gave no reaction under similar conditions. This indicated that the transformation observed above was due to the 2537 Å excitation and also showed that this source had no significant output above 3000 Å.

Reports of quenching and sensitization studies of enones have appeared (31,34,37). It was decided to investigate the effect of sensitization and quenching on a steroidal enone such as testosterone. Testosterone was a convenient substrate for study since it gives only two primary photoproducts which are easily resolvable by v.p.c. study.

Benzophenone was chosen as a photosensitizer since its intersystem crossing efficiency was known to be 100% (105). A sample of testosterone was prepared in tertiary butyl alcohol. Benzophenone was added to the solution in a concentration sufficient to allow it to absorb greater than 95% of the incident light. The actinometer for this study was a like sample of testosterone without benzophenone. The irradiation was

conducted in Pyrex in a Rayonet photochemical reactor chamber using the "black light" lamps whose principle output is in the 3500 Å region. After two hours the sample with benzophenone showed a trace amount of photoproduct formation while the testosterone alone showed no appreciable reaction. After six hours the benzophenone solution showed that greater than 60% of the testosterone had been consumed and only traces of lumi-testosterone and photo-testosterone were observed. The sample containing testosterone alone showed less than 5% destruction of testosterone and traces of the photoproducts were observed. After ten hours the benzophenone solution had consumed greater than 95% of the testosterone, but photoproduct formation to give lumi-testosterone and photo-testosterone was less than 5%. The solution containing only testosterone had reacted to an extent of about 10% to yield lumi-testosterone (178) and photo-testosterone (179). It appears that benzophenone sensitizes the destruction of testosterone, but not the formation of the usually observed photoproducts such as 178 and 179.

A similar experiment was conducted to study the ability of ferric dipivaloyl methane (FDM) to quench the formation of the photoproducts of testosterone. FDM had previously been found to be successful in quenching enone triplets (31). A solution of testosterone in tertiary butyl alcohol was prepared. Ferric dipivaloyl methane was added in a concentration such that greater than 93% of the light would be absorbed by the testosterone. A similar solution of testosterone without FDM was prepared to serve as an actinometer. Irradiation of the samples for periods of two, six and ten

hours established that the reaction of testosterone to yield lumi-testosterone and photo-testosterone proceeds as efficiently in the presence as in the absence of FDM. It can be concluded that ferric dipivaloyl methane exhibits no appreciable quenching of the photochemical reaction of testosterone under the above conditions.

Testosterone was also irradiated in the presence of dibenzothiophene as a photosensitizer. Dibenzothiophene has found some previous use in photosensitized reactions (37). The exact intersystem crossing efficiency is not known for dibenzothiophene. However, it has been determined that its efficiency lies between 33% and 100% (105). A filter solution containing nickel sulfate and cobalt sulfate was used to isolate the 3130 Å line of the mercury arc since both testosterone and dibenzothiophene absorb in this region. Above 3600 Å only testosterone has an appreciable absorption. The concentration of dibenzothiophene was adjusted so that it absorbed greater than 95% of the incident light. Tertiary butyl alcohol was employed as the solvent. An identical sample without dibenzothiophene was used as an actinometer. Irradiation for periods of up to fifty hours indicate that the reaction of testosterone to yield lumi-testosterone (178) and photo-testosterone (179) proceed as well in the presence as in the absence of dibenzothiophene. Essentially the same ratios of products are formed and the destruction of testosterone with time is not more complex in the presence of dibenzothiophene. This indicated that dibenzothiophene was an efficient photosensitizer of the reactions of testosterone.

This is in contrast to the result observed with benzophenone where enone was destroyed but significant formation of lumi-testosterone and photo-testosterone was not observed.

Photochemistry of Progesterone

At the time this study was initiated there were no reports of the photochemistry of a bifunctional enone, although several examples had been studied in cross-conjugated cyclohexadienones (See Historical Section). Progesterone (227) seemed an ideal choice for entry into this type of investigation. The molecule possessed both an α,β-unsaturated ketone moiety and a saturated ketone. It was possible that under appropriate conditions such a ketone might exhibit selective reactivity at one of the two centers.

Irradiation of progesterone (227) in tertiary butyl alcohol with light above 3000 Å gave five photoproducts. For convenience the compounds were given the trivial names of photo #1 through photo #5. Photoproducts #1, 2, 3, and 5 were separated by chromatography on alumina. Photo #4 and progesterone were separated by rechromatography on Florisil. Progesterone (227) was recovered in 18% yield, photo #1 (228) in 11%, photo #2 (229) in 8%, photo #3 (230) in 5%, photo #4 (231) in 19% and photo #5 (232) in 11% yield.

Photo #1 (228) gave a m.p. 197.5-99.5 °C with $[\alpha]_D^{27} = +134°$ (c = 1.83, $CHCl_3$). The compound exhibited a $\lambda_{max}^{EtOH} = 241_{m\mu}$ ($\varepsilon = 13,600$) suggestive of an α,β-unsaturated ketone. The infrared spectrum is shown in Figure 4 on page 63 and indicated the presence of an alcohol (2.80-

2.90 μ) and an α,β-unsaturated ketone (6.01 and 6.18 μ). The n.m.r. spectrum is reproduced in Figure 5 on page 65. The n.m.r. spectrum showed a six proton singlet at 8.88 τ which was resolved into two three proton singlets at 9.02 and 8.67 τ in pyridine showing that there were two non-equivalent methyl groups which exhibited the same chemical shift in $CDCl_3$ solution. These singlets were assigned to the C-19 and C-21 methyl groups. Part of the broad singlet at 8.35 τ was shown to be due to a hydroxyl proton by deuterium exchange. The proton at 4.28 τ was assigned to the olefinic proton at C-4.

The absence of a singlet due to the C-18 methyl group in the n.m.r. spectrum of photo #1 and the absence of the C-21 methyl of the C-20 ketone at 7.95-8.00 τ indicated that these groups were probably involved in the formation of the alcohol. The absence of a broad absorption in the 5.5-6.5 τ region of the spectrum due to a methine or methylene on a carbon bearing an alcohol supported the assumption that the alcohol in question was tertiary. The structure 228 was tetatively assigned to photo #1.

A report appeared in the literature that irradiation of Δ^5-pregnen-3β-acetoxy-20-one gave a cyclobutanol which on hydrolysis gave the steroidal alcohol 234 (95). Subsequent oxidation gave the corresponding ketone 228. The stereochemistry of the diol was later shown to be as shown for 234.

The synthesis of 228 which has the structure proposed for photo #1 was approached via the alcohol 233. Irradiation of Δ^5-pregnen-3β-ol-20-

one (233) in tertiary butyl alcohol gave 61% of the diol 234 with m.p. 224.5-5.5 °C and a band in the infrared showing alcohol (2.80-2.90 μ). The n.m.r. spectrum of 234 is shown in Figure 6 on page 79. The three proton singlets at 9.08 and 8.90 τ are assigned to the C-21 and C-19 methyl groups respectively. The broad band at 7.90-7.95 τ was shown to be due to two hydroxyl protons by deuterium exchange. The broad absorption at 4.68 τ was assigned to the olefinic proton at C-5. The spectral data of the diol is consistent with structure 234. The melting point of the diol 234 was reported to be 224-5 °C and this agrees well with the sample obtained in our laboratory (95). Oxidation of the diol gave a ketone with m.p. 191-2 °C, $[\alpha]_D$ = +130 (c = 0.77, $CHCl_3$), λ_{max}^{EtOH} = 243 mμ (ε = 14,500) and bands in the infrared at 2.76, 6.01 and 6.17 μ (95). These properties compare favorably with those of photo #1 (228) isolated from the irradiation of progesterone (227).

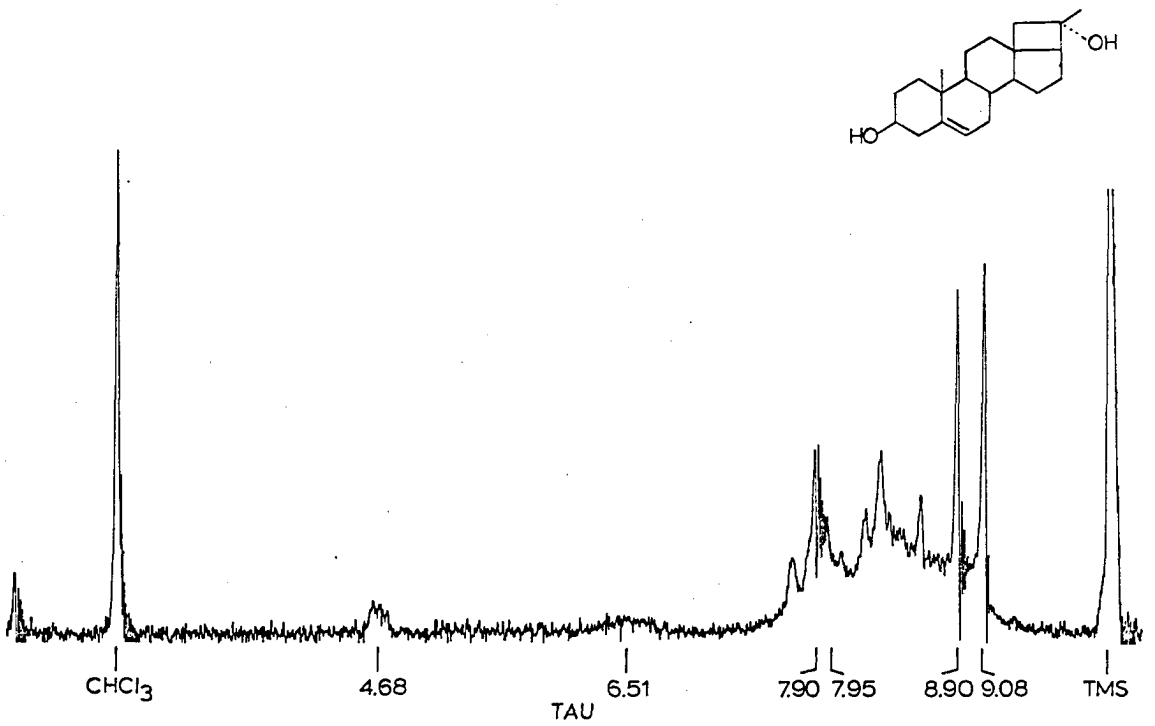
The steroidal diol 234 was oxidized by aluminum isopropoxide in toluene to give 56% of the keto-alcohol 228 with m.p. 194-5 °C. A mixed melting point with a sample of photo #1 obtained by the irradiation of progesterone with m.p. 193-5 °C gave a mixed m.p. of 193-5 °C. The infrared spectra of the two samples in KBr were superimposable. The infrared spectrum in KBr is shown on page 63 in Figure 4. This established the structure of photo #1 of progesterone as that shown for 228.

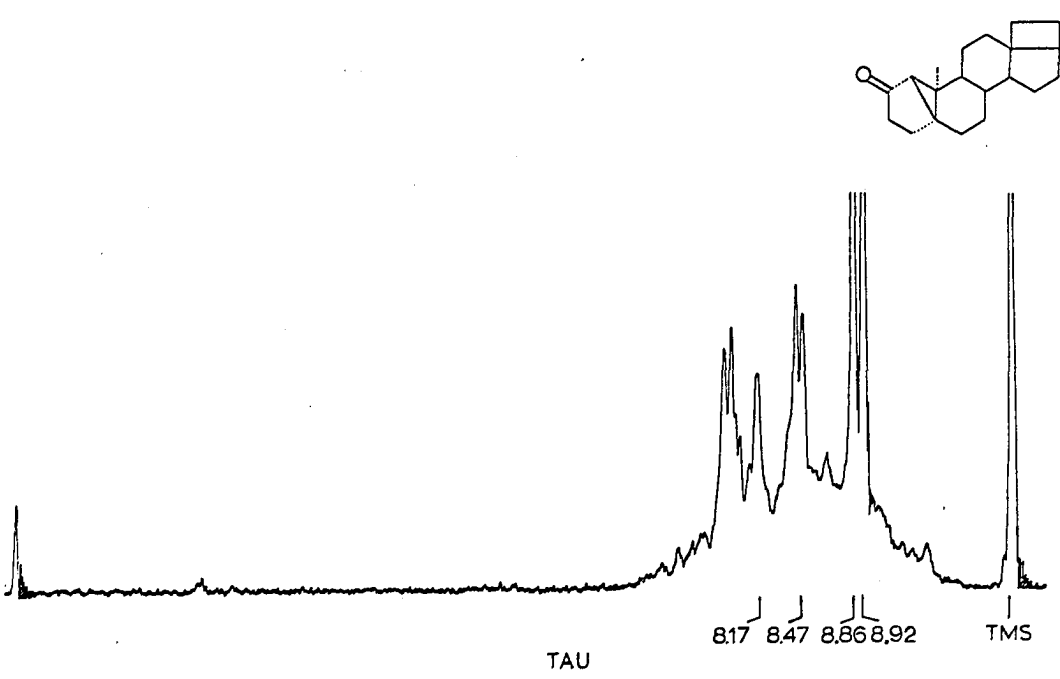
In subsequent work Jeger (Cereghetti et al., 97) prepared the C-20 epimer of 228 and found it to melt at 186-7 °C or lower than the C-20 epimer with structure 228.

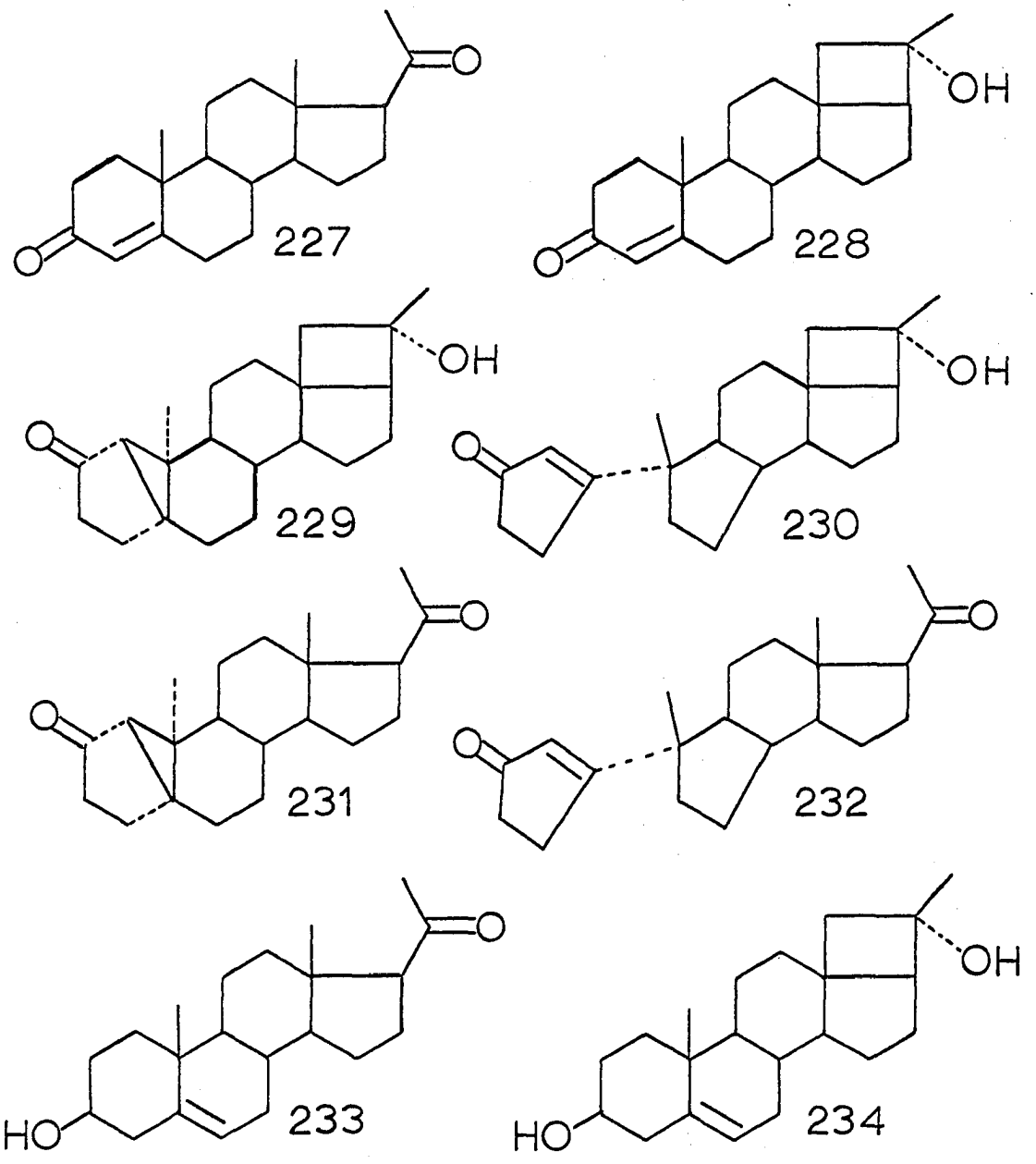
Figure 6. Nuclear magnetic resonance spectra

Top - (20S)-3β,20-Dihydroxy-Δ^5-18,20-cyclo-pregnen (234) ($CDCl_3$)

Bottom - Photo #2 (229) of progesterone ($CDCl_3$)

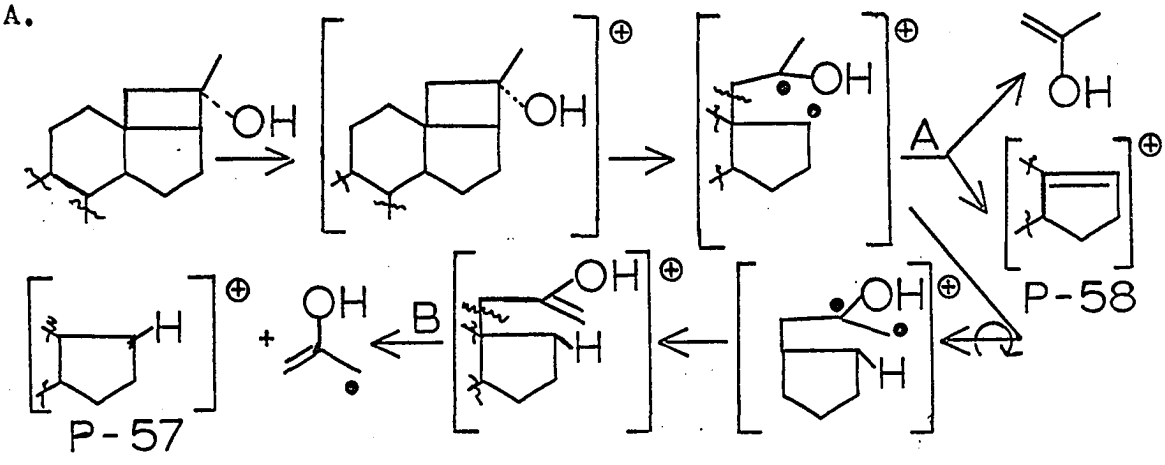

OH
HO
CHCl3
4.68
6.51
7.90
7.95
8.90
9.08
TMS
TAU


OH
8.17
8.47
8.86
8.92
TMS
TAU



The mass spectrum of photo #1 was examined to see what effect the strained cyclobutanol ring would have on the fragmentation pattern. Photo #1 (228) gave m/e values of 314 (57%, P^+), 257 (64%) and 256 (64%) as the only significant peaks in the spectrum. At 16 e.v. the m/e peaks 256 and 257 still predominate over 314.

The scheme of fragmentation is presented below. It is tempting to view the base peak at m/e 256 as resulting from cleavage by path A to give acetone. Path B gives a loss of 57 with the charge being carried by the remainder of the steroid skeleton. This is also the case in path A.



Each of these paths has a partial analogy in the cleavage of larger cyclic alcohols (103). However, in the case of the larger cyclic alcohols the fragments m/e 57 and 58 leave as charged species. In the example studied here the charge is carried by the remainder of the steroid skeleton, presumably by the oxygen at C-3. The facile loss of the fragments of weight 57 and 58 essentially represent the only significant cleavage of photo #1 (228). The fragmentation from the A and B ring systems of the Δ^4-3-keto steroid system which is usually facile is almost completely suppressed in this case (103).

Photo #2 (229) gave m.p. 254-6 °C with $[\alpha]_D^{27}$ = 93.4° (c = 2.08, $CHCl_3$). The ultraviolet spectrum gave λ_{max}^{EtOH} = 212 mμ (ε = 5,250). The infrared spectrum is shown in Figure 4 on page 63 and indicated the presence of an alcohol (2.80-2.90 μ) and a ketone (5.88 μ).

The position of the ketone band in the infrared spectrum and the ultraviolet absorption suggested that the A and B rings of photo #2 were structurally analogous to those of lumi-testosterone (178) and lumi-testosterone acetate (172) (15,19).

The n.m.r. spectrum of photo #2 is shown in Figure 6 on page 79. The three proton singlets at 8.92 and 8.86 τ are assigned to the C-18 and C-21 methyl groups. The broad peak at 8.17 τ was shown to be due to a single hydroxyl proton by deuterium exchange. There were two peaks in the region 8.4-8.5 τ so the assignment of a cyclopropyl proton could not be made with certainty. The presence of a hydroxyl proton with the corresponding absence of absorption in the 5.5-6.5 τ region indicated that the alcohol was tertiary. This conclusion was supported by the observation of a singlet in the n.m.r. spectrum of photo #2 in dimethyl sulfoxide (106).

The absence of the C-21 methyl of a methyl ketone and the C-19 methyl group in the n.m.r. spectrum of photo #2 (229) indicated that it was these groups which were involved in cyclobutanol formation.

The mass spectrum gave peaks at m/e 314 (27%, P^+), 257 (52%), 256 (35%), 123 (100%) and 109 (32%). At low electron voltage the m/e 123 peak decreases very rapidly and becomes less intense than the 109 peak. However, the major peaks remain m/e 257, 256 and 314. The presence of the fragments m/e 257 and 256 in the mass spectrum support the presence of a cyclobutanol in photo #2. The stereochemistry of the cyclobutanol is assigned as in 229 in analogy with that of photo #1.

The presence of the m/e peaks at 123 and 109 support the presence of the cyclopropyl cyclopentanone system in ring A. However, the ratio of the 123 and 109 peaks were the reverse of that observed for the model compounds 172 and 178. It is felt that this is due to a modification of the fragmentation pattern due to the presence of the cyclobutanol ring system. In the model compounds the m/e 123 and 109 peaks were the only significant peaks in the spectrum and this was not the case in photo #2 (229).

The data presented above support the assignment of the structure as shown in 229 to photo #2 of progesterone. Additional support for this assignment was obtained by the preparation of the monobenzylidine derivative 235 of photo #2.

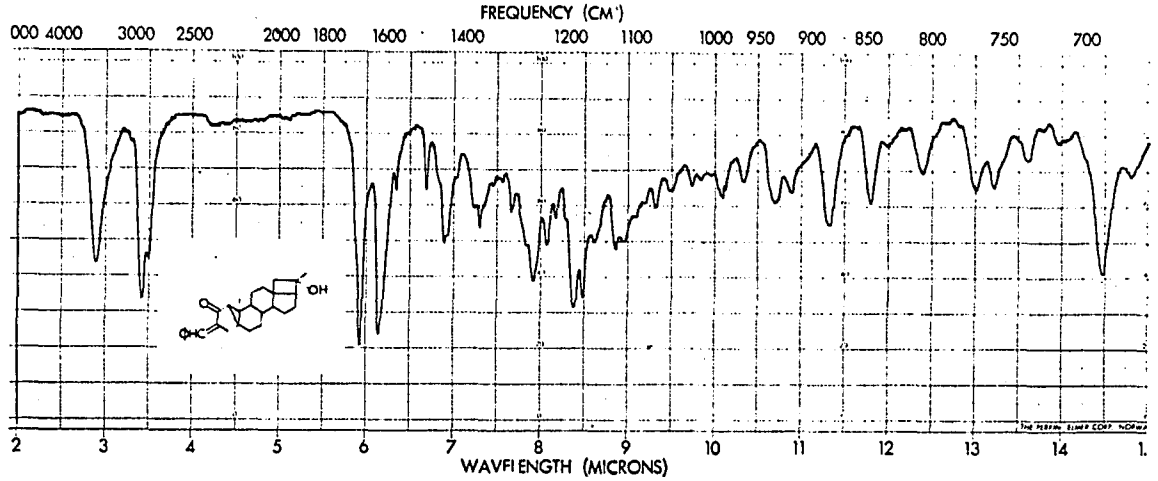
Treatment of photo #2 (229) with benzaldehyde in methanolic potassium hydroxide gave the monobenzylidine derivative 235 with m.p. 218-20 °C and λ_{max}^{EtOH} = 299 mμ (ε = 24,900), 230 mμ (ε = 9,680) and 224 mμ (ε = 9,600). The infrared spectrum of 235 is shown in Figure 7 on page 85 and indicated the presence of an alcohol (2.80 μ), a ketone (5.93 μ) and the benzylidine function (6.15 and 14.45 μ). The n.m.r. spectrum is reproduced in Figure 8 on page 87. The two singlets at 8.94 and 8.88 τ which integrated for three protons each are assigned to the C-19 and C-21 methyl groups. The singlet at 8.40 τ was assigned to the cyclopropyl methine at C-1. The 8.2-8.3 τ region was decreased by deuterium exchange and indicated the presence of a hydroxyl proton. The two proton

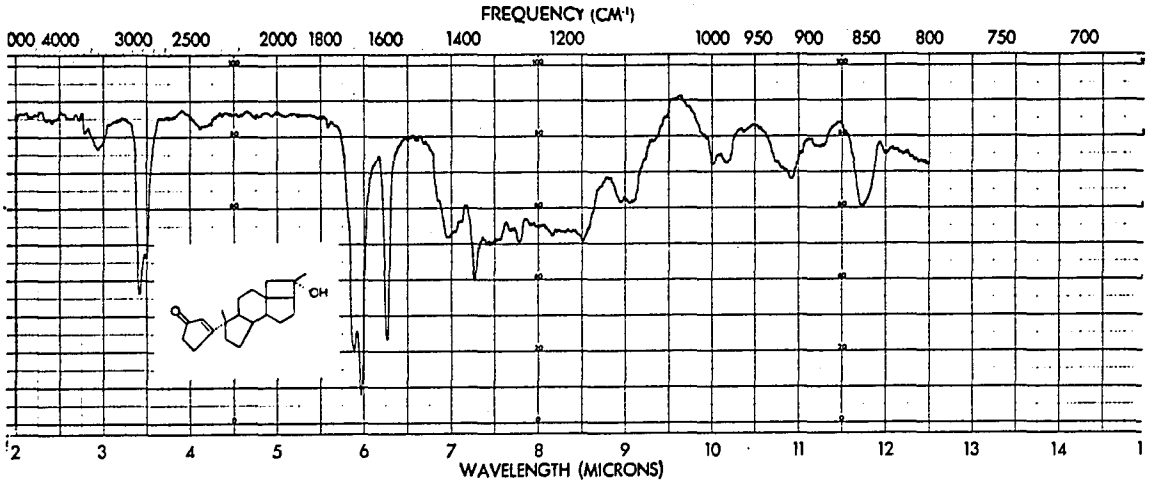
Figure 7. Infrared spectra

Top - (20S)-20-Hydroxy-3-benzylidene-10α-methyl-1β,5β-cyclo-18,20-cyclo-pregnan-2-one (235) (KBr Pellet)

Middle - Photo #3 (230) of progesterone ($CHCl_3$)

Bottom - Photo #4 (231) of progesterone (KBr Pellet)


FREQUENCY (CM⁻¹)
000 4000 3000 2500 2000 1800 1600 1400 1200 1100 1000 950 900 850 800 750 700
OH
2 3 4 5 6 7 8 9 10 11 12 13 14
WAVELENGTH (MICRONS)


FREQUENCY (CM⁻¹)
000 4000 3000 2500 2000 1800 1600 1400 1200 1000 950 900 850 800 750 700
OH
2 3 4 5 6 7 8 9 10 11 12 13 14
WAVELENGTH (MICRONS)

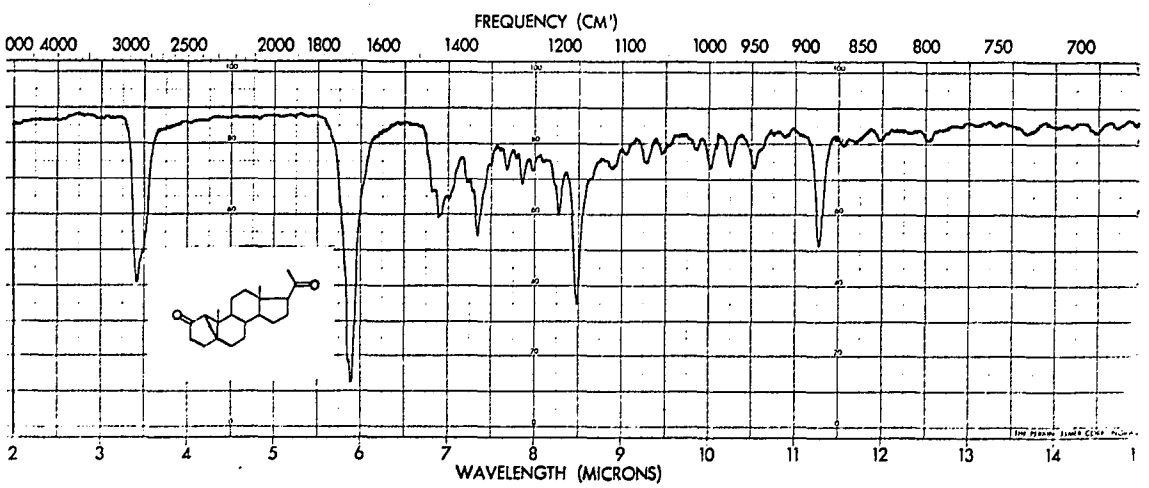
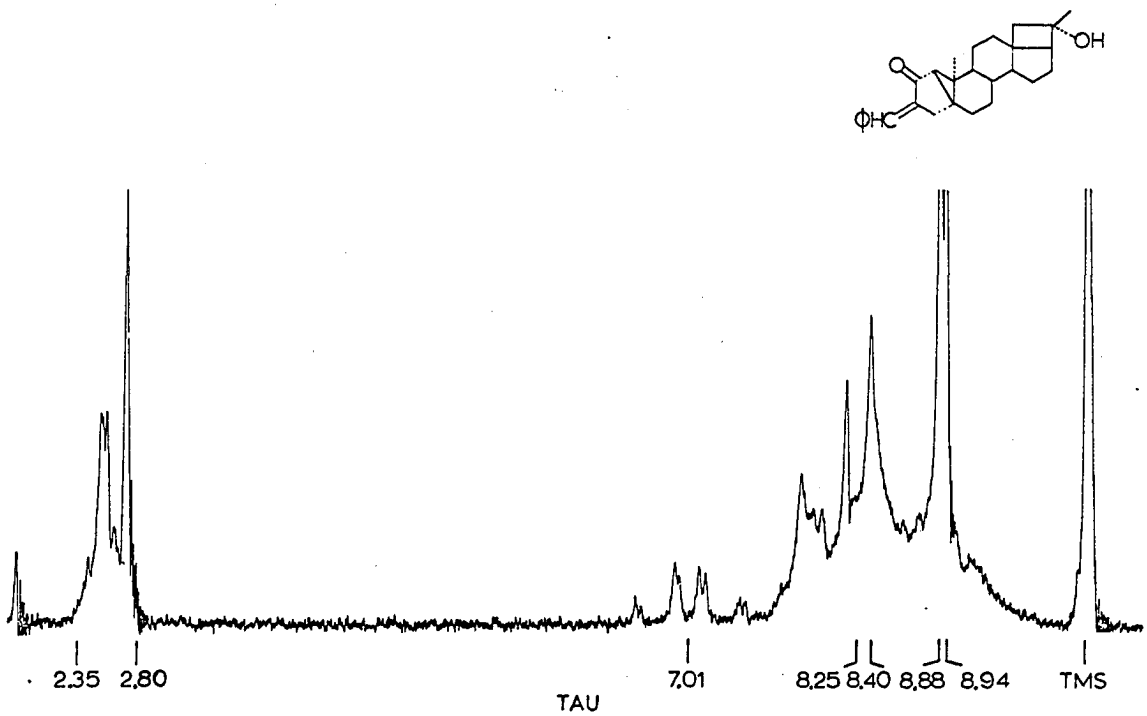
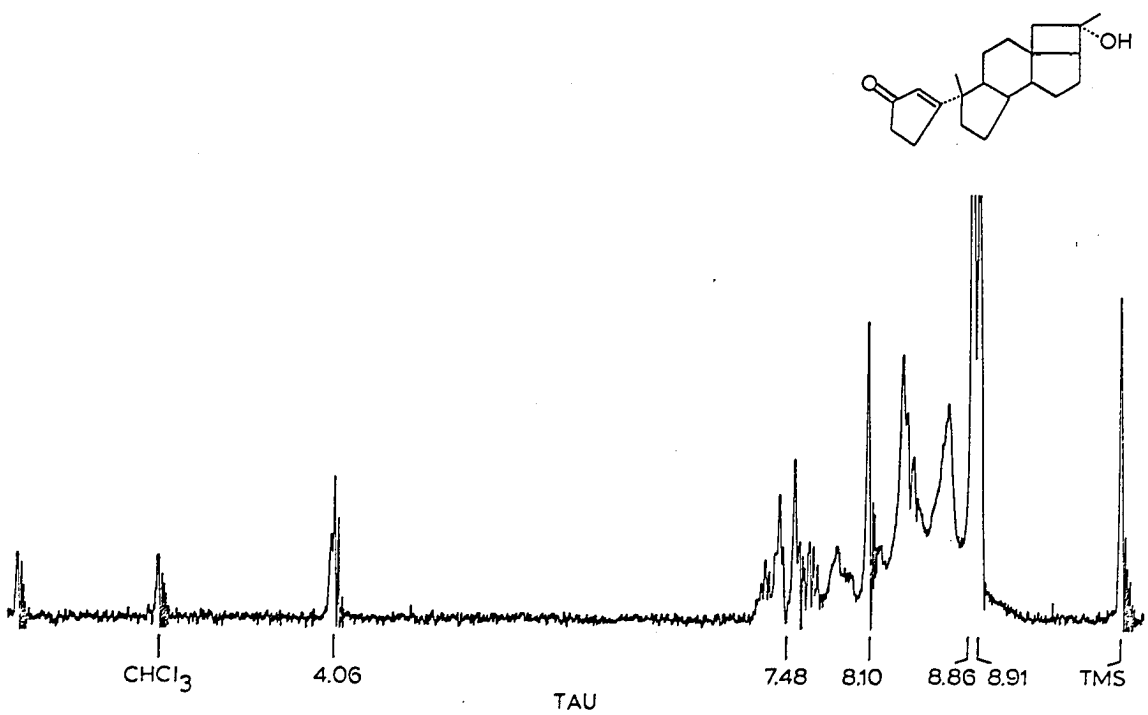

FREQUENCY (CM⁻¹)
000 4000 3000 2500 2000 1800 1600 1400 1200 1100 1000 950 900 850 800 750 700
2 3 4 5 6 7 8 9 10 11 12 13 14
WAVELENGTH (MICRONS)

Figure 8. Nuclear magnetic resonance spectra

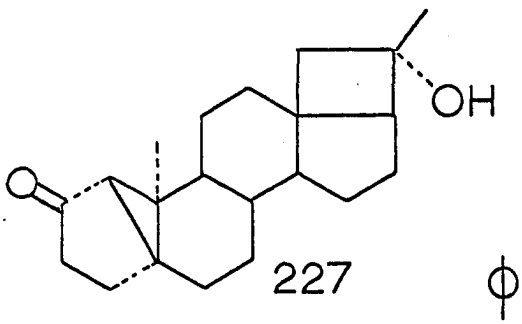
Top - (20S)-20-Hydroxy-3-benzylidene-10α-methyl-1β,5β-cyclo-18,20-cyclo-pregnan-2-one (235) ($CDCl_3$)

Bottom - Photo #3 (230) of progesterone ($CDCl_3$)

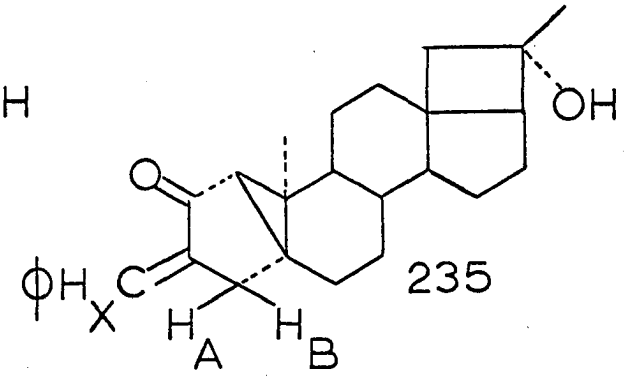

OH
ΦHC
2.35
2.80
7.01
8.25
8.40
8.88
8.94
TMS
TAU


OH
CHCl3
4.06
7.48
8.10
8.86
8.91
TMS
TAU

absorption centered at 7.01 τ was assigned to the AB portion of an ABX system. The X portion was buried in the aromatic absorption at 2.35-2.80 τ.



227



235

Analysis of the AB portion of the ABX system by assignment of lines 1, 3, 5 and 7 to the A nucleus and lines 2, 4, 6 and 8 to the B nucleus gave a value of J_{AB} = 18 c.p.s. The same value of J_{AB} is obtained if lines 1, 3, 6 and 8 and lines 2, 4, 5 and 7 are assigned to the A and B nuclei respectively. The assignment of the quartets as in the first case indicated that $J_{AX} = J_{BX}$ and that J_{AX} = 2.2 c.p.s. Assignment as in the second case indicated that $J_{AX} = -J_{BX}$. However, no further information about the relative magnitude of J_{AX} or J_{BX} could be obtained from the AB portion of the spectrum in the second case.

An unambiguous choice between these two possibilities could be made by analysis of the X portion of the spectrum. However, this was not possible in this case since the X portion was buried in the aromatic region of the spectrum.

The value of J_{AB} of 18 c.p.s. is consistent with the value of J_{AB} obtained from the analysis of systems similar to that observed for 235

(15,31). The value of $J_{AX} = J_{BX} = 2.2$ c.p.s. which is obtained from the analysis of the spectrum by assigning lines 1, 3, 5 and 7 and lines 2, 4, 6 and 8 to the A and B nuclei respectively is also consistent with that found in systems of similar structure (15).

The ultraviolet and n.m.r. data for 235 are consistent with that obtained by Griswold (15) and Rettig (31) for similar systems. The large value of J_{AB} would be expected from a strained system such as is present in 235. The absence of further splitting of the AB portion of the spectrum precludes any adjacent protons. The formation of only a monobenzylidine derivative indicated that the carbonyl must be flanked by a tri- or tetra-substituted carbon on one side and a di-substituted system on the other. The presence of the sharp singlet at 8.40 τ supports the assignment of C-1 as a tri-substituted position.

On the basis of the above data, the structure of photo #2 of progesterone is considered secure as shown in 229.

Photo #3 (230) of progesterone gave m.p. 135-6.5 °C with $[\alpha]_D^{26} = +76.8°$ (c = 1.43, $CHCl_3$). The ultraviolet spectrum gave $\lambda_{max}^{95\ EtOH} = 232$ mμ ($\varepsilon = 17{,}600$). The infrared spectrum is reproduced in Figure 8 on page 87. The infrared indicated the presence of an alcohol (2.85-2.90 μ) and an α,β-unsaturated ketone (5.87, 5.95 and 6.26 μ). The similarity of the ultraviolet spectrum and the infrared spectrum of photo #3 to those of photo-testosterone and photo-testosterone acetate gave the first clue to the structure of the A and B rings of photo #3 (15).

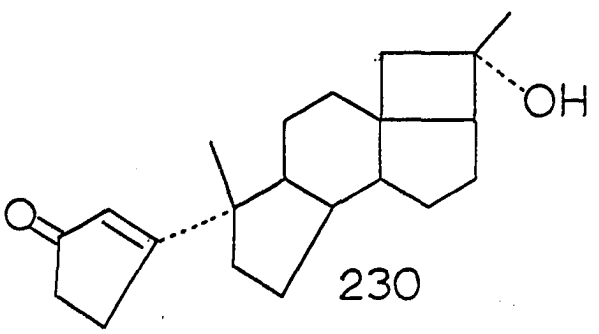
The n.m.r. spectrum of photo #3 (230) is shown in Figure 7 on page 85. The three proton singlets at 8.91 and 8.86 τ are assigned to the C-19 and C-21 methyl groups. The singlet at 8.10 τ was shown to be due to a single hydroxyl proton by deuterium exchange. A four proton multiplet was centered at 7.48 τ and a highly split olefinic proton at 4.06 τ.

The mass spectrum of photo #3 gave m/e peaks at 314 (9.2%, P^+), 257 (16%), 256 (21%), 123 (100%) and 109 (8.3%). At low ionizing voltage the m/e 123 peak decreased very rapidly and became about equal to the 109 peak. The peaks at m/e 256, 257 and 314 were the predominant peaks in the spectrum at low e.v.

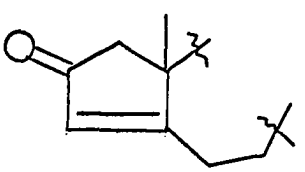
The absence of the C-21 methyl ketone in the n.m.r. spectrum coupled with the absence of the C-18 methyl again suggested that these groups were involved in cyclobutanol formation. The presence of a hydroxyl proton and the absence of absorption in the 5.5-6.5 τ region indicated that the alcohol was tertiary. The m/e peaks in the mass spectrum at 257 and 256 supported this postulate. On the basis of this data the structure of the C and D rings of photo #3 was assigned as shown in 230. The stereochemistry at C-20 is assigned in analogy with photo #1 and photo #2.

The doublet carbonyl band in the infrared spectrum of photo #3 strongly suggests the presence of a 3-substituted 2-cyclopentenone similar to that of photo-testosterone. The region at 7.48 τ in the n.m.r. spectrum of photo #3 was virtually identical to that of photo-testosterone and photo-testosterone acetate. The pattern in the 7.48 τ region in the n.m.r. spectrum of 230 was considered as the ABCD portion of an ABCDX

spectrum which resulted from the coupling of the five protons on the 3-substituted 2-cyclopentenone ring. For purposes of interpretation it was assumed that the A and B protons and the C and D protons were nearly chemically equivalent. This assumption was supported by the previously discussed case of photo-testosterone-d_5 (226). This assumption would allow the ABCDX spectrum to be viewed more simply as an A_2B_2X spectrum. The region at 7.48 τ was then interpreted as the A_2B_2 portion of an A_2B_2X system with the X portion being the olefinic proton at 4.06 τ. The lower half of the four proton multiplet integrated for two protons and these were assigned to the methylenes at C-4 of the 2-cyclopentenone ring. The upper half of the multiplet also integrated for two protons and these were assigned to the methylenes at C-5 of the 2-cyclopentenone ring system. The absorption at 4.06 τ is consistent with that of an α-proton on an enone system. Since no other olefinic protons were observed, it was concluded that the system was 3-substituted with no further substitution.



230



236

The ratio of the m/e 123 to 109 peaks in the mass spectrum of photo #3 and their behavior at low electron voltage is consistent with that

observed for the model compounds, photo-testosterone and photo-testosterone acetate.

The only other reasonable structural alternative for photo #3 would be a system with the partial structure 236. Such a compound might exhibit a doublet carbonyl band in the infrared and have an ultraviolet absorption maximum similar to that of photo #3. However, the n.m.r. spectrum of 236 would be inconsistent with that observed for photo #3. In a system such as 236 there would be two types of methylenes. Those at C-1 would be expected to appear at higher field and resemble those of photo #3. However, the second two methylenes at C-5 would be further split by the adjacent protons at C-6. This type of pattern is not observed in the n.m.r. spectrum of photo #3 where the A_2B_2 pattern has a high degree of symmetry.

The mass spectrum of 236 would be expected to give as the major fragment m/e 110 as the result of di-allylic cleavage. Such cleavage is the preferred route of fragmentation for similar systems (103). Since the m/e fragment 110 is not observed in the spectrum of photo #3 a structure such as 236 can again be eliminated.

On the basis of the above data photo #3 of progesterone was assigned the structure as shown in 230. The stereochemistry at C-10 is assigned in analogy with similar systems (See Historical Section).

Photo #4 (231) of progesterone gave m.p. 121-3 °C with $[\alpha]_D^{26} = +147°$ (c = 2.02, $CHCl_3$). The ultraviolet spectrum of photo #4 gave $\lambda_{max}^{95\ EtOH} = 205\ m\mu$ ($\varepsilon = 6,380$). The infrared spectrum of photo #4 in KBr

is shown in Figure 7 on page 85 and in chloroform in Figure 9 on page 95. The infrared spectrum in KBr indicated the presence of a methyl ketone (5.86 and 7.38 μ) and possibly a cyclopropyl cyclopentanone (5.88 μ). The ultraviolet and infrared spectra of photo #4 suggested that the A and B ring structure might be similar to that of photo #2 (229).

The n.m.r. spectrum of photo #4 is reproduced in Figure 10 on page 97. The two singlets at 9.41 and 8.87 τ which integrated for three protons each were assigned to the C-18 and C-19 methyl groups respectively. The sharp three proton singlet at 7.95 τ was assigned to the C-21 methyl group of a methyl ketone. The one proton singlet at 8.43 τ was assigned to the cyclopropyl proton at C-1.

The mass spectrum of photo #4 gave peaks at m/e 314 (89%, P^+), 123 (59%) and 109 (100%). At 18 e.v. and below only m/e 314 and 109 remained significant. The ratio of the 109 to 123 m/e peaks in the spectrum of photo #4 and their behavior at low electron voltage show excellent agreement with those of the model compounds, lumi-testosterone and lumi-testosterone acetate.

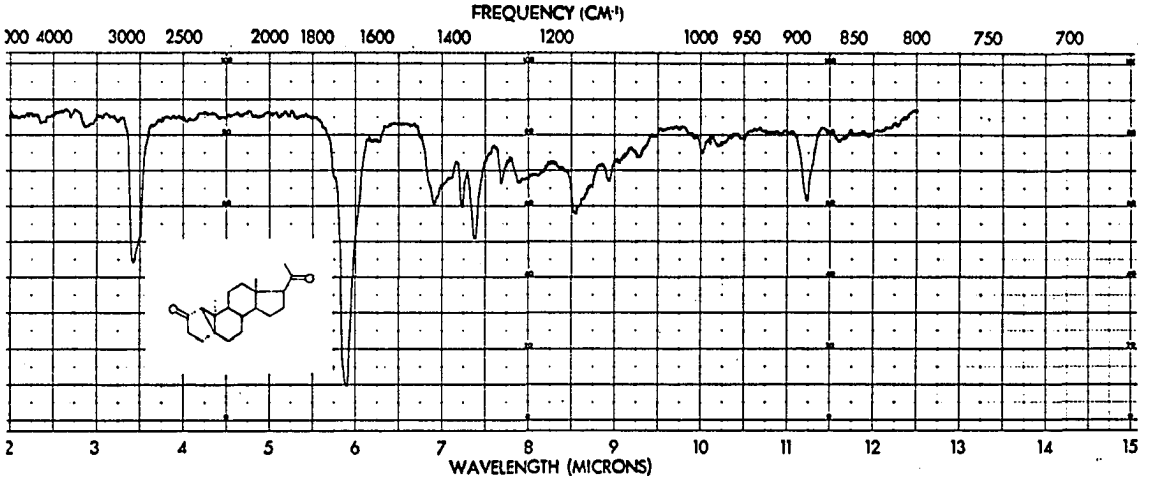
The infrared and n.m.r. evidence support the presence of a methyl ketone in photo #4. It is assumed that this ketone is the methyl ketone at C-17 as in the parent molecule progesterone. This was shown to be correct by an independent synthesis of photo #4 described later. The spectral data also support the assignment of the lumi-type structure to

Figure 9. Infrared spectra

Top - Photo #4 (231) of progesterone ($CHCl_3$)

Middle - Photo #5 (232) of progesterone ($CHCl_3$)

Bottom - Photo #1-A (240) of Δ^4-pregnen-20β-ol-3-one ($CDCl_3$)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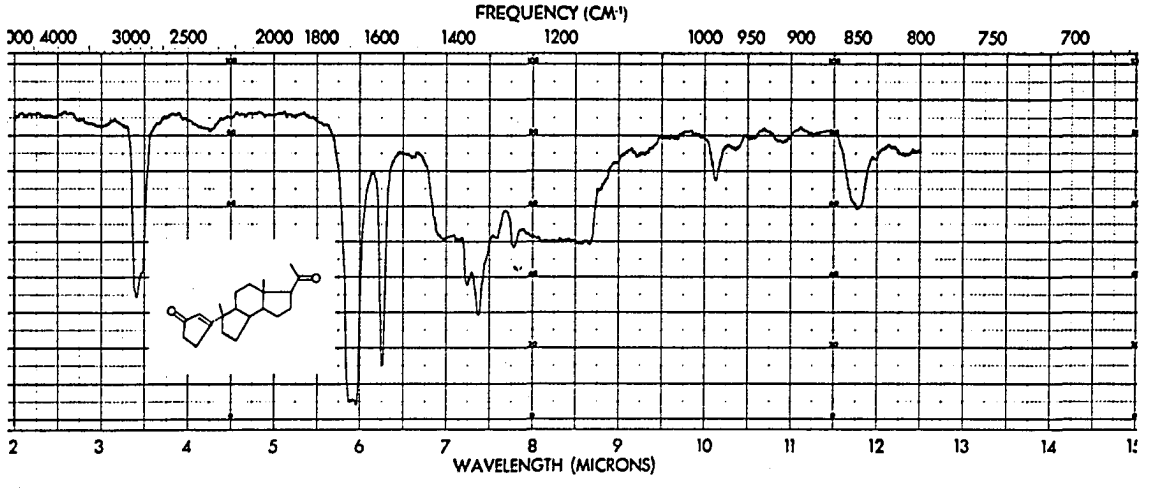
WAVELENGTH (MICRONS)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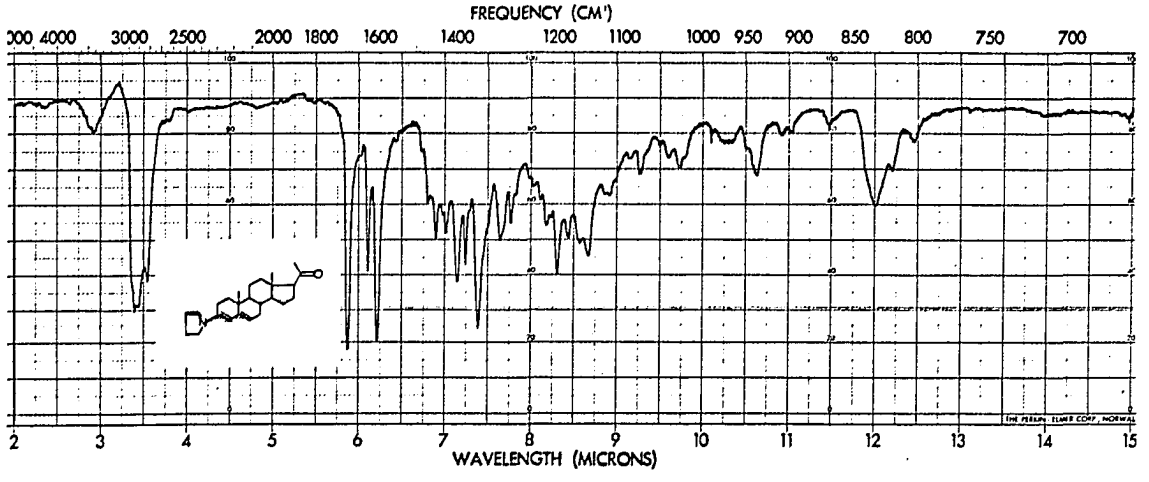
WAVELENGTH (MICRONS)


FREQUENCY (CM-1)
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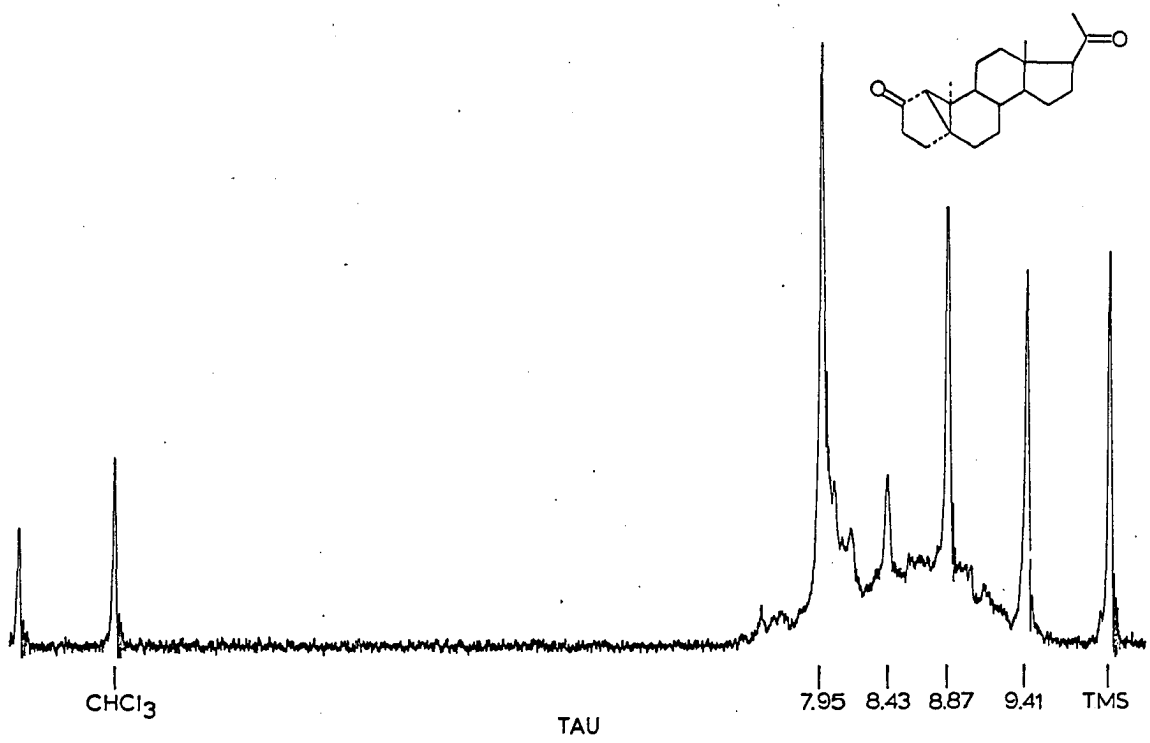
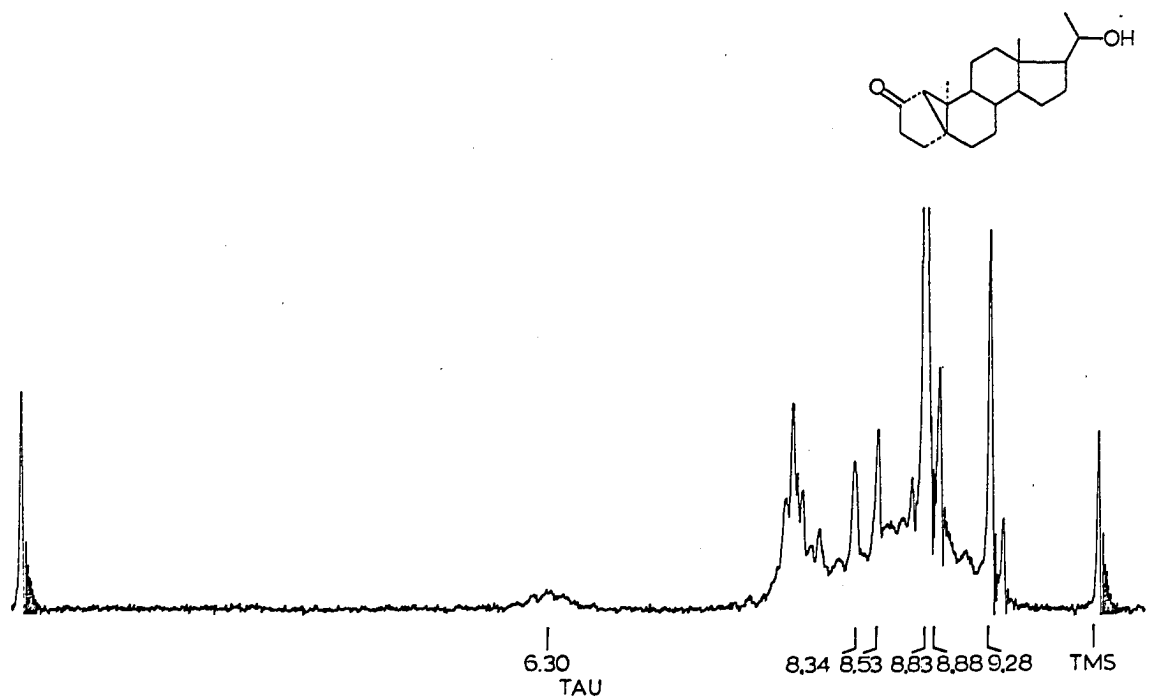
2 3 4 5 6 7 8 9 10 11 12 13 14 15
WAVELENGTH (MICRONS)

Figure 10. Nuclear magnetic resonance spectra

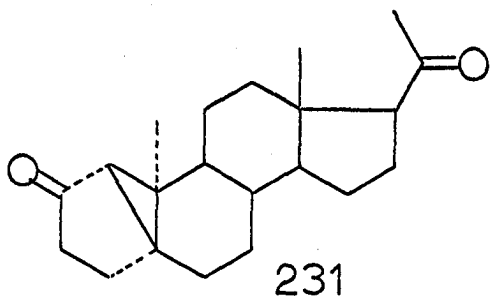
Top - Photo #4 (231) of progesterone ($CDCl_3$)

Bottom - Photo #1-A (240) of Δ^4-pregnen-20β-ol-3-one ($CDCl_3$)

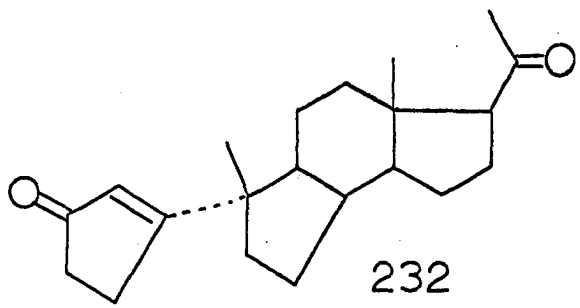

CHCl3
TAU
7.95
8.43
8.87
9.41
TMS


OH
6.30
TAU
8.34
8.53
8.83
8.88
9.28
TMS

the A and B rings of photo #4. On the basis of the above data the structure shown in 231 is assigned to photo #4 of progesterone.



231

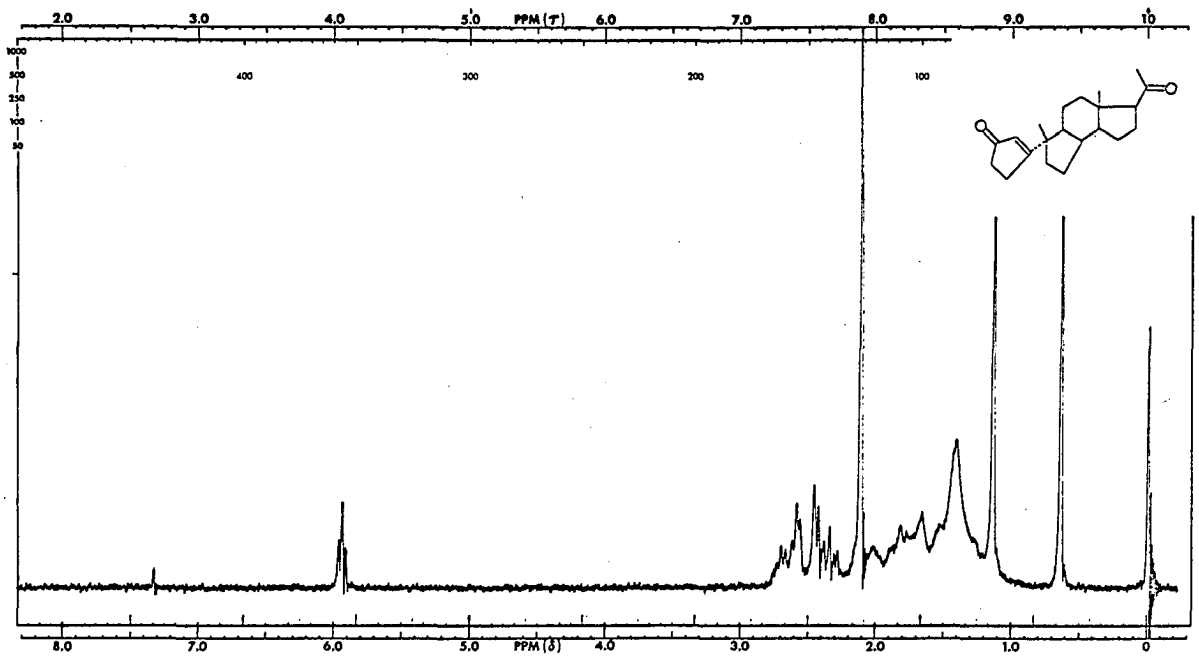


232

Photo #5 (232) of progesterone resisted all attempts at crystallization. The infrared spectrum of photo #5 is shown in Figure 9 on page 95. The infrared gave evidence of the presence of a methyl ketone (5.88 and 7.38 μ) and of an α,β-unsaturated ketone (5.88, 5.95 and 6.26 μ). The infrared spectrum was suggestive of the β-substituted cyclopentenone type of structure for the A and B rings of photo #5.

The n.m.r. spectrum of photo #5 is reproduced in Figure 11 on page 100. The n.m.r. spectrum showed two singlets of three protons each at 9.38 and 8.88 τ assigned to the C-19 and C-18 methyl groups respectively. The sharp singlet at 7.94 τ was assigned to the C-21 methyl group of the ketone at C-20. There was a four proton multiplet centered at 7.46 τ and a highly split olefinic proton at 4.08 τ. This structural feature was virtually identical to the ABCDX pattern seen in the n.m.r. spectra of photo #3, photo-testosterone and photo-testosterone acetate. As in the previous examples, the ABCDX pattern may be more simply viewed as an A_2B_2X spectrum.

Figure 11. Nuclear magnetic resonance spectrum of Photo #5 (232) of progesterone ($CDCl_3$)


2.0
3.0
4.0
5.0
PPM (τ)
6.0
7.0
8.0
9.0
10
1000
500
250
100
50
400
300
200
100
8.0
7.0
6.0
5.0
PPM (δ)
4.0
3.0
2.0
1.0
0

The similarity of the infrared and n.m.r. spectra of photo #5 to those of photo #3 led to the assignment of the ring A and B structure as for photo #3. The presence of the methyl ketone in the n.m.r. spectrum of photo #5 led to the assignment of the C and D ring structure as for photo #4. The structure proposed for photo #5 of progesterone is that shown as 232. This was confirmed by the synthesis of photo #5 by a different route which will be discussed later.

The variety of products isolated from the irradiation of progesterone (227) in tertiary butyl alcohol with light greater than 3000 Å indicated that the molecule exhibited no selective reactivity as regards the various functional groups.

An examination of the ultraviolet spectrum of progesterone indicated that the $n \rightarrow \pi^*$ absorption band of the saturated ketone was buried under the tail of the $\pi \rightarrow \pi^*$ band of the enone. The $n \rightarrow \pi^*$ band of the enone had its maximum in the region of 3000 Å, but tailed well above 3600 Å with an extinction coefficient of the order of 7.

It was decided to irradiate progesterone with light greater than 3600 Å. The 3660 Å line of the mercury arc was isolated by means of a copper sulfate filter solution and was used to irradiate progesterone.

The irradiation of progesterone with the isolated 3660 Å line in tertiary butyl alcohol gave photo #4 (231) in 26% yield, photo #5 (232) in 9% yield and 8% of recovered progesterone. The irradiation gave a large amount of amorphous polymeric material but the presence of other rearrangement products could not be detected.

Photo #4 was identified by comparison of its infrared spectrum, melting point and mixed melting point with that of authentic material isolated previously.

Photo #5 was identified by comparison of its infrared and n.m.r. spectra, v.p.c. and thin layer behavior with an authentic sample isolated from the broad arc irradiation of progesterone.

A similar irradiation of progesterone (227) in tertiary butyl alcohol was preformed in the presence of dibenzothiophene using the broad mercury arc in Pyrex. The concentration of dibenzothiophene was such that it absorbed greater than 98% of the light below 3600 Å. However, progesterone absorbs more strongly than dibenzothiophene at wave lengths greater than 3600 Å. Above 3600 Å it was found that dibenzothiophene absorbed 22% of the light and progesterone absorbed the remainder.

Dibenzothiophene has been shown to have a triplet energy of 69.3 kcal./mole with the lowest triplet apparently the $\pi \rightarrow \pi^*$ triplet (105). Thus dibenzothiophene might function as both an internal filter and a photosensitizer.

Irradiation of progesterone in tertiary butyl alcohol in the presence of dibenzothiophene gave two products. Photo #4 (231) was isolated in 30% yield, photo #5 (232) in 24% yield and 14% of progesterone was recovered. The amount of polymeric material found in this irradiation was significantly less than that found in the irradiation at 3660 Å. The reaction seemed to proceed at a rate that was equal to or slightly greater than that at 3660 Å.

The identity of the photoproducts isolated from the irradiation mixture was accomplished by a comparison of their properties with those of the authentic materials isolated previously.

A similar irradiation of Δ^5-pregnen-3β-ol-20-one (233) in tertiary butyl alcohol in the presence of dibenzothiophene resulted in the recovery of unreacted starting material. This indicated the inability of dibenzothiophene to transfer its triplet energy to the saturated ketone function. This agrees with the result observed with progesterone above. A similar solution of 233 without dibenzothiophene underwent greater than 50% conversion to photoproducts under like conditions.

Progesterone has a strong absorption in the 2300-2600 Å region due to the $\pi \rightarrow \pi^*$ transition to the enone. Irradiation of progesterone (227) in tertiary butyl alcohol with a low pressure mercury arc gave rise to only two photoproducts. Photo #4 (231) was isolated in 29% yield, photo #5 (232) in 14% yield and 13% of unreacted progesterone was recovered. No other photoproducts were detected from this reaction. The identity of photo #4 and photo #5 was established by comparison of the properties of the isolated compounds with those of the authentic materials isolated previously.

The above experiments showed conclusively that an α,β-unsaturated ketone could be preferentially excited in the presence of a saturated ketone and could react to yield the usual type of photoproducts.

An attempt to find a method for preferential excitation of a saturated ketone was then initiated. Saturated ketones have an absorption

at 2700-2900 Å due to an n → π* excitation. It was probable that this band extended into the region of 3130 Å. If the extinction coefficient of the saturated ketone was larger than that of the unsaturated ketone in this region, a selective excitation and thus reaction might be achieved.

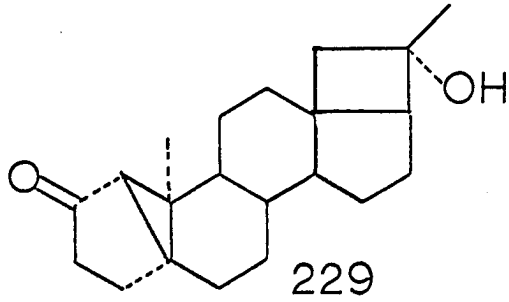
Irradiation of progesterone (227) in tertiary butyl alcohol with the 3130 Å line of the mercury arc, isolated by means of a nickel sulfate-cobalt sulfate filter solution, gave only one significant product. Column chromatography on alumina gave photo #1 (228) in 18% yield and recovered progesterone in 58% yield. Any other type of rearranged photoproducts resulting from this irradiation were present is less than 3%. The identity of the product isolated above was confirmed as photo #1 by comparison of its melting point, mixed melting point and infrared spectrum in KBr with that of an authentic sample.

Longer periods of irradiation gave products resulting from the reaction of the enone moiety as well as the saturated ketone as shown by v.p.c. This is expected since both ketones have absorption in this region of the spectrum.

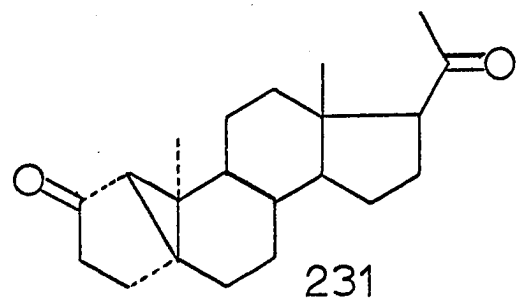
The selective formation of photo #1 (228) is possible because the extinction coefficient of the saturated ketone is larger than that of the enone in this region of the spectrum or its reaction path is more efficient or both.

It had been reported that irradiation of the cyclopropyl cyclopentanone type of photoproduct such as photo #2 (229) gave rise to the parent enone in a reversible process (10). The cyclopropyl cyclopentanone

was also considered as giving rise to the other observed photoproducts in analogy with the chemistry of cross-conjugated dienones (See Historical Section). This report was not in agreement with that observed by other workers (31). It was decided to investigate this type of process using photo #2 (229) of progesterone. Irradiation of photo #2 in tertiary butyl alcohol at 3000-3700 Å in Pyrex or at 2537 Å in quartz did not give rise of any further rearranged products as shown by v.p.c. The infrared spectrum of the reisolated material was virtually identical to that of photo #2 before irradiation. Under similar conditions progesterone had reacted to the extent of 30-50% to yield the usual type of photoproducts as shown by v.p.c. Longer periods of irradiation would result in the conversion of photo #2 (229) to substances which were not v.p.c. volatile, but in all cases it was stable to further rearrangement to any of the usual photoproducts.



229



231

A similar study with photo #4 (231) at 3000-3700 Å in Pyrex in tertiary butyl alcohol solution was undertaken. Irradiation of photo #4 under these conditions gave only photo #2 (229) as shown by v.p.c. analysis.

A similar study using photo #4 and benzophenone in a concentration such that benzophenone absorbed greater than 96% of the incident light gave essentially the same product distribution as observed with photo #4 alone as shown by v.p.c. analysis. The reaction in the presence of benzophenone proceeded with essentially the same efficiency as the unsensitized reaction. This indicated that benzophenone was capable of transferring its triplet energy to the saturated ketone function.

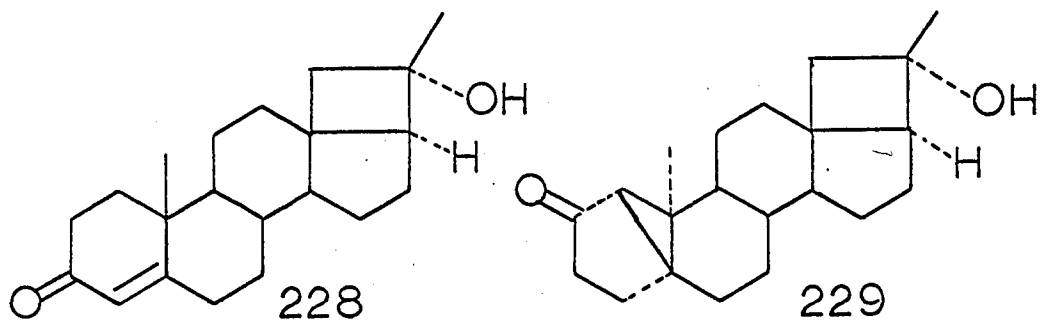
Photochemistry of (20S)-20-Hydroxy-Δ^4-18,20-cyclo-pregnen-3-one (228)

In order to confirm the stereochemical assignments of photo #2 (229) and photo #3 (230), the irradiation of photo #1 (228) was initiated. Photo #1 was prepared by the oxidation of the diol 234 as previously described.

Irradiation of photo #1 in tertiary butyl alcohol gave two photoproducts, photo #2 and photo #3. Photo #2 (229) was isolated in 26% yield, photo #3 (230) in 20% yield and 27% of photo #1 was recovered unchanged.

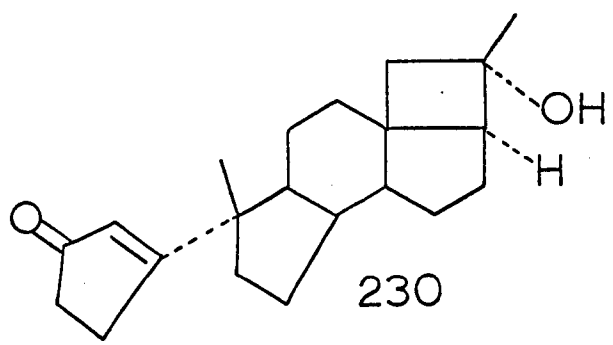
The photo #2 and photo #3 isolated from the irradiation of photo #1 were identical in every respect with the authentic samples prepared by the irradiation of progesterone.

The cyclobutanol ring system is not an absorbing chromaphore and is left unchanged upon irradiation. Thus this establishes the stereochemistry of the C and D ring systems of photo #2 and photo #3 as that shown in 229 and 230 respectively.



228

229



230

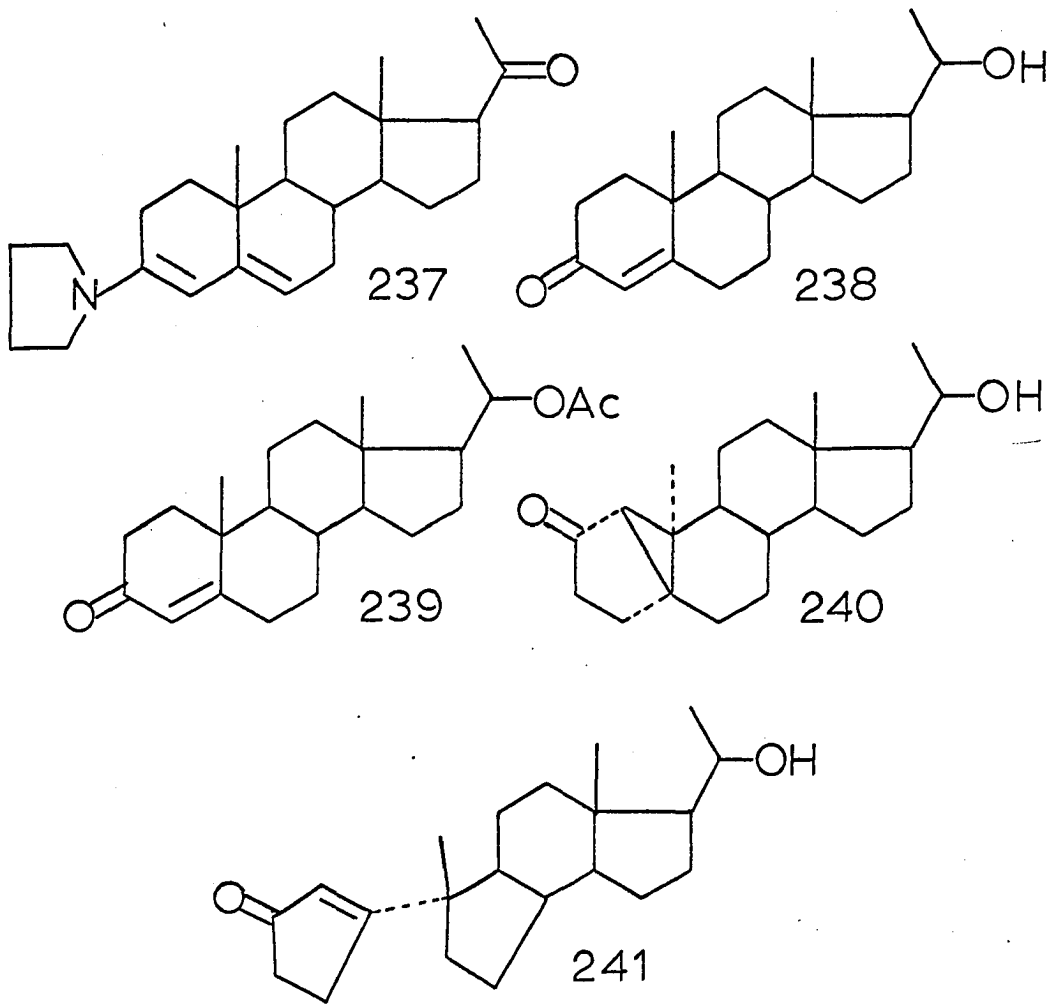
Photochemistry of Δ^4-Pregnen-20β-ol-3-one (238)

In order to establish the absolute configuration of photo #4 (231) and photo #5 (232) an investigation of the photochemistry of Δ^4-pregnen-20β-ol-3-one (238) was undertaken.

Treatment of progesterone (227) with pyrrolidine gave the enamine 237 whose properties were consistent with the literature values (107). The infrared spectrum of 237 is shown in Figure 9 on page 95. Reduction of the enamine with lithium aluminum hydride in ether followed by hydrolysis gave Δ^4-pregnen-20β-ol-3-one (238) as the major product with m.p. 171-5 °C compared to the literature value of 171-2 °C (108). The infrared spectrum shown in Figure 12 on page 112 was consistent with the structure 238. Acetylation of 238 gave Δ^4-pregnen-20β-acetoxy-3-one

(239) with m.p. 156-9 °C compared with a literature value of 159-9.5 °C (108). The infrared spectrum of the acetate 239 is given in Figure 12 on page 112.

Oxidation of the alcohol 238 gave progesterone (227) showing that no gross structural changes had occurred in the synthetic sequence.



Irradiation of Δ^4-pregnen-20β-ol-3-one (238) in tertiary butyl alcohol gave two photoproducts. Photo #1-A (240) was isolated in 24% yield, photo #2-A (241) in 21% yield and 10% of starting material was recovered.

Photo #1-A (240) gave m.p. 238-40 °C with $[\alpha]_D^{26}$ = +50.8° (c = 1.115, $CHCl_3$). The ultraviolet spectrum exhibited $\lambda_{max}^{95\ EtOH}$ = 210 mμ (ε = 6,810). The infrared spectrum is shown in Figure 12 on page 112. The infrared indicated the presence of an alcohol (2.86 μ) and a ketone (5.90 μ). The similarity of the ultraviolet and infrared spectra of photo #1-A to those of photo #2 and photo #4 of progesterone gave the first clue to its structure.

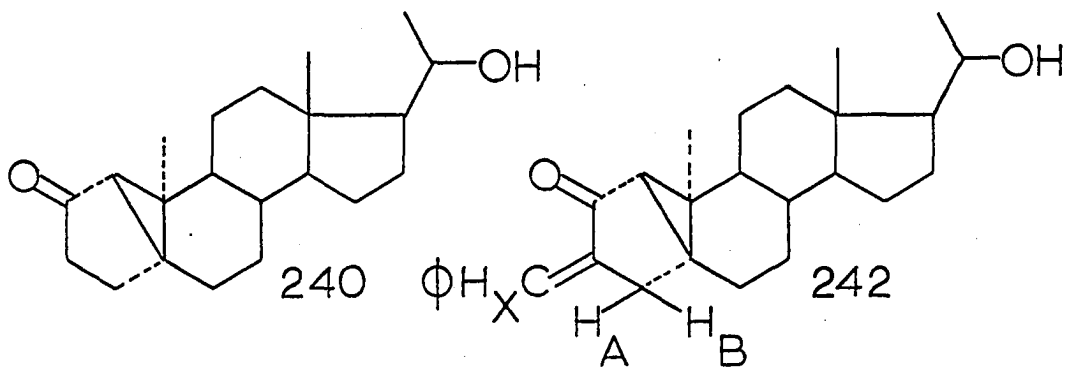
The n.m.r. spectrum of photo #1-A (240) is shown in Figure 10 on page 97. The singlets at 9.28 and 8.83 were assigned to the C-18 and C-19 methyl groups respectively. A doublet with J = 7 c.p.s. was centered at 8.88 τ and was assigned to the C-21 methyl group. This assignment was confirmed by application of the double resonance technique to the broad multiplet at 6.30 τ which was assigned to the C-20 methine. The one proton singlet at 8.53 τ was due to the hydroxyl proton as shown by deuterium exchange. The singlet at 8.34 τ was assigned to the cyclopropyl methine at C-1.

The mass spectrum gave peaks at m/e values of 316 (56%, P^+), 123 (56%) and 109 (100%) at 70 e.v. At 18 e.v. and below, only m/e 109 and 316 remain significant.

The infrared and ultraviolet spectra are consistent with the assignment of the cyclopropyl cyclopentanone structure for photo #1-A. The absence of any olefinic protons in the n.m.r. spectrum and the presence of the sharp singlet at 8.34 τ also support this assignment. The m/e peaks at 123 and 109 and their behavior at low electron voltage are in

excellent agreement with the behavior observed in the model compounds described previously.

The n.m.r. spectrum supports the assignment of the C and D ring structure of photo #1-A as identical to that of the starting material. On the basis of the above information the structure 240 is assigned to photo #1-A.



Further evidence for the structure of photo #1-A was obtained by the preparation of its monobenzylidine derivative 242. Treatment of photo #1-A (240) with methanolic potassium hydroxide and benzaldehyde gave 242 with m.p. 206-7 °C. The ultraviolet spectrum gave λ_{max}^{EtOH} = 299 mμ (ε = 27,300), 230 mμ (ε = 10,700) and 224 mμ (ε = 10,500). The infrared spectrum is shown in Figure 13 on page 114. The infrared indicated the presence of an alcohol (2.87 μ), a ketone (5.92 μ) and the benzylidine moiety (6.15 and 14.60 μ). These data are in excellent agreement with those of similar benzylidine derivatives previously prepared (15,31).

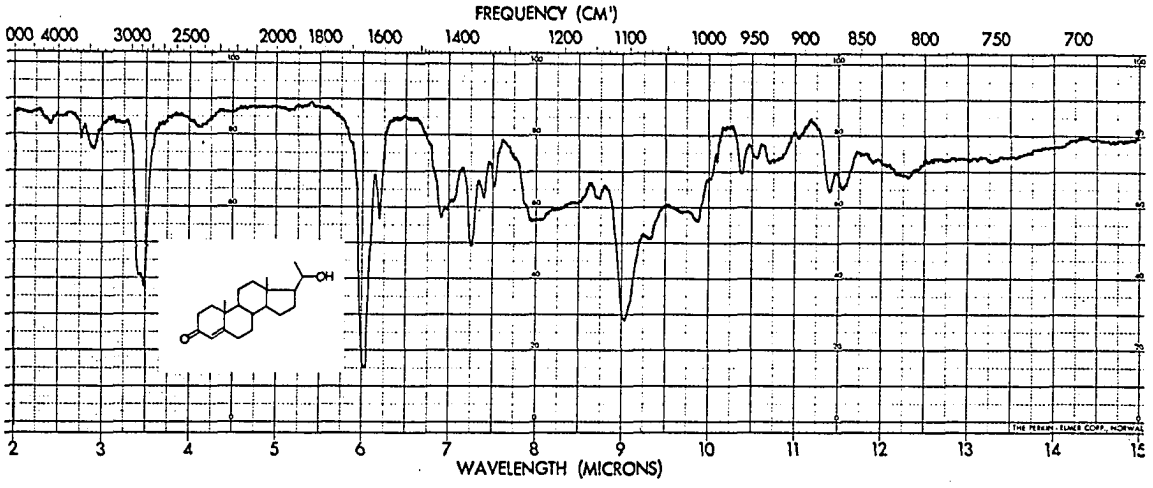
The n.m.r. spectrum of 242 is reproduced in Figure 14 on page 116. The three proton singlets at 9.22 and 8.92 τ are assigned to the C-18

Figure 12. Infrared spectra

Top - Δ^4-pregnen-20β-ol-3-one (238) ($CHCl_3$)

Middle - Δ^4-pregnen-20β-acetoxy-3-one (239) (KBr Pellet)

Bottom - Photo #1-A (240) of Δ^4-pregnen-20β-ol-3-one (KBr Pellet)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OH
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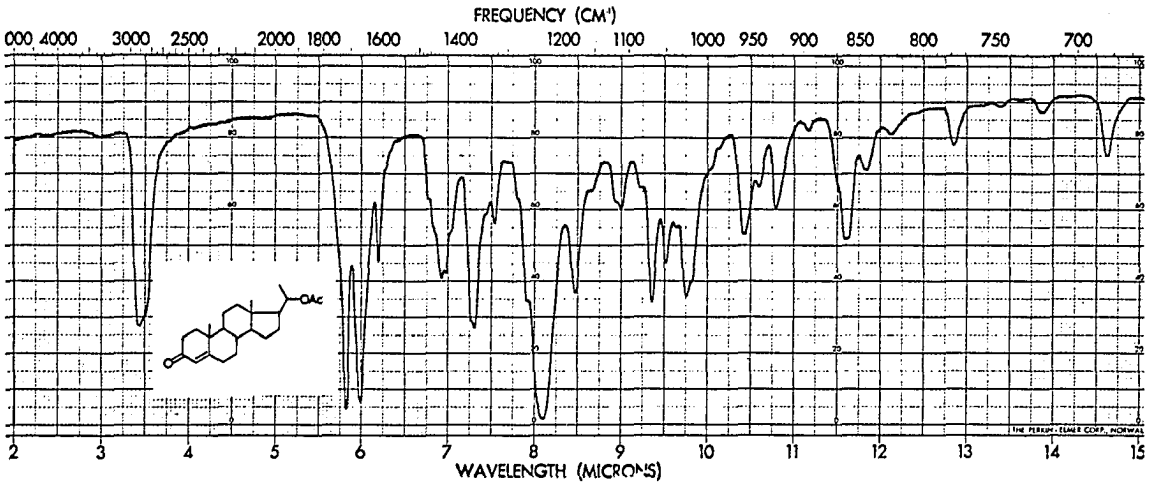
WAVELENGTH (MICRONS)


FREQUENCY (CM')
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OAc
2 3 4 5 6 7 8 9 10 11 12 13 14 15
WAVELENGTH (MICRONS)

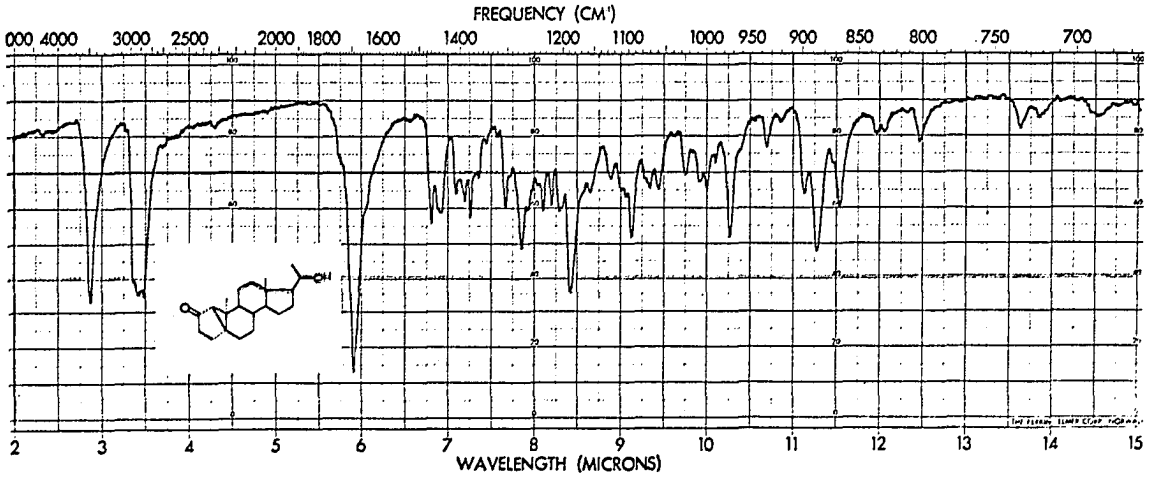
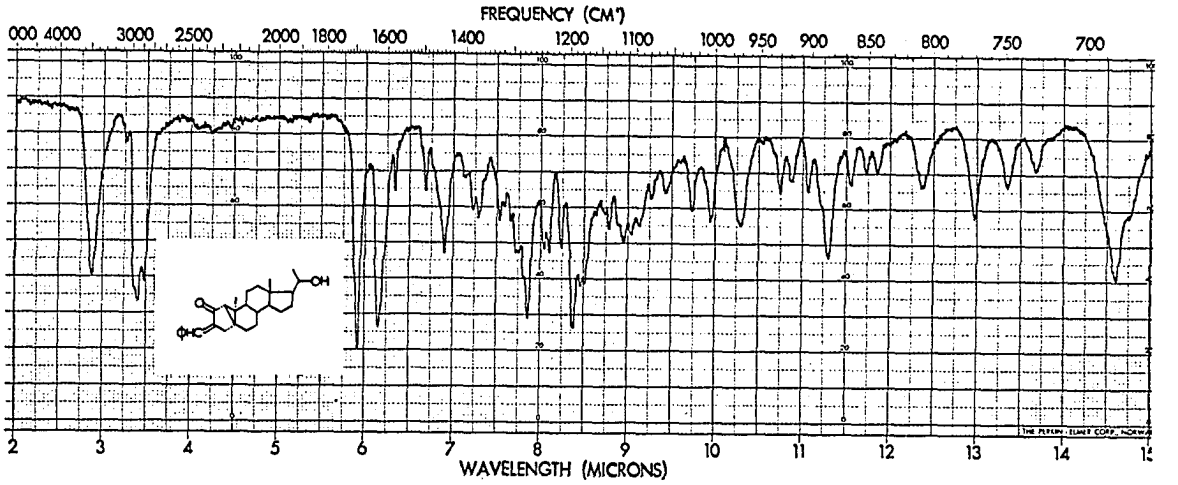

FREQUENCY (CM')
000 4000 3000 2500 2000 1800 1600 1400 1200 1100 1000 950 900 850 800 750 700
OH
2 3 4 5 6 7 8 9 10 11 12 13 14 15
WAVELENGTH (MICRONS)

Figure 13. Infrared spectra

Top - 3-Benzylidene-10α-methyl-1β,5β-cyclopregnan-20β-hydroxy-2-one (242) (KBr Pellet)

Middle - 10α-Methyl-1β,5β-cyclopregnan-20β-acetoxy-2-one (244) (KBr Pellet)

Bottom - Photo #2-A (241) of Δ^4-pregnen-20β-ol-3-one (KBr Pellet)


FREQUENCY (CM⁻¹)
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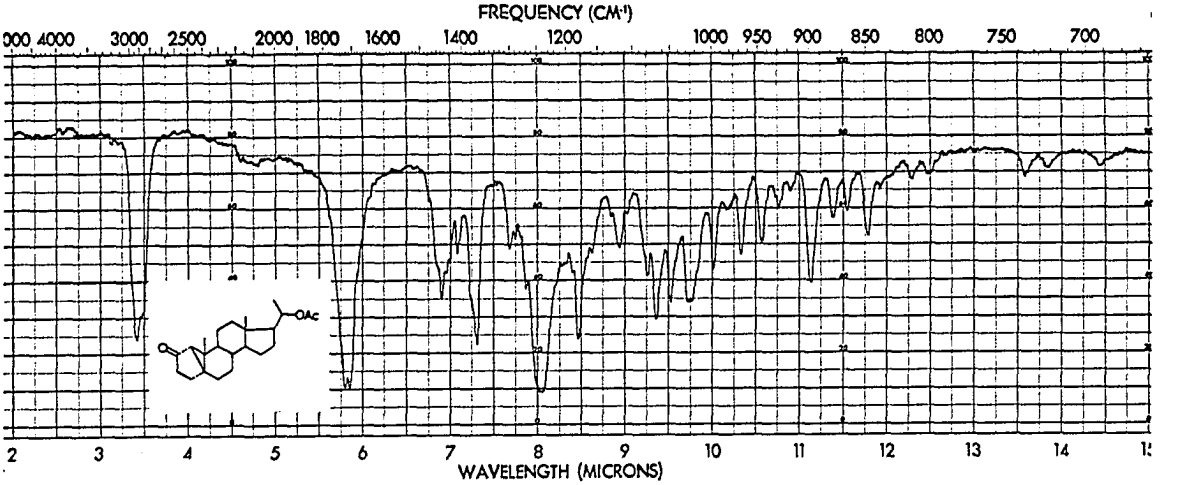
OH
2 3 4 5 6 7 8 9 10 11 12 13 14
WAVELENGTH (MICRONS)


FREQUENCY (CM⁻¹)
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OAc
2 3 4 5 6 7 8 9 10 11 12 13 14
WAVELENGTH (MICRONS)

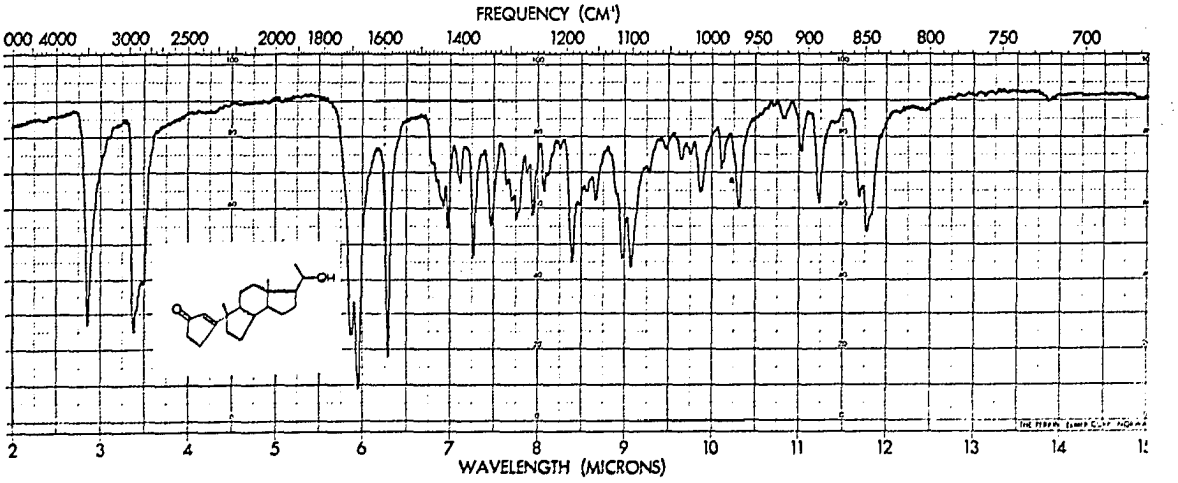
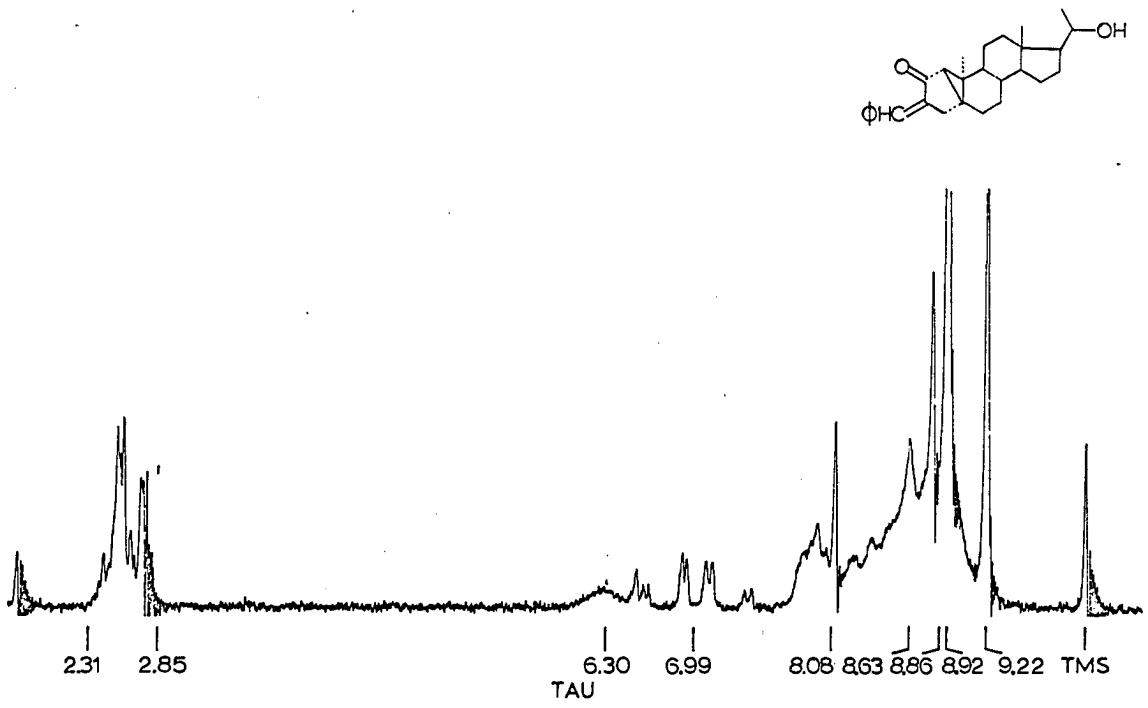
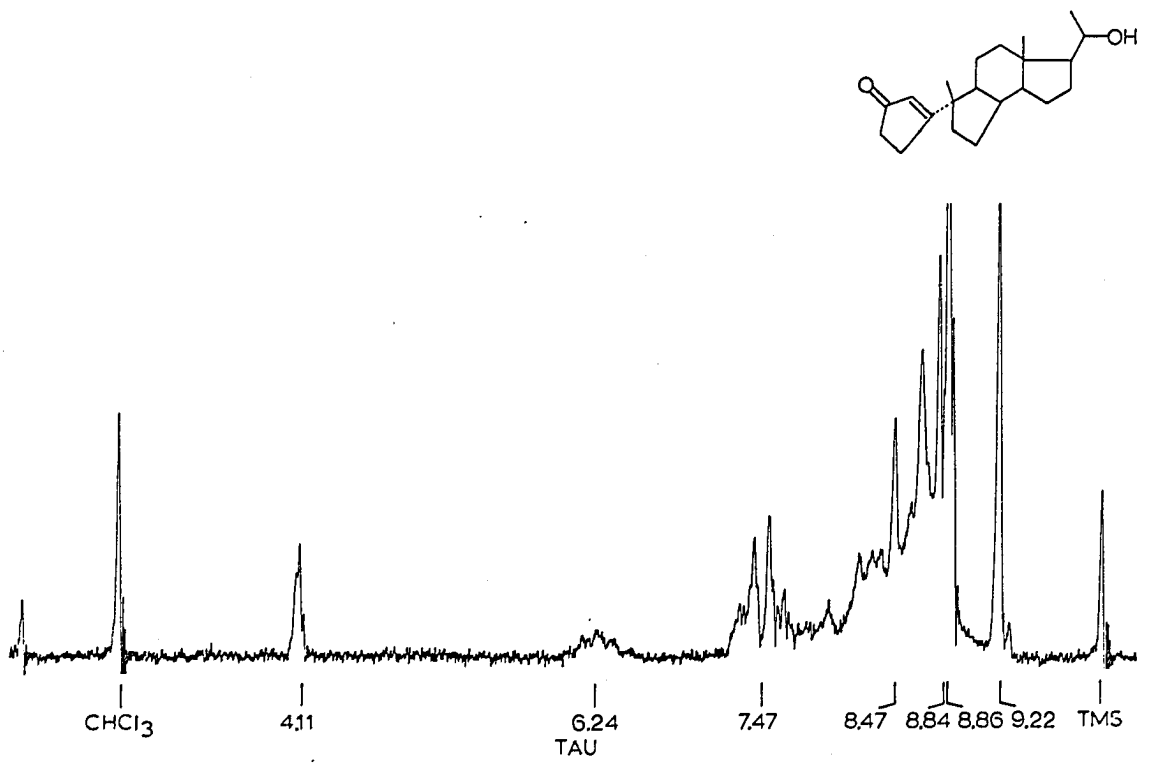

FREQUENCY (CM⁻¹)
4000 3000 2500 2000 1800 1600 1400 1200 1100 1000 950 900 850 800 750 700
OH
2 3 4 5 6 7 8 9 10 11 12 13 14
WAVELENGTH (MICRONS)

Figure 14. Nuclear magnetic resonance spectra

Top - 3-Benzylidene-10α-methyl-1β,5β-cyclopregnan-20β-hydroxy-2-one (242) ($CDCl_3$)

Bottom - Photo #2-A (241) of Δ^4-pregnen-20β-ol-3-one ($CDCl_3$)


OH
ΦHC
2.31
2.85
6.30
6.99
8.08
8.63
8.86
8.92
9.22
TMS
TAU


OH
CHCl3
4.11
6.24
7.47
8.47
8.84
8.86
9.22
TMS
TAU

and C-19 methyl groups respectively. The doublet with J = 7 c.p.s. centered at 8.86 τ is assigned to the C-21 methyl group. The broad singlet at 8.63 τ was assigned to the hydroxyl proton by deuterium exchange. The sharp singlet at 8.08 τ is assigned to the cyclopropyl methine at C-1. The two proton multiplet centered at 6.99 τ is assigned to the methylenes at C-4. The pattern was interpreted as an ABX system with the X portion buried in the aromatic absorption at 2.31-2.85 τ.

There were two possible assignments for the A and B quartets of the ABX system. In the first case lines 1, 3, 5 and 7 of the AB pattern were assigned to the A nucleus and lines 2, 4, 6 and 8 to the B nucleus. This assignment gave a value of J_{AB} = 19 c.p.s. Another possible assignment was that of lines 1, 3, 6 and 8 and lines 2, 4, 5 and 7 to the two quartets. This also gave a value of J_{AB} = 19 c.p.s. Analysis of the system with the quartets assigned as in the first case indicated that $J_{AX} = J_{BX}$ and that J_{AX} = 2.4 c.p.s. The analysis of the system with the quartets as assigned in the second case indicated that $J_{AX} = -J_{BX}$, but the absolute magnitude of the coupling constant could not be determined without analysis of the X portion of the spectrum.

An unambiguous choice between the two assignments would be possible by analysis of the X portion of the spectrum. However, this was not possible in this case since the X portion is buried in the aromatic absorption.

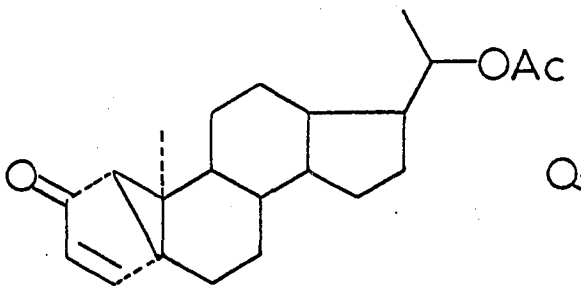
The value of J_{AB} = 19 c.p.s. is consistent with the data obtained for similar systems (15,31). The value of $J_{AX} = J_{BX}$ = 2.4 c.p.s. obtained from analysis in the first case is also consistent with that found in a system similar to 242 (15).

The n.m.r. spectrum is entirely consistent with the structure shown in 242. The formation of only the monobenzylidine derivative precludes the availability of two positions α to the carbonyl. The lack of further splitting of the AB portion of the ABX pattern indicated that the adjacent center was tetra-substituted. The presence of the sharp one proton singlet at 8.08 τ indicated that the other position α to the carbonyl was tri-substituted.

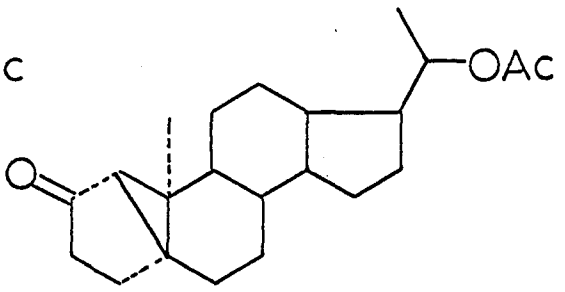
On the basis of the above data the structure of photo #1-A of Δ^4-pregnen-20β-ol-3-one (238) was assigned as shown in 240.

Oxidation of photo #1-A with aqueous CrO_3/H_2SO_4 in acetone gave a compound with an identical melting point, infrared spectrum and v.p.c. retention time as photo #4 (231) of progesterone. A mixed melting point of the two samples gave no depression. This confirms the assignment of the stereochemistry at C-17 of photo #4.

A report appeared in the patent literature on the preparation of a compound which should have been the 20β-acetoxy analogue of photo #1-A (109). The compound in the patent literature was prepared by the irradiation of the cross-conjugated 20β-acetoxy analogue of 238 to yield 243. Hydrogenation of 243 then gave a compound of proposed structure 244. The properties reported for compound 244 were m.p. 161-2 °C and



243



244

λ_{max}^{EtOH} = 238 mμ (ε = 2,190). The ultraviolet data is inconsistent with the structure proposed for 244 in the patent literature. Acetylation of photo #1-A (240) obtained by the irradiation of 238 gave an acetate with m.p. 147-8 °C and λ_{max}^{EtOH} = 211 mμ (ε = 6,260). The infrared spectrum is shown in Figure 13 on page 114. The data for the acetate prepared from photo #1-A are entirely consistent with the structure 244 proposed for the acetate. The ultraviolet spectrum for the acetate prepared in the patent literature is consistent with structure 243 rather than 244.

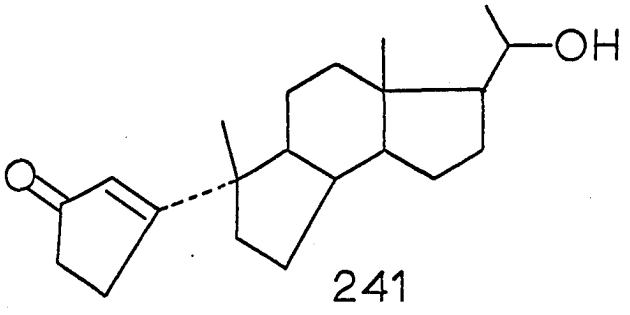
Photo #2-A (241) of Δ^4-pregnen-20 -ol-3-one (238) gave a m.p. 175-7 °C with $[\alpha]_D^{26}$ = +34.9° (c = 1.61, $CHCl_3$). The ultraviolet spectrum showed λ_{max}^{EtOH} = 232 mμ (ε = 19,400). The infrared spectrum is reproduced in Figure 13 on page 114. The infrared indicated the presence of an alcohol (2.86 μ) and an α,β-unsaturated ketone (5.86, 5.95 and 6.28 μ). The similarity of the infrared and ultraviolet spectra to those of photo #3 and photo #5 of progesterone gave the first clue to the structure of photo #2-A.

The n.m.r. spectrum of photo #2-A (241) is given in Figure 14 on page 116. The singlets at 9.22 and 8.86 τ were assigned to the C-18 and C-19 methyl groups respectively. The doublet with J = 7 c.p.s. centered at 8.84 τ was assigned to the C-21 methyl group and the broad multiplet at 6.24 τ to the C-20 methine. These assignments were confirmed by the application of the double resonance technique. The singlet at 8.47 τ was shown to be due to the hydroxyl proton by deuterium exchange. The four proton multiplet centered at 7.47 τ was assigned to the methylenes at C-4 and C-5 of the 2-cyclopentenone ring. The highly split olefinic proton at 4.11 τ was assigned to the methine at C-2 of the 2-cyclopentenone ring.

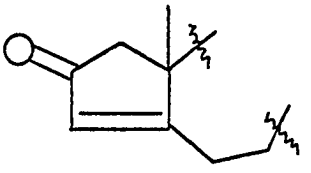
The four proton multiplet centered at 7.47 τ was virtually identical to that observed in photo #3 of progesterone where the pattern was the ABCD portion of an ABCDX spectrum. In the case of photo #3 the simplifying assumption was made that the A and B protons and the C and D protons were nearly chemically equivalent. This would allow the spectrum to be viewed more simply as an A_2B_2X system. This assumption was supported by the spectrum of photo-testosterone-d_5 (226). The same assumptions were made in the case of photo #2-A (241) and this allowed the ABCDX spectrum to be viewed more simply as an A_2B_2X system. The two protons in the lower field portion of the multiplet centered at 7.47 τ were assigned to the A_2 protons which were the methylenes at C-4 of the 2-cyclopentenone ring. The two protons at upper field were assigned to the B_2 protons which were those at C-5 of the 2-cyclopentenone ring. The X proton was assigned to the olefinic proton at 4.11 τ. The position of

the olefinic proton was consistent with its presence at C-2 of the 2-cyclopentenone ring. The absence of any other olefinic protons indicated that the ring was 3-substituted.

The mass spectrum of photo #2-A (241) gave m/e values of 316 (35%, P^+), 123 (100%) and 109 (52%) at 70 e.v. At 18 e.v. and below, only 109 and 316 remain significant. The mass spectral behavior of photo #2-A is in excellent agreement with that observed for the model compounds, photo-testosterone and photo-testosterone acetate.



241



236

The only reasonable structural alternative for photo #2-A would be a system with the partial structure 236. The n.m.r. spectrum of 236 would be expected to resemble that of the A_2B_2X pattern of photo #2-A. However the two protons at higher field would be the methylenes at C-1 and these would not be a highly split as those observed in the spectrum of photo #2-A. The protons at lower field would be those at C-5 and these should exhibit a very complex pattern due to coupling with the protons at C-6 which in turn would be coupled with those at C-7. In contrast to this pattern the observed multiplet in photo #2-A has a high degree of symmetry.

The major fragment from the mass spectrum of 236 would be that at m/e 110 as the product of di-allylic cleavage as is observed in systems of

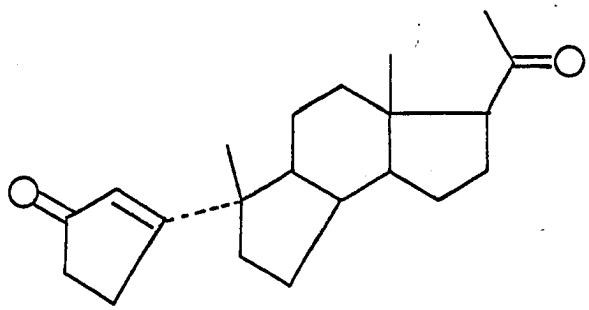
similar structure (103). Such a fragment is not present in the mass spectrum of photo #2-A.

On the basis of the above data, a structure such as 236 can be eliminated from consideration. The structure 241 is consistent with all of the data and is proposed for photo #2-A of Δ^4-pregnen-20β-ol-3-one (238).

Oxidation of photo #2-A (241) with aqueous CrO_3/H_2SO_4 in acetone gave a compound with the identical infrared and n.m.r. spectra of photo #5 (232) of progesterone. The v.p.c. retention time and thin layer behavior on silica gel and alumina plates were also identical to that of photo #5 (232). Crystallization from hexane gave white crystals with m.p. 77-8 °C and $[\alpha]_D^{26} = +156°$ (c = 1.19, $CHCl_3$). The ultraviolet spectrum gave $\lambda_{max}^{EtOH} = 232$ mμ (ε = 19,000). The infrared and n.m.r. spectra were identical to those of photo #5 shown in Figure 9 on page 95 and Figure 11 on page 100 respectively.

The mass spectrum of the crystalline material gave peaks at m/e 314 (64%, P^+), 123 (100%) and 109 (36%) at 70 e.v. At 15 e.v. and below the peaks at m/e 314 and 109 were the only significant peaks in the spectrum. The mass spectral behavior of photo #5 is in excellent agreement with that observed for the model compounds, photo-testosterone and photo-testosterone acetate.

The conversion of photo #2-A (241) to photo #5 of progesterone establishes the stereochemistry at C-17 in photo #5 as that shown for 232. The difficulty of obtaining photo #5 is crystalline form from



232

other sources is probably partially due to the fact that photo #5 is a low melting solid and such compounds in the steroid series are notorious for their desire to remain oils and partly due to the presence of small amounts of impurities in other samples of photo #5. Evidently these impurities are absent in the photo #5 (232) prepared by the oxidation of photo #2-A (241).

Photochemistry of Δ^5-Pregnen-3β-acetoxy-20-one (245)

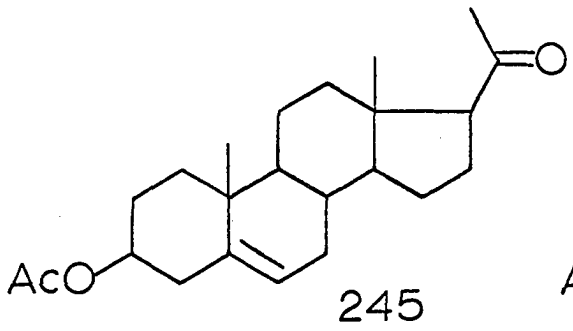
The irradiation of progesterone (227) in tertiary butyl alcohol led to the isolation of three products containing the cyclobutanol ring system. In all examples of this irradiation only one of the two possible epimeric alcohols was isolated. Due to the complexity of the irradiation mixture, a small amount of the other possible epimer could have been overlooked, but if it was a significant part of the mixture it should have been observed. Likewise, the irradiation of Δ^5-pregnen-3β-ol-20-one (233) in tertiary butyl alcohol led to the isolation of only one of the two epimeric alcohols. The stereochemistry of the alcohol isolated in each case was that assigned in the structure of photo #1 (228) of progesterone.

These results are in agreement with the work of Jeger (Buchschacher et al., 95) in which he reported the isolation of only one epimeric alcohol from the irradiation of Δ^5-pregnen-3β-acetoxy-20-one (245) in hexane. However, they are in contrast to later reports by Yang and Yang (96) and Jeger (Cereghetti et al., 97) that two epimeric alcohols were found upon irradiation of compounds of similar structure in ethanol and methanol solutions.

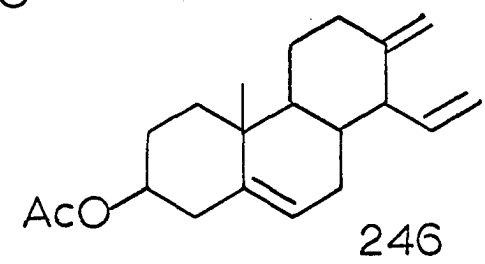
This suggested that the variance of epimer production with solvent might be a case of a novel solvent effect in a photochemical reaction and possibly could give some evidence about the mechanistic nature of the reaction.

The model system chosen for study was Δ^5-pregnen-3β-acetoxy-20-one (245). This system was an excellent model compound since its stereochemical requirements in the B, C and D rings would be the same as those of progesterone. It and similar systems have been studied previously and thus the expected products were known compounds which could be characterized by spectral means (95,96,97).

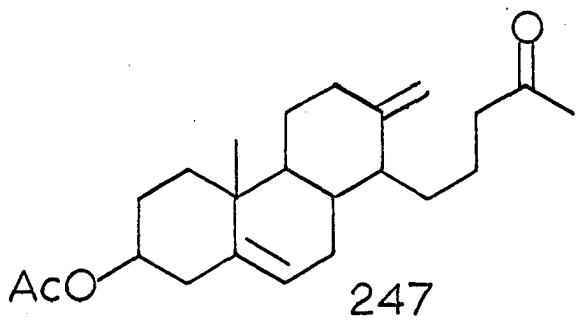
Irradiation of Δ^5-pregnen-3β-acetoxy-20-one (245) in methyl alcohol gave four photoproducts. These were given the trivial names of photo A (246), photo B (247), photo C (248) and photo D (249). The compounds were isolated by column chromatography on alumina. Recovered starting material was isolated in 5% yield, photo A (246) in 11%, photo B (247) in 40%, photo C (248) in 11% and photo D (249) in 32% yield.



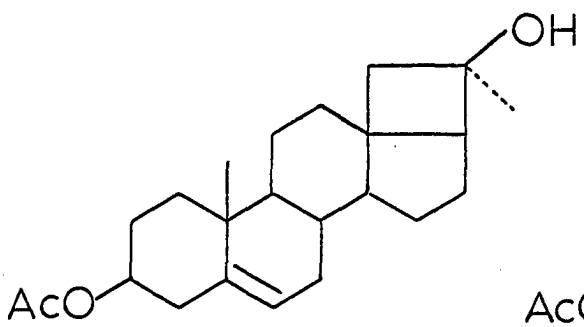
245



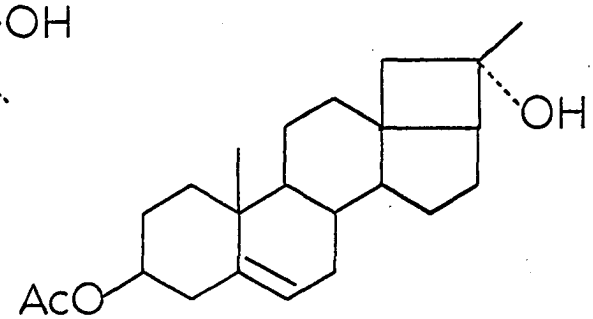
246



247



248



249

Photo A was isolated as a viscous oil. The infrared spectrum is shown in Figure 15 on page 128. The infrared spectrum indicated the presence of an acetate (5.80 and 7.9-8.1 μ), olefinic groups (6.08 μ), a monosubstituted olefin (10.93 μ) and a geminal disubstituted olefin (11.14 μ). The compound showed only end absorption in the ultraviolet spectrum. The n.m.r. spectrum of photo A (246) is reproduced in Figure

16 on page 130 and was most informative. The compound gave a three proton singlet at 9.05 τ which was assigned to the C-19 methyl group. The sharp three proton singlet at 8.08 τ was assigned to the acetate methyl of the 3β-acetoxy group. The complex region at 6.0-4.0 τ integrated for seven protons and was assigned as due to the six olefinic protons plus the methine at C-3. The upfield region of the spectrum integrated for twenty one protons.

The structure of photo A (246) is consistent with the above data. The absence of the C-21 methyl group which should appear at 7.9-8.0 τ and the C-18 methyl group which should appear at 9.3-9.5 τ indicate that the molecule has undergone extensive rearrangement. The acetate methyl and the C-19 methyl are present at the expected positions. The spectrum integrates for twenty eight protons which is not consistent with a material isomeric with the starting material. A structure such as 246 would be expected to have seven protons at low field. These would be the six olefinic protons and the methine at C-3. There would be twenty one at higher field and this is also observed.

The above data support the assignment of 246 as the structure of photo A. The data above is in excellent agreement with that of the identical compound prepared by Jeger (Cereghetti et al., 97). This type of product has also been isolated from the irradiation of other 20-keto steroids (95,96).

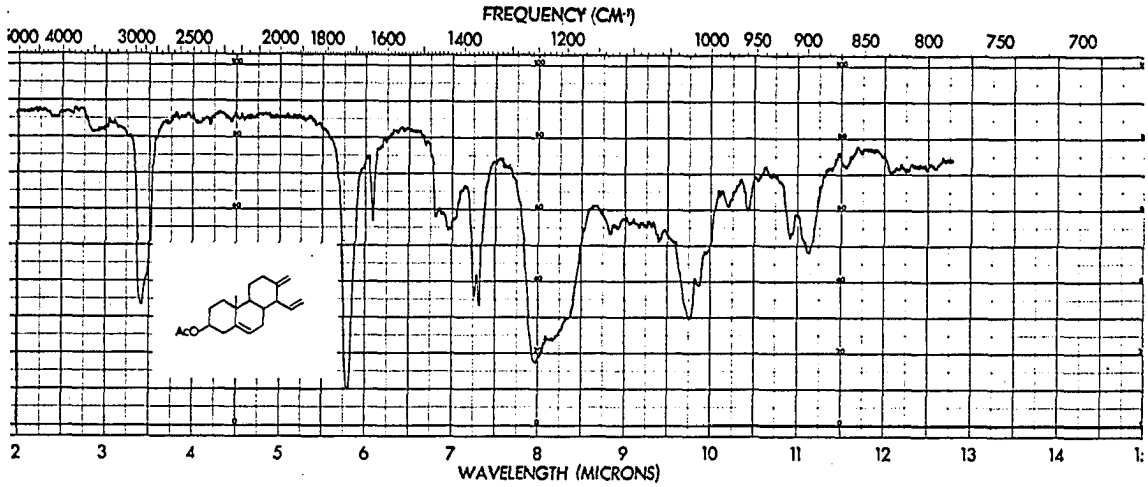
Further evidence for the structure of photo A (246) comes from the observation that it is the prime product of the irradiation of photo B

Figure 15. Infrared spectra

Top - Photo A (246) of Δ^5-pregnen-3β-acetoxy-20-one ($CHCl_3$)

Middle - Photo B (247) of Δ^5-pregnen-3β-acetoxy-20-one ($CHCl_3$)

Bottom - 3β-Hydroxy-20-keto-$\Delta^{5;13(18)}$-13,17-seco-pregnadiene (250) ($CHCl_3$)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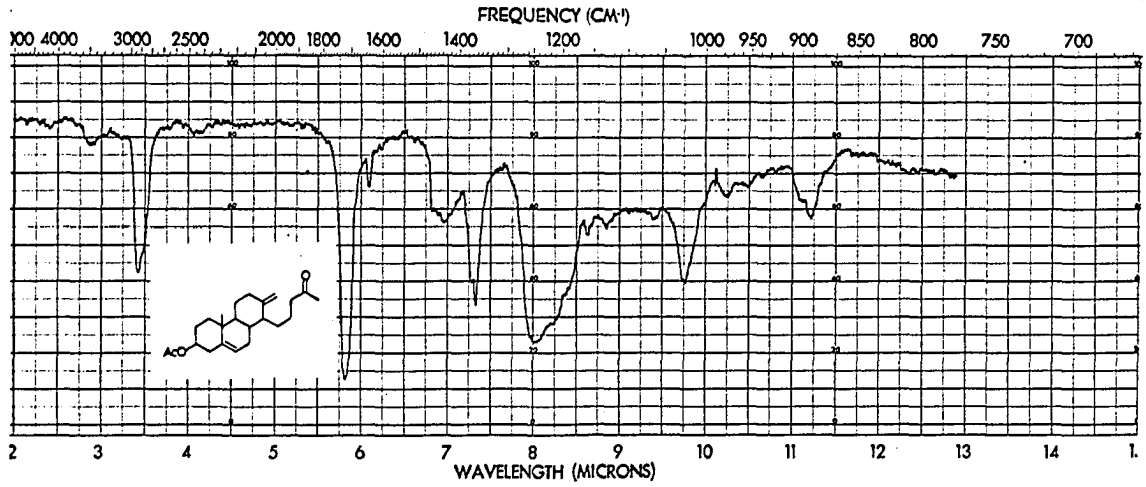
AcO
2 3 4 5 6 7 8 9 10 11 12 13 14
WAVELENGTH (MICRONS)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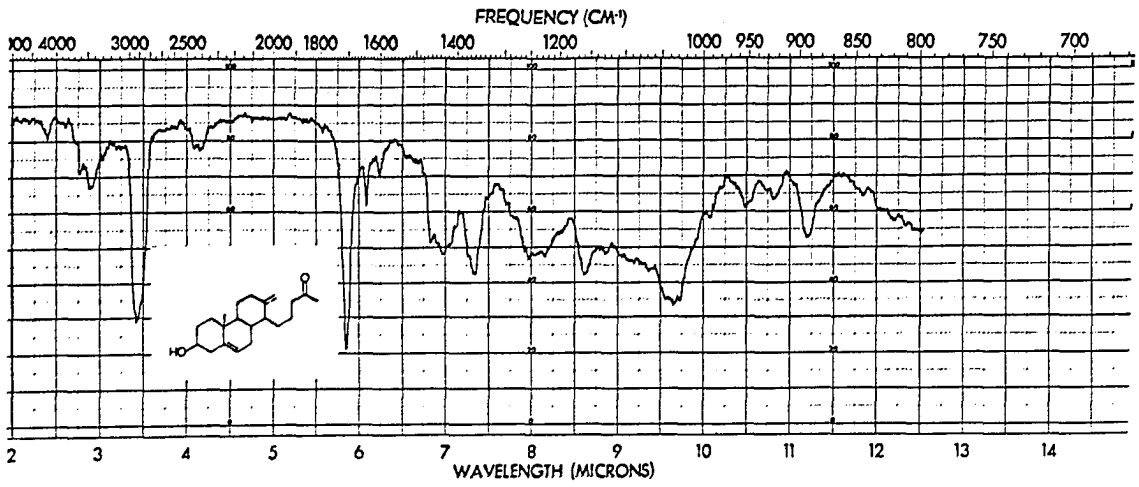
FREQUENCY (CM-1)
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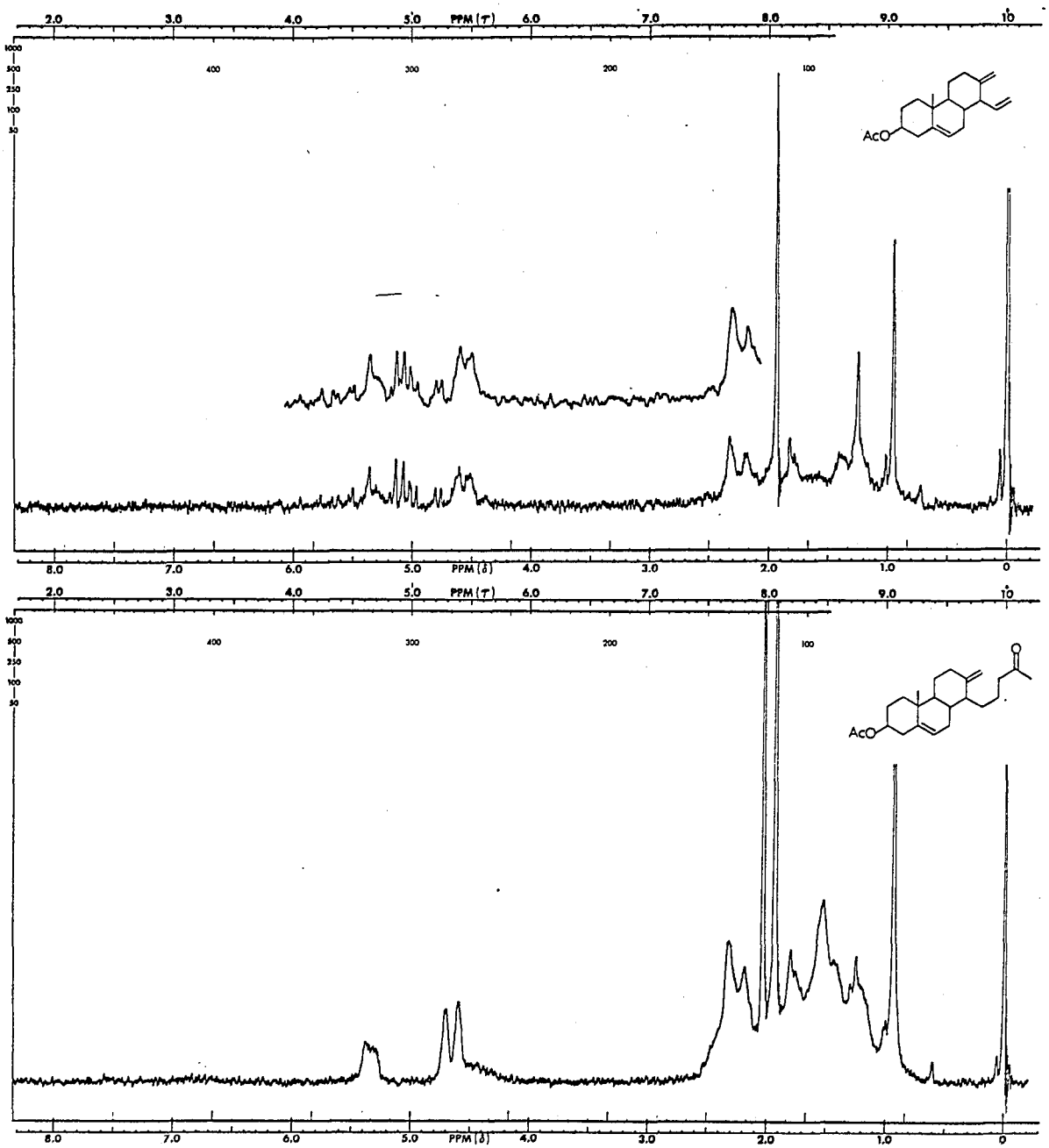
HO
2 3 4 5 6 7 8 9 10 11 12 13 14
WAVELENGTH (MICRONS)

Figure 16. Nuclear magnetic resonance spectra

Top - Photo A (246) of Δ^5-pregnen-3β-acetoxy-20-one (CCl_4)

Bottom - Photo B (247) of Δ^5-pregnen-3β-acetoxy-20-one (CCl_4)

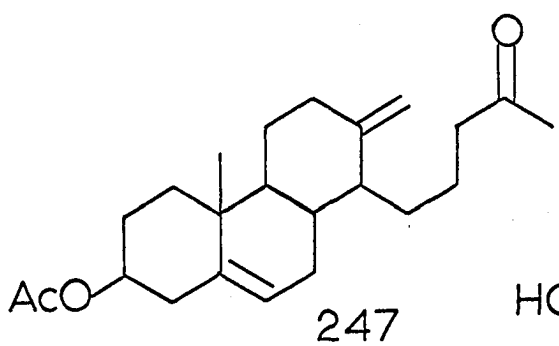

2.0
3.0
4.0
5.0
PPM (τ)
6.0
7.0
8.0
9.0
10
AcO
8.0
7.0
6.0
5.0
PPM (δ)
4.0
3.0
2.0
1.0
0
AcO

(247) in methanol. Its formation is the result of a type II cleavage of photo B. This type of path has been previously observed (97).

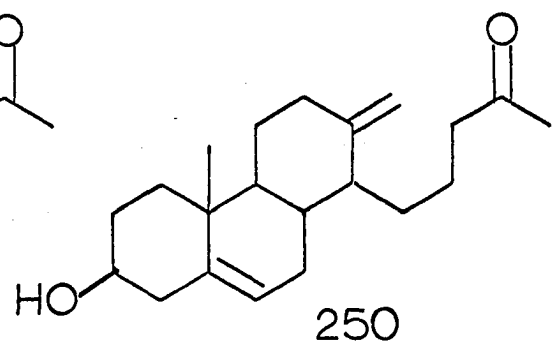
Photo B (247) was also isolated as an oil and resisted all attempts at crystallization. The infrared spectrum is shown in Figure 15 on page 128. The infrared indicated that photo B contained an acetate (5.80 μ shoulder and 7.9-8.1 μ), a methyl ketone (5.84 μ and 7.30 μ shoulder), olefinic unsaturation (6.08 μ) and a geminal disubstituted olefin (11.22 μ). The n.m.r. spectrum of photo B is shown in Figure 16 on page 130. The n.m.r. spectrum showed three proton singlets at 9.06, 8.08 and 7.98 τ and a three proton grouping at 5.1-5.8 τ and a single olefinic proton at 4.68 τ. The spectrum integrated for 34 protons.

The proton integral of photo B indicated that it was isomeric with the starting material. The singlets at 9.06 and 8.08 τ were assigned to the C-19 and acetate methyls respectively. The olefinic proton at 4.68 τ was assigned to the proton at C-6. The singlet at 7.98 τ was assigned to the C-21 methyl group of the methyl ketone. The three proton grouping at 5.1-5.8 τ was interpreted as follows. The broad absorption centered at 5.5 τ was assigned to the methine at C-3. The slightly broadened singlets at 5.28 and 5.38 τ were assigned to the two protons of the geminal substituted olefinic system. The absence of the C-18 methyl group in the n.m.r. spectrum of photo B indicated that it was this group which had been converted to the geminal olefin. The absence of any further splitting of these peaks confirms their assignment as those of a geminal substituted olefin.

The data presented above are consistent with the assignment of the structure of photo B as shown 247. The gross structural features of photo B are in excellent agreement with compounds of similar structure isolated by other workers (95,96,97).



247



250

Treatment of photo B (247) with methanolic potassium hydroxide gave the hydrolysis product 250. The infrared spectrum of 250 is given in Figure 15 on page 128. The infrared indicated the presence of an alcohol (2.90 μ), a methyl ketone (5.86 μ and 7.38 μ shoulder), olefinic groups (6.08 μ) and a geminal disubstituted olefin (11.20 μ). the n.m.r. spectrum is reproduced in Figure 17 on page 135. The spectrum integrated for thirty two protons. The three proton singlets at 9.08 and 7.96 τ were assigned to the C-19 methyl group and the C-21 methyl group of the methyl ketone respectively. The broad singlet at 7.48 τ was assigned to the hydroxyl proton of the alcohol at C-3 by deuterium exchange. The broad multiplet at 6.64 τ assigned to the methine at C-3. Its shift in the hydrolyzed compound 250 is consistent with this assignment. The two broad singlets at 5.40 and 5.30 τ are due to the geminal methylene protons

of the transformed C-18 methyl group. The olefinic absorption at 4.75 τ was assigned to the proton at C-6.

The spectral data presented above are in excellent agreement with that of the identical compound prepared by Yang and Yang (96) with the structure 250.

On the basis of its spectral similarity to known compounds and its conversion to the known alcohol 250 the structure of photo B of Δ^5-pregnen-3β-acetoxy-20-one is regarded as established as shown in structure 247.

Photo C (248) gave a m.p. 139-40.5 °C with $[\alpha]_D = -32.6°$ (c = 1.66, $CHCl_3$). The infrared spectrum of photo C is shown in Figure 18 on page 137. The infrared indicated the presence of an alcohol (2.90 μ) and an acetate (5.80 and 8.0-8.2 μ). The n.m.r. spectrum of photo C is shown in Figure 17 on page 135. The spectrum integrated for thirty four protons. The three proton singlets at 9.10, 8.98 and 8.08 τ were assigned to the C-21 methyl group, the C-19 methyl group and the acetate methyl respectively. The sharp singlet at 8.58 τ was due to a hydroxyl proton as shown by deuterium exchange. The broad absorption at 5.56 τ was assigned to the methine at C-3. The olefinic proton at 4.64 τ was assigned to the olefinic hydrogen at C-6.

The mass spectrum of photo C gave peaks at m/e 358 (< 0.1%, P^+), 298 (76%), 241 (28%) and 240 (100%). The peak at m/e 298 corresponds to P-60 and is ascribed to loss of CH_3CO_2H from photo C (248). The peaks at m/e 241 and 240 correspond to the loss of CH_3CO_2H followed by the loss

Figure 17. Nuclear magnetic resonance spectra

Top - 3β-Hydroxy-20-keto-$\Delta^{5;13(18)}$-13,17-seco-pregnadiene (250) (CCl_4)

Bottom - Photo C (248) of Δ^5-pregnen-3β-acetoxy-20-one (CCl_4)

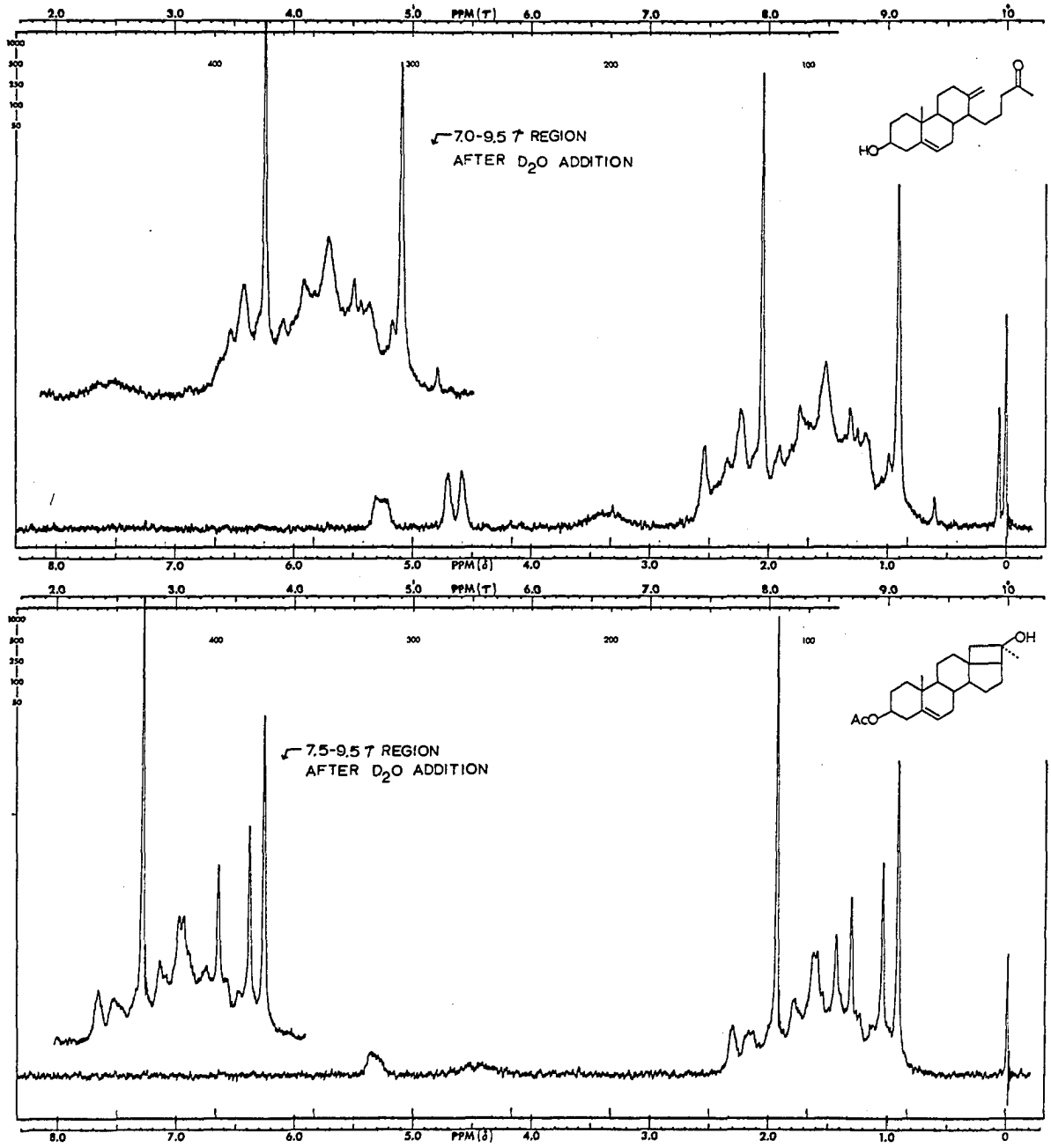
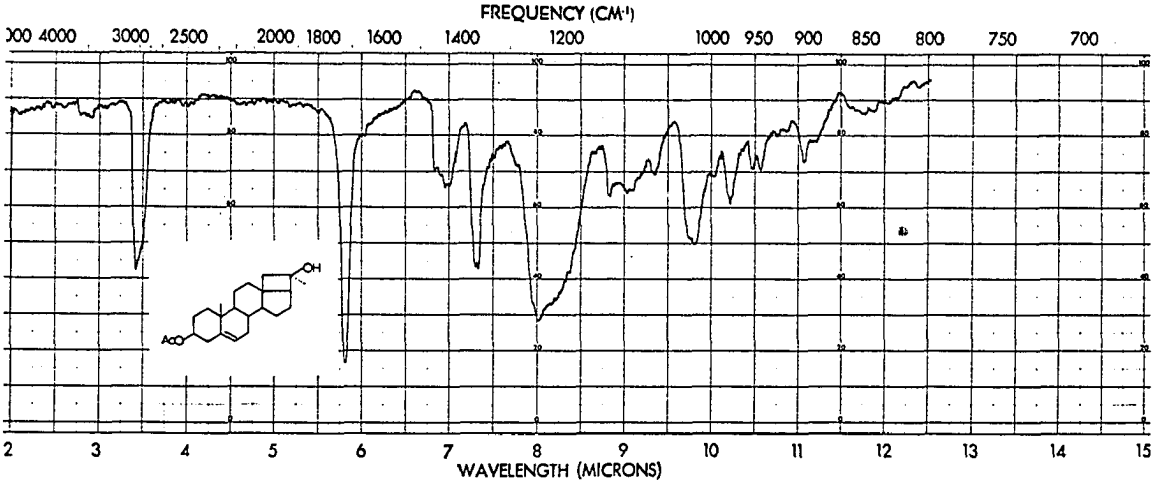

PPM(τ)
PPM(δ)
7.0-9.5 τ REGION
AFTER D2O ADDITION
HO
7.5-9.5 τ REGION
AFTER D2O ADDITION
AcO
OH

Figure 18. Infrared spectra

Top - Photo C (248) of Δ^5-pregnen-3β-acetoxy-20-one ($CHCl_3$)

Bottom - Photo D (249) of Δ^5-pregnen-3β-acetoxy-20-one ($CHCl_3$)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AcO
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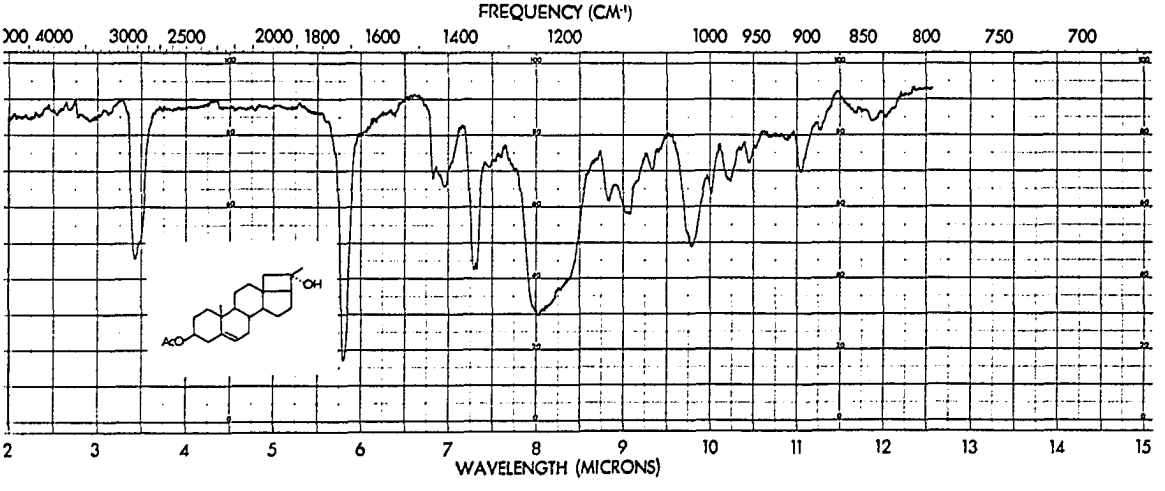
WAVELENGTH (MICRONS)


FREQUENCY (CM-1)
000 4000 3000 2500 2000 1800 1600 1400 1200 1000 950 900 850 800 750 700
OH
AcO
2 3 4 5 6 7 8 9 10 11 12 13 14 15
WAVELENGTH (MICRONS)

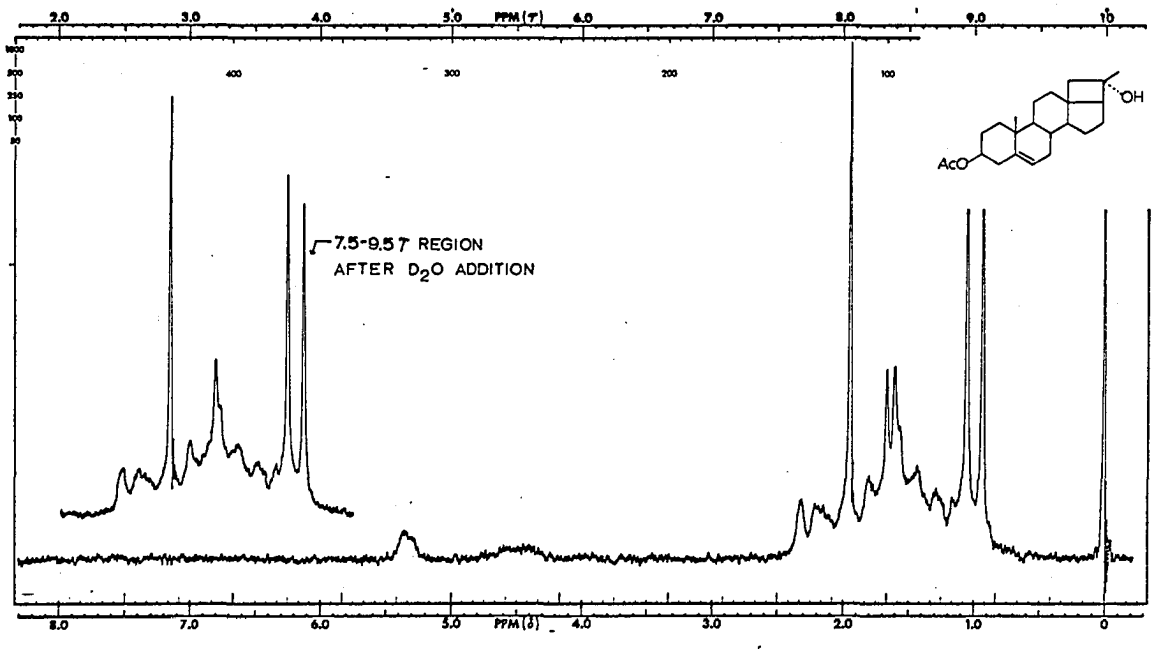
of CH_2COCH_3 and CH_3COCH_3 respectively in the same type of path as was postulated for photo #1 (228).

The absence of the C-18 methyl in the 9.3 τ region and of the C-21 methyl in the 7.95 τ region of photo C are strongly suggestive of the involvement of these groups in cyclobutanol formation. The infrared, n.m.r. and mass spectral data are consistent with this assumption. The stereochemistry at C-20 of photo C is assigned by comparison of its properties with the identical compound isolated by Jeger (Cereghetti et al., 97). The stereochemistry of Jerger's compound was assigned on the basis of independent synthesis and assigned structure 248. The compound prepared by Jeger gave m.p. 139-40 °C with $[\alpha]_D = -49°$ (c = 0.86, $CHCl_3$). the spectral data and physical properties of the compound prepared by Jeger are in good agreement with those of photo C isolated above. On the basis of this data the structure 248 is assigned as the structure of photo C.

Irradiation of photo C (248) in methanol resulted in the recovery of unchanged photo C indicating that it was stable to further transformations under the conditions of the experiment.

Photo D (249) gave m.p. 151-2 °C with $[\alpha]_D = -46.8°$ (c = 1.72, $CHCl_3$). The infrared spectrum of photo D is shown in Figure 18 on page 137. The infrared indicated the presence of an alcohol (2.7-2.9 μ) and an acetate (5.80 and 7.95-8.20 μ). The n.m.r. spectrum of photo D is reproduced in Figure 19 on page 140. The three proton singlets at 9.10, 8.98 and 8.06 τ are assigned to the C-21 methyl group, the C-19 methyl

Figure 19. Nuclear magnetic resonance spectrum of photo D (249) of Δ^5-pregnen-3β-acetoxy-20-one (CCl_4)

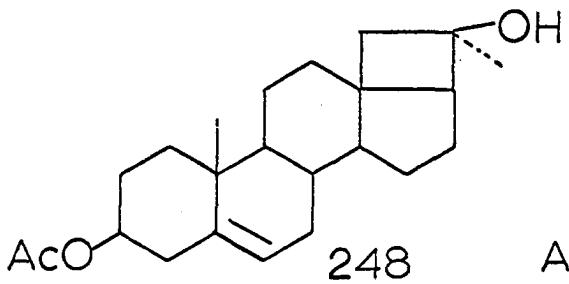

2.0
3.0
4.0
5.0
PPM(τ)
6.0
7.0
8.0
9.0
10
400
300
200
100
OH
AcO
7.5-9.5 τ REGION
AFTER D2O ADDITION
8.0
7.0
6.0
5.0
PPM(δ)
4.0
3.0
2.0
1.0
0

group and the acetate methyl respectively. The sharp singlet at 8.32 τ was shown to be due to an alcohol proton by deuterium exchange. The broad multiplet centered at 5.5 τ was assigned to the methine at C-3. The olefinic proton centered at 4.65 τ was due to the proton at C-6. The spectrum integrated for 34 protons indicating a material isomeric with the starting material.

The mass spectrum of photo D (249) gave peaks at m/e 358 (< 0.1%, P^+), 298 (79%), 241 (28%) and 240 (100%) at 70 e.v. The sources of the various fragments were assigned as in the case of photo C (248). The similarity of the mass spectra of photo C and photo D led to the conclusion that they were alcohols epimeric at C-20. The similarity of the infrared and n.m.r. spectra also support this assumption.

Jeger (Buchschacher et al., 95) isolated a compound with the proposed structure 249. The properties given for this molecule were m.p. 145-6 °C with $[\alpha]_D$ = -51° (c = 0.78, $CHCl_3$). The spectral data for photo D isolated above are in excellent agreement with those of the known compound. The melting point of the photo D obtained above is higher than that quoted by Jeger. However, this point is not considered serious since the acetate of structure 249 prepared by Jeger was converted to the diol 234 and the ketone 228. The diol 234 and the ketone 228 have been prepared in the course of this work and have been found to have properties which are in excellent agreement with those of the compounds prepared by Jeger (Buchschacher et al., 95).

On the basis of the above data, the structure of photo D of Δ^5-pregnen-3β-ol-20-one (245) is assigned as shown in structure 249.



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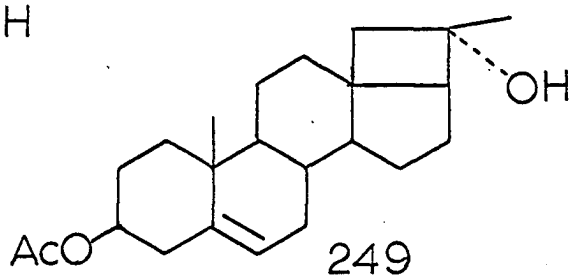
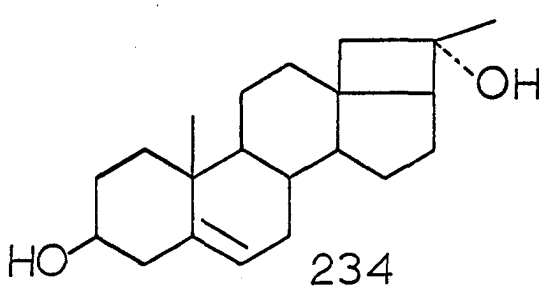


249



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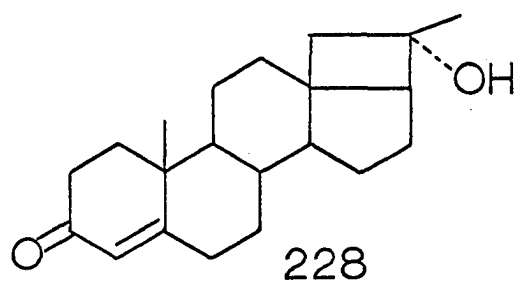


228

Irradiation of photo D (249) in methanol under the same conditions as were used for photo C resulted in the recovery of unchanged photo D. This indicated that photo D was stable to any further photochemical rearrangements under the irradiation conditions.

In order to study the photochemistry of Δ^5-pregnen-3β-acetoxy-20-one (245) in other solvents, a technique for the isolation and identification of the various photoproducts was developed. It was found that column chromatography on alumina gave separation of the photoproducts. The order of elution was photo A, starting material, photo B, photo C and photo D. Isolated photo A was identified by comparison of its v.p.c. retention time and infrared spectrum with that of an authentic sample. Isolated photo B and starting material were also identified by comparison of their v.p.c. retention times and infrared spectra with those of the

authentic materials. The photo C and photo D isolated by column chromatography were identified by comparison of their infrared spectra and thin layer behavior on alumina plates with those of authentic samples. This isolation and identification scheme was shown to give reproducible results by checking duplicate runs in selected cases.

Solvents were chosen which would have a wide range of steric and electronic effects. Those selected were methanol, 95% ethanol, absolute ethanol, benzene, isopropyl alcohol, dimethyl sulfoxide, glacial acetic acid, pyridine, cyclohexane and tertiary butyl alcohol. The results are presented in Table 1.

Table 1. Results of the irradiation of Δ^5-pregnen-3β-ol-20-one (245) in various solvents

Solvent	Time hours	Per cent Starting material	A	B	C	D	Ratio D/C	Lit. val.
Methanol	5 1/2	5.4	10.8	39.6	11.4	31.7	2.8/1	3/1 (96)
95% Ethanol	5 1/2	4.8	8.8	32.2	12.2	33.5	2.75/1	3/1 (97)
95% Ethanol	5 1/2	3.1	9.0	28.8	12.5	34.9	2.8/1	3/1 (97)
Absolute ethanol	5 1/2	2.0	17.2	27.9	12.0	34.7	2.9/1	
Benzene	11	18.8	5.8	11.8	6.1	19.3	3.16/1	
Benzene	11	17.1	8.0	18.5	5.4	16.8	3.12/1	
Isopropyl alcohol	5 1/2	2.2	2.2	11.1	10.7	38.9	3.6/1	
Dimethyl sulfoxide	14	12.5	6.5	35.2	7.3	35.2	4.8/1	

Table 1 (Continued)

Solvent	Time hours	Per cent Starting material	A	B	C	D	Ratio D/C	Lit. val.
Glacial acetic acid	11	9.4	13.8	39.5	5.9	30.6	5.2/1	
Pyridine	11	20.9	5.9	6.5	6.6	37.4	5.7/1	
Cyclo-hexane	11	5.2	14.0	18.2	4.8	36.2	7.5/1	34% D[a]
Cyclo-hexane	8[b]	4.4	15.4	21.3	6.0	42.3	7.05/1	34% D[a]
t-Butyl alcohol	5 1/2	2.4	2.2	10.2	5.5	44.4	8.1/1	

[a]Stated yield of the only product isolated from irradiation in n-hexane solution (95).

[b]Irradiation vessel of slightly different design used which permitted more of the solution to be exposed to the arc.

It can be seen that the results obtained provide a gradual change in the ratio of D/C from 2.8/1 in methanol to 8.1/1 in tertiary butyl alcohol. The values obtained in this work were in good agreement with those available in the literature for similar experiments.

The following table of the physical properties of the solvents used is included for comparison.

Table 2. Physical properties of solvents used

Solvent	Dipole moment (110)	Dielectric constant (110)	Refractive index (110)
Methanol	1.70	33.63	1.3312
Ethanol	1.69	24.30	1.3624
Benzene	0	2.27	1.5011
Isopropyl alcohol	1.60	18.3	1.3778
Dimethyl sulfoxide	3.90 (111)	45 (112)	1.4787 (113)
Glacial acetic acid	1.74	6.15	1.3718
Pyridine	2.28 (114)	12.3	1.5092
Cyclohexane	0	2.02	1.4290
t-Butyl alcohol	1.64	10.9	1.3878

Discussion of the Photochemistry of Enones

A significant number of steroidal Δ^4-3-keto steroids were examined in the course of this work. In all cases the major products resulting from the irradiation of such ketones in tertiary butyl alcohol were the cyclopropyl cyclopentanones and the 3-substituted 2-cyclopentenones. This established the generality of this type of reaction path for systems with the Δ^4-3-keto structural features.

The isolation of five photoproducts from the irradiation of progesterone (227) with light of wave length greater than 3000 Å suggested three possible modes of reaction. It was possible that the enone and the saturated ketone were both absorbing light and then reacting in a manner consistent with their known paths or the enone might transfer energy via some type of process to the saturated ketone or the saturated ketone might perform a similar function with respect to the enone chromaphore. The fact that the fragmentation products of the type isolated in the irradiation of Δ^5-pregnen-3β-ol-20-one (245) were not isolated here is probably due to the fact that these products would be formed in amounts of the order of 1-2 per cent and thus escaped detection.

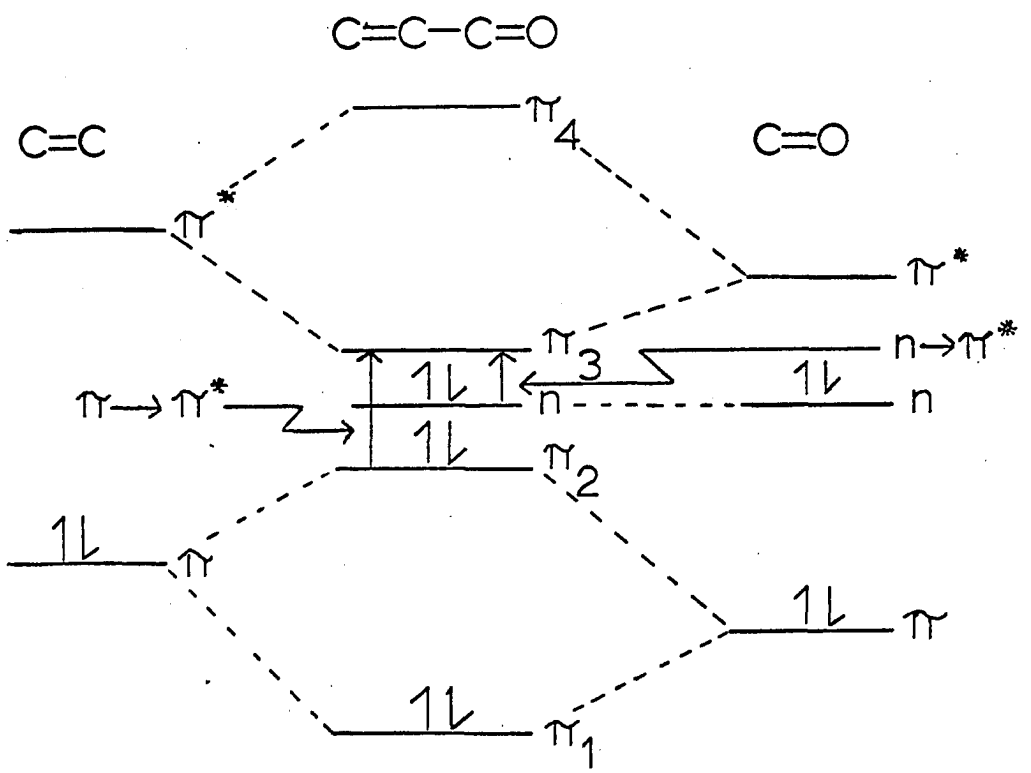
The observation that the enone could be selectively excited at 3660 Å to give the usual type of enone photoproducts without giving rise to products via the 20-keto group ruled out the possibility that the enone was involved in any type of intramolecular or intermolecular energy transfer process with the 20-keto group.

The similar experiment with light at 3130 Å involving excitation of the 20-keto group followed by its characteristic reactions eliminated the possibility that it was involved in any type of intramolecular or intermolecular energy transfer process with the enone.

Thus the first possibility appears to be the one most consistent with the observed experimental data. This result should prove useful in synthesis since it indicates that selective excitation is possible in practice as well as in theory. This type of process should be most

efficient when the two absorbing chromophores are separated by a difference in absorption maxima or extinction coefficient or both.

There are two methods possible for excitation of the enone chromaphore. One involves the lower energy n → π* transition and the other the higher energy π → π* transition. These transitions are shown schematically below (115). The n → π* excitation has been extensively



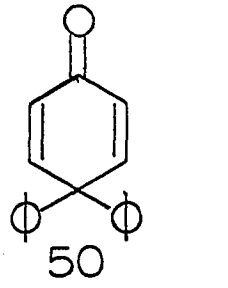
studied (See Historical Section). This work is the first example of a study of the π → π* excitation path for enone photoproducts, although it has found application in the case of cross-conjugated dienones (See Historical Section).

In the case of 4,4-diphenylcyclohexadienone (50) the n → π* process has been viewed as the initial formation of the n → π* singlet followed

by intersystem crossing to the triplet which then by a series of steps involving bond alternation, electron demotion and rearrangement finally gives rise to products (43). A similar route was proposed for the photochemistry of santonin (104) in which it was postulated that the initially formed $n \rightarrow \pi^*$ singlet underwent internal conversion to the $\pi \rightarrow \pi^*$ triplet which then led to products (61). One of the distinguishing features of dienone photochemistry is the relative efficiency of the reactions. The quantum yields which have been determined are in the range 0.8-1.0. The reactions of these systems are also highly stereoselective with regard to product formation.

In contrast to the high quantum yields obtained for the cross-conjugated dienones, those of enones appear to be much lower. The quantum yields reported for 44 and 16 are 8.4×10^{-3} and 3.8×10^{-3} respectively. These reactions still retain their stereoselectivity with regard to product formation. Rettig (31) has found a value of 6.5×10^{-3} for the quantum yield for the production of the lumi-isomer (187) from 4,4-dimethylcyclohexenone (186).

Zimmerman and Swenton (43) found that 50 could be sensitized by acetophenone to give triplets, but that the reaction was too rapid to be quenched. In contrast to this result it was found that the enones 44 and 16 could be both sensitized by triplet photosensitizers and quenched by triplet quenchers in certain solvents (73). A similar result was also observed in the case of 44 by Chapman *et al.* (37). Zimmerman *et al.* (73) also observed significant products due to hydrogen abstraction in solvents



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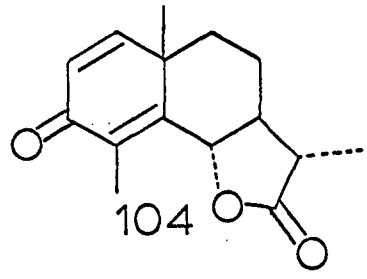

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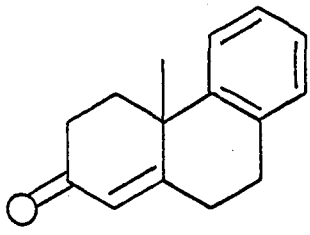

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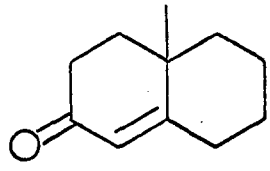

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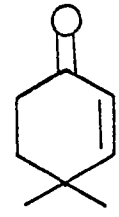

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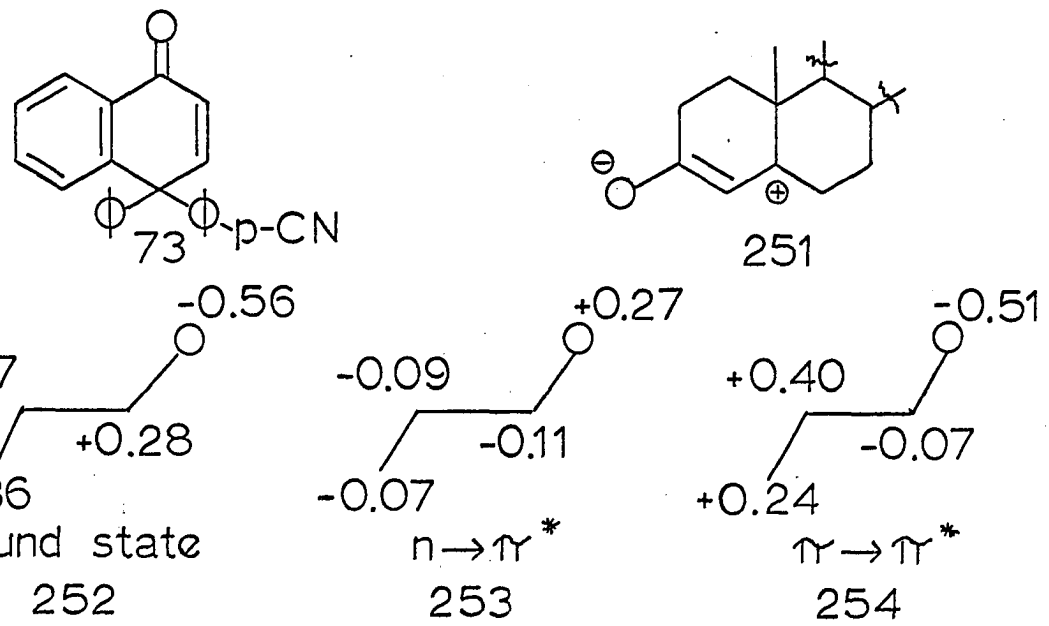
with available α-hydrogens in the case of 44. He interprets the results of the photochemistry of the phenanthrone 44 as the result of one of three possible mechanistic sequences. Either the n → π* or π → π* triplet is a precursor to both rearrangement and hydrogen abstraction or two triplets are in rapid equilibrium with one responsible for each reaction or hydrogen abstraction rates may vary for aromatic enones such as 44 versus enones like 16 and so 44 reacts to give hydrogen abstraction products while 16 does not. On the basis of the available data a meaningful distinction could not be made among these choices.

If an n → π* state was involved in the reaction, theory predicts that the β-carbon atom of the enone should be electron rich rather than electron poor as pictured in the polar intermediate 251. Experiments with 73 have indicated that the p-cyano-phenyl migrates to the β-carbon to a greater extent than phenyl (44).

Recent calculations on the excited state dipole of formaldehyde have shown that it is less than the ground state dipole, but not by as large as would be expected from the simple n → π* excitation scheme (116). This is due to electron "tunneling" or the feedback of the electron density to the more electronegative oxygen atom in the excited state. The β-carbon of an n → π* excited enone may not be as electron poor as pictured in the simple representation 252 (117). If the n → π* state then is converted to another reactive species, a system such as 251 may well be involved. If a π → π* state is involved by formation from the ground state 252, then it would be expected to have a charge distribution similar to 254 which is analogous to the polar species 251.



It is generally accepted that the lowest lying triplet state is involved in photochemical rearrangements unless two triplet states of similar energy are possible (12). The singlet-triplet splittings for

$n \rightarrow \pi^*$ states are less than those for $\pi \rightarrow \pi^*$ states. If a $\pi \rightarrow \pi^*$ singlet is lowest in energy then the $\pi \rightarrow \pi^*$ triplet will also lie lowest. However, if the $n \rightarrow \pi^*$ singlet is lowest, the lowest triplet state cannot be readily assigned. If the $n \rightarrow \pi^*$ triplet lies lowest, the most probable route from the initially formed $n \rightarrow \pi^*$ singlet would be intersystem crossing to the $n \rightarrow \pi^*$ triplet. If a $\pi \rightarrow \pi^*$ triplet lies lowest, the most probable route from the initially formed $n \rightarrow \pi^*$ singlet would be intersystem crossing to the $n \rightarrow \pi^*$ triplet followed by internal conversion to the $\pi \rightarrow \pi^*$ triplet (12).

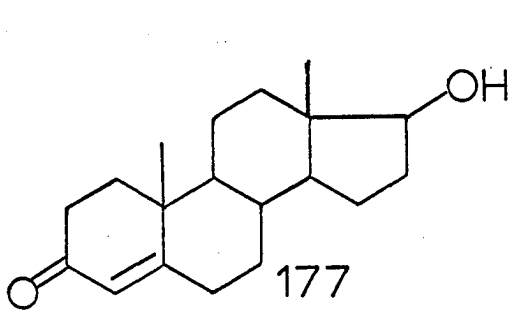
The energy of the lowest lying triplet state of enones is difficult to determine since phosphorescence is not a common property of these systems. Fisch and Richards (61) have placed the triplet energy of santonin (104) at about 68 kcal./mole and have assigned this to the $\pi \rightarrow \pi^*$ triplet. Zimmerman et al. (73) has placed the triplet energy of the phenanthrone 44 in the region of 73-71 kcal./mole. The phosphorescence emission of 44 was not well defined. Corey et al. (23) has estimated the energy of the $n \rightarrow \pi^*$ singlet and triplet at 85 and 75 kcal./mole respectively. He also estimates that the $\pi \rightarrow \pi^*$ triplet states of enones should lie in the region of 60 kcal./mole and be lower in energy than the $n \rightarrow \pi^*$ triplet. The energy of the energy of the $n \rightarrow \pi^*$ singlet and $\pi \rightarrow \pi^*$ singlet can be estimated from the absorption maxima and lie in the region of 92-87 and 124-114 kcal./mole respectively. The energy separation of the $n \rightarrow \pi^*$ singlet and triplet has been estimated at 10-16 kcal./mole (23). This gives a value of 82-71 kcal./mole for the $n \rightarrow \pi^*$ triplet. If one takes conjugated dienes as models for the $\pi \rightarrow \pi^*$ state, an energy

separation of the order of 60-65 kcal./mole is obtained for the singlet-triplet separation (118). This would lead to a value of 65-55 kcal./mole for the $\pi \rightarrow \pi^*$ triplet of enones. This agrees well with the prediction made by Corey et al. (23).

Hammond and Leermakers (119) have shown that for certain aromatic ketones the $n \rightarrow \pi^*$ triplet is a very superior hydrogen abstracting species compared to a $\pi \rightarrow \pi^*$ triplet. This may be a general conclusion as evidenced by the observation of Zimmerman et al. (73).

Hammond and Saltiel (120) have shown that the transfer of triplet energy by triplet sensitizers is a diffusion controlled process. Benzophenone has an intersystem crossing efficiency from the $n \rightarrow \pi^*$ singlet to the corresponding triplet of 100 per cent. The energy of this triplet has been determined to be 69.2 kcal./mole (105). Irradiation of testosterone (177) in the presence of benzophenone greatly accelerated the destruction of starting material, but did not give rise to the usually observed photoproducts in tertiary butyl alcohol. Under the conditions of the experiment benzophenone would be expected to give rise to enone triplets, presumably $n \rightarrow \pi^*$ triplets. Since these triplets did not enter into a process yielding the usual type of photoproducts, it is concluded that they must have reacted to yield addition products with benzophenone itself or combined to yield pinacol type products of the kind observed by Zimmerman et al. (73) or formed dimeric materials. Hydrogen abstraction would not be a particularly favorable process in tertiary butyl alcohol since this solvent lacks a suitable α-hydrogen. Benzophenone is also

capable of transferring its triplet energy to saturated ketones as evidenced in the sensitization of the reaction of 231. This would place the energy of the n → π* triplet of the 20-keto group as in the neighborhood of 69 kcal./mole.



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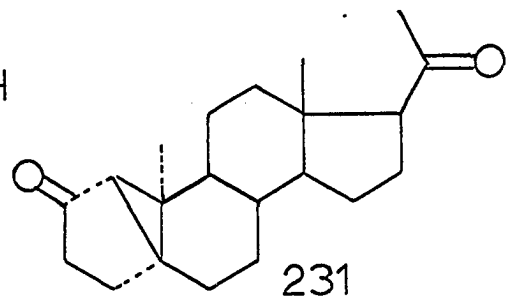

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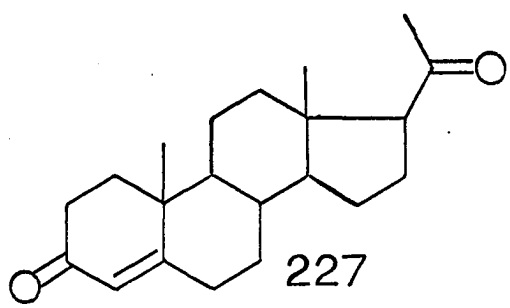

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In contrast to the benzophenone sensitization, dibenzothiophene has been shown to efficiently sensitize both the conversion of testosterone (177) and progesterone (227) to the cyclopropyl cyclopentanone and the cyclopentenone type of photoproducts by irradiation in tertiary butyl alcohol. Dibenzothiophene has also been shown to be ineffective in transferring energy to the saturated 20-keto group as evidenced by the irradiation of Δ^5-pregnen-3β-ol-20-one (233) in its presence. The triplet energy of dibenzothiophene has been found experimentally to be 69.3 kcal./mole in polar solvents (105). The triplet exhibits the behavior expected for a π → π* triplet. The intersystem crossing efficiency for dibenzothiophene has not been quantitatively determined, but has been shown to

be between 33-100 per cent by a qualitative method (105). Thus a significant amount of dibenzothiophene triplets would be available for energy transfer.

The triplet energies of benzophenone and dibenzothiophene are 69.2 and 69.3 kcal./mole respectively (105). Acetophenone with an $n \rightarrow \pi^*$ triplet energy of 76.3 kcal./mole has also been observed to sensitize enone reactions (73). Since the energies of benzophenone and dibenzothiophene are equal to within experimental error, their differences in reactivity may result from the two different types of triplets that they form. If the $n \rightarrow \pi^*$ triplet and the $\pi \rightarrow \pi^*$ triplet of the enone lie relatively close in energy as is possible from the results of previous calculations, then energy transfer between the $n \rightarrow \pi^*$ triplet of benzophenone might be expected to be more efficient to the $n \rightarrow \pi^*$ triplet of the enone than to the $\pi \rightarrow \pi^*$ triplet of the enone. A similar argument would apply in the case of the transfer of $\pi \rightarrow \pi^*$ triplet energy from dibenzothiophene. The differences in the reaction modes of the two sensitized reactions would then be the result of the high concentrations of the two different but almost isoenergetic states formed by photosensitization. This postulate receives support from the work of Zimmerman *et al.* (73) and from that of Trecker *et al.* (16) where two different triplets are postulated to account for the photochemical dimerization reactions of 3,4,4-trimethyl-2-cyclohexenone.

The inability of ferric dipivaloyl methane (FDM) to quench the photochemical reactions of testosterone (177) in tertiary butyl alcohol may

result from some sort of selective solvation cage which inhibits quenching or could be the result of a facile path of conversion to a ground state reactive intermediate in this solvent which would be immune to quenching. This result obtained in this work is supported by a similar result obtained by Zimmerman et al. (73) in the case of the octalone 16 which was resistant to the effects of quenchers in tertiary butyl alcohol but not in solvents such as benzene. The fact that the phenanthrone 44 can be quenched under similar conditions may be the result of its longer residency in the excited state due to some effect of the phenanthrone system which is absent in 16 (37,73).

In the case of the $\pi \rightarrow \pi^*$ excitation at 2537 Å the $\pi \rightarrow \pi^*$ singlet would be formed. If the $n \rightarrow \pi^*$ triplet and the $\pi \rightarrow \pi^*$ triplet were of similar energy, it would be expected that intersystem crossing to the $\pi \rightarrow \pi^*$ triplet would be preferred on the basis of symmetry. This process might not be extremely efficient due to the large difference in singlet-triplet energy and other processes might intervene (12). The $n \rightarrow \pi^*$ triplet could also result via internal conversion from the $\pi \rightarrow \pi^*$ state. The irradiation of testosterone (177) and progesterone (227) at 2537 Å gave rise to the cyclopropyl cyclopentanone and cyclopentenone photoproducts in yields comparable to those obtained via the $n \rightarrow \pi^*$ excitation.

The possible intermediacy of two closely energetic triplets in the photochemistry of enones is especially appealing in view of the variety of products formed (See Historical Section). The dimerization reactions, reductions, addition of the α-carbon of alcoholic solvents and pinacol

formation are suggestive of a radical type of species. The products of molecular rearrangement and addition of water and the addition of alcohols by formation of carbon-oxygen bonds are suggestive of an intermediate with polar character such as 251.

The conversion of the $n \rightarrow \pi^*$ triplet to a species with a large degree of radical character could lead to products characteristic of radical reactions. The $n \rightarrow \pi^*$ triplet could undergo conversion to the $\pi \rightarrow \pi^*$ triplet which could then decay to a polar species giving rearranged products. The effect of various solvents could be rationalized on the basis of one state being favored at the expense of the other. Calculations have shown that excitation leads to a redistribution of π-electrons and alters the structure of the molecule as compared to the ground state (121). However, the exact nature of the excited state geometry has not been determined, so the effect of solvents may be more subtle than for the corresponding ground state reactions.

On the basis of these observations the author favors the mechanistic sequence shown in Charts 2 and 3 on pages 158 and 160 respectively. The sequence shown is for the photochemistry of testosterone (177), but the sequence is applicable to enones of similar structure.

Once the $n \rightarrow \pi^*$ triplet is converted to the reactive radical species 255, it can then react in the manner characteristic of a diradical species. This diradical species can give rise to the dimeric species observed in photochemical reactions by addition to another unexcited steroid molecule. Coupling of the radicals at the ketone carbon would lead to the pinacol

Chart 2. Mechanistic scheme for enones (Part I)

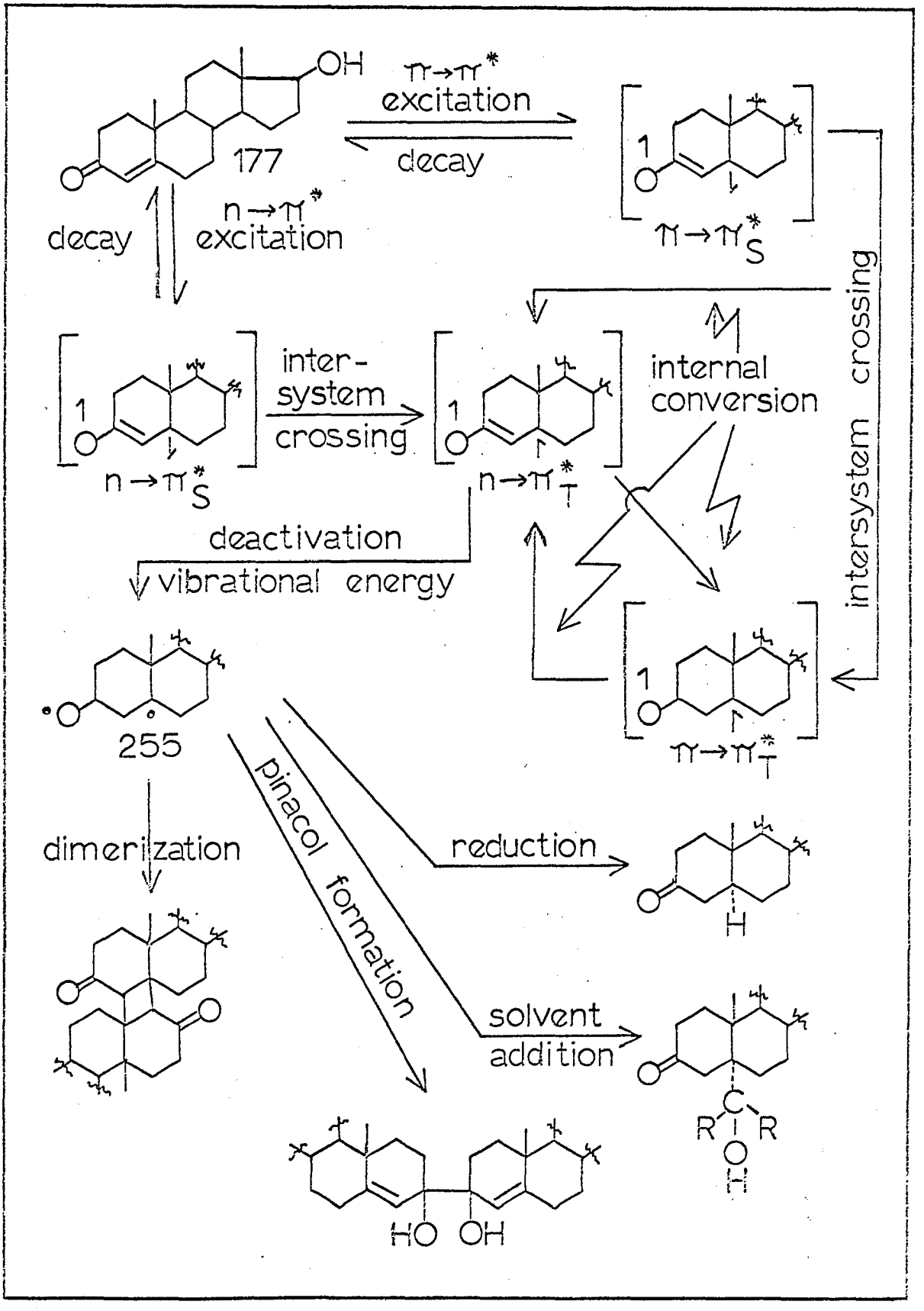
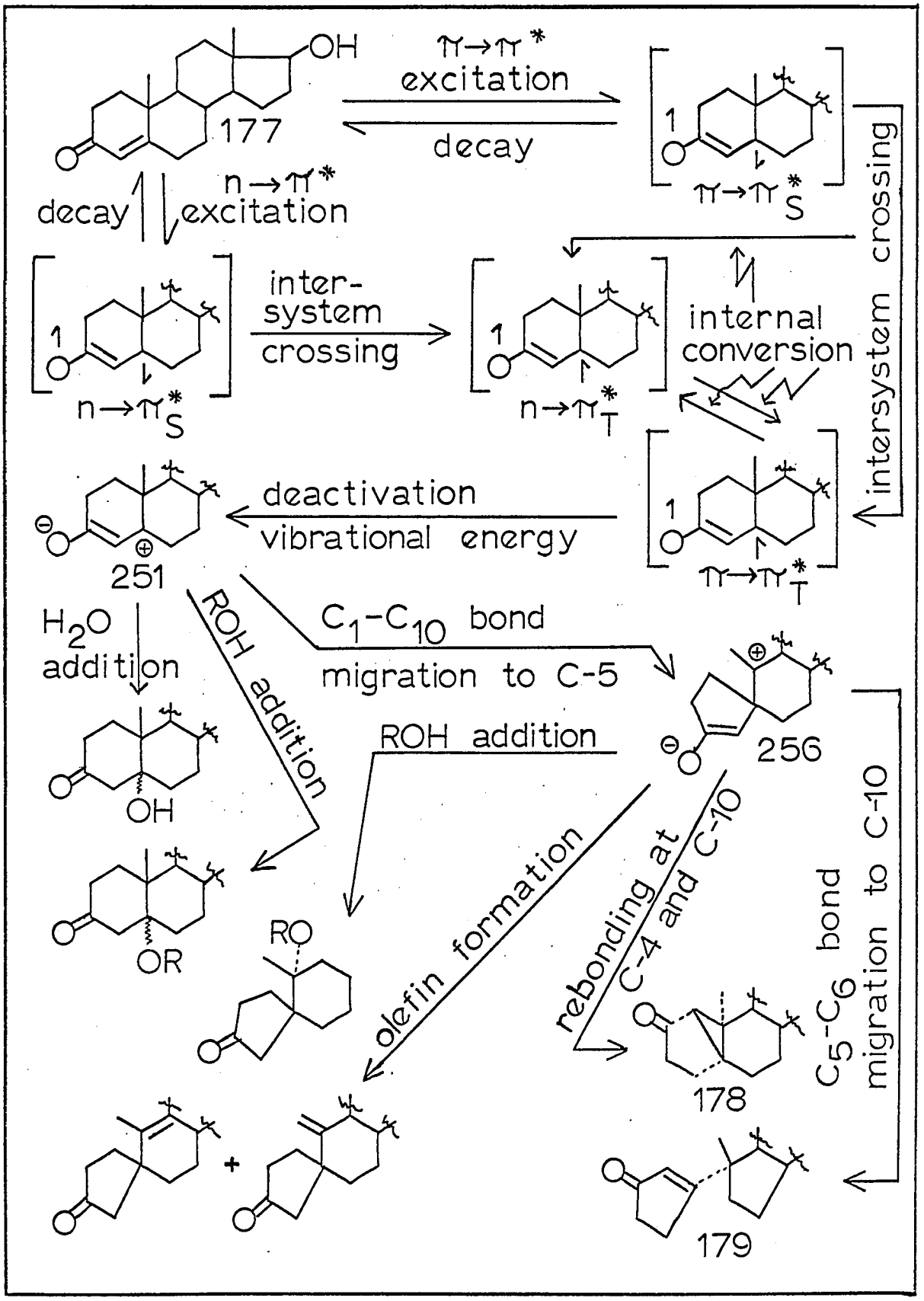

OH
177
π→π*
excitation
decay
decay
n→π*
excitation
1
π→π*S
inter-
system
crossing
1
n→π*S
1
n→π*T
internal
conversion
intersystem crossing
deactivation
vibrational energy
1
π→π*T
255
dimerization
pinacol formation
reduction
H
solvent
addition
C
R
R
O
H
HO
OH

Chart 3. Mechanistic scheme for enones (Part II)


OH
177
π→π*
excitation
decay
1
π→π*S
decay
n→π*
excitation
inter-
system
crossing
n→π*S
1
n→π*T
internal
conversion
intersystem crossing
deactivation
vibrational energy
251
1
π→π*T
H2O
addition
OH
ROH addition
C1-C10 bond
migration to C-5
ROH addition
256
OR
RO
olefin formation
rebonding at
C-4 and C-10
C5-C6 bond
migration to C-10
178
179

type of products observed by Zimmerman et al. (73) in the case of the phenanthrone 44 and by Jeger (Nann et al., 19) in the case of testosterone.

The addition of the α-carbon of alcohols to excited enones is also most easily rationalized by a hydrogen abstraction process involving the α-hydrogens of the alcohol. The radical species formed in this process then adds to the enone by the α-carbon. This process can also occur with ethers with abstractable α-hydrogen atoms (19).

The photochemical reduction of enones can also follow a similar path. In this case the oxygen of the diradical species might abstract an α-hydrogen of an alcoholic solvent and this would be followed by a second abstraction by the α-carbon of the excited enone. Such a mechanism has been proposed to account for the reduction processes observed in solution (33). The fact that tertiary butyl alcohol has no available α-hydrogens would account for the extreme slowness of these types of reactions when it is employed as a solvent.

The intermediate 251 is proposed as coming from the $\pi \rightarrow \pi^*$ triplet state. This intermediate can undergo solvent addition reactions in certain solvents. However, these types of reactions are largely forbidden in tertiary butyl alcohol because of its large steric bulk and thus the intermediate 251 should find conversion to 256 a favored process in this solvent. The intermediate 256 cannot give rise to the 5/7 fused ring systems observed in the case of santonin and other cross-conjugated

dienenones because no facile route exists to this type of product in the case of simple enones.

Solvent attact at C-10 in 256 is permitted in simple systems, but is prevented by steric requirements in the case of steroids. If a bulky solvent like tertiary butyl alcohol is involved in the solvation of C-10, then intermolecular nucleophilic attack would also be unfavorable. It should be noted that Kropp (54) has observed a significant steric effect in the case of nucleophilic attack on 97 (See Historical Section).

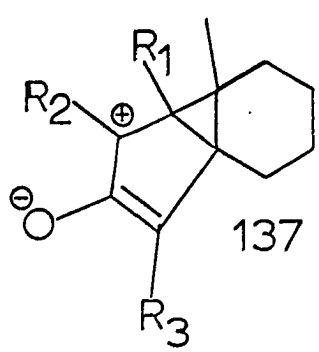
Loss of a proton from 256 to yield an olefin would compete with other processes of bond migration. The loss of a proton would be most favored when the charge at C-10 is stabilized in a significant manner. The only reported case of olefin formation is in the phenanthrone 44 where C-10 is benzilic (37). The product is formed in only a small amount in tertiary butyl alcohol and has been shown to be the product of a dark reaction in aqueous acetic acid. This indicates that bond migration in species 256 is preferred over olefin formation.

Once the intermediate 256 is formed, it may undergo return of electrons from the front side to yield the cyclopropyl cyclopentanone with the observed stereochemistry. Due to the nature of this process, only one C-10 epimer can be formed. Attack is possible only from the front side in intermediate 256 and this leads to the formation of the 10α-methyl epimer.

An alternate route available to 251 is an S_Ni type of displacement of the C_5-C_6 bond to C-10 yielding the cyclopentenone. An examination of molecular models shows that the S_Ni type of displacement of the C_5-C_6 bond

should result in only one isomer if the process is concerted. The displacement would be such that attack at the front side of C-10 would be favored. The predicted isomer from this process is the only one which has ever been isolated from the photochemistry of enones (See Historical Section).

In theory the C_9-C_{10} bond migration to C-5 from the intermediate 251 which has been observed in cross-conjugated dienones should be possible. However, the absence of the extra double bond in the enone system does not allow the formation of an intermediate such as 137. In the case of the cross-conjugated dienones the presence of the extra double bond allows the formation of a tetra-substituted carbon at C-10. With the system constrained in this manner, the driving force for migration of the C_9-C_{10} bond is the formation of a lumi-type product. In the intermediate 256 the migration of the C_9-C_{10} bond to C-5 with the formation of a carbonium ion at C-10 would lead to interactions between the C-18 and C-19



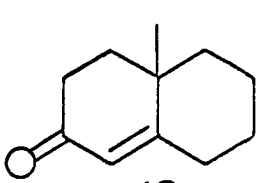
this path is sterically unfavorable and is not observed in the simple enones where the constraint of a system such as 137 is not possible. The

migration of the C-19 methyl to C-5 from intermediate 251 is an unfavorable process relative to the migration of the C_1-C_{10} bond and so is not observed.

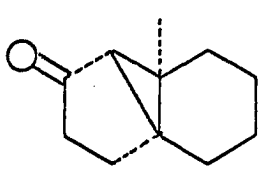
The mechanistic scheme allows for interconversion between the $n \rightarrow \pi^*$ and $\pi \rightarrow \pi^*$ triplets. Such interconversion would be favored if the states are close in energy. The reactive species can also be reached from the $\pi \rightarrow \pi^*$ singlet by intersystem crossing and internal conversion.

The fact that lumi-testosterone (178) is stable to irradiation shows that it is not an intermediate in the further formation of products. The cyclopentenone type of photoproduct, such as photo-testosterone (179), has been shown to react to give a solvent addition product, but no others (19). The fact that both photoproducts appear together in the irradiation of enones suggests that a common intermediate such as 256 is involved.

The lumi-product 185 is the only product formed in the irradiation of 16. This may be the result of a preference for the C_4-C_{10} bond formation from intermediate 256 rather than a displacement to give the cyclopentenone type of product. The steric bulk of the steroidal systems may also favor the formation of the cyclopentenones, since it seems to be an exclusive property of these systems.



16



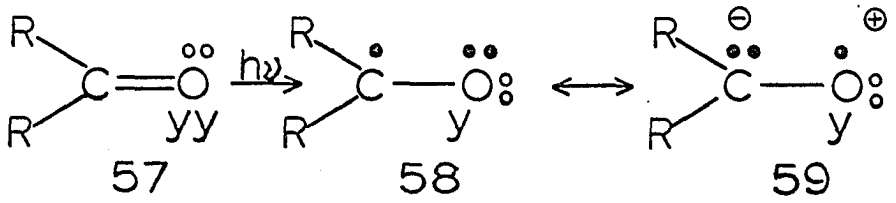
185

An attempt has been made to develop a reasonable mechanistic path to account for the formation of the observed photoproducts resulting from the irradiation of 3,4,4-trialkyl-2-cyclohexenones of which Δ^4-3-keto steroids are one example. The results of studies on known systems were incorporated where possible in this reaction sequence. As with all proposed mechanistic interpretations, it is subject to change. It is hoped that it will serve some use in the prediction of product types in a proposed photochemical scheme and also aid in the choice of conditions for irradiation.

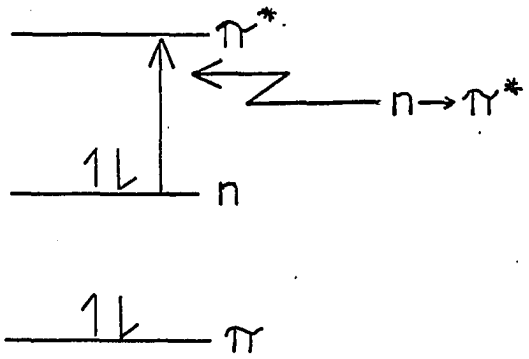
Discussion of the Photochemistry of Δ^5-pregnen-3β-acetoxy-20-one (245)

The only low energy path for excitation of a saturated ketone is that of the $n \rightarrow \pi^*$ transition. This may be pictured in valence bond terms as removal of a p_y electron from oxygen and its placement on carbon as shown in 57, 58 and 59. The molecular orbital picture is also shown below. The polar state 59 may be somewhat less polar than pictured due to electron feedback (115). However, the electron deficient nature of the oxygen is manifested in the hydrogen abstraction reactions which are characteristic of saturated ketones in their excited states (See Historical Section).

The chemistry of saturated ketones in solution is almost exclusively that of the Norrish Type II process and cyclobutanol formation (See Historical Section). These were the types of processes found in this work with ketone 245. The exact energy of the $n \rightarrow \pi^*$ triplet of the 20-keto



57 58 59



steroid is not known, but would be expected to be in the region of 70 kcal./mole as evidenced by benzophenone sensitization of its reactions. Recently the triplet state of acetone was examined and found to sensitize phosphorescence from biacetyl which has a triplet energy of 54-57 kcal./mole (122). The half-life of the acetone triplet was estimated to be of the order of 10^{-6} seconds. The 20-keto group of a steroid would be expected to exhibit a similar triplet energy.

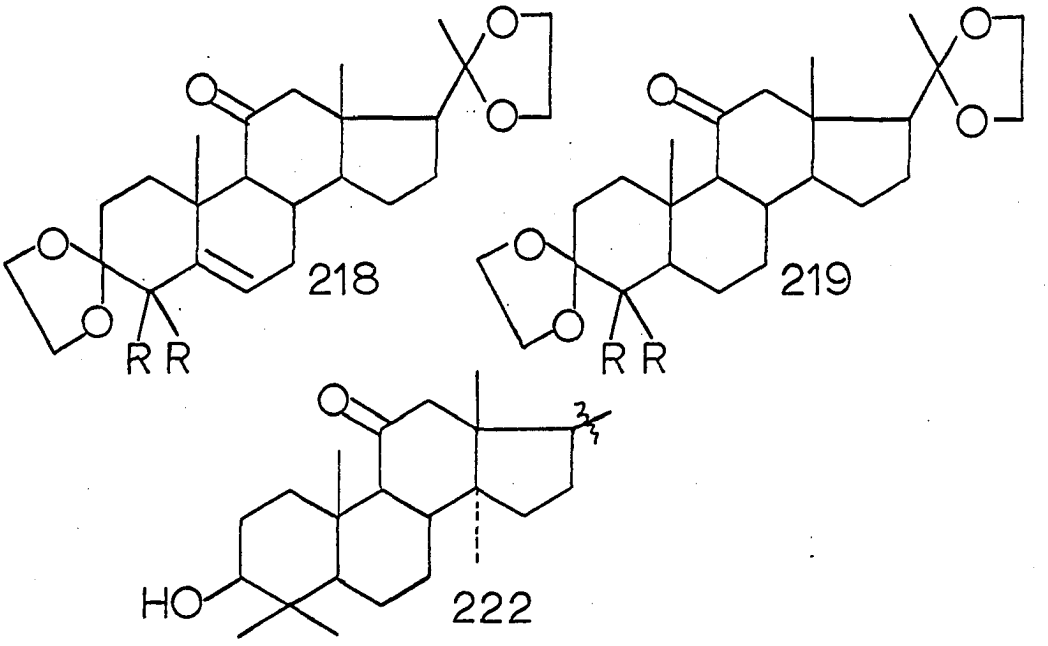
Various mechanisms have been proposed for the types of reaction encountered in the solution photochemistry of saturated ketones. Jeger (Buchschacher *et al.*, 95) proposed a concerted cyclic mechanism. Later Yang and Yang (96) and Jeger (Cereghetti *et al.*, 97) proposed that a two step mechanism was the most probable mechanistic route. Recently Wagner

and Hammond (91) and Dougherty (93) have suggested that both the singlet and triplet n → π* states are involved in the reaction. Experimental evidence also indicated that the hydrogen abstracting ability should not differ greatly for the singlet and triplet n → π* states of saturated ketones (92). These mechanisms all propose that hydrogen abstraction is involved in the initial stage of the reaction.

The choice of a 20-keto steroid for study is useful in that it permits an evaluation of steric factors on the course of the reaction. The steroid skeleton provides a rigid framework in the reacting area which is not possible in the acyclic cases. This should favor the closure to cyclobutanols over cleavage to acetone and an olefin. In the cases studied in this work, the cyclobutanols were consistently the major products. However, cleavage products were also formed in significant amounts in all cases studied.

The effects of substituients on the course of the closure reaction has been investigated by Jeger (Iriarte et al., 101). He found that the amount of C_{19}-C_{11} ring closure product formed from 218 and 219 increased when the hydrogens at C-4 were replaced with geminal methyl groups. This was rationalized as the result of a steric effect in which the C-19 methyl group became displaced toward the C-11 ketone and thus was in a more favorable position for ring closure in the methyl substituted cases. In another unique example, compound 222 reacted exclusively to give the C_{11}-C_{18} methyl closure product (102). This was considered as due to the alteration of the steroid conformation by the introduction of the 14α-

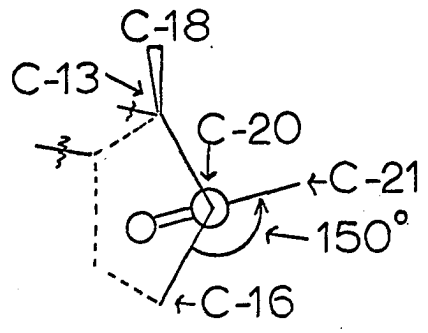
methyl substituent. This reaction shows the marked sensitivity of the ring closure reaction to steric factors. An examination of molecular models indicated that the 14α-methyl group might cause an alteration in the preferred conformation of ring C and thus bring the 11-keto function into closer proximity to the C-18 methyl group.



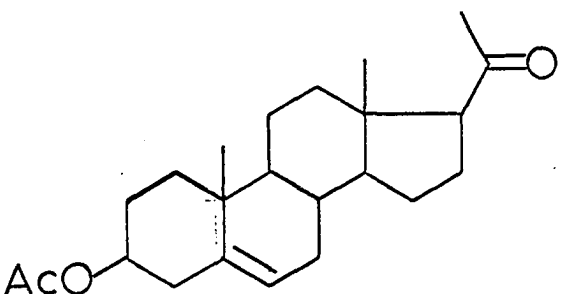
Examination of molecular models suggests that a 20-keto steroid such as 245 should have a preferred conformation in which the C-21 methyl group is placed behind ring D of the steroid skeleton and the 20-keto group lies over ring D. This was confirmed in the recent studies of Wellman and Djerassi (123) and Allinger et al. (124). These workers found that the conformation shown as 257 was the preferred conformation for such steroidal ketones.

If a concerted cyclic mechanism was involved, one would expect that the major products would result from the preferred ground state confor-

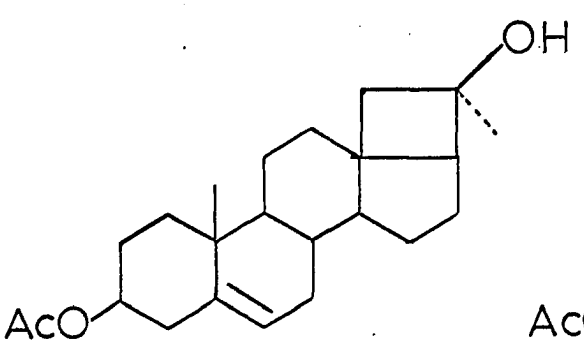
mation since this conformation would be the one available at the moment of excitation. This leads to the prediction that 248 should be the major product if such a mechanistic path were operative. Examination of the data show that 248 is the minor cyclobutanol formed in all cases studied. Even if one permitted the formation of the least favored conformation of 245 which would place the C-21 methyl group over the plane of ring D and allowed this conformation to react to give 249. It would be expected that the ratio of 249:248 should be relatively invarient with solvent changes since an intramolecular cyclic process should not be greatly effected by solvent changes. Examination of the experimental data shows that not only does the ratio of 248:249 vary with solvent, but there is



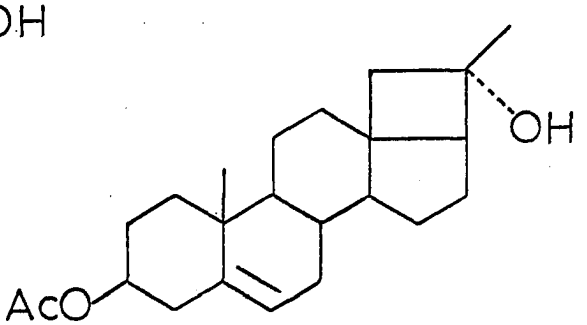
257



245



248



249

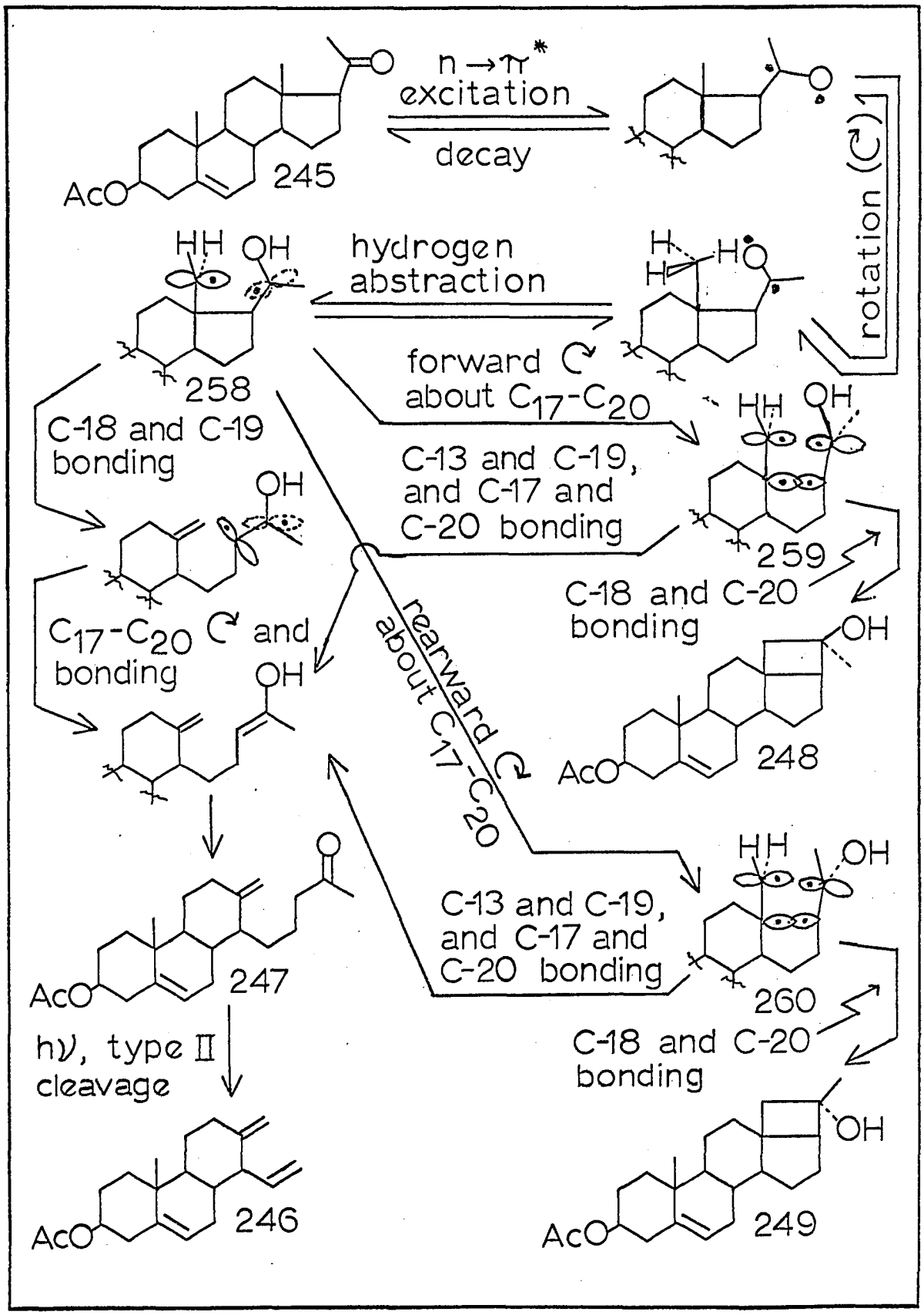
a wide variation between solvents which should be very similar in their effect on a cyclic process such as benzene and cyclohexane.

If one considers the steric requirements for a cyclic four center process like the one suggested by Jeger (Buchschacher et al., 95), it is found that the hydrogen abstracting p-orbital of oxygen cannot be brought into proximity with the hydrogen of the C-18 methyl group in a manner which would allow bonding between the C-18 methyl radical once it is formed and the C-20 carbon. In fact, it is found that a situation of no significant overlap is produced unless rotation is allowed about the C_{17}-C_{20} bond. Thus the evidence is in opposition to the operation of a four center one step cyclic type of process and such a route is eliminated from further consideration.

A two step process is subject to fewer restrictions than the cyclic one step route. It has been proposed that the initial step of such a process would be the abstraction of a γ-hydrogen atom by the excited carbonyl function (94). The species produced would resemble a diradical and it was this intermediate which could then lead to the observed products.

In the case of Δ^5-pregnen-3β-acetoxy-20-one (245) this process can be viewed in the manner shown in Chart 4 on page 172. The initial $n \rightarrow \pi^*$ excitation process produces an electronically excited ketone diradical species which may then rotate so that overlap with a C-19 methyl hydrogen is possible. This would result in the abstraction of a γ-hydrogen atom producing a radical type of species at C-19 and at C-20 such as 258. The

Chart 4. Mechanistic scheme for Δ^5-pregnen-3β-acetoxy-20-one (245)


n → π* excitation
decay
245
AcO
rotation (C)1
hydrogen abstraction
HH OH
258
forward C about C17-C20
C-18 and C-19 bonding
C-13 and C-19, and C-17 and C-20 bonding
HH OH
259
C-18 and C-20 bonding
OH
C17-C20 C and bonding
OH
rearward about C17-C20
248
AcO
HH OH
C-13 and C-19, and C-17 and C-20 bonding
260
C-18 and C-20 bonding
OH
247
AcO
hν, type II cleavage
246
AcO
249
AcO

process here may also be reversible (92). At this stage C_{19}-C_{13} bonding would yield an olefinic species which by a rotation about the C_{17}-C_{20} bond could give rise to the enolic form of 247. Collapse of the enol would then yield 247.

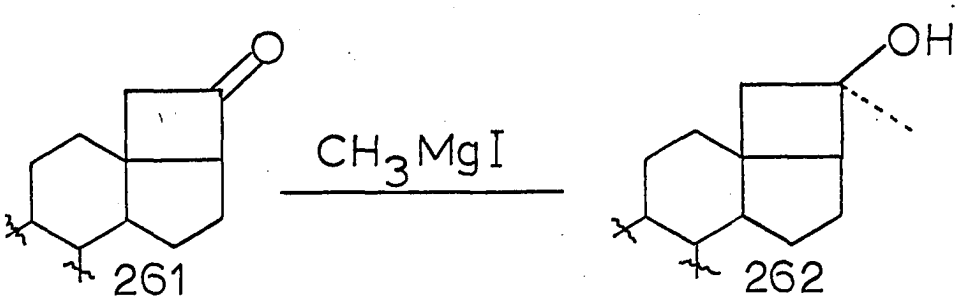
An alternate route is possible by rotation about the C_{17}-C_{20} bond to give either 259 or 260. The intermediates could collapse by C_{19}-C_{13} and C_{20}-C_{17} bonding to yield the enolic form of 247. Compound 247 is the intermediate compound involved in the formation of 246 by a type II cleavage. This path was shown to be correct by the irradiation of 247 in this work and has been confirmed by other workers (95).

An alternate γ-hydrogen abstraction involving the hydrogen at C-15 is not favorable since the conformation of ring D of the steroid skeleton is such that this hydrogen is not in a position which allows sufficient overlap for abstraction.

A forward rotation about the C_{17}-C_{20} bond of 258 gives rise to 259 which by bonding at C-19 and C-20 yields the observed alcohol (248). Examination of molecular models indicates that this alcohol has the least strained conformation of the two possible epimeric alcohols. A rearward rotation about the C_{17}-C_{20} bond of 258 gives the intermediate 260. By bonding at C-19 and C-20, this intermediate gives the cyclobutanol 249. This alcohol has the C-21 methyl group over ring D and gives an alcohol with more steric hindrance than that of the opposite epimer. Both cyclobutanols have been shown to be stable to further irradiation.

Examination of the experimental data indicates that the more hindered alcohol 249 is always produced over the less hindered epimer 248. This suggests that the species 258 has a favored mode of rotation which favors the formation of 249 over 248. In terms of a mechanistic interpretation this would involve the favored formation of the intermediate 260 over 259.

If the back side of an intermediate such as 258 is less hindered than the front side, one might expect the approach of solvent to occur from the back side. Back side approach has been shown to be preferred by Jeger (Cereghetti et al., 97). He synthesized the alcohol 262 by treatment of 261 with methyl magnesium iodide. This indicated that the approach of solvent molecules in an intermediate such as 258 would be most favored from the back side.



The intermediate species 258 contains an alcohol function for which hydrogen bonding should be a favored process. If solvent approach from the rear and hydrogen bonding are favored, then the rotation to give 260 over 259 should occur. As the steric bulk of the solvent alcohol is increased, more of the intermediate 260 should be favored over 259 and this in turn should give more of the cyclobutanol 249 rather than 248.

The experimental data shown in Table 1 on page 143 support this observation. As one goes from methanol to tertiary butyl alcohol, the ratio of 249:248 increases from 2.8:1 to 8.1:1. Solvents such as ethanol and methanol would be expected to give about the same ratio of products and this is observed. As the steric bulk of the solvent increases, the only way that the intermediate 258 can obtain sufficient hydrogen bonding is by a rearward rotation eventually resulting in the production of 249. The postulate of hydrogen bonding in the intermediate 258 also receives support from the data obtained in acetic acid acid and dimethyl sulfoxide as solvents. Dimethyl sulfoxide has a configuration similar to that of isopropyl alcohol. Dimethyl sulfoxide can coordinate with alcoholic groups via oxygen and sulfur and this should make it even more influential in such a process. The ratio of photo D (249):photo C (248) is 4.8:1 in dimethyl sulfoxide versus 3.6:1 for isopropyl alcohol. This is in good agreement with the prediction made on the basis of hydrogen bonding in the intermediate 258. Glacial acetic acid exists as the dimer in solution. Thus it has a significant steric bulk. It is possible that acetic acid coordinates via the oxygens of the carbonyl group and also forms hydrogen bonds with the oxygen of the intermediate 258 by use of the acid protons. In accord with this assumption the ratio of photo D:photo C is 5.2:1.

In the case of the alcoholic solvents and acetic acid, two types of hydrogen bonding are possible. The proton of the alcohol or acid may hydrogen bond with the oxygen of the hydrogen abstracted intermediate 258 and the oxygen of the alcohol may form a hydrogen bond with the proton of

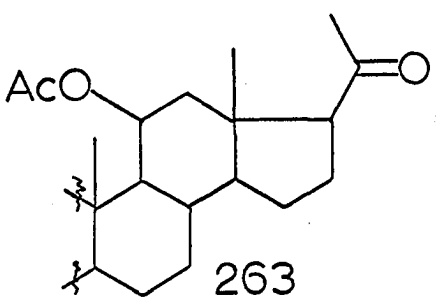
the hydrogen abstracted intermediate. A similar case exists for dimethyl sulfoxide which can coordinate through oxygen and sulfur.

In pyridine the only significant type of bonding would be that which results by the overlap of the available electron pair on nitrogen with the proton of the intermediate 258. This type of overlap would be more effective from the back side of the steroid system and would favor the production of photo D (249) over photo C (248). The effect of this type of overlap should be less than that for a bulky alcohol like tertiary butyl alcohol. This is observed since the ratio of photo D:photo C is 5.7:1 for pyridine and 8.1:1 for tertiary butyl alcohol. The ratio for pyridine is also larger than that observed for dimethyl sulfoxide and acetic acid and indicates that the complex formed in the case of pyridine must have significant steric bulk.

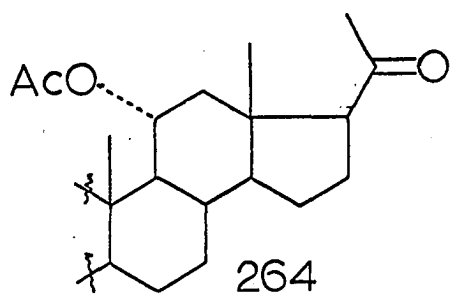
The contrast between benzene and pyridine is also instructive. In a situation where no bonding or complexing is involved, benzene and pyridine would be expected to act similarly as solvents. However, this is not observed. Benzene gives a ratio which is almost identical to that of the sterically small alcohols while pyridine gives a significant enhancement of the photo D:photo C ratio. The chief difference between the two solvents is the presence of the lone electron pair on the nitrogen of pyridine. Benzene lacks this type of ability for bonding and this gives a ratio which is less than that of pyridine. This observation supports the postulate that hydrogen bonding in the hydrogen bonded intermediate 258

is significant in determining the product ratio of the two epimeric cyclobutanols.

Further support for this type of bonding comes from the work of Wehrli et al. (125). These workers studied the irradiation of the steroids 263 and 264. The irradiation of the 11β-isomer 263 gave two epimeric alcohols similar to photo D (249) and photo C (248). The ratio of the epimers was 5:1. Irradiation of the 11α-isomer 264 gave the cyclobutanol with the stereochemistry identical to that of photo D (249) as the only isolated product.



263



264

An examination of molecular models shows that in 263 the 11β-acetate is capable of disrupting the solvent shell in the region of ring D. This decreases the formation of solvent hydrogen bonding which would lead to an intermediate like 259 which could then give rise to the alcohol with stereochemistry similar to that of photo C (248). The 11β-acetoxy group does not greatly affect the back side of the ring where hydrogen bonding would give the intermediate 260 which would give a cyclobutanol similar to photo D (249). The 11β-isomer also has the capacity to hydrogen bond with the intermediate which leads to the major cyclobutanol. The 11α-isomer gives only one isolated cyclobutanol. This

compound has a stereochemistry at C-20 which is identical to that of photo D (249). The acetate of 264 can still coordinate with an intermediate such as 260 to give the cyclobutanol. However, the acetate cannot affect the front side of ring D. The absence of any cyclobutanol resulting from an intermediate such as 259 is unexpected. This could be the result of the formation of a highly ordered solvation shell in the region behind ring D. The 11α-acetate would have to be the main cause of such an odering. This solvation could then make the formation of 260 favored to the exclusion of an intermediate such as 259. Brown and Klimisch (126) have observed a similar coordination effect in the solvolysis of arenesulfonates in tertiary butyl alcohol. In any case the 11-substituted compounds exhibit a behavior which is significantly different from that of the corresponding compounds lacking such a substituent. The results are best interpreted as involving the acetate substituent.

Solvents such as benzene and cyclohexane are not capable of involvement in hydrogen bonding, and yet they influence the ratio of photo D:photo C. Benzene gives the same ratio of photo D:photo C as is observed for the sterically small alcohols such as methanol and ethanol. This indicates that there is an inherent preference in the 20-keto system for the formation of photo D (249) over photo C (248) since benzene would be expected to be an inert solvent with respect to any type of coordination.

Cyclohexane gives a rather unexpected result. The rates of the reaction in benzene and cyclohexane are comparable and yet cyclohexane gives a ratio of photo D:photo C of 7.5:1 which approaches that observed

in tertiary butyl alcohol. Cyclohexane would not be expected to be capable of hydrogen bond formation and its solvating ability would also be expected to be less than that of benzene since cyclohexane lacks a π-system. The earlier results obtained with alcoholic solvents suggest that two types of influences may be felt in the reactions leading to the formation of cyclobutanols. One is the formation of hydrogen bonds with the intermediate 258 and the other would be a steric bulk effect causing the intermediate 258 to undergo a favored rearward rotation which would eventually lead to the formation of 249. For the solvents discussed thus far, both effects lie in the same direction. For a solvent like tertiary butyl alcohol, the formation of hydrogen bonds and solvation are both favored from the rear giving a preference for the formation of photo D (249). With a solvent like dimethyl sulfoxide, hydrogen bonding and solvation from the front side could occur, but both are more favored from the rear.

The results obtained with cyclohexane cannot be readily explained in terms of a hydrogen bonded intermediate. In the absence of available hydrogen bonding, the solvation shell of 258 may undergo changes which are not readily obvious. The manner in which cyclohexane influences the formation of photo C and photo D is not well understood at present.

The results obtained from the irradiation of Δ^5-pregnen-3β-acetoxy-20-one (245) in various solvents support the operation of a two step process in the photochemical reactions of saturated ketones in solution. The first step is the abstraction of a γ-hydrogen atom by the excited

ketone to give a diradical species. This species may then give rise to olefinic products or lead to cyclobutanol formation in a process which has been shown to be solvent dependent. The factors of selective solvation and hydrogen bond formation with the intermediate produced by hydrogen abstraction both appear to be important.

The results in tertiary butyl alcohol explain the isolation of only one epimeric alcohol from the irradiation of progesterone (227). This investigation constitutes the first known example of an intermolecular solvent effect on the photochemical reactions of saturated ketones. The experimental results can be accommodated by the involvement of either the singlet state, triplet state or both in the reaction since the hydrogen abstracting efficiency of the two states does not vary greatly (92). The determining factor in such cases will be the lifetime of the intermediate formed by hydrogen abstraction. If the lifetime is sufficient to allow the various rotations necessary for product formation, then the formation of the cyclobutanols should occur. If a singlet species can meet these requirements in a given case, it should be capable of reaction. The triplet state would also be favored because of its longer lifetime.

The solvent dependance of the reaction provides a unique method of controlling the steric course of a photochemical reaction. This method should be applicable to the synthesis of other cyclobutanol systems.

EXPERIMENTAL

Instruments and Methods

All melting points were measured on a Kofler microscope hot stage equipped with a polarizer and are uncorrected.

All vapor phase chromatography (v.p.c.) measurements were made on a Chromalab instrument manufactured by the Glowall Corporation, Glenside, Pennsylvania. The column used was a twelve foot, 3/16 inch glass column packed with 1% General Electric SE-30 on acid washed chromasorb P (80-100 mesh).

All ultraviolet spectra were obtained in 95% ethanol, unless otherwise noted, on a Beckman Model DK-2A spectrophotometer.

All infrared spectra were recorded on a Perkin-Elmer Model 21 spectrometer.

All nuclear magnetic resonance (n.m.r.) spectra were taken on a Varian Associates Model HR-60 or A-60 spectrometer at 60 Mc. The HR-60 spectra were calibrated by the side band technique using the side band of tetramethyl silane as an internal standard. The chemical shift values are reported in tau (τ) units. All spectra were in deuteriochloroform unless otherwise noted.

All mass spectra were taken on an Atlas CH-4 mass spectrometer at 70 electron voltes (e.v.) unless otherwise noted.

All elemental analyses were performed by Spang Microanalytical Laboratory, Ann Arbor, Michigan or by Schwarzkopf Microanalytical Laboratory, Woodside, New York.

Experimental for the Photochemistry of Testosterone (177)

Irradiation of testosterone (177) in tertiary butyl alcohol

Testosterone (177, 7.5 g., 0.026 mole) was dissolved in two liters of tertiary butyl alcohol in a two liter irradiation vessel. The solution was purged with nitrogen for 20 minutes, sealed and irradiated for 42 hours using a Hanovia 550 watt medium pressure mercury arc suspended in a water cooled Pyrex jacket. After irradiation the solvent was removed by use of a rotary evaporator. The residue was dissolved in 30 ml. of benzene and pipetted onto a 4.5 x 25 cm. column of Woelm activity II neutral alumina prepared by adding 10 ml. of water to 340 g. of alumina. Elution was begun using Skelly B and followed by v.p.c. The results are given below.

Substance	Solvent	Weight (g.)	Yield (%)
testosterone and lumi-testosterone (178)	100 Skelly B, 50 Skelly B-50 benzene	4.902	65.5
photo-testosterone (179)	75 ether-25 benzene, 90 ether-10 $CHCl_3$	2.117	28.2
column stripping and polymer	75 ether-25 $CHCl_3$, 95 $CHCl_3$-5 methanol	0.466	6.2
	Total	7.485	99.9

The mixture of testosterone and lumi-testosterone (178) was re-chromatographed on a 3.5 x 30 cm. column of 140 g. of Florisil. The material was placed on the column in benzene (20 ml.) and elution was begun with Skelly B and followed by v.p.c. From this column 1.322 g.

of lumi-testosterone was eluted with 90% benzene-10% ether. A mixture of testosterone and lumi-testosterone (3.250 g.) was also obtained.

Attempted separation of the mixture of testosterone and lumi-testosterone by chromatography on silica gel was unsuccessful and 3.066 g. of material was recovered.

Fractional recrystallization of the 3.066 g. mixture from acetone-hexane gave 0.850 g. of lumi-testosterone. Further fractional recrystallization from methanol-water gave 0.180 g. of lumi-testosterone. The total amount of lumi-testosterone isolated was 1.322 + 0.850 + 0.180 = 2.352 g.

Fractional recrystallization of the mixture (3.006 g.) from acetone-hexane gave 0.916 g. of testosterone. Further fractional recrystallization from methanol-water gave 0.744 g. of testosterone. The total amount of testosterone isolated was 1.660 g.

The total yield of photoproducts and recovered starting material was as follows.

Compound	Weight (g.)	Yield (%)
testosterone (177)	1.660	22.2
lumi-testosterone (178)	2.352	31.4
photo-testosterone (179)	2.117	28.2
total	6.129	81.8

The recovered testosterone was recrystallized twice from methanol-water to give white crystals with m.p. 153-154 °C. A mixed melting point with an authentic sample gave no depression. The infrared spectrum and

v.p.c. retention time of the recovered material were identical to those of the authentic material.

Lumi-testosterone (178) was recrystallized from methanol-water to give white crystals with m.p. 204-205 °C. The infrared spectrum is shown in Figure 1 on page 54. The melting point and infrared spectrum of 178 are identical to those reported by Griswold (15). The mass spectrum of lumi-testosterone gave peaks at m/e 288 (90%, P^+), 123 (58%) and 109 (100%). At 18 e.v. and below only m/e 109 and 288 remain significant.

Photo-testosterone (179) was recrystallized from methanol-water to give white crystals with m.p. 149-150 °C. The infrared spectrum is shown in Figure 1 on page 54. The infrared spectrum and melting point of photo-testosterone are virtually identical to those of the identical compound prepared by Griswold (15). The mass spectrum of photo-testosterone gave peaks at m/e 288 (46%, P^+), 123 (100%) and 109 (54%). At 18 e.v. and below only 109 and 288 remain significant.

Preparation of 10α-methyl-1β,5β-androstan-17β-acetate-2-one (172)

Lumi-testosterone (178, 120 mg., 4.16×10^{-4} mole) was dissolved in 10 ml. of pyridine and 10 ml. of acetic anhydride. The solution was stirred overnight, poured over crushed ice and extracted with 3 x 75 ml. portions of benzene. The benzene extracts were combined, washed with 2 x 50 ml. portions of water, 2 x 75 ml. protions of 5% hydrochloric acid, 2 x 75 ml. portions of water, 1 x 75 ml. portion of 5% potassium carbonate and 2 x 75 ml. portions of water. The benzene layer was dried over

anhydrous magnesium sulfate, filtered and the benzene evaporated by use of a rotary evaporator.

The residue was crystallized from methanol-water to give 115 mg. (84%) of white needles with m.p. 167-169 °C of lumi-testosterone acetate (172). The infrared spectrum is shown in Figure 1 on page 54. The melting point and infrared spectrum are virtually identical to that of the identical compound prepared by Griswold (15). The mass spectrum of lumi-testosterone acetate gave peaks at m/e 330 (69%, P^+), 287 (21%), 269 (21%), 123 (47%) and 109 (100%). At 18 e.v. and below only m/e 109 and 330 remain significant.

Preparation of 3α-(3-keto-1-cyclopenten-1-yl)-3β,5aβ-dimethyl-6β-acetoxy-as-hydrindacene (173)

Photo-testosterone (179, 130 mg., 4.50×10^{-4} mole) was dissolved in 10 ml. of pyridine and 10 ml. of acetic anhydride. The solution was stirred overnight, poured over crushed ice and extracted with 3 x 75 ml. portions of benzene. The benzene extracts were washed with 2 x 75 ml. portions of water, 2 x 75 ml. portions of 5% hydrochloric acid, 1 x 75 ml. portion of water, 2 x 75 ml. portions of 5% sodium carbonate solution and 2 x 75 ml. portions of water. The benzene layer was then dried over anhydrous magnesium sulfate, filtered and the benzene removed under reduced pressure by use of a rotary evaporator. The residue was crystallized from ether-pentane to give 70 mg. (48%) of photo-testosterone acetate (173) as white crystals with m.p. 109-109.5 °C. A mixed melting

point with an authentic sample prepared by Griswold (15) gave no depression. The infrared spectrum is shown in Figure 2 on page 56 and is identical with that of Griswold (15).

The mass spectrum of photo-testosterone acetate gave peaks at m/e 330 (57%, P^+), 287 (22%), 269 (18%), 123 (100%) and 109 (24%). At 13 e.v. and below only m/e 109 and 330 remain significant.

Irradiation of testosterone (177) in tertiary butyl alcohol, in tertiary butyl alcohol plus benzophenone and in tertiary butyl alcohol plus ferric dipivaloyl methane

Testosterone (177, 100 mg., 3.50×10^{-4} mole) was placed in each of three 30 ml. Pyrex test tubes. To one tube 25 ml. of nitrogen purged tertiary butyl alcohol was added, to another 338 mg. of benzophenone followed by 25 ml. of nitrogen purged tertiary butyl alcohol and to the third 25 ml. of a nitrogen purged 2.8×10^{-6} molar solution of ferric dipivaloyl methane (FDM) in tertiary butyl alcohol.

For benzophenone at 360 mμ, $\varepsilon = 61$ and for testosterone at 360 mμ, $\varepsilon = 7.3$. The solution was 0.074 molar in benzophenone and 0.014 molar in testosterone. The per cent of the light absorbed by the benzophenone was $(100)(0.074)(61)/[(0.074)(61) + (0.014)(7.3)] = 97.8\%$.

For ferric dipivaloyl methane at 360 mμ, $\varepsilon = 2{,}500$. The per cent of the light absorbed by the ferric dipivaloyl methane was $(100)(2.8 \times 10^{-6})(2{,}500)/[(2.8 \times 10^{-6})(2{,}500) + (0.014)(7.3)] = 6.3\%$.

The tubes were capped and irradiated using the "black light" lamps of a Rayonet photochemical reactor. The tubes were placed in the center of

the reactor chamber for irradiation. The output of the "black light" lamps is mainly in the 3400-3600 Å region. The irradiation was followed by v.p.c. After two hours the testosterone was greater than 25% consummed in the tube with benzophenone and no reaction could be detected in the tubes containing testosterone and testosterone and FDM. After six hours the benzophenone solution showed greater than 75% destruction of testosterone and only minor amounts of lumi-testosterone and photo-testosterone. The other tubes had reacted to give these two photoproducts is about 5% yield. After ten hours the tube with benzophenone showed greater than 95% destruction of testosterone and less than 2% of the photoproducts lumi-testosterone (178) and photo-testosterone (179). The tubes containing testosterone and testosterone plus FDM gave the same ratio of photo-testosterone to lumi-testosterone after this time. The extent of reaction in these tubes was about 10%. Irradiation was discontinued after this time.

Irradiation of testosterone (177) in the presence of dibenzothiophene at 3130 Å

Two Pyrex test tubes were prepared each containing testosterone (177, 30 mg., 1.1×10^{-4} mole) and 10 ml. of nitrogen purged tertiary butyl alcohol. To one of the tubes dibenzothiophene (40 mg.) was also added. The solutions were immersed in a beaker of filtering solution prepared by dissolving 46 g. of nickel sulfate hexahydrate and 14 g. of cobalt sulfate heptahydrate in each 100 ml. of water. This solution is transparent in

the 3100-3200 Å region and filters out light below 3100 Å and above 3200 Å (127). The minimum thickness of the filter solution was 2 cm.

The tertiary butyl alcohol solution was 1.04×10^{-2} molar in testosterone and 2.16×10^{-2} molar in dibenzothiophene. At 3130 Å dibenzothiophene has an ε value of 2,080 and testosterone has an ε value of 86.5. The per cent of the light absorbed by dibenzothiophene is (100) $(2.16 \times 10^{-2})(2,080)/[(2.16 \times 10^{-2})(2,080) + (1.04 \times 10^{-2})(86.5)] = 98\%$.

The solutions were irradiated using a Hanovia 550 watt medium pressure mercury arc in a water cooled Pyrex jacket. The reaction was followed by v.p.c. Samples were taken at 18, 47.5 and 95 hours. The extent of reaction was measured by comparing the ratios of lumi-testosterone (178) and photo-testosterone (179) to remaining starting material. After 18 hours the ratio was 0.15:1 for testosterone and 0.12:1 for testosterone plus dibenzothiophene. After 47.5 hours the ratios were 0.36:1 and 0.30:1 respectively and after 95 hours the ratios were 1.8:1 and 1.1:1 respectively. The reaction of testosterone to give products which are not v.p.c. volatile was about the same in the sensitized and unsensitized reactions and no other v.p.c. volatile products were observed.

Irradiation of testosterone (177) at 2537 Å in tertiary butyl alcohol

Testosterone (177, 2.00 g., 6.95×10^{-3} mole) was dissolved in 170 ml. of tertiary butyl alcohol in a quartz irradiation vessel, purged with nitrogen for 15 minutes and sealed. The solution was irradiated for 126 hours using a low pressure external mercury arc placed about 1 cm. from the quartz vessel.

After irradiation the solvent was removed under reduced pressure using a rotary evaporator. The residue was dissolved in 30 ml. of benzene and pipetted onto a 2.5 x 35 cm. column of Woelm activity II neutral alumina prepared by adding 4.5 ml. of water to 150 g. of alumina. Elution was begun using Skelly B and followed by v.p.c. The results of the chromatography are given below.

Compound	Solvent	Weight (g.)	Yield (%)
forerun	100 Skelly B, 95 benzene-5 ether	0.172	8.6
testosterone	90 benzene-10 ether	0.274	13.7
lumi-testosterone (178)	75 benzene-25 ether	0.636	31.8
photo-testosterone (179)	50 benzene-50 ether	0.526	26.3
polymer and column stripping	100 ether, 95 $CHCl_3$-5 methanol	0.450	19.6
	total	2.058	103.0

Recovered testosterone was identified by comparison of its infrared spectrum and v.p.c. retention time with an authentic sample.

Lumi-testosterone (178) was recrystallized three times from methanol-water to give white crystals with m.p. 203-205 °C. A mixed melting point with an authentic sample of photo-testosterone gave no depression. The infrared spectrum of photo-testosterone was identical with that of an authentic sample whose spectrum is shown in Figure 1 on page 54.

Photo-testosterone (179) was recrystallized from methanol-water five times to give white crystals with m.p. 149-150 °C. A mixed melting point

with an authentic sample gave no depression. The infrared spectrum of the photo-testosterone isolated above was identical with that of an authentic sample whose spectrum is reproduced in Figure 1 on page 54.

A similar irradiation of testosterone (10 mg.) in 10 ml. of tertiary butyl alcohol in a Pyrex test tube produced no visible reaction after 14 hours while a similar sample in a quartz vessel gave greater than 60% conversion after 10 hours. This indicated that the low pressure mercury arc had no significant output above 3000 Å.

Preparation of testosterone-2,2,4,6,6-d_5 (224)

Testosterone (177, 5.00 g., 0.0174 mole) was dissolved in 80 ml. of deuteriomethanol (CH_3OD). The CH_3OD was 98.8% deuterated as shown by n.m.r. analysis using the ^{13}C side band technique. To this mixture 4.0 g. of sodium methoxide was added and the mixture was refluxed under nitrogen for 53 hours. After this time the flask was equipped with a distillation head and 40 ml. of the deuteriomethanol was distilled. The remaining solution was cooled, diluted with 50 ml. of D_2O and extracted with 4 x 100 ml. portions of ether. The ether extracts were washed with 1 x 200 ml. portion of water, with 1 x 200 ml. portion of 5% hydrochloric acid and with 3 x 200 ml. portions of water. The ether extracts were dried over anhydrous magnesium sulfate, filtered and the solvent removed under reduced pressure using a rotary evaporator.

The residue was recrystallized twice from methanol-water to give 4.6 g. (91%) of testosterone-d_5 (224) with m.p. 153-154 °C. A mixed melting point with a sample of testosterone (177) gave no depression. The

v.p.c. retention time of 224 was identical with that of testosterone. Testosterone-d_5 had an ultraviolet spectrum which gave $\lambda_{max}^{95\ EtOH}$ = 240 mμ (ε = 15,900). The infrared spectrum is shown in Figure 2 on page 56. The n.m.r. spectrum is reproduced in Figure 3 on page 61. Analysis of the mass spectrum of testosterone-d_5 gave d_5 = 70.2%, d_4 = 25.6% and d_3 = 4.2%. The analysis used the peaks at m/e 293, 292, 291 and 290 after correcting for the ^{13}C content using 1.1% ^{13}C as the correction factor.

Irradiation of testosterone-2,2,4,6,6-d_5 (224)

Testosterone-d_5 (224, 4.00 g., 0.0136 mole) was dissolved in 700 ml. of sodium dried tertiary butyl alcohol and placed in an irradiation vessel. The solution was irradiated for 25 hours using a Hanovia 550 watt medium pressure mecury arc in a water cooled Pyrex immersion jacket. Nitrogen was bubbled through the solution during irradiation. After irradiation the tertiary butyl alcohol was removed under reduced pressure using a rotary evaporator. The residue was dissolved in chloroform and ether, dried over anhydrous magnesium sulfate, filtered and the solvent removed under reduced pressure.

A sample of testosterone-d_5 lost deuterium content on column chromatography on alumina, so this method of separation was not used.

Fractional recrystallization from acetone-hexane gave 0.724 g. (18%) of lumi-testosterone-d_5 (225) with m.p. 202-204 °C. A mixed melting point with an authentic sample of lumi-testosterone gave no depression. The v.p.c. retention times of the deuterated and undeuterated material were identical. The infrared spectrum of lumi-testosterone-d_5 is shown

in Figure 2 on page 56. The n.m.r. spectrum is reproduced in Figure 3 on page 61. The mass spectrum of lumi-testosterone-d_5 at 70 e.v. gave m/e peaks at 293 (72%, P^+), 292 (28%), 291 (5.5%), 290 (0.5%), 128 (57%), 127 (38%), 113 (100%) and 112 (48%). At 17 e.v. only the m/e peaks at 112, 113 and those of the parent ion remained significant. The extent of deuteration was calculated to be d_5 = 67.5%, d_4 = 27.6% and d_3 = 4.9% in the manner described for testosterone-d_5.

After removal of the lumi-testosterone-d_5, fractional recrystallization from ether-pentane gave 0.406 g. (10.2%) of photo-testosterone-d_5 (226). A sample was recrystallized four times from methanol-water to give white plates with m.p. 148.5-150 °C. A mixed melting point with a sample of photo-testosterone gave no depression. The v.p.c. retention times of the two samples were identical. The infrared spectrum and n.m.r. spectrum of photo-testosterone-d_5 (226) are reproduced in Figures 4 and 5 on pages 63 and 65 respectively. The mass spectrum of photo-testosterone-d_5 gave m/e peaks at 293 (53%, P^+), 292 (22%), 291 (4.6%), 290 (0.48%), 128 (100%), 127 (48%), 113 (65%) and 112 (30%). At 17 e.v. and below only m/e peaks at 112, 113 and those of the parent ion remain significant. The deuterium content was calculated to be d_5 = 65.4%, d_4 = 28.5% and d_3 = 6.1% in the same manner as described for testosterone-d_5.

Experimental for the Photochemistry of Progesterone (227)

Irradiation of progesterone (227) in tertiary butyl alcohol with 3000-3700 Å light

Progesterone (227, 8.00 g., 0.0253 mole) was dissolved in two liters of tertiary butyl alcohol in a two liter irradiation vessel. The solution was purged with nitrogen for 30 minutes, sealed and irradiated for a period of 24 hours using a Hanovia 550 watt medium pressure mercury arc in a water cooled Pyrex immersion jacket. After irradiation the solvent was removed under reduced pressure using a rotary evaporator. The residue was dissolved in 50 ml. of benzene and pipetted onto a 4.0 x 24 cm. column of Woelm activity II neutral alumina prepared by adding 10.5 ml. of water to 350 g. of alumina. Elution was begun with Skelly B and followed by v.p.c. The chromatographic scheme is presented below.

Compound	Solvent	Weight (g.)
forerun, photo #4 and progesterone	100 Skelly B, 50 Skelly B-50 benzene	3.229
photo #4 (231)	75 benzene-25 Skelly B	0.387
progesterone (227)	75 benzene-25 Skelly B	0.310
photo #5 (232)	95 benzene-b Skelly B, 100 benzene	0.880
7 unidentified products	90 benzene-10 ether	0.235
photo #1 (228)	90 benzene-10 ether, 75 benzene-25 ether	0.865
photo #2 (229)	75 benzene-25 ether 10 benzene-90 ether	0.634

photo #3 (230)	95 ether-5 benzene 50 ether-50 $CHCl_3$	0.424
column stripping and amorphous polymer	75 $CHCl_3$-25 ether 75 $CHCl_3$-25 methanol	1.118
	total	8.082

The combined fractions with a weight of 3.229 g. were dissolved in 30 ml. of benzene and pipetted onto a 2.0 x 29 cm. column of 90 g. of Florisil (60-100 mesh). Elution was begun using Skelly B and followed by v.p.c. The chromatographic scheme is presented below.

Compound	Solvent	Weight (g.)
waste	100 Skelly B, 100 benzene	0.140
photo #4 (231)	90 benzene-10 ether 75 benzene-25 ether	1.136
progesterone (227)	50 benzene-50 ether	1.116
column stripping	50 benzene-50 ether 75 $CHCl_3$-25 methanol	0.051
	total	2.443

The total yield of photoproducts is given below.

Compound	Weight (g.)	Yield (%)
progesterone (227)	1.426	17.8
photo #1 (228)	0.865	10.8
photo #2 (229)	0.634	7.9
photo #3 (230)	0.424	5.3

photo #4 (231)	1.523	19.0
photo #5 (232)	0.880	11.0
total	5.752	71.8

Recovered progesterone was identified by comparison of its infrared spectrum and v.p.c. retention time with that of an authentic sample.

Photo #1 (228) was recrystallized three times from acetone-hexane to give colorless plates with m.p. 197.5-199.5 °C and $[\alpha]_D^{27}$ = +134° (c = 1.83, $CHCl_3$). The ultraviolet spectrum gave $\lambda_{max}^{95\ EtOH}$ = 241 mμ (ε = 13,900). The infrared spectrum in KBr is shown in Figure 4 on page 63. The n.m.r. spectrum is reproduced in Figure 5 on page 65. The mass spectrum of photo #1 (228) at 70 e.v. gave peaks at m/e 314 (54%, P^+), 257 (63%) and 256 (100%). At 16 e.v. these three peaks remain as the only significant peaks in the spectrum.

Anal. Calc. for $C_{21}H_{30}O_2$: C, 80.21; H, 9.61. Found: C, 80.05: H, 9.42.

Photo #2 (229) was recrystallized twice from acetone-hexane to give white crystals with m.p. 254-256 °C and $[\alpha]_D^{27}$ = +93.4°, (c = 2.08, $CHCl_3$). The ultraviolet spectrum gave $\lambda_{max}^{95\ EtOH}$ = 212 mμ (ε = 5,250). The infrared spectrum is shown in Figure 4 on page 63 and the n.m.r. spectrum is reproduced in Figure 6 on page 79. The mass spectrum gave peaks at m/e 314 (18%, P^+), 257 (52%), 256 (35%), 123 (100%) and 109 (31%). At lower electron voltage the peak at m/e 123 falls in intensity at a faster rate than the m/e 109 peak. At 15 e.v. the peaks at 109 and 123 are small and

about equal and those at 314, 257 and 256 are the major peaks in the spectrum.

Anal. Calc. for $C_{21}H_{30}O_2$: C, 80.21; H, 9.61. Found: C, 80.41; H, 9.71.

Photo #3 (230) was recrystallized three times from hexane to give white crystals with m.p. 135-136.5 °C and $[\alpha]_D^{26}$ = +76.8, (c = 1.43, $CHCl_3$). The ultraviolet spectrum gave $\lambda_{max}^{95\ EtOH}$ = 232 mμ (ε = 17,600). The infrared and n.m.r. spectra are reproduced in Figures 7 and 8 on pages 85 and 87 respectively.

The mass spectrum of photo #3 gave m/e peaks at 314 (9.4%, P^+), 257 (16%), 256 (21%), 123 (100%) and 109 (8.0%). At low electron voltage the intensity of the m/e 123 peak drops sharply. At 15 e.v. both 109 and 123 are small and about equal and m/e 256, 257 and 314 are the only significant peaks in the spectrum.

Anal. Calc. for $C_{21}H_{30}O_2$: C, 80.21; H, 9.61. Found: C, 80.15; H, 9.62.

Photo #4 (231) was recrystallized three times from hexane to give white crystals with m.p. 122-123 °C with $[\alpha]_D^{26}$ = +147°, (c = 2.02, $CHCl_3$). The ultraviolet spectrum gave $\lambda_{max}^{95\ EtOH}$ = 205 mμ, ε = 6,380. The infrared spectrum in KBr is shown in Figure 4 on page 85 and that in chloroform in Figure 9 on page 95. The n.m.r. spectrum is reproduced in Figure 10 on page 97.

The mass spectrum of photo #4 gave peaks at m/e 314 (89%, P^+), 123 (59%) and 109 (100%). At 18 e.v. and below only m/e 314 and 109 remain significant.

Anal. Calc. for $C_{21}H_{30}O_2$: C, 80.21; H, 9.61. Found: C, 80.09; H, 9.64.

Photo #5 (232) resisted all attempts at crystallization. The ultraviolet spectrum gave $\lambda_{max}^{95\ EtOH}$ = 232 mμ. The infrared spectrum and n.m.r. spectrum are shown in Figures 9 and 11 on pages 95 and 100 respectively. The infrared and n.m.r. spectra of photo #5 isolated from the irradiation of progesterone are identical with those of photo #5 with m.p. 77-78 °C obtained by the oxidation of photo #2-A (241) of Δ^4-pregnen-20β-ol-3-one. The v.p.c. retention time and thin layer behavior on silica gel and alumina plates of the two samples were also identical.

Irradiation of progesterone (227) in tertiary butyl alcohol with 3660 Å light

Progesterone (227, 2.00 g., 0.00632 mole) was dissolved in 200 ml. of tertiary butyl alcohol in a one liter Pyrex Berzelius beaker. A Pyrex cooling jacket with a distance of about 1.8 cm. between its inner and outer walls was lowered into the beaker. A Hanovia 550 watt medium pressure mercury arc was placed in the inner chamber of the cooling jacket. A solution of saturated copper sulfate was circulated in the chamber between the lamp and the tertiary butyl alcohol solution. The saturated copper sulfate solution served as both a coolant and filter solution for isolation of the 3660 Å line of the mercury arc (127).

The solution was irradiated for a period of 70 hours with nitrogen purging the system during irradiation. After irradiation the solvent was

removed under reduced pressure by use of a rotary evaporator. The residue was dissolved in 20 ml. of benzene and pipetted onto a 2.5 x 30 cm. column of 80 g. of Florisil (60-100 mesh). Elution was begun with Skelly B and followed by v.p.c. The results of chromatography are presented below.

Compound	Solvent	Weight (g.)
forerun	100 Skelly B, 95 benzene-5 Skelly B	0.044
photo #4 (231)	100 benzene, 95 benzene-5 ether	0.472
photo #4, photo #5 (232) and progesterone	95 benzene-5 ether	0.102
photo #5 and progesterone	75 ether-25 benzene	0.558
photo #5 and polymer	100 ether	0.300
column stripping	100 ether, 80 $CHCl_3$-20 methanol	0.274
	total	1.750

The fractions of 0.102, 0.558 and 0.300 g. were combined, dissolved in 20 ml. of benzene and pipetted onto a 2.2 x 19 cm. column of Woelm activity II neutral alumina prepared by adding 2.3 ml. of water to 75 g. of alumina. Elution was begun with Skelly B and followed by v.p.c. The chromatographic scheme is given below.

Compound	Solvent	Weight (g.)
forerun	100 Skelly B, 95 benzene-5 Skelly B	0.030
progesterone	95 benzene-5 Skelly B	0.154
photo #4	100 benzene	0.033
photo #5	100 benzene, 90 benzene-10 ether	0.177
amorphous polymer	75 benzene-25 ether, 100 $CHCl_3$	0.152
column stripping	100 $CHCl_3$, 100 methanol	0.248
	total	0.794

The isolated yields of the photoproducts are presented below.

Compound	Weight (g.)	Yield (%)
progesterone	0.154	7.7
photo #4 (231)	0.505	25.3
photo #5 (232)	0.177	8.9
total	0.836	41.9

Recovered progesterone was identified by comparison of its infrared spectrum and v.p.c. retention time with that of an authentic sample.

Photo #4 (231) was recrystallized from methanol-water to give m.p. 120.5-122.5 °C. A mixed melting point with an authentic sample of photo #4 isolated from the broad arc irradiation of progesterone with m.p. 121-123 °C gave a mixed melting point of 120.5-122.5 °C or essentially no depression. The v.p.c. retention time of the two samples was identical. The infrared spectrum of the photo #4 isolated above was identical

with that of the authentic sample whose spectrum is shown in Figure 9 on page 95.

Photo #5 (232) resisted all attempts at crystallization. The photo #5 isolated above gave the same retention time on v.p.c. and thin layer plates of silica gel and alumina as the photo #5 isolated from the broad arc irradiation of progesterone. The n.m.r. and infrared spectra of the photo #5 isolated above were identical to those of the authentic material whose spectra are reproduced in Figures 9 and 11 on pages 95 and 100 respectively.

Irradiation of progesterone (227) in tertiary butyl alcohol with 3130 Å light

Progesterone (227, 1.5 g., 0.0047 mole) was dissolved in 200 ml. of tertiary butyl alcohol in a one liter Pyrex Berzelius beaker. The Pyrex cooling jacket used in this experiment was as described for the previous irradiation of progesterone at 3660 Å. A solution containing 46 g. of nickel sulfate hexahydrate and 14 g. of colbalt sulfate heptahydrate for each 100 ml. of water was pumped through the cooling jacket. This solution served as both the coolant and filtering solution which isolated the 3130 Å line of the mercury arc (127). The minimum thickness of the filter solution surrounding the lamp was 1.8 cm.

A Hanovia 550 watt medium pressure mercury arc was placed in the inner well of the cooling jacket and the solution was irradiated for 10 hours. Nitrogen was bubbled through the solution during irradiation. After irradiation the tertiary butyl alcohol was removed under reduced

pressure using a rotary evaporator. The residue was dissolved in 20 ml. of benzene and pipetted onto a 2.5 x 19 cm. column of Woelm activity II neutral alumina prepared by adding 2.5 ml. of water to 80 g. of alumina. The elution was begun with Skelly B and followed by v.p.c. The results of the column are given below.

Compound	Solvent	Weight (g.)	Yield (%)
forerun	100 Skelly B, 75 Skelly B-25 benzene	0.016	1
progesterone	50 Skelly B-50 benzene, 95 benzene-5 ether	0.872	58
amorphous polymer	90 benzene-10 ether	0.044	3
photo #1 (228)	90 benzene-10 ether, 50 benzene-50 ether	0.268	18
column stripping	75 ether-25 benzene 90 $CHCl_3$-10 methanol	0.206	14
	total	1.408	94

Progesterone was obtained in 58% yield and was identified by comparison of its v.p.c. retention time and infrared spectrum in chloroform with those of an authentic sample.

Photo #1 (228) was obtained in 18% yield. The compound was recrystallized twice from methanol-water and once from ether-pentane to give white crystals with m.p. 194-196 °C. An authentic sample of photo #1 from the broad arc irradiation of progesterone with m.p. 195-197 °C gave a mixed melting point of 194-196.5 °C or essentially no depression. The infrared spectrum of the photo #1 isolated above was identical to that of

authentic photo #1 whose spectrum in KBr is shown in Figure 4 on page 63. The v.p.c. retention times of the two samples were also identical.

Irradiation of progesterone (227) in tertiary butyl alcohol in the presence of dibenzothiophene

Progesterone (227, 1.95 g., 0.00622 mole) and dibenzothiophene (2.68 g., 0.0141 mole) with m.p. 98.5-99.0 °C were dissolved in 650 ml. of tertiary butyl alcohol. At 313 mμ dibenzothiophene has $\varepsilon = 2{,}080$ and progesterone has $\varepsilon = 88$. The solution is 0.00955 molar in progesterone and 0.0218 molar in dibenzothiophene. At 313 mμ the per cent of the light absorbed by dibenzothiophene is $(100)(0.0218)(2{,}080)/[(0.0218)(2{,}080) + (0.00955)(88)] = (100)(45.4)/(46.2) = 98.4\%$. At 360 mμ progesterone has $\varepsilon = 6$ and dibenzothiophene has $\varepsilon = 0.77$. The per cent of the light absorbed by dibenzothiophene at 360 mμ is $(100)(0.0218)(0.77)/[(0.0218)(0.77) + (0.00955)(6.0)] = (100)(0.0168)/(0.0741) = 22.6\%$ In this case dibenzothiophene acts as a photosensitizer below 360 mμ, but absorbs only 22% of the light above 360 mμ. The ability of dibenzothiophene to sensitize enone reactions has been shown with testosterone at 313 mμ on page 187. Above 360 mμ dibenzothiophene absorbs only 22.6% of the light and allows the enone reactions like those on page 182 to occur.

The solution was irradiated for 45 hours using a Hanovia 550 watt medium pressure mercury arc in a water cooled Pyrex jacket. Nitrogen was bubbled through the solution during irradiation. After irradiation the solvent was removed under reduced pressure using a rotary evaporator. The residue was dissolved in 30 ml. of benzene and pipetted onto a 2.9 x 31

cm. column of Woelm activity II neutral alumina prepared by adding 4.5 ml. of water to 150 g. of alumina. Elution was begun with Skelly B and followed by v.p.c. Dibenzothiophene (2.4 g.) was eluted immediately with Skelly B. The steroidal material was eluted as follows.

Compound	Solvent	Weight (g.)
forerun	100 Skelly B, 60 benzene-40 Skelly B	0.078
photo #4 (231) and progesterone	75 benzene-25 Skelly B	0.796
photo #4 and photo #5 (232)	10 Skelly B-90 benzene	0.656
column stripping	100 benzene, 100 $CHCl_3$	0.400
	total	1.930

The mixture of photo #4 and progesterone weighing 0.796 g. was dissolved in 20 ml. of benzene and pipetted onto a 2 x 19 cm. column of 32 g. of Florisil (60-100 mesh). Elution was begun with Skelly B and followed by v.p.c. The results of the column are given below.

Compound	Solvent	Weight (g.)
forerun	100 Skelly B, 100 benzene	0.090
photo #4	95 benzene-5 ether	0.412
progesterone	90 benzene-10 ether, 75 benzene-25 ether	0.276
	total	0.778

The mixture of photo #4 and photo #5 weighing 0.656 g. was dissolved in 20 ml. of benzene and pipetted onto a 2 x 19 cm. column of 32 g. of

Florisil (60-100 mesh). Elution was begun with Skelly B and followed by v.p.c. The chromatographic scheme is presented below.

Compound	Solvent	Weight (g.)
forerun	100 Skelly B, 10 Skelly B 90 benzene	0.010
photo #4	95 benzene-5 Skelly B	0.168
photo #5	100 benzene, 90 benzene-10 ether	0.470
column stripping	90 ether-10 $CHCl_3$, 100 $CHCl_3$	0.002
	total	0.650

The total yields were as follows.

Compound	Weight (g.)	Yield (%)
progesterone (227)	0.276	14.2
photo #4 (231)	0.580	29.8
photo #5 (232)	0.470	24.2
total	1.326	68.2

Recovered progesterone was identified by comparison of its v.p.c. retention time and infrared spectrum with that of authentic material.

Photo #4 (231) was recrystallized twice from methanol-water and once from ether-pentane to give white crystals with m.p. 120-122 °C. A mixed melting point with a sample of photo #4 from the broad arc irradiation of progesterone with m.p. 120-122 °C gave a mixed melting point which showed no depression. The infrared spectrum of the photo #4

isolated above was identical with that of an authentic sample whose spectrum is shown in Figure 9 on page 95. The v.p.c. retention times of the two samples were also identical.

Photo #5 (232) resisted all attempts at crystallization. Its v.p.c. retention time and thin layer movement on alumina and silica gel thin layer plates were identical to that of an authentic sample isolated from the broad arc irradiation of progesterone. The infrared spectrum and n.m.r. spectrum of the photo #5 isolated above were virtually identical to those of the authentic material whose spectra are shown in Figures 9 and 11 on pages 95 and 100 respectively.

The relative rate of the reaction here may be compared to that of progesterone irradiated at 3660 Å using a copper sulfate filtering solution which is described on page 197. In the irradiation of progesterone in the presence of dibenzothiophene, 45 hours were required for the formation of 29.8% of photo #4, 24.2% of photo #5 and 14.2% of recovered progesterone. In the irradiation of progesterone at 3660 Å using a copper sulfate filtering solution, 70 hours were required for the formation of 25.5% of photo #4, 9% of photo #5 and 8% of recovered starting material. Thus the reaction in the presence of dibenzothiophene appears to be somewhat cleaner and also gives a higher yield of rearranged products.

Irradiation of progesterone (227) in tertiary butyl alcohol at 2537 Å

Progesterone (227, 2.00 g., 0.00632 mole) was dissolved in 170 ml. of tertiary butyl alcohol in a quartz irradiation vessel, purged with

nitrogen for 15 minutes and sealed. The solution was irradiated for 138 hours using a low pressure mercury arc placed about 1 cm. from the quartz vessel. The solution was stirred magnetically during irradiation. After irradiation the solvent was removed under reduced pressure using a rotary evaporator. The residue was dissolved in 30 ml. of benzene and pipetted onto a 2.0 x 29 cm. column of 90 g. of Florisil (60-100) mesh. Elution was initiated with Skelly B and followed by v.p.c. The chromatographic scheme is presented below.

Compound	Solvent	Weight (g.)
forerun	100 Skelly B, 75 benzene-25 Skelly B	0.026
photo #4 (231)	100 benzene	0.500
photo #4, progesterone and photo #5	95 benzene-5, ether 75 benzene-25 ether	0.948
polymer	50 benzene-50 ether	0.340
column stripping	100 $CHCl_3$, 100 methanol	0.206
	total	2.020

The fractions of weight 0.948 g. and 0.340 g. were combined, dissolved in 20 ml. of benzene and pipetted onto a 2.5 x 24 cm. column of Woelm activity II neutral alumina prepared by the addition of 3.0 ml. of water to 100 g. of alumina. Elution was begun with Skelly B and followed by v.p.c. The chromatographic scheme is presented below.

Compound	Solvent	Weight (g.)
forerun	100 Skelly B, 75 benzene-25 Skelly B	0.026
progesterone	90 benzene-10 Skelly B	0.258
photo #5	95 benzene-5 Skelly B, 95 benzene-5 ether	0.269
photo #4	95 benzene-5 ether	0.081
polymer	90 benzene-10 ether, 100 ether	0.190
column stripping	100 $CHCl_3$	0.382
	total	1.206

The total yield of photo-products and recovered starting material is as follows.

Compound	Weight (g.)	Yield (%)
progesterone (227)	0.258	12.9
photo #4 (231)	0.581	29.1
photo #5 (232)	0.269	13.5
total	1.108	55.5

Recovered progesterone was identified by comparison of its v.p.c. retention time and infrared spectrum with that of an authentic sample.

Photo #4 (231) was recrystallized twice from methanol-water to give white crystals with m.p. 121-123 °C. A mixed melting point with an authentic sample of photo #4 melting at 121-123 °C gave no depression. The v.p.c. retention times of the two samples were identical. The infra-

red spectrum of the photo #4 isolated above was virtually identical to that of the authentic material whose spectrum is shown in Figure 9 on page 95.

Photo #5 (232) resisted all attempts at crystallization. The sample isolated above had the same v.p.c. retention time and rate of movement on thin layer plates of alumina and silica gel as those of an authentic sample. The infrared and n.m.r. spectra of the sample isolated above were virtually identical to those of the authentic material whose spectra are shown in Figures 9 and 11 on pages 95 and 100 respectively.

Irradiation of (20S)-20-hydroxy-10α-methyl-1β,5β-cyclo-18,20-cyclo-pregnan-2-one (229) in Pyrex

Photo #2 (229, 14 mg., 4.5 x 10^{-5} mole) was dissolved in 3 ml. of tertiary butyl alcohol in a Pyrex test tube, purged with nitrogen for 10 minutes and sealed. A similar tube was prepared using progesterone. The tubes were placed 0.5 cm. distant from a Hanovia 550 watt medium pressure mercury arc contained in a Pyrex water cooled jacket and were irradiated for a period of 5.5 hours.

After this time the extent of reaction was determined by v.p.c. analysis. Progesterone had reacted to an extent greater than 60% to yield the five usually formed photoproducts. Photo #2 (229) had decreased by about 35-40% but failed to give any trace of any other photoproduct. The infrared spectrum of photo #2 in chloroform after removal of the solvent was virtually identical to that of the authentic material.

Irradiation of (20S)-20 hydroxy-10α-methyl-1β,5β-cyclo-18,20-cyclo-pregnan-2-one (229) in quartz

Photo #2 (229, 14 mg., 4.5×10^{-5} mole) was dissolved in 3 ml. of nitrogen purged tertiary butyl alcohol in a quartz ultraviolet cell and sealed. A similar solution of progesterone was also prepared as a standard. The solutions were placed 0.5 cm. distant from a low pressure mercury arc and were irradiated for 9 hours. After this time the extent of reaction was determined by v.p.c. analysis. Progesterone had reacted to the extent of 60% to give the five usually formed photoproducts. Photo #2 had decreased in concentration by 20-25% but gave no trace of any other photoproduct by v.p.c.

The infrared spectrum in chloroform of photo #2 after removal of the solvent was virtually identical to that of an authentic sample.

Irradiation of 10α-methyl-1β,5β-cyclo-pregnan-2,20-dione (231) in the presence of benzophenone

Photo #4 (231, 14 mg., 4.5×10^{-5} mole) was dissolved in 3 ml. of nitrogen purged tertiary butyl alcohol in a Pyrex test tube and sealed. A similar tube was prepared by dissolving photo #4 (12 mg., 3.8×10^{-5} mole) and benzophenone (41.5 mg., 2.28×10^{-4} mole) in 3 ml. of nitrogen purged tertiary butyl alcohol in a Pyrex test tube. This tube was also sealed. The concentration of photo #4 in the tube containing benzophenone was 0.0127 molar and that of benzophenone was 0.076 molar. The extinction coefficient of benzophenone at 313 mμ is 130 and that of photo #4 is 25.6. At 313 mμ the per cent of the light absorbed by

benzophenone is (100)(0.076)(130)/[(0.076)(130) + (0.0127)(25.6)] = 96.5%. At 360 mμ the extinction coefficient of benzophenone is 61 and that of photo #4 is 4.9. The per cent of the light absorbed by benzophenone at 360 mμ is (100)(0.076)(61)/[(0.076)(61) + (0.0127)(4.9)] = 98.6%.

The solutions were placed about 0.5 cm. distant from a Hanovia 550 watt medium pressure mercury arc contained in a Pyrex water cooled jacket and irradiated for 5.5 hours.

After this time the solutions were subjected to v.p.c. analysis. The solution containing only photo #4 underwent photodecomposition to the extent of 40% but gave a ratio of photo #2 (229):photo #4 of 3:1. The tube containing benzophenone and photo #4 gave an extent of photodecomposition and ratio of photo #2:photo #4 which were essentially the same as those of the unsentized irradiation. Photo #2 (229) was the only observed photoproduct in both cases and resulted from reaction of the 20-keto group of photo #4.

Preparation of (20S)-20-hydroxy-3-benzylidene-10α-methyl-1β,5β-cyclo-18,20-cyclo-pregnan-2-one (235)

Photo #2 (229, 100 mg., 3.18×10^{-4} mole) was dissolved in 15 ml. of 1 N methanolic potassium hydroxide. To this solution was added 0.8 ml. of freshly distilled benzaldehyde. The mixture was sealed, shaken and let stand for 4 days. After this time the solution was diluted with 30 ml. of water and extracted with 3 x 50 ml. portions of ether. The ether extracts were combined, dried over anhydrous magnesium sulfate, filtered and the ether removed under reduced pressure using a rotary evaporator.

The residue was recrystallized from methanol-water to give 35 mg. (28%) of the monobenzylidene derivative 235 with m.p. 218-220 °C. Compound 235 gave a ultraviolet spectrum with $\lambda_{max}^{95\ EtOH}$ = 299 mμ (ε 24,900), 230 mμ (ε 9,800) and 224 mμ (ε 9,600). The infrared spectrum in KBr is shown in Figure 7 on page 85. The n.m.r. spectrum is reproduced in Figure 8 on page 87.

Anal. Calc. for $C_{28}H_{34}O_2$: C, 83.75; H, 8.52. Found: C, 83.70; H, 8.64.

Experimental for the Photochemistry of (20S)-20 Hydroxy-Δ^4-18,20-cyclo-pregnen-3-one (228)

Irradiation of Δ^5-pregnen-3β-ol-20-one (233)

Δ^5-Pregnen-3β-ol-20-one (233, 8.00 g., 0.0253 mole) was dissolved in two liters of tertiary butyl alcohol in a two liter Pyrex irradiation vessel, purged with nitrogen for 0.5 hour and sealed. The solution was irradiated using a Hanovia 550 watt medium pressure mercury arc contained in a water cooled Pyrex jacket. The cooling jacket was then immersed in the two liter irradiation vessel. The course of the irradiation was followed by v.p.c. The irradiation was terminated after 42 hours when no starting material could be detected by v.p.c.

The solvent was removed under reduced pressure using a rotary evaporator. The residue was dissolved in 30 ml. of chloroform and pipetted onto a 4.4 x 15 cm. column of Woelm activity III neutral alumina prepared by adding 12 ml. of water to 200 g. of alumina. Elution was begun with Skelly B and followed by v.p.c.

(20S)-3β,20-Dihydroxy-Δ^5-18,20 cyclo-pregnen (234) was eluted with solvent mixtures ranging from 60% Skelly B-40% benzene to 30% ether-70% benzene to give 4.88 g. (61%). Recrystallization three times from methanol-water gave 3.80 g. of 234 as white crystals with m.p. 224.5-225.5 °C. The infrared spectrum of 234 in nujol gave bands at 2.90 μ (hydroxyl) and 3.4-3.5 μ (carbon-hydrogen bonding). The melting point of 234 is in good agreement with the identical compound prepared in a similar manner by Jeger (Buchschacher et al., 95) with m.p. 224-225 °C. The n.m.r. spectrum of 234 is shown in Figure 6 on page 79.

Irradiation of Δ^5-pregnen-3β-ol-20-one (233) in the presence of dibenzothiophene

Δ^5-Pregnen-3β-ol-20-one (233, 15 mg., 4.8×10^{-5} mole) was added to each of two Pyrex test tubes. To one tube dibenzothiophene (20 mg., 1.10×10^{-4} mole) was also added. Tertiary butyl alcohol (5 ml.) was added to each tube. The tubes were purged with nitrogen for 5 minutes and sealed.

The solutions were 0.0095 molar in Δ^5-pregnen-3β-ol-20-one and the solution containing dibenzothiophene was 0.022 molar in dibenzothiophene. At 313 mμ the extinction coefficient of dibenzothiophene is 2,080 and that of 233 is 17.6. The per cent of the light absorbed by dibenzothiophene at 313 mμ is $(100)(0.022)(2,080)/[(0.022)(2,080) + (0.0095)(17.6)] = 99.5\%$. At 360 mμ the extinction coefficient of dibenzothiophene is 0.77 and that of 233 is 4.0. The per cent of the light absorbed by dibenzothiophene at 360 mμ is $(100)(0.022)(0.77)/[(0.022)(0.77) + (0.0095)(4.0)] = 30\%$.

The solutions were placed 0.5 cm. distant from a Pyrex water cooled jacket containing a Hanovia 550 watt medium pressure mercury arc. The solutions were irradiated for a period of three hours. After this time a v.p.c. analysis showed that the tube containing only 233 had reacted to give a 50-50 mixture of 233 and the cyclobutanol 234. The tube containing 233 plus dibenzothiophene showed no reaction by v.p.c. analysis.

The solvent was removed from the tube containing dibenzothiophene and 233 by use of a rotary evaporator. The residue was dissolved in 2 ml. of chloroform and towered through a column of 10 g. of Florisil (60-100 mesh). The dibenzothiophene was eluted with 100% benzene and 233 was eluted with 50% benzene-50% ether. The infrared spectrum of the recovered 233 in chloroform was virtually identical with that of an authentic sample. The reisolated Δ^5-pregnen-3β-ol-20-one (233) was recrystallized twice from methanol-water to give m.p. 187-188 °C. A mixed melting point with an authentic sample gave no depression.

Preparation of (20S)-20-hydroxy-Δ^4-18,20-cyclo-pregnen-3-one (228)

(20S)-3β,20-Dihydroxy-Δ^5-18,20-cyclo-pregnen (234, 4.00 g., 0.0127 mole) was dissolved in 350 ml. of sodium dried toluene and 48 ml. of freshly distilled cyclohexanone and placed in a 500 ml. 2-necked flask. The flask was equipped with a dropping funnel and a distilling head for downward distillation. To insure anhydrous conditions, 125 ml. of toluene was distilled from the mixture. A solution of 6.0 g. of aluminum isopropoxide in 70 ml. of toluene was added dropwise over a period of 45

minutes. After the addition, distillation was continued for an additional 45 minutes.

The contents of the flask were then split into two parts. A saturated solution of Rochelle Salt (40 ml.) was added to each portion and the solutions were subjected to steam distillation for 30 minutes. Each portion was then cooled and extracted with 4 x 125 ml. portions of chloroform. The chloroform extracts were combined, washed with 4 x 125 ml. portions of water, dried over anhydrous magnesium sulfate and filtered. The chloroform was removed under reduced pressure using a rotary evaporator.

The residue was dissolved in 30 ml. of benzene and chromatographed on a 2.5 x 23 cm. column of Woelm activity III neutral alumina prepared by adding 6 ml. of water to 100 g. of alumina. Elution with 50% benzene-50% ether gave (20S)-20-hydroxy-Δ^4-pregnen-3-one (228). The material was recrystallized from methanol-water to give 1.787 g. of material with m.p. 193-196 °C.

The first fractions from the column were combined and dissolved in benzene. The benzene solution was then pipetted onto a 2.5 x 23 cm. column of 100 g. of Woelm activity I neutral alumina. Compound 228 was eluted with 100% ether. Recrystallization from methanol-water gave 0.473 g. of material with m.p. 182-193 °C. The total yield of crystalline material was 2.26 g. or 56%.

A sample of 228 was recrystallized from acetone-hexane to give m.p. 197.5-199.5 °C. A mixed melting point with an authentic sample of photo

#1 (228) of progesterone, obtained from the broad arc irradiation of progesterone, gave no depression. The infrared spectrum of 228 prepared here was superimposable with that of an authentic sample whose spectrum is shown in Figure 4 on page 63.

Jeger (Buchschacher et al., 95) prepared the (20S)-epimer 228 and reported a melting point of 191-192 °C. The (20R)-epimer has also been prepared with a melting point of 186-187 °C (97). Yang and Yang (96) have also prepared the (20S)- and (20R)-epimers and reported melting points of 204-205 °C and 163-165 °C respectively.

Irradiation of (20S)-20-hydroxy-Δ^4-18,20-cyclo-pregnen-3-one (228) in tertiary butyl alcohol

Photo #1 (228, 2.5 g., 0.0079 mole) prepared by the oxidation of (20S)-3β,20-dihydroxy-Δ^5-18,20 cyclo-pregnen (234) was dissolved in 650 ml. of tertiary butyl alcohol in a Pyrex irradiation vessel. The solution was irradiated using a Hanovia 550 watt medium pressure mercury arc contained in a water cooled Pyrex immersion jacket. Nitrogen was bubbled through the solution during irradiation. The irradiation was stopped after 18 hours and the solvent was removed under reduced pressure using a rotary evaporator.

The residue was dissolved in 30 ml. of a 50-50 mixture of chloroform and benzene and pipetted onto a 2.5 x 30 cm. column of Woelm activicy II neutral alumina prepared by adding 4 ml. of water to 130 g. of alumina. Elution was begun using Skelly B and was followed by v.p.c. The chromatographic scheme is given below.

Compound	Solvent	Weight (g.)
forerun	100 Skelly B, 90 benzene-10 Skelly B	0.160
photo #1 (228)	90 benzene-10 ether	0.676
photo #2 (229)	90 benzene-10 ether	0.048
photo #2 and photo #3 (230)	75 benzene-25 ether, 100 $CHCl_3$	1.211
polymer and column stripping	50 $CHCl_3$-50 methanol	0.254
	total	2.349

The fractions containing photo #2 and photo #3 with a weight of 1.211 g. were dissolved in 10 ml. of chloroform and pipetted onto a 2.0 x 19.5 cm. column of 90 g. of Florisil (60-100 mesh). Elution was begun with Skelly B and was followed by v.p.c. The chromatographic scheme is given below.

Compound	Solvent	Weight (g.)
forerun	100 Skelly B, 90 benzene-10 Skelly B	0.061
photo #2	90 benzene-10 Skelly B, 95 benzene-5 ether	0.601
photo #3	90 benzene-10 ether, 50 benzene-50 ether	0.492
polymer	50 benzene-50 ether, 50 $CHCl_3$-50 methanol	0.060
	total	1.214

The total yield of photoproducts and recovered starting material is as follows.

Compound	Weight (g.)	Yield (%)
photo #1 (228)	0.676	27.0
photo #2 (229)	0.649	26.0
photo #3 (230)	0.492	19.7
total	1.817	72.7

Photo #1 was recrystallized from acetone-hexane to give white crystals with m.p. 197.5-199.5 °C. A mixed melting point with an authentic sample gave no depression. The infrared spectrum of the photo #1 isolated above in KBr was identical with that of an authentic sample whose spectrum is shown in Figure 4 on page 63.

Photo #2 (229) was recrystallized from acetone-hexane to give white crystals with m.p. 254-256 °C. A mixed melting point with an authentic sample of photo #2 isolated from the broad arc irradiation of progesterone gave no depression. The infrared spectrum of the photo #2 isolated above was virtually identical with that of an authentic sample whose spectrum is shown in Figure 4 on page 63.

Photo #3 (230) was recrystallized three times from hexane to give white crystals with m.p. 135-136.5 °C. A mixed melting point with an authentic sample of photo #3 isolated from the broad arc irradiation of progesterone gave no depression. The infrared spectrum of the photo #3 isolated above was virtually identical with that of an authentic

sample whose spectrum is shown in Figure 7 on page 85. The v.p.c. retention times of the two samples were also identical.

Experimental for the Photochemistry of Δ^4-Pregnen-20β-ol-3-one (238)

Preparation of 3-(N-pyrrolidinyl)-3,5-pregnadiene-20-one (237)

Progesterone (227, 8.0 g., 0.025 mole) was dissolved in 100 ml. of warm methanol. The solution was stirred with a magnetic stirrer and continually purged with nitrogen. To this solution 5 ml. of freshly distilled pyrrolidine was added. A yellow precipitate formed within one minute. Stirring was continued for one hour. After this time the solution was cooled in an ice bath and filtered to give 8.99 g. (96.2%) of the enamine 237.

The enamine 237 gave m.p. 172-175 °C with decomposition. Compound 237 gave a ultraviolet spectrum with $\lambda_{max}^{95\ EtOH}$ = 279 mμ. Literature values given for 237 are m.p. 170-175 °C with decomposition and $\lambda_{max}^{95\ EtOH}$ = 281 mμ (107). The infrared spectrum of 237 in KBr is reproduced in Figure 9 on page 95.

Preparation of Δ^4-pregnen-20β-ol-3-one (238)

3-(N-Pyrrolidinyl)-3,5-pregnadiene-20-one (237, 9.0 g., 0.025 mole) was dissolved in 100 ml. of benzene and added dropwise to a solution of 3.6 g. of lithium aluminum hydride in 480 ml. of anhydrous ether. After refluxing for 40 minutes, the solution was cooled to room

temperature and 30 ml. of ethyl acetate and 50 ml. of water were added cautiously to the solution. The mixture was concentrated at reduced pressure by use of a rotary evaporator. A solution of 11 g. of sodium acetate, 12 ml. of glacial acetic acid and 200 ml. of water was added to the concentrated solution. The resulting mixture was refluxed for two hours.

After this time the mixture was cooled to room temperature and 300 ml. of 2 N hydrochloric acid was added. The solution was cooled and extracted with 3 x 300 ml. portions of ether. The ether extracts were combined and concentrated to 500 ml. The ether solution was then washed with 3 x 300 ml. portions of water, 3 x 300 ml. portions of saturated sodium bicarbonate and 3 x 300 ml. portions of water. The ether extracts were then dried over anhydrous magnesium sulfate, filtered and the ether removed under reduced pressure by use of a rotary evaporator. After drying the crude yield was 7.6 g. or 98% of Δ^4-pregnen-20β-ol-3-one (238).

Several recrystallizations from ether-pentane gave white crystals with m.p. 171-175 °C. This compares with literature values of m.p. 171-172 °C (108) and 174-175 °C (128) for the β-alcohol and m.p. 161-162 °C (128) for the α-alcohol. The infrared spectrum of 238 is shown in Figure 12 on page 112.

Preparation of Δ^4-pregnen-20β-acetoxy-3-one (239)

Δ^4-Pregnen-20β-ol-3-one (238, 100 mg., 3.17×10^{-4} mole) was dissolved in 10 ml. of pyridine and 10 ml. of acetic anhydride and let stir overnight. The solution was then poured over crushed ice and

extracted with 4 x 100 ml. portions of benzene. The benzene extracts were combined and washed with 2 x 100 ml. portions of water, 3 x 100 ml. portions of 5% hydrochloric acid, 2 x 100 ml. portions of water, 3 x 100 ml. portions of saturated sodium bicarbonate and 3 x 100 ml. portions of water. The benzene extracts were dried over anhydrous magnesium sulfate, filtered and the benzene removed under reduced pressure by use of a rotary evaporator. The residue was recrystallized three times from ether-pentane to give 50 mg. (44%) of Δ^4-pregnen-20β-acetoxy-3-one (239) as white crystals with m.p. 156-159 °C. Literature values for the melting point of the β-acetate are 159-159.5 °C (108) and 161-162 °C (128) and for the α-acetate 138.5-139.5 °C (128). The infrared spectrum of 239 is shown in Figure 12 on page 112.

Oxidation of Δ^4-pregnen-20β-ol-3-one (238)

Δ^4-Pregnen-20β-ol-3-one (238, 100 mg., 3.17×10^{-4} mole) was dissolved in 10 ml. of acetone and cooled to ice bath temperature. An oxidizing solution was prepared by adding 2.68 g. of chromium trioxide to 5 ml. of water followed by 2.2 ml. of concentrated sulfuric acid. The total volume was brought to 10 ml. by the addition of more water. This solution was added dropwise to the acetone solution of 238. The addition was stopped when the reddish color of unreduced oxidizing solution persisted. The reaction was stirred for an additional 5 minutes and then added to 100 ml. of saturated potassium carbonate solution.

The potassium carbonate solution was extracted with 3 x 100 ml. portions of ether. The ether extracts were combined and washed with 2 x 75 ml. portions of water, dried over anhydrous magnesium sulfate, filtered and the ether removed under reduced pressure using a rotary evaporator.

The residue was recrystallized from ether-pentane to give 76 mg. (76%) of progesterone (227) as white crystals with m.p. 128-129.5 °C. A mixed melting point with an authentic sample of progesterone gave no depression. The infrared spectrum of the progesterone isolated above was taken in a KBr pellet and was identical to that of an authentic sample of progesterone.

Irradiation of Δ^4-pregnen-20β-ol-3-one (238) in tertiary butyl alcohol

Δ^4-Pregnen-20β-ol-3-one (238, 2.00 g., 0.00632 mole) was dissolved in 650 ml. of tertiary butyl alcohol. The solution was irradiated using a Hanovia 550 watt medium pressure mercury arc contained in a water cooled Pyrex immersion jacket. Nitrogen was bubbled through the solution during irradiation. The irradiation was stopped after 20 hours.

After irradiation the solvent was removed under reduced pressure using a rotary evaporator. The residue was dissolved in 30 ml. of benzene and pipetted onto a 2.5 x 27.5 cm. column of Woelm activity II neutral alumina prepared by adding 3.6 ml. of water to 120 g. of alumina. Elution was begun with Skelly B and followed by v.p.c. The chromatographic scheme is given below.

Compound	Solvent	Weight (g.)
forerun	100 Skelly B, 75 benzene-25 Skelly B	0.270
starting material (238)	100 benzene	0.031
starting material and photo #1-A (240)	90 benzene-10 ether	0.534
photo #1-A	75 benzene-25 ether	0.195
photo #2-A (241)	75 benzene-25 ether, 100 ether	0.420
column stripping and polymer	95 ether-5 $CHCl_3$, 100 methanol	0.407
	total	1.857

The fractions containing photo #1-A and starting material were combined, dissolved in 10 ml. of chloroform and pipetted onto a 2 x 9.7 cm. column of 30 g. of Florisil (60-100 mesh). Elution was begun with Skelly B and followed by v.p.c. The chromatographic scheme is given below.

Compound	Solvent	Weight (g.)
waste	100 Skelly B, 100 benzene	0.057
photo #1-A	95 benzene-5 ether, 90 benzene-10 ether	0.290
starting material	75 benzene-25 ether, 100 $CHCl_3$	0.174
	total	0.521

The yield of the photoproducts and starting material from all sources is given below.

Compound	Weight (g.)	Yield (%)
starting material (238)	0.205	10.2
photo #1-A (240)	0.485	24.2
photo #2-A (241)	0.420	21.0
total	1.110	55.4

Recovered Δ^4-pregnen-20β-ol-3-one (238) was identified by comparison of its infrared spectrum in chloroform and its v.p.c. retention time with that of an authentic sample.

Photo #1-A (240) was recrystallized from ether-pentane to give white crystals with m.p. 238-240 °C and $[\alpha]_D^{26}$ = +50.8° (c = 1.15, $CHCl_3$). The ultraviolet spectrum of photo #1-A gave $\lambda_{max}^{95\ EtOH}$ = 210 mμ (ε = 6,810). The infrared spectrum of photo #1-A is shown in Figure 12 on page 112 and the n.m.r. spectrum is reproduced in Figure 10 on page 97.

The mass spectrum of photo #1-A (240) gave m/e peaks at 316 (56%, P^+), 123 (56%) and 109 (100%). At 18 e.v. and below, only m/e peaks at 316 and 109 remain significant.

Anal. Calc. for $C_{21}H_{32}O_2$: C, 79.69; H, 10.19. Found: C, 79.44; H, 10.07.

Photo #2-A (241) was recrystallized from ether-pentane to give white plates with m.p. 174-177 °C and $[\alpha]_D^{26}$ = +34.9° (c = 1.61, $CHCl_3$). The ultraviolet spectrum of photo #2-A gave $\lambda_{max}^{95\ EtOH}$ = 232 mμ (ε = 19,400).

The infrared spectrum and n.m.r. spectrum are reproduced in Figures 13 and 14 on pages 114 and 116 respectively.

The mass spectrum of photo #2-A (241) gave m/e peaks at 316 (35%, P^+), 123 (100%) and 109 (52%). At 15 e.v. and below, only m/e peaks at 316 and 109 remain significant.

Anal. Calc. For $C_{21}H_{32}O_2$: C, 79.69; H, 10.19. Found: C, 79.70; H, 10.38.

Preparation of 3-benzylidene-10α-methyl-1β,5β-cyclopregnan-20β-hydroxy-2-one (242)

Photo #1-A (240, 100 mg., 3.17×10^{-4} mole) was dissolved in 15 ml. of 1 N methanolic potassium hydroxide. To this was added 0.7 ml. of freshly distilled benzaldehyde. The resulting solution was stoppered, shaken and let stand for seven days. After this time 20 ml. of distilled water was added dropwise to the solution with cooling. A slightly yellow precipitate formed and was collected by suction filtration. The solid was recrystallized twice from methanol-water to give 118 mg. (92%) of fine white needles of the mono-benzylidene derivative 242 with m.p. 206-207.5 °C. The ultraviolet spectrum of 242 gave $\lambda_{max}^{95\ EtOH}$ = 299 mμ (ε = 27,300), 230 mμ (ε = 10,700) and 224 mμ (ε = 10,500). The infrared and n.m.r. spectra of 242 are reproduced in Figures 13 and 14 on pages 114 and 116 respectively.

Anal. Calc. for $C_{28}H_{36}O_2$: C, 83.12; H, 8.97. Found: C, 82.98; H, 9.15.

Preparation of 10α-methyl-1β,5β-cyclopregnan-20β-acetoxy-2-one (244)

Photo #1-A (240, 100 mg., 3.17×10^{-4} mole) was dissolved in 10 ml. of pyridine and 7 ml. of acetic anhydride and let stir at room temperature for 2.5 hours. The solution was then poured over crushed ice and extracted with 3 x 60 ml. portions of benzene. The benzene extracts were combined and washed with 2 x 50 ml. portions of water, 2 x 50 ml. portions of 5% hydrochloric acid, 1 x 50 ml. portion of water, 2 x 50 ml. portions of 10% sodium carbonate and 2 x 50 ml. portions of water. The benzene extracts were dried over anhydrous magnesium sulfate, filtered and the benzene removed under reduced pressure using a rotary evaporator.

The remaining solid was recrystallized twice from hexane to give 63 mg. (56%) of the acetate 244 as white crystals with m.p. 147-148 °C. The ultraviolet spectrum gave $\lambda_{max}^{95\ EtOH} = 211$ mμ ($\varepsilon = 6{,}260$). The infrared spectrum in KBr is shown in Figure 13 on page 114.

Anal. Calc. for $C_{23}H_{34}O_3$: C, 77.09; H, 9.47. Found: C, 76.93; H, 9.34.

Preparation of 10α-methyl-1β,5β-cyclopregnan-2,20-dione (231)

Photo #1-A (240, 105 mg., 3.33×10^{-4} mole) was dissolved in 15 ml. of acetone and cooled to ice bath temperature. An oxidizing solution was prepared by adding 2.68 g. of chromium trioxide to 5 ml. of water followed by 2.2 ml. of concentrated sulfuric acid. The total volume was brought up to 10 ml. by the addition of sufficient water. This solution

was added dropwise to the cooled acetone solution of 240 until the reddish color of the unreduced oxidizing solution persisted. Stirring was continued for an additional 5 minutes. The acetone solution was then poured into 150 ml. of saturated potassium carbonate solution. The resulting mixture was extracted with 3 x 100 ml. portions of ether. The ether extracts were combined, washed with 2 x 100 ml. portions of water, dried over anhydrous magnesium sulfate, filtered and the ether removed under reduced pressure using a rotary evaporator.

The remaining solid was recrystallized twice from hexane to give 73 mg. (69%) of photo #4 (231) of progesterone as white crystals with m.p. 121-123 °C. A mixed melting point with an authentic sample of photo #4 gave no depression.

The v.p.c. retention time of the photo #4 isolated here was identical with that of an authentic sample. The infrared spectrum of photo #4 (231) obtained by the oxidation of photo #1-A was virtually identical with that of an authentic sample of photo #4 whose spectrum is shown in Figure 9 on page 95.

Preparation of 3β-(3-keto-1-cyclopenten-yl)-3β-5aβ-dimethyl-6β-acetyl-as-hydrindacene (232)

Photo #2-A (241, 150 mg., 4.76 x 10^{-4} mole) was dissolved in 12 ml. of acetone and cooled in an ice bath. An oxidizing solution was prepared by adding 2.68 g. of chromium trioxide to 5 ml. of water followed by 2.2 ml. of concentrated sulfuric acid. The total volume was brought up to 10 ml. by the addition of sufficient water. This solution was added

dropwise with stirring to the acetone solution of photo #2-A. Addition was discontinued when the reddish color of the unreduced oxidizing solution persisted. Stirring was continued for an additional 5 minutes.

The acetone solution was then added to 150 ml. of saturated potassium carbonate solution. The resulting solution was extracted with 5 x 100 ml. portions of ether. The ether extracts were combined, washed with 4 x 100 ml. portions of water, dried over anhydrous magnesium sulfate, filtered and the ether removed under reduced pressure using a rotary evaporator.

The remaining oil was crystallized from hexane to give 117 mg. (78%) of photo #5 (232) of progesterone as white crystals with m.p. 77-78 °C and $[\alpha]_D$ = +156° (c = 1.19, $CHCl_3$). The ultraviolet spectrum gave $\lambda_{max}^{95\ EtOH}$ = 232 mμ (ε = 19,000). The v.p.c. retention time and thin layer behavior on alumina and silica gel thin layer plates for the oxidation product of photo #2-A was identical to that of authentic photo #5 isolated from the broad arc irradiation of progesterone (227). The infrared spectrum in chloroform and the n.m.r. spectrum of the photo #5 prepared above were identical to those of the authentic material whose spectra are reproduced in Figures 9 and 11 on pages 95 and 100 respectively.

The mass spectrum of photo #5 (232) gave m/e peaks at 314 (64%, P^+), 123 (100%) and 109 (36%) at 70 e.v. At lower electron voltage the m/e 123 peak decreases in intensity very rapidly and at 15 e.v. the peaks at m/e 314 and 109 are the most significant peaks in the spectrum.

Anal. Calc. for $C_{21}H_{30}O_2$: C, 80.21; H, 9.61. Found: C, 80.24; H, 9.50.

Photochemistry of Δ^5-Pregnen-3β-acetoxy-20-one (245)

Irradiation of Δ^5-pregnen-3β-acetoxy-20-one (245) in methyl alcohol

Δ^5-Pregnen-3β-acetoxy-20-one (245, 1.00 g., 2.79×10^{-3} mole) was dissolved in 250 ml. of anhydrous methyl alcohol and irradiated for 5.5 hours using a Hanovia 550 watt medium pressure mercury arc contained in a Pyrex water cooled immersion jacket. Nitrogen was bubbled through the solution during irradiation. After irradiation the solvent was removed under reduced pressure by use of a rotary evaporator.

The remaining oil was dissolved in 30 ml. of benzene and pipetted onto a 2.0 x 16 cm. column of Woelm activity III neutral alumina prepared by adding 3 ml. of water to 50 g. of alumina. Elution was begun with Skelly B and was followed by v.p.c. and thin layer chromatography using alumina plates. The chromatographic scheme is presented below.

Compound	Solvent	Weight (g.)
photo A (246)	100 Skelly B	0.108
starting material	95 Skelly B-5 benzene	0.054
photo B (247)	95 Skelly B-5 benzene 90 Skelly B-10 benzene	0.396
photo C (248)	90 Skelly B-10 benzene	0.114
photo D (249)	75 Skelly B-25 benzene 50 Skelly B-50 benzene	0.317
column stripping	100 $CHCl_3$	0.040
	total	1.029

The yields of the various photoproducts are given below.

Compound	Weight (g.)	Yield (%)
photo A (246)	0.108	10.8
starting material	0.054	5.4
photo B (247)	0.396	39.6
photo C (248)	0.114	11.4
photo D (249)	0.317	31.7
total	0.989	98.9

Recovered Δ^5-pregnen-3β-acetoxy-20-one (245) was identified by comparison of its infrared spectrum in chloroform and its v.p.c. retention time with that of an authentic sample.

Photo A (246) was identified as a product of the type II cleavage of photo B (247) by comparison of its infrared and n.m.r. spectra with that of the identical compound (97) and similar compounds (95,96,97) in the literature. The infrared spectrum of photo A is shown in Figure 15 on page 128. The n.m.r. spectrum is reproduced in Figure 16 on page 130. Photo A gave only end absorption in the ultraviolet region. The purity of photo A was determined by v.p.c. and thin layer analysis on alumina.

Photo B (247) resisted all attempts at crystallization. The compound was found to be homogenous by v.p.c. and thin layer chromatography on alumina. The identity of photo B was established by comparison of its infrared and n.m.r. spectra with those of similar compounds found in the chemical literature (95,96,97). The infrared and n.m.r. spectra of photo

B (247) are reproduced in Figures 15 and 16 on pages 128 and 130 respectively.

Photo C (248) was recrystallized from ether-pentane to give fine needles with m.p. 139-140.5 °C and $[\alpha]_D^{27}$ = -32.6° (c = 1.66, $CHCl_3$). This compares with a literature value of m.p. 139-140 °C with $[\alpha]_D$ = -49° (c = 0.86, $CHCl_3$) (97). The infrared and n.m.r. spectra of photo C are in excellent agreement with those in the literature for the identical compound. The infrared and n.m.r. spectra of photo C (248) are reproduced in Figures 18 and 17 on pages 137 and 135 respectively.

The mass spectrum of photo C (248) at 70 e.v. gave m/e peaks at 298 (76%), 241 (28%) and 240 (100%). The parent ion at m/e 358 was less than 0.1% of the base peak.

Photo D (249) was recrystallized from ether-pentane to give white plates with m.p. 151-152 °C and $[\alpha]_D^{27}$ = -46.8° (c = 1.72, $CHCl_3$). This compares with a literature value of m.p. 145-146 °C with $[\alpha]_D$ = -51° (c = 0.78, $CHCl_3$) (95). The infrared and n.m.r. spectra of photo D are in excellent agreement with those given in the literature. The infrared and n.m.r. spectra of photo D (249) are reproduced in Figures 18 and 19 on pages 137 and 140 respectively.

The mass spectrum of photo D (249) at 70 e.v. gave m/e peaks at 298 (79%), 241 (28%) and 240 (100%). The parent ion at m/e 358 was less than 0.1% of the base peak of the spectrum.

Subsequent irradiations were carried out using the same volume of solvent and weight of starting material as for the methanol irradiation.

In these cases the oil remaining after solvent removal was chromatographed as for the methanol irradiation. The same solvent systems were employed and the products were eluted in the same order.

For subsequent irradiations, the starting material was identified by its v.p.c. retention time. Photo A was identified by its v.p.c. retention time and thin layer behavior on alumina. Photo B was identified by its v.p.c. retention time and by thin layer chromatography on alumina plates. Photo C and photo D were identified by their infrared spectra in chloroform and their thin layer chromatography behavior on alumina plates.

Irradiation of Δ^5-pregnen-3β-acetoxy-20-one (245) in 95% ethanol

Δ^5-Pregnen-3β-acetoxy-20-one (245, 1.00 g., 2.79×10^{-3} mole) was dissolved in 250 ml. of 95% ethanol and irradiated for 5.5 hours in the manner described for methanol on page 228. After removal of the solvent, the material was chromatographed as described for the methanol irradiation. The results are given below.

Compound	Fraction weight (g.)	Photoproduct (g.)	Yield (%)
photo A (246)	0.088	0.088	8.8
starting material	0.048	0.048	4.8
photo B (247)	0.322	0.322	32.2
photo C (248)	0.122	0.122	12.2
photo D (249)	0.335	0.335	33.5
column stripping	0.072	-	-
total	0.987	0.915	91.5

A second irradiation was performed under the identical conditions. The results are given below.

Compound	Fraction weight (g.)	Photoproduct (g.)	Yield (%)
photo A (246)	0.090	0.090	9.0
starting material	0.031	0.031	3.1
photo B (247)	0.288	0.288	28.8
photo C (248)	0.125	0.125	12.5
photo D (249)	0.349	0.349	34.9
column stripping	0.124	-	-
total	1.007	0.883	88.3

Irradiation of Δ^5-pregnen-3β-acetoxy-20-one (245) in absolute ethanol

Δ^5-Pregnen-3β-acetoxy-20-one (245, 1.00 g. 2.79×10^{-3} mole) was irradiated in 250 ml. of absolute ethanol for 5.5 hours in the manner described for methanol on page 228. After irradiation the solvent was removed and the material chromatographed as described for the methanol irradiation. The results are presented below.

Compound	Fraction weight (g.)	Photoproduct (g.)	Yield (%)
photo A (246)	0.172	0.172	17.2
starting material	0.020	0.020	2.0
photo B (247)	0.279	0.279	27.9
photo C (248)	0.120	0.120	12.0

photo D (249)	0.347	0.347	34.7
column stripping	0.091	-	-
total	1.029	0.938	93.8

Irradiation of Δ^5-pregnen-3β-acetoxy-20-one (245) in benzene

Δ^5-Pregnen-3β-acetoxy-20-one (245, 1.00 g., 2.79×10^{-3} mole) was dissolved in 250 ml. of benzene and irradiated for 11 hours in the manner described for methanol on page 228. After irradiation the solvent was removed and the residue chromatographed as in the methanol irradiation. The results are given below.

Compound	Fraction weight (g.)	Photoproduct (g.)	Yield (%)
photo A (246)	0.058	0.058	5.8
starting material	0.188	0.188	18.8
photo B (247)	0.118	0.118	11.8
photo C (248)	0.061	0.061	6.1
photo D (249)	0.193	0.193	19.3
column stripping	0.281	-	-
total	0.899	0.618	61.8

A second irradiation was performed. The solution was irradiated for a period of 15 hours. The solvent was then removed and the material chromatographed. The results are presented below.

Compound	Fraction weight (g.)	Photoproduct (g.)	Yield (%)
photo A (246)	0.080	0.080	8.0
starting material	0.171	0.171	17.1
photo B (247)	0.185	0.185	18.5
photo C (248)	0.054	0.054	5.4
photo D (249)	0.168	0.168	16.8
column stripping	0.310	-	-
total	0.968	0.658	65.8

Irradiation of Δ^5-pregnen-3β-acetoxy-20-one (245) in isopropyl alcohol

Δ^5-Pregnen-3β-acetoxy-20-one (245, 1.00 g., 2.79×10^{-3} mole) was dissolved in 250 ml. of isopropyl alcohol, irradiated for 5.5 hours and chromatographed after solvent removal in the manner described for methanol on page 228. The results are given below.

Compound	Fraction weight (g.)	Photoproduct (g.)	Yield (%)
photo A (246)	0.022	0.022	2.2
3 minor products	0.038	-	-
starting material	0.022	0.022	2.2
photo B (247)	0.111	0.111	11.1
photo C (248)	0.107	0.107	10.7
photo D (249)	0.389	0.389	38.9
column stripping	0.272	-	-
total	0.961	0.651	65.1

Irradiation of Δ^5-pregnen-3β-acetoxy-20-one (245) in dimethyl sulfoxide

Δ^5-Pregnen-3β-acetoxy-20-one (245, 1.00 g., 2.79×10^{-3} mole) was dissolved in 250 ml. of dimethyl sulfoxide and irradiated for 14 hours using the apparatus described for the methanol irradiation on page 228. After irradiation the mixture was diluted to 3 liters with water and split into two parts. Each part was extracted with 4 x 300 ml. portions of ether. The ether extracts were combined, washed with 5 x 200 ml. portions of water, dried over anhydrous magnesium sulfate, filtered and the ether removed under reduced pressure by use of a rotary evaporator. The mixture was examined by v.p.c. before and after extraction and showed no change in the ratios of the components present.

The residues from the two extractions were combined and chromatographed as described for the methanol irradiation. The results are given below.

Compound	Fraction weight (g.)	Photoproduct (g.)	Yield (%)
photo A (246)	0.065	0.065	6.5
3 minor products	0.020	-	-
starting material	0.125	0.125	12.5
photo B (247)	0.352	0.352	35.2
photo C (248)	0.073	0.073	7.3
photo D (249)	0.352	0.352	35.2
column stripping	0.071	-	-
total	1.058	0.967	96.7

Irradiation of Δ^5-pregnen-3β-acetoxy-20-one (245) in glacial acetic acid

Δ^5-Pregnen-3β-acetoxy-20-one (245, 1.00 g., 2.79×10^{-3} mole) was dissolved in 250 ml. of glacial acetic acid and irradiated for 11 hours using the apparatus described for the methanol irradiation on page 228.

After irradiation the solution was diluted to 3 liters with water and split into two parts. Each part was extracted with 4 x 300 ml. portions of ether. The ether extracts were combined and washed with 1 x 300 ml. portion of water, 2 x 200 ml. portions of 5% potassium carbonate and 3 x 200 ml. portions of water. The ether extracts from both parts were combined, dried over anhydrous magnesium sulfate, filtered and the ether removed under reduced pressure using a rotary evaporator. The residue remaining after extraction was examined by v.p.c. and was found to have the same composition as that of the mixture before extraction. The residue was then chromatographed in the manner described for the methanol irradiation on page 228. The results are presented below.

Compound	Fraction weight (g.)	Photoproduct (g.)	Yield (%)
photo A (246)	0.138	0.138	13.8
starting material	0.094	0.094	9.4
photo B (247)	0.395	0.395	39.5
photo C (248)	0.059	0.059	5.9
photo D (249)	0.306	0.306	30.6
column stripping	0.024	-	-
total	1.016	0.992	99.2

Irradiation of Δ^5-pregnen-3β-acetoxy-20-one (245) in pyridine

Δ^5-Pregnen-3β-acetoxy-20-one (245, 1.00 g., 2.79×10^{-3} mole) was dissolved in 250 ml. of pyridine and irradiated for 11 hours using the apparatus described on page 228 for the irradiation of 245 in methanol solution.

After irradiation the pyridine was removed under reduced pressure using a rotary evaporator. The residue was dissolved in 300 ml. of benzene and washed with 2 x 150 ml. portions of 5% hydrochloric acid followed by 2 x 150 ml. portions of water. The benzene extracts were dried over anhydrous magnesium sulfate and filtered. The benzene was removed under reduced pressure by use of a rotary evaporator. A v.p.c. analysis of the residue before and after extraction showed that no change in the concentrations of the various products had taken place. The material was then chromatographed in the same manner as previously described for the methanol irradiation on page 228. The results of the chromatography are given below.

Compound	Fraction weight (g.)	Photoproducts (g.)	Yield (%)
photo A (246)	0.059	0.059	5.9
starting material	0.209	0.209	20.9
photo B (247)	0.065	0.065	6.5
photo C (248)	0.066	0.066	6.6
photo D (249)	0.374	0.374	37.4
column stripping	0.213	-	-
total	0.986	0.773	77.3

Irradiation of Δ^5-pregnen-3β-acetoxy-20-one (245) in cyclohexane

Δ^5-Pregnen-3β-acetoxy-20-one (245, 1.00 g., 2.79×10^{-3} mole) was dissolved in 250 ml. of cyclohexane and irradiated for 11 hours using the same apparatus as was used in the methanol irradiation described on page 228. After irradiation the solvent was removed, and the residue was chromatographed in the same manner as described for the methanol irradiation. The results are presented below.

Compound	Fraction weight (g.)	Photoproduct (g.)	Yield (%)
photo A (246)	0.147	0.147	14.7
3 minor products	0.056	-	-
starting material	0.052	0.052	5.2
5 minor products	0.041	-	-
photo B (247)	0.182	0.182	18.2
photo C (248)	0.048	0.048	4.8
photo D (249)	0.362	0.362	36.2
column stripping	0.170	-	-
total	1.058	0.791	79.1

A second run was also made in cyclohexane. An irradiation vessel of slightly different dimensions was used which shortened the time of irradiation to 8 hours. The solvent was removed and the material was chromatographed as above. The results are given below.

Compound	Fraction weight (g.)	Photoproduct (g.)	Yield (%)
photo A (246)	0.154	0.154	15.4
3 minor products	0.043	0	-
starting material	0.044	0.044	4.4
5 minor products	0.041	-	-
photo B (247)	0.213	0.213	21.3
photo C (248)	0.060	0.060	6.0
photo D (249)	0.423	0.423	42.3
column stripping	0.053	-	-
total	1.031	0.894	89.4

Irradiation of Δ^5-pregnen-3β-acetoxy-20-one (245) in tertiary butyl alcohol

Δ^5-Pregnen-3β-acetoxy-20-one (245, 1.00 g., 2.79×10^{-3} mole) was dissolved in 250 ml. of tertiary butyl alcohol and irradiated for 5.5 hours in the same apparatus as was used in the methanol irradiation described on page 228. After irradiation the solvent was removed, and the residue was chromatographed in the manner described for the methanol irradiation. The results are given below.

Compound	Fraction weight (g.)	Photoproduct (g.)	Yield (%)
photo A (246)	0.022	0.022	2.2
4 minor products	0.040	-	-
starting material	0.024	0.024	2.4
photo B (247)	0.102	0.102	10.2

photo C (248)	0.055	0.055	5.5
photo D (249)	0.444	0.444	44.4
column stripping	0.326	-	-
total	1.013	0.647	64.7

Irradiation of 3β-acetoxy-20-keto-$\Delta^{5;13(18)}$-13,17-seco-pregnadiene (247) in methyl alcohol

Photo B (247, 40 mg., 1.1 x 10^{-5} mole) was dissolved in 10 ml. of methyl alcohol in a Pyrex test tube. A similar solution of Δ^{5}-pregnen-3β-acetoxy-20-one (245, 40 mg., 1.1 x 10^{-5} mole) was also prepared in 10 ml. of methyl alcohol in a Pyrex test tube. The tubes were purged with nitrogen for 10 minutes, sealed and placed in a holder which was 0.5 cm. distant from a water cooled Pyrex jacket containing a Hanovia 550 watt medium pressure mercury arc. The solutions were irradiated for 2.5 hours. After this time the tubes were subjected to v.p.c. analysis.

The tube containing Δ^{5}-pregnen-3β-acetoxy-20-one showed 65-70% conversion to the products photo A, photo B, photo C and photo D. The tube containing photo B (247) gave photo A (246) or (-)-β-vinyl-2-methylene-4bβ-methyl-7β-acetoxy-Δ^{8a}-4aα,10αβ-dodecahydro-phenanthren as the only observed product in 30-35% yield.

Irradiation of (20R)-3β-acetoxy-20-hydroxy-Δ^{5}-18,20-cyclo-pregnene (248) in methyl alcohol

Photo C (248, 40 mg., 1.1 x 10^{-5} mole) was dissolved in 10 ml. of methyl alcohol in a Pyrex test tube. The solution was purged with nitrogen for 10 minutes and sealed. The solution was placed 0.5 cm.

distant from a water cooled Pyrex jacket containing a Hanovia 550 watt medium pressure mercury arc and irradiated for a period of 2.5 hours.

After irradiation v.p.c. analysis indicated that no change had taken place. The solvent was removed under reduced pressure by use of a rotary evaporator. The infrared spectrum of the recovered photo C was virtually identical to that of an authentic sample whose spectrum is shown in Figure 18 on page 137. The n.m.r. spectrum of the recovered material was taken in carbon tetrachloride and was virtually identical with that of an authentic sample whose spectrum is shown in Figure 17 on page 135.

Photo C (248) was recrystallized from ether-pentane to give 28 mg. of white crystals with m.p. 139-140.5 °C. A mixed melting point with an authentic sample of photo C (248) gave no depression.

Irradiation of (20S)-3β-acetoxy-20-hydroxy-Δ^5-18,20-cyclo-pregnene (249) in methyl alcohol

Photo D (249, 40 mg., 1.1×10^{-5} mole) was dissolved in 10 ml. of methyl alcohol in a Pyrex test tube. The solution was purged with nitrogen for 10 minutes and sealed. The tube was placed 0.5 cm. distant from a Pyrex water cooled jacket containing a Hanovia 550 watt medium pressure mercury arc and was irradiated for a period of 2.5 hours. After irradiation a v.p.c. analysis indicated that no change had taken place.

The solvent was removed under reduced pressure by use of a rotary evaporator. The infrared spectrum of the recovered photo D in chloroform

was virtually identical to that of an authentic sample whose spectrum is shown in Figure 18 on page 137.

The n.m.r. spectrum of the recovered photo D in carbon tetrachloride was also virtually identical with that of an authentic sample whose spectrum is reproduced in Figure 19 on page 140.

Photo D (249) was recrystallized from ether-pentane to give 30 mg. of white crystals with m.p. 150-152 °C. A mixed melting point with an authentic sample of photo D with m.p. 151-152 °C gave a mixed melting point of 150-152 °C or essentially no depression.

Preparation of 3β-hydroxy-20-keto-$\Delta^{5;13(18)}$-13,17-seco-pregnadiene (250)

Photo B (247, 150 mg., 4.20×10^{-5} mole) was dissolved in 30 ml. of 1 N methanolic potassium hydroxide and refluxed for 5 hours. After this time the mixture was cooled and diluted to 150 ml. with distilled water. The solution was extracted with 3 x 50 ml. portions of ether. The ether extracts were combined and washed with 2 x 50 ml. portions of distilled water, dried over anhydrous magnesium sulfate, filtered and the ether removed under reduced pressure by use of a rotary evaporator.

The residue was dissolved in 10 ml. of benzene and towered through a 1.0 x 10 cm. column of 20 g. of Florisil (60-100 mesh). Elution with benzene gave 92 mg. (68%) of 3β-hydroxy-20-keto-$\Delta^{5;13(18)}$-13,17-seco-pregnadiene (250) as an oil which resisted recrystallization. The purity of the material was checked by v.p.c.

The infrared spectrum of 250 is shown in Figure 15 on page 128. The n.m.r. spectrum of 250 is reproduced in Figure 17 on page 137.

SUMMARY

The mass spectral fragmentation patterns of the two major photoproducts resulting from the irradiation of Δ^4-3-keto steroids were studied. In the case of testosterone (177), the source of the fragments from the 2-bicyclo[3.1.0]hexanone 178 and the 3-substituted 2-cyclopentenone 179 were confirmed by the study of the photoproducts resulting from the irradiation of testosterone-2,2,4,6,6-d_5 (224).

The photochemical reactions of various Δ^4-3-keto steroids were studied in tertiary butyl alcohol solution using 2537 Å light, 3130 Å light and 3660 Å light. It was found that the photochemical rearrangements to 2-bicyclo[3.1.0]hexanones and 3-substituted 2-cyclopentenones proceed well at these wave lengths.

It was found that at 2537 Å and 3660 Å saturated ketones are essentially unreactive. Using 3130 Å light it was found that the saturated 20-keto group of progesterone (227) could be made to undergo reaction at a rate which was greater than that of the Δ^4-3-keto chromaphore. This selectivity is apparently the result of the greater extinction coefficient and efficiency of reaction of the 20-keto group in comparison with the Δ^4-3-keto chromaphore in this wavelength region.

The irradiation of Δ^5-pregnen-3β-acetoxy-20-one (245) was found to yield four photoproducts. One of the products was a keto-olefin which was isomeric with the starting material. The keto-olefin 247 was converted to a diene 246 on further irradiation. This pathway was the result of a type II cleavage reaction of 247. The other two products

resulting from the irradiation of (245) were found to be epimeric cyclobutanols which resulted from photochemical ring closure involving the C-18 methyl group and the 20-keto group of the ketone 245.

A novel solvent effect was observed in the ring closure reaction yielding cyclobutanols. This effect was studied using a variety of solvents. The results indicated that the preference for the formation of the (20S)-isomer 249 over the (20R)-isomer 248 could be increased significantly by the appropriate choice of solvent. The effect was interpreted as being due to the selective solvation of a diradical intermediate produced in the reaction.

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ACKNOWLEDGMENTS

The author wishes to thank his parents for their encouragement and patience throughout the course of his education. He especially wishes to thank his mother for the many sacrifices she made, which enabled him to continue his education after the death of his father.

The author wishes to acknowledge and thank Dr. O. L. Chapman for his guidance, encouragement and patience during the course of this investigation. The author would also like to acknowledge Dr. W. C. Wildman, Dr. R. W. King and Dr. T. H. Kinstle for giving freely of their time in discussing various parts of this work. The author also acknowledges the graduate students of the organic division for their assistance and patience during many discussions.

The author acknowledges the National Science Foundation for support from June, 1964 to June, 1966, and the Procter and Gamble Company for a summer fellowship from June to September, 1966.