Remote Oxidation of Steroids by Photolysis of Attached Benzophenone Groups[1a,b]

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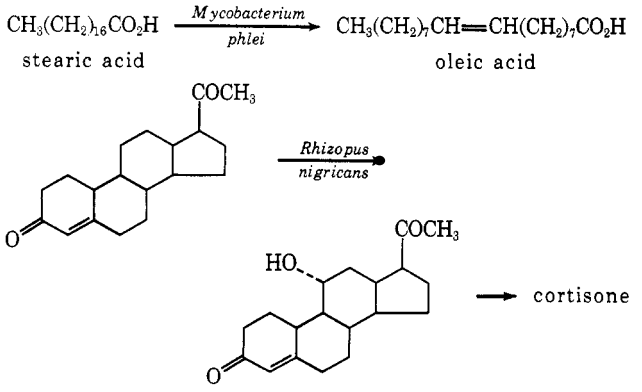
Abstract: Steroid esters of benzophenonecarboxylic acids, benzophenoneacetic acids, and homologs are prepared. Circular dichroism studies indicate that in some of these compounds the benzophenone chromophore can pack on the steroid; these data and phosphorescence lifetime data are interpretable in terms of conformation predicted from molecular models. On irradiation, various of these esters undergo intramolecular attack by the attached benzophenone on the steroid hydrogens. The products can be predicted from molecular models, and considerable control of steroid functionalization can be achieved by appropriate choice of reagent. Controls establish that this photochemistry is directed mainly by the geometry of the ester. Starting with 3α-cholestanol, appropriate esters can direct a photochemical dehydrogenation exclusively into ring D, at the opposite end of the molecule, leading to useful remote functionalization.

Much attention has recently been focused on the attempt to understand enzymatic reactions in simple chemical terms. The major effort has been concerned with explaining the extraordinarily high rates of enzyme-catalyzed processes, and duplicating such rates with chemical model systems. However, in many respects the high rates of enzymatic reactions are not their most interesting feature in terms of organic synthesis. Enzymes are able to carry out some remarkably selective reactions, *e.g.*, the selective dehydrogenation of stearic acid to oleic acid, and this kind of selectivity is of greater practical interest. Thus, currently industrial chemists carry out ester hydrolysis with normal chemical means, even though enzymatic hydrolyses are much faster under mild conditions, because the more brutal conditions required for chemical hydrolysis do not, in fact, represent a real problem. However, in the manufacture of corticosteroids industrially the oxygen atom in ring C is commonly introduced by a microbiological fermentation. The high selectivity of enzymatic processes makes this a very efficient and selective oxidation of an otherwise unactivated position in the steroid, and chemists cannot replace this enzymatic process by simple resort to more brutal chemical conditions.



Interestingly, although the kind of selectivity exemplified above is really of greater practical interest to synthetic chemists than would be a duplication of catalytic hydrolysis rates, it also should be more accessible. Only when model systems achieve catalysis by factors of the order of 10^{10} do they begin to be interesting as models for enzymatic hydrolysis, but no such factors are required in models for selectivity. If a random chemical reaction could simply be accelerated at a particular atom by a factor of 10^2, the resulting selective attack on that atom could be highly practical. Accelerations by factors as large as 10^{10} seem to be difficult to achieve in model systems, but modest accelerations of 10^2 or greater are commonly attainable by simple proximity effects. It thus occurred to us some time ago that the field of model enzyme studies had already reached a sophistication at which it should be possible to achieve chemically useful selectivity by imposing orientation on some otherwise unselective functionalization reactions.

Of course, proximity effects have been observed in the past to lead to selective attack on unactivated and otherwise unreactive chemical positions. Such processes as the Barton reaction,[2] the Loeffler–Freytag reaction,[3] the Yang photolysis,[4] the Heusler reaction,[5] and a variety of relatives all involve the production of a reactive heteroatom radical in a molecule which then, by intramolecular attack on a hydrogen atom located six atoms away, initiates functionalization of a position which is not chemically activated in the usual sense.

Such processes have proven to be eminently practical in organic synthesis, but they do not really illustrate the type of thing we want. A functional group within the substrate is, in fact, used to attack a particular atom; while it does not "activate" that atom in the normal electronic sense, there is still the restriction that only positions with a certain close relationship to the functional group can be attacked. Furthermore, the attack occurs from within the molecule, rather than by

(1) (a) Support of this work by the National Institutes of Health is gratefully acknowledged. (b) The phosphorescence lifetimes were determined with the kind assistance of Professor N. Turro, using an apparatus constructed by him. (c) NIH Postdoctoral Fellow, 1969–1970. (d) NIH Postdoctoral Fellow, 1970–1972. (e) NIH Predoctoral Fellow, 1968–1971.

(2) M. Akhtar, *Advan. Photochem.*, **2**, 263 (1964).
(3) K. Loeffler and C. Freytag, *Ber.*, **42**, 3427 (1909).
(4) N. C. Yang and D. D. H. Yang, *J. Amer. Chem. Soc.*, **80**, 2913 (1958).
(5) K. Heusler and J. Kalvoda, *Angew. Chem., Int. Ed. Engl.*, **3**, 525 (1964).

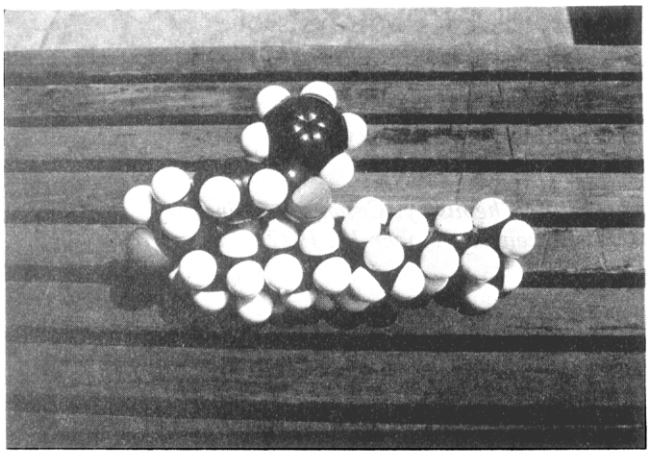


Figure 1. A molecular model of the benzophenone-4-propionic acid ester of 3α-cholestanol (Ic), showing the accessibility of steroid hydrogens to the ketonic oxygen.

an external oriented reagent such as the enzyme. Finally, the distances over which attack can occur are small. It would not be possible, for instance, to use this type of intramolecular process to introduce a functional group at carbon 11 of a steroid utilizing any of the commonly available functional groups, such as oxygen atoms at position 3 or on the side chain at position 17.

However, there is no special reason that an intramolecular process need operate over a six-membered ring. The critical point in determining the probability of attack is the number of degrees of freedom which must be frozen out. While this is favorable in the case of a small ring, such as a six-membered ring, it is also possible to have a favorable entropy term over much larger ring sizes if large sections of the ring are rigid and do not require loss of freedom in the transition state. Thus, it seemed to us that it should be possible to carry out directed attack on a particular atom within a molecule or complex even if the formal ring size is very large, provided the reagent and substrate are rigid so that the process is not hopelessly improbable.

We thus define as "remote oxidation" a process in which we attach a rigid reagent to a substrate and then carry out a directed functionalization of that substrate at a relatively large distance from the point of attachment. For instance, if the reagent is attached to an oxygen at C-3 in ring A of a steroid, directed attack on hydrogens as far away as those on C-9, 14, or 17 at the opposite end of the molecule certainly qualify as being remote oxidations.

The reagents which we have explored in the most detail are derivatives of benzophenone[6a,b] which carry carboxyl groups so that they can be attached to steroidal alcohols as temporary esters. On irradiation the benzophenone is excited to its triplet state, whose oxygen atom is capable of attacking unactivated C–H bonds. A disadvantage of this choice is that the benzophenone triplet has some chemical preference for attacking tertiary hydrogens rather than secondary;[7] thus geometry is not the only determinant of the position of attack, as we would have preferred. The use of a direct photolytic reaction, whose quantum yield must be less than 1, may also not be completely practical for serious synthetic applications. Furthermore, the decision to attach the reagent to the substrate, rather than simply complex it, removes some generality from the scheme. Subsequent to our exploration of the use of an attached benzophenone, we have in fact been able to generalize our chemistry to the use of complexing,[8] rather than attachment, of reagent and substrate and also to the use of free-radical processes[9] which do not proceed with low quantum yields. These will be described in future publications.

Although the current work was designed with functionalization of steroids in mind, and rigid steroids are most suitable for this kind of process, it was first explored and reported using flexible substrates.[10] These introduce a number of special difficulties in that the coiling of substrates such as 1-octadecanol introduces some randomness in both the initially attacked position and also in the subsequent chemistry. With steroids, these problems are diminished.

The substrates examined were 3α-cholestanol, 5α-androstan-17β-ol, and 5β-cholan-24-ol. 3β-Cholestanol and 3α-coprostanol (AB cis) were also examined, but did not undergo remote oxidation (*vide infra*). As reagents we utilized benzophenone-4-carboxylic acid, benzophenone-4-acetic acid, benzophenone-4-propionic acid, and benzophenone-4-pentanoic acid. In the meta series benzophenone-3-carboxylic acid and benzophenone-3-acetic acid were examined, and the ortho derivatives benzophenone-2-carboxylic acid and benzophenone-2-acetic acid were also explored. With androstan-17β-ol, benzophenone-4-hexanoic acid was used.

Models show that certain combinations of these substrates and reagents would be expected to lead to selective oxidations. Thus, as Figure 1 shows, a model of the benzophenone-4-propionic acid ester of 3α-cholestanol can pack in such a way that the carbonyl oxygen of the benzophenone is in contact with axial hydrogens of the steroid. In particular, this model shows that carbonyl oxygen can swing in an arc which allows it to contact hydrogens of C-12, -14, and -7. On this basis, one might expect that these hydrogens could be attacked if the material were activated by light. By contrast, in the benzophenone-4-carboxylic acid ester of 3α-cholestanol the rigid reagent and rigid substrate form a V (Figure 2) in which it is expected that the carbonyl oxygen could not reach and attack substrate hydrogens intramolecularly.

The intermediate case, the benzophenone-4-acetic acid ester of 3α-cholestanol, does permit the carbonyl oxygen to reach the steroid, but the reagent and substrate are not parallel as in the propionic ester derivative. With four methylene groups, the benzophenone-4-pentanoic ester of 3α-cholestanol, the reagent and substrate can be parallel, but now the carbonyl group of the benzophenone is moved up into ring D where it can contact hydrogens on C-14 and C-17.

Esters of 3β-cholestanol do not pack well in models. The 3β position is of course equatorial, so the reagent and substrate start off in an extended relationship, and

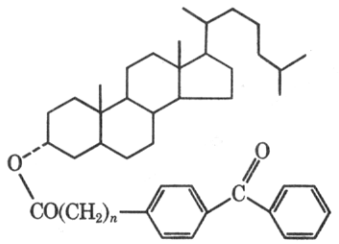
(6) (a) R. Breslow and S. W. Baldwin, *J. Amer. Chem. Soc.*, **92**, 732 (1970); (b) R. Breslow and P. Kalicky, *ibid.*, **93**, 3540 (1971).

(7) C. Walling and M. Gibian, *J. Amer. Chem. Soc.*, **87**, 3361 (1965).

(8) R. Breslow and P. C. Scholl, *J. Amer. Chem. Soc.*, **93**, 2331 (1971).

(9) R. Breslow, J. A. Dale, P. Kalicky, S. Y. Liu, and W. N. Washburn, *J. Amer. Chem. Soc.*, **94**, 3276 (1972), and subsequent unpublished work involving attached reagents.

(10) R. Breslow and M. Winnik, *J. Amer. Chem. Soc.*, **91**, 3083 (1969).



I

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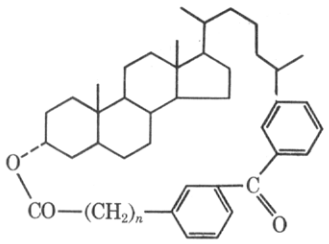

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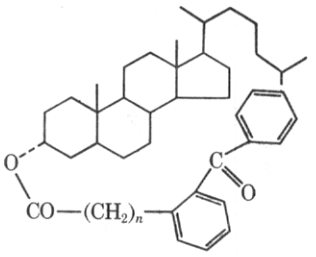

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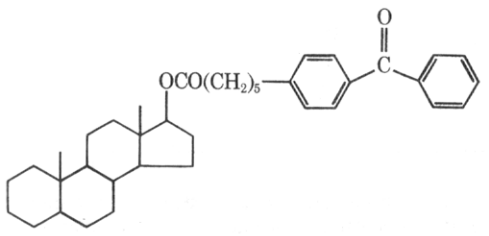
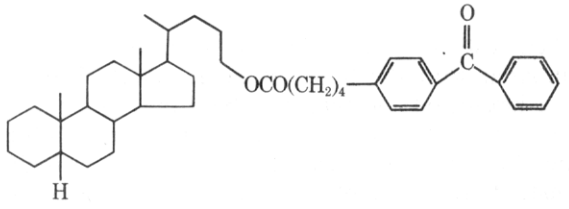


IV



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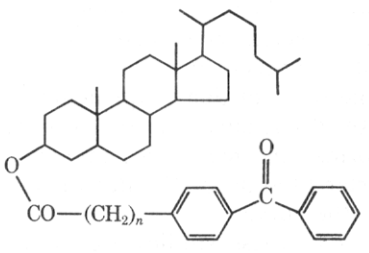

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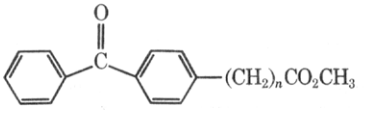

VII

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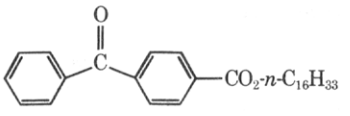


VIII

considerable curling of the reagent is required to bring it under the substrate (models and our results suggest

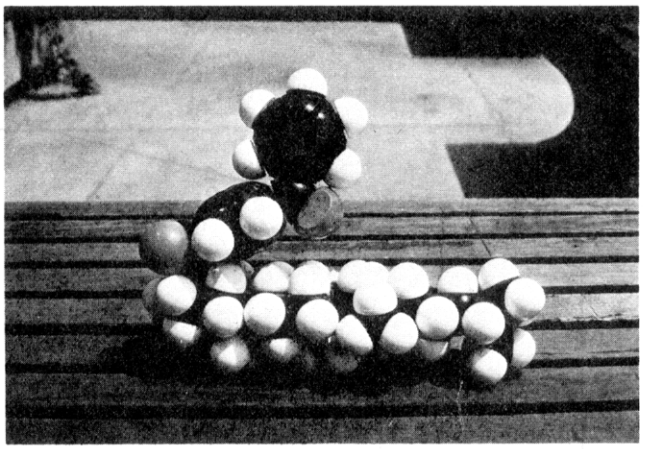


Figure 2. A molecular model of the benzophenone-4-carboxylic acid ester of 3α-cholestanol (Ia), which indicates the reason that Ia does not undergo intramolecular photochemical reactions and shows only weak circular dichroism.

that attack does not occur easily on the top of the steroid, since the angular methyl groups at C-10 and C-13 tend to introduce steric repulsions to close approach on the β side). Although a model suggests that the benzophenone-4-pentanoic ester of 3β-cholestanol could curl so as to permit attack on the α side of the steroid, such a process is apparently improbable and we have no direct evidence for it.

Physical Studies

Some evidence on the packing of the steroid esters of our benzophenone derivatives comes from circular dichroism studies. The benzophenone chromophore is not chiral, but it can develop circular dichroism when it is attached to the chiral steroid. The CD spectra of various of our steroid esters were determined at the n,π^* transition wavelength for the benzophenone, and the results are listed in Table I. Intermolecular controls, with mixtures of unattached steroids and benzophenones, showed no CD in the 300–380-nm region. It is

Table I. CD Spectra of Esters (Room Temperature, 10^{-3} *M*)

Ester	Solvent	$\Delta\epsilon \pm 10\%$	λ_{max} (nm) $\pm$ 3 nm
Ia	Benzene	+0.030	347
	Acetonitrile	+0.058	345
	Methanol	+0.054[a]	340
Ib	Benzene	+0.106	345
	Hexane	+0.120	347
	Acetonitrile	+0.202	345
	Methanol	+0.224[a]	340
Ic	Benzene	+0.127	347
	Hexane	+0.180	347
	Carbon tetrachloride	+0.202	344
	Acetonitrile	+0.257	342
	Methanol	+0.267[a]	344
Id	Benzene	0 ± 0.020	
	Hexane	0 ± 0.020	
	Acetonitrile	−0.242	342
	Methanol	−0.220[a]	345
VIa	Benzene	+0.041	347
	Acetonitrile	+0.030	345
VIc	Benzene	0 ± 0.020	
	Acetonitrile	0 ± 0.020	
	Methanol	0 ± 0.020[a]	

[a] Saturated solution (about 5×10^{-4} *M*).

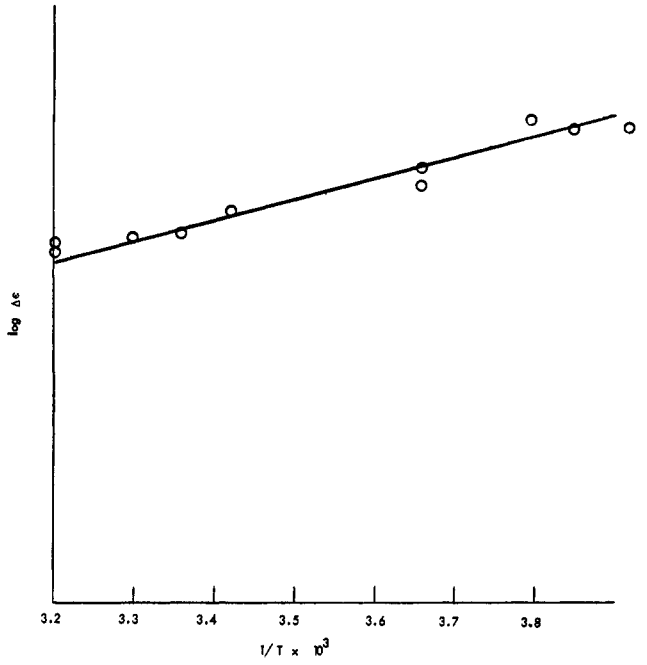


Figure 3. The variation of the circular dichroism of Ic in acetonitrile with temperature.

undoubtedly significant that ester Ia, which cannot pack onto the steroid according to our models, shows only a small circular dichroism even though the benzophenone system is directly attached to the chiral steriod. By contrast, larger effects are seen with ester Ib, Ic, and Id, in which models reveal that the benzophenone can pack on the steroid and in which, as will be described, there is significant intramolecular photochemistry involving such packing. Furthermore, the esters of 3β-cholestanol, VIa and VIc, show only small effects consistent with our argument that such equatorial attachments will make packing difficult.

A temperature study was done of the CD spectra of esters Ic and Id in acetonitrile and in hexane solvents. Ester Id showed no temperature dependence; there was a significant circular dichroism, with $\Delta\epsilon$ of -0.230 ± 0.020, constant over the temperature range -13 to $+40°$ in acetonitrile, while in hexane the $\Delta\epsilon$ was 0 over this temperature range. For ester Ic the $\Delta\epsilon$ at $-18°$ was twice the value at 40°. These and intermediate points fit on Arrhenius-type plot with a slope indicating $\Delta H°$ of -3.7 kcal/mol in acetonitrile (Figure 3) and -3.5 kcal/mol in hexane.

The detailed interpretation of these $\Delta\epsilon$'s is difficult. The data seem to suggest that in Ic the chiral conformation, presumably a packed conformation, is frozen in as we lower the temperature. The temperature independence of the CD spectrum for Id in acetonitrile seems to suggest that it is in this chiral conformation at all temperatures examined. However, other interpretations of these data are certainly possible. In any case, they do suggest a detectable population of a chiral packed conformation in the case of the substrates for which, as we describe below, intramolecular photochemistry is detectable.

Phosphorescence lifetimes of various of these materials have also been determined at room temperature in 1,1,2-trifluorotrichloroethane.[1b] The benzophenone triplet lifetimes of the cases in which a substrate is attached (esters Ia, Ic, VIc, and VIII, at 10^{-3} M) were compared with the lifetimes of an unattached steroid (or 1-hexadecyl) acetate and benzophenonone methyl ester, each at $10^{-3}M$. In this way the effect on the lifetime of an intramolecular interaction, such as hydrogen transfer to the benzophenone triplet, could be compared with the results for an intermolecular system at the same concentration. Whenever a short phosphorescence lifetime was detected, benzophenone was added in an independent experiment in order to determine that the short lifetime was not due to quenching by impurities; in all cases the decay curve was then nonlogarithmic and both the normal lifetime for benzophenone and the reported shorter lifetime of the derivative could be dissected from the curve.

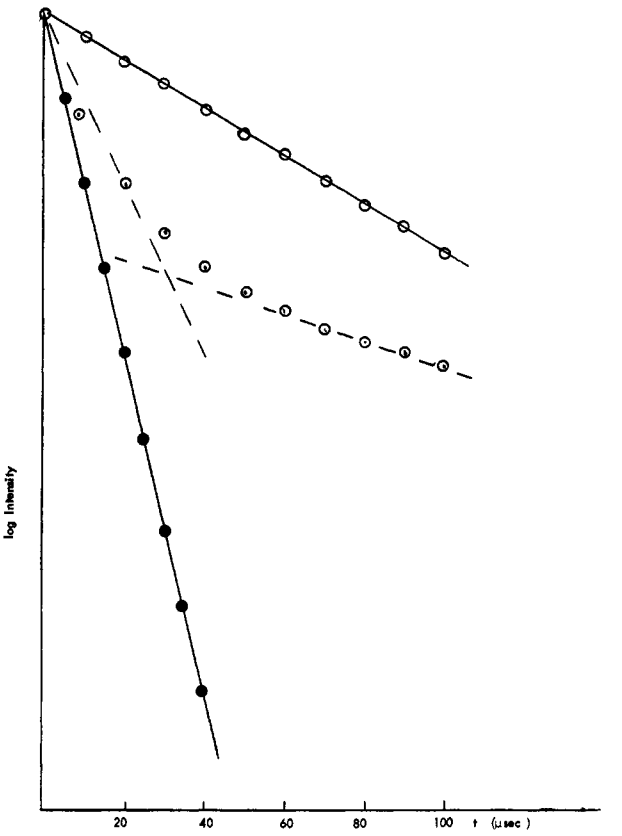


Figure 4. Phosphorescence decay: (●) Ic; (○) equimolar mixture of VIIb and 3α-cholestanyl acetate; (⊙) equimolar mixture of Ic and benzophenone.

The results of these studies are presented in Table II. In Figure 4 are illustrated three typical decay

Table II

Compd	τ, μsec	E_t, kcal/mol
Benzophenone	90	69.0
VIIa + 3α-cholestanyl acetate	80	66.2
VIIb + 3α-cholestanyl acetate	65	69.0
Ia	68	66.2
Ic	10	69.0
VIIa + n-hexadecyl acetate	73	66.2
VIII	13	66.2
VIIc	20	69.0
VIc	15	60.0

Table III. Steroidal Olefins Derived from Benzophenone–Steroid Esters on Irradiation in Benzene at 10^{-3} M

Substrate	% direct olefin	% lactone	Olefin distribution Δ6	Δ7	Δ14	Δ8(14)	Δ16	Δ5	Δ9(11)
Ia, IIa, IIIa, IIIb, VIa–c	None	None							
Ib	55	0			100				
Ic	35	50			100				
Ic (lactone cleavage)			20	49		31			
Id (in benzene)	55	10			43		57		
Id (in acetone)	55				30		70		
IIb	5	95							
IIb (lactone cleavage)			28	16				30	34

plots, from which these phosphorescence lifetimes were determined. The general result is that long phosphorescence lifetimes (60–90 μsec) were found for the cases in which a benzophenone is not attached to a steroid and also for compound Ia in which the V shape of the molecule prevents close approach of the excited carbonyl group to the steroid hydrogens. By contrast, compound Ic, in which models and CD spectra show that good packing can occur, has a very short lifetime, corresponding to the intramolecular photochemistry we report below. In compound VIII there is also intramolecular photochemistry, as we have described elsewhere.[10]

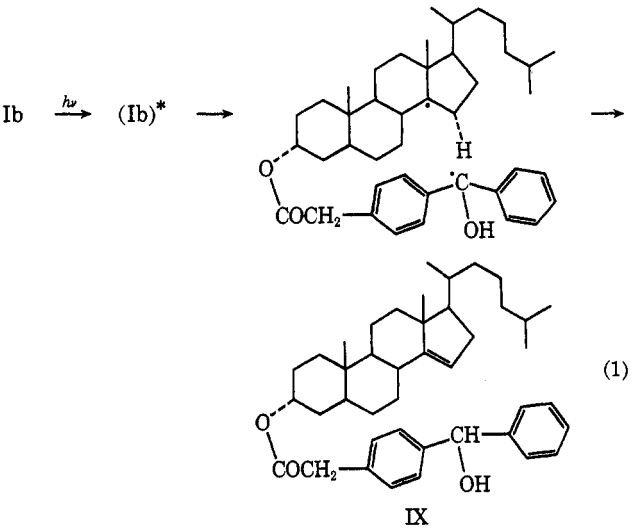
Phosphorescence quenching need not involve determinable photochemistry, however. Thus, in compound VIIc the very short phosphorescence lifetime apparently results from the approach of the long-chain ester group to the benzophenone carbonyl, leading either to undetectable temporary chemical changes or to triplet relaxation by spin–orbit coupling. In any case, no detectable photochemical transformation of compound VIIc occurred on photolysis.

Quantum yields for disappearance of the benzophenone carbonyl group were determined in a few cases. Thus, at 10^{-3} M concentration in benzene, the intramolecular photochemistry of ester Ic involved a quantum yield of approximately 0.16, four times larger than the quantum yield for photochemical reaction of $10^{-3}M$ solution of VIIb with 3α-cholestanyl acetate. In the latter case all the photochemistry was intermolecular, and in fact involved attack of the benzophenone component VIIb on the solvent, not on the steroid. The quantum yield for photoexcited benzophenone attack on solvent benzene has been reported to be 0.05.[11] Although detailed studies were not undertaken in many cases, controls were always performed to establish that the quantum yield for a proposed intramolecular process was significantly larger than the quantum yield for any possible competing intermolecular reactions.

Products of Photolysis of Steroid Esters (Table III). Preparative photolyses were generally run with concentrations of 10^{-3} M in purified benzene solution. The choice of benzene solvent, which reacts with excited benzophenone with quantum yield of 0.04, meant that only intramolecular functionalizations with reasonable quantum yields could compete with the reaction with solvent. As described below, some studies were also done with other solvents. However, the control reactions run in benzene demonstrate that this solvent also completely suppresses intermolecular attack of a benzophenone on another steroid at 10^{-3} M, so all the products of steroid functionalization obtained under these conditions are in fact entirely the result of intramolecular functionalization.

The benzophenone-4-carboxylic acid ester of 3α-cholestanol (Ia) does not functionalize the steroid on irradiation. The slow photochemical disappearance of the benzophenone carbonyl is due to reaction with the benzene solvent, since on hydrolysis 3α-cholestanol is recovered unchanged. This is consistent with the suggestion from models that the benzophenone carbonyl oxygen cannot reach any of the steroid hydrogens. Similarly, the benzophenone-3-carboxylic acid ester of 3α-cholestanol (IIa), on irradiation, yields only products derived from attack on solvent with no functionalization of the steroid. In the case of benzophenone-2-carboxylic esters (IIIa) or the benzophenone 2-acetic ester of 3α-cholestanol (IIIb) there is also no attack on the steroid.

The benzophenone-4-acetic ester of 3α-cholestanol (Ib) gives a strikingly specific steroid functionalization, however. On irradiation under these conditions the benzophenone carbonyl disappears approximately four times as rapidly as in the solvent attacks described above, and the product is IX, an ester in which the 14 and 15 hydrogens of the steroid have been transferred to the benzophenone carbonyl (eq 1). This is the only



(1)

IX

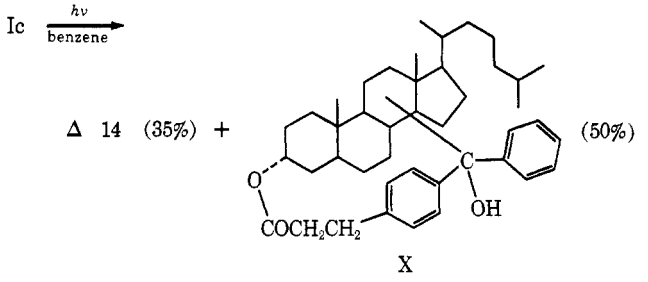
steroidal product detectable, and it is formed in 55% yield, by nmr analysis, together with unfunctionalized steroid in which the benzophenone carbonyl has reacted with solvent or impurities.

From models and our other data the sequence involved in the selective introduction of this double bond is undoubtedly as shown. The oxygen of the excited

(11) A. Beckett and G. Porter, *Trans. Faraday Soc.*, 57, 1686 (1961).

benzophenone abstracts the axial hydrogen on carbon 14, and the resulting diradical then transfers the α hydrogen from C-15 to the benzhydryl radical to complete the process. This is the only course open to the intermediate diradical (except for an undetected possible reversal of the original hydrogen abstraction). With only an acetic acid chain linking the rigid steroid to the rigid benzophenone the steric problems involved in closing the diradical to form a new carbon–carbon bond are apparently too formidable. If the diradical is instead to undergo a hydrogen transfer to form a steroidal olefin, the only hydrogen which can be reached is that on C-15. This is because in our reaction both the first hydrogen abstraction and also the second process, in this case a hydrogen transfer, are directed by the stereochemical possibilities. Even though an 8(14) olefin is also quite stable, the intermediate diradical cannot undergo a transfer of the 8 hydrogen which is located on the β inaccessible side of the steroid in the diradical intermediate. The intermolecular controls, described below, indicate that both the first hydrogen transfer and also the subsequent fate of the diradical are in fact being directed by the orientation we have imposed.

With the benzophenone-4-propionic acid ester of 3α-cholestanol (Ic), a new type of process comes in. Direct irradiation does produce a 35% yield of steroidal olefin by hydrogen transfer, which is again the Δ14 olefin for the reasons described above. However, there is also produced a 50% yield of a product mixture (X) in which new carbon–carbon bonds have been



X

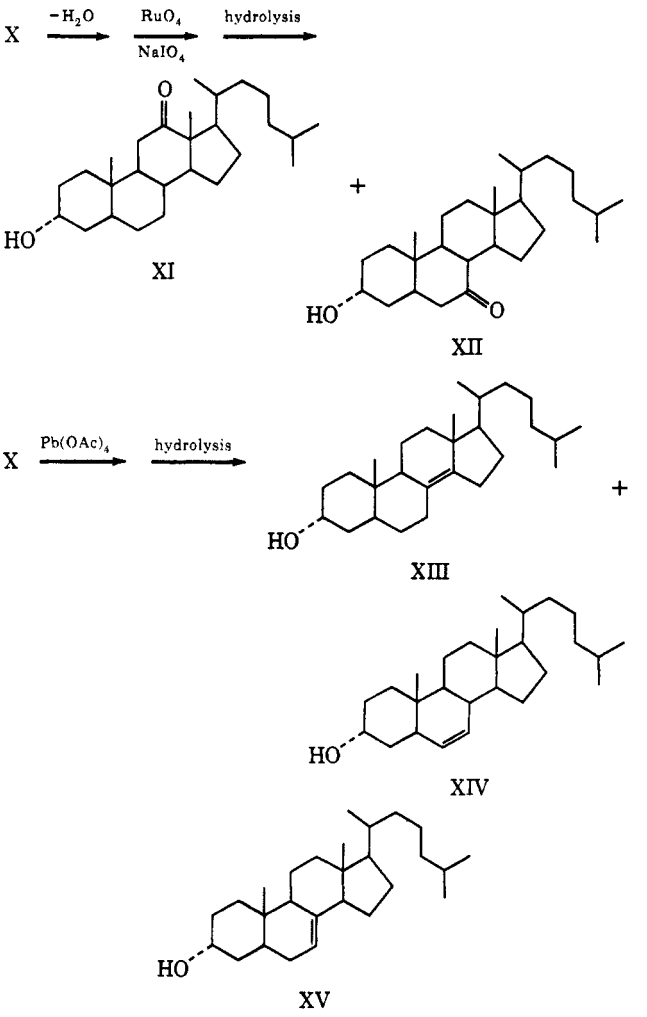
formed by insertion of the benzophenone carbonyl into steroidal C–H bonds. This results from coupling of the intermediate diradical in this more flexible case, and it leads to a more complicated functionalization of the steroid.

As we have described previously,[6a] this large ring lactone product (X) can be in part dehydrated, and the resulting olefin oxidatively cleaved to produce keto steroids. Very low yields of 12-ketocholestan-3α-ol (XI) and 7-ketocholestan-3α-ol (XII) are obtained in this way (Scheme I). The most useful degradation to establish the products in this reaction is a direct cleavage of the lactone material by lead tetraacetate[12] oxidation. This involves oxidation of the benzhydrol to an intermediate which undergoes cleavage of the bond to the steroid, and the resulting steroidal intermediate is then oxidized further to steroidal olefin. In this case, the olefin is not introduced by an intramolecular hydrogen transfer, and normal chemical factors determine the composition of this material.

As we show in Table III, the product of lead tetraacetate cleavage of the lactone material from this

(12) M. Amorose, D. Arigoni, and O. Jeger, *Helv. Chem. Acta*, **45**, 2674 (1962).

Scheme I

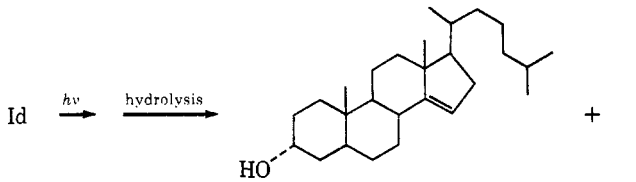


photolysis contains 30% $\Delta^{8(14)}$-cholesten-3α-ol (XIII). We believe this is derived from a lactone in which the new carbon–carbon bond is formed to carbon 14 of the steroid, the same carbon which is attacked in the steroid olefin production. Oxidation of an intermediate of this type would be expected to lead to the stable Δ8(14) olefin. In addition, most of the other 70% of the product is a mixture of Δ^6- and Δ^7-cholesten-3α-ols (compounds XIV and XV, respectively) which we believe are derived from a lactone originally attached at steroid carbon 7. The 7α hydrogen is also axial, and in models it is very close to the hydrogen at 14 and is within the arc which the benzophenone carbonyl can describe.

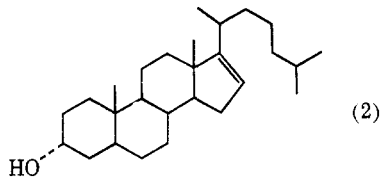
The reaction of Ic is less selective that that of Ib, since attack on carbons 7, 14, and to a minor extent 12 have been detected. Furthermore, in Ic the attack on C-14 leads to two alternative subsequent processes for the intermediate diradical, carbon–carbon bond formation and hydrogen transfer. In spite of this diminished selectivity there is no doubt that orientation factors are at work here. The intermolecular controls described below indicate that the large proportion of attack on a secondary hydrogen at C-7 would not be expected from an undirected process. The controls also indicate that the efficiency of attack on the steroid, rather than solvent, is due entirely to the intramolecular orientation we have achieved.

If the chain is extended some ambiguity arises in our

expectations. Thus in the case of Id, the benzophenone-4-pentanoic acid ester of 3α-cholestanol, one might simply have observed a more random attack on a variety of accessible hydrogens in the steroid. However, if these molecules prefer to pack with a reasonably compact conformation, then a model of such a compact arrangement indicates that the benzophenone carbonyl will now be moved up opposite the center of ring D in the steroid, and thus in a position to attack hydrogens on the tertiary C-14 and C-17. This is the result we have actually observed, and it is the result reported by Baldwin, *et al.*,[13] who also have photolyzed this ester. Table III shows that we obtain a 55% direct yield of olefin together with a small amount of lactone. The olefin is a mixture of Δ^{14}-cholesten-3α-ol (XVI) and Δ^{16}-cholesten-3α-ol (XVII) (eq 2).



XVI



XVII (2)

The specific formation of these two olefins is again sensible in terms of the orientation effect imposed in our molecule. The two tertiary hydrogens abstracted are the pseudoaxial hydrogens at C-14 and C-17, and they are attacked first by the benzophenone oxygen. In the intermediate diradicals which result there is again specific hydrogen transfer. The 14 radical can only transfer the α hydrogen on C-15, while the 17 radical can only transfer the α hydrogen on C-16. Models indicate that side chain C-20 is not accessible in the intermediate diradical. The choice of which hydrogen to attack initially, 14 or 17, is quite subtle since these are 1,3-pseudodiaxial with respect to each other and the oxygen may well lie between them. Thus the selection is influenced by very minor conformational effects associated with changes in solvent. As Table III shows, the proportion of these two olefins can be changed over a reasonable range by changing solvents.

In the meta-substituted series, the benzophenone-3-acetic acid ester of 3α-cholestanol (IIb) gave only 5% of steroidal olefin on direct irradiation, together with 95% of a mixture of lactones. On cleavage of this mixture with lead tetraacetate the Δ^{6}-cholesten-3α-ol (XIV) and Δ^{7}-cholesten-3α-ol (XV) were obtained, presumably from a lactone inserted at C-7. In addition, a Δ^{5}-cholesten-3α-ol and a $\Delta^{9(11)}$-cholesten-3α-ol were obtained. These olefin yields are listed in Table III. It should be noted that the ratio of Δ^{6}- to Δ^{7}-cholestenol is not uniform throughout our series, but this is still consistent with the hypothesis that they are derived from lactones attached at C-7. Lactones at C-7 derived from different starting materials will differ in the mode of attachment to C-3; more to the point, the two epimeric lactones derived from attachment at C-7 which differ in the configuration around the benzhydryl carbon need not be formed in constant proportion.

A general description of the products derived from compound IIb is that the benzophenone oxygen has attacked the three axial hydrogens on the α side of ring B. This attack on the hydrogens on C-5, -7, and -9 is expected from examination of molecular models. Although there certainly is some element of randomness in the set of products produced, it is striking that we can use this relatively short meta linkage between a benzophenone and the 3 position in ring A of a steroid to direct attack into ring B, while with the longer para linkage in compound Id we were able to direct attack exclusively into ring D starting from the same point of attachment.

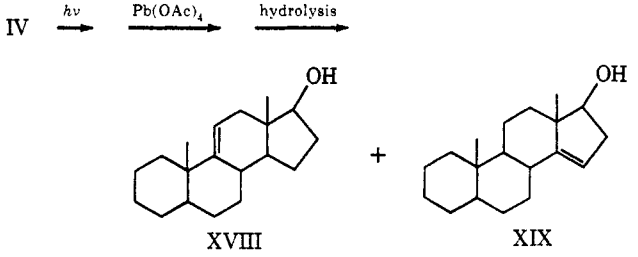
Two steroids were examined in which a benzophenone was attached through its ortho position to 3α-cholestanol. The benzophenone-2-carboxylic ester of 3α-cholestanol (IIIa) on photolysis afforded only reaction with solvent. Although in molecular models it is possible to reach steroid hydrogens with the carbonyl oxygen of this compound, models also suggest that in this system there would be crowding of α hydrogens in ring A by the packed benzene ring. Similarly, the benzophenone-2-acetic acid ester of 3α-cholestanol (IIIb) does not functionalize the steroid. In this case one might expect photoenolization of the benzophenone acetic acid system to be the major process occurring in any case, so the failure of this molecule to attack the steroid is not surprising. The failure of 3α-coprostanol derivatives to undergo remote oxidation may reflect a problem in packing, since the steroid is not flat at the A/B junction.

A few cases have also been examined in which benzophenone groups were attached at positions other than 3α on a steroid. 3β-Cholestanyl esters of various benzophenonecarboxylic acids were examined, but in every case slow photochemistry involved only attack on the solvent and the steroid was recovered unchanged. Remarkably, this was true even when the benzophenone-4-pentanoic acid ester of 3β-cholestanol was irradiated in 1,2-difluorotetrachloroethane. A fast photochemical disappearance of the benzophenone carbonyl was accompanied by no functionalization of the steroid, which could be recovered completely unchanged. This may well reflect intermolecular attack of one benzophenone derivative on the nonsteroidal hydrogens of another, but it does not represent useful functionalization possibilities.

Several compounds were examined in which a benzophenone was attached to groups on ring D of the steroid. When the benzophenone-4-hexanoic acid ester (IV) of 17β-hydroxy-5α-androstane was prepared and photolyzed in 1,1,2-trifluorotrichloroethane at 2.3×10^{-4} *M*, an intramolecular functionalization reaction occurred. Lead tetraacetate cleavage of the resulting insertion product and hydrolysis afforded approximately 50% of unfunctionalized steroid and 20% of a 3.3:1 mixture of $\Delta^{9(11)}$- and Δ^{14}-androsten-17β-ols (compounds XVIII and XIX, respectively). Irradiation of a 10^{-3} *M* benzene solution of this ester with lead tetraacetate cleavage of the entire photoproduct mixture

(13) J. E. Baldwin, A. K. Bhatnagar, and R. W. Harper, *Chem. Commun.*, 659 (1970).

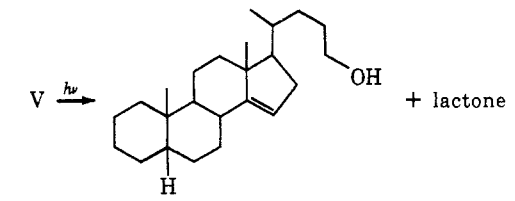
and hydrolysis afforded a 60% recovery of the starting steroid and a 20% yield of a 2:1 mixture of $\Delta^{9(11)}$-androsten-17β-ol (XVIII) and Δ^{14}-androsten-17β-ol (XIX). In compound IV the ester is originally on the



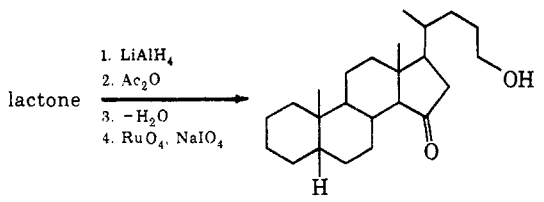
XVIII XIX

β side of the steroid, but apparently it is able to curl under and permit the benzophenone to attack the α face. However, the chain is sufficiently flexible that we are not seeing major orientation effects here. In comparison with an intermolecular control reaction (see below) we are probably achieving here principally an increased probability of attack on the steroid.

A much longer flexible chain is involved in the benzophenone-4-pentanoic ester of 5β-cholan-24-ol (V). Here ten atoms unite the rigid steroid framework with the rigid benzophenone reagent, and yet on photolysis and mild hydrolysis compound V is converted to a 25% yield of Δ^{14}-cholen-24-ol (XX), and a 45% yield of a lactone fraction. This lactone was reduced with lithium aluminum hydride, acetylated, and dehydrated. Cleavage of the resulting diphenylethylene derivative with ruthenium tetroxide and sodium periodate afforded a 16% yield of 15-ketocholan-24-ol (XXI) as the only steroidal ketone.



XX



XXI

Obviously, the course of this reaction is complex, and the yield of identified products is not quantitative. However, it is clear that a major attack in this case has occurred on C-14 and -15 of the steroid, in the same ring D to which the very long chain is attached. Our interpretation of this result is that the ten-atom chain is not in fact free to adopt more or less any conformation; instead there is a tendency for the hydrocarbon section of it to be extended, and for a bend to occur at the ester group. If a model is constructed with this principle incorporated, the steroidal side chain in the extended form and the benzophenone side chain brought back along it, the result is to put the benzophenone system under ring D and accounts for our observations. In this case, it is obvious that even with the potential flexibility of attachment there is a considerable directing influence by the geometry of the system, since attack on C-15 is never observed in intermolecular processes, and is undoubtedly the result of a proximity effect.

The identification of all these products is described in the Experimental Section, but a few general points should be made. Most of our products have been directly related experimentally to known steroids, so that the position of the new double bond or carbonyl group is proven by a direct comparison. In a few minor cases the identifications are based on spectroscopy, in particular nmr. There are excellent correlations of the steroid angular methyl shifts[14] (and the vinyl hydrogen in unsaturated steroids)[15] with the position of a double bond or carbonyl group. Thus the use of nmr to assign the position of a new double bond or carbonyl group is probably as reliable as correlation with "known" compounds. All of our assignments are consistent with these spectroscopic criteria.

Intermolecular Controls

Irradiation of a 10^{-3} *M* benzene solution of 3α-cholestanyl acetate and either benzophenone or methyl *p*-benzoylbenzoate caused slow steady destruction of the benzophenone carbonyl but no functionalization of the steroid. Irradiation of a 10^{-3} *M* solution of 3α-cholestanyl acetate and benzophenone in 1,1,2-trifluorotrichloroethane under our standard conditions gave a slow disappearance of the benzophenone chromophore, with approximately 50% gone in 12 hr. Lead tetraacetate oxidation, base hydrolysis, and chromatography on the total reaction mixture afforded 8% of steroidal olefinic alcohol along with 92% of recovered starting steroid. Nmr analysis of the steroidal olefin showed it to be a 1:2 mixture of $\Delta^{9(11)}$-cholesten-3α-ol and Δ^{14}-cholesten-3α-ol. Irradiation of benzophenone alone in this Freon solvent also led to slow decomposition of the benzophenone. Thus in 3α-substituted cholestanyl derivatives the most reactive positions for intermolecular attack by benzophenone triplet are at C-9 and C-14. This is consistent with the results of our studies on simple free-radical halogenations of steroids.[9]

While in some of our current intramolecular studies using benzophenones attached to steroids there was attack on C-9 and C-14, only in the case of the 17β-androstanol ester (IV) is there any pattern corresponding to the result of random intermolecular attack. Even in the case of IV we achieve steroid functionalization in benzene, in which the intermolecular process does not attack the steroid, so that a high local concentration was achieved by the attachment of reagent to substrate. In all the other cases there was additionally a major directing effect of the attachment, geometry playing an important role in determining both the ease of reaction and also the specificity of the functionalization reaction.

(14) N. S. Bhacca and D. w. Williams, "Applications of NMR Spectroscopy in Organic Chemistry," Holden-Day, San Francisco, Calif., 1964, pp 19–24. We calculate predicted nmr methyl resonances for those few steroidal olefins whose skeleta are not included in these tables by applying the tabulated changes, on introduction of a specific unsaturation, to the observed methyl signals in the saturated precursor.

(15) G. M. L. Cragg, C. W. Davey, D. N. Hall, G. D. Meakins, E. E. Richards, and T. L. Whateley, *J. Chem. Soc.*, 1266 (1966).

Future Developments

While real elements of control have thus been achieved, it is obvious that much better control would bring further synthetic advantages. All of the cases we describe here involve only a single point of attachment between reagent and substrate, and the development of reagents which are attached or complexed at several points in a well-defined way to the substrate would clearly be an important development. Additionally, the chemistry we have described utilizes benzophenone photochemistry for the functionalization process. In other work we have been able to show that simple free-radical chain functionalization can also be directed in very much the same way by using the principle we have developed here. Thus, it seems likely that remote oxidation or remote functionalization will, in fact, prove to be generally applicable to a variety of chemical processes, and not just to the photochemical process we have illustrated here.

Experimental Section

Benzene used in irradiations was purified by first stirring over concentrated sulfuric acid for 1 day, then decanting it and refluxing it with phosphorus pentoxide for several hours before distillation. The carbon tetrachloride used was Baker's Spectrophotometric grade, the acetonitrile was MC & B's Chromatoquality grade. The 1,1,2-trifluorotrichloroethane was distilled before use; it was shown by nmr to contain no detectable protonic material. The tetrachlorodifluoroethane (Genesolv C, a mixture of the 1,1,2,2 and 1,1,1,2 isomers) was also distilled before use and also contained no detectable hydrogen-containing component.

The 20% silver nitrate impregnated silica gel was prepared by adding a saturated solution of 14 g of silver nitrate to 70 g of silica gel, and the slurry was shaken in a stoppered blackened 500-ml flask for 40 min. Most of the water was then removed on a rotary evaporator, the flask heated at 80° while attached to a vacuum pump for 3 hr, and the silica gel stored in a brown bottle covered with aluminum foil.

Vpc Analyses of Mixtures of Cholesten-3α-ols. The steroid alcohols were first converted to their methyl ethers. A solution of 3–40 mg of the alcohol mixture in 6 ml of tetrahydrofuran was treated with sodium hydride (washed free of mineral oil) until the evolution of hydrogen had ceased. Methyl iodide (1 ml) was then added and the solution stirred at room temperature for 6–12 hr, when the excess base was quenched first with methanol, then with water. The ether soluble portion of the products was analyzed directly on a Hewlett-Packard Model 5750 instrument using a 0.25 in. × 8 ft 5% diethylene glycol succinate column at 206° with a flow rate of 125 ml/min. The retention times for the steroid methyl ethers were 60–80 min and, in increasing order, were: Δ16, Δ8(14), Δ9(11), Δ14, Δ6, Δ5, Δ7. The retention time for the saturated 3α-cholestanol (ether) was the same as that for the Δ8(14) compound; thus the olefins were separated from the saturated steroid by absorption chromatography on 20% silver nitrate impregnated silica gel.

To perform this separation, the steroid mixture was placed on a column of 100 times the mixture weight of silica gel–silver nitrate and the column was eluted with 3–5% ether–hexane. This brought off the saturated alcohol. Next, 20% ether–hexane afforded the olefin mixture. These columns were never used more than once.

At the temperature used for analysis, the 5% DEGS vpc column started a slow decomposition; thus standard sample injections were done just before and just after each analysis injection. Under these conditions the DEGS column had a lifetime of 20–50 hr (or 3–10 analyses).

Preparation of the Benzophenone Carboxylic Acids. The *o*- and *p*-benzoylbenzoic acids were commercial materials. The *m*-benzoylbenzoic acid was prepared from *m*-methylbenzophenone and had a mp of 160–161° (lit.[16] mp 162.5–163.2°).

The *m*- and *p*-benzoylphenylacetic acids were prepared by the method of Bonner.[17] The para isomer melted at 110–111° (lit.[17] mp 111°) and the meta isomer at 114–115° (lit.[18] mp 112–113°).

***o*-Benzoylphenylacetic Acid.** To a solution of phenylmagnesium bromide prepared from 6.301 g (40 mmol) of bromobenzene and 1.020 g (42 mmol) of magnesium in 100 ml of anhydrous ether was added dropwise 4.831 g (36.4 mmol) of 1-indanone in 100 ml of ether. This solution was stirred at room temperature overnight, then poured into ice–hydrochloric acid, and extracted into ether, and this ether solution was dried (sodium sulfate) and the solvent removed *in vacuo*. The resulting orange oil was dissolved in 125 ml of benzene, 600 mg of *p*-toluenesulfonic acid was added, and the solution was boiled for 3 hr. The cooled solution was washed with 5% sodium hydroxide and then water, dried over sodium sulfate, and distilled. The material distilling at 110–115° (0.1 mm) was collected to afford 5.282 g (27.3 mmol, 75% yield based on ketone) of 1-phenylindene. The ir and nmr spectra of this material agreed with those reported.[19]

A total of 3.972 g (20.7 mmol) of this material was then oxidized to the *o*-benzoylphenylacetic acid by the method of Lemieux[20] to afford 2.370 g (9.9 mmol, 48%) of the desired acid, mp 116–118° (methanol) (lit.[21] mp 118°).

ω-(*p*-Benzoyl)phenylalkanoic Acids. The propanoic, butanoic, pentanoic, hexanoic, and nonanoic acid derivatives were all prepared by Friedel–Crafts benzoylation of the corresponding ω-phenyl-*n*-alkyl acid methyl esters by the method of Borsche.[22] The acids, obtained in 45–60% yield, were: *p*-benzoyl-3-phenylpropanoic, mp 96–98° (lit.[22] mp 97°); *p*-benzoyl-4-phenylbutanoic, mp 44–47°; *p*-benzoyl-5-phenylpentanoic, mp 55–58°; *p*-benzoyl-6-phenylhexanoic, oil; and *p*-benzoyl-9-phenylnonanoic, mp 67–68°.

5α-Cholestan-3α-ol. 5α-Cholestan-3β-ol was oxidized to the ketone with chromic acid by the method of Bruce.[23] This ketone was reduced to the α-ol using iridium trichloride[24] or platinum and hydrogen.[25] The product was purified by crystallization and chromatography until only a trace of the 3β-ol was present, and melted at 183–184° (lit.[26] mp 182°).

Androstan-17β-ol. A mixture of 10 g (34.5 mmol) of androstan-17β-ol-3-one, 15 g of potassium hydroxide, 6 g of hydrazine, and 150 g of diethylene glycol was heated at reflux for 30 min, the condenser removed, and the water distilled out over 2 hr. The solution was cooled and the product extracted into benzene; the organic phase was washed several times with water and dried over magnesium sulfate. The solvent was removed *in vacuo* and the product crystallized from ether–hexane to afford 5.7 g (57%) of androstan-17β-ol, mp 166–167.5° (lit.[27] mp 165.5–166.5°). The 60-MHz nmr spectrum of this material revealed axial methyl resonances at 44 and 47 Hz from TMS and the 17α proton as a multiplet centered at 220 Hz from TMS.

Cholan-24-ol. To 8 g (21.3 mmol) of lithocholic acid in 800 ml of acetone was added 6 ml of a solution prepared by diluting 13.35 g of chromium trioxide and 12 ml of sulfuric acid to 50 ml with water. The mixture was stirred at room temperature for 30 min, the acetone removed at reduced pressure, and the residue extracted with ether and water. The ethereal solution was dried over magnesium sulfate and the solvent removed to afford 7 g of erude 3-ketolithocholic acid which was used without further purification.

The 3-ketolithocholic acid, 6 g of hydrazine, 18 g of potassium hydroxide, 180 ml of diethylene glycol, and 30 ml of methanol were mixed and heated at reflux for 45 min. The condenser was then removed and the methanol and water were distilled off over 2 hr. This mixture was then cooled and extracted into benzene which was washed several times with water. The benzene solution was dried over magnesium sulfate and the solvent removed to

(16) W. N. White, R. Schlitt, and D. Gwynn, *J. Org. Chem.*, **26**, 3613 (1961).

(17) J. A. Zderic, M. J. Kubitschek, and W. A. Bonner, *J. Org. Chem.*, **26**, 1635 (1961).

(18) D. E. Bays and R. V. Foster, S. African Patent 6804,682; *Chem. Abstr.*, **71**, 91097s (1969).

(19) L. Skattebøl and B. Boulette, *J. Org. Chem.*, **31**, 84 (1966).

(20) R. U. Lemieux and E. Rudloff, *Can. J. Chem.*, **33**, 1701 (1955).

(21) J. Thibault and P. Maitte, *Bull. Soc. Chim. Fr.*, 915 (1969).

(22) W. Borsche and F. Sinn, *Justus Liebigs Ann. Chem.*, **553**, 260 (1942).

(23) W. E. Bruce, "Organic Syntheses," Collect. Vol. II, Wiley, New York, N. Y., 1943, p 139.

(24) E. L. Eliel, T. W. Doyle, R. O. Hutchins, and E. C. Gilbert, *Org. Syn.*, **50**, 13 (1970).

(25) J. T. Edward and J. M. Ferland, *Can. J. Chem.*, **44**, 1311 (1966).

(26) O. Diels and E. Abderhalden, *Ber.*, **39**, 884 (1906).

(27) W. V. Ruyle, A. E. Erickson, A. Lovell, and E. M. Chamberlin, *J. Org. Chem.*, **25**, 1260 (1960).

afford 6.2 g of crude 5β-cholanic acid. This material was used without further purification.

To a solution of 6.2 g of cholanic acid in 50 ml of ether and 50 ml of tetrahydrofuran was added 1.9 g of lithium aluminum hydride in 50 ml of ether at such a rate that a gentle reflux was maintained. After completion of the addition, the mixture was heated at reflux for an additional 30 min and then 1.9 ml of water was slowly added. Finally, 8 ml of 4% sodium hydroxide solution was added, the mixture filtered, the filtrate dried over sodium sulfate, and the solvent removed *in vacuo* to afford 5.6 g of cholan-24-ol (76%), mp 127–129° (lit.[28] mp 129.5–130.5°). In the 60-MHz nmr spectrum of this compound the axial methyl resonances occur at 40 and 55.5 Hz from TMS and the hydroxyl-bearing carbon protons at 220 Hz from TMS.

Steroidal Ester Preparations. Typically, the steroidal esters of the benzophenone carboxylic acids were prepared through the reaction of the alcohol with appropriate acid chloride in dry benzene in the presence of 1 equiv of pyridine. The one exception was the *o*-benzoylbenzoate (*vide infra*). The products from these reactions were then purified by chromatography on silica gel. Elution with 5% ether–hexane afforded ester uncontaminated with alcohol.

The esters were, in general, clear glasses. The exceptions were the cholestan-3α-yl benzoylbenzoates which were solids: para (Ia) mp 78–79°; meta (IIa) mp 65–67°; ortho (IIIa) mp 82–83°. The spectra of these compounds were unexceptionable: ir (NaCl) 1708 and 1665 cm^{-1}; nmr ($CDCl_3$) (cholestan-3α-yl series) δ 0.68–2.17 (46 H, steroid envelope), 5.00 (1 H, 3β-H), and 7.22–7.82 (9 H, arom). In particular, the angular methyl signals were at 40.5 and 47.0 Hz from TMS. The androstan-17β-yl hexanoate (IV) displayed only one angular methyl resonance at 47.0 Hz and the 17α-proton absorption was a broad triplet with further splitting at 276 Hz. The cholan-24-yl pentanoate (V) showed angular methyl resonances at 38.0 and 54.5 Hz and the two protons on C-24 absorbed at 247 Hz as a broadened triplet.

In the acetic acid derivatives there was an additional signal at δ 3.67 (Ib and IIb) or 3.85 (IIIb) (2 H, singlet, benzylic CH_2). The propanoate ester methylene chain absorbed as a multiplet at δ 2.42–3.22 (4 H). In the pentanoate, hexanoate, and nonanoate derivatives the additional signals from the methylene chain overlapped the steroid envelope and extended to δ 3.00. All of the esters showed the appropriate parent ions in their mass spectra.

5α-Cholest-6-en-3α-ol (XIV). This material, obtained from the irradiations, was recrystallized several times from ethanol and acetone, mp 160.5–162.5° (lit.[29] mp 162°). The mass spectrum showed a parent at *m/e* 386, and the nmr spectrum showed angular methyl resonances at 41.6 and 45.2 Hz from TMS (calcd[14] at 42.8 and 46.0).

5α-Cholest-7-en-3α-ol (XV). The compound isolated after irradiation was in every respect identical with that prepared independently. 5α-Cholesta-5,7-dien-3β-yl benzoate was converted[15] to the 5α-cholest-7-en-3β-ol. This alcohol was epimerized to the α-ol by oxidation to the ketone with chromic acid[23] and then reduction to a mixture of the α and β alcohols with hydrogen and platinum.[25] Separation by silica gel chromatography afforded 5α-cholest-7-en-3α-ol, mp 174–176° (lit.[30] mp 175–176°). The nmr spectrum of this compound showed angular methyl resonances at 32.0 and 48.0 Hz (calcd[14] at 32.4 and 48.1 Hz).

5α-Cholest-8(14)-en-3α-ol (XIII). This olefin, isolated after irradiation, had mp 141–145° after recrystallization from methanol. The partial spectra were: ir ($CHCl_3$) 3600, 3450 cm^{-1}; nmr ($CDCl_3$) angular methyl resonances at 42.5 and 51.0 Hz (calcd[14] at 41.7 and 51.9 Hz); mass spectrum (75 eV) *m/e* 386.

Anal. Calcd for $C_{27}H_{46}O$: C, 83.87; H, 11.99. Found: C, 83.51; H, 11.64.

Oxidation of this material with Jones reagent and reduction with lithium tri-*tert*-butoxy aluminum hydride afforded the β alcohol, mp 118–121° (lit.[31] mp 119–120°), mmp 118–121° with authentic material.

5α-Cholest-14-en-3α-ol (XVI). This compound, isolated after irradiation, was recrystallized from acetonitrile several times, mp 128–129°.[32] Partial spectra were: ir ($CHCl_3$) 3600 and 3450 cm^{-1}; nmr ($CDCl_3$) angular methyl resonances at 49.5 and 55.5 Hz and vinyl proton absorption at 308 Hz (calcd[14,15] at 49.0, 55.0, and 304 Hz), *m/e* 386.

Anal. Calcd for $C_{27}H_{46}O$: C, 83.87; H, 11.99. Found: C, 83.72; H, 11.89.

Oxidation of the α alcohol and reduction of this product to the β alcohol as in the case of the 8(14)-ene produced a white solid, mp 130–131° (lit.[33] mp 130–131°), mmp (with authentic material) 129–130°.

5α-Cholest-16-en-3α-ol (XVII). The olefin isolated after irradiation was recrystallized from ethanol, mp 133–136°. Partial spectra were: ir ($CHCl_3$) 3600 and 3450 cm^{-1}; nmr ($CDCl_3$) angular methyl resonances at 63 and 47 Hz, vinyl proton resonance at 318 Hz; *m/e* 386.

Anal. Calcd for $C_{27}H_{46}O$: C, 83.87; H, 11.99. Found: C, 83.81; H, 11.72.

5α-Cholest-9(11)-en-3α-ol. The olefin isolated after irradiation was recrystallized from ethanol, mp 164–167°.[34] The nmr spectrum ($CDCl_3$) showed methyl resonances at 36 and 57 Hz and the vinyl proton signal at 316 Hz (methyl signals calcd[14] at 35.5 and 57 Hz) and was identical with the spectrum of authentic material prepared as described below. The mass spectrum of this compound showed a parent peak at *m/e* 386.

Synthesis of 5α-Cholest-9(11)-en-3α-ol. 5α-Cholesta-7,9-dien-3β-yl acetate (570 mg, 1.33 mmol), prepared by the method of Heusser,[35] was dissolved in 15 ml of methylene chloride at 0°. *m*-Chloroperbenzoic acid was added slowly until the tlc of the reaction mixture showed the starting diene to be gone. This solution was poured into water and washed with 5% sodium bicarbonate solution. The solvent was removed and the crude epoxide was converted without further purification to 11-keto-5α-cholest-8-en-3β-yl acetate by the method of Heusser.[35] To the epoxide, dissolved in 15 ml of benzene, 5 drops of boron trifluoride-etherate was added and the solution stirred for 3 days at room temperature. It was then poured into water and extracted with ether. The ether solution was washed with sodium bicarbonate solution and dried over magnesium sulfate. The solvent was removed *in vacuo* and the residue chromatographed on silica gel; 40% chloroform–petroleum ether afforded 340 mg (0.77 mmol, 56%) of the desired enone. By nmr analysis, about 15% of this material was the 7-ene and 85% the 8-ene. The infrared spectrum of this crude material ($CHCl_3$) showed absorptions at 1755 and 1680 cm^{-1}.

Without further purification this material was converted to 5α-cholestan-11α-ol-3-one. The 11-keto-5α-cholest-8-en-3β-yl acetate (340 mg, 0.77 mmol) in 20 ml of ether was added to 60 ml of ammonia containing 0.5 g of lithium. This solution was allowed to reflux for 2 hr and was then quenched with methanol. After evaporation of the ammonia, the solution was poured into water and extracted with ether. This ether solution was dried and the solvent removed to afford 230 mg of crude 5α-cholestane-3β,11α-diol.[36] This crude diol was directly oxidized.[37] The diol was added to 16 ml of toluene containing 6 ml of cyclohexanone and 0.4 g of aluminum isopropoxide and this solution heated at reflux for 1 hr. It was then poured into dilute hydrochloric acid, and extracted with ether, the ether solution dried, and the solvent removed to afford a residue which was chromatographed on silica gel. Using 50% chloroform–petroleum ether, 90 mg (30%) of 5α-cholestan-11α-ol-3-one was eluted.

The crude 5α-cholestan-11α-ol-3-one (90 mg, 0.22 mmol) was dissolved in 5 ml of pyridine at 0°, 0.3 ml of methanesulfonyl chloride was added, and the solution stirred at 0° for 15 hr. After quenching with water, extraction into ether, washing with dilute hydrochloric acid and saturated sodium carbonate, and drying over magnesium sulfate and solvent removal, the sulfonic ester was dissolved in 10 ml of *N,N*-dimethylformamide and 1.0 g of lithium chloride added. This solution was heated at 100° for 2.5 hr, poured into water, and extracted three times with ether. The ether extracts were washed with water and dried. After removal of the solvent, the residue was chromatographed on silica gel; 25%

(28) R. T. Blickenstaff and R. C. Chang, *J. Amer. Chem. Soc.*, **80**, 2726 (1958).

(29) C. W. Shoppe, T. F. Holley, and G. P. Newsoroff, *J. Chem. Soc.*, 2349 (1965).

(30) D. E. Evans and G. H, R. Summers, *J. Chem. Soc.*, 4821 (1956).

(31) F. Hunziker, F. X. Müllner, K. G. Reuteler, and H. Schaltegger, *Helv. Chim. Acta*, **38**, 1316 (1955).

(32) This compound apparently forms a 1:1 complex with solvent alcohol. For a mp of 165–167°, see ref 6a.

(33) F. Schenck, K. Buchholz, and O. Wiese, *Chem. Ber.*, **69**, 2696 (1936).

(34) The melting point of a slightly less pure sample is reported to be 155–157° in ref 9.

(35) H. Heusser, K. Heusler, K. Eichenberger, C. G. Honegger, and O. Jeger, *Helv. Chim. Acta*, **35**, 295 (1952).

(36) F. Sondheimer, O. Mancera, G. Rosenkranz, and C. Djerassi, *J. Amer. Chem. Soc.*, **75**, 1282 (1953).

(37) O. Mancera, J. Romo, F. Sondheimer, G. Rosenkranz, and C. Djerassi, *J. Org. Chem.*, **17**, 1066 (1952).

chloroform–petroleum ether eluted 48 mg (56%) of 5α-cholest-9(11)-en-3-one.[38] The nmr spectrum of this material showed angular methyl resonances at 37 and 69 Hz from TMS. The calculated positions[14] are 38 and 72 Hz.

A solution of 48 mg (0.125 mmol) of the cholest-9(11)-en-3-one in 15 ml of dimethoxyethane was treated with excess lithium aluminum hydride at 100°. Standard work-up afforded the α and β alcohols in a 1:9 ratio. They were separated by tlc on silica gel.

5α-Cholestan-3α-ol-12-one (XI). The isolated material was recrystallized from methanol, mp 165–167°. Partial spectral data were: ir ($CHCl_3$) 3600, 3450, and 1710 cm^{-1}; nmr ($CDCl_3$) methyl resonances at 62.0 and 52.0 Hz (calcd[14] at 62.5 and 53.0 Hz), *m/e* 402.

Anal. Calcd for $C_{27}H_{46}O_2$: C, 80.54; H, 11.51. Found: C, 80.61; H, 11.40.

Jones oxidation of this compound afforded 5α-cholestane-3,12-dione, mp 186–177°; identical in all respects with authentic compound prepared as described below.

5α-Cholestane-3,12-dione. The bis-formate of deoxycholic acid was prepared in 56% yield by the procedure of Hoehn and Moffet,[39] mp 191–193° (lit.[39] mp 195–196°). This material was converted to the acyl chloride and then treated with diisopropylcadmium[40] in benzene at 25° for 40 hr to afford the 24-keto steroid, in 62% yield, which was directly reduced (Wolff–Kishner) and hydrolyzed to the coprostane-3,12-diol (79% yield). Jones oxidation of this compound proceeded in 89% yield to give coprostane-3,12-dione, mp 128–131° (lit.[40] mp 138–138.5°). Bromination and dehydrobromination then afforded the cholest-4-ene-3,12-dione, mp 112–116° (lit.[40] mp 117–118°). Lithium in liquid ammonia reduction of the α,β-unsaturated ketone gave the saturated diketone, mp 187–188°.

5α-Cholestan-3α-ol-7-one (XII). This material was isolated as a mixture with the 12-keto isomer; the partial 220-MHz nmr spectrum ($CDCl_3$): methyl resonances at 229 and 144 Hz from TMS (calcd[14] 232 and 148 Hz). The 5α-cholestan-3α-ol-12-one had methyl resonances at 229 and 193.5 Hz (calcd[14] at 228 and 194 Hz). 3α-Cholestanol has 220-MHz nmr methyl resonances at 172 and 146 Hz.

Androst-9(11)-en-17β-ol (XVIII). The material isolated after irradiation was crystallized from ethanol, mp 158–159° (lit.[41] mp 160.5–162°). The nmr spectrum of this compound showed angular methyl resonances at 42.0 and 56.0 Hz and vinyl proton resonance at 321 Hz (calcd[14,15] at 40.5, 56.5, and 314 Hz). In the mass spectrum the parent ion was at *m/e* 274.

Androst-14-en-17β-ol (XIX). This material, in its nmr spectrum, had methyl resonances at 48.0 and 58.0 Hz and a vinyl proton signal at 304 Hz (calcd[14,15] at 48.5, 59.5, and 302 Hz).

Chol-14-en-24-ol (XX). This material crystallized from methanol, mp 99–101°, mass spectrum parent ion at *m/e* 344. The methyl resonances in the nmr spectrum occurred at 54.0 and 56.0 Hz (calcd[14] at 55.0 and 56.0). The vinyl proton resonance came at 309 Hz.

Cholan-24-ol-15-one (XXI). The nmr spectrum of this material showed methyl singlets at 44.5 and 55.5 Hz (calcd[14] at 44.5 and 56.0 Hz). The mass spectrum showed a parent ion at *m/e* 360 and the infrared spectrum displayed a carbonyl resonance at 1740 cm^{-1}.

Irradiation of Steroidal Benzophenone Carboxylic Esters. The procedure was always the same unless noted, although the time required for the disappearance of the benzophenone carbonyl chromophore depended on the length of the methylene chain and the steroid substrate involved, and on the solvent.

Example. 5α-Cholestan-3α-yl 3-(*p*-benzoyl)phenylpropanoate (Ic) (930 mg, 1.5 mmol) was dissolved in 1.7 l. of purified benzene. The solution was degassed for several hours with purified argon. The photolysis lamp, suspended in a jacketed, water-cooled immersion well, was a 450-W medium-pressure Hanovia lamp. A uranium glass filter was used and the course of the reaction was monitored by following the ir absorption of the benzophenone carbonyl chromophore. After 1.25 hr, the reaction was finished. The solvent was removed and the nmr spectrum of the photomixture determined. The 3β-proton absorption at δ 5.0 was split into two absorptions: a peak at 5.0 and at 4.65. The absorption at 4.65 was due to lactone (X) formation (55% by integration) and, in addition, vinylic proton absorption (Δ^{14}-cholestenol ester) at δ 5.15 integrated for 25% of the mixture. This photomixture was hydrolyzed by reflux for 1.5 hr in a mixture of 150 ml of methanol, 40 ml of dioxane, and 10 ml of water containing 12.5 g of potassium hydroxide. Under these conditions the lactones do not hydrolyze but the simple esters do. The hydrolysis solution was poured into a saturated sodium chloride solution and extracted three times with ether. The ether extracts were dried, the solvent was removed, and the residue was chromatographed on silica gel; 7% ether–petroleum ether eluted a lactone weighing 270 mg followed by a 1:2 mixture of 3α-cholestanol and Δ^{14}-cholestenol weighing 211 mg. Ether eluted another lactone (207 mg) and methanol eluted an amorphous material (120 mg).

Lead Tetraacetate Cleavage of Lactones.[13] The lactone (207 mg, 0.32 mmol) was dissolved in 35 ml of cyclohexane to which was added 1.5 g of lead tetraacetate and 0.4 g of calcium carbonate in an anhydrous atmosphere. This solution was refluxed for 10–16 hr, and filtered hot and the filtrate washed with water, a potassium iodide solution, a sodium thiosulfate solution, and a saturated sodium bicarbonate solution. The ethereal solution was then dried over magnesium sulfate, the solvent removed *in vacuo*, and the spectra were taken; the nmr spectrum indicated the presence of acetates and olefins; the ir spectrum indicated that most of the benzophenone carbonyl chromophore had been restored. This material was hydrolyzed by reflux for 2 hr in aqueous methanol with potassium hydroxide, and the neutral product mixture from this chromatographed on silica gel. With 7% ether was eluted a mixture of cholestenols weighing 30 mg (20%).

Irradiation of 5α-Cholestan-3α-yl 3-(*p*-Benzoyl)phenylpropanoate (Ic) in Carbon Tetrachloride. A solution of 793 mg of the ester (1.27 mmol) in 900 ml of carbon tetrachloride (1.4×10^{-3} *M*) was irradiated through a uranium glass filter for 12 hr. Removal of solvent afforded 1.11 g of a yellow oil whose infrared spectrum showed no benzophenone carbonyl.

A solution of this material in 100 ml of methanol, 5 ml of water, 25 ml of *p*-dioxane, and 8 g of potassium hydroxide was heated at reflux under a nitrogen atmosphere for 1.5 hr, cooled, and extracted with water after the addition of ether. The ether solution was dried and the solvent removed to afford 748 mg of material possessing considerable ester carbonyl absorption (1730 cm^{-1}) in its infrared spectrum. This material was then chromatographed on 74 g of silica gel. Elution with 10% ether–cyclohexane produced 277 mg of lactone (35% from starting ester).

A portion of the lactone isolated in this way (264 mg, 0.42 mmol) was treated with excess lithium aluminum hydride in refluxing ether for 3.5 hr to afford 269 mg of triol. This triol was then diacetylated by allowing it to stand in 10 ml of dry pyridine with 2 ml of acetic anhydride at room temperature for 16 hr. The diacetate, isolated by concentrating the solution *in vacuo*, was 281 mg of oil which had an ir spectrum ($CHCl_3$) 1735 cm^{-1} and a nmr spectrum ($CDCl_3$) δ 1.95 s (6 H, acetyl CH_3).

Dehydration of this material with thionyl chloride in pyridine (0.5 ml) afforded 103 mg of crude diphenylethylene derivative. This olefin was dissolved in 20 ml of acetone and 3 ml of a 0.03 *M* ruthenium tetroxide in carbon tetrachloride solution was added. Over a period of 12 hr a total of 1.2 g of sodium periodate (5.5 mmol) in 24 ml of water was added, and the excess oxidant then destroyed by the addition of 3 ml of isopropyl alcohol.

A total of 173 mg of neutral organic material was isolated from this reaction and was chromatographed on 20 g of silica gel. Elution with 10% ether–hexane afforded 31 mg of 5α-cholestan-12-on-3α-yl acetate whose mass spectrum showed a parent of *m/e* 444. Base hydrolysis afforded 27 mg of 5α-cholestan-3α-ol-12-one (XI).

Irradiation of Androstan-17β-yl 6-(*p*-Benzoyl)phenylhexanoate (IV). A solution of 470 mg (0.85 mmol) of the ester in 900 ml of benzene was irradiated under standard conditions for 2 hr. The benzophenone carbonyl chromophore was then completely absent. The photoproduct mixture was then oxidized by 10 hr heating at reflux in 100 ml of cyclohexane with 3 g of lead tetraacetate and 0.7 g of calcium carbonate. This produced 606 mg of crude neutral material which was hydrolyzed by reflux for 3 hr in 100 ml of methanol, 20 ml of *p*-dioxane, and 5 g of potassium hydroxide. The neutral material isolated from this reaction was chromatographed on 25 g of silica gel; 10% ether–petroleum ether eluted 187 mg of purified steroid. This material was then chromatographed on 10 g of 20% silver nitrate–silica gel to afford 128 mg (60%) of androstan-17β-ol and 40.5 mg (20%) of two steroid olefins, the androst-9(11)-en-17β-ol (XVIII) and the androst-14-en-17β-ol (XIX). Their ratio was 1:2 as determined by integration of the vinyl proton signals in the 100-MHz nmr.

(38) von L. Ehmann, K. Heusler, C. Meystre, P. Wieland, G. Anner, and A. Wettstein, *Helv. Chem. Acta*, **42**, 2548 (1959).
(39) W. M. Hoehn and R. B. Moffet, *J. Amer. Chem. Soc.*, **67**, 740 (1945).
(40) D. N. Kirk and V. Petrov, *J. Chem. Soc.*, 1691 (1959).
(41) W. Klyne and S. Palmer, *J. Chem. Soc.*, 4545 (1958).

Irradiation of Cholan-24-yl 5-(*p*-Benzoyl)phenylpentanoate (V). Irradiation of 475 mg (0.78 mmol) of this ester in 900 ml of benzene for 2 hr and standard work-up (lead tetraacetate, hydrolysis, chromatography) afforded 48 mg (17%) of cholan-24-ol and 59 mg (22%) of chol-14-en-ol (XX). A similar irradiation of 1.150 g (1.72 mmol) of this ester in 1800 ml of benzene and oxidative work-up (acetylation, dehydration, and ruthenium tetroxide oxidation, as in the case of the irradiation of the cholestan-3α-yl propionate ester in carbon tetrachloride) afforded 51 mg (8%) of cholan-24-ol-15-one (XXI).

Control Irradiations. Irradiation under our standard conditions of 602 mg (3.32 mmol) of resublimed benzophenone in 150 ml of 1,1,2-trichlorotrifluoroethane for 15.5 hr caused the disappearance of *ca.* 50% of the benzophenone carbonyl chromophore.

Benzophenone (612 mg, 3.40 mmol) and 3α-cholestanyl acetate (594 mg, 1.40 mmol) in 150 ml of 1,1,2-trichlorotrifluoroethane were irradiated for 12 hr. Roughly half of the benzophenone carbonyl chromophore had disappeared at this time. Lead tetraacetate oxidation, base hydrolysis, and silver nitrate–silica gel chromatography afforded 41 mg of steroidal olefin alcohol. Nmr analysis of this material showed it to be a 1:2 mixture of the cholest-9(11)-en-3α-ol and cholest-14-en-3α-ol (XVI) in a yield of 7.7%.

Irradiation of a 10^{-3} *M* benzene solution of 3α-cholestanyl acetate also 10^{-3} *M* in benzophenone or methyl *p*-benzoylbenzoate brought about rapid (2 hr) disappearance of the benzophenone carbonyl chromophore but no detectable modification of the steroid component.

Preparative Irradiation of 5α-Cholestan-3α-yl (*p*-Benzoyl)phenylacetate (Ib). Irradiation of a combined total of 11.296 g (18.5 mmol) of the ester in three equal batches each in 5.0 l. of benzene, each for 10 hr, and base hydrolysis of the combined photoproduct mixture afforded 4.911 g of neutral steroid mixture and 6.041 g of acidic material, chiefly, benzhydrol-4-acetic acid. The nmr of the neutral material contained no aromatic signals, and indicated a mixture of 5α-cholestan-3α-ol and 5α-cholest-14-en-3α-ol. Chromatography of the mixture on 20% silver nitrate–silica gel afforded 1.549 g of 5α-cholestan-3α-ol and 2.483 g (44% isolated yield) of 5α-cholest-14-en-3α-ol (XVI).

Phosphorescence Lifetimes.[1b] All esters were given a final purification by passage through an alumina column, eluted with carbon tetrachloride. The solvent, 1,1,2-trichlorotrifluoroethane, was distilled and passed through an alumina column. All glassware was cleaned with chromic acid, then 10% sodium hydroxide solution, and finally rinsed 4 times with distilled water and dried at 50° in a stream of nitrogen. Benzophenone, methyl *p*-benzoylbenzoate, and 3α-cholestanyl acetate were further purified by sublimation.

The 5-ml samples in Pyrex tubes were degassed by 8–11 cycles of the freeze–pump–thaw routine and sealed frozen under vacuum. The flash was a Xenon Corp. nanolamp with a decay lifetime of 5 μsec under the conditions used. The lamp light was filtered free of visible light and the phototube filters removed light of $\lambda < 480$ nm. The fast-rise-time oscilloscope was self-triggered by the signal and this signal recorded using a polaroid camera. Emission spectra from the same samples were obtained on a Hitachi spectrophosphorimeter with excitation at 350 nm.

Circular Dichroism Spectra. The spectra were recorded on a Cary Model 60 instrument with each component at 10^{-3} *M* in purified solvents. The instrument calibration was checked with 5α-cholestan-3-one in dioxane, $\Delta\epsilon$ +1.095 at 280 nm (lit.[42] $\Delta\epsilon$ +1.132 at 280 nm). Temperature control was accomplished using a jacketed 1-cm cell through the jacket of which was circulated methanol from a thermostatic bath and pump with electronic-temperature controller.

(42) L. Velluz, M. Legrand, and M. Grosjean, "Optical Circular Dichroism," Academic Press, New York, N. Y., 1965, pp 84–85.

Electrolyte Effects on the Cationic Micelle Catalyzed Decarboxylation of 6-Nitrobenzisoxazole-3-carboxylate Anion[1,2]

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Abstract: The unimolecular decarboxylation of 6-nitrobenzisoxazole-3-carboxylate ion is strongly catalyzed by micelles of cationic and nonionic surfactants. The catalysis by cationic micelles can be enhanced by adding some electrolytes or nonionic surfactants or by using dicationic surfactants, indicating that the catalysis is sensitive to changes in micellar structure and charge density. The mode of incorporation of aromatic sulfonate and carboxylate anions into cationic micelles has been investigated by nmr spectroscopy and by electrochemical and viscosity measurements, and the effects of such incorporated anions on micellar catalysis and structure are discussed. It appears that the anions insert into the micelle with the aryl groups fitting between the ammonium head groups of the surfactant.

Micellar catalysis is observed when reactants are taken into the micellar pseudophase and there have a greater reactivity than in the bulk solution.[5–10] Analogies between enzyme and micellar catalysis have been widely discussed,[6–10] but are discounted[8] because micellar catalysis generally lacks the substrate specificity and high catalytic activity of enzymes. Reactions occurring on micelles are akin to those occurring on lipid–protein interfaces, especially because micelles, like lipid bilayers, are easily structurally altered by

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(5) E. F. Duynstee and E. G. Grunwald, *J. Amer. Chem. Soc.*, **81**, 4540, 4542 (1959).

(6) R. B. Dunlap and E. H. Cordes, *J. Amer. Chem. Soc.*, **90**, 4395 (1968).

(7) E. M. Cordes and R. B. Dunlap, *Accounts Chem. Res.*, **2**, 329 (1969).

(8) H. Morawetz, *Advan. Catal. Relat. Subj.*, **20**, 341 (1969).

(9) E. J. Fendler and J. H. Fendler, *Advan. Phys. Org. Chem.*, **8**, 271 (1970).

(10) T. C. Bruice, *Enzymes, 3rd Ed.*, **2**, 217 (1970).