(3) P. Chaquin, B. Furth, and J. Kossanyi, *C. R. Hebd. Seances Acad. Sci., Ser. C*, **279**, 359 (1974).
(4) Pentane solution; medium-pressure Hg lamp; (a) 0.04 M, Pyrex; (b) 0.04 and 0.1 M methylnaphthalene, Vycor.
(5) J. R. Scheffer, K. S. Bhandari, Y. M. Ngan, and D. K. Schmidt, *Tetrahedron Lett.*, 1413 (1973).
(6) P. Chaquin and C. Lang, unpublished results.
(7) R. M. Silverstein, R. G. Brownlee, T. E. Bellas, O. L. Wood, and L. E. Browne, *Science*, **159**, 889 (1968); R. M. Silverstein, *J. Chem. Educ.*, **45**, 794 (1968).
(8) T. E. Bellas, R. G. Brownlee, and R. M. Silverstein, *Tetrahedron*, **25**, 5149 (1969); H. H. Wasserman and E. H. Barber, *J. Am. Chem. Soc.*, **91**, 3674 (1969); B. P. Mundy, R. D. Otzenberger, and A. R. DeBernardis, *J. Org. Chem.*, **36**, 2390 (1971); K. Mori, *Tetrahedron*, **30**, 4223 (1974); J. Knolle and H. J. Schäfer, *Angew. Chem., Int. Ed. Engl.*, **14**, 758 (1975).
(9) K. Alder, H. Offermanns, and E. Rüden, *Chem. Ber.*, **74**, 905 (1941).
(10) G. Stork and S. R. Dowd, *J. Am. Chem. Soc.*, **85**, 2178 (1963).
(11) G. Buchi and J. E. Powell, Jr., *J. Am. Chem. Soc.*, **92**, 3126 (1970).

Selective Halogenation of Steroids Using Attached Aryl Iodide Templates†

Ronald Breslow,* Richard J. Corcoran, Barry B. Snider, Ronald J. Doll, Pyare L. Khanna, and Ronald Kaleya

Contribution from the Department of Chemistry, Columbia University, New York, New York 10027. *Received July 1, 1976*

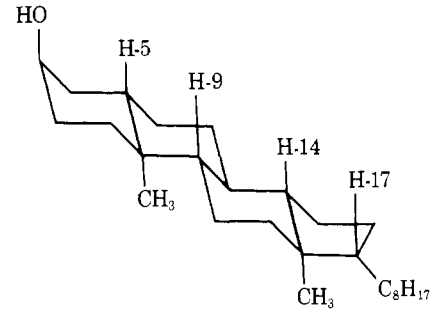
Abstract: The free radical chlorination of steroids by phenyliodine dichloride in aromatic solvents can be rather selective, leading to functionalization at unactivated tertiary positions. This process involves a solvent complex of the chlorine atom and can be directed by substituents in the substrate. More selectivity is achieved by a different mechanism when the aryliodine dichloride reagent is directly attached to the substrate. Thus 3α-cholestanyl *m*-iodobenzoate dichloride undergoes internal hydrogen abstraction in a free radical chain process to afford a 9α-chlorosteroid. The process is directed by the geometric relationship between substrate and reagent, and other geometries can be used to direct functionalization at C-14 or at C-17. A variant is the radical relay process, in which the intermediate chloroiodoaryl radical is generated by chlorine atom transfer to a template molecule attached to the substrate. Here too, geometric relationships can be adjusted to direct the reactions. The processes are illustrated by a cortisone synthesis, by the conversions of sitosterol and cholesterol to androsterone, and by synthesis of a cardenolide intermediate. In one case the template directed halogenation of an unactivated carbon took place even in the presence of an unprotected enone system.

Some years ago, we initiated a program to introduce certain enzymatic principles into the design of specific organic functionalization reactions. The essential idea[1] was that the selectivity of enzymatic reactions is determined in large part by the geometric demands of the reagent, rather than by the intrinsic reactivity pattern of the substrate. This is in marked contrast to the usual synthetic chemical style, in which functional group manipulation is used to adjust the substrate reactivity so as to produce a desired result.

Our first approach to this area involved the use of benzophenone photochemistry.[2] Various derivatives of benzophenone were attached to flexible substrates and to steroids and were then photolyzed. This led to attack on unactivated positions in the substrate dictated by the geometrical relationship between the substrate and the attached reagent. Good control was achieved using this technique, but such photochemistry with quantum yield less than unity is of limited practical synthetic interest. Therefore, a few years ago we set out to devise similar reactions by which free radical chain halogenation processes could be directed in this same general fashion. We hoped to attach a reagent to a substrate and then have the reagent carry out a free radical halogenation whose selectivity would be determined by the precise geometrical relationship between the reagent and substrate.

In our search for a suitable rigid free radical halogenating reagent, we were drawn to phenyliodine dichloride, which has great selectivity[3] for tertiary hydrogens compared with secondary or primary CH bonds. Such a reagent promised to let us combine chemical selectivity of this sort with geometrical control. While this is not ideal in terms of our ultimate goal, in which geometrical control alone is to determine reactivity, such a combination of factors has certain practical advantages in permitting selective functionalizations. We had found in our benzophenone photochemistry[2] that with only one point of connection between substrate and reagent, the ester link at which they were joined, we frequently saw attack at several positions in a steroid because the reagent could swing in an arc under the substrate hydrogens. With a reagent which has a large chemical preference for tertiary hydrogens, such motion is not a problem in steroid functionalization. The tertiary hydrogens on the α face of a steroid are distributed radially from the oxygen at carbon 3, so any arc whose center is that oxygen is likely to encounter only one of these tertiary hydrogens. We thus set out to attach aryl iodides to steroid substrates, in order to carry out intramolecular halogenations using the corresponding aryliodine dichlorides.

First we undertook a short study[4] of the selectivity of unattached phenyliodine dichloride in steroid functionalization.



3α-cholestanol

With convenient concentrations of various steroids and phenyliodine dichloride in nonaromatic solvents, such as methylene chloride, no appreciable amount of halogenation of the steroid was observed when a free radical process was

† Dedicated to R. B. Woodward on the occasion of his sixtieth birthday.

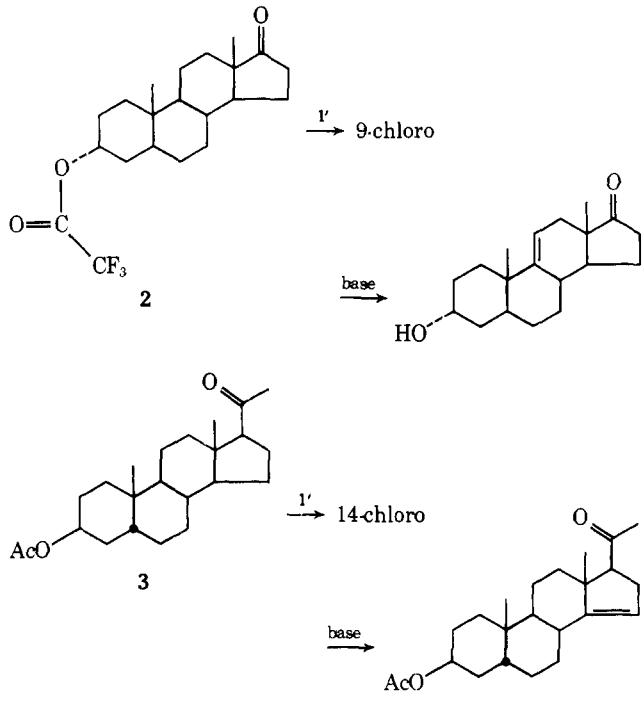
initiated. These free radical halogenations are most conveniently initiated by simple photolysis, although, as is described in the Experimental Section, other methods can be used. It is known that phenyliodine dichloride undergoes a light-induced self-decomposition to produce chloroiodobenzene and other products.[5] This process, which may involve a rearrangement of the intermediate radical **1**, apparently occurs more rapidly than does attack on the steroid in dilute solution. However, in aromatic solvents such as benzene or chlorobenzene, the steroids are halogenated; with 3β-cholestanyl acetate for instance the process is directed to halogenate largely at carbons 9 and 14 of the steroid. Thus, there is a preference for attack on tertiary α-hydrogens, specifically those axial on six-membered rings away from any polar substituents. We have used this polar effect to direct halogenation with such a random reagent specifically into the 9 position of androsterone trifluoracetate (**2**), with resulting introduction of the synthetically important 9(11) double bond.[6]

At first, we believed[4] that the aromatic solvent might be stabilizing the chloroiodophenyl radical **1** by complexing. However, it is now almost certain that instead the aromatic solvent complexes the chlorine atom of **1** and removes it from iodobenzene to produce a simple solvated chlorine **1'**; this is then the hydrogen abstracter in this reaction. The evidence for this is twofold. First of all, we find essentially the same selectivity if we simply halogenate steroids in benzene solution with Cl_2 photolytically, so that the chlorine atom complexed to benzene behaves in the same way as does the reagent generated in our system. Secondly, in the intramolecular halogenations with attached reagents to be described below, aromatic solvents promote intermolecular halogenations. This is most easily understood if the aromatic solvent carries off the chlorine atom from a radical intermediate and thus leads to intermolecular halogenation. It might be added that while the σ complex of a chlorine atom on iodobenzene must be more stable than is the π complex of a chlorine with the benzene solvent, the concentration of the solvent molecules is much higher than is that of the reagent. Thus it would not be surprising that the chlorine atom σ-iodobenzene complex could be converted to the benzene π complex.

$$C_6H_5ICl_2 \xrightarrow{h\nu} \underset{\mathbf{1}}{C_6H_5\dot{I}Cl} \xrightarrow{\text{benzene}} C_6H_5I + \underset{\mathbf{1'}}{\text{C}_6\text{H}_5\text{Cl}\cdot}$$

However this process is performed, it can have attractive selectivity in some cases. Thus, we have also reported[7] that under similar conditions the keto ester **3** with an A/B cis junction can be selectively halogenated at carbon 14 to produce an interesting intermediate useful in the synthesis of cardenolides. In this case, a combination of conformational and polar effects directs the random halogenation essentially exclusively to carbon 14.

Several other reports have appeared of selective functionalizations related to these simple halogenations. Thus, Mazur has reported[8] moderately selective hydroxylations of steroids under free radical conditions, although curiously he found that hydroxyl radical did not attack the C-9 hydrogen which is always a major point of attack in our chemistry. Furthermore, Barton et al. have recently reported[9] the selective fluorination of steroids using F_2. Although the mechanism Barton suggested is a direct electrophilic fluorination, it seems more likely that this process involves the frequently discussed[10] direct reaction between a hydrocarbon and F_2 to generate a pair of radicals. In the gas phase this reaction is usually then followed by rapid free radical chain processes, but in the low-temperature liquid-phase reaction described by Barton, these chains can be suppressed, and the principal product probably arises from a cage recombination of the carbon radical with the fluorine atom. Barton observes similar polar effects to those we had reported previously[6] for our selective chlorination reaction, and the yield and selectivity in his process seem to be comparable to or slightly better than those we can achieve with our selective chlorination in aromatic solvents.



$$t\text{-R-H} + F_2 \longrightarrow t\text{-R}\cdot + \text{H-F} + \text{F}\cdot (\longleftrightarrow \text{R}^+ + \text{HF} + \text{F}^-)$$

$$\text{cage recombination} \downarrow \qquad \Delta H^\circ = -8 \text{ kcal/mol}$$

$$t\text{-R-F}$$

Attached Aryl Iodine Dichlorides. Guided by molecular models, we constructed the *m*-iodobenzoate ester of 3α-cholestanol and converted it with Cl_2 to the corresponding dichloride (**4**). During this conversion the steroid is unaffected (it can be recovered unchanged on saponification). When this dichloride is briefly irradiated with a sunlamp, a free radical halogenation of the steroid ensues. Other radical initiating methods have also been used (cf. Experimental Section).

In our original report, this reaction was performed in chlorobenzene,[6] in which case the reaction led to 43% of the Δ9(11)-cholesten-3-ol acetate, after saponification (with concomitant dehydrochlorination) and acetylation. However, 35% of the 3α-cholestanol (acetate) was recovered, and 9% of the Δ14 cholestenol derivative was also formed along with 2% of the Δ5 olefinic product. Androstane was included in this reaction as a control, and it was halogenated to the extent of 20%, so intermolecular halogenations are accompanying a selective intramolecular process.

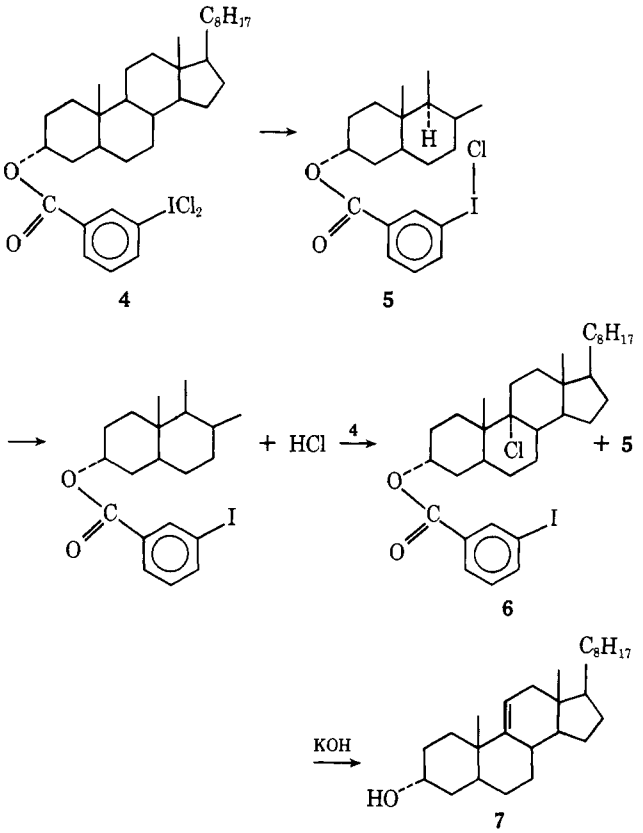
This mixture is formed because the aromatic solvent is able to carry off the chlorine atom from the intermediate radical **5** and permit it to attack substrates in a random fashion. If instead the halogenation is performed in a nonaromatic solvent such as methylene chloride, then a very high conversion of the starting material is achieved and there is furthermore no significant amount of attack at C-5 or C-14. There is also no functionalization of externally added androstane.

The product 9α-chloro steroid **6** can be isolated and characterized, but in this and related reactions it is most convenient to carry out a saponification–dehydrochlorination and characterize the product as the derived 9(11) olefin (**7**). The yields

Table I. Isolated Olefins from Template Directed Halogenation, then Dehydrohalogenation

Substrate (concn, M)	Solvent	Added $C_6H_5ICl_2$ concn, M	% conversion	Product distribution Δ9(11)	Δ14	Δ16	Polar[a]
2 (0.01)	Benzene	0.01	75	58			35[b]
3 (0.01)	Benzene	0.01	66		54		39[b]
4 (0.001)	CH_2Cl_2		92	62.3	3.3		34.5
4 (0.001)	Cyclohexane		61	78.4	8.1		13.5
4 (0.01)	CH_2Cl_2		82	80.7	4		16
4 (0.001)	Benzene		66	66	14		17[c]
8 (0.01)	CH_2Cl_2		54		55		45
10 (0.01)	CH_2Cl_2		50.5	48	25		26
11 (0.01)	CH_2Cl_2	0.01	78.4	84			16[d]
12 (0.01)	CH_2Cl_2	0.01	48.8	51	22.5		26.6
13 (0.01)	CH_2Cl_2	0.01	0				
14 (0.01)	CH_2Cl_2	0.01	0				
15 (0.01)	CH_2Cl_2	0.01	40	54			46
16 Dichloride (0.01)	CH_2Cl_2		57		54		46
17 (0.01)	CH_2Cl_2	0.012	88			61	15
19 (0.01)	CH_2Cl_2	0.01	39.5	6	24.5	27.6	41.7
20 (0.01)	CCl_4	0.011	56			66	33
21 (0.001)	$CHCl_3$	0.002	100			48[e]	
22 (0.01)	CH_2Cl_2	0.015	100	88[e]			
23 (0.0003)	CH_2Cl_2	0.00045	100	77[e]			
26 (0.01)	CH_2Cl_2	0.01	22	53			47
26 (0.001)	Benzene	0.001	37.5	31	15.5		42[f]

[a] The product of rearrangement or further halogenation of intermediates. [b] The Δ5 olefin was also formed in ~7% yield. [c] With 1 equiv of androstane present, 21% of the androstane is functionalized. [d] No detectable functionalization of added androstane. [e] Isolated yield, based on starting material. [f] The Δ5 olefin was also formed in 11% yield.



of various products from these reactions under several conditions are listed in Table I.

Molecular models suggest that the dichloride **8** derived from the *p*-iodophenylacetic acid ester of 3α-cholestanol should be able to halogenate at C-14. In both cases these predictions from models are based on the assumption that the intermediate chloroiodoaryl radical has fundamentally the same geometry as that of the precursor aryliodine dichloride. In the solid phase, the latter is known[11] to have the iodine hybridized as a trigonal bipyramid, with the chlorines occupying the two apical positions and the Cl-I-Cl line perpendicular to the phenyl plane. We furthermore assume, in constructing the models for the hydrogen abstraction transition state, that it is the chlorine atom, not the iodine atom, which abstracts the hydrogen. Abstraction by the iodine had been suggested,[12] but it seems energetically unlikely. The full strength of the H-Cl bond would be required in order that the breaking of the C-H bond not be greatly endothermic. This argues for a one-step abstraction by chlorine rather than a two-step process, first abstraction by iodine, followed by an HCl loss from an intermediate tricoordinated iodine. The molecular models are also constructed with the ester in its preferred extended (nonlactone) conformation.[13]

Since a number of conformational points have to be kept in mind, such predictions from models may seem somewhat arbitrary. Thus we have examined other ways to predict the selectivities in these systems. One method involves mapping onto the steroid skeleton the geometrical change in going from a known template to a new template. To illustrate, in the conversion from a *m*-iodobenzoate to a *p*-iodophenylacetate, the iodine atom has been moved two carbons farther from the steroid oxygen. This should then put it two atoms farther out on the steroid skeleton, under C-14 (or C-12, a secondary hydrogen).

An alternative way to remove some of the arbitrary character from the inspection of models is to calculate distances using the known x-ray structures of steroids and other components of our systems. This has been done using a simple Cartesian coordinate program,[14] and the results are displayed in Table II. As with the models, we must make some conformational choices, dictated by considerations of steric crowding and known conformational preferences. The table shows that such calculations correctly correlate the radial distance between a steroid oxygen and the hydrogen being abstracted with the radial distance between that same oxygen and the chlorine on the reagent which is carrying out the abstraction. However,

Table II. Calculated Distances in Steroids and Reagents

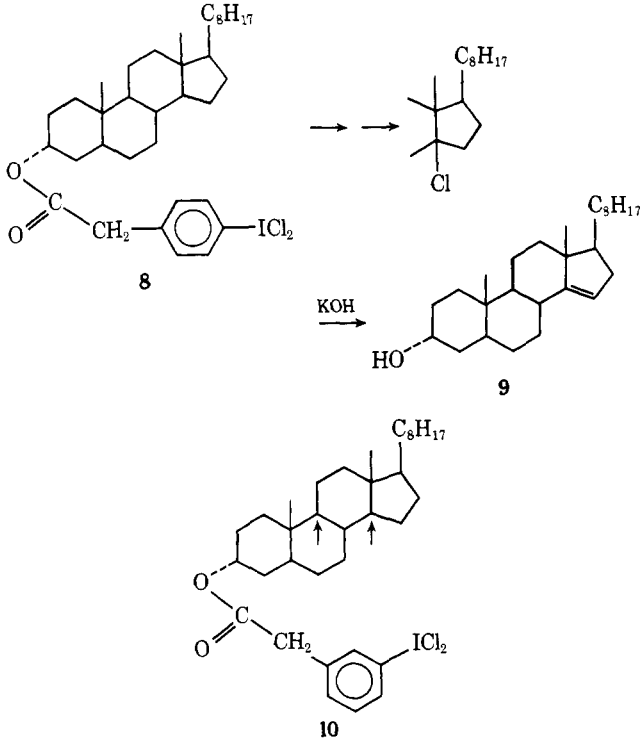
Steroids (A/B trans) Oxygen	Hydrogen	Distance, Å[a]
3α	9α	4.41
3α	14α	6.52
3α	17α	8.49
7α	17α	5.04[b]

Reagent-chlorine atom σ complex[c]	Oxygen-chlorine distance, Å[d]
m-Iodobenzoate	4.27
p-Iodophenylacetate	6.84
m-Iodophenylacetate	5.24
4'-Iodo-3-biphenylcarboxylate (**3**)	8.68
4-(*p*-Iodophenyl)butyrate	8.11

[a] Calculated from x-ray crystal diffraction data for 5α-androstan-3α,17β-diol.[38] [b] Calculated from average values of steroidal molecular dimensions.[39] [c] Standard bond lengths and angles appropriate to straight-chain alkanes in their most stable conformation were assumed. Ph-I and I-Cl bond lengths and the Ph-I-Cl bond angle were taken from x-ray data for $PhICl_2$.[11] Reasonable conformations for the reagents were assumed.[14] [d] The distances between the ester oxygen and a chlorine atom attached to the iodine were calculated from the Cartesian coordinates of the atoms involved.[40] The ester group was assumed to be in the nonlactone conformation.[13]

there seems to be no advantage to this method over the examination of models, provided that the same careful conformational choices are made.

As predicted from all of these considerations, the *p*-iodophenylacetate of 3α-cholestanol, when converted to its dichloride **8** and submitted to our free radical initiating conditions, does perform a selective halogenation at C-14. With

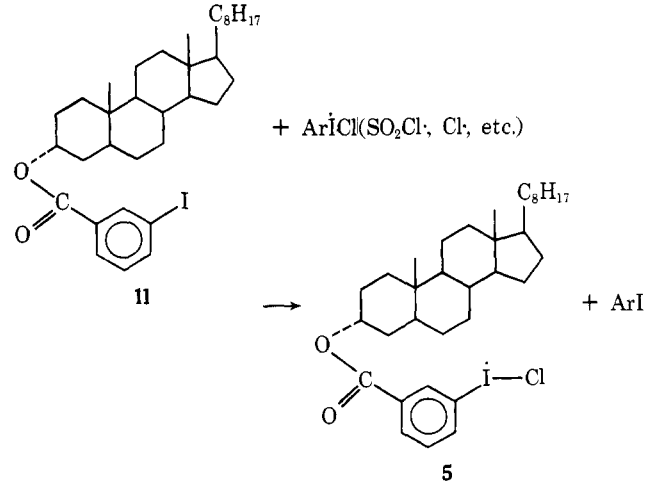


aromatic solvents[6] we again get some evidence of chlorine atom transfer to the solvent with accompanying intermolecular chemistry, but in nonaromatic solvents there is no detectable amount of halogenation at C-9 or any of the other tertiary positions of the steroid except for C-14. However, a significant fraction of the product is what we describe as "polar material". Previous studies[15] indicate that this results from olefin production during the halogenation process itself, and consequent halogenations of the olefinic product to more highly functionalized materials. As we will describe below, under carefully controlled conditions a template carrying a sulfur rather than an iodine atom gives a much higher yield of this C-14 halogenation, with much less of the accompanying side products.

When the *m*-iodophenylacetate ester **10** of 3α-cholestanol is prepared and converted to its dichloride, the intramolecular reaction leads to halogenation at both C-9 and C-14. This reaction was established to be purely intramolecular by the finding that accompanying androstane was not functionalized (in a nonaromatic solvent). The result is predicted from models and the consideration of the general geometric points made above. Extending the *m*-iodobenzoate by one carbon moves the iodine under C-8, which has a hydrogen on the β side of the steroid and cannot be attacked. However, it also puts the iodine exactly between the axial hydrogens at C-9 and C-14; a slight motion allows the reagent to attack either one. It is interesting that the ratio of attack on these two positions (Table I) is actually fairly close to unity. This particular reaction is not of synthetic interest, but it is an interesting indication of the extent to which molecular models or geometrical arguments can be used to predict the selectivity of these reactions. The result will also be used below as a test for a particular mechanistic point.

Radical Relay Mechanism. In some respects, the sequence described above is not quite optimal. After the attachment of an iodoaryl template to the substrate, that template is converted to the aryliodine dichloride with Cl_2, and a free radical halogenation reaction is then initiated. In a particular practical application which we wish to pursue, the synthesis of cortisone (vide infra), this treatment with Cl_2 led to some side reactions in other parts of the molecule. However, the species **5** which removes hydrogen from the substrate can be considered a σ complex of Cl· with an iodoaryl group. It thus occurred to us that this species might also be generated by external transfer of a chlorine atom to the aryl iodide itself, by-passing the necessity for the preparation of an aryliodine dichloride.

We have called the mechanism envisioned a radical relay process.[16] In it a species bearing a chlorine atom (Cl·, SO_2Cl·, ArICl·, etc.) attacks substrate **11.** However, instead of per-



forming its normal attack on a hydrogen of the substrate, it instead relays the chlorine atom to the iodine of the attached template to generate intermediate **5.** This would then direct hydrogen abstraction with geometric control by the template.

It might be wondered why there should be any preference for a mechanism in which the external halogenating agent uses an additional step before the substrate hydrogen is removed.

This is a common situation in a number of reactions, and the two-step process is frequently preferred. As an example which was discussed first by us some years ago,[17] there is an entropy advantage to the common two-step mechanism for enzymatic hydrolysis. Many hydrolytic enzymes do not use a water molecule to attack the substrate directly but instead use an enzymatic group to make an intermediate, and then hydrolyze that intermediate in the second step. This indirect sequence has the advantage that the external reagent water is not tied down until the translational entropy of one of the fragments of the substrate has been recovered. Similarly, in the radical relay halogenation mechanism the advantage to the two-step sequence using an external ArICl· to transfer the chlorine is of the same form. That is, the external reagent can recover the translational entropy of the ArI fragment before the restricted geometry of the transition state for hydrogen abstraction is imposed.

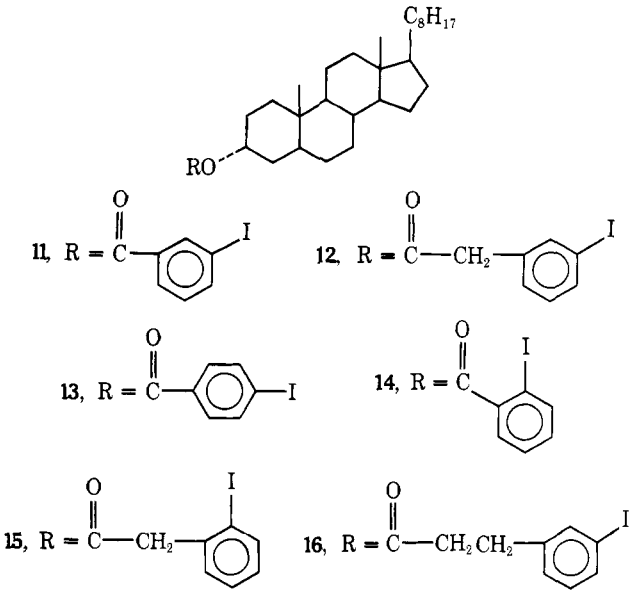
On this basis one might expect a preference for the radical relay mechanism; this is what we observe. Treatment of the *m*-iodobenzoate **11** with phenyliodine dichloride in CH_2Cl_2 solution leads to no halogen exchange when the solution is allowed to stand, and similarly no halogen exchange can be detected starting with the attached aryliodine dichloride **4** and free iodobenzene under the same conditions. However, when the solution of **11** with phenyliodine dichloride is briefly irradiated with a sunlamp, a very rapid halogenation of the steroid occurs, and the exclusive monohalogenated product is the 9-chloro steroid in excellent yield (Table I). Samples of the reaction mixture taken during the photolysis did not show the characteristic NMR spectrum of **4** either. Thus, we conclude that externally generated chloroiodophenyl radical transfers its chlorine to the iodoaryl template of **11,** presumably reversibly, but that the attack on the substrate occurs exclusively from the resulting radical **5** and is thus completely selective.

Since external chloroiodophenyl radical, if it attacked the steroid directly, would have halogenated at C-14 as well, it is apparent that the radical relay mechanism is preferred over such a direct attack. Other evidence for this is that we are able to perform this reaction in the solvents in which chloroiodophenyl radical undergoes decomposition rather than attack the steroids. Thus, the iodoaryl template attached in intermediate **11** both catalyzes the halogenation and directs it specifically according to the geometry of the intermediate radical **5.**

We have another piece of evidence that precisely the same radical intermediate is involved in the radical relay process as in the process starting from an attached aryliodine dichloride. That is, the *m*-iodophenylacetate ester of cholestanol (**12**) gives the same mixture of the C-9 and C-14 chloro steroids under radical relay conditions as it does when starting with the aryliodine dichloride (**10**) directly attached to the steroid.

The radical relay process has the advantage that one less step is performed on the substrate. Furthermore, milder reagents can be used and an excess of the chlorinating agent can be available to achieve complete conversion of the substrate. Thus we generally have selected this as the process of choice in our template directed halogenations. It should be pointed out that in his classic work on halogenation by arene complexes of Cl·, Russell suggested[18] that iodobenzene forms a σ complex with Cl· at the iodine. This is the species we are suggesting as our intermediate.

Other Templates and Other Attachments. When 3α-cholestanyl *p*-iodobenzoate (**13**) was used in the radical relay reaction, no steroid functionalization resulted. As was found with a simple benzophenone-*p*-carboxylic acid ester of cholestanol,[2] models show that the *p*-iodobenzoate ester is held in the shape of a V, and the chlorine attached to iodine cannot reach the steroid. Similarly, the *o*-iodobenzoate ester of 3α-cholestanol (**14**) did not undergo functionalization under these conditions. Apparently steric crowding prevents this potential template

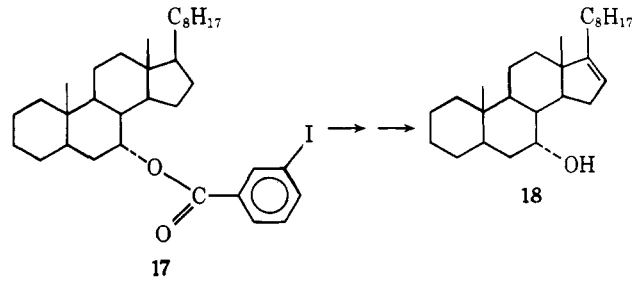


from attaining a reactive conformation. However, *o*-iodophenylacetic acid can serve as a template in **15** to direct halogenation to C-9. The yield is not as good as that with the *m*-iodobenzoate, but the product is the same: an *o*-iodophenylacetate is topographically similar to a *m*-iodobenzoate in the relationship between the iodine and ester groups.

For the same reason, a *m*-iodophenylpropionate is essentially equivalent to a *p*-iodophenylacetate ester. That is, starting with *m*-iodophenylacetic acid, the distance between the iodine and the ester groups can be lengthened by one bond, either by inserting an extra methylene group into the chain or by moving the iodine from the meta to the para position. Thus, the *m*-iodophenylpropionate ester of 3α-cholestanol also undergoes halogenation at C-14, as did the *p*-iodophenylacetate ester.

Halogenation at C-9 is of interest in the preparation of corticosteroids, which is discussed below. The functionalization at C-14, especially in the A/B cis series, is of interest in the production of cadenolides. The remaining centers of practical interest are at C-17 or in the side chain. Sitosterol is an abundant plant sterol which could serve as an important precursor of steroid hormones and drugs if an efficient side chain removal procedure were available. Thus, we turned our attention to the use of our template methods for achieving such side chain removal.

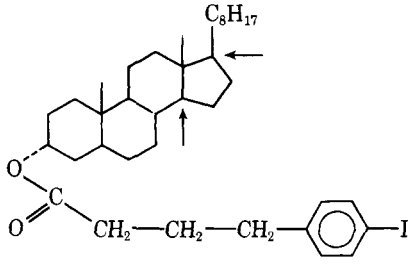
The first system examined was simply designed to see whether the otherwise rather inactive C-17 hydrogen could be selectively removed with an appropriate template method. The *m*-iodobenzoate ester of 7α-cholestanol **17** was prepared and submitted to the radical relay conditions. The principal product was the 17-chloro steroid, which proved to be somewhat unstable with respect to a rearrangement involving migration of the angular methyl group. Accordingly, the product was directly converted by saponification–dehydrochlorination to the Δ16 olefin **18** in good yield (Table I). As the calculations in Table II show, the distance between C-7 and C-17 is comparable with that in the *m*-iodobenzoate template, and models



17 18

confirm this. Moving the ester attachment from C-3 to C-7 on the steroid involves a four bond displacement, and this similarly displaces the position of attack by four bonds from the C-9 to the C-17 hydrogen.

A method to achieve the correct geometry starting at C-3 might be to consider that the C-3 *p*-iodophenylacetate directed halogenation to C-14. If we extend the chain by two more carbons to make **19,** the iodine would be moved out two atoms

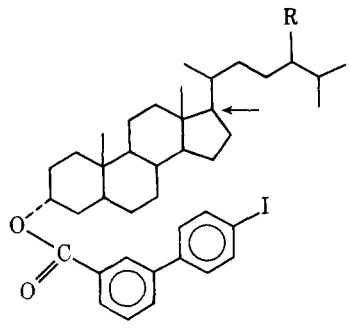


19

farther, under C-17. As Table I shows, this was partially successful, but such an extension by a flexible polymethylene chain leads to the possibility of several conformations, and permits some attack at C-14. Thus, a more rigid chain extender was required.[19]

The most obvious way to incorporate the three methylenes of *p*-iodophenylbutyric acid into a rigid system is to make them part of a ring. On the basis of other considerations, we also concluded that a template which would perform this halogenation is 4-iodobiphenyl-3′-carboxylic acid. It is apparent that this can be considered to be a derivative of the phenylbutyrate in which the fully extended conformation is locked. Alternatively, it may be noted that the *m*-iodobenzoate directed halogenation to C-9, and that C-17 simply lies one six-membered ring farther away. Of course, six-membered ring C is not aromatic, but the two-dimensional projection of a chair cyclohexane is very close to the geometry of a benzene ring. It also should be added that in a model the iodine in compound **20** did lie under C-17, and the calculated distance (Table II) was also similar to that required.

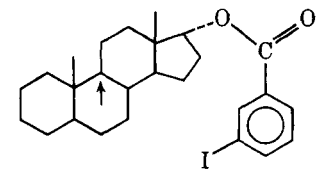
As Table I shows, application of our radical relay conditions to compound **20** directed halogenation to C-17 with no evi-



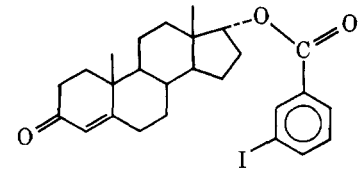
20, R = H
21, R = Et

dence for halogenation of any of the other steroid positions. A good yield of the Δ16 olefin was thus obtained. Furthermore, the same sequence could be applied to the ester **21** derived from sitosterol. Again, an excellent conversion of this material to the Δ16 derivative was observed. The use of these compounds for the removal of the side chain[20] will be discussed below.

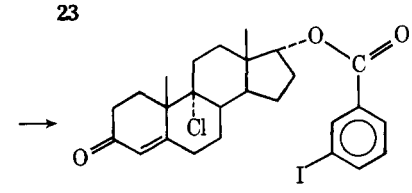
One other point was investigated in conjunction with some considerations in corticosteroid synthesis. The distance from C-17 to C-9 is essentially identical with that from C-3 to C-9, so a *m*-iodobenzoate ester of 17α-androstanol (**22**) was prepared and submitted to the radical relay conditions. As Table I indicates, a highly selective halogenation of C-9 also occurred



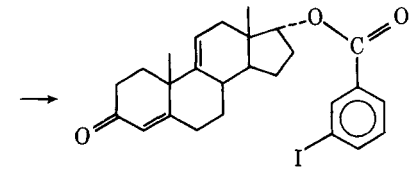
22



23



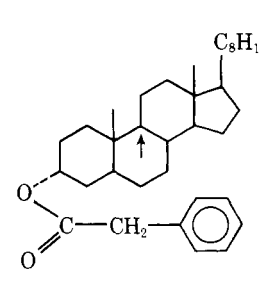
24



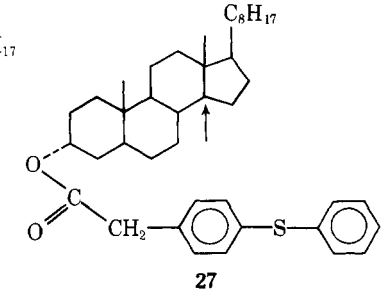
25

in this system, with good yield. Since these halogenations seemed to be so selective, it was of interest to see whether they could be carried out even in the presence of functionality which might normally direct a random halogenation process. Accordingly, the *m*-iodobenzoate ester of 17-epitestosterone **23** was prepared. In this compound a radical relay halogenation should also direct functionalization to C-9, but this is of course not activated by any of the functional groups. It was problematical whether a halogenation of this kind, directed to an unactivated position, could compete with halogenations involving the enone system. In fact, as Table I shows, the radical relay halogenation was fully competitive and an excellent yield of the 9-chloro derivative **24** was obtained. This could be dehydrochlorinated under mild conditions to the 9(11) olefin (**25**). The overall process thus seems to have considerable promise for corticosteroid synthesis.

Russell's work on chlorine atom complexes with aromatic compounds[18] suggested that a simple aromatic ring, and also an aryl sulfide, might be able to serve as templates. When the simple phenylacetate ester of 3α-cholestanol (**26**) was sub-



26



27

mitted to our radical relay conditions we did find some halogenation of the steroid in a nonaromatic solvent, which would not have been observed without the aromatic ring template. Furthermore, there was a preference for halogenation at C-9, although the preference is not as striking as is that for our iodoaryl templates (Table I). Thus, a simple aromatic ring template seems to be less useful than one carrying a heteroatom

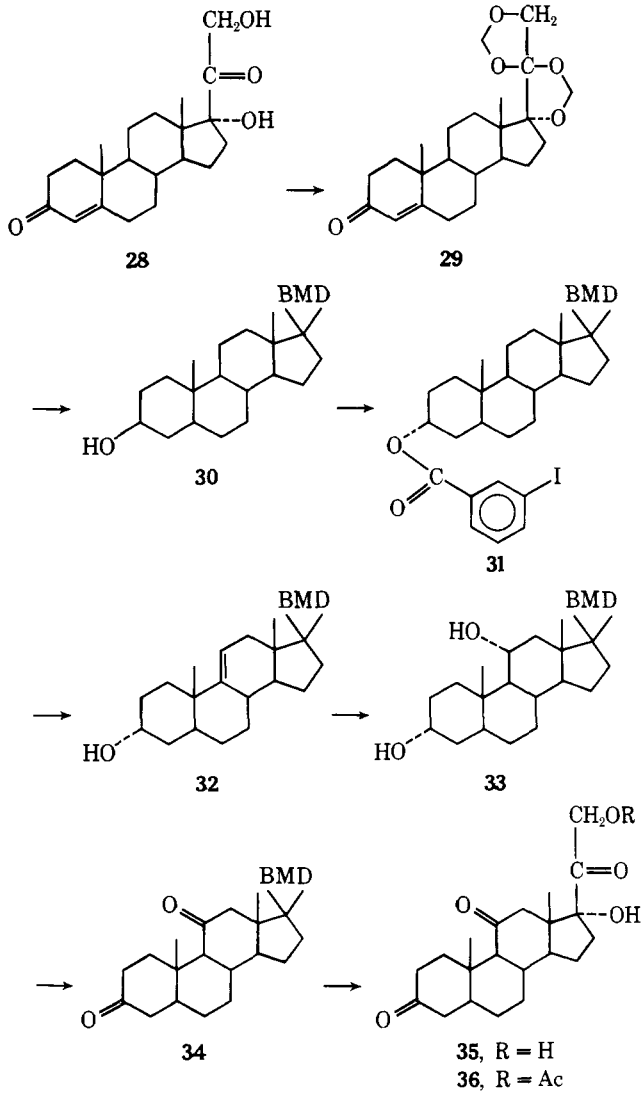
which can be used as a specific point of attachment of the chlorine atom.

We have reported elsewhere[21] that a diphenyl sulfide template can be used in a radical relay halogenation with SO_2Cl_2 to direct halogenation at C-14 in compound **27** with very good yield. We have also described[22] use of the *m*-iodobenzoate **11** in an electrochemical template-directed halogenation at C-9 in a yield comparable with that we obtain under our normal free radical conditions.

Conversion of Cortexolone to Dihydrocortisone. As a specific practical application of our template methods, we decided to apply them to the introduction of the C-11 oxygen of a corticosteroid. Arbitrarily, we chose to start with cortexolone (**28**), although in a realistic synthetic sequence our functionalization reaction should be performed on an earlier intermediate in the synthesis of cortexolone.

Cortexolone was protected[23] by treatment with formalin and HCl to the bis(methylenedioxy) derivative **29,** and this was then reduced with lithium in ammonia, ethanol, and ether to the corresponding saturated 3β-alcohol **30** (Scheme I). With

Scheme I



m-iodobenzoic acid, triphenylphosphine, and azodicarboxylic ester this underwent the convenient inversion–esterification reaction[24] to produce the *m*-iodobenzoate **31,** which was then submitted to our radical relay conditions (using either phenyliodine dichloride or sulfuryl chloride). The product 9-chloro derivative could be detected spectroscopically, but for convenience the product was directly saponified and dehydrohalogenated to afford the unsaturated steroidal alcohol **32,** isolated as the corresponding acetate. Then **32** was hydroborated[25] and oxidized with alkaline hydrogen peroxide to afford the diol **33,** and this was oxidized to the corresponding dione **34** with Jones' reagent. Deprotection with HF[26] afforded dihydrocortisone[27] **35.** On acetylation this afforded dihydrocortisone acetate[28] **36,** identical with authentic material in every respect. The overall yield in the entire sequence starting from cortexolone is 30%, and the sequence by which intermediate **32** is converted to diol **33** goes in a 68% overall yield. Since the conversion of dihydrocortisone acetate **36** to cortisone acetate[29] and also to prednisolone acetate[30] are both well known, our procedure accomplishes new syntheses of both of these compounds.

Removal of the Side Chain from Cholesterol and Sitosterol. As another practical application of our techniques, we wanted to convert available sterols to useful hormone intermediates. We have described above how templates can be used to introduce halogen at C-17 in sterol derivatives. The particular cases of most practical interest involve the use of biphenyl template in **20** and **21,** prepared by inversion–esterification.

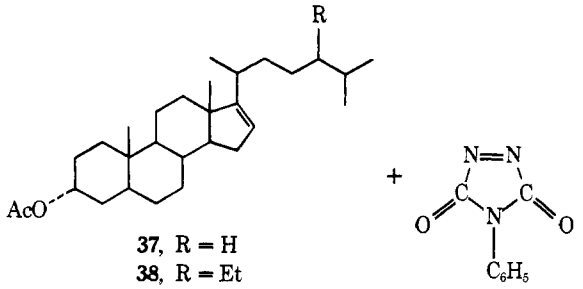
In both cases, as Table I indicates, a good yield of the Δ16 unsaturated steroid was obtained after saponification–dehydrochlorination of the 17-chloro derivative obtained from radical relay halogenation. However, we were not able to find any conditions in which the 17-chloro compound could be dehydrohalogenated directly to the 17(20) olefin. This probably reflects the instability[31] of the 17(20) double bond, because of the steric crowding introduced between side chain atoms and C-12 of ring C. Accordingly, there seems to be no way to move the double bond into the 17(20) position by equilibration, so we were forced to devise a method which supplies chemical energy to drive it.

Various attempts at allylic halogenation proved abortive, apparently because the hydrogens at C-15 are at least comparable in reactivity with the hydrogen at C-20. However, we found that compound **37** underwent a facile ene reaction with *N*-phenyltriazolinedione, and this was also true of compound **38** derived from sitosterol. The reaction appears to be highly regio- and stereoselective, and only a small amount of another isomer can be detected. This high selectivity is undoubtedly the result of a mechanism in which the enophile initiates attack on the unhindered end of the double bond, and thus perforce must remove the allylic hydrogen from the more hindered side.

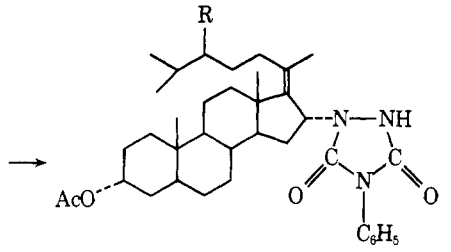
The resulting derivatives **39** and **40** could in principle be submitted to selective oxidative reactions, and we have examined various transformations of these materials. However, the simplest route to a steroid hormone intermediate starts with the reductive removal of the addend with lithium in ethylamine.[32] Such a reduction proceeds through the allylic anion, which could in principle have protonated at C-20 or at C-16. In the first case we would have restored our original Δ16 double bond, but we considered this an unlikely course for the reaction to take. Protonation at C-16 involves a less hindered transition state, in which as well the negative charge is being localized on a secondary, rather than tertiary, carbon. In fact, in both the cholesterol and sitosterol series the reduction goes essentially exclusively in this fashion, with the production of the *Z* isomer[33] of the Δ17(20) sterol derivatives **41** and **42.**

We found it convenient to saponify the 3-acetate before this reduction, to prevent hydrogenolysis at C-3. The reduction product was then reacetylated and ozonized to afford androsterone acetate (**43**) in good overall yield. Other transformations of these intermediates can be envisioned in which a 17-acetyl group might be left behind with removal of only a portion of the side chain. However, the 17-keto steroid produced by the sequence we have described is a useful intermediate in the synthesis of a variety of medicinally active steroid hormones.

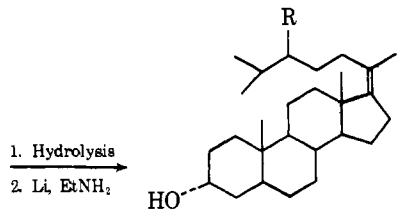
In the coprostanol series (A/B cis fusion) a template must



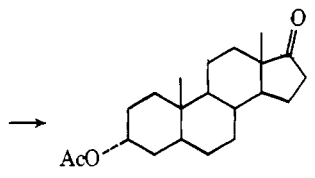
37, R = H
38, R = Et



39, R = H
40, R = Et

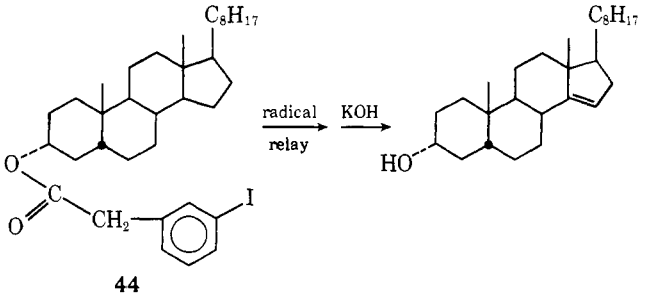


41, R = H
42, R = Et



43

not only be of the right length but also be able to curve[35] along the now angular steroid. Models suggested that **44** should be suitable for attack at C-14, and this proved correct.[7] Such 14-functionalization in the A/B cis series is attractive for cardenolide synthesis.



44

Our results show that template-directed reactions have great potential for selective synthesis. Furthermore, they show that predictions of selectivity can be made with some confidence. The generalization of these concepts should thus be a fruitful activity.

Experimental Section

Iodoaryl Acids. Most of the template acids were known compounds and were prepared by standard procedures. 4′-Iodobiphenyl-3-carboxylic acid, mp 219–221 °C, was prepared from the methyl ester of biphenyl-3-carboxylic acid[36] by refluxing it (6.24 g, 30 mmol) with potassium iodate (1.290 g), iodine (3.045 g), water (13 ml), acetic acid (27 ml), and sulfuric acid (2 ml) for 9 h,[37] then treating the solution with SO_2 until it was light yellow. On cooling the mixture to room temperature, the product acid crystallized (7.28 g, 75% yield) and was essentially pure. It could be recrystallized from chloroform–acetone. In the NMR the compound showed a broad four-hydrogen multiplet at δ 7.33–8.17, a two-hydrogen doublet at δ 7.83 (J = 8 Hz) and a two-hydrogen doublet at δ 7.48 (J = 8 Hz). The CI mass spectrum showed major peaks at m/e 325, 324, 307, and 198.

Preparation of the Steroid-Template Esters. All of these esters could be made by reaction of the appropriate acid chloride and alcohol under standard conditions. In addition, esters of aromatic carboxylic acids could be prepared in good yield by the Bose inversion-esterification method,[24] producing the α esters from the corresponding β steroidal alcohols. An example of each procedure is described.

Acid Chloride Method for the Production of 5α-Cholestan-3α-yl *m*-Iodobenzoate (11). 3α-Cholestanol (4.85 g, 12.5 mmol) and *m*-iodobenzoyl chloride (3.37 g, 12.7 mmol) were dissolved in 20 ml of dry benzene, and 2 ml of pyridine were added. The mixture was heated at 80 °C under nitrogen for 8 h. The solvent was removed on a rotary evaporator and the residue diluted with 200 ml of ether. This was washed twice each with 25-ml portions of both 10% hydrochloric acid and sodium bicarbonate. The organic layer was dried ($MgSO_4$) and evaporated, and the residue was recrystallized from ethanol to afford 6.6 g (84% yield) of colorless crystals: mp 89.5–90.5 °C; NMR ($CDCl_3$) δ 8.38 (t, 1 H, J = 1.5 Hz), 7.95 (tt, 2 H, J = 8, 1.5 Hz), 7.18 (t, 1 H, J = 8 Hz), 5.28 (broad, 1 H, $W_{1/2}$ = 8 Hz, 3β-H), side chain methyls at 0.91 and 0.81, axial methyls at 0.83 and 0.66. Anal. ($C_{34}H_{51}O_2I$) C, H, I.

Preparation by the Inversion–Esterification Methods. 3β-Cholestanol (17.34 g, 44.6 mmol), *m*-iodobenzoic acid (10 g, 40.3 mmol), and triphenylphosphine (11.69 g, 44.6 mmol) were dissolved in 500 ml of dry tetrahydrofuran. Then diethyl azodicarboxylate (7.76 g, 44.6 mmol) in 70 ml of tetrahydrofuran was added, and the solution was stirred under N_2 for 8 h. The solvent was removed and the product purified by rough silica chromatography and recrystallization from ethanol. A yield of 21.1 g (85%) of ester was obtained identical with the above material.

5α-Cholestan-3α-yl *o*-Iodophenylacetate (15). Treatment of 3α-cholestanol (1.50 g, 3.87 mmol) with *o*-iodophenyl acetyl chloride (1.11 g, 3.97 mmol) gave 2.06 g (84% yield) of the ester after recrystallization from cold pentane: mp 110–112 °C; NMR ($CDCl_3$) δ 7.84 (d, 1 H, J = 8 Hz), 7.33, 7.23 (singlets) and 6.8–7.1 (m, 3 H total), 5.03 (broad s, $W_{1/2}$ = 7 Hz, 3β-H), 3.78 (s, 2 H, $-CH_2-$), axial methyls at 0.65 and 0.75. Anal. ($C_{35}H_{53}O_2I$) C, H, I.

5α-Cholestan-3α-yl *m*-Iodophenylacetate (12). This was prepared by the acid chloride method, affording a 90% yield of the ester after column chromatography on silica gel (5% ether/petroleum ether): mp 88–90 °C; IR (CS_2) 1720 cm^{-1}; NMR ($CDCl_3$) δ 7.48–7.6 and 6.95–7.35 (m, 4 H), 5.00 (broad, 1 H, $W_{1/2}$ = 8 Hz, 3β-H), 3.55 (s, 2 H, $-CH_2-$), axial methyls at 0.74 and 0.64. Anal. ($C_{35}H_{53}O_2I$) C, H, I

5α-Cholestan-3α-yl *p*-Iodophenylacetate. The acid chloride method gave the ester in 91% yield: mp 95–97 °C; IR (CCl_4) 1725 cm^{-1}; NMR ($CDCl_3$) δ 7.70, 7.75, 7.10 and 6.97 (4 H, aromatic), 3.47 (s, 2 H, $-CH_2-$), axial methyls at 0.76 and 0.65. Anal. ($C_{35}H_{53}O_2I$) C, H, I.

5α-Cholestan-3α-yl β-(*p*-Iodophenyl)propionate. The acid chloride procedure gave an 88% yield of colorless crystals after recrystallization from ethanol: mp 107–109 °C; NMR ($CDCl_3$) δ 7.55 (d, 2 H, J = 8 Hz), 6.91 (d, 2 H, J = 8 Hz), 5.00 (broad, 1 H, $W_{1/2}$ = 8 Hz, 3β-H), 2.90 and 2.60 (A_2B_2 m, 4 H, J = 6 Hz), axial methyls at 0.77 (19-CH_3) and 0.66 (18-CH_3) Hz.

5α-Cholestan-3α-yl γ-(*p*-Iodophenyl)butyrate (19). This was also prepared via the acid chloride method, giving colorless crystals (EtOH): mp 91–94 °C; NMR ($CDCl_3$) δ 6.8–7.75 (four singlets, 4 H), 5.05 (broad, 1 H, 3β-H), 2.20–2.85 (m, 6 H, $-(CH_2)_3-$), axial methyls at 0.80 and 0.65.

5α-Cholestan-3α-yl δ-(*p*-Iodophenyl)valerate. The same method gave the valerate (EtOH): mp 63–65 °C; NMR ($CDCl_3$) δ 7.58 (d, 2 H, J = 8 Hz), 6.91 (d, 2 H, J = 8 Hz), 5.02 (broad, 1 H, 3β-H), 2.58 (broad t, 2 H, J = 7 Hz), 2.32 (broad t, 2 H, J = 7 Hz), axial methyls at 0.79 and 0.63.

5α-Cholestan-3α-yl 4′-Iodobiphenyl-3-carboxylate (20). The inversion-esterification procedure followed by column chromatography on silica gel (5% ether/petroleum ether) and recrystallization from ethanol/hexane gave the ester in 61% yield: mp 117–118.5 °C; IR

($CHCl_3$) 2950 and 1715 cm^{-1}; NMR ($CDCl_3$) δ 7.2–8.3 (m, 8 H), 5.30 (broad s, 1 H, 3β-H); axial methyls at 0.84 and 0.67; mass spectrum (CI) *m/e* 695, 694, 693, 568, 567, 371, and 369.

5α-Cholestan-3α-yl *m*-Iodophenylpropionate (16). The acid chloride method was used, giving the oily ester with CH_3 NMR signals at δ 0.64 and 0.76 and *m/e* 646.

5α-Cholestan-7α-yl *m*-Iodobenzoate (17). The inversion–esterification reaction gave the oily ester in 44% yield: IR ($CHCl_3$) 2950, 1720, and 1250 cm^{-1}; NMR ($CDCl_3$) δ 8.37 (m, 1 H), 7.95 (m of t, 2 H, J = 8 Hz), 7.18 (t, 1 H, J = 8 Hz), 5.16 (broad, 1 H, 3β-H); axial methyls at 0.85 and 0.68; mass spectrum (CI) *m/e* 619, 618, 617, 491, and 371.

5β-Cholestan-3α-yl *m*-iodophenylacetate (44) was prepared by the acid chloride method as an oil: IR ($CHCl_3$) 1725 cm^{-1}; NMR ($CDCl_3$) δ 7.55 (m, 2 H), 6.85–7.3 (m, 2 H), 4.74 (broad, 1 H, 3β-H), 3.50 (s, 2 H, $-CH_2-$); side chain methyls at 0.97 and 0.82; mass spectrum *m/e* 632 (M^+), 370, 230, 217, 216, and 215.

3α-(4′-Iodobiphenyl-3-carboxylate)-24-ethylcholestane (21) was prepared by the inversion–esterification procedure from stigmastanol in 57% yield: mp 130.5–132 °C; IR ($CHCl_3$) 2940, 2860, 1710 cm^{-1}. Anal. ($C_{42}H_{59}O_2I$) C, H.

17α-Androstanyl *m*-iodobenzoate (22), mp 118–120 °C, *m/e* 506, was prepared by the acid chloride method.

17-Epitestosterone *m*-iodobenzoate (23) could be prepared either by the acid chloride method or by inversion–esterification in 45% yield. The compound had mp 184–185 °C and *m/e* 518.

Template Directed Halogenations. The dichlorides of the steroidal esters were always made in the same manner, and a representative example is given below. After 1 month in the dark at 0 °C, the compounds still had ca. 90% of the theoretical active chlorine.

5α-Cholestan-3α-yl *m*-Iodophenylacetate Dichloride (10). The *m*-iodophenylacetate (900 mg, 1.28 mmol) was dissolved in 20 ml of *n*-pentane at 0 °C. Chlorine was bubbled into the solution. After 10 min a yellow, crystalline precipitate formed. Isolation and drying by suction filtration gave 872.6 mg (97% yield) of the dichloride. On some occasions chilling in a dry ice–acetone bath was necessary to initiate crystallization. More of the dichloride could be obtained by treating the filtrate with chlorine. The compound had mp 117–118.5 °C (gas evolution); NMR ($CDCl_3$) δ 8.14 (m, 1 H), 7.0–7.7 (m, 3 H), 5.00 (broad, 1 H, 3β-H), 3.68 (s, 2 H, $-CH_2-$); axial methyls at 0.76 and 0.65.

In the same fashion the dichloride of cholestanyl *m*-iodobenzoate (**4**) was prepared in 96% yield: mp 112–114 °C (gas evolution); NMR (CH_2Cl_2), partial spectrum, δ 9.11 (t, 1 H, J = 1.5 Hz), 8.55 (tt, 2 H, J = 1.5, 8 Hz), 7.83 (t, 1 H, J = 8 Hz).

5α-Cholestan-3α-yl *o*-iodophenylacetate dichloride, 88% yield, 5α-cholestan-3α-yl *p*-iodophenylacetate dichloride (**8**), 94% yield, mp 99–101 °C (gas evolution), and 5α-androstan-3α-yl *p*-iodophenylacetate dichloride, 80% yield, were also prepared in the same way.

Halogenation by the Attached Aryliodine Dichlorides. The appropriate amount of freshly prepared steroidal iodoaryl dichloride ester (about 1 mmol) was placed in a three-necked, round bottom flask equipped with a magnetic stirring bar, reflux condenser and drying tube, nitrogen inlet, and a thermometer. The required amount of solvent was added, and the solution was deoxygenated with nitrogen for 30 min. Photolysis was carried out using a G.E. 275-W sunlamp placed 6 in. away from the apparatus. The temperature was maintained at ~25 °C with an ice–water bath. The progress of the reaction was followed by using potassium iodide–starch paper, which would cease to give a positive test when all the active halogen compound was gone. The end of the reaction was also indicated by a change in color of the solution from pale yellow to deep yellow or pink (I_2).

Workup of the reaction mixture involved removal of the solvent on a rotary evaporator, followed by repeated addition and evaporation of carbon tetrachloride to remove traces of iodine. The residue was treated with a mixture of 15 ml of 10% potassium hydroxide in methanol and 15 ml of dioxane at 80 °C for 1 h to cleave the ester and dehydrochlorinate the chlorosteroids formed during the photolysis. The solvent was evaporated, and 100 ml of a saturated brine solution were added. This was extracted with five 100-ml portions of ether. The organic layer was dried ($MgSO_4$) and evaporated to give a mixture of cholestanol and cholestenols. Cases in which androstane was present to detect intermolecular chlorination also contained androstane and androstenes in this mixture. These were separated from the steroidal alcohols by column chromatography on silica gel (petroleum ether). Elution with ether afforded the steroidal alcohols.

The alcohols were acetylated with 2 ml of acetic anhydride and 2 ml of pyridine together in 20 ml of dry benzene at 80 °C overnight. The solvent was evaporated and the residue taken up in 200 ml of ether. Two washings of this with 25-ml portions of 10% hydrochloric acid and 10% sodium bicarbonate, drying ($MgSO_4$), and evaporation gave the acetates in quantitative yield.

Halogenations by the Radical Relay Method. The same procedure was used except that the parent iodo compounds were used instead of the dichlorides. In addition, 1 or more equivalents of iodobenzene dichloride were included in the photolysis mixture.

Nonphotolytic Initiation of the Halogenations. A solution of cuprous acetate was added dropwise by syringe to a 10^{-2} M solution of 3α-cholestanyl *m*-iodobenzoate dichloride (**4**) in a 50:50 mixture of acetonitrile and methylene chloride until the reaction mixture turned blue. Iodide–starch paper gave a negative test. Standard workup showed the presence of a 50% yield of the Δ9(11) olefin and 50% of unfunctionalized steroid. A similar reaction using the parent *m*-iodobenzoate **11,** iodobenzene dichloride and cuprous acetate at 10^{-2} M gave a 30% yield of the olefin.

A 10^{-2} M solution of *m*-iodobenzoate **11** in carbon tetrachloride containing 1.2 equiv of iodobenzene dichloride and 10 mol % of benzoyl peroxide was heated at reflux for 1 h under nitrogen. The usual treatment gave 15% starting material, 75% Δ9(11) olefin and 10% polar material.

In the absence of an initiator, a 10^{-2} M solution of **11** and iodobenzene dichloride in carbon tetrachloride was heated at reflux for 10 h giving 25% unfunctionalized steroid, 50% of the Δ9(11) olefin, and 25% polar material.

Radical Relay Halogenation Using Sulfuryl Chloride. A 10^{-2} M solution of 3α-cholestanyl *m*-iodobenzoate (**11**) in carbon tetrachloride containing 1.2 equiv of sulfuryl chloride and 10 mol % of benzoyl peroxide was heated at reflux under nitrogen for 5 h. Standard workup gave the Δ9(11) olefin in 75% yield as well as 10% polar and 15% starting materials by NMR analysis. The same reaction using AIBN as the initiator (18 h at reflux) gave ~35% of the olefin and 65% unfunctionalized steroid. If no initiator was used, no functionalization occurred after 96 h at reflux.

Control Reaction for the Radical Relay Mechanism. The ester **11** (61.9 mg, 0.1 mmol) and iodobenzene dichloride (27.5 mg, 0.1 mmol) were dissolved in 2 ml of methylene chloride (with Me_4Si) and placed in an NMR tube. Freshly prepared dichloride **4** (69.0 mg, 0.1 mmol) and iodobenzene (0.1 mmol) were dissolved in 2 ml of methylene chloride and placed in another NMR tube. Spectra of each of the separate components of the mixtures were taken in methylene chloride. The downfield portion of the NMR spectra of the two mixtures was observed for any evidence of exchange of chlorine from one iodo compound to the other.

Formation of iodobenzene dichloride, NMR (CH_2Cl_2) δ 8.30 (m) and 7.67 (m), from iodobenzene, NMR (CH_2Cl_2) δ 7.83 (m) and 7.33 (m), would give an easily detectable signal in the NMR spectrum. In the same manner, formation of the ester dichloride **4,** NMR (CH_2Cl_2) δ 9.12 (t), 8.55 (tt), 7.83 (t), from the parent iodo ester **11,** NMR (CH_2Cl_2) δ 8.53 (t), 8.12 (tt), 7.33 (t), can also be observed. In neither case, however, was there observed any chlorine transfer after 18 h standing at room temperature in the dark. The limit of detection was found to be 5–10% by the addition of small quantities of **4** to the solution of **11** and iodobenzene dichloride.

Analysis and Identification of the Products. The steroidal acetate products were separated by careful column chromatography on 20% silver nitrate on silica gel with ether–petroleum ether. The products could also be separated by liquid chromatography of the steroid benzoates on microporasil with hexane. The 5α-cholest-9(11)-ene-3α-ol and 5α-cholest-14-ene-3α-ol were identified by comparison with authentic samples.[2] The 5α-cholest-16-ene-3α-ol had mp 119–120 °C (reported[2] mp 133–136 °C) and showed IR ($CHCl_3$) 2950, 1460, and 1380 cm^{-1}; NMR ($CDCl_3$) δ 5.28 (broad, 1 H, vinyl H), 4.05 (broad, 1 H, 3-H), 0.99 (d, 3H J = 7 Hz, 21-CH_3), 0.88 (d, 6 H, J = 6 Hz, 26- and 27-CH_3's); axial methyls at 0.88 and 0.75; mass spectrum (CI) *m/e* 387, 386 (M^+), 385, and 369.

17α-Hydroxy-5α-androst-9(11)-ene was identified by its *m/e* 274 and characteristic NMR signals for the 18 methyl (δ 0.78) and 19 methyl (δ 0.93) as well as the C-11 vinyl proton at δ 5.33–5.45.

Radical relay halogenation of epitestosterone *m*-iodobenzoate (**23**) afforded the isolated 9-chloro derivative (**24**) of the starting ester, mp 169–170 °C, *m/e* 552. In the NMR the 18 methyl appeared at δ 0.87,

while the 19 methyl appeared at δ 1.45. This material is sensitive to base, but a brief exposure at room temperature to a slight excess of aqueous silver perchlorate in acetone converted it to the Δ9(11)-dehydroepitestosterone *m*-iodobenzoate (**25**) in 96% yield, mp 117–120 °C. This unsaturated ester had *m/e* 516 and NMR signals at δ 0.83 and 1.35 for the 18 and 19 methyl groups, as well as the C-11 vinyl proton at δ 5.37–5.57.

Large Scale Preparation of 5α-Cholest-9(11)-en-3α-yl Acetate. 5α-Cholestan-3α-yl *m*-iodobenzoate (18.51 g, 29.9 mmol) was dissolved in 200 ml of *n*-pentane and chilled to 0 °C. Chlorine was bubbled into the solution. After 15 min the dichloride **11** was obtained as a yellow, crystalline precipitate. Isolation of this by suction filtration and drying in vacuo gave 17.6 g (85% yield). This was dissolved in 3 l. of methylene chloride (8.5×10^{-3} M) and deoxygenated with nitrogen for 1.5 h. The orange solution was irradiated with a 275-W sunlamp for 2 h, when the mixture became pale green. Iodide-starch paper gave a negative test. Base hydrolysis and standard workup gave the crude olefin. Acidification of the aqueous layer from the saponification workup resulted in a 94% recovery (5.98 g) of pure *m*-iodobenzoic acid.

Acetylation of the steroid, followed by chromatography on 200 g of 20% silver nitrate–silica gel gave 2.27 g (21%) of 3α-cholestanyl acetate, 7.14 g (66%) of Δ9(11)-cholestenyl acetate, and 0.39 g (4%) of Δ14-cholestenyl acetate plus 0.93 g (9%) of polar material. Recrystallization of the Δ9(11) olefin from ethanol gave 5.58 g of the pure compound. A second and third crop increased the yield to 6.26 g.

Conversion of Cortexolone to Dihydrocortisone. Cortexolone (**28**) (20.2 g, 58.30 mmol) was added to a mixture of chloroform (1000 ml), concentrated hydrochloric acid (400 ml), and 37% formalin (400 ml). The two-phase mixture was stirred 30 h at 25 °C, and the organic layer was separated. The aqueous layer was extracted twice with chloroform. The combined organic layers were washed with 10% $NaHCO_3$ solution, dried, and evaporated. The resulting oil was triturated with petroleum ether giving 23.35 g (104% of 85% pure material). A sample was recrystallized once from ethanol giving white crystals, mp 243–247 °C. The compound (**29**) had the expected NMR and IR spectra.

The crude bismethylenedioxy derivative **29** (22.35 g) was dissolved in ca. 200 ml of methylene chloride and added to a 5-l. three-necked flask and the methylene chloride removed at aspirator pressure with a heat gun. Ether (300 ml) and ethanol (300 ml) were added. Then 2 l. of liquid ammonia were added by distillation with a condensing bath at −78 °C. After the ammonia had condensed, the −78 °C bath was removed, and the solution was stirred magnetically, and 12 g of lithium wire (12 × 25 cm × ⅛ in. diameter) was added in small pieces over the course of 1 h. The ammonia was allowed to evaporate overnight under nitrogen flow. Ether (300 ml) and water (1000 ml) were added. The aqueous layer was separated and extracted three times with methylene chloride. The combined organic layers were washed with dilute sulfuric acid and water and dried over magnesium sulfate and evaporated, giving 19.55 g of crude **30.** A portion was recrystallized twice from methanol giving white crystals, mp 242–247 °C. Anal. ($C_{23}H_{36}O_5$) C, H.

The compound had expected IR and NMR spectra.

The crude sterol **30** (13.12 g, 33.43 mmol) prepared from 37.45 mmol of cortexolone, triphenyl phosphine (15.72 g, 60.0 mmol, 1.8 equiv), and *m*-iodobenzoic acid (10.00 g, 40.32 mmol, 1.2 equiv) were dissolved in 400 ml of anhydrous THF. A solution of diethylazodicarboxylate (10.65 g, 60 mmol, 1.8 equiv) in 50 ml of THF was added dropwise to the stirred solution. The reaction mixture was stirred overnight, the solution was evaporated in vacuo to 100 ml, and 50 g of silica gel was added. The mixture was evaporated to dryness and the resulting powder poured on top of a column of 300 g of silica gel packed in petroleum ether. The column was eluted with petroleum ether:ether mixtures. The desired product **31** was eluted with 10–15% petroleum ether:ether giving 14 g of pure **31** (60% based on **30**). A sample was recrystallized from methanol giving white crystals, mp 173–174 °C. Anal ($C_{30}H_{39}O_6I$) C, H, I.

The compound showed the expected NMR and IR spectra.

A 100-mg sample of iodobenzoate **31** was dissolved in 5 ml of dioxane, and 5 ml of 10% KOH in methanol was added. The solution was refluxed for 1 h, cooled, and poured into 50 ml of water. This was extracted with three portions of methylene chloride, and the combined organic layers were dried over magnesium sulfate and evaporated giving a quantitative yield of the corresponding alcohol. An analytic sample was recrystallized from methanol giving a product with mp 179.5–180 °C. Anal. ($C_{23}H_{36}O_5$) C, H.

The compound gave the expected IR and NMR spectra.

The iodobenzoate **31** (8.00 g, 12.85 mmol) was dissolved in 1286 ml of purified methylene chloride. Iodobenzene dichloride (4.244 g, 15.432 mmol, 1.2 equiv) was added. The solution was degassed for 30 min and photolyzed with a sunlamp for 1 h. The solution was kept at a temperature of 10–20 °C by use of an ice–water bath. The color changed from green to pink after 45 min. The solution was evaporated to dryness giving a brownish oil.

The crude photolysis product was taken up in 120 ml of dioxane and 120 ml of 10% KOH in methanol was added. The solution was refluxed for 2 h and diluted with water. Most of the solvent was removed in vacuo. More water was added, and the mixture was extracted with four portions of methylene chloride. The combined organic layers were washed with water, dried, and evaporated giving 5.603 of almost colorless oil which crystallized on standing.

A portion of the crude **32** was purified by silver nitrate–silica gel chromatography of the corresponding acetate. The remaining material was carried onto the next step without purification.

Crude **32** (0.573 g) was dissolved in a mixture of 5 ml of pyridine and 2 ml of acetic anhydride and heated at 80 °C for 4 h. Water (1 ml) was added, and the solution was stirred 1 h at 25 °C. It was then poured into 50 ml of water and extracted with three portions of methylene chloride. The methylene chloride extracts were washed three times with copper sulfate solution, once with sodium bicarbonate solution, and dried and evaporated, giving 568 mg of orange oil. This was placed on a column of 30 g of 20% silver nitrate on silica gel packed in petroleum ether. Elution with 0–3% ether in petroleum ether gave 38 mg of unfunctionalized material (6.6%). Elution with 5–16% ether:petroleum ether gave 424 mg of **32** acetate (74.5%). Elution with 30–100% ether in petroleum ether gave 61.37 mg (11%) of polar material. A portion of the **32** acetate was recrystallized from methanol, giving material with mp 168.5–169.5 °C. Anal. ($C_{25}H_{36}O_6$) C, H.

The infrared and NMR spectra were as expected, in particular the 18 methyl signal at δ 0.77 and the 19 methyl signal at δ 0.94, together with a C-11 vinyl signal at δ 5.33.

Radical relay halogenation could also be done using sulfuryl chloride. The iodobenzoate **31** (2.370 g, 3.807 mmol), benzoyl peroxide (0.083 g), and sulfuryl chloride (0.48 ml) were dissolved in 400 ml of carbon tetrachloride. This solution was refluxed for 9 h under N_2. (The reaction can be followed in this case by TLC in 3:1 petroleum ether: ether using ceric spray.) The solution was evaporated and hydrolyzed as previously described. The resulting material was hydroborated and purified as described (vide infra), giving 0.906 g of pure **33** (58% from **31**).

The crude olefin **32** (5.03 g), obtained from 11.518 mmol of **31,** was dissolved in 150 ml of anhydrous tetrahydrofuran. A solution of 1 M borane in THF (48 ml) was added dropwise at 0 °C. Gas evolution occurred immediately. The solution was stirred 12 h at 25 °C. Then 50 ml of 3 N sodium hydroxide solution was added. Vigorous gas evolution occurred. Fifty milliliters of 30% hydrogen peroxide was added, and the mixture was allowed to stir 6 h at 25 °C. The solution was acidified with concentrated hydrochloric acid and extracted with four portions of methylene chloride. The organic layer was washed with sodium sulfate solution, dried, and evaporated giving 5.410 g of crude product. This was dissolved in ether and put on a column of 150 g of silica gel in 1:1 ether:petroleum ether. Elution with ether gave 417 mg (8%) of unfunctionalized 3α-ol and 3.190 g (68% from **31**) of dihydroxy steroid **33.** A portion was recrystallized from benzene–cyclohexane giving white crystals, mp 177–178 °C. Anal. ($C_{23}H_{36}O_6$) C, H.

The 18 methyl signal came at δ 0.83 and the 19 methyl signal at δ 0.93.

The steroid diol **33** (2.748 g, 6.727 mmol) was dissolved in 80 ml of acetone and cooled to 0 °C. Jones' reagent (2.67 M in Cr(VI), 4 ml) was added dropwise, giving residual yellow color in the solution. After stirring 15 min, 15 ml of isopropanol was added. The solution was stirred an additional 10 min, poured into water, and evaporated partially. The residual solution was extracted with four portions of methylene chloride which was dried and evaporated giving 2.63 g (96%) of pure dione (**34**). A sample was recrystallized from methanol giving material with mp 215–220 °C. Anal. ($C_{23}H_{32}O_5$) C, H.

In the NMR, the 18 methyl appeared at δ 0.80, the 19 methyl at δ 1.25, while the infrared showed a strong band at 1715 cm^{-1}.

The bismethylenedioxy dione **34** (2.16 g, 5.34 mmol) was dissolved

in a mixture of ca. 30 ml of tetrahydrofuran and 60 ml of 48% HF. More THF and acid were added to make a homogeneous solution. (The reaction is done in a polyethylene bottle.) The solution was stirred for 3 days at 25 °C. Some solid potassium carbonate was added (vigorous gas evolution) and then 300 ml of water. This mixture was extracted with four portions of methylene chloride which were dried and evaporated giving 2.045 g of crude product. A portion was recrystallized from methanol and then from acetone, giving white crystals of **35**, mp 216–218 °C (lit.[27] mp 217–221 °C). The spectra were as expected.

Dihydrocortisone **35** (1.822 g, crude) was dissolved in a mixture of pyridine and 4 ml of Ac_2O. The solution was stirred 6 h at 25 °C, 2 ml of water was added, and the solution was stirred overnight. The reaction mixture was poured into methylene chloride which was washed with 5% HCl solution, 10% sodium bicarbonate, and water, dried, and evaporated, giving 1.924 g of material. Chromatography on 50 g of silica gel gave 1.560 g (80% from **34**) of pure dihydrocortisone acetate (**36**), mp 220–225 °C. Two recrystallizations from acetone gave material of mp 235–237 °C (lit.[28] mp 235–237 °C), mixed mp 234–236 °C. The spectra were identical with those of an authentic sample.

Removal of the Steroid Side Chain. A similar sequence was carried through in both the cholesterol and the sitosterol series. Sitosterol was hydrogenated to stigmastanol, which was converted by inversion–esterification to the 3α-4′-iodobiphenyl-3-carboxylate ester **21.**

This ester was submitted to the radical relay conditions with a 100% excess of iodobenzene dichloride in chloroform by irradiation with two 275-W sunlamps for 20 min. This was repeated twice, so that a total of 8.8 g of ester was utilized. The solvent was removed and the total product saponified and dehydrohalogenated with methanolic KOH in dioxane in the standard fashion.

The product was 6.0 g of crude 3α-hydroxy-24-ethylcholest-16-ene as a colorless oil, which was acetylated and chromatographed on silver nitrate–silica gel. The pure unsaturated acetate **38** was collected as a colorless oil (2.6 g, 48% yield overall) with the expected infrared and NMR spectra, including the 18 methyl at δ 0.82, the 19 methyl at δ 0.76, and the 21 methyl as a doublet at δ 0.99. Anal. ($C_{31}H_{54}O_2$) C, H.

A solution of **38** (1.3 g, 2.9 mmol) and *N*-phenyltriazolinedione (0.93 g, 5.3 mmol) in 200 ml CH_2Cl_2 was stirred at 25 °C under N_2. After 8 days, the solvent was removed and the product chromatographed to afford the adduct **40** (0.93 g, 51% yield) as a white solid with mp 118–122 °C.

This adduct (150 mg, 0.24 mmol) was saponified with 10 ml dioxane and 10 ml 10% methanolic KOH at room temperature for 10 h. The crude alcoholic product was then dissolved in 20 ml of ethylamine in a flask equipped with a dry ice condenser, and lithium (42 mg, 6 mg-atom) was added. The blue solution was stirred for 1 h, and then 5 ml of ether and 1 ml of methanol were added. After standard workup, crude 3α-hydroxy-24-ethylcholest-17(20)-ene (**42**) was isolated as a colorless oil (92 mg, 95% yield). This oil was directly acetylated to afford the corresponding acetate, which showed a methyl signal in the NMR at δ 1.55 for the C-21 methyl on a double bond. This olefin was then ozonized in the standard way to afford androsterone acetate (**43**), identical in all respects with authentic material.

In a similar fashion, cholesterol was converted to the 3α-acetoxycholest-16-ene (**37**), and this was treated with *N*-phenyltriazolinedione in methylene chloride at 25 °C for 24 h to provide the ene adduct **39** in 65% yield. Saponification of this material followed by reduction with lithium in ethylamine afforded (*Z*)-Δ17(20)-3α-cholestenol (**41**), mp 133–135 °C, in 74% yield. This also was acetylated and ozonized to afford androsterone acetate (**43**), identical with authentic material.

Acknowledgment. Support of this work by the National Institutes of Health and the National Science Foundation is gratefully acknowledged. R.J.C. held a National Science Foundation Predoctoral Fellowship, and B.B.S. and R.J.D. held National Institutes of Health Postdoctoral Fellowships, which are also gratefully acknowledged.

References and Notes

(1) R. Breslow, *Chem. Soc. Rev.*, **1**, 553 (1972).
(2) R. Breslow and M. A. Winnik, *J. Am. Chem. Soc.*, **91**, 3083 (1969); R. Breslow and S. W. Baldwin, *ibid.*, **92**, 732 (1970); R. Breslow and P. C. Scholl, *ibid.*, **93**, 2332 (1971); R. Breslow, S. Baldwin, T. Flechtner, P. Kalicky, S. Liu, and W. Washburn, *ibid.*, **95**, 3251 (1973); R. L. Wife, D. Prezant, and R. Breslow, *Tetrahedron Lett.*, 517 (1976).
(3) D. D. Tanner and P. B. Van Bostelen, *J. Org. Chem.*, **32**, 1517 (1967).
(4) R. Breslow, J. A. Dale, P. Kalicky, S. Y. Liu, and W. N. Washburn, *J. Am. Chem. Soc.*, **94**, 3276 (1972).
(5) E. B. Merkushev and V. S. Raida, *Zh. Org. Khim.*, **10**, 405 (1974).
(6) R. Breslow, R. Corcoran, J. A. Dale, S. Liu, and P. Kalicky, *J. Am. Chem. Soc.*, **96**, 1973 (1974).
(7) R. J. Corcoran, *Tetrahedron Lett.*, 317 (1976).
(8) A. Rotman and Y. Mazur, *J. Am. Chem. Soc.*, **94**, 6228 (1972).
(9) D. H. R. Barton, R. H. Hesse, R. F. Markwell, M. M. Pechet, and S. Rosen, *J. Am. Chem. Soc.*, **98**, 3034, 3036 (1976).
(10) Cf. M. L. Poutsma in "Free Radicals", Vol. II, J. Kochi, Ed., Wiley, New York, N.Y., 1973, p 169.
(11) E. M. Archer and T. G. D. van Schalkwyk, *Acta Crystallogr.*, **6**, 88 (1953).
(12) Reference 3. See also ref 10, p 204, for the alternative.
(13) A. McL. Mathieson, *Tetrahedron Lett.*, 4137 (1965).
(14) For details, see the Ph.D. Thesis of Richard J. Corcoran, Columbia University, New York, N.Y. 1976.
(15) Reference 6, footnote 5.
(16) R. Breslow, R. J. Corcoran, and B. B. Snider, *J. Am. Chem. Soc.*, **96**, 6791 (1974).
(17) R. Breslow, "Organic Reaction Mechanisms", 2d Ed., W. A. Benjamin, New York, N.Y., 1969, p 63.
(18) G. A. Russell, *J. Am. Chem. Soc.*, **80**, 4987 (1958).
(19) An interesting alternating effect is seen in the *p*-iodophenylalkanoic esters. That is, template-directed halogenation is observed with one methylene or three methylenes, but not with two or four (or zero). If the polymethylene chain exists chiefly in an extended conformation, such an alternating effect is expected, since only the odd methylene compounds turn the aromatic ring back toward the steroid. With substitution this effect was not expected or observed.
(20) When the *m*-iodophenylpropionate was attached at C-5 instead of C-3, the site of halogenation was moved from C-14 out by two carbons to C-17. Since available sterols have a 5,6 double bond which permits the preparation of such an ester, this could also be of practical interest.
(21) R. Breslow, R. L. Wife, and D. Prezant, *Tetrahedron Lett.*, 1925 (1976).
(22) R. Breslow and R. Goodin, *Tetrahedron Lett.*, in press.
(23) R. E. Beyler, F. Hoffman, R. M. Moriarty, and L. H. Sarett, *J. Org. Chem.*, **26**, 2421 (1961).
(24) A. K. Bose, B. Lal, W. A. Hoffman, and M. S. Manhas, *Tetrahedron Lett.*, 1619 (1973).
(25) M. Nussim and F. Sondheimer, *Chem. Ind. (London)*, 400 (1960).
(26) J. B. Siddall, F. Alvarez, and A. Ruiz, *Neth. Appl.*, 6 607 490 (1967); *Chem. Abstr.*, **66**, P115875u (1967).
(27) R. M. Evans, G. F. H. Green, J. S. Hunt, A. G. Long, B. Mooney, and G. H. Philipps, *J. Chem. Soc.*, 1529 (1958).
(28) J. Pataki, G. Rosenkranz, and C. Djerassi, *J. Am. Chem. Soc.*, **74**, 5615 (1952).
(29) R. M. Evans, J. C. Hamlet, J. S. Hunt, P. G. Jones, A. G. Long, J. F. Oughton, L. Stephenson, T. Walker, and B. M. Wilson, *J. Chem. Soc.*, 4356 (1956).
(30) Ch. Meystre, H. Frey, W. Voser, and A. Wettstein, *Helv. Chim. Acta*, **38**, 734 (1956).
(31) N. K. Chaudhuri, R. Nickolson, J. G. Williams, and M. Gut, *J. Org. Chem.*, **34**, 3767 (1969).
(32) Cf. A. S. Hallsworth, H. B. Henbest, and T. I. Wrigley, *J. Chem. Soc.*, 1969 (1957).
(33) The NMR signal of the 21-CH_3 of **41** occurs at 93 Hz. In the *E* isomer the corresponding absorption occurs at 101 Hz.[31] This dependence of the chemical shift of the methyl group has been previously observed in Δ17(20) pregnenes.[34]
(34) M. Tanabe and R. H. Peters, *J. Org. Chem.*, **36**, 2403 (1971).
(35) Cf. P. Kalicky, Ph.D. Thesis, Columbia University, New York, N.Y., 1973, p 14.
(36) D. H. Hey, F. C. Saunders, and G. H. Williams, *J. Chem. Soc.*, 554 (1961).
(37) J. T. Plati, W. H. Strain, and S. L. Warren, *J. Am. Chem. Soc.*, **65**, 1273 (1943).
(38) G. Precioqoux, B. Bustella, C. Courseille, and M. Hospital, *Cryst. Struct. Commun.*, **1**, 265 (1972).
(39) Specialist Periodical Reports, "Terpenoids and Steroids", Vol. 4, Part II, The Chemical Society, London, 1974, Chapter 3; G. H. Geise, C. Altona, and C. Romers, *Tetrahedron*, **23**, 439 (1967) and **24**, 13 (1968).
(40) H. B. Thompson, *J. Chem. Phys.*, **47**, 3407 (1967); R. L. Hilderbrandt, *ibid.*, **51**, 1654 (1969).