of the mechanism of this unusual reaction are under current investigation.

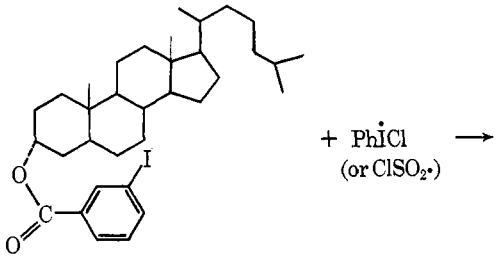
Acknowledgment. We thank the donors of the Petroleum Research Fund, administered by the American Chemical Society, for the support of this research.

L. S. Hegedus,* E. L. Waterman
Department of Chemistry, Colorado State University
Fort Collins, Colorado 80521
Received July 27, 1974

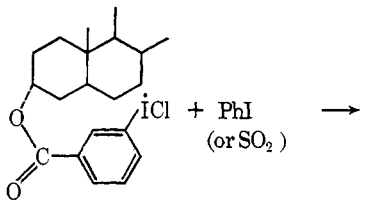
Remote Functionalization of Steroids by a Radical Relay Mechanism

Sir:

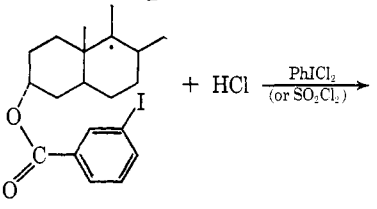
We have described the use of phenyliodine dichloride in steroid functionalizations[1] and the conversion of this intermolecular halogenation process into a directed intramolecular reaction.[2] For example, 3β-cholestanol was converted with *m*-iodobenzoic acid and triphenylphosphine–diethyl azodicarboxylate into the *m*-iodobenzoate of 3α-cholestanol (**1**) in 85% yield by the very useful inversion–esterification procedure.[3] This was converted with Cl_2 to the attached $ArICl_2$ derivative, and on brief irradiation this afforded the *m*-iodobenzoate of 9α-chloro-3α-cholestanol (**4**) as the major product.[2] The important intermediate in the hydrogen abstraction from the steroid is species **2**, which can be considered to be a σ-complex of Cl· with the attached aryl iodide. We now wish to report that **2** can instead be generated by transfer of a chlorine atom to **1** from an external radical reagent species. The overall process **1** → **2** → **3** → **4** has a number of advantages over the direct use of an aryl dichloride prepared from an attached aryl iodide such as **1**. Thus an excess of the chlorinating agent can be used, and exposure of sensitive substrates to Cl_2 is avoided. These advantages made possible the cortisone acetate synthesis described in the accompanying communication.[4]



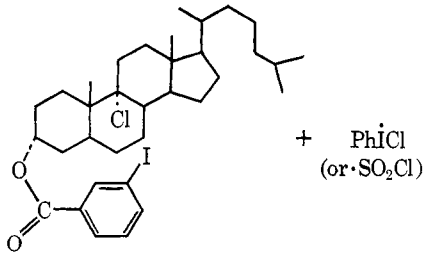
1



2

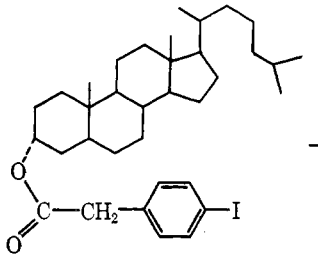


3

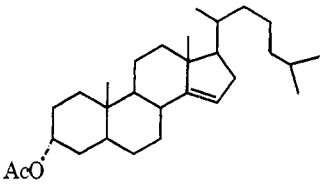


4

A solution of **1** (742 mg, 1.20 mmol) and $PhICl_2$ (330 mg, 1.20 mmol) in 120 ml of CH_2Cl_2 was irradiated with a 275-W sunlamp for 25 min at 25° under N_2. Saponification, acetylation, and chromatography afforded 18.4% of unfunctionalized 3α-cholestanol acetate and 66% $\Delta^{9(11)}$-cholestene-3α-ol acetate (80% yield corrected for recovered starting material) with 12% of polar impurities and no detectable amount of a Δ^{14}-cholestenol derivative. By contrast, the same reaction conditions applied to the *p*-iodophenyl acetate of 3α-cholestanol (**5**) led to 55% recovery of unfunctionalized steroid and 18% production of Δ^{14}-cholestanol acetate with 27% of polar impurities and no detectable amount of $\Delta^{9(11)}$-steroid derivative. The preference of **1** to undergo chlorination of C-9 while **5** is



5



6

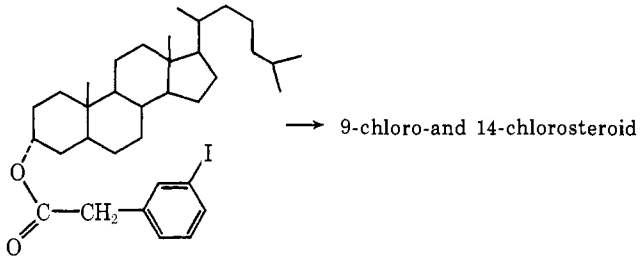
chlorinated at C-14 are those expected from molecular models if hydrogen is being abstracted by a chlorine atom attached to iodine, and they are the same preferences we have previously observed[2] starting with the aryl iodine dichlorides derived from **1** and **5**. Thus, the most trivial explanations of these observations would be conversion of **1** to the corresponding dichloride by reaction with $PhICl_2$, but this is excluded by direct equilibration studies. The characteristic aryl proton nmr of **1** dichloride cannot be observed after 18 hr equilibration of **1** with $PhICl_2$ in the dark at 0.05 *M* in CH_2Cl_2 solution nor can equilibration be detected (within 10%) starting with **1** dichloride and PhI after the same time. Aliquots withdrawn during the irradiation of **1** with $PhICl_2$ also reveal no detectable amount of **1** dichloride.

Further observations support the mechanism shown. It should be possible to transfer Cl· to **1** from other species, and we find that this can be done using sulfuryl chloride. Thus a 0.01 *M* solution of **1** in CCl_4 with

(1) R. Breslow, J. A. Dale, P. Kalicky, S. Y. Liu, and W. N. Washburn, *J. Amer. Chem. Soc.*, **94**, 3276 (1972).
(2) R. Breslow, R. Corcoran, J. A. Dale, S. Y. Liu, and P. Kalicky *J. Amer. Chem. Soc.*, **96**, 1973 (1974).
(3) A. K. Bose, B. Lal, W. A. Hoffman, and M. S. Manhas, *Tetrahedron Lett.*, 1619 (1973).
(4) R. Breslow, B. B. Snider, and R. J. Corcoran, *J. Amer. Chem. Soc.*, **96**, 6792 (1974).

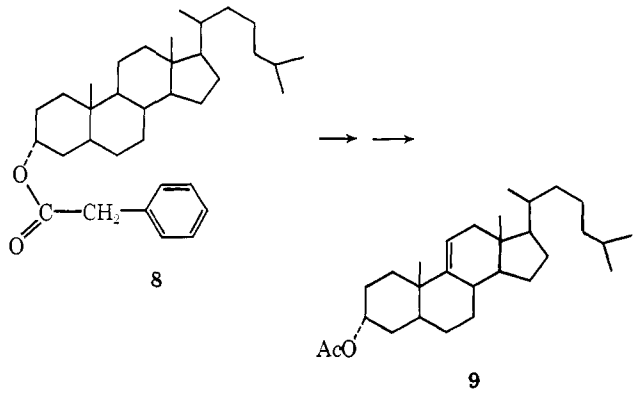
1.2 equiv of SO_2Cl_2 was heated for 22 hr at reflux in the presence of 10 mol % benzoyl peroxide to afford **4** and recovered **1** in yields comparable to those obtained with $PhICl_2$. In the absence of the peroxide radical initiator, **1** was recovered unchanged (if it had formed the corresponding dichloride, thermally initiated chlorination would have occurred). If 3α-cholestanyl benzoate is used in the SO_2Cl_2–peroxide reaction, the steroid is not chlorinated; thus the iodine atom both promotes and directs the halogenation.

Another point in favor of species **2** as the intermediate in these indirect halogenations comes from the results with **7**, the *m*-iodophenylacetate ester.[5] Models show that the chlorine atom on this iodine can reach both C-9 and C-14, and we find that the dichloride of **7** does chlorinate both of these positions in the simple intramolecular process. The identical mixture is obtained from radical relay halogenation of **7** using external $PhICl_2$.



7

The simple benzoate of 3α-cholestanol is not halogenated to an appreciable extent by $PhICl_2$ under our conditions (in CH_2Cl_2) and this is also true in the cortisone series described in the accompanying paper. Intermolecular halogenations by $PhICl_2$ work really well only in aromatic solvents. Such solvent effects suggest that some kind of aromatic complexing[6] of the intermediate PhICl· may be important for intermolecular processes, although it is not required for an intramolecular halogenation by an attached $ArICl_2$ reagent or for the radical relay mechanism. This indicated that it might be possible to use aromatic ring complexing to direct a halogenation process. Accordingly, we examined the halogenation of the phenylacetate of 3α-cholestanol (**8**) with $PhICl_2$ in various solvents. In benzene solution, we obtain an equal ratio of attack on C-9 and C-14 characteristic of external attack on other simple 3α-cholestanol derivatives. However, in CH_2Cl_2 solution we still get some halogenation of the steroid, showing that this attached phenyl can replace solvent benzene. There is 22% conversion of **8** to a mixture of 47% of polar products and 53% of the 9(11) olefin with no detectable amount of a Δ^{14} derivative.



8 **9**

Thus, an attached phenyl ring in **8** can indeed direct the halogenation by complexing with PhICl·. Molecular models show that the phenyl ring of **8** can lie under C-9 of the steroid; rather than shielding this position, this apparently results in delivery of a complexed reagent.

Although aromatic complexing can direct a halogenation, the strikingly different result with the iodo esters and the esters lacking the iodine atom clearly indicate that the major interactions in the halogenations of **1**, **5**, and **7** are with the iodine atoms themselves. This is also true for chlorine atoms "solvated" by iodobenzene in contrast to benzene solvent.[6]

The most reasonable interpretation of the selective halogenation of **1** is the radical relay mechanism shown. It should be noted that this mechanism for intermolecular halogenation has the usual entropy advantage characteristic of two-step processes involving a neighboring catalytic group[7] and furthermore that this mechanism should be quite general. While the relay transfer of other radicals by other complexing atoms or groups may be useful variants, the current versions of this process (including the thermal reaction using SO_2Cl_2 and radical initiators) are particularly attractive ways to functionalize ring C of steroids.

Acknowledgment. Experimental assistance by Mr. Steven Thompson and financial support of this work by the National Institutes of Health are gratefully acknowledged.

(5) Prepared by esterification of 3α-cholestanol. The compound was characterized by analysis and spectra, and had mp 88–90°.

(6) G. A. Russell, *J. Amer. Chem. Soc.*, 80, 4987 (1958). Note in particular the evidence for complexes involving one chlorine atom and *two* arenes.

(7) *Cf.* R. Breslow, "Organic Reaction Mechanisms," 2nd ed, W. A. Benjamin, New York, N. Y., 1969, p 63.

(8) NSF Predoctoral Fellow.

Ronald Breslow,* Richard J. Corcoran,[8] Barry B. Snider
Department of Chemistry, Columbia University
New York, New York 10027
Received July 29, 1974

A Cortisone Synthesis Using Remote Oxidation

Sir:

We have developed reactions[1-3] by which it is possible to introduce functionality into unactivated positions of substances such as steroids, using rigid oriented reagents which can attack at a large distance from their point of original attachment. The invention of this class of reactions, which we refer to as remote oxidation or remote functionalization, was actually inspired by considering the processes by which corticosteroids are produced biologically. Both in adrenal biosynthesis and in preparative reactions utilizing microbiological fermentation, a steroid without function-

(1) R. Breslow, S. Baldwin, T. Flechtner, P. Kalicky, S. Liu, and W. Washburn, *J. Amer. Chem. Soc.*, **95**, 3251 (1973).

(2) R. Breslow, R. Corcoran, J. A. Dale, S. Liu, and P. Kalicky, *J. Amer. Chem. Soc.*, **96**, 1973 (1974).

(3) R. Breslow, R. J. Corcoran, and B. B. Snider, *J. Amer. Chem. Soc.*, **96**, 6791 (1974).