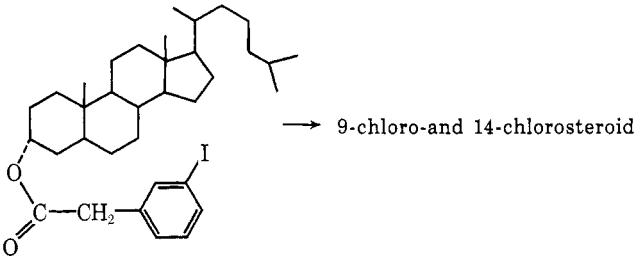
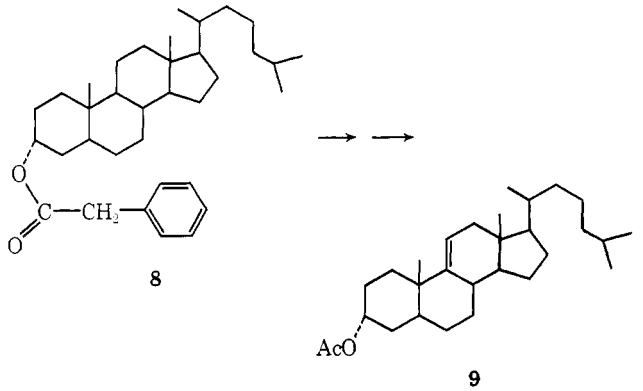
1.2 equiv of SO_2Cl_2 was heated for 22 hr at reflux in the presence of 10 mol % benzoyl peroxide to afford **4** and recovered **1** in yields comparable to those obtained with $PhICl_2$. In the absence of the peroxide radical initiator, **1** was recovered unchanged (if it had formed the corresponding 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 $PhICl\cdot$ 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 $PhICl\cdot$. 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.

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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).

ality in ring C is oxygenated at position 11 because of stereochemical constraints within an enzyme–substrate complex. We have imitated these constraints by our remote functionalization procedures, and have demonstrated with them that it is possible to achieve selective steroid functionalization in ring C or D starting with a rigid reagent attached to C-3 of ring A of the steroid. We now wish to report a synthesis of cortisone utilizing such a process for the critical introduction of oxygen at C-11 in ring C. The sequence illustrates the ease with which these methods can be applied and the high yields now attainable.

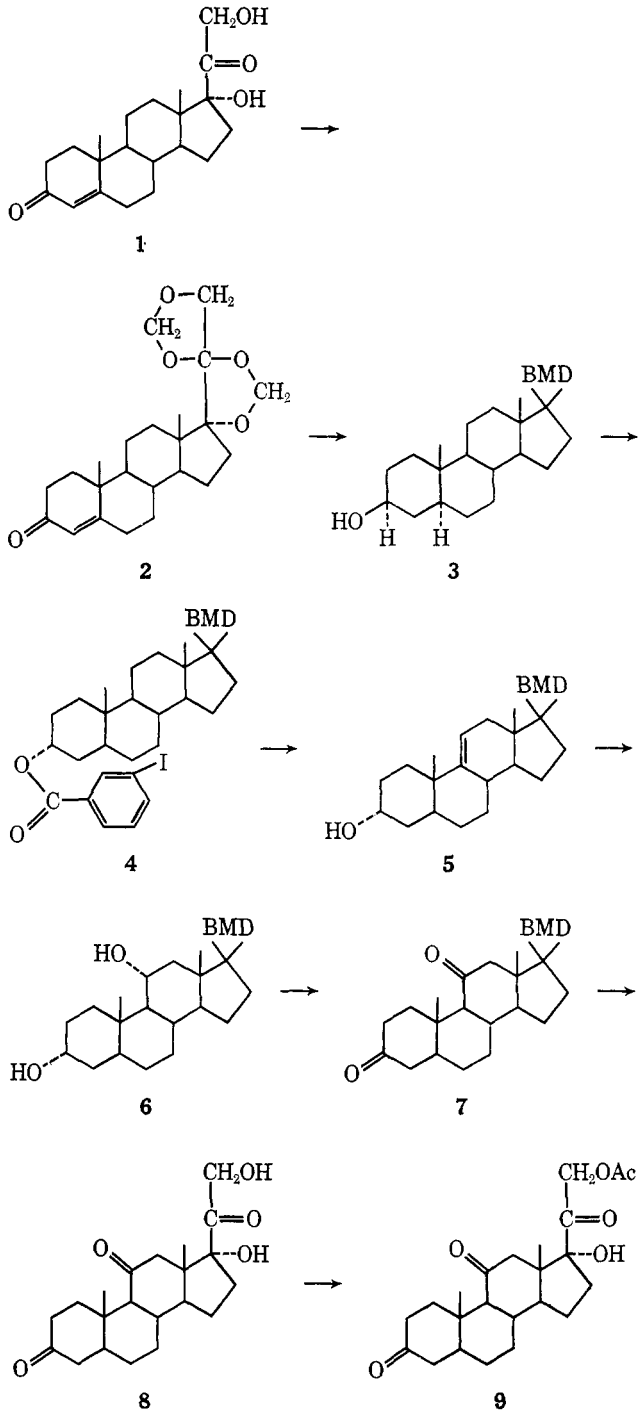
Since we were fundamentally interested in the ring C functionalization process, we initiated our synthesis with cortexolone (**1**) which contains all the functionality of cortisone except for a keto group at C-11. Cortexolone was converted with formalin and HCl into the BMD derivative **2**,[4] which by reduction with lithium (NH_3–ethanol–ether) afforded the saturated 3β-alcohol **3**,[5] mp 242–247° (Scheme I). This was converted to the corresponding α ester with *m*-iodobenzoic acid by the extremely convenient inversion–esterification procedure,[6] utilizing triphenylphosphine and azodicarboxylic ester. The *m*-iodobenzoate **4**,[5] mp 173–174°, was obtained in 60% overall yield from cortexolone (**1**).

We had originally intended to apply our procedure of remote functionalization using an attached aryliodine dichloride.[2] Indeed the dichloride corresponding to **4** had already been prepared by us in the cholestanol series and shown to direct halogenation to C-9, so that the 9(11) double bond was easily introduced. However, direct chlorination of **4** led to some attack on the BMD protecting group. Accordingly, we have devised a new procedure,[3] which proves to be even more convenient and effective than our previously described halogenation using attached aryliodine dichlorides. A 0.01 *M* solution of **4** in CH_2Cl_2 with 1.2 equiv of phenyliodine dichloride was briefly irradiated with an ordinary sunlamp, and the product was then dehydrohalogenated and saponified with methanolic KOH to afford the unsaturated steroidal alcohol **5**. This was isolated as the acetate,[5] mp 168.5–169.5°, in 74.5% yield from **4**.

This process does not involve conversion of **4** into its corresponding dichloride, but instead utilizes reaction of an external ArICl radical with **4**. The external radical apparently transfers a chlorine atom to the iodine of **4**, to generate an intermediate radical whose chlorine is now uniquely positioned to abstract the 9 hydrogen of the steroid. A study of this novel radical relay process is reported in the accompanying communication.[3] It should be mentioned that a simple benzoate corresponding to **4** undergoes very little functionalization under these same conditions and does not produce an appreciable yield of **5**.

We have found[3] that radical relay halogenation can also be performed using SO_2Cl_2 and benzoyl peroxide with thermal initiation. This nonphotochemical procedure, utilizing inexpensive reagents, also converts **4** to **5** in a yield comparable to that described above.

Scheme I



The olefin **5** was hydroborated[7] and oxidized with alkaline hydrogen peroxide under standard conditions to afford the 3α-11α-diol **6**,[5] mp 180–181°, in 68% overall yield from **4**. With Jones' reagent this was converted to the corresponding dione **7**,[5] mp 215–220°, in 96% yield, which was deprotected with 48% HF in tetrahydrofuran[8] to afford dihydrocortisone **8**,[9] mp 216–218° (lit.[9] mp 217–221°) in 85% yield. This was converted to dihydrocortisone acetate[10] **9**, mp 235–

(4) R. E. Beyler, F. Hoffman, R. M. Moriarty, and L. H. Sarett, *J. Org. Chem.*, **26**, 2421 (1961).
(5) Characterized by correct combustion analytical and spectroscopic data.
(6) A. K. Bose, B. Lal, W. A. Hoffman, III, and M. S. Manhas, *Tetrahedron Lett.*, 1619 (1973).
(7) M. Nussim and F. Sondheimer, *Chem. Ind. (London)*, 400 (1960).
(8) J. B. Siddall, F. Alvarez, and A. Ruiz, *Neth. Appl.*, 6,607,490 (1967); *Chem. Abstr.*, **66**, P115875*u* (1967).
(9) R. M. Evans, G. F. H. Green, J. S. Hunt, A. G. Long, B. Mooney, and G. H. Philipps, *J. Chem. Soc.*, 1529 (1958).
(10) J. Pataki, G. Rosenkranz, and C. Djerassi, *J. Amer. Chem. Soc.*, **74**, 5615 (1952).

237° (lit.[10] mp 234–236°) in 95% yield, identical with authentic material. The overall yield in the entire sequence is 30% starting from cortexolone (**1**).

The conversion of **9** to cortisone acetate in 42% yield is already known,[11] and **9** can also be converted to prednisolone acetate.[12] Thus, our procedure accomplishes new syntheses of both of these compounds. Although the conversion of **1** to cortisone acetate involves a number of steps and proceeds in an overall yield of only 12.5%, this is largely because of the arbitrary choice of starting material. The remote functionalization reaction itself, by which the ring C functionality is introduced, proceeds in good yield and with excellent selectivity. In appropriate sequences it should furnish an attractive alternative to the microbiological functionalization methods currently in use.

Acknowledgment. Financial support of this work by the National Institutes of Health is gratefully acknowledged.

(11) 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).
(12) Ch. Meystre, H. Frey, W. Voser, and A. Wettstein, *Helv. Chim. Acta*, **39**, 734 (1956).
(13) NSF Predoctoral Fellow.

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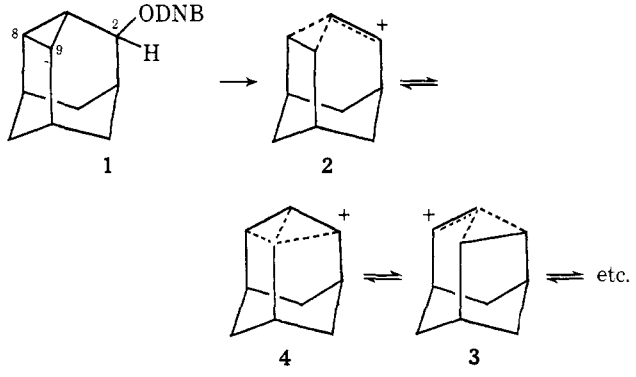
Stable Carbocations. CLXXV.[1] 8,9-Dehydro-2-adamantyl Cations

Sir:

In an attempt to generate a cyclopropylcarbinyl cation that would be geometrically defined and of potential C_{3v} symmetry, Baldwin and Foglesong examined the solvolysis of 8,9-dehydro-2-adamantyl 3,5-dinitrobenzoate (**1**).[2] They found that solvolysis of **1**

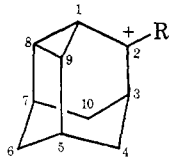


1 **2** **4** **3**

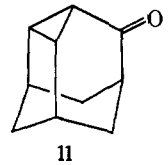
occurs with the marked rate acceleration characteristic of cyclopropylcarbinyl systems,[3] and (*via* labeling studies) that the original 2, 8, and 9 positions of **1** achieve nearly complete equivalence during solvolysis.[2] Baldwin and Foglesong suggested the bridged, nonclassical representation **2** for the charge-delocalized 8,9-dehydro-2-adamantyl cation and proposed that scrambling occurred *via* migration of the C_8–C_9 bond to give **3**, etc. The ion-linking degenerate cyclopropylcarbinyl cations **2** and **3** were represented as bicyclobutonium ion **4**.[2] Recently, we have studied by nmr the structures of cyclopropylcarbinyl cations **5**–**7** under stable ion

5 **6**, R = H; **7**, R = CH_3

conditions.[4] It is apparent from these studies that although the primary cyclopropylcarbinyl cation **5** is a rapidly equilibrating *nonclassical* ion, both the secondary (**6**) and tertiary (**7**) ions are *classical* ions with varying degrees of charge delocalization into the cyclopropane ring.[4] In view of these studies, we now wish to report the direct observation of the 8,9-dehydro-2-adamantyl (**8**) and 2-methyl-8,9-dehydro-2-adamantyl (**9**) cations under stable ion conditions.



8, R = H
9, R = CH_3
10, R = OH



11

The parent secondary ion **8** and the tertiary ion **9** were prepared from the corresponding alcohols[5,6] in FSO_3H–SO_2ClF (SO_2) solutions at −120 and −78°, respectively. The pmr spectrum of ion **8** (Figure 1a) shows a deshielded doublet of doublets at δ 7.96 (three protons), a quartet at 4.92 (one proton), and two broad peaks at 3.20 and 2.60 (three and six protons, respectively). In contrast, the bridgehead proton H_1 in ion **9** (Figure 1b) is a triplet, since it is coupled with two equivalent protons (H_8 and H_9). The latter appear as a broad multiplet at δ 5.69. Moreover, the two H_6 methylene protons in **9** are *non*equivalent and display an AB quartet centered at δ 2.60 (J = 11.2 Hz). Similarly, the two H_6 methylene protons in protonated 8,9-dehydro-2-adamantanone (**10**) (prepared from ketone **11**[5] in FSO_3H–SO_2ClF solution) appear as an AB quartet centered at δ 2.45 (J = 11.0 Hz).[7]

In order to further define the structures of the 8,9-dehydro-2-adamantyl cations, we have obtained their Fourier transform (FT) ^{13}C nmr spectra. The complete cmr parameters with resonance assignments for ions **8**–**10** are summarized in Table I. As is apparent, the cmr spectra of ions **8** and **9** are strikingly different. Consistent with a rapidly equilibrating system, the ^{13}C nmr spectrum of **8** shows only four carbon resonances. In contrast, tertiary ion **9** displays the behavior char-

(1) Part CLXXIV: G. A. Olah, H. C. Lin, and D. A. Forsyth, *J. Amer. Chem. Soc.*, in press.
(2) J. E. Baldwin and W. D. Foglesong, *J. Amer. Chem. Soc.*, **90**, 4303, 4311 (1968).
(3) For a review see K. B. Wiberg, B. A. Hess, Jr., and A. J. Ashe, III, in "Carbonium Ions," Vol. III, G. A. Olah and P. v. R. Schleyer, Ed., Wiley-Interscience, New York, N. Y., 1972, Chapter 26.
(4) G. A. Olah, C. I. Jeuell, D. P. Kelly, and R. D. Porter, *J. Amer. Chem. Soc.*, **94**, 146 (1972).
(5) R. K. Murray, Jr., and K. A. Babiak, *Tetrahedron Lett.*, 319 (1974).
(6) R. K. Murray, Jr., and K. A. Babiak, *Tetrahedron Lett.*, 311 (1974).
(7) The hydroxy proton absorption at δ 12.84 in ion **10** is a sharp singlet at −80°, which gradually becomes broadened as the temperature rises and collapses with the acid peak at −30°. Upon cooling to −80°, the original singlet is reformed.