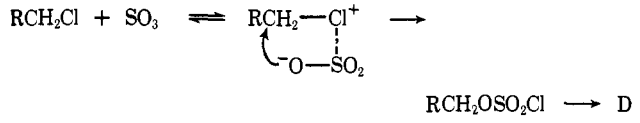
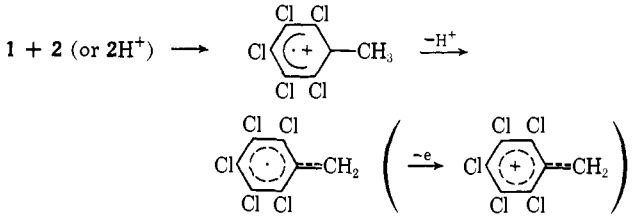
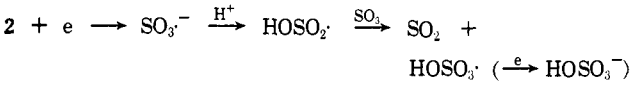


(b) Electrophilic attack on the π-bond system by **2** (or protonated **2**), resulting in the formation of radical cations,[15] is suggested by the intensely colored solutions and by the detection of free radicals by esr. The





effect of substituents on rate (methyl increases, nitro group retards or impedes) is accommodated by either mechanism. Conceivably, however, two or more competing mechanisms, yielding similar or related products, may occur simultaneously.

(15) Electron-rich aromatic systems readily form radical cations on dissolution in concentrated sulfuric acid or oleum.[16]

(16) M. K. Carter and G. Vincow, *J. Chem. Phys.*, 47, 302 (1967); J. R. Bolton and A. Carrington, *Proc. Chem. Soc.*, 174 (1961); S. I. Weissman, E. deBoer, and J. J. Conradi, *J. Chem. Phys.*, 26, 963 (1957); K. D. J. Root and M. T. Rogers, *J. Magn. Resonance*, 1, 568 (1969).

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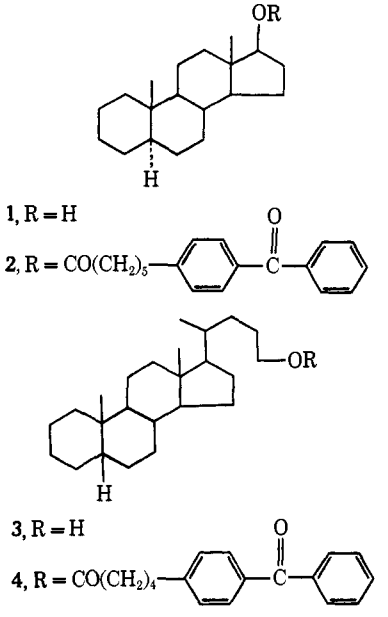
Remote Oxidation of Steroids by Reagents Attached to Ring D. Introduction of a 9(11) Double Bond

Sir:

We have reported[1,2] a process, remote oxidation, in which unactivated carbons can be functionalized by intramolecular hydrogen abstraction using a rigid benzophenone reagent attached to a functional group of the substrate. The resulting diradical may couple, resulting in overall insertion of the benzophenone carbonyl into a substrate C–H bond; alternatively, hydrogen transfer in the diradical leads directly to introduction of a substrate double bond, with reduction of the benzophenone carbonyl. The carbinol products of C–H insertion may be dehydrated and oxidized, leading to substrates into which a carbonyl has been introduced, or the carbinols may be fragmented with lead tetraacetate to produce substrate-derived olefins.

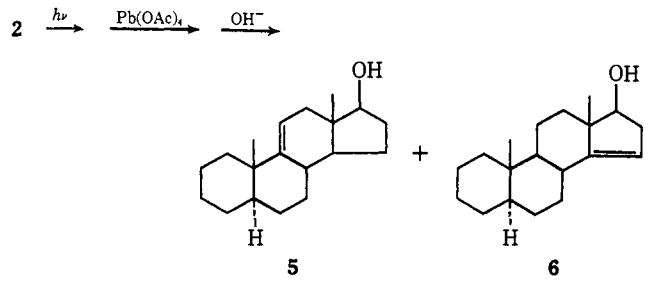
The process was initially described for flexible long-chain alcohol substrates,[1] but it has been extended to steroids.[2,3] By attachment of a rigid benzophenone reagent to 3α-cholestanol, we have been able to functionalize the steroid selectively at C-7, -12, and -14.[4] In an extension, we have shown[5] that simple complexing of a steroid carboxylic acid with a reagent carboxylic acid permitted us to perform selective functionalization at C-16. However, all of the steroid cases which have been reported up to this time have involved a 3α attachment to an AB trans steroid, and it is naturally of interest to inquire how general the process is.[6]

We now wish to report that remote oxidation is successful if a benzophenone reagent is initially attached directly to ring D in androstan-17β-ol (**1**), or to the side-chain C-24 of cholan-24-ol (**3**). Interestingly, these attachments to the β side of the steroid still lead to attack on the α side, by a curling under of the connecting chains, and they permit functionalizations at C-14, -15, and -9. This last result is of the greatest significance, since it leads to the introduction of a 9(11) double bond which, by functionalizing C-11, allows an entry[7] into the important 11-oxygenated corticosteroid structures.



Photolysis of a 900-ml 10^{-3} *M* solution of **2** in purified benzene for 3 hr (450-W medium-pressure lamp, uranium glass filter), and lead tetraacetate cleavage of the entire product, followed by hydrolysis, leads to a 60% recovery of the starting steroid and the isolation of 20% of a mixture of $\Delta^{9(11)}$-androsten-17β-ol (**5**) and Δ^{14}-androsten-17β-ol (**6**). Photolysis of **2** in 1,1,2-trifluoro-1,2,2-trichloroethane followed by an identical processing affords similar results. The ratio of **5** to **6** is 2:1 in benzene and 4:1 in the fluorocarbon solvent. The initial photoproduct can alternatively be separated into a fraction containing **6** and a lactone fraction (from insertion of the benzophenone carbonyl into steroid C–H bonds); cleavage of this lactone by lead tetraacetate produces only the $\Delta^{9(11)}$ olefin **5**. However, oxidation of the entire photoproduct and chromatographic separation of **5** and **6** is more convenient.

(1) R. Breslow and M. Winnik, *J. Amer. Chem. Soc.*, **91**, 3083 (1969).
(2) R. Breslow and S. W. Baldwin, *ibid.*, **92**, 732 (1970).
(3) J. E. Baldwin, A. K. Bhatnagar, and R. W. Harper, *Chem. Commun.*, 659 (1970).
(4) Unpublished work of W. Washburn shows that functionalization at C-7 accompanies the processes described in ref 2.
(5) R. Breslow and P. Scholl, *J. Amer. Chem. Soc.*, in press.
(6) We have found that the chemistry of ref 2 cannot be trivially extended to 3β,5α or 3α,5β steroids.
(7) For examples of the conversion of $\Delta^{9(11)}$ steroids not only to 11-oxygenated corticosteroids, but also to even more useful 9-halo-11-oxo steroids, *cf.* L. F. Fieser and M. Fieser, "Steroids," Van Nostrand-Reinhold, New York, N. Y., 1959, pp 681–692.



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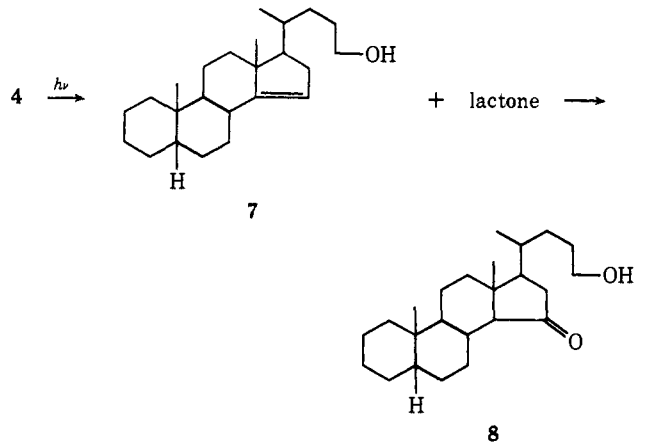
The structure of **5**, *m/e* 274, is indicated by its mp, 158–159° (lit.[8] 160.5–162°), and its highly characteristic nmr spectrum. The vinyl proton is centered at δ 5.34 (expected[9a] value δ 5.27). Angular methyl resonance positions for the C-18 and C-19 groups vary characteristically with the double bond position,[9b] and our signals (60 MHz) at 42.0 and 56.0 Hz agree with the predicted[9b] values of 40.5 and 56.5 Hz.[10] The closest methyl signals for an alternative position of the double bond, Δ^{14}, are predicted at 48.5 and 59.5 Hz, in poor agreement with the values above but in excellent agreement with the values of 48.0 and 58.0 observed for the compound assigned structure **6**. The vinyl proton of **6** has its characteristic signal at δ 5.07 (predicted[9a] δ 5.04), quite different from other[9a] steroid vinyl positions.

Photolysis of a 10^{-3} *M* solution of **4** in purified benzene (450-W medium-pressure lamp, uranium glass filter) followed by basic hydrolysis affords a 25% yield of the hitherto unreported Δ^{14}-cholen-24-ol (**7**), mp 99–100° (*m/e* 344), and a 45% yield of a lactone fraction.[11] This lactone was reduced with lithium aluminum hydride, acetylated with acetic anhydride in pyridine, and dehydrated with thionyl chloride in pyridine. The resulting diphenylethylene derived from **4** was submitted to oxidation with ruthenium tetroxide and sodium periodate, followed by chromatography. The only steroidal ketone detectable, isolated in 16% yield based on the total lactone fraction, was the hitherto unreported 15-keto-cholan-24-ol (**8**) (*m/e* 360).



7 8

(8) W. Klyne and S. Palmer, *J. Chem. Soc.*, 4545 (1958). Their multistep synthesis starts with a cortisone derivative.

(9) (a) G. M. L. Cragg, C. W. Davey, D. N. Hall, G. D. Meakins, E. E. Richards, and T. L. Whateley, *J. Chem. Soc.*, 1266 (1966); (b) calculated from the tables in N. Bhacca and D. H. Williams, "Application of Nmr Spectroscopy in Organic Chemistry; Illustrations from the Steroid Field," Holden-Day, San Francisco, Calif., 1964.

(10) These data also agree with those for other $\Delta^{9(11)}$ steroids prepared in unpublished remote oxidation work by W. Washburn.

(11) Oxidation of this lactone with lead tetraacetate produces no olefinic cleavage products.

The structure of **7** is indicated by its vinyl nmr resonance at δ 5.15, and its C-18 and C-19 resonances at 54.0 and 56.0 Hz. For this skeleton the predicted[9b] values for **7** are 55.0 and 56.0 Hz, while the closest alternative (excluded also by the vinyl nmr), Δ^{11}, would come at 45.0 and 53.5 Hz. The structure of **8** is indicated by the infrared band for a cyclopentanone at 1740 cm^{-1}, and methyl nmr signals at 44.5 and 55.5 Hz (predicted[9b] 44.5 and 56 Hz). The alternative 16-oxo structure would have[5,12] these signals at 50.5 and 57 Hz.

It is interesting that, in the previous examples,[2,3,5] attachment of a benzophenone residue to the rigid steroid nucleus by a flexible chain of atoms led to attack quite remote from the position of attachment at 3α. By contrast, in **4** we may consider that the benzophenone is attached by a long chain, partly from the reagent and partly the side chain of the steroid, leading from C-17 of the steroid nucleus; however, attack occurs at C-14 and C-15, only a few atoms from the point of attachment of the flexible chain. Apparently in this case the chain doubles back under itself as a loop, and the flat benzophenone system lies underneath ring D of the steroid. In the photolysis of **2** the two products arise from initial attack of the benzophenone carbonyl group on carbon–hydrogen bonds at C-9 and C-14, again on the α side of the steroid even though the chain was attached β. The flexibility in **2** and **4** makes *a priori* predictions of these positions of attack difficult. However, the observation that in **2** the major product, in respectable conversion, is the $\Delta^{9(11)}$ olefin **5** indicates further the synthetic potential of remote oxidation.

(12) J. Jacques, M. Minssen, D. Varech, and J. Basselier, *Bull. Soc. Chim. Fr.*, 77 (1965).

(13) NIH Predoctoral Trainee. Support of this work by the National Institutes of Health is gratefully acknowledged.

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Nitrogen-15 Magnetic Resonance Spectroscopy. Solvent Effects on $^1J(^{15}NH)$ and Hydrogen Bonding in Ortho-Substituted Anilines

Sir:

Nmr evidence for the existence of hydrogen bonding has come primarily from chemical shift investigations of the proton(s) involved in the hydrogen-bonded complex X—H···Y,[1] although recent reports indicate that new insights may be provided by chemical shift studies of the heteronuclei which serve as the hydrogen donors (X) and acceptors (Y).[2]

To the extent that hydrogen bonding alters the nature of the X–H bond, one might expect this to be reflected in the one-bond X–H spin coupling. Solvent dependence of $^1J(^{15}NH)$ in aniline[3] and its ring-sub-

(1) J. W. Emsley, J. Feeney, and L. H. Sutcliffe, "High Resolution Nuclear Magnetic Resonance Spectroscopy," Vol. 1, Pergamon Press, Oxford, 1965, p 534.

(2) A. E. Florin and M. Alei, Jr., *J. Chem. Phys.*, 47, 4268 (1967); A. E. Florin and M. Alei, Jr., *J. Phys. Chem.*, 73, 863 (1969); J. Reuben, *J. Amer. Chem. Soc.*, 91, 5725 (1969); W. M. Litchman, M. Alei, Jr., and A. E. Florin, *ibid.*, 91, 6574 (1969); 92, 4828 (1970); H. Saito and K. Nukada, *ibid.*, 93, 1072 (1971); H. Saito, Y. Tanaka, and K. Nukada, *ibid.*, 93, 1077 (1971).

(3) L. Paolillo and E. D. Becker, *J. Magn. Resonance*, 2, 168 (1970).