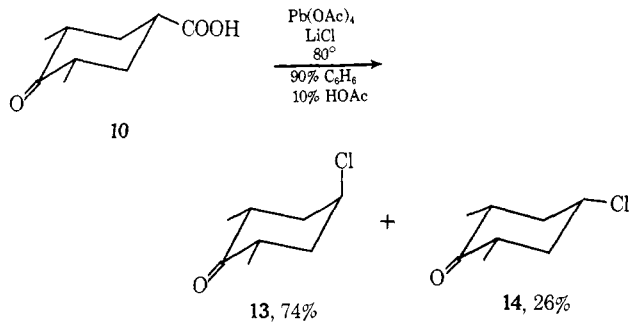

Jones oxidations[15] of chloro alcohols to chloro ketones and conversions of chloro ketones with sulfur tetrafluoride[14] into chlorodifluorides were stereospecific, so that independent product syntheses **11** → **13** → **7** and **12** → **14** → **8** proceeded in good yield without detectible epimerization.

Acknowledgment. We wish to thank the National Science Foundation, the Research Corporation, and an anonymous donor for support of this work. The 100-MHz nmr spectrometer was purchased with the aid of matching funds from National Science Foundation Grant No. GP-8171.

(15) J. Meinwald, J. Crandall, and W. E. Hymans, *Org. Syn.*, **45**, 77 (1965); R. G. Curtis, I. Heilbron, E. R. H. Jones, and G. F. Woods, *J. Chem. Soc.*, 457 (1953).

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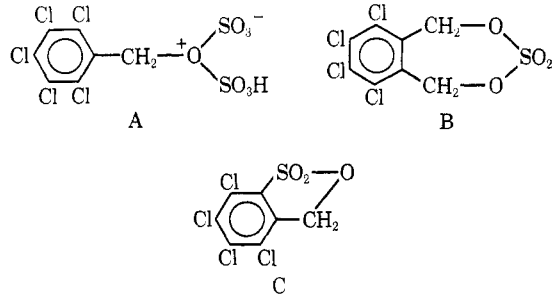
Selective Oxidations by Sulfur Trioxide

Sir:

Although it has been recognized for some time that sulfur trioxide is a powerful oxidant, its use as such for organic compounds has not so far been developed. The main reason for not utilizing its oxidizing properties was the indiscriminate reaction pattern it exhibited when it was contacted with a variety of substrates, mainly hydrocarbons. With paraffins and olefins, it gave messy, intractable reaction mixtures due to the intermeshing of various, not fully clarified oxidation, rearrangement, condensation, polymerization, sulfonation, and sulfation reactions, the complex nature of which apparently discouraged the consideration of sulfur trioxide as a manageable oxidizing agent. In contrast, its use as a sulfonating agent for unsaturated compounds and as a sulfating agent for alcohols is well developed and amply documented.[1]

We now wish to demonstrate that sulfur trioxide can be of considerable synthetic value as an oxidant when used with the proper reaction partners. These are organic compounds in which some parts of the molecule are protected by appropriate substitution while others remain susceptible to oxidation by sulfur trioxide. The reaction of 2,3,4,5,6-pentachlorotoluene (**1**) provides a representative example.

When 26.4 g (0.1 mol) of **1**[2a] was added in one portion to an excess (200 ml) of liquid (stabilized) sulfur trioxide (**2**), and the resultant mixture was refluxed with good stirring, an intensely blue color developed, accompanied with the evolution of sulfur dioxide, which continued for 2–3 hr and amounted to 0.1 mol. After removal of excess **2**, 45.2 g of a greenish gray solid, **3**, with the composition of $C_7H_3Cl_5O_7S_2$ was recovered. The latter, on addition to water, followed by heating of the resultant aqueous slurry to reflux, precipitated 26.6 g of a white, powdery material which after dissolution in acetic acid[3] and reprecipitation yielded 24.5 g (91%) of 2,3,4,5,6-pentachlorobenzyl alcohol (**4**), mp 195.0–196.5°. When **3** was added directly to aqueous sodium hydroxide or ammonium hydroxide solutions, the corresponding salts of the hydrogen sulfate ester of **4** were obtained. These data and reactions suggest that **3** is the hydrogen sulfate ester of **4** solvated by 1 mol of **2** as shown in structure A. This was confirmed by its nmr spectrum, run in **2** at the end of the heating period, which showed that the proton peak of **1** at δ 2.52 had completely disappeared and that two new peaks at δ 6.29 and 9.2 were present in a 2:1 ratio.[4] The former corresponds to the two benzylic hydrogens and the latter to the acidic proton of the sulfuric acid moiety in A.[5–7] In corroboration of structure A, **3** was prepared also from **4** and **2**.



The oxidation reaction illustrated with **1** was found to be of a rather wide scope and includes not only chlorinated, fluorinated, and brominated toluenes, but the halogenated xylenes and higher methylbenzenes as well. For instance, the reaction of tetrachloro or tetrabromo *m*- and *p*-xylenes provides a convenient, one-step preparation of the corresponding xylylene diols.[8] These reactions seem to be characteristic of the methyl side chains, since *ar*-pentachloroethylbenzene yields *ar*-pentachloro-β-*trans*-styrenesulfonic acid and *ar*-pentachlorocumene forms *ar*-pentachlorobenzenesulfonic acid. When the aromatic nuclei are not fully protected by substitution, sulfonation may accompany the oxidation reaction. With hydrogens in

(1) E. E. Gilbert, "Sulfonation and Related Reactions," Interscience, New York, N. Y., 1965.

(2) (a) P. G. Harvey, F. Smith, M. Stacey, and J. C. Tatlow, *J. Appl. Chem.*, **4**, 325 (1954); (b) S. D. Ross and M Markarian, *J. Amer. Chem. Soc.*, **71**, 2756 (1949).

(3) The small amount of material insoluble in acetic acid was identified as *ar*-decachlorodibenzyl ether, mp 223–225°, and a mixture of *ar*-decachlorodiphenylmethane and isomeric *ar*-nonachlorophenyltolylmethanes. *ar*-Pentafluorotoluene yielded a somewhat higher proportion of alkylation products.

(4) The chemical shift of the low-field peak is somewhat variable during the reaction between δ 9.2 and 9.6.

(5) The chemical shift of the benzylic protons at δ 6.29 of **3** is at an intermediate position between that of hydrogen sulfate ester of **4** (δ 5.05 in DMSO) and those of the benzylic cations (*e.g.*, pentamethylbenzyl cation at δ 8.66 in SbF_5–SO_2 solution[6]).

(6) J. M. Bollinger, M. B. Comisarow, C. A. Cupas, and G. A. Olah, *J. Amer. Chem. Soc.*, **89**, 5687 (1967).

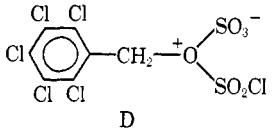
(7) The preferred *Chemical Abstracts* name of A is pentachlorobenzyldisulfooxonium hydroxide inner salt: Dr. K. L. Loening, Chemical Abstracts Service, personal communication.

(8) Tetrahalo-*o*-xylenes give predominantly the corresponding cyclic sulfates as the hydrolysis product, *e.g.*, B.

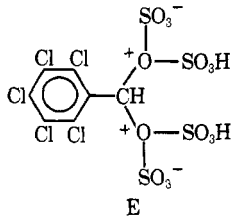
the meta or para position to the methyl group, sulfonic acids, and in the ortho position, sultones are produced. For instance, 2,3,4,5-tetrachlorotoluene yields C (δ 5.38 in $CDCl_3$) and 2,4,5-trichlorotoluene yields some of the corresponding trichloro analog (δ 5.35 and 7.74).

Compounds with structures analogous to A are obtained from benzylic chlorides and **2**. For instance, pentachlorobenzyl chloride[2b] yields D. This and related compounds also undergo the characteristic reactions of A (*vide infra*).[9]

A significant extension of this novel oxidation reaction was realized when the heating of **1** in excess **2** was extended to 24 hr. In a slower, but continuous reaction, 1 more mol equiv of sulfur dioxide was evolved and a product with the composition of $C_7H_3Cl_5O_{14}S_4$ (**5**) was obtained, which on hydrolysis yielded pentachlorobenzaldehyde, mp 201–203°, in nearly quantitative conversion. The hydrolysis and nmr data (δ at 10.15 and 8.9) indicate structure E for **5**.



D



E

Similarly, 2,3,4,5,6-pentabromotoluene yielded quantitatively pentabromobenzaldehyde, mp 281–283°. Both aldehydes were completely free of the corresponding acids, probably as a result of steric crowding in E, which prevents the removal of the third hydrogen from the benzylic carbon.

The aldehyde-forming reaction seems to be characteristic of polyhalotoluenes and meta-substituted benzenes (*m*-xylene and mesitylene), since tetrahalo-*o*- and *p*-xylenes yield, even after extended refluxing, only the diols or the cyclic sulfates after hydrolysis.

Both the benzyldisulfooxonium and benzalbis(disulfooxonium) compounds undergo a variety of displacement reactions, usually cleanly and in good yield, a feature which renders these highly reactive compounds of considerable synthetic value. A few illustrative reactions are shown with A as one of the reactants (R = pentachlorophenyl substituent).

$$A + CCl_4 \text{ (or } CHCl_3) \longrightarrow RCH_2Cl \quad (1)$$

$$A + CBr_4 \longrightarrow RCH_2Br \quad (2)$$

$$A + Br_2 \longrightarrow RBr \quad (3)$$

$$A + PhH \longrightarrow RCH_2Ph \quad (4)$$

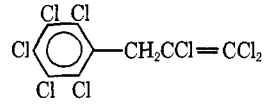
$$A + CH_3CN \longrightarrow RCH_2NHCOCH_3 \quad (5)$$

$$A + HCCl{=}CCl_2 \xrightarrow{H_2SO_4} RCH_2CHClCOOH \quad (6)$$

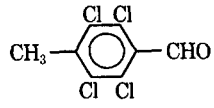
$$A + Cl_2C{=}CCl_2 \xrightarrow{H_2SO_4} RCH_2CCl_2COOH \quad (7)[10]$$

With difunctional analogs of A (as, *e.g.*, those derived from xylenes or E), the corresponding difunctional products are obtained. For instance, reaction 6 yields with tetrahalo-*o*-, -*m*-, and -*p*-xylenes the corresponding α,α'-dichlorobenzenedipropionic acids in 63–98% conversion.

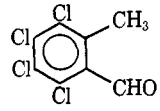
A noteworthy difference between the reactions of A and D was encountered with the haloolefins. Whereas A and trichloroethylene (**6**) yielded predominantly (in the presence of sulfuric acid quantitatively) the benzenepropionic acid, D and **6** formed halocarbons, mainly the octachloroallylbenzene F (δ 4.38 in DMSO), and α,α'-2,3,5,6-hexachloro-*p*-xylene and **6** formed the corresponding bis(trichloroallyl)tetrachlorobenzene (δ 3.74 in C_6D_6).[11]



F



G

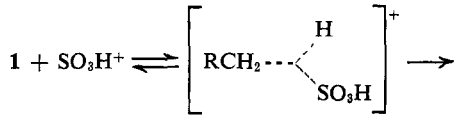


H

A further variation in the basic oxidation pattern was obtained when **2** was utilized in the presence of sulfuric acid. Thus, while tetrachloro-*p*-xylene and tetrachloro-*o*-xylene yielded with neat **2**, after hydrolysis, tetrachloro-*p*-xylylenediol and B, respectively, they formed, on reaction with an excess of 20% oleum, the corresponding tolualdehydes.[12]

Although a detailed discussion of the mechanism of the formation of A and of its reactions is deferred to the comprehensive publication, the two major mechanisms that attract primary consideration can be briefly outlined as follows.

(a) Electrophilic Sulfonation of the C–H σ Bond. Very recently Olah and coworkers proposed an intriguing, general mechanistic pathway initiated by direct attack of the electrophilic reagent on the shared electron pair of single bonded atoms, resulting in the formation of a two-electron, three-center bonded intermediate.[13] Applied to our examples, the formation of A can be derived as follows (R is pentachlorophenyl)



$$[RCH_2OSO_2H_2]^+ \xrightarrow[SO_3]{-H^+} SO_2 + RCH_2OSO_3H \longrightarrow A$$

The addition of a small amount of sulfuric acid to **2** increases the rate of SO_2 evolution, presumably by the enhancement of its electrophilic character *via* protonation.

In its insertion into the C–Cl bond, **2** is visualized to first coordinate with the unshared electrons of chlorine, followed by an internal displacement step.[14]

(9) When *ar*-polyhalobenzylic bromides are dissolved in **2**, bromine is liberated and the side chain is quantitatively replaced by bromine (*e.g.*, pentachlorobenzyl bromide yields bromopentachlorobenzene, α,α'-2,3,5,6-hexabromo-*p*-xylene yields hexabromobenzene).

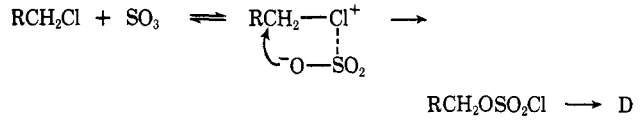
(10) Depending on the reaction conditions, variable amounts of RCH=CClCOOH were also produced. Both acids can be dehydrochlorinated to RC≡CCOOH.

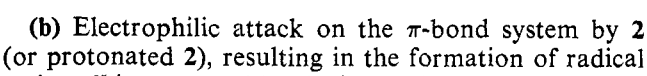
(11) The dichloroethylenes, as well as tribromoethylene and various chloromethyl-*ar*-polybromobenzenes, behave analogously.

(12) More interestingly, but explicably, even *ar*-tetrachloro-*p*-xylylene-α,α'-diol and α,α'-2,3,5,6-hexachloro-*p*-xylene became converted to *ar*-tetrachloro-*p*-tolualdehyde by oleum.

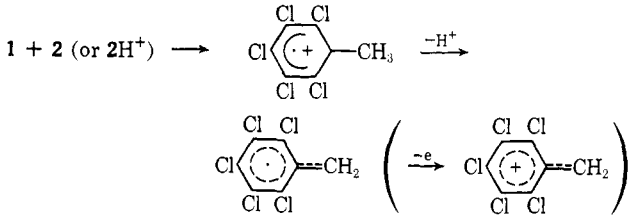
(13) G. A. Olah, Y. Halpern, J. Shen, and Y. K. Mo, *J. Amer. Chem. Soc.*, **93**, 1251 (1971); G. A. Olah and J. A. Olah, *ibid.*, **93**, 1256 (1971); G. A. Olah and H. C. Lin, *ibid.*, **93**, 1259 (1971). We thank Professor Olah for calling our attention to his mechanism.

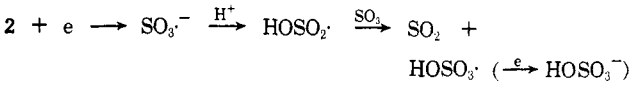
(14) *ar*-Polyhalobenzal chlorides react similarly and yield mono- and di-insertion products.





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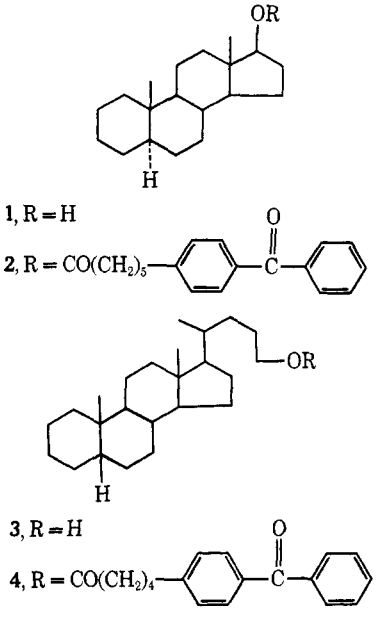
Remote Oxidation of Steroids by Reagents Attached to Ring D. Introduction of a 9(11) Double Bond

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.