Registry No. **5**, 88106-71-2; **6**, 38323-04-5; *parf*-**14**, 88106-72-3; *pref*-**14**, 88106-73-4; *parf*-**15**, 88106-74-5; *pref*-**15**, 88106-75-6; *parf*-**16**, 88106-76-7; *pref*-**16**, 88106-77-8; *parf*-**17**, 88106-78-9; *pref*-**17**, 88106-79-0; *parf*-**18**, 88106-80-3; *pref*-**18**, 88130-58-9; *parf*-**19**, 88106-81-4; **20**, 2362-61-0; PMHS, 26403-67-8; DBTO, 17068-56-3; TMEDA, 110-18-9; 18-crown-6, 17455-13-9; CH_3MgI, 917-64-6; *i*-PrMgI, 920-39-8; PhMgBr, 100-58-3; CH_3Li, 917-54-4; $(CH_3)_2CuLi$, 15681-48-8; Ph_2CuLi, 23402-69-9; D_2, 7782-39-0; potassium tri-*sec*-butylhydridoborate, 54575-49-4; lithium tri-*tert*-butylhydridoaluminate, 17476-04-9; sodium hydridotrimethoxyborate, 16940-17-3; 9-borabicyclononane, 280-64-8; sodium bis(1,4-dioxapentyl)dihydroaluminate, 22722-98-1; sodium cyanotrihydroborate, 25895-60-7; 2-phenylpropanal, 93-53-8; malononitrile, 109-77-3; dimethyl malonate, 108-59-8; 2-phenylcyclohexanone, 1444-65-1; 3-phenyl-2-butanone, 769-59-5; aluminum isopropoxide, 555-31-7; diborane, 19287-45-7; sodium tetrahydridoborate, 16940-66-2; lithium tetrahydridoaluminate, 16853-85-3; 2-methylcyclopentanone, 1120-72-5; 2-isopropylcyclohexanone, 1004-77-9; *tert*-butyllithium, 594-19-4; 2-methylcyclohexanone, 583-60-8.

Reactivity-Selectivity in the Swern Oxidation of Alcohols Using Dimethyl Sulfoxide-Oxalyl Chloride[1]

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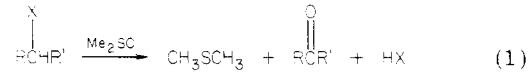
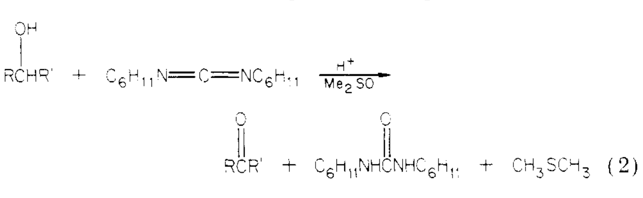
The competitive oxidation of a mixture of two alcohols by less than an equivalent amount of oxidant under the conditions developed by Swern (reaction of the alcohol at -60 °C with $Me_2SCl^+Cl^-$ (**4**) generated from $(COCl)_2$ and Me_2SO in CH_2Cl_2 followed by reaction with Et_3N) shows significant selectivity, with crowded alcohols and those bearing electron-withdrawing substituents being less reactive. Experiments in which the order of mixing of the alcohols and the oxidant are changed and the time of reaction varied establish that the process involves initial fast formation of a mixture of alkoxydimethylsulfonium ions $ROSMe_2^+$ (**1**), which equilibrate at a slower rate with the residual alcohols. Addition of Et_3N rapidly converts the existing mixture of **1** to carbonyl products. Intramolecular and intermolecular H/D isotope effects are consistent with this mechanistic scheme. In a practical application of these reactivity principles the steroid **33** with a crowded 11β-OH group was oxidized smoothly in 58% yield to the 11-ketone **34**, whereas the 9α-fluoro substituent present in **36** inhibited the reaction, and ketone was formed in only 5% yield.

The first use of dimethyl sulfoxide (Me_2SO) as an oxidizing agent was by Kornblum and co-workers,[2] who showed that alkyl halides and tosylates are converted to carbonyl compounds by Me_2SO at room temperature or with heating (eq 1). A variety of procedures using Me_2SO with electrophilic "activators" have subsequently been developed and reviewed.[3]

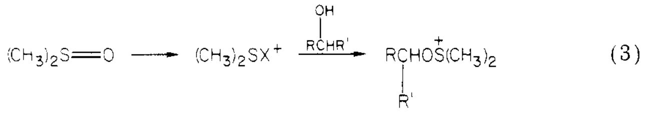


$$\underset{X}{RCHR'} \xrightarrow{Me_2SO} CH_3SCH_3 + R\overset{O}{\overset{\|}{C}}R' + HX \qquad (1)$$

The widely used Moffatt[3b] procedure involves reaction of the alcohol, Me_2SO, dicyclohexylcarbodiimide (DCC), and an acid at room temperature (eq 2). Some of the electrophilic activators used with Me_2SO in the other procedures include acetic anhydride, trifluoroacetic anhydride, SO_3-pyridine, P_2O_5, *t*-BuOCl, halogens, *N*-halosuccinimides, and oxalyl chloride. These latter reactions evidently all proceed through the formation of activated dimethylsulfonium species Me_2SX^+, which react with the alcohol to form an alkoxysulfonium ion **1** (eq 3), which then reacts with base to give an ylide **2** that reacts intramolecularly to form the carbonyl product (eq 4). The Moffatt procedure evidently also involves the ylide **2**, but this is formed in an intramolecular reaction in which a nitrogen of the DCC acts as the base.[3b] Formation of (methylthio)methyl esters **3**, a common side reaction in these procedures, evidently also occurs through the intermediacy of **2** (eq 5).

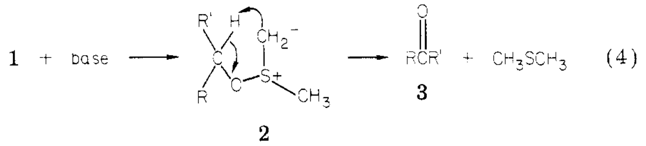


$$\overset{OH}{RCHR'} + C_6H_{11}N{=}C{=}NC_6H_{11} \xrightarrow[Me_2SO]{H^+} R\overset{O}{\overset{\|}{C}}R' + C_6H_{11}NH\overset{O}{\overset{\|}{C}}NHC_6H_{11} + CH_3SCH_3 \qquad (2)$$



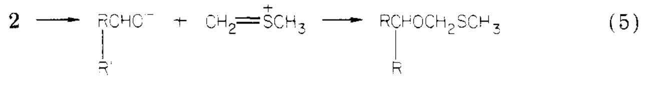
$$(CH_3)_2S{=}O \longrightarrow (CH_3)_2SX^+ \xrightarrow{\overset{OH}{RCHR'}} \underset{R'}{RCHO}\overset{+}{S}(CH_3)_2 \qquad (3)$$

1



$$1 + \text{base} \longrightarrow \qquad \longrightarrow R\overset{O}{\overset{\|}{C}}R' + CH_3SCH_3 \qquad (4)$$

2 **3**



$$2 \longrightarrow \underset{R'}{RCHO^-} + CH_2{=}\overset{+}{S}CH_3 \longrightarrow \underset{R}{RCHOCH_2SCH_3} \qquad (5)$$

3

Particularly convenient reaction conditions developed by Swern[3c,4] involve reaction of Me_2SO with oxalyl chloride

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(1) Contribution No. 663 from the Institute of Organic Chemistry. This article is dedicated to the memory of the late Professor Swern.

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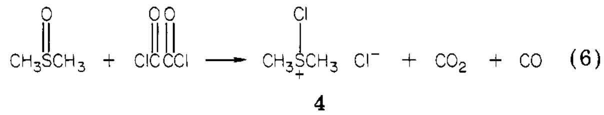
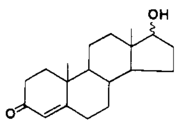
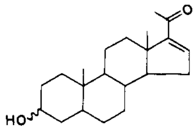
in methylene chloride at –60 °C to give chlorodimethylsulfonium chloride (**4**, eq 6), which is reacted with the alcohol at –60 °C followed by Et_3N. Yields in this reaction generally exceed 95% and there is minimal formation of **3**. The reactive reagent **4** can be prepared directly from chlorine and dimethyl sulfide (eq 7),[5,6] but the high yields and convenience of the procedure of eq 6 are especially advantageous.

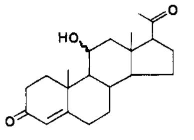

$$\mathrm{CH_3\overset{O}{\overset{\|}{S}}CH_3 + Cl\overset{O}{\overset{\|}{C}}\overset{O}{\overset{\|}{C}}Cl \longrightarrow \underset{\textbf{4}}{CH_3\underset{+}{\overset{Cl}{\overset{|}{S}}}CH_3\ Cl^-} + CO_2 + CO} \qquad (6)$$

$$\mathrm{Cl_2 + CH_3SCH_3 \longrightarrow \textbf{4}} \qquad (7)$$

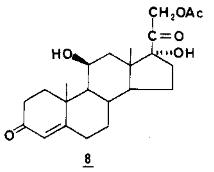
There have been a few indications that Me_2SO-based oxidations may be useful for achieving selective oxidations. For example, semiquantitative rate studies in the Moffatt oxidation[3b,7] of the epimers **5a** and **5b** and of **6a** and **6b** showed that the α and β OH isomers were of similar reactivity for each substrate. In contrast, while 11α-hydroxyprogesterone **7a** was smoothly oxidized to the 11-keto product, the 11β-hydroxy isomer **7b**, which has a more hindered axial OH group, was unreactive under the same conditions.

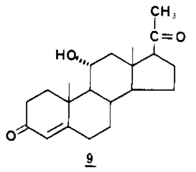

5a,b


6a,b


7a,b

A seemingly contrary pattern of reactivity was observed by using the Me_2SO–acetic anhydride reagent, which gave a 53% yield of 11-keto product from **8** after 92 h at room temperature, whereas **9** gave 56% of the corresponding (methylthio)methyl ether and 30% of the corresponding keto product.[8] The successful oxidation of the axial 11β-OH of **8** under these conditions is in contrast to the failure of **7b** to react with the Me_2SO–DCC reagent. A possible cause of this difference is the higher temperature used in the former example, and the relatively high yield of (methylthio)methyl ether from **9** may also be due to the same cause. The oxidation of **9** gave the corresponding ketone in "essentially quantitative yield" by using the oxidant generated from Me_2SO and trifluoroacetic anhydride at –60 °C followed by reaction with triethylamine at either –60 °C or room temperature.[9]


8


9

Selective oxidation of unactivated primary or secondary alcohols in the presence of benzylic or allylic alcohols has been effected by using Me_2SO and trifluoroacetic anhydride.[9b] The success of this method arises from the solvolysis of the benzylic or allylic sulfoxonium salts to give trifluoroacetates, which are not oxidized. The details of this process have not been established, but possibly a direct displacement is involved (eq 8). This reaction is related to the conversion of allylic and benzylic sulfoxonium salts to chlorides at –25 °C.[10] The possibility of prior dissociation of the sulfoxonium salt to Me_2SO and a carbocation cannot be excluded, but in one example an unsymmetrical alcohol gave the chloride without rearrangement,[10] which argues against formation of an intermediate ion.

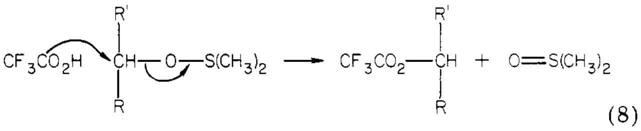

$$\mathrm{CF_3CO_2H\ \ \overset{R'}{\underset{R}{CH}}{-}O{-}S(CH_3)_2 \longrightarrow CF_3CO_2{-}\overset{R'}{\underset{R}{CH}} + O{=}S(CH_3)_2} \qquad (8)$$

Table I. Effect of the Percentage of Total Oxidation on k_{rel}(3-Octanol)/(1-Phenylethanol) and K_{equil}([3-Octanone][1-Phenylethanol]/[3-Octanol][Acetophenone])

	% oxidation			
	60	52	45	35
$k_{rel}{}^a$	3.1	3.3	4.1	5.9
$K_{equil}{}^a$	5.8	5.5	6.5	8.8

[a] ±10%.

The goal of the present research has been to explore the scope of the Swern oxidation procedure in selective oxidations. It is hoped that the knowledge gained in this study will assist in the development of highly selective oxidations.

Results

Competitive oxidations were carried out by generation of chlorodimethylsulfonium chloride (**4**) by the addition of Me_2SO to oxalyl chloride in CH_2Cl_2 at –60 °C and addition of this reagent to an equimolar mixture of two alcohols in CH_2Cl_2 at –60 °C. After 15 min at –60 °C, Et_3N was added to complete the oxidation and the product composition was determined by gas chromatography. Usually 1 equiv of **4** was added to 1 equiv each of the two alcohols, but in other experiments the amount of oxidant was varied from one-quarter to three-quarters of the total amount of alcohol. In these experiments the solutions were always clear and homogeneous during the addition of the oxidant to the alcohols. The solutions then became cloudy during the 15-min stirring time but clarified immediately on the addition of Et_3N. All of these alcohols were shown to give greater than 95% yields of the corresponding carbonyl products when oxidized alone.

Relative rates as defined by the Shaw–Ingold expression (eq 9)[11] where i and f represent the initial and final con-

$$k_{rel}(R^aOH)/(R^bOH) = [\log([R^aOH]_f/[R^aOH]_i)]/[\log([R^bOH]_f/[R^bOH]_i)] \quad (9)$$

centrations of the alcohols, respectively, were calculated for each competition. This equation would be applicable to a situation where the reagent **4** reacted competitively and irreversibly with the alcohols R^aOH and R^bOH to form alkoxydimethylsulfonium ions **1**, which gave the carbonyl

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(5) (a) Corey, E. J.; Kim, C. U. *J. Am. Chem. Soc.* **1972**, *94*, 7586–7587. (b) Corey, E. J.; Kim, C. U. *Tetrahedron Lett.* **1974**, 287–290. (c) Corey, E. J.; Kim, C. U. *J. Org. Chem.* **1973**, *38*, 1233–1234.

(6) Gauvreau, J. R.; Poignant, S.; Martin, G. J. *Tetrahedron Lett.* **1980**, *21*, 1319–1322.

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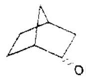
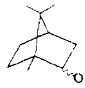
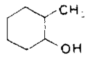
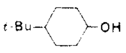
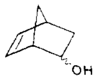
(9) (a) Huang, S. L.; Omura, K.; Swern, D. *Synthesis* **1978**, 297–299. (b) Omura, K.; Sharma, A. K.; Swern, D. *J. Org. Chem.* **1976**, *41*, 957–962.

(10) Corey, E. J.; Kim, C. U.; Takeda, M. *Tetrahedron Lett.* **1972**, 4339–4342.

(11) (a) Russell, G. A. In "Technique of Organic Chemistry"; Friess, S. L., Lewis, E. S., Weissberger, A., Eds.; Interscience: New York, 1961, Vol. 8, Part 1, Chapter 8; pp 344, 358. (b) Ingold, C. K.; Shaw, F. R. *J. Chem. Soc.* **1927**, 2918–2926.

Table II. Values of k_{rel}[a] and K_{equil}[b] for Alcohols ROH Relative to $PhCHOHCH_3$ at 50 ± 3% Total Oxidation

ROH		k_{rel}	K_{equil}
	exo (**10**)	4.6[c]	8.1
	endo (**11**)	3.6[c]	6.3
	exo (**12**))	3.6[d]	5.9
	endo (**13**)	3.8	6.3
	cis (**14**)	3.3[c]	5.2
	trans (**15**)	2.9[c]	4.4
	cis (**16**)	2.4[c,e]	3.6
	trans (**17**)	2.8[c,e]	4.6
cycloheptanol	**18**	3.6	5.7
3-octanol	**19**	3.3	5.5
	exo (**20**)	2.9[f]	4.1
	endo (**21**)	2.0[f]	2.4
p-$TolCHOHCH_3$	**22**	1.6	1.8
1-octanol	**23**	1.5	1.8
$PhCHOHCH_3$	**24**	1.0	1.0
$PhCH_2OH$	**25**	0.69	0.61
t-Bu_2CHOH	**26**	0.30	0.20
p-$CF_3C_6H_4CHOHCH_3$	**27**	0.21	0.12
Ph_2CHOH	**28**	0.20	0.097
$PhCHOHCF_3$	**29**	0.004[g]	7×10^{-4}

[a] Obtained from eq 9. Experimental comparison to 1-phenylethanol unless noted. [b] Equation 10. [c] Obtained from an indirect comparison. [d] Obtained by direct comparison to the endo isomer. [e] Determined by using a commercial mixture containing 30% **16** and 70% **17**. [f] Determined by using a commercial mixture containing 26% **20** and 74% **21**. [g] Upper limit assuming a maximum amount of 1% oxidation of **29** (see text).

products on addition of triethylamine. These k_{rel} values were found to be reproducible to ±10% for a given percentage of total oxidation but varied according to the percentage of oxidation. An example of this behavior is shown in Table I. Similar trends were observed for other pairs of alcohols.

An alternative treatment of the data was also carried out. This treatment assumes that the Et_3N traps a chemical equilibrium involving the alcohols R^aOH and R^bOH and alkoxydimethylsulfonium ions $R^aOS(CH_3)_2^+$ and $R^bOS(CH_3)_2^+$ to give carbonyl products from the sulfonium ions. Values of K_{eq} were calculated by using eq 10, in which f

$$K_{eq} = \frac{[R^aOH]_f[\text{carbonyl product b}]}{[R^bOH]_f[\text{carbonyl product a}]} \qquad (10)$$

refers to the concentration of an alcohol at the end of the reaction and the carbonyl products are derived from oxidation of the corresponding alcohols. These values (Table I) also varied with the extent of oxidation.

The variations of k_{rel} and K_{equil} (Table I) with concentration follow a similar pattern, with larger differences between pairs of alcohols corresponding to lower percentages of oxidation. Therefore, for a common basis of comparison of a series of alcohols, k_{rel} values for 50% total oxidation are listed in Table II, with 1-phenylethanol as the standard of comparison. In several cases the relative reactivities of pairs of alcohols were measured directly and compared to values calculated from the reactivities relative to 1-phenylethanol. As shown in Table III the agreement between these directly and indirectly observed reactivities was quite satisfactory. Some of the k_{rel} values listed in Table II were obtained by such indirect comparisons.

Table III. Comparison of Observed Values of k_{rel} (R^aOH/R^bOH) Compared to Values Calculated from k_{rel} ($ROH/PhCHOHCH_3$)

R^aOH	R^bOH	k_{rel}(obsd)	k_{rel}(calcd)
13	**19**	1.1	1.2
13	**26**	12	12
13	**28**	19	19
25	**28**	2.9	3.3
27	**28**	1.8	1.1
22	**27**	5.7	7.4

Table IV. Effect of Order of Mixing and Time of Reaction on Competitive Oxidation of 3-Octanol (**19**) and 1-Phenylethanol (**24**) at -60 °C

addition mode	% oxdn	time,[a] min	k_{rel}(**19**/**24**)	K_{equil}
oxidant to ROH	50	15	3.3	5.5
oxidant to ROH	45	1	3.1	4.5
oxidant to ROH	25	60	4.6	5.6
oxidant to ROH	48	60	3.9	6.4
oxidant to ROH	73	60	2.5	5.5
ROH to oxidant[b]	48	1	2.3	3.1
19, then **24**, to oxidant	53	2	11	34
19, then **24**, to oxidant	50	10	5.1	9.8
24, then **19**, to oxidant	49	2	0.18	0.087
24, then **19**, to oxidant	54	15	1.3	1.4

[a] Time after completion of mixing of all reagents. [b] Mixture of the two alcohols added to the oxidant.

Values of K_{equil} are also listed in Table II.

The k_{rel} value for $PhCHOHCF_3$ (**29**) is an upper limit because when 1 equiv each of **29** and $PhCHOHCH_3$ (**24**) were reacted with 0.92 equiv of oxidant, no oxidation product from **29** was observed. When 1.34 equiv of oxidant was used there was no residual **24** detectable and **29** was 34% oxidized.

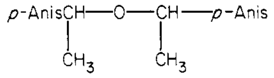
The effect of the order of mixing of the reagents was tested in experiments in which first one and then the other alcohol was added to the oxidant **4** at -60 °C, and then Et_3N was added after varying time intervals. It was found that when **4** was added to a mixture of 3-octanol (**19**) and 1-phenylethanol (**24**) and the solution aged 15 min, 3-octanol was 3.3 times more reactive (Tables I and II). However, when 3-octanol was added first to the oxidant followed by 1-phenylethanol then the k_{rel} values of 3-octanol were 11 and 5.1 for 2- and 10-min mixing times of **24**, respectively. When the order of addition of these alcohols was reversed the k_{rel} of the 3-octanol was 0.18 and 1.3 for 2- and 15-min aging time after addition of the 3-octanol. In these reactions with sequential addition of the alcohols to the oxidant, the solutions became cloudy after the addition of the first alcohol but cleared rapidly on the addition of Et_3N. In further experiments in which the oxidant was added to the alcohol mixture at -50 °C and the solutions were aged 60 min for 25%, 48%, and 73% total oxidation, K_{equil} values were 5.6, 6.4, and 5.4, respectively, and k_{rel} values were 4.6, 3.9, and 2.5, respectively. All these results are summarized in Table IV.

The reaction of PhCHDOH with excess oxidant was studied to measure isotope effects on the oxidation. The product benzaldehyde was analyzed by ^1H NMR and by mass spectrometry. Each analytical method revealed a 2-fold preference for the formation of PhCD=O relative to PhCH=O (eq 11). In a second experiment the reaction

$$\text{PhCHDOH} \xrightarrow[\text{2. Et}_3\text{N}]{\text{1. Me}_2\text{SCl}^+\text{Cl}^-} \underset{72 \pm 2\%}{\text{PhCD=O}} + \underset{28 \pm 2\%}{\text{PhCH=O}} \qquad (11)$$

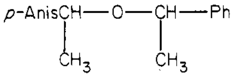
of a mixture of 1 equiv each of $PhCHOHCH_3$ and $PhCDOHCH_3$ with 1 equiv of oxidant was examined. Analysis of the residual alcohol by ^1H NMR showed that the two isotopic isomers were still present in a 1.0 to 1.0 (±5%) ratio.

The reaction of a mixture of 1-*p*-anisylethanol (**30**) and 1-phenylethanol (**24**) at –60 °C gave 26% acetophenone, 24% p-AnisCOCH$_3$, 4% of **31**, and 6% of **32**. The yields



$p\text{-AnisCH(CH}_3\text{)}\text{–O–CH(CH}_3\text{)–}p\text{-Anis}$

31

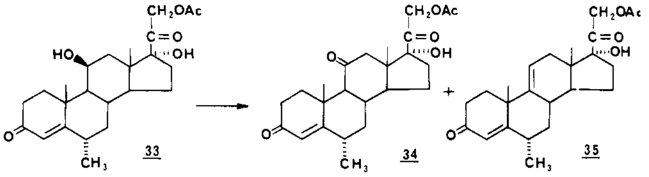


$p\text{-AnisCH(CH}_3\text{)–O–CH(CH}_3\text{)–Ph}$

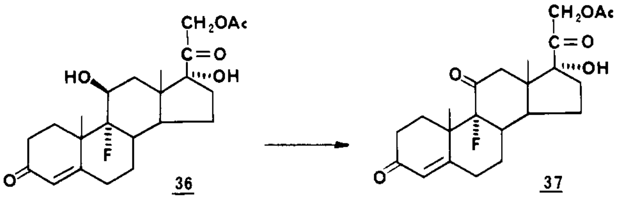
32

of **31** and **32** increased if the reaction was conducted at higher temperature.

The reaction of 6α-methylhydrocortisone acetate (**33**) with excess oxidant at –60 °C for 15 min followed by addition of Et$_3$N at –60 °C gave after chromatography 58% ketone **34** along with 13% of the dehydration product **35**. Residual starting material was estimated as less than 2%.



In contrast, oxidation of 9α-fluorohydrocortisone acetate (**36**) under the same conditions gave 5% of the ketone **37** and 89% starting material after chromatography. When **36** was reacted for 120 h at –20 °C with excess oxidant and then treated with Et$_3$N, analysis by TLC of the product revealed that at least nine components were present, including **37** and the starting material, but none appeared to comprise more than 25% of the mixture, which was not examined further.



Discussion

On the basis of previous work and the experiments reported herein, the mechanism shown in eq 12–14 can be

$$\mathrm{Me_2S^+Cl + Cl^- + ROH \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} Me_2S^+OR + Cl^- + HCl} \qquad (12)$$

$$\mathrm{Me_2S^+OR^a + R^bOH \underset{k_{-2}}{\overset{k_2}{\rightleftharpoons}} Me_2S^+OR^b + R^aOH} \qquad (13)$$

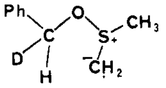
$$\mathrm{Me_2S^+OR + Et_3N \xrightarrow{k_3} carbonyl\ product} \qquad (14)$$

drawn for the competitive oxidation of alcohols with chlorodimethylsulfonium chloride (**4**) followed by Et$_3$N. The results summarized in Table IV in which the order of mixing of 3-octanol (**19**) and 1-phenylethanol (**24**) and the oxidant are changed and the aging time is varied are strongly indicative of this mechanism. Thus, if the alcohols are added sequentially to the oxidant and the aging time is brief, there is a strong preference for oxidation of the first added alcohol. This indicates that the forward reaction of eq 12 and the reaction of eq 14 are fast on the time scale of these experiments.

The fact that the relative amounts of oxidation of the two alcohols changes with time shows that equilibration according to eq 13 is occurring. The fact that the K_{equil} values defined by eq 10 became invariant at 5.9 ± 0.5, with the percentage of oxidation within the accuracy of the measurements after 1-h aging at –50 °C, shows that the equilibrium is effectively established after this time. Exchange of the alkoxy groups of alkoxydimethylsulfonium ions with alcohols under other conditions has been demonstrated previously.[12]

When a mixture of the alcohols reacts with the oxidant, the initial mixture of alkoxysulfonium ions and alcohols is a kinetic and not an equilibrium product. If this initial mixture could be trapped without any equilibration then k_{rel} values derived from eq 9 would correctly represent the true relative reactivities of the alcohols. However, equilibration does proceed, and the apparent k_{rel} values are not constant. For the standard 15-min aging time of the reactions reported in Table II, partial equilibration has occurred so neither k_{rel} values defined by eq 9 nor K_{equil} values defined by eq 10 are strictly applicable. However, for 50% total oxidation under these conditions either k_{rel} or K_{equil} values give a reproducible and consistent ranking of the relative reactivities of the alcohols and can be used for interpretive and predictive purposes. If complete equilibration were achieved, the K_{equil} values would evidently follow the same trends but with larger differences betwen the alcohols. For such values to be obtained, an excessive effort would be required, and no additional understanding of the factors affecting reactivities would be obtained.

The isotope effect experiments support these interpretations. Thus, in the competitive oxidation of PhCHOHCH$_3$ and PhCDOHCH$_3$; no noticeable isotope effect on the reaction of the alcohols with the oxidant (eq 12) or the equilibration of eq 13 is expected, and none is observed. The 2-fold preference of PhCHDOH for loss of H relative to D appears plausible for the breakdown of the intermediate ylide **38**, for even though this process is



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exothermic there is still an activation barrier that is less for proton abstraction. This isotope effect $k(\mathrm{H})/k(\mathrm{D})$ of 2.6 ± 0.3 differs from that of 7 found for chromic acid oxidation of 2-propanol,[13a] but this appears reasonable as the reaction of eq 4 involving a five-membered cyclic transition state is more comparable to olefin-forming pyrolyses of sulfoxides or *N*-oxides.[13b,c] These reactions show isotope effects in the range of 2 to 3 and also have five-atom cyclic transition states where the hydrogen atom transfer is nonlinear.

Two trends predominate in the relative rate data in Table II. Electron-withdrawing substituents in the alcohol decrease the k_{rel} values, as shown convincingly by the series of 1-arylethanols, where the *p*-methyl group increases the k_{rel} to 1.6 and a *p*-trifluoromethyl causes a 5-fold decrease to 0.21. The effect is even more pronounced in PhCHOHCF$_3$, which is drastically less reactive, and also appears to be important in the greater reactivity of secondary as opposed to primary alcohols (e.g., PhCHOHCH$_3$ compared to PhCH$_2$OH, 3-octanol compared to 1-octanol). The electron-withdrawing effect of the homoallylic double bond is probably also responsible for the lower reactivity of the norbornenols **20** and **21** compared to the norbornanols **10** and **11**, and a similar effect of the phenyl

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[12] (a) Torssell, K. *Acta Chem. Scand.* **1967**, *21*, 1–14. (b) Johnson, C. R.; Phillips, W. G. *J. Org. Chem.* **1967**, *32*, 1926–1931.

[13] (a) Westheimer, F. H.; Nicolaides, N. *J. Am. Chem. Soc.* **1949**, *71*, 25–28. (d) Chiao, W.-B.; Saunders, W. H., Jr. *Ibid.* **1978**, *100*, 2802–2805. (e) Kwart, H.; Brechbiel, M. *Ibid.* **1981**, *103*, 4650–4652.

group would be operative in the 1-arylcarbinols as well. The electron-withdrawing groups in all these cases would destabilize the intermediate alkoxydimethylsulfonium ions **1** and decrease the reactivity of the corresponding alcohol.

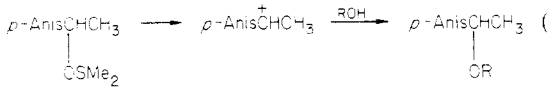
A trend to lower reactivity for more crowded alcohols is also apparent. This effect evidently arises from destabilization of more crowded alkoxysulfonium ion due to nonbonding interactions of the dimethylsulfonium group with the alkoxy portion of the molecule. This effect is most obvious in the low reactivity of di-*tert*-butylcarbinol (**26**) but also appears to be evident in the fact that in every case the less crowded epimer of the pairs **10**/**11**, **12**/**13**, **16**/**17**, and **20**/**21** is more reactive.

For most of these molecules the steric effect is, however, rather small. Thus, **10** is only slightly more reactive than **12**, and as already noted there are two examples where a primary alcohol is less reactive than a corresponding secondary alcohol. The low reactivity of benzhydrol (**28**) may be partly due to steric factors, but the electron-withdrawing effect of the two aryl rings is probably important as well.

The consequences of the steric and electronic influences on reactivity are illustrated in the oxidations of the hydrocortisones **33** and **36**. As has been demonstrated by Swern and co-workers,[4] crowded alcohols give some of the highest oxidation yields in this procedure, and the efficient oxidation of the very crowded 11β-OH group in **33** is consistent with this behavior. However, in **36** the deactivating influence of the 9α-fluoro is so strong that oxidation is inefficient at −60 °C, and other reactions predominate at higher temperature.

The reactivity trends in the Swern oxidation provide an interesting contrast to the widely studied chromic acid oxidation of alcohols.[14,15] In this latter reaction there is strong evidence that the product stability affects the reactivity so that more crowded alcohols are more reactive. The opposing reactivity trends for the chromic acid and Swern oxidations is instructive and offers promise of useful application in synthesis.

The formation of the ethers **31** and **32** from the competitive reaction of 1-*p*-anisylethanol (**30**) is readily understood on the basis of the solvolysis of the dimethylsulfonium derivative of this alcohol (eq 15). This process



$$p\text{-AnisCH(O}\overset{+}{\text{S}}\text{Me}_2\text{)CH}_3 \longrightarrow p\text{-Anis}\overset{+}{\text{C}}\text{HCH}_3 \xrightarrow{\text{ROH}} p\text{-AnisCH(OR)CH}_3 \quad (15)$$

is favored by the strong electron-donating effect of the substituent and could involve either a displacement of Me_2SO by the alcohol or prior ionization to a discrete intermediate as shown.

Experimental Section

Alcohols were obtained from commercial sources or by $LiAlH_4$ reduction of ketones, except for $PhCHDOH$ and $PhCDOHCH_3$, which were prepared by $LiAlD_4$ reduction of benzaldehyde and acetophenone, respectively. Oxalyl chloride (15 mL, Aldrich Gold Label) was diluted with 75 mL of CH_2Cl_2 and stored in a bottle with a Teflon brand stopcock and septum opening. Methylene chloride (Burdick and Jackson, glass distilled) was stored over molecular sieves. Triethylamine was distilled from CaH_2 and stored over molecular sieves. Dimethyl sulfoxide was distilled at reduced pressure from CaH_2 and stored over molecular sieves. All transfers of solutions were carried out by using glass syringes and positive nitrogen pressure. Gas chromatographic analyses were carried out by using a Hewlett-Packard 402 instrument with a 1 m × 8 mm Carbowax 20M column. Preparative separations were carried out on a Chromatotron centrifugal radial thin-layer chromatograph from Harrison Research. All glassware was dried in vacuo overnight at 150 °C and cooled in a dessicator before use. Reactions were conducted under a N_2 atmosphere.

Competitive oxidations were conducted by generating the oxidant in a 50-mL three-necked flask equipped with a magnetic stirrer and rubber septa and connected by a double-tipped needle to a 100-mL three-necked flask fitted with a magnetic stirrer, drying tube, and thermometer. Neat Me_2SO (0.5 mL, 7 mmol) was added dropwise to a stirred solution of 1.3 mL (2.5 mmol) of the 1.9 M stock solution of oxalyl chloride in CH_2Cl_2 in 30 mL of CH_2Cl_2 stirred at −60 °C in the 50-mL flask. After 5 min of stirring, the solution was forced by N_2 pressure through the double-tipped needle into a solution of 2.50 mmol each of two alcohols in 50 mL of CH_2Cl_2 stirred at −60 °C or below in the 100-mL flask. Addition took about 2 min and the solution remained clear throughout the addition. Then the solution was stirred for 15 min at −60 °C, during which time the solution usually became cloudy. In some of the experiments different amounts of oxidant and different reaction times were used, as reported in Table IV. Then 2.5 mL of Et_3N was injected into the solution, which rapidly clarified. The solution was warmed to room temperature and poured into 100-mL of H_2O, the layers were separated, and the aqueous layer was extracted twice with CH_2Cl_2. The combined organic layers were washed once with 2 M HCl and with $NaHCO_3$, with a reextraction of each aqueous layer with CH_2Cl_2. The resulting solution was analyzed directly by VPC, along with a small portion of the starting alcohol mixture to determine response factors. Response factors for a number of the carbonyl compounds were checked and found to equal those of the corresponding alcohols, so these were always taken as identical.

The product chromatograms showed only traces of materials besides the starting alcohols and the product carbonyls, so the yields of the alcohols and carbonyls were normalized to 100% for calculation of k_{rel} and K_{equil} values by eq 9 and 10, respectively. The oxidations of the individual alcohols with excess oxidant have all been found to give the corresponding ketone or aldehyde in at least 95% yield. For the examples reported in Table II beginning with equimolar amounts of two alcohols, the residual alcohol and the corresponding product for each component made up 50 ± 3% of the final mixture, and the total extent of oxidation was 50 ± 3% in every case. A number of other alcohols with five and six carbon atoms were also examined, but these appeared to give incomplete material balances so are not included in the results.

The effect of the order of mixing was tested by generating a solution of oxidant in a 100-mL three-necked flask, under N_2, equipped with a magnetic stirrer, thermometer, drying tube, and septum cap by adding 0.5 mL of Me_2SO to 2.5 mmol of oxalyl chloride in 50 mL of CH_2Cl_2 at −60 °C. After 5 min, 2.50 mmol of an alcohol in 15 mL of CH_2Cl_2 was added, keeping the temperature at −60 °C or below. This solution was stirred for 5 min at −60 °C and usually became cloudy. Then a second alcohol in 15 mL of CH_2Cl_2 was added as quickly as possible, keeping the temperature at −60 °C, and after a suitable time interval the reaction was quenched by injection of 2.5 mL of Et_3N and worked up as above. In one case the two alcohols were added together to the oxidant.

Partial reaction of an equimolar mixture of 1-phenylethanol (**24**) and 1-*p*-anisylethanol (**30**) gave 32% and 52% consumption of **24** and **30**, respectively. Products observed were acetophenone (26%), $p\text{-AnisCOCH}_3$ (24%), **31** (4%), and **32** (6%). The latter two compounds were identified by their mass spectrometric molecular weights.

In a preparative oxidation of 6α-methylhydrocortisone acetate (**33**) the alcohol (0.401 g, 0.958 mmol) in 25 mL of CH_2Cl_2 was added to a stirred solution of oxidant prepared from 1 mL (11 mmol) of $(COCl)_2$ and 1.7 mL (22 mmol) of Me_2SO in 25 mL of CH_2Cl_2 at −55 °C. After 15 min of stirring at −60 °C, 5 mL Et_3N

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(14) (a) Wiberg, K. B. In "Oxidation in Organic Chemistry"; Wiberg, K. B., Ed.; Academic Press: New York, 1965, Part A, Chapter 2, p 160. (b) Lee, D. G. In "Oxidation; Techniques and Applications in Organic Synthesis"; Augustine, R. L., Ed; Marcel Dekker: New York, 1969. (c) Stewart, R. "Oxidation Mechanisms"; Benjamin: New York, 1964; Chapter 4.

(15) Müller, P.; Perlberger, J.-C. *J. Am. Chem. Soc.* 1976, *98*, 8407–8413.

was added and the solution was worked up as in the preparative runs. The crude product was separated on the Chromatotron using 2% MeOH in CH_2Cl_2 to give a leading band (0.067 g, yellow color, sulfur odor, unidentified), a second band identified as 6α-methyl-17α-hydroxy-21-acetoxy-4,9(11)-pregnadiene-3,20-dione (**35**,[16] 0.050 g, 0.12 mmol, 12%), and finally 6α-methylcortisone acetate (**34**, 0.230 g, 58%).

Addition of 9α-fluorohydrocortisone acetate (**36**,[17] 0.218 g, 0.516 mmol) in 45 mL of CH_2Cl_2 to 11 mmol of oxidant in 30 mL of CH_2Cl_2 was carried out as for **33**. After workup, separation of the crude product from a 15-min reaction at −60 °C on the Chromatotron using 2% MeOH in CH_2Cl_2 gave 0.010 g (0.024 mmol, 5%) of 9α-fluorocortisone acetate (**37**)[18] and 0.202 g (89%) of recovered **36**. When the reaction was repeated and continued for 120 h at −20 °C, the crude product showed at least nine major spots on TLC. Two of these corresponded in R_f value to **36** and **37**, but none appeared to comprise more than 25% of the mixture, which was not examined further.

Registry No. **4**, 23372-58-9; **10**, 497-37-0; **11**, 497-36-9; **12**, 124-76-5; **13**, 507-70-0; **14**, 7443-70-1; **15**, 7443-52-9; **16**, 937-05-3; **17**, 21862-63-5; **18**, 502-41-0; **19**, 589-98-0; **20**, 2890-98-4; **21**, 694-97-3; **22**, 536-50-5; **23**, 111-87-5; **24**, 98-85-1; **25**, 100-51-6; **26**, 75-84-3; **27**, 1737-26-4; **28**, 91-01-0; **29**, 340-04-5; **30**, 3319-15-1; **31**, 88288-58-8; **32**, 88288-59-9; **33**, 88288-60-2; **36**, 514-36-3; Me_2SO, 67-68-5; $(COCl)_2$, 79-37-8.

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(16) Spero, G. B.; Thompson, J. L.; Lincoln, F. H.; Schneider, W. P.; Hogg, J. A. *J. Am. Chem. Soc.* **1957**, *79*, 1515–1516.

(17) (a) Eardley, S.; Green, G. F. H.; Long, A. G. *J. Chem. Soc.* **1965**, 148–155. (b) Burn, D.; Kirk, D. N.; Petrow, V. *Tetrahedron* **1965**, *21*, 1619–1624.

(18) Fried, J.; Sabo, E. F. *J. Am. Chem. Soc.* **1954**, *76*, 1455–1456.

Reaction of Tetramethyl-1,2-dioxetane with Phosphines: Deuterium Isotope Effects

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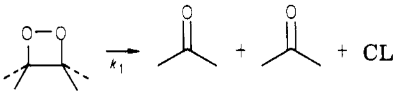
The reaction of tetramethyl-1,2-dioxetane (**1**) in C_6D_6 with methyldiphenylphosphine (**2a**), methyl-d_3-diphenylphosphine (**2d**), dimethylphenylphosphine (**2c**), and dimethyl-d_6-phenylphosphine (**2d**) produced the corresponding 2,2-dihydro-4,4,5,5-tetramethyl-2,2,2-trisubstituted-1,3,2-dioxaphospholanes **3a–d** in 90% yield or better. The phosphoranes were characterized by ^1H and ^{31}P NMR spectroscopy and by their thermal decomposition (60 °C) to tetramethyloxirane and the corresponding phosphine oxides. Kinetic studies of the rate of phosphorane formation in benzene were carried out by the chemiluminescence method. The reaction was found to be of the first order with respect to **1** and to the phosphines. Inverse deuterium isotope effects were observed for the reaction of **1** with phosphines **2a–d**. The value of k_{CH_3}/k_{CD_3} obtained with phosphines **2a,b** was found to be 0.94 ± 0.01 while that with phosphines **2c,d** was found to be 0.91 ± 0.01. The rates of phosphorane formation for the reaction of tetramethyl-d_{12}-1,2-dioxetane (**1d**) with **2a,c** and triphenylphosphine were also investigated and compared to those for reaction with **1**. For all three phosphines, the rate constants with **1d** were slower than those obtained with **1** ($k_H/k_D = 1.06 \pm 0.02$). This result is in marked contrast with the results obtained with the deuterated phosphines. The results are consistent with a concerted insertion of the phosphine into the peroxy bond of the dioxetane.

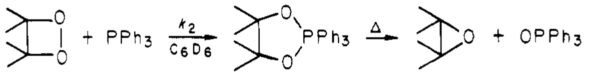
1,2-Dioxetanes have been studied extensively because of their unique chemiluminescent thermal decomposition to two carbonyl fragments (reaction 1).[2] Under controlled conditions, dioxetanes have been shown to undergo a number of interesting reactions (metal ion catalyzed decomposition,[3a] BF_3-catalyzed rearrangement,[3b] reduction to 1,2-glycols,[3c] insertion into the peroxy bond[4–6]) in which no excited products are formed.[2] The reaction of trivalent phosphorus compounds with dioxetanes is the most studied nonthermolytic reaction of dioxetanes. In 1973, the reaction of triphenylphosphine with tetramethyl-1,2-dioxetane was shown[4] to produce an isolable phosphorane, the thermal decomposition of which resulted in the formation of the expoxide and the phosphine oxide (Scheme I). Previously, Denney had shown[7] that the reaction of



(1)

CL = chemiluminescence

Scheme I



94%

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(1) Fellow of the Camille and Henry Dreyfus Foundation, 1981–1986.

(2) For reviews, see: (a) Wilson, T. *MTP Int. Rev. Sci.: Phys. Chem. Ser. Two* **1976** *9*, 265. (b) Adam, W. *Adv. Heterocycl. Chem.* **1977**, *21*, 437. (c) Horn, K. A.; Schmidt, S. P.; Schuster, G. B.; *Mol. Photochem.* **1978–9**, *9(1)*, 1. (d) Bartlett, P. D.; Landis, M. E. "Singlet Oxygen"; Wassermann, H. H., Murray, R. W., Eds.; Academic Press: New York, 1979; p 243. (e) Baumstark, A. L. "Singlet Oxygen"; Frimer A., Ed.; CRC Press–Uniscience, in press.

(3) (a) Wilson, T.; Landis, M. E.; Baumstark, A. L.; Bartlett, P. D. *J. Am. Chem. Soc.* **1973**, *95*, 4765. (b) Bartlett, P. D.; Baumstark, A. L.; Landis, M. E. *Ibid.* **1977**, *99*, 1890. (c) Kopecky, K. R.; Filby, J. E.; Mumford, C.; Lockwood, P. A.; Ding, J. *Can. J. Chem.* **1975** *53*, 1103.

(4) Bartlett, P. D.; Baumstark, A. L.; Landis, M. E. *J. Am. Chem. Soc.* **1973**, *95*, 6486.

(5) Baumstark, A. L.; Landis, M. E.; Brooks, P. J. *J. Org. Chem.* **1979**, *44*, 4251.

(6) (a) Campbell, B. S.; Denney, D. B.; Denney, D. Z.; Shik, L. S. *J. Am. Chem. Soc.* **1975**, *97*, 3850. (b) Wasserman, H.; Saito, I. *Ibid.* **1975**, *97*, 905.

(7) (a) Denney, D. B.; Relles, H. M. *J. Am. Chem. Soc.* **1964**, *86*, 3897. (b) Denney, D. B.; Jones, D. H. *Ibid.* **1969**, *91*, 5821. (c) Denney, D. B.; Denney, D. Z.; Hall, C. D.; Marsi, K. L. *Ibid.* **1972**, *94*, 245.

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