The Neighboring Sulfonium Group in Ester Hydrolysis

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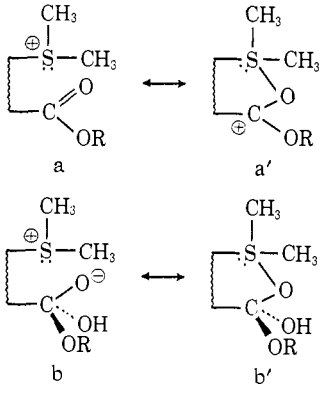
Abstract: The alkaline hydrolysis of methyl 2-dimethylsulfoniophenylacetate *p*-toluenesulfonate (*o*-**5**) proceeds 5.2 times faster than that of the 4 isomer (*p*-**5**). With a correction for steric effects, the ratio is 14. The 2-dimethylsulfonio ester is hydrolyzed 356 times faster than the 2-isopropyl ester, and the 4-dimethylsulfonio ester is hydrolyzed 25 times faster than the 4-isopropyl ester. From these data and proton resonance spectra, it is concluded that the neighboring sulfonium group in these compounds exhibits a small rate-enhancing effect on ester hydrolysis, probably *via* a field effect rather than by covalent bonding between sulfur and oxygen.

The role of neighboring functional groups in intramolecular nucleophilic catalysis of ester hydrolysis is clearly established and has been the topic of extensive researches.[1] The intervention of intramolecular electrophilic catalysis in alkaline ester hydrolysis has been advanced in the case of hydroxylic hydrogen,[2] and is thought to be of the general acid type. Such electrophilic catalysis has not been reported for other electrophiles, perhaps due to the paucity of functional groups which are potentially capable of serving in this capacity. The extensive distribution of sulfonium compounds in biological systems[3] and the well-documented propensity of sulfur for d orbital resonance[4] suggested that a neighboring sulfonium group might function as such an electrophilic group, capable of the intramolecular catalysis of alkaline ester hydrolysis, either by bonding with, or inducing polarization in the carbonyl group (a, a′) or by stabilizing the tetrahedral intermediate (b, b′) in ester hydrolysis, or both. Either effect should lead to a rate increase. The object of the work described in this paper was to prepare esters containing

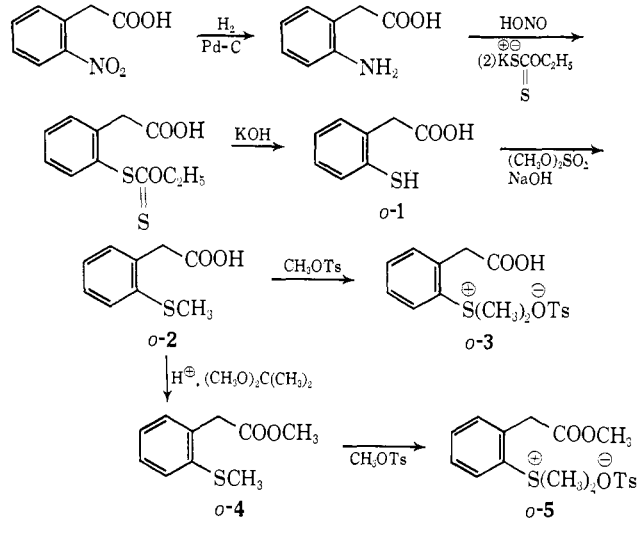


sulfonium groups disposed in space so as to favor the incursion of such an effect and to examine the hydrolysis rates of these esters when compared to isomeric systems incapable of intramolecular catalysis.

Results and Discussion

The substrates selected for this study were methyl 2-dimethylsulfoniophenylacetate *p*-toluenesulfonate (*o*-**5**) and the 4-substituted isomer (*p*-**5**). Their preparation is shown in Charts I and II. Their selection

Chart I



was predicated on the well-defined rigid geometry imparted by the aromatic ring and by the insulating effect of the α-methylene group, which would operate so as to minimize direct resonance interaction between the sulfur and carbonyl carbon. Inductive effect differences between the *ortho* and *para* isomers should also be small, since the effect is already attenuated by four bonds in the *ortho* isomer.

In order to assess the magnitude of *ortho* steric effects, which are substantial in the case of substituted benzoates,[5] methyl 2- and 4-isopropyl phenylacetates were prepared and their hydrolytic behavior was examined under the same conditions as employed for the sulfonio esters. The assumption was made that an isopropyl group simulates a dimethylsulfonio group in steric requirement. The preparation of the isopropyl substituted esters is shown in Chart III.

(1) (a) B. Capon, *Quart. Rev.* (London), **18**, 45 (1964); (b) T. C. Bruice and S. J. Benkovic, "Bioorganic Mechanisms," W. A. Benjamin, Inc., New York, N. Y., 1966; (c) M. L. Bender, *Chem. Rev.*, **60**, 53 (1960).

(2) (a) H. B. Henbest and B. J. Lovell, *J. Chem. Soc.*, 1965 (1957); (b) H. G. Zachan and W. Karau, *Ber.*, **93**, 1830 (1960); (c) H. Morawetz and I. Oreskes, *J. Am. Chem. Soc.*, **80**, 2591 (1958); (d) H. Morawetz and J. Shaffer, *ibid.*, **84**, 3783 (1962); (e) B. Capon, *Tetrahedron Letters*, 911 (1963).

(3) F. Schlenk, "Progress in the Chemistry of Organic Natural Products," Vol. XXIII, L. Zechmeister, Ed., Springer-Verlag, Berlin, 1965, pp 61–104.

(4) (a) G. Cilento, *Chem. Rev.*, **60**, 147 (1960); (b) C. C. Price and S. Oae, "Sulfur Bonding," Ronald Press Co., New York, N. Y., 1962; (c) W. von E. Doering and A. K. Hoffmann, *J. Am. Chem. Soc.*, 77, 521 (1955); (d) L. Goodman, A. H. Konstam, and L. H. Sommer, *ibid.*, 87, 1012 (1965); (e) P. Haake, W. B. Miller, and D. B. Tyssee, *ibid.*, **86**, 3255 (1964).

(5) (a) M. Hojo, M. Utaka, and Z. Yoskida, *Tetrahedron Letters*, 19 (1966); (b) *ibid.*, 25 (1966).

Chart II

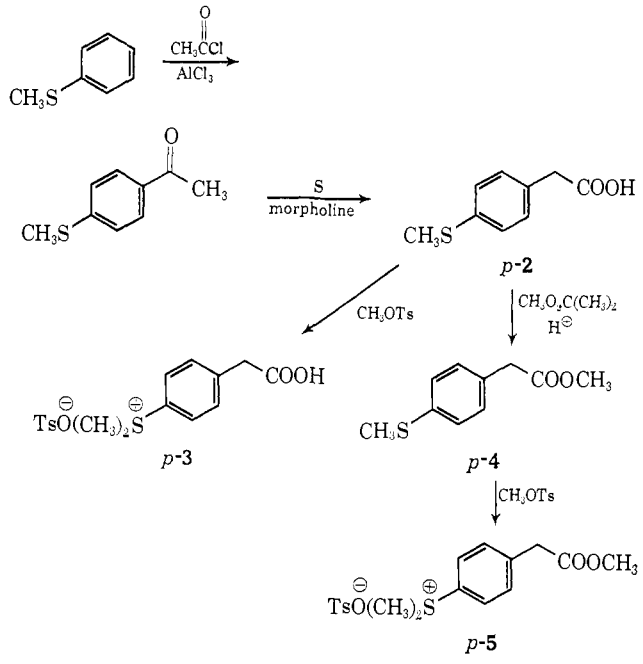
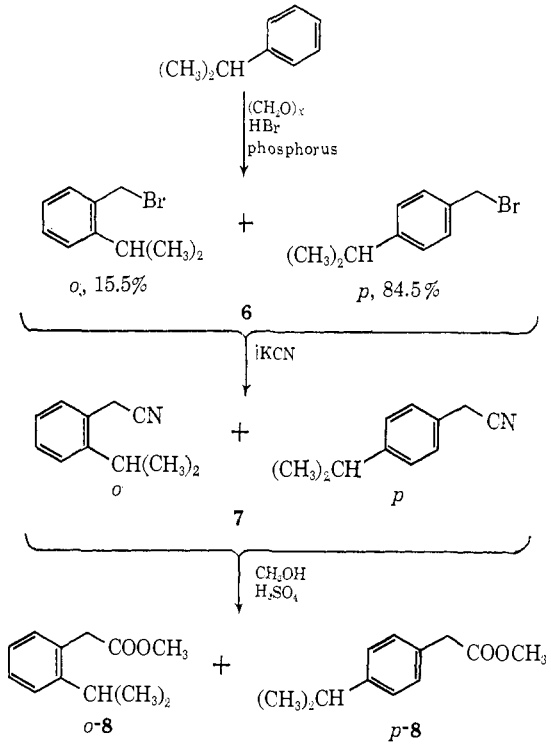


Chart III



Hydrolysis rates were measured titrimetrically at constant pH using 50% v/v aqueous dioxane as solvent. A plot of log C_0/C_t *vs.* time gave a straight line for several half-lives. Rate constants were measured under conditions of similar ionic strength, although the effect of added salt was very small. A sample run is shown in Figure 1. The pseudo-first-order rate constants were calculated by the method of least squares using a simple computer program[6] and are shown in Table I. A graph of log k *vs.* pH for the two sulfonio esters gave good parallel straight lines over the pH range 7.2–10.3 with a slope of 1.0 (Figure 2). Thus, both esters follow the simple rate expression $-\mathrm{d(ester)}/\mathrm{d}t = k(\mathrm{ester})(\mathrm{OH}^-)$. A summary of the calculated second-order rate constants for hydrolysis of the four esters at 69.5° is given in Table II. It can be seen that the *o*-sulfonio ester (*o*-**5**) is hydrolyzed 5.2 times faster than its *para* isomer (*p*-**5**). This rate order is reversed for the isopropyl esters (*o*-**8** and *p*-**8**)

(6) J. Casanova, Jr., and E. R. Weaver, *J. Chem. Educ.*, **42**, 137 (1965).

Table I. The Hydrolysis Rates of Methyl 4-Dimethylsulfoniophenylacetate *p*-Toluenesulfonate, Methyl 2-Dimethylsulfoniophenylacetate *p*-Toluenesulfonate, Methyl 4-Isopropylphenylacetate, and Methyl 2-Isopropylphenylacetate in 50% Aqueous Dioxane at Constant pH

Compd	Temp, °C	pH_{app}	10^6k_1, sec^{-1}	10^6k_1, av, sec^{-1}
o-**5**	69.5	10.33	16,800 17,200 17,000	17,000 ± 200
p-**5**			3,450 3,810 3,580	3,619 ± 133
o-**5**		8.84	665 638	651 ± 14
p-**5**			121 131	126 ± 5
o-**5**		8.56	295 344 351	330 ± 23
p-**5**			65.5 67.0	66.2 ± 0.8
o-**5**		7.17	12.9 13.2	13.1 ± 0.2
p-**5**			1.95 2.49	2.22 ± 0.29
o-**5**	59.6	10.33	7,530 2,200 7,000	7,243 ± 191
p-**5**			1,570 1,553	1,550 ± 20
o-**5**	54.2	10.33	4,950 4,990	4,970 ± 20
p-**5**			929 884	907 ± 22
o-**5**	49.8	10.33	3,190 2,910 2,620 2,600	2,830 ± 220
p-**5**			500 501 572	524 ± 32
o-**8**	69.5	9.68	12.9 10.6	11.8 ± 1.1
p-**8**			32.9 29.9 35.2 33.1	32.8 ± 1.4

Table II. Second-Order Rate Constants for the Alkaline Hydrolysis of Methyl 4-Dimethylsulfoniophenylacetate *p*-Toluenesulfonate, Methyl 2-Dimethylsulfoniophenylacetate *p*-Toluenesulfonate, Methyl 4-Isopropylphenylacetate, and Methyl 2-Isopropylphenylacetate at 69.5° in 50% Aqueous Dioxane

Ester	k_2, l. $mole^{-1}$ sec^{-1}	k_{ortho}/k_{para}	$k_{S^+}/k_{Pr\text{-}i}$
o-**5**	88.3 ± 4.8	5.2	356
p-**5**	17.1 ± 1.2		25
o-**8**	0.248 ± 0.002	0.36	
p-**8**	0.687 ± 0.003		

When the *ortho:para* rate ratio for sulfonium ester hydrolysis is corrected for steric rate retardation, which would operate in the hindered *ortho* ester but not in the

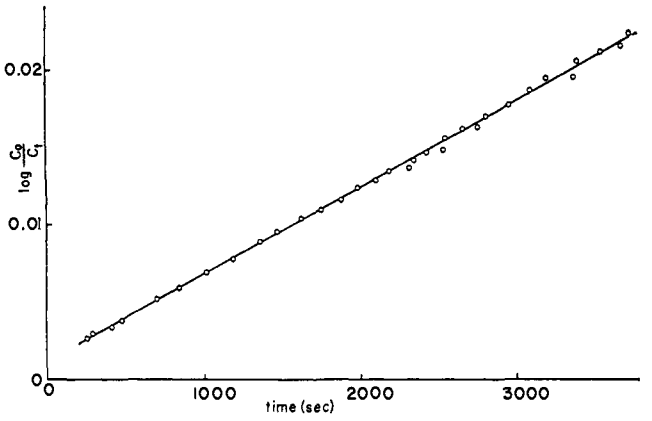


Figure 1. Log C_0/C_t *vs.* time for the hydrolysis of methyl 2-dimethylsulfoniophenylacetate *p*-toluenesulfonate in 50% aqueous dioxane at pH 7.17 and 69.5° (run 026).

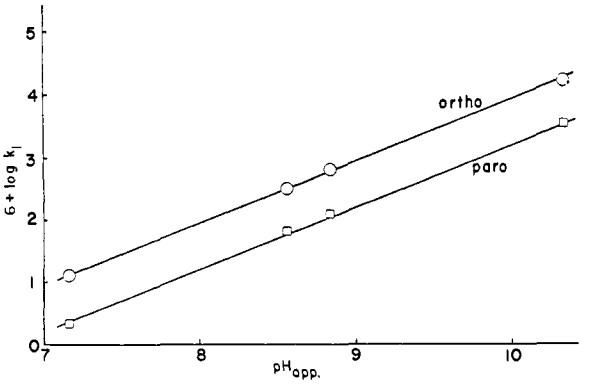


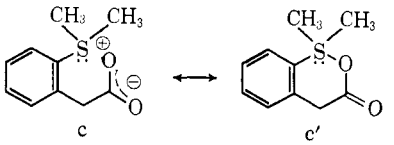
Figure 2. The pH–rate profile for the alkaline hydrolysis of methyl 4-dimethylsulfoniophenylacetate *p*-toluenesulfonate (*p*-**5**) and methyl 2-dimethylsulfoniophenylacetate *p*-toluenesulfonate (*o*-**5**).

para, by dividing by the *ortho*:*para* rate ratio obtained for the isopropyl esters (*o*-**8** and *p*-**8**), the ratio becomes 14. Contrasted with the magnitude of rate acceleration values which have been observed for systems in which nucleophilic neighboring group assistance is thought to occur efficiently[7] (10^2–10^6), the enhanced reactivity in the present case is hardly significant.

To assess the importance of a neighboring sulfonium ion in stabilizing a negatively charged carboxyl derivative, the pK_a was measured for 2- and 4-dimethylsulfoniophenylacetic acids (*o*-**3** and *p*-**3**). These values are shown in Table III. Although the resonance-stabilized carboxylate anion with a delocalized negative charge must be a poor model for the anticipated tetrahedral intermediate with a full negative charge localized on one oxygen atom, both effects operate in the same direction and the difference in acidity between the two acids should give an indication of the importance of stabilization of the tetrahedral intermediate during ester hydrolysis. The *o*-sulfonium acid (*o*-**3**) is seen to be more than 100 times stronger an acid than the corresponding methylthio acid (*o*-**2**), whereas the ratio between the *para* acids (*p*-**3** and *p*-**2**) is close to 10. However, the difference in acidity between *o*-**3** and *p*-**3** is only 0.75 p*K* unit, which does not suggest considerable stabilization of the carboxylate anion by the neighboring sulfonium ion. In its ultimate form, stabilization could take the form of covalent bonding between the carboxylate anion and the sulfonium sulfur atom (c′).

Table III. Acidity Constants of Carboxylic Acids Prepared in This Study, Measured in 45.0% w/w Dioxane–Water at 29°

Compd	pK_a
o-**2**	6.16
p-**2**	5.95
o-**3**	4.07
p-**3**	4.82



(7) A. Streitwieser, "Solvolytic Displacement Reactions," McGraw-Hill Book Co., Inc., New York, N. Y., 1962, pp 104–126.

The proton resonance spectra of the sulfonio acids (*o*- and *p*-**3**) in 2 *N* DCl and 2 *N* NaOD in D_2O were determined, and the chemical shift of the dimethylsulfonio protons was measured with respect to the chemical shift of the same protons in pure D_2O. If the covalent form (c′) made a significant contribution to the structure of the anion, then the methyl protons should show a substantial increase in shielding as the medium was changed from acidic to basic, and the species present became the carboxylate anion. The results of these measurements are shown in Table IV. Although the *ortho* zwitterion shows a slightly greater shielding than the *para*, the magnitude of the difference does not warrant invoking structure c′ as a significant contributing form.

Table IV. The Chemical Shift of the Dimethylsulfonio Protons of 4-Dimethylsulfoniophenylacetic Acid and 2-Dimethylsulfoniophenylacetic Acid Measured in 2 *N* HCl and 2 *N* NaOH

	Chemical shift, cps[a]	
Compd	2 *N* HCl	2 *N* NaOH
o-**3**	+6.5[b]	−17.0
p-**3**	+7.5	−4.5

[a] Relative to the chemical shift of the dimethylsulfonio group in pure D_2O. [b] A positive number designated a shift downfield from the standard.

It might be anticipated that if the transition state for hydrolysis of *ortho* ester (*o*-**5**) involved covalent bonding to sulfur (b′) this difference would be reflected in a more negative $\Delta S^{\pm}$ for the *ortho* than for the *para* ester because of greater constraint in such a transition state. The activation parameters for the sulfonium esters were determined from the second-order rate constants for hydrolysis at pH 10.33 using rate measurements at four temperatures. The calculated values of E_a and $\Delta S^{\pm}$ are shown in Table V. The near coincidence of both the activation energy and the activation entropy for the two sulfonio esters suggests again that the rate differences between the esters should not be attributed to any fundamental differences in the mode of reaction.

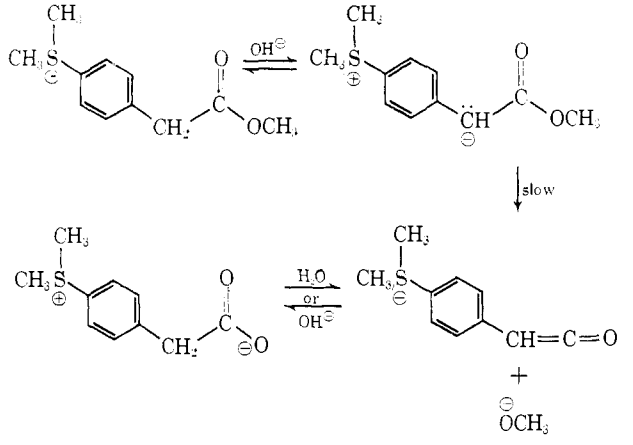
The magnitude and sign of the entropy of activation is itself very unusual and warrants comment. Most reactions which are bimolecular in the rate-controlling

Table V. Activation Parameters for the Hydrolysis of Methyl 2-Dimethylsulfoniophenylacetate *p*-Toluenesulfonate and Methyl 4-Dimethylsulfoniophenylacetate *p*-Toluenesulfonate at pH 10.33

Compd	E_a, kcal/mole[a]	$\Delta S^{\neq}$, eu[b]
o-**5**	20.0 ± 1.0	+6.4 ± 2.9
p-**5**	21.6 ± 1.0	+7.9 ± 2.9

[a] Calculated graphically from a plot of log k_2 *vs.* $1/T$. These values are, within experimental error, the same as the values obtained from the expression $E_a = RT_1T_2 \ln (k_2/k_1)/(T_2T_1)$. [b] Calculated from the expression $k_2 = (ek_BT/h) \exp(\Delta S^{\neq}/R) \exp(-E_a/RT)$. L. L. Schaleger and F. A. Long, *Advan. Phys. Org. Chem.*, **1**, 1 (1963).

step exhibit an entropy of activation of about −20 eu.[8] Although the magnitude of the activation energy observed here is similar to that reported for many ester hydrolysis reactions, the entropy of activation is 15–30 eu greater than anticipated.[9] One interpretation of this result is that ester hydrolysis in the present case (both *ortho* and *para*) is not bimolecular in the rate-controlling step. A reasonable mechanism involving a ketene intermediate can be devised to accommodate that interpretation.[10]



Inductive and resonance stabilization of the enolate anion renders this mechanism an attractive possibility. Suggestions of the operation of this mechanism in the literature are rare.[11] A necessary condition for the intervention of this novel pathway is that the rate of exchange of α-hydrogen be at least as fast as the over-all hydrolysis rate. This has been determined to be the case for the *para* ester *p*-**3**, for which k_2(exchange per hydrogen)/k_2(hydrolysis) is 8. Other experiments designed to test the interpretation stated above are in progress.

A recent report[12] of the kinetics of alkaline hydrolysis of several substituted ethyl acetates included the bromide salt of ethyl dimethylsulfonium acetate. The rate differences observed were attributed largely to electrostatic effects of substituent charges and dipoles, rather than to inductive effects. The possibility of covalent bonding between sulfur and the carbonyl group of the ester was not discussed. Inductive effects were dismissed as small in the sulfur-substituted series, based on the questionable assumption that electronegativity differences should be small in the series $RS^-(CH_3)_2$, $RSCH_3$, and RS^-. In addition, the data presented by these authors gives a straight line when plotted as log k_2 *vs.* σ^*. Under the circumstances we feel that it would be premature to dismiss an inductive effect as unimportant in the sulfonium salts.

The magnitude of the *ortho*:*para* ratio for the sulfonio esters is small enough so that it could be interpreted in terms of an inductive effect alone. This is contrary to our assumption at the onset of this study. To the extent that the hydrolysis of sulfonium esters *o*-**5** and *p*-**5** follows a normal hydrolytic sequence, a supposition to which some doubt has been raised here, it is evident that neighboring sulfonium sulfur exerts a surprisingly small electrophilic enhancement of the rate of ester hydrolysis.

Experimental Section

***o*-Mercaptophenylacetic Acid (1).** This compound was prepared by the method of Pascal and Tarbell.[13] The acid did not crystallize and was used directly in the preparation of the sulfide. The yield was 22%.

2-(Methylthio)phenylacetic Acid (*o*-2). A solution of 4.0 g of *o*-mercaptophenylacetic acid in 15 ml of absolute ethanol was added slowly to a warm solution of 3.01 g (0.024 mole) of dimethyl sulfate in 15 ml of 33% aqueous sodium hydroxide and heated at reflux for 0.5 hr. The ethanol was removed *in vacuo*, and approximately 10 ml of water was added. The solution was acidified with 6 *N* HCl and solid appeared. The solid recrystallized from chloroform, 1.31 g (30%), mp 127–129°. An infrared spectrum in chloroform showed strong absorption at 1715 cm^{-1} (s), 3600–2500 cm^{-1} (nl). An nmr spectrum in $CDCl_3$ with tetramethylsilane as an internal standard showed a complex multiplet, centered at 7.32 ppm, a singlet at 3.86 ppm, and a singlet at 2.44 ppm with the area ratio 4:2:3, respectively.

Anal. Calcd for $C_9H_{10}O_2S$: C, 59.31; H, 5.53; S, 17.59. Found: C, 58.91; H, 5.55; S, 17.59.

2-Dimethylsulfoniophenylacetic Acid *p*-Toluenesulfonate (*o*-3). 2-(Methylthio)phenylacetic acid (0.5 g, 2.7 mmoles), 1.0 g (5.4 mmoles) of methyl *p*-toluenesulfonate (Eastman, distilled), and 5 ml of toluene (reagent grade, dried over sodium) were heated overnight. An oil separated and the toluene was decanted. The oil was crystallized by trituration with methanol. The white solid was twice recrystallized by dissolving it in acetone containing a few milliliters of ethanol and then adding ethyl acetate to give 0.28 g (27%) of white solid, mp 153.0–153.5°.

Anal. Calcd for $C_{17}H_{20}O_5S_2$: C, 55.41; H, 5.47; S, 17.40. Found: C, 55.38; H, 5.55; S, 17.22.

4-(Methylthio)phenylacetic Acid (*p*-2). This compound was prepared in 45% yield by the method of Elderfield and Burgess,[14] mp 93–95° (lit.[14] 94–95°).

4-Dimethylsulfoniophenylacetic Acid *p*-Toluenesulfonate (*p*-3). 4-(Methylthio)phenylacetic acid (1 g, 5.4 mmoles), 2.0 g (10.8 mmoles) of methyl *p*-toluenesulfonate (Eastman, distilled), and 10 ml of anhydrous toluene were refluxed for 6 hr. The solid which had formed was collected on a filter and washed with benzene. The solid was twice recrystallized from ethanol–ethyl acetate to give 0.80 g (41%) of white solid, mp 180–182°.

Anal. Calcd for $C_{17}H_{20}O_5S_2$: C, 55.41; H, 5.47; S, 17.40. Found: C, 55.47; H, 5.56; S, 17.08.

pK_a Determinations. A standard solution of sodium hydroxide (0.0498 *N*) in 55.0% (by weight) of distilled water and 45.0% (by

(8) K. B. Wilberg, "Physical Organic Chemistry," John Wiley and Sons, Inc., New York, N. Y., 1964, p 387.

(9) M. L. Bender, R. D. Ginger, and J. P. Unik, *J. Am. Chem. Soc.*, **80**, 1044 (1958); A. Fischer, W. J. Mitchell, G. S. Ogilvie, J. Packer, J. E. Packer, and J. Vaughn, *J. Chem. Soc.*, 1426 (1958); E. Tommila, A. Nurro, R. Muren, S. Merenheimo, and E. Vuorinen, *Suomen Kemistilehti*, **32B**, 115 (1959); K. J. Laidler and D. Cheu, *Trans. Faraday Soc.*, **5b**, 1026 (1958); J. E. Earley, C. E. O'Rourke, L. B. Clapp, J. O. Edwards, and B. C. Lawes, *J. Am. Chem. Soc.*, **80**, 3458 (1958); A. Moffat and H. Hunt, *ibid.*, **81**, 2082 (1959); S. Sarel, L.Tsai, and M. S. Newman, *ibid.*, **78**, 5420 (1956); T. C. Bruice and G. L. Schmir, *ibid.*, **79**, 1663 (1957); G. L. Nolan and E. S. Amis, *J. Phys. Chem.*, **65**, 1556 (1961); ref 1c, p 11.

(10) The authors are indebted to E. Cordes for pointing out this possibility.

(11) W. A. Remers, R. H. Roth, and M. J. Weiss, *J. Org. Chem.*, **30**, 2901 (1965); ref 1c, p 8.

(12) R. P. Bell and B. A. W. Coller, *Trans. Faraday Soc.*, **61**, 1445 (1965).

(13) I. I. Pascal and D. S. Tarbell, *J. Am. Chem. Soc.*, **79**, 6015 (1957).

(14) R. C. Elderfield and K. L. Burgess, *ibid.*, **82**, 1975 (1960).

weight) of dioxane (purified by the Hess and Frahm method[15]) was the titrant. The general method of Albert and Serjeant[16] was used to determine the pK_a values. The sample was dissolved in 55.0% (by weight) of water and 45.0% (by weight) of dioxane. A Leeds and Northrup pH meter was used, and the meter was standardized with both phthalate buffer (pH 4.00) and phosphate buffer (pH 6.86) before and after the measurements. During the measurement of pH, prepurified nitrogen gas was bubbled through Fieser's solution,[17] reaction solvent, and into the cell. The calculation of the pK_a values was carried out as described elsewhere.[16] Corrections for the hydrogen ion concentration were applied.

Methyl 4-(Methylthio)phenylacetate (*p*-4). A solution of 5.5 g (20 mmoles) of 4-(methylthio)phenylacetic acid, 10 ml of methanol (reagent grade), 10 ml of 2,2-dimethoxypropane (Dow Chemical Co.), and a few milligrams of *p*-toluenesulfonic acid monohydrate was stirred overnight at room temperature. The solution was concentrated *in vacuo* and then taken up in chloroform and washed in sodium bicarbonate and saturated aqueous sodium chloride. The dried chloroform solution was concentrated to give a tan liquid. Distillation of this liquid gave 3.0 g (51%), bp 178–180° (0.5 mm) [lit.[18] 179–181° (3 mm)]. An infrared spectrum in chloroform showed no absorption between 3600 and 3200 cm^{-1} and strong absorption at 1735 cm^{-1}.

Methyl 4-Dimethylsulfoniophenylacetate *p*-Toluenesulfonate (*p*-5). Methyl ester *p*-4 (3 g, 0.015 mole) and methyl *p*-toluenesulfonate (3.6 g, 0.019 mole) (Eastman, distilled) were heated at 100° for 3 hr. After cooling to room temperature the reaction mixture solidified. The solid was first washed with ethyl ether and then collected on a filter. Recrystallization from dioxane–methanol gave 5.0 g (87%) of a white solid, mp 145–147°.

Anal. Calcd for $C_{18}H_{22}O_5S_2$: C, 56.52; H, 5.80; S, 16.77. Found: C, 56.35; H, 5.80; S, 16.40.

Methyl 2-(Methylthio)phenylacetate (*o*-4). A solution of 3.7 g (0.020 mole) of 2-(methylthio)phenylacetic acid, 15 ml of absolute methanol, 10 ml of 2,2-dimethoxypropane (Dow Chemical Co.), and a few milligrams of *p*-toluenesulfonic acid monohydrate was heated at reflux for 4 hr. The dark solution was concentrated *in vacuo*, taken up in chloroform, and washed with sodium bicarbonate solution and saturated aqueous sodium chloride solution. The chloroform solution was dried and distilled to give 2.8 g (72%) bp 99–100° (0.75 mm); $n^{21}D$ 1.5632. An infrared spectrum in chloroform showed no absorption between 3600 and 3200 cm^{-1} and strong absorption at 1730 cm^{-1}.

Anal. Calcd for $C_{10}H_{12}O_2S$: C, 61.20; H, 6.16; S, 16.34. Found: C, 61.14; H, 6.08; S, 16.13.

Methyl 2-Dimethylsulfoniophenylacetate *p*-Toluenesulfonate (*o*-5). A solution of 2.8 g (0.014 mole) of methyl ester *o*-4 and 3.2 g (0.017 mole) of methyl *p*-toluenesulfonate (Eastman, distilled) was heated at 100° for 3 hr. The reaction mixture was cooled to room temperature and a solid formed which was washed with ethyl ether and collected on a filter. The white solid was recrystallized from 2-butanol to give 2.5 g (46%) of a white solid, mp 156–158°. A second crop of 1.2 g (22%) was obtained.

Anal. Calcd for $C_{18}H_{22}O_5S_2$: C, 56.52; H, 5.80; S, 16.77. Found: C, 56.15; H, 5.74; S, 16.54.

2- and 4-Isopropylbenzyl Bromides (*o*- and *p*-6). Into a solution of 120 ml of (48%) HBr, 93 g of cumene, 39 g of paraformaldehyde, and 200 mg of red phosphorus, gaseous HBr was bubbled for 6 hr while the mixture was stirred vigorously. After 20 min the reaction mixture because hot and was cooled for 30 min in an ice bath until all paraformaldehyde was dissolved and no further exothermic reaction was observed. It was then held at 55° for 18 hr. The organic layer was separated, washed with water, and dried over $MgSO_4$.

Distillation at 64° (0.5 mm) yielded 141.8 g (77%) [lit.[19] bp 126–130° (20 mm)].

2- and 4-Isopropylbenzyl Cyanides (*o*- and *p*-7). Potassium cyanide (60 g) was dissolved with stirring in 70 ml of water. After addition of 60 ml of ethanol, the solution was cooled with ice and 140 g of the bromide (*o*- and *p*-6) in 60 ml of ethanol was added over a period of 30 min. The reaction mixture was then stirred at room temperature for 2 hr. The solid KBr was removed by filtration and the alcohol evaporated. The oily layer was washed with water and extracted with ether. The ether solution was dried over $MgSO_4$ and evaporated. Distillation on a Vigreux column, 92° (0.5 mm), yielded 96.5 g (93%) of product.

Methyl 2- and 4-Isopropylphenyl Acetates (*o*- and *p*-8). The mixed cyanides (*o*- and *p*-7), 96.5 g, in 180 ml of methanol and 80 ml of concentrated sulfuric acid were refluxed for 20 hr. Water was added, and the resulting oil was extracted into ether, washed with 10% $NaHCO_3$ and water, dried, and distilled, bp 68–83° (0.5 mm), 77 g (66%). This material was distilled on a spinning-band column and collected in three fractions (see Table VI). The first distillation fraction was separated by preparative glpc on a 10-ft Carbowax 20M column, 185°, and the esters (**8**) collected were redistilled.

Table VI

Bp, °C (0.5 mm)	Glpc, % *ortho*	Glpc, % *para*	Wt, g
86–90	27.5	72.5	15
96	15	85	40
96–98	6	94	15

Anal. Calcd for $C_{12}H_{16}O_2$ [*ortho:* bp 78° (1 mm)]: C, 74.96; H, 8.39. Found: C, 74.94; H, 8.43. Found [*para:* bp 80° (0.2 mm)]: C, 75.39; H, 8.51.

Kinetics Procedure. The dioxane used was commercial grade, purified by the method of Hess and Frahm.[15] Standard sodium hydroxide solutions were prepared in the reaction solvent so that the composition of the solvent would not be changed during the reaction. The concentration of the sodium hydroxide solution was between 10^{-3} and 10^{-2} *N*, so as to give about 2 ml volume change, depending on the rate of the hydrolysis reaction.

A solution (50 ml) of 50.0% (by volume) dioxane and 50.0% (by volume) water was pipetted into a jacketed reaction cell which was equipped with a Beckman amber glass electrode and a Beckman silver chloride reference electrode, an automatic buret, the tip of which was immersed in the reaction solution, and a water condenser. The reaction solution was stirred magnetically under an atmosphere of prepurified nitrogen. The solvent was allowed to equilibrate thermally for 1 hr in the cell. During the equilibration period, the pH of the solution was adjusted to the desired regulation point by the addition of a very small amount of either acid or base. Either 100 or 50 mg of sample was added to the reaction cell.

Base was added automatically in small increments to maintain the pH constant to ±0.04 unit. The buret was driven by a relay which was activated by imbalance in a 1:10 scale-expanded pH meter. The results were recorded automatically on a chart. First-order rate constants were calculated by the method of least squares using an IBM 1620 computer.[5]

The nature of the hydrolysis products was confirmed by carrying out several reactions in nmr tubes and identifying methanol and the carboxylic acids which formed by their characteristic spectra.

α-Methylene Exchange and Hydrolysis Rates by Nmr. A sample of *p*-5 (54.7 mg, 0.143 mmole) was dissolved in 0.50 ml of K_3BO_3–H_3BO_3 buffer in D_2O (pH 10.69), and the sample was immediately frozen to −78°. The proton resonance spectrum was followed at 36.5° as a function of time. The α-methylene exchange rate was calculated by comparing one-half of the methylene peak integral to an internal standard (3 H from the *p*-toluenesulfonate anion). A plot of log [0.5(area CH_2)/area CH_3(tosyl)] *vs.* time gave a straight line, from which a pseudo-first-order rate constant for α-hydrogen exchange was obtained. The result is shown below. By determining the area under the ester CH_3 peak, relative to that under the tosyl CH_3 peak during the reaction, or by plotting a graph of log [area CH_3(ester)]/[area CH_3(ester) + area CH_3(methanol)] *vs.* time, a straight line could be obtained which measured the over-all hy-

Table VII

	10^4k_1, sec^{-1}	k_2, l. $mole^{-1}$ sec^{-1}
Exchange, per H	18	3.7
Hydrolysis	2.3	0.47

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drolysis rate constant. The values are shown below, and compare quite favorably with those obtained by the titrimetric method shown in Table VII.

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Dimethyl Sulfoxide–Acid Anhydride Mixtures for the Oxidation of Alcohols

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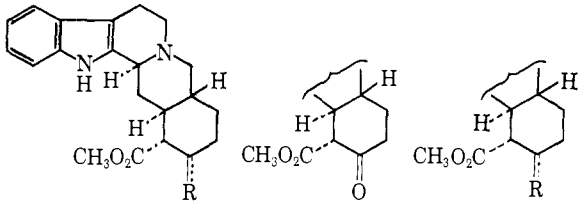
Abstract: Oxidation of alcohols with dimethyl sulfoxide and acetic anhydride is reported. The conversion of secondary hydroxyl functions to ketones in a variety of alkaloids and steroids occurs in moderate to excellent yields. The dimethyl sulfoxide–acetic anhydride oxidation procedure is particularly useful for oxidation of sterically hindered hydroxyl groups and for oxidation of hydroxyl functions in sensitive molecules such as indole alkaloids. The mechanism of oxidation is discussed. By-products often formed are methylthiomethyl ethers of the starting alcohols.

Our continued interest in improved methods for the oxidation of secondary hydroxyl groups of indole alkaloids[1] to ketones led to the discovery of a novel method of oxidation of alcohols to their corresponding carbonyl derivatives with dimethyl sulfoxide (DMSO) and acetic anhydride.[2] Oxidation of alcohols with acetic anhydride–DMSO is a mild oxidative method and is particularly useful with indole alkaloids which are sensitive to nonselective oxidizing reagents. In addition this procedure gives good yields with sterically hindered hydroxyl groups and has been applied to a number of steroids. However, it is obvious that this method will fail in cases where alcohols are rapidly acetylated under the conditions of the reaction, for O-acetylation will then effectively compete with oxidation.

In general, the procedure consists of stirring a solution of the alcohol in a mixture of DMSO and acetic anhydride for 15–24 hr at room temperature. Dimethyl sulfoxide has been used as both solvent and reagent, although there is no reason to believe that an inert diluent is deleterious. In our original experiments a ratio of 20 moles of acetic anhydride to 1 mole of alcohol was employed; however, such a large excess of acetic anhydride is not necessary. Successful oxidations have been carried out with 3–5 moles of anhydride per mole of alcohol.

Optimal conditions for the reaction and variations which could be employed were determined using yohimbine (**1**) as substrate. The reaction of **1** (1 mmole), 3 ml of DMSO, and 2 ml (*ca.* 20 mmoles) of acetic anhydride was followed by periodically removing aliquots and determining the extent of reaction by thin layer chromatography (tlc) on silica gel. In 4–5 hr the reaction was approximately 50% complete and in 12 hr no more starting material remained. Yohimbinone[3] (**3**) was isolated in 80% yield at the end of this time. No reduction in the yield was observed on decreasing the molar ratio of alcohol **1** to acetic anhydride to 1:5.



1, R = –H, ···OH
2, R = –OH, ···H

3

4, R = –H, ···OCH_2SCH_3
5, R = –OCH_2SCH_3, ···H

Certain other acid anhydrides can be used in place of acetic anhydride. Benzoic anhydride (17 moles) and yohimbine (1 mole) in DMSO at room temperature for 22 hr afforded 82% of β-keto ester **3**. However trifluoroacetic anhydride and *p*-toluenesulfonic anhydride were not effective. Based on plausible mechanistic considerations (*vide infra*) anhydrides unreactive to DMSO should be unsatisfactory as should overly reactive ones. Phosphorus pentoxide[4] and polyphosphoric acid were studied briefly with the following results. Yohimbine (**1**) (1 mole) and phosphorus pentoxide (1 mole) in DMSO at 65° for 18 hr gave yohimbinone (**3**) in 45% yield. Polyphosphoric acid and **1** at room temperature for 41 hr afforded **3** in 51%

(1) For a previous study of oxidation of alcohols see J. D. Albright and L. Goldman, *J. Org. Chem.*, **30**, 1107 (1965).

(2) See J. D. Albright and L. Goldman, *J. Am. Chem. Soc.*, **87**, 4214 (1965), for preliminary communication of this work; for application of this method in the carbohydrate field see W. Sowa and G. H. S. Thomas, *Can. J. Chem.*, **44**, 836 (1966).

(3) M.-M. Janot, R. Goutarel, E. W. Warnhoff, and A. Le Hir, *Bull. Soc. Chim. France*, 637 (1961).

(4) The oxidation of alcohols to ketones in the carbohydrate field with DMSO–phosphorus pentoxide has been described recently: K. Onodera, S. Hirano, and N. Kashimura, *J. Am. Chem. Soc.*, **87**, 4651 (1965).