

Biologically Oriented Organic Sulfur Chemistry. I. Reactions of Thiols with Highly Reactive Carbonyl Compounds¹

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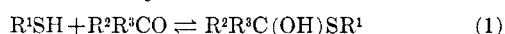
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Approximate equilibrium constants (K) were obtained for the uncatalyzed reaction of 1-propanethiol with various carbonyl compounds in methylene chloride solution, leading to the formation of α -hydroxy sulfides. Many of the carbonyl compounds were of a highly reactive type, typified by a propensity to form isolable hydrates. The values of K obtained ranged from nearly 0 to in excess of 10^4 . In instances where values of K were equal to or greater than about 10^2 , the α -hydroxy sulfides formed could not be converted in the presence of acid catalyst and excess thiol into mercaptals or mercaptoles. However, where K values were in the range of about 0 – 10^2 , the well-established conversion into mercaptals or mercaptoles could be achieved readily in the presence of hydrogen chloride or boron trifluoride. Values of K with chloral and tertiary thiols were similar to those with 1-propanethiol. 1-Dodecanethiol was much more sluggish in its reaction with chloral than were short-chain primary or tertiary thiols.

For some years we have been interested in substances which would react with radioprotective aminoalkane-thiols in such a way as to reduce toxicity and improve protective activity of the thiol, thereby enhancing the usefulness of the structure for protection against otherwise lethal effects of ionizing radiation.² A similar approach deserves investigation with the tertiary thiol, penicillamine, which is of interest in relation to rheumatoid arthritis (as well as to other diseases), but which unfortunately has problems of toxicity associated with its use.³

Since a number of reactive carbonyl compounds have long been known to form isolable hydrates, it seemed that they might similarly form hemimercaptals or hemimercaptoles (α -hydroxy sulfides) with radioprotective thiols, or with penicillamine, as shown in eq 1. Such products might have worthwhile medicinal properties in being stable solids of reduced toxicity and/or improved activity.



Knowledge of the relative stability of α -hydroxy sulfides thus was desirable as a basis for attempted preparation of those which might be reasonably stable, as well as to suggest carbonyl compounds which would exemplify as great a range of stabilities as feasible (because of the possible variation of medicinal activity with stability). A study of equilibrium constants (K) for eq 1 therefore was undertaken.

Comparatively little attention has been given to the formation of α -hydroxy sulfides. Johns and Hixon measured the dissociation constants of hemimercaptals formed in the reaction in benzene of chloral with several thiols by a method based on depression of freezing points.⁴ Moore later obtained results similar to those of Johns and Hixon, using a vapor pressure method.⁵ Lienhard and Jencks recently determined rate and equilibrium constants for the reaction of a series of thiols with acetaldehyde and several other simple carbonyl compounds to form the corresponding

α -hydroxy sulfides in aqueous media.⁶ They followed the reactions by changes in the uv absorbance of the carbonyl group. They suggested that reaction occurred by specific base catalyzed and general acid catalyzed pathways and that the mechanism of the general acid catalyzed reaction involves proton donation to the unhydrated carbonyl group. The rather limited amount of preparative work on α -hydroxy sulfides has been summarized by Reid⁷ and by Schöberl and Wagner.⁸

For our purpose, study of carbonyl compounds which are sufficiently reactive to give isolable hydrates seemed more promising than of normal carbonyl compounds, although some of the latter type, such as acetone, acetaldehyde, ethyl acetoacetate, and benzaldehyde, were included for comparison.

Selection of 1-propanethiol for use in this study was made after investigating the reaction of chloral with 1-dodecanethiol, 2-acetamidoethanethiol, and 1-propanethiol. 1-Dodecanethiol was an unsuitable choice since it did not react with chloral in methylene chloride solution in 14 days, whereas 1-propanethiol came to equilibrium under corresponding conditions within one day. The hemimercaptal from the reaction of 1-dodecanethiol with chloral was readily formed by mixture of the liquid reactants,⁹ but when it was dissolved in methylene chloride its rate of dissociation was so slow that the system was never observed to come to equilibrium, although, under similar conditions in the presence of 0.2 *M* boron trifluoride etherate, the system came to equilibrium within 3 days. A possible explanation for this abnormally low reactivity is that, owing to the long aliphatic sidechain, an entropy factor unfavorably retards both the formation and dissociation of the hemimercaptal. The other two thiols reacted quite rapidly with chloral in the neat state in quite exothermic reactions; similar behavior occurred with the other carbonyl compounds. Another factor favoring 1-propanethiol was its lack of polar groups which might influence the stability of an α -hydroxy sulfide, if formed, or which might lead to ir absorption maxima which could confuse ir interpretations.

(1) This investigation was supported by the U. S. Army Medical Research and Development Command, Department of the Army, under Research Contract No. DA-49-193-MD-2030 and by Public Health Service Research Grant No. 1 RO1 AM11685 from the National Institute of Arthritis and Metabolic Diseases.

(2) Cf. Paper XXVII and earlier papers in the series entitled "Organic Disulfides and Related Substances;" L. Field and R. B. Barbee, *J. Org. Chem.*, **34**, 1792 (1969).

(3) I. A. Jaffe, *Arthritis Rheumat.*, **8**, 1064 (1965).

(4) I. B. Johns and R. M. Hixon, *J. Amer. Chem. Soc.*, **56**, 1333 (1934).

(5) F. B. Moore, *Iowa State Coll. J. Sci.*, **16**, 99 (1941); *Chem. Abstr.*, **36**, 4396 (1942).

(6) G. E. Lienhard and W. P. Jencks, *J. Amer. Chem. Soc.*, **88**, 3982 (1966).

(7) E. E. Reid, "Organic Chemistry of Bivalent Sulfur," Vol. III, Chemical Publishing Co. Inc., New York, N. Y., 1960, p 320.

(8) A. Schöberl and A. Wagner, in "Methoden der Organischen Chemie (Houben-Weyl)," Vol. 9, E. Müller Ed., G. Thieme Verlag, Stuttgart, 1955, p 199.

(9) Cf. R. L. Frank, S. S. Drake, P. V. Smith, Jr., and C. Stevens, *J. Polym. Sci.*, **3**, 50 (1948).

TABLE I
APPROXIMATE EQUILIBRIUM CONSTANTS (K) FOR THE REACTION OF PRIMARY THIOLS WITH CARBONYL COMPOUNDS^a

Parent carbonyl compound	ν_{\max} of C(O), cm^{-1}	K , approx	Methods	ν_{\max}		Product in presence of acid catalyst
				(O-H), cm^{-1}	(C-OH), cm^{-1}	
Ketones						
CH_3COCH_3	1720	0, 0	<i>b, c; b, d</i>			Mercaptole ^e
CF_3COCF_3	1800	<i>ca.</i> 10^3 - 10^5	<i>b, f</i>	3530	1085	α -Hydroxy sulfide
$\text{C}_2\text{H}_5\text{O}_2\text{CCOCO}_2\text{C}_2\text{H}_5$	1770	$>10^3$, ($>10^4$)	<i>b, c (c, g)</i>	3490	1035	α -Hydroxy sulfide
$\text{CH}_3\text{COCO}_2\text{H}$	1798	2×10^0	<i>b, c</i>	Weak	Weak	Mercaptole ^e
$\text{CH}_3\text{COCH}_2\text{CO}_2\text{C}_2\text{H}_5$	1740	<i>ca.</i> 0	<i>b, c</i>			Mercaptole
$\alpha\text{-C}_6\text{H}_4(\text{CO})_2$	1750 or 1760	$>10^3$, $>10^3$	<i>b, c; g, h</i>	3510	Uncertain	α -Hydroxy sulfide
Aldehydes						
$\text{C}_6\text{H}_5\text{COCHO}$	1738	$>10^3$, $>10^3$	<i>b, c; c, g</i>	3480	1070	α -Hydroxy sulfide
Br_3CCHO	1748	3×10^1 , 3×10^1	<i>b, c</i>	3525	1040	Mercaptal ^f
Cl_3CCHO	1770	3, 5, 8×10^2	<i>b, d, i</i>	3540	1055	α -Hydroxy sulfide
<i>j</i>		8×10^2	<i>b, j</i>	3450	1085	α -Hydroxy sulfide
<i>k</i>		1×10^2	<i>b, k</i>	3540	1055	α -Hydroxy sulfide
CH_3CHO	1730	0	<i>b, d</i>			Mercaptal ^e
$\text{C}_6\text{H}_5\text{CHO}$	1700	5×10^0	<i>b, d</i>	Weak	Weak	Mercaptal
$\text{C}_6\text{F}_5\text{CHO}$	1720	5×10^0	<i>b, c</i>	3575	1025	Mercaptal

^a At ambient temperatures of *ca.* 28°. 1-Propanethiol was used in all instances unless otherwise specified. ^b Method using ir absorption. ^c Calculated after dilution of the neat mixture of 1 molar proportion of carbonyl compound and 2.5 molar proportions of 1-propanethiol with CH_2Cl_2 and equilibration by dissociation. ^d Calculated after equilibration of a mixture of solutions in CH_2Cl_2 of 1 molar proportion of carbonyl compound and 2.5 molar proportions of 1-propanethiol. ^e Residual carbonyl absorption in the ir suggested incomplete conversion into mercaptal or mercaptole. ^f Excess hexafluoroacetone was condensed into 2.16 g of 1-propanethiol at *ca.* -70°. The mixture was evacuated briefly at room temperature to constant weight (yield of the α -hydroxy sulfide, 101%), dissolved in CH_2Cl_2 , and allowed to equilibrate by dissociation. ^g Measured using uv. ^h Procedure as in footnote *c*, but using benzene as solvent. ⁱ Values of 3×10^2 , 5×10^2 , and 8×10^2 were obtained in replicate experiments. ^j As in footnote *c* but using 1 molar proportion of 2-acetamidoethanethiol. ^k As in footnote *c* but using a 1 molar proportion of 1-dodecanethiol in a solution 0.2 *M* with respect to boron trifluoride etherate (which, of course, may have had an effect on the value of K); the ir frequencies of OH and C-OH were determined in the absence of the boron trifluoride.

For the evaluation of K , a Beer's law curve for the selected carbonyl compound in methylene chloride was prepared either using a suitable uv absorption maximum or the carbonyl ir absorption maximum in the range of 1700-1800 cm^{-1} (*cf.* Table I). The carbonyl compound usually was then mixed with about 2.5 molar proportions of 1-propanethiol (in the absence of acid or solvent) and characteristics of the reaction such as evolution of heat, formation of water, color change, etc., were observed, as described in the Experimental Section (where behavior of other carbonyl compounds unsuitable for inclusion in Table I also is mentioned). The mixture then was dissolved in methylene chloride and its uv or ir spectrum was examined from time to time until equilibrium by dissociation was achieved. The equilibrium constants (K), calculated as described in the Experimental Section, are given in Table I. They are considered to be rather approximate values because the temperature was not rigorously controlled, because the amount of carbonyl compound left after reaction often was too small to be measured accurately using our methods, and occasionally because of other features mentioned later or as footnotes to Table I. Nevertheless, the values of 3 - 8×10^2 for chloral and 1-propanethiol (Table I) agree reasonably with those of 4 - 6×10^2 determined by Johns and Hixon for ethane- and butanethiol.⁴

The production of O-H and C-OH ir absorption maxima in the regions 3450-3575 and 1025-1085 cm^{-1} , respectively (Table I), confirmed the formation of α -hydroxy sulfides, but the frequency of the absorption seemed to show no useful correlation with the value of K . The carbonyl frequency itself also showed no useful correlation with K . In some instances, K values were measured after achieving equilibration by

both dissociation of preformed α -hydroxy sulfide in CH_2Cl_2 and by reaction of the carbonyl compound in CH_2Cl_2 with thiol in CH_2Cl_2 , good agreement being observed in all cases investigated. That α -hydroxy sulfides, rather than mercaptals or mercaptoles, were initial products is further confirmed by the literature cited above, by remarks below dealing with subsequent formation of mercaptals and mercaptoles, and by isolation of α -hydroxy sulfides from reaction of several compounds of high K value with 2-aminoethanethiol hydrochloride.¹⁰

Coupled with these observations, in each instance we thought it of added value to study similar systems in the presence of acid catalyst (hydrogen chloride or boron trifluoride) to observe the possibility of conversion of the α -hydroxy sulfide into mercaptal or mercaptole, as estimated by formation of water or by spectral changes.

In the instances of the carbonyl compounds which do not form isolable hydrates (*i.e.*, acetone, ethylacetate, pyruvic acid, acetaldehyde, pentafluorobenzaldehyde, and benzaldehyde), Table I shows that little or no α -hydroxy sulfide was formed ($K \sim 0$), as was evidenced by only small initial changes in the carbonyl absorbance. However, upon addition of the acid catalyst the expected substantial conversion into a mercaptal or mercaptole occurred in most cases, as indicated by virtually complete disappearance of the carbonyl absorption and separation of considerable amounts of water from the methylene chloride used as the solvent.

In marked contrast, Table I shows that the carbonyl compounds which are well known to form isolable

(10) Details to be published elsewhere.

hydrates, and in this sense are "highly reactive," underwent substantial conversion into the α -hydroxy sulfides. These α -hydroxy sulfides could not be significantly converted into mercaptals or mercaptoles in the presence of the acid catalysts and the remaining approximately 1.5 molar proportions of 1-propanethiol. Some support for this conclusion was afforded by our inability to note any formation of water, although an amount corresponding to less than 1% conversion of the α -hydroxy sulfide can be seen easily in pure methylene chloride. Since the solubility of water in the actual systems seemed rather variable, however, a firmer basis for the conclusion is that the ir absorption spectra of solutions of the stable α -hydroxy sulfides showed no significant change after addition of the acid catalyst.

These observations suggest the generalization that carbonyl compounds which are sufficiently reactive to form isolable hydrates also are sufficiently reactive to form α -hydroxy sulfides, rather than mercaptals or mercaptoles, and that these α -hydroxy sulfides indeed cannot even be readily converted into mercaptals or mercaptoles; Table I suggests that this behavior holds when the value of K equals or exceeds about 10^2 . The converse also seems true, that carbonyl compounds which show relatively little tendency to form isolable hydrates show little tendency to form α -hydroxy sulfides (K below about 10^2) and show the usual marked tendency to form mercaptals or mercaptoles in the presence of an acid catalyst. One should bear in mind, however, that changes in circumstances could have a marked effect on these generalizations. For example, the hemimercaptole of hexafluoroacetone and 1-propanethiol disappeared rather rapidly under vacuum; dissociation to the gaseous ketone might be involved, as well as volatilization; irreversible dissociation also would be expected if a thiol component were readily oxidized.

The main factor leading to stabilization of an α -hydroxy sulfide of 1-propanethiol appears to be the presence of an electron-withdrawing group in the α position. The results presented in Table I suggest that the stabilities decrease in this order: $C_6H_5C(O)$, bis CO, bis CO_2Et , $CF_3 > CCl_3 > CBr_3 > C_6F_5$, $C_6H_5 > CH_3(CO_2H) > CH_3(CH_2CO_2Et)$, CH_3 . This order resembles that which might be expected from the order of Taft polar substituent constants, where data are available (*e.g.*, $CCl_3 > CHF_2 > CO_2ME \gg C_6H_5 > CH_3$).¹¹ If the stabilizing group is in the β position (*e.g.*, CO_2Et in ethyl acetoacetate), the stabilizing effect is very greatly reduced.

The most attractive explanation for the inability of α hydroxy sulfides having α -electron-withdrawing groups to be further converted in the presence of acid into mercaptals or mercaptoles is that the electron-withdrawing group, which perhaps strengthens the C-OH bond and reduces the basicity of the OH, destabilizes the transition state leading to the formation of the carbonium ion, which presumably is essential in the conversion. Steric influences also may play a role; for example, hexachloroacetone which on reaction with a thiol might be expected to yield a stable α -hydroxy sulfide, was completely unreactive.

Because of the interest mentioned in tertiary thiols like penicillamine, it was desirable also to study the reaction of a tertiary thiol with a carbonyl compound having a value of K intermediate among those which formed α -hydroxy sulfides. The reaction system chosen was that of chloral with 2-methyl-2-propanethiol (penicillamine itself is too sparingly soluble in methylene chloride). The K value (measured by either formation or dissociation) for this reaction was 1.5×10^2 , approximately one-third of the value obtained using 1-propanethiol. The rapidity of equilibration was roughly comparable for the primary and tertiary thiols. Since it was available to us,¹⁰ the thiol $HSC(CH_3)_2CH_2CH_2OH$ also was studied with chloral. In this instance, a K value of 1.3×10^3 was obtained (about three times the value obtained using 1-propanethiol and nearly ten times that using 2-methyl-2-propanethiol). The alternative product, $Cl_3CCH(OH)O(CH_2)_2C(CH_3)_2SH$, cannot be excluded entirely, but seemed unlikely to be more than a minor component, at most, since no ir frequency for SH was seen at equilibrium. This enhanced stability may reflect a stabilizing effect of the side-chain hydroxyl group on the α -hydroxy sulfide. This reaction when carried out neat appeared to be somewhat more exothermic than the one using 2-methyl-2-propanethiol. Cyclization to significant amounts of 2-(trichloromethyl)-4,4-dimethyl-1,3-oxathiane with this thiol seems unlikely, since the ir spectrum was consistent only with the α -hydroxy sulfide structure and since no water formation was detected, even after the product had been kept in methylene chloride for 4 days. In this case, equilibration following either reaction of the aldehyde and thiol or dissociation of the adduct seemed to occur about ten times faster with the hydroxythiol than with 2-methyl-2-propanethiol. The observations of a more noticeable exothermic reaction and a more rapid occurrence of equilibration for systems with a higher value of K were consistent with impressions from the studies using 1-propanethiol.

Experimental Section¹²

Determination of Values of K .—For each carbonyl compound studied, either the C=O ir stretching frequency or an appropriate uv absorption maximum was used to construct a Beer's Law curve and this in turn was used to determine residual content of carbonyl compound after reaction with the thiol; therefrom, the constant K , measured at equilibrium (*i.e.*, at constancy of absorbance) for the particular reaction, was calculated using

$$K = [R^2R^3C(OH)SR^1]/[R^2R^3CO][R^1SH] \quad (2)$$

which $[R^2R^3CO]$ was taken as the concentration of carbonyl compound measured, $[R^2R^3C(OH)SR^1]$ as equal to the decrease in $[R^2R^3CO]$, and $[R^1SH]$ as $[R^1SH]$ initial - $[R^2R^3C(OH)SR^1]$. Measurements and calculations were carried out in the same fashion irrespective of whether the thiol and carbonyl compounds were first mixed in CH_2Cl_2 or, for dissociation, were first mixed neat and later diluted (dissociation then usually being evidenced by increased absorption on standing). Simultaneous observations of semiquantitative kinetic and other characteristics also were made, and comments on these are made below.

(12) Infrared spectra were obtained using a Beckman Model IR-10 spectrophotometer with a matched pair of 0.1-mm NaCl cavity cells. Unless otherwise specified, methylene chloride (Matheson Coleman and Bell "Spectro-quality") was used as solvent. Ultraviolet or visible spectra were obtained using a Cary Model 14 spectrophotometer. All starting materials were the best commercial grades, unless otherwise mentioned; they were suitably purified when necessary.

(11) J. Hine, "Physical Organic Chemistry," McGraw Hill Book Co., Inc., New York, N. Y., 1962, p 97.

In several experiments using di- or tricarbonyl compounds, overlapping C=O bands in the ir hindered accurate quantitative measurements and, consequently, K values were measured, in these instances, using absorption bands in the visible or uv regions.

Description of an experiment will illustrate the general methods used and some of the deviations necessary. Freshly redistilled diethyl oxomalonate (0.428 g, 2.46 mmol) and 1-propanethiol (0.443 g, 5.82 mmol; approximately 2.4 molar proportions) were mixed. (This method was usually followed as an alternative to mixture in solution, as a convenient check, because formation of the product is rapid and more nearly complete, and because by use of the neat reactants dissociation of a product was involved and the equilibration seemed more certain.) There was evolution of much heat and the diethyl oxomalonate was immediately decolorized. After 20 min the mixture was made up to 25 ml with CH_2Cl_2 and the spectrum of the solution was examined. The absorption bands at 1770 (shoulder) cm^{-1} in the ir and the uv absorption band at 369 $\text{m}\mu$ ($\log \epsilon$ 1.49) had disappeared. The ir spectrum showed bands at 3490 (OH), 1035 (C—OH), and 1750 (ester —CO—) cm^{-1} . Because of the proximity of the ir absorption of the ketone carbonyl (1770 cm^{-1}) to that of the ester, only an approximate minimum value of K could be determined by the ir technique. K was better approximated using a uv band at 369 $\text{m}\mu$ ($\log \epsilon$ 1.49). When equilibrium was assured by constancy of the uv spectrum (*ca.* 1 hr in this instance) the amount of residual oxomalonate was too small to be measured. An estimate from the Beer's law plot suggested that a concentration of 0.0003 mol/l. would have been barely detectable and this value was used for $[\text{R}^2\text{R}^3\text{CO}]$ in eq 2; taking $[\text{R}^2\text{R}^3\text{C}(\text{OH})\text{SR}^1]$ as 0.0981 mol/l. and $[\text{R}^1\text{SH}]$ as 0.1347 mol/l. thus gave $K = 2.4 \times 10^3$; the actual value must have exceeded this. The value of $>10^4$ (Table I) was obtained similarly but at a higher concentration. Subsequent passage of HCl caused no changes in the ir spectrum and no visible formation of water, hence the conclusion (Table I) that the α -hydroxy sulfide was unchanged.

Reaction of Particular Carbonyl Compounds with 1-Propanethiol. A. **Ketones.** Acetone.—In the absence of HCl there was no diminution of carbonyl absorption in the ir. The mercaptole was formed when HCl gas was introduced, as evidenced by an exothermic reaction, by formation of water (none visible earlier), and by ir spectral changes not attributable to formation of an α -hydroxy sulfide.

sym-Dichloroacetone.—This reacted rapidly and exothermically with 1-propanethiol, liberating both HCl and H_2O ; an intense red color developed within minutes. The ir spectrum suggested formation of an unstable mercaptole, but the cause of the red color is not understood. Perhaps this reaction is autocatalyzed by acid.

1,1,1-Trifluoroacetone.—Surprisingly, the ir spectrum showed that, in the absence or presence of HCl, no reaction occurred.

Hexafluoroacetone.—The reaction of hexafluoroacetone with 1-propanethiol was followed by the procedure described in footnote *f* of Table I. Because of the slight solubility of hexafluoroacetone in CH_2Cl_2 the concentration of the carbonyl compound had to be estimated using a Beer's law curve constructed for acetone or hexachloroacetone. Because of the nature of these assumptions the calculated value of K should be regarded as approximate at best. Interestingly, 7.3 g of the liquid hemimercaptole of hexafluoroacetone and 1-propanethiol disappeared in 5 hr at a pressure of 5 mm and in 30 min at one of 1 mm (*ca.* 28°); there was no ebullition, but the hemimercaptole could be recovered in a receiver cooled with liquid N_2 .

Hexafluoroacetone Trihydrate.—No reaction was apparent with 1-propanethiol in the absence or presence of HCl. This illustrates the high stability of such hydrates; it can be compared with our observation that trifluoroacetaldehyde hydrate did not react with 2-aminoethanethiol hydrochloride.¹⁰

Hexachloroacetone.—No reaction occurred with 1-propanethiol in the absence or presence of HCl under any conditions tried.

Diethyl Oxomalonate.—This ester was freshly redistilled from its hydrate over P_2O_5 .¹³ It reacted extremely rapidly and exothermically with 1-propanethiol giving the α -hydroxy sulfide as described above. Study of the reaction in the uv of a 0.0163 M

solution of diethyl oxomalonate in CH_2Cl_2 with a 0.042 M solution of 1-propanethiol in CH_2Cl_2 suggested a time of half-reaction of *ca.* 8 min.

Pyruvic Acid.—An exothermic reaction occurred with 1-propanethiol. An ir spectrum of the neat mixture suggested some conversion into the α -hydroxy sulfide. However, on dilution with CHCl_3 , the α -hydroxy sulfide dissociated almost completely; the value of K obtained after dissociation is given in Table I. In the presence of HCl, some conversion into the mercaptole was achieved.

Ethyl Acetoacetate.—The α -hydroxy sulfide could not be detected in the neat state or in CH_2Cl_2 . A neat mixture of the carbonyl compound and 1-propanethiol gave, in the presence of HCl, a typical exothermic reaction in which water was formed. Examination of the ir spectrum of a CH_2Cl_2 solution of the mixture then suggested virtually complete conversion into the mercaptole.

Indan-1,2,3-trione.—This compound was insufficiently soluble in CH_2Cl_2 for accurate ir measurements, although the α -hydroxy sulfide formed when it reacted with 1-propanethiol was quite soluble in CH_2Cl_2 . Coupled with this, the presence of three carbonyl bands at 1730, 1750, and 1760 cm^{-1} in the ir spectrum of indan-1,2,3-trione in CH_2Cl_2 made interpretation of changes in this region difficult. As a consequence of these observations, benzene was used as solvent, advantage being taken of the maximum of the triketone at 612 $\text{m}\mu$ ($\log \epsilon$ 1.46). The reaction neat of the purple triketone with 1-propanethiol was exothermic and, within seconds, gave solid α -hydroxy sulfide as pale yellow needles. The C—OH frequency of the product was displaced by over 80 cm^{-1} from the usual range and no definite assignment could be made.

B. Aldehydes. Phenylglyoxal Monomer.—This was distilled from phenylglyoxal hydrate or from polyphenylglyoxal.¹⁴ The monomer was used within 24 hr of distillation. Its reaction with 1-propanethiol forming an α -hydroxysulfide was rapid and exothermic, decolorization being virtually instantaneous. The ketone carbonyl absorption at 1680 cm^{-1} overlapped at its base with the aldehyde carbonyl absorption at 1738 cm^{-1} and quantitative measurement by ir of K was not precise. However, by using the absorption maximum at 425 $\text{m}\mu$ ($\log \epsilon$ 1.32) of phenylglyoxal in CH_2Cl_2 a minimum K value of 10^8 was obtained. After saturation of the mixture with HCl, no conversion into mercaptal or mixed mercaptal-mercaptole was observed. Although conversion into α -hydroxy sulfide was essentially complete, solutions were pale yellow, apparently because of the tail of an intense absorption band in the near-uv.

Bromal.—Mixture with 1-propanethiol in the usual way (neat) gave an α -hydroxy sulfide which was stable in CH_2Cl_2 for several days (no change in the ir spectrum). In the presence of HCl the mixture gradually became brown and H_2O separated; the brown solution then showed an unexplained second ir absorption maximum at 1732 cm^{-1} in addition to the maximum of bromal at 1748 cm^{-1} . Treatment with HCl resulted in the complete and immediate loss of the absorption maxima of the α -hydroxy sulfide at 3525 and 1040 cm^{-1} . These results suggest the formation of an unstable mercaptal, although side reactions may have been significant.

Chloral.—Chloral reacted rapidly and exothermically in the neat state with 1-propanethiol, 2-acetamidoethanethiol, or 1-dodecanethiol⁹ to give the respective α -hydroxy sulfides. The α -hydroxy sulfides from 1-propanethiol and 1-dodecanethiol absorb in the ir at 3540, 1055, and 1763 (weak) cm^{-1} , while, in the spectrum of the α -hydroxy sulfide from 2-acetamidoethanethiol, the corresponding frequencies occur at 3450 and 1085 cm^{-1} . A solution of chloral (0.2 M) in CH_2Cl_2 equilibrated with 1-propanethiol (0.3 M) within 1 day and with 2-acetamidoethanethiol (0.3 M) within 4 days, but no reaction whatever could be detected with 1-dodecanethiol after 14 days. In the presence of acid catalyst (HCl saturation or 0.2 M with respect to boron trifluoride etherate) in CH_2Cl_2 , 1-propanethiol and 2-acetamidoethanethiol reacted rapidly to give the α -hydroxy sulfides, but the trend of decreasing —CO— absorbance suggested that 1-dodecanethiol would have taken at least 300 days to equilibrate. The α -hydroxy sulfide from 1-dodecanethiol was prepared using the method of Frank, Drake, Smith, and Stevens⁹ and came to equilibrium in CH_2Cl_2

(13) R. S. Curtiss and E. K. Stracham, *J. Amer. Chem. Soc.*, **33**, 396 (1911).

(14) H. A. Riley and A. R. Gray, "Organic Syntheses," Coll. Vol. II, John Wiley & Sons, Inc., New York, N. Y., 1943, p 509.

containing boron trifluoride etherate (0.2 *M* solution) in about 3 days. The calculated *K* was about 10^2 , in contrast to the value of $3-8 \times 10^2$ for the reactions of 1-propanethiol or 2-acetamidoethanethiol. The value of $3-8 \times 10^2$ compares favorably with those of $4-6 \times 10^2$ measured by Johns and Hixon for the reaction of chloral with ethanethiol or 1-butanethiol using a freezing point depression method.⁴

The reaction of chloral with 2-methyl-2-propanethiol also was studied for comparison and gave a *K* of *ca.* 1.5×10^2 in CH_2Cl_2 ; the spectrum of the α -hydroxy sulfide which resulted had maxima at 3540 and 1055 cm^{-1} . The time of equilibration (*ca.* 2 days) of the neat chloral-thiol mixture appeared to be about double that of the corresponding chloral-1-propanethiol mixture. The reaction of the tertiary thiol $\text{HSC}(\text{CH}_3)_2\text{CH}_2\text{CH}_2\text{OH}$ with chloral gave a *K* value of 1.3×10^3 , the time of equilibration under the conditions used with 2-methyl-2-propanethiol being about 4 hr. The ir spectrum of this α -hydroxy sulfide had maxima at 3520 and 1085 cm^{-1} .

Acetaldehyde.—This did not react in any amount detected with 1-propanethiol, 2-acetamidoethanethiol, or 1-dodecanethiol

in CH_2Cl_2 in the absence of acid. In the presence of HCl or boron trifluoride etherate the corresponding mercaptal formed (see footnote *e*, Table I).

Formaldehyde.—Paraldehyde or *s*-trioxane with 1-propanethiol showed no reaction. In the presence of HCl, exothermic conversion into mercaptal occurred.

Benzaldehyde.—In the absence of HCl, slight conversion into an α -hydroxy sulfide occurred, as indicated by diminution in the $-\text{CO}-$ absorption at 1700 cm^{-1} and by weak absorptions produced at 3510 and 1100 (1085) cm^{-1} . In the presence of HCl, substantial conversion into the expected mercaptal occurred.

Pentafluorobenzaldehyde.—This gave a reaction similar to that given by benzaldehyde, the spectrum of the mixture in CH_2Cl_2 having absorption maxima of medium intensity at 3575 and 1025 cm^{-1} . However, the calculated *K* was only 5×10^2 (benzaldehyde, 5×10^3). This lower *K* than expected must be due to a cancellation of electronic effects on the aromatic ring.

Registry No.—1-Propanethiol, 107-03-9.

Methanesulfenyl Chloride. V. The Spontaneous Decomposition of Methanesulfenyl Chloride and Methylsulfur Trichloride^{1a}

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Methanesulfenyl chloride, CH_3SCl , on standing for a few hours at room temperature begins to decompose into methyl chloride, methyldisulfur chloride, methyl disulfide, methyl trisulfide, and methyl tetrasulfide as major products as indicated by the nmr spectra of decomposition mixtures. Minor peaks in the spectrum correspond to the δ chemical shifts of methyl chloromethyl disulfide and dichloromethyl methyl sulfide. Other products were hydrogen chloride, sulfur dichloride, elementary sulfur, and, in some cases, on long standing an unidentified solid. Methylsulfur trichloride decomposes rapidly when the crystalline solid is heated a few degrees above room temperature. The nmr spectrum of the decomposition mixture indicates that the principal products are chloromethanesulfenyl chloride (*ca.* 60%) and methanesulfenyl chloride (*ca.* 20%). Other products identified by their peaks in the nmr spectrum are methyldisulfur chloride, methyltrisulfur chloride, methyltetrasulfur chloride, bischloromethyl disulfide, and dichloromethanesulfenyl chloride. In addition, hydrogen chloride and sulfur dichloride were also products of the decomposition. Uncertainty exists as to whether the decomposition of CH_3SCl takes place by an ionic or free-radical mechanism. An esr study of the decomposition showed no signals to indicate an appreciable concentration of free radicals. Methyl disulfide, irradiated at liquid nitrogen temperature, produced an esr spectrum with clearly defined signals believed to indicate the $\text{CH}_3\text{S}\cdot$ radical. This radical appears to be highly reactive and cannot be stabilized on Vycor glass at room temperature. The failure to observe esr signals in decomposing CH_3SCl may possibly be due to the high reactivity of radical intermediates resulting in a low steady state concentration.

Methanesulfenyl chloride, CH_3SCl , and methylsulfur trichloride, CH_3SCl_3 , are two highly reactive compounds which, if treated properly, enter into stoichiometric reactions and yield products which can be isolated in high yield.^{2,3} If CH_3SCl is allowed to stand a few hours, or if CH_3SCl_3 is warmed only a few degrees above room temperature, however, the compounds undergo profound decompositions, yielding mixtures which defy separation or analysis by conventional means.

Since the two original compounds contain single carbon atoms, most of the decomposition products are

capable of yielding sharp singlet peaks in the nmr spectra. Recent experience in our laboratory as well as previous studies by others have shown that nmr affords an excellent means for identifying individual closely related sulfur compounds in complex mixtures.^{4,5}

Although there remain a number of uncertainties regarding the identity of some products formed in the decompositions, and the mechanisms by which the products are formed, it seems appropriate to report at this time the products identified. Later work may clarify some of the unsolved questions but the departure of the junior authors and the stinking character of the materials involved discourage further work at the present time.

There are previous reports concerning the instability of these compounds. In his original description of

(1) (a) Taken in part from the Ph.D. Thesis of R. V. Norton, University of Maine, 1967, and from the M. S. Thesis of R. L. Weichman, University of Maine, 1966. (b) To whom inquiries concerning this paper may be sent. (c) To whom the senior author is indebted for carrying out the esr study of the decomposition of CH_3SCl at Princeton University.

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