by the addition of water, dissolved in ethyl acetate, and washed with 15-ml portions of 1 *N* sodium bicarbonate, water, 1 *N* hydrochloric acid, and water. The solution was filtered through sodium sulfate, evaporated, and crystallized from ethyl acetate–ether to yield 1.52 g, mp 178.5–181° (37.5%) of XXIII. Recrystallization from ethyl acetate raised the melting point to 184–185°, $[\alpha]^{24}D$ −17.2° (*c* 1, DMF).

Anal. Calcd for $C_{50}H_{49}N_3O_6S_2$: C, 70.73; H, 5.86; N, 4.91; S, 7.67. Found: C, 70.48; H, 5.79; N, 4.93; S, 7.53.

The tripeptide derivative (XXIII) was also prepared in 62% yield from the reaction of *p*-nitrophenyl N-carbobenzoxy-S-trityl-L-cysteinate with the crude hydrobromide derivative. The sample of XXIII obtained by this procedure melted at 183.5–185°, $[\alpha]^{24}D$ −17.2° (*c* 1, DMF). A mixture melting point with XXIII obtained *via* the DCC method was not depressed.

Benzhydryl S-Benzhydryl-L-cysteinylglycinate Tosylate (XXIVa).—A mixture of 2.35 g (5 mmoles) of XXI and 2.07 g (5 mmoles) of benzhydrylglycinate tosylate in 30 ml of chloroform was treated with 1.03 g (5 mmoles) of DCC. The reaction mixture was stirred at 0° for 1 hr and at room temperature for 15 hr. The filtered reaction mixture was dissolved in 30 ml of acetone, filtered, and treated with 5.4 ml of 1 *N* hydrochloric acid. After 15 min the solvent was evaporated and the residue was treated with 20 ml of 0.25 *N* sodium hydroxide followed by 50 ml of ether. The ether layer was washed with water, dried, and treated with 0.95 g (5 mmoles) of *p*-toluenesulfonic acid. The ether was removed and the residue was crystallized from a methylene chloride–ether mixture to give 1.48 g (44%) of XXIV as a white powder: mp 152–153°; $[\alpha]^{20}D$ 16.6° (*c* 1, DMF); paper chromatography, one spot (ninhydrin) R_f 0.96 (system A).

Anal. Calcd for $C_{38}H_{38}N_2O_6S_2$: C, 66.84; H, 5.61; N, 4.10; S, 9.39. Found: C, 66.63; H, 5.88; N, 4.27; S, 9.24.

Benzhydryl N-Carbobenzoxy-S-trityl-L-cysteinyl-S-benzhydryl-L-cysteinylglycinate (XXVa).—A mixture of 1.14 g (2 mmoles) of N-carbobenzoxy-S-trityl-L-cysteine N,N-diethylamine salt and 1.33 g (2 mmoles) of XXIVa in 20 ml of chloroform was treated with 0.41 g (2 mmoles) of DCC. The reaction mixture was stirred at 0° for 1 hr and at room temperature for 22 hr. The filtered solution was washed with 5-ml portions of 5% sodium bicarbonate, water, 1 *N* hydrochloric acid, and water, and dried. Removal of the solvent and crystallization of the residue from ethyl acetate gave 1.15 g (59%) of XXVa, mp 184–185°, $[\alpha]^{20}D$ −27.8° (*c* 1, DMF).

Anal. Calcd for $C_{60}H_{55}N_3O_6S_2$: C, 73.67; H, 5.67; N, 4.30; S, 6.56. Found: C, 73.85; H, 5.87; N, 4.49; S, 6.54.

***p*-Nitrophenyl S-Benzhydryl-L-cysteinylglycinate Tosylate Salt (XXIVb).**—A mixture containing 6.12 g (13.2 mmoles) of XXI and 3.66 g of *p*-nitrophenylglycinate hydrobromide in 60 ml of chloroform was treated with 2.72 g (13.2 mmoles) of DCC; the mixture was stirred at 0° for 1 hr and at room temperature for 14 hr. The filtrate from the reaction mixture was evaporated and the residue was dissolved in 40 ml of acetone. The solution was treated with 1.44 g (13.2 mmoles) of *p*-toluenesulfonic acid monohydrate and the product XXIVb was collected: 4.2 g (50%); mp 167–168°; $[\alpha]^{20}D$ 21.5° (*c* 1, DMF); paper chromatography, one spot (ultraviolet analysis, ninhydrin) R_f 0.92 (system A).

Anal. Calcd for $C_{31}H_{31}N_3O_8S_2$: C, 58.38; H, 4.90; N, 6.59; S, 10.06. Found: C, 58.29; H, 4.87; N, 6.48; S, 10.26.

***p*-Nitrophenyl N-Carbobenzoxy-S-trityl-L-cysteinyl-S-benzhydryl-L-cysteinylglycinate (XXVb).**—A solution containing 1.14 g (2 mmoles) of N-carbobenzoxy-S-trityl-L-cysteine and 1.27 g (2 mmoles) of XXIVb in 20 ml of chloroform was treated with 0.41 g (2 mmoles) of DCC. The mixture was stirred for 1 hr at 0° and at room temperature for 17 hr. The filtered reaction mixture was washed with 5-ml portions of 5% sodium bicarbonate, water, 1 *N* hydrochloric acid, and water, and dried. Removal of the chloroform and crystallization of the residue from ethyl acetate provide 1.13 g (71%) of XXVb, mp 187–190°, tlc homogeneous (system B), $[\alpha]^{20}D$ −11.1° (*c* 1, DMF).

Anal. Calcd for $C_{54}H_{48}N_4O_8S_2$: C, 68.62; H, 5.12; N, 5.93; S, 6.79. Found: C, 68.76; H, 5.65; N, 6.02; S, 6.89.

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The Reaction of Methanesulfenyl Chloride with Alkoxides and Alcohols. Preparation of Aliphatic Sulfenate and Sulfinate Esters

T. L. MOORE AND D. E. O'CONNOR

The Procter and Gamble Company, Miami Valley Laboratories, Cincinnati, Ohio 45239

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Methanesulfenyl chloride reacts with an equimolar or greater ratio of lithium *n*-pentyloxide, 4-methyl-2-pentyloxide, or *t*-butoxide in 1,2-dimethoxyethane at −40 to −60° to give the corresponding methanesulfenate esters, CH_3SOR, in 40–75% yields. Keys to the successful isolation of the sulfenate esters are use of the alkoxide rather than alcohol and the strict avoidance of an excess of sulfenyl chloride. When a 0.5 *M* excess of methanesulfenyl chloride is employed with lithium *n*-pentyloxide or 4-methyl-2-pentyloxide, the corresponding sulfinate esters, $CH_3\overset{\overset{O}{\uparrow}}{S}OR$, are formed in good yield. However, reaction with lithium *t*-butoxide gives the sulfenate ester, even with an excess of methanesulfenyl chloride. The methanesulfenate esters derived from primary and secondary alcohols are converted by air, or most oxidizing agents, to the corresponding sulfinate esters. These results are interpreted in terms of competition between sulfenate ester and alkoxide or alcohol for methanesulfenyl chloride.

Sulfenate esters, RSOR′, in which R is aromatic[1] or halogenated alkyl[2] are well known. However, we are aware of only two references to isolation of a sulfenate ester in which R and R′ are simple aliphatic groups—the preparation of **1** by the route indicated in eq 1[3]

$$C_2H_5SSCN + NaOC_2H_5 \longrightarrow \underset{\mathbf{1}}{C_2H_5SOC_2H_5} + NaSCN \quad (1)$$

$$(t\text{-}C_4H_9S\text{-})_2Hg + 2I_2 \longrightarrow HgI_2 + 2t\text{-}C_4H_9SI \xrightarrow{C_2H_5O^-} \underset{\mathbf{2}}{2t\text{-}C_4H_9SOC_2H_5} \quad (2)$$

and of **2** by the route of eq 2.[4] A more recent attempt by Douglass to prepare methyl methanesulfenate by reaction of methanesulfenyl chloride with methanol

(1) N. Kharasch, S. J. Potempa, and H. L. Wehrmeister, *Chem. Rev.*, **39**, 269 (1946); N. Kharasch, D. P. McQuarrie, and C. M. Buess, *J. Am. Chem. Soc.*, **75**, 2658 (1953).

(2) F. A. Drahowzal in "Organic Sulfur Compounds," Vol. I, N. Kharasch, Ed., Pergamon Press Inc., New York, N.Y., 1961, p 361, and references therein.

(3) A. Meuwsen and H. Gebhardt, *Ber.*, **70**, 792 (1937). The remarkable stability of $C_2H_5SOC_2H_5$ to "autoxidation," SeO_2, N_2O_4, and $KMnO_4$ described by these authors casts some doubt on the accuracy of their structural assignment in light of the instability to oxidation that we observed for primary, secondary, and tertiary methanesulfenates.

(4) (a) H. Rheinboldt and E. Motzkus, *ibid.*, **72**, 657 (1939); H. Rheinboldt, *Rev. Brasil. Chim.* (São Paulo), **4**, 169 (1937); *Chem. Abstr.*, **32**, 484 (1938); (b) J. A. Barltrop, P. M. Hays, and M. Calvin, *J. Am. Chem. Soc.*, **76**, 4348 (1954).

TABLE I

PREPARATION AND PROPERTIES OF SOME SULFENATE (CH_3SOR) AND SULFINATE ($CH_3\overset{O}{\overset{\uparrow}{S}}OR$) ESTERS

Compd	Structure	Yield, %	Bp, °C (mm)	C, % Calcd	C, % Found	H, % Calcd	H, % Found	S, % Calcd	S, % Found	O (direct), % Calcd	O (direct), % Found
3	$CH_3SOC_5H_{11}$	35, 74[a]	57–58 (15)	53.7	53.4	10.5	10.5	23.8	23.7	11.9	12.7
4	$CH_3SOCHCH_2CH(CH_3)_2$ (CH₃ branch)	48	57.5 (17)	56.7	54.5	10.8	10.4	21.6	21.6	10.8	10.9
5	$CH_3SOC(CH_3)_3$	45	53 (75)		[b]						
6	$CH_3\overset{O}{\overset{\uparrow}{S}}OC_5H_{11}$	84	95–96 (15)	48.0	47.4	9.3	9.1	21.3	21.5	21.3	22.1
7	$CH_3\overset{O}{\overset{\uparrow}{S}}OCHCH_2CH(CH_3)_2$ (CH₃ branch)	77	97 (15)	51.2	50.5	9.7	9.7	19.5	19.5	19.5	20.5

[a] Using a 2:1 ratio of lithium pentyloxide to methanesulfenyl chloride. [b] We were unable to obtain satisfactory analyses for this compound, although spectroscopic data indicated high purity. The sulfenate esters exploded during combustion on several occasions, and with **5** mild combustion conditions gave low carbon values indicating incomplete combustion of the tertiary butyl group.

gave methyl chloride, dimethyl disulfide, methyl methanethiosulfonate, and hydrogen chloride.[5]

We have examined in some detail the reactions of methanesulfenyl chloride with alcohols and alkoxides and report the preparation and some of the properties of the sulfenate and sulfinate esters formed.

Results

The results are presented in sequence for three different sets of reaction conditions which, while superficially of the same general reaction type, give strikingly different reaction products. These are as follows: (A) addition of methanesulfenyl chloride to 1 equiv or more of an alkoxide; (B) addition of a 0.5 *M* or greater excess of methanesulfenyl chloride to an alkoxide; and (C) addition of methanesulfenyl chloride to an alcohol. The methanesulfenyl chloride was prepared by the direct, low-temperature chlorination of dimethyl disulfide.[5a]

(A) The addition of 1 equiv or less of methanesulfenyl chloride to a soluble alkoxide in ethereal solvent at temperatures of −20 to −60° gave moderate yields of the sulfenate esters (eq 3). Table I summarizes the

$$CH_3SCl + LiOC_5H_{11} \longrightarrow CH_3SOC_5H_{11} + LiCl \quad (3)$$

preparation and some of the properties of three methanesulfenate esters of representative primary, secondary, and tertiary alcohols. The yields of sulfenate esters listed in Table I are from reactions employing a 1:1 stoichiometry. Use of a 2:1 *M* excess of *n*-pentyloxide led to an increase in sulfenate ester yield from 35 to 74%, based on sulfenyl chloride (this is consistent with the reaction scheme as is presented in the Discussion).

(B) When the reaction was run using a 1.5:1 or greater ratio of methanesulfenyl chloride to lithium *n*-pentyloxide or 4-methyl-2-pentyloxide, the corresponding sulfinate ester was formed in good yield (eq 4).[6] However, reaction with lithium *t*-butoxide under the same conditions gave the sulfenate ester in 35% yield and no sulfinate. This procedure is a convenient method for preparing primary and secondary sulfinate esters, although one-half of the alkoxide and two-thirds of the methanesulfenyl chloride are converted to other products. The yields of sulfinate esters reported in Table I were calculated from the stoichiometry of eq 4.

$$3CH_3SCl + 2LiOR \longrightarrow CH_3\overset{O}{\overset{\uparrow}{S}}OR + CH_3SSCH_3 + RCl + 2LiCl \quad (4)$$

When *n*-pentyl or 4-methyl-2-pentyl methanesulfenate was allowed to react with a 0.5 mole ratio of methanesulfenyl chloride under the same conditions (low temperature, 1,2-dimethoxyethane solvent), the same products, excepting lithium chloride, were formed (eq 5). In a typical experiment, reaction of 0.005

$$CH_3SCl + 2CH_3SOR \longrightarrow CH_3\overset{O}{\overset{\uparrow}{S}}OR + CH_3SSCH_3 + RCl \quad (5)$$

R = *n*-C_5H_{11}, $CH(CH_3)CH_2CH(CH_3)_2$

mole of sulfenyl chloride with 0.01 mole of sulfenate ester gave 0.0045 mole of sulfinate ester, 0.0041 mole of disulfide, and 0.0039 mole of alkyl chloride, thus providing the basis for the stoichiometry of eq 4 and 5.

In order to test the possibility that a thiolsulfinate is an intermediate in the reaction shown in eq 5, methyl methanethiolsulfinate was prepared by a variation of the method of Small, *et al.*,[7] and was treated with *n*-pentyl methanesulfenate (**3**). These two materials reacted rapidly at 0 to −10° in methylene chloride to give *n*-pentyl methanesulfinate (**6**) and dimethyl disulfide (eq 6), thus fulfilling the requirement of such an intermediate (see Discussion).

(5) (a) I. B. Douglass, *J. Org. Chem.*, **24**, 2004 (1959); (b) I. B. Douglass and D. A. Koop, *ibid.*, **27**, 1398 (1962).

(6) Aliphatic and aromatic sulfinate esters are well known and are accessible by several routes. See I. B. Douglass, *ibid.*, **30**, 633 (1965), and references cited therein.

(7) (a) L. D. Small, J. H. Bailey, and C. J. Cavallito, *J. Am. Chem. Soc.*, **69**, 1710 (1947). We observed considerable difficulty in handling the thiolsulfinate; it appeared to decompose on standing at room temperature. The nmr of the freshly distilled product was consistent with that of methyl methanethiolsulfinate, but, after standing for 30 hr at room temperature, the nmr suggested a mixture consisting predominantly of dimethyl disulfide and methyl methanethiolsulfonate. The boiling point reported by Small, *et al.*, appears closer to that of the thiolsulfonate **12**; such a disproportionation would, of course, give a mixture with elemental analyses unchanged from those of the thiolsulfinate. (b) The disproportionation of ethyl ethanethiolsulfinate was shown to be acid catalyzed;[5b] J. L. Kice and G. B. Large [*Tetrahedron Letters*, **No. 40**, 3537 (1965)] and D. Barnard [*J. Chem. Soc.*, 4675 (1957)] have shown that aromatic thiolsulfinates undergo acid-catalyzed disproportionation.

$$\underset{\mathbf{3}}{CH_3SOC_5H_{11}} + CH_3\overset{\overset{O}{\uparrow}}{S}SCH_3 \longrightarrow \underset{\mathbf{6}}{CH_3\overset{\overset{O}{\uparrow}}{S}OC_5H_{11}} + \underset{\mathbf{11}}{CH_3SSCH_3} \quad (6)$$

An inverse addition experiment in which lithium *n*-pentyloxide in 1,2-dimethoxyethane was added to methanesulfenyl chloride at −50° gave only *n*-pentyl methanesulfinate, dimethyl disulfide, and *n*-pentyl chloride. These conditions were quite similar to those in the reaction of an excess of methanesulfenyl chloride with alkoxide in that an excess of the sulfenyl chloride was present in the reaction mixture and, as would be expected, the reaction followed the same course.

(C) The reaction of methanesulfenyl chloride with excess methanol or *n*-pentyl alcohol gave dimethyl disulfide, methyl methanethiolsulfonate, and methyl or *n*-pentyl chloride (eq 7), in agreement with the findings of Douglass.

$$4CH_3SCl + 2ROH \longrightarrow \underset{\mathbf{11}}{CH_3SSCH_3} + \underset{\mathbf{12}}{CH_3\overset{\overset{O}{\uparrow}}{S}SCH_3\overset{\overset{O}{\downarrow}}{}} + 2RCl + 2HCl \quad (7)$$

R = CH_3, *n*-C_5H_{11}

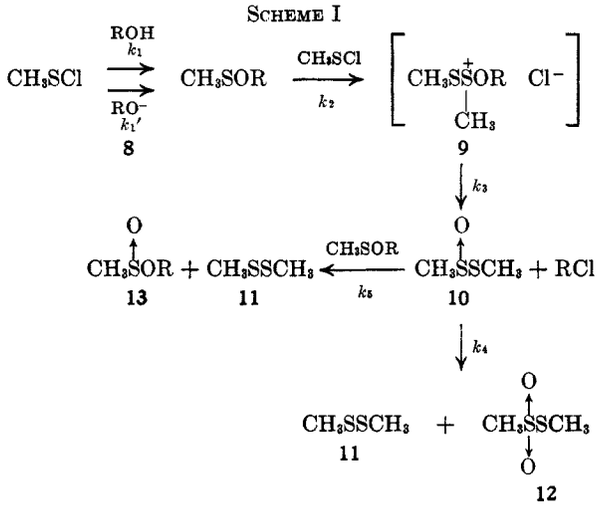
The reagent system of choice for the preparation of the sulfenate esters listed in Table I is lithium alkoxide in 1,2-dimethoxyethane. The anhydrous alkoxide solution is easily prepared by adding methyllithium in ether to a solution of alcohol in 1,2-dimethoxyethane. The lithium alkoxides are more soluble at low temperature in this solvent than in their parent alcohols. Since preparation of sulfenates depends upon the high reactivity of the alkoxide (see Discussion), it follows that solubility of the alkoxide is important. Hydrogen bonding in the protic solvent might also reduce the alkoxide reactivity relative to that in 1,2-dimethoxyethane. For example, a reaction using lithium *n*-pentyloxide in *n*-pentyl alcohol at −40° gave only a 14% yield of sulfenate ester. The other products of this reaction were the same as those obtained when an excess of methanesulfenyl chloride was used. Bis(2-methoxyethyl) ether is also a suitable solvent. Choice of solvent should be dictated by the ease of its separation from the desired product. Diethyl ether is a poorer solvent for the alkoxide, and lower yields of sulfenate esters were obtained with it.

These sulfenate esters were stable to distillation, and **4** and **5** were stable for long periods at room temperature without special handling. The primary sulfenate **3**, however, decomposed on standing at room temperature unless air was rigorously excluded. Compound **3** was rapidly converted to the sulfinate ester **6** when air was bubbled through it. Compounds **3**, **4**, and **5** rapidly reduced selenium dioxide to red selenium (*cf.* ref 3), decolorized potassium permanganate, and converted potassium dichromate to chromic ion. The sulfenate esters did not decolorize methanolic iodine solution, but did cause oxidation of an acidic methanolic potassium iodide solution (strong iodine color formed). The product formed in good yield from the oxidation of **3** with 1 equiv of methanolic potassium permanganate was the corresponding sulfinate ester **6**. Thus, the alkyl sulfenate esters behave as compounds of intermediate oxidation state which can be oxidized (to sulfinate ester and presumably to higher oxidation states) and reduced. (Their reaction products with iodide ion were not characterized but were presumably disulfide or mercaptan–disulfide mixtures.[8])

Discussion

The different courses of the reaction under conditions A, B, and C above can best be explained by reference to Scheme I. Reaction of methanesulfenyl chloride

SCHEME I



with a soluble or finely dispersed alkoxide proceeds as anticipated to give the desired sulfenate ester. When equivalent amounts of sulfenyl chloride and alkoxide are used, the principal side reaction which limits the yield of sulfenate ester is further reaction of the sulfenate with sulfenyl chloride. When the ratio of alkoxide to sulfenyl chloride is raised, the yield of sulfenate increases. This suggests that k_1' and k_2 are of similar magnitude and that increasing alkoxide concentration is simply increasing the rate of the alkoxide–sulfenyl chloride reaction at the expense of the competing sulfenate ester–sulfenyl chloride reaction.

When an excess of sulfenyl chloride is employed (case B) the sulfinate ester **13** is formed in good yield, but no sulfenate is isolated. Under these conditions, as in case A, **8** is apparently formed first. However, **8** can react with the excess sulfenyl chloride to give the thiolsulfinate **10** and alkyl chloride. The **10** can then react further with the remaining sulfenate ester which had built up in the early stages of the reaction to give the sulfinate ester **13** and dimethyl disulfide **11**.[9]

(8) The reaction of mercaptan with iodine to give disulfide is reversible. See E. E. Reid, "Organic Chemistry of Bivalent Sulfur," Vol. I, Chemical Publishing Co., New York, N. Y., 1958, p 124; J. R. Sampey and E. E. Reid, *J. Am. Chem. Soc.*, **54**, 3404 (1932); J. W. Kimball, R. L. Kramer, and E. E. Reid, *ibid.*, **43**, 1199 (1921).

(9) A possible alternative route for sulfinate ester formation is that proposed by Douglass[5b] who has shown that **10** can react with methanesulfenyl chloride to form dimethyl disulfide and methanesulfinyl chloride which could then react with alcohol or alkoxide to give the sulfinate ester. The difference in the two pathways centers around whether the thiolsulfinate **10** reacts with the sulfenate ester or the sulfenyl chloride. In cases A and B where sulfenyl chloride was added to alkoxide we favor the reaction of **10** with sulfenate ester because **10**, which must be present only in very low concentration, probably could not compete effectively with the alkoxide for sulfenyl chloride. The sulfenate ester, on the other hand, is present in substantial quantities during the reaction. However, we cannot exclude the other possibility and it is not apparent to us how one could easily distinguish between these two pathways, since the isolated steps of both have been demonstrated to be possible.

The first step of the proposed sequence whereby the sulfenate ester **8** is converted to **13** was tested by carrying out the reaction of *n*-pentyl methanesulfenate with methanesulfenyl chloride. The fact that these two materials reacted rapidly to give the expected products (eq 5) lends credibility to the proposed reaction path. This reaction of sulfenate with sulfenyl chloride is similar to the reactions of methanesulfenyl chloride with methyl thiolacetate, methyl methanethiolsulfonate, and ethyl ethanethiolsulfinate reported by Douglass[5a] and to the work of Morrison who showed that both trialkyl phosphites[10] **14** and esters of benzenephosphonous acid[11] **15** react rapidly with methanesulfenyl chloride to give alkyl chloride and good yields of the analogous tertiary phosphorothioates and thiophosphonates, respectively.

$$\underset{\mathbf{14}}{CH_3SCl + P(OR)_3} \longrightarrow [CH_3SP^+(OR)_3 + Cl^-] \longrightarrow RCl + CH_3S\overset{\overset{O}{\uparrow}}{P}(OR)_2 \quad (8)$$

$$CH_3SCl + \underset{\mathbf{15}}{C_6H_5P(OR)_2} \longrightarrow [CH_3S\overset{\overset{C_6H_5}{|}}{\underset{+}{P}}(OR)_2 + Cl^-] \longrightarrow RCl + CH_3S\overset{\overset{O}{\uparrow}}{\underset{\underset{C_6H_5}{|}}{P}}OR \quad (9)$$

No direct evidence for formation of **9** was obtained, presumably since it reacted too rapidly, even at low temperature, to be isolated. However, **9** seems to be the most reasonable intermediate from reaction of **8** and sulfenyl chloride.[12]

Some evidence bearing on the intermediacy of the thiolsulfinate **10** in the proposed sequence was obtained. Compound **10** was prepared independently[7a] and was found to react rapidly with **8** to form the sulfinate **13** and disulfide **11**. Unless stored at Dry Ice temperature, **10** decomposed on standing to give principally dimethyl disulfide **11** and thiolsulfonate **12**[7] (eq 10). Since **10**

$$\underset{\mathbf{10}}{2CH_3\overset{\overset{O}{\uparrow}}{S}SCH_3} \longrightarrow \underset{\mathbf{12}}{CH_3\overset{\overset{O}{\uparrow}}{\underset{\underset{O}{\downarrow}}{S}}SCH_3} + \underset{\mathbf{11}}{CH_3SSCH_3} \quad (10)$$

readily undergoes disproportionation and readily oxidizes sulfenate to sulfinate (eq 6), it fulfills both requirements for its participation in Scheme I.

The different course of the reaction in the two cases B and C can best be explained as follows. When methanesulfenyl chloride is added to an alcohol (case C), the methanesulfenate is formed just as in the alkoxide reaction. However, the sulfenate ester thus formed reacts faster with the remaining sulfenyl chloride than the alcohol does and this reaction leads to **10**, just as in case B. It is at this point that the courses of the two reactions differ. In case C hydrogen chloride is formed from the sulfenyl chloride–alcohol reaction and probably exerts a strong catalytic effect on the disproportionation reaction (k_4).[7b] In the absence of hydrogen chloride (case B), $k_5 > k_4$; *i.e.*, **10** reacts much more rapidly with **8** to give **13** than it disproportionates to give **12**. However, when hydrogen chloride is present to catalyze the disproportionation, $k_4 > k_5$. A second factor that could be involved is the difference in concentration of sulfenate ester **8** in the two cases. The reaction of methanesulfenyl chloride with alcohol (case C) is probably much slower than its reaction with alkoxide (case B) so that the concentration of **8** is much lower in case C. Its lower concentration would reduce its rate of reaction with **10**, thus making the disproportionation reaction more favorable.

Of these two possibilities, the presence of acid appears to have much the greater effect on the course of the reaction. The great effect of acid was demonstrated by carrying out the alcohol–sulfenyl chloride reaction in the presence of a base (pyridine) that would remove the acid as it was formed, but which was not strong enough to form the alkoxide ion from the alcohol. When the reaction of methanesulfenyl chloride with *n*-pentyl alcohol was carried out in the presence of pyridine, the sulfinate ester **13** was formed in 35% yield (based on the stoichiometry of eq 4) while less than 2% of the thiolsulfonate **12** was obtained. The inverse addition experiment described above also bears on this point. The addition of the alkoxide to the methanesulfenyl chloride would ensure that the concentration of sulfenate ester **8** was low. Still, under these conditions, the sulfinate, not the thiolsulfonate, was formed. Thus, the available evidence indicates that the critical difference between the reactions of case B and case C is the presence of acid in the latter.

In summary, the scheme shown in Scheme I accounts very nicely for the different reaction courses followed under conditions A B, and C in terms of well-accepted principles. For example, it is quite reasonable to expect alkoxide to react much more rapidly than alcohol with methanesulfenyl chloride. Furthermore, the reaction of methanesulfenyl chloride with sulfenate ester has been shown to give the sulfinate ester, dimethyl disulfide, and an alkyl chloride as required by the reaction scheme. Finally, the proposed intermediate thiosulfinate **10**, which by Scheme I is the required precursor to the products observed in cases B and C, has been prepared and shown to form these products rapidly under the reaction conditions of B and C.

Experimental Section

Nmr spectra were obtained on 5–10% solutions in carbon tetrachloride using a Varian HA-100 spectrometer and are reported in τ units. Infrared spectra were obtained on a Perkin-Elmer Infracord spectrophotometer.

Methanesulfenyl Chloride.—Methanesulfenyl chloride was prepared by the reaction of dimethyl disulfide with chlorine at low temperature to give methanesulfenyl chloride directly.[5a] The methanesulfenyl chloride so formed can be stored for several weeks in a closed container at Dry Ice temperature without change in appearance. However, the yield of sulfenate ester was much reduced when using sulfenyl chloride which had been stored in this manner for 4 weeks. Samples of the sulfenyl chloride prepared by the direct chlorination procedure were titrated with 0.10 N sodium hydroxide, consuming exactly 1.33 equiv

(10) D. C. Morrison, *J. Am. Chem. Soc.*, **77**, 181 (1955).

(11) D. C. Morrison, *J. Org. Chem.*, **21**, 705 (1956).

(12) Compound **9** is pictured as an ionic intermediate, but we do not mean to preclude the possibility that the reaction may be concerted or involve a tight ion pair. In this regard it should be noted that the reaction of **3** or **4** with methanesulfenyl chloride remained homogeneous in 1,2-dimethoxyethane or methylene chloride even at low temperature where an ionic species such as **9** might be expected to crystallize. Furthermore, no dialkyl ether, which would arise from reaction of **9** with alcohol instead of chloride ion, was observed even when a large excess of alcohol was allowed to react with methanesulfenyl chloride.

of hydroxide per sulfenyl chloride as predicted,[13] indicating that the crude sulfenyl chloride was of very high purity.

n-**Pentyl Methanesulfenate.**—*n*-Pentyl alcohol (17.6 g, 0.20 mole) was dissolved in 100 ml of anhydrous 1,2-dimethoxyethane and the mixture cooled to −10 to −30°. To this solution was added 120 ml of methyllithium solution in diethyl ether (Foote Mineral Co., 1.67 *M*, 0.20 mole) dropwise with vigorous stirring and cooling. After addition was completed, the temperature of the solution was lowered to −30 to −60° and 16.5 g (0.20 mole) of previously prepared methanesulfenyl chloride was added dropwise with vigorous stirring. After warming to room temperature, 100 ml of chloroform was added and the solution extracted with two 100-ml portions of water. The organic layer was separated and dried over anhydrous magnesium sulfate, and the solvent was stripped under aspirator vacuum. The residue was distilled, giving 9.4 g of pentyl methanesulfenate, bp 57–58° (15 mm), yield 35%. Analytical data are summarized in Table I. Lower boiling fractions were shown by gas chromatography to contain *n*-pentyl alcohol, *n*-pentyl chloride, and dimethyl disulfide. Higher boiling fractions were shown to contain *n*-pentyl methanesulfinate and a trace of methyl methanethiolsulfonate. Analytical samples were prepared by preparative gas chromatography on a 10 ft × $^3/_8$ in. XE-60 column. The nmr spectrum of *n*-pentyl methanesulfenate displayed a singlet at τ 7.32 (area 3.0) due to S–CH_3, a triplet at 6.40 (area 2.0, J = 6.8 cps) due to the activated methylene group, and multiplets at 8.4, 8.7 and 9.1 (total area 6.9) due to the remaining aliphatic hydrogens. The infrared spectra of the aliphatic sulfenate esters do not display any prominent bands associated with the sulfenate linkage, but show fingerprint absorptions very similar to those of the parent alcohols.

4-Methyl-2-pentyl Methanesulfenate.—4-Methylpentan-2-ol (20.4 g, 0.20 mole) in 100 ml of 1,2-dimethoxyethane was converted to its lithium salt as described above. To this was added at −40 to −50° 16.5 g (0.20 mole) of methanesulfenyl chloride. After work-up as described above and distillation there was isolated 14.2 g, 48% yield, of the corresponding methanesulfenate ester boiling at 57.5° (17 mm). The lower boiling fractions were shown by gas chromatography to contain dimethyl disulfide and starting alcohol and the higher boiling fractions to contain the corresponding sulfinate ester and traces of methyl methanethiolsulfonate. The nmr spectrum of the sulfenate ester displayed the CH_3S singlet at τ 7.33 (area 3.0), the activated methinyl multiplet at 6.35 (area 1.0), the 2-methyl doublet at 8.78 (area 3.1, J = 6.0 cps), the doublet from the terminal methyls at 9.05 (area 6.1, J = 5.9 cps), and a broad multiplet from 8.1 to 8.7 (area 3.1) for the remaining hydrogens.

t-**Butyl Methanesulfenate.**—*t*-Butyl alcohol (14.85 g, 0.20 mole) was converted to its lithium salt as above and treated at −40 to −60° with 16.5 g (0.20 mole) of methanesulfenyl chloride. After the usual work-up there was isolated 10.8 g of *t*-butyl methanesulfenate boiling at 53° (75 mm), yield 45%. In this case no higher boiling fraction was observed. The nmr spectrum consisted of singlets at τ 7.37 (area 3.0) and 8.77 (area 9.0).

n-**Pentyl Methanesulfinate.**—A 0.20-mole quantity of lithium *n*-pentyloxide was prepared as described above and to this solution at −40 to −50° was added dropwise 24.7 g (0.30 mole) of methanesulfenyl chloride. After the same work-up as described above, distillation of the solution gave no fraction corresponding to *n*-pentyl methanesulfenate but, rather, 12.6 g of *n*-pentyl methanesulfinate boiling at 95–96° (15 mm). The yield was 84%, calculated on a stoichiometry which requires two alkoxide molecules for each sulfinate ester formed. The lower boiling fractions were found to contain a trace of starting alcohol and considerable quantities of *n*-pentyl chloride and dimethyl disulfide. The nmr spectrum of the sulfinate displayed the CH_3SO_2 singlet at τ 7.58 (area 3.0),[14] a triplet at 6.13 (area 2.0, J = 5.8 cps) due to the methylene adjacent to oxygen, and multiplets centered at 8.35, 8.68, and 9.1 (total area 8.9) from the hydrocarbon chain. The infrared spectrum displayed the fingerprint absorptions characteristic of the parent alcohol and the sulfenate ester, but also a strong band at 1130 cm^{-1} characteristic of the

RSO– group.[15]

4-Methyl-2-pentyl Methanesulfinate.—A 10.2-g (0.10 mole) quantity of 4-methylpentane-2-ol was converted to its lithium salt in 1,2-dimethoxyethane as described above. To this solution at −30 to −50° was added dropwise with vigorous stirring 12.4 g (0.15 mole) of methanesulfenyl chloride. The solution was allowed to warm to room temperature and stirring was continued for 30 min. After work-up as described above and distillation there was obtained 6.5 g, 79% yield, of the sulfinate ester, bp 97° (15 mm). The nmr spectrum displayed the CH_3SO_2 singlet at τ 7.58 (area 3.0), a multiplet centered at 5.74 (area 1.0) due to the activated methinyl hydrogen, a doublet centered at 9.11 (area 5.9, J = 6.0 cps) from the terminal methyl groups, and a series of multiplets from 8.4 to 8.9 (area 5.9) from the remaining hydrogens.[16] The infrared spectrum showed the characteristic[15] sulfinate band at 1135 cm^{-1}.

Reaction of *n*-Pentyl Methanesulfenate with Methanesulfenyl Chloride.—A solution of 3.4 g (0.025 mole) of *n*-pentyl methanesulfenate in 10 ml of methylene chloride was cooled to −10° and, under an argon atmosphere, 1.03 g (0.0125 mole) of methanesulfenyl chloride was added dropwise at this temperature. After stirring for 15 min at −10°, a sample was withdrawn and injected directly for gas chromatographic analysis on a 10 ft × $^1/_4$ in. XE-60 column. Only a trace of sulfenate ester (<5%) remained, and *n*-pentyl methanesulfinate, *n*-pentyl chloride, and dimethyl disulfide were present in approximately 60% yield. The reaction was warmed to room temperature and allowed to stand for 1 hr. Calibration of the chromatograph response with authentic samples of the products permitted calculation of the actual amounts present. The quantities found after stirring for 1 hr were *n*-pentyl methanesulfinate, 0.011 mole (88%); dimethyl disulfide, 0.0105 mole; and *n*-pentyl chloride, 0.010 mole.

Methyl Methanethiosulfinate.—In a modification of the procedure of Small, *et al.*,[7a] 18.8 g (0.20 mole) of dimethyl disulfide was dissolved in 1500 ml of chloroform and 38 g (0.20 mole) of 40% peracetic acid (FMC Corp.) was added dropwise at room temperature. Vigorous cooling was required to keep the reaction temperature below 25°. Immediately after completion of addition, 53 g (0.50 mole) of anhydrous sodium carbonate was added and the heterogenous mixture was stirred at room temperature for 15 min. The mixture was filtered and the solution was passed through a 10-cm filter funnel containing about 75 g each of anhydrous sodium carbonate and anhydrous magnesium sulfate to ensure removal of acid and water. The chloroform solution was stripped under aspirator vacuum and the residue was distilled through a simple Vigreux head. There was no forerun, and 17.8 g (81% yield) of a fraction boiling at 65° (1.1 mm) was collected. A second cut boiling from 65 to 75°, but comprising only 0.5 g, was also collected. Gas chromatographic analysis on a 10 ft × $^1/_4$ in. Apiezon column indicated greater than 95% purity for cut 1, with the principal impurity being methyl methanethiosulfonate. Cut 2 was a mixture of the thiolsulfinate and thiolsulfonate in an approximately 1:6 ratio.

Cut 1 was used for reaction studies and for nmr and infrared analysis of the thiolsulfinate. A preparative gas chromatographic collection was used for elemental analysis.

Anal. Calcd: C, 21.8; H, 5.5; S, 58.2; O, 14.5. Found: C, 22.2; H, 5.6; S, 55.6; O, 14.9 (direct).

The nmr spectrum of methyl methanethiolsulfinate consists of two singlets of equal area located at τ 7.08 and 7.48. On standing at room temperature for a few days, the thiolsulfinate peaks are replaced by new peaks corresponding to dimethyl disulfide (τ 7.63) and methyl methanethiolsulfonate (two equal singlets at 6.80 and 7.40).[14] The infrared spectrum of the thiolsulfinate (pure liquid sample) displayed a strong band at 1090 cm^{-1} [14] and a medium one at 948 cm^{-1}.

A sample of the thiolsulfonate collected from cut 2 by preparative gas chromatography on a 10 ft × $^3/_8$ in. XE-60 column was identified by its nmr spectrum (equal singlets at τ 6.80 and 7.39), its very characteristic infrared spectrum (strong bands at 1310

(13) The hydrolysis of sulfenyl halides is summarized by A. Burawoy in ref 2, pp 293–295.

(14) The resonance of CH_3SO_2 at higher field than that of CH_3SO in the sulfenate esters is very surprising in light of the usual progression to lower field with increasing oxidation state for methyl bound to sulfur. For a compilation of SCH_3 chemical shifts, see G. R. Pettit, I. B. Douglass, and R. A. Hill, *Can. J. Chem.*, **42** (10), 2357 (1964). The activated protons adjacent to oxygen, however, show the normal order; *i.e.*, the methylene hydrogens in the sulfenate occur at higher field (τ 6.40) than those of the sulfinate (6.13). These same sequences are observed for the secondary sulfenate–sulfinate pair.

(15) S. Detoni and D. Hadzi, *J. Chem. Soc.*, 3163 (1955).

(16) The methyl group adjacent to the sulfinate ester oxygen function appears here as a multiplet, although in the parent alcohol and in the sulfinate ester it appears as a clean doublet. This may be due to the existence of different chemical shifts for the methyl groups of the two diastereomers or to a difference in methyl chemical shifts for different conformers, or both.

and 1130 cm^{-1} characteristic of the SO_2 chromophore and a strong band at 745 cm^{-1} in the spectrum of the pure liquid), and its elemental analysis.

Anal. Calcd: C, 19.1; H, 4.8; S, 50.8; O, 25.4. Found: C, 19.1; H, 5.0; S, 50.8; O, 25.2 (direct).

Reaction of Methyl Methanethiolsulfinate with *n*-Pentyl Methanesulfenate.—A solution of 0.50 g (0.0037 mole) of *n*-pentyl methanesulfenate in 5 ml of methylene chloride was cooled to −10° and a solution of 0.41 g (0.0037 mole) of methyl methanethiolsulfinate in 5 ml of methylene chloride was added dropwise with cooling to maintain the reaction temperature at −10°. After the reaction was allowed to stir for 10 min at 0°, a sample of the reaction solution was injected directly into the gas chromatograph. A small amount of sulfenate remained, but dimethyl disulfide and *n*-pentyl methanesulfinate (identified by comparison of their retention times with those of authentic samples) were the major products present. After 0.5 hr, no sulfenate ester could be detected in the reaction mixture.

Oxidations of Methanesulfenate Esters.—To a solution of 1.34 g (0.01 mole) of *n*-pentyl methanesulfenate in 5 ml of methanol was added dropwise 1.05 g (0.0067 mole) of potassium permanganate dissolved in 10 ml of methanol. A brown precipitate, presumably manganese dioxide, formed during the course of the addition. The solution was filtered and a sample was injected into the gas chromatograph. *n*-Pentyl methanesulfinate, identified by comparison of its retention time with that of an authentic sample, was the only volatile product other than methanol in the reaction mixture.

Approximately 1% solutions in methanol of potassium permanganate, sodium dichromate, iodine, and selenium dioxide were prepared and added dropwise to approximately 10% solutions of the three sulfenate esters in methanol. All three esters behaved in a similar manner toward each of the reagents tested. Potassium permanganate gave very rapid decoloration with concomitant manganese dioxide formation. Sodium dichromate solution remained yellow until 1 drop of acetic or hydrochloric acid was added, whereupon the solution turned the pale green color characteristic of chromic ion. The selenium dioxide solutions slowly turned red-orange and deposited a dark red-orange sludge characteristic of selenium. The iodine solutions gave no color change on addition to the ester solutions, even with 1 drop of hydrochloric acid. When a few drops of 5% potassium iodide in 50% acetic acid–water was added to the esters, followed by 1 drop of starch solution, a dark blue color formed in a few seconds, presumably indicating oxidation of iodide ion to iodine.

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The Synthesis of 4,6-Dihydrothieno[3,4-*b*]thiophene

D. W. H. MacDowell and Timothy B. Patrick

Department of Chemistry, West Virginia University, Morgantown, West Virginia

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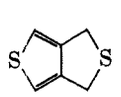
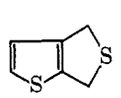
The synthesis of the title compound (II) along with several new 2,3-disubstituted thiophenes is described. Nuclear magnetic resonance and ultraviolet spectra of II are discussed with respect to possible ring strain in the thiophene nucleus.

The synthesis of a thiophene derivative exhibiting a possible ring-strain or Mills–Nixon-type effect has been described by Wynberg and Zwanenburg.[1]

In this work, which reported an elegant synthesis of 1H,3H-thieno[3,4-*c*]thiophene (I), it was claimed that the system containing a five-membered ring fused (3,4) to the thiophene ring exhibited slightly diminished aromatic properties. This was postulated to result possibly from the strain involved in having the two five-membered rings fused together and attention was directed to the desirability of an investigation of compound II. Recently Wynberg and co-workers[2] have synthesized compounds II and IX. The synthesis of II and IX by a different method is reported below.



I



II

Metallation of 3-thiophene aldehyde ethylene acetal[3] (III) followed by formylation with N,N-dimethylformamide gave a 74% yield of 2-formyl-3-thiophene aldehyde ethylene acetal (IV). Hydrolysis of IV with dilute hydrochloric acid furnished 2,3-thiophenedicarboxaldehyde (V) in 80% yield. This compound, prepared independently by us, has also been reported recently by two groups of French workers.[4,5] Conversion of V to VII by way of VI was carried out as indicated in Scheme I. The title compound, 4,6-dihydrothieno[3,4-*b*]thiophene (II), a colorless liquid, bp 70.5–71° (0.7 mm), was prepared in 27% yield by treating VII with sodium sulfide nonahydrate in dimethylformamide solution. The liquid decomposed on standing at room temperature for 1 day, but could be kept with a minimum of decomposition at −5° for several days. Attempts to prepare this compound in methanol solution by the methods of Wynberg and Zwanenburg[1] or Cava[6] gave low yields of mixtures of II and 2,3-bis(methoxymethyl)thiophene (VIII) as evidenced by infrared spectra. The dimethoxy compound (VIII) is readily produced by heating the dibromide (VII) in methanol solution. The 2,3-bis(bromomethyl)thiophene (VII) was treated with the sodium salt of ethyl mercaptan to yield 2,3-bis[(ethylthio)methyl]thiophene (IX) in 67% yield. This compound served as a model compound with which to compare the spectral properties of II.

Discussion

Wynberg and Zwanenburg[1] demonstrated that, on comparison of I with the model (X, Table I) using nmr spectroscopy, the thiophene 2-hydrogen atom was shifted to a higher field while the ultraviolet maximum absorption at 246 mμ was shifted to shorter wavelength. These effects were stated to possibly arise from a small perturbation of the π-orbital delocalization in the thiophene ring.

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