

TABLE V
 PROPERTIES OF ISOBUTYRALDIMINES

Imine	Bp, °C	d_4^{25}	t_1 , °C	n_D^{25}	t_2 , °C	Calcd, %			Found, %		
						C	H	N	C	H	N
<i>i</i> -PrCH=N(CH ₂) ₃ OMe	160	0.820	35	1.4245	25	67.09	11.82	9.93	67.07	11.97	9.79
<i>i</i> -PrCH=NCH ₂ CH ₂ OMe	142	0.839	35	1.4139	25	65.07	11.70	10.84	64.93	11.80	10.67
<i>i</i> -PrCH=NCH ₂ CH ₂ NMe ₂	110 ^a	0.796	25	1.4283	27	67.54	12.76	19.70	67.67	12.88	19.48
<i>i</i> -PrCH=NCH ₂ CH(OMe) ₂	127 ^b	0.899	25	1.4237	27	60.34	10.76	8.80	60.52	10.93	8.64
<i>i</i> -PrCH=NCH ₂ CF ₃ ^c	102	1.036	26	1.3632	27.5	47.07	6.58	9.14	47.28	6.67	9.17
<i>i</i> -PrCH=NCH ₂ CN	35 ^d			1.4326	28	65.43	9.15	25.42	65.34	9.42	25.40
<i>i</i> -PrCH=NCH ₂ C≡CH	132	0.841	26	1.4443	26	77.01	10.16	12.83	76.92	10.23	12.97
<i>i</i> -PrCH=NCH ₂ C ₆ H ₅	66 ^e	0.856	26	1.5079	26	81.94	9.38	8.69	81.84	9.32	8.74

^a At 138 mm. ^b At 143 mm. ^c Calcd: F, 37.23. Found: F, 37.12. ^d At 2.5 mm. ^e At 0.26 mm.

It may be that some of the deviations from linearity in the plot in Figure 1 arise from complications that affect only the pK_a values.

Experimental Section

Unless otherwise stated, the experimental methods were the same as those used previously.²

Aminoacetonitrile bisulfate and glycinamide hydrochloride were recrystallized from 95% ethanol and dried in a desiccator. All the other amines used were tested by gas-liquid partition chromatography and found to contain less than 0.5% impurity, except for 2,2,2-trifluoroethylamine, which contained about 1.5% impurity.

Imines.—The various imines were prepared from isobutyraldehyde and the appropriate primary amine by methods like that described previously,² except in the cases of the 2,2-dimethoxy-

ethyl and the 2,2,2-trifluoroethyl compounds, where magnesium sulfate was used as the drying agent instead of potassium hydroxide, and the case of N-isobutylideneaminoacetonitrile, which was prepared as follows. A mixture of 15.4 g (0.1 mol) of aminoacetonitrile bisulfate and 18 g (0.18 mol) of triethylamine was stirred at 0° while 7.2 g (0.1 mol) of isobutyraldehyde was added. After 2 hr the reaction mixture was dried over molecular sieves, Type 5A, and distilled under vacuum. Data on the imines prepared are listed in Table V. Attempts to isolate N-isobutylidene-glycinamide were unsuccessful.

Registry No.—Isobutyraldehyde, 78-84-2.

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A New Addition Reaction of Chloromethyl Methyl Sulfide to Olefins in Sulfuric Acid. A New Synthesis of 3-(Methylthio)propionaldehyde

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Chloromethyl methyl sulfide (10) has been found to add to vinyl chloride in sulfuric acid to give 3-(methylthio)propionaldehyde. The addition reaction of 10 with other olefins was investigated, but similar reactions did not occur in the case of cyclohexene, acrylonitrile, or 1-chlorocyclohexene.

Presently, *dl*-methionine, an essential amino acid, is produced from acrolein and methanethiol.¹ The present study has been undertaken to find a new synthetic route from dimethyl sulfide and vinyl chloride (11). The chlorination of dimethyl sulfide is known to give chloromethyl methyl sulfide (10)² in good yields. The electrophilic addition of α -chloro ethers to olefins has been widely investigated³ but the analogous reaction of α -chloro sulfides seems not to have been, presumably because of the weak reactivities of the sulfides compared with the ethers.⁴ The Markovnikov addition of 10 to 11 would give rise to 1,1-dichloro-3-(methylthio)propane (1), which might in turn be converted into *dl*-methionine.

On exploring this possibility, it has been found that 10 adds to 11 in the presence of aluminum chloride yielding 1 in low yield. This result has led to the

investigation of other Lewis acids as catalysts for this reaction, and to success with sulfuric acid.

Reaction of Chloromethyl Methyl Sulfide with Vinyl Chloride in Sulfuric Acid.—When the sulfide 10 was treated with sulfuric acid, it gradually dissolved with the evolution of hydrogen chloride to give a clear solution. The solution was allowed to react with 11 in a pressure vessel, and 3-(methylthio)propionaldehyde (4) was found in the ether extract of the hydrolysate of the reaction mixture and was isolated as its 2,4-dinitrophenylhydrazone (13a). A part of unreacted 10 was recovered as the methylthiomethyl derivatives of the hydrazine (15a), one of which was isolated and identified as 1-(2,4-dinitrophenyl)-1,2-bis(methylthio-methyl)hydrazine (15b). There were also found some by-products, among which formaldehyde and acetaldehyde were isolated as 13b and 13c, respectively. From the ether extract of the original hydrolysate, bis(methylthio)methane (5),⁵ *cis*- and *trans*-1,3-bis(methylthio)propene (6a and b), and 3-(methylthio)propionaldehyde dimethyl mercaptal (9) were separated

(1) J. R. Catch, A. H. Cook, A. R. Graham, and I. Heilbron, *J. Chem. Soc.*, 1609 (1947); E. Pierson, M. Giella, and M. Tishler, *J. Amer. Chem. Soc.*, **70**, 1450 (1948).

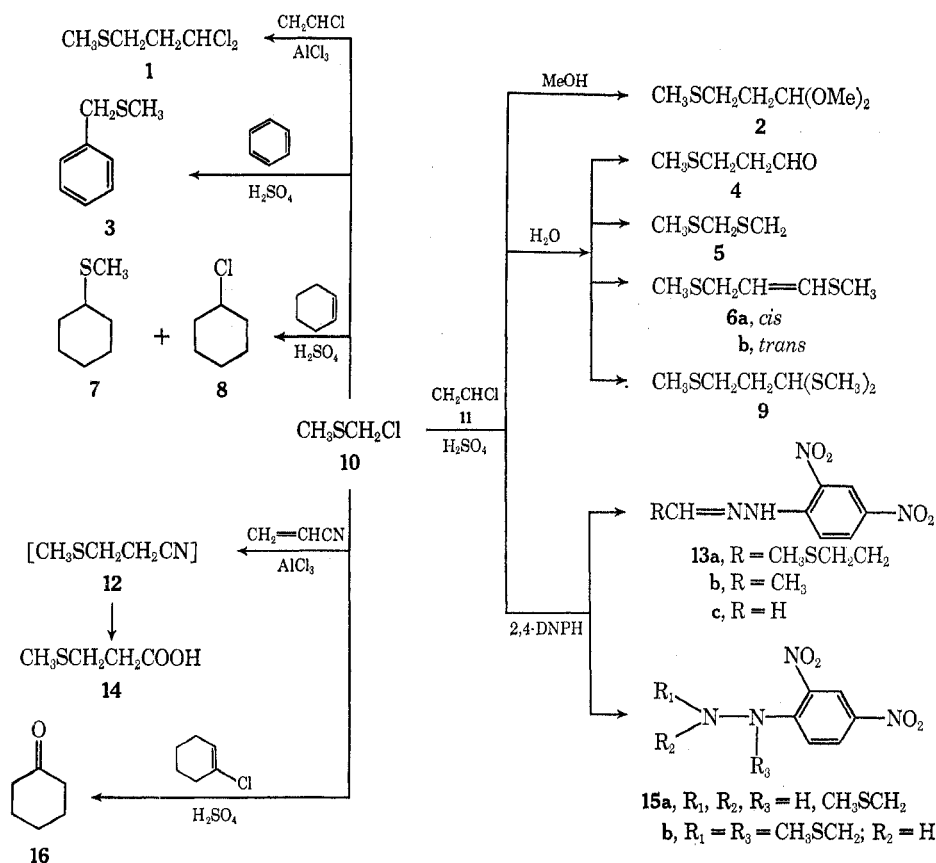
(2) F. Boberg, G. Winter, and J. Moos, *Ann. Chem.*, **616**, 1 (1958); W. E. Truce, G. H. Birum, and E. T. McBee, *J. Amer. Chem. Soc.*, **74**, 3594 (1952).

(3) S. A. Vartanyan and A. O. Tosunyan, *Russ. Chem. Rev.*, **34**, 267 (1965).

(4) H. Böhme, *Chem. Ber.*, **74**, 248 (1941).

(5) L. Horner and P. Kaiser, *Ann. Chem.*, **626**, 19 (1959).

SCHEME I



by vpc and identified by nmr. The methanolysis of the initial reaction mixture gave 3-(methylthio)propionaldehyde dimethyl acetal (2). Good yields were obtained when amounts greater than 4 mol of sulfuric acid of above 95% concentration to 1 mol of 10 were used and the reaction was carried out at around 0°. Among other catalysts, chlorosulfonic acid has been found to be effective, but the yields were generally inferior to those obtained using sulfuric acid.

Reaction with Other Olefins.—When treated with 10 in sulfuric acid, benzene gave benzyl methyl sulfide (3), suggesting electrophilic attack of the methylthio-methyl cation. A similar result has been reported for the reaction of 10 with *o*-nitrophenol in the presence of aluminum chloride,⁶ but the reaction of 10 in sulfuric acid with vinyl acetate, vinyl ethyl ether, or styrene gave only the polymerization product. Cyclohexene yielded cyclohexyl methyl sulfide (7) and chlorocyclohexane (8) as the result of the addition of methanethiol and hydrogen chloride originated from 10.⁷ The reaction of 1-chlorocyclohexene gave only cyclohexanone (16) as the hydrolyzed product. Acrylonitrile gave 3-(methylthio)propionitrile (12), the identity of which was confirmed by converting the product into 3-(methylthio)propionic acid (14). These results seem to suggest that the olefin would have to be intact in the reaction medium to be attacked by the methylthio-methyl cation.

Experimental Section

All melting points are uncorrected. The nmr spectra were measured with a Varian A-60 spectrometer. Chemical shifts

(6) S. W. Long and R. D. Moss, U. S. Patent 2,976,325 (1961); *Chem. Abstr.*, **55**, 16484h (1961).

(7) H. Böhme, H. Fischer, and R. Frank, *Ann. Chem.*, **563**, 54 (1949).

were determined using the δ convention relative to tetramethylsilane (TMS) as internal standard. Ultraviolet absorption spectra were taken with a Hitachi Type EPS-2U automatic recording spectrophotometer, and infrared absorption spectra were measured with Jasco Model IR-S spectrophotometer. Analyses by vpc were carried out using a Shimadzu GC-2B apparatus with a 4 mm \times 3 m, 10% Carbowax 20M on 40–60 mesh Chromosorb W column. The concentration of sulfuric acid or oleum was determined by melting point.⁸

3-Methylthio-1,1-dichloropropane (1).—To powdered aluminum chloride (12 g, 0.09 mol) in 40 ml of methylene chloride was added with stirring 7.7 g (0.08 mol) of 10 at 10°. The mixture was stirred for 20 min at 10° and transferred to a pressure vessel; 11 (5.6 g, 0.09 mol) was added. The mixture was kept for 2 days at room temperature with occasional shaking, then poured into 100 ml of 3 *N* hydrochloric acid, and extracted with ether which was washed with water, dried over calcium chloride, and evaporated. Distillation of the residue gave 0.45 g, bp 40–42° (1 mm), of 1. The identity of the product was confirmed by nmr, compared with that of authentic 1 prepared from 4 by the method of Hill and Tyson.⁹

3-(Methylthio)propionaldehyde 2,4-Dinitrophenylhydrazone (13a).—To 98% sulfuric acid (19.6 g, 0.2 mol) was added 10 (3.8 g, 0.04 mol) at 0–2°, dropwise and with stirring. After 5 min at 0°, the mixture was transferred to a cooled pressure vessel and 11 (3.7 g, 0.06 mol) was added. The mixture was kept for 4 hr at 0° with occasional shaking and then poured into a solution of 2,4-dinitrophenylhydrazine (16 g, 0.08 mol) in 800 ml of 6 *N* sulfuric acid to give crude hydrazone (11.4 g). A mixture of accurately weighed samples of *t*-butyl alcohol and the hydrazone was analyzed by nmr in pyridine. From the peak ratios of the methyl signals of 13a (δ 2.07, s, CH_3S), 13b (δ 1.95 and 1.85, d, $J = 6$ Hz, CH_2CH), and 15a (δ 2.2–2.4, m, CH_3S) to that of *t*-butyl alcohol, it was found that the hydrazone contained 7.9 g of 13a (70% from 10), 1.7 g of 13b (13% from 11), and 15a, the methylthio groups of which corresponded to 8 mol % of the amount of 10 employed. Recrystallization from methanol gave

(8) C. M. Gable, H. F. Betz, and S. H. Maron, *J. Amer. Chem. Soc.*, **72**, 1445 (1950).

(9) A. J. Hill and F. Tyson, *ibid.*, **50**, 172 (1928).

13a (mp 120.5°), the ir and nmr of which were identical with those of the hydrazone prepared from authentic 4.

3-(Methylthio)propionaldehyde Dimethyl Acetal (2).—The reaction mixture, worked up as in the previous experiment from 10 (7.6 g, 0.08 mol), in oleum (31.2 g, SO₃ 6.8%) with 11 (7.4 g, 0.12 mol), was poured into 200 ml of anhydrous methanol and boiled under reflux for 2 hr. The solution was poured into sodium bicarbonate solution and extracted with ether. The extract was washed with water, dried over magnesium sulfate, filtered, and evaporated. Distillation of the residue gave 3.0 g (25%), bp 72–78° (15 mm), of 2. The identity was confirmed by nmr, compared with that of authentic 2 prepared from 4 and methanol by the conventional method.

Identification of Side Products.—A reaction mixture, worked up as in the previous experiment from 10 (7.6 g, 0.08 mole), in 100% sulfuric acid (63 g, 0.64 mol) and 11 (7.4 g, 0.12 mol), was poured into 400 ml of water-ice slurry and extracted with chloroform which was washed with sodium bicarbonate solution and water, dried over magnesium sulfate, and filtered. The vpc of the extract at 122° with helium gas flow rate of 78 ml/min exhibited the peaks of 4 [retention time (*t_r*) 7.0 min] and 5 (*t_r* 3.8 min) along with two peaks at *t_r* of 14.3 (A) and 17.5 min (B). Vpc also showed the peak of 9 (*t_r* 21.4 min) at 150° with helium gas flow rate of 60 ml/min. The identity was confirmed by comparison with the *t_r* of authentic compounds. The compounds A and B were separated by vpc. Elemental analysis showed that both compounds have a composition close to C₈H₁₀S₂. The nmr spectrum of A (CCl₄) exhibited 3 H singlets at δ 2.02 (CH₃SCH₃) and 2.26 (CH₃SCH=C), a 2 H doublet at 3.12 (*J* = 8 Hz SCH₂CH=C), a 1 H multiplet at 5.2–5.8 (CH₂CH=CHS), and a 1 H doublet at 6.12 (CH_A=CH_BS, *J_{AB}* = 9 Hz) along with small peaks of impurities at 1.9–2.5. Compound B exhibited a very similar nmr spectrum at δ 1.98 (s, 3), 2.25 (s, 3), 3.12 (d, 2, *J* = 8 Hz), 4.9–5.7 (m, 1), and 6.05 (d, 1, CH_A=CH_BS, *J_{AB}* = 15 Hz), along with small peaks of impurities at 1.9–2.5. These results and the fact that *J_{AB}* of B is larger than that of A indicate that A and B are 6a and 6b, respectively.

Sulfuric acid (100%, 2.5 g, 0.025 mol) followed by 10 (3.8 g, 0.04 mol) was added dropwise to trimethyl phosphate (10 ml) at 0–4°. After 5 min, the solution was allowed to react with 11 (3.7 g, 0.06 mol) in a pressure vessel at 0° for 3 hr. The mixture was poured into a solution of 2,4-dinitrophenylhydrazine (16 g, 0.08 mol) in 6 *N* sulfuric acid (800 ml). The orange-red precipitate was filtered, washed with water, and dried. Recrystallization from benzene gave yellow needles of 13c, the identity of which was confirmed by infrared spectrum. The mother liquor was evaporated and the residue was chromatographed over alumina. From the petroleum ether-benzene (4:1) eluate, a yellow prism of 15b, mp 97–98° (recrystallized from petroleum ether-benzene), was obtained: λ_{max}^{EtOH} 342 mμ (ε 17,200);¹⁰ nmr (C₆D₆) δ 1.85 (s, 6, SCH₃), 3.70 (broad s, 2, NCH₃S), 3.71 (broad s, 2, NCH₂S), 6.9–8.7 (m, 3, ArH), and 9.26 (broad s, 1, NH). The nmr spectrum (pyridine) indicated that it corresponds to one of the peaks of the side product 15a (δ 2.2–2.4).

(10) The hydrazone 13a had the uv absorption maximum (EtOH) of 360 mμ (ε 31,900).

Anal. Calcd for C₁₀H₁₄N₄O₄S₂: C, 37.72; H, 4.43; N, 17.60, S, 20.14. Found: C, 38.09; H, 4.62; N, 17.69; S, 20.10.

Reactions of 10 in Sulfuric Acid. A. With Benzene.—To oleum (SO₃ 5.7%, 68 g) was added 10 (16 g, 0.17 mol), dropwise and with stirring at 0–2°, followed by 13 g of benzene (0.17 mol). After being kept for 2 hr at 0–2° and overnight at room temperature, the mixture was poured into 150 ml of water-ice slurry and extracted with ether which was dried over magnesium sulfate and evaporated. Distillation of the residue gave 6.7 g (29%), bp 94–96° (18 mm), of 3: nmr (CCl₄) δ 1.86 (s, 3, SCH₃), 3.53 (s, 2, CH₂S), and 7.20 (s, 5, ArH).

Anal. Calcd for C₈H₁₀S: C, 69.51; H, 7.29; S, 23.20. Found: C, 69.36; H, 7.53; S, 23.40.

B. With Cyclohexene.—Sulfide 10 (16 g, 0.17 mol) was added dropwise with stirring to oleum (SO₃ 5.7%, 68 g) followed by cyclohexene (13.7 g, 0.17 mol) at 0–2°. After 3 hr at 0°, the mixture was poured into 200 ml of water-ice slurry and extracted with ether; the extract was dried over sodium sulfate and evaporated. Distillation gave an oil (5.4 g), bp 131–132.5°, which was identified as 8 containing about 10% 5 by nmr and vpc, compared with those of authentic samples.

The mother liquor of the ether extract was boiled under reflux for 2 hr, neutralized with sodium hydroxide solution, and extracted with ether; the extract was dried over sodium sulfate and evaporated. Distillation of the residue gave 2.0 g (9%), bp 59–62° (11.5 mm), of an oil, rectification of which gave 7: bp 59.5–60.5° (13 mm); nmr (CCl₄) δ 2.00 (s, 3, SCH₃), 1.0–2.2 (broad hump 10, CH₂), and 2.2–2.7 (broad hump, 1, CHS).

Anal. Calcd for C₇H₁₄S: C, 64.55; H, 10.83; S, 24.62. Found: C, 64.39; H, 10.86; S, 25.16.

C. With Acrylonitrile.—Sulfide 10 (16 g, 0.17 mol) was added with stirring to oleum (SO₃ 5.7%, 68 g) followed by acrylonitrile (8.9, 0.18 mol) at 0–2°. After 4 hr at 0°, the mixture was poured into 200 ml of water-ice slurry and extracted with ether. The aqueous layer was made slightly alkaline with sodium hydroxide solution, the deposited sodium sulfate removed by decantation, and the solution boiled under reflux for 4 hr. It was then acidified with sulfuric acid and extracted with ether; the extract was dried over sodium sulfate and evaporated. Distillation of the residual oil gave 7.1 g (35%), bp 135–135.5° (19 mm), of 14: ir 1710 cm⁻¹ (C=O); nmr (CCl₄) δ 2.12 (s, 3, SCH₃), 2.68 (m, 4, CH₂CH₂S), and 11.32 (s, 1, COOH).

Anal. Calcd for C₈H₈O₂S: C, 39.98; H, 6.71; S, 26.68. Found: C, 39.97; H, 6.78; S, 26.47.

Registry No.—Sulfuric acid, 7664-93-9; 1, 22433-40-5; 2, 13214-29-4; 3, 766-92-7; 6a, 22433-04-1; 6b, 22433-05-2; 7, 7133-37-1; 10, 2373-51-5; 13a, 7372-49-8; 14, 646-01-5; 15a, 22433-47-2; 15b, 22433-48-3.

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