BULLETIN OF THE CHEMICAL SOCIETY OF JAPAN VOL. 43 1890—1892 (1970)

Synthesis of 2-Substituted Ethyl Hydrodisulfides

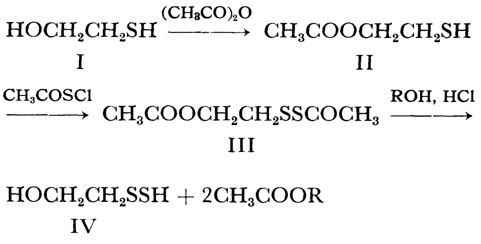
Jitsuo TSURUGI, Yasuo ABE and Shunichi KAWAMURA

Radiation Center of Osaka Prefecture, Shinke-cho, Sakai, Osaka

(Received December 8, 1969)

Alkyl hydrodisulfides synthesized so far are methyl,[1] ethyl,[1] benzyl,[1,2] benzhydryl[2] and trityl[3] hydrodisulfides, the latter three of which have been reported sufficiently stable for a few weeks. Compounds containing hydrodisulfide group (–SSH) have been postulated by biochemists as intermediates of various enzymatic reactions.[4-6] However, alanyl hydrodisulfide $HOCOCH(NH_2)CH_2SSH$, which has been called thiocysteine and proposed as an intermediate of enzymatic cleavage of cystine by Cavallini,[4] has never been isolated. Only circumstantial evidence is available to support the intermediate formation of thiocysteine[4-6] and similar polysulfidic species containing labile sulfur.[7,8] This note describes the synthesis or attempted synthesis of mono-2-substituted ethyl hydrodisulfides.

2-Hydroxyethyl hydrodisulfide (IV) was prepared as indicated in Scheme 1 by the Böhme method.[1] In Scheme 1, prior conversion of 2-mercaptoethanol (I) to 2-acetoxyethanethiol (II) was necessary, because direct reaction of I with acetyl sulfenyl chloride yielded an oily mixture, suggesting that hydroxyl group of I was also attacked by acetyl sulfenyl chloride. Compound II was then allowed to react with acetyl sulfenyl chloride to yield 2-acetoxyethyl acetyl disulfide (III). Alcoholysis of III with anhydrous methanolic or ethanolic hydrogen chloride produced IV almost quantitatively as viscous oil along with methyl or ethyl acetate. Alcoholysis of both $R'SS-COCH_3$ and CH_3CO-OR'' bonds of III apparently took place simultaneously. Compound IV seems unstable even at room temperature. Slight and continuous evolution of hydrogen sulfide was observed during alcoholysis, isolation and storing. Although analysis was carried out immediately after isolation, analytical values did not completely agree with calculated ones. However, NMR spectra showed the corresponding protons (–SSH, –OH and ethylenic ones) and no other signals. These results suggest that IV was contaminated with a trace amount of the corresponding trisulfide.

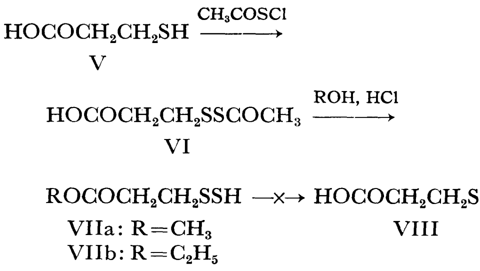


$$\underset{\text{I}}{HOCH_2CH_2SH} \xrightarrow{(CH_3CO)_2O} \underset{\text{II}}{CH_3COOCH_2CH_2SH} \xrightarrow{CH_3COSCl} \underset{\text{III}}{CH_3COOCH_2CH_2SSCOCH_3} \xrightarrow{ROH,\ HCl} \underset{\text{IV}}{HOCH_2CH_2SSH} + 2CH_3COOR$$

Scheme 1

Contrary to our expectation that the introduction of hydroxyl group would make the hydrodisulfide water-soluble, IV was found to be insoluble in water and to decompose slowly on contact with water as evidenced by the evolution of hydrogen sulfide. More stable aralkyl hydrodisulfides also were reported to decompose on contact with water.[9]

Preparation of 2-carboxyethyl hydrodisulfide (VIII) was attempted next, as indicated in Scheme 2. Unlike Scheme 1, sulfenyl chloride reacted with 2-mercaptopropionic acid (V) exclusively on the sulfur side. Esterification took place during the alcoholysis of 2-carboxyethyl acetyl disulfide (VI). Thus 2-carboalkoxyethyl hydrodisulfides (VIIa, VIIb) were separated as oily substances in good yields. Neither hydrolysis of VII to the corresponding acid (VIII) with hydrochloric acid



$$\underset{\text{V}}{HOCOCH_2CH_2SH} \xrightarrow{CH_3COSCl} \underset{\text{VI}}{HOCOCH_2CH_2SSCOCH_3} \xrightarrow{ROH,\ HCl} \underset{\substack{\text{VIIa: } R=CH_3 \\ \text{VIIb: } R=C_2H_5}}{ROCOCH_2CH_2SSH} \xrightarrow{\times} \underset{\text{VIII}}{HOCOCH_2CH_2SSH}$$

Scheme 2

---

[1] H. Böhme and G. Zinner, *Ann.*, **585**, 142 (1954).

[2] J. Tsurugi and T. Nakabayashi, *J. Org. Chem.*, **24**, 807 (1959).

[3] T. Nakabayashi, J. Tsurugi and T. Yabuta, *ibid.*, **29**, 1236 (1964).

[4] D. Cavallini, C. De Marco, B. Mondovi and B. G. Mori, *Enzymologia*, **22**, 161 (1960).

[5] M. Flavin, *J. Biol. Chem.*, **237**, 768 (1962).

[6] J. Loiselet and F. Chatagner, *Bull. Soc. Chim. Biol.*, **48**, 595 (1966).

[7] O. Gawron and G. Odstrchel, *J. Amer. Chem. Soc.*, **89**, 3263 (1967).

[8] J. L. Wood and N. Catsimpoolas, *J. Biol. Chem.*, **238**, 2887 (1963); N. Catsimpoolas and J. L. Wood, *ibid.*, **239** 4132 (1964); **241**, 1790 (1966).

[9] S. Kawamura, Y. Abe and J. Tsurugi, *J. Org. Chem.*, **34**, 3633 (1969).

nor transesterification of VII to VIII with formic acid was successful, because the susceptibility of hydrodisulfide group to hydrolysis led to unidentified products. Instability, slight disagreement of analytical data, and NMR spectral evidence, all of which are similar to those of IV, indicate that VIIa may be also contaminated with a trace amount of the corresponding trisulfide. Compound VIIb, on the contrary, shows good coincidence of analytical data. The behavior of VII toward water was similar to that of IV.

Spectroscopic data of hydrodisulfides IV and VII are shown in Table 1 along with those of the starting thiols I and V. Proton of hydrodisulfide group of IV and VII is exchangeable with that of water, because their peaks in NMR were diminished without change in the remaining parts of the spectra by shaking with deuterated water. Although the hydrodisulfides are unstable in the presence of water as mentioned above, the decomposition of IV and VII did not disturb the NMR spectral determination. The singlet peak of each hydrodisulfide group is found in a much lower field than the triplet center of the corresponding thiol, presumably because of the anisotropic effect of additional sulfur atom. IR spectra also show that SH stretching frequency of each hydrodisulfide group is slightly lower than that of the corresponding thiol. This fact suggests that the lowering of force constant between S and H is caused by the effect of neighboring S–S bond.

TABLE 1. SPECTROSCOPIC DATA

Compound	NMR (δ, ppm)	IR (cm^{-1})
$HOCH_2CH_2\mathbf{SSH}$(IV)	3.09 (s)	2,500 (m)
$HOCH_2CH_2\mathbf{SH}$(I)	1.45 (t)	2,560 (w)
$CH_3OCOCH_2CH_2\mathbf{SSH}$(VIIa)	3.00 (s)	2,510 (m)
$C_2H_5OCOCH_2CH_2\mathbf{SSH}$(VIIb)	3.06 (s)	2,510 (m)
$HOCOCH_2CH_2\mathbf{SH}$(V)	1.59 (*t*)	2,600 (w)

Synthesis of 2-aminoethyl acetyl disulfide and 2-acetamidoethyl acetyl disulfide (IX) by the Böhme method was not successful. Synthesis of IX was realized, however, by the Field[10] method as shown below. By ethanolysis of IX an oily

$$CH_3CONHCH_2CH_2SSO_2CH_2CH_2NHCOCH_3$$

$$+\ CH_3COSH \longrightarrow \underset{\text{IX}}{CH_3CONHCH_2CH_2SSCOCH_3}$$

$$+\ CH_3CONHCH_2CH_2SO_2H$$

substance and ethyl acetate were obtained. The oily substance continued to evolve hydrogen sulfide during and after the evaporation of the solvent, and after one night decomposed to unidentified yellow solids, which were insoluble in most organic solvents. Although direct evidence for the formation of 2-acetamidoethyl hydrodisulfide could not be obtained, indications are the formation of ethyl acetate on ethanolysis, and a positive result in the lead acetate test characteristic for hydrodisulfides.[11] We previously reported that amines can decompose aralkyl hydrodisulfide (benzyl, benzhydryl and trityl hydrodisulfides) at room temperature.[12] The instability of this oily substance may be ascribed to the introduction of an amino group into hydrodisulfide molecule. Judging from the instability of this compound and the failure of synthesis of 2-aminoethyl hydrodisulfide, it may be concluded that the isolation of alanyl hydrodisulfide, which is considered to be an intermediate of cystine decomposition, would be difficult, even if it is formed during the enzymatic reaction.

Experimental

Commercial 2-mercaptoethanol and 2-mercaptopropionic acid was distilled under reduced pressure before use. Other reagents and solvents were commercial products. NMR spectra were taken on a JNM 3H-60 spectrometer with tetramethylsilane as an internal standard and IR spectra were obtained on a JASCO IR-S spectrometer.

2-Acetoxyethyl Acetyl Disulfide (III). 2-Acetoxyethanethiol (II) was prepared from 2-mercaptoethanol by the method of Miles and Owen,[13] bp 57°C/16 mmHg (lit, 62—64°C/16 mmHg). To a solution of II (15.0 g, 0.125 mol) in anhydrous ether, freshly distilled acetyl sulfenyl chloride[14] (15.2 g, 0.137 mol) in absolute ether was added with stirring at 0—5°C under a nitrogen atmosphere. Gaseous hydrogen chloride was evolved gradually. After being kept standing overnight the reaction mixture was separated off, and volatiles were removed *in vacuo*. Highly viscous oil of III was obtained in near 100% yield and proved to be pure enough for the following synthesis. Distillation did not change the properties of the product. The IR spectrum (neat) showed a strong C=O band at 1740 cm^{-1}. The NMR spectrum (10% in CCl_4) was consistent with the structure of III having two kinds of acetyl group, $OCOCH_3$, δ 2.03 and $SCOCH_3$, δ 2.43. Both IR and NMR spectra indicated no peak corresponding to sulfhydryl group.

Found: C, 36.96; H, 5.50; S, 33.35%. Calcd for $C_6H_{10}O_3S_2$: C, 37.09; H, 5.19; S, 33.01%.

2-Hydroxyethyl Hydrodisulfide (IV). To a solution of III (1 g, 5.15 mmol) in absolute methanol was added a few m*l* (0.7—2) of 5N methanolic hydrogen chloride, and the solution was kept standing for *ca.* 3 hr at room temperature. Complete removal of volatiles

---

[10] L. Field, T. C. Owen, R. R. Crenshaw and A. W. Bryan, *J. Amer. Chem. Soc.*, **83**, 4414 (1961); L. Field and J. D. Buckman, *J. Org. Chem.*, **32**, 3467 (1967).

[11] T. Nakabayashi and J. Tsurugi, *ibid.*, **28**, 813 (1963).

[12] J. Tsurugi, Y. Abe, T. Nakabayashi, S. Kawamura, T. Kitao and M. Niwa, accepted by *J. Org. Chem.*

[13] L. W. C. Miles and L. N. Owen, *J. Chem. Soc.*, **1952**, 821.

[14] H. Böhme and M. Clement, *Ann.*, **576**, 65 (1962).

(hydrogen chloride, methanol and methyl acetate) by a rotary evaporator in a vacuum gave viscous oil of IV quantitatively. The IR spectrum (neat) exhibited a medium band at 2500 cm^{-1} characteristic for sulfhydryl groups of hydrodisulfides (*cf.* Table 1). NMR spectrum (10% in $CDCl_3$) showed a characteristic signal for singlet proton of –SSH at δ 3.09 which was exchangeable with deuteron in D_2O, as well as hydroxylic δ 3.4—4.2 (*cf.* OH of I, δ 4.12—4.60) and ethylenic protons. Qualitative test by lead acetate gave a black precipitate which resulted from the hydrodisulfide group.[11)]

Found: C, 22.43; H, 5.56; S, 56.62%. Calcd for $C_2H_6OS_2$: C, 21.80; H, 5.49; S, 58.19%.

2-Carboxyethyl Acetyl Disulfide (VI). In the same way as for the preparation of III, VI was obtained quantitatively as white crystals from freshly distilled 2-mercaptopropionic acid (11.3 g, 0.106 mol) and acetyl sulfenyl chloride (26.9 g, 0.267 mol). The crystals were recrystallized from carbon tetrachloride, mp 69—70°C. The IR spectrum (KBr) showed a broad band at 1690 cm^{-1} ($SCOCH_3$). The NMR spectrum (10% in $CDCl_3$) indicated signals at δ 2.49 ($SCOCH_3$), and δ 11.70 (COOH).

Found: C, 33.20; H, 4.71; S, 35.72%. Calcd for $C_5H_8O_3S_2$: C, 33.32; H, 4.47; S, 35.58%.

2-Carboalkoxyethyl Hydrodisulfide (VII). VI (1 g, 5.55 mmol) was suspended in anhydrous methanol or ethanol (4 m*l*) with magnetic stirring. To this was added 5N methanolic or ethanolic hydrogen chloride (3 m*l*). Disulfide VI was gradually dissolved in alcohol as alcoholysis proceeded. After 3 hr, volatiles were removed by using a rotary evaporator (*in vacuo*) at room temperature. 2-Carbomethoxyethyl (VIIa) or 2-carboethoxyethyl hydrodisulfide (VIIb) was obtained as an oily substance. IR spectra (neat) of both VIIa and VIIb showed bands at 2510 cm^{-1} corresponding to hydrodisulfide group (*cf.* Table 1). NMR signals (10% in $CDCl_3$) of SSH proton were at δ 3.00 (VIIa) and δ 3.06 (VIIb) (*cf.* Table 1), and other reasonable signals were found. Addition of lead acetate solution to VII gave a black precipitate.[11)]

Found: C, 31.75; H, 5.30; S, 39.49%. Calcd for $C_4H_8O_2S_2$ (VIIa): C, 31.56; H, 5.30; S, 42.13%.

Found: C, 36.26; H, 6.02; S, 38.35%. Calcd for $C_5H_{10}O_2S_2$ (VIIb): C, 36.12; H, 6.06; S, 38.57%.

Reaction of 2-Acetamidoethyl Acetyl Disulfide in Alcoholic Hydrogen Chloride. 2-Acetamidoethyl acetyl disulfide[10)] was allowed to react with alcoholic hydrogen chloride under the conditions similar to those in the case of VII. After volatiles were completely evaporated, an oil remained. After a few minutes, the oily substance decomposed with evolution of hydrogen sulfide and solidified. The solid was washed with acetone and dried *in vacuo*, mp 143—146°C (unidentified). IR spectrum (KBr) showed that $SCOCH_3$ group (1734 cm^{-1}) was removed by the above treatment. In NMR (DMSO-d_6), neither the signal corresponding to $SCOCH_3$ nor SSH was found. The oily material, immediately after its formation, produced black precipitates by treatment with lead acetate solution.[11)]