Russian Chemical Bulletin, International Edition, Vol. 52, No. 4, pp. 958—960, April, 2003

Sulfur-containing carboxylic acids

6.* The syntheses of 3,3´-sulfinyldipropionic and 2,2´-sulfinyldiacetic acids

T. P. Vasil´eva

A. N. Nesmeyanov Institute of Organoelement Compounds, Russian Academy of Sciences,
28 ul. Vavilova, 119991 Moscow, Russian Federation.
Fax: +7 (095) 135 5085. E-mail: kolomiets@ineos.ac.ru

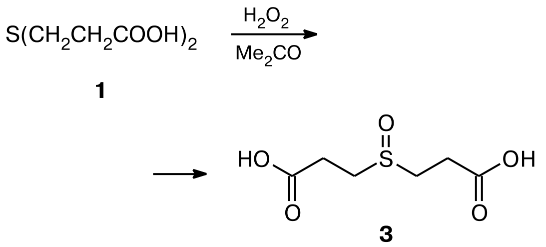
Pure sulfoxides of thiodialiphatic acids were obtained in high yields by oxidation of the corresponding sulfides in organic solvents. 3,3´-Sulfinyldipropionic acid was obtained by the reaction of hydrogen peroxide with thiodipropionic acid in acetone. 2,2´-Sulfinyldiacetic acid was synthesized by the reaction of thiodiglycolic acid with H_2O_2 in acetone containing acetic acid (26 mol %). Pure 2,2´-sulfinyldiacetic acid was found to be stable in storage rather than labile as reported previously.

Key words: thiodipropionic acid, thiodiglycolic acid, oxidation, 3,3´-sulfinyldipropionic acid, 2,2´-sulfinyldiacetic acid, stability.

In continuation of the studies[1,2] devoted to sulfur-containing carboxylic acids, we investigated oxidation of 3,3´-thiodipropionic (**1**) and thiodiglycolic (**2**) acids. Some sulfoxides (*e.g.*, those containing methyl,[3] *tert*-butyl, vinyl,[4] aryl,[5] and acylaminoethyl[3] radicals) are known to have pronounced radioprotective properties and be nontoxic, as distinct from corresponding sulfides. For this reason, functionalized sulfoxides, especially carboxyl-containing ones, can be of interest as intermediates for the synthesis of new biologically active substances. The goal of the present work was to select optimum conditions for the synthesis of sulfinyldialiphatic acids and study the effects of the solvent and the sulfide structure on the oxidation course.

Oxidation of sulfur-containing acids **1** and **2** into the corresponding sulfoxides, namely, 3,3´-sulfinyldipropionic (**3**) and 2,2´-sulfinyldiacetic acids (**4**), has been poorly studied to date. The known procedures afford impure sulfoxides **3** [6,7] and **4**.[8—12] Thus, the oxidation of thiodipropionic acid **1** (pre-neutralized with KOH) with hydrogen peroxide in water is completed over 24 h to give, along with sulfoxide **3**,[7] 3,3´-sulfonyldipropionic acid as a by-product of its further oxidation. Alternatively, sulfoxide **3** can be obtained by the reaction of sulfide **1** with H_2O_2 in acetone for 2 days.[6] However, the oxidation product under these conditions contains a significant admixture of the starting sulfide **1** (MS and TLC data). The yield and purity of oxidation product **3** were increased by extending the reaction time to 5 days (Scheme 1).

Scheme 1



Oxidation of thiodiglycolic acid **2** yielded highly impure products. As a rule, sulfoxide **4** obtained earlier[8—12] was not purified, and its purity was not checked. That is the reason why the literature data on its melting point show a large discrepancy: from 79—80 °C (with excess H_2O_2 in the absence of a solvent)[8] and 109 °C (with bromine water)[12] to 119 °C (with excess H_2O_2 in water[9] or acetone[10]) and 119—121 °C (with ozone in water).[11] Earlier,[9] the reaction of excess hydrogen peroxide with sulfide **2** in water was reported to be the optimum method for the synthesis of compound **4** (m.p. 119 °C). When repeated by us, the synthesis gave an oxidation product (m.p. 80—100 °C) containing sulfoxide **4**, the starting sulfide **2**, the corresponding sulfone (2,2´-sulfonyldiacetic acid (**5**)), and other admixtures. Obviously, other previous products[8—11] were crude sulfoxide **4** containing different amounts of compounds **2** and **5**. Thus, the oxidation of sulfide **2** in water affords impure sulfoxide **4**. Apparently, water provokes side reactions. In addition, the solvent should be removed to isolate the oxidation product, and sulfoxide **4** partly decomposes when heated in aqueous solutions.[9,10] These undesirable effects seemed to be quite avoidable if acetone is used instead of water as a solvent. However, it turned out that the oxidation rate

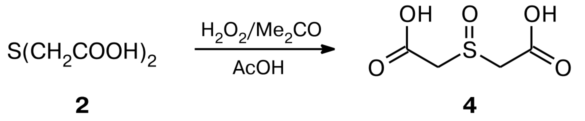
---

* For Part 5, see Ref. 1.

Published in Russian in *Izvestiya Akademii Nauk. Seriya Khimicheskaya,* No. 4, pp. 908—910, April, 2003.

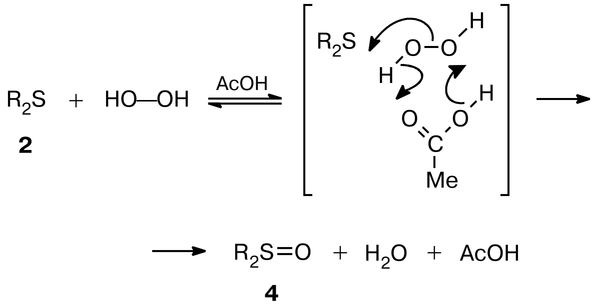
of thiodiacetic acid **2** in acetone is lower than in water. Moreover, sulfide **2** is much harder to react with H_2O_2 in acetone than thiodipropionic acid **1**: under the reaction conditions for sulfoxide **3** (see Scheme 1), the oxidation of sulfide **2** was only half completed. A similar tendency was observed earlier in the oxidation of these acids with hydrogen peroxide in water; the rate constant for **2** is much lower (0.003) than for **1** (0.17).[7] We found the optimum conditions for the synthesis of sulfoxide **4** by oxidation of sulfide **2** with hydrogen peroxide in acetone containing ~26 mol % acetic acid (Scheme 2).

Scheme 2



Under these mild conditions, the oxidation rate is satisfactory, and no decomposition of **4** or further oxidation occur. The accelerating effect of AcOH can be explained by the reaction mechanism involving proton transfer and the formation of a trimolecular cyclic intermediate (Scheme 3).

Scheme 3



R = CH_2COOH

Sulfoxide **4** can be purified by soft methods in $Me_2CO—C_6H_6$ or $MeOH—Et_2O$ systems. Crystallization from water, which was used to purify propionic analog **3**,[6] is unsuitable for compound **4**. The melting point of pure compound **4** was found to be 142—143 °C. In the previous studies,[8—11] the products obtained were not purified and hence sulfoxide **4** had lower melting points. Complete decomposition of sulfoxide **4** (m.p. 119 °C) on storage at 20 °C within two months[9] is mainly due to the presence of sulfide **2** and sulfone **5**. The behavior of its analog **3** is quite different; for this reason, we studied the stability of **4** in storage. Like sulfoxide **3**, pure compound **4** (m.p. 142—143 °C) was found to be stable at 20 °C for 6.5 months.

The purity of the sulfoxides **3** and **4** obtained was confirmed by TLC, ^1H NMR, and elemental analysis data, as well as by a special titrimetric reductive method developed for sulfoxides.[13]

It is worth noting that the protons of the sulfur-bound methylene group are nonequivalent because of the pyramidal structure of the sulfoxide substituent in S-monooxides **3** and **4**. In ^1H NMR spectra, they are manifested as a multiplet (for **3**) or a quadruplet AB system (for **4**). Meanwhile their signals appear as singlets at δ 3.13 (DMSO-d_6) or 3.52 (acetone-d_6 [14]) for the corresponding sulfide **2** and at δ 4.47 (acetone-d_6[14]) for sulfone **5**.

Thus, it was shown that dialkyl sulfides containing an electron-withdrawing β- and especially α-carboxy group are more resistant to oxidation.

Hence, we developed preparative methods for the selective oxidation of thiodialiphatic acids into sulfoxides with an easily accessible oxidant, modified the method for the synthesis of 3,3´-sulfinyldipropionic acid (**3**), and obtained for the first time stable sulfinyldiacetic acid (**4**) in the individual state.

Experimental

The starting sulfides, namely, 3,3´-thiodipropionic (**1**) and thiodiglycolic (**2**) acids (Fluka Chemie AG), were used as received. Acetone (analytical grade) was not purified. Other, domestic solvents (AcOH, benzene, and ether) were purified by standard methods. ^1H NMR spectra were recorded on a Bruker AMX-400 instrument with HMDS as the internal standard. The course of the reaction was monitored and the purity of sulfoxides was checked by TLC on Silufol plates (Czech Republic) in $EtOH—CHCl_3$ (1 : 3) (*A*), $Me_2CO—CHCl_3$, (1 : 1) (*B*) and (3 : 1) (*C*) (visualization with iodine vapor), as well as by the titrimetric reductive method as described earlier.[13]

Complete oxidation of sulfides into sulfoxides **3** and **4** was indicated by a negative test with aqueous KI/HCl for peroxide.

Caution! The use of a large excess of H_2O_2 (> 10—20%) in the synthesis of compounds **3** and **4** can yield explosive acetone peroxide! For safety purposes, isolation of sulfoxides **3** and **4** should be preceded by analysis for peroxides and the reaction mixture should be evacuated at $T < 56—60$ °C.

3,3´-Sulfinyldipropionic acid (3). Aqueous 50.8% H_2O_2 (1.65 g, 24.7 mmol) was added at 0 °C to a solution of compound **1** (4 g, 22.5 mmol) in 73 mL of Me_2CO, and the reaction mixture was left in a refrigerator for three days. The precipitate that formed was filtered off and washed with cold acetone and ether to give compound **3** (0.87 g), m.p. 112—114 °C. The filtrate containing, along with sulfoxide **3**, unreacted H_2O_2 (test with KI/H^+) and sulfide **1** (TLC/*A*), was allowed to stand in the dark at ~20 °C for the reaction to be completed. Two days later, the precipitate that formed was separated as described above to give compound **3** (1.36 g), m.p. 112—114 °C. The mother liquor was evaporated *in vacuo* to dryness, and the residue was washed with ether to give an additional 1.91 g of acid **3**, m.p. 111—114 °C. The total yield of sulfoxide **3** was 4.14 g (95%). The purity of compound **3** was confirmed by TLC (R_f 0.72/*A*) and ^1H NMR data. Recrystallization of compound **3** from water (as described earlier[6]) does not increase the melting point but results in considerable weight losses and thus seems to be inexpedient.

Found (%): C, 37.00; H, 5.26; S, 16.48. $C_6H_{10}O_5S$. Calculated (%): C, 37.11; H, 5.15; S, 16.49. ^{1}H NMR (AcOH-d$_4$), δ: 2.94 (t, 2 H, CH_2CO, J = 6.8 Hz); 3.24 (m, 2 H, CH_2SO).

According to the previous method,[6] the yield of pure compound **3** with m.p. 112 °C (water) (*cf.* Refs. 6, 7: m.p. 114 °C) was only 33%; concentration of the mother liquor gave an additional amount of product **3** (43%), m.p. 109—112 °C, containing ~10% sulfide **1** (R_f 0.9/A).

2,2´-Sulfinyldiacetic acid 4. ***A.*** Aqueous 50.8% H_2O_2 (8.08 g, 0.12 mol) was added at 0 °C to a solution of acid **2** (15 g, 0.1 mol) in 135 mL of Me_2CO. The reaction mixture was left in a refrigerator for three days and then kept (while periodically stirring without access for light) at ~20 °C for 26 h and at ~35 °C for 2 h. The ratio of **4** : **2** in the resulting solution (in system B) was ≈ 1 : 1 (TLC data).

B. Aqueous 50.8% H_2O_2 (8.08 g, 0.12 mol) was added at 0 °C to a solution of acid **2** (15 g, 0.1 mol) in a mixture of Me_2CO (135 mL) and AcOH (1.5 mL, 26 mmol). The reaction mixture was left in a refrigerator for three days and then at ~20 °C for two days. The reaction mixture was stirred at ~35—47 °C until H_2O_2 disappeared (~5.5 h) and evaporated *in vacuo* to dryness. The residue was washed with Et_2O and dried *in vacuo* over P_2O_5 to give a white powder (14.9 g, m.p. 119—124 °C) containing compounds **4** (~90%), **2** (~10%), and sulfone **5** (trace amounts) (TLC/B and ^{1}H NMR/DMSO-d$_6$ data). Sulfone **5** as a reference substance for TLC was prepared according to the known procedure.[15] Pure sulfoxide **4** was obtained by reprecipitation from hot Me_2CO with benzene (yield 72%, m.p. 141—142 °C) or precipitation from a methanolic solution with Et_2O (yield 55%, m.p. 142—143 °C) (*cf.* Refs. 8—10: R_f 0.1—0.18/B, 0.38—0.44/C).

Attempts to recrystallize compound **4** from water (as described in Ref. 5 for sulfoxide **3**) failed: a sample of **4** (1 g, m.p. 119—124 °C) dissolved in 5 mL of water at 63 °C gave no precipitate upon cooling. Found (%): C, 28.84; H, 3.59; S, 19.27; reductive equivalent[12] (E) 82.5. $C_4H_6O_5S$. Calculated (%): C, 28.92; H, 3.61; S, 19.28; E, 83 (M/2). ^{1}H NMR (DMSO-d$_6$), δ: 3.69 (q, 4 H, two overlapping AB systems, CH_2SCH_2, δ_A 3.6, δ_B 3.78, J_{AB} = 14.7 Hz); 5.21 (br.s, 2 H, 2 COOH).

Compound **4** was also synthesized as described earlier[8] (except that the reaction mixture was concentrated at 38—50 °C (~23 Torr) rather than over H_2SO_4 in a vacuum desiccator). The yield of the product was 84%, m.p. 80—100 °C. Along with sulfoxide **4** (R_f 0.18), the product contained admixtures of the starting sulfide **2** (R_f 0.56), the corresponding sulfone **5** (R_f 0.41), and unidentified substances (TLC/B data). Previously,[9] compound **4** was obtained in 70% yield (m.p. 119 °C).

References

1. T. P. Vasil´eva, A. O. Mozzhukhin, M. Yu. Antipin, and Yu. T. Struchkov, *Izv. Akad. Nauk, Ser. Khim.*, 1992, 1766 [*Bull. Russ. Acad. Sci., Div. Chem. Sci.*, 1992, **41**, 1368].
2. T. P. Vasil´eva, A. F. Kolomiets, E. I. Mysov, and A. V. Fokin, *Izv. Akad. Nauk, Ser. Khim.*, 1997, 1230 [*Russ. Chem. Bull.*, 1997, **46**, 1181 (Engl. Transl.)].
3. V. V. Znamenskii, A. D. Efremov, V. M. Bystrova, and T. P. Vasil´eva, *Khim.-Farm. Zh.*, 1986, **20**, 942 [*Pharm. Chem. J.*, 1986, **20** (Engl. Transl.)].
4. V. G. Yashunskii, *Usp. Khim.*, 1975, **44**, 564 [*Russ. Chem. Rev.*, 1975, **44**, 260 (Engl. Transl.)].
5. V. G. Yashunskii and V. Yu. Kovtun, *Usp. Khim.*, 1985, **54**, 138 [*Russ. Chem. Rev.*, 1985, **54**, 76 (Engl. Transl.)].
6. E. Larsson, *Svensk. Kem. Tids.*, 1943, **55**, 29.
7. E. Larsson, *Trans. Chalmers Univ. Technol.*, *Gothenburg* No. **59**, 1947, 3; *Chem. Abstrs.*, 1948, **42**, 7248b.
8. M. Gazdar and S. Smiles, *J. Chem. Soc.*, 1908, **93**, 1833.
9. H. Oddy and V. Dodson, *Ohio J. Sci.*, 1949, **49**, 149; *Chem. Abstrs.*, 1949, **43**, 9032g.
10. K. Jonsson, *Svensk. Kem. Tids.*, 1923, **34**, 192; *Chem. Abstrs.*, 1923, **17**, 1428.
11. L. Horner, H. Schaefer, and W. Ludwig, *Chem. Ber.*, 1958, **91**, 75.
12. E. Larsson, *Svensk. Kem. Tids.*, 1940, **52**, 9; *Chem. Abstrs.*, 1940, **34**, 4054.
13. S. Allenmark, *Acta Chem. Scand.*, 1966, **20**, 910.
14. M. Brink, *Acta Chem. Scand.*, 1966, **20**, 2882.
15. H. Backer, *Rec. Trav. Chim. Pays-Bas*, 1953, **72**, 119.

Received April 12, 2002;
in revised form August 22, 2002