

## Studies of Thioacids and Their Derivatives

## XIII.\* Thiohydroxamic Acids

K. A. JENSEN, O. BUCHARDT and C. CHRISTOPHERSEN

*Chemical Laboratory II (General and Organic Chemistry), University of Copenhagen, The H. C. Ørsted Institute, Copenhagen, Denmark*

The reaction between carboxymethyl dithioates and hydroxylamine has been devised as a general method for preparing thiohydroxamic acids. In some cases, however, only the corresponding nitriles could be isolated. According to infrared spectroscopy the thiohydroxamic acids are *N*-hydroxythioamides,  $R-C(SNHOH)$ , which do not tautomerize appreciably to thiohydroximic acids,  $R-C(SH)=NOH$ . Coordination compounds of the type  $[(RCSNHO)_2M]$  ( $M = Ni$  or  $Cu$ ) are derived from the thioamide form. On addition of a strong base they are transformed into derivatives of the thiohydroximic acid, *e.g.*  $[(RCSNO)_2M]Na_2$ , and this transformation is accompanied by a more spectacular change of the infrared spectrum than the formation of the neutral complexes.

The recent papers by Mizukami and Nagata<sup>1-3</sup> on thiohydroxamic acids prompt us to report some results from work carried out in this laboratory since 1961.

At the beginning of our investigation a few thiohydroxamic acids had been prepared from dithio acids and hydroxylamine<sup>4,5</sup> or from the reaction of hydroxamic chlorides with hydrogen sulfide.<sup>6</sup> More recently some thiohydroxamic acids have also been prepared from nitrile oxides and hydrogen sulfide.<sup>7</sup> We have used the reaction of carboxymethyl esters of dithio acids<sup>8</sup> with hydroxylamine as a general method for the preparation of thiohydroxamic acids. Although this method is not in principle different from the use of free dithio acids or of the ethyl esters used by the Japanese authors it offers great advantages because the carboxymethyl esters are stable crystalline compounds which can be stored indefinitely and because they are soluble in aqueous sodium hydroxide so that the reaction can be carried out in aqueous solution. In addition to some of the compounds obtained by Bachetti and Alemagna<sup>5,6</sup> we have by this method prepared several new thiohydroxamic acids (Table 1),

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Table 1. Thiohydroxamic acids, R-CSNHOH (and their Ni- and Cu-complexes).

R	Formula	M.p., °C	Analyses (C, H, N, S)
<i>o</i> -MeOC <sub>6</sub> H <sub>4</sub>	C <sub>8</sub> H <sub>9</sub> NO <sub>2</sub> S	76.5–77	Calc.: 52.46; 4.95; 7.65; 17.47 Found: 52.25; 4.80; 7.47; 17.42
»	(Ni-salt) C <sub>16</sub> H <sub>16</sub> N <sub>2</sub> NiO <sub>4</sub> S <sub>2</sub>		Calc.: 45.42; 3.79; 6.62 Found: 45.70; 3.79; 6.66
»	(Cu-salt) C <sub>16</sub> H <sub>16</sub> CuN <sub>2</sub> O <sub>4</sub> S <sub>2</sub>		Calc.: 44.91; 3.74; 6.55 Found: 44.98; 3.70; 6.40
<i>p</i> -MeOC <sub>6</sub> H <sub>4</sub>	C <sub>8</sub> H <sub>9</sub> NO <sub>2</sub> S	117–118	Calc.: 52.46; 4.95; 7.65; 17.47 Found: 52.30; 4.84; 7.77; 17.30
<i>o</i> -Pr <sup>n</sup> OC <sub>6</sub> H <sub>4</sub>	C <sub>10</sub> H <sub>13</sub> NO <sub>2</sub> S	59–60	Calc.: 56.85; 6.20; 6.63; 15.18 Found: 56.60; 5.98; 6.50; 15.03
<i>o</i> -Pr <sup>i</sup> OC <sub>6</sub> H <sub>4</sub>	C <sub>10</sub> H <sub>13</sub> NO <sub>2</sub> S	80–81	Found: 56.92; 6.15; 6.47; 15.02
<i>o</i> -Bu <sup>n</sup> OC <sub>6</sub> H <sub>4</sub>	C <sub>11</sub> H <sub>15</sub> NO <sub>2</sub> S	91–92	Calc.: 58.64; 6.70; 6.22; 14.21 Found: 58.20; 6.40; 6.14; 14.38
»	(Ni-salt) C <sub>22</sub> H <sub>28</sub> N <sub>2</sub> NiO <sub>4</sub> S <sub>2</sub>		Calc.: 52.3; 5.55; 5.55 Found: 52.0; 5.41; 5.70
»	(Cu-salt) C <sub>22</sub> H <sub>28</sub> CuN <sub>2</sub> O <sub>4</sub> S <sub>2</sub>		Calc.: 51.9; 5.50; 5.50 Found: 50.6; 5.51; 5.51
2-Furyl	C <sub>5</sub> H <sub>5</sub> NO <sub>2</sub> S	92–93	Calc.: 41.96; 3.52; 9.79; 22.38 Found: 41.84; 3.65; 9.54; 22.54

among which the *o*-alkoxybenzothiohydroxamic acids are very stable crystalline substances. *o*-Butoxybenzothiohydroxamic acid has been kept for more than two years in a refrigerator without any change, as indicated by m.p. and infrared spectrum. In contrast, some of the known thiohydroxamic acids, especially benzothiohydroxamic acid, acetothiohydroxamic, and phenylacetothiohydroxamic acid, are rather unstable and easily decompose into nitriles, sulfur, and water. In attempts to prepare  $\beta$ -phenylpropiothiohydroxamic acid, thiophene-2-carbothiohydroxamic acid, pyrrole-2-carbothiohydroxamic acid, and indole-3-carbothiohydroxamic acid we have only been able to isolate the nitriles.

The infrared spectra of all the thiohydroxamic acids investigated, recorded from KBr discs, showed no SH stretching band. Since this is located in an otherwise empty region (near 2600 cm<sup>-1</sup>) of the infrared spectrum, even a very weak absorption would have been discovered. It can therefore be concluded that these compounds in the solid state are generally not thiohydroxamic acids, R-C(=NOH)SH, but thiohydroxamic acids, *i.e.* *N*-hydroxythioamides, R-C(=S)NHOH.

Nagata and Mizukami<sup>2</sup> report that solutions of the thiohydroxamic acids show a weak SH band. We have also repeatedly observed such a band, but rigorous purification by recrystallization of aromatic crystalline thiohydroxamic acids and recording of the spectra immediately after dissolution of the compounds have always afforded spectra without any perceptible SH band, so we are inclined to ascribe any SH band to impurities, either originally present or originating from beginning decomposition. An exception seems to be phenylacetothiohydroxamic acid which showed an SH band ( $2580\text{ cm}^{-1}$ ) in  $\text{CS}_2$  solution which persisted after recrystallization. For this compound, however, another tautomerism than the hydroximic-hydroxamic acid tautomerism is also possible, *viz.* the formation of molecules with the structure  $\text{RCH}=\text{C}(\text{SH})\text{NHOH}$ .

All the thiohydroxamic acids investigated show absorption bands near  $1420\text{ cm}^{-1}$ ,  $1350\text{ cm}^{-1}$ ,  $1080\text{ cm}^{-1}$ ,  $700\text{ cm}^{-1}$ , and  $620\text{ cm}^{-1}$  which represent the thioamide B, C, D, F, and G bands, discussed by Jensen and Nielsen.<sup>9</sup> They are affected by *S*-alkylation or the formation of coordination compounds (Table 2), the first four bands being shifted to higher frequencies and the last

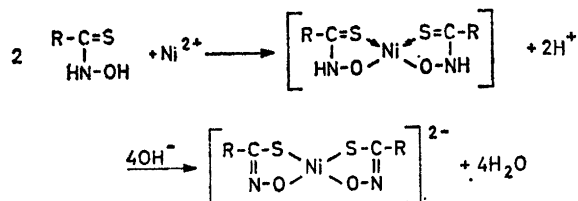
Table 2. Characteristic infrared bands ( $\text{cm}^{-1}$ ) of thiohydroxamic acids and their metal compounds.

Compound	B	C	D	F	G	OH
<i>o</i> -MeOC <sub>6</sub> H <sub>4</sub> CSNHOH	1420 s	1335 s	1070 s	705 m	612 s	1222 s
( <i>o</i> -MeOC <sub>6</sub> H <sub>4</sub> CSNHO) <sub>2</sub> Ni	1460 m	1360 s	1080 s	710 w	585 w	»
[( <i>o</i> -MeOC <sub>6</sub> H <sub>4</sub> CSNO) <sub>2</sub> Ni]Na <sub>2</sub>	1460 m	1530 m	1090 vw	715 w	580 w	»
( <i>o</i> -MeOC <sub>6</sub> H <sub>4</sub> CSNHO) <sub>2</sub> Cu	1460 m	1370 s	1100 s	720 m	580 w	»
[( <i>o</i> -MeOC <sub>6</sub> H <sub>4</sub> CSNO) <sub>2</sub> Cu]Na <sub>2</sub>	1460 m	1520 m	1100 vw	715 w	580 w	»
<i>o</i> -Bu <sup>n</sup> OC <sub>6</sub> H <sub>4</sub> CSNHOH	1420 s	1344 s	1070 s	700 m	620 w	1220 vs
( <i>o</i> -Bu <sup>n</sup> OC <sub>6</sub> H <sub>4</sub> CSNHO) <sub>2</sub> Ni	1460 s	1385 s	1085 s	705 m	580 vw	»
( <i>o</i> -Bu <sup>n</sup> OC <sub>6</sub> H <sub>4</sub> CSNHO) <sub>2</sub> Cu	1460 s	1385 s	1095 s	715 m	610 vw	»

one to lower frequencies. A band near  $1200\text{ cm}^{-1}$  disappears in the spectra of the coordination compounds and is assigned to the OH group. We do not agree with Nagata and Mizukami that a band near  $1570\text{ cm}^{-1}$  is a thioamide band because it appears practically unchanged in the spectra of the metal compounds. The band near  $1420\text{ cm}^{-1}$  was ascribed by Nagata and Mizukami to the OH group but it appears also in the spectra of the metal compounds which contain no OH group.

On addition of a nickel(II) or copper(II) salt to an ethanolic solution of a thiohydroxamic acid a yellowish (Ni) or brownish (Cu) precipitate is formed immediately and although the solution becomes strongly acid the precipitation is practically complete. These metal compounds contain the metal ion and the thiohydroxamic anion exactly in the proportion 1:2 and their properties indicate that they should be formulated as inner complex salts. According to an X-ray investigation by Sato *et al.*<sup>10</sup> this type of compound contains 5-membered rings so that the metal ion is bonded to the oxygen atom and not — as is usual in coordination compounds of oximes — to nitrogen. The

fact that the infrared spectra of these metal compounds differ comparatively little from the spectra of the thiohydroxamic acids — except for the disappearance of the band ascribed to the OH group — shows that they are derived from the thiohydroxamic form in which the hydrogen of the OH group has been replaced by the metal ion. However, the metal complexes dissolve easily in excess strong base with the formation of an orange-yellow (Ni) or red-brown (Cu) solution, so that also the NH group has an acid character. The infrared spectra of the complexes thus formed show a much more pronounced shift of the thioamide bands than those of the complexes formed in acid solution. A strong band near  $960\text{ cm}^{-1}$  — found both in the spectra of the thiohydroxamic acids and the neutral complexes and assigned to N—H deformation — has disappeared in the spectra of the anionic complexes and the band at  $1420\text{ cm}^{-1}$  is shifted to  $1530\text{ cm}^{-1}$ . This is very characteristic and is indicative of a change from the structure  $\text{S}=\text{C}-\text{N}$  to the structure  $\text{S}-\text{C}=\text{N}$ :



According to Huisgen *et al.*,<sup>11</sup> benzothiohydroxamic acid reacts with dichloro(diphenyl)methane (benzophenone dichloride) to form 2,2,4-triphenyl-1,3,5-oxathizole. This preparation could easily be repeated but no corresponding compounds could be prepared from *o*-alkoxybenzothiohydroxamic acids. It should be mentioned that benzothiohydroxamic acid also does not form heterocyclic compounds easily. Attempts were made to prepare oxathiazoles and some new types of heterocyclic compounds by reaction of benzothiohydroxamic acid and various other thiohydroxamic acids with benzylidene chloride, benzaldehyde, crotonaldehyde, acetone, benzophenone, phenylboron dichloride, and phenylphosphorus dichloride, but in all cases with negative results (frequently the thiohydroxamic acid decomposed with the formation of free sulfur).

#### EXPERIMENTAL

*Thiohydroxamic acids.* The carboxymethyl dithioate,<sup>8</sup>  $\text{RCSSCH}_2\text{COOH}$  (10 mmoles) was dissolved in 10 ml of 1 N NaOH, a solution of 11 mmoles of hydroxylammonium chloride in 11 ml of 1 N NaOH was added with cooling and the pH was adjusted to 7. The reddish colour of the solution disappeared more or less rapidly. Compounds with an aromatic-aliphatic ( $\text{C}_6\text{H}_5\text{CH}_2$ ,  $\text{C}_6\text{H}_5\text{CH}_2\text{CH}_2$ ) or heterocyclic radical, R, reacted very rapidly, most compounds with aromatic R rather slowly. To complete the reaction the solutions were stirred for 2–24 h at room temperature. The solution was made acid with acetic acid and extracted with ether, and the ethereal fractions were washed with water and dried with anhydrous magnesium sulfate, and the ether was removed by evaporation. The crude products may be contaminated by unchanged carboxymethyl ester and should be recrystallized until their infrared spectra show no absorption near  $1700\text{ cm}^{-1}$ . Benzene-petroleum ether (2:3) or ether-petroleum ether (1:1) were used for recrystallization. The compounds are colourless or light yellow.

From carboxymethyl  $\beta$ -phenyldithiopropionate a crystalline precipitate, which is probably the thiohydroxamic acid, separated in aqueous solution, but was transformed in the course of a few minutes into the oily nitrile. From the crude nitrile well-developed crystals of elemental sulfur separated after some days. Also from carboxymethyl 2-pyrrolicarboodithioate and carboxymethyl 2-thiophenecarboodithioate only the oily nitriles (strong nitrile bands at *ca.* 2200  $\text{cm}^{-1}$ ) were obtained. From carboxymethyl 3-indolecarboodithioate<sup>8</sup> a slightly soluble precipitate was formed the appearance of which changed conspicuously in the course of 24 h. The resulting compound was found to be 3-indolecarbonitrile (3-cyanoindole). Yield 50 % after purification by dissolution in chloroform or benzene and precipitation by addition of pentane to the filtered solution. (Found: C 75.45; H 4.57; N 19.46. Calc. for  $\text{C}_8\text{H}_6\text{N}_2$ : C 76.04; H 4.25; N 19.71). M.p. 176–177°C (lit.<sup>12</sup> 178°). The primary product was found to be the hydroxylammonium salt of the carboxymethyl ester, containing one mole water of crystallization after recrystallization from ethanol. (Found: C 43.87; H 4.50; N 9.05; S 21.19. Calc. for  $\text{C}_8\text{H}_7\text{NCSSCH}_2\text{COONH}_3\text{OH}\cdot\text{H}_2\text{O}$  or  $\text{C}_{11}\text{H}_{14}\text{N}_2\text{O}_4\text{S}_2$ : C 43.71; H 4.64; N 9.27; S 21.19). Its infrared spectrum agrees with the formulation as a salt of a carboxylic acid. On dissolution in aqueous sodium hydroxide and addition of hydrochloric acid, the original carboxymethyl ester precipitated.

Table 1 contains the analytical data for the new thiohydroxamic acids and for *p*-methoxybenzothiohydroxamic acid. The latter was described by Bachetti and Alemagna, but the m.p. found for our product deviates rather much from that given in Ref. 5 and seemed to indicate transformation into another compound. The infrared spectrum of the molten and resolidified substance was, however, unchanged. In addition, the following known compounds were prepared in 70–80 % yields by the method described here: benzothiohydroxamic acid (characterized as the *S*-benzyl derivative, m.p. 121–122°C, lit.<sup>4-5</sup> 120–122°), phenylacetothiohydroxamic acid (m.p. 72–73, lit.<sup>5</sup> 74–75°), and *p*-chlorobenzothiohydroxamic acid (m.p. 91–92°C, lit.<sup>5</sup> 93–94°).

The *o*-alkoxybenzothiohydroxamic acids are quite stable. The *o*-butoxy derivative could be recovered quantitatively and unchanged after boiling of its solution in toluene for one hour and it could be sublimed without change at 100°C and 0.1 mm Hg. However, on heating for 3 days in a sublimation apparatus at atmospheric pressure an oil collected on the “cold finger”; it showed a sharp absorption band at 2200  $\text{cm}^{-1}$ , characteristic of nitriles. Since light promoted discoloration of the compounds, their light sensitivity was tested: KBr-discs containing 1 mg of the compounds were irradiated in a quartz apparatus for several hours, but no change of the infrared spectra occurred.

*Metal compounds.* On addition of a solution of nickel(II) or copper(II) chloride to an ethanolic solution of the thiohydroxamic acid, the complex compound precipitates immediately. The nickel compounds are orange-coloured, the copper compounds have either a greenish-grey (*o*- and *p*-methoxybenzothiohydroxamates) or reddish-brown colour. The compounds dissolve in excess NaOH to give an orange or red-brown solution, respectively. Infrared spectra of the sodium salts were recorded after evaporation of the solutions *in vacuo*. The nickel and copper compounds of *o*-methoxy- and *o*-butoxybenzothiohydroxamic acids were isolated by filtration and showed practically correct analyses after washing with ethanol and ether and drying (Table 2). They are insoluble in water and in most organic solvents, but easily soluble in chloroform.

*Infrared spectra* were recorded on a Perkin Elmer Model 337 grating spectrophotometer from KBr discs or solutions in chloroform (both thiohydroxamic acids and inner complex salts) and carbon disulfide (only the thiohydroxamic acids). Table 2 shows the thioamide bands for two thiohydroxamic acids, but similar values have been found for the other thiohydroxamic acids. The absorption maxima were practically unchanged, whether they were recorded from KBr or solutions.

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