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Synthesis of 4-Ethyl-5-Ethylimino-[1,2,4]-Dithiazolidin-3-Trithione through Ethyl-(4-Ethyl-5-Thioxo-[1,2,4]-Dithiazolidin-3-ylidene)ammonium Oxopentachlorotungstate(VI) Hydrolysis and the Dimroth Rearrangement in It on Heating

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Abstract—We demonstrate that the previously synthesized product of ethyl isothiocyanate insertion into tungsten hexachloride, WCl_5{N(Et)C(S)N(Et)C(S)Cl}, whose partial hydrolysis yields {N(Et)C(S)–S–S–C=NH(Et)}[$WOCl_5$] (**I**), can be used as a source of biologically active heterocyclic compounds. ^{1}H and ^{13}C NMR and gas chromatography–mass spectrometry data show that reaction of **I** with a saturated aqueous Na_2CO_3 solution yields a number of thiazolidine heterocycles, mostly 4-ethyl-5-ethylimino-[1,2,4]-dithiazolidin-3-trithione. The thermal Dimroth rearrangement leads to the formation of 2,4-diethyl-[1,2,4]-dithiazolidin-3,5-dithione and the products of partial hydrolysis of both heterocycles: 4-ethyl-5-ethylimino-[1,2,4]-dithiazolidin-3-on and 2,4-diethyl-3-thioxo-[1,2,4]-dithiazolidin-5-on.

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INTRODUCTION

The synthesis and properties of thiazolidine compounds have attracted considerable attention because they possess high reactivity in various chemical transformations. These derivatives were shown to offer a wide range of biological activities. In particular, penicillin compounds are known to contain thiazolidine as a component, and the healing power of this type of drug substance is due to this ring.

As shown earlier, the reaction of WCl_6 with EtNCS in dichloroethane leads to the insertion of two isothiocyanate molecules into one tungsten–chlorine bond, yielding WCl_5{N(Et)C(S)N(Et)C(S)Cl}[1]. It is shown as well that holding the addition product in an excess of EtNCS in the presence of trace levels of atmospheric moisture causes its partial hydrolysis, which, according to X-ray diffraction results [1], leads to partial cyclization of the hydrolyzed ligand, yielding {$\overline{\text{N(Et)C(S)–S–S–C}}$=NH(Et)}[$WOCl_5$] (**I**), containing a dithiazolidin derivative as a cation.

In this paper, we report NMR and gas chromatography–mass spectrometry studies of the hydrolysis of **I** and describe counter synthesis necessary to identify the organic products of the hydrolysis of **I**.

†Deceased.

EXPERIMENTAL

Hydrolysis of I. To carry out the reaction, we used earlier prepared, structurally characterized crystals of **I** [1], Na_2CO_3 (analytical grade), absolute ether, and hexane (analytical grade).

To a weighed amount of **I** (1.05 g, 20 mL) was added a saturated aqueous Na_2CO_3 solution. As a result, the solution took on a turquoise color, a yellow oily product was formed on the bottom of the flask, and HCl gas evolved. The oil was extracted with 10 mL of ethyl ether, boiled down to 10 mL under vacuum, and left to stand until complete ether vaporization. Next, the isolated compound was recrystallized from hexane and characterized by ^{1}H and ^{13}C NMR and gas chromatography–mass spectrometry.

^{1}H and ^{13}C NMR spectra were taken on a Bruker AC 200 spectrometer at working frequencies of 200.13 and 50.3 MHz, respectively, using a deuterium lock. The ^{1}H and ^{13}C chemical shifts were determined relative to tetramethylsilane. The signals from the CH_2 and CH_3 groups in the ^{13}C NMR spectra were assigned by the DEPT method using a 135° editing pulse [2]. The signals in the proton and carbon NMR spectra were correlated using a two-dimensional heterocorrelated experiment: ^{13}C, ^{1}H-CORR [3]. Signals from tertiary carbon atoms were accumulated and assigned using selective polarization transfer from protons having sca-

lar spin–spin interaction with a ^{13}C nucleus through several bonds (INEPT LR) [4].

Gas chromatography–mass spectrometry experiments were carried out on an Automass 150 spectrometer (Delsi-Nermag, France) in electron impact mode (ionization energy of 70 eV). Chromatographic separation was performed with an OV-1 capillary column (inner diameter, 0.25 mm; length, 25 m; He carrier gas, 0.75 atm). Chromatographic modes: injector with a split ratio of 1 : 40; $t_{inj} = 300°C$; injected sample volume, 0.5 μL; initial column temperature, 100°C (2 min); temperature program, 10°C/min to 270°C.

Counter synthesis. 4-Ethyl-5-ethylimino-[1,2,4]-dithiazolidin-3-thione (**II**) was prepared as described by Freund [5]. We used ethyl isothiocyanate (Fluka), Na_2CO_3 (analytical grade), bromine dried over concentrated H_2SO_4, *n*-octane distilled twice over CaH_2, chloroform (analytical grade), and absolute ether.

To a bromine solution (5 mL) in octane (100 mL) was added in small portions with constant stirring an ethyl isothiocyanate solution (9 mL) in octane (9 mL). The reaction was highly exothermic and yielded a dark vinous oil, which was separated from the solution by filtration, washed with octane, and dried to constant weight.

The oily product was decomposed by water (200 mL) over a period of three days. To the resultant pale yellow solution was added Na_2CO_3 until CO_2 evolution ceased. The dark yellow oil resulting from the hydrolysis was extracted with ethyl ether (150 mL), and the extract was dried using a roughing pump.

The product, having the form of yellow oil, was treated with water. As a result, light yellow oil (**II**) was formed on the flask wall. It was filtered off, dissolved in chloroform on the filter, and used to identify the organic product by ^1H and ^{13}C NMR (table) and gas chromatography–mass spectrometry. In addition, when the reaction was left to stand, yellow crystals precipitated from the solution. The crystals were also characterized by NMR spectroscopy (table, **V**).

Since the sample to be analyzed by mass spectrometry was passed through a high-temperature zone (above 150°C), we performed an additional NMR characterization of a solution of **II** in $CDCl_3$ after holding **II** at 160°C for 55 min, which indicated the formation of a mixture of four compounds (table, **II**–**V**).

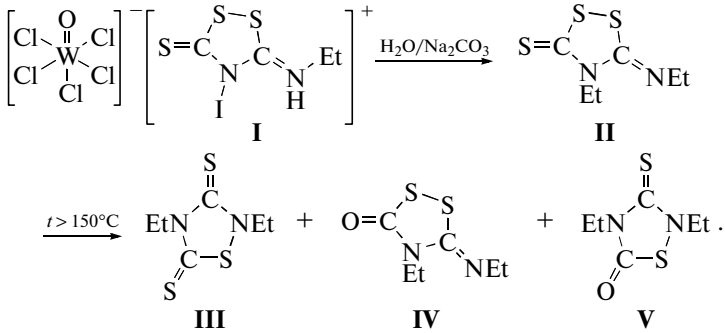
It is remarkable that the addition of Na_2CO_3 led not only to the formation of dark yellow oil (**II**) but also to the precipitation of yellow crystals (**VI**), in contrast to what was reported by Freund [5]. According to X-ray diffraction data, which agreed well with earlier results [6], the crystals consisted of crystalline sulfur, S_8.

The structure of **VI** was determined by X-ray diffraction on an Enraf-Nonius CAD-4 single-crystal automatic diffractometer (4 (λ MoK_α, graphite monochromator).

RESULTS AND DISCUSSION

The present ^{13}C and ^1H NMR spectroscopy results (table) demonstrate that the organic product resulting from the hydrolysis of **I** is a five-membered dithiazole ring: 4-ethyl-5-ethylimino-[1,2,4]-dithiazolidin-3-thione (**II**).

What is surprising at first sight is that the mass spectrum of the reaction product shows two mass 190 peaks and two mass 260 peaks, indicating that the sample contains, in addition to **II** (dithiazole derivative) and **III** (its bond isomer), two isomeric compounds formed through partial hydrolysis of the above compounds: the oxo derivatives **IV** and **V**:



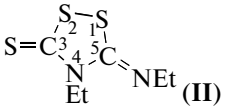
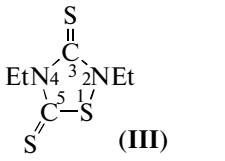
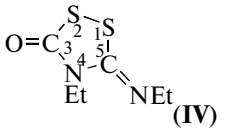
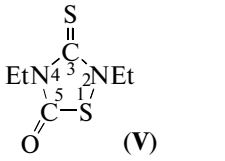
I **II** **III** **IV** **V**

Additional studies showed that the observed distinctions between NMR and mass spectrometry results were due to the difference in temperature programs.

In particular, the NMR spectrum of the solution of **II** after heat treatment indicated the presence of the same four compounds (table) as after passing **II** through a high-temperature zone in gas chromatography–mass spectrometry characterization.

These transformations, resulting in bond isomerization of **II** followed by the hydrolysis of both isomers,

Parameters of the ^{1}H and ^{13}C NMR spectra of the organic compounds isolated in $CDCl_3$ at 298 K

Compound	Position	Group	δ, ppm	^{3}J, Hz	δ, ppm
			proton NMR		^{13}C
 **(II)**	4	CH_3	1.167 *t*	6.95	10.76
	4	CH_2	4.21 *q*	6.95	45.51
	5	CH_3	1.25 *t*	7.18	15.3
	5	CH_2	3.36 *q*	7.18	47.5
	5	C	–	–	152.03
	3	C	–	–	192.45
 **(III)**	4	CH_3	1.25 *t*	7.24	10.89
	4	CH_2	4.39 *q*	7.24	44.19
	2	CH_3	1.31 *t*	7.22	12.79
	2	CH_2	4.03 *q*	7.22	44.06
	3	C	–	–	175.7
	5	C	–	–	187.63
 **(IV)**	4	CH_3	1.21 *t*	7.16	11.77
	4	CH_2	4.01 *q*	7.16	39.93
	5	CH_3	1.23 *t*	7.27	13.81
	5	CH_2	3.65 *q*	7.27	39.75
	5	C	–	–	153.4
	3	C	–	–	187.3
 **(V)**	4	CH_3	1.23 *t*	7.1	12.1
	4	CH_2	4.06 *q*	7.1	44.1
	2	CH_3	1.29 *t*	7.1	12.7
	2	CH_2	4.03 *q*	7.1	41.7
	5	C	–	–	166.9
	3	C	–	–	174.9

constitute an example of the thermal Dimroth rearrangement, often encountered in heteroaromatic compounds [7]. They are accompanied by preliminary ring opening in the hydrolysis of **II**, followed by the formation of its bond isomer (**III**) and oxo derivatives corresponding to **II** and **III** (**IV** and **V**, respectively).

It is remarkable that a similar thermal rearrangement was identified previously in X-ray diffraction characterization of complete [8] or partial [9] hydrolysis products: symmetric and asymmetric triazine rings obtained through EtNCO insertion into WCl_6 under various temperature conditions. In particular, in the case of an ethyl isocyanate derivative, raising the synthesis temperature from 20°C to the boiling point of the reaction mixture leads to bond isomerization, like in this study. In both cases, all of the isocyanate groups in the structure of the heterocycles in the thermolysis products are linked to one another only through CN bonds, in contrast to their analogs synthesized without heating.

CONCLUSIONS

The present results suggest that ethyl isothiocyanate insertion into tungsten hexachloride and subsequent hydrolysis of the reaction product can be used for modeling and creating drugs based on complexes containing dithiazole rings. Moreover, these reactions can be thought of as a direct path to the preparation of 4-ethyl-5-ethylimino-[1,2,4]-dithiazolidin-3-thione (**II**), its bond isomer (**III**), and their oxo derivatives (**IV** and **V**), which may exhibit biological activity.

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