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Dedicated to Full Member of the Russian Academy of Sciences G.A. Tolstikov on his 75th anniversary

1,1,1- and 1,1,3-Trihalo-2-sulfanylpropan-2-ols: New Preparatively Accessible Synthons

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Abstract—A procedure has been developed for the synthesis of 1,1,1-trichloro-2-sulfanylpropan-2-ol and 1,1,3-tribromo-2-sulfanylpropan-2-ol via acid-catalyzed addition of hydrogen sulfide to the corresponding ketones. The stability of the resulting hydroxy thiols was estimated by analyzing the potential energy surface for the reaction of 1,1,1-trichloropropan-2-one with hydrogen sulfide in the presence of hydrogen chloride. In addition, quantum-chemical analysis of rotational isomerism of 1,1,1-trichloro-2-sulfanylpropan-2-ol was performed.

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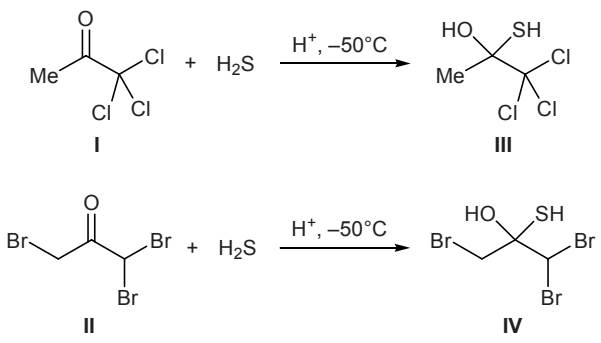
Geminal hydroxy thiols have been poorly studied, for there are no reliable methods for their preparation. Nevertheless, interest in such structures is related to their high reactivity and the possibility of using them in the synthesis of various acyclic, heterocyclic, macrocyclic, and polymeric systems possessing practically important properties.

It is known [1] that reactions of hydrogen sulfide with carbonyl compounds involve intermediate formation of the corresponding geminal hydroxy thiols. These intermediates were detected by experimental methods; however, it was very difficult or impossible to isolate them as individual substances. Geminal hydroxy thiols that are stable under usual conditions were synthesized for the first time by reaction of polyfluorinated ketones with hydrogen sulfide in a sealed ampule under high pressure at 80°C [2].

We previously showed that the stability of the C(OH)SH moiety depends on the number of halogen atoms in the initial ketone molecule [3, 4]. Reactions of α,α′-dihalo ketones in aprotic solvent stop at the stage of formation of hydroxy thiol due to stabilization via interaction between the SH and OH protons, on the one hand, and halogen atoms, on the other. Presumably, in protic medium, these limitations are partially removed, thus favoring elimination of water with formation of thiones [4].

In the present work we examined the effect of three halogen atoms on the stability of hydroxy thiol intermediates. The only product of the reaction of 1,1,1-trichloropropan-2-one (**I**) or 1,1,3-tribromopropan-2-one (**II**) with hydrogen sulfide at –50°C, regardless of the solvent (diethyl ether or methanol), was the corresponding geminal hydroxy thiol, 1,1,1-trichloro-2-sulfanylpropan-2-ol (**III**) or 1,1,3-tribromo-2-sulfanylpropan-2-ol (**IV**), which was formed in 81–85% yield (Scheme 1). The structure of compounds **III** and **IV** was confirmed by the IR and ^{1}H and ^{13}C NMR spectra.

Scheme 1.



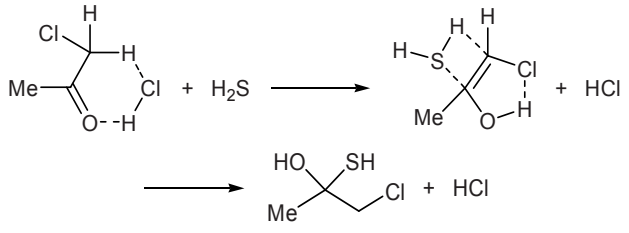
Their IR spectra (neat) characteristically contained absorption bands due to S–H [2578 (**III**), 2562 cm^{-1} (**IV**)] and O–H groups [3447 (**III**), 3446 cm^{-1} (**IV**)]. In the ^1H NMR spectra, the SH and OH protons appeared at δ 3.11 (SH, **III**), 1.56 (SH, **IV**), 3.68 (OH, **III**), and 3.68 ppm (OH, **IV**). The C(SH)OH carbon nucleus resonated in the ^{13}C NMR spectrum at δ_C 91.72 and 84.75 ppm for compounds **III** and **IV**, respectively.

Above −5°C, compounds **III** and **IV** lose hydrogen sulfide molecule. This follows from the appearance of IR absorption bands at 1739 and 1732 cm^{-1}, corresponding to stretching vibrations of the carbonyl group in initial ketones **I** and **II**, in addition to SH and OH absorption. In the ^{13}C NMR spectra, a signal at δ_C 195.01 ppm was observed, which is typical of carbonyl carbon atom.

In order to elucidate factors responsible for the stability of hydroxy thiol intermediates in reactions of halogenated acetone with hydrogen sulfide and its relation with the number of α-halogen atoms, we examined the potential energy surface for the reaction of 1,1,1-trichloropropan-2-one (**I**) with hydrogen sulfide in the presence of hydrogen chloride, leading to 1,1,1-trichloro-2-sulfanylpropan-2-ol (**III**); also, quantum-chemical analysis of rotational isomerism of compound **III** was performed. The calculations were performed using Gaussian 98 software package [5] with 6-311+G(3*df*) basis set. The molecular structures and gradient channel connecting them were simulated in terms of the density functional theory (DFT) using B3LYP three-parameter functional [6]. The calculation details were described previously [7].

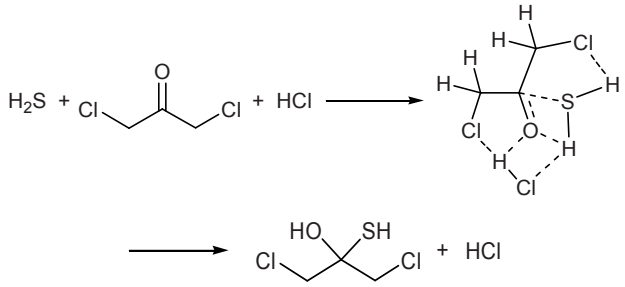
According to the experimental data, the mechanism of formation of hydroxy thiols in reactions of halogenated ketones with hydrogen sulfide in the presence of hydrogen chloride is determined on the number of halogen atoms in the α-positions with respect to the carbonyl group and is almost independent of the halogen nature (F, Cl, Br) [7, 8]. Therefore, the calculations were performed for chlorinated acetones. The reaction of α-chloroacetone with H_2S in the presence of HCl includes two steps with intermediate formation of the corresponding enol form, where hydrogen chloride acts as mediator (Scheme 2). The rate-determining step is the reaction of hydrogen sulfide with the active enol form (E_{act} = 232.5 kJ/mol, according to the B3LYP/LANL2DZ calculations [8]).

Scheme 2.



1,3-Dichloropropan-2-one reacts preferentially along a one-step path involving direct nucleophilic attack by hydrogen sulfide on the carbonyl group (E_{act} = 184.3 kJ/mol, B3LYP/6-311+P(3*df*) [7]). In this case, reaction of hydrogen chloride molecule at the carbonyl group reduces the order of the C=O bond, which facilitates proton addition at the π-orbital of the oxygen atom.

Scheme 3.

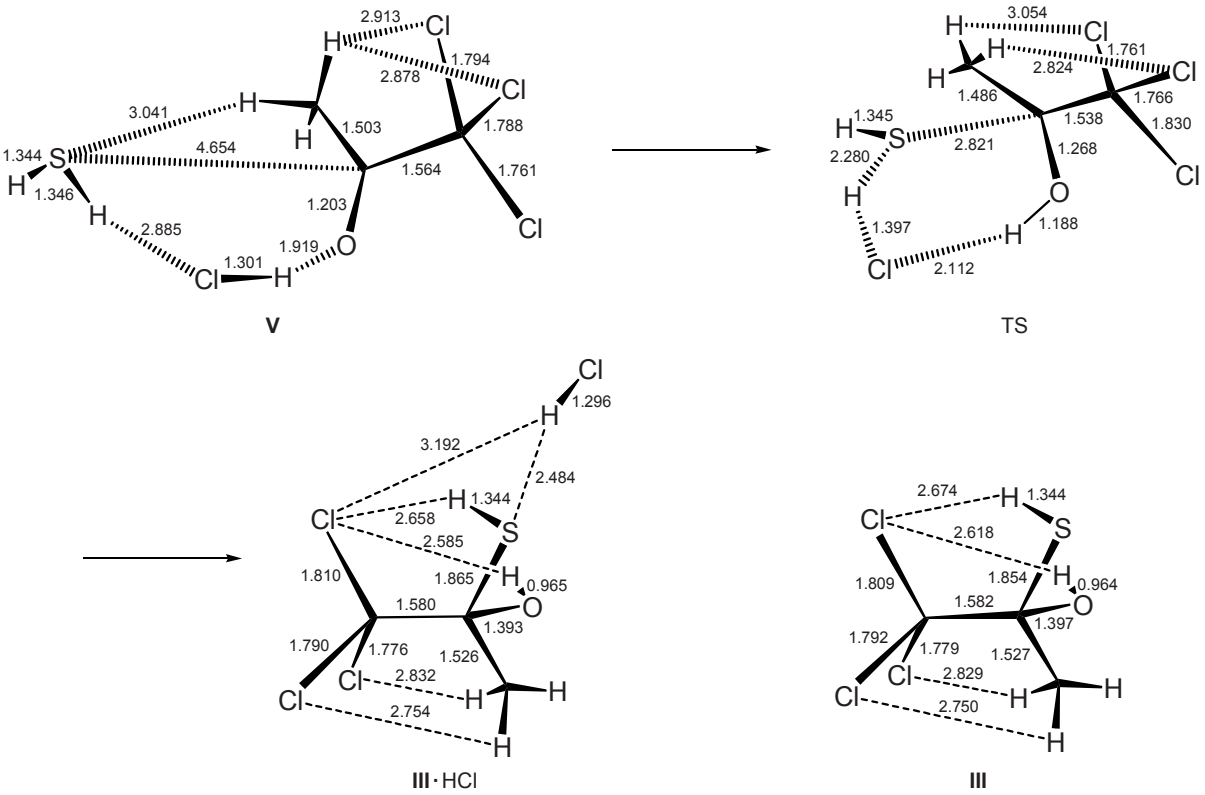


The results of calculations showed that the optimal gradient channel for the formation of hydroxy thiol from 1,1,1-chloropropan-2-one differs from those considered above. It includes intermolecular proton shifts. The potential energy surface for the reaction of ketone **I** with H_2S and HCl was analyzed following the pro-

Total energies (E_{tot}, a.u.),[a] energies of zero-point harmonic vibrations (ZPE, a.u.), relative energies (Δ*E*, kJ/mol), imaginary or least harmonic frequencies (*iw*/w_1, cm^{-1}), and dipole moments (μ, D) of the initial reactants, transition state, and products in the reaction of 1,1,1-trichloropropan-2-one with hydrogen sulfide and hydrogen chloride, calculated at the B3LYP/6-311+G(3*df*) level

Structure	$-E_{tot}$	ZPE	Δ*E*	*iw*/w_1	μ
I·HCl·H_2S	2432.34876	0.08612	0.0	23	1.73
TS	2432.28388	0.08573	169.2	*i*942	2.98
III·HCl	2432.34275	0.08644	8.7	12	2.19
III	1971.50392	0.07789	–	79	0.45
I	1572.08107	0.05565	–	57	2.36
HCl	460.83411	0.00667	–	2924	1.12
H_2S	399.42329	0.01498	–	1219	0.97

[a] 1 a.u. = 2622.9897 kJ/mol.



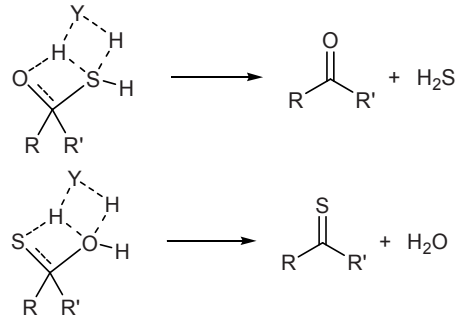
Structures and principal geometric parameters (interatomic distances, Å) of isolated molecule **III**, trimolecular complex **V**, bimolecular complex **III**·HCl, and the corresponding transition state TS according to the B3LYP/6-311+G(3*df*) calculations.

cedures described in [7, 8] for trimolecular system **I**·HCl·H_2S (**V**).

The energy of stabilization of prereaction complex **V** was estimated as the difference in the total energy of the complex and the sum of the energies of the optimized components and was 27.0 kJ/mol (see table). The structures and principal geometric parameters of complex **V** are given in figure. Complex **V** is stabilized by formation of a set of intermolecular hydrogen bonds which determine the optimal reaction channel. The reaction involves joint prototropic shifts, followed by attack by the thiol group on the electrophilic carbon center (see figure). The activation barrier for the formation of structure **III**·HCl is 169.2 kJ/mol; i.e., it is lower by 14.2 kJ/mol than the barrier to analogous reaction of 1,3-dichloropropan-2-one [7]. The transition state of the reaction **I**·HCl·H_2S → **III**·HCl and its structural parameters are given in figure. The thermodynamic stability of bimolecular structure **III**·HCl is insignificantly lower than that of prereaction complex **V** (ΔE = 8.7 kJ/mol).

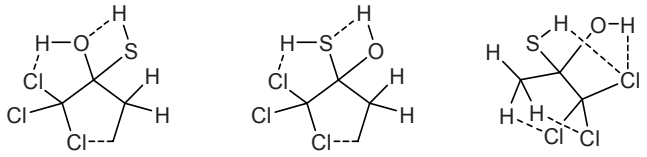
Hydroxy thiol structure is capable of losing either hydrogen sulfide or water molecule to produce the corresponding ketone or thione, respectively, as a result of intramolecular autoprotonation promoted by proton-donor molecules in the nearest environment (Scheme 4).

Scheme 4.



The predominant reaction channel is determined by rotational state of hydroxy thiol, which is related in turn to orientation of the SH and OH protons and halogen atoms. According to our previous data [7], rotamers **A** and **B** are the most favorable for elimination, while rotamer **C** is unfavorable.

Interconversions of rotamers **A**–**C** are characterized by activation barriers exceeding 30 kJ/mol, which rule out rotational transformations in low-temperature re-



A B C

actions. Unlike 1,3-dichloro-2-sulfanylpropan-2-ol which gives rise to a large number of spectroscopically distinguishable rotational states [7] (the stability range of the most thermodynamically favorable rotamers **A**–**C** does not exceed 4.1 kJ/mol), rotamers **A** and **B** of isolated molecule **III** degenerate into **C**. Presumably, this is the main factor responsible for the formation of relatively stable hydroxy thiol in the low-temperature reaction of 1,1,1-trichloropropan-2-one (**I**) with hydrogen sulfide.

Thus we have developed a procedure for the synthesis of first representatives of the geminal hydroxy thiol series, containing three halogen atoms in the α-positions with respect to the C(SH)OH moiety. The presence of several halogen atoms considerably extends the synthetic potential of these compounds from the viewpoint of obtaining new cyclic and heterocyclic systems, including those possessing biological activity.

EXPERIMENTAL

The ^{1}H and ^{13}C NMR spectra were recorded on a Bruker DPX-400 instrument (400 and 100 MHz, respectively) from solutions in $CDCl_3$. The IR spectra were measured on an IFS-25 spectrometer from thin films (neat). The progress of reactions and the purity of products were monitored by TLC on Silufol UV-254 plates using chloroform as eluent. Trihaloketones **I** [9] and **II** [10] were synthesized by known methods. We failed to perform elemental analysis of compounds **III** and **IV** because of their instability under usual conditions.

1,1,1-Trichloro-2-sulfanylpropan-2-ol (III). A solution of 1 g (6.2 mmol) of 1,1,1-trichloropropan-2-one (**I**) in 10 ml of anhydrous methanol was saturated with hydrogen chloride at −10°C and cooled to −50°C, and hydrogen sulfide was passed through the solution over a period of 10–12 h until the initial ketone disappeared completely. The mixture was purged with argon to remove excess hydrogen chloride and hydrogen sulfide, 50 ml of diethyl ether cooled to −60°C was added, and the mixture was quickly washed with ice-cold water until neutral reaction. The organic layer was dried over $CaCl_2$ and evaporated under reduced pressure. Yield 0.98 g (81%), colorless viscous liquid, which is stable below −5°C. IR spectrum, ν, cm^{-1}: 2578 (S–H), 3447 (O–H). ^{1}H NMR spectrum, δ, ppm: 1.99 s (3H, CH_3), 3.11 s (1H, SH), 3.68 s (1H, OH). ^{13}C NMR spectrum, δ_C, ppm: 27.32 (CH_3), 91.72 (HSCOH), 107.84 (CCl_3). ^{1}H NMR spectrum of initial ketone **I**, δ, ppm: 2.60 s (3H, CH_3). ^{13}C NMR spectrum of initial ketone **I**, δ_C, ppm: 21.61 (CH_3), 96.29 (CCl_3), 187.60 (C=O).

1,1,3-Tribromo-2-sulfanylpropan-2-ol (IV) was synthesized in a similar way from 1 g (3.4 mmol) of 1,1,3-tribromopropan-2-one (**II**). Yield 0.94 g (85%), colorless viscous liquid, which is stable below −5°C. IR spectrum, ν, cm^{-1}: 2562 (S–H), 3446 (O–H). ^{1}H NMR spectrum, δ, ppm: 1.56 s (1H, SH), 3.68 s (1H, OH), 3.94 d and 4.02 d (1H each, CH_2Br, *AB* system, J = 11.18 Hz), 6.08 s (1H, CH). ^{13}C NMR spectrum, δ_C, ppm: 40.05 (CH_2), 53.16 (CH), 85.74 (HSCOH). ^{1}H NMR spectrum of initial ketone **II**, δ, ppm: 4.44 q (2H, CH_2), 6.12 s (1H, CH). ^{13}C NMR spectrum of initial ketone **II**, δ_C, ppm: 27.38 (CH_2), 38.57 (CH), 188.01 (C=O).

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