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Studies on oxidative transformations of thiols, sulfides and alcohols in the presence of chlorine dioxide

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Abstract: Our recent studies on the chemical reactivity of chlorine dioxide in the reactions with sulfur and oxygen containing compounds are reviewed. A special attention is given to chlorine dioxide interaction with alkyl, aryl, heteroaryl, monoterpenyl thiols, sulfides and disulfides. The data on the oxidation of monoterpene alcohols and phenols are also presented. The directions of reactions depending on the structure of the compounds were identified.

Keywords: alcohols; chlorine dioxide; disulfides; heteroaryl; Mendeleev XX; oxidation; phenols; sulfides; terpenoids; thiols.

Introductions

The oxidative transformations under the action of organic and inorganic oxidants are one of the most common methods of the conversion of different classes of organic compounds. Oxidation processes play an important role in nature, chemical engineering and organic synthesis.

The simplest triatomic oxidants (chlorine dioxide, ozone, etc.) are of particular interest among a large number of oxidants and oxidation systems.

Chlorine dioxide (ClO_2) is a commercial product and is used in the pulp and paper industry in bleaching cellulose fibers, as well as in water treatment and disinfection [1, 2].

It is highly soluble in water and organic solvents, which makes possible to use it in different media and change the way of adding reagents.

The structural features of the molecule of chlorine dioxide such as the presence of an unpaired electron and two reaction centers (chlorine and oxygen) determine its properties different from those of other oxidants.

Compared to the chlorine or hypochlorous acid the chlorine dioxide primarily acts as an oxidant rather than as a chlorinating agent.

The physical and chemical properties of chlorine dioxide, methods of synthesis, industrial applications have been described and also the results of studies of chlorine dioxide interaction with aromatic compounds,

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olefins, phenols, amines, aliphatic alcohols and some carbonyl compounds in aqueous media have been summarized in monographs [3, 4].

The kinetic studies and mechanism of the reaction of chlorine dioxide with some classes of organic compounds have benn discussed in the reviews [5, 6].

In this review, we summarize the results of the investigations of chlorine dioxide reaction with sulfur- and oxygen-containing organic compounds obtained in the Institute of Chemistry of the Komi Science Centre of Ural Branch of the Russian Academy of Sciences.

Reactions with organosulfur compounds

The products of oxidation of organosulfur compounds are widely used in chemical industry and medicine. Dialkyl and diaryl thiosulfinates and thiosulfonates have shown bactericidal and fungicidal activities. Sulfonyl chlorides are used in the production of detergents, ion exchange resins, elastomers, pharmaceuticals, dyestuffs, herbicides. Like a sulfonic acid the sulfonyl chlorides are important intermediates in organic synthesis and are used in the synthesis of sulfonic acid esters and as soft alkylation agents in organic synthesis. Sulfonic acids are used to obtain azo dyes, medicinal substances (sulfonamides), ion exchange resins, electroplating additives, catalysts and others. Sulfoxides and sulfones are used as metal extractants and complexing agents, flotation agents, pharmaceuticals and are involved in fine organic synthesis. Most of the drugs belong to the class of heterocyclic compounds. Their biological activity primarily depends on the nature of the substituents, which makes the chemical modification of heteroarylthioles a promising direction in the search for new biologically active substances [7, 8].

Reactions with thiols and disulfides

The studies of ClO_2 reaction with organic thiols and disulfides have shown that the substrate structure has a major effect on the product composition, and the reaction conditions such as the molar ratio of the reactants, the nature of the solvent and the method of mixing the reactants affect the yield of the products. Two main methods of mixing reagents were used:

method *a*–the chlorine dioxide (gas or solution) is added in doses to an organic solution of organosulfur compounds;

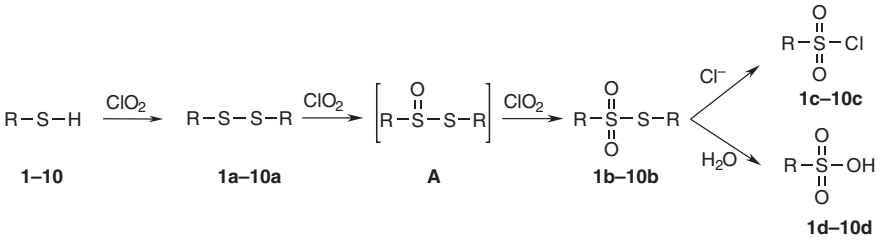
method *b*–solution of organosulfur compounds is added in doses to an organic or aqueous solution of chlorine dioxide.

It was revealed that the main products of reactions between ClO_2 and thiols are disulfides, thiosulfonate, sulfonyl chlorides, and sulfonic acid, less commonly are trisulfides, sulfinyl chlorides, ketones, esters [9–17].

The synthesis of sulfonyl chlorides by oxidation of thiols and disulfides with chlorine dioxide is a new reaction, which was first described in our papers [10, 12]. Sulfonyl chlorides in industry and laboratory are prepared by interaction of aliphatic hydrocarbons with sulfuryl halides or mixture of chlorine and sulfur dioxide, by oxidative chlorination of thiols, sulfides, disulfides; by oxidation of sulfinyl chlorides; by reacting of the sulfonic acid and their derivatives with PCl_5, $COCl_2$, thionyl chloride, chlorine, chlorosulfonic acid. Sulfonyl halides are also formed by the reaction of organomagnesium compounds with sulfuryl halide or diazonium salt with sulfur dioxide and $CuCl_2$ [18]. However, all these methods have certain disadvantages associated with the harsh reaction conditions and side reactions. We have developed a method of synthesis of sulfonyl chlorides, which is convenient and easy to use and gives a high yield (up to 88 %), does not require additional reaction conditions, such as heating, cooling, pressure variation.

Reactions alkyl, aryl thiol and disulfides

In the first step of the oxidation of alkyl and aryl thiol by ClO_2 the corresponding disulfides **1a–10a** in 86–98 % yield are produced [7] (Scheme 1).



R = C_6H_{13} (**1**), $C_{16}H_{33}$ (**2**), C_2H_4OH (**3**), $C_6H_5CH_2$ (**4**), *n*-$CH_3C_6H_4$ (**5**), C_2H_5 (**6**), C_4H_9 (**7**), C_6H_5 (**8**), *n*-$NO_2C_6H_4$ (**9**), $CH_2CH(NH_2)COOH$ (**10**).

Scheme 1: Reactions of chlorine dioxide with alkyl- and aryl thiol and disulfides.

Increasing the molar ratio of the thiol-oxidant leads to the formation of thiosulfonates **1b–10b** [12], followed by sulfonyl chlorides **1c–9c** [10, 12].

For example, in the oxidation of hexanethiol **1** in dichloromethane in a molar ratio of thiol-oxidant of 1:0.5 the main product is dihexyl disulfide **1a** (98 %); and oxidation in a molar ratio of thiol-oxidant of 1:2 results in a mixture of disulfide **1a** thiolsulfonate **1b** and sulfunylchloride **1c** in 24 %, 65 % and 11 % yields, respectively. In the presence of water in reaction mixture the products of complete oxidation of thiols are sulfonic acids **1d**–**9d** with 64–95 % yields [16]. Good water solubility of cysteine **10** and ClO_2 allows to complete the reaction in an aqueous medium for 0.5 h in the ratio of thiol-oxidant of 1:3 producing the appropriate sulfonic acid **10d** in a quantitative yield.

The reaction temperature affects the reaction rate and selectivity. For example, oxidation of diethyl disulfide **6a** at room temperature in chloroform with an equimolar amount of chlorine dioxide for 1 h leads to the formation of diethyl thiosulfonate **6b** with the selectivity of 75 % and complete conversion. Oxidation disulfide **6a** at 0 °C leads to an increase the reaction time by eight times, but the selectivity reaches 90 %.

Oxidation of disulfide **6a** at 0 °C increases the reaction time by eight times, but the selectivity reaches 90 %.

For obtaining thiosulfates, the method of mixing reagents is preferable when the chlorine dioxide is added in doses to an organic solution of thiol or disulfide (method *a*, oxidation in the case of oxidant shortage).

For example, in the oxidation of dihexyl disulfide **1a** in dichloromethane for 1 h in a molar ratio of substrate-oxidant ratio of 1:2 the yield of dihexyl thiosulfonate **1b** is 73 %.

In the case when the solution of dihexyl disulfide **1a** is added in doses to the solution of chlorine dioxide (method *b*, oxidation with the oxidant present in excess), the yield of thiolsulfonate **1b** is 18 % and the main product is sulfonyl chloride **1c**.

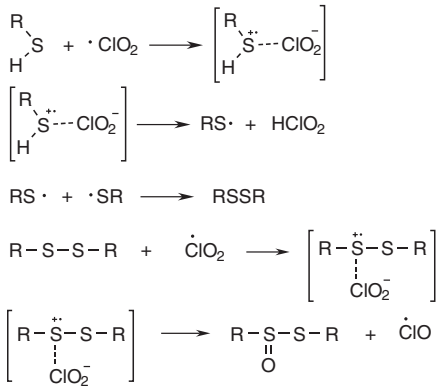
The influence of the solvent nature on the conversion of substrates and yields of the corresponding thiosulfonates and sulfonyl chlorides was found. Thus, in the oxidation of dibenzyl **4a** and dibutyl **7a** disulfides in hexane ($\varepsilon = 1.88$) and dichloromethane ($\varepsilon = 8.93$) in the ratio of oxidant-disulfide of 1:1 for 1 h the conversion of disulfides increases [from 45 % (in hexane) to 86 % (in dichloromethane) for **4a** and from 29 to 78 % for **7a**, respectively]. The yields of the corresponding thiosulfonates increase from 20 to 61 % (for **4**b) and from 25 to 59 % (for **7b**), respectively.

Identified regularities are consistent with data obtained by colleagues in previous studies [19, 20], where the kinetics of chlorine dioxide reactions with thiols has been studied by spectrophotometric method considering the rate of consumption of chlorine dioxide at $\lambda = 354–362$ nm in various solvents.

It has been found that kinetics obeys the equation of the first order in all solvents with excess of substrate by 10 times in a wide range of temperatures with the high correlation coefficient ($r > 0.98$) of ClO_2 consumption.

It has been shown that with increasing of solvent polarity (from heptane to acetonitrile) the constant rate of reaction between propanethiol and chlorine dioxide increases by more than four orders indicating the formation of the transient polar complex which is stabilized by solvation with a solvent. In the papers [19, 21] a mechanism of the oxidation to the stage of formation of thiosulfinates has been proposed.

It should be noted that according to our data [9–12] the thiosulfinates **A** (Scheme 2) are produced in minor amounts, their content in the mixture estimated by NMR is not more than 5–7 %, which is probably due to the



Scheme 2: Formation of thiosulfinates.

high activity of chlorine dioxide, which has two oxygen atoms in the molecule. This scheme can be extended to the stage of formation of thiosulfonates and sulfonyl chlorides (Scheme 3).

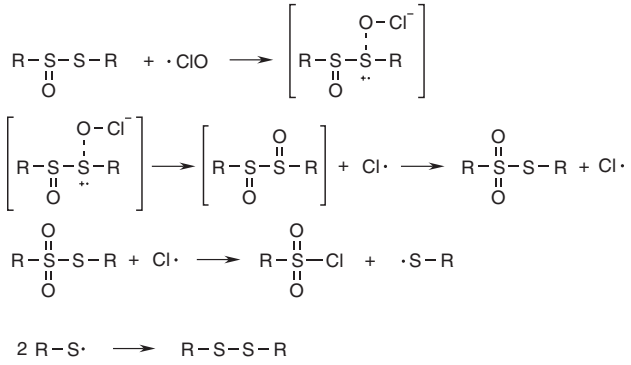
Oxidation of diaryl disulfides is difficult due to reduced electron density of the sulfur atom, especially in the presence of electron withdrawing substituents in benzene ring. Thus, the conversion of 4,4-dinitrodiphenyl disulfide **9a** by oxidation with a fourfold excess of chlorine dioxide in dichloromethane for 1 day does not exceed 30 %, and under the same conditions the conversion of 4,4′-dimethyldiphenyl disulfide **5a** is complete.

Within the framework of the Taft equation the dependence of the reactivity of thiols and sulfides on their structure was studied [21].

It was found that the introduction of electron withdrawing substituents into the molecule of sulfide reduces reaction rate constant under substrate-excess conditions, but in the case of thiols the rate constant is increased. This is probably due to the fact that the key step of the reaction of the thiol with chlorine dioxide is the acid dissociation forming the thiolate anion RS^-, which is further oxidized to thiyl radical RS.

The oxidation of diaryl disulfides with ClO_2 occurres not only slower than of dialkyl disulfides but less selectively so that the reaction of diphenyl disulfide **8a** with chlorine dioxide is used as a model for the catalytic oxidation. The vanadyl acetyl acetonate $VO(acac)_2$ in an amount of 10 mol.% is used as oxidation catalyst, which had previously [22] performed well in the oxidation of sulfoxides to sulfones. Reactions are carried out in solvents of different polarity: hexane, dichloromethane and acetonitrile. The main products of the oxidation of disulfide **8a** in acetonitrile without catalyst are tiolsulfonate **8b**, sulfonylchloride **8c**, acid **8**d and others, the main products of the oxidation of dichloromethane, along with products **8b–d**, are the methyl esters of benzenesulfonic and benzenesulfinic acids (products of the reaction of substrate with a solvent) with a total content in mixture up to 25 %. Disulfide **8a** does not react with dioxide chlorine in the hexane.

Conversion of disulfide **8a** in acetonitrile under catalysis in a molar ratio of substrate-oxidant of 1:3 increases from 85 % to 100 %, and the yield of diphenyl thiolsulfonate **8b** is 85 %, while the non-catalytic



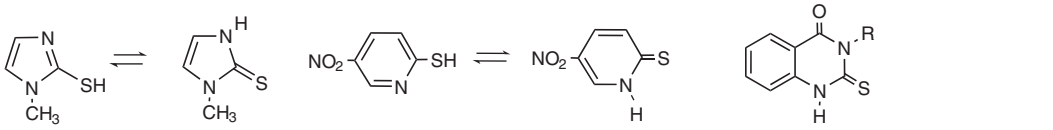
Scheme 3: Formation of thiosulfonates and sulfonyl chlorides.

oxidation provides a 15 % yield. In the presence of $VO(acac)_2$ the yield of sulfonylchloride **8c** increases from 12 % to 96 % in the ratio of substrate to oxidant of 1:4 [13, 17].

The reactions with heterocyclic thiols-thione

The characteristic feature of this class of compounds is their ability to thiol-thione tautomerism, which leads to a variety of properties and their difference from the alkyl and aryl thiols. The state of the tautomeric equilibrium depends on the solvent and affects the oxidation results. The main products of the complete oxidation depending on the structure of the substrate and the reaction conditions are the sulfonic acids or ketones; the thiosulfonates and sulfonyl chlorides are not formed [13, 14, 16].

The nitrogen-containing thiols-thiones are taken as the substrates: 1-methyl-1*H*-imidazol-2-thiol (**11**), 5-nitropyridine-2-thiol (**12**), 3-methyl- (**13**), 3-allyl (**14**) and 3-phenyl-2-sulfanylquinazolin-4(*3H*)-ones (**15**).



11 **12** **13–15**

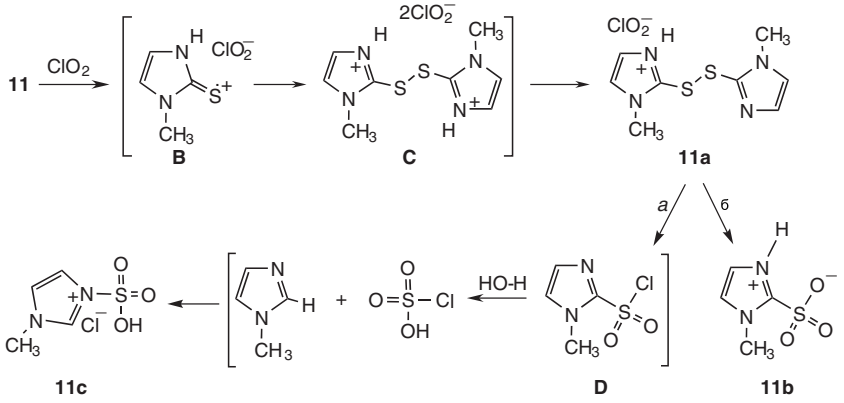
R = CH_3 (**13**); R = CH_2-CH = CH_2 (**14**); R = Ph (**15**)

Depending on the conditions, the main products of oxidation of thiol **11** with chlorine dioxide are 2,2-disulfanediyl*bis*(1-methylimidazole) hydrochlorite (**11a**), 1-methylimidazole-2-sulfonic acid (**11b**), and 1-methyl-3- sulfo-3*H*-imidazolium chloride (**11c**) (Scheme 4) [12].

In the first step the cation radical **B** and chlorite anion are generated, and combination of radical cations **B** gives disulfide **C** which is successively deprotonated by ClO_2^- as a base. The stability of disulfide mono- and dications depends on the thiol structure, solvent nature and temperature [23] and in this case the reaction stops at the formation of disulfide **11a**. The best yields of **11a** (65–78 %) were obtained in the oxidation of **11** with ClO_2 in benzene and methylene chloride at the substrate-to-oxidant molar ratio being 1:2.

The yields of sulfonic acids **11b**, **11c** depend on the method of mixing the reactants and a solvent. The use of the method *b* in the oxidation in water with a threefold excess of chlorine dioxide allows to obtain acid **11b** in 96 % yield, while the method *a* provides the yield under 42 %, and in these conditions the major product is acid **11c** in 58 % yield. By oxidation of thione **11** in acetonitrile according to the method *b* the yields of **11b** and **11c** are 69 % and 24 %, respectively, whereas their yields via the method *a* are 28 and 63 %, respectively.

The reactions by the methods *a* and *b* probably proceed via various intermediates and lead to different products. Presumably, cleavage of the C–S bond occurs in intermediate sulfonyl chloride **D** which is typically



B **C** **11a** **11c** **D** **11b**

Scheme 4: Reaction of chlorine dioxide with 1-methyl-2-sulfanilimidazole **11**.

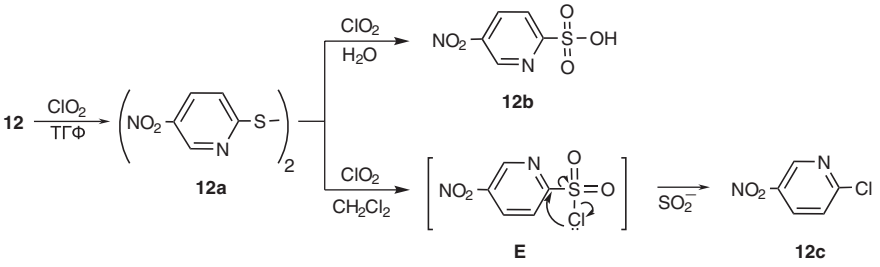
formed in the oxidation of alkyl- and aryl thiols with chlorine dioxide. If the excess oxidant is initially present in the reaction mixture (method *b*), sulfonic acid **11c** is likely to be formed without intermediacy of sulfonyl chloride **D**. If the amount of chlorine dioxide is initially insufficient (method *a*), the role of an oxidant is played by the reduction products of ClO_2, i.e. chlorite or hypochlorite ions or radicals, which are reduced to chloride ions or chlorine radicals [21, 24], and the latter are involved in the formation of intermediate **D**.

According to the data of X-ray analysis the molecule of **11b** exists in zwitterionic form [14]. The crystal packing of **11b** is represented by dimers linked through strong intermolecular hydrogen bonds.

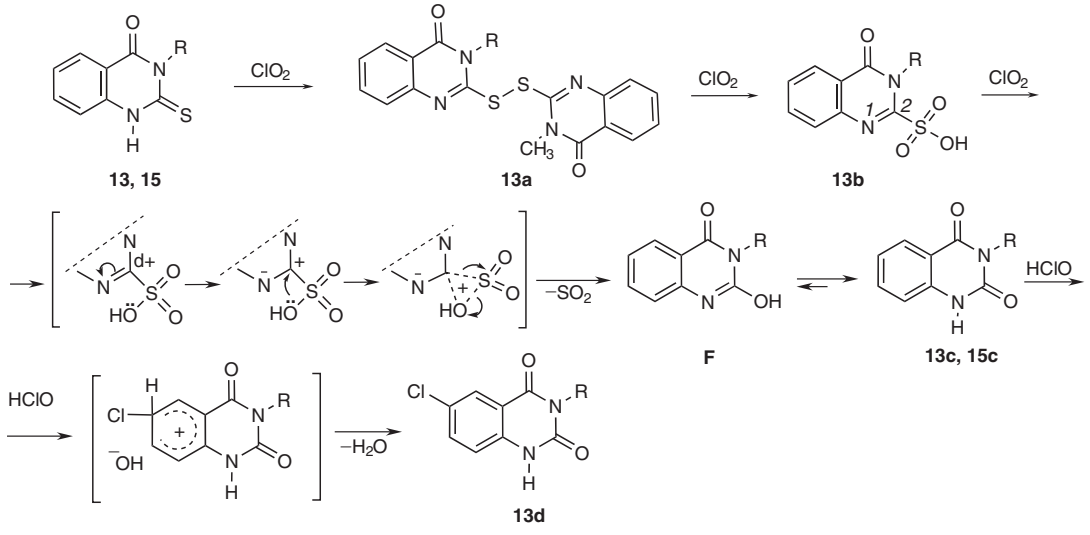
1,2-Bis(5-nitro-pyridin-2-yl)-disulfide **12a** and 5-nitro-pyridin-2-sulfonic acid **12b** in the ratio of 2:1 respectively were obtained by the oxidation of the thiol **12** (Scheme 5) with a twofold excess of the oxidant in tetrahydrofuran or water according to the method *a* [16]. The use of $VO(acac)_2$ increases the yield of **12a** to 96 %. The yield of the acid **12b** increases up to 57 % with a fourfold excess of the oxidant and 2-chloro-5-nitropyridine **12c** in 13 % yield is formed. Ammonia addition under the same conditions leads to quantitative formation of the ammonium sulfonate salt **12b** (94 % by ^{1}H NMR) but in dichloromethane the reaction is directed towards the formation of **12c** (50 %). Perhaps the compound **12c** is produced under an intramolecular nucleophilic substitution reaction S_NAE (addition-elimination) in sulfonyl chloride **E**.

Products of complete oxidation of quinazolinone thiols with various substituents at N^3 position of compounds **13**–**15** by chlorine dioxide are ketones **13c**–**15c** (Schemes 6 and 7) [16]. Benzene, acetic acid, acetonitrile, methanol, dichloromethane and pyridine are used as the solvents.

The reaction of thiol **13** has been studied in more detail [13, 16]. As a result of its oxidation by chlorine dioxide in various conditions 2,2′-disulfanediyl-bis(3-methylquinozalin-4(*3H*)-one) (**13a**)

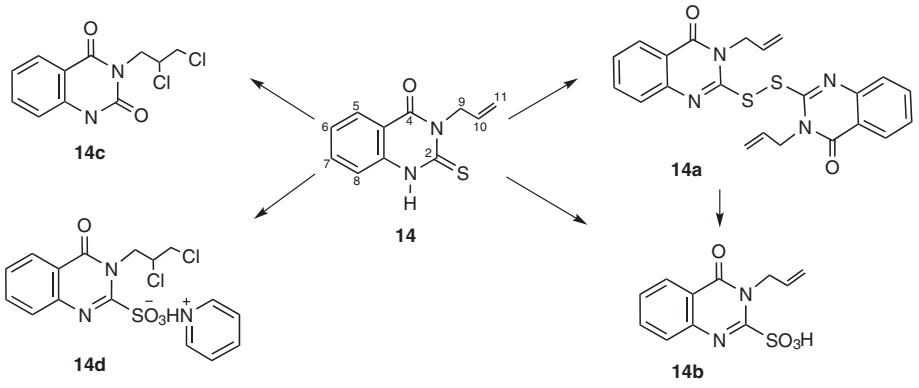


Scheme 5: Reaction of chlorine dioxide with 5-nitropyridine-2-thiol **12**.



R = CH_3 (**13**), Ph(**15**).

Scheme 6: Reaction of chlorine dioxide with 3-methyl- (**13**) and 3-phenyl- (**15**) 2-sulfanilhinazolin-4(*3H*)-ones.



Scheme 7: Reaction products of 3-allyl-2-sulfanylquinazolin-4(*3H*)-one **14** with chlorine dioxide.

3,4-dihydro-3-methyl-4-oxo-quinozalin-2-sulfonic acid (**13b**), 3-methylquinozalin-2,4(*1H,3H*)-dione (**13c**), 3-methyl-6-chloroquinozalin-2,4(*1H,3H*)-dione (**13d**) were obtained (Scheme 6).

At the first stage of thiol **13** oxidation with an equimolar amount of chlorine dioxide in methanol for half an hour the disulfide **13a** is formed in 42 % yield. The maximum quantity of acid **13b** (45 % by ^{1}H NMR) is observed in the oxidation with a threefold excess of ClO_2 in low-polar benzene ($\varepsilon = 2.28$). This is probably due to the low polarity of the solvent and the presence of π-electron system performing the role of weak hydrogen bond acceptors. In the more polar pyridine ($\varepsilon = 13.23$) a relatively high content of acid **13b** (34 %) is caused by stabilization of hydrogen bonds between the hydroxyl group of acid and pyridine. In contrast, in proton solvents (methanol and acetic acid) an unstabilized by specific interactions sulfonic group has the highest reactivity and is easily cleaved from molecule. As a result, dione **13c** is produced. It was confirmed by ^{1}H NMR on the ratio of products in the reaction mixture versus time. Probably the reaction proceeds under an intramolecular nucleophilic substitution mechanism (Scheme 6).

In the aprotic dichloromethane and benzene the main product of reaction of thiol **13** with a threefold excess of chlorine dioxide is the lactim form of the compound **13c** (the compound **F**). Its amount in a mixture of tautomers according to the ^{1}H NMR spectrum (solvent: DMSO-d^6) varies between 65–82 %. Possibly, the compound **F** is stabilized via formation of intermolecular associates (N...H–O) due to the lack of solvation. The proton-donor solvents (acetic acid, methanol, water) promote tautomeric conversion to the lactam form.

The influence of the solvent nature on the conversion of thiol **13** in reactions with chlorine dioxide and yields of oxidation products have been studied. It is shown that in oxidation of thiol **13** with chlorine dioxide in the ratio of 1:1 the conversion of the thiol **13** increases with increasing of polarity among aprotic solvents (benzene < dichloromethane < pyridine < acetonitrile) from 13 % [in benzene ($\varepsilon = 2.28$)] to 52 % [in acetonitrile ($\varepsilon = 38.0$)]. This relationship indicates that the transition state is more polar than the starting reagents.

It is revealed that the presence of water even in catalytic amounts causes chlorination of the benzene ring of dione **13c** to the position C^6 forming the dione **13d** (Scheme 6). Thus, under oxidation of thiol **13** by ClO_2 in a molar ratio of 1:2 in aqueous pyridine for 0.25 h (method *b*) the amount of dione **13d** in the reaction mixture is 35–50 %, while in the reaction in anhydrous pyridine the dione **13d** is not present in the reaction mixture. This is apparently due to the formation of hypochlorous acid according to the equations:

$$RSH + 2ClO_2 = RSO_3H + Cl^{\cdot} + ClO^{\cdot}$$

$$Cl^{\cdot} + ClO^{\cdot} = Cl_2O$$

$$Cl_2O + H_2O = 2HClO.$$

At the substitution of H atom in the benzene ring by Cl atom a new molecule of water is formed which can participate again in a similar process. The position of Cl atom in dion **13d** is consistent with the rules of orientation of electrophilic substitution. Groups C=O (*meta* orientant) and NH (*ortho* and *para* orientant) consistently direct the electrophile to atoms C^6 and C^8, but probably atom C^6 is more spatially available.

In the reactions of thiol **14** the chlorination of double bond of the allyl substituents takes place (Scheme 7). Dione **14c** is formed as the main product in the oxidation with a twofold excess of the oxidant in acetic acid and methanol for 2 h, but in this case, the conversion of thiol **14** does not exceed 50 %. A mixture of dione **14b** and acid **14c** in the ratio of 1:2, respectively is formed in aqueous pyridine, and in this case the reaction time is reduced by 4 times with complete conversion of thiol **14**.

In the NMR spectra of dione **14c** the signals of atoms C^{10} (43.60 ppm), H^{10} (4.35 ppm) and C^{11} (51.21 ppm), H^{11} (4.46 ppm) are observed in the strong field relative to similar signals of thiol **14** (132.27, 5.92 ppm and 117.58, 5.19 ppm, respectively). The double bond disappears and chlorination occurs to its both sides. IR spectrum of dione **14c** has an additional band C=O (1708 cm^{-1}) (Supplementary data).

In dry pyridine alongside with the compounds **14b** and **14c** the pyridinium salt **14d** is formed (13 %). The starting compound is destroyed by oxidation with an equimolar amount of chlorine dioxide in THF, disulfide **14a** is isolated in amount of 10 %.

Similarly, in the reaction of thiol **14** with chlorine dioxide the conversion of thiol **15** does not exceed of 50 % in aqueous methanol or acetic acid with a twofold excess of the oxidant, while in aqueous pyridine the conversion is complete and dione **15c** is selectively formed.

Thus, the effect of substituents at N^3 position and of the solvent on the oxidation of thiols **13**–**15** has been detected. The presence of electron-donating methyl group promotes the oxidation of S atom. Therefore, when carrying out the reaction in acetic acid in a molar ratio of oxidant-thione of 1:2 for 1.5–2 h, the conversion of thiol **13** reaches 100 %, although for thiols **14**, **15** it does not exceed 50 %.

Proton-donor solvents (acetic acid, methanol) reduce the rate of oxidation unlike the basic pyridine. Dry pyridine prevents the formation of chlorinated products.

Reactions with terpene thiols

An important direction in the modern organic synthesis is the search for new physiologically active substances, in particular, by chemical modification of natural compounds. Monoterpenoids are considered as one of the most interesting and promising classes of natural compounds from the point of view of their synthetic properties. They possess bactericidal, analgesic and expectorant activities, are used as antiseptics, fungicides, anti-viral agents. Introduction of sulfonyl group into the terpene molecule can increase solubility in water, reduce toxicity of the compound while maintaining its biological activity, and expand its spectrum [25]. A high antioxidant activity of terpene thiols and disulfides was shown in the paper [26].

However, functionalization of terpene compounds by the introduction of the sulfonyl group into the molecule using common methods is complicated due to the high lability of terpene fragment.

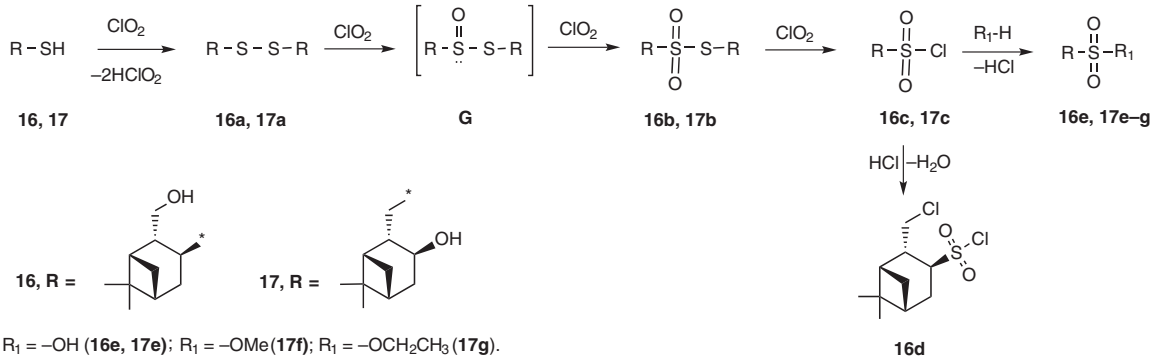
We [15, 17] propose the synthesis of S–, O–, N–, Cl– containing terpenoids via obtaining of appropriate thiols and their further oxidation by ClO_2.

The pinane and isobornane thiols were synthesized as the starting substrates: 3-sulfanylmyrtanol **16** [27], 10-sulfanylisopinocampheol **17** [28], isobornanethiol **18** [29] and 10-sulfanylisoborneol **19** [30]. It was found that the reactivity of the examined thiols decreases in the series **17** > **16** > **19** > **18**. The conversions of **18, 19, 16** and **17** were 26, 50, 78 and 100 %, respectively, in the oxidation with 0.5 equiv of ClO_2 in hexane–water (reaction time 0.5 h). This is probably due to the steric availability of sulfur atom to the oxidant molecules.

Corresponding disulfides **16a–19a** are traditionally the main products in the first step of oxidation of thiols by ClO_2 (Schemes 8 and 10). The maximum yields of disulfides **16a**, **17a** and **19a** are obtained by the oxidation in hexane or chloroform by equimolar amount of ClO_2 and are equal 79–92 %. Disulfide **18a** in 78 % yield is obtained by the oxidation of thiol **18** only in more polar dichloromethane with a two fold excess of ClO_2.

Pinane disulfides **16a** and **17a** are commonly oxidized with ClO_2 to the corresponding thiosulfinates **G**; however, their concentration in the reaction mixtures in different solvents in different reactant ratios does not exceed 5 %. Thiosulfinates **G** are rapidly oxidized to thiosulfonates **16b** and **17b** which are more stable in the reaction medium.

The maximum yields of **16b** and **17b** are 46 and 58 %, respectively, when the oxidation is performed in methylene chloride with an equimolar amount of the oxidant. Raising the molar ratio of thiol–ClO_2 to 1:2 or



Scheme 8: Reactions of ClO_2 with pinane hydroxythiol **16**, **17**.

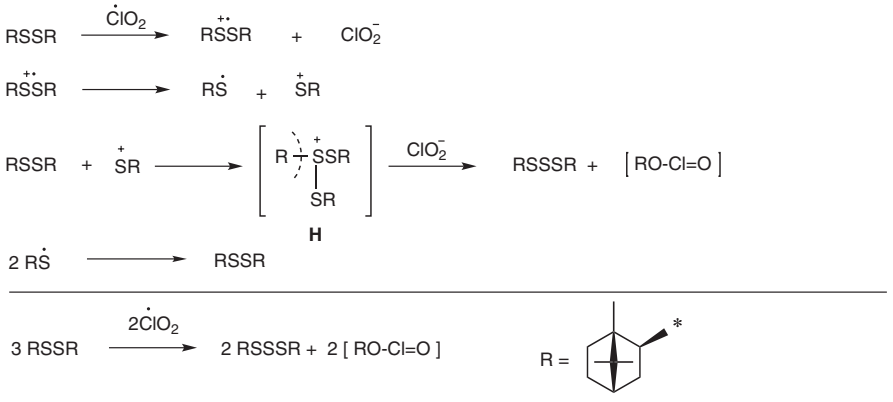
1:3 in hexane–water or methylene chloride leads to the formation of sulfonyl chlorides **16c**, **17c** (up to 70 %, according to the NMR data). Increase of the reaction time to 2 h in the oxidation of **16** favors the accumulation of sulfonyl chloride **16d**.

In the reactions of thiol **18** with ClO_2 a new direction with the formation of trisulfide **18b** (78 % yield) has been detected, which is not typical for the oxidation reactions of alkyl and aryl thiols (Schemes 9 and 10) [15]. Probably, thrisulfide is formed according to the Scheme 9. It is known [31] that the formation of a radical cation is the first step of ClO_2 oxidation of disulfides. Further fragmentation of the radical cation gives a sulfenium cation RS^+ and the $RS^\bullet$ radical. The sulfenium cation reacts with another disulfide molecule to form an intermediate trisulfide cation **H**. Through the action of nucleophile, e.g. ClO_2^-, the R–S bond of intermediate **H** breaks to provide trisulfide **18b** and an unstable compound of the chlorite type ROClO. The $RS^\bullet$ radicals dimerize to give a new disulfide molecule.

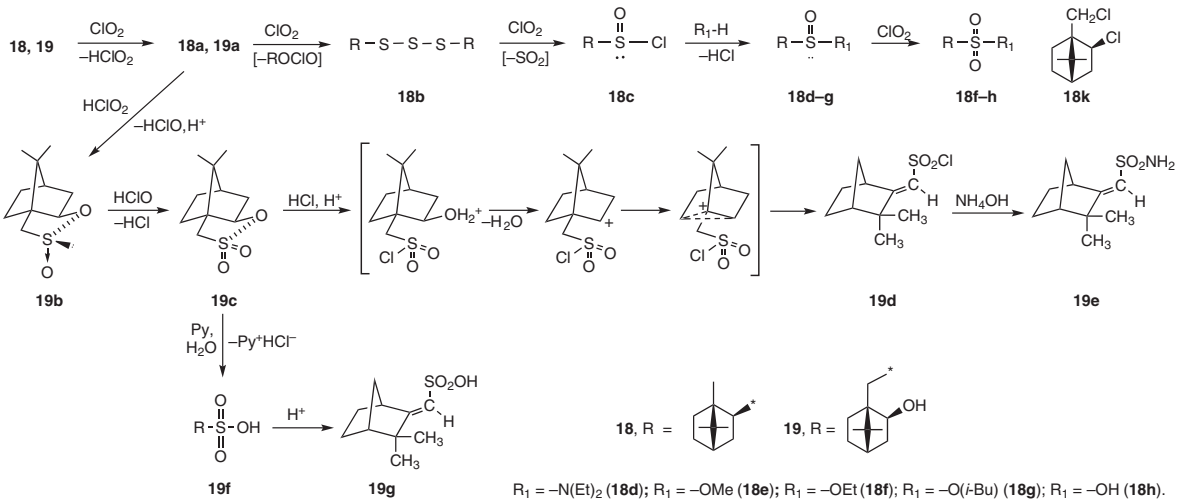
Mass spectrum of trisulfide **18b** reveals the molecular ion peak with *m/z* 370. There are no peaks in the IR spectrum characteristic for the S=O and SO_2 groups. Retention of the isobornyl skeleton is shown by the 2D NMR techniques (HSQC, COSY, NOESY and HMBC) (Supplementary data). Elemental analysis data confirm the trisulfide composition.

The formation of thiosulfinates, thiosulfonates and sulfonyl chlorides in reactions of thiol **18** with ClO_2 is not observed. Deep oxidation leads to the formation of a probably sterically less hindered stereoisomer of sulfinyl chloride **18c** (*de* 47 %). Reaction of sulfinyl chloride **18c** with diethylamine leads to the mixture of diastereomeric sulfinamides **18d** (*de* 10 %). Reducing of the diastereomeric purity of the product **18d** suggests that the amidation of **18c** follows mainly the S_N1-mechanism. The low values of *de* (10–18 %) are also obtained for substance **18e**–**g**.

In the reactions of thiols **17**, **18** with ClO_2 in alcohol medium the alcoholysis of sulfinyl and sulfonyl chloride occurs to form the corresponding sulfonic **17f**, **17g**, **18h**, **18i** and sulfinic **18f**, **18g** esters (Scheme 8 and 10).



Scheme 9: Proposed scheme of formation of diisobornyl trisulfide **18b**.



Scheme 10: Reaction of chlorine dioxide with isobornane thiols **18, 19**.

The sulfinic esters **18f, 18g** are oxidized to sulfonic esters **18h, 18i** in high yields (78–85 %). The esters **18h, 18i** are adducts $C_{10}H_{17}SO_2OR{\cdot}ROH$, in which molecules are probably linked by a strong hydrogen bond.

Dichloro-substituted derivative **18k** with content up to 45 % (^{1}H NMR data) is the predominant by-product of the ClO_2 oxidation of disulfide **18** in organic solvents. Addition of pyridine to the reaction mixture leads to a noticeable decrease in the content of the by-product **18k** in the reaction mixture and to an increase in the target product yields, since pyridine binds free H^+ and Cl^-. Thus, the yields of esters **18h, 18i** in the reactions in the presence of pyridine increase from 50 to 85 % (^{1}H NMR data) [15].

The oxidation of thiol **19** with two equiv of chlorine dioxide in methylene chloride gives sultine **19b** as a single diastereoisomer (*de* 100 %) whose configuration was previously identified as S_S [17] (Scheme 10). The sultine **19b** is formed up to 70 % for 0.25 h. No analogous ring closure is observed in the reactions with pinane derivatives **16** and **17**. Presumably, the intramolecular ring closure is favored by *exo* orientation of the hydroxy group in **19**. The sulfanyl and hydroxy groups in **16** and **17** reside at different sides of the ring in the *endo* and *exo* positions, respectively.

Apart from sultine **19b**, up to 28 % of sultone **19c** is formed. Prolonged reaction (1 h) leads to the formation of camphenesulfonyl chloride **19d** (up to 55 % in the reaction mixture). The rearrangement is promoted by accumulation of protons in the reaction mixture. The corresponding sulfonamide **19e** is quantitatively obtained under reaction of **19d** with ammonia.

Thiols **16**–**19** react with two equiv of ClO_2 in aqueous pyridine to give sulfonic acids **16e**, **17e** (Scheme 8), **18h** and the mixtures **19g** and **19f** (Scheme 10).

In summary, the direction of reaction depends on the class of compounds and conditions. It was shown that for the alkyl, aryl and terpenyl thiols the increase of the molar ratio of thiol-oxidant leads to a growing of oxidation state of sulfur: disulfides - thiosulfonates - sulfonyl chlorides - sulfonic acid. Substitution of sulfur atom by hydrogen, oxygen, chlorine is characteristic for the heterocyclic thiols. The formation of sulfonyl chlorides and isobornane trisulfide by chlorine dioxide oxidation of thiols was first described.

Terpenoids functionalized with sulfur-, oxygen-, nitrogen-, and chlorine-containing groups have been synthesized by oxidation of hydroxy thiols of the pinane and isobornane series with chlorine dioxide. Unlike pinane derivatives, the oxidation of isobornane hydroxy thiols is characterized by high selectivity with respect to sulfinyl derivatives. Steric structure of the isobornane fragment determines oxidant coordination predominantly at one side of the molecule. Isobornane hydroxy thiol undergoes cyclization to give the corresponding sultine as a single diastereoisomer. The formation of thiosulfonates indicates stability of the S–S bond in the pinane derivatives, while no analogous products with isobornane fragment are formed.

A shortage of chlorine dioxide in the reaction mixture leads to chlorinated products, regardless of classes of compounds. The presence of pyridine prevents the chlorination.

Reactions with sulfides

Recently there are a lot of studies in organosulfur chemistry devoted to sulfoxides showing great promise as not only extractants, ligands to metals, flotation agents, and drugs but also reagents for fine organic synthesis.

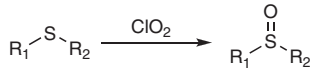
Despite a variety of oxidants for sulfides, only some of them can ensure selective sulfoxide formation, without further oxidation. Since new methods for chemo-, stereo-, and enantioselective oxidation of sulfides are required, a search for new oxidative systems [32–35] is still a challenge. The data on oxidation of alkyl-, phenyl-, benzyl-, oxo- and terpenyl-substituted and nitrogen-containing heterocyclic sulfides with chlorine dioxide are given in the review [36]. The oxidation is highly chemoselective and moderately stereo- and enantioselective.

Reactions with alkyl-, arylsulfides

In papers [35, 37–42] regularities of oxidation of sulfides to sulfoxides (molar ratio of substrate-oxidant, temperature, solvent, reagent mixing methods) were studied. Using the example of symmetrical and asymmetrical dialkyl-, alkylaryl-, diaryl-, dibenzylsulfides **20–33** it was found that the chemoselectivity of oxidation of sulfides to sulfoxides is achieved when the molar ratio of sulfide: ClO_2 equals 1:0.5 at room temperature. The sulfoxides **20a–33a** in 95–100 % yield were produced (Scheme 11).

The reaction is not selective by the sulfide oxidation with excess of chlorine dioxide: the main reaction products are sulfoxides, sulfones, their yields do not exceed 30 %. By-products of the reaction are chlorinated sulfoxides, disulfides and esters which must be formed by homolytic rupture of the connection C–S. The reactions of sulfides with chlorine dioxide proceed quickly and selectively but sulfoxides are oxidized slowly with a small conversion and a large number of by-products. Therefore, the oxidation reaction of sulfoxides to sulfones can be a good model for the catalytic oxidation. Since the oxidation of sulfoxides by ClO_2 in the absence of catalysts is not selective and leads to the formation of chlorinated products, we used the catalysts $Cr(acac)_3$, $MoO_2(acac)_2$, $Mo(CO)_6$, $VO(acac)_2$. When using $MoO_2(acac)_2$, $Mo(CO)_6$, $Cr(acac)_3$ in CH_2Cl_2, $CHCl_3$, CH_3COOH significant catalytic effect is not detected. The high selectivity of the oxidation of sulfoxides **34a–41a** by chlorine dioxide is found in the presence of $VO(acac)_2$ (the yield of sulfones **34b**–**41b** comes up to 96 %) (Scheme 12). Sulfoxides oxidation scheme in the presence of $VO(acac)_2$ is proposed. Using NMR and EPR spectroscopy methods it was shown that the reaction proceeds via the oxo transfer mechanism [22, 43].

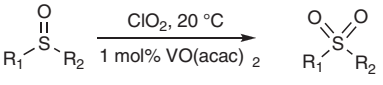
In the article [44] the kinetics and mechanism of the reaction between chlorine dioxide and dimethyl sulfoxide **34a** were studied in the tetrachloromethane solution. Data on the time-dependent changes of ClO_2



20–33 **20a–33a**

$R_1 = R_2 =$ Me (**20, 20a**); R_1 = Me, R_2 = Et (**21, 21a**); R_1 = Me, R_2 = Bu (**22, 22a**); R_1 = Me, R_2 = Ph (**23, 23a**); $R_1 = R_2$ = Pr (**24, 24a**); R_2 = Pr, $R_1 = C_6H_{13}$ (**25, 25a**); $R_1 = R_2$ = Bu (**26, 26a**); $R_1 = R_2$ = i-Bu (**27, 27a**); $R_1 = R_2$ = Ph (**28, 28a**); R_1 = Ph; $R_2 = C_6H_{13}$(**29, 29a**); $R_1 = R_2 = C_8H_{17}$ (**30, 30a**); $R_1 = R_2$ = p-Tol (**31, 31a**); $R_1 = R_2$ = Bn (**32, 32a**); $R_1 = R_2$ = п-BrC_6H_4 (**33, 33a**)

Scheme 11: Reaction of chlorine dioxide with monofunctional sulfides.



34a–41a **34b–41b**

$R_1 = R_2$=Me (**34a, 34b**); R_1= Me, R_2= Bu (**35a, 35b**); R_1=Me, R_2=Ph (**36a, 36b**); $R_1 = R_2$= Pr (**37a, 37b**); R_1= Me, R_2= Pr (**38a, 38b**); $R_1 = R_2$= Ph (**39a, 39b**); R_1= Pr, R_2= Bu (**40a, 40b**); R_1= Ph; R_2= Bn (**41a, 41b**)

Scheme 12: Reaction of chlorine dioxide with sulfoxides.

concentration were obtained using ESR method by measurements of integral intensities of ESR signals. It was shown that the thermal decomposition of chlorine dioxide and the reaction with DMSO take place simultaneously with comparable rates. At low concentrations ClO_2 decomposes by the monomolecular mechanism, but the bimolecular decomposition becomes predominant as the concentration is increased. The rate constants of the thermal decomposition of ClO_2 ($1.4 \cdot 10^{-5}$ c^{-1}, 28 °C) and the interaction with DMSO were determined at low concentrations of ClO_2 ($0.6 \cdot 10^{-5}$ c^{-1}, 28 °C). Probable mechanism of interaction between ClO_2 and DMSO was proposed.

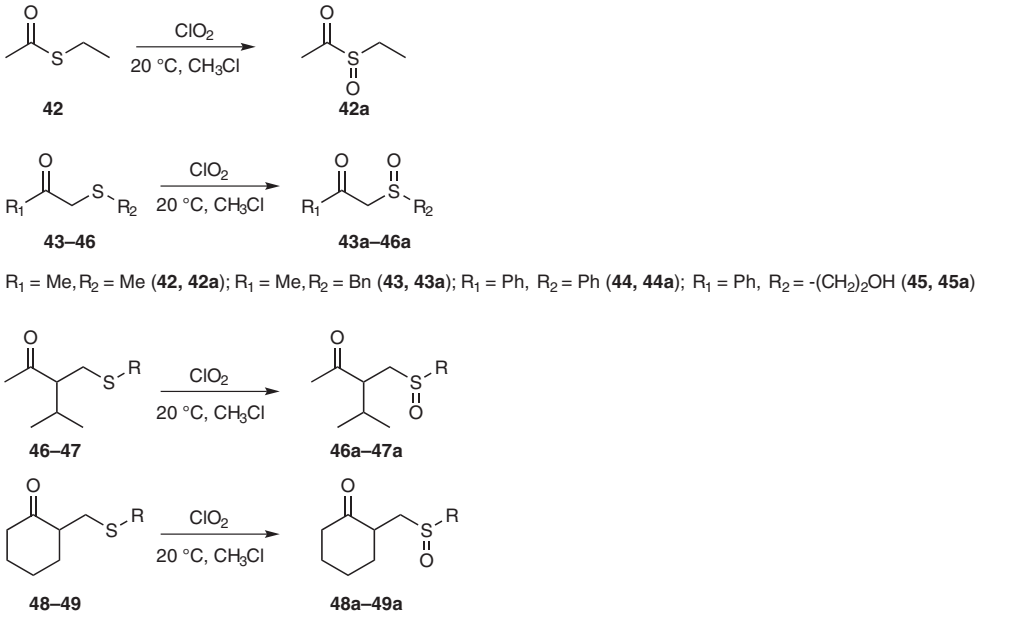
Reaction with ketosulfides and heteroaryl sulfides

Chemoselective oxidation of α, β- and γ-ketosulfides **42–49** is carried out under mild conditions (molar ratio sulfide : ClO_2, 1:0.5, room temperature) with a good yield of sulfoxides **42a–49a** (85–95 %), whereas using *tert*-butyl hydroperoxide (TBHP) the reaction should be conducted at a temperature of 0 °C and ketosulfides to oxidant molar ratio of 1:1 for similar results (Scheme 13) [45].

The high chemoselectivity is achieved by oxidation of polyfunctional and nitrogen-containing heterocyclic sulfides containing triazole, tetrazole, imidazole and benzimidazole groups (Scheme 14) [46, 47]. Oxidation was carried out using different oxidant supply methods: aqueous ClO_2, ClO_2 solution in an organic solvent, by sparging of gaseous ClO_2 through reaction mixture. It was found that the process of oxidant supply almost did not affect the yield of reaction products, as well as in the reaction of dialkyl and diaryl sulfides [41] with chlorine dioxide. Oxidation of sulfides **50–59** by ClO_2 at 20 °C and the molar ratio of the sulfide-oxidant of 1:1 leads to the formation of sulfoxides **50a**–**59a** without sulfones impurities.

It should be noted that the unsubstituted imidazole and benzimidazole containing sulfides **60–63** are chemoselectively oxidized by chlorine dioxide to the corresponding sulfoxide with yields of up to 89 %, without formation of chlorinated products (Scheme 15).

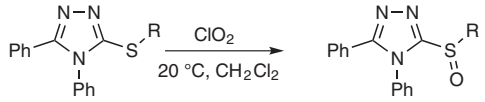
The oxidation of *N*-substituted imidazole sulfide **64** by ClO_2 leads to the formation of sulfoxide with yield less than 8 % and the major reaction product is a chlorine-containing compound 2-(5-chloro-1-methyl-1*H*-imidazol-2-ylsulfanyl)-1-phenylethanone (**64c**) (Scheme 16) [48].



R_1 = Me, R_2 = Me (**42, 42a**); R_1 = Me, R_2 = Bn (**43, 43a**); R_1 = Ph, R_2 = Ph (**44, 44a**); R_1 = Ph, R_2 = $-(CH_2)_2OH$ (**45, 45a**)

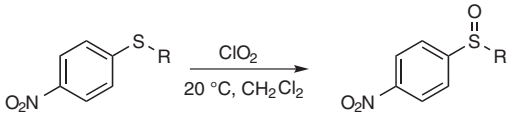
R = H-C_6H_{13} (**46, 46a**, **30, 30a**); R = Bn (**47, 47a, 49, 49a**)

Scheme 13: Reaction of chlorine dioxide with ketosulfides **42–49**.



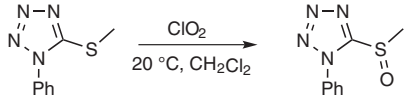
50–53 **50a–53a**

R = Me, 80 % (**50, 50a**); Et, 73 % (**51, 51a**); Pr, 68 % (**52, 52a**); Bn, 89 % (**53, 53a**)



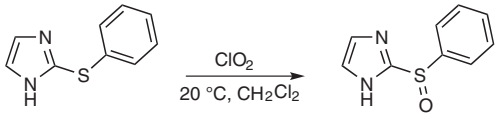
54–58 **54a–58a**

R = Me, 81 % (**54, 54a**); Et, 80 % (**55, 55a**); Pr, 78 % (**56, 56a**); Bu, 75 % (**57, 57a**); Bn, 89 % (**58, 58a**)

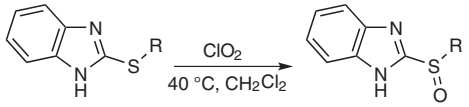


59 **59a, 75 %**

Scheme 14: Reactions of chlorine dioxide with aryl and heteroaryl sulfides **50–59**.



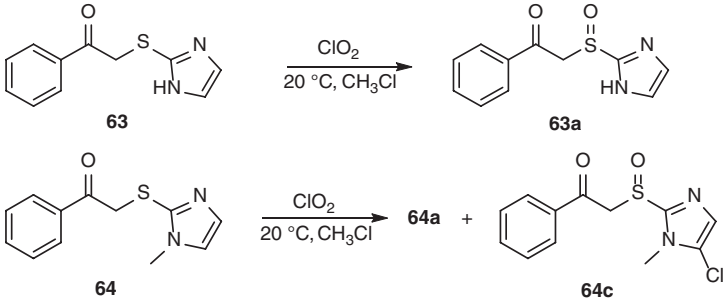
60 **60a, 78 %**



61–62 **61a–62a**

R = Me, 89 % (**61, 61a**); Bn, 65 % (**62, 62a**)

Scheme 15: Reactions of chlorine dioxide with imidazole and benzimidazole sulfides **60–62**.



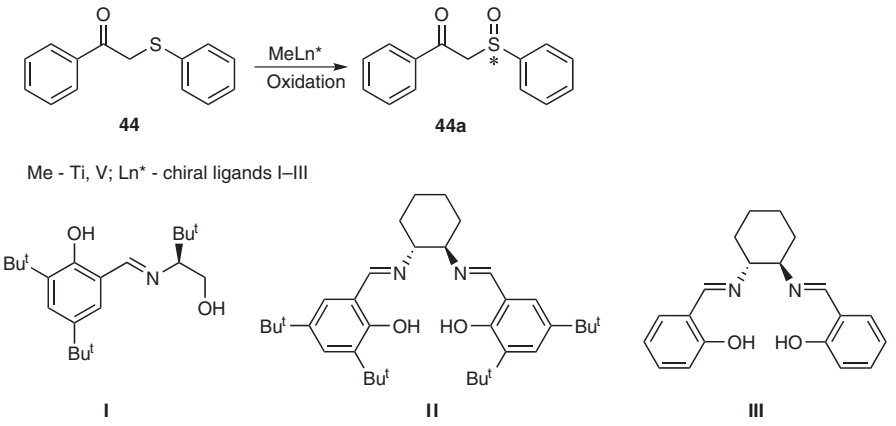
63 **63a**

64 **64c**

Scheme 16: Reactions of chlorine dioxide with imidazole sulfides **63–64**.

Chlorine dioxide in the asymmetric oxidation reactions

Due to the fact that chlorine dioxide has not been previously used in the asymmetric oxidation reactions, it was the subject of concern. We used two approaches to produce chiral sulfoxides: asymmetric oxidation of corresponding prochiral sulfide to enantiomerically enriched sulfoxides and asymmetric synthesis in which



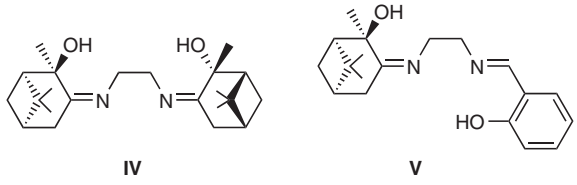
Scheme 17: Asymmetric oxidation of ketosulfide **44** by chlorine dioxide using Bolm system.

the sulfinyl group is introduced into the existing optically active compound (an asymmetric oxidation of optically active substrates).

Catalyst systems based on complexes of transition metals (vanadium, titanium) with a chiral organic ligands are of great interest for asymmetric sulfoxidation. The use of chlorine dioxide in the modified Sharpless system ($Ti(OPr^i)_4$-(+)-diethyl tartrate) in the oxidation of phenyl phenacyl sulfide **44** leads to an increased yield of the sulfoxide (from 62 % to 80 %) but decreases the enantioselectivity up to 7 % as compared with TBHP (52 % *ee*) or cumene hydroperoxide (69 % *ee*). It should be noted that the formation of the opposite enantiomer of ketosulfoxide **44a** occurs.

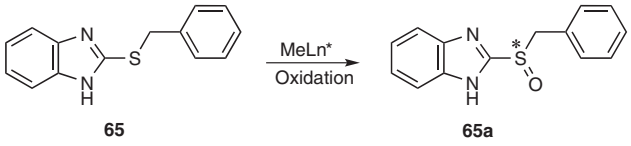
Reduction of enantioselectivity was also observed when H_2O_2 was replaced by ClO_2 in Bolm catalyst systems with complexes $VO(acac)_2$ with chiral Schiff bases (I–III) (Scheme 17) [49–51]. Thus, in the oxidation of **44** by Bolm system with H_2O_2 and ligand I sulfoxide **44a** is formed with 59 % *ee*, while using ClO_2 in chloroform gives only –27 % *ee*.

The opposite result is obtained when chlorine dioxide is employed in catalytic systems based on $VO(acac)_2$ and $Ti(Oi–Pr)_4$ complexes with chiral ligands **IV** and **V** [52]. Combination of these ligands with $VO(acac)_2$ and ClO_2 allows a noticeable increase in the enantioselectivity compared to that achieved in the oxidation with H_2O_2: from 8 to 15 % *ee* (ligand **IV**) and from 3 to 32 % *ee* (with ligand **V**).



As with sulfide **44**, asymmetric oxidation of 2-benzylthio-1*H*-benzimidazole **65** with ClO_2 in the presence of titanium(IV) and vanadium(IV) complexes with chiral ligands **I**–**III** is less enantioselective than the oxidation with H_2O_2 and organic peroxides. However, the yield of 2-benzylsulfinyl-1*H*-benzimidazole **65a** is increased (Scheme 18) [53, 54]. Possibly, chlorine dioxide is a more active oxidizing agent. It is found that by its participating in the Bolm system opposite enantiomer of sulfoxide is formed, as well as at asymmetric sulfoxidation of **26**. Perhaps this is due to a change in the stereochemistry of the reaction by the action of chlorine dioxide on the catalyst complex. Low enantiomeric yield is probably due to the destruction of the catalytic complex by the action of highly active chlorine dioxide.

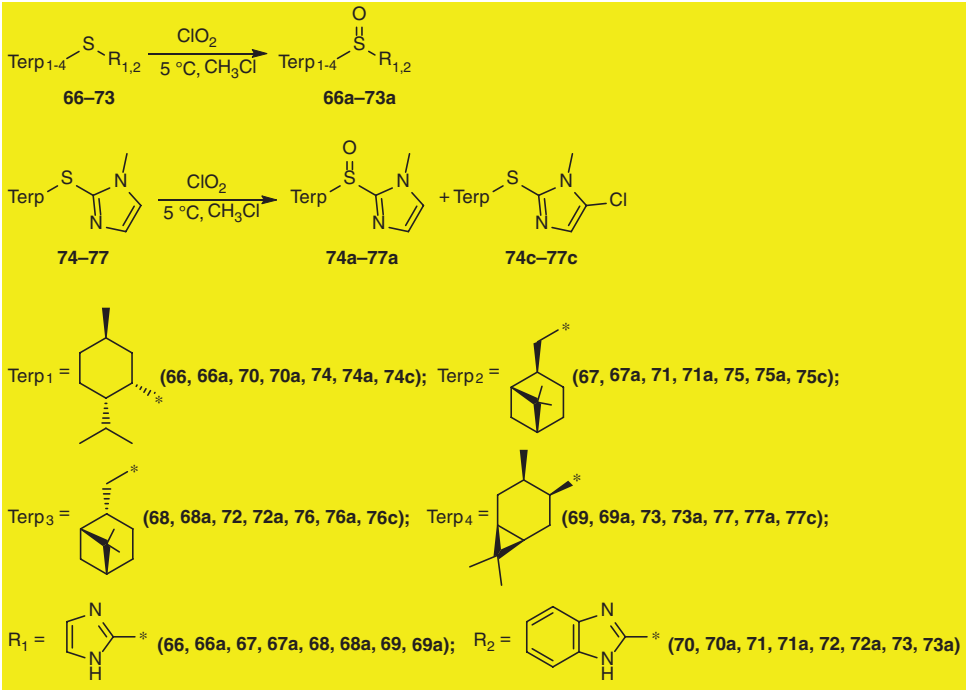
The reactions of asymmetric oxidation of optically active monoterpenylsulfanylimidazoles by chlorine dioxide occurring with high chemo- and moderate stereoselectivity were studied (Scheme 19). Reactions of chlorine dioxide with unsubstituted (benz)imidazolyl sulfides **66–73** containing the menthane, carane, and pinane moieties afford the corresponding sulfoxides **66a–73a** in 71–91 % yields with *de* 10–37 % [55]. It should



65 **65a**

Me - Ti, V; Ln* - chiral ligands I–V

Scheme 18: Asymmetric oxidation of sulfide **65** by chlorine dioxide.



Scheme 19: Asymmetric oxidation of optically active monoterpenylsulfanylimidazoles **66–77** by chlorine dioxide.

be noted that the synthesis of menthyl and caranyl sulfoxides is more stereoselective (*de* 16–30 %) than the synthesis of myrtanyl sulfoxides (*de* 10–14 %). Presumably, replacement of the neomenthyl moiety in a substrate molecule by the caranyl one gives rise to great steric hindrances that preclude chlorine dioxide from attacking and as a result the stereoselectivity of the reaction increases from *de* 16 to 37 %. In myrtanylsulfanylimidazoles the chiral induction of the asymmetric centers distant from the prochiral center is too weak to ensure the high *de* of the resulting sulfoxides.

It was found that in the reaction of *N*-substituted 1-methyl-2-terpenylsulfanylimidazoles **74–77** with chlorine dioxide, the major products were chlorinated compounds **74c–77c** (yields 76–84 %). The corresponding sulfoxides were isolated as a minor product in yields of 6–17 %.

Summing up, the chlorine dioxide acts as a chemoselective oxidant of sulfides. Asymmetric sulfoxidation with ClO_2 is moderately stereo- and enantioselective. Compared to the oxidation with hydroperoxides and peroxy acids, the reactions with ClO_2 mainly yield the opposite sulfoxide enantiomer.

Reactions of chlorine dioxide with alcohols

There is little data on the chlorine dioxide reactivity with aliphatic alcohols. Lower alcohols are relatively resistant to chlorine dioxide. Thus, ethanol and 1,3-butanediol react with an excess of chlorine dioxide only

under extreme conditions (pH = 1, 70–80 °C) to form a mixture of aldehydes and carboxylic acids [3]. Glucose in the acidic medium is oxidized without destroying -CH_2OH groups of the ring, also transforming into aldehyde and carboxyl derivatives.

The kinetics of chlorine dioxide reactions with a number of alcohols in aqueous media was investigated in [56–58], and the oxidation of methanol [55] and isopropanol [58] was studied in detail. It was found that the reaction is first order in both alcohol and chlorine dioxide. The reaction rate constants determined from initial rates increase with increasing solution ionic strength. Investigation of the effect of inorganic salts on the reaction rate showed that chlorides, nitrates, phosphates and bromides accelerate the reaction, while sulfates slow it down. In the oxidation of methanol and isopropanol isotope effect is observed when water is replaced with D_2O: $k_{H_2O}/k_{D_2O} = 1.59$ and 1.78, respectively. The dependence of the rate constant on pH of the solution has a complicated character: at pH = 3.0–5.9 rate constant decreases with increasing of pH and increases sharply in the range of pH 6.3–6.7. According to the authors [56–58], this is attributed to the reaction of the anion RO^- with chlorine dioxide. With further increase of pH the reaction rate decreases again [58]. The activation energy of the oxidation reaction of monohydric alcohols decreases in the order [56]: $CH_3OH > C_2H_5OH > n\text{-}C_3H_7OH > n\text{-}C_4H_9OH > i\text{-}C_4H_9OH > i\text{-}C_3H_7OH >> CH_3CH(OH)CH_2CH_3$.

Reactions with terpene alcohols

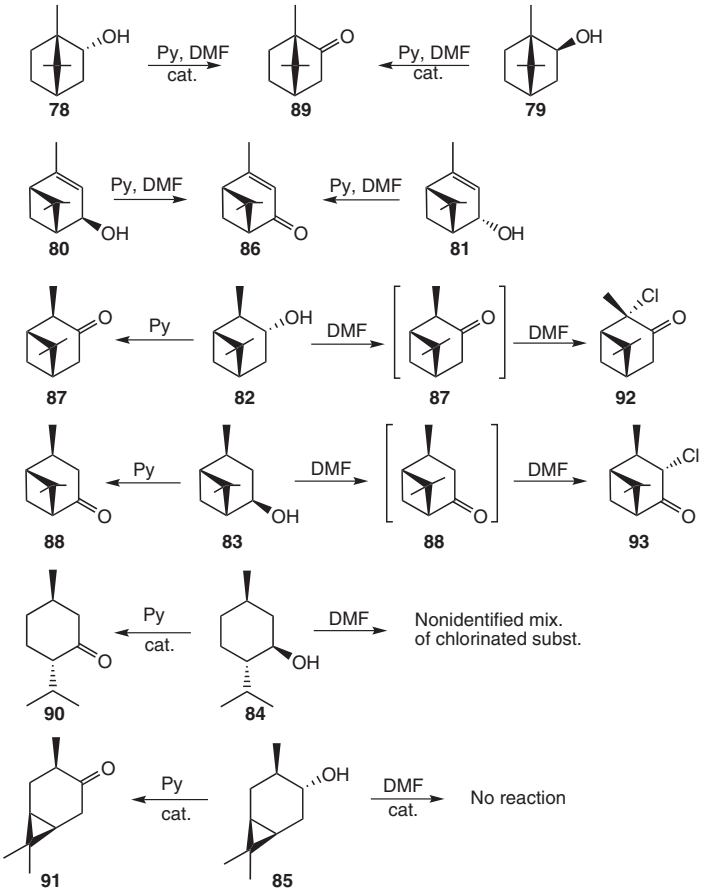
Terpenic α-hydroxyketones are important building blocks for the total synthesis of natural products; furthermore, they are widely used in preparation of chiral catalysts for various asymmetric reactions [59, 60]. Two well known groups of the mentioned substances are derivatives of 2α-hydroxypinan-3-one, easily obtained in both enantiomer forms via oxidation of α-pinene with $KMnO_4$. Hydroxyketone derivatives of 3-carene are less available due to the absence of preparatory single-stage methods of their synthesis. In this work we report on an easy and selective procedure to prepare α-hydroxyketones of bornane, carane and pinane types using chlorine dioxide.

α-Chloroketones are widely used as intermediate products in the synthesis of heterocyclic compounds, epoxides (Darsens condensation), α-alkyl(aryl) thiocarbonyl compounds, β-ketoesters, etc [61]. Numerous methods for the preparation of α-chloroketones are known, most of which are based on the α-chlorination of ketones with gaseous chlorine, *N*-chlorosuccinimide, sulfuryl chloride, selenonyl chloride, copper (II) chloride, trichloroisocyanuric acid, $NaClO_2$–$Mn(acac)_3$–Al_2O_3, and a polymeric analog of *N*,*N*-dichloro-4-methylbenzenesulfonamide in the presence of acid catalysts. However, only a few examples of a direct transformation of secondary alcohols into α-chloroketones have been reported. We found that the system chlorine dioxide–dimethylformamide in combination with or without a catalytic amount of $MoCl_5$, $CeCl_3$, $ZrOCl_2$, or $VO(acac)_2$ induces oxidative chlorination of a number of bicyclic terpene alcohols and vicinal diols. 2α-Chloropinan-3-one, 3α-chloro-10β-pinan-4-one, 5α-chloro-3α-hydroxycaran-4- one, 5β-chloro-3β-hydroxycaran-4-one, and 4α-chloro-2α-hydroxypinan-3-one were synthesized in good preparative yields.

Secondary terpenic alcohol oxidation by ClO_2

Herein we report on oxidation of secondary terpene alcohols: borneol (**78**), isoborneol (**79**), *cis*- (**80**) and *trans*-verbenol (**81**), isopinocampheol (**82**), neoisoverbanol (**83**), menthol (**84**) and isocaranol-4 (**85**) by ClO_2 in pyridine and dimethylformamide with or without catalysts – $ZrOCl_2$, $VO(acac)_2$, $MoCl_5$, $Mo(CO)_6$.

The alcohols of pinane structure *cis*- (**80**) and *trans*-verbenol (**81**), isopinocampheol (**82**), neoisoverbanol (**83**) are most easily oxidized. Oxidation of alcohols **80–83** proceeds readily without a catalyst in pyridine in 2–4 h at room temperature with 89–100 % conversion, selectivity of verbenone **86** formation is 76–79 %, isopinocamphone **87** and *cis*-verbanone **88** – 95–100 %, whereas oxidation of alcohols **78**, **79**, **84** is carried out better using a catalyst (Scheme 20). The selectivity of camphor **89** and menthone **90** formation is 98–100 %. The exclusive reaction product is menthone **90**, whereas oxidation of **84** by Cr^{+6} compounds almost always



Scheme 20: Reaction of chlorine dioxide with secondary terpenic alcohols.

produces a certain amount of isomenthone [62]. Conversion of isocaranol-4 **85** for 3 h is 78 %, selectivity of isocaranone-4 **91** formation – 91 %. In the presence of $MoCl_5$ the conversion of **85** is 100 %, but the selectivity decreases to 83 % [63].

When using DMF instead of pyridine the compounds **78–81** are converted into camphor **89** and verbenone **86**, respectively, with high selectivity, alcohols **82–84** are subjected to oxidative chlorination [63]. The oxidative chlorination of alcohol **82** in DMF in the absence of a catalyst is fairly slow. The complete conversion of the substrate is attained only in 12 h, but addition of a catalyst ($ZrOCl_2$, $VO(acac)_2$, $MoCl_5$) strongly accelerates the reaction. The selectivity for 2α-chloropinan-3-one **92** is 70–76 % (yield 71 %). Unlike compound **82**, oxidative chlorination of alcohol **83** is very fast with no use of the catalyst (yield 63 %). By contrast, addition of catalysts reduces the concentration of 3α-chloro-10β-pinan-4-one **93** in the reaction mixture. The result of menthone oxidation in DMF is the mixture of four chlorinated products. Unexpectedly, isocaran-4-ol **85** in DMF is neither oxidized nor chlorinated [63].

Oxidation of terpenic diols

Herein we report on oxidation by ClO_2 of terpenoid diols: 3α,4α- (**94**), 3α,4β- (**95**), 3β,4β- (**96**), 3β,4α-caranediols (**97**), 2α,3α- (**98**), 2α,3β-pinanediols (**99**), 2-*exo*-,3-*exo*-bornanediol (**100**), 3α, 4β-pinanediol (**101**) in pyridine and dimethylformamide with or without catalysts – $ZrOCl_2$, $VO(acac)_2$, $MoCl_5$, $Mo(CO)_6$, $CeCl_3$ [64].

The oxidation of vicinal diols with the formation of carbonyl compounds and a carboxylic acid is a well-known process. As expected, the major factor affecting the oxidation rate was the oxidant attack on C–H

bond, the compounds **95, 96** and **99**, having less sterically hindered proton at C^4 or C^3, were the fastest to be oxidized. Full conversion was observed within 1–3 h, the selectivity of ketols **102–104** formation being 84–90 % (Scheme 21). The corresponding acids **105** and **106** were obtained in minor amounts (10–16 %). In the cases of the most sterically hindered carane-based diols **94** and **97** full conversion could not be reached even in 5–7 h, the selectivity of ketols formation was 80–81 %.

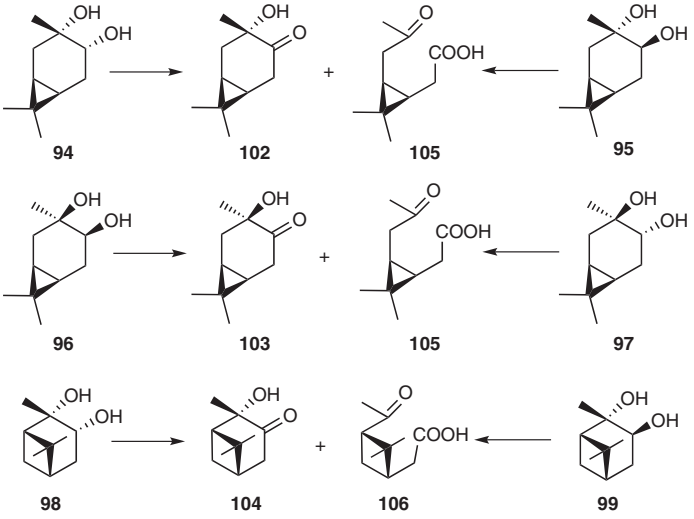
We performed the oxidation of 3α,4α-caranediol in the presence of catalysts. Ni(II), Co(II), Cr(III), and VO acetylacetonates slowed down the oxidation process, instead of accelerating it. As an example, in the presence of the most active of acetylacetonates used, $VO(acac)_2$, the conversion of **94** in 3 h was 40 %, being 58 % in the absence of any catalyst. The selectivity of ketol **102** formation was below 80 %. In the presence of molybdenum containing catalysts the oxidation was not accelerated as well, however, the ketol formation selectivity was somewhat increased under such conditions, to 89–91 % instead of 84 %.

Compound **107** was the only product of the prolonged (15 h) oxidation of diol **94** with chlorine dioxide in dimethylformamide medium (Scheme 22). GLC analysis of the products in the course of the reaction revealed that after 3 h the reaction was completed to 50 %; the content of hydroxyketone **102** was 42 %, and that of chlorinated derivative **107** was 4 %. After 7 h of the reaction duration, at 65 % overall conversion, the ketol content was down to 37 %, and that of the chlorinated derivative was up to 22 %. Within 15 h diol **94** conversion was full (99 %), the content of **107** was reached 76 % [64].

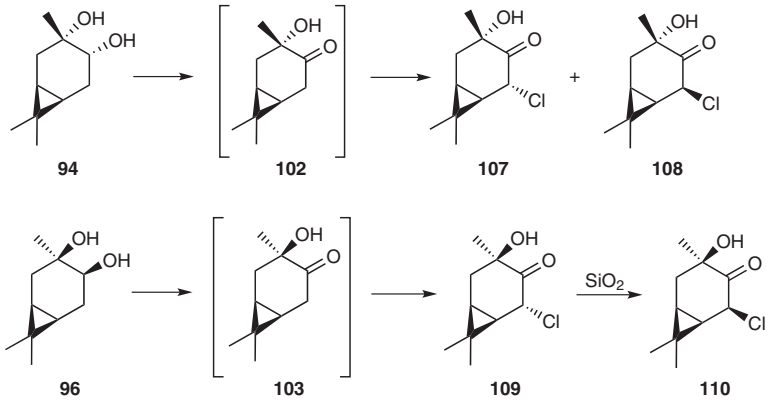
In order to accelerate oxidative chlorination of diol **94**, the reaction temperature was raised to 40 °C, catalysts ($ZrOCl_2$, $MoCl_5$, $CeCl_3$) were added, and the concentration of $CeCl_3$ was increased from 1.5 to 9.0 mol%. The optimal conditions for the formation of compound **107** were room temperature, reaction time 7 h, and $CeCl_3$ concentration 5–9 mol% (Scheme 22). The isolated yield of compound **107** was 51 %. We also succeeded in isolating pure isomer **108** whose fraction in the product mixture was as low as 3–5 % [63].

The oxidation of carane-3β,4β-diol **96** with ClO_2 in DMF (5–6 h) afforded 5α-chloro-3β-hydroxycaran-4-one (**109**, $t_R = 16.56$ min) with a selectivity of 91 %. An attempt to isolate chloroketone **109** by silica gel column chromatography (hexane–Et_2O) led to its complete isomerization to 5β-chloro-3β-hydroxycaran-4-one (**110**, $t_R = 17.61$ min). Neither oxidation nor chlorination occurred when diols **94** and **96** dissolved in DMF were treated with an aqueous solution of chlorine dioxide. After 24 h, the pure initial compounds were recovered from the reaction mixtures [63].

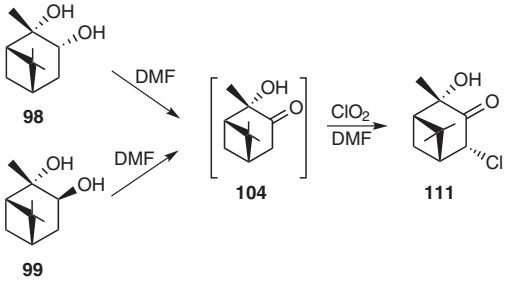
Diol **98** was fairly rapidly oxidized with ClO_2–DMF even in the absence of a catalyst (7 h, 100 % conversion); however, the chlorination of 2α-hydroxypinan-3-one **104** thus obtained was much slower (Scheme 23). Only after 48 h in the presence of 5 mol% of $CeCl_3$ the concentration of chlorohydroxyketone **111** attained 90 %. The oxidative chlorination of isomeric pinane-2α,3β-diol **99** was characterized by lower rate and selectivity.



Scheme 21: Reaction of chlorine dioxide with terpenic diols in pyridine.



Scheme 22: Reaction of chlorine dioxide with terpenic diols in DMF.



Scheme 23: Oxidation of pinane diols **98**, **99** by chlorine dioxide.

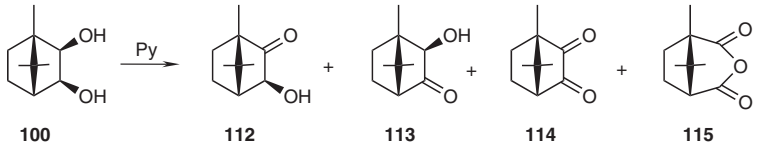
After 6 h, the conversion of diol **99** was 79 %, and the product mixture contained 45 % of hydroxy ketone **104** and 9 % of chlorohydroxyketone **111**, while the other products were not identified [63].

Bornanediol **100** was extremely rapidly oxidized with chlorine dioxide in pyridine: the conversion was practically 100 % after 1 h [65]. The major products were isomeric ketols, 3β-hydroxycamphor **112** and 2β-hydroxyepicamphor **113**, 74–80 % in total (Scheme 24). Besides those products, the reaction mixture contained 10–15 % of camphorquinone **114** and 9–10 % of camphor anhydride **115**. When the reaction run longer (up to 3 h), the ketols content was down to 50 %, and camphor anhydride yield was up to 40 %, yield of camphorquinone being almost the same (12–15 %).

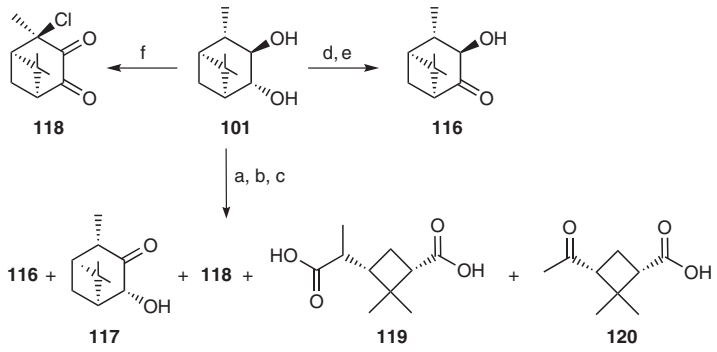
With $VO(acac)_2$ or $MoCl_5$ as catalyst, selectivity of the ketols **112** and **113** formation was up to 85–87 %, and the isomers ratio was somewhat shifted in favor of formation of exo-2-hydroxyepicamphor **113**. When DMF was used as solvent instead of pyridine, the oxidation was significantly slowed down: conversion of the starting diol **100** was of 26 % within 1 h. However, longer reaction run (3 h) or using of the catalyst ($VO(acac)_2$ or $MoCl_5$) resulted in a complete conversion of the diol with selectivity of 95–99 % with respect to ketols. Under those conditions, only tiny amounts of camphorquinone and camphor anhydride were formed [65].

Oxidation of 3α,4β-pinanediol **101** in pyridine without any catalyst or with $VO(acac)_2$ yielded a complex mixture of products that could be separated into the neutral and the acidic fractions via treatment with aqueous $NaHCO_3$ (5 wt%). In the neutral fraction two isomeric ketols were identified: 3α-hydroxy-10β-pinane-4-one **116** and 4β-hydroxy-10β-pinane-3-one **117** (Scheme 25) along with the chlorinated derivative 2α-chloropinane-3,4-dione **118**. Among acidic products, pinocamphor acid **119** was isolated, and *cis*-pinonic acid **120** was identified. Molybdenum containing catalysts decreased the diol **101** conversion to 35–54 %, but selectivity of the α-ketols formation was up to 60–68 %. In all the cases, 3α-hydroxy-10β-pinane-4-one was the major isomer [65].

When DMF was used instead of pyridine, both without any catalyst or in the presence of $Mo(CO)_6$ or $MoCl_5$, α-hydroxyketone **116** was practically the only reaction product, selectivity of its formation being independent of heating up to 40 °C as well as cooling down to 0 °C. Compound **116** was isolated via chromatography on



Scheme 24: Oxidation of Bornanediol **100** by chlorine dioxide.



Scheme 25: Interaction of pinane diol **101** with chlorine dioxide. (a) ClO_2, Py; (b) ClO_2, Py, Mo(II); (c) ClO_2, Py, $VO(acac)_2$; (d) ClO_2, DMF; (e) ClO_2, DMF, Mo(II); (f) ClO_2, DMF, $VO(acac)_2$.

SiO_2; mp 57–58 °C and $[\alpha]_D$+73.6° (after recrystallization from hexane–Et_2O mixture). In the case of ClO_2–DMF–$VO(acac)_2$ oxidative system, the major product of diol **101** oxidation was chlorinated diketone **118** [65].

Thus, oxidative dehydrogenation of terpenic secondary alcohols and *sec-tert* vicinal diols with ClO_2 in pyridine produces the respective ketones and hydroxyketones with high selectivity and excellent preparative yields. The reactivity of diols relative to ClO_2 mainly depends on the stereochemistry of hydroxyl groups.

Oxidative dehydrogenation of *sec-*, *sec-* vicinal diols in pyridine yielded hydroxylketones, diketones, acids, and chlorinated products. In DMF, both without any catalyst and in the presence of Mo-containing catalyst α-hydroxyketones were obtained with high selectivity. *exo*-Positioning of hydroxyl groups in bornane-2,3-diol affords equal accessibility of C–H bonds for the oxidants attack, and in most cases practically equimolar mixture of isomeric α-hydroxyketones was formed. In 3α,4β-pinanediol, the proton at C^4 atom was sterically hindered, and 3-hydroxypinane-4-one prevailed in the products, or even was the only isomer.

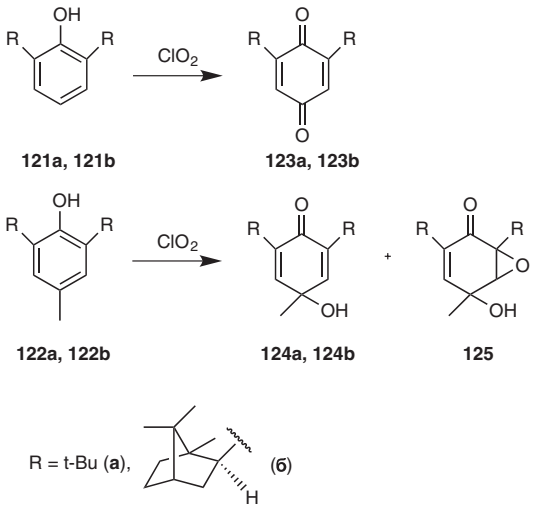
The system ClO_2–DMF acts as not only an oxidant but also a chlorinating agent. The product structure (α-chloroketone or α-chlorohydroxyketone) is determined by both substrate nature and stereochemical orientation of the hydroxy groups in initial isomeric terpene diols. *cis*-Diols are converted into the corresponding chlorohydroxyketones with fairly high selectivity, whereas the oxidative chlorination of *trans*-diols is much less selective. In some cases, the system ClO_2–DMF may be recommended for one-pot preparation of α-chloroketones or α-chlorohydroxyketones.

The reactions with terpenophenols

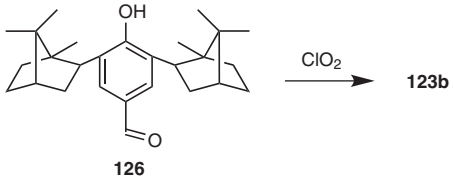
Quinone derivatives constitute important groups of natural compounds such as dyes, pigments, antibiotics, vitamins, etc. They are used as reagents in synthesis, polymer modifiers and stabilizers, and catalysts of chemical reactions. Development of procedures for the synthesis of quinones from sterically hindered phenols attracts interest from a practical viewpoint.

Oxidation of phenols with chlorine dioxide (ClO_2) was studied in [66–68]; it was shown that 2,6-disubstituted phenols are thus oxidized to the corresponding 1,4-quinones (yield 67–95 %) or diphenoquinones; 2,4-disubstituted phenols react with ClO_2 to form 4-alkyl-*p*-quinols.

In the works [69–71] we examined oxidation of sterically hindered phenols **121a**, **121b**, **122a**, and **122b** with chlorine dioxide in pyridine on cooling or in DMF at 20 °C (Scheme 26). The oxidation of 2,6-di-*tert*-butylphenol



Scheme 26: Reaction of chlorine dioxide with sterically hindered phenols.



Scheme 27: Oxidation of 3,5-diisobornyl-4-hydroxybenzaldehyde **126** with chlorine dioxide.

121a gave 2,6-di-*tert*-butylbenzoquinone **123a** [66]. By oxidation of 2,6-diisobornylphenol **122b** we obtained previously unknown 2,6-diisobornyl-1,4-benzoquinone **123b**. Its structure was confirmed by IR and NMR spectroscopy.

Oxidation of 4-methyl-substituted phenols **122a** and **122b** with ClO_2 afforded 2,6-dialkyl-4-hydroxy-4-methyl-2,5-cyclohexadien-1-ones **124a** and **124b**. No chlorination products were detected in the reaction mixtures. When phenol **122a** was oxidized in pyridine on cooling, the substrate-to-oxidant molar ratio being 1:3, a mixture of products was formed. It was separated by column chromatography to isolate major product **124a** and 1.5 % of 1,3-di-tert-butyl-5-hydroxy-5-methyl-7-oxabicyclo-[4.1.0]hept-3-en-2-one **125a**.

Quinone **123b** was also obtained instead of the expected carboxy derivative in the oxidation of 3,5-diisobornyl-4-hydroxybenzaldehyde **126** with chlorine dioxide (Scheme 27). The yield of **123b** was 80 % when the reaction was carried out in dimethylformamide at 20 °C. Presumably, the reaction is accompanied by oxidative decarboxylation. Chlorine dioxide is a fairly potent oxidant, reactions with its participation occur at a high rate, and we failed to isolate hydroxybenzoic acid. Quinone **123b** was formed in 36 % yield by oxidation of **126** in pyridine on cooling with the use of three equiv of ClO_2; the product was isolated after prolonged keeping of the reaction mixture.

Thus oxidation with chlorine dioxide of sterically hindered phenols having a methyl group in the *para* position with respect to the OH group yields 4-hydroxy-4-methyl-2,5-cyclohexadien-1-ones. Phenols having no substituent in the *para* position with respect to the hydroxy group, as well as 4-hydroxybenzaldehyde derivative, are converted into the corresponding 1,4-benzoquinones.

Conclusions

Over the last 10–15 years we have obtained important results on the reactivity of chlorine dioxide with organic compounds. New synthetic possibilities of chlorine dioxide in reactions of the chemo- and stereoselective

oxidation of thiols, sulfides and alcohols have been shown. A new reaction of thiols and disulfides with chlorine dioxide to produce sulfonyl chlorides has been discovered. Catalysis in the oxidation reactions with chlorine dioxide of oxygen- and organosulfur compounds was first used and the asymmetric sulfide oxidation reactions were studied.

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