Reactions of 2-mercaptoacetic acid with mucochloric acid and its derivatives*

A. R. Kurbangalieva,[a] N. F. Devyatova,[a] L. S. Kosolapova,[a] O. A. Lodochnikova,[b] E. A. Berdnikov,[a] I. A. Litvinov,[b] and G. A. Chmutova[a]*

[a]*Kazan State University,*
18 ul. Kremlevskaya, 420008 Kazan, Russian Federation.
Fax: +7 (843) 231 5416. E-mail: Almira.Kurbangalieva@ksu.ru
[b]*A. E. Arbuzov Institute of Organic and Physical Chemistry,*
Kazan Research Center of the Russian Academy of Sciences,
8 ul. Akad. Arbuzova, 420088 Kazan, Russian Federation.
Fax: +7 (843) 273 2253

The stable products of reactions of mucochloric acid and some of its ethers with 2-mercaptoacetic acid were synthesized and characterized. The variation of experimental conditions allowed targeted introduction of a sulfur-containing fragment into particular position of the heterocycle: the reaction in aqueous potassium hydroxide gives 3-substituted 2(5*H*)-furanone, the triethylamine additive in nonaqueous solvents facilitates the formation of 4-substituted products, and acid catalysis results in the replacement of the hydroxy (methoxy) group at C(5). (3,4-Dichloro-2-oxo-2,5-dihydrofuran-5-ylthio)ethanoic acid and (3-chloro-5-hydroxy-2-oxo-2,5-dihydrofuran-4-ylthio)ethanoic acid were characterized by X-ray diffraction; their crystal and gas-phase structures were discussed. The 5-monosubstituted product crystallizes as a racemate, while 4-monosubstituted product, as a conglomerate.

Key words: mucochloric acid, mercaptoacetic acid, 2(5*H*)-furanones, sulfides, X-ray diffraction, quantum chemical calculations.

Mucochloric acid (3,4-dichloro-5-hydroxy-2(5*H*)-furanone) is one of the most readily accessible and reactive representatives of five-membered oxygen-containing heterocycles whose derivatives play an important role in both theoretical and applied organic chemistry. 2(5*H*)-Furanone structural fragments are parts of natural biologically active compounds such as clavacin, penicillic acid, vitamin C, and synthetic pharmaceutical substances.[1—4] The interest in mucochloric acid from the standpoint of theoretical and experimental organic chemistry is due to its structural features (ring—chain tautomerism) and to the presence of a number of reaction centers owing to which this acid and its derivatives can be involved, as effective building blocks, in reactions with nucleophilic, electrophilic, and other reagents.[1] A large number of publications are devoted to reactions of 2(5*H*)-furanones with N-, C-, O-, and P-nucleophiles; however, among reactions with S-nucleophiles, only those with thiols were described.[5—11]

Our recent studies of reactions of mucochloric acid with various sulfur-containing nucleophiles[11—13] were mainly aimed at elucidating the conditions for selective thiolation, preparation of sulfides of different structural types, investigation of their spatial and electronic structures, and the possibilities to be involved in intermolecular contacts. This appears especially important in view of the hypothetical high biological activity of this class of compound as predicted by the PASS (Prediction of Activity Spectra for Substances) program[14,15] available on the Internet (most likely are antiinflammatory, dermatological, and antiarthritic activities and antiviral, antiatherosclerotic, antipruritic, and hypolipidemic actions).

Previously, we studied the reactions of mucochloric acid and some its derivatives with substituted thiophenols and found conditions for selective introduction of arylthio substituents into various positions of the furanone ring.[11] The use of sulfur-containing binucleophilic reagents (ethane-1,2-dithiol[12] and 2-mercaptoethanol[13]) furnished nucleophilic substitution products including mono- and bicyclic and unexpectedly acyclic ones.

The purpose of this work was to study the reactivity of mucochloric acid, its ethers, and some other derivatives with respect to 2-mercaptoacetic acid and to prepare and characterize the fine structure of products containing a

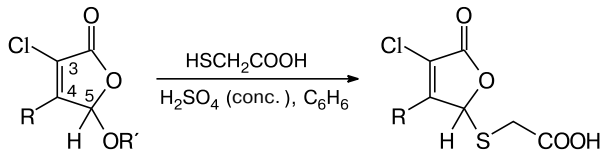
* Dedicated to Academician A. I. Konovalov on his 75th birthday.

Published in Russian in *Izvestiya Akademii Nauk. Seriya Khimicheskaya,* No. 1, pp. 126—133, January, 2009.
1066-5285/09/5801-0126

2-mercaptoacetic acid fragment in heterocycle positions 3, 4, and 5.

The reactions of mucochloric acid **1** and its methyl ether **2** with 2-mercaptoacetic acid carried out in benzene in the presence of catalytic amounts of concentrated sulfuric acid resulted in the product of replacement of the hydroxy group at the C(5) atom of the lactone ring (Scheme 1).

Scheme 1



1—5 **6, 7**

R = Cl (**1**—**4**, **6**), *p*-TolS (**5**, **7**); R′ = H (**1**, **5**), Me (**2**), Et (**3**), Pr^i (**4**)

Similar reactions with ethyl (**3**) and isopropyl (**4**) mucochlorates did not proceed even on long-term refluxing of the reactants. Only the starting ethers and 2-mercaptoacetic acid were recovered from the reaction mixtures. On increasing the reaction temperature, resinification of the reaction mixtures took place.

The reaction of 4-(*p*-tolylthio)-substituted furanone **5** with 2-mercaptoacetic acid in the presence of concentrated sulfuric acid follows a similar route with replacement of the hydroxy group to give sulfide **7** (see Scheme 1).

The structures of new compounds **6** and **7** were proved by IR and ^{1}H NMR spectroscopy; the structure of compound **6** was additionally confirmed by X-ray diffraction study. According to X-ray diffraction data (Fig. 1, Table 1), the five-membered ring is planar (within 0.009(4) Å), which is typical of both the proper mucochloric acid[16] and the products of its reactions with thiophenols.[11] The molecules of **6** in the crystal occur in a "coiled" conformation in which the terminal carbonyl group C(7)=O(7) and the endocyclic bond O(1)—C(2) are spatially proximate. The structure has short contacts, C(7)...O(1) (3.071(4) Å) and C(2)...O(7) (3.032(5) Å) (the sum of the van der Waals radii of oxygen and carbon is 3.22 Å). Taking into account the polarity of the carbonyl group (a partial negative charge on oxygen and a partial positive charge on carbon) and the electron lone pair of the ring oxygen atom, the stability of this unexpected conformation of molecules in the crystal can be attributed to through-space electrostatic interactions of oppositely charged atoms (see Fig. 1).

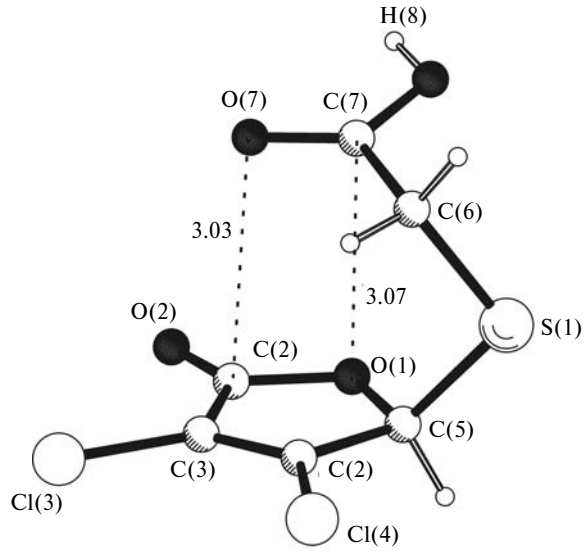
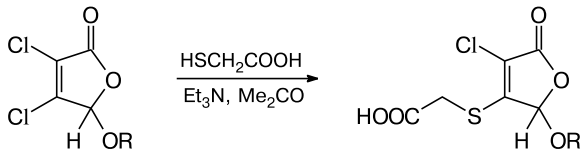


Fig. 1. Geometry of molecule **6** in the crystal. Interatomic distances (in Å) are marked by dashed line.

Previously,[9,11] it was shown that in the presence of basic substances, 3,4-dichloro-2(5*H*)-furanones react with S-nucleophiles with substitution of chlorine in position 4 of the lactone ring. The reactions of mucochloric acid **1** and its alkoxy derivatives **2—4** with 2-mercaptoacetic acid in the presence of triethylamine in acetone follow a similar route resulting in the products of replacement of chlorine at the C(4) atom in the lactone ring **8—11** (Scheme 2).

Scheme 2



1—4 **8—11**

R = H (**1**, **8**), Me (**2**, **9**), Et (**3**, **10**), Pr^i (**4**, **11**)

The structures of new sulfides **8—11** was proved by IR and NMR spectroscopy. The IR spectra of compounds **8—11** contain a narrow band for the C=C stretching vibrations in the γ-lactone ring at 1590—1595 cm^{-1}, two strong signals at 1654—1723 and 1725—1772 cm^{-1} for C=O stretching vibrations of carboxylic acids and γ-lactone ring, respectively, and a group of broadened bands at 2500—3300 cm^{-1} due to ν(OH) stretching vibrations of the carboxy group. The ^{1}H NMR spectra of sulfides **8—11** typically exhibit a singlet for the H(5) methine proton with δ 6.25—6.43 and an AB quadruplet with δ 4.0—4.3 corresponding to the methylene protons in the 2-mercaptoacetic acid fragment.

The structure of compound **8** in the crystalline state was confirmed by X-ray diffraction (Fig. 2, Table 1). The conformation of this compound differs from that observed

Table 1. Selected geometric parameters (bond lengths (*d*), bond angles (ω), and torsion angles (τ)) of compounds **6** and **8** in the crystals from X-ray diffraction data and in the gas phase from B3LYP/6-31G(d,p) quantum chemical calculations

Parameter	**6**			**8**	
	X-Ray diffraction	Monomer*	Dimer*	X-Ray diffraction	Monomer*
Bond			*d*/Å		
S(1)—C(5)	1.793(3)	1.831	1.831	—	—
S(1)—C(4)	—	—	—	1.714(8)	1.746
S(1)—C(6)	1.801(3)	1.838	1.838	1.80(1)	1.844
O(1)—C(2)	1.370(5)	1.381	1.379	1.34(1)	1.380
O(1)—C(5)	1.440(4)	1.433	1.434	1.45(1)	1.433
O(2)—C(2)	1.190(6)	1.197	1.198	1.21(1)	1.199
O(7)—C(7)	1.221(4)	1.211	1.233	1.22(1)	1.207
O(8)—C(7)	1.298(4)	1.347	1.309	1.32(1)	1.355
C(2)—C(3)	1.462(6)	1.491	1.490	1.47(1)	1.483
C(3)—C(4)	1.324(5)	1.339	1.339	1.35(1)	1.345
C(4)—C(5)	1.492(5)	1.509	1.509	1.50(1)	1.527
C(6)—C(7)	1.505(4)	1.517	1.516	1.52(1)	1.516
Angle			ω/deg		
C(5)—S(1)—C(6)	102.1(1)	102.8	102.7	—	—
C(4)—S(1)—C(6)	—	—	—	103.4(4)	104.1
C(2)—O(1)—C(5)	110.0(3)	110.8	110.8	110.9(7)	110.7
O(1)—C(2)—O(2)	121.3(4)	123.2	123.2	123(1)	123.2
O(2)—C(2)—C(3)	131.4(4)	129.8	129.7	128.8(9)	129.8
O(1)—C(2)—C(3)	107.3(3)	107.0	107.1	107.9(7)	106.9
C(2)—C(3)—C(4)	109.4(3)	108.6	108.6	109.3(8)	110.1
C(3)—C(4)—C(5)	109.2(3)	109.4	109.4	107.8(7)	107.5
O(1)—C(5)—C(4)	104.0(3)	104.2	104.2	104.1(6)	104.8
S(1)—C(6)—C(7)	113.5(2)	114.2	113.9	109.4(6)	113.7
O(7)—C(7)—C(6)	121.4(3)	124.2	120.7	124.5(9)	124.7
O(8)—C(7)—C(6)	114.6(3)	112.1	113.8	113.7(7)	112.0
O(7)—C(7)—O(8)	124.0(3)	123.7	125.5	121.8(9)	123.3
Angle			τ/deg		
C(6)—S(1)—C(5)—C(4)	50.2(3)	−48.1	−49.9	—	—
C(5)—S(1)—C(6)—C(7)	68.3(3)	−67.4	−68.6	—	—
C(6)—S(1)—C(4)—C(5)	—	—	—	17.5(9)	10.9
C(4)—S(1)—C(6)—C(7)	—	—	—	79.4(7)	87.4

* Gas.

for molecule **6**, in particular, it is nearly eclipsed along the S(1)—C(4) bond (the corresponding torsion angle is 17.5(9)°), which gives rise to stereochemical conditions for the conjugation of the sulfur lone pair with the C(3)=C(4) multiple bond. The decrease in the C(4)—S(1) bond length to 1.714(9) Å (*cf.*: in the crystal of **6** the length of this bond is 1.794(3) Å) may serve as evidence for this conjugation. The conformation along the S(1)—C(6) bond is nearly staggered, the corresponding torsion angle being equal to 79.4(7)°.

The significant difference between the spatial structures of the crystalline state of compounds **6** and **8** was an incentive for more thorough studies of the structure of these compounds. Having assumed that conformations of the two molecules in the free state should be similar and the unusual spatial structure of 5-substituted sulfide in the crystal is due to a packing effect and to a different motif of intermolecular H-bonding compared to that in the 4-substituted derivative, we carried out the B3LYP/6-31G(d,p) DFT calculations for structures of **6** and **8** in the gas-phase taking account of the possibility of existence of

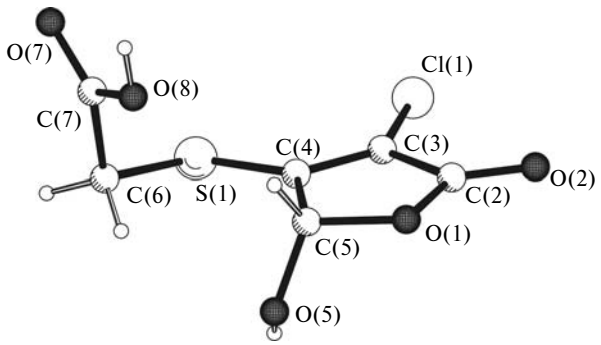


Fig. 2. Geometry of molecule **8** in the crystal.

different conformations and additionally studied the crystal packing motifs for both compounds by X-ray diffraction. The experimental and theoretical geometric parameters of both structures were found to be rather similar (see Table 1). As expected, the most stable conformations of individual compounds **6** and **8** (gas phase) are nearly the same: the substituent SCH_2COOH has a zigzag conformation and is directed away from the furanone ring; the "X-ray-like" structure of compound **6** is 1.39 kcal mol^{-1} lower in energy; the stability of the latter twisted conformation is largely determined by through-space electrostatic interactions (according to calculation, the O(7)...C(2) and C(7)...O(1) distances are 3.032 and 3.070 Å, respectively, the charges on the O(7), C(7), C(2), and O(1) atoms are −0.447, 0.584, 0.640, and −0.460, respectively; the numbering is shown in Fig. 1). However, the crystal packing motifs of these compounds are considerably different.

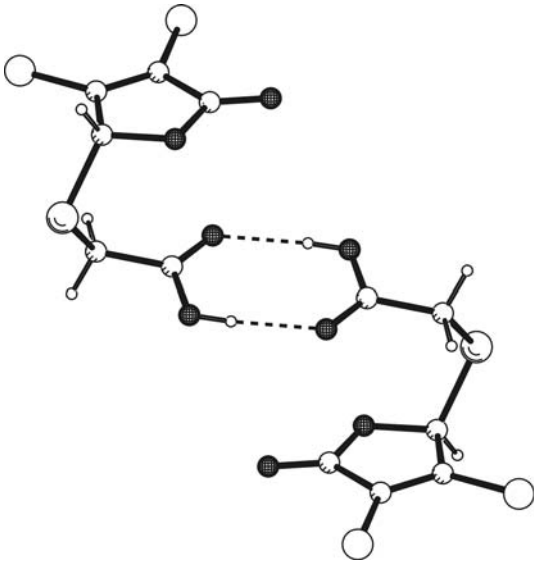


Fig. 3. Hydrogen-bonded dimer of molecules **6**.

Compound **6** crystallizes as a racemate (space group $P\bar{1}$). Neighboring molecules **6**, which represent an enantiomeric pair, are connected to centrosymmetric S-shaped dimers through classical hydrogen bond O(8)—H(8)...O(7) (H(8)...O(7), 1.86 Å; O(7)...O(8), 2.679(4) Å; O(8)—H(8)...O(7), 173°) (Fig. 3). The intermolecular hydrogen bonds are strong ($\delta\Delta G_{298}$ = −4.33 kcal mol^{-1} per hydrogen bond). Unlike compound **6**, in the case of compound **8**, X-ray diffraction data indicate the presence of one enantiomer in the crystal (space group $P2_1$), which may attest to conglomerate crystallization. The system of hydrogen bonds

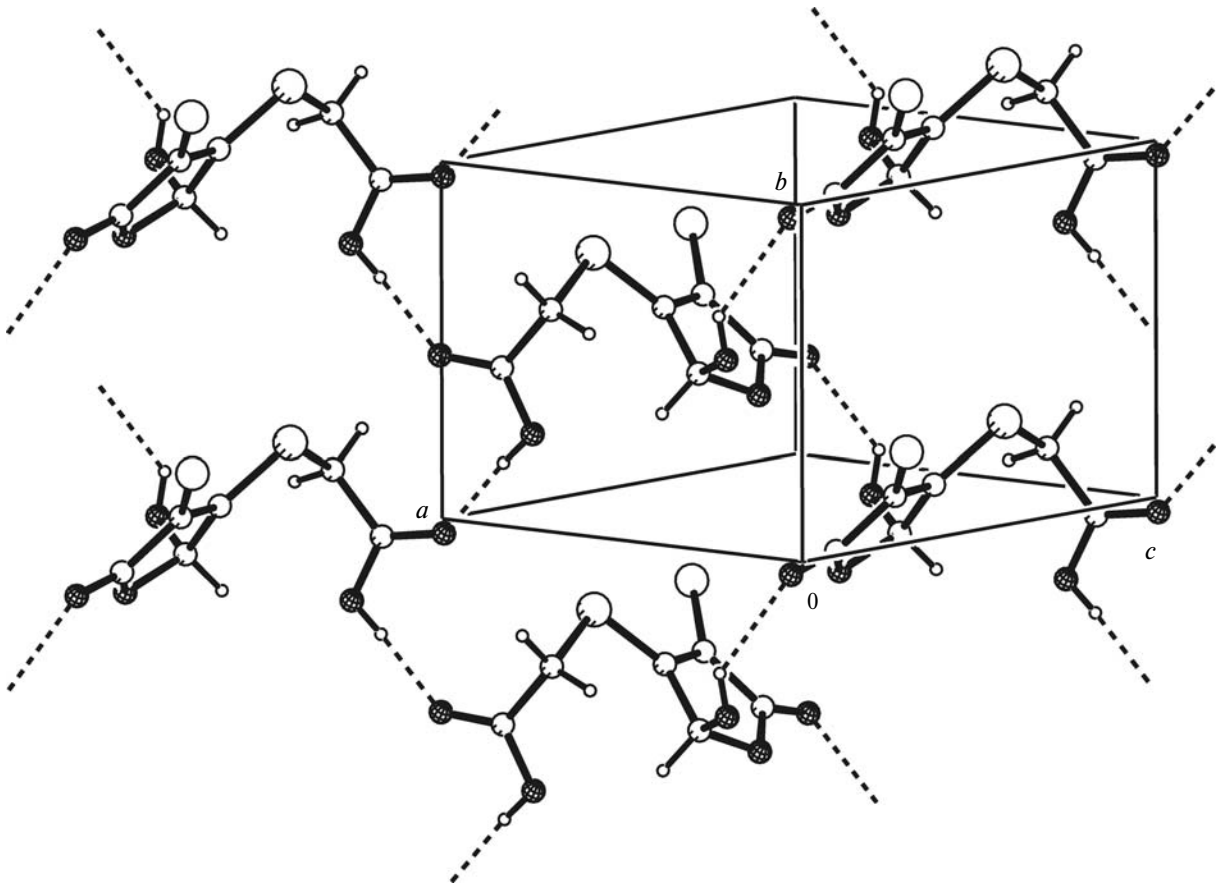
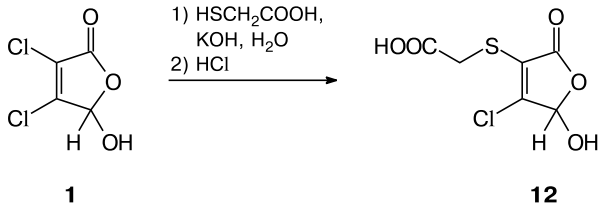


Fig. 4. Network of hydrogen-bonded molecules **8**.

in the crystal of compound **8** is much more complicated than that in **6** due to the presence of an additional donor center, a hydroxy group. In this case, the classical dimer is probably no longer the most favorable supramolecular associate. Hydrogen bonds of two types (Fig. 4) combine molecules **8** into networks along a crystal cell diagonal. Parameters of the O(5)—H(5)...O(2′) bond [$1 - x$, $-1/2 + y$, $1 - z$]: H(5)...O(2′), 2.05 Å; O(5)...O(2′), 2.84(1) Å; O(5)—H(5)...O(2′), 162°; parameters of the O(8)—H(8)...O(7′) bond [$2 - x$, $1/2 + y$, $-z$]: H(8)...O(7′), 1.78 Å; O(8)...O(7′), 2.59(1) Å; O(5)—H(5)...O(2′), 173°.

The reaction of mucochloric acid **1** with 2-mercaptoacetic acid in the presence of alkali followed by treatment of the reaction mixture with dilute HCl gave a product of chlorine substitution at C(3), compound **12** (Scheme 3). Unlike the ^{1}H NMR spectrum of compound **8** (4-substitution product), in the spectrum of compound **12**, the methine proton and the proton of the hydroxy group at C(5) are responsible for doublets, which can be attributed to the lack of intramolecular exchange interactions between the hydroxyl and carboxyl protons in the 3-regioisomer product molecule **12**.

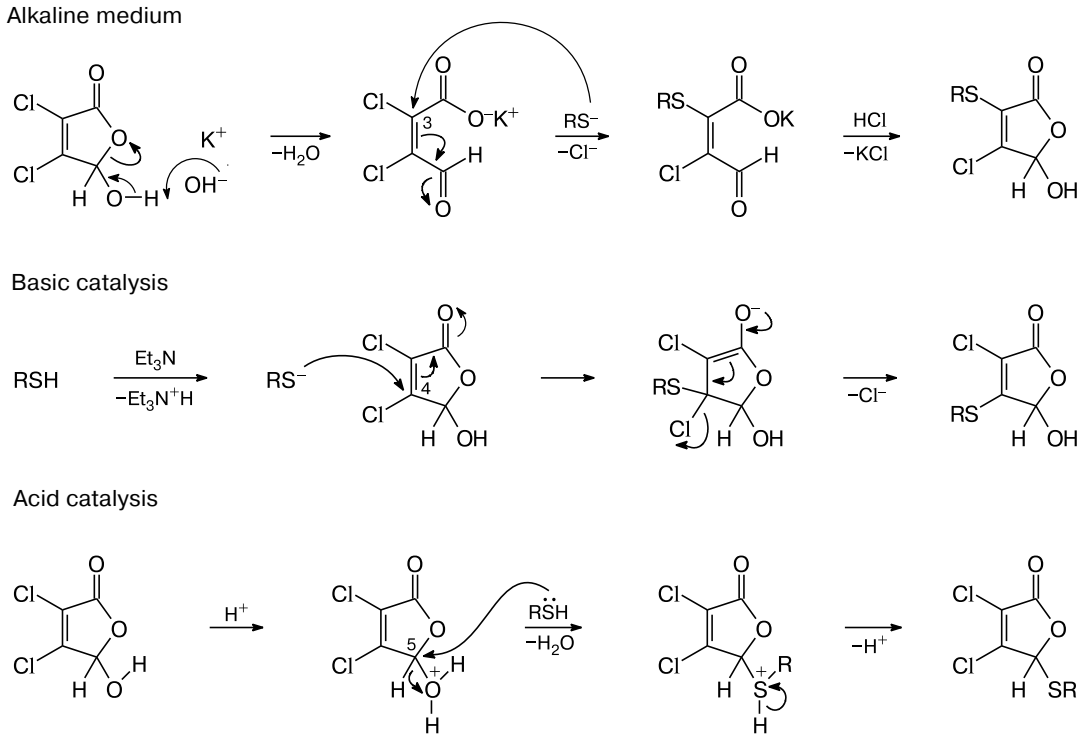
Scheme 3



It is noteworthy that selective introduction of ArS group to positions 3, 4, and 5 of mucochloric acid molecule in previously studied[11] reactions with substituted thiophenols or the SCH_2COOH group in reactions with 2-mercaptoacetic acid proceed under similar experimental conditions. In the presence of acidic and basic compounds, the attack of the S-nucleophile is directed on different sites; the difference in regioselectivity is evidently due to different reaction mechanisms. The mechanisms we propose for the formation of the 3-, 4-, and 5-substituted products under different reaction conditions are shown in Scheme 4.

In alkaline medium, the lactone ring is opened and potassium mucochlorate is formed;[17] in its molecule, the C(3) atom is the most electron deficient site attacked by the thiolate ion as a result of greater mesomeric effect of the carbonyl group compared to the carboxy group. In the reactions carried out in the presence of triethylamine, the C(4) atom is, in our opinion, most susceptible to nucleophilic attack, and halogen is replaced according to the generally accepted nucleophilic vinylic substitution pattern.[18] With acid catalysis, the increased electrophilicity of the C(5) atom in the protonated mucochloric acid

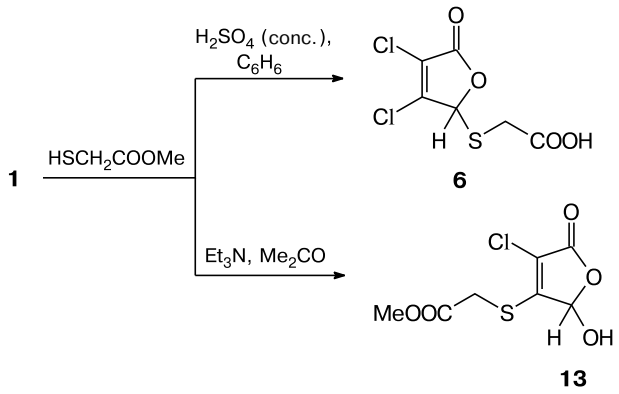
Scheme 4



directs the RSH attack on the C(5) atom of the lactone ring; this is followed by elimination of the water molecule and the proton to give 5-thiosubstituted mucochloric acid derivatives.

The reaction of mucochloric acid with methyl 2-mercaptoacetate in basic and acidic media leads to the following results. The reaction carried out in the presence of triethylamine in acetone gives the expected product of chlorine replacement at C(4) atom of the lactone ring of **13** (Scheme 5). In the case of acid catalysis, the above-described sulfide **6** was isolated as a result of hydrolysis of the ester fragment COOMe.

Scheme 5



In summary, by varying the conditions for performing reactions of mucochloric acid, its ethers, and its thioether with 2-mercaptoacetic acid, it is possible, as in the case of aromatic thiols,[11] to selectively obtain 3-, 4-, and 5-monosubstituted products. Ethers **2**—**4** and sulfide **5** react with aromatic and aliphatic thiols similarly to the proper mucochloric acid. The 5-monosubstituted product (**6**) crystallizes as a racemate to give dimers usual for carboxylic acids. In the crystal of 4-monosubstituted product (**8**), a branched system of hydrogen bonds is formed owing to the simultaneous presence of hydroxy and carboxy groups in the molecule. A different type of crystal packing (more complicated system of intermolecular interactions) may be responsible for the conglomerate crystallization of compound **8** in a homochiral space group.

Experimental

IR spectra of crystalline samples were recorded on a Tensor-27 FT spectrometer (Bruker) in the 4000—400 cm^{-1} range (Nujol was used as the carrier, the sample was placed between KBr plates). The NMR spectra were recorded on a Varian Unity-300 spectrometer (299.94 (^{1}H) and 75.13 MHz (^{13}C)) for solutions in acetone-d_6 at 25 °C. The chemical shift was referred to residual proton signals of acetone-d_6. The melting points were measured on a Boetius hot stage and were not corrected. TLC analysis was carried out on Silufol UV-254 plates (elution with hexane—diethyl ether, 1 : 3 v/v).

Mucochloric acid **1** (Shostka Chemical Reagents Plant, Ukraine) was recrystalized from water, m.p. 127 °C. 3,4-Dichloro-5-methoxy-2(5*H*)-furanone[19] (**2**), 3,4-dichloro-5-ethoxy-2(5*H*)-furanone[20] (**3**), 3,4-dichloro-5-isopropoxy-2(5*H*)-furanone[19] (**4**), and 3-chloro-5-hydroxy-4-[(4-methylphenyl)thio]-2(5*H*)-furanone[11] (**5**) were synthesized by known procedures.

(3,4-Dichloro-2-oxo-2,5-dihydrofuran-5-ylthio)ethanoic acid (6). ***A.*** Compound **1** (1.50 g, 8.88 mmol) and 2-mercaptoacetic acid (0.62 mL, 8.88 mmol) were dissolved in anhydrous benzene (30 mL) in a round-bottom flask equipped with a Dean—Stark trap and a reflux condenser. Concentrated sulfuric acid (0.024 mL, 5 mol.%) was added to the resulting solution. The reaction mixture was refluxed to complete consumption of compound **1** (16 h) according to TLC monitoring. The reaction mixture was cooled and the resulting yellow precipitate was filtered off and recrystallized from benzene. Yield 89%, white-colored plate crystals, m.p. 114 °C, R_f 0.54. Found (%): C, 29.48; H, 1.32; Cl, 28.87; S, 13.28. $C_6H_4Cl_2O_4S$. Calculated (%): C, 29.65; H, 1.66; Cl, 29.17; S, 13.19. IR, ν/cm^{-1}: 3160, 2689, 2575 (OH); 1799, 1698 (C=O); 1622 (C=C). ^{1}H NMR, δ: 3.45, 3.47 (AB quadruplet, 1 H each, SCH_2, J = 15.5 Hz); 6.57 (s, 1 H, H(5)).

B. Ether **2** (1.00 g, 3.60 mmol) was refluxed with 2-mercaptoacetic acid (0.25 mL, 3.60 mmol) in benzene (30 mL) in the presence of concentrated sulfuric acid (0.003 mL, 5 mol.%) for 26 h. The yield of compound **6** was 35%.

C. Compound **1** (1.00 g, 5.9 mmol) was refluxed with methyl 2-mercaptoacetate (0.44 mL, 5.9 mmol) in benzene (30 mL) in the presence of concentrated sulfuric acid (0.03 mL, 0.59 mmol) for 16 h. The yield of compound **6** was 42%.

[3-Chloro-4-(4-methylphenylthio)-2-oxo-2,5-dihydrofuran-5-ylthio]ethanoic acid (7) was synthesized similarly to compound **6** from sulfide **5** (0.70 g, 2.72 mmol), 2-mercaptoacetic acid (0.19 mL, 2.72 mmol), and concentrated sulfuric acid (0.007 mL, 5 mol.%), reaction time 21 h. Yield 68%, m.p. 142—144 °C (from a CCl_4—CH_2Cl_2 mixture), R_f 0.25. Found (%): C, 47.09; H, 3.18; Cl, 10.64; S, 19.25. $C_{13}H_{11}ClO_4S_2$. Calculated (%): C, 47.20; H, 3.35; Cl, 10.72; S, 19.39. IR, ν/cm^{-1}: 3176, 2678, 2563 (OH); 1768, 1704 (C=O); 1574 (C=C). ^{1}H NMR, δ: 2.38 (s, 3 H, Me); 3.29, 3.39 (AB quadruplet, 1 H each, SCH_2, J = 15.3 Hz); 6.23 (s, 1 H, H(5)); 7.30, 7.60 (AA´BB´ system, 4 H, H arom., $N = {}^3J_{A,B} + {}^5J_{A,B'}$ = 8.0 Hz).

(3-Chloro-5-hydroxy-2-oxo-2,5-dihydrofuran-4-ylthio)ethanoic acid (8). A solution of 2-mercaptoacetic acid (0.62 mL, 8.88 mmol) in acetone (6 mL) and then a solution of triethylamine (1.24 mL, 8.88 mmol) in acetone (4 mL) were added dropwise with vigorous stirring to a solution of mucochloric acid **1** (1.5 g, 8.88 mmol) in acetone (10 mL). The reaction mixture was refluxed for 4 h and the end of the reaction was determined by TLC. The white precipitate of $Et_3N \cdot HCl$ was filtered off and washed with acetone. The filtrate was concentrated *in vacuo* and the dark oily residue was purified by column chromatography (elution with hexane—ether, 1 : 3) followed by recrystallization of the main fraction from CH_2Cl_2. Yield 56%, white-colored precipitate, m.p. 114 °C, R_f 0.28. Found (%): C, 32.41; H, 2.45; Cl, 15.99; S, 14.27. $C_6H_5ClO_5S$. Calculated (%): C, 32.08; H, 2.24; Cl, 15.78; S, 14.28. IR, ν/cm^{-1}: 3296, 2685, 2564 (OH); 1725, 1654 (C=O); 1589 (C=C). ^{1}H NMR, δ: 4.09, 4.29 (AB quadruplet, 1 H each, SCH_2, J = 16.5 Hz); 6.43 (s, 1 H, H(5)).

(3-Chloro-5-methoxy-2-oxo-2,5-dihydrofuran-4-ylthio)-ethanoic acid (9) was synthesized similarly to compound **8** from ether **2** (0.41 g, 2.23 mmol), 2-mercaptoacetic acid (0.16 mL, 2.23 mmol), and triethylamine (0.31 mL, 2.23 mmol). Yield

46%, white-colored precipitate, m.p. 95 °C (from a CCl_4—benzene mixture), R_f 0.48. Found (%): C, 34.92; H, 2.76; Cl, 14.72; S, 13.28. $C_7H_7ClO_5S$. Calculated (%): C, 35.23; H, 2.96; Cl, 14.86; S, 13.44. IR, ν/cm^{-1}: 3093, 2731, 2597 (OH); 1772, 1700 (C=O); 1595 (C=C). ^{1}H NMR, δ: 3.57 (s, 3 H, OMe); 4.07, 4.21 (AB quadruplet, 1 H each, SCH_2, J = 16.3 Hz); 6.25 (s, 1 H, H(5)).

(3-Chloro-5-ethoxy-2-oxo-2,5-dihydrofuran-4-ylthio)ethanoic acid (10) was prepared similarly to compound **8** from ether **3** (0.92 g, 4.67 mmol), 2-mercaptoacetic acid (0.33 mL, 4.68 mmol), and triethylamine (0.65 mL, 4.68 mmol). Yield 52%, colorless crystals, m.p. 93—94 °C (from a hexane—benzene mixture), R_f 0.55. Found (%): C, 38.12; H, 3.46; Cl, 14.00; S, 12.58. $C_8H_9ClO_5S$. Calculated (%): C, 38.03; H, 3.59; Cl, 14.03; S, 12.69. IR, ν/cm^{-1}: 3095, 2706, 2599 (OH); 1768, 1723 (C=O); 1590 (C=C). ^{1}H NMR, δ: 1.28 (t, 3 H, Me, ^3J = 7.2 Hz); 3.85, 3.90 (both m, 1 H each, OCH_2, ^2J = 9.5 Hz, ^3J = 7.2 Hz); 4.06, 4.22 (AB quadruplet, 1 H each, SCH_2, J = 16.6 Hz); 6.29 (s, 1 H, H(5)).

(3-Chloro-5-isopropoxy-2-oxo-2,5-dihydrofuran-4-ylthio)-ethanoic acid (11) was synthesized similarly to compound **8** from ether **4** (1.00 g, 4.74 mmol), mercaptoacetic acid (0.33 mL, 4.74 mmol), and triethylamine (0.66 mL, 4.74 mmol), reaction time 2 h. Yield 48%, colorless crystals, m.p. 89—90 °C (from a petroleum ether—benzene mixture), R_f 0.49. Found (%): C, 40.23; H, 3.98; Cl, 13.24; S, 11.89. $C_9H_{11}ClO_5S$. Calculated (%): C, 40.53; H, 4.16; Cl, 13.29; S, 12.02. IR, ν/cm^{-1}: 3221, 2679, 2576 (OH); 1770, 1721 (C=O); 1594 (C=C). ^{1}H NMR, δ: 1.29, 1.33 (both d, 3 H each, Me, J = 6.1 Hz); 4.07, 4.24 (AB quadruplet, 1 H each, SCH_2, J = 16.5 Hz); 4.22 (sept, 1 H, CH, J = 6.1 Hz); 6.35 (s, 1 H, H(5)).

(4-Chloro-5-hydroxy-2-oxo-2,5-dihydrofuran-3-ylthio)ethanoic acid (12). A solution of mercaptoacetic acid (0.41 mL, 5.9 mmol) and potassium hydroxide (0.66 g, 11.84 mmol) in water (12 mL) was added dropwise with vigorous stirring to a solution of mucochloric acid **1** (1 g, 5.9 mmol) and potassium hydroxide (0.33 g, 5.9 mmol) in water (12 mL). The reaction mixture was stirred for 2 h, acidified with dilute hydrochloric acid to pH 2, and evacuated to dryness. The oily residue was purified by column chromatography (elution with a hexane—diethyl ether mixture, 1 : 3), and the product was recrystallized from chloroform. Yield 39%, m.p. 86 °C, R_f 0.44. Found (%): C, 31.96; H, 2.01; Cl, 15.72; S, 14.11. $C_6H_5ClO_5S$. Calculated (%): C, 32.08; H, 2.24; Cl, 15.78; S, 14.28. IR, ν/cm^{-1}: 3311, 2682, 2569 (OH); 1760, 1705 (C=O); 1598 (C=C). ^{1}H NMR, δ: 4.08, 4.12 (AB quadruplet, 1 H each, SCH_2, J = 16.2 Hz); 6.13 (d, 1 H, H(5), J = 8.4 Hz); 7.30 (d, 1 H, OH, J = 8.4 Hz).

Methyl (3-chloro-5-hydroxy-2-oxo-2,5-dihydrofuran-4-ylthio)acetate (13) was synthesized similarly to compound **8** from compound **1** (1.0 g, 5.9 mmol), methyl mercaptoacetate (0.44 mL, 5.9 mmol), and triethylamine (0.83 mL, 5.9 mmol) in acetone, reaction time 4 h. Yield 31%, m.p. 68 °C (from CCl_4), R_f 0.38. Found (%): C, 35.35; H, 2.45; Cl, 14.47; S, 13.57. $C_7H_7ClO_5S$. Calculated (%): C, 35.23; H, 2.96; Cl, 14.86; S, 13.44. IR, ν/cm^{-1}: 3365 (OH); 1772, 1734 (C=O); 1591 (C=C). ^{1}H NMR, δ: 3.75 (s, 3 H, Me); 4.09, 4.30 (AB quadruplet, 1 H each, SCH_2, J = 16.3 Hz); 6.42 (s, 1 H, H(5)); 7.38 (br, 1 H, OH).

X-Ray diffraction analysis. The single crystals of compounds **6** and **8** were prepared by crystallization from benzene. The X-ray diffraction experiments were carried out on an Enraf-Nonius CAD 4 diffractometer (graphite monochromator, λ(Cu-Kα) = 1.54184 Å, 293 K, ω/2θ-scanning). The crystal data and selected structure refinement parameters for **6** and **8** are summarized in Table 2. The absorption corrections were applied using the experimental azimuthal scanning curves (T_{min}/T_{max} = 0.7981/0.9968 for the crystal of **6** and T_{min}/T_{max} = = 0.9061/0.9982 for the crystal of **8**). The structure was solved by the direct method.[21] The positions and thermal parameters of non-hydrogen atoms were refined in the isotropic and then in the anisotropic approximation by the full-matrix least-squares method. The hydrogen atoms were placed into geometrically calculated positions and included in the refinement in the riding model. All calculations were carried out using SHELXL-97 software.[22]

Table 2. Crystal parameters of compounds **6** and **8** and X-ray diffraction experiment details

Parameter	**6**	**8**
Molecular formula	$C_6H_4Cl_2O_4S$	$C_6H_5ClO_5S$
M	243.05	224.61
Crystal system	Triclinic	Monoclinic
Space group	$P\bar{1}$	$P2_1$
a/Å	6.9452(7)	7.775(3)
b/Å	7.4525(8)	6.542(1)
c/Å	9.942(1)	8.865(2)
α/deg	108.895(9)	90.00
β/deg	99.925(3)	102.67(2)
γ/deg	101.027(2)	90.00
V/Å^3	462.41(8)	439.9(2)
Z	2	2
d_{calc}/g cm^{-3}	1.746	1.696
μ/cm^{-1}	83.08	60.34
Scanning range	4.86 ≤ θ ≥ 74.24	5.11 ≤ θ ≥ 74.20
Number of measured reflections (R_{int})	1947 (0.077)	1022 (0.1167)
Number of reflections with $I \geq 2\sigma(I)$	1729	669
Number of refined parameters	120	119
R_1 ($I \geq 2\sigma(I)$)	0.0837	0.0625
wR_2 (for all reflections)	0.2059	0.1789

The structures of compounds **6** and **8** were calculated by the B3LYP/6-31G(d,p) method using the Gaussian-98 program (see Ref. 23) with full geometry optimization without symmetry limitations; for all stationary points the matrix of second derivatives was calculated. The structures had only positive frequencies.

This work was supported by the CRDF and the Russian Federation Ministry of Education and Science (Basic Research and Higher Education Program, joint grant REC KSU 007, No. Y2-C-07-17).

References

1. F. Bellina, R. Rossi, *Curr. Org. Chem.*, 2004, **8**, 1089.
2. A. A. Avetisyan, M. T. Dangyan, *Usp. Khim.*, 1977, **46**, 1250 [*Russ. Chem. Rev. (Engl. Transl.)*, 1977, **46**].
3. Y. S. Rao, *Chem. Rev.*, 1976, **76**, 625.

4. N. B. Carter, A. E. Nadany, J. B. Sweeney, *J. Chem. Soc., Perkin Trans. 1*, 2002, **21**, 2324.
5. W. Gumulka, J. Kokosinski, *Pol. Organika*, 1976, 45.
6. T. I. Bobrova, S. D. Volodkovich, S. S. Kukalenko, *Zh. Obshch. Khim.*, 1975, **45**, 1123 [*J. Gen. Chem. USSR (Engl. Transl.)*, 1975, **45**].
7. Jpn Pat. 63170370; *Chem. Abstrs*, 1989, **110**, 8030.
8. Jpn Pat. 63170371; *Chem. Abstrs*, 1989, **110**, 8031.
9. Ger. Offen. Pat. 2032709; *Chem. Abstrs*, 1972, **76**, 140252c.
10. S. Ducher, A. Michet, *Bull. Soc. Chim. Fr.*, 1976, **11**, 1923.
11. A. R. Kurbangalieva, N. F. Devyatova, A. V. Bogdanov, E. A. Berdnikov, T. G. Mannafov, D. B. Krivolapov, I. A. Litvinov, G. A. Chmutova, *Phosphorus, Sulfur, Silicon, Relat. Elem.*, 2007, **182**, 607.
12. A. R. Kurbangalieva, N. F. Devyatova, L. S. Kosolapova, L. Z. Latypova, G. A. Chmutova, *XVIII Mendeleevskii S´ezd po Obshchei i Prikladnoi Khimii (Moscow, September 23—28, 2007)* [*XVIII Mendeleev Congress on General and Applied Chemistry (Moscow, September 23—28, 2007)*], Abstrs, Moscow, 2007, **1**, 194 (in Russian).
13. N. F. Devyatova, L. S. Kosolapova, A. R. Kurbangalieva, E. A. Berdnikov, O. A. Lodochnikova, I. A. Litvinov, G. A. Chmutova, *Zh. Org. Khim. (Engl. Transl.)*, 2008, **44**, 1237 [*Russ. J. Org. Chem.*, 2008, **44**, 1235].
14. T. A. Gloriozova, D. A. Filimonov, A. A. Lagunin, V. V. Poroikov, *Khim.-Farm. Zhurn.*, 1998, **32**, 32 [*Pharm. Chem. J. (Engl. Transl.)*, 1998, **32**, 658].
15. V. Poroikov, D. Filimonov, *Predictive Toxicology*, 2005, 459.
16. E. J. Valente, J. F. Fuller, J. D. Ball, *Acta Crystallogr., Sect. B*, 1998, **54**, 162.
17. N. P. Buu-Hoï, M. Dufour, P. Jacquignon, *Bull. Soc. Chim. Fr.*, 1971, **8**, 2999.
18. Z. Rappoport, *Acc. Chem. Res.*, 1981, **14**, 7.
19. P. L. Fishbein, H. W. Moore, *Synth. Commun.*, 1989, **19**, 3283.
20. D. T. Mowry, *J. Am. Chem. Soc.*, 1950, **72**, 2535.
21. A. Altomare, G. Cascarano, C. Giacovazzo, D. Virerbo, *Acta Crystallogr., Sect. A*, 1991, **47**, 744.
22. G. M. Sheldrick, *SHELXL97, A Computer Program for Crystal Structure Determination*, Göttingen University, Göttingen (Germany), 1997.
23. M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, V. G. Zakrzewski, J. A. Montgomery, R. E. Stratmann, J. C. Burant, S. Dapprich, J. M. Millam, A. D. Daniels, K. N. Kudin, M. C. Strain, O. Farkas, J. Tomasi, V. Barone, M. Cossi, R. Cammi, B. Mennucci, C. Pomelli, C. Adamo, S. Clifford, J. Ochterski, G. A. Petersson, P. Y. Ayala, Q. Cui, K. Morokuma, D. K. Malick, A. D. Rabuck, K. Raghavachari, J. B. Foresman, J. Cioslowski, J. V. Ortiz, A. G. Baboul, B. B. Stefanov, G. Liu, A. Liashenko, P. Piskorz, I. Komaromi, R. Gomperts, R. L. Martin, D. J. Fox, T. Keith, M. A. Al-Laham, C. Y. Peng, A. Nanayakkara, C. Gonzalez, M. Challacombe, P. M. W. Gill, B. G. Johnson, W. Chen, M. W. Wong, J. L. Andres, M. Head-Gordon, E. S. Replogle, J. A. Pople, *GAUSSIAN 98, Revision A.7*, Gaussian, Inc., Pittsburgh PA (USA), 1998.

Received June 3, 2008;
in revised form July 31, 2008