PREPARATION AND ALKALINE HYDROLYSIS OF HALOLACTONES OF 1,1-DIOXO-2-THIOLEN-4-YLACETIC ACIDS

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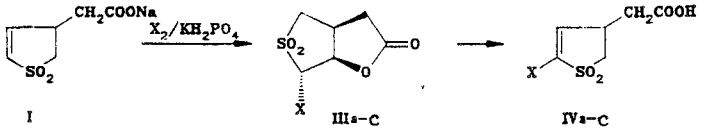
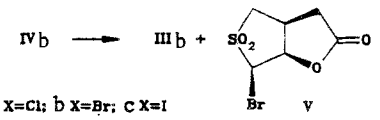
Halolactonization of an aqueous solution of a salt of 1,1-dioxo-2-thiolen-4-ylacetic acid gave lactones of 1,1-dioxo-2-halo-cis-3-hydroxythiolan-4-ylacetic acids, which on alkaline hydrolysis form 1,1-dioxo-2-thiolen-4-ylacetic acids. The mechanism for the reaction is given.

It is known that halolactones possess a number of valuable synthetic properties and are used as intermediates in the preparation of natural biologically active substances and their synthetic analogs [1, 2]. For this reason it was of interest to prepare analogous derivatives of thiolan-1,1-dioxide. The synthesis of the lactone of 1,1-dioxo-3-hydrothiolan-4-ylacetic acid (II) was described in [3]; however, the preparation of the analogous halolactones has not been reported. In this paper we report the first synthesis of halolactones obtained by the lactonization of salts of the acid I in aqueous solution (Table 1):





III, IV a X=Cl; b X=Br; c X=I

The compounds prepared were white crystalline substances, poorly soluble in water and chloroform, but readily soluble in acetone and hot alcohol. Acidification of solutions of these compounds in 1 N NaOH gave the acids IVa-c (Table 1). These acids, in contrast to the lactones are readily soluble in hot water. Refluxing an aqueous solution of the acid IVb for 1 h gave a mixture of the isomeric halolactones IIb and V.

The structure of the halolactones was determined by ^{13}C and ^{1}H NMR spectroscopy (see Table 2 and Fig. 1). Assignments of peaks were made based on chemical shifts, and the nature of peak-splitting, and by comparison with reported data [4, 5].

TABLE 1. Characteristics of Synthesized Compounds

Compound	T_{mp}, °C †	IR spectra, cm^{-1}			Found, %		Empirical formula	Calculated, %		Yield, %
		ν_{SO_2}	$\nu_{C=O}$	$\nu_{C=C}$	S	Hal		S	Hal	
IIIa	157—159	1160, 1330	1780	—	15.5	17.3	$C_6H_7ClO_4S$	15.2	16.8	56
IIIb	135—137	1155, 1315	1780	—	12.7	30.4	$C_6H_7BrO_4S$	12.6	31.4	88
IIIc	193—196	1140, 1325	1795	—	10.7	39.3	$C_6H_7IO_4S$	10.6	42.0	51
IVa	122—123.5	1140, 1305	1685	1600	15.1	17.3	$C_6H_7ClO_4S$	15.2	16.8	60
IVb	125—126	1140, 1305	1695	1600	12.5	31.2	$C_6H_7BrO_4S$	12.6	31.4	82
IVc	137—139	1145, 1300	1720	1640	10.8	39.3	$C_6H_7IO_4S$	10.6	42.0	89
V	179—185	1165, 1328	1780	—	12.8	31.2	$C_6H_7BrO_4S$	12.6	31.4	27

†Compounds IIIa and b and V were recrystallized from ethanol, IVa-c from 0.01 N HCl, compound IIIc from glacial acetic acid.

*Deceased.

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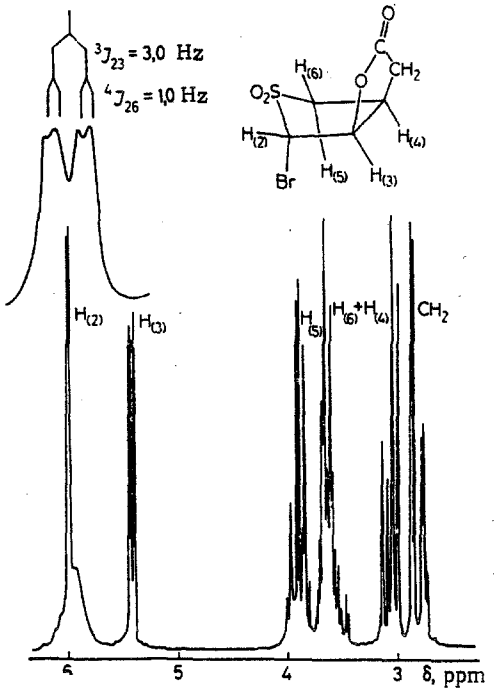
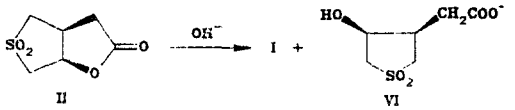


Fig. 1. NMR spectrum of the lactone IIIb in deuteropyridine.

The orientation of the halogen atom, and the configuration of the molecule were determined from the magnitude of the coupling constant for the vicinal protons of the 1,1-dioxothiolan ring. To do this, we used a coupling constant-torsion angle equation [6], which relates the magnitude of $^3J_{HH}$ with the dihedral angle between the interacting atoms and includes a correlation for the electronegativity of the substituents. The constants J_{23}, J_{13}, J_{34}, J_{45}, and J_{46} were calculated and compared with experimentally obtained data (see Table 3). The dihedral angles, which are necessary for the calculation, were determined from Newman projections of the corresponding ethane-like fragments of possible conformers and isomers of the molecules of the lactones II, IIIa, b, and V. The best correspondence of calculated and experimental values of $^3J_{HH}$ were found for cis-coupling of the lactone and dioxothiolan rings, and the conformation of the molecule, is shown in Fig. 1 for the lactone IIIb. This conformation has been reported for other bicyclic derivatives of thiolan-1,1-dioxide with cis-structure [4, 7].

By a similar method, it was found that in the lactones IIIa and b, the halogen atom is in the trans-orientation to the oxygen atom of the lactone ring, while in the lactone V it is in the cis-position. The occurrence of a long-range constant $^4J_{26}$ in the PMR spectrum of the lactone IIIb confirms the suggested orientation of the halogen atom and the conformation of the molecule (see Fig. 1).

It is known that lactones form hydroxyacids on alkaline hydrolysis [8]. However, esters of 3-hydroxythiolan-1,1-dioxide in alkaline medium mainly split off a carboxylic acid to give 2-thiolene-1,1-dioxide, which the authors of [9] explain by the increase in the α-CH-acidity of the hydroxyderivatives of thiolan-1,1-dioxide. The alkaline cleavage of lactone II can be expected to proceed simultaneously in two directions:



II VI

In fact, treatment of the lactone II with an equimolar quantity of 1 N NaOH gave solutions in which, according to ^{13}C NMR spectroscopy, the molar ratio of unsaturated acid I and oxyacid VI is 35:65. By a similar method [10] it was also found that the quantity of the acid I in this solution was eqivalent to 35% of the starting lactone. The free hydroxyacid could not be isolated since on acidification it cyclized to the lactone II.

In a separate experiment, it was shown that the acid I, under conditions of hydrolysis of the lactone II, did not combine with water, consequently, the hydroxyacid VI must be

TABLE 2. Chemical Shifts for Carbon Atoms of 1,1-Dioxo-2-thiolen-4-ylacetic Acid (I) and Some of Its Derivatives, ppm (internal standard — TMS)

Compound	Solvent	$C_{(2)}$	$C_{(3)}$ (d)	$C_{(4)}$ (d)	$C_{(5)}$ (t)	CH_2 (t)	C=O (s)
I*	H_2O	127,3 d	144,9	35,0	51,3	39,2	176,5
II	Acetone-D_6	54,2 t	77,4	34,0	54,2	34,1	175,1
IIIb	Acetone-D_6	58,2 d	83,9	31,9	51,1	33,7	174,4
IIIb	CF_3COOH	56,6 d	85,2	31,9	50,6	34,5	—
IVb	CF_3COOH	121,2 s	142,4	35,5	52,6	37,4	176,7
V	CF_3COOH	57,1 d	78,9	32,5	51,0	35,8	180,3
VI*	H_2O	59,1 t	68,1	38,0	51,3	34,2	177,6

*Sodium salt.

TABLE 3. Experimental and Calculated Coupling Constants for the Vicinal Protons of the 1,1-Dioxothiolan Ring of the Lactones of 1,1-Dioxo-cis-3-hydroxythiolan-4-ylacetic Acids, Hz*

Compound	J_{34}		J_{45}		J_{46}		J_{13}		J_{23}	
	exp.	calc.	exp.	calc.	exp.	calc.	exp.	calc.	exp.	calc.
IIIa	8,1	8,3	9,6	9,6	3	4,7	—	5,2	1,8	2,2
IIIb	8,3	8,5	9,7	9,6	3	4,7	—	5,2	3,0	2,1
V	8,3	8,5	—	9,6	—	4,7	5,5	5,2	—	2,1
II	8,0	8,0	—	9,6	—	4,7	5.5	5,5	3,0	3,0

*Spectra taken in deuteropyridine (IIIa, b, V) and deuterochloroform (II).

formed directly from the lactone II. This is in agreement with the increase in the content of the acid I in the mixture when the hydrolysis temperature is increased. Thus, carrying out the reaction at 11, 20, and 68°C, gave yields of the unsaturated acid I corresponding to 25, 35, and 52% of the starting lactone, respectively. The authors of [9] found that in the hydrolysis of the esters of 3-hydroxythiolan-1,1-dioxide, this relationship was reversed, but they showed that part of the alcohol was formed by addition of water to 2-thiolen-1,1-dioxide.

Alkaline hydrolysis of the halolactones IIIa-c goes considerably faster than that of the lactone II. Moreover, the main product is the unsaturated acid (according to analytical data, equivalent to at least 95% of the amount of starting lactone). The difference in the amount of unsaturated acid formed by hydrolysis of the lactones II and III can be explained as follows. According to [8], the stage which determines the rate of the reaction of hydrolysis of the lactones to hydroxyacids, is attack by the hydroxyl ion on the carbonyl carbon atom. In lactones of type III, the halogen atom is remote from the carbonyl group, as a result of which it differs little in reactivity from the carbonyl group of the lactone II. Therefore both types of lactone are hydrolyzed to the hydroxyacid at essentially the same rate.

At the same time, the halogen atom α to the sulfonyl group in the lactones of type III increases the CH-acidity of the single hydrogen atom, and this leads to an increase in the rate of cleavage of the lactone ring to give the anion of the unsaturated acid.

Thus, halolactonization of 1,1-dioxo-2-thiolen-4-ylacetic acid gave the corresponding bicyclic cis-coupled halolactones in good yield. In dilute alkali, these split to give 1,1-dioxo-2-halogen-2-thiolen-4-ylacetic acids. Under similar conditions, lactones which do not contain a halogen atom form a mixture of hydroxyacids and unsaturated acids.

EXPERIMENTAL

NMR spectra were recorded on a Bruker CXP-200 spectrometer (200 MHz for the ^1H series and 50.32 MHz for the ^{13}C series). IR spectra were obtained on a UR-20 apparatus (KBr pellets). 1,1-Dioxo-2-thiolen-4-ylacetic acid (I) and the lactone of 1,1-dioxo-cis-3-oxythiolan-4-ylacetic acid (II) were obtained by the method given in [3].

Lactone of 1,1-Dioxo-trans-2-chloro-cis-3-hydroxythiolan-4-ylacetic Acid (IIIa). A solution of 1.76 g (0.01 mole) of the acid I in 50 ml of water was neutralized (phenolphtha-

lein) with 1 N NaOH, and 5 ml of a solution of 1.7 g KH_2PO_4 in 50 ml of water added. Chlorine was slowly bubbled through the reaction mixture until it turned green. The precipitated material was filtered off, washed on the filter with water, and dried.

Lactone of 1,1-Dioxo-trans-2-bromo-cis-3-hydroxythiolan-4-ylacetic Acid (IIIb). To a solution of the sodium salt of the acid I and KH_2PO_4, obtained as described above, with vigorous mixing with a magnetic stirrer was added dropwise 0.53 ml (0.01 mole) of bromine over a period of 20-30 min. A light-colored precipitate of the lactone began to separate 1-2 minutes after the start of the bromine addition. When all the bromine had been added, the suspension was mixed for a further 30 min, the precipitated material filtered off, washed on the filter with water, dried, and if necessary recrystallized from alcohol.

Lactone of 1,1-Dioxo-trans-2-iodo-cis-3-hydroxythiolan-4-ylacetic Acid (IIIc). To a stirred solution of the sodium salt of the acid I and KH_2PO_4, obtained as described above, was added a solution of 3.52 g (0.01 mole) of iodine in 11 ml 20% solution of potassium iodide. The dark solution was mixed for 2 h and left for 2 days at 20°C. The black precipitate was filtered off, washed on the filter with water, and dissolved in acetone, and twice the volume of water added. It was left in an open vessel overnight and the precipitated material then filtered off, washed with water, and dried.

Lactone of 1,1-Dioxo-cis-2-bromo-3-hydroxythiolan-4-ylacetic Acid (V). A mixture of 2.6 g (0.01 mole) of the acid IVb and 20 ml of water in a flask fitted with a reflux condenser was refluxed for 1 h. The mixture was cooled and left to stand for 1-2 days; the oily product did not crystallize. The residue was triturated, 12 ml of alcohol added, the mixture refluxed for 10-15 min, and the hot solution filtered. The insoluble precipitate of the lactone V was washed with alcohol and dried, and, if necessary, recrystallized from acetic acid. The acid IVb crystallized from the alcohol solution on cooling. It was filtered off, the filtrate evaporated to dryness in vacuum, and the dry residue treated with a cold 2% solution of $NaHCO_3$. An insoluble residue of the lactone IIIb (0.12 g, 3%) was obtained.

1,1-Dioxo-2-halogen-2-thiolen-4-ylacetic Acids (IVa-c). In a conical flask with magnetic stirrer, held in a thermostated water bath, was placed 0.01 mole of the lactone and one drop of an alcoholic solution of phenolphthalein. 1 N NaOH was slowly added until one drop of alkali produced a permanent coloration. The alkaline reaction mixture was filtered, and to the filtrate was added 2 ml (0.02 mole) of concentrated hydrochloric acid and the mixture cooled. The clear oil which separated was triturated to give a powder, which was filtered off, washed with cold water, and dried. Alkaline hydrolysis of the lactone II was carried out in the same way.

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