ATTEMPTED CYCLIZATION OF HALOTHIOL ESTERS TO β-THIOLACTONES

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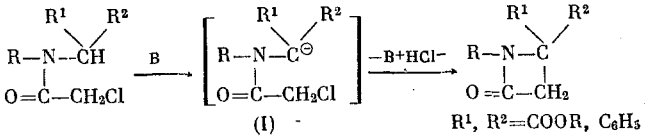
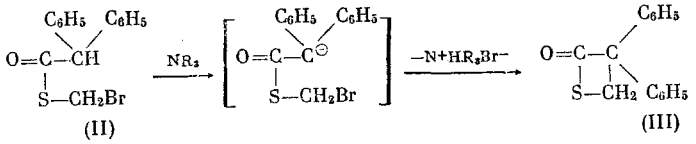
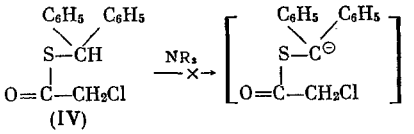
One of the methods for the preparation of β-lactams is the cyclization of the corresponding N-substituted α-chloroacetamidomalonates with the formation of a new C—C bond [1]. A necessary step of this cyclization is the formation of the intermediate carbanion (I)



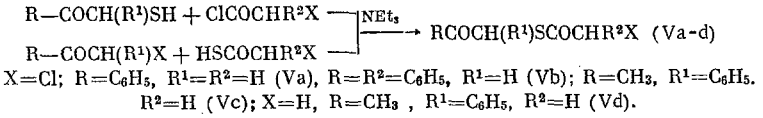
This principle could be realized in the cyclization of the bromomethyl ester of diphenylthiolacetic acid (II), which easily forms α,α-diphenyl-β-thiolactone (III)



The chloromethyl ester of the diphenylthiolacetic acid reacts with somewhat greater difficulty. We had previously obtained this thiolactone by the reaction of H_2S with the acid chloride of α,α-diphenyl-β-chloropropionic acid [2]. However, the β,β-diphenyl-β-thiolactone cannot be obtained from the isomeric (II) diphenyl ester of chlorothiolacetic acid (IV) due to the lower lability of the hydrogen atom and the impossibility of forming the carbanion under these conditions



In order to facilitate the formation of the carbanion we synthesized the thiol esters (V), which bear a keto group in series with either a methylene or a methyl group. The latter were obtained either by the acylation of mercaptoketones with the acid chlorides of α-halocarboxylic acids or by the alkylation of α-halothiolcarboxylic acids with haloketones in the presence of triethylamine



The constants of the obtained thiol esters are given in Table 1. However, instead of the desired β-thiolactones, the treatment of (Va—c) with Et_3N respectively gave the 2,3-dihydro-1,4-oxathiin-2-ones (VIa—c) (Table 2).

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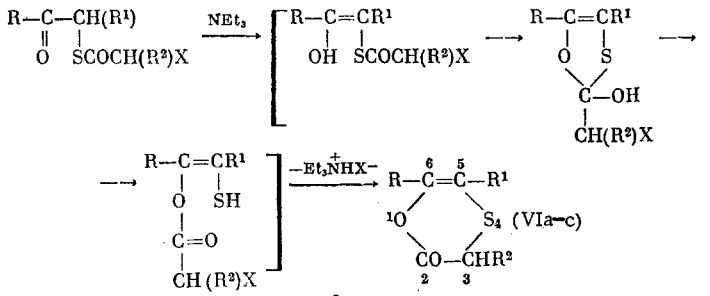
TABLE 1

Compound	Formula	Yield, %	Bp, °C (p, mm of Hg), and Mp, °C (solvent)	Found, %				Empirical formula	Calculated, %				Method
				C	H	S	Cl		C	H	S	Cl	
	$(C_6H_5)_2CHSCOCH_3$	95	55—56 (hexane)	74,27	5,59	14,2		$C_{15}H_{14}OS$	74,40	5,78	13,22		2
(IV)	$(C_6H_5)_2CHSCOCH_2Br$	50	47			10,31	25,22	$C_{15}H_{13}BrOS$			9,97	24,92	1
	$(C_6H_5)_2CHSCOCHClC_6H_5$	65	69	71,65	4,75	8,59	9,23	$C_{21}H_{17}ClOS$	71,48	4,82	9,08	9,93	1
	$C_6H_5COCH_2SCOCH_3$	74	120 (5) 44 (petroleum ether)	61,25	5,12	15,75		$C_{10}H_{10}O_2S$	61,85	5,15	16,50		1
(Va)	$C_6H_5COCH_2SCOCH_2Cl$	90/88	54 (petroleum ether)	52,72	4,01	14,02	15,36	$C_{10}H_9ClO_2S$	52,63	3,95	14,04	15,56	1/2
	$C_6H_5COCH_2OCOCH_2Br$	87	82 (alcohol)	46,77	3,56	—	31,08	$C_{10}H_9BrO_3$	46,69	3,50	—	31,12	1
(Vb)	$C_6H_5COCH_2SCOCHClC_6H_5$	80	78	62,28	4,25	10,45	11,44	$C_{16}H_{13}ClO_2S$	63,05	4,24	10,51	11,66	2
	$C_6H_5COCH_2SCOCHClCH_2Cl$	90	37	47,86	3,48	11,75	24,22	$C_{11}H_{10}Cl_2O_2S$	47,63	3,61	11,55	25,63	1
(Vc)	$C_6H_5CH(COCH_3)SCOCH_2Cl$	71	46—47 (petroleum ether)	54,31	4,51	13,44	13,84	$C_{11}H_{11}ClO_2S$	54,43	4,53	13,19	14,55	2

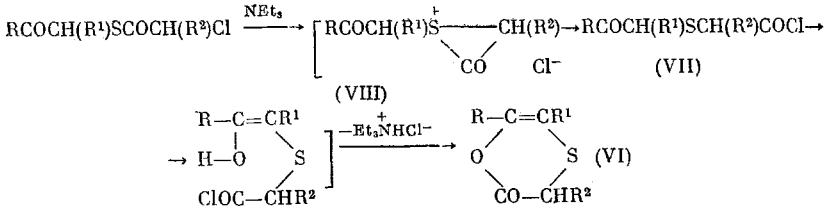
TABLE 2

Compound	Yield, %	Bp, °C (p, mm of Hg), and Mp, °C (solvent)	Found, %			Empirical formula	Calculated, %		
			C	H	S		H	C	S
(VIa)	87	97 (CCl_4)	62,23	4,31	16,39	$C_{10}H_8O_2S$	62,50	4,20	16,68
(VIb)	90	105 (0,01)	64,67	5,06	15,74	$C_{11}H_{11}O_2S$	63,77	4,85	15,53
(VIc)	76	124 (CH_3OH)	70,86	4,74	11,98	$C_{16}H_{12}O_2S$	71,65	4,48	11,93

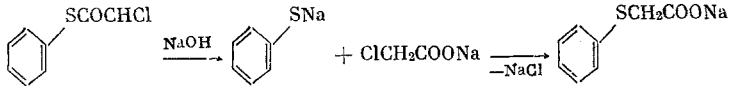


It is possible that when Et_3N acts on the thiol esters (V) they initially undergo enolization, followed by migration of the chloroacetyl moiety from the sulfur atom to the oxygen atom and subsequent intramolecular alkylation of the sulfur atom with closure of the ring. It should be mentioned that in (Vd) a migration of the acetyl moiety fails to occur under analogous conditions.

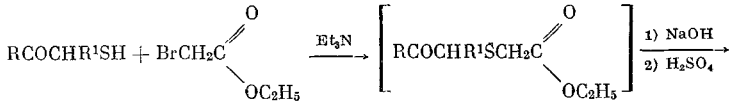
Analogous to the α-halothio esters [3], the most probable route for the formation of (VIa—c) is the isomerization of (Va—c) under the influence of Et_3N to the acid chlorides of the α-mercaptophenacylacetic acid (VII) via the intermediate episulfonium ion (VIII). The subsequent intramolecular acylation by the acid chloride (VII) at the oxygen atom of the enol form leads to (VI)



The known rearrangement of the chloroacetyl moiety to the thiophenol occurs under the influence of aqueous NaOH solution [4] according to the scheme:



These transformations are confirmed by the easy cyclization of (VII), which is synthesized by the alkylation of ω-mercaptoacetophenone with ethyl bromoacetate, to compound (VI)



Even when treated with thionyl chloride, phenacylmercaptoacetic acid (IXa) is spontaneously cyclized to (VIa) in high yield. The role of the episulfonium ion (VIII) in these transformations is also confirmed by the absence of isomerization to the oxygen analog (Va), the phenacyl ester of chloroacetic acid (X), which remains unchanged under analogous conditions. This confirms the known fact that the oxygen atom exerts a smaller influence on the lability of protons than does the sulfur atom [5]. Compound (X) was obtained by the alkylation of ω-bromoacetophenone with bromoacetic acid in the presence of Et_3N

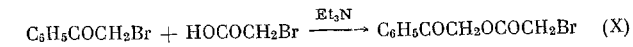
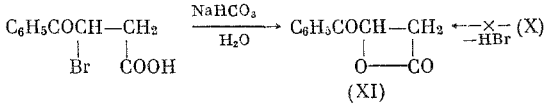


TABLE 3

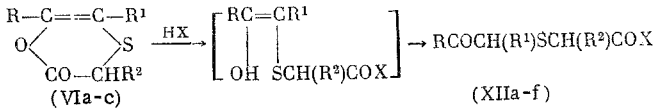
Compound	Yield, %	Mp, °C	Found, %			Empirical formula	Calculated, %		
			C	H	S		H	C	S
(XIIa)	95	102—103	57,26	5,18	15,17	$C_{10}H_{11}NO_2S$	57,41	5,26	15,26
(XIIb)	86	122—123	68,22	5,69	10,70	$C_{17}H_{17}NO_2I$	68,23	5,68	10,70
(XIIc)	93	185	66,90	5,24	11,31	$C_{16}H_{15}NO_2S$	67,37	5,26	11,27
(XIId)	66	119—120	58,20	5,86	14,40 *	$C_{11}H_{13}NO_2S$	59,10	5,83	14,35
(XIIe)	70	20—22	58,31	5,36	14,12	$C_{11}H_{12}O_3S$	58,88	5,35	14,28
(XIIf)	83	72	68,23	5,33	11,30	$C_{17}H_{16}O_3S$	68,00	5,3	10,70

*Found: N 6.33%. Calculated: N 6.28%.

β-Benzoyl-β-propiolactone (XI) could not be obtained from the corresponding ester (X); it was obtained in known manner from the Na salt of β-benzoyl-β-bromopropionic acid [6]



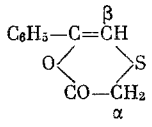
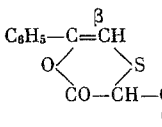
Compounds (VIa—c) are cyclic unsaturated γ-lactones and possess well-defined acylating properties. They are easily cleaved to give either the corresponding carboxylic acids (IXa, b) or their derivatives (XIIa)



X=NH_2, R=R^2=H, R^1=C_6H_5 (XIIa); X=$HNCH_2C_6H_5$, R=R^2=H, R^1=C_6H_5 (XIIb);
X=NH_2, R=H, R^1=R^2=C_6H_5 (XIIc); X=NH_2, R=CH_3, R^1=C_6H_5, R^2=H (XIId);
X=OCH_3, R=R^2=H, R^1=C_6H_5 (XIIe); X=OCH_3, R=H, R^1=R^2=C_6H_5 (XIIf).

The cleavage of (VIa, b) with 0.5 N NaOH in alcohol at ~20°, or with aqueous $NaHCO_3$ solution at 100°, gave (IXa, b) in quantitative yield. The treatment of (VIa—c) with amines or methanol in the presence of acid catalysts (H_2SO_4) gave the corresponding amides or esters of carboxylic acids (XIIa—f) (Table 3). The methyl ester (XIIe) was also obtained from (IXa) and CH_2N_2. Aniline does not react with (VIa) even when heated in CCl_4 for a long time.

TABLE 4

Compound	ν, cm^{-1}			Chemical shift of protons, ppm		J, Hz
	ketone	ester	lactone	α	β	
$C_6H_5COCH_2SCOCH_2Cl$	1695	1675		4,33 (s)	4,17 (a)	
$C_6H_5COCH_2SCOCH(C_6H_5)Cl$	1700	1680				
	1618 C=C		1760	3,28	6,17	
	1620 C=C		1760	4,51	6,18	1,9
$C_6H_5CO—CH(β)—CH_2(α)$ O—CO	1695		1840	3,74	5,45	6,5
$C_6H_5COCH—CH—C_6H_5$ [6] O—CO	1700		1820	5,09	5,33	3,3
$C_6H_5COCH_2OCOCH_2Cl$	1700	1780				
$C_6H_5COCH_2SCH_2COOH$	—			3,10 (s)	3,82 (s)	

The structure of compounds (VIa—b) follows not only from their method of preparation and chemical properties, but is also confirmed by the NMR and IR spectra, the data for which are given in Table 4.

Intense bands are present in the IR spectra of (VIa—c) in the 1760 cm^{-1} region, which are characteristic for the carbonyl group of an ester, while the frequencies that are characteristic for a ketone carbonyl are absent. The IR spectra of the oxygen analogs of the β-benzoyl-β-lactones contain two characteristic frequencies for the lactone carbonyl (1840 and 1830 cm^{-1}) and for the ketone carbonyl (1695 and 1700 cm^{-1}).

EXPERIMENTAL METHOD

α-Hydroxymethyl Ester of Diphenylthiolacetic Acid (XIII). As described in [7], a mixture of equimolar amounts of diphenylthiolacetic acid and paraform was heated on the water bath until solution was complete. The mixture was extracted with petroleum ether to give (XIII) in 40.1% yield, mp 53° (from petroleum ether). Found: C 69.99; H 5.48; S 12.00%. $C_{15}H_{14}O_2S$. Calculated: C 69.76; H 5.43; S 12.40%.

Chloromethyl Ester of Diphenylthiolacetic Acid (XIV). With cooling in ice water, 1.3 g of $SOCl_2$ and 1 g of pyridine were added to 2.58 g of (XIII) in 10 ml of absolute ether. The mixture was allowed to stand at ~20° for 24 h. We obtained (XIV) in 53.1% yield, mp 62° (from petroleum ether). Compound (II) was obtained in a similar manner from (XIII) and PBr_3 in 65.7% yield, mp 66° (from alcohol). Found: C 64.91; H 4.83; Cl 13.73; S 11.39%. $C_{15}H_{13}ClOS$. Calculated: C 65.10; H 4.70; Cl 12.83; S 11.57%. Found: C 56.97; H 4.08; S 10.37; Br 24.75%. $C_{15}H_{13}BrOS$. Calculated: C 56.05; H 4.05; S 9.96; Br 24.92%.

α,α-Diphenyl-β-thiolactone (III). To 1 g of (II) in 20 ml of absolute ether was added an equivalent amount of Et_3N in 10 ml of absolute ether. The mixture was allowed to stand overnight at ~20°. Then the triethylamine hydrobromide was filtered (~100% yield), and the filtrate was evaporated in vacuo. The oily residue was extracted with hot heptane to give (III) in 31.3% yield, mp 54-55° [2], ν 1755 cm^{-1}.

Preparation of Thiol Esters (Va—c). 1. With stirring, 0.01 M of Et_3N in 50 ml of absolute ether was added to a mixture of equimolar amounts (0.01 mole) of thiolchloroacetic acid and the appropriate bromo derivative of the ketone in absolute ether (100 ml), and the mixture was allowed to stand overnight at ~20°. The triethylamine hydrobromide was filtered, and the ether was evaporated in vacuo.

2. With stirring, 0.01 M of Et_3N in 50 ml of absolute ether was added in drops to a mixture of the mercaptoketone and the appropriate acid chloride of the carboxylic acid (0.01 mole of each) in 100 ml of absolute ether at 0°. The temperature of the mixture was gradually brought up to room temperature and it was allowed to stand for 30 min. The triethylamine hydrochloride was filtered, and the filtrate was evaporated in vacuo. The residue was either distilled or recrystallized (see Table 1).

Phenacylmercaptoacetic Acid (IXa). To 0.1 mole of phenacylmercaptan and 0.1 mole of ethyl bromoacetate in 100 ml of absolute ether was added 0.1 M of Et_3N in 20 ml of absolute ether. The mixture was heated for 3 h, the triethylamine hydrobromide was filtered, the ether was evaporated in vacuo, and the residue was treated with 5% aqueous NaOH solution. The obtained solution was washed with ether, and then acidified with 10% HCl solution. Compound (IXa) was obtained in 80% yield, mp 100-101° (from CH_3OH). Found: C 62.23; H 4.31; S 16.39%. $C_{10}H_{10}O_3S$. Calculated: C 62.50; H 4.20; S 16.68%. In a similar manner, $C_6H_5CH(SCH_2COOH)COCH_3$ (IXb) was obtained from $C_6H_5CH(SH)COCH_3$ and ethyl bromoacetate in 74% yield, mp 47-48° (from alcohol). Found: C 58.51; H 5.07; S 14.69%. $C_{11}H_{12}O_3S$. Calculated: C 58.93; H 5.34; S 14.24%.

2,3-Dihydro-1,4-oxathiin-2-ones (VIa—c). 1. An equivalent amount of Et_3N in 10 ml of absolute ether was added to 1 g of (Va) in 20 ml of absolute ether. The mixture was allowed to stand overnight at ~20°, and then it was refluxed for 50 min. The triethylamine hydrochloride was filtered, and the filtrate was evaporated in vacuo. Compound (VI) was obtained (see Table 2).

2. A mixture of 0.7 g of phenacylmercaptoacetic acid (IXa) and 10 ml of $SOCl_2$ was heated under reflux for 2 h. The excess $SOCl_2$ was vacuum-distilled. We obtained (VIa) in 60% yield, mp 97°. The mixed melting point with a sample from the preceding experiment was not depressed. Compound (VIb) was obtained in a similar manner from (IXb) in 47% yield.

β-Benzoyl-β-propiolactone (XI). A solution of 0.42 g of NaOH in 5 ml of water was added to 1.3 g of β-bromo-β-benzoylpropionic acid in 20 ml of ether. The mixture was stirred vigorously for 5 h, and the ether layer was separated, dried over $MgSO_4$, and evaporated in vacuo. We obtained (XI) in 30% yield, mp 103° (from alcohol). Found: C 68.22; H 4.70%. $C_{10}H_8O_3$. Calculated: C 68.18; H 4.54%.

CONCLUSIONS

1. A new route was proposed for the preparation of α,α-diphenyl-β-thiolactone from the corresponding bromomethyl ester of diphenylthiolacetic acid in the presence of triethylamine, which includes the formation of a new C—C bond.

2. The phenacyl esters of thiolchloroacetic acid undergo rearrangement in the presence of triethylamine and form 2,3-dihydro-1,4-oxathiin-2-ones.

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