Olin Mathieson Chemical Corporation, Chemicals Division

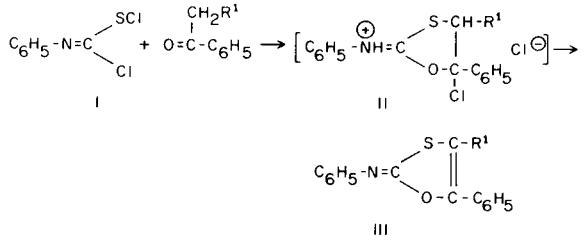
Chlorination of Isothiocyanates. VIII. (1) Reaction of *S*-Chloroisothiocarbamoyl Chlorides with Aliphatic and Cycloaliphatic Ketones

G. Ottmann, G. D. Vickers and H. Hooks, Jr.

Reported is the synthesis of various derivatives of 2-imino-5-chloro-1,3-oxathiolanes, 2-imino-1,3-oxathioles and 1,3-thiazolin-2-ones from *N*-aryl- and *N*-alkyl-*S*-chloroisothiocarbamoyl chlorides and ketones.

Recently, we reported on the reaction of *N*-aryl substituted *S*-chloroisothiocarbamoyl chlorides (I) (2) with aryl alkyl ketones, which leads directly to the hydrochlorides of 2-arylimino-5-aryl-1,3-oxathioles (III) (1). Attempts to elucidate the mechanism of this reaction failed since no intermediates such as the hypothetical compound II were obtained (Scheme 1).

Scheme I



I II III

However, we have now isolated the relatively stable 2-imino-5-chloro-1,3-oxathiolane hydrochlorides (IV) as defined intermediates from the reactions of *N*-aryl and *N*-alkyl-*S*-chloroisothiocarbamoyl chlorides with aliphatic and cycloaliphatic ketones, as well as from the reaction of *N*-alkyl derivatives of I with aryl ketones. Depending on reaction conditions, compounds IV can be converted either to 2-imino-1,3-oxathioles (Scheme 2, Table I) via the rather labile 2-imino-5-chloro-1,3-oxathiolanes (V) or to 1,3-thiazolin-2-ones (IX) (Scheme 2, Table V).

The first step of the reaction sequence leading to compounds IV probably consists of an addition of the -SCl moiety of I to the enolized form of the ketone by analogy with the reaction of simple sulfenyl chlorides with acetone (3) to form β-keto sulfides (4). However, in contrast to the latter reaction, stabilization of the hypothetical intermediate VIII does not occur by α-elimination of hydrogen chloride but by a ring closure reaction and intramolecular neutralization of hydrogen chloride (Scheme 3).

Principal by-products of the reaction are isothiocyanates, self-condensation products of the ketones employed, *e.g.*, 2-cyclohexylidene cyclohexanone and chlorination products of aryl alkyl ketones, *e.g.*, α-chloropropiophenone.

The conversion of the hydrochlorides IV to the parent bases, 2-imino-5-chloro-1,3-oxathiolanes (V) succeeds only with a tertiary amine under anhydrous conditions. Most compounds V are only stable if stored in a sealed container at below -25°. Above 0°, β-elimination of hydrogen chloride ensues more or less rapidly with the hydrogen chloride being trapped intramolecularly to form 2-imino-1,3-oxathiole hydrochlorides (VI). The exothermic formation of compounds VI is facilitated by warming compounds V to 50-60° or by heating in an aprotic solvent. A greatly increased stability was observed among some 2-arylimino-5-chloro-1,3-oxathiolanes having a tetramethylene bridge connecting the C(4)- and C(5)-atoms. Thus, 2-phenylimino-5-chloro-4,5-tetramethylene-1,3-oxathiolane (Ve), m.p. 96°, requires heating to 104° to induce hydrogen chloride elimination. The rapid conversion of V to VI, except for Ve, did not allow determination of physical properties of 2-imimo-5-chloro-1,3-oxathiolanes (V), however, infrared absorption and NMR-spectra were obtained in some cases (Tables II and III). The hydrochlorides VI can be converted to their free bases, 2-imino-1,3-oxathioles (VII), either by triethylamine under anhydrous conditions or by aqueous alkali hydroxides. 2-Imino-1,3-oxathioles are also obtained without isolating V and VI, if compounds IV are treated with 2 moles of triethylamine in heptane, whereby the first mole is added at between 0° to 10° and the second mole at above 50°.

The reaction path and structures shown in Scheme 2 are supported by the results of NMR-studies and are exemplified for the reactions of *N*-butyl-*S*-chloroisothiocarbamoyl chloride with acetone (IVa-VIIa) (Table II) and with propiophenone (IVf-VIIf) (Table III), respectively. Thus, the cyclic structures of compounds IV and V are evidenced by two unequivalent protons attached to the C(4)-atom in (IVa) and (Va). The resonance signals at 4.17 ppm and

TABLE I

2-Imino-1,3-oxathioles

R	R^1	R^2	(IV) Yield (a), %	(IV) M.p., °C	(VI) Yield (b), %	(VI) M.p., °C	Empirical Formula	Yield (b), %	M.p., °C	Bp. °C (mm Hg)	n_D (C°)	(VII) Calculated. % C	H	N	S	C	Found. % H	N	S	λ max mμ (log ε)
(a) C_4H_9	H	CH_3	58	–	58	163-164	$C_8H_{13}NOS$	74	28-28.5			56.12	7.65	8.18	18.69	56.51	8.03	7.81	18.90	–
(b) C_4H_9		$-(CH_2)_4-$	63	102-104	81	85-87	$C_{11}H_{17}NOS$	51.5	–	117-119(0.3)	1.5292(25)	62.54	8.11	6.63	15.15	62.38	8.16	6.50	15.27	–
(c) C_6H_5	H	CH_3	75	166-168	91	174-175	$C_{10}H_9NOS$	68	48-49	119-120(0.2)	1.6162(23)	62.81	4.74	7.32	16.73	62.66	4.50	7.21	16.76	280 (3.90)
(d) C_6H_5	C_4H_9	CH_3	78	105-107	51	110.5-112	$C_{14}H_{17}NOS$	42.5	–	152(0.2)	1.5765(26)	67.99	6.93	5.67	12.94	68.09	6.93	5.28	13.07	283 (3.86)
(e) C_6H_5		$-(CH_2)_4-$	60	109-111	81	163-164	$C_{13}H_{13}NOS$	81	83-83.5	–	–	67.52	5.67	6.06	13.84	67.89	5.77	6.38	13.96	284 (3.88)
(f) C_4H_9	CH_3	C_6H_5	39	104	100	153-154	$C_{14}H_{17}NOS$	68	31.5-32	–	–	67.99	6.93	5.67	12.94	68.38	7.39	5.68	12.90	–
(g) C_4H_9	H	C_6H_5	68	100-101	–	143-144	$C_{13}H_{15}NOS$	67	60.5-61	–	–	66.93	6.48	6.01	13.72	67.10	6.76	6.09	13.99	–

(a) Yield is based on the N-chloroisothiocarbamoyl chloride charged. (b) Yield is based on compounds IV.

TABLE II

Proton NMR of Compounds IVa, Va, VIa and VIIa from the Reaction of *N*-Butyl-*S*-Chloroisothiocarbamoyl Chloride with Acetone (R = n-C_4H_9; R^1 = H; R^2 = CH_3). Chemical Shift δ in ppm and Coupling Constant J in Hz.

		δ	Multiplicity	J
(IVa)	CH_3Butyl	0.94	p.t. (a)	
	CH_2CH_2	1.1-2.1	broad	
	CH_3Ring	2.44	1	
	CH_2N	3.56	3	6
	CH_2Ring	4.17	2	13
	CH_2Ring	4.52	2	13
(Va)	CH_3Butyl	0.93	p.t. (a)	
	CH_2CH_2	1.15-2.02	broad	
	CH_3Ring	2.15	1	
	CH_2N	3.18	3	6
	CH_2Ring	3.67	2	13
	CH_2Ring	3.77	2	13
(VIa)	CH_3Butyl	0.97	p.t. (a)	
	CH_2CH_2	1.15-2.10	broad	
	CH_3Ring	2.36	2	1.3
	CH_2N	3.64	3	7
	CHRing	6.82	4	1.3
(VIIa)	CH_3Butyl	0.93	p.t. (a)	
	CH_2CH_2	1.10-1.95	broad	
	CH_3Ring	2.06	2	1.3
	CH_2N	3.02	3	6
	CHRing	5.73	4	1.3

(a) Perturbed triplet.

4.52 ppm of relative unit intensity, each having the multiplicity 2, are caused by the unsymmetric substitution on C(5). If compounds IVa and Va had a non-cyclic structure, only a single peak of relative intensity 2 would be expected. The formation of a >C=C< bond by hydrogen chloride-elimination from V is supported, *e.g.* by the coupling (J=1.3 HZ) of the C(4) proton of VIa and VIIa to the methyl group attached to the C(5)-atom. The proton resonance spectra of the hydrochlorides IVa, VIa, IVf and VIf, respectively, differ from those of the corresponding bases Va, VIIa, Vf and VIIf to the extent that the resonance signals of the former are shifted to lower field as expected. The proton NMR signals for compounds VIIb-e are compiled in Table IV. Additional support for the structure assignment of compounds VII was gathered from IR and UV-absorption spectra, and

Scheme 2

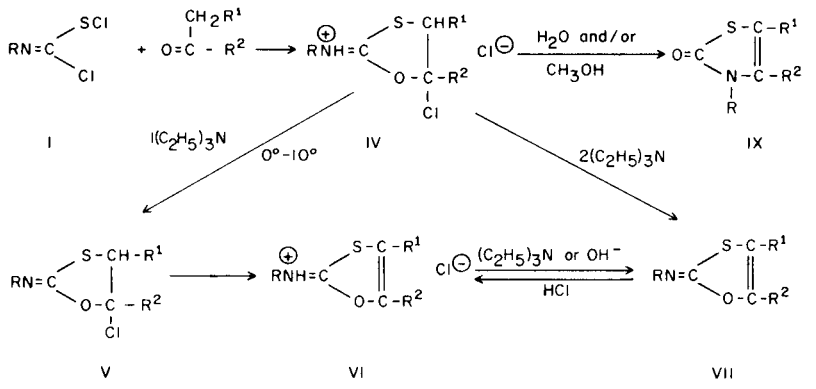


TABLE III

Proton NMR of Compounds IVf, Vf, VIf and VIIf from the Reaction of *N*-Butyl-*S*-Chloroisothiocarbamoyl Chloride with Propiophenone (R = n-C_4H_9; R^1 = CH_3; R^2 = C_6H_5). Chemical Shift δ in ppm and Coupling Constant J in Hz.

		δ	Multiplicity	J
(IVf)	CH_3Butyl	0.98	p.t. (a)	
	CH_2CH_2	1.15-2.23	broad	
	CH_3Ring	1.22	2	7
	CH_2N	3.79	3	6
	CHRing	4.93	4	7
	C_6H_5	7.56	1	
(Vf)	CH_3Butyl	0.93	broad	
	CH_2CH_2	1.15-2.34	broad	
	CH_3Ring	1.22	2	7
	CH_2N	3.40	p.t. (a)	
	CHRing	4.12	4	7
	C_6H_5	7.32-7.84	m (b)	
(VIf)	CH_3Butyl	0.98	p.t. (a)	
	CH_2CH_2	1.17-2.23	broad	
	CH_3Ring	2.46	1	
	CH_2N	3.73	3	7
	C_6H_5	7.55	1	
(VIIf)	CH_3Butyl	0.94	p.t. (a)	
	CH_2CH_2	1.15-2.00	broad	
	CH_3Ring	2.20	1	
	CH_2N	3.06	3	6
	C_6H_5	7.23-7.68	m (b)	

(a) Perturbed triplet. (b) Multiplet.

TABLE IV

Proton NMR of Derivatives of 2-Imino-1,3-oxathiole. Chemical Shift δ in ppm and Coupling Constant J in Hz.

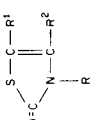
		δ	Multiplicity	J
(VIIb)	CH_3Butyl	0.93	p.t. (a)	
	CH_2CH_2Butyl	1.13-2.03	broad	
	CH_2N	3.02	3	6
	CH_2Allyl	2.32	m (b)	
	CH_2CH_2Cyclohexane	1.77	m (b)	
(VIIc)	CH_3	1.99	2	1.3
	CH	5.58	4	1.3
	C_6H_5	6.82-7.54	m (b)	
(VIId)	CH_3Butyl	0.95	p.t. (a)	
	CH_2CH_2Butyl	1.05-1.63	broad	
	CH_2N	2.27	3	6
	CH_3Ring	2.01	1	
	C_6H_5	6.85-7.55	m (b)	
(VIIe)	CH_2Allyl	2.26	m (b)	
	CH_2CH_2Cyclohexane	1.72	m (b)	
	C_6H_5	6.82-7.57	m (b)	

(a) Perturbed triplet. (b) Multiplet.

from mass spectroscopy. The most distinguishable infrared absorption of compounds VII are at between 1665 and 1680 cm^{-1} for C=N, and at between 1630 and 1650 cm^{-1} for C=C. 2-Phenylimino-5-chloro-4,5-tetramethylene-1,3-oxathiolane (Ve) has only one absorption in this region, namely at 1660 cm^{-1} for C=N. In agreement with structure VII are also the UV-spectra of the 2-phenylimino

TABLE V

1,3-Thiazolin-2-ones (IX)



R	R^1	R^2	Compounds IV Yield (a), %	M.p., °C	Empirical Formula	Yield (b), %	M.p., °C	C	H	N	S	Calculated, % C	H	N	S	Found, % C	H	N	S	λ max mμ (log ε)
(a) C_6H_5	H	CH_3	69	166-168	$C_{10}H_9NOS$	75	147.5-148	62.82	4.71	7.33	16.75	63.13	4.86	7.47	16.76	234 (3.80)
(b) p-$NO_2C_6H_4$	H	CH_3	59	188-190	$C_{10}H_8N_2O_3S$	94	158-159	50.85	3.41	11.86	–	50.76	4.10	11.75	–	–
(c) C_6H_5	CH_3	CH_3	69.5	waxy	$C_{11}H_{11}NOS$	56	103-103.5	64.45	5.40	6.84	15.60	64.87	5.71	6.66	15.88	238 (3.78)
(d) C_6H_5	$COOC_2H_5$	CH_3	56	116-121	$C_{13}H_{13}NO_3S$	58	103.5-104.5	59.31	4.98	5.33	12.17	59.47	5.16	5.57	12.16	–
(e) C_6H_5	-$(CH_2)_4$-		60	109-111	$C_{13}H_{13}NOS$	70	153-154	67.52	5.67	6.06	13.84	67.57	5.85	6.00	13.63	231 (3.91)
(f) p-ClC_6H_4	-$(CH_2)_4$-		56.5	165-167	$C_{13}H_{12}ClNOS$	92	115-116	58.76	4.55	5.27	12.04	58.99	4.48	5.62	11.60	240 (3.83)
(g) p-$CH_3OC_6H_4$	-$(CH_2)_4$-		37	119-120	$C_{14}H_{15}NO_2S$	94	116-117	64.35	5.79	5.36	12.25	64.02	5.70	5.58	12.43	252 (3.77)

(a) Yield is based on the S-chloroisothiocarbamoyl chloride charged. (b) Yield is based on compounds IV.

TABLE VI

Proton NMR of some Derivatives of 1,3-thiazolin-2-ones (IX) Chemical Shift in ppm and coupling constant J in Hz

		δ	Multiplicity	J
(IXa)	CH_3	1.84	2	1.5
	CH	5.81	4	1.5
	C_6H_5	7.3	m (a)	
(IXb)	CH_3	1.96	2	1.5
	CH	5.95	4	1.5
	C_6H_4	7.48 8.37	4	9.0
(IXc)	CH_3	1.76	4	1.0
	CH_3	2.12	4	1.0
	C_6H_5	7.35	m (a)	
(IXg)	$(CH_2)_4$	1.6-2.6	m (a)	
	CH_3O	3.8	1	
	C_6H_4	6.92 7.17	4	9.0

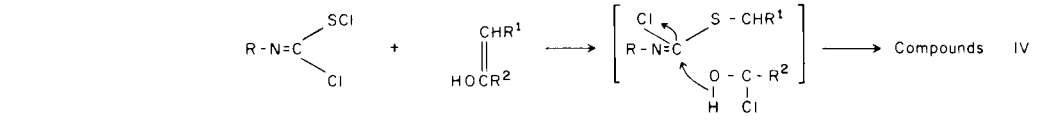
(a) Multiplet.

derivatives of VII (Table I) (7).

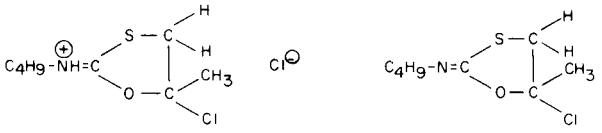
As mentioned above, 2-imino-5-chloro-1,3-oxathiolane hydrochlorides (IV) can either form 2-imino-1,3-oxathioles (VII) via V or rearrange to 1,3-thiazolin-2-ones (IX) (Scheme 2, Table V). The formation of the latter compounds takes place if the very moisture-sensitive compounds IV or V are brought in contact with water or alcohol or a mixture of both. The very exothermic reaction proceeds under heavy hydrogen chloride evolution and precipitation of the reaction products - which are not basic enough to form stable hydrochlorides - in a crystalline state.

Considering the high reactivity of the chlorine atom in 2-imino-5-chloro-1,3-oxathiolanes (V), it is proposed that the rearrangement of compounds IV or V to 1,3-thiazolin-2-ones (IX) proceeds through a carbonium ion intermediate as shown in Scheme 3. The structure of compounds IX is supported by NMR, IR, UV, and mass spectroscopy, and - last but not least - by direct comparison with 1,3-thiazolin-2-ones synthesized by an independent route (8). Thus, compound IXa is identical with 3-phenyl-4-methyl-1,3-thiazolin-2-one obtained from mercaptoacetone and phenylisocyanate. The identity was likewise shown in case of 3-phenyl-4,5-dimethyl-1,3-thiazolin-2-one. Unlike compounds VII (R=phenyl), the UV-absorption

Scheme 3

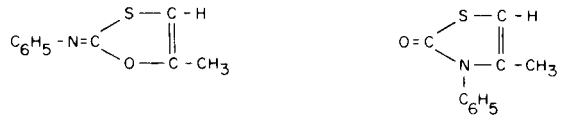


I VIII



IVa Va

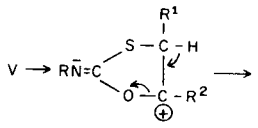
VIa VIIa

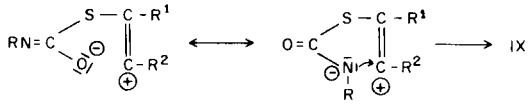


VIIc IXa

spectra (Table V) of *N*-aryl substituted compounds IX give - in agreement with the assigned structure - no indication of a bathochromic shift caused by conjugation of the >C=*N*- chromophore with the π-electron system of the aromatic nucleus.

Scheme 4





The mass spectra of compounds VII and IX will be discussed as part of a separate comprehensive paper (9). It will be shown that mass spectroscopy permits to distinguish unequivocally between structures VII and IX. As an example, the mass spectrum of VIIc has the predominant peaks at m/e 43, $(CH_3CO)^+$, and at m/e 149, $(C_6H_5NCSCH_2)^+$, after loss of ketene. In contrast, the spectrum of IXa shows neither fragment and loses no ketene, but has the principle peak at m/e 118, $(C_6H_5NCCH_3)^+$. Both compounds give, upon electron bombardment, fragments at m/e 45, identified as $(CHS)^+$.

Acknowledgment.

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EXPERIMENTAL

Melting points were determined in a modified Thiele Apparatus; melting and boiling points are not corrected. The H^1 NMR spectra were obtained on a Varian A-60 instrument, and the chemical shift data are expressed in parts per million relative to tetramethyl silane. Ultraviolet spectra were recorded by a Cary Spectrophotometer, Model 14. Spectrograde acetonitrile was used as solvent. Infrared spectra were taken on a Perkin-Elmer infracord spectrophotometer 137B. Vapor phase chromatography column used: 6 ft., 0.25" O. D., aluminum 0.032" wall, 30% SE 30 on Chromosorb W (60-80 mesh).

2-Butylimino-5-methyl-5-chloro-1,3-oxathiolane Hydrochloride (IVa). (General Procedure for the Preparation of Compounds IVa-g).

To a stirred solution of 35 g. (0.6 mole) of acetone in 250 ml. of hexane was added dropwise a solution of 75 g. (0.4 mole) of *N*-butyl-*S*-chloroisothiocarbamoyl chloride in 50 ml. of pentane over a period of 1.5 hours. The very exothermic reaction was moderated by external cooling, and a temperature of 25° was maintained. After standing at room temperature for 4.5 hours and at 0° for 20 hours, the reaction mixture was filtered, the filter cake was washed with hexane and immediately transferred to a vacuum dessicator for drying, yield, 57 g.

2-Butylimino-5-methyl-1,3-oxathiole Hydrochloride (VIa). (General Procedure for the Preparation of Compounds VIa-g).

To an agitated and ice-cooled slurry of 36 g. (0.147 mole) of compound IVa in 400 ml. of anhydrous ether was added dropwise a solution of 16.5 g. (0.16 mole) of triethylamine in 80 ml. of ether. After standing for 4 hours at room temperature, triethylamine hydrochloride (20.4 g.) was separated by filtration, and the solvent was removed from the filtrate *in vacuo* at 0-5° to afford 30 g. of 2-butylimino-5-methyl-5-chloro-1,3-oxathiolane (Va) in form of a pale yellow colored oil. Upon warming to room temperature, this liquid solidified spontaneously with evolution of

heat to give 30 g. of 2-butylimino-5-methyl-1,3-oxathiole hydrochloride (VIa), which was washed with ice cold toluene to remove small amounts of a contaminating oil. Yield after washing, 27.6 g.

2-Butylimino-5-methyl-1,3-oxathiole (VIIa). (General Procedure for the Preparation of VIIa-g).

The hydrochloride VIa (19.7 g.) was allowed to react with triethylamine (10 g.) in 250 ml. of ether. The crude oily reaction product was dissolved in 50 ml. of pentane, treated with decolorizing charcoal and stored at -25° for 15 hours to facilitate the separation of 12 g. of pure VIIa in form of hard bulky crystals. A second recrystallization increased the melting point by only 0.5°.

Compound VIIa gave with hydrogen chloride in ether a precipitate which proved to be identical (by m.p., IR and NMR) with the hydrochloride VIa.

2-Phenylimino-5-chloro-4,5-tetramethylene-1,3-oxathiolane (Ve).

To 98 g. of cyclohexanone in 250 ml. of anhydrous ether was added dropwise with stirring 103 g. of *N*-phenyl-*S*-chloroisothiocarbamoyl chloride over a period of 2.5 hours. The very exothermic reaction was moderated to 20° by means of external cooling. The reaction mixture was stirred for 18 hours at room temperature to complete the precipitation of 2-phenylimino-5-chloro-4,5-tetramethylene-1,3-oxathiolane hydrochloride which was separated by filtration, washed with pentane and dried to yield 120 g.

To a slurry of this hydrochloride in 800 ml. of anhydrous ether was added dropwise a solution of 88 g. of triethylamine in 100 ml. of ether. A mixture containing 105 g. of reaction product and triethylamine hydrochloride were separated by filtration. An additional amount of 45 g. was obtained from the filtrate by alternating freezing and concentrating procedures. The combined solid portions were recrystallized from 1200 ml. of heptane leaving triethylamine hydrochloride undissolved and yielding 73 g. of pure Ve, m.p. 95-95°.

Anal. Calcd. for $C_{13}H_{14}ClNOS$: C, 58.32; H, 5.27; Cl, 13.25; N, 5.23; S, 11.95. Found: C, 58.61; H, 5.68; Cl, 13.40; N, 5.60; S, 12.07.

Heating compound Ve above its melting point, caused its conversion to 2-phenylimino-4,5-tetramethylene-1,3-oxathiole hydrochloride (VIe) which was indicated by a sudden resolidification of the melt at 104°.

3-Phenyl-4-methyl-1,3-thiazolin-2-one (IXa). (General Procedure for the Preparation of 1,3-Thiazolin-2-ones).

(a) Twenty g. of 2-phenylimino-5-methyl-1,3-oxathiolane hydrochloride (IVc) was added portionwise with stirring to 100 ml. of water. After exothermic reaction had ceased, the reaction mixture was boiled, treated with charcoal and filtered. Upon cooling, 12.3 g. of 3-phenyl-4-methyl-1,3-thiazolin-2-one (IXa) crystallized in white needles.

(b) In a similar fashion, 20 g. of (IVc) was added to 100 ml. of methanol. After an induction period, the reaction mixture became very hot and evolved hydrogen chloride heavily. After boiling for 5 minutes the reaction mixture was allowed to cool to 0°, thereby precipitating 13 g. of IXa in form of white needle-like prisms.

A mixed melting point of the compounds obtained under (a) and (b) with an authentic sample synthesized from α-mercaptoacetone and phenyl isothiocyanate, did not show any depression.

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