

Isothiazoles I: 4-Isothiazolin-3-ones. A General Synthesis from 3,3'-Dithiodipropionamides

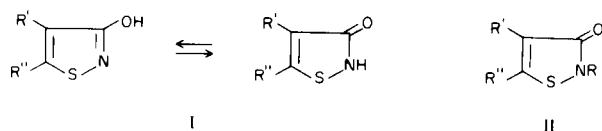
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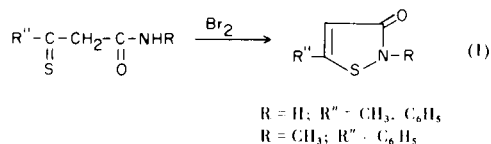
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The syntheses of 3-hydroxyisothiazole, 4-methyl-3-hydroxyisothiazole, and a comprehensive series of the respective 2-substituted-4-isothiazolin-3-ones have been achieved by the one-step chlorination-cyclization of the corresponding 3,3'-dithiodipropionamides. In several instances, 5-chloro-4-isothiazolin-3-ones were isolated as side products; however, no 4-chloro-4-isothiazolin-3-ones were evident in the reaction mixtures. These observations, coupled with the exclusive 4- or 4,5-halogenation of several preformed 4-isothiazolin-3-ones, support a proposed reaction pathway involving introduction of chlorine α to the sulfur atom in intermediate reaction products.

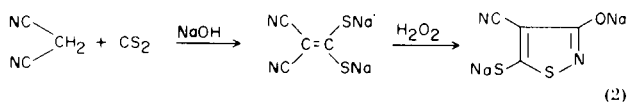
Since its first synthesis in 1956 by Adams and Slack (1), the mononuclear isothiazole ring system has undergone increasing investigation, and numerous syntheses yielding a variety of substituted derivatives have now been described (2). Substantially less has been reported on 3-hydroxyisothiazoles (I) and the closely related 2-substituted-4-isothiazolin-3-one systems (II), however. Goerdeler



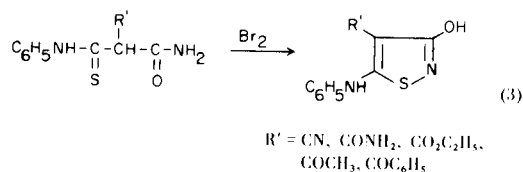
and Mittler (3) in 1963 reported the syntheses of 5-methyl- and 5-phenyl-3-hydroxyisothiazoles as well as 2-methyl-5-phenyl-4-isothiazolin-3-one by bromination of the appropriately substituted thioacylacetamides (eq. 1). Hatchard



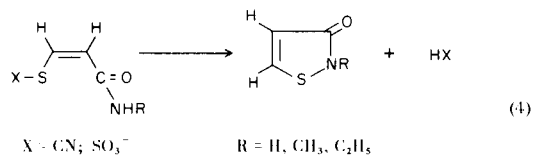
(4), also in 1963, described the synthesis of the disodium salt of 3-hydroxy-4-cyano-5-mercaptoisothiazole by the hydrogen peroxide oxidation of di(sodiummercapto)methyl-malononitrile (eq. 2). Goerdeler and Keuser (5) in



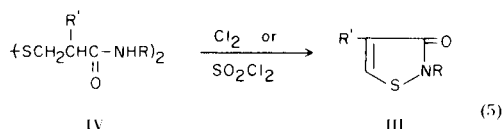
1964 reported the preparation of several 5-anilino-3-hydroxyisothiazoles by the bromination of the respective thiomalonamide derivatives (eq. 3). The first reported



synthesis of the parent 3-hydroxyisothiazole itself, however, was *via* the cyclization of *cis*-3-thiocyano- and thio-sulfatoacrylamide in 1964 by Crow and Leonard (6), who also described the preparation of 2-methyl- and 2-ethyl-4-isothiazolin-3-ones from the corresponding amides by the same method (eq. 4).



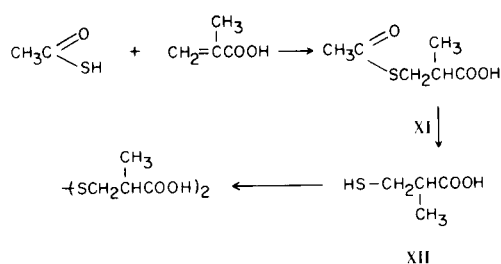
We now wish to report a very simple, convenient, and high yield synthesis of 3-hydroxyisothiazole (III; $R = R' = H$), 4-methyl-3-hydroxyisothiazole (III; $R = H, R' = CH_3$), and a comprehensive series of the respective 2-substituted-4-isothiazolin-3-ones (III; $R \neq H$) by the chlorine or sulfuryl chloride induced cyclization of readily available 3,3'-dithiodipropionamides (IV) (eq. 5). The reaction



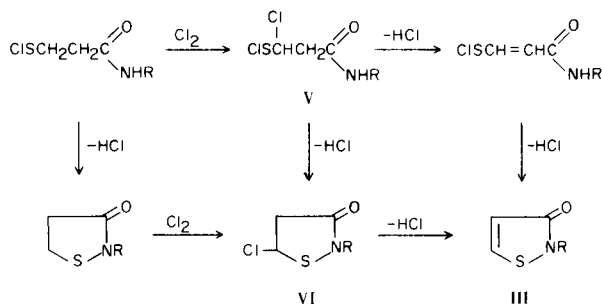
is conveniently performed by the introduction of a slight excess of three equivalents of the chlorinating agent to the amide slurry or solution in toluene, ethylene dichloride, or ethyl acetate at 0-50°. Conversion is quite rapid and essentially complete at the termination of the chlorine addition. Isothiazolin-3-one products (III) may be isolated from the reaction mixture either as their generally insoluble hydrochloride salts or alternatively as the free bases by suitable aqueous work-up; the isothiazolone bases are sufficiently weak that their hydrochloride salts are essentially completely dissociated in water. The use of pyridine as an internal acid scavenger during the reaction offered no advantages; in fact, the products were obtained in lower yield and purity. The preparations of a large variety of 4-isothiazolin-3-ones by this method are summarized in Table I; little effort was made to optimize the reported yields.

A major advantage of this preparative route is the ready availability of the 3,3'-dithiodipropionamide intermediates (IV), conveniently prepared by amidation, *via* the acid chlorides, of the corresponding diacids. 3,3'-Dithiodipropionic acid is commercially available (Evans Chemetics, Inc.), while 3,3'-dithiodiisobutyric acid may be prepared by the hydrogen peroxide oxidation of β -mercaptoisobutyric acid (XII), in turn obtained by hydrolysis of β -thioacetoxyisobutyric acid (XI), the addition product of methacrylic and thioacetic acids (Scheme I).

SCHEME I

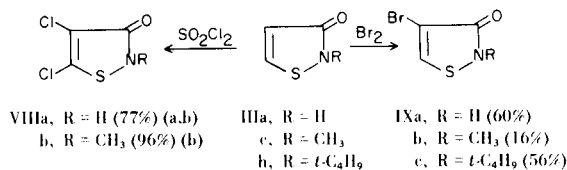


SCHEME II



Accepting the well established chlorinolysis of dialkyl disulfides to sulfenyl halides (7) as the initial step in 4-isothiazolin-3-one product formation (eq. 5), the most likely mechanistic pathway is indicated in Scheme II. It is clear that for the unsaturated 4-isothiazolin-3-one nucleus (III) to result *via* Scheme II, an atom of chlorine must first be introduced either α or β to sulfur. A preference for α -chlorination is suggested in the literature (8) and supported here by the isolation in several instances (Table II) of 5-chloro-4-isothiazolin-3-ones (VII), likely descendants of further chlorination of either of the possible monochlorinated intermediates, V or VI. Indeed, these 5-chlorinated derivatives may be obtained as major products by appropriate manipulation of reaction stoichiometry and conditions (9). Although they may also result from the dehydrochlorination of α,β -dichloro analogs of V or VI, theoretical considerations would appear to favor α,α -intermediacy. Significantly no 4-mono chlorinated by-products were observed in the reaction mixtures, although the presence of 4,5-dichloro derivatives (VIIe) was noted. In contrast, direct halogenation of III afforded only 4- and 4,5-dihalo-4-isothiazolin-3-ones (Scheme III), quite

SCHEME III



(a) A small quantity of 4-chloro-4-isothiazolin-3-one was isolated.
 (b) No evidence for 5-chloro-4-isothiazolin-3-ones was obtained.

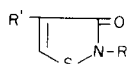
in line with the known preference for electrophilic substitution at the 4-position in simple isothiazoles (2). Thus it appears certain that the 5-chloro substituent of the by-products VII must also be introduced prior to formation of the 4-isothiazolin-3-one nucleus.

The positions of the halogens in compounds VIIa, c,d,f and IXa-c were shown by NMR spectral data (Table V). Thus the 4-protons of VIIa,c,d,f appeared at δ 6.10-6.50 (deuteriochloroform) while the 5-protons of IXa-c were evident at δ 8.80 (DMF) and δ 8.13-7.93 (deuteriochloroform), respectively. These assignments were unambiguously confirmed by the NMR analysis of the unequivocal 4-methyl-4-isothiazolin-3-ones IIIb, IIId, and IIIr which showed 5-proton absorption in the range of δ 7.57-7.92 (deuteriochloroform).

EXPERIMENTAL

Melting points were determined using a Thomas-Hoover capillary melting point apparatus; all melting and boiling points are uncorrected. The ultraviolet absorption spectra were recorded on

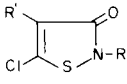
TABLE I
4-Isothiazolin-3-ones (III)



Compound	R	R'	M.p. °C	B.p. °C (mm)	Solvent	Chlor Agent	Yield %
IIIa	H	H	73-74 (a,b)		EtOAc	Cl ₂	75
IIIb	H	CH ₃	105-109 (c)		EDC	SO ₂ Cl ₂	47
IIIc	CH ₃	H	48-50 (d)	93 (0.03)	EDC	SO ₂ Cl ₂	33
III d	CH ₃	CH ₃	78-80 (e)		EDC	SO ₂ Cl ₂	54
IIIe	C ₂ H ₅	H	59-61 (f)	72 (0.3)	EDC	SO ₂ Cl ₂	53
III f	C ₃ H _{7-n}	H		65 (0.1)	EDC	SO ₂ Cl ₂	85
IIIg	C ₄ H _{9-n}	H		96 (0.03)	Toluene	Cl ₂	92
IIIh	C ₄ H _{9-t}	H	85-86 (c)		Toluene	SO ₂ Cl ₂	80
IIIi	C ₅ H _{11-n}	H		118 (0.05)	EtOAc	Cl ₂	82
IIIj	C ₅ H ₉ (cyclo)	H	118-119 (a)		EtOAc	Cl ₂	52
IIIk	C ₆ H _{13-n}	H		102 (0.03)	EDC	SO ₂ Cl ₂	89
III l	C ₆ H ₁₁ (cyclo)	H	114-115 (a)		EDC	SO ₂ Cl ₂	65
III m	C ₈ H _{17-n}	H		142 (0.03)	Toluene	Cl ₂	96
III n	C ₈ H _{17-t}	H	101-102 (g)		Toluene	Cl ₂	94
III o	CH ₂ CH(C ₂ H ₅)C ₄ H _{9-n}	H		119 (0.01)	Toluene	SO ₂ Cl ₂	48
III p	C ₉ H _{19-n}	H	30-31 (h)		Toluene	SO ₂ Cl ₂	48
III q	C ₁₀ H _{21-n}	H	41-42 (h)		Toluene	Cl ₂	96
III r	C ₁₂ H _{25-n}	H	46-49 (c)		EDC	SO ₂ Cl ₂	41
III s	C ₁₄ H _{29-n}	H	53-55 (i)		EDC	SO ₂ Cl ₂	56
III t	CH ₂ C ₆ H ₅	H	78-80 (c)		EDC	SO ₂ Cl ₂	47
III u	CH ₂ C ₆ H ₄ Cl-2	H	99-100		EDC	SO ₂ Cl ₂	73
III v	CH ₂ C ₆ H ₄ Cl-4	H	90-92 (a)		EDC	SO ₂ Cl ₂	40
III w	CH ₂ C ₆ H ₄ OCH ₃ -4	H	80-82		EDC	SO ₂ Cl ₂	36
III x	CH ₂ C ₆ H ₄ CH ₃ -4	H	76-77 (c)		EDC	SO ₂ Cl ₂	40
III y	CH ₂ C ₆ H ₃ Cl ₂ -2,4	H	122-124		EDC	SO ₂ Cl ₂	72
III z	CH ₂ C ₆ H ₃ Cl ₂ -3,4	H	87-89		EDC	SO ₂ Cl ₂	72
III aa	CH(CH ₃)C ₆ H ₅	H		138 (0.01)	Toluene	SO ₂ Cl ₂	49
III bb	C ₂ H ₄ C ₆ H ₅	H	76-78 (c)		EDC	SO ₂ Cl ₂	44
III cc	C ₂ H ₄ CN	H	85-86 (j)		EtOAc	SO ₂ Cl ₂	44
III dd	C ₂ H ₄ CO ₂ CH ₃	H		120 (0.02)	EDC	Cl ₂	50
III ee	C ₂ H ₄ Cl	H	64-66	100 (0.02)	EtOAc	Cl ₂	46
III ff	C ₂ H ₄ OC ₂ H ₅	H		90 (0.04)	Toluene	Cl ₂	62
III gg	C ₂ H ₄ OC ₆ H ₅	H	78-81		Toluene	Cl ₂	14
III hh	C ₂ H ₄ CH ₂ Cl	H	45-48	124 (0.03)	EtOAc	Cl ₂	85
III ii	C ₆ H ₅	H	91-92 (j)		EtOAc	SO ₂ Cl ₂	37
III jj	C ₆ H ₄ Cl-2	H	90-91 (j)		EtOAc	SO ₂ Cl ₂	48
III kk	C ₆ H ₄ Cl-3	H	119-122 (j)		Toluene	SO ₂ Cl ₂	67
III ll	C ₆ H ₄ Cl-4	H	142-144 (j)		Toluene	SO ₂ Cl ₂	71
III mm	C ₆ H ₄ NO ₂ -4	H	188-190 (k)		Toluene	SO ₂ Cl ₂	61
III nn	C ₆ H ₄ CO ₂ C ₂ H ₅ -4	H	141-142 (j)		Toluene	SO ₂ Cl ₂	78
III oo	C ₆ H ₃ Cl ₂ -2,4	H	155-157 (j)		Toluene	SO ₂ Cl ₂	73
III pp	C ₆ H ₃ Cl ₂ -2,3	H	130-134 (j)		Toluene	SO ₂ Cl ₂	57
III qq	C ₆ H ₃ Cl ₂ -2,5	H	145-147 (a)		Toluene	SO ₂ Cl ₂	30
III rr	C ₆ H ₃ Cl ₂ -3,4	CH ₃	166-168 (g)		EtOAc	SO ₂ Cl ₂	67

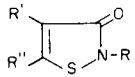
(a) Recrystallized from benzene. (b) Lit. (6) m.p. 74-75°. (c) Recrystallized from benzene-hexane. (d) Lit. (6) m.p. 50-51°. (e) Recrystallized from heptane. (f) Lit. (6) m.p. 61-62°. (g) Recrystallized from ethyl acetate. (h) Recrystallized from hexane. (i) Recrystallized from ligroin (90-120°). (j) Recrystallized from toluene. (k) Recrystallized from ethanol.

TABLE II
5-Chloro-4-isothiazolin-3-ones (VII)

Compound			M.p. °C	Yield %
	R	R'		
VIIa	H	H	95-96 (a)	15
VIIb	H	CH ₃	125-126 (b)	18
VIIc	CH ₃	H	54-55 (c)	13
VIIId	CH ₂ C ₆ H ₅	H	58-59 (d)	12
VIIe	CH ₂ C ₆ H ₅	Cl	62-64 (d)	27
VIIIf	C ₂ H ₄ C ₆ H ₅	H	55-59 (e)	2

(a) Recrystallized from water. (b) Recrystallized from chloroform. (c) Recrystallized from ligroin (60-90°). (d) Recrystallized from heptane. (e) Recrystallized from benzene-hexane.

TABLE III
Halogenation of 4-Isothiazolin-3-ones

Compound				M.p. °C	Yield %
	R	R'	R''		
VIIIa	H	Cl	Cl	151-154 (a)	77
VIIIb	CH ₃	Cl	Cl	121-123 (b)	96
IXa	H	Br	H	198-199 (c)	60
IXb	CH ₃	Br	H	94-97 (d)	16
IXc	C ₄ H ₉ t	Br	H	150-153 (e)	56

(a) Recrystallized from benzene-ethanol. (b) Recrystallized from chloroform. (c) Recrystallized from ethyl acetate. (d) Recrystallized from ligroin. (e) Recrystallized from ether.

a Perkin Elmer Model 202 Ultraviolet-Visible Spectrophotometer, and NMR spectra were recorded on a Varian T-60 Spectrometer. Elemental analyses were performed by the analytical department of the Research Division of the Rohm and Haas Company.

3,3'-Dithiodipropionyl Dichloride (X)

In a 12 liter flask fitted with a mechanical stirrer and hydrogen chloride scrubber was placed 3150 g. (15 moles) of 3,3'-dithiodipropionic acid and one ml. of pyridine. To this flask was then added 7000 g. (58.7 moles) of thionyl chloride, and the mixture was stirred at 25° for 2 days. The resulting clear amber solution was then concentrated on the steam bath under the reduced pressure of a water aspirator to give approximately the theoretical amount (3705 g.) of X which was used without further purification.

3,3'-Dithiodipropionamide Preparations.

3,3'-Dithiodipropionamide (IV). The following procedure illustrates the general Method A.

In a 5 liter flask equipped with a heavy duty stirrer, thermometer, and dropping funnel was placed a mixture of 600 ml. of

benzene and 810 g. (13.3 moles) of 28% aqueous ammonia. To this mixture was added a solution of 741 g. (3.00 moles) of X in 1200 ml. of benzene at such a rate as to keep the reaction temperature below 35°. Near the end of the addition water was added as required to thin the mixture for efficient stirring. The thick suspension was then filtered, and the solid was pressed on the filter and dried to yield 573 g. (92%) of IVa, m.p. 169-171°.

N,N'-Dicyclohexyl-3,3'-dithiodipropionamide (IVj). The following procedure illustrates the general Method B.

In a 3 liter flask equipped with a mechanical stirrer, thermometer, and dropping funnel, was placed a solution of 396 g. (4.00 moles) of cyclohexylamine in 1 liter of ethylene dichloride. To this solution was then added dropwise a solution of 247 g. (1.0 mole) of X, keeping the temperature below 45°. After addition the mixture was allowed to stir for a few hours and to cool to room temperature. The thick paste was filtered by suction and dried. The dried solid was then washed free of cyclohexylamine hydrochloride by slurring in 300 ml. of water. The insoluble solid was collected and dried to yield 328 g. (92%) of IVj, m.p. 159-160°.

N,N'-Di-n-octyl-3,3'-dithiodipropionamide (IVk). The following procedure illustrates the general Method C.

In a 1 liter flask with a stirrer, a thermometer, and a dropping funnel was placed a mixture of 119 g. (1.0 mole) of n-octylamine, 200 ml. of toluene, and 160 g. (1.0 mole) of 25% aqueous sodium hydroxide solution. A solution of 123.5 g. (0.50 mole) of X in 200 ml. of toluene was then added dropwise, keeping the temperature below 35°. The thick, off-white paste was then filtered by suction, and the solid product dried to yield 127 g. (59%) of IVk, m.p. 126-127°.

N,N'-Bis-(3,4-dichlorobenzyl)-3,3'-dithiodipropionamide (IVx). The following procedure illustrates the general procedure D.

In a 1 liter flask with a stirrer, thermometer, and dropping funnel was placed a mixture of 88 g. (0.50 mole) of 3,4-dichlorobenzylamine, 50.5 g. (0.50 mole) of triethylamine, and 250 ml. of ethylene dichloride. To this solution was added dropwise a solution of 61.8 g. (0.25 mole) of X in 150 ml. of ethylene dichloride, keeping the temperature below 30° with an ice bath. After addition the reaction mixture was allowed to stir at 25° for several hours. The suspension was filtered by suction, and the solid dried. The dry solid was washed thoroughly with water, collected, and dried to yield 108 g. (83%) of IVx, m.p. 125-130°.

N,N'-Bis-(2-carboxyethyl)-3,3'-dithiodipropionamide.

To a solution of 44.5 g. (0.50 mole) of β-alanine and 20 g. (0.50 mole) of sodium hydroxide in 200 ml. of water at 10° were added simultaneously, dropwise, 61.7 g. (0.25 mole) of X and a solution of 20 g. (0.50 mole) of sodium hydroxide in 50 ml. of water. The temperature was maintained between 10-20° during the addition which required about 15 minutes. After stirring for 2 hours a trace of tan solid was removed by filtration, and the dark brown filtrate was then acidified by dropwise addition of concentrated hydrochloric acid. The resulting tan solid was collected by filtration and dried in vacuum to yield 83.1 g. (93%) of N,N'-bis-(2-carboxyethyl)-3,3'-dithiodipropionamide, m.p. 174-176° from water.

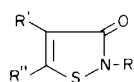
N,N'-Bis-(2-carbomethoxyethyl)-3,3'-dithiodipropionamide (IVbb).

A solution of 176 g. (0.50 mole) of N,N'-bis-(2-carboxyethyl)-3,3'-dithiodipropionamide and 320 g. (10 moles) of absolute methanol was heated at reflux for 2.75 hours, during which time

TABLE IV
Elemental Analysis of 4-Isothiazolin-3-ones

Compound	Formula	Calcd.					Found				
		C	H	N	S	Cl	C	H	N	S	Cl
IIIa	C ₃ H ₃ NOS	35.64	2.97	13.86	31.68		35.48	3.08	13.74	31.80	
b	C ₄ H ₅ NOS	41.74	4.35	12.17			41.81	4.33	12.07		
c	C ₄ H ₅ NOS	41.74	4.35	12.17	27.83		41.54	4.45	11.81	27.96	
d	C ₅ H ₇ NOS	46.50	5.42	10.86	24.81		46.51	5.52	10.83	24.63	
e	C ₅ H ₇ NOS	46.50	5.42	10.86	24.81		46.62	5.37	11.01	24.41	
f	C ₆ H ₉ NOS	50.34	6.29	9.79	22.38		50.28	6.17	9.83	22.30	
g	C ₇ H ₁₁ NOS	53.50	7.01	8.92	20.38		53.36	7.19	8.87	20.25	
h	C ₇ H ₁₁ NOS	53.50	7.01	8.92	20.38		53.37	7.00	8.89	20.52	
i	C ₈ H ₁₃ NOS	56.14	7.60	8.19	18.71		56.09	7.86	8.14	18.40	
j	C ₈ H ₁₁ NOS	56.80	6.51	8.28	18.94		56.84	6.59	8.32	18.82	
k	C ₉ H ₁₅ NOS	58.38	8.11	7.57	17.30		58.30	8.39	7.53	17.38	
l	C ₉ H ₁₃ NOS	59.02	7.10	7.65	17.49		59.18	6.95	7.59	17.41	
m	C ₁₁ H ₁₉ NOS	61.97	8.92	6.57	15.02		61.88	8.90	6.52	15.29	
n	C ₁₁ H ₁₉ NOS	61.97	8.92	6.57	15.02		61.99	8.92	6.54	15.00	
o	C ₁₁ H ₁₉ NOS	61.97	8.92	6.57	15.02		61.67	8.96	6.51	15.02	
p	C ₁₂ H ₂₁ NOS	63.45	9.29	6.17	14.10		63.34	9.55	6.08	14.00	
q	C ₁₃ H ₂₃ NOS	64.73	9.55	5.81	13.32		64.66	9.76	5.62	13.00	
r	C ₁₅ H ₂₇ NOS	66.92	10.04	5.20	11.90		66.98	9.90	5.25	11.72	
s	C ₁₇ H ₃₁ NOS	68.75	10.43	4.73	10.77		68.86	10.61	4.68	10.88	
t	C ₁₀ H ₉ NOS	62.83	4.71	7.33	16.75		62.82	4.84	7.22	16.97	
u	C ₁₀ H ₈ ClNOS	53.21	3.55	6.28	14.19	15.74	53.39	3.69	6.18	13.95	15.96
v	C ₁₀ H ₈ ClNOS	53.21	3.55	6.28	14.19	15.74	53.59	3.59	6.17	14.42	15.76
w	C ₁₁ H ₁₁ NO ₂ S	59.73	4.98	6.33	14.48		59.74	4.96	6.25	14.58	
x	C ₁₁ H ₁₁ NOS	64.39	5.37	6.83	15.61		64.60	5.32	6.60	15.60	
y	C ₁₀ H ₇ Cl ₂ NOS	46.15	2.69	5.38	12.31	27.31	46.18	2.80	5.25	12.46	26.85
z	C ₁₀ H ₇ Cl ₂ NOS	46.15	2.69	5.38	12.31	27.31	45.87	2.62	5.15	12.12	27.33
aa	C ₁₁ H ₁₁ NOS	64.41	5.36	6.83	15.61		64.15	5.55	6.77	15.55	
bb	C ₁₁ H ₁₁ NOS	64.41	5.36	6.83	15.61		64.35	5.49	6.75	15.40	
cc	C ₆ H ₆ N ₂ OS	46.73	3.90	18.17	20.79		46.68	3.92	18.25	20.20	
dd	C ₇ H ₉ NO ₃ S	44.92	4.81	7.49	17.12		44.69	4.92	7.41	17.02	
ee	C ₅ H ₆ ClNOS	36.70	3.67	8.56	19.57	21.71	36.63	3.83	8.48	19.51	21.36
ff	C ₇ H ₁₁ NO ₂ S	48.55	6.36	8.09	18.49		48.95	6.42	7.98	18.16	
gg	C ₁₁ H ₁₁ NO ₂ S	59.73	4.98	6.34	14.48		59.61	5.15	6.23	14.28	
hh	C ₆ H ₈ ClNOS	40.56	4.51	7.83	18.03		40.07	4.70	7.72	17.82	
ii	C ₉ H ₇ NOS	61.02	3.95	7.92	18.06		61.31	4.03	7.86	17.70	
jj	C ₉ H ₆ ClNOS	51.06	2.84	6.62	15.12		51.06	2.82	6.55	14.82	
kk	C ₉ H ₆ ClNOS	51.06	2.84	6.62	15.12		51.26	3.00	6.55	14.98	
ll	C ₉ H ₆ ClNOS	51.06	2.84	6.62	15.12	16.78	51.02	2.59	6.42	14.88	16.55
mm	C ₉ H ₆ N ₂ O ₃ S	48.65	2.72	12.61	14.41		48.62	2.78	12.77	13.99	
nn	C ₁₂ H ₁₁ NO ₂ S	57.83	4.44	5.62	12.85		58.12	4.46	5.70	12.79	
oo	C ₉ H ₅ Cl ₂ NOS	43.90	2.05	5.69	13.01		44.13	2.08	5.53	12.88	
pp	C ₉ H ₅ Cl ₂ NOS	43.90	2.05	5.69	13.01		43.70	2.16	5.60	12.69	
qq	C ₉ H ₅ Cl ₂ NOS	43.90	2.05	5.69	13.01		43.71	2.08	5.58	12.85	
rr	C ₁₀ H ₇ Cl ₂ NOS	46.15	2.69	5.39	12.31	27.31	45.92	2.80	5.59	12.65	27.13
VIIa	C ₃ H ₂ ClNOS	26.57	1.48	10.33	23.62	26.20	26.88	1.29	10.28	23.53	26.26
b	C ₄ H ₄ ClNOS	32.11	2.68	9.37	21.47	23.75	32.34	2.76	9.23	21.53	23.69
c	C ₄ H ₄ ClNOS	32.11	2.68	9.37	21.47	23.75	31.91	2.56	9.19	21.44	23.95
d	C ₁₀ H ₈ ClNOS	53.22	3.55	6.21	14.19	15.74	53.19	3.46	6.18	13.80	15.01
e	C ₁₀ H ₇ Cl ₂ NOS	46.15	2.69	5.38	12.31	27.31	46.43	2.81	5.33	12.48	27.97
f	C ₁₁ H ₁₀ ClNOS	55.12	4.18	5.87	13.36	14.78	55.22	3.95	5.62	13.16	14.51
VIIIa	C ₃ HCl ₂ NOS	21.18	0.59	8.24	18.83		21.11	0.49	8.06	18.80	
b	C ₄ H ₃ Cl ₂ NOS	26.09	1.63	7.61	17.39		26.20	1.72	7.46	17.44	
IXa	C ₃ H ₂ BrNOS	20.00	1.12	7.78	17.79		20.20	1.17	7.73	17.74	
b	C ₄ H ₄ BrNOS	24.73	2.06	7.22			24.97	2.14	7.12		
c	C ₇ H ₁₀ BrNOS	35.58	4.27	5.93	13.58		35.83	4.27	6.00	13.28	

TABLE V
Nuclear Magnetic Resonance and Ultraviolet Absorption
Spectral Data for 4-Isothiazolin-3-ones



Compound	R	R'	R''	Chemical Shifts, δ (a,b)			Coupling Constant, Hz $J_{4,5}$	UV (Methanol)	
				R	R'	R''		λ max ($m\mu$)	$\log \epsilon$
IIIa (c)	H	H	H	10.80 (s)	6.48 (d)	8.28 (d)	5.0	257	3.92
IXa (d)	H	Br	H			8.80 (s)		267	3.88
IIIb	H	CH ₃	H	12.67 (s)	2.08 (s)	7.92 (s)		262	3.90
VIIa	H	H	Cl	11.48 (s)	6.50 (s)			262	3.90
VIIb	H	CH ₃	Cl	12.00 (s)	2.05 (s)			262	3.92
IIIc (c)	CH ₃	H	H	3.27 (s)	6.05 (d)	7.98 (d)	6.0	278	3.87
IXb	CH ₃	Br	H	3.38 (s)		8.13 (s)			
III d	CH ₃	CH ₃	H	3.27 (s)	1.95 (s)	7.57 (m)		274	4.09
VIIc	CH ₃	H	Cl	3.25 (s)	6.20 (s)			277	3.82
VIIIb	CH ₃	Cl	Cl	3.33 (s)				279	4.09
IIIe (f)	C ₂ H ₅	H	H	1.33 (t)	6.09 (d)	7.98 (d)	6.5	279	3.92
III f	C ₃ H _{7-n}	H	H	3.90 (q)	0.93 (t)	5.94 (d)	6.5	279	3.88
				1.65 (m)		7.85 (d)			
				3.73 (t)					
IIIg	C ₄ H _{9-n}	H	H	0.95 (m)	6.12 (d)	8.37 (d)	6.0	276	3.95
				1.50 (m)					
				3.73 (t)					
IIIh	C ₄ H _{9-t}	H	H	1.63 (s)	6.09 (d)	7.85 (d)	6.0	278	3.94
IXc	C ₄ H _{9-t}	Br	H	1.63 (s)		7.93 (s)			
IIIk	C ₆ H _{13-n}	H	H	0.88 (t)	6.09 (d)	8.03 (d)	6.0	279	3.90
				1.32 (s)					
				1.67 (m)					
				3.73 (t)					
III l	C ₆ H ₁₁ (cyclo)	H	H	1.38 (m)	6.05 (d)	7.93 (d)	6.5	280	3.92
				4.27 (m)					
III m	C ₈ H _{17-n}	H	H	0.87 (m)	5.83 (d)	7.82 (d)	7.0	280	3.88
				1.27 (s)					
				1.67 (m)					
				3.72 (t)					
III n	C ₈ H _{17-t}	H	H	0.92 (s)	6.05 (d)	7.82 (d)	6.5	280	3.90
				1.65 (s)					
				2.12 (s)					
III r	C ₁₂ H _{25-n}	H	H	0.88 (m)	6.10 (d)	7.98 (d)	6.5	277	3.89
				1.25 (s)					
				3.77 (t)					
III bb	CH ₂ CH ₂ C ₆ H ₅	H	H	2.95 (m)	6.14 (d)	7.89 (d)	6.5		
				3.98 (m)					
				7.17 (s)					
VII f	CH ₂ CH ₂ C ₆ H ₅	H	Cl	2.73 (t)	6.10 (s)				
				4.45 (t)					
				7.12 (s)					
III t	CH ₂ C ₆ H ₅	H	H	5.07 (s)	6.45 (d)	8.27 (d)	6.0	278	3.89
				7.53 (s)					
VII d	CH ₂ C ₆ H ₅	H	Cl	4.83 (s)	6.24 (s)			280	3.80
				7.30 (s)					
VII e	CH ₂ C ₆ H ₅	Cl	Cl	4.98 (s)					
				7.42 (s)					

TABLE V (Continued)

Compound	Chemical Shifts, δ (a,b)			Coupling Constant, Hz			λ max (m μ)	log ϵ
	R	R'	R''	R	R'	R''		
IIIi	C ₆ H ₅	H	H	7.54 (m)	6.30 (d)	8.16 (d)	6.0	
IIIr	C ₆ H ₅ Cl ₂ -3,4	CH ₃	H	7.71 (s)	2.05 (s)	7.71 (s)		
				7.40 (s)				

(a) All NMR spectra were determined in deuterated chloroform solution, with tetramethylsilane as an internal reference, unless otherwise noted. (b) The multiplicity of the absorption is shown in brackets: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet. (c) Lit. (6) NMR δ 12.63 (s, N-H), 6.57 (d, $J_{4,5}$ 4.6 Hz, 4-H), 8.42 (d, $J_{4,5}$ 4.6 Hz, 5-H). (d) NMR determined in dimethylformamide solution. (e) Lit. (6) NMR δ 3.37 (s, CH₃), 6.28 (d, $J_{4,5}$ 6.5 Hz, 4-H), 8.29 (d, $J_{4,5}$ 6.5 Hz, 5-H). (f) Lit. (6) NMR δ 1.33 (t, CH₃), 3.88 (q, CH₂), 6.28 (d, $J_{4,5}$ 6.5 Hz, 4-H), 8.23 (d, $J_{4,5}$ 6.5 Hz, 5-H).

one gram aliquots of the reaction mixture were removed and titrated with 0.1 *N* sodium hydroxide solution for residual acid. When titration indicated that the reaction was over 93% complete, the mixture was cooled to room temperature and yielded in three crops 117 g. (62%) of IVbb, m.p. 124-125° after recrystallization from methanol.

N,N'-Di-*n*-tetradecyl-3,3'-dithiodipropionamide (IVq).

In a reaction flask equipped with a Dean-Stark trap was heated a mixture of 42 g. (0.20 mole) of dithiodipropionic acid, 85.2 g. (0.40 mole) of *n*-tetradecylamine, and 350 ml. of dry xylene. After 3 hours at reflux, 4 ml. of water had been collected, and a solution had formed. The reflux temperature was maintained overnight. At the end of this time the odor of hydrogen sulfide was evident, and the trap contained 6.3 ml. of water (theoretical amount 7.2 ml.). On cooling of the reaction solution IVq separated as a grey solid which was collected and dried to yield 47 g. (39%), m.p. 123-126° after recrystallization from toluene.

β -Thioacetoxyisobutyric Acid (XI).

In a 500 ml. flask with a stirrer, thermometer, and dropping funnel was placed 172 g. (2.0 moles) of methacrylic acid. Then 152 g. (2.0 moles) of thioacetic acid was added dropwise over one hour. The solution was allowed to stand for several days at room temperature, during which time a solid separated. The suspension was filtered giving 38 g. of XI as a white solid. The filtrate was cooled in dry-ice to precipitate an additional 175 g. of product XI. The combined solids were then triturated with hexane, giving 157 g. (49%) of XI, m.p. 39-41° (lit. (10) b.p. 143-144° (4 mm)).

β -Mercaptoisobutyric Acid (XII).

In a two liter flask containing 80 g. (2.0 moles) of sodium hydroxide in 675 ml. of water under a nitrogen atmosphere was added 100 g. (0.62 mole) of XI. After stirring at room temperature for 5 hours, the clear yellow solution was acidified with 400 ml. of 1:1 aqueous sulfuric acid giving an emulsion containing some pale pink gum. Both the emulsion and gum were extracted with ether, and the ether was dried over anhydrous magnesium sulfate. Evaporation gave 79 g. of crude XII as a yellow-orange oil, which was used without further purification.

3,3'-Dithiodiisobutyric Acid.

To a solution of 17 g. (0.425 mole) of sodium hydroxide in 160 ml. of water was added 50 g. (0.42 mole) of crude XII. The solution was maintained at 45° during the dropwise addition of 21 ml. (0.215 mole) of 35% hydrogen peroxide. After addition

the reaction was allowed to stand for several hours at room temperature and was then acidified with concentrated hydrochloric acid. The precipitate was collected by filtration and dried to give 23 g. (48%) of 3,3'-dithiodiisobutyric acid, m.p. 83-84° (lit. (11) m.p. 86-87°).

3,3'-Dithiodipropionamide Cyclizations. The following procedures are typical illustrations of the general method.

3-Hydroxyisothiazole (IIIa).

In a two liter flask with stirrer, a thermometer, and a gas inlet tube was placed 208 g. (1.0 mole) of IVa and one liter of anhydrous ethyl acetate. The resulting slurry was warmed to 40°, and 224 g. (3.5 moles) of chlorine gas was added over 2 hours beneath the surface of the liquid, maintaining the temperature at 40-50°. Hydrogen chloride began to evolve fairly rapidly after about 1.5 hours. At the completion of addition the cream colored suspension was cooled to room temperature and was filtered. The solid precipitate was washed with ethyl acetate on the filter and then was resuspended in one liter of this solvent.

The slurry was cooled to 10°, and 20% aqueous sodium hydroxide was added until the aqueous phase was pH 4.5 (about 380 g., 1.90 moles of base was required). The organic phase was then separated and evaporated under reduced pressure to yield 150 g. (75%) of IIIa, m.p. 73-74° from benzene (lit. (6) m.p. 74-75°).

3-Hydroxyisothiazole (IIIa) and 5-Chloro-3-hydroxyisothiazoles (VIIa).

To a suspension of 20.8 g. (0.10 mole) of IVa in 500 ml. of ethylene dichloride at 10-15° was added dropwise 42.5 g. (0.315 mole) of sulfuryl chloride. After addition the suspension was allowed to come to room temperature and was stirred for several hours. The solid was then removed by filtration and was dissolved in 100 ml. of warm water. On cooling of the aqueous solution 4 g. (15%) of VIIa separated as tan crystals, m.p. 95-96° after recrystallization from water. The aqueous filtrate was then continuously ether extracted to yield 11.2 g. (55%) of IIIa, m.p. 73-74° (benzene) (lit. (6) m.p. 74-75°).

4-Methyl-3-hydroxyisothiazole (IIIb) and 5-Chloro-4-methyl-3-hydroxyisothiazole (VIIb).

To a suspension of 11.8 g. (0.05 mole) of IVqq in 200 ml. of ethylene dichloride at 20-25° was added slowly a solution of 21.3 g. (0.15 mole) of sulfuryl chloride in 30 ml. of ethylene dichloride. During this addition a gummy material formed but turned to a granular solid on continued stirring overnight. On

TABLE VI (Continued)

Compound	R	R'	Method (a)	Yield %	M.p. °C	Formula	Elemental Analysis, %							
							Calcd.			Found				
							H	N	S	C	H	N	S	
ii	C ₆ H ₄ Cl ₃	H	C	84	150-152	C ₁₈ H ₁₈ Cl ₂ N ₂ O ₂ S ₂	50.53	4.20	6.52	14.92	50.64	4.15	6.45	15.08
j	C ₆ H ₄ Cl ₄	H	C	86	179-186	C ₁₈ H ₁₈ Cl ₂ N ₂ O ₂ S ₂	(f)							
kk	C ₆ H ₄ NO ₂ -4	H	C	93	204-210	C ₁₈ H ₁₈ N ₄ O ₆ S ₂	48.00	4.00	12.45	14.25	48.12	3.88	12.27	14.46
ll	C ₆ H ₄ CO ₂ C ₂ H ₅ -4	H	C	92	172-174	C ₂₄ H ₂₀ N ₂ O ₆ S ₂	43.73	3.24	5.64	12.81	43.05	3.25	5.60	12.70
mm	C ₆ H ₃ Cl ₂ -2,4	H	C	73	150-152	C ₁₈ H ₁₆ Cl ₄ N ₂ O ₂ S ₂	43.73	3.24	5.62	12.96	43.05	3.25	5.60	12.70
nn	C ₆ H ₃ Cl ₂ -2,3	H	C	77	173-178	C ₁₈ H ₁₆ Cl ₄ N ₂ O ₂ S ₂				12.96				12.48
oo	C ₆ H ₃ Cl ₂ -2,5	H	C	56	157-162	C ₁₈ H ₁₆ Cl ₄ N ₂ O ₂ S ₂			5.62	12.96			6.00	13.05
pp	C ₆ H ₃ Cl ₂ -3,4	H	C	91	104-109	C ₁₈ H ₁₆ Cl ₄ N ₂ O ₂ S ₂	43.73	3.24	5.62	12.96	43.55	3.05	5.86	27.65
qq	H	CH ₃	A	96	—	C ₈ H ₁₆ N ₂ O ₂ S ₂				27.12				
rr	CH ₃	CH ₃	A	87	—	C ₁₀ H ₂₀ N ₂ O ₂ S ₂			10.61				10.46	
ss	C ₆ H ₃ Cl ₂ -3,4	CH ₃	B	72	—	C ₂₀ H ₂₀ Cl ₄ N ₂ O ₂ S ₂			5.32	12.17			5.32	11.96

(a) See the Experimental for typical examples. (b) Recrystallized from ethyl acetate. (c) See the Experimental for preparation. (d) Recrystallized from toluene. (e) Recrystallized from ethanol. (f) No elemental analysis was obtained.

filtration 9.15 g. of white solid was obtained. The filtrate was evaporated, and the residue dissolved in ether. The ether solution was washed with water and dried over anhydrous magnesium sulfate. Evaporation gave 3.0 g. of IIIb, m.p. 105-109° from benzene-hexane. The original solid precipitate from above was treated with 100 ml. of hot water. Filtration gave 2.8 g. (18%) of VIIIb, m.p. 125-126° from chloroform. Extraction of the aqueous filtrate with ether, and evaporation of the ether yielded 2.4 g. additional IIIb, giving a total amount of 5.4 g. (47%).

2-Methyl-4-isothiazolin-3-one (IIIc).

To a slurry of 71 g. (0.30 mole) of IVb in one liter of ethylene dichloride at 10-15° was added dropwise over a period of 1.5 hours 122 g. (0.90 mole) of sulfonyl chloride. After stirring for several hours at room temperature the reaction was filtered to give a white solid precipitate. This material was dissolved in 200 ml. of water, and the aqueous solution was continuously ether extracted overnight. The ether extract was diluted with chloroform to dissolve some oil which had separated, and the solution was dried over magnesium sulfate. Evaporation then gave 23 g. (33%) of IIIc, b.p. 93° (0.03 mm), m.p. 48-50° (lit. (6) m.p. 50-51°). This product was extremely hygroscopic and turned to an oil almost immediately when exposed to atmospheric conditions.

5-Chloro-2-methyl-4-isothiazolin-3-one (VIIc).

To a slurry of 23.6 g. (0.10 mole) of IVb in 350 ml. of ethylene dichloride at 10-15° was added 54 g. (0.40 mole) of sulfonyl chloride over a period of 1.25 hours. The mixture was stirred for an additional 6 hours. Water (75 ml.) was then added to the cold mixture, and the resulting layers were separated. The ethylene dichloride layer was dried over magnesium sulfate and evaporated to an oil which solidified on standing. Recrystallization of this solid from ligroin (60-90°) gave 4 g. (13%) of VIIc, m.p. 54-55°.

2-n-Butyl-4-isothiazolin-3-one (IIIg).

To a suspension of 192 g. (0.60 mole) of IVe in 600 ml. of toluene at 40° was added 134 g. (1.90 mole) of chlorine over a period of one hour. After addition the mixture was evaporated under reduced pressure to give the light tan solid hydrochloride. This solid was added to a mixture of 300 ml. of water and 200 ml. of ether. Solid sodium bicarbonate was added in portions until the aqueous phase was at a pH of 7-8. The layers were then separated, and the water extracted with 3 x 200 ml. additional portions of ether. The combined ether extracts were dried over anhydrous magnesium sulfate, and the ether was evaporated to leave a dark oil. Vacuum distillation of this oil gave 173 g. (92%) of IIIg, b.p. 90-105° (0.4-0.8 mm), which on redistillation gave b.p. 96° (0.3 mm).

2-t-Octyl-4-isothiazolin-3-one (IIIh).

To a suspension of 208 g. (0.48 mole) of IVI in 480 ml. of toluene at 20-50° was added 107 g. (1.50 mole) of chlorine over a period of one hour. After addition the clear orange solution was allowed to cool and was then washed with 3 x 500 ml. portions of water. The toluene phase was then dried over anhydrous magnesium sulfate and evaporated under reduced pressure to give 193 g. (94%) of IIIh, m.p. 88-93°. Recrystallization of this material from ethyl acetate gave IIIh, as a white solid, m.p. 101-102°.

2-Benzyl-4-isothiazolin-3-one (IIIi) and 2-Benzyl-5-chloro-4-isothiazolin-3-one (VIIi).

To a suspension of 58.2 g. (0.15 mole) of IVr in 500 ml. of

ethylene dichloride at 10-15° was added dropwise 63.6 g. (0.47 mole) of sulfuryl chloride. After stirring overnight the clear, light amber solution was concentrated under reduced pressure to about 0.5 volume. A cream-colored solid separated and was collected by suction filtration. This solid was then slurried in 200 ml. of water, filtered, and dried to give 27 g. (47%) of III_t, m.p. 78-80°, not changed by recrystallization from benzene-hexane. The original ethylene dichloride filtrate was then evaporated under reduced pressure to leave a brown oil. Charcoal decolorization of this material in benzene, and crystallization from heptane gave 8 g. (12%) of VIId, m.p. 58-59°.

2-Benzyl-4,5-dichloro-4-isothiazolin-3-one (VHe).

To a suspension of 15 g. (0.039 mole) of IVr in 155 ml. of ethylene dichloride at 15° was added dropwise 38.4 g. (0.27 mole) of sulfuryl chloride. After addition the clear solution was allowed to stir at room temperature overnight. The solution was then evaporated under reduced pressure to give an amber oil. This oil was extracted with boiling heptane; on cooling a pale yellow solid separated. This solid on recrystallization from heptane yielded 5.5 g. (27%) of VIIe, m.p. 62-64°.

2-(4-Chlorophenyl)-4-isothiazolin-3-one (IIII).

To a suspension of 136 g. (0.32 mole) of IVjj in 320 ml. of toluene at 40-45° was added over a period of one hour 129 g. (0.96 mole) of sulfuryl chloride. During the addition the reaction mixture thickened considerably, and an additional 450 ml. of toluene was added to ease the stirring. After the addition the mixture was stirred for 0.5 hour and filtered. This solid was dried and then slurried in 600 ml. of water. Filtration and drying gave 96 g. (71%) of IIII, m.p. 142-144° after recrystallization from toluene.

4,5-Dichloro-3-hydroxyisothiazole (VIIIa).

To a solution of 5.1 g. (0.050 mole) of IIIa in 100 ml. of ethyl acetate at -5° was added 6.75 g. (0.050 mole) of sulfuryl chloride over a period of 20 minutes. The mixture was then allowed to warm to room temperature and stir overnight. Filtration of the mixture gave 2.6 g. (76%) of IIIa hydrochloride. The filtrate upon evaporation yielded 6.4 g. of a solid-oil residue. Trituration of this mixture with water then gave 3.3 g. (77% based on sulfuryl chloride) of VIIIa, m.p. 151-154° from benzene-ethanol.

4-Chloro-3-hydroxyisothiazole.

To a solution of 10.1 g. (0.1 mole) of IIIa in 100 ml. of EDC at 5-10° was added over a period of 45 minutes a solution of 13.5 g. (0.1 mole) of sulfuryl chloride in 10 ml. of EDC. Upon completion of the addition, the solid which had separated was collected, but turned to gum on the filter. This material was dissolved in water and extracted continuously with ether. Evaporation of the dried extracts gave 6.0 g. of the starting IIIa. The EDC filtrate from above was evaporated to a gummy solid. This material was dissolved in hot water, filtered to remove some tarry matter, and cooled to yield 0.5 g. of crude 4,5-dichloro-3-hydroxyisothiazole (VIIIa), m.p. 146-150°. The aqueous filtrate was then extracted continuously with ether. The dried extract on evaporation gave a gummy solid, which upon crystallization from EDC yielded 0.4 g. of 4-chloro-3-hydroxyisothiazole, m.p. 167-172°. This product was not purified further, but NMR analysis corroborated the assigned structure, δ (deuterated acetone) 8.80 (s, 5H).

4-Bromo-3-hydroxyisothiazole (IXa).

To a solution of 5.1 g. (0.050 mole) of IIIa in 100 ml. of ethyl

acetate at -5° was added dropwise 8 g. (0.050 mole) of bromine. The resulting suspension was allowed to come to room temperature and stir for several hours. The resulting slurry was then evaporated to an oil-solid residue, which on trituration with water gave 5.3 g. (60%) of IXa, m.p. 198-199° from ethyl acetate.

4,5-Dichloro-2-methyl-4-isothiazolin-3-one (VIIIb).

To a solution of 5.2 g. (0.045 mole) of IIIc in 100 ml. of ethyl acetate at -70° was added 6.08 g. (0.045 mole) of sulfuryl chloride over 45 minutes. The reaction was stirred at this temperature for 4 hours, and was then allowed to come to room temperature. The ethyl acetate was removed by evaporation from the reaction slurry, and the solid thus obtained was extracted with benzene. Filtration and evaporation of the benzene gave 4 g. (96% based on sulfuryl chloride) of VIIIb, m.p. 121-123° from chloroform.

4-Bromo-2-methyl-4-isothiazolin-3-one (IXb).

To a solution of 5.0 g. (0.043 mole) of IIIc in 100 ml. of ethylene dichloride at 0-5° was added dropwise over 35 minutes a solution of 6.94 g. (0.043 mole) of bromine in 25 ml. of ethylene dichloride. After addition the mixture was allowed to warm to room temperature and to stir for several hours. The mixture was then filtered to yield a red solid, which on solution in water and ether extraction gave 1.3 g. (16%) of IXb, m.p. 94-97° from ligroin (90-120°).

4-Bromo-2-*t*-butyl-4-isothiazolin-3-one (IXc).

To a solution of 7.8 g. (0.05 mole) of IIIh and 5.0 g. (0.05 mole) of triethylamine in 50 ml. of ethyl acetate was added at -5-0° over 15 minutes 8.0 g. (0.05 mole) of bromine in 20 ml. of ethyl acetate. A precipitate formed at once, and after 2.5 hours at room temperature the mixture was evaporated to a solid residue. This material was slurried first in water and then in ether to yield 6.6 g. (56%) of IXc, m.p. 150-153° from ether.

REFERENCES

- (1) A. Adams and R. Slack, *Chem. Ind.* (London), 1232 (1956).
- (2) A. R. Katritzky, Ed., "Advances in Heterocyclic Chemistry", Vol. 4, 111, Academic Press, New York and London, 1965.
- (3) J. Goerdeler and W. Mittler, *Chem. Ber.*, **96**, 944 (1963).
- (4) W. R. Hatchard, *J. Org. Chem.*, **28**, 2163 (1963).
- (5) J. Goerdeler and U. Keuser, *Chem. Ber.*, **97**, (11), 3106 (1964).
- (6a) W. D. Crow and N. F. Leonard, *Tetrahedron Letters*, 1477 (1964); (b) *J. Org. Chem.*, **30**, 2660 (1965).
- (7a) N. Kharasch, S. J. Potempa, and H. L. Wehrmeister, *Chem. Rev.*, **39**, 283 (1946); (b) I. B. Douglass, "Alkanesulfonyl Chlorides and Related Compounds", Vol. I, N. Kharasch, Ed., Pergamon Press, Inc., New York, N. Y., 1961, p. 350. (c) A. Luttringhaus and R. Schneider, *Angew. Chem. Int. Ed. Engl.*, **3**, 67 (1964).
- (8a) E. N. Givens and H. Kwart, *J. Am. Chem. Soc.*, **90**, 378 (1968). (b) K. R. Brower and I. B. Douglass, *ibid.*, **73**, 5787 (1951). (c) I. B. Douglass, K. R. Brower, and F. T. Martin, *ibid.*, **74**, 5770 (1952). (d) H. Brintzinger and H. Ellwanger, *Chem. Ber.*, **87**, 300 (1954).
- (9) G. A. Miller, E. D. Weiler, M. Hausman, "Isothiazoles II", *J. Heterocyclic Chem.*, **8**, 581 (1971).
- (10) E. Schjanberg, *Ber.*, **74**, 1751 (1941).
- (11) J. G. Murphy and J. F. Mulvaney, U. S. Patent 2,623,066 (1952).