Isothiazoles II: 5-Chloro-4-isothiazolin-3-ones

G. A. Miller, E. D. Weiler, and M. Hausman

Research Division, Rohm and Haas Company, Spring House, Pennsylvania 19477

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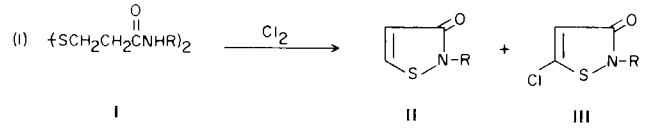
Quantitative gas chromatographic analysis of the 3-hydroxyisothiazole product distributions formed in the chlorine induced cyclization of 3,3′-dithiodipropionamide and 3-mercaptopropionamide has led to reaction conditions which yield respectively 3-hydroxyisothiazole, 5-chloro-3-hydroxyisothiazole, or 4,5-dichloro-3-hydroxyisothiazole as the predominant product. The 4-chloro analog was found in only small quantity. Similar glc analysis of the cyclization of *N,N′*-dimethyl-3,3′-dithiodipropionamide showed 5-chloro-2-methyl-4-isothiazolin-3-one to be the major 4-isothiazolin-3-one product under varied conditions. Also, a representative series of 5-chloro-2-substituted-4-isothiazolin-3-ones were prepared under extrapolated reaction conditions.

In a previous investigation (1) the chlorine induced cyclization of 3,3′-dithiodipropionamides (I) (eq. 1) was found to be a convenient and general synthesis of the 4-isothiazolin-3-one ring system II. Also in that study several 5-chloro-4-isothiazolin-3-ones (III) were identified as minor reaction products. Since reaction 1 is the only

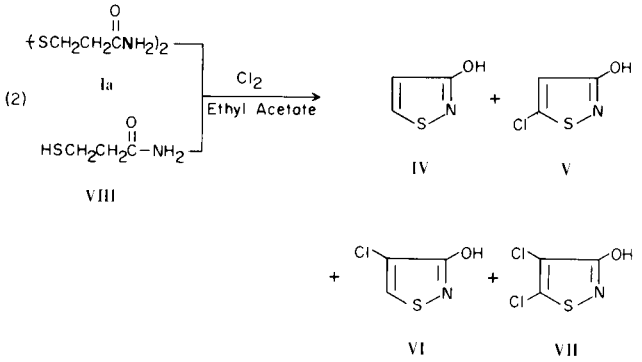


known source of III, the present work was conducted to determine quantitatively the product distributions of representative reactions and to manipulate conditions to allow the synthesis of additional examples of these derivatives.

3-Hydroxyisothiazole.

The 3-hydroxyisothiazole IV-VII product distributions obtained by the chlorination (eq. 2) of 3,3′-dithiodipropionamide (Ia) and the corresponding mercaptan VIII under varied conditions were determined by internal standard gas chromatographic analysis (Tables I and II).

Examination of reaction 2 showed considerable effect of chlorine equivalence, concentration, and temperature on product distribution. In fact, proper selection of these reaction variables yielded as the predominant product either 3-hydroxyisothiazole (IV, exp 1), 5-chloro-3-hydroxyisothiazole (V, exp 17), or 4,5-dichloro-3-hydroxyisothiazole (VII, exp 10). As expected from previous work (1) only trace amounts of 4-chloro-3-hydroxyisothiazole VI were obtained.



The mercaptoamide VIII usually gave a higher percentage of 5-chlorination than the disulfide Ia, although reactions of the two amides under identical conditions were not possible due to unmanageable gumming of the reaction mixtures under the same amide and chlorine modes of addition.

The incremental amide addition procedure was viewed as a means to limit the amide excess, thereby increasing the possibility of competitive chlorination of reaction intermediates (1) to yield 5-chlorinated products. However, little difference in product distribution was found using normal or incremental addition of either amide (compare exp 2-5 and 12-16). Nevertheless, the incremental addition had the practical advantage of avoiding reaction gumming or balling-up, particularly encountered with the mercaptoamide VIII, and provided a more manageable reaction slurry with disulfide-amide Ia at > 1 mole/l concentration.

TABLE I

Chlorination of 3,3′-Dithiodipropionamide (Ia)

Experiment	Mode of Add'n	Temp °C	Conc (b)	Equiv Cl_2	Yield % (c)	Purity % (d)	Composition % (a) IV	V	VI	VII	Comment
1	Normal	45	1	3.0	51	77	78	17	0	5	
2	"	45	2	3.0	37	72	36	53	0	11	Very thick reaction mixture
3	Incremental	25		3.0		Terminated due to gumming					Cl_2 ahead of amide
4	"	25		3.0		" " " "					Amide ahead of Cl_2
5	"	45	2	3.0	51	77	38	56	0	6	" " "
6	"	45	3	3.0	63	70	49	43	0	8	" " "
7	"	45	4	3.0	59	72	53	43	0	4	" " "
8	"	45	2	5.0	74	81	24	50	0	26	" " "
9	"	45	3	5.0	75	75	19	41	0	40	" " "
10	"	45	4	5.0	61	71	7	8	6	79	" " "

(a) Determined by internal standard glc analysis. (b) Moles of amide/per liter of ethyl acetate. (c) Based on a molecular weight of 136. (d) Total 3-hydroxyisothiazole content of the reaction product was determined by internal standard glc analysis.

TABLE II

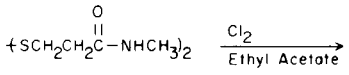
Chlorination of 3-Mercaptopropionamide (VIII)

Experiment	Mode of Add'n	Temp °C	Conc (b)	Equiv Cl_2	Yield % (c)	Purity % (d)	Composition % (a) IV	V	VI	VII	Comment
11	Normal	25	1.33	2.5	69	81	11	80	0	9	Transient gumming
12	"	25	1.33	3.0	83	88	13	74	1	12	" "
13	"	25	1.33	3.5	84	84	13	68	1	18	" "
14	"	45	1.33	3.0	78	83	12	66	2	20	" "
15	Incremental	25	1.33	3.0		Terminated due to gumming					Amide ahead of Cl_2
16	"	25	1.33	3.0	75	86	9	75	1	14	Cl_2 ahead of Amide
17	"	25	2.0	3.0	67	84	6	86	0	8	" " "
18	"	25	4.0	3.0	54	79	6	80	0	14	" " "
19	"	25	6.0	3.0	65	75	19	69	0	12	" " "
20	"	25	8.0	3.0	66	84	32	57	0	11	" " "
21	"	25	8.0	3.5	73	88	44	40	1	15	" " "
22	"	45	8.0	3.0	87	75	25	55	0	20	" " "
23	"	45	6.0	3.0	74	85	30	53	0	17	" " "
24	"	10	6.0	3.0	36	71	11	72	0	17	" " "

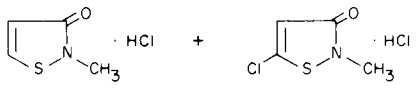
(a) Determined by internal standard glc. (b) Moles of amide/per liter of ethyl acetate. (c) Based on molecular weight of 136. (d) Total 3-hydroxyisothiazole content of the reaction product determined by internal standard glc.

2-Methyl-4-isothiazolin-3-one.

The chlorination-cyclization (eq. 3) of *N,N'*-dimethyl-3,3'-dithiodipropionamide (Ib) was examined in ethyl acetate varying the chlorine equivalence, the temperature, the concentration, and the mode of amide addition. The insoluble hydrochloride product mixtures were isolated by filtration and were analyzed by internal standard glc (Table III). In every reaction the hydrochloride product consisted of essentially only the 4-isothiazolin-3-ones IX and X. The ethyl acetate filtrates yielded on complete evaporation uncharacterized oils and small quantities of 4,5-dichloro-2-methyl-4-isothiazolin-3-one.

(3) 

Ib



IX X

Reaction 3 gave a reaction product consistently high in the 5-chlorinated product X (53-100 percent) and was not markedly influenced by reaction variables other than the chlorine equivalence. Use of 5.25 equivalents of chlorine, approximately stoichiometric for complete 5-chlorination, conveniently gave pure X (exp 11), although in poor yield (24%). At 3.15 chlorine equivalents, about stoichiometric for the non-chlorinated product IX, a 53:47 ratio of X to IX was formed in 56% yield (exp 7).

5-Chloro-2-substituted-4-isothiazolin-3-ones.

Based upon the results obtained in the formation of 5-chloro-3-hydroxyisothiazole (V) and 5-chloro-2-methyl-4-isothiazolin-3-one (X) several representative dithiodipropionamides (I) were cyclized to the respective 5-chloro-4-isothiazolin-3-ones (III) in low yields of isolated pure products (Table IV). The experimental conditions of these reactions - 4.1 equivalents of chlorine, incremental amide addition, 0°, and one mole/l concentration - were considered condusive to formation of 5-chlorinated products, but no effort was made to optimize the individual reactions.

The crude reaction mixtures obtained by this procedure consisted mainly of the 5-chlorinated products, the unchlorinated analogs II, and the 4,5-dichlorinated derivatives. The desired 5-chloro-4-isothiazolin-3-ones were isolated and purified by column chromatography, distillation, crystallization, and combinations of these techniques. The typical (1) nuclear magnetic resonance absorption of the 5-chloro products in the range δ 6.26-6.33 for the 4-H was of considerable aid as a guide in the identification, isolation, and purification of III.

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 a Perkin Elmer Model 202 Ultraviolet-Visible Spectrophotometer, and nmr spectra were recorded on a Varian T-60 Spectrometer. All nmr spectra were determined in deuterated chloroform solution with tetramethylsilane as an internal reference; the multi-

TABLE III

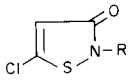
Chlorination of *N,N'*-Dimethyl-3,3'-dithiodipropionamide (Ib)

Experiment	Mode of Add'n	Temp °C	Conc (b)	Equiv Cl_2	Yield % (c)	Composition % (a) IX	X
1	Normal (d)	0	1	4.75	76	29	71
2	"	0	1	5.25	74	23	77
3	"	0	1	5.50	70	18	82
4	"	0	0.5	5.25	80	21	79
5	"	15	0.5	5.25	70	16	84
6	"	30	0.5	5.25	75	22	78
7	Incremental (e)	15	1	3.15	56	47	53
8	"	15	1	3.79	60	31	69
9	"	15	1	4.10	72	13	87
10	"	15	1	4.43	44	13	87
11	"	15	1	5.25	24	0	100
12	"	30	1	4.10	74	20	80
13	"	40	1	4.10	76	13	87

(a) Determined by internal standard glc analysis. (b) Moles of amide/per liter of ethyl acetate. (c) Based on a molecular weight of 186. (d) Amide Ib was prepared by aminolysis of dimethyl 3,3'-dithiodipropionate. (e) Amide Ib was prepared according to reference (1).

TABLE IV

5-Chloro-4-isothiazolin-3-ones (III)



R	b.p./m.p. °C	Yield %	Emperical Formula	Elemental Analysis Calcd. C	H	N	S	Found C	H	N	S
C_2H_5	63-64 (0.5 mm)	25	C_5H_6ClNOS	36.69	3.67	8.50	19.57	36.89	3.54	8.59	19.86
C_3H_7-*n*	61-62 (0.1)	22	C_6H_8ClNOS	40.56	4.51	7.89	18.03	40.41	4.73	7.75	18.09
C_4H_9-*n*	82-84 (0.1)	15	$C_7H_{10}ClNOS$	43.87	5.26	7.30	16.73	44.09	5.20	7.34	16.79
C_6H_{13}-*n*	87-94 (0.002)	17	$C_9H_{14}ClNOS$	49.20	6.38	6.38	14.58	49.12	6.34	6.19	14.55
C_8H_{17}-*n*	119-122 (0.001)	18	$C_{11}H_{18}ClNOS$	53.33	7.27	5.66	12.93	53.32	7.52	5.65	13.10
C_6H_5	118-120 (a)	16	C_9H_6ClNOS	51.06	2.84	6.62	15.15	51.03	3.06	6.50	14.94

(a) Recrystallized from methanol.

plicity of the absorption is shown in brackets: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet. Elemental analyses were performed by the analytical department of the Research Division of the Rohm and Haas Company.

The 3-hydroxyisothiazole (IV-VII) product mixtures were determined by internal standard gas chromatographic analysis with a Varian Aerograph Model 204 flame-ionization gas chromatograph. Durene was used as an internal standard, and the 3-hydroxyisothiazoles were converted prior to injection to their trimethylsilyl derivatives employing Regisil (Regis Chemical Co.), bis-(trimethylsilyl)trifluoroacetamide, in pyridine. A 10 ft. x 1/8 in. stainless steel column with a packing of 10% DC-11 on 80-100 mesh Gas Chrom Q at 130° achieved separation of the 3-hydroxyisothiazole components.

The 2-methyl-4-isothiazolin-3-one (IX and X) product mixtures were determined by internal standard gas chromatographic analysis with a Varian Aerograph Model 1700 flame-ionization gas chromatograph. A 4 1/2 ft. x 1/8 in. glass column with a packing of 7% OV-225 on 80-100 mesh Gas Chrom Q, Sylil 8 treated, at 135° allowed separation of the product components. Bibenzyl was utilized as an internal standard, and the samples were injected in pyridine solution.

The pure samples of 3-hydroxyisothiazoles IV-VII and 2-methyl-4-isothiazolin-3-ones IX and X required for internal standard glc were prepared as previously described (1). The dithiodipropionamide starting materials were prepared by aminolysis of dithiodipropionyl dichloride (1) and of the corresponding dimethyl ester.

2-Methoxyethyl 3-Mercaptopropionate.

A mixture of 53 g. (0.50 mole) of β-mercaptopropionic acid, 48 g. (0.63 mole) of 2-methoxyethanol, 2 ml. of concentrated sulfuric acid, and 88 ml. of benzene was heated at reflux, with a Dean-Stark trap provided for water removal. After 12.3 ml. of 2-methoxyethanol-water azeotrope had been removed, the benzene reaction solution was washed with 15% aqueous bicarbonate solution, and then with water. The oil obtained by evaporation was then distilled to give 60.5 g. (74%) of 2-methoxyethyl 3-mercaptopropionate, b.p. 64-66° (0.05 mm.).

Anal. Calcd. for $C_6H_{12}O_3S$: C, 43.95; H, 7.32; S, 19.50. Found: C, 43.63; H, 7.07; S, 19.58.

3-Mercaptopropionamide (VIII).

To 164 g. (2.73 moles) of 28.2% aqueous ammonium hydroxide was added dropwise over one hour 190 g. (1.16 moles) of 2-methoxyethyl 3-mercaptopropionate. Very little exotherm occurred, and after stirring for several hours the slurry was evaporated under vacuum at room temperature to leave a white solid residue. The last traces of water were then removed by azeotropic distillation with benzene to give finally 102 g. (85%) of VIII as a white granular solid, m.p. 95-97°.

Anal. Calcd. for C_3H_7NOS: C, 34.27; H, 6.66; N, 13.33; S, 30.45. Found: C, 34.41; H, 6.30; N, 13.15; S, 30.76.

3,3′-Dithiodipropionamide (Ia) (2).

A mixture of 630 g. (3.0 moles) of 3,3′-dithiodipropionic acid, 2520 g. (42 moles) of ethylene glycol, and 8.5 g. of concentrated sulfuric acid was stirred and heated at 100-110° under a vacuum of 25 mm. The reaction was continued under these conditions until two successive samples taken from the reaction solution gave the same acid number on titration. The reaction solution was then cooled to 25°. To 494 g. (0.5 mole) of this solution was added at 25-30° 52 g. (3.05 moles) of anhydrous ammonia over 90 minutes. The reaction was then stirred at 25° for 21 hours, during which time a precipitate began to form. The thick reaction slurry was then diluted with 1200 ml. of water; the solid was collected by filtration, washed thoroughly with water, and air dried to yield 83 g. (80%) of Ia, m.p. 170-172° (lit. (1) m.p. 169-171°).

3-Hydroxyisothiazoles (IV-VII).

The following experiments illustrate the general chlorination procedures employed.

(a) 3-Mercaptopropionamide (VIII).

(1) Normal addition.

A slurry of 10.5 g. (0.10 mole) of VIII in 75 ml. of anhydrous ethyl acetate (99.5%) was treated over 0.5 hour at 25° with 21.3 g. (0.3 mole) of chlorine gas which was added at a constant rate beneath the surface of the slurry. A short period of mild gumming or balling occurred early in the addition

but disappeared. At the completion of the chlorination, the reaction was allowed to stir at 25° over an additional one hour. The slurry was then diluted to about 150 ml. volume with ethyl acetate, and 10% aqueous sodium hydroxide solution was added at 20-25° until the aqueous phase was at *p*H 4.5-5.0. The layers were then separated, and the ethyl acetate solution was dried over anhydrous magnesium sulfate. Evaporation of the solvent then gave 11.3 g. of the crude mixture of 3-hydroxyisothiazoles which was analyzed by internal standard glc.

(2) Incremental addition.

To 50 ml. of anhydrous ethyl acetate at 25° was added 2.13 g. (0.03 mole) of chlorine gas at a rate of 0.71 g./minute. Then, maintaining the same chlorine addition rate, ten 1.05 g. (0.01 mole) portions of VIII were added at 3 minute intervals, keeping the temperature at 25° by cooling. The chlorine addition was terminated with the addition of the final amide portion. Following the addition the reaction slurry was treated as in a-1 to yield 9.15 g. of the crude 3-hydroxyisothiazole mixture.

In order to employ a higher equivalence of chlorine, the feed rate was adjusted to the appropriate level. To change the final slurry concentration, the total number of incremental additions was adjusted. Also, the portionwise amide addition was best accomplished through a wide-mouth, ground-glass addition funnel while applying a slight vacuum to the reaction flask. As a point of caution, chlorine reacts exothermically with ethyl acetate at temperatures higher than 35°; therefore, to carry out reactions at higher than 25° the chlorination was allowed to exotherm to the desired temperature after the initial portions of amide had been added.

(b) 3,3′-Dithiodipropionamide (Ia).

(1) Normal addition.

To a slurry of 20.8 g. (0.1 mole) of Ia in anhydrous ethyl acetate at the desired concentration level was added at 45° over 1 hour 21.3 g. (0.30 mole) of chlorine beneath the surface of the liquid. After the addition the slurry was treated as in a-1 to yield the crude mixture of 3-hydroxyisothiazoles.

(2) Incremental addition.

To 50 ml. of anhydrous ethyl acetate was added 2.08 g. (0.01 mole) of Ia. The reaction was then controlled to 45° and chlorine was added beneath the surface of the reaction at a rate of 0.35 g. (0.005 mole/minute) while eighteen 1.04 g. (0.005 mole) portions of amide were added at 3 minute intervals. The chlorine addition was continued at the initial rate for 6 minutes after the final amide portion. Following completion of addition the reaction slurry was treated as in a-1 to yield 14.0 g. of crude 3-hydroxyisothiazole mixture.

To increase the chlorine equivalence the feed rate was appropriately adjusted, and to increase the final slurry concentration the total number of amide portions was properly selected.

N,N-Dimethyl-3,3-dithiodipropionamide (Ib).

The following experiment illustrates the general ester aminolysis procedure employed.

To 132 g. (0.5 mole) of dimethyl 3,3-dithiodipropionate was added slowly a solution of 97 g. (1.25 mole) of 40% aqueous methylamine and 0.3 g. of concentrated hydrochloric acid in 162 ml. of water while maintaining the temperature near 5°. The solution was stirred at 5° for several hours and then allowed to warm to room temperature over night. The white, paste-like precipitate which had formed was filtered, washed with a small amount of water, and dried to provide 95 g. (80%) of Ib, m.p. 110-113° (lit. (1) m.p. 105-108°).

2-Methyl-4-isothiazolin-3-ones (IX and X).

The following experiments illustrate the general chlorination procedures utilized.

(1) Normal addition.

To a suspension of 23.6 g. (0.1 mole) of Ib in 100 ml. of anhydrous ethyl acetate at 0° was added 37.3 g. (0.525 mole) of chlorine over one hour. After completion of the chlorine addition, the reaction slurry was allowed to warm to room temperature and filtered; the precipitate was washed with small amounts of ethyl acetate and dried to give 26.0 g. of the mixture of IX and X which was analyzed by internal standard glc.

(2) Incremental addition.

To a slurry of 1.18 g. (0.005 mole) of Ib (1) in 100 ml. of anhydrous ethyl acetate at 15° was added 29.1 g. (0.410 mole) of chlorine over one hour while 38 portions (0.59 g., 0.0025 mole) of Ib were added simultaneously at 1.5 minute intervals. The thick, white slurry was allowed to warm to room temperature and was filtered to give 27.0 g. of the mixture of IX and X which was analyzed by internal standard glc.

5-Chloro-2-ethyl-4-isothiazolin-3-one.

To a slurry of 5.28 g. (0.02 mole) of *N,N′*-diethyl-3,3′-dithiodipropionamide (Ic) in 400 ml. of ethyl acetate at 0° was added 116.5 g. (1.64 moles) of chlorine over one hour while 38 portions (2.64 g., 0.01 mole) of Ic were added simultaneously at 1.5 minute intervals. The thick, white slurry was allowed to warm to room temperature and was filtered to give 69.1 g. of hydrochloride salt product. The filtrate on concentration yielded an additional 61.1 g. of this product. The hydrochloride salt was neutralized with aqueous sodium bicarbonate solution and ether extracted. The ether solution was dried over anhydrous magnesium sulfate and evaporated to give a slightly yellow oil. Vacuum distillation of this oil gave 16.3 g. (25%) of 5-chloro-2-ethyl-4-isothiazolin-3-one, b.p. 64° (0.5 mm); $n_D^{24.5}$ 1.5698; uv max (95% ethanol) 277 mμ (log ε 3.84); nmr δ 6.26 (s, 1, 4-H), 1.22 (t, 3, CH_3), 3.81 (q, 2, CH_2).

5-Chloro-2-*n*-propyl-4-isothiazolin-3-one.

To a slurry of 5.84 g. (0.02 mole) of *N,N′*-di-*n*-propyl-3,3′-dithiodipropionamide (Id) (1) in 400 ml. of ethyl acetate at 0° was added 116.5 g. (1.64 moles) of chlorine over one hour while 38 portions (2.92 g., 0.01 mole) of Id were added simultaneously at 1.5 minute intervals. During the addition the reaction mixture became progressively thicker. The slurry was allowed to warm to room temperature and was concentrated to yield after filtration 107 g. of crude hydrochloride salt product. The hydrochloride salt was neutralized with an aqueous sodium bicarbonate solution and ether extracted. The ether solution was dried over anhydrous magnesium sulfate and evaporated to yield a slightly yellow oil. Vacuum distillation of this oil gave 15.7 g. (22%) of 5-chloro-2-*n*-propyl-4-isothiazolin-3-one, b.p. 61-62° (0.10 mm); $n_D^{24.5}$ 1.5570; uv max (95% ethanol) 278 mμ (log ε 3.84); nmr δ 6.31 (s, 1, 4-H), 0.93 (t, 3, CH_3), 1.73 (m, 2, CH_2CH_3), 3.75 (t, 2, N-CH_2).

5-Chloro-2-*n*-butyl-4-isothiazolin-3-one.

To a slurry of 4.8 g. (0.015 mole) of *N,N′*-di-*n*-butyl-3,3′-dithiodipropionamide (Ie) (1) in 300 ml. of ethyl acetate at 0° was added 87.3 g. (1.23 moles) of chlorine over one hour while 38 portions (2.5 g., 0.007 mole) of Ie were added simultaneously at 1.5 minute intervals. The mixture was allowed to warm to room temperature and was then poured into 1500 ml. of water. The organic layer was separated, and the aqueous solution was extracted several times with ether. The combined organic solution

was washed with water, dried over anhydrous magnesium sulfate, and the ether removed to afford 90 g. of crude oil product. The oil was subjected to dry column chromatography (3) on Woelm Alumina, and the major 5-chloro-4-isothiazolin-3-one containing fractions were combined and distilled to give 8.0 g. (15%) of 5-chloro-2-*n*-butyl-4-isothiazolin-3-one, b.p. 82-84° (0.1 mm); $n_D^{24.5}$ 1.5409; uv max (95% ethanol) 278 mμ (log ε 3.80); nmr δ 6.27 (s, 1, 4-H), 0.95 (t, 3, CH_3), 1.60 (m, 4, C_2H_4), 3.75 (t, 2, N-CH_2).

5-Chloro-2-*n*-hexyl-4-isothiazolin-3-one.

To a slurry of 7.52 g. (0.02 mole) of *N,N'*-di-*n*-hexyl-3,3'-dithiodipropionamide (If) (1) in 400 ml. of ethyl acetate at 0° was added 116.5 g. (1.64 moles) of chlorine over one hour while 38 portions (3.76 g., 0.01 mole) of If was added simultaneously at 1.5 minute intervals. The reaction slurry was allowed to warm to room temperature and was then poured into 1500 ml. of water. The organic phase was separated, and the aqueous phase was extracted several times with ether. The combined organic solution was washed with water, dried over anhydrous magnesium sulfate, and the solvent was removed under reduced pressure to give 136 g. of crude oil product. The oil was subjected to dry column chromatography (3) on Woelm Alumina, and the major 5-chloro-4-isothiazolin-3-one containing fractions were combined and vacuum distilled to give 14.8 g. (17%) 5-chloro-2-*n*-hexyl-4-isothiazolin-3-one, b.p. 87-94° (0.002 mm); $n_D^{24.5}$ 1.5286; uv max (95% ethanol) 287 mμ (log ε 3.82); nmr δ 6.27 (s, 1, 4-H), 0.87 (t, 3, CH_3), 1.10-2.16 (m, 8, C_4H_8), 3.75 (t, 2, N-CH_2).

5-Chloro-2-*n*-octyl-4-isothiazolin-3-one.

To a slurry of 10.8 g. (0.025 mole) of *N,N'*-di-*n*-octyl-3,3'-dithiodipropionamide (Ig) (1) in 500 ml. of ethyl acetate at 0° was added 146 g. (2.05 moles) of chlorine over one hour while 38 portions (5.4 g., 0.0125 mole) of Ig were added simultaneously at 1.5 minute intervals. The mixture was allowed to warm to room temperature, and the slurry was concentrated to yield after filtration 266 g. of crude hydrochloride salt product. The hydrochloride salt was neutralized with aqueous sodium bicarbonate and ether extracted. The ether solution was dried over anhydrous magnesium sulfate and evaporated to give a dark oil. Vacuum distillation of this oil gave 22.3 g. (18%) of 5-chloro-2-*n*-octyl-4-isothiazolin-3-one, b.p. 119-122° (0.001 mm); $n_D^{24.5}$ 1.5214; uv max (95% ethanol) 278 mμ (log ε 3.84); nmr δ 6.27 (s, 1, 4-H), 0.87 (t, 3, CH_3), 1.07-2.05 (m, 12, C_6H_{12}), 3.75 (t, 2, N-CH_2).

5-Chloro-2-phenyl-4-isothiazolin-3-one.

To a slurry of *N,N'*-diphenyl-3,3'-dithiodipropionamide (Ih) (1) in 400 ml. of ethyl acetate at 0° was added 116.5 g. (1.64 moles) of chlorine over one hour while 38 portions (3.8 g., 0.01 mole) of Ih were added simultaneously at 1.5 minute intervals. The reaction slurry was allowed to warm to room temperature, and filtration afforded 56.8 g. of crude hydrochloride salt product. Trituration of the salt with water and repeated recrystallizations of the precipitate from methanol yielded 26.8 g. (16%) of 5-chloro-2-phenyl-4-isothiazolin-3-one, m.p. 118-120°; uv max (95% ethanol) 286 mμ (log ε 3.86); nmr δ 6.33 (s, 1, 4-H), 7.10-7.70 (m, 5, C_6H_5).

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