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Bromination of 4-isothiazolin-3-ones, I, gave the 4-bromo derivatives, III, in good yields, while formation of 4,5-dibromo derivatives, IV, was much more difficult. In contrast, chlorination of I, even under mild conditions, gave primarily 4,5-dichloro derivatives, VI, and lesser amounts of the 4-chloro derivatives, V. Vigorous bromination of the 4-methyl analog of I gave the 5-bromo derivatives, VIII, whereas mild chlorination gave predominantly the 4,5,5-trichloro derivatives, X.

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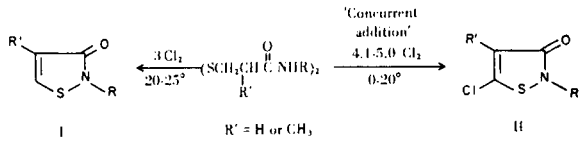
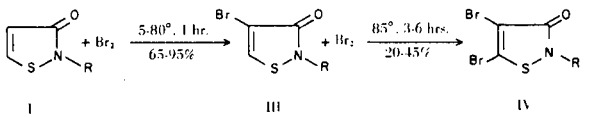
In a previous publication (1) we described a convenient and general synthesis of 4-isothiazolin-3-ones, I, by the chlorine induced cyclization of 3,3′-dithiodipropionamides and 3,3′-dithiodiisobutyramides. A variation of this general method, an incremental concurrent addition procedure, was developed to favor formation of 5-chloro-4-isothiazolin-3-one derivatives, II (2).

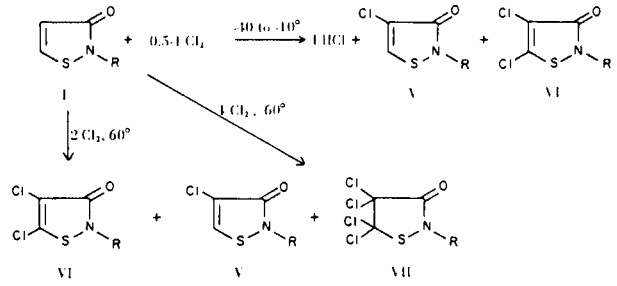



We now wish to report a dramatic difference in behavior of bromine and chlorine toward 4-isothiazolin-3-ones, I. Position-4 in I (R′ = H) is prone to electrophilic attack. Thus, bromination of I with one equivalent of bromine at temperatures between 5 and 80° gave the 4-bromo derivatives, III, in excellent yields. It was not possible, however, to obtain exclusively the 4,5-dibromo derivatives, IV, in one step from I even when 100 to 200% excess of bromine was used and the reaction mixture was heated at 80° for 24 hours. The reaction stalled after formation of the 4-bromo and a small amount of 4,5-dibromo derivative. Further bromination of crude or pure 4-bromo derivatives with an excess of bromine was sluggish even at elevated temperature and was always incomplete, most probably due to steric hindrance. The bulky bromine atom in the 4-position retards the addition of bromine across the double bond which must precede dehydrobromination. Furthermore, bromination was increasingly resisted as the alkyl group in the 2-position was replaced by aralkyl and then by cyclohexyl and, finally, was completely prevented by the 4-chlorophenyl

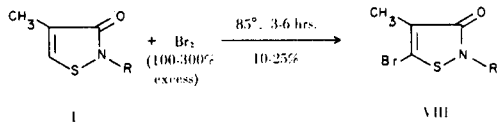



group even under more stringent conditions.

In contrast, it was not possible to stop chlorination of I at the mono chloro stage, even under very mild conditions. For example, chlorination of 2-*n*-octyl or 2-(4-chlorophenyl)-4-isothiazolin-3-one, I, with 0.5 to 1 equivalent of chlorine or sulfuryl chloride between -40 to -10° in various solvents gave starting material as the hydrochloride and an approximate 1:2 mixture of the 4-chloro, V, and 4,5-dichloro, VI, derivatives. Action of two equivalents of chlorine on I at 25 or 60° gave the 4,5-dichloro derivative, VI, as the major product with some 4,4,5,5-tetrachloro, VII, and 4-chloro, VI, derivatives (1), while exhaustive chlorination with excess of chlorine gave a similar mixture containing VII as the major product (3).




The bromination of various 4-methyl-2-substituted-4-isothiazolin-3-ones, I (R′ = $CH_3$), with 100% excess bromine at 80° was also very sluggish and the 5-bromo derivatives, VIII, were obtained only in a poor yield with a recovery of the starting material.

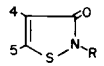



When the alkyl chain length was increased from $C_8$ to $C_{14}$, only a trace amount of 5-bromo derivative could be found, even though a large excess (300%) of bromine was used It is noteworthy that unlike the 4-bromo-2-(4-chlorophenyl) derivative, the 4-methyl analog could be converted to the 5-bromo derivative; the yield, however, was very poor.

In contrast to bromination, the chlorination reaction of I (R′ = $CH_3$) was so facile and rapid that it was not possible to stop it at the 5-chloro stage, IX, even though the reaction was carried out at room temperature using one equivalent of sulfuryl chloride. Unlike bromine, two equivalents of chlorine or sulfuryl chloride readily gave

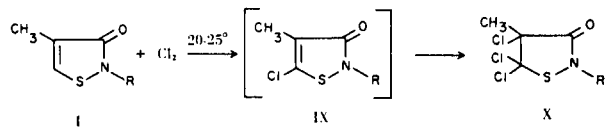
TABLE I

Bromo Derivatives of 2-Substituted-4-isothiazolin-3-ones



| R | 4 | 5 | M.p. or B.p. °C | Recrystallization Solvent | Yield % | Empirical Formula | Calcd. C | Calcd. H | Calcd. N | Calcd. S | Calcd. Br | Found C | Found H | Found N | Found S | Found Br |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| $CH_3$ | Br | Br | 150-153 | Methanol | 22 (a) | $C_4H_3Br_2NOS$ | 17.58 | 1.10 | 5.13 | 11.72 | — | 17.59 | 1.05 | 5.16 | 11.79 | — |
| $CH_3$ | $CH_3$ | Br | 80-83 | Ether | 9 | $C_5H_6BrNOS$ | 28.56 | 2.91 | 6.73 | 15.41 | — | 29.14 | 2.76 | 6.70 | 15.26 | — |
| $C_4H_9$-*n* | Br | H | 135-145/ 0.25 mm | – | 35 | $C_7H_{10}BrNOS$ | 35.59 | 4.24 | 5.93 | 13.56 | 33.90 | 36.18 | 4.39 | 6.19 | 13.58 | 33.95 |
| $C_4H_9$-*n* | Br | Br | 49-52 | Ether | 26 (a) | $C_7H_9Br_2NOS$ | 26.68 | 2.89 | 4.45 | 10.18 | — | 26.78 | 2.92 | 4.35 | 10.31 | — |
| $C_4H_9$-*n* | $CH_3$ | Br | 81-85/ 0.1 mm | – | 15 | $C_8H_{12}BrNOS$ | 38.40 | 4.84 | 5.60 | 12.81 | — | 38.86 | 5.24 | 5.81 | 12.48 | — |
| $C_4H_9$-*sec* | $CH_3$ | Br | 92-95/ 0.5 mm | – | 24 | $C_8H_{12}BrNOS$ | 38.40 | 4.84 | 5.60 | 12.81 | — | 39.00 | 4.80 | 5.76 | 12.65 | — |
| $C_6H_{11}$*cyclo* | Br | H | 157-160 | Ethyl Acetate | 75 | $C_9H_{12}BrNOS$ | 41.22 | 4.58 | 5.34 | 12.21 | 30.53 | 40.77 | 4.62 | 5.20 | 12.31 | 30.78 |
| $C_6H_{11}$*cyclo* | Br | Br | 167-169 | Ethyl Acetate | 20 (b) | $C_9H_{11}Br_2NOS$ | 31.67 | 3.22 | 4.10 | 9.38 | 46.92 | 31.79 | 3.24 | 4.28 | 9.47 | 46.48 |
| $C_6H_{13}$-*n* | Br | H | 64-66 | *n*-Hexane | 86 | $C_9H_{14}BrNOS$ | 40.91 | 5.30 | 5.30 | 12.12 | — | 40.86 | 5.41 | 5.60 | 11.87 | — |
| $C_6H_{13}$-*n* | Br | Br | 64-66 | Ethanol | 37 (a) | $C_9H_{13}Br_2NOS$ | 31.50 | 3.83 | 4.08 | 9.34 | — | 31.64 | 4.09 | 4.24 | 9.15 | — |
| $C_8H_{17}$-*n* | Br | H | 47-49 | *n*-Hexane | 65 | $C_{11}H_{18}BrNOS$ | 45.21 | 6.16 | 4.79 | 10.96 | 27.42 | 45.18 | 6.23 | 4.80 | 10.73 | 27.90 |
| $C_8H_{17}$-*n* | Br | Br | 58-60 | Ether | 20 (a) | $C_{11}H_{17}Br_2NOS$ | 35.59 | 4.63 | 3.77 | 8.64 | — | 35.77 | 4.58 | 3.73 | 8.61 | — |
| $C_8H_{17}$-*n* | $CH_3$ | Br | 128-135/ 0.25 mm | – | 20 | $C_{12}H_{20}BrNOS$ | 47.05 | 6.59 | 4.57 | 10.47 | — | 47.51 | 6.66 | 4.53 | 10.48 | — |
| $C_{10}H_{21}$-*n* | Br | H | 38-40 | *n*-Hexane | 81 | $C_{13}H_{22}BrNOS$ | 48.75 | 6.88 | 4.38 | 10.00 | 25.00 | 48.86 | 7.04 | 4.62 | 9.92 | 25.19 |
| $C_{10}H_{21}$-*n* | Br | Br | 65-67 | *n*-Pentane | 45 (a) | $C_{13}H_{21}Br_2NOS$ | 39.12 | 5.30 | 3.51 | 8.03 | 40.03 | 39.56 | 5.35 | 3.42 | 8.82 | 39.65 |
| $C_{12}H_{25}$-*n* | Br | H | 46-48 | *n*-Pentane | 86 | $C_{15}H_{26}BrNOS$ | 51.72 | 7.52 | 4.02 | 9.21 | 22.94 | 51.82 | 7.79 | 3.98 | 9.31 | 23.21 |
| $C_{12}H_{25}$-*n* | Br | Br | 67-69 | *n*-Hexane | 41 (b) | $C_{15}H_{25}Br_2NOS$ | 42.17 | 5.90 | 3.28 | 7.50 | 37.39 | 42.57 | 6.02 | 3.23 | 7.86 | 36.68 |
| $C_6H_4Cl$ (4) | Br | H | 194-196 | Ethyl Acetate | 95 | $C_9H_5BrClNOS$ | 37.18 | 1.72 | 4.82 | 11.02 | 27.54 | 37.35 | 1.60 | 4.58 | 10.98 | 27.99 |
| $C_6H_4Cl$ (4) | $CH_3$ | Br | 120-122 | – | 9 | $C_{10}H_7BrClNOS$ | 39.45 | 2.32 | 4.60 | 10.53 | — | 39.81 | 2.34 | 4.33 | 10.54 | — |
| $CH_2C_6H_4Cl$ (4) | Br | H | 134-136 | 2-Propanol | 73 | $C_{10}H_7BrClNOS$ | 39.45 | 2.32 | 4.60 | 10.53 | 26.21 (c) | 39.12 | 2.28 | 4.64 | 10.57 | 25.92 (c) |
| $C_2H_4C_6H_5$ | Br | H | 110-112 | Ethyl Acetate | 63 | $C_{11}H_{10}BrNOS$ | 46.49 | 3.55 | 4.93 | 11.28 | 28.12 | 46.24 | 3.39 | 4.95 | 11.07 | 28.49 |
| $C_2H_4C_6H_5$ | Br | Br | 111-113 | Ethyl Acetate | 32 (b) | $C_{11}H_9Br_2NOS$ | 36.39 | 2.50 | 3.86 | 8.83 | 44.02 | 36.86 | 2.60 | 3.76 | 8.50 | 43.83 |

(a) Based on 4-isothiazolin-3-one. (b) Based on 4-bromo-4-isothiazolin-3-one. (c) Calcd. Cl, 11.64; Found 11.51.



I IX X

the 4,5,5-trichloro derivatives, X, in high yields (3).

The crude products were purified by recrystallization, distillation or by dry column chromatography. Elemental analysis, ir and nmr spectral data are consistent with the assigned structures. Table I summarizes the pertinent data on bromo derivatives of 2-substituted-4-isothiazolin-3-ones. No effort was made to optimize the reported yields.

## EXPERIMENTAL

Melting points were determined using a Thomas-Hoover capillary melting point apparatus, and are uncorrected. Ir spectra were taken as mineral oil mulls on a Perkin-Elmer Infracord, Model 137. Elemental analyses were performed by the analytical department of the Research Division of the Rohm and Haas Company. The following experiments illustrate the general reaction procedures employed.

4-Bromo-2-cyclohexyl-4-isothiazolin-3-one.

To a solution of 229.0 g. (1.25 moles) of 2-cyclohexyl-4-isothiazolin-3-one in 2.5 l. of dry ethyl acetate was added dropwise 200 g. (1.25 moles) of bromine. The mixture was heated to 80°, allowed to cool to room temperature and then concentrated to dryness under reduced pressure. The residue was dissolved in chloroform, washed several times with water, dried (magnesium sulfate) and concentrated to give 322 g. of a solid. Recrystallization from ethyl acetate gave 240 g. (75%) of the product, m.p. 157-160°; ir: 6.1 $\mu$ (C=O).

4,5-Dibromo-2-cyclohexyl-4-isothiazolin-3-one.

To a solution of 150 g. (0.57 mole) of 4-bromo-2-cyclohexyl-4-isothiazolin-3-one in 1 l. of dry 1:1 (v:v) *N,N*-dimethylformamide:ethyl acetate was added dropwise 91.2 g. (0.57 mole) of bromine. The mixture was heated under reflux at 80° for 16 hours. Tlc (silica gel, diisopropyl ether) indicated incomplete conversion. An additional 91.2 g. (0.57 mole) bromine was added and heating continued for 3 hours. Tlc still indicated incomplete conversion. The mixture was concentrated, poured into water and extracted into chloroform. The chloroform extract was washed (water) and concentrated to give a mushy solid. The residue was triturated with 200 ml. of methanol and filtered to give 68.7 g. of a white solid. Recrystallization (2X) from methanol gave 38.6 g. (20%) of the desired product, m.p. 167-169°; ir: 6.1 $\mu$ (C=O).

4-Bromo-2-phenethyl-4-isothiazolin-3-one.

To a solution of 41.0 g. (0.2 mole) of 2-phenethyl-4-isothiazolin-3-one in 300 ml. of dry 1:1 (v:v) DMF:ethyl acetate was added dropwise 96.0 g. (0.6 mole) of bromine and the mixture heated to 80° for 3 hours. Tlc indicated the presence of 4-bromo as the major product and a very small amount of 4,5-dibromo derivative. The mixture was concentrated and the residue was dissolved in chloroform. The solution was washed with aqueous sodium bicarbonate, followed by water, dried (magnesium sulfate) and concentrated. The residue was recrystallized from ethyl acetate to give 35.7 g. (63%) of the product, m.p. 105-107°; ir: 6.1 $\mu$ (C=O).

4,5-Dibromo-2-phenethyl-4-isothiazolin-3-one.

To a solution of 30.36 g. (0.11 mole) of 4-bromo-2-phenethyl-4-isothiazolin-3-one in 250 ml. of dry 1:1 (v:v) DMF:ethyl acetate was added 51.3 g. (0.32 mole) of bromine and the mixture was heated at 80° for a period of 4.5 hours. The work-up as above gave 36.2 g. of a crude product, which was found to be a mixture of ~ 1:1 4-bromo and 4,5-dibromo derivatives by nmr analysis. These two derivatives could not be separated by fractional cryatallization from ethyl acetate. Dry column chromatography (trichloroethylene, silica gel) gave 14.5 g. (36%) of the product as an off-white solid. Final crystallization from 80 ml. of ethyl acetate gave 12.6 g. (32%) of pure 4,5-dibromo compound, m.p. 111-113°; ir: 6.05 $\mu$ (C=O).

4,5-Dibromo-2-methyl-4-isothiazolin-3-one.

To a solution of 111.0 g. (0.96 mole) of 2-methyl-4-isothiazolin-3-one in 300 ml. of dry 1:1 (v:v) DMF:ethyl acetate was added in portions a total of 180.0 g. (1.0 mole) of bromine. A vigorous reaction accompanied the addition of each portion of bromine and occasional external cooling was used to keep the temperature of the mixture below 70°. The mixture was allowed to cool to room temperature and was then concentrated. The residue was dissolved in chloroform, washed several times with water, dried (magnesium sulfate) and concentrated to give crude 4-bromo-2-methyl-4-isothiazolin-3-one. Bromination of this intermediate was carried out using the same quantities of bromine and solvents as before. The temperature was kept in the range of 70-80° by heating for 2.5 hours. The mixture was worked up as described above. The crude product was washed with methanol to give 60 g. (22%) of product, m.p. 150-153°; ir: 6.10 $\mu$ (C=O).

4,5-Dibromo-2-*n*-octyl-4-isothiazolin-3-one.

To a solution of 21.3 g. (0.1 mole) of 2-*n*-octyl-4-isothiazolin-3-one in 100 ml. of dry 1:1 (v:v) DMF:ethyl acetate was added 48.0 g. (0.3 mole) of bromine. The temperature of the mixture rose to 65° and was held in the range of 60-70° for 2.75 hours by external heating. The ethyl acetate was then removed under reduced pressure and the residue diluted with approximately 300 ml. of water. The layers were separated and the organic layer was washed several times with water, then dissolved in chloroform, dried (magnesium sulfate) and concentrated to give crude 4-bromo-2-*n*-octyl-4-isothiazolin-3-one. Bromination of this material using the same quantities of reagents and reaction conditions gave 35.3 g. of crude 4,5-dibromo-2-*n*-octyl-4-isothiazolin-3-one. The material was washed with heptane and the heptane-soluble portion was recrystallized from ether to give 7.4 g. (20%) of pure product, m.p. 58.5-60.5°; ir: 6.10 $\mu$ (C=O).

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

To a stirred solution of 150 g. (0.7 mole) of 2-*n*-octyl-4-isothiazolin-3-one in 1 l. of ethyl acetate was added dropwise 94.5 g. (0.7 mole) of sulfuryl chloride while maintaining the temperature below -10°. At the end of addition, the mixture was degassed and filtered to recover 70.3 g. (40%) of hydrochloride salt of starting material. The filtrate was concentrated to give 112.1 g. of a mushy residue which was found to be a mixture of ~ 1:2 4-chloro (Rf 0.40) and 4,5-dichloro (Rf 0.57) derivatives by nmr analysis. The residue, 40 g., was separated by dry column chromatography (diisopropyl ether, silica gel) to give 13.1 g. (35%) of the product, m.p. 33-35° (hexane); ir: 6.1 $\mu$ (C=O).

*Anal.* Calcd. for $C_{11}H_{18}ClNOS$: C, 53.32; H, 7.32; N, 5.65; Cl, 14.31; S, 12.94. Found: C, 53.02; H, 7.24; N, 5.83; Cl, 14.73; S, 13.01.

4,5-Dichloro-2-*n*-octyl-4-isothiazolin-3-one.

To a solution of 833 g. (3.9 mole) of 2-*n*-octyl-4-isothiazolin-3-one in 950 ml. of ethyl acetate was added dropwise 1053 g. (7.8 moles) of sulfuryl chloride over a period of 3 hours while maintaining the temperature at 70°. At the end of addition, the solvent was removed under reduced pressure at 50° to give 1122 g. of a viscous liquid residue. Glc analysis showed the crude product to contain 21.4% of the 4,4,5,5-tetrachloro derivative, 59.0% of 4,5-dichloro derivative and 19.5% of the 4-chloro derivative with respective Rf values of 0.64, 0.55, and 0.4 on tlc (silica, IPE). The crude product was crystallized from 1.4 l. of hexane to give 563 g. (51%) of the product; 99.1% pure (by glc), m.p. 44-46°; ir: 5.95 $\mu$ (C=O).

*Anal.* Calcd. for $C_{11}H_{17}Cl_2NOS$: C, 46.80; H, 6.07; N, 4.96; Cl, 25.12; S, 11.36. Found: C, 46.58; H, 6.15; N, 4.97; Cl, 25.52; S, 11.51.

5-Bromo-2-*n*-butyl-4-methyl-4-isothiazolin-3-one.

To a solution of 5.5 g. (0.03 mole) of 2-*n*-butyl-4-methyl-4-isothiazolin-3-one in 30 ml. of dry 1:1 (v:v) DMF:ethyl acetate was added 10.2 g. (0.06 mole) of bromine. The temperature of the mixture rose to approximately 60° and was held in the range of 60-65° by external heating for 2 hours. The mixture was then concentrated and the residue washed several times with water. The oil was dissolved in chloroform, dried (magnesium sulfate) and concentrated to give 5.6 g. (70%) of crude product which was purified first by dry column chromatography (1% acetone in benzene, silica gel; product Rf $\approx$ 0.4) then by distillation to give 1.2 g. (15%) of product, b.p. 81-85°/0.1 mm; ir: 6.10 $\mu$ (C=O).

5-Bromo-4-methyl-2-*n*-octyl-4-isothiazolin-3-one.

To a solution of 15.0 g. (0.07 mole) of 4-methyl-2-*n*-octyl-4-isothiazolin-3-one in 60 ml. of dry 1:1 (v:v) DMF:ethyl acetate was added 23.0 g. (0.13 mole) of bromine. The temperature of the mixture rose to approximately 80° and was held at 80-85° for 1.5 hours by external heating. The ethyl acetate was then removed and the residue was washed several times with water, taken up in chloroform, dried (magnesium sulfate) and concentrated. Hexane extraction and evaporation of the hexane gave 11.2 g. of material which was further purified by dry column chromatography (1% acetone in benzene, silica gel) followed by distillation to give 4.0 g. (20%) of product; b.p. 128-135°/0.25 mm; ir: 6.05 $\mu$ (C=O).

5-Bromo-4-methyl-2-(4-chlorophenyl)-4-isothiazolin-3-one.

To a solution of 4.5 g. (0.02 mole) of 2-(4-chlorophenyl)-4-methyl-4-isothiazolin-3-one in 100 ml. dry 1:1 (v:v) DMF:ethyl acetate was added 3.2 g. (0.02 mole) of bromine at room temperature. The mixture was heated to 85° for a period of 3 hours. Tlc (silica, IPE) showed formation of the 5-bromo derivative in trace amount. An additional 3.2 g. (0.02 mole) of bromine was added and heating continued for 5 hours. Tlc showed the presence of the desired product (Rf 0.53) in small amount and a substantial amount of unchanged starting material. The reaction mixture was worked up as above to give 4.1 g. of a crude product. Dry column chromatography (diisopropyl ether, silica gel) provided 0.56 g. (9.2%) of the product, m.p. 120-122°; ir: 6.05 $\mu$ (C=O).

4,5,5-Trichloro-4-methyl-2-(4-chlorophenyl)isothiazolidin-3-one.

To a slurry of 4.5 g. (0.02 mole) of 2-(4-chlorophenyl)-4-methyl-4-isothiazolin-3-one in 150 ml. of ethyl acetate was added dropwise 2.7 g. (0.02 mole) of sulfuryl chloride. The mixture was stirred for 1 hour. Tlc (silica, IPE) showed the trichloro derivative (Rf 0.61), traces of the 5-chloro derivative (Rf 0.54) and unchanged starting material (0.28). An additional 2.7 g. (0.02 mole) of sulfuryl chloride was added and stirred 1 hour at 40°. The reaction mixture was concentrated to dryness, the residue dissolved in 100 ml. of ether, washed, dried (magnesium sulfate) and concentrated to give 4.6 g. of crude product. Further purification *via* dry column chromatography (diisopropyl ether, silica gel) gave 3.95 g. (60%) of the solid product, m.p. 71-73°; ir: 5.8 $\mu$ (C=O).

*Anal.* Calcd. for $C_{10}H_7Cl_4NOS$: C, 36.29; H, 2.13; Cl, 42.83; N, 4.23; S, 9.68. Found: C, 35.84; H, 2.14; Cl, 42.78; N, 3.99; S, 9.76.

Acknowledgement.

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