Anal. Calcd. for $C_2H_9N_{11}$: C, 12.83; H, 4.85; N, 82.32. Found: C, 12.87; H, 3.57; N, 83.07.

C.—Procedure B was followed except that 14.7 g. (0.1 mole) of potassium dicyanoguanidine was used instead of the sodium dicyanamide and the filtered, hot solution immediately was acidified with 25 ml. of hydrochloric acid. The product was removed after the solution had cooled to 25°, washed with cold water, and air-dried; the yield was 11.6 g. (67%). Recrystallization from water gave rosettes of coarse, white needles, whose infrared spectrum was identical with that for **31** monohydrate made by methods A or B.

Anal. Calcd. for $C_2H_3N_9 \cdot H_2O$: C, 14.04; H, 2.95; N, 73.67. Found: C, 14.00, 14.23; H, 2.90, 2.95; N, 73.36, 73.72.

N-(1-Methyl-5-tetrazolyl)-N-(5-tetrazolyl)amine.—A solution consisting of 0.95 g. of **34**, 0.42 g. of sodium azide, and 0.62 g. of trimethylammonium chloride in 10 ml. of water was heated overnight on the steam bath, acidified with 3 ml. of concentrated hydrochloric acid, and cooled to 0°. The yield of precipitated solid after filtration, washing, and drying was 0.5 g. Only 35 mg. of the title compound was recovered, as the less-soluble fraction, after fractional crystallization from water; the bulk of the material proved to be **8**. Recrystallization from water gave rosettes of white needles, decomposing at 242–243°.

Anal. Calcd. for $C_3H_5N_9$: C, 21.56; H, 3.02; N, 75.43. Found: C, 21.51; H, 3.56; N, 74.94.

The Synthesis of Isothiazoles. I. 3,5-Dichloro-4-isothiazolecarbonitrile and Its Derivatives

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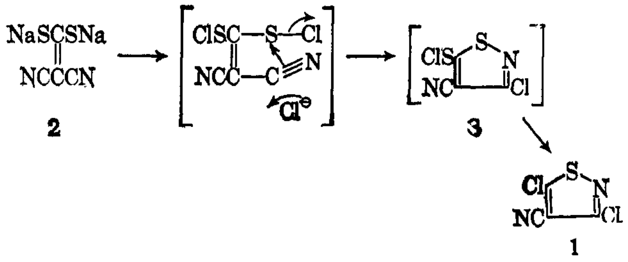
Received August 26, 1963

In a new synthesis of isothiazoles, 3,5-dichloro-4-isothiazolecarbonitrile (1) has been prepared by the treatment of di(sodiomercapto)methylenemalononitrile (2) with excess chlorine in boiling carbon tetrachloride. Nucleophilic reagents react with 1 under mild conditions to replace the chlorine atom in the 5-position. A series of 5-substituted 3-chloro-4-isothiazolecarbonitriles has been prepared from amines, alkoxides, phenolates, and anionic sulfur reagents. Replacement of both halogens of compound 1 resulted in a mixture of 3,5-disubstituted isothiazoles and products formed by ring opening. Hydrolysis of the 3,5-disubstituted 4-isothiazolecarbonitriles led to amide, acid, and ester derivatives.

Few syntheses of mononuclear isothiazoles have been described and, indeed, until recently, this heterocycle has been unknown. The first preparation of isothiazole and its derivatives stemmed from a classical synthesis by oxidation of an aminobenzisothiazole.[1] Subsequently the same workers[2] described the synthesis of 5-aminoisothiazole derivatives by a ring closure involving oxidation of substituted β-iminothioamides, a synthesis discovered and extended independently by Goerdeler.[3] In other syntheses, isothiazole and simple alkylisothiazoles have been made by cyclization of sodium acrolein-3-thiosulfate or acrolein-3-thiocyanate in liquid ammonia[4] and by the hot-tube reaction of olefins, sulfur dioxide, and ammonia.[5] 3,5-Diphenylisothiazole has been prepared from diphenyl dithiolium perchlorate.[6]

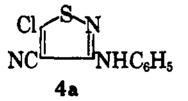
We now have found that substituted isothiazoles may be synthesized by ring closure of 2-cyano-1-mercaptoethylene derivatives. The present paper reports the synthesis of 3,5-dichloro-4-isothiazolecarbonitrile (1) in 57% yield by treatment of di(sodiomercapto)methylenemalononitrile (2) with excess chlorine in boiling carbon tetrachloride. Compound 1 has proved to be a reactive intermediate for preparation of variously substituted isothiazole derivatives. It is a stable, white, crystalline solid, m.p. 65–66°, that is insoluble in water, very soluble in organic solvents, and readily purified by recrystallization or sublimation.



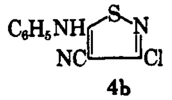
The reaction probably proceeds by a mechanism involving conversion of the bismercaptide to a bissulfenyl halide that cyclizes by addition of a sulfenyl halide or sulfenium ion to the nitrile to form the isothiazolesulfenyl halide intermediate (**3**). In the presence of excess chlorine, **3** is converted to **1** and sulfur chlorides by a process similar to the overchlorination of trichlorosulfenyl chloride to form carbon tetrachloride.[7]

An analogous 3,5-dibromo-4-isothiazolecarbonitrile was prepared in low yield by the action of bromine on 2.

Reaction with Nucleophilic Reagents.—Nucleophilic agents react with 1 under mild conditions to replace one of the chlorine atoms. It is not immediately apparent which chlorine is more active since valid arguments may be proposed for the high activity of either. The 3-chlorine atom might be considered analogous to that of an imino chloride or of an α-chloro nitrogen heterocycle, both of which show high reactivity. On the other hand, the 5-chlorine atom is analogous to that of an α-chlorothiophene where activity is increased by the nitrile group. The structure of the monosubstitution product from aniline might be either **4a** or **4b**.



4a



4b

That replacement of halogen occurred in the 5-position

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(1) A. Adams and R. Slack, *Chem. Ind.* (London), 1232 (1956).

(2) A. Adams and R. Slack, *J. Chem. Soc.*, 3061 (1959).

(3) (a) J. Goerdeler and H. W. Pohland, *Chem. Ber.*, **94**, 2950 (1961); (b) **96**, 526 (1963); (c) J. Goerdeler and W. Mittler, *ibid.*, **96**, 944 (1963); (d) J. Goerdeler and H. Horn, *ibid.*, **96**, 1550 (1963).

(4) F. Wille, *Angew. Chem.*, **74**, 467 (1962).

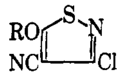
(5) F. Hubenett, F. H. Flock, and H. Hofman, *ibid.*, **74**, 653 (1962).

(6) D. Leaver and W. A. H. Robertson, *Proc. Chem. Soc.*, 252 (1960).

(7) G. Sosnovsky, *Chem. Rev.*, **58**, 509 (1958).

TABLE I

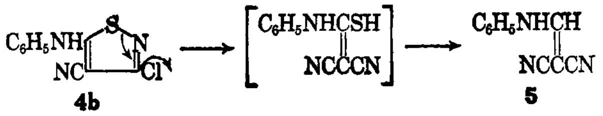
5-ALKOXY- AND 5-ARYLOXY-3-CHLORO-4-ISOTHIAZOLECARBONITRILES



R	Yield, %	M.p., °C.	Formula	Analysis, %				λ_{max}^{alc}, mμ (ε)
					C	H	Other	
CH_3	76[a,b]	106.5–107.5	$C_5H_3ON_2ClS$	Calcd.	34.4	1.72	174[c]	247 (6300)
				Found	34.2	1.97	174	
C_2H_5	94[d]	59.5–60.5	$C_6H_5ON_2ClS$	Calcd.	38.2	2.67		248 (6840)
				Found	38.1	2.94		
$C_6H_5CH_2$	e	136–138	$C_{11}H_7ON_2ClS$	Calcd.	52.7	2.81	11.1[f]	246 (8380)
				Found	51.6	2.62	10.8	
C_6H_5	84[d]	69–71	$C_{10}H_5ON_2ClS$	Calcd.	50.7	2.14		250 (8900)
				Found	50.0	2.14		
p-ClC_6H_4	92[g]	87.5–88.5	$C_{10}H_4N_2OSCl$	Calcd.	44.3	1.47	26.2[h]	252 (10,000)
				Found	44.4	1.27	26.1	

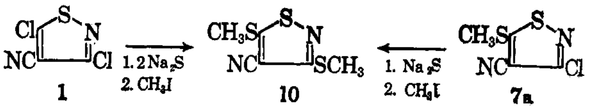
[a] $NaOCH_3$ in THF, 60% yield with Na_2CO_3 in methanol. [b] Excess ether–alcohol. [c] Mol. wt. mass spec. [d] Excess aqueous alcohol. [e] From $NaOCH_2C_6H$ on **7a**, yield not calculated. [f] % nitrogen. [g] Excess methanol. [h] % chlorine.

rather than the 3-position was demonstrated by the Raney nickel desulfurization[2] of the monoanilino product (**4a** or **b**) to give the known anilinomethylenemalononitrile[8] (**5**) which could arise only from **4b** by a ring-opening reaction regenerating a nitrile group.



4b **5**

Replacement of both halogen atoms of **1** did not occur readily nor in a straightforward manner. Only monosubstitution products were obtained when solutions of the dichloro compound (**1**) in nonpolar solvents were treated with an excess of ammonia or alkylamines. Under more strenuous conditions, replacement of the 3-chlorine also occurred, but this reaction was complicated by ring-opening reactions apparently stemming from attack of the nucleophile on the sulfur atom. For example, addition of one molar equivalent of **1** to an aqueous alcoholic solution of two molar equivalents of sodium sulfide, followed by alkylation with methyl iodide, yielded a mixture of 3,5-bis(methylthio)-4-isothiazolecarbonitrile (**10**) and 1,1-bis(methylthio)-2,2-dicyanoethylene (**11**).[9] The same products were isolated from reaction of 3-chloro-5-methylthio-4-isothiazolecarbonitrile (**7a**) with one mole of sodium sulfide followed by alkylation.



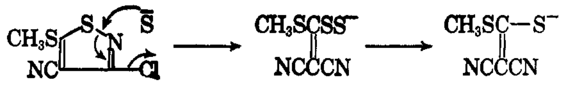
1 **10** **7a**

and

$(CH_3S)_2C{=}C(CN)_2$

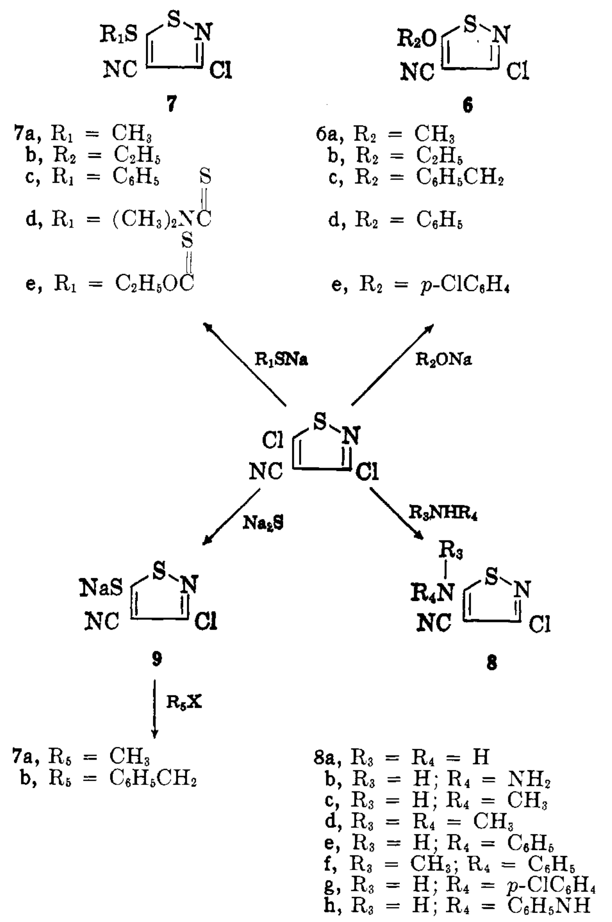
11

The formation of the dicyanoethylene apparently occurred by attack of the sulfide anion on the ring sulfur with ejection of the chloride ion and collapse to the nitrile.



5-Substituted 3-Chloro-4-isothiazolecarbonitriles.—A number of 5-substituted 3-chloro-4-cyanoisothiazoles were prepared according to Scheme I. Yields, physical properties, and analytical data for these derivatives are summarized in Tables I to III.

SCHEME I



7 **6** **9** **8**

7a, $R_1 = CH_3$
b, $R_2 = C_2H_5$
c, $R_1 = C_6H_5$
d, $R_1 = (CH_3)_2NC(=S)$
e, $R_1 = C_2H_5OC(=S)$

6a, $R_2 = CH_3$
b, $R_2 = C_2H_5$
c, $R_2 = C_6H_5CH_2$
d, $R_2 = C_6H_5$
e, $R_2 = p\text{-}ClC_6H_4$

7a, $R_5 = CH_3$
b, $R_5 = C_6H_5CH_2$

8a, $R_3 = R_4 = H$
b, $R_3 = H$; $R_4 = NH_2$
c, $R_3 = H$; $R_4 = CH_3$
d, $R_3 = R_4 = CH_3$
e, $R_3 = H$; $R_4 = C_6H_5$
f, $R_3 = CH_3$; $R_4 = C_6H_5$
g, $R_3 = H$; $R_4 = p\text{-}ClC_6H_4$
h, $R_3 = H$; $R_4 = C_6H_5NH$

Dichloroisothiazolecarbonitrile (**1**) is not affected by boiling methanol or ethanol in the absence of base. In the presence of sodium carbonate, however, the methoxy derivative was formed in 60% yield, and the ethoxy derivative was formed in 96% yield from the respective alcoholic solutions. Reaction with equimolar quantities of sodioalcoholates or phenolates in 1,2-dimeth-

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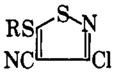
(8) C. C. Price and V. Boekelheide, *J. Am. Chem. Soc.*, **68**, 1246 (1946).

(9) J. D. Kendall and H. D. Edwards, U. S. Patent 2,493,071 (1950).

TABLE II

5-SUBSTITUTED THIO-3-CHLORO-4-ISOTHIAZOLECARBONITRILE

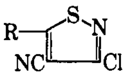


R	Yield, %	M.p., °C.	Formula		Analysis, % C	H	Other	λ_{max}^{alc}, mμ	(ε)
C_6H^c	50^a	108.5–110	$C_{10}H_5N_2S_2Cl$	Calcd.	47.5	1.98	11.1^b	287	(9450)
				Found	46.1	1.99	11.0	ch 274	(8400)
CH_3	$73^{c,d}$	75–76	$C_5H_3N_2ClS_2$	Calcd.	31.5	1.58		288	(10,400)
				Found	32.8	1.72		222	(12,500)
C_2H_5	65^e	64.5–65	$C_6H_5N_2ClS_2$	Calcd.	35.2	2.47	31.3^f	288	(9550)
				Found	35.3	2.64	31.9	223	(11,450)
$(CH_3)_2N\overset{\overset{S}{\Vert}}{C}$	62^g	145–146.5	$C_7H_6N_3ClS_3$	Calcd.	31.9	2.99		295	(10,400)
				Found	31.9	2.49		272	(18,700)
$C_2HSO\overset{\overset{S}{\Vert}}{C}$	16^d	94.5–95.5	$C_7H_5ON_2ClS$	Calcd.	31.7	1.91	10.6^b	304	(11,100)
				Found	31.8	2.14	10.8	277	(8400)
								269	(8500)
$C_6H_5CH_2$	$60^{a,c}$	78–78.5	$C_{11}H_7N_2Cl_2S_2$	Calcd.	49.5	2.65	10.4^b	288	(10,000)
				Found	49.3	2.59	10.4	218	(17,000)

[a] From methanol. [b] % nitrogen. [c] By reaction of 1 with Na_2S followed by alkylation. [d] From petroleum ether. [e] Isolated as by-product of sodium ethyl xanthate with 1. [f] % sulfur. [g] From benzene–hexane.

TABLE III

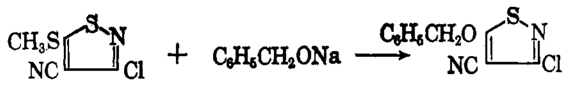
5-AMINO-3-CHLORO-4-ISOTHIAZOLECARBONITRILE DERIVATIVES



R	Yield, %	M.p., °C.	Formula		Analysis, % C	H	Other	λ_{max},[a] mμ	(ε)
H_2N	92^b	210–212	$C_4H_2N_3ClS$	Calcd.	30.1	1.25	26.3^c	259^d	(7930)
				Found	30.5	1.46	26.6		
H_2NNH	91^c	150 dec.	$C_4H_3N_4ClS$	Calcd.	27.5	1.72	18.3^e	268	(9700)
				Found	27.8	1.80	18.6	220	(21,100)
CH_3NH	98^f	198–199	$C_5H_4N_3ClS$	Calcd.	34.6	2.32	18.4^e	270	(10,600)
				Found	35.0	2.50	18.6	219	(21,000)
$(CH_3)_2N$	86^f	103.5–104.5	$C_6H_6N_3ClS$	Calcd.	38.2	3.22	17.0^e	277	(11,400)
				Found	38.3	3.29	17.1	221	(20,400)
C_6H_5NH	80^f	193–193.5	$C_{10}H_6N_3ClS$	Calcd.	17.8^c		15.1^g	301^d	(14,600)
				Found	17.2		14.8		
$C_6H_5\underset{\underset{CH_3}{\vert}}{N}$	85	94.5–95	$C_{11}H_8N_3ClS$	Calcd.	52.9	3.32		282	(10,800)
				Found	53.0	3.31		222	(19,500)
p-ClC_6H_4NH	96^f	261–263	$C_{10}H_5N_3Cl_2S$	Calcd.	44.4	1.85	11.7^b	301	(15,700)
				Found	44.5	2.16	10.8	227	(19,700)
C_6H_5NHNH	100^f	130 dec.	$C_{10}H_7N_4ClS$	Calcd.	47.9	2.81	12.7^e	268^d	(10,600)
				Found	47.4	3.07	12.8		

[a] In alcohol unless noted. [b] From benzene. [c] % nitrogen. [d] In methylene chloride. [e] % sulfur. [f] From methanol. [g] % chlorine.

oxyethane or tetrahydrofuran gave high yields of the corresponding ethers. The benzyl ether (**6c**) was prepared indirectly by reaction of sodium benzylate with 3-chloro-5-methylthio-4-isothiazolecarbonitrile (**7a**) in tetrahydrofuran.



7a **6c**

With anionic sulfur reagents, 1 readily yielded derivatives of 5-mercaptoisothiazole. Methyl, ethyl, and phenyl mercaptides gave the corresponding thioethers. The dimethylammonium salt of N,N-dimethyldithiocarbamic acid[10] yielded the dithiocarbamate ester (**7d**), and sodium ethyl xanthate gave the ethyl dithiocarbonate ester (**7e**). The latter compound was obtained in only 16% yield along with a 65% yield of 5-ethylthio-3-chloro-4-isothiazolecarbonitrile (**7b**). This result was surprising until it was found that the dithiocarbonate was thermally unstable. Attempted sublimation of the ethyl dithiocarbonate ester converted it to the ethylthio derivative (**7b**) apparently by loss of COS. A second route to thioether derivatives involved the preparation of the 5-sodiomercapto derivative (**9**) from 3,5-dichloro-4-isothiazolecarbonitrile (**1**) and an equivalent of sodium sulfide and subsequent alkylation with an alkyl halide. 5-Methylthio- and 5-benzylthio-3-chloroisothiazolecarbonitriles (**7a** and **7b**) were made in this way.

Reaction of tetrahydrofuran solutions of 3,5-dichloro-4-isothiazolecarbonitrile (**1**) with excess ammonia, methylamine, or dimethylamine gave the corresponding 5-amino derivatives in high yields. Similarly, high yields of amine derivatives were obtained from methanol solutions of the dichloro compound with 2 moles of hydrazine, aniline, N-methylaniline, p-chloroaniline, and phenylhydrazine. 5-Amino-3-chloroisothiazolecarbonitrile (**8a**) is not appreciably basic as evidenced by its failure to form salts with anhydrous hydrogen chloride. It was diazotized with difficulty, and the diazonium compound coupled to β-

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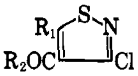
(10) de M. M. Delepine, *Compt. rend.*, **134**, 714 (1902).

TABLE IV



3-CHLORO-5-SUBSTITUTED 4-ISOTHIAZOLECARBOXYLIC ACIDS, ESTERS, AND AMIDES

R_1	R_2	Yield, %	M.p., °C.	Formula	Analysis, %				λ_{max}^{alc}, mμ (ε)
						C	H	Other	
Cl	H_2N	96[a]	168–168.5	$C_4H_2N_2OCl_2S$	Calcd.	24.3	1.0	14.2[b]	256 (6550)
					Found	24.4	0.9	13.3	259[c] (6680)
H_2N	H_2N	100[a]	198–199	$C_4H_4N_3$	Calcd.	27.0	2.2		267 (9450)
					Found	27.6	2.5		222 (24,500)
CH_3O	H_2N	82[d]	185–186	$C_5H_5N_2O_2ClS$	Calcd.	31.2	2.6		244 (6250)
					Found	31.4	2.6		
Cl	CH_3NH	93[a]	105–106	$C_5H_4N_2OCl_2S$	Calcd.	28.4	1.9		256 (7230)
					Found	29.0	2.2		
Cl	C_6H_5NH	94[a]	143.5–144.5	$C_{10}H_6ON_2Cl_2S$	Calcd.	44.0	2.2		254 (16,000)
					Found	44.2	2.4		
Cl	*o*-tolylNH	93[a]	173–174.5	$C_{11}H_8N_2OCl_2S$	Calcd.	46.0	2.8		256 (10,820)
					Found	46.0	2.8		228 (10,380)
Cl	*o*-$H_2NC_6H_4NH$	83[a]	187–188	$C_{10}H_7N_3OCl_2S$	Calcd.	41.6	2.4		298 (3830)
					Found	42.3	2.7		260 (9210)
$(CH_3)_2N$	C_6H_5NH	92[a]	156–157	$C_{12}H_{12}N_3OClS$	Calcd.	51.1	4.3		
					Found	51.3	4.5		
CH_3NH	*o*-tolylNH	98[a]	131–133	$C_{12}H_{12}N_3OCl$	Calcd.	51.2	4.3		
					Found	50.7	4.3		
CH_3O	HO	73[e]	180–182	$C_5H_4O_3NClS$	Calcd.			7.2[b]	243 (6240)
					Found			7.4	
Cl	HO	77[f]	155–156	$C_4HO_2NCl_2S$	Calcd.		198[i]	7.1[b]	259 (6540)
					Found		198	7.0	
CH_3O	CH_3O	100[g]	72–73	$C_6H_6O_3NClS$	Calcd.	34.7	2.9	6.7[b]	243 (6950)
					Found	35.2	3.2	6.8	
Cl	CH_3O	90[h]	35.5–36.5	$C_5H_3O_3NCl_2S$	Calcd.	28.5	1.4		258 (6100)
					Found	28.7	1.7		

[a] From methanol. [b] % nitrogen. [c] In CH_2Cl_2. [d] From alcohol. [e] From water. [f] From benzene. [g] From benzene–hexane. [h] Purified by sublimation. [i] Neut. equiv.

naphthol to give a violet dye. The dye was prepared more conveniently by the potassium ferricyanide oxidative coupling[11] of the hydrazine derivative **8b** with β-naphthol.

Alkylation of 3-chloro-5-methylamino-4-isothiazolecarbonitrile (**8c**) with methyl iodide gave the 5-dimethylamino derivative (**8d**) without apparent ring alkylation.

4-Isothiazolecarboxylic Acids, Esters, and Amides.—A number of 3,5-disubstituted 4-isothiazolecarboxylic acids, esters, and amides were prepared from the 4-isothiazolecarbonitriles. Yields, physical properties, and analytical data for these derivatives are summarized in Table IV. The 5-chloro-, 5-amino-, and 5-methoxy-3-chloro-4-isothiazolecarboxamides were prepared by solution of the appropriate nitrile in sulfuric acid and subsequent reaction with water. The N-substituted 3,5-dichloroisothiazolecarboxamides were prepared by the reaction of 3,5-dichloroisothiazolecarbonyl chloride with the appropriate amine in ether or tetrahydrofuran. The 3,5-dichloroisothiazolecarboxamides also underwent replacement of the 5-chlorine atom on treatment with nucleophilic agents. In this way, 3-chloro-5-dimethylamino-4-isothiazolecarboxanilide was prepared from 3,5-dichloro-4-isothiazolecarboxanilide and dimethylamine, and 3-chloro-5-methylamino-4-isothiazolecarboxy-*o*-toluidide was prepared from 3,5-dichloroisothiazolecarboxy-*o*-toluidide and methylamine.

Two 4-isothiazolecarboxylic acids, 3,5-dichloro- and 3-chloro-5-methoxy-, were prepared by the nitrous acid hydrolysis of the amides.[12] The dichloro acid was converted to the acid chloride with thionyl chloride and thence with methanol to the methyl ester. The methyl ester of 3-chloro-5-methoxy-4-isothiazolecarboxylic acid was prepared by the action of diazomethane on the acid.

Experimental[13]

Di(alkalimercapto)methylenemalononitriles (2).[9] Sodio Derivative.—Malononitrile (66 g., 1 mole) was added slowly to a stirred suspension of 80 g. (2 moles) of sodium hydroxide in 900 ml. of alcohol while the temperature of the mixture was maintained at 10–15°. Carbon disulfide (76 g., 1 mole) was added dropwise with cooling over a period of 30 min., and the resulting heavy, yellow slurry was stirred an additional hour at room temperature. Filtration, washing with alcohol, and drying at 80° in a vacuum oven for 24 hr. gave 170 g. (90%) of light tan, hydroscopic powder; $\lambda_{max}^{H_2O}$ 341 mμ (ε 20,800), 307 (15,600), 271 (2830); λ_{max}^{alc} 341 mμ (ε 22,800), 313 (14,000), 271 (4250). The infrared spectrum (Nujol) showed three bands for CN at 4.55 (m), 460 (s), 4.77 (w), and a band at 7.6 μ for $C{=}CS_2$.

Anal. Calcd. for $C_4N_2S_2Na_2$: S, 34.4. Found: S, 33.2.

The dipotassium salt was prepared in 80% yield from potassium hydroxide, malononitrile, and carbon disulfide[14]; $\lambda_{max}^{H_2O}$ 345 mμ (ε 18,500), sh 310 (9600); λ_{max}^{alc} 341 mμ (ε 21,400), sh 313 (9200), 272 (6900).

Anal. Calcd. for $C_4N_2S_2K_2$: S, 29.2. Found: S, 28.5.

3,5-Dichloro-4-isothiazolecarbonitrile (1).—Chlorine was

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(11) S. Hunig, H. Balli, H. Nother, and H. Geiger, *Ann.*, **628**, 75 (1959).

(12)(a) Sudborough, *J. Chem. Soc.*, **67**, 601 (1895); (b) N. Sperber, D. Papa, and E. Schwenk, *J. Am. Chem. Soc.*, **70**, 3091 (1948).

(13) All melting points are uncorrected. Infrared spectra, measured on a Perkin-Elmer Model 21, appeared to be consistent with the structures proposed for all compounds described. Ultraviolet spectra were measured on a Cary Model 14.

(14) W. R. Hatchard, U. S. Patent 3,048,596 (1962).

passed into a stirred slurry of 110 g. of anhydrous **2** (dried to constant weight over phosphoric anhydride at 80° under vacuum) in 800 ml. of distilled carbon tetrachloride for 2 hr. Heat evolution caused the mixture to reflux for the first hour, but during the second hour the mixture cooled to about 40°. The warm reaction mixture was filtered, and the residue was washed with carbon tetrachloride. The combined washes and filtrate was distilled through a Claisen stillhead on a steam bath to remove carbon tetrachloride and sulfur chlorides, and then the residue was steam distilled to give a white solid distillate that weighed 60 g. (57% yield). Recrystallization from petroleum ether (b.p. 60–80°) gave **1**, m.p. 64–65°; $\lambda_{\max}^{\text{isooctane}}$ 240 mμ (ϵ 4650), 263 (7160), sh 270 (6300). The infrared spectrum showed major bands at 4.5 (conj. CN), 6.65, and 7.52 μ (C=CS and/or C=C–N).

Anal. Calcd. for $C_4N_2Cl_2S$: C, 26.8; Cl, 39.6; S, 17.9; mol. wt., 179. Found: C, 27.1; Cl, 39.4; S, 17.8; mol. wt., 196 (Rast, acetone).

3,5-Dibromo-4-isothiazolecarbonitrile.—At room temperature, 64 g. (0.4 mole) of bromine was added dropwise over 0.5 hr. to a slurry of 3.72 g. (0.20 mole) of **2** in 400 ml. of carbon tetrachloride. The temperature rose to 30° during the addition. After being stirred 1.25 hr. at 40–55° (external heat), the reaction mixture was filtered, and the filtrate was distilled, first at atmospheric pressure and then at reduced pressure, to remove solvent and sulfur bromides. At a pot temperature of about 130° at 1 mm., a small quantity of white crystals formed in the stillhead. Collection and resublimation gave 3,5-dibromo-4-isothiazolecarbonitrile, m.p. 98–98.5°; $\lambda_{\max}^{CH_2Cl_2}$ 253 mμ (ϵ 6350), 267 (6850), sh 274 (6040). The infrared spectrum showed bands at 4.48 (CN), 6.70, and 7.65 μ.

5-Alkoxy- and 5-Aryloxy-3-chloro-4-isothiazolecarbonitriles.—The following preparations are typical of those in Table I.

5-Ethoxy-3-chloro-4-isothiazolecarbonitrile (6b).—A mixture of 2.5 g. (14 mmoles) of **1**, 1.45 g. (14 mmoles) of anhydrous sodium carbonate, and 25 ml. of ethanol was heated under reflux overnight, concentrated on a steam bath under a helices-packed column, and diluted with water. The precipitated solid, after collection and drying, weighed 2.5 g. (96% yield) and melted at 58–59°. An analytical sample purified by sublimation melted at 59.5–60.5°.

5-*p*-Chlorophenoxy-3-chloro-4-isothiazolecarbonitrile (6e).—A solution of 14.3 g. (0.08 mole) of **1** in 20 ml. of 1,2-dimethoxyethane was added at room temperature to a solution of 10.02 g. (0.08 mole) of *p*-chlorophenol, 3.6 g. (0.079 mole) of sodium hydroxide, and 250 ml. of 1,2-dimethoxyethane, and the mixture was heated under reflux for 3 hr. Filtration, evaporation of the filtrate, and recrystallization of the residue from aqueous methanol gave 19.9 g. (92% yield) of white crystals that melted at 87.5–88.5°

5-Benzyloxy-3-chloro-4-isothiazolecarbonitrile (6c).—A mixture of 1.08 g. (0.01 mole) of benzyl alcohol, 0.46 g. (0.01 mole) of 52% sodium hydride emulsion, and 25 ml. of tetrahydrofuran was stirred at room temperature for 30 min. To this mixture was added 1.90 g. (0.01 mole) of **7a**, and the mixture was stirred 1 hr., concentrated by evaporation at reduced pressure, and diluted with water. The crystals that formed were collected and extracted with hot cyclohexane. A crystalline fraction obtained from the cyclohexane melted at 111–130°. Recrystallization from methanol gave white needles of **6c**, m.p. 136–138°.

3-Chloro-5-Substituted Thio-4-isothiazolecarbonitrile Derivatives.—The following syntheses are illustrative of the compounds in Table II.

Method A. 3-Chloro-5-N,N-dimethyldithiocarbamoyl-4-isothiazolecarbonitrile (7d).—A mixture of 3.58 g. (0.02 mole) of **1**, 3.32 g. (0.02 mole) of dimethylammonium N,N-dimethyldithiocarbamate,[10] and 10 ml. of methanol was boiled on a steam bath for 1 hr., cooled, and filtered to give 3.55 g. (62%) of white crystals that melted at 145–147°. Recrystallization from a benzene–hexane mixture gave a product that melted at 145–146.5°. In some cases, concentration of the reaction mixture and dilution with water was required to effect crystallization.

Method B. 3-Chloro-5-methylthio-4-isothiazolecarbonitrile (7a).—A solution of 1.79 g. (0.01 mole) of **1** in 20 ml. of methanol was added dropwise over 15 min. with stirring to a warm solution of 2.40 g. (0.01 mole) of sodium sulfide nonahydrate in 5 ml. of water and 50 ml. of methanol. After 1 hr., the reaction mixture was evaporated at reduced pressure to give a reddish solid residue. The solid was triturated in ethyl ether, and the insoluble portion was redissolved in methanol. Methyl iodide (5 g.) was added, and the mixture was heated under reflux 20 min., then evaporated. The residue was washed with water and air-dried to give 1.38 g. (73% yield) of crystals that melted at 72–73°. An identical product (by infrared) was prepared from sodium methylmercaptide and **1** by method A.

Reaction of 3,5-Dichloro-4-isothiazolecarbonitrile with Sodium Ethyl Xanthate to Yield 5-Ethoxythiocarbonylthio-3-chloro-4-isothiazolecarbonitrile (7e) and 5-Ethylthio-3-chloro-4-isothiazolecarbonitrile (7b).—A solution of 31.2 g. (0.20 mole) of sodium ethyl xanthate in 250 ml. of acetone was mixed with a solution of 35.8 g. (0.20 mole) of **1** in 250 ml. of acetone, and the mixture was stirred with warming for 25 min. and then filtered. The filtrate was evaporated at reduced pressure to small volume and diluted with petroleum ether. Crystals that formed were collected (12 g., m.p. 68–71.5°) and recrystallized from benzene and then from aqueous acetone to give 8.2 g. (16% yield) of **7e**, m.p. 98–99°. Evaporation of filtrates and trituration in a little petroleum ether gave 30 g. of crystals, m.p. 52–104°. This crop was heated on a steam bath for 1 hr. to give 26 g. (65% yield) of white crystals that melted at 65–67°. Determination of a mixture melting point and comparison of the infrared spectrum with that of a known sample showed this product to be **7b**.

Reaction of 3,5-Dichloro-4-isothiazolecarbonitrile (1 Mole) with Sodium Sulfide (2 Moles).—A solution of 1.79 g. (0.01 mole) of **1** in 20 ml. of methanol was added over 15 min. to a warm solution of 4.80 g. (0.02 mole) of sodium sulfide nonahydrate in 5 ml. of water and 50 ml. of methanol, and the mixture was stirred under reflux an additional 10 min. The mixture was cooled, and 2.84 g. (0.02 mole) of methyl iodide was added. After 20 min., the mixture was evaporated under reduced pressure, and the residue was washed with water and filtered. The water-insoluble residue (0.8 g.) melted at 68–71° after recrystallization from methanol and had an infrared spectrum identical with that of **7a**. The aqueous filtrate was evaporated to dryness, and the residue was stirred with excess methyl iodide for 30 min. and again evaporated. The residue was extracted with hot cyclohexane, and from the extract was obtained 0.24 g. of white needles, m.p. 60–64°. Recrystallization from methanol gave needles that melted at 69–71° and whose infrared spectrum was identical with that of **11**.[9]

In another experiment using the same quantities of starting materials, the reaction mixture was heated under reflux 3.5 hr. before the addition of excess (4 ml.) methyl iodide. After 30 min. the reaction mixture was cooled and filtered to give 0.76 g. of white crystals. Recrystallization from methanol gave a product that melted at 130–131.5° and was identified as **10** by elemental analyses and absorption spectra: $\lambda_{\max}^{\text{alc}}$ 284 mμ (ϵ 13,300), 230 (11,700), 215 (11,100); the infrared spectrum showed bands at 4.50 (CN), 6.65, 6.79, and 7.6 μ.

Anal. Calcd. for $C_6H_6N_2S_3$: C, 35.6; H, 2.9; S, 47.5. Found: C, 35.8; H, 2.9; S, 47.9.

5-Amino-3-chloro-4-isothiazolecarbonitrile Derivatives.—The following examples illustrate preparations of derivatives included in Table III.

5-Amino-3-chloro-4-isothiazolecarbonitrile (8a).—Dry ammonia gas was passed into a refluxing solution of 10.0 g. (56 mmoles) of **1** in 500 ml. of purified tetrahydrofuran for 7 hr., and the reaction mixture was allowed to stand overnight at room temperature. Filtration, concentration to a small volume, and dilution with benzene caused crystallization of tan needles that weighed 8.17 g. (92%) and melted at 208–209°. Recrystallization from a methanol–benzene mixture after treatment with decolorizing charcoal gave white needles that melted at 210–212°.

3-Chloro-5-(β-phenylhydrazino)-4-isothiazolecarbonitrile (8h).—A mixture of 8.95 g. (0.05 mole) of **1** and 10.8 g. (0.10 mole) of phenylhydrazine in 75 ml. of methanol was heated under reflux for 2 hr., then evaporated at reduced pressure to give a yellowish solid. Trituration, first in petroleum ether and then in water, gave 12.4 g. (100%) of white solid that melted at 135° dec. An analytical sample was crystallized from methanol.

3-Chloro-5-hydrazino-4-isothiazolecarbonitrile (8b).—Ten grams (0.20 mole) of hydrazine hydrate in 25 ml. of methanol was added dropwise at room temperature to a stirred solution of 17.9 g. (0.01 mole) of **1** in 250 ml. of methanol, and the mixture was stirred 3 hr. at room temperature. Concentration and dilution with water gave 16.0 g. (91%) of the hydrazine derivative. Two recrystallizations from methanol gave an analytical sample that melted with decomposition when placed in a bath at 150°.

The hydrazine derivative was soluble in aqueous sodium hydroxide and was reprecipitated unchanged by acid. Reaction of the hydrazine derivative with an acetone–methanol mixture gave the azine as white needles that melted with decomposition at 204–205° when immersed in the bath at 200°; λ_{max}^{alc} 296 mμ (ε 16,000), 228 (16,000).

Anal. Calcd. for $C_7H_7N_4ClS$: C, 39.2; H, 3.26; N, 26.2; Cl, 16.5. Found: C, 40.6; H, 3.3; N, 26.3; Cl, 16.1.

Reaction Product of 3-Chloro-5-hydrazino-4-isothiazolecarbonitrile (18b) and β-Naphthol.—A mixture of 1.45 g. (0.011 mole) of β-naphthol and 1.74 g. (0.01 mole) of the hydrazinoisothiazole **8b** in 100 ml. of methanol was stirred at room temperature as 10 g. of 10% sodium hydroxide solution was added dropwise. The solution became light violet. The addition of a solution of 10 g. of potassium ferricyanide in 50 ml. of water and 40 ml. of methanol caused the formation of a slurry which was largely dissolved by the addition of another 100 ml. of water. After being stirred 15 min., the solution was filtered to give 0.98 g. of maroon solid, m.p. 265–270° (31% yield). An analytical sample, crystallized from benzene–chloroform mixture, melted at 281–283°; $\lambda_{max}^{CH_2Cl_2}$ 290 mμ (ε 10,300), 300 (9800), 320 (4750), 430 (13,000), 465 (14,600), 550 (3900).

Anal. Calcd. for $C_{14}H_8ON_4ClS$: C, 53.4; H, 2.6; N, 17.7. Found: C, 53.4, 53.7; H, 2.3, 2.4; N, 17.9.

Preparation of 3,5-Disubstituted 4-Isothiazolecarboxamides (Table IV). Amides unsubstituted on nitrogen were prepared by dissolving the corresponding nitrile in 6–8 times its weight of concentrated sulfuric acid, warming the solution on a steam bath for 20 min., and allowing the mixture to stand 18 hr. at room temperature. The products were precipitated by dilution in ice-water and were recrystallized from aqueous alcohol.

4-N-Substituted amides of 3,5-dichloroisothiazole were prepared by reaction of the acid chloride with an excess of the amine in ether or tetrahydrofuran by usual procedures.[15]

o-(3-Chloro-5-methylamino-4-isothiazolecarboxy)toluidide and 3-chloro-5-dimethylamino-4-isothiazolecarbanilide were made by the reaction of the corresponding N-substituted 3,5-dichloroisothiazolecarboxamides in ethereal solution with an excess of gaseous methylamine and dimethylamine, respectively.

4-Isothiazolecarboxylic Acids.—The two acids described in Table IV were prepared by a modification of the method of Sudborough[12] as given below.

3,5-Dichloro-4-isothiazolecarboxylic Acid.—A solution of 3.1 g. (0.045 mole) of sodium nitrite in 10 ml. of water was added over 15 min. to a cold (5–10°) stirred solution of 5.91 g. (0.03 mole) of 3,5-dichloroisothiazolecarboxamide in a mixture of 40 ml. of sulfuric acid and 10 ml. of water. The addition was made through a tube dipping below the surface of the reaction mixture at such a rate that the temperature was maintained at 10–15° and the formation of red fumes was minimized. After addition was complete, the reaction mixture was stirred for 30 min. at room temperature, 20 min. at 50–60° when much foaming occurred, and then poured into an ice–water mixture. The precipitated solid was collected on a filter, dissolved in aqueous sodium carbonate solution, and the solution was treated with decolorizing charcoal and filtered. Acidification of the filtrate gave 3.65 g. of white solid that melted at 155–155.5°. An additional 0.94 g. of acid was obtained by ether extraction of the aqueous, acidic filtrate (total yield 77%). Recrystallization from benzene and sublimation gave an analytical sample that melted at 155–156°.

The acid chloride, prepared by refluxing the acid with an excess of thionyl chloride for 6 hr., boiled at 102° (8 mm.), $n^{25}D$ 1.5945.

Desulfurization of 5-Anilino-3-chloro-4-isothiazolecarbonitrile.—A mixture of 5.0 g. of **8e** 150 ml. of ethanol, and about 25 g. of Raney nickel was heated under reflux overnight, filtered to remove the catalyst, and evaporated under reduced pressure. The residue was washed with water to remove soluble salts and then extracted with hot benzene. Crystallization from the extracts yielded 0.23 g. of light tan crystals that melted at 230–235°. Recrystallization from methanol gave 0.20 g. of crystals, m.p. 244–247°. The infrared spectrum of the product was identical with that of anilinomethylenemalonitrile.[8]

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[15] N. D. Cheronis and J. B. Entrikin, "Semimicro Qualitative Organic Analysis," Interscience Publishers, Inc., New York, N. Y., 1957, p. 356.

The Synthesis of Isothiazoles. II. 3,5-Dimercapto-4-isothiazolecarbonitrile and Its Derivatives

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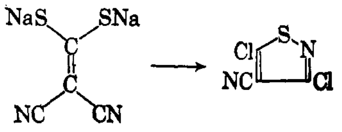
Received August 26, 1963

Salts of 3,5-dimercapto-4-isothiazolecarbonitrile were formed by the reaction of salts of dimercaptomethylenemalononitrile with sulfur in boiling methanol. These novel dimercaptoisothiazole salts have been converted to a variety of alkylthio-, acylthio-, and alkylsulfonylisothiazolecarbonitrile derivatives. Hydrolysis gave a series of 3,5-bis(methylthio)-4-isothiazolecarboxylic acid, ester, and amide derivatives.

Earlier we described the preparation of 3,5-dichloro-4-isothiazolecarbonitrile (**2**) by the ring closure of di-(sodiomercapto)methylenemalononitrile (**1**) with excess chlorine.[1,2] The dichlorocyanoisothiazole (**2**) provides a route to a number of isothiazole derivatives by replacement and hydrolysis reactions.



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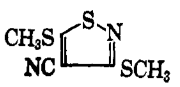
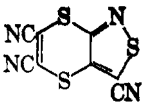


3

One of the products of the earlier described replacement reactions of **2** was 3,5-bis(methylthio)isothiazolecarbonitrile (**3**). With the exception of **3** and similar compounds mentioned in our first paper, no mononuclear isothiazoles having a sulfur atom bonded directly to the heterocyclic ring have been described. However, complex isothiazoles **4** and **5** having sulfur atoms bonded to positions 3 and 4 recently have been reported from this laboratory.[3,4]



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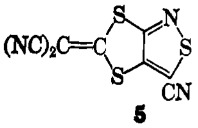

5

The present paper reports the synthesis of salts of 3,5-dimercapto-4-isothiazolecarbonitrile (**6**) and their conversion to a number of isothiazole derivatives substituted with sulfur. The new 3,5-dimercaptoisothiazole salts (**6**) were prepared by reaction of a dibasic salt of dimercaptomethylenemalononitrile with sulfur. For example, a boiling methanol solution of the di-

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[1] Part I, W. R. Hatchard, *J. Org. Chem.*, **29**, 660 (1964).

[2] W. R. Hatchard, *ibid.*, **28**, 2163 (1963).

[3] H. E. Simmons, R. D. Vest, D. C. Blomstrom, J. R. Roland, and T. L. Cairns, *J. Am. Chem. Soc.*, **84**, 4746 (1962).

[4] W. R. Hatchard, U. S. Patent 3,048,596 (1962).