Bis(3-chloro-4-cyanoisothiazol-5-yl) Sulfide

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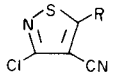
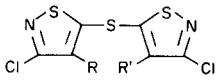
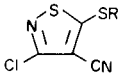
We wish to report a novel reaction which was encountered during attempts to prepare 3-chloro-4,5-dicyanoisothiazole (I). When 3,5-dichloro-4-cyanoisothiazole (II) (1) was allowed to react between 160-250° with one equivalent of cuprous cyanide, instead of the expected 3-chloro-4,5-dicyanoisothiazole (I), the previously unknown bis(3-chloro-4-cyanoisothiazol-5-yl) sulfide (III) was isolated. The best yields were observed at the upper end of the temperature range (20-24% based on converted II).



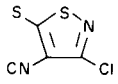
I R = CN
II R = Cl



III R, R' = CN
IV R = $CONH_2$; R' = CN
V R, R' = $CONH_2$



VI R = Na



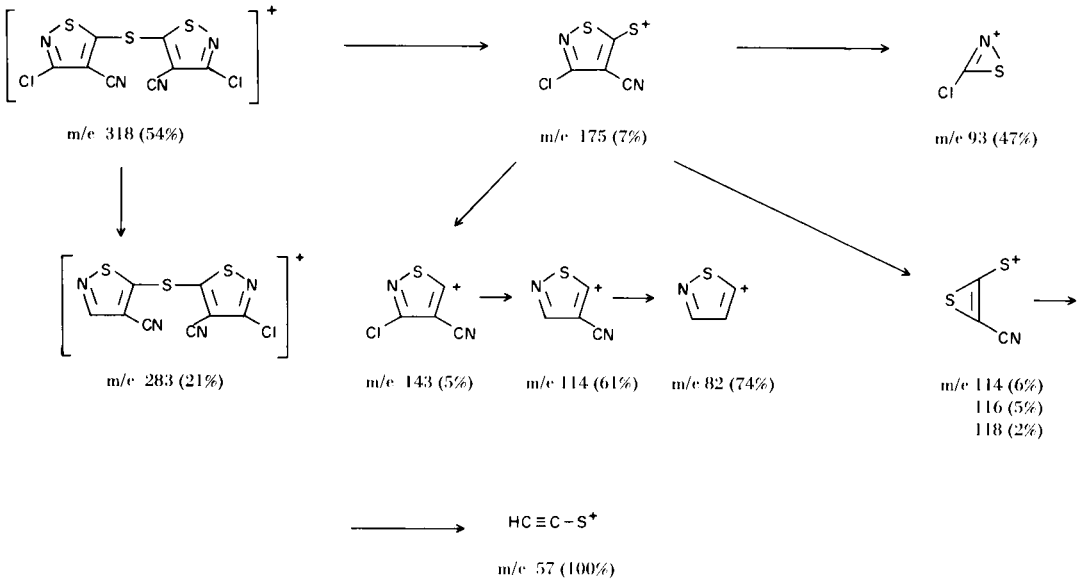
VII R =

The structural assignment for sulfide III was based on elemental analysis, infrared and mass spectra and comparison with an authentic sample prepared from II and sodium sulfide. Sulfide III analyzed for $C_8Cl_2N_4S_3$ and had an absorption band at 4.43 μm indicating the presence of a cyano- but not thiocyano- or isothiocyano- function. The mass spectrum showed a molecular ion of 318 consistent with the molecular formula $C_8Cl_2N_4S_3$. The isotope ratios observed for $M^+/M^+ + 1$, $M^+/M^+ + 2$, $M^+/M^+ + 3$, and $M^+/M^+ + 4$ (9.0, 1.3, 1.4 and 6.0, respectively) are in accord with the presence of two chlorine atoms and at least one sulfur atom in the molecule. The base peak at m/e 57 results from complete fragmentation of the isothiazole ring. In Scheme I, structures are assigned to the more important fragments present in the mass spectrum of III. They are in agreement with those of other isothiazoles (2,3).

Structures isomeric with III and resulting by displacement of one or both chlorine atoms at C-3 in one or both isothiazole moieties are ruled out by the much higher reactivity of chlorine at C-5 in II observed in nucleophilic substitutions (1).

Although the function of cuprous cyanide in the formation of sulfide III is not clear, its presence is necessary as indicated by the fact that when compound II was heated alone at 205° for three hours, no sulfide was detected and II was recovered quantitatively. Neither copper powder nor cuprous thiocyanide under the same

SCHEME I



conditions reacted with II to give sulfide III. In both cases only unreacted II was recovered.

The sulfide III could be prepared in several other ways. Hatchard had found that when II was allowed to react with one equivalent of sodium sulfide in methanol and oxidized *in situ* with iodine, disulfide VII was formed in 34% yield (4). If, however, II was allowed to react with only one half equivalent of sodium sulfide, the intermediate sodium salt VI reacted readily with the remaining II to form III even when no special precautions were taken to avoid oxidation of VI to VII.

Similarly II could be converted into III by fusion with sodium sulfide at 205°. Sulfide III was also obtained when II was treated with potassium thiocyanate in methanolic solution or fusion at 205°. The reactions in solution resulted in somewhat higher yields.

The presence of two cyano functions in sulfide III could be demonstrated by stepwise hydrolysis. When sulfide III was hydrolyzed in sulfuric acid, a mono- and a dicarboxamide (IV and V) were isolated. They were characterized by elemental analysis and ir spectra. A somewhat diminished cyano absorption band at 4.4 μm was observed in IV and none was observed in V. These observations were in accord with the appearance of amide absorption bands at 6.0 and 6.03 μm, respectively.

EXPERIMENTAL

Bis(3-chloro-4-cyanoisothiazol-5-yl) Sulfide (III) From 3,5-Dichloro-4-cyanoisothiazole (II) and Cuprous Cyanide.

An intimate mixture of II (1.79 g., 0.01 mole) and Cu (I) cyanide (0,89 g., 0.01 mole) was placed in a round bottom flask, equipped with a condenser and heated at 250° in an oil bath for 3 hours. Then unreacted II (800 mg., 48%) was removed by vacuum distillation. The remaining residue was triturated several times with methylene chloride. Excess solvent was removed and III crystallized as a light yellow solid (208 mg., 24%, m.p. 128-132°); ir (chloroform) 4.43, 6.74, 7.40, 7.55, and 9.10 μm; uv max (ethanol) 323 (ε, 4,500), 275 (ε, 11,450) and 241 nm (ε, 8,200); mass spectrum (70 eV, 50 μA) m/e (relative intensity) 320 (42), 318 (54), 286 (32), 114 (61), 93 (47), 82 (74), 71 (57), 69 (71), 57 (100), 56 (94).

Anal. Calcd. for $C_8Cl_2N_4S_3$: C, 30.10; Cl, 22.21; N, 17.55. Found: C, 29.86; Cl, 22.25; N, 17.17.

Sulfide III from II and Sodium Sulfide.

A solution of II (1.8 g., 0.01 mole) in 25 ml. of methanol was added dropwise into a clear solution of sodium sulfide (1.2 g., 0.005 mole) in 20 ml. of methanol at 40-50°. The mixture was then heated under reflux for two hours. The solution was concentrated after filtration to almost dryness. The resulting solid product was recrystallized to give 0.61 g. of impure sulfide III. Traces of starting material II were detected in the mother liquor by tlc.

Sulfide III was further purified by vacuum sublimation followed by recrystallization from methanol. The pure III, m.p. 129-131°, had an identical infrared spectrum and R_f value as compared with III obtained by the other two methods.

Sulfide III from II and Potassium Thiocyanate.

A mixture of II (1.8 g., 0.01 mole), potassium thiocyanate (0.97 g., 0.01 mole) and methanol (20 ml.) was heated under reflux for 75 minutes. After cooling to 25° and filtering, the methanolic solution was concentrated. A light yellow solid crystallized (0.7 g., 43%, m.p. 128-134°). After having been recrystallized from methanol (m.p. 129-133°), the compound was identified as III. In addition, the following data was obtained ir (chloroform), 4.41, 6.72, 7.40, 7.55, and 9.12 μm; mass spectrum (70 eV, 10 μA), m/e (rel. intensity) 320 (77), 318 (100), 286 (1.4), 114 (26), 93 (9), 82 (15).

(3-Chloro-4-cyanoisothiazol-5-yl) (3-Chloro-4-carboxamidoisothiazol-5-yl) Sulfide (IV) and Bis(3-chloro-4-carboxamidoisothiazol-5-yl) Sulfide (V).

A mixture of 200 mg. of III and 5 ml. of concentrated sulfuric acid was allowed to stand for four hours. The clear solution was poured into crushed ice. The bright yellow precipitate (m.p. 108-125°) was collected. After three recrystallizations from methanol-chloroform, the monocarboxamide IV was obtained (50 mg., 23.8% yield, m.p. 193-195°); ir (potassium bromide), 2.89, 3.16, 4.44, 6.0, 6.27, 6.78, and 9.18 μm; uv max (ethanol) 270 nm (ε, 10,200).

Anal. Calcd. for $C_8H_2Cl_2N_4OS_3$: C, 28.49; H, 0.60; N, 16.61. Found: C, 27.90; H, 0.62; N, 16.10.

From the mother liquor of IV, a second hydrolysis product was isolated. This was recrystallized to give 35 mg. (15.6%) of light yellow crystals of V, m.p. 230-233°; ir (potassium bromide), 3.0, 5.98, 6.03, 6.71, and 7.80 μm; uv max (ethanol) 269 nm (ε, 14,500).

Anal. Calcd. for $C_8H_4Cl_2N_4O_2S_3$: C, 27.05; H, 1.14; N, 15.77. Found: 27.00; H, 1.13; N, 15.40.

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Received March 12, 1970 Princeton, N. J. 08540