BULLETIN OF THE CHEMICAL SOCIETY OF JAPAN VOL. 42 1152—1153 (1969)

The Reaction of 3-Chloro-benzo[*d*]isothiazole with Thiophenols

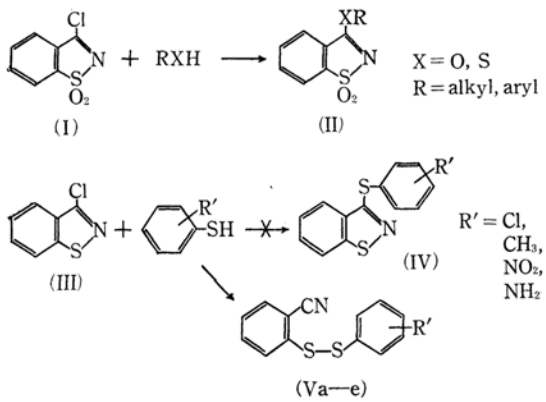
Suzuo WATANABE

Central Research Laboratories, Meiji Seika Kaisha, Ltd., Morooka-cho, Kohoku-ku, Yokohama

(Received August 5, 1968)

The condensation of 3-chloro-benzo[*d*]isothiazole 1,1-dioxide (saccharin chloride) (I) with alcohols, phenols, or mercaptans was reported to give a series of saccharin derivatives (II),[1] which have distinct melting points, so they have been used for the identification of alcohols, phenols, or mercaptans.

The present report deals with the reaction of thiophenols with 3-chloro-benzo[*d*]isothiazole (III).[2]



When III was treated with substituted thiophenols at 40°C, a vigorous evolution of hydrogen chloride gas occured. By adding ethanol to the reaction mixture, the crystalline product was obtained in yield of 87—28%.

This product was not the expected compound, 3-arylthio-benzo[*d*]isothiazoles (IV), but aryl *o*-cyanophenyl disulfides (V), which are listed in Table 1.

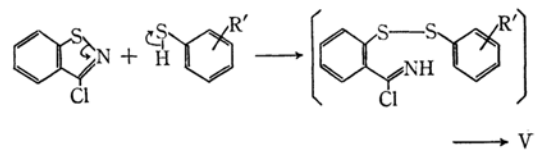
The structure of the compounds Va—e was determined by their elemental analyses and infrared spectra, which showed a characteristic band at 2210 cm^{-1} due to –CN group. To confirm the structure, Vc was reduced with lithium aluminum hydride to *p*-methylthiophenol, which was identified by its melting point and by the reaction with 2,4-dinitrochlorobenzene to *p*-tolyl 2,4-dinitrophenyl sulfide.

It was reported[3] that 2-substituted-benzo[*d*]isothiazole-3(2)-ones were reacted with aniline to afford *o*-(*N*-substituted carbamoyl)-benzenesulfenanilides. When III was treated with alcohols or aniline, no reaction occurred and starting materials were recovered.

Table 1. Disulfides by the reaction of 3-chloro-benzo[*d*]isothiazole with thiophenols

	R	Yield (%)	Mp (°C)	Anal. % N	Found / Calcd S
Va	*p*-Cl	87.0	47.0—49.0	5.23 5.04	— —
Vb	*o*-CH_3	31.5	58.0—60.0	5.50 5.44	24.98 24.92
Vc	*p*-CH_3	67.0	53.5—55.0	5.21 5.44	24.68 24.92
Vd	*p*-NO_2	28.0	92.0—93.0	9.90 9.72	22.19 22.21
Ve	*o*-NH_2	33.5	83.0—86.0	10.98 10.82	24.82 24.78

The reaction mechanism of III with thiophenols was thought to be as follows.



The compounds Va–e showed moderate antibacterial and antifungal activities. The minimum inhibition concentrations (MIC) are listed in Table 2.

Experimental

Two typical examples for the reaction of III with thiophenols were described below.

p-Chlorophenyl o-Cyanophenyl Disulfide (Va). *p*-Chlorothiophenol (8.7 g) was added to 3-chloro-benzo[*d*]isothiazole (III) (10.2 g) with shaking in small portions at 40°C. The reaction mixture was thoroughly shaken until the vigorous evolution of hydrogen chloride gas stopped, and then allowed to stand in an ice box overnight. Ethanol (20 *ml*) was added to the reaction mixture, and the resulting suspension was thoroughly

1) J. R. Meadow and J. C. Cavagnol, *J. Org. Chem.*, **16**, 1582 (1951); *ibid.*, **17**, 488 (1952).

2) A. Reissert, *Ber.*, **61**, 1681 (1928).

3) R. G. Bartlett, L. E. Hart and E. W. McClelland, *J. Chem. Soc.*, **1939**, 760.

stirred over a period of 15 min, then crystals were collected, washed with ethanol and dried. Recrystallization from ethanol gave 14.5 g (87.0%) of *p*-chlorophenyl *o*-cyanophenyl disulfide, mp 47.0—49.0°C. Found: C, 56.55; H, 3.39; N, 5.23%. Calcd for $C_{13}H_8ClNS_2$: C, 56.21; H, 2.90; N, 5.04%.

***o*-Aminophenyl *o*-Cyanophenyl Disulfide (Ve).** 3-Chlorobenzo[*d*]isothiazole (10.2 g) was added to *o*-aminothiophenol (14.8 g) with shaking in small portions. The reaction mixture was thoroughly shaken for an additional 15 min, and then allowed to stand in an ice box overnight. Crystalline precipitate was filtered and washed with ethanol (25 m*l*). The filtrate and the washings were combined, concentrated *in vacuo* to a half volume, and cooled, then crystals which separated were collected. Further concentration of the mother liquor to 7 m*l* yielded more crystals. The entire crystals were recrystallized from ethanol, the yield of *o*-aminophenyl *o*-cyanophenyl disulfide was 5.2 g (33.5%), mp 83.0—86.0°C. Found: C, 60.81; H, 4.37; N, 10.98; S, 24.82%. Calcd for $C_{13}H_{10}N_2S_2$: C, 60.40; H, 3.89; N, 10.82; S, 24.78%.

TABLE 2. ANTIMICROBIAL ACTIVITIES OF Va—e (MIC; mcg/m*l*)

Name of test oganisms	Va	Vb	Vc	Vd	Ve
S. aureus 209P	2.0	2.0	3.9	12.5	7.8
E. coli IAM 1253	>500	>500	>500	500	>500
Mycobacterum 607	7.8	15.6	15.6	31.2	31.2
Candida albicans IAM	7.8	15.6	15.6	500	7.8
Xanthomonas oryzae	7.8	15.6	15.6	500	7.8
Asp. niger ATCC 6275	>500	>500	>500	>500	500
Pir. Sasaki	7.8	125	7.8	500	15.6