Antifungal Agents I.
5-Substituted-3-(trichloromethyl)-1,2,4-thiadiazoles

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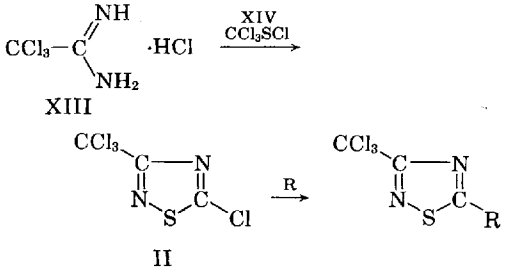
Some 5-substituted-3-(trichloromethyl)-1,2,4-thiadiazoles were synthesized by the nucleophilic displacement of the Cl^- ion of 5-chloro-3-(trichloromethyl)-1,2,4-thiadiazole for evaluation as soil fungicides. An interesting O → N migration of the β-hydroxyethyl substituent was observed during the synthesis of 5-(2-hydroxyethoxy)-3-(trichloromethyl)-1,2,4-thiadiazole. All these compounds retained 60–80 per cent of the over-all fungicidal activity of the analogous 5-ethoxy-3-(trichloromethyl)-1,2,4-thiadiazole.

THE DISCOVERY of 5-ethoxy-3-(trichloromethyl)-1,2,4-thiadiazole as an effective soil fungicide (1, 2) led the authors to synthesize the compounds listed in Table I (compounds III–VIII). The objectives were to decrease the volatility of the parent compound and to determine the structure-activity relationships in this series.



Trichloroacetamidine hydrochloride (XIII) was reacted with trichloromethanesulfenyl chloride (XIV) to give a 56% yield of II (3). The displacement of the Cl^- ion of II by the appropriate nucleophiles gave compounds III through VIII. The reactions were achieved by the slow addition of the appropriate nucleophiles, dissolved in suitable solvents, to a solution of II, and stirring for several hours at room temperature. The above general procedure is necessitated because of the instability of the allylic chlorines toward strong bases, especially at elevated temperatures. Furthermore, it takes advantage of the high reactivity of the chlorine at the 5-position toward nucleophilic displacements.

Compound VIII was obtained in almost quantitative yields following the general procedure outlined. A v.p.c. analysis[1] indicated the material to be of 90–95% purity. However, distillation of VIII *in vacuo* led to extensive desulfurization, and a 30% yield of an isomeric mixture (X) was obtained. On the basis of the spectral data,[2] the mixture was estimated to contain approximately 75% of VIII, the major component of the remainder being the *N*-alkylated product (XI). The thermal isomerization could proceed through the mechanism shown in Scheme I.

The fact that the propoxy derivative (VII) distilled unchanged and that it could not be isomerized by heating at 155–165° suggests that the transition state (XII) for the formation of XI may have some ionic character, being stabilized by the polar —OH group.

Attempts to obtain IX by reacting II with the anion $-P(OC_2H_5)_2$ (4), following the general procedure, failed. Although its formation was indicated [I.R., λ $CHCl_3$ 9.7 μ (aryl phosphate)] (5), isolation procedures led to extensive decomposition, and a mixture of unidentified products was obtained. The nature of this reaction was not studied further.

EXPERIMENTAL

All melting points were taken on a Thomas-Hoover melting point apparatus and are uncorrected. The v.p.c. separation was performed on K-22A column at 142° and 30 ml./min. gas flow. The infrared spectra were determined with samples in the form of Nujol mulls, and NMR spectra in deuteriochloroform in the presence of deuterium oxide with tetramethylsilane as the internal standard.

Substituted Thiadiazoles (Table I; III–VIII). General Procedure.—The appropriate nucleophile (0.1 mole) dissolved in a suitable solvent (chloroform or the alcohols from which the nucleophiles were generated) was added dropwise with stirring to a solution of 0.1 mole of 5-chloro-3-(trichloromethyl)-1,2,4-thiadiazole (II) dissolved in the same solvent. The mixture was then stirred for 4–6 hr., and allowed to stand overnight at room temperature. After removal of the solvent *in vacuo*, the product was isolated either by distillation under reduced pressure or by crystallization.

Pertinent data are listed in Table I.

5-(2-Hydroxyethoxy)-3-(trichloromethyl)-1,2,4-thiadiazole (VIII).—Sodium methylate, 2.83 Gm., was dissolved in 30 ml. of absolute methanol, and to this solution 31 Gm. of ethylene glycol, dissolved in 20 ml. of absolute methanol, was added. The mixture was concentrated to remove the methanol, and the remaining solution was then added dropwise at room temperature to a solution of 11.9 Gm. of II in 100 ml. of ether. The reaction mixture was stirred overnight, washed with water, and then dried over $MgSO_4$. Removal of ether gave 12.1 Gm. (92.4%) of the product as a thick pale yellow viscous oil. λ 2.95 μ, broad (bonded OH), and 6.55 μ (C=N), τ 5.25 (t, O—CH_2) and τ 5.95 (t, CH_2).

Anal.—Calcd. for $C_5H_5Cl_3N_2O_2S$: C, 22.51; H, 1.88; N, 10.84. Found: C, 21.87; H, 2.09; N, 10.99.

A v.p.c. analysis indicated the material to be 90–95% pure.

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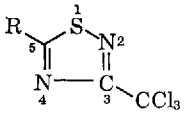
[1] The v.p.c. analysis was determined by Mr. A. Niedermayer.

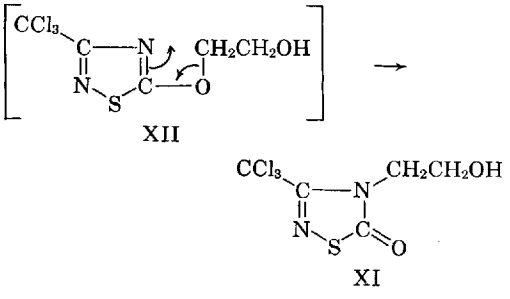
[2] The spectral data were furnished by Miss B. Keeler and Dr. A. Cohen.

TABLE I.—COMPOUNDS SYNTHESIZED



Compd.	R	M.p. or b.p., °C. (mm.)	Formula	Anal., %[a] Calcd.	Found
I	$-OCH_2CH_3$				
II	$-Cl$	53–55/0.05			
III	$-OCH(CH_3)_2$	70/0.02	$C_6H_7Cl_3N_2OS$	Cl, 40.66	40.68
				N, 10.71	10.96
				S, 12.26	12.61
IV	$-NH-NH_2$	182–183	$C_3H_3Cl_3N_4S$	Cl, 45.57	45.50
				N, 24.00	23.76
V	$-NH-OH$	170–171	$C_3H_2Cl_3N_3OS$	Cl, 45.37	45.36
				N, 17.92	17.60
VI	$-NH-O-CH_2-\phi$	153–155	$C_{10}H_8Cl_3N_3OS$	Cl, 32.78	32.94
				N, 12.95	12.97
VII	$-O-CH_2-CH_2-CH_3$	103.5–104/1.4	$C_6H_7Cl_3N_2OS$	Cl, 40.66	40.99
				N, 10.71	10.88
				S, 12.26	12.49
VIII	$-O-CH_2-CH_2-OH$				
IX	$-P(=O)(OC_2H_5)_2$				

[a] The microanalyses were conducted by Mr. J. Alicino.



XII

XI

Scheme I

Isomerization of 5-(2-Hydroxyethoxy)-3-(trichloromethyl)-1,2,4-thiadiazole (VIII → XI).—Ten grams of VIII was distilled *in vacuo* under nitrogen, and the fraction that distilled at 153–158°/0.6–0.7 mm. was collected as a thick yellow liquid, weighing 2.8 Gm. λ 2.95 μ broad (bonded OH), 5.85 μ (C=O) and 6.55 μ (C=N); τ 5.25 (t, O—CH_2), τ 5.51 (t, N—CH_2), and τ 5.95 (t, CH_2).

Anal.—Calcd. for $C_5H_5Cl_3N_2O_2S$: C, 22.51; H, 1.88; Cl, 40.48; N, 10.84. Found: C, 22.79; H, 1.92; Cl, 40.37; N, 10.63.

An attempted v.p.c. separation on K-122A column was not successful.

On the basis of the relative intensities of the C=N band at 6.55 μ, XI was estimated to be present to the extent of about 25%.

BIOLOGICAL TESTING

Compounds III–VIII were screened as soil fungicides[3] against 3 different pathogenic fungi, *Fusarium*, *Rhizoctonium*, and *Pythium*. Although no definite pattern of structure-activity relationships was discernible, all these compounds retained about 60–80% of the over-all activity of the analogous 5-ethoxy-3-(trichloromethyl)-1,2,4-thiadiazole. However, in general, they were more phytotoxic than I.

REFERENCES

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(5) Nakaniski, K., "Infrared Absorption Spectroscopy—Practical," Holden-Day, Inc., San Francisco, Calif., 1962, p. 56.

[3] The authors thank Dr. S. Cohen for the biological results.