

The Squibb Institute for Medical Research

## 5-Ethoxy-3-(trichloromethyl)-1,2,4-oxadiazole (I)

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5-Ethoxy-3-(trichloromethyl)-1,2,4-oxadiazole (V) was synthesized to elucidate the chemistry involved in the preparation of the hitherto unreported alkoxy-1,2,4-oxadiazoles and to determine the effect of the isosteric replacement of sulfur by oxygen on anti-fungal activity. Heating the "amino-oxime" tautomer II of trichloroacetamidoxime with ethyl chloroformate furnished exclusively the *O*-acylated product III. The *trans* configuration of III accounts for its resistance to cyclize under a variety of conditions, in contrast to the general behaviour of acylated amidoximes. Pyrolysis of III at 160° yielded IV which exists in the keto form. Refluxing IV with ethyl iodide in the presence of silver oxide gave an isomeric mixture which was separated by v.p.c. to give V and VI. Compound V retained 60% of the overall activity of the corresponding sulfur analog.

The discovery of the useful antifungal activity exhibited by 5-ethoxy-3-(trichloromethyl)-1,2,4-thiadiazole (2) prompted us to synthesize the corresponding oxygen analog. We were interested in determining the effect of the isosteric replacement of sulfur by oxygen on antifungal activity. Furthermore, since until recently (3), no alkoxy and/or alkyl substituted 1,2,4-oxadiazole has been reported (4), an elucidation of the chemistry involved in its synthesis appeared of interest to us for possible further development of this type of compounds.

The synthesis of 5-ethoxy-3-(trichloromethyl)-1,2,4-oxadiazole (V) has been achieved in satisfactory yields through the following sequence of reactions (Chart I).

Trichloroacetonitrile was allowed to react with hydroxylamine base to give II in 59% yield. However, the use of a mixture of hydroxylamine hydrochloride and potassium carbonate in the above reaction (5) gave a lower yield of II (25-37%). The much higher yield in the former case could be ascribed to the greater concentration of the preformed nucleophile, and the absence of salt effects.

Recent infrared and n.m.r. studies on related amidoxime (3, 6) reveal that amidoximes exist exclusively as one (VIIIb) of the two possible tautomers VIIIa and VIIIb. The infrared spectrum of II showed

two sharp NH<sub>2</sub> bands at 2.90 and 2.98 μ, and a broad bonded hydroxyl at 3.0-3.5 μ (7) in agreement with the "amino-oxime" structure of amidoximes. Confirmation of this structure was obtained from the n.m.r. spectrum (8), which indicates one proton at τ 0.87 (s, OH), and two protons at τ 4.98 (s, NH<sub>2</sub>).

Heating two molar equivalents of II with one equivalent of ethyl chloroformate at 75° furnished an 85% yield of III, one equivalent of the amidoxime functioning as the acid acceptor. The use of bases like triethylamine, in the above reaction gave lower yields (*ca.* 65%) of the product III. Although halogenated acetamidoximes have been reported to yield *N*-acylated products (5), we found no evidence of *N*-acylation occurring in this case (9). Infrared and n.m.r. data established III to be wholly the *O*-acylated product. The infrared spectrum of III revealed the absence of the broad hydroxyl peak at 3.0-3.5 μ, and the persistence of the two NH<sub>2</sub> bands at 2.86, and 2.95 μ. The n.m.r. spectrum showed the following protons (8): τ 5.64 (q, O-CH<sub>2</sub>), τ 8.70 (t, CH<sub>3</sub>), two protons at τ 4.63 (s, NH<sub>2</sub>), and no signal at τ 0.87 (absence of N-OH).

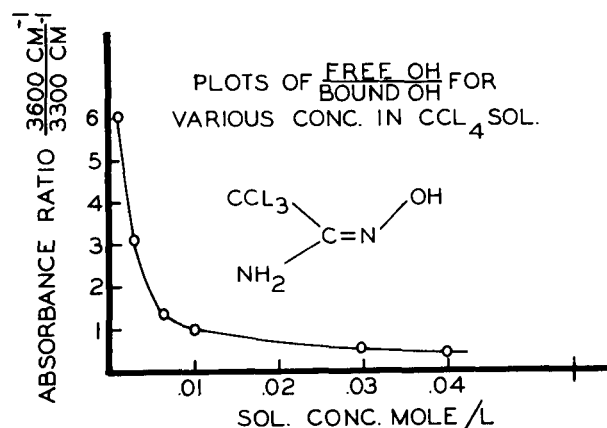
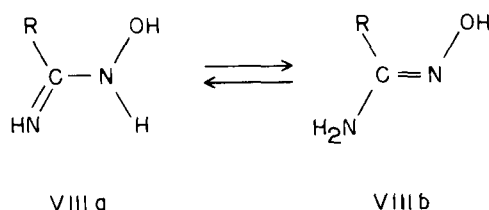
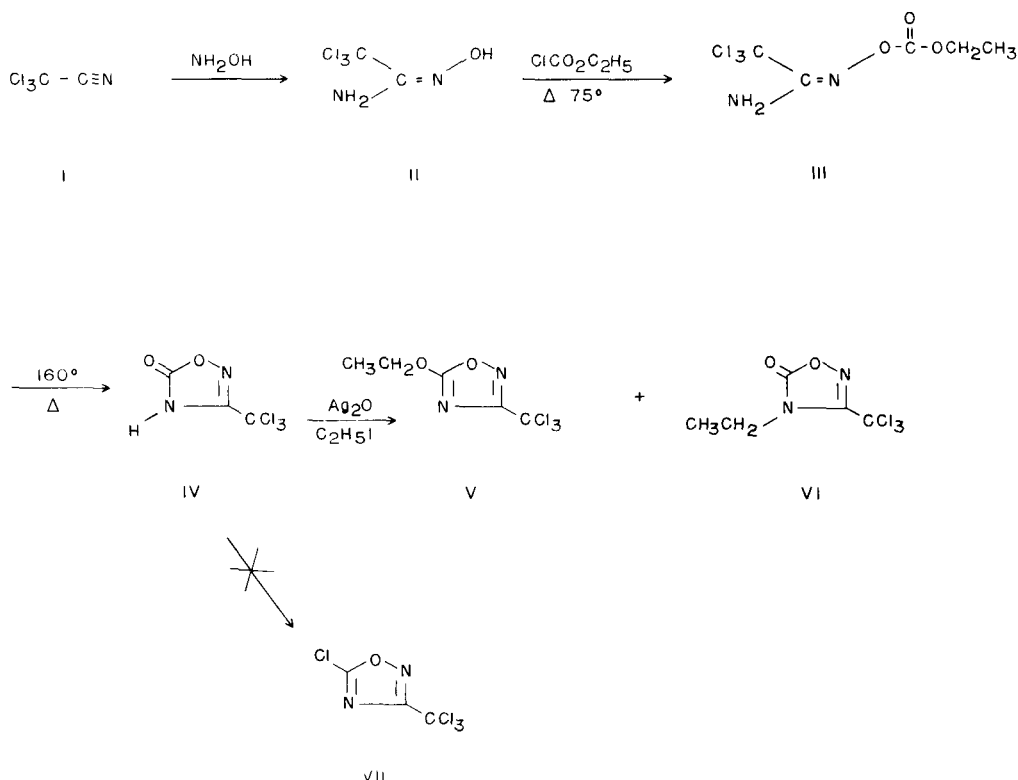


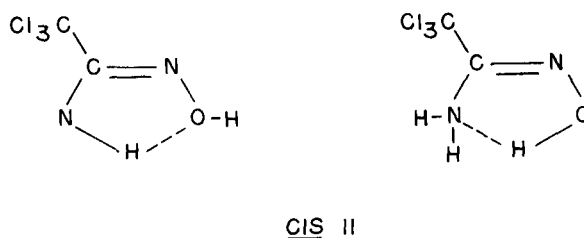
FIGURE 1

CHART I



The cyclization of III proved to be difficult and a variety of reaction conditions (heating with acetic acid, pyridine, water, benzene or ethanol) was tried (10) before a satisfactory procedure was worked out. At first, this phenomenon appeared surprising in view of the fact that acylated amidoximes are well-known to cyclize readily (3, 5b, 6, 11). However, a detailed examination of II and III showed that they exist in the *trans* form, ( $\text{NH}_2$  and O-H or O-R are *trans*) needing a high energy of activation for the cyclization to occur. The assignment of the *trans* arrangement is based on the following observations. The infrared spectrum of II in dilute carbon tetrachloride solution ( $< 0.002 M$ ) exhibited the stretching frequency of both a nonbonded hydroxyl at  $3600 \text{ cm}^{-1}$  and a bonded hydroxyl band at  $3300 \text{ cm}^{-1}$ . The ratio of the free and bound hydroxyl absorbances were found to be concentration dependent (Figure 1). This concentration dependence suggests intermolecular hydrogen bonding (12). From models, it becomes obvious, that in the *cis* form, steric crowding around the  $\text{Cl}_3\text{CC}=\text{N}$  bond would preclude intermolecular hydrogen bonding. In addition, intramolecular hydrogen bonding should predominate due to *cis* orientation. Therefore, the favoured geometry of II is a *trans* arrangement of the  $\text{NH}_2$  and OH groups. The acylation reaction ( $\text{II} \rightarrow \text{III}$ ) does not involve any bond breaking or making processes around the  $\text{C}=\text{N}$  bond

and hence the *trans* arrangement is preserved in III. Confirmation of this structure was obtained from the infrared spectrum, which indicates no bonding interactions even in the solid state. Should compound III be *cis*, we would expect strong intramolecular bonding.



Recognizing the *trans* geometry of III, drastic reaction conditions were chosen to achieve the desired ring closure. Compound III was pyrolyzed at  $160^\circ$  to give a 41% yield of IV. Compound IV exists in the keto form as shown by infrared and n.m.r. data:  $\lambda$  3.17 (broad, bonded NH), 5.62 (s,  $\text{C}=\text{O}$ ) and  $6.32 \mu$  ( $\text{C}=\text{N}$ ): single proton peak at  $\tau$  0.85 (NH). This is in keeping with the general observation of Katritzky, *et al.*, (13) who have

shown that 5-membered heterocycles with hetero atoms-1,2 and a potential 5-hydroxy group exist predominantly in the keto form. All attempts to convert IV→VII failed (14) under a variety of reaction conditions, further substantiating the lack of enolic character of the carbonyl at position 5 in IV.

The treatment of IV with an excess of ethyl iodide in the presence of silver oxide resulted in a strong exothermic initial reaction, and produced a 78% yield of an isomeric mixture. Spectral analyses identified the mixture to be a composite of V and VI;  $\lambda$  5.55 (C=O), 6.20 (C=N), and 7.7, 9.75  $\mu$  (aromatic ether);  $\tau$  5.32 (q, O-CH<sub>2</sub>), and  $\tau$  8.47 (t, CH<sub>3</sub>). By v.p.c. (15), the mixture of isomers was resolved into 87% of V [ $\lambda$  6.20 (C=O), and 7.7, 9.75  $\mu$  (aromatic ether);  $\tau$  5.32 (q, O-CH<sub>2</sub>), and  $\tau$  8.47 (t, CH<sub>3</sub>)], and 10% of VI [ $\lambda$  5.55 (s, C=O), 6.20  $\mu$  (C=N); and  $\tau$  5.96 (q, N-CH<sub>2</sub>), and  $\tau$  8.47 (t, CH<sub>3</sub>)]. Surprisingly, in related five membered ring systems, no *N*-alkylation was observed, under the same experimental conditions (16).

#### Biological Testing.

Compound V was screened (17) as a soil fungicide against three different pathogenic fungi *Fusarium*, *Rhizoctonium* and *Pythium*. It retained 60% of the overall activity of the corresponding sulfur analog.

#### EXPERIMENTAL (18)

##### 2,2,2-Trichloroacetamidoxime (II).

###### Method (a).

A solution of 72.3 g. (0.5 mole) of trichloroacetonitrile in 100 ml. of anhydrous ether was added dropwise with stirring at a temperature of 5-10° to a suspension of 16.5 g. (0.5 mole) of hydroxylamine in 1.5 l. of anhydrous ether (addition time, 1.5 hours). Stirring at 5-10° was continued for an additional hour. The mixture was then washed with 25 ml. of ice cold water, and the ethereal solution was dried over anhydrous magnesium sulfate. Evaporation of the ether gave 67.5 g. of a yellowish-white solid, m.p. 115-119°. It was crystallized from a 1:1 mixture of benzene and hexane to give 52.5 g. (59%) of shiny white crystals, m.p. 125°. An analytical sample was obtained by a further crystallization from the same solvent mixture, m.p. 128°.

*Anal.* Calcd. for C<sub>2</sub>H<sub>3</sub>Cl<sub>3</sub>N<sub>2</sub>O: C, 13.54; H, 1.71; N, 15.79; Cl, 59.95. Found: C, 13.38; H, 1.95; N, 16.04; Cl, 60.20.

###### Method (b).

To a solution of 3.54 g. of hydroxylamine hydrochloride, and 3.54 g. of potassium carbonate in 20 ml. of water, 7.2 g. of I was added in the cold and the mixture stirred for 3 hours in the ice bath. Crystallization of the oily white solid from a mixture of benzene and hexane afforded 3.2 g. (32%) of II.

##### O-Ethoxycarbonyl-2,2,2-trichloroacetamidoxime (III).

###### Method (a).

A stirred mixture of 8.9 g. of 2,2,2-trichloroacetamidoxime and 7.5 ml. of ethyl chloroformate was placed in an oil bath and the temperature of the oil bath raised slowly during 30 minutes to 75°. At 75°, the reaction mixture (half solid, half liquid) was removed from the heating bath and stirred for 15 minutes. The exothermic reaction (temperature rising to 85°) subsided during this time. The mixture was again heated to 80-90° for an additional 15 minutes, and subsequently allowed to cool. The addition of 30 ml. of dry ether resulted in the precipitation of 6.2 g. (93%) of II as the hydrochloride. The ether solution was washed with water (30 ml.) and dried over anhydrous magnesium sulfate. Slow evaporation of ether gave 5.2 g. (85% yield, based on the recovered starting material) of white crystals, m.p. 97-103°. Crystallization from carbon tetrachloride gave an analytical sample, m.p. 105-105.5°.

*Anal.* Calcd. for C<sub>8</sub>H<sub>7</sub>Cl<sub>3</sub>N<sub>2</sub>O<sub>3</sub>: C, 24.06; H, 2.82; N, 11.22; Cl, 42.64. Found: C, 24.21; H, 3.07; N, 10.94; Cl, 42.48.

###### Method (b).

To a solution of 4.96 g. of II and 4.5 ml. of pyridine in 300 ml. of ethanol, 2.6 ml. of ethyl chloroformate in 30 ml. of benzene was added and the mixture heated under reflux for an hour. Isolation as in Part A gave 4.1 g. (59%) of III.

##### 3-(Trichloromethyl)- $\Delta^2$ -1,2,4-oxadiazolin-5-one (IV).

Compound III, 24.95 g. (0.1 mole) was pyrolyzed at 160° (preheated oil bath) for 45 minutes. By this time, the reaction was essentially complete as indicated by the very sluggish evolution of gas and lack of NH bands at  $\lambda$  2.86 and 2.95  $\mu$  in the infrared spectrum. On cooling, a thick yellow oil was obtained which solidified on the addition of hexane and scratching, 19.2 g., m.p. 103-125°. Two crystallizations from a mixture of chloroform and hexane gave 8.5 g. (41%) of white crystals, m.p. 129-131°. One further crystallization from carbon tetrachloride gave an analytical sample, m.p. 131-132°.

*Anal.* Calcd. for C<sub>3</sub>H<sub>3</sub>OCl<sub>3</sub>N<sub>2</sub>: C, 17.71; H, 0.50; Cl, 52.27; N, 13.76. Found: C, 17.62; H, 0.55; Cl, 51.98; N, 13.74.

##### 5-Ethoxy-3-(trichloromethyl)-1,2,4-oxadiazole (V).

Ethyl iodide (10 ml.) was added cautiously (reaction exothermic, strong cooling necessary) to a mixture of 2.03 g. (10 mmoles) of IV and 2.3 g. (10 mmoles) of silver oxide and then heated under reflux with stirring for 3 hours. The mixture was filtered and the excess of ethyl iodide removed *in vacuo* to give 1.8 g. (78%) of a pale yellow oil, b.p. 100-110°/2 mm.

By v.p.c. the above mixture was resolved into 87% of V and 10% of VI.

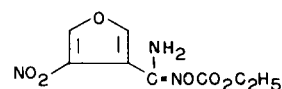
*Anal.* Calcd. for C<sub>6</sub>H<sub>5</sub>Cl<sub>3</sub>N<sub>2</sub>O<sub>2</sub>: C, 25.94; H, 2.18; Cl, 45.95; N, 12.11. Found: C, 25.71; H, 2.23; Cl, 45.41; N, 12.42.

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and pyridine for long periods. In our hands, this procedure, when applied to convert IV→VII, led to the isolation of chlorine-free products. This is not surprising in view of the instability of the allylic chlorines at the 3-position towards bases at high temperatures.  
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