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Metal Coordination Compounds of Thiabendazole

Several metal coordination compounds of the fungicide thiabendazole, 2-(4'-thiazolyl)benzimidazole (TBZ), have been prepared and the solubilities in water and the pH of the solutions

have been determined. Fungicidal activity of the compounds = TBZ against an isolate of *Penicillium* and of *Fusarium*.

Thiabendazole, 2-(4'-thiazolyl)benzimidazole (TBZ), has been widely used for plant disease control since its fungicidal properties were reported by Staron and Allard (1964). In an earlier investigation (Miller *et al.*, 1971), the formation of metal salts of TBZ were noted which were similar to metal salts of the parent compound benzimidazole, as reported by Skraup (1919) and Feigl and Gleich (1928). The present compounds herein reported are believed to be coordination compounds of thiabendazole, similar to the nickel compounds of 2-(hydroxymethyl)benzimidazole and methylbenzimidazole, as reported by Artemenko and Chistyakova (1970), and the cobalt compounds of 2-benzylbenzimidazole, as reported by Artemenko *et al.* (1972). The formulas were NiL_2X_2 or NiL_3X_2 and CoL_2X_2 , in which L = benzimidazole derivative and X = one of several monovalent anions.

This report describes the synthesis and some physical and biological properties of several of these coordination compounds.

EXPERIMENTAL SECTION

The 1:1:2 molar ratio (metal-TBZ-chloride) cupric compound was prepared by dissolving 1.5 g of TBZ in 40 ml of boiling ethanol containing 0.27 ml of 12 N HCl and adding 1.28 g of $CuCl_2 \cdot 2H_2O$ in ~25 ml of ethanol. The pale green $CuTBZCl_2$ precipitated at once. The mixture was refluxed ~2 hr on the steam bath. The compound was separated by centrifugation and washed in the centrifuge tube with ethanol.

The 1:1:2 zinc compound was prepared by dissolving 1.5 g of TBZ in 50 ml of boiling ethanol and adding 1.0 g of $ZnCl_2$. The white $ZnTBZCl_2$ quickly precipitated. The mixture was refluxed for ~2 hr and filtered hot. The insoluble crystals were purified by ethanol extraction in a ASTM Method D147 extraction apparatus (VWR Scientific =27630-000). As crystals formed in the solvent the solvent was poured off, and further crystallization occurred on cooling. More ethanol was added to the extraction apparatus and the extraction continued until the crude $ZnTBZCl_2$ had been dissolved and crystallized.

Cupric 1:2:2 compound was prepared by dissolving 2.0 g of TBZ and 0.86 g of $CuCl_2 \cdot 2H_2O$ in 100 ml of hot water containing 0.85 ml of 12 N HCl. The solution was warmed on the steam bath for ~2 hr. Dark green crystals formed. An additional 500 ml of boiling water was added and

stirred on a hot plate to effect solution. The solution was filtered hot and the filtrate allowed to crystallize. This compound may be recrystallized from ethanol using the ASTM extraction apparatus in the same manner as the $ZnTBZCl_2$ to give green $Cu(TBZ)_2Cl_2 \cdot 2H_2O$.

The cobalt 1:2:2 compound was prepared in the same manner as the $Cu(TBZ)_2Cl_2 \cdot 2H_2O$, except that 1.2 g of $CoCl_2 \cdot 6H_2O$ was used with 2.0 g of TBZ. The solution was filtered hot and evaporated to dryness at room temperature. The dry crude cobalt TBZ chloride was extracted in an ASTM extraction apparatus with ethanol. The pink ethanol-insoluble compound remaining in the thimble was $Co(TBZ)_2Cl_2 \cdot 2H_2O$.

Zinc 1:2:4 compound was prepared by dissolving 14.6 g of TBZ in 200 ml of hot water containing 7.0 ml of 12 N HCl. When the solution was complete, 4.5 g of $ZnCl_2$ in 20 ml of 6 N HCl was added and the solution heated (~95°) on the steam bath for 1 hr. The solution was filtered hot and the filtrate evaporated to dryness on the steam bath. The dry crude compound was transferred to a thimble and extracted with hot ethanol in an ASTM extraction apparatus. The $Zn(TBZ)_2Cl_4$ was very soluble in ethanol and was quickly separated from the small amount of insoluble $ZnTBZCl_2$. On cooling the solution, crystals of $Zn(TBZ)_2Cl_4$ separated.

The 1:2:2 nickel compound was prepared by dissolving 2.0 g of TBZ and 1.2 g of $NiCl_2 \cdot 6H_2O$ in 100 ml of water containing 5.0 ml of 12 N HCl and warming on the steam bath for ~2 hr. The solution was filtered hot and evaporated to dryness on the steam bath. The dried material was placed in a thimble of an ASTM extraction apparatus and extracted with ethanol. Any $Ni(TBZ)_3Cl_2$ present was rapidly extracted by the hot ethanol, and the pale blue powder remaining in the thimble was $Ni(TBZ)_2Cl_2 \cdot 2H_2O$.

The 1:3:2 nickel compound was prepared by dissolving 3.0 g of TBZ and 1.2 g of $NiCl_2 \cdot 6H_2O$ in 100 ml of ethanol and refluxing 15 min on the steam bath. The solution was filtered hot and evaporated to incipient crystal formation. Recrystallization of the purple crystals of $Ni(TBZ)_3Cl_2 \cdot 3H_2O$ was from ethanol.

Cobalt TBZ gluconate (GLU) was prepared by heating 10 mM each of $CoCO_3$ and glucono-*d*-lactone in 100 ml of water on the steam bath until most of the carbonate had dissolved. The solution was filtered and 10 mM of TBZ was added. The heating on the steam bath was continued

Table I. Metal Complexes of Thiabendazole

Molar ^a ratio	Analysis, calcd/found			Color	Mp	Water solubility, as TBZ mg/ml	pH 1 mg/ml in water	Inhibitory concentration, $\mu\text{g/ml}$ of TBZ	
	Metal	TBZ	Cl					<i>Penicillium</i>	<i>Fusarium</i>
	Cu								
1:1:2	18.9/18.6	59.9/59.6	21.2/20.8	Pale green	286-290	1.8	3.7	7	
1:2:2·2H ₂ O	11.4/11.1	70.0/70.1	12.4/12.0	Deep green	264	1.5	3.9	9	61
	Zn								
1:1:2	19.4/19.1	59.6/60.2	21.0/20.2	White	>300	1.4	4.8		
1:2:4	10.7/10.4	66.0/66.0	23.3/22.6	White	280	5.8	3.2	7	53
	Co								
1:2:2·2H ₂ O	10.4/10.4	70.8/70.8	12.5/12.8	Pink	>300	2.0	5.2	9	51
1:1:2·2H ₂ O	8.6/8.5	29.2/29.1	b	Pink	166	5.5	4.9	5	
	Ni								
1:2:2·2H ₂ O	10.3/10.7	70.8/71.2	12.5/12.6	Pale blue	>300	1.4	4.6		
1:3:2·3H ₂ O	7.5/7.0	76.6/76.1	9.0/9.0	Purple	298	2.2	4.2	9	55

^a Metal:TBZ:anion. ^b Gluconate.

for 2-3 hr. The solution was filtered hot and the filtrate was evaporated to ~25 ml on the steam bath. The solution was allowed to crystallize overnight. Pink crystals of CoTBZ(GLU)₂·2H₂O separated.

The yields of pure material were 40-60%. For analysis the compounds were hydrolyzed in 6 N HCl at steam bath temperature for 1-2 hr. The metal analyses were by methods reported by Sandell (1959). TBZ was determined by absorbance of an aliquot of the digest in 0.1 N HCl measured at 302 nm (Merck and Co., 1967). For chloride analysis, the sample was dissolved in dilute nitric acid and titrated by the procedure of Caldwell and Moyer (1935). The compounds and some of the properties are listed in Table I. All the compounds except for CoTBZ(GLU)₂ have melting points near or over 300° (the melting point of TBZ was 304-305°; Brown *et al.*, 1961).

The approximate water solubility of the compounds was determined by machine shaking of excess compound with water at room temperature for at least 4 hr. The solutions were filtered, in some instances through a packed Celite column to remove colloidal material. The clear solutions were diluted with 0.1 N HCl and the absorbance was determined at 302 nm to measure the amount of TBZ present. The water solubility of TBZ was determined to be 1-2 $\mu\text{g/ml}$, less than the 30 $\mu\text{g/ml}$ reported by Merck and Co. The Zn(TBZ)₂Cl₄ and CoTBZ(GLU)₂ were the most soluble. The solubility of TBZHCl as TBZ was 18.2 mg/ml, and the pH was 3.3. The solubility of this salt was some ten times the solubility of TBZ at the pH of 3.3 reported by Merck and Co. (1963).

The water solutions of Cu(TBZ)₂Cl₂, CuTBZCl₂, Zn(TBZ)₂Cl₄, Ni(TBZ)₂Cl₂, and CoTBZ(GLU)₂ were stable; the other solutions gradually decomposed with separation of colloidal material after standing a few days.

The materials to be bioassayed were dissolved in water and the concentration was determined by spectroscopy at 302 nm in 0.1 N HCl. Serial dilutions were made in water. Each concentration was 0.707 times the preceding one. Sterile blank Bacto concentration disks were dipped in the solution, the excess liquid was removed, and the disk was placed on seeded potato dextrose agar in a petri dish. The control level was considered to be the minimum concentration required to produce a clear zone around the

disk. The test organisms were a *Penicillium* spp. and *Fusarium* spp. isolated by one of us (C.J.G.) from infected iris bulbs. The control level of active ingredient of commercially formulated TBZ determined by this bioassay was 11 $\mu\text{g/ml}$ for *Penicillium* and 92 $\mu\text{g/ml}$ for *Fusarium*. The activity of the synthetic materials may reflect water solubility rather than greater potency. However, these data from several bioassays indicate that the fungicidal activity of the coordination compounds is at least equal to the activity of formulated TBZ.

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