SOME COORDINATION COMPOUNDS OF 6-MERCAPTOPURINE

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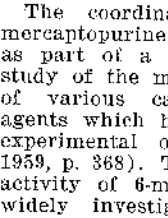
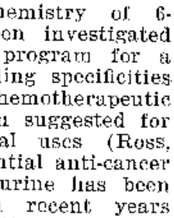
ABSTRACT.—A number of bis chelates of 6-mercaptopurine with divalent metals have been synthesized and characterized. A presumably dinuclear complex has been isolated with copper (I) thiocyanate.

The coordination chemistry of 6-mercaptopurine has been investigated as part of a general program for a study of the metal-binding specificities of various cancer chemotherapeutic agents which have been suggested for experimental or clinical uses (Ross, 1959, p. 368). The potential anti-cancer activity of 6-mercaptopurine has been widely investigated in recent years (Brockman, 1963, p. 1191) (Elion, 1963, p. 1207). Details of our experimental work are given at the end of this paper.

The structure of 6-mercaptopurine, I, with an ionizable mercapto group *peri* to a tertiary heterocyclic nitrogen atom is formally analogous to that of 8-hydroxyquinoline, II, and the well-known avidity of II for a wide variety of metallic cations (Hollingshead, 1954) suggests that 6-mercaptopurine might be expected to exhibit similar behavior.



I



II

However, the coordination chemistry of 6-mercaptopurine has received only slight attention. The most significant investigation was undertaken by Freiser and his coworkers (1959). They determined the aqueous formation constants for complexes of this ligand with Ni(II), Co(II), Pb(II), and Zn(II). No one seems to have reported the isolation and characterization of such complexes.

The synthetic procedure employed in the preparation of divalent metal complexes of 6-mercaptopurine was based upon the general reaction, $M(C_2H_3O_2)_2 \cdot (0\text{-}4)H_2O + 2C_5H_4N_4S \cdot H_2O = M(C_5H_3N_4S)_2 \cdot (0\text{-}2)H_2O + 2HC_2H_3O_2 + (2\text{-}6)H_2O$, where M = Co(II), Ni(II), Zn(II), Cd(II), Hg(II), and Pb(II). Methanol was employed as a solvent with the single exception of the cobalt (II) case in which the use of dimethylformamide was found to yield a purer product. The reactions proceed smoothly and the yields are moderate to high. Purification of the resulting complexes is relatively simple since all of the starting materials and extraneous products are soluble in hot methanol whereas the complexes are insoluble in that solvent. Hence, solvent extraction offers a convenient purification technique.

The complexes attract and hold water tenaciously. Several of the compounds analyze as the dihydrates even after drying for 24 hours in a vacuum at 100°. The nickel (II) compound may be isolated as a monohydrate but, on standing exposed to the air, it readily acquires a second molecule of water.

The actual presence of waters of hydration, as indicated by the elemental analyses, was confirmed by the infrared spectra of these compounds as well as by a study of their thermal stabilities. Thus, the spectra of the hydrated species show strong absorption in the 3400-3500 cm^{-1} region whereas this region is empty in the case of anhydrous species. More convincing, since several of the spectra were run after exposure of the sample to air, were thermal stability studies which showed that each of the hydrated species lost 5-10% of its initial weight at 200°. This loss corresponds to the removal of 1-2 water molecules. In most cases there is a plateau of relative stability beyond this point, extending as high as 350°.

All of the complexes are soluble with decomposition in strong acids or bases and relatively insoluble in water and most polar organic solvents.

6-Mercaptopurine, in the manner common to thiol ligands, reduces copper(II) to copper(I) prior to complex formation. In order to avoid the complications inherent in such a stepwise reaction, a copper (I) complex of 6-mercaptopurine was prepared by the direct reaction of copper(I) thiocyanate and the ligand. The reaction proceeds slowly in methanol and is characterized by a gradual color change from pale yellow to deep cherry red. The product isolated after 24 hours analyzes as a 1:1 adduct, Cu($C_5H_4N_4S$) (SCN). This species is diamagnetic. It may be a dimer with thiocyanate bridges but no suitable solvent for a molecular weight determination has been found. Hence, full characterization of this species must await further study.

PROCEDURES

Thermal stability studies were conducted with a simple thermogravimetric balance constructed by Judd (1958). Infra-red spectra were obtained as KBr disks and fluorolube mulls using a Beckman Model IR-5 spectrophotometer.

Sythesis of bis (6-mercaptopurinato) lead (II).-6-Mercaptopurine hydrate (0.68 g, 0.004 mole) was placed in a 500 ml., one-necked, round-bottom flask and dissolved with 200 ml. of absolute methanol. Lead acetate trihydrate (0.76 g, 0.002 mole) was added to the solution and the mixture was slurried with a magnetic stirrer. The flask was equipped with a water-cooled condenser and the mixture was placed under gentle reflux. After 24 hours the reaction mixture was filtered. The chunks of yellow solid product were ground to a powder, placed in a Soxhlet extractor, and extracted with hot methanol for 24 hours. The yield was 1.00 g (82%). (Analysis: Calculated for $C_{10}H_6N_8S_2Pb$: C, 23.57; H, 1.19; N, 21.99. Found: C, 23.59; H, 1.58; N, 21.83).

The following compounds were prepared under conditions similar to the formation of bis (6-mercaptopurinato) lead (II):

> bis (6-mercaptopurinato) mercury (II), yield 94%. Analysis: Calculated for $C_{10}H_6N_8S_2Hg$: C, 23.88; H, 1.20; N, 22.28. Found: C, 23.85; H, 1.33; N, 21.90.
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> bis (6-mercaptopurinato) cadmium (II) dihydrate, yield 75%. Analysis: Calculated for $C_{10}H_6N_8S_2Cd \cdot 2H_2O$: C, 26.64; H, 2.24; N, 24.86. Found: C, 26.51; H, 1.81; N, 24.68.
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> bis (6-mercaptopurinato) zinc (II) dihydrate, yield 67%. Analysis: Calculated for $C_{10}H_6N_8S_2Zn \cdot 2H_2O$: C, 29.75; H, 2.50; N, 27.75. Found: C, 29.84; H, 2.05; N, 28.26.
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> bis (6-mercaptopurinato) nickel (II) monohydrate, yield 87%. Analysis: Calculated for $C_{10}H_6N_8S_2Ni \cdot H_2O$: C, 31.69; H, 2.13; N, 29.56. Found: C, 31.73; H, 2.56; N, 29.75.

Synthesis of a copper (I) complex of 6-mercaptopurine 6-Mercaptopurine hydrate (1.10 g, 0.006 mole) and copper (I) thiocyanate (0.36 g, 0.003 mole) were slurried in 200 ml. of absolute methanol in a 500 ml. one-necked, round-bottom flask. The flask was equipped with a water-cooled condenser and the mixture was placed under gentle reflux. After 24 hours the mixture had changed from a pale yellow hue to a bright cherry red. The solid product was filtered, extracted with hot methanol for 24 hours and dried *in vacuo* for 24 hours. The yield was 0.78 g (93%). (Analysis: Calculated for $C_5H_4N_4S \cdot Cu$ SCN: C, 26.32; H, 1.47; N, 25.58. Found: C, 26.38; H, 1.44; N, 25.51).

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