

Metal Ions and Biological Activity. Part I. Copper Complexes of Isonicotinic Acid Hydrazide

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Copper complexes with isonicotinic acid hydrazide in both the valence states have been described. A general method for the preparation of 1:1 Cu (II) complexes is also described.

Isonicotinic acid hydrazide, commonly known as isoniazid, has been shown to behave as bidentate in its chelate with bivalent metal ions. Fallah *et al.*¹ studied its behaviour with copper ions conductometrically and spectrophotometrically and showed the presence of $[C_5H_4NC(=N.NH_2)O]_2Cu$. Albert² found bivalent metal ion to react with 1 or 2 moles of isoniazid to form $[C_5H_4NC(=N.NH_2)O]M^{1+}$ (I) and $[C_5H_4NC(=N.NH_2)O]_2M(II)$. With copper sulphate, Sorokin prepared a light blue compound of composition $C_6H_{11}O_7 \cdot N_3S \cdot Cu$, but its structure was not proposed. Wojahn⁴ showed that with mercury, isoniazid formed an ion-dipole complex of molecular formula $(Isoniazid)_2(HgCl_2)_3$. Isoniazid antagonises the toxic effect of heavy metals, especially copper, on organisms (*C. coligy* and *S. garattini*)⁵; also its copper complex inhibits the autorepiration of tubercle bacteria at a relatively low concentration with respect to that of isoniazid. The inhibiting effect of isoniazid on the growth of tubercle bacteria on egg medium has been reported by Pothmann and Stuttgart⁶ through the copper complex. It has been observed that 1:1 copper complex of isoniazid is biologically important and 1:2 copper complex reverts to 1:1 state in many biological processes⁷. Since the formation of 1:1 copper isoniazid complex has not been fully investigated, the present work has been undertaken with a view to studying the formation of these complexes with different acid radicals attached to it. Since such complexes are formed by addition of isoniazid solution to a water-soluble copper salt in molecular ratio, it has not been possible to prepare such complexes with acid radicals, such as oxalate or phosphate, attached to 1:1 complex. A general method for the preparation of such complexes was found through metathesis of isoniazid-copper (II) acetate complex by the corresponding alkali salts.

All these complexes may be represented by the formula $[C_5H_4N.C(=N.NH_2)O].CuX_n \cdot nH_2O$, where X is a monovalent acid radical. Compound ($X=I$) could not be prepared since the iodine, liberated on addition of alkali iodide to copper acetate solution, oxidised isoniazid to bis-niazid. All these complexes are light green in colour, insoluble in water, ethanol, chloroform but soluble in pyridine. These are decomposed by mineral acids and

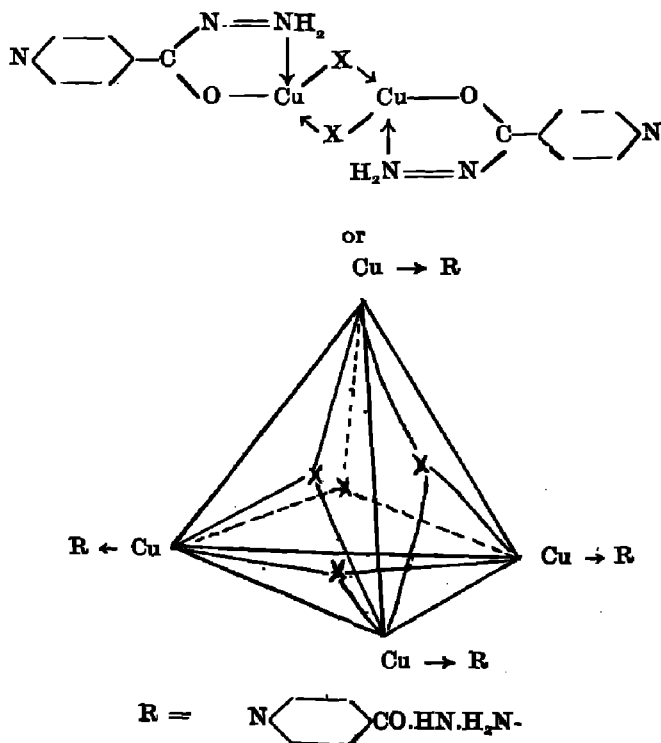
1. *Experientia*, 1952, 8, 298; *Helv. Chim. Acta*, 1953, 36, 3.
2. *Experientia*, 1953, 9, 370.
3. *Arch. Pharm.*, 1954, 287, 45.
4. *Atti Soc. Lombarda Sci. Med. Biol.*, 1953, 8, 45.
5. *Chem. Abs.*, 1955, 49, 14160.
7. William *et al.*, *J. Amer. Pharm. Assoc.*, 1959, 41, 282.

on warming with alkali hydroxides, nitrogen is evolved with formation of an orange-red precipitate.

When isoniazid is added to copper acetate solution prior to that of alkali salts, another yellowish green copper complex of empirical formula $C_6H_6N_3OCuX$ ($X=Cl$ or Br) (III) is formed where copper is present in mono and divalent states. On treating the complex with dilute nitric acid, a white compound separated which on analysis was found to be cuprous chloride or bromide. On treatment with sodium bicarbonatesolution, the complex was converted into a brownish yellow complex of molecular formula, (Isoniazid)- $Cu_2(HCO_3)_2$. Further work for the determination of the structure of this complex is under progress.

Cuprous Complexes of Isoniazid

No complex of isoniazid with copper (I) has been reported so far. The presence of copper (I) in complex (III) indicates that isoniazid may form cuprous complexes as well. These have been prepared as yellow- or orange-coloured compounds from cuprous chloride, bromide, iodide, and thiocyanate and are insoluble in water, ethanol, chloroform, but readily soluble in pyridine. The empirical formulas correspond to $C_6H_6ON_3CuX$ ($X=Cl, Br, I, \& CNS$). In view of the well-known tetrahedral configuration exhibited by cuprous complexes, these may be represented as :



METAL IONS AND BIOLOGICAL ACTIVITY

TABLE I

Compounds.	Colour.	%Carbon.		%Hydrogen.		%Nitrogen.		%Copper.		%X.		Total isoniazid.	
		Found.	Reqd.	Found.	Reqd.	Found.	Reqd.	Found.	Reqd.	Found.	Reqd.	Found.	Reqd.
A. Mono-isoniazid Cu(II) complexes.													
1. Chloride $C_6H_6ON_3CuCl \cdot 2H_2O$	Green	26.50	26.50	3.46	3.69	15.36	15.49	23.64	23.44	13.18	13.09	50.76	50.55
2. Bromide $C_6H_6ON_3CuBr \cdot 2H_2O$	"	22.04	22.82	3.32	3.16	13.06	13.31	20.33	20.13	25.48	25.35	43.69	43.42
3. Nitrate $C_6H_6ON_3Cu(NO_3) \cdot 2H_2O$	"	24.08	24.20	3.48	3.36	10.08	10.82	21.72	21.35	46.50	46.05
4. Sulphate $C_6H_6ON_3Cu(HSO_4) \cdot 2H_2O$	White-green	21.60	21.65	3.45	3.30	12.70	12.63	19.12	19.10	9.04	9.62	41.58	41.20
5. Oxalate $C_6H_6ON_3Cu(HC_2O_4) \cdot 2H_2O$	Green	29.38	29.58	3.06	3.38	12.80	12.94	19.39	19.58	42.52	42.22
6. Phosphate $C_6H_6ON_3Cu(H_2PO_4) \cdot 2H_2O$.	Light greenish violet	21.64	21.65	3.54	3.61	12.62	12.63	19.17	19.10	41.50	41.20
B. Mono-isoniazid Cu(I) complexes.													
1. Chloride $(C_6H_6ON_3CuCl)$	Orange	30.42	30.63	2.83	2.55	18.00	17.87	27.11	27.08	15.38	15.10	58.51	58.29
2. Bromide $(C_6H_6ON_3CuBr)$	Yellow	25.92	25.76	2.46	2.14	15.14	15.02	22.85	22.78	28.66	28.62	49.20	49.01
3. Iodide $(C_6H_6ON_3CuI)$	Light yellow	22.00	22.05	2.01	1.83	12.80	12.86	19.56	19.46	39.01	38.89	42.08	41.96
4. Thiocyanate $(C_6H_6ON_3Cu(CNS))$	Yellow	32.56	32.62	2.45	2.33	21.58	21.74	24.80	24.69	53.34	53.20

In the first case isoniazid behaves as a bidentate, but in the second case it behaves as a monodentate. Further work on determination of molecular weight and magnetic susceptibility is under progress.

General Method for the Preparation

Monoisoniazid Copper (II) Complexes.—To a solution of neutral copper acetate $\text{Cu}(\text{CH}_3\text{COO})_2 \cdot \text{H}_2\text{O}$ (2 g.) in water (50 ml) containing acetic acid (2 drops) was added a solution of an equivalent amount of sodium salt followed by addition of isoniazid (1.37 g.) in water (20 ml). The light green copper (II) complexes, recorded in Table IA, were filtered, washed with water, ethanol, and ether, and air-dried.

The analyses of copper and total isoniazid in these complexes were carried out in the following manner.

Copper was precipitated as copper sulphide from a solution of known weight of the complex in HCl (dilute), filtered, and determined iodometrically. For determination of total isoniazid, the filtrate was aerated to remove H_2S , neutralised with ammonium hydroxide, and made slightly acidic with dilute acetic acid; 5% ethanolic solution of salicylaldehyde was then added to it and the whole heated on a water bath for 45 mins. and cooled. The precipitated salicylaldehyde-isonicotinic acid hydrazide was filtered, washed with 1% ethanol, and dried at 100° to a constant weight.

Monoisoniazid Copper (I) Complexes.—Cuprous complexes of isoniazid with cuprous chloride, bromide, iodide, and thiocyanate were prepared by the following method.

A known weight of cuprous compound was dissolved in large excess of a solution of the corresponding sodium salt. On addition of a solution of an equivalent amount of isoniazid in water, yellow or yellowish orange precipitate of cuprous complex separated almost quantitatively. This was filtered, washed with water, ethanol, and ether, and dried in a vacuum desiccator. The complexes are recorded in Table I B.

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