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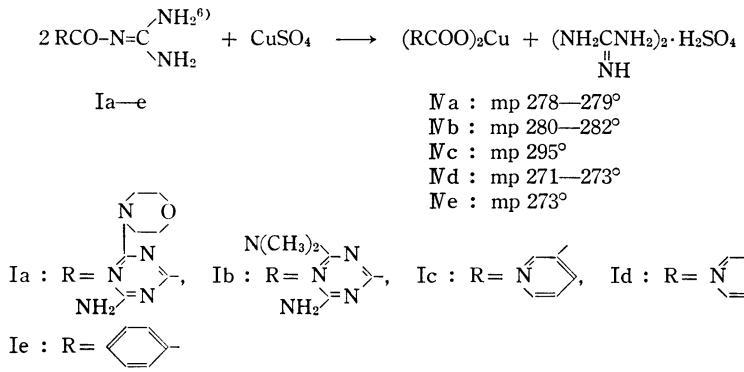
Cupric Ion Catalyzed Guanidide Hydrolysis

The antiviral effect of the inorganic salts of guanidine on several pathogenic viruses in the cell culture has been reported by the authors[1] and other research groups.[2] Subsequently, Ueda and his coleagues have demonstrated that the antiviral activity of several acyl guanidines, particularly N-amidino-4-amino-6-morpholino-*s*-triazine-2-carboxamide[3] (Ia) and 1-methyl-4-(amidinocarbamoyl)pyrimidinium iodide[4] (II), is stronger than that of guanidine salts, and postulated that the appearance of the activity of Ia and II may be due to the liberation of guanidine salt after incorporation of the compounds into the host cells.[5]

Since acyl guanidines are susceptible to the acid catalyzed hydrolysis, it is expected that the guanidide bond will be susceptible to metal ion catalysis. Thus, the author conceived an idea that the mechanism of the liberation of guanidine salt in the host cells might be explained by assuming the catalytic action of metal ions for the hydrolysis of Ia or II. This paper describes the effect of cupric ion on the hydrolysis of acyl gaunidines.

Into 20 ml of aq. solution of Ia (2.66 g, 1/100 mole) was added 25 ml of 5% $CuSO_4$ solution (1/200 mole, pH of the solution was 4.5) at room temperature. Precipitation completed immediately after addition of $CuSO_4$ solution, and the precipitate (A) was separated from the filtrate (B) by filtration. The precipitate, A, was confirmed to be the cupric salt of 4-amino-6-morpholino-*s*-triazine-2-carboxylic acid (III) from the following evidence: i) The known compound, III,[3] was obtained upon treatment of A with H_2S. ii) The cupric salt of III was unequivocally prepared from III and $CuSO_4$. A solid obtained from evaporation of the filtrate, B, was identical with guanidine sulfate as compared by the infrared (IR) spectra. A similar result was further obtained from the reaction of N-amidino-4-amino-6-dimethylamino-*s*-triazine-2-carboxamide[3a] (Ib), 3- and 4-(amidinocarbamoyl)pyridine[4] (Ic and Id) or benzoyl guanidine (Ie) with $CuSO_4$.

Hydrolysis of I did not take place in dilute hydrochloric acid at room temperature when



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2) *a*) D. Crowther and J. Melnick, *Virology*, **15**, 65 (1961); *b*) W.A. Rightsel, J.R. Dice, R.J. McAlpine, E.A. Timm, I.W. McLean, G.J. Dixon and F.M. Schabel, *Science*, **134**, 558 (1961).
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6) The present acyl guanidines were assumed to have the acylimino form, but not the acylamino form, RCONHC(=NH)NH_2, since the IR spectra (KBr) showed the NH_2 band at 3300—3400 cm^{-1} but no imino absorption.

the pH was between 4.0 and 7.0, while hydrolysis of I with Cu^{2+} (pH 4.5—7.0) proceeded too rapidly to measure the rate constant. Since acyl hydrazines are known to form the stable 5-membered chelate ring compounds,[7] acyl guanidines are expected to form a similar metal complex. It appears probable that the catalytic effect of Cu^{2+} is due to the formation of the metal complex. The presumed reaction mechanism is described in Chart 1. It is analogous to the acid catalyzed hydrolysis of carboxamides. The mechanism involves the formation of the carbonium cation in a 6-membered chelate ring (V), followed by the hydration into (VI), and subsequently the rearrangement of hydrogen to form the tetrahedral intermediate (VII).

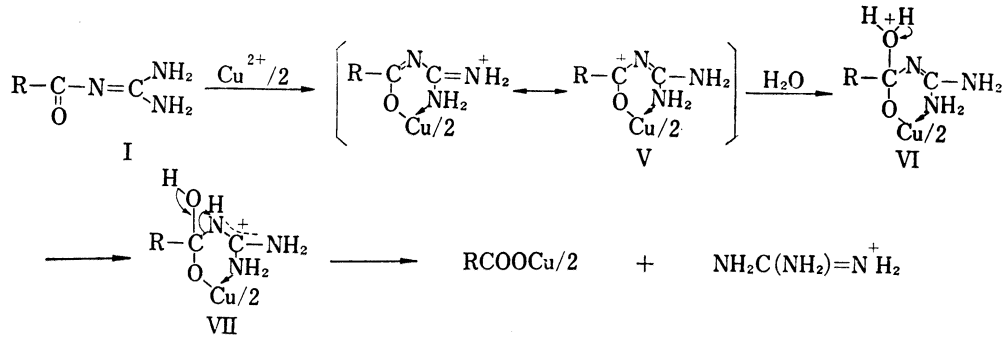

Chart 1

In order to clarify the correlation between metal ions and the hydrolysis of Ia or II in the tissue cell systems, further works are now in progress.

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On the Structure of Kidjolanin and the Position of the Esterlinkage of Penupogenin

The isolation of sarcostin (I), utendin (II), and tomentogenin from the stems of *Marsdenia tomentosa* DECNE (Asclepiadaceae, Japanese name: Kijoran) has been reported previously and the structure (III) was given for tomentogenin.[1] In this communication, we wish to describe the isolation and the structure of a new aglycone, kidjolanin, from the same stems and the position of the ester linkage of penupogenin[2] (IV).

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