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Cyclizations of Thioureas with a Hydroxy Group at the β-Position of the *N*-Substituent. I. Reaction with Cupric Acetate

Yoshio IWAKURA, Tadahiro KAYA[*1] and Keisuke KURITA

Department of Synthetic Chemistry, Faculty of Engineering, The University of Tokyo, Bunkyo-ku, Tokyo

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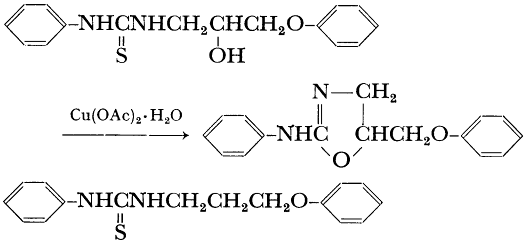
The reaction of 1-(3-phenoxy-2-hydroxypropyl)-3-phenyl-2-thiourea (thiourea I) with cupric acetate was investigated. The desulfurization reaction by the cupric ion proceeded in refluxing ethanol to yield 2-anilino-5-phenoxymethyl-2-oxazoline. At room temperature, thiourea I and cupric acetate gave a copper complex and the oxazoline. When the complex was heated in ethanol, the same oxazoline and thiourea I were obtained, along with inorganic copper compounds. On the basis of an investigation of the structure of the complex and the decomposition of the complex, the reaction mechanism involving copper-complex formation was discussed. On the other hand, the reaction of 1-(3-phenoxypropyl)-3-phenyl-2-thiourea with cupric acetate under the same conditions gave 1-(3-phenoxypropyl)-3-phenyl-3-acetylurea.

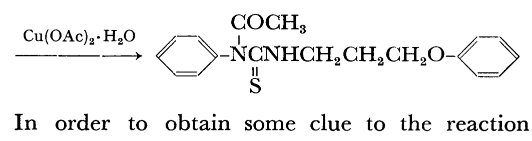
The desulfurization reaction of thiourea bearing a hydroxy group at the β-position of the *N*-substituent (hydroxythiourea) to give an oxazoline derivative was first reported by Söderbaum,1) who used mercuric oxide to effect such a desulfurization-cyclization reaction. This method was later elaborated by Dains and his co-workers.2,3) However, their version requires the use of a large excess of the metal oxide to complete the reaction. Adcock and his co-workers4–6) used methyl iodide for such a desulfurization of hydroxythioureas.

In an earlier paper,7) it was reported that 2-anilino-5-phenoxymethyl-2-oxazoline was obtained from 1-(3-phenoxy-2-hydroxypropyl)-3-phenyl-2-thiourea by treatment with *p*-toluenesulfonyl chloride. As part of a continuing investigation of the cyclization reaction of hydroxythiourea, the reaction of 1-(3-phenoxy-2-hydroxypropyl)-3-phenyl-2-thiourea with cupric acetate was attempted with the expectation that the oxazoline derivative would be formed by a homogeneous reaction.

Results and Discussion

The reaction of 1-(3-phenoxy-2-hydroxypropyl)-3-phenyl-2-thiourea (thiourea I) with an equimolar amount of cupric acetate proceeded readily in refluxing ethanol to give 2-anilino-5-phenoxymethyl-2-oxazoline in a 73% yield along with some blue-black inorganic precipitate. On the other hand, 1-(3-phenoxypropyl)-3-phenyl-2-thiourea (thiourea II), which has no hydroxy group, was found to afford 1-(3-phenoxypropyl)-3-phenyl-3-acetylurea in an 83% yield, along with a black, inorganic precipitate, under the same reaction conditions.





In order to obtain some clue to the reaction mechanism, the reaction of thiourea I and cupric acetate was examined at room temperature. When the solutions of thiourea I and cupric acetate in 70% aqueous dioxane were mixed at room temperature, a brown-black solution resulted and the color of the solution immediately turned yellow. From the yellow solution, yellow crystals containing copper (complex I) appeared gradually.

[*1] Present address: Sankyo Chemical Industries, Ltd., 3-Chome, Ginza, Chuo-ku, Tokyo.

1) H. G. Söderbaum, *Ber.*, **28**, 1897 (1895).

2) F. B. Dains, R. Q. Brewster, J. S. Blair and W. C. Thompson, *J. Amer. Chem. Soc.*, **44**, 2637 (1922).

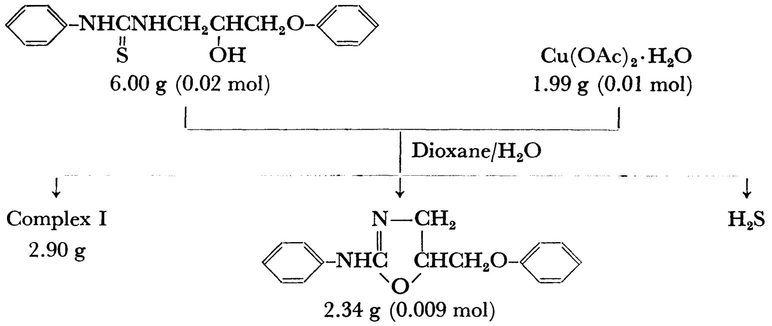
3) F. B. Dains, R. Q. Brewster, I. L. Malm, A. W. Miller, R. V. Maneval and J. A. Sultzaberger, *ibid.*, **47**, 1981 (1925).

4) B. Adcock, A. Lawson and D. H. Miles, *J. Chem. Soc.*, **1961**, 5120.

5) B. Adcock and A. Lawson, *ibid.*, **1965**, 474.

6) B. Adcock and A. Lawson, *ibid.*, *C*, **1966**, 65.

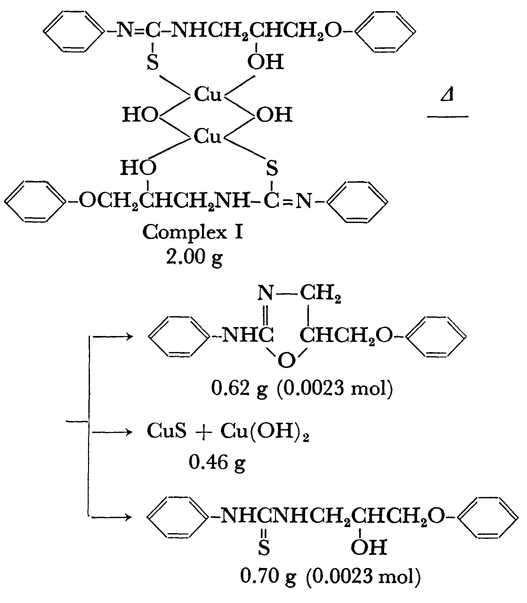
7) Y. Iwakura, K. Kurita and F. Hayano, *J. Polym. Sci.*, in press.



When the moler ratio of thiourea I to cupric acetate was exactly 2 : 1, only the oxazoline and acetic acid were found in the mother liquor obtained after the filtration of complex I from the reaction mixture mentioned above, while neither of the reactants remained unchanged. However, if the ratio was less than 2 : 1, the cupric acetate remained unchanged; on the contrary, if the ratio was larger than 2 : 1, thiourea I was recovered. These facts suggest that the formation of complex I and the oxazoline requires only a half mole of cupric acetate for each mole of thiourea I. Furthermore, a quantitative study of the reaction showed that two moles of thiourea I gave one mole of the oxazoline when the molar ratio of thiourea I to cupric acetate was just 2 : 1. This indicates that one of the two moles of thiourea I added was consumed in the formation of complex I. The elemental analysis of complex I indicated that it contained thiourea I and copper in a 1 : 1 ratio. These results are summarized in the following diagram, along with the quantitative relationship of the materials. Hydrogen sulfide was detected in the reaction mixture by gas chromatography.

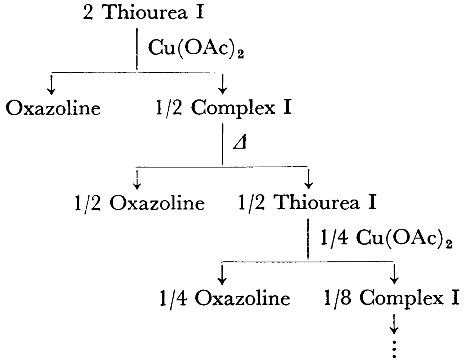
Complex I is soluble in polar solvents, such as dimethylformamide and dimethyl sulfoxide, but insoluble in usual organic solvents, such as dioxane, toluene, benzene, methanol, and acetone. These facts suggest that the complex has a polymeric rather than a monomeric structure. From the elemental analysis, the empirical formula, $C_{16}H_{18}N_2SO_3Cu$, was obtained; this formula corresponded well with the composition, thiourea I·Cu·OH. On the basis of these facts, a dimeric olation structure was considered for complex I, since it is well known that a copper complex is apt to form a dimeric olation structure in an aqueous medium. The ESR measurement and particularly the thermoanalysis of the complex, to be described below, seemed to support the structure. Complex I showed a sharp signal in the ESR; this indicated that the copper was in the cupric rather than the cuprous state. The complex prepared from thiourea I and cuprous chloride showed no signal in the ESR.

When complex I was heated while suspended in refluxing ethanol, it gradually decomposed, giving rise to a blue-black powdery material which was insoluble in ethanol. From the ethanolic solution, the oxazoline and thiourea I were obtained in equimolar amounts. The blue-black powder was considered to be a 1 : 1 mixture of cupric sulfide and cupric hydroxide on the basis of the following facts: (1) The sulfur content of the powder was found to be 17.00%, this value was in good agreement with the calculated value, 16.67%. (2) In a thermogravimetric analysis, the powder showed a 9.00% weight loss after being kept at 350°C for 4 hr in a nitrogen atmosphere. If the cupric hydroxide in the mixture loses water to give cupric oxide, the weight loss should be 9.30%. After heating, the color of the powder was black, suggesting a change from cupric hydroxide (blue) to the oxide (black). Complex I and its decomposition in boiling ethanol may be depicted thus:



Thus, on the basis of theses data, the reaction scheme between two moles of thiourea I and one mole of cupric acetate at room temperature was presumed to be as follows. Two molecules of thiourea I were co-ordinated to a cupric ion at the initial stage; then one molecule of thiourea I was removed to produce the oxazoline and hydrogen sulfide, and simultaneously the co-ordinated water was changed to hydroxide to form the olation structure.

If it is assumed that the reaction of thiourea I with cupric acetate in refluxing ethanol also proceeds *via* the formation of complex I, the whole reaction sequence between equimolar amounts of thiourea I and cupric acetate at an elevated temperature would be as follows. Two moles of thiourea I and one mole of cupric acetate react to give one mole of the oxazoline and a half mole of complex I. Then complex I decomposes to give a half mole of the oxazoline and a half mole of thiourea I, along with inorganic materials. The half mole of thiourea I freed from complex I again reacts with a quarter mole of cupric acetate to repeat the sequence. Therefore, the minimum amount of cupric acetate required to convert one mole of thiourea I to the oxazoline completely should be 2/3 mol.



This sequence may be summarized as in the following equation.

$$2\ \text{Thiourea I} + 4/3\ Cu(OAc)_2 \longrightarrow 2\ \text{Oxazoline}$$

The experimental results showed that the reaction of one mole of thiourea I with 2/3 mol of cupric acetate in refluxing ethanol gave the oxazoline in a 67% yield, with no recovery of thiourea I or cupric acetate.

Figure 1 represents the infrared to far-infrared spectra of thiourea I, complex I, and the oxazoline.

The copper complex of thiourea II (complex II) was obtained by the procedure described for the preparation of complex I. The results of the elemental analysis of complex II agreed well with the calculated value for the 1 : 1 complex of thiourea II and copper. In contrast to complex I, complex II showed no signal in the ESR and was soluble even in a non-polar solvent such as benzene. From these facts, this complex may be considered to consist of thiourea II and copper in a cuprous state in a 1 : 1 ratio and to have no polymeric olation structure. Therefore, the mechanism of the reaction of cupric acetate with thiourea I and that with thiourea II are considered to be quite different; in the latter case, the cupric ion has been reduced to the cuprous ion during the formation of complex II. This problem is under investigation.

Figure 2 represents the infrared to far-infrared spectra of thiourea II, complex II, and the *N*-acylurea.

Experimental

1-(3-Phenoxy-2-hydroxypropyl)-3-phenyl-2-thiourea. This compound, prepared from 1-phenyl-3-amino-2-propanol and phenyl isothiocyanate, has been reported previously.[7]

3-Phenoxypropylamine. This compound was pre-

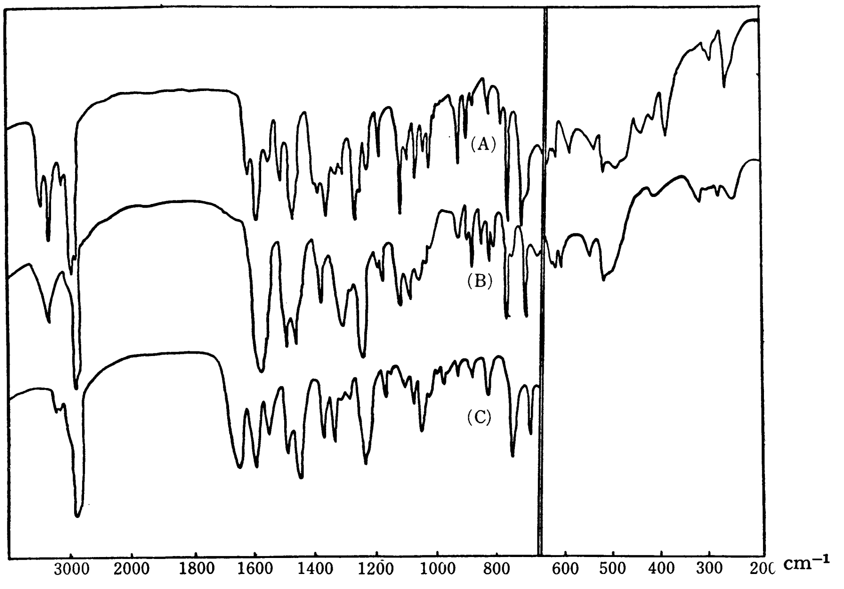


Fig. 1. Infrared to far-infrared spectra of thiourea I (A), complex I (B), and the oxazoline (C), (Nujol).

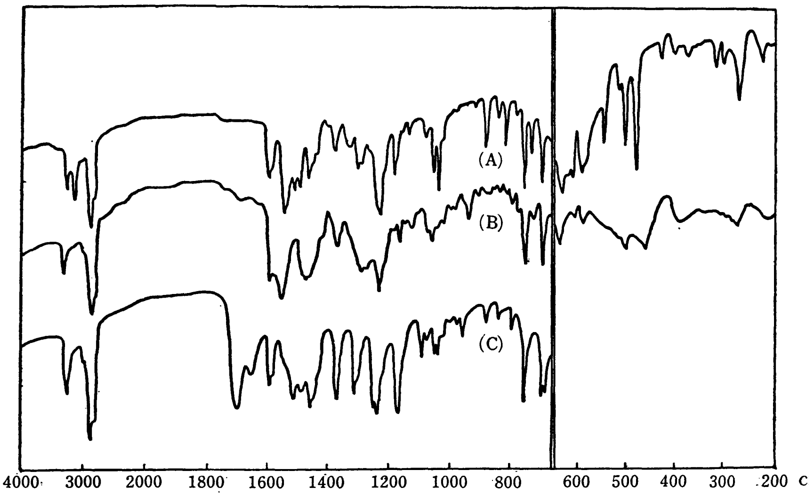


Fig. 2. Infrared to far-infrared spectra of thiourea II (A), complex II (B), and the *N*-acylurea (C), (Nujol).

pared from 3-phenoxypropyl bromide[8] and was synthesized from phenol, 1,3-dibromopropane, and potassium phthalimide according to the Gabriel synthesis. The yield was 64%, bp 138—139°C/23 mmHg.

1-(3-Phenoxypropyl)-3-phenyl-2-thiourea. Into a solution of 15.1 g (0.1 mol) of 3-phenoxypropylamine in 100 m*l* of methanol, we stirred 13.5 g (0.1 mol) of phenyl isothiocyanate, drop by drop, over a period of 30 min. The mixture was then stirred for 4 hr at room temperature; then the solvent was evaporated under reduced pressure. The residual white solid was recrystallized from toluene to give 25.4 g (89.0%) of the product; mp 89—90°C.

Found: C, 67.39; H, 6.42; N, 9.57%. Calcd for $C_{16}H_{18}N_2SO$: C, 67.10; H, 6.33; N, 9.78%.

2-Anilino-5-phenoxymethyl-2-oxazoline. 1-(3-Phenoxy-2-hydroxypropyl)-3-phenyl-2-thiourea (1 g; 0.0033 mol) was refluxed with 0.66 g (0.0033 mol) of cupric acetate monohydrate in 20 m*l* of ethanol. After 5 hr heating, the blue-black precipitate was filtered off and the filtrate was evaporated under reduced pressure. The residue was dissolved in 20 m*l* of toluene and extracted with dilute hydrochloric acid. On the basification of the aqueous extract with aqueous sodium hydroxide, 0.6 g (73%) of 2-anilino-5-phenoxymethyl-2-oxazoline was obtained; this was identical with the authentic sample prepared by the dehydration of 1-(3-phenoxy-2-hydroxypropyl)-3-phenylurea.[7]

1-(3-Phenoxypropyl)-3-phenyl-3-acetylurea. To a solution of 0.95 g (0.0033 mol) of 1-(3-phenoxypropyl)-3-phenyl-2-thiourea in 20 m*l* of ethanol, we added a solution of 0.66 g (0.0033 mol) of cupric acetate monohydrate in 30 m*l* of ethanol. After the mixture had been refluxed for 7 hr, the black precipitate which had formed was filtered off. The filtrate was evaporated under reduced pressure, and the residual solid was recrystallized from *n*-hexane to give 0.86 g (83%) of colorless needles, mp 84°C.

Found: C, 69.40; H, 6.53; N, 8.88% Calcd for $C_{18}H_{20}N_2O_3$: C, 69.21; H, 6.45; N, 8.97%

Reaction of 1-(3-Phenoxy-2-hydroxypropyl)-3-phenyl-2-thiourea with Cupric Acetate at Room Temperature. Cupric acetate monohydrate (1.99 g; 0.01 mol), dissolved in 120 m*l* of 70% aqueous dioxane, was added to a solution of 6.00 g (0.02 mol) of 1-(3-phenoxy-2-hydroxypropyl)-3-phenyl-2-thiourea in 120 m*l* of 70% aqueous dioxane. The mixture immediately became a brown-black solution, and then the solution turned yellow. When this yellow solution was allowed to stand yellow crystals began to appear. The mixture was allowed to stand at room temperature for 6 hr. The crystals were then collected by filtration and weighed 2.90 g; mp 115°C (decomposition).

Found: C, 49.71; H, 4.88; N, 7.51; Cu, 16.66%. Calcd for $C_{32}H_{36}N_4S_2O_6Cu_2$: C, 50.18; H, 5.00; N, 7.32; Cu, 16.59%.

The filtrate was evaporated under reduced pressure, and the residue was dissolved in toluene. The toluene solutions was extracted with dilute hydrochloric acid, and the aqueous extract was basified with aqueous sodium hydroxide to precipitate 2-anilino-5-phenoxymethyl-2-oxazoline in a yield of 2.34 g.

Copper Complex from Thiourea I and Cuprous Chloride. To a solution of 1.00 g (0.0033 mol) of 1-(3-phenoxy-2-hydroxypropyl)-3-phenyl-2-thiourea in 30 m*l* of 70% aqueous dioxane, we added a solution of 0.33 g (0.0033 mol) of cuprous chloride and 0.3 g of sodium chloride, which was added to dissolve the cuprous chloride, in 50 m*l* of 70% aqueous dioxane at room temperature. Aqueous sodium hydroxide was added to the reaction mixture to maintain the pH at 6.8, which was the value of the reaction mixture of the thiourea I and cupric acetate, since the complex was not formed in the low pH region. The precipitated yellow crystals weighed 0.95 g; mp 134°C (decomposition).

Reaction of 1-(3-Phenoxypropyl)-3-phenyl-2-thiourea with Cupric Acetate at Room Temperature. Cupric acetate monohydrate (0.697 g; 0.0033 mol) was dissolved in 40 m*l* of 70% aqueous dioxane, and then the solution was slowly added to a solution of 2.00 g

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[8] C. S. Marvel and A. L. Tanenbaum, "Organic Syntheses," Coll. Vol. I, p. 435 (1956).

(0.0067 mol) of 1-(3-phenoxypropyl)-3-phenyl-2-thiourea in 40 m*l* of 70% aqueous dioxane. The brown-black mixture changed to yellow, and yellow crystals gradually precipitated. The mixture was kept at room temperature for 6 hr. The crystals were then filtered off; they weighed 0.86 g; mp 104°C (decomposition).

Found: C, 55.31; H, 5.16; N, 8.38%. Calcd for $C_{16}H_{17}N_2SOCu$: C, 54.92; H, 5.18; N, 8.01%.

The filtrate was evaporated, and the residue was dissolved in toluene; the organic solution was washed with aqueous sodium hydroxide to remove the acetic acid, and then with water, and dried over sodium sulfate. The solvent was evaporated to give 0.80 g of 1-(3-phenoxypropyl)-3-phenyl-3-acetylurea.

Thermal Decomposition of Complex I. Complex I (2.00 g) was heated in 60 m*l* of refluxing ethanol for 7 hr heterogeneously. The yellow-orange complex decomposed, giving a blue-black powder. The blue-black powder was filtered, washed with ethanol and weighed; 0.46 g. The filtrate was evaporated under reduced pressure, and the residue was dissolved in toluene. The toluene solution was extracted with dilute hydrochloric acid. When the organic layer was evaporated, 0.70 g of thiourea I was obtained, while, from the aqueous extract, 0.62 g of 2-anilino-5-phenoxymethyl-2-oxazoline was obtained by basification.