

SYNTHESIS OF SOME METAL CHELATES AS

ANTITUMOR AGENTS

By

OLAMAY CHEN

Bachelor of Science

Taiwan Provincial

Cheng-Kung University

Tainan, Taiwan

Republic of China

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Thesis Approved:

Ernest M. Hedrick

Thesis Adviser

John E. Moore

D. D. Durham

Dean of the Graduate College

658397

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CHAPTER I

INTRODUCTION

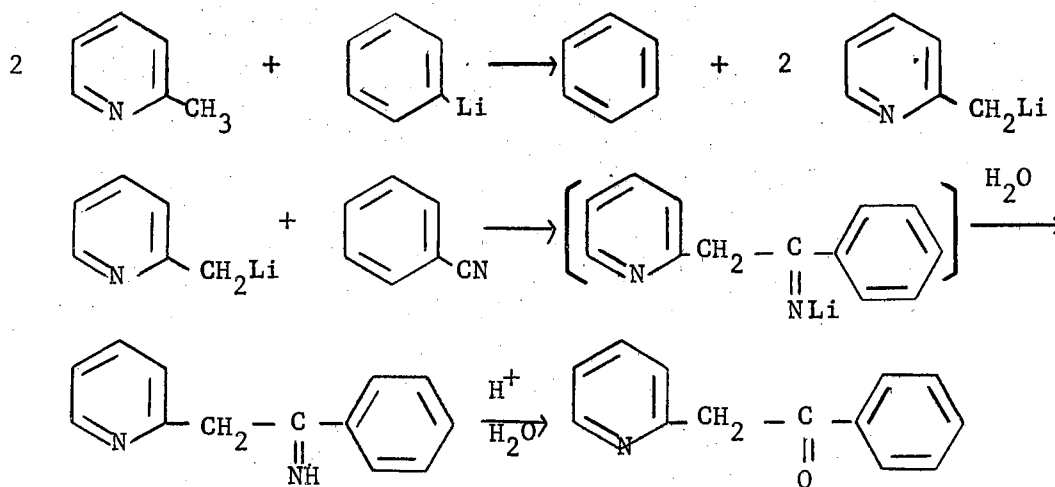
Metal compounds of some organic ligands have shown their effect in biological oxidation-reduction systems. For instance the copper chelate of kethoxal bis(thiosemicarbazone) (1) has shown significant inhibition of tumor growth in mice. In this investigation, some chelate compounds were synthesized in the hope of gaining an understanding of their nature and the properties which make them so indispensable to biological oxidation and reduction, which might have some usefulness in medicines.

Several organic compounds were synthesized. 2-Picolyl phenyl ketone was prepared by the general method of Levine and his co-workers (2). In this method 2-picoline was first reacted with phenyllithium to form the lithium salt, which was then condensed with the ester to yield the ketone. Five saturated secondary aromatic amines were prepared by reduction of the corresponding Schiff bases with lithium aluminum hydride. Since lithium aluminum hydride was first used in reductions, many compounds have been reduced by use of this compound. We made these secondary amines by this method, and compared the yield and properties with same compounds made by other methods. These six compounds were reacted with cobalt(II), copper(II), and nickel(II) salts. Some of them formed chelates with all of these metals. Some failed to form chelates with nickel(II) or cobalt(II) or both.

CHAPTER II

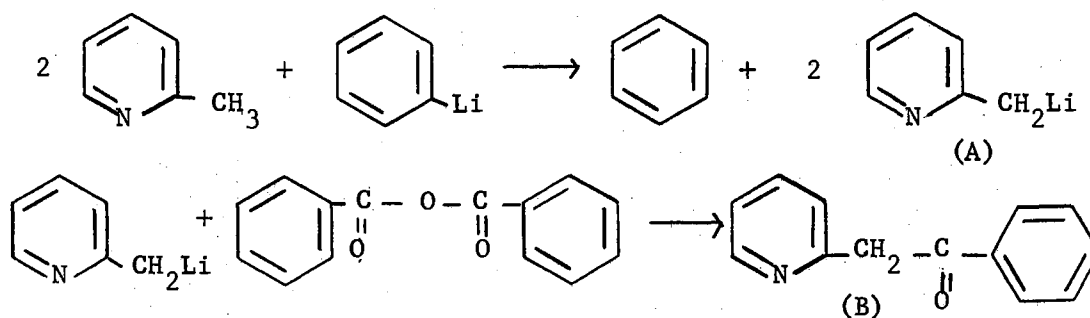
HISTORICAL

2-Picolyl phenyl ketone has been made by various synthetic methods. For example Wibaut and de Jong (3) reported in 1949 the synthesis of this compound according to the following method. 2-Picoline is first reacted with phenyllithium to form the lithium salt, which is then condensed with benzonitrile; decomposition of the product with acidified water yields the ketone. By this method a 30% yield based on 2-picoline was reported whereas Levine and his co-workers obtained an 80.2% yield. The probable course of the reaction according to Wibaut and de Jong may be represented by the equations:

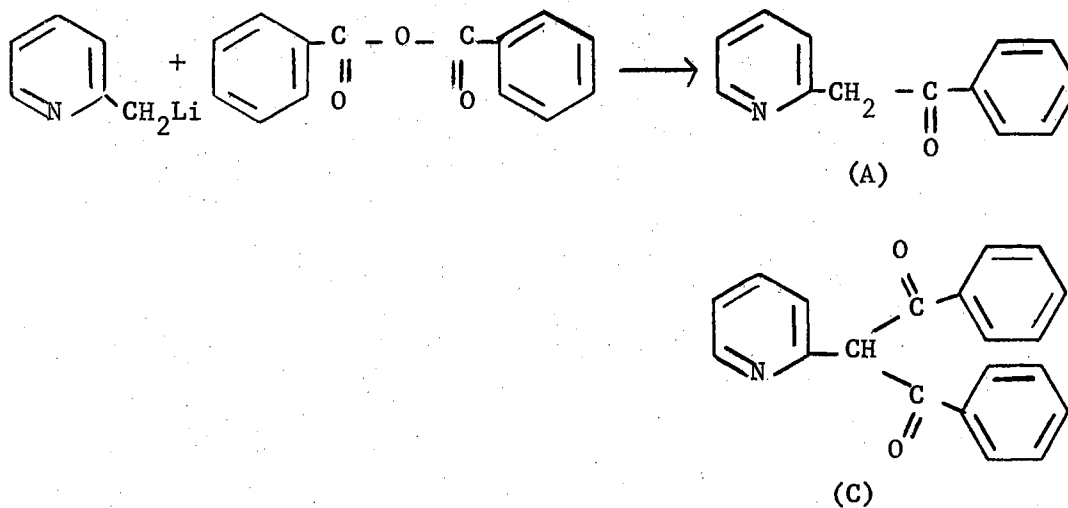


Kloppenburger and co-workers (4) also prepared this compound by the interaction of benzoyl chloride or benzoic anhydride on 2-picolyllithium. They found a melting point of 54° for the ketonic base purified via the

picrate. Their procedure may be represented as below:

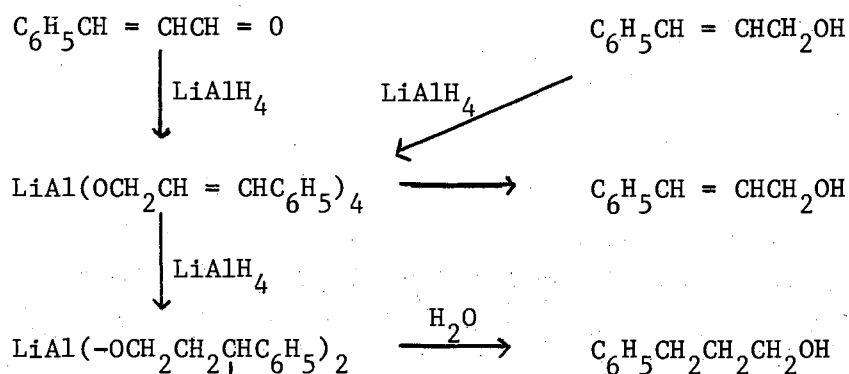


According to the report of Kloppenbrug and Wibaut, the formation of 2-picolyl phenyl ketone (B) is entirely analogous to the formation of 2-picolyl methyl ketone from 2-picolyllithium and acetic anhydride. In the reaction with benzoic anhydride a small amount of base having the composition of $C_{20}H_{15}O_2N$ which was probable 2-phridyldibenzoylmethane (C) is also formed.

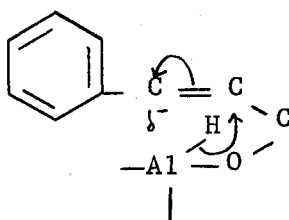


In the year 1964, Harry Nelson (5) reported a series of 2-picolyl ketones. He made those compounds (including 2-picolyl phenyl ketone) by the general method of Levine and co-workers and made several metal chelates of each compound using ethanol as the solvent, he obtained the metal chelates of 2-picolyl phenyl ketone, with copper(II), cobalt(II) and nickel(II) solutions.

In 1946, Finhold and his co-workers (6) reported the preparation of lithium aluminum hydride. Nystrom and Brown (7) reduced some organic compounds such as aldehydes, ketones, esters, and acid chlorides with lithium aluminum hydride. Later, they found that the reduction of unsaturated aldehydes occurs in two successive stages (8) and that the attack upon the double bond takes place as a slower reaction which follows the reduction of the carbonyl group:



It was observed that allyl alcohol is not reduced at room temperature by lithium aluminum hydride. In 1949 summer, Chanley, and Sobotka (9) reported that lithium aluminum hydride serves for partial hydrogenation of the triple bond to a double bond in cyclohexenylbutynol, Benedict and Russell (10) reduced acetylenedicarboxylic acid to 2-butene-1,4-diol (bp 128-130°) by using lithium aluminum hydride. Hamlin and Weston (11) used lithium aluminum hydride to reduce unsaturated nitro compounds to saturated amines. From the evidence accumulated it appears that the reduction of an unsaturated compound is readily accomplished if an O-Al or N-Al bond is able to form close to the unsaturated center. In the reduction of cinnamaldehyde, it is possible to attribute the driving force to formation of the benzyl carbanion in the transition state:



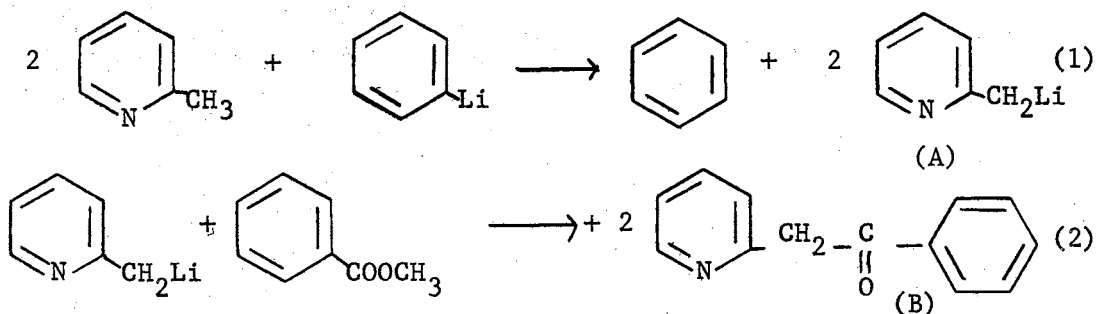
In 1956 Sommers and Aaland (12) prepared some secondary aliphatic amines from the corresponding Schiff bases by using lithium aluminum hydride with good yields.

The five aromatic amines which were made in this investigation had been formed earlier by different methods (except α -(p-dimethylaminoanilino)-o-cresol). For example, α -anilino-o-cresol was prepared by Robertson in 1952 (13) by dissolving substituted phenols in an aldehyde and then hydrogenating with Raney nickel under reduced pressure (74-120°/4 mm.). α -(p-Toluidino)-o-cresol has been made in 1953 by Castle (14) by reduction of the Schiff base with lithium aluminum hydride. Horii and co-workers (15) also made this compound by reduction with sodium borohydride. α -(p-Anisidino)-o-cresol was prepared by Hantzsch and Wechsler (16) by reducing the Schiff base with sodium borohydride. E. Schering (17) prepared α -(p-hydroxyanilino-o-cresol) by reducing 4-(salicylidineamino)phenol with zinc metal under nitrogen. Beretka and co-workers (18) had made α -anilino-o-cresol in 1964 by reducing the Schiff base with Raney nickel and used this compound to form metal chelates. They tried three metal solutions, cobalt(II), copper(II), and nickel(II), but only formed the chelate with copper acetate, a dark green solid (mp 186°) of composition $C_{15}H_{15}NO_3$ which is a 1:1 complex.

CHAPTER III

INTRODUCTION TO EXPERIMENTAL WORK

In this investigation, we prepared 2-picolyl phenyl ketone according to the procedure suggested by Levine and his co-workers in 1951. They synthesized this compound by reacting 2-picoline with phenyllithium to form the lithium salt and then condensing the product with ester to yield the ketone. The acylation may be represented by the following equations:

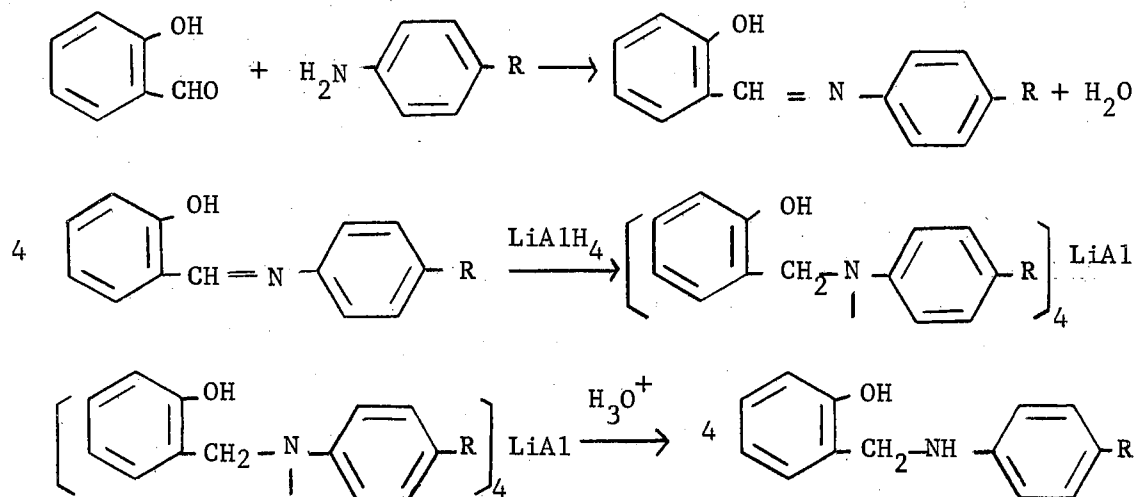


The 2-picoline is first converted to its lithium derivative (A) by an acid-base reaction with phenyllithium (Equation 1). In Equation (2), (A) is acylated by the ester to give the ketone (B). In this method the compound obtained was first purified by repeated recrystallization from light petroleum (34°) as described by Wibaut and de Jong (3). According to their report, the compound which is purified by this method rapidly changes to a brown resinous mass on standing in the air. For this reason Bergmann and Rosenthal (19) gave no elemental analysis although they prepared 2-picolyl phenyl ketone. Therefore, Kloppenburg and Wibaut (4) suggested a purification method involving repeated

recrystallization of the picrate and recovery of the 2-picolyyl phenyl ketone. In our experiments, it appears that this compound is light-sensitive and remains quite stable if kept in a brown bottle covered with aluminum foil after recrystallization from light petroleum.

Three metal chelates were obtained by reacting this compound with cobalt(II), nickel(II), and copper(II) salts according to the method suggested by Harry Nelson (4) using ethanol as the solvent.

α -Anilino-o-cresol, α -(p-toluidino)-o-cresol, α -(p-anisidino)-o-cresol, α -(p-dimethylaminoanilino)-o-cresol, and α -(p-hydroxyanilino)-o-cresol were prepared by reduction of the corresponding Schiff bases with lithium aluminum hydride. The Schiff bases were formed by the method of Campbell and Sommers (20) by heating equal moles of aldehyde and amine together. The reduction method was reported by Nystrom and Brown (21) with lithium aluminum hydride and dry ether as the solvent. The reaction could be represented by the following equations:



where R=H, CH₃, OCH₃, N(CH₃)₂, and OH.

From these compounds were prepared metal chelates with cobalt(II), copper(II), and nickel(II) solutions according to the method of Beretka

and his co-workers (18) with ethanol as the solvent. Some of these compounds formed chelates with all three metal ions, but some of them did not. Details will be included in experimental work part.

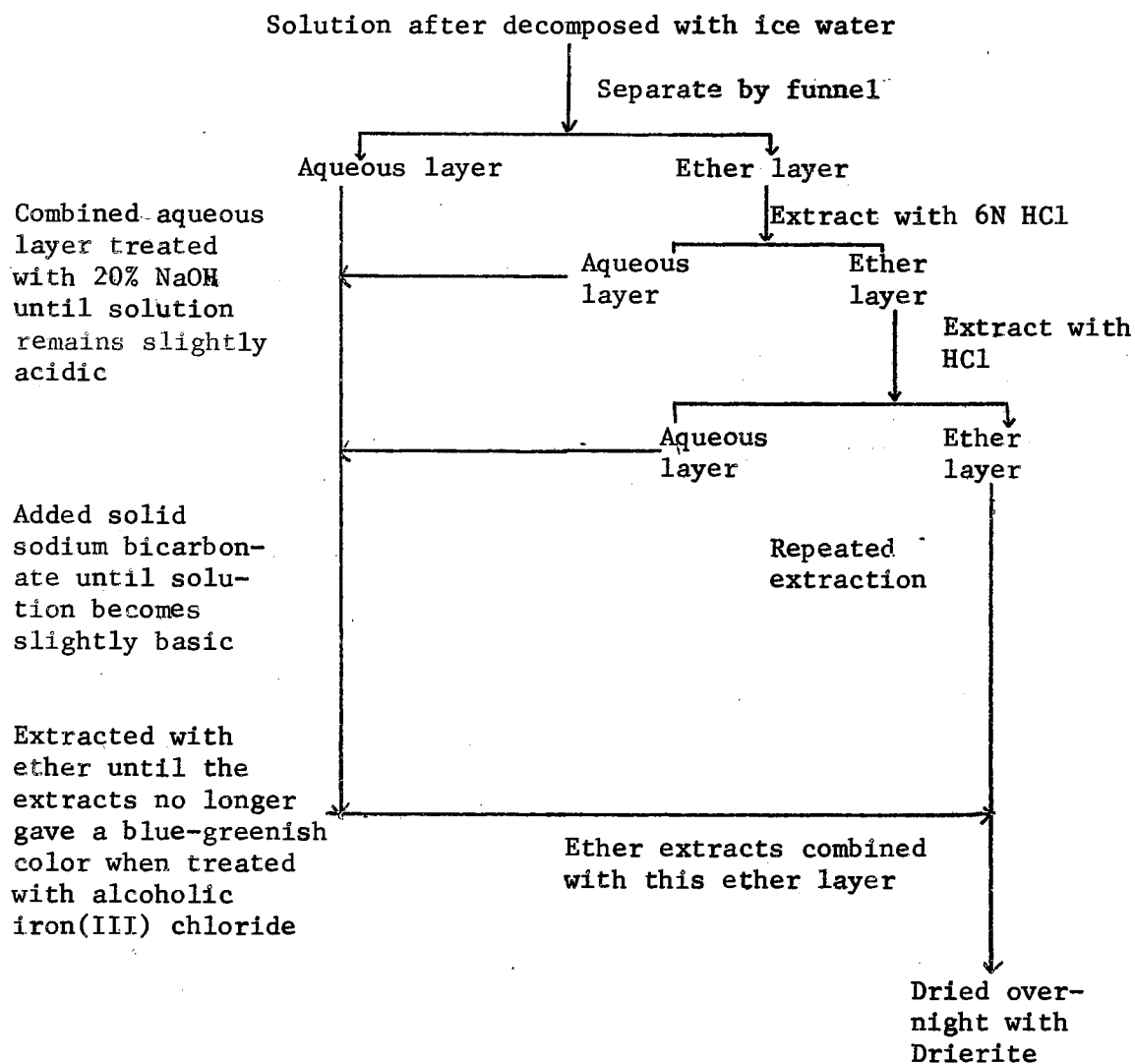
CHAPTER IV

EXPERIMENTAL WORK

Preparation of 2-picoly1 phenyl ketone, $2-C_5H_4NCH_2COC_6H_5$ and its metal chelates.

This compound was synthesized according to the method reported by Levine and his co-workers (2). In a 1500-ml. three-neck round-bottom flask equipped with ground-glass joints and fitted with a glass stirrer, an addition funnel, and a reflux ice cold condenser (protected from atmospheric moisture by a drying tube filled with Drierite), 33.6 g. (0.4 moles) of phenyllithium (from bromobenzene and small pieces of metal lithium) was prepared in 500 ml. of anhydrous ether. 2-Picoline (37.2 g. or 0.4 moles) was added to the mixture in a 20-minute period, and then the solution was refluxed for 30 minutes; the conversion of the 2-picolyllithium was assumed to be quantitative. To the rapidly stirred solution of the 2-picolyllithium, 30 g. (0.2 moles) of ethyl benzoate dissolved in 25 ml. of anhydrous ether was added over a 30-minute period so that the ether refluxed rapidly. After the ethyl benzoate was added, the reaction mixture was refluxed for 30 minutes further on a water bath, then 75 ml. of water was added slowly and the mixture poured into 100 ml. of 6N hydrochloric acid and 500 g. of ice. The mixture was filtered to get rid of the precipitate; the ether layer and aqueous layer were separated. The ether phase was extracted several times with 6N hydrochloric acid. The combined aqueous solution was

treated with 20% sodium hydroxide solution until the solution remained slightly acidic. Solid sodium bicarbonate was added until the solution was slightly basic. The basic solution was extracted with ether for several times until the extracts no longer gave a blue-greenish color with alcoholic iron(III) chloride. The combined ether solution was dried over night with Drierite and the ether was distilled by heating



on a water bath. The residue upon fractional vacuum distillation gave at $210^{\circ}/2$ mm. a pale yellow solid which on recrystallization from light

petroleum gave a pale-yellow crystalline compound, mp 52.5-53° (Goldberg (2), 52.5-54°). Yield, 44.4%.

The chelates were made according to the method reported by Nelson (5) using ethanol as the solvent. An excess of the ketone dissolved in 50-100 ml. of ethanol was added to the copper(II) perchlorate solution, nickel(II) sulfate solution, and cobalt(II) perchlorate solution. The pH of the mixture was adjusted to 4-5 for copper(II), 6-7 for nickel(II), and 5-6 for cobalt(II) with perchloric acid or sodium hydroxide solution. After the precipitate settled, the chelate was filtered and washed with copious amounts of water and dilute ethanol in order to remove any free original reagent. Chelates were dried under vacuum. From 2-picolyyl phenyl ketone three metal chelates were obtained: copper(II) chelate, dark green solid, mp 108°; cobalt(II) chelate, light brown solid, mp 166°; and nickel(II) chelate, light green solid, mp over 300°. The yields are 87.27%, 51.29%, and 67.80% respectively.

Preparation of α -anilino- o -cresol, o -HOC₆H₄CH₂NHC₆H₅.

The Schiff base was made by the method of Campbell and Sommers (20) by heating equal molar amounts of salicylaldehyde and aniline under nitrogen gas. Freshly distilled salicylaldehyde (30.55 g. or 0.25 moles) dissolved in 100 ml. of ethanol was used and 16.5 g. (0.125 moles) of aniline was added with stirring. The solution was heated until the color of the mixture deepened no more. The mixture was cooled to room temperature and put in the refrigerator overnight, the pale yellow crystals were filtered and washed with dilute ethanol solution. The product, recrystallized from warmed ethanol, gave yellow crystals, mp 49° (Beretka (18) 49°). This aldimine was reduced to

saturated α -anilino-o-cresol by the method reported by Sommers and Aaland (12). Yield, 56.37%.

The reaction was done under a nitrogen atmosphere. In a 1000-ml. three-neck round-bottom flask equipped with ground-glass joints and fitted with a glass stirrer, an addition funnel, and a reflux ice-cold condenser. The aldimine (13 g. or 0.066 moles) dissolved in 100 ml. of anhydrous ether was added during one hour into the flask in which the same number of moles of lithium aluminum hydride dissolved in 400 ml. of dry ether had been placed. The mixture was well stirred and refluxed for six hours (until all the aldimine color disappeared). After removing the heater, the flask was cooled in an ice bath. Ice water (15 ml.) was added dropwise (until all the grey color of lithium aluminum hydride turned to white), and the suspension was allowed to stand overnight. The mixture was filtered, the filtrate including ether washings was collected, and all the ether was evaporated on a water bath. The white crystals were recrystallized from chloroform, which gave crystals, mp 113.5° (Bamberger (22) 113°). The yield was 24.66% of the theoretical.

Preparation of α -(p-toluidino)-o-cresol, $\text{o-HOC}_6\text{H}_4\text{CH}_2\text{NHC}_6\text{H}_4\text{CH}_3\text{-p}$.

Equal moles of salicylaldehyde and p-toluidine were heated as described before. The Schiff base was recrystallized from warm ethanol. The pale-yellow crystals so obtained, mp $98-99^{\circ}$ (Jaillard (23) 100°), were dried in desiccator. This aldimine (35.97 g. or 0.123 moles) was added slowly during an hour to 4.75 g. (0.123 moles) of lithium aluminum hydride dissolved in 400 ml. of anhydrous ether. The equipment was the same as before. After refluxing for six hours there was still some

yellow color of aldimine, so reflux was continued for two more hours until the yellow color had disappeared. Then the mixture was decomposed with 20 ml. of ice water (the amount of added water was determined by the suspension changing from grey to white but excess of water should be avoided otherwise the mixture will convert to a gelatinous emulsion which is very difficult either to filter or to extract). The mixture after standing overnight was filtered, the filtrate and the ether washings were collected, and the ether distilled. Recrystallization from chloroform gave white crystals, mp 121° (Horii (15) 120°). The yield was 29.91%.

Preparation of α -(p-anisidino)-o-cresol, $\text{o-HOC}_6\text{H}_4\text{CH}_2\text{NHC}_6\text{H}_4\text{OCH}_3\text{-p}$.

The Schiff base was made by mixing equal amounts of salicylaldehyde and p-anisidine in ethanol and heating under a nitrogen atmosphere until the color no longer deepened. The yellow crystals which resulted were recrystallized from ethanol, mp 85° (Hantzsch (16) 86°). This aldimine was reduced with lithium aluminum hydride according to the same method as above. In this experiment 34.05 g. (0.15 moles) of aldimine was reduced with 5.7 g. (0.15 mole) of lithium aluminum hydride. The reflux time was six hours and the amount of ice water added for decomposition was 20 ml. The white crystals were recrystallized from benzene giving white crystals, mp 126° (Hantzsch (16) $127\text{-}128^{\circ}$). Yield 37.96%.

Preparation of α -(p-dimethylaminoanilino)-o-cresol, $\text{o-HOC}_6\text{H}_4\text{CH}_2\text{NHC}_6\text{H}_4\text{N(CH}_3)_2\text{-p}$.

Equal molar quantities of salicylaldehyde and N,N-dimethyl-p-

phenylenediamine were mixed in ethanol. A longer heating time was required for this reaction; almost one hour was needed before the color deepened no more. When the reaction mixture was cooled in a refrigerator, it gave a black precipitate. This was washed with cold dilute ethanol to get rid of all the unreacted amine, and orange crystals were obtained mp 134° (Moore (24) $134-135^{\circ}$). This compound was reduced with lithium aluminum hydride as described before, except that reflux time was seven hours and decomposition was done with 18 ml. of ice-cold water. After extraction by ether and evaporation on a water bath, the residue was recrystallized from chloroform. Pale yellow crystals were formed, mp 98° . The yield was 33.79%.

Preparation of α -(p-hydroxyanilino)-o-cresol, $\text{o-HOC}_6\text{H}_4\text{CH}_2\text{NHC}_6\text{H}_4\text{OH-p}$.

The Schiff base was made by mixing equal amounts of salicylaldehyde and p-aminophenol in ethanol as described before. Brown crystals mp $136-137^{\circ}$ (Haegeler (25) 137°) were obtained. This compound was reduced according to the method used before but the reflux time was eight hours and 25 ml. of ice cold water was used for decomposition. Pale yellow crystals, mp 121° (E. Schering (17) $122-123^{\circ}$) were obtained.

Preparation of metal chelates.

Metal chelates of the above five secondary aromatic amine were prepared according to the method of Beretka and his co-workers (18). Since 2:1 complexes were expected, the organic compounds were dissolved in ethanol and half molar quantities of copper(II) nitrate, cobalt(II) nitrate, and nickel(II) sulfate solutions were added. The pH was adjusted to 4-5 for copper(II), 5-6 for cobalt(II) and 6-7 for nickel(II).

For α -anilino-o-cresol, dark green copper(II) chelate, mp 107° , was obtained, but no chelates with cobalt(II) and nickel(II) metal solutions were found. This also had been reported by Beretka (18). From his compound he got the copper(II) chelate only. From the reaction of α -(p-toluidino)-o-cresol with metal solutions, three chelates were obtained: copper(II) chelate, olive green solid, mp 115° ; cobalt(II) chelate, green solid, mp 119° , and nickel(II) chelate, pale green solid, mp 117° . α -(p-Anisidino)-o-cresol reacted with the metal solutions to give the copper chelate, dark green solid, mp 177° , but failed to form chelates with cobalt(II) and nickel(II) ions. α -(p-Dimethylaminoanilino)-o-cresol failed to form chelates with cobalt(II) and nickel(II) solutions, but gave a copper(II) chelate when reacted with copper(II) nitrate solutions, brown red solid, mp 113° . From α -(p-hydroxyanilino)-o-cresol was obtained the copper(II) chelate, dark green solid, mp over 300° , and the cobalt(II) chelate, green solid which decomposed at 195° , but no chelate with nickel(II)sulfate solution.

CHAPTER V

RESULTS

In this investigation, eleven metal chelates were synthesized for antitumor testing. The physical constants and analysis for these compounds are summarized below:

1. α -Picolyyl phenyl ketone

Copper chelate

dark green solid, mp 107°

formula: $(C_{13}H_{10}NOCu)OH$

%N: found, 5.21; Calc., 5.04.

Cobalt chelate

brown green solid, mp over 300°

formula: $(C_{13}H_{10}NOCo)OH$

%N: found, 5.02; Calc., 5.13.

Nickel chelate

pale green solid, mp 116°

formula: $(C_{13}H_{10}NONi)_2SO_4$

%N: found, 4.43; Calc., 4.62.

2. α -Anilino-o-cresol

Copper chelate

dark green solid, mp 107°

formula: $C_{26}H_{24}N_2O_2Cu$

%N: found, 5.90; Calc., 6.09

3. α -(p-Toluidino)-o-cresol

- Copper chelate olive green solid, mp 115°
 formula: $C_{28}H_{28}N_2O_2Cu$
 %N: found, 5.51; Calc., 5.74.
- Cobalt chelate pale green solid, mp 119°
 formula: $C_{28}H_{28}N_2O_2Co$
 %N: found, 5.82; Calc., 5.79.
- Nickel chelate pale green solid, mp 117°
 formula: $(C_{14}H_{14}NONi)_2SO_4$
 %N: found, 4.41; Calc., 4.39.
4. α -(p-Anisidino)-o-cresol
- Copper chelate dark green solid, mp 177°
 formula: $C_{28}H_{28}N_2O_4Cu$
 %N: found, 5.60; Calc., 5.39.
5. α -(p-Dimethylaminoanilino)-o-cresol
- Copper chelate brown red solid, mp 113°
 formula: $(C_{15}H_{17}ON_2Cu)OH$
 %N: found, 8.70; Calc., 8.01.
6. α -(p-Hydroxyanilino)-o-cresol
- Copper chelate dark green solid, mp over 300°
 formula $C_{26}H_{24}N_2O_4Cu$
 %N: found, 5.33; Calc., 5.69.
- Cobalt chelate green solid, mp 195° d
 formula: $C_{26}H_{24}N_2O_4Co$
 %N: found, 5.80; Calc., 5.75.

CHAPTER VI

DISCUSSION

This investigation confirms that copper(II) ions form chelates with organic ligands more readily than cobalt(II) or nickel(II) ions do. All of our six compounds can form copper(II) chelates, but not all form nickel(II) or cobalt(II) chelates.

Attempts were made to make ethylenediamine derivatives of these Schiff bases. According to the report of Schönerberger and Bauer (26) using magnesium-magnesium iodide mixture, they succeeded in making ethylenediamine derivatives of many benzylidene alkylamines. The same method was tried with salicylideneaniline as the original reagent. No dimer was obtained but only the monomer. Synthesis of the dimer was also attempted (27) by reducing the salicylideneaniline with activated aluminum in alcoholic solution. No dimer was obtained by this method.

CHAPTER VII

SUMMARY

The six compounds 2-picoly1 phenyl ketone, α -anilino-o-cresol, α -(p-anisidino)-o-cresol, α -(p-toluidino)-o-cresol, α -(p-dimethylamino-anilino)-o-cresol, and α -(p-hydroxyanilino)-o-cresol and their eleven metal chelates were made in this experiment. Only 2-picoly1 phenyl ketone was made by reacting 2-picoline with phenyllithium to form the lithium salt which is then condensed with the ester to yield the ketone. The other five compounds were made by reducing the corresponding Schiff bases with lithium aluminum hydride. Their metal chelates were prepared by method suggested by Nelson (5) dissolving the compounds in ethanol then adding metal ions directly to form complexes.

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VITA

Olamay Chen

Candidate for the Degree of

Master of Science

Thesis: SYNTHESIS OF SOME METAL CHELATES AS ANTITUMOR AGENTS

Major Field: Chemistry

Biographical:

Personal Data: Born at Chekiang, China, September 5, 1942, the daughter of Mr. and Mrs. T. C. Chen.

Education: Bachelor of Science Degree, Taiwan Provincial Cheng-Kung University, Tainan, Taiwan Republic of China, 1960-1964.