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Macro Chelate Rings. I. Synthesis of 2,7-Dimethyl-4,5-bis(salicylideneaminomethyl)acridone as a Quadridentate Chelating Agent and Its Metal Complexes

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2,7-Dimethyl-4,5-bis(salicylideneaminomethyl)acridone, which may form a quadridentate metal complex involving a ten-membered chelate ring, was synthesized by a sequence of steps and characterized. A monomeric cobalt(II) complex of the ligand was isolated and examined.

A number of six- or less-membered metal chelates have been synthesized, but there have been few, if any, characterized complexes with eight- or more-membered chelate rings in spite of the interest in the configuration of the complex.

In order to find a suitable metal complex which is sterically controlled for our ultimate object of making an asymmetric synthesis of an organic compound, we attempted to synthesize a novel quadridentate chelating agent, 2,7-dimethyl-4,5-bis(salicylideneaminomethyl)acridone (I), which may form a ten-membered chelate ring in addition to two six-membered chelate rings by complex formation.

As is generally known, a purely organic macro ring compound is considered to be difficult to obtain without the selection of a suitable cyclization reaction and strict reaction conditions. In chelate compounds as well, an eight- or more-membered solitary chelate ring would not seem to form a stable metal complex because of the extreme weakness of the chelate effect. A considerably stable inner complex, however, may be formed if a macro chelate ring is fortified with an adjoining six-membered chelate ring on each side. Actually, some stable chelates of the ligand derived from salicylaldehyde and hexamethylenediamine have been obtained.

From this fact it seems possible to isolate a metal chelate of the liganed (I) in a stable form. However, no chelating agent similar to our ligand has ever been synthesized. The hydrogen atom attached to the nitrogen atom in the acridone nucleus may hinder the complex formation. Moreover, the ligand is unique in that the two phenolic oxygen atoms and two azomethin nitrogen atoms in the ligand molecule can not coordinate to the four sites of a square, planar central atom, as shown by a model consideration. Therefore, it seems necessary for the chelate to take a tetrahedral or octahedral configuration.

Therefore, in this work the synthesis of 2,7-dimethyl-4,5-bis(salicylideneaminomethyl) acridone (I) was explored as well as the complex formation.

Results and Discussion

The synthetic scheme of the organic moiety is shown in Chart 1. As the starting material, 2,7-dimethylacridone (V), in which the most reactive sites of acridone are blocked by methyl groups, was prepared by the Jourdan-Ullmann-Goldberg method from *p*-bromotoluene and 2-amino-5-methylbenzoic acid, which had been synthesized by a new method. Since the aminomethyl derivatives of acridone were not known, several routes were attempted. Among these, only direct aminomethylation was successful. 2,7-Dimethylacridone (V) was treated with *N*-hydroxymethylphthalimide or *N*-hydroxymethylbenzamide in concentrated sulfuric acid, and the condensation product (VI or VII) was hydrolyzed with hydrobromic acid to give 2,7-dimethyl-di(aminomethyl)acridone dihydrobromide (VIII). The di(aminomethyl)derivative was stable only in its salt form; the isolation of the free diamine was unsuccessful. Because of the instability of free diamine, the positions of the substitution were tentatively assigned to the 4 and 5 positions by analogy with the electrophilic substitutions of 2,7-dichloro and 2,7-dibromoacridone.[1] This 2,7-dimethyl-4,5-di(aminomethyl) acridone dihydrobromide was treated with salicylaldehyde to give 2,7-dimethyl-4,5-bis(salicylideneaminomethyl)acridone (I), the structure of which was confirmed by elementary analysis; its infrared spectrum supported the existence of a chelated azomethin group at 1625 cm^{-1}.

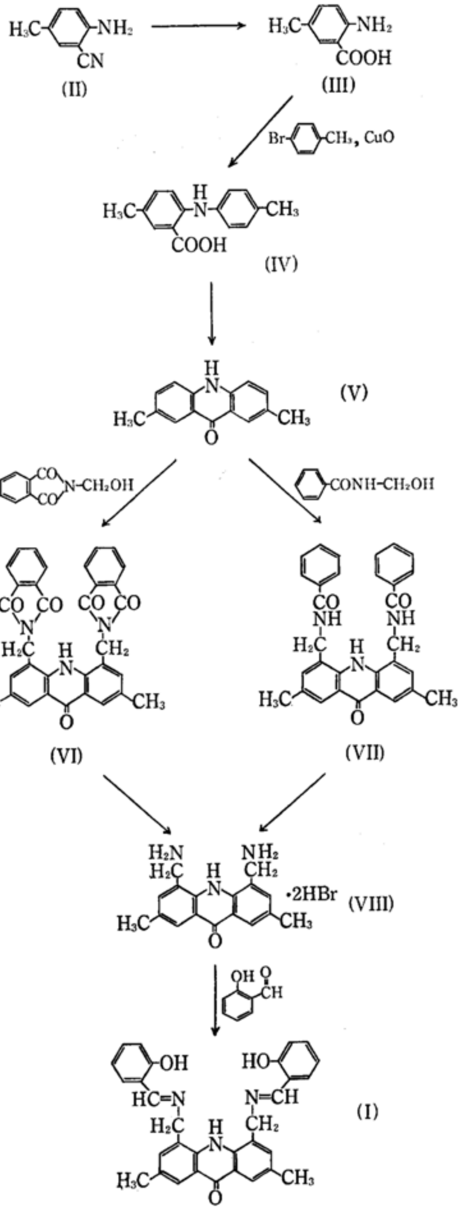

Chart 1.

The compound (I) formed metal complexes with several metal salts, such as cobalt(II) and nickel(II) acetates. Of these the cobalt(II) complex (IX) was so stable as to be isolable in a pure state; its structure was determined by elementary analysis, by molecular-weight determination by vapor pressure in methanol, and by the shift of the C=N strectching vibration from 1625 to 1620 cm^{-1}. On the other hand, no recognizable shifts of the C=O and N–H stretching vibrations in the acridone nucleus were observed upon complex formation, the respective peaks being at 3270 and 1625 cm^{-1}. This fact means that the acridone nucleus does not change to the 9-hydroxyacridine nucleus upon prototropy; accordingly, the nitrogen atom in the acridone nucleus does not participate in the complex formation. The quinquedentate structure shown

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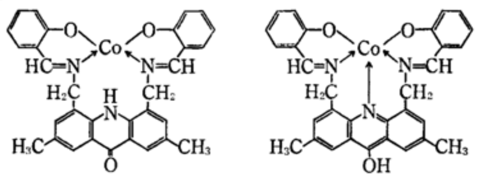
[1] M. Ionescu and D. Postescu, *Studia Univ. Babes-Bolyai, Ser. Chem.*, **11**(1), 73 (1966).



(IXa) (IXb)

Chart 2.

in formula (IXb) could thus be excluded, and the quadridentate structure (IXa) was chosen as that of the cobalt(II) complex (Chart 2[*1]). The hydrogen atom attached to the nitrogen atom in the acridone nucleus was, unexpectedly, shown not to hinder the complex formation. Although the cobalt(II) complex did not have sufficient stability because of the steric strain probably due to the macro ring, our experiments have shown that the matal complex involving a ten-membered chelate ring is possibly so stable as to be isolable in a pure state.

Experimental

2-Amino-5-methylbenzonitrile (II). A mixture of 3-bromo-4-aminotoluene (186 g, 1 mol) and cuprous cyanide (100 g, 1.1 mol) in *N,N*-dimethylformamide (250 m*l*) was refluxed. Cuprous cyanide was dissolved within about 10 min. After a period of 3 hr, the reaction mixture was poured into a solution of sodium cyanide (200 g) in water (700 m*l*). The entire mixture was heated on a water bath for 1 hr and then cooled. The upper organic layer was separated, and the aqueous layer was extracted with benzene (300 m*l*). After the combined mixture of the organic layers had been dried over anhydrous sodium sulfate and the solvent had been removed by distillation, the residue was subjected to vacuum distillation; a fraction (97 g) boiling at 94—102°C/2 mmHg and solidifying immediately on cooling was collected to give 2-amino-5-methylbenzonitrile. A sample crystallized from ethanol consisted of colorless needles with a mp of 60—61°C.

The compound obtained by this new method was identified by the coincidence of our description with that of Findeklee's report.[2]

2-Amino-5-methylbenzoic Acid (III). 2-Amino-5-methylbenzonitrile (61 g, 0.5 mol) was hydrolyzed in a solution prepared by adding ethanol (500 m*l*) to a solution of sodium hydroxide (80 g) in water (100 m*l*). The sodium salt which separated after 7 hr was collected and dissolved in water (500 m*l*). The aqueous solution was neutralized with hydrochloric acid to give 2-amino-5-methylbenzoic acid, the subsequent crystallization of which from benzene gave colorless needles with a mp of 173°C.

The product was identified by the coincidence of our descritpion with that of Findeklee's report.[3]

2-(*p*-Tolylamino)-5-methylbenzoic Acid (IV). A mixture of 2-amino-5-methylbenzoic acid (40 g, 0.25 mol), *p*-bromotoluene (43 g, 0.25 mol), copper(II) oxide (0.5 g), and anhydrous potassium carbonate (18 g) in quinoline (100 m*l*) was refluxed at 240°C for 3 hr. After the excess *p*-bromotoluene and quinoline had been removed by steam distillation, the remaining dark-brown reaction mixture was boiled with active charcoal (5 g) for 5 min and then filtered. The filtrate, on acidification with hydrochloric acid, separated a dark yellowish green precipitate which was then crystallized from ethanol to give pale yellow prisms (50 g) with a mp of 184—186°C.

Found: C, 74.89; H, 6.36; N, 5.87%. Calcd for $C_{15}H_{15}NO_2$: C, 74.67; H, 6.27; N, 5.80%.

2-Amino-5-methylbenzoic acid and excess *p*-bromotoluene formed yellow crystals of 2-bis(*p*-tolyl)amino-5-methylbenzoic acid, which in turn yielded *N*-*p*-tolyl-2,7-dimethylacridone with a mp of 217—219°C.

2,7-Dimethylacridone (V). A solution of 2-(*p*-tolylamino)-5-methylbenzoic acid (50 g) in concentrated sulfuric acid (200 m*l*) was heated on a water bath for 4 hr. After having been cooled, the reaction mixture was poured onto ice. The yellow precipitate was collected by filtration. After any impurities had been removed by boiling with a 10% aqueous sodium carbonate solution, the insoluble residue was crystallized from dioxane or acetic acid to give yellow needles (28 g) with a mp of above 300°C. The overall yield from 2-amino-5-methylbenzoic acid was 55%.

Found: C, 80.99; H, 5.99; N, 6.58%. Calcd for $C_{15}H_{13}NO$: C, 80.69; H, 5.87; N, 6.27%.

The use of an excess of sulfuric acid led to the formation of a compound of an unknown structure, the composition of which was close to $C_{15}H_{14}NO_5SNa$.

2,7-Dimethyl-4,5-bis(phthalimidomethyl)acridone (VI). 2,7-Dimethylacridone (2.23 g, 0.01 mol) and *N*-hydroxymethylphthalimide (3.54 g, 0.023 mol) were dissolved in concentrated sulfuric acid (50 m*l*), and then the solution was left standing at room temperature for a week. The reaction mixture was then poured onto ice to give a yellow precipitate; this precipitate was collected by suction, treated in a 10% sodium bicarbonate solution (300 m*l*), collected by filtration, and washed with water and then with ethanol. The yield was almost quantitative. An analytical sample was crystallized from acetic acid to give pale yellow needles with a mp of above 300°C.

Found: C, 72.93; H, 4.46; N, 7.46%. Calcd for $C_{33}H_{23}N_3O_5$: C, 73.19; H, 4.28; N, 7.76%.

The use of a large excess of *N*-hydroxymethylphthalimide resulted in the formation of an insoluble substance, of an unknown structure, apparently containing more than two, probably six, phthalimidomethyl groups.

Found: C, 69.11; H, 3.88; N, 7.89%. Calcd for $C_{69}H_{43}N_7O_{13}\cdot H_2O$: C, 69.29; H, 3.79; N, 8.20%.

2,7-Dimethyl-4,5-bis(benzamidomethyl)acridone (VII). A mixture of 2,7-dimethylacridone (1.1 g, 0.005 mol) and *N*-hydroxymethylbenzamide (1.8 g, 0.012 mol) in concentrated sulfuric acid (50 m*l*) was left standing at room temperature for ten days, and then the reaction mixture was poured onto ice. The yellow precipitate was collected by filtration. After having been boiled in a 10% aqueous sodium bicarbonate solution, it was collected, washed with water, and crystallized from a methanol-dioxane mixture to give pale yellow needles (2.2 g) with a mp of above 300°C.

Found: C, 75.81; H, 5.82; N, 8.42%. Calcd for $C_{31}H_{27}N_3O_3$: C, 76.03; H, 5.56; N, 8.58%.

[*1] Two water molecules which may be coordinated to the cobalt atom are eliminated in this chart.

2) W. Findeklee, *Ber.*, **38**, 3544 (1905).

3) W. Findeklee, *ibid.*, **38**, 3555 (1905).

2,7-Dimethyl-4,5-di(aminomethyl)acridone Dihydrobromide (VIII). A mixture of 2,7-dimethyl-4,5-bis(phthalimidomethyl)acridone (5 g) in acetic acid (50 m*l*) and 40% hydrobromic acid (50 m*l*) was refluxed in an oil bath for 2 days. The yellow needles (400 mg) which separated were collected by filtration and washed with a small amount of ethanol.

Found: C, 43.87; H, 4.86; N, 8.98%. Calcd for $C_{17}H_{21}N_3OBr_2$: C, 44.27; H, 5.03; N, 9.11%.

This dihydrobromide (200 mg) was also obtained in a comparable yield by refluxing 2,7-dimethyl-4,5-bis-(benzamidomethyl)acridone (2 g) in a mixture of acetic acid (30 m*l*) and 40% hydrobromic acid (30 m*l*) for 7 hr. In this case, the reaction time could be shortened for a comparably easy hydrolysis. These dihydrobromides were confirmed to be the same by the coincidence of the two infrared spectra.

The diamine seemed to be stable only in its salt form; attempts to isolate the free diamine failed, giving only a black paste.

2,7-Dimethyl-4,5-bis (salicylideneaminomethyl)-acridone (I). An acidic solution of 2,7-dimethyl-4,5-di(aminomethyl)acridone dihydrobromide (50 mg) and salicylaldehyde (50 mg) in 50% ethanol (30 m*l*) was neutralized with a 10% sodium bicarbonate solution to separate dark pink needles; these needles were collected by filtration and recrystallized three times from dioxane to give pink needles (30 mg) with a mp of 227—229°C. UV (ethanol): 31600 (6770), 25600 (5460) and 24700 cm^{-1} (ε 6190). IR (KBr disk): 3270 (N–H) and 1625 cm^{-1} (C=O and C=N).

Found: C, 76.24; H, 5.63; N, 8.51%. Calcd for $C_{31}H_{27}N_3O_3$: C, 76.05; H, 5.56; N, 8.58%.

Cobalt(II) Complex of 2,7-Dimethyl-4,5-bis(salicylideneaminomethyl)acridone (IX). A mixture of 2,7-dimethyl-4,5-bis (salicylideneaminomethyl) acridone (30 mg) and cobalt(II) acetate tetrahydrate (25 mg) in ethanol (25 m*l*) was heated on a water bath for 3 hr to give a reddish-brown precipitate; this precpitate was collected by filtration and washed with a small amount of ethanol. It was soluble in pyridine, dioxane, and *N,N*-dimethylformamide. UV (ethanol): 20000 (2100), 17500 (1100) and 7300 cm^{-1} (ε 480). IR (KBr disk): 3270 (N–H), 1625 (C=O) and 1620 cm^{-1} (C=N).

Found: C, 64.29; H, 4.77; N, 7.21; Co, 10.15%, mol wt, 590 (methanol). Calcd for $C_{31}H_{25}N_3O_3Co \cdot 2H_2O$: C, 63.92; H, 5.02; N, 7.21; Co, 10.12%, mol wt, 582.5.

Nickel(II) Complex of 2,7-Dimethyl-4,5-bis(salicylideneaminomethyl)acridone (X). A mixture of 2,7-dimethyl-4,5-bis (salicylideneaminomethyl) acridone (30 mg) and nickel(II) acetate tetrahydrate (25 mg) in ethanol (25 m*l*) was heated on a water bath for 1 hr. The precipitate was collected by filtration and washed with a small amount of ethanol to give a yellowish-brown powder.

Found: C, 63.37; H, 4.57; N, 7.53%. Calcd for $C_{31}H_{25}N_3O_3Ni \cdot 2H_2O$: C, 63.94; H, 5.02; N, 7.22%.