and that of salicylaldehyde. As to the type of carbonyl group, thiolic acid ester is the strongest and the chelating ability decreases in the order of thiolic acid ester, ester, amide, and ketone.

The authors extend their gratitude to Prof. T. Uno for his helpful advices.

Summary

Stabilities of copper, palladium, nickel, cobalt, and iron chelates of various tyres of ligands involving the mercapto and the carbonyl group were compared each other by measuring the pH at 50% extractability of the chelates into chloroform and at incipient chelate formation. From the results of these experiments, relationship between chelating abilities and chemical structures of the ligands was confirmed. The ligands which involve conjugated double bond in their chelate ring and those involve thiolic acid ester group were found to have stronger chelating ability.

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181. Shigeru Kobayashi and Chizuru Kuraishi : A Synthesis of 2′-Acetyl-5,5′,6-trimethoxy-2-biphenylcarboxylic Acid.

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In the course of the project to synthesize hydroxyapogalanthamine,[1] the transformation product of galanthamine by hydroiodic acid, an attempt was made to prepare key intermediate 2′-carboxy-5,5′,6′-trimethoxy-2′-biphenylacetic acid (X) via 2′-acetyl-5,5′,6-trimethoxy-2-biphenylcarboxylic acid (IX : R=H).

As a starting material for the synthesis of the latter compound, 2′-iodo-4′-methoxyacetophenone (II : R=Me) reported by Oki[2] was necessary. He claimed to obtain this as a sole product, m.p. 68~70°, by the Friedel-Crafts reaction of 3-iodoanisole (I) with acetyl chloride in the presence of aluminum chloride. On repetition of this reaction under the identical conditions as used by him, two major products, compound A, $C_9H_9O_2I$, m.p. 45~47° and compound C, $C_8H_7O_2I$, m.p. 52~54° and two minor ones, compound B, $C_9H_9O_2I$, m.p. 70~71° and compound D, $C_8H_7O_2I$, m.p. 131~132° were isolated. Among them the compounds A and B were non-phenolic while the compounds C and D were phenolic. Obviously Oki isolated only the compound B from the reaction mixture and assigned to it the structure 2′-iodo-4′-methoxyacetophenone (II : R=Me) without any convincing evidence. Since, oxidation of the compound B with potassium hypochlorite yielded 4-iodo-2-methoxybenzoic acid (VI), identical with an authentic sample obtained by the methylation of methyl 2-hydroxy-4-iodobenzoate (V)[3] followed by hydrolysis, this should be 2′-methoxy-4′-iodoacetophenone (III : R=Me). In accordance with this assignment, the compound B was shown to be identical with the pro-

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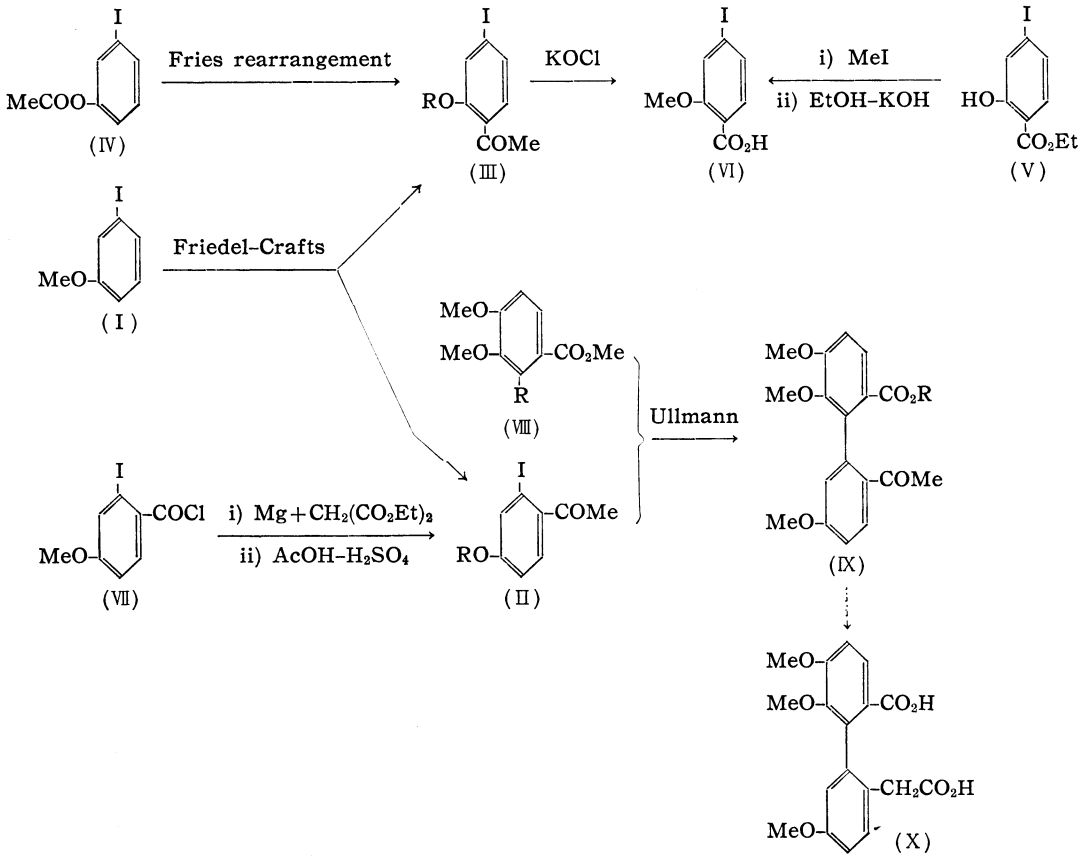
duct of the same structure prepared by the method as reported by Chen, Chang, Shi and Li[4] who obtained 2′-methoxy-4′-iodoacetophenone (Ⅲ : R=Me) by the Fries rearrangement of 3-iodophenyl acetate (Ⅳ), followed by the methylation of the resulting 2′-hydroxy-4′-iodoacetophenone (Ⅲ : R=H). They confirmed the structure of their compounds by direct comparison with the product obtained by the Sandmeyer reaction of 2′-methoxy-4′-aminoacetophenone in the presence of potassium iodide

The compound C was proved to be 2′-hydroxy-4′-iodoacetophenone (Ⅲ : R=H) by converting it into the compound B with methyl iodide in an alkaline solution. Doubtlessly, this must have been formed as a result of the demethylation of the compound B by the action of aluminum chloride used as a catalyst.

The compound A was shown to be 2′-iodo-4′-methoxyacetophenone (Ⅱ : R=Me) by a comparison with the compound prepared by interaction of 2-iodo-4-methoxybenzoyl chloride (Ⅶ) and diethyl malonate using magnesium as a condensing agent, followed by subsequent hydrolysis and decarboxylation in acetic acid containing sulfuric acid.

The compound D was identified as 2′-iodo-4′-hydroxyacetophenone (Ⅱ : R=H) which was prepared by the demethylation of the compound A with hydrobromic acid.

Thus it has been shown conclusively that the Friedel-Crafts acetylation of 3-iodoanisole afforded, contrary to the Oki's findings, 2′-iodo-4′-methoxy- and 2′-hydroxy-4′-iodo-acetophenone in predominant yields whereas 2′-methoxy-4′-iodo- and 2′-iodo-4-hydroxyacetophenone can only be obtained in very lower yields.



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The Ullmann condensation of 2′-iodo-4′-methoxyacetophenone (II : R=Me) thus obtained with methyl 2-bromo- or 2-iodo-veratrate (VIII : R=Br or I) in the presence of copper bronze in a sealed tube gave, after fractionation and hydrolysis, 2′-acetyl-5,5′,6-trimethoxy-2-biphenylcarboxylic acid (IX : R=H) in a poor yield. Therefore extremely low overall yield of this compound precluded its use for the conversion into 2′-carboxy-5,5′,6′-trimethoxy-2-biphenylacetic acid (X) by the Willgerodt reaction.

Experimental*2

Friedel-Crafts Reaction of 3-Iodoanisole——To a cooled mixture of 3-iodoanisole (8 g.), $AlCl_3$ (5.3 g.), and CS_2 (10 cc.), was added gradually AcCl (2.6 cc.) during 20 min. The mixture was stirred for 30 min. at room temperature and then boiled gently for further 30 min. After decantation of the upper CS_2 layer, ice and HCl were added to the residue and the mixture was extracted with benzene, which was washed with 10% NaOH and H_2O, dried over $CaCl_2$, and concentrated. Fractional distillation of the residue (8.7 g.) gave the first fraction as an orange-yellow oil (1.9 g.), b.p_3 92～134°, which was discarded, and the second fraction as an orange oil (3.8 g.), b.p_3 142～148°, from which the compounds A and B were isolated as follows :

On trituration with petr. ether the second fraction gave compound A (1.8 g.), colorless long prisms, m.p. 45～47° (from the same solvent). *Anal.* Calcd. for $C_9H_9O_2I$: C, 39.15; H, 3.28. Found : C, 39.40; H, 3.42. 2,4-Dinitrophenylhydrazone was prepared in the usual manner and crystallized from AcOEt-EtOH as orange needles, m.p. 137～140°. *Anal.* Calcd. for $C_{15}H_{13}O_5N_4I$: C, 39.48; H, 2.87; N, 12.28. Found : C, 39.79; H, 2.29; N, 12.87.

The compound A was identical with an authentic specimen of 2′-iodo-4′-methoxyacetophenone prepared from 2′-iodo-4′-methoxybenzoic acid described below, as shown by mixed m.p. and IR comparison.

After removing the petr. ether from the mother-liquors from the compound A, the residue was chromatographed in benzene-petr. ether (1 : 9) on alumina to give, after elution with the same solvent mixture, white needles of compound B, m.p. 70～71° (from petr. ether). *Anal.* Calcd. for $C_9H_9O_2I$: C, 39.15; H, 3.28. Found : C, 39.43; H, 3.58. 2,4-Dinitrophenylhydrazone was crystallized from AcOEt-EtOH as orange needles, m.p. 195～197°. *Anal.* Calcd. for $C_{15}H_{13}O_5N_4I$: C, 39.48; H, 2.87; N, 12.28. Found : C, 39.82; H, 2.67; N, 12.97.

The compound B was identified as 2′-methoxy-4′-iodo-acetophenone obtained by the methylation of 2′-hydroxy-4′-iodoacetophenone by mixed m.p. and comparison of IR spectra.

Further elution through the column with the same solvent mixture afforded a trace of 2′-iodo-4′-methoxyacetophenone.

The 10% NaOH washings separated above from the benzene layer were acidified with HCl and extracted with Et_2O. After evaporation of the solvent, the residue (2.1 g.) yielded the compounds C and D as follows :

Trituration of the residue with MeOH gave 1.3 g. of the compound C (2′-hydroxy-4′-iodoacetophenone) as white needles, m.p. 52～54° (from MeOH). (reported[4] m.p. 53～54°). *Anal.* Calcd. for $C_8H_7O_2I$: C, 36.67; H, 2.69. Found : C, 37.13; H, 2.87.

A mixture of the compound C (0.6 g.), K_2CO_3 (0.2 g.), MeI (2 g.), and Me_2CO (6 cc.) was refluxed for 5 hr. After working up in the usual manner, the methylated product was crystallized from petr. ether to afford white needles, m.p. 70～71°. Found : C, 39.39; H, 3.23. It showed no depression of m.p. with the compound B (2′-methoxy-4′-iodoacetophenone) and the IR spectra were also identical.

The MeOH mother-liquors from the compound C was evaporated to dryness and the residue was chromatographed in benzene through alumina. The first benzene eluate gave a trace of the compound C and the second benzene eluate afforded, on crystallization from benzene, white needles of the compound D, m.p. 131～132°. *Anal.* Calcd. for $C_8H_7O_2I$: C, 36.67; H, 2.69. Found : C, 36.87; H, 2.69.

A mixture of 2′-iodo-4′-methoxyacetophenone (0.2 g.), 48% HBr (3 cc.), and AcOH (3 cc.) was heated in a sealed tube at 100° for 3.5 hr. After removing the starting material (87 mg.) in the usual manner, the resulting demethylated product was recrystallized from benzene to give needles of 2′-iodo-4′-hydroxyacetophenone (54 mg.), m.p. 131～132°. Found : C, 37.02; H, 2.66. This compound was shown to be identical with the compound D by mixed m.p. and IR comparison.

2′-Iodo-4′-methoxyacetophenone from 2-Iodo-4-methoxybenzoic Acid——To a suspension of Mg (1.6 g.) in dry Et_2O (2 cc.), CCl_4 (0.15 g.), and anhyd. EtOH (42 cc.), was added a solution of diethyl malonate (10 g.) in anhyd. EtOH (6 cc.) and Et_2O (7.2 cc.), and the mixture was heated under reflux for 6 hr. until most of Mg dissolved in solution. To 3 g. of the above whole mixture (38 g.), was

*2 All melting points are uncorrected.

added dropwise during 10 min. an ethereal solution (6 cc.) of 2-iodo-4-methoxybenzoyl chloride, which was obtained by the treatment of the corresponding acid (10.9 g.) with $SOCl_2$ (4 cc.), and the whole was refluxed for 3.5 hr. After removal of the Et_2O, a mixture of AcOH (5 cc.), conc. H_2SO_4 (0.7 cc.), and H_2O (3.5 cc.) was added to the residue and refluxed for 4 hr. The cooled mixture was made alkaline with 20% NaOH and extracted with Et_2O. After working up, the product was distilled *in vacuo*. The fraction, $b.p_3$ 139~140°, was a yellow oil (0.2 g.) which was crystallized from petr. ether as white needles of 2-iodo-4-methoxyacetophenone, m.p. 45~47°. Found : C, 39.45; H, 3.18.

2'-Hydroxy-4'-iodoacetophenone and its Methyl Ether from 3-Iodophenyl Acetate——By the procedure reported by Chen *et al.*,[4] a mixture of 3-iodophenyl acetate (5.5 g), nitrobenzene (30 cc), and $AlCl_3$ (0.7 g.) was heated at 120° for 2 hr. After cooling, the mixture was taken up in Et_2O, which was extracted with 15% NaOH. The alkaline extracts were treated with charcoal, acidified with HCl, and extracted with Et_2O. After removal of the solvent, the residue (2.5 g.) was crystallized from MeOH to give white long prisms of 2'-hydroxy-4'-iodoacetophenone, m.p. 52~54°, (reported[4] m.p. 53~54°). Found : C, 36.78; H, 2.85.

Methylation of 2'-hydroxy-4'-iodoacetophenone (0.6 g.) by the method used above gave 2'-methoxy-4'-iodo-acetophenone, m.p. 70~71°. Found : C, 39.43; H, 3.15.

4-Iodo-2-methoxybenzoic Acid——(i) From compound B : Cl_2 was passed into a solution of 24% KOH (10.5 g.), until the solution became neutral to litmus and then 1% KOH (1 cc.) was added. To this solution was added dropwise a solution of the compound B (0.5 g.) in MeOH (20 cc.) at −10° during 25 min. The mixture was kept at this temperature for 2 hr., at 0° for 2 hr., then at 15° for a further 1.5 hr. and worked up in the usual manner. The resulting acid (0.2 g.) was crystallized from Et_2O to afford white plates, m.p. and mixed m.p. 146~148°, identical in IR spectrum with an authenti csample of 2-methoxy-4-iodobenzoic acid obtained below in (ii). *Anal.* Calcd. for $C_8H_7O_3I$: C, 34.56; H, 2.54. Found : C, 34.91; H, 2.47.

(ii) From methyl 2-hydroxy-4-iodobenzoate : Methyl 2-hydroxy-4-iodobenzoate was prepared from *p*-aminosalicylic acid by the method reported by Brenaus *et al.*[3] A mixture of the ester (1.5 g.), Me_2CO (200 cc.), MeI (7.5 g.), and K_2CO_3 (0.8 g.) was heated under reflux for 5 hr. and worked up in the usual way. Resulting methyl 2-methoxy-4-iodobenzoate (1.5 g.) was hydrolyzed by refluxing in 8% EtOH-KOH (300 cc.) for 1 hr. The product was crystallized from petr. ether to give white plates of 2-methoxy-4-iodobenzoic acid, m.p. 146~148°. (reported[5] m.p. 150°). *Anal.* Calcd. for $C_8H_7O_3I$: C, 34.56; H, 2.54. Found : C, 34.86; H, 2.54.

Methyl 2-Iodoveratrate——To a mixture of methyl 2-aminoveratrate (3 g.)[6] in 10% H_2SO_4 (22.5 g.), was added 10% $NaNO_2$ solution (10 cc.) at 3° and stirred for 1 hr. A solution of 10% KI (48 cc.) was added to the mixture at 3°, and the whole kept at 15° for 3 hr., then at 60° for a further 30 min., and extracted with $CHCl_3$. Working up in the usual way gave an orange residue (4.8 g) which was chromatographed in benzene on alumina and recrystallized from MeOH to give white needles of methyl 2-iodoveratrate, m.p. 46~47°. *Anal.* Calcd. for $C_{10}H_{11}O_4I$: C, 37.29; H, 3.44. Found : C, 37.67; H, 3.38.

2'-Acetyl-5,5',6-trimethoxy-2-biphenylcarboxylic Acid and its Methyl Ester——2'-Iodo-4'-methoxyacetophenone (3 g.), methyl 2-bromoveratrate (1 g.)[6] and copper bronze (3 g.) were heated in a sealed tube at 220° for 4 hr. The reaction mixture was taken up in $CHCl_3$, which was evaporated, and the residue was extracted with Et_2O. The extract was evaporated to dryness and distilled at 0.01 mm. and 72~100° to give a solid (0.5 g.) which was discarded. The residue (1.9 g.) remained in the flask was hydrolyzed by refluxing in 10% EtOH-KOH (200 cc.) for 1.5 hr. After working up, the resulting acidic fraction was fractionally crystallized from Et_2O to give, together with 5,6,5',6'-tetramethoxy-2, 2'-biphenyldicarboxylic acid (30 mg.), 2'-acetyl-5,5',6-trimethoxy-2-biphenylcarboxylic acid (60 mg.) as white needles, m.p. 176~177.5°. *Anal.* Calcd. for $C_{18}H_{18}O_8$: C, 65.44; H, 5.49. Found : C, 65.62; H, 5.47.

In a similar manner, the Ullmann condensation of 2-iodo-4-methoxyacetophenone (2.6 g.) with methyl 2-iodoveratrate (1 g.) in the presence of copper bronze (2 g.) and hydrolysis of the resulting product gave 2'-acetyl-5,5',6-trimethoxy-2-biphenylcarboxylic acid (130 mg.), identical with the above product.

Treatment of the keto-carboxylic acid (30 mg.) with $NH_2OH \cdot HCl$ (0.1 g.) in pyridine (0.5 cc.) and EtOH (0.5 cc.) in a sealed tube at 120° for 2 hr. yielded its oxime as cubes, m.p. 243~245.5° (from MeOH) .*Anal.* Calcd. for $C_{18}H_{19}O_6N$: C, 62.60; H, 5.55; N, 4.06. Found : C, 62.85; H, 5.50; N, 4.04.

A mixture of the keto-carboxylic acid (0.16 g.), MeOH (70 cc.), and conc. H_2SO_4 (2.8 cc.) was heated under reflux for 5 hr. Methyl 2'-acetyl-5,5',6-trimethoxy-2-biphenylcarboxylate thus obtained formed cubes, m.p. 82~84° (from Et_2O). *Anal.* Calcd. for $C_{19}H_{20}O_6$: C, 66.27 ; H, 5.85. Found : C, 66.69 ; H, 6.07.

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Summary

It has been found that the Friedel-Crafts reaction of 3-iodoanisole with acetyl chloride yielded, contrary to Oki's report, four products, 2′-hydroxy-4′-iodo-, 2′-iodo-4′-hydroxy, 2′-iodo-4′-methoxy-, and 2′-methoxy-4′-iodoacetophenone.

The Ullmann condensation of 2′-iodo-4′-methoxyacetophenone with methyl 2-bromo- or 2-iodo-veratrate, followed by hydrolysis, gave, in a poor yield, 2′-acetyl-5,5′6-trimethoxy-2-biphenylcarboxylic acid which was characterized as its oxime as well as its methyl ester.

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186. Takanobu Itai[*1] and Genzō Itō[*2] : Potential Anti-Cancer Agents. VII.[1] Azido-purine Derivatives.

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As 6-azidopurine[2] and 7-azidomethyl-8-chlorotheophylline[3] have been known to show anti-cancer action, an attempt was made to synthesize some azido derivatives of purine for screening their action. Starting from 2,6-dichloro-7-methylpurine (I) and 2,6,8-trichloro-7-methylpurine (II), the former had been synthesized from theobromine with phosphorus oxychloride,[4] and the latter with phosphorus oxychloride and phosphorus pentachloride.[5] Azido group was produced by an usual approach, that is, chloro group was changed to hydrazino group by heating with hydrazine, and then by the reaction with nitrous acid to azide group. In order to prove their structure, these azido derivatives were reduced to amino derivatives and compared with amino derivatives already known in literatures. If not, amino derivatives were synthesized from corresponding chloro derivatives by heating with ammonia.

Fischer[6] had already reported 6-hydrazinopurine by heating 6-chloro-compound with anhydrous hydrazine, and Montgomery[7] also studied 2- and 6-derivatives examining the reactivity of chlorine atom.

In the experiments of this series, at first, (I) and (II) were converted to 2-chloro-6-ethoxy-7-methylpurine[4] (III), 2,6-dichloro-8-ethoxy-7-methylpurine[8] (IV), and 2-chloro-6,8-diethoxy-7-methylpurine[4] (V). By heating (I), (II), (III), (IV), and (V) with 80%

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