

Aldol Condensation of Aldehydes with Ketones Promoted by the Copper(II) Ion. Orientation to the Chemical Model for Metalloaldolases

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The aldol condensation reactions of aromatic aldehydes such as **1** through **4** and **7** through **13**, and aliphatic aldehydes such as **5** and **6**, with a number of ketones promoted by the copper(II) ion were examined. The reactions were specifically promoted by the copper(II) ion, while such metal ions as zinc, cobalt(II), manganese(II), and magnesium were quite inactive as catalysts. All the aldehydes but **7** and **8** reacted with all the aliphatic ketones except ethyl acetoacetate, acetonitrile, and nitromethane to varying degrees in the Claisen-Schmidt type of reaction. Acetylacetone gave a condensation product of the Knoevenagel type. In the reaction of aldehydes with 2-butanone, aldehydes regioselectively attacked the methylene group at C₃ of 2-butanone. Amines inhibited the reaction, while the coexistence effect of zinc or cobalt(II) was observed. It was shown that there existed a substrate selectivity depending greatly on the kinds of ketones in the reaction promoted by the copper(II) ion. As a consequence, possible intermediates in the reaction were proposed and the relationship of the aldol condensation reaction promoted by the copper(II) ion with the metalloaldolases was discussed, particularly in the light of the role of the metal ions in both catalytic mechanisms.

The aldol-condensation reaction is generally catalyzed by strong bases, such as alkali-metal hydroxide or alkoxide, or strong acids, such as hydrochloric or sulfuric acid.¹⁾ However, no instances of an aldol condensation catalyzed by a transition-metal ion have been reported. This must be because there is no requirement of new catalysts superior to such bases or acids for general organic synthesis. In relation to enzymatic reactions, however, Rutter reported an important phylogenetic analysis in 1964 where he showed that there were two types of aldolases with distinct catalytic elements and molecular characteristics.²⁾ One type of aldolase (according to Rutter, Class I aldolases) catalyzes the aldol condensation of D-glyceraldehyde 3-phosphate with dihydroxyacetone phosphate to form fructose 1,6-diphosphate *via* a Schiff-base intermediate; the other type of aldolase (Class II aldolases) needs divalent metal ions to promote the same condensation reaction, the intermediate of which is evidently different from that of Class I aldolases. Later works by Rutter and his co-workers,³⁻⁵⁾ and by other groups⁶⁾ have given evidence of the presence of these two types of aldolases, and the catalytic mechanisms have been discussed. However, it has remained chemically unsolved whether or not the aldol-condensation reaction is really catalyzed by the transition-metal ion. On the other hand, we incidentally found the novel aldol-condensation reaction promoted by the copper(II) ion of 2,6-dimethoxybenzaldehyde with acetone in the course of our studies concerning the demethylation of methoxy-substituted aromatic aldehydes,⁷⁾ and we briefly reported that the copper(II) ion specifically promoted the aldol condensation of acetone with several aromatic aldehydes to give benzylideneacetones.⁸⁾ In order to ascertain the scope and limitations of the aldol condensation promoted by the copper(II) ion and in order to approach a chemical elucidation of the role of metal ion in the catalytic mechanism of metalloaldolases, the method was further applied to the condensation of aliphatic and aromatic ketones with aliphatic and aromatic aldehydes. In this paper, the results obtained will be reported in detail and the relationship of the

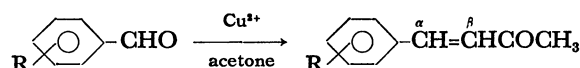
aldol-condensation reaction promoted by the copper(II) ion with enzymatic reactions will be discussed.

Results and Discussion

Reaction Systems. As aldehydes, benzaldehyde (**1**), *o*-anisaldehyde (**2**), *p*-anisaldehyde (**3**), 2,6-dimethoxybenzaldehyde (**4**), propanal (**5**), pentanal (**6**), salicylaldehyde (**7**), *p*-chlorobenzaldehyde (**8**), furfural (**9**), 2-thiophenecarbaldehyde (**10**), 2-pyridinecarbaldehyde (**11**), 3-pyridinecarbaldehyde (**12**), and 4-pyridinecarbaldehyde (**13**) were arbitrarily chosen. Acetone, 2-butanone, 2-pentanone, cyclopentanone, cyclohexanone, acetophenone, acetylacetone, and ethyl acetoacetate were used as ketones. Also, solvents with an active methylene group, such as acetonitrile and nitromethane, were examined as ketone analogues. In a typical experiment, we employed, unless otherwise stated, the procedure described in a previous report⁸⁾ where 8—10 mmol of a (hydrated) metal ion, such as zinc, cobalt(II), manganese(II), magnesium, or copper(II), all of which were selected in relation to the prothetic metal ions for the Class II aldolases,⁹⁾ and 5 mmol of an aldehyde were stirred in 20—30 ml (an excess amount) of the solvent ketone at room temperature. Also, on the basis of analogy with the enhancement effect of nucleophilic attack upon the addition of the zinc ion,⁹⁾ an amount of zinc chloride equimolar to that of the copper(II) ions was added to the reaction system.

Condensation of Aldehydes with Acetone. The results obtained in the presence of the copper(II) ion alone and in the coexistence of copper(II) and zinc ions are summarized in Table I; the table shows that the yield of the condensation product after a comparable or shorter reaction time was strikingly increased by the addition of the zinc ion and that the **7** and **8** aldehydes gave no condensation product, presumably because of the occupation of the catalytic site of the metal ion by the electron-rich substituent or because of the decreasing electrophilicity of the aldehyde group as a result of the inductive and resonance effects of the

TABLE 1. THE CONDENSATION OF AROMATIC ALDEHYDES WITH ACETONE IN THE PRESENCE OF CUPRIC ION ALONE AND IN THE COEXISTENCE OF CUPRIC AND ZINC IONS



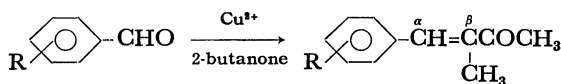
Aldehyde	R	Configuration of double bond of the product ^{a)}	Yield (%) of benzylideneacetones ^{c)}			
			Cu ²⁺ catal.	Reac. time, h	Cu ²⁺ -Zn ²⁺ catal.	Reac. time, h
1	H	E ¹⁰⁾	2	51	26	50
2	2-OCH ₃	E ¹¹⁾	trace	64	12	44
3	4-OCH ₃	E ¹²⁾	4	84	20	65
4	2,6-di-OCH ₃	E ¹³⁾	34	43	73	40
7	2-OH	—	— ^{b)}	68	— ^{b)}	67
8	4-Cl	—	— ^{b)}	52	— ^{b)}	52

a) The configuration of the double bond was determined by the coupling constants of NMR spectra. b) No reaction occurred and the starting material was recovered. c) Yield after the column chromatographic separation.

substituents. It was also of interest, from the synthetical point of view, that the copper(II) ion-promoted reaction of **4** in the coexistence of the zinc ion gave 2,6-dimethoxybenzylideneacetone in a considerably high yields. Furthermore, the yield of 2-methoxybenzylideneacetone in the coexistence of copper(II) and zinc ions was dramatically ameliorated when acetone was purified (Fig. 1). The aliphatic aldehydes, **5** and **6**, appeared to give no condensation product with acetone.

Condensation of Aldehydes with 2-Butanone. The reactions of 2-butanone with the aldehydes **1** through **6** and **9** through **13** in the presence of the copper(II) ion alone and in the coexistence of the copper(II) and zinc ions were examined. The results obtained are listed in Tables 2 and 3. It is of particular interest to note that all aldehydes attack the methylene group at C₃ of 2-butanone, but not the methyl group at C₁. The regioselectivity suggests that the copper(II) ion functions as a proton-like catalyst because it has been generally known that the mineral-acid-catalyzed aldol condensation of aldehydes with 2-butanone preferentially occurs at C₃, while the strong base-catalyzed aldol condensation preferentially occurs at C₁.¹⁾ Also, it was demonstrated

TABLE 2. THE CONDENSATION OF AROMATIC ALDEHYDES WITH 2-BUTANONE IN THE PRESENCE OF CUPRIC ION ALONE AND IN THE COEXISTENCE OF CUPRIC AND ZINC IONS



Aldehyde	R	Yield (%) of 3-benzylidene-2-butanones ^{a)}				Ref. ^{b)}
		Cu ²⁺ catal.	Reac. time, h	Cu ²⁺ -Zn ²⁺ catal.	Reac. time, h	
1	H	91	41	88	41	14)
2	2-OCH ₃	48	28	63	44	15)
3	4-OCH ₃	40	44	63	44	16)
4	2,6-di-OCH ₃	45	20	23	20	

a) Yield after the column chromatographic separation. b) The condensation product obtained was identified in comparison with the reference cited.

TABLE 3. THE CONDENSATION OF ALDEHYDES WITH 2-BUTANONE IN THE PRESENCE OF CUPRIC ION ALONE AND IN THE COEXISTENCE OF CUPRIC AND ZINC IONS

Aldehyde	Product	Yield (%)			
		Cu ²⁺ catal.	Reac. time, h	Cu ²⁺ -Zn ²⁺ catal.	Reac. time, h
5	dehyd ^{a)}	3 ^{c)}	48	2 ^{c)}	24
6	dehyd	—	—	27 ^{c)}	19
9	dehyd	15 ^{d)}	22	15 ^{d)}	22
10	dehyd	33 ^{e)}	24	77 ^{e)}	24
11	add ^{b)}	70 ^{d)}	24	70 ^{d)}	24
12	add	40 ^{d)}	20	0	20
13	add	80 ^{d)}	22	30 ^{d)}	22

a) The condensation reaction gave dehydrated product, RCH=C(CH₃)COOCH₃, where R was the group in the aldehyde RCHO. b) The condensation reaction afforded addition product, RCH(OH)CH(CH₃)COCH₃, where R was the group in the aldehyde RCHO. c) Yield after the column chromatographic separation. d) On the basis of TLC spot. e) On the basis of gas chromatographic analysis (see Experimental part).

that the additional effect of the zinc ion was not so remarkable as has been shown in the case of acetone. It was of interest that the pyridinecarbaldehydes **11** through **13** gave only aldol-addition products to 2-butanone, but not dehydrated products, as was shown in all the other aldehydes, and that the aliphatic aldehydes **5** and **6** gave also the condensation products, unlike the case of acetone, but in a lower yield. The fact that the condensation of pyridinecarbaldehydes with 2-butanone gave the addition product led us to predict that the reaction of benzaldehydes with 2-butanone in the presence of pyridine would also afford the non-dehydrated product. However, no addition product was obtained; pyridine acted only as an inhibitor of the reaction.

Condensation of Miscellaneous Ketones and their Analogues with Aldehydes. The reactants and the results obtained are briefly shown in Table 4; no condensation product of aryl methyl ketone, β-keto ester, or alkyl (carbon number > 3) methyl ketone was obtained in the presence of a copper(II) or copper(II)-zinc catalyst.

TABLE 4. THE CONDENSATION OF MISCELLANEOUS KETONES WITH ALDEHYDES IN THE PRESENCE OF CUPRIC ION OR IN THE COEXISTENCE OF CUPRIC AND ZINC IONS

Aldehyde	Ketone	Catalyst ^{a)}	Reac. time, h	Yield (%) ^{b)}
3	Acetophenone	A	139	N
3	Acetophenone	B	139	N
1	2-Pentanone	A	24	N
2	2-Pentanone	A	24	N
3	2-Pentanone	A	24	N
4	2-Pentanone	A	24	N
2	Acetylacetone	A	29	47
2	Acetylacetone	B	23	14
2	Ethyl acetoacetate	A	7 days	N
3	Acetonitrile	A	47	N
3	Acetonitrile	B	47	N
2	Nitromethane	A	23	N
2	Nitromethane	B	23	N

a) A; $\text{CuCl}_2 \cdot 2\text{H}_2\text{O}$ and B; $\text{CuCl}_2 \cdot 2\text{H}_2\text{O} - \text{ZnCl}_2$. b) yield after the column chromatographic separation and N represents non-reaction.

In addition, solvents with an active methylene group, such as acetonitrile and nitromethane, gave no condensation product with aldehydes in spite of the formation of certain copper complexes. On the other hand, of interest was the formation of 3-(2-methoxybenzylidene)-2,4-pentanedione (**14**) by the reaction of **2** with acetylacetone, while the reaction was not induced when bis(acetylacetonato)copper(II), which had previously been prepared by the reaction of copper(II) chloride dihydrate with twice the equimolar amount of acetylacetone, was treated with **2** in benzene. This seemed to indicate that it might be crucially important in the aldol condensation promoted by the copper(II) ion that the copper(II) ion was bound to the carbonyl moiety weakly, not tightly. Furthermore, it should be noted that, from the synthetical point of view, the formation of **14** was the first example of the Knoevenagel-type aldol condensation under weak acidic conditions; the reaction has usually been run in the presence of primary or secondary amines, ammonia, pyridine, or piperidine.¹⁷⁾

Catalytic Activity of the Metal Ion. It is of particular interest to learn, in relation to the enzymatic reaction, whether the aldol condensation promoted by the copper(II) ion is specific for the copper(II) ion or equally applicable to other metal ions. In order to elucidate the specificity, zinc, magnesium, cobalt(II), and manganese(II) were examined under conditions similar to those of the copper(II) ion series. However, none of these metal ions which were prothetic to the Class II aldolases promoted the Claisen-Schmidt aldol condensation; that is, the aldol condensation promoted by the metal ion was specific for the copper(II) ion. The reaction was, however, affected by the addition of zinc or cobalt(II) in some aldehydes (see Experimental). As regards the effect of the counter anion of the copper(II) ion, copper(II) acetate was also effective in the condensation of **3** with acetone; the yield of the product was, however, considerably decreased in comparison with that catalyzed by copper(II) chloride.

Effect of Molar Ratio of $\text{Zn}^{2+}/\text{Cu}^{2+}$ on the Condensation Reaction.

The observations that the reaction yield of the aldol condensation promoted by the copper(II) ion depended greatly on the kinds of ketones and that it was greatly or slightly affected in the coexistence of the zinc ion led us to examine the possibility of the substrate selectivity of the aldol condensation. Thus, the effect of the molar ratio of $\text{Zn}^{2+}/\text{Cu}^{2+}$ on the yields of the condensation reaction of *o*-anisaldehyde (**2**) as a representative aldehyde with acetone, 2-butanone, 2-pentanone, cyclopentanone, and cyclohexanone respectively was investigated. The results obtained are illustrated by plotting the molar ratio of $\text{Zn}^{2+}/\text{Cu}^{2+}$ vs. the yield of the condensation product in Fig. 1. In the experi-

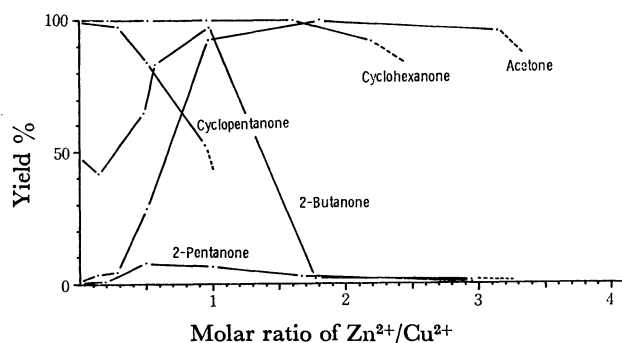


Fig. 1. The effect of the molar ratio of $\text{Zn}^{2+}/\text{Cu}^{2+}$ on the condensation yield of various ketones with *o*-anisaldehyde (**2**).

ments, purified acetone was used, and a series of the reactions for each ketone was set up to keep consistency with respect to the reaction time and temperature in order to normalize the data. Also, the reaction yield was estimated by analyzing the gas chromatogram on the basis of the theoretical equation derived from several assumptions (see Experimental). The molar ratio of $\text{Cu}^{2+}/\mathbf{2}$ was at most 2, and that of $\text{Zn}^{2+}/\mathbf{2}$, at most 2. Figure 1 shows the following characteristic features; there is certainly a substrate selectivity in the condensation reaction in the presence of the copper(II) ion alone, since acetone and 2-pentanone hardly reacted with **2**, while cyclopentanone and cyclohexanone quantitatively gave the condensation product. In any cases, the condensation reaction was not induced without the copper(II) ion, and the zinc ion coexisting in the system affected the yield positively or negatively. Additionally, there was the optimum molar ratio of $\text{Zn}^{2+}/\text{Cu}^{2+}$ to give the product in the best yield. The range showing the optimum ratio is limited in the case of 2-butanone, whereas it is very wide for acetone.

Scope and Limitation of the Aldol Condensation Promoted by the Copper(II) Ion.

In view of the stoichiometry of the reaction, 0.05 mol of **2** was treated with a mixture of 0.05 mol of 2-butanone, 0.01 mol of copper(II) chloride dihydrate, and 0.01 mol of zinc chloride in 30 ml of ethanol for 122 h. However, no benzylideneacetone derivative was obtained, and almost all of the starting materials were recovered. On the other hand, the reaction in which **3** and imidazole were added to the previously prepared acetone-copper(II) complex in the excess amount of acetone also gave no condensation

product. In addition, when the acetone-copper(II) complex which had previously been prepared was added to the mixture of **2** and 2-butanone, 3-(2-methoxybenzylidene)-2-butanone was produced after 28 h but no 2-methoxybenzylideneacetone was produced. Furthermore, it was of interest that methyl salicylate was formed in a 19% yield when **2** and the 2-butanone-copper(II) complex, previously prepared, were stirred in benzene for 48 h.

These observations, together with the afore-mentioned results, permit us to draw some conclusions with regard to the scope and limitations of the aldol condensation promoted by the copper(II) ion. That is, (a) the reaction will not stoichiometrically proceed with respect to ketone and thus should be conducted in a ketone solvent, which means that only liquid ketone can be used as a reactant for aldehyde. (b) A stable ketone-copper(II) complex such as bis(acetylacetonato)copper(II) is unsuitable for the condensation with an aldehyde, while such an unstable ketone-copper(II) complex as acetone-copper(II), 2-butanone-copper(II), or an intermediately formed copper(II) complex in a mixture of acetylacetonate, aldehyde, and copper(II) ions will be effective for the condensation. This seems to be the case where enzymes catalyze the reactions in biological systems. (c) Ketone analogues with active hydrogen(s), such as acetonitrile, nitromethane, and the β -keto esters, are inactive in relation to the copper(II) ion. In the latter particularly, the hydrolysis of the ester rather than the condensation is promoted by copper(II) ion. (d) Aryl alkyl ketones will be unsuitable, while aliphatic ketones can be used. As regards aldehydes, hydroxyl, halogeno, and nitro substituents will inhibit the condensation, while the methoxy group and hetero atoms in the aromatic ring will allow the reaction.

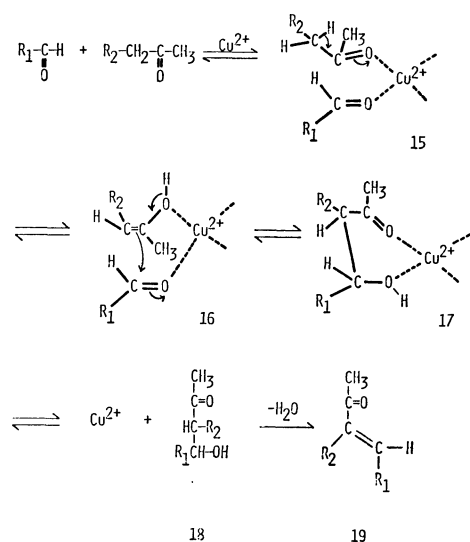
Role of the Metal Ion in the Catalytic Mechanism of Metalloaldolases. The most remarkable feature of the aldol condensation promoted by the copper(II) ion is that the mixed condensation of aldehyde with ketone exclusively predominates over the self condensa-

tion of ketone, even if large excess amounts of ketone are present. This can be explained by the assumption that the ligation power of aldehydes to the copper(II) ion slightly predominates over that of ketones; thus, in the equilibrium, the copper(II) ion, present in twice the equimolar amount of aldehyde, coordinates both aldehyde and ketone. In fact, this assumption seems to be reasonable because the color of the intermediately formed copper(II) complex in the reaction medium depends on the kinds of aldehydes and ketones used. In addition, such an intermediate will explain the inactivity of such metal ions as zinc, cobalt(II), magnesium, and manganese(II) in the consideration of coordination chemistry.¹⁸⁾

Thus, we can deduce the processes of the aldol condensation promoted by the copper(II) ion from the initial formation of the mixed copper(II) complex of aldehyde and ketone, as is shown in Scheme 1. That is, in the initially formed copper(II) complex (**15**)-copper assists the enolization of ketone to give the intermediate (**16**), which then nucleophilically attacks the aldehyde moiety activated by the copper(II) ion to afford **17**. Subsequently, **17** releases the metal ion to prepare the addition product (**18**), which is then dehydrated to give **19** in almost all the aldehydes but the pyridinecarbaldehydes. In this reaction scheme, the dual role of the copper(II) ion, the enolization of ketone and the activation of aldehyde, is emphasized. If the mechanism has reality, it resembles the one proposed for the Class II aldolases with respect to the role of the metal ion.

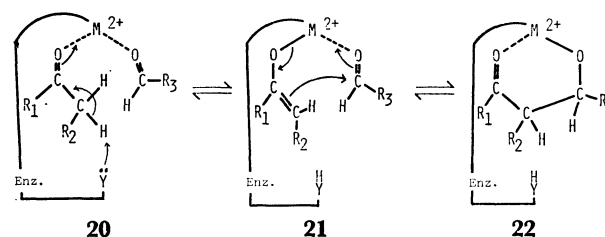
As regards the mechanism of the action of the Class I aldolases, direct chemical evidence has been provided by many workers.^{6a,19,20)} Alternatively, as for the role of the metal ion in the catalytic mechanism of the Class II aldolases which require a divalent metal ion and are not inhibited in the presence of sodium borohydride, Rutter and his co-workers have proposed some intermediates, which can be illustrated as **20**, **21**, and **22** in Scheme 2.³⁻⁶⁾ Now, the similarity of the dual role of the copper(II) ion in the aldol condensation promoted by the copper(II) ion to that of the metal ion in the Class II aldolases is apparent, and the mixed complex is likely to exist in both the chemical and enzymatic processes.

We are, however, confronted with a large gap regarding indispensable metal ions for the aldol condensation between the chemical model and the natural metalloaldolases, in which Zn^{2+} , Co^{2+} , Ni^{2+} , Mn^{2+} , and Fe^{2+} restore the enzymatic activity to varying degrees, while Cu^{2+} , Hg^{2+} , Cd^{2+} , Mg^{2+} , and Fe^{3+} fail to restore activity to any measurable extent.³⁾ Although a hasty



R_1 =Aryl or Alkyl R_2 =Alkyl

Scheme 1.



Scheme 2.

judgment may lead to an erroneous conclusion, we now consider that the gap is caused by the protein effects in enzyme such as proximity, orientation, strain, and microenvironmental factors; that is, the topochemical configuration of the catalytic site of a metal ion in the absence of an enzyme will be changed by these effects in the presence of enzyme. It is important to note that the coordination number and, thus, the stereochemical outcome are determined largely by the size and charge of the metal ion and ligand.¹⁹⁾ The investigation of the problem with which we are here concerned will bring about further fruitful results.

Experimental

The IR spectra were obtained using a Shimadzu IR-27 apparatus. The ¹H-NMR spectra were recorded on a Varian HA-100D apparatus, with tetramethylsilane as the internal standard. The chemical shift and the coupling constant were represented by δ and Hz units respectively. The mass spectra and exact mass measurements were obtained using a Japan Electron Optics Lab. Model JMS-OISG instrument. Merck Art. 7734 (E. Merck, Darmstadt) was used for the preparative separation of the products on a silica gel column by elution chromatography, and Wakogel B-5 FM (Wako Pure Chem. Ind.), for the thin-layer chromatography (TLC). The measurements of the gas chromatography were performed by a Shimadzu GC-4A gas chromatograph with a flame ionization detector, using a 1.8 m \times 3 mm glass tube column packed with 5% Silicone GE-30 on Shimalite W 60–80 mesh and using helium gas as the carrier. The melting points are uncorrected. The elemental analyses were performed by the staff of the Organic Microanalysis Lab. in our Institute.

Materials. All the ketones and aldehydes, **1** through **13**, are commercially available. Purified acetone was obtained by drying over Drierite after treatment with potassium permanganate, followed by distillation.²¹⁾ Copper(II) chloride dihydrate, zinc chloride, magnesium chloride hexahydrate, manganese(II) chloride tetrahydrate, cobalt(II) chloride, and copper(II) acetate monohydrate were used as metal chloride; all of them were commercially available.

Reaction Systems. The general procedure was described above. In the examination of the coexistence of copper(II) and zinc ions, an amount of zinc chloride equimolar to that of copper(II) chloride dihydrate was used unless otherwise stated. Although benzaldehydes are easily oxidized to the corresponding benzoic acid, the reaction system prevented the oxidation to a small extent, as has been shown by the comparative studies of the reaction of 2-butanone with benzaldehyde in the absence and in the presence of nitrogen gas. The final point of the reaction was decided by monitoring the TLC spots. After the completion of the reaction, the mixture was hydrolyzed by the addition of water and filtered through celite to remove the emulsive metal hydroxides. The filtrate was then extracted with ethyl acetate. The organic layer was dried over anhydrous sodium or magnesium sulfate, and the solvents were evaporated under reduced pressure. The residue was chromatographed on a silica gel column to give the products. In the case of the estimation of the yield by the aid of gas chromatography, the extract with ethyl acetate was used.

Analysis of Gas Chromatogram. In the case of the column chromatographic separation of the product, "yield" represents the real theoretical percentage of the product to the starting aldehyde. On the other hand, in the case of the

estimation of the product yield by the use of gas chromatography, "yield" is evaluated on the basis of the following assumptions: (a) on the gas chromatogram, the product of the height of a band and the width of the band at half of its height nearly equals the relative area, which is directly proportional to the gram-molecular weight of the compound, and (b) the side products except for the condensation product are negligible (all the aldehyde consumed is converted to the condensation product). This second assumption (b) has a practical significance in this condensation reaction. According to these assumptions, the product yield ($Y_{\%}$) based on the gas chromatogram can generally be calculated by means of the following equation: $Y_{\%} = 100 r / (1 + r)$, where r is the molar ratio of the condensation product to the aldehyde remaining on the gas chromatogram. Therefore, we can obtain the product yield by the estimation of r , which is calculated by the area ratio of the aldehyde to the product.

Under the conditions of the gas chromatograph (injection temp, 222 °C; detector oven temp, 230 °C; column temp, 89–189 °C (10 °C per min)) and a pressure of helium gas of 1.2–1.39 kg/cm², the retention times of *o*-anisaldehyde (**2**) and the condensation products were as follows: **2** was 5; 2-methoxybenzylideneacetone, 10; 3-(2-methoxybenzylidene)-2-butanone, 10; 3-(2-methoxybenzylidene)-2-pentanone, 12.7; 2-(2-methoxybenzylidene)cyclopentanone, 14; 2-(2-methoxybenzylidene)cyclohexanone, 9; 3-(2-methoxybenzylidene)-2,4-pentanedione, 10.5; and 3-(2-furylmethylidene)-2-butanone, 20 min. Under an injection temp of 260 °C, a detector oven temp. of 220 °C, a column temp of 100–200 °C (10 °C per min), and a pressure of helium gas of 1.0–1.4 kg/cm², the retention time of 3-(2-thienylmethylidene)-2-butanone was 7, and that of thiophenecarbaldehyde, 1.8 min.

Additional Effect of Anhydrous CoCl₂ on the Aldol Condensation Promoted by the Copper(II) Ion. Various amounts of anhydrous CoCl₂ were added to the usual reaction system, and the mixture was stirred at the ambient temperature for 38 h. After a usual work-up, the yields of the product, 3-(2-methoxybenzylidene)-2-butanone, were determined on the basis of the analysis of the gas chromatogram. When 10, 5, 2.5, and 1.25 mmol of anhydrous CoCl₂ coexisted, the yields of the product were 59, 63, 69, and 70% respectively.

Condensation Product. Benzylideneacetone;¹⁰⁾ NMR (CCl₄); 2.32 (3H, s, $-\text{COCH}_3$), 6.65 (1H, d, $J=16.5$, $C_{\beta}\text{-H}$), and 7.45 (1H, d, $J=16.5$, $C_{\alpha}\text{-H}$).

2-Methoxybenzylideneacetone¹¹⁾ [mp 44–46 °C (lit, 50 °C)]; NMR (CCl₄); 2.34 (3H, s, $-\text{COCH}_3$), 3.90 (3H, s, $-\text{OCH}_3$), 6.66 (1H, d, $J=17.0$, $C_{\beta}\text{-H}$), and 7.80 (1H, d, $J=17.0$, $C_{\alpha}\text{-H}$).

4-Methoxybenzylideneacetone¹²⁾ [mp 70–72 °C (lit, 73 °C)]; NMR (CCl₄); 2.26 (3H, s, $-\text{COCH}_3$), 3.82 (3H, s, $-\text{OCH}_3$), 6.50 (1H, d, $J=16.0$, $C_{\beta}\text{-H}$), and 7.37 (1H, d, $J=16.0$, $C_{\alpha}\text{-H}$).

2,6-Dimethoxybenzylideneacetone¹³⁾ [mp 89–91 °C (lit, 88–90 °C)]; NMR (CCl₄); 2.26 (3H, s, $-\text{COCH}_3$), 3.88 (6H, s, $-\text{OCH}_3$), 6.97 (1H, d, $J=16.6$, $C_{\beta}\text{-H}$), and 7.77 (1H, d, $J=16.6$, $C_{\alpha}\text{-H}$).

3-Benzylidene-2-butanone;¹⁴⁾ NMR (CCl₄); 2.01 (3H, s, $\text{C}=\text{C}-\text{CH}_3$), 2.40 (3H, s, $-\text{COCH}_3$), and 7.35 (1H, s, $C_{\alpha}\text{-H}$).

3-(2-Methoxybenzylidene)-2-butanone¹⁵⁾; NMR (CCl₄); 1.95 (3H, s, $\text{C}=\text{C}-\text{CH}_3$), 2.42 (3H, s, $-\text{COCH}_3$), 3.87 (3H, s, $-\text{OCH}_3$), and 7.63 (1H, s, $C_{\alpha}\text{-H}$).

3-(4-Methoxybenzylidene)-2-butanone¹⁶⁾; NMR (CCl₄); 2.02 (3H, s, $\text{C}=\text{C}-\text{CH}_3$), 2.37 (3H, s, $-\text{COCH}_3$), 3.82 (3H, s, $-\text{OCH}_3$), and 7.36 (1H, s, $C_{\alpha}\text{-H}$).

3-(2,6-Dimethoxybenzylidene)-2-butanone; pale yellow crystals, mp 78–80 °C. Found: C, 70.59; H, 7.18%. Calcd for C₁₃H₁₆O₃: C, 70.89; H, 7.32%. NMR (CCl₄); 1.61 (3H,

s, C=C-CH₃), 2.40 (3H, s, -COCH₃), 3.80 (6H, s, -OCH₃), and 7.23 (1H, s, C_α-H).

3-(2-Thienylmethylidene)-2-butanone; a pale yellow liquid. Found: C, 65.17; H, 6.08; S, 19.10%. Calcd for C₉H₁₀OS: C, 65.03; H, 6.06; S, 19.29%. NMR (CCl₄); 2.10 (3H, d, *J*=0.7, C_β-CH₃), 2.36 (3H, s, -COCH₃), 7.09 (1H, d-d, *J*=3.75 and 5.0, ring C₄-H), 7.25 (1H, broad d, *J*=3.75, ring C₅-H), 7.46 (1H, broad d, *J*=5.0, ring C₂-H), and 7.58 (1H, d, *J*=0.7, C_α-H).

3-(2-Methoxybenzylidene)-2,4-pentanedione; light yellow crystals, mp 96–98 °C. Found: C, 71.51; H, 6.47%. Calcd for C₁₃H₁₄O₃: C, 71.54; H, 6.47%. IR (neat); 1705 and 1685 cm⁻¹. NMR (CCl₄); 2.15 and 2.35 (3H each, s, two -COCH₃), 3.85 (3H, s, -OCH₃), and 7.71 (1H, s, C_α-H).

3-Methyl-3-octen-2-one; a pale yellow liquid. Found: C, 76.94; H, 11.14%. Calcd for C₉H₁₆O (140.22): C, 77.09; H, 11.50%. MS; *m/e* 140 (parent). Exact mass measurement; Calcd, 140.120; Found, 140.123. NMR (CCl₄); 0.98 (3H, m, -CH₃), 1.43 (4H, m, -CH₂CH₂-), 1.72 (3H, s, C₃-CH₃), 2.00 (2H, m, -CH₂-), 2.22 (3H, s, -COCH₃), and 6.51 (1H, broad t, *J*=7.5, -CH=C).

4-Hydroxy-3-methyl-4-(2-pyridyl)-2-butanone; colorless crystals, mp 72–74 °C (sublimation). MS; *m/e* 179 (parent). exact mass measurement; Calcd for C₁₀H₁₃O₂N, 179.094; Found, 179.099. NMR (CCl₄); 0.93 and 1.05 (3H each, d, *J*=7.0, C₃-CH₃) (ratio, 8:5) and 2.11 and 2.18 (3H each, s, -COCH₃) (ratio, 5:8). These results gave evidence of the presence of rotamers between C_α and C_β of the side chain.

4-Hydroxy-3-methyl-4-(3-pyridyl)-2-butanone; a pale yellow liquid. MS; *m/e* 179 (parent). Exact mass measurement; Calcd for C₁₀H₁₃O₂N, 179.094; Found, 179.092. NMR (CDCl₃); 0.92 and 1.08 (3H each, d, *J*=7.0, C₃-CH₃) (ratio, 96:117), and 2.18 and 2.24 (3H each, s, -COCH₃) (ratio, 75:78). These results gave evidence of the presence of rotamers between C_α and C_β of the side chain.

4-Hydroxy-3-methyl-4-(4-pyridyl)-2-butanone; a pale yellow viscous liquid. Found: C, 66.92; H, 7.34; N, 7.78%. Calcd for C₁₀H₁₃O₂N (179.21): C, 67.02; H, 7.31; N, 7.82%. MS; *m/e* 179 (parent). Exact mass measurement; Calcd, 179.094; Found, 179.097. NMR (CDCl₃); 2.21 and 2.22 (3H each, s, -COCH₃) (ratio, 1:1). Those results gave evidence of the presence of rotamers between C_α and C_β of the side chain.

Methyl salicylate; yield, 19%, exact mass measurement, Calcd for C₉H₈O₃, 152.047; Found, 152.049. IR (neat); 3530 (OH) and 1740 (C=O) cm⁻¹. NMR (CCl₄); 3.82 (3H, s, -OCH₃).

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