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The Knoevenagel Reactions of Aldehydes with Carboxy Compounds. I. Reactions of *p*-Nitrobenzaldehyde with Active Methine Compounds

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The Knoevenagel reactions of *p*-nitrobenzaldehyde (**1**) with β-keto acids, methylmalonic (**2a**) and α-methylacetoacetic acids (**2b**) were carried out in the presence of a tertiary amine such as pyridine. We have isolated the corresponding β-hydroxy intermediate (**3a**) by the reaction of **2a** which positively suggested the reaction proceeded by the Hann and Lapworth mechanism. A kinetic study using ^{1}H NMR revealed the existence of the reversibility between the starting materials and the β-hydroxy intermediate and that the rate determining step was decarboxylattion. But, when using the secondary amine, both the β-hydroxy acid and the corresponding condensation product were obtained via this reaction. These findings led to the conclusion that the reaction proceeded according to the two competing mechanisms, i.e., the Hann and Lapworth and Knoevenagel mechanisms. It was further clarified that either the decarboxylation step or the formation of the bis(dialkylamino) derivative was the rate determining step. The stereoselectivity of the β-hydroxy saturated compound has been closely related to the fact that the conformation of the intermediate possesses an intramolecular hydrogen bond to a hydroxyl group.

Some mechanisms,[1] depending on the kind of amine catalysts, have been proposed for the Knoevenagel reaction between an aldehyde and an active methylene compound. The Hann and Lapworth mechanisms[2] containing a β-hydroxy intermediate was expected when using tertiary amines. The Knoevenagel mechanism[3] has been predicted for the reaction which gives a condensation product via a bis(dialkylamino) derivative formed from a secondary amine and an aldehyde. However, these expectations were not realized because the condensation product was mainly obtained in both mechanisms.

For active methylene compounds such as malonic, cyanoacetic, and acetoacetic acids which accompanies decarboxylation, it is not yet clear that either dehydration or decarboxylation preferentially proceeds from the β-hydroxy intermediate in the presence of a tertiary amine.

An active methine compound such as β-keto acid was reacted with an aromatic aldehyde instead of an active methylene one. Gensler et al.[4] have reported that reaction of *p*-nitrobenzaldehyde with methylmalonic acid at 90 °C in the presence of piperidine–pyridine gave the corresponding cinnamic acid, but Fujiwara et al.[5] obtained 3-hydroxy-2-methyl-3-(*p*-nitrophenyl)propionic acid via the same reaction in pyridine. Yuan et al.[6] have considered the reaction mechanism operated by both catalysts at room temperature. However, the intermediate could not be confirmed in all cases. Tanikaga et al.[7] have reported that various aromatic aldehydes reacted with active methylene compounds in the presence of piperidine to isolate bispiperidides and that this reaction proceeded via the Knoevenagel mechanism. Lopez et al.[8] have shown that 2,3-*O*-isopropylidene-D-glyceraldehyde and α-methylacetoacetic acid reacted in toluene in the presence of diethylamine to give the β-ketol and α,β-enone. Inoue et al.[9] have stated that the reaction of *m*-nitrobenzaldehyde with *p*-nitrophenylacetic acid in the presence of secondary amines also proceeded via the Hann and Lapworth mechanism, i.e., the reaction proceeded via the β-hydroxy intermediate as in the case of tertiary amine catalysts. Thus, the mechanism for the Knoevenagel reaction accompanying decarboxylation is not yet clear.

To elucidate these problems, we carried out the Knoevenagel reactions of *p*-nitrobenzaldehyde (**1**) with methylmalonic (**2a**) and α-methylacetoacetic acids (**2b**) using secondary and tertiary amines. We report the isolation of the β-hydroxy intermediate and the mechanistic determination of the role of amines.

Results and Discussion

Synthesis of the β-Hydroxy Intermediate 3a and the β-Hydroxy Acid 4a. To a mixture of **1** (0.03 mol) and **2a** (0.06 mol), pyridine (0.18 mol) was added at room temperature and the mixture was kept for 6 h. The reaction time was determined in advance by ^{1}H NMR. From the residue remaining after the removal of the unreacted substances the β-hydroxy intermediate, **3a**, was isolated in a 54% yield after extraction with ether under acidic conditions (pH 2).

The β-hydroxy acid, **4a**, was obtained in a 46% yield by decarboxylation of the corresponding β-hydroxy intermediate. The structure of **4a** was identified with ^{1}H NMR, IR, and elemental analyses. The threo- and erythro-compound, **4a**, have been distinguished and their configurations were established by ^{1}H NMR at 4.89 (J=8.4 Hz) and 5.71 (J=4.2 Hz), respectively.

It may be affirmed by the isolation of **3a** that this

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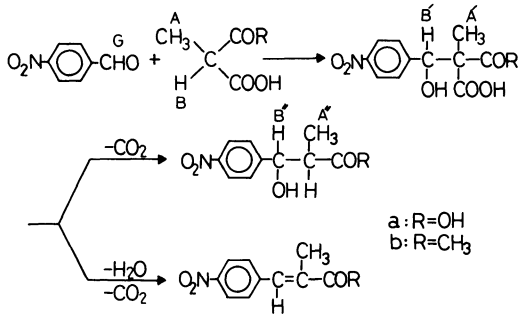
reaction proceeded via the Hann and Lapworth mechanism.

Kinetic Studies on Addition and Decarboxylation Stages. A mixture of **1**, **2a** (1.04 mmol, each) and pyridine-d_5 (3.11 mmol) was put into a sealed NMR tube and the reaction was run for 30 days at room temperature, then the ^{1}H NMR spectra of the mixture were measured. The signals were assigned as follows (Scheme 1): A, A′, and A″ are methyl proton signals of **2a**, **3a**, and **4a**, respectively, B for α-CH signal of **2a**, and B′ and B″ for β-CH signals of **3a** and **4a**, respectively and G refers to the proton signal of an aldehyde, where the intergral of B″ was calculated by the total amount of β-CH signals of the threo- and erythro- β-hydroxy acids. The integrated intensities of their signals are the mean values of more than three observed values. Relative concentrations of the compounds were calculated by the total amount of the groups (A+A′+A″).

Time dependences of the relative concentration of **3a** and **4a** measured by ^{1}H NMR during 30 days are shown in Fig. 1. The concentration of the β-hydroxy intermediate, **3a**, showed a maximum in about 3.5 h, while the β-hydroxy acid, **4a**, began to appear after 24 h.

The different formation times between **3a** and **4a** have suggested that the rate of the decarboxylation reaction was slower than that of the addition reaction at room temperature under these reaction conditions.



Scheme 1.

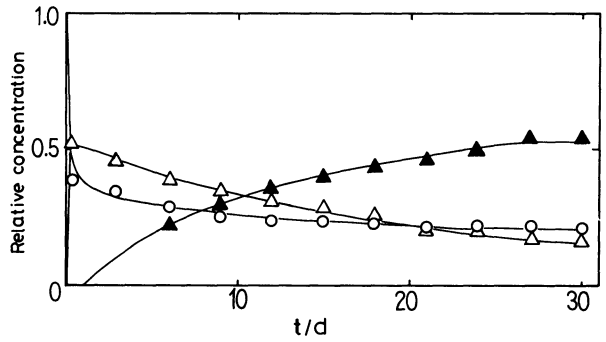


Fig. 1. Reaction of **1** with **2a** in the presence of pyridine and DMSO at room temperature. ○: Starting material, △: β-hydroxy intermediate, ▲: β-hydroxy acid.

Figure 2 shows the initial part of Fig. 1. From this figure it can be assumed that the concentrations of **3a** become almost unchangeable after 200 min. Further, when the **3a** isolated in pure form was dissolved in pyridine at room temperature, a part of **3a** was cleaved into **1** and **2a**. This result has suggested the reversible reaction between starting materials and the intermediate, in accordance with the reports by Kinastowski et al.[10] They have demonstrated that there is a linear relation between the rate constant and the concentration of the catalyst at an addition stage and that the catalytic rate was fairly faster than the rate of the spontaneous chemical reaction. In practice, we have experienced great difficultly in calculating the rate sequence, **1**+**2**⇄**3**→**4**. To overcome this difficulty, an analysis based on a preequilibrium was considered. We tried to conveniently determine the apparent reaction rates at a constant catalytic concentration by dividing it into two stages: (a) the addition stage, and (b) the decarboxylation stage.

(a) The Addition Stage. From Fig. 2, we assumed that there exists a reversibility between second-order (forward reaction k_1) and first-order (reverse reaction k_2) rates and that the concentration of an aldehyde (C_1) is equal to that of an active methine compound (C_2), that is, $C_1=C_2$. The rate constants are expressed by:

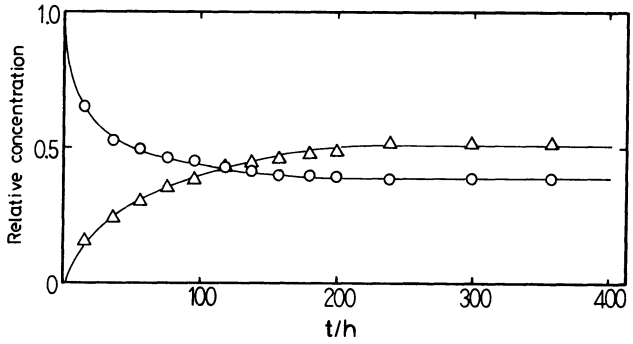


Fig. 2. Reaction of **1** with **2a** in the presence of pyridine and DMSO at room temperature. ○: Starting material, △: β-hydroxy intermediate

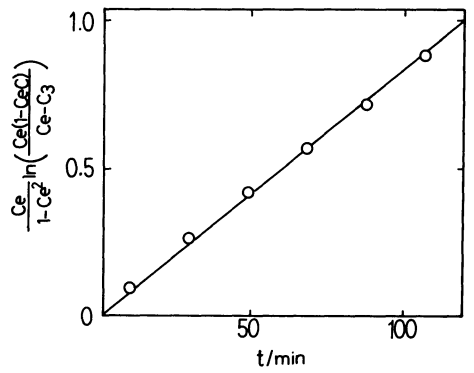


Fig. 3. Second-order plots vs. time in the reaction of **1** with **2a**.

$$k_1 t = \frac{C_e}{1 - C_e} \ln \frac{C_e(1 - C_e C_3)}{C_e - C_3}, \quad (1)$$

$$k_2 = \frac{k_1(C_0 - C_e)^2}{C_e}, \quad (2)$$

where C_0 is the initial concentration of aldehyde, and C_3 and C_e are the concentration and the preequilibrium concentrations of the β-hydroxy intermediate, respectively. In Fig. 3, the right side of Eq. 1 is plotted against reaction time. The plot gives a satisfactory straight line passing through the origin, from which the rate constants, $k_1=4.56\times10^{-1}$ and $k_2=1.98\times10^{-1}$ h^{-1}, and the preequilibrium constant, $K(=k_1/k_2)=$ 2.30, could be estimated.

(b) The Decarboxylation Stage. By using the C_e value determined from Fig. 2, the rate of decarboxylation originating from the β-hydroxy intermediate was calculated by assuming a first-order reaction (k_3):

$$k_3 t = \ln \frac{C_e}{C_e - C_4}, \quad (3)$$

where C_4 is the concentration of the β-hydroxy acid. Figure 4 shows the relation between the right side in Eq. 3 and reaction time. As shown in this figure, a satisfactory straight line was also suggested by the results of a regression analysis. The rate constant, k_3, was 4.17×10^{-3} h^{-1}. The decarboxylation rate in this system was 10^{-2}-fold slower than the addition one. The reactions of *p*-substituted (cf. CN, Br) benzaldehydes with **2a** showed the same results.

We may firmly suggest that there is a reversibility between the starting materials and the β-hydroxy intermediate, and that the decarboxylation process is the rate determining step. The careful and exact observations by NMR have indicated that the β-hydroxy acid consisted of threo and erythro isomers and that the reaction rate of threo isomer was faster than that of the erythro. These details will be demonstrated later.

The Knoevenagel Reaction in the Presence of Piperidine. For the Knoevenagel reaction in the presence of a tertiary amine, the Hann and Lapworth mechanism was firmly demonstrated by our experiments. On the other hand, for the reaction promoted by the presence of secondary amines, another mechanism has been proposed by Knoevenagel himself; the catalyst reacts with an aldehyde to form a bis(dialkylamino) derivative, which then reacts with an active methylene compound to produce an unsaturated compound. However, the Knoevenagel reaction catalyzed by a secondary amine as reported by Lopez or Inoue et al. cannot be explained only by the Knoevenagel mechanism. To elucidate the complete mechanism of the reaction conducted in the presence of secondary amines, we studied similar reaction at room temperature by the use of ^{1}H NMR. To a solution of **1** and **2a** (1.04 mmol, each) in CD_3CN, piperidine was added dropwise (1/10, 1/3 and 1 mole per mole of aldehyde). Time dependences of the relative concentrations of **3a**, **4a** and α,β-unsaturated compound **6a** measured with ^{1}H NMR during 100 h are shown in Fig. 5. In all cases of the added piperidine, the β-CH-proton signal of **3a** appeared at δ 5.5 immediately after the initiation of the reaction. The concentration of this intermediate increased with increasing piperidine. After the appearance of the β-CH signal, **6a** was recognized. The product, **4a**, increased as the piperidine was decreased (1/10 and 1/3 mole per mole of an aldehyde). But, since the

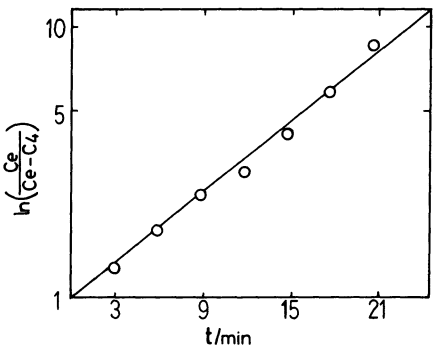


Fig. 4. First-order plots vs. time in the reaction of **1** with **2a**.

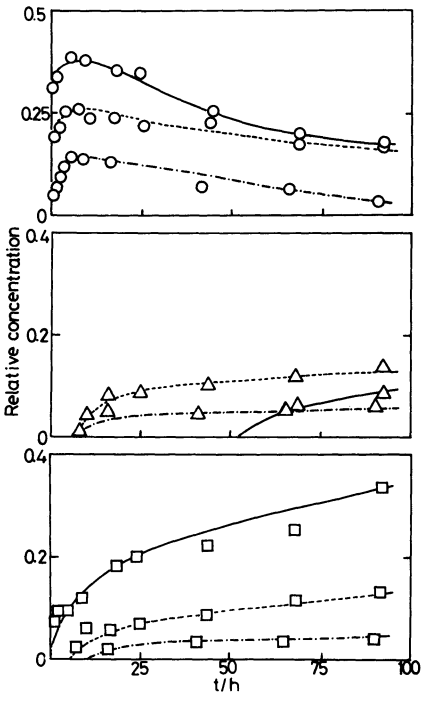


Fig. 5. Reaction of **1** with **2a** in the presence of piperidine. Piperidine concn. (mole per mole of aldehyde): —— (1 equiv), ------ (1/3 equiv), -·-·- (1/10 equiv). ○: β-Hydroxy intermediate, △: β-hydroxy acid, □: α,β-unsaturated compound.

dehydration from both the β-hydroxy intermediate and the β-hydroxy acid is usually difficult to occur under such reaction conditions, we have no convictions about the formation of **6a**. Therefore, the reactions of the β-hydroxy intermediate with amine catalysts were subsequently carried out.

Reaction from the β-Hydroxy Intermediate 3a. The reactions using **3a** (1.04 mmol) as a starting material were carried out in an NMR tube at room temperature with the $CDCl_3$–DMSO-d_6 solutions of piperidine (0.35 mmol) or pyridine (1.04 mmol). Time dependences of the relative concentrations of reactants in the presence of piperidine measured with ^1H NMR for 200 h are shown in Fig. 6. In both systems, **1** and **2a** were immediately produced and **4a** was obtained in a small amount. In the presence of piperidine, **6a**, which was not obtained in the presence of pyridine, was produced after the formation of **1** and **2a**. Further, when piperidine (2 mmol) was added to a solution of **1** (1 mmol) in $CDCl_3$, this solution showed the CH-proton signal of bispiperidide (**5a**) at δ 3.5. **6a** was produced immediately after addition of **2a** to the CD_3CN solution of **5a**. It gave additional credence that **3a** was easily decomposed into **1** and **2a** in the presence of piperidine, whereas only **4a** was obtained in the presence of pyridine. The product ratio, **4a**/**6a**, was dependent on the quantity of added piperidine. Judging from this fact, we may safely say that a slight amount of piperidine promotes the decarboxylation of **3a**, as supported by the study of Patai et al.[11] In other words, **6a** was not directly supplied by either the dehydration of **3a** or **4a**, but produced by the reaction via the Knoevenagel mechanism. From the above results there may exist a different mechanism between the presence of pyridine or piperidine. Therefore, we can advance the suggestion that the reaction accompanying the decarboxylation in the presence of piperidine proceeds by two competing mechanisms; the Hann and Lapworth(path A) and the Knoevenagel (path B) mechanisms as shown in Scheme 2, and that both decarboxylation from **3a** and the formation of **5a** are the rate determining steps of these competing reactions.

Reaction in the Presence of Various Secondary Amine Catalysts. Several reactions of **1** with **2a** were carried out in toluene–DMSO at room temperature using several kinds of secondary amines such as piperidine, morpholine, diethylamine, and dicyclohexylamine, in order to make a comparison with the reaction using the tertiary amine such as pyridine. The results are shown in Table 1. In all cases using the secondary amines as a catalyst, the mixture of **4a** and **6a** was obtained, but in pyridine, **6a** was not formed. The product ratio, **4a**/**6a**, depended on the type of the secondary amine catalyst, i.e., the yield of **6a** was somewhat higher than that of **4a**, when piperidine and morpholine were used, while that of **4a** was preferentially produced when diethylamine and dicyclohexylamine were used.

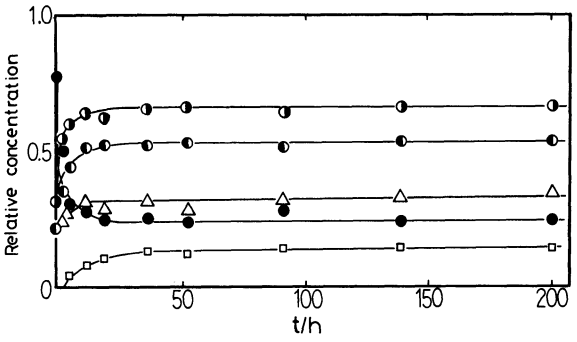
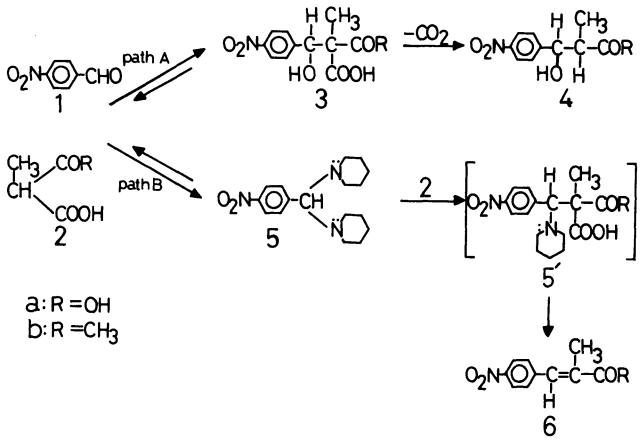


Fig. 6. Reaction from β-hydroxy intermediate in the presence of piperidine (1/3 equiv). ●: β-Hydroxy intermediate, ◐: **1**, ◑: **2a**, △: β-hydroxy acid, □: α,β-unsaturated compound.



Scheme 2.

Table 1. Reaction of **1** with **2a**

Catalyst	pK_a	Yield/%		Selectivity	
		4a	**6a**	Erythro	: Threo
Pyridine	5.2	92.1	—	16	84
Piperidine	11.2	42.2	54.4	12	88
Morpholine	8.5	35.9	58.7	16	84
Diethylamine	10.8	81.3	15.5	10	90
Dicyclohexylamine	11.2	85.4	8.3	7	93
—[a]		—	—	59	41

a) This is not estimated from isolated product.

These results have given active support to the existence of the two competing mechanisms. In the reactions of **1** with diethylamine or dicyclohexylamine in $CDCl_3$ solutions in an NMR tube at room temperature, the bis(dialkylamino) derivatives can be hardly recognized. The order of the difficulty for detection of bis(dialkylamino) derivatives is as follows: dicyclohexylamine>diethylamine≫morpholine, piperidine.

We may thus conclude that the yield of the bis(dialkylamino) derivative increased by decreasing the steric hindrance of the secondary amines in accordance with the previously mentioned results.

Reaction of α-Methylacetoacetic Acid (2b). To verify the existence of another rate determining step, namely the difficulty of the decarboxylation, the reaction of **1** with **2b**, which was easier than **2a** during decarboxylation, was carried out using various secondary and tertiary amines in toluene. The reaction finished at −18 °C for a short period, about 2 days, compared well with the reaction of **2a** done for one month at room temperature. The β-hydroxy intermediate could not be determined due to the rapid decarboxylation. The yields of **4b** and **6b** are shown in Table 2. **4b** was preferentially obtained in all cases, but of these, **6b** was slightly produced using only secondary amines. The ratio of **4b** to **6b** varied with the kind of secondary amines and this tendency was somewhat similar to that of the reaction with **2a**.

We concluded that **1** reacted with α-substituted active methine compounds accompanying decarboxylation in the presence of secondary amines to afford the preferential formation of the β-hydroxy acid, when the active methine compound possible for decarboxylation and/or bulky amines were used. The existence of competing pathways in the reaction mentioned above was thus reconfirmed.

Stereochemistry of the Knoevenagel Reaction. In the Knoevenagel reaction of **1** with **2a**, the stereochemical data were also tabulated in Tables 1 and 2. The threo/erythro ratios were determined by ^1H NMR and compared with the results of Yuan et al. It was inconclusive that the stereoselective formation of the product was explainable by kind, bulkiness, and pK_a of the catalyst. But, we could draw a clear distinction between the presence or the absence of catalysts in both cases. Also, there was a subtle difference between the two active methine compounds. The ratio of the erythro isomer in the case of the reaction with **2b** is somewhat high.

Moreover, the reactions with **2b** were run with varying amounts of pyridine, giving the results shown in Table 3. The formation of the threo isomer was inclined to increase with an increase in pyridine while using 9-fold moles of pyridine, the *threo*-**4b** was obtained exclusively, although **2b** itself is apt to evolve carbon dioxide, resulting in a lower yield of **4b**. The basicity of the reaction system may contribute to this trend.

In general, the β-hydroxy intermediate obtained by the Knoevenagel reaction in the presence of a tertiary amine would be a mixture of diastereomers. For the Knoevenagel reaction with a planar prochiral compound, e.g., **1**, **3b** may include the threo isomer equivalent to the erythro, although **3b** could not be isolated. The fact will be experimentally verified in a subsequent paper on the reaction of **1** with *p*-nitrophenylacetic acid.[12] So, when the difference in the stereoselectivity of the saturated product can be detected, the fact is undoubtedly due to the decarboxylation stage initiated from the intermediate. In this reaction, it is theorized that the conformations cannot be exchanged in the course of the decarboxylation since we believe that the reaction conditions are hard to produce epimerization between threo and erythro isomers.[13] In addition, the coupling constants of **4b** (J=8.0 and 4.0 Hz) also correspond to those of **4a**. On an analogous discussion of Yuan et al., **3b** seems to possess an intramolecular hydrogen bonding.

Table 3. Reaction of **1** with **2b** in Pyridine

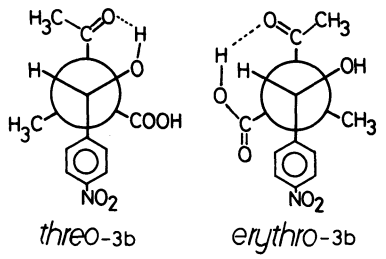
Pyridine/mol[a]	Yield/% **4b**	Selectivity Erythro : Threo
0.1	60.1	33 : 67
0.5	57.8	50 : 50
1.5	31.4	25 : 75
4.0	32.7	16 : 84
9.0	28.7	0 : 100

a) Per mole of aldehyde.

Table 2. Reaction of **1** with **2a** in Toluene

Catalyst	pK_a	Yield/% **4a**	**6b**	Selectivity Erythro : Threo
Pyridine	5.2	88.9	—	37 : 63
2,6-Lutidine[a]	6.7	93.7	—	8 : 92
DABCO[a]	8.6	98.1	—	15 : 85
Piperidine	11.2	83.7	14.3	12 : 88
Morpholine	8.5	82.9	17.0	27 : 73
Diethylamine	10.8	89.0	9.5	22 : 78
Dicyclohexylamine	11.2	94.0	4.9	27 : 73
—		64.1	—	67 : 33

a) These reactions were carried out without toluene.



Scheme 3.

The intramolecular hydrogen bonding suggests to us the reactivity or stability of the intermediate, which will be demonstrated in a forthcoming report.

Taking into account the above statements, the conformations of **3b** are illustrated in Scheme 3. Each is invariable during decarboxylation. Further, the conformations of the corresponding saturated compounds were deduced by Karplus' equation.

When β-keto acids are used as the active methine compounds, we must consider the decarboxylation from a few types; the keto acid[14] or the hydroxy acid type,[15] and in the presence or in the absence of amine catalysts. The acetyl group of **3b** is able to be linked to both hydroxyl and carboxyl groups by intramolecular hydrogen bonding. In the absence of amine catalysts, we may propose the mechanism which would induce the spontaneous decarboxylation of the keto acid type instead of the hydroxy acid one. This argument is suggested by the fact that the erythro isomer was preferentially obtained. The representation of the erythro isomer is then carried out by a figure of conformation of the intramolecular bonding between acetyl and carboxyl groups.

On the contrary, the acetyl group of the threo conformation prefers the hydroxyl group to the carboxyl. This conformation is more stable than the other in the presence of amine catalysts, since the reverse reaction forming starting materials is relatively difficult to produce owing to the hydrogen bond.

Accordingly, the amine catalyst at first draws a free proton from the carboxyl group, and subsequently accelerates the decarboxylation of *threo*-**3b**, while it acts on the reversible reaction of *erythro*-**3b**. This might be supported by the fact that the appearance of *threo*-**4b** was easier and that in excess pyridine the threo isomer was exclusively produced.

Experimental

The melting points were measured with a Yanagimoto Melting-point Apparatus and are presented without correction. Solvents and other commercially obtained materials were purified by distillation. The IR spectra were recorded with a Shimadzu IRA-435 spectrometer and the ^{1}H NMR spectra using a JEOL JNM-MH100 (100 MHz) or a JEOL GX-400 (400 MHz) spectrometer with TMS as an internal standard. GLC analysis was performed on a Shimadzu GC-6AM gas chromatography using FID detector. All analyses were carried out on 2 m×3 mm in 10% Silicone SE-30.

β-Hydroxy Intermediate 3a. A mixture of **1** (0.03 mmol), **2a** (0.06 mmol), and pyridine (0.18 mmol) was kept at room temperature for 6 h. To the mixture was added 4 M HCl (1 M=1 mol dm^{-3}) until pH 2. Then the mixture, except pyridine, was extracted with ether. After the ether was evaporated, dil. Na_2CO_3 was added to the residue to pH 11, then an unreacted aldehyde was extracted with benzene. The remaining aqueous solution was acidified (pH 2) with concd. HCl, extracted with ether, and the ether solution was washed with water, and dried with anhydrous Na_2SO_4. After removing the remaining ether, pale yellowish crystals obtained were recrystallized from methanol–water solution (4.36 g, 54% yield). Mp 130—131 °C; Found: C, 49.29; H, 4.12; N, 5.04%. Calcd for $C_{11}H_{11}O_7N$: C, 49.08; H, 4.12; N, 5.20%. ^{1}H NMR (400 MHz) δ=1.289 (s, 3H), 5.534 (s, 1H), 7.619, 8.137 (2d, 4H), 10.285 (s, 3H). IR(KBr) 3500, 1710, 1350 cm^{-1}.

3-Hydroxy-2-methyl-3-(*p*-nitrophenyl)propionic Acid (4a). A mixture of **1** (0.03 mol), **2a** (0.06 mol) and pyridine (0.18 mol) was kept at room temperature for a month, and was added 4 M HCl until pH 2. The mixture was extracted with ether. After the ether was evaporated, dil. Na_2CO_3 was added to the residue to pH 11, then an unreacted aldehyde was extracted with benzene. The aqueous solution was acidified (pH 2) with concd. HCl and again was extracted with ether. The extract was washed with water, and dried with anhydrous Na_2SO_4. Ether was evaporated and the residue was recrystallized from methanol–water solution. (3.10 g, 46% yield); mp 139—141 °C. Found: C, 53.41; H, 5.01; N, 6.01%. Calcd for $C_{10}H_{11}O_5N$; C, 53.33; H, 4.93; N, 6.22%; ^{1}H NMR($CDCl_3$) δ=5.66 (br, 1H), 8.97 (br, 1H), 8.16, 7.58 (dd, 4H), 5.71 (d, β-CH, *J*=4.2 Hz, erythro), 4.89 (d, β-CH, *J*=8.4 Hz, threo), 2.80 (m, α-CH,erythro), 2.67 (m, α-CH, threo), 1.15 (d, CH_3, erythro), 0.95 (d, CH_3, threo); IR (KBr) 3500, 1710, 1350 cm^{-1}.

Bispiperidide (5a). A mixture of **1** (1 mol) and piperidine (3 mol) was kept at room temperature for about 5 h, and subsequently the reaction mixture was freeze-dried to yield quantitatively red brown crystals. Mp 79—82 °C; ^{1}H NMR ($CDCl_3$) δ=8.15—7.35 (dd, 4H), 3.65 (s, 1H), 2.30, 1.45 (dd, 10H).

Preparation of 6a from 5a and 2a. A mixture of (0.041 mol) **2a** and **5a** (0.041 mol) was kept at room temperature for about 4 days, and into the mixture 4M HCl was poured until pH 2 to yield crude yellowish crystals. They were recrystallized from methanol–water solution (7.38 g, 87% yield). Mp 205—206 °C; ^{1}H NMR ($CDCl_3$) δ=8.15, 7.35 (dd, 4H), 7.72 (s, 1H), 2.00 (s, 3H); IR (KBr) 1710, 1680, 1510, 1350, 860 cm^{-1}.

α-Methylacetoacetic Acid (2b). To α-methylacetoacetic acid ethyl ester (0.1 mol) 1 M NaOH aqueous solution (110 ml) was dropped at room temperature for about 12 h, the solution was extracted with ether (50 ml×2), concentrated until one-third volume, to which dil. H_2SO_4 (H_2SO_4=15 ml:3.5 ml) was added in the ice bath, saturated with NaCl, and extracted with ether. The extraction was continued until no α-methylacetoacetic acid in water layer was detected with $FeCl_3$ test. The extract was dried with anhydrous Na_2SO_4. Ether was evaporated in the ice-water bath to obtain the product (8.8 g, 76% yield). ^{1}H NMR

($CDCl_3$) δ=7.6—8.0 (br, 1H), 3.4 (q, 1H), 2.2 (s, 3H), 1.3 (d, 3H).

4-Hydroxy-3-methyl-4-(*p*-nitrophenyl)-2-butanone (4b) and 3-Methyl-4-(*p*-nitrophenyl)-3-buten-2-one (6b). A mixture of **1** (0.05 mol), **2b** (0.1 mol), and pyridine (0.025 mol) was kept at −50 °C in the Dry Ice bath, to −18 °C for 48 h under closed pressure, and opened in the nitrogen atmosphere. The reaction was continued until a disappearance of an aldehyde signal of **1** in an NMR spectrum. The unreacted catalyst was excluded from the solution in vacuo and the residue was washed with benzene to precipitate yellowish crystals, 4-hydroxy-3-methyl-4-(*p*-nitrophenyl)-2-butanone (4.21 g, 37.8% yield). Mp 93—95 °C; ^{1}H NMR ($CDCl_3$) δ=8.24, 7.60 (dd, 4H), 5.32 (d, β-CH, J=4.0 Hz, erythro), 4.92 (d, β-CH, J=8.0 Hz, threo), 4.60 (br, 1H), 2.96 (q, 1H), 2.26 (s, CH_3, erythro), 2.24 (s, CH_3, threo), 1.04 (d, α-CH_3, erythro), 0.98 (d, α-CH_3, threo); IR (KBr) 3400, 1710, 1510, 1350 cm^{-1}.

On the other hand, using piperidine–pyridine (0.1 mol, each) the same method was performed to obtain the mixture **4b** and **6b**. The residue was washed with benzene, and with additional methanol to yield crystals, 3-methyl-4-(*p*-nitrophenyl)-3-buten-2-one (0.27 g, 2.6% yield). Mp 205—206 °C; ^{1}H NMR ($CDCl_3$) δ=8.28—7.76 (dd+s, 5H), 2.40 (s, 3H, E), 2.00 (s, 3H); IR (KBr) 1650, 1510, 1350 cm^{-1}

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