Ambident Ion. VI. Kinetical and Thermodynamical Control in the Acylation of β-Dicarbonyl Compounds. Acetylation of Benzoylacetone and Benzoylacetonate Anion

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Kinetically as well as thermodynamically controlled steps have been established in acetylation of ambident ion. Acetylation of sodium benzoylacetonate in pyridine gave initially the kinetically controlled product (I) which isomerized gradually to the thermodynamically controlled (II). *C*-Acetylation product (III) was formed by the reaction of benzoylacetonate ion with *O*-acetylbenzoylacetones at higher temperatures. Comparison of the results in the acetylation of benzoylacetone with those of its sodium salt suggested that enolate anion was the reacting species in both processes of *O*- and *C*-acetylation. Isomerization between I and II was suppressed in α-picoline or 2,6-lutidine solution. Utilizing these results we have prepared three kinds of acetylated products I, II, and III readily in high selectivity.

Alkylation of enolate anions has been extensively studied, but not the acylation of enolates.[1-3]

In this paper we wish to report on the acetylation of benzoylacetone which shows a marked duality in the reaction process, *viz.*, kinetically controlled and thermodynamically controlled processes. Acetylation of the salts of benzoylacetone is expected to give two *O*-acetylated products (I) and (II) and one *C*-acetylated one (III) (Eq. 1). It was found that solvents effected the product distribution remarkably.

$$(PhCOCHCOCH_3)^-Na^+ + AcCl \longrightarrow \underset{\text{(I)}}{PhCOCH{=}C(OAc){-}CH_3} + \underset{\text{(II)}}{PhC(OAc){=}CHCOCH_3} + \underset{\text{(III)}}{PhCOCH(Ac)COCH_3} \quad (1)$$

Solvent Effects on the Product Distribution in Acetylation of Sodium Benzoylacetonate. The results of the acetylation of sodium benzoylacetonate with acetyl chloride in several solvents are shown in Table 1.

Total yields including *O*- and *C*-acylated products in ether solvents increased in the order: ethyl ether< dimethoxyethane<diglyme. This suggests that the solvating power to Na^+ plays an important role.[4] The contents of III in the product decreased in the order: ether>dimethoxyethane>diglyme, and those of II increased in the reverse order. This suggests that *O*-acetylation is more favored when the reaction medium is more favorable for the dissociation of the sodium salt to enolate anion. Benzene is distinguished from the others in giving III as the major product. In *N,N*-dimethylformamide, no formation of *C*-acetylated product was detected and the ratio of I/II was 79/21, being much higher than the other cases at 0°C. The ratio, however, changed to 19/81 when acetylation was carried out at 50°C.

Table 1. Solvent effects on the product distribution in the acetylation of sodium benzoylacetonate

Solvent[a]	Reaction temp. °C	Time hr	Yield[b] %	Composition I%	II%	III%
Ether	38	24	31.0	18	45	37
DME	0	24	32.8	21	59	20
DGM	0	24	45.1	22	78	0
Benzene	12	24	26.2	4	6	90
DMF	0	24	32.9	79	21	0
DMF	50	24	26.3	19	81	0

a) DME: 1,2-dimethoxyethane; DGM: diethylene glycol dimethyl ether (diglyme).
b) Based on sodium salt.

Isomerization between the two *O*-acetylated compounds at a higher reaction temperature was confirmed experimentally as shown in Table 2. The same phenomenon was also realized in acetylation in pyridine as mentioned later.

Acetylation of Benzoylacetone and its Sodium Salt in Pyridine at 0°C (O-acetylation). It is well known that the acylation of β-dicarbonyl compounds in pyridine proceeds smoothly and gives *O*-acylation products exclusively, but the reaction mechanism is open to question.[5] By comparing the results in the acetylation of benzoylacetone with those of its sodium salt, the intervention of enolate anion as a reacting species was examined. Changes of the product compositions during the course of the reaction are shown in Figs. 1 and 2.

1) W. R. Gilkerson, W. J. Argersinger, Jr., and W. E. McEwen, *J. Amer. Chem. Soc.*, **76**, 41 (1954), and the references cited therein.
2) W. M. Muir, P. D. Ritchie, and D. J. Lyman, *J. Org. Chem.*, **31**, 3790 (1966), and the references cited therein.
3) M. Suama, Y. Murata, and K. Ichikawa, *Nippon Kagaku Zasshi*, **91**, 162, 168 (1970).
4) H. O. House, and V. Kramer, *J. Org. Chem.*, **27**, 4146 (1962).
5) McEwen *et al.* (*J. Amer. Chem. Soc.*, **76**, 41 (1954).) proposed a reaction mechanism through the intermediate (IV) which has been denied in Ref. 3.

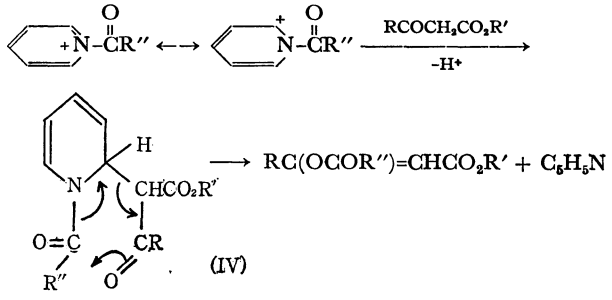


Table 2. Acetylation of sodium benzoylacetonate in DMF at 50°C

Reaction time hr	Yield %	Composition		
		I%	II%	III%
0.25	59	56	24	20
2.0	59	34	41	25

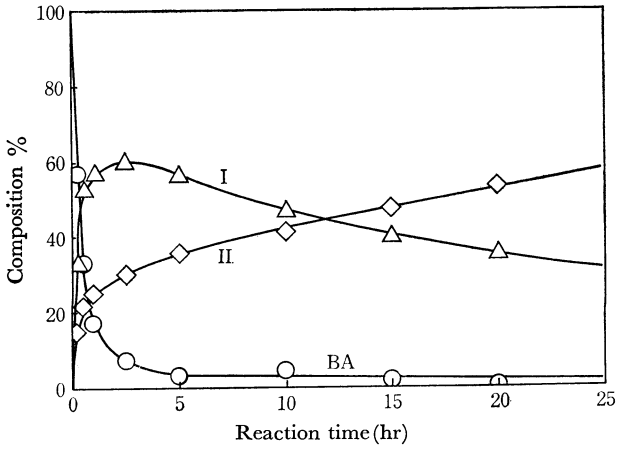


Fig. 1. Acetylation of benzoylacetone (BA) in pyridine at 0°C.

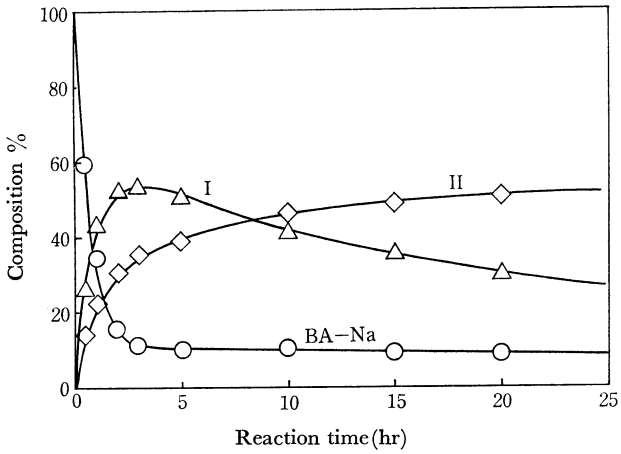


Fig. 2. Acetylation of sodium benzoylacetonate (BA-Na) in pyridine at 0°C.

In each case, acetylation was complete in about 2 hr, and afforded I and II nearly in quantitative yield and only a trace amount of III. Kinetic preference for the formation of I to II can be attributed to the steric hindrance of phenyl group, since no acetylation occurred in the case of dibenzoylmethane under the reaction conditions.

Figures 1 and 2 clearly show that the isomerization of I to II occurred. In the reactions of ambidents, these kinds of isomerization have scarcely been considered so far. However, our data indicate that it is necessary to distinguish the competitive reactions from the isomerization reactions in order to discuss the reactivity of two reaction sites.

Controlled experiments showed that the mutual isomerization between I and II occurred in pyridine and the equilibrium ratio of I to II was about 19/81 at 0°C. The results of the isomerization are shown in Figs. 3 and 4.

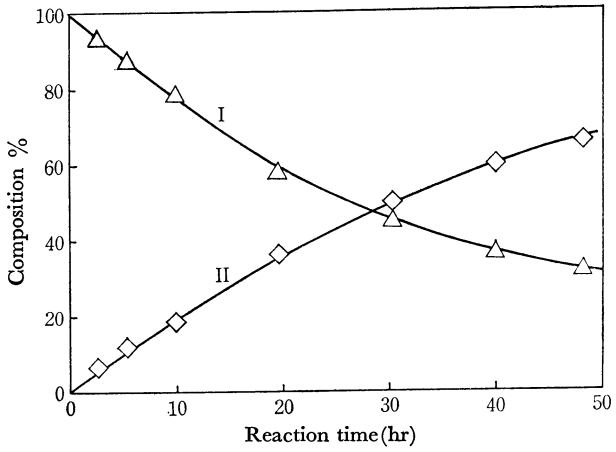


Fig. 3. Isomerization of I to II in pyridine at 0°C.

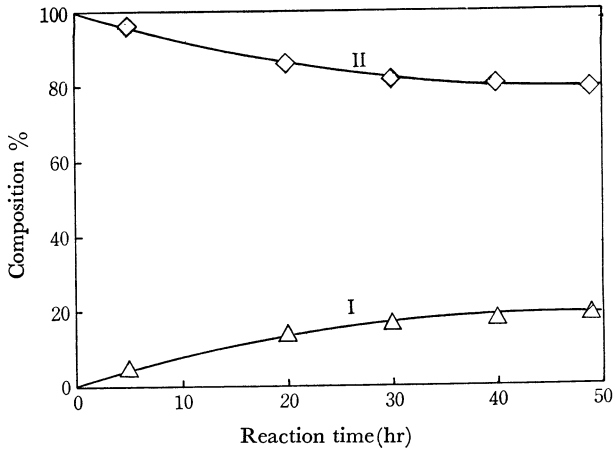
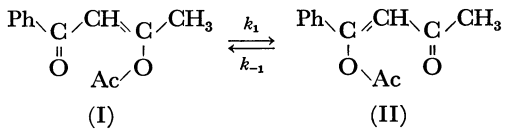


Fig. 4. Isomerization of II to I in pyridine at 0°C.



Isomerization was of first order with respect to both I and II, and the pseudo-first order rate constants were $k_1=0.85\times10^{-5}$ sec^{-1} and $k_{-1}=0.20\times10^{-5}$ sec^{-1}, respectively. Considering the absence of any other acylating agents and substrate except solvents in these experiments, the isomerization seems to be an intramolecular rearrangement caused by the assistance of pyridine base.

Under the reaction conditions of Figs. 1 and 2, the rate of isomerization was smaller than that of acetylation, and the effect of the isomerization can be neglected in the early period of the reaction. In the cases of benzoylacetone and its salt, *C*-acetylated product formation was a minor process and the relative ratios of I to II were about 2.0/1.0 in the early stage of the reactions.

The results and similarities in the composition patterns of Figs. 1 and 2 suggest that in the acetylation of benzoylacetone also, enolate anion is the reacting species which is formed by the deprotonation from benzoylacetone by the action of pyridine base. However, the direct acylation process of keto-enol tautomers by acetylpyridinium cation[3] is not yet

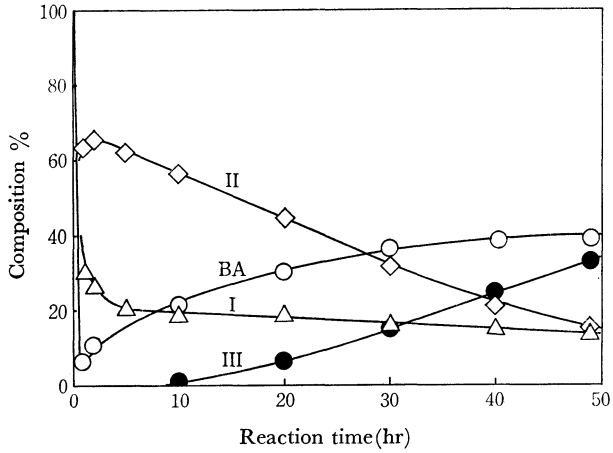


Fig. 5. Acetylation of benzoylacetone in pyridine at 50°C.

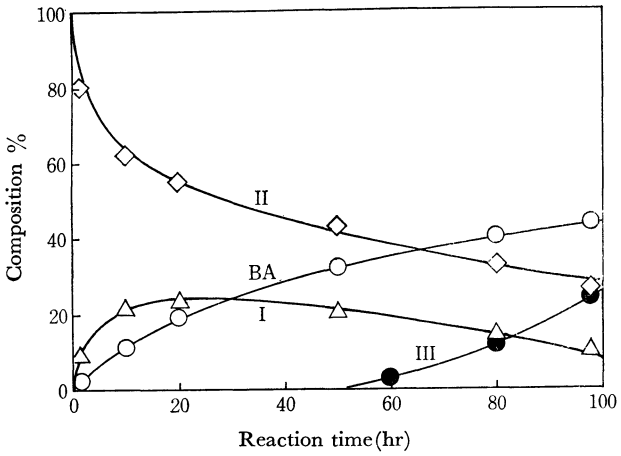


Fig. 6. Isomerization and decompsition of II in pyridine at 50°C.

completely excluded.

Acetylation of Benzoylacetone in Pyridine at 50°C (C-Acetylated Benzoylacetone Formation). When acetylation was carried out at 50°C, the composition of the reaction mixtures changed with reaction time as shown in Fig. 5.

During the course of the reaction, III was formed which was a minor product in the acetylation at 0°C as mentioned before. As shown in Fig. 6, when II was kept at 50°C in pyridine, III and benzoylacetone were formed, suggesting that the formation of III and benzoylacetone resulted from the isomerization and decomposition of II. Figures 5 and 6 indicate that the formation of benzoylacetone takes place before the formation of III. When an equimolar mixture of II and benzoylacetone were kept at 50°C in pyridine, formation of III was very slow. However, when sodium salt of benzoylacetone was used instead of benzoylacetone, the formation of III was favored. Consequently, in the process of *C*-acetylation the reacting species is also enolate anion.

Mutual Isomerizations between I and II in Methylpyridines. I and II isomerized mutually in pyridine at 0°C through first order kinetics. The isomerization in methylpyridines was also examined and the results are shown in Tables 3 and 4.

Introduction of methyl group into the 2- and/or

Table 3. Isomerization of I at 0°C in methylpyridines

Solvent	Reaction time hr	Composition			
		BA[a]%	I%	II%	III%
α-Picoline	53	2	89	6	3
γ-Picoline	53	9	25	66	0
2,6-Lutidine	53	1	92	7	0

a) BA: benzoylacetone

Table 4. Isomerization of II at 50°C in methylpyridnes

Solvent	Reaction time hr	Composition			
		BA%	I%	II%	III%
α-Picoline	53	2	13	85	0
γ-Picoline	53	41	10	9	40
2,6-Lutidine	47	0	12	82	0

6-position of pyridine nucleus suppressed the isomerization effectively, but the methyl group in 4-position showed no such inhibition. This indicates that steric bulkiness around the basic nitrogen atom is largely reflected upon the catalytic activity of pyridine base in the isomerization process. However, acetylation of benzoylacetone in α-picoline gave I selectively in high yield (70%) in the reaction at 0°C for 23 hr. Thus, the 2-methyl group which suppresses the isomerization does not effect the first step acetylation rate. The result is very useful for the preparation of I.

Conclusion

The reaction courses of acetylation of benzoylacetone and its sodium salt have been established as follows:

$$(PhCOCHCOCH_3)^-Na^+ + CH_3COCl \xrightarrow{\text{in ethers}} I + II + III$$

$$PhCOCH_2COCH_3 \overset{\text{pyridine}}{\rightleftharpoons} (PhCOCHCOCH_3)^- + \text{N-acetylpyridinium}$$

$$PhCOCH{=}C(OAc)CH_3\ (I) \quad \overset{\text{in pyridine, 0°C}}{\rightleftharpoons} \quad PhC(OAc){=}CHCOCH_3\ (II)$$

$$I \text{ and } II \xrightarrow{\text{pyridine, 50°C}} PhCOCH_2COCH_3 \overset{\text{pyridine, 50°C}}{\rightleftharpoons}$$

$$(PhCOCHCOCH_3)^- \xrightarrow[\text{pyridine, 50°C}]{\text{I or II}} PhCOCHCOCH_3\ (III)$$

(Ac)

In the acetylation of sodium salt of benzoylacetone in ethers the dissociation into enolate anion favored *O*-acetylation, suggesting that enolate anion is a reacting species in the *O*-acetylation. By comparison of the acylation of benzoylacetone with that of sodium salt, the intervention of enolate anion is also probable in the *O*-acetylation of benzoylacetone itself. The formation of *C*-acetylation product in pyridine at a higher reaction temperature clearly shows that the

enolate anion is acylated by enol ester as pointed out by Muir *et al.*[2]

In the acetylation in pyridine, consecutive mutual isomerizations between I and II proceed even at 0°C. The isomerization is first order reaction with each enol ester I and II and seems to be intramolecular rearrangement reaction. The isomerization can be retarded by the introduction of methyl group into the 2- and/or 6-position of pyridine ring. At a higher temperature further isomerization into III occurred, being an intermolecular migration of acetyl group from the enol ester to enolate anion.

Selection of the reaction condition in the acetylation of benzoylacetone makes it possible to obtain three kinds of acetylated products I, II, and III selectively. Thus, in acetylation in pyridine at 50°C for more than 80 hr, III could be obtained in a selectivity of 83%. Futher, in the acetylation in α-picoline at 0°C, I was formed in 76% selectivity and II was obtained in the selectivity of 77% after a reaction at 0°C for 80 hr. Utilizing these reactions three kinds of acetylated products are readily prepared.

Experimental

Infrared spectra were recorded on a Hitachi EPI-G2. The ultraviolet absorption spectra were determined with a Hitachi EPS-3T spectrophotometer. Nuclear magnetic resonance spectra were recorded on Japan Electronic Optics JNM-3H-60 and JNM-MH-60 using tetramethylsilane as the internal standard in deuteriochloroform. Thin layer chromatography was carried out on silica gel G and developed with benzene or *n*-hexane-ethyl acetate mixtures (90: 10, and 80:20). The spots were detected by standing in an atmosphere of iodine.

Reagents. Benzoylacetone was prepared by the method of Claisen[6] and purified by vacuum distillation and recrystallization from *n*-hexane in 68% yield, bp 104—108°C/2—5mmHg (lit, 132/14 mmHg), mp 56.4—56.6°C (reported 60—61°C). The IR spectrum of the sample was identical with that of Sadtler's data No. 476K and No. 5437. Sodium salt of benzoylacetone was prepared by the reaction of benzoylacetone and sodium metal in dry ether under reflux in the presence of a catalytic amount of ethanol. The white powder precipitated was collected, washed with ether and dried *in vacuo*. Acetyl chloride was purified by distillation of GR grade reagent and stored under nitrogen in a sealed ampule, bp 51.2—51.4°C. Pyridine, α-picoline, γ-picoline, 2,6-lutidine, dimethylformamide, dimethoxyethane, and ethylene glycol dimethyl ether were purified by the procedures described previously.[3]

Analysis of the Composition of the Reaction Mixture. Because of the thermal instability of I, II, and III, glc method was very troublesome. We developed an electronic computer program which determined the concentration of each components by analyzing UV spectra of the reaction mixtures. Aliquots of the reaction mixture were diluted with methanol in order to stop the reaction. UV absorptions were measured and expressed in numerical absorptions in the wave length range 258—334 mμ in every milimicron and the concentration of each component was obtained by the program using computer HARP-5020. The accuracy of the concentration obtained by this method was ±5% in absolute values. It was confirmed that Lambert-Beer's law and the additivity of the absorptions of the components existing in the system holdand the absorptions of the other components except for those cited in Table 5 do not disturb the analysis in this range of concentrations.

Table 5. Ultraviolet absorption of each component

Compound	λ_{max}(mμ)	$\varepsilon_{max} \times 10^{-4}$
Benzoylacetone	309	1.51
	249	0.574
Sodium benzoylacetonate	309	1.05
	247	0.584
I	262	1.89
II	280	1.47
III	280	1.08
	252	1.50

Identification of Acetylated Products. 4-Phenyl-2-acetoxy-2-buten-4-one (I): 16.2 g of benzoylacetone (0.1 mol) was dissolved in 50 g of α-picoline in a flask equipped with a mechanical stirrer, dropping funnel, and a silica gel tube and cooled on an ice-water bath. Acetyl chloride 11.8 g (0.15 mole) was added in portions at a rate which kept the reaction temperature below 4°C. The progress of the reaction was checked by UV spectrum during a period of 10 hr. The reaction mixture was poured into dilute hydrochloric acid. and the neutralized mixture was extracted with ether. After the usual work-up an oily product was obtained which afforded yellow crystals on cooling at −20°C. The crystals were collected and recrystallized from petroleum ether to yield 3.6 g of I, mp 32.5—33.0°C, bp 108—117°C/0.5 mmHg. Found: C, 70.77; H, 5.85%. Calcd for $C_{12}H_{12}O_3$: C, 70.57; H, 5.92%. IR (KBr) 1750 (s, $\nu_{C=O}$ enol ester), 1680 (s, $\nu_{C=O}$ benzoyl), 1630 (s, $\nu_{C=C}$), 1450, 1380 (m, δCH_3), 1230, 1147 (vs, ν_{C-O} ester), 780, and 710 cm^{-1} (s, phenyl). NMR ($CDCl_3$) τ 7.76 (s, 3H, acetoxy), 7.57 (d, 3H, J=1.1 Hz, $-CH=C(OAc)C\underline{H}_3$), 3.17 (q, 1H, J=1.1 Hz, vinyl proton), and 2.0—2.8 (m, 5H, ArH). UV λ_{max}^{MeOH}=281 mμ (ε=1.55×10⁴).

1-Phenyl-1-acetoxy-1-buten-3-one (II): The acetylation of benzoylacetone was carried out in pyridine at 0°C for 24 hr. After a similar working-up as above, the oily product was separated into I and II by means of column chromatography (Wakogel C-200, 30φ×420, elutant: benzene and then ethyl acetate). Recrystallization of crude solid from petroleum ether afforded colorless crystals II mp 38.2—38.5°C, bp 119—123°C/0.5 mmHg. Found: C, 70.73; H, 5.93%. Calcd for $C_{12}H_{12}O_3$: C, 70.57; H, 5.92%. IR (KBr) 1770 (s, $\nu_{C=O}$ enol ester), 1690 (s, $\nu_{C=O}$ acetyl), 1600 (s, $\nu_{C=C}$), 1450, 1362 (m, δCH_3), 1200, 1160 (vs, ν_{C-O} ester), 765, and 690 cm^{-1} (s, phenyl). NMR ($CDCl_3$) τ 7.75 (s, 3H, acetoxy) 7.65 (s, 3H, acetyl), 3.48 (s, 1H, vinyl proton), 2.0—2.6 (m, 5H, ArH). UV λ_{max}^{MeOH}=262 mμ (ε=1.98×10⁴).

ω,ω-Diacetylacetophenone (III): III was prepared by the Schotten-Baumann reaction[7] and purified by vacuum distillation and recrystallization from methanol or petroleum ether in a yield of 42%, mp 28.9—29.4°C (reported 35.0°C), bp 132—135°C/5 mmHg. Found: C, 70.80; H, 5.93%. Calcd for $C_{12}H_{12}O_3$: C, 70.57; H, 5.92%. IR (KBr) 1655 (*vs*, $\nu_{C=O}$ intramolecular H-bonded), 1590 (s, $\nu_{C=C}$ enol form), 1450, 1360 (m, δCH_3), 730, and 700 cm^{-1} (s, phenyl). NMR ($CDCl_3$) τ 7.92 (s, 6H, two acetyl), 1.8—2.6

6) L. Claisen, *Ber.*, **38**, 695 (1905).

7) L. Claisen, *Ann.*, **291**, 63 (1896).

(m, 5H, ArH), −7.20 (broad s, 0.8H, enol OH). UV λ_{max}^{MeOH} =253 mμ ($\varepsilon=1.59\times10^4$), and 280 mμ ($1.08\times10^4$).

I and II could be decisively identified by means of NMR—the presence of fine long-range coupling between methyl and vinyl ptotons of $-C\underline{H}=C(OAc)C\underline{H}_3$ in I. Purity of the samples could be readily determined by taking advantage of the signals of vinyl protons.

Acetylation of Sodium Benzoylacetonate. The sodium salt (20 mmol) was dissolved in 50 g of solvent and acetyl chloride (22 mmol) was added under cooling when necessary. A similar treatment of the reaction mixture as mentioned above gave an oily product which was analyzed by glpc (OV-17 5%, 2m, 130°C) with *trans*-stilbene as an internal standard. Besides the glpc analysis, UV technique was also applied directly to the reaction mixture.

Acetylation of Benzoylacetone and Sodium Benzoylacetonate in Pyridine at 0°C. 11.8 g of acetyl chloride (0.15 mol) was added to 35.0 g of pyridine under stirring on an ice-water bath. Pyridine (15.0 g) solution of benzoylacetone 16.2 g (0.10 mol) was added into the suspension of acetylpyridinium chloride in pyridine and aliquots were analyzed by means of UV technique. Acetylation of sodium benzoylacetonate at 0°C was carried out in a similar way.

Acetylation of Benzoylacetone and its Sodium Salt in Pyridine at 50°C. Acetyl chloride (0.15 mol) was added to pyridine (50g) solution of benzoylacetone sodium salt (0.10 mol) at 50°C. Previous addition of acetyl chloride as mentioned above in the experiments at 0°C failed to give rise to reproducibility of the results.

Acetylation of Benzoylacetone in α-Picoline at 0° and 50°C. The procedure is described in the preparation of I. The change of composition was followed by means of UV technique. In the reaction at 0°C, the ratios of I/II were constant (4.8± 0.4) all through the reaction for 8 hr up to 90% conversion. In the reaction at 50°C, acylation was complete in 0.5 hr (cf. at 0°C, 75% conversion after the reaction for 2 hr) but slow isomerization of I to II was observed.

Isomerization between I and II in Pyridine at 0°C. Ca. 1g of pyridine solution of I or II (0.1—2.0 mol/*l*) was kept at 0°C and aliquots were analyzed by means of UV technique at proper time intervals. The changes of composition are shown in Figs. 3 and 4. The plot of $\ln[([I]_0-[I]_e)/([I]-[I]_e)]$ *vs.* reaction time gave a common straight line through the origin over the range of twenty times initial concentration of I or II. From the slope of the straight line (1.05×10^{-5} sec^{-1}) and the equilibrium ratio of I to II (19/81), k_1 (0.85×10^{-5}) and k_{-1}(0.20×10^{-5} sec^{-1}) were obtained.

Isomerization between I and II in Methylpyridines. Ca. 180 mg of methylpyridine solution of I or II (2.0 mol/*l*) was kept at 0 or 50°C and aliquots were analyzed in a similar way. Isomerization was also examined in DMF, dimethoxyethane, diglyme, acetonitrile, and benzene at 50°C but no isomerization was detected. In triethylamine, however, II isomerized to a mixture after the reaction at 50°C for 47 hr, whose composition was benzoylacetone 31, I 18, II 43, and III 8%.