SYNTHESIS OF SOME N-HETEROCYCLES USING ACETOACETAMIDE DERIVATIVES

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Reaction of ethyl acetoacetate (1), ethyl β-aminocrotonate (2), acetoacetamide (3), and β-aminocrotonamide (4) with carboxylic acid derivatives, aldehydes, ketones, and diketene results in the formation of N-heterocycles. This article gives a detailed survey of the reactions of these compounds and related derivatives.

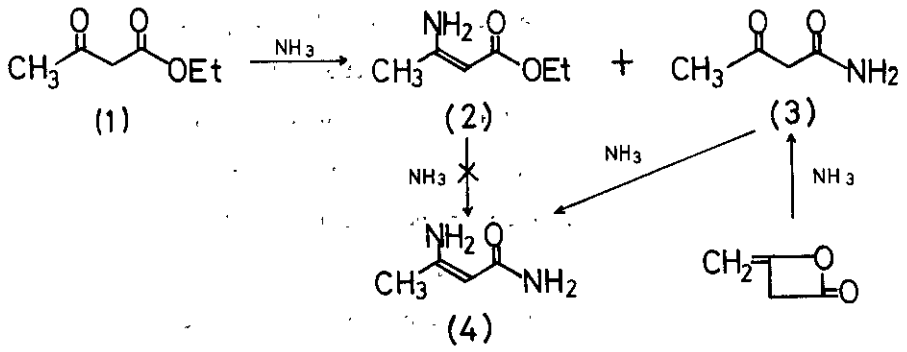
Introduction

In 1878, Precht[1] obtained a colorless oil, $C_6H_{11}O_2N$(2), by passing dry ammonia gas over ethyl acetoacetate (1). Duisberg[2] reinvestigated this reaction in detail, and observed an increase in the yield of 2 by using 25% ammonium hydroxide, together with a small amount of a crystalline substance, $C_4H_7O_2N$(3). Later, Claisen[3] reported that the yield of 3 rose when 1 was kept in 10% ammonium hydroxide at room temperature for several weeks (30-40% yield as a crude product).

Though both 2 and 3 were speculated to be amide derivatives of acetoacetic acid, erroneous structures were proposed for them since elemental analysis was the only criterion for this proposal at that time. However, ethyl β-aminocrotonate[4] and acetoacetamide[3] were proposed as the structures of 2 and 3, respectively. In these reactions, ethyl β-aminocrotonate (2) could be isolated easily by distillation, but acetoacetamide (3) was difficult to isolate and moreover, the yield was low.

Chick and Wilsmore[5] reported that by introduction of dry ammonia gas into an anhydrous ether solution of diketene, compound 3 was precipitated as white crystals. Further introduction of ammonia caused 3 to change to a yellow oil. Though this oily substance could not be purified by crystallization or distillation, its structure was presumed to be β-aminocrotonamide (4) by them.

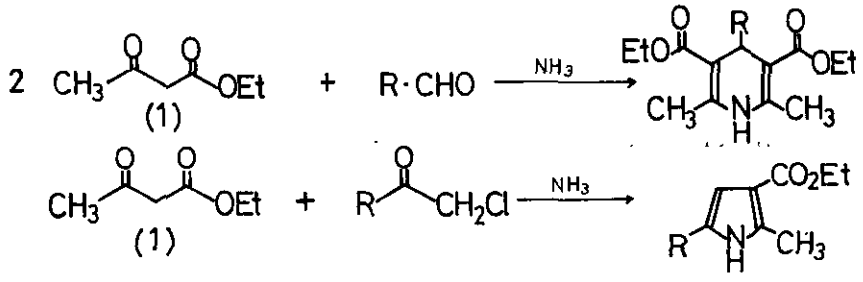
Chart 1



The present authors reinvestigated this reaction, and isolated 4 as pure crystals and established its structure as β-aminocrotonamide (4).[6] Even when 2 was treated with ammonia under the same condition as described above, it was not transformed into 4.

Ethyl acetoacetate (1), a typical β-ketoester, is considered an important reagent in the field of synthetic chemistry. Thus, many papers concerning the reactivity of 1 have been published. For example, in the synthesis of heterocyclic compounds, the so-called Hantzsch's pyridine synthesis[7] is carried out by the condensation of ethyl acetoacetate, aldehyde and ammonia. Applying this method to α-haloketone[8] or α-haloaldehyde,[9] instead of simple aldehydes a large number of pyrrole derivatives can be synthesized.

Chart 2



As a matter of fact, 2 is assumed to be the intermediate in these reactions, and some reports concerning the use of 2 in the synthesis of the pyridine ring have been published.[10]

The reactivity of ethyl β-aminocrotonate (2) has been investigated in relative detail. That of 3, however, and especially 4 is

barely known, because both 3 and 4 were difficult to obtain. In contrast, 2 was prepared easily from ethyl acetoacetate (1) as mentioned above.

Recently, because of the availability of diketene, and the ready preparation of 3 and 4, some reports concerning the reactivity of the latter compounds have been published.

The scope of this review is to compare the related reactions of 3 and 4 with those of 1 and 2, with especial emphasis on the synthesis N-heterocyclic compounds.

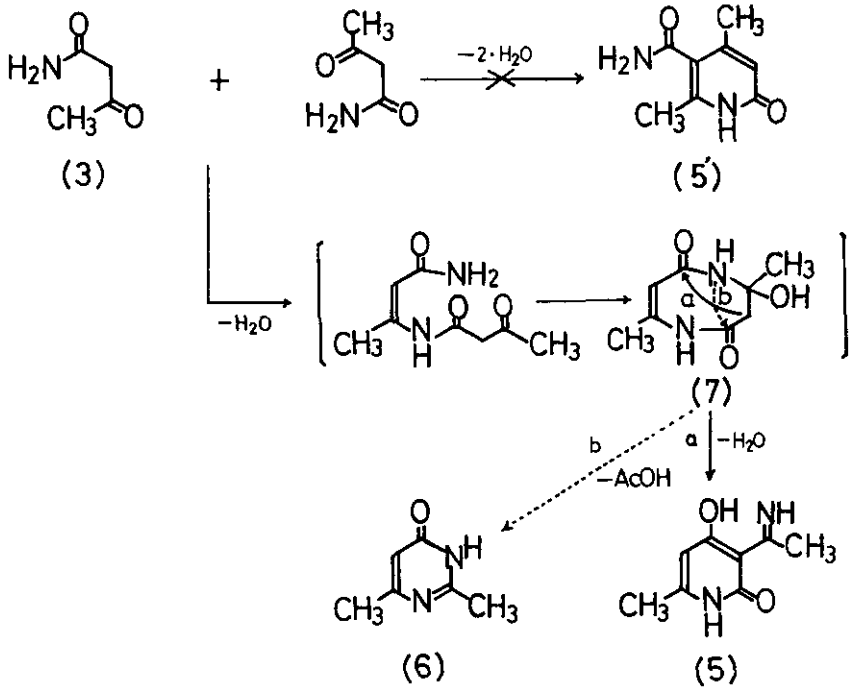
I. Thermal Reaction of Acetoacetamide (3) and β-Aminocrotonamide (4)

Neither 1 nor 2 is decomposed by heating, and both can be purified by distillation. It is very difficult, however, to purify 3 and 4 by distillation because of thermal decomposition.

Claisen[3] found that heating of acetoacetamide (3) gave a crystalline substance, $C_8H_{18}O_2N_2$, to which the structure of 4,6-dimethyl-2(1H)-pyridone-5-carboxamide (5'), the intermolecular condensation product of 3, was proposed.

The present authors[11,12] elucidated that the structure was not 5' but 3-acetimidoyl-4-hydroxy-6-methyl-2(1H)-pyridone (5). Moreover, in this reaction the main product was not 5 but 2,6-dimethyl-4(3H)-pyrimidone (6). Although the mechanism of this reaction is obscure, the formations of pyridone (5) and pyrimidone (6) can be explained as follows : two moles of 3 would give β-acetoacetamidocrotonamide which cyclizes to the eight-membered intermediate (7), ring contraction of which along path-a and path-b would give rise to 5 and 6, respectively.

Chart 3



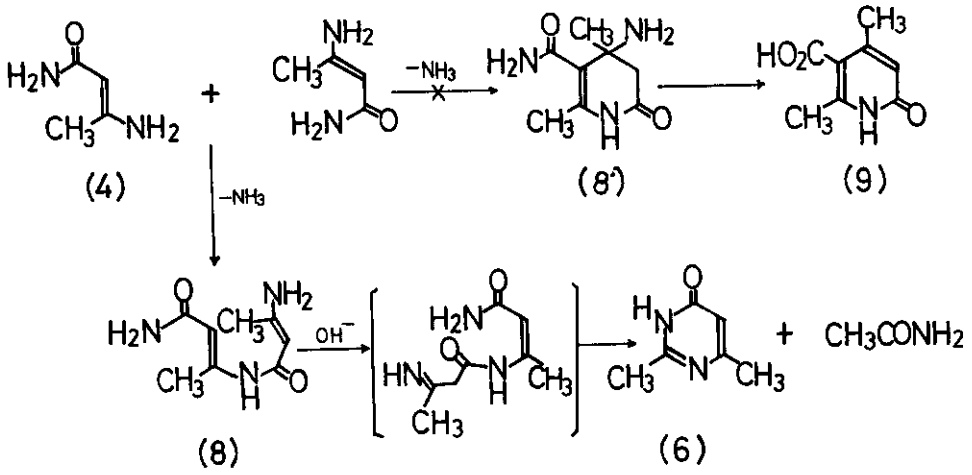
Later, a report concerning the thermolysis reaction of β-aminocrotonamide similar to the above method was published. By passing excess ammonia gas over diketene Chick and Wilsmore[5] obtained a yellow oil, the structure of which was elucidated as 4. This compound was difficult to purify by distillation and, on heating, was transformed into crystals, mp 197°, $C_8H_{13}O_2N_3$ (8), whose structure were considered as 4-amino-3,4-dihydro-4,6-dimethyl-2(1H)-pyridone-5-carboxamide (8') at that time.

The present authors[6] reinvestigated this reaction, and proved

structure (8') to be erroneous, and proposed β-(β'-amino-crotonamido)crotonamide (8) as the reasonable structure. Compound 8 was transformed into 2,6-dimethyl-4(3H)-pyrimidone (6), and acetamide by hydrolysis. However, the formation of 4,6-dimethyl-2(1H)-pyridone-5-carboxylic acid (9), reported by Chick and Wilsmore, was not obserbed.

Considering these reactions 3 and 4 appear to be worthy starting material in the synthesis of pyrimidine derivatives.

Chart 4



II. Acylation Reaction

Though acylation reactions of 1 and 2 by acyl chloride or acid anhydride have long been known,[13] those of 3 and 4 have been scarcely studied. The authors investigated the reaction of 4 with acylating reagents in detail, and developed a new synthetic approach

to pyrimidine derivatives using acyl derivatives of 4.

When β-aminocrotonamide (4) was warmed in acetic anhydride or boiled under reflux with acetic anhydride in chloroform, β-acetamidocrotonamide (10, R=CH_3) was obtained. Compound 10 can also be obtained from the reaction of 4 with acetyl chloride in pyridine with ice-cooling.

Usually, aliphatic acylation reaction proceeds smoothly by using acid anhydride. On the other hand, aromatic acylation by acyl halide, under Schotten-Baumann reaction condition, gives a good result.

For example, 4 was heated with acetic anhydride in chloroform to give (10, R=CH_3) in 74% yield. Employing the same procedure, aliphatic derivatives (10) such as ethyl(R=CH_3CH_2), n-propyl(R=$CH_3CH_2CH_2$) and isopropyl(R=$(CH_3)_2CH$) were obtained in relatively good yield (74%, 68% and 62%, respectively).

On the contrary, the use of benzoic anhydride gave a 31% yield of 10(R=C_6H_5). However, the yield of 10 was improved up to 75% by treatment of 4 with benzoyl chloride in pyridine. On the other hand, applying the acetyl chloride-pyridine method the yield of 10 (R=CH_3) dropped to 49%.[14]

When 4 was acetylated with ketene, the carbon at the α-position was attacked predominantly. For example, α-acetyl-β-aminocrotonamide (11) was obtained by passing ketene gas into an acetone solution of 4 at room temperature.

Treatment of 4 with ketene in the presence of pyridine as a catalyst resulted in the formation of C,N-diacetyl derivative (12) together with 11. Since 12 can not be obtained from the reaction

of 10 with ketene, it might be formed via 11.

Acetylation of 4 with isopropenyl acetate gave only 10, which means that the carbon at α-position of 4 is not reactive toward this acylating agent.[15]

When 11 was heated in acetic acid-acetic anhydride mixture, 5-acetyl-2,6-dimethyl-4(3H)-pyrimidone (13) was obtained. It seems that 13 might be formed via α-acetyl-β-acetamidocrotonamide (12), by subsequent acetylation of 11. Actually, direct heating or heating of compound 12 in a 10% NaOH solution also led to the formation of 13 in good yield. Compound 10 was also transformed into pyrimidone derivative (14) by heating.

As mentioned above, heating of acetoacetamide (3) or β-aminocrotonamide (4) followed by treatment with alkali gave rise to 2,6-dimethyl-4(3H)-pyrimidone (6 or 14, R=CH_3). β-Acylaminocrotonamide can be speculated as an intermediate in these reactions. Therefore, a new synthetic approach may be expected by investigation on the ring closure reaction of 10.

Investigations to find the favorite condition for this type of ring closure reaction came to the conclusion that heating or treatment of 10 with alkali are the best conditions for the preparation of pyrimidone derivatives. For example, 10(R=CH_3) was heated in an oil bath at 200°C for a few minutes to give the ring closed compound (14, R=CH_3) in 50% yield. On the other hand, boiling of 10 in tetralin gave 14 in 95% yield. Compound 14 was also obtained in good yield by heating of 10 in NaOH or NaOEt-EtOH. The results are summarized in Table 1.

Chart 5

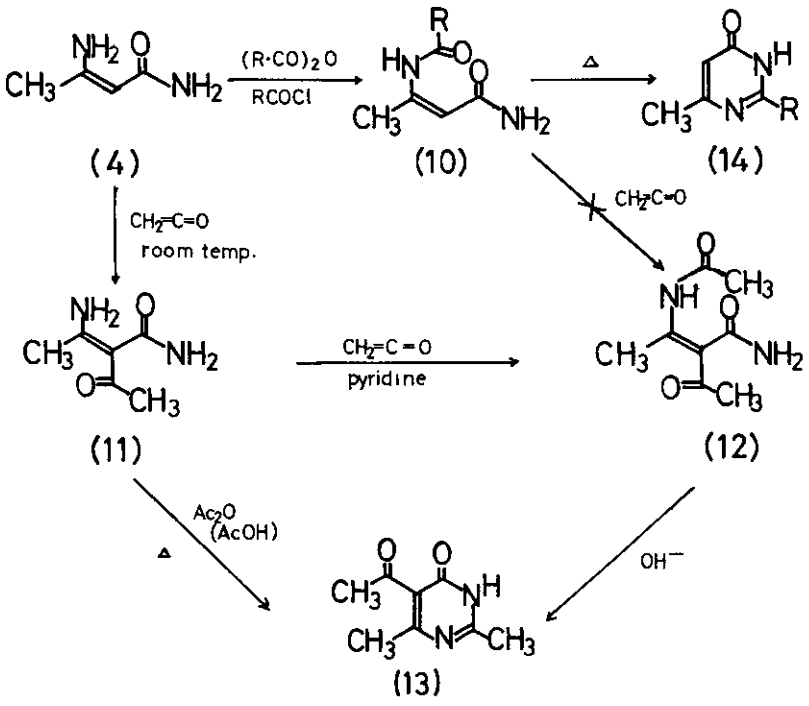


Table 1

(10) $\xrightarrow{\Delta}$ (14)

R	Solvent	Reaction Temp. (°C)	Yield (%)
methyl	none	220	52
ethyl	"	"	62
n-propyl	"	"	67
isopropyl	"	"	74
phenyl	"	"	27
methyl	tetralin	reflux	95
ethyl	"	"	86
n-propyl	"	"	73
isopropyl	"	"	77
phenyl	"	"	32
methyl	10% NaOH	80	95
phenyl	"	"	83

When 4 was heated with esters such as ethyl isolactate in the presence of sodium ethoxide in ethanol, 2-isopropyl-6-methyl-4(3H)-pyrimidone (14, R=isopropyl) was obtained in one step. If the yields (ca. 40%) can be improved in this reaction, this method would be of value from synthetic point of view.[16]

As a whole, these synthetic approaches of pyrimidine ring mentioned above[14,16,17] involve the following advantages; that is, the starting material (4) can be prepared in almost quantitative yield by treatment of diketene with ammonia, and acylation of 4 or subsequent ring closure reaction to pyrimidone proceeds quite easily.

III. Reaction with α,β-Unsaturated Carboxylic Acid Derivatives

As mentioned previously, β-aminocrotonamide (4) reacts with acid anhydride to give β-acylamino derivatives (10), further cyclization of which results in the formation of pyrimidone derivatives (14).

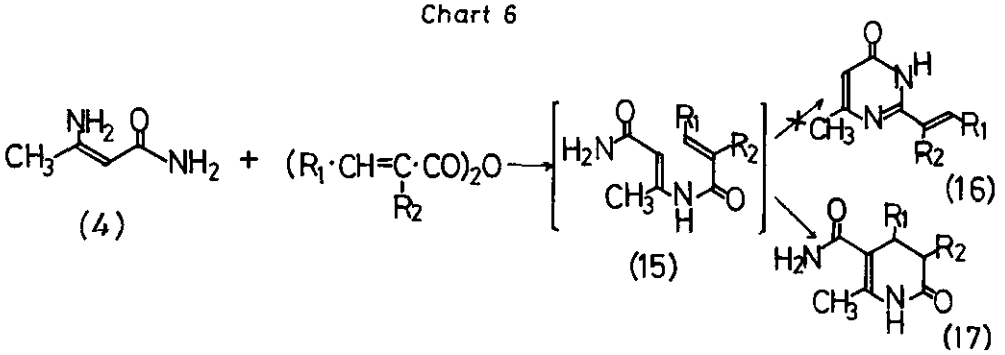
Applying the same method by the use of α,β-unsaturated carboxylic acid anhydrides, the expected 2-alkenyl-6-methyl-4(3H)-pyrimidone (16) was not isolated, but pyridone derivative (17) was obtained, instead. Thus, refluxing of a mixture of 4 and acrylic anhydride in chloroform gave crystals, which were not the expected N-acyl derivative (15), but 6-methyl-3,4-dihydro-2(1H)-pyridone-5-carboxamide (17, R_1=R_2=H). In the same fashion, the reaction with crotonic anhydride, and methacrylic anhydride gave the related 17.[18]

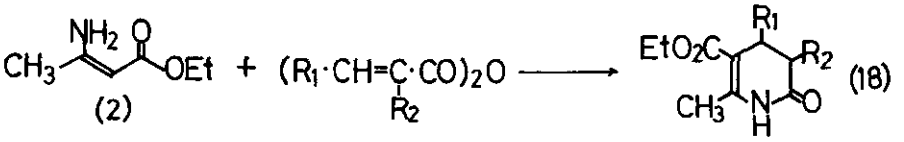
Though acylated compound (15) was not isolated in this reaction, it could be speculated as an intermediate. Namely, it seems likely that the first step of the reaction is acylation of the β-amino

moiety of (4) to give 15, followed by cyclization to form 17.

The similar reaction can be expected in the case of ethyl β-aminocrotonate (2). In fact, 2 was allowed to react with acrylic, crotonic, and methacrylic anhydride under the same condition to yield the corresponding 6-methyl-3,4-dihydro-2(1H)-pyridone-5-carboxylate derivatives (18).[18] These reactions are thought to be the Michael additions.[19]

Chart 6



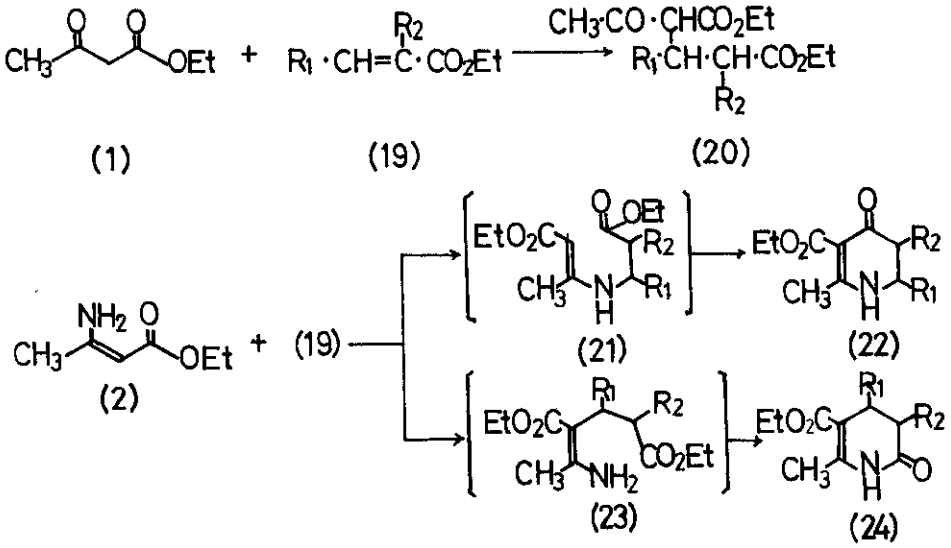


For instance, ethyl acetoacetate easily reacts with ethyl acrylate (19, R_1=R_2=H) in the presence of a catalyst such as sodium ethoxide to afford diethyl α-acetylglutarate (20, R_1=R_2=H).[20]

Schmidt[21] reported the reaction of ethyl β-aminocrotonate (2) with ethyl acrylate (19, R_1=R_2=H) in the presence of sodium ethoxide to give ethyl 2-methyl-5,6-dihydro-4(1H)-pyridone-3-carboxylate (22).

Later, Becker[22] reinvestigated the same reaction, and reported the structure of the product was not 22, but its isomer, ethyl 6-methyl-3,4-dihydro-2(1H)-pyridone-5-carboxylate (24). Namely, reaction does not proceed through the addition to the amino group of 2 to form the adduct (21), but the Michael addition of 19 to the α-carbon of 2 takes place to afford the intermediate (23), through which compound (24) is formed.

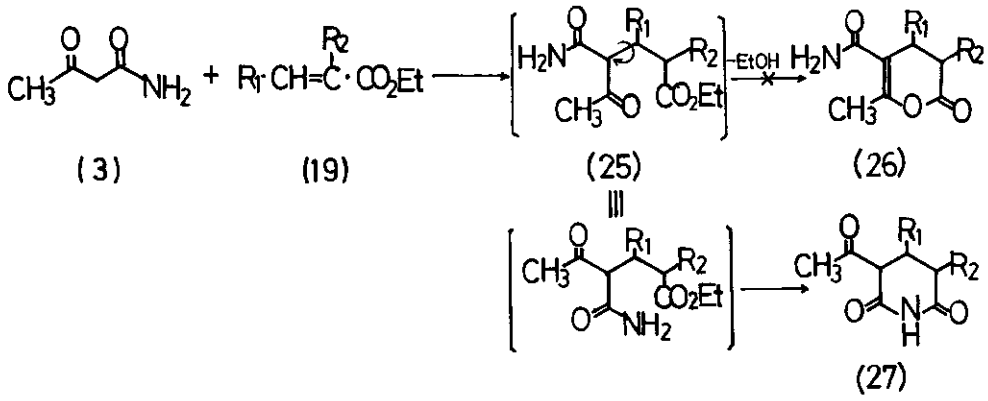
Chart 7



Acetoacetamide (3) reacts with ethyl acrylate under the same reaction condition to give 3-acetylglutarimide (27, R_1=R_2=H). Therefore, it is clear that 19 added to 3 by Michael addition to yield 25, which transformed into 27 by the ring closure between amido and ester group, but the ring closure to 26 was not observed.

Ethyl crotonate, ethyl methacrylate, and ethyl cinnamate also showed the same type of reactivity giving the corresponding glutarimide derivatives (27).[23]

Chart 8



Moreover, Michael reaction of 4 showed interesting results.[24] Thus, ethyl acrylate (19, R_1=R_2=H) was allowed to react with 4 in the presence of sodium ethoxide to afford 3-acetimidoylglutarimide (29, R_1=R_2=H), and 2-(2-ethoxyethyl)-6-methyl-4(3H)-pyrimidone (32) (R_1=R_2=H). Using potassium t-butoxide instead of sodium ethoxide, 29 and 2-vinyl-6-methyl-4(3H)-pyrimidone (16, R_1=R_2=H) were obtained.

Though the mechanisms of these reactions are not clear, 29 seems to be formed by ring closure of the Michael adduct intermediate (28).

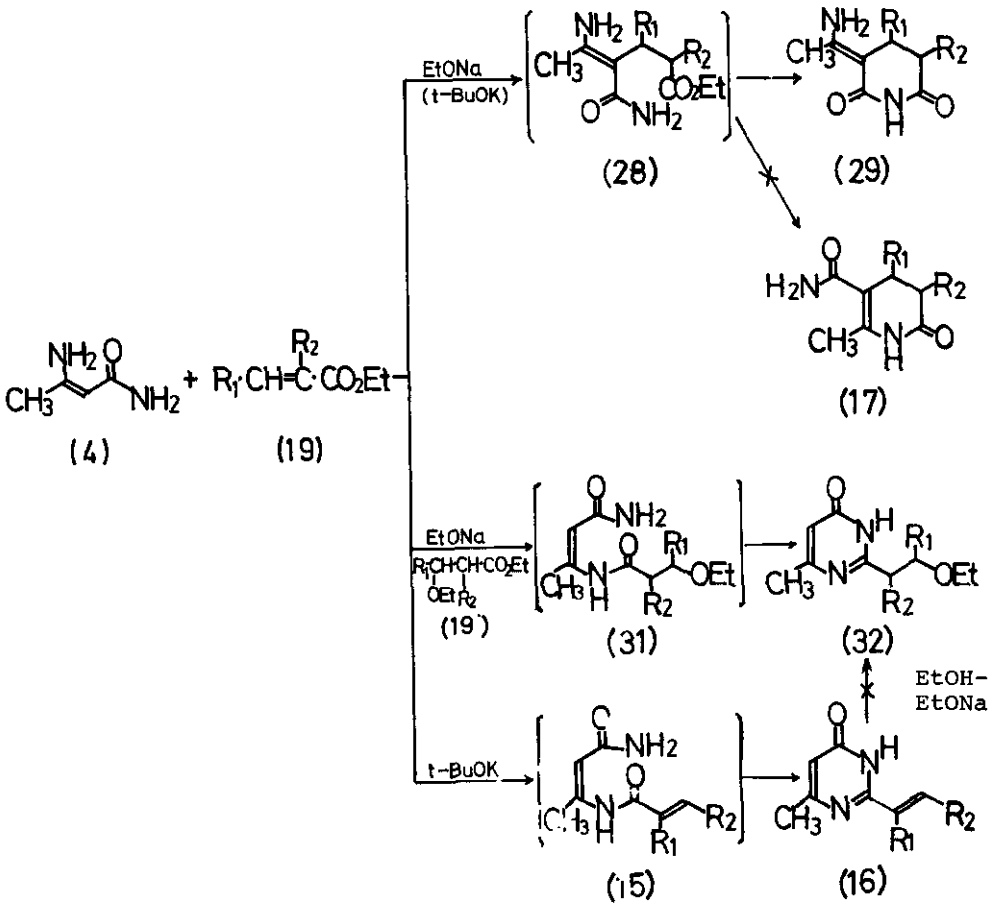
Because the formation of the pyridone derivative (17) corresponding to 24, obtained from Michael reaction of 2 by Becker,[22] was not observed, it is reasonable to think that comparing the two nitrogen moieties of 28, the amido nitrogen is more active for ring closure than the enamine nitrogen.

It is clear that 2-substituted pyrimidone derivatives (32 and 16) were formed by the acylation of β-amino group with ester,

followed by ring closure to pyridone in the presence of a base as mentioned above. Especially, in the formation of 32, it is reasonable to assume that on treatment with EtOH-NaOEt, the unsaturated ester (19) was first transformed into β-ethoxy derivative, $EtOCHR_1CHR_2CO_2Et$ (19'), through which the pyrimidone nucleus was formed.

Difficulty in the transformation of 16 into 32 while using EtOH-EtONa is another proof to support the above mechanism.

Chart 9



IV. Reaction with Aldehydes

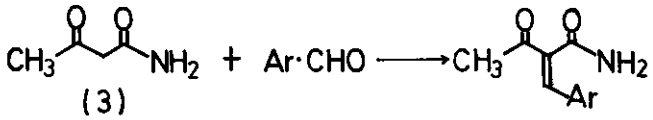
As described previously, the reaction of ethyl acetoacetate (1) or ethyl β-aminocrotonate (2) with aldehyde has been investigated in detail in Hantzsch's pyridine synthesis. However, little is known about the reactivity of 3 or 4 towards aldehydes.

Wilson[25] reported the reaction of acetoacetamide (3) with formaldehyde to give the bis type compound, $CH_2[CH(COCH_3)CONH_2]_2$. Actually, 3 hardly reacts with aldehyde. For example, in the presence of a basic catalyst, 3 reacts with aromatic aldehyde to give benzylidene derivative (33) in rather low yield.[26] Though 3-acetylcoumarin (34) was obtained from the reaction of salicylaldehyde with 3, it is thought to be formed via the benzylidene type intermediate, which is shown in Chart 10.

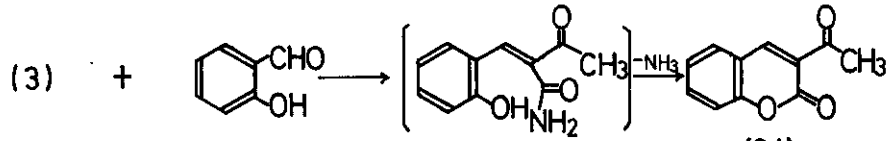
Furthermore, when 3 was allowed to react with benzaldehyde in alcoholic ammonia according to Hantzsch's synthesis method, the expected pyridone derivative (35) was obtained in 42% yield. Compound 35 was also obtained in 45% yield by treatment of 4 with benzaldehyde in ethanol. Similarly, following the Hantzsch's synthesis, treatment of a mixture of 3 and 4 with benzaldehyde in ethanol gave a 22% yield of 35. However, the formation of pyridone derivatives was not observed in the reaction of 3 or 4 with aliphatic aldehydes.

Though triethylamine is effective for Hantzsch's synthesis as a basic catalyst, the use of KOH-EtOH or NaOEt-EtOH instead of triethylamine did not give the pyridine derivative, but gave pyrimidone. For example, 4 was heated with benzaldehyde in ethanol in

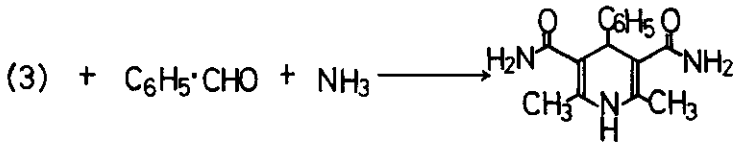
Chart 10



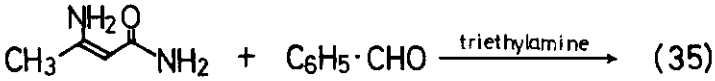
(3)　　(33)



(34)

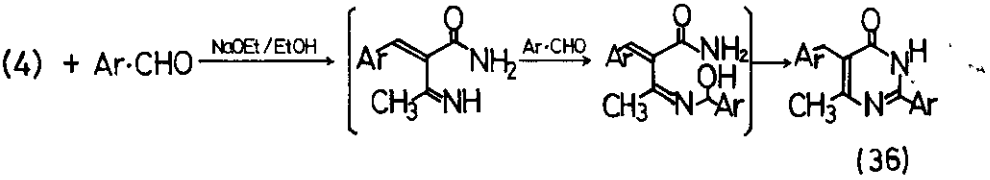


(35)　(42%)



(4)　(35)　(45%)

(35)　(22%)



(36)

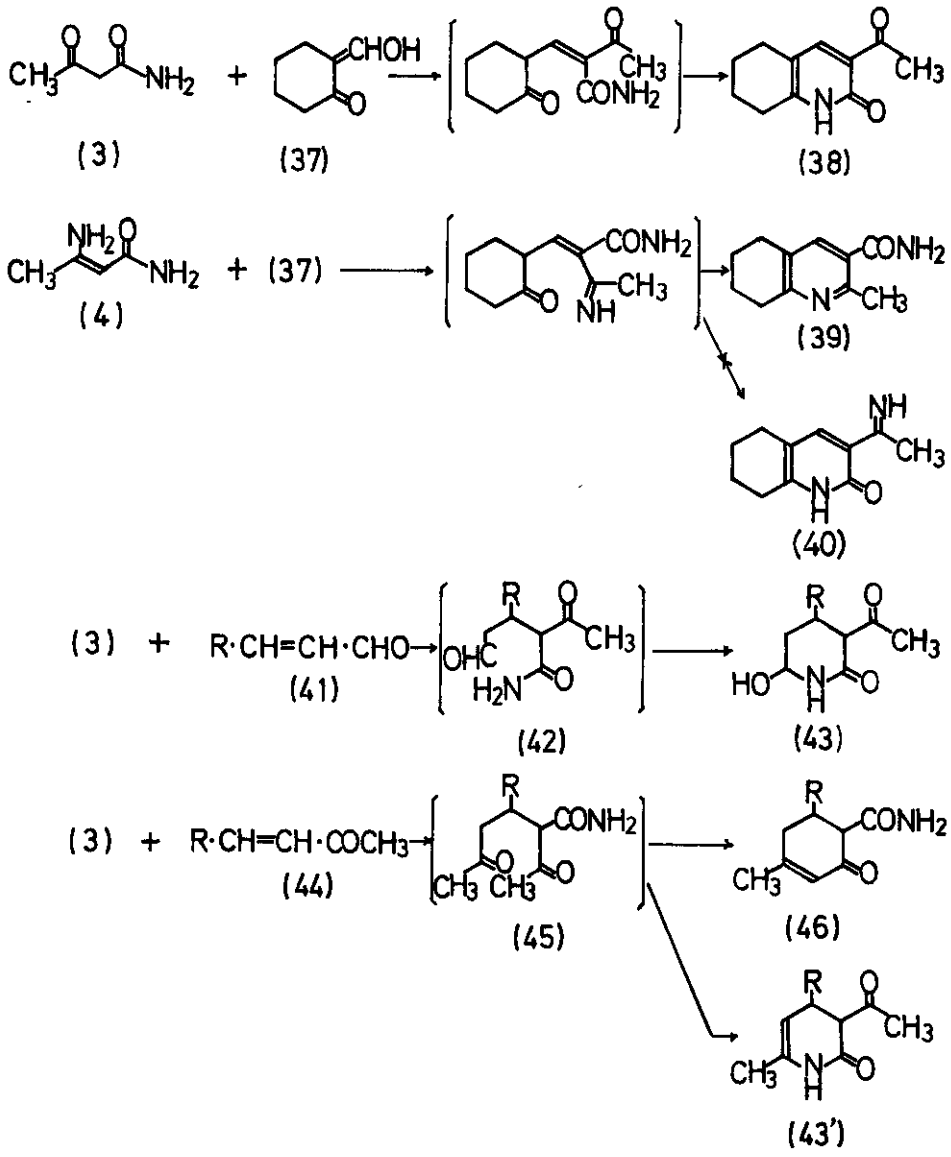
the presence of KOH to give 36 (Ar=C_6H_5) in 90% yield. But under the same condition, aliphatic aldehyde hardly reacts with 4.[26]

1-Hydroxymethylenecyclohexanone (37) was allowed to react with 3 to give 3-acetyl-5,6,7,8-tetrahydrocarbostyril (38). It is clear that alkylidene derivative is an intermediate of this reaction. Employing the similar condition, the reaction of 37 with 4 did not give 40, but tetrahydroquinaldine derivative (39). The mechanism concerning the course of cyclization is not clear at present.

The reaction of 3 with α,β-unsaturated aldehyde (41) and ketone (44) also shows an interesting result. Namely, a solution of 3 and crotonaldehyde (41, R=CH_3) in absolute ethanol was heated in the presence of triethylamine to afford 3-acetyl-5-hydroxy-4-methyl-2(1H)-piperidone (43, R=CH_3). The similar reaction with cinnamaldehyde (41, R=C_6H_5), afforded the acetyl-2-piperidone derivative (43, R=C_6H_5). Therefore, in this reaction the intermediate is not an alkylidene type compound, but a Michael addition type compound (42).

When, however, an α,β-unsaturated ketone such as benzalacetone (44, R=C_6H_5) was allowed to react with 3 under the same condition, the cyclohexene derivative (46) was obtained as a major product together with the piperidone type compound (43', R=C_6H_5) corresponding to 43. Although the intermediate of this reaction is the Michael adduct type compound (45), as described previously, cyclization was carried out by the aldol type condensation reaction.[27]

Chart 11



V. Reaction with Diketene

When ethyl acetoacetate (1) was allowed to react with diketene in the presence of a basic catalyst, ethyl 6-methyl-β-resorcylate (47) and ethyl 2,6-dimethyl-4H-4-pyrone-3-carboxylate (48) were obtained. The yields of 47 and 48 were strongly influenced by the reaction conditions. For instance, when 1 was allowed to react with diketene in the presence of triethylamine, hardly any β-resorcylate (47) was obtained (below 1%), and the pyrone derivative (48) was the main product (ca. 35%). When, however, 1 was allowed to react with diketene, after metalation with NaH in tetrahydrofuran, the yields of 47 and 48 were reversed.

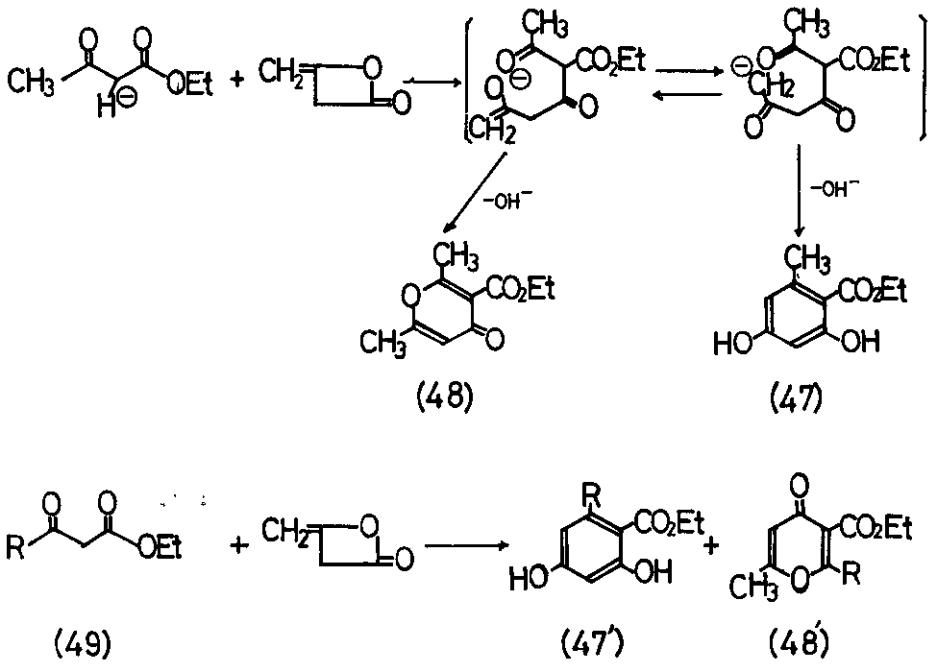
As shown in Chart 12, both of 47 and 48 would be formed via the α-acetoacetyl derivative of 1.

Compound 47 corresponds to the ester of orsellinic acid which is known as a lichen metabolite. Using this reaction, several kinds of β-resorcylate derivatives (47) were prepared from common β-ketoesters (49). Thus, ethyl β-ketocapronate (49, R=n-propyl) was treated with diketene under the same condition as described above to give ethyl divarate (47', R=n-propyl). Employing the same procedure, ethyl olivetolcarboxylate (47', R=n-pentyl) and ethyl sphaeropherol carboxylate (47', R=n-heptyl) were obtained from ethyl β-ketocaprylate (49, R=n-pentyl), and ethyl β-ketocaprinoate (49, R=n-heptyl), respectively.

Though the yield in this reaction is about 35-40%, in the case of improvement, this synthetic approach of β-resorcylate derivatives seems to be superior to the conventional methods owing to

the fewer number of steps.[28]

Chart 12



It has been reported that ethyl β-aminocrotonate (2 or 50, R=H) was acetylated with acetic anhydride or acetyl chloride to give the N-acetyl derivative, whereas using ketene as an acetylating reagent the C-acetylated compound was obtained.

As ketene and diketene are intramolecular anhydrides of acetic acid and acetoacetic acid, respectively, the behavior of diketene as an acylating reagent towards 2 is of interest. As a result, the reaction of 2 with diketene gave ethyl 2,6-dimethyl-4(1H)-pyridone-3-carboxylate (52, R=H). It is clear, therefore, that the intermediate of this reaction is ethyl α-acetoacetyl-β-aminocrotonate

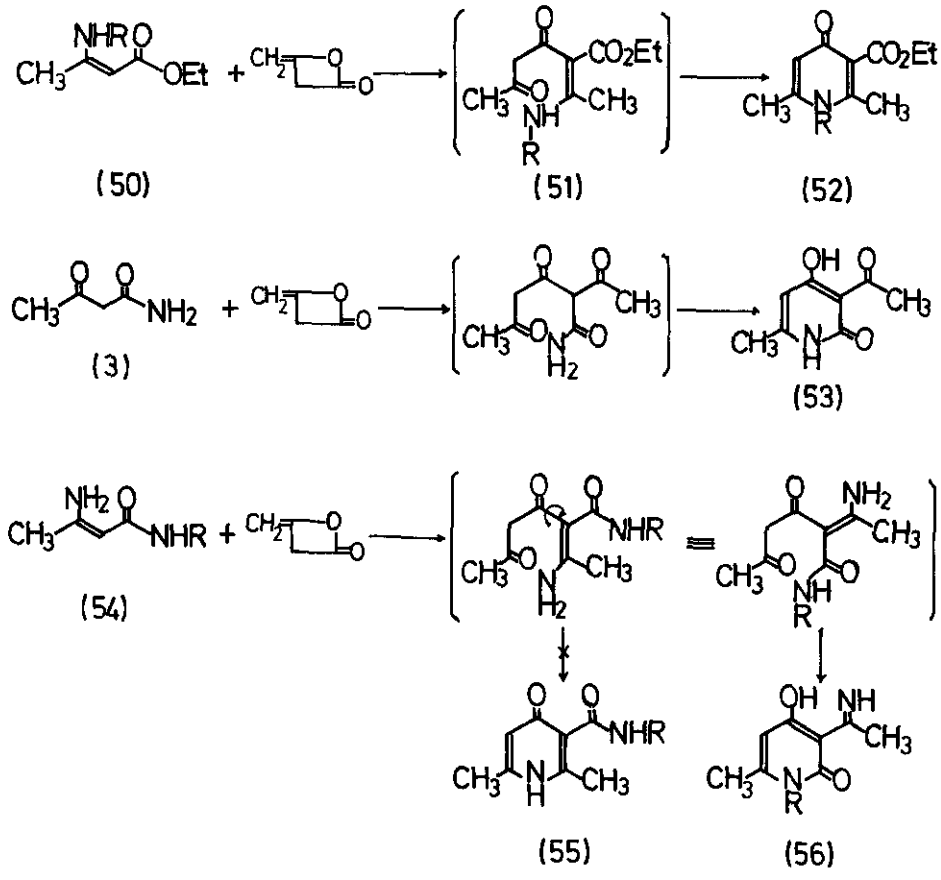
(51, R=H), formed by acylation of α-carbon of 2. Employing the same procedure, ethyl β-anilinocrotonate (50, R=phenyl) reacted with diketene to give the corresponding 4-pyridone carboxylic ester (52, R=phenyl).[29,30,31]

Acetoacetamide (3) was refluxed with diketene in benzene in the presence of triethylamine to give 3-acetyl-4-hydroxy-6-methyl-2(1H)-pyridone (53).[32] Furthermore, when this reaction was carried out in aqueous sodium hydroxide with ice-cooling, 53 was obtained in better yield.[33] In this case diketene attacks the α-carbon of 3 in the first stage to form α-acetoacetylacetoacetamide as an intermediate.

In addition, β-aminocrotonamide (4 or 54, R=H) also reacts with diketene easily to afford a pyridone derivative. In this reaction the amido nitrogen of 4 or 54(R=H) participates in the cyclization to give 3-acetimidoyl-4-hydroxy-6-methyl-2(1H)-pyridone (56, R=H) as that of acetoacetamide (3) does. However, in this case the formation of 2,6-dimethyl-4(1H)-pyridone-3-carboxamide (55), which would be generated by participation of β-amino group, was not observed. Similarly, only 56($R=CH_3$) was obtained from N-methylamido compound (54, $R=CH_3$) in low yield, but 55($R=CH_3$) was not isolated.[15]

Moreover, each of 1, 2, 3 and 4 reacts with diketene to give the corresponding cyclized compounds, and their intermediates are α-acetoacetyl derivatives, formed by the electrophilic attack of diketene to α-carbon of 1-4. However, it is noteworthy that the direction of the subsequent cyclization reaction is different in each case.

Chart 13

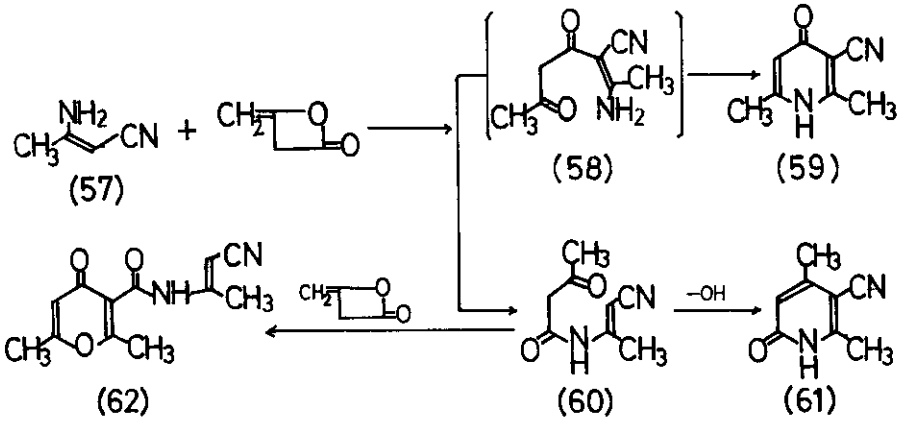


Finally, β-aminocrotononitrile (57), related to acetoacetamide derivatives, reacted with diketene to give 3-cyano-2,6-dimethyl-4(1H)-pyridone (59) and β-acetoacetamidocrotononitrile (60). The yields of 59 and 60 are reaction condition dependent.

As described previously in the reaction of 1-4, it is obvious that 59 is formed via the α-acetoacetyl intermediate. Using excess

of diketene, 62 was also obtained. Furthermore, 60 was heated with alkali to transform easily into the cyclized compound (61).[30]

Chart 14



Conclusion

The reactions of amino derivatives of acetoacetic acid were described in this review. Especially, our attentions were focused upon the synthesis of heterocyclic compounds using 3 and 4. In future, the reactions of these compounds should be investigated in more detail from view point of not only their own reactivities but also synthetic approach of heterocycles.

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References

1) H. Precht, Ber., 11, 1193 (1878).

2) C. Duisberg, Annalen., 213, 133 (1882).

3) L. Claisen and K. Meyer, Ber., 35, 583 (1902).

4) J. N. Collie, Annalen., 226, 294 (1884).

5) F. Chick and N. T. M. Wilsmore, J. Chem. Soc., 97, 1978 (1910).

6) T. Kato, H. Yamanaka and T. Shibata, Tetrahedron, 23, 2965 (1967).

7) A. Hantzsch, Annalen, 231, 37 (1885).

8) A. Hantzsch, Ber., 23, 1474 (1890).

9) E. Benary, Ber., 44, 495 (1911).

10) e.g., R. C. Elderfield, Heterocyclic Compounds, 1, 462 (1959), John Wiley & Sons, Inc., New York.

11) T. Kato, H. Yamanaka, and T. Shibata, Chem. and Pharm. Bull. (Japan), 15, 921 (1967).

12) T. Kato, H. Yamanaka, T. Shibata, and J. Kawamata, Chem. and Pharm. Bull. (Japan), 16, 1835 (1968).

13) (a) L. Claisen and H. Hasse, Ber., 33, 3775 (1900); (b) M. Viscontini and H. Köhler, Helv. Chim. Acta, 37, 41 (1951); (c) J. N. Collie, Annalen, 226, 294 (1884); (d) E. Benary, Ber., 42, 3912 (1909); (e) T. Kato, H. Yamanaka, and J. Kawamata, J. Pharm.

Soc. Japan, 89, 1637 (1969).

14) T. Kato, H. Yamanaka, and T. Shibata, J. Pharm. Soc. Japan, 87, 955 (1967).

15) T. Kato, H. Yamanaka, and J. Kawamata, Chem. and Pharm. Bull. (Japan), 17, 1889 (1969).

16) T. Kato, H. Yamanaka, and S. Konno, J. Pharm. Soc. Japan, 90, 509 (1970).

17) T. Kato, H. Yamanaka, and J. Kawamata, J. Pharm. Soc. Japan, 89, 460 (1969).

18) T. Kato, H. Yamanaka, and J. Kawamata, Chem. and Pharm. Bull. (Japan), 17, 2411 (1969).

19) e.g., E. D. Bergmann, Org. Reactions, Vol. 10, R. Adams Ed., John Wiley & Sons, Inc., New York, 1959, p. 179.

20) N. F. Albertson, J. Amer. Chem. Soc., 70, 669 (1948).

21) U. Schmidt, Angew. Chem., 69, 138 (1957).

22) H. G. O. Becker, J. prakt. Chem., 12, 294 (1961).

23) T. Kato and M. Noda, Chem. and Pharm. Bull. (Japan), 22, 2947 (1974).

24) T. Kato, H. Yamanaka, H. Fukumi, and M. Noda, J. Pharm. Soc. Japan, 93, 1437 (1973).

25) B. D. Wilson, J. Org. Chem., 28, 314 (1963).

26) T. Kato, H. Yamanaka, S. Konno, and H. Shimomura, J. Pharm. Soc. Japan, 90, 606 (1970).

27) T. Kato, M. Noda, submitted for publication.

28) T. Kato and T. Hozumi, Chem. and Pharm. Bull (Japan), 20, 1574 (1974).

29) E. Ziegler, I. Herbst, and Th. Kappe, Monatsh., 100, 132 (1969).

30) T. Kato, H. Yamanaka, and T. Hozumi, J. Pharm. Soc. Japan, 91,

740 (1971).

31) T. Kato, H. Yamanaka, Y. Yamamoto, and T. Sakamoto, J. Pharm. Soc. Japan, 90, 613 (1970).

32) S. Seto, H. Sasaki and K. Ogura, Bull. Chem. Soc. Japan, 39, 281 (1966).

33) T. Kato and Y. Kubota, J. Pharm. Soc. Japan, 89, 1477 (1969).

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