Recent Synthetic Studies Using Diketene

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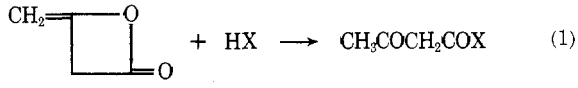
In 1908, Chick and Wilsmore[1] isolated a pungent oil during the course of the preparation of ketene monomer. They postulated that it was a dimer of ketene and suggested that the structure CH_3CO-$CH{=}C{=}O$ (acetylketene) best represented the reactions of the new compound. Since then, because of its extraordinary reactivity and utility, diketene has received increasing attention in both academic and industrial research. Though diketene is a small molecule, $C_4H_4O_2$, it took 40 years to establish its structure definitely as 4-methylene-2-oxetanone (**1**).[2]

The present Account describes recent synthetic research utilizing diketene.[3] Emphasis is placed on reactions of diketene with nitrogen compounds such as amines to give N-heterocyclic compounds.

Most reactions of diketene fall into the category of addition reactions with concomitant opening of the β-lactone ring. Diketene is an enol lactone of acetoacetic acid, and its most typical reaction is acylation of a nucleophile to give an acetoacetic acid derivative (see eq 1).



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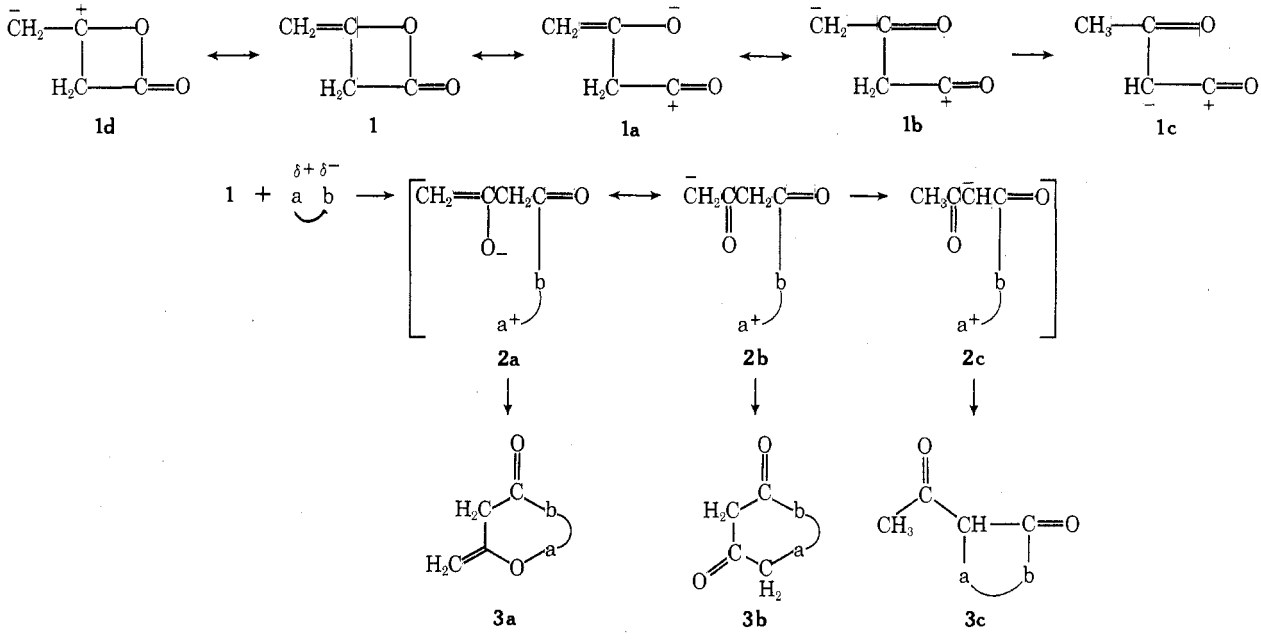
X = OH, NH_2, NHR, OR, halogen, etc.

Other typical reactions involve cycloaddition of double bonds to diketene to give heterocyclic compounds; these also involve opening of the β-lactone ring of diketene. These reactions do not however appear to be concerted cycloadditions.[4]

For the purpose of symbolizing the reactivity of diketene, it is convenient to refer to structural representations **1a–d** (see eq 2). Of these, **1a** and **1b** are no-bond resonance structures, and **1d** is also a canonical form. **1c** is not a canonical form of diketene, but rather a tautomeric form.

Actually, a more fundamental understanding of the diverse patterns of reactivity of diketene is obtained by consideration of the probable dipolar intermediates which result from heterolytic cleavage of the β-lactone ring through attack on the carbonyl carbon by the nucleophilic terminus of an attacking double or triple bond. As shown in eq 3, if the attacking reagent has polarity $a^{\delta+}$–$b^{\delta-}$, the immediate product of heterolytic cleavage is a resonance hybrid of structures **2a** and **2b**, and it may subsequently cyclize to structure **3a** and/or **3b** in consequence of the fact that both nucleophilic oxygen and a nucleophilic carbon exist in the intermediate. Alternatively, tautomerization to structure **2c** may occur, and cyclization affords product **3c**. For convenience



Tetsuzo Kato was born in Soma, Fukushima Prefecture, and did his undergraduate work at Tokyo Imperial University, from which he graduated in 1943. His Ph.D. studies were also done at Tokyo, under Eiji Ochiai. He was Assistant Professor and then Professor at the Tokyo College of Pharmacy, Women's Division, 1951–1959, except for 1 year spent in postdoctoral work with J. F. Bunnett at the University of North Carolina. Since 1959, he has been Professor in the Pharmaceutical Institute of Tohoku University.

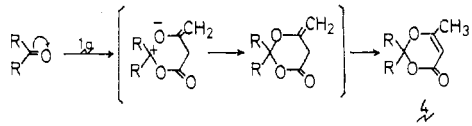
(1) F. Chick and N. T. M. Wilsmore, *J. Chem. Soc.*, **93**, 946 (1908).

(2) *E.g.*, (a) A. B. Boese Jr., *Ind. Eng. Chem.*, **32**, 16 (1940); (b) C. D. Hurd and C. A. Blanchard, *J. Amer. Chem. Soc.*, **72**, 1461 (1950).

(3) For reviews previously reported see (a) G. Quadbeck, *Angew. Chem.*, **68**, 351 (1956); (b) R. N. Lacey, "Advances in Organic Chemistry, Methods and Results," Vol. 2, Interscience, New York, N. Y., 1960, p 240; (c) R. N. Lacey, "The Chemistry of Alkenes," S. Patai, Ed., Interscience, London, 1964, p 1182; (d) Y. Etienne and N. Fischer, "The Chemistry of Heterocy-

of notation I will refer to forms **1a–1d** in pointing out the pattern of reactivity which prevails in particular cases.

For example, the reaction of diketene with a ketone, such as acetone or acetophenone, which gives a dioxane derivative (**4**),[5] can be considered a 1,4 dipolar addition of the C=O double bond of the ketone to **1a** (eq 4). 1,4 dipolar addition of the C=N double bond of 1-benzylpyrazoline (**5**) to **1b** gives rise to a pyrazolopyridone derivative (**6**)[6] (eq 5). In some of the reactions discussed below, we will encounter reactivity such as suggested by form **1c**; *e.g.*, see the formation of **44** from **43** in eq 7.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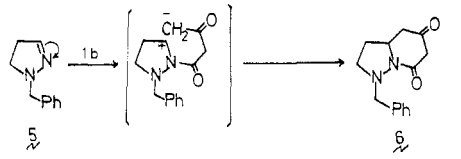

(5)

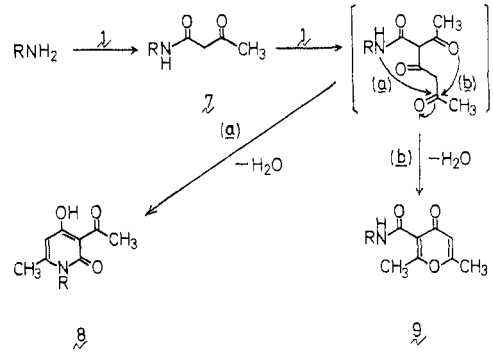
Some reactions of diketene involve only the olefinic double bond, keeping the β-lactone ring intact. For instance, the homolytic addition of mercaptans to diketene gives rise to γ-alkylthio-β-butyrolactones.[7] Similarly, β-butyrolactone is obtained in 93% yield by reduction of diketene with palladium on charcoal at 0°.[8]

Reaction with Amines to Give Pyridone and Pyrone Derivatives

It has long been known that primary amines react with diketene to give acetoacetamides (**7**) in good yield. Although there have been many reports concerning reactions of diketene with primary and secondary amines, the products described have been mostly limited to acetoacetamides (**7**).[9] However, when we carried out the reaction in the presence of a basic catalyst, such as triethylamine, we obtained either a 1-substituted 3-acetyl-4-hydroxy-6-methyl-2-pyridone (**8**) or an N-substituted 2,6-dimethyl-4-pyrone-3-carboxamide (**9**). For instance, aniline reacted with diketene in benzene to give acetoacetanilide (**7**, R = Ph), but reaction in the presence of a catalytic amount of triethylamine afforded a 40% yield of **8** (R = Ph) accompanied by a 3% yield of **7** (R = Ph). Several *para*-substituted anilines (anisidine, toluidine, *p*-bromoaniline, and ethyl *p*-aminobenzoate) also were converted to pyridone derivatives (**8**). However, *p*-nitroaniline gave the pyrone derivative (**9**, R = *p*-nitrophenyl) in 16% yield as well as an acetoacetamide (**7**).[10]

Aliphatic amines also gave acetoacetamides (**7**), but reaction in an NaOH solution in the cold afforded both **8** and **7**. For instance, methylamine gave a 28% yield of a pyridone derivative (**8**, R = Me). Similarly, ethylamine, *n*-propylamine, benzylamine, and ethanolamine gave rise to N-substituted pyridones (**8**). However, isopropylamine, *tert*-butylamine and cyclohexylamine afforded pyrone derivatives (**9**).[11] Amino heterocycles, such as 3- and 4-aminopyridines,[12] and aminotropolone[13,14] reacted with diketene to give pyridones (**8**) or pyrone type compounds (**9**).

Though the mechanism of the formation of pyridones (**8**) and pyrones (**9**) is not clear at present, the basicity of the starting amine seems to influence the product formed. With aliphatic amines, formation of **9** is favored by bulkiness in the alkyl group. If the alkyl group is bulky like *tert*-butyl, ring closure along pathway b is easier than along pathway a, resulting in the formation of **9**.



Reaction with Enamines to Give N-Heterocycles

Although there is a considerable literature dealing with the reaction of enamines with ketene, little attention had been given to their reactions with diketene. Hünig[15a] and Millward[15b] reported reactions of diketene with enamines such as 1-morpholinocyclohexene and 1-dimethylamino-4-methylcyclohexa-1,3-diene to give 2-methyl-5,6,7,8-tetrahydrochromone and 2,6-dimethyl-7,8-dihydrochromone, respectively.

The enamines discussed in the literature are mostly those in which the nitrogen atom is tertiary. Our work has principally concerned reactions of so-called secondary and primary enamines of structural types of C=C—NHR and C=C—NH_2, respectively.

Ziegler[16] reported that ethyl β-aminocrotonate (or

clic Compounds. Heterocyclic Compounds with Three- and Four-membered Rings," Part 2, A. Weissberger, Ed., Interscience, New York, N. Y., 1964, p 733; (e) L. F. Fieser and M. Fieser, "Reagents for Organic Synthesis," Wiley, New York, N. Y., 1964, p 264; (f) D. Borrmann in "Houben-Weyl's Methoden der Organischen Chemie," E. Müller, Ed., Band VII/4, Georg Thieme Verlag, Stuttgart, 1968, p 226.

(4) *E.g.*, (a) R. Huisgen, R. Grashey, and J. Sauer, "Cycloaddition Reaction of Alkenes," S. Patai Ed., Interscience, London, 1964, p 741; (b) H. Ulrich, "Cycloaddition Reactions of Heterocumulens," Academic Press, New York, N. Y., 1967, p 22.

(5) M. F. Carroll and A. R. Bader, *J. Amer. Chem. Soc.*, **75**, 5400 (1953).

(6) Farbwerke Hoechst A.-G., French Patent, 1,441,937 (1966); *Chem. Abstr.*, **66**, 55492*e* (1967).

(7) C. W. Theobald, U. S. Patent, 2,763,664 (1956); *Chem. Abstr.*, **49**, 4722*a* (1955).

(8) J. Sixt, U. S. Patent 2,763,664 (1956); *Chem. Abstr.*, **51**, 5117*c* (1957).

(9) *E.g.*, (a) R. N. Lacey and E. E. Connolly, British Patent 715,896 (1954); *Chem. Abstr.*, **49**, 13290*d* (1955); (b) A. Stocker, German Patent 1,142,859 (1963); *Chem. Abstr.*, **59**, 7377*a* (1963).

(10) T. Kato and Y. Kubota, *Yakugaku Zasshi*, **87**, 1212 (1967).

(11) T. Kato and Y. Kubota, *Yakugaku Zasshi*, **89**, 1477 (1969).

(12) (a) T. Kato, H. Yamanaka, T. Niitsuma, K. Wagatsuma, and M. Oizumi, *Chem. Pharm. Bull.*, **12**, 916 (1964); (b) T. Kato, H. Yamanaka, and H. Moriya, *Yakugaku Zasshi*, **84**, 1201 (1964); (c) T. Kato, H. Yamanaka, N. Katagiri, and S. Masuda, *Chem. Pharm. Bull.*, **20**, 133 (1972).

(13) S. Seto, H. Sasaki, and K. Ogura, *Bull. Chem. Soc. Jap.*, **39**, 281 (1966).

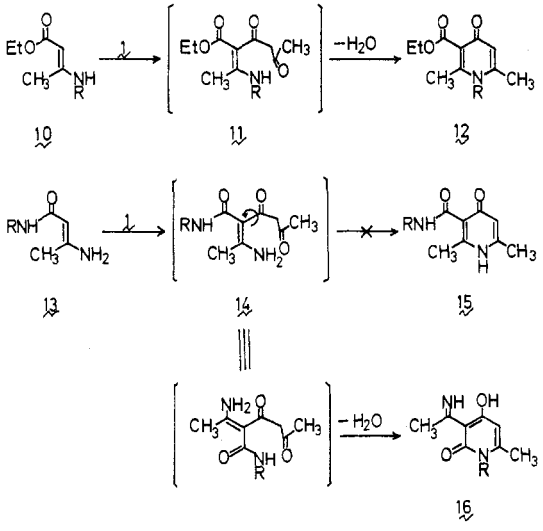
(14) H. Toda, *Yakugaku Zasshi*, **87**, 1351 (1967).

(15) (a) S. Hünig, E. Benzing, and K. Hübner, *Chem. Ber.*, **94**, 486 (1961); (b) B. B. Millward, *J. Chem. Soc.*, 26 (1960).

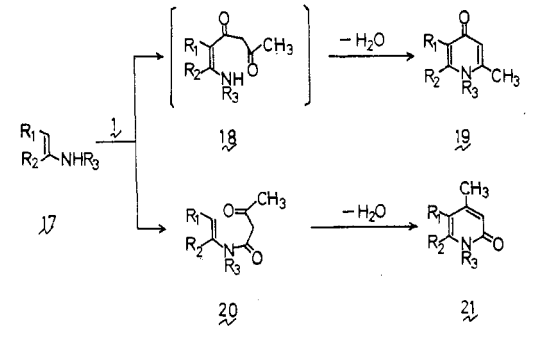
(16) E. Ziegler, I. Herbst, and Th. Kappe, *Monatsh. Chem.*, **100**, 132 (1969).

β-anilino-) (**10**, R = H, Ph) reacted with diketene to give ethyl 2,6-dimethyl-4-pyridone-3-carboxylate (**12**, R = H, Ph). However, reaction of β-aminocrotonamide (**13**, R = H, Me) under the same conditions did not give the corresponding 2,6-dimethyl-4-pyridone derivative (**15**, R = H, Me), but rather 3-acetimidoyl-4-hydroxy-6-methyl-2-pyridone (**16**, R = H, Me).[17]

The first stage of both reactions was presumably the same, giving *C*-acetoacetyl derivatives (**11** and **14**) as intermediates, but the amide nitrogen of **14**, even in the case of a secondary amide (**14**, R = Me), seemed to be more active than the enamine nitrogen, resulting in ring closure to **16**.



Usually, such enamines as **17** (where R_1 = CO_2Et, COMe, COPh; R_2 = Me, Ph; R_3 = H, Ph) afford the corresponding 4-pyridone derivative (**19**).[16,18-20] However, with β-aminocrotononitrile (**17**, R_1 = CN, R_2 = Me, R_3 = H) and β-aminocinnamonitrile (**17**, R_1 = CN, R_2 = Ph, R_3 = H) there was not only acetoacetylation of their enamine carbons to give **19** *via* **18**, but also acetoacetylation of their enamine nitrogens to form acetoacetamides (**20**, R_1 = CN, R_2 = Me, Ph, R_3 = H). The latter, on treatment with alkali, cyclized readily to 5-cyano-4,6-dimethyl-2-pyridone and 5-cyano-4-methyl-6-phenyl-2-pyridone (**21**, R_1 = CN, R_2 = Me, Ph, R_3 = H).[19]



(17) T. Kato, H. Yamanaka, J. Kawamata, and H. Shimomura, *Chem. Pharm. Bull.*, **17**, 1889 (1969).
(18) T. Kato, H. Yamanaka, Y. Yamamoto, and T. Sakamoto, *Yakugaku Zasshi*, **90**, 613 (1970).
(19) T. Kato, H. Yamanaka, and T. Hozumi, *Yakugaku Zasshi*, **91**, 740 (1971).
(20) P. Caramella and A. Querci, *Synthesis*, 42 (1972).

Reaction with C=N Double Bonds to Give N-Heterocycles

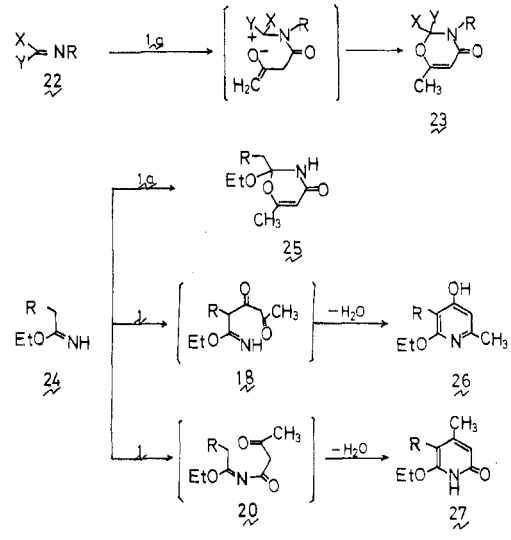
It is well known that diketene reacts with urea, thiourea, amidines, and guanidine to give pyrimidine derivatives.[21] Lacey,[22] who investigated these reactions in detail, found that some urea derivatives such as S-alkylthioureas (*e.g.*, **22**, R = H, X = NH_2, Y = SR) did not afford the pyrimidones expected by analogy with the well-known reactions of *S*-alkylthioureas with acetoacetic ester. Instead, they gave 3,4-dihydro-2-alkylthio-2-amino-6-methyl-2*H*-1,3-oxazin-4-one derivatives (**23**, R = H, X = NH_2, Y = SR), from which 2-alkylthio-6-methyl-4-pyrimidones were obtained by treatment with a basic catalyst.

Similarly, N,N′-disubstituted derivatives of *S*-alkylisothioureas (**22**, X = NHR, Y = SR) and *N,N′*-diphenylguanidines (**22**, R Ph, X = NHPh, Y = NH_2) gave the corresponding 1,3-oxazine derivatives (**23**). Such oxazine derivatives were also obtainable by the reactions of diketene with carbodiimide[23] and ammonium thiocyanate.[24]

Ketimines such as benzhydrylidenimine (**22**, R = H, X = Y = Ph), 1,2-diphenylethylidenimine (**22**, R = H, X = Ph, Y = $PhCH_2$), and 1-phenylpropylidenimine (**22**, R = H, X = Ph, Y = Et) reacted with diketene to give the corresponding oxazine derivatives (**23**) in good yield.[25] Also, addition of diketene to the C=N double bond of an imidate like ethyl benzimidate (**22**, R = H, X = Ph, Y = OEt) gave rise to a cyclic oxazine adduct (**23**, R = H, X = Ph, Y = OEt). Aliphatic imidates like ethyl acetimidate (**24**, R = H) and ethyl phenacetimidate (**24**, R = $PhCH_2$) were converted to the corresponding 1,3-oxazine derivatives (**25**).[26]

Such reactions to give oxazine derivatives (**23**, **25**) are in effect 1,4 additions of the C=N double bond to diketene, as suggested by structure **1a**.

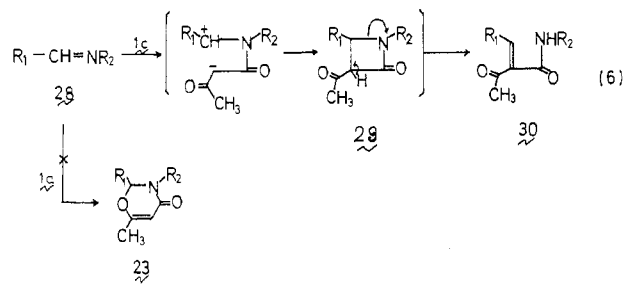
On the other hand, reaction of diketene with imid-



(21) *E.g.*, (a) A. B. Boese Jr. U. S. Patent 2,138,756 (1938); (b) R. N. Lacey, British Patent 699,812 (1953); *Chem. Abstr.*, **49**, 2527*f* (1955).
(22) R. N. Lacey, *J. Chem. Soc.*, 846 (1958).
(23) R. N. Lacey and W. R. Ward, *J. Chem. Soc.*, 2134 (1958).
(24) V. Gunar, L. Overchkina, and S. Zavyalov, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1078 (1965).
(25) T. Kato and T. Sakamoto, *Yakugaku Zasshi*, **87**, 1322 (1967).
(26) T. Kato and Y. Yamamoto, *Chem. Pharm. Bull.*, **15**, 1334 (1967).
(27) T. Kato, H. Yamanaka, Y. Yamamoto, and M. Kondo, *Yakugaku Zasshi*, **92**, 886 (1972).

ates such as ethyl 1-ethoxyformimidoylacetate (**24**, R = CO_2Et) and ethyl cyanoacetimidate (**24**, R = CN) did not afford an oxazine adduct (**25**) but gave ethyl 2-ethoxy-4-hydroxy-6-methylpyridine-3-carboxylate (**26**, R = CO_2Et) and 6-ethoxy-4-methyl-2-pyridone-5-carbonitrile (**27**, R = CN), respectively.[27] These reactions resemble the reactions of enamines described above. Imidates of type **24**, in which R is an electron-attracting group such as CN or ethoxycarbonyl, presumably exist at least in part as enamine tautomers similar to that of β-aminocrotononitrile (**17**, R_1 = CN, R_2 = Me, R_3 = H). In consequence, *C*- and *N*-acetoacetyl derivatives (**18**, **20**) are formed as intermediates, and they undergo ring closure to 4- and 2-pyridone derivatives (**26**, **27**), respectively.

Addition of diketene to the C=N double bond of Schiff bases (**28**) also afforded adducts. However, the products were not oxazines (**23**) but α-alkylideneacetoacetamide (**30**).[28] Although details of the mechanism of formation of **30** are not clear at present, a likely pathway is shown in eq 6. Addition of diketene, as suggested by structure **1c**, to the C=N double bond of the Schiff base is postulated to give rise to the four-membered cyclo intermediate **29**, which, by prototropy, is transformed to **30**. This mechanism accounts for the fission of the C=N double bond of the Schiff base.

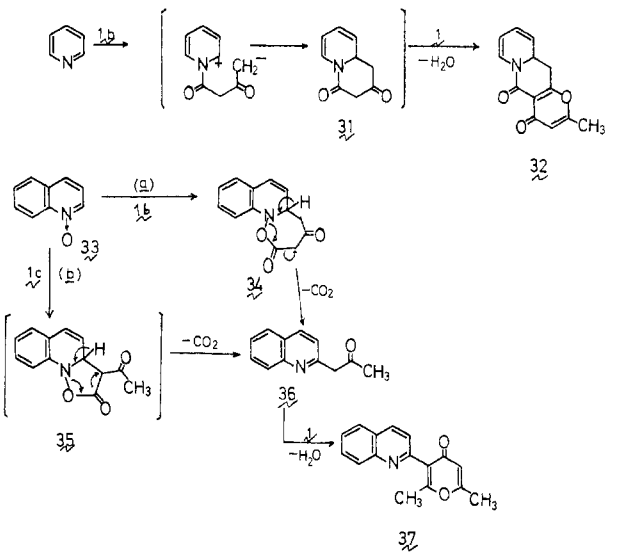


Reaction with Pyridine and Quinoline Derivatives

Pyridine is known to be an effective catalyst for the dimerization of diketene to dehydroacetic acid.[1] However, we found that reaction of diketene and pyridine afforded a small amount of a pure bright yellow crystalline substance,[29] which is known as the Wollenberg compound (**32**). This compound was originally prepared by passing ketene gas into pyridine.[30,31]

The first stage of this reaction is perhaps 1,4 addition of the C=N double bond of pyridine to diketene as suggested by canonical form **1b** to give an intermediate quinolizine derivative (**31**), which reacts with another mole of diketene to give the Wollenberg compound (**32**). Quinoline, isoquinoline, and phenanthridine also reacted with diketene to give Wollenberg type compounds, and in much better yields.[29,32-34]

Pyridine *N*-oxide was recovered unchanged from attempted reaction with diketene, but quinoline *N*-oxide (**33**) reacted giving 3-(2′-quinolyl)-2,6-dimethyl-4-pyrone (**37**).[35,36] Though there are several possible mechanisms, it seems probable that the initial step is cycloaddition of quinoline *N*-oxide to diketene as suggested by either the **1b** or **1c** structure to form, respectively, an intermediate oxazepinoquinoline derivative (**34**) (path a) or an isoxazoloquinoline derivative (**35**) (path b). Both intermediates can undergo decarboxylation to give 2-acetonylquinoline (**36**), which can react with another mole of diketene, followed by cyclization to give **37**. Actually, the reaction of quinoline *N*-oxide with excess diketene in acetic acid at room temperature afforded **36** as a stable product. On treatment with diketene, **36** was converted to **37** in very good yield.

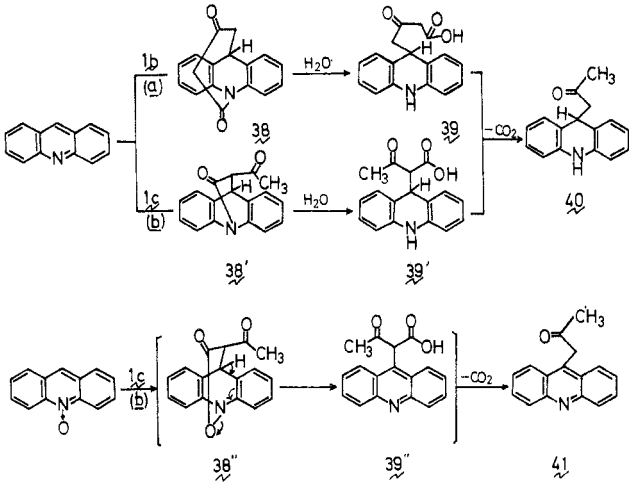


Acridine and acridine *N*-oxide reacted with diketene to give 9-acetonylacridan (**40**) and 9-acetonylacridine (**41**), respectively.[37,38] A probable mechanism is as follows: cycloaddition of diketene to the 9 and 10 positions of acridine gives a 9,10-bridged acridan intermediate, either the dibenzo-1-azabicyclo[4.2.2]decane derivative (**38**) (path a) or the dibenzo-1-azabicyclo[2.2.2]octane derivative (**38′**) (path b). Whichever is formed is then transformed to γ-(9-acridanyl)acetoacetic acid (**39**) or α-(9-acridanyl)acetoacetic acid (**39′**), respectively, and subsequent decarboxylation gives 9-acetonylacridan (**40**).

A similar pathway is suggested for the reaction of acridine *N*-oxide. Addition of diketene (**1c**) to the oxygen and the C-9 of acridine *N*-oxide gives rise to the dibenzo-1-aza-2-oxabicyclo[3.2.2]nonane derivative (**38″**) which can be further transformed to α-(9-acridyl)acetoacetic acid (**39″**). Decarboxylation of **39″** gives **41**.

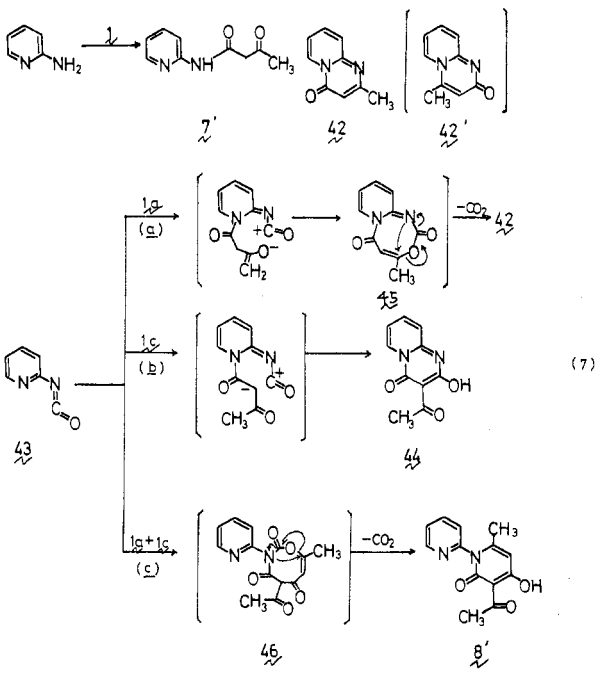
As described above, the reactions of 3- and 4-aminopyridines with diketene produced 2-pyridone (**8**) and 4-pyrone (**9**) derivatives.[13] However, 2-aminopy-

(28) (a) T. Kato and Y. Yamamoto, *Chem. Pharm. Bull.*, **13**, 959 (1965); (b) T. Kato, Y. Yamamoto, H. Sekita, and T. Sakamoto, *Yakugaku Zasshi*, **87**, 691 (1967).
(29) T. Kato, T. Kitakawa, and Y. Yamamoto, *Yakugaku Zasshi*, **83**, 267 (1963).
(30) O. Wollenberg, *Chem. Ber.*, **67**, 1675 (1934).
(31) J. A. Berson and W. M. Jones, *J. Amer. Chem. Soc.*, **78**, 1625 (1956).
(32) T. Kato and T. Kitakawa, *Yakugaku Zasshi*, **84**, 874 (1964).
(33) T. Kato and Y. Yamamoto, *Chem. Pharm. Bull.*, **14**, 752 (1966).
(34) T. Kato and T. Kawamata, *Yakugaku Zasshi*, **87**, 597 (1967).
(35) T. Kato and H. Yamanaka, *Chem. Pharm. Bull.*, **12**, 18 (1964).
(36) T. Kato, H. Yamanaka, T. Sakamoto, and T. Shiraishi, *Chem. Pharm. Bull.*, **22**, 1206 (1974).
(37) T. Kato and Y. Yamamoto, *Chem. Pharm. Bull.*, **15**, 1426 (1967).
(38) T. Kato, T. Chiba, and M. Daneshtalab, *Heterocycles*, **2**, 315 (1974).



ridine did not give a 2-pyridone (8) or 4-pyrone (9) derivative, but rather 2-acetoacetamidopyridine (7′ or 7, R = 2-pyridyl) and 2-methyl-4*H*-pyrido[1,2-*a*]pyrimidin-4-one (42).[13,39,40] It is noteworthy that though 4-methyl-2*H*-pyrido[1,2-*a*]pyrimidin-2-one (42′) would be expected to form, only the 4-one derivative (42) was obtained.

Reaction of 2-pyridyl isocyanate (43) with diketene gave rise to 42, 3-acetyl-2-hydroxy-4*H*-pyrido[1,2-*a*]pyrimidin-4-one (44), and 3-acetyl-4-hydroxy-6-methyl-1-(2-pyridyl)-2-pyridone (8′ or 8, R = 2-pyridyl).[41] A plausible mechanism for the formation of these products is shown in eq 7: namely, diketene adds, as suggested by canonical form **1a**, to the ring nitrogen and isocyanate carbon of 43 to produce the pyridooxadiazocine intermediate (45) (path a). Rearrangement of the latter, accompanied by decarboxylation, gives rise to 42. 44 probably is obtained by the addition of diketene along path b as suggested by structure **1c**. Furthermore, addition of 2 mol of diketene to the N=C double bond of the isocyanate group (path c) perhaps gives a 1,3-oxazocine type intermediate (46), which, on ring contraction, is transformed to acetylpyridone derivative (8′ or 8, R = 2-pyridyl).

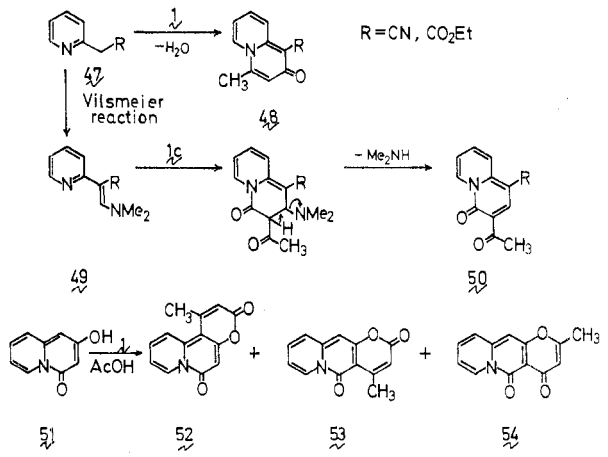


(7)

Reaction of 2-pyridineacetonitrile (47, R = CN) with diketene gave rise to 4-methyl-2-oxo-2*H*-quinolizine-1-carbonitrile (48, R = CN).[42] This reaction is similar to the reaction of a secondary enamine which gives a 2-pyridone derivative. That is to say, addition of diketene to the active methylene of the cyanomethyl moiety gives the C-acetoacetylated product, followed by ring closure to give 48.

Vilsmeier reactions of 47 (R = CN, CO_2Et) afforded enamines such as 49 (R = CN, CO_2Et), which reacted with diketene giving quinolizine derivatives (50).[43] This can be explained by 1,4 addition of diketene to 49 as suggested by structure **1c**.

Kappe[44] reported the reaction of 2-hydroxy-4-oxo-4*H*-quinolizine (51) with diketene in acetic acid to give pyranoquinolizine derivatives, 52, 53, and 54, in 60, 5, and 2% yields, respectively. It is of interest to note that 54 is the dehydro derivative of the Wollenberg compound (32).



Cycloaddition to the C=C Double Bond of Diketene to Give Spiro Compounds

As already mentioned, diketene undergoes a variety of ring-opening reactions to afford acetoacetyl derivatives and heterocyclic compounds. However, little is known about reactions of the C=C double bond which occur while the integrity of the β-lactone linkage is maintained. As described previously, catalytic reduction of diketene gives β-butyrolactone in good yield.[9] Also, reactions of alkylthiols with diketene gave rise to the lactone derivatives, γ-alkylthio-β-butyrolactones.[8,45]

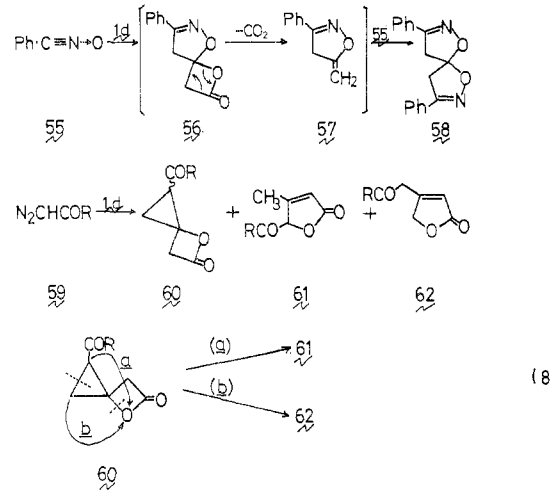
d'Alontres[46] reported the reaction of benzonitrile oxide (55) with diketene to give 3,3′-diphenyl-5,5′-spiro[2-isoxazoline] (58) in 35% yield. In this reaction, a substance containing a β-lactone ring, namely 56, is a probable intermediate. Decarboxylation to 57

(39) T. Kato, H. Yamanaka, N. Katagiri, and S. Masuda, *Chem. Pharm. Bull.*, **20**, 142 (1972).
(40) H. L. Yale, B. Toepelitz, J. Z. Gougoutas, and M. Puar, *J. Heterocycl. Chem.*, **10**, 123 (1973).
(41) T. Kato and S. Masuda, *Chem. Pharm. Bull.*, **22**, 1542 (1974).
(42) (a) T. Kato and T. Atsumi, *Yakugaku Zasshi*, **87**, 961 (1967); (b) Th. Kappe, I. Herbst, and E. Ziegler, *Monatsh. Chem.*, **100**, 136 (1969).
(43) T. Kato and T. Chiba, *Yakugaku Zasshi*, **89**, 464 (1969).
(44) Th. Kappe and Y. Linnau, *Justus Liebigs Ann. Chem.*, 761 25 (1972).
(45) G. A. Hull, F. A. Daniher, and T. F. Conway, *J. Org. Chem.*, **37**, 1837 (1972).
(46) G. Stagno d'Alontres, G. Cum, and M. Gattuso, *Ric. Sci.*, **37**, 750 (1967).

and addition of another molecule of **55** give **58.** Similarly, it is reported that *C*-benzoyl-*N*-phenylazomethine oxide undergoes similar reactions for which spiro compounds have been proposed as intermediates.[47]

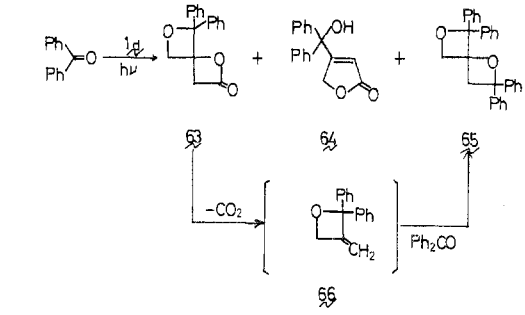
When diazoacetophenone (**59**, R = Ph) was heated with diketene in the presence of copper powder, two isomeric spiro compounds, *trans*-2-benzoyl-1-hydroxycyclopropaneacetic acid β-lactone and its cis isomer (**60**, R = Ph), were obtained. A similar reaction with ethyl diazoacetate (**59**, R = OEt) afforded the spiro product (**60**, R = OEt), ethyl 2,5-dihydro-3-methylfuran-5-one-2-carboxylate (**61**, R = OEt), and ethyl 2,5-dihydrofuran-2-one-4-acetate (**62**, R = OEt).[48]

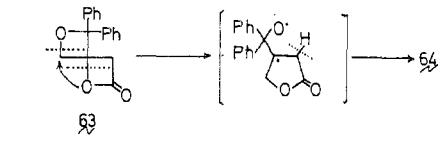
There are several possible mechanisms for the formation of these products. A likely possibility is that addition of a carbene generated from the diazo compound (**59**) to the C=C double bond of diketene gives the spiro compound **60.** Rearrangement along path a or b then yields isomer **61** or **62**, respectively (eq 8). The mechanism of rearrangement is uncertain.



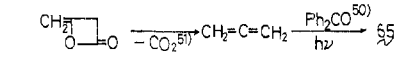
(8)

As described previously, heterolytic addition of diketene to ketones such as acetone and acetophenone gives rise to cycloadducts, 2,2-disubstituted 6-methyl-1,3-dioxan-4-ones (**4**) (eq 4). However, photoreaction of ketones with diketene gives spiro compounds.[49] For instance, when benzophenone was allowed to react with diketene under irradiation with ultraviolet light, a 25% yield of 2,2-diphenyl-3-hydroxy-3-oxetaneacetic acid β-lactone (**63**), a 9% yield of 4-diphenylhydroxymethyl-2,5-dihydrofuran-2-one (**64**), and a 25% yield of 1,1,6,6-tetraphenyl-2,5-dioxaspiro[3.3]heptane (**65**) were obtained. The formation of such products can be explained as follows: photoaddition of the benzophenone carbonyl to the olefinic double bond of diketene in form **1d** produces the spirooxetane derivative **63.** Somewhat as **62** is obtained from **60**, **64** would be obtainable from **63** (eq 9). The formation of **65** can be explained similarly to the formation of **58** from **55**, that is, decarboxylation of **63** gives rise to the oxetane intermediate (**66**), to which benzophenone adds to give **65.** Spirooxetane **65** is a known compound, which was prepared by the photoaddition of benzophenone to allene.[50] Since decomposition of diketene yields allene under certain conditions,[51] this is another possible pathway to **65** (eq 10).





(9)



(10)

Synthesis of Peptides, Antibiotics, Amino Acids, and Lichen Metabolites

This section is concerned with the synthesis of natural products and concentrates on the chemistry of diketene products, rather than on reactions of diketene itself.

Diketene reacts with α-amino esters to give 5-substituted 3-acetyl-tetramic acids.[52] Applying this reaction, Büchi[3e,53] reported the reaction of diketene with *S*-benzyl-L-cysteine ethyl ester to give 3-acetyl-5-benzylthiomethyltetramic acid, from which holomycin, an antibiotic isolated from *Streptomyces griseus*, was prepared.

D'Angeli[3e,54] reported that α-*N*-acetoacetylamino acids (AcA-aa) were obtained in high yield by the reaction of amino acids with diketene in the presence of sodium hydroxide. Condensation with amino acid esters or analogous nucleophiles under standard conditions yields N-AcA-peptides. The acetoacetyl group was selectively removed by hydroxylamine hydrochloride. The resulting peptide was easily separated from the isoxazoline which was produced from the acetoacetyl moiety. Almost quantitative retention of configuration was observed in the synthesis of a few oligopeptides.

Bromination of diketene followed by ethanolysis gives rise to ethyl γ-bromoacetoacetate (**68**).[1] D'Alo[55] used this compound as a starting material

(47) M. C. Aversa, G. Cum, G. Stagno d'Alontres, and N. Uccella, *J. Chem. Soc., Perkin Trans. 1*, 222 (1972).

(48) T. Kato and N. Katagiri, *Chem. Pharm. Bull.*, **21**, 729 (1973).

(49) T. Kato, M. Sato, and Y. Kitagawa, *Chem. Pharm. Bull.*, submitted for publication.

(50) *E.g.*, (a) D. R. Arnold and A. H. Glick, *Chem. Commun.*, 813 (1966); (b) H. Gotthard, R. Steinmetz, and G. S. Hammond, *J. Org. Chem.*, **33**, 2774 (1968).

(51) R. T. Conley and T. F. Futledge, U. S. Patent 2,818,456 (1957); *Chem. Abstr.*, **52**, 6391*f* (1958).

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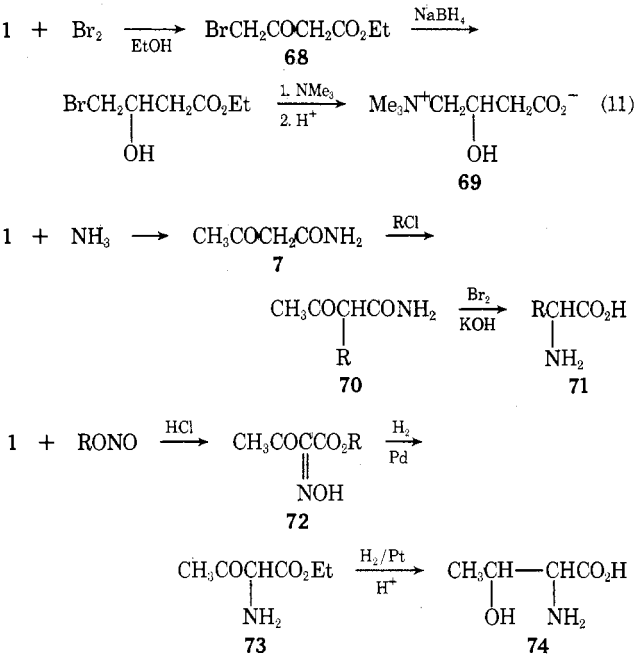
(55) F. D'Alo and A. Masserini, *Farmaco (Pavia), Ed. Sci.*, **19**, 30 (1964).

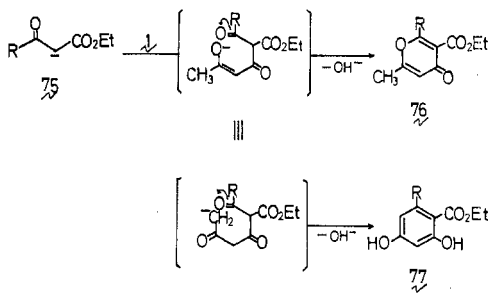
for the synthesis of carnitine (**69**), a betaine derivative found in the flesh of horses, hogs, and calves (eq 11).

Acetoacetamide (**7**) is most readily prepared from the reaction of diketene with ammonia.[1,56] Yamato[57] used this sequence in the first stage of a novel and simple method for the synthesis of α-amino acids (**71**). Acetoacetamide (**7**) was treated with an alkyl halide to give an α-alkylacetoacetamide (**70**), which, on treatment with bromine in a KOH solution, was transformed to an α-amino acid (**71**). For example, reaction of α-isobutylacetoacetamide (**70**, R = isobutyl) gave *dl*-leucine in 50% yield. This is a simultaneous Hofmann and haloform reaction of the amide and acetyl moiety of **70**.

When dry HCl was bubbled into a solution of diketene and an alkyl nitrite, such as ethyl nitrite or amyl nitrite, in ether at room temperature, alkyl α-hydroxyiminoacetoacetate (**72**) was obtained in *ca.* 60% yield. Catalytic reduction of **72** (R = Et) with Pd/C in ethanolic hydrochloride gave a quantitative yield of ethyl α-aminoacetoacetate (**73**), which, upon further catalytic reduction with Pt/C in water, followed by hydrolysis, afforded α-amino-β-hydroxybutyric acid (**74**), from which threonine and allothreonine were isolated.[58]



When ethyl acetoacetate (**75**, R = Me) was allowed to react with diketene in the presence of NaH in tetrahydrofuran, ethyl 2,4-dihydroxy-6-methylbenzoate (**77**, R = Me) and ethyl 2,6-dimethyl-4-pyrone-3-carboxylate (**76**, R = Me) were obtained in 38 and 7% yields, respectively.[59] Hydrolysis of **77** (R = Me) with dilute alkali at room temperature afforded orsellinic acid, a known metabolite of lichens and fungi. Similarly, β-keto esters like ethyl β-ketocaproate (**75**, R = n-C_3H_7), ethyl β-ketocaprylate (**75**, R = n-C_5H_{11}), and ethyl β-ketocaprinoate (**75**, R = n-C_7H_{15}) reacted with diketene to yield esters of lichen metabolites, ethyl divarate (**77**, R = n-C_3H_7), ethyl olivetolcarboxylate (**77**, R = n-C_5H_{11}), and ethyl sphaeropherolcarboxylate (**77**, R = n-C_7H_{15}), respectively, in about 40% yield.



Since orsellinic acid is a precursor of a number of other natural products, and the synthetic methods previously reported for such metabolites are not always satisfactory, our method provides a more accessible route to these products.

Conclusions

The most fundamental reaction of diketene is addition, and falls into the following categories: (a) addition to give acetoacetyl derivatives; (b) addition to give cyclic (mostly heterocyclic) compounds, and (c) addition of the C=C double bond of diketene to give β-butyrolactone derivatives. The first two modes of reaction (a and b) usually involve ionic mechanisms. In contrast, the last (c) usually involves radical intermediates.[45]

In this Account much emphasis has been placed on use of diketene for the synthesis of heterocyclic compounds. Employment of diketene reactions for the synthesis of natural products should attract considerable interest in the future.

The author wishes to acknowledge his many coworkers, who are named in the references, for their intellectual and experimental contributions to our work.

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(59) T. Kato and T. Hozumi, *Chem. Pharm. Bull.*, **20**, 1574 (1972).