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169. **Tetsuzo Kato and Yutaka Yamamoto :** Studies on Ketene and Its Derivatives. XVII.*[1] Reaction of Diketene with Imidates.

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Reactions of diketene with iminoethers such as benziminoethylether and phenacetiminoethylether were investigated. Refluxing of benziminoethylether with diketene in ether afforded 2-ethoxy-6-methyl-2-phenyl-3,4-dihydro-2*H*-1,3-oxazin-4-one (I) and 6-methyl-2-phenyl-4*H*-1,3-oxazin-4-one (II). Phenacetiminoethylether reacted with diketene to give 2-benzyl-2-ethoxy-6-methyl-3,4-dihydro-2*H*-1,3-oxazin-4-one (IV), 3-acetyl-2,6-dibenzyl-4-hydroxypyrimidine (V) and N-acetoacetyl-α-phenylacetamide (VI). The structure assignments of these compounds were described.

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Previous works in this series[1~3] have shown the reactions of diketene with the C=N double bond of aromatic heterocycles such as quinoline or that of Schiff bases to give the Wollenberg's compound[4,5] or the alkylidene acetoacetamides respectively. The continuous investigation was undertaken to see if the C=NH double bond such as imidates was reacted with diketene in a similar fashion as reported before. And we found that the reaction proceeded in a different manner to result in the formation of the oxazine derivatives, which is reported in the present paper.

When a solution of benziminoethylether and diketene in ether was refluxed, colorless needles, m.p. 87~88° (I), and colorless needles, m.p. 140~141.5° (II), were obtained. Elemental analyses and molecular weight determinations provided their empirical formulae as $C_{13}H_{15}O_3N$ (I) and $C_{11}H_9O_2N$ (II) respectively.

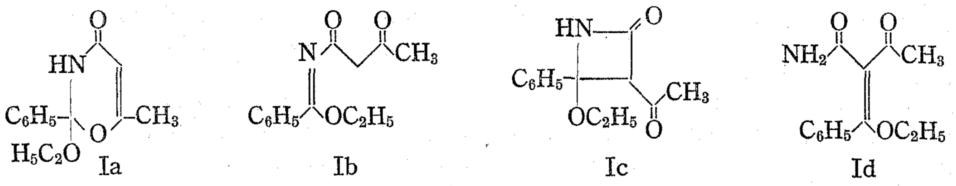
Ia Ib Ic Id

Chart 1.

Of the four probable structures (Ia~d) for the former compound (I), we propose the structure Ia is the most reasonable one on the basis of spectral data. Infrared spectrum of I indicated the existence of NH at 3425 cm^{-1} and only one carbonyl band at 1681 cm^{-1}. The existence of these absorption bands contradicts the possibilities of the structures Ib and Ic.*[3] The NMR spectrum of I shows such signals of methyl protons and olefinic proton as are observed in the case of the allyl group. No signal due to the enolic proton was observed. These data described above contradict the structure Id

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*[1] Part XVI : T. Kato, Y. Yamamoto, H. Sekita, T. Sakamoto : Yakugaku Zasshi, **87**, 691 (1967).

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*[3] If the structure Ic were correct, the absorption of the four membered imide carbonyl could be observed at *ca.* 1745 cm^{-1} (K. Nakanishi : IR Absorption Spectroscopy-Practical, p. 52, Nanzando (1960)).

1) T. Kato, T. Kitagawa, Y. Yamamoto : Yakugaku Zasshi, **83**, 267 (1963).
2) T. Kato, T. Kitagawa : *Ibid.*, **84**, 874 (1964).
3) *Idem* : This Bulletin, **13**, 959 (1965).
4) O. Wollenberg : Ber., **67**, 1675 (1934).
5) J. Berson, W. Jones : J. Am. Chem. Soc., **78**, 1625 (1956).

and support the structure of 2-ethoxy-6-methyl-2-phenyl-3,4-dihydro-2*H*-1,3-oxazin-4-one (Ia) as the most probable structure for the compound I.

Refluxing of I in benzene afforded readily compound II. Treatment of II with NH_3 gave 4-hydroxy-6-methyl-2-phenylpyrimidine (III) in good yield. The structure of III was confirmed by the comparison of its infrared spectrum and the mixed melting point determination with an authentic sample.6) In the infrared spectrum of II the carbonyl band was observed at $1678\,cm^{-1}$, but no band due to NH or OH was appeared in the region of $3000\,cm^{-1}$. The NMR spectrum of II was essentially similar with that of I, and indicated the existence of methyl and olefinic protons. From these data the structure of II was confirmed to be 6-methyl-2-phenyl-4*H*-1,3-oxazin-4-one.

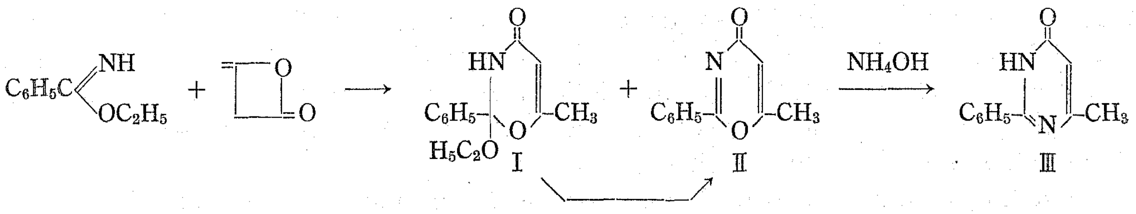

Chart 2.

The reaction of phenacetiminoethylether with diketene under the same condition as above gave colorless needles, m.p. 114∼115° (IV), and colorless needles, m.p. 166∼167.5° (V). Besides, using ether, benzene or acetone containing water as a solvent, compound of m.p. 147∼148° (VI) was obtained as a by-product. Elemental analyses of these compounds provided their empirical formulae as $C_{14}H_{17}O_3N$ (IV), $C_{20}H_{18}O_2N_2$ (V), and $C_{12}H_{13}O_3N$ (VI) respectively.

On heating without a solvent or refluxing in benzene in the presence of acetic acid as a catalyst, IV was converted to compound V. Treatment of IV with ammonia in ethanol gave 2-benzyl-4-hydroxy-6-methylpyrimidine (VII), whose infrared spectrum was identical in every respect with that of an authentic sample7) and no depression in melting point was observed on admixture. Infrared spectrum of IV showed NH band at

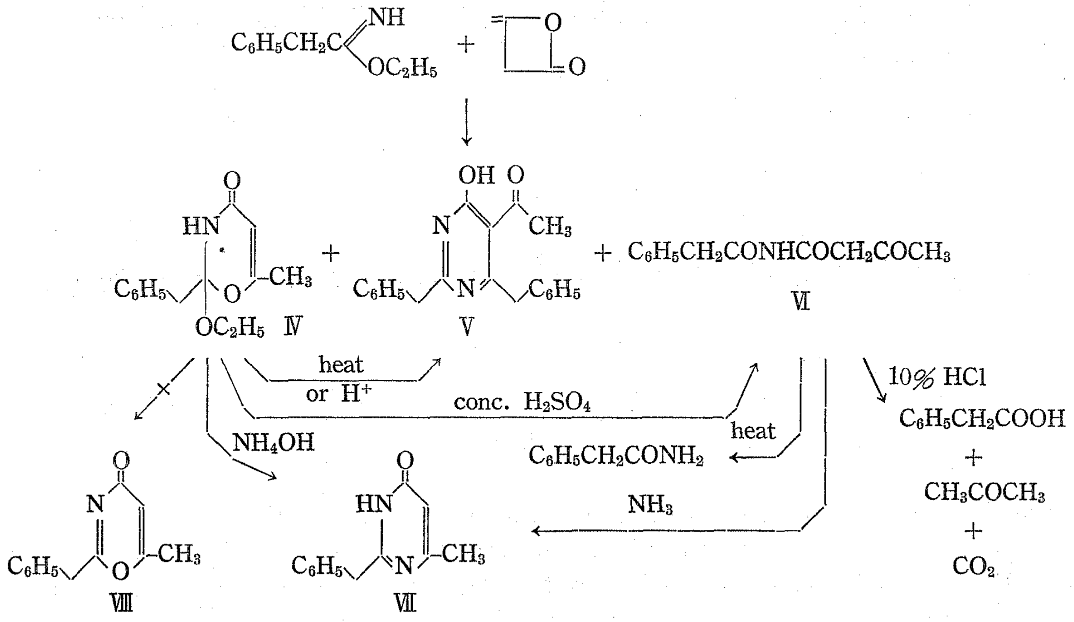

Chart 3.

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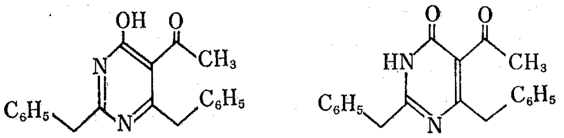
6) A. Pinner: Ber., **23**, 3820 (1890).
7) E. Ochiai, K. Yanai: Yakugaku Zasshi, **60**, 493 (1940).

3401 cm^{-1} and carbonyl band at 1678 cm^{-1}. The NMR spectrum of IV was essentially identical with that of I, that is, characteristic signals due to the 2-substituted 1-propenyl group were observed at 1.95 p.p.m. (methyl protons) and at 5.03 p.p.m. (olefinic proton). These data described above support the structure of 2-benzyl-2-ethoxy-6-methyl-3,4-dihydro-2*H*-1,3-oxazin-4-one for compound IV.

The infrared absorption spectrum of compound V showed the characteristic broad band near 2900 cm^{-1} and the carbonyl band at 1650 cm^{-1}. The NMR spectrum of V indicated the existence of one methyl, two mehylenes and two phenyl groups. Besides, the broad signal due to an enolic proton was observed at 13.3 p.p.m. Although there are some considerable structures for compound V, the spectral data above mentioned support the structure Va or Vb as the most probable one. Acturelly, the infrared spectrum of 4-hydroxypyrimidines usually shows a characteristic broad band at 2900 cm^{-1}, and NMR spectra of III and VII exhibited a broad peak at 13 p.p.m. On the other hand, in the case of the NMR spectum of the acetoacetyl compound, the signal owing to the enolic proton is usually appeared near 13 p.p.m. Accordingly, we assigned the structure of compound V being either Va or Vb.

Though the details of the mechanism of the formation of V is not clear for the present, a likely pathway is shown in Chart 5.



Va Vb

Chart 4.

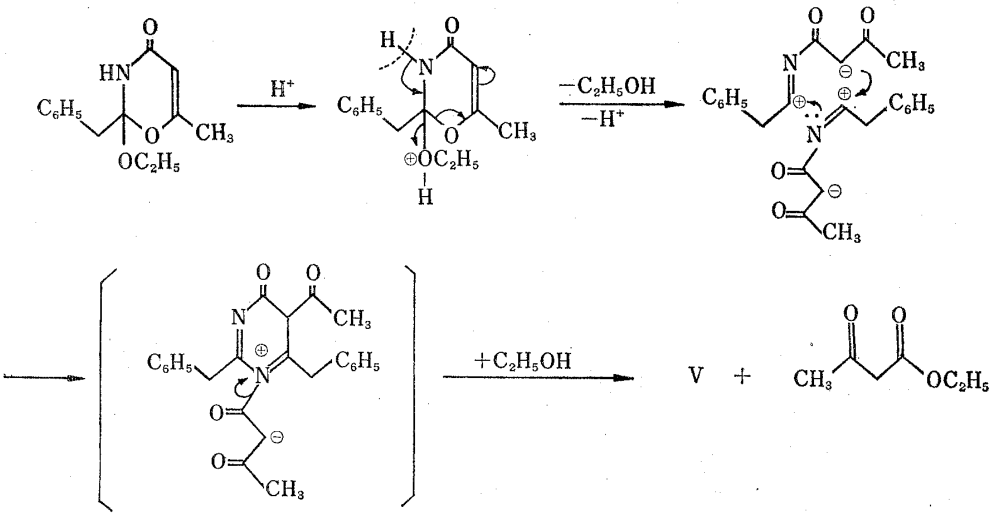
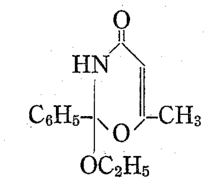
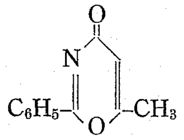
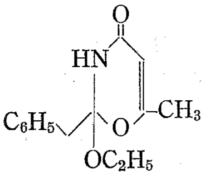
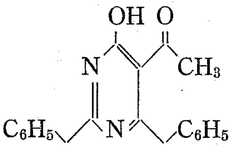
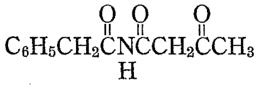


Chart 5.

On passing through a column of neutral alumina using ether as a solvent, IV was easily hydrolyzed to yield compound VI, which was also obtained by the treatment of IV with sulfuric acid. Hydrolysis of VI with 10% HCl gave phenylacetic acid, acetone and carbon dioxide. On heating compound VI was converted to α-phenylacetamide. Treatment of V with liq. ammonia afforded 2-benzyl-4-hydroxy-6-methylpyrimidine (VII). The infrared spectrum of VI showed an NH band at 3436 cm^{-1} and carbonyl bands at 1727, 1704 and 1692 (sh.) cm^{-1}. As shown in Table I, in the NMR spectrum of VI methyl protons (3H, 2.25 p.p.m., singlet), two methylenes (2H, 3.69 p.p.m., singlet; 2H, 3.81 p.p.m, singlet) and ring protons (5H, 7.26 p.p.m., sharp) were observed. Also, it was found that the enol form could be existed in about 30%. From the data mentioned above, VI was confirmed to be N-acetoacetyl-α-phenylacetamide.

Attempts to obtain 2-benzyl-6-methyl-4*H*-1,3-oxazin-4-one (VIII) from IV were unsuccessful.

Table I.

	Compound	δ (p.p.m.)	No. of Protons obs.		J (c/s)
I		1.21	3H	t.	7
		2.33	3H	d.	0.9
		3.7	2H	q.	7
		6.08	1H	q.	0.9
		7.45~8.3	6H (ring H + NH)		
II		2.3	3H	d.	0.8
		6.04	1H	q.	0.8
		7.45~8.3	5H		
IV		1.2	3H	t.	7
		1.95	3H	d.	0.8
		3.18	2H	s.	
		3.61	2H	q.	7
		5.03	1H	q.	0.8
		6.3	1H (NH)	broad	
		7.25	5H		
V		2.45	3H	s.	
		3.9	2H	s.	
		4.01	2H	s.	
		7.25	10H		
		13.3	1H	broad	
VI	 $C_6H_5CH_2\overset{O}{\overset{\|}{C}}\underset{H}{N}\overset{O}{\overset{\|}{C}}CH_2\overset{O}{\overset{\|}{C}}CH_3$	2.0	3H/3	s.	
		2.25	3H	s.	
		3.69	2H	s.	
		3.75	2H/3	s.	
		3.81	2H	s.	
		6.08	1H/3	s.	
		7.26	5H	s.	
		9.18	1H (NH)	broad	

$CDCl_3$ solvent. Relative to tetramethylsilane at 60 Mc.
s=singlet, d=doublet, t=triplet, q=quartet.

Experimental

Reaction of Diketene with Benziminoethylether——A solution of benziminoethylether (6 g.) and diketene (6 g.) in ether (10 ml.) was refluxed for 5 hr. After cooling, petroleum ether (b.p. 35~45°, 50 ml.) was added to the reaction mixture and allowed to stand at room temperature. A yellow oil separated was solidified on cooling, which was collected by suction and washed with ether. The ether washing was condensed and the residue was recrystallized from ether-petroleum ether to give I, colorless needles, m.p. 87~88°. Yield, 2 g. (21.3%). *Anal.* Calcd. for $C_{13}H_{15}O_3N$ (I): C, 66.93; H, 6.48; N, 6.01. Found: C, 66.87; H, 6.26; N, 6.17. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3185, 1695. The ether insoluble substance was purified by recrystallization from ether to give II, colorless prism, m.p. 140~141.5°. Yield, 1.2 g. (16%). *Anal.* Calcd. for $C_{11}H_9O_2N$ (II): C, 70.58; H, 4.85; N, 7.48. Found: C, 70.29; H, 4.99; N, 7.66. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1678.

Reaction of II with Ammonia——In a sealed tube, a solution of II (0.5 g.) in ethanolic NH_3 (15 ml. of EtOH and 15 ml. of 28% NH_4OH) was heated at 80~85° for 5 hr. After cooling, the reaction mitxure was condensed under reduced pressure to give a crystalline substance, which was collected by filtration and recrystallized from acetone giving colorless needles (III), m.p. 214.5~216°, undepressed on admixture with an authentic sample prepared by the method reported by Pinner.6) The filtrate was extracted with $CHCl_3$. From the $CHCl_3$ extract, a small amount of III was obtained. Total yield, 0.3 g. (60%). IR $\nu_{max}^{CHCl_3}$ cm^{-1} : 2700~3200 (broad), 1661. NMR ($CDCl_3$) p.p.m. : 2.39 (-$C\underline{H}_3$); 6.3 ($>C\underline{H}$); 7.48~8.3 (ring H); 13.3 ($N\underline{H}$, broad).

Reaction of Diketene with Phenacetiminoethylether——A solution of phenacetiminoethylether (11.5 g.) and diketene (11.85 g.) in ether (50 ml.) was refluxed for 6 hr. Crystalline solid separated was collected by filtration, washed with ether and recrystallized from ether to give IV as colorless needles, m.p. 114~115°, 9.5 g. (54.6%). *Anal.* Calcd. for $C_{14}H_{17}O_3N$ (IV) : C, 67.99; H, 6.93; N, 5.66. Found : C, 67.86; H, 6.74; N, 5.86. IR $\nu_{max}^{CHCl_3}$ cm^{-1} : 3401, 1678.

The filtrate was condensed under reduced pressure at 50° and allowed to stand at room temperature to give a crystalline substance, which was collected and recrystallized from MeOH to give V as colorless needles, m.p. 166~167.5°, 3 g. (27%). *Anal.* Calcd. for $C_{20}H_{18}O_2N_2$ (V) : C, 75.45; H, 5.70; N, 8.80. Found : C, 75.71; H, 5.92; N, 8.83. IR $\nu_{max}^{CHCl_3}$ cm^{-1} : 3125~2740 (broad), 1650.

Treatment of IV with Sulfuric Acid——The adduct IV (0.2 g.) was dissolved in conc. sulfuric acid (2 ml.). The mixture was warmed on a steam bath for a few minutes and poured into ice. The precipitate appeared was collected and purified by crystallization from EtOH to give VI (0.14 g.) as colorless needles, m.p. 147~148°. *Anal.* Calcd. for $C_{12}H_{13}O_3N$ (VI) : C, 65.74; H, 5.98; N, 6.39. Found : C, 66.01; H, 5.97; N, 6.52. IR $\nu_{max}^{CHCl_3}$ cm^{-1} : 3436, 1727, 1704, 1692 (sh.).

Reaction of IV to give V——i) The adduct IV (2 g.) was heated at 140~145° (bath temperature) for about 20 min. and allowed to stand at room temperature to give a crystalline substance, which was collected, and recrystallized from MeOH to give V (0.8 g.), whose melting point was undepressed on admixture with a specimen obtained in the above run. The residue was purified by distillation giving an oil (0.3 g.) of b.p. 180~190° (bath temperature), which was characterized as ethyl acetoacetate by the comparison of its IR spectrum with that of an authentic sample.

ii) To a suspension of IV (0.3 g.) in benzene (10 ml.) was added a few drops of AcOH. The mixture was refluxed for 1 hr. and condensed to give a crystalline substance. Recrystallization from MeOH gave colorless needles, m.p. 166~167.5°, undepressed on admixture with a specimen of V obtained in the above run. Yield, 0.17 g.

Reaction of IV with Ammonia——A solution of IV (1 g.) in ethanolic NH_3 (10 ml. of EtOH and 20 ml. of 28% NH_4OH) was refluxed. After 1 hr. 10 ml. of NH_4OH was added, and the mixture was refluxed for an additional 2 hr. and condensed under reduced pressure. Crystals separated were collected and recrystallized from benzene to give VII as colorless needles, m.p. 169~170°, undepressed on admixture with an authentic sample of VII7) (m.p. 169~170°, reported m.p. 175°). IR $\nu_{max}^{CHCl_3}$ cm^{-1} : 2700~3000 (broad), 1664. NMR ($CDCl_3$) p.p.m. : 2.25 (-$C\underline{H}_3$, d. J=0.8 c.p.s.); 3.9 ($>C\underline{H}_2$ s.); 6.11 ($>C\underline{H}$, q. J=0.8 c.p.s.); 7.1~7.4 (ring H); 13 ($N\underline{H}$, broad).

Reaction of VI with Ammonia——In a sealed tube, VI (0.37 g.) and liq. NH_3 (5 ml.) were placed. The mixture was allowed to stand at room temperature for 30 min. After evaporation of NH_3, the residue was purified by recrystallization from benzene to give VII, m.p. 169~170°, undepressed on admixture with a specimen of VII obtained in the above run.