peptides containing tyrosine and estrogens and so on, and the other, CySDE and thioglycollate which may be concerned with -S-S- group of oxytocin.

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104. Tetsuzo Kato and Yutaka Yamamoto: Studies on Ketene and Its Derivatives. XI.[*1] Reaction of Diketene with Phenanthridine.

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In 1934, Wollenberg[1] obtained a pure, bright yellow, crystalline substance by passing ketene gas into pyridine, the stoichiometry being $C_5H_5N+4C_2H_2O=C_{13}H_{11}O_3N$(I) $+H_2O$. He made preliminary studies but did not propose a structure. Berson and Jones[2] designated this substance as a Wollenberg's adduct, and after having studied in detail chiefly by degradative investigation they proposed the structure being a dihydropyranoquinolizinedione, either I-a or I-b as shown in Chart 1.

On the other hand, Chick and Wilsmore[3] reported that diketene reacted with pyridine or quinoline yielding crystalline substances, which, however, did not contain nitrogen. They described that pyridine or quinoline seemed to act merely as a catalytic agent, since they could be readily washed out from the mixture, leaving a residue of dehydroacetic acid.

As reported previously,[4] when this reaction was re-examined in our laboratory, the results obtained were at variance with those noted by Chick and Wilsmore. Pyridine does not only a catalyst, but also reacts with diketene forming a so-called Wollenberg's compound (I). In the case of quinoline or isoquinoline, reactions proceed smoothly to give Wollenberg's type compounds (II,III). Furthermore, we proposed the correct structure of these compounds being rather I-a type than I-b type, after having been made the structural assignment on the basis of those infrared absorption spectra.[5]

Recently, the similar conclusion was reported by Taylor[6], who investigated a Wollenberg's compound by degradative reactions establishing the correct structure as 2-methyl-10 *a*, 11-dihydro-4*H*,5*H*-pyrano [2,3-*b*]quinolizine-4,5-dione (I-a).

This reaction might well involve the addition of two moles of diketene with the C=N double bond in a heterocyclic ring, followed by dehydration giving a dihydropyranoquinolizine ring system. This paper describes an unexpected reaction of diketene with phenanthridine under the same condition to give an intermediate adduct as a stable substance, which was not isolated in the case of pyridine, quinoline or isoquinoline.

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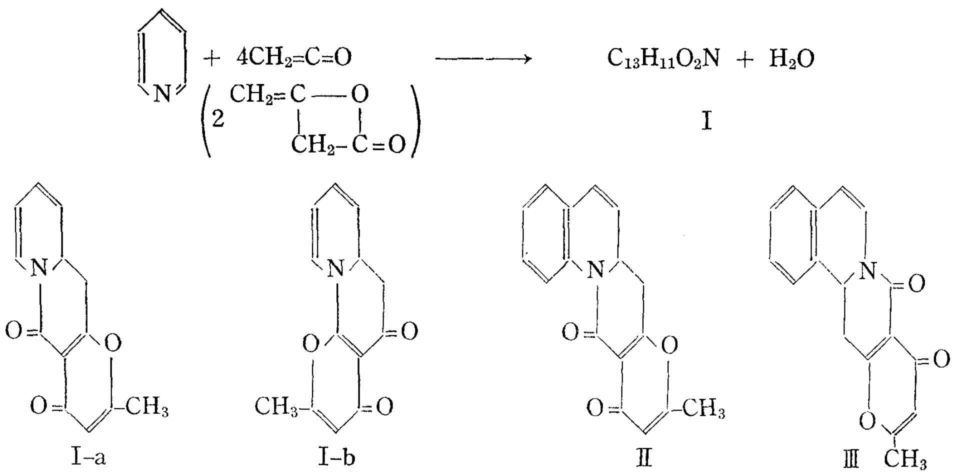

Chart 1.

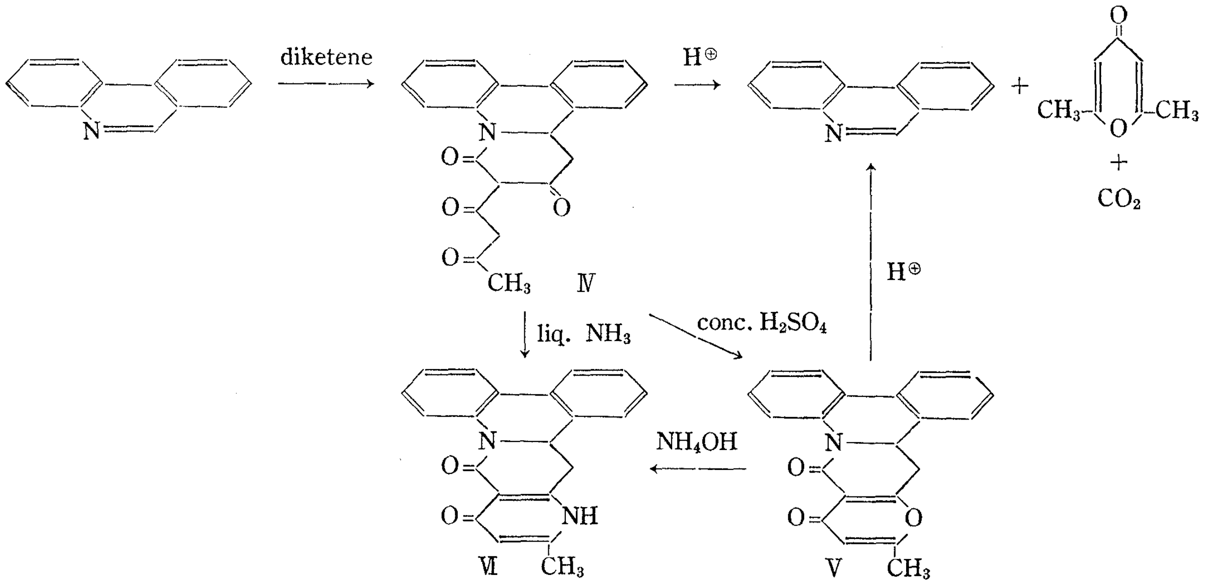

Chart 2.

Refluxing of a solution of diketene and phenanthridine in acetone gave colorless needles of m.p. 185~186° (decomp.). Elemental analysis and molecular weight determination provided its empirical formula $C_{21}H_{17}O_4N$ (IV), which is consisted with the adduct structure formed from one mole of phenanthridine and two moles of diketene, but not with the Wollenberg's type structure (V).

Hydrolysis of IV with hydrochloric acid afforded phenanthridine, 2,6-dimethyl-4-pyrone and carbon dioxide. In considering these facts, we assumed that the structure of IV might be a molecular compound between phenanthridine and dehydroacetic acid which was formed by dimerization of diketene. However, this assumption was contradicted by the following facts; that is, 1) isolation of phenanthridine by alumina chromatography failed, 2) efforts to obtain a molecular compound between dehydroacetic acid and phenanthridine were unsuccesful, and 3) in the mass spectrum of IV a parent peak occurs at m/e 347, and no $C_8H_8O_4$ ion (dehydroacetic acid) is present in this spectrum.

The infrared absorption spectrum of IV exhibits a characteristic peak at 1724 cm^{-1}, which eliminates in the case of compound (V), and the nuclear magnetic resonance (NMR) absorption spectrum is shown in Table I.

TABLE I. Nuclear Magnetic Resonance Spectra[a]

Compound	τ-Value[b]	Multiplicity
IV	7.74(3H)	singlet
	6.25, 5.83(2H)	AB quartet (J=15 c.p.s.)
	6.7 (2H)	multiplet
	5.2 (1H)	〃
	−7.7 (1H)	broad
V	7.73(3H)	doublet (J=0.3 c.p.s.)
	6.47(2H)	multiplet
	5.14(1H)	〃
	3.92(1H)	quartet (J=0.3 c.p.s.)
VI	7.51(3H)	doublet (J=0.3 c.p.s.)
	6.2 (2H)	multiplet
	5.08(1H)	〃
	3.43(1H)	quartet (J=0.3 c.p.s.)

[a] Spectra were obtained on a Varian A-60 spectrometer using $CDCl_3$ as solvent and tetramethylsilane as internal standard.

[b] Aromatic ring protons of phenanthridine were not assigned.

Treatment of IV with conc. sulfuric acid in ethanol gave a Wollenberg's type compound (V), for which both the infrared and ultraviolet absorption spectra suggestive of I-a type structure. Reaction of IV with ammonia afforded a pyridone structure compound (VI), which was also obtainable from V as shown in Chart 2.

It is of interest to see that hydrolysis of IV as well as V under acidic conditions gave phenanthridine. Similarly, I and II were hydrolyzed under the same condition to give pyridine and quinoline respectively.

Although the detailes of the mechanism of hydrolysis is not clear for the present, a likely pathway is shown in Chart 3.

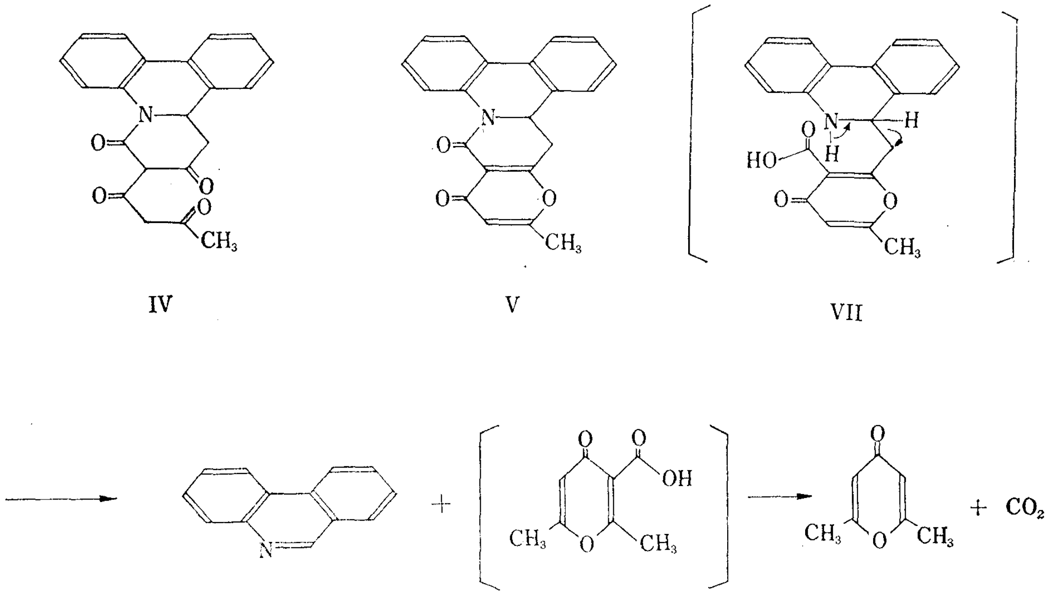

Chart 3.

That is, it will be easily understood that the dehydration of IV gave V under acidic conditions, and the subsequent stage might well involve the hydrolysis of amide to give compound (VII), followed by prototropy to result in the fission of C-C linkage to give phenanthridine and Ⅷ which transformed to 2,6-dimethyl-4-pyrone by decarboxylation.

Experimental

Reaction of Diketene with Phenanthridine——A solution of phenanthridine (15 g.) and diketene (30 g.) in 50 ml. of acetone was refluxed for 5.5 hr. The reaction mixture was condensed under reduced pressure to give a reddish residue, to which MeOH was added and scrubbed with a glass rod to give a crystalline solid. Recrystallization from $CHCl_3$-EtOH afforded colorless needles of m.p. 185~186°(decomp.), 8 g. (27%). *Anal.* Calcd. for $C_{21}H_{17}O_4N$ (Ⅳ): C, 72.61; H, 4.93; N, 4.03. mol. wt., 347.35. Found: C, 72.36; H, 4.89; N, 4.21. mol. wt. (mass spectroscopy), 347. IR ν_{max}^{KBr} cm^{-1} : 1724, 1664, 1616, 1587 (shoulder), 1570 (shoulder), 1560.

Reaction of IV with Conc. Sulfuric Acid——To a suspension of 1 g. of Ⅳ in 50 ml. of EtOH, was added a few drops of conc. H_2SO_4. The mixture was heated in a sealed tube on a steam bath for 30 min. After being condensed to 10 ml., the reaction mixture was allowed to stand at room temperature. Crystals separated were collected. Recrystallization from EtOH gave light brown needles of m.p. 238°(decomp.), 0.4 g. (43%). *Anal.* Calcd. for $C_{21}H_{15}O_3N$ (Ⅴ): C, 76.58; H, 4.59; N, 4.25. Found: C, 76.88; H, 4.77; N, 4.28. IR ν_{max}^{KBr} cm^{-1} : 1681, 1653 (shoulder), 1608.

Reaction of IV with Liq. Ammonia——In a pyrex sealed tube 0.5 g. of Ⅳ, 40 ml. of EtOH and 10 ml. of liq. NH_3 were placed. The reaction mixture was allowed to stand at room temperature for 2 hr. After evaporation of NH_3 and EtOH, the resulted crystalline solid was recrystallized from EtOH to give colorless needles of m.p. 251°(decomp.), 0.38 g. (80%). *Anal.* Calcd. for $C_{21}H_{16}O_2N_2$ (Ⅵ) : C, 76.81; H, 4.91: N, 8.53. Found : C, 76.60; H, 4.66; N, 8.56. IR ν_{max}^{KBr} cm^{-1} : 1642, 1608 (shoulder), 1585.

Reaction of V with Ammonia——In a sealed tube 150 mg. of Ⅴ, 10 ml. of EtOH and 15 ml. of NH_4OH (28%) were placed. The reaction mixture was heated in a steam bath for 1 hr. After evaporation of NH_3 and the solvent, the resulted crystalline solid was recrystallized from EtOH to give Ⅵ (m.p. 249~250°(decomp.)), whose infrared spectrum was identical with that of a specimin obtained in the above run.

Hydrolysis of IV——A suspension of 0.6 g. of Ⅳ in 25 ml. of 15% HCl was refluxed for 4 hr. The reaction mixture turned gradually to a clear solution, and evolution of CO_2 gas was identified (as $BaCO_3$). After cooling the mixture was condensed *in vacuo*, made alkaline with K_2CO_3, and extracted with $CHCl_3$. The $CHCl_3$ soluble fraction was dried over anhydrous K_2CO_3, evaporated to give a residue, which was purified by crystallization from petroleum ether giving 0.31 g. of phenanthridine (m.p. 107°) and 0.07 g. of 2,6-dimethyl-4-pyrone (m.p. 131~132°), both of whose melting point test did not depress with the corresponding authentic samples.

Ⅳ (0.5 g.), conc. HCl (3 ml.) and 95% EtOH (20 ml.) were placed in a pyrex sealed tube, and the mixture was heated at 100° for 2 hr. Employing the same treatment as above, phenanthridine (0.22 g.) and 2,6-dimethyl-4-pyrone (0.1 g.) were obtained.

Following the similar procedure given for the above run, the reaction of Ⅳ (0.5 g.) with 15 ml. of conc. HCl at 110~115° for 5 hr. afforded 0.15 g. of phenanthridine and 0.05 g. of 2,6-dimethyl-4-pyrone.

Hydrolysis of V——A suspension of Ⅴ (0.15 g.) in 10 ml. of 20% HCl was refluxed for 3 hr. After cooling, the reaction mixture was made alkaline with K_2CO_3 and extracted with ether. The ether layer was dried over K_2CO_3, condensed to give a crystalline solid. Recrystallization from petroleum ether gave 0.06 g. of phenanthridine and 0.02 g. of 2,6-dimethyl-4-pyrone.

Summary

Diketene reacts with phenanthridine giving an adduct (Ⅳ). Treatment of Ⅳ with conc. sulfuric acid in ethanol affords a Wollenberg's type compound (Ⅴ). Both of Ⅳ and Ⅴ react with ammonia to give a pyridone compound (Ⅵ). Hydrolysis of Ⅳ and Ⅴ in acidic solution gives phenanthridine, 2,6-dimethyl-4-pyrone and carbon dioxide.

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