STUDIES ON THE REACTIVITY OF ISOQUINOLINE AND RELATED COMPOUNDS. II. ADDITION REACTION OF DIKETENE WITH ISOQUINOLINE AND RELATED COMPOUNDS IN ACIDIC MEDIA.

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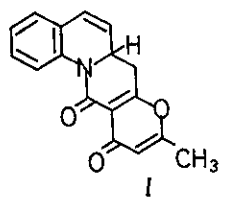
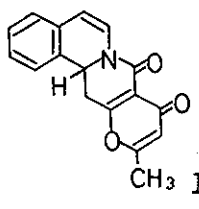
Addition of diketene in formic, acetic or propionic acid to isoquinoline afforded 1-acetonyl-2-acyl-1,2-dihydroisoquinoline (Va-c) in satisfactory yields. The same reaction was observed to occur in phthalazine and 1,6-naphthyridine.

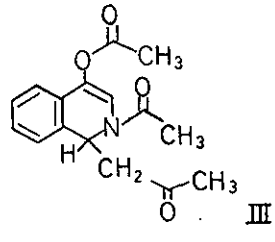
Recently, Kato, et al.[1] reported that diketene reacted with azanaphthalenes such as quinoline and isoquinoline in a nonpolar aprotic solvent to give the so-called Wollenberg type compounds (tetracyclic benzoquinolizine derivatives) (I and II). On the other hand, the authors[2] observed that addition reaction of diketene to 4-acetoxyisoquinoline in acetic acid yielded 1-acetonyl-



I



II

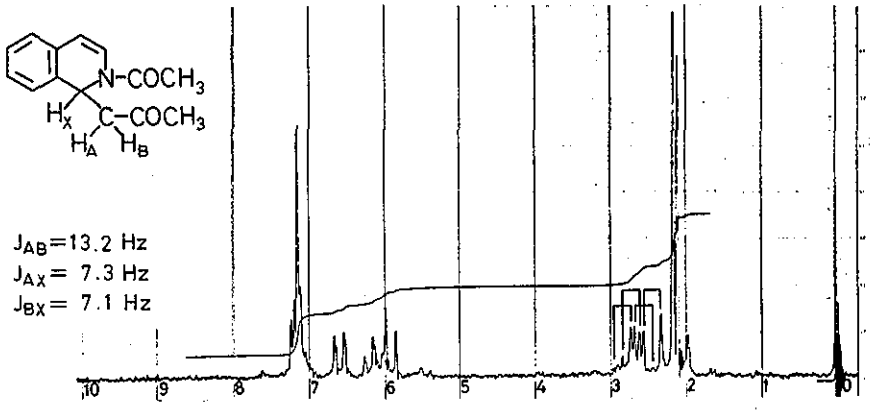


III

2-acetyl-4-acetoxy-1,2-dihydroisoquinoline (III). This fact predicts that in acidic medium the reaction of diketene with aromatic heterocycles might undergo in a path way different from the case when a nonpolar aprotic solvent is used.

In accord with this expectation, we investigated the reaction of diketene with isoquinoline (IV) and related compounds using carboxylic acids as solvents, which is described in this communication.

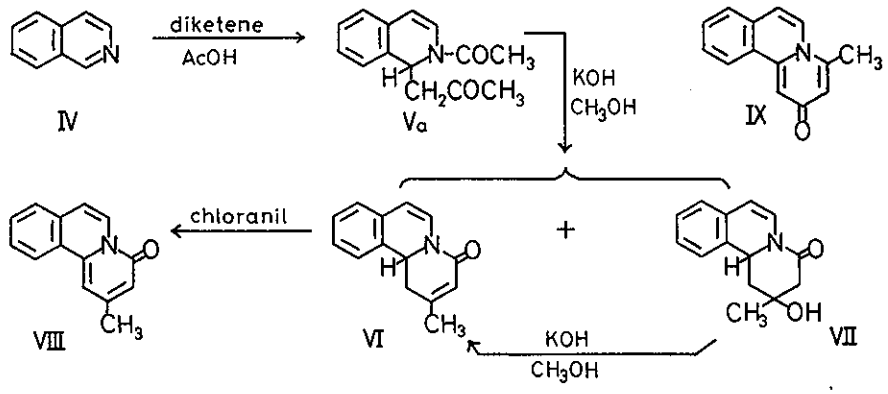
When IV was allowed to react with five molar excess of diketene in glacial acetic acid at 20-30° for 10 hr, a dark red liquid was obtained. Purification of the reaction muxture by column chromatography (Al_2O_3-Et_2O) gave pale yellow crystals of 100-101°(43%), $C_{14}H_{15}O_2N$ (Va). The IR spectrum ($CHCl_3$) of Va shows absorption bands at 1670 and 1710 cm^{-1}, which are assignable to the amide and the aiphatic ketone carbonyl groups, respectively. As shown below, the NMR spectrum ($CDCl_3$) of Va exhibits signals due to two acetyl methyls and a $-\overset{|}{C}H-CH_2-$ group. Analysis of the NMR spectrum with the aid of double resonance experiments shows that signals due to the $-\overset{|}{C}H-CH_2-$ group are



observed as an ABX type multiplet. The NMR spectrum also suggests the existence of the rotamers due to the N-acetyl group.

Based on these spectral data, the structure of Va has been proposed as 1-acetonyl-2-acetyl-1,2-dihydroisoquinoline which was confirmed as follows.

On heating with KOH in CH_3OH, Va was converted into pale yellow prisms of mp 113-116°(47%), $C_{14}H_{13}ON$ (VI) together with the formation of colorless needles of mp 136-137°(17%), $C_{14}H_{15}O_2N$ (VII) as a by-product.



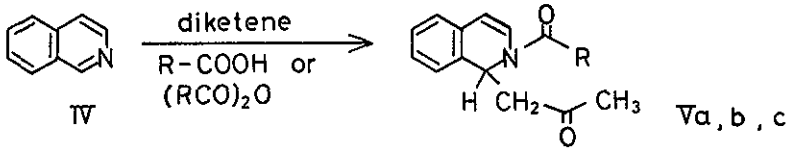
Based on the spectral data and the empirical formula, the structures of VI and VII were assigned 2-methyl-4-oxo-1,11b-dihydro-4H-benzo[a]quinolizine and 2-hydroxy-2-methyl-4-oxo-2,-3,4,11b-tetrahydro-4H-benzo[a]quinolizine, respectively. In fact, VII was trasformed into VI by the treatment with KOH under the identical conditions given for the above reaction.

Oxidation of VI with chloranil in benzene afforded its dehydro compound of mp 147-148°(94%), $C_{14}H_{11}ON$ (VIII) whose NMR spectrum showed no signal owing to the methine and methylene protons, and the IR spectrum exhibited an absorption band at 1670 cm^{-1}

owing to the 2-pyridone structure. As reported in the preceding paper[2], we have already obtained 2-oxo-4-methyl-2H-benzo[a]-quinolizine (IX) which was not identical with VIII.

From these observations, it is reasonably concluded that VIII must have the structure of 2-methyl-4-oxo-4H-benzo[a]quinolizine and that the structures of Va, VI, and VII assigned above were also correct.

Following a manner similar to that given for the reaction in acetic acid, IV was treated with diketene in formic acid, propionic acid, acetic anhydride and propionic anhydride to give the corresponding N-acyl derivatives (Va,b,c). The results summarized in the table indicate that the N-acetyl group of Va is not derived from diketene, but from the acid used as a solvent.



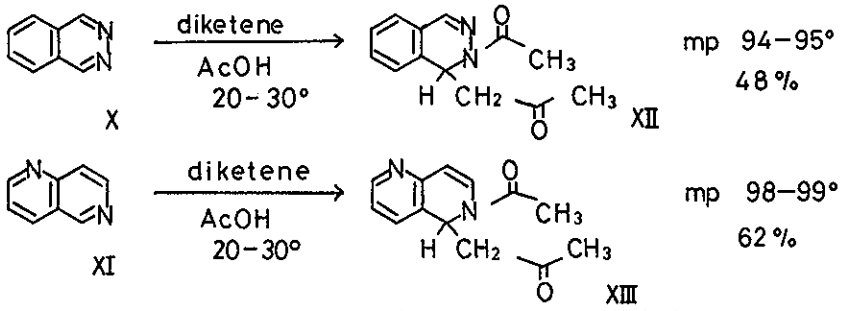
IV Va, b, c

Compd No.	R	bp or mp	Medium	Yield (%)
Va	CH_3	mp 100-101°	$(CH_3CO)_2O$	40
Vb	H	bp 160-170° (2mmHg)	HCOOH	56
Vc	C_2H_5	bp 150-160° (2mmHg)	C_2H_5COOH	35
Vc	C_2H_5		$(C_2H_5CO)_2O$	41

Further attempts were made to extend this reaction to other heteroaromatics, such as quinoline, quinoxaline, phthalazine (X), and 1,6-naphthyridine (XI). Although the reaction of quinoline and quinoxaline with diketene resulted in the recovery of the starting materials, X and XI were converted to the expected

products (XII), $C_{13}H_{14}O_2N_2$, and XIII, $C_{13}H_{14}O_2N_2$, respectively.

In the NMR spectrum of XIII, a signal due to the ring proton appeared at 8.4 ppm as a double doublet (J=4.5Hz and 1.5Hz), which evidently proved that the addition reaction of diketene to XI occurred at the isoquinoline type carbon-nitrogen double bond. Therefore the structure of XIII was represented as shown below.



Although the reason for different reactivities between isoquinoline and quinoline toward diketene in acetic acid remains obscure at present, this reaction has provided a facile synthetic method for isoquinoline derivatives.

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