ADDITION OF ACID ANHYDRIDES TO THE NITROGEN-CARBON DOUBLE BOND OF ISOQUINOLINE RINGS

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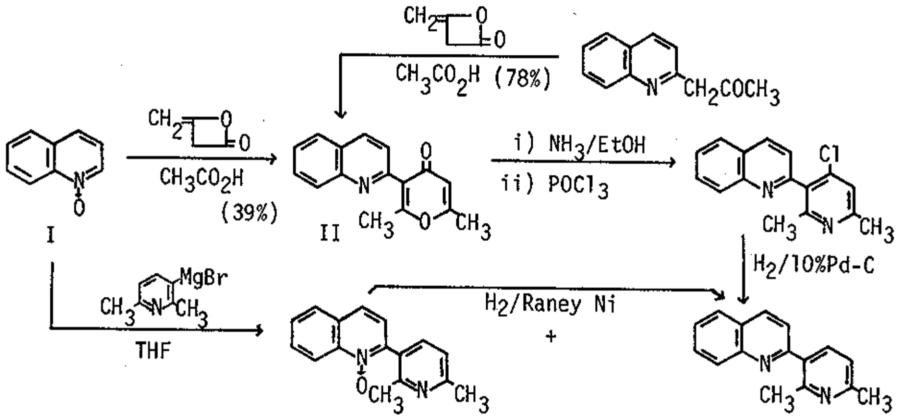
The unique addition reaction of such reagents as diketene in acidic media, acetic anhydride and the active methylene compounds in acetic anhydride to the C=N double bond of isoquinoline was investigated. Isoquinoline derivatives possessing a carbon substituent at the 1-position were synthesized through this method.

The reaction of diketene with quinoline and isoquinoline in a non-polar solvent was reported to give the tetracyclic benzoquinolizines.[1,2] This promoted us to investigate the reaction of diketene with quinoline 1-oxide (I) and isoquinoline 2-oxide (III). During the course of this investigation, a novel addition of acid anhydrides to isoquinoline-like heteroaromatic rings was observed. In this paper we wish to give an outline of our recent studies on this field.

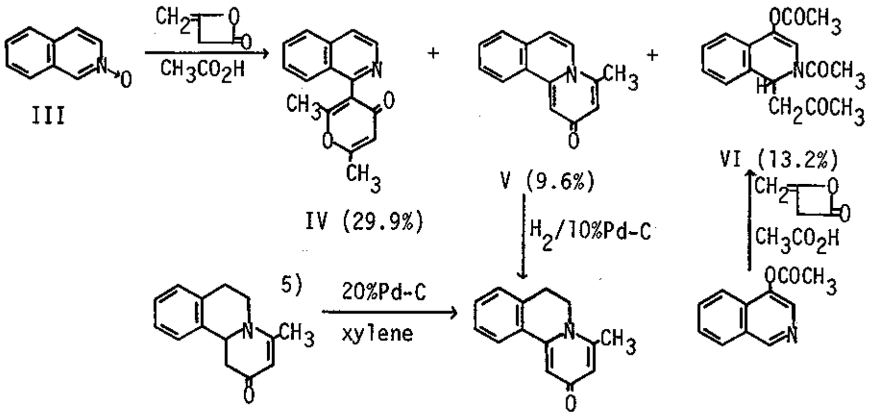
When quinoline 1-oxide (I) was warmed at 40-50° in acetic acid with excess diketene, the quinolyl-γ-pyrone (II) was obtained.[3] The structure II was determined by the usual spectroscopy



and the chemical reactions as shown above.

When the reaction was performed with less than 1 mole eq. diketene in acetic acid, 2-acetonylquinoline was isolated. On treatment with excess diketene in acetic acid, this compound was readily converted into II. This observation may suggest 2-acetonylquinoline to be the reaction intermediate.

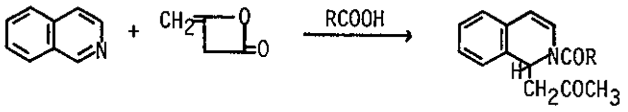
In order to compare with I, isoquinoline 2-oxide (III) was allowed to react with diketene under identical conditions. In



this case, the three products (IV, V, VI) were obtained.[4)]

The tentative reaction mechanism was represented on the next page. The formation of VI suggests that diketene may react with isoquinoline in the presence of a carboxylic acid to give the acetonylisoquinoline (VII).[7)]

Table 1

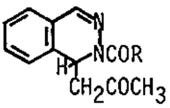


VIIa-e

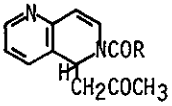
R		Yield (%)	
		in the absence of triethylamine	in the presence of triethylamine
H	(VIIa)	56	74
CH_3	(VIIb)	43	64
CH_3CH_2	(VIIc)	35	58
$CH_3CH{=}CH$	(VIId)	—	21.5
$CH_3OCOCH_2CH_2$	(VIIe)	—	33

Indeed, this presumption was ascertained by the results summarized in Table 1. As shown in Table 2, phthalazine and 1,6-naphthyridine were readily converted into the same type products (VIII, IX). On the contrary, quinoline and quinoxaline were recovered when they were treated with diketene under identical conditions.

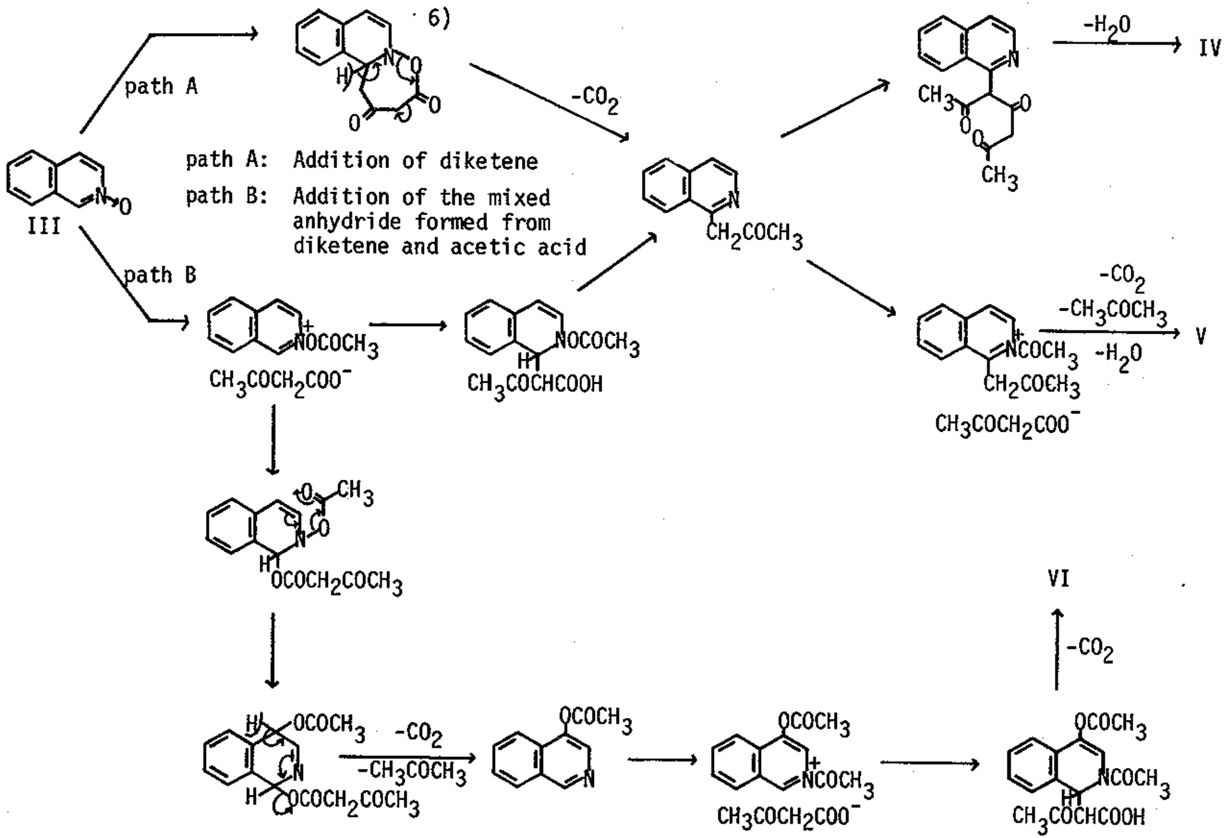
Table 2



	R	Yield(%)
VIIIa:	H	62
VIIIb:	CH_3	48
VIIIc:	CH_3CH_2	69



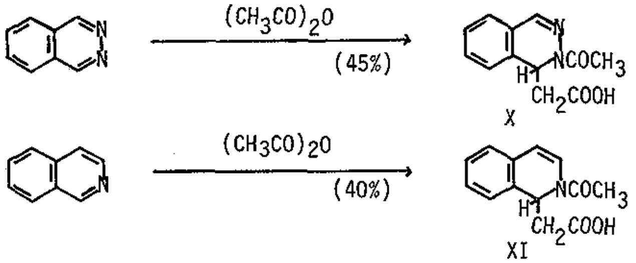
	R	Yield(%)
IXa:	H	60
IXb:	CH_3	62



path A: Addition of diketene

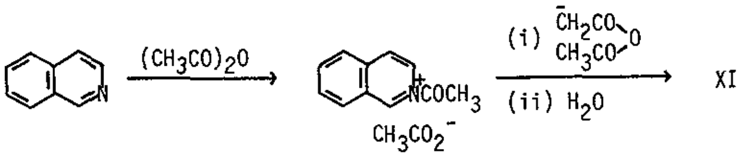
path B: Addition of the mixed anhydride formed from diketene and acetic acid

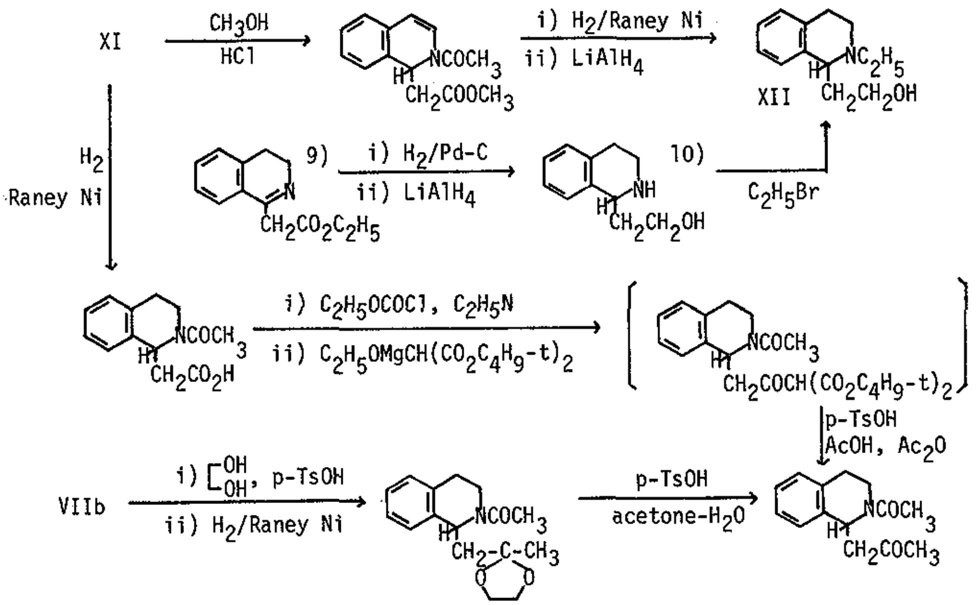
During the course of this investigation, it was unexpectedly found that acetic anhydride itself added to phthalazine without adding any catalyst. From the spectral data, the 1-phthalazineacetic acid structure (X) was assigned to the product. In a similar manner, isoquinoline was transformed into the adduct (XI) whose structure was confirmed by the chemical methods[8)] shown on the next page.



Namely, compound XI was reduced to the tetrahydroisoquinolineethanol (XII) which was identical with the authentic specimen. The structural relation between XI and VIIb was also established by the chemical modifications as shown on the next page. Quinoline and quinoxaline were observed to give none of addition products with acetic anhydride.

The mechanism of the addition of acetic anhydride to isoquinoline was assumed to be in analogy with that of the Perkin reaction.

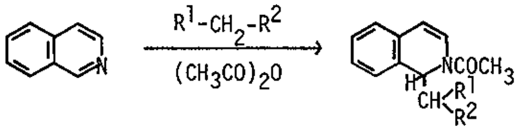




It is, therefore, conceivable that a different carbanion generated from active methylene compounds in the reaction mixture may attack the C=N double bond of isoquinoline to give the adducts competitively with the carbanion from acetic acid.

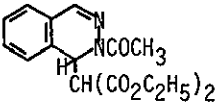
In fact, isoquinoline reacted with such active methylene (or methyl) compounds as shown in Table 3 to afford the 1-substituted isoquinoline (XII). Like the addition of diketene or acetic anhydride the addition of the active methylene compounds were observed to occur on phthalazine and 1,6-naphthyridine giving the corresponding products (XIII, XIV).

Table 3

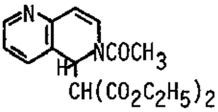


XII

Active Methyl(Methylene) Compds.	Yield	
	XII	XI
acetone	(R^1=H, R^2=$COCH_3$) 12 %	24.5 %
acetophenone	(R^1=H, R^2=COC_6H_5) 12 %	14.2 %
γ-picoline	(R^1=H, R^2=4-pyridiyl) 35 %	———
lepidine	(R^1=H, R^2=4-quinolyl) 50 %	———
ethyl malonate	(R^1=R^2=$CO_2C_2H_5$) 40 %	3.5 %
ethyl acetoacetate	(R^1=H, R^2=$COCH_3$) 7 %	1.7 %
ethyl benzoylacetate	(R^1=H, R^2=COC_6H_5) 14 %	5.5 %
phenylacetic acid	(R^1=C_6H_5, R^2=CO_2H) 32 % and 10.5 % (diastereomers)	———



XIII (54.5 %)



XIV (33 %)

Although the different reactivity between quinoline and isoquinoline towards the addition of this type is not explained at present, these reactions described above provide a simple synthetic way to 1,2-dihydroisoquinolines possessing a carbon substituent at the 1-position.

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