[Chem. Pharm. Bull. 13(8) 912~920 (1965)] UDC 547.831.1.07

118. Masatomo Hamana and Hiroshi Noda : Studies on Tertiary Amine Oxides. XXIV.*1 Reactions of Aromatic N-Oxides with Enamines of Cyclohexanone in the Presence of Acylating Agents. (1).*2

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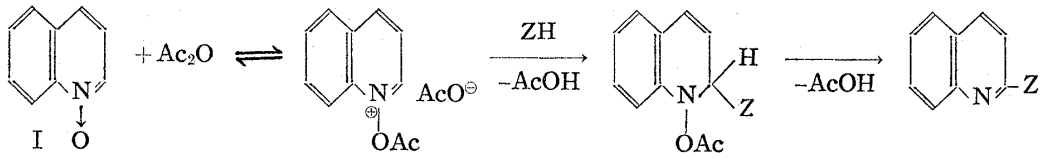
A previous paper of this series[1] has shown that quinoline 1-oxide reacts smoothly with compounds containing reactive hydrogens, *e.g.* ethyl cyanoacetate, in the presence of acetic anhydride, producing the corresponding 2-substituted quinolines in good yields according to the following equation.



ZH : Active hydrogen compounds, *e.g.* $NCCH_2CO_2C_2H_5$, CH_3COCN, $O_2NCH_2CO_2C_2H_5$

This reaction seems apparently promising for introduction of a carbon-substituent into N-heteroaromatic nuclei *via* its N-oxide, but its application suffers from some limitations. Namely, no reaction occurs with somewhat less reactive compounds such as phenylacetonitrile, acetophenone or acetone, and the reactivity is much decreased with pyridine 1-oxide. Okamoto and Takayama[2] have described that 1-methoxyquinolinium iodide reacts with acetone in a caustic alkaline solution to give 2-acetonylquinoline, but again its yield is very low.

With the aim of widening the scope of this kind of reaction we studied the reaction of aromatic N-oxides and a variety of active hydrogen compounds and found that cyclohexanone, which was inactive as it was, could readily enter into the reaction under likewise mild condition when employed as an enamine.

When benzoyl chloride (1.2 equiv.) was added to an ice-cooled solution of quinoline 1-oxide (I) and morpholine enamine of cyclohexanone (2 equiv.) in chloroform, an exothermic reaction ensued and the solution displayed a deep red coloration. Standing overnight at room temperature and treating of the reaction mixture with 20% hydrochloric acid gave 2-(2-quinolyl)cyclohexanone (II) as a major product (73.4%), accompanied by small amounts of by-products. II had an empirical formula $C_{15}H_{15}ON$ and was crystallized from methanol as orange prisms, m.p. 121~122°, forming the corresponding oxime, $C_{15}H_{16}ON_2$, white leaflets, m.p. 190~192°. When the ethanolic solution of II and potassium hydroxide was refluxed for a long period, 2-quinolinehexanoic acid (III), m.p. 105~107°, was obtained. Oxidation of II with hydrogen peroxide in acetic acid yielded quinaldic acid 1-oxide (IV).[3] II was reduced with sodium borohydride in ethanol to an alcohol (V), m.p. 124~125°, which was dehydrated by warming with acetic anhydride, followed by catalytic dehydrogenation with selenium into the known 2-phenylquinoline (VI)[4] (see Chart 1).

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*1 Part XXIII. M. Yamazaki, Y. Chono, K. Noda, M. Hamana : Yakugaku Zasshi, **85**, 62 (1965).
*2 A part of the work has been preliminarily reported in this Bulletin, **11**, 1331 (1963).
*3 Katakasu, Fukuoka (浜名政和, 野田浩司).
1) H. Hamana, M. Yamazaki : This Bulletin, **11**, 415 (1963).
2) T. Okamoto, H. Takayama : *Ibid.*, **11**, 514 (1963).
3) Y. Hamada : Yakugaku Zasshi, **79**, 908 (1959).
4) K. Ziegler, H. Zeiser : Ann., **485**, 174 (1931).

II gave no color with ferric chloride, and its infrared spectrum in Nujol lacked any ketonic band but showed a strong absorption at 1613 cm^{-1} characteristic of enol C=C bond (Fig. 1a). The ultraviolet spectrum in ethanol showed absorption in the region of significantly long wave length (λ_{max}^{EtOH} mμ (log ε) : 216.5 (4.57), 278 (3.95), 440 (3.89)). On the other hand, the spectrum in N-hydrochloric acid was similar to 2-alkylquinolines (λ_{max}^{NHCl} mμ (log ε) : 237 (4.57), 317 (4.06)) (Fig. 2a). These facts suggested that II existed predominantly as an enol form and an intramolecular hydrogen bond was formed between the enol hydroxyl group and the nitrogen of quinoline ring (IIb), in the same manner as in analogous 2-substituted quinolines.[2,5,6]

It was subsequently examined how the reaction would be affected by the nature of acylating agent and also of the basic moiety of cyclohexanone enamine, and the results in Table I was obtained. The order of effectiveness of acylating agents was as follows : benzoyl chloride>tosyl chloride>acetic anhydride~acetyl chloride. But the fact that the difference was not so marked was remarkably contrast to the original reactions[1] which were found to be profoundly affected by the nature of acylating agent. Among the commonest enamines, morpholine-, piperidine-, and pyrrolidine-enamine, the first was the most reactive one, the last being the least. This order of enamines was apparently in accordance with that reported in acylation of enamines.[7,8]

The influences of the amounts of reagents on the yield of II were next explored in reaction of I, morpholine enamine and benzoyl chloride. Best result was obtained when the mole ratio of I, benzoyl chloride and the enamine was 1:1:2 (Exp. No. 1), and a fairly good yield was given in the ratio of 1:1:1 (Exp. No. 9). No increase in yield was observed by employment of an exess of enamine (Exp. No. 10), unsatisfactory fruits being obtained conversely when triethylamine was used as a neutralizing agent (Exp. No. 11 and 12) (Table II).

Table I. The Reactions of Quinoline 1-Oxide with Cyclohexanone Enamines in the Presence of Acylating Agent

Exper. No.	Quinoline 1-oxide (g.) 1 equiv.	Enamine of cyclohexanone (g.) 2 equiv.		Acylating agent (g.) 1 equiv.		Product g. (%) II	VII	A	B
1	4.35	morpholine	10	PhCOCl	5.06	4.95 (73.4)		0.04 (0.72)	0.07 (0.65)
2	1.45	〃	3.34	TsCl	2.29	1.49 (66.2)			
3	0.48	piperidine	1.1	PhCOCl	0.58	0.46 (61.4)	0.06 (8)		
4	1.45	〃	3.3	TsCl	2.29	1.24 (55.1)		trace	
5	0.48	〃	1.1	AcCl	0.32	0.41 (54.7)	0.015 (2)		
6	0.48	〃	1.1	Ac_2O	0.41	0.4 (53.4)	0.04 (5.34)		
7	1.45	pyrrolidine	3.02	PhCOCl	1.74	1.11 (49.3)		0.134 (7.3)	
8	1.45	〃	3.02	TsCl	2.29	0.12 (5.3)			

5) R. F. Branch : Nature, **177**, 671 (1956); **179**, 42 (1957).
6) R. F. Branch, A. H. Beckett, D. B. Cowell : Tetrahedron, **19**, 401, 413 (1963).
7) S. Hünig, E. Benzing, E. Lücke : Chem. Ber., **90**, 2833 (1957).
8) G. Stork, A. Brizzolara, H. Landesman, J. Szmuskovicz, R. Terrell : J. Am. Chem. Soc., **85**, 207 (1963).

Table II. The Effect of the Mole Ratio of Reactants in the Reaction of Quinoline 1-Oxide

Exper. No.	Quinoline 1-oxide g. (equiv.)	Morpholine enamine of cyclohexanone g. (equiv.)	PhCOCl g. (equiv.)	$(C_2H_5)_3N$ g. (equiv.)	Product g. (%)		
					II	A	B
9	1.45 (1)	1.84 (1)	1.55 (1)	—	1.49 (66.2)	0.02 (1.1)	
1	4.35 (1)	10 (2)	5.06 (1)	—	4.95 (73.4)	0.04 (0.72)	0.07 (0.65)
10	0.48 (1)	2.46 (4)	0.52 (1)	—	0.49 (65.3)		
11	1.45 (1)	1.84 (1)	1.55 (1)	1.12 (1)	1.19 (52.9)	0.02 (1.1)	
12	1.45 (1)	1.84 (1)	1.55 (1)	2.24 (2)	0.93 (41.3)		

In some reactions mentioned above, a few kinds of by-products were also isolated. Among these compounds 2-(4-quinolyl)cyclohexanone (VII), an isomer of II, was only one characterized. VII, colorless prisms of m.p. 125°, formed in 8% yield from the reaction of I, piperidine enamine and benzoyl chloride, and was converted into 4-phenylquinoline[9] by reduction with sodium borohydride followed by selenium dehydrogenation. In connection with this, it was also found that treatment of I with ethyl 2-oxocyclohexanecarboxylate according to the original procedure[1] and hydrolysis of the product gave only a trace of 2-(4-quinolyl)cyclohexanone (VII) (0.7%). Further, two kinds of by-products (A and B) gave analytical values in agreement with the empirical formulae of 2,6-bis(2-quinolyl)cyclohexanone and 2-(2-quinolyl)-6-benzoylcyclohexanone, respectively. However, the lack of material prevented from further structural elucidation. On the other hand, any attempt to increase the yield of A or B by changing the amount of I and/or benzoyl chloride failed, and resulted in the formation of the mixture of untractable products.

While the reactivity of pyridine 1-oxide (IX) was much lower as compared with that of quinoline 1-oxide in the former reaction,[1] the new procedure using enamines of cyclohexanone yielded the expected product, 2-(2-pyridyl)cyclohexanone (X) in very good yields. X was a pale yellow, viscous oil, $b.p_{0.13}$ 138~140°, giving an oxime, m.p.

Table III. The Reactions of Pyridine 1-Oxide with Cyclohexanone Enamines in the Presence of Acylating Agent

Pyridine 1-oxide (g.) 1 equiv.	Enamine of cyclohexanone (g.) 2 equiv.		Acylating agent (g.) 1 equiv.		Product g. (%)	
					X	C[a]
1.88	morpholine	7.26	PhCOCl	3.33	2.88 (83.3)	
1.43	piperidine	5.47	〃	2.54	1.79 (68)	
1.04	pyrrolidine	3.64	〃	1.85	0.8 (40)	
1.42	morpholine	5.47	TsCl	3.41	1.57 (60)	0.022 (0.84)

a) 2-(4-pyridyl)cyclohexanone

9) J. Kenner, F. S. Statham: J. Chem. Soc., 1935, 301.

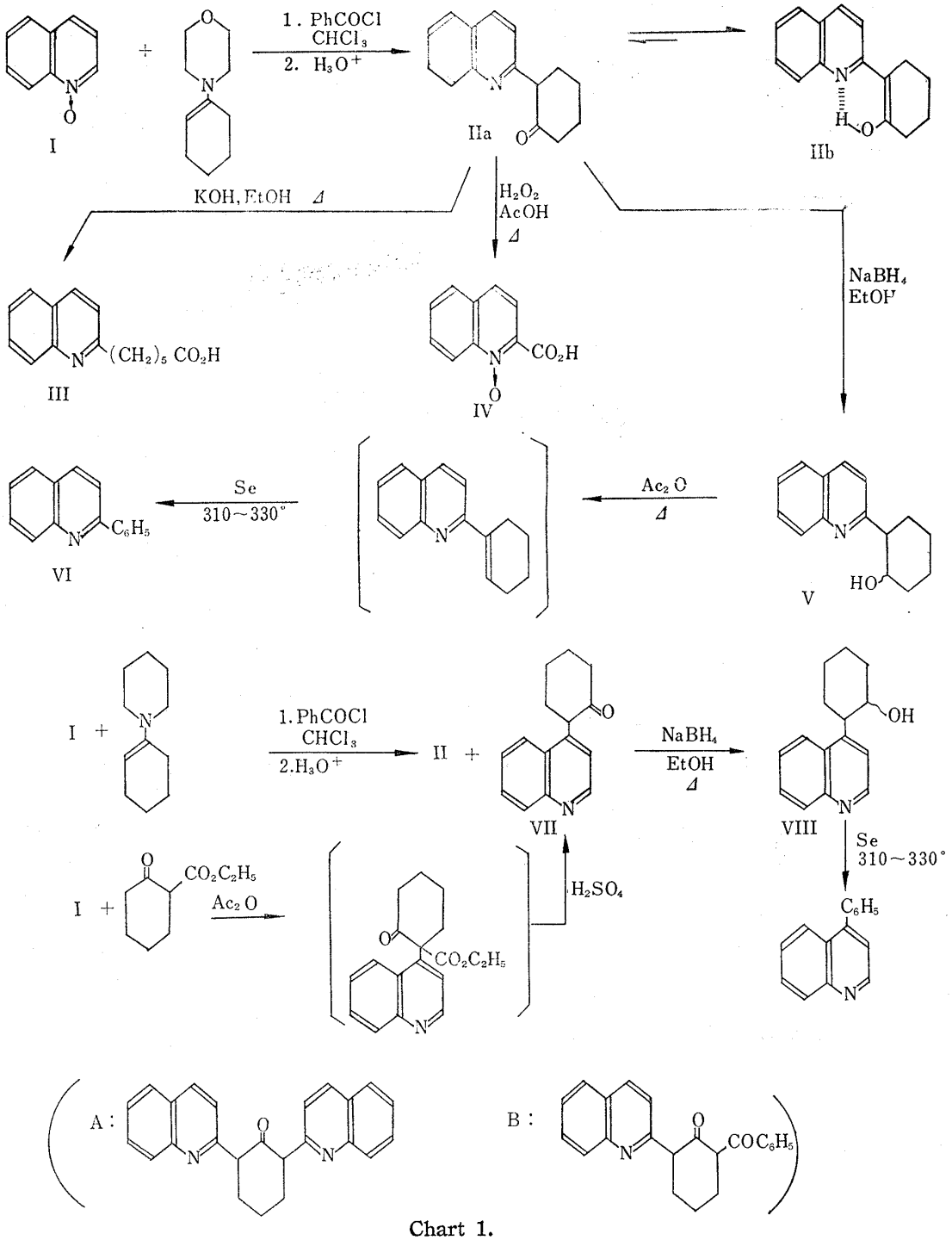


Chart 1.

125°, and a picrate, m.p. 158~160°. X was oxidized to picolinic acid 1-oxide[10] by hydrogen peroxide and acetic acid. From the reaction using the morpholine enamine and tosyl chloride a trace of 2-(4-pyridyl) cyclohexanone[11] was also isolated as a by-product. The effects of the nature of acylating agents and the enamines were practically the same as in the case of I (Table III), except the reaction using acetic anhydride as the acylating agent which produced a number of untractable products (Chart 2).

10) O. Diels, R. Meyer : Ann., **513**, 129 (1934); R. Adams, S. Miyano : J. Am. Chem. Soc., **76**, 3168 (1954).

11) W. von E. Doering, W. E. McEwen : J. Am. Chem. Soc., **73**, 2104 (1951).

The infrared and ultraviolet spectra of X were fairly different from those of the corresponding quinoline derivative (II). The infrared spectrum showed absorption bands for intramolecular hydrogen bond of a chelate form, ketonic group and enol C=C bond, at 2778~2439 (with fine structures), 1715 and 1624 cm^{-1}, respectively (Fig. 1b). The ultraviolet spectrum showed little change in ethanol or N-hydrochloric acid : that is at 260 or 262 mμ respectively, corresponding to that of 2-alkylpyridines (Fig. 2b). These observations showed that X existed as a mixture of keto (Xa) and enol form (Xb), the former being dominant.

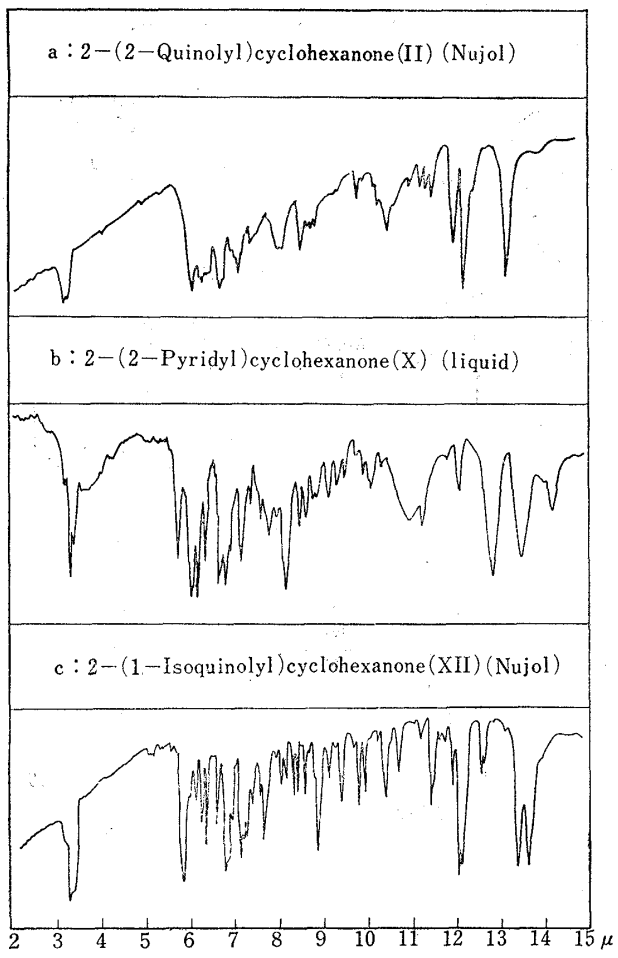


Fig. 1. Infrared Spectra

Isoquinoline 2-oxide (XI) reacted in the same manner with morpholine enamine of cyclohexanone and benzoyl chloride, producing 2-(1-isoquinolyl)-cyclohexanone (XII), m.p. 141.5~143.5°, in 73.3% yield. XII was reduced with sodium borohydride to the corresponding alcohol (XIII), which was converted by selenium dehydrogenation to 1-phenylisoquinoline[4] (Chart 2). The infrared spectrum of XII exhibited ketonic absorption band at 1695 cm^{-1} but lacked bands for hydrogen bond and enol C=C bond (Fig. 1c). Therefore, XII existed exclusively as a keto form. This would suggest that coplanarity required for the formation of a resonance-stabilized enol was hindered by the steric repulsion between the hydrogen atoms at the 8-position of isoquinoline and at the 3-position of cyclohexanone (XII′).

Since quinoline 1-oxide did not react with enamines of cyclohexanone without acylating agent, the role of which is essential for initiation of the

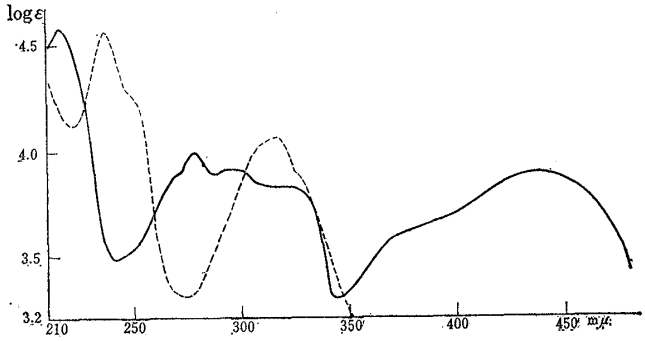


Fig. 2a. Ultraviolet Spectra of 2-(2-Quinolyl)-cyclohexanone (II)

——— in EtOH
– – – – – in *N*HCl

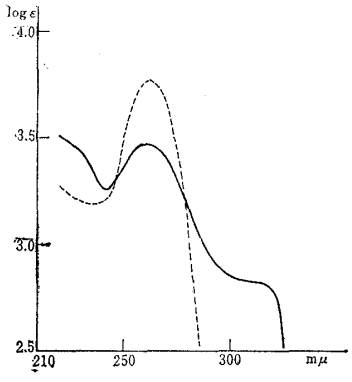


Fig. 2b. Ultraviolet Spectra of 2-(pyridyl)cyclohexanone (X)

——— in EtOH
– – – – – in *N*HCl

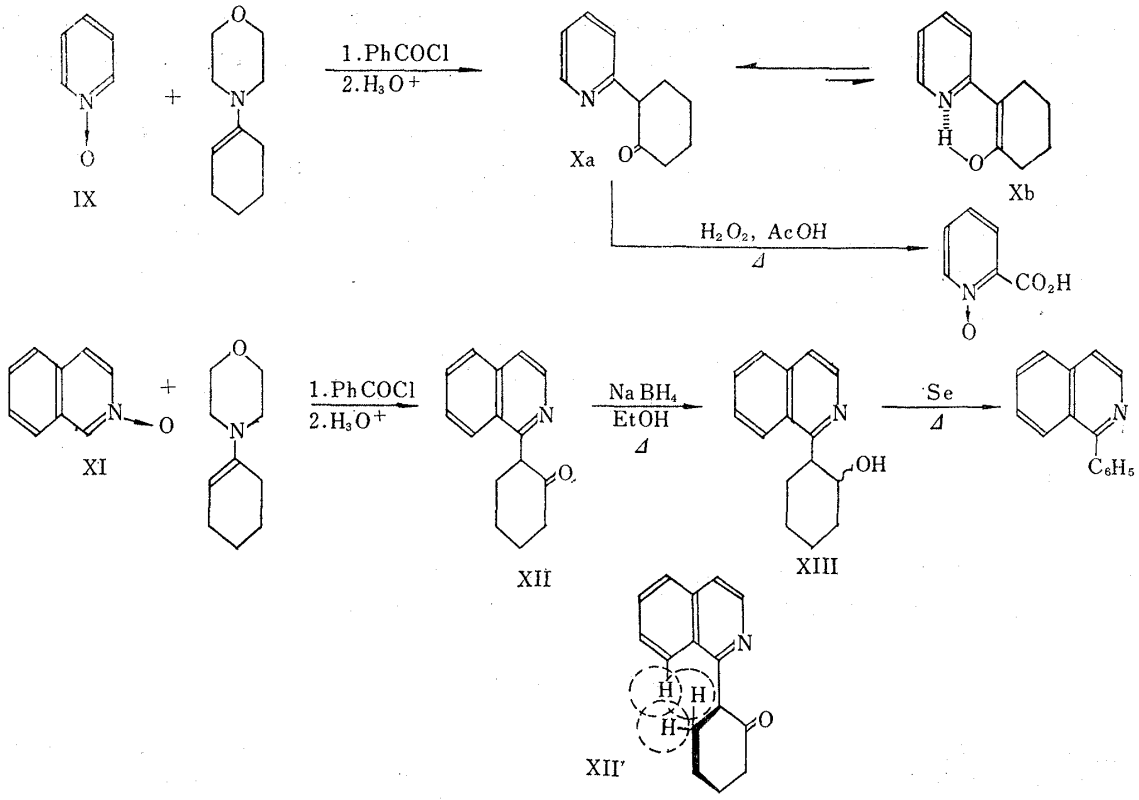
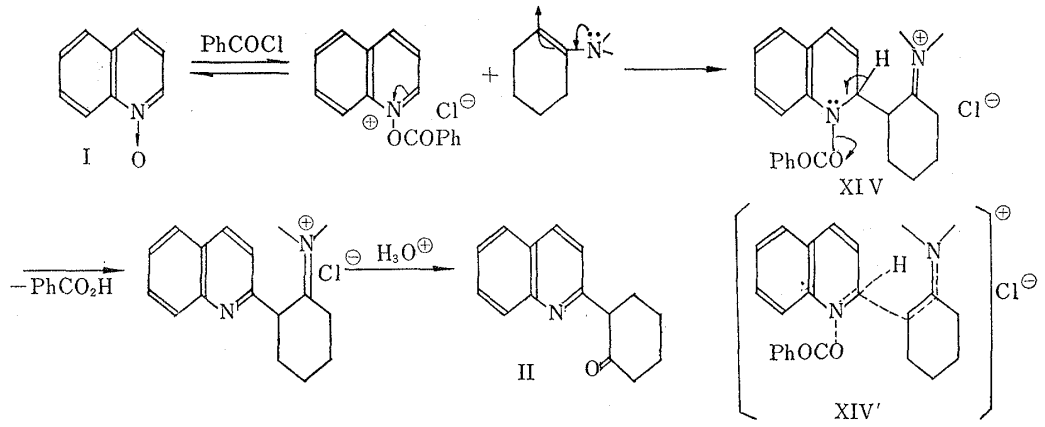


Chart 2.

reaction. Taking account of the analogous nucleophilic reactions of acyl adducts of aromatic N-oxides,[12] the reaction should be considered to proceed by the following addition-elimination process. Judging from the Stuart model, however, the transition state (XIV) is too sterically crowded to exist as such. Thus, the fission and formation of bonds must take place simultaneously by the concerted mechanism, and it would be better to formulate the transition state as XIV'. It is very surprising that the enamine was introduced preferentially into the α-position of ring nitrogen in spite of such an unfavorable steric environment, especially in the case of isoquinoline 2-oxide.

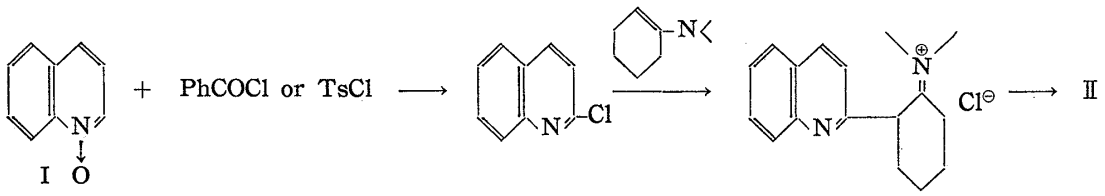


From the standpoint of enamine chemistry, essential feature of the present reaction is not conceivable as direct arylation of enamine, but might be regarded as a type of reaction with electrophilic olefin.[8] If so, the order of reactivity of the enamines is

12) *a*) E. Ochiai : Ann. Rept. ITSUU Lab. (Tokyo), **12**, 43 (1962). *b*) M. Hamana, M. Yamazaki : This Bulletin, **11**, 411 (1963). *c*) S. Oae, S. Kozuka : Tetrahedron, **20**, 2691 (1964).

expected to be reversed to the experimental one. The discrepancy may be probably due to the fact that stability of enamine is overwhelming its inherent reactivity in these reactions.

Kuehne[13] has reported that 2-chloroquinoline reacts with pyrrolidine enamine of cyclohexanone to give none of 2-(2-quinolyl)cyclohexanone (II) but 2-pyrrolidinoquinoline in an unsatisfactory yield. We also tried the reaction of 4-chloroquinoline 1-oxide with morpholine enamine of cyclohexanone in hot dioxane without any acylating agent, and obtained 4-morpholinoquinoline[14] as a sole product in 61.2% yield. These results may exclude the following alternative course.



Further work on the various derivatives of aromatic N-oxide are now under way in this Laboratory and the results will be published shortly.

Experimental*4

Reactions of Quinoline 1-Oxide with Enamine of Cyclohexanone——1) (Exp. No. 1) To an ice-cooled solution of quinoline 1-oxide (I) (4.34 g.) and morpholine enamine of cyclohexanone (10 g.) in $CHCl_3$ (30 ml.), PhCOCl (5.06 g.) was added dropwise with stirring. After standing overnight at room temperture, the reaction mixture was poured into 20% HCl (60 ml.), concentrated on a water-bath under reduced pressure, and the residue was dissolved again in 20 % HCl and washed with benzene-ether. The acidic solution was made alkaline with solid K_2CO_3 and extracted with benzene and $CHCl_3$ successively. Evaporation of benzene left a solid, which was recrystallized from MeOH to yield 4.59 g. of 2-(2-quinolyl)cyclohexanone (II), orange prisms, m.p. 121~122°. *Anal.* Calcd. for $C_{15}H_{15}ON$: C, 79.97; H, 6.71; N, 6.22. Found : C, 79.95; H, 6.72; N, 5.75.

The methanolic mother liquor was evaporated, taken up in benzene and passed through an alumina column; the first eluate gave an additional 0.36 g. of II, and the second furnished 0.04 g. of A which was recrystallized from acetone to brownish yellow prisms, m.p. 200~201° (decomp.). *Anal.* Calcd. for $C_{24}H_{20}ON_2 \cdot H_2O$: C, 77.89; H, 5.94; N, 7.57. Found : C, 78.03; H, 5.72; N, 7.52.

The residue from the $CHCl_3$ extract was purified by chromatography in benzene on alumina and recrystallized from MeOH to give 0.07 g. of B, light yellow prisms, m.p. 218~220°. *Anal.* Calcd. for $C_{22}H_{19}O_2N \cdot H_2O$: C, 76.06; H, 6.09; N, 4.03. Found : C, 75.91; H, 6.04; N, 4.04.

2) (Exp. No. 3) I (0.48 g.), piperidine enamine (1.1 g.) and PhCOCl (0.58 g.) were allowed to react in the same manner as described above. After treating the reaction mixture with dil. HCl, all basic products were taken up in $CHCl_3$. The $CHCl_3$ solution was evaporated, and the residue was recrystallized from MeOH to yield 0.33 g. of II. The materials from the mother liquor were chromatographed on alumina using benzene and then $CHCl_3$ for elution. The first fraction afforded an additional 0.13 g. of II, and the second was recrystallized from AcOEt-petr. benzin to give 0.06 g. of 2-(4-quinolyl)cyclohexanone (VII), colorless prisms, m.p. 124~125°. *Anal.* Calcd. for $C_{15}H_{15}ON$: C, 79.97; H, 6.71; N, 6.22. Found : C, 79.59; H, 6.66; N, 6.26.

3) (Exp. No. 11) When I (1.45 g.) was similarly treated with morpholine enamine (1.84 g.), Et_3N (1.12 g.) and PhCOCl (1.55 g.) in $CHCl_3$ (10 ml.), white crystals deposited from the reaction mixture. On working up as described in 2), 1.19 g. of II and 0.02 g. of A were obtained.

Reactions of 2-(2-Quinolyl)cyclohexanone (II)——1) Oxime: A mixture of II (2.25 g.)-EtOH (15 ml.), $NH_2OH \cdot HCl$ (0.77 g.)-H_2O (3 ml.) and KOH (0.76 g.)-H_2O (4 ml.) was heated under reflux for 2 hr. After cooling, the mixture was poured on 100 ml. of ice-water containing 0.2 ml. of AcOH. The resultant light yellow precipitates were collected, washed with H_2O and ether, and recrystallized from EtOH to give 2.4 g. (quant.) of the oxime, white leaflets, m.p. 190~192°. *Anal.* Calcd. for $C_{15}H_{16}ON_2$: C, 74.97; H, 6.71; N, 11.66. Found : C, 75.04; H, 7.00; N, 11.21.

*4 All melting and boiling points were uncorrected.

13) M. E. Kuehne : J. Am. Chem. Soc., **84**, 837 (1962).
14) T. Itai : Yakugaku Zasshi, **66B**, 170 (1946).

2) Acid-hydrolysis of II with KOH-EtOH : A mixture of II (1.2 g.), KOH (1.1 g.), H_2O (5 ml.) and EtOH (20 ml.) was refluxed on a water-bath. After 18 hr., 0.5 g. of KOH was added and heating was continued for further 39 hr. The solution was evaporated *in vacuo* and the residue was dissolved in H_2O, shaken with $CHCl_3$ and made weakly acidic with dil. HCl to separate an oil. This was extracted with $CHCl_3$ followed by triturating with ether to give a solid. Recrystallization from AcOEt yielded 0.6 g. (46.2%) of 2-quinolinehexanoic acid (III), colorless plates, m.p. 105~106°. *Anal.* Calcd. for $C_{15}H_{17}O_2N$: C, 74.05; H, 7.04; N, 5.76. Found : C, 74.28; H, 7.12; N, 5.44.

3) Oxidation of II with H_2O_2-AcOH : A mixture of II (0.3 g.), 30% H_2O_2 (5 ml.) and glacial AcOH (10 ml.) was warmed at 70~80° in a water-bath. After 6 hr., 3 ml. of 30% H_2O_2 was further added and the whole was kept for 6 hr. at the same temperature. The reaction mixture was evaporated *in vacuo* to give a white solid, which was dissolved in 2*N* KOH and shaken with $CHCl_3$. The alkaline solution was made weakly acidic with dil. HCl to afford a white precipitate which was extracted with $CHCl_3$. The $CHCl_3$ extract gave 0.11 g. (41%) of quinaldic acid 1-oxide[3] (IV), yellow needles, m.p. 168~169.5° (MeOH), which was proved to be identical with an authentic sample[3] by admixture and by comparison of their IR spectra. *Anal.* Calcd. for $C_{10}H_7O_3N$: C, 63.49; H, 3.73; N, 7.41. Found : C, 63.23; H, 3.96; N, 7.63.

On refluxing IV (0.2 g.) with Ac_2O (5 ml.) for 2 hr.,[15] carbostyril, m.p. 194~196°, was obtained in 78% yield (0.12 g.).

4) Reduction of II with $NaBH_4$: A solution of II (0.8 g.) and $NaBH_4$ (0.06 g.) in anhyd. EtOH (20 ml.) was refluxed for 2 hr. The solvent was distilled off under reduced pressure, and the residue was treated with H_2O and extracted with $CHCl_3$. The solvent was evaporated and the solidified residue was recrystallized from benzene to give 0.78 g. (97%) of V, white powders, m.p. 124~125°. *Anal.* Calcd. for $C_{15}H_{17}ON$: C, 79.26; H, 7.54; N, 6.16. Found : C, 79.03; H, 7.36; N, 6.05.

5) 2-Phenylquinoline (VI) from V: A mixture of V (0.23g.) and Ac_2O (5 ml.) was heated on a water-bath for 5 hr. The reaction mixture was evaporated *in vacuo*, and the residue was treated with K_2CO_3 solution and extracted with $CHCl_3$. The crude product was directly heated with Se (1 g.) at 310~340° for 3.5 hr., cooled and extracted with MeOH. The product was dissolved in ether and purified by alumina chromatography to afford 0.13 g. (63%) of VI, colorless crystals (EtOH-H_2O), m.p. 82~84°, which was shown identical with an authentic sample[4] of 2-phenylquinoline by admixture and by comparison of their IR spectra.

4-Phenylquinoline from 2-(4-Quinolyl)cyclohexanone (VII)——As described for the reduction of II, VII (0.4 g.) was treated with $NaBH_4$ (0.075 g.) in boiling EtOH (25 ml.) for 3 hr., and similar treatment of the reaction mixture yielded 0.35 g. (86%) of an alcohol (VIII), m.p. 109~110° (CCl_4-petr. benzin). *Anal.* Calcd. for $C_{15}H_{17}ON$: C, 79.26; H, 7.54; N, 6.16. Found : C, 79.03; H, 7.72; N, 6.35.

VIII (0.3 g.) was heated with Se (1 g.) at 310~330° for 3 hr. The product was extracted with MeOH and then purified by chromatography in ether on alumina to give 4-phenylquinoline[9] as an oil, which was derived to 0.25 g. of picrate, m.p. 223~224° (EtOH).

Reaction of Quinoline 1-Oxide (I) with Ethyl 2-Oxocyclohexanecarboxylate in the Presence of Acetic Anhydride——To a mixture of I (1.45 g.) and Ac_2O (1.3 g.) was added ethyl 2-oxocyclohexanecarboxylate (2.21 g.) and the whole was kept at 40~50° for 20 hr. An excess of EtOH was added to the resultant orange solution and then the solvent was evaporated *in vacuo*. The residue was treated with a saturated $NaHCO_3$ solution and extracted with $CHCl_3$. The extracted substances were dissolved in benzene and chromatographed on alumina. A yellow oil was eluted with benzene and then 0.82 g. (55%) of unreacted I with AcOEt. A solution of the former in 50% H_2SO_4 (7 ml.) was refluxed for 1 hr., cooled, washed with ether, basified with solid K_2CO_3 and extracted with $CHCl_3$. A product obtained on evaporation of $CHCl_3$ was purified by passing its ether solution through alumina column and recrystallized from petr. benzin (b.p. 60~64°) to give 0.015 g. (0.7%) of 2-(4-quinolyl)cyclohexanone (VII), m.p. 125~127°, undepressed on admixture with a specimen obtained above (Exp. No. 3).

Reaction of Pyridine 1-Oxide (IX) with Morpholine Enamine of Cyclohexanone——1) To an ice-cooled solution of IX (1.88 g.) and morpholine enamine of cyclohexanone (7.26 g.) in $CHCl_3$ (10 ml.) was added PhCOCl (3.33 g.) with stirring, and the solution was kept standing at room temperature for 3 days. The reaction mixture was poured into 20% HCl (50 ml.) and evaporated under reduced pressure. The residue was dissolved in 5% HCl, washed with benzene-ether mixture, made alkaline with solid K_2CO_3 and extracted with $CHCl_3$. After removing $CHCl_3$, the residue was distilled at reduced pressure. A distillate of $b.p_{0.13}$ 138~140° was collected to afford 2.88 g. of 2-(2-pyridyl)cyclohexanone (X); picrate, m.p. 158~160° (EtOH). *Anal.* Calcd. for $C_{11}H_{13}ON \cdot C_6H_3O_7N_3$: C, 50.50; H, 3.99; N, 13.86. Found : C, 50.40; H, 4.14 ;N, 14.01. Oxime, colorless needles, m.p. 125° (EtOH-H_2O). *Anal.* Calcd. for $C_{11}H_{14}ON_2$: C, 69.44; H, 7.42; N, 14.73. Found : C, 69.46; H, 7.60; N, 14.71.

2) A mixture of IX (1.42 g.), morpholine enamine (5.47 g.) and TsCl (4.41 g.) was treated as described above. A yellow distillate, $b.p_3$ 95~100°, was purified by alumina chromatography using benzene and then ether to give 1.57 g. of X and 0.022 g. of 2-(4-pyridyl)cyclohexanone,[11] m.p. 105~106° (petr. benzin).

15) M. Hamana, M. Yamazaki : Yakugaku Zasshi, 81, 574 (1961).

Anal. Calcd. for $C_{11}H_{13}ON$: C, 75.40; H, 7.48; N, 7.99. Found: C, 75.11; H, 7.50; N, 7.47.

Oxidation of X with Hydrogen Peroxide and Acetic Acid——A mixture of X (0.5 g.), 30% H_2O_2 (8 ml.) and AcOH (15 ml.) was warmed at 70~80° on a water-bath for 3 hr., and then 30% H_2O_2 (8 ml.) was added and the mixture was kept for further 6 hr. at the same temperature. The reaction mixture was evaporated *in vacuo*, and the residue was recrystallized from EtOH to give 0.2 g. of picolinic acid 1-oxide,[10] colorless rods, m.p. 163~164° (decomp.), undepressed on admixture with an authentic sample.

Reaction of Isoquinoline 2-Oxide (XI) with Morpholine Enamine of Cyclohexanone——To an ice-cooled solution of XI (2.90 g.) and morpholine enamine (7.36 g.) in $CHCl_3$ (20 ml.) was added dropwise PhCOCl (3.66 g.) with sirring. The resultant orange-red mixture was kept standing overnight at room temperature and then treated with 20% HCl (40 ml.). The whole was allowed to stand for 2 hr. with occasional shaking, and the aqueous solution was separated and extracted with $CHCl_3$. The combined $CHCl_3$ solution on evaporation gave a solid, which was washed with ether and recrystallized from MeOH to give 0.32 g. of 2-(1-isoquinolyl)cyclohexanone (XII), colorless needles, m.p. 141.5~143.5°. The acidic solution was basified with solid K_2CO_3 and extracted with $CHCl_3$ to give additional 1.16 g. of XII on recrystallization from MeOH. The mother liquor was evaporated, and the residue was purified by alumina chromatography in benzene to afford additional 1.82 g. of XII. The total yield of XII was 3.3 g. *Anal.* Calcd. for $C_{15}H_{15}ON$: C, 79.97; H, 6.71; N, 6.22. Found: C, 80.17; H, 6.88; N, 6.22.

1-Phenylisoquinoline from 2-(1-Isoquinolyl)cyclohexanone (XII)——1) Reduction of XII (0.225 g.) with $NaBH_4$ (0.015 g.) in anhyd. EtOH (10 ml.) was carried out and processed as described earlier to give 0.226 g. (99%) of an alcohol (XIII), colorless and viscous oil, b.$p_{0.04}$ 160~170° (bath temp.). Picrolonate, m.p. 223~224° (decomp.). *Anal.* Calcd. for $C_{15}H_{17}ON \cdot C_{10}H_8O_5N_4$: C, 61.09; H, 5.13; N, 14.25. Found: C, 61.29; H, 5.11; N, 14.04.

2) A mixture of XIII (0.45 g.) and Se (2 g.) was heated at 310~340° for 4 hr. The product was purified by alumina chromatography in benzene, and recrystallized from petr. benzin to yield 0.123 g. of 1-phenylisoquinoline,[4] m.p. 93~95°. *Anal.* Calcd. for $C_{15}H_{11}N$: C, 87.77; H, 5.40; N, 6.82. Found: C, 87.50; H, 5.43; N, 6.84.

Reaction of 4-Chloroquinoline 1-Oxide with Morpholine Enamine of Cyclohexanone——A solution of 4-chloroquinoline 1-oxide (1.8 g.) and the morpholine enamine (3.68 g.) in anhyd. dioxane (20 ml.) was heated under reflux for 12 hr., and then evaporated *in vacuo*. The residue was taken up in $CHCl_3$, thoroughly shaken with H_2O (20 ml.) and kept standing overnight. The aqueous layer was made alkaline with $NaHCO_3$, separated and extracted further with $CHCl_3$. The combined $CHCl_3$ solution was evaporated and the residue was distilled at reduced pressure to give 1.32 g. (61.2%) of 4-morpholinoquinoline,[14] b.p_2 180° (bath temp.). Picrate, m.p. 222~224°.

A part of expenses for this work was defrayed by the Grant-in-Aid for Scientific Research from the Ministry of Education, which is gratefully acknowledged. Thanks are also due to Messrs. J. Uchida and H. Hara for technical assistance, to Messrs. M. Shido, K. Ishimura, Mrs. S. Matsuba, Miss Y. Takahashi, and Miss T. Tahara for elemental analysis, and Mr. H. Matsui and Miss K. Soeda for the measurement of absorption spectra.

Summary

Quinoline 1-oxide reacted smoothly with cyclohexanone enamines in the presence of acylating agent, producing 2-(2-quinolyl)cyclohexanone as a major product in a good yield after treatment of the reaction mixture with hydrochloric acid. The effectiveness of acylating agents was as follows: benzoyl chloride>tosyl chloride>acetic anhydride~acetyl chloride. The sequence of the reactivity of enamines was morpholine->piperidine->pyrrolidine-enamine. The reaction of pyridine 1-oxide and isoquinoline 2-oxide similarly proceeded in good yields, 2-(2-pyridyl)- and 2-(1-isoquinolyl)-cyclohexanone being obtained, respectively. The structural elucidation of the products was effected by chemical methods and the examinations of their infrared and ultraviolet spectra.

(Received February 23, 1965)