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Studies on Quinoline and Isoquinoline Derivatives. III.[1] Reaction of Quinoline 1-Oxide with 2-Substituted Ethyl Acetimidates

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In order to introduce a carbon substituent to the α-position of the quinoline ring, the condensation of quinoline 1-oxide (VII) with the primary enamines, such as ethyl 2-ethoxycarbonyl-(IIIb), ethyl 2-benzoyl-(IIId), ethyl 2-cyanoacetimidate (IIIe), and 2-ethoxycarbonylacetamidine (IIIc), was investigated. The reaction of VII in the presence of benzoyl chloride afforded the following products: ethyl 2-ethoxycarbonyl-2-(2-quinolyl)acetimidate (VIII), 65%; ethyl 2-benzoyl-2-(2-quinolyl)acetimidate (X), 54%; ethyl 2-cyano-2-(2-quinolyl)acetimidate (XI), 29%; ethyl 2-diaminomethylene-2-quinolylacetate (XII), 62%.

The similar reaction proceeded in the case of isoquinoline 2-oxide.

Keywords——quinoline 1-oxide; isoquinoline 2-oxide; carbon carbon-bond formation; ethyl ethoxycarbonylacetimidate; ethoxycarbonylacetamidine; 2-substituted quinoline; 1-substituted isoquinoline

We have reported in the previous paper[3] of this series, 5-amino-3-methylisoxazole or 3-methyl-5-isoxazolone reacted with quinoline 1-oxide giving the 2-(4-isoxazolyl)quinoline derivatives. The catalytic reduction of the products over Raney nickel brought about the ring fission of the isoxazole moiety, however, the β-dicarbonyl side chains intermedially formed, was cleaved during purification of the products to give the monocarbonyl derivatives.

In order to introduce a bifunctional side chain into the α-position of quinoline rings, we investigated the reaction of quinloine 1-oxide with some 2-substituted ethyl acetimidates and acetamidines, because the following facts were reported of the reactivity of the imidates and amidines.

Namely, instead of 4,6-dimethyl-2-pyrimidineacetamide (I), 2-amino-4,6-dimethyl-3-pyridinecarboxamide (II) was reported to be obtained by the reaction of 2-carbamoylacetamidine (IIIa) with acetylacetone.[4] The acylation of ethyl 2-ethoxycarbonylacetimidate (IIIb) with diketene was shown to give the 4-pyridone (IV),[5] and the formation of the 2-pyridone (V) was not observed. The reaction of 2-ethoxycarbonylacetamidine (IIIc) with phenyl isothiocyanate was also reported to give the product (VI) possessing a thioanilide group at the β-carbon atom.[6]

Accordingly, it is presumable that ethyl 2-ethoxycarbonylacetimidate (IIIb)[7] and related compounds may react with quinoline 1-oxide according to the method reported by Hamana *et al.* on the reaction of morpholine (or piperidine) enamines.[8]

1) Part II: H. Yamanaka, M. Shiraiwa, K. Edo, and T. Sakamoto, *Chem. Pharm. Bull.* (Tokyo), **27**, 270 (1979).
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3) H. Yamanaka, H. Egawa, and T. Sakamoto, *Chem. Pharm. Bull.* (Tokyo), **26**, 2759 (1978).
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6) J. Goerdeler and U. Keuser, *Chem. Ber.*, **97**, 3106 (1964).
7) The improved procedure for the synthesis of this compound will be given in the subsequent paper.
8) M. Hamana and H. Noda, *Chem. Pharm. Bull.* (Tokyo), **13**, 912 (1965).

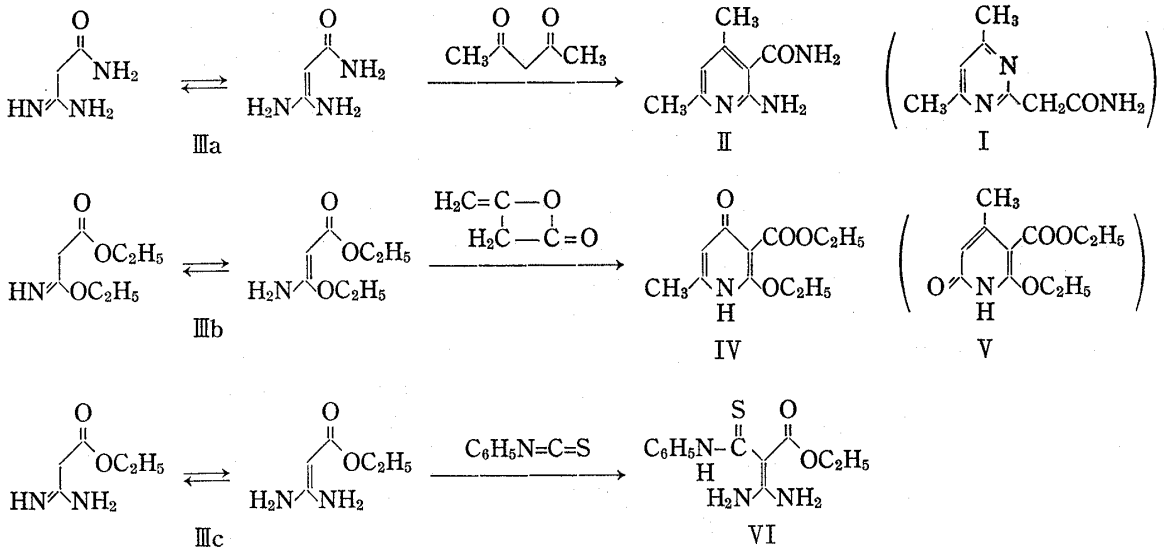

Chart 1

A solution of quinoline 1-oxide (VII), the imidate (IIIb) and benzoyl chloride in chloroform was allowed to stand overnight at room temperature giving pale yellow crystals of mp 146° in satisfactory yield. Elemental analysis established the empirical formula of the product (VIII) as $C_{16}H_{18}N_2O_3$. The hydrolysis of VIII with dilute hydrochloric acid at room

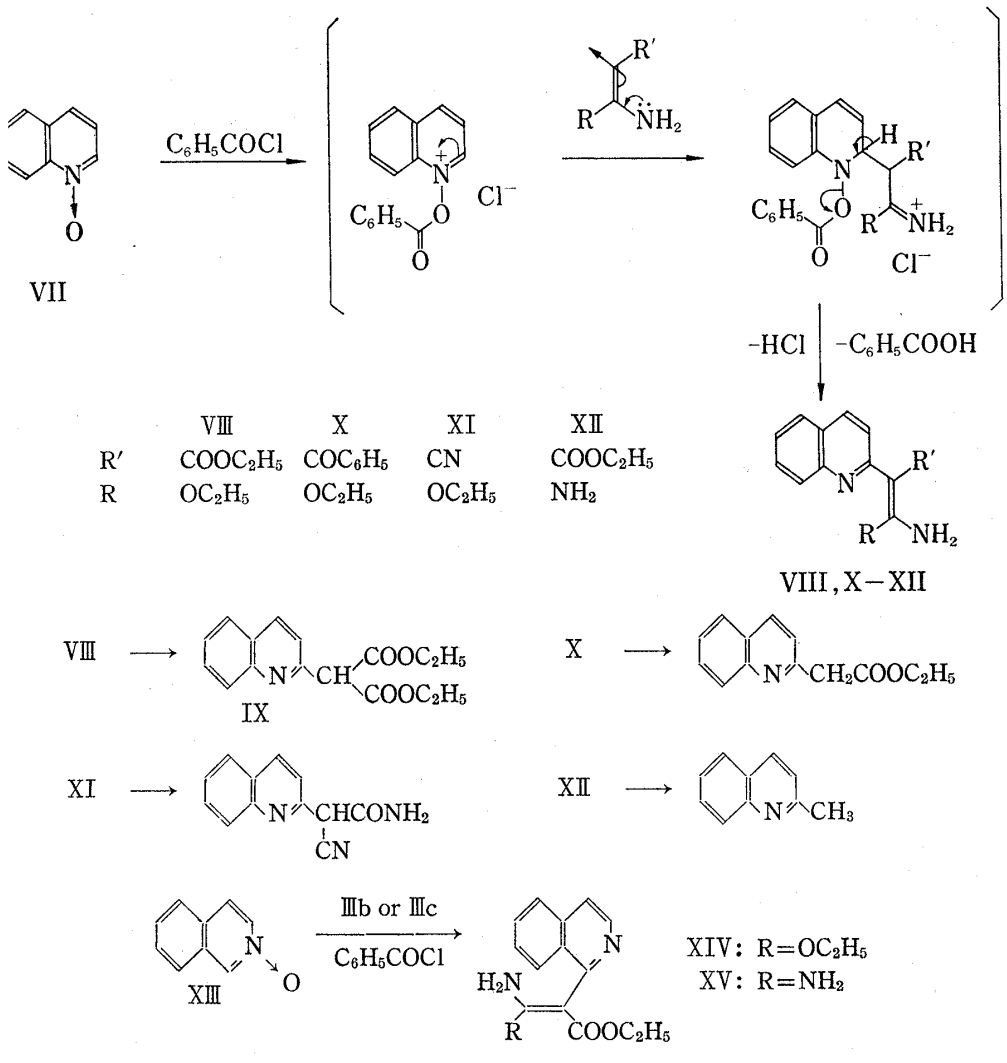

Chart 2

temperature gave diethyl 2-quinolylmalonate (IX) which was identical with the authentic specimen prepared by the method according to literature.[9] The nuclear magnetic resonance (NMR) and the infrared (IR) spectra of VIII exhibit that an imidate moiety was still retained on the side chain introduced. Therefore, ethyl 2-ethoxycarbonyl-2-(2-quinolyl)acetimidate structure was reasonably assigned to the product (VIII).

Also, ethyl 2-benzoylacetimidate (IIId)[10] and ethyl 2-cyanoacetimidate (IIIe)[11] were allowed to react with VII to give the 2-substituted quinolines, ethyl 2-benzoyl-2-(2-quinolyl)- (X) and ethyl 2-cyano-2-(2-quinolyl)acetimidate (XI), as expected.

Acid hydrolysis of X and XI with dilute hydrochloric acid under mild conditions afforded ethyl 2-quinolylacetate[12] and 2-quinolylcyanoacetamide[13] respectively.

As well as IIIb,d,e, the amidine (IIIc) condensed with VII in the presence of benzoyl chloride to give the corresponding product (XII), $C_{14}H_{15}N_3O_2$, in good yield. Acid hydrolysis of XII under the same conditions as in the case of VIII failed to give any significant product, however, XII was converted to 2-methylquinoline by heating it with dilute hydrochloric acid. Based on the above result and the NMR spectrum of XII not showing the presence of any methylene group, the structure of XII was proposed to be ethyl 2-diaminomethylene-2-quinolylacetate.

In order to extend the carbon-carbon bond formation of this type to other heteroaromatic N-oxide, pyridine 1-oxide and isoquinoline 2-oxide (XIII) were tested to react with IIIb,c. while the reaction of pyridine 1-oxide with IIIb in the presence of acylating agents resulted on the recovery of the starting N-oxide, IIIb,c readily reacted with XIII to give ethyl 2-ethoxycarbonyl-2-(1-isoquinolyl)acetimidate (XIV) and ethyl 2-diaminomethylene-1-isoquinolylacetate (XV), respectively.

As shown in the experimental section, the results of elemental analyses and the spectral data of XIV and XV were in full agreement with their assigned structure.

Although the geometrical isomerism of VIII, X, XI, XIV have not been determined in this stage, the condensation of heteroaromatic N-oxides with the primary enamines (IIIb,c) might provide one of the facile method for the synthesis of the quinoline and isoquinoline derivatives possessing a bifunctional side chain at the α-position of the rings.

Experimental[14]

Ethyl 2-Ethoxycarbonyl-2-(2-quinolyl)acetimidate (VIII)——1.45 g (0.01 mol) of quinoline 1-oxide (VII) and 3.20 g (0.02 mol) of 2-ethoxycarbonylacetimidate (IIIb)[7] were dissolved in 10 ml of $CHCl_3$ and the solution was cooled in ice-bath. Thereto 1.68 g (0.012 mol) of benzoyl chloride in 10 ml of $CHCl_3$ was added slowly. The reaction mixture was stirred at room temperature for 3 hr, and then allowed to stand overnight. The mixture was washed with 60 ml of 3 N Na_2CO_3 and dried over anhydrous K_2CO_3. The solvent was evaporated *in vacuo* and the residual crystals were washed with ether. Recrystallization from acetone–peteroleum ether gave 1.87 g (65%) of yellow prisms (VIII), mp 145—146.° *Anal.* Calcd. for $C_{16}H_{18}N_2O_3$: C, 67.11; H, 6.34; N, 9.78. Found; C, 67.04; H, 6.27; N, 9.91. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3500, 3320, 1740. NMR ($CDCl_3$): 1.00—1.50 (6H, m), 3.90—4.50 (4.4H, m), 4.90 (0.6H, s), 7.00—8.40 (7H, m).

Diethyl 2-Quinolylmalonate (IX)——1.0 g (0.004 mol) of VIII was dissolved in 20 ml of 10% HCl and the solution was allowed to stand at room temperature overnight. The reaction mixture was made strongly basic with K_2CO_3 and then extracted with ether. The extracts were dried over anhydrous K_2CO_3. After evaporating the solvent, the residue was recrystallized from petroleum ether giving 0.7 g (70%) of yellow prisms (IX), mp 73—74.° A mixed melting point with the authentic sample[9] showed no depression.

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14) All melting points were uncorrected. IR spectra measurements were performed with a JASCO IRA-1 spectrometer. NMR spectra were taken at 60 MHz with a Hitachi-Perkin-Elmer R-20 spectrometer. Chemical shifts were expressed in ppm downfield from TMS as internal standard. The following abbreviations were used. s=singlet, d=doublet, t=triplet, m=multiplet, and b=broad.

Ethyl 2-Benzoyl-2-(2-quinolyl)acetimidate (X)——1.45 g (0.01 mol) of VII was dissolved in 10 ml of $CHCl_3$ and the solution was cooled in ice-bath and thereto 1.7 g (0.012 mol) of benzoyl chloride in 10 ml of $CHCl_3$ was added with stirring. Then the mixture was allowed to stand overnight. To the solution, 3.8 g (0.02 mol) of IIId[10] in 15 ml of $CHCl_3$ was added and the mixture was stirred at room temperature overnight. The precipitate was filtered and the filtrate was washed with 10% Na_2CO_3 and dried over anhydrous K_2CO_3. The solvent was evaporated *in vacuo* and the residual oil was purified on a column of silica gel by elution with CH_3OH giving yellow oil. Crystallization from ether–petroleum ether gave 1.7 g (54%) of yellow crystals, mp 161—162.5°. *Anal.* Calcd. for $C_{20}H_{18}N_2O_2$: C, 75.45; H, 5.70; N, 8.80. Found; C, 75.41; H, 5.81; N, 8.60. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3510, 3300, 1640. NMR ($CDCl_3$): 1.08 (3H, t, J=7.0 Hz), 4.05 (2H, q, J=7.0 Hz), 3.80—4.30 (0.5H, b), 7.00—8.00 (12.5H, m).

Ethyl 2-Quinolylacetate——0.32 g (0.001 mol) of X was dissolved in 10 ml of 10% HCl and the solution was stirred at room temperature for 5 hr. The reaction mixture was neutrallized with K_2CO_3 and the separated oil was extracted with ether. After drying over anhydrous K_2CO_3, the solvent was evaporated *in vacuo* and the residual oil was purified on a column of alumina by elution with ether giving 0.1 g (47%) of ethyl 2-quinolylacetate; picrate mp 153—154° (dec.), lit.[12] mp 152—153° (dec.). NMR (CCl_4); 1.22 (3H, t, J=7 Hz), 3.88 (2H, s), 4.1 (2H, q, J=7 Hz), 7.2—8.0 (6H, m).

Ethyl 2-Cyano-2-(2-quinolyl)acetimidate (XI)——1.45 g (0.01 mol) of VII in 10 ml of $CHCl_3$ was cooled in ice-bath and stirred. Thereto 1.7 g (0.012 mol) of benzoyl chloride on 10 ml of $CHCl_3$ was added and the mixture was allowed to stand at room temperature overnight. To the solution 2.3 g (0.02 mol) of IIIe[11] in 15 ml of $CHCl_3$ was added slowly and the mixture was stirred at room temperature overnight. The precipitate was filtered and the filtrate was washed with 10% Na_2CO_3 and dried over anhydrous K_2CO_3. The solvent was evaporated *in vacuo* and the residual oil was chromatographed on a silica gel column by elution with ether–ethyl acetate (1: 1). Recrystallization from ethyl acetate–petroleum ether gave 0.7 g (29%) of yellow prisms (XI), mp 182—183°. *Anal.* Calcd. for $C_{14}H_{13}N_3O$: C, 70.27; H, 5.48; N, 17.56. Found: C, 70.05; H, 5.69; N, 17.48. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3500, 3350, 2200. NMR ($CDCl_3$): 1.50 (3H, t, J=7.0 Hz), 4.25 (2H, q, J=7.0 Hz), 7.20—8.10 (8H, m, 2H were exchanged by D_2O).

2-Quinolylcyanoacetamide——0.3 g (0.0013 mol) of XI was dissolved in 10% HCl (15 ml)–EtOH (15 ml) and the mixture was heated at 50—60° for 3 hr. After evaporating EtOH, the aqueous solution was neutrallized with K_2CO_3 and then extracted with $CHCl_3$. The extracts were dried over anhydrous K_2CO_3 and the solvent was evaporated *in vacuo*. The residual cyrstals were recrystallized from CH_3OH giving 0.05 g (23%) of yellow prisms, mp 248—249.5°. A mixed melting point with the authentic sample[13] showed no depression.

Ethyl 2-Diaminomethylene-2-quinolylacetate (XII)——1.45 g (0.01 mol) of VII in 10 ml of $CHCl_3$ was cooled in ice-bath and stirred. Thereto 1.7 g (0.012 mol) of benzoyl chloride in 10 ml of $CHCl_3$ was added and the solution was left at room temperature overnight. To the solution, 1.3 g (0.01 mol) of IIIc[7] in 20 ml of $CHCl_3$ was added and allowed to stand at room temperature for 3 days. The mixture was extracted with 10% HCl and the extracts were made basic with K_2CO_3. The separated oil was extracted with ether and the extracts were dried over K_2CO_3. After evaporating the solvent, the residue was chromatographed on a silica gel column by elution with ether. Recrystallization from ether–petroleum ether gave 1.6 g (62%) of yellow prisms (XII), mp 99—100°. *Anal.* Calcd. for $C_{14}H_{15}N_3O_2$: C, 65.35; H, 5.88; N, 16.33. Found; C, 65.34; H, 6.00; N, 16.33. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3450, 3260, 1640 (Sh), 1590. NMR ($CDCl_3$): 1.25 (3H, t, J= 7 Hz), 4.20 (2H, q, J=7.0 Hz), 6.40—8.30 (10H, m, 4H were exchanged by D_2O).

Ethyl 2-Ethoxycarbonyl-2-(1-isoquinolyl)acetate (XIV)——4.35 g (0.03 mol) of XIII in 30 ml of $CHCl_3$ was cooled in ice-bath and stirred. Thereto 5.10 g (0.036 mol) of benzoyl chloride in 30 ml of $CHCl_3$ was added and the solution was left at room temperature overnight. The mixture was washed with 10% NaOH and dried over anhydrous Na_2SO_4. The solvent was evaporated *in vacuo* and the residue was chromatographed on an alumina column by elution with CH_3OH. Recrystallization from acetone gave 4.6 g (54%) of yellow prisms (XIV), mp 138—140°. *Anal.* Calcd. for $C_{16}H_{18}N_2O_3$: C, 67.11; H, 6.34; N, 9.78. Found: C, 67.03; H, 6.59; N, 9.98. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3300, 3170, 1660. NMR ($CDCl_3$): 0.80—1.40 (6H, m), 3.60—4.50 (4H, m), 5.49 (1H, s, exchanged by D_2O), 7.20—8.60 (7H, m).

Ethyl 2-Diaminomethylene-2-(1-isoquinolyl)acetate (XV)——1.45 g (0.01 mol) of XIII in 10 ml of $CHCl_3$ was cooled in ice-bath and stirred. Thereto 1.7 g (0.012 mol) of benzoyl chloride in 10 ml of $CHCl_3$ was added and the mixture was left at room temperature overnight. To the solution, 1.3 g (0.01 mol) of IIIc in 15 ml of $CHCl_3$ was added and the mixture was allowed to stand at room temperature overnight. The precipitate was collected by filtration and recrystallized from EtOH–AcOEt giving 0.85 g (30%) of yellow prisms (XV), mp 193—194.5°. *Anal.* Calcd. for $C_{14}H_{15}N_3O_2$: C, 65.35; H, 5.88; N, 16.33. Found: C, 65.17; H, 5.74; N, 16.19. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3500, 3300, 1640. NMR ($CDCl_3$): 0.85 (3H, t, J=7 Hz), 3.85 (2H, q, J=7.0 Hz), 5.00—6.40 (2H, b), 7.30—8.50 (8H, m).

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