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Studies on Quinoline and Isoquinoline Derivatives. I. Condensation of Quinoline and Isoquinoline N-Oxides with Isoxazoles

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In order to introduce a carbon function to the 2-position of quinoline, the reaction of quinoline 1-oxide with some isoxazole derivatives whose 4-positions are free, was investigated. The products, such as 2-(5-amino-3-methyl-4-isoxazolyl)-, 2-(5-ethylamino-3-methyl-4-isoxazolyl)-, 2-(5-hydroxy-3-methyl-4-isoxazolyl)-, and 2-(5-ethoxy-3-methyl-4-isoxazolyl)-quinolines were hydrogenated in the presence of Raney nickel catalyst to give the quinoline derivatives possessing the desired side chains. Treatment of 2-(5-hydroxy-3-methyl-4-isoxazolyl)quinoline with excess phosphoryl chloride afforded 2-(5-chloro-3-methyl-4-isoxazolyl)quinoline whose chlorine atom could be substituted by diethylamine and ethoxide ion.

These reactions were equally applied to isoquinoline 2-oxide yielding the corresponding products.

Keywords——2-(5-substituted-3-methyl-4-isoxazolyl)quinolines; 1-(5-substituted-3-methyl-4-isoxazolyl)isoquinolines; hydrogenation of isoxazoles; chlorination of 5-hydroxyisoxazoles; 2-(2-aminopropyl)quinoline; 1-(2-aminopropyl)isoquinoline; 5-ethylamino-3-methylisoxazole; quinoline 1-oxide; isoquinoline 2-oxide

Hamana, *et al.* reported that the reaction of quinoline 1-oxide with enamines or active methylene compounds in the presence of appropriate acylating reagents offers the advantage of widespread applicability and experimental simplicity to introduce a carbon substituent at the 2-position of quinoline rings.[2a,b]

On the other hand, it is well known that on catalytic hydrogenation over Raney nickel, the nitrogen-oxygen bond of isoxazole rings cleaves to give β-dicarbonyl compounds. For instance, 3,5-dimethylisoxazole and 5-amino-3-phenylisoxazole are converted to 4-amino-3-penten-2-one and 3-aminocinnamamide, respectively.[3a,b]

It was also reported that isoxazoles in which the 4-position is free are halogenated, nitrated, or sulfonated at this position. Since the presence of an amino group on the ring facilitates such electrophilic substitution, 5-amino-3-phenylisoxazole is readily formylated at the 4-position by Vilsmeier reagent to give 5-amino-4-formyl-3-phenylisoxazole.[4] Further, 5-isoxazolones unsubstituted at the 4-position are known to contain an active methylene

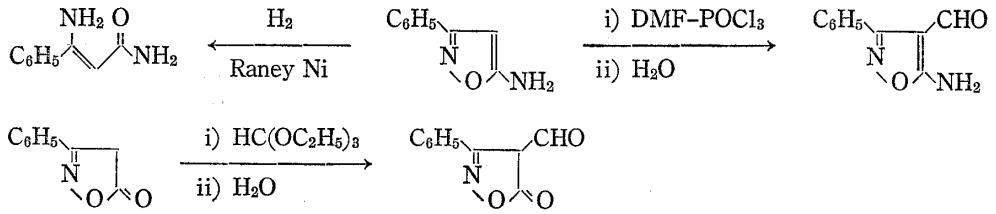

Chart 1

1) Location: *Aobayama, Sendai 980, Japan.*
2) *a*) M. Hamana and H. Noda, *Chem. Pharm. Bull.* (Tokyo), **11**, 1331 (1963); *b*) M. Hamana and M. Yamazaki, *Chem. Pharm. Bull.* (Tokyo), **11**, 415 (1963).
3) *a*) G.S. D'Alcontres, *Gazz. Chim. Ital.*, **80**, 441 (1950); *b*) G. Shaw and G. Sugowdz, *J. Chem. Soc.*, **1954**, 665.
4) H. Yamanaka, T. Sakamoto, and A. Shiozawa, *Heterocycles*, **7**, 51 (1977).

group, *e.g.* 3-phenyl-5-isoxazolone condenses with ethyl orthoformate to yield 4-formyl-3-phenyl-5-isoxazolone.[5]

From these points of view, our interest was focussed on the condensation of aromatic amine N-oxides with 5-aminoisoxazoles and 5-isoxazolones in order to introduce a functional side chain into the α-position of aromatic heterocycles.

When quinoline 1-oxide (I) was heated with 5-amino-3-methylisoxazole (IIIa) in chloroform in the presence of benzoyl chloride, pale yellow prisms (IVa) were obtained. The elemental analysis of IVa established its empirical formula to be $C_{13}H_{10}N_3O$, which suggested IVa being a condensation product of I and IIIa with loss of one molecule of water. The infrared (IR) spectrum of IVa shows absorption bands at 3350 and 3240 cm^{-1}, but no band due to an N-oxide group is observed. The nuclear magnetic resonance (NMR) spectrum exhibits signals owing to six aromatic ring protons at 8.0—9.25 ppm together with a singlet (3H) at 2.65 ppm. Based on these data the structure of the product (IVa) was proposed to be 2-(5-amino-3-methyl-4-isoxazolyl)quinoline.

The catalytic hydrogenation of IVa over Raney nickel and subsequent purification by column chromatography on Al_2O_3 afforded colorless needles (Va) whose melting point (191—

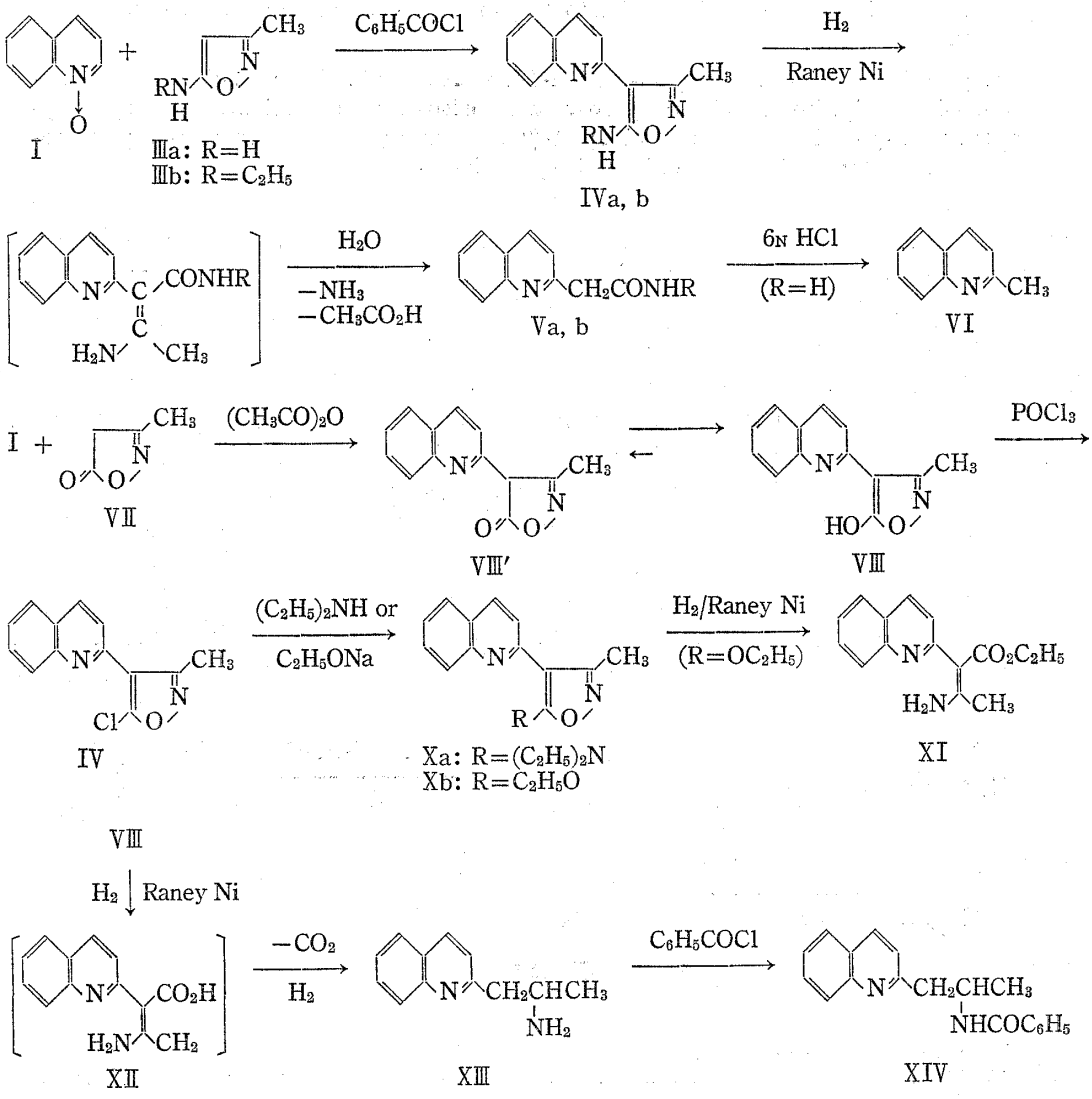

Chart 2

5) P. Papini and S. Checchi, *Gazz. Chim. Ital.*, **82**, 730 (1953).

192°) is in close agreement with that of quinoline-2-acetamide (lit.[6] mp 191—193°). The spectral data of Va are consistent with the assigned structure. Furthermore, acid hydrolysis of Va gave rise to 2-methylquinoline (VI).

The reaction of I with 5-ethylamino-3-methylisoxazole (IIIb) readily prepared by the lithium aluminum hydride reduction of N-(3-methyl-5-isoxazolyl)acetamide, afforded the corresponding 5-ethylamino derivative (IVb) under the same conditions. Upon catalytic hydrogenation IVb was transformed to N-ethyl-2-quinolineacetamide (Vb). The elemental analyses and spectral data of IVb and Vb are consistent with the expected structures.

According to the similar manner[2b] given for the reaction of I with active methylene compounds, 3-methyl-5-isoxazolone (VII) was treated with I in chloroform in the presence of acetic anhydride to give 2-(5-hydroxy-3-methyl-4-isoxazolyl)quinoline (VIII). In the IR spectrum of VIII, no absorption band assignable to a carbonyl group is observed. The NMR spectrum of VIII shows signals owing to a methyl group at 2.43 ppm as a singlet (3H) and a hydroxyl group at 13.0—14.0 ppm. These spectral data suggest that the enol content in the tautomerism (VIII⇌VIII') may approach immeasurably close to 100%.

On treatment with excess phosphoryl chloride VIII was converted to 2-(5-chloro-3-methyl-4-isoxazolyl)quinoline (IX), although VII could not be chlorinated to 5-chloro-3-methylisoxazole under the same conditions. The chlorine atom of IX was considerably reactive toward nucleophilic reagents and readily replaced with diethylamine or ethoxide ion to give the corresponding diethylamino or ethoxyl derivatives (Xa, b).

The ring cleavage reaction of VIII by means of catalytic hydrogenation gave a liquid [bp 114—116° (3 mmHg)] (XIII) which reacted with benzoyl chloride to yield the benzoate (XIV). From the spectral data of XIV, the structure of XIII was determined to be 2-(2-aminopropyl)quinoline. Accordingly, it is considered that the carboxylic acid (XII) initially formed is converted into XIII by spontaneous decarboxylation. The catalytic reduction of

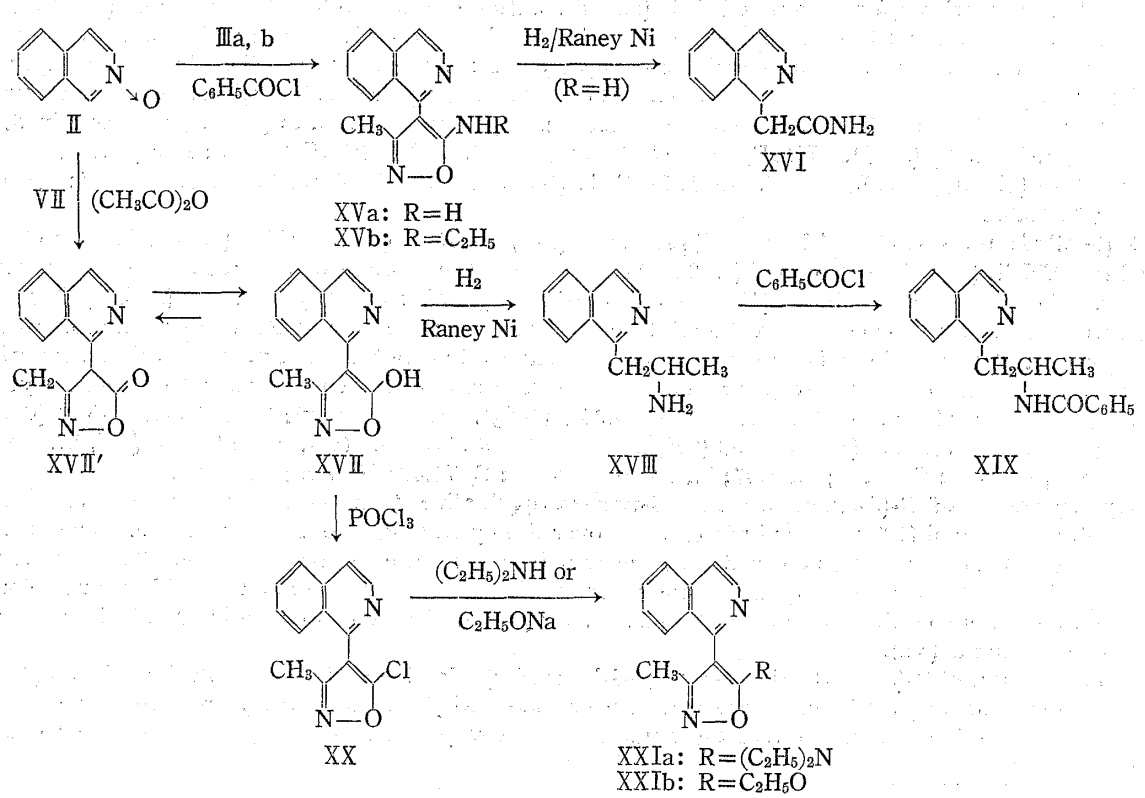

Chart 3

6) F. Zymalkowski and W. Schauer, *Arch. Pharm.*, **290**, 218 (1957).

Xb afforded ethyl 3-amino-2-(2-quinolyl)crotonate (XI) in good yield. This observation suggests that the decarboxylation might take place prior to the reduction of the side chain double bond of XII.

The reactions described above, were equally applicable to isoquinoline 2-oxide (II) to give the corresponding 1-substituted isoquinolines. Thus the reaction of II with IIIa, b in the presence of benzoyl chloride afforded 1-(5-amino-3-methyl-4-isoxazolyl)isoquinoline (XVa), and 1-(5-ethylamino-3-methyl-4-isoxazolyl)isoquinoline (XVb), respectively. The condensation of II and VII in the presence of acetic anhydride also gave the expected product, 1-(5-hydroxy-3-methyl-4-isoxazolyl)isoquinoline (XVII). The spectral data show that, as well as VIII, this compound exists in an enol form (XVII), rather than a keto form (XVII') in a chloroform solution.

On catalytic hydrogenation over Raney nickel, XVa and XVII were transformed into the corresponding 1-substituted isoquinolines, 1-isoquinolineacetamide (XVI), and 1-(2-aminopropyl)isoquinoline (XVIII) whose structure was confirmed by converting it to the benzoate XIX.

Further, the chlorination of XVII with excess phosphoryl chloride and the subsequent treatment of the chloride (XX) with diethylamine or sodium ethoxide also afforded the desired derivatives (XXIa, b). As shown in the experimental section, the spectral data of all the derivatives (XIX—XXIa, b) are satisfactory to their proposed structures.

In conclusion, the synthetic utilities of the isoxazoles in the field of N-oxide chemistry were recognized.

Experimental[7]

2-(5-Amino-3-methyl-4-isoxazolyl)quinoline (IVa)——Benzoyl chloride (3.37 g, 0.024 mol) was added to a $CHCl_3$ (40 ml) solution of quinoline 1-oxide (I) (2.90 g, 0.02 mol) under ice-cooling. After the cold solution had been stirred for 40 min, a $CHCl_3$ (20 ml) solution of 5-amino-3-methylisoxazole (IIIa) (2.35 g, 0.024 mol) was added and the mixture was stirred for 40 min at room temperature followed by reflux for 4 hr. The mixture was made alkaline with 3 N Na_2CO_3 and extracted with $CHCl_3$. The $CHCl_3$ layer was dried over Na_2SO_4 and the $CHCl_3$ was removed. The residue was purified by Al_2O_3 column chromatography using ether and $CHCl_3$ as eluants. From the $CHCl_3$ eluate pale yellow needles (MeOH) were obtained, mp 201—203°, yield 1.62 g (35%). IR ν_{max}^{KBr} cm^{-1}: 3350, 3240, 1640. NMR (CF_3COOH) δ: 2.65 (3H, s), 8.0—9.5 (5H, m), 9.15 (1H, d, J=9.0). *Anal.* Calcd. for $C_{13}H_{11}N_3O$: C, 69.32; H, 4.92; N, 18.66. Found: C, 69.00; H, 5.12; N, 18.65.

2-(5-Ethylamino-3-methyl-4-isoxazolyl)quinoline (IVb)——Benzoyl chloride (1.40 g, 0.01 mol) was added to a $CHCl_3$ (20 ml) solution of I (1.59 g, 0.011 mol) and the mixture was stirred at room temperature for 2 hr. To this solution a $CHCl_3$ (20 ml) solution of 5-ethylamino-3-methylisoxazole (IIIb) (1.26 g, 0.01 mol) was added under ice-cooling and the mixture was stirred for 35 min at room temperature followed by reflux for 5 hr. The reaction mixture was worked up as above to give the crude product which was purified by Al_2O_3 column chromatography (benzene). The benzene eluate was concentrated to give pale yellow needles (ether–petr. ether), mp 111—113°, yield 0.35 g (14%). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3200, 1640. NMR ($CDCl_3$) δ: 1.37 (3H, t, J=6.8), 2.50 (3H, s), 3.58 (2H, dq, J=6.0, 6.8), 7.3—8.1 (6H, m), 8.8—9.3 (1H, b). *Anal.* Calcd. for $C_{15}H_{15}N_3O$: C, 71.12; H, 5.97; N, 16.59. Found: C, 71.43; H, 5.90; N, 16.83.

Hydrogenation of 2-(5-Amino-3-methyl-4-isoxazolyl)quinoline (IVa)——A solution of IVa (1.12 g, 0.005 mol) in methanol (100 ml) was hydrogenated over Raney Ni (1 g) at ordinary pressure. The catalyst was filtered and the filtrate was concentrated under reduced pressure to give a residue. The residue was purified by Al_2O_3 column chromatography using ether and $CHCl_3$ as eluants. From the $CHCl_3$ eluate colorless needles (EtOAc) were obtained mp 191—192°, yield 0.70 g (75%). This compound is identical with authentic 2-quinolineacetamide (Va).

Hydrogenation of 2-(5-Ethylamino-3-methyl-4-isoxazolyl)quinoline (IVb)——A solution of IVb (0.52 g, 0.002 mol) in methanol (40 ml) was hydrogenated over Raney Ni (0.5 g) at ordinary pressure. The mixture was worked up similarly as above and the crude product was purified by Al_2O_3 column chromatography

7) All melting points and boiling points are uncorrected. The IR spectra were taken with a JASCO IRA-1 spectrometer and the NMR spectra with a Hitachi R-20 spectrometer. The chemical shifts are expressed by δ and the coupling constants by Herz (Hz). Following abrreviations are used: singlet (s), doublet (d), triplet (t), quartet (q), multiplet (m), double quartet (dq), broad (b).

(ether) to give Vb as pale yellow scales (ether–petr. ether), mp 108—110°, yield 0.27 g (63%). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3440, 1660. NMR ($CDCl_3$) δ: 1.10 (3H, t, J=7.2), 3.30 (2H, dq, J=5.7, 7.2), 3.89 (2H, s), 7.3—8.2 (7H, m). *Anal.* Calcd. for $C_{13}H_{14}N_2O$ (Vb): C, 72.87; H, 6.59; N, 13.08. Found: C, 72.95; H, 6.41; N, 13.14.

Hydrolysis of 2-Quinolineacetamide (Va)——After a mixture of Va (0.40 g, 0.02 mol) and 6 N HCl (10 ml) had been refluxed for 2 hr, the mixture was made alkaline with 3 N Na_2CO_3 and concentrated under reduced pressure. The residue was extracted with hot $CHCl_3$ and the $CHCl_3$ layer dried over K_2CO_3. The $CHCl_3$ was removed and the residue was distilled under reduced pressure to give a colorless liquid, bp 90° (14 mmHg), yield 0.20 g (65%). This compound is identical with authentic 2-methylquinoline.

1-(5-Amino-3-methyl-4-isoxazolyl)isoquinoline (XVa)——According to a similar manner for the preparation of IVa, IIIa (1.77 g, 0.018 mol) was added to a mixture of isoquinoline 2-oxide (II) (1.45 g, 0.01 mol), benzoyl chloride (1.69 g, 0.012 mol) and $CHCl_3$ (20 ml), and the mixture was stirred for 30 min at room temperature followed by reflux for 3 hr. The resulting precipitate was filtered, suspended in 3 N Na_2CO_3 and extracted with $CHCl_3$. The extract was purified by Al_2O_3 column chromatography using ether and $CHCl_3$. From the $CHCl_3$ eluate pale yellow needles (XVa) (benzene) were obtained, mp 174—176°, yield 1.0 g (45%). IR ν_{max}^{KBr} cm^{-1}: 3500, 3400, 1650. NMR ($CDCl_3$) δ: 2.20 (3H, s), 5.0—5.3 (2H, b), 7.3—8.1 (5H, m), 8.51 (1H, d, J=5.3). *Anal.* Calcd. for $C_{13}H_{11}N_3O$: C, 69.32; H, 4.92; N, 18.66. Found: C, 69.00; H, 5.19; N, 18.38.

1-(5-Ethylamino-3-methyl-4-isoxazolyl)isoquinoline (XVb)——According to a similar manner for the preparation of IVa, IIIb (1.51 g, 0.012 mol) was added to a mixture of II (1.45 g, 0.01 mol), benzoyl chloride (1.54 g, 0.011 mol) and $CHCl_3$ (20 ml) under ice-cooling. After the mixture had been stirred at room temperature for 8 hr, 3 N Na_2CO_3 was added. The crude product obtained by $CHCl_3$ extraction was purified by Al_2O_3 column chromatography (benzene) to give pale yellow prisms (XVb) (ether–petr. ether), mp 107—108°, yield 0.45 g (17%). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3420, 1635. NMR ($CDCl_3$) δ: 1.21 (3H, t, J=6.8), 2.16 (3H, s), 3.43 (2H, dq, J=7.5, 6.8), 5.6—6.0 (1H, b), 7.4—8.1 (5H, m), 8.45 (1H, d, J=6.0). *Anal.* Calcd. for $C_{15}H_{15}N_3O$: C, 71.12; H, 5.97; N, 16.59. Found: C, 71.37; H, 6.05, N, 16.63.

Hydrogenation of 1-(5-Amino-3-methyl-4-isoxazolyl)isoquinoline (XVa)——A solution of XVa (1.12 g, 0.005 mol) in methanol (100 ml) was hydrogenated over Raney Ni (1 g) at ordinary pressure. The mixture was worked up in the same manner as with IVa and the crude product was purified by Al_2O_3 column chromatography using ether and $CHCl_3$ as eluants. From the $CHCl_3$ eluate colorless needles (acetone) was obtained, mp 209—211°, yield 0.74 g (80%). This compound is identical with authentic 1-isoquinolineacetamide (XVI).

2-(5-Hydroxy-3-methyl-4-isoxazolyl)quinoline (VIII)——To a $CHCl_3$ (40 ml) solution of I (11.6 g, 0.08 mol) was added a $CHCl_3$ (20 ml) solution of acetic anhydride (8.2 g, 0.08 mol) and the mixture was stirred for 4 hr at room temperature. To this solution a $CHCl_3$ (20 ml) solution of VII (9.6 g, 0.096 mol) was added and stirred for 20 hr at room temperature. The mixture was washed with 3 N HCl then with 1 N $NaHCO_3$, and dried over Na_2SO_4. The $CHCl_3$ was removed and the crude product was recrystallized from benzene–$CHCl_3$ to give yellow needles (VIII), mp 244—245° (dec.), yield 7.9 g (44%). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1650. NMR ($CDCl_3$) δ: 2.43 (3H, s), 7.3—8.0 (4H, m), 7.38 (1H, d, J=9.0), 8.05 (1H, d, J=9.0), 13.0—14.0 (1H, b). *Anal.* Calcd. for $C_{13}H_{10}N_2O_2$: C, 69.01; H, 4.46; N, 12.38. Found: C, 68.95; H, 4.34; N, 12.56.

1-(5-Hydroxy-3-methyl-4-isoxazolyl)isoquinoline (XVII)——a) According to the same manner described above, a $CHCl_3$ (20 ml) solution of VII (24 g, 0.24 mol) was added to a $CHCl_3$ (80 ml) solution of II (29 g, 0.2 mol) and acetic anhydride (20.4 g, 0.2 mol). The mixture was stirred for 18 hr at room temperature and the resulting precipitate was filtered and recrystallized from tetrahydrofuran to give yellow needles (XVII), mp 253—255° (dec.), yield 10 g (22%). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1640. NMR (CF_3COOH) δ: 2.51 (3H, s), 8.0—8.8 (6H, m), 12.5—13.5 (1H, b). *Anal.* Calcd. for $C_{13}H_{10}N_2O_2$: C, 69.01; H, 4.46; N, 12.38. Found: C, 68.94; H, 4.26; N, 12.43.

b) To a $CHCl_3$ (60 ml) solution of II (10.2 g, 0.07 mol) and VII (7.7 g, 0.07 mol) was added benzoyl chloride (9.8 g, 0.07 mol). The mixture was stirred at room temperature for 10 hr and extracted with 3 N NaOH. The aqueous layer was acidified with 3 N HCl to give precipitate. The precipitate was filtered, washed with 1 N $NaHCO_3$ and H_2O then with a small amount of methanol and recrystallized from tetrahydrofuran to give yellow needles, yield 7.2 g (45%).

Hydrogenation of 2-(5-Hydroxy-3-methyl-4-isoxazolyl)quinoline (VIII)——A solution of VIII (1.13 g, 0.005 mol) in methanol (60 ml) and conc. NH_4OH (20 ml) was hydrogenated over Raney Ni (1 g) at a pressure of 3.1 kg/cm². The catalyst was filtered off and the methanol was removed under reduced pressure. The resulting aqueous solution was extracted with $CHCl_3$. The $CHCl_3$ layer was dried over K_2CO_3 and the $CHCl_3$ was removed. The residue was purified by Al_2O_3 column chromatography using ether, $CHCl_3$ and then methanol as eluants. From the methanol eluate a liquid [bp 114—116° (3 mmHg), 0.3 g] was obtained. The liquid was shaken with benzoyl chloride (0.25 ml) and 3 N NaOH (2 ml) to give XIV as colorless needles (acetone), mp 155—156°, yield 0.43 g (31%). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3320, 1660. NMR ($CDCl_3$) δ: 1.28 (3H, d, J=6.8), 2.8—3.6 (2H, m), 4.3—4.9 (1H, m), 7.2—8.5 (12H, m). *Anal.* Calcd. for $C_{19}H_{18}N_2O$ (XIV): C, 78.59; H, 6.25; N, 9.65. Found: C, 78.95; H, 6.20; N, 9.91.

Hydrogenation of 1-(5-Hydroxy-3-methyl-4-isoxazolyl)isoquinoline (XVII)——A solution of XVII (1.13 g, 0.005 mol) in methanol (40 ml) and conc. NH_4OH (20 ml) was hydrogenated over Raney Ni (1 g) at ordinary pressure. The mixture was worked up similarly as above and the residue was purified by Al_2O_3

column chromatography using ether, $CHCl_3$ and then methanol as eluants. From the methanol eluate a pale yellow liquid [bp ~120° (3 mmHg), 0.37 g] was obtained which was converted to a benzoate with benzoyl chloride (0.3 ml) and 3 N NaOH (2 ml). The benzoate was recrystallized from benzene to give colorless needles, mp 130—132°, yield 0.35 g (25%). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3320, 1670. NMR ($CDCl_3$) δ: 1.31 (3H, d, J=6.8), 3.53 (2H, m), 4.4—4.9 (1H, m), 7.2—8.4 (11H, m), 8.45 (1H, d, J=5.3). *Anal.* Calcd. for $C_{19}H_{18}N_2O$ (XIX): C, 78.59; H, 6.25; N, 9.65. Found: C, 78.50; H, 6.21; N, 9.45.

2-(5-Chloro-3-methyl-4-isoxazolyl)quinoline (IX)——A mixture of $POCl_3$ (30 ml), Et_3N (1.7 ml) and VIII (2.71 g, 0.012 mol) was refluxed for 1 hr. Excess $POCl_3$ and Et_3N was removed under reduced pressure and the residue was poured into ice-cooled conc. NH_4OH. The aqueous layer was extracted with $CHCl_3$ and then the $CHCl_3$ was removed. The residue was purified by Al_2O_3 column chromatography (benzene) to give colorless needles (ether–petr. ether), mp 120—122°, yield 2.68 g (91%). NMR ($CDCl_3$) δ: 2.62 (3H, s), 7.4—8.4 (6H, m). *Anal.* Calcd. for $C_{13}H_9ClN_2O$: C, 63.80; H, 3.68; Cl, 14.52; N, 11.45. Found: C, 63.71; H, 3.77; Cl, 14.44; N, 11.34.

1-(5-Chloro-3-methyl-4-isoxazolyl)isoquinoline (XX)——According to the same method described above, XVII (6.78 g, 0.03 mol) was chlorinated with $POCl_3$ (60 ml) and Et_3N (4.2 ml), and the mixture was worked up in the usual way. The crude product was purified by Al_2O_3 column chromatography (benzene) to give colorless needles (benzene), mp 102—104°, yield 6.2 g (85%). NMR ($CDCl_3$) δ: 2.26 (3H, s), 7.5—8.0 (5H, m), 8.60 (1H, d, J=5.3). *Anal.* Calcd. for $C_{13}H_9ClN_2O$: C, 63.80; H, 3.68; Cl, 14.52; N, 11.45. Found: C, 63.72; H, 3.69; Cl, 14.62; N, 11.34.

2-(5-Diethylamino-3-methyl-4-isoxazolyl)quinoline (Xa)——A mixture of IX (0.49 g, 0.002 mol) and Et_2NH (20 ml) in a sealed tube was heated at 100° for 5 hr. The resulting precipitate ($Et_2\overset{+}{N}H_2Cl^-$) was filtered off and the filtrate was concentrated to dryness under reduced pressure. The residue was purified by Al_2O_3 column chromatography (ether) to give a pale yellow liquid, bp 126° (0.05 mmHg), yield 0.56 g (96%). NMR ($CDCl_3$) δ: 1.15 (6H, t, J=6.8), 2.52 (3H, s), 3.48 (4H, q, J=6.8), 7.3—7.9 (5H, m), 8.50 (1H, d, J=8.3). *Anal.* Calcd. for $C_{17}H_{19}N_3O$: C, 72.57; H, 6.81; N, 14.94. Found: C, 72.25; H, 6.90; N, 14.74.

1-(5-Diethylamino-3-methyl-4-isoxazolyl)isoquinoline (XXIa)——A mixture of XX (0.49 g, 0.002 mol) and Et_2NH (20 ml) in a sealed tube was heated at 100° for 5 hr. The mixture was worked up as above to give a pale yellow liquid, bp 118° (0.15 mmHg), yield 0.50 g (89%). NMR ($CDCl_3$) δ: 0.92 (6H, t, J=6.8), 1.90 (3H, s), 3.12 (4H, q, J=6.8), 7.3—8.1 (5H, m), 8.55 (1H, d, J=5.3). *Anal.* Calcd. for $C_{17}H_{19}N_3O$: C, 72.57; H, 6.81; N, 14.94. Found: C, 72.73; H, 6.97; N, 15.00.

2-(5-Ethoxy-3-methyl-4-isoxazolyl)quinoline (Xb)——To an abs. EtOH–EtONa solution prepared from abs. EtOH (40 ml) and metallic sodium (0.37 g) was added IX (1.96 g, 0.008 mol) and the mixture was refluxed for 3 hr. After the EtOH had been removed, H_2O was added to the residue and the H_2O layer extracted with $CHCl_3$. The $CHCl_3$ was removed to afford colorless needles (ether–petr. ether), mp 96—97°, yield 1.67 g (83%). NMR ($CDCl_3$) δ: 1.50 (3H, t, J=6.8), 2.70 (3H, s), 4.55 (2H, q, J=6.8), 7.3—8.2 (6H, m). *Anal.* Calcd. for $C_{15}H_{14}N_2O_2$: C, 70.85; H, 5.55; N, 11.02. Found: C, 70.82; H, 5.51; N, 11.06.

1-(5-Ethoxy-3-methyl-4-isoxazolyl)isoquinoline (XXIb)——According to the same method described above, XX (3.68 g, 0.015 mol) was refluxed for 3 hr in abs. EtOH–EtONa prepared from abs. EtOH (50 ml) and metallic sodium (0.69 g). The mixture was worked up as above to give colorless needles (ether–petr. ether), mp 91—93°, yield 3.10 g (82%). NMR ($CDCl_3$) δ: 1.33 (3H, t, J=7.0), 2.25 (3H, s), 4.43 (2H, q, J=7.0), 7.5—8.1 (5H, m), 8.58 (1H, d, J=6.0). *Anal.* Calcd. for $C_{15}H_{14}N_2O_2$: C, 70.85; H, 5.55; N, 11.02. Found: C, 70.72; H, 5.49; N, 10.84.

Hydrogenation of 2-(5-Ethoxy-3-methyl-4-isoxazolyl)quinoline (Xb)——A methanol (80 ml) solution of Xb (1.26 g, 0.005 mol) was hydrogenated over Raney Ni (1 g) at ordinary pressure. The catalyst was filtered off and the filtrate was concentrated under reduced pressure. After water had been added to the residue, the mixture was extracted with $CHCl_3$. The $CHCl_3$ was removed and the crude product was recrystallized from ether–petr. ether to give colorless prisms (XI), mp 112°, yield 0.90 g (71%). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3520, 3320, 1665. NMR ($CDCl_3$) δ: 1.12 (3H, t, J=7.0), 1.90 (1H, s), 4.16 (2H, q, J=7.0), 7.30—8.30 (8H, m). *Anal.* Calcd. for $C_{15}H_{16}N_2O_2$: C, 70.29; H, 6.29; N, 10.93. Found: C, 70.26; H, 6.09; N, 11.28.

5-Ethylamino-3-methylisoxazole (IIIb)——To an anhydrous tetrahydrofuran solution (80 ml) of N-(3-methyl-5-isoxazolyl)acetamide (7.0 g, 0.05 mol) was portionwise added $LiAlH_4$ (2.14 g, 0.056 mol) under ice-cooling and the mixture was refluxed for 5 hr. Water was added to the mixture and the precipitate was filtered. The filtrate was concentrated under reduced pressure and the crude product was recrystallized from ether–petr. ether to give colorless needles, mp 80—82°, yield 5.1 g (81%). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3440, 1620. NMR ($CDCl_3$) δ: 1.20 (3H, t, J=7.2), 2.12 (3H, s), 3.17 (2H, dq, J=6.0, 7.2), 4.2—4.9 (1H, b), 4.78 (1H, s). *Anal.* Calcd. for $C_6H_{10}N_2O$: C, 57.11; H, 7.99; N, 22.21. Found: C, 56.83; H, 7.85; N, 22.38.

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