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Studies on 1-Alkyl-2(1*H*)-pyridone Derivatives. XXII.[1] The Friedel-Crafts Reaction of 1-Methyl-2(1*H*)-pyridone and Its Homologs with Benzoyl Chloride

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The Friedel-Crafts reaction of 1-methyl-2(1*H*)-pyridone (I), 1-methyl-2(1*H*)-quinolone (II), and 2-methyl-1(2*H*)-isoquinolone (III) with benzoyl chloride was successfully carried out. I gave products identified as 5-benzoyl-1-methyl-2(1*H*)-pyridone (IV), 3-benzoyl-1-methyl-2(1*H*)-pyridone (V), and 3,5-dibenzoyl-1-methyl-2(1*H*)-pyridone (VI). II gave 3-benzoyl-1-methyl-2(1*H*)-quinolone (VII) and 6-benzoyl-1-methyl-2(1*H*)-quinolone (VIII), and III gave 4-benzoyl-2-methyl-1(2*H*)-isoquinolone (IX) and 5-benzoyl-2-methyl-1(2*H*)-isoquinolone (X).

1-Methyl-2(1*H*)-pyridone (I) is prepared from pyridine in two steps[3] and can be reverted to pyridine.[4] Electrophilic reactions of I take place at 3- and/or 5-position,[5] different from that in pyridine N-oxide.[6] From these facts, I and its homologs, 1-methyl-2(1*H*)-quinolone (II) and 2-methyl-1(2*H*)-isoquinolone (III), are rather interesting as the intermediates for the syntheses of the derivatives of pyridine and its homologs.

In previous works of this series, the Friedel-Crafts reactions of II[7] and III[8] with aliphatic acid chloride were carried out, but, as reported by Adams, *et al.*,[9] this reaction of I was unsuccessful. In the present series, the Friedel-Crafts reaction of I was successfully carried out with benzoyl chloride and the same reactions of II and III were also attained, and these are reported herein.

A mixture of I, benzoyl chloride, and aluminum chloride was heated at 180° for 48 hr to yield three kinds of product (IV, V, and VI), besides the recovery of I (7.1%). The compound (IV) was obtained in 30.9% yield as a colorless crystalline powder (from benzene) of mp 178—179°, which is similar to that of 5-benzoyl-1-methyl-2(1*H*)-pyridone in literature[10] (mp 181—182°). The structure of IV was proved chemically as shown in Chart 1. The Friedel-Crafts reaction of benzene with 1-methyl-2(1*H*)-pyridone-5-carbonyl chloride, which was derived from 1-methyl-2(1*H*)-pyridone-5-carboxylic acid,[11] gave 5-benzoyl-1-methyl-2(1*H*)-pyridone (82.1%), whose infrared (IR) spectrum was completely superimposable with that of IV. Consequently, IV is 5-benzoyl-1-methyl-2(1*H*)-pyridone. With consideration of the foregoing reaction of I,[5] it seems quite natural that the main product of this reaction is a 5-substituted compound.

The compound (V) was obtained as pale brown pillars (from benzene) of mp 115—116° in 12.4% yield. The structure of V was also proved chemically as shown in Chart 1. The

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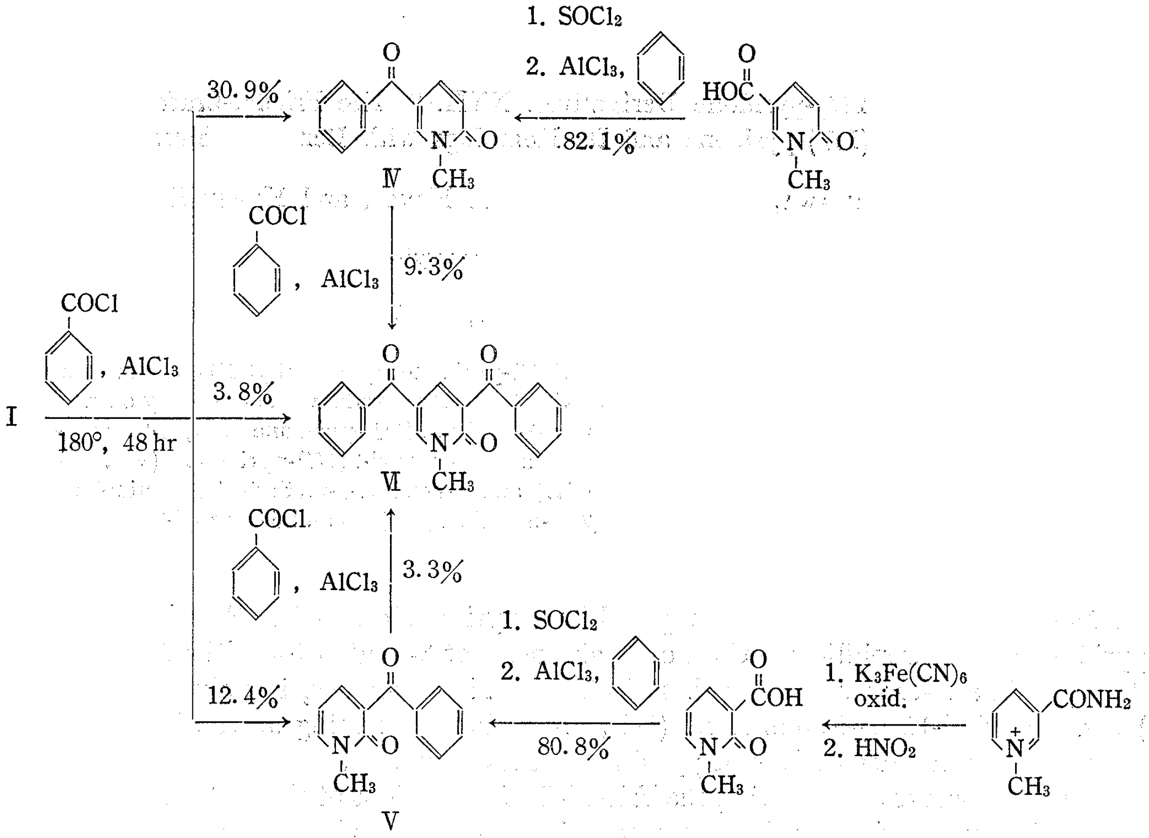

Chart 1

Friedel-Crafts reaction of benzene with 1-methyl-2(1*H*)-pyridone-3-carbonyl chloride, which was derived from 1-methyl-2(1*H*)-pyridone-3-carboxylic acid synthesized in a good yield by the modification of the method of Bradlow and Vanderwerf,[11] gave 3-benzoyl-1-methyl-2-(1*H*)-pyridone (80.8%), whose IR spectrum was completely superimposable with that of V. Therefore, V is 3-benzoyl-1-methyl-2(1*H*)-pyridone.

The minor product, VI was obtained as pale brown pillars (from benzene) of 158—160° in 3.8% yield. Mass spectrum and elemental analytical values of VI corresponded to I with the introduction of two benzoyl groups. This is of interest because it is contrary to general concept of the Friedel-Crafts reaction. In order to confirm the above fact, the Friedel-Crafts reaction of 5-benzoylpyridone (IV) and 3-benzoylpyridone (V) with benzoyl chloride was carried out, as shown in Chart 1, and the products of these reactions were identified by IR and nuclear magnetic resonance (NMR) spectral comparison with those of VI. This examination shows that the structure of VI is 3,5-dibenzoyl-1-methyl-2(1*H*)-pyridone and that benzoylation of benzoylpyridone does proceed, though in a poor yield [9.3% from 5-benzoyl compound (IV) and 3.3% from 3-benzoyl compound (V)].

A mixture of II, benzoyl chloride, and aluminum chloride was heated in an oil bath at 120° for 48 hr to yield two kinds of product (VII and VIII). Their mass spectra (263 M^+) showed that their molecular weight corresponded to II with an introduction of one benzoyl group. The compound (VII) was obtained as pale yellow needles (from benzene), mp 140—142°, in 2.3% yield. In the NMR spectrum of VII, signals for AB quartet of 3,4-protons in that of II (Fig. 1) have disappeared and a new signal of a proton on the pyridone ring appeared as a singlet, but the signals of the protons on the benzene ring of VII were similar to that of II. If the benzoyl group was in 4-position, the signal for the proton at 5-position, *peri* to the benzoyl group, should shift to a lower magnetic field due to the anisotropy of its carbonyl but this was not the case in NMR spectrum of VII. Consequently, the benzoyl group must be located at 3-position and the structure of VII would be 3-benzoyl-1-methyl-2(1*H*)-quinolone.

The compound (VIII) was obtained in 28.3% yield as a colorless crystalline powder (from benzene) of mp 128—129°. The NMR spectrum of VIII (Fig. 1) showed the presence of 3,4-protons on the pyridone ring as AB quartet. Some signals of the protons on the benzene ring of VIII appeared as a doublet ($J=2$ Hz) for one proton at 8.21 ppm and as quartet ($J=2$ Hz) for one proton at 8.05 ppm, and these shifted to a lower magnetic field due to the effect of the carbonyl in the benzoyl group on the benzene ring compared to that of II. These data suggested that the benzoyl group should be located at 6- or 7-position. Chemical proof of the location of benzoyl group was attempted but did not succeed. Therefore, the structure of VIII was not unambiguously determined but, according to the previous paper of this series,[5,7] the electrophilic substitution reaction on the benzene ring of II occurred only at 6-position, and it seems likely that VIII would be formulated as 6-benzoyl-1-methyl-2(1*H*)-quinolone.

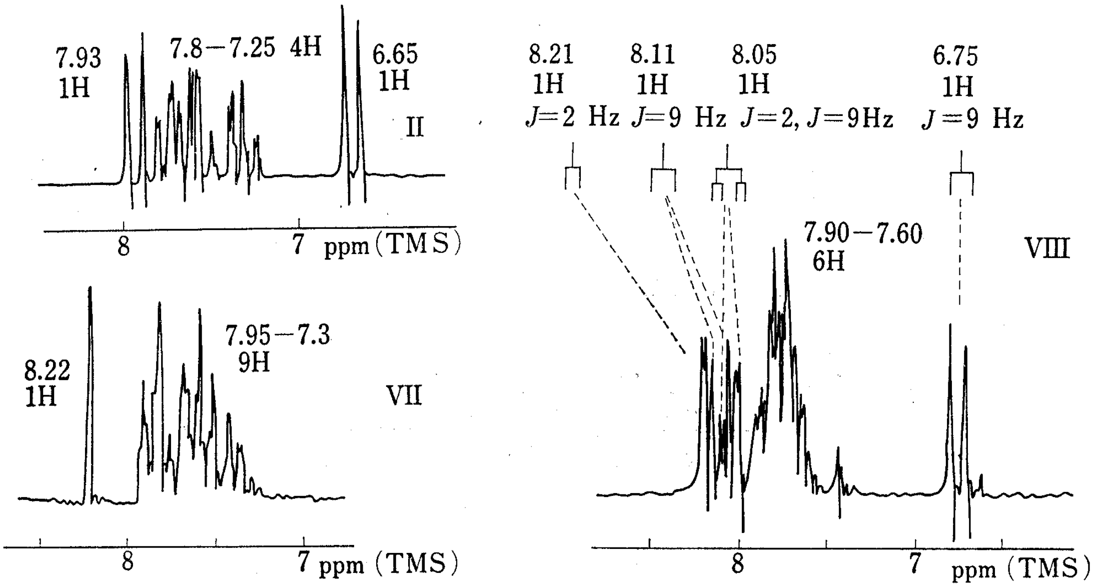

Fig. 1. NMR Spectra of II, VII and VIII (in Me_2SO-d_6) (100 MHz)

A mixture of III, benzoyl chloride, and aluminum chloride was heated in an oil bath at 120° for 1 week and gave two kinds of product (IX and X). Their mass spectra (263 M^+) showed that their molecular weight corresponded to III with an introduction of one benzoyl group. IX was obtained in 21.6% yield as pale red needles (from benzene) of mp 130—131°, which is similar to that of 4-benzoyl-2-methyl-1(2*H*)-isoquinolone in literature[12] (mp 131—132°). In NMR spectral comparison of IX and III (Fig. 2), signals for AB quartet of 3,4-protons in the spectrum of III disappeared in that of IX, and the lowest signal (around 8.4 ppm) in the spectrum of III, assigned to the proton at 8-position, changed to the signal for two protons in that of IX. These data showed that the location of benzoyl group is 4-position and the signal for the proton at 5-position, which is affected by the strong anisotropy of benzoyl group at *peri* position, shifted to a far lower magnetic field (around 8.4 ppm). Therefore, the structure of IX is 4-benzoyl-2-methyl-1(2*H*)-isoquinolone.

X was obtained in 19.5% yield as pale yellow pillars (from benzene) of mp 128—129°. The NMR spectrum of X (Fig. 3) showed signals for AB quartet of 3,4-protons on the pyridone ring, and the signal for the proton at 4-position shifted to a lower magnetic field than that of III. The signal at the lowest magnetic field, assigned to the proton at 8-position, showed the presence of *ortho* and *meta* coupling constant. These data reveal that the location of the substituent is not on the pyridone ring of X, and the protons on the benzene ring of X

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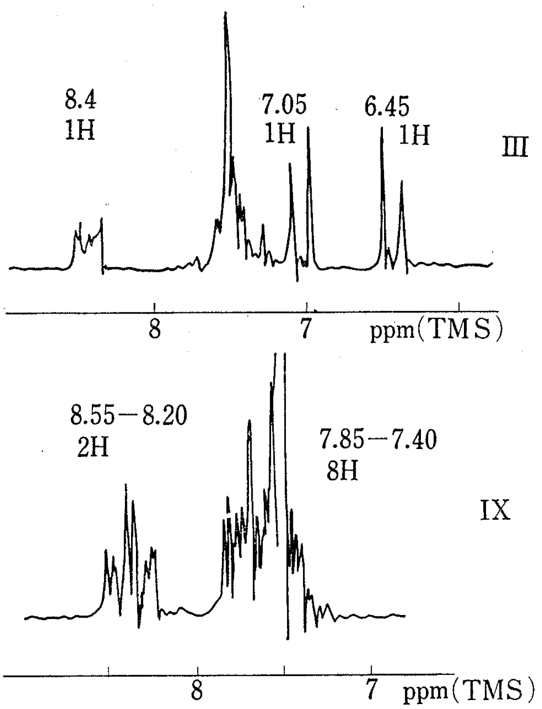

Fig. 2. NMR Spectra of III and IX (in $CDCl_3$) (60 MHz)

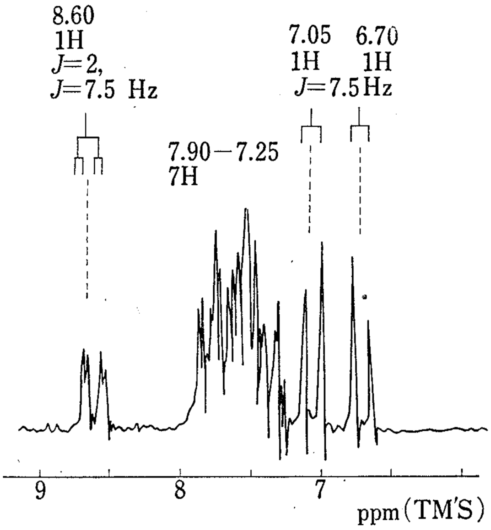

Fig. 3. NMR Spectrum of X (in $CDCl_3$) (60 MHz)

are located at 6-, 7-, and 8-positions. Therefore, the benzoyl group must be located at 5-position and the structure of X is 5-benzoyl-2-methyl-1(2*H*)-isoquinolone.

The results of the benzoylation of II and III are shown in Chart 2.

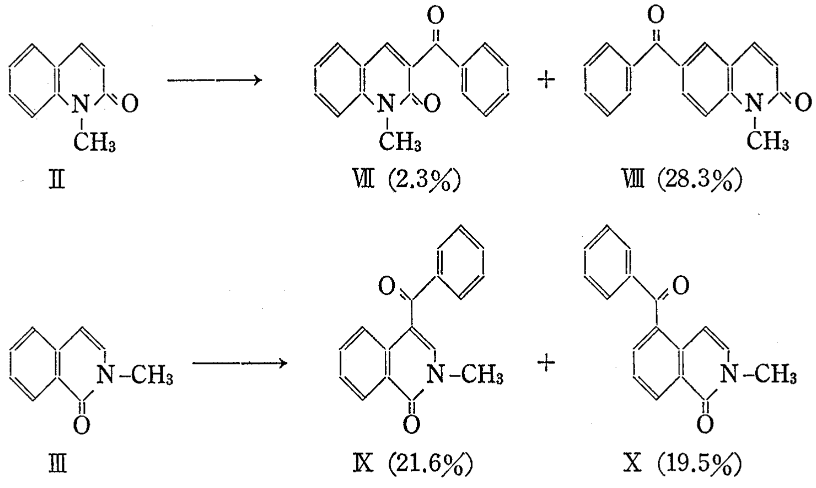

Chart 2

Experimental[13]

Reaction of 1-Methyl-2(1*H*)-pyridone (I) and Benzoyl Chloride (BzCl)——A mixture of 11.0 g of BzCl and 3.6 g of $AlCl_3$, mixed under anhydrous condition, was warmed until $AlCl_3$ was completely dissolved in BzCl. The warmed mixture was cooled in ice water, by which the whole crystallized, and added dropwise with 3 g of I,and the mixture was heated in an oil bath of 180° for 48 hr. The reaction mixture was poured into ice water, basified with NaOH soln., and the mixture was extracted with $CHCl_3$. The $CHCl_3$ extract was dried over $MgSO_4$, evaporated, and the residue was passed through a column of silica gel. The column eluted with

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[13] All melting points are uncorrected.

benzene–acetone (10: 1) gave five fractions. The first fraction was a mixture of BzCl and BzOH, and the fifth was the recovered I (0.215 g, 7.1%). The second was recrystallized from benzene to 0.302 g (3.83%) of 3,5-dibenzoyl-1-methyl-2(1*H*)-pyridone, (VI) as pale brown pillars, mp 158—160°. Admixture of VI with an authentic sample of VI, prepared by a different routes, did not depress the melting point. Mass Spectrum *m/e*: 317 (M^+). *Anal.* Calcd. for $C_{20}H_{15}O_3N$: C, 75.69; H, 4.76; N, 4.41. Found: C, 76.06; H, 4.98; N, 4.48. IR ν_{max}^{Nujol} cm^{-1}: 1860, 1675 (C=O), 800, 780, 700 (δ-CH). UV λ_{max}^{EtOH} mμ (log ε): 210 (4.37), 253 (4.17), 295 (4.16), 330 (3.42). NMR (in $CDCl_3$) ppm: 3.67 (3H, singlet, N–CH_3), 7.45—7.95 (10H, multiplet, benzene-H), 8.17 (1H, *J*=2 Hz, C-4 or C-6H), 8.26 (1H, *J*=2 Hz, C-4 or C-6H).

The third was recrystallized from benzene to 1.874 g (30.9%) of 5-benzoyl-1-methyl-2(1*H*)-pyridone (IV) as a colorless crystalline powder, mp 178—179°, alone and in admixture with an authentic sample of IV (reported[10]) mp 181—182°). Mass Spectrum *m/e*: 213 (M^+). *Anal.* Calcd. for $C_{13}H_{11}O_2N$: C, 73.22; H, 5.20; N, 6.57. Found: C, 73.24; H, 5.27; N, 6.57. NMR (in $CDCl_3$) ppm: 3.60 (3H, singlet, N–CH_3), 6.60 (1H, doublet, *J*=9 Hz, C-3H), 7.5—7.75 (5H, multiplet, benzene-H), 7.87 (1H, *J*=9, *J*=2 Hz, C-4H), 8.10 (1H, *J*=2 Hz, C-6H).

The fourth was recrystallized from benzene to 0.730 g (12.4%) of 3-benzoyl-1-methyl-2(1H)-pyridone (V) as pale brown pillars, mp 115—116°, undepressed on admixture with an authentic sample of V. Mass Spectrum *m/e*: 213 (M^+). *Anal.* Calcd. for $C_{13}H_{11}O_2N$: C, 73.22; H, 5.20; N, 6.57. Found: C, 73.24; H, 5.23; N, 6.53. IR ν_{max}^{Nujol} cm^{-1}: 1665, 1655 (C=O), 860, 815, 775, 700 (δ-CH). UV λ_{max}^{EtOH} mμ (log ε): 210 (4.31), 252 (3.86), 330 (3.51). NMR (in $CDCl_3$) ppm: 3.59 (3H, singlet, N–CH_3), 6.29 (1H, triplet, *J*=7.5 Hz, C-5H), 7.40—7.90 (7H, multiplet, C-4, C-6H and benzene-H).

Synthesis of IV——A mixture of 3 g of 1-methyl-2(1*H*)-pyridone-5-carboxylic acid[11]) and 20 g of $SOCl_2$ was heated in an oil bath at 80° for 4 hr. After evaporation of excess $SOCl_2$, the residue of yellow crystals was dissolved in 25 g of anhyd. benzene, 4 g of $AlCl_3$ was added, and the mixture was heated in an oil bath at 80° for 3 hr. The reaction mixture was poured into ice water, basified with NaOH soln., and extracted with $CHCl_3$. The $CHCl_3$ extract was dried over $MgSO_4$, evaporated, and the residue was recrystallized from benzene to a colorless crystalline powder, mp 182—184° (reported[10]) mp 181—182°). Yield, 3.424 g (82.1%).

Synthesis of 1-Methyl-2(1*H*)-pyridone-3-carbamoyl Amide——Me_2SO_4 (36 g) was added dropwise to nicotinic amide (30 g), the mixture was warmed in a water bath for 1 hr, and poured into 500 ml of H_2O. To the solution, 234 g of powdered $K_3Fe(CN)_6$ was added, the solution was cooled below 0°, and 72 g of granulated KOH was added with stirring during 1 hr, maintaining the temperature below 0°. After stirring for additional 30 min, the solution was salted out with NaCl and extracted with $CHCl_3$. The $CHCl_3$ extract was dried over $MgSO_4$, evaporated, and the residue was recrystallized from H_2O to pale yellow needles, mp 216—217° (reported[11]) mp 217—218°). Yield, 14.8 g (39.7%). IR ν_{max}^{Nujol} cm^{-1}: 3300, 3150 (amide NH_2), 1680, 1660 (C=O), 810, 770 (δ-CH). NMR (in CF_3COOH) ppm: 4.20 (3H, singlet, N–CH_3), 7.50 (1H, quartet, *J*=9, *J*=7.5 Hz, C-3H), 8.48 (1H, quartet, *J*=7.5, *J*=2 Hz, C-6H), 9.00 (1H, quartet, *J*=9, *J*=2 Hz, C-4H).

Synthesis of 1-Methyl-2(1*H*)-pyridone-3-carboxylic Acid——To a solution of 25 ml of conc. HCl and 5 g of 1-methyl-2(1*H*)-pyridone-3-carbamoyl amide dissolved in 30 ml of H_2O, 9 g of $NaNO_2$ was added with stirring during 1 hr. After stirring for additional 2 hr, $(NH_2)_2CO$ was added, basified with KOH, and extracted with $CHCl_3$ to remove the unreacted amide. The aqueous layer was acidified with conc. HCl, salted out with NaCl, and extracted with $CHCl_3$. The $CHCl_3$ extract was dried over $MgSO_4$ and evaporated to give practically pure compound as colorless crystals (4.9 g, 98%) melting at 182—184° (reported[11]) mp 183°), alone and in admixture with 1-methyl-2(1*H*)-pyridone-3-carboxylic acid. NMR (in $CDCl_3$) ppm: 3.72 (3H, singlet, N–CH_3), 6.55 (1H, quartet, *J*=8, *J*=7.5 Hz, C-5H), 7.68 (1H, quartet, *J*=7.5, *J*=2 Hz, C-6H), 8.52 (1H, quartet, *J*=8, *J*=2 Hz, C-4H).

Synthesis of V——A mixture of 3 g of 1-methyl-2(1*H*)-pyridone-3-carboxylic acid and 25 g of $SOCl_2$ was heated in an oil bath at 80° for 3.5 hr. After evaporation of excess $SOCl_2$, the residue of yellow crystals was dissolved in 25 g of anhyd. benzene, 4 g of $AlCl_3$ was added, and the mixture was heated in an oil bath at 80° for 4.5 hr. The reaction mixture was poured into ice water, basified with NaOH, and extracted with $CHCl_3$. The $CHCl_3$ extract was dried over $MgSO_4$ and evaporated to give practically pure compound as pale brown pillars (3.3 g, 80.8%) melting at 114°.

Synthesis of VI——a) Reaction of IV and BzCl: A mixture of 1.98 g of BzCl and 0.62 g of $AlCl_3$ was warmed until $AlCl_3$ completely dissolved in BzCl. The warmed mixture was cooled in ice water, by which the whole crystallized, 1 g of IV was added. This mixture was heated and treated in the same way as in the Friedel-Crafts reaction of I and BzCl. The column of silica gel was eluted with benzene–acetone (10: 1), and the second fraction gave 0.13 g (9.3%) of VI, mp 158—160°. The third gave 0.9 g (90%) of recovered IV.

b) Reaction of V and BzCl: A mixture of 1.98 g of BzCl and 0.62 g of $AlCl_3$ was warmed until $AlCl_3$ was completely dissolved in BzCl and cooled in ice water. To this mixture, 1 g of V was added and the mixture was treated as in the foregoing (a). The column of silica gel was eluted with benzene–acetone (10: 1) and the second fraction gave 0.05 g (3.3%) of VI, whose melting point (mp 158—160°) was not depressed when it was mixed with the above dibenzoylpyridone. The third gave 0.85 g (85%) of recovered V.

Reaction of 1-Methyl-2(1*H*)-quinolone (II) and BzCl——A mixture of 13.2 g of BzCl and 15.3 g of $AlCl_3$ was cooled in ice water, 3 g of II was added, and the mixture was heated in an oil bath at 120° for 48 hr. The reaction mixture was treated as in the foregoing (a) and (b), and the product was passed through a column of silica gel. The column eluted with benzene–acetone (13: 1) gave four fractions. The first fraction was an oil and the fourth was the recovered II (0.42 g, 13.8%). The second was recrystallized from benzene to 0.117 g (2.3%) of 3-benzoyl-1-methyl-2(1*H*)-quinolone (VII) as pale yellow needles, mp 140—142°. Mass spectrum *m/e*: 263 (M$^+$). *Anal.* Calcd. for $C_{17}H_{13}O_2N$: C, 77.55; H, 4.98; N, 5.32. Found: C, 77.92; H, 5.05; N, 5.43. IR $\nu_{\max}^{\text{Nujol}}$ cm^{-1}: 1670, 1655 (C=O), 820, 770, 750, 700 (δ-CH). UV $\lambda_{\max}^{\text{EtOH}}$ mμ (log ε): 210 (4.52), 231.5 (4.51), 250 (4.29), 289 (4.03), 350 (3.96). NMR (in DMSO-d_6) ppm: 3.37 (3H, singlet, N–CH_3), 7.3—7.95 (9H, multiplet, aromatic H), 8.22 (1H, singlet, C-4H).

The third was recrystallized from benzene to 1.43 g (28.3%) of 6-benzoyl-1-methyl-2(1*H*)-quinolone (VIII) as a colorless crystalline powder, mp 128—129°. Mass Spectrum *m/e*: 263 (M$^+$). *Anal.* Calcd. for $C_{17}H_{13}O_2N$: C, 77.55; H, 4.98; N, 5.32. Found: C, 77.76; H, 4.81; N, 5.48. IR $\nu_{\max}^{\text{Nujol}}$ cm^{-1}: 1670, 1660 (C=O), 835, 750, 700 (δ-CH). UV $\lambda_{\max}^{\text{EtOH}}$ mμ (log ε): 210 (4.39), 227 (4.36), 255 (4.57), 265 (4.65), 325 (4.10), 336 (3.99), 347 (3.89). NMR (in DMSO-d_6) ppm: 3.75 (3H, singlet, N–CH_3), 6.75 (1H, doublet, $J=9$ Hz, C-3H), 7.6—7.9 (6H, multiplet, C-8H and benzene-H), 8.05 (1H, quartet, $J=9$, $J=2$ Hz, C-7H), 8.11 (1H, doublet, $J=9$ Hz, C-4H), 8.21 (1H, doublet, $J=2$ Hz, C-5H).

Reaction of 2-Methyl-1(2*H*)-isoquinolone (III) and BzCl——A mixture of 12.3 g of BzCl and 14.9 g of $AlCl_3$ was warmed until $AlCl_3$ was completely dissolved in BzCl, and cooled in ice water. To the cooled mixture, 3 g of III was added and the mixture was heated in an oil bath at 120° for 1 week. The reaction mixture was treated as in the foregoing cases and the product was passed through a column of silica gel. The column eluted with benzene–acetone (10: 1) gave three fractions and the first was an oil. The second was recrystallized from benzene to 1.09 g (21.6%) of 4-benzoyl-2-methyl-1(2*H*)-isoquinolone (IX) as pale red needles, mp 130—131° (reported[12]) mp 131—132°). Mass Spectrum *m/e*: 263 (M$^+$). *Anal.* Calcd. for $C_{17}H_{13}O_2N$: C, 77.55; H, 4.98; N, 5.32. Found: C, 77.83; H, 5.05; N, 5.17. IR $\nu_{\max}^{\text{Nujol}}$ cm^{-1}: 1655, 1640 (C=O), 785, 700 (δ-CH). UV $\lambda_{\max}^{\text{EtOH}}$ mμ (log ε): 210 (4.93), 215 (4.39), 242 (4.26), 314 (3.69), 326 (3.74), 340 (3.27). NMR (in $CDCl_3$) ppm: 3.59 (3H, singlet, N–CH_3), 7.4—7.75 (8H, multiplet, C-3, C-6, C-7H and benzene-H), 8.2—8.55 (2H, multiplet, C-5, C-8H).

The third was recrystallized from benzene to 0.98 g (19.5%) of 5-benzoyl-2-methyl-1(2*H*)-isoquinolone (X) as pale yellow pillars, mp 128—129°. Mass Spectrum *m/e*: 263 (M$^+$). *Anal.* Calcd. for $C_{17}H_{13}O_2N$: C, 77.55; H, 4.98; N, 5.32. Found: C, 77.68; H, 4.86; N, 5.34. IR $\nu_{\max}^{\text{Nujol}}$ cm^{-1}: 1665 (C=O), 820, 770, 750, 700 (δ-CH). UV $\lambda_{\max}^{\text{EtOH}}$ mμ (log ε): 210 (4.51), 218 (4.51), 260 (4.17). NMR (in $CDCl_3$) ppm: 3.60 (3H, singlet, N–CH_3), 6.70 (1H, doublet, $J=7.5$ Hz, C-4H), 7.05 (1H, doublet, $J=7.5$ Hz, C-3H), 7.25—7.9 (7H, multiplet, C-6, C-7H and benzene-H), 8.60 (1H, quartet, $J=7.5$, $J=2$ Hz, C-8H).

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