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Studies on 1-Alkyl-2(1*H*)-pyridone Derivatives. XVI.[1] The Friedel-Crafts Reaction of 2-Methyl-1(2*H*)-isoquinolone

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The Friedel–Crafts reaction of 2-methyl-1(2*H*)-isoquinolone (I) gave products identified as 4- and 7-acetylated compounds (III and IV), 4-, 5-, and 7-propionylated compounds (VII, VIII, and IX), and 5- and 7-butyrylated compounds (V and VI).

In previous work of this series, the reaction of 2-methyl-1(2*H*)-isoquinolone (I) with formaldehyde and hydrochloric acid was mentioned,[3] and the Mannich reaction of I was carried out.[4] The products in these reactions were the compounds substituted at 4-position only. The Friedel–Crafts reaction of 1-methyl-2(1*H*)-quinolone[5] (II) gave 6-acetylated, 3-propionylated, and 6-propionylated compounds, whereas the reaction of II with formaldehyde and hydrochloric acid[6] gave a product substituted at 6-position only. In the present work, the Friedel–Crafts reaction of I was carried out and some new observations on this reaction are described herein.

A mixture of 5 g of I and 25 g of aluminum chloride, with dropwise addition of 15 g of acetyl chloride, was heated in an oil bath at 50—55° for 24 hr. The cooled reaction mixture was basified with sodium hydroxide and was extracted with chloroform. The dried extract was passed through a chromatographic column over alumina and afforded two kinds of acetylated product (III and IV). III, $C_{12}H_{11}O_2N$, formed pale yellow needles, mp 133—135°, yield, 2.5 g (40.4%). The analytical value of III corresponded to I with introduction of one acetyl group and its infrared (IR) spectrum (in Nujol) exhibited absorptions for acetyl C=O at 1680 cm^{-1}, for amide C=O at 1660 cm^{-1}, and for adjacent four hydrogens on the aromatic ring at 770 cm^{-1}. The nuclear magnetic resonance (NMR) spectrum of III (in $CDCl_3$) (Fig. 1) showed signals at 2.52 ppm (3H, singlet, $COCH_3$) and at 3.64 ppm (3H, singlet, N–CH_3), while the signals for AB quartet in the NMR spectrum of I at 6.43 ppm (1H, doublet, C4–H) and 7.05 ppm (1H, doublet, C3–H) disappeared and a new signal appeared as a singlet at 7.88 ppm (1H, C3–H or C4–H), and III was found to be a compound having a substituent on the pyridone ring. The NMR spectrum of III further showed signals at 7.57 ppm (2H, multiplet), 8.35 ppm (1H, quartet), and 8.85 ppm (1H, doublet), whereas that of I showed signals at 7.50 ppm (3H, multiplet, C5, C6, C7–H) and 8.42 ppm (1H, quartet, C8–H). According to these NMR spectral data, the signals at 8.35 ppm and 8.85 ppm would be assigned to the protons at 5- and 8- positions, respectively and considerable lower shifts of these signals would be attributed to the anisotropy and electronic effects, respectively, of the acetyl carbonyl group at 4- position. Consequently, III would be formulated as 4-acetyl-2-methyl-1-(2*H*)-isoquinolone.

IV, $C_{12}H_{11}O_2N$, formed colorless pillars, mp 152—153°, yield, 0.43 g (6.9%). The analytical value of IV corresponded to I with introduction of one acetyl group, and its IR spec-

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3) H. Tomisawa, K. Saito, H. Hongo, and R. Fujita, *Chem. Pharm. Bull.* (Tokyo), **18**, 937 (1970).
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6) H. Tomisawa, Y. Kobayashi, H. Hongo, and R. Fujita, *Chem. Pharm. Bull.* (Tokyo), **18**, 932 (1970).

trum (in Nujol) exhibited absorption for acetyl C=O at 1680 cm^{-1}, for amide C=O at 1660 cm^{-1}, and for adjacent two hydrogens in the aromatic ring at 845 cm^{-1}. In the NMR spectrum of IV (in $CDCl_3$) (Fig. 2), the signals for 3,4-protons were present as an AB quartet at 6.47 and 7.17 ppm, the same as in that of I, and suggesting IV to be a compound having a substituent on the benzene ring. The NMR spectrum of IV further showed the signals at 7.50

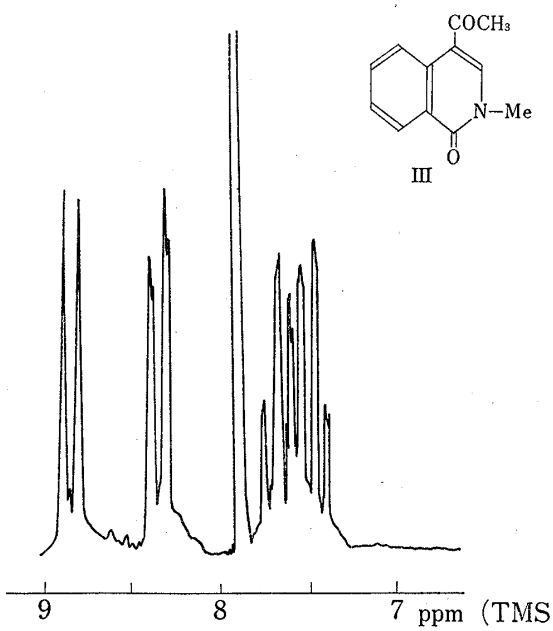

Fig. 1. NMR Spectrum of III (in $CDCl_3$) (100 Mcps)

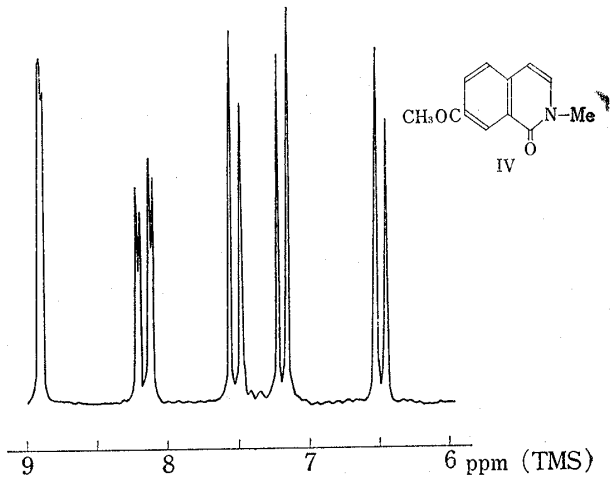

Fig. 2. NMR Spectrum of IV (in $CDCl_3$) (100 Mcps)

ppm (1H, doublet, J=7.5 cps), 8.15 ppm (1H, quartet, J=7.5, J=2.0 cps), and 8.90 ppm (1H, doublet, J=2.0 cps). On comparison of the NMR spectrum of IV with that of I, it can be considered that lower shifts of two signals, which are assigned to the proton at 8-position (8.42 ppm in I) and one of the protons at 5-, 6-, and 7-positions (7.50 ppm in I), respectively, would be attributed to the anisotropy of the acetyl carbonyl at 7-position. Consequently, IV would be formulated as 7-acetyl-2-methyl-1(2*H*)-isoquinolone.

A mixture of 20 g of I and 98 g of aluminum chloride, with dropwise addition of 52.8 g of butyryl chloride, was heated in an oil bath at 100° for 9 hr. Two kinds of acylated products (V and VI) were obtained. V, $C_{14}H_{15}O_2N$, formed pale yellow needles, mp 136—137°, 0.459 g. Its IR spectrum (in Nujol) showed absorptions for butyryl C=O at 1680 cm^{-1}, for amide C=O at 1665 cm^{-1}, and for hydrogens on the aromatic ring at 815 cm^{-1} which were different from those of 4- and 7-acylated compounds. The ultraviolet (UV) spectra of acylated compounds (Figures. 3 and 4) suggested that location of the substituent in V might be different from that of 4- and 7-acylated compounds. The NMR data of V (in $CDCl_3$) are shown in Table I and Fig. 5, where the signals are arbitrarily desiganted as A, B, C, D, and E. The chemical shift of A is in almost the same position as that of the proton at 8-position of I. Since a spin coupling constant of 0.5 cps was observed between A and D (probably through "cross-ring coupling[7]), these protons can be assigned to those at 8- and 4-positions, respectively. The signals of B, C, and E can, therefore, be assigned to those due to protons at 6-, 7-, and 3-positions, respectively. Comparison of the NMR spectra of V and I showed that the signal for the proton at 5-position in I has disappeared, and those at 4- and 6-positions have shifted to a lower magnetic field. Consequently, the structure of V would be formulated as 5-butyryl-2-methyl-1(2*H*)-isoquinolone.

7) M. Martin-Smith, S.T. Reid, and S. Sternhell, *Tetrahedron Letters*, **1965**, 2393.

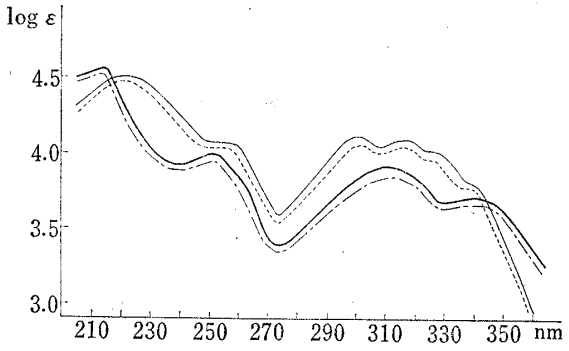

Fig. 3. UV Spectra of 4-, and 5-Acylated Compounds (in EtOH)
------: III, ——: VII, ——: V, ·—·: IX

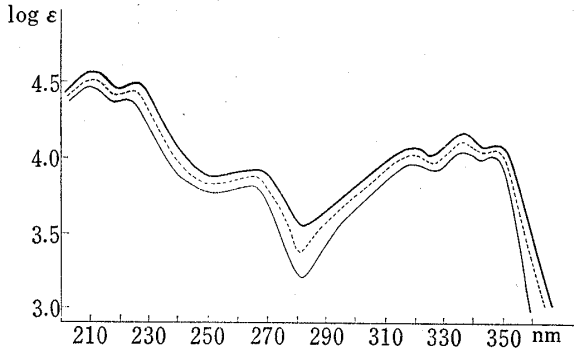

Fig. 4. UV Spectra of 7-Acylated Compounds (in EtOH)
——: IV, ——: VI, ------: VIII

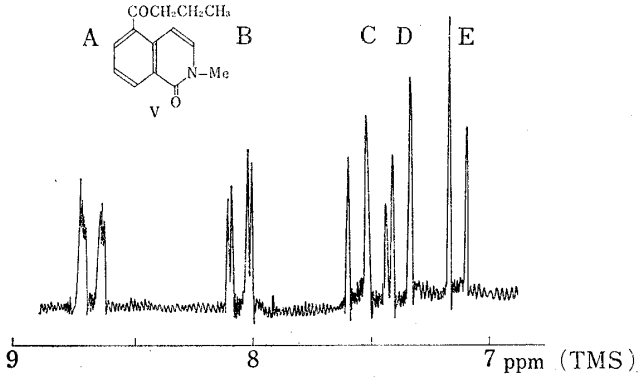

Fig. 5. NMR spectrum of V (in $CDCl_3$) (100 Mcps)

Table I. NMR Spectrum[a] of V in $CDCl_3$

	Chemical shift (ppm)	Coupling constant (J), cps
A	8.63	J_{AC}=8.0, J_{AB}=2.0, J_{AD}=0.5
B	8.05	J_{BC}=8.0, J_{BA}=2.0
C	7.52	J_{CB}=8.0, J_{CA}=8.0
D	7.36	J_{DE}=7.5, J_{DA}=0.5
E	7.13	J_{ED}=7.5

a) Tetramethylsilane was used as internal standard.

VI, $C_{14}H_{15}O_2N$, formed colorless plates, mp 107—108°, 0.21 g. Its IR, UV (Fig. 4), and NMR (Table II) spectra were similar to those of 7-acylated compound, and from these spectral data, VI would be formulated as 7-butyryl-2-methyl-1(2*H*)-isoquinolone.

Table II. NMR Signals of 4-, 5-, and 7-Acylated Compounds (ppm[a], in $CDCl_3$)

Compound	C3-H	C4-H	C5-H	C6-H	C7-H	C8-H	N-CH_3
4-CH_3CO (III)	7.88(s)	—	8.35(q)	7.57(m)		8.85(q)	3.64(s)
4-C_2H_5CO (VII)	7.90(s)	—	8.44(q)	7.62(m)		8.86(q)	3.67(s)
5-C_2H_5CO (IX)	7.18(d)	7.42(d)	—	8.08(q)	7.55(t)	8.65(q)	3.65(s)
5-C_3H_7CO (V)	7.13(d)	7.36(d)	—	8.05(q)	7.52(t)	8.63(q)	3.62(s)
7-CH_3CO (IV)	7.17(d)	6.47(d)	7.50(d)	8.15(q)	—	8.90(d)	3.60(s)
7-C_2H_5CO (VIII)	7.20(d)	6.52(d)	7.49(d)	8.24(q)	—	8.97(d)	3.63(s)
7-C_3H_7CO (VI)	7.21(d)	6.52(d)	7.56(d)	8.22(q)	—	8.97(d)	3.63(s)

a) Tetramethylsilane was used as internal standard.

A mixture of 10 g of I and 49 g of aluminum chloride, with dropwise addition of 29 g of propionyl chloride, was heated in an oil bath at 80° for 15 hr and three kinds of acylated products (VII, VIII and IX) were obtained. VII, $C_{13}H_{13}O_2N$, formed pale yellow needles, mp 164—165°, VIII, $C_{13}H_{13}O_2N$, formed colorless needles, mp 153—155°, IX, $C_{13}H_{13}O_2N$, formed pale yellow powder, mp 104—105°. The structures of VII, VIII, and IX were decided from the similarity of their IR, UV (Figures. 3 and 4), and NMR (Table II) spectra respectively with those of 4-acetylated (III), 7-acetylated (IV), and 5-butyrylated (V) compounds. Therefore,

VII would be formulated as 2-methyl-4-propionyl-1(2*H*)-isoquinolone, VIII as 2-methyl-7-propionyl-1(2*H*)-isoquinolone, and IX as 2-methyl-5-propionyl-1(2*H*)-isoquinolone.

In previous work of this series,[3,4] only 4-substituted isoquinolone was obtained, but in the present case, the Friedel–Crafts reaction of I gave the products having one acyl group at 4-, 5-, or 7-positions.

Experimental[8]

Reaction of 2-Methyl-1(2*H*)-isoquinolone (I) and Acetyl Chloride——To a mixture of 5 g of I and 25 g of $AlCl_3$, 15 g of AcCl was added dropwise and the mixture was warmed in an oil bath of 50—55° for 24 hr. The cooled mixture was poured into ice water, basified with NaOH, and extracted with $CHCl_3$. The $CHCl_3$ extract was dried over $MgSO_4$, evaporated, and the residue was passed through a column of Al_2O_3, elution of which afforded three fractions. The first fraction eluted with hexane–benzene (2: 1) was the recovered I (1.79 g, 35.8%). The second fraction eluted with hexane-benezene (2: 1) was evaporated and the residue was recrystallized from benzene to 2.5 g (40.4%) of 4-acetyl-2-methyl-1(2*H*)-isoquinolone (III) as pale yellow needles, mp 133—135°. *Anal.* Calcd. for $C_{12}H_{11}O_2N$: C, 71.62; H, 5.51; N, 6.96. Found: C, 71.53; H, 5.54; N, 7.01. IR ν_{max}^{Nujol} cm^{-1}: 1680 (C=O), 1660 (amide C=O), 770 (δ-CH). UV λ_{max}^{EtOH} nm (log ε): 221.5 (4.49), 260 (3.96), 304 (4.06), 312 (4.03), 325 (3.96), 339 (3.75). NMR (in $CDCl_3$) ppm: 2.52 (3H, singlet, $COCH_3$), 3.64 (3H, singlet, N-CH_3), 7.57 (2H, multiplet, J=7.5, J=2.0 cps, C6-H, C7-H), 7.88 (1H, singlet, C3-H), 8.35 (1H, quartet, J=7.5, J=2.0 cps, C5-H), 8.85 (1H, quartet, J=7.5, J=2.0 cps, C8-H).

The third fraction eluted with hexane–benzene (1: 1) was evaporated and the residue was recrystallized from benzene to 0.43 g (6.9%) of 7-acetyl-2-methyl-1(2*H*)-isoquinolone (IV) as colorless pillars, mp 152—153°. *Anal.* Calcd. for $C_{12}H_{11}O_2N$: C, 71.62; H, 5.51; N, 6.96. Found: C, 71.62; H, 5.53; N, 7.00. IR ν_{max}^{Nujol} cm^{-1}: 1680 (C=O), 1660 (amide C=O), 845 (δ-CH). UV λ_{max}^{EtOH} nm (log ε): 213 (4.52), 223 (4.49), 266 (3.77), 317 (4.03), 332 (4.12), 343 (4.07). NMR (in $CDCl_3$) ppm: 2.68 (3H, singlet, $COCH_3$), 3.60 (3H, singlet, N-CH_3), 6.47 (1H, doublet, J=7.5 cps, C4-H), 7.17 (1H, doublet, J=7.5 cps, C3-H), 7.50 (1H, doublet, J=7.5 cps, C5-H), 8.15 (1H, quartet, J=7.5, J=2.0 cps, C6-H), 8.90 (1H, doublet, J=2.0 cps, C8-H).

Reaction of 2-Methyl-1(2*H*)-isoquinolone (I) and Butyryl Chloride——To a mixture of 20 g of I and 98 g of $AlCl_3$, 52.8 g of butyryl chloride was added dropwise and the mixture was heated in an oil bath at 100° for 9 hr. The cooled mixture was treated as in the foregoing case and the $CHCl_3$ extract was passed through a column of Al_2O_3. The fraction eluted with hexane–benzene (3: 1) was the recovered I (1.8 g, 9.0%). Further, elution of the column with hexane–benzene (2: 1) gave the first fraction, with hexane–benzene (1: 2), the second, and with benzene, the third fraction. These fractions were all a mixture of some compounds. The second fraction was evaporated and the residue was treated with ether. The part insoluble in ether at room temperature was collected by filtration and recrystallized from benzene to pale yellow needles (V), mp 136—137°. The ether solution was passed through a column of silica gel. The fraction eluted with benzene–EtOAc (1: 3) was evaporated and the residue was recrystllized from ether to colorless plates (VI), mp 107—108°.

The first and the third fractions were treated in the same way as the second fraction, and further crops of V and VI were obtained. 5-Butyryl-2-methyl-1(2*H*)-isoquinolone (V): Yield, 0.459 g (1.81%). *Anal.* Calcd. for $C_{14}H_{15}O_2N$: C, 73.34; H, 6.59; N, 6.11. Found: C, 73.09; H, 6.56; N, 6.16. IR ν_{max}^{Nujol} cm^{-1}: 1680 (C=O), 1665 (amide C=O), 815 (δ-CH). UV λ_{max}^{EtOH} nm (log ε): 215 (4.56), 256 (3.98), 310 (3.92), 342 (3.70). NMR (in $CDCl_3$) ppm: 1.03 (3H, triplet, J=7.5 cps, C-CH_3), 1.82 (2H, sextet, J=7.5 cps, CO-C-$\underline{CH_2}$-), 3.00 (2H, triplet, J=7.5 cps, CO-$\underline{CH_2}$-), 3.62 (3H, singlet, N-CH_3), 7.13 (1H, doublet, J=7.5 cps, C3-H), 7.36 (1H, doublet, J=7.5 cps, C4-H), 7.52 (1H, triplet, J=8.0 cps, C7-H), 8.05 (1H, quartet, J=8.0, J=2.0 cps, C6-H), 8.63 (1H, quartet, J=8.0, J=2.0 cps, C8-H). 7-Butyryl-2-methyl-1(2*H*)-isoquinoline (VI): Yield, 0.21 g (0.82%). *Anal.* Calcd. for $C_{14}H_{15}O_2N$: C, 73.34; H, 6.59; N, 6.11. Found: C, 73.01; H, 6.48; N, 6.18. IR ν_{max}^{Nujol} cm^{-1}: 1680 (C=O), 1670 (amide C=O), 850 (δ-CH). UV λ_{max}^{EtOH} nm (log ε): 215 (4.54), 225 (4.50), 267 (3.93), 318 (4.07), 334 (4.14), 346 (4.09). NMR (in $CDCl_3$) ppm: 1.03 (3H, triplet, J=7.5 cps, C-CH_3), 1.82 (2H, sextet, J=7.5 cps, C-$\underline{CH_2}$-C), 3.08 (2H, triplet, J=7.5 cps, CO-$\underline{CH_2}$-), 3.63 (3H, singlet, N-CH_3), 6.52 (1H, doublet, J=7.5 cps, C4-H), 7.21 (1H, doublet, J=7.5 cps, C3-H), 7.56 (1H, doublet, J=8.0 cps, C5-H), 8.22 (1H, quartet, J=8.0, J=2.0 cps, C6-H), 8.97 (1H, doublet, J=2.0 cps, C8-H).

Reaction of 2-Methyl-1(2*H*)-isoquinolone (I) and Propionyl Chloride——To a mixture of 10 g of I and 49 g of $AlCl_3$, 29 g of propionyl chloride was added dropwise and the mixture was heated in an oil bath at 80° for 15 hr. The reaction mixture was treated as in the foregoing cases and the $CHCl_3$ extract was passed through a column of Al_2O_3. The fraction eluted with hexane–benzene (6: 1) was the recovered I (0.65 g, 6.5%). The fraction eluted with benzene was evaporated and a mixture of three kinds of propionylated compound was obtained as 3.4 g (25.1%) of yellow crystals. The mixture was recrystallized from benzene

8) All melting points are uncorrected.

to 0.62 g of 4-propionyl compound (VII) as yellow needles, mp 164—165°. The recrystallization mother liquor was further recrystallized from benzene to 0.155 g of 7-propionyl compound (VIII) as colorless needles, mp 153—155°. This mother liquor was again evaporated, the residue was treated with ether and the part insoluble in ether was collected by filtration. The ether solution was evaporated and the residue was passed through a column of silica gel. The column was eluted with benzene–acetone (20:1); the first fraction gave 0.227 g of VII, the second gave 0.121 g of 5-propionyl compound (IX) as pale yellow powder, mp 104—105°, and the third gave 0.13 g of VIII. 2-Methyl-4-propionyl-1(2*H*)-isoquinolone (VII): Yield, 0.847 g (6.3%). *Anal.* Calcd. for $C_{13}H_{13}O_2N$: C, 72.54; H, 6.09; N, 6.51. Found: C, 72.41; H, 6.13; N, 6.54. IR ν_{max}^{Nujol} cm^{-1}: 1680 (C=O), 1665 (amide C=O), 775 (δ-CH). UV λ_{max}^{EtOH} nm (log ε): 221.7 (4.49), 258 (3.95), 304 (4.08), 312 (4.04), 325 (3.99), 339 (3.80). NMR (in $CDCl_3$) ppm: 1.25 (3H, triplet, J=7.5 cps, C-CH_3), 2.91 (2H, quartet, J=7.5 cps, CO-$\underline{CH_2}$-), 3.67 (3H, singlet, N-CH_3), 7.62 (2H, multiplet, J=7.5, J=2.0 cps, C6-H, C7-H), 7.90 (1H, singlet, C3-H), 8.44 (1H, quartet, J=7.5, J=2.0 cps, C5-H), 8.86 (1H, quartet, J=7.5, J=2.0 cps, C8-H).

2-Methyl-7-propionyl-1(2*H*)-isoquinolone (VIII): Yield, 0.285 g (2.1%). *Anal.* Calcd. for $C_{13}H_{13}O_2N$: C, 72.54; H, 6.09; N, 6.51. Found: C, 72.60; H, 6.13; N, 6.53. IR ν_{max}^{Nujol} cm^{-1}: 1680 (C=O), 1670 (amide C=O), 850 (δ-CH). UV λ_{max}^{EtOH} nm (log ε): 213 (4.51), 225 (4.49), 266 (3.81), 317 (4.04), 332 (4.11), 343 (4.04). NMR (in $CDCl_3$) ppm: 1.25 (3H, triplet, J=7.5 cps, C-CH_3), 3.14 (2H, quartet, J=7.5 cps, CO-$\underline{CH_2}$-), 3.63 (3H, singlet, N-CH_3), 6.52 (1H, doublet, J=7.5 cps, C4-H), 7.20 (1H, doublet, J=7.5 cps, C3-H), 7.49 (1H, doublet, J=8.0 cps, C5-H), 8.24 (1H, quartet, J=8.0, J=2.0 cps, C6-H), 8.97 (1H, doublet, J=2.0 cps, C8-H).

2-Methyl-5-propionyl-1(2*H*)-isoquinolone (IX): Yield, 0.121 g (0.9%). *Anal.* Calcd. for $C_{13}H_{13}O_2N$: C, 72.54; H, 6.09; N, 6.51. Found: C, 72.71; H, 6.17; N, 6.53. IR ν_{max}^{Nujol} cm^{-1}: 1680 (C=O), 1670 (amide C=O), 815 (δ-CH). UV λ_{max}^{EtOH} nm (log ε): 215 (4.54), 253 (3.96), 309 (3.88), 342 (3.64). NMR (in $CDCl_3$) ppm: 1.32 (3H, triplet, J=7.5 cps, C-CH_3), 3.12 (2H, quartet, J=7.5 cps, CO-$\underline{CH_2}$-), 3.65 (3H, singlet, N-CH_3), 7.18 (1H, doublet, J=7.5 cps, C3-H), 7.42 (1H, doublet, J=7.5 cps, C4-H), 7.55 (1H, triplet, J=8.0 cps, C7-H), 8.08 (1H, quartet, J=8.0, J=2.0 cps, C6-H), 8.65 (1H, quartet, J=8.0, J=2.0 cps, C8-H).

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