Chem. Pharm. Bull. 18(5) 919—924 (1970)

UDC 547.823.04

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

Hiroshi Tomisawa, Masao Watanabe, Reiko Fujita, and Hiroshi Hongo

Tohoku College of Pharmacy[2]

(Received December 3, 1969)

The Friedel-Crafts reaction of 1-methyl-2(1*H*)-quinolone (I) was carried out. The products identified were 6-acetylated compound (II), 3-propionylated (V) and 6-propionylated (IV), and also 3- and 6-substituted compounds by butyrylation and valerylation.

1-Methyl-2(1*H*)-quinolone (I) is easily synthesized from quinoline in two steps,[3] and it is possible to revert it back to quinoline.[4] It has resonance limit formulae shown in Chart 1, and electrophilic substitution reaction seems possible at 3-, 6-, and 8-positions. In fact, nitration is known to occur at 6-position.[5] In quinoline 1-oxide, substitution reaction occurs at 4-position,[6] differing from that of I. From these facts, various reactions attempted on I would offer a new method for syntheses of quinoline derivatives.

In the present series of work, the Friedel-Crafts reaction of I was attempted as one of electrophilic substitution reactions, and introduction of a carbon chain into the quinolone ring was successfully carried out.

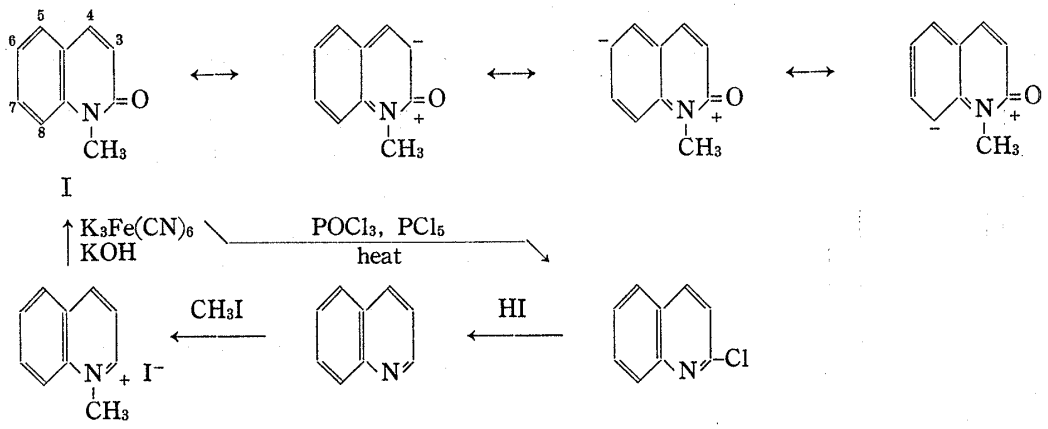

Chart 1

A mixture of 20 g of I and 200 g of aluminium chloride, with dropwise addition of 92 g of acetyl chloride, was heated in an oil bath at 50—55° for two weeks, and a compound (II) of $C_{12}H_{11}O_2N$ was obtained as yellow needles, mp 164°, in 10 g (37.5%) yield. The infrared (IR) spectrum of II (in KBr) showed absorption for acetyl C=O at 1683 cm^{-1}, amide C=O at 1665 cm^{-1}, aromatic ring hydrogen at 895 cm^{-1}, adjacent two hydrogens in the pyridone ring at 832 cm^{-1}. These spectral data suggested a 6- or 7-acetyl compound. The structure of II was proved chemically as shown in Chart 2. The Huang-Minlon reduction of II gave a

1) Part VIII: H. Tomisawa, H. Hongo, and H. Haruta, *Yakugaku Zasshi*, **87**, 554 (1967).
2) Location; *Nankozawa, Odawara, Sendai.*
3) H. Decker, *J. Prakt. Chem.*, **47**, 31 (1893).
4) P. Friedlender and H. Ostmaier, *Ber.*, **15**, 333 (1882).
5) A. Mittasch, *J. Prakt. Chem.*, **68**, 103 (1903).
6) E. Ochiai, M.O. Ishikawa, and Z. Sai, *Yakugaku Zasshi*, **63**, 280 (1943).

product (III) whose IR spectrum was completely superimposable with that of 6-ethyl-1-methyl-2(1*H*)-quinolone (III), obtained by derivation of 6-ethylquinoline to its methiodide[7] and its oxidation with potassium ferricyanide to III. Consequently, II is 6-acetyl-1-methyl-2(1*H*)-quinolone.

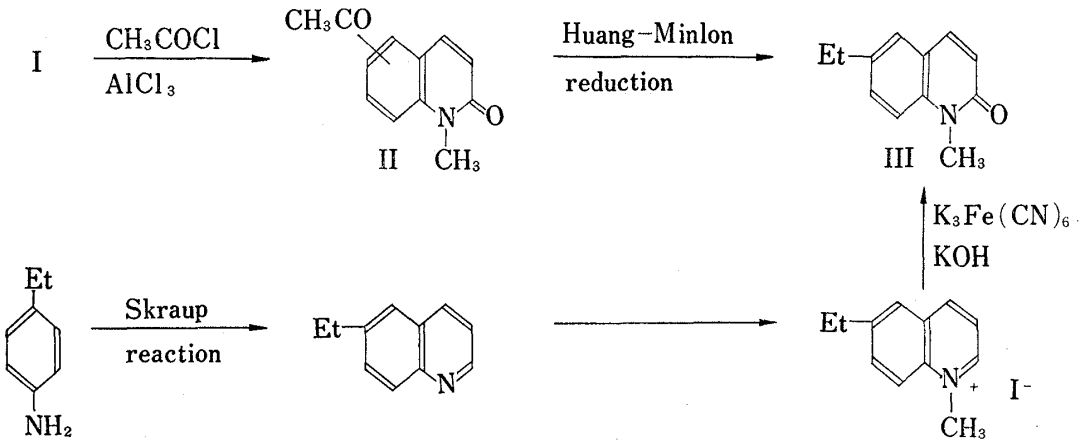

Chart 2

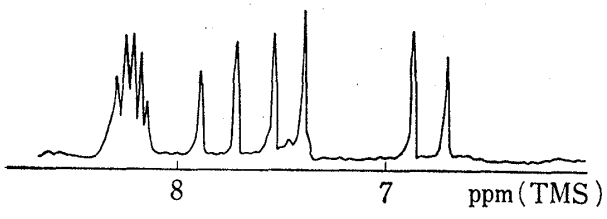

Fig. 1. NMR Spectrum of II (in $CDCl_3$) (60 Mcps)

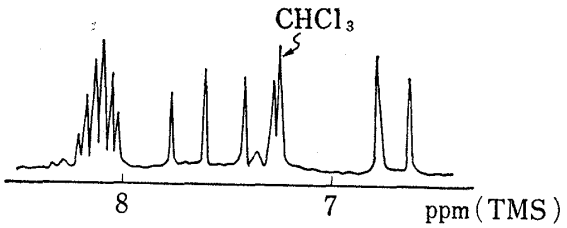

Fig. 3. NMR Spectrum of IV (in $CDCl_3$) (60 Mcps)

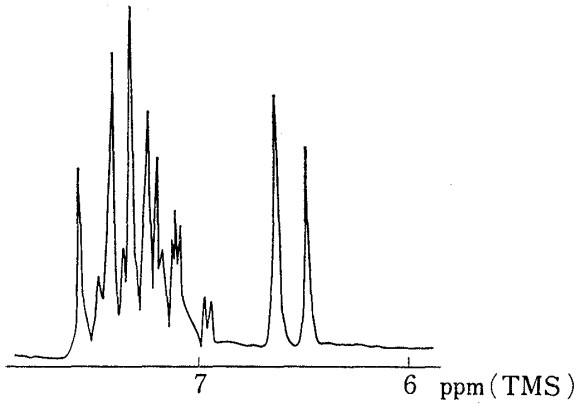

Fig. 2. NMR Spectrum of I (in$CDCl_3$) (60 Mcps)

The nuclear magnetic resonance (NMR) spectrum (Fig. 1) of II (in $CDCl_3$) also showed the presence of 3, 4-protons on the pyridone ring as AB quartet at 6.8 ppm (1H, J=9 cps) and 7.8 ppm (1H, J=9 cps).[8]

The protons on the benzene ring of I (Fig. 2) appeared as a multiplet at around 7.25 ppm for 4H, but in II, the signals appeared as a multiplet for 2H at 8.2 ppm, and as a doublet for 1H at 7.45 ppm (J=9 cps) due to the effect of C=O in the acetyl group. These data deny the presence of a substituent at 3-, 4-, 5-, and 8-position and is compatible with the structure for a 6-substituted compound. II is also obtained by the reaction of I and acetic anhydride but yield of the product is lowered (13.7%).

A mixture of 5 g of I and 50 g of aluminium chloride, with dropwise addition of 10 g propionyl chloride, was heated in an oil bath at 80° for 2 weeks and two kinds of acylated product (IV and V) were obtained. IV, $C_{13}H_{13}O_2N$, formed yellow needles, mp 172—174°; yielded, 0.08 g (1.2%). Its IR spectrum (in Nujol) showed absorptions for C=O in the propionyl group at 1680 cm^{-1}, amide C=O at 1655 cm^{-1}, adjacent two hydrogens in the pyridone ring at 840 cm^{-1}, and adjacent two hydrogens in the benzene ring at 820 cm^{-1}. In the NMR

7) W.S. Emeron, R.A. Heimsch, and T.M. Patic Jr., *J. Am. Chem. Soc.*, **75**, 2256 (1953).
8) L.M. Jackman and J.A. Elvidge, *J. Chem. Soc.*, **1961**, 859.

spectrum (Fig. 3) of IV (in $CDCl_3$), 3,4-proton signals were present as AB quartet at 6.7 and 7.7 ppm (J=9 cps), and the protons on the benzene ring as 2H at 8.1 ppm and 1H at 7.35 ppm. These data and the fact that its ultraviolet (UV) spectrum (Fig. 4) was quite similar to that of the 6-acetyl compound (II) indicated that IV is 1-methyl-6-propionyl-2(1*H*)-quinolone.

V, $C_{13}H_{13}O_2N$, formed yellow needles, mp 130—132°, in 0.4 g (5.9%) yield. Its IR spectrum (in Nujol) showed absorptions for C=O in the propionyl group at 1680 cm^{-1}, amide C=O at 1655 cm^{-1}, one H in the aromatic ring at 899 cm^{-1}, and adjacent four hydrogens at 770 cm^{-1}. It is clear that V is different from either II or IV. The NMR spectrum (Fig. 5) of V (in $CDCl_3$) showed signals at 1.2 ppm (3H, triplet, J=7 cps, $CO-C-CH_3$), 3.2 ppm (2H, quartet, J=7 cps, $CO-CH_2-$), 3.75 ppm (3H, singlet, $N-CH_3$), and the four protons on the benzene ring as a multiplet at around 7.4 ppm. With the disappearance of a signal for AB quartet of 3,4-protons, a signal appeared newly at 8.3 ppm (1H, singlet), and it is known that V is a compound having a substituent on the pyridone ring. Jackman and others[8] assigned the chemical shift of protons on the pyridone ring as shown in Chart 3.

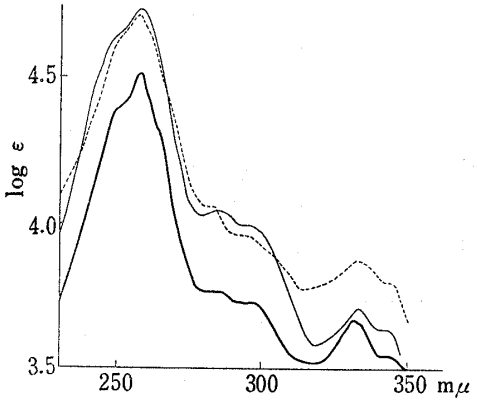

Fig. 4. UV Spectra of II, IV and VI (in EtOH)

II: ——, IV: ---, VI: ——

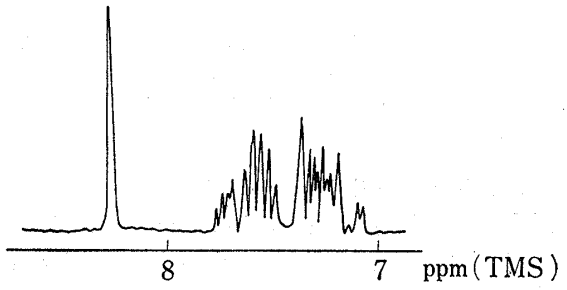

Fig. 5. NMR Spectrum of V (in $CDCl_3$) (60Mcps)

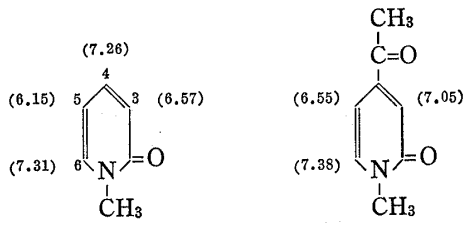

Chart 3

Comparison of this shift and the chemical shift of 4-acetyl-1-methyl-2(1*H*)-pyridone (Chart 3) shows that the proton signals for 3,5-protons have shifted *ca.* 0.45 ppm to a lower magnetic field by the introduction of an acetyl group. The signal at 8.3 ppm in V is about 1.6 ppm to the lower magnetic field than the signal (6.7 ppm) for 3-proton on the pyridone ring of IV, and is 0.95 ppm to the lower magnetic field than the signal (7.35 ppm) for 4-proton. However, it seems more appropriate to assign the signal at 8.3 ppm to the proton at 4-position in V. According to this assignment, the acetyl group would be in 3-position and the lower shift can be accounted only for the proton in 4-position. If the acetyl group were in the 4-position (*i.e.*, giving the signal at 8.3 ppm to the proton at 3-position), the proton at 5-position of the benzene ring should to a lower magnetic field and this is contrary to the spectral data. Consequently, V is 1-methyl-3-propionyl-2(1*H*)-quinolone.

The reaction of I with butyryl chloride gave 6-butyryl-1-methyl-2(1*H*)-quinolone (VI) and 3-butyryl-1-methyl-2(1*H*)-quinolone (VII),

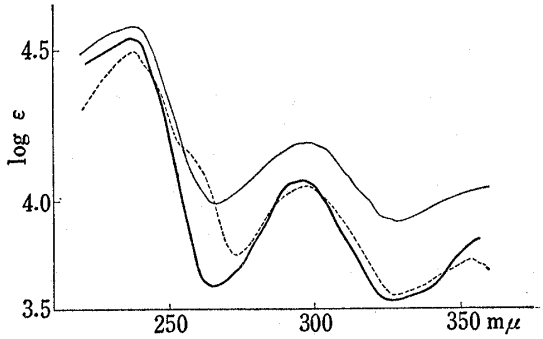

Fig. 6. UV Spectra of V, VII and IX (in EtOH)

V: ——, VII: ——, IX: ------

and that of I with valeryl chloride produced 1-methyl-6-valeryl-2(1H)-quinone (VIII) and 1-methyl-3-valeryl-2(1*H*)-quinolone (IX). The structure of these compounds was determined by spectral comparison (Fig. 6 and Tables I and II)

Table I. NMR Signals of 6-Acyl Compounds (ppm, in $CDCl_3$)

Compound	C_3-H	C_4-H	C_5,C_7-H	C_8-H
6-Acetyl (II)	6.80(d)	7.80(d)	8.20(m)	7.45(d)
6-Propionyl (IV)	6.70(d)	7.70(d)	8.10(m)	7.35(d)
6-Butyryl (VI)	6.70(d)	7.70(d)	8.10(m)	7.35(d)

Table II. NMR Signals of 3-Acyl Compounds (ppm,in $CDCl_3$)

Compound	C_4-H	C_5,C_6,C_7,C_8-H
3-Propionyl (V)	8.28(s)	7.45(m)
3-Butyryl (VII)	8.30(s)	7.45(m)
3-Valeryl (IX)	8.30(s)	7.45(m)

Reaction condition and yield of product are listed in Table III. It was found that electrophilic substitution reaction occurs at 3- and 6-positions by the Friedel–Crafts reaction of I and that the formation ratio of these isomer depends on the temperature and time of the reaction. These formation ratios were obtained from gas chromatography.

Table III. Reaction Conditions and Yields

Reagent	Temp. (°C)	1 week			2 weeks		
		Total yield (%)	Yield 3-	Ratio 6-	Total yield (%)	Yield 3-	Ratio 6-
Acetyl chloride	50				37.5	0	100
Acetic anhydride	130	16.6	0	100	13.7	0	100
Propionyl chloride	80	4.9	20	80	32.3	80	20
	100				10.1	93	7
Butyryl chloride	80	2.4	7	93	9.5	100	0
	100				13.3	3	97
Valeryl chloride	80				0	0	0
	100	1.7	100	0	2.6	94	6

Experimental[9]

Reaction of 1-Methyl-2(1*H*)-quinolone (I) and Acetyl Chloride——To a mixture of 20 g of I and 200 g of $AlCl_3$, mixed under anhydrous condition, 92 g of AcCl was added dropwise and the mixture was warmed in an oil bath of 50—55° for 1 hr. Further 92 g of AcCl was added and the mixture was heated at the same temperature for 2 weeks. The cooled mixture was poured into ice water, basified with 40% NaOH, and the mixture was extracted with benzene. The benzene extract was dried over $MgSO_4$, evaporated, and the residue was recrystallized from benzene to pale yellow needles (II), mp 164°. The recrystallization mother liquor was passed through a column of Al_2O_3 and the column was eluted with benzene–hexane (3:1) mixture from which further crop of II was obtained. Total yield, 10 g (37.5%). *Anal.* Calcd. for $C_{12}H_{11}O_2N$: C, 71.62; H, 5.51; N, 6.96. Found: C, 71.50; H, 5.52; N, 6.91. IR ν_{max}^{KBr} cm^{-1}: 1683 (C=O), 1665 (amide C=O), 895, 832 (δ C–H). UV λ_{max}^{EtOH} mμ (log ε): 250 (4.40), 257 (4.51), 285 (3.78), 298 (3.74), 334 (3.68), 346

9) All melting points are uncorrected.

(3.55). NMR (in $CDCl_3$) ppm: 2.7 (3H, singlet, $-COCH_3$), 3.8 (3H, signlet, $N-CH_3$), 6.8 (1H, doublet, $J=9$ cps, C_3-H), 7.45 (1H, doublet, $J=9$ cps, C_8-H), 7.8 (1H, doublet, $J=9$ cps, C_4-H), 8.2 (2H, multiplet, C_5, C_7-H).

Reaction of I and Acetic Anhydride——A mixture of 5 g of I and 125 g of $AlCl_3$, mixed under anhydrous condition, was added dropwise with 15 g of Ac_2O and the mixture was heated in an oil bath at 130° for 1 hr. Further 15 g of Ac_2O was added and the mixture was heated for 1 week at the same temperature. Treatment of the reaction mixture as in the foregoing case afforded 0.5 g (13.7%) of II.

Reaction of I and Propionyl Chloride——A mixture of 5 g of I and 50 g of $AlCl_3$, mixed under anhydrous condition, was added dropwise with 10 g of propionyl chloride and heated in an oil bath at 80° for 1 hr. Further 10 g of propionyl chloride was added and the mixture was heated for 2 weeks at the same temperature. The reaction mixture was treated as in the foregoing case and the product was separated by column chromatography over Al_2O_3. The fraction eluted with benzene was evaporated and the residue was recrystallized from benzene to 0.08 g (1.2%) of 1-methyl-6-propionyl-2(1*H*)-quinolone (IV) as yellow needles, mp 172—174°. *Anal.* Calcd. for $C_{13}H_{13}O_2N$: C, 72.54; H, 6.09; N, 6.51. Found: C, 72.55; H, 5.96; N, 6.31. IR ν_{max}^{Nujol} cm^{-1}: 1680 (C=O), 1655 (amide C=O), 840, 820 (δ C–H). UV λ_{max}^{EtOH} mμ (log ε): 252 (4.64), 257 (4.72), 284 (4.06), 295 (3.97), 333 (3.89), 346 (3.80). NMR (in $CDCl_3$) ppm: 1.25 (3H, triplet, $J=7$ cps, $C-CH_3$), 2.05 (2H, quartet, $J=7$ cps, $-COCH_2-$), 3.70 (3H, singlet, $N-CH_3$), 6.70 (1H, doublet, $J=9$ cps, C_3-H), 7.35 (1H, doublet, $J=9$ cps, C_8-H), 7.70 (1H, doublet, $J=9$ cps, C_4-H), 8.10 (2H, multiplet, C_5, C_7-H).

The column was further eluted with benzene–hexane (2:1) mixture and the residue left after evaporation of the solvent was recrystallized from benzene to 0.4 g (5.9%) of 1-methyl-3-propionyl-2(1*H*)-quinolone (V) as yellow needles, mp 130—132°. *Anal.* Calcd. for $C_{13}H_{13}O_2N$: C, 72.54; H, 6.09; N, 6.51. Found: C, 72.55; H, 5.9; N, 6.31. IR ν_{max}^{Nujol} cm^{-1}: 1680 (C=O), 1655 (amide C=O), 899, 770 (δ C–H). UV λ_{max}^{EtOH} mμ (log ε): 237 (4.56), 295 (4.08), 362 (3.88). NMR (in $CDCl_3$) ppm: 1.20 (3H, triplet, $J=7$ cps, $C-CH_3$), 3.20 (2H, quartet, $J=7$ cps, $-COCH_2-$), 3.75 (3H, singlet, $N-CH_3$), 7.45 (4H, multiplet, C_5, C_6, C_7, C_8-H), 8.28 (1H, singlet, C_4-H).

Gas Chromatography: Retention time (min): 4.6 (III), 2.7 (IV). Unit area ratio of III: IV=1:1.3. Measured on Shimazu Gas Chromatograph Model GC-IB FID. Column, Silicone SE-30, 1.5% on Shimalite 3 mm/×1.5. Temperature of the column, 205°, injection 300°, detector 240°. Carrier N_2 gas flow, 60 ml/min, H_2 flow, 45 ml/min, air 2 l/min. Recorder sensitivity, 100°; range, 3.2; chart drive, 1 cm/min.

Reaction of I and Butyryl Chloride——1) To an anhydrous mixture of 5 g of I and 50 g of $AlCl_3$, 10 g of butyryl chloride was added dropwise and the mixture was heated in an oil bath of 100° for 1 hr. Further 10 g of butyryl chloride was added and the mixture was heated at the same temperature for 2 weeks. The reaction mixture was treated as in the foregoing cases and the product was separated by column chromatography over Al_2O_3. The fraction eluted with benzene–hexane (3:1) mixture was recrystallized from benzene to 0.17 g (2.4%) of 6-butyryl-1-methyl-2(1*H*)-quinolone (VI) as yellow needles, mp 145—146°. *Anal.* Calcd. for $C_{14}H_{15}O_2N$: C, 73.34; H, 6.59; N, 6.11. Found: C, 73.21; H, 6.36; N, 6.37. IR ν_{max}^{Nujol} cm^{-1}: 1660 (C=O), 1655 (amide C=O), 890, 837, 815 (δ C–H). UV λ_{max}^{EtOH} mμ (log ε): 252 (4.66), 258 (4.74), 285 (4.06), 297 (4.00), 334 (3.72), 348 (3.65). NMR (in $CDCl_3$) ppm: 1.05 (3H, triplet, $J=7$ cps, $C-CH_3$), 1.75 (2H, sextet, $J=7$ cps, $-CO-C-CH_2-$), 2.95 (2H, triplet, $J=7$ cps, $-CO-CH_2-$), 3.70 (3H, singlet, $N-CH_3$), 6.70 (1H, doublet, $J=9$ cps, C_3-H), 7.35 (1H, doublet, $J=9$ cps, C_8-H), 7.70 (1H, doublet, $J=9$ cps, C_4-H), 8.10 (2H, multiplet, C_5, C_7-H).

Gas Chromatography: Carried out under the same conditions as in the foregoing case. Retention time was 4.6 min (the peak at 2.7 min indicate the presence of 1/15 of the 3-butyryl compound (VII)).

2) Anhydrous mixture of 5 g of I and 50 g of $AlCl_3$, added dropwise with 10 g of butyryl chloride, was heated in a water bath of 80° for 1 hr, further 5 g of butyryl chloride was added, and heated for 2 weeks at the same temperature. The reaction mixture was treated as in the foregoing cases and the prodcut was separated by column chromatography over Al_2O_3.

The fraction eluted with benzene–hexane was evaporated and the residue was crystallized from benzene to 0.68 g (9.5%) of 3-butyryl-1-methyl-2(1*H*)-quinolone (VII) as yellow needles, mp 91—92°. *Anal.* Calcd. for $C_{14}H_{15}O_2N$: N, 6.11. Found: N, 5.94. IR ν_{max}^{Nujol} cm^{-1}: 1695 (C=O), 1655 (amide C=O), 770 (δ C–H). UV λ_{max}^{EtOH} mμ (log ε): 237 (4.6), 296 (4.20), 365 (4.04). NMR (in $CDCl_3$) ppm: 0.97 (3H, triplet, $J=7$ cps, $C-CH_3$), 1.70 (2H, multiplet, $-CO-C-CH_2-$), 3.15 (2H, triplet, $J=7$ cps, $-CO-CH_2-$), 3.71 (3H, singlet, $N-CH_3$), 7.45 (4H, multiplet, C_5,C_6,C_7,C_8-H), 8.30 (1H, singlet, C_4-H).

Gas Chromatography: Carried out under the same conditions as above. Retention time, 2.7 min.

Reaction of I and Valeryl Chloride——To an anhydrous mixture of 5 g of I and 50 g of $AlCl_3$, 10 g of valeryl chloride was added dropwise and the mixture was heated in an oil bath of 100° for 1 hr. Further 10 g of valeryl chloride was added and the mixture was heated under the same condition for 2 weeks. The reaction mixture was treated as in the foregoing and the product was separated by column chromatography over Al_2O_3.

The fraction eluted with benzene–hexane (2:1) mixture was evaporated and the residue was recrystallized from benzene to 0.2 g (2.6%) of 1-methyl-3-valeryl-2(1*H*)-quinolone (IX) as pale yellow needles, mp 83—84°. *Anal.* Calcd. for $C_{15}H_{17}O_2N$: C, 74.05; H, 7.05; N, 5.76. Found: C, 74.43; H, 7.30; N, 5.38. IR ν_{max}^{Nujol} cm^{-1}: 1683 (C=O), 1655 (amide C=O), 895, 775 (δ C–H). UV λ_{max}^{EtOH} mμ (log ε): 237 (4.52), 296 (4.06), 365 (3.83). NMR (in $CDCl_3$) ppm: 1.10 (5H, multiplet, $-CH_2-CH_3$), 1.70 (2H, multiplet, $-CO-C-CH_2-$),

3.20 (2H, triplet, $J=7$ cps, $-CO-CH_2-$), 3.75 (3H, singlet, $N-CH_3$), 7.45 (4H, multiplet, C_5,C_6,C_7,C_8–H), 8.30 (1H, singlet, C_4–H).

Gas Chromatography: Carried out under the same conditions as above. Retention time, 2.7 min (The peak at 4.6 min shows the presence of 1/13 of 6-valeryl compound (VIII)).

Synthesis of 6-Ethyl-1-methyl-2(1*H*)-quinolone (III)——1) To a solution of 1 g of KOH dissolved in 10 ml of ethylene glycol with application of heat, 0.21 g of the 6-acetyl compound (II) and 1 g of 80% $NH_2NH_2\cdot H_2O$ were added and the mixture was refluxed for 1 hr. The temperature was then raised to 200—210° to distill off excess $NH_2NH_2\cdot H_2O$, and again refluxed at 190—200° for 3 hr. When cooled, the reaction mixture was poured into a large amount of H_2O and extracted with benzene. Evaporation of benzene from the extract under a reduced pressure left 0.21 g of pale yellow oil which was purified by distillation at a highly reduced pressure to collect a fraction boiling at 130—150° (0.05 mmHg) as a viscous oil. Picrate, mp 114°. Chloroplatinate, mp 160—170° (decomp.). *Anal.* Calcd. for $C_{18}H_{16}O_8N_4$ (picrate): C, 51.92; H, 3.87; N, 13.45. Found: C, 51.95; H, 3.92; N, 13.25. IR ν_{max}^{Nujol} cm^{-1}: 1660 (amide C=O), 890, 835, 823 (δ C–H). UV λ_{max}^{EtOH} mμ (log ε): 274 (3.85), 283 (3.84), 341 (3.67).

2) A solution of 1 g of 6-ethyl-1-methyl-2(1*H*)-quinolone methiodide[7] and 4 g of $K_3Fe(CN)_6$ dissolved in 5 ml of H_2O was cooled in ice, 100 ml of 2% KOH was added dropwise, and the mixture was stirred for 8 hr. The mixture was covered with benzene and allowed to stand over night. This was extracted with benzene, and evaporation of the solvent from the extract under a reduced pressure afforded 0.6 g of pale yellow oil whose IR spectrum was identical with that of 6-ethyl-1-methyl-2(1*H*)-quinolone (III).

Synthesis of 4-Acetyl-1-methyl-2(1*H*)-pyridone——An alkohol-free alkoxide was prepared by dissolving 0.8 g of Na in 12 ml of abs. EtOH. A solution of 4 g of 4-ethoxycarbonyl-1-methyl-2(1*H*)-pyridone[10] dissolved in 11.4 g of AcOEt was added dropwise into this NaOEt and the mixture was stirred for 10 hr while heating in an oil bath of 100°. After standing over night, the mixture was dissolved in 50 ml of H_2SO_4 and extracted with benzene to remove the unreacted ester. Mother liquid was acidified by the addition of 25 ml of conc. HCl and stirred for 3 hr while heating in an oil bath of 100°. This mixture was basified with K_2CO_3 and extracted with benzene. After evaporation of bezene from the extract, the residue was recrystallized from benzene to pale yellow needles, mp 144—145°.[11] Yield, 1.54 g (46.2%). IR ν_{max}^{Nujol} cm^{-1}: 1680 (C=O), 1660 (amide C=O), 890, 800, 760 (δ C–H). NMR (in $CDCl_3$) ppm: 2.50 (3H, singlet, $-COCH_3$), 3.55 (3H, singlet, $N-CH_3$), 6.55 (1H, quartet, $J=6$, 3 cps, C_5–H), 7.05 (1H, doublet, $J=3$ cps, C_3–H), 7.38 (1H, doublet, $J=6$ cps, C_6–H).

Acknowledgement The authers are indebted Mr. Fusao Sakakibara of this College for elemental analyses, to the Analysis Center of the Institute of Pharmacy, Tohoku University School of Medicine, for elemental analyses and for IR and NMR spectral measurements, and Prof. Mitsuru Uchiyama of Tohoku University for gas chromatographic data.

10) M.H. Fronk and H.S. Mosher, *J. Org. Chem.*, **24**, 196 (1959).
11) S. Sugasawa and M. Kirisawa, *Chem. Pharm. Bull.* (Tokyo), **6**, 615 (1958).