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Studies on 1-Alkyl-2(1*H*)-pyridone Derivatives. XII.[1] Reaction of 2-Methyl-1(2*H*)-isoquinolone with Formaldehyde and Hydrochloric Acid

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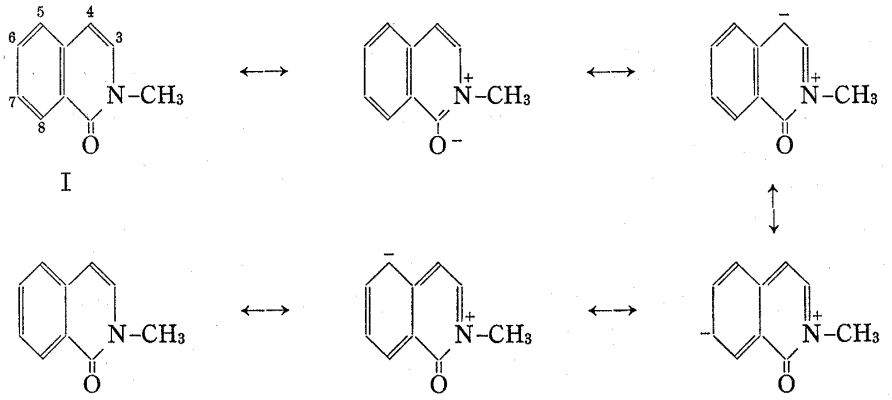
Reaction of 2-methyl-1(2*H*)-isoquinolone (I) with formaldehyde and conc. hydrochloric acid was carried out and it was found that the product differed according to reaction conditions. The products obtained and their structure identified were 4-hydroxymethyl-2-methyl-1(2*H*)-isoquinolone (II), 4,4′-methylene-bis[2-methyl-1(2*H*)-isoquinolone] (III), and 4-chloromethyl-2-methyl-1(2*H*)-isoquinolone (IV).

2-Methyl-1(2*H*)-isoquinolone (I) is easily prepared in two steps from isoquinoline[3] and can be reverted to isoquinoline in two steps.[4] Isoquinoline and its N-oxide are active to electrophilic substitution in 5- and 8-position but I is assumed to have active positions different from those of isoquinoline because there has been a report on the bromination of the pyridone ring in I[5] and from the resonance limiting formulae (Chart 1). From these facts, various reaction attempted on I would offer a new synthetic route to isoquinoline derivatives and should be of interest.

In the present series of work, reaction of I with formaldehyde and hydrochloric acid was carried out as one of the electrophilic substitution reaction on I.



I

Chart 1

A mixture of 10 g of I, 4.2 g of paraformaldehyde, and 25 ml of conc. hydrochloric acid was stirred in an oil bath of 100° for 3.5 hr, 42.5 g of crystalline sodium acetate and 12.9 g of acetic anhydride were added, and the mixture was further stirred at 100° for 2 hr. The cooled reaction mixture was basified with potassium carbonate and extracted with chloroform. The

1) Part XI: H. Tomisawa, Y. Kobayashi, H. Hongo, and R. Fujita, *Chem. Pharm. Bull.* (Tokyo), **18**, 930 (1970).
2) Location: *Nankozawa, Odawara, Sendai.*
3) H. Decker, *J. prakt. Chem.*, **47**, 37 (1893).
4) S. Gabriel and J. Colman, *Ber.*, **33**, 985 (1900).
5) E. Bamberger and W. Frew, *Ber.*, **27**, 206 (1894).

dried extract was passed through a chromatographic column over alumina and afforded 3.2 g (27%) of colorless needles (II), mp 209—210°, $C_{11}H_{11}O_2N$, and 3.3 g (32%) of colorless plates (III), mp 302—304°, $C_{21}H_{18}O_2N_2$. The analytical value of II corresponds to I with introduction of one hydroxymethyl group and its infrared (IR) spectrum (in Nujol) exhibited absorptions for OH at 3350 cm^{-1}, for amide C=O at 1645 cm^{-1}, for C–O at 1020 cm^{-1}, and for adjacent four H in the aromatic ring at 750 cm^{-1}, same as that of I. The nuclear magnetic resonance (NMR) spectrum of II (in CF_3COOH) (Fig. 1) exhibited signals at 4.08 ppm (3H, singlet, N–CH_3), and at 5.78 ppm (2H, singlet, –$C\underline{H}_2OH$), while the signals for AB quartet in I (Fig. 2) at 7.6—7.8 ppm disappeared and appeared as a singlet at 7.83 ppm. According to the NMR assignment of protons on the pyridone ring by Jackman and others,[6] the signal in the higher magnetic field than the AB quartet should be the proton at 4-position of the isoquinolone ring. Comparison of the NMR spectra of I and II suggests the disappearance of the signal in the higher magnetic field and, therefore, II seems to be 4-hydroxymethyl-1(2*H*)-isoquinolone.

However, the difference of the chemical shift (0.15 ppm) of the AB quartet signal of I is so small that it would be difficult to determine the structure merely from this point. The NMR spectrum of II further shows signals at 7.88—8.15 ppm (3H, multiplet, C_5, C_6, C_7–H) and at 8.65 ppm (1H, doublet, J=7.5 cps, C_8–H).

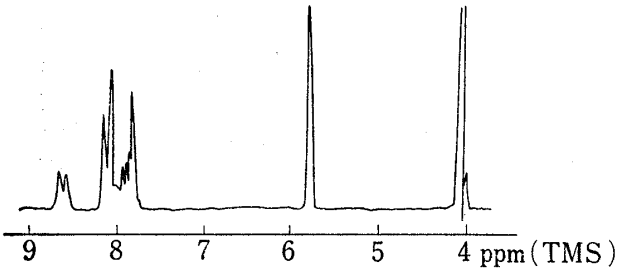


Fig. 1. NMR Spectrum of II in CF_3COOH (100 Mcps)

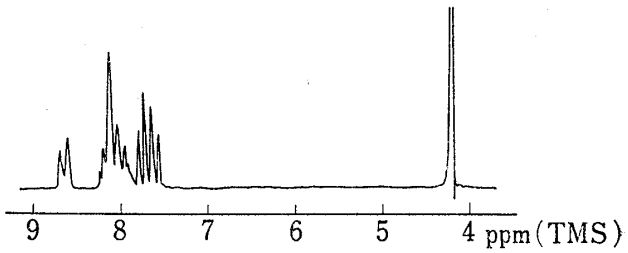


Fig. 2. NMR Spectrum of I in CF_3COOH (100 Mcps)

The IR spectrum of III (in Nujol) shows absorptions for amide C=O at 1650 cm^{-1} and for adjacent four H in the aromatic ring at 760 cm^{-1}, suggesting a substitution in the pyridone ring. The NMR spectrum (Fig. 3) of III (in CF_3COOH) has signals at 4.03 ppm (3H, singlet, N–CH_3), 4.75 ppm (1H, singlet), 7.85—8.20 ppm (3H, multiplet, C_5, C_6, C_7–H), 8.73 ppm (1H, doublet, J=7.5 cps, C_8–H), and at 7.38 ppm (1H, singlet) for a proton on the pyridone ring. The fact that the signal at 4.75 ppm must be assigned to one hydrogen cannot be explained unless this signal is taken as two hydrogens and giving a bimolecular structure of two isoquinolone rings situated symmetrically and connected by a methylene linkage for III. Compared to the NMR spectrum of I (Fig. 2), the proton on the pyridone ring of III appears in too high a magnetic field and it is difficult to decide whether it is for the proton in 3- or 4-position.

The fact that the substituent in II and III is in the same position was proved by chemical means (Chart 2). The product obtained by heating I and II with conc. hydrochloric acid at 100° for 2.5 hr was completely identical with III, both in mixed melting point determination and in IR spectra.

A mixture of 2 g of I, 0.8 g of paraformaldehyde, 10.4 ml of conc. hydrochloric acid, and 10 ml of acetic anhydride was stirred at room temperature for 215 hr, hydrochloric acid and acetic anhydride was distilled off under a reduced pressure, and the residue was extracted with hexane. The hexane extract afforded 0.6 g (23%) of colorless needles (IV), mp 279—282°, $C_{11}H_{10}ONCl$. The residual solution left after hexane extraction afforded 1.6 g (77%) of III. The analytical values of IV corresponded to I with introduction of one chloromethyl group, and its IR spectrum showed absorptions for amide C=O at 1650

6) L.M. Jackman and J.A. Elvidge, *J. Chem. Soc.*, **1961**, 859.

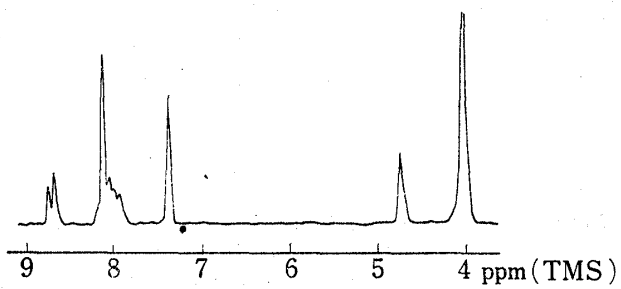


Fig. 3. NMR Spectrum of III in CF_3COOH (100 Mcps)

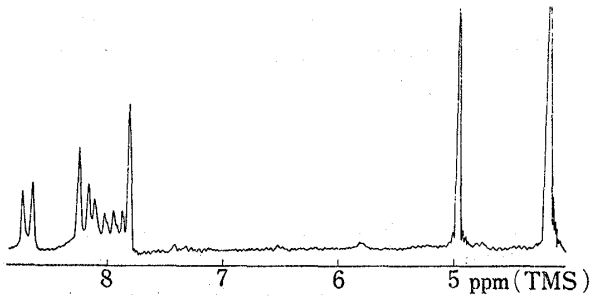


Fig. 4. NMR Spectrum of IV in CF_3COOH (100 Mcps)

cm^{-1} and adjacent four hydrogens in the aromatic ring at 750 cm^{-1}, suggesting a substituion into the pyridone ring. The NMR spectrum (Fig. 4) of IV (in CF_3COOH) exhibited signals at 4.15 ppm (3H, singlet, N–CH_3), 4.95 ppm (2H, singlet, –CH_2Cl), 7.87—8.35 ppm (3H, multiplet, C_5, C_6, C_7–H), and 8.69 ppm (1H, doublet, C_8–H), with the proton on the pyridone ring appearing at 7.80 ppm (1H, singlet), same as in that of II, and suggesting IV to be a 4-chloromethyl compound. In order to confirm further its structure, the following examinations were made. IV, differing from II or III, was soluble in $CDCl_3$ and the NMR spectra of I and IV in $CDCl_3$ were compared. In the NMR spectrum of I (Fig. 5), the AB quartet of proton at 4- and 3- positions appear respectively at 6.45 and 7.02 ppm, with a difference of 0.57 ppm, and in that of IV (Fig. 6), the signal at 6.45 ppm has disappeared and that of the proton in 3-position remains as a singlet at 7.19 ppm. Consequently, IV is 4-chloromethyl-2-methyl-1(2*H*)-isoquinolone. Since heating of II with thionyl chloride at 90° for 2 hr gives a product which is completely identical with IV in melting point and IR spectrum, the presence of a substituent in II and III in the same position as in IV has been proved chemically (Chart 2). Therefore, II is 4-hydroxymethyl-2-methyl-1(2*H*)-isoquinolone and III is 4,4′-methylene-bis(2-methyl-1(2*H*)-isoquinolone). The shift of the proton at 3-position in III to an abnormally high magne-

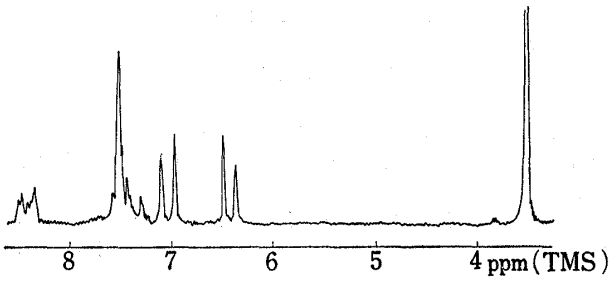


Fig. 5. NMR Spectrum of I in $CDCl_3$ (60 Mcps)

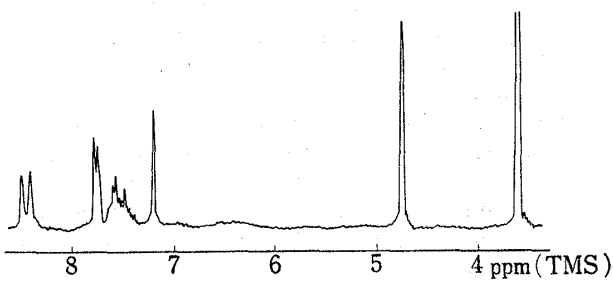


Fig. 6. NMR Spectrum of IV in $CDCl_3$ (100 Mcps)

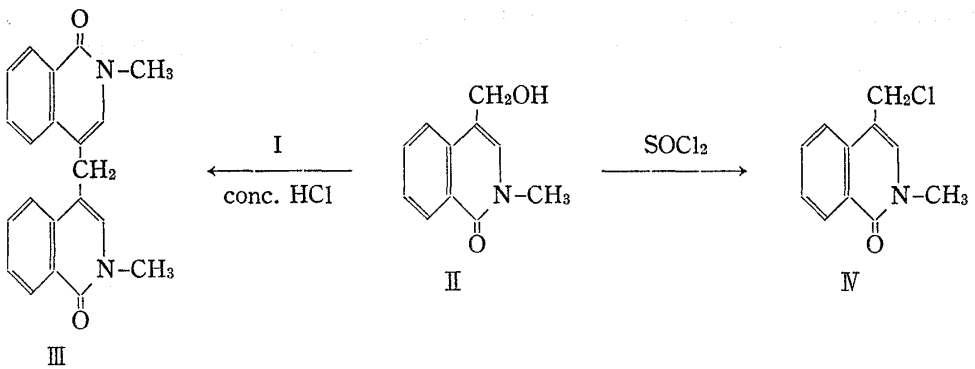


Chart 2

tic field must be to the anisotropy of the isoquinolone ring. It should be added that III can be obtained quantitatively by dissolving 2 g of I and 0.8 g of paraformaldehyde in 25 ml of ethanol saturated with hydrogen chloride and stirring this mixture at 100° for 2 hr.

Experimental[7]

Reaction of 2-Methyl-1(2*H*)-isoquinolone (I) with Paraformaldehyde and Conc. Hydrochloric Acid——A mixture of 10 g of I, 4.2 g of paraformaldehyde, and 25 ml of conc. HCl was stirred in an oil bath of 100° for 3.5 hr, 12.9 g of Ac_2O and 42.5 g of $AcONa \cdot 3H_2O$ were added, and the mixture was stirred for 2 hr at the same temperature. The cooled reaction mixture was basified with K_2CO_3 and extracted with $CHCl_3$. The $CHCl_3$ extract was dried over $MgSO_4$, the solvent was evaporated under a reduced pressure, and the resinous residue in benzene solution was submitted to column chromatography over Al_2O_3. The fraction eluted with benzene–$CHCl_3$ (5:1) was evaporated and the residue was recrystallized from $CHCl_3$ to 3.2 g (27%) of 4-hydroxymethyl-2-methyl-1(2*H*)-isoquinolone (II) as colorless prisms, mp 209—210°. *Anal.* Calcd. for $C_{11}H_{11}O_2N$: C, 69.82; H, 5.86; N, 7.40. Found: C, 69.96; H, 5.72; N, 7.40. IR ν_{max}^{Nujol} cm^{-1}: 3350 (O–H), 1645 (amide C=O), 1020 (C–O), 900, 750 (δ C–H). NMR (in CF_3COOH) ppm: 4.08 (3H, singlet, N–CH_3), 5.78 (2H, singlet, –CH_2–), 7.83 (1H, singlet, C_3–H), 7.88—8.15 (3H, multiplet, C_5, C_6, C_7–H), 8.65 (1H, doublet, J=7.5 cps, C_8–H). UV λ_{max}^{EtOH} mμ (log ε): 227 (4.23), 244 (3.87), 253 (3.82), 285 (3.93), 294 (3.95), 320 (3.63), 330 (3.69), 340 (3.57).

Elution of the column further with $CHCl_3$ gave 3.3 g (32%) of 4,4′-methylene-bis[2-methyl-1(2*H*)-isoquinolone] (III) as colorless plates (from $CHCl_3$), mp 302—304°. *Anal.* Calcd. for $C_{21}H_{18}O_2N_2$: C, 76.36; H, 5.49; N, 8.48. Found: C, 76.66; H, 5.51; N, 8.55. IR ν_{max}^{Nujol} cm^{-1}: 1650 (amide C=O), 880, 760 (δ C–H). NMR (in CF_3COOH) ppm: 4.03 (6H, singlet, N,N′–CH_3), 4.75 (2H, singlet, –CH_2–), 7.38 (2H, singlet, C_3,C_3′–H), 7.85—8.20 (6H, multiplet, C_5,C_6,C_7,C_5′,C_6,′C_7′–H), 8.73 (2H, doublet, J=7.5 cps, C_8,C_8′–H). UV λ_{max}^{EtOH} mμ (log ε): 227 (4.54), 246 (4.21), 252 (4.17), 292 (4.32), 298 (4.23), 326 (4.03), 338 (4.09), 348 (3.97).

Syntheses of III and 4-Chloromethyl-2-methyl-1(2*H*)-isoquinolone (IV)——A mixture of 2 g of I, 0.8 g of paraformaldehyde, 10.4 ml of conc. HCl, and 10 ml of Ac_2O was stirred at room temperature for 215 hr, the solvent was evaporated in a reduced pressure, and the residue was extracted with warm hexane. The solvent was evaporated from the extract in a reduced pressure and the residue was recrystallized from acetone to 0.6 g (23%) of colorless needles (IV), mp 279—282° (sublimated at 145°). *Anal.* Calcd. for $C_{11}H_{10}ONCl$: C, 63.62; H, 4.85; N, 6.74. Found: C, 63.56; H, 4.76; N, 6.67. IR ν_{max}^{Nujol} cm^{-1}: 1650 (amide C=O), 900, 750 (δ C–H). NMR (in CF_3COOH) ppm: 4.15 (3H, singlet, N–CH_3), 4.95 (2H, singlet, –CH_2–), 7.80 (1H, singlet, C_3–H), 7.87—8.35 (3H, multiplet, C_5,C_6,C_7–H), 8.69 (1H, doublet, J=7.5 cps, C_8–H). NMR (in $CDCl_3$) ppm: 3.58 (3H, singlet, N–CH_3), 4.72 (2H, singlet, –CH_2–), 7.19 (1H, singlet, C_3–H), 7.4—7.8 (3H, multiplet, C_5,C_6,C_7–H), 8.46 (1H, doublet, J=7.5 cps, C_8–H). UV λ_{max}^{EtOH} mμ (log ε): 226 (4.26), 242 (3.94), 253 (3.86), 285 (3.91), 294 (3.92), 320 (3.62), 330 (3.68), 342 (3.53).

The residue left after extraction with warm hexane was recrystallized from $CHCl_3$ and 1.6 g (77%) of III was obtained.

Synthesis of III——A mixture of 2 g of I, 0.8 g of paraformaldehyde, and 25 ml of EtOH saturated with HCl was stirred in an oil bath of 100° for 2 hr, EtOH was evaporated in a reduced pressure, and the residue was recrystallized from $CHCl_3$ to 2.0 g (97%) of III.

Reaction of I and II——A solution of 45.6 mg of I and 33.5 mg of II dissolved in excess conc. HCl was heated in an oil bath of 100° for 2.5 hr, HCl was evaporated under a reduced pressure, and the residue was recrystallized from $CHCl_3$ to 45.3 mg (77%) of III.

Reaction of II and Thionyl Chloride——A mixture of 61 mg of II and 2.0 g of $SOCl_2$ was refluxed in an oil bath of 90° for 2 hr, $SOCl_2$ was evaporated in a reduced pressure, and the residue was recrystallized from acetone to 60 mg (91%) of IV.

Acknowledgement The authors are indebted to Mr. F. Sakakibara of this College for elemental analysis and to the Analysis Center of the Institute of Pharmaceutical Sciences, Tohoku University, for elemental analysis and NMR spectral measurement.

7) All melting points are uncorrected.