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Studies on 1-Alkyl-2(1*H*)-pyridone Derivatives. XIV.[1] The Mannich Reactions of 1-Methyl-2(1*H*)-pyridone and 2-Methyl-1(2*H*)-isoquinolone

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1-Methyl-2(1*H*)-pyridone (I) is easily synthesized from pyridine in two steps,[3] and it is possible to revert it back to pyridine.[4] 2-Methyl-1(2*H*)-isoquinolone (II) is prepared from isoquinoline[5] and can be reverted to isoquinoline.[6] With consideration for the resonance theory, the electrophilic substitution reaction seems to occur at the 3- and 5-positions of I, and at the 4-,5- and 7- positions of II. In a previous work of this series,[7,8] the reactions of I and II with formaldehyde in the presence of hydrochloric acid were carried out, and these reactions took place at the 5-position of I and the 4-position of II. From many evidences, the Mannich reaction seems to be similar to the reactions which were mentioned in a previous paper.[7,8] However, the Mannich reactions of I and II are expected to occur not only at the 5-position of I and the 4-position of II but also at the others. Kamiya, *et al.*[9] have successfully carried out the Mannich reactions of 2(1*H*)-pyridone and 3-hydroxy-2(1*H*)-pyridone. But the Mannich reactions of I and II have not been reported. In the present series, the Mannich reactions of I and II were carried out and some observations on these reactions are described herein.

A mixture of I, dimethylamine hydrochloride, and 37% formalin was gently refluxed for 48 hr. Treatment of the reaction mixture with benzene and chloroform, followed by chromatographic separation on silica gel, afforded two kinds of products (III and IV), besides the recovery of I (60%).

III, $C_{13}H_{14}O_2N_2 \cdot H_2O$, was obtained as colorless pillars, mp 241—243°, in 21.9% yield. The ion peak in the mass spectrum of III occurred at *m/e* 230 (M^+). The infrared (IR) spectrum (Nujol) of III showed absorptions for amide C=O at 1650 cm^{-1} and adjacent two hydrogens in the pyridone ring at 830 cm^{-1}. From these spectral data, substitution seems to have occurred at 4- or 5-position. The protons on the pyridone ring in the nuclear magnetic resonance (NMR) spectrum (in CF_3COOH) of III appeared as the signals at 4.10 ppm (1H, singlet), 7.39 ppm (1H, doublet, J=9 cps), and 7.85—8.10 ppm (2H). The fact that the signal at 4.10 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 pyridone rings situated symmetrically and connected by a methylene linkage for III. According to Elvidge and Jackman,[10] the peak at 7.39 ppm would be the proton at the 3- or 5-position, and there would be an adjacent proton from the coupling constant of 9 cps. The peak at 7.85—8.10 ppm

1) Part XIII: H. Tomisawa, R. Fujita, K. Noguchi and H. Hongo, *Chem. Pharm. Bull.* (Tokyo), **18**, 941 (1970).
2) Location: *Nankozawa, Odawara, Sendai.*
3) E.A. Prill and S.M. McElvain, "Organic Syntheses," Collected Vol. II, 1943, p. 419.
4) O. Fischer and M. Chur, *J. Prakt. Chem.*, [2] **93**, 363 (1916); A.H. Berrie, G.T. Newhold, and F.S. Spring, *J. Chem. Soc.*, **1951**, 2590.
5) H. Decker, *J. Prakt. Chem.*, **47**, 37 (1893).
6) S. Gabriel and J. Colman, *Ber.*, **33**, 985 (1900).
7) H. Tomisawa, Y. Kobayashi, H. Hongo and R. Fujita, *Chem. Pharm. Bull.* (Tokyo), **18**, 932 (1970).
8) H. Tomisawa, K. Saito, H. Hongo and R. Fujita, *Chem. Pharm. Bull.* (Tokyo), **18**, 937 (1970).
9) A. Nakamura and S. Kamiya, *Chem. Pharm. Bull.* (Tokyo), **16**, 1466 (1968).
10) J.A. Elvidge and L.M. Jackman, *J. Chem. Soc.*, **1961**, 859.

would be assigned to the protons at the 4- and 6- positions. From these spectral data, III would be formulated as 5,5′-methylene-bis[1-methyl-2(1*H*)-pyridone].

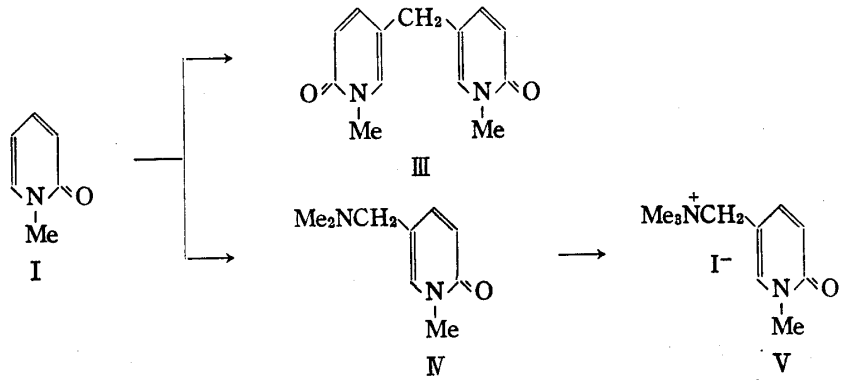

Chart 1

IV was obtained as yellow oil in 11.1% yield. Treatment of IV with methyl iodide in methanol gave fine pale yellow pillars (V), mp 185—187°, $C_9H_{14}ON_2 \cdot CH_3I$, in 55.7% yield. The IR spectrum (Nujol) of V showed absorptions due to amide C=O at 1660 cm^{-1} and adjacent two hydrogens in the pyridone ring at 850 cm^{-1}. The protons on the pyridone ring in the NMR spectrum (in CF_3COOH) of V appeared as the signals at 7.68 ppm (1H, doublet, J=9 cps), 8.41 ppm (1H, broad doublet, J=9 cps), and 8.66 ppm (1H). From these data and above mentioned report,[10] the peak at 7.68 ppm would be the proton at the 3-position and the protons at the 4- and 6- positions would be existed at around 8.5 ppm (2H). Therefore, V would be formulated as 5-dimethylaminomethyl-1-methyl-2(1*H*)-pyridone methiodide and IV as 5-dimethylaminomethyl-1-methyl-2(1*H*)-pyridone.

A mixture of II[11], dimethylamine hydrochloride, paraformaldehyde, conc. hydrochloric acid, and ethanol was gently refluxed for 91 hr. The result of which, colorless plates (VI), mp 302—304°, was obtained by filtration in 34.6% yield and was completely identical with 4,4′-methylene-bis[2-methyl-(12*H*)-isoquinolone][8] by mixed melting point determination and IR spectral comparison. The filtrate was made basic with potassium carbonate and extracted with benzene. Evaporation of extract afforded colorless plates (VII) (15%), mp 114.5—115.5°, $C_{13}H_{16}ON_2$, besides the recovery of II (46%).

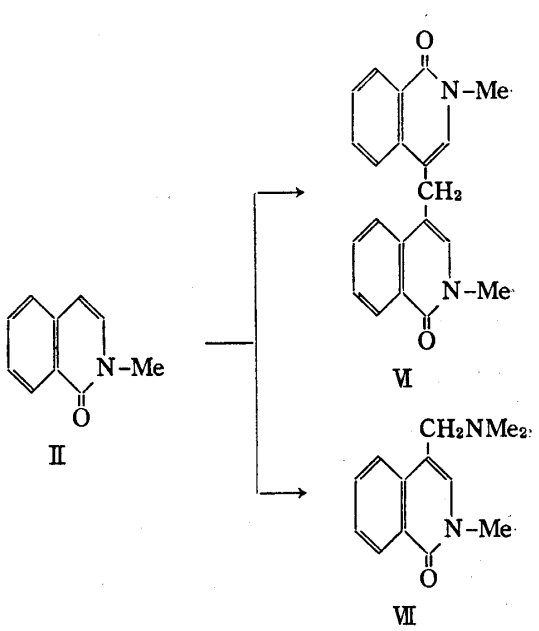

Chart 2

The IR spectrum (Nujol) of VII exhibited the absorption due to amide C=O at 1620 cm^{-1} and that of adjacent four aromatic hydrogens at 765 cm^{-1}, suggesting no substituent in benzene ring. The NMR spectrum (in $CDCl_3$) of VII showed that the signals for a pair of AB doublets (at 6.45 ppm for C_4-H, and at 7.07 ppm for C_3-H) in II disappeared. On the other hand, there appeared a singlet at 6.92 ppm, which would be assigned to the 3-position proton. The NMR spectrum of VII further shows the signals at 7.27—7.95 ppm (C_5, C_6, C_7-H) and 8.35 ppm (C_8-H).

11) Joseph M. Muchowski (Bristol Laboratories of Canada) recently wrote us a private letter. It was described that he also carried out the same reaction, but the only product, formed in low yield, was VI. These will be come out with the Canadian Journal of Chemistry.

From these spectral data, VII would be formulated as 4-dimethylaminomethyl-2-methyl-1(2*H*)-isoquinolone.

When this reaction was carried out using water as the solvent, VI was obtained in quantitative yield.

Making a comparison between these Mannich reactions and the reactions which were reported in a previous paper,[7,8] the substituted positions were the same positions, which were the 5-position of I and the 4-position of II in both reactions. The methylene-bis compound (VI) was given in both reactions of II, but another methylene-bis compound (III) was obtained only in the Mannich reaction of I.

Experimental[12]

The Mannich Reaction of 1-Methyl-2(1*H*)-pyridone with Dimethylamine Hydrochloride——A mixture of 10 g of I, 9.4 g of dimethylamine hydrochloride, and 10 g of 37% formalin was gently refluxed for 48 hr. The cooled reaction mixture was extracted with benzene. The benzene extract was dried over $MgSO_4$ and the solvent was evaporated under a reduced pressure. Chromatography of the residue with $CHCl_3$–MeOH (1: 1) on silica gel afforded two fractions. The first was the recovery of I as a pale yellow oil (6.0 g, 60%). The second was recrystallized from $CHCl_3$ to give 0.9 g of 5,5′-methylene-bis[1-methyl-2(1*H*)-pyridone] (III) as colorless pillars, mp 241—243°. *Anal.* Calcd. for $C_{13}H_{14}O_2N_2 \cdot H_2O$: C, 62.89; H, 6.50; N, 11.28. Found: C, 63.11; H, 6.46; N, 11.55. IR ν_{max}^{Nujol} cm^{-1}: 1650 (amide C=O), 830 (δ C-H). NMR (in CF_3COOH) ppm: 4.02 (6H, singlet, N,N′-Me), 4.10 (2H, singlet, $-CH_2-$), 7.39 (2H, doublet, $J=9$ cps, C_3, C_3'-H), 7.85—8.10 (4H, multiplet, C_4,C_6,C_4',C_6'-H). Mass Spectrum (*m/e*): 230 (M^+).

Mother liquid was made basic with potassium hydroxide and extracted with $CHCl_3$. The $CHCl_3$ extract was dried over $MgSO_4$, the solvent was evaporated, and the residue was submitted to column chromatography over silica gel. Elution with $CHCl_3$–MeOH (2: 3) afforded III [1.6 g; total yield, 2.5 g (21.9%)], and then 5-dimethylaminomethyl-1-methyl-2(1*H*)-pyridone (IV) as a pale yellow oil. Yield, 1.7 g (11.1%).

When the reaction time was reduced to 24 hr and the other conditions were the same, the products obtained were 1.1 g (9.6%) of III, 1.5 g (9.8%) of IV, and 5.8 g (58%) of the recovery of I. When the reaction time was prolonged to 94 hr, the products were 2.9 g (25.4%) of III, 0.8 g (5.2%) of IV, and 5.6 g (56%) of the recovery of I.

5-Dimethylaminomethyl-1-methyl-2(1*H*)-pyridone Methiodide (V)——A mixture of 310 mg of IV and 10 g of CH_3I was gently refluxed for 2 hr, and CH_3I was evaporated. The residue was recrystallized from MeOH–$CHCl_3$ to give 320 mg (55.7%) of V as pale yellow pillars, mp 185—187°. *Anal.* Calcd. for $C_{10}H_{17}ON_2I$: C, 38.97; H, 5.56; N, 9.09. Found: C, 38.80; H, 5.54; N, 8.93. IR ν_{max}^{Nujol} cm^{-1}: 1660 (amide C=O), 850 (δ C-H). NMR (in CF_3COOH) ppm: 3.32 (9H, singlet, $-N^+Me_3$), 4.11 (3H, singlet, N-Me), 4.80 (2H, singlet, $-CH_2-$), 7.68 (1H, doublet, $J=9$ cps, C_3-H), 8.41 (1H, broad doublet, $J=9$ cps, C_4-H), 8.66 (1H, broad singlet, C_6-H).

The Mannich Reaction of 2-Methyl-1(2H)-isoquinolone with Dimethylamine Hydrochloride——A solution of 5 g of II, 7.7 g of dimethylamine hydrochloride, 1.9 g of paraformaldehyde, and 0.1 ml of conc. HCl in 20 ml of EtOH was refluxed for 91 hr and allowed to stand overnight at room temperature. The precipitates formed were collected by filtration and recrystallized from EtOH to give colorless plates 4,4′-methylene-bis[2-methyl-1(2*H*)-isoquinolone] (VI), mp 302—304°. Yield, 1.8 g (34.6%). Mass Spectrum (*m/e*): 330 (M^+). The filtrate was evaporated under a reduced pressure and the residue was poured into water and extracted with benzene. The solvent was evaporated from the extract from which 2.3 g (46%) of II was recovered.

Mother liquid was made basic with potassium carbonate and extracted with benzene. The benzene extract was dried over $MgSO_4$, the solvent was evaporated, and the residue was recrystallized from hexane to afford 0.95 g (15%) of 4-dimethylaminomethyl-2-methyl-1(2*H*)-isoquinolone (VII) as colorless plates, mp 114.5—115.5°. *Anal.* Calcd. for $C_{13}H_{16}ON_2$: C, 72.19; H, 7.46; N, 12.95. Found: C, 72.39; H, 7.66; N, 12.94. IR ν_{max}^{Nujol} cm^{-1}: 1620 (amide C=O), 765 (δ C-H). NMR (in $CDCl_3$) ppm: 2.25 (6H, singlet, $-NMe_2$), 3.37 (2H, singlet, $-CH_2-$), 3.55 (3H, singlet, N-Me), 6.92 (1H, singlet, C_3-H), 7.27—7.95 (3H, multiplet, C_5,C_6,C_7-H), 8.35 (1H, multiplet, C_8-H).

The other reaction conditions: a) A solution of 5 g of II, 3 g of $(Me)_2NH \cdot HCl$, 1 g of paraformaldehyde, and 0.1 ml of conc. HCl in 14 ml of EtOH was refluxed for 24 hr. The products were 1 g (19.2%) of VI, 0.6 g (8.8%) of VII, and 3.4 g (68%) of the recovery of II.

12) All melting points are uncorrected.

b) A mixture of 5 g of II, 7.7 g of $(Me)_2NH \cdot HCl$, 1.9 g of paraformaldehyde, 0.1 ml of conc. HCl, and 26 ml of H_2O was refluxed for 14 hr. The products were 5.1 g (98.1%) of VI and 2.7 mg of VII.

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Synthèse de δ-Lactones. II.[1] Preparation d'Aryl-6 δ-Lactones par Application de la Reaction de Friedel et Crafts[2]

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Dans un précédent mémoire,[1] nous avons envisagé une méthode de préparation, à partir de la dihydrorésorcine, des alcoyl-6, alcényl-6 et aralcoyl-6 δ-lactones, composés utiles comme matière des parfums. Nous décrivons dans ce mémoire la synthèse d'aryl-6 δ-lactones qui sont également intéressants dans le domaine de la parfumerie. Le but que nous aovns poursuivi dans ce travail était de découvrir une méthode avantageuse pour l'obtention des aryl-6 δ-lactones. Pour cela, nous avons particulièrement étudié, par application de la réaction de Friedel et Crafts sur des homologues benzéniques, la préparation d'acides γ-aroylbutyriques qui peuvent conduire facilement aux δ-lactones attendus en passant par des acides δ-hydroxylés.

C'est ainsi qu'en faisant agir, à température ne dépassant pas 0°, le chlorure de γ-carbéthoxybutyroyle sur le benzène ou sur ses dérivés alcoylés ou alcoxylés dans le tétrachlorure d'acétylène en présence de chlorure d'alminium comme agent de condensation (dans le cas de l'action sur le benzène, on peut utiliser un excès de benzène sans solvant), nous avons obtenu des γ-aroylbutyrates d'éthyles (I) que l'on peut ensuite hydrolyser, par traitement dans une solution alcoolique de potasse, en acides γ-aroylbutyriques (II) correspondants. Nous avons réalisé la condensation du chlorure de γ-carbéthoxybutyroyle sur le thiophène, en employant le benzène comme solvant et en présence de chlorure stannique, pour former le γ-thiénoylbutyrate d'éthyle qui s'hydrolyse également en acides γ-thiénoylbutyrique. Le Tableau I montre dix acides du type II ainsi formés.

Cette méthode d'obtention des acides II donne meilleur rendement que celle qui consiste à faire agir directement l'anhydride glutarique sur le noyau aromatique, méthode habituelle pour la formation des acides δ-cétoniques du type II.[4] Cela pourrait s'expliquer par le fait que, dans notre méthode, la réaction de Friedel et Crafts pour former les esters I peut s'effectuer aisément à basse température, grâce à l'utilisation du chlorure de γ-carbéthoxy-

1) Mémoire I: A. Ijima, H. Mizuno et K. Takahashi, *Chem. Pharm. Bull.* (Tokyo), **19**, 1053 (1971).
2) Ce travail a été présenté à la 91e réunion annuelle de la Société pharmaceutique du Japon, à Fukuoka, le 7 avril 1971.
3) Adresse: *Yado-cho, Tanashi-shi, Tokyo.*
4) *a*) A. Ali, R.D. Desai, R.F. Hunter et S.M.M. Muhammad, *J. Chem. Soc.*, **1937**, 1013; *b*) F.D. Carter, J.L. Simosen et H.O. Williams, *J. Chem. Soc.*, **1940**, 451; *c*) L.F. Fieser et ses coll., *J. Am. Chem. Soc.*, **70**, 3197 (1948); *d*) S.G.P. Plant et M.E. Tombinson, *J. Chem. Soc.*, **1935**, 856; *e*) P. Cagniant et A. Deluzarche, *Compt. Rend.*, **222**, 1301 (1946).