used are s=singlet and d=doublet. Mass, IR, and UV spectra were taken on Hitachi RMU-6, Hitachi EPI-S2, and Hitachi ESP-2U spectrometers, respectively. TLC was performed on silica gel (Kiesel gel GF_{254}, Merck). Column chromatography was run on silica gel (100 mesh), Mallinckrodt).

Isolation of Kakkatin (I)——The dried powdered Chinese *Pueraria* flowers (500 g) purchased on Hong Kong market were extracted with 70% MeOH (5 liters). After removal of MeOH under reduced pressure, aqueous concentrate was obtained, To the aqueous concentrate was added ether with stirring, A crude isoflavone mixture (1 g) was deposited at the H_2O–ether interface and collected by filtration. The mixture was submitted to column chromatography on silica gel, using $CHCl_3$–MeOH (17: 3) as an eluent. The residue from the first eluate was recrystallized from MeOH several times to give colorless needles (I) (300 mg), mp over 290°. *Anal.* Calcd. for $C_{16}H_{12}O_5$: C, 67.60; H, 4.26. Found: C, 67.41; H, 4.20.

Acetylation of I——A mixture of I (20 mg), acetic anhydride (0.5 ml) and pyridine (0.5 ml) was allowed to stand over night at room temperature. After the usual work-up, recrystallization from acetone gave colorless needles (II) (20 mg), mp 235—238°. *Anal.* Calcd. for $C_{20}H_{16}O_7$: C, 65.21; H, 4.38. Found: C, 64.90; H, 4.25. UV λ_{max}^{EtOH} nm (log ε): 254 (4.54), 325 (3.93). IR ν_{max}^{KBr} cm^{-1}: 1760, 1610, 1570, 1480. NMR δ (in $CDCl_3$): 2.32 (s, 3H), 2.46 (s, 3H), 3.94 (s, 3H), 7.16 (d, J=8.5 Hz, 2H), 7.24 (s, 1H), 7.58 (d, J=8.5 Hz, 2H), 7.74 (s, 1H), 7.97 (s, 1H). Mass Spectrum *m/e*: 368 (M^+).

Methylation of I——A mixture of I (30 mg), dimethyl sulfate (2.0 ml), K_2CO_3 (3.0 g) and dry acetone (30 ml) was refluxed for 5 hr. The inorganic salts were removed by filtration, and the filtrate was evaporated to give a residue which was heated with aqueous NaOH for 10 min. Resulting precipitates were collected and recrystallized from 95% EtOH to give the white crystalls (III) (15 mg), mp 178—180°. UV λ_{max}^{EtOH} nm (log ε): 263 (4.48), 320 (4.03). IR ν_{max}^{KBr} cm^{-1}: 1620, 1590, 1500, 1450, 1430.

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A New Method for the Preparation of 2-Hydroxymethyl-3-quinolinecarboxylic Acid Lactone Derivatives

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The reaction of 2-acetoxymethyl-3-acetylquinolines (V, VI) with sodium hydride gave 2-hydroxymethyl-3-quinolinecarboxylic acid lactones (IX, X), presumably formed with the migration of acetyl group. On the other hand, the fact that the reaction of 3-acetyl-2-benzoyloxymethylquinoline (VIII) with sodium hydride gave a lactone (IX) and acetophenone would strongly support for the mechanism of the lactone formation with the acyl migration.

Recently[2] we reported the convenient synthesis of 3-acetylquinaldine 1-oxide derivatives (III, IV) by the reductive cyclization of *o*-nitrobenzylideneacetylacetones (I, II).

In 1958 Fehnel[3] had reported, as studies of quinoline analogs of podophyllotoxin, for the preparation of 2-hydroxymethyl-3-quinolinecarboxylic acid lactone (IX) by a Friedländer condensation of *o*-aminobenzaldehyde with tetronic acid. In the present paper, we wish

1) Location: *2-10-65, Kawai, Matsubara, Osaka, 580, Japan.*
2) T. Kurihara, H. Sano, and H. Hirano, *Chem. Pharm. Bull.* (Tokyo), **23**, 1155 (1975).
3) E.A. Fehnel, *J. Org. Chem.*, **23**, 432 (1958); E.A. Fehnel, J.A. Deyrup, and M.B. Davidson, *ibid.*, **23**, 1996 (1958).

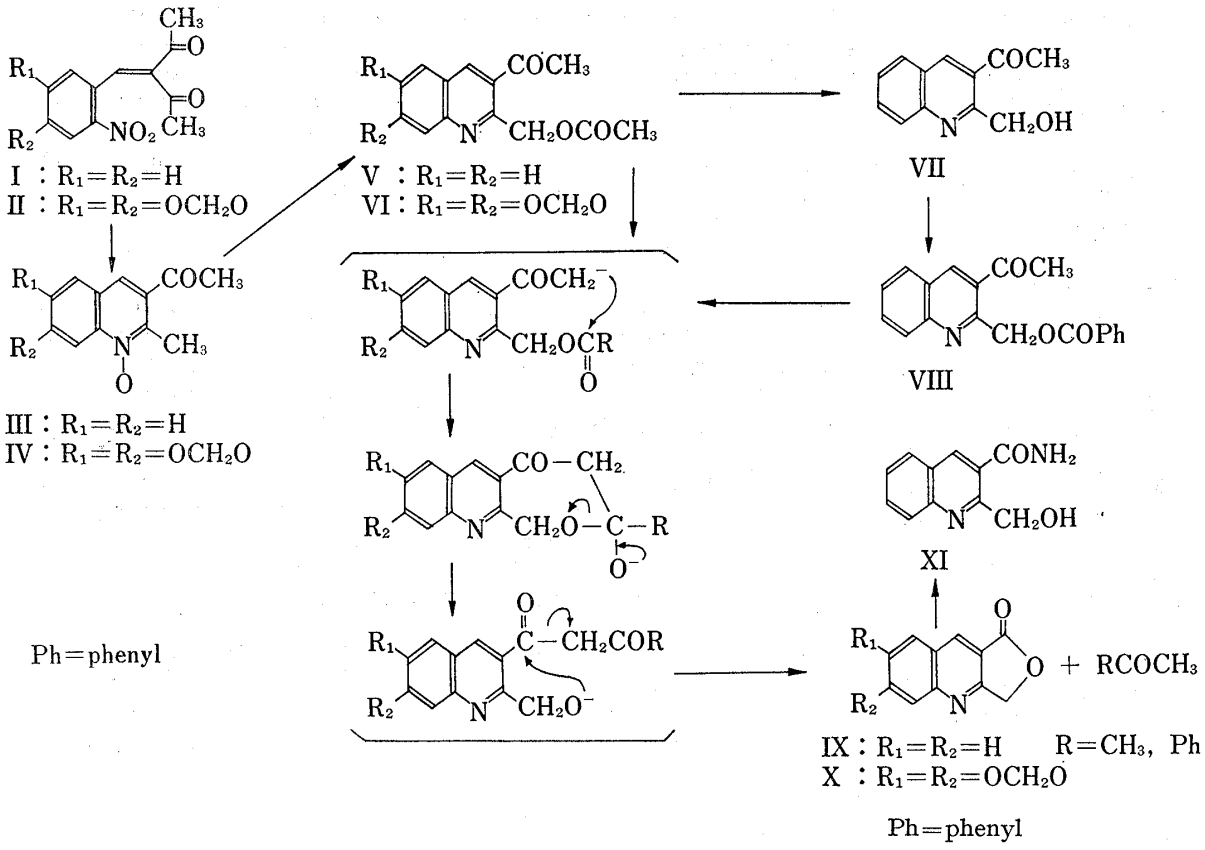

Chart 1

to report a new method for the preparation of lactones (IX, X) starting from the N-oxides (III, IV).

Refluxing of 3-acetylquinaldine 1-oxide (III) with excess acetic anhydride[4] afforded 2-acetoxymethyl-3-acetylquinoline (V) in 65% yield. Heating of this acetate (V) with sodium hydride in anhydrous benzene for 1 hour gave a product (IX), mp 221—222°, in 68% yield having an empirical formura of $C_{11}H_7O_2N$. The infrared (IR) spectrum of this product showed the absorption attributed to a five membered lactone at 1770 cm^{-1}. It was proved finally identical with an authentic 2-hydroxymethyl-3-quinolinecarboxylic acid lactone prepared according to the method of Fehnel. Similarly reaction of 3-acetyl-6,7-methylenedioxyquinaldine 1-oxide (IV) with acetic anhydride gave 2-acetoxymethyl-3-acetyl-6,7-methylenedioxyquinoline (VI), which was subsequently treated with sodium hydride in anhydrous benzene to give 2-hydroxymethyl-6,7-methylenedioxy-3-quinolinecarboxylic acid lactone (X), mp 290—294°, in a yield of 72%. These reaction course can be reasonably rationalized by the initial formation of seven membered-ring intermediate followed by the migration of acetyl group and by the attack of the anion at carbonyl carbon to make lactones (IX, X) and acetone, which could not be isolated.

On the other hand, reaction of 3-acetyl-2-benzoyloxymethylquinoline (VIII), prepared by benzoylation of 3-acetyl-2-hydroxymethylquinoline (VII), with sodium hydride in anhydrous benzene gave a lactone (IX) and acetophenone, which were identical with the anthentic samples by comparison of their retention times of gas chromatography (GLC), respectively. This result would strongly support for the mechanism of the lactone formation with acyl migration.

4) S. Ginsburg and I.B. Wilson, *J. Am. Chem. Soc.*, **79**, 481 (1957).

Experimental

All melting points are uncorrected. IR and ultraviolet (UV) spectra were recorded on a JASCO Model IRA-1 and Shimadzu UV-200 spectrophotometers. Nuclear magnetic resonance (NMR) spectra were measured with a Varian A-60D spectrometer using tetramethylsilane as internal reference. Mass spectrum was taken with Hitachi Mass Spectrometer RMU-7L. Gas chromatographies were measured on a Shimadzu 4-BMPF gas chromatograph, employing SE-30.

2-Acetoxymethyl-3-acetylquinoline (V)——A mixture of III (10 g) in acetic anhydride (35 ml) was refluxed for 1 hr. Removal of the excess acetic anhydride *in vacuo* gave a black solid. After decomposition of the remaining trace of acetic anhydride with saturated $NaHCO_3$, the mixture was extracted with $CHCl_3$. The $CHCl_3$ extract was washed with water, dried over anhyd. Na_2SO_4, and evaporated. The residual solid was combined with sand and extracted with *n*-hexane in a Soxhlet apparatus for 2 days. After cooling precipitated crystals were collected to give 7.9 g (62%) of V. Recrystallization from ligroin gave an analytical sample as pale yellow needles, mp 113—114°. IR ν_{max}^{KBr} cm^{-1}: 1740 (ester), 1680 (CO). NMR ($CDCl_3$) δ: 2.22 (3H, s, $OCOC\underline{H}_3$), 2.72 (3H, s, $COC\underline{H}_3$), 5.67 (2H, s, $C\underline{H}_2O$), 8.55 (1H, s, C_4–H). *Anal.* Calcd. for $C_{14}H_{13}O_3N$: C, 69.12; H, 5.39; N, 5.76. Found: C, 69.05; H, 5.54; N, 5.81.

2-Acetoxymethyl-3-acetyl-6,7-methylenedioxyquinoline (VI)——A mixture of IV (2 g) in acetic anhydride (7 ml) was treated in the same manner as described for the synthesis of V to give 1.9 g (81%) of VI. Recrystallization from benzene gave an analytical sample as pale yellow needles, mp 176—177°. IR ν_{max}^{KBr} cm^{-1}: 1738 (ester), 1660 (CO). NMR ($CDCl_3$) δ: 2.20 (3H, s, $OCOC\underline{H}_3$), 2.68 (3H, s, $COC\underline{H}_3$), 5.60 (2H, s, $C\underline{H}_2O$), 6.15 (2H, s, OCH_2O), 8.37 (1H, s, C_4–H). *Anal.* Calcd. for $C_{15}H_{13}O_5N$: C, 62.71; H, 4.56; N, 4.88. Found: C, 62.86; H, 4.82; N, 4.72.

2-Hydroxymethyl-3-quinolinecarboxylic Acid Lactone (IX)——To a stirred suspension of 50% NaH (1.0 g) in anhyd. benzene (10 ml) was added a solution of V (3.0 g) in anhyd. benzene (10 ml) dropwise at room temperature under N_2 atomosphere. After refluxing for 0.5 hr, the mixture was cooled and poured into ice-water. The mixture was neutralized with dil. AcOH and extracted with $CHCl_3$. The $CHCl_3$ extract was washed with water, dried over anhyd. Na_2SO_4, and evaporated to give a pasty solid. Recrystallization from MeOH gave 1.55 g (68%) of IX as pale yellow plates, mp 221—222°, lit.[3] mp 217—219°. IR ν_{max}^{KBr} cm^{-1}: 1770 (lactone). UV λ_{max}^{EtOH} mμ (log ε): 243 (4.75), 297 (3.72). NMR ($CDCl_3$) δ: 5.50 (2H, s, $C\underline{H}_2O$), 8.80 (1H, s, C_4–H). Mass Spectrum *m/e*: 185 (M^+). *Anal.* Calcd. for $C_{11}H_7O_2N$: C, 71.35; H, 3.81; N, 7.56. Found: C, 71.12; H, 3.83; N, 7.50. Upon treatment of IX with ammonia in EtOH at room temperature was 2-hydroxymethyl-3-quinolinecarboxyamide (XI) obtained as colorless leaflets, mp 181—182°, which was recrystallized from MeOH. *Anal.* Calcd. for $C_{11}H_{10}O_2N_2$: C, 65.33; H, 4.98; N, 13.86. Found: C, 65.10; H, 4.98; N, 13.86.

2-Hydroxymethyl-6,7-methylenedioxy-3-quinolinecarboxylic Acid Lactone (X)——A mixture of VI (1.9 g) and 50% NaH (1.2 g) in anhyd. benzene (20 ml) was treated in the same manner as described for the synthesis of IX to give 1.03 g (72%) of X. Recrystallization from EtOH–benzene gave an analytical sample as pale yellow needles, mp 290—294°. IR ν_{max}^{KBr} cm^{-1}: 1767 (lactone). UV λ_{max}^{EtOH} mμ (log ε): 250 (4.78), 301 (3.85). NMR (d_6-DMSO) δ: 5.48 (2H, s, $C\underline{H}_2O$), 6.31 (2H, s, $OC\underline{H}_2O$), 8.73 (1H, s, C_4–H). *Anal.* Calcd. for $C_{12}H_7O_4N$: C, 62.89; H, 3.08; N, 6.11. Found: C, 62.83; H, 3.29; N, 5.89.

3-Acetyl-2-hydroxymethylquinoline (VII)——To a solution of V (2 g) in EtOH (20 ml) was added a solution of KOH (0.5 g) dissolved in water (2 ml) and the reaction mixture was heated at 40° for 2 hr. After evaporation of the solvent *in vacuo*, the resulting residue was diluted with water. The mixture was extracted with $CHCl_3$. The $CHCl_3$ extract was washed with water, dried over anhyd. Na_2SO_4, and evaporated. The residue was recrystallized from AcOEt to give an analytical sample as colorless needles, mp 104—105°. IR ν_{max}^{KBr} cm^{-1}: 3380 (OH), 1680 (CO). *Anal.* Calcd. for $C_{12}H_{11}O_2N$: C, 71.62; H, 5.51; N, 6.96; Found: C, 71.97; H, 5.68; N, 6.64.

3-Acetyl-2-benzoyloxymethylquinoline (VIII)——To a stirred solution of VII (2 g) in pyridine (10 ml) was added benzoyl chloride (1.5 g) under ice cooling. The reaction mixture was heated at 60° for 10 hr and poured into ice-water. After extraction with $CHCl_3$, the $CHCl_3$ extract was washed with water several times, dried over anhyd. Na_2SO_4, and evaporated to give a crystalline residue. Recrystallization from MeOH gave an analytical sample (1.8 g) as colorless needles, mp 122—123°. IR ν_{max}^{KBr} cm^{-1}: 1720 (ester), 1680 (CO). NMR ($CDCl_3$) δ: 2.71 (3H, s, $COC\underline{H}_3$), 5.91 (2H, s, $C\underline{H}_2O$), 8.58 (1H, s, C_4–H). *Anal.* Calcd. for $C_{19}H_{15}O_3N$: C, 74.74; H, 4.95; N, 4.59. Found: C, 74.46; H, 4.79; N, 4.26.

Reaction of VIII with Sodium Hydride——A mixture of VIII (0.1 g) and 50% NaH (0.085 g) in anhyd. benzene (5 ml) was treated in the same manner as described for the synthesis of IX. The isolated mixture showed two peaks of lactone (IX) and acetophenone on GLC, each identical with those of the authentic samples, respectively.

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