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Novel Synthesis of Quinoline Derivatives with Triethyl Phosphite[1]

Tetsuji Kametani, Kiyosato Nyu, Tohru Yamanaka,
Haruhiko Yagi, and Kunio Ogasawara

Pharmaceutical Institute, Tohoku University[2]

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Treatment of ethyl 4,5-dimethoxy-2-nitrobenzylidenemalonate (III), ethyl 4-benzyloxy-5-methoxy-2-nitrobenzylidenemalonate (IV), and ethyl 4,5-methylenedioxy-2-nitrobenzylidenemalonate (V) with triethyl phosphite at 160—170° for 20 hr afforded 2-ethoxy-3-ethoxycarbonyl-6,7-dimethoxyquinoline (VI), 7-benzyloxy-2-ethoxy-3-ethoxycarbonyl-6-methoxyquinoline (VII), and 2-ethoxy-3-ethoxycarbonyl-6,7-methylenedioxyquinoline (VIII), respectively, in 53—68% yield. On the other hand, the 6-benzyloxy-2-ethoxycarbonyl-5-methoxyindole (XIII) was obtained with the same treatment of ethyl 4-benzyloxy-3-methoxy-2-nitrocinnamate (XII).

The reaction of aromatic nitro compounds with triethyl phosphite has hitherto been investigated by many researchers.[3–16] Among them, Sundberg, *et al.*[7] reported that deoxygenation of 2-nitrostyrene derivatives by triethyl phosphite gave the indole derivatives. Meanwhile, we have reported that the compound (I), whose carbonyl and 2-nitrophenyl groups were oriented in relation to *cis* conformation each other, was reacted with triethyl phosphite to give the quinoline derivative (II) in an excellent yield.[9] We now report that the novel synthesis of the quinoline derivatives by the reaction of triethyl phosphite with the 2-nitrobenzylidenemalonates (III), (IV), and (V), whose 2-nitrophenyl groups are oriented against one of two carbonyl groups in *cis* conformation.

Treatment of ethyl 4,5-dimethoxy-2-nitrobenzylidenemalonate (III), ethyl 4-benzyloxy-5-methoxy-2-nitrobenzylidenemalonate (IV), and ethyl 4,5-methylenedioxy-2-nitrobenzylidenemalonate (V) with five equivalent moles of triethyl phosphite at 160—170° for 20 hr in a current of nitrogen afforded the quinoline derivatives (VI), (VII), and (VIII), respectively. The structure of the above cyclization products were supported by their infrared (IR) spectra which showed the absorptions due to ester carbonyl group at 1710—1720 cm^{-1} and C=N double bond at 1605—1627 cm^{-1}. The nuclear magnetic resonance (NMR) spectra of the above products showed the one-proton singlet at 8.26—8.47 ppm which was assigned to the typical aromatic proton at the C_4-position of quinoline skeleton, highly deshielded by the aromatization and the anisotropy of the neighbouring benzene ring.

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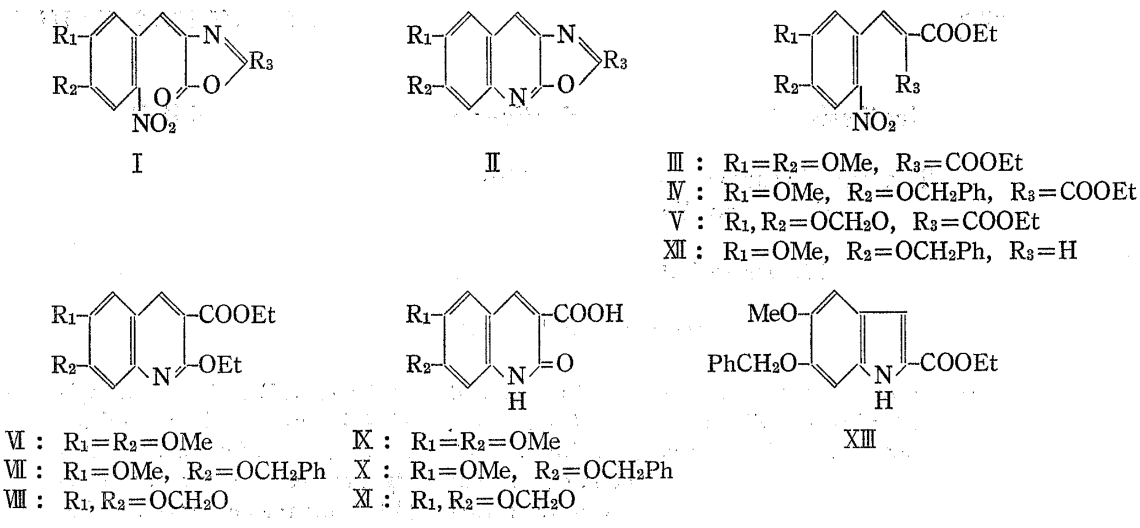

I

II

III : $R_1=R_2=OMe$, $R_3=COOEt$
IV : $R_1=OMe$, $R_2=OCH_2Ph$, $R_3=COOEt$
V : $R_1, R_2=OCH_2O$, $R_3=COOEt$
XII : $R_1=OMe$, $R_2=OCH_2Ph$, $R_3=H$

VI : $R_1=R_2=OMe$
VII : $R_1=OMe$, $R_2=OCH_2Ph$
VIII : $R_1, R_2=OCH_2O$

IX : $R_1=R_2=OMe$
X : $R_1=OMe$, $R_2=OCH_2Ph$
XI : $R_1, R_2=OCH_2O$

XIII

Chart 1

Further, hydrolysis of the above compounds (VI), (VII), and (VIII) with hydrochloric acid gave the corresponding quinolone derivatives, (IX), (X), and (XI), thus unambiguously confirming the structures of cyclization products.

On the other hand, ethyl 4-benzyloxy-3-methoxy-2-nitrocinnamate (XII) was synthesised by the standard method and its carbonyl and nitro groups were confirmed to be oriented in the *trans* conformation which was revealed by the large coupling constant ($J=16$ cps) of two olefinic protons in its NMR spectrum. The same treatment of XII with triethyl phosphite gave the expected indole derivative, namely 6-benzyloxy-2-ethoxycarbonyl-5-methoxyindole (XIII), in 56% yield. The structure of the above product (XIII) was supported by its IR spectrum which showed N–H stretching and ester carbonyl absorption at 3400 and 1688 cm^{-1}, respectively. The NMR spectrum showed the typical aromatic proton of the C_3-position of the indole skeleton at 6.82 ppm.

These facts are in accord with that of Sundberg's results. Namely, when both 2-nitrophenyl and carbonyl groups were in relation to *trans* conformation, the formation of the indoles has been proved, whereas the compounds with reverse conformation such as III, IV, and V afforded our expected quinoline derivatives. Thus this reaction provides the novel synthesis of the quinoline derivatives having various substituents.

Experimental

Melting points were uncorrected. The infrared (IR) spectra were taken with a Hitachi EPI-S_2 spectrophotometer, and the nuclear magnetic resonance (NMR) spectra were run on a Hitachi H-60 spectrometer using tetramethylsilane as an internal reference.

Diethyl 4,5-Dimethoxy-2-nitrobenzylidenemalonate (III)——A mixture of 10 g of 2-nitroveratraldehyde, 20 g of diethyl malonate, 100 ml of dry pyridine, and 10 drops of piperidine was refluxed for 2 hr in a dark place. After cooling, the reaction mixture was poured into 1 liter of cold water with vigorous stirring and the resulting crystals were collected, washed with dil. HCl and dried. Recrystallization from EtOH gave 6.9 g. (41%) of needles, mp 123—125°. *Anal.* Calcd. for $C_{16}H_{19}O_8N$: C, 54.39; H, 5.42; N, 3.96. Found: C, 54.49; H, 5.69; N, 4.32. IR ν_{max} cm^{-1} ($CHCl_3$): 1725 (C=O) and 1575 (>C=C<). NMR δ ($CDCl_3$): 1.10, 1.36 (each 3H, two triplets, $J=7$ cps, $2\times CH_2C\underline{H}_3$), 3.97 (each 3H, two singlets, $2\times OC\underline{H}_3$), 4.10, 4.32 (each 2H ,two quartets, $J=7$ cps, $2\times C\underline{H}_2CH_3$), 6.92 (1H, singlet, C_6–$\underline{H}$), 7.85 (1H, singlet, C_3–$\underline{H}$), 8.19 (1H, singlet, olefinic proton).

Diethyl 4-Benzyloxy-5-methoxy-2-nitrobenzylidenemalonate (IV)——A mixture of 5 g of 2-nitrobenzylvanillin, 10 g of diethyl malonate, 50 ml of pyridine, and 5 drops of piperidine was refluxed for 2 hr in a dark place. After cooling, the reaction mixture was poured into 500 ml of ice–water with vigorous stirring, and the resulting crystals were collected by filtration, washed successively with dil. HCl and water, and dried. Recrystallization from EtOH gave 5.0 g (63%) of yellowish needles, mp 112—114°. *Anal.* Calcd. for $C_{22}H_{23}O_8N$: C, 61.53; H, 5.40; N, 3.26. Found: C, 62.08; H, 5.31; N, 3.30. IR ν_{max} cm^{-1} ($CHCl_3$): 1725 (C=O) and 1575 ($\rangle C{=}C\langle$). NMR δ ($CDCl_3$): 1.08, 1.33 (each 3H, two triplets, $J=7$ cps, $2\times CH_2C\underline{H}_3$), 4.08, 4.20 (each 2H, two quartets, $J=7$ cps, $2\times C\underline{H}_2CH_3$), 5.18 (2H, singlet, $OC\underline{H}_2Ph$), 6.88 (1H, singlet, C_6–$\underline{H}$), 7.38 (5H, singlet, $OCH_2C_6\underline{H}_5$), 7.78 (1H, singlet, C_3–$\underline{H}$), 8.14 (1H, singlet, olefinic proton).

Diethyl 4,5-Methylenedioxy-2-nitrobenzylidenemalonate (V)——A mixture of 4 g of 2-nitropiperonal, 3.2 g of diethyl malonate, 3 g of $KHCO_3$ and 7.2 ml of Ac_2O was heated at 100° for 2 hr. After cooling, the reaction mixture was poured into 300 ml of cold water and the precipitated oil was extracted with ether. The extract was washed with sat. Na_2CO_3 solution and water, dried over Na_2SO_4 and evaporated to give yellowish crystals. Recrystallization from EtOH–H_2O gave 4.4 g (60%) of yellowish needles, mp 63—65°. *Anal.* Calcd. for $C_{15}H_{15}O_8N$: C, 53.41; H, 4.48; N, 4.15. Found: C, 53.71; H, 4.63; N, 4.47. IR ν_{max} cm^{-1} ($CHCl_3$): 1720 (C=O) and 1610 ($\rangle C{=}C\langle$). NMR δ ($CDCl_3$) 1.20, 1.30 (each 3H, two triplets, $J=7$ cps, $2\times CH_2C\underline{H}_3$) 4.15, 4.32 (each 2H, two quartets, $J=7$ cps, $2\times C\underline{H}_2CH_3$), 6.16 (2H, singlet, –$OC\underline{H}_2O$), 6.81 (1H, singlet, C_6–$\underline{H}$), 7.15 (1H, singlet, C_3–$\underline{H}$), 8.09 (1H, singlet, olefinic proton).

2-Ethoxy-3-ethoxycarbonyl-6,7-dimethoxyquinoline (VI)——A mixture of 3 g of ethyl nitrobenzylidenemalonate (III) and 8.3 g of triethyl phosphite was refluxed at 150—160° for 20 hr in a current of nitrogen. The excess reagent was removed by distillation under reduced pressure and the resultant syrup was triturated with a small amount of EtOH to give yellowish crystals, whose recrystallization from EtOH gave 1.8 g (61%) of colorless needles, mp 92—94°. *Anal.* Calcd. for $C_{16}H_{19}O_5N$: C, 62.94; H, 6.27; N, 4.59. Found: C, 63.43; H, 6.61; N, 4.94. IR ν_{max} cm^{-1} ($CHCl_3$): 1718 (C=O) and 1627 ($\rangle N{=}C\langle$). NMR δ($CDCl_3$): 1.40, 1.47 (each 3H, two triplets, $J=7$ cps, $2\times CH_2C\underline{H}_3$), 3.96, 4.01 (each 3H, two singlets, $2\times OC\underline{H}_3$), 4.38, 4.55 (each 2H, two quartets, $J=7$ cps, $2\times C\underline{H}_2CH_3$), 7.00 (1H, singlet, C_5–H or C_8–H), 7.14 (1H, singlet, C_5–$\underline{H}$ or C_8–$\underline{H}$), 8.45 (1H, singlet, C_4–$\underline{H}$).

7-Benzyloxy-2-ethoxy-3-ethoxycarbonyl-6-methoxyquinoline (VII)——A mixture of 1.8 g of ethyl nitrobenzylidenemalonate (IV) and 5 g of triethyl phosphite was refluxed at 150—160° for 20 hr in a current of nitrogen. The excess reagent was removed by distillation under reduced pressure and the resultant syrup was triturated with a small amount of EtOH to give yellow crystals. Recrystallization from EtOH–H_2O gave 1.2 g (68%) of pale yellowish needles, mp 95—98°. *Anal.* Calcd. for $C_{22}H_{23}O_5N$: C, 69.27; H, 6.08; N, 3.67. Found: C, 69.75; H, 5.80; N, 3.77. IR ν_{max} cm^{-1} ($CHCl_3$): 1711 (C=O) and 1620 ($\rangle C{=}N\langle$). NMR δ ($CDCl_3$): 1.41, 1.47 (each 3H, two triplets, $J=7$ cps, $2\times CH_2C\underline{H}_3$), 3.96 (3H, singlet, $OC\underline{H}_3$), 4.38, 4.54 (each 2H, two quartets, $J=7$ cps, $2\times C\underline{H}_2CH_3$), 5.28 (2H, singlet, $OC\underline{H}_2Ph$), 7.04 (1H, singlet, C_5–$\underline{H}$ or C_8–$\underline{H}$), 7.18—7.56 (6H, multiplet, C_6H_5 and C_8–$\underline{H}$ or C_5–$\underline{H}$), 8.47 (1H, singlet, C_4–$\underline{H}$).

2-Ethoxy-3-ethoxycarbonyl-6,7-methylenedioxyquinoline (VIII)——A mixture of 1.8 g of ethyl nitrobenzylidenemalonate (V) and 9.4 g of triethyl phosphite was refluxed at 160—170° for 20 hr in a current of nitrogen. The excess reagent was removed by distillation under reduced pressure and the resultant syrup was triturated with a small amount of EtOH to give pale brownish crystals, whose recrystallization from EtOH gave 0.8 g (53%) of pale brownish needles, mp 129—130°. *Anal.* Calcd. for $C_{15}H_{15}O_5N$: C, 62.28; H, 5.23; N, 4.84. Found: C, 62.01; H, 5.17; N, 4.88. IR ν_{max} cm^{-1} ($CHCl_3$): 1713 (C=O) and 1605 (–$N{=}C\langle$). NMR δ (CCl_4) 1.40, 1.46 (each 3H, two triplets, $J=7$ cps, $2\times C\underline{H}_2CH_3$), 4.35, 4.46 (each 2H, two quartets, $J=7$ cps, $2\times C\underline{H}_2CH_3$), 6.02 (2H, singlet, $OC\underline{H}_2O$), 6.88 (1H, singlet, C_5–$\underline{H}$ or C_8–$\underline{H}$), 6.99 (1H, singlet, C_8–$\underline{H}$ or C_5–$\underline{H}$), 8.26 (1H, singlet, C_4–$\underline{H}$).

1,2-Dihydro-6,7-dimethoxy-2-oxo-3-quinolinecarboxylic Acid (IX)——A mixture of 0.2 g of VI, 5 ml of EtOH, and 5 ml of conc. HCl solution was refluxed for 30 min. After cooling, the precipitated crystals were collected and recrystallized from dimethylformamide–EtOH to give 0.18 g of yellowish needles, mp>270°. *Anal.* Calcd. for $C_{12}H_{11}O_5N$: C, 57.83; H, 4.45; N, 5.62. Found: C, 57.99; H, 4.26; N, 5.28. IR ν_{max} cm^{-1} (KBr): 2900—3100 (carboxyl OH), 1710 (C=O), and 1650 (lactam C=O). NMR δ (CF_3CO_2H): 4.13, 4.19 (each 3H, two singlets, $2\times OC\underline{H}_3$), 7.39 (1H, singlet C_5–$\underline{H}$ or C_8–$\underline{H}$), 7.39 (1H, singlet, C_8–$\underline{H}$ or C_5–$\underline{H}$), 9.32 (1H, singlet, C_4–$\underline{H}$).

7-Benzyloxy-1,2-dihydro-6-methoxy-2-oxo-3-quinolinecarboxylic Acid (X)——A mixture of 0.2 g of VII, 2.5 ml of EtOH, and 2.5 ml of conc. HCl solution was refluxed for 30 min. After cooling, the precipitated crystals were collected and recrystallized from dimethylformamide–EtOH to give 0.1 g of yellowish brown needles, mp>280°. *Anal.* Calcd. for $C_{18}H_{15}O_5N$: N, 4.31. Found: N, 4.66. IR ν_{max} cm^{-1} (KBr): 3150—2800 (carboxyl OH), 1725 (C=O), and 1655 (lactam C=O). NMR δ (CF_3CO_2H): 4.10 (3H, singlet, $OC\underline{H}_3$), 5.40 (2H, singlet, $OC\underline{H}_2C_6H_5$), 7.25 (1H, singlet, C_5–$\underline{H}$ or C_8–$\underline{H}$), 7.40 (1H, singlet, C_8–$\underline{H}$ or C_5–$\underline{H}$), 7.45 (5H, singlet, $OCH_2C_6\underline{H}_5$), 9.25 (1H, singlet, C_4–$\underline{H}$).

1,2-Dihydro-6,7-methylenedioxy-2-oxo-3-quinolinecarboxylic Acid (XI)——A mixture of 0.3 g of VIII, 2.5 ml of EtOH, and 2.5 ml of conc. HCl solution was refluxed for 30 min. After cooling, the precipitated crystals were collected and recrystallized from dimethylformamide–EtOH to give 0.2 g of pale brown needles, mp>280°. *Anal.* Calcd. for $C_{11}H_7O_5N$: C, 56.66; H, 3.03; N, 6.01. Found: C, 56.18; H, 3.41; N, 6.01. IR ν_{max} cm^{-1} (KBr): 3150—2900 (carboxyl OH), 1705 (C=O), and 1648 (lactam C=O). NMR δ (CF_3CO_2H): 6.37 (2H, singlet, $OC\underline{H}_2O$), 7.40 (1H, singlet, C_5–$\underline{H}$ or C_8–$\underline{H}$), 7.46 (1H, singlet, C_8–$\underline{H}$ or C_5–$\underline{H}$), 9.31 (1H, singlet, C_4–$\underline{H}$).

Ethyl 4-Benzyloxy-5-methoxy-2-nitrocinnamate (XII)——To a mixture of 50 ml of AcOH and 10 ml of conc. HNO_3 ($d=1.38$) was added portionwise 6.2 g of ethyl 4-benzyloxy-3-methoxycinnamate within 30 min under stirring at 15° and the stirring was continued for further 1 hr. The reaction mixture was poured onto

500 ml of ice–water and the resulting yellowish crystals were collected. Recrystallization from EtOH gave 7.0 g of yellowish needles, mp 127—128°. *Anal.* Calcd. for $C_{19}H_{19}O_6N$: C, 63.86; N, 5.36; N, 3.92. Found: C, 63.81; H, 5.58; N, 4.05. IR ν_{max} cm^{-1} ($CHCl_3$): 1708 (C=O), 1570 ($>C=C<$), 1505 and 1327 (NO_2). NMR δ (CCl_4): 1.33 (3H, triplet, J=6.6 cps, $CH_2C\underline{H}_3$), 3.94 (3H, singlet, $OC\underline{H}_3$), 4.22 (2H, quartet, J=6.6 cps, $C\underline{H}_2CH_3$), 5.12 (2H, singlet, $OC\underline{H}_2Ph$), 6.12, 8.11 (each 1H, two doublets, J=16 cps, 2 × olefinic protons), 6.90 (1H, singlet, C_3–$\underline{H}$), 7.35 (5H, singlet, $OCH_2C_6\underline{H}_5$), 7.61 (1H, singlet, C_5–$\underline{H}$).

6-Benzyloxy-2-ethoxycarbonyl-5-methoxyindole (XIII)——A mixture of 3.2 g of XII and 8.3 g of triethyl phosphite was refluxed for 20 hr at 150—160° in a current of N_2. The excess reagent was removed by distillation under reduced pressure and the resultant syrup was treated with a small amount of EtOH to give pale yellowish crystals, whose recrystallization from EtOH gave 1.7 g (56%) of pale yellowish needles, mp 135—136°. *Anal.* Calcd. for $C_{19}H_{19}O_4N$: C, 70.14; H, 5.89: N, 4.31. Found: C, 70.00; H, 6.04; N, 4.24. IR ν_{max} cm^{-1} ($CHCl_3$): 3400 (NH), 1688 (C=O), and 1630 ($>C=C<$). NMR δ ($CDCl_3$): 1.38 (3H, triplet, J=6.5 cps, $CH_2C\underline{H}_3$), 3.91 (3H, singlet, $OC\underline{H}_3$), 4.35 (2H, quartet, J=6.5 cps, $C\underline{H}_2CH_3$), 5.16 (2H, singlet, $OC\underline{H}_2Ph$), 6.82 (1H, singlet, aromatic proton), 7.05 (2H, singlet, aromatic protons), 7.37 (5H, broad singlet, $OCH_2C_6\underline{H}_5$), 8.95 (1H, broad singlet, $N\underline{H}$).

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