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Polycyclic N-Hetero Compounds. V.[1] A Novel Synthesis of Isoquinoline by the Vilsmeier Reaction of Phenylacetonitriles

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A novel synthesis of 3-chloro- or 3-chloro-4-formylisoquinolines by the Vilsmeier reaction of phenylacetonitriles is described. 3,5-Dimethoxyphenylacetonitrile (I) afforded 3-chloro-6,8-dimethoxyisoquinoline (II) in a good yield and a small amount of 3-chloro-6,8-dimethoxy-4-formyl isoquinoline (III). Other phenylacetonitriles (V) afforded 3-chloro-4-formylisoquinoline derivatives (VI) only. The mechanism of this reaction is proposed.

In the synthetic process of agrimonolide,[3] we planned the introduction of a formyl group into the 2-position of 3,5-dimethoxyphenylacetonitrile (I) by the Vilsmeier reaction using dimethylformamide and phosphoryl chloride, but unexpectedly 3-chloro-6,8-dimethoxyisoquinoline (II) and a small amount of 3-chloro-4-formyl-6,8-dimethoxyisoquinoline (III) were obtained. The former was already reported by us.[4] White and Straus[5] also obtained II by the Gattermann reaction of I, but they did not isolate III. III had no C≡N band but the formyl C=O band at 1670 cm^{-1} in its infrared (IR) spectrum, and its nuclear magnetic resonance (NMR) spectrum showed aromatic protons at τ 3.43 (1H, d,[6] $J=2$ Hz), 1.90 (1H, d,[6] $J=2$ Hz), 0.76 (1H, s) attributed to C_8, C_5, C_1–H of isoquinoline ring respectively and formyl proton at τ -0.70. The signal of C_5 proton of III shifted to a lower field compared with that of II, because of formyl group of *peri*-position. Emsly, *et al.*[7] stated that the *peri*-position-H of 1-naphthaldehyde shifted to a lower field by *ca.* 1.5 ppm than the α-proton of naphthalene.

Both the Vilsmeier reaction and the Gattermann reaction are important methods of arylformylation, and it is of interest that both reactions of I give II.

Although White and Straus[5] did not isolate 3-chloro-6,7-dimethoxyisoquinoline from the Gattermann reaction of 3,4-dimethoxyphenylacetonitrile (Vb), we tried to generalize our novel isoquinoline synthesis by using various phenylacetonitriles (V). The isolated products were small amounts of 3-chloro-4-formylisoquinolines (VI). It has been said[8] that the Vilsmeier reaction for active methylenes resulted in C-formylated derivatives. As it is unknown the formyl group was introduced into 4-position of III whether before or after the cyclization to isoquinoline, the Vilsmeier reaction of II was carried out. The thin-layer chromatography (TLC) of the reaction mixture had no spot of III, and the main product was 3-chloro-6,8-dimethoxy-5-formylisoquinoline (IV). In the case of 3,5-dimethoxy derivative

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[1] Part IV: T. Koyama, T. Hirota, M. Ikeda, T. Satoh, A. Iwadoh, and S. Ohmori, *Chem. Pharm. Bull.* (Tokyo), in press.

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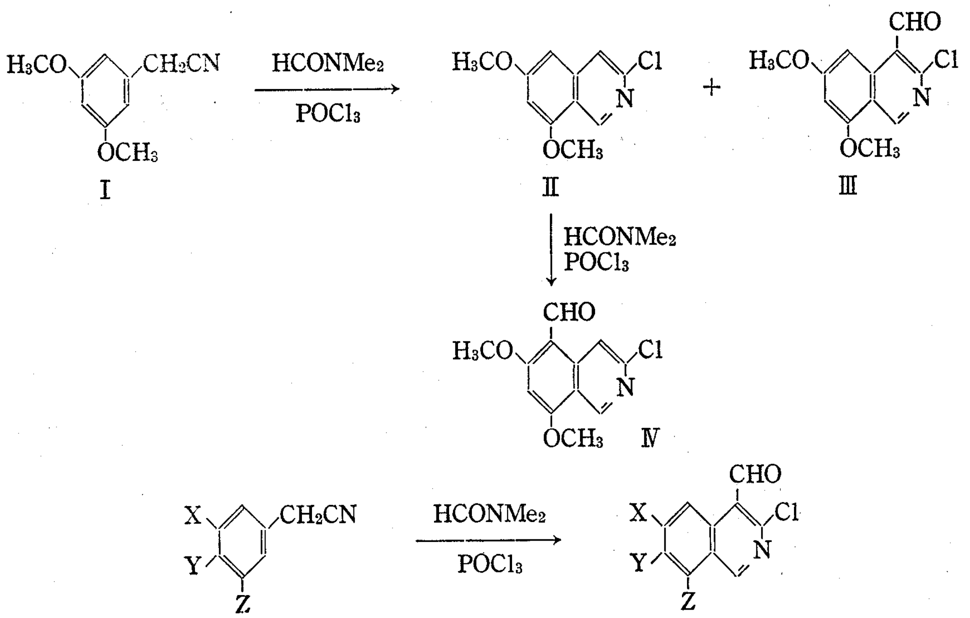

Va : $X=OCH_3$, Y, Z=H
Vb : X, $Y=OCH_3$, Z=H
Vc : X, $Y=OCH_2O$, Z=H
Vd : X, Y, $Z=OCH_3$
Ve : X, $Z=CH_3$, Y=H

VIa : $X=OCH_3$, Y, Z=H
VIb : X, $Y=OCH_3$, Z=H
VIc : X, $Y=OCH_2O$, Z=H
VId : X, Y, $Z=OCH_3$
VIe : X, $Z=CH_3$, Y=H

Chart 1

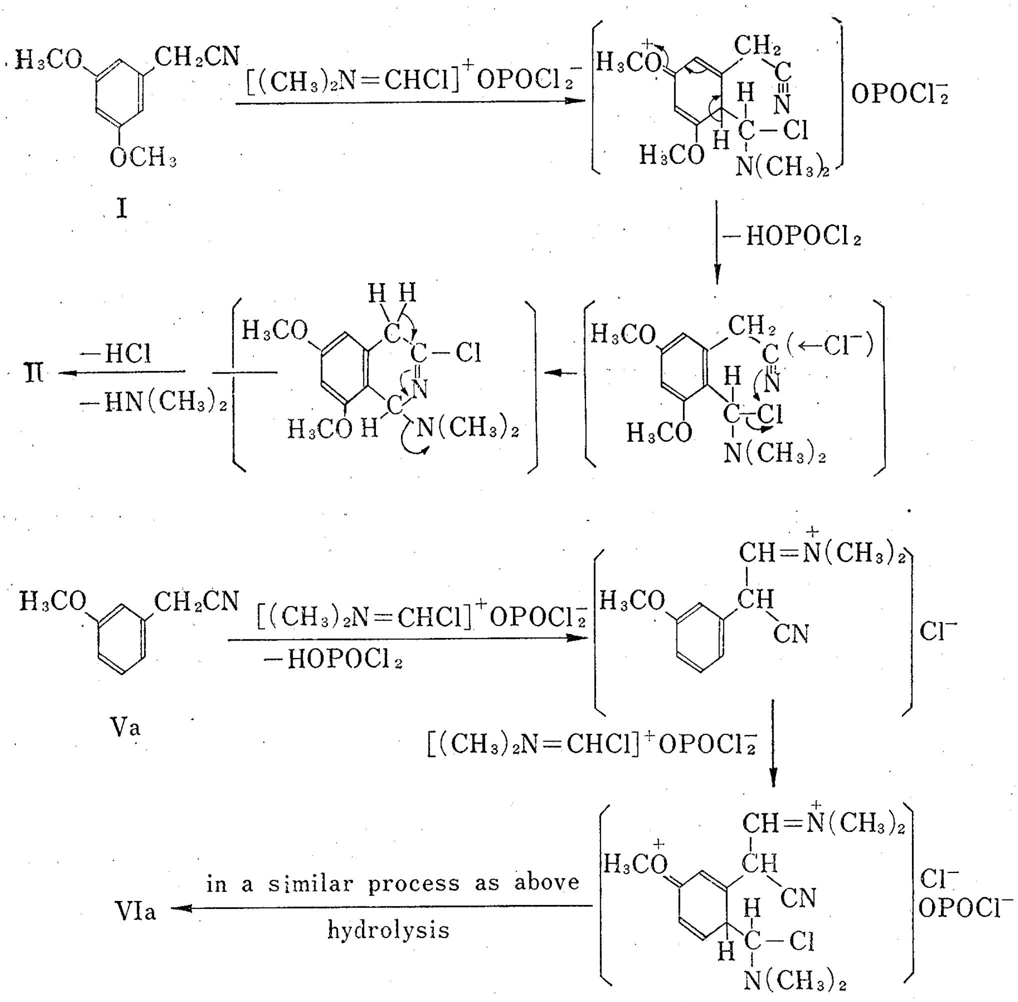

Chart 2

(I), II was obtained in a good yield (65%) because of the ease of substitution of Vilsmeier reagent into the benzene ring, and in other cases, small amounts of VI (less than 10%) were obtained. Therefore, it is suggested that, in the formylation of V, the methylene group was preferentialy formylated, and the yield of isoquinolines was lower than II. Thus we propose the reaction mechanism of these isoquinoline synthesis shown in Chart 2.

Experimental

Melting points are uncorrected. NMR spectra were taken on a Hitachi Model R-22 spectrometer (90 MHz) or Japan Electron Optics Laboratory JNM C-60-H (60 MHz) in $CDCl_3$, except where otherwise noted, with tetramethylsilane as an internal standard (τ value), s, singlet; d, doublet; dd, double doublet; b, broad. IR spectra were taken on a Japan Spectroscopic Company DS-301 spectrometer in KBr disk. Mass spectra were taken on a Japan Electron Optics Laboratory OL-SG spectrometer with a direct inlet system.

Vilsmeier Reaction of 3,5-Dimethoxyphenylacetonitrile (I)——To a mixture of 3.54 g of I and 1.46 g of $HCONMe_2$, 3.06 g of $POCl_3$ was added dropwise under cooling, the mixture was stirred at 20° for 1 hr and further at 90—95° for 2 hr, and allowed to stand at room temperature for 15 hr. The reaction mixture was refluxed for 0.5 hr with 30 ml of dil. HCl, cooled, made alkaline with dil. NaOH, and extracted with $(C_2H_5)_2O$–$CHCl_3$ (1: 1), The organic layer was washed with H_2O, dried over Na_2SO_4, and the solvent was evaporated. The yellowish crystalline residue was recrystallized from dil. EtOH to 3-chloro-6,8-dimethoxyisoquinoline[4] (II), as pale yellow needles, mp 159—160° (reported[5] mp 160—161°). Yield, 2.75 g (62%). The above mother liquid was evaporated to dryness and the residue was chromatographed over alumina, eluted with benzene. The first fraction of benzene eluate was recrystallized from dil. EtOH to 86 mg (*ca.* 3%) of III as pale yellow needles, mp 159—160°, identical with the above material (mixed mp, IR, and TLC). Recrystallization of the second fraction of benzene eluate from benzene–cyclohexane gave 24 mg (*ca.* 1%) of 3-chloro-6,8-dimethoxy-4-formylisoquinoline (III) as pale yellow needles, mp 226—229°. *Anal.* Calcd. for $C_{12}H_{10}O_3NCl$: C, 57.29; H, 3.98; N, 5.57. Found: C, 57.45; H, 4.11; N, 5.40. IR $\nu_{\max}^{\mathrm{KBr}}$ cm^{-1}: 1674 (C=O). NMR: 6.03, 5.98 (each 3H, s, 2-OCH_3), 3.43 (1H, d, J=2.5 Hz, C_7-H), 1.90 (1H, d, J=2.5 Hz, C_5-H), 0.76 (1H, s, C_1-H), −0.70 (1H, s, –CHO). Mass Spectrum: m/e (M^+)=251. Beilstein test: positive.

Vilsmeier Reaction of II——To a solution of 0.78 g of II in 10 ml of $HCONMe_2$, 0.5 ml of $POCl_3$ was added dropwise under cooling and the mixture was stirred at 20—25° for 2 hr, and the temperature was raised gradually to 100—110° during 0.5 hr, then the mixture was stirred at the temperature additional 2 hr. After the reaction mixture was allowed to stand overnight, 20 ml of dil. HCl was added and the mixture was stirred at 80—90° for 0.5 hr. The resulting solution was diluted with *ca.* 2 volumes of H_2O and extracted with $(C_2H_5)_2O$: CH_2Cl_2 (1: 1). The organic layer was washed with H_2O, dried over Na_2SO_4, and the solvent was evaporated. There was no spot of III on TLC. The residue was recrystallized from benzene to 0.32 g (40%) of 3-chloro-6,8-dimethoxy-5-formylisoquinoline (IV) as colorless needles, mp 195—196°. *Anal.* Calcd. for $C_{12}H_{10}O_3NCl$: C, 57.29; H, 3.98; N, 5.57. Found: C, 57.35; H, 4.06; N, 5.38. IR $\nu_{\max}^{\mathrm{KBr}}$ cm^{-1}: 1665 (C=O). NMR: 5.95, 5.91 (each 3H, s, 2-OCH_3), 3.53 (1H, s, C_7-H), 1.89, 1.84 (each 1H, s, C_4, C_1-H), −0.65 (1H, s, –CHO).

Vilsmeier Reaction of 3-Methoxyphenylacetonitrile (Va)——To a mixture of 2.95 g of Va and 1.5 g of $HCONMe_2$, 3.37 g of $POCl_3$ was added dropwise under cooling and the mixture was stirred at 20° for 1 hr and further at 110—120° for 2 hr. After the reaction mixture was allowed to stand overnight at room temperature, 50 ml of dil. HCl was added and the mixture was stirred at 95—100° for 1 hr. When cooled, the solution was made alkaline with Na_2CO_3 and extracted with $(C_2H_5)_2O$, then with $CHCl_3$. Each extract was washed with H_2O independently, dried over Na_2SO_4, and the solvent was evaporated. The $(C_2H_5)_2O$ extract was chromatographed over alumina with benzene. The first fraction eluted with benzene was recrystallized from dil. EtOH to 0.08 g (4%) of 3-chloro-6-methoxy-4-formylisoquinoline (VIa) as pale yellow needles, mp 155—156°. *Anal.* Calcd. for $C_{11}H_8O_2NCl$: C, 59.59; H, 3.61; N, 6.32. Found: C, 59.70; H, 3.55; N, 6.48. Mass Spectrum: m/e (M^+)=221. IR $\nu_{\max}^{\mathrm{KBr}}$ cm^{-1}: 1675 (C=O). NMR: 6.01 (3H, s, OCH_3), 2.75 (1H, dd, J=8 Hz, J=2.5 Hz, C_7-H), 2.15 (1H, d, J=8 Hz, C_8-H), 1.44 (1H, d, J=2.5 Hz, C_5-H), 0.92 (1H, s, C_1-H), −0.70 (1H, s, –CHO). Beilstein test: positive. 2,4-Dinitrophenylhydrazone: Light orange needles, mp 241—242°, from dioxane. Pure material was not isolated from the dark brown tarry $CHCl_3$ extract.

Vilsmeier Reaction of 3,4-Dimethoxyphenylacetonitrile (Vb)——To a mixture of 3.5 g of Vb and 1.6 g of $HCONMe_2$, 3.5 g of $POCl_3$ was added dropwise under cooling and the mixture was stirred at room temperature for 1 hr and then at 100° for 2 hr. After allowing to stand overnight at room temperature, the reaction mixture was heated with 50 ml of dil. HCl for 0.5 hr. When cooled, 2 volumes of H_2O was added to the solution, which was made alkaline with Na_2CO_3, and extracted with $(C_2H_5)_2O$. The extract was washed with H_2O, dried over Na_2SO_4, and $(C_2H_5)_2O$ was evaporated. The yellowish crystalline residue was recrystallized from dil. EtOH to 0.18 g (7.5%) of 3-chloro-6,7-dimethoxy-4-formylisoquinoline (VIb) as pale yellow needles, mp 199—201°. *Anal.* Calcd. for $C_{12}H_{10}O_3NCl$: C, 57.29; H, 3.98; N, 5.57. Found: C, 57.11; H, 4.14; N, 5.65. Mass Spectrum: m/e (M^+)=251. IR $\nu_{\max}^{\mathrm{KBr}}$ cm^{-1}: 1674 (C=O). NMR: 5.95, 5.90 (each 3H, s, 2-OCH_3), 2.87 (1H, s, C_8-H), 1.41 (1H, s, C_5-H), 1.12 (1H, s, C_1-H), −0.65 (1H, s, -CHO). Beilstein test: positive. The dark brown tarry material remained in the mother liquid after $(C_2H_5)_2O$ extraction was extracted with $CHCl_3$ but pure compound could not be isolated.

Vilsmeier Reaction of 3,4-Methylenedioxyphenylacetonitrile (Vc)——To a mixture of 3.3 g of Vc and 2.9 g of $HCONMe_2$, 6.1 g of $POCl_3$ was added dropwise under cooling and the mixture was stirred at room temperature for 1 hr and further at 100—110° for 3 hr. When cooled, 50 ml of dil. HCl was added to the reaction mixture and the solution was refluxed for 0.5 hr. When cooled, the solution was made alkaline with dil. Na_2CO_3 and extracted with $(C_2H_5)_2O$. The extract was washed with H_2O, dried over Na_2SO_4, and the solvent was evaporated. The residue was recrystallized repeatedly from dil. EtOH to 0.14 g (6.1%) 3-chloro-4-formyl-6,7-methylenedioxyisoquinoline (VIc) as pale yellow needles, mp 244—245°. *Anal.* Calcd. for $C_{11}H_6O_3NCl$: C, 56.05; H, 2.55; N, 5.94. Found: C, 56.30; H, 2.50; N, 5.80. Mass Spectrum: *m/e* (M^+)=235. IR $\nu_{\max}^{\text{KBr}}$ cm^{-1}: 1681 (C=O). NMR (CF_3COOD): 3.55 (2H, s, OCH_2O), 2.36 (1H, s, C_8-H), 1.18 (1H, s, C_5-H), 0.75 (1H, s, C_1-H), −0.75 (1H, s, -CHO). Beilstein test: positive. The dark brown material remaining in the mother liquid after $(C_2H_5)_2O$ extraction was extracted with $CHCl_3$ but pure compound could not be isolated.

Vilsmeier Reaction of 3,4,5-Trimethoxyphenylacetonitrile (Vd)——To a mixture of 0.9 g of Vd and 0.9 g of $HCONMe_2$, 2.0 g of $POCl_3$ was added dropwise under cooling and the mixture was stirred at room temperature for 1 hr and then at 100—110° for 3 hr. When cooled, the reaction mixture was heated with dil. HCl (15 ml) at 90° for 0.5 hr. The solution was diluted with 2 volumes of H_2O, made alkaline with dil. Na_2CO_3, and extracted with $(C_2H_5)_2O$-$CHCl_3$ (1:1). The organic layer was washed with H_2O, dried over Na_2SO_4, and the solvent was evaporated. The residue was chromatographed over alumina with benzene. Recrystallization of benzene eluate from dil. EtOH gave 96 mg (8%) of 3-chloro-6,7,8-trimethoxy-4-formyl-isoquinoline (VId) as pale yellow needles, mp 159—161°. *Anal.* Calcd. for $C_{13}H_{12}O_4NCl$: C, 55.41; H, 4.26; N, 4.94. Found: C, 55.60; H, 4.11; N, 5.16. Mass Spectrum: *m/e* (M^+)=281. IR $\nu_{\max}^{\text{KBr}}$ cm^{-1}: 1673 (C=O). NMR: 6.11, 5.95, 5.89 (each 3H, 3-OCH_3), 1.58 (1H, s, C_5-H), 0.77 (1H, s, C_1-H), −0.74 (1H, s, -CHO).

Vilsmeier Reaction of 3,5-Dimethylphenylacetonitrile (Ve)——To a solution of 2.9 g of Ve in 10 ml of $HCONMe_2$, 3.5 g of $POCl_3$ was added dropwise under cooling and the solution was stirred at room temperature for 1 hr and then at 110—120° for 4 hr. When cooled, the reaction mixture was refluxed with 30 ml of dil. HCl, diluted with *ca.* 2 volumes of H_2O, made alkaline with Na_2CO_3, and extracted with $(C_2H_5)_2O$. The extract was washed with H_2O, dried over Na_2SO_4, $(C_2H_5)_2O$ was evaporated. The residue was chromatographed over alumina with benzene. Recrystallization of benzene eluate from benzene–cyclohexane gave 65 mg (*ca.* 3%) of 3-chloro-6,8-dimethyl-4-formyl-isoquinoline (VIe) as pale yellow needles, mp 134—136°. *Anal.* Calcd. for $C_{12}H_{10}ONCl$: C, 65.60; H, 4.56; N, 6.33. Found: C, 65.41; H, 4.62; N, 6.44. Mass Spectrum: *m/e* (M^+)=219. IR $\nu_{\max}^{\text{KBr}}$ cm^{-1}: 1680 (C=O). NMR: 7.45, 7.32 (each 3H, s, 2-CH_3), 2.90 (1H, bs, C_7-H), 1.45 (1H, bs, C_5-H), 1.13 (1H, s, C_1-H), −0.68 (1H, s, -CHO). Beilstein test: positive.

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