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Polycyclic N-Hetero Compounds. XV.[1] The Vilsmeier Reaction of Phenylacetonitriles. II[2]

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The Vilsmeier reaction of phenylacetonitriles to obtain intermediates of isoquinoline cyclization was described (refer to Chart 1). Phenylacetonitrile (I) gave β-dimethylamino-α-phenylacrylonitrile (II), α-formyl- (III) and α,N-diformyl- (IV) α-phenylacetamide, and 5,7-dioxo-2,6-diphenyl-4-aza-2-heptenamide (VI). *m*-Methoxyphenylacetonitrile (VII) gave α-(*m*-methoxyphenyl)-β-dimethylaminoacrylonitrile (VIII) and 3,5-bis(*m*-methoxyphenyl)-6-(N,N-dimethylaminomethyleneamino)-2(1H)-pyridone (IX). *p*-Methoxyphenylacetonitrile (XI) gave 2-[α-(β-carbamoyl)-*p*-methoxystyryl)amino]-6-chloro-3,5-bis(*p*-methoxyphenyl)pyridine (XII). 3,5-Dimethoxyphenylacetonitrile (XIV) gave 3-chloro-6,8-dimethoxyisoquinoline (XV) and 3-chloro-5-hydroxymethyl-6,8-dimethoxyisoquinoline (XVI). Phenylacetamides (V, X, XIII, XVII) were also obtained from respective nitriles (I, VII, XI, XIV).

Keywords——Vilsmeier reaction; dimethylformamide; phosphoryl chloride; phenylacetonitriles; formylation; pyridine cyclization; isoquinoline cyclization

In the previous paper,[2] it was shown as a novel isoquinoline synthesis that the Vilsmeier reaction of phenylacetonitriles, using dimethylformamide and phosphoryl chloride, afforded 3-chloro or 3-chloro-4-formylisoquinolines. In the previous reaction condition, isoquinoline derivatives were only isolated. To obtain the intermediates of isoquinoline cyclization, products under more moderate reaction condition than the previous were investigated. The present paper describes these results.

As shown in Chart 1, phenylacetonitrile (I), *m*-methoxyphenylacetonitrile (VII), *p*-methoxyphenylacetonitrile (XI), and 3,5-dimethoxyphenylacetonitrile (XIV) were used as starting materials.

The Vilsmeier reagent was prepared with dimethylformamide and phosphoryl chloride at 10—12° for 0.5 hr under stirring without moisture and the reaction with phenylacetonitriles was carried out at 60—70° for 0.5—4 hr.

The Vilsmeier reaction of I afforded β-dimethylamino-α-phenylacrylonitrile (II), α-formyl-α-phenylacetamide (III), α,N-diformyl-α-phenylacetamide (IV), phenylacetamide (V),[4] and 5,7-dioxo-2,6-diphenyl-4-aza-2-heptenamide (VI). But formylation product at benzene ring could not be isolated. II was already synthesized by Novelli, *et al.*[5] on heating I with dimethylformamide, and mp and spectral data (infrared (IR) and proton magnetic resonance (PMR) spectra) agreed with their specimen, *i. e.*, phenyl group and vinyl proton of II situated in *cis* configuration. The IR spectrum of III in KBr disk showed N–H bands at 3420, 3180, and 1630 cm^{-1}, C=O band at 1660 cm^{-1}, and hydrogen bonded broad O–H band at *ca.* 2700

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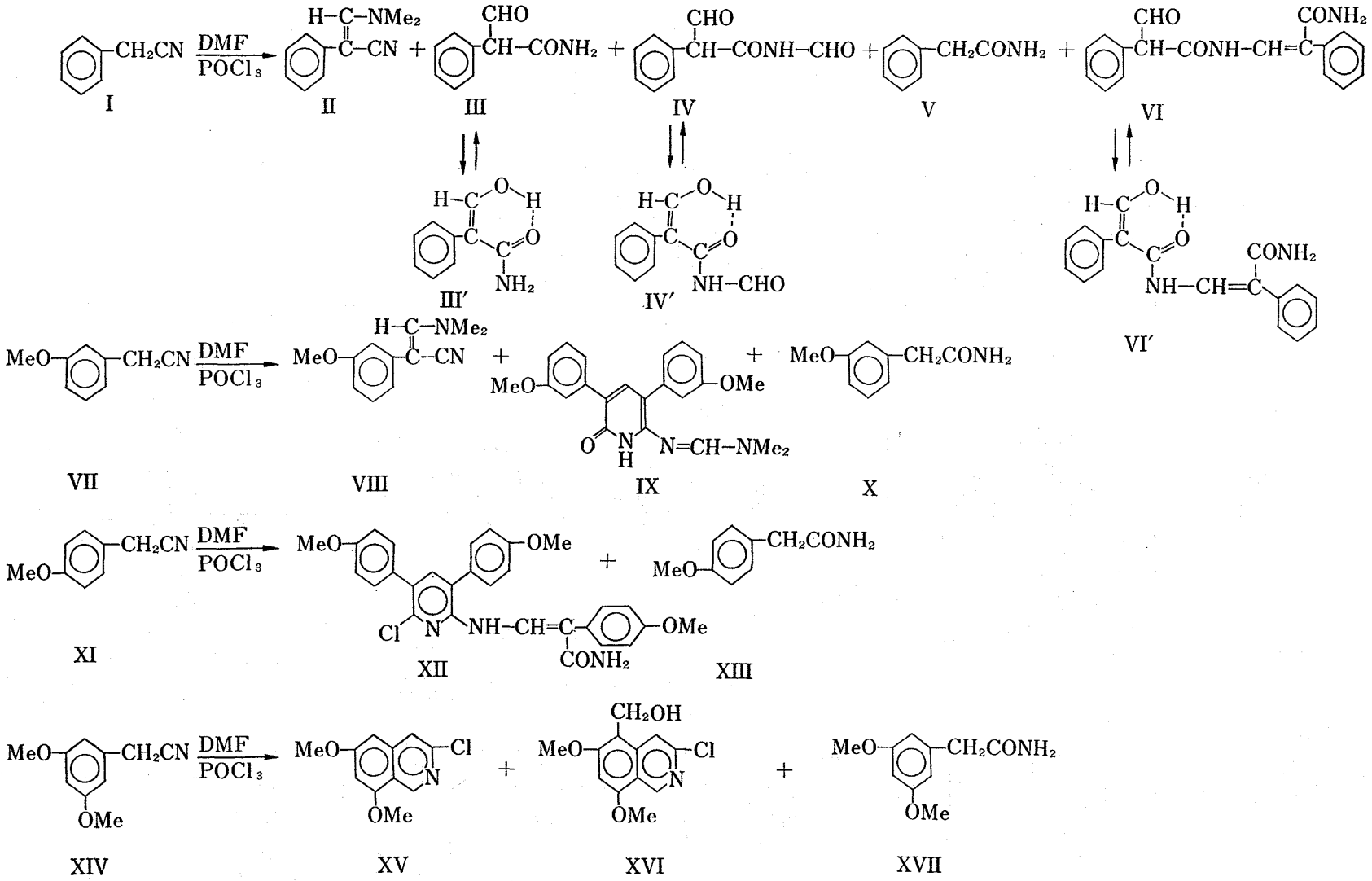

Chart 1

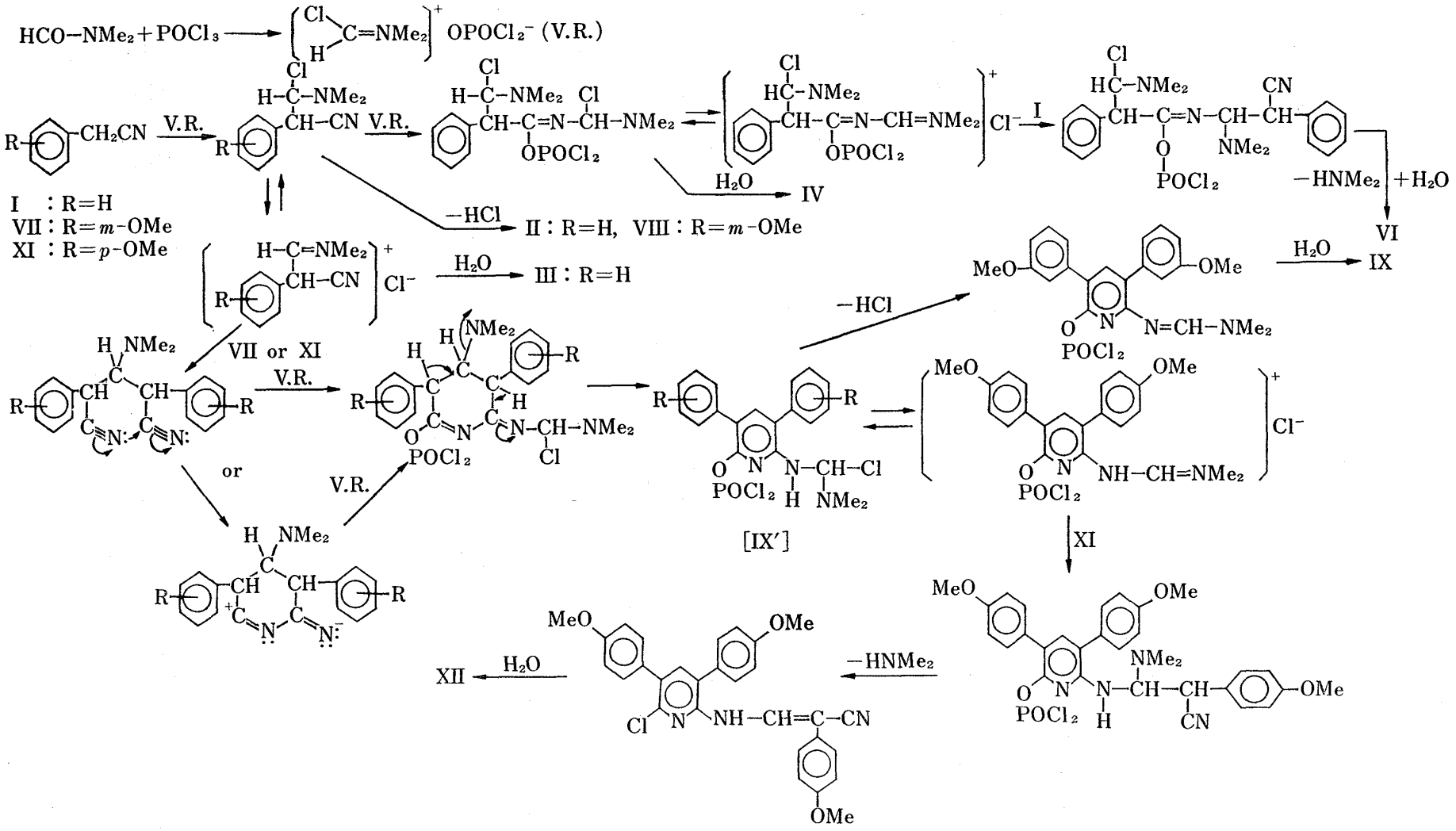

Chart 2

cm^{-1}. The PMR spectrum of III exhibited two-proton broad absorption at δ 5.40 attributable to NH_2, six-proton multiplet at δ 7.32 for phenyl and vinyl protons, and one-proton doublet at δ 13.65 (J=11 Hz) for OH. NH_2 and OH signals were disappeared with few drops of D_2O. The IR spectrum of IV in KBr disk showed N–H band at 3340 cm^{-1}, C=O bands at 1726 and 1645 cm^{-1}, and hydrogen bonded broad O–H band at *ca.* 2800 cm^{-1} and its PMR spectrum exhibited six-proton multiplet at δ 7.36 attributable to phenyl and vinyl protons, one-proton broad absorption (D_2O exchange) at δ 7.78 for NH, one proton doublet (J=10 Hz) at δ 9.18 for N-formyl proton which was changed to singlet with few drops of D_2O, and one-proton doublet (J=12 Hz) at δ 12.93 for OH which was disappeared with D_2O exchange. The α-formyl groups of III and IV seem to be enolated and chelations characteristic of β-dicarbonyl compounds are presumed by the above data. Therefore, it can be presumed that the structures of III and IV seem to be transformed into III′ and IV′. Perhaps α-formyl group of VI seems to be chelated as well as III′ and IV′. These presumable mechanistic pathways are summarized in Chart 2.

The Vilsmeier reaction of VII gave α-(*m*-methoxyphenyl)-β-dimethylaminoacrylonitrile (VIII), 3,5-bis(*m*-methoxyphenyl)-6-(N,N-dimethylaminomethyleneamino)-2(1H)-pyridone (IX), and *m*-methoxyphenylacetamide (X).[6] Since the chemical shifts of dimethylamino group and vinyl proton of VIII were similar to those of II, phenyl group and vinyl proton seem to be situated in *cis* configuration as analogous to II. The molecular formula of IX agreed with $C_{22}H_{23}N_3O_3$ by elemental analysis and mass spectroscopy. The IR spectrum of IX showed N–H band at 2950 cm^{-1} and C=O band at 1635 cm^{-1} similar to that of 2(1H)-pyridone and its PMR spectrum exhibited N-methyl groups at δ 2.67 and 2.92, methoxyl groups at δ 3.77 and 3.79, aromatic protons at δ 6.60—7.50 as multiplet, and one-proton singlets at δ 7.76 and 8.09 due to pyridone C-4 and azomethine protons. The presumable formation mechanism of IX is indicated in Chart 2.

The Vilsmeier reaction of XI afforded 2-(β-carbamoyl-*p*-methoxystyrylamino)-6-chloro-3,5-bis(*p*-methoxyphenyl)pyridine (XII) and *p*-methoxyphenylacetamide (XIII).[6] The formation of XII appears to be condensation of unisolable intermediate [IX′] (Chart 2) similar to IX with additional one molecule of XI at side chain carbon. The presumable formation mechanism of XII is indicated in Chart 2.

The Vilsmeier reaction of XIV afforded 3-chloro-6,8-dimethoxyisoquinoline (XV), 3-chloro-5-hydroxymethyl-6,8-dimethoxyisoquinoline (XVI), and 3,5-dimethoxyphenylacetamide (XVII).[7] XV was identified with authentic sample reported in our laboratory.[2] The IR spectrum of XVI showed O–H band at 3310 cm^{-1} and its PMR spectrum in deuterotrifluoroacetic acid exhibited two methoxyl signals at δ 4.20 and 4.23, methylene signal at δ 5.80 as singlet, and each one-proton sharp singlets at δ 6.95, 8.11, and 9.49 due to C-7, C-4, and C-1 protons, respectively. Moreover the ultra violet spectrum of XVI in EtOH was similar to that of XV (XV: 314 nm, 324 nm (shoulder); XVI: 317 nm, 329 nm (shoulder)). In the previous paper,[2] we reported the presumable formation mechanism and the product of the Vilsmeier reaction of XV (3-chloro-5-formyl-6,8-dimethoxyisoquinoline (XV′)). Although the formation of XVI seems to be the reduction of XV′ with formic acid formed, a certain mechanism is under investigation. The analogous observation was reported by Remer and Weiss,[8] who obtained 4-chloro-5-dimethylaminomethylindoles from 4-oxo-4,5,6,7-tetrahydroindoles by the Vilsmeier reaction.

The above phenylacetamides (V, X, XIII, and XVII), which appeared to be formed by hydrolysis of phenylacetonitriles (I, VII, XI, and XIV), were identified with authentic samples prepared from phenylacetyl chlorides and aqueous ammonia (mixed mp, IR, PMR, and TLC).

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Experimental

Melting points are uncorrected. IR spectra were recorded on Nippon Bunko DS-301 spectrometer in KBr. PMR spectra were taken with Hitachi R-22 spectrometer (90 MHz) in $CDCl_3$, except where otherwise noted, with tetramethylsilane as an internal standard (δ value), s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; b, broad. Mass spectra (MS) were obtained with Shimadzu LKB-9000 instrument at 70 eV ionization potential.

The Vilsmeier Reaction of Phenylacetonitrile (I)——To the Vilsmeier reagent prepared from 4.38 g of dimethylformamide (DMF) and 9.21 g of $POCl_3$ at 10—12° for 0.5 hr, 5.85 g of I was added under cooling with stirring. The mixture was warmed gradually to 65—70° and stirred at the temperature for 4 hr. After cooled, *ca.* 5-fold of H_2O was added to the reaction mixture under cooling. The resulting solution was extracted with ether (A), the H_2O layer was basified with Na_2CO_3, then extracted with CH_2Cl_2 (B). The basic H_2O layer was acidified with AcOH again and extracted with ether (C). Each extract was washed with sat. NaCl solution, dried, and evaporated, independently. The residue of the first ether extract (A) was recrystallized from benzene-*n*-hexane (*ca.* 3: 1) to give 1.30 g (13.6%) of α,N-diformyl-α-phenylacetamide (IV) as colorless needles, mp 119—120°. *Anal.* Calcd. for $C_{10}H_9NO_3$: C, 62.82; H, 4.75; N, 7.33. Found: C, 62.94; H, 4.77; N, 7.52. MS *m/e*: 191 (M^+). The IR and PMR spectral data of IV are shown in The text. The residue of the CH_2Cl_2 extract from basic medium (B) was recrystallized from benzene to give 0.35 g of phenylacetamide (V) as colorless plates, mp 155—156° (reported mp 156°[4]), identical with the authentic sample prepared from phenylacetyl chloride and aqueous NH_3 (mixed mp, IR, and TLC). The above mother benzene solution was chromatographed over silica gel with benzene and then $CHCl_3$. After evaporation of the benzene eluate, the residue was recrystallized from cyclohexane to give 0.09 g (1%) of β-dimethylamino-α-phenylacrylonitrile (II) as colorless needles, mp 79°, agreed with the authentic sample reported by Novelli, *et al.*[5] (mp, IR, and PMR). *Anal.* Calcd. for $C_{11}H_{12}N_2$: C, 76.71; H, 7.02; N, 16.27. Found: C, 76.42; H, 6.95; N, 16.25. MS *m/e*: 172 (M^+). After evaporation of the $CHCl_3$ eluate, the residue was recrystallized from benzene to give 0.16 g of V as colorless plates, mp 155—156°, overall yield 0.51 g (7.6%). The ether extract from AcOH acidic medium was chromatographed over silica gel with benzene and then CH_2Cl_2. After evaporation of the benzene eluate, the residue was recrystallized from cyclohexane to give 0.25 g (3.1%) of α-formyl-α-phenylacetamide (III) as colorless needles, mp 107—109°. *Anal.* Calcd. for $C_9H_9NO_2$: C, 66.24; H, 5.56; N, 8.58. Found: C, 66.36; H, 5.55; N, 8.61. MS *m/e*: 163 (M^+). The IR and PMR spectral data of III are shown in the text. After evaporation of the CH_2Cl_2 eluate, the residue was recrystallized from benzene to give 0.09 g (0.6%) of 5,7-dioxo-2,6-diphenyl-4-aza-2-heptenamide (VI) as pale yellow granules, mp 201—203°. *Anal.* Calcd. for $C_{18}H_{16}N_2O_3$: C, 70.11; H, 5.23; N, 9.09. Found: C, 69.94; H, 5.05; N, 8.91. MS *m/e*: 308 (M^+). IR ν_{max}^{KBr} cm^{-1}: 3470, 3370, 3130 (broad) (N–H, O–H), 1675, 1650 (C=O). PMR: 5.58 (2H, b, NH_2, D_2O exchange), 7.15 (12H, m, 2-phenyl-H, O–CH=C, NH, only 1H D_2O exchange), 8.13, 8.28 (1H, both added, each s, N–CH=C, which seems to be attributable to *cis-trans* isomer), 13.32 (1H, bd, $J=12$ Hz, OH, D_2O exchange).

The Vilsmeier Reaction of *m*-Methoxyphenylacetonitrile (VII)——To the Vilsmeier reagent prepared from 1.75 g of DMF and 3.07 g of $POCl_3$ at 10—12° for 0.5 hr, 2.94 g of VII was added and the mixture was stirred at 70° for 3 hr. After cooled, *ca.* 5-fold of H_2O was added to the reaction mixture. The resulting solution was extracted with ether (A), the H_2O layer was basified with Na_2CO_3, then extracted with ether (B) followed by CH_2Cl_2 (C). Each extract was worked up as usual. The residue of the first ether extract (A) distilled under reduced pressure to give 1.1 g (37.8%) of unchanged VII. The residues of the ether (B) and CH_2Cl_2 (C) extracts were combined (same spots on TLC) and the oily crystals were recrystallized from 80% MeOH to give 0.19 g (10.7%) of 3,5-bis(*m*-methoxyphenyl)-6-(N,N-dimethylaminomethyleneamino)-2(1H)-pyridone (IX) as pale yellow needles, mp 192—195°. For elemental analysis, the crystals were twice recrystallized from benzene–cyclohexane, mp 194—195°. *Anal.* Calcd. for $C_{22}H_{23}N_3O_3$: C, 70.01, H, 6.14; N, 11.13. Found: C, 70.14; H, 6.20; N, 10.87. MS *m/e*: 377 (M^+). The IR and PMR spectral data are shown in the text. The above mother liquor was evaporated to dryness and the cold benzene-insoluble fraction of the residue was recrystallized from benzene to give 0.10 g of *m*-methoxyphenylacetamide (X) as colorless plates, mp 125—126°, agreed with the authentic sample reported by Yonemitsu and Naruto[6] (mp, IR, and PMR). *Anal.* Calcd. for $C_9H_{11}NO_2$: C, 65.44; H, 6.71; N, 8.48. Found: C, 65.58; H, 6.70; N, 8.35. MS *m/e*: 165 (M^+). The above benzene-soluble fraction of the residue was chromatographed over silica gel with benzene–CH_2Cl_2 and then benzene–EtOH. After evaporation of the benzene–CH_2Cl_2 (5: 1) eluate, the residue was recrystallized from *n*-hexane to give 0.05 g (2%) of α-(*m*-methoxyphenyl)-β-dimethylaminoacrylonitrile (VIII) as colorless needles, mp 74—75°. *Anal.* Calcd. for $C_{12}H_{14}N_2O$: C, 71.26; H, 6.98; N, 13.85. Found: C, 71.44; H, 7.02; N, 13.82. MS *m/e*: 202 (M^+). IR ν_{max}^{KBr} cm^{-1}: 2180 (C≡N). PMR: 3.20 (6H, s, $N(CH_3)_2$), 3.78 (3H, s, OCH_3), 6.91 (1H, s, CH=C), 6.40—7.32 (4H, m, phenyl-H). After evaporation of the benzene–EtOH (9: 1) eluate, the residue was recrystallized from benzene–cyclohexane to give 0.16 g of X as colorless plates, mp 125—126°, identical with the above amide X, overall yield 0.26 g (9.9%).

The Vilsmeier Reaction of *p*-Methoxyphenylacetonitrile (XI)——To the Vilsmeier reagent prepared from 3.51 g of DMF and 7.37 g of $POCl_3$ at 10—12° for 0.5 hr, 5.88 g of XI was added and the mixture was stirred

at 65—70° for 4 hr. After cooled, *ca.* 5-fold of H_2O was added to the reaction mixture. The resulting solution was extracted with ether (A) followed by CH_2Cl_2 (B), the H_2O layer was basified with Na_2CO_3, then extracted with CH_2Cl_2 (C). Each extract was worked up as usual. The ether extract (A) was chromatographed over alumina with benzene. The benzene eluate contained 1.32 g (22.5%) of unchanged XI. The residue of the CH_2Cl_2 extract (B) from acidic medium was recrystallized from benzene to give 0.27 g of *p*-methoxyphenylacetamide (XIII)[6] as colorless scales, mp 181—182°, identical with the authentic sample prepared from *p*-methoxyphenylacetyl chloride and aqueous ammonia. The above mother benzene solution was evaporated to dryness and chromatographed over with CH_2Cl_2 and then with AcOEt. After evaporation of the CH_2Cl_2 eluate, the residue was recrystallized from cyclohexane to give 0.08 g (1.5%) of 2-(β-carbamoyl-*p*-methoxystyrylamino)-6-chloro-3,5-bis(*p*-methoxyphenyl)pyridine (XII) as colorless needles, mp 190—192°. *Anal.* Calcd. for $C_{29}H_{26}ClN_3O_4$: C, 67.51; H, 5.04; N, 8.15. Found: C, 67.78; H, 5.15; N, 8.02. IR ν_{max}^{KBr} cm^{-1}: 3400—(broad), 1610 (N–H), 1660 (C=O). PMR: 3.77, 3.81 (6H, 3H, each s, 3-OCH_3, which were split to three singlets with expansion (×5)), 4.35, 5.29 (1H, 2H, b, NH, NH_2, D_2O exchange), 6.74—7.43 (12H, 3-A_2B_2 q, J=8—9 Hz, 3-phenyl-H), 7.37 (1H, s, N–CH=C), 7.95 (1H, s, pyridine 4-H). MS *m/e*: 515 (M^+), P: P+1=3: 1. Beilstein test: positive. After evaporation of the AcOEt eluate, the residue was recrystallized from benzene to give 0.11 g of XIII as colorless scales, mp 181—182°, identical with the above amide XIII, overall yield 0.38 g (7.4%).

The Vilsmeier Reaction of 3,5-Dimethoxyphenylacetonitrile (XIV)——To the Vilsmeier reagent prepared from 0.54 g of DMF and 1.14 g of $POCl_3$ at 10—12° for 0.5 hr, 1.10 g of XIV was added and the mixture was stirred at 60—65° for 0.5 hr. After cooled, *ca.* 5-fold of H_2O was added to the reaction mixture. The resulting solution was extracted with CH_2Cl_2 (A), the H_2O layer was basified with Na_2CO_3, then extracted with CH_2Cl_2 (B). Each extract was worked up as usual. The residue of the first CH_2Cl_2 extract (A) was recrystallized from dil. EtOH to give 0.54 g of 3-chloro-6,8-dimethoxyisoquinoline (XV) as pale yellow needles, mp 159—160°, identical with the specimen previously reported in our laboratory[2] (mixed mp, IR, and TLC). The above mother liquor was evaporated to dryness and the residue was chromatographed over alumina with benzene and then $CHCl_3$. After evaporation of the first benzene eluate, the residue was recrystallized from cyclohexane to give 0.06 g (5.5%) of unaltered XIV as colorless needles, mp 53° and recrystallization of the residue of the second benzene eluate from cyclohexane gave 0.13 g of XV as colorless needles, mp 160°, identical with above isoquinoline XV, overall yield 0.68 g (52%). After evaporation of the first $CHCl_3$ eluate, the residue was recrystallized from benzene to give 0.05 g (3.4%) of 3-chloro-5-hydroxymethyl-6,8-dimethoxyisoquinoline (XVI) as pale yellow needles, mp 256—258° with positive Beilstein test. *Anal.* Calcd. for $C_{12}H_{12}ClNO_3$: C, 56.84; H, 4.73; N, 5.52. Found: C, 57.09; H, 4.61; N, 5.43. MS *m/e*: 253 (M^+), P: P+1=3: 1. The IR and PMR spectral data are shown in the text. After evaporation of the second $CHCl_3$ eluate, the residue was recrystallized from benzene to give 0.04 g (3.5%) of 3,5-dimethoxyphenylacetamide (XVII)[7] as colorless needles, mp 126—127°, identical with the authentic sample prepared from 3,5-dimethoxyphenylacetyl chloride and aqueous ammonia.

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