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Polycyclic N-Hetero Compounds. XVI.[1] Reactions of Benzyl Ketones with Formamide or Acetamide

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Reaction of α-acyl-α-(*m*-chlorophenyl)acetonitrile (II) with formamide gave enamines (III) and 4-aminopyrimidines (IV). III could be converted to IV by the same treatment with formamide. 4-Acetamido-5-(3,5-dimethylphenyl)pyrimidine (Ve) gave 1,3,10-triazaphenanthrene (VI) with polyphosphoric acid, although cyclization of *m*-chloro- (Va) and *m*-methyl- (Vd) phenyl derivatives were unsuccessful (Chart 1). Reactions of α-acyl-α-(3,5-dimethoxyphenyl)acetonitrile (VII) with acetamide gave 6-alkyl-5-(3,5-dimethoxyphenyl)-2-methyl-4(3H)-pyrimidinone (VIII) which were converted to 4-chloro derivatives (X) with $POCl_3$. Treatment of 3,5-dimethoxybenzyl alkyl ketones (XI) with acetamide gave 3-alkyl-1-methylisoquinolines (XII) and analogous reaction of 3,4-methylenedioxyphenylacetone (XIV) gave naphthalene derivative (XV) (Chart 2).

Keywords——benzyl ketones; formamide; acetamide; pyrimidines; isoquinolines; 1,3,10-triazaphenanthrene; modified Vilsmeier reaction; Bischler-Napieralski reaction

In the previous paper,[3] it was reported that the reactions of α-acylphenylacetonitriles with formamide in the presence of phosphoryl chloride (called the modified Vilsmeier reaction) gave 3-substituted 4-isoquinolinecarbonitriles or 6-substituted 4-amino-5-arylpyrimidines for a variety of substituents at phenyl group. In order to investigate the limitation between isoquinoline and pyrimidine formation, the modified Vilsmeier reaction of α-acyl-*m*-chlorophenylacetonitriles (IIa, b, c) were carried out.

As shown in Chart 1, α-formyl-(IIa), α-acetyl- (IIb), and α-benzoyl- (IIc) *m*-chlorophenylacetonitriles, which were synthesized by ester condensation of *m*-chlorophenylacetonitrile (I) and respective esters in the presence of sodium ethoxide, were used as starting materials.

To the cold formamide solutions of these acyl derivatives were added phosphoryl chloride dropwise under cooling with stirring and then the mixtures were heated at 120—140°. The modified Vilsmeier reaction of IIa and IIb afforded respective enamines (IIIa and IIIb) and 4-amino-5-(*m*-chlorophenyl)pyrimidines (IVa and IVb). But same reaction of IIc afforded only IIIc. These enamines IIIa, IIIb, and IIIc, intermediates[3] of pyrimidine formation, were attempted to similar reaction and expectedly afforded respective pyrimidines IVa, IVb, and IVc.

Davies and Piggott[4] reported that the reaction of α-acetylphenylacetonitrile with formamide under dry ammonia stream at 180° gave 4-amino-5-phenylpyrimidine without isola-

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[1] Part XV: T. Hirota, T. Koyama, T. Nanba, and M. Yamato, *Chem. Pharm. Bull.* (Tokyo), **25**, 2838 (1977).

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[3] *a*) T. Koyama, T. Hirota, I. Itoh, M. Toda, and M. Yamato, *Tetrahedron Lett.*, **1968**, 4631; *b*) T. Koyama, T. Hirota, M. Toda, K. Iwai, M. Minami, and M. Yamato, *Yakugaku Zasshi*, **89**, 1334 (1969); *c*) T. Koyama, M. Toda, T. Hirota, M. Hashimoto, and M. Yamato, *Yakugaku Zasshi*, **89**, 1688 (1969); *d*) T. Koyama, M. Toda, T. Hirota, and M. Yamato, *Yakugaku Zasshi*, **90**, 8 (1970); *e*) T. Koyama, T. Hirota, T. Matsumura, and M. Yamato, *Yakugaku Zasshi*, **92**, 1233 (1972).

[4] W.H. Davies and H.A. Piggott, *J. Chem. Soc.*, **1945**, 347.

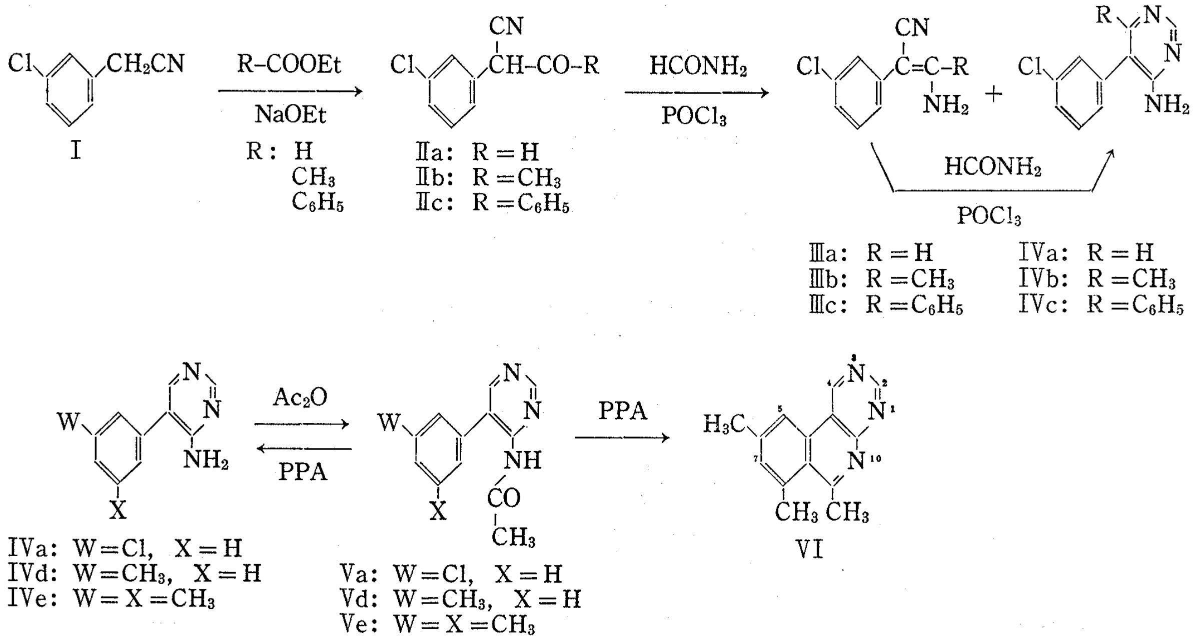

Chart 1

tion of 4-amino-6-methyl-5-phenylpyrimidine. They described the pyrimidine formation as the condensation of phenylacetonitrile, formed by elimination of α-acetyl group, with formamide. In our reaction conditions, however, 6-substituted pyrimidines were obtained without elimination of α-acyl groups as described in earlier reports.[3b–e)]

As described in our earlier reports,[5)] 4-amino-5-arylpyrimidines are convenient materials for synthesis of 1,3,10-triazaphenanthrenes. As shown in Chart 1, acetylation of IVa with acetic anhydride gave acetamido derivative (Va). The Bischler-Napieralski reaction of Va with polyphosphoric acid (PPA) did not afforded 1,3,10-triazaphenanthrene but deacetylation was resulted. Similarly, acetylation of 4-amino-5-(*m*-methylphenyl)pyrimidine (IVd) and 4-amino-5-(3,5-dimethylphenyl)pyrimidine (IVe), which were already reported in our laboratory,[3e)] gave respective acetamido derivatives (Vd, Ve). When the Bischler-Napieralski reaction of Vd was carried out with PPA, deacetylated IVd was only obtained. However, same reaction of Ve with PPA afforded 6,8,9-trimethyl-1,3,10-triazaphenanthrene (VI) with small amount of IVe. The proton magnetic resonance (PMR) spectrum of VI exhibited two one-proton singlets at δ 9.94 and 9.42 attributable to C-4 and C-2, two one-proton broad singlets at δ 8.32 and 7.35 for C-5 and C-7 (each lower field shift of C-4 and C-5 protons was due to the anisotropic effect[6)] of benzene or pyrimidine ring), and methyl groups at δ 3.22, 2.95, and 2.57. Moreover the similarity of the ultraviolet (UV) spectra of VI and 6,8-dimethyl-1,3,10-triazaphenanthrene, reported in our laboratory,[5b)] supported the structure of VI as 1,3,10-triazaphenanthrene skeleton.

On the basis of the previous papers[3)] and the above results, the authors were interested in carrying out the modified Vilsmeier reaction of α-acylphenylacetonitriles with acetamide in stead of formamide.

As shown in Chart 2, the modified Vilsmeier reaction of α-acetyl- (VIIa) and α-propionyl- (VIIb) 3,5-dimethoxyphenylacetonitriles, which were favorable for isoquinoline cyclization, was carried out with acetamide and phosphoryl chloride. However, 6-alkyl-5-(3,5-dimethoxyphenyl)-2-methyl-4-pyrimidones (VIIIa, b) were obtained without any isoquinoline deriva-

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5) *a*) T. Koyama, T. Hirota, M. Yamato, and N. Ohta, *Yakugaku Zasshi*, **93**, 330 (1973); *b*) T. Koyama, T. Hirota, Y. Shinohara, S. Fukuoka, M. Yamato, and S. Ohmori, *Chem. Pharm. Bull.* (Tokyo), 23, 494 (1975).

6) H.H. Perkampus, T. Bluhm, and J.V. Knop, *Z. Naturforsch.*, **27a**, 310 (1972).

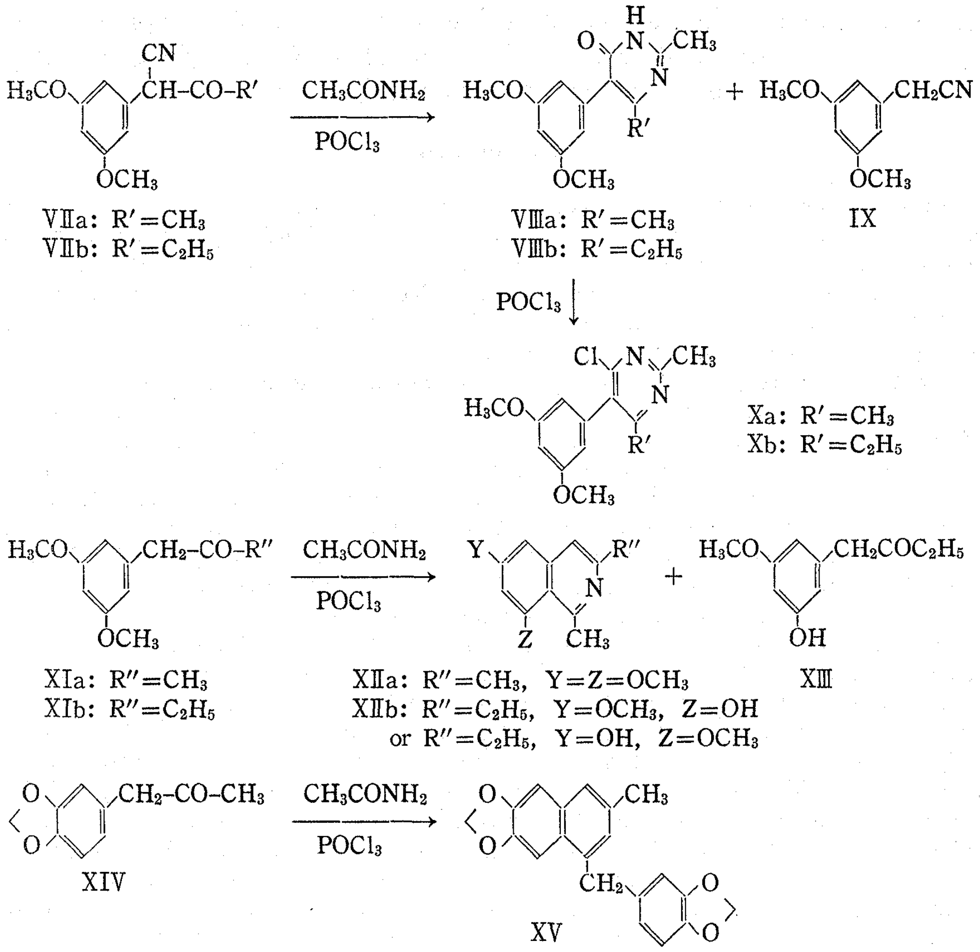

Chart 2

tives. The infrared (IR) spectrum of VIIIb showed C=O band at 1645 cm^{-1} and its PMR spectrum exhibited ethyl group at δ 1.15 (3H) and 2.50 (2H) as three-four pattern, methyl signal at δ 2.40 as singlet, methoxyl groups at δ 3.75 as singlet, phenyl protons at δ 6.40 as broad singlet, and D_2O exchangeable NH proton at δ 12.0—13.1 as broad absorption. VIIIa had also similar data in IR and PMR spectra. Treatment of these pyrimidones with refluxing phosphoryl chloride afforded 4-chloropyrimidines (Xa, b).

As pyrimidone (VIII) formation was due to β-ketonitrile structure of VII, the same reaction of benzyl ketones without cyano group were attempted to carried out, As shown in chart 2, the modified Vilsmeier reaction of 3,5-dimethoxyphenylacetone (XIa) with acetamide afforded expectedly 6,8-dimethoxy-1,3-dimethylisoquinoline (XIIa), but the similar reaction of ethyl derivative (XIb) gave 3-ethyl-6 (or 8) -hydroxy-8 (or 6)-methoxy-1-methylisoquinoline (XIIb) which was interpreted as demethylation by hydrogen chloride formed during the reaction. The analogous reaction of 3,4-methylenedioxyphenylacetone (XIV) afforded 3-methyl-6,7-methylenedioxy-1-(3,4-methylenedioxybenzyl)naphthalene (XV), which was similar to formation of 2,3-methylenedioxy-6-(3,4-methylenedioxyphenyl)naphthalene by treatment of homopiperonal with formamide in the presecne of phosphoryl chloride in our laboratory[7] or with acetic acid in the presence of hydrochloric acid by Entmann and Robinson.[8]

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7) T. Koyama, M. Toda, T. Hirota, Y. Katsuse, and M. Yamato, *Yakugaku Zasshi*, **90**, 11 (1970).

8) H. Entmann and R. Robinson, *J. Chem. Soc.*, **1933**, 1530.

Analogous isoquinoline formations by using acetamide and phosphoryl chloride were reported by Kametani[9] and Tamayo, *et al.*[10] with safrol, O-methyleugenol, isosafrol, and O-methylisoeugenol. But they obtained 3,4-dihydroisoquinolines.

Experimental

Melting points are uncorrected. IR spectra were recorded on a Nippon Bunko DS-301 or DS-403 spectrometer in KBr disk. Mass spectra were taken on a Hitachi RMU-7M spectrometer or Japan Electron Optics Laboratory OL-SG spectrometer. UV spectra were taken on a Hitachi EPS-2 spectrophotometer in 99% EtOH. PMR spectra were taken on a Japan Electron Optics Laboratory C-60-H (60 MHz) or Hitachi R-22 (90 MHz) spectrometer with tetramethylsilane as an internal standard (δ value), s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; b, broad.

The Modified Vilsmeier Reaction of α-Formyl-α-(*m*-chlorophenyl)acetonitrile (IIa)——To 1.4 g of IIa in 20 ml of $HCONH_2$ was added dropwise 1.5 ml of $POCl_3$ under cooling, and the mixture was heated at 120° for 8 hr. After cooled, the reaction mixture was poured into H_2O, made basic with Na_2CO_3, and extracted with $CHCl_3$. The $CHCl_3$ layer was washed with H_2O, dried over Na_2SO_4, and evaporated. The residue was chromatographed over alumina with benzene. After evaporation of the benzene eluate, the residue was recrystallized from benzene–cyclohexane (*ca.* 2: 1) to give 0.32 g (23%) of β-amino-α-(*m*-chlorophenyl)-acrylonitrile (IIIa) as pale yellow needles, mp 118—119°. *Anal.* Calcd. for $C_9H_7ClN_2$: C, 60.50; H, 3.92; N, 15.69. Found: C, 60.25; H, 3.82; N, 15.91. IR $\nu_{\max}^{\text{KBr}}$ cm^{-1}: 3430, 3335, 3170, and 1650 (N–H), 2218 (C≡N). Recrystallization of the residue of the ether eluate from benzene gave 0.11 g (6.5%) of 4-amino-5-(*m*-chlorophenyl)pyrimidine (IVa) as colorless needles, mp 121—122°. *Anal.* Calcd. for $C_{10}H_8ClN_3$: C, 58.39; H, 3.89; N, 20.44. Found: C, 58.62; H, 3.77; N, 20.40. IR $\nu_{\max}^{\text{KBr}}$ cm^{-1}: 3350, 3180, and 1645 (N–H). PMR ($CDCl_3$): 5.32 (2H, b, NH_2, D_2O exchange), 7.31 (4H, m, phenyl-H), 8.19, 8.49 (each 1H, s, pyrimidine-H).

The Modified Vilsmeier Reaction of IIIa——To 1.0 g of IIIa in 10 ml of $HCONH_2$ was added dropwise 1.0 ml of $POCl_3$, and the mixture was heated at 130—140° for 8 hr. The reaction mixture was worked up as described above. The residue was recrystallized from benzene to give 0.21 g (18.3%) of IVa as colorless needles, mp 121—122°, identical with the above pyrimidine (mixed mp, IR, and PMR).

The Modified Vilsmeier Reaction of α-Acetyl-α-(*m*-chlorophenyl)acetonitrile (IIb)——To 1.9 g of IIb in 20 ml of $HCONH_2$ was added dropwise 1.9 g of $POCl_3$, and the mixture was heated at 120° for 5 hr. The reaction mixture was worked up as usual and the residue was chromatographed over alumina with benzene and then ether. After evaporation of the benzene eluate, the residue was recrystallized from benzene–cyclohexane (*ca.* 1: 1) to give 0.31 g (16%) of β-amino-α-(*m*-chlorophenyl)crotononitrile (IIIb) as pale yellow needles, mp 120—121°. *Anal.* Calcd. for $C_{10}H_9ClN_2$: C, 62.34; H, 4.68; N, 14.55. Found: C, 62.41; H, 4.60; N, 14.79. IR $\nu_{\max}^{\text{KBr}}$ cm^{-1}: 3455, 3320, 3215, and 1642 (N–H), 2218 (C≡N). PMR ($CDCl_3$): 2.75 (3H, s, CH_3), 4.80 (2H, b, NH_2, D_2O exchange), 7.29 (4H, m, phenyl-H). After evaporation of the ether eluate, the residue was recrystallized from benzene–cyclohexane to give 0.21 g (9.5%) of 4-amino-5-(*m*-chlorophenyl)-6-methylpyrimidine (IVb) as pale yellow needles, mp 180—181.5°. *Anal.* Calcd. for $C_{11}H_{10}ClN_3$: C, 60.14; H, 4.56; N, 19.13. Found: C, 60.37; H, 4.60; N, 19.18. IR $\nu_{\max}^{\text{KBr}}$ cm^{-1}: 3310, 3120, and 1630 (N–H). PMR ($CDCl_3$): 2.17 (3H, s, CH_3), 5.16 (2H, b, NH_2, D_2O exchange), 7.30 (4H, m, phenyl-H), 8.46 (1H, s, pyrimidine-H).

The Modified Vilsmeier Reaction of IIIb——To 0.6 g of IIIb in 10 ml of $HCONH_2$ was added dropwise 1 ml of $POCl_3$, and the mixture was heated at 130—140° for 7 hr. The reaction mixture was treated as usual. The residue was recrystallized from benzene–cyclohexane to give 0.30 g (44%) of IVb as pale yellow needles, mp 180—181.5°, identical with the above pyrimidine (mixed mp, IR, and PMR).

The Modified Vilsmeier Reaction of α-Benzoyl-α-(*m*-chlorophenyl)acetonitrile (IIc)——To 1.9 g of IIc in 20 ml of $HCONH_2$ was added dropwise 1.9 ml of $POCl_3$, and the mixture was heated at 120° for 8 hr. The reaction mixture was treated as usual and the residue was recrystallized from benzene–cyclohexane to give 0.75 g (30%) of β-amino-α-(*m*-chlorophenyl)cinnamonitrile (IIIc) as pale yellow needles, mp 118—119.5°. *Anal.* Calcd. for $C_{15}H_{11}ClN_2$: C, 70.73; H, 4.32; N, 11.00. Found: C, 70.81; H, 4.11; N, 11.12. IR $\nu_{\max}^{\text{KBr}}$ cm^{-1}: 3450, 3330, 3230, and 1626 (N–H), 2220 (C≡N). PMR ($CDCl_3$): 5.05 (2H, b, NH_2, D_2O exchange), 7.31 (9H, m, phenyl-H).

The Modified Vilsmeier Reaction of IIIc——To 1.4 g of IIIc in 15 ml of $HCONH_2$ was added 1.2 ml of $POCl_3$ and the mixture was heated at 130—140° for 12 hr. The reaction mixture was treated as usual and the residue was recrystallized from benzene to give 0.48 g (30.5%) of 4-amino-5-(*m*-chlorophenyl)-6-phenylpyrimidine (IVc) as colorless needles, mp 201—202°. *Anal.* Calcd. for $C_{16}H_{12}ClN_3$: C, 68.21; H, 4.26; N, 14.92. Found: C, 68.01; H, 4.04; N, 14.71. IR $\nu_{\max}^{\text{KBr}}$ cm^{-1}: 3470, 3285, and 1631 (N–H). PMR (acetone-d_6): 5.67 (2H, b, NH_2, D_2O exchange), 7.10 (9H, m, phenyl-H), 8.42 (1H, s, pyrimidine-H).

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9) T. Kametani, *Yakugaku Zasshi*, **72**, 1090, 1537 (1952).

10) M.L. Tamayo, R.M. Pelaez, and E.S. Alvarenz, *Anales Real Soc. Espan. Fis. Quim.* (Madrid), **51B**, 276 (1955).

Acetylation of IVa with Ac_2O——A mixture of 2.05 g of IVa, 15 ml of Ac_2O, and 0.5 ml of conc. H_2SO_4 was refluxed for 5 hr and then poured into H_2O. The resulting solution was neutralized with dil. NaOH and extracted with $CHCl_3$. After drying and removal of solvent, a solid was obtained which after recrystallization from benzene gave 4-acetamido-5-(*m*-chlorophenyl)pyrimidine (Va) as pale yellow needles, mp 141—142°, yield 1.40 g (56%). *Anal.* Calcd. for $C_{12}H_{10}ClN_3O$: C, 58.18; H, 4.04; N, 16.97. Found: C, 58.29; H, 4.11; N, 16.80. IR ν_{max}^{KBr} cm^{-1}: 3360 (N–H), 1680 (C=O).

Reaction of Va with PPA——A mixture of 0.5 g of Va and 10 g of PPA was heated at 130—140° for 10 hr with stirring. After the addition of H_2O to the reaction mixture, the resulting solution was made basic with Na_2CO_3, then extracted with $CHCl_3$. The $CHCl_3$ layer was washed with H_2O, dried over Na_2SO_4, and evaporated. The residue was recrystallized from benzene–cyclohexane to give 0.31 g (75%) of IVa as colorless needles, mp 121—122°, identical with the above starting material IVa (mixed mp and IR).

Acetylation of 4-Amino-5-(*m*-methylphenyl)pyrimidine (IVd)[3e] with Ac_2O——A mixture of 2.0 g of IVd, 15 ml of Ac_2O, and 0.5 ml of conc. H_2SO_4 was refluxed for 6 hr. The resulting solution was neutralized with dil. NaOH, then extracted with $CHCl_3$. After drying (Na_2SO_4) and removal of solvent, a solid was obtained which after recrystallization from benzene–cyclohexane gave 4-acetamido-5-(*m*-methylphenyl)-pyrimidine (Vd) as pale yellow needles, mp 135—136°, yield 0.98 g (40%). *Anal.* Calcd. for $C_{13}H_{13}N_3O$: C, 68.70; H, 5.77; N, 18.49. Found: C, 68.81; H, 5.70; N, 18.60. IR ν_{max}^{KBr} cm^{-1}: 1675 (C=O), 3370 (N–H).

Reaction of Vd with PPA——A mixture of 0.45 g of Vd and 10 g of PPA was heated at 140—150° for 15 hr with stirring. The reaction mixture was treated as described in Va. The residue was recrystallized from benzene–cyclohexane to give 0.29 g (80%) of IVd as pale yellow needles, mp and mixed mp 117—118°.

Acetylation of 4-Amino-5-(3,5-dimethylphenyl)pyrimidine (IVe)[3e] with Ac_2O——A mixture of 2.0 g of IVe, 7 ml of Ac_2O, and 14 ml of AcOH was refluxed for 4 hr. The reaction mixture was treated as described in IVa. The residue was recrystallized from benzene to give 2.05 g (84.7%) of 4-acetamido-5-(3,5-dimethylphenyl)pyrimidine (Ve) as pale yellow needles, mp 156—157°. *Anal.* Calcd. for $C_{14}H_{15}N_3O$: C, 69.69; H, 6.27; N, 17.42. Found: C, 69.82; H, 6.35; N, 17.30. IR ν_{max}^{KBr} cm^{-1}: 1679 (C=O), 3378 (N–H).

Reaction of Ve with PPA——A mixture of 1.0 g of Ve and 20 g of PPA was heated at 140° for 14 hr with stirring. The reaction mixture was treated as described in Va. Recrystallization of the residue from EtOH gave 0.35 g (37.6%) of 6,8,9-trimethyl-1,3,10-triazaphenanthrene (VI) as pale yellow needles, mp 178—180°. *Anal.* Calcd. for $C_{14}H_{13}N_3$: C, 75.31; H, 5.87; N, 18.82. Found: C, 75.10; H, 5.93; N, 18.71. MS *m/e*: 223 (M^+). The PMR spectrum data of VI is shown in the text. UV λ_{max}^{EtOH} nm (log ε): 270 (4.41), 303 (3.91), 337 (3.80), 353 (3.81). The mother EtOH solution was evaporated to dryness. Repeated recrystallization of the residue from benzene–cyclohexane gave 0.05 g (6%) of IVe as pale yellow needles, mp 126—128°, identical with the above starting material IVe.

Reaction of α-Acetyl-α-(3,5-dimethoxyphenyl)acetonitrile (VIIa) with CH_3CONH_2——A mixture of 2.2 g of VIIa, 10 g of CH_3CONH_2, and 3.5 g of $POCl_3$ was heated at 160—170° for 8 hr with stirring. After cooled, *ca.* 10-fold of H_2O was added to the reaction mixture and the resulting solution was extracted with ether. The H_2O layer was made basic with Na_2CO_3, then extracted with $CHCl_3$. Each extract was washed with H_2O, dried over Na_2SO_4, and evaporated, independently. The former ether extract was chromatographed over alumina with benzene. After evaporation of the benzene eluate, the residue was recrystallized from cyclohexane gave 0.11 g (6.1%) of 3,5-dimethoxyphenylacetonitrile (IX) as colorless needles, mp 53°, identical with the authentic sample (mixed mp and IR). The latter $CHCl_3$ was evaporated to dryness and the residue was recrystallized from benzene to give 1.28 g (58%) of 5-(3,5-dimethoxyphenyl)-2,6-dimethyl-4(3H)-pyrimidinone (VIIIa) as colorless needles, mp 192—193°. *Anal.* Calcd. for $C_{14}H_{16}N_2O_3$: C, 64.60; H, 6.20; N, 10.76. Found: C, 64.84; H, 6.32; N, 10.61. MS *m/e*: 260 (M^+). IR ν_{max}^{KBr} cm^{-1}: 1649 (C=O). PMR ($CDCl_3$): 2.18, 2.33 (each 3H, s, 2-CH_3), 3.73 (6H, s, 2-OCH_3), 6.35 (3H, br. s, phenyl-H), 11.9—13.1 (1H, b, NH, D_2O exchange).

Reaction of α-Propionyl-α-(3,5-dimethoxyphenyl)acetonitrile (VIIb) with CH_3CONH_2——A mixture of 1.2 g of VIIb, 5.0 g of CH_3CONH_2, and 2.0 g of $POCl_3$ was heated at 160—170° for 8 hr with stirring. The reaction mixture was treated as described in VIIa. The ether extract from acidic medium was chromatographed over alumina with benzene. After evaporation of the benzene eluate, the residue was recrystallized from cyclohexane to give 0.08 g (9%) of IX as colorless needles, mp 53°, identical with the above nitrile IX. After evaporation of the $CHCl_3$ extract from Na_2CO_3 basic medium was recrystallized from benzene to give 0.63 g (45%) of 6-ethyl-5-(3,5-dimethoxyphenyl)-2-methyl-4(3H)-pyrimidinone (VIIIb) as colorless needles, mp 199—201°. *Anal.* Calcd. for $C_{15}H_{18}N_2O_3$: C, 65.67; H, 6.61; N, 10.21. Found: C, 65.87; H, 6.80; N, 10.17. MS *m/e*: 274.130 (Calcd. for $C_{15}H_{18}N_2O_3$: 274.132). The IR and PMR data of VIIIb are shown in the text.

Reaction of VIIIa with $POCl_3$——A mixture of 0.26 g of VIIIa and 2.0 g of $POCl_3$ was heated at 120° for 1 hr. The resulting solution was poured into H_2O, made basic with Na_2CO_3, and extracted with $CHCl_3$. The $CHCl_3$ layer was washed with H_2O, dried over Na_2SO_4, and evaporated. The residue was recrystallized from benzene-cyclohexane to give 0.20 g (71%) of 4-chloro-5-(3,5-dimethoxyphenyl)-2,6-dimethylpyrimidine (Xa) as pale yellow needles, mp 127—128°. *Anal.* Calcd. for $C_{14}H_{15}ClN_2O_2$: C, 60.32; H, 5.39; N, 10.05. Found: C, 60.58; H, 5.50; N, 9.80. Beilstein test: positive.

Reaction of VIIIb with $POCl_3$——A mixture of 0.27 g of VIIIb and 2.0 g of $POCl_3$ was heated at 120° for 1 hr. The resulting solution was treated as described in VIIIa. Recrystallization of the residue from benzene–cyclohexane gave 0.17 g (59%) of 4-chloro-6-ethyl-5-(3,5-dimethoxyphenyl)-2-methylpyrimidine (Xb) as pale yellow needles, mp 132—133°. *Anal.* Calcd. for $C_{15}H_{17}ClN_2O_2$: C, 61.54; H, 5.81; N, 9.57. Found: C, 61.80; H, 5.71; N, 9.38. Beilstein test: positive.

Reaction of 3,5-Dimethoxyphenylacetone (XIa) with CH_3CONH_2——A mixture of 1.9 g of XIa, 7.0 g of CH_3CONH_2, and 3.0 g of $POCl_3$ was heated at 140—150° for 6 hr with stirring. The reaction mixture was treated as described in VIIa. The ether extract from acidic medium was chromatographed over alumina with benzene and then ether. The benzene eluate gave 0.23 g (12%) of unchanged XIa, identified by the IR and PMR spectra. After evaporation of the ether eluate, the residue was recrystallized from cyclohexane to give 0.05 g of 1,3-dimethyl-6,8-dimethoxyisoquinoline (XIIa) as colorless needles, mp 91°. The $CHCl_3$ extract from Na_2CO_3 basic medium was recrystallized from cyclohexane to give 0.12 g of XIIa as colorless needles, mp 91°, overall yield 0.17 g (9%). *Anal.* Calcd. for $C_{13}H_{15}NO_2$: C, 71.86; H, 6.96; N, 6.45. Found: C, 71.58; H, 7.12; N, 6.23. MS *m/e*: 217.112 (Calcd. for $C_{13}H_{15}NO_2$: 217.110). PMR ($CDCl_3$): 2.55, 2.97 (each 3H, s, 2-CH_3), 3.85, 3.88 (each 3H, s, 2-OCH_3), 6.40, 6.49 (each 1H, AB q, $J=2$ Hz, 5-H, 7-H), 7.09 (1H, s, 4-H).

Reaction of 1-(3,5-Dimethoxyphenyl)-2-butanone (XIb) with CH_3CONH_2——A mixture of 1.1 g of XIb, 5 g of CH_3CONH_2, and 5 g of $POCl_3$ was heated at 150—160° for 8 hr with stirring. After the addition of H_2O to the reaction mixture, the resulting solution was extracted with ether followed by $CHCl_3$. The H_2O layer was made basic with Na_2CO_3, then extracted with $CHCl_3$. Each extract was washed with H_2O, dried over Na_2SO_4, and evaporated, independently. The ether extract was chromatographed over alumina with benzene. After elution of benzene, ether and $CHCl_3$, the MeOH eluate was subjected to high vacuum distillation with long test tube (*ca.* 40 cm) to give 0.08 g (8%) of 1-(3-hydroxy-5-methoxyphenyl)-2-butanone (XIII), bp 105—108°/below 0.5 mmHg. *Anal.* Calcd. for $C_{11}H_{14}O_3$: C, 68.02; H, 7.27. Found: C, 68.30; H, 7.02. MS *m/e*: 194 (M^+). IR ν_{max}^{KBr} cm^{-1}: 3380 (O–H), 1720 (C=O). The residues of the $CHCl_3$ extracts from acidic and basic medium (same spots on TLC) was recrystallized from AcOEt to give 0.08 g (7%) of 3-ethyl-6(or 8)-hydroxy-8(or 6)-methoxy-1-methylisoquinoline (XIIb) as pale yellow needles, mp 201—204°. *Anal.* Calcd. for $C_{13}H_{15}NO_2$: C, 71.86; H, 6.96; N, 6.45. Found: C, 71.59; H, 6.93; N, 6.12. MS *m/e*: 217 (M^+). IR ν_{max}^{KBr} cm^{-1}: ~2500 (O–H). PMR (acetone-d_6 with few drops of CF_3COOD): 1.40 (3H, t, $J=7$ Hz, $CH_2C\underline{H}_3$), 3.07 (2H, q, $J=7$ Hz, $C\underline{H}_2CH_3$), 3.25 (3H, s, CH_3), 3.95 (3H, s, OCH_3), 6.70, 6.78 (each 1H, AB q, $J=2$ Hz, 5-H, 7-H), 7.50 (1H, s, 4-H).

Reaction of 3,4-Methylenedioxyphenylacetone (XIV) with CH_3CONH_2——A mixture of 1.0 g of XIV, 5.0 g of CH_3CONH_2, and 2.0 g of $POCl_3$ was heated at 140—150° for 6 hr with stirring. The reaction mixture was treated as described in VIIa. The ether extract from acidic medium was chromatographed over alumina. After elution of benzene and ether, the residue of the $CHCl_3$ eluate was recrystallized from EtOH to give 0.81 g (45%) of 3-methyl-6,7-methylenedioxy-1-(3,4-methylenedioxybenzyl)naphthalene (XV) as colorless needles, mp 105—106°. *Anal.* Calcd. for $C_{20}H_{16}O_4$: C, 74.99; H, 5.03. Found: C, 74.80; H, 5.14. MS *m/e*: 320 (M^+). PMR ($CDCl_3$): 2.45 (3H, s, CH_3), 4.18 (2H, s, CH_2), 5.78, 5.95 (each 2H, s, 2-OCH_2O), 6.64 (3H, br. s, piperonyl-H), 6.99 (2H, br. s, 5-H, 8-H), 7.20, 7.29 (each 1H, br. s, 2-H, 4-H).

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