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Studies on Pyrimidine Derivatives. XIII.[1] Reaction of 4-Alkoxypyrimidine 1-Oxides with Phenyl Isocyanate and Phenyl Isothiocyanate

Hiroshi Yamanaka, Setsuko Niitsuma, and Takao Sakamoto

Pharmaceutical Institute, Tohoku University[2]

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Like pyridine 1-oxide, 4-ethyl-6-methylpyrimidine 1-oxide reacts with phenyl isocyanate; the products in the latter case are 2-anilino-4-ethoxy-6-methylpyrimidine and 1,3-diphenyl-1-(4-ethoxy-6-methyl-2-pyrimidinyl)urea. In contrast to this reaction, phenyl isothiocyanate transformed the same N-oxide into 7-methyl-3-phenyl-2,3-dihydrooxazolo[4,5-*d*]pyrimidine-2-thione.

Keywords——pyrimidine 1-oxides; 1,3-dipolar cycloaddition; sigmatropic rearrangement; 2-anilinopyrimidines; 1,3-diphenyl-1-(2-pyrimidinyl)ureas; 7-methyl-3-phenyl-2,3-dihydrooxazolo[4,5-*d*]pyrimidine-2-thione

Many reports[3–7] have been published on 1,3-dipolar cycloaddition between aromatic amine N-oxides and dipolarophiles. A typical example is the reaction of pyridine 1-oxide with phenyl isocyanate to give 2-anilinopyridine.[3] In our preceding paper[1] 4,6-disubstituted pyrimidine 1-oxides were reported to react with dimethyl acetylenedicarboxylate to give dimethyl α-oxo-α′-(4,6-disubstituted-2-pyrimidinyl)succinates as virtual products. In the present paper, we deal mainly with the formation of an unusual product, *via* sigmatropic rearrangement of a primary adduct formed from pyrimidine N-oxides and phenyl isothiocyanate.

First, the reaction of 4-ethoxy-6-methylpyrimidine 1-oxide (Ia) with phenyl isocyanate was investigated. A mixture of Ia and phenyl isocyanate was heated at 95—105° for 5 hr to give 1,3-diphenyl-1-(4-ethoxy-6-methyl-2-pyrimidinyl)urea (IIIa), mp 115.5°, together with 2-anilino-4-ethoxy-6-methylpyrimidine (IIa), mp 72—73°. The latter was identical with an authentic specimen prepared by the reaction of 2-anilino-4-chloro-6-methylpyrimidine[8] with sodium ethoxide.

The infrared (IR) spectrum (KBr) of IIIa exhibits a carbonyl absorption band at 1700 cm^{-1} and no band due to an N-oxide group is observed. The nuclear magnetic resonance (NMR) spectrum of IIIa indicates the presence of two phenyl groups at δ 7.00—7.80 (10H, m), a pyrimidine ring proton at δ 6.16 (1H, s), and an amide proton at δ 13.00—14.30 (1H, broad). These spectral data are consistent with the proposed structure. Furthermore, the treatment of IIa with phenyl isocyanate gave rise to IIIa in 60% yield. Accordingly, IIa is considered to be an intermediate in the formation of IIIa. The use of an equimolar amount of phenyl isocyanate with respect to Ia did not prevent the formation of IIIa as a contaminant of the main product IIa. Similar reactions of Ib—d with phenyl isocyanate proceeded analogously to give II and/or III.

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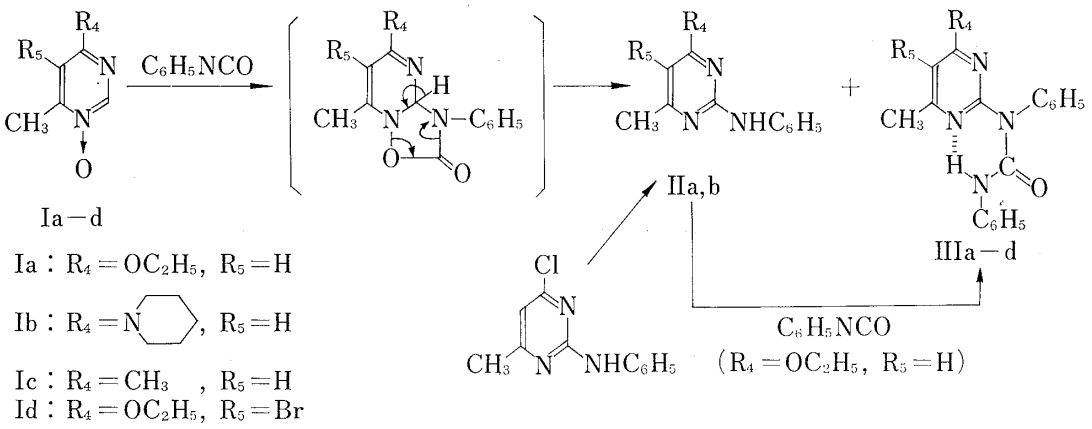

Chart 1

On the other hand, the reaction of Ia with phenyl isothiocyanate in chloroform at room temperature for 45 hr afforded an unexpected product (IVa), mp 145.5—147°, instead of IIa or the 2-thiourea derivative. The structure of this product was elucidated as follows. The empirical formula, $C_{12}H_9N_3OS$ was established by elemental analysis and mass spectrometry [m/e=243 (M^+)]. The IR spectrum ($CHCl_3$) of IVa shows absorption bands at 1650 and 1120 cm^{-1} due to a carbon-nitrogen double bond and a thiocarbonyl group, respectively. The NMR spectrum ($CDCl_3$) of IVa shows a signal at δ 8.68 (1H, s) which could be assigned to the proton located at the 2-position of a pyrimidine ring. However, no signal corresponding to the proton of the 5-position of a pyrimidine ring was observed. On hydrolysis with ethanolic potassium hydroxide, IVa was transformed into 4-anilino-5-hydroxy-6-methylpyrimidine (V), mp 238—239° (dec.). The same compound was also obtained by means of

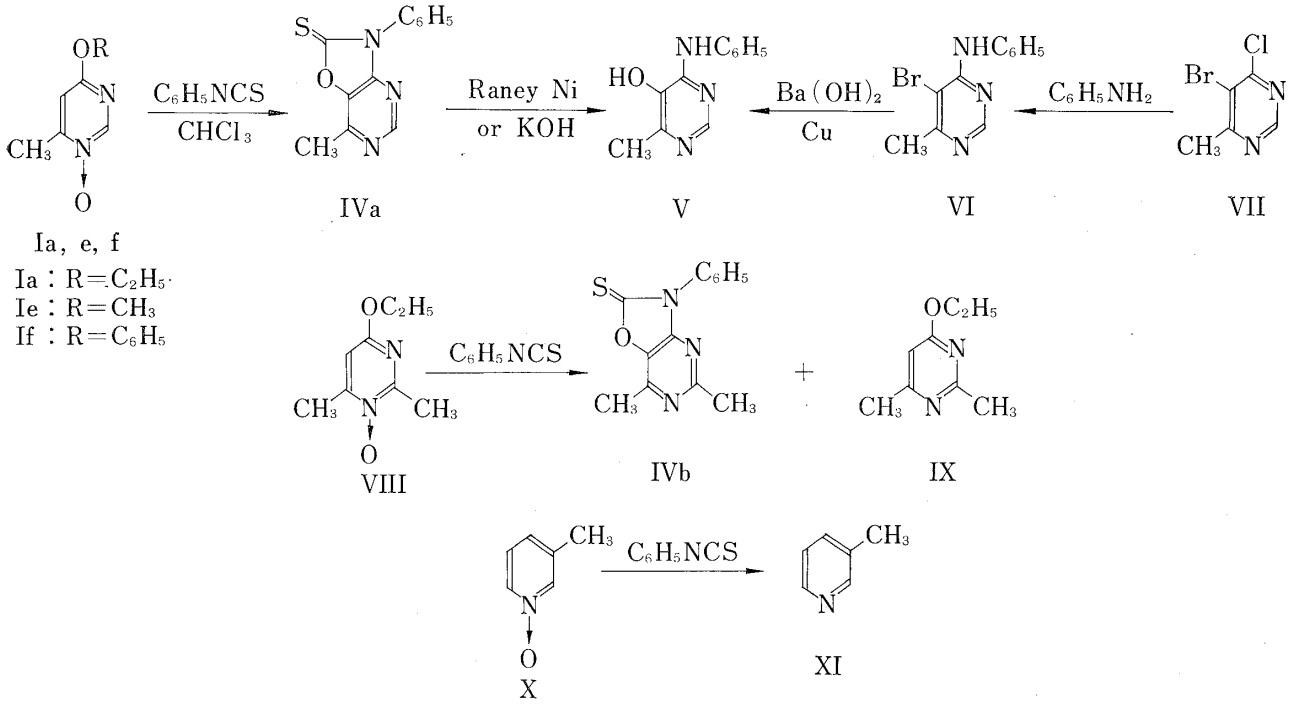

Chart 2

Raney nickel desulfurization of IVa. Using the method of Bray,[9] 4-anilino-5-bromo-6-methylpyrimidine (VI), derived from 4-chloro-5-bromo-6-methylpyrimidine (VII),[10] was heated with barium hydroxide in the presence of copper powder in a sealed tube at 185—190° for 10 hr to give 4-anilino-5-hydroxy-6-methylpyrimidine, which was identical with V. Based on these observations, the 7-methyl-3-phenyl-2,3-dihydrooxazolo[4,5-*d*]pyrimidine-2-thione structure was assigned to the product (IVa). The same product was also obtained from the reactions of 4-methoxy- and 4-phenoxy-6-methylpyrimidine 1-oxides (Ie, f) with phenyl isothiocyanate, clearly demonstrating replacement of the 4-alkoxyl groups by the reagent.

In order to obtain some information on the reaction pathway, the reaction of 4-ethoxy-2,6-dimethylpyrimidine 1-oxide (VIII) with phenyl isothiocyanate was carried out. Although the main product was 4-ethoxy-2,6-dimethylpyrimidine (IX), the methyl homolog of IVa, *i.e.* 5,7-dimethyl-3-phenyl-2,3-dihydrooxazolo[4,5-*d*]pyrimidine (IVb), was also isolated in 1.7 % yield. Similar deoxygenation in the reaction of 3-methylpyridine (XI) has been described by Hisano.[11]

A probable mechanism for these reaction[12] is illustrated in Chart 3, showing the formation of IX and IV from the same intermediate (XII). Namely, when the primary intermediate (XII) cyclizes between the carbon atom of the 2-position and the sulfur atom on the side chain, the oxathiazolidine intermediate (XIII) is the expected product. Subsequent elimination of phenyl isocyanate from XIII, accompanied by the liberation of sulfur may explain the formation of IX.

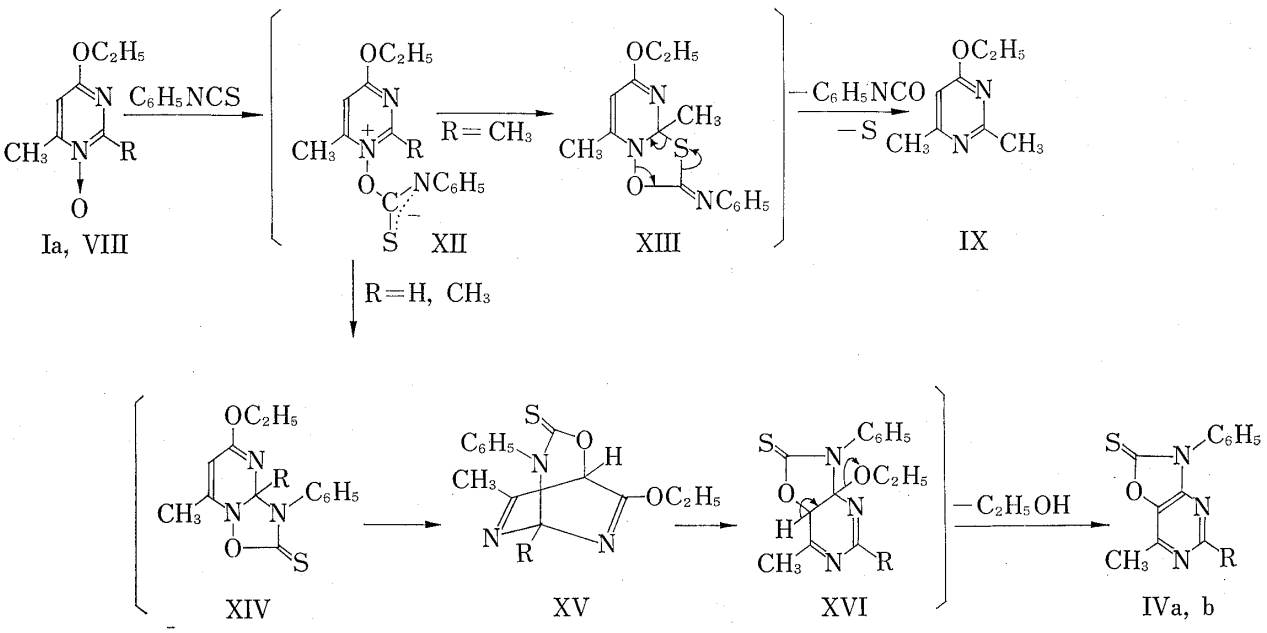

Chart 3

Alternatively, the oxadiazolidine intermediate (XIV) could arise from the primary intermediate (XII), if it cyclizes between the carbon atom and the nitrogen atom on the side chain. The reaction sequence leading to the final product (IV) from XIV may involve two 1,3-sigmatropic rearrangements *via* intermediates XV and XVI.

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12) The reaction mechanism reported preliminarily in Heterocycles requires revision along the lines presented in this paper [H. Yamanaka, S. Niitsuma, T. Sakamoto, and M. Mizugaki, *Heterocycles*, **5**, 255 (1976)].

Experimental[13]

Reaction of Ia—d with Phenyl Isocyanate——General Procedure: Phenyl isocyanate was added to a solution of Ia—d in $CHCl_3$, and the $CHCl_3$ was removed to give a residue, which was then heated at 95—105° for 5 hr. After cooling, the reaction mixture was passed through a column of Al_2O_3 using C_6H_6 as an eluent to give a mixture of two compounds. This crude product was recrystallized to yield IIIa—d, while the mother liquor gave II.

Reaction of Ia with Phenyl Isocyanate——Compounds IIa and IIIa (crude mixture, 0.68 g) were obtained from Ia (0.62 g, 0.004 mol), phenyl isocyanate (1.19 g, 0.01 mol), and $CHCl_3$ (10 ml) according to the general procedure.

IIa: Colorless prisms (petr. ether), mp 72—73°. Yield 115 mg (12%). *Anal.* Calcd. for $C_{13}H_{15}N_3O$: C, 68.10; H, 6.59; N, 18.33. Found: C, 68.14; H, 6.44; N, 18.36. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3440. NMR ($CDCl_3$) δ: 1.37 (3H, t, J=6.8 Hz), 2.30 (3H, s), 3.42 (2H, q, J=6.8 Hz), 6.01 (1H, s), 6.90—7.70 (6H, m). This compound was identical with an authentic sample of 2-anilino-4-ethoxy-6-methylpyrimidine, prepared from 2-anilino-4-chloro-6-methylpyrimidine, by mixed melting point test and comparison of spectral data.

IIIa: Colorless needles (ether), mp 115.5°. Yield 560 mg (40%). *Anal.* Calcd. for $C_{20}H_{20}N_4O_2$: C, 68.95; H, 5.79; N, 16.08. Found: C, 69.11; H, 5.75; N, 16.26. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1700. NMR ($CDCl_3$) δ: 1.02 (3H, t, J=6.8 Hz), 2.47 (3H, s), 3.83 (2H, q, J=6.8 Hz), 6.16 (1H, s), 7.00—7.80 (10H, m), 13.00—14.30 (1H, broad). This compound was identical with an authentic sample prepared from IIa and phenyl isocyanate.

Reaction of Ib with Phenyl Isocyanate——Compounds IIb and IIIb were obtained from Ib (480 mg, 0.0025 mol), phenyl isocyanate (714 mg, 0.006 mol), and $CHCl_3$ (7 ml) according to the general procedure.

IIb: Colorless prisms (ether–petr. ether), mp 135.5—137°. *Anal.* Calcd. for $C_{16}H_{20}N_4$: C, 71.61; H, 7.51; N, 20.88. Found: C, 71.38; H, 7.31; N, 20.87. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3445. NMR ($CDCl_3$) δ: 1.62 (6H, broad s), 2.23 (3H, s), 3.40—3.80 (4H, m), 5.90 (1H, s), 6.70—7.80 (6H, m). This compound was identical with an authentic sample of 2-anilino-6-methyl-4-piperidinopyrimidine prepared from 2-anilino-4-chloro-6-methylpyrimidine by mixed melting point test and comparison of spectral data.

IIIb: Colorless needles (ether), mp 130—132°. *Anal.* Calcd. for $C_{23}H_{25}N_5O$: C, 71.29; H, 6.50; N, 18.08. Found: C, 70.94; H, 6.31; N, 18.23. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1690. NMR ($CDCl_3$) δ: 1.15—1.80 (6H, m), 2.38 (3H, s), 3.08—3.40 (4H, m), 5.97 (1H, s), 6.80—7.80 (10H, m), 13.45 (1H, broad s).

Reaction of Ic with Phenyl Isocyanate——Compound IIIc was obtained from Ic (0.62 g, 0.005 mol), phenyl isocyanate (1.79 g, 0.015 mol), and $CHCl_3$ (6 ml) according to the general procedure. Colorless needles (acetone), mp 151—153°. *Anal.* Calcd. for $C_{19}H_{18}N_4O$: C, 71.67; H, 5.70; N, 17.60. Found: C, 71.32; H, 5.60; N, 17.96. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1700. NMR ($CDCl_3$) δ: 2.37 (6H, s), 6.63 (1H, s), 6.80—7.80 (10H, m), 12.50—13.20 (1H, broad).

Reaction of Id with Phenyl Isocyanate——Compound IIId was obtained from Id (0.58 g, 0.0025 mol), phenyl isocyanate (0.6 g, 0.005 mol), and $CHCl_3$ (5 ml) according to the general procedure. Colorless needles (petr. benzine), mp 113—113.5°. *Anal.* Calcd. for $C_{20}H_{19}BrN_4O_2$: C, 56.08; H, 4.48; Br, 18.66; N, 13.08. Found: C, 56.14; H, 4.40; Br, 18.40; N, 13.31. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1700. NMR ($CDCl_3$) δ: 1.05 (3H, t, J=7.1 Hz), 2.61 (3H, s), 3.89 (2H, q, J=7.1 Hz), 6.80—7.90 (10H, m), 12.72 (1H, broad s).

Reaction of IIa with Phenyl Isocyanate——Phenyl isocyanate (0.36 g, 0.003 mol) was added to a solution of IIa (0.69 g, 0.003 mol) in $CHCl_3$ (6 ml), and the $CHCl_3$ was removed to give a residue which was heated at 95—105° for 2 hr. After cooling, the resulting crystalline solid was recrystallized from ether to give IIIa. Colorless needles, mp 115.5—116°. Yield 0.62 g (60%).

2-Anilino-4-ethoxy-6-methylpyrimidine (IIa)——An ethanolic solution (11 ml) of 2-anilino-4-chloro-6-methylpyrimidine[8] (1.54 g, 0.007 mol) was added to an ice-cooled ethanolic solution of sodium ethoxide (prepared from 0.32 g (0.014 g atom) of metallic sodium and 6 ml of abs. EtOH) with stirring, and the mixture was refluxed for 2 hr. After removal of the EtOH, water was added to the residue, and the resulting oil was extracted with ether. The ether extract was dried and evaporated to give a colorless crystalline solid (IIa), which was recrystallized from petr. ether. Colorless prisms, mp 72—73°. Yield 1.40 g (88%).

2-Anilino-6-methyl-4-piperidinopyrimidine (IIb)——A mixture of 2-anilino-4-chloro-6-methylpyrimidine[8] (0.44 g, 0.002 mol) and piperidine (1.70 g, 0.02 mol) was refluxed for 2 hr. After removal of the excess piperidine under reduced pressure, the residue was dissolved in $CHCl_3$, washed with 1 N HCl, and dried over anhyd. K_2CO_3. The $CHCl_3$ was removed to give the crude product, which was recrystallized from ether–petr. ether. Pale brown prisms, mp 135—136°.

Reaction of Ia, e, f with Phenyl Isothiocyanate——General Procedure: A solution of Ia, e, f (1.0 equivalent) and phenyl isothiocyanate (1.0 equivalent) in $CHCl_3$ was allowed to stand at room temperature for 45 hr. The reaction mixture was diluted with $CHCl_3$, washed with 3 N HCl and with 3 N NaOH, then dried over

13) All melting points and boiling points are uncorrected. IR spectra were measured with a JASCO IRA-1 spectrometer and NMR spectra were taken at 60 MHz with a Hitachi-Perkin-Elmer spectrometer. Chemical shifts are expressed as δ (ppm) using tetramethylsilane (TMS) as an internal standard. The following abbreviations are used: s=singlet, t=triplet, q=quartet, and m=multiplet. Mass spectra (MS) were measured with a Hitachi RMU-7 spectrometer.

anhyd. K_2CO_3. After evaporation of the $CHCl_3$, the residue was purified by column chromatography (Al_2O_3–C_6H_6), followed by recrystallization from ether. IVa: colorless needles, mp 145.5—147°. *Anal.* Calcd. for $C_{12}H_9N_3OS$: C, 59.22; H, 3.73; N, 17.28; S, 13.19. Found: C, 59.58; H, 3.76; N, 17.83; S, 12.93. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1650, 1120. NMR ($CDCl_3$) δ: 2.68 (3H, s), 7.56 (5H, s), 8.68 (1H, s). MS *m/e*: 243 (M^+), 142, 77, 51.

Reaction of Ia with Phenyl Isothiocyanate——Compound IVa was obtained from Ia (920 mg, 0.006 mol), phenyl isothiocyanate (0.81 g, 0.006 mol), and $CHCl_3$ (2 ml) according to the general procedure. Yield 0.55 g (38%).

Reaction of Ie with Phenyl Isothiocyanate——Compound IVa was obtained from Ie (1.4 g, 0.01 mol), phenyl isothiocyanate (1.35 g, 0.01 mol), and $CHCl_3$ (5 ml) according to the general procedure. Yield 0.73 g (30%).

Reaction of If with Phenyl Isothiocyanate——Compound IVa was obtained from If (606 mg, 0.003 mol), phenyl isothiocyanate (405 mg, 0.003 mol), and $CHCl_3$ (1.5 ml) according to the general procedure. Yield 221 mg (30%).

Reaction of VIII with Phenyl Isothiocyanate——A solution of VIII (1.18 g, 0.007 mol) and phenyl isothiocyanate (0.95 g, 0.007 mol) in $CHCl_3$ (3 ml) was allowed to stand for 45 hr. The reaction mixture was diluted with $CHCl_3$, extracted with 3 N HCl and with 3 N NaOH, then dried over anhyd. K_2CO_3. The $CHCl_3$ was removed and the residue was passed through a column of Al_2O_3 using petr. ether–ether (2: 1) as an eluent. The crude product was recrystallized from ether to give colorless needles (IVb), mp 201—202°. Yield 30 mg (1.7%). *Anal.* Calcd. for $C_{13}H_{11}N_3OS$: C, 60.68; H, 4.31; N, 16.33; S, 12.46. Found: C, 60.79; H, 4.49; N, 16.38; S, 12.25. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1650, 1120. NMR ($CDCl_3$) δ: 2.67 (6H, s), 7.66 (5H, s). The 3 N HCl extract was neutralized with 3 N NaOH and extracted with $CHCl_3$. The $CHCl_3$ extract was dried and concentrated to give a residue, which was purified by column chromatography (Al_2O_3–ether) to yield a colorless liquid (IX), bp 98° (45 mmHg). Yield 351 mg (33%). This compound was identical with an authentic sample of 4-ethoxy-2,6-dimethylpyrimidine by comparison of spectral data.

4-Anilino-5-hydroxy-6-methylpyrimidine (V)——i) Raney Ni catalyst (prepared from 5 g of Ni–Al alloy powder) was added to a hot solution of IVa (1.46 g, 0.006 mol) in MeOH (35 ml), and the mixture was refluxed for 3 hr. After cooling, Raney Ni was filtered off and the filtrate was concentrated under reduced pressure. 3 N NaOH and $CHCl_3$ were added to the residue and insoluble material was removed by filtration. The $CHCl_3$ layer of the filtrate was extracted several times with 3 N NaOH, and the combined 3 N NaOH solution was neutralized with 6 N HCl. The crystals which separated were collected and recrystallized from MeOH to give colorless needles, mp 242—247° (dec.). Yield 534 mg (44%). *Anal.* Calcd. for $C_{11}H_{11}N_3O$: C, 65.67; H, 5.51; N, 20.88. Found: C, 65.63; H, 5.39; N, 20.98. IR ν_{max}^{KBr} cm^{-1}: 3335, 3280, 2800—2200. NMR (CF_3COOH) δ: 2.66 (3H, s), 7.47 (5H, s), 8.50 (1H, s). This compound was identical with an authentic sample of 4-anilino-5-hydroxy-6-methylpyrimidine, obtained by method iii), by comparison of spectral data. Methyl ether (prepared from V and CH_2N_2 in ether): colorless needles (ether–petr. ether), mp 140—142°. *Anal.* Calcd. for $C_{12}H_{13}N_3O$: C, 66.95; H, 6.09; N, 19.52. Found: C, 66.84; H, 6.09; N, 19.72. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3435. NMR ($CDCl_3$) δ: 2.44 (3H, s), 3.82 (3H, s), 6.90—7.82 (6H, m), 8.41 (1H, s). This compound was identical with the authentic methyl ether obtained by method iii), by mixed melting point test and comparison of spectral data.

ii) Compound IVa (1.46 g, 0.006 mol) was added to a solution of KOH (2 g, 0.036 mol) in EtOH (20 ml) and the mixture was refluxed for 2 hr. After removal of the EtOH under reduced pressure, the residue was dissolved in water and washed with ether. The aqueous solution was neutralized with 3 N HCl to precipitate crystals, which were collected and recrystallized from MeOH mp 238—239° (dec.). Yield 1.01 g (84%). This compound was identical with V prepared by method iii). Methyl ether: colorless prisms (ether–petr. ether), mp 140—141.5°. This was identical with the authentic methyl ether obtained by method iii).

iii) Compound VI (2.11 g, 0.008 mol), $Ba(OH)_2 \cdot 8H_2O$ (6.33 g, 0.02 mol), Cu powder (50 mg), and water (24 ml) were heated in a sealed tube at 185—190° for 10 hr. The reaction mixture, after addition of water (25 ml), was boiled for 1 hr to remove NH_3 then filtered. The filtrate was neutralized with conc. H_2SO_4 and evaporated to dryness under reduced pressure. The residue was extracted with boiling EtOH, and the EtOH extract was evaporated to dryness under reduced pressure. The residue was dissolved in 3 N NaOH (20 ml), washed with $CHCl_3$ and neutralized with 3 N HCl. The precipitated crystals were collected and recrystallized from MeOH to give pale brown needles. mp 227—239° (dec.). Yield 186 mg (12%). Methyl ether: colorless needles, mp 139.5—141° (ether–petr. ether).

4-Anilino-5-bromo-6-methylpyrimidine (VI)——A stirred mixture of 5-bromo-4-chloro-6-methylpyrimidine[10] (VII) (6.01 g, 0.029 mol) and aniline (27 g, 0.29 mol) was heated at 100° for 2 hr. After removal of the excess aniline under reduced pressure, the residue was partitioned between $CHCl_3$ and water. The $CHCl_3$ phase was washed with 1 N HCl and evaporated down to give a pale brown crystalline solid, which was recrystallized from ether–petr. ether. Colorless prisms, mp 92—93°. Yield 5.54 g (72%). *Anal.* Calcd. for $C_{11}H_{10}BrN_3$: C, 50.03; H, 3.79; Br, 30.26; N, 15.91. Found: C, 50.18; H, 3.82; Br, 30.33; N, 16.15. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3425. NMR ($CDCl_3$) δ: 2.54 (3H, s), 7.07—7.70 (5H, m), 6.80—7.80 (1H, broad), 8.43 (1H, s).

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