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Studies on Pyrimidine Derivatives. XVI.[1] Site Selectivity in the Homolytic Substitution of Simple Pyrimidines

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Pyrimidine derivatives in which both the 2- and 4-positions are free exhibited site selectivity in their reactions with radicals generated in redox systems. Namely, 6-phenyl- (I), 6-methylpyrimidine (XV), and 5,6,7,8-tetrahydroquinazoline (XVII) reacted with radicals such as $R\dot{C}O$, $R_2N\dot{C}O$, $EtO\dot{C}O$, and $\dot{C}H_2OH$ to give predominantly the 4-substituted products. Except in the reaction of I with the N,N-dimethylcarbamoyl radical, the formation of the corresponding 2-substituted isomers was not observed.

Keywords——homolytic acylations; homolytic hydroxymethylation; site selective reaction; 4-substituted 6-phenylpyrimidines; 2-substituted 6-phenylpyrimidines; cross-coupling reaction; oxidation of methylpyrimidines

In the preceding paper of this series, we reported the synthesis of pyrimidinyl methanols,[3] ketones,[1] and amides[1] by means of the homolytic substitution reactions developed by Minisci and co-workers.[4-6] For example, 2,6-disubstituted pyrimidines were converted into 2,6-disubstituted 4-acylpyrimidines.

During the investigation mentioned above, we observed high site selectivity in the homolytic reactions of simple pyrimidine derivatives in which the 2- and 4-positions are both free. In the present paper we report an investigation of the reactions of 6-phenylpyrimidine 4-methylpyrimidine, and 5,6,7,8-tetrahydroquinazoline with radicals generated in the Minisci-type redox system to give 4-substituted products selectively.

When 6-phenylpyrimidine (I) was treated with acetaldehyde (6 mol eq.), ferrous sulfate (6 mol eq.), and *t*-butyl hydroperoxide (6 mol eq.), in aq. sulfuric acid (2 mol eq.) at a temperature not exceeding 20° for 15 min, colorless needles (IIa), $C_{12}H_{10}N_2O$, mp 54—55.5°, were obtained as the sole product in 53% yield. This compound, mp 51—52.5°, was also formed in 20% yield by the reaction of I with pyruvic acid in the presence of silver nitrate and ammonium peroxydisulfate. In the nuclear magnetic resonance (NMR) spectrum of IIa, two singlet signsls (1H each) due to the ring protons were observed at 8.22 and 9.28 ppm, together with a signal due to an acetyl methyl group (2.72 ppm, 3H, s). This clearly demonstrated the 2-position of the product to be unsubstituted.

Furthermore, the Wolff-Kishner reduction of IIa afforded 4-ethyl-6-phenylpyrimidine (III) which was identical with an authentic specimen prepared by the cross-coupling reaction of 4-chloro-6-phenylpyrimidine (IV) with ethylmagnesium bromide in the presence of a nickel-phosphine complex catalyst.

Based on these results, the structure of the product was unequivocally determined to be 4-acetyl-6-phenylpyrimidine (IIa).

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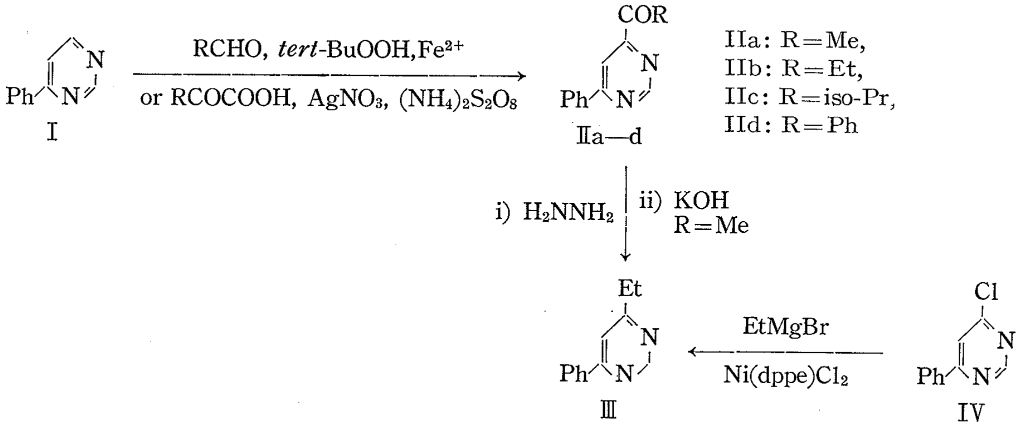

Chart 1

Similarly, the reaction of I with aldehydes such as propionaldehyde, isobutyraldehyde, and benzaldehyde under similar conditions gave rise to 4-propionyl- (IIb), 4-isobutyroyl- (IIc), and 4-benzoyl-6-phenylpyrimidine (IId) selectively, although the yields did not exceed 50%. Compound IId was also obtained in 18.5% yield by the reaction of I with phenylglyoxylic acid in the presence of $(NH_4)_2S_2O_8$ and $AgNO_3$. Elemental analyses, NMR, and infrared (IR) spectra of compounds IIb—d were in full agreement with the assigned structures. In all cases formation of the 2-substituted isomer was not observed, as ascertained by gas chromatographic analysis of the crude product.

The site selectivities of homolytic amidation, ethoxycarbonylation, and hydroxymethylation of the pyrimidine ring were then investigated. Prior to the investigation, the authentic pyrimidinecarboxamides (VIIIa, b, c, XII) were prepared as follows. 6-Phenylpyrimidine-4-carboxylic acid (VI), obtained by selenium dioxide oxidation of 4-methyl-6-phenylpyrimidine (V), was converted to the methyl ester (VIIa) in the usual manner. This ester was treated with excess ammonia, methylamine, or dimethylamine at room temperature to give 6-phenylpyrimidine-4-carboxamide (VIIIa), mp 174—176°, N-methyl-6-phenylpyrimidine-4-carboxamide (VIIIb), mp 59—60°, or N,N-dimethyl-6-phenylpyrimidine-4-carboxamide (VIIIc), mp 117—118°, respectively.

In order to ensure accurate gas chromatographic analysis of the products, the positional isomer, N,N-dimethyl-6-phenylpyrimidine-2-carboxamide(XII), was also synthesized. Namely, 2-methyl-6-phenylpyrimidine (IX) was oxidized with selenium dioxide to 6-phenylpyrimidine-2-carboxylic acid (X), which was converted to XII, mp 73—75°, *via* its methyl ester (XI), mp 83—84°.

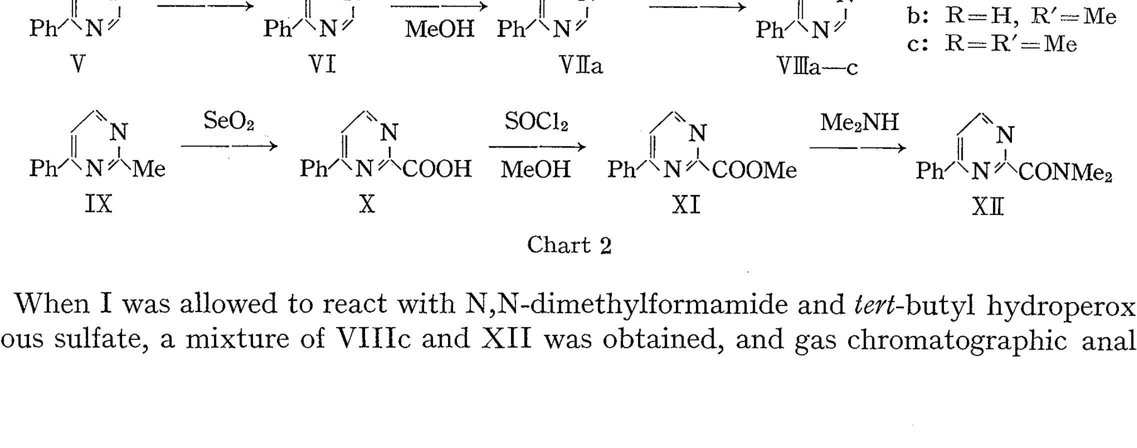

Chart 2

When I was allowed to react with N,N-dimethylformamide and *tert*-butyl hydroperoxide-ferrous sulfate, a mixture of VIIIc and XII was obtained, and gas chromatographic analysis showed the ratio of VIIIc and XII to be 2: 1. While both isomers were detected in the above amidation, a gas chromatogram of the crude product from the reaction of I with N-methylformamide under identical conditions showed no peak due to any by-product, and VIIIb was isolated in 23% yield. Similarly, the homolytic amidation of I with formamide gave 6-phenylpyrimidine-4-carboxamide (VIIIa), mp 187—188°, 55%, as the sole product. The spectral data for these products are consistent with amide group location at the 4-position.

The homolytic ethoxycarbonylation of I, using ethyl pyruvate and hydrogen peroxide in the presence of ferrous ions, produced VIIb selectively, although the yield was disappointing.

For comparison with these homolytic acylations, the hydroxymethylation of I with the hydroxymethyl radical generated from methanol and ammonium peroxydisulfate was examined. Even in this case the product was simple, and pure 6-phenylpyrimidine-4-methanol (XIII) was obtained by chromatography. Sodium borohydride reduction of VIIb gave the same 4-hydroxymethyl compound (XIII).

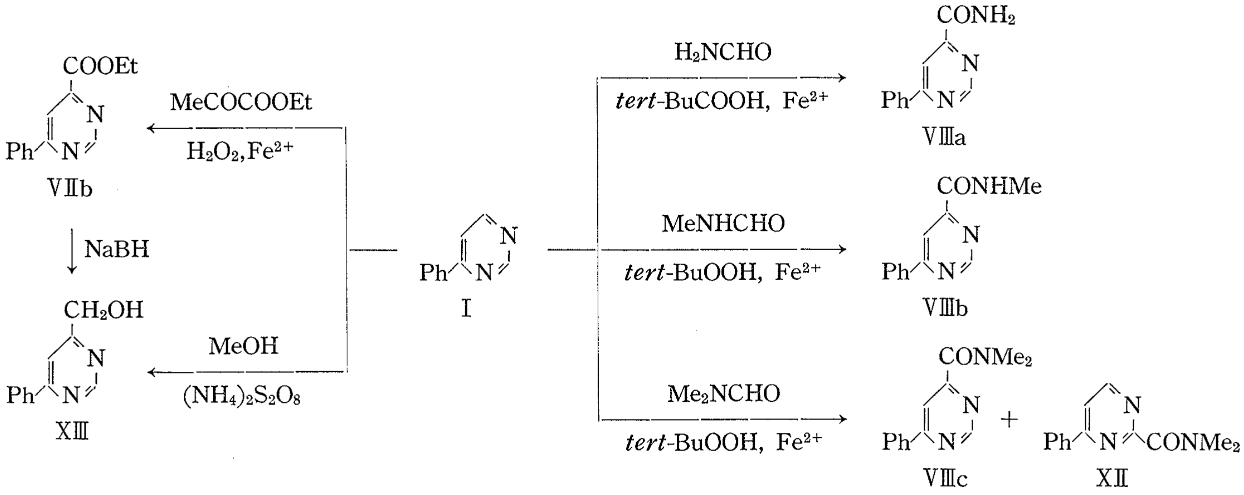

Chart 3

The selectivity described above seems to be general with pyrimidine derivatives. Namely, acetylation of 6-methylpyrimidine (XIV) and 5,6,7,8-tetrahydroquinazoline (XVII), using pyruvic acid in the redox system, gave rise to 4-acetyl-6-methylpyrimidine (XVI) and 4-acetyl-5,6,7,8-tetrahydroquinazoline (XVIII), respectively. In both cases, neither the 2-acetyl isomer nor the 2,4-diacetyl compound was obtained.

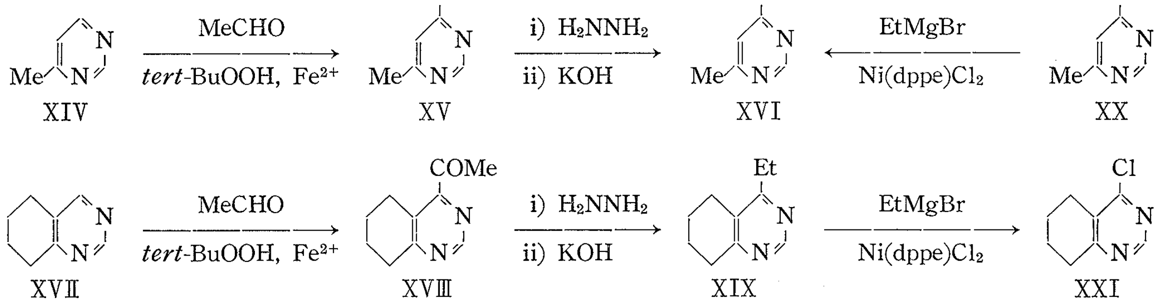

Chart 4

As illustrated in Chart 5, the acetylation[5] of quinoline is known to give three products, 2,4-diacetyl- (XXII), 2-acetyl- (XXIII), and 4-acetyl-quinoline (XXIV), in a ratio of 53:22:25. This demonstrates that there is no site selectivity as regards substitution at the α- and

γ-positions of the quinoline ring, in contrast to our results with the substitution of pyrimidines, in which specificity was observed in the synthesis of simple derivatives.

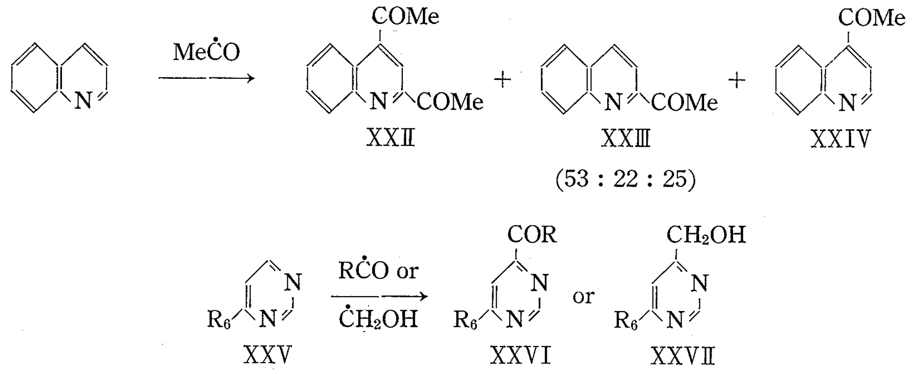

Chart 5

Experimental

All melting points and boiling points are uncorrected. IR spectra were measured with a JASCO IRA-1 spectrometer. NMR spectra were obtained at 60 MHz with a Hitachi-Perkin-Elmer R-20 spectrometer. Chemical shifts are expressed by ppm downfield from TMS as an internal standard. The following abbreviations are used: s=singlet, d=doublet, t=triplet, q=quartet, and m=multiplet.

General Procedure for Acylation with α-Keto Acids

An aq. solution of $(NH_4)_2S_2O_8$ (0.02 mol in 40 ml H_2O) was added to a solution of the pyrimidine (0.01 mol), $AgNO_3$ (0.001 mol), the α-keto acid (0.02 mol), and conc. H_2SO_4 (3 ml) in H_2O (30 ml) at 50° with stirring. The reaction mixture was stirred at 50° for 1.5 hr, then extracted with $CHCl_3$. The $CHCl_3$ extract was washed with 3 N NaOH and dried over K_2CO_3.

4-Acetyl-6-phenylpyrimidine (IIa)——The crude product was obtained from 6-phenylpyrimidine (I) (3.12 g, 0.02 mol) and pyruvic acid (3.52 g, 0.04 mol) according to the general procedure. This was purified by SiO_2 column chromatography using C_6H_6 as an eluant. Recrystallization from petr. ether gave colorless needles, mp 51—52.5°. Yield 0.79 g (20%). IR $\nu_{\max}^{\mathrm{CHCl_3}}$ cm^{-1}: 1710. NMR ($CDCl_3$) ppm: 2.72 (3H, s), 7.30—7.60 (3H, m), 8.00—8.20 (2H, m), 8.22 (1H, s), 9.28 (1H, s). *Anal.* Calcd for $C_{12}H_{10}N_2O$: C, 72.71; H, 5.09; N, 14.13. Found: C, 72.74; H, 5.02; N, 14.01.

4-Benzoyl-6-phenylpyrimidine (IId)——The crude product was obtained from I (1.56 g, 0.01 mol) and phenylglyoxylic acid (3.0 g, 0.02 mol) according to the general procedure. This was purified by SiO_2 column chromatography using $CHCl_3$ as an eluant. Recrystallization from MeOH gave colorless needles, mp 80—81°. Yield 0.48 g (18.5%). IR $\nu_{\max}^{\mathrm{CHCl_3}}$ cm^{-1}: 1680. NMR ($CDCl_3$) ppm: 7.37—7.83 (6H, m), 8.07—8.50 (5H, m), 9.45 (1H, s). *Anal.* Calcd for $C_{17}H_{12}N_2O$: C, 78.44; H, 4.65; N, 10.76. Found: C, 78.40; H, 4.71; N, 10.58.

General Procedure for Acylation with Aldehydes

A solution of $FeSO_4 \cdot 7H_2O$ (0.06 mol) in H_2O (40 ml) and 70% *tert*-butyl hydroperoxide (0.06 mol) were separately but simultaneously added to a stirred and cooled (10—20°) mixture of the pyrimidine (0.01 mol), 4 M H_2SO_4 (5 ml), and the aldehyde (0.06 mol). The reaction mixture was stirred at 10—20° for 15 min, then extracted with $CHCl_3$. The crude product was purified by recrystallization, distillation or column chromatography.

4-Acetyl-6-phenylpyrimidine (IIa)——The crude product was obtained from I (1.56 g, 0.01 mol) and 90% acetaldehyde (2.94 g, 0.06 mol) according to the general procedure. This was purified by SiO_2 column chromatography using C_6H_6 as an eluant. Recrystallization from hexane gave colorless needles, mp 54—55.5°. Yield 1.05 g (53%).

6-Phenyl-4-propionylpyrimidine (IIb)——The crude product was obtained from I (1.56 g, 0.01 mol) and propionaldehyde (3.5 g, 0.06 mol) according to the general procedure. This was purified by SiO_2 column chromatography using C_6H_6 as an eluant. Vacuum distillation gave a colorless liquid, bp 140—141° (5 mmHg). Yield 1.07 g (51%). IR $\nu_{\max}^{\mathrm{CHCl_3}}$ cm^{-1}: 1720. NMR (CCl_4) ppm: 1.20 (3H, t, J=7.0 Hz), 3.20 (2H, q, J=7.0 Hz), 7.30—7.60 (3H, m), 8.00—8.40 (3H, m), 9.27 (1H, s). *Anal.* Calcd for $C_{13}H_{12}N_2O$: C, 73.56; H, 5.70; N, 13.20. Found: C, 73.55; H, 5.71; N, 12.89.

4-Isobutyroyl-6-phenylpyrimidine (IIc)——The crude product was obtained from I (1.56 g, 0.01 mol) and isobutyraldehyde (4.32 g, 0.06 mol) according to the general procedure. This was purified by vacuum distillation to give a colorless liquid, bp 120—121° (3 mmHg). Yield 0.8 g (35%). IR $\nu_{\max}^{\mathrm{CHCl_3}}$ cm^{-1}: 1710. NMR (CCl_4) ppm: 1.22 (6H, d, J=7.0 Hz), 4.03 (1H, septet, J=7.0 Hz), 7.37—7.63 (3H, m), 8.08—8.33 (3H, m), 9.29 (1H, s). An analytical sample was obtained as the tosylhydrazone (EtOH), mp 142°. *Anal.* Calcd for $C_{21}H_{22}N_4O_2S$: C, 63.93; H, 5.62; N, 14.20. Found: C, 64.14; H, 5.60; N, 14.19.

4-Benzoyl-6-phenylpyrimidine (IId)——The crude extract was obtained from I (1.56 g, 0.01 mol) and benzaldehyde (6.4 g, 0.06 mol) according to the general procedure, although in this case acetic acid (15 ml) was added to provide a homogeneous solution. After the removal of benzaldehyde by steam distillation, the crude product was purified by SiO_2 column chromatography using $CHCl_3$ as an eluant. Recrystallization from MeOH gave colorless needles, mp 78—79°. Yield 0.73 g (28%).

4-Acetyl-6-methylpyrimidine (XV)——The crude product was obtained from 6-methylpyrimidine (XIV) (1.88 g, 0.02 mol) and 90% acetaldehyde (5.86 g, 0.12 mol) according to the general procedure. This was distilled under reduced pressure to give a colorless solid, bp 85—95° (15 mmHg). Yield 0.91 g (34%). Recrystallization from ether–petr. ether gave colorless needles, mp 74—76°. IR $\nu_{\max}^{\mathrm{CHCl_3}}$ $\mathrm{cm^{-1}}$: 1708. NMR ($CDCl_3$) ppm: 2.54 (3H, s), 2.71 (3H, s), 7.78 (1H, s), 9.25 (1H, s). *Anal.* Calcd for $C_7H_8N_2O$: C, 61.75; H, 5.92; N, 20.58. Found: C, 61.54; H, 6.00; N, 20.52.

4-Acetyl-5,6,7,8-tetrahydroquinazoline (XVIII)——The crude product was obtained from 5,6,7,8-tetrahydroquinazoline (XVIII) (2.68 g, 0.02 mol) and 90% acetaldehyde (5.86 g, 0.12 mol) according to the general procedure. Vacuum distillation gave a colorless liquid, bp 140° (20 mmHg). Yield 1.2 g (34%). IR $\nu_{\max}^{\mathrm{CHCl_3}}$ $\mathrm{cm^{-1}}$: 1720. NMR (CCl_4) ppm: 1.67—2.17 (4H, m), 2.60 (3H, s), 2.77—3.30 (4H, m), 8.86 (1H, s). An analytical sample was obtained as the semicarbazone (EtOH). *Anal.* Calcd for $C_{11}H_{15}N_5O$: C, 56.63; H, 6.48; N, 30.03. Found: C, 56.86; H, 6.58; N, 30.00.

General Procedure for Amidation with Formamides

A solution of $FeSO_4 \cdot 7H_2O$ (0.06 mol) in H_2O (40 ml) and 70% *tert*-butyl hydroperoxide (0.06 mol) were separately but simultaneously added to a stirred and cooled (10—20°) mixture of the pyrimidine (0.01 mol), 4 M H_2SO_4 (10 ml, 0.04 mol), and the formamide (15 ml). The reaction mixture was stirred at 10—20° for 1 hr.

6-Phenylpyrimidine-4-carboxamide (VIIIa)——Compound I (1.56 g, 0.01 mol) was allowed to react with formamide according to the general procedure. The reaction mixture was diluted with H_2O and extracted with AcOEt. The crude product was purified by SiO_2 column chromatography using AcOEt as an eluant. Recrystallization from C_6H_6 gave colorless needles, mp 187—188°. Yield 1.1 g (55%). IR $\nu_{\max}^{\mathrm{KBr}}$ $\mathrm{cm^{-1}}$: 3460, 3418, 1711. NMR (CF_3COOH) ppm: 7.86—8.13 (3H, m), 8.20—8.46 (2H, m), 8.52—8.78 (1H, broad), 9.30 (1H, s), 9.79 (1H, s). *Anal.* Calcd for $C_{11}H_9N_3O$: C, 66.32; H, 4.55; N, 21.10. Found: C, 66.45; H, 4.46; N, 21.08.

N-Methyl-6-phenylpyrimidine-4-carboxamide (VIIIb)——Compound I (1.56 g, 0.01 mol) was allowed to react with N-methylformamide according to the general procedure. The reaction mixture was diluted with H_2O and extracted with AcOEt. The crude product was purified by SiO_2 column chromatography using $CHCl_3$: AcOEt (10: 1) as an eluant. Recrystallization from ether–pentane gave colorless needles, mp 53—55°. Yield 0.49 g (23%). IR $\nu_{\max}^{\mathrm{KBr}}$ $\mathrm{cm^{-1}}$: 3340, 1665. NMR ($CDCl_3$) ppm: 3.06 (3H, d, $J=5.0$ Hz), 7.43—7.67 (3H, m), 8.00—8.33 (3H, m), 8.57 (1H, s), 9.23 (1H, s). *Anal.* Calcd for $C_{12}H_{11}N_3O$: C, 67.59; H, 5.20; N, 19.71. Found: C, 67.59; H, 5.32; N, 20.03.

Reaction of I with N,N-dimethylformamide——Compound I (1.56 g, 0.01 mol) was allowed to react with N,N-dimethylformamide according to the general procedure. The reaction mixture was diluted with H_2O and extracted with C_6H_6. The crude product was analysed by gas chromatography (FID). Column, OV 17 2 m; carrier gas (N_2), 60 ml/min; column temperature, 270°. The crude product was distilled under reduced preseure to remove I (0.69 g, 44%). The residue was purified by SiO_2 column chromatography using $CHCl_3$: AcOEt (5: 1) as an eluant. The first fraction afforded colorless needles (VIIIc), mp 116—117°, which were recrystallized from hexane. Yield 0.33 g (14%). IR $\nu_{\max}^{\mathrm{KBr}}$ $\mathrm{cm^{-1}}$: 1646. NMR ($CDCl_3$) ppm: 3.18 (6H, s), 7.52—7.77 (3H, m), 8.07—8.40 (3H, m), 9.35 (1H, s). *Anal.* Calcd for $C_{13}H_{13}N_3O$: C, 68.70; H, 5.77; N, 18.49. Found: C, 69.03; H, 5.75; N, 18.44. The second fraction gave colorless prisms (XII), mp 71—73°, which were recrystallized from ether. Yield 45 mg (2%). IR $\nu_{\max}^{\mathrm{KBr}}$ $\mathrm{cm^{-1}}$: 1641. NMR ($CDCl_3$) ppm: 3.02 (3H, s), 3.18 (3H, s), 7.43—7.65 (3H, m), 7.75 (1H, d, $J=6.0$ Hz), 8.08—8.35 (2H, m), 8.87 (1H, d, $J=6.0$ Hz). *Anal.* Calcd for $C_{13}H_{13}N_3O$: C, 68.70; H, 5.77; N, 18.49. Found: C, 69.06; H, 6.02; N, 18.31.

Ethoxycarbonylation of I with Ethyl Pyruvate

An aq. solution of H_2O_2 (30%, 3.4 g, 0.03 mol) was added dropwise to ethyl pyruvate (5.2 g, 0.045 mol) with stirring and cooling (−10—0°). After stirring the mixture at −10—0° for 15 min, it was added to a mixture of I (1.56 g, 0.01 mol), $FeSO_4 \cdot 7H_2O$ (6.8 g, 0.03 mol), conc. H_2SO_4 (3 g), and H_2O (4 ml) at −5—0°. This reaction mixture was stirred at −5—5° for 15 min, then poured into ice-water, and extracted with $CHCl_3$.

The extract was washed with H_2O. Purification of the crude product by SiO_2 column chromatography using $CHCl_3$ as an eluant, gave a colorless liquid (VIIb). Yield 0.38 g (17%). This compound was identical with an authentic specimen.

Hydroxymethylation of I with Methyl Alcohol

A mixture of I (1.56 g, 0.01 mol), H_2O (9 ml), MeOH (18 ml), conc. H_2SO_4 (0.7 ml), and $(NH_4)_2S_2O_8$ (2.5 g) was refluxed for 1 hr. The reaction mixture was concentrated under reduced pressure and the residue was diluted with H_2O, made alkaline with K_2CO_3, then extracted with $CHCl_3$. The crude product was purified by SiO_2 column chromatography using C_6H_6: acetone (20: 1) as an eluant. The first fraction afforded the starting pyrimidine (0.545 g, 35%). The second fraction gave pale yellow needles (XIII), mp 77—79°, which were recrystallized from C_6H_6–hexane. Yield 0.54 g (29%). IR $\nu_{\max}^{\text{KBr}}$ cm^{-1}: 3200 (broad). NMR ($CDCl_3$) ppm: 4.04 (1H, s), 4.80 (2H, s), 7.40—7.62 (3H, m), 7.77 (1H, s), 7.98—8.21 (2H, m), 9.18 (1H, s). *Anal.* Calcd for $C_{11}H_{10}N_2O$: C, 70.95; H, 5.41; N, 15.05. Found: C, 71.40; H, 5.48; N, 14.86.

Wolff-Kishner Reduction of 4-Acetylpyrimidines

4-Ethyl-6-phenylpyrimidine (III)——A mixture of IIa (0.5 g, 2.52 mmol), $H_2NNH_2 \cdot H_2O$ (5 g), and diethyleneglycol (10 ml) was refluxed for 2 hr. Potassium hydroxide (2 g) was added and the mixture was heated gradually to 160° during distillation under normal pressure. The mixture was kept at this temperature for 1 hr, then diluted with H_2O and extracted with ether. The crude product was distilled under reduced pressure to give a colorless liquid, bp 98—100° (3.5 mmHg). Yield 0.44 g (94%). NMR (CCl_4) ppm: 1.33 (3H, t, J=7.0 Hz), 2.80 (2H, q, J=7.0 Hz), 7.30—7.60 (4H, m), 7.97—8.13 (2H, m), 9.05 (1H, s). Picrate mp 182—183° (EtOH) (lit.[7] mp 185—187°).

4-Ethyl-6-methylpyrimidine (XVI)——A mixture of XV (0.396 g, 2.9 mmol), $H_2NNH_2 \cdot H_2O$ (0.5 g), and EtOH (5 ml) was refluxed for 2 hr. The reaction mixture was concentrated under reduced pressure, then diethyleneglycol (1.5 ml) and KOH (150 mg) were added to the residue and the mixture was heated at 170° for 2 hr. Purification of the crude mixture by Al_2O_3 column chromatography using ether as an eluant gave a colorless liquid. Yield 0.27 g (76%). NMR ($CDCl_3$) ppm: 1.27 (3H, t, J=7.5 Hz), 2.48 (3H, s), 2.75 (2H, q, J=7.5 Hz), 7.06 (1H, s), 8.98 (1H, s). An analytical sample was obtained as the styphnate (C_6H_6), mp 126—127° (dec.). *Anal.* Calcd for $C_{13}H_{13}N_5O_8$: C, 42.51; H, 3.57; N, 19.07. Found: C, 42.55; H, 3.51; N, 18.95.

4-Ethyl-5,6,7,8-tetrahydroquinazoline (XIX)——A mixture of XVIII (0.64 g, 3.63 mmol), $H_2NNH_2 \cdot H_2O$ (0.61 g), and EtOH (5 ml) was refluxed for 2 hr. After concentration of the reaction mixture, diethyleneglycol (2 ml) and KOH (0.21 g) was added to the residue, followed by heating at 170° for 2 hr. Purification of the crude mixture by Al_2O_3 column chromatography using ether as an eluant gave a colorless liquid. Yield 0.475 g (82%). NMR (CCl_4) ppm: 1.24 (3H, t, J=7.5 Hz), 1.70—2.00 (4H, m), 2.45—2.95 (6H, m), 8.80 (1H, s). An analytical sample was obtained as the picrate, mp 89—90° (C_6H_6). *Anal.* Calcd for $C_{16}H_{17}N_5O_7$: C, 49.10; H, 4.38; N, 17.90. Found: C, 49.03; H, 4.26; N, 17.78.

Grignard Coupling of 4-Chloropyrimidines

4-Ethyl-6-phenylpyrimidine (III)——An ethereal solution (20 ml) of 4-chloro-6-phenylpyrimidine (IV) (1.0 g, 5.2 mmol) was added to a solution of ethylmagnesium bromide [prepared from 0.28 g (0.012 g atom) of Mg and 1.24 g (0.011 mol) of ethyl bromide] and $Ni[Ph_2P(CH_2)_2PPh_2]Cl_2$ [$Ni(dppe)Cl_2$, 10 mg] in anhyd. ether (10 ml) with stirring and cooling (−15°). After stirring the mixture at room temperature for 3 hr, aq. NH_4Cl was added and the mixture was extracted with ether. Removal of the ether gave a colorless liquid. Yield 0.456 g (47%). Picrate mp 182—183°.

4-Ethyl-6-methylpyrimidine (XVI)——An ethereal solution (90 ml) of 4-chloro-6-methylpyrimidine (XX) (5.14 g, 0.04 mol) was added to a solution of ethylmagnesium bromide [prepared from 2.14 g (0.088 g atom) of Mg and 9.59 g (0.088 mol) of ethyl bromide] and $Ni(dppe)Cl_2$ (220 mg) in anhyd. ether (40 ml) with ice-cooling (−10°) and stirring. The mixture was stirred at −10° for 3 hr, then aq. NH_4Cl was added and the mixture was extracted with CH_2Cl_2. Removal of the CH_2Cl_2 gave a colorless liquid, bp 97—98° (60 mmHg). Yield 3.29 g (67%). Styphnate (C_6H_6) mp 126—129.5° (dec.).

4-Ethyl-5,6,7,8-tetrahydroquinazoline (XIX)——An ethereal solution (20 ml) of ethylmagnesium bromide [prepared from 0.63 g (0.026 g atom) of Mg and 2.7 g (0.025 mol) of ethyl bromide] was added to an ethereal solution (20 ml) of 4-chloro-5,6,7,8-tetrahydroquinazoline (XXI) (1.5 g, 0.009 mol) and $Ni(dppe)Cl_2$ (70 mg) with ice-cooling and stirring. After the mixture had been stirred under ice-cooling for 5 hr, water was added and the mixture was extracted with ether. Removal of the ether gave a colorless liquid. Yield 1.23 g (84%). Picrate (C_6H_6), mp 89—90°.

Methyl 6 Phenylpyrimidine-4-carboxylate (VIIa)——A mixture of 4-methyl-6-phenylpyrimidine (V) (2.0 g, 0.012 mol), SeO_2 (2.1 g, 0.019 mol), and pyridine (30 ml) was refluxed for 6 hr. The precipitated selenium was filtered off, then the pyridine was removed under reduced pressure, 3 N NaOH (5 ml) was added to the residue, and the mixture was washed with CH_2Cl_2. The aqueous layer was neutralized with 3 N HCl (5 ml) and the mixture was evaporated to dryness under reduced pressure. The residue was dissolved in MeOH (40 ml), then $SOCl_2$ (5 ml) was added with ice-cooling. The mixture was allowed to stand at room temperature for 10 hr. The MeOH was removed under reduced pressure, 1 N $NaHCO_3$ was added to the residue, and the mixture was extracted with $CHCl_3$. The crude product was passed through a short column of Al_2O_3 using C_6H_6 as an eluant. Recrystallization from ether–hexane gave colorless needles, mp 71—73°. Yield 1.56 g (62%). IR $\nu_{\max}^{\text{KBr}}$ cm^{-1}: 1726. NMR ($CDCl_3$) ppm: 4.04 (3H, s), 7.40—7.70 (3H, m), 8.10—8.30 (2H, m), 8.44 (1H, s), 9.41 (1H, s). *Anal.* Calcd for $C_{12}H_{10}N_2O_2$: C, 67.28; H, 4.71; N, 13.08. Found: C, 67.09; H, 4.70; N, 13.16.

Ethyl 6-Phenylpyrimidine-4-carboxylate (VIIb)——Thionyl chloride (4 ml) was added to a solution of 6-phenylpyrimidine-4-carboxylic acid (VI) (0.45 g, 2.25 mmol) and abs. EtOH (40 ml) with ice-cooling,

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[7] H. Bredereck, R. Gompper, and G. Morlock, *Chem. Ber.*, 90, 942 (1957).

and the mixture was stirred at room temperature for 10 hr. The EtOH was removed under reduced pressure and the residue was poured into ice-water. The mixture was made alkaline with $NaHCO_3$ and extracted with CH_2Cl_2. The crude product was purified by Al_2O_3 column chromatography using $CHCl_3$ as an eluant. Recrystallization from hexane gave colorless needles, mp 54.5—55°. Yield 0.248 g (48.3%). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1724. NMR ($CDCl_3$) ppm: 1.48 (3H, t, J=7.0 Hz), 4.55 (2H, q, J=7.0 Hz), 7.45—7.70 (3H, m), 8.10—8.33 (2H, m), 8.45 (1H, s), 9.46 (1H, s). *Anal.* Calcd for $C_{13}H_{12}N_2O_2$: C, 68.41; H, 5.30; N, 12.27. Found: C, 68.76; H, 5.37; N, 12.53.

6-Phenylpyrimidine-2-carboxylic Acid (X)——A mixture of 2-methyl-6-phenylpyrimidine (IX) (1.0 g, 0.006 mol), SeO_2 (0.98 g, 0.009 mol), and pyridine (20 ml) was refluxed for 5 hr. The precipitated selenium was filtered off, then the pyridine was removed under reduced pressure. The residue was dissolved in 3 N NaOH and the mixture was washed with CH_2Cl_2, acidified with 3 N HCl, and extracted with $CHCl_3$. The crude product was recrystallized from C_6H_6 to give colorless needles, mp 154—156°. Yield 0.67 g (57%). IR ν_{max}^{KBr} cm^{-1}: 3200—2200 (broad), 1735, 1711. NMR (CF_3COOH) ppm: 7.60—7.80 (3H, m), 8.40—8.78 (3H, m), 9.15 (1H, d, J=7.0 Hz). *Anal.* Calcd for $C_{11}H_8N_2O_2$: C, 65.99; H, 4.03; N, 13.99. Found: C, 66.24; H, 4.16; N, 14.24.

Methyl 6-Phenylpyrimidine-2-carboxylate (XI)——Thionyl chloride (2 ml) was added to a cold solution of X (0.65 g, 3.25 mmol) and MeOH (20 ml) and the mixture was stirred at room temperature for 10 hr. After removing the MeOH under reduced pressure, the residue, was made alkaline with 1 N $NaHCO_3$ and the mixture was extracted with CH_2Cl_2. The crude product was purified by SiO_2 column chromatography using $CHCl_3$ as an eluant. Recrystallization from hexane gave colorless needles, mp 83—84°. Yield 0.69 g (99%). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1741. NMR ($CDCl_3$) ppm: 4.07 (3H, s), 7.47—7.68 (3H, m), 7.86 (1H, d, J=6.0 Hz), 8.10—8.33 (2H, m), 8.95 (1H, d, J=6.0 Hz). *Anal.* Calcd for $C_{12}H_{10}N_2O_2$: C, 67.28; H, 4.71; N, 13.08. Found: C, 67.47; H, 4.62; N, 13.13.

Conversion of Pyrimidine Carboxylic Esters to Amides

6-Phenylpyrimidine-4-carboxamide (VIIIa)——A solution of VIIa (0.3 g, 1.4 mmol), MeOH (10 ml), and 28% NH_4OH (3 ml) was allowed to stand at room temperature for 10 hr. After removing the MeOH under reduced pressure, the residue was purified by SiO_2 column chromatography using AcOEt as an eluant. Recrystallization from C_6H_6 gave colorless needles, mp 174—176°. Yield 180 mg (65%).

N-Methyl-6-phenylpyrimidine-4-carboxamide (VIIIb)——A solution of VIIa (0.61 g, 2.85 mmol), 40% aq. methylamine (5 ml), and MeOH (20 ml) was allowed to stand at room temperature for 10 hr. After removal of the MeOH under reduced pressure, the residue was purified by SiO_2 column chromatography using $CHCl_3$: AcOEt (10: 1) as an eluant. Recrystallization from ether–hexane gave colorless needles, mp 59—60°. Yield 344 mg (56.6%).

N,N-Dimethyl-6-phenylpyrimidine-4-carboxamide (VIIIc)——A solution of VIIa (0.109 g, 0.47 mmol), 40% aq. dimethylamine (2 ml), and MeOH (5 ml) was allowed to stand at room temperature for 10 hr. After removal of the MeOH under reduced pressure, the residue was passed through a short column of Al_2O_3 using $CHCl_3$ as an eluant. Recrystallization from hexane gave colorless needles, mp 117—118°. Yield 76.7 mg (66.4%).

N,N-Dimethyl-6-phenylpyrimidine-2-carboxamide (XII)——A solution of XI (0.23 g, 1.1 mmol), 40% aq. dimethylamine (1 ml), and MeOH (3 ml) was allowed to stand at room temperature for 10 hr. After removal of the MeOH under reduced pressure, the residue was purified by SiO_2 column chromatography using $CHCl_3$ as an eluant. Recrystallization from ether gave colorless needles, mp 73—75°. Yield 0.162 g (65%).

Reduction of Ethyl 6-Phenylpyrimidine-4-carboxylate with $NaBH_4$

A mixture of VIIb (0.5 g, 2.2 mmol), $NaBH_4$ (0.83 g, 2.3 mmol), and MeOH (10 ml) was refluxed for 2 hr. After removal of the MeOH, aq. K_2CO_3 was added to the residue and the mixture was extracted with CH_2Cl_2. The crude product was purified by SiO_2 column chromatography using ether as an eluant. Recrystallization from ether–pentane gave colorless needles (XIII), mp 79—80°. Yield 0.21 g (50%).

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