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Polycyclic N-Hetero Compounds. XVII.[1] Reactions of Heterocyclic Active Methyl Group with Formamide or Trisformylaminomethane

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Pyrimidine formation from active methyl group on heterocycles is described. 2-Methyl-pyridine (I), -quinoline (III), -pyrazine (IX), -benzothiazole (XX), 2,4-dimethyl-quinoline (VII), and -thiazole (XIII) were successful in pyrimidine formation. 2-Methyl-imidazole (XI), -benzimidazole (XV), -benzoxazole (XVI), and 2,4-dimethyloxazole (XII) were unsuccessful. Compound (III) gave pyrazine (V) and pyridine (VI) derivatives and pyridine formation occurred also in XX.

Keywords——formamide; trisformylaminomethane; heterocyclic active methyl group; pyridine; pyrazine; azoles; pyrimidine formation; pyridine formation; pyrazine formation

In the earlier papers[3] of this series, we reported that the reaction of methylpyridines with formamide or of methylpyrimidines with trisformylaminomethane or formamide-phosphoryl chloride afforded pyrimidinyl pyridines or pyrimidines. The present paper deals with the

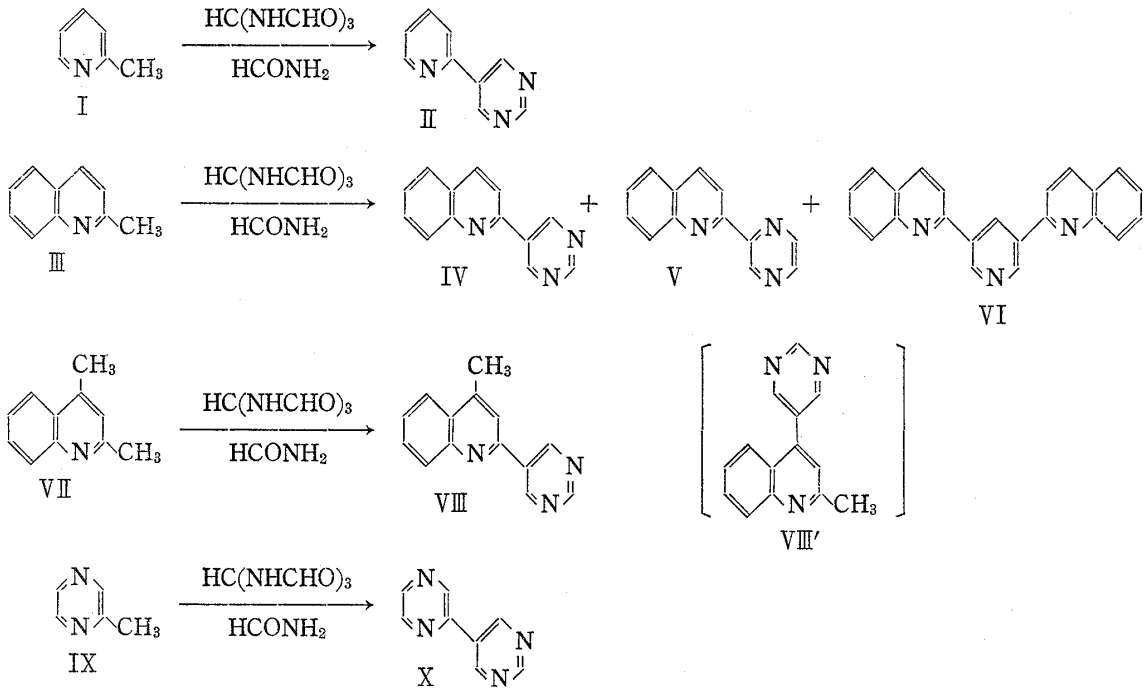


Chart 1

1) Part XVI: T. Hirota, T. Koyama, T. Nanba, M. Yamato, and T. Matsumura, *Chem. Pharm. Bull.* (Tokyo), "in press."
2) Location: *1-1, Tsushima-naka 1-chome, Okayama 700, Japan.*
3) *a*) T. Koyama, T. Hirota, C. Basho, T. Nanba, S. Ohmori, and M. Yamato, *Chem. Pharm. Bull.* (Tokyo), **25**, 1923 (1977); *b*) T. Koyama, T. Hirota, C. Basho, Y. Sato, Y. Watanabe, S. Matsumoto, Y. Shinohara, S. Ohmori, and M. Yamato, *Chem. Pharm. Bull.* (Tokyo), **23**, 2158 (1975); *c*) T. Koyama, T. Hirota, C. Basho, Y. Watanabe, Y. Kitauchi, Y. Sato, S. Ohmori, and M. Yamato, *Chem. Pharm. Bull.* (Tokyo), **24**, 1459 (1976).

reaction of analogous heterocycles (Chart 1) or azoles (Chart 2) with formamide or trisformylaminomethane to give pyrimidinyl heterocycles.

As shown in Chart 1, 2-methylpyridine (I), 2-methylquinoline (III), 2,4-dimethylquinoline, and 2-methylpyrazine (IX) were used as starting materials.

Reaction of I with trisformylaminomethane afforded 5-(2-pyridyl)pyrimidine (II) and that of III with same reagent afforded 2-(5-pyrimidinyl)quinoline (IV), 2-(2-pyrazinyl)quinoline (V), and 3,5-bis(2-quinolyl)pyridine (VI). These products were identified with authentic samples prepared from I or III with formamide in our laboratory and the formation mechanisms of V and VI were also proposed in that report.[3a)]

Similar reaction of VII with trisformylaminomethane gave 4-methyl-2-(5-pyrimidinyl)-quinoline (VIII). The position of pyrimidinyl group formed was determined by the chemical shifts of pyrimidine ring protons in nuclear magnetic resonance (NMR) in deuterochloroform. Whereas IV exhibited two-proton singlet (pyrimidine 4,6-H, δ 9.66) at lower field than one-proton singlet (pyrimidine 2-H, δ 9.33), 4-(5-pyrimidinyl)quinoline[3a)] resulted reversal (pyrimidine 4,6-H, δ 8.87, 2-H δ 9.33). The fact was interpreted as paramagnetic effect of nitrogen atom of quinoline ring. The chemical shifts of pyrimidine ring protons of VIII exhibited two-proton singlet at δ 9.38 and one-proton singlet at δ 9.18. Consequently the structure of VIII was more favorable than VIII'. Similar reaction of IX with trisformylaminomethane gave expectedly 5-(2-pyrazinyl)pyrimidine (X). Also in this case, two-proton singlet appeared at lower field than one-proton singlet in deuterochloroform.

As shown in Chart 2, 2-methylimidazole (XI), 2,4-dimethyloxazole (XII), 2,4-dimethylthiazole (XIII), and their benzologes (XV, XVI, and XX) were used as starting azoles.

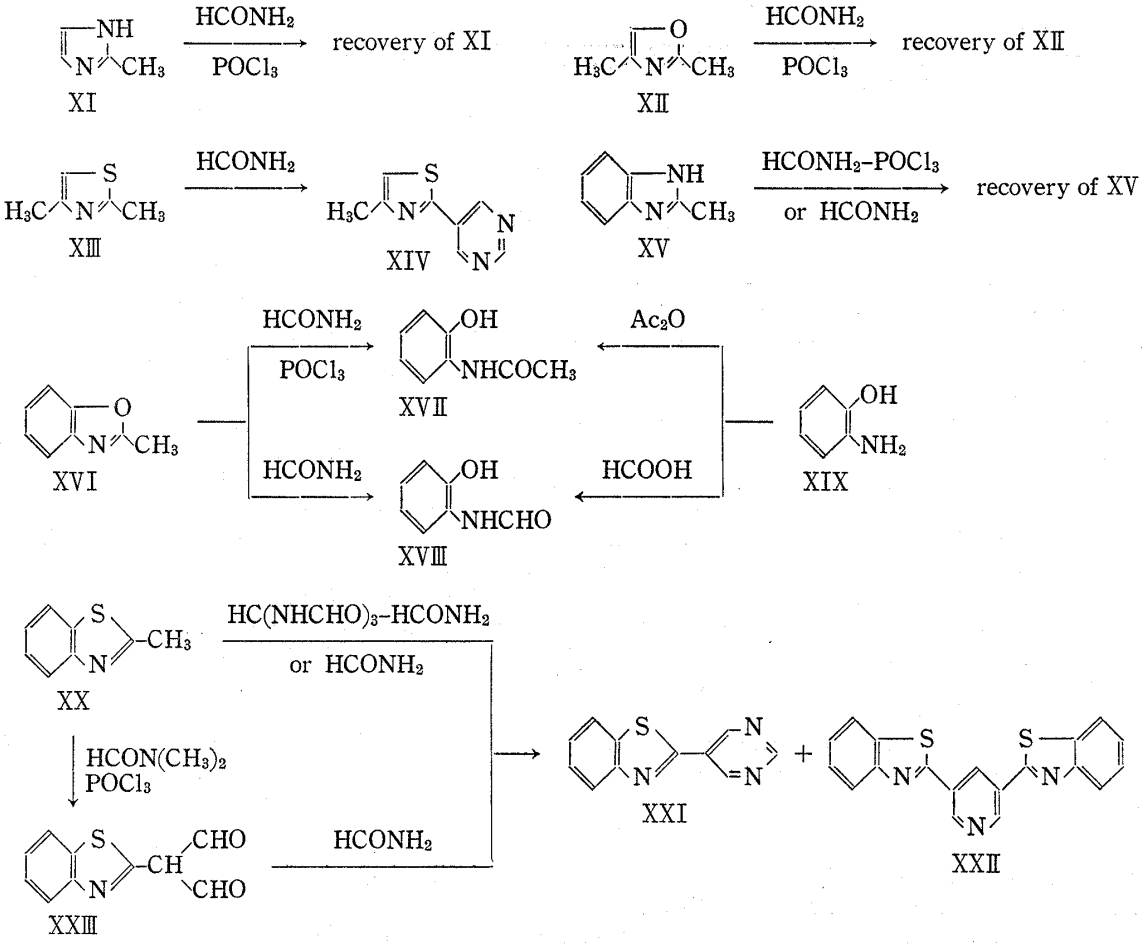
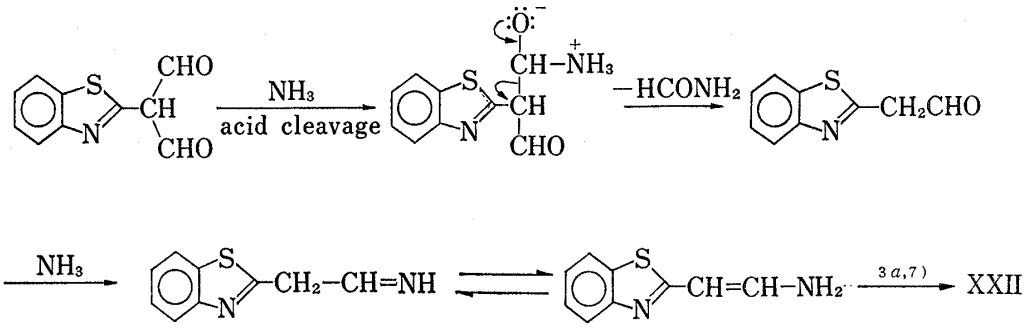


Chart 2

Although XI and XII were unchanged by heating with formamide–phosphoryl chloride at 90—100° at atmospheric pressure or in autoclave, XIII afforded 4-methyl-2-(5-pyrimidinyl)-thiazole (XIV) by heating with formamide only. Reaction of XV with formamide–phosphoryl chloride or with formamide only recovered starting material. On heating XVI with formamide–phosphoryl chloride or with formamide only, cleavage of oxazole ring resulted and *o*-hydroxyacetanilide (XVII) or *o*-hydroxyformanilide (XVIII) was obtained. XVII and XVIII were identified with authentic samples prepared from *o*-aminophenol (XIX), and acetic anhydride[4] or formic acid.[5]

Reaction of XX with formamide or trisformylaminomethane gave both 2-(5-pyrimidinyl)-benzothiazole (XXI) and 3,5-bis(2-benzothiazolyl)pyridine (XXII). XXI was already synthesized by Jayanth, *et al.*[6] by heating 2-(2-benzothiazolyl)malonaldehyde (XXIII) with formamide. For identification of XXI, XXIII, which was synthesized by Vilsmeier reaction of XX, was heated with formamide according to the condition of Jayanth, *et al.*[6] XXI was obtained as major product of this reaction, and identified with our product. But in our case, XXII was also obtained as a minor product. The formation of XXII was not reported by Jayanth, *et. al.*[6] and its presumable formation mechanism is shown in Chart 3. Pyridine ring formation of arylacetaldimine–enamine tautomer was described in earlier reports.[3a,7]



NH_3: thermal decomposition product of $HCONH_2$

Chart 3

Experimental

Melting points are uncorrected. Infrared (IR) spectra were recorded on Nippon Bunko DS-301 spectrometer. NMR spectra were taken on a Hitachi R-22 spectrometer (90 MHz) 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. Ultraviolet (UV) spectra were taken on a Hitachi ESP-2 spectrophotometer.

Reaction of 2-Methylpyridine (I) with HC(NHCHO)$_3$——A mixture of 9.8 ml of I, 28.1 g of $HC(NHCHO)_3$, and 25 ml of $HCONH_2$ was heated at 160—180° for 18 hr in autoclave with stirring. After cooled, *ca.* 50 ml of H_2O was added to the reaction mixture and the resulting solution was extracted with ether. The ether layer was washed with small amount of sat. NaCl solution, dried over Na_2SO_4, and evaporated. The oily residue was distilled to give 4.9 ml of unaltered I (50%). The distillation residue was recrystallized from cyclohexane to give 0.54 g of 5-(2-pyridyl)pyrimidine (II) as colorless needles, mp 131—132°. The above H_2O layer extracted with ether was continuously extracted with benzene for 14 hr. The benzene layer was dried over Na_2SO_4 and evaporated. Recrystallization of the residue gave 0.22 g of II as colorless needles, mp 131—132°, overall yield 0.76 g (9.6%). *Anal.* Calcd. for $C_9H_7N_3$: C, 68.77; H, 4.49; N, 26.74. Found: C, 68.44; H, 4.61; N, 26.49, identical with the authentic sample[3a] (mixed mp, IR, NMR, and thin-layer chromatography (TLC)).

Reaction of 2-Methylquinoline (III) with HC(NHCHO)$_3$——A mixture of 13.5 ml of III, 28.1 g of $HC(NHCHO)_3$, and 25 ml of $HCONH_2$ was heated at 165—170° for 20 hr with stirring. After cooled, the reaction mixture was poured into *ca.* 100 ml of H_2O and extracted with ether. The ether layer was worked up as

4) L.C. Raiford and C.E. Greinder, *J. Am. Chem. Soc.*, **46**, 430 (1924).
5) E. Bamberger, *Chem. Ber.*, **36**, 2042 (1903).
6) M.R. Jayanth, H.A. Naik, D.R. Tatke, and S. Sechadri, *Indian J. Chem.*, **11**, 1112 (1973).
7) D.R. Eckroth, *Chem. Ind.* (London), **1976**, 920.

usual. The residue was recrystallized from ether followed by cyclohexane to give 3.66 g of 2-(5-pyrimidinyl)-quinoline (IV) as colorless feathers, mp 139—140°. The filtrate was fractionated with preparative TLC (Merck, Kieselguhr PF_{254}; acetone: benzene: cyclohexane=2: 1: 1). The fraction of *Rf* value *ca.* 0.6—0.7 was collected and recrystallized from cyclohexane to give 0.17 g of IV as colorless feathers, mp 139—140°, overall yield 3.83 g (18.8%). *Anal.* Calcd. for $C_{13}H_9N_3$: C, 75.34; H, 4.38; N, 20.28. Found: C, 75.34; H, 4.37; N, 20.31. The fraction of *Rf* value *ca.* 0.4 was collected and recrystallized from cyclohexane to give 0.10 g (0.5%) of 2-(2-pyrazinyl)quinoline (V) as colorless fine needles, mp 156—157°. *Anal.* Calcd. for $C_{13}H_9N_3$: C, 75.34; H, 4.38; N, 20.28. Found: C, 75.40; H, 4.36; N, 20.13. The above H_2O layer extracted with ether was extracted with $CHCl_3$ and the $CHCl_3$ layer was worked up as usual. The residue was recrystallized from EtOH to give 3,5-bis(2-quinolyl)pyridine (VI) as colorless feathers, mp 233—234°. *Anal.* Calcd. for $C_{23}H_{15}N_3$: C, 82.86; H, 4.54; N, 12.61. Found: C, 82.63; H, 4.55; N, 12.55. Above three products (IV, V, VI) were identified with authentic samples[3a] (mixed mp, IR, NMR, and TLC).

Reaction of 2,4-Dimethylquinoline (VII) with $HC(NHCHO)_3$——A mixture of 7.4 ml of VII, 28.1 g of $HC(NHCHO)_3$, and 20 ml of $HCONH_2$ was heated at 170—180° for 24 hr with stirring. After cooled, *ca.* 50 ml of H_2O was added to the reaction mixture and the resulting solution was continuously extracted with ether. The ether layer was dried over Na_2SO_4 and evaporated. Recrystallization of the residue from cyclohexane gave 0.95 g (8.6%) of 4-methyl-2-(5-pyrimidinyl)quinoline (VIII) as colorless needles, mp 157—159°. For elemental analysis, the crystals were subjected to vacuum sublimation (80—100°/0.01 mmHg) and the sublimate was recrystallized from cyclohexane to give colorless needles, mp 158—159.5°. *Anal.* Calcd. for $C_{14}H_{11}N_3$: C, 75.99; H, 5.01; N, 18.99. Found: C, 76.25; H, 5.02; N, 18.88. MS *m/e*: 221 (M^+). UV λ_{max}^{EtOH} nm (log ε): 213 (4.64), 238.5 (4.40), 243.5 (4.59), 249 (4.73), 255 (4.77), 261 (4.67), 267.5 (3.86), 311 (3.80). NMR ($CDCl_3$): 2.73 (3H, s, CH_3), 7.60 (1H, s, quinoline C-3-H), 7.53, 7.70 (each 1H, bt, J=6.5 Hz, quinoline C-6,7-H), 7.96 (1H, dd, J=7 Hz, 2 Hz, quinoline C-5-H), 8.10 (1H, dd, J=7 Hz, 2 Hz, quinoline C-8-H), 9.18 (1H, s, pyrimidine C-2-H), 9.38 (2H, s, pyrimidine C-4,6-H).

Reaction of 2-Methylpyrazine (IX) with $HC(NHCHO)_3$——A mixture of 9.2 ml of IX, 28.1 g of $HC(NHCHO)_3$, 25 ml of $HCONH_2$, and 0.8 g of *p*-toluenesulfonic acid was heated at 165—170° for 10 hr in autoclave with stirring. After cooled, *ca.* 50 ml of H_2O was added to the reaction mixture and the resulting solution was continuously extracted with $CHCl_3$ for 16 hr. The $CHCl_3$ layer was woked up as usual and the residue was distilled under reduced pressure. The fraction of bp 85—90°/0.003 mmHg was recrystallized from petro. ether to give 0.95 g (6%) of 5-(2-pyrazinyl)pyrimidine (X) as colorless fine needles, mp 125—129°. For elemental analysis, the crystals were subjected to vacuum sublimation and the sublimate at 90—93°/0.003 mmHg was recrystallized from petro. ether to give colorless needles, mp 128—129°. *Anal.* Calcd. for $C_8H_6N_4$: C, 60.75; H, 3.82; N, 35.43. Found: C, 60.60; H, 3.80; N, 35.21. MS *m/e*: 158 (M^+). UV λ_{max}^{EtOH} nm (log ε): 235 (3.73), 249.5 (3.59), 258.5 (3.63), 281 (3.78). NMR ($CDCl_3$): 8.59 (1H, d, J=2.6 Hz, pyrazine C-5-H), 8.66 (1H, dd, J=2.6 Hz, 1.2 Hz, pyrazine C-6-H), 9.01 (1H, d, J=1.2 Hz, pyrazine C-3-H), 9.24 (1H, s, pyrimidine C-2-H), 9.30 (2H, s, pyrimidine C-4,6-H).

Reaction of 2,4-Dimethylthiazole (XIII) with $HCONH_2$——A mixture of 5.3 ml of XIII and 20 ml of $HCONH_2$ was heated at 170—180° for 34 hr with stirring. After cooled, *ca.* 30 ml of H_2O was added to the reaction mixture and the resulting solution was continuously extracted with benzene for 16 hr. The benzene layer was dried over Na_2SO_4 and evaporated. The residue was distilled under reduced pressure and the fraction of bp 70—80°/0.003 mmHg was recrystallized from cyclohexane to give 0.57 g (6.7%) of 4-methyl-2-(5-pyrimidinyl)thiazole (XIV) as colorless needles, mp 95—96.5°. *Anal.* Calcd. for $C_8H_7N_3S$: C, 54.23; H, 3.98; N, 23.72. Found: C, 54.29; H, 3.91; N, 23.65. MS *m/e*: 177 (M^+). UV λ_{max}^{EtOH} nm (log ε): 211 (3.87), 230 (3.91), 299 (4.41). NMR ($CDCl_3$): 2.56 (3H, d, J=1 Hz, CH_3), 7.10 (1H, q, J=1 Hz, thiazole C-5-H), 9.34 (3H, s, pyrimidine C-2,4,6-H).

Reaction of 2-Methylbenzoxazole (XVI) with $HCONH_2$-$POCl_3$——To 12 ml of $HCONH_2$, 5.5 ml of $POCl_3$ was added at 5—10° under stirring and after the addition was completed, stirring was continued for additional 0.5 hr. To the mixture, 3.0 ml of XVI was added at once and the resulting mixture was stirred at 60—70° for 6 hr followed by at 90—100° for 17 hr. After cooled, *ca.* 50 ml of H_2O was added to the reaction mixture, basified with Na_2CO_3, and extracted with ether. The ether layer was worked up as usual and the residue was recrystallized from dil. EtOH to give 0.61 g (25%) of *o*-hydroxyacetanilide (XVII) as colorless plates, mp 202—203.5°, identical with the authentic sample[4] (mixed mp, IR, and TLC).

Reaction of XVI with $HCONH_2$——A mixture of 5.8 ml of XVI and 20 ml of $HCONH_2$ was heated at 160—180° for 44 hr under N_2 stream. After cooled, *ca.* 30 ml of H_2O was added to the reaction mixture and the resulting solution was continuously extracted with benzene for 20 hr. The benzene layer was dried over Na_2SO_4 and evaporated and the hot cyclohexane-soluble fraction of the residue gave 1.5 ml (26%) of XVI. The hot cyclohexane-insoluble fraction was recrystallized from $CHCl_3$ to give 1.05 g (15.5%) of *o*-hydroxyformanilide (XVIII) as colorless plates, mp 127.5—129°, identical with the authentic sample[5] (mixed mp, IR, NMR, and TLC).

Reaction of 2-Methylbenzothiazole (XX) with $HCONH_2$——A mixture of 6.3 ml of XX and 20 ml of $HCONH_2$ was heated at 170—180° for 4 days with stirring. After cooled, *ca.* 50 ml of H_2O was added to the reaction mixture and the resulting solution was continuously extracted with ether for 16 hr. The ether layer was dried over Na_2SO_4 and evaporated. The residue was recrystallized from benzene to give 0.53 g

(6.4%) of 3,5-bis(benzothiazolyl)pyridine (XXII) as pale yellow fine plates, mp 241.5—243°. *Anal.* Calcd. for $C_{19}H_{11}N_3S_2$: C, 66.08; H, 3.21; N, 12.17. Found: C, 65.96; H, 3.25; N, 11.99. MS *m/e*: 345 (M^+). UV $\lambda_{max}^{CHCl_3}$ nm (log ε): 253 (4.36), 311 (4.68). NMR ($CDCl_3$): 7.54 (4H, m), 7.99 (2H, m), 8.17 (2H, m) benzothiazolyl-4,5,6,7-H, 9.03 (1H, t, $J=2$ Hz, pyridine C-4-H), 9.29 (2H, d, $J=2$ Hz, pyridine C-2,6-H). The mother benzene solution was distilled under reduced pressure to give 1.2 ml (19%) of XX (bp 37—40°/0.003 mmHg) and 0.18 g (1.8%) of 2-(5-pyrimidinyl)benzothiazole (XXI)[6] (bp 100—110°/0.003 mmHg) which was recrystallized from petro. ether to give colorless needles, mp 121—122°. *Anal.* Calcd. for $C_{11}H_7N_3S$: C, 61.97; H, 3.31; N, 19.71. Found: C, 61.82; H, 3.40; N, 19.59. UV λ_{max}^{EtOH} nm (log ε): 207 (4.63), 222.5 (4.54), 252 (4.28), 256 (4.28), 298 (4.53). NMR ($CDCl_3$): 7.56, 7.96 (each 2H, m, benzothiazole-H), 9.20 (1H, s, pyrimidine C-2-H), 9.29 (2H, s, pyrimidine C-4,6-H).

Reaction of XX with $HC(NHCHO)_3$——A mixture of 18.6 ml of XX, 28.1 g of $HC(NHCHO)_3$, and 30 ml of $HCONH_2$ was heated at 170—180° for 40 hr with stirring. After cooled, *ca.* 60 ml of H_2O was added to the reaction mixture and the resulting solution was continuously extracted with ether for 18 hr. The ether layer was dried over Na_2SO_4 and evaporated. The residue contained oil and crystals was filtered and the crystals were recrystallized from benzene to give 2.34 g (13.5%) of XXII as pale yellow fine plates, mp 241—243°, identical with the above XXII (mixed mp, IR, and TLC). The first oily filtrate was subjected to vacuum distillation to give 5.3 ml (28%) of XX, bp 123°/25 mmHg. Although the formation of XXI was observed in this residue on TLC, isolation was unsuccessful.

Reaction of 2-(2-Benzothiazolyl)malonaldehyde (XXIII)[6] with $HCONH_2$——A mixture of 0.51 g of XXIII and 4 ml of $HCONH_2$ was heated at 220—230° for 2 hr. After cooled, *ca.* 10 ml of H_2O was added to the reaction mixture and the resulting solution was extracted with $CHCl_3$. The $CHCl_3$ layer was worked up as usual and the residue was recrystallized from cyclohexane to give mixture of XXI and XXII, which was subjected to high vacuum sublimation. The sublimate at 80°/0.003 mmHg was recrystallized from cyclohexane to give 0.27 g (51%) of XXI as colorless fine needles, mp 121°. The residue of vacuum sublimation was recrystallized from benzene to give 0.06 g (14.5%) of XXII as colorless fine plates, mp 241—243°, identical with the above XXII (mixed mp, IR, and TLC).

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