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Studies on Pyrimidine Derivatives. VIII.[1] Ring-Cleavage Reaction of 4,6-Dimethylpyrimidine 1-Oxide

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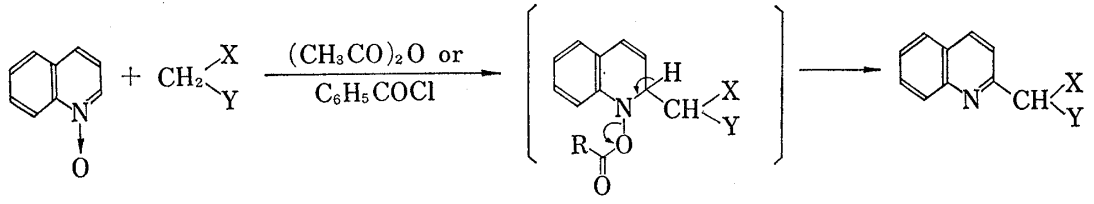
Unlike quinoline and isoquinoline N-oxides, 4,6-dimethylpyrimidine 1-oxide reacted with active methylene compounds such as malononitrile, ethyl cyanoacetate, and ethyl ethoxycarbonylacetimidate to give ring-opened products. In these cases, none of pyrimidine derivatives with a substituent at the 2-position were isolated.

On the other hand, the pyrimidine 1-oxide was condensed with 5-amino-3-methylisoxazole to give 2-(5-amino-3-methyl-4-isoxazolyl)-4,6-dimethylpyrimidine.

Comparing these two reactions, the driving force of the ring-fission of the reaction intermediates was discussed.

Keywords——4,6-dimethylpyrimidine 1-oxide; ring-cleavage reaction; active methylene compound; ethyl 2-ethoxycarbonylacetimidate; 5-amino-3-methylisoxazole; ethyl 4-ethoxy-2-methyl-5-pyrimidinecarboxylate

It is well known that the treatment of quinoline 1-oxides with active methylene compounds, in the presence of an appropriate acylating agent, gives the products possessing a carbon substituent at the α-position of the ring.[3] Previously, we have reported that the active methylene compounds such as 2-ethoxycarbonylacetamidine, ethyl 2-ethoxycarbonylacetimidate and the related ethyl imidates readily reacted with quinoline and isoquinoline N-oxides introducing a side chain with an imidate or amidine moiety to the α-position of the rings.[4]



X=CN; $COCH_3$; $C(=NH)OC_2H_5$; $C(=NH)NH_2$

Y=CN; $CO_2C_2H_5$; $CO_2C_2H_5$; $CO_2C_2H_5$

Chart 1

In order to synthesize pyrimidine derivatives containing a carbon function at the 2-position, we examined the reaction of the above reagents with 4,6-dimethylpyrimidine 1-oxide (I) and found the pyrimidine ring being cleaved, unlike quinoline and isoquinoline N-oxides, when the attacking nucleophiles contain an active hydrogen atom. In this paper we wish to report the details of these reactions.

1) Part VII: H. Yamanaka, K. Edo, F. Shoji, S. Konno, T. Sakamoto, and M. Mizugaki, *Chem. Pharm. Bull.* (Tokyo), **26**, 2160 (1978).
2) Location: *Aobayama, Sendai 980, Japan.*
3) *a*) M. Hamana and M. Yamazaki, *Chem. Pharm. Bull.* (Tokyo), **11**, 415 (1963); *b*) P. Bruni and G. Guerra, *Ann. Chim.* (Rome), **57**, 688 (1967) [*C.A.*, **67**, 16679*y* (1967)].
4) H. Yamanaka, S. Konno, M. Komatsu, and S. Ogawa, "Abstracts of the 9th Congress of Heterocyclic Chemistry," Fukuoka, 1976, p. 146.

According to the manner given for the reaction of quinoline 1-oxide with active methylene compounds, 4,6-dimethylpyrimidine 1-oxide (I) was allowed to react with malononitrile (II) in the presence of acetic anhydride to afford an adduct as pale yellow needles (IVa), mp 132° (dec.), in 93% yield. The elemental analysis exhibited the empirical formula of IVa to be $C_{11}H_{12}N_4O_2$. The infrared (IR) spectrum ($CHCl_3$) of IVa reveals the characteristic bands of cyano groups at 2190 cm^{-1} and an ester carbonyl group at 1760 cm^{-1}.

Based on these data, the cyclic (IIIa) and the open chain structure (IVa) were both assignable to the adduct, however, the following findings from the nuclear magnetic resonance (NMR) spectrum of the adduct contradicted the cyclic structure (IIIa). Namely, on the NMR spectrum ($CDCl_3$) of the adduct, there are observed signals at 7.69 ppm (1H, d, J=14.0 Hz) and 11.20—12.20 ppm (1H, broad d, J=14.0 Hz) as a pair of doublet along with signals due to three methyl groups. Analysis of the spectrum with the aid of a double resonance technique, shows these two doublets being coupled each other. The doublet at 11.20—12.20 ppm was assigned to an N–H proton, because it vanished with the addition of deuterium oxide.

Accordingly, it was reasonably concluded that the structure of the adduct was IVa which might be formed *via* the primary adduct (IIIa). None of evidence on the ring-chain tautomerism between IIIa and IVa was observed on the NMR spectrum.

While aminomethylenemalononitrile (V), mp 145—147° (lit.[5] mp 146°), was obtained in 42% yield by treatment of IVa with hydrochloric acid at room temperature, no 4,6-dimethyl-

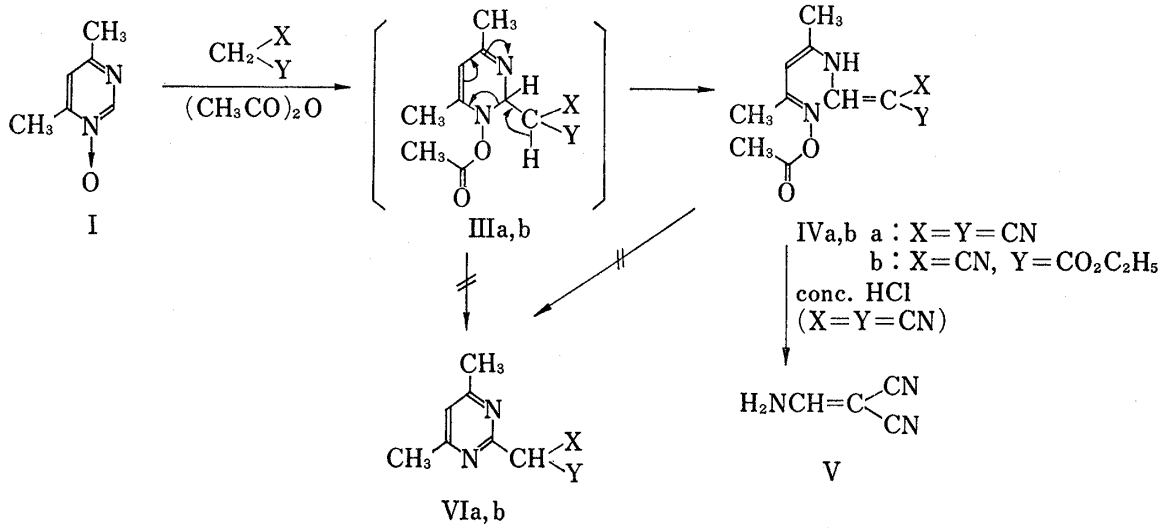


Chart 2

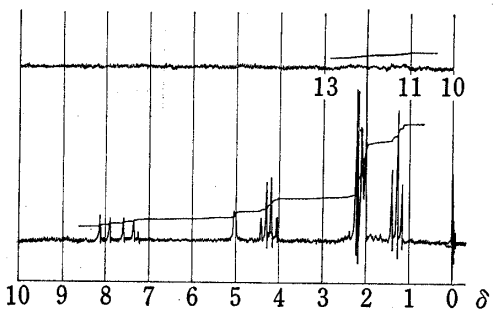


Fig. 1. NMR Spectrum of IVb in $CDCl_3$ (without D_2O)

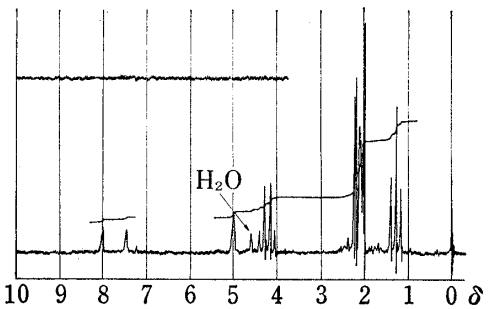


Fig. 2. NMR Spectrum of IVb in $CDCl_3$ (with D_2O)

5) A. Ishiwata, *Takamine Kenkyusho Nempo*, **9**, 21 (1957) [*Chem. Abstr.*, **55**, 1439c (1961)].

2-pyrimidinemalononitrile (VIa) was isolated by the thermal decomposition or the alkaline hydrolysis of IVa.

As well as II, ethyl cyanoacetate (VII) reacted with I to give an analogous adduct (IVb), $C_{13}H_{17}N_3O_4$, mp 127—128.5°, in 67% yield. As shown in Fig. 1 and 2, the NMR spectrum of the adduct reveals signals due to an olefinic proton [7.49 ppm (0.5 H, d, J=13.5 Hz), 8.03 ppm (0.5 H, d, J=14.0 Hz)] and an N–H proton [10.90—11.80 (0.5 H, broad), 11.80—12.70, (0.5 H, broad)]. The latter signals disappeared with addition of deuterium oxide accompanying with the change of the splitting pattern of the former signals from two doublets to two singlets. Although acid hydrolysis of the adduct gave no significant product, these spectral data suggest that the adduct also has the open chain structure (IVb).

Further, on the basis of the splitting pattern of the signals due to the methyl group (see Experimental), the olefinic proton, and the N–H proton, the adduct was presumed to be a 1:1 mixture of the E and Z isomers attributed to a $-C(H)=C(CN)(COOEt)$ moiety.

In order to prevent the pyrimidine N-oxide from cleaving the ring, ethyl 2-ethoxycarbonylacetimidate (VIII) was then adopted to react with I. It has been reported that[6] 1-morpholinocyclohexene readily condensed with pyrimidine N-oxide in the presence of benzoyl chloride to give the 2-substituted pyrimidine derivatives and that[4] in a chloroform solution of VIII, the enamine content on the enamine-ketimine tautomers is closely to 75%.

Thus, the pyrimidine 1-oxide (I) was allowed to react with VIII under the conditions given for the reaction of pyrimidine N-oxides with 1-morpholinocyclohexene yielding pale yellow needles (X), mp 114° (dec.), $C_{20}H_{25}N_3O_5$, in 61% yield. In the NMR spectrum ($CDCl_3$) of X, there are observed signals at 4.96 ppm (1H, broad, >C=CH–), 7.00—7.70 ppm (3H, m, phenyl ring protons), 7.80—8.70 ppm (4H, m, phenyl ring protons, >NCH=C<, and NH) and 11.00—12.50 (1H, broad, NH) along with the signals owing to two methyl and two ethyl groups.

When the spectrum was taken in the presence of deuterium oxide, the areal intensity of signals appeared at 7.80—8.70 ppm was reduced to three quarters, in addition to disappearance of the broad signal at 11.0—12.5 ppm. Accordingly it is obvious that the signals at 7.80—8.70 ppm are composed of signals due to two ring protons of a benzoyl group, one

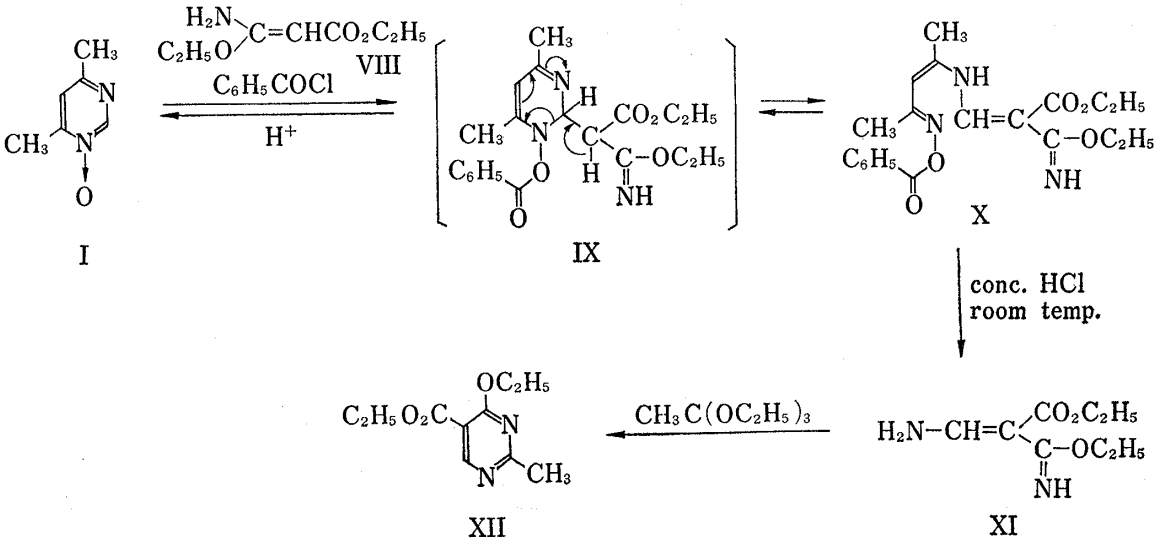


Chart 3

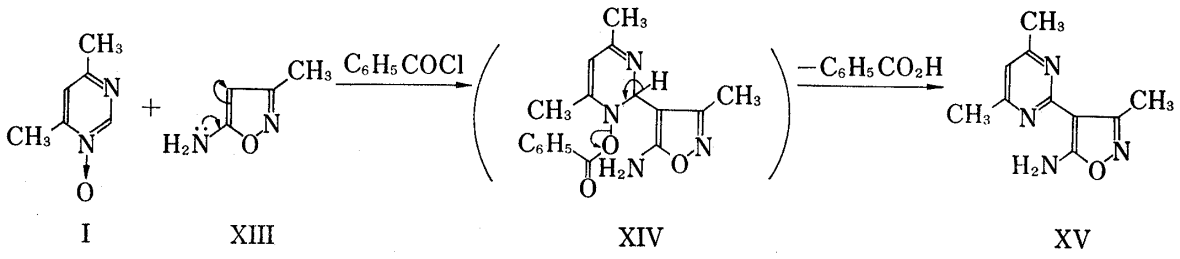
6) H. Yamanaka, S. Niitsuma, Y. Bannai, and T. Sakamoto, *Chem. Pharm. Bull.* (Tokyo), **23**, 2591 (1975).

olefinic proton and one N–H proton. These observations on the NMR spectra indicated that, contrary to the expectation, the adduct has an open chain structure (X) as in the case of IVa, b. However, the splitting pattern of the NMR signals corresponding to *E* and *Z* isomers was not recognized.

Treatment of X in concentrated hydrochloric acid afforded colorless crystallines (XI), mp 97—99°, $C_8H_{14}N_2O_3$, in 39% yield together with 38% yield of I. When XI was heated with excess ethyl orthoacetate, ethyl 4-ethoxy-2-methyl-5-pyrimidinecarboxylate (XII), mp 53—55°, was obtained which was identical with the authentic specimen prepared from ethyl 2-methyl-4-oxo-3,4-dihydro-5-pyrimidinecarboxylate.[7] Based on this finding and the spectral data of XI, the structure of this compound was assignable to ethyl 2-aminomethylene-2-ethoxycarbonylacetimidate (XI), even though the compounds of this type were previously believed to be unstable in a mineral acid.

Finally, the reaction of I with 5-amino-3-methylisoxazole (XIII) was investigated, since this compound was known to attack nucleophilically quinoline and isoquinoline N-oxides,[8] forming a carbon-carbon bond at the α-position of the rings.

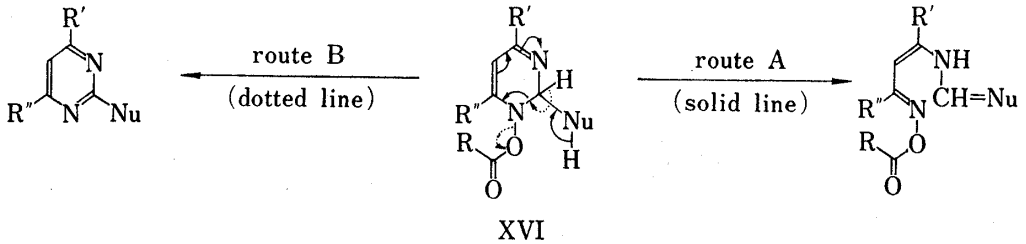
Thus, to a chloroform solution of I and XIII, an equimolecular amount of benzoyl chloride was added under ice-cooling to give colorless needles (XV), mp 199—200°, $C_{10}H_{12}N_4O$, in 7% yield. This product (XV) was stable in hot concentrated hydrochloric acid and as described in experimental section, the spectral data of XV were in good agreement with a 2-(5-amino-3-methyl-4-isoxazolyl)-4,6-dimethylpyrimidine structure.



I XIII XIV XV

Chart 4

Throughout this investigation, the reaction path ways of pyrimidine N-oxides with nucleophiles may be briefly summed up as follows. When the adducts (XVI) initially formed contain an active hydrogen atom at the α-carbon atom of the 2-substituents, XVI decay to give the open chain compounds (route A). The reactions with active methylene compounds and with VIII may proceed through this route. The ring transformation of pyrimidine N-oxides into isoxazoles[9] is also included in this route, although it was performed under acidic conditions.



XVI

Chart 5

7) S. Mizukami and E. Hirai, *J. Org. Chem.*, **31**, 1199 (1966).
8) H. Yamanaka, H. Egawa, and T. Sakamoto, *Chem. Pharm. Bull.* (Tokyo), **26**, 2759 (1978).
9) T Kato, H. Yamanaka, and N. Yasuda, *J. Org. Chem.*, **32**,3593 (1967).

In the case of the adducts (XVI) possessing no active hydrogen atom at the α-carbon atom, XVI are aromatized to the 2-substituted pyrimidine derivatives (route B). The Reissert-Henze reaction,[10] the condensation of morpholine enamines,[6] and that of 5-amino-3-methylisoxazole with pyrimidine N-oxides are considered to belong in this category.

Since the ring-cleavage reaction of pyridine, quinoline and isoquinoline N-oxides with active methylene compounds has not been reported, the driving force of the ring fission of pyrimidine N-oxides may be electron-withdrawing effect of another tertiary nitrogen atom located in pyrimidine rings.

Experimental[11]

Reaction of 4,6-Dimethylpyrimidine 1-Oxide (I) with Malononitrile in the Presence of Acetic Anhydride——A mixture of I (2.48 g, 0.02 mol), malononitrile (2.00 g, 0.03 mol), and acetic anhydride (10 ml) was briefly warmed on a water bath under vigorous stirring until the mixture became to a clear solution. After the solution had been stood at room temperature for 24 hr, the resulting precipitates were filtered and washed with ether giving pale yellow crystals, mp 132° (dec.), yield 4.34 g (93%). *Anal.* Calcd. for $C_{11}H_{12}N_4O_2$ (IVa): C, 56.89; H, 5.21; N, 24.13. Found: C, 56.71; H, 5.24; N, 24.42. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3000 (broad), 2190, 1760. NMR ($CDCl_3$) δ: 2.07 (3H, s), 2.15 (3H, s), 2.18 (3H, s), 5.10 (1H, broad s), 7.69 (1H, d, J=14.0), 11.20—12.20 (1H, broad d, J=14.0).

Reaction of I with Ethyl Cyanoacetate in the Presence of Acetic Anhydride——A mixture of I (2.48 g, 0.02 mol), ethyl cyanoacetate (2.72 g, 0.024 mol), and acetic anhydride (4 ml) was briefly warmed on a water bath under vigorous stirring until the mixture became to a clear solution. After the solution had been stood at −4° for 48 hr, the resulting precipitates were filtered and recrystallized from acetone–petr. benzine to afford pale yellow prisms, mp 127—128.5°, yield 3.72 g (67%). *Anal.* Calcd. for $C_{13}H_{17}N_3O_4$ (IVb): C, 55.90; H, 6.14; N, 15.05. Found: C, 55.74; H, 6.23; N, 14.81. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3100 (broad), 2200, 1765, 1700. NMR ($CDCl_3$) δ: 1.30 (3H, t, J=7.0), 2.04 (3H, s), 2.11 (1.5 H, s), 2.13 (1.5 H, s), 2.21 (1.5 H, s) 2.25 (1.5 H, s), 4.24 (2H, q, J=7.0), 5.04 (1H, broad s), 7.49 (0.5 H, d, J=13.5), 8.03 (0.5 H, d, J=14.0), 10.90—11.80 (0.5 H, broad), 11.80—12.70 (0.5 H, broad).

Reaction of I with Ethyl 2-Ethoxycarbonylacetimidate (VIII) in the Presence of Benzoyl Chloride——To a $CHCl_3$ (20 ml) solution of I (4.96 g, 0.04 mol) and VIII (9.60 g, 0.06 mol) was added benzoyl chloride (6.80 g, 0.048 mol) under ice-cooling and the mixture was stirred for 10 min. Petr. benzine (30 ml) was added to the mixture and the resulting precipitates were filtered and washed with petr. benzine (30 ml). The precipitates were dissolved in water (100 ml) by heating on a water bath and the solution was immediately cooled to room temperature, washed with ether, made alkaline with K_2CO_3, and extracted with benzene. The benzene was removed under reduced pressure to give pale yellow needles which were recrystallized from ether, mp 114° (dec.), yield 9.47 g (61%). *Anal.* Calcd. for $C_{20}H_{25}N_3O_5$ (X): C, 62.00; H, 6.50; N, 10.85. Found: C, 61.93; H, 6.48; N, 10.79. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3310, 3200, 1750, 1700. NMR ($CDCl_3$) δ: 1.20 (3H, t, J=7.0), 1.30 (3H, t, J=7.0), 2.11 (3H, s) 2.14 (3H, s), 4.21 (2H, q, J=7.0), 4.29 (2H, q, J=7.0), 4.96 (1H, broad s), 7.00—7.70 (3H, m), 7.80—8.70 (4H, m), 11.00—12.50 (1H, broad).

Hydrolysis of IVa with Concentrated Hydrochloric Acid——A mixture of IVa (2.32 g, 0.01 mol), conc. HCl (20 ml), and ether (50 ml) was stirred for 24 hr at room temperature. After separation of the ethereal layer, the aqueous solution was diluted with water (40 ml) and extracted with ether. The combined ethereal extracts were dried over Na_2SO_4 and the ether was removed to afford colorless needles which were recrystallized from acetone–benzene, mp 145—147°, yield 0.39 g (42%). This compound is identical with the authentic aminomethylenemalononitrile.[5]

Hydrolysis of X with Concentrated Hydrochloric Acid——A mixture of X (2.00 g, 0.005 mol) and conc. HCl (10 ml) was stood at room temperature for 12 hr. The mixture was washed with ether, diluted with water (10 ml), made alkaline with K_2CO_3, and extracted with ether. The extract was concentrated to give a residue. The residue was purified by Al_2O_3 column chromatography (ether) to afford colorless needles which were recrystallized from ether–petr. benzine, mp 97.5—99°, yield 0.38 g (39%). From the aqueous mother liquor, 4,6-dimethylpyrimidine 1-oxide (I) was obtained in 38% yield. *Anal.* Calcd. for $C_8H_{14}N_2O_3$ (XI): C, 51.60; H, 7.58; N, 15.04. Found: C, 51.63; H, 7.56; N, 15.26. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3520, 3400, 3320, 1680. NMR ($CDCl_3$) δ: 1.29 (3H, t, J=7.0), 1.36 (3H, t, J=7.0), 4.21 (2H, q, J=7.0), 4.34 (2H, q, J=7.0), 5.80—6.70 (1H, broad), 7.70—9.00 (3H, broad).

10) H. Yamanaka, *Chem. Pharm. Bull.* (Tokyo), **6**, 633 (1958).

11) All melting points are uncorrected. The IR spectra were taken with a JASCO IRA-1 spectrometer and the NMR spectra with a Hitachi R-20 spectrometer. The chemical shift of signals is expressed by δ and the coupling constants by Herz. Following abbreviations are used: singlet (s), doublet (d), triplet (t), quartet (q), and multiplet (m).

Ethyl 4-Ethoxy-2-methyl-5-pyrimidinecarboxylate (XII)——A mixture of XI (0.56 g, 0.03 mol) and ethyl orthoacetate (0.97 g, 0.06 mol) was heated at 130° for 2.5 hr followed by addition of 10% HCl (10 ml). The mixture was washed with ether, made alkaline with K_2CO_3, and extracted with ether. The ether was removed and the residue was purified by Al_2O_3 column chromatography (ether). The ether was removed to give colorless needles which were recrystallized from petr. benzine, mp 53—55°, yield 0.20 g (34%).

2-(5-Amino-3-methyl-4-isoxazolyl)-4,6-dimethylpyrimidine (XV)——To a $CHCl_3$ (6 ml) solution of I (1.24 g, 0.01 mol) and benzoyl chloride (1.69 g, 0.012 mol) was added a $CHCl_3$ (4 ml) solution of XIII (1.18 g, 0.012 mol) with stirring at −4° and the mixture kept at the same temperature for 24 hr. The reaction mixture was extracted with 3 N HCl and the extract was made alkaline with K_2CO_3 and extracted with ether. The ether extract was washed with 3 N NaOH and H_2O and dried over K_2CO_3. The ether was removed and the residue was purified by Al_2O_3 column chromatography (ether) to give colorless needles which were recrystallized from benzene, mp 198—200°, yield 0.14 g (7%). *Anal.* Calcd. for $C_{10}H_{12}N_4O$: C, 58.81; H, 5.92; N, 27.44. Found: C, 58.96; H, 5.91; N, 27.49. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3500, 3300. NMR ($CDCl_3$) δ: 2.40 (6H, s), 2.55 (3H, s), 6.66 (1H, s), 6.10—7.30 (2H, broad).

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