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Synthesis of Compounds related to Antitumor Agents. V.[1] On the Reaction of Aliphatic Carboxylates with 2,4-Diamino-5-hydroxy-6-methylpyrimidine

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In a previous paper, we described the reaction of some aromatic carboxylates with 2,4-diamino-5-hydroxy-6-methylpyrimidine. In continuation with this work, this paper deals with the synthesis of oxazolo[4,5-*d*]pyrimidines, pyrimido[5,4-*b*][1,4]oxazines and pyrimido-[5,4-*b*][1,4]oxazepines by the reaction of 2,4-diamino-5-hydroxy-6-methylpyrimidine with aliphatic carboxylates.

Keywords——nucleoside base having purine analogy; pyrimidine derivatives; aliphatic carboxylates; diethyl malonate; diethyl bromomalonate; maleic anhydride

In the synthesis of nucleoside base having purine analogy, we have reported the syntheses of oxazolo[4,5-*d*]pyrimidine derivatives from 2,4-diamino-5-hydroxy-6-methylpyrimidine(I). In a previous paper,[1] we described that 5 hydroxyl group of I attacked to some aromatic carboxylates as a nucleophile. This paper deals with the reaction of I with aliphatic carboxylates.

A fusion of I in diethyl malonate at 140—150° afforded ethyl β-ethoxy-β-hydroxy-β-(2,3-diamino-6-methylpyrimidine-5-yl)oxypropylcarboxylate(II) in 30% yield. The structure of II was evident from its elementary analysis and the presence of methylene signal and two ethyl signals in nuclear magnetic resonance (NMR) spectrum.

Treatment of the hemiacetal (II) with acetic acid afforded two compounds (III and IV), which were separated by fractional recrystallization from ethanol; one of them was obtained as colorless prisms, mp 166.5—168°, and its infrared (IR) spectrum showed the disappearance of ester carbonyl band. The other compound was formed as colorless needles, mp 152—153°, whose ultraviolet (UV) spectrum showed the same absorption maximum of some oxazolo[4,5-*d*]pyrimidines[3] synthesized in this laboratory. These IR spectra of III and IV exhibited characteristic absorption peaks of primary amine near 3425—3320 cm^{-1}. Therefore, the former was assigned to 2-amino-9-acetyl-6-ethoxy-6-hydroxy-4-methyl-7H-pyrimido[5,4-*b*][1,4]oxazepin-8-one(III) and the latter to 5-amino-3-acetyl-2-ethoxycarbonylmethyl-7-methyl-oxazolo-[4,5-*d*]pyrimidine (IV). Since the yield of IV was very small amount, further investigation could not be carried out.

Further evidence for the structure of III was given by the following facts. Refluxing III in ethanol for several hours gave 2-amino-9-acetyl-4-methyl-7H-pyrimido[5,4-*b*][1,4]oxazepin-6,8-dione (VI), which were also obtained from 2-(2,4-diamino-6-methylpyrimidine-5-yl)-oxycarbonylacetic acid hydrochloride (V) and acetic acid-pyridine. The IR spectrum of IV showed a characteristic absorption peak of lactone at 1770 cm^{-1}. Subsequently, VI was hydrolyzed in 10% HCl to give 2-(2,4-diamino-5-hydroxy-6-methylpyrimidine-4-yl)carbamoylacetic acid(VII). Compounds (VII) was cyclized to 2-amino-4-methyl-7H-pyrimido[5,4-*b*]-[1,4]oxazepin-6,8(9H)-dione(VIII) by heating in dimethyl sulfoxide for 5 hours, which was identical with the compound derived from I and malonyl chloride.

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[1] Part IV: T. Kato, N. Oda, and I. Ito, *Chem. Pharm. Bull.* (Tokyo), 24, 2461 (1976).

[2] Location: *Tanabe-dori, Mizuho-ku, Nagoya.*

[3] I. Ito, N. Oda, and T. Kato, *Chem. Pharm. Bull.* (Tokyo), 24, 1189 (1976).

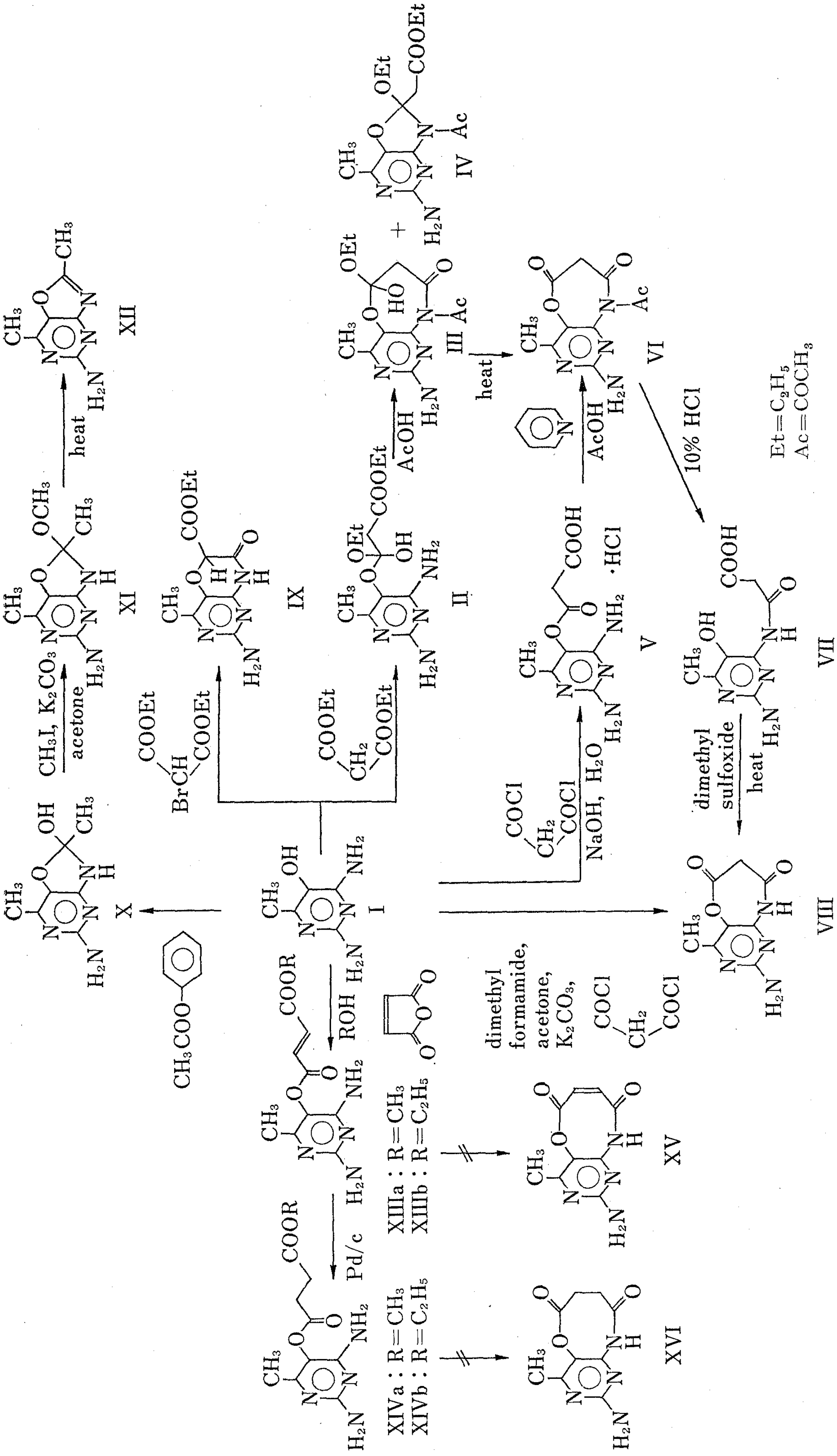
I
II
III
IV
V
VI
VII
VIII
IX
X
XI
XII
XIIIa : R=CH$_3$
XIIIb : R=C$_2$H$_5$
XIVa : R=CH$_3$
XIVb : R=C$_2$H$_5$
XV
XVI
CH$_3$COO-C$_6$H$_5$
CH$_3$I, K$_2$CO$_3$
acetone
heat
BrCH(COOEt)$_2$
CH$_2$(COOEt)$_2$
AcOH
CH$_2$(COCl)$_2$
NaOH, H$_2$O
·HCl
10% HCl
dimethyl sulfoxide
heat
ROH
Pd/c
dimethyl formamide, acetone, K$_2$CO$_3$,
CH$_2$(COCl)$_2$
Et=C$_2$H$_5$
Ac=COCH$_3$

Chart 1

When I was allowed to react with diethyl bromomalonate, instead of diethyl malonate, the product obtained was not the hemiacetal such as II but 2-amino-6-ethoxycarbonyl-4-methyl-pyrimido[5,4-*b*][1,4]oxazin-7(8H)-one (IX). The structure of IX was confirmed by the appearance of methine signal at δ 5.64 in the NMR spectrum and by the bathochromic shift to 312 $m\mu$, which was similar to that of some pyrimido[5,4-*b*][1,4]oxazines.[3] That IX was obtained, seemed to be attributable to the resonance stabilization of the carbonium ion by the α-bromine substituent of diethyl bromomalonate.[4]

Refluxing I with phenyl acetate in ethanol afforded 5-amino-2-hydroxy-2,7-dimethyl-3H-oxazolo[4,5-*d*]pyrimidine (X) in 40% yield. The carbinolamine (X) was converted to 5-amino-2,7-dimethyl-oxazolo[4,5-*d*]pyrimidine (XII), according to the method described previously.[1]

We attempted to synthesize the pyrimidines having eight membered condensed ring. On treatment of I with maleic anhydride in alcohol, alkyl 3-(2,4-diamino-6-methylpyrimidine-5-yl)oxycarbonyl-2-propylen carboxylates (XIIIa and XIIIb) were obtained in 40—50% yield. Compounds (XIIIa and XIIIb) were reduced with 5% palladium on charcoal to give alkyl 3-(2,4-diamino-6-methylpyrimidine-5-yl)oxycarbonylpropyl carboxylates (XIVa and XIVb), whose NMR spectra showed the methylene signals as a A_2B_2 pattern at δ 2.40 in place of olefinic protons of XIIIa and XIIIb as a AB pattern at δ 5.90 and δ 6.35 ($J=12$ cps). However, attempts to prepare the eight membered condensed compounds (XV and XVI) from the compounds (XIIIa, XIIIb, XIVa, and XIVb) obtained were unsuccessful, and other routes to synthesize XV and XVI are now under investigation.

Experimental

All melting points were measured on a Yanagimoto Melting Points Apparatus and are uncorrected. IR spectra were taken on a JASCO infrared spectrophotometer IR-S. UV spectra were measured on a Hitachi EPS-3T spectrophotometer. NMR spectra were run on a JEOL JNM-MH-100 spectrometer using tetramethylsilane as an internal standard.

Ethyl β-Ethoxy-β-hydroxy-β-(2,4-diamino-6-methylpyrimidine-5-yl)oxypropyl Carboxylate (II)——A mixture of 0.5 g of I and 3 ml of diethyl malonate was heated on an oil bath at 140—150° for a few min. After cooled, the deposited crystals were washed ether and recrystallized from ethanol. mp 109—110°, colorless needles, 0.3 g (30%). IR ν_{max}^{KBr} cm^{-1}: 1740 (ester carbonyl). NMR ($CDCl_3$: $(CD_3)_2SO=2:1$) δ: 1.20 (6H, triplet, $J=7$ cps, $2\times$-$CH_2C\underline{H}_3$), 2.15 (3H, singlet, -CH_3), 3.10 (2H, singlet, -CH_2-), 4.04 (4H, quartet, $J=7$ cps, $2\times$-$C\underline{H}_2CH_3$), 7.20—7.80 (5H, broad singlet, exchanged with D_2O, $2\times$-NH_2, -OH). *Anal.* Calcd. for $C_{12}H_{20}O_5N_4$: C, 47.99; H, 6.71; N, 18.66. Found: C, 47.87; H, 6.66; N, 18.51.

2-Amino-9-acetyl-6-ethoxy-6-hydroxy-4-methyl-7H-pyrimido[5,4-*b*][1,4]oxazepin-8-one(III) and 5-Amino-3-acetyl-2-ethoxycarbonylmethyl-7-methyl-oxazolo[4,5-*d*]pyrimidine (IV)——A mixture of 0.3 g of II and 5 ml of acetic acid was heated on a water bath at 40—50° for 10 min. After evaporation of the solvent in *vacuo* below 40°, the residue were washed with 50% ethanol under cooling and the deposited crystals were collected.

These compounds were recrystallized from a small amount of ethanol to give III and IV. III, mp 166.5—168°, colorless prisms, 89 mg (30%). IR ν_{max}^{KBr} cm^{-1}: 1710, 1680 (amido carbonyl). NMR ($CDCl_3$) δ: 1.25 (3H, triplet, $J=7$ cps, -$CH_2C\underline{H}_3$), 2.20, 2.30 (6H, each singlet, $2\times$-CH_3), 3.65 (2H, singlet, -CH_2-), 4.10 (2H, quartet, $J=7$ cps, -$C\underline{H}_2CH_3$). *Anal.* Calcd. for $C_{12}H_{16}O_5N_4$: C, 48.65; H, 5.44; N, 18.91. Found: C, 48.32; H, 5.60; N, 19.00. IV, mp 152—153°, colorless needles, 16 mg (5%). IR ν_{max}^{KBr} cm^{-1}: 1750 (ester carbonyl), 1710 (amido carbonyl). UV λ_{max}^{EtOH} $m\mu$ (log ε): 302 (3.97). NMR ($CDCl_3$) δ: 1.25 (6H, triplet, $J=7$ cps, $2\times$-$CH_2C\underline{H}_3$), 2.15, 2.20 (6H, each singlet, $2\times$-CH_3), 3.25 (2H, singlet, -CH_2-), 4.10 (4H, quartet, $J=7$ cps, $2\times$-$C\underline{H}_2CH_3$). *Anal.* Calcd. for $C_{14}H_{20}O_5N_4$: C, 51.85; H, 6.22; N, 17.27. Found: C, 51.62; H, 5.98; N, 17.38.

2-(2,4-Diamino-6-methylpyrimidine-5-yl)oxycarbonylacetic Acid Hydrochloride (V)——To a solution of 0.5 g of I, 0.5 g of sodium hydroxide and 8 ml of water was added 0.3 g of malonyl chloride under cooling. The mixture was stirred for 30 min at room temperature and the deposited crystals were collected. It was recrystallized from ethanol to give V. mp 220—222° (decomp.), colorless prisms, 0.4 g (45%). *Anal.* Calcd. for $C_8H_{11}O_4N_4Cl$: C, 36.58; H, 4.22; N, 21.33. Found: C, 36.69; H, 4.39; N, 21.69.

2-Amino-9-acetyl-4-methyl-7H-pyrimido[5,4-*b*][1,4]oxazepin-6,8-dione (VI)——1) A mixture of 50 mg of III and 10 ml of ethanol was refluxed for 8 hr. After evaporation of the solvent, the residues were recrystallized from ethanol. mp 182—183°, colorless needles, 30 mg (70%).

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4) P. Salomma, "The Chemistry of the Carbonyl Group," ed by S. Patai, Interscience Publishers Inc., New York, 1966, p. 182.

2) A mixture of 0.5 g of V, 10 ml of acetic acid and 10 ml of pyridine was heated at 80—90° for 3 hr. After evaporation of the solvent, the residues were washed with 50% ethanol and the deposited crystals were recrystallized from ethanol. 0.3 g (65%). IR $\nu_{\max}^{\text{KBr}}$ cm^{-1}: 3425, 3320 (primary amine), 1760 (lactone), 1710, 1675 (amido carbonyl). NMR ($CDCl_3$: $(CD_3)_2SO=1:2$) δ 2.25, 2.30 (6H, each singlet, 2×-CH_3), 3.60 (2H, singlet, -CH_2-). *Anal.* Calcd. for $C_{10}H_{10}O_4N_4$: C, 48.00; H, 4.03; N, 22.39. Found: C, 47.82; H, 4.32; 22.51.

2-(2,4-Diamino-5-hydroxy-6-methylpyrimidine-5-yl)carbamoylacetic Acid (VII)——A mixture of 0.3 g of VI and 10 ml of 10% HCl was heated at 80—90° for 1 hr. After evaporation of the solvent, the residues were recrystallized from 50% ethanol. mp 193—195° (decomp.), colorless prisms, 0.1 g (40%). IR $\nu_{\max}^{\text{KBr}}$ cm^{-1}: 1700 (carboxylic acid), 1680, 1675 (amido carbonyl). *Anal.* Calcd. for $C_8H_{10}O_4N_4$: C, 42.48; H, 4.46; N, 24.77. Found: C, 42.30; H, 4.50; N, 24.80.

2-Amino-4-methyl-7H-pyrimido[5,4-*b*][1,4]oxazepin-6,8(9H)-dione (VIII)——1) A mixture of 0.1 g of VII and 2 ml of dimethyl sulfoxide was heated on an oil bath at 140—150° for 20 min. After cooled, 2 ml of water was added to the solution and the mixture was allowed to stand at room temperature for 10 hr. The deposited crystals were collected and recrystallized from ethanol. mp 201—202°, colorless prisms, 32 mg (35%).

2) To a solution of 0.5 g of I, 0.2 g of potassium carbonate, 4 ml of dimethylformamide and 4 ml of acetone was added 0.5 g of malonyl chloride under cooled. The mixture was heated at 40—50° for 5 hr. After cooled, the deposited crystals were collected and washed with water. The unsoluble crystals were recrystallized from ethanol. 0.18 g (25%). IR $\nu_{\max}^{\text{KBr}}$ cm^{-1}: 1770 (lactone), 1695 (amido carbonyl). NMR ($(CD_3)_2SO$) δ: 2.30 (3H, singlet, -CH_3), 3.70 (2H, singlet, -CH_2-). *Anal.* Calcd. for $C_8H_8O_3N_4$: C, 46.16; H, 3.87; N, 26.91. Found: C, 45.88; H, 3.80; N, 26.77.

2-Amino-6-ethoxycarbonyl-4-methyl-pyrimido[5,4-*b*][1,4]oxazin-7(8H)-one (IX)——A mixture of 0.3 g of I, 0.5 g of diethyl bromomalonate and 10 ml of ethanol was refluxed for 10 min. After cooled, the deposited crystals were collected and recrystallized from dry dimethylformamide. mp>300°, colorless needles, 0.19 g (37%). IR $\nu_{\max}^{\text{KBr}}$ cm^{-1}: 1735 (ester carbonyl), 1665 (amido carbonyl). NMR (CF_3COOD) δ: 2.30 (3H, singlet, -CH_3), 5.64 (1H, singlet, methine proton). UV $\lambda_{\max}^{\text{EtOH}}$ mμ (log ε): 300 (3.87). *Anal.* Calcd. for $C_{10}H_{12}O_4N_4$: C, 47.62; H, 4.80; N, 22.21. Found: C, 47.78; H, 5.11; N, 22.38.

5-Amino-2-hydroxy-2,7-dimethyl-3H-oxazolo[4,5-*d*]pyrimidine (X)——A mixture of 0.5 g of I, 0.5 g of phenyl acetate and 10 ml of ethanol was refluxed for 2 hr. After evaporation of the solvent, the residues were crystallized from ether and recrystallized from isopropyl alcohol. mp 172—173°, pale yellow needles, 0.34 g (55%). UV $\lambda_{\max}^{\text{EtOH}}$ mμ (log ε): 302 (3.99). *Anal.* Calcd. for $C_7H_{10}O_2N_4$: C, 46.15; H, 5.53; N, 30.75. Found: C, 46.35; H, 5.67; N, 30.92.

5-Amino-2-methoxy-2,7-dimethyl-3H-oxazolo[4,5-*d*]pyrimidine (XI)——A mixture of 0.3 g of X, 0.2 g of potassium carbonate, 20 ml of acetone and 0.5 g of methyl iodide was stirred for 20 hr at room temperature. After evaporation of the solvent, the residue were washed with water and the insoluble crystals were recrystallized from ethanol. mp 245—250° (decomp.), yellow needles, 0.2 g (62%). *Anal.* Calcd. for $C_8H_{12}O_2N_4$: C, 48.97; H, 6.16; N, 28.56. Found: C, 49.03; H, 6.23; N, 28.72.

5-Amino-2,7-dimethyl-oxazolo[4,5-*d*]pyrimidine (XII)——A mixture of 0.3 g of XI and 20 ml of ethanol was refluxed for 20 hr. After cooled, the deposited crystals were collected and recrystallized from ethanol. mp >300°, yellow needles, 80 mg (30%). *Anal.* Calcd. for $C_7H_8ON_4$: C, 51.21; H, 4.91; N, 34.13. Found: C, 51.50; H, 5.30; N, 34.39.

Alkyl 3-(2,4-Diamino-6-methylpyrimidine-5-yl)oxycarbonyl-2-propylen Carboxylates (XIIIa and XIIIb)——A mixture of 2 g of I, 2 g of maleic anhydride and 30 ml of alcohol was refluxed for a few min and the mixture was allowed to stand for 3 hr at room temperature. After evaporation of the solvent, the residues were crystallized from ether and the deposited crystals were recrystallized from alcohol. XIIIa, R=CH_3, mp 157—158°, colorless prisms, 1.35 g (40%). NMR ($CDCl_3$: $(CD_3)_2SO=1:1$) δ: 2.10 (3H, singlet, -CH_3), 3.60 (3H, singlet, -OCH_3), 5.90, 6.35 (2H, each doublet, $J=12$ cps, olefinic protons). *Anal.* Calcd. for $C_{10}H_{12}O_4N_4$: C, 47.62; H, 4.80; N, 22.21. Found: C, 47.33; H, 4.92; N, 22.47. XIIIb, R=C_2H_5, mp 105—107°, colorless needles 1.8 g (50%). *Anal.* Calcd. for $C_{11}H_{14}O_4N_4$: C, 49.62; H, 5.30; N, 21.04. Found: C, 50.00; H, 5.38; N, 20.88.

Alkyl 3-(2,4-Diamino-6-methylpyrimidine-5-yl)oxycarbonylpropyl Carboxylates (XIVa and XIVb)——A solution of 1 g of XIIIa or XIIIb in 50 ml of alcohol was hydrogenated over 1 g of 5% palladium on charcoal. The catalyst was filtered and the filtrate was evaporated to dryness. The residues were recrystallized from alcohol. XIVa, R-CH_3, mp 167—170° (decomp.), colorless prisms, 0.55 g (55%). NMR ($(CD_3)_2SO$: $CDCl_3=2:1$) δ: 2.10 (3H, singlet, -CH_3), 2.40 (4H, multiplet, A_2B_2 pattern, -CH_2CH_2-), 3.65 (3H, singlet, -OCH_3). *Anal.* Calcd. for $C_{10}H_{14}O_4N_4$: C, 47.24; H, 5.55; N, 22.04. Found: C, 47.33; H, 5.47; N, 22.39. XIVb, R=CH_2CH_3, mp 155°, colorless needles, 0.4 g (40%). *Anal.* Calcd. for $C_{11}H_{16}O_4N_4$: C, 49.25; H, 6.02; N, 20.88. Found: C, 49.40; H, 6.22; N, 20.91.

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