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Azole Series. III.[1] Reactions of 2-Acylamino-2-cyanoacetamides leading to 5-Aminooxazole-4-carboxamides and to Oxazolo[5,4-*d*]pyrimidines

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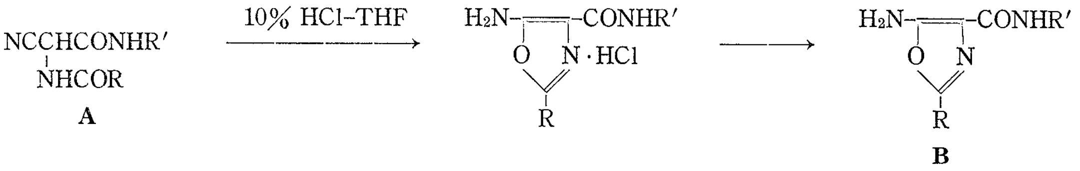
A series of 5-aminooxazole-4-carboxamides were obtained from 2-acylamino-2-cyanoacetamides by influence of hydrogen chloride. From these products syntheses of the corresponding oxazolo[5,4-*d*]pyrimidines were performed by the methods through 5-ethoxymethyleneaminooxazole-4-carboxamides as intermediates.

Although the previous paper in this field has reported the direct formations of 5-acylaminooxazole-4-carboxamides from 2-acylamino-2-cyanoacetamides and the ring closures of the resulting products to oxazolo[5,4-*d*]pyrimidines, this synthetic path does not seem satisfactory because of the low yields in the latter reactions. In continuing investigation, a synthetic path of oxazolo[5,4-*d*]pyrimidines through 5-aminooxazole-4-carboxamides other than the 5-acylamino compounds was found to be more convenient for their preparations.

On survey of literature several papers[1,3] reported the 5-aminooxazole formations from α-acylaminonitriles by catalytic action of acids. The formations of 5-aminooxazole-4-carboxamide hydrochlorides from 2-acylamino-2-cyanoacetamides were successfully performed by influence of hydrogen chloride in tetrahydrofuran. With four substrates, *i.e.*, 2-formamido- and 2-acetamido- derivatives of cyanoacetamide and of N-methylcyanoacetamide, the reactions smoothly proceeded in 10% hydrogen chloride-containing tetrahydrofuran mostly at room temperature to give the corresponding oxazole compounds as shown in Chart 1.



		A	B
R=H	R'=H	I	V
R=CH_3	R'=H	II	VI
R=H	R'=CH_3	III	VII
R=CH_3	R'=CH_3	IV	VIII

Chart 1

The hydrochlorides could not be in good keeping because of the decomposition to the starting 2-acylamino-2-cyanoacetamides. The free 5-aminooxazole-4-carboxamide obtained by treatment with sodium bicarbonate or silver oxide were more stable than the hydrochlorides. None of these 5-aminooxazole-4-carboxamides have been reported previously. Their structures were deduced by elemental analyses, and by infrared (IR), ultraviolet (UV) and nuclear magnetic resonance (NMR) spectroscopy. The UV spectra of these compounds have maxima at 257—262 mμ.

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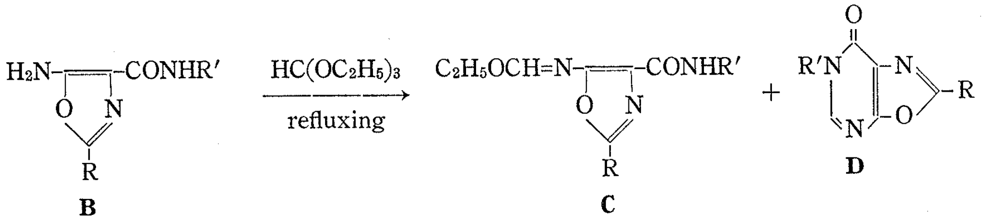
1) Part II: M. Sekiya, J. Suzuki and Y. Kakiya, *Chem. Pharm. Bull.* (Tokyo), **18**, 1233 (1970).
2) Location: *2-2-1, Oshika, Shizuoka.*
3) J. Lichtenberger and J.P. Fleury, *Bull. Soc. Chim. France*, **1956**, 1184; M. Grifantini and M.L. Stein, *Ann. Chim.* (Rome), **55**, 576 (1965); H.J. Barber, P.Z. Gregory, R. Slack, C.E. Stickings and A.M. Woolman, "The Chemistry of Penicillin," Princeton University Press, 1948, p. 701.

Conversions of 5-aminooxazole-4-carboxamides to 5-ethoxymethyleneaminooxazole-4-carboxamides were performed by refluxing with ethyl orthoformate. In these reactions spontaneous formations of oxazolo[5,4-*d*]pyrimidines were also observed to occur by succeeding pyrimidine ring closures. These product formations from V—VIII are summarised in Chart 2. The ethoxymethylene derivative of VIII could not be isolated because of difficulty of crystallization and therefore, the raw product was subjected to the succeeding reaction without purification.



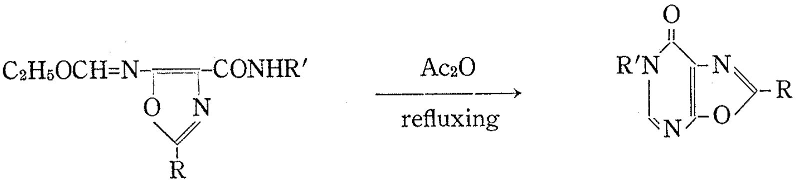
		B	C	D
R=H	R'=H	V	IX	
R=CH_3	R'=H	VI	X	XIII
R=H	R'=CH_3	VII	XI	XIV
R=CH_3	R'=CH_3	VIII	XII[a]	XV

a) Raw material not purified as crystals.

Chart 2

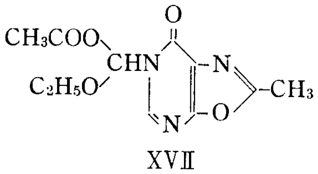
Assignment of ethoxymethyleneaminooxazole-4-carboxamides were made by elemental analyses and NMR and UV spectroscopy. The NMR spectra of these materials are consistent with the presence of ethoxymethyleneamino groupings by the following assignments: triplet at τ 8.60 to methyl hydrogens of ethyl, quartet at τ 5.55—5.62 to methylene hydrogens of ethyl, and singlet at τ 1.09—1.78 to methylidyne hydrogen.

5-Ethoxymethyleneaminooxazole-4-carboxamides, IX—XII, were smoothly converted into the corresponding oxazolo[5,4-*d*]pyrimidines, XVI, XIII—XV, respectively, when refluxed with acetic anhydride.



The compounds, XVI and XIII were identical with those obtained in the previously published paper[1] by noting exact correspondence of their UV, IR and NMR spectra. The analogous compounds, XIV and XV gave the similar UV spectra, and the corresponding NMR spectra, which are consistent with the assigned structures. Both the IR spectra of XIV and XV showed lack of a broad band at 2860—2870 cm^{-1} appeared in those of XVI and XIII. This band is indicative of hydrogen bond of NH hydrogen at 6 position and the observation is suggestive of substitution of methyl at 6 position in XIV and XV.

Trials for conversions of the 5-aminooxazole-4-carboxamides directly into oxazolo[5,4-*d*]-pyrimidines were also successfull by means of heating with a mixture of ethyl orthoformate and acetic anhydride. Compounds, VII and VIII gave XIV and XV in good yields, however, from V and VI, yields of XVI and XIII were lower because of byproduct formation. Crystals of a byproduct were isolated in the reaction with VI, recrystallization of which from ethyl acetate gave leaflets, mp 97—98°. We deduced formula, XVII for this material from the following data.



XVII

Data of the elemental analysis and determination of the molecular weight gave the molecular formula of $C_{11}H_{13}O_5N_3$. An observed UV spectrum resembled that of 2-methyloxazolo[5,4-*d*]pyrimidine-7-ol (XIII), suggesting the presence of oxazolo[5,4-*d*]pyrimidine skeleton. The compound was easily hydrolyzed to XIII by heating with water at 90°. An NMR spectrum was indicative of the existence of acetoxyethoxymethyl grouping $(CH_3COO\underset{|}{C}HOC_2H_5)$. Signals for the ethoxy hydrogens appeared as triplet at τ 8.71 to $C\underline{H}_3$ and multiplet from τ 6.35 to 5.82 to $C\underline{H}_2\langle$, which would be expected from the signals of diethyl acetal reported in the previous paper.[4] Methin hydrogen of $-NC\underline{H}\langle{}^{O-}_{O-}$ and methyl hydrogens of acetoxy appeared as two sets of singlets at τ 2.25 and τ 7.86. The presence of the carbonyl of the acetoxy was also seen at 1760 cm^{-1} in an IR spectrum.

Experimental

Formation of 5-Aminooxazole-4-carboxamides from 2-Acylamino-2-cyanoacetamides——5-Aminooxazole-4-carboxamide (V): To 30 ml of dry HCl–THF (content of HCl: 10%) 2.3 g of 2-formamido-2-cyanoacetamide (I) was suspended and stirred at room temperature for 4 days. The suspensing material was collected by filtration and desiccated *in vacuo* over sodium hydroxide pellets, mp 148—150° (decomp.). This material could not be purified, because of its instability for the reverse decomposition to the starting material. Its aqueous solution showed a single maximum absorption at 261 mμ, characteristic of 5-aminooxazole-4-carboxamide hydrochloride. An aqueous solution of the hydrochloride was treated with silver oxide freshly prepared from 6.8 g of silver nitrate. After filtration, the filtrate was concentrated under reduced pressure below 40°, to give solid residue, which was recrystallized from THF. Yield, 1.9 g (82.6%). An analytical sample was obtained on further recrystallization from THF, white prisms, mp 127—128°. UV λ_{max}^{EtOH} mμ (log ε): 258 (4.22). IR ν_{max}^{KBr} cm^{-1}: 3450, 3400 (NH_2), 1660 (CO). NMR τ (in D_2O): 2.53 (1H, singlet, $\rangle C\underline{H}$). *Anal.* Calcd. for $C_4H_5O_2N_3$: C, 37.80; H, 3.97; N, 33.06. Found: C, 37.98; H, 4.07; N, 33.25.

2-Methyl-5-aminooxazole-4-carboxamide (VI): To 75 ml of dry HCl–THF (content of HCl: 10%) 7.1 g of 2-acetamido-2-cyanoacetamide (II) was suspended. After stirring at room temperature for 4 days, the suspensing material was collected by filtration and desiccated *in vacuo* over sodium hydroxide pellets, mp 172—173° (decomp.). An aqueous solution of the product showed a single maximum absorption at 263 mμ. This material was suspended in 50 ml of water and sodium bicarbonate was added to give the free oxazole compound, weighing 6.9 g. Recrystallization from ethanol gave white leaflets, mp 157—158°. Yield, 5.2 g (73.1%). UV λ_{max}^{EtOH} mμ (log ε): 262 (4.20). IR ν_{max}^{KBr} cm^{-1}: 3490, 3410 (NH_2), 1665 (CO). *Anal.* Calcd. for $C_5H_7O_2N_3$: C, 42.55; H, 5.00; N, 29.78. Found: C, 42.80; H, 5.17; N, 29.81.

5-Aminooxazole-4-N-methylcarboxamide (VII): To 70 ml of dry HCl–THF (content of HCl: 10%) 5.64 g of 2-formamido-2-cyano-N-methylacetamide (III) was suspended. The mixture was warmed with stirring at 60—62° on a water-bath for 2.5 hr. On cool, the suspensing material was collected by filtration and desiccated *in vacuo* over sodium hydroxide pellets, mp 116—120° (decomp.). An aqueous solution of the product showed a single maximum absorption at 259.5 mμ. This material was suspended in 4 ml of water and neutralized by addition of sodium bicarbonate. The insoluble materials were collected by filtration, dried and extracted with boiling THF. After standing overnight, the deposited crystals were filtered and combined with a second crop obtained on concentration of the filtrate. Yield, 3.8 g (67.9%), mp 132—135°. An analytical sample was obtained as white prisms from THF, mp 137—138°. UV λ_{max}^{EtOH} mμ (log ε): 257 (4.21). IR ν_{max}^{KBr} cm^{-1}: 3430, 3350 (NH_2), 1650 (CO). *Anal.* Calcd. for $C_5H_7O_2N_3$: C, 42.55; H, 5.00; N, 29.78. Found: C, 42.29; H, 5.26; N, 29.65.

2-Methyl-5-aminooxazole-4-N-methylcarboxamide (VIII): To 35 ml of dry HCl–THF (content of HCl: 10%) 3.1 g of 2-acetamido-2-cyano-N-methylacetamide (IV) was suspended. After stirring at room temperature for 4 days, the suspensing material was collected by filtration and desiccated *in vacuo* over sodium hydroxide pellets, mp 134—137° (decomp.). An aqueous solution of the product showed a single maximum absorption at 262 mμ. This material was suspended in 3 ml of water and neutralized by addition of sodium bicarbonate. The precipitates were filtered and recrystallized from $CHCl_3$ to give white plates, mp 130—131°. Yield, 2.2 g (71.0%). UV λ_{max}^{EtOH} mμ (log ε): 260.5 (4.18). IR ν_{max}^{KBr} cm^{-1}: 3350, 3330 (NH_2), 1660 (CO). NMR τ (in $CDCl_3$): 7.67 (3H, singlet, $\rangle CC\underline{H}_3$), 7.07 (3H, doublet, $J=5$ cps, $-NHC\underline{H}_3$), 4.67 (2H,

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[4] K. Nukada and U. Maeda, *Bull. Chem. Soc. Japan*, 32, 655 (1959); K. Nukada, *ibid.*, 33, 1606 (1960).

broad, NH_2), 3.60 (1H, broad, $N\underline{H}CH_3$). *Anal.* Calcd. for $C_6H_9O_2N_3$: C, 46.44; H, 5.85; N, 27.08. Found: C, 46.17; H, 5.82; N, 27.02.

Formations of 5-Ethoxymethyleneaminooxazole-4-carboxamides from 5-Aminooxazole-4-carboxamides with Ethyl Orthoformate——5-Ethoxymethyleneaminooxazole-4-carboxamide (IX): To 15 ml of ethyl orthoformate 1.0 g of V was added. The mixture become homogeneous on refluxing was refluxed for 1 hr on an oil–bath. On cool, the deposited crystals were collected by filtration, weighing 0.9 g, mp 146—148°. An analytical sample was obtained as white leaflets by recrystallization from ethyl orthoformate, mp 149—150°. UV $\lambda_{\max}^{\mathrm{EtOH}}$ mμ (log ε): 222 (4.01), 277.5 (3.99). IR $\nu_{\max}^{\mathrm{KBr}}$ cm^{-1}: 1675 (CO). NMR τ (in $CDCl_3$): 8.60 (3H, triplet, J=7.5 cps, $C\underline{H}_3CH_2$), 5.61 (2H, quartet, J=7.5 cps, $CH_3C\underline{H}_2$), 1.98 (1H, singlet, O–C$\underline{H}$=N), 1.78 (1H, singlet, O–C$\underline{H}$=N). *Anal.* Calcd. for $C_7H_9O_3N_3$: C, 45.90; H, 4.95; N, 22.94. Found: C, 45.79; H, 5.12; N, 22.55. The solid residue obtained on concentration of the filtrate under reduced pressure was extracted with hot ethyl orthoformate. An additional amount of the above material was obtained from this ethyl orthoformate extract. Total yield, 1.1 g (78.6%). The material insoluble ethyl orthoformate was identified as I.

2-Methyl-5-ethoxymethyleneaminooxazole-4-carboxamide (X): To 21 ml of ethyl orthoformate 1.4 g of VI was added. The suspension was refluxed on an oil–bath. After about 5 hr, the crystals insoluble on refluxing were filtered, weighing 0.1 g, mp 268—275° (decomp.), which were identified as 2-methyloxazolo[5,4-*d*]pyrimidine-7-ol (XIII) by comparison of its IR and UV spectrum with those of the authentic sample prepared by another route.[1] The filtrate was allowed to stand at room temperature overnight. The deposited crystals were filtered and extracted with hot ethyl acetate. Insoluble material was shown to be additional XIII. Total yield, 0.6 g (40%). The extract was chilled in a refrigerator overnight to give white crystals, weighing 0.8 g, mp 141—143°. A second crop of identical material (0.1 g, total yield, 47.1%) was obtained on concentration of the mother liquor. Recrystallization from ethyl acetate gave white needles, mp 143—144°. UV $\lambda_{\max}^{\mathrm{EtOH}}$ mμ (log ε): 222.5 (4.05), 284.5 (4.02). IR $\nu_{\max}^{\mathrm{KBr}}$ cm^{-1}: 1678 (CO). NMR τ (in $CDCl_3$): 8.60 (3H, triplet, J=7.5 cps, $C\underline{H}_3CH_2$), 7.60 (3H, singlet, $\rangle CC\underline{H}_3$), 5.62 (2H, quartet, J=7.5 cps, $CH_3C\underline{H}_2$), 1.35 (1H, singlet, O–C$\underline{H}$=N). *Anal.* Calcd. for $C_8H_{11}O_3N_3$: C, 48.72; H, 5.62; N, 21.31. Found: C, 48.50; H, 5.60; N, 21.41.

5-Ethoxymethyleneaminooxazole-4-N-methylcarboxamide (XI): To 15 ml of ethyl orthoformate 0.99 g of VII was added. The mixture become homogeneous on refluxing was heated and refluxed for 2 hr. The reaction solution was concentrated under reduced pressure and the resulting residue was extracted with hot ethyl acetate. Insoluble material, yielding 0.06 g (5.7%), mp 185—187°, was identified as 6-methyloxazolo[5,4-*d*]pyrimidine-7-one (XIV) by comparison of its IR and UV spectrum with those of a specimen obtained by the reaction described later. The ethyl acetate extract was chilled in a refrigerator to give white crystals, weighing 1.0 g, mp 74—77°. A second crop of identical material (0.1 g, total yield 75.4%) was obtained on concentration of the mother liquor. Recrystallization from ethyl acetate gave white needles, mp 82—84°. UV $\lambda_{\max}^{\mathrm{EtOH}}$ mμ (log ε): 222.5 (4.08), 277 (4.04). IR $\nu_{\max}^{\mathrm{KBr}}$ cm^{-1}: 1668 (CO). NMR τ (in $CDCl_3$): 8.58 (3H, triplet, J=7.5 cps, $C\underline{H}_3CH_2$), 7.03 (3H, doublet, J=5 cps, $NHC\underline{H}_3$), 5.55 (2H, quartet, J=7.5 cps, $CH_3C\underline{H}_2$), 2.40 (1H, singlet, O–C$\underline{H}$–N), 1.09 (1H, singlet, O–C$\underline{H}$=N). *Anal.* Calcd. for $C_8H_{11}O_3N_3$: C, 48.72; H, 5.62; N, 21.31. Found: C, 48.78; H, 5.61; N, 21.77.

Formations of Oxazolo[5,4-*d*]pyrimidine-7-ols——Oxazolo[5,4-*d*]pyrimidine-7-ol (XVI): i) To 18 ml of acetic anhydride 1.83 g of IX was added. The mixture was refluxed for 10 min on an oil–bath. After standing in a refrigerator the deposited crystals were filtered, weighing 0.87 g, mp>300°. A second crop of identical material (0.18 g, total yield, 77.1%) was obtained on concentration of the filtrate. This material was identified as XVI by comparison of its IR and UV spectrum with those of the authentic sample prepared by another route.[1]

ii) To a mixture of 9.5 ml of acetic anhydride and 9.5 ml of ethyl orthoformate 1.27 g of V was added. The mixture was refluxed for 1.5 hr. The reaction solution was concentrated under reduced pressure. The resulting resinous residue was dissolved in a small amount of chloroform and allowed to stand in a refrigerator overnight. The deposited crystals were filtered, washed with chloroform and dried. Yield, 0.61 g (44.5%), mp>300°.

2-Methyloxazolo[5,4-*d*]pyrimidine-7-ol (XIII): i) To 10 ml of acetic anhydride 0.98 g of X was added. The mixture was refluxed for 10 min. After standing in a refrigerator overnight, the white needles was filtered, weighing 0.46 g, mp 275—278° (decomp.). A second crop of identical material (0.91 g, total yield, 85.5%) was obtained on concentration of the filtrate under reduced pressure. This material was identified as XIII by comparison of its IR and UV spectrum with those of an authentic sample.

ii) To a mixture of 10.4 ml of acetic anhydride and 10.4 ml of ethyl orthoformate 1.4 g of VI was added. The mixture was refluxed for 30 min. After standing in a refrigerator overnight, the deposited precipitates were collected by filtration, weighing 0.33 g, mp 276—277° (decomp.). The filtrate was concentrated under reduced pressure and the resulting residue was triturated with a small amount of ethanol and filtered, weighing 0.35 g, mp 272—274° (decomp.). Total yield, 45.0%. These materials were identified as XIII by comparison of its IR and UV spectrum with those of an authentic sample.

The filtrate was sufficiently chilled in a refrigerator. The deposited crystals were collected by filtration and dried, yielding 0.76 g (28.6%), mp 89—92°. Recrystallization from ethyl acetate gave white leaflets, mp 96—97°. UV $\lambda_{\max}^{\mathrm{EtOH}}$ mμ (log ε): 235 (3.93) shoulder, 239 (3.97), 245 (3.45) shoulder, 277 (3.70). IR $\nu_{\max}^{\mathrm{KBr}}$ cm^{-1}: 1760 (CH_3COO-). NMR τ (in $CDCl_3$): 8.71 (3H, triplet, $J=7.2$ cps, $C\underline{H}_3CH_2$), 7.86 (3H, singlet, $C\underline{H}_3CO$), 7.38 (3H, singlet, ⫽$CC\underline{H}_3$), 6.35—5.82 (2H, multiplet, $CH_3C\underline{H}_2$), 2.25 $\left(1H, \text{singlet}, -NCH\Big\langle{}^{O-}_{O-}\right)$, 1.67 (1H, singlet, ⫽$C\underline{H}$ (pyrimidine)). Molecular weight Calcd. for $C_{11}H_{13}O_5N_3$: 267.24. Found: 271.1 (vapor pressure lowering method). *Anal.* Calcd. for $C_{11}H_{13}O_5N_3$: C, 49.43; H, 4.90; N, 15.73. Found: C, 49.49; H, 5.03; N, 15.72.

An aqueous solution of this compound was heated for 1 hr on a boiling water–bath. On cool, the precipitates were collected by filtration and identified as XIII by comparison of its IR and UV spectrum with those of an authentic sample. Additional amount of XIII was obtained on concentration of the filtrate. The yield was theoretical.

6-Methyloxazolo[5,4-*d*]pyrimidine-7-one (XIV): i) To 5 ml of acetic anhydride 500 mg of XI was added. The mixture was refluxed for 10 min. The reaction solution was concentrated under reduced pressure to give a solid residue, which was washed with a small amount of ethyl acetate and filtered, weighing 322 mg (85.2%). Recrystallization from methanol gave white leaflets, mp 187.5—188°. UV $\lambda_{\max}^{\mathrm{EtOH}}$ mμ (log ε): 232.5 (3.91) shoulder, 238.5 (3.97), 244.5 (3.89) shoulder, 272 (3.73). IR $\nu_{\max}^{\mathrm{KBr}}$ cm^{-1}: 1700 (CO). NMR τ (in CF_3COOH): 6.03 (3H, singlet, $>NC\underline{H}_3$), 1.32 (1H, singlet, ⫽$C\underline{H}$ (oxazole)), 1.17 (1H, singlet, ⫽$C\underline{H}$ (pyrimidine)). *Anal.* Calcd. for $C_6H_5O_2N_3$: C, 47.68; H, 3.34; N, 27.81. Found: C, 47.45; H, 3.40; N, 27.58.

ii) To a mixture of 8.5 ml of acetic anhydride and 8.5 ml of ethyl orthoformate 1.13 g of VII was added. The mixture was refluxed for 5 hr. The reaction solution was concentrated under reduced pressure. The resulting solid residue was washed with a small amount of ethyl acetate and filtered. Yield, 1.05 g (86.5%), mp 186—188°.

2,6-Dimethyloxazolo[5,4-*d*]pyrimidine-7-one (XV): i) To 45 ml of ethyl orthoformate 3.1 g of VIII was added. The suspension was refluxed for 2 hr. Upon partial concentration of under reduced pressure fine needles were crystallized from the reaction mixture. This material was shown to be 2,6-dimethyloxazolo[5,4-*d*]pyrimidine-7-one (XV), weighing 0.3 g (9.0%) on filtration, mp 193—197°. The filtrate was concentrated under reduced pressure. The resulting pasty residue was triturated ethyl acetate to give white powder, weighing 0.3 g (9.7%) on filtration, mp 149—152°, which was identified as IV. The filtrate was evaporated to give pasty residue which showed two maxima absorption at 227 and 283 mμ in ethanol resembled to other analogous 5-ethoxymethyleneaminooxazole compounds. Because of difficulty for crystallization, the paste was without purification, submitted to the following oxazolo[5,4-*d*]pyrimidine formation reaction.

To 30 ml of acetic anhydride the paste was added and the mixture was refluxed for 10 min. The reaction solution was concentrated under reduced pressure. The resulting crystalline residue was triturated with ethyl acetate, and the crystals were collected by filtration, weighing 2.1 g, mp 193—197°. Recrystallization from methanol gave white needles, mp 201—202.° Yield, 1.76 g (53.3% based on VIII). UV $\lambda_{\max}^{\mathrm{EtOH}}$ mμ (log ε): 235 (3.96) shoulder, 239.5 (4.02), 245.5 (3.96) shoulder, 275.5 (3.77). IR $\nu_{\max}^{\mathrm{KBr}}$ cm^{-1}:1715 (CO). NMR τ (in CF_3COOH): 7.07 (3H, singlet, ⫽$CC\underline{H}_3$), 6.05 (3H, singlet, $>NC\underline{H}_3$), 1.18 (1H, singlet, ⫽$C\underline{H}$ (pyrimidine)). *Anal.* Calcd. for $C_7H_7O_2N_3$: C, 50.91; H, 4.27; N, 25.45. Found: C, 50.82; H, 4.35; N, 25.23.

ii) To a mixture of 11.7 ml of acetic anhydride and 11.7 ml of ethyl orthoformate 1.55 g of VIII was added. The mixture was heated under reflux for 4 hr. The reaction solution was concentrated under reduced pressure to give a solid residue which was washed with ethyl acetate and filtered, yielding 1.39 g (84.2%), mp 197—200°.

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