UDC 547.859.3.07

100. Yasuo Makisumi : Studies on the Azaindolizine Compounds. X.*2 Synthesis of 5,7-Disubstituted Pyrazolo[1,5-*a*]pyrimidines.

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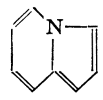
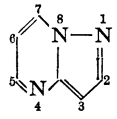
In the previous papers of this series, the author reported on the synthesis and the reactivity of the *s*-triazolo[1,5-*a*]pyrimidine derivatives.

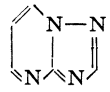
In order to investige on the general property and reactivity of the azaindolizine compounds, the synthesis of the derivatives of pyrazolo[1,5-*a*]pyrimidine (I) possessing the similar structure to *s*-triazolo[1,5-*a*]pyrimidine (II) as one of the azaindolizine compounds was attempted.



indolizine



(I)



(II)

The present paper describes the synthesis of 5,7-disubstituted pyrazolo[1,5-*a*]pyrimidines by means of the condensation of 1,3-dicarbonyl compounds with 5-aminopyrazole (III) and its derivatives.

As the starting compounds, (III) and its derivatives were prepared by the methods reported by Schmidt and Druey.[1,2]

Condensation of ethyl acetoacetate with (III) in boiling glacial acetic acid gave a product (IV), $C_7H_7ON_3$, m.p. 298~299°, in a good yield. When ethanol instead of glacial acetic acid was used as the solvent, (IV) was obtained in 60% yield, but the yield of (IV) was improved to the theoretical one by the addition of a small amount of dehydrous zinc cnloride. On the other hand, reaction of ethyl acetoacetate with (III) without solvent at room temperature gave a product (V), $C_9H_{13}O_2N_3$, m.p. 102°, in a good yield. This product showed an absorption band at 293 mμ (log ε 4.30) in the ultraviolet region, absorption bands of the NH groups of ring and side chain, and that of the C=O group of ester in the infrared region (see Table I). Moreover, (V) was negative to the reaction of the aromatic primary amines using sodium pentacyanoaquoferriate. These results support that the structure of (V) is ethyl 3-(5-pyrazolylamino)crotonate. When (V) was heated with glacial acetic acid, the condensate (IV) was also obtained in a good yield.

The similar reactions on 1-phenyl-5-aminopyrazole[2] (VI) were carried out in order to compare with the above results. Reaction of ethyl acetoacetate with (VI) without solvent at room temperature afforded ethyl 3-(1-phenyl-5-pyrazolylamino)crotonate (VII), whose structure was confirmed by means of the absorption spectral analysis and the colorlized reaction of the aromatic primary amines as well as (V) (see Table I). Heating of (VII) with glacial acetic acid gave 1-phenyl-6-methylpyrazolo[3,4-*b*]pyridin-4-ol (VIII), which was also obtained by condensation of ethyl acetoacetate with (VI) in glacial acetic acid at refluxing temeprature. This compound (VIII) shows the lactam carbonyl band at 1629 cm^{-1} which correspond to that of pyridone-(4).

From results of these reactions, it was considered that the structure of the con-

*1 Fukushima-ku, Osaka (牧角徳夫).

*2 Y. Makisumi : This Bulletin, **9**, 883 (1961).

1) P. Schmidt, J. Druey : Helv. Chim. Acta, **39**, 986 (1956).

2) *Idem* : *Ibid.*, **41**, 306 (1958).

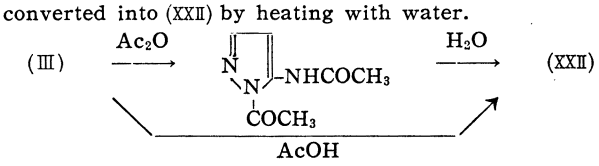
densate (IV) of ethyl acetoacetate with (III) would be either 5-methylpyrazolo[1,5-*a*]pyrimidin-7-ol or 6-methylpyrazolo[3,4-*b*]pyridin-4-ol (IX).

In order to establish the structure of (IV), the similar reactions of ethyl acetoacetate with 4-substituted 5-aminopyrazoles were carried out. Treatment of ethyl acetoacetate with ethyl 5-amino-4-pyrazolecarboxylate[1] (X) without solvent at room temperature gave ethyl 3-(4-ethoxycarbonyl-5-pyrazolylamino)crotonate (XI), whose structure was also confirmed by the same method as (V) (see Table I). Heating of (XI) in glacial acetic acid or in the presence of sodium ethoxide in ethanol afforded ethyl 5-methyl-7-hydroxypyrazolo[1,5-*a*]pyrimidine-3-carboxylate (XII), which was also obtained by condensation of ethyl acetoacetate with (X) in boiling glacial acetic acid in a good yield. Saponification of the ester (XII) with aqueous sodium hydroxide gave the corresponding carboxylic acid (XIII), which was decarboxylated to 5-methylpyrazolo[1,5-*a*]pyrimidin-7-ol, m.p. 298~299°, by heating at 260~270° in a reduced pressure or heating in 40% sulfuric acid. This compound was identified with the preceding condensate (IV) by mixed melting point determination and infrared spectral comparison. Moreover, condensation of ethyl acetoacetate with 5-amino-4-pyrazolecarbonitrile[3] (XIV) in glacial acetic acid at refluxing temperature for three hours gave 5-methyl-7-hydroxypyrazolo[1,5-*a*]pyrimidine-3-carbonitrile (XV). When this compound was heated with 40% sulfuric acid for four hours, hydrolysis and following decarboxylation occurred and a product, m.p. 298~299°, was obtained, which was also identified with (IV). From these results, the structure of (IV) was established to be 5-methylpyrazolo[1,5-*a*]pyrimidin-7-ol.

Heating of acetylacetone with (X) in the presence of a few drops of piperidine in ethanol for ten hours gave ethyl 5,7-dimethylpyrazolo[1,5-*a*]pyrimidine-3-carboxylate (XVI), which was converted to the corresponding carboxylic acid (XVII) by saponification with aqueous sodium hydroxide. Decarboxylation of the acid (XVII) by heating at 200° or with 40% sulfuric acid afforded 5,7-dimethylpyrazolo[1,5-*a*]pyrimidine (XVIII), which was also obtained by heating of the ester (XVI) with 40% sulfuric acid. On the other hand, condensation of acetylacetone with (III) in the presence of a few drops of piperidine in boiling ethanol gave a product, m.p. 40~40.5°, which was identified with (XVIII).

Condensation of ethyl cyanoacetate with (III) and (X) in the presence of sodium ethoxide in ethanol was carried out and a 7-aminopyrazolo[1,5-*a*]pyrimidin-5-ol (XIX) and its 3-carboxylic ester (XX) were obtained. The positions of the hydroxyl and amino groups of these products were confirmed by the following experiments. When a mixture of ethyl cyanoacetate and (III) was heated at 160~170° for two hours, a substance (XXI), m.p. 212° (decomp.), was obtained. This product showed a similar curve to that of 5-acetamidopyrazole*[3] (XXII) in the ultraviolet region and absorption bands of C≡N and CONH in the infrared region. Moreover, (XXI) was negative to the characteristic reaction of the aromatic primary amine. Therefore, the structure of (XXI) was established to be 5-(2-cyanoacetamido)pyrazole. Heating of (XXI) in glacial acetic acid afforded an isomeric compound, m.p. 305° (decomp.). This product showed an absorption band of NH_2 and no C≡N band in the infrared spectrum, and that was identified with the condensate (XIX) by the infrared spectral comparison. On the other hand, the ester (XX) was

*[3] 5-Acetamidopyrazole (XXII), m.p. 223~224° was prepared by reaction of (III) with glacial acetic acid. Acetylation of (III) using acetic anhydride gave 1-acetyl-5-acetamidopyrazole, m.p. 190.5~191.5°, which was easily converted into (XXII) by heating with water.



3) G. H. Hitchings, E. A. Falco: U. S. Pat. 2,759,947 (1956) (C. A., **51**, 11391 (1957)).

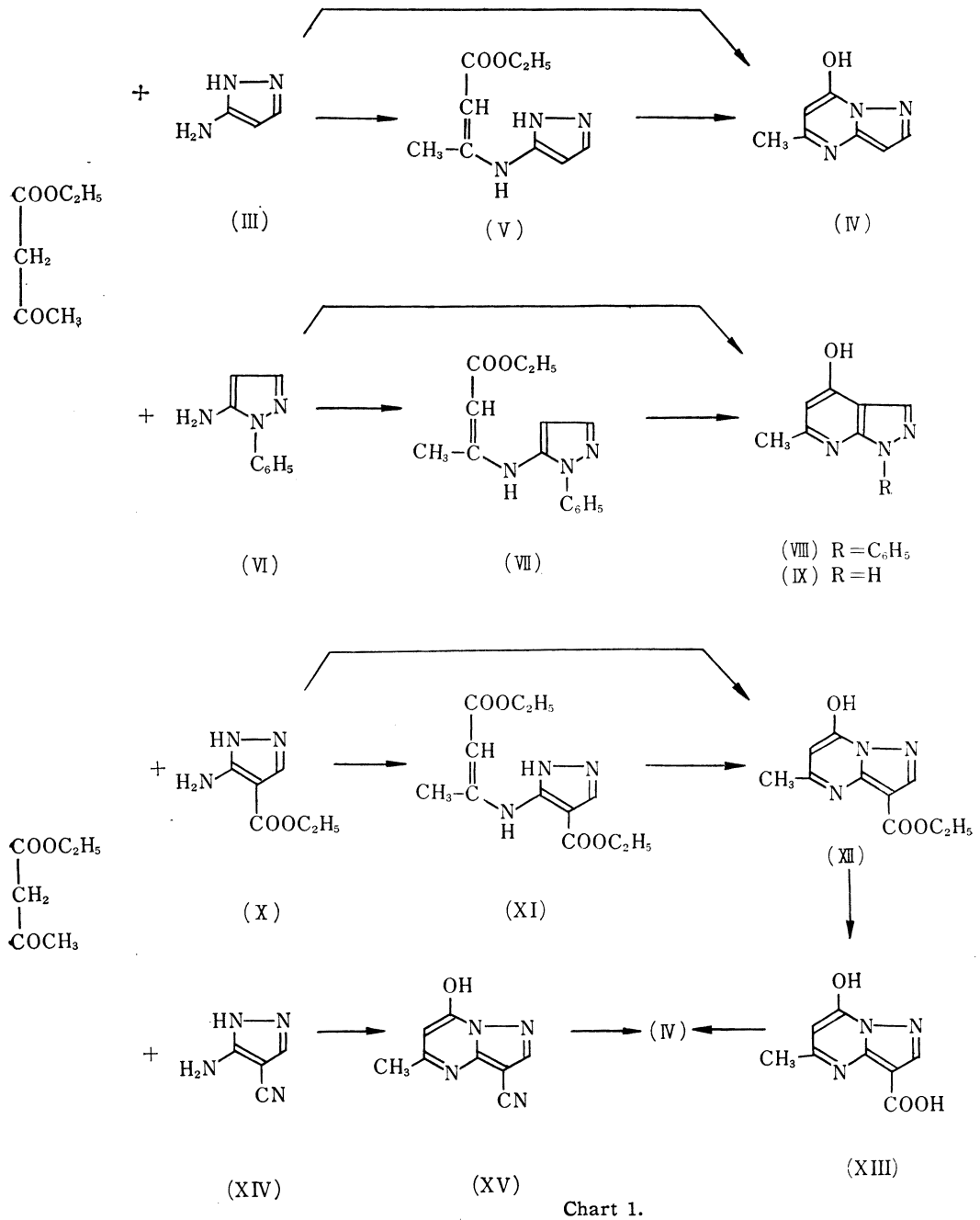


Chart 1.

Table I. Infrared Spectra of the 5-Aminopyrazole Derivatives ($\nu_{max}^{CHCl_3}$ in cm^{-1})

Compd.	Ring NH	Side chain NH	C=O	C=C	NH_2[a]
(V)	3532	3238	1651	1621	—
(VII)	—	3282	1661	1622	—
(XI)	3469	3268	1702 1666	1623	—

a) All compounds were negative for the colorlized reaction of the aromatic primary amines using sodium pentacyanoaquoferriate.

converted by saponification with aqueous sodium hydroxide to the corresponding carboxylic acid (XXIII). This acid was decarboxylated by heating at 260° in a reduced pressure to a substance, m.p. 305°(decomp.), which was also identified with (XIX). From these

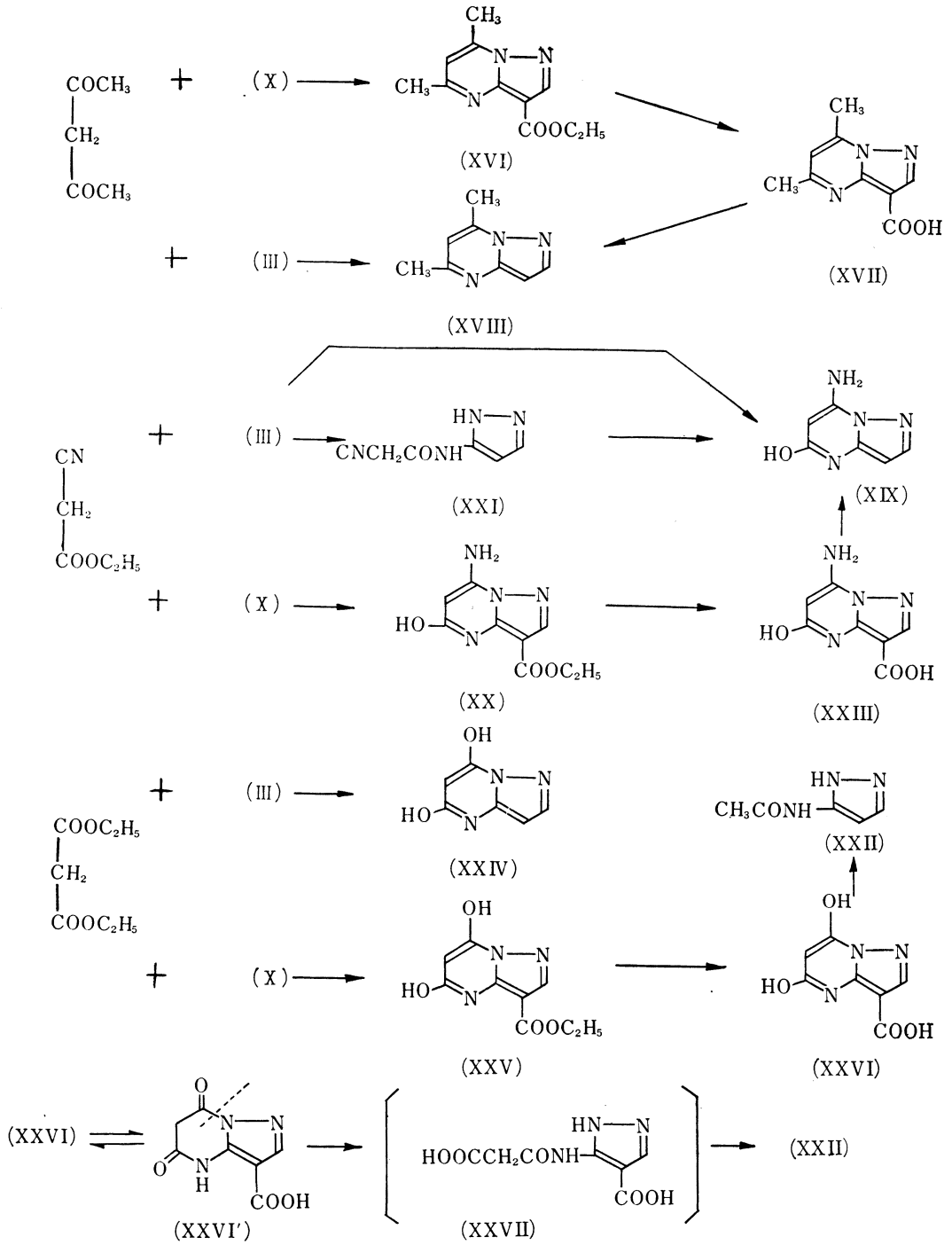


Chart 2.

results, the structures of the condensates (XIX and XX) were established to be 7-amino-pyrazolo[1,5-*a*]pyrimidin-5-ol and its 3-carboxylic ester.

Similarly, condensation of diethyl malonate with (III) and (X) in the presence of sodium ethoxide in ethanol gave pyrazolo[1,5-*a*]pyrimidine-5,7-diol (XXIV) and its 3-carboxylic ester (XXV). The latter was saponified to the corresponding carboxylic acid (XXVI) by heating with aqueous sodium hydroxide. Decarboxylation of this acid by heating at 235° did not afford (XXIV) and 5-acetamidopyrazole (XXII) was obtained. This reaction seems to be the result of the following mechanism. Ring cleavage between 7- and

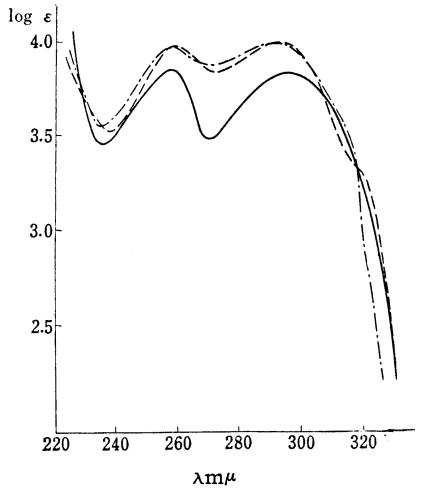


Fig. 1. Ultraviolet Absorption Spectra (in EtOH)

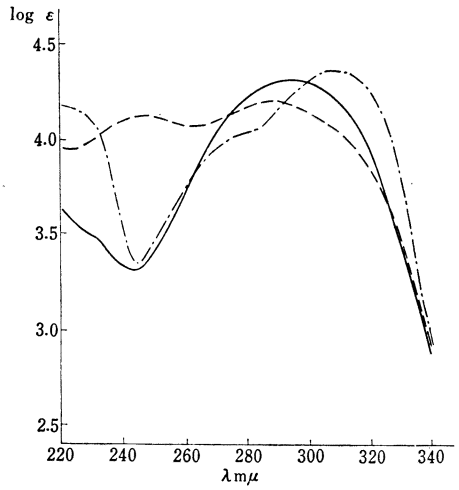
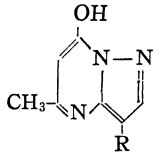
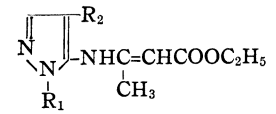


Fig. 2. Ultraviolet Absorption Spectra (in EtOH)



——— (IV) R=H
– – – (XII) R=$COOC_2H_5$
-·-·- (XV) R=CN



——— (V) $R_1=R_2=H$
– – – (VII) $R_1=C_6H_5$, $R_2=H$
-·-·- (XI) $R_1=H$, $R_2=COOC_2H_5$

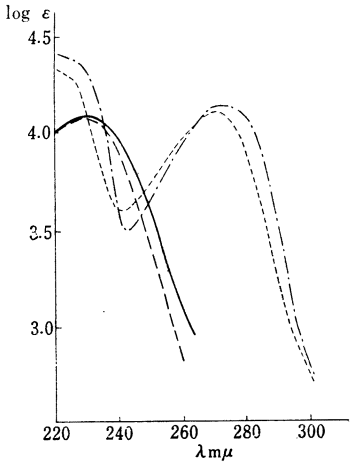
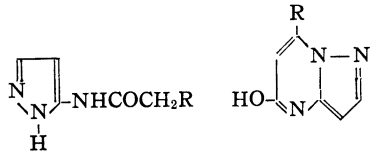


Fig. 3. Ultraviolet Absorption Spectra (in EtOH)



——— (XXI) R=CN
– – – (XXII) R=H
-·-·- (XIX) R=NH_2
····· (XXIV) R=OH

8-position to the dicarboxylic acid (XXVII) and subsequent decarboxylation of (XXVII) would produce (XXII).

The infrared spectra of the pyrazolo[1,5-*a*]pyrimidine derivatives which obtained here, was measured, as it was considered that the hydroxyl and amino groups at 5- and 7-positions of pyrazolo[1,5-*a*]pyrimidine ring would possess the property of the tautomerism as well as those at 2-, 4-, and 6-positions of the pyrimidine ring. Consequently, it was observed that the hydroxyl group at 5- and 7-positions shows the lactam form and the amino group at 7-position shows the amino form in the neutral medium. These results are analogous to those of the pyrimidine derivatives.

Experimental*4

Ethyl 3-(5-Pyrazolylamino)crotonate (V)——A mixture of 1.3 g. of ethyl acetoacetate and 0.8 g. of (III) was allowed to stand at room temperature overnight and the resulting solid was recrystallized from EtOH to 1.69 g. of colorless prisms, m.p. 102°. *Anal.* Calcd. for $C_9H_{13}O_2N_3$: C, 55.37; H, 6.71; N, 21.53. Found: C, 55.28; H, 6.63; N, 21.58. UV: λ_{max}^{EtOH} 293 mμ (log ε 4.30). IR: see Table I.

Ethyl 3-(1-Phenyl-5-pyrazolylamino)crotonate (VII)——A mixture of 1.3 g. of ethyl acetoacetate and 1.6 g. of (VI) was allowed to stand at room temperature overnight and the resulting solid was recrystallized from petr. benzin to 2.06 g. of colorless prisms, m.p. 80~81°. *Anal.* Calcd. for $C_{15}H_{17}O_2N_3$: C, 66.40; H, 6.32; N, 15.49. Found: C, 66.67; H, 6.24; N, 15.77. UV λ_{max}^{EtOH} mμ (log ε): 246 (4.11), 287 (4.18). IR: see Table I.

Ethyl 3-(4-Ethoxycarbonyl-5-pyrazolylamino)crotonate (XI)——A mixture of 1.3 g. of ethylacetoacetate and 1.55 g. of (X) was unified by warming and allowed to stand overnight at room temperature. The reaction mixture which solidified, was recrystallized from EtOH to 2.18 g. of white needles, m.p. 175~176°. *Anal.* Calcd. for $C_{12}H_{17}O_4N_3$: C, 53.92; H, 6.41; N, 15.72. Found: C, 54.14; H, 6.47; N, 15.55. UV λ_{max}^{EtOH} mμ (log ε): 278 (shoulder), 308 (4.35). IR: see Table I.

1-Phenyl-6-methylpyrazolo[3,4-*b*]pyridin-4-ol (VIII)——a) A mixture of 1.3 g. of ethyl acetoactate and 1.6 g. of (VI) in 5 cc. of AcOH was refluxed for 4 hr. After removal of the solvent, the residue was recrystallized from EtOH to 1.95 g. of colorless pillars, m.p. 188~189°. *Anal.* Calcd. for $C_{13}H_{11}ON_3$: C, 69.32; H, 4.92; N, 18.66. Found: C, 69.56; H, 4.86; N, 18.83. UV λ_{max}^{EtOH} mμ (log ε): 254 (4.32), 292 (4.01). IR: ν_{max}^{Nujol} 1629 cm^{-1} (lactan C=O).

b) One gram of (VII) was heated with 3 cc. of AcOH under reflux for 3 hr. and the reaction mixture was treated by the same method as above giving 0.86 g. of colorless pillars, m.p. 188~189°. It showed no depression of melting point on admixture with (VIII) obtained as above.

Ethyl 5-Methyl-7-hydroxypyrazolo[1,5-*a*]pyrimidine-3-carboxylate (XII)——a) A mixture of 1.3 g. of ethyl acetoacetate and 1.55 g. of (X) in 3 cc. of AcOH was refluxed for 2.5 hr. The reaction mixture was diluted with H_2O, the resulting crystals were collected by filtration, washed with H_2O, and dried giving 2.03 g. of white crystals, which were recrystallized from EtOH to colorless needles, m.p. 218~220°. *Anal.* Calcd. for $C_{10}H_{11}O_3N_3$: C, 54.29; H, 5.01; N, 19.00. Found: C, 54.49; H, 5.03; N, 18.82. UV λ_{max}^{EtOH} mμ (log ε): 259 (4.05), 292 (4.07). IR ν_{max}^{Nujol} cm^{-1}: 1708 (ester C=O), 1669 (lactam C=O).

b) A mixture of 0.5 g. of (XI) and 2 cc. of AcOH was refluxed for 2 hr., and the reaction mixture was treated as above to give 0.4 g. of colorless needles, m.p. 218~220°, which was identified as (XII) by mixed melting point and IR spectra.

c) To a solution of 0.09 g. of Na in 10 cc. of dehyd. EtOH, 1 g. of (XI) was added and the mixture was reflxed for 10 hr. After cool, the precipitated Na salt was collected by filtration, dissolved in H_2O, and acidified with dil. HCl. The resulting white crystals were collected, washed with H_2O, and recrystallized from EtOH to 0.75 g. of colorless needles, m.p. 218~220°. This was also identified with the samples described in (a) and (b), by mixed melting point and IR spectra.

5-Methyl-7-hydroxypyrazolo[1,5-*a*]pyrimidine-3-carboxylic Acid (XIII)——A solution of 0.5 g. of (XII) in 5 cc. of 10% NaOH was heated on a steam bath for 2 hr. and the reaction mixture was diluted with H_2O (to dissolve the precipitated Na salt of (XIII)). The resulting clear solution was treated with charcoal, and acidified with 10% HCl. The resulting white crystals (0.45 g.) were collected, washed with H_2O, and recrystallized from 60% EtOH to colorless needles, m.p. 296~297° (decomp.). *Anal.* Calcd. for $C_8H_7O_3N_3$: C, 49.74; H, 3.65; N, 21.76. Found: C, 50.03; H, 3.76; N, 21.70.

*4 All melting points are uncorrected. Infrared spectra were measured with the Kōken Infrared Spectrophotometer, Model DS-301, and ultraviolet spectra were taken with the Hitachi Recording Spectrophotometer, EPS-2.

5-Methyl-7-hydroxypyrazolo[1,5-*a*]pyrimidine-3-carbonitrile (XV)——A mixture of 1.3 g. of ethyl acetoacetate and 0.94 g. of (XIV) in 2.5 cc. of AcOH was refluxed for 2.5 hr. After cool, the resulting crystals were collected by filtration, washed with EtOH, and recrystallized from EtOH to give 1.5 g. of white needles, m.p. 313°(decomp.). *Anal.* Calcd. for $C_8H_6ON_4$: C, 55.17; H, 3.47; N, 32.17. Found: C, 55.37; H, 3.58; N, 31.92. UV λ_{max}^{EtOH} mμ (log ε): 257 (3.99), 291 (4.02). IR ν_{max}^{Nujol} cm^{-1}: 2237 (C≡N), 1679 (lactam C=O).

5-Methylpyrazolo[1,5-*a*]pyrimidin-7-ol (IV)——a) A mixture of 1.3 g. of ethyl acetoacetate and 0.83 g. of (III) in 5 cc. of AcOH was refluxed for 2 hr. and the reaction mixture was diluted with H_2O. The resulting crystals were collected by filtration, washed with H_2O, and recrystallized from EtOH to 1.38 g. of colorless pillars, m.p. 298~299°. *Anal.* Calcd. for $C_7H_7ON_3$: C, 56.38; H, 4.72; N, 28.19. Found: C, 56.49; H, 4.92; N, 28.02. UV λ_{max}^{EtOH} mμ (log ε): 257 (3.83), 293 (3.83), IR ν_{max}^{Nujol} 1692 cm^{-1}(lactam C=O).

b) A solution of 1.0 g. of (V) in 3 cc. of AcOH was refluxed for 2 hr. and the reaction mixture was treated by the method as above to give 0.86 g. of colorless pillars, m.p. 298~299°. *Anal.* Calcd. for $C_7H_7ON_3$: C, 56.38; H, 4.72. Found: C, 56.41; H, 4.79.

c) To a mixture of 0.3 g. of ethyl acetoacetate and 0.2 g. of (III) in 5 cc. of dehyd. EtOH, 0.05 g. of dehyd. $ZnCl_2$ was added and the mixture was refluxed for 3 hr. After cool, the resulting crystals were collected by filtration, washed with H_2O, and recrystallized from EtOH to give 0.32 g. of colorless pillars, m.p. 298~299°. *Anal.* Calcd. for $C_7H_7ON_3$ C, 56.38; H, 4.72; N, 28.19. Found: C, 56.02; H, 4.79; N, 28.21.

d) A mixture of 0.5 g. of (XIII) and 1.5 cc. of 40% H_2SO_4 was refluxed for 3 hr. and the reaction mixture was ajusted to pH 5~6 by addition of 10% NaOH. The precipitated crystals were collected by filtration, washed with H_2O, and recrystallized from EtOH to 0.32 g. of colorless pillars, m.p. 298~299°. *Anal.* Calcd. for $C_7H_7ON_3$: C, 56.38; H, 4.72; N, 28.19. Found: C, 56.45; H, 4.89; N, 28.24.

e) A mixture of 0.5 g. of (XV) and 1.5 cc. of 40% H_2SO_4 was refluxed for 4 hr. and the reaction mixture was treated by the method as above to give 0.4 g. of colorless pillars, m,p, 298~299°. *Anal.* Calcd. for $C_7H_7ON_3$: C, 56.38; H, 4.72. Found: C, 56.31; H, 4.68. All products which prepared in (b) to (e) were identified with the sample (IV) described in (a) by the mixed melting point and IR spectra.

Ethyl 5,7-Dimethylpyrazolo[1,5-*a*]pyrimidine-3-carboxylate (XVI)——To a mixture of 1.3 g. of acetylacetone and 2 g. of (X) in 20 cc. of dehyd. EtOH, 3 drops of piperidine were added and this mixture was refluxed for 10 hr. After removal of the solvent to dryness, the residue was purified by Al_2O_3 chromatography with benzene to give 2.1 g. of crystals. Recrystallization from petr benzin. gave colorless pillars, m.p. 107~107.5. *Anal.* Calcd. for $C_{11}H_{13}O_2N_3$: C, 60.26; H, 5.98; N, 19.54. Found: C, 60.44; H, 6.09; N, 19.54. UV λ_{max}^{EtOH} mμ (log ε): 225 (4.47), 237 (4.36), 285 (3.75), 305 (3.75).

5,7-Dimethylpyrazolo[1,5-*a*]pyrimidine-3-carboxylic Acid (XVII)——A mixture of 0.5 g. of (XVI) and 5 cc. of 10% NaOH was heated on a steam bath for 2 hr. After cool, the resulting Na salt was collected by filtration, dissolved in H_2O, treated with charcoal, and acidified with 10% HCl. The precipitated white crystals were collected by filtration and recrystallized from benzene to 0.31 g. of colorless needles, m.p. 178~179°. *Anal.* Calcd. for $C_9H_9O_2N_3$: C, 56.54; H, 4.75; N, 21.98. Found: C, 56.74; H, 4.74; N, 21.84.

5,7-Dimethylpyrazolo[1,5-*a*]pyrimidine (XVIII)——a) 0.5 g. of (XVII) was heated at 200° for 20 min., by which the crystals were decomposed and liquefied completely. After cool, the resulting product was dissolved in benzene and purified by Al_2O_3 chromatography giving 0.34 g. of white crystals, m.p. 37~39°. Recrystallization from petr. benzin gave white needles, m. p. 40~40.5°. *Anal.* Calcd. for $C_8H_9N_3$: C, 65.28; H, 6.16; N, 28.55. Found: C, 65.37; H, 6.32; N, 28.26. UV λ_{max}^{EtOH} mμ (log ε): 229 (4.62), 277.5 (3.29), 312 (3.20).

b) A mixture of 0.5 g. of(XVII)and 2.5 cc of 40% H_2SO_4 was refluxed for 3 hr. After cool, the reaction mixture was basified with 15% NaOH and extracted with $CHCl_3$. The extract was concebenzene to 0.35 g. ntrated to dryness, the residue was dissolved in benzene, and purified by Al_2O_3 chroma tography with of white crystals, m.p. 39~40°. Recrystallization from petr. benzin gave white needles, m.p. 40~40.5°. It showed no depression of melting point on admixture with (XVIII) obtained as above.

c) A mixture of 0.5 g. of (XVI) and 2.5 cc. of 40% H_2SO_4 was treated by the same procedure as above (b) to give 0.26 g. of colorless needles (XVIII), m.p. 40~40.5°.

d) To a mixture of 2 g. of acetylacetone and 1.65 g. of (III) in 30 cc. of dehyd. EtOH, 3 drops of piperidine were added and the mixture was refluxed for 12 hr. After removal of the solvent, the residue was purified by Al_2O_3 chromatography with benzene to 2.4 g. of white crystals. Recrystallization from petr. benzin gave white needles, m.p. 40~40.5°. *Anal.* Calcd. for $C_8H_9N_3$: C, 65.28; H, 6.16; N, 28.55. Found: C, 65.32; H, 6.35; N, 28.45. This sample showed no depression on admixture with the samples prepared by the method (a) to (c) described above.

5-(2-Cyanoacetamido)pyrazole (XXI)——A mixture of 2 g. of ethyl cyanoacetate and 1 g. of (III)

was heated at 160~170° for 2 hr. The reaction product which solidified after cool, was collected, washed with Et_2O, and recrystallized from 60% EtOH to 1.05 g. colorless prisms, m.p. 211~212°(decomp.). *Anal.* Calcd. for $C_6H_6ON_4$: C, 48.00; H, 4.03; N, 37.32. Found: C, 47.95; H, 4.37; N, 37.15. UV: λ_{max}^{EtOH} 230 mμ (log ε 4.08). IR ν_{max}^{Nujol} cm^{-1}: 3333 (ring NH), 3210 (amide NH), 2278 (C≡N), 1699 (C=O).

Ethyl 5-Hydroxy-7-aminopyrazolo[1,5-a]pyrimidine-3-carboxylate (XX)——To a solution of 0.3 g. of Na in 30 cc. of dehyd. EtOH, 1.5 g. of ethyl cyanoacetate and 2 g. of (X) were added and the mixture was refluxed for 5 hr. After cool, the precipitated Na salt was collected, dissolved in H_2O, filtered with charcoal, and the filtrate was acidified with AcOH. The resulting precipitate was collected, washed with H_2O, and recrystallized from 50% EtOH to 1.95 g. of colorless needles, m.p. 236~237°. *Anal.* Calcd. for $C_9H_{10}O_3N_4$: C, 48.65; H, 4.54; N, 25.22. Found: C, 48.46; H, 4.61; N, 25.31. UV λ_{max}^{EtOH} mμ (log ε): 242 (4.31), 268 (4.18). IR ν_{max}^{Nujol} cm^{-1}: 3370, 3152 (NH_2), 1727 (ester C=O), 1664 (lactam C=O).

5-Hydroxy-7-aminopyrazolo[1,5-*a*]pyrimidine-3-carboxylic Acid (XXIII)——A solution of 0.5 g. of (XX) in 5 cc. of 10% NaOH was heated on a steam bath for 2 hr. and the reaction mixture was filtered with charcoal. The filtrate was acidified with AcOH, the resulting precipitate was collected by filtration, washed with H_2O, and recrystallized from 60% EtOH to 0.21 g. of colorless needles, m.p. 296°(decomp.). *Anal.* Calcd. for $C_7H_6O_3N_4$: C, 43.30; H, 3.12; N, 28.86. Found: C, 43.12; H, 3.23; N, 28.75.

7-Aminopyrazolo[1,5-*a*]pyrimidin-5-ol (XIX)——a) To a solution of 1.15 g. of Na in 50 cc. of dehyd. EtOH, 5.7 g. of ethyl cyanoacetate and 4.15 g. of (III) were added and the mixture was refluxed for 8 hr. After cool, the precipitated Na salt was collected by filtration, dissolved in H_2O, filtered with charcoal, and the filtrate was acidified with AcOH. The resulting precipitate was collected by filtration, washed with H_2O, and recrystallized from 60% EtOH to give 4.6 g. of colorless needles, m.p. 306°(decomp.). *Anal.* Calcd. for $C_6H_6ON_4$: C, 48.00; H, 4.03; N, 37.32. Found: C, 48.02; H, 4.26; N, 37.16. UV: λ_{max}^{EtOH} 273 mμ (log ε 4.14). IR ν_{max}^{Nujol} cm^{-1}: 3317, 3226 (NH_2), 1663 (lactam C=O).

b) A solution of 0.7 g. of (XXI) in 5 cc. of AcOH was heated on a steam bath for 5 hr. After cool, the resulting crystals were collected by filtration, washed with EtOH, and recrystallized from 60% EtOH to 0.52 g. of colorless needles, m.p. 306°(decomp.). *Anal.* Calcd. for $C_6H_6ON_4$: C, 48.00; H, 4.03; N, 37.32. Found: C, 48.15; H, 4.21; N, 37.45. This was identified by the IR spectrum with sample (XIX) prepared by the method of (a).

c) 0.1 g. of (XXIII) was heated at 260~270° in a pressure of 5 mm. Hg. After cool, the product was recrystallized from 60% EtOH to 0.05 g. of colorless needles, m.p. 304°(decomp.). This was also identified with the samples described in (a) and (b), by the IR spectral comparison.

Pyrazolo[1,5-*a*]pyrimidine-5,7-diol (XXIV)——To a solution of 2 g. of Na in 50 cc. of dehyd. EtOH, 7 g. of diethyl malonate and 3.5 g. of (III) were added and the mixture was refluxed for 5 hr. After cool, the precipitated Na salt was collected by filtration, dissolved in H_2O, treated with charcoal, and acidified with 10% HCl giving 8.5 g. of white crystals. Reprecipitation with alkali and acid gave white needles, m.p. 239~240°(decomp.). *Anal.* Calcd. for $C_6H_5O_2N_3$: C, 47.68; H, 3.33; N, 27.81. Found: C, 47.90; H, 3.51; N, 27.65, UV: λ_{max}^{EtOH} 271 mμ (log ε 4.10). IR: ν_{max}^{Nujol} 1655 cm^{-1}(lactam C=O).

Ethyl 5.7-Dihydroxypyrazolo[1,5-*a*]pyrimidine-3-carboxylate (XXV)——To a solution of 0.6 g. of Na in 30 cc. of dehyd. EtOH, 2.1 g. of diethyl malonate and 2 g. of (X) were added and the mixture was refluxed for 5 hr. After cool, the precipitated Na salt was collected by filtration, dissolved in H_2O, and acidified with 10% HCl. The resulting precipitate was collected by filtration, washed with H_2O, and recrystallized from H_2O to 1.9 g. of colorless needles, m.p. 186~187°(decomp.). *Anal.* Calcd. for $C_9H_9O_4N_3 \cdot H_2O$: C, 44.81; H, 4.60; N, 17.42. Found: C, 44.98; H, 4.86; N, 17.51. UV: λ_{max}^{EtOH} 256.5 mμ (log ε 4.10). IR ν_{max}^{Nujol} cm^{-1}: 1697 (ester C=O), 1673 (lactam C=O).

5,7-Dihydroxypyrazolo[1,5-*a*]pyrimidine-3-carboxylic Acid (XXVI)——A solution of 0.5 g. of (XXV) in 2.7 cc. of 10% NaOH was heated on a steam bath for 1 hr. and the reaction mixture was filtered with charcoal. The filtrate was acidified with 10% HCl, the resulting precipitate was collected by filtration, washed with H_2O, and recrystallized from H_2O to 0.1 g. of white leaflets, m.p. 229°(decomp.). *Anal.* Calcd for $C_7H_5O_4N_3 \cdot H_2O$: C, 39.44; H, 3.31; N, 19.72. Found: C, 39.55; H, 3.23; N, 19.99.

Decarboxylation of (XXVI)——0.1 g. of (XXVI) was heated at 235° for 5 min.. by which the crystals were decomposed and liquefied completely. After cool, the resulting product was recrystallized from 50% EtOH to 0.05 g. of colorless prisms, m.p. 223~224°, which was identified with (XXII) by the mixed melting point determination and the IR spectral comparison.

Acetylation of (III)——a) A mixture of 0.5 g. of (III) and 2 cc. of AcOH was refluxed for 1 hr. and the excess AcOH was removed in a reduced pressure. The residue was recrystallized from EtOH to 0.55 g. of 5-acetamidopyrazole (XXII) as colorless prisms, m.p. 223~224°. *Anal.* Calcd. for $C_5H_7ON_3$: C, 47.99; H, 5.64; N, 33.58. Found: C, 47.86; H, 5.71; N, 33.59. UV: λ_{max}^{EtOH} 230 mμ (log ε 4.07). IR: ν_{max}^{Nujol} 1660 cm^{-1}(C=O). This product was a negative test for the reaction of free amino groups using sodium pentacyanoaquoferriate

b) A mixture of 0.5 g. of (III) and 2 cc. of Ac_2O was heated on a steam bath for 15 min. and the resulting crystals were collected by filtration, washed with dehyd. EtOH, and dried to 0.68 g. of 14-acetyl-5-acetamidopyrazole, m.p. 190~191°. Recrystallization from dehyd. EtOH gave colorless needles, m.p. 190.5~191.5°. *Anal.* Calcd. for $C_7H_9O_2N_3$: C, 50.29; H, 5.43; N, 25.14. Found: C, 50.32; H, 5.57; N, 25.23. IR ν_{max}^{Nujol} cm^{-1}: 1738 (C=O of ring N), 1661 (C=O of amino).

This compound was heated with H_2O on a steam bath for 15 min. After cool, the resulting crystals were collected by filtration and dried to colorless prisms, m.p. 223~224°, which was identified with (XXII) by the mixed melting point determination and the infrared spectral comparison.

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Summary

Condensation of 1,3-dicarbonyl compounds with 5-aminopyrazole (III) and its 3-carboxylic ester (X) was examined and several kinds of 5,7-disubstituted pyrazolo[1,5-*a*]-pyrimidines were obtained. It was observed by the infrared spectrum that the hydroxyl group at 5- and 7-positions of pyrazolo[1,5-*a*]pyrimidine ring shows the lactam form in the neutral medium,

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101. Yasuo Makisumi: Studies on the Azaindolizine Compounds. XI.*2 Synthesis of 6,7-Disubstituted Pyrazolo[1,5-*a*]pyrimidines.

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In the foregoing paper*2, the author reported on the synthesis of 5,7-disubstituted pyrazolo[1,5-*a*]pyrimidines by means of the condensation of 1,3-dicarbonyl compounds with 5-aminopyrazole (I) and its derivatives.

In the present paper, the condensation of 2-ethoxymethylene-1,3-dicarbonyl compounds with (I) to give 6,7-disubstituted pyrazolo[1,5-*a*]pyrimidines is described.

Condensation of ethyl 2-cyano-3-ethoxyacrylate with (I) in boiling ethanol gave a product (II), $C_9H_{10}O_2N_4$, m.p. 186°. However, when glacial acetic acid instead of ethanol was used as the solvent, an isomeric compound of (II), m.p. 147°, (III) was obtained. The former showed an absorption band at 311 mμ (log ε 4.37) in the ultraviolet region and absorption bands of the groups ring NH, side chain NH, C≡N, and ester C=O in the infrared region (see Table I). Moreover, (II) was negative for the reaction of the aromatic primary amines using sodium pentacyanoaquoferriate. These results support that the structure of (II) is ethyl 2-cyano-3-(5-pyrazolylamino)acrylate. The latter compound (III) showed absorption bands at 3537, 3373 (NH_2), and 1710 (ester C=O) in the infrared spectrum (in $CHCl_3$) and (III) was identified with the product which obtained by teratment of (II) with boiling glacial acetic acid. Therefore, the structure of (III) was established to be ethyl 7-aminopyrazolo[1,5-*a*]pyrimidine-6-carboxylate. (III) was also

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