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

(Research Laboratory, Shionogi & Co., Ltd. *1)

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 com-pounds was attempted.

The present paper describes the synthesis of 5, 7-disubstituted pyrazolo [1, 5-a] pyrimi-dines 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 pro-
duct (IV), C7H7ON3, 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), C9H13O2N3, m. p. 102°, in a good yield.
This product showed an absorption band at 293mμ (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 reac-tion 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 (VI), 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 (VII), 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 1629cm-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).

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densate (W) of ethyl acetoacetate with (III) would be either 5-methylpyrazolo[1,5-a]pyri-midin-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-pyrazolecarboxylateo (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-hydroxy-pyrazolo[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]pyrilnidin-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 aceto-acetate with with 5-amino-4-pyrazolecarbonitrilea) (XIV) in glacial acetic acid at refluxing tem-perature for three hours gave 5-methyl-7-hydroxypyrazolo[1, 5-a]pyrimidine-3-carbo-nitrile (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 eth-oxide in ethanol was carried out and a 7-aminopyrazolo[1,5-c]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-acetarnidopyrazole *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 reac tion 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
isolneric compound, m. p. 305° (decomp.). This product showed an absorption band of
NH2 and no C≡N band in the infrared spectrum, and that was identified with the con-

densate (XIX) by the infrared spectral comparison. On the other hand, the ester (XX) was

*3 5-Acetamidopyrazole (XXE), 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)).

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Chart 1.

TABLE I. Infrared Spectra of the 5-Aminopyrazole Derivatives (ν CHCl3 max in cm-1)

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

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converted by saponification with aqueous sodium hydroxide to the corresponding carbo-

xylic 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.

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8-position to the dicarboxylic acid (XXVII) and subsequent decarboxylation of (XXVII) would produce (XXII).
The infrared spectra of the pyrazolo[1, 5-cdpyrimidine derivatives which obtairied 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. Con-sequently, 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 1.3g. of ethyl acetoacetate and 0.8g. of
(III) was allowed to stand at room temperature overnight and the resulting solid was recrystallized
from EtOH to 1.69g. of colorless prisms, m. p. 102°. Anal. Calcd. for C9H13O2N3: C, 55.37; H, 6.71;
N, 21.53. Found: C, 55.28; H, 6.63; N, 21.58. UV: λ EtOH max 293 mp (logε 4.30). IR: see Table I.

Ethyl 3-(1-Phenyl-5-pyrazolylamino)crotonate (VII) A mixture of 1.3g. of ethyl acetoacetate
and 1.6g. of (VI) was allowed to stand at room temperature overnight and the resulting solid was
recrystallized from petr. benzin to 2.06g. of colorless prisms, m. p. 80～81°. Anal. Calcd. for C15H17O2N3:
C, 66.40; H, 6.32; N, 15.49. Found: C, 66.67; H, 6.24; N, 15.77. UV λ EtOH max mμ (logε): 246 (4.11),

287 (4.18). IR: see Table I.
Ethyl 3-(4-Ethoxycarbonyl-5-pyrazolylamino)crotonate (XI) A mixture of 1.3g. of ethylaceto-
acetate and 1.55g. of (X) was unified by warming and allowed to stand overnight at room tempera-
ture. The reaction mixture which solidified, was recrystallized from EtOH to 2.18g. of white needles,
m. p. 175～176°. Anal. Calcd. for C12H17O4N3: C, 53.92; H, 6.41; N, 15.72. Fomd: C, 54.14; H, 6.47;
N, 15.55. UV λ EtOH max mμ (logε): 278 (shoulder), 308 (4.35). IR: see Table I.

1-Phenyl-6-methylpyrazolo[3, 4-b]pyridin-4-ol (VIII)-a) A mixture of 1.3g. of ethyl acetoactate
and 1.6g. of (VI) in 5cc. of AcOH was refluxed for 4 hr. After removal of the solvent, the residue
was recrystallized from EtOH to 1.95g. of colorless pillars, m. p. 188～189°. Anal. Calcd. for C13H11-

ON3: C, 69.32; H, 4.92; N, 18.66. Found: C, 69.56; H, 4.86; N, 18.83. UV λ EtOH max mμ (logε): 254
(4.32), 292 (4.01). IR: ν Nujol max 1629cm-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 0.86g. of colorless pillars, m. p. 188～189°. It
showed no depression of melting point on admixture with (WI) obtained as above.
Ethyl 5-Methyl-7-hydroxypyrazolo[1,5-a]pyrimidine-3-carboxylate (XII) a) A mixture of 1.3g.
of ethyl acetoacetate and 1.55g. of (X) in 3cc. of AcOH was refluxed for 2.5 hr. The reaction mix-ture was diluted with H2O, the resulting crystals were collected by filtration, washed with H2O, and dried giving 2.03g. of white crystals, which were recrystallized from EtOH to colorless needles,
m. p. 218～220°. Anal. Calcd. for C10H11O3N3: C, 54.29; H, 5.01; N, 19.00. Found: C, 54.49; H,
5.03; N, 18.82. UV λ EtOH max mμ (logε): 259 (4.05), 292 (4.07). IR ν Nujol max cm-1: 1708 (ester C=O), 1669

(lactam C=O).
b) A mixture of 0.5g. of (XI) and 2cc. of AcOH was refluxed for 2 hr., and the reaction mixture
was treated as above to give 0.4g. of colorless needles, m. p. 218～220°, which was identified as (XII)

by mixed melting point and IR spectra.
c) To a solution of 0.09g. of Na in 10cc. of dehyd. EtOH, 1g. of (XI) was added and the mix-ture was refixed for 10 hr. After cool, the precipitated Na salt was collected by filtration, dissolved in H2O, and acidified with dii. HCl. The resulting white crystals were collected, washed with H2O,
and recrystallized from EtOH to 0.75g. 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 0.5g. of
(XII) in 5cc. of 10% NaOH was heated on a steam bath for 2 hr. and the reaction mixture was diluted with H2O (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 (0.45g.) were col-lected, washed with H2O, and recrystallized from 60% EtOH to colorless needles, m. p. 296～297° (decomp.). Anal. Calcd. for C8H7O3N3: 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 KOken Infrared
Spectrophotometer, Model DS-301, and ultraviolet spectra were taken with the Hitachi Recording
Spectrophotometer, EPS-2.

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b) A mixture of 0.5g. of (III) and 2cc. of Ac2O was heated on a steam bath for 15min. and the resulting crystals were collected by filtration, washed with dehyd. EtOH, and dried to 0.68g. of 14-
acety1-5-acetamidopyrazole, m. p.190～191°. Recrystallization from dehyd. EtOH gave colorless ne-
edles, m. p. 190.5～191.5°. Anal. Calcd. for C7H9O2N3: C, 50.29; H, 5.43; N, 25.14. Found: C, 50.32;
H, 5.57; N, 25.23. IR ν Nujol max cm-1: 1738 (C=O of ring N), 1661 (C=O of amino).

This compound was heated with H2O on a steam bath for 15min. After cool, the resulting
crystals were collected by filtration and dried to colorless prisms, m. p.223～224°, which was identi-

filed 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-car-boxylic 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.

(Research Laboratory, Shionogi & Co., Ltd.*1)

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 com-
pounds 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), C9H10O2N4, m. p. 186°. However, when glacial acetic acid instead of ethanol

was used as the solvent, an isomeric compound of (II), m. p. 1470, (III) was obtained.
The former showed an absorption band at 311mμ (logε 4.37) in the ultraviolet region
and absorption bands of the groups ring NH, side chain NH, C•ßN, 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 com-
pound (III) showed absorption bands at 3537, 3373 (NH,), and 1710 (ester C=O) in the infra-
red spectrum (in CHCl3) 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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*2 Part X. Y. Makisumi: This Bulletin, 10, 612 (1962)

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