[Chem. Pharm. Bull. 13(10)1207~1220(1965)] UDC 547.779.07

155. Akira Takamizawa and Yoshio Hamashima: Syntheses of Pyrazole Derivatives. XI.*1 Acetylation Products of 7-Aminopyrazolo[1,5-*a*]pyrimidines. Supplement.

(*Shionogi Research Laboratory, Shionogi & Co., Ltd.**2)

In the earlier papers[1] of this series it was described that acetylation of 7-amino-2,3-dimethylpyrazolo[1,5-*a*]pyrimidine (I) and 7-amino-2,3,6-trimethylpyrazolo[1,5-*a*]-pyrimidine (II) gave a 7-acetamido compound (III) and a 7-diacetylamino compound (V), respectively, and that the difference in reactivity between them might depend upon the basicity of the amino groups due to the steric effect of substituents at the C-6 position of the bicyclic systems. The present work is to study in more detail the reactivity of the amino groups of this series of compounds.

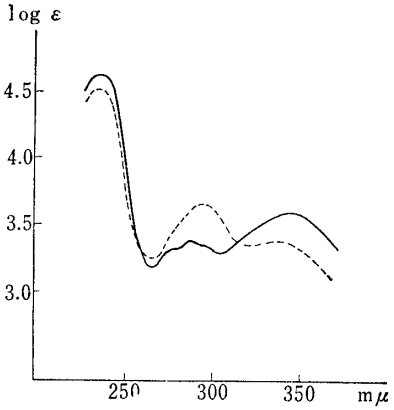


Fig. 1. Ultraviolet Absorption Spectra of III and IX in Ethanol
—— III —— — IX

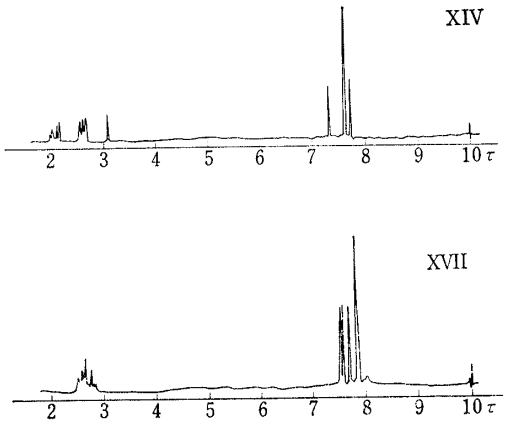
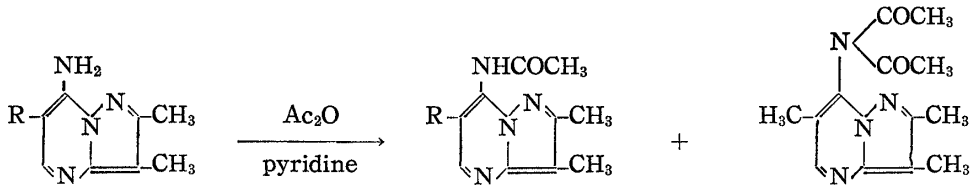
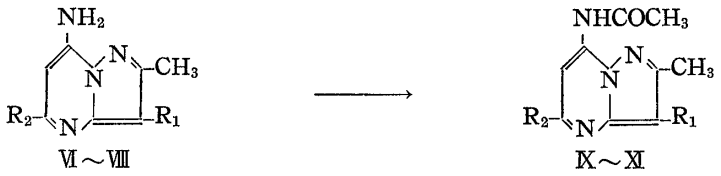


Fig. 2. Nuclear Magnetic Resonance Spectra of XIV and XVII ($CDCl_3$, 60 Mc.p.s.)



I : R=H
II : R=CH_3
III : R=H
IV : R=CH_3
V

Chart 1.

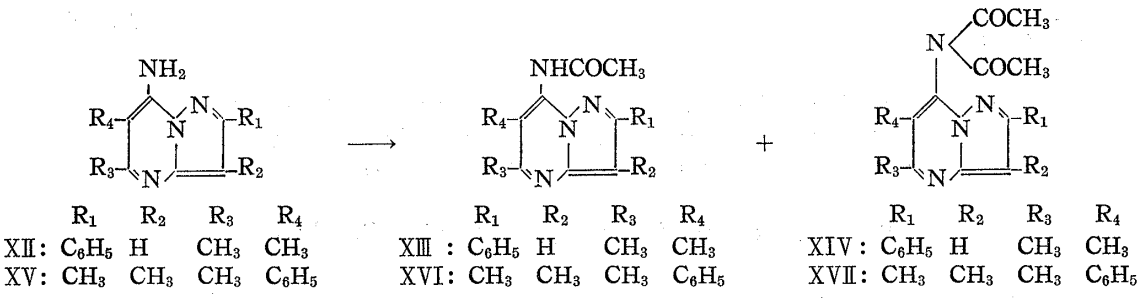


VI～VIII IX～XI

VI : R_1=H, R_2=CH_3
VII : R_1=H, R_2=C_6H_5
VIII : R_1=CH_3, R_2=C_6H_5
IX : R_1=H, R_2=CH_3
X : R_1=H, R_2=C_6H_5
XI : R_1=CH_3, R_2=C_6H_5

Chart 2.

*1 Part X. S. Hayashi: Yakugaku Zasshi, **85**, 442 (1965).
*2 Sagisu, Fukushima-ku, Osaka (高見沢 映, 浜島好男).
1) A. Takamizawa, Y. Hamashima: This Bulletin, **13**, 142 (1965).



	R_1	R_2	R_3	R_4
XII	C_6H_5	H	CH_3	CH_3
XIII	C_6H_5	H	CH_3	CH_3
XIV	C_6H_5	H	CH_3	CH_3
XV	CH_3	CH_3	CH_3	C_6H_5
XVI	CH_3	CH_3	CH_3	C_6H_5
XVII	CH_3	CH_3	CH_3	C_6H_5

Chart 3.

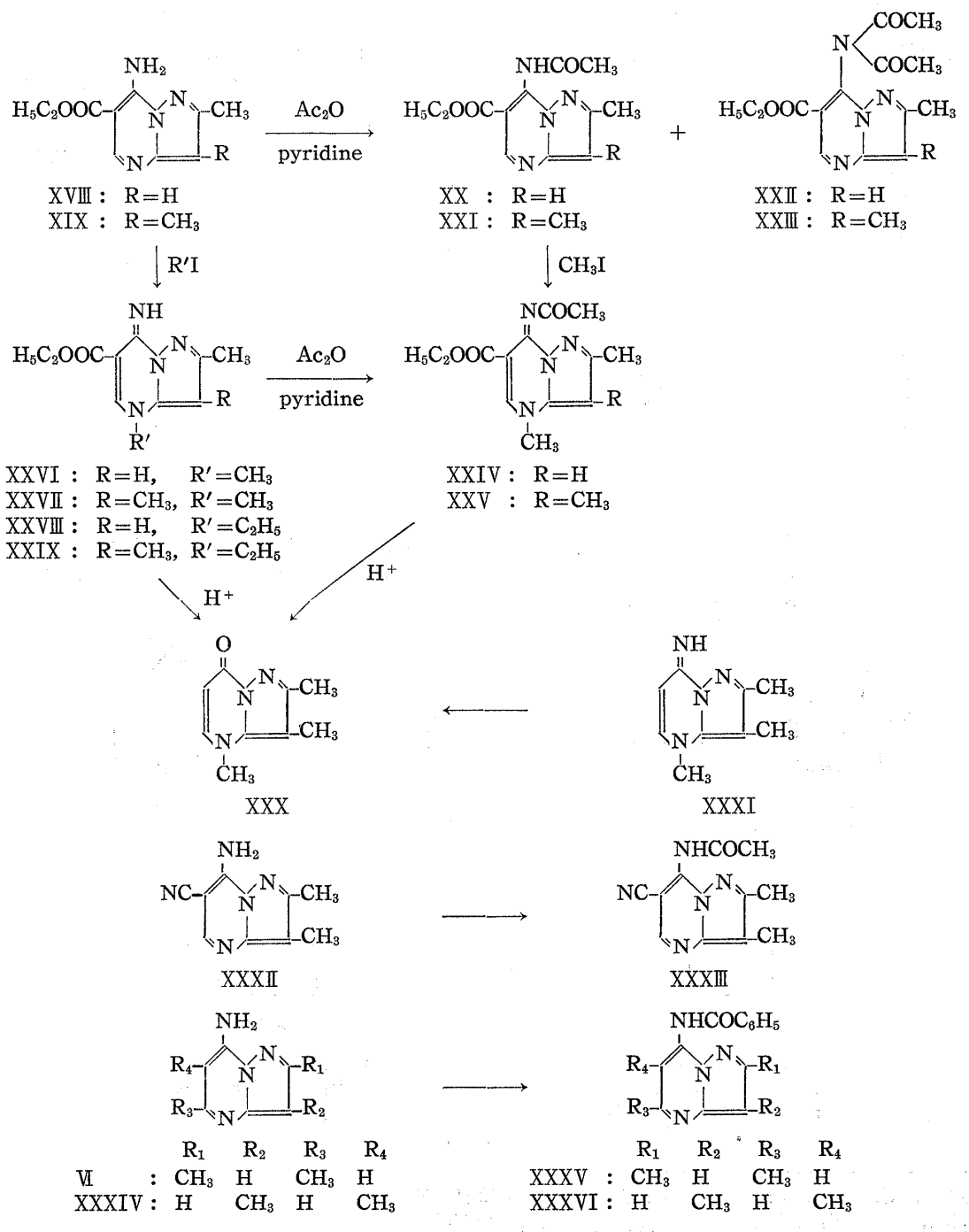


Chart 4.

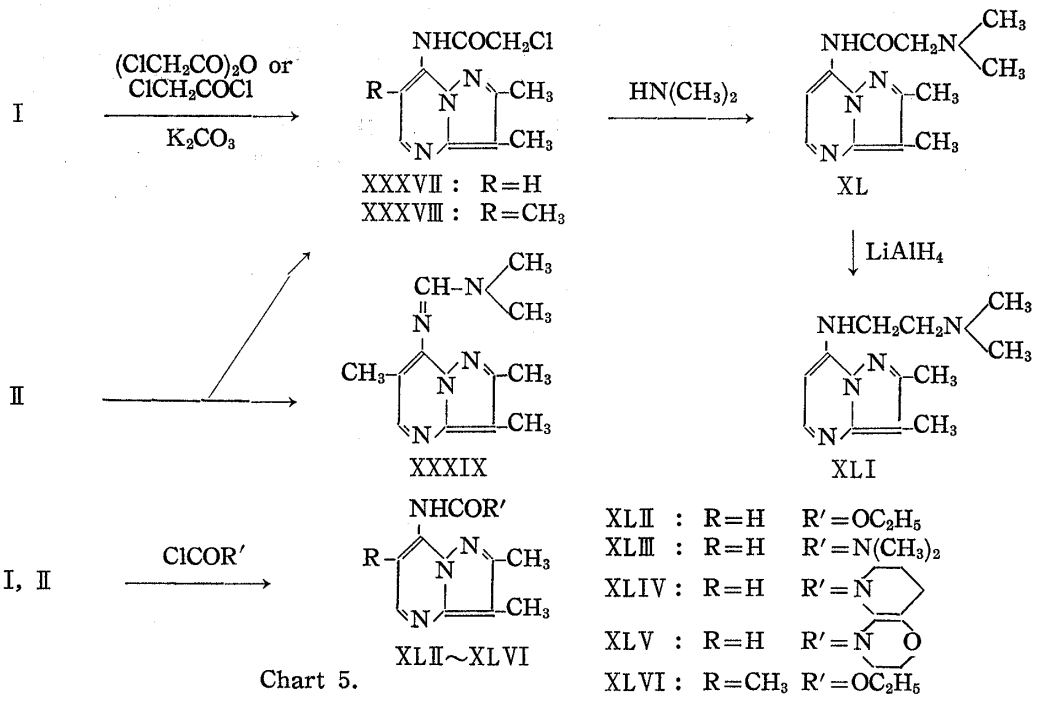
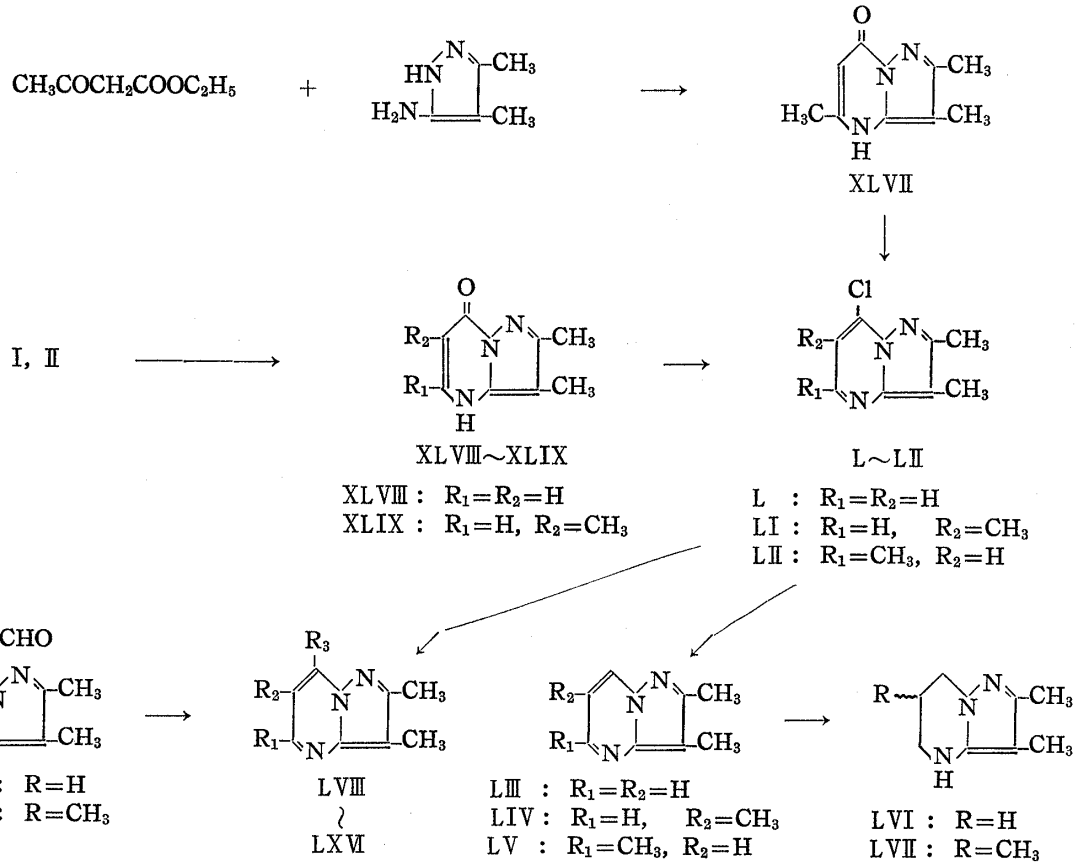


Chart 5.



	R_1	R_2	R_3
LVIII :	H	H	$NHCH_3$
LIX :	H	CH_3	$NHCH_3$
LX :	CH_3	H	$NHCH_3$
LXI :	H	H	$N(CH_3)_2$
LXII :	H	CH_3	$N(CH_3)_2$

	R_1	R_2	R_3
LXIII :	CH_3	H	$N(CH_3)_2$
LXIV :	CH_3	H	N
LXV :	H	H	$NHCH_2CON(CH_3)_2$
LXVI :	H	CH_3	$NHCH_2CON(CH_3)_2$

Chart 6.

Treatment of 7-amino-2,5-dimethylpyrazolo[1,5-*a*]pyrimidine (Ⅵ)[2] with either acetic anhydride or acetyl chloride in pyridine afforded the compound (Ⅸ), $C_{10}H_{20}ON_4$ as colorless crystals, m.p. 83~84°, showing an NH infrared band at 3183 cm^{-1}. The compound exhibited an ultraviolet absorption spectrum [λ_{max} mμ (log ε): 237.5 (4.53), 295.5 (3.67), and 336 (3.23)] whose maxima correspond to those [λ_{max} mμ (log ε): 235.5 (4.67), 280 (3.33, sh), 288 (3.39), 296.5 (3.34, sh) and 343 (3.61)] of Ⅲ (Fig. 1). The proton magnetic resonance (NMR) spectrum showed a singlet signal peak at 0.83 τ due to the NH proton of the 7-acylamino group.[1] Similarly, acetylation of 2-methyl-5-phenyl-7-amino- and 5-phenyl-7-amino-2,3-dimethylpyrazolo[1,5-*a*]pyrimidines (Ⅶ) and (Ⅷ) afforded the 7-acetamido compounds (Ⅹ) and (Ⅺ), respectively. The NMR spectra of Ⅹ and Ⅺ showed NH proton signals at 0.90 and 0.92 τ, respectively. These large shifts of the NH proton signals to low fields are in marked contrast to the NH proton signals of 4-alkyl substituted-7-imino-4,7-dihydropyrazolo[1,5-*a*]pyrimidines[1] which appear at about 2.67~5.37 τ.

On the other hand, acetylation of 2-phenyl-7-amino-5,6-dimethylpyrazolo[1,5-*a*]-pyrimidine (Ⅻ) gave the diacetate (XIV), m.p. 168~169°. The NMR spectrum of this diacetate showed signals of the acetyl groups as a coalescing sharp singlet at 7.65 τ. XIV was hydrolyzed to 2-phenyl-7-acetamido-5,6-dimethylpyrazolo[1,5-*a*]pyrimidine (XIII) through aluminum oxide chromatography. Since XIII exhibited an ultraviolet spectrum very similar to that of XIV, it is clear that its ring system did not undergo any change during this hydrolysis.

Mild acetylation of 6-phenyl-7-amino-2,3,5-trimethylpyrazolo[1,5-*a*]pyrimidine (XV) afforded a monoacetate (XVI), m.p. 228~229°, which on further acetylation led to the diacetate (XVII), $C_{19}H_{20}O_2N_4 \cdot 1/2H_2O$, m.p. 105°. In the NMR spectrum of XVII two methyl signals of acetyl groups appear at 7.81 τ as a coalescing sharp singlet. Both XVII and XVI gave very similar ultraviolet spectra [λ_{max} mμ (log ε): 247 (4.75), 296.5 (3.46), 341 (3.19) in XVII; λ_{max} mμ (log ε): 244 (4.72), 295.5 (3.62), 339 (3.27) in XVI]. The above experimental results indicate that acetylation took place at the 7-amino group to give a diacetate when an alkyl or aryl substituent was present at C-6. Next, we have examined a similar reaction on compounds bearing the ethoxycarbonyl or cyano group at C-6. Since both ethoxycarbonyl and cyano groups have rather high electronegativity, it might be expected that basicity of the 7-amino group should be reduced, and its reactivity decreased. Furthermore, the 7-amino group might undergo more severe steric hindrance by the ethoxycarbonyl group of angled structure than by the cyano group of rectilinear structure, and thus its reactivity should be different in 6-ethoxycarbonyl- and 6-cyano derivatives. Actually, acetylation of ethyl 2-methyl-7-amino- and ethyl 7-amino-2,3-dimethylpyrazolo[1,5-*a*]pyrimidine-6-carboxylates (XVIII) and (XIX) by acetic anhydride in pyridine readily gave the diacetates (XXII), m.p. 100~103° and (XXIII), m.p. 83~85°, respectively. These diacetates were hydrolyzed by alumina chromatography to give the monoacetates (XX), m.p. 169~170° and (XXI), m.p. 143~145°. Acetylation of XX and XXI gave back XXII and XXIII, respectively. The ultraviolet spectra of XX and XXI are similar to those of XXII and XXIII, respectively. Furthermore, in the NMR spectra of XXII and XXIII, the two methyl signals for the acetyl groups appear as a coalescing singlet at 7.69 and 7.70 τ, respectively. Methylation of XX and XXI afforded in good yields ethyl 7-acetylimino-2,4-dimethyl-4,7-dihydropyrazolo[1,5-*a*]pyrimidine-6-carboxylate (XXIV), m.p. 144~146°, and ethyl 7-acetylimino-2,3,4-trimethyl-4,7-dihydropyrazolo[1,5-*a*]pyrimidine-6-carboxylate (XXV), m.p. 178~180°, respectively. The structures of XXIV and XXV were confirmed by comparison with the authentic samples prepared by the acetylation of ethyl 7-imino-2,4-dimethyl-

2) A. Takamizawa, S. Hayashi, Y. Hamashima, R. Kido: Yakugaku Zasshi, 83, 313 (1963).

4,7-dihydropyrazolo[1,5-*a*]pyrimidine-6-carboxylate (XXVI) and ethyl 7-imino-2,3,4-trimethyl-4,7-dihydropyrazolo[1,5-*a*]pyrimidine-6-carboxylate (XXVII), respectively. XXVI and XXVII were derived easily by the methylation of XVIII and XIX, respectively. Ethyl 2-methyl-4-ethyl-7-imino- and ethyl 4-ethyl-7-imino-2,3-dimethyl-4,7-dihydropyrazolo-[1,5-*a*]pyrimidine (XXVIII) and (XXIX) were also obtained by the ethylation of XVIII and XIX, respectively. Both XXV and XXVII were decomposed by acid to give 2,3,4-trimethylpyrazolo[1,5-*a*]pyrimidin-7(4*H*)-one (XXX),[1] which had been prepared previously. Contrary to our expectations, acetylation of 7-amino-2,3-dimethylpyrazolo[1,5-*a*]pyrimidine-6-carbonitrile (XXXII) yielded only a monoacetate (XXXIII), m.p. 204~205°, even under various reaction conditions tried. The ultraviolet spectrum of XXXIII is very similar to that of XXI, showing absorption maxima at 251.5 mμ (log ε 4.62), 306 (3.57), 318 (3.59), and 346 (3.31). Moreover, the NMR signal for the NH group appears at 0.71 τ, which is characteristic of the 7-acetamido group. Thus, XXXIII can be formulated as 7-acetamido-2,3-dimethylpyrazolo[1,5-*a*]pyrimidine-6-carbonitrile. The above experimental results suggest that the differences of reactivity[3,4] between these series are dependent mainly upon the degree of strain of the amino group being caused by the spatial extension of the substituent at C-6. Since the coplanarity of the amino group to pyrazolo[1,5-*a*]pyrimidine ring system would be hindered by the substituents such as methyl, phenyl, or ethoxycarbonyl group having rather large spatial extension, tne basicity of the amino group would be increased and as a result a diacetate would be expected to form. On the other hand, the spatial extension of a hydrogen or cyano group would be smaller to hinder the coplanarity of the amino group, and therefore the basicity of the amino group would be decreased to give only a monoacetate.

Benzoylation of 7-amino-2,5-dimethyl- and 7-amino-3,6-dimethylpyrazolo[1,5-*a*]-pyrimidine (VI), and (XXXIV) afforded onyl 7-benzamido-2,5-dimethyl and 7-benzamido-3,6-dimethylpyrazolo[1,5-*a*]pyrimidine (XXXV), m.p. 138~139°, and (XXXVI), m.p. 187~188°, respectively. These results may be ascribable to rather lower reactivity and spatial factor of the benzoyl group itself.

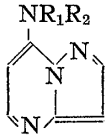
The fact that acetylation took place at the 7-amino group makes it possible to prepare various kinds of 7-acylaminopyrazolo[1,5-*a*]pyrimidines. Treatment of I with either chloracetyl chloride or chloracetic anhydride in chloroform afforded easily 7-(2-chloracetamido)-2,3-dimethylpyrazolo[1,5-*a*]pyrimidine (XXXVII), m.p. 175°. It had absorption maxima at 237 mμ (log ε 4.61), 280 (3.29, sh), 289.5 (3.35), 299 (3.26, sh), and 346 (3.61). On the other hand, reaction of II with chloracetyl chloride in chloroform did not proceed, but on treatment with chloracetic anhydride using either dimethylformamide or chloroform as a solvent, II yielded 7-(2-chloracetamido)-2,3,6-trimethylpyrazolo[1,5-*a*]pyrimidine (XXXVIII), m.p. 152~153°. However, when chloracetyl chloride and dimethylformamide were used, unexpected yellow crystals, m.p. 119° ($C_{12}H_{17}N_5$), were obtained instead of XXXVIII, which had no NH absorption band in the infrared spe-ctrum. This product exhibited ultraviolet absorption maxima at 241.5 mμ (log ε 4.44), 273.5 (4.05), and 371 (3.85), and in the NMR spectrum, two methyl signals at 6.90 τ as a coalescing sharp singlet and one proton (-N=CH-) at 0.71 τ. These spectroscopic data suggested that this compound must be 7-(dimethylaminomethylideneamino)-2,3,6-trimethylpyrazolo[1,5-*a*]pyrimidine (XXXIX). To confirm this, II was treated with acetyl chloride in dimethylformamide, whereby XXXIX and 7-acetylamino-2,3,6-trimethylpyrazolo[1,5-*a*]pyrimidine[1] (IV) were obtained. Reaction of XXXVII with dimethylamine afforded 7-(2-dimethylaminoacetamido)-2,3-dimethylpyrazolo[1,5-*a*]pyrimidine (XL), m.p.

3) H.C. Brown, A. Cahn : J. Am. Chem. Soc., **72**, 2939 (1950).
4) A.E. Remick : "Electronic Interpretation of Org. Chem.," Ed. 2, p. 318 (1949), John Wiley & Sons, New York.

168~170°. XL was reduced with lithium aluminum hydride in tetrahydrofuran to give 7-(2-dimethylaminoethylamino)-2,3-dimethylpyrazolo[1,5-*a*]pyrimidine (XLI), m.p. 103~104°. The structures of the products (XL), and (XLI) were deduced from the data of their elemental analyses and ultraviolet spectra (Table I). On reaction with ethyl chloroformate, I gave XLII as colorless needles, m.p. 113°. Treatment of I with alkylcarbamoyl chlorides gave the alkyl ureas (XLIII~XLV). II was less reactive than I with either alkyl chloroformates or alkylcarbamoyl chlorides, and in this case only ethyl 2,3,6-trimethylpyrazolo[1,5-*a*]pyrimidine-7-carbamate (XLVI), m.p. 133~135°, was obtained in poor yield.

Our attention was next directed to the syntheses of 7-alkylaminopyrazolo[1,5-*a*]-pyrimidine derivatives. It was reported[2,5] previously that 7-aminopyrazolo[1,5-*a*]-pyrimidines were easily hydrolyzed to pyrazolo[1,5-*a*]pyrimidin-7(4*H*)-ones. The

Table I. Ultraviolet Spectra of 7-Aminopyrazolo[1,5-*a*]pyrimidines and Related Compounds (in 95% EtOH)

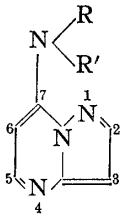


Compd. No.	λ_{max} mμ (log ε)											
IX	237.5	(4.53)				295	(3.67)				336	(3.23)
XVI	244	(4.72)				295.5	(3.62)				339	(3.27)
XVII	247	(4.75)				296.5	(3.46)				341	(3.19)
XX	245	(4.62)				298	(3.54)				334	(3.44)
XXI	246	(4.63)				299	(3.53)				340	(3.29)
XXII	250	(4.62)				297	(3.50)				330	(3.24)
XXIII	256	(4.64)				300	(3.52)	320	(3.39 sh)		348	(3.15)
XXXIII	251.5	(4.62)				306	(3.57)	318	(3.59)		346	(3.31)
XXXV	238	(4.60)				284.5	(3.63)				331	(3.82)
XXXVII	237	(4.61)	280	(3.29 sh)		289.5	(3.35)	299	(3.26 sh)		346	(3.61)
XXXVIII	239.5	(4.64)				295	(3.22)	310	(3.16)		348	(3.37)
XXXIX	241.5	(4.44)				273.5	(4.05)				371	(3.85)
XL	235.5	(4.64)	280	(3.32 sh)		289	(3.38)	298	(3.29 sh)		346	(3.63)
XLI	225	(4.55)	281.5	(3.77 〃)		290.5	(3.81)				323	(3.83)
XLII	232.5	(4.63)				287	(3.44)	297	(3.43)		336	(3.59)
XLIII	233	(4.67)	276	(3.25 sh)		286.5	(3.50)	295.5	(3.52)		332	(3.69)
XLIV	232.5	(4.63)				285.5	(3.54)	294	(3.57)		329	(3.82)
XLIV[a)]	232.5	(4.66)	276	(3.38 sh)		285.5	(3.54)	294	(3.57)		329	(3.74)
XLVI	238	(4.66)	282.5	(3.21 〃)		292.5	(3.28)	308	(3.21 sh)		342	(3.39)
L	238	(4.69)	283	(3.17 〃)		293.5	(3.24)	302	(3.10 〃)		343	(3.21)
LI	239.5	(4.87)	286	(3.18 〃)		296	(3.23)	310	(3.16)		344	(3.24)
LII	240.5	(4.67)	283	(3.26 〃)		292	(3.29)	301	(3.18 sh)		338	(3.16)
LIII	237.5	(4.40)	283.5	(2.93)		290	(2.94)	304	(2.75 〃)		344	(2.79)
LIV	239.5	(4.66)	285	(3.14 sh)		294	(3.15)	309	(3.06)		345	(3.06)
LV	238.5	(4.65)	281	(3.23)		289.5	(3.23)	299	(3.04 sh)		332	(2.98)
LVI	245	(3.82)										
LVII	244	(3.82)										
LX	228.5	(4.59)				290.5	(3.85)				316	(3.80)
LXI	231	(4.55)	287	(3.61 sh)		296.5	(3.67)				338	(3.83)
LXII	238	(4.57)	266	(3.67 〃)		291	(3.57)	303	(3.47 sh)		350	(3.76)
LXIII	234	(4.62)	288	(3.70 〃)		298	(3.78)				330	(3.85)
LXIV	236	(4.64)	288	(3.60 〃)		298.5	(3.68)				332	(3.78)
LXVI	233	(4.63)	285	(3.62 〃)		294	(3.70)				336	(3.80)

a) Hydrochloride

5) Y. Makisumi: This Bulletin, **10**, 621 (1962).

TABLE II. Nuclear Magnetic Resonance Data on 7-Aminopyrazolo[1,5-*a*]pyrimidine Derivatives and Related Compounds (60 Mc.p.s.)[a]



Compd. No.	C-2[c]	C-3[c]	C-5[c]	C-6[c]	N-R	N-R′
IX	7.59 (Me)	3.75 (H)	7.47 (Me)	2.57 (H)	0.83 (H)	7.67 (COMe)
X	7.54 (〃)	3.60 (〃)	1.82～2.64[m] (Ph)	1.92 (〃)	0.90 (〃)	7.68 (〃)
XI	7.64 (〃)	7.74 (Me)	1.82～2.67[m] (〃)	2.04 (〃)	0.92 (〃)	7.70 (〃)
XIV	1.96～2.68[m] (Ph)	3.10 (H)	7.37 (Me)	7.78 (Me)	7.65 (COMe)	7.65 (〃)
XVI	7.55 or 7.57 (Me)	7.65 (Me)	7.55 or 7.57 (〃)	2.49～2.92[m] (Ph)	1.13 (H)	7.78 (〃)
XVII	7.61 (〃)	7.68 (〃)	7.58 (〃)	2.52～2.93[m] (〃)	7.81 (COMe)	7.81 (〃)
XX	7.52 (〃)	3.52 (H)	1.26 (H)		0.26 (H)	7.65 (〃)
XXI	7.55 (〃)	7.72 or 7.63 (Me)	1.30 (〃)		0.53 (〃)	7.63 or 7.72 (〃)
XXII	7.49 (〃)	3.37 (H)	1.03 (〃)		7.69 (COMe)	7.69 (〃)
XXIII	7.52 (〃)	7.70 (Me)	1.05 (〃)		7.70 (〃)	7.70 (〃)
XXXIII	7.52 or 7.56 (〃)	7.73 (〃)	1.68 (〃)		0.71 (H)	7.56 or 7.52 (〃)
XXXV	7.51 (〃)	3.71 (H)	7.41 (Me)	2.52 (H)	0.10 (〃)	1.92～2.53[m] (COC_6H_5)
XXXVI	1.69 (H)	7.68 (Me)	2.24 (H)	7.68 (Me)	0.21 (〃)	1.95～2.62[m] (〃)
XLII	7.60 (Me)	7.74 (〃)	1.74[d] (〃) $J_{5,6}=5.5$	2.74[d] (H)	1.34 (〃)	
XLIII	7.61 (〃)	7.73 (〃)	1.75[d] (〃) $J_{5,6}=10.0$	2.63[d] (〃)	1.23 (〃)	6.88 ($CONMe_2$)
XLVI	7.61 (〃)	7.71 (〃)	1.80 (〃)	7.75 (Me)	1.80 (〃)	
LVIII	7.61 (〃)	7.76 (〃)	1.85[d] (〃) $J_{5,6}=5.0$	4.25[d] (H)	3.64 (〃)	6.98[d] (Me)[b] J=5.5
LIX	7.63 (〃)	7.58 or 7.78 (〃)	2.08 (〃)	7.78 or 7.58 (Me)	3.69 (〃)	6.69[d] (〃)[b] J=5.7
LX	7.63 (〃)	7.78 (〃)	7.52 (Me)	4.35 (H)	3.65 (〃)	7.03[d] (〃)[b] J=5.2
LXI	7.56 (〃)	7.73 (〃)	1.88[d] (H) $J_{5,6}=5.0$	4.18[d] (〃)	6.72 (Me)	6.72 (〃)
LXII			1.94 (〃)		6.81 (〃)	6.81 (〃)
LXIII	7.60 (〃)	7.77 (〃)	7.52 (Me)	4.25 (〃)	6.77 (〃)	6.77 (〃)
L	7.49 (〃)	7.69 (〃)	1.76[d] (H) $J_{5,6}=4.5$	3.20[d] (〃)		
LI	7.52 (〃)	7.61 (〃)	1.86 (〃)	7.72 (Me)		
LII	7.55 (〃)	7.74 (〃)	7.47 (Me)	3.87 (H)		

a) Observed on about 10% (w/v) solutions in deuteriochloroform. Multiplicities of signals are represented as d (doublet), and m (multiplet).
b) Became singlet by D_2O addition.
c) The assignment of chemical shifts for C-methyl groups were mainly due to the rule of 7-aminopyrazolo[1,5-*a*]pyrimidines reported previously, thus the assignments are not always justifiable.

7-oxo-derivatives (XLVIII) and (XLIX), obtained by acid hydrolysis of I and II, respectively, and XLVII[6] were then chlorinated with phosphoryl chloride to 7-chloro-2,3-dimethyl-, 7-chloro-2,3,6-trimethyl, and 7-chloro-2,3,5-trimethylpyrazolo[1,5-*a*]pyrimidines (L), (LI), and (LII), respectively. L was hydrogenated over palladized charcoal to give 2,3-dimethylpyrazolo[1,5-*a*]pyrimidine (LIII), m.p. 54°, λ_{max} mμ (log ε): 237.5 (4.40), 283.5 (2.93), 290 (2.94), 304 (2.75), and 344 (2.79). Similarly, LI and LII were also hydrogenated to give 2,3,6- and 2,3,5-trimethylpyrazolo[1,5-*a*]pyrimidine (LIV), m.p. 110°, and (LV), m.p. 81° in good yields. On further hydrogenation, LIII and LIV led to 2,3-dimethyl-, and 2,3,6-trimethyl-4,5,6,7-tetrahydropyrazolo[1,5-*a*]pyrimidines (LVI), m.p. 141~142°, and (LVII), m.p. 169~170°. LVI and LVII show an absorption maximum at 245 and 244 mμ, respectively, which is typical of 5-amino-3,4-dimethylpyrazole (232 mμ). In their NMR spectra, methyl signals at C-2 and C-3 both appear as a singlet. These spectroscopic evidence confirmed the structures of LVI and LVII. Reaction of alkylamines with L~LII afforded corresponding 7-alkylaminopyrazolo[1,5-*a*]pyrimidine (LVIII~LXVI). The structures of LVIII and LIX were confirmed by preparing them by lithium aluminum hydride reduction[1] from 7-formamido-2,3-dimethyl-, and 7-formamido-2,3,6-trimethylpyrazolo[1,5-*a*]pyrimidines (LXVII) and (LXVIII),[1] respectively. It is interesting to note that in LVIII and LIX the N-methyl groups coupled to their adjacent NH protons show their signals as doublets at 6.98 (J=5.5 c.p.s.) and 6.69 τ (J=5.7 c.p.s.), respectively, which turn into singlets by the addition of a small amount of deuterium oxide to the examined solutions.

Experimental*3

7-Acetamido-2,5-dimethylpyrazolo[1,5-*a*]pyrimidine (IX)——a) A mixture of 2.0 g. of VI, 10 ml. of Ac_2O and 20 ml. of pyridine was heated at 105° for 5.5 hr. The reaction mixture was concentrated and the residue was extracted with $CHCl_3$. The crystalline residue after removal of the solvent was recrystallized from ether to give colorless needles, m.p. 83~84°. Yield, 1.8 g. (71%). *Anal.* Calcd. for $C_{10}H_{20}ON_4$: C, 58.81; H, 5.92; N, 27.44. Found: C, 59.15; H, 5.98; N, 26.92. IR λ_{max}^{Nujol} cm^{-1}: 3183 (NH), 1703 (C=O).

b) A solution of 1.0 g. of VI in 10 ml. of pyridine was cooled in ice-water. To this solution was added dropwise 1.2 g. of AcCl under stirring. After being reacted at 100° for 2 hr., the reaction mixture was concentrated. The residue was extracted with $CHCl_3$ and the organic solution was washed with aq. K_2CO_3, H_2O and dried over $MgSO_4$. The crystalline residue after removal of the solvent was recrystallized to give IX as colorless needles, which was identified by the mixture melting point determination.

2-Methyl-5-phenyl-7-acetamidopyrazolo[1,5-*a*]pyrimidine (X)——A mixture of 500 mg. of VII, 3 ml. of Ac_2O, and 8 ml. of pyridine was heated at 110~115° for 1.5 hr., the mixture was concentrated to leave brown oil, which was solidified. Recrystallization of the solids gave X as colorless plates, m.p. 196~198°. Yield, 450 mg. (75%). *Anal.* Calcd. for $C_{15}H_{14}ON_4$: C, 67.65; H, 5.30; N, 21.04. Found: C, 67.63; H, 5.40; N, 21.00. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3326 (NH), 1717 (C=O).

5-Phenyl-7-acetamido-2,3-dimethylpyrazolo[1,5-*a*]pyrimidine (XI)——Prepared by the same method as X. Yellow needles (from ether), m.p. 165~166°. Yield, 84.8%. *Anal.* Calcd. for $C_{16}H_{16}ON_4$: C, 68.55; H, 5.75; N, 19.99. Found: C, 68.53; H, 5.88; N, 19.73. IR ν_{max}^{Nujol} cm^{-1}: 3300 (NH), 1721 (C=O).

2-Phenyl-7-diacetylamino-5,6-dimethylpyrazolo[1,5-*a*]pyrimidine (XIV)——A mixture of 500 mg. of XII, 5 ml. of Ac_2O, and 15 ml. of pyridine was heated at 100° for 3 hr., the reaction mixture was concentrated and the residue was extracted with $CHCl_3$. The organic solution was washed with K_2CO_3, H_2O, and dried. The residue after removal of the solvent was recrystallized from MeOH to give diacetate as colorless needles, m.p. 168~169°. Yield, 84.7%. *Anal.* Calcd. for $C_{18}H_{18}O_2N_4$: C, 67.06; H, 5.63; N, 17.38. Found: C, 67.67; H, 5.77; N, 17.48.

Acetylation of XV——A mixture of 500 mg. of XV, 5 ml. of Ac_2O and 15 ml. of pyridine was heated at 100° for 12 hr. The reaction mixture was concentrated to leave brown oil, which was submitted to Al_2O_3 (neutral) chromatography using $CHCl_3$ as a solvent. From the first eluate was given colorless crys-

*3 All melting points are uncorrected.

6) Y. Makisumi: This Bulletin, **10**, 612 (1962).

tals, which were recrystallized from acetone to give monoacetate (XVI), m.p. 228~229°. Yield, 490 mg. (90.5%). *Anal.* Calcd. for $C_{17}H_{18}ON_4$: C, 69.37; H, 6.16; N, 19.04. Found: C, 69.01; H, 6.39; N, 18.56.

Monoacetate (XVI) (200 mg.) was heated with Ac_2O (3 ml.) in pyridine (5 ml.) at 115° for 6 hr., the reaction mixture was concentrated. The residue gradually solidified, which was recrystallized from hexane to give diacetate (XVII) as yellow rocks, m.p. 105°. Yield, 210 mg. (89.6%). *Anal.* Calcd. for $C_{19}H_{20}O_2N_4 \cdot 1/2H_2O$: C, 66.10; H, 6.17; N, 16.24; O, 11.58. Found: C, 65.69; H, 6.34; N, 16.07; O, 12.24.

Acetylation of XVIII——A mixture of 1.0 g. of XVIII, 10 ml. of Ac_2O and 20 ml. of pyridine was heated in a sealed tube at 110° for 15 hr. The dark brown reaction mixture was concentrated, the residue was dissolved in EtOAc and the organic solution was washed with chilled aq. K_2CO_3, H_2O and dried. The solution after being treated with active carbon was concentrated under vacuum. The residues crystallized by adding small amount of ether, the solids obtained were recrystallized from acetone-ether to give colorless scales, m.p. 169~170°. Yield, 388 mg. *Anal.* Calcd. for $C_{12}H_{14}O_3N_4$: C, 54.95; H, 5.38; N, 21.37. Found: C, 54.96; H, 5.53; N, 21.51. IR ν_{max}^{Nujol} cm^{-1}: 3220 (NH), 1712, 1694 (C=O).

From the ether solution were obtained yellow crystals. Recrystallization of the crystals from ether-hexane gave XXII as light yellow scales, m.p. 100~103°. Yield, 102 mg. *Anal.* Calcd. for $C_{14}H_{16}O_4N_4$: C, 55.25; H, 5.30; N, 18.41. Found: C, 55.38; H, 5.47; N, 19.19. IR ν_{max} cm^{-1}: 1735, 1717, 1702 (C=O).

XXII was chromatographed on Al_2O_3 (Merck, standardized) with $CHCl_3$ to give XX in good yield.

Acetylation of XIX——A mixture of 1.5 g. of XIX, 8 ml. of Ac_2O, and 15 ml. of pyridine was heated in a sealed tube at 110° for 15 hr. The dark brown reaction mixture was concentrated, the residue was dissolved in EtOAc and the organic layer was treated with active carbon and then washed with chilled 10% K_2CO_3 and dried. The oily residue after removal of the solvent gradually solidified, which was recrystallized from hexane to give XXIII as light yellow scales, m.p. 83~85°. Yield, 1.55 g. (75.5%). *Anal.* Calcd. for $C_{15}H_{18}O_4N_4$: C, 56.59; H, 5.70; N, 17.60. Found: C, 56.81; H, 5.75; N, 17.52. IR ν_{max}^{Nujol} cm^{-1}: 1730, 1721 (C=O).

XXIII was chromatographed on Al_2O_3 in EtOAc to give monoacetate (XXI) as light yellow needles, m.p. 143~145°. *Anal.* Calcd. for $C_{13}H_{16}O_3N_4$: C, 56.51; H, 5.84; N, 20.28. Found: C, 56.56; H, 5.99; N, 20.46. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3375 (NH), 1726 (C=O).

Ethyl 7-Imino-2,4-dimethyl-4,7-dihydropyrazolo[1,5-*a*]pyrimidin-6-carboxylate (XXVI)——A mixture of 1.1 g. of XVIII, 0.71 g. of CH_3I in 30 ml. of acetone was heated in a sealed tube at 100° for 6 hr. After cooling, the reaction mixture was concentrated and the residue was recrystallized from MeOH-ether to give colorless needles, m.p. 152° (decomp.). *Anal.* Calcd. for $C_{11}H_{14}O_2N_4 \cdot HI \cdot H_2O$: C, 34.75; H, 4.51; N, 14.73; O, 12.61. Found: C, 35.48; H, 4.83; N, 14.79; O, 11.94.

The hydriodide was dissolved in H_2O and neutralized with K_2CO_3, precipitated crystals were filtered and washed. The crystals were recrystallized from acetone to give colorless sticks, m.p. 208° (decomp.). *Anal.* Calcd. for $C_{11}H_{14}O_2N_4 \cdot H_2O$: C, 52.37; H, 6.39; N, 22.21. Found: C, 51.96; H, 6.76; N, 22.82. UV λ_{max}^{EtOH} mμ (log ε): 228 (4.40), 289 (3.95), 327 (4.00).

NMR (τ) in $CDCl_3$: 4.24[s] (3-H), 2.23[s] (5-H), 6.44[s] (N-Me), 7.65[s] (2-Me), 2.25[b] (NH).

Ethyl 7-Imino-2,3,4-trimethyl-4,7-dihydropyrazolo[1,5-*a*]pyrimidin-6-carboxylate (XXVII)——A mixture of 2.0 g. of XIX and 1.21 g. of CH_3I in 20 ml. of acetone was heated in a sealed tube at 110° for 6 hr. After cooling, the precipitated solids were filtered and washed with acetone. Recrystallization of the solids gave XXVII as colorless sticks, m.p. 205° (decomp.). Yield, 1.42 g. (44.5%). *Anal.* Calcd. for $C_{12}H_{16}O_2N_4 \cdot HI$: C, 38.38; H, 4.56; N, 14.83. Found: C, 37.82; H, 4.66; N, 15.13.

The hydriodide was dissolved in H_2O and neutralized with K_2CO_3. The precipitated solides were filtered and recrystallized from acetone to give colorless needles, m.p. 228° (decomp.). *Anal.* Calcd. for $C_{12}H_{16}O_2N_4$: C, 58.05; H, 6.50; N, 22.57. Found: C, 57.80; H, 6.71; N, 22.47. UV λ_{max}^{EtOH} mμ (log ε): 233 (4.39), 279 (3.97), 295 (3.92, sh), 325 (3.95).

NMR (τ) in $CDCl_3$: 2.28 (5-H), 2.58[b] (NH), 6.21 (N-Me), 7.71 (2-Me), 7.77 (3-Me).

Ethyl 7-Acetylimino-2,4-dimethylpyrazolo[1,5-*a*]pyrimidin-6-carboxylate (XXIV)——a) To a suspension of XXVI (500 mg.) in pyridine (10 ml.) was added 5 ml. of Ac_2O under cooling. The mixture was stirred at room temperature for 5.5 hr. The light yellow reaction mixture was concentrated under reduced pressure. Recrystallization of the residue from acetone-ether gave colorless needles, m.p. 144~146°. Yield, 570 mg. (96.5%). *Anal.* Calcd. for $C_{13}H_{16}O_3N_4$: C, 56.53; H, 5.84; N, 20.25. Found: C, 56.33; H, 6.08; N, 19.83. UV λ_{max}^{EtOH} mμ (log ε): 226 (4.30), 281.5 (3.99), 325 (4.04).

NMR (τ) in $CDCl_3$: 2.06[s] (5-H), 4.11[s] (3-H), 6.33[s] (N-Me), 7.64 or 7.66 (2-Me), 7.66 or 7.64 (COMe).

b) A mixture of 500 mg. of XX and 500 mg. of CH_3I in 10 ml. of acetone was heated in a sealed tube at 100° for 5 hr. After cooling, the precipitated solids were collected and washed with acetone. The solids were dissolved in H_2O and neutralized with aq. Na_2CO_3. The precipitated solids were extracted with $CHCl_3$ and dried. The residue after removal of the solvent was recrystallized from acetone-ether to give XXIV as colorless needles, m.p. 143°, which was proved to be identical with the sample prepared by the method described in a) by a comparison of their IR spectra.

Ethyl 7-Acetylimino-2,3,4-trimethyl-4,7-dihydropyrazolo[1,5-*a*]pyrimidin-6-carboxylate (XXV)——a) To a suspension of XXVII (500 mg.) in pyridine (10 ml.) was added 5 ml. of Ac_2O under cooling. The mixture became clear solution under stirring at room temperature for 3.5 hr. The reaction mixture was concentrated to leave light brown residue. Recrystallization of the residue from acetone to give light yellow needles, m.p. 178~180°. Yield, 520 mg. *Anal.* Calcd. for $C_{14}H_{18}O_3N_4$: C, 57.92; H, 6.25; N, 19.30. Found: C, 58.02; H, 6.46; N, 19.39. UV λ_{max}^{EtOH} mμ (log ε): 230 (4.24), 285 (4.10), 330 (4.02).

NMR (τ) in $CDCl_3$: 2.13 (5-H), 6.13 (N-Me), 7.66, 7.65, 7.78 (Me × 3).

b) A mixture of 200 mg. of XXI and 200 mg. of CH_3I in 10 ml. acetone was heated in a sealed tube at 100° for 5 hr. After cooling, the reaction mixture was concentrated *in vacuo*. The residue was suspended in H_2O and washed with EtOAc. The aqueous layer was neutralized with Na_2CO_3 and extracted with $CHCl_3$. The residue after removal of the solvent was recrystallized from ether to give XXV as pale yellow needles, m.p. 176°. Yield, 23 mg.

Hydrolysis of XXVII——XXV (130 mg.) in 10 ml. of 20% HCl was refluxed for 24 hr. and concentrated. The brown residue was redissolved in H_2O and neutralized with K_2CO_3, the precipitated crystals were extracted with $CHCl_3$ and $CHCl_3$ extract was washed with H_2O and dried. The residue after removal of the solvent was chromatographed over Al_2O_3 using acetone as a solvent. Colorless crystals (17 mg.)obtained had an m.p. 235°, and were identified as XXX with the authentic sample by the mixed melting point determination and a comparison of IR spectra.

Ethyl 2-Methyl-4-ethyl-7-imino-4,7-dihydropyrazolo[1,5-*a*]pyrimidin-6-carboxylate (XXVIII)——A mixture of 2.2 g. of XVIII and 1.6 g. of C_2H_5I in 30 ml. of acetone was heated in a sealed tube at 110° for 6.5 hr. After cooling, the solid (raw material, 480 mg.) was filtered off. The filtrate was concentrated and the residue (2.66 g.) was suspended in H_2O and the insoluble mass was filtered off (420 mg.). The filtrate was neutralized with K_2CO_3, the precipitated crystals were extracted with $CHCl_3$ and $CHCl_3$ extract was washed and dried. The residue after removal of the solvent was recrystallized from EtOAc to give colorless plates, m.p. 155~156°. Yield, 564 mg. *Anal.* Calcd. for $C_{12}H_{16}O_2N_4$: C, 58.05; H, 6.50; N, 22.57. Found: C, 58.24; H, 6.58; N, 22.49.

Ethyl 4-Ethyl-7-imino-2,3-dimethyl-4,7-dihydropyrazolo[1,5-*a*]pyrimidin-6-carboxylate (XXIX)——A mixture of 2.0 g. of XIX and 1.42 g. of C_2H_5I in 30 ml. of acetone was heated at 100° for 19 hr. After being cooled, the precipitated solid (raw material, 316 mg.) was filtered off, the fiiltrate was concentrated and the residue was suspended in H_2O, the insoluble mass (raw material, 680 mg.) was filtered off. The filtrate was concentrated and the residue was recrystallized from acetone to give colorless needles, m.p. 185° (decomp.). Yield, 1.2 g. (70.2%). *Anal.* Calcd. for $C_{13}H_{18}O_2N_4 \cdot HI$: C, 40.00; H, 4.90; N, 14.68. Found: C, 38.73; H, 5.00; N, 14.70. UV λ_{max}^{EtOH} mμ (log ε): 230 (4.55), 289 (4.08); 328 (3.72).

The hydriodide was neutralized with K_2CO_3, the free base obtained was recrystallized from acetone-ether to give colorless sticks, m.p. 181~182°. *Anal.* Calcd. for $C_{13}H_{18}O_2N_4$: C, 59.42; H, 6.92; N, 21.36. Found: C, 59.21; H, 7.08; N, 21.27. UV λ_{max}^{EtOH} mμ (log ε): 232.5 (4.36), 277 (3.97), 295 (3.88, sh), 328 (3.94).

7-Acetamido-2,3-dimethylpyrazolo[1,5-*a*]pyrimidin-6-carbonitrile (XXXIII)——a) A suspension of 500 mg. of XXXII, 10 ml. of pyridine and 5 ml. of Ac_2O was stirred at room temperature for 25 hr. becoming to clear solution. After being stirred more 5 hr., the reaction mixture was concentrated under reduced pressure (bath temp., below 50°). The residue was recrystallized from MeOH-EtOAc to give XXXIII as pale yellow sticks, m.p. 204~205°. *Anal.* Calcd. for $C_{11}H_{11}ON_5$: C, 57.63; H, 4.84; N, 30.55. Found: C, 57.74; H, 4.97; N, 30.49.

b) A mixture of XXXII (1.0 g.), Ac_2O (10 ml.), and pyridine (20 ml.) was heated at 110° for 8 hr. The brown reaction mixture was concentrated and the dark brown residue was dissolved in EtOAc, the EtOAc extract was passed through active carbon to be obtained pale yellow solution. IR spectrum of the residue after removal of the solvent showed the identity with that of XXXIII obtained above. The residue after being solidified was recrystallized from EtOAc to give pale yellow sticks, m.p. 203~205°, which was proved to be identical with XXXIII obtained by method a). Yield, 305 mg.

7-Benzamido-2,5-dimethylpyrazolo[1,5-*a*]pyrimidine (XXXV)——To a solution of 1.0 g. of VI in 10 ml. of pyridine was added dropwise 1.86 g. of benzoyl chloride under stirring and ice cooling, the mixture then was heated at 110° for 1 hr. The brown reaction mixture was concentrated and extracted with $CHCl_3$, the $CHCl_3$ extract was washed with K_2CO_3, H_2O and dried. The yellow residue after removal of the solvent was recrystallized from ether to give yellow rhombs., m.p. 138~139°. Yield, 1.2 g. *Anal.* Calcd. for $C_{15}H_{14}ON_4$: C, 67.65; H, 5.30; N, 21.04. Found: C, 67.59; H, 5.51; N, 20.67.

7-Benzamido-3,6-dimethylpyrazolo[1,5-*a*]pyrimidine (XXXVI)——To a solution of 250 mg. of XXXIV in 3 ml. of pyridine was added 465 mg. of benzoylchloride and was treated by the same method mentioned above. Thin-layer chromatograph (SiO_2-EtOAc) showed single spot. Recrystallization from ether gave colorless needles, m.p. 187~188°. Yield, 200 mg. *Anal.* Calcd. for $C_{15}H_{14}ON_4$: C, 67.65; H, 5.30; N, 21.04. Found: C, 67.89; H, 5.50; N, 21.38.

7-(2-Chloracetamido)-2,3-dimethylpyrazolo[1,5-*a*]pyrimidine (XXXVII)——a) To a suspension of I (5.7 g.) and 5.0 g. of K_2CO_3 in 40 ml. of DMF (dimethylformamide) was added dropwise 4.0 g. of $ClCH_2COCl$ under ice cooling and stirring. The mixture was heated on a steam bath for 6 hr. After being

cooled, the mixture was concentrated under reduced pressure. The residue was extracted with $CHCl_3$ and the $CHCl_3$ extract was washed with K_2CO_3, H_2O and dried. Aqueous layer was neutralized with K_2CO_3 and the precipitated solid was filtered to recover the raw material (3.1 g.). The organic layer was concentrated and the residue was passed through Al_2O_3 column using $CHCl_3$. The solids obtained was recrystallized from MeOH to give colorless needles, m.p. 175°. Yield, 1.94 g. (50.6%). *Anal.* Calcd. for $C_{10}H_{11}ON_4Cl$: C, 50.35; H, 4.65; N, 23.50. Found : C, 50.12; H, 4.81; N, 23.52.

b) A mixture of 5.0 g. of I and 5.27 g. of chloracetic anhydride in 100 ml. of $CHCl_3$ was heated to reflux for 6.5 hr. After cooling, the precipitated solids were filtered off and the filtrate was washed with Na_2CO_3, H_2O, dried, and chromatographed over Al_2O_3. The residue after evaporated the solvent was recrystallized from MeOH to give colorless needles, m.p. 176°, which was identified as XXXVII by the mixture melting point determination and comparison of the IR spectra.

7-(2-Chloracetamido)-2,3,6-trimethylpyrazolo[1,5-*a*]pyrimidine (XXXVIII)——A mixture of II (1.0 g.) and chloracetic anhydride (1.0 g.) in $CHCl_3$ was heated to reflux for 5 hr. After being cooled, the precipitated solids were filtered and the filtrate was washed with K_2CO_3, H_2O and dried. Recrystallization of the residue from MeOH after removal of the solvent afforded XXXVIII as colorless needles, m.p. 152~153°. Yield, 960 mg. *Anal.* Calcd. for $C_{11}H_{13}ON_4Cl \cdot 1/2H_2O$: C, 50.48; H, 5.40; N, 21.41. Found : C, 50.21; H, 5.65; N, 21.77.

7-(Dimethylaminomethylideneamino)-2,3,6-trimethylpyrazolo[1,5-*a*]pyrimidine (XXXIX)——a) II (1.76 g.) was dissolved in DMF (20 ml.) by warming, the solution was then cooled with ice-water bath. To the solution was added chloracetyl chloride (1.13 g.), the mixture was heated on a steam bath for 1 hr. The dark brown reaction mixture was concentrated and extracted with $CHCl_3$ and the organic layer was washed with chilled 5% K_2CO_3, H_2O and dried. The residue after removal of the solvent was passed through Al_2O_3 column using $CHCl_3$. The residue after removal of the solvent was recrystallized from ether to give yellow rhombs., m.p. 119°. Yield, 634 mg. *Anal.* Calcd. for $C_{12}H_{17}N_5$: C, 62.31; H, 7.41 ; N, 30.28. Found : C, 62.39; H, 7.48; N, 29.52.

NMR (τ) in $CDCl_3$: 0.71 (-CH=N-), 1.87 (5-H), 6.90 (N-Me × 2) 7.59 (Me), 7.75 (Me × 2).

b) II (1.0 g.) was dissolved in DMF (15 ml.). To the mixture was added dropwise 0.45 g. of CH_3COCl under ice-water cooling, the solution was heated on a steam bath for 3 hr. and concentrated under reduced pressure. The residue was extracted with $CHCl_3$ and $CHCl_3$ extract was passed through Al_2O_3 column using $CHCl_3$ as a solvent. The residues after removal of the solvent was recrystallized from ether to give XXXIX as yellow rhombs., m.p. 119° (26.8%). From the mother liquid was obtained light yellow needles, m.p. 180°, which was proved to be identical with 7-acetamido-2,3,6-trimethylpyrazolo-[1,5-*a*]pyrimidine (IV) by the mixture melting point and the IR comparison determinations.

7-(2-Dimethylaminoacetamido)-2, 3-dimethylpyrazolo [1, 5-*a*]pyrimidine (XL)——XXXVII (1.68 g.) was dissolved in $CHCl_3$ containing 1.27 g. of $HN(CH_3)_2$. The solution was heated in a sealed tube at 105° for 6.5 hr. After cooling, the reaction mixture was washed with H_2O and dried. The brown residue after removal of the solvent was recrystallized from acetone to give colorless needles, m.p. 168~170°. Yield, 1.28 g. (76.2%). *Anal.* Calcd. for $C_{12}H_{17}ON_5$: C, 58.28; H, 6.93; N, 28.32. Found : C, 58.26; H. 6.96; N, 28.38.

Hydrochloride in yellow needles from MeOH-ether, m.p. 188° (decomp.). *Anal.* Calcd. for $C_{12}H_{17}ON_5 \cdot 2HCl \cdot H_2O$: C, 42.65; H, 6.25; N, 20.70. Found : C, 42.69; H, 6.57; N, 20.99.

7-(2-Dimethylaminoethylamino)-2,3-dimethylpyrazolo[1,5-*a*]pyrimidine (XLI)——To a THF (tetrahydrofaran) (50 ml.) containing 400 mg. of $LiAlH_4$ was added dropwise XL (490 mg.) in THF under ice-water cooling and stirring. The mixture was then heated to reflux for 10 hr. with stirring. After cooling, the reaction mixture was decomposed by the ordinary methed. The THF layer was concentrated and the residue was extracted with $CHCl_3$, and the $CHCl_3$ extract was washed with H_2O and dried. The oily residue after removal of the solvent was chromatographed on Al_2O_3 using $CHCl_3$ as a solvent. Elution with $CHCl_3$ afforded a product as colorless sticks. m.p. 103~104°. Yield, 150 mg. *Anal.* Calcd. for $C_{12}H_{19}N_5$: C, 61.77; H, 8.21; N, 30.02. Found : C, 62.01; H, 8.11; N, 29.74.

Ethyl 2,3-Dimethylpyrazolo[1,5-*a*]pyrimidine-7-carbamate (XLII)——To a solution of I (1.5 g.) in 15 ml. of pyridine was added dropwise 2.02 g. of $ClCOOC_2H_5$ under ice cooling, the mixture was gradually heated to 70~80° and reacted at the temperatures for more 2 hr. The brown reaction mixture was then concentrated to dryness, the residue was extracted with $CHCl_3$ and the $CHCl_3$ extract was washed with K_2CO_3, H_2O and dried. Recrystallization of the residue after removal of the solvent afforded XLII as colorless sticks, m.p. 113°. Yield, 1.2 g. *Anal.* Calcd. for $C_{11}H_{14}O_2N_4$: C, 56.40; H, 6.02; N, 23.92. Found : C, 56.54; H, 6.12; N, 23.95.

Hydrochloride in yellow plates from acetone, m.p. 188° (decomp.). *Anal.* Calcd. for $C_{11}H_{14}O_2N_4 \cdot HCl$: C, 48.80; H, 5.58; N, 20.69. Found : C, 48.77; H, 5.76; N, 20.71.

7-(3,3-Dimethylureido)-2,3-dimethylpyrazolo[1,5-*a*]pyrimidine (XLIII)——A mixture of I (500 mg.) and $ClCON(CH_3)_2$ (660 mg.) in pyridine (4 ml.) was heated on gentle refluxing for 3.5 hr. The reaction mixture was concentrated, the residue was extracted with $CHCl_3$ and the $CHCl_3$ extract was washed with

K_2CO_3, H_2O and dried. The residue after removal of the solvent was submitted to Al_2O_3 chromatography. Elution with $CHCl_3$ afforded XLIII as light yellow crystals, which was recrystallized from acetone to give light yellow plates, m.p. 163°. *Anal.* Calcd. for $C_{11}H_{15}ON_5$: C, 56.63; H, 6.48; N, 30.03. Found: C, 56.80; H, 6.56; N, 29.72.

Hydrochloride as yellow needles from EtOH–acetone, m.p. 210~213° (decomp.). *Anal.* Calcd. for $C_{11}H_{15}ON_5 \cdot HCl$: C, 48.98; H, 5.97; N, 25.96. Found: C, 49.41; H, 6.18; N, 25.77.

7-(Piperidinocarbonylamino)-2,3-dimethylpyrazolo[1,5-*a*]pyrimidine (XLIV)——A mixture of 1.62 g. of I, piperidinocarbonyi chloride (2.95 g.) in 20 ml. of pyridine was treated by the method mentioned above. Colorless scales (from ether), m.p. 126°. *Anal.* Calcd. for $C_{14}H_{19}ON_5$: C, 61.52; H, 7.01; N, 25.62. Found: C, 61.61; H, 7.14; N, 25.42.

Hydrochloride as yellow thin plates, m.p. 213° (decomp.). *Anal.* Calcd. for $C_{14}H_{19}ON_5 \cdot HCl$: C, 54.27; H, 6.51; N, 22.61. Found: C, 54.20; H, 6.82; N, 22.61.

7-(Morphorincarbonylamino)-2,3-dimethylpyrazolo[1,5-*a*]pyrimidine (XLV)——Yellow plates (from acetone), m.p. 208° (decomp.). *Anal.* Calcd. for $C_{13}H_{17}O_2N_5 \cdot HCl$: C, 50.07; H, 5.82; N, 22.46. Found: C, 49.95; H, 6.19; N, 22.17.

Ethyl 2,3,6-Trimethylpyrazolo[1,5-*a*]pyrimidine-7-carbamate (XLVI)——A mixture of 2.0 g. of II, 2.46 g. of $ClCOOC_2H_5$ in 30 ml. of pyridine was warmed at 50° for 2 hr. The reaction mixture was concentrated, the residue was dissolved in H_2O and neutralized with K_2CO_3 and extracted with $CHCl_3$. The residue after removal of the solvent was submitted to Al_2O_3 chromatography. Elution with $CHCl_3$ gave the product (250 mg.), which was recrystallized from ether to give XLVI as colorless sticks, m.p. 133~135°. *Anal.* Calcd. for $C_{12}H_{16}O_2N_4$: C, 58.05; H, 6.50; N, 22.57. Found: C, 58.08; H, 6.56; N, 22.33.

The second elution product was proved to be the raw material (1.3 g.).

7-Chloro-2,3-dimethylpyrazolo[1,5-*a*]pyrimidine (L)——A mixture of 200 mg. of XLVIII and 10 ml. of $POCl_3$ was heated to reflux for 3 hr. The excess $POCl_3$ was removed by distillation *in vacuo*, and the residue was decomposed with crushed ice, neutralized with conc. NH_4OH and extracted with $CHCl_3$. The $CHCl_3$ extract after being dried was concentrated to leave yellow residues. The residues were chromatographed over Al_2O_3. Elution with ether gave the product (193 mg., 90%), which was recrystallized from ether to give L as light green needles, m.p. 113°. *Anal.* Calcd. for $C_8H_8N_3Cl$: C, 52.90; H, 4.43; N, 23.16. Found: C, 52.72; H, 4.48; N, 23.27.

7-Chloro-2,3,6-trimethylpyrazolo[1,5-*a*]pyrimidine (LI)——A mixture of 1.5 g. of II and 20 ml. of $POCl_3$ was treated by the ordinary method to give LI as light green rhombs., m.p. 122° (acetone). Yield, 1.42 g. (86%). *Anal.* Calcd. for $C_9H_{10}N_3Cl$: C, 55.25; H, 5.12; N, 21.47. Found: C, 55.19; H, 5.30; N, 21.70.

7-Chloro-2,3,5-trimethylpyrazolo[1,5-*a*]pyrimidine (LII)——Light green needles, m.p. 79°. Yield, 87%. *Anal.* Calcd. for $C_9H_{10}N_3Cl$: C, 55.25; H, 5.12; N, 21.47. Found: C, 55.39; H, 5.27; N, 21.54.

2,3-Dimethylpyrazolo[1,5-*a*]pyrimidine (LIII)——To a solution of 615 mg. of L and 600 mg. of NaOAc in 30 ml. of MeOH was added 500 mg. of 5% palladized charcoal. The mixture was stirred under hydrogen at room temperature and atmospheric pressure (uptake of hydrogen, 76 ml. within 5 min.). The catalyst was filtered off and filtrate was concentrated *in vacuo*, and extracted with $CHCl_3$. The $CHCl_3$ extract was washed successively with Na_2CO_3, H_2O and dried over $MgSO_4$. The crystalline residue after removal of the solvent was recrystallized from hexane to give LIII as colorless needles, m.p. 54°. Yield, 480 mg. (96%). *Anal.* Calcd. for $C_8H_9N_3$: C, 65.28; H, 6.16; N, 28.55. Found: C, 65.19; H, 6.25; N, 28.17.

2,3,6-Trimethylpyrazolo[1,5-*a*]pyrimidine (LIV)——A mixture of 500 mg. of LII, 500 mg. of NaOAc, and 500 mg. of 5% palladized charcoal in 30 ml. of MeOH was worked up by the method mentioned above to give LIV as light green sticks, m.p. 110°. Yield, 350 mg. (85%). *Anal.* Calcd. for $C_9H_{11}N_3$: C, 67.05; H, 6.88; N, 26.07. Found: C, 67.27; H, 7.08; N, 26.18.

Hydrochloride in yellow needles from acetone, m.p. 188~189°. *Anal.* Calcd. for $C_9H_{11}N_3 \cdot HCl$: C, 54.68; H, 6.12; N, 21.27. Found: C, 54.74; H, 6.21; N, 21.59.

2,3,5-Trimethylpyrazolo[1,5-*a*]pyrimidine (LV)——A mixture of LII (213 mg.), NaOAc (200 mg.) and 5% palladized charcoal (500 mg.) in MeOH (20 ml.) was treated by the method mentioned above to give LV, which was recrystallized from hexane to give colorless needles, m.p. 81°. Yield, 156 mg. (88.7%). *Anal.* Calcd. for $C_9H_{11}N_3$: C, 67.05; H, 6.88; N, 26.07. Found: C, 67.85; H, 6.83; N, 25.65.

Hydrochloride in yellow sticks from acetone, m.p. 179°. *Anal.* Calcd. for $C_9H_{11}N_3 \cdot HCl$: C, 54.68; H, 6.12; N, 21.27. Found: C, 54.91; H, 6.32; N, 21.08.

2,3-Dimethyl-4,5,6,7-tetrahydropyrazolo[1,5-*a*]pyrimidine (LVI)——To a solution of 225 mg. of LIII in 20 ml. of MeOH was added 500 mg. of 5% Pd-C. The mixture was stirred under hydrogen at room temperature and atmospheric pressure (uptake of hydrogen, 76 ml. within 2 hr., theor. 68.8 ml.). The catalyst was filtered off and the filtrate was concentrated *in vacuo*. The crystalline residue was recrystallized from ether to give LVI as colorless needles, m.p. 141~142°. Yield, 176 mg. (76.2%). *Anal.* Calcd. for $C_8H_{13}N_3$: C, 63.54; H, 8.67; N, 27.79. Found: C, 63.25; H, 8.49; N, 28.22. NMR (τ) in $CDCl_3$: 7.92 (2-Me), 3.25 (3-Me).

2,3,6-Trimethyl-4,5,6,7-tetrahydropyrazolo[1,5-*a*]pyrimidine (LVII)——A mixture of 250 mg. of LIV and 500 mg. of 5% Pd-C in 20 ml. of MeOH was worked up by the method mentioned above (uptake of hydrogen, 65.3 ml. within 4.5 hr., theor. 69.7 ml.). Recrystallization from ether afforded LVII as colorless thin plates, m.p. 169~170°. Yield, 185 mg. (72.5%). *Anal.* Calcd. for $C_9H_{15}N_3$: C, 65.42; H, 9.15; N, 25.43. Found: C, 65.25; H, 9.18; N, 25.52.

NMR (τ) in $CDCl_3$: 7.92 (2-Me), 8.25 (3-Me), 9.05[d] (6-Me, J=6.8).

7-Methylamino-2,3-dimethylpyrazolo[1,5-*a*]pyrimidine (LVIII)——A mixture of L (300 mg.) and excess NH_2CH_3 in $CHCl_3$ was heated in a sealed tube at 150° for 8 hr. After being cooled, the reaction mixture was washed with H_2O and the organic layer was dried over $MgSO_4$. The brown residue after removal of the solvent was submitted to Al_2O_3 chromatograph. Elution with $CHCl_3$ gave the product (LVIII), which was recrystallized from ether to give LVIII as colorless plates, m.p. 145~146°, which was proved to be identical with the sample derived from the hydrogenation of 7-formamido-2,3-dimethylpyrazolo[1,5-*a*]pyrimidine (LXVII) described previously.[1]

7-Methylamino-2,3,6-trimethylpyrazolo[1,5-*a*]pyrimidine (LIX)——Colorless rhombs., m.p. 157°, which was proved to be identical with the sample prepared by the $LiAlH_4$ reduction of 7-formamido-2,3,6-trimethylpyrazolo[1,5-*a*]pyrimidine by the direct comparison of their IR spectra. Yield, 82.4%.

7-Methylamino-2,3,5-trimethylpyrazolo[1,5-*a*]pyrimidine (LX)——Colorless prisms (ether), m.p. 174°. Yield, 79%. *Anal.* Calcd. for $C_{10}H_{14}N_4$: C, 63.13; H, 7.42; N, 29.25. Found: C, 63.18; H, 7.47; N, 29.48.

7-Dimethylamino-2,3-dimethylpyrazolo[1,5-*a*]pyrimidine (LXI)——A mixture of 170 mg. of L and excess $NH(CH_3)_2$ in $CHCl_3$ was heated in a sealed tube at 150° for 7 hr. After being cooled, the brown reaction mixture washed with NaOH, H_2O and dried. The residue was chromatographed on Al_2O_3. Elution with $CHCl_3$, followed by recrystallization from hexane gave LXI as colorless needles, m.p. 71°. Yield, 130 mg. (75.6%). *Anal.* Calcd. for $C_{10}H_{14}N_4 \cdot H_2O$: C, 57.67; H, 7.74; N, 26.90. Found: C, 57.61; H, 7.70; N, 26.85.

Hydrochloride in light yellow rhombs. from MeOH-acetone, m.p. 240° (decomp.). *Anal.* Calcd. for $C_{10}H_{14}N_4 \cdot HCl$: C, 53.00; H, 6.66; N, 24.72. Found: C, 52.97; H, 6.79; N, 25.70.

7-Dimethylamino-2,3,6-trimethylpyrazolo[1,5-*a*]pyrimidine (LXII)——Light green rhombs. (hexane), m.p. 69°. Yield, 73%. *Anal.* Calcd. for $C_{11}H_{16}N_4$: C, 64.67; H, 7.90; N, 27.43. Found: C, 64.55; H, 7.98; N, 27.26.

Hydrochloride in yellow scales from MeOH-acetone, m.p. 206° (decomp.). *Anal.* Calcd. for $C_{11}H_{16}N_4 \cdot HCl$: C, 54.87; H, 7.12; N, 23.28. Found: C, 55.02; H, 7.13; N, 23.06.

7-Dimethylamino-2,3,5-trimethylpyrazolo[1,5-*a*]pyrimidine (LXIII)——Colorless needles from hexane, m.p. 84°. Yield, 77%. *Anal.* Calcd. for $C_{11}H_{16}N_4 \cdot H_2O$: C, 59.43; H, 8.16; N, 25.21. Found: C, 59.39; H, 8.20; N, 25.30.

Hydrochloride in colorless needles from MeOH-acetone, m.p. 250° (decomp.). *Anal.* Calcd. for $C_{11}H_{16}N_4 \cdot HCl \cdot H_2O$: C, 50.99; H, 7.34; N, 21.61. Found: C, 51.06; H, 7.57; N, 21.51.

2,3,5-Trimethyl-7-piperidinopyrazolo[1,5-*a*]pyrimidine (LXIV)——Colorless thin plates from ether, m.p. 132°. Yield, 60.2%. *Anal.* Calcd. for $C_{14}H_{20}N_4$: C, 68.82; H, 8.25; N, 22.93. Found: C, 68.79; H, 8.33; N, 23.28.

Hydrochloride in light yellow needles from acetone, m.p. 205°. *Anal.* Calcd. for $C_{14}H_{20}N_4 \cdot HCl \cdot H_2O$: C, 56.25; H, 7.76; N, 18.73; H_2O, 6.02. Found: C, 56.20; H, 7.80; N, 19.17; H_2O, 5.85.

7-(Dimethylcarbamoylmethylamino)-2,3-dimethylpyrazolo[1,5-*a*]pyrimidine (LXV)——A mixture of 600 mg. of L and 850 mg. of glycine dimethylamide[7] in 20 ml. of $CHCl_3$ was heated to reflux for 5 hr. After cooling, the brown reaction mixture was washed successively with 10% NaOH, H_2O and dried over anhydrous K_2CO_3. The residue after removal of the solvent was submitted to chromatograph on Al_2O_3 (neutral). Elution with $CHCl_3$, followed by recrystallization from EtOAc gave LXV as colorless thin plates, m.p. 185~186°. Yield, 400 mg. (49%). *Anal.* Calcd. for $C_{12}H_{17}ON_5$: C, 58.28; H, 6.93; N, 28.32. Found: C, 58.57; H, 7.22; 27.98.

Hydrochloride in colorless needles from MeOH-acetone, m.p. 248° (decomp.). *Anal.* Calcd. for $C_{12}H_{17}ON_5 \cdot HCl \cdot H_2O$: C, 47.75; H, 6.68; N, 23.21. Found: C, 47.89; H, 6.96; N, 23.37.

7-(Dimethylcarbamoylmethylamino)-2,3,6-trimethylpyrazolo[1,5-*a*]pyrimidine (LXVI)——Colorless needles from EtOAc, m.p. 177°. Yield, 34.7%. *Anal.* Calcd. for $C_{13}H_{19}ON_5$: C, 59.75; H, 7.33; N, 26.80. Found: C, 59.80; H, 7.42; N, 26.68.

Hydrochloride was very labile and could not be isolated.

The authors are grateful to Emeritus Prof. E. Ochiai and Dr. K. Takeda, Director of this laboratory for their continuing encouragement. Thanks are also due to Dr. K. Tori of this laboratory for his helpful discussion on the NMR spectra and to Mr. S. Sakai for skilled technical help.

7) W. E. Hanby, S. G. Waley, J. Watson: J. Chem. Soc., **1950**, 3009.

Summary

In connection with the study of the acetylation of 7-aminopyrazolo[1,5-*a*]pyrimidines, further studies on the acetylation were investigated. Mono- and diacetates were obtained from the compounds being substituted with methyl-, phenyl-, or ethoxycarbonyl group at the C-6 position and only monoacetates being unsubstituted or with a cyano group at the C-6 position. The reason for this was confirmed to be the steric effect of the substituents at the C-6 position.

Various 7-acylamino (XXXVII～XL, XLII～XLVI), 7-alkylamino (XLI, LVIII～LXVI), and 7-H pyrazolo[1,5-*a*]pyrimidines (LIII～LV) were also derived.

(Received April 26, 1965)

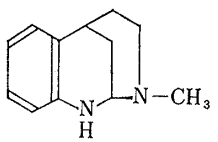
[Chem. Pharm. Bull. 13(10)1220～1224(1965)]

UDC 615.782-012 : 547.833.07

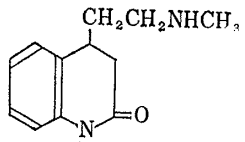
156. Tetsuji Kametani, Kazuo Kigasawa,[*1] and Mineharu Hiiragi[*2] : Azabenzomorphane and Related Compounds. VII.[*3] Synthesis of 1,2,3,4,5,6-Hexahydro-2,6-methanobenzo[*d*][1,3]diazocine Derivatives.[*4]

(*Pharmaceutical Institute, Tohoku University School of Medicine*[*1] *and Research Laboratories, Grelan Pharmaceutical Co., Ltd.*[*2])

In the previous paper[*3, 1~3] four kinds of azabenzomorphane derivatives were synthesized. In this paper will be described some results of synthetical experiments of 1,2,3,4,5,6-hexahydro-2,6-methanobenzo[*d*][1,3]diazocine derivatives, which appeared to have some analgesic activity.



I



II

Since the skeleton of the azabenzomorphane derivatives as above has not been synthesized yet, methods for its synthesis were examined using 1-methyl-4-carboxymethylcarbostyril (III) as a starting material.

Reductive cyclization of 4-(2-methylaminoethyl)-3,4-dihydrocarbostyril (II) gave the compound (I)[*3] in an excellent yield, whose structure was characterized by infrared, ultraviolet, nuclear magnetic resonance spectra and analytical data. Reductive cyclization of 1-methyl-4-(2-aminoethyl)-3,4-dihydrocarbostyril (Xa) and 1-methyl-4-(2-methylaminoethyl)-3,4-dihydrocarbostyril (Xb) also gave, respectively, 1-methyl- (XIa) 1,3-dimethyl-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[*d*][1,3]diazocine (XIb).

---

*1 Kita-4-bancho, Sendai (亀谷哲治, 気賀沢和雄).
*2 Shinmachi-3-chome, Setagaya-ku, Tokyo (柊木峯治).
*3 Part VI : T. Kametani, K. Kigasawa, M. Hiiragi : Yakugaku Zasshi, **85**, 871 (1965).
*4 This forms part CXX of "Studies on the Syntheses of Heterocyclic Compounds" by Tetsuji Kametani.

1) T. Kametani, *et al.* : Yakugaku Zasshi, **84**, 405 (1964).
2) T. Kametani, K. Kigasawa, M. Hiiragi, H. Ishimaru : This Bulletin, **13**, 295 (1965).
3) T. Kametani, K. Kigasawa, T. Hayasaka : *Ibid.*, **13**, 300 (1965).