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162. Akira Takamizawa, Kentaro Hirai, Teruyuki Ishiba, and Yoshihiro Matsumoto : Studies on Pyrimidine Derivatives and Related Compounds. XLIX.*1 Several Reactions of 1-[(2-Methyl-4-amino-5-pyrimidinyl)methyl]-3-alkyl-4-(2-hydroxyethyl)-5-methylimidazolium Salts.

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1-[(2-Methyl-4-amino-5-pyrimidinyl)methyl]-3-alkyl-4-(2-hydroxyethyl)-5-methylimidazolium salts reacted with diethyl benzoylphosphonate after treatment with triethylamine to give O-benzoate. However, the treatment with dimethylsulfinyl carbanion in dimethylsulfoxide gave iminochrome type compounds (Ⅵ, XIX), imidazole (XXVI), and azomethine compounds (Ⅶ, XX, XXⅧ). The difference of lability between imidazolium and thiazolium C-2 protons was shown by NMR measurements.

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In the previous paper,[1] it was reported that diethyl acylphosphonates (I) reacted with thiamine (Ⅱ) after treatment with triethylamine to give dihydropyrimido[4′,5′-4,5]-pyrimido[2,3-*c*][1,4]thiazine derivatives (Ⅲ).

In order to see if this novel reaction is applicable to other azolium compounds than thiazolium salt, reactions with imidazolium salts were attempted.

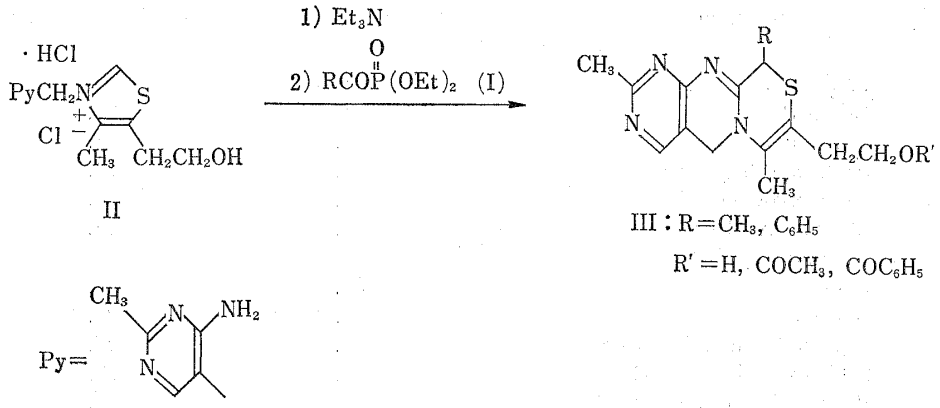

Chart 1.

First, 1-[(2-methyl-4-amino-5-pyrimidinyl)methyl]-3-benzyl-4-(2-hydroxyethyl)-5-methylimidazolium salt (Ⅳ)[2] was allowed to react with diethyl benzoylphosphonate after treatment with triethylamine in a similar condition as carried out for thiamine (Ⅱ).[1] No rearrangement was observed to give O-benzoyl derivative (Ⅴ). Since triethylamine was considered to be too weak as the base to pull out the proton on imidazolium C-2 position, methylsulfinyl carbonion[3] was used as the strong base. After treatment of Ⅳ with methylsulfinyl carbanion in dimethylsulfoxide (DMSO), diethyl benzoyl (or

*1 Part XLⅧ. A. Takamizawa, K. Inazu, S. Nakanishi, H. Ito, H. Sato, M. Ando, A. Akahori, R. Yamamoto : Vitamins (Japan), **36**, 35 (1967).

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1) A. Takamizawa, Y. Hamashima, Y. Sato, H. Sato, S. Tanaka, H, Ito, Y. Mori : J. Org. Chem., **31**, 2951 (1966).

2) T. Masuda : Yakugaku Zasshi, **81**, 541 (1961).

3) E. J. Corey, M. Chaykovsky : J. Am. Chem. Soc., **87**, 1345 (1965).

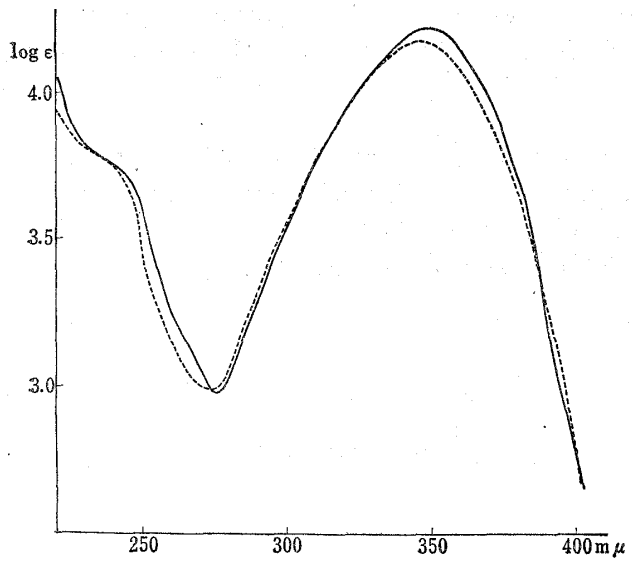


Fig. 1. Ultraviolet Spectra of Ⅵ (——) and XIX (-----) (in EtOH)

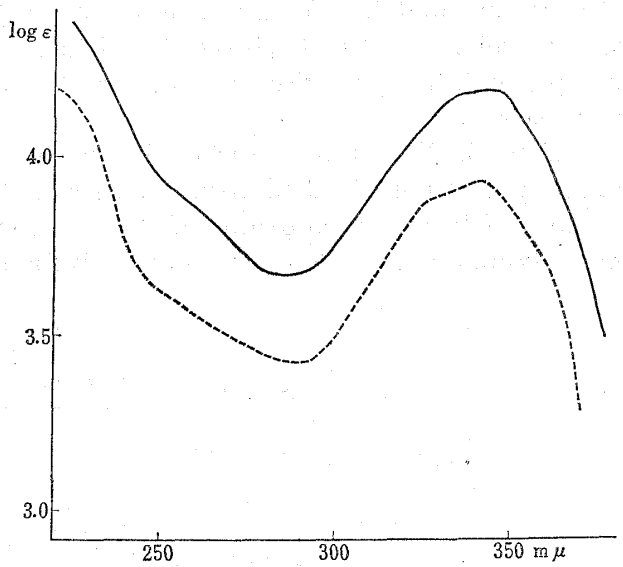


Fig. 2. Ultraviolet Spectra of Ⅶ (——) and XX (-----) (in EtOH)

acetyl) phosphonate was added at room temperature. Purification of the reaction product gave, $C_{19}H_{21}ON_5$, m. p. 176~178° and Ⅶ, $C_{19}H_{23}ON_5$, m. p. 214~215°. UV spectrum of Ⅵ showed the maximum at 350 mμ (log ε 4.25) (Fig. 1) and Ⅵ showed remarkable fluorescence suggesting the presence of polycyclic system. Infrared (IR) spectrum showed no bands due to NH_2 and N-CHO groups, but OH band was seen at 1048 cm^{-1}. Acetylation of Ⅵ afforded monoacetate (Ⅷ). IR spectrum of Ⅷ showed no OH band, instead the bands due to acetyl group were seen at 1738, 1249, and 1029 cm^{-1}. Nuclear magnetic resonance (NMR) spectrum[4] of Ⅷ exhibited the proton signals as follows: 7.98^s $\left(\text{CH}_3\right\rangle=\Big)$, 7.85^s ($OCOCH_3$), 7.48^s (pyrimidine C-2-CH_3), 7.33^t (J=7, -$C\underline{H}_2$-CH_2O-), 6.15^t (J=7, -$CH_2C\underline{H}_2O$-), 4.90^s (pyrimidine C-5-$C\underline{H}_2$-), 4.82^s ($C\underline{H}_2$-C_6H_5), 2.75^s (CH_2-$C_6\underline{H}_5$), 2.12^s (pyrimidine C-6-H). From these facts, the structure of Ⅵ was confirmed to be 1-benzyl-2-(2-hydroxyethyl)-3,8-dimethyl-1,5-dihydroimidazo[1,2-*a*]pyrimido[4,5-*d*]pyrimidine.

On the other hand, Ⅶ exhibited the maximum at 345 mμ (log ε 4.20) with the shoulder at 333 mμ in its ultraviolet (UV) spectrum (Fig. 2), but no fluorescence was shown. From UV data, the presence of an extensive conjugation system was suggested. IR spectrum of Ⅶ exhibited NH_2 bands at 3316 and 3138 cm^{-1}. NMR spectrum of Ⅶ showed the proton signals at 7.93^s $\left(\text{CH}_3\right\rangle=\Big)$, 7.52^s (pyrimidine C-2-CH_3), 5.37^s (-$C\underline{H}_2$-C_6H_5), and 2.78^b (-$CH_2C_6\underline{H}_5$). Three singlets at 2.13, 1.93, and 1.84τ suggested the presence of pyrimidine C-6, N-CHO, and -CH=N- protons. Further, the signals corresponding to ethyl group were seen at 8.93 and 7.58τ as triplet and quartet (J=7), respectively. Therefore, the structure for Ⅶ was considered to be N-[(2-methyl-4-amino-5-pyrimidinyl)methylidene]-1-methyl-2-(N-formyl)benzylamino-1-butenylamine. In order to confirm this structure, Ⅶ was hydrolyzed by hydrochloric acid to give the crystals of m. p. 175° (decomp.), $C_6H_7ON_3$ (Ⅸ) and an oil (Ⅹ). NMR spectrum of Ⅸ showed three singlets at 7.43, 1.45, and 0.15τ corresponding to pyrimidine C-2-CH_3,

4) NMR spectra were recorded on a Varian A-60 spectrometer by using solution in $CDCl_3$ or D_2O containing tetramethylsilane (TMS) or sodium 2,2-dimethyl-2-silapentane-5-sulfonate (DSS) as internal references; Chemical shifts (τ), coupling constants (J, c.p.s.). Peak multiplicities are presented by s (singlet), d (doublet), t (triplet), and b (broad).

C-6-proton, and C-5-formyl groups, respectively. Therefore, this crystalline product was found to be 2-methyl-4-amino-5-formylpyrimidine. The identity with an authentic sample obtained by the method of Miyatake, *et al.*[5] was confirmed by their IR comparison.

The oil (X) obtained above showed the strong C=O band at 1710 cm^{-1} in its IR spectrum, but no N-CHO band was seen. The structure of this oil (X) was considered to be 3-N-benzylaminopentanone-2. To confirm this structure, the synthesis of 3-N-benzylaminopentanone-2 was made. Butanone-2 (XI) was chlorinated by SO_2Cl_2 to give

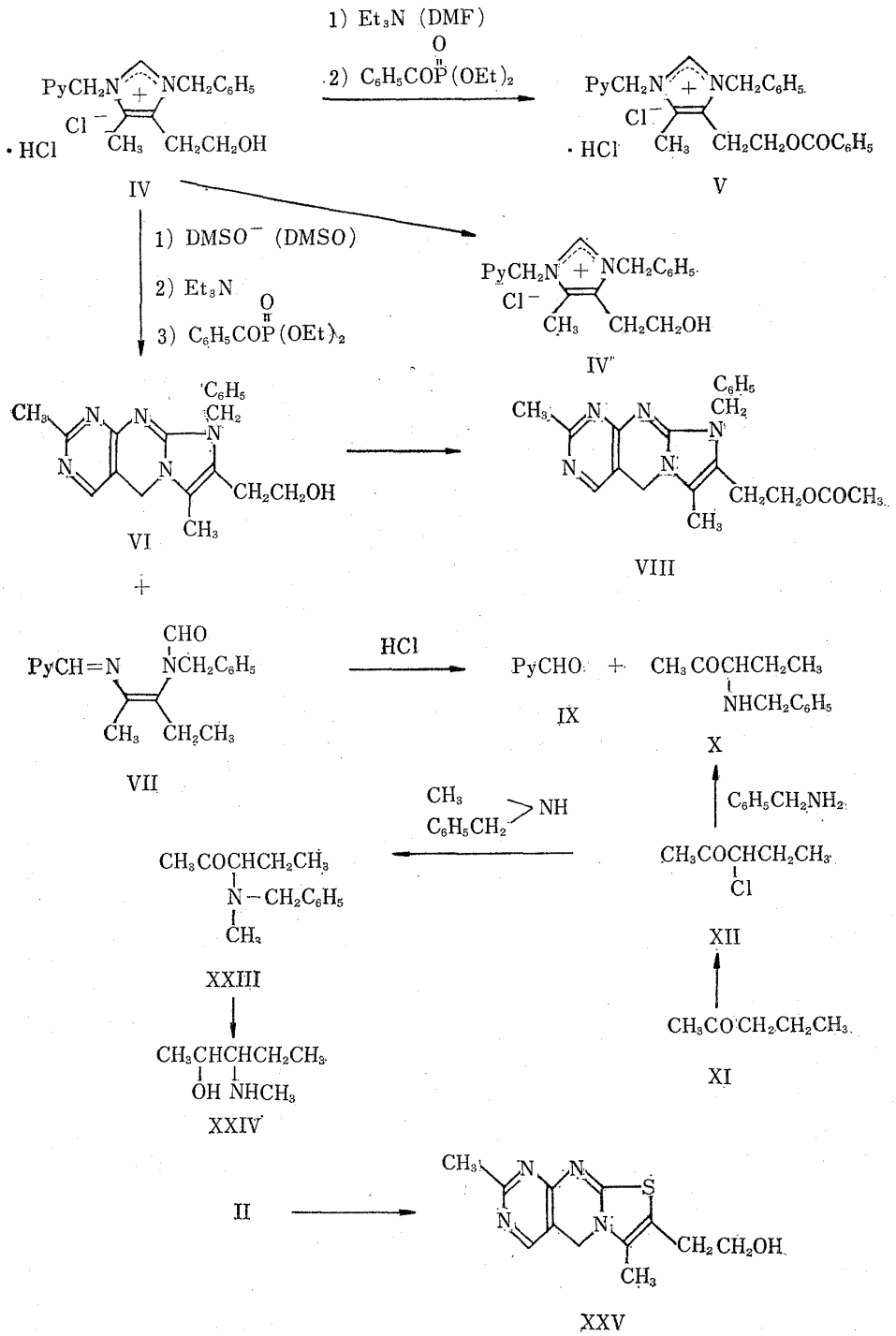


Chart 2.

5) K. Miyatake, M. Tsunoo : Yakugaku Zasshi, **72**, 630 (1952).

3-chlorobutanone-2 (XII), which reacted with benzylamine to give 3-N-benzylaminopentanone-2 as the oil of b.$p_{0.6}$ 90~91°. The hydrolyzed product (X) was found to be identical by direct comparison (IR and thin-layer chromatogram) with 3-N-benzylaminopentanone-2 synthesized above (Fig. 3). Thus, the structure of VII was confirmed.

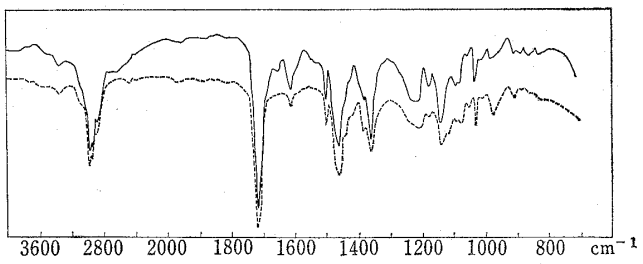


Fig. 3. IR Spectra of X (—— from VII) (------ from XII) (in $CHCl_3$)

It was found that the reaction with imidazolium salt proceeded in a different way from thiazolium to give unexpected products. To see if this reaction proceeds in other imidazolium salts, the reaction with 1-[(2-methyl-4-amino-5-pyrimidinyl)methyl]-3,5-dimethyl-4-(2-hydroxyethyl)imidazolium salt (XIII) was attempted. To obtain XIII, 1-[(2-methyl-4-amino-5-pyrimidinyl)methyl]-4-(2-hydroxyethyl)-5-methylimidazole (XIV)[2] was heated with excess of methyl iodide to give the dimethiodide, $C_{14}H_{23}ON_5I_2$ (XV), as the crystals of m. p. 240° (decomp.). NMR spectrum of XV showed two $\overset{+}{>}N\text{-}CH_3$ signals at 6.12 and 6.15τ. It has been shown that the addition of methyl iodide to ethyl 2-methyl-4-amino-5-pyrimidinecarboxylate occurred at pyrimidine 1-N.[6] Therefore, the addition of CH_3^+ was considered to occur at pyrimidine 1-N and imidazole 3-N. Acetylation of XV with acetic anhydride-acetic acid gave O-acetate (XVI). O-Acetate (XVII) obtained from XIV by heating with acetic anhydride-acetic acid, which was refluxed with excess of methyl iodide to give dimethiodide, and the identity with XVI was confirmed by IR comparison.

On the other hand, when XIV was heated with one equivalent amount of methyl iodide in a bomb, monomethiodide XIII was obtained as the crystals of m. p. 233° (decomp.). Acetylation of XIII gave O-acetate (XVIII).

XIII obtained here was treated with dimethylsulfinyl carbanion in dimethylsulfoxide followed by addition of triethylamine and acylphosphonate. From the reaction mixture, two compounds, XIX ($C_{13}H_{17}ON_5$) and XX ($C_{13}H_{19}ON_5$), were obtained as the crystals of m.p. 179~182° and m. p. 232~235°, respectively. XIX showed the maximum at 347 mμ (log ε 4.18) in its UV spectrum (Fig. 1), and also showed remarkable fluorescence similarly as VI. IR spectrum of XIX exhibited OH band at about 3500 and 1050 cm^{-1}, but no N-CHO and NH_2 bands were shown. Acetylation of XIX with pyridine-acetic anhydride gave O-acetate XXI. NMR spectrum of XXI exhibited the proton signals as follows: 7.93^s $\left(CH_3\right>=\left)$, 7.87^s ($OCOCH_3$), 7.52^s (pyrimidine C-2-CH_3), 6.58^s ($>N\text{-}CH_3$), 7.22^t ($-\underline{CH_2}CH_2O-$), 5.87^t ($-CH_2\underline{CH_2}O-$), 4.97^s (bridged methylene), 2.13^s (pyrimidine C-6-H). From these facts, the structure of XIX was confirmed to be 2-(2-hydroxyethyl)-1,3,8-trimethyl-1,5-dihydroimidazo[1,2-*a*]pyrimido[4,5-*d*]pyrimidine.

Although XX showed no fluorescence, UV spectrum showed the maximum at 343 mμ (log ε 3.93) with the shoulder at 330 mμ (Fig. 2) suggesting the presence of an extensive conjugation. NMR spectrum of XX showed the three singlets at 7.93 $\left(CH_3\right>=\left)$, 7.48 (pyrimidine C-2-CH_3), and 7.00τ ($>NCH_3$). The presence of ethyl group was shown by the triplet (J=7) at 8.92τ and the quartet (J=7) at 7.57τ. The three singlets at 2.13, 1.78, and 1.71τ were assumed to be corresponding to the pyrimidine C-6, N-CHO, and -CH=N- protons, respectively. Therefore, the structure of XX was considered to be

6) E. Hirai: This Bulletin, **14**, 861 (1966).

N-[(2-methyl-4-amino-5-pyrimidinyl)methylidene]-1-methyl-2-(N-formyl)methylamino-1-butenylamine. Acid hydrolysis of XX gave 2-methyl-4-amino-5-formylpyrimidine (IX) and an oil. This oil was assumed to be 3-N-methylaminopentanone-2 (XXII) analogously as X.

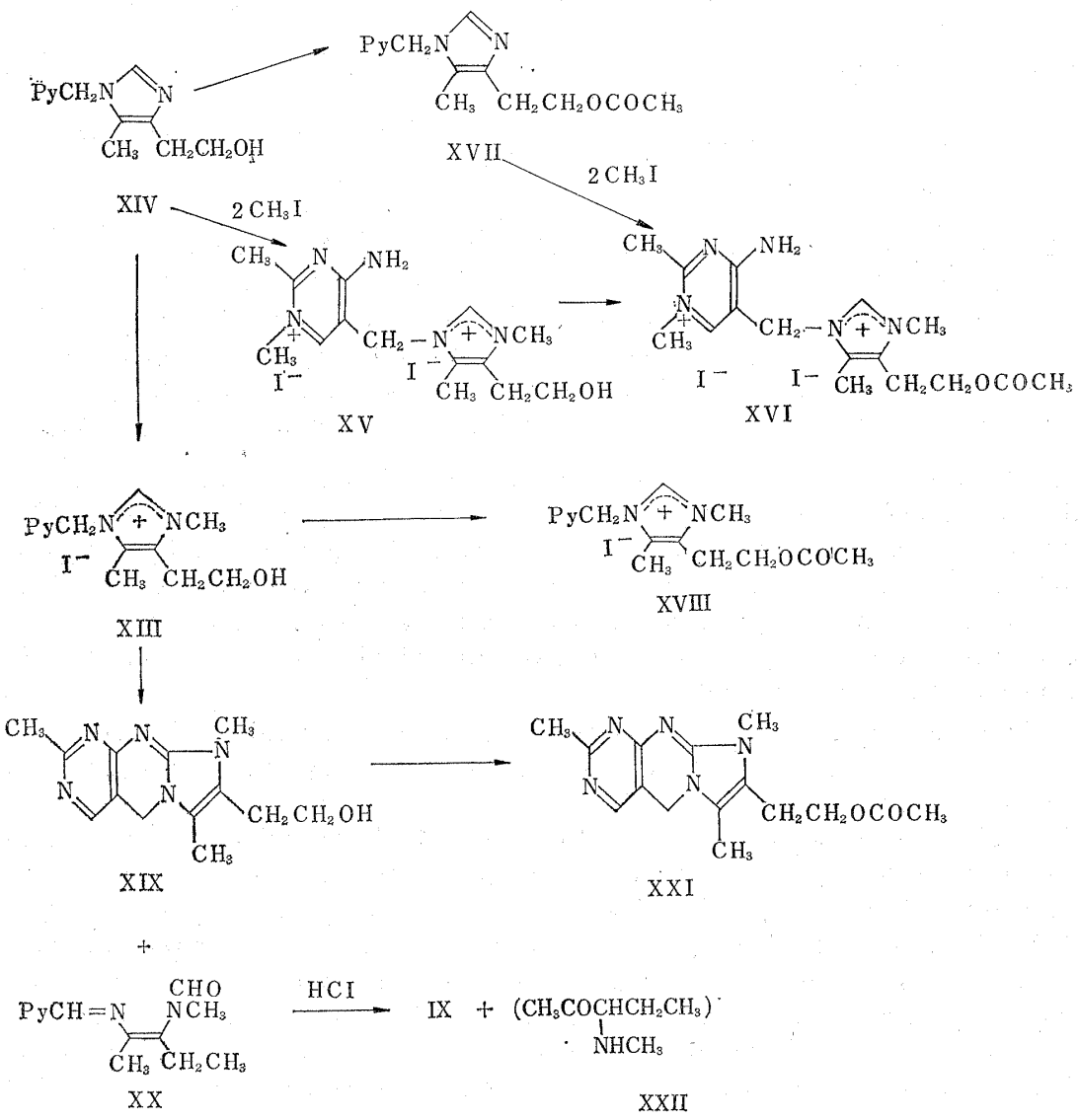


Chart 3.

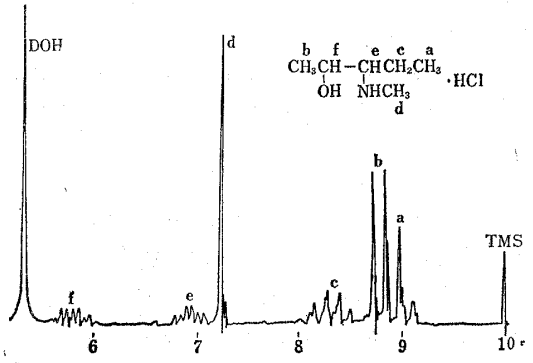


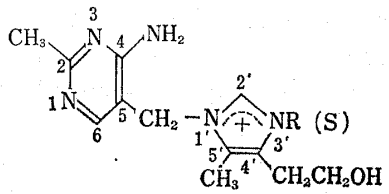
Fig. 4. Nuclear Magnetic Resonance Spectrum of XXIV (in D_2O)

The attempt to synthesize XXII was made by debenzylation of 3-N-benzyl-N-methylaminopentanone-2 (XXIII) derived from XII. Hydrogenation of XXIII afforded 2-hydroxy-3-(N-methylamino)pentane (XXIV) as hydrochloride of m. p. 101~103°, and NMR spectrum of XXIV well explained the structure as shown in Fig. 4.

It is well known that thiochrome (XXV) is easily formed from thiamine (II) by alkaline oxidation. However, Masuda[2] reported that the formation of no fluorescent product was

observed from imidazolium salts by the action of ferricyanate in alkaline solution. In contrast to this, fluorescent iminochrome type compounds (Ⅵ, XIX) were able to obtain from imidazolium salts by using methylsulfinyl carbanion in dimethylsulfoxide. These facts suggest that the abstraction of the imidazolium C-2 proton to give ylid (XXX) or carbene (XXXI)[7] is not so easy as that of the thiazolium C-2 proton in thiamine. In NMR spectra of imidazolium salts (Table I), it was observed that the signals of the imidazolium C-2 protons are less deshielded than that of the thiazolium C-2 proton to

Table I. Nuclear Magnetic Resonance Spectra[a]



Compound	5′-CH_3	2-CH_3	Bridged CH_2	6-H	2′-H	$\overset{+}{\rangle}NCH_3$
Ⅱ	7.42	7.33	4.38	1.92	0.28	
Ⅱ′ (monochloride)	7.48	7.37	4.50	1.90	—	
Ⅳ	7.63	7.31	4.58 4.48	1.98	1.12	
Ⅳ′ (monochloride)	7.56	7.42	4.58 4.42	1.85	1.15	
XV	7.65	7.30	4.70	1.98	1.22	6.15 6.12
XIII	7.68	7.53	4.82	2.05	1.55	6.13

a) Spectra were recorded on a Varian A-60 spectrometer by using solution in D_2O containing DSS as an internal reference. Chemical shifts are presented by τ-value.

appear at about 1.2τ. Deuterium exchange of the thiazolium C-2 proton was first demonstrated by Breslow.[8] Examination of the deuterium exchange in imidazolium the C-2 protons was made by NMR spectra measurements. As shown in Fig. 5, the

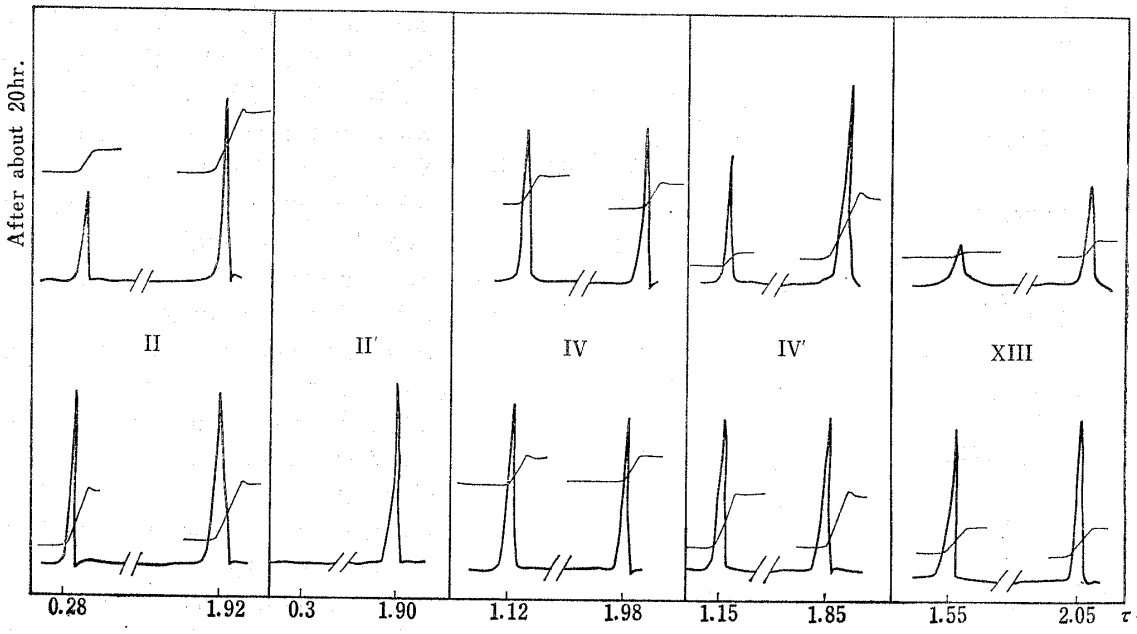


Fig. 5. Nuclear Magnetic Resonance Spectra of Ⅱ, Ⅱ′, Ⅳ, Ⅳ′, and XIII (in D_2O)

7) H. W. Wanzlick : Angew. Chem. Int. Ed., **1**, 75 (1962).
8) R. Breslow : J. Am. Chem. Soc., **80**, 3719 (1958).

intensity of the signal of the imidazolium C-2 proton in Ⅳ after standing in D_2O solution for 20 hours was as almost same as the biginning. But considerable deuterium exchange was observed in the thiazolium C-2 proton in thiamine. The signal of the thiazolium C-2 proton in thiamine monochloride was no detectable in D_2O solution due to rapid deuterium exchange, but the intensities of the signals of the imidazolium C-2 protons decreased to about a half to a third of the biginnings after standing for 20 hours in D_2O solution.

Recently, Olofson, *et al.*[9] reported rapid deuterium exchange rate of the C-2 proton of N,N′-dimethylimidazolium salt, but the results obtained here showed the lability of the C-2 proton of imidazolium ring was less than that of thiazolium ring. One of this reason was considered to be ascribed to the existence of d-σ overlap of the electron pair of the anion with an empty d-orbital of sulfur in thiazolium ring.

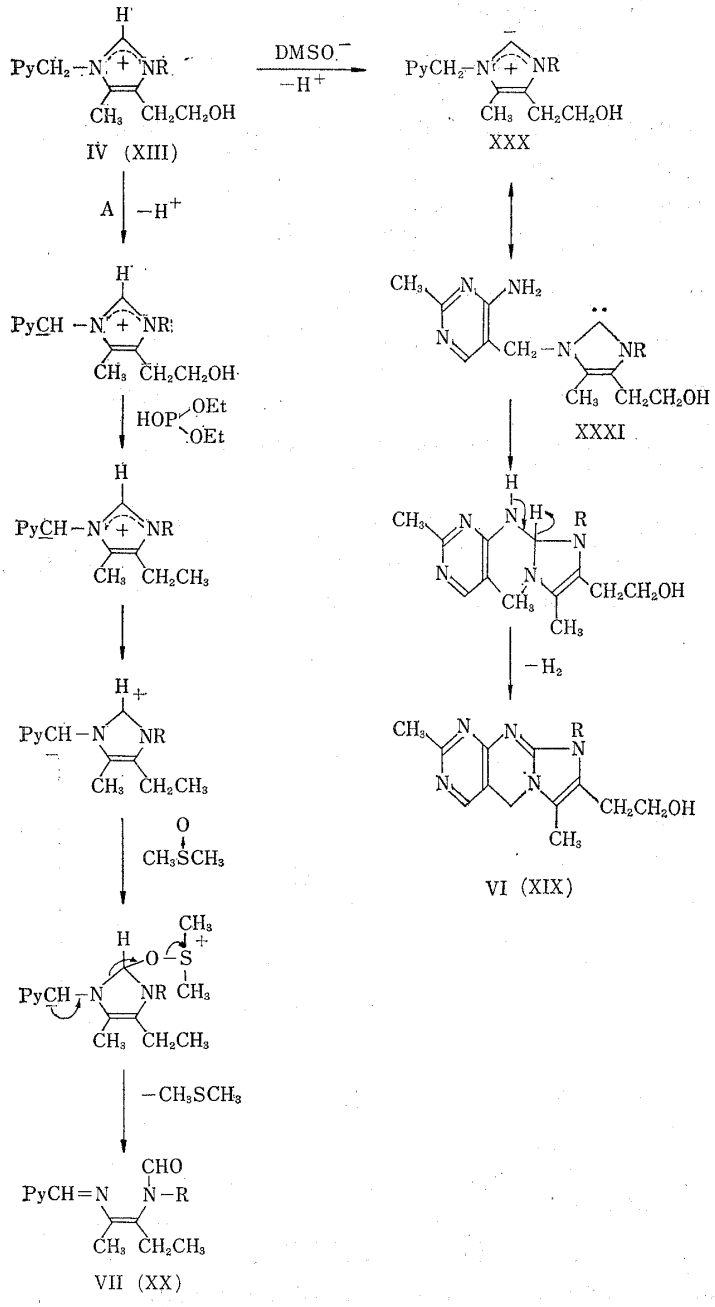


Chart 4. (continued)

The formation of Ⅵ (XIX) and Ⅶ (XX) may be explained as shown in Chart 4. The abstraction of the imidazolium C-2 proton leads to the formation of the iminochrome type compound (Ⅵ, XIX). Abstraction of the proton of bridged methylene by methylsulfinyl carbanion following abstraction of oxygen by diethylphosphite formed from I will take course A to give Ⅶ (XX) *via* oxysulfonium salt.[10] Abstraction of the proton at the allylic position following dehydration will take course B to give Ⅶ (XX) *via* pseudo base.

When Ⅳ was heated in the presence of dimethylsulfinyl carbanion in dimethylsulfoxide solution at 60°, Ⅵ and the crystals of m. p. 152~153°, $C_{13}H_{16}ON_2$ (XXVI), were obtained. UV spectrum of XXVI showed only end absorption. NMR spectrum of this compound explained the structure to be 1-benzyl-4-methyl-5-hydroxyethylimidazole. In this case, the cleavage reaction occurred to give imidazole and pyrimidine moieties. The latter was obtained as amorphous powder, and its UV spectrum showed the maxima at 237 and 278 mμ in ethanol and at 253 mμ in acid solution. Acetylation of crude product gave O-acetylimidazole derivative XXVII as an oil and a small amount of the crystals of

9) R. A. Olofson, W. R. Thompson, J. S. Michelman : *Ibid.*, **86**, 1865 (1964).

m.p. 164~167°, $C_{13}H_{18}O_2N_4$ (XXIX). UV spectrum of XXIX showed the maximum at 337 mμ with the shoulder at 325 mμ suggesting the existence of the conjugation system. NMR spectrum showed the signals corresponding to $CH_3\rangle=$ and $OCOCH_3$ protons at 7.93τ. The singlet due to pyrimidine C-2-CH_3 protons appeared at 7.47τ and the triplet (J=7) corresponding to $-CH_2-\underline{C}H_2O-$ group appeared at 5.85τ. Two singlets corresponding to pyrimidine C-6 and -CH=N- protons appeared at 1.78 and 1.70τ, respectively. Further, one olefinic proton signal appeared as triplet (J=7) at 4.65τ and $-\underline{C}H_2CH_2O-$ protons appeared at about 7.32τ as broad quartet. Hydrolysis of XXVIII also gave IX. From these facts, the structure of XXVIII was considered to be N-[(2-methyl-4-amino-5-pyrimidinyl)methylidene]-1-methyl-4-(2-hydroxyethyl)-1-butenylamine.

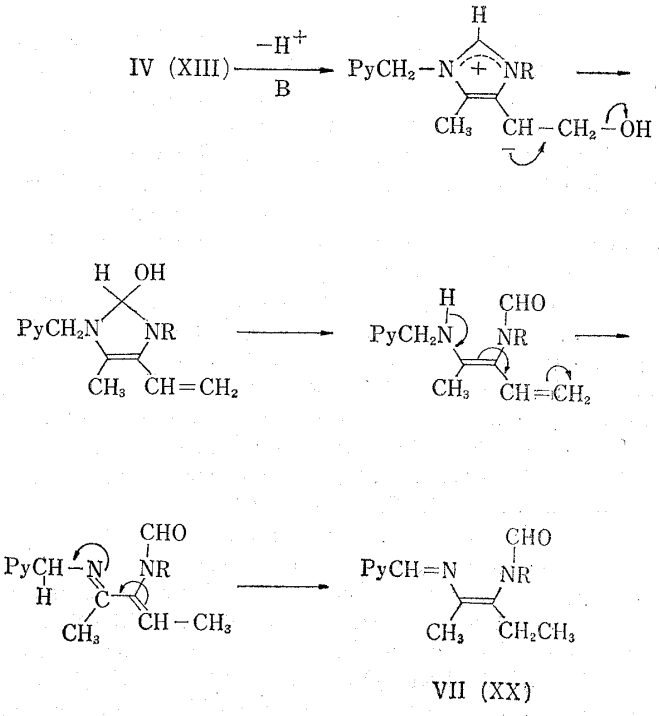


Chart 4.

Further study on these reactions is now in progress.

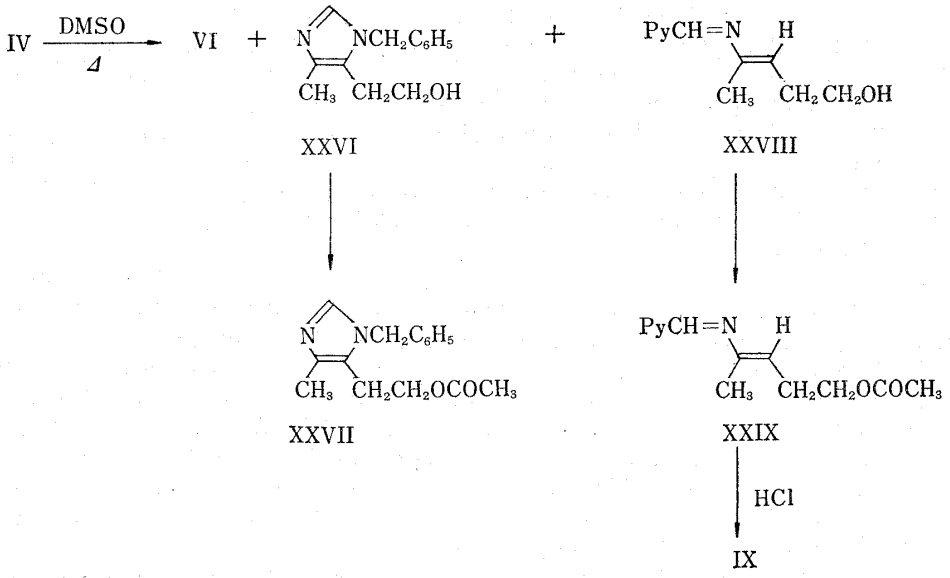


Chart 5.

Experimental*3

1-[(2-Methyl-4-amino-5-pyrimidinyl)methyl]-3-benzyl-4-(2-benzoyloxyethyl)-5-methylimidazolium Chloride Hydrochloride (V)——To a suspension of 4.19 g. of IV in 20 ml. of dimethylformamide, 4.04 g. of triethylamine was added with stirring and cooling. After stirring for 30 min. at room temperature, 4.84 g.

*3 Melting points and boiling points are uncorrected.

10) Recently, several reactions through oxysulfonium salt have been reported. D. H. R. Barton: J. Chem. Soc. **1964**, 1855; I. Lillien: J. Org. Chem., **29**, 1631 (1964); H. W. Johnson: *Ibid.*, **29**, 246 (1964).

of diethyl benzoylphosphonate was added and stirred for 4.5 hr. at room temperature. UV spectrum of this reaction mixture showed no absorption at about 350 mμ. After heating at 90~100° for 19 hr., the reaction mixture was concentrated *in vacuo* and the residue was added $CHCl_3$ to collect separated material which was recrystallized from dil. EtOH to give colorless needles, m.p. 230~236°(decomp.). *Anal.* Calcd. for $C_{26}H_{29}O_2N_5Cl_2$: C, 59.54; H, 5.53; N, 13.63; Cl, 13.52. Found: C, 59.43; H, 6.19; N, 13.63; Cl, 13.92.

1-Benzyl-2-(2-hydroxyethyl)-3,8-dimethyl-1,5-dihydroimidazo[1,2-*a*]pyrimido[4,5-*d*]pyrimidine (VI) and N-[(2-Methyl-4-amino-5-pyrimidinyl)methylidene]-1-methyl-2-(N-formyl)benzylamino-1-butenylamine (VII)——a) To 25 ml. of anhyd. DMSO, 1.35 g. of sodium hydride (50% mineral oil dispersion; Metal Hydrides, Inc.) was added and heated with stirring at 60~70° until the evolution of hydrogen ceased under N_2 stream. To this solution, 6.3 g. of IV was added and stirred at room temperature under N_2 atmosphere. To this solution, 3.03 g. of triethylamine and 2.7 g. of diethyl acetylphosphonate were added and stirred for 2 days at room temperature. To this reaction mixture, H_2O was added and extracted with $CHCl_3$. The $CHCl_3$ extract was washed with H_2O, dried over $MgSO_4$, and evaporated to give crystalline residue. Recrystallization from MeOH–AcOEt gave 0.25 g. of crystals which were recrystallized from benzene to give colorless prisms, m.p. 214~215°(VII). IR ν_{max}^{Nujol} cm^{-1}: 3260, 3100, 1660, 1635, 740. UV λ_{max}^{EtOH} mμ (log ε): 345 (4.20), shoulder 333 (4.18). NMR (τ, $CDCl_3$): 7.93[s] (3H), 7.52[s] (3H), 5.37[s] (2H), 2.78[b] (5H), 2.13[s] (1H), 1.93[s] (1H), 1.84[s] (1H). PPC[*4]: Rf 0.90. *Anal.* Calcd. for $C_{19}H_{23}ON_5$: C, 67.63; H, 6.87; N, 20.76. Found: C, 67.40; H, 7.04; N, 20.61.

From the recrystallization filtrate, 0.65 g. of yellow crystals were slowly separated. Recrystallization from MeOH–AcOEt gave pale yellow prisms, m.p. 176~178°(VI). IR ν_{max}^{Nujol} cm^{-1}: 3350, 1048. UV λ_{max}^{EtOH} mμ (log ε): 350 (4.25). PPC: Rf 0.73 (yellowish fluorescence). *Anal.* Calcd. for $C_{19}H_{21}ON_5$: C, 68.04; H, 6.31; N, 20.88. Found: C, 67.79; H, 6.53; N, 20.73.

b) Diethyl benzoylphosphonate instead of diethyl acetylphosphonate gave same products.

1-Benzyl-2-(2-acetyloxyethyl)-3,8-dimethyl-1,5-dihydroimidazo[1,2-*a*]pyrimido[4,5-*d*]pyrimidine (VIII)——To a suspension of 0.2 g. of VI in 2 ml. of anhyd. pyridine, 1.0 g. of Ac_2O was added and allowed to stand overnight at room temperature. To this reaction mixture, dil. $NaHCO_3$ was added and extracted with $CHCl_3$. The $CHCl_3$ extract was washed with H_2O, dried over $MgSO_4$, and evaporated. Residue was treated with Et_2O to give 0.17 g. of pale brown prisms, m.p. 136~138°, which were recrystallized from Me_2CO–AcOEt to give colorless prisms, m.p. 167~169°. IR ν_{max}^{Nujol} cm^{-1}: 1738, 1249, 1029. UV λ_{max}^{EtOH} mμ (log ε): 348 (4.29). NMR (τ, $CDCl_3$): 7.98[s] (3H), 7.85[s] (3H), 7.48[s] (3H), 7.33[t] (J=7, 2H), 6.15[t] (J=7, 2H), 4.90[s] (2H), 4.82[s] (2H), 2.75[s] (5H), 2.12[s] (1H). PPC: Rf 0.84 (yellowish fluorescence). *Anal.* Calcd. for $C_{21}H_{23}O_2N_5$: C, 66.82; H, 6.14; N, 18.56. Found: C, 66.60; H, 6.58; N, 18.47.

Hydrolysis of VII——A solution of 0.1 g. of VII in 2 ml. of 10% HCl was heated on a steam bath for 10 min. After neutralization of the reaction mixture with Na_2CO_3, extracted with $CHCl_3$. The $CHCl_3$ extract was washed with H_2O, dried over $MgSO_4$, and evaporated to give 0.071 g. of the residue showing the spots at Rf 0.41 and 0.69 by TLC (Al_2O_3, $CHCl_3$). Preparative TLC (Al_2O_3, $CHCl_3$) gave 0.021 g. of 2-methyl-4-amino-5-formylpyrimidine (IX), m.p. 175°(decomp.) (H_2O), as colorless needles which proved to be identical with an authentic sample synthesized by other route[5] by IR comparison. TLC (Al_2O_3, $CHCl_3$): Rf 0.41. NMR (τ, $CDCl_3$): 7.43[s] (3H), 1.45 (1H), 0.15 (1H). *Anal.* Calcd. for $C_6H_7ON_3$: C, 52.54; H, 5.15; N, 30.64; Found: C, 52.48; H, 5.26; N, 30.03.

The product corresponding to Rf 0.69 was separated in preparative TLC (Al_2O_3, $CHCl_3$) to give an oil (X) which proved to be identical with 3-N-benzylaminopentanone-2 synthesized by following method.

3-(N-Benzylamino)pentanone-2 (X)——3-Chloropentanone-2 (XII) was obtained as colorless oil of $b.p_{55}$ 57~59° from XI by reaction with SO_2Cl_2. A mixture of 7.5 g. of benzylamine and 3.6 g. of XII was heated on a steam bath for 2 hr. Ether was added to the reaction mixture to separate henzylamine hydrochloride. Ether filtrate was washed with H_2O and shaken with dil. HCl. HCl layer was made alkaline with NaOH and extracted with CH_2Cl_2. The CH_2Cl_2 extract was washed with H_2O, dried over $MaSO_4$, and evaporated to leave 3.2 g. of yellow oil. After purification with Al_2O_3 chromatography, distilled in reduced pressure to give pale yellow oil of $b.p_{0.6}$ 90°. TLC (Al_2O_3, $CHCl_3$): Rf 0.69. *Anal.* Calcd. for $C_{12}H_{17}ON$: C, 75.35; H, 8.96; N, 7.32. Found: C, 75.36; H, 8.96; N, 8.08.

1-[(2-Methyl-4-amino-5-pyrimidinyl)methyl]-4-(2-acetyloxyethyl)-5-methylimidazole (XVII)——A mixture of 8.0 g. of 1-[(2-methyl-4-amino-5-pyrimidinyl)methyl]-4-(2-hydroxyethyl)-5-methylimidazole (XIV),[2] 10 ml. of Ac_2O, and 20 ml. of AcOH was heated on a steam bath for 2 hr. Reaction mixture was concentrated and added dil. $NaHCO_3$ to collect separated 6.65 g. of crystals. Recrystallization from Me_2CO gave colorless prisms, m.p. 165~167°. *Anal.* Calcd. for $C_{14}H_{19}O_2N_5 \cdot H_2O$: C, 54.71; H, 6.89; N, 22.79; H_2O, 5.86. Found: C, 54.89; H, 7.25; N, 22.90; H_2O, 6.22.

1-[(1,2-Dimethyl-4-amino-5-pyrimidinium)methyl]-3,5-dimethyl-4-(2-hydroxyethyl)imidazolium Diiodide (XV)——A mixture of 10 g. of XIV, 8 g. of MeI, and 40 ml. of MeOH was refluxed for 5 hr. on a steam bath. The reaction mixture was concentrated *in vacuo* and AcOEt was added to the residue. Collected crystals were recrystallized from MeOH to give 8.9 g. of colorless prisms, m.p. 240°(decomp.).

[*4] Paper chromatography (PPC): BuOH, AcOH, H_2O (4:1:5), ascending method. Dragendorff reagent.

Anal. Calcd. for $C_{14}H_{23}ON_5I_2$: C, 31.65; H, 4.36; N, 13.19; I, 47.78. Found: C, 31.81; H, 4.57; N, 13.18; I, 47.59.

1-[(1,2-Dimethyl-4-amino-5-pyrimidinium)methyl]-3,5-dimethyl-4-(2-acetyloxyethyl)imidazolium Diiodide (XVI)——a) A mixture of 4.2 g. of XIV, 2.47 g. of MeI, and 35 ml. of MeOH was heated in a bomb for 5 hr. at 110°. After removal of MeOH, residue was treated with dil. Me_2CO to give 3.0 g. of the crystals. Recrystallization from EtOH gave colorless needles, m.p. 215~216°(decomp.). *Anal.* Calcd. for $C_{16}H_{25}O_2N_5I_2$: C, 33.30; H, 4.37; N, 12.20; I, 43.97. Found: C, 33.61; H, 4.62; N, 12.27; I, 43.76.

b) A mixture of 2.0 g. of XV, 4 ml. of AcOH, and 2 ml. of Ac_2O was heated on a steam bath for 2 hr. The reaction mixture was concentrated *in vacuo* and Me_2CO was added to the residue to give 1.4 g. of XVI. Identity with the sample obtained above a) was shown by IR comparison.

1-[(2-Methyl-4-amino-5-pyrimidinyl)methyl]-3,5-dimethyl-4-(2-hydroxyethyl)imidazolium Iodide (XIII)——A mixture of 7.95 g. of XIV, 4.26 g. of MeI, and 60 ml. of MeOH in a bomb was heated on a steam bath for 5.5 hr. The reaction mixture was concentrated *in vacuo* and the residue was added Me_2CO to give the crystals. Recrystallization from MeOH–AcOEt gave 5.4 g. of colorless prisms, m.p. 233° (decomp.). *Anal.* Calcd. for $C_{13}H_{20}ON_5I$: C, 40.11; H, 5.18; N, 17.99; I, 32.61. Found: C, 40.46; H, 5.31; N, 18.03; I, 32.48.

1-[(2-Methyl-4-amino-5-pyrimidinyl)methyl]-3,5-dimethyl-4-(2-acetyloxyethyl)imidazolium Iodide (XVIII)——A mixture of 0.57 g. of XIII, 1.2 ml. of AcOH, and 0.6 ml. of Ac_2O was heated on a steam bath for 45 min. The reaction mixture was concentrated *in vacuo*, and the residue was treated with Et_2O–petr. ether to give the crystals. Recrystallization from AcOEt–Me_2CO gave 0.6 g. of colorless prisms, m.p. 112~113°. *Anal.* Calcd. for $C_{15}H_{22}O_2N_5I \cdot H_2O$: C, 40.10; H, 5.38; N, 15.89; I, 28.25; H_2O, 4.00. Found: C, 39.94; H, 5.42; N, 15.35; I, 29.16; H_2O, 4.17.

2-(2-Hydroxyethyl)-1,3,8-trimethyl-1,5-dihydroimidazo[1,2-*a*]pyrimido[4,5-*d*]pyrimidine (XIX) and N-[(2-Methyl-4-amino-5-pyrimidinyl)methylidene]-1-methyl-2-(N-formyl)methylamino-1-butenylamine (XX)——To 16 ml. of anhyd. DMSO, 0.48 g. of sodium hydride (50% mineral oil dispersion) was added and heated with stirring at 60~70° until the evolution of hydrogen ceased under N_2 stream. To this solution, 3.8 g. of XIII was added at room temperature under N_2 atmosphere. To this solution, 2.02 g. of triethylamine and 2.42 g. of diethyl benzoylphosphonate were added to appear the UV maximum at 346 mμ. After standing overnight at room temperature, 100 ml. of H_2O was added and extracted with $CHCl_3$. The $CHCl_3$ extract was dried over $MgSO_4$ and evaporated. The residue was treated with Et_2O to give 0.35 g. of the crystals. Recrystallization from MeOH–AcOEt gave colorless prisms, m.p. 232~233°(XX). IR ν_{max}^{Nujol} cm^{-1}: 3316, 3138, 1666, 1643. UV λ_{max}^{EtOH} mμ (log ε): 343 (3.93), shoulder 330 (3.90). PPC: Rf 0.64 (no fluorescence). NMR (τ, $CDCl_3$): 7.93^s (3H), 7.48^s (3H), 7.00^s (3H), 8.92^t (J=7, 3H), 7.57^q (J=7, 2H), 2.13^s (1H), 1.78^s (1H), 1.71^s (1H). *Anal.* Calcd. for $C_{13}H_{19}ON_5$: C, 59.75; H, 7.33; N, 26.80. Found: C, 59.82; H, 7.61; N, 26.44. The aqueous layer was extracted with *i*-BuOH, and the *i*-BuOH extract was washed with H_2O, dried over $MgSO_4$, and evaporated. Residue was treated with Et_2O–Me_2CO to give 0.2 g. of the crystals. Recrystallization from MeOH–Me_2CO gave colorless needles, m.p. 179~182°(XIX). UV λ_{max}^{EtOH} mμ (log ε): 347 (4.18). PPC: Rf 0.28 (yellowish fluorescence). *Anal.* Calcd. for $C_{13}H_{17}ON_5$: C, 60.21; H, 6.61; N, 27.01. Found: C, 59.56; H, 6.98; N, 27.54.

2-(2-Acetyloxyethyl)-1,3,8-trimethyl-1,5-dihydroimidazo[1,2-*a*]pyrimido[4,5-*d*]pyrimidine (XXI)——A mixture of 0.064 g. of XIX, 0.5 ml. of Ac_2O, and 1 ml. of anhyd. pyridine was warmed to become yellow solution. After standing overnight at room temperature, H_2O was added, made alkaline with Na_2CO_3, and extracted with $CHCl_3$. The $CHCl_3$ extract was washed with H_2O, dried over $MgSO_4$, and evaporated. Residue was treated with Et_2O to give 0.045 g. of the crystals. Recrystallization from Me_2CO–AcOEt gave almost colorless needles, m.p. 90~92°. IR ν_{max}^{Nujol} cm^{-1}: 1738, 1243, 1055. NMR (τ, $CDCl_3$): 7.93^s (3H), 7.87^s (3H), 7.52^s (3H), 6.58^s (3H), 7.22^t (J=7, 2H), 5.87^t (J=7, 2H), 4.97^s (2H), 2.13^s (1H). PPC: Rf 0.39 (yellowish fluorescence).

Hydrolysis of XX——A solution of 0.085 g. of XX in 0.5 ml. of conc. HCl was allowed to stand overnight at room temperature. The reaction mixture was made alkaline with dil. Na_2CO_3 and extracted with $CHCl_3$. The $CHCl_3$ extract was dried over $MgSO_4$, and evaporated. Recrystallization of the residue from AcOEt gave IX which proved to be identical with an authentic sample by IR comparison. The oil obtained from the filtrate showed the spot on TLC at Rf 0.71 (Al_2O_3, $CHCl_3$).

3-N-Benzyl-N-methylaminopentanone-2 (XXIII)——A solution of 4.0 g. of XII and 10 g. of N-benzyl-N-methylamine in 40 ml. of xylene was refluxed for 9 hr. in an oil bath. The reaction mixture was concentrated *in vacuo*, the residue was added dil. $NaHCO_3$, and extracted with $CHCl_3$. The $CHCl_3$ extract was dried over $MgSO_4$ and evaporated. The residue was added 20 ml. of Ac_2O and heated on a steam bath for 1 hr. The reaction mixture was concentrated *in vacuo*, and the residue was added dil. HCl, and washed with $CHCl_3$. The HCl layer was made alkaline with K_2CO_3 and extracted with $CHCl_3$. The $CHCl_3$ extract was dried over $MgSO_4$, and evaporated to give 2.4 g. of brown oil. This oil was chromatographed on Al_2O_3 with $CHCl_3$ and the fraction corresponding to Rf 0.88 on TLC was collected and $CHCl_3$ was removed. The residual oil was distilled in reduced pressure to give colorless oil of b.$p_{0.6}$ 89°. IR: $\nu_{C=O}^{CHCl_3}$ 1710 cm^{-1}. *Anal.* Calcd. for $C_{13}H_{19}ON$: C, 76.05; H, 9.33; N, 6.82. Found: C, 76.31; H, 9.36; N, 6.85.

2-Hydroxy-3-(N-methylamino)pentane (XXIV)——A mixture of 0.6 ml. of 8.5% $PdCl_2$, 0.10 g. of Norit A, and 6.5 ml. of MeOH was shaken in H_2 atmosphere. To this Pd-C suspension, a solution of 0.54 g. of XXIII in 6 ml. of MeOH was added and shaken in H_2 atmosphere for 3 hr. (absorbed 80 ml. of H_2). The reaction mixture was filtered and the filtrate was concentrated *in vacuo*. The residual oil was slowly solidified and treated with Me_2CO to give 0.135 g. of colorless crystals, m.p. 101~103°. NMR (τ, D_2O): 8.90^t (J=7, 3H), 8.80^d (J=7, 3H), 8.37^q (J=7, 2H), 7.25^s (3H), 6.95^{t-d} (J=7, 3.5; 1H), 5.80^{d-q} (J=7, 3.5 1H). *Anal.* Calcd. for $C_6H_{16}ONCl$: C, 46.89; H, 10.50; N, 9.12; Cl, 23.08. Found: C, 46.81; H, 10.61; N, 9.18; Cl, 22.90.

1-Benzyl-4-methyl-5-hydroxyethylimidazole (XXVI)——To 20 ml. of anhyd. DMSO, 0.82 g. of sodium hydride (50% mineral oil dispersion) was added and heated with stirring at 60~70° until the evolution of hydrogen ceased under N_2 stream. To this solution, 6.4 g. of IV was added and heated at 60° for 10 hr. To the reaction mixture, H_2O was added, washed with petr. benzine, and extracted with $CHCl_3$, dried over $MgSO_4$ and evaporated, and treated with AcOEt to give the crystals. Recrystallization from AcOEt gave colorless prisms, m.p. 152~153°. IR ν_{max}^{Nujol} cm^{-1}: 1600, 1501, 1079, 747. NMR (τ, $CDCl_3$): 7.85^s (CH_3), 7.33^t (J=7, $-C\underline{H}_2CH_2O-$), 6.73^s (OH, disappeared by D_2O addition), 6.40^t (J=7, $CH_2C\underline{H}_2O$), 4.92^s ($C_6H_5C\underline{H}_2$). PPC: Rf 0.66. *Anal.* Calcd. for $C_{13}H_{16}ON_2$: C, 72.19; H, 7.46; N, 12.95. Found: C, 71.81; H, 7.46; N, 12.94. The aqueous layer was extracted with *i*-BuOH, dried over $MgSO_4$, and evaporated *in vacuo* to give the amorphous powder, m.p. 183~186°. UV: λ_{max}^{EtOH} 237, 279 mμ; $\lambda_{max}^{EtOH\text{-}HCl}$ 257 mμ.

N-[(2-Methyl-4-amino-5-pyrimidinyl)methylidene]-1-methyl-4-acetoxy-1-butenylamine (XXIX)——To 10 ml. of anhyd. DMSO, 0.48 g. of sodium hydride (50% oil dispersion) was added and heated with stirring at 66° for 1 hr. under N_2 stream until the evolution of hydrogen ceased. To this solution, 3.74 g. of IV was added and stirred for 1 hr. at 60°. After standing overnight at room temperature, 50 ml. of H_2O was added, washed with petr. benzine, and extracted with $CHCl_3$. The $CHCl_3$ extract was dried over $MgSO_4$, evaporated, and added AcOEt to the residue. Separated crystals (0.42 g., m.p. 145~146°) were collected. From the AcOEt filtrate, 0.05 g. of IV was obtained as yellow pillars. Identity with an authentic sample was shown by IR comparison.

Above crystals of m.p. 145~146° were found to be a mixture of XXVI and a small amount of XXVIII by showing the maximum at 337 mμ in UV spectrum. To a suspension of 0.2 g. of above mixture in 3 ml. of pyridine, 1 ml. of Ac_2O was added and allowed to stand overnight at room temperature. The reaction mixture was concentrated *in vacuo*, the residue was added to dil. $NaHCO_3$, and extracted with $CHCl_3$. The $CHCl_3$ extract was dried over $MgSO_4$, evaporated, and the residue was recrystallized from AcOEt to give 0.02 g. of colorless needles, m.p. 164~167°. PCC: Rf 0.66 (pink red). IR ν_{max}^{Nujol} cm^{-1}: 1738, 1726, 1250, 1040. UV λ_{max}^{EtOH} mμ (log ε): 337 (3.49), shoulder 325. NMR (τ, $CDCl_3$): 7.98^{b-s} (6H), 7.47^s (3H), 7.32^{b-q} (2H), 5.85^t (J=7, 2H), 4.65^t (J=7, 1H), 1.78^s (1H), 1.70^s (1H). *Anal.* Calcd. for $C_{13}H_{18}O_2N_4$: C, 59.52; H, 6.92; N, 21.36. Found: C, 58.99; H, 6.83; N, 21.16. From the filtrate, 1-benzyl-4-methyl-5-acetyloxyethylimidazole (XXVII) was obtained as an oil.

Hydrolysis of XXIX——A solution of 0.02 g. of XXIX in 2 ml. of dil. HCl was heated on a steam bath for 5 min. After washing with CH_2Cl_2, HCl layer was made alkaline with NaOH solution and extracted with $CHCl_3$. The $CHCl_3$ extract was dried over $MgSO_4$ and evaporated to give IX which proved to be identical with an authentic sample by IR comparison.

IV·monochloride (IV′)——IV·chloride·hydrochloride hemihydrate (41.9 g.) was added to 16.3 ml. of 28% NH_4OH and stirred for 15 min. with cooling. After standing overnight, separated crystals were collected and recrystallized from EtOH to give colorless prisms, m.p. 208~210°(decomp.). *Anal.* Calcd. for $C_{19}H_{24}ON_5Cl\cdot H_2O$: C, 58.22; H, 6.69; N, 17.87; Cl, 9.05. Found: C, 58.17; H, 6.79; N, 17.71; Cl, 9.10.

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