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56. Akira Takamizawa and Kentaro Hirai : Studies on the Pyrimidine Derivatives. XXVII.*1 Reactions of Amidines with 3-Ethoxy-2-methoxymethylenepropionitrile, 3-Ethoxy-2-ethoxymethoxymethylpropionitrile, Ethyl 3-Ethoxy-2-methoxymethylenepropionate, and Ethyl 3-Ethoxy-2-ethoxymethoxymethylpropionate.

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In earlier experiments on the synthesis of vitamin B_1 we found that acetamidine reacted with 3-ethoxy-2-methoxymethylenepropionitrile (I) to give 4-amino-5-ethoxymethyl-2-methylpyrimidine (II),[1] with 3-ethoxy-2-ethoxymethoxymethylpropionitrile (III) it gave 5-acetamidomethyl-4-amino-2-methylpyrimidine (V) *via* 2,7-dimethyl-5,6-dihydropyrimido[4,5-*d*]pyrimidine (IV),[1] and with ethyl 3-ethoxy-2-methoxymethylenepropionate (VI) 5-ethoxymethyl-2-methyl-4-pyrimidinol (VII) was obtained.[2]

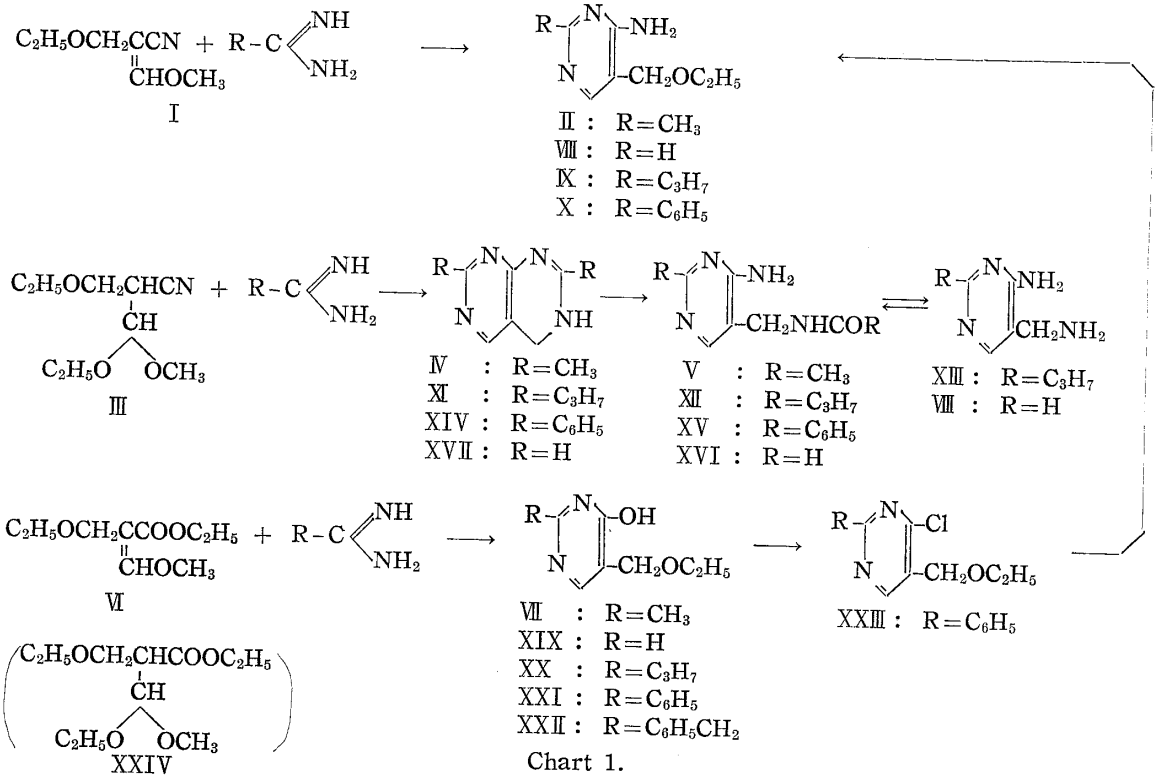

Chart 1.

*1 Part XXVI : Vitamins (Kyoto), in contribution.

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1) A. Takamizawa, K. Ikawa, K. Tori : Yakugaku Zasshi, **78**, 647 (1958).
2) A. Takamizawa : *Ibid.*, **74**, 756 (1954).

Recently, Ogawa, *et al.*[3] synthesized 2-ethyl homologues of II and V by using propioamidine, and described the biological action on animals and microbes.

The present study is concerned with the reaction of various amidine derivatives with I, III, and VI. First of all, we obtained 4-amino-5-ethoxymethylpyrimidine (VIII) from the reaction of I with formamidine in ethanol solution. In a similar way, I reacted with butanamidine to give 4-amino-5-ethoxymethyl-2-propylpyrimidine (IX), and with benzamidine (I) gave 4-amino-5-ethoxymethyl-2-phenylpyrimidine (X).

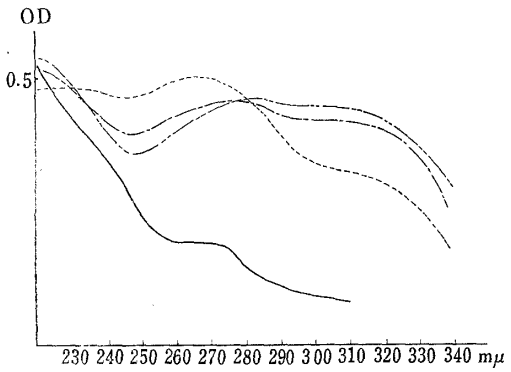


Fig. 1. Ultraviolet Spectra of the Reaction Mixture at the Different Time

——— Before heating
– – – – – After 1 hr. refluxing
– – – – – After 2 hr. refluxing
——— After 5 hr. refluxing

Two molar equivalent of butanamidine reacted with III in ethanol solution and the process of the reaction was traced by ultraviolet absorption spectra of the reaction mixture (Fig. 1). After refluxing for one hour, an absorption maximum at about 265 mμ appeared and the formation of the intermediate was suggested,[1] by continued refluxing the maximum shifted to 300 mμ. When no change in ultraviolet spectrum was seen after 5 hours, the reaction mixture was concentrated to give crystals of m.p. 96°. The ultraviolet spectrum of this compound showed the maximum at 298 mμ and conjugation with pyrimidine was supposed. From the elemental analysis and the nuclear magnetic resonance spectrum, the structure of this compound was confirmed to be 2,7-dipropyl-5,6-dihydropyrimido[4,5-*d*]pyrimidine (XI). XI was hydrolyzed under mild conditions to give 4-amino-5-butyramidomethyl-2-propylpyrimidine (XII), which was hydrolyzed again to afford 4-amino-5-aminomethyl-2-propylpyrimidine (XIII). XIII was converted into the original XII by the reaction with butyryl chloride.

Also, III reacted with benzamidine to yield 2,7-diphenyl-5,6-dihydropyrimido[4,5-*d*]-pyrimidine (XIV), which was hydrolyzed to give 4-amino-5-benzamidomethyl-2-phenylpyrimidine (XV). With formamidine, III gave 4-amino-5-formamidomethylpyrimidine (XVI), and although dihydropyrimidopyrimidine (XVII) could not be isolated as crystals the formation of XVII was confirmed by the ultraviolet spectrum of the reaction mixture, showing the absorption maximum at about 300 mμ. Hydrolysis of XVI yielded 4-amino-5-aminomethylpyrimidine (XVIII), which was converted into XVI by the action of formamide.

The reaction of VI with formamidine gave 5-ethoxymethyl-4-pyrimidinol (XIX), with butanamidine it gave 5-ethoxymethyl-2-propyl-4-pyrimidinol (XX), with benzamidine 5-ethoxymethyl-2-phenyl-4-pyrimidinol (XXI) was obtained, and with phenylacetamidine it yielded 2-benzyl-5-ethoxymethyl-4-pyrimidinol (XXII).

Treatment of XXI with phosphoryl chloride afforded 4-chloro-5-ethoxymethyl-2-phenylpyrimidine (XXIII). The reaction of XXIII with ammonia in ethanol gave an amino compound which was identical with X obtained from the reaction of I with benzamidine.

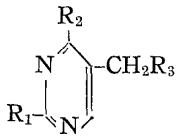
The reaction of benzamidine with acetal ester compound (ethyl 3-ethoxy-2-ethoxymethoxymethylpropionate (XXIV))[4] also gave XXI and the difference in the reaction pattern between the reactions using acetal ester (XXIV) and enol ester (VI) was not seen.

3) S. Ogawa, *et al.*: Vitamins (Kyoto), **27**, 75, 325 (1963), *Ibid.*, **28**, 238 (1963).
4) A. Takamizawa, K. Tokuyama, H. Sato: Yakugaku Zasshi, **79**, 664 (1959).

This result was analogous to the early experiment[4] using acetamidine and more detailed experiment has not been made.

Experimental*3

General Procedure for Synthesis of 2-Substituted 4-Amino-5-ethoxymethylpyrimidine——To a solution of 0.01 mole of Na in 10 ml. of abs. EtOH, 0.01 mole of amidine·HCl (formamidine, butyramidine or benzamidine) was added, and the mixture was allowed to stand at room temperature for 1 hr. To this mixture, 0.01 mole of 3-ethoxy-2-methoxymethylenepropionitrile (I) was added and refluxed for 5 hr. The reaction mixture was filtered and the filtrate was evaporated *in vacuo*, the residue was purified with Al_2O_3 column chromatography (Ⅷ), distillation (Ⅸ), or recrystallization (Ⅹ). IR $\nu_{C\text{-}O\text{-}C}^{Nujol}$ cm^{-1}: 1075～1090. NMR*4: τ=8.75～8.79 (CH_3, triplet J=7 c.p.s.), 6.48～6.52 (-CH_2-, quartet J=7 c.p.s.), 5.54～5.58 ( , 4.28,～4.45 (NH_2), 1.87～1.90 (6-H), 1.47 (2-H). The data for the compounds are listed in Tables Ⅰ and Ⅱ.

Table Ⅰ. 

Compd. No.	Subitituents R_1	R_2	R_3	m.p. (°C)	Appearance	Yield (%)
Ⅷ	H	NH_2	OC_2H_5	ca. 79	hygroscopic prisms	61
Ⅷ·picrate	〃	〃	〃	186 (decomp.)	yellow needles[a]	
Ⅷ·HCl	〃	〃	〃	196 (〃)	colorless needles[b]	
Ⅸ	C_3H_7	〃	〃	42 (108～115/1 mm. Hg)	pale yellow prisms	51.3
Ⅹ	C_6H_5	〃	〃	132	colorless prisms[c]	44
Ⅻ	C_3H_7	〃	$NHCOC_3H_7$	179	colorless needles[d]	26 (from butyramidine)
XV	C_6H_5	〃	$NHCOC_6H_5$	219～220	colorless rhombics	47 (from XIV)
XVI	H	〃	NHCHO	171～172	colorless prisms[e]	6.6 (from formamidine)
XVI·picrate	〃	〃	〃	265 (decomp.)	yellow prisms[a]	
XVⅢ·HCl	〃	〃	NH_2	290<	colorless needles[b]	97.2
XⅢ·HCl	C_3H_7	〃	〃	210	colorless prisms	79.2
XIX	H	OH	OC_2H_5	98	colorless needles	27
XX	C_3H_7	〃	〃	131	〃 [f]	25
XXI	C_6H_5	〃	〃	157	colorless scales[f]	53
XXⅡ	$C_6H_5CH_2$	〃	〃	148	colorless rhombics[f]	7.2

Recryst. from *a*) EtOH; *b*) aq. EtOH; *c*) benzene-petr. ether; *d*) H_2O; *e*) Me_2CO; *f*) AcOEt.

General Procedure for Synthesis of 2,7-Disubstituted 5,6-Dihydropyrimido[4,5-*d*]pyrimidine——A solution of 0.02 mole of Na, 0.02 mole of amidine·HCl (butyramidine or benzamidine), and 0.01 mole of Ⅲ in 20 ml. of abs. EtOH was refluxed for 5 hr. The reaction mixture was filtered and the filtrate was evaporated *in vacuo*. The residue was purified with Al_2O_3 column chromatography (Ⅺ) or recrystallization from EtOH-AcOEt (XIV). After collection of Ⅺ, the residue was hydrolyzed with 20 ml. of H_2O and 0.3 g. (12.7%) of Ⅻ was obtained. NMR: τ=5.10～5.45 (C-5 methylene), 1.75～1.93 (4-H). The data for the compounds are listed in Table Ⅲ.

General Procedure for Synthesis of 2-Substituted 4-Amino-5-acylaminomethylpyrimidine——a) A solution of 0.001 mole of 2,7-disubstituted 5,6-dihydropyrimido[4,5-*d*]pyrimidine in 3 ml. of 10% NaOH and 10 ml. of EtOH was refluxed for 2 hr. The separated crystals were collected and recrystallized (XV).

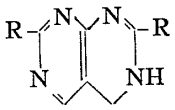
*3 All melting points are uncorrected.

*4 The NMR spectra were taken with a Varian A-60 spectrometer in $CDCl_3$ solution containing $Si(CH_3)_4$ as an internal reference.

Table II. Analytical and Ultraviolet Spectral Data

Compd. No.	Formula	Analysis (%) Calcd. C	H	N	Found C	H	N	UV λ_{max}^{EtOH} mμ (log ε)
VIII·picrate	$C_{13}H_{14}O_8N_6$	40.84	3.69	21.98	41.18	3.85	21.64	
VIII·HCl	$C_7H_{12}ON_3Cl$	44.31	6.38	22.15	43.70	6.56	22.03	
IX	$C_{10}H_{17}ON_3$	61.51	8.78	21.53	61.74	8.78	20.58	234.5 (3.97), 273 (3.66)
X	$C_{13}H_{15}ON_3$	68.10	6.59	18.32	67.61	6.61	17.81	240 (3.75), 281.7 (3.94)
XII	$C_{12}H_{20}ON_4$	60.98	8.53	23.71	61.45	8.70	23.82	236 (3.93), 277.8 (3.75)
XV	$C_{18}H_{16}ON_4$	71.03	5.30	18.41	71.02	5.51	18.23	238 (4.49), 284 (3.99)
XVI	$C_6H_8ON_4$	47.37	5.30	36.83	47.12	5.42	35.66	235.5 (3.99), 274 (3.63)
XVI·picrate	$C_{12}H_{11}O_8N_7$	37.80	2.91	25.73	38.29	3.47	25.46	
XVIII·HCl	$C_5H_{10}N_4Cl_2$	30.47	5.11	28.43	30.73	5.46	28.25	
XIII·HCl	$C_8H_{16}N_4Cl_2$	40.17	6.75		40.43	6.92		235 (3.95), 262 (3.73)
XIX	$C_7H_{10}O_2N_2$	54.53	6.54	18.17	54.23	6.61	17.87	224.3 (3.80), 270 (3.62)
XX	$C_{10}H_{16}O_2N_2$	61.20	8.22	14.28	61.41	8.26	14.00	224.2 (4.15), 275 (4.18)
XXI	$C_{13}H_{14}O_2N_2$	67.81	6.13	12.17	67.62	6.16	12.54	241.5 (4.10), 293.7 (3.95)
XXII	$C_{14}H_{16}O_2N_2$	68.83	6.60	11.97	69.11	6.71	11.44	223.3 (shoulder 3.92), 256 (3.83)

Table III.



Compd. No.	Substituent R	m.p. (°C)	Appearance	Yield (%)	Formula	Analysis (%) Calcd. C	H	N	Found C	H	N	UV λ_{max}^{EtOH} mμ (log ε)
XI	C_3H_7	96	colorless prisms	4.6	$C_{12}H_{15}N_4$	66.02	8.31	25.67	65.43	8.31	25.21	298
XIV	C_6H_5	212	pale yellow prisms	22.7	$C_{18}H_{14}N_4$	75.51	4.93	19.57	75.81	5.03	19.04	254 (4.42) 315 (3.78)

b) The residue obtained in the synthesis of 2,7-disubstituted 5,6-dihydropyrimido[4,5-*d*]pyrimidine was added 20 ml. of H_2O and boiled for 1 hr. Separated crystals were collected and recrystallized (XII, XVI). The data for the compounds were listed in Tables I and II.

General Procedure for Synthesis of 2-Substituted 4-Amino-5-aminomethylpyrimidine——A solution of 0.02 mole of 4-amino-5-acylaminomethylpyrimidine in 6 ml. of 10% HCl was heated at 70° for 1 hr. (XVIII), or in 13 ml. of 14% EtOH-HCl at 130° for 6.5 hr. (XIII). The reaction mixture was concentrated to give the crystals and washed with EtOH to give XVIII and XIII, respectively as hydrochloride. The hydrochloride obtained was dissolved in H_2O and neutralized with $NaHCO_3$ and evaporated *in vacuo*. The residue (XVIII) was refluxed with 0.5 g. of NH_2CHO for 4 hr. in an oil bath. To the reaction mixture, EtOH was added and filtered. The filtrate was evaporated *in vacuo*, and the residue was dissolved in EtOH and picric acid solution was added. The separated crystals were collected and recrystallized from EtOH to give the yellow needles, m.p. 211° (decomp.), which was identified by IR spectra as the picrate of XVI. XIII·HCl (0.12 g.) was neutralized as above and dissolved in 3 ml. of pyridine. To this solution, 0.06 g. of butyryl chloride was added and heated at 120° for 3 hr. To the reaction mixture, H_2O was added and extracted with $CHCl_3$. After drying over anhyd. $MgSO_4$, $CHCl_3$ was removed. H_2O was added to the residue and separated crystals, m.p. 175~176°, were collected. It was identified by IR spectra as XII.

General Procedure for Synthesis of 2-Substituted 5-Ethoxymethyl-4-pyrimidinol——A solution of 0.02 mole of Na, 0.02 mole of amidine·HCl (formamidine, butyramidine, benzamidine, or phenylacetamidine), and 0.02 mole of VI in 20 ml. of abs. EtOH was stirred for 3 hr. below 10° and for 2 hr. at 40°. The reaction mixture was filtered and the filtrate was concentrated *in vacuo*. To the residue, 4 ml. of 10% NaOH was added and heated on the steam bath. The reaction mixture was adjusted to pH 6 by adding

AcOH. Extracted with $CHCl_3$, dried over anhyd. $MgSO_4$ and $CHCl_3$ was removed. The residual crystals were washed with Et_2O. The data for the compounds are listed in Tables I and II.

4-Chloro-5-ethoxymethyl-2-phenylpyrimidine (XXIII)——The mixture of 1 g. of XXI and 8 ml. of $POCl_3$ was heated at 78° for 3 hr. The reaction mixture was evaporated *in vacuo*, the residue was added H_2O and neutralized with $NaHCO_3$ and extracted with $CHCl_3$. After drying over anhyd. $MgSO_4$, $CHCl_3$ was removed to afford the prisms, m.p. 88°(1.05 g.).

Recrystallized from Et_2O-petr. ether to give 0.7 g. of colorless prisms, m.p. 91°. *Anal.* Calcd. for $C_{13}H_{13}ON_2Cl$: C, 62.77; H, 5.27; N, 11.26; Cl, 14.26. Found: C, 62.70; H, 5.33; N, 11.16; Cl, 14.17.

Amination of XXIII——The solution of 0.5 g. of XXIII in 10 ml. of 15% NH_3-EtOH was heated at 140° for 3 hr. The reaction mixture was evaporated *in vacuo*, the residue was added dil. $NaHCO_3$ solution and extracted with $CHCl_3$. After drying over anhyd. $MgSO_4$, $CHCl_3$ was removed to afford 0.3 g. of prisms, m.p. 131°. Recrystallized from benzene-petr. benzin to give 0.28 g. of colorless prisms, m.p. 134°. It was identified by IR spectra as X.

Reaction of Benzamidine with Ethyl 3-Ethoxy-2-ethoxymethoxymethylpropionate (XXIV)——A solution of 0.46 g. of Na, 3.8 g. of benzamidine·HCl, and 2.34 g. of XXIV in 20 ml. of abs. EtOH was treated as described in the synthesis of 2-substituted 5-ethoxymethyl-4-pyrimidinol and 0.5 g. of XXI was obtained. The identity with the product obtained above was confirmed by the comparison of IR spectra.

The authors express their deep gratitude to Prof. M. Tomita, Prof. S. Uyeo of Kyoto University, and Dr. K. Takeda, Director of this laboratory, for their encouragement throughout this work. Thanks are also due to Drs. T. Kubota, Y. Matsui, and K. Tori for UV, IR, and NMR spectral measurements, to the members of Analysis Room of this laboratory for elemental analyses, and to Mr. T. Ishiba for his assistance.

Summary

The reaction of 3-ethoxy-2-methoxymethylenepropionitrile (I) with various kind of amidine gave 2-alkyl(aryl)-4-amino-5-ethoxymethylpyrimidine derivatives. The reaction of 3-ethoxy-2-methoxyethoxymethylpropionitrile (III) with various amidine derivatives afforded 2,7-dialkyl(aryl)-5,6-dihydropyrimido[4,5-*d*]pyrimidine, which was converted into 2-alkyl(aryl)-4-amino-5-acylaminomethylpyrimidine. The reaction with ethyl 3-ethoxy-2-methoxymethylenepropionate (VI) or ethyl 3-ethoxy-2-ethoxymethoxymethylpropionate (XXIV) yielded 2-alkyl(aryl)-5-ethoxymethyl-4-pyrimidinol. 2-Phenyl derivative (XXI) was converted into 4-amino compound through 4-chloro compound.

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