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Studies on the Syntheses of N-Heterocyclic Compounds. II.[1] Pyrimido[4,5-*e*]-, Pyridazino[3,4-*e*]- and Pyrido-[4,3-*e*]-1,2,3,5-tetrahydro[1,4]oxazepine-5-one

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Various pyrimido[4,5-*e*][1,4]oxazepines (III) were synthesized by the reaction of 2-substituted-4-chloro-5-ethoxycarbonylpyrimidines (I) with N-substituted ethanolamines (II). The reaction was further applied to the syntheses of the pyridazino[3,4-*e*][1,4]-oxazepines (XX) and pyrido[4,3-*e*][1,4]oxazepines (XXII). In the course of this study an N-O rearrangement at 4-position of 2-phenyl-4-(N-phenyl-2-hydroxyethylamino)-5-ethoxycarbonylpyrimidine (Vc) was found.

In the preceding paper,[1] we reported that reaction between 2-methylthio-4-chloro-5-ethoxycarbonylpyrimidine[3] (Ia) and diethanolamine (IIa) gave a new cyclization product (IIIa). In this paper, various types of condensed-ring compounds of the oxazepine series have been synthesized by application of the above cyclization reaction. Treatment of a 2-substituted pyrimidine (Ia—g) with a substituted ethanolamine (IIb—j) gave the corre-

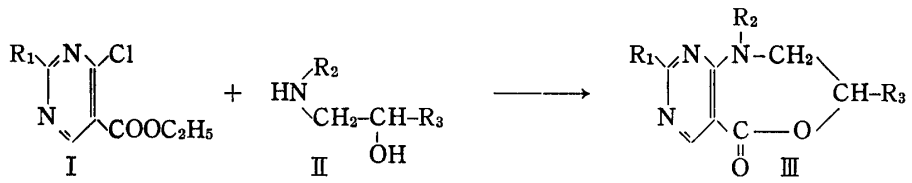
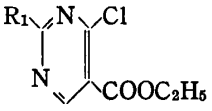
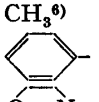
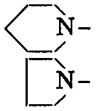


Chart 1

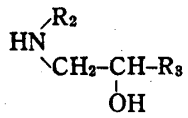
Table I. 2-Substituted-4-chloro-5-ethoxycarbonylpyrimidines (I)



I	R_1	mp (°C)	Yield (%)	Formula	Calcd. (%) C	H	N	Found (%) C	H	N
a	CH_3S[3]	—	—	—	—	—	—	—	—	—
b	CH_3[6]	—	—	—	—	—	—	—	—	—
c		125—126	91.6	$C_{13}H_{11}O_2N_2Cl$	59.44	4.22	10.67	59.16	4.00	10.28
d		85—86	90.0	$C_{11}H_{14}O_3N_3Cl$	48.63	5.19	15.47	48.66	5.16	15.48
e		48—49	93.0	$C_{12}H_{16}O_2N_3Cl$	53.63	5.59	15.64	53.70	5.39	15.59
f		60	93.5	$C_{11}H_{14}O_2N_3Cl$	51.67	5.52	16.43	51.45	5.57	16.86
g		95—97	83.0	$C_{12}H_{10}O_2N_3Cl$	54.66	3.82	15.94	54.32	3.61	15.67

1) S. Yurugi, M. Tomimoto, and T. Fushimi, *Ann. Rept. Takeda Research Lab.*, **28**, 1 (1969).
2) Location: *Juso, Higashiyodogawa-ku, Osaka.*
3) C.W. Todd, J.H. Fletcher, and D.S. Tarbell, *J. Am. Chem. Soc.*, **65**, 350 (1943).

Table II. N-Substituted Ethanolamines (II)



II	R_2	R_3	II	R_2	R_3
a	$-CH_2-CH_2-OH$	H	g	$-C_2H_4N(CH_3)_2$	H
b	CH_3	H	h	$-C_2H_4OC_2H_5$	H
c	$-CH_2-\underset{OH}{CH}-CH_3$	CH_3	i	$-C_2H_4N$ 	H
d	C_2H_5	H	j	$-C_3H_6N$ 	H
e	$-CH_2-$ 	H	k		H
f	$-C_2H_4N(C_2H_5)_2$	H	l	H	H

sponding 1,8-disubstituted-1,2,3,5-tetrahydropyrimido[4,5-*e*][1,4]oxazepine-5-one (IIIb-B) in a high yield. The physical constants of IIIb-B are shown in Table III.

Reaction of 2-piperidino-4-benzenesulfonyloxy-5-ethoxycarbonylpyrimidine (IV) which has benzenesulfonyloxy group in place of the chlorine atom in I with diethanolamine (IIa) gave the corresponding pyrimido[4,5-*e*][1,4]oxazepine (IIIy).

In an attempt to form an eight-membered ring by similar reaction, N-(2-dimethylaminoethyl)aminopropanol having one more methylene than II was allowed to react with Id. However, the objective compound was not obtained, but the substituted compound (VI) was isolated.

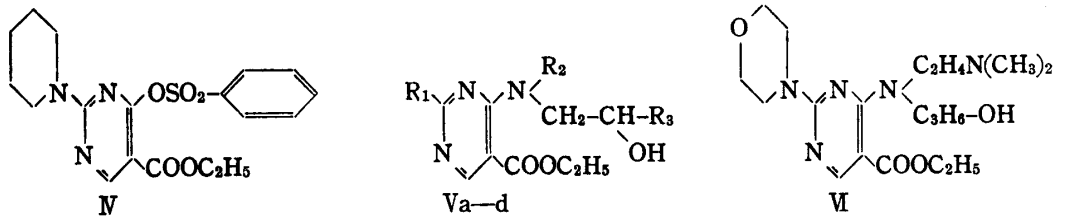


Chart 2

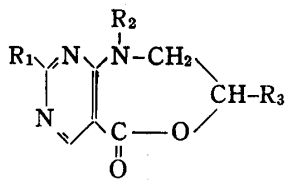
No cyclization was observed in the case of the reaction of I with ethanolamine (III) and N-phenylethanolamine (IIk), but only the substituted products (Va—d) were obtained. Since oxazepines (III) were not formed starting from Va—d under a variety of conditions, these compounds may not be intermediates of the cyclization reaction.

Reaction of Ia with IIb and of Ic with IIe afforded a mixture of IIIb and Ve and of IIIl and Vf, respectively. Thus, different type of 4-substituted pyrimidines (Ve, f) were obtained under a milder condition by reaction between I and II. While, reaction of Ia with IIa and IIc gave only the cyclization products (IIIa, c) under a mild condition similar to the above. The result seems to demonstrate that the amines (IIa, c) having two 2-hydroxyethyl groups are more readily cyclized than the amines having one 2-hydroxyethyl group.

Attempts to cyclize the compound (Vf) to IIIl in boiling acetone, alcohol or chloroform resulted in recovery of the starting material even if the hydrochloride of IIe was added to accelerate the reaction. Refluxing of Vf in amylalcohol, however, induced this cyclization to obtain IIIl in 30% yield for 7 hr and in 91% yield for 70 hr. This reaction was not catalyzed with an acid or alkali.

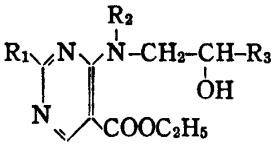
The mechanism of the reaction is thus presumed as follow: The compounds (V) would not be intermediates for the pyrimido[4,5-*e*][1,4]oxazepine (III) in view of the fact that V

TABLE III. 1,8-Disubstituted-5-oxo-1,2,3,5-tetrahydropyrimido[4,5-*e*][1,4]oxazepine (III)

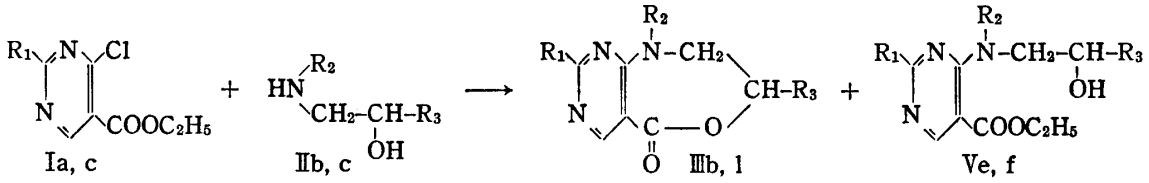


III	R_1	R_2	R_3	mp (°C)	Yield (%)	Formula	Calcd. (%) C	H	N	Found (%) C	H	N
a	CH_3S	C_2H_4-OH	H	145	91.3	$C_{10}H_{13}O_3N_3S$	47.05	5.13	16.46	46.81	5.19	16.27
b	CH_3S	CH_3	H	182—183	90.4	$C_9H_{11}O_2N_3S$	47.98	4.92	18.65	48.08	4.86	18.63
c	CH_3S	$-CH_2-CH(OH)-CH_3$	CH_3	145—147	82.2	$C_{12}H_{17}O_3N_3S$	50.87	6.05	14.83	50.56	6.04	14.74
d	CH_3S	C_2H_5	H	155	93.3	$C_{10}H_{13}O_2N_3S$	50.19	5.44	17.57	49.98	5.44	17.43
e	CH_3S	CH_2-Ph	H	130—131	95.8	$C_{15}H_{15}O_2N_3S$	59.78	5.02	13.94	60.03	4.86	13.97
f	CH_3S	$C_2H_4N(C_2H_5)_2$	H	61—63	30.0	$C_{14}H_{22}O_2N_4S$	54.17	7.15	18.05	53.07	7.03	17.85
g	CH_3	CH_2-Ph	H	122—123	67.1	$C_{15}H_{15}O_2N_3$	66.91	5.62	15.61	66.82	5.49	15.40
h	CH_3	C_2H_4-OH	H	110—112	54.1	$C_{10}H_{13}O_2N_3$	53.81	5.88	18.80	54.67	6.14	17.63
i	Ph-	C_2H_4-OH	H	150—152	95.2	$C_{15}H_{15}O_3N_3$	63.15	5.30	14.73	63.25	5.36	14.49
j	Ph-	CH_3	H	151—152	81.2	$C_{14}H_{13}O_2N_3$	65.87	5.13	16.46	65.93	5.18	16.57
k	Ph-	C_2H_5	H	115—117	84.0	$C_{15}H_{15}O_2N_3$	66.90	5.61	15.60	66.48	5.40	15.31
l	Ph-	CH_2-Ph	H	216—217	79.5	$C_{20}H_{17}O_2N_3$	72.49	5.17	12.68	72.58	5.17	12.56
m	Ph-	$-CH_2-CH(OH)-CH_3$	CH_3	142—143	71.5	$C_{17}H_{18}O_3N_3$	65.38	5.81	13.45	65.23	6.13	13.67
n	Ph-	$C_2H_4N(CH_3)_2$	H	108—110	43.0	$C_{17}H_{20}O_2N_4$	67.08	6.62	15.78	66.85	6.60	15.28
o	Ph-	$C_2N_4N(C_2H_5)_2$	H	110	42.5	$C_{19}H_{24}O_2N_4$	67.03	7.11	16.46	67.06	6.98	16.43
p	Ph-	$C_2H_4OC_2H_5$	H	90—91	78.3	$C_{17}H_{19}O_3N_3$	65.16	6.11	13.41	64.92	6.16	13.46
q	Ph-	C_2H_4-morpholino	H	105—108	59.3	$C_{19}H_{22}O_3N_4$	64.39	6.26	15.81	64.32	6.27	16.09
r	Ph-	C_3H_6-piperidino	H	90—91	78.3	$C_{21}H_{26}O_2N_4$	65.16	6.11	13.41	64.92	6.16	13.46
s	morpholino-	C_2H_4OH	H	148—149	99.0	$C_{13}H_{18}O_4N_4$	53.05	6.16	19.04	52.97	6.10	19.10
t	morpholino-	CH_3	H	185	87.5	$C_{12}H_{16}O_3N_4$	54.54	6.10	21.20	54.40	5.90	21.37
u	morpholino-	$-CH_2-CH(OH)-CH_3$	CH_3	120—121	63.8	$C_{15}H_{22}O_4N_4 \cdot H_2O$	52.93	7.11	16.46	53.66	7.10	16.78
v	morpholino-	$C_2N_4N(C_2H_5)_2$	H	86—89	62.8	$C_{17}H_{27}O_3N_5$	58.43	7.79	20.04	56.48	7.54	19.47
w	piperidino-	CH_3	H	108—110	47.4	$C_{13}H_{18}O_2N_4$	59.52	6.92	21.36	59.17	6.60	21.27
x	piperidino-	$-CH_2-CH(OH)-CH_3$	CH_3	95—97	79.0	$C_{16}H_{24}O_3N_4$	59.98	7.54	17.49	59.55	7.47	17.37
y	piperidino-	C_2H_4OH	H	78—80	93.0	$C_{14}H_{20}O_3N_4 \cdot 1.5H_2O$	52.66	7.21	17.55	52.61	7.27	17.48
z	pyrrolidino-	CH_3	H	180	94.3	$C_{12}H_{16}O_2N_4$	58.05	6.50	22.57	57.84	6.50	22.69
A	pyrrolidino-	$-CH_2-CH(OH)-CH_3$	CH_3	118—120	49.8	$C_{15}H_{22}O_3N_4$	58.82	7.23	18.30	57.98	7.46	18.05
B	4-pyridyl-	C_2H_4-OH	H	156—158	92.0	$C_{14}H_{14}O_3N_4$	58.73	4.93	19.54	58.58	4.90	19.54

Table IV. 2-Substituted-4-(N-substituted-2-hydroxyethylamino)-5-ethoxycarbonylpyrimidine (V)

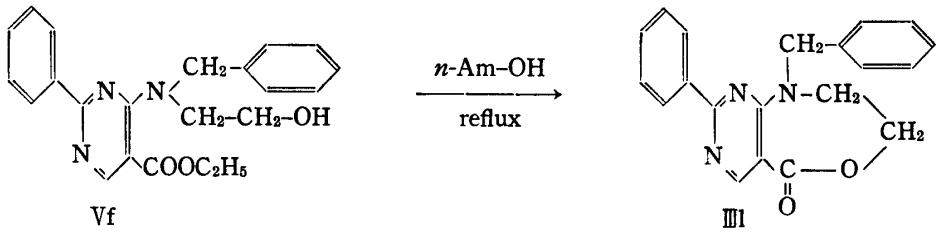


V	R_1	R_2	R_3	mp (°C)	Yield (%)	Formula	Calcd. (%) C	H	N	Found (%) C	H	N
a	CH_3S		H	113—115	75.8	$C_{16}H_{19}O_3N_3S$	57.64	5.74	12.60	57.48	5.72	12.63
b	CH_3S	H	H	161	90.6	$C_{10}H_{15}O_3N_3S$	46.68	5.88	16.33	46.61	5.91	16.54
c			H	95—98	69.5	$C_{21}H_{21}O_3N_3$	69.40	5.83	11.56	68.81	5.79	11.58
d		H	H	133—134	95.0	$C_{15}H_{17}O_3N_3$	62.72	5.92	14.63	63.02	5.28	14.44



Ia, c IIb, c IIIb, 1 Ve, f

Chart 3



Vf III

Chart 4

did not give III under an ordinary condition of the cyclization. Possible intermediates are the addition products (VII). The compounds (VII) would undergo cyclization to give the pyrimido[4,5-*e*][1,4]oxazepine (III) *via* VIII at a higher temperature, whereas at a lower temperature the elimination of hydrogen chloride would occur prior to the cyclization. The difficulty of cyclization from V may be interpreted by the double-bond character of C-N bond at the 4-position.

It was already described that III (R_2=R_3=H) and IIk (R_2=phenyl, R_3=H) failed to give the cyclized compounds in the reaction with I. The products of the reaction of Ic with excess III in refluxing amylalcohol were also non-cyclized compounds (IX and X). The reaction of IIk with Ic was continually followed by the thin-layer chromatography (TLC). On elongation of the reaction time, there appeared an additional spot on the TLC. The same spot was also observed when Vc was heated in dioxane. The new compound was isolated from the reaction solution of Vc in dioxane. Although the elemental analysis and the molecular ion peak in the mass spectrum were the same as those of Vc, other physico-chemical data were quite different. The nuclear magnetic resonance (NMR) spectrum of this compound showed the signals ethoxycarbonyl group shifted to a lower field as compared with that of Vc. In the infrared (IR) spectrum the absorption of ethoxycarbonyl group observed at 1770 cm^{-1} in Vc showed a lower shift to 1760 cm^{-1}.

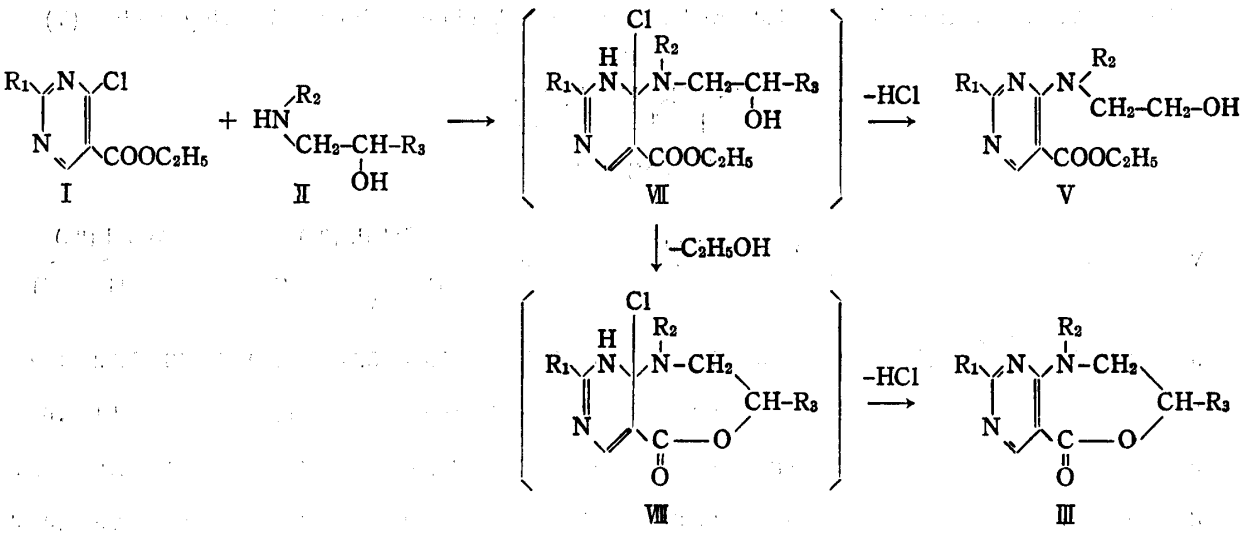


Chart 5

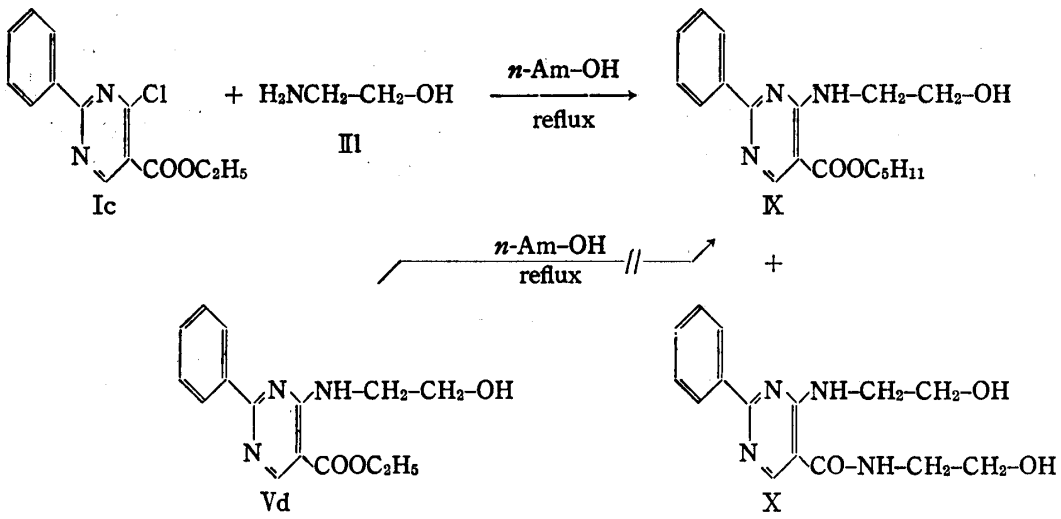


Chart 6

These observation led us to assume that the unknown compound would be an isomer of Vc which has the structure shown by XIa. To confirm this assumption we tried the acetylation of both Vc and XIa. The acetylated compounds XII and XIII showed different data in IR spectrum. Thus, $\nu_{C=O}$ in the spectrum of XII was found at 1735 cm^{-1} which was assigned to the O-acetate of Vc, while that of XIII was found at 1655 cm^{-1} showing to be $\nu_{C=O}$ of N-acetate.

Further evidence for the structure can be seen in the ultraviolet (UV) spectrum. The spectrum of Vc in methanol showed the absorption maximum at 267 mμ, and that of XIa showed the maximum at 248 mμ and 287 mμ. These absorption maxima did not shifted in acidic medium. This result parallels those found in the spectra of 2-phenyl-4-piperidino-5-ethoxycarbonylpyrimidine (XIV) and 2-phenyl-4-methoxy-5-methoxycarbonylpyrimidine (XV), the former has a structure similar to Vc and shows only one maximum at 266 mμ and the latter whose structure corresponds to XIa shows two maxima at 265 mμ and 287 mμ. These observations support the proposed structure (XIa) for the rearrangement products. This N-O rearrangement on the pyrimidine nucleus also observed on Va. 2-Phenyl-4-(N-phenyl-2-hydroxyethyl)aminopyrimidine (XVI), however, failed to undergo this rearrangement, suggesting the participation of the ethoxycarbonyl group at 5-position.

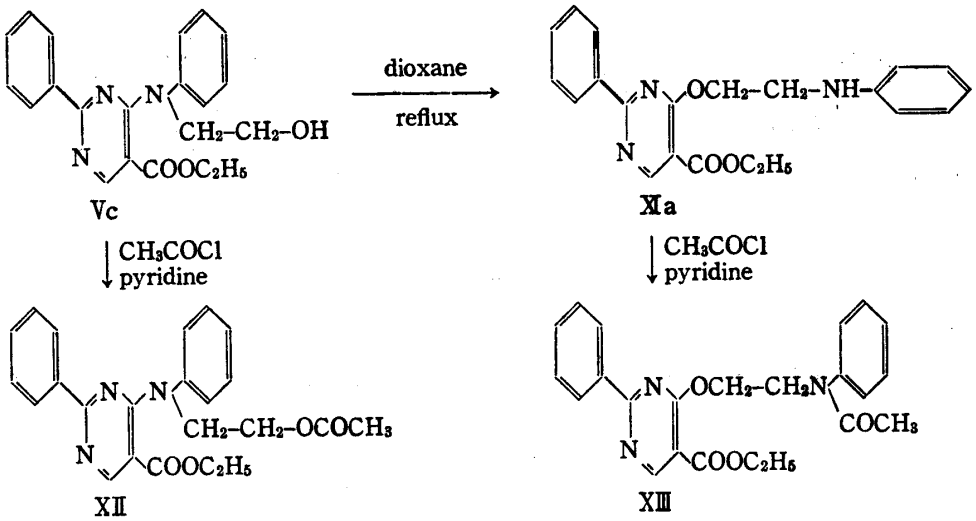


Chart 7

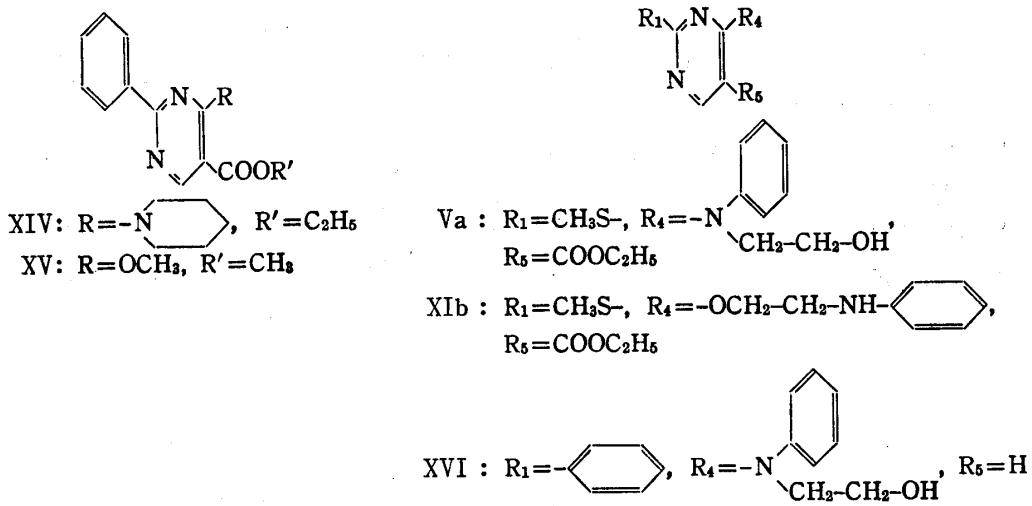


Chart 8

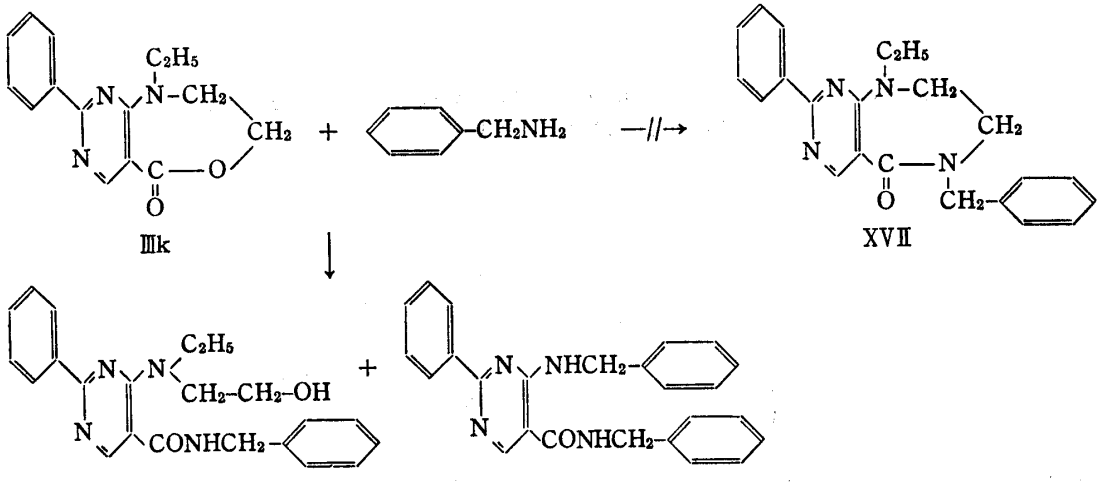
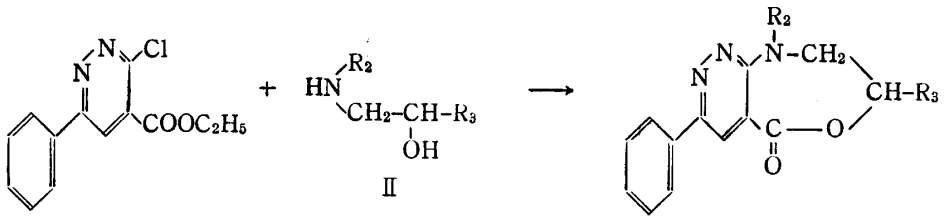


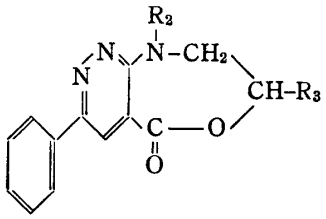
Chart 9



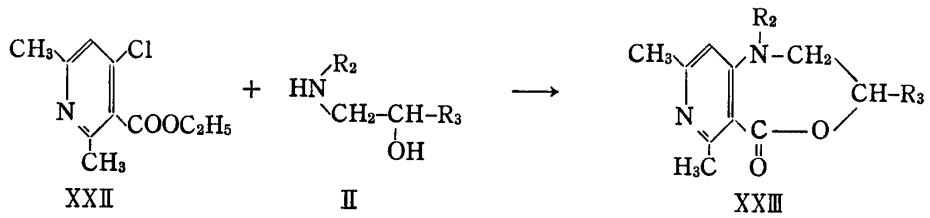
XX II XXI

Chart 10

Table V. 1,3,7-Trisubstituted-5-oxo-1,2,3,5-tetrahydropyridazino[4,3-*e*][1,4]oxazepine (XXI)



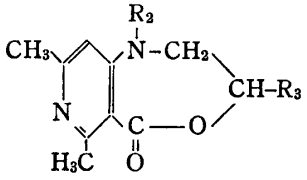
XXI	R_2	R_3	mp (°C)	Yield (%)	Formula	Calcd. (%) C	H	N	Found (%) C	H	N
a	CH_2-CH_2-OH	H	121—123	40.5	$C_{15}H_{15}O_3N_3 \cdot \frac{1}{3}CHCl_3$	56.66	4.74	12.92	56.10	4.90	13.01
b	CH_2-CH(OH)-CH_3	CH_3	117—120	74.0	$C_{17}H_{19}O_3N_3 \cdot \frac{1}{3}CHCl_3$	58.76	5.45	11.86	58.73	5.61	11.81
c	CH_2-C$_6$H$_5$	H	137—138	61.0	$C_{20}H_{17}O_3N_3 \cdot \frac{1}{3}CHCl_3$	65.80	4.67	11.33	65.54	4.71	11.39



XXII II XXIII

Chart 11

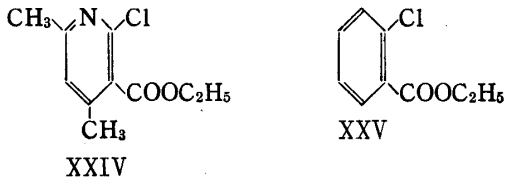
Table VI. 1-Substituted-5-oxo-6,8-dimethyl-1,2,3,5-tetrahydropyrido-[4,3-*e*][1,4]oxazepine (XXIII)



XXIII	R_2	R_3	mp (°C)	Yield (%)	Formula	Cacld. (%) C	H	N	Found (%) C	H	N
a	CH_2-CH_2-OH	H	140—142	39.8	$C_{12}H_{16}O_3N_2$	61.00	6.83	11.86	61.06	6.92	12.02
b	CH_3	H	165	48.3	$C_{11}H_{14}O_2N_2$	64.06	6.84	13.58	64.31	6.88	13.50

Recently Irwin, *et al.*[4] have reported that reaction between a 2-alkylpyrido[3,2-*d*][1,3]-oxazine-4-one and an aliphatic or aromatic amine gives the pyrido[3,2-*d*]pyrimidine-4-one. We applied this reaction to the reaction between 1-ethyl-8-phenyl-1,2,3,5-tetrahydropyrimido-[4,5-*e*][1,4]oxazepine-5-one (IIIk) and benzylamine. On accounts of the easy cleavage of the oxazepine ring, two ring-opened compound XVIII and XIX were obtained instead of the objective compound, pyrimido[4,5-*e*]diazepine.

Finally some other aromatic compounds were similarly allowed to react with N-substituted ethanolamine (II). Reaction of II with 3-chloro-4-ethoxycarbonyl-6-phenylpyridazine (XX) and 2,6-dimethyl-3-ethoxycarbonyl-4-chloropyridine[5] (XXII) proceeded in a similar manner to give cyclized compounds, pyridazino-[4,3-*e*][1,4]oxazepine (XXI) and pyrido-[4,3-*e*][1,4]-oxazepine (XXIII), respectively. On the contrary, reaction with 2-chloro-3-ethoxycarbonyl-4,6-dimethylpyridine (XXIV) and ethyl 2-chlorobenzoate (XXV) were unsuccessful.



XXIV XXV

Chart 12

Experimental

2-Substituted-4-chloro-5-ethoxycarbonylpyrimidines (I) (Table I)——a) 2-Methyl,[6] 2-phenyl-,[7] 2-morpholino-,[3] 2-piperidino-[3] and 2-pyrrolidino-4-hydroxy-5-ethoxycarbonylpyrimidine[1] were prepared according to the methods in literature.

b) 2-(3-Pyridyl)-4-hydroxy-5-ethoxycarbonylpyrimidine was synthesized according to the following method: To a solution of 3-carbamidinopyridine hydrochloride[8] (3.2 g) in EtOH (20 ml) was added a solution of sodium (0.92 g) in EtOH (20 ml) under cooling. Dimethylethoxymethylenemalonate was dropwise added to the mixture. The reaction mixture was stirred under cooling for 2 hr and allowed to stand overnight at room temperature. After evaporation *in vacuo*, the residue was dissolved in 10% HCl, neutralized with NH_4OH and the precipitate was collected. Recrystallization from EtOH gave 2-(3-pyridyl)-4-hydroxy-5-ethoxycarbonylpyrimidine (3.6 g, 73.4%), mp 265—270° (decomp.). *Anal.* Calcd. for $C_{12}H_{11}O_3N_3$: C, 58.77; H, 4.52; N, 17.14. Found: C, 58.51; H, 4.38; N, 16.88.

c) General Procedure: To a 2-substituted-4-hydroxy-5-ethoxycarbonylpyrimidine was added 5-fold volumes of $POCl_3$. The mixture was refluxed for 2—3 hr. After evaporation of $POCl_3$ *in vacuo*, the residue was poured portionwise with stirring on crushed ice, collected and washed throughly with H_2O to give colorless needles of I. Recrystallization from EtOH gave colorless needles of I.

N-Substituted Ethanolamines (II) (Table II)——a) Among the amines used in the present investigation, diethanolamine, diisopropanolamine, ethanolamine, N-methyl-, N-ethyl- and N-phenyl-ethanolamines were obtained from commercial sources. N-Benzyl-,[9] N-(2-diethylaminoethyl)-,[10] N-(2-dimethylaminoethyl)-[11] and N-(2-ethoxyethyl)ethanolamines[12] were prepared by the methods in literature.

b) N-(2-Morpholinoethyl)ethanolamine (IIi): A mixture of 2-morpholinoethylchloride and 3 mole equivalent of ethanolamine was heated at 130—150° for 4 hr. After cooling, water was added to the reaction mixture and it was saturated with NaCl. The given oil was extracted with $CHCl_3$, dried over $MgSO_4$. The extract was evaporated and the residue was destillated to give IIi, 58.8% yield, bp 160° (14 mmHg). *Anal.* Calcd. for $C_8H_{18}O_2N_2$: C, 55.14; H, 10.14; N, 16.08. Found: C, 54.68; H, 10.42; N, 16.27.

c) N-(3-Piperidinopropyl)ethanolamine (IIj): By using 3-piperidinopropylchloride in place of 2-morpholinoethylchloride in the above reaction b), IIj was obtained by the same procedure as described above in a 69.5% yield, bp 150—160°. *Anal.* Calcd. for $C_{10}H_{22}ON_2$: C, 64.47; H, 11.90; N, 15.04. Found: C, 64.42; H, 11.74; N, 14.89.

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General Procedure for the Syntheses of 1,3,8-Trisubstituted-5-oxo-1,2,3,5-tetrahydropyrimido[4,5-*e*][1,4]-oxazepine (III) (Table III)——To a hot solution of 2-substituted-4-chloro-5-ethoxycarbonylpyrimidine (Ia—j) (containing 4-benzenesulfonyloxypyrimidine derivatives (IV)) (1.0 g) in acetone (20 ml) was added N-substituted ethanolamine (II) (3.0 g) with stirring and the mixture was refluxed for 1—2 hr. After removal of the solvent *in vacuo*, the residue was treated with H_2O (100 ml) and the crystals were collected by filtration. Recrystallization from EtOH gave IIIa-B. EtOH, $CHCl_3$, THF, ether, C_6H_6 and dioxane were also usable as solvent in the place of acetone.

2-Piperidino-4-benzenesulfonyloxy-5-ethoxycarbonylpyrimidine (IV)——2-Piperidino-4-hydroxy-5-ethoxycarbonylpyrimidine (1.0 g) was dissolved in a 8% NaOH aqueous solution (50 ml) and to the stirred solution was dropped benzenesulfonylchloride (706 mg) at 50—60°. After stirring for 40 min, the resulting crystals were filtered. Recrystallization from *n*-hexane gave 0.55 g (37.5%) of IV, mp 98—99°. *Anal.* Calcd. for $C_{18}H_{21}O_5N_3S$: C, 55.24; H, 5.39; N, 10.74. Found: C, 55.37; H, 5.56; N, 10.57.

2-Substituted-4-(N-substituted-2-hydroxyethylamino)-5-ethoxycarbonylpyrimidines (Va—d) (Table IV)——2-Substituted-4-chloro-5-ethoxycarbonylpyrimidine (Ia—d) (0.01 mole) and N-substituted ethanolamine (II) (0.02 mole) were dissolved in acetone (100 ml) (or EtOH, $CHCl_3$) and refluxed for 2 hr. After removal of the solvent, the residue was treated with H_2O and the crystals were filtered. Recrystallization from EtOH gave (Va—d).

N-(2-Dimethylaminoethyl)aminopropylalcohol——2-Dimethylaminoethylchloride (15.0 g) and propanolamine (35.3 g) were dissolved in dioxane (50 ml) and refluxed for 15 hr. After removal of the solvent *in vacuo*, the residue was made alkaline with aq. K_2CO_3 and extracted with ether. The ether layer was dried over $MgSO_4$ and evaporated. The residue was fractionated by distillation to give 3.0 g (14%), bp 130—135° (20 mmHg). *Anal.* Calcd. for $C_7H_{18}ON_2$: C, 57.49; H, 12.41; N, 19.61. Found: C, 57.10; H, 12.52; N, 19.51.

The Isolation of V from III in the Reaction of I with II——a) To a stirred solution of Ia (3.0 g) in acetone (30 ml) was dropped N-methylethanolamine (IIb) (3.0 g) at room temperature. After a little while, the solvent was evaporated off *in vacuo*. The residue was treated with H_2O and the crystals were collected by filtration. Recrystallization from EtOH gave IIIb (0.7 g, 24.1%), mp 182—183°. The mother liquor was evaporated to dryness and the residue was treated with H_2O to give Ve (2.1 g, 60.0%), mp 78—79° (recrystallized from EtOH). *Anal.* Calcd. for $C_{11}H_{17}O_3N_3S$: C, 48.96; H, 6.32; N, 15.49. Found: C, 48.59; H, 6.46; N, 15.19.

b) To a stirred solution of Ic (2.6 g) in $CHCl_3$ (200 ml) was dropped N-benzylethanolamine (IIe) (3.8 g) under cooling with ice and salt. After 5 hr, the solvent was evaporated to dryness at the room temperature. The residue was treated with H_2O and the crystals were filtered. Recrystallization from EtOH gave IIIl (1.0 g, 30.3%), mp 216—217°. The mother liquor was condensed to a half volume *in vacuo*. On standing, Vf was given as needles (1.9 g, 53.0%), mp 133—134°. *Anal.* Calcd. for $C_{21}H_{23}O_3N_3$: C, 70.03; H, 6.10; N, 11.41. Found: C, 70.07; H, 5.97; N, 11.20.

The Ring-closure Reaction of 2-Phenyl-4-(N-benzyl-2-hydroxyethylamino)-5-ethoxycarbonylpyrimidine (Vf)——A solution of Vf (377 mg) in amyl alcohol (20 ml) was refluxed for 72 hr. After cooling, the crystals were filtered and recrystallized from EtOH to obtain IIIl (300 mg, 91%), mp 216—217°.

The Reaction of Ic with III in Amyl Alcohol——A solution of Ic (2.6 g) and III (2.5 ml) in amyl alcohol (100 ml) was refluxed for 76 hr and the solvent was evaporated *in vacuo*. The residue was treated with H_2O and the resulting crystals were filtered, dried and extracted with boiling ether. Ether insoluble substance was recrystallized from EtOH to give 2-phenyl-4-(2-hydroxyethylamino)-5-(2-hydroxyethylcarbamoyl)pyrimidine (X) (1.4 g, 46%), mp 189—190°. This substance was recognized from IR, NMR and elementary analysis. IR cm^{-1} (Nujol): 3350, 3280, 3200 (OH, NH), 1642 (CONH). NMR (in d_6-DMSO) τ: 6.45 (m) 6H ($-CH_2-$), 5.26 (m) 2H ($-CH_2-$), 2.50 (m), 1.60 (m) 5H (C_6H_5), 1.25 (s) 1H (ring proton). *Anal.* Calcd. for $C_{18}H_{23}O_3N_3$: C, 65.65; H, 6.99; N, 12.77. Found: C, 65.36; H, 6.95; N, 12.69. Ether soluble substance was obtained after evaporation of ether. Recrystallization from EtOH gave IX, 750 mg (23%), mp 72—73°. IR cm^{-1} (Nujol): 3270, 3200 (OH, NH), 1695 ($COOC_5H_{11}$). NMR (in $CDCl_3$) τ: 8.0—9.3 (m) 9H (C_4H_9), 6.12 (m) 4H ($-N-CH_2-CH_2-O-$), 5.71 (t) 2H ($-COOCH_2-$), 2.50 (m), 1.57 (m) 5H (C_6H_5), 1.07 (s) 1H (ring proton).

The Rearrangement Reaction of 2-Phenyl-4-(N-phenyl-2-hydroxyethylamino)-5-ethoxycarbonylpyrimidine (Vc)——a) A solution of Vc (1.0 g) in dioxane (10 ml) was refluxed for 10 hr and the solvent was condensed to the half volume. On standing, 2-phenyl-4-(2-phenylaminoethoxy)-5-ethoxycarbonylpyrimidine (XIa) crystallized out, which was filtered, 0.5 g (50%), mp 111—113°. Mass spectrum of XIa showed *m/e*: 363 (M^+). NMR (in $CDCl_3$) τ: 8.60 (3H, triplet, CH_3), 6.80 (H, singlet, CH), 6.36 (2H, triplet, CH_2), 5.58 (2H, quartet, CH_2), 5.16 (2H, triplet, CH_2), 2.42—3.40, 1.50 (10H, multiplet, $2C_6H_5$), 0.80 (H, singlet, CH). *Anal.* Calcd. for $C_{21}H_{21}O_3N_3$: C, 69.40; H, 5.83; N, 11.56. Found: C, 69.05; H, 5.51; N, 11.22.

b) A solution of Ic (2.6 g) and IIk (2.75 g) in dioxane (10 ml) was refluxed for 10 hr. On standing, XIa crystallized out, which was filtered and washed with a small volume of EtOH, 1.8 g (50%).

The Rearrangement Reaction of 2-Methylthio-4-(N-phenyl-2-hydroxyethylamino)-5-ethoxycarbonylpyrimidine (Va)——Va (1.0 g) was handled in the same manner with the case of Vc to give 0.62 g (62%) of

2-methylthio-4-(2-phenylaminoethoxy)-5-ethoxycarbonylpyrimidine (XIb), mp 88—89°. *Anal.* Calcd. for $C_{16}H_{19}O_3N_3$: C, 57.81; H, 5.70; N, 12.61. Found: C, 57.61; H, 5.25; N, 12.43. Mass spectrum of Xb showed *m/e*: 333 (M^+). NMR (in $CDCl_3$) τ: 8.63 (3H, triplet, CH_3), 7.44 (3H, singlet, CH_3), 6.43 (2H, triplet, CH_2), 5.63 (2H, triplet, CH_2), 5.63 (2H, quartet, CH_2), 5.32 (2H, triplet, CH_2), 2.65—3.38 (10H, multiplet, $2C_6H_5$), 0.85 (H, singlet, CH). UV λ_{max}^{EtOH} mμ (ε): 248 (16900), 290 (19000).

Acetylation of Vc——To a mixture of Vc (0.5 g) in pyridine (1.0 ml) was dropped acetylchloride with cooling and the mixture was allowed to stand at room temperature overnight, then poured into H_2O. The separated oil was extracted with $CHCl_3$, dried and the solvent was evaporated to dryness. The residue was then chromatographed on silica gel (50 g). The elution with a solvent system of acetone–benzene (2: 15) afforded 0.4 g (71.7%) of 2-phenyl-4-(N-phenyl-2-acetoxyethylamino)-5-ethoxycarbonylpyrimidine (XII), mp 120—122°. IR cm^{-1} (Nujol): 1735 (CH_3-CO-O). *Anal.* Calcd. for $C_{23}H_{23}O_4N_3$: C, 68.13; H, 5.72; N, 10.37. Found: C, 68.39; H, 5.95; N, 10.27.

Acetylation of XIa——A solution of Xa (0.7 g) in pyridine (1.5 ml) and acetylchloride (3.3 g) was handled in same manner with the case of Vc to give 0.5 g (89.7%) of 2-phenyl-4-(N-acetyl)-phenylaminoethoxy-5-ethoxycarbonylpyrimidine (XIII). mp 91—92°. IR cm^{-1} (Nujol): 1655 (CH_3CO-N). *Anal.* Calcd. for $C_{23}H_{23}O_4N_3$: C, 68.13; H, 5.72; N, 10.37. Found: C, 68.13; H, 5.63; N, 10.37.

2-Phenyl-4-piperidino-5-ethoxycarbonylpyrimidine (XIV)——A mixture of Ic (1.0 g) and piperidine (680 mg) in EtOH (50 ml) was refluxed for 3 hr. After removal of the solvent, the residue was treated with H_2O and the resulting crystals were filtered. Recrystallization from EtOH gave XIV (0.9 g, 78%), mp 95—96°. UV λ_{max}^{MeOH} mμ (ε): 266 (34800). *Anal.* Calcd. for $C_{18}H_{21}O_3N_3$: C, 69.45; H, 6.75; N, 13.51. Found: C, 69.60; H, 6.82; N, 13.55.

2-Phenyl-4-methoxy-5-methoxycarbonylpyrimidine (XV)——Ic (1.0 g) was dissolved in a solution of MeONa prepared from Na (216 mg) and MeOH (50 ml) and refluxed for 2 hr. After cooling, the resulting crystals were filtered and washed with H_2O to give XV (0.8 g, 81%), mp 120—121° (recrystallized from EtOH). UV λ_{max}^{MeOH} mμ (ε): 265 (15000), 287 (23300). *Anal.* Calcd. for $C_{13}H_{12}O_3N_2$: C, 63.93; H, 4.92; N, 11.48. Found: C, 63.83; H, 4.90; N, 11.52.

2-Phenyl-4-(N-phenyl-2-hydroxyethylamino)pyrimidine (XVI)——A mixture of 2-phenyl-4-chloropyrimidine[13] (0.4 g) and N-phenylethanolamine (IIk) (1.0 g) in dioxane (2 ml) was refluxed for 2 hr. After removal of the solvent, the residue was then chromatographed on silica gel (80 g). The elution with a solvent system of acetone–benzene (2: 15) afforded 0.2 g of XVI, mp 120—122°. *Anal.* Calcd. for $C_{18}H_{17}ON_3$: C, 74.20; H, 5.88; N, 14.42. Found: C, 74.03; H, 5.77; N, 14.29.

The Reaction of IIIk with Benzylamine——a) 2-Phenyl-4-(N-ethyl-2-hydroxyethylamino)-5-benzylcarbamoylpyrimidine (XVIII): A mixture of IIIk (0.2 g) and benzylamine (5 ml) was heated in an oil bath at 100° for 2 hr and then at 120—130° for 30 min. The excess amine was removed by evaporation and H_2O was added to the residue to give the crystals which was crystallized from aqueous EtOH to give XVIII (0.2 g), mp 127—128°. *Anal.* Calcd. for $C_{22}H_{24}O_2N_4$: C, 70.19; H, 6.43; N, 14.88. Found: C, 70.08; H, 6.46; N, 14.85.

b) 2-Phenyl-4-benzylamino-5-benzylcarbamoylpyrimidine (XIX): A mixture of IIIk (2.0 g) and benzylamine (50 ml) was heated in an oil bath at 120° for 2 hr and at 140° for 1 hr. After removal of the excess amine, the residue was chromatographed on silica gel (150 g). The elution with a solvent system of acetone–benzene (1: 2) afforded XIX (0.2 g, 6.1%), mp 148—149°. *Anal.* Calcd. for $C_{25}H_{22}ON_4$: C, 76.11; H, 5.62; N, 14.21. Found: C, 75.45; H, 5.60; N, 14.15.

3-Chloro-4-ethoxycarbonyl-6-phenylpyridazine (XX)——a) 3-Hydroxy-4-ethoxycarbonyl-6-phenylpyridazine: To a solution of 3-hydroxy-4-ethoxycarbonyl-6-phenyl-4,5-dihydropyridazine[14] (12.8 g) in AcOH (300 ml) was added Br_2 (12.2 g) at room temperature and the mixture was allowed to stand overnight. To a reaction mixture was added a great deal of H_2O as much as the crystals did not crystallized out any more, filtered, dried and recrystallized from EtOH to give 10.3 g (80%) of 3-hydroxypyridazine compound, mp 145—147°. *Anal.* Calcd. for $C_{13}H_{12}O_3N_2$: C, 63.93; H, 4.92; N, 11.48. Found: C, 63.47; H, 4.96; N, 11.48.

b) A mixture of the above obtained pyridazine (10 g) and $POCl_3$ (20 ml) was heated at 70—80° for 2 hr. After removal of excess $POCl_3$, the residue was treated with crushed ice. The resulting crystals were recrystallized from petroleum ether to give XX (9.0 g, 85%), mp 45—46°. *Anal.* Calcd. for $C_{13}H_{11}O_2N_2Cl$: C, 56.29; H, 2.99; N, 11.93. Found: C, 56.06; H, 3.07; N, 11.73.

General Procedure for the Syntheses of 1,3-Disubstituted-7-oxo-1,2,3,5-tetrahydropyridazino[3,4-*e*][1,4]-oxazepine (XXI)——A solution of XX (1.0 g) and N-substituted ethanolamine (II) (3.0 g) in EtOH (20 ml) was refluxed for 3 hr. After removal of the solvent *in vacuo*, the residue was extracted with $CHCl_3$. The $CHCl_3$ layer was evaporated to dryness and the residue was chromatographed on silica gel (80 g). The elution with a solvent system of acetone–benzene afforded XXI which was crystallized from EtOH.

General Procedure for the Syntheses of 1-Substituted-6,8-dimethyl-5-oxo-1,2,3,5-tetrahydropyrido[4,3-*e*]-[1,4]oxazepine (XXIII)——A solution of XXII (1.5 g) and II (3.0 g) was heated in sealed tube for 4 hr at

13) S. Ruhemann and A.S. Hemmy, *Chem. Ber.*, **30**, 2029 (1902).
14) Th. Curtius, *J. Prakt. Chem.*, (2) **50**, 508 (1894).

165°. After cooling, the resulting crystals were filtered and chromatographed on a silica gel (100 g). The elution with acetone afforded XXIII.

2-Chloro-3-ethoxycarbonyl-4,6-dimethylpyridine (XXIV)——A mixture of 2-hydroxy-3-ethoxycarbonyl-4,6-dimethylpyridine[15] (1.3 g), $POCl_3$ (25 ml) and PCl_5 (5.0 g) was refluxed for 5 hr. After removal of $POCl_3$ *in vacuo*, the residue was treated with the crushed ice and the resulting oil was extracted with $CHCl_3$. The $CHCl_3$ layer was evaporated to give XXIV (650 mg, 45%) as an oil. TLC (developed with a solvent system acetone–benzene (1:4)): *Rf* 0.8. IR (nujol) cm^{-1}: 1726, 1280, 1245, 1080 ($-COOC_2H_5$) (The bands of 3280, 1647, 1550 (-CONH-) in the starting material disappeared). NMR (in $CDCl_3$): τ 8.59 (3H, triplet, CH_3), 7.68 (3H, singlet, CH_3), 7.48 (3H, singlet, CH_3), 5.66 (2H, quartet, CH_2), 3.02 (H, singlet, CH).

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