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Synthesis of 5-Amino-4(3*H*)-pyrimidinones. II.[1] Synthesis of 5-Acyl- and 5-Alkylamino-3-phenyl-6-methyl-4(3*H*)-pyrimidinones and Determination of Their Analgesic and Antiinflammatory Activities

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N-Acylation and *N*-alkylation of 5-amino-6-methyl-3-phenyl-4(3*H*)-pyrimidinone (I) were carried out and the products were examined for analgesic and antiinflammatory activities. The reaction of I with α-bromopropionyl bromide or chloroacetyl chloride followed by treatment with 40% aqueous dimethylamine gave 5-(α-dimethylaminopropionamido)- or 5-(*N*,*N*-dimethylglycyl)amino-6-methyl-3-phenyl-4(3*H*)-pyrimidinone (IIc or IIe). The reaction of 3,4-dihydro-1,6-dimethyl-5-dimethylamino-4-oxo-3-phenylpyrimidinium iodide (IV) with several alkylamines such as propylamine, isobutylamine, *sec*-butylamine, and allylamine in acetonitrile gave 5-alkylamino-3,4-dihydro-1,6-dimethyl-4-oxo-3-phenylpyrimidinium iodides (IVa—d), whose reduction with sodium borohydride in methanol gave 5-alkylamino-1,2-dihydro-1,6-dimethyl-3-phenyl-4(3*H*)-pyrimidinones (VIIa—d). The reaction of I with benzaldehyde or *p*-methoxybenzaldehyde gave 5-benzylidene (or *p*-methoxybenzylidene)amino-6-methyl-3-phenyl-4(3*H*)-pyrimidinones (VIIIa, b). Compounds I and VIIIa showed analgesic and antiinflammatory activities in mice and rats.

Keywords——4-oxo-3,4-dihydropyrimidinium iodide; 5-amino-3,4-dihydro-4-oxopyrimidine; alkylamination; analgesic activity; antiinflammatory activity

Pyrimidines and pyrimidinones are important intermediates for the syntheses of a number of compounds which have potential biological activities.[2] Previously we found the novel ring transformation of 4-aminoantipyrines to 5-amino-4(3*H*)-pyrimidinones.[1] The latter compounds contain a partial structure related to aminopyrine[3] which possesses analgesic and antipyretic activities. Thus it appeared interesting to synthesize derivatives of 5-amino-4(3*H*)-pyrimidinones and to examine their pharmacological activities. We wish to report here the *N*-acylation and the *N*-alkylation of 5-amino-4(3*H*)-pyrimidinones, and the analgesic and antiinflammatory actions of the products.

Chemistry

The *N*-acylation and *N*-alkylation of 5-amino-6-methyl-3-phenyl-4(3*H*)-pyrimidinone[1] (I) were carried out as depicted in Chart 1 and Chart 2. Acetylation of I with acetic anhydride and acetic acid gave 5-acetamido-6-methyl-3-phenyl-4(3*H*)-pyrimidinone (IIa) in 78% yield. Aminopropylon[4] has a dimethylaminopropionamido group in its molecule. Thus, the reaction of I with α-bromopropionyl bromide was carried out to give 5-(α-bromopropionamido)-6-methyl-3-phenyl-4(3*H*)-pyrimidinone (IIb), whose treatment with 40% aqueous dimethylamine gave 5-(α-dimethylaminopropionamido)-6-methyl-3-phenyl-4(3*H*)-pyrimidinone (IIc) in 67% yield. Similar reaction with chloroacetyl chloride followed by treatment with 40% aqueous dimethylamine afforded 5-(*N*,*N*-dimethylglycyl)amino-6-methyl-3-phenyl-4(3*H*)-pyrimidinone (IIe) in 70% yield.

For *N*-alkylation, the reaction of I with alkyl halide in the presence of sodium hydride was attempted initially. However, this method met with failure, resulting in recovery of the starting material or giving a resinous tar. An attempt to displace the dimethylamino group of 5-dimethylamino-6-methyl-3-phenyl-4(3*H*)-pyrimidinone[5] (III) with some other amino groups was also unsuccessful. Thus, 3,4-dihydro-5-dimethylamino-1,6-dimethyl-4-oxo-3-phenylpyrimidinium iodide (IV) was prepared, since it should be more susceptible to nucleophilic attack. Treatment of III with methyl iodide in *N*,*N*-dimethylformamide (DMF) gave IV, whose structure was confirmed by reducing it with sodium borohydride to give 1,6-dimethyl-5-dimethylamino-1,2-dihydro-3-phenyl-4(3*H*)-pyrimidinone (V). The nuclear magnetic resonance (NMR) spectrum, mass spectrum and elemental analysis of V agreed well with the assigned structure. When a mixture of IV and an appropriate alkylamine in acetonitrile was refluxed on a mantle heater, nucleophilic substitution of alkylamines at the C-5 position proceeded smoothly. The reactions with propylamine, isobutylamine, allylamine, and *sec*-butylamine gave 5-alkylamino-3,4-dihydro-1,6-dimethyl-4-oxo-3-phenylpyrimidinium iodides (VIa—d), whose reduction with sodium borohydride in methanol afforded 5-alkylamino-1,2-dihydro-1,6-dimethyl-3-phenyl-4(3*H*)-pyrimidinones (VIIa—d). This method is facile and would be useful for the synthesis of 5-alkylaminopyrimidinones from 5-dimethylamino compounds.

The reaction of I with benzaldehyde or *p*-methoxybenzaldehyde gave 5-benzylidene (or *p*-methoxybenzylidene)amino-6-methyl-3-phenyl-4(3*H*)-pyrimidinone (VIIIa or VIIIb) in 75—76% yield.

I

IIa : R=Ac
IIb : R=COCHBr
|
Me

IIc : R=COCHN(Me)(Me)
|
Me

IId : R=$COCH_2Cl$

IIe : R=$COCH_2N(Me)(Me)$

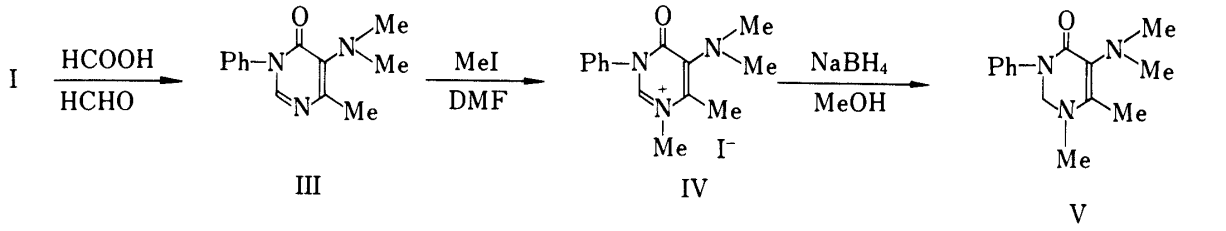
Chart 1

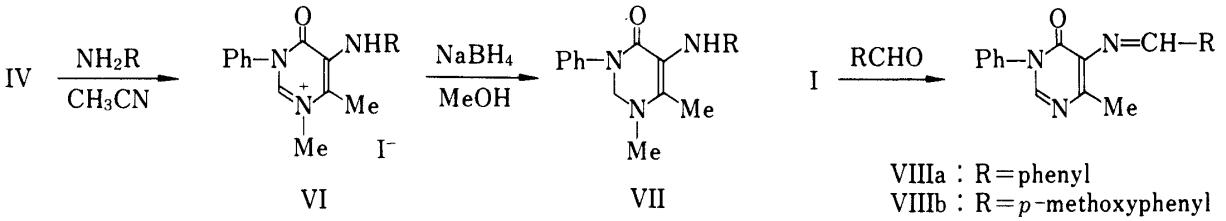
An attempt to introduce a hydroxy group into the C-2 position of IV in the presence of sodium hydroxide in methanol resulted in the formation of 2-dimethylamino-*N*-formyl-3-methylamino-*N*-phenyl-crotonamide (IX), whose structure was deduced from the NMR spectrum. The signal of the methyl group of the *N*-methylamino moiety was observed at δ 3.02 ppm as a doublet (J=2 Hz), which became a singlet on addition of D_2O. Another possible isomer (IX′) was not detected.

Analgesic and Antiinflammatory Activities

The analgesic and antiinflammatory activities of 5-acyl- or 5-alkylamino-1-phenyl-6-methyl-4(3*H*)-pyrimidinones and related compounds (I, IIa—c, e, IV, V, VIa, b, d, VIIa—d, VIIIa, b, IX) were examined. These pharmacological results are shown in Table I.

(A) Analgesic Activity Testing: Test compounds were administered orally to ddy male mice (*ca.* 20 g) at a dose of 100 mg/kg. Ten animals were used to test each dose. Half an hour





VIa : R=$CH_2CH_2CH_3$
VIb : R=$CH_2CH(CH_3)_2$
VIc : R=CH_2-CH=CH_2
VId : R=CH(CH_3)-CH_2CH_3

VIIa : R=$CH_2CH_2CH_3$
VIIb : R=$CH_2CH(CH_3)_2$
VIIc : R=CH_3-CH=CH_2
VIId : R=CH(CH_3)-CH_2CH_3

Chart 2

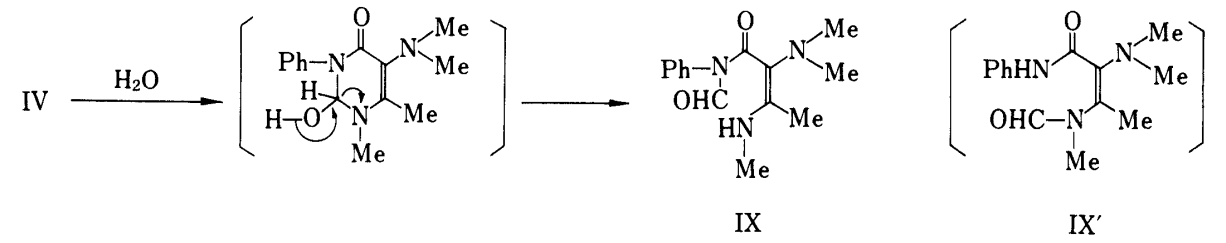


Chart 3

later, writhing was induced in the mice by intraperitoneal injection of 0.7% acetic acid (10 ml/kg) and the number of wriths was counted in each animal for 10 min. The percent inhibition was calculated from the difference in the count between the treated group and the control group.

(B) Carrageenin Edema Testing: Six male Wistar strain rats weighing 100—120 g were used. Test compounds were administered orally at a dose of 100 mg/kg. One hour later, 0.1 ml of 0.5% carrageenin was injected *s.c.* under the plantar surface of a hind paw. The foot volume was measured in each animal at 3 h, and the percent swelling (foot edema) was calculated. The percent diminution due to a test compound was computed from the difference in percent swelling between the treated group and the control group.

Among the test compounds, I and VIIIa showed analgesic and antiinflammatory activities.

Experimental

All melting points were determined on a Yanagimoto micro melting point apparatus and are uncorrected. Infrared (IR) spectra were measured with an IR-S machine from Nihon Bunko Spectroscopic Co., Ltd. Mass spectra (MS) were obtained on a Hitachi M-52 mass spectrometer. NMR spectra were measured with a Japan Electron Optics Laboratory Co., JNM-100 spectrometer using tetramethylsilane as an internal standard. Abbreviations are as follows: s, singlet; d, doublet; q, quartet; br, broad.

5-Acetamido-6-methyl-3-phenyl-4(3*H*)-pyrimidinone (IIa)——Compound (I) (2 g) was dissolved in a mixture of

Table I. Analgesic and Antiinflammatory Activities of 5-Acyl- and 5-Alkylamino-1-phenyl-6-methyl-4(3*H*)-pyrimidinones and Related Compounds

Compd.	Inhibition (%)	
	AcOH writhing (100 mg/kg, *p.o.*) mouse (ddy, ♂)	Carrageenin edema (100 mg/kg, *p.o.*) rat (Wistar, ♂)
I	83.7	48.0
IIa	44.8	1.0
IIb	30.9	2.6
IIc	27.9	0
IIe	47.7	3.3
IV	48.5	3.3
V	a)	42.2
VIa	27.8	13.1
VIb	27.2	10.7
VId	30.0	11.2
VIIa	29.1	15.0
VIIb	43.0	23.5
VIIc	46.9	2.4
VIId	38.8	9.2
VIIIa	72.5	33.7
VIIIb	50.9	15.4
IX	37.7	0.7
Tiaramide	60—70	30—50
Phenylbutazone	10—20	30—50

a) All animals died.

acetic anhydride (10 ml) and acetic acid (10 ml) and the solution was allowed to stand overnight. The acetic anhydride and the acetic acid were distilled off. The residue was recrystallized from ethanol to obtain colorless needles of mp 174—175 °C. Yield 1.9 g (78%). *Anal.* Calcd for $C_{13}H_{13}N_3O_2$: C, 64.18; H, 5.39; N, 17.28. Found: C, 64.25; H, 5.66; N, 17.41.

5-(α-Bromopropionamido)-6-methyl-3-phenyl-4(3*H*)-pyrimidinone (IIb)——A solution of α-bromopropionyl bromide (2 g) in dichloromethane (10 ml) was added dropwise to a solution of I (2 g) in dichloromethane (30 ml) under cooling with ice and the mixture was stirred for 30 min. Water was added to the reaction mixture, which was then extracted with chloroform. The solvent was distilled off and the residue was recrystallized from ethanol to give colorless prisms of mp 187—188 °C. Yield 2.3 g (67%). NMR ($CDCl_3$) δ: 1.80 (3H, d, J=7 Hz, CH–Me), 2.30 (3H, s, Me), 4.45 (1H, q, J=7 Hz, Me–CH), 7.25—7.55 (5H, m, aromatic protons), 8.02 (1H, s, pyrimidone C-2 proton), 8.50 (1H, s, NH, lost on D_2O-exchange). *Anal.* Calcd for $C_{14}H_{14}BrN_3O_2$: C, 50.02; H, 4.20; N, 12.50. Found: C, 50.31; H, 4.33; N, 12.56.

5-(α-Dimethylamino)propionamido-6-methyl-3-phenyl-4(3*H*)-pyrimidinone (IIc)——Dimethylamine (40% aqueous solution, 20 ml) was added to a mixture of IIb (4 g) and benzene (80 ml). The mixture was stirred at room temperature for 4 h, and then refluxed for 1 h. The benzene layer was separated and dried with anhydrous sodium sulfate. The benzene was distilled off and the residue was recrystallized from ether, mp 88—90 °C. Yield 3.1 g (51%). NMR ($CDCl_3$) δ: 1.30 (3H, d, J=7 Hz, Me–CH), 2.34 (3H, s, Me), 2.35 (6H, s, $-N<^{Me}_{Me}$), 3.15 (1H, q, J=7 Hz, Me–CH), 7.30—7.55 (5H, m, aromatic protons), 8.00 (1H, s, pyrimidone C-2 proton), 9.10 (1H, br, NH, lost on D_2O-exchange). MS *m/z*: 300 (M^+). *Anal.* Calcd for $C_{16}H_{20}N_4O_2$: C, 63.98; H, 6.71; N, 18.65. Found: C, 63.87; H, 6.56; N, 18.68.

5-(Chloroacetylamino)-6-methyl-3-phenyl-4(3*H*)-pyrimidinone (IId)——A solution of chloroacetyl chloride (1.2 g) in dichloromethane (10 ml) was added dropwise to a solution of I (2 g) in dichloromethane (30 ml) under cooling with ice and the mixture was stirred for 30 min. Water was added to the reaction mixture, which was extracted with chloroform. The chloroform layer was dried. The solvent was distilled off, and the residue was recrystallized from

ethanol to give colorless prisms of mp 129—130 °C. Yield 2.1 g (75%). *Anal.* Calcd for $C_{13}H_{12}ClN_3O_3$: C, 56.22; H, 4.36; N, 15.13. Found: C, 56.21; H, 4.33; N, 15.09.

5-(*N*,*N*-Dimethylglycyl)amino-6-methyl-3-phenyl-4(3*H*)-pyrimidinone (IIe)——Dimethylamine (40% aqueous solution, 5 ml) was added to a mixture of IId (1 g) and benzene (30 ml). The mixture was stirred at room temperature for 4 h, and then refluxed for 1 h. The benzene layer was separated and dried over anhydrous sodium sulfate. The benzene was distilled off and the residue was recrystallized from ether, colorless prisms of mp 85—87 °C. Yield 1.1 g (70%). NMR ($CDCl_3$) δ: 2.35 (3H, s, $\diagup\!\!\!=\!\!\diagdown$Me), 2.40 (6H, s, $-N\lesssim^{Me}_{Me}$), 3.10 (2H, s, $-CH_2-$), 7.30—7.50 (5H, m, aromatic protons), 8.00 (1H, s, pyrimidone C-2 proton), 8.95 (1H, br, NH, lost on D_2O-exchange). MS *m/z*: 286 (M^+). *Anal.* Calcd for $C_{15}H_{18}N_4O_2$: C, 62.92; H, 6.34; N, 19.57. Found: C, 63.08; H, 6.59; N, 19.84.

5-Dimethylamino-6-methyl-3-phenyl-4(3*H*)-pyrimidinone (III)——A mixture of I (2 g), 98% formic acid (2 ml) and 35% formalin (4 ml) was heated on a water bath (90—100 °C) for 3 h. The mixture was poured into water and extracted with chloroform. The extract was washed with water and dried over anhydrous sodium sulfate. The chloroform was distilled off and the residue was recrystallized from ether to give colorless needles of mp 115—116 °C. Yield 1.6 g (70%). IR ν_{max}^{KBr} cm^{-1}: 1650 (C=O). NMR ($CDCl_3$) δ: 2.40 (3H, s, $\diagup\!\!\!=\!\!\diagdown$Me), 2.80 (6H, s, $-N\lesssim^{Me}_{Me}$), 7.30—7.60 (5H, m, aromatic protons), 8.00 (1H, s, pyrimidine ring C-2 proton). MS *m/z*: 229 (M^+). *Anal.* Calcd for $C_{13}H_{15}N_3O$: C, 68.10; H, 6.59; N, 18.33. Found: C, 68.03; H, 6.66; N, 18.52.

3,4-Dihydro-1,6-dimethyl-5-dimethylamino-4-oxo-3-phenylpyrimidinium Iodide (IV)——A mixture of III (1.4 g), methyl iodide (2 ml) and DMF (50 ml) was stirred under cooling with ice for 1 h, then solvent was distilled off. The residue was recrystallized from ethanol to give prisms of mp 211—213 °C. Yield 1.5 g (62%). NMR ($CDCl_3$) δ: 2.44 (3H, s, $\diagup\!\!\!=\!\!\diagdown$Me), 2.80 (6H, s, $-N\lesssim^{Me}_{Me}$), 3.92 (3H, s, $\gtrsim^{+}$N–Me), 7.45—7.75 (5H, m, aromatic protons), 9.80 (1H, s, pyrimidine ring C-2 proton). *Anal.* Calcd for $C_{14}H_{18}IN_3O$: 45.30; H, 4.89; N, 11.32. Found: C, 45.39; H, 4.61; N, 11.55.

1,6-Dimethyl-5-dimethylamino-1,2-dihydro-3-phenyl-4(3*H*)-pyrimidinone (V)——Sodium borohydride (1.7 g) was added to a solution of IV (1.7 g) in methanol (60 ml). The mixture was refluxed with stirring for 2 h. The solvent was distilled off, and water was added to the residue. The aqueous layer was extracted with chloroform. The extract was washed with water and dried over anhydrous sodium sulfate. The solvent was distilled off and the residue was recrystallized from methanol to give colorless prisms of mp 122—124 °C. Yield 0.8 g (76%). NMR ($CDCl_3$) δ: 2.10 (3H, s, $\diagup\!\!\!=\!\!\diagdown$Me), 2.70 (6H, s, $-N\lesssim^{Me}_{Me}$), 2.90 (3H, s, N–Me), 4.65 (2H, s, N–CH_2–N), 7.10—7.45 (5H, m, aromatic protons). MS *m/z*: 245 (M^+). *Anal.* Calcd for $C_{14}H_{19}N_3O$: C, 68.54; H, 7.81; N, 17.13. Found: C, 68.29; H, 7.91; N, 16.83.

General Procedure for the Preparation of 5-Alkylamino-3,4-dihydro-1,6-dimethyl-4-oxo-3-phenylpyrimidinium Iodides (VIa—d)——A mixture of IV (0.01 mol), alkylamine (0.01 mol) and acetonitrile (50 ml) was refluxed with stirring for 3 h, then the solvent was distilled off. The residue was column-chromatographed on silica gel and eluted first with chloroform and then with ethanol. The ethanol eluate was collected and the solvent was distilled off. The residue was recrystallized from ethanol.

Table II. 5-Alkylamino-3,4-dihydro-1,6-dimethyl-4-oxo-3-phenylpyrimidinium Iodides

Compd. No.	mp (°C)	Yield (%)	Formula	Analysis (%) Calcd (Found)		
				C	H	N
VIa	188—190	53	$C_{15}H_{20}IN_3O$	46.77 (46.91)	5.23 5.42	10.91 11.06)
VIb	185—187	45	$C_{16}H_{22}IN_3O$	48.13 (48.05)	5.55 5.54	10.52 10.64)
VIc	174—175	40	$C_{15}H_{18}IN_3O$	47.01 (47.26)	4.73 5.01	10.96 11.10)
VId	147—150	49	$C_{16}H_{22}IN_3O$	48.13 (48.31)	5.55 5.76	10.52 10.84)

Table III. 5-Alkylamino-1,2-dihydro-1,6-dimethyl-3-phenyl-4(3*H*)-pyrimidinone Dihydrochlorides

Compd. No.	mp (°C) (dec.)	Yield (%)	Formula	Analysis (%) Calcd (Found)		
				C	H	N
VIIa	107—111	92	$C_{15}H_{23}Cl_2N_3O$	54.22	6.98	12.65
				(53.98	6.69	12.73)
VIIb	100—105	90	$C_{16}H_{25}Cl_2N_3O$	55.49	7.28	12.13
				(55.20	7.56	12.41)
VIIc	106—110	95	$C_{15}H_{21}Cl_2N_3O$	54.55	6.41	12.72
				(54.29	6.70	12.54)
VIId	80—83	96	$C_{16}H_{25}Cl_2N_3O$	55.49	7.28	12.13
				(55.25	7.44	12.39)

General Procedure for the Preparation of 5-Alkylamino-1,2-dihydro-1,6-dimethyl-3-phenyl-4(3*H*)-pyrimidinone Dihydrochlorides (VIIa—d)——Sodium borohydride (0.1 mol) was added to a solution of VIa—d (0.01 mol) in methanol (100 ml). The mixture was refluxed with stirring for 2 h. The solvent was distilled off and water was added to the residue. The aqueous layer was extracted with chloroform. The extract was washed with water and dried over anhydrous sodium sulfate. The solvent was distilled off. The residue was purified by column chromatography on silica gel, eluting with chloroform. The product was dissolved in ethanol which contained hydrogen chloride. Evaporation of the ethanol gave the dihydrochloride of VIIa—d.

5-Benzylideneamino-6-methyl-3-phenyl-4(3*H*)-pyrimidinone (VIIIa)——A mixture of I (1 g) and benzaldehyde (5 g) was refluxed for 1 h to obtain a clear solution, which was then cooled. The resulting crystals were washed with ether and recrystallized from ethanol to give prisms of mp 143—145 °C. Yield 1.1 g (76%). IR ν_{max}^{KBr} cm^{-1}: 1670 (C=O). NMR ($CDCl_3$) δ: 2.60 (3H, s, –Me), 7.30—7.99 (10H, m, aromatic protons), 8.00 (1H, s, pyrimidone C-2 proton), 9.52 (1H, s, –N=CH–). *Anal.* Calcd for $C_{18}H_{15}N_3O$: C, 74.72; H, 5.23; N, 14.53. Found: C, 74.46; H, 5.37; N, 14.30.

5-(*p*-Methoxybenzylideneamino)-6-methyl-3-phenyl-4(3*H*)-pyrimidinone (VIIIb)——A mixture of I (1 g) and *p*-methoxybenzaldehyde (6 g) was refluxed for 1 h to obtain a clear solution, which was then cooled. The resulting crystals were washed with ether and recrystallized from ethanol to give prisms of mp 147—149 °C. Yield 1.2 g (75%). IR ν_{max}^{KBr} cm^{-1}: 1670 (C=O). NMR ($CDCl_3$) δ: 2.60 (3H, s, –Me), 3.85 (3H, s, OMe), 6.90—7.90 (9H, m, aromatic protons), 8.00 (1H, s, pyrimidone C-2 proton), 9.40 (1H, s, –N=CH–). *Anal.* Calcd for $C_{19}H_{17}N_3O_2$: C, 71.45; H, 5.37; N, 13.16. Found: C, 71.53; H, 5.40; N, 12.94.

2-Dimethylamino-*N*-formyl-3-methylamino-*N*-phenylcrotonamide (IX)——Aqueous 20% sodium hydroxide (2 ml) was added to a solution of IV (2.5 g) in methanol (50 ml) and the mixture was stirred at room temperature for 1 h. The solvent was distilled off. Water was added to the residue and the solution was extracted with chloroform. The extract was washed with water and dried over anhydrous sodium sulfate. The chloroform was distilled off and the residue was recrystallized from methanol–ether (1 : 1) to give colorless prisms of mp 120—121 °C. Yield 0.9 g (51%). NMR ($CDCl_3$) δ: 1.90 (3H, s, C–Me), 2.70 (6H, s, $-N<^{Me}_{Me}$), 3.02 (3H, d, J=2 Hz, –NH–Me), 7.10—7.98 (6H, m, aromatic protons and –CHO). MS *m/z*: 261 (M^+). *Anal.* Calcd for $C_{14}H_{19}N_3O_2$: C, 64.34; H, 7.33; N, 16.08. Found: C, 64.37; H, 7.28; N, 16.09.

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5) This compound was synthesized from I by means of the Eschweiler–Clark reaction in 70% yield. Senda *et al.* also synthesized the dihydrobromide of III by the reaction of 5-bromo-6-methyl-3-phenyl-4(3*H*)-pyrimidinone with dimethylamine in a sealed tube in 15% yield [S. Senda, K. Hirota and O. Otani, *Yakugaku Zasshi*, **94**, 571 (1974)].