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Studies on Pyrimidinylpyrazoles. I. Syntheses of 1- and 2-Pyrimidinyl-3-methylpyrazolin-5-one Derivatives[1,2]

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In order to find new analgesics and anti-inflammatories, 1- and 2-pyrimidinyl-3-methylpyrazolin-5-one derivatives (III and VII) were synthesized from hydrazinopyrimidines (I) and ethyl acetoacetate or ketene dimer, and then methylated to afford 1- and 2-pyrimidinyl-3-methyl-5-methoxypyrazoles (IV and VIII), 1-pyrimidinyl-2,3-dimethylpyrazolin-5-ones (V), and 2-pyrimidinyl-1,3-dimethylpyrazolin-5-ones (IX). Physical properties of these derivatives were also described.

Since the first pyrazolinone was developed by Knorr in 1883, many papers have been published on phenylpyrazolin-5-one analgesics. There have been several reports[4] on the synthetic and pharmacological studies on 1- or 2-heterocyclyl-pyrazolin-5-one derivatives.

The present authors have now synthesized 1- and 2-pyrimidinyl-3-methylpyrazolin-5-one derivatives and their O- and N-methylated derivatives of the pyrazolinone moiety in the course of our search for new analgesics and anti-inflammatories, and the relationship between chemical structure and pharmacological activity of these compounds was studied. The present paper is concerned with the synthetic studies on 1- and 2-pyrimidinyl-3-methylpyrazolin-5-one derivatives.

Syntheses of 1-Pyrimidinyl-3-methylpyrazolin-5-one Derivatives

The syntheses of 1-pyrimidinylpyrazole derivatives were carried out in a manner similar to that described by Knorr.[5] 1-Pyrimidinyl-3-methylpyrazolin-5-ones (III) were synthesized by the cyclization of ethyl 3-(pyrimidinylhydrazono)butyrates (II) with alkali, which were obtained from hydrazinopyrimidines (I) and ethyl acetoacetate.

Then, III were methylated with dimethyl sulfate and sodium methoxide in dimethylformamide or with an ether solution of diazomethane to afford a mixture of 1-pyrimidinyl-3-methyl-5-methoxypyrazoles (IV) and 1-pyrimidinyl-2,3-dimethyl-3-pyrazolin-5-ones (V) which were separated by chromatography on alumina or by extraction. Melting points and yields of III, IV, and V obtained here are shown in Tables I, II, and III, respectively.

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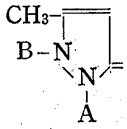
1) This work was presented at the 88th Annual Meeting of the Pharmaceutical Society of Japan, Tokyo, April 1968.

2) In this series, nomenclature and numbering system are adopted as follows:



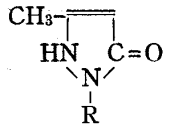
A=pyrimidinyl groups, B=H : 1-pyrimidinyl-3-methylpyrazolin-5-ones

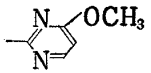
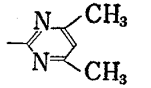
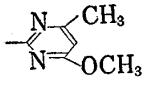
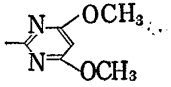
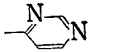
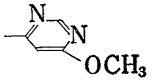
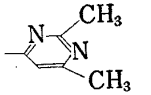
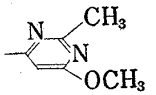
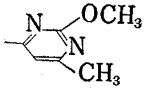
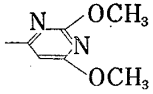
A=H, B=pyrimidinyl groups : 2-pyrimidinyl-3-methylpyrazolin-5-ones

3) Location: *Minamifunabori-cho, Edogawa-ku, Tokyo.*

4) *a*) A. Vystrčil and J. Vidlička, *Chem. Listy*, **45**, 407 (1951); *b*) R. Giuliano and G. Leonardi, *Farmaco.* (Pavia) *Ed. Sci.*, **12**, 394 (1957); *c*) H. Beyer and D. Stehwien, *Arch. Pharm.*, **286**, 13 (1953); *d*) H. Bredereck, A. Bräuninger, D. Hayer and H. Vollmann, *Chem. Ber.*, **92**, 2937 (1959); *e*) A. Ebnöther, E. Jucker and A. Lindermann, *Helv. Chim. Acta*, **42**, 1201 (1959); *f*) J. Büchi, P. Fabiani, H.V. Frey, A. Hofstetter and A. Schorno, *Helv. Chim. Acta*, **49**, 272 (1966).

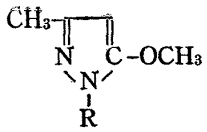
TABLE I. 1-Pyrimidinyl-3-methylpyrazolin-5-ones



No.	R	mp (°C)	Yield (%)	IR $\nu_{C=O}^{KBr}$ cm^{-1}	Formula	Analysis (%) Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
1		101	82	1638 (m)	$C_9H_{10}O_2N_4$	52.42	4.89	27.17	52.80	4.85	26.92
2		112[a]	85	1631 (m)	$C_{10}H_{12}ON_4$	58.81	5.92	27.44	58.63	6.00	27.32
3		102	85	1632 (m)	$C_{10}H_{12}O_2N_4 \cdot H_2O$	50.42	5.92	23.52	50.40	5.76	23.34
4		181—183	85	1635 (m)	$C_{10}H_{12}O_3N_4$	50.84	5.12	23.72	50.60	5.27	23.95
5		189—190	67	1643 (vs)	$C_8H_8ON_4$	54.54	4.58	31.80	54.75	4.82	31.42
6		183—184	68.5	1650 (vs)	$C_9H_{10}O_2N_4$	52.42	4.89	27.17	52.43	4.53	26.62
7		127	50	1633 (vs)	$C_{10}H_{12}ON_4$	58.81	5.92	27.44	58.87	5.87	27.65
8		148	84	1638 (vs)	$C_{10}H_{12}O_2N_4$	54.54	5.49	25.44	54.53	5.82	25.47
9		154	80	1638 (vs)	$C_{10}H_{12}O_2N_4$	54.54	5.49	25.44	54.85	5.62	25.85
10		148	80.5	1645 (vs)	$C_{10}H_{12}O_3N_4$	50.84	5.12	23.72	51.13	5.04	23.65

a) R. Giuliano and G. Leonardi[4b] reported mp 112° as dihydrate.

Table II. 1-Pyrimidinyl-3-methyl-5-methoxypyrazoles



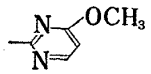
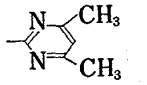
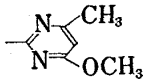
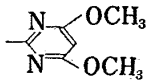
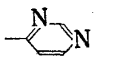
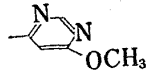
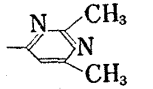
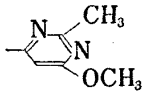
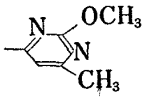
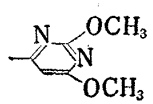
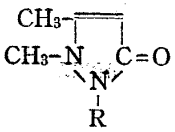
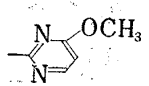
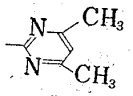
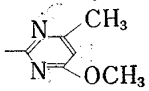
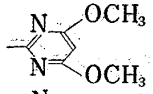
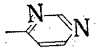
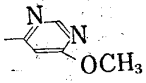
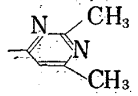
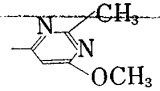
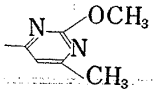
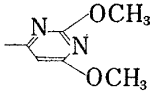
No.	R	mp (°C)	Yield (%)	Formula	Analysis (%) Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
11		104—106	26.4	$C_{10}H_{12}O_2N_4$	54.54	5.49	25.44	54.67	5.53	25.51
12		94—96	23.7	$C_{11}H_{14}ON_4$	60.53	6.47	25.67	60.68	6.32	25.33
13		90	48.0	$C_{11}H_{14}O_2N_4$	56.40	6.02	23.92	56.31	6.08	23.66
14		102—104	26.0	$C_{11}H_{14}O_3N_2$	52.79	5.64	22.39	52.68	5.62	23.30
15		87	11.1	$C_9H_{10}ON_4$	56.83	5.30	29.46	56.61	5.35	29.69
16		124	23.0	$C_{10}H_{12}O_2N_4$	54.54	5.49	25.44	54.82	5.52	25.52
17		90	16.5	$C_{11}H_{14}ON_4$	60.53	6.47	25.67	60.63	6.46	25.81
18		115—118	23.3	$C_{11}H_{14}O_2N_4$	56.40	6.02	23.92	56.49	6.07	23.51
19		122—124	30.0	$C_{11}H_{14}O_2N_4$	56.40	6.02	23.92	56.65	6.05	24.17
20		126	15.5	$C_{11}H_{14}O_3N_2$	52.79	5.64	22.39	52.80	5.90	22.64

TABLE III. 1-Pyrimidinyl-2,3-dimethyl-3-pyrazolin-5-ones



No.	R	mp (°C)	Yield (%)	IR $\nu_{C=O}^{KBr}$ cm^{-1}	Formula	Analysis (%) Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
21		100—102	23.0	1665 (vs)	$C_{10}H_{12}O_2N_4$	54.54	5.49	25.44	54.63	5.40	25.57
22		176[a]	49.7	1659 (vs)	$C_{11}H_{14}ON_4$	60.53	6.47	25.67	60.66	6.55	25.52
23		118—120	19.0	1663 (vs)	$C_{11}H_{14}O_2N_4$	56.40	6.02	23.92	56.14	5.95	23.55
24		97—99	23.2	1677 (vs)	$C_{11}H_{14}O_3N_4$	52.79	5.64	22.39	52.81	5.70	22.27
25		134	20.0	1683 (vs)	$C_9H_{10}ON_4$	56.83	5.30	29.46	56.78	5.08	29.31
26		124	27.0	1670 (vs)	$C_{10}H_{12}O_2N_4$	54.54	5.49	25.44	54.68	5.48	25.63
27		124	17.9	1663 (vs)	$C_{11}H_{14}ON_4$	60.53	6.47	25.67	60.69	6.55	25.32
28		115—117	34.8	1672 (vs)	$C_{11}H_{14}O_2N_4$	56.40	6.02	23.92	56.49	5.97	23.81
29		130	24.3	1680 (vs)	$C_{11}H_{14}O_2N_4$	56.40	6.02	23.92	56.56	6.21	23.49
30		109	21.4	1685 (vs)	$C_{11}H_{14}O_3N_4$	52.79	5.64	22.39	52.97	5.56	22.40

a) Reported mp 162—163°,[4b]

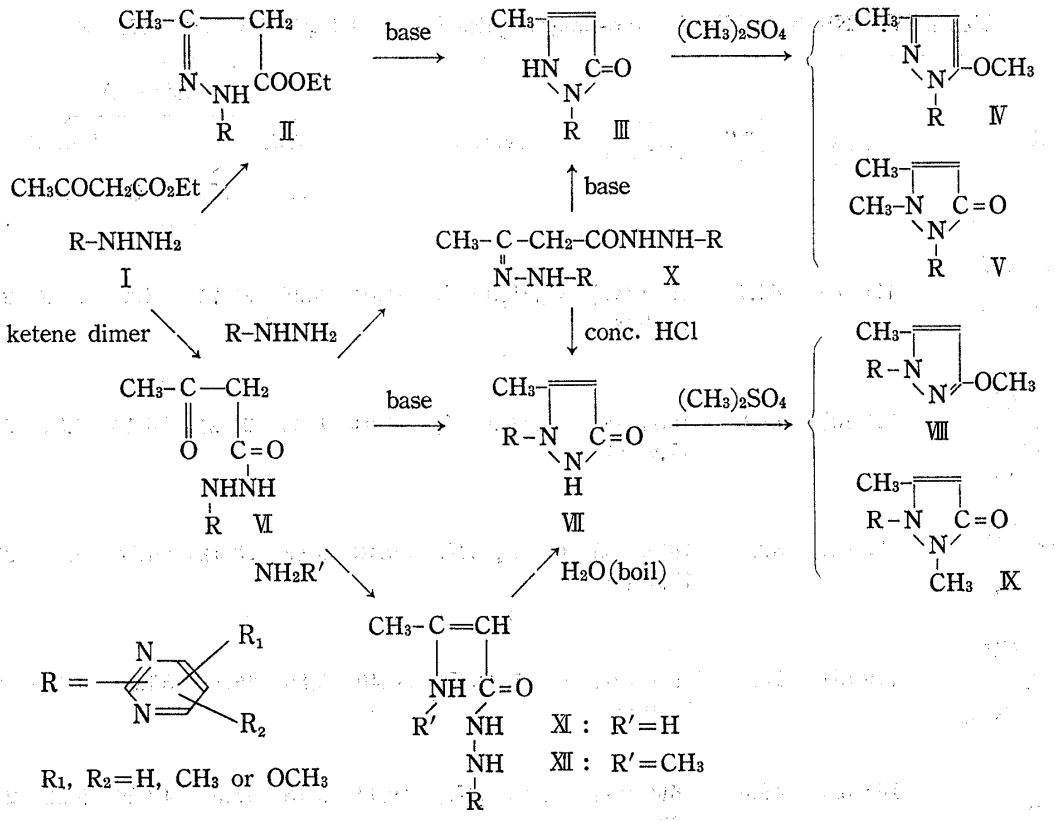


Chart 1

Syntheses of 2-Pyrimidinyl-3-methylpyrazolin-5-one Derivatives

Lecher, *et al.*[6] have reported that N^2-phenyl-3-(phenylhydrazono)butyrohydrazide (XIII) is obtained from phenylhydrazine and ketene dimer, and that XIII gives 2-phenyl-3-methylpyrazolin-5-one by treatment with hydrochloric acid, while the reaction of XIII with alkali gives 1-phenyl-3-methylpyrazolin-5-one.

We found that the reaction of equimolar amount of I and ketene dimer in dioxane solution gave N^2-pyrimidinyl-3-oxo-butyrohydrazides (VI) and that further treatment of equimolar amount of I and VI gave N^2-pyrimidinyl-3-(pyrimidinylhydrazono)butyrohydrazides (X). This result is of interest in contrast with the fact that the reaction of phenylhydrazine with ketene dimer always gives only XIII at low temperature and no compound corresponding to VI is formed under any conditions. The structure of VI was confirmed by their infrared absorption spectra in which the C=O bands of acetyl and amide groups appeared in the 1710 and 1660 cm^{-1} regions, respectively, and by their NMR spectra in DMSO-d_6 which revealed two broad signals assigned to the protons of –NH-NH– and a two-proton signal due to $-COCH_2CO-$ at 3.6 ppm.

Reaction of X with alkali afforded III in a good yield, whereas treatment of X with hydrochloric acid gave 2-pyrimidinyl-3-methylpyrazolin-5-ones (VII). On the other hand, it was found that VII is obtained by treatment of VI with aqueous ammonia or aqueous amines in a good yield. This is an excellent and convenient method for the syntheses of VII. VII thus obtained were methylated in the manner described above for 1-pyrimidinylpyrazolinone compounds and resulting products were separated to give 2-pyrimidinyl-3-methyl-5-methoxypyrazoles (VIII) and 2-pyrimidinyl-1,3-dimethyl-3-pyrazolin-5-ones (IX). Further, treatment of VI with aqueous ammonia and aqueous monomethylamine at room temperature afforded crystals, whose structures were confirmed by infrared spectra (νNH_2 band in the

5) L. Knorr, *Chem. Ber.*, **16**, 2597 (1883).
6) H.Z. Lecher, R.P. Parker and R.C. Conn, *J. Am. Chem. Soc.*, **66**, 1959 (1944).

TABLE IV. N^2-Pyrimidinyl-3-oxo-butyrohydrazide $CH_3COCH_2CONHNH-R$

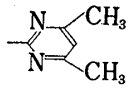
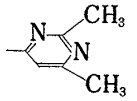
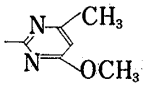
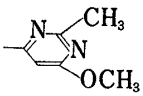
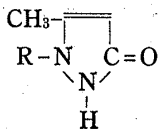
R	mp (°C)	Yield (%)	IR $\nu_{C=O}^{KBr}$ cm^{-1}	Formula	Analysis (%) Calcd. C	H	N	Found C	H	N
	176 (d)	61.7	1658 (vs) 1719 (s)	$C_{10}H_{14}O_2N_4$	54.04	6.35	25.21	54.27	6.53	25.49
	173 (d)	63.0	1666 (vs) 1725 (s)	$C_{10}H_{14}O_2N_4$	54.04	6.35	25.21	54.16	6.51	25.42
	155 (d)	52.0	1658 (vs) 1720 (s)	$C_{10}H_{14}O_3N_4$	50.40	5.88	23.48	50.64	5.60	23.83
	179 (d)	70.1	1660 (vs) 1710 (s)	$C_{10}H_{14}O_3N_4$	50.40	5.88	23.48	50.60	6.10	23.75
	168 (d)	49.0	1690 (vs) 1720 (sh)	$C_8H_{10}O_2N_4$	49.44	5.18	28.88	49.56	5.52	28.57

TABLE V. 2-Pyrimidinyl-3-methylpyrazolin-5-ones 

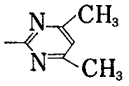
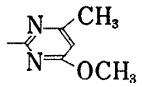
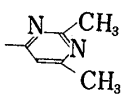
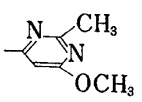
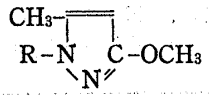
No.	R	mp (°C)	Yield (%)	Formula	Analysis (%) Calcd. C	H	N	Found C	H	N
31		242	82.5	$C_{10}H_{12}ON_4$	58.81	5.92	27.44	58.63	6.00	27.32
32		229	89.0	$C_{10}H_{12}O_2N_4 \cdot H_2O$	50.42	5.92	23.52	50.40	5.76	23.34
33		215	78.3	$C_8H_8ON_4$	54.54	4.58	31.80	54.61	4.55	31.24
34		193	84.0	$C_{10}H_{12}ON_4$	58.81	5.92	27.44	59.08	6.11	27.22
35		198	84.2	$C_{10}H_{12}O_2N_4$	54.54	5.49	25.44	54.40	5.63	25.86

Table VI. 2-Pyrimidinyl-3-methyl-5-methoxypyrazoles



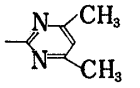
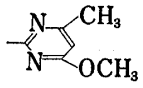
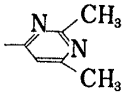
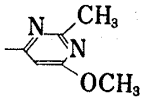
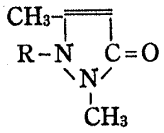
No.	R	mp (°C)	Yield (%)	Formula	Analysis (%) Calcd. C	H	N	Found C	H	N
36		75—76	25.9	$C_{11}H_{14}ON_4$	60.53	6.47	25.67	60.74	6.45	25.35
37		102	44.8	$C_{11}H_{14}O_2N_4$	56.40	6.02	23.91	56.51	6.18	23.95
38		94—96	31.0	$C_9H_{10}ON_4$	56.83	5.30	29.46	56.57	5.39	29.22
39		48—50	53.0	$C_{11}H_{14}ON_4$	60.53	6.47	25.67	60.72	6.61	25.68
40		76—78	52.8	$C_{11}H_{14}O_2N_4$	56.40	6.02	23.91	56.48	6.30	24.59

Table VII. 2-Pyrimidinyl-1,3-dimethyl-3-pyrazolin-5-ones



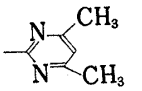
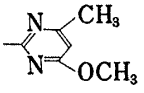
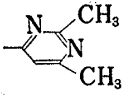
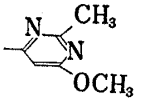
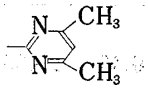
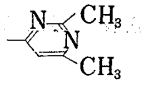
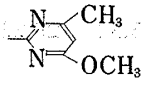
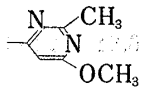
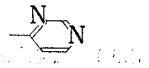
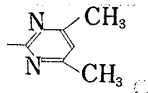
No.	R	mp (°C)	Yield (%)	IR $\nu_{C=O}^{KBr}$ cm^{-1}	Formula	Analysis (%) Calcd. C	H	N	Found C	H	N
41		111—113	39.0	1667 (vs)	$C_{11}H_{14}ON_4$	60.53	6.47	25.67	61.09	6.67	25.72
42		116—118	13.2	1668 (vs)	$C_{11}H_{14}O_2N_4$	56.40	6.02	23.91	56.42	5.99	23.53
43		141—142	27.0	1662 (m) 1683 (vs)	$C_{11}H_{14}ON_4$	60.53	6.47	25.67	60.83	6.43	25.60
44		122—124	18.9	1643 (vs)	$C_{11}H_{14}O_2N_4$	56.40	6.02	23.91	56.51	5.98	24.25

TABLE VIII. N^2-Pyrimidinyl-3-aminocrotonohydrazides (XI) and N^2-Pyrimidinyl-3-methylaminocrotonohydrazides (XII)

CH_3–C=CH CONHNH–R
HN–R′

R	R′	mp (°C)	Yield (%)	IR $\nu_{C=O}^{KBr}$ cm^{-1}	Formula	Analysis (%) Calcd. C	H	N	Found C	H	N
	H	194 (d)	84	1620 1650 (sh)	$C_{10}H_{15}ON_5$	54.40	6.84	31.60	54.44	6.97	31.47
	H	162 (d)	91	1620 (sh) 1655 (sh)	$C_{10}H_{15}ON_5$	54.40	6.84	31.60	54.53	7.02	31.63
	H	174 (d)	87	1625 (sh) 1650 (sh)	$C_{10}H_{15}O_2N_5$	50.70	6.37	29.51	50.37	6.37	29.88
	H	137 (d)	95	1628 1650 (sh)	$C_{10}H_{15}O_2N_5$	50.70	6.37	29.51	51.14	6.21	29.84
	H	173 (d)	89	1631 (sh) 1654 (sh)	$C_8H_{11}ON_5$	49.73	5.74	36.25	50.01	5.93	36.23
	CH_3	159 (d)	64.5	1637 1655 (sh)	$C_{11}H_{17}O_2N_5$	52.60	6.77	27.90	52.90	6.85	28.11

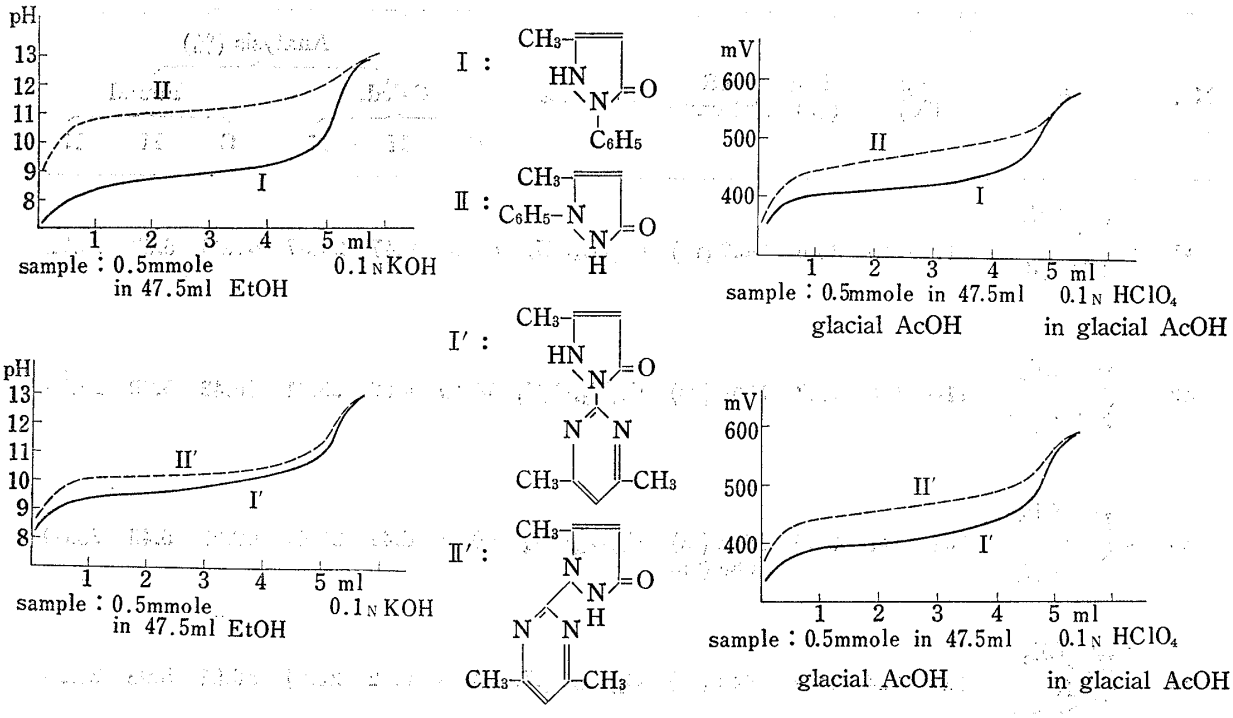


Fig. 1. Potentiometric Titration for Comparison of 1- and 2-Substd.-pyrazolin-5-ones

3350—3400 cm^{-1} regions) and NMR spectra (a proton signal of C_2 at 4.42 ppm in $DMSOd_6$) to be N^2-pyrimidinyl-3-aminocrotonohydrazides (XI) and N^2-pyrimidinyl-3-methylaminocrotonohydrazides (XII). On heating in water, they were converted to the same compound (VII). Melting points and yields of VI, VII, VIII, IX, XI, and XII obtained here are shown in Tables IV—VIII.

The synthesized compounds were tested for analgesic, antipyretic, and anti-inflammatory activity. The compound No. 13 showed the strongest analgesic and anti-inflammatory action. Detailed pharmacological studies will be reported in part IV of this series.

Physical Properties

The potentiometric titration and UV absorption spectra of III and VII were compared with those of 1-phenyl-3-methylpyrazolin-5-one and 2-phenyl-3-methylpyrazolin-5-one.

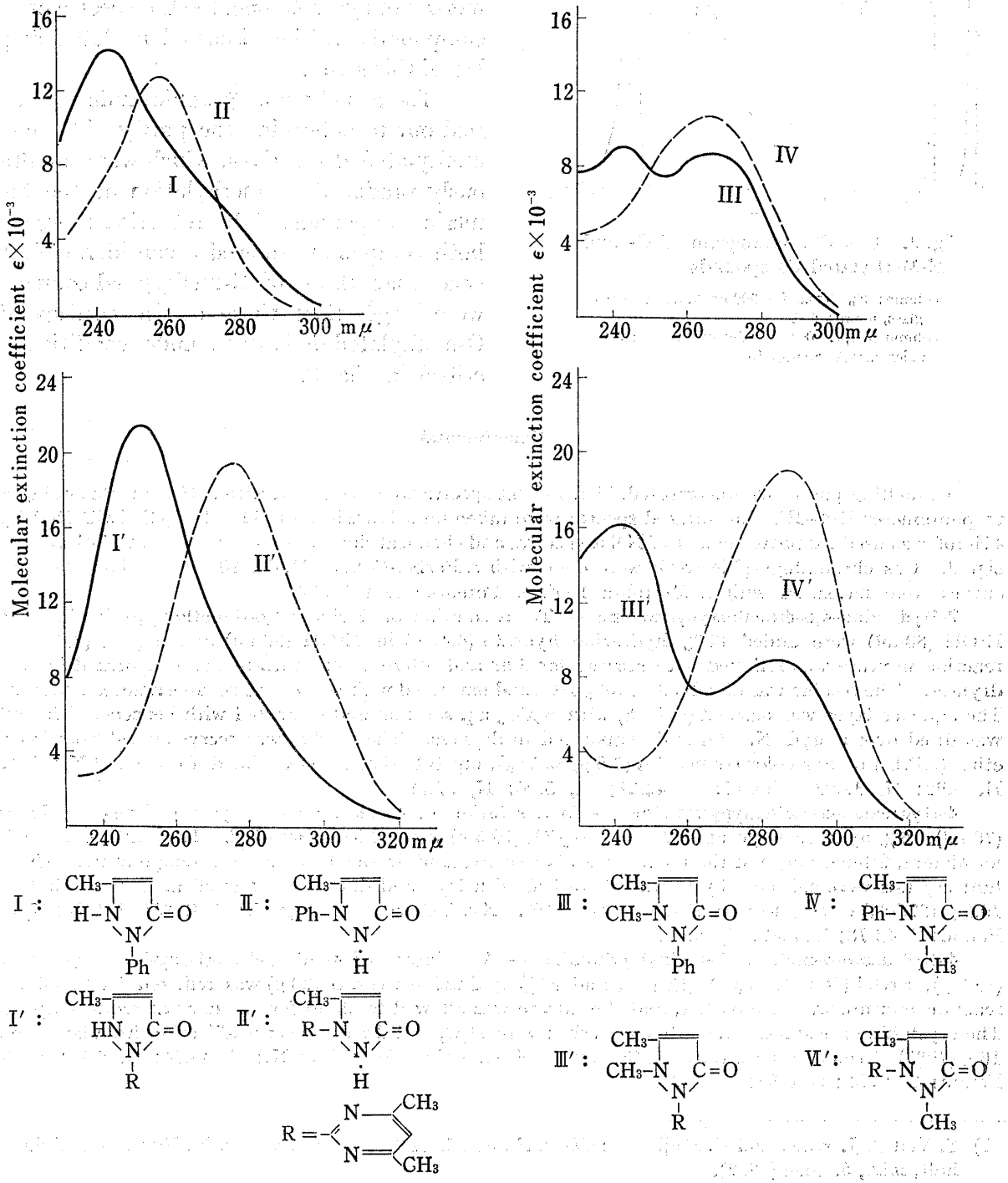


Fig. 2. UV Spectra for Comparison of 1- and 2-Substd.-pyrazolin-5-ones in MeOH

These results are shown in Fig. 1 and 2. Previously, Veibel, *et al.*[7] reported that 1-phenylpyrazolin-5-one was not only a stronger acid but also a stronger base than 2-phenyl derivative from the results of the potentiometric titrations. Similar titrations of 1- and 2-pyrimidinylpyrazolin-5-ones were examined, and they obviously exhibited the same tendency as 1- and 2-phenyl analogs, respectively, in acidity and basicity.

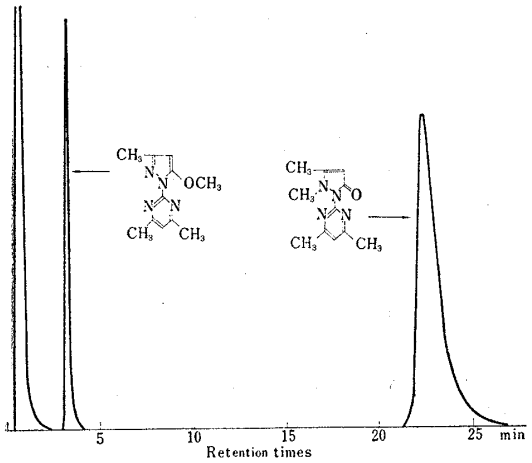


Fig. 3. Gas Chromatogram of O- and N-Methylated Compounds

column: 2% Versamide 900 on Anakrom ABS glass, 6 mm×6 ft
column temp.: 200° detector temp.: 210°
carrier gas: Ar 80 ml/min

The UV spectra of 1- and 2-pyrimidinylpyrazolin-5-ones in methanol solution provided a result similar to that of 1- and 2-phenyl derivatives, the 2-substituted derivatives absorbing in a longer wavelength than 1-substituted derivatives. In connection with tautomerism of pyrazolinone, the UV spectra of these compounds will be discussed in detail in part III of this series.

The gas chromatographic studeis were carried out to determine the purity of O- and N-methylated derivatives, which were simultaneously produced by methylation of the tautomeric compounds. The retention times of the both compounds showed a considerable difference that those of N-methylated compounds were longer than those of the corresponding O-methylated derivatives under conditions described in Fig. 3.

Experimental

All melting points are uncorrected. Ultraviolet spectra were measured with a Hitachi Recording Spectrophotometer EPS-2U, and infrared spectra were taken on a Hitachi EPI-G2. The JEOLCO Model JNM 4H-100 was used for measurement of NMR spectra, and chemical shift showed in ppm from TMS as standard signal. Gas chromatographic work were done with a Barber-Colman Model 10. Potentiometric titration curves were measured with a Metrohm Herisau Potentiograph E-336.

2-Hydrazino-4,6-dimethoxypyrimidine——To a solution of 2-chloro-4,6-dimethoxypyrimidine (9 g) in EtOH (80 ml) were added 80% hydrazine hydrate (6.45 g) in EtOH (50 ml) and K_2CO_3 (3.6 g). The reaction mixture was refluxed with stirring for 3 hr and filtered. The filtrate was evaporated *in vacuo* to dryness. The residue was dissolved in 10% HCl, and extracted with benzene to remove a unreacted material. The aqueous layer was basified (pH=8) with K_2CO_3 aq. solution and extracted with benzene. The extract was dried over anhyd. Na_2SO_4 and evaporated to dryness. The residue was recrystallized from isopropyl ether (I.P.E.) to give colorless needles (7.5 g, 85.7%), mp 101—104°. *Anal.* Calcd. for $C_6H_{10}O_2N_4$: C, 42.35; H, 5.92; N, 32.93. Found: C, 42.21; H, 5.96; N, 32.59.

4-Hydrazino-6-methoxypyrimidine——To a solution of 4-chloro-6-methoxypyrimidine (83 g) in EtOH (70 ml), 80% hydrazine hydrate (72 g) and K_2CO_3 (79.5 g) were added at 60—70°. The mixture was refluxed for 40 min, filtered hot, and the filtrate was allowed to stand for one hour at room temperature. The resultant crystals were collected by filtration, washed with H_2O and dried. Recrystallization from EtOH gave 70.5 g (87.5%) of colorless needles, mp 148—149°. *Anal.* Calcd. for $C_5H_8ON_4$: C, 42.85; H, 5.75; N, 39.98. Found: C, 42.78; H, 5.82; N, 39.61.

4-Hydrazino-6-methoxy-2-methylpyrimidine——A mixture of 4-chloro-6-methoxy-2-methylpyrimidine (13.7 g), EtOH (50 ml), K_2CO_3 (12.1 g), and 80% hydrazine hydrate (20 g) was refluxed for 20 min. The reaction mixture was filtered hot, and the filtrate was allowed to stand for one hour at room temperature. The crystalline precipitate was filtered, washed with H_2O, and dried. Recrystallization from benzene gave 10 g (79%) of colorless needles, mp 148—149°. *Anal.* Calcd. for $C_6H_{10}ON_4$: C, 46.74; H, 6.54; N, 36.34. Found: C, 46.58; H, 6.53; N, 36.24.

7) S. Veibel, J. Kjaer and E. Plejl, *Acta Chem. Scand.*, **5**, 1283 (1951); S. Veibel, K. Eggersen and S.C. Linholt, *ibid.*, **6**, 1066 (1952).
8) H. Vanderhaeghe and M. Claesen, *Bull. Soc. Chim. Belg.*, **68**, 30 (1959).

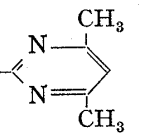
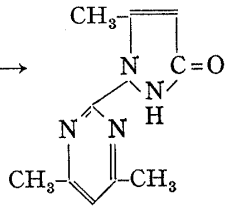
2-Hydrazino-4-methoxy-6-methylpyrimidine and 4-Hydrazino-2-methoxy-6-methylpyrimidine——To a solution of crude 2-chloro-4-methoxy-6-methylpyrimidine (50 g) in EtOH (100 ml), which was prepared from 2,4-dichloro-6-methylpyrimidine according to the method of Vandehaeghe, *et al.*[8] were added 80% hydrazine hydrate (64.5 g) in EtOH (200 ml) and K_2CO_3 (43.5 g). The mixture was refluxed with stirring for 3 hr, filtered hot, and the filtrate was allowed to stand for one hour at room temperature. The resultant crystals were collected, washed with a small amount of H_2O, and dried. Recrystallization from EtOH gave 35.2 g (72.5%) of 2-hydrazino-4-methoxy-6-methylpyrimidine as colorless needles, mp 113—114° (Lit.[9] mp 112.5—114°). From the mother liquor obtained by filtration of pure 2-hydrazino-4-methoxy-6-methylpyrimidine, 4-hydrazino-2-methoxy-6-methylpyrimidine was obtained in a poor yield. mp 154—156°. *Anal.* Calcd. for $C_6H_{10}ON_4$: C, 46.74; H, 6.54; N, 36.34. Found: C, 46.83; H, 6.51; N, 36.50.

1-Pyrimidinyl-3-methylpyrazolin-5-one Derivatives (III) (Table I)——A mixture of 2- or 4-hydrazinopyrimidine derivative (1 mole), equal volume of MeOH and ethyl acetoacetate (1.1 mole) was refluxed for 2 hr. To the mixture was added 3N NaOH (1.1 mole), and the mixture was refluxed for 10—60 min and evaporated *in vacuo* to syrup which was dissolved in H_2O and neutralized with AcOH. The crystalline precipitate was filtered, washed with H_2O, and dried. The crude product was obtained in 90—97% yield. Recrystallization from I.P.E. or benzene gave III as colorless needles. The yield was 65—85%.

Methylation of 1-Pyrimidinyl-3-methylpyrazolin-5-one Derivatives (III) (Tables II and III)——Method A: To a solution of III (0.2 mole) in 3 times volumes of dimethylformamide or MeOH were added a solution of sodium methoxide (Na, 0.6 gram atom in 250 ml of MeOH), and dimethyl sulfate (0.6 mole) at 35—45° with stirring. The mixture was refluxed for 4 hr. After removal of the solvent *in vacuo*, the syrup obtained was dissolved in H_2O (600 ml), basified with 10% NaOH, and extracted 3 times with 400 ml portions of benzene. The combined extract was dried over anhyd. Na_2SO_4, and removal of the solvent afforded a yellow syrup which was distilled. The distillate solidified on standing, and the solid was recrystallized from isopropyl ether to give 1-pyrimidinyl-3-methyl-5-methoxypyrazole derivatives (IV) in 40—48% yield.

Method B: To a solution of III (15 mmole), MeOH (50 ml) and NaOH (32 mmole) was added dropwise dimethyl sulfate (32 mmole) at 60° with stirring, and the mixture was refluxed for 2.5 hr. After removal of the solvent, the residue was dissolved in H_2O (30 ml), basified with 10% NaOH, and extracted with benzene (200 ml). The extract was dried over anhyd. Na_2SO_4 and evaporated. The residue was dissolved in a small amount of benzene, chromatographed on neutral Al_2O_3 (30 g). The column was eluted initially with cyclohexane and then benzene. The first fraction eluted with cyclohexane afforded 1-pyrimidinyl-3-methyl-5-methoxypyrazole derivatives (IV) and the second fraction eluted with benzene gave 1-pyrimidinyl-2,3-dimethyl-3-pyrazolin-5-one derivatives (V).

Method C: To a solution of III (1 g), MeOH (1 ml), and ether (9 ml) was added a large excess of diazomethane–ether solution. The mixture was allowed to stand for 3 hr at room temperature. After decomposing the excess diazomethane with a small amount of AcOH. The ether solution was evaporated, and the residue was chromatographed on neutral Al_2O_3 (15 g). Fractions eluted with cyclohexane were recrystallized from isopropyl ether to give IV in yield 45—50%.

Table IX. $CH_3COCH_2CONHNH$–  ⟶ 

Bases	Reaction conditions		Yield (%)
	Temp. (°C)	Times	
NH_4OH	90—100	30 min	82.5
CH_3NH_2	90—100	30 min	73.5
$(CH_3)_2NH$	25	12 hr	75.5
$(CH_3)_3N$	25	48 hr	72.0
Aniline	25	48 hr	22.6
Piperidine	25	24 hr	54.0
$NaHCO_3$	80—90	60 min	63.3
Na_2CO_3	80—90	60 min	49.0
NaOH	80—90	60 min	55.0
$Ca(OH)_2$	80—90	60 min	31.8

9) K. Shirakawa, S. Ban, and M. Yoneda, *Yakugaku Zasshi*, 73, 598 (1953).

N^2-Pyrimidinyl-3-oxobutyrohydrazide Derivatives (VI) (Table IV)——A suspension of I (10 mmole) in dioxane (5 ml) was added dropwise to a solution of ketene dimer (10.5 mmole) in dioxane (5 ml) with vigorous stirring at 5—10°. The mixture was heated then at 60—70° for 5—30 min until a clear solution was obtained, and the mixture was cooled or concentrated *in vacuo* rapidly. The precipitated crystals were collected and recrystallized from EtOH or acetone–EtOH. The yield was 52—70%.

General Synthetic Procedure of 2-Pyrimidinyl-3-methylpyrazolin-5-ones (VII) (Tables V and IX)——A mixture of VI (1 g) and 20% NH_4OH (5 ml) was stirred at 90—100° for 30 min and concentrated *in vacuo*. The concentrate was acidified with acetic acid and the crystalline precipitate was filtered, washed with H_2O, and dried. The yield was 78—89%. The results of a typical example of this reaction under various conditions were shown in Table IX.

N^2-(4,6-Dimethyl-2-pyrimidinyl)-3-[1-(4,6-dimethyl-2-pyrimidinyl)]-hydrazonobutyrohydrazide (X)——To a stirred solution of ketene dimer (0.1 mole) in dioxane (50 ml), a suspension of 2-hydrazino-4,6-dimethylpyrimidine (0.2 mole) in dioxane (100 ml) was added dropwise at 20—25° and stirred for another 2 hr at the same temperature. The solvent was evaporated *in vacuo*, and a small amount of H_2O was added to the concentrate. The precipitated crystals were collected and recrystallized from acetone–EtOH rapidly to give X as colorless needles, mp 134—135° (decomp.). *Anal.* Calcd. for $C_{16}H_{22}ON_8 \cdot 1.5H_2O$: C, 52.02; H 6.82; N, 30.33. Found: C, 51.88; H, 6.93; N, 30.75.

Reaction of X with Alkali——A mixture of X (2 mmoles), 10% NaOH (2 ml) and EtOH (2 ml) was heated at 90° for 30 min and evaporated *in vacuo*. The residue was dissolved in H_2O (10 ml) and extracted with $CHCl_3$ to remove a liberated 4,6-dimethyl-2-hydrazinopyrimidine. The aqueous layer was acidified with AcOH and extracted with $CHCl_3$. The extract was dried over anhyd. Na_2SO_4 and evaporated to give 1-(4,6-dimethyl-2-pyrimidinyl)-3-methylpyrazolin-5-one, mp 112°. The yield was 80%.

Reaction of X with conc. HCl——X (2 mmoles) was dissolved in conc. HCl (1 ml) and the mixture was allowed to stand overnight at room temperature. The precipitated crystals were collected by filtration. The HCl salt of 2-(4,6-dimethyl-2-pyrimidinyl)-3-methylpyrazolin-5-one thus obtained was dissolved in H_2O and adjusted to pH 4 to afford free 2-(4,6-dimethyl-2-pyrimidinyl)-3-methylpyrazolin-5-one. The yield from X was *ca.* 35%.

N^2-Pyrimidinyl-3-aminocrotonohydrazides (XI) and N^2-Pyrimidinyl-3-methylaminocrotonohydrazides (XII) (Table VIII)——VI (1 g) was dissolved in 20% aqueous ammonia (5 ml) or aqueous monomethylamine (5 ml), allowed to stand for 1—2 hr at room temperature. The precipitated crystals were filtered, washed with H_2O, and dried. XI or XII was obtained as prisms in a good yield.

Preparation of VII from XI or XII——A suspension of XI (or XII) (1 g) in H_2O (10 ml) was heated for 30 min at 80—90°. After cooling, the mixture was adjusted to pH 4 with AcOH and the precipitated crystals were collected, washed with water and dried. The yield was 78—89%.

Methylation of 2-Pyrimidinyl-3-methylpyrazolin-5-one Derivatives (VII) (Tables VI and VII)——Methylation of VII was carried out in a manner similar to Method B described above for II.

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