Summary

The behaviors of various 4,5-di- and 3,4,5-trisubstituted 1-phenyl-6(1*H*)-pyridazinone against caustic alkali and hydrobromic acid were investigated. From these data, the mechanism of the ring-contraction from pyridazinone to pyrazolone, as shown in Chart 1, was discussed. Action of 1-phenyl-4,5-dichloro-6(1*H*)-pyridazinone with boiling caustic alkali took place the ring-contraction to give unexpected 1-phenyl-3-hydroxy-5-pyrazolecarboxylic acid. The mechanism of this reaction was also assumed as shown in Chart 4. Moreover, the reactivity of chlorines on 1-phenyl-3,4,5-trichloro-6(1*H*)-pyridazinone was elucidated to increase in the order 4-, 5-, 3-position from the result of its methoxylation reaction.

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25. Jiro Kinugawa, Michihiko Ochiai, Chikashi Matsumura, and Hiroichi Yamamoto : Studies on Fungicides. VII.*1 Synthesis and Antifungal Activity of Some Pyrazole Derivatives.*2

(*Research Laboratories, Takeda Chemical Industries, Ltd.**3)

The preceding paper*1 described the synthesis of various 4-thiocyanato- and 4-carbamoylthio-pyrazoles and di(4-pyrazolyl)disulfides.

In this paper, the syntheses of some thiocyanatopyrazoles and 4-mercaptopyrazole derivatives and the antifungal activities of these compounds as well as those described in the preceding paper are recorded.

The impetus for undertaking these studies arose from the early observations of McNew, *et al.*,[1] who reported the antifungal activity of 4-nitrosopyrazoles, and that of Kosuge and Okeda,[2] who reported that 3-alkylpyrazoles have a similar antimicrobial activity.

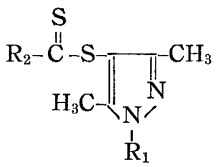
Synthesis of Pyrazole Derivatives

Thiocyanatopyrazoles and 4-mercaptopyrazole derivatives were synthesized according to the scheme shown in Chart 1.

3-Methyl-4-thiocyanato-2-pyrazolin-5-one (II) was obtained by the reaction of 3-methyl-4-bromo-2-pyrazolin-5-one (I) with ammonium thiocyanate. Treatment of the sodium salt of 1-phenyl-3-methyl-4-benzoyl-5-mercaptopyrazole (III) with cyanogen bromide afforded 1-phenyl-3-methyl-4-benzoyl-5-thiocyanatopyrazole (IV). S-Diacetylmethyl alkyl dithiocarbonates (VIIa) and diacetylmethyl N,N-disubstituted dithiocarbamates (VIIb) were obtained by the reaction of 3-chloro-2,4-pentanedione (VI) with alkyl xanthates

*1 Part VI : This Bulletin, **12**, 23 (1964).
*2 This paper was presented at the Kinki Branch Meeting of Pharmaceutical Society of Japan, Kyoto, June, 1963.
*3 Juso-nishino-cho, Higashiyodogawa-ku, Osaka (衣川二郎, 落合道彦, 松村 親, 山本弘一).
1) G.L. McNew, N.K. Sundholm : Phytopathology, **39**, 721 (1949).
2) T. Kosuge, H. Okeda : J. Biochem., **41**, 183 (1954), etc.

TABLE I. 4-(N,N-Disubstituted thiocarbamoylthio)- and 4-Alkoxythiocarbonylthiopyrazoles



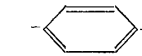
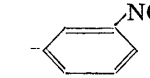
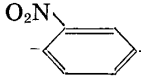
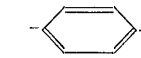
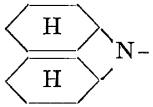
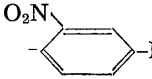
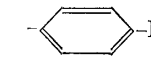
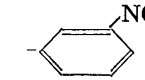
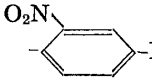
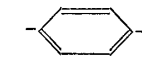
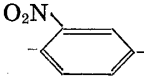
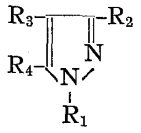
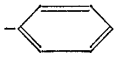
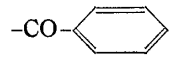
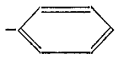
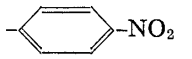
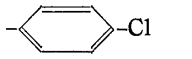
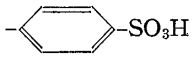
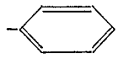
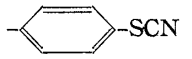
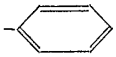
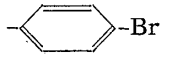
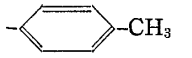
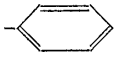
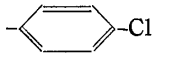
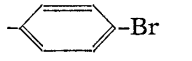
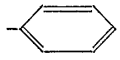
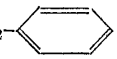
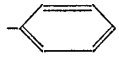
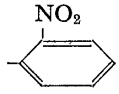
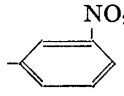
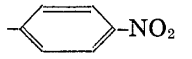
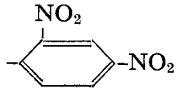
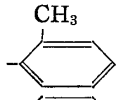
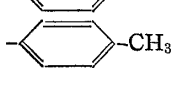
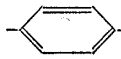
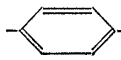
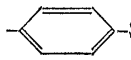
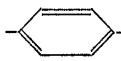
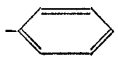
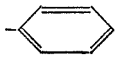
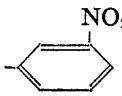
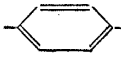
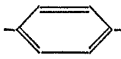
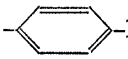
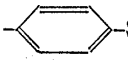
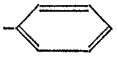
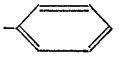
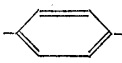
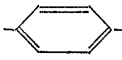
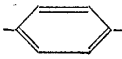
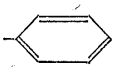
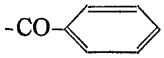
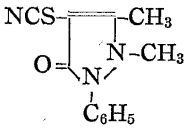
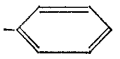
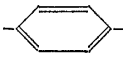
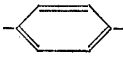
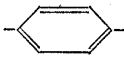
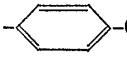
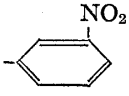
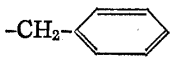
R_1	R_2	m.p. (°C)	Yield (%)	Recrystallization solvent	Appearance	Formula	Analysis					
							Calcd.			Found		
							C	H	N	C	H	N
H	$(CH_3)_2N$-	171.5～172.5	88	dil. MeOH	colorless needles	$C_8H_{13}N_3S_2$	44.63	6.08	—	44.52	6.19	—
	〃	137～139	80	EtOH	greenish prisms	$C_{14}H_{16}O_2N_4S_2$	49.98	4.79	—	50.32	4.88	—
	〃	139～140	89	MeOH	yellow prisms	〃	49.98	4.79	—	49.92	4.82	—
	〃	183～184	89	〃	〃	$C_{14}H_{15}O_4N_5S_2$	44.09	3.96	—	44.17	3.99	—
	〃	125～126	62	EtOH	colorless prisms	$C_{14}H_{16}N_3ClS$	51.60	4.91	—	51.71	5.20	—
H	$(C_2H_5)_2N$-	123～124	87	benzene-hexane	colorless needles	$C_{10}H_{17}N_3S_2$	49.36	7.04	17.27	49.26	7.15	16.96
〃		187～188	76	〃	colorless crystals	$C_{18}H_{27}N_3S_2$	61.85	7.78	—	61.54	8.33	—
	〃	141～142	78	EtOH	yellow needles	$C_{24}H_{29}O_4N_5S_2$	55.90	5.66	13.58	55.98	5.78	13.36
	C_2H_5O-	88～89.5	81	MeOH	yellow crystals	$C_{14}H_{15}O_3N_3S_2$	49.83	4.48	—	49.70	4.72	—
	〃	73～75	62	benzene-hexane	yellow needles	〃	—	—	12.45	—	—	12.21
	〃	127～129	52	〃	yellow crystals	$C_{14}H_{14}O_5N_4S_2$	43.96	3.63	—	44.35	4.13	—
	$(CH_3)_2CHO$-	91.5	57	EtOH	yellowish prisms	$C_{15}H_{17}O_3N_3S_2$	51.26	4.87	11.95	50.93	5.00	11.66
	〃	102～103	51	benzene-hexane	yellow crystals	$C_{15}H_{16}O_5N_4S_2$	45.44	4.06	—	45.12	4.39	—

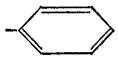
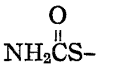
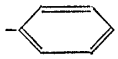
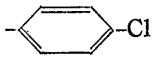
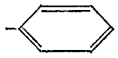
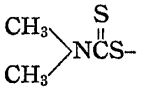
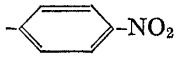
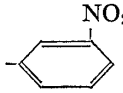
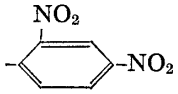
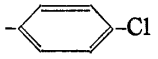
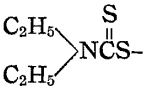
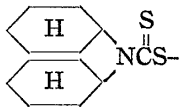
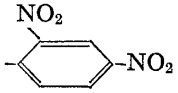
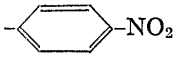
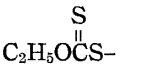
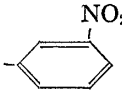
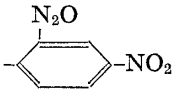
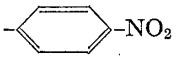
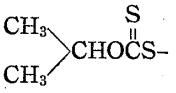
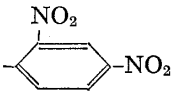
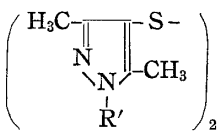
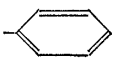
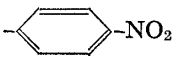
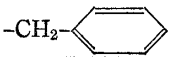
TABLE II. Antifungal Activity of Pyrazole Derivatives
(Minimum Inhibitory Concentration (μg./ml.))



No.	R_1	R_2	R_3	R_4	*Piricularia oryzae*	*Phytophthora infestans*	*Colletotrichum lagenarium*
1	H	$-CH_3$	H	$-CH_3$	>100	>100	>100
2	〃	〃	Br	〃	>100	>100	>100
3	$-CH_3$	〃	H	〃	>100	>100	>100
4	$-CH_2-C_6H_5$	〃	〃	〃	100	>100	100
5	$-C_6H_5$	〃	〃	〃	>100	>100	>100
6	$-C_6H_4(NO_2)$	〃	〃	〃	>100	>100	>100
7	$-C_6H_4(NO_2)$	〃	〃	〃	< 3.9	>100	< 3.9
8	$-C_6H_4-NO_2$	〃	〃	〃	>100	>100	>100
9	$-C_6H_3(NO_2)-NO_2$	〃	〃	〃	< 3.9	>100	< 3.9
10	$-C_6H_4(CH_3)$	〃	〃	〃	>100	>100	>100
11	$-C_6H_4-CH_3$	〃	〃	〃	>100	>100	>100
12	$-C_6H_4-Cl$	〃	〃	〃	50	>100	100
13	$-C_6H_4-SO_3H$	〃	〃	〃	50	>100	50
14	$-C_6H_4-OH$	〃	〃	〃	>100	>100	>100
15	$-C_6H_4(NO_2)$	〃	〃	$-C_6H_5$	62.5	>100	62.5
16	$-C_6H_4(NO_2)$	〃	〃	〃	>100	>100	>100
17	$-C_6H_3(NO_2)-NO_2$	〃	〃	$-CH_3$	>100	>100	>100
18	$-C_6H_3(NO_2)-NO_2$	〃	〃	〃	>100	>100	>100
19	$-CONH_2$	〃	〃	〃	>100	>100	>100
20	〃	$-C_6H_5$	〃	〃	50	>100	50
21	$-COCH_2CN$	$-CH_3$	〃	〃	>100	>100	>100
22	$-CO-C_6H_5$	〃	〃	〃	100	>100	100
23	$-C_6H_5$	H	$-CO_2C_2H_5$	$-OH$	>100	>100	>100
24	〃	〃	〃	$-CH_3$	62.5	>100	>100
25	〃	〃	〃	$-NH_2$	>100	>100	>100

26		H	H	$-NH_2$	100	>100	100
27	〃	$-CH_3$	〃	Cl	>100	>100	100
28	〃	〃		〃	>100	>100	>100
29	〃	〃	〃	-SH	>100	>100	>100
30	H	〃	H	-OH	>100	>100	>100
31	〃	〃	Br	〃	15.62	62.5	62.5
32		〃	H	〃	>100	>100	>100
33	〃	〃	Br	〃	62.5	>100	62.5
34		〃	H	〃	100	>100	50
35		〃	〃	〃	100	>100	100
36		〃	〃	〃	>100	>100	>100
37		$-NH_2$	〃	〃	100	>100	100
38		$-CH_3$	〃	$-CH_3$	10	15	7.5
39	〃	〃	〃		< 3.12	>100	6.25
40	〃	〃	〃	-OH	100	>100	100
41		〃	〃	$-CH_3$	100	>100	100
42		〃	〃		12.5	>100	12.5
43		〃	〃	〃	100	>100	100
44		〃	〃	〃	6.25	>100	25
45		H	-CN	$-NH_2$	>100	>100	>100
46	H	$-CH_3$	-SCN	$-CH_3$	>100	100	100
47	$-CH_3$	〃	〃	〃	50	>100	50
48	$-CH_2-$ 	〃	〃	〃	50	100	25
49		〃	〃	〃	31.25	62.5	31.25
50		〃	〃	〃	12.5	>100	25
51		〃	〃	〃	< 3.9	< 3.9	< 3.9
52		〃	〃	〃	31.25	>100	15.62
53		〃	〃	〃	50	>100	100
54		〃	〃	〃	6.25	>100	25
55		〃	〃	〃	100	>100	100

56		$-CH_3$	-SCN	$-CH_3$	12.5	>100	25
57		〃	〃	〃	6.25	>100	>100
58		〃	〃	〃	>100	>100	>100
59		〃	〃	〃	< 3.12	100	< 3.12
60	$-CONH_2$	〃	〃	〃	50	100	50
61		〃	〃		12.5	>100	50
62		〃	〃	〃	12.5	>100	12.5
63		〃	〃	〃	25	>100	100
64		〃	〃	〃	50	>100	100
65		〃	〃	〃	12.5	>100	12.5
66		〃	〃	〃	12.5	>100	100
67		H	〃	$-NH_2$	12.5	100	12.5
68	H	$-CH_3$	〃	-OH	>100	>100	>100
69		〃	〃	〃	>100	>100	>100
70		〃	〃	〃	100	>100	100
71		〃	〃	〃	>100	>100	>100
72		〃	〃	〃	>100	>100	>100
73		$-NH_2$	〃	〃	>100	>100	>100
74	〃	$-CH_3$		-SCN	>100	>100	>100
75					>100	>100	>100
76		$-CH_3$	$NH_2\overset{O}{\overset{\|}{C}}S-$	$-CH_3$	12.5	>100	>100
77		〃	〃	〃	50	>100	>100
78		〃	〃	〃	>100	>100	>100
79		〃	〃	〃	>100	>100	>100
80		〃	〃	〃	100	>100	>100
81		〃	〃	〃	>100	>100	>100
82		〃	〃	〃	100	>100	>100

83		$-CH_3$			>100	>100	>100
84		〃	〃	〃	>100	>100	>100
85		〃	〃	-OH	>100	>100	>100
86	H	〃		$-CH_3$	>100	>100	>100
87		〃	〃	〃	>100	>100	>100
88		〃	〃	〃	>100	>100	>100
89		〃	〃	〃	>100	>100	>100
90		〃	〃	〃	50	>100	50
91	H	〃		〃	100	>100	>100
92	〃	〃		〃	>100	>100	>100
93		〃	〃	〃	100	>100	100
94		〃		〃	6.25	>100	50
95		〃	〃	〃	6.25	>100	>6.25
96		〃	〃	〃	25	>100	50
97		〃		〃	6.25	>100	>100
98		〃	〃	〃	< 3.12	>100	>100
	 R′						
99					6.25	>100	>100
100					>100	>100	>100
101					25	—	>100

4-Thiocyanato-2-pyrazolin-5-ones are represented in the enol form.

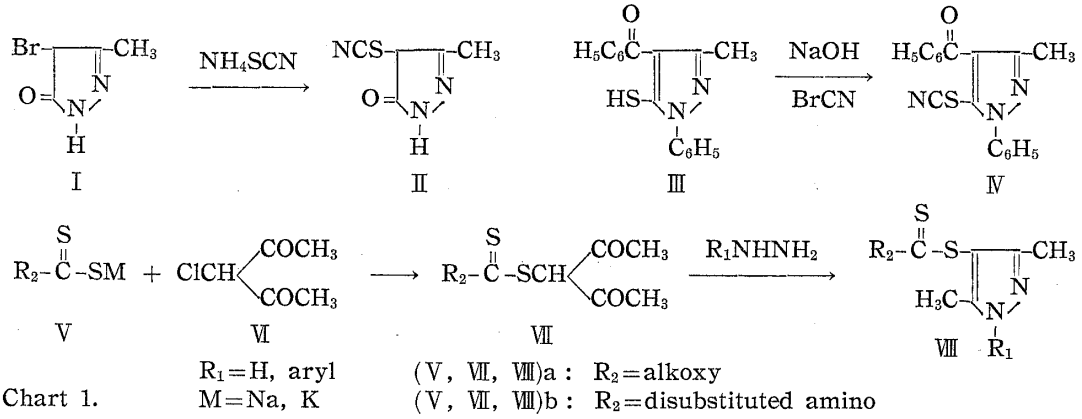


Chart 1.

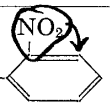
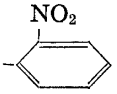
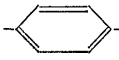
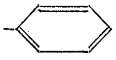
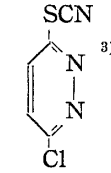
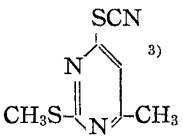
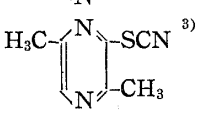
R_1=H, aryl (V, Ⅶ, Ⅷ)a : R_2=alkoxy
M=Na, K (V, Ⅶ, Ⅷ)b : R_2=disubstituted amino

(Va) and N,N-disubstituted dithiocarbamates (Vb) respectively. On treatment with hydrazines, Ⅶa and Ⅶb gave 4-alkoxythiocarbonylthio-3,5-dimethylpyrazoles (Ⅷa) and 4-(N,N-disubstituted thiocarbamoylthio)-3,5-dimethylpyrazoles (Ⅷb) respectively in good yields. The list of the compounds thus obtained and their production yields are given in Table I.

Antifunagl Activity

Antifungal activities of these compounds and those synthesized in the preceding paper were tested against *Piricularia oryzae, Phytophthora infestans, Colletotrichum la-*

Table Ⅲ. Antifungal Activity of Pyrazole Derivatives and Related Compounds (Minimum Inhibitory Concentration (μg./ml.))

No.	Compound	Ⅰ	Ⅱ	Ⅲ	Ⅳ	Ⅴ	Ⅵ	Ⅶ	Ⅷ
51		< 3.9	15.62	< 3.9	< 3.9	< 3.9	< 3.9	< 3.9	31.25
50		12.5			>100	25			
52		31.25	>100	12.5	>100	15.62	31.25	>100	>100
49		31.25	12.5	62.5	62.5	31.25	62.5	31.25	62.5
	 [3]	7.5	2	3.5	1	20	20	20	5
	 [3]	< 5	15	< 5	< 5	< 5	7.5	20	10
	 [3]	7.5	20	5	10	< 5	10	10	15

Ⅰ : *Piriculria oryzae* Ⅱ : *Gibberella fujikuroi* Ⅲ : *Ustilago zeae* Ⅳ : *Phytophthora infestans*
Ⅴ : *Colletotrichum lagenarium* Ⅵ : *Glomerella cingulata* Ⅶ : *Alternaria kikuchiana* Ⅷ : *Candida albicans*

genarium and *Candida albicans*, etc. by the agar streak-dilution method. The results obtained with 101 compounds are summarized in Table II.

As can be seen in the Table, the compounds No. 7, 9, 31, 38, 42, 44, 49, 50, 51, 52, 54, 56, 59, 62, 65, 67, 94, and 95, showed excellent antifungal activities. Among these compounds, No. 51 is most effective. The antifungal spectra of this compound and the related compounds against various other fungi were then tested and the results are shown in Table III.

It is interesting to note that compound No. 51 has the highest antifungal activity in the test and also shows a broad antifungal spectrum, the compound being superior to any of the thiocyanatodiazines which were described in the previous papers.[3]

Experimental[*4]

3-Methyl-4-thiocyanato-2-pyrazolin-5-one (II)——A solution of 1.8 g. of 3-methyl-4-bromo-2-pyrazolin-5-one (I) and 1.5 g. of NH_4SCN in 20 ml. of EtOH was refluxed for 30 min. The reaction mixture was concentrated to about 5 ml. and 20 ml. of H_2O was added. The separated solid was recrystallized from EtOH to colorless needles, m.p. 191~193°; yield, 1.3 g. *Anal.* Calcd. for $C_5H_5ON_3S$: C, 39.36; H, 3.24; N, 27.09. Found: C, 39.45; H, 3.43; N, 27.38.

1-Phenyl-3-methyl-4-benzoyl-5-thiocyanatopyrazole (IV)——To a solution of 1.5 g. of 1-phenyl-3-methyl-4-benzoyl-5-mercaptopyrazole (III) and 0.2 g. of NaOH in 25 ml. of H_2O was added with stirring within 1 min. at 10° a solution of 0.7 g. of BrCN in 6 ml. of EtOH. After a few minutes, the separated solid was collected and recrystallized from benzene-hexane to yellowish crystals, m.p. 126~127°; yield, 1.4 g. *Anal.* Calcd. for $C_{18}H_{13}ON_3S$: C, 67.70; H, 4.10. Found: C, 67.97; H, 4.18.

Table IVa. Dithiocarbonic Acid Derivatives $R-\overset{\overset{S}{\|}}{C}-SCH(COCH_3)_2$

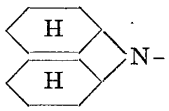
No.		m.p. (b.p.) (C°)	Yield (%)	Recrystallization solvent	Appearance
1	$(CH_3)_2N-$	55~56	71	dil. MeOH	colorless scales
2	$(C_2H_5)_2N-$	44~45	81	dil. EtOH	colorless crystals
3		122	57	dil. Me_2CO	colorless scales
4	C_2H_5O-	(b.$p_{0.02}$ 81~82)	86		yellow oil
5	$(CH_3)_2CHO-$	(b.$p_{0.07}$ 89~91)	83		〃

Table IVb. Analytical Data of Compounds shown in Table IVa

No.	Formula	Calcd.			Found		
		C	H	N	C	H	N
1	$C_8H_{13}O_2NS_2$	43.81	5.97	6.39	43.85	6.11	6.70
2	$C_{10}H_{17}O_2NS_2$	48.56	6.92	5.66	48.50	6.95	5.48
3	$C_{18}H_{27}O_2NS_2$	61.15	7.69	3.96	61.12	8.27	3.84
4	$C_8H_{12}O_3S_2$	43.61	5.49	—	43.23	5.51	—
5	$C_9H_{14}O_3S_2$	46.13	6.02	—	46.03	6.00	—

[*4] All melting points are uncorrected.

3) Part IV: Yakugaku Zasshi, 83, 767 (1963); Part V: *Ibid.*, 83, 1086 (1963).

General Method for Synthesis of S-Diacetylmethyl Alkyl Dithiocarbonate (VIIa) and Diacetylmethyl N,N-disubstituted Dithiocarbamate (VIIb)——To an aqueous solution of a slight excess of alkali salt of alkylxanthic acid (Va) or N,N-disubstituted dithiocarbamic acid (Vb) was added an EtOH solution of 3-chloro-2,4-pentanedione (Ⅵ) in small portions, while the solution was stirred at room temperature. After stirring for further 2 hr., the reaction mixture was left to stand overnight. The separated oil or solid was purified in the usual way. The compounds thus obtained and the yields thereof are shown in Table Ⅳ.

1-(*p*-Nitrophenyl)-4-ethoxythiocarbonylthio-3,5-dimethylpyrazole (No. 94)——To a solution of 4.4 g. (0.02 mole) of S-diacetylmethyl ethyl dithiocarbonate in 20 ml. of EtOH was added 3.1 g. (0.02 mole) of *p*-nitrophenylhydrazine and 0.2 ml. of conc. HCl. The reaction mixture was refluxed for 30 min. and 30 ml. of H_2O was added after cooling. The separated oil solidified on standing, which was recrystallized from MeOH to yield yellow crystals. Analytical data and other 4-alkoxythiocarbonylthio-3,5-dimethylpyrazoles obtained in a similar way are listed in Table I.

4-(N,N-Dimethylthiocarbamoylthio)-3,5-dimethylpyrazole (No. 86)——To a solution of 3 g. of diacetylmethyl N,N-dimethyldithiocarbamate in 10 ml. of EtOH was added dropwise 0.9 g. of hydrazine hydrate. The reaction mixture was refluxed for 10 min. and 10 ml. of H_2O was added after cooling. The separated solid was recrystallized from MeOH to give colorless needles. Analytical data and other 4-(N,N-disubstituted thiocarbamoylthio)-3,5-dimethylpyrazoles obtained in a similar way are listed in Table I.

Antifungal Test——A sample was dissolved in sterillized distd. H_2O or a small quantity of hydrophilic organic solvent, the solution was then diluted to a desired concentration with sterillized distd. H_2O, and finally mixed with a glucose-bouillon agar (pH 7) in petri dishes to make a series of dilutions.

The spores or cells of a test organism, which had been previously incubated 10～14 days at 27° on potato agar slants, were suspended in saline H_2O. Then the suspension was streaked on the agar plates. After incubating 5 days at 25～27°, minimum concentration for complete inhibition of growth was measured.

Discussion

The relationship between the structure and antifungal activities of these pyrazoles against *Piricularia oryzae* and *Colletotrichum lagenarium* will be discussed briefly.

I) Substituents in the 4-Position

The most reasonable conclusions to be drawn from the data are as follows.

a) Almost all of the pyrazoles having a thiocyanato group are effective in the tests. Introduction of a thiocyanato group into a pyrazole ring causes an enhancement of the antifungal activities except two cases (Compounds No. 9, 13).

b) Some of the pyrazoles substituted with an alkoxythiocarbonylthio group are also effective, but less potent than the corresponding thiocyanatopyrazoles.

c) Pyrazoles with N,N-disubstituted thiocarbamoylthio- or carbamoylthio group and di(4-pyrazolyl)disulfides are almost ineffective.

d) Pyrazoles with other substituents are mostly ineffective except a few compounds (No. 7, 9, 31).

II) 4-Thiocyanatopyrazoles

a) Pyrazole ring——It may well be that introduction of a thiocyanato group into 2-pyrazolin-5-ones mostly decreases the antifungal activity of the parent compound, the observation being contrary to those made on pyrazoles. This may coincide with the finding of McNew, *et al.*,[1] who stated that 4-nitrosopyrazoles are highly antifungal while 4-nitrosopyrazolinones are less effective, thus demonstrating that the pyrazole ring plays an important role in the case of 4-thiocyanatopyrazoles.

b) Substituents in the 1-position——It may well be that the antifungal activity of 4-thiocyanatopyrazoles having a substituent in the 1-position decreases in the order of phenyl, benzyl, methyl group and hydrogen. This tendency also seems to coincide with the earlier finding of McNew, *et al.* made on 4-nitrosopyrazoles.

c) Substituents in the 3- and 5-positions——Comparison of the activities of 3,5-dimethylpyrazole derivatives with those of 3-methyl-5-phenylpyrazole derivatives shows that the former has higher activities, though the difference is not remarkable.

d) Effect of a Substituent on a Phenyl Ring at the 1-Position of the Pyrazole—— Among the 4-nitroso-3,5-dimethylpyrazoles, 1-(*p*-chlorophenyl)- and 1-*p*-tolyl derivatives were most antifungal,[1] but in the series of 4-thiocyanato-3,5-dimethylpyrazoles, 1-(*m*-nitrophenyl)derivative was most effective. Substituents on the phenyl ring at the 1-position of 3-methyl-4-thiocyanato-1,5-diphenylpyrazole, however, did not exert remarkable effects on the antifungal activity.

The authors express their deep gratitude to Dr. S. Kuwada, ex-Director of these Laboratories, for his encouragement and to Dr. T. Matsukawa for his helpful advice.

Thanks are also due to Mr. M. Kan for elemental analyses and to Mr. H. Nakamachi and Miss T. Hiratsuka for optical measurements.

Summary

4-Alkoxythiocarbonylthio- and 4-(N,N-disubstituted thiocarbamoylthio)pyrazoles and two thiocyanatopyrazoles were synthesized.

Antifungal activities of these compounds as well as those described in the preceding paper were tested.

In conclusion, 4-thiocyanatopyrazoles showed high antifungal activities of which 1-(*m*-nitrophenyl)-4-thiocyanato-3,5-dimethylpyrazole was most effective.

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26. Tadashi Sasaki, Ken Kanematsu, Katsumaro Minamoto,[*1] and Hajime Fujimura[*2] : Researches on Morphine-like Analgesics. I. Syntheses and Analgesic Activity of Desylamine Derivatives.

(*Department of Pharmacy, Tokyo College of Science,*[*1] *and Institute of Chemical Research, Kyoto University*[*2])

For the purpose of elucidating the relationship between effective partial structure of morphine skeleton (I′) and analgesic action, several compounds possessing the A-C rings in the morphine skeleton as the basic structure were synthesized. This papar is concerned with the synthesis of 2-dialkylamino-2-phenylacetophenone, the Mannich reaction of deoxybenzoin and the behavior of its product in the succeeding reaction.

The original report by Dodds, *et al.*[1] that diphenylethylamines and in particular 2-amino-1,2-diphenylethanol relieved pain associated with carcinoma in human subjects appears to have been a specialized circumstance.

Later they reported the failure to detect the production of analgesia by these compounds in rats. In 1960, (−)N,N-dimethyl-1,2-diphenylethylamine derived from (−)1,2-diphenylethylamine was found to be 0.33~0.5 times as potent as (−)morphine by Fujimura, *et al.*, whereas the (+)enantiomorph shows almost no activity.[2] Recently,

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1) E.C. Dodds, *et al.* : J. Physiol., **104**, 47 (1945); Nature **151**, 614 (1943). C.M. Suter : "Medicinal, Chemistry" Vol. **1**, 399 (1951).

2) K. Ogiu, H. Fujimura, Y. Yamakawa : Yakugaku Zasshi, **80**, 283 (1960).