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5. Jiro Kinugawa and Michihiko Ochiai : Studies on Fungicides. VI.*1 Synthesis of Thiocyanatopyrazoles.*2

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Horsfall and Rich[1] suggested that a thiocyanato compound needs a second electronegative group in the molecule to make it effectively fungicidal. In previous papers*1,2) we reported the synthesis of several thiocyanatodiazines which have electronegative nitrogen atoms in the molecule. Some of these thiocyanatodiazines were shown to be highly antifungal.

This paper describes the synthesis of thiocyanatopyrazoles which appears to have received little attention previously. Direct thiocyanation of the five-membered heterocyclic compounds, such as pyrrole,[3] thiophene,[4] furan,[5] indole[6] and aminothiazole derivatives,[7] with thiocyanic acid salts and halogen[8] has been reported. As to the six-membered heterocyclic compounds such as pyridine, pyrimidine and quinoline, the direct thiocyanation has been reported only in the case of the compound which has a hydroxyl and/or an amino group in the ring.[9] In the field of the diazoles, direct-thiocyanation of imidazole[10] and 1-phenylpyrazole[11] (I) has been reported to be unsuccessful. Finar, *et al.*[11] obtained 1-phenyl-4-thiocyanatopyrazole (II) in poor yield *via* the 4-mercuric compounds (III) (Chart 1).

Thiocyanation of Pyrazole Derivatives

The thiocyanation with thiocyanogen or with thiocyanic acid salts and halogen is generally considered to be initiated by an electrophilic attack of a thiocyanato cation. Therefore it will be pertinent to assume that a thiocyanation may be feasible for pyrazoles having electron-releasing substituents. Since it has been reported that the methyl group is sufficiently effective for this kind of reaction,[12] first of all the thiocyanation of 1-phenyl-3,5-dimethylpyrazole (IV) was attempted.

When IV was treated with ammonium thiocyanate and bromine in glacial acetic acid at 10°, a colorless crystalline monothiocyanated compound (V) was obtained in 75% yield.

Other substituted pyrazoles were also thiocyanated in a similar way. The thiocyanatopyrazoles thus obtained are shown in Table I.

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*1 Part V : Yakugaku Zasshi, **83**, 1086 (1963).

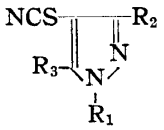
*2 This paper was presented at the Kinki Branch Meeting of Pharmaceutical Society of Japan, Kyoto, June, 1963.

*3 Juso-nishino-cho, Higashiyodogawa-ku, Osaka (衣川二郎, 落合道彦).

1) J.G. Horsfall, S. Rich : Indian Phytopathology, **6**, 1 (1953).
2) Part IV : Yakugaku Zasshi, **83**, 767, 1086 (1963).
3) S. Gronowitz, A. Hörnfeldt, B. Gestblom, R.A. Hoffman : J. Org. Chem., **26**, 2615 (1961); E. Söderbäck, S. Gronowitz, A. Hörnfeldt : Acta Chem. Scand., **15**, 227 (1961).
4) E. Söderbäck : Acta Chem. Scand., **8**, 1851 (1954).
5) S. Gronowitz, G. Soerlin : Arkiv Kemi., **19**, 515 (1962).
6) M.S. Grant, R. Snyder : J. Am. Chem. Soc., **82**, 2742 (1960).
7) C.D. Hurd, H.L. Wehrmeister : *Ibid.*, **71**, 4007 (1949).
8) J.L. Wood : "Org. Reactions" **3**, 240 (1946).
9) A. Maggiolo : J. Am. Chem. Soc., **73**, 5815 (1951).
10) R.E. Koeppe, J.L. Wood : *Ibid.*, **75**, 4655 (1953).
11) I.L. Finar, K.E. Godfrey : J. Chem. Soc., **1954**, 2293.
12) K. Takatori, H. Nishida : Yakugaku Zasshi, **71**, 1367 (1951); K. Takatori, S. Asano : *Ibid.*, **80**, 789 (1960).

Table I. Thiocyanatopyrazoles

No.	R_1	R_2	R_3	m.p. (C°)	Yield (%)	Recrystallization solvent
1	H	$-CH_3$	$-CH_3$	71.5～73.5 ($b.p_{2.5}$ 155～157)	54	Et_2O-ligroin
2	$-CH_3$	〃	〃	55～56 ($b.p_{1.0}$ 104～106)	54	
3	$-CH_2-C_6H_5$	〃	〃	84.5～85.5	77	hexane
4	$-CONH_2$	〃	〃	150～152	35	EtOH
5	$-C_6H_5$	〃	〃	98～99.5	75	〃
6	$-C_6H_4(2-O_2N)$	〃	〃	101～102	87	〃
7	$-C_6H_4(2-NO_2)$	〃	〃	113～114	86	〃
8	$-C_6H_4-NO_2$	〃	〃	90～91	88	〃
9	$-C_6H_3(2-O_2N)-NO_2$	〃	〃	137.5～138.5	51	〃
10	$-C_6H_4(2-H_3C)$	〃	〃	48～49	76	ligroin
11	$-C_6H_4-CH_3$	〃	〃	87～89	66	hexane
12	$-C_6H_4-Cl$	〃	〃	103～105	78	dil. EtOH
13	$-C_6H_4-Br$	〃	〃	109～110	86	Me_2CO-hexane
14	$-C_6H_4-SO_3H$	〃	〃	287～293	61	EtOH
15	$-C_6H_4-SCN$	〃	〃	85～86.5	80	benzene-hexane
16	$-C_6H_5$	〃	$-C_6H_5$	81～83	60	hexane
17	$-C_6H_4(2-NO_2)$	〃	〃	119～120	62	EtOH
18	$-C_6H_4-NO_2$	〃	〃	120～122	77	〃
19	$-C_6H_4-Cl$	〃	〃	122.5～123.5	68	〃
20	$-C_6H_4-Br$	〃	〃	127.5～128.5	80	〃
21	$-C_6H_4-SCN$	〃	〃	118～119	60	〃
22	$-C_6H_5$	-H	$-NH_2$	120～121	73	dil. Me_2CO



Appearance	Formula	Analysis					
		Calcd.			Found		
		C	H	N	C	H	N
colorless prisms	$C_6H_7N_3S$	47.03	4.60	27.42	46.42	4.98	26.93
colorless crystals	$C_7H_9N_3S$	50.28	5.42	—	50.04	5.69	—
colorless needles	$C_{13}H_{13}N_3S$	64.17	5.38	17.27	63.99	5.26	17.16
yellowish prisms	$C_7H_8ON_4S$	42.84	4.11	28.55	42.80	4.36	28.75
colorless prisms	$C_{12}H_{11}N_3S$	62.85	4.83	18.32	63.03	5.01	18.32
〃	$C_{12}H_{10}O_2N_4S$	52.54	3.67	20.79	52.24	3.89	20.60
colorless needles	〃	〃	〃	〃	52.35	3.51	20.84
yellowish prisms	〃	〃	〃	〃	52.25	4.00	20.98
yellowish plates	$C_{12}H_9O_4N_5S$	45.13	2.84	22.04	45.03	2.53	22.11
colorless crystals	$C_{13}H_{13}N_3S$	64.17	5.38	17.27	64.34	5.45	17.06
〃	〃	〃	〃	〃	64.15	5.65	17.15
yellowish prisms	$C_{12}H_{10}N_3ClS$	54.65	3.82	—	54.37	4.02	—
colorless needles	$C_{12}H_{10}N_3BrS$	46.76	3.27	13.63	46.51	3.58	13.54
colorless plates	$C_{12}H_{11}O_3N_3S_2$	—	—	13.58	—	—	13.51
colorless needles	$C_{13}H_{10}N_4S_2$	—	—	19.57	—	—	19.23
colorless crystals	$C_{17}H_{13}N_3S$	70.09	4.49	14.42	70.36	4.47	14.71
〃	$C_{17}H_{12}O_2N_4S$	—	—	16.68	—	—	16.55
colorless needles	〃	60.99	3.59	16.68	60.36	3.58	16.56
〃	$C_{17}H_{12}N_3ClS$	62.66	3.71	12.89	62.21	3.86	13.15
〃	$C_{17}H_{12}N_3BrS$	55.15	3.26	11.35	55.09	3.40	11.26
colorless crystals	$C_{18}H_{12}N_4S_2$	62.05	3.47	16.08	61.75	3.53	15.89
〃	$C_{10}H_8N_4S$	55.55	3.76	25.91	55.63	4.05	26.21

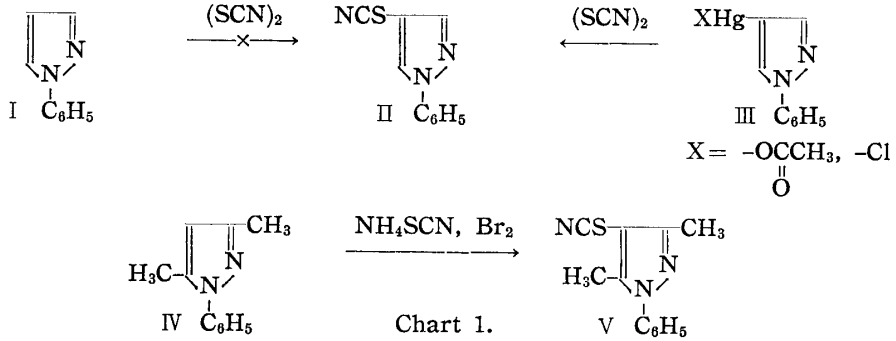
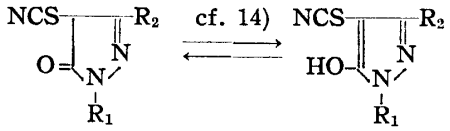


Chart 1.

Table I indicates that 3,5-dimethyl- and 3-methyl-5-phenylpyrazole derivatives both of which have, in the 1-position of pyrazole ring, phenyl group bearing electronegative substituent such as nitro or sulfo group, are also thiocyanated in good yield. Somewhat lower yield in the thiocyanation of 1-(2,4-dinitrophenyl)-3,5-dimethylpyrazole would probably due to the decrease of the electron density in the pyrazole ring caused by two electron-withdrawing substituents. 3-Methyl-5-phenylpyrazole derivatives are thiocyanated in lower yields in comparison with the corresponding 3,5-dimethyl derivatives, and 1-(2,4-dinitrophenyl)-3-methyl-5-phenylpyrazole was recovered unchanged. Pyrazole derivatives which are rather inactive for electrophilic reactions or pyrazoles substituted in the 4-position, for instance, 1-phenyl-3-methyl-5-chloropyrazole, 1-phenyl-4-ethoxycarbonyl-5-hydroxypyrazole, 1-phenyl-4-ethoxycarbonyl-5-aminopyrazole, 1-phenyl-4-ethoxycarbonyl-5-methylpyrazole, 1-phenyl-4-cyano-5-aminopyrazole were recovered unchanged.

In a similar procedure, 2-pyrazolin-5-ones were also thiocyanated. Thiocyanato-2-pyrazolin-5-ones thus obtained are shown in Table II.

Table IIa. 4-Thiocyanato-2-pyrazolin-5-ones 

No.	R_1	R_2	m.p. (°C)	Yield (%)	Recrystallization solvent	Appearance
1	-C6H5	$-CH_3$	131~132	71	dil. EtOH	yellowish crystals
2	-C6H4-NO2	〃	146~148	79	〃	yellowish needles
3	-C6H4-Cl	〃	132~134	78	dil. Me_2CO	colorless crystals
4	-C6H4-SCN	〃	115~120	76	〃	colorless scales
5	-C6H4	$-NH_2$	176~178	67	EtOH	colorless crystals

Table IIb. Analytical Data of Compounds shown in Table IIa

No.	Formula	Calcd.			Found		
		C	H	N	C	H	N
1	$C_{11}H_9ON_3S$	57.14	3.92	18.17	56.96	4.09	18.73
2	$C_{11}H_8ON_4S$	—	—	20.28	—	—	20.58
3	$C_{11}H_8ON_3ClS$	49.72	3.03	—	49.62	2.78	—
4	$C_{12}H_8ON_4S_2$	49.98	2.79	19.43	49.54	2.98	19.41
5	$C_{10}H_8ON_4S$	51.72	3.47	24.13	51.60	3.57	23.84

Location of the Thiocyanato Group

The position of the thiocyanato group was determined in the case of thiocyanated compounds of 1-phenyl-3,5-dimethylpyrazole (V) and 1-phenyl-3-methyl-2-pyrazolin-5-one (X) by the reactions shown in Chart 2.

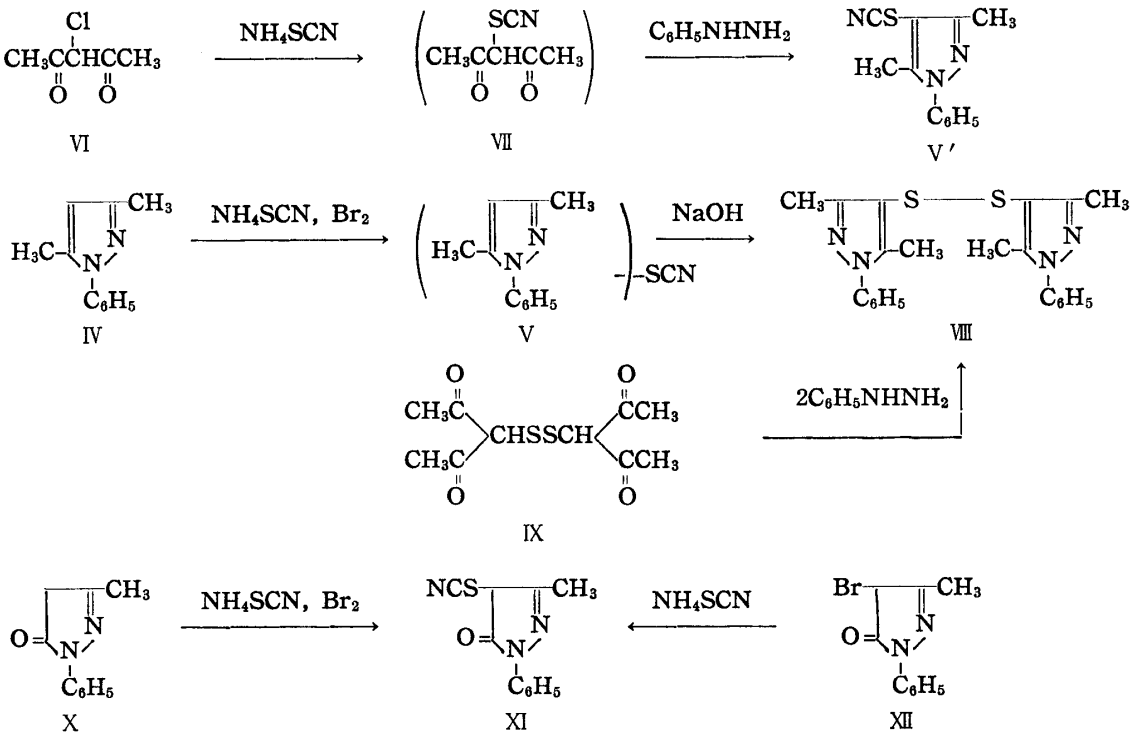


Chart 2.

Treatment of 3-chloro-2,4-pentanedione (VI) with ammonium thiocyanate caused precipitation of ammonium chloride. When phenylhydrazine was added to this reaction mixture, without isolating the anticipated 3-thiocyanato-2,4-pentanedione (VII), a colorless crystalline compound (V′) was obtained, which was identical with the thiocyanated compound (V) of 1-phenyl-3,5-dimethylpyrazole (IV) by the mixed melting point determination and the comparison of infrared spctra. Treatment of V with alkali gave a compound, which was identical with 1,1′-diphenyl-3,3′,5,5′-tetramethyl-4,4′-dithiodipyrazole (VIII),[13] obtainable from bis(diacetylmethyl)disulfide (IX) and phenylhydrazine. The elemental analysis, mixed melting point determination and comparison of infrared spectra comfirmed the identity.

Reaction of 1-phenyl-3-methyl-4-bromo-2-pyrazolin-5-one (XII) with ammonium thiocyanate afforded a crystalline compound which was identical with the thiocyanated compound (XI) of 1-phenyl-3-methyl-2-pyrazolin-5-one (X). These results show that the thiocyanation of pyrazoles and 2-pyrazolin-5-ones gave the 4-thiocyanato derivatives.

This was further confirmed by the nuclear magnetic resonance spectra (Table III).

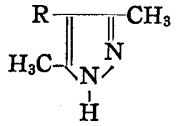
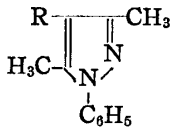
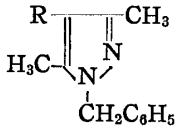
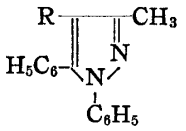
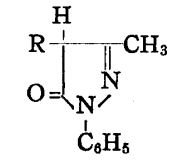
Table III indicates that the thiocyanato derivatives have no proton on C-4 atom of the pyrazole ring, and that 1-phenyl-3-methyl-4-thiocyanato-2-pyrazolin-5-one (XI) possibly exists in the enol form in dimethylsulfoxide solution.

Infrared and Ultraviolet Absorption Spectra

Infrared and ultraviolet spectra of the 4-thiocyanatopyrazoles and 4-thiocyanato-2-pyrazolin-5-ones are summarized in Tables IV and V respectively.

13) F. Magnani : Gazz. chim. ital., **23**, II 418 (1893).

TABLE III. Nuclear Magnetic Resonance Spectra of Pyrazole Derivatives (Measured at 60 Mc. by Varian A-60)

Structure	R	Solvent	τ value: $-CH_3$	τ value: H-ring	τ value: ϕ-H	τ value: $-CH_2-$	τ value: NCS-ring
	H	CCl_4	7.76 s	4.33 s	—	—	—
	SCN	〃	7.66 s	no peak	—	—	—
	H	〃	7.86 s 7.76 s	4.19 s	2.75m	—	—
	SCN	〃	7.64 s 7.56 s	no peak	2.63m	—	—
	H	〃	7.95 s 7.84 s	4.36 s	2.97m	4.95 s	—
	SCN	〃	7.73 s 7.68 s	no peak	2.85m	4.86 s	—
	H	〃	7.73 s	3.90 s	2.90m	—	—
	SCN	〃	7.52 s	no peak	2.84m	—	—
	H	DMSO	7.89 s	4.67 s	2.50m	no peak	—
	SCN	〃	7.72 s	no peak	2.49m	—	no peak

m: multiplet s: singlet

TABLE IV. Infrared and Ultraviolet Absorption Spectra of 4-Thiocyanatopyrazoles

No.	IR spectra SCN (cm^{-1})	UV spectra max. (mμ)	UV spectra log ε	No.	IR spectra SCN (cm^{-1})	UV spectra max. (mμ)	UV spectra log ε
1	2160	—	—	12	2155	251.5	4.173
2	2160	—	—	13	2150	252	4.204
3	2150	—	—	14	2160	253	4.164
4	2160	238	3.918	15	2160	262.5	4.269
5	2155	246	4.056	16	2150	251	4.179
6	2155	233	4.100	17	2150	255.5	4.116
7	2170	251	4.330	18	2160	301.5	4.173
8	2155	299	4.164	19	2160	256	4.230
9	2170	290	3.863	20	2160	257.5	4.257
10	2155	226	3.917	21	2160	266	4.296
11	2155	245	4.091	22	2160	/	/

IR spectra: in KBr UV spectra: in EtOH

Table V. Infrared and Ultraviolet Absorption Spectra of 4-Thiocyanato-2-pyrazolin-5-ones

No.	IR spectra : absorption bands (cm^{-1})				UV spectra	
	OH	SCN	C=O	C=N	max. (mμ)	log ε
1	3450	2150	1630	1590	231.5	4.155
2	3450	2160	1640	1610	236	4.075
3	3400	2160	1630	1600	252	4.305
4	3400	2160	1620	1590	267	4.283
5	(3350)	2170	1640	1600	247	4.136

IR spectra : in KBr UV spectra : in EtOH

A sharp band was observed in the region of 2150~2170 cm^{-1} in each 4-thiocyanatopyrazole, the band being attributable to the CN stretching vibration of the thiocyanato group. In the case of 2-pyrazolin-5-one derivatives, the infrared bands occurring in the regions of 3400 cm^{-1} and 1630 cm^{-1} are attributed to the OH and C=O groups[14] respectively, thus indicating that 4-thiocyanato-2-pyrazolin-5-ones are the mixture of the enol and the keto forms in the solid state.

Reactions of Thiocyanatopyrazoles

It has been known[15] that a thiocyanato compound affords a thiolcarbamate on treatment with sulfuric acid containing some water. When 1-phenyl-4-thiocyanato-3,5-dimethylpyrazole (V) was treated with 90% sulfuric acid, a crystalline substance was obtained. The elemental analysis of the product was in agreement with that of the thiolcarbamate derivatives (XIII).

The infrared spectrum of the product (Fig. 1) showed that the absorption band at 2155 cm^{-1}, attributed to the CN stretching vibration of the thiocyanato group, had disappeared and that the bands attributed to the NH_2 and C=O groups appeared.

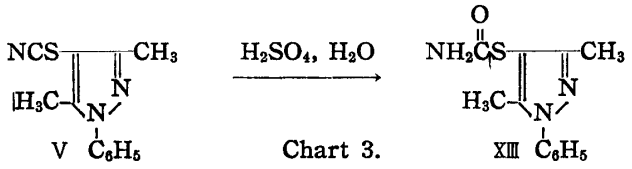


Chart 3.

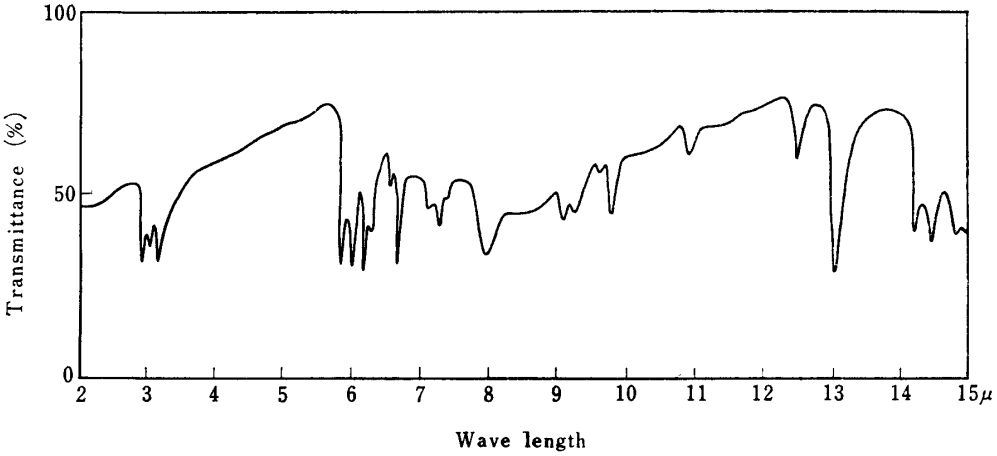
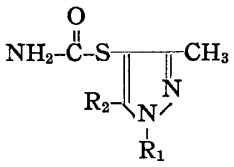


Fig. 1. Infrared Absorption Spectrum of 1-Phenyl-4-carbamoyl-3,5-dimethylthiopyrazole (KBr)

14) P.E. Gagnon, J.L. Biovin, Y. Laflamme : Can. J. Chem., **34**, 530 (1956).
15) Houben-Weyl : "Methoden der organishen Chemie" (IV) **9**, 835.

Table VIa. 4-Carbamoylthiopyrazoles



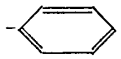
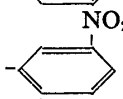
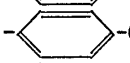
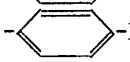
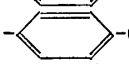
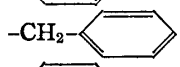
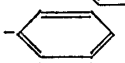
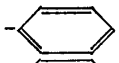
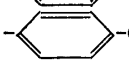
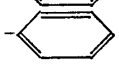
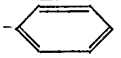
No.	R_1	R_2	m.p. (°C)	Yield (%)	Recrystallization solvent	Appearance
1		$-CH_3$	148~149	79	dil. EtOH	colorless crystals
2		〃	156~158	84	〃	yellowish prisms
3		〃	187	80	DMF	colorless scales
4		〃	147~149	75	dil. EtOH	colorless prisms
5		〃	166~168	84	〃	〃
6		〃	142~143	77	〃	colorless needles
7		〃	146~148	86	〃	colorless prisms
8			173~175	73	〃	〃
9			185~186	78	〃	〃
10		$-OH$	167~168	83	DMF	colorless needles

Table VIb. Analytical Data of Compounds shown in Table VIa

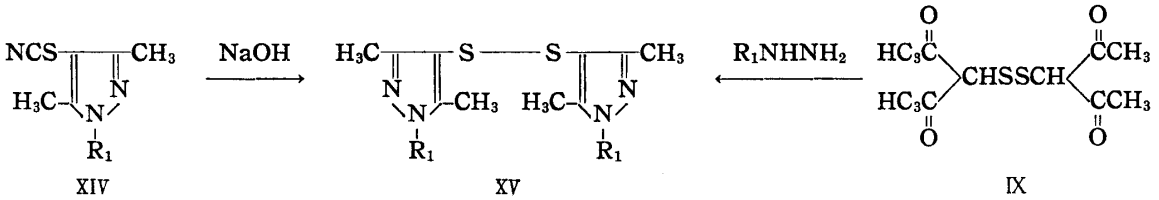
No.	Formula	Calcd.			Found		
		C	H	N	C	H	N
1	$C_{12}H_{13}ON_3S$	58.27	5.29	16.91	58.04	5.41	16.31
2	$C_{12}H_{12}O_3N_4S$	49.30	4.13	—	49.56	4.39	—
3	〃	〃	〃	—	49.44	4.33	—
4	$C_{12}H_{12}ON_3ClS$	51.16	4.29	14.91	50.88	4.48	14.66
5	$C_{12}H_{12}ON_3BrS$	44.18	3.70	12.88	44.19	3.68	12.57
6	$C_{13}H_{15}ON_3S$	59.75	5.74	—	59.86	5.91	—
7	〃	〃	〃	16.08	59.94	5.91	15.83
8	$C_{17}H_{15}ON_3S$	66.01	4.88	—	66.65	4.95	—
9	$C_{17}H_{14}ON_3ClS$	59.38	4.10	—	59.50	4.47	—
10	$C_{11}H_{11}ON_3S$	53.01	4.44	16.86	53.13	4.65	16.59

4-Carbamoylthiopyrazoles obtained in a similar way are shown in Table VI.

4-Thiocyanatopyrazoles, when refluxed in an aqueous ethanol containing sodium hydroxide, gave 4,4′-dithiodipyrazoles (XV), which were identical with the disulfides obtained by the reaction of bis(diacetylmethyl)disulfide (IX) with the hydrazine derivatives (Chart 4).

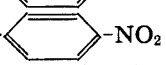
On the contrary to the earlier observation[16] that the thiocyanatopyrimidines undergo thermal isomerization to isothiocyanato derivatives, attempted isomerization of the thiocyanatopyrazole under various conditions resulted in the recovery of the starting material.

16) J.B. Johnson, W.F. Storey: Am. Chem. J., **40**, 131 (1908); Y. Chi, Y. Chen: J. Chem. Eng., (China), **5**, 35 (1938).



XIV XV IX

XIV, XV a: R_1= 

b: R_1= 

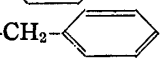
c: R_1= 

Chart 4.

Consideration on the Mechanism of the Thiocyanation

It is generally accepted that the thiocyanation with thiocyanic acid salts and halogen takes place through the action of the thiocyanato cation which is formed *via* intermediate thiocyanogen (Formulae (1) in Chart 5). Recently Kaji[17] proposed a mechanism in which he postulated that the thiocyanation does not proceed through the intermediate thiocyanogen but proceeds through the thiocyanato cation directly formed from the thiocyanic acid salt and halogen (Formulae (2) in Chart 5).

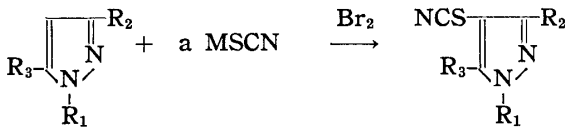
$$
\begin{aligned}
&2MSCN + Br_2 \longrightarrow (SCN)_2 + 2MBr\\
&(SCN)_2 \longrightarrow SCN^+ + SCN^-\\
&RH + SCN^+ \longrightarrow RSCN + H^+\\
&\hline
&RH + 2MSCN + Br_2 \longrightarrow RSCN + 2MBr + HSCN
\end{aligned}
\quad (1)
$$

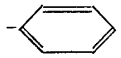
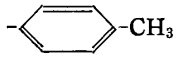
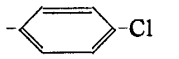
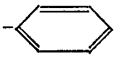
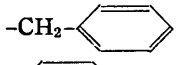
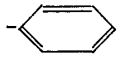
$$
\begin{aligned}
&MSCN + Br_2 \longrightarrow BrSCN + MBr\\
&BrSCN \longrightarrow SCN^+ + Br^-\\
&RH + SCN^+ \longrightarrow RSCN + H^+\\
&\hline
&RH + MSCN + Br_2 \longrightarrow RSCN + MBr + HBr
\end{aligned}
\quad (2)
$$

M=NH_4, Na, K

Chart 5.

TABLE VII. Yield of Thiocyanatopyrazoles



R_1	R_2	R_3	a	M	Yield (%)
	$-CH_3$	$-CH_3$	2	NH_4	75
	〃	〃	1	〃	77
	〃	〃	1	Na	74
	〃	〃	1	K	78
	〃	〃	2	NH_4	66
	〃	〃	1	〃	71
	〃		2	〃	68
	〃	〃	1	〃	88
	〃	$-CH_3$	2	〃	77
	〃	〃	1	〃	68
	〃	$-OH$	2	〃	71
	〃	〃	1	〃	77

17) Y. Kaji: Nippon Kagaku Zasshi, **81**, 1776 (1960).

Accordingly the stoichiometric relation is different for both mechanisms; the quantity of the thiocyanic acid salt required for reaction differs. In order to examine this relation the thiocyanation was reinvestigated stoichiometrically. The results are shown in Table Ⅶ.

As is shown in Table Ⅶ, so far as the thiocyanation of the pyrazoles is concerned, the minimum requirement of the thiocyanic acid salt to insure the good yield of the thiocyanation reaction can be decreased to half the quantity hitherto used. This seems to support the Kaji's proposal.

Antimicrobial data will be reported elsewhere.

Experimental*4

1-Phenyl-4-thiocyanato-3,5-dimethylpyrazole (V)——a) To a solution of 5.1 g. (0.03 mole) of 1-phenyl-3,5-dimethylpyrazole (Ⅳ) and 4.6 g. (0.06 mole) of NH_4SCN in 20 ml. of glacial acetic acid was added dropwise with stirring over a period of 25 min. at 7~8° a solution of 4.8 g. (0.03 mole) of bromine in 10 ml. of glacial acetic acid. After being stirred for 30 min. the reaction mixture was poured into 300 ml. of H_2O. The separated solid was recrystallized from EtOH to colorless prisms, m.p. 98~99.5°; yield, 5.1 g. Analytical data are shown in Table I.

b) By the use of NH_4SCN or NaSCN and KSCN in place of NH_4SCN in an equimolar to 1-phenyl-3,5-dimethylpyrazole the same compound was obtained in good yield (Table Ⅶ).

c) To a solution of 1.2 g. of NH_4SCN in 10 ml. of EtOH was added 2 g. of 3-chloro-2,4-pentanedione (Ⅵ) under ice-cooling. The reaction mixture was kept standing for 30 min. during which time NH_4Cl precipitated. Phenylhydrazine (1.6 g,), 5 ml. of H_2O and 0.2 ml. of conc. HCl were added to this. After warming at 60° for 10 min. the reaction mixture was cooled in an ice bath. The separated solid was recrystallized from EtOH to colorless prisms, m.p. 98~99.5°; yield, 0.7 g. *Anal.* Calcd. for $C_{12}H_{11}N_3S$: C, 62.85; H, 4.83; N, 18.32. Found: C, 62.59; H, 5.04; N, 18.62.

Other thiocyanatopyrazoles obtained according to the method a) are shown in Table I.

1-Phenyl-3-methyl-4-thiocyanato-2-pyrazolin-5-one (XI)——a) To a solution of 17.4 g. (0.1 mole) of 1-phenyl-3-methyl-2-pyrazolin-5-one (X) and 15.2 g. (0.2 mole) of NH_4SCN in 50 ml. of glacial AcOH was added dropwise with stirring over a period of 35 min. at 10~15° a solution of 16 g. (0.1 mole) of bromine in 20 ml. of glacial AcOH. After 5 min. the reaction mixture poured into 500 ml. of H_2O. The separated solid was recrystallized from dil. EtOH to yellowish crystals, m.p. 131~132°; yield, 16.5 g. Analytical data are shown in Table Ⅱ.

b) To a solution of 1 g. of 1-phenyl-3-methyl-4-bromo-2-pyrazolin-5-one (XⅡ) in 10 ml. of EtOH was added 1 g. of NH_4SCN. The reaction mixture was refluxed for 10 min. After cooling, 10 ml. of H_2O was added. The separated solid was recrysatllized from dil. EtOH to yellowish crystals, m.p. 131°; yield, 0.8 g. This compound was confirmed to be identical with a sample obtained in a) by the mixed melting point determination.

Other 4-thiocyanato-2-pyrazolin-5-ones obtained according to the method a) are shown in Table Ⅱ.

1,1′-Diphenyl-3,3′,5,5′-tetramethyl-4,4′-dithiodipyrazole (VIII, XVa)——To a mixture of 10 ml. of EtOH and 10 ml. of 10% aq. NaOH was added 2 g. of 1-phenyl-4-thiocyanato-3,5-dimethylpyrazole (V). The reaction mixture was refluxed for 3 hr. and kept standing over night. The separated solid was recrystallized from hexane to colorless prisms, m.p. 77~79°; yield, 0.7 g. *Anal.* Calcd. for $C_{22}H_{22}N_4S_2$: C, 64.99; H, 5.45. Found: C, 64.70; H, 5.57.

The identity of this compound with a sample obtained from bis(diacetylmethyl) disulfide (Ⅸ) and phenylhydrazine[13] was established by the mixed melting point determination and the comparison of the IR spectrum.

1,1′-Bis(*p*-nitrophenyl)-3,3′,5,5′-tetramethyl-4,4′-dithiodipyrazole (XVb)——a) To a mixture of 10 ml. of EtOH and 10 ml. of 10% aq. NaOH was added 2 g. of 1-(*p*-nitrophenyl)-4-thiocyanato-3,5-dimethylpyrazole (XⅣb). The reaction mixture was refluxed for 2.5 hr. and 20 ml. of H_2O was added. The separated solid was recrystallized from Me_2CO to colorless crystals, m.p. 182~183°; yield, 1.1 g. *Anal.* Calcd. for $C_{22}H_{20}O_4N_6S_2$: C, 53.20; H, 4.05. Found: C, 53.45; H, 4.10.

b) To 30 ml. of EtOH was added 2 g. of bis(diacetylmethyl)disulfide (Ⅸ), 2.4 g. of 4-nitrophenylhydrazine and 2 ml. of 10% HCl. The reaction mixture was refluxed for one hr. The separated solid was recrystallized from DMF to colorless crystals, m.p. 182~183°; yield, 3.5 g. *Anal.* Calcd. for $C_{22}H_{20}O_4N_6S_2$: C, 53.20; H, 4.05; S, 12.91. Found: C, 53.11; H, 4.16; S, 12.81.

*4 All melting points are uncorrected.

The disulfide obtained by the both methods was identical by the mixed melting point determination and the comparison of the IR spectrum.

1,1′-Dibenzyl-3,3′,5,5′-tetramethyl-4,4′-dithiodipyrazole (XVc)——By the method a) described for the synthesis of 1,1′-bis(*p*-nitrophenyl)-3,3′,5,5′-tetramethyl-4,4′-dithiodipyrazole (XVb), colorless prisms were obtained in 77% yield, m.p. 104~105°. *Anal.* Calcd. for $C_{24}H_{26}N_4S_2$: C, 66.32; H, 6.03; N, 12.89. Found : C, 66.67; H, 6.24; N, 12.92.

General Method for Synthesis of 4-Carbamoylthiopyrazoles——To 5~10 times quantity of 90% H_2SO_4 was added 4-thiocyanatopyrazoles and the mixture was kept at 10° for 48 hr. The mixture was poured into ice-water and neutralized with 5% aq. NaOH. The separated solid was recrystallized from the solvent shown in Table VI.

Isomerization to Isothiocyanato Derivatives——Attempts were made to isomerize 1-(*p*-nitrophenyl)-4-thiocyanato-3,5-dimethylpyrazole (XIVb) to the isothiocyanato derivative under several conditions. Conditions employed were (1) refluxed for 10 hr. in toluene, (2) 180~190° for 10 hr. in toluene, (3) 170~180° for 10 hr. in toluene in the presence of anhyd. $ZnCl_2$, (4) 170~180° for 10 hr. in EtOH. In all cases the compound was recovered unchanged.

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 Dr. Y. Asahi for his aid in interpretation of the NMR spectra, to Mr. M. Kan for elemental analyses and to Messrs. T. Shima and H. Nakamachi and Miss T. Hiratsuka for optical measurement.

Summary

During the course of our synthetic approach to find out antifungal agents, new thiocyanatopyrazoles were synthesized by the direct thiocyanation reaction.

Some of the reactions of thiocyanatopyrazoles were also described.

(Received August 20, 1963)

[Chem. Pharm. Bull. 12 (1) 33 ~ 40]

UDC 547.841.64.07

6. Masao Tomita and Shin-ichi Ueda : Studies on the Dibenzo-*p*-dioxin (Diphenylene Dioxide) Derivatives. XXXVIII.*1 The Color Reaction of Dibenzo-*p*-dioxin Derivatives in Concentrated Sulfuric Acid with Oxidizing Agents. The Detection by Electron Spin Resonance Spectra.*2

(*Faculty of Pharmaceutical Sciences, Kyoto University**3)

Tomita[1] discovered that all substances possessing a dibenzo-*p*-dioxin skeleton (I) gave blue to bluish green coloration in concentrated sulfuric acid with an oxidizing agent such as potassium nitrate, concentrated nitric acid, potassium bichromate, potassium permanganate, ferric chloride, potassium chlorate, manganese dioxide or hydrogen peroxide. This color reaction can be utilized for qualitative identification of dibenzo-*p*-dioxin derivatives.

However, octachlorodibenzo-*p*-dioxin (XIX) and octabromodibenzo-*p*-dioxin (XX) prepared by the present authors and a coworker[2] do not undergo this color reaction. In

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*1 Part XXXVII. S. Ueda : Yakugaku Zasshi, **83**, 805 (1963).

*2 Preliminary communication : Tetrahedron Letters, No. 18, 1189 (1963).

*3 Yoshida-konoe-cho, Sakyo-ku, Kyoto (富田真雄, 上田伸一).

1) M. Tomita : Yakugaku Zasshi, **52**. 889 (1932); *Ibid.*, **54**, 891 (1934).

2) M. Tomita, S. Ueda, M. Narisada : *Ibid.*, **79**, 186 (1959).