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UDC 547.852.2.07

24. Yoshifumi Maki and Kazunaga Obata : Studies of Rearrangement Reaction. VIII.*1 Ring-Contraction from Pyridazinone Derivatives to Pyrazolone Derivatives. (3).

(*Gifu College of Pharmacy**2)

In the previous papers,*2,1) it has been demonstrated that 1-phenyl-3,5-dichloro-6(1*H*)-pyridazinone (I) (R=Cl) undergoes the ring-contraction by treatment with boiling aqueous sodium hydroxide to give 1-phenyl-3-hydroxy-5-pyrazolecarboxylic acid (III), and the reaction mechanism has been assumed as shown in Chart 1. The behaviors of 1-phenyl-6(1*H*)-pyridazinone*2 derivatives, bearing various substituent groups at 3,4-, 3,5-, and 5-positions, on treatment with boiling 10% aqueous sodium hydroxide or 47% hydrobromic acid have been also investigated. These results have shown that the ring-contraction reaction takes place by applying such starting materials and conditions as hydroxyl groups are introduced into both of 3- and 5-positions of the pyridazinone ring to form the possible intermediate (a).

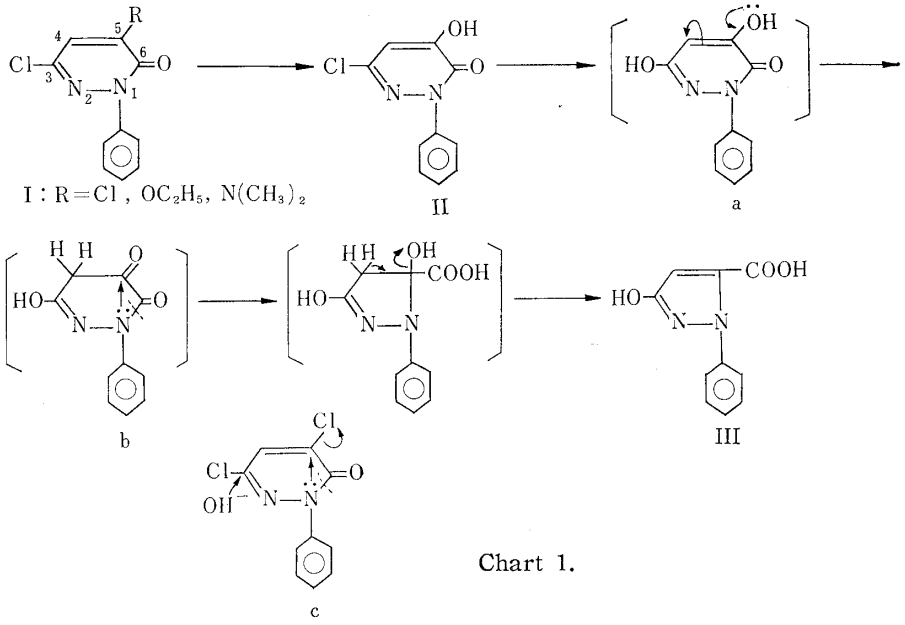

Chart 1.

For example,1) 1-phenyl-3,5-diethoxy-6(1*H*)-pyridazinone (IV) (R=C_2H_5), 1-phenyl-5-methoxy-6(1*H*)-pyridazinone (V), and 1-phenyl-3,4-dichloro-6(1*H*)-pyridazinone (VI) were converted into the corresponding hydroxy compounds (IV′, V′, and VI′) by action with boiling 10% aqueous sodium hydroxide with no ring-contraction. However, when IV and IV′ were treated with boiling 47% hydrobromic acid, III was obtained in a good yield. On the contrary, V and 1-phenyl-3,4-dimethoxy-6(1*H*)-pyridazinone (VII) did not transformed into the corresponding carboxylic acid (V″) and (VI″) by action of 47% hydrobromic acid, but into hydroxy compounds (V′ and VI′).

The present investigation was undertaken to see if 4,5-di- and 3,4,5-trisubstituted 1-phenyl-6(1*H*)-pyridazinone would suffer the ring-contraction by applying the condi-

*1 Part VII. (2) : Yakugaku Zasshi, **83**, 819 (1963).
*2 Kokonoe-cho, Gifu (牧 敬文, 小畑和永).
1) Y. Maki, H. Kizu, K. Obata : *Ibid.* **83**, 725 (1963).

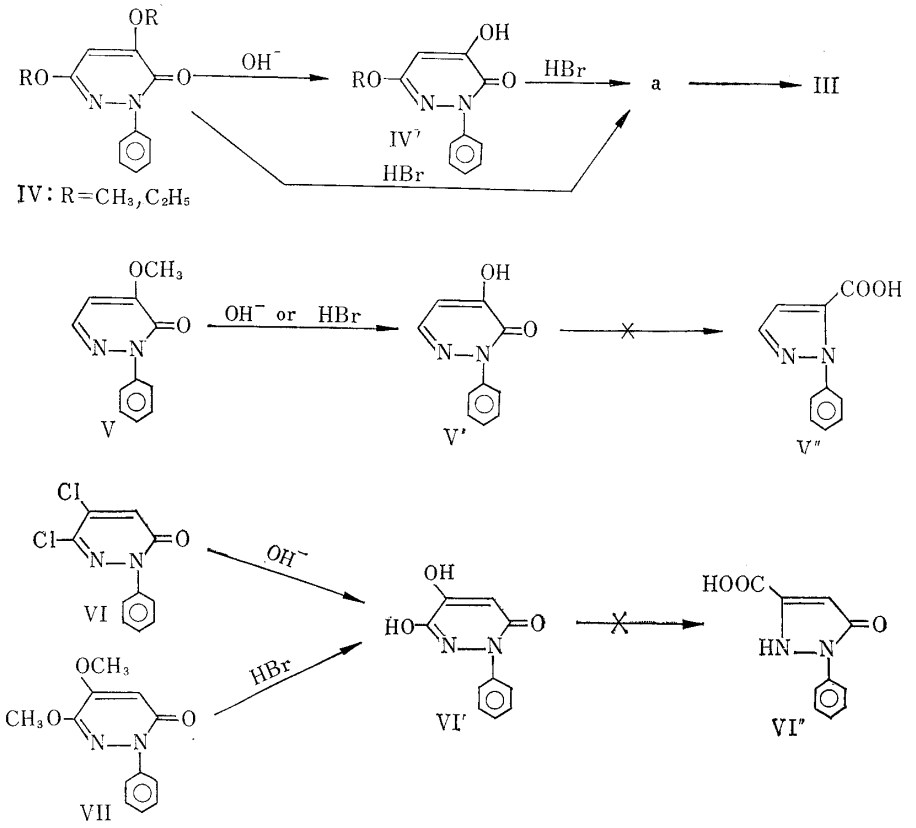

Chart 2.

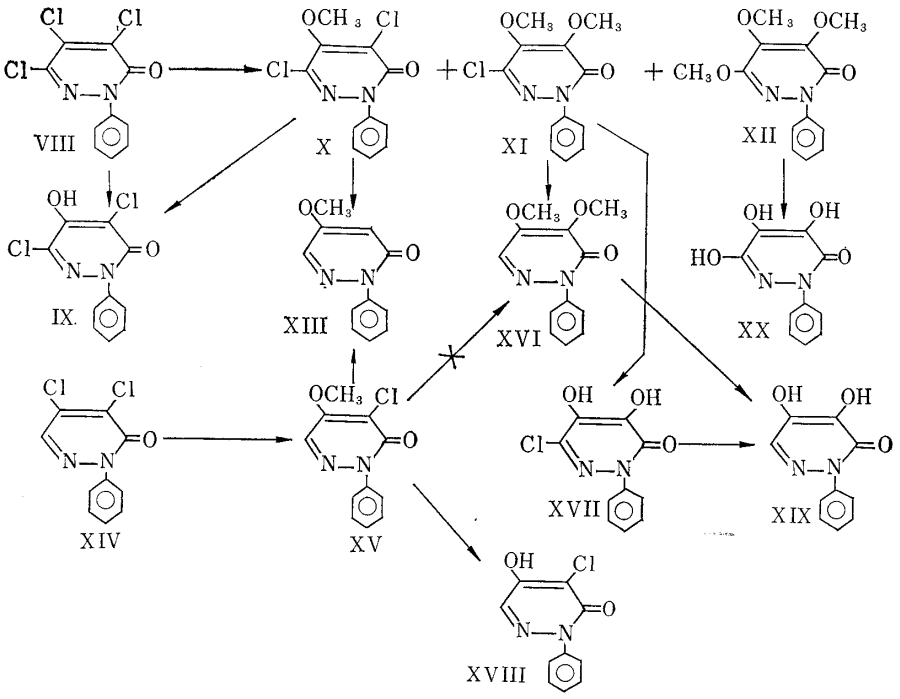

Chart 3.

tions similar to earlier work.*[2] On the basis of the data so obtained, the scope and mechanism of this reaction will be discussed below.

The reaction of 1-phenyl-3,4,5-trichloro-6(1*H*)-pyridazinone (Ⅷ)*[2] with boiling 5% aqueous sodium hydroxide did not give any crystaline substance, but with methanolic sodium hydroxide produced 1-phenyl-4-hydroxy-3,5-dichloro-6(1*H*)-pyridazinone (Ⅸ),

m.p. 254°, giving a positive ferric chloride test, identical with a specimen prepared by hydrolysis of 1-phenyl-4-methoxy-3,5-dichloro-6(1*H*)-pyridazinone (X), which structure was elucidated as mentioned below.

Since the behaviors of Ⅷ against caustic alkali has not proved consistently successful for examining the posibility of the ring-contraction, it was thought advisable to investigate the reaction of 1-phenyl-3,4,5-trimethoxy-6(1*H*)-pyridazinone (XII) with 47% hydrobromic acid.

When Ⅷ was allowed to react with sodium methoxide at room temperature, three substances, A m.p. 144°, B m.p. 119° and C m.p. 104°, were separated in uncertained yield from the resulting reaction mixture.

The reactivity of halogen atom on 1-phenyl-6(1*H*)-pyridazinone ring may be considered to increase in the order 4->5->3-position from the results of studies of nucleophilic substitution on dihalogenated (3·4, 4·5, and 3·5)-1-phenyl-6(1*H*)-pyridazinone by J. Druey, *et al.*[2,3]

According to their analytical value, A, B, and C may be assigned to each of the compounds which were formed by displacing stepwisely three chlorines of Ⅷ with methoxy groups. Therefore, clarifying positions of methoxy groups on A, B, and C appears to be also valuable for comparing chemically reactivity of halogen atom at each position on 1-phenyl-6(1*H*)-pyridazinone ring.

The first substance, A, was catalitically dehalogenated over paladium-charcoal to give 1-phenyl-4-methoxy-6(1*H*)-pyridazinone (XIII), m.p. 94°. No depression in melting point was observed in admixture of XIII with a specimen prepared by dehalogenation of 1-phenyl-4-methoxy-5-chloro-6(1*H*)-pyridazinone (XV) starting from XIV. Accordingly, A should be represented by the structure (X).

The second substance, B, giving a positive halogen test, yielded dehalogenated compound, m.p. 142°, by the catalitic hydrogenation with paladium-charcoal. The structure of the dehalogenated compound was certified to be 1-phenyl-4,5-dimethoxy-6(1*H*)-pyridazinone (XVI) according to comparison of infrared spectrum and melting point depression on admixture of any pair of position isomers, 1-phenyl-3,4-dimethoxy-6(1*H*)-pyridazinone (Ⅶ), m.p. 225°, and 1-phenyl-3,5-dimethoxy-6(1*H*)-pyridazinone (Ⅳ) (R=CH_3), m.p. 142°.*[2] This fact makes it possible to assign to structure (XI) for B. An attempt to synthesize XVI from XV by interaction with sodium methoxide failed due to inactivity of chlorine at 5-position of XV, and led to formation of XVIII by hydrolysis of methoxy group.

The third substance, C, is the desirable 1-phenyl-3,4,5-trimethoxy-6(1*H*)-pyridazinone (XII). Its structure is supported by a negative halogen test, agreement of analytical value and no hydroxy band in its infrared spectrum. Yield of XII was capable of increasing by the prolonged reaction time.

Isolation of such products as X, XI, and XII in the methoxylation of Ⅷ shows apparently that the activity of chlorine increase in the order 4->5->3-position.

If the cleavage of N_1-C_6 bond occurs after formation of intermediate, b, the key points in the hypothetical mechanism of the ring-contraction reaction (Chart 1) would be as following : 1) the formation of the intermediate, 1-phenyl-3,5-dihydroxy-6(1*H*)-pyridazinone (a) *via* 1-phenyl-3-chloro-5-hydroxy-6(1*H*)-pyridazinone (Ⅱ). 2) prototropy to diketone (b) from a.

On the other hand, the alternative concerted mechanism as shown in c might be also assumed.

2) J. Druey, *et al.* : Helv. Chem. Acta., **37**, 510 (1954).
3) *Idem* : *Ibid.*, **37**, 523 (1954).

In order to make a choice between these alternative explanation, the separation of intermediate was attempted.

When 3,5-dichloro compounds (I) (R=Cl) was treated by three equimolar of aqueous sodium hydroxide, followed by adding methyl iodide, 1-phenyl-3-methoxy-5-pyrazolecarboxylic acid[1] was obtained from reaction mixture after neutralization by acetic acid, but any intermediate was not isolated.

However, when I (R=Cl) was refluxed with methanolic sodium hydroxide, 1-phenyl-3-chloro-5-hydroxy-6(1*H*)-pyridazinone (II), m.p. 207~208°, reported previously,[1] was separated, and II underwent the ring-contraction by heating with 10% sodium hydroxide to give III in the similar manner to I (R=Cl).

In view of above facts, the most reasonable conclusion to be drawn from available data is that the ring-contraction proceeds through intermediate (II) without concerted mechanism (c).

As pointed out in the beginning of this paper, IV was converted into III by heating with 47% hydrobromic acid, and also in this case it appears that the reaction would take place through formation of the intermediate (a) by hydrolysis of methoxy group on IV and prototropy from a to diketone (b). On this assumption, examining the behavior of XII against 47% hydrobromic acid seemed of interest for the following reason : the resulting 3,4,5-trihydroxy compound (XX) did not transform into the corresponding diketone, for hydroxyl group at 4-position inhibits prototropy of hydroxyl group at 5-position. If the ring-contraction reaction involved the formation of such α-diketone as b, it should not take place in XX.

In the fact, XII was converted into XX by treating with boiling 47% hydrobromic acid without the ring-contraction. The structure of XX was supported by showing hydroxy band at 3200, 2900~2400 cm^{-1} and lactam carbonyl band at 1640 cm^{-1} in infrared spectrum.

Furthermore, treatment of XI with 47% hydrobromic acid afforded 1-phenyl-3-chloro-4,5-dihydroxy-6(1*H*)-pyridazinone (XVII) in good yield, which was dehalogenated catalitically over paladium-charcoal to 1-phenyl-4,5-dihydroxy-6(1*H*)-pyridazinone (XIX), m.p. 197°, showing no carboxyl band in infrared spectrum.

From these results, it may be concluded that a requirement for the ring-contraction is formation of α-diketone as shown in Chart 1.

The behaviors of XIV and XVI against boiling caustic alkali or 47% hydrobromic acid is very interesting for discussing the scope and limitation of the ring-contraction.

XVI was converted into XIX by heating with 47% hydrobromic acid without the ring-contraction.

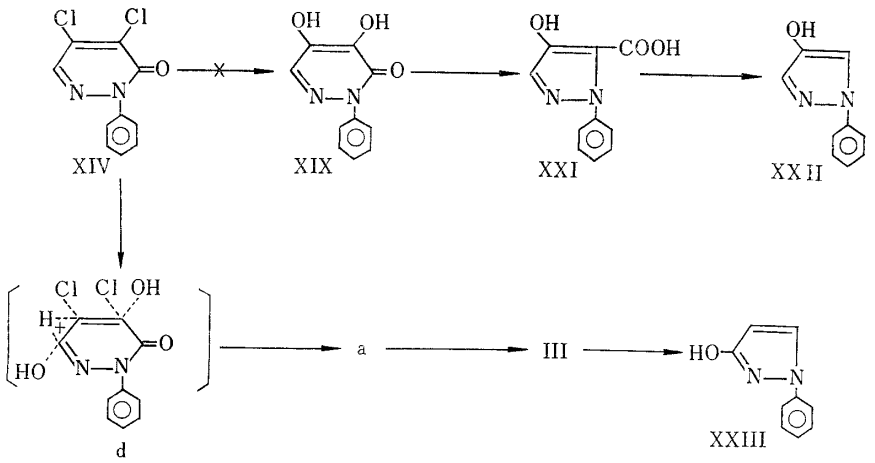

Chart 4.

When XIV was drastically heated with 10% sodium hydroxide, followed by acidification with 10% sulfuric acid, the crystaline mass, m.p. 260° (decomp.), was obtained. Since the product showed absorption band of carboxyl at 2900~2400, 1700 cm^{-1} in infrared spectrum, its structure would be supposed to be 1-phenyl-4-hydroxy-5-pyrazolecarboxylic acid (XXII), although that violate the preceding limitation of the ring-contraction.

Heating the carboxylic acid in a sealed tube without solvent, afforded decarboxylation product, m.p. 155°, in good yield. This decarboxylation product is well concordant with 1-phenyl-3-hydroxy pyrazole[4] (XXIII) prepared by decarboxylation of III rather than expected 1-phenyl-4-hydroxypyrazole[5] (XXII) in both of melting point and infrared spectrum. The derivatives,[1] methyl esther, m.p. 211°, and monoacetate, m.p. 171°~172°, derived from this carboxylic acid showed no melting point depression on admixture with specimens from III.

Apparently, these facts show that the reaction of XIV with sodium hydroxide afforded unexpected III.

For this interesting reaction, we might suggest the mechanism as shown in chart 4, d, involving so-called *cine*-substitution through bridge cation.

The above data could also support the suggestion that introduction of hydroxy group at both of 3- and 5-positions of the ring in the course of reaction is necessary for ring-contraction.

Experimental

1-Phenyl-3-chloro-5-hydroxy-6(1*H*)-pyridazinone (II)——A mixture of I, 0.5 g., 10 ml. of 5% NaOH and 7 ml. of MeOH was refluxed for 4 hr. After having been cooled, the reaction mixture was acidified by 50% H_2SO_4, and the resulting precipitates were recrystallized from MeOH to give II, m.p. 207~208°. Yield : 0.3 g. *Anal.* Calcd. for $C_{10}H_7O_2N_2Cl$: C, 53.95; H, 3.14. Found : C, 54.00; H, 3.45. II was identical with a specimen prepared by the reaction of I (R=OC_2H_5) with 47% HBr, as reported previously.*2

Action of 1-Phenyl-3,4,5-trichloro-6(1*H*)-pyridazinone (VIII) with Methanolic Alkali——To a solution of 0.5 g. of VIII in 10 ml. of MeOH was added 20 ml. of 5% NaOH. The reaction mixture was refluxed for 5 min. After allowing the resulting clear solution to stand at room temperature during overnight, the insoluble substances were separated by filtration, and then the filtrate was acidified by 50% H_2SO_4. The resulting precipitates were recrystallized from MeOH to give 100 mg. of 1-phenyl-4-hydroxy-3,5-dichloro-6(1*H*)-pyridazinone (IX), colorless needles, m.p. 253~254°. No melting point depression was observed on admixture with a sample prepared by the interaction of IX and 47% HBr, as described below.

Action of 1-Phenyl-3,4,5-trichloro-6(1*H*)-pyridazinone (VIII) with Sodium Methoxide——To a solution of 3.5 g. of Na metal dissolved in 150 ml. of MeOH was added 3.5 g. of V in 150 ml. of MeOH under cooling by an ice-water bath. After reaction mixture was allowed to stand at room temperature for 24 hr., the separated crystals were collected by filtration, washed with H_2O, and recrystallized from MeOH to give monomethoxy compound (X), colorless needles, m.p. 142~144°. *Anal.* Calcd. for $C_{11}H_8O_2N_2Cl_2$: C, 48.75; H, 2.97. Found : C, 48.83; H, 3.16.

After removal of X, the reaction mixture was concentrated to the halves of original volume, and diluted by 10 ml. of H_2O. The resulting precipitates were collected by filtration, and recrystallized from MeOH to give dimethoxy compound (XI), colorless needles, m.p. 119~120°. *Anal.* Calcd. for $C_{12}H_{11}O_3N_2Cl$: C, 54.03; H, 4.12. Found : C, 54.27; H, 4.28.

Moreover, the mother liquor was evaporated under reduced pressure to dryness, and the residue thus obtained was recrystallized from hexane to give trimethoxy compound (XII) as colorless prisms, m.p. 102~103°. *Anal.* Calcd. for $C_{13}H_{14}O_4N_2$: C, 59.53; H, 5.38; N, 10.68. Found : C, 58.95; H, 5.32; N, 10.52.

The yield of XII was occasionally very poor in the above mentioned procedure, but increased by prolonging the reaction time from 24 hr. to 72 hr.

4) A. Michaelis, *et al.* : Ber., **40**, 1020 (1907).
5) L. Wolff, A. Lüttringhaus : Ann., **313**, 1 (1900).

1-Phenyl-4-hydroxy-3,5-dichloro-6(1*H*)-pyridazinone (IX)——X was heated with excess 47% HBr at 130° for 2 hr., and after having been cooled the resulting clear solution was diluted with H_2O. The precipitates so obtained were recrystallized from MeOH to give IX, colorless needles, m.p. 253~254°, in fairly quantitative yield. *Anal.* Calcd. for $C_{10}H_6O_2N_2Cl_2$: C, 46.09; H, 2.33. Found : C, 46.30; H, 2.40.

1-Phenyl-4-methoxy-6(1*H*)-pyridazinone (XIII)——To a solution of 0.3 g. of X in 50 ml. of EtOH was added 1.5 g. of 5% Pd-C. The mixture was reduced by catalytic hydrogenation at room temperature and atmospheric pressure (uptake of H_2, 2.2 moles for 3 hr.). After removal of catalyst, the solvent was evaporated under reduced pressure to yield oily residue. The oily residue crystallized spontaneously on adding hexane. Recrystallization from benzene gave 0.1 g. of XIII as colorless needles, m.p. 92~93°. *Anal.* Calcd. for $C_{11}H_{10}O_2N_2$: C, 65.33; H, 4.99. Found : C, 64.20; H, 4.64. XIII was identical with sample prepared from XV by the similar catalitic hydrogenation, on admixture and IR comparison. XIII also showed depression on admixture with 1-phenyl-5-methoxy-6(1*H*)-pyridazinone (V),*2 m.p. 99~101°.

1-Phenyl-4-methoxy-5-chloro-6(1*H*)-pyridazinone (XV)——To a solution of 1 g. of Na metal dissolved in 30 ml. of MeOH was added 0.5 g. of XIV in MeOH. A mixture allowed to stand at room temperature for 48 hr., and then crystals separated were collected by filtration, washed with H_2O and dried. Recrystallization from MeOH afforded XV melting at 157~158° as colorless needles. The mother liquor was evaporated into about one-fifth under reduced pressure, diluted with H_2O, and the precipitated crystals (XV), m.p. 157~158°, were collected. Total yield 0.3 g. *Anal.* Calcd. for $C_{11}H_9O_2N_2Cl$: C, 55.82; H, 3.83. Found : C, 55.80; H, 3.88.

1-Phenyl-4-hydroxy-5-chloro-6(1*H*)-pyridazinone (XVIII)——To a solution of 1 g. of Na metal dissolved in 40 ml. of MeOH was added 0.5 g. of XV in MeOH. A mixture was refluxed at 130° for 4 hr., cooled, diluted with H_2O, and acidified with dil. H_2SO_4. The separated crystals were recrystallized from MeOH to give 0.3 g. of XVIII as colorless needles, m.p. 247°, giving a positive $FeCl_3$ test. IR ν_{max}^{Nujol} cm^{-1} : 3200, 1650. *Anal.* Calcd. for $C_{10}H_7O_2N_2Cl$: C, 53.93; H, 3.14. Found : C, 53.83; H, 3.09. XVIII was also obtained from XV by interaction of 47% HBr as described above for IX. XVIII was distinguished from position isomer, II and 1-phenyl-4-hydroxy-5-chloro-6(1*H*)-pyridazinone[2] by admixture and IR comparison.

1-Phenyl-4,5-dihydroxy-6(1*H*)-pyridazinone (XIX)——XI was reduced by catalytic hydrogenation to give XVI, colorless prisms, m.p. 140~142°(from EtOH-MeOH). The method used here was virtually identical with that described for XIII. *Anal.* Calcd. for $C_{12}H_{12}O_3N_2$: C, 62.06; H, 5.21. Found: C, 62.07; H, 4.98.

A mixture of 0.05 g. of XVI and 5 ml. of 47% HBr was heated at 130~140° for 3 hr., cooled, diluted with two times volume of H_2O. The precipitates thus obtained were recrystallized from MeOH-benzene (1:1) to give 0.02 g. of XIX, colorless needles, m.p. 196~197°. IR ν_{max}^{Nujol} cm^{-1} : 3200, 1630. *Anal.* Calcd. for $C_{10}H_8O_3N_2$: C, 58.82; H, 3.92. Found : C, 58.76; H, 3.81.

XIX was also obtained by following route : XI was submitted to 47% HBr hydrolysis to convert into XVII, colorless needles, m.p. 223~224°, from benzene-MeOH (5:1). *Anal.* Calcd. for $C_{10}H_7O_3N_2Cl$: C, 50.31; H, 2.94. Found : C, 50.40; H, 2.86. XVII was reduced by catalytic hydrogenation to yield XIX, m.p. 196°, according to the procedure described for XIII.

Action of 1-Phenyl-3,4,5-trimethoxy-6(1*H*)-pyridazinone (XII) with 47% Hydrobromic Acid——A mixture of 0.2g. of XII and 8 ml. of 47% HBr was refluxed at 130° for 3 hr. After having been cooled, a reaction mixture was diluted by a large amount of H_2O, and allowed to stand for 24 hr. The crystals so obtained were recrystallized repeatedly from Et_2O-Me_2CO (1:1) to give 0.05 g. of XX, colorless needles, m.p. 230~231°. IR ν_{max}^{Nujol} cm^{-1} : 3200, 2400~2900, 1640. *Anal.* Calcd. for $C_{10}H_8O_4N_2$: C, 54.55; H, 3.66. Found : C, 53.09; H, 3.76.

Rearrangement of 1-Phenyl-4,5-dichloro-6(1*H*)-pyridazinone (XIV) to 1-Phenyl-3-hydroxy-5-pyrazolecarboxylic Acid (III)——A mixture of 4.0 g. of XIV and 60 ml. of 5% NaOH was heated at 130° for 5 hr. On cooling, a reaction mixture was filtered to separate insoluble substances, and acidified with 50% H_2SO_4. Recrystallization of the separated precipitates from EtOH afforded 2.2 g. of III, colorless prisms, m.p. 259~260°(decomp.). IR ν_{max}^{Nujol} cm^{-1} : 3400, 2400~2800, 1700. *Anal.* Calcd. for $C_{10}H_8O_3N_2$: C, 58.82; H, 3.95. Found : C, 58.59; H, 4.00. The derivatives of III, methyl esther, m.p. 214°, and monoacetate, m.p. 171~172°, was identified by admixture with authentic samples in the previous work.*2

The authors express their deep gratitude to Prof. Dr. E. Miyamichi, the president of this college, and Dr. T. Takahashi, Hon. Prof. of Kyoto University, for their encouragement throughout this work. Thanks are also due to members of the pharmaceutical room of Scientific Research Institute for Production Development for IR measurement and Miss K. Masuda, analytical room of this college, for elemental microanalysis.

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

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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.