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148. Takenari Nakagome, Atsuko Misaki, and Toshiaki Komatsu : Synthesis of Pyridazine Derivatives. XIII.*1 Synthesis of N^1-(2-methyl-3-oxo-2,3-dihydro-4-pyridazinyl)-sulfanilamide Derivatives.*2

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Of a number of N^1-4-pyridazinylsulfanilamides prepared by the present authors, N^1-(3-oxo-2,3-dihydro-4-pyridazinyl)-sulfanilamides (II) as well as N^1-(3,6-dimethoxy-4-pyridazinyl)sulfanilamide (I) have shown[1,2] pronounced antimicrobial activities *in vitro*. In contrast, therapeutic effects of N^1-(3-oxo-2,3-dihydro-4-pyridazinyl)sulfanilamides (II) against experimental infections of mice have heen found to decrease.[2] From these results and the fact that only a few reports[3~6] have hitherto been available concerning the synthesis of this series of N^1-heterocyclic sulfonamides having an oxo group and an alkylated nitrogen atom adjacent to an oxo group, it appeared of interest to prepare the structurally related sulfonamides of 2-methyl-3(2*H*)-pyridazinone derivatives.

1. Amino-2-methyl-3(2*H*)pyridazinones

Synthetic routes of amino-2-methyl-3(2*H*)pyridazinones used as essential intermediates are shown in Chart 2 and 3.

Chlormaleic anhydride (IV)[7~9] was condensed with methylhydrazine sulfate in aqueous medium to yield a mixture of two products in a ratio of 1:1, which were separated by difference of their solubility. Chlorination of these condensation products (V and VI) with phosphorus oxychloride produced dichloro derivatives (VII and VIII), and each dichloro derivative gave, on treatment with aqueous ammonium hydroxide, a sole monoamino compounds (IX and X) respectively. Two isomeric condensation products are theoretically possible to be produced in the reaction of IV with methylhydrazine and monoamino derivatives (IX and X) resulting from the amination may have any of four possible structures. The structures of these compounds were proved as follows.

First, the constitution of 2-methyl-4-amino-6-chloro-3(2*H*)pyridazinone (IX) was proved by synthesis from 4-amino-6-chloro-3(2*H*)pyridazinone (XVII), the structure of which had been proved by Kuraishi.[10] On treatment of XVII with dimethyl sulfate in dilute sodium hydroxide solution, there were obtained two methylated compounds, the principal one of which was identical with the above-mentioned aminated product (IX). Since in IX the position of the methyl group is pre-fixed, this experiment indicates that the rest of the molecule of IX have a structure similar to XVII.

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*1 Part XII. T. Nakagome, A. Kobayashi, A. Misaki : This Bulletin, **14**, 1074 (1966).

*2 Presented at the 85th Annual Meeting of the Pharmaceutical Society of Japan at Tokushima, Oct. 28, 1965.

*3 Kasugade-cho, Konohana-ku, Osaka (中込孟也, 三崎敦子, 小松敏昭).

1) Presented at the 9th Annual Meeting of the Japan Society of Chemotherapy. Chemotherapy, **9**, 411 (1961) (abstract).
2) Presented at the 11th Annual Meeting of the Japan Society of Chemothrapy (June, 1964).
3) W.G. Overend, L.F. Wiggins : J. Chem. Soc., **1947**, 549.
4) R.F. Homer, H. Gregory, W.G. Overend, L.F. Wiggins : *Ibid.*, **1948**, 2195.
5) W. Logemann, L. Caprio, K. Artini : C.A., **53**, 18052 (1959).
6) I. Satoda, N. Yoshida, K. Mori : Yakugaku Zasshi, **77**, 703 (1957).
7) A.M. Cliford : U.S. Pat., 2,432,470, Dec. 9, 1947 (C.A., **41**, 2277i).
8) Reppe, *et al.* : Ann. d. Chem., **596**, 157 (1955).
9) Yu.A. Baskakov, N.N. Mel'nikov : Zhur. Obshchei Khim., **24**, 1216 (1954) (C.A., **49**, 12484 (1955)).
10) T. Kuraishi : This Bulletin, **6**, 331 (1958).

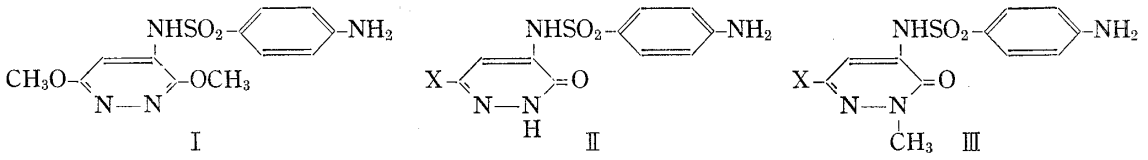


Chart 1. X=H, CH_3, Cl, OCH_3

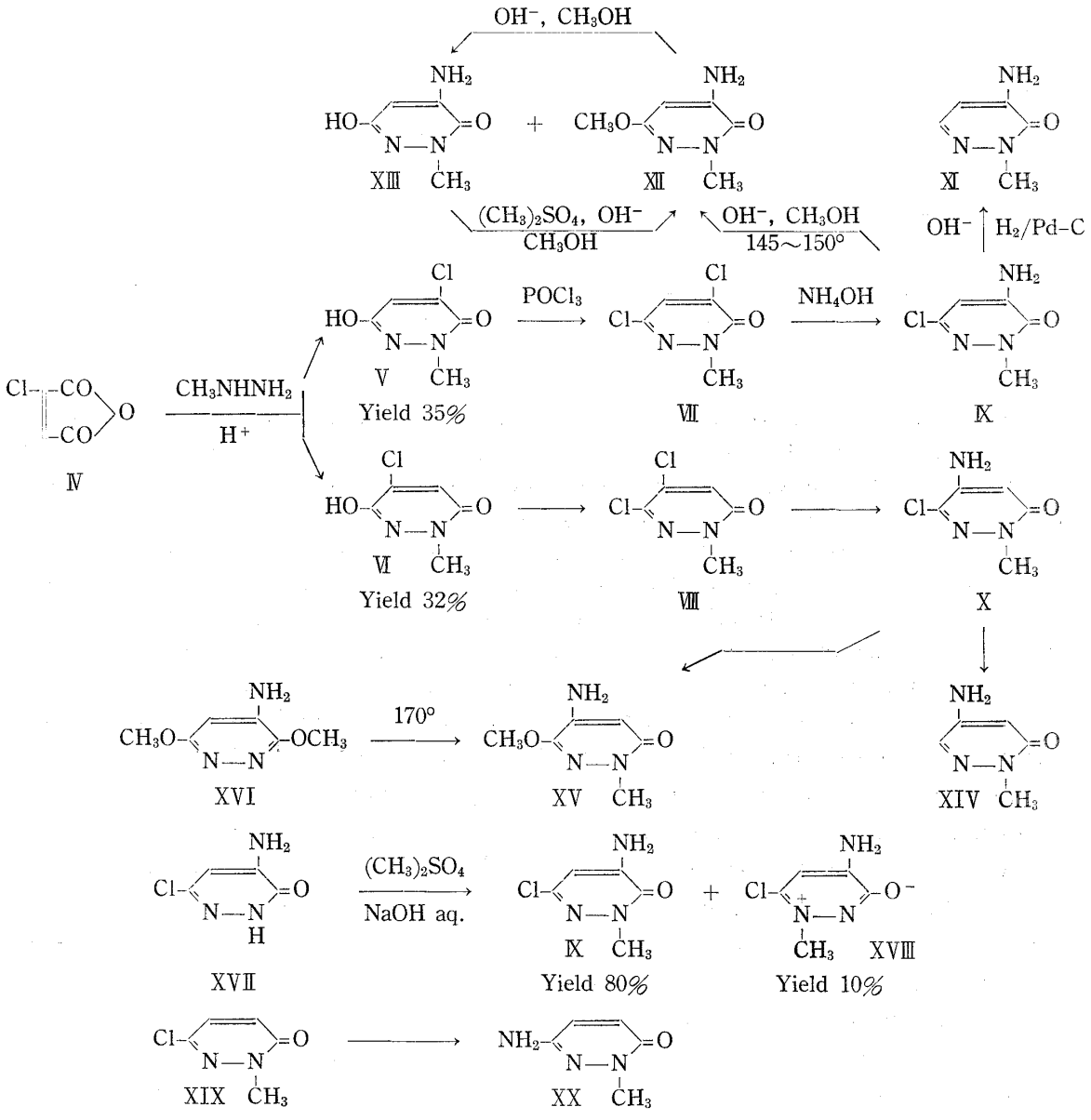


Chart 2.

Thus, Ⅸ is 2-methyl-4-amino-6-chloro-3(2*H*)pyridazinone and it follows that intermediates (Ⅴ and Ⅶ) to Ⅸ are 2-methyl-4-chloro-6-hydroxy-3(2*H*)pyridazinone (Ⅴ) and 2-methyl-4,6-dichloro-3(2*H*)pyridazinone (Ⅶ) and isomeric Ⅵ and Ⅷ are 2-methyl-5-chloro-6-hydroxy-3(2*H*)pyridazinone (Ⅵ) and 2-methyl-5,6-dichloro-3(2*H*)pyridazinone (Ⅷ) respectively.

The second product (XVⅢ) in the methylation whose structure has been assigned as anhydronium compound of 1-methyl-3-hydroxy-4-amino-6-chloropyridazinium hydroxide, will de described in a later paper.

Compound (Ⅸ) yielded 2-methyl-4-amino-3(2*H*)pyridazinone (Ⅺ) by catalytic dehalogenation over palladium on charcoal in dilute sodium hydroxide solution, and gave

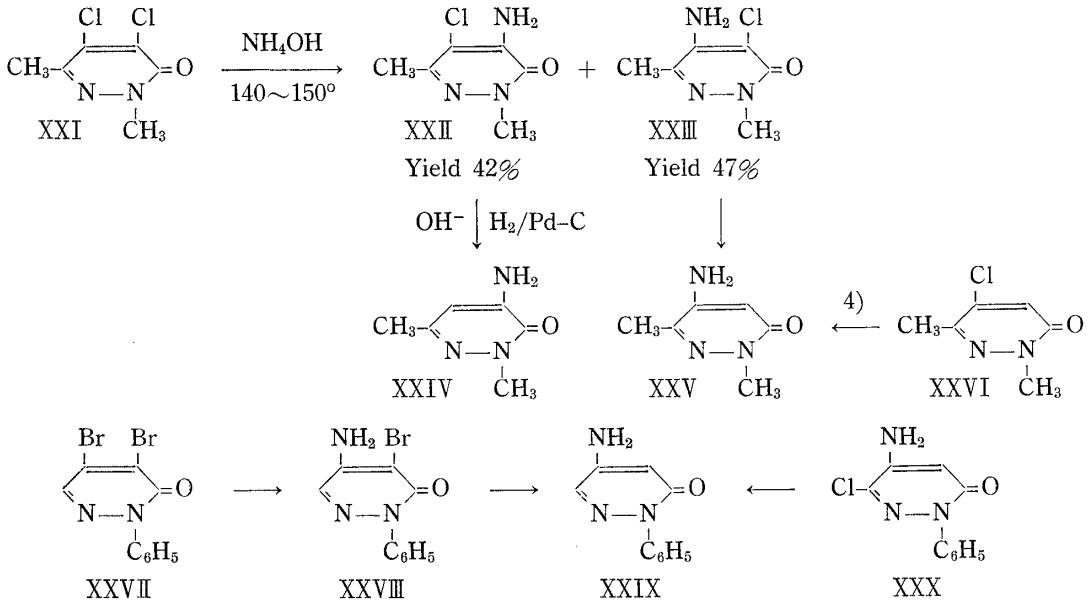


Chart 3.

2-methyl-4-amino-6-methoxy-3(2*H*)pyridazinone (XII) by heating with sodium methoxide or caustic alkali in methanol, both in good yields. In the latter reaction heating for longer hours led to cleavage of the methoxy group at position 6, with formation of 2-methyl-4-amino-6-hydroxy-3(2*H*)pyridazinone (XIII), the constitution of which was proved by its conversion into XII by the action of methyl iodide and pottasium hydroxide in methanol. A similar series of reactions was carried out with X. Elimination of a chlorine atom of X by catalytic reduction resulted in the formation of a halogen-free compound (XIV), which was not identical with the material (XX) obtained from 2-methyl-6-chloro-3(2*H*)pyridazinone (XIX)[11] by treatment with aqueous ammonia.

Since XX must be 2-methyl-6-amino-3(2*H*)pyridazinone from the method of preparation, it follows that XIV must be 2-methyl-5-amino-3(2*H*)pyridazinone and X itself must be 2-methyl-5-amino-6-chloro-3(2*H*)pyridazinone. Replacement of a chlorine atom with the methoxy function afforded 2-methyl-5-amino-6-methoxy-3(2*H*)pyridazinone (XV). Alternatively, when 4-amino-3,6-dimethoxypyridazine (XVI) was heated at 170° for 0.5 hour, the migration of the methyl group of the methoxy group at 3 position took place to a ring nitrogen atom in 2 position, and XV was formed as a sole product.

2-Methyl-4-amino-6-methyl-3(2*H*)pyridazinone (XXIV) was prepared by a synthetic process shown in Chart 3. When 2,6-dimethyl-4,5-dichloro-3(2*H*)pyridazinone (XXI), prepared by the method of Wiggins, *et al.*[12] was allowed to react with aqueous ammonium hydroxide at 140~150°, two monoamino compounds were produced, which were separable by virtue of their different basicities. The basic component (XXIII) was dehalogenated by catalytic hydrogenation in the presence of palladium charcoal as catalyst yielding XXV identical with 5-amino-2,6-dimethyl-3(2*H*)pyridazinone which was alternatively prepared from 5-chloro-2,6-dimethyl-3(2*H*)pyridazinone (XXVI) by treatment with an aqueous ammonia according to the method of Wiggins, *et al.*[4] The isomeric XXII, less basic substance, is, therefore, 4-amino-5-chloro-2,6-dimethyl-3(2*H*)-pyridazinone. Catalytic dehalogenation of XXII gave 4-amino-2,6-dimethyl-3(2*H*)pyridazinone (XXIV).

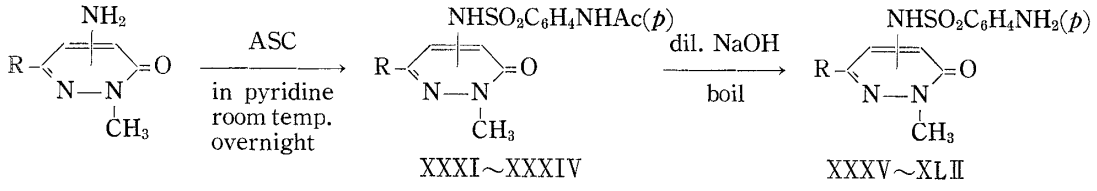
11) K. Eichenberger, A. Staehelin, J. Druey: Helv. Chim. Acta, **37**, 837 (1954).
12) R. F. Homer, H. Gregory, L. F. Wiggins: J. Chem. Soc., **1948**, 2191.

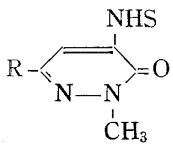
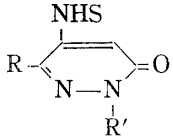
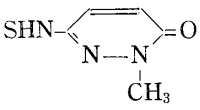
2-Phenyl-5-amino-3(2*H*)pyridazinone (XXIX) was similarly obtained*4 from 2-phenyl-5-amino-6-chloro-3(2*H*)pyridazinone (XXX)[13] by catalytic hydrogenation. It could be more advantageously prepared from 2-phenyl-4,5-dibromo-3(2*H*)pyridazinone (XXVIII).

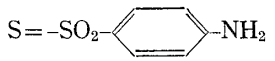
2. N^1-(2-Methyl (or phenyl)-3-oxo-2,3-dihydropyridazinyl)sulfanilamide

Introduction of the sulfanilamide residue was carried out by means of the usual procedure. Thus, these resulting amino-3(2*H*)pyridazinone derivatives (IX), (XI,) (XII), (XIV), (XV), (XX), (XXIV) and (XXIX) were condensed with *p*-acetylsulfanilyl chloride in pyridine to yield N^1-(2-methyl (or phenyl)-3-oxo-2,3-dihydro-4-pyridazinyl)-N^4-acetylsulfanilamides (XXXI～XXXIV) which, on hydrolysis with dilute sodium hydroxide solution, were converted into the desired N^1-(2-methyl(or phenyl)-3-oxo-2,3-dihydro-4-pyridazinyl)sulfanilamides (XXXV～XLII).

Table I. N^1-(2-Methyl-2,3-dihydro-3-oxo-4-pyridazinyl)sulfanilamide



	Comp. No.	Substituent R′	Substituent R	Yield (%) from amine	Yield (%) from N^4-acetate	Appearance	m.p. (°C)
	XXXV		H		90	colorless needles	233 (MeOH)
						colorless needles	247～248(H_2O)
	XXXVI		CH_3	62		colorless leaflets	200～201
	XXXVII		Cl		74	colorless prisms	185～186
	XXXVIII		OCH_3		92	colorless prisms	215
	XXXIX	CH_3	H	59		colorless scales	256～257
	XL	CH_3	OCH_3		86	colorless leaflets	206.5
	XLI	C_6H_5	H	34		colorless needles	230～231
	XLII			87		colorless needles	208

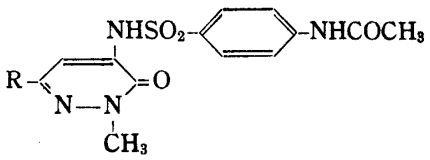


It seemed of interest that, of these sulfonamides listed in Table I, those having the sulfanilamide residue at 4 position of pyridazine nucleus, regardless of the 6-substituents, have been found to possess marked bacteriostatic activities against various microorganisms *in vitro*.[2]

*4 Recently reported by K. Dury : Angew. Chem., **77**, 282 (1965).

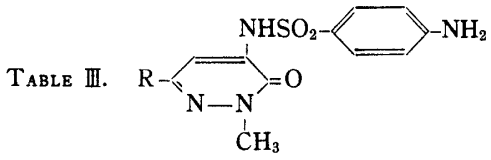
13) J. Druey, Kd. Meier, B.H. Ringier : Helv. Chim. Acta, **37**, 523 (1954).

TABLE II.



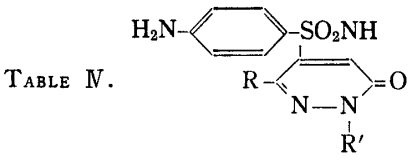
Comp. No.	R	Yield (%)	Appearance	m.p. (℃)	Formulae	Analysis Calcd. C	H	N	Found C	H	N
XXXI	H	84	colorless scales	270～271	$C_{13}H_{14}O_4N_4S$	48.45	4.38	17.39	48.58	4.48	17.17
XXXII	Cl	50	colorless scales	234.5～235	$C_{13}H_{13}O_4N_4SCl$	43.76	3.67	15.70	44.36	3.66	14.83
XXXIII	OCH_3	86	colorless prisms	242～243	$C_{14}H_{16}O_5N_4S$	47.73	4.58	15.90	47.86	4.67	15.41
XXXIV	OCH_3	57	colorless prisms	264	$C_{14}H_{16}O_5N_4S$	47.73	4.58	15.90	48.16	4.81	15.90

TABLE III.



Comp. No.	m.p. (℃)	R	Formulae	Analysis Calcd. C	H	N	Found C	H	N
XXXV	233	H	$C_{11}H_{12}O_3N_4S$	47.14	4.32	20.89	47.36	4.39	20.21
	247～248	H					47.15	4.33	20.24
XXXVI		CH_3	$C_{12}H_{14}O_3N_4S$	48.98	4.80	19.04	49.32	5.07	19.16
XXXVII		Cl	$C_{11}H_{11}O_3N_4SCl$	41.98	3.52	17.80	42.42	3.88	17.50
XXXVIII		OCH_3	$C_{12}H_{14}O_3N_4S$	46.45	4.55	18.06	46.55	4.55	18.14

TABLE IV.



Comp. No.	R	R′	Formulae	Analysis Calcd. C	H	N	Found C	H	N
XXXIX	H	CH_3	$C_{11}H_{12}O_3N_4S$	47.14	4.32	19.99	47.02	4.33	20.39
XL	OCH_3	CH_3	$C_{12}H_{14}O_4N_4S$	46.45	4.55	18.06	46.52	4.68	17.81
XLI	H	C_6H_5	$C_{16}H_{14}O_3N_4S$	56.14	4.12	16.37	56.45	4.29	16.05
XLII (3-sulfanilamido)		CH_3	$C_{11}H_{12}O_3N_4S$	47.14	4.32	19.99	47.39	4.22	19.77

Experimental*5

Condensation of Chloromaleic Anhydride (IV) with Methylhydrazine Sulfate——To a boiling solution of 21.6 g. (0.15 mole) of methylhydrazine sulfate in 200 ml. of water was added 20 g. (0.15 mole) of IV and boiling was continued for 2.5 hr. The crystals which separated on cooling were collected, boiled with ca. 80 ml. of MeOH and 5.7 g. of insoluble colorless prisms was filtered, m.p. 257°. Concentration of the filtrate to 30 ml. gave a second crop, 1.95 g., m.p. 257°, total 7.65 g. (32%). *Anal.* Calcd. for $C_5H_5O_2N_2Cl$ (2-methyl-5-chloro-6-hydroxy-3(2*H*)pyridazinone (VI)): C, 37.40; H, 3.14; N, 17.45. Found: C, 37.23; H, 3.46; N, 17.08. Evaporation of the methanolic filtrate and recrystallization of the residue from ether yielded 3.6 g. of colorless needles melting at 184~188° and 1.65 g. of a second crop, m.p. 182~187°. The aqueous filtrate from the crude mixture was concentrated and the precipitate which separated on cooling was recrystallized from ether giving further 3.1 g. of colorless needles, m.p. 186~189°. Recrystallization of the combined crystals (8.35 g. (35%)) of 2-methyl-4-chloro-6-hydroxy-3(2*H*)pyridazinone (V) raised the m.p. to 185~186°. *Anal.* Calcd. for $C_5H_5O_2N_2Cl$: C, 37.40; H, 3.14; N, 17.45. Found: C, 37.39; H, 3.40; N, 17.10.

2-Methyl-4,6-dichloro-3(2*H*)pyridazinone (VII)——A mixture of 6.0 g. of 2-methyl-4-chloro-6-hydroxy-3(2*H*)pyridazinone (V) and 60 ml. of $POCl_3$ was heated for 30 min. at 100°. Excess phosphorus oxychloride was remove *in vacuo*, and the residue was poured into ice water, made alkaline with 28% NH_4OH, extracted with ether. The ether was removed by distillation, and the residue dissolved in benzene and poured on alumina column for chromatography. The initial fraction afforded 0.71 g. (10%) of VII as yellow needles, m.p. 75.5~76° after recrystallization from *n*-hexane. The filtrate, upon concentration, gave an additional 0.07 g. (1%) of VII, m.p. 73~75°. *Anal.* Calcd. for $C_5H_4ON_2Cl_2$: C, 33.82; H, 2.25; N, 15.65. Found: C, 34.43; H, 2.44; N, 15.68. In addition to VII, there were obtained 0.11 g. of yellow crystals, m.p. 207~211° which were scarcely soluble in *n*-hexane. *Anal.* Found: C, 40.30; H, 1.82; N, 18.00; Cl, 33.78.

2-Methyl-5,6-dichloro-3(2*H*)pyridazinone (VIII)——A mixture of 5.3 g. of VI and 50 ml. of $POCl_3$ was heated for 30 min. at 100°. The reaction mixture was worked up as described above for VII. Recrystallization of the product from $(iso\text{-}Pr)_2O$ gave 3.97 g. (64%) of VIII melting at 97~98° and 0.17 g. (2.7%) of a second crop as pale yellow needles, m.p. 94~98°. *Anal.* Calcd. for $C_5H_4ON_2Cl_2$: C, 33.82; H, 2.25; N, 15.65. Found: C, 34.62; H, 2.32; N, 15.10.

2-Methyl-4-amino-6-chloro-3(2*H*)pyridazinone (IX)——A mixture of 0.2 g. of VII, 10 ml. of NH_4OH (28%), and 10 ml. of water was heated at 140~150° (bath) for 10 hr. in an autoclave. The resulting solution was evaporated to dryness under reduced pressure, and the residue was extracted with boiling AcOEt. The residue (0.19 g., m.p. 122~131°) obtained by concentration of the extract was dissolved in $CHCl_3$, passed through an alumina column for decoloration. Removal of $CHCl_3$ by distillation left 0.13 g. (73%) of the product which was recrystallized from AcOEt to colorless needles, m.p. 145~145.5°. *Anal.* Calcd. for $C_5H_6ON_3Cl$: C, 37.61; H, 3.79; N, 26.32. Found: C, 38.17; H, 4.00; N, 26.12.

2-Methyl-5-amino-6-chloro-3(2*H*)pyridazinone (X)——A mixture of 0.5 g. of VIII, 15 ml. of 28% NH_4OH, and 15 ml. of water was heated at 140~150° (bath) for 10 hr. in an autoclave. Colorless needles, almost pure X separated on cooling, were filtered, 0.23 g. (52.3%), m.p. 166.5~168°. Concentration of the filtrate gave an additional crop, which was recrystallized from AcOEt to colorless plates, m.p. 167~168°. Yield 0.06 g., total 66%. The analytical sample, colorless plates, m.p. 168~169°, was obtained by recrystallization from AcOEt. *Anal.* Calcd. for $C_5H_6ON_3Cl$: C, 37.63; H, 3.79; N, 26.33; Cl, 22.22. Found: C, 38.47; H, 3.79; N, 26.38; Cl, 22.23.

2-Methyl-4-amino-3(2*H*)pyridazinone (XI)——A mixture of 44 g. of IX, 15 g. of 5% Pd on charcoal and 275 ml. of *N* NaOH was shakan with H_2 at an atmospheric pressure. After about 8 hr. 1 mole of H_2 was taken up. The catalyst was filtered and 30 g. (87%) of XI was obtained as colorless needles, m.p. 174~175° after concentration of the filtrate and chilling. This was recrystallized from AcOEt to colorless rods, m.p. 175~176°. *Anal.* Calcd. for $C_5H_7ON_3$: C, 47.99; H, 5.64; N, 33.58. Found: C, 48.20; H, 5.84; N, 33.58.

2-Methyl-5-amino-3(2*H*)pyridazinone (XIV)——A mixture of 0.2 g. of X, 0.2 g. of 5% Pd on charcoal, 1.5 ml. of *N* NaOH and 30 ml. of H_2O was shaken with H_2 at an atmospheric pressure. The absorption of hydrogen ceased after 38 ml. of H_2 was taken up. After removal of the catalyst, the filtrate was neutralized with 2*N* HCl and evaporated *in vacuo* to dryness. Extraction of the residue with boiling AcOEt, and removal of AcOEt by distillation afforded 0.14 g. (87.5%) of XIV, m.p. 192.5~193.5°, which was recrystallized from AcOEt to colorless plates, m.p. 193.5~194.5°, 0.12 g. (76.5%). Concentration of the mother liquor gave 0.03 g. (19%) of an additional crop. *Anal.* Calcd. for $C_5H_7ON_3$: C, 47.99; H, 5.64; N, 33.58. Found: C, 47.36; H, 5.98; N, 33.00.

2-Methyl-4-amino-6-methoxy-3(2*H*)pyridazinone (XII)——i) From IX. A mixture of 150 g. (0.968 mole) of IX, 122.5 g. (1.9 moles) of KOH (purity 86%) (or 70 g. of NaOH) and 1200 ml. of MeOH was heated

*5 All melting points are uncorrected. Infrared and ultraviolet spectra were respectively measured with a Shimadzu IR Infrared Spectrophotometer and a Shimadzu RS-27 Recording Spectrophotometer.

at 140° for 4 hr. in an autoclave. After removal of MeOH the residue was triturated with water for filtration. There was obtained 118.5 g. of XII, m.p. 159~160°. The analytical sample, colorless prisms, m.p. 159~160°, was obtained after recrystallization from MeOH or H_2O with charcoal treatment. *Anal.* Calcd. for $C_6H_9O_2N_3$: C, 46.44; H, 5.85; N, 27.08. Found: C, 46.59; H, 6.08; N, 26.62.

ii) From XIII. To a stirred solution of 1 g. of XIII (0.0071 mole) in 20 ml. of methanolic potassium hydroxide containing 0.53 g. of KOH, 1.1 g. (0.0087 mole) of dimethyl sulfate was added dropwise. The mixture was then refluxed for 1 hr. After cooling, the precipitated inorganic material was removed by filtration, and the filtrate concentrated and 5 ml. of water added to the residue, whereupon 0.49 g (45%) of crude XII precipitated and was separated from the mixture by filtration. The filtrate (filtrate A) was set aside to be examined later. Recrystallization of the crude (XII) from water gave 0.3 g. (35.6%) of colorless needles, m.p. 159~160°, undepressed when mixed with an authentic sample of XII. The IR spectra of the two samples were identical. The aqueous filtrate (filtrate A) was concentrated *in vacuo* to ca. 10 ml. Extraction with $CHCl_3$ and evaporation of the extract left 0.17 g. of a mixture of XII and the starting material (XIII). The aqueous layer was further concentrated and the concentrate was acidified to pH 3 with 6*N* HCl. The separated crystals, weighing 0.15 g. (15%), m.p. 242~244°, were recrystallized from EtOH giving 0.11 g. (11%) of the starting material, m.p. 248~250°, undepressed on admixture with an authentic sample of XIII. The aqueous filtrate was again evaporated to dryness, the residue was extracted with boiling abs. EtOH, and the ethanolic extract was filtered. After evaporation of the EtOH, the residue was dissolved in $CHCl_3$–MeOH mixture, and the solution was poured on alumina column for chromatography. Elution with $CHCl_3$ furnished 0.15 g. (13.7%) of colorless plates, m.p. 188~189°, which were not identified. Recrystallization from EtOH raised the melting point to 189~190°. *Anal.* Calcd. for $C_6H_9O_2N_3$: C, 46.44; H, 5.85; N, 27.08. Found: C, 47.26; H, 5.91; N, 27.52.

2-Methyl-5-amino-6-methoxy-3(2*H*)pyridazinone (XV)——i) From X. A solution of 0.5 g. (0.0313 mole) of X in 30 ml. of MeOH containing 0.5 g. (0.076 mole) of 86% KOH was heated at 140~150° (bath temp.) for 7 hr. in a sealed tube. The resulting solution was evaporated to dryness and water (20~30 ml.) was added to the residue. Extraction with $CHCl_3$, drying and evaporation of the extract left behind 0.33 g. (69%) of XV. This was crystallized from MeOH–AcOEt with charcoal treatment gave 0.18 g. (37.5%) of colorless plates, m.p. 196~197° and a second crop 0.12 g. (25%), m.p. 193~194°. *Anal.* Calcd. for $C_6H_9O_2N_3$: C, 46.44; H, 5.85; N, 27.08. Found: C, 47.07; H, 5.88; N, 26.55.

ii) From XVI. Five g. of XVI was heated at 170° for 0.5 hr. The molten crystals again resolidified. The product was dissolved in MeOH, and AcOEt was added until crystals began to separate. Recrystallization from MeOH–AcOEt with alumina treatment for decoloration gave 2.2 g. (45%) of yellow needles, m.p. 195~196°, undepressed on admixture with a sample of XV prepared from X. Concentration of the mother liquor gave a further crop, 1.1 g. (33%), m.p. 192~194°.

2-Methyl-4-amino-6-hydroxy-3(2*H*)pyridazinone (XIII)——A mixture of 20 g. (0.133 mole) of XII, 35.2 g. (0.533 mole) of KOH (purity 85%)and 300 ml. of MeOH was heated at 150° in an autoclave for 10 hr. After cooling the deposited crystals were collected, and dissolved in 20 ml. of water. Acidification with HCl to pH 5, caused the precipitation of 5.8 g. (31%) of XIII, m.p. 250.5~251°. The filtrate (filtrate A) was set aside to be examined later. The methanolic filtrate was evaporated to dryness, and the residue was washed with ca. 120 ml. of water to give 4.7 g. (23.5%) of the crude (XII), m.p. 157~159°. This material was recrystallized from AcOEt to give 4.4 g. (22%) of colorless plates, m.p. 160~160.5, undepressed on admixture with the starting material (XII). The aqueous filtrate from XII was extracted with $CHCl_3$, and the extract was evaporated. Recrystallization of the residue from AcOEt gave an additional crop of the starting material, m.p. 157~158°, yield 0.5 g.; total 5.2 g. (26%). The aqueous layer from $CHCl_3$ extraction was concentrated to 120 ml. The crude (XIII) was precipitated by addition of 6*N* HCl at pH 7.0~6.6, weighing 4.4 g. (22.1%), m.p. 246~247° (filtrate B). Recrystallization from MeOH afforded 3.9 g. (20.4%) of pale yellow needles of XIII, m.p. 249~249.5°.

The filtrate A and B were combined and evaporated to dryness *in vacuo*. The residue was extracted with boiling EtOH and the extract was filtered while being hot and evaporated to dryness. The solution of the product, dissolved in 2*N* NaOH, was adjusted with 6*N* HCl to pH 7.0~5.5, producing 1.6 g. (6.8%) of crude XIII, m.p. 248°. This was recrystallized from MeOH to give 1.3 g. (1.1%) of a second crop, m.p. 247~249°. Total yield of crude XIII; 11.8 g. (62%). *Anal.* Calcd. for $C_5H_7O_2N_3$: C, 42.55; H, 5.00; N, 29.78. Found: C, 42.71; H, 5.20; N, 29.89.

2-Methyl-6-amino-3(2*H*)pyridazinone (XX)——A mixture of 3 g. of XIX and 60 ml. of 28% NH_4OH was heated in an autoclave at 155~160° (bath temp.) for 20 hr. The reaction mixture was evaporated to dryness, extracted with boiling AcOEt and the extract was filtered while being hot and evaporated. The residue was dissolved in $CHCl_3$ and the solution was poured onto an alumina column for chromatography. The fractions which showed one spot of Rf 0.23 on thin-layer chromatography (TLC) (Silica Gel plate, $CHCl_3$–MeOH (9:1) solvent, detected by I_2 vapor) were combined and $CHCl_3$ was removed to give 0.51 g. (21%) of the crude (XX), which was purified by repeated recrystallization from EtOH giving yellow needles, m.p. 220~221°. *Anal.* Calcd. for $C_5H_7ON_3$: C, 47.99; H, 5.64; N, 33.58. Found: C, 48.49; H, 5.96; N, 33.59.

Methylation of 4-Amino-6-chloro-3(2*H*)pyridazinone (XVII) with Dimethyl Sulfate will be reported in the following paper.[14]

Amination of 2,6-Dimethyl-4,5-dichloro-3(2*H*)pyridazinone (XXI)——A mixture of 4 g. of XXI, 20 ml. of 28% NH_4OH and 20 ml. of water was heated at 140~150° (bath temp.) for 10 hr. in an autoclave. The solution was evaporated to dryness. The residue was dissolved in 40 ml. of 6*N* HCl and the solution resulting was extracted with $CHCl_3$. After drying over anhyd. Na_2SO_4, the $CHCl_3$ was distilled off and the residue (1.5 g., 42%) was recrystallized from acetone giving colorless rhombs, m.p. 169~170°. Yield 0.7 g. (19.5%). *Anal.* Calcd. for $C_6H_8ON_3Cl$ (4-amino-5-chloro-2,6-dimethyl-3(2*H*)pyridazinone (XXII)): C, 41.47; H, 4.61; N, 24.19. Found: C, 41.65; H, 4.68; N, 24.49. The aqueous hydrochloric acid layer was made alkaline with dil. NaOH. Extraction with $CHCl_3$ and removal of the solvent left 1.7 g. (47%) of the residue, which was recrystallized from acetone to colorless plates, m.p. 190~191°. Yield, 1.2 g. (33.4%). *Anal.* Calcd. for $C_6H_8ON_3Cl$ (2,6-dimethyl-4-chloro-5-amino-3(2*H*)pyridazinone (XXIII)): C, 41.47; H, 4.61; N, 24.19. Found: C, 41.10; H, 4.59; N, 23.56.

4-Amino-2,6-dimethyl-3(2*H*)pyridazinone (XXIV)——A mixture of 0.2 g. of XXII, 1 ml. of 28% NH_4OH, 20 ml. of MeOH and 5% Pd on charcoal was shaken with hydrogen under atmospheric pressure. The catalyst was filtered, the filtrate was evaporated to dryness and the residue was extracted with boiling AcOEt. The extract was evaporated, 0.13 g. (81%) of crude XXIV being obtained. Recrystallization from AcOEt afforded 0.11 g. (69%) of colorless plates, m.p. 141~142°. *Anal.* Calcd. for $C_6H_9ON_3$: C, 51.78; H, 6.52; N, 30.20. Found: C, 51.73; H, 6.77; N, 30.53. Picrate, yellow plates, m.p. 161~162° (from EtOH). *Anal.* Calcd. for $C_6H_9ON_3 \cdot C_6H_3O_7N_3$: C, 39.13 H, 3.28; N, 22.82. Found: C, 38.60; H, 3.62; N, 22.34. Hydrochloride, m.p. 232° (decomp.) (from EtOH or H_2O).

5-Amino-2,6-dimethyl-3(2*H*)pyridazinone (XXV)——i) From XXIII. A mixture of 1 g. of XXIII, 6 ml. of 28% NH_4OH, 50 ml. of MeOH and 2 g. of 5% Pd-C was shaken with hydrogen under atmospheric pressure, and worked up in the same manner as described for XXIV, except that the crude product was recrystallized from acetone to give 0.55 g. (69%) of XXV, colorless prisms, m.p. 168~169°. *Anal.* Calcd. for $C_6H_9ON_3$: C, 51.78; H, 6.52; N, 30.20. Found: C, 51.29; H, 6.36; N, 30.40. Picrate; m.p. 163~164°, yellow prisms (EtOH). *Anal.* Calcd. for $C_6H_9ON_3 \cdot C_6H_3O_7N_3$: C, 39.13; H, 3.28; N, 22.82. Found: C, 39.44; H, 3.51; N, 22.19. Hydrochloride, m.p. 266~267° (decomp.). *Anal.* Calcd. for $C_6H_{10}ON_3Cl$: C, 40.97; H, 5.69; N, 23.90. Found: C, 41.07; H, 5.69; N, 23.62. 5-Acetamide compound colorless needles, m.p. 232~233°, was prepared by treatment with boiling Ac_2O. *Anal.* Calcd. for $C_8H_{11}O_2N_3$: C, 53.03; H, 6.13; N, 23.19. Found: C, 52.75; H, 5.96; N, 22.91. Homer, *et al.*[4] record m.p. 163° for the base (XXV), m.p. 130° for the picrate, m.p. 245° (decomp.) for the hydrochloride, m.p. 227° for the acetamide.

ii) From 5-chloro-2,6-dimethyl-3(2*H*)pyridazinone (XXVI). The procedure of Homer *et al.*[4] was partly modified as follows. A mixture of 2 g. of XXVI and aqueous ammonia (28% NH_4OH 70 ml. and water 70 ml.) was heated at 140~150° in an autoclave for 50 hr. The mixture was evaporated to dryness under reduced pressure and the residue was extracted with two 50 ml. portions of boiling AcOEt. Evaporation of the solvent from AcOEt extract left 1.4 g. (80%) of XXV, m.p. 162~165°, which separated as colorless prisms after recrystallization from acetone, m.p. 168~169°, undepressed on admixture with a sample prepared in i).

2-Phenyl-4-bromo-5-amino-3(2*H*)pyridazinone (XXVIII)——A mixture of 20 g. of 2-phenyl-4,5-dibromo-3(2*H*)pyridazinone (XXVII), 100 ml. of 28% NH_4OH and 100 ml. of water was heated in an autoclave at 130° (bath temp.) for 10 hr. On concentration of the solution the crystals which separated were collected to give 13 g. (83%) of the crude product, which was recrystallized from EtOH forming colorless scales, m.p. 220~221°. Yield, 9 g. (57%). *Anal.* Calcd. for $C_{10}H_8ON_3Br$: C, 45.09; H, 3.00; N, 15.78. Found: C, 44.91; H, 2.82; N, 16.33.

2-Phenyl-5-amino-3(2*H*)pyridazinone (XXIX)——2-Phenyl-4-bromo-5-amino-3(2*H*)pyridazinone(XXVIII)or 2-phenyl-5-amino-6-chloro-3(2*H*)pyridazinone (XXX) was dissolved in *N* NaOH solution. The solution was mixed with almost an equal amount of 5% Pd-C and shaken with H_2 at an atmospheric pressure. After the reduction was complete, the catalyst was filtered off and the filtrate was concentrated and chilled. The precipitated (XXIX) was recrystallized from water or EtOH to colorless prisms, m.p. 209~211°. A mixture of both samples prepared from XXVIII and XXX showed no depression of melting point on admixture. *Anal.* Calcd. for $C_{10}H_9ON_3$: C, 64.16; H, 4.85; N, 22.45. Found: C, 64.64; H, 4.96; N, 22.22.

Preparation of N^1-(2-Methyl-3-oxo-2,3-dihydro-4-pyridazinyl)-N^4-acetylsulfanilamides——To a stirred mixture of 2-methyl-4-amino-3(2*H*)pyridazinone in ten fold excess of pyridine was added 10% excess of the stoichiometric amount of acetylsulfanilyl chloride below 10° with external cooling. The resulting mixture was stirred and kept at room temperature overnight, and then poured into ice water containing an equivalent amount of NaOH. The pyridine was removed by distillation under reduced pressure, and the N^4-acetylsulfanilamide which separated was collected. The analytical sample was obtained after recrystallization from MeOH (Table II). The reaction conditions were not necessarily optimal, and better yields of the products would have been given. The starting material was recovered from the aqueous filtrate after concentration *in vacuo*, neutralization and chilling, and was identified by mixture melting point determination.

14) Part XIV. T. Nakagome, A. Misaki, A. Murano: This Bulletin, **14**, 1090 (1966).

The sulfonamides (XXXVI), (XXXIX), (XLI), (XLII) were prepared from XXIV, XV, XX, XXIX, according to the following procedure, without isolating the intermediate N^4-acetates.

Preparation of N^1-(2-Methyl(or phenyl)-3-oxo-2,3-dihydro-4-pyridazinyl)sulfanilamides——The N^4-acetylsulfonamide was dissolved in ten times the amount of 10% NaOH solution and the solution was refluxed for 1 hr. The filtered solution was acidified with HCl to pH 4.0. The precipitated sulfonamide was collected, washed and dried. Yield, quantitative. The product was purified by recrystallization from MeOH or EtOH.

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Summary

Five kinds of N^1-(2-methyl-3-oxo-2,3-dihydro-4(or 5)-pyridazinyl)sulfanilamides were prepared starting from chloromaleic anhydride. In addition, three kinds of N^1-(2-methyl(or phenyl)-3-oxo-2,3-dihydro-4(or 5)-pyridazinyl)sulfanilamides were also prepared.

It is of interest that of these sulfonamides prepared, those substituted with the sulfanilamide group at 4-position of pyridazine nucleus have shown marked activities *in vitro*.

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149. Takenari Nakagome, Atsuko Misaki,*1 and Atsushi Murano*2 : Synthesis of Pyridazine Derivatives. XIV.*3 On the Methylation of 4-Amino-3(2*H*)pyridazinone Derivatives.*4

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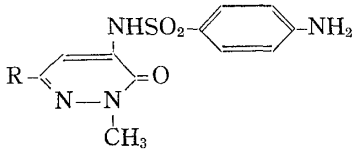
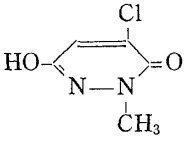
In Part XIII*3 of this series, we have described the preparation of a series of N^1-(2-methyl-3-oxo-6-substituted-2,3-dihydro-4-pyridazinyl)sulfanilamides (Chart 1, A~D), and the intermediates required in their synthesis from chloromaleic anhydride. Some of these sulfonamides showed marked promise as chemotherapeutic agents.



A : R=H B : R=CH_3
C : R=Cl D : R=OCH_3



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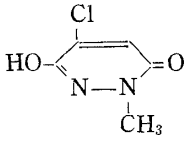

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Chart 1.

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