phosphate in dimethylformamide followed by removal of the protecting group. Similarly, from isopropylidene-adenosine, -guanosine, -cytidine and -uridine, the corresponding 5′-nucleotides were obtained and from thymidine, its mono- and di-phosphate. Furthermore, inosine 5′-phosphate and 5′-diphosphate were prepared by heating isopropylidene inosine with tri-*n*-butylammonium-pyrophosphate or -polyphosphate.

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146. Takenari Nakagome, Akira Kobayashi, Atsuko Misaki, Toshiaki Komatsu*1, Toru Mori, and Seiichi Nakanishi*2: Synthesis of Pyridazine Derivatives. XI.*3 Synthesis of N^1-4-Pyridazinylsulfanilamide Derivatives.*4

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In an earlier paper[1] of this series, the synthesis of a series of N^1-4-pyridazinylsulfanilamides including N^1-(3,6-dimethoxy-4-pyridazinyl)sulfanilamide[1,2] (XII) was reported. A superior chemotherapeutic activity[3] of XII prompted further study on the synthetic procedure[1] of XII. The present paper describes the new finding which have been revealed in the course of the study.

It has already been reported[1] that 4-amino-3,6-dichloropyridazine (I), on treatment with one molecular proportion of sodium methoxide or caustic alkali in methanol, yielded 3-methoxy compound (II) in good yield, and with an excess of the reagent at an elevated temperature it gave two products, *i.e.*, 4-amino-3,6-dimethoxypyridazine (III) and an alkali-soluble by-product which afforded 4-amino-6-chloro-3(2*H*)pyridazinone (IV) after recrystallization from water.

Thin-layer chromatographic study of the crude alkali-soluble product showed an additional spot besides (IV). It was found possible to separate the crude mixture, by fractional acidification of the alkaline solution of the mixture, with the result that less acidic 4-amino-6-methoxy-3(2*H*)pyridazinone (V), m.p. 276~277° was obtained in addition to the known 4-amino-6-chloro-3(2*H*)pyridazinone (IV), m.p. 300~301°, in a ratio of 1:9. Structural elucidation of V is dealt with later. By heating with methyl alcoholic sodium methoxide or caustic alkali, V was obtained from III, but not from IV. These experiments indicate that mechanisim of the reaction is such that II is first formed from I, and then the replacement of chlorine atom and the demethylation in II take place side by side to yield III and IV respectively, and subsequently part of III suffers cleavage of methoxy group at 3 position to give V.

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*3 Part X. T. Nakagome: Yakugaku Zasshi, **83**, 934 (1963).
*4 Presented at the 85th Annual Meeting of the Pharmaceutical Society of Japan at Tokushima, Oct. 28, 1965.

1) Part VI. T. Nakagome, T. Hayama, T. Komatsu, Y. Eda: Yakugaku Zasshi, **82**, 1103 (1962).
2) M. Yanai, T. Kuraishi, T. Kinoshita: *ibid.*, **81**, 708 (1961).
3) Presented at the 9th Annual Meeting of the Japan Society of Chemotherapy. Chemotherapy, **9**, 411 (1961) (abstract).

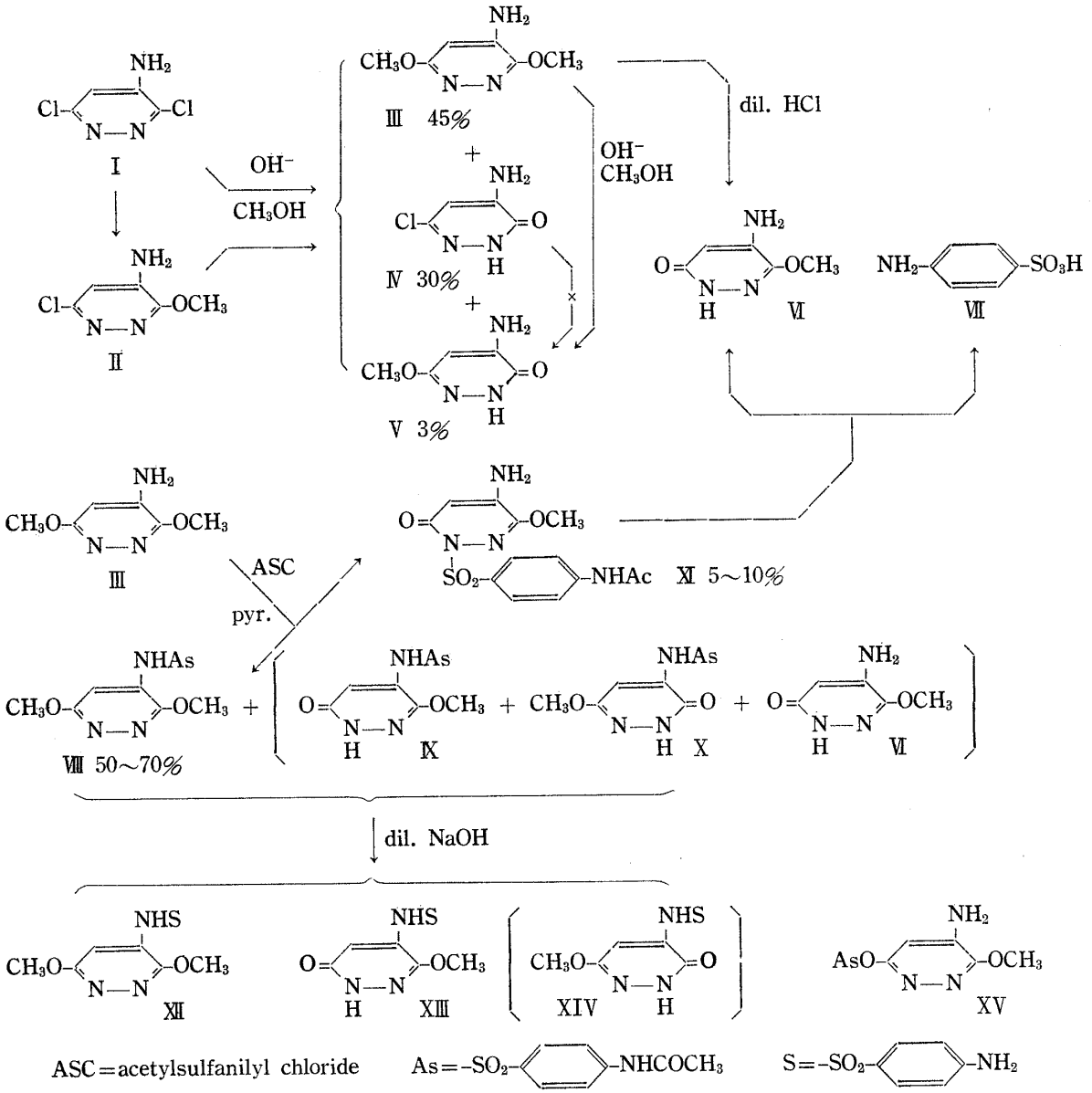


Chart 1.

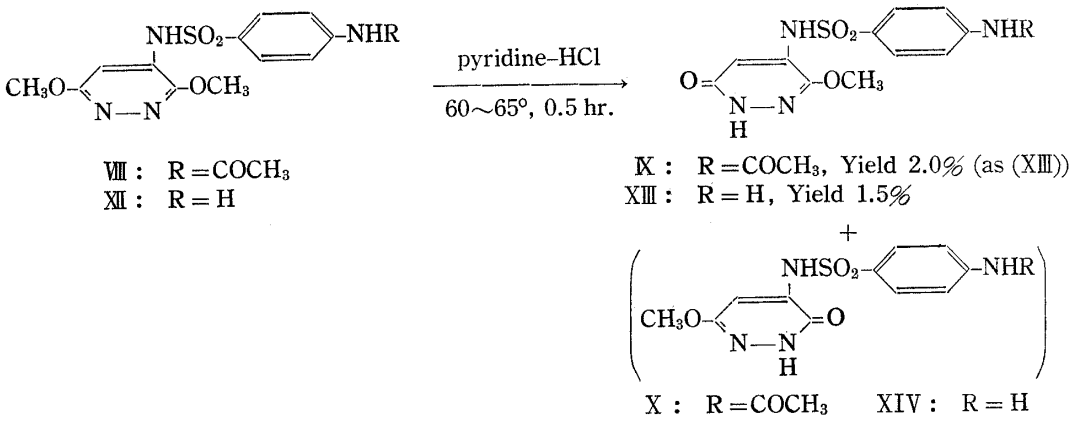


Chart 2.

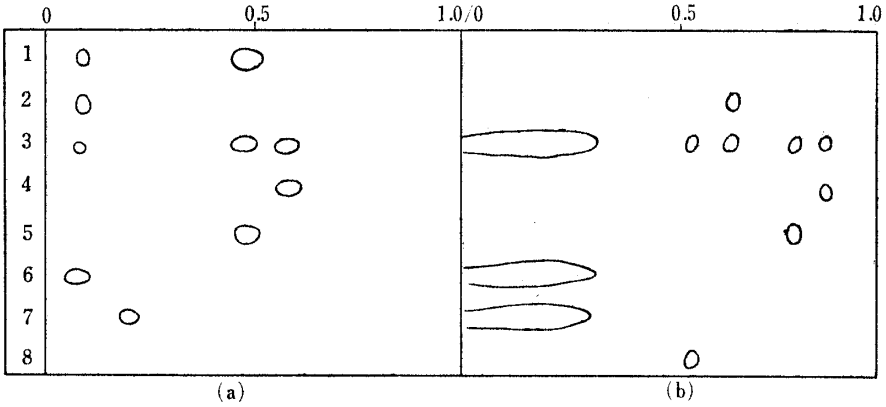


Fig. 1. Thin-layer Chromatogram of a Product from the Reaction of Ⅲ and ASC in Pyridine

Layer: Silica Gel G, activated at 105° for 30 min.
Detection: I_2 vapor
Samples: 1. An acidic fraction (crude Ⅷ) 2. A non-acidic fraction (Ⅺ) 3. A filtrate 4. Ⅲ 5. Ⅷ 6. Ⅸ 7. Ⅹ 8. Ⅵ
Solvent: (a) $CHCl_3$-acetone-AcOH (7:3:0.05), 10 cm., twice developed with the same solvent system
(b) $CHCl_3$-MeOH (8:2), 10 cm.

In Part Ⅵ,[1] N^1-(3,6-dimethoxy-4-pyridazinyl)-N^4-acetylsulfanilamide (Ⅷ) and an akali-insoluble substance (Ⅺ) have been obtained by the reaction of Ⅲ with acetylsulfanilyl chloride (ASC) in pyridine solution. The subsequent study revealed the formation of additional by-products and elucidated the constitution of the neutral substance (Ⅺ).

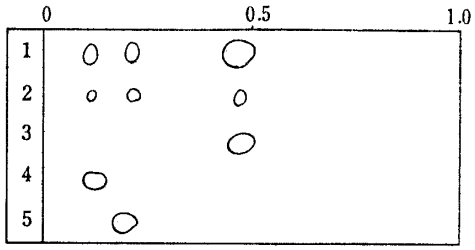


Fig. 2. Thin-layer Chromatogram of a Product from the Alkali Hydrolysis of an Acidic Fraction (crude Ⅷ)

Layer: Silica Gel G, activated at 105° for 30 min.
Detection: Diazonium Reagent
Solvent: $CHCl_3$-acetone-AcOH (7:3:0.05), 10 cm.
Sample: 1. An acidic fraction
2. A filtrate
3. Ⅻ
4. ⅩⅢ
5. ⅩⅣ

The condensation was carried out at 0~5° overnight using 0.95 mole of ASC and the product was divided into three fractions; first, the non-acidic and acidic crystalline solids were separated successively by filtration, then aqueous filtrate being left. Thin-layer chromatographic study indicated the presence of Ⅷ, Ⅸ, Ⅺ, Ⅵ and starting material (Ⅲ) in the aqueous filtrate, as illustrated in Fig. 1. When the acidic fraction (crude Ⅷ) was subjected to hydrolysis with dilute aqueous sodium hydroxide solution, it gave a product which was found to be a mixture of three sulfonamides by thin-layer chromatographic examination (Fig. 2). Attempt was made to separate these products by taking advantage of difference of their isoelectric points and, Ⅻ and ⅩⅢ were isolated. The results of the reaction between Ⅲ and acetylsulfanilyl chloride followed by hydrolysis of the acidic product with dilute sodium hydroxide is shown in Table Ⅱ, from which it is seen that when the condensation reaction was carried out at 0~5°, a yield of ⅩⅢ was only 1%, and it increased at higher temperature. The similar demethylation reaction has been reported by Klötzer and Schantl[4] who described that N^1-(2-hydroxy-4-pyrimidinyl)sulfanilamide was obtained by reactoin of 2-methoxy-4-aminopyrimidine (XXI) with acetylsulfanilyl chloride in pyridine and by treatment of N^1-(2-methoxy-4-pyrimidinyl)sulfanilamide, prepared by an alternative method, with pyridine containing

4) W. Klötzer, J. Schantl: Monatsh. Chem., **94**, 1175 (1963).

20% ether-hydrochloric acid on a steam bath. Nitta, *et al.*[5] have also reported similar observation in the reaction of XXI with *p*-nitrobenzenesulfonyl chloride.

Many reports have been available concerning the cleavage of ether linkage of phenolethers using pyridine hydrochloride as a reagent, since a series of studies by Prey.[6] Treatment of VIII and XII with pyridine hydrochloride led to the cleavage of methoxy group as expected (Chart 2). The formation of IX and X from VIII was detected by thin-layer chromatography, and after hydrolysis XIII was separated in addition to XII. The yield of the demethylated product (XIII), however, was lower comparing with that of the reaction of III with acetylsulfanilyl chloride under the same reaction conditions. The formation of demethylated products (IX), (X) and (VI) in the reaction mentioned above, therefore, might be caused by the action of pyridine hydrochloride upon VIII or III, although it is not attributable only to pyridine hydrochloride. The formation of XIV was proved by thin-layer chromatography but this failed to be isolated. Treatment of XI with pyridine at 100° resulted in the recovery of the unchanged starting material. Compound (IX) was failed to be obtained by the reaction of VI and acetylsulfanilyl chloride in pyridine.*5 Thus, both conceivable reaction sequences (III)→(VI)→(IX) and (XI)→(IX) were excluded. Thin-layer chromatographic examination showed no formation of XIII or XIV when VIII was refluxed with dilute sodium hydroxide solution.

The sulfonamide (XIII), readily obtained from XII as mentioned above, gave a positive diazo reaction and was soluble in dilute bicarbonate solution, a behavior which is characteristic of N^1-heterocyclic sulfonamides. The assignment of the structure (XIII) to the compound was substantiated by the fact that it was not identical with N^1-(3-oxo-6-methoxy-2,3-dihydro-4-pyridazinyl)sulfanilamide (XIV) prepared from 4-amino-6-methoxy-3(2*H*)pyridazinone (V).

A non-acidic substance (XI) remained unchanged when boiled in water. However, by heating with dilute sodium hydroxide solution it afforded sulfanilic acid (VII) and 3-methoxy-4-amino-6(1*H*)pyridazinone (VI). The constitution of VI was proved by its synthesis through a sequence of reactions starting from known 3-methoxy-4-methyl-6(1*H*)-pyridazinone (XVII)[7] as shown in Chart 4. Dichromate-sulfuric acid oxidation of XVII gave the carboxylic acid (XVIII) which by the action of methanolic hydrogen chloride was readily transformed into the methyl ester (XIX) and then into the carbamyl derivative (XX) on treatment with methanolic ammonia. The Hoffmann degradation product of XX must be 3-methoxy-4-amino-6(1*H*)pyridazinone (VI) from the method of preparation. The same compound (VI) was also obtained by refluxing 4-amino-3,6-dimethoxypyridazine (III) with dilute hydrochloric acid or with pyridine hydrochloride. In the latter reaction with the pyridine hydrochloride, however, VI was accompanied by small amount of V. The constitution of the isomeric (V) was, therefore, 4-amino-6-methoxy-3(2*H*)pyridazinone as represented in Chart 1.

The non-acidic product from the condensation between III and acetylsulfanilyl chloride in pyridine may have either of the structures (XI) or (XV). It has been shown by the present authors that 3-methoxy-6-pyridazinol *p*-toluenesulfonate is less resistant to hydrolysis than 2-*p*-toluenesulfonyl-6-methoxy-3(2*H*)pyridazinone, and the former undergoes hydrolysis by boiling with water whereas the latter does not. This

*5 The reaction gave a product which was presumed to be a mixture of the O-sulfonate and the N^1-sulfonyl compound (unpublished work).

5) Y. Nitta, K. Okui, K. Ito, M. Togo: This Bulletin, **13**, 568 (1965).
6) V. Prey: Chem. Ber., **74**, 1219 (1941); **75**, 350, 445 (1942).
7) Part V. T. Nakagome: Yakugaku Zasshi, **82**, 1005 (1962).

observation will be described more fully in a subsequent paper.[8] Considering the stability of the product in question in boiling water, it seems reasonable to allocate the structure (XI) to it.

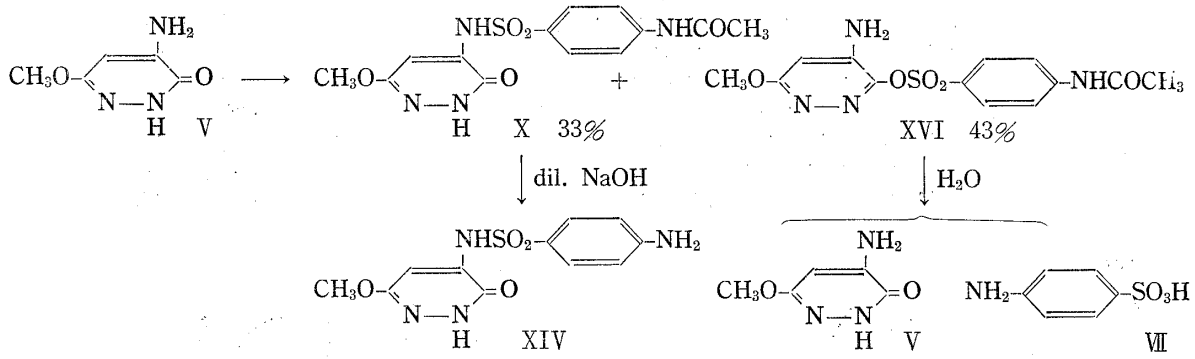


Chart 3.

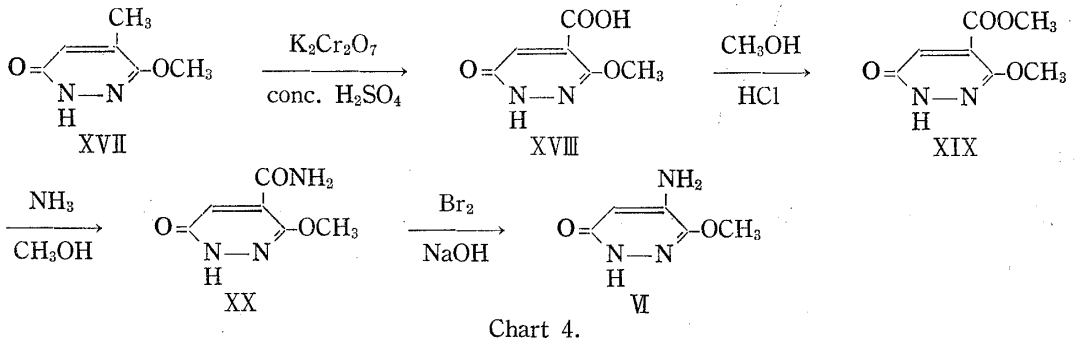


Chart 4.

In view of a marked antimicrobial activity *in vitro* of several N^1-(3-oxo-2,3-dihydro-4-pyridazinyl)sulfanilamides with or without substituents at 6-position of the pyridazine nucleus which were prepared in the previous work,[1] it was of interest to synthesize a sulfonamide of this series, N^1-(3-oxo-6-methoxy-2,3-dihydro-4-pyridazinyl)sulfanilamide (XIV).

When V was allowed to react with acetylsulfanilyl chloride in pyridine according to the usual procedure, it yielded two products, as shown in Chart 3. The desired sulfonamide (XIV) was obtained from the acidic product (X) by hydrolysis with dilute sodium hydroxide solution. The sulfonamide (X) and (XIV) must be N^1-(3-oxo-6-methoxy-2,3-dihydro-4-pyridazinyl)-N^4-acetylsulfanilamide and N^1-(3-oxo-6-methoxy-2,3-dihydro-4-pyridazinyl)sulfanilamide respectively as represented in Chart 3, because of their solubility in dilute aqueous alkali and the method of preparation.

The second product (XVI), insoluble in dilute sodium hydroxide solution, gave 4-amino-6-methoxy-3(2*H*)pyridazinone (V) and sulfanilic acid (VII) when boiled in water. It follows that the constitution of the product is 4-amino-6-methoxy-3-pyridazinol *p*-acetamidobenzenesulfonate, as shown in Chart 3. The ester linkage in XVI seems to be responsible for its susceptibility to hydrolysis.

The sulfonamide (XIV) was investigated bacteriostatically in our laboratory and was found to possess a very high bacteriostatic activity *in vitro* against various microorganisms. These results have already been reported elsewhere.[9]

The 4- and 5-aminopyridazinone derivatives in this and subsequent papers were formulated by amino-3(2*H*)pyridazinone structures. With respect to the hydroxy group, the oxo formulation was supported by the similarity of the ultraviolet spectra

8) Part XII. T. Nakagome, A. Kobayashi, A. Misaki: This Bulletin, **14**, 1074 (1966).
9) Presented at the 11th Annual Meeting of the Japan Society of Chemotherapy, June, 1964.

Table I. Ultraviolet Spectral Values

Compound (Fig. 3~5)	λ_{max}^{EtOH} mμ (log ε)
(a) 4-Amino-3(2*H*)pyridazinone[11]	290 (4.04)
(b) 2-Methyl-4-amino-3(2*H*)pyridazinone[11]	295 (4.04)
(c) 3-Methoxy-4-aminopyridazine[13,14]	251.5 (3.96), 275 (3.89)
(d) 4-Amino-6-methyl-3(2*H*)pyridazinone[1]	291 (4.02)
(e) 4-Amino-2,6-dimethyl-3(2*H*)pyridazinone[12]	294.5 (4.01)
(f) 3-Methoxy-4-amino-6-methylpyridazine[15,16]	250.5 (3.90), 278 (3.86)
(g) 5-Amino-3(2*H*)pyridazinone[12]	274 (3.72)
(h) 2-Methyl-5-amino-3(2*H*)pyridazinone[11]	277.5 (3.79)

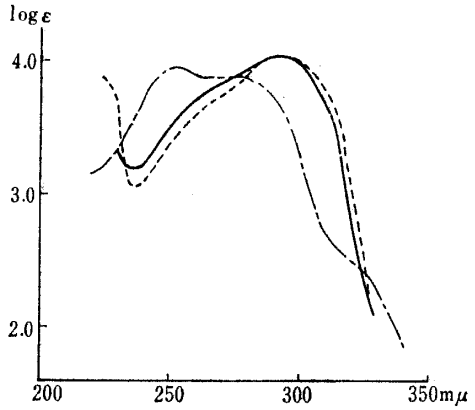
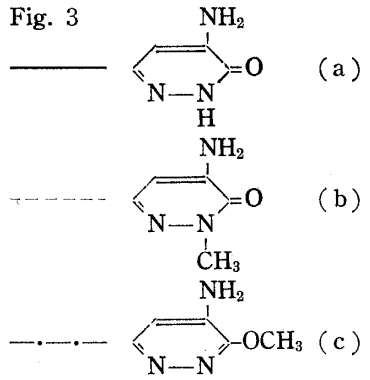


Fig. 3



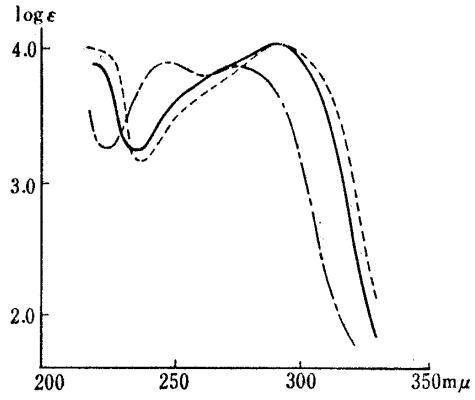
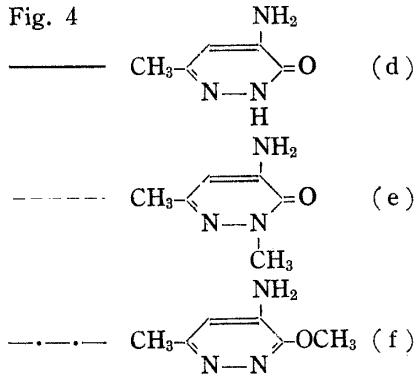


Fig. 4



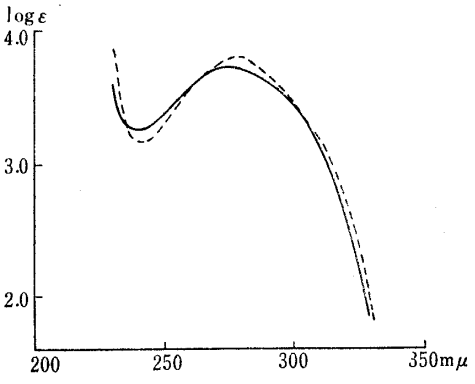
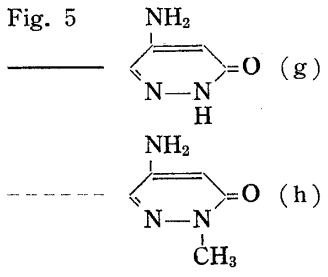


Fig. 5



of these compounds (a, d, g in Fig. 3~5) to those of 2-methyl-4- and 5-amino-3(2*H*)pyridazinone derivatives and by the fact that the spectra of (a) and (d) were different from those of 3-methoxy compounds, as shown in Fig. 3~5. For the supposed amino structure there was no investigation made. The amino structure was assumed by analogy with many heterocyclic amino compounds and amino pyrimidinones.[10]

10) A. R. Katritzky, A. J. Boulton, J. M. Lagowski: "Advances in Heterocyclic Chemistry," Vol. 1, 311 (1962). Academic Press, New York and London.
11) T. Kuraishi: This Bulletin, **6**, 331 (1958).
12) Part XIII. T. Nakagome, A. Misaki, T. Komatsu: This Bulletin, **14**, 1082 (1966).
13) H. Igeta: This Bulletin, 8, 550 (1960).

Experimental*6

Reaction of 4-Amino-3,6-dichloropyridazine (I) with Potassium Hydroxide——To a solution of 23.8 g. of KOH dissolved in 250 ml. of MeOH 15 g. of I was added and the mixture was heated in an autoclave at 150° for 1.5 hr. The resulting mixture was filtered to remove KCl and the filtrate was evaporated to dryness. The residue was triturated with 20 ml. of water, cooled, and filtered to give 6.35 g. (44.8%) of 4-amino-3,6-dimethoxypyridazine (III), m.p. 175~177°. Recrystallization from water afforded colorless rods, m.p. 177~178°, undepressed on admixture with an authentic specimen.[17] Yield, 5.8 g. (41%). The aqueous mother liquor from the crude (III) was neutralized with HCl and the resulting precipitate was filtered, weighing 5.7 g. (43%), m.p. 260~268°.

Ten g. of this solid was dissolved in dilute sodium hydroxide, treated with charcoal and the product fractionally reprecipitated by the addition of HCl in five portions.

		m.p. (°C)	Beilstein reaction	TLC*7
No. 1 (pH >12.5)	0.7 g.	274~275	—	0.46
No. 2 (pH 12.5~12.0)	0.4 g.	274~275	±	0.46
No. 3 (pH 12.0~11.5)	0.7 g.	264~265	+	0.46, 0.56
No. 4 (pH 11.5~11.25)	0.4 g.	279~280	+	0.46, 0.56
No. 5 (pH <11.25)	7.6 g.	278~280	+	0.56

The first two precipitates were combined and recrystallized from MeOH, giving 0.7 g. (3%) of 4-amino-6-methoxy-3(2*H*)pyridazinone (V), m.p. 276~277°. *Anal.* Calcd. for $C_5H_7O_2N_3$: C, 42.55; H, 5.00; N, 29.78. Found: C, 42.50; H, 5.06; N, 29.42. Recrystallization of the last fraction from MeOH gave 6.7 g. (29%) of 4-amino-6-chloro-3(2*H*)pyridazinone (IV) as colorless scales, m.p. 300~301°, undepressed on admixture with a sample prepared by the method of Kuraishi.[11] The IR spectra of the two samples were identical. *Anal.* Calcd. for $C_4H_4ON_3Cl$: C, 32.99; H, 2.75; N, 28.87. Found: C, 33.02; H, 2.77; N, 28.51.

Reaction of III with Potassium Hydroxide——A solution of 96.5 g. (0.62 mole) of III and 225 g. (3.45 moles) of potassium hydroxide dissolved in 960 ml. of MeOH was heated in an autoclave at 160~165° for 2 hr. The solution was evaporated, and the residue was dissolved in water (500 ml.) and filtered. The filtrate was neutralized with HCl and the precipitate was filtered. Yield, 59.1 g. (67.4%), m.p. 264~273°. The methanolic solution of the crude product was boiled with charcoal, and the charcoal was removed by filtration. Almost all of the solvent was removed from the solution by evaporation, which resulted in the precipitation of 45 g. of colorless prisms, m.p. 277~278°. The melting point of a mixture with the material (V) prepared in the previous experiment was not depressed.

Reaction of III with Acetylsulfanilyl Chloride (ASC)——i) To a stirred solution of 5.5 g. of III in 30 ml. of pyridine was added with cooling below 10° 7.9 g. (0.95 times of calculated amount) of ASC and the resulting solution was maintained at the same temperature overnight. The reaction mixture was poured into ice water (200 ml.), containing sufficient sodium hydroxide to give pH of 7. The solution was concentrated *in vacuo*, water (150 ml.) was added and the solution was concentrated to a small volume. The cooled residue was made alkaline with dil. aq. NaOH and filtered. The insoluble solid, 2-*p*-acetylaminobenzenesulfonyl-5-amino-6-methoxy-3(2*H*)pyridazinone (XI), weighing 1.37 g. (11.4%), m.p. 200~212°, was purified by dissolving in pyridine and adding water, to give 0.85 g. (7.1%) of colorless prisms of m.p. 215~217° and 0.165 g. (1.4%) of second crop, m.p. 211~212°. *Anal.* Calcd. for $C_{13}H_{14}O_5N_4S$: C, 46.16; H, 4.17; N, 16.56. Found: C, 46.15; H, 4.31; N, 16.32. The alkaline filtrate was adjusted with HCl to pH 3, giving 7.3 g. (58.3%) of crude N^1-(3,6-dimethoxy-4-pyridazinyl)-N^4-acetylsulfanilamide (VIII), m.p. 200° (decomp.). TLC of the product showed the presence of VIII and IX (Fig. 1). This was again dissolved in dil. aq. NaOH solution and conc. HCl was added to the solution until pH 6 was attained. This caused the precipitation of 6.9 g. (55%) of pure VIII of m.p. 206~207°, which was recrystallized from MeOH to give colorless prisms, m.p. 206~207°, undepressed on admixture with an authentic sample.[1] The filtrate from

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

*7 AcOEt solvent, Sillica Gel G plate, detected by I_2 vapor.

14) Part I. T. Nakagome: Yakugaku Zasshi, **82**, 554 (1961).
15) Part IV. *Idem*: *Ibid.*, **82**, 253 (1962).
16) M. Ogata, H. Kano: This Bulletin, **11**, 29 (1963).
17) T. Itai, H. Igeta: Yakugaku Zasshi, **75**, 966 (1955).

the crude (Ⅷ) was made alkaline, evaporated *in vacuo*, and 1.35 g. (24.6%) of crystals which separated out on cooling were collected. Recrystallization from water formed colorless rhombs, melting at 177~177.5°, undepressed on admixture with starting material. Yield 1.05 g. (18%). The aqueous filtrates from pure Ⅷ and from crude Ⅲ were combined and evaporated *in vacuo*. The residue was heated with dil. NaOH solution under reflux for 1 hr., 0.3 g. of white powder was precipitated by addition of dil. HCl at pH 3. The product was recrystallized from MeOH yielding 0.05 g. (0.5%) of N^1-(3-oxo-6-methoxy-2,3-dihydro-5-pyridazinyl)sulfanilamide (XIII), m.p. 266°. *Anal.* Calcd. for $C_{11}H_{12}O_4N_4S$: C, 44.60; H, 4.08; N, 18.91; S, 10.80. Found: C, 44.52; H, 4.39; N, 19.22; S, 10.48. The methanolic mother liquor was evaporated to dryness and 0.06 g. of XII recovered by dissolving the residue in dil. NaOH solution and precipitation with HCl.

ii) Ⅲ was reacted with ASC in the same manner as described in i). After evaporation of pyridine and water *in vacuo*, the residue was digested with 120 ml. of dil. NaOH and filtered. Hydrolysis was effected by refluxing the filtrate for 45 min. The sulfonamide was fractionally precipitated by the addition of dil. HCl. The first fraction, which was precipitated within a pH range 7.5~6.0 and melted at 189~190°, was pure XII. The second fraction, melting within a range 250~260°, was precipitated within a pH range 6.0~3.0, and filtered after standing for 12 hr. This was purified by recrystallization from MeOH. The starting material was recovered by concentration and cooling the filtrate.

Table Ⅱ.

Exp. No.	Reaction temp. (°C)	Reaction time	ASC (mole ratio)	Yield(%) XII	XIII	XI	recovered Ⅲ
1	0	overnight	0.95	54	1.0	11.4	18
2	〃	〃	1.25	64	1.6	6.3	3.6
3	〃	〃	1.44	68	3.2	7.6	—
4	60~65	0.5 hr.	1.25	52	8.2	9.2	—
5	room temp.	overnight	1.25	52	8.1	9.0	—

Reaction of N^1-(3,6-Dimethoxy-4-pyridazinyl)sulfanilamide (XII) with Pyridine Hydrochloride——A solution of 7 g. of XII and 3 g. of pyridine hydrochloride in 30 ml. of pyridine was allowed to stand overnight with ice cooling, and heated at 60~65° for 30 min. After cooling the mixture was poured into sufficient dil. aq. NaOH to give pH of 7 and concentrated *in vacuo* to remove pyridine. The precipitated product was collected by filtration. This crude product was shown to contain XII, XIII and XIV by thin-layer chromatographic examination according to the procedure represented in Fig. 2. The crude product was dissolved in dil. aq. NaOH, neutralized with HCl to pH 6 to give XII, 6.65 g. (93.5%), m.p. 190~190.5°. Evaporation of the filtrate to 100 ml., acidification with HCl to pH 2.5 and filtration gave 0.35 g. of crude XIII which was purified by washing with boiling MeOH. Yield, 0.1 g. (1.5%), m.p. 273°.

Reaction of VIII with Pyridine Hydrochloride——The treatment of a solution of 7.95 g. of Ⅷ and 3 g. of pyridine hydrochloride in 30 ml. of pyridine in the same manner as described above for the reaction of XII and pyridine hydrochloride and subsequent hydrolysis of the product with 80 ml. of 2*N* NaOH afforded 6.75 g. (96.3%) of XII and 0.14 g. (2%) of XIII, m.p. 270°. The presence of Ⅷ, Ⅸ and Ⅹ in the crude product from the reaction between Ⅷ and pyridine hydrochloride was proved by thin-layer chromatographic examination according to the procedure represented in Fig. 1.

Acetylation of XIII——A slurry of 0.7 g. of XIII in 6 ml. of 75% AcOH was treated with 1.1 ml. of Ac_2O. After 30 min. stirring, the mixture was poured into ice water and filtered. There was obtained 0.7 g. of N^1-(3-oxo-6-methoxy-2,3-dihydro-5-pyridazinyl)-N^4-acetylsulfanilamide (Ⅸ), m.p. 274°. Recrystallization from MeOH did not raise the melting point. *Anal.* Calcd. for $C_{13}H_{14}O_5N_4S$: C, 46.30; H, 4.29; N, 16.57. Found: C, 46.37; H, 4.27; N, 16.31.

3-Methoxy-4-amino-6(1*H*)pyridazinone (VI)——i) From Ⅲ. A solution of 0.5 g. of Ⅲ in 10 ml. of 2*N* HCl was refluxed for 15 hr. After cooling, the solution was made alkaline with Na_2CO_3, and evaporated to dryness. The residue was washed with small quantity of water and filtered, yielding 0.34 g. of Ⅵ, m.p. 254~258°. Recrystallization from EtOH gave 0.27 g. (60%) of colorless prisms melting at 266°. *Anal.* Calcd. for $C_5H_7O_2N_3$: C, 42.55; H, 5.00; N, 29.78. Found: C, 43.19; H, 5.07; N, 29.57. Hydrochloride; m.p. 217~218° (decomp.). *Anal.* Calcd. for $C_5H_7O_2N_3 \cdot HCl$: C, 33.81; H, 4.54; N, 23.66. Found: C, 34.66; H, 4.83; N, 23.60.

ii) From XX. To a stirred solution of 0.7 g. of 3-oxo-6-methoxy-2,3-dihydro-5-pyridazinecarboxamide (XX) in 20 ml. of water containing 1.05 g. of NaOH was added dropwise 0.72 g. of bromine with cooling. After stirring was continued for 45 min., the ice bath was removed and the temperature was raised to room temperature for 1 hr. and then the mixture was heated on the boiling water bath for 10 min. The

cooled solution was neutralized with HCl and concentrated *in vacuo* to a small volume. The precipitated crystals were recrystallized from EtOH (charcoal treatment) giving 0.3 g. of colorless prisms melting at 268°, and a second crop, 0.1 g., m.p. 268~269°, yield 69%. This product was identified with VI prepared from III as described above by mixture melting point and comparison of IR spectra.

Reaction of III with Pyridine Hydrochloride——A solution of 3 g. of III and 3 g. of pyridine hydrochloride in 30 ml. of pyridine was refluxed for 3 hr. The resulting solution was poured into water containing sufficient amount of NaOH to give pH of 7. The solution was concentrated *in vacuo* to dryness, was added and again the solution was concentrated to dryness. The residue was rinsed with *N* HCl and filtered. The insoluble material, weighing 0.22 g. (8.2%) and melting at 269~272°, was purified by recrystallization from water. The melting point was raised to 276.5~277°. No depression of the melting point was observed when mixed with V described above. The filtrate from crude V was concentrated *in vacuo*, made alkaline with Na_2CO_3, cooled and filtered, giving 0.98 g. (36%) of colorless prisms, m.p. 260°. Recrystallization from water raised the melting point to 266°. No melting point depression was observed when mixed with VI prepared in the previous experiment.

Hydrolysis of XI——A mixture of 2 g. of XI and 20 ml. of 2*N* NaOH was refluxed for 1.5 hr. The resulting solution was acidified with HCl, then neutralized with Na_2CO_3, concentrated to 5~10 ml., cooled and filtered (mother liquor A). The solid was extracted with boiling EtOH. The EtOH was distilled from the extract, leaving 1.44 g. of crude VI which was purified by recrystallization from water. Yield 0.5 g. (60%), m.p. 259~259.5°. Additional recrystallization from MeOH gave 0.48 g. of colorless prisms, identical to a sample prepared from III by mixed melting point and comparison of IR spectra. The insoluble material in boiling EtOH was dissolved in water, and made alkaline with Na_2CO_3. The filtered solution was acidified with HCl to give 0.25 g. (22.1%) of colorless crystals of m.p. >300°, which were identified with an authentic sample of sulfanilic acid by comparison of IR spectra. Acidification to the mother liquor A with HCl, concentration to a small volume, and recrystallization of the precipitate from water gave additional crop (0.12 g.) of sulfanilic acid; total 0.37 g. (33%).

Reaction of V with ASC——To a stirred mixture of 2.8 g. (0.02 mole) of V and 60 ml. of pyridine was added 5.1 g. (0.022 mole) of ASC with cooling. The resulting mixture was stirred at room temperature overnight and then poured into ice water containing 10 ml. of 2*N* NaOH. The solution was concentrated *in vacuo* below 40°, water was added, and again the solution was concentrated to a small volume. The residue was made alkaline with NaOH solution with cooling, the insoluble solid was filtered, washed and dried *in vacuo*, giving 2.9 g. (43.2%) of 4-amino-6-methoxy-3-pyridazinol *p*-acetylaminobenzenesulfonate (XVI), m.p. 163~165°. Recrystallization from pyridine-water formed pale brown prisms, m.p. 167~169°. *Anal.* Calcd. for $C_{13}H_{14}O_5N_4S$: C, 46.16; H, 4.17; N, 16.56. Found: C, 46.78; H, 4.66; N, 16.44. From the alkaline mother liquor 2.2 g. (32.8%) of crude N^1-(3-oxo-6-methoxy-2,3-dihydro-4-pyridazinyl)-N^4-acetylsulfanilamide (X), m.p. 255~256° was precipitated by the addition of HCl. Recrystallization from MeOH formed colorless needles, m.p. 261° (decomp.). *Anal.* Calcd. for $C_{13}H_{14}O_5N_4S$: C, 46.16; H, 4.17; N, 16.56. Found: C, 46.28; H, 4.28; N, 16.63.

N^1-(3-Oxo-6-methoxy-2,3-dihydro-4-pyridazinyl)sulfanilamide (XIV)——A solution of 1 g. of X in 15 ml. of 2*N* NaOH was refluxed for 1 hr. Precipitation by acidification with dil. HCl gave 0.75 g. (86%) of XIV, m.p. 252.5°, which was recrystallized from MeOH to give colorless needles, m.p. 248~248.5°. *Anal.* Calcd. for $C_{11}H_{12}O_4N_4S$: C, 44.60; H, 4.08; N, 18.91. Found: C, 44.60; H, 4.45; N, 18.92.

Hydrolysis of XVI——A mixture of 2 g. of XVI and 20 ml. of water was refluxed for 1 hr. The cooled mixture was made alkaline with 10% Na_2CO_3 solution and insoluble V was filtered, giving 0.71 g. (85%), m.p. 280°, undepressed when admixed with V obtained above (from I). The IR spectra of the two samples were identical. The filtrate was evaporated and the residue was recrystallized from water, yielding 0.5 g. (50%) of colorless crystals, m.p. >300°, which were identified with a sample of sulfanilic acid by comparison of IR spectra.

3-Oxo-6-methoxy-2,3-dihydro-5-pyridazinecarboxylic Acid (XVIII)——To a stirred solution of 10 g. of 5-methyl-6-methoxy-3(2*H*)pyridazinone (XVII)[7] in 60 ml. of conc. H_2SO_4 was gradually added 27 g. of $K_2Cr_2O_7$ mixed with 120 ml. of conc. H_2SO_4, the temperature being maintained at 20° with external cooling. Stirring was continued for further 2 hr., then the ice bath was removed and the mixture was allowed to stand overnight. The reaction mixture was poured into 1.2 L. of ice water, and the separated crystals were collected, dissolved in aq. $NaHCO_3$ solution, treated with charcoal, and filtered. On acidification with HCl there was obtained 3.1 g. (25.6%) of XVIII, m.p. 259° (decomp.), which after recrystallization from water, melted at 261.5° (decomp.). *Anal.* Calcd. for $C_6H_6O_4N_2$: C, 42.36; H, 3.56; N, 16.47. Found: C, 42.14; H, 3.53; N, 16.59.

Methyl 3-Oxo-6-methoxy-2,3-dihydro-5-pyridazinecarboxylate (XIX)——A mixture of 2 g. of XVIII in 50 ml. of MeOH containing 0.2 g. of dry HCl was heated under reflux for 6 hr. The reaction mixture was evaporated to dryness, and aq. $NaHCO_3$ solution was added to the residue. Extraction with $CHCl_3$ and evaporation of the extract left 1.9 g. (88%) of XIX, m.p. 175~177°, which formed colorless leaflets melting at 178~179° on recrystallization from MeOH. *Anal.* Calcd. for $C_7H_8O_4N_2$: C, 45.65; H, 4.38; N, 15.21. Found: C, 45.92; H, 4.54; N, 15.23.

3-Oxo-6-methoxy-2,3-dihydro-5-pyridazinecarboxamide (XX)——To a stirred solution of 30 ml. of MeOH saturated with NH_3 at 0° was added with cooling 0.33 g. of XIX. The ester dissolved and amide began to deposit. The reaction mixture was stirred and cooled overnight, and evaporated to one-third of the original volume. The filtered crystals were recrystallized from water, giving XX as colorless needles, m.p. 265~266°. Yield, quantitative. *Anal.* Calcd. for $C_6H_7O_3N_3$: C, 42.60; H, 4.17; N, 24.85. Found: C, 42.89; H, 4.31; N, 25.03.

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Summary

Reactions of 4-amino-3,6-dichloropyridazine (I) with caustic alkali in methanol and of 4-amino-3,6-dimethoxypyridazine (III) with acetylsulfanilchloride in pyridine were studied. In the former reaction, the reaction sequence to the formation of (III), 4-amino-6-chloro-(IV) and 4-amino-6-methoxy-3(2*H*)pyridazinone (V) was clarified. In the latter condensation reaction, it was found by thin-layer chromatography that 2-*p*-acetylaminobenzenesulfonyl-5-amino-6-methoxy-3(2*H*)pyridazinone (XI), two demethylated compounds (IX and X) of N^1-(3,6-dimethoxy-4-pyridazinyl)-N^4-acetylsulfanilamide (VIII) as well as the main product (VIII) were produced and their structures were proved. The demethylation reactions of VIII and its deacetylated compound (XII) with pyridine hydrochloride were examined.

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147. Takenari Nakagome, Akira Kobayashi, and Atsuko Misaki: Synthesis of Pyridazine Derivatives. XII.*1 Reaction of Amino-3(2*H*)pyridazinone Derivatives with Tosyl Chloride.

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In a previous work of this series,*1 4-amino-3,6-dimethoxypyridazine (XV) and 4-amino-6-methoxy-3(2*H*)pyridazinone (I) was reacted with acetylsulfanilyl chloride in pyridine with the object of preparing hitherto unknown N^1-4-pyridazinylsulfanilamides after subsequent deacetylation. The reaction was not quite simple and, besides desired N^1-4-pyridazinyl-N^4-acetylsulfanilamides some neutral substances were formed, whose structures, postulated as XIX and XX (Chart 3) have not yet been conclusive. The present work was undertaken in order to obtain further evidences supporting the foregoing assumption and for this purpose the reaction of some pyridazine and pyridazinone derivatives with tosyl chloride was investigated.

*1 Part XI. T. Nakagome, A. Kobayashi, A. Misaki, T. Komatsu, T. Mori, S. Nakanishi: This Bulletin, **14**, 1065 (1966).

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