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Syntheses of Pyrimido[4,5-*c*]pyridazine Derivatives. I. A Novel Reaction of α-Diazo-β-oxo-5-(4-chloropyrimidine)propionate with Hydrazine leading to 1,2-Dihydro-4-hydroxypyrimido[4,5-*c*]pyridazine-3-carboxamide[1]

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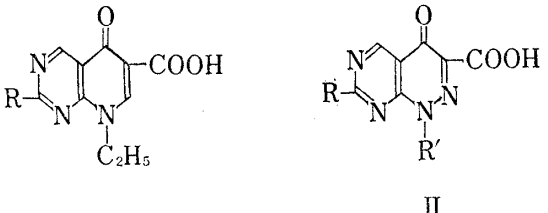
A reaction of ethyl α-diazo-β-oxo-5-(4-chloro-2-methylthiopyrimidine)propionate (III) with hydrazine hydrate in ethanol afforded 1,2-dihydro-4-hydroxy-7-methylthiopyrimido-[4,5-*c*]pyridazine-3-carboxamide (VII), of which structure was determined by chemical and infrared, ultraviolet, nuclear magnetic resonance and mass spectral evidences: VII was acetylated to 1,2-diacetyl-4-hydroxy-1,2-dihydro-7-methylthiopyrimido[4,5-*c*]pyridazine-3-carboxamide (XI) and 4-acetoxy-9-acetyl-1-methyl-7-methylthio imidazo[3′,4′: 2,3]-pyridazo[6,5-*d*]pyrimidin-3(9*H*)-one (XII), which were interconvertible. Both XI and XII were converted to 9-acetyl-4-hydroxy-1-methyl-7-methylthioimidazo[3′,4′: 2,3]-pyridazo[6,5-*d*]pyrimidin-3(9*H*)-one (XIII). The hydrolyzed product (X) of VII was treated with alkaline permanganate to give 6-methylthio-1*H*-pyrazolo[3,4-*d*]pyrimidine-3-carboxylic acid (XIV), which was subjected to decarbonylation and desulfurization. The formation mechanism of VII was discussed.

Treatment of the acid (X) with benzoyl peroxide in ethanol in the presence of triethylamine afforded ethyl 1,4-dihydro-7-methylthio-4-oxopyrimido[4,5-*c*]pyridazine-3-carboxylate(XVII). The corresponding acid (XVIII) is a key intermediate for syntheses of 1,4-dihydro-4-oxopyrimido[4,5-*c*]pyridazine-3-carboxylic acids, which would be expected as antibacterial agents.

It was found that 5,8-dihydro-5-oxopyrido[2,3-*d*]pyrimidine-6-carboxylic acid derivatives (piromidic acid Ia[3] and pipemidic acid Ib[4]) have excellent antibacterial activities against gram-negative bacteria and also moderate activities against some positive bacteria such as staphylococci. These findings prompted us to synthesize 1,4-dihydro-4-oxopyrimido[4,5-*c*]-pyridazine-3-carboxylic acid derivatives (II), of which skeleton has one more nitrogen atom than the pyrido[2,3-*d*]pyrimidine ring in Ia and Ib, in hopes of further developing useful antibacterial agents.



II

Ia : R = −N⟨ ⟩

Ib : R = −N⟨ ⟩NH

Chart 1

During the course of our study on the reactivities of ethyl α-diazo-β-oxo-5-(4-chloro-2-methylthiopyrimidine)propionate (III) obtained from reaction of 4-chloro-2-methylthiopyrimidine-5-carbonyl chloride with ethyl diazoacetate, it was observed that treatment of III with aqueous hydrobromic acid in ethanol gave quantitatively ethyl 5-hydroxy-2-methyl-

1) A part of this work was presented as a communication: S. Minami, Y. Kimura, T. Miyamoto, and J. Matsumoto, *Tetrahedron Letters*, **1974**, 3893.
2) Location: *Enoki-cho 33–94, Suita, Osaka.*
3) Generic name of 8-ethyl-5,8-dihydro-5-oxo-2-pyrrolidinopyrido[2,3-*d*]pyrimidine-6-carboxylic acid. S. Minami, T. Shono, and J. Matsumoto, *Chem. Pharm. Bull.* (Tokyo), **19**, 1426 (1971).
4) Generic name of 8-ethyl-5,8-dihydro-5-oxo-2-(1-piperazinyl) pyrido[2,3-*d*]pyrimidine-6-carboxylic acid. J. Matsumoto, and S. Minami, *J. Med. Chem.*, **18**, 74 (1975).

thiofuro[2,3-*d*]pyrimidine-6-carboxylate (IV). α-Diazoketones undergo the acid-catalyzed decomposition with loss of nitrogen and an addition of HA which represents H_2O, HCl, AcOH, *etc.*[5] This fact suggests that ethyl α-diazo-β-oxo-5-(4-hydrazino-2-methylthiopyrimidine)-propionate (V), if available, would be subjected to the similar reaction on an acid-treatment and afford ethyl 1,2,3,4-tetrahydro-7-methylthio-4-oxopyrimido[4,5-*c*]pyridazine-3-carboxylate (VI) or its equivalent, which may be a synthetic intermediate for our desirable compound II.

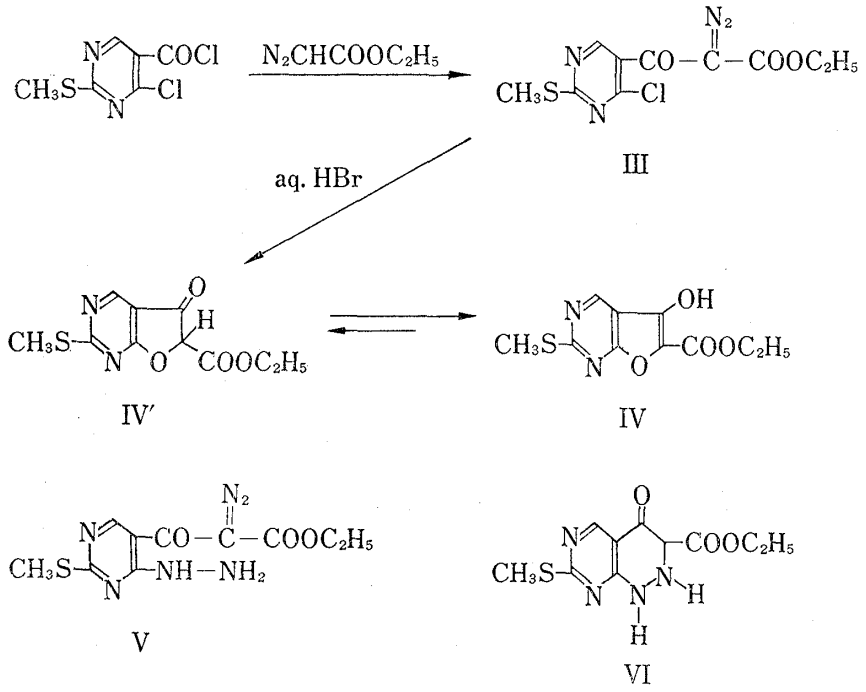


Chart 2

An attempted reaction of III with a 1.5-fold molar amount of hydrazine hydrate at 0—5° in a mixture of benzene and ethanol gave 1,2-dihydro-4-hydroxy-7-methylthiopyrimido-[4,5-*c*]pyridazine-3-carboxamide (VII) in 24.2% yield, instead of an expected compound V, together with 5,5′-bis(ethoxycarbonyldiazoacetyl)-3,3′-bismethylthio-4,4′-hydrazopyrimidine

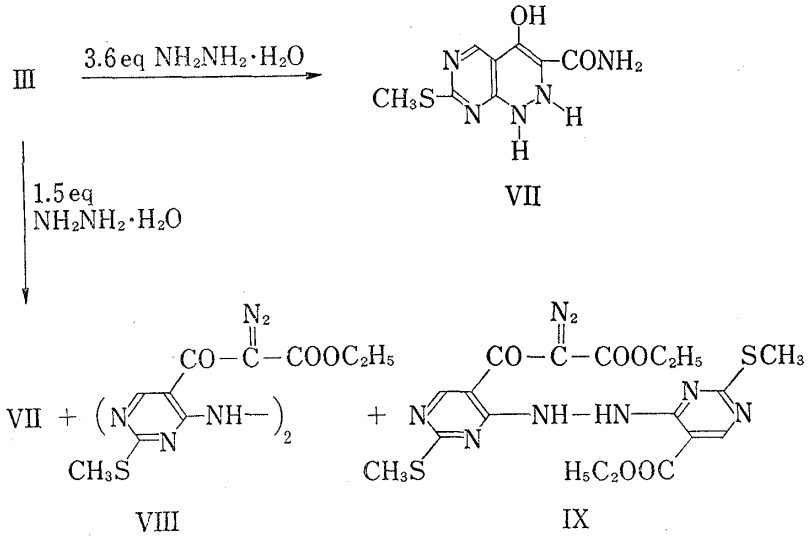


Chart 3

5) C.E. McCauley and C.V. King, *J. Am. Chem. Soc.*, **74**, 6221 (1952); H. Dahn and H. Gold, *Helv. Chim. Acta*, **46**, 983 (1963), and cited references.

(VIII) and 1-(5-ethoxycarbonyl-2-methylthio-4-pyrimidinyl)-2-(5-ethoxycarbonyldiazoacetyl-2-methylthio-4-pyrimidinyl)hydrazine (IX) in 47.3% and 19.5% yields, respectively. A nearly quantitative formation of VII was best effected by treating III with a 3.6-fold molar amount of hydrazine hydrate at 8—20° in ethanol as a result of examinations of the molar ratio of hydrazine hydrate to III. This paper deals with the structural elucidation of VII.

The carboxamide (VII) underwent hydrolysis with 5% aqueous hydrochloric acid in ethanol to give 1,2-dihydro-4-hydroxy-7-methylthiopyrimido[4,5-*c*]pyridazine-3-carboxylic acid (X). The conjugation of a keto or enol group with the pyrimidine chromophore was suggested by the ultraviolet (UV) spectra showing bathochromic shifts; *i.e.*, the maximum bands at 275 and 320 nm of VII (in water) shifted to 295 and 384 nm (in 0.01N NaOH), respectively, and the maximum bands at 226 and 278 nm of X (in water) to 256 and 308 nm (in 0.01N NaOH), respectively.

Acetylation of VII with acetic anhydride at 50° produced 1,2-diacetyl-4-hydroxy-1,2-dihydro-7-methylthiopyrimido[4,5-*c*]pyridazine-3-carboxamide (XI) in 86% yield. The nuclear magnetic resonance (NMR) spectrum of XI exhibits a signal at 12.3 ppm which is assignable to the proton of the hydroxyl group deshielded probably due to a hydrogen bonding with the carboxamide group, indicating the *ortho* location of these groups. Treatment of VII with acetic anhydride at 120° afforded 4-acetoxy-9-acetyl-1-methyl-7-methylthioimidazo-[3′,4′: 2,3]pyridazo[6,5-*d*]pyrimidin-3(9*H*)-one (XII) in 96% yield, which was identical with that obtained by further treatment of XI with acetic anhydride at 120°. Treatment of XII with aqueous 1N sodium hydroxide at 80° gave back XI in 43% yield. The NMR spectrum of XII shows no longer the signal ascribable to the labile protons as possessed by XI but a new signal at 2.74 ppm attributable to methyl protons on the imidazole ring which arises from intramolecular dehydration between the carboxamide and acetamide groups; hence the two groups were revealed to be adjacent each other in position. The anhydro-diacetate (XII) in which the presence of an enol acetate function was suggested by its infrared (IR) band at 1730 cm^{-1} was easily hydrolyzed with 28% aqueous ammonia to give, as expected, 9-acetyl-4-hydroxy-1-methyl-7-methylthioimidazo[3′,4′: 2,3]pyridazo[6,5-*d*]pyrimidin-3(9*H*)-one (XIII) in 72% yield. Alternatively, the formation of XIII from XI by heating was demonstrated by the mass spectrum of XI showing the fragmentation pattern due to XIII (Fig. 1).

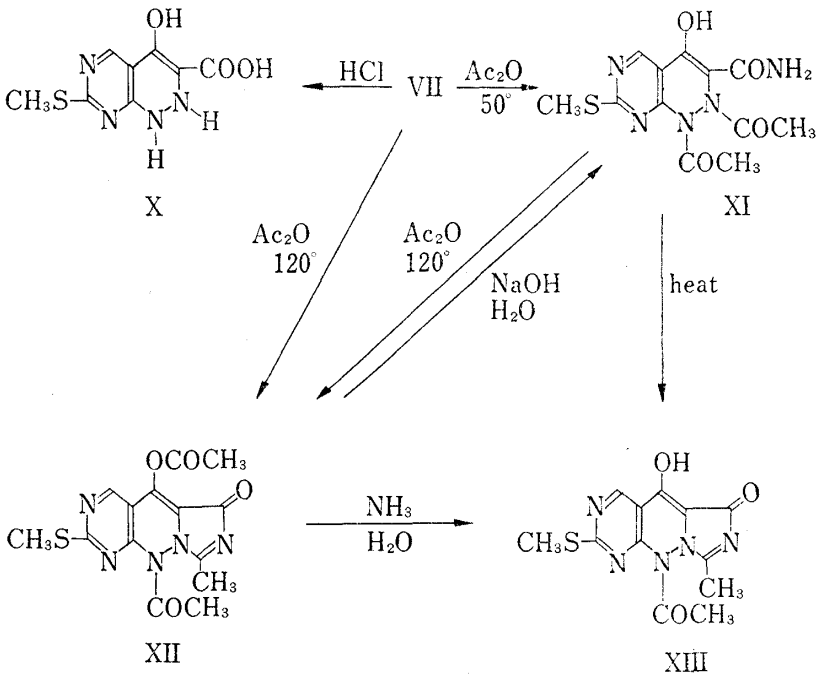


Chart 4

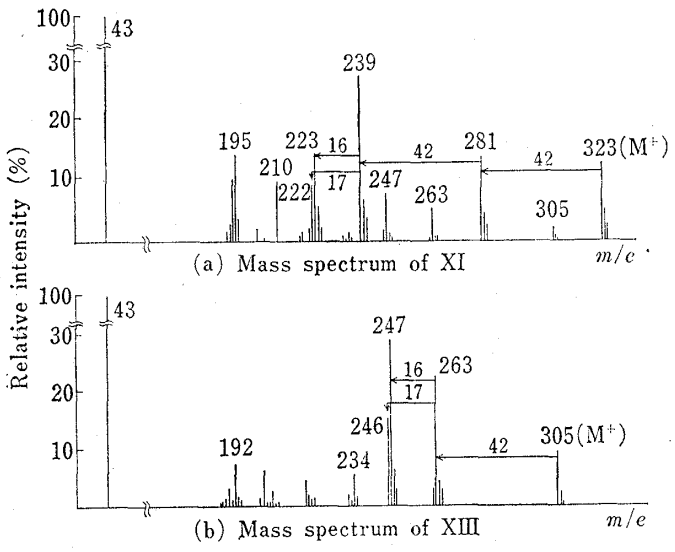


Fig. 1

Oxidation of X with potassium permanganate in aqueous 0.1N sodium hydroxide afforded 6-methylthio-1*H*-pyrazolo[3,4-*d*]pyrimidine-3-carboxylic acid (XIV) in 70.2% yield, which arose from a bond migration followed by dehydration and decarbonylation of the resulting α-ketocarboxylic acid. In order to confirm the structure, XIV was converted by heating at 300° into 6-methylthio-1*H*-pyrazolo-[3,4-*d*]pyrimidine (XV) in 76% yield, followed by desulfurization with Raney nickel into 1*H*-pyrazolo[3,4-*d*]pyrimidine (XVI) which was identical in all respects with the sample prepared according to the literature.[6] This fact demonstrates that a hydrazino group is present at position 4 on the pyrimidine ring of X and hence of VII.

Treatment of X with an excess of benzoyl peroxide in ethanol in the presence of triethylamine caused dehydrogenation along with esterification to afford ethyl 1,4-dihydro-7-methylthio-4-oxopyrimido[4,5-*c*]pyridazine-3-carboxylate (XVII) in 50% yield. Subsequently XVII was hydrolyzed to 1,4-dihydro-7-methylthio-4-oxopyrimido[4,5-*c*]pyridazine-3-carboxylic acid (XVIII) in 82% yield which is a key intermediate for syntheses of our desirable compounds II.

The compound VII and its derivatives (X—XVIII) thus are best formulated as the assigned structures in good agreement with their spectral and chemical evidences. Further

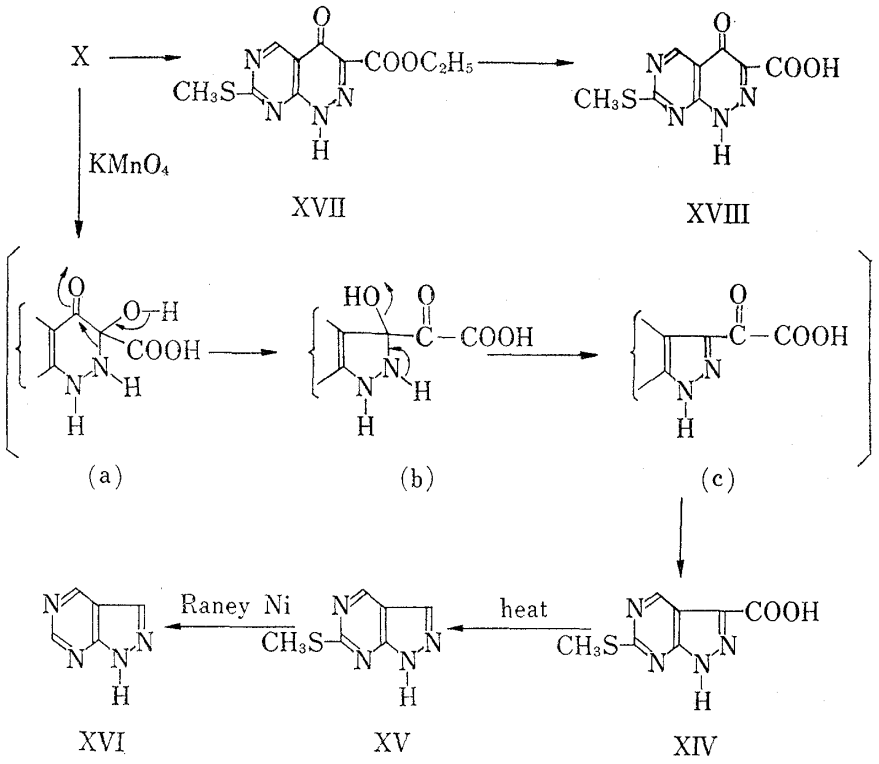


Chart 5

6) R.K. Robins, *J. Am. Chem. Soc.*, **78**, 784 (1956).

structural confirmation of these compounds was carried out by means of an alternative synthesis of the ester XVII, which will be reported in our next paper.

The formation of VII from the reaction of III with hydrazine is reasonably explained by a probable mechanistic pathway as given in Chart 6; thus, both the position 4 on the pyrimidine ring and the positively charged nitrogen of the diazo group are subjected at first to nucleophilic displacement with hydrazine to form an intermediate (d), which subsequently converts into a tetrazolone (e) by ring closure, and then the hydrazino group attacks the α-carbon with simultaneous ruptures of C–N and N–N bonds, resulting in the formation of VII along with hydrogen azide. This mechanism was rationalized by detection of hydrogen azide in the reaction mixture as silver and ferric azides by Feigl's procedure.[7]

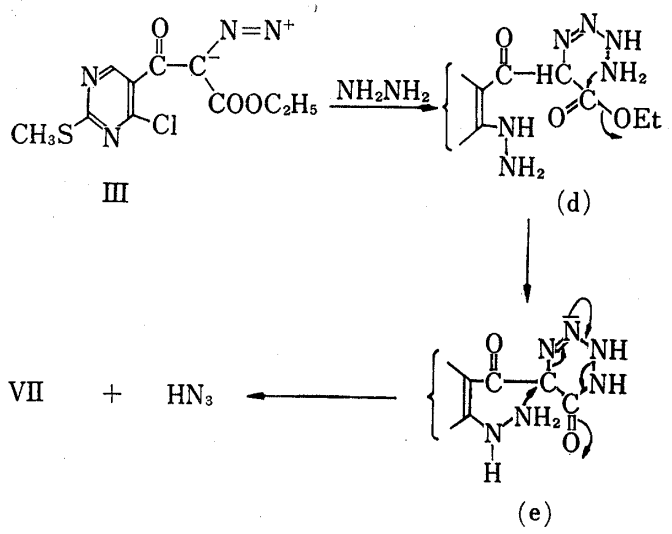


Chart 6

No precedent for reaction of the α-carbon in a class of α-diazo-β-oxopropionates with nucleophiles in an alkaline condition has known so far. It is of interest that this new type of reaction of III with hydrazine took place to form the 1,2-dihydropyrimido[4,5-*c*]-pyridazine derivatives (VII). Compound (VII) served through XVIII as an important intermediate for syntheses of our aimed compounds (II), which will be published later.

Experimental

Melting points were determined on a Yanagimoto micro melting point apparatus and are uncorrected. IR spectra were recorded in potassium bromide disk on a Hitachi EPI spectrometer. UV spectra were measured with a Hitachi EPS-2U spectrometer. NMR spectra were taken with tetramethylsilane as an internal standard on a Varian A-60 spectrometer. Mass spectra were taken with a Hitachi RMU-6L spectrometer with the direct sample inlet system. Organic extracts were dried over anhyd. Na_2SO_4 or $MgSO_4$. All evaporation were performed on a rotary evaporator *in vacuo*.

Reaction of 4-Chloro-2-methylthiopyrimidine-5-carbonylchloride with Ethyl Diazoacetate——A mixture of 4-chloro-2-methylthiopyrimidine-5-carbonylchloride[8] (30 g) and ethyl diazoacetate (30 g) was stirred at 45—50° for 12 hr. The reaction mixture was concentrated to dryness below 50°. The residue was triturated with hexane. The resulting precipitate was collected by filtration to give 3.1 g (11.7%) of 4-chloro-2-methylthiopyrimidine-5-carboxylic anhydride (III'). The product was recrystallized from hexane, mp 117—118°. *Anal.* Calcd. for $C_{12}H_8O_3N_4S_2Cl_2$: C, 36.84; H, 2.06; N, 14.32; S, 16.40; Cl, 18.12. Found: C, 36.96; H, 1.94; N, 14.50; S, 16.80; Cl, 17.96. IR cm^{-1}: 1800, 1740 (C=O). NMR ($CDCl_3$) δ: 2.67 (3H, s, SCH_3), 9.06 (1H, s, C_6–H).

The filtrate was evaporated to dryness. The resulting residue was chromatographed on neutral Al_2O_3 (column; 7.0×20.0 cm) with AcOEt. A crude product was recrystallized from hexane to give 25.1 g (62.1%) of ethyl α-diazo-β-oxo-5-(4-chloro-2-methyl thio pyrimidine)propionate (III) as colorless needles, mp 63—64°. *Anal.* Calcd. for $C_{10}H_9O_3N_4SCl$: C, 39.94; H, 3.02; N, 18.63; S, 10.66; Cl, 11.79. Found: C, 39.78; H, 2.88; N, 18.63; S, 10.80; Cl, 12.09. IR cm^{-1}: 2150 (N_2), 1715, 1635 (C=O). NMR ($CDCl_3$) δ: 1.25 (3H, t, J=7.5 Hz, $CH_2\underline{CH_3}$), 2.60 (3H, s, SCH_3), 4.25 (2H, q, J=7.5 Hz, $C\underline{H_2}CH_3$), 8.37 (1H, s, C_4-H). UV λ_{max}^{EtOH} nm: 222, 279.

Ethyl 5-Hydroxy-2-methylthiofuro[2,3-*d*]pyrimidine-6-carboxylate (IV)——To a stirred suspension of III (350 mg) in EtOH (5 ml) was added 40% aq HBr (2 ml) at room temperature. The mixture was heated at 50° for 5 min and cooled. The resulting crystals were collected and recrystallized from EtOH to give 270 mg (91.2%) of IV as colorless needles, mp 147—148°. *Anal.* Calcd. for $C_{10}H_{10}O_4N_2S$: C, 47.24; H, 3.96; N, 11.02;

7) F. Feigl, "Spot Tests in Inorganic Analysis," 5th ed. (Asian ed.), Maruzen Co., Ltd., Tokyo, 1961 p. 286.
8) H.L. Wheeler and C.O. Johns, *Am. Chem. J.*, **40**, 233 (1908).

S, 12.61. Found: C, 47.07; H, 3.99; N, 10.98; S, 12.84. IR cm^{-1}: 1670, 1600 (C=O). The NMR spectrum of IV shows that IV and its tautomer, ethyl 5,6-dihydro-2-methylthio-5-oxofuro[2,3-*d*]pyrimidine-6-carboxylate (IV'), exist in *ca.* 1 : 2 molar ratio as an equilibrium mixture in a $CHCl_3$ solution. NMR ($CDCl_3$) for IV, δ: 1.45 (3H, t, J=7 Hz, $CH_2C\underline{H}_3$), 2.63 (3H, s, SCH_3), 4.49 (2H, q, J=7 Hz, $C\underline{H}_2CH_3$), 8.98 (1H, s, C_4-H); for IV', δ: 1.33 (3H, t, J=7 Hz, $CH_2C\underline{H}_3$), 2.63 (3H, s, SCH_3), 4.36 (2H, q, J=7 Hz, $C\underline{H}_2CH_3$), 5.28 (1H, s, C_6-H), 8.78 (1H, s, C_4-H). Mass Spectrum *m/e*: 254 (M^+).

Reaction of III with Hydrazine Hydrate——(A) Using 1.5 eq. of $NH_2NH_2\cdot H_2O$: To a stirred solution of III (10 g) in a mixture of benzene (30 ml) and EtOH (15 ml) was added a solution of $NH_2NH_2\cdot H_2O$ (2.16 g) in EtOH (5 ml) at 0—5° over a period of 10 min. The stirred mixture was kept below 5° for 1 hr and allowed to stand at room temperature overnight. The resulting precipitate was collected by filtration, washed with a mixed solvent of benzene (10 ml) and EtOH (10 ml), and extracted with $CHCl_3$ (120 ml). The insoluble fraction was washed with water (15 ml) to give 1.95 g (24.2%) of 1,2-dihydro-4-hydroxy-7-methylthiopyrimido-[4,5-*c*]pyridazine-3-carboxamide (VII) which was reprecipitated from 1N NaOH with 10% aq. AcOH to give brown solid, mp 260—265° (decomp). *Anal.* Calcd. for $C_8H_9O_2N_5S$: C, 40.16; H, 3.79; N, 29.27; S, 13.40. Found: C, 40.06; H, 3.61; N, 28.85; S, 13.44. IR cm^{-1}: 1650 (sh, C=O), 1640 (sh, C=O). NMR (DMSO-d_6) δ: 2.61 (3H, s, SCH_3), 5.82 (5H, br, exchangeable with D_2O), 8.93 (1H, s, C_5–H). UV $\lambda_{max}^{H_2O}$ nm: 235, 275, 320; $\lambda_{max}^{0.01N\ NaOH}$ nm: 234, 295, 384. Mass Spectrum *m/e*: 239 (M^+).

The $CHCl_3$ extract was concentrated to dryness and the residue was recrystallized from tetrahydrofuran to give 2.4 g (47.3%) of 5,5'-bis(ethoxycarbonyldiazoacetyl)-3,3'-bismethylthio-4,4'-hydrazopyrimidine (VIII) as yellow needles, mp 175—176°. *Anal.* Calcd. for $C_{20}H_{20}O_6N_{10}S_2$: C, 42.86; H, 3.60; N, 24.98; S, 11.44. Found: C, 43.10; H, 3.35; N, 24.78; S, 11.68. IR cm^{-1}: 2140, 2125 (N_2), 1715, 1600 (C=O).

After the initial filtrate had been allowed to stand for 3 weeks, yellow crystals separated out, collected by filtration, and recrystallized from EtOH to give 1.6 g (19.5%) of 1-(5-ethoxycarbonyl-2-methylthio-4-pyrimidinyl)-2-(5-ethoxycarbonyldiazoacetyl-2-methylthio-4-pyrimidinyl)hydrazine (IX) as yellow needles, mp 165—166° (decomp). *Anal.* Calcd. for $C_{18}H_{20}O_5N_8S_2$: C, 43.89; H, 4.09; N, 22.75; S, 13.02. Found: C, 43.87; H, 3.88; N, 22.83; S, 13.30. IR cm^{-1}: 2145 (N_2), 1700, 1675, 1590 (C=O).

(B) Using 3.6 eq. of $NH_2NH_2\cdot H_2O$: To a stirred solution of III (40 g) in EtOH (1.5 liter) was added dropwise a solution of $NH_2NH_2\cdot H_2O$ (2.5 g) in EtOH (120 ml) below 10° over a period of 20 min, during which time precipitates appeared gradually. The reaction mixture was stirred at room temperature for 1 hr and allowed to stand overnight. The precipitates were collected by filtration, washed with water, and dissolved in 1N NaOH. The solution was filtered and the filtrate was acidified with 30% aq. AcOH. The precipitate was collected and washed successively with water, EtOH and ether to give 32 g of VII (nearly 100%).

(C) Detection of Hydrogen Azide: The filtrate, obtained from the original reaction mixture, was served to detection of the hydrogen azide formed during the reaction. The test were carried out according to Feigl's procedure[7] by uses of $AgNO_3$ and $FeCl_3$.

Hydrolysis of VII to 1,2-Dihydro-4-hydroxy-7-methylthiopyrimido[4,5-*c*]pyridazine-3-carboxylic Acid (X)——A suspension of VII (10 g) in a mixture containing 5% aq. HCl (240 ml) and EtOH (1.6 liter) was heated to reflux for 5 hr. The reaction mixture was filtered to remove a small amount of red precipitates, and the filtrate was treated with charcoal by refluxing for 30 min, during which period colorless needles separated out gradually. The resulted crystals were collected along with the charcoal by filtration, and dissolved in 1N NaOH (50 ml). The alkaline solution was filtered to remove the charcoal, and the filtrate was acidified with 30% aq. AcOH to give precipitates, which were collected and washed with water to give the crude product. The initial filtrate, separated from the crystals and charcoal, was cooled on an ice-bath to give an additional crop of the product, which was collected and combined with the first crop. The combined product (X), weighing 6.78 g (64.5%), was purified by recrystallization from EtOH, mp 250—252° (decomp). *Anal.* Calcd. for $C_8H_8O_3N_4S$: C, 40.00; H, 3.35; N, 23.32; S; 13.34. Found: C, 40.13; H, 3.26; N, 23.26; S, 13.20. IR cm^{-1}: 3325, 3225 (OH, NH), 1650, 1640 (C=O). NMR (DMSO-d_6) δ: 2.61 (3H, s, SCH_3), 6.00 (2H, br, exchangeable with D_2O), 8.90 (1H, s, C_5–H), 10.00 (2H, br, exchangeable with D_2O). UV $\lambda_{max}^{H_2O}$ nm: 226, 278. $\lambda_{max}^{0.01N\ NaOH}$ nm: 256, 308. Mass Spectrum *m/e*: 240 (M^+).

Acetylation of VII to 1,2-Diacetyl-4-hydroxy-1,2-dihydro-7-methylthiopyrimido[4,5-*c*]pyridazine-3-carboxamide (XI)——A mixture of VII (500 mg) and Ac_2O (15 ml) was kept at 50° for 30 min with stirring and then an excess of Ac_2O was evaporated. The resulting residue was washed with EtOH (30 ml) to give 580 mg (86%) of XI which was recrystallized from EtOH to give colorless prisms, mp 291—292°. *Anal.* Calcd. for $C_{12}H_{13}O_4N_5S$: C, 44.58; H, 4.05; N, 21.67; S, 9.90. Found: C, 44.45; H, 3.82; N, 21.72; S, 9.95. IR cm^{-1}: 3250 (OH), 1690, 1660 (C=O). NMR (DMSO-d_6) δ: 2.11 (3H, s, $COCH_3$), 2.18 (3H, s, $COCH_3$), 2.57 (3H, s, SCH_3), 8.97 (1H, s, C_5–H), 9.65 (1H, s, NH, exchangeable with D_2O), 10.79 (1H, s, NH, exchangeable with D_2O), 12.30 (1H, br, OH, exchangeable with D_2O). UV λ_{max}^{EtOH} nm (log ε): 277 (4.20), 340 (4.34). Mass Spectrum *m/e*: 323 (M^+).

Acetylation of VII to 4-Acetoxy-9-acetyl-1-methyl-7-methylthioimidazo[3',4': 2,3]pyridazo[6,5-*d*]pyrimidin-3(9*H*)-one (XII)——A mixture of VII (500 mg) and Ac_2O (10 ml) was heated at 120° for 2.5 hr. After evaporation of excess Ac_2O, the residue was triturated with water (10 ml) to give precipitates. The precipitate was collected and washed with water to give 710 mg (98%) of XII, which was recrystallized from $CHCl_3$–EtOH to give colorless prisms, mp 224—225°. *Anal.* Calcd. for $C_{14}H_{13}O_4N_5S$: C, 48.41; H, 3.77; N, 20.16; S, 9.21.

Found: C, 48.72; H, 3.64; N, 19.81; S, 9.31. IR cm^{-1}: 1730, 1715, 1690, 1630 (C=O). NMR ($CDCl_3$) δ: 2.38 (6H, s, 2 $COCH_3$), 2.54 (3H, s, SCH_3), 2.74 (3H, s, CH_3), 9.03 (1H, s, C_5–H). UV λ_{max}^{EtOH} nm (log ε): 245 (3.97), 296 (3.94), 332 (4.10), 345 (4.15). Mass Spectrum *m/e*: 347 (M^+).

Acetylation of XI to XII——A mixture of XI (110 mg) and Ac_2O (5 ml) was heated at 120° for 1.5 hr. The reaction mixture was worked up as described above, and 112 mg (96%) of XII was obtained, which was identical in all respects with the sample derived from VII.

Hydrolysis of XII to XI——A mixture of XII (200 mg), 1N NaOH (5 ml) and EtOH (5 ml) was heated at 80° for 5 min. The ethanol was evaporated. To the residual solution was added water (10 ml), and the mixture was acidified with 10% aq. HCl. The resulting precipitates were collected and washed with water to give 80 mg (42%) of XI which was identical in all respects with an authentic sample.

Hydrolysis of XII to 9-Acetyl-4-hydroxy-1-methyl-7-methylthioimidazo[3′,4′: 2,3]pyridazo[6,5-*d*]pyrimidin-3(9H)-one (XIII)——A mixture of XII (120 mg) and 28% NH_4OH (10 ml) was heated at 55° for 10 min, and then acidified with 30% aq. AcOH. The resulting precipitates were collected and washed with water to give 80 mg (71.6%) of XIII which was recrystallized from EtOH to give colorless prisms, mp 219—221°. *Anal.* Calcd. for $C_{12}H_{11}O_3N_5S$: C, 47.20; H, 3.63; N, 22.94; S, 10.50. Found: C, 47.19; H, 3.36; N, 22.80; S, 10.74. IR cm^{-1}: 3500 (OH), 1700, 1680, 1630 (C=O). NMR (DMSO-d_6) δ: 2.15 (3H, s, $COCH_3$), 2.58 (3H, s, SCH_3), 2.68 (3H, s, CH_3), 9.15 (1H, s, C_5–H), 10.92 (1H, br, OH, exchangeable with D_2O). UV λ_{max}^{EtOH} nm (log ε): 244 (4.16), 294 (4.10), 330 (4.25), 344 (4.35). Mass Spectrum *m/e*: 305 (M^+).

6-Methylthio-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-carboxylic Acid (XIV)——To a stirred solution of X (2.0 g) in 2% NaOH was added 0.5% aq. $KMnO_4$ (200 ml) during 20 min. After being heated at 40° for 10 min, the mixture was kept at room temperature for 3 hr, and filtered to remove the precipitated MnO_2. The filtrate was acidified with 30% aq. AcOH, giving a small amount of the precipitate which was removed by filtration. The resulting yellow filtrate was further acidified with 10% aq. HCl, and cooled. The resulting crystals were collected, washed with water and recrystallized from EtOH to give 1.23 g (70.2%) of XIV, mp 291—292°. *Anal.* Calcd. for $C_7H_6O_2N_4S$: C, 39.99; H, 2.88; N, 26.65; S, 15.25. Found: C, 39.99; H, 2.91; N, 26.74; S, 14.84. IR cm^{-1}: 1720 (C=O). NMR (DMSO-d_6) δ: 2.60 (3H, s, SCH_3), 9.20 (1H, s, C_4–H), 14.3 (1H, br, COOH, exchangeable with D_2O). Mass Spectrum *m/e*: 210 (M^+).

6-Methylthio-1*H*-pyrazolo[3,4-*d*]pyrimidine (XV)——XIV (70 mg) was heated above 300° under reduced pressure (40 mmHg) to give sublimates, which weighed 42 mg (76%) of XV, mp 216—217°. *Anal.* Calcd. for $C_6H_6N_4S$: C, 43.35; H, 3.64; N, 33.76; S, 19.29. Found: C, 43.56; H, 3.38; N, 33.88; S, 19.44. IR cm^{-1}: 3100 (NH). NMR (DMSO-d_6) δ: 2.58 (3H, s, SCH_3), 8.25 (1H, s, C_3–H), 9.12 (1H, s, C_4–H). Mass Spectrum *m/e*: 166 (M^+).

1*H*-Pyrazolo[3,4-*d*]pyrimidine (XVI)——A mixture of XV (450 mg), EtOH (150 ml) and Raney Ni (about 0.2 g) was stirred at 60° for 5 hr. The reaction mixture was filtered to remove the catalyst and the filtrate was concentrated to dryness. The residue was extracted with toluene (50 ml). The extract was concentrated to dryness, and the residue was triturated with cold EtOH to give 15 mg (4.6%) of XVI, mp 204—209°, which was identical with the sample prepared according to the literature.[6] *Anal.* Calcd. for $C_5H_4N_4$: C, 49.99; H, 3.36; N, 46.65. Found: C, 49.70; H, 3.04; N, 46.82.

Ethyl 1,4-Dihydro-7-methylthio-4-oxopyrimido[4,5-*c*]pyridazine-3-carboxylate (XVII)——To a stirred suspension of X (9.6 g) in absolute EtOH (0.8 liter) was added Et_3N (4.4 g). The mixture was maintained at room temperature for 2 hr with stirring. To the solution was added benzoyl peroxide in three 6 g-portions for each 30 min interval. The reaction mixture was heated at 45° for 5 hr with stirring and allowed to stand overnight at room temperature. The resulting precipitates were collected by filtration. The filtrate was concentrated to a 1/8 volume and cooled to give an additional precipitate, which was collected by filtration. The combined precipitates were recrystallized from EtOH to give 5.3 g (50%) of XVII as colorless prisms, mp 269—270° *Anal.* Calcd. for $C_{10}H_{10}O_3N_4S$: C, 45.11; H, 3.79; N, 21.04; S, 12.04. Found: C, 45.06; H, 3.67; N, 21.14; S, 12.09. IR cm^{-1}: 1710, 1640 (C=O). NMR (DMSO-d_6) δ: 1.33 (3H, t, J=7 Hz) $CH_2\underline{CH_3}$), 2.62 (3H, s, SCH_3), 4.37 (2H, q, J=7 Hz, $\underline{CH_2}CH_3$), 9.20 (1H, s, C_5–H), 14.00 (1H, br, NH, exchangeable with D_2O). UV λ_{max}^{EtOH} nm (log ε): 270 (4.48), 345 (4.10), 350sh (4.09). Mass Spectrum *m/e*: 266 (M^+).

1,4-Dihydro-7-methylthio-4-oxopyrimido[4,5-*c*]pyridazine-3-carboxylic Acid (XVIII)——A mixture of XVII (1.3 g), 1N NaOH (20 ml) and EtOH (20 ml) was heated at 90° for 10 min and then cooled. The reaction mixture was acidified with 1N aq HCl to give 950 mg (82%) of XVIII which was recrystallized from EtOH to give colorless prisms, mp 278.5—279.5° (decomp). *Anal.* Calcd. for $C_8H_6O_3N_4S$: C, 40.03; H, 2.60; N, 23.34; S, 13.36. Found: C, 40.06; H, 2.59; N, 23.10; S, 13.18. IR cm^{-1}: 1720, 1630 (C=O).