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Syntheses of Pyrimido[4,5-*c*]pyridazine Derivatives. II.[1] A Novel Reaction of α-Diazo-β-oxo-5-(4-chloropyrimidine)propionate with Triphenyl Phosphine leading to 1,4-Dihydro-4-oxopyrimido-[4,5-*c*]pyridazine-3-carboxylate

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A new and convenient synthetic method was presented for the derivatives of the pyrimido[4,5-*c*]pyridazine. Reactions of α-diazo-β-oxo-5-(4-chloro-2-substituted pyrimidine)propionates (**1a**—**c**) with triphenyl phosphine afforded ethyl 1,4-dihydro-4-oxo-7-substituted pyrimido[4,5-*c*]pyridazine-3-carboxylates (**3a**—**c**) in good yields. α-Diazo-β-oxo-5-(4-methoxy-2-methylthiopyrimidine)propionate (**5a**), when treated with triphenyl phosphine in the same conditions, yielded {[1-ethoxycarbonyl-2-oxo-2-(4-methoxy-2-methylthio-5-pyrimidinyl)ethylidene]hydrazono}triphenyl phosphorane (**6a**) which was an intermediate for the 7-methylthio derivative (**3a**). The conversion of **6a** into **3a** was effected by treating with aqueous alcohol *via* ethyl α-hydrazono-β-oxo-5-(4-methoxy-2-methylthiopyrimidine)propionate (**7a**). The 2-phenyl derivative (**5b**) gave the 7-phenyl analog (**3b**). Reaction mechanisms for **1** leading to **3** were discussed.

Keywords——reductive cyclization; triphenyl phosphine; reduction of α-diazo-β-oxopropionates; derivatives of phosphazine; derivatives of pyrimido[4,5-*c*]pyridazine

In the previous paper,[1] we reported the synthesis of ethyl 1,4-dihydro-7-methylthio-4-oxopyrimido[4,5-*c*]pyridazine-3-carboxylate (**3a**) from ethyl α-diazo-β-oxo-5-(4-chloro-2-methylthiopyrimidine)propionate (**1a**) *via* three steps.

This paper deals with an alternate synthesis of **3a** involving a new reaction of **1a** with triphenyl phosphine.

It is well known that α-diazo-β-oxopropionate (I) forms a phosphazine (II) by reacting with triphenyl phosphine, followed by hydrolysis of II to the corresponding hydrazone (III).[3]

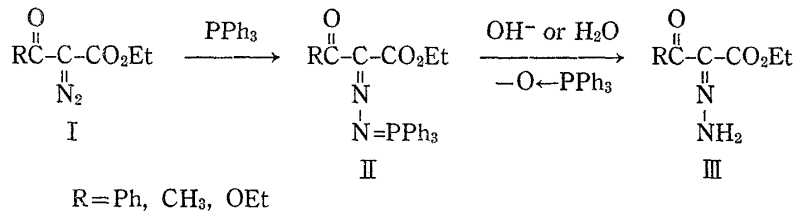

Chart 1

It is expected that **1** would react similarly with triphenyl phosphine to form phosphazines (**2**), which would be convertible to pyrimido[4,5-*c*]pyridazines (**3**) under appropriate reaction conditions. Phosphonium salts (**4**) besides **2** are also possible as the reaction products, because **1** has another reactive center, *i.e.*, C-4 position, in the molecule. The possibility of forming **4**, however, seems likely to be excluded owing to the less basicity and

1) Part I: Y. Kimura, T. Miyamoto, J. Matsumoto, and S. Minami, *Chem. Pharm. Bull.* (Tokyo), **24**, 2637 (1976).
2) Location: *Enoki-cho 33-94, Suita, Osaka, 564, Japan.*
3) H. Staudinger and G. Lüscher, *Helv. Chim. Acta*, **5**, 75 (1922); H.J. Bestmann and H.K. Koln, *Chem. Ber.*, **96**, 1948 (1963).

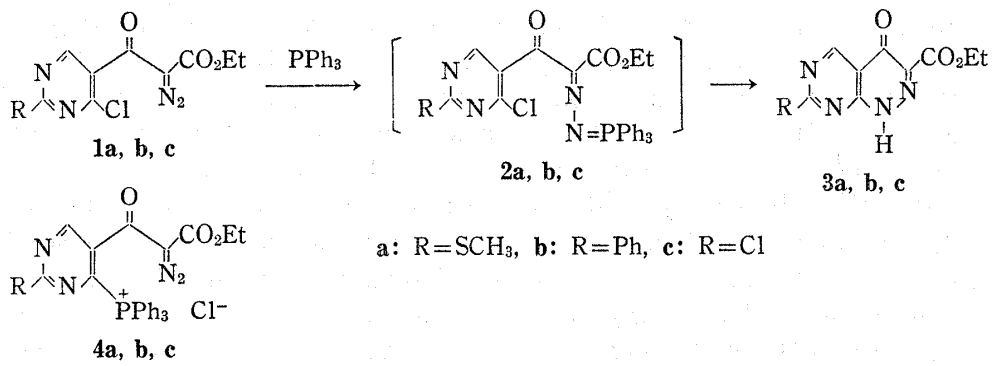

Chart 2

larger bulkiness of triphenyl phosphine. In fact, treatment of **1** with triphenyl phosphine gave directly the desired product (**3**). Thus when **1a** was allowed to react with triphenyl phosphine in diisopropyl ether at room temperature, pale yellow precipitates gradually appeared during a course of the reaction. The precipitate thus obtained was recrystallized from 80% aq. ethanol to give a pure sample of **3a**, which was identical in all respects with an authentic species.[1] Analogously, the reaction of **1b** and **1c** with triphenyl phosphine afforded the corresponding pyrimido[4,5-*c*]pyridazine derivatives **3b** and **3c** in 80 and 37% yield, respectively.

It is of interest to clarify the mechanism of this reaction. In order to determine the stage in which the ring closure took place, ethyl α-diazo-β-oxo-5-(4-methoxy-2-methylthiopyrimidine)propionate (**5a**) bearing a less active methoxy group was subjected to the same reaction in hopes of isolating any intermediate. In fact, **3a** was prepared stepwise from **5a**

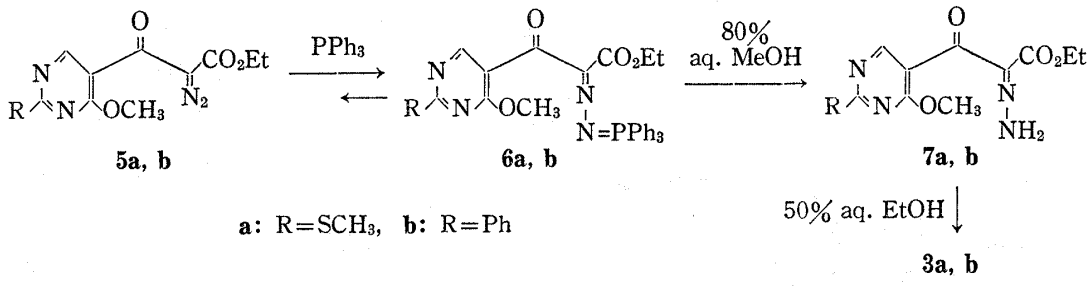

Chart 3

through the intermediary phosphazine (**6a**) and the hydrazone (**7a**), both of which were isolated, as expected, in contrast with the case of **1a**. Thus treatment of **5a** with triphenyl phosphine in a similar manner afforded a yellow precipitate. The precipitate was found to be the phosphazine (**6a**). The structure **6a** was confirmed by elemental analysis, and spectral evidences [infrared (IR) and nuclear magnetic resonance (NMR) spectra]; IR spectrum of **6a** lacks the N≡N absorption band at 2140 cm^{-1} observed in the spectrum of **5a**.

It was found that **6a** dissociated gradually into **5a** and triphenyl phosphine in a solvent such as $CHCl_3$, benzene, and dimethylformamide. This phenomenon was observed by NMR spectrum ($CDCl_3$) of **6a** showing that a ratio of **5a** to **6a** increased gradually. It was understood that **6a** was so hardly soluble in diisopropyl ether that the reaction proceeded to deposit **6a**. The similar phenomenon had been reported in regard with acyl phosphazines.[4] The phosphazine (**6a**) was refluxed in 80% aq. methanol for 3 hr to afford mainly the hydrazone (**7a**), together with **3a**, **5a**, and an unidentified compound (**8**) (mp 136—137°),[5] as by-products. The main product (**7a**) (mp 100—105°) was revealed to be a mixture of two

4) H.J. Bestmann and L. Göthlich, *Ann.*, **655**, 1 (1962).
5) The structural determination of **8** is in progress.

compounds by its NMR spectrum. Fractional recrystallization from isopropanol divided essentially the mixture into compounds A (mp 112—113°) and B (mp 103—105°). Although elemental analyses of both compounds agreed equally with $C_{11}H_{14}N_4O_4S$, considerable differences between A and B were observed in their spectra. Thus, in their IR spectra (KBr), NH_2 absorption bands appeared clearly at 3320 and 3180 cm^{-1} in A and at 3300 and 3160 cm^{-1} in B. Also, C=O absorption bands appeared at 1695 and 1600—1550 cm^{-1} in A and at 1675 and 1635 cm^{-1} in B. In their NMR spectra ($CDCl_3$), an NH_2 signal appeared at δ 9.94 (2H, broad singlet) in A and at δ 9.25 (2H, broad singlet) in B, but the signals due to the other protons were essentially the same in both compounds. Those data demonstrated that both compounds A and B were hydrazones isomeric in geometry with respect to the C=N bond, although its geometry remains to be solved. The hydrazone (**7a**), consisting of the two isomers, was converted effectively into **3a** by refluxing with 50% aq. ethanol for 10 hr. In a similar manner, ethyl α-diazo-β-oxo-5-(4-methoxy-2-phenylpyrimidine)propionate (**5b**) was treated with triphenyl phosphine followed by heating with aq.ethanol, without isolation of the intermediates in this case, to give **3b** in 30% over-yield.

Possible mechanisms for the reaction of **1** with triphenyl phosphine are given in Chart 4. In analogy to the case of **5a, 1** reacts with triphenyl phosphine to yield at first the phosphazine (**2**) which is hydrolyzed *via* **11** to give the hydrazone (**12**), together with triphenyl phosphine oxide, followed by the successive cyclization to **3** (path a). The intermediate **11** may alternatively undergo the ring closure prior to the elimination of triphenyl phosphine oxide to give **10** which then converts into **3**. Another probable pathway leading to **3** is shown

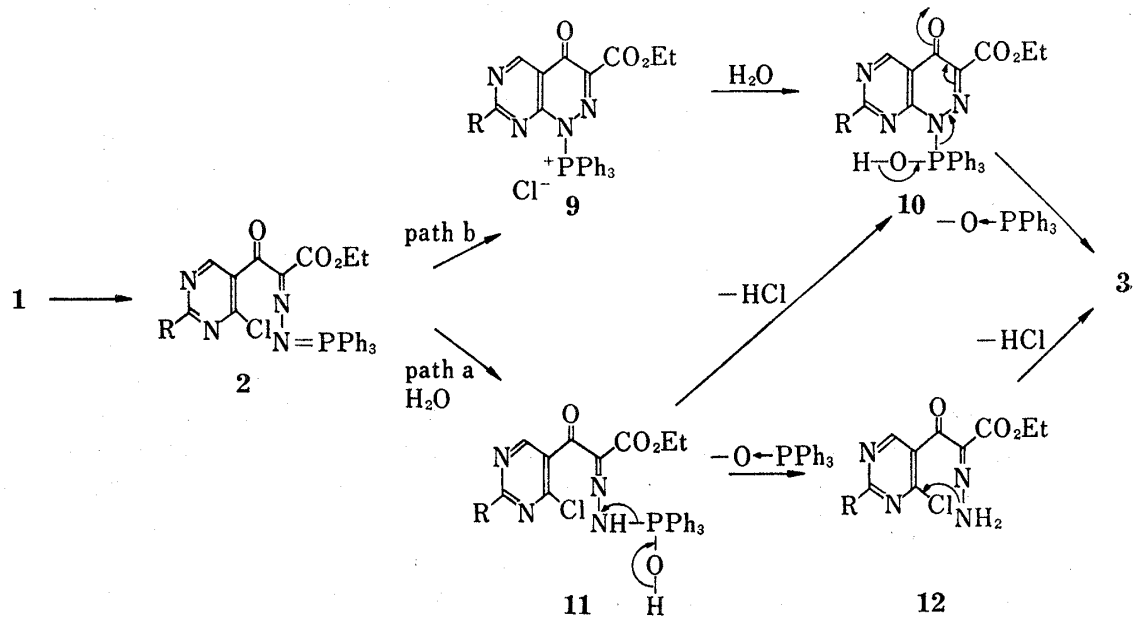

Chart 4

by the reaction sequences **2**→**9**→**10**→**3** (path b) in considering the presence of the more reactive chloro group than the methoxy group. Thus the phosphazine (**2**) undergoes the intramolecular cyclization between the activated nitrogen atom bonded to the phosphorus atom and the active C-4 position situated properly on the pyrimidine ring to result in forming the phosphonium salt (**9**) under mild conditions. The precipitate separating out during a course of the reaction is likely to be the salt (**9**), although no definitive characterization of the precipitate could be made because of its lability. When the precipitate was once isolated from the mixture, its IR spectrum was practically the same to that of **3**.

The reactivities of triethyl and triphenyl phosphites with **1a** were examined in place of triphenyl phosphine. As a result, triethyl phosphite gave **3a** in 37% yield, while triphenyl phosphite failed to react with **1a** in the same conditions.

This work presents a further evidence for correctness of the structure assigned previously[1] to **3a** as well as an alternate and convenient synthetic method for the derivatives of the pyrimido[4,5-*c*]pyridazine.

Experimental

All melting points were determined on a Yanagimoto micro melting point apparatus and not corrected. IR spectra were recorded on a Hitachi model 215 spectrometer. NMR spectra were taken with tetramethylsilane as an internal standard on a Varian A-60 spectrometer, unless otherwise noted.

Ethyl α-Diazo-β-oxo-5-(4-chloro-2-methylthiopyrimidine)propionate (1a)——According to the procedure described previously,[1] **1a** was prepared from 4-chloro-2-methylthiopyrimidine-5-carbonyl chloride and ethyl diazoacetate.

Ethyl α-Diazo-β-oxo-5-(4-chloro-2-phenylpyrimidine)propionate (1b)——A suspension of 4-chloro-2-phenylpyrimidine-5-carbonyl chloride (10.7 g), prepared from 4-hydroxy-2-phenylpyrimidine-5-carboxylic acid[6] by treating with $POCl_3$, and ethyl diazoacetate (10 g) was stirred at 10° for 10 min and then heated to 65°. The mixture gradually became a clear solution with evolution of the gas and then was kept for 7 hr at the same temperature. The reaction mixture was allowed to stand overnight. The resulting precipitate was collected by filtration to give **1b** (7.6 g, 57.5%), colorless prisms, mp 97—98° (benzene–hexane). *Anal.* Calcd. for $C_{15}H_{11}ClN_4O_3$: C, 54.47; H, 3.35; Cl, 10.72; N, 16.94. Found: C, 54.34; H, 3.07; Cl, 10.86; N, 16.93. IR (KBr) cm^{-1}: 2160 (N_2), 1720, 1645 (C=O). NMR ($CDCl_3$) δ: 1.20 (3H, t, $J=7$ Hz, $CH_2\underline{CH_3}$), 4.23 (2H, q, $J=7$ Hz, $\underline{CH_2}CH_3$), *ca.* 7.5 (3H, phenyl protons), *ca.* 8.5 (2H, phenyl protons), 8.65 (1H, s, C_6–H).

Ethyl α-Diazo-β-oxo-5-(2,4-dichloropyrimidine)propionate (1c)——A mixture of 2,4-dichloropyrimidine-5-carbonyl chloride (5 g),[7] and ethyl diazoacetate (10 g) was stirred under ice-cooling. After evolution of the gas ceased, the reaction mixture was heated at 45—50° for 24 hr and concentrated to dryness below 50°. The oily residue was chromatographed on a silica gel with $CHCl_3$. The oily product **1c** (5 g, 73%) was obtained and used for the next step without analysis and further purification. IR (liq. film) cm^{-1}: 2160 (N_2), 1720, 1640 (C=O). NMR ($CDCl_3$) δ: 1.25 (3H, t, $J=7$ Hz, $CH_2\underline{CH_3}$), 4.25 (2H, q, $J=7$ Hz, $\underline{CH_2}CH_3$), 8.48 (1H, s, C_6–H).

Ethyl 1,4-Dihydro-4-oxo-7-methylthiopyrimido[4,5-*c*]pyridazine-3-carboxylate (3a)——(A) To a stirred solution of **1a** (6 g) in iso-Pr_2O (100 ml) was added a solution of triphenyl phosphine (PPh_3) (6 g) in iso-Pr_2O (150 ml) at room temperature. After several minutes, pale yellow precipitates appeared gradually. After stirring for 2 hr, the reaction mixture was heated at 60—70° for 1.5 hr and allowed to stand overnight at room temperature. The resulting precipitate, showing a negative Beilstein test, was collected by filtration to give 7.5 g of the crude product, which was then recrystallized from 80% aq. EtOH to give **3a** (4.0 g, 76%), colorless prisms, mp 269—270° (EtOH). *Anal.* Calcd. for $C_{10}H_{10}N_4O_3S$: C, 45.11; H, 3.79; N, 21.04; S, 12.04. Found: C, 45.23; H, 3.59; N, 20.77; S, 12.32. The product **3a** was identical in all respects with an authentic species.[1] Triphenyl phosphine oxide was obtained from the mother-liquor of the recrystallization of **3a**.

(B) To a stirred solution of **1a** (300 mg) in iso-Pr_2O (30 ml) was added triethyl phosphite (180 mg) at room temperature, and the mixture was refluxed for 10 hr. The resulting precipitate was collected by filtration to give **3a** (100 mg, 37.6%). An excess of triethyl phosphite and triethyl phosphate formed during a course of the reaction were readily removed by washing with EtOH or H_2O.

Ethyl 1,4-Dihydro-4-oxo-7-phenylpyrimido[4,5-*c*]pyridazine-3-carboxylate (3b)——(A) To a stirred solution of **1b** (1.1 g) in a mixture of iso-Pr_2O (20 ml) and dry $CHCl_3$ (10 ml) was added a solution of PPh_3 (1.0 g) in iso-Pr_2O (12 ml) at room temperature. The mixture was allowed to stand overnight at room temperature. The resulting yellow precipitate was collected by filtration. This product (1.35 g), which showed a negative Beilstein test, was refluxed for 1.5 hr with 60% aq. EtOH to give **3b** (800 mg, 80%), colorless prisms, mp 256—257° (EtOH). *Anal.* Calcd. for $C_{15}H_{12}N_4O_3$: C, 60.80; H, 4.08; N, 18.91. Found: C, 60.73; H, 3.86; N, 18.85. NMR (DMSO-d_6) δ: 1.33 (3H, t, $J=7$ Hz, $CH_2\underline{CH_3}$), 4.38 (2H, q, $J=7$ Hz, $\underline{CH_2}CH_3$), 9.50 (1H, s, C_5–H).

(B) To a stirred solution of **5b** (370 mg) in iso-Pr_2O (15 ml) was added a solution of PPh_3 in iso-Pr_2O (10 ml) at room temperature. After stirring for 2 hr, the mixture was refluxed for 5 hr and concentrated to dryness. The resulting residue was refluxed for 6 hr with 80% aq. EtOH (40 ml), and then the mixture concentrated to one-third volume. The resulting precipitate on cooling was collected by filtration to give **3b** (100 mg, 30%).

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7) Geigy, J.R., A.G., Brit. Patent 1182086 (1970) [*C.A.*, **72**, 100736 (1970)].

Ethyl 7-Chloro-1,4-dihydro-4-oxopyrimido[4,5-*c*]pyridazine-3-carboxylate (3c) ——To a stirred solution of **1c** (3.2 g) in iso-Pr_2O (80 ml) was added a solution of PPh_3 (3.5 g) in iso-Pr_2O (50 ml) at room temperature. After several minutes, pale yellow precipitates appeared. After stirring for 30 min, the reaction mixture was heated at 50—60° for 5 min and cooled. The resulting precipitate was collected by filtration and recrystallized from EtOH to give a crude product (1.05 g, 37%), mp 206—207°. For analysis the sample was further purified by chromatography on a silica gel with AcOEt to give **3c** as colorless needles, mp 209—210° (EtOH). *Anal.* Calcd. for $C_9H_7ClN_4O_3$: C, 42.45; H, 2.77; Cl, 13.92; N, 22.00. Found: C, 42.66; H, 2.51; Cl, 13.74; N, 21.73. NMR (DMSO-d_6) δ: 1.32 (3H, t, $J=7$ Hz, $CH_2C\underline{H}_3$), 4.35 (2H, q, $J=7$ Hz, $C\underline{H}_2CH_3$), 9.38 (1H, s, C_5–H), 14.67 (1H, br, NH or OH, exchangeable with D_2O). IR (KBr) cm^{-1}: 1715, 1610 (C=O).

Ethyl α-Diazo-β-oxo-5-(4-methoxy-2-methylthiopyrimidine)propionate (5a)——4-Methoxy-2-methylthiopyrimidine-5-carbonyl chloride (7.2 g), prepared by hydrolysis of 4-methoxy-2-methylthiopyrimidine-5-carboxylate[8] followed by treatment with $SOCl_2$, was allowed to react with ethyl diazoacetate (14 g) under ice-cooling. After evolution of the gas ceased, the reaction mixture was heated at 45—50° for 24 hr and concentrated to dryness below 50°. The oily residue was chromatographed on neutral Al_2O_3 with AcOEt. The oily product **5a** (9.0 g, 92%) was obtained and used for the next step without analysis and further purification. IR (liq. film) cm^{-1}: 2140 (N_2), 1715, 1620 (C=O). NMR ($CDCl_3$) δ: 1.25 (3H, t, $J=7$ Hz, $CH_2C\underline{H}_3$), 2.58 (3H, s, SCH_3), 4.00 (3H, s, OCH_3), 4.25 (2H, q, $J=7$ Hz, $C\underline{H}_2CH_3$), 8.33 (1H, s, C_6–H).

Ethyl α-Diazo-β-oxo-5-(4-methoxy-2-phenylpyrimidine)propionate (5b)——4-Methoxy-2-phenylpyrimidine-5-carbonyl chloride (1.15 g), prepared by hydrolysis of 4-methoxy-2-phenylpyrimidine-5-carboxylate[9] followed by treatment with $SOCl_2$, was allowed to react with ethyl diazoacetate (3 g) under ice-cooling. After evolution of the gas ceased, the reaction mixture was heated at 60° for 2 hr and concentrated to dryness below 50°. The oily residue was chromatographed on silica gel with $CHCl_3$. The oily product **5b** (500 mg, 35%) was obtained and used for the next step without analysis and further purification. IR (liq. film) cm^{-1}: 2140 (N_2), 1715, 1620 (C=O). NMR ($CDCl_3$) δ: 1.22 (3H, t, $J=7$ Hz, $CH_2C\underline{H}_3$), 1.40 (3H, s, OCH_3), 4.17 (2H, q, $J=7$ Hz, $C\underline{H}_2CH_3$), *ca.* 7.4 (3H, phenyl protons), *ca.* 8.5 (2H, phenyl protons), 8.50 (1H, s, C_6–H).

{[1-Ethoxycarbonyl-2-oxo-2-(4-methoxy-2-methylthio-5-pyrimidinyl) ethylidene] hydrazono} triphenyl phosphorane (6a)——To a stirred solution of **5a** (3.83 g) in iso-Pr_2O (30 ml) was added PPh_3 (5.12 g) at room temperature. After being kept at the same temperature for 45 min, the reaction mixture was heated at 50° for 3.5 hr. The resulting precipitate on cooling was collected by filtration to give **6a** (4.6 g, 64%), yellow prisms, mp 117—118 (benzene–hexane). *Anal.* Calcd. for $C_{29}H_{27}N_4O_4PS$: C, 62.35; H, 4.87; N, 10.03; P, 5.46; S, 5.74. Found: C, 62.64; H, 4.72; N, 9.82; P, 5.54; S, 5.89. IR (KBr) cm^{-1}: 1720, 1620 (C=O). NMR ($CDCl_3$) (100 MHz, Varian HA-100 D) δ: 1.40 (3H, t, $J=7$ Hz, $CH_2C\underline{H}_3$), 2.55 (3H, s, SCH_3), 3.63 (3H, s, OCH_3), 4.45 (2H, q, $J=7$ Hz, $C\underline{H}_2CH_3$), *ca.* 7.5 (15H, phenyl protons), 8.03 (1H, s, C_6–H).

Hydrolysis of 6a——A mixture of **6a** (3.4 g) and 80% aq. MeOH (30 ml) was refluxed for 3 hr. After cooling, the resulting precipitate was collected by filtration to give **3a** (300 mg, 18.5%). The filtrate was concentrated to dryness. The residue was extracted with $CHCl_3$, and the $CHCl_3$ evaporated to leave an oil which was chromatographed on a silica gel (column: 4.5×20 cm) with $CHCl_3$. The first fraction gave the diazo compound (**5a**) (30 mg, 1.7%). From the second fraction, an unidentified compound (**8**) (170 mg) was obtained, which was recrystallized from EtOH to give 100 mg, colorless prisms, mp 136—137°. *Anal.* Calcd. for $C_{11}H_{12}N_4O_3S$ (**8**): C, 47.13; H, 4.32; N, 19.99; S, 11.44. Found: C, 47.18; H, 4.05; N, 19.65; S, 11.83. The third fraction gave 1.34 g of a pale yellow oil, which was crystallized from iso-PrOH to afford ethyl α-hydrazono-β-oxo-5-(4-methoxy-2-methylthiopyrimidine)propionate (**7a**) (800 mg, 43.6%). The hydrazone (**7a**) was found to be a mixture of two compounds and divided into compounds A (350 mg) and B (100 mg) by fractional recrystallization from iso-PrOH. The two compounds were not distinguishable by TLC [Merck silica gel 60 F_{254}; solvent: a) AcOEt, b) $CHCl_3$–HCO_2Et–HCO_2H (10: 20: 1, v/v)]. Compound A: colorless prisms, mp 112—113° (iso-PrOH). *Anal.* Calcd. for $C_{11}H_{14}N_4O_4S$: C, 44.29; H, 4.73; N, 18.78. Found: C, 44.32; H, 4.58; N, 18.79. NMR ($CDCl_3$) (100 MHz) δ: 1.22 (3H, t, $J=7$ Hz, $CH_2C\underline{H}_3$), 2.58 (3H, s, SCH_3), 3.98 (3H, s, OCH_3), 4.20 (2H, q, $J=7$ Hz, $C\underline{H}_2CH_3$), 8.48 (1H, s, C_6–H), 9.94 (2H, br, NH_2, exchangeable with D_2O). Compound B: colorless prisms, mp 103—105° (iso-PrOH). *Anal.* Calcd. for $C_{11}H_{14}N_4O_4S$: C, 44.29; H, 4.73; N, 18.78. Found: C, 44.35; H, 4.65; N, 18.63. NMR ($CDCl_3$) (100 MHz) δ: 1.24 (3H, t, $J=7$ Hz, $CH_2C\underline{H}_3$), 2.58 (3H, s, SCH_3), 3.97 (3H, s, OCH_3), 4.25 (2H, q, $J=7$ Hz, $C\underline{H}_2CH_3$), 8.48 (1H, s, C_6–H), 9.25 (2H, br, NH_2, exchangeable with D_2O).

Conversion of 7a into 3a——The hydrazone (**7a**) (150 mg) was refluxed with 50% aq. EtOH (10 ml) for 10 hr. The reaction mixture was concentrated to one-third volume and cooled. The resulting precipitate was collected by filtration to give **3a** (80 mg, 60%).

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8) R.S. Shadbolt and T.L.V. Ulbricht, *J. Chem. Soc.* (*C*), **1967**, 1172.
9) S. Yurugi, M. Hieda, T. Fushimi, and T. Tomimoto, *Chem. Pharm. Bull.* (Tokyo), **19**, 2354 (1971).