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Syntheses of the Urinary Metabolites of 1-(4-Methoxy-6-methyl-2-pyrimidinyl)-3-methyl-5-methoxypyrazole (Mepirizole,[1] DA-398[2])

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All the metabolites (UAM-1, UNM-1, UNM-2, UNM-4, and URM-1), which were isolated from the urine of rats and rabbits administered 1-(4-methoxy-6-methyl-2-pyrimidinyl)-3-methyl-5-methoxypyrazole (mepirizole, DA-398) were synthesized and their structures were established by direct comparison with the synthetic samples.

In the preceding paper,[4] it was shown that five metabolites[5] were isolated as crystals from the urine of rats and rabbits administered with mepirizole and their chemical structures were elucidated. In order to confirm the structures of these metabolites and to investigate their pharmacological properties, syntheses of these metabolites were carried out and this paper deals with the method for their synthesis.

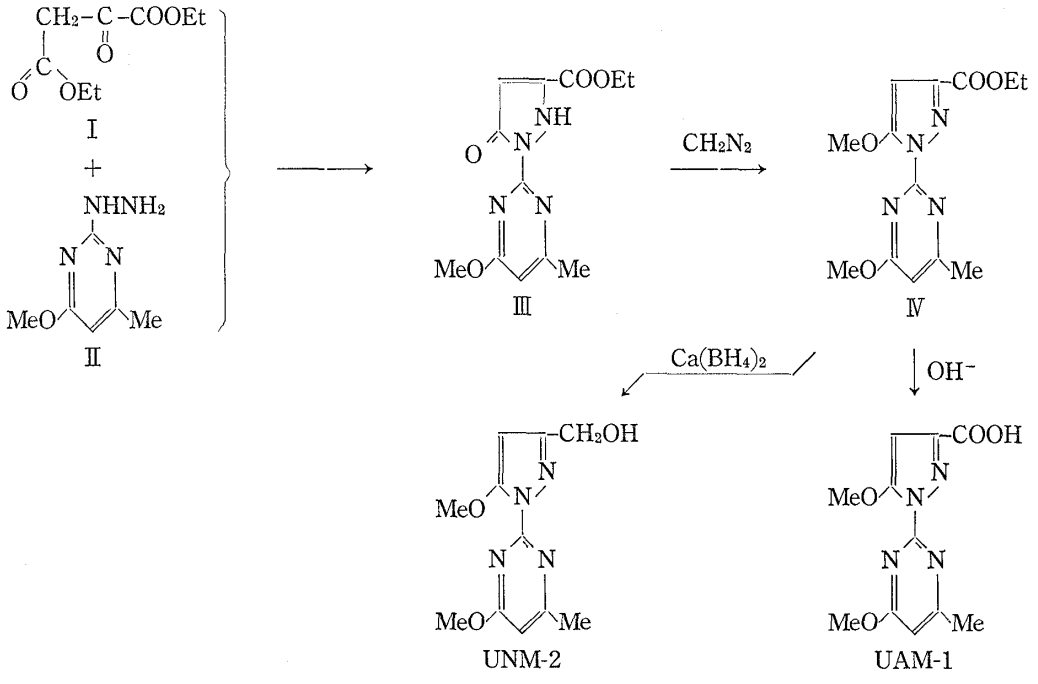

Chart 1

1) Japanese accepted name.
2) Presented in part at the 89th Annual Meeting of the Pharmaceutical Society of Japan, Nagoya, April, 1969 and at the Meeting of Kyushu Branch, the Pharmaceutical Society of Japan, Fukuoka, September 1969.
3) Location: *Minamifunabori-cho, Edogawa-ku, Tokyo.*
4) E. Takabatake, R. Kodama, Y. Tanaka, R. Dohmori, H. Tachizasa, and T. Naito, *Chem. Pharm. Bull.* (Tokyo), **18**, 1889 (1970).
5) In the preceding paper,[4] the five metabolites were adopted the names of UAM-1, UNM-1, UNM-2, UNM-4 and URM-1.

Synthesis of 1-(4-Methoxy-6-methyl-2-pyrimidinyl)-5-methoxypyrazole-3-carboxylic Acid (UAM-1)

UAM-1 was synthesized by the route shown in Chart 1. According to the general method[6] of synthesizing pyrazolone-3-carboxylic acid derivatives, the 3-ethoxycarbonylpyrazolone compound (III) was obtained by cyclization of diethyl oxalacetate (I) with 2-hydrazino-4-methoxy-6-methylpyrimidine (II). III was methylated with diazomethane in methanol–ether solution and the O-methylated compound (IV) so obtained was hydrolyzed with alkali to give 1-(4-methoxy-6-methyl-2-pyrimidinyl)-5-methoxypyrazole-3-carboxylic acid (UAM-1), mp 193—195°.

Synthesis of 1-(4-Methoxy-6-methyl-2-pyrimidinyl)-3-hydroxymethyl-5-methoxypyrazole (UNM-2)

The reduction of IV with calcium borohydride in tetrahydrofuran afforded 1-(4-methoxy-6-methyl-2-pyrimidinyl)-3-hydroxymethyl-5-methoxypyrazole (UNM-2), mp 135°, in a satisfactory yield. The yield of UNM-2 was lower by the use of sodium borohydride.

Synthesis of 1-(4-Methoxy-5-hydroxy-6-methyl-2-pyrimidinyl)-3-methyl-5-methoxypyrazole (UNM-1)

Since the 4-position of pyrazole ring is obviously liable to electrophilic attack, the tempting attempt to introduce a hydroxyl group *via* halogeno or amino group only into the pyrimidine ring of pyrimidinylpyrazole derivative was rejected. Therefore, a long sequence shown in Chart 2 was chosen for the synthesis of UNM-1.

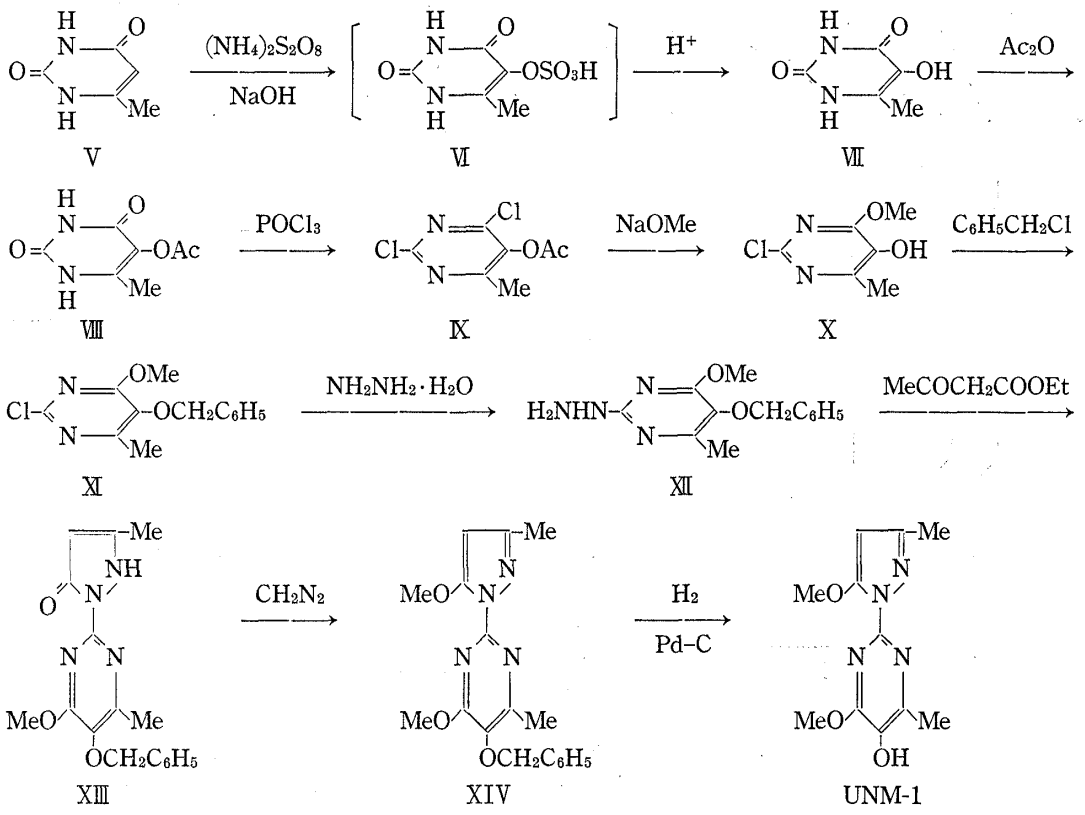

Chart 2

The Elbs persulfate oxidation introduced to pyrimidine series by Hull[7] is a valuable method for the synthesis of 5-hydroxypyrimidines. Thus, in accordance with his procedure,

6) E. Koike, H. Iida, and A. Kashioka, *Kogyo Kagaku Zasshi*, **57**, 123 (1954).
7) R. Hull, *J. Chem. Soc.*, **1956**, 2033.

hydroxylation of 6-methyluracil (V) was examined. The sulfate ester (VI) of 5-hydroxy-6-methyluracil, which was obtained by the treatment of V with ammonium persulfate in 3N sodium hydroxide solution, without isolation, was hydrolyzed with hydrochloric acid to give 5-hydroxy-6-methyluracil (VII). The yield of VII was about 50% from V. The compound (VII) gave a deep blue color with ferric chloride and its nuclear magnetic resonance (NMR) spectrum (in NaOD) indicated the disappearance of a proton signal due to 5-position of pyrimidine ring. Heating of VII with acetic anhydride gave the monoacetate[8] (VIII) decomposing at 295°.

VIII was converted into the dichloropyrimidine compound (IX) by treatment with phosphoryl chloride and dimethylaniline. Although the treatment of IX with one mole of sodium methoxide caused only deacetylation, heating of IX with 10 molar equivalent sodium methoxide in methanol gave the monochloro-monomethoxy-pyrimidine compound (X) in a good yield. The hydroxyl group of X was protected by treatment with benzyl chloride and the reaction of the resulting benzyloxypyrimidine compound (XI) with hydrazine hydrate in the presence of potassium carbonate afforded the 2-hydrazinopyrimidine compound (XII). The pyrimidinylpyrazole compound (XIII), which was prepared from XII and ethyl acetoacetate, was methylated with diazomethane, followed by hydrogenolysis over palladium charcoal to give 1-(4-methoxy-5-hydroxy-6-methyl-2-pyrimidinyl)-3-methyl-5-methoxypyrazole (UNM-1), mp 203°.

Synthesis of 1-(4-Methoxy-6-methyl-2-pyrimidinyl)-3-methyl-4-hydroxy-5-methoxypyrazole Sulfate (URM-1)

The synthesis of URM-1 is outlined in Chart 3. The pyrazole compound (XVI) was not obtained by refluxing ethyl 2-acetoxyacetoacetate[11] (XV) with the hydrazinopyrimidine compound (II) in ethanol, in the presence of acid or alkali. However, it was obtained in 42% yield by heating a mixture of XV and II in toluene for 12 hours. XVI was converted

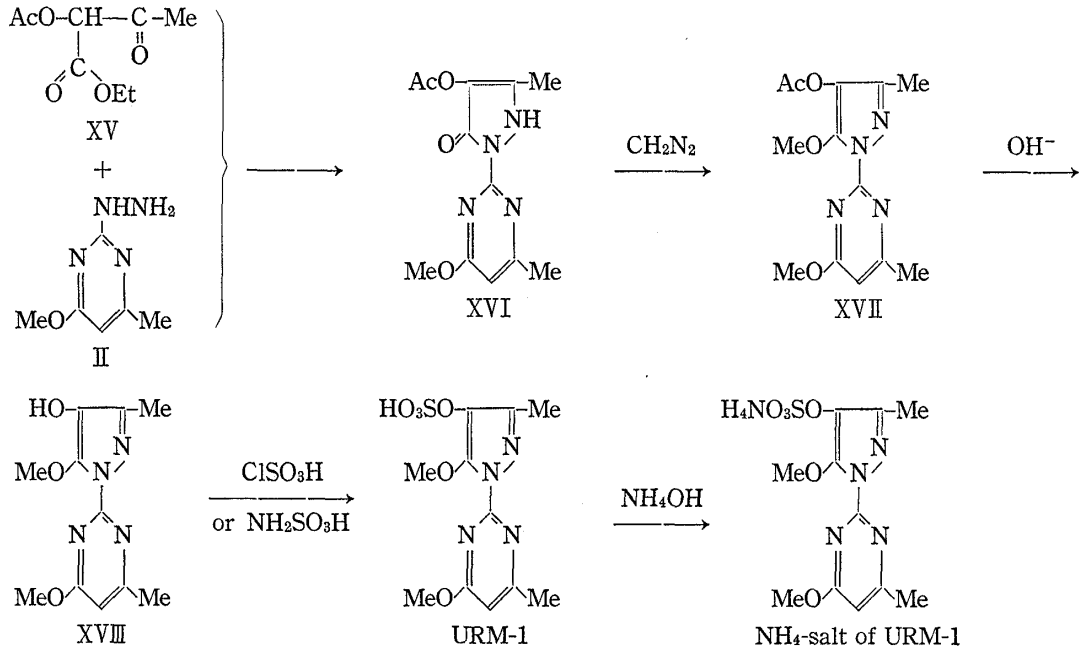

Chart 3

8) Behrend, *et al.*[9] reported that 5-hydroxy-6-methyluracil (VII) was obtained by $KMnO_4$-oxidation of 6-methyluracil (V) in a poor yield and its acetate (VIII) decomposed at 238—241°. Hufschmidt[10] followed up their procedure and corrected the melting point of VIII as 285—290°.

9) R. Behrend and R. Grünewald, *Ann. Chem.*, **323**, 178 (1902).

10) C. Hufschmidt, *Ann. Chem.*, **343**, 164 (1905).

11) H. Henecke, *Chem. Ber.*, **81**, 179 (1948).

into the O-methyl compound (XVII) by treatment with diazomethane and XVII was hydrolyzed to the 4-hydroxypyrazole compound[12] (XVIII), mp 195—198°.

In general, the sulfate esters of alcohols have been prepared by the application of chlorosulfonic acid[13] or sulfamic acid.[14] By the reaction of XVIII with chlorosulfonic acid or sulfamic acid in pyridine, the sulfate ester (URM-1) was prepared in about 60% yield. The ester obtained above was converted into the ammonium salt, mp 204—207° (decomp.), for identification with the metabolite.

Synthesis of 1-(4-Hydroxymethyl-6-methoxy-2-pyrimidinyl)-3-methyl-5-methoxypyrazole(UNM-4)

UNM-4 was synthesized by the route illustrated in Chart 4. The ring closure reaction of 2-hydrazino-4-hydroxymethyl-6-pyrimidone[15] (XIX) with ethyl acetoacetate gave the pyrazolone compound (XX)in a good yield. On treatment with a large excess of diazomethane, XX afforded 1-(4-hydroxymethyl-6-methoxy-2-pyrimidinyl)-3-methyl-5-methoxypyrazole (UNM-4), mp 155—157°.

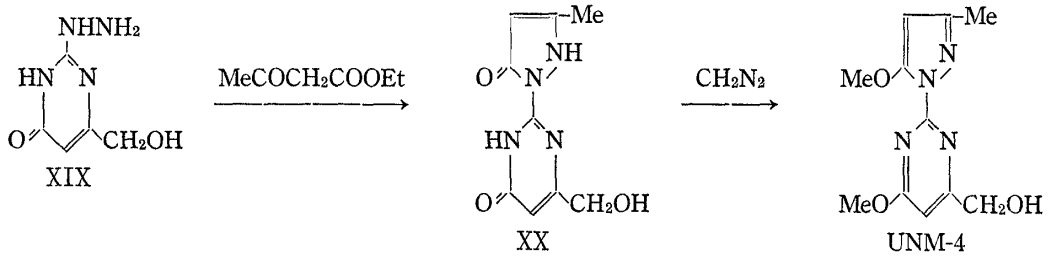

Chart 4

The five compounds obtained above were identical with the metabolites (UAM-1, UNM-1, UNM-2, UNM-4, and URM-1) isolated from the urine of rats and rabbits administered mepirizole by direct comparison (mp, ultraviolet (UV), infrared (IR), NMR, and TLC).

Experimental

All melting points were uncorrected. The IR spectra were taken with a Hitachi EPI-G2 Spectrophotometer. The ultraviolet spectra were measured with a Hitachi Recording Spectrophotometer EPS-2U. A JEOLCO Model JNM 4H-100 Spectrometer was used for measurement of NMR spectra and chemical shift showed in ppm from TMS as standard signal.

Ethyl 1-(4-Methoxy-6-methyl-2-pyrimidinyl)-3-pyrazolin-5-one-3-carboxylate (III)——A mixture of 2-hydrazino-4-methoxy-6-methylpyrimidine (40 g), diethyl oxalacetate (97.5 g) and EtOH (300 ml) was refluxed for 2 hr. After cooling, a solution of Na (15.5 g) in EtOH (250 ml) was added and the mixture was refluxed for another one hour. After evaporation of the solvent, the residue was dissolved in H_2O and the insoluble material was removed by filtration. The filtrate was acidified with AcOH and the resulting precipitate was collected by filtration and dried. Recrystallization from benzene gave III (41 g, 56.7%) as colorless needles, mp 187—188°. *Anal.* Calcd. for $C_{12}H_{14}O_4N_4$: C, 51.79; H, 5.07; N, 20.14. Found: C, 52.23; H, 5.25; N, 19.74.

Ethyl 1-(4-Methoxy-6-methyl-2-pyrimidinyl)-5-methoxypyrazole-3-carboxylate (IV)——To a suspension of III (27 g) in MeOH (100 ml) was added a large excess of diazomethane–ether solution and the mixture was allowed to stand overnight at room temperature. The solvent was evaporated and the residue was treated with ether. The solid separated was recrystallized from MeOH–H_2O to give IV (20.5 g, 72.4%) as colorless needles, mp 110—111°. *Anal.* Calcd. for $C_{13}H_{16}O_4N_4$: C, 53.42; H, 5.52; N, 19.18. Found: C, 53.46; H, 5.62; N, 19.02.

12) In the preceding paper,[4] this compound was isolated from the urine of rabbits administered mepirizole and received the name "UNM-5."
13) I. Tanaka, *Jap. Saf. Forces Med. J.*, 3, 811 (1956).
14) J.P. Joseph, J.P. Dusza, and S. Bernstein, *Steroid*, 7, 577 (1966).
15) H. Vanderhaeghe and M. Claesen, *Bull. Soc. Chim. Belg.*, 68, 30 (1959).

1-(4-Methoxy-6-methyl-2-pyrimidinyl)-5-methoxypyrazole-3-carboxylic Acid (UAM-1)——A mixture of IV (2.92 g) and 5% NaOH (12 ml) was warmed for 10—30 min on a steam-bath with stirring. After cooling, the reaction mixture was acidified with AcOH and the solid separated was collected and dried. Recrystallization from MeOH–H_2O gave 1-(4-methoxy-6-methyl-2-pyrimidinyl)-5-methoxypyrazole-3-carboxylic acid (1.8 g, 68.2%) as colorless needles, mp 193—195°. *Anal.* Calcd. for $C_{11}H_{12}O_4N_4$: C, 50.00; H, 4.58; N, 21.20. Found: C, 49.85; H, 4.70; N, 21.02. IR ν_{max}^{KBr} cm^{-1}: 1720 (C=O). UV λ_{max}^{MeOH} mμ (log ε): 251 (4.21). NMR (CD_3OD) ppm: 2.43 (3H, singlet, CH_3), 3.93 (6H, singlet, $2\times OCH_3$), 6.17 (1H, singlet, pyrazole-C_4–H), 6.58 (1H, singlet, pyrimidine-C_5–H).

1-(4-Methoxy-6-methyl-2-pyrimidinyl)-3-hydroxymethyl-5-methoxypyrazole (UNM-2)——To a solution of $NaBH_4$ (2.27 g) in tetrahydrofuran (100 ml) was added anhyd. $CaCl_2$ (3.3 g) with stirring and the mixture was stirred at room temperature for one hour. To the reaction mixture was added a solution of IV (5.84 g) in tetrahydrofuran (100 ml) and the mixture was stirred at room temperature for another 10 hr. After evaporation of the solvent *in vacuo* to dryness, the residue was treated with 10% NaOH and extracted with $CHCl_3$. The extract was washed with H_2O and dried over anhyd. Na_2SO_4 and evaporated. The residue was recrystallized from EtOH to give 1-(4-methoxy-6-methyl-2-pyrimidinyl)-3-hydroxymethyl-5-methoxypyrazole (3.8 g, 76.0%) as colorless prisms, mp 135—137°. *Anal.* Calcd. for $C_{11}H_{14}O_3N_4$: C, 52.79; H, 5.64; N, 22.39. Found: C, 52.42; H, 5.68; N, 22.70. UV λ_{max}^{MeOH} mμ (log ε): 251 (4.21). NMR (CD_3OD) ppm: 2.44 (3H, singlet, CH_3), 4.00, 4.02 (each 3H, two singlets, $2\times OCH_3$), 4.57 (2H, singlet, $-CH_2-$), 5.88 (1H, singlet, pyrazole-C_4–H), 6.60 (1H, singlet, pyrimidine-C_5–H).

5-Hydroxy-6-methyluracil (VII)——Ammonium persulfate (855 g) in H_2O (1750 ml) was added dropwise to a stirred ice-cold solution of 6-methyluracil (315 g) in 3N NaOH (5500 ml) during 2 hr. The reaction mixture was stirred at 5—8° for another one hour and allowed to stand overnight at room temperature. The solution was acidified (pH 4) with conc. HCl and evaporated *in vacuo* to dryness. To the residue was added 5N HCl (2000 ml) and the mixture was refluxed for 2 hr and allowed to stand overnight at room temperature. The resulting precipitate was filtered, washed with H_2O and dried. Recrystallization from H_2O gave VII (176.5 g, 49.7%) as colorless prisms, mp >300°. *Anal.* Calcd. for $C_5H_6O_3N_2$: C, 42.25; H, 4.26; N, 19.71. Found: C, 41.95; H, 4.23; N, 91.40. The compound gave a deep blue color with ferric chloride and showed only one signal due to the methyl group in NMR spectrum (in NaOD).

5-Acetoxy-6-methyluracil (VIII)——A mixture of VII (142 g) and Ac_2O (8400 ml) was refluxed for 3 hr. After removal of insoluble material by filtration, the filtrate was allowed to stand overnight at room temperature. The crystals separated were collected and the filtrate was concentrated *in vacuo* to give further crops. These crystals were combined and recrystallized from H_2O to give VIII (158 g, 85.9%) as colorless prisms, mp 295° (decomp.). *Anal.* Calcd. for $C_7H_8O_4N_2$: C, 45.65; H, 4.38; N, 15.21. Found: C, 45.36; H, 4.36; N, 14.99.

2,4-Dichloro-5-acetoxy-6-methylpyrimidine (IX)——A mixture of VIII (133 g), $POCl_3$ (1300 ml) and dimethylaniline (133 ml) was refluxed for 1.5 hr on an oil bath. The excess of $POCl_3$ was removed *in vacuo* and the residue was poured into ice-water. The resulting solution was extracted with ether and the extract was washed with H_2O and dried over anhyd. Na_2SO_4. The solvent was evaporated and the residue was distilled to give IX (114 g, 71.4%), bp 135—137° (6 mmHg), which solidified on cooling as colorless needles, mp 78—80°. *Anal.* Calcd. for $C_7H_6O_2N_2Cl_2$: C, 38.03; H, 2.74; N, 12.68; Cl, 32.08. Found: C, 38.44; H, 2.76; N, 12.37; Cl, 31.83.

2-Chloro-4-methoxy-5-hydroxy-6-methylpyrimidine (X)——IX (45 g) was added to a solution of Na (47.5 g) in MeOH (1640 ml) and the mixture was refluxed for 10 hr. The solvent was evaporated. The residue was dissolved in H_2O, acidified with HCl and extracted with $CHCl_3$. The extract was washed with H_2O and dried over anhyd. Na_2SO_4. After evaporation of the solvent, the residue was recrystallized from EtOH to give X (32.0 g, 89.6%) as colorless needles, mp 149—150°. *Anal.* Calcd. for $C_6H_7O_2N_2Cl$: C, 41.27; H, 4.04; N, 16.05; Cl, 20.31. Found: C, 41.18; H, 4.31; N, 16.35; Cl, 20.52.

2-Chloro-4-methoxy-5-benzyloxy-6-methylpyrimidine (XI)——Benzyl chloride (126.6 g) was added to a solution of Na (2.3 g), MeOH (400 ml) and X (17.5 g). The mixture was refluxed with stirring for one hour and concentrated *in vacuo*. The residue was treated with H_2O and the solution was basified with 10% NaOH and then extracted with benzene. The extract was washed with H_2O and dried over anhyd. Na_2SO_4. After evaporation of the solvent, the residue was distilled to yield XI (20 g, 75.5%) as colorless syrup, bp 175—177° (6 mmHg). *Anal.* Calcd. for $C_{13}H_{13}O_2N_2Cl$: C, 58.98; H, 4.95; N, 10.59; Cl, 13.40. Found: C, 59.09; H, 4.81; N, 10.39; Cl, 13.49.

2-Hydrazino-4-methoxy-5-benzyloxy-6-methylpyrimidine (XII)——To a stirred mixture of XI (10.6 g) in EtOH (100 ml) and K_2CO_3 (5.52 g) was added dropwise a solution of 80% $NH_2NH_2\cdot H_2O$ (25.0 g) in EtOH (50 ml) at 70—80° over a period of one hour. The reaction mixture was stirred at the same temperature for another one hour. After removal of the solvent, the residue was treated with H_2O and the solution was basified with NaOH and then extracted with $CHCl_3$. The extract was washed with H_2O, dried over anhyd. Na_2SO_4 and evaporated *in vacuo* to dryness. Recrystallization of the residue from EtOH gave XII (6.5 g, 62.5%) as colorless needles, mp 96—97°. *Anal.* Calcd. for $C_{13}H_{16}O_2N_4$: C, 59.98; H, 6.20; N, 21.53. Found: C, 59.67; H, 6.24; N, 21.53.

1-(4-Methoxy-5-benzyloxy-6-methyl-2-pyrimidinyl)-3-methyl-3-pyrazolin-5-one (XIII)——A mixture of XII (1.3 g), ethyl acetoacetate (1.0 g) and MeOH (40 ml) was refluxed for 30 min. To the reaction mixture was added a solution of NaOH (0.22 g) in 80% aqueous MeOH (6 ml). The mixture was refluxed for 30 min and then concentrated to syrup *in vacuo*. The residue was dissolved in H_2O, neutralized with AcOH and extracted with $CHCl_3$. The extract was washed with H_2O and dried over anhyd. Na_2SO_4. After evaporation of the solvent, the residue was recrystallized from EtOH to give XIII (1.2 g, 73.5%) as a colorless powder, mp 146—148°. *Anal.* Calcd. for $C_{17}H_{18}O_3N_4$: C, 62.56; H, 5.56; N, 17.17. Found: C, 62.25; H, 5.87; N, 17.02.

1-(4-Methoxy-5-benzyloxy-6-methyl-2-pyrimidinyl)-3-methyl-5-methoxypyrazole (XIV)——To a solution of XIII (6.52 g) in $CHCl_3$ (32.5 ml) was added a large excess of diazomethane–ether solution and the mixture was allowed to stand for 20 hr at room temperature. The solvent was evaporated and the residue was treated with 10% NaOH and then extracted with benzene. The extract was dried over anhyd. Na_2SO_4 and concentrated. The residue was dissolved in benzene and chromatographed on Al_2O_3. The crude product obtained from the eluate with benzene was recrystallized from cyclohexane to give XIV (3.38 g, 49.7%) as colorless needles, mp 65°. *Anal.* Calcd. for $C_{18}H_{20}O_3N_4$: C, 63.51; H, 5.92; N, 16.46. Found: C, 63.23; H, 6.13; N, 15.99.

1-(4-Methoxy-5-hydroxy-6-methyl-2-pyrimidinyl)-3-methyl-5-methoxypyrazole (UNM-1)——A mixture of XIV (6.5 g), 10% Pd–C (3 g) and MeOH (200 ml) was submitted to reduction at ordinary temperature and pressure. One molar equivalent of H_2 was absorbed within about one hour. After removal of the catalyst, the solvent was evaporated and the residue was recrystallized from MeOH to give 1-(4-methoxy-5-hydroxy-6-methyl-2-pyrimidinyl)-3-methyl-5-methoxypyrazole (3.5 g, 73.7%) as colorless prisms, mp 203—205°. *Anal.* Calcd. for $C_{11}H_{14}O_3N_4$: C, 52.79; H, 5.64; N, 22.39. Found: C, 52.43; H, 5.46; N, 22.48. UV λ_{max}^{MeOH} mμ (log ε): 256 (4.24). NMR (CD_3OD) ppm: 2.23, 2.38 (each 3H, two singlets, $2\times CH_3$), 3.92, 4.05 (each 3H, two singlets, $2\times OCH_3$), 5.63 (1H, pyrazole-C_4–H).

1-(4-Methoxy-6-methyl-2-pyrimidinyl)-3-methyl-4-acetoxy-3-pyrazolin-5-one (XVI)——A mixture of 2-hydrazino-4-methoxy-6-methylpyrimidine (123 g), ethyl 2-acetoxyacetoacetate[11] (150 g) and EtOH (1000 ml) was refluxed for one hour. After evaporation of the solvent, toluene (1000 ml) was added to the residue and the mixture was refluxed for 12 hr. After cooling, the solution was washed with 10% AcOH and dried over anhyd. Na_2SO_4. After evaporation of the solvent, the residue was treated with ether and the resulting crystals were recrystallized from benzene–cyclohexane to give XVI (95 g, 42.7%) as colorless prisms, mp 143—145°. *Anal.* Calcd. for $C_{12}H_{14}O_4N_4$: C, 51.79; H, 5.07; N, 20.14. Found: C, 51.62; H, 5.01; N, 19.95.

1-(4-Methoxy-6-methyl-2-pyrimidinyl)-3-methyl-4-acetoxy-5-methoxypyrazole (XVII)——To a solution of XVI (27.8 g) in $CHCl_3$ (60 ml) was added an excess of diazomethane–ether solution. After the mixture had stood overnight, the solvent was evaporated and the residue was dissolved in benzene. The benzene solution was washed with 10% NaOH and dried over anhyd. Na_2SO_4. The solution was concentrated *in vacuo* and the residue was chromatographed on Al_2O_3. The eluate with benzene was concentrated to dryness and the residue was recrystallized from cyclohexane to give XVII (13.3 g, 45.5%) as colorless columns, mp 95—98°. *Anal.* Calcd. for $C_{13}H_{16}O_4N_4$: C, 53.42; H, 5.52; N, 19.17. Found: C, 53.06; H, 5.22; N, 18.85.

1-(4-Methoxy-6-methyl-2-pyrimidinyl)-3-methyl-4-hydroxy-5-methoxypyrazole[12] (XVIII)——A mixture of XVII (13.2 g) and 5% NaOH (225 ml) was warmed at 50—60° with stirring for 30 min. After cooling, the reaction mixture was neutralized with AcOH and extracted with $CHCl_3$. The extract was washed with H_2O, dried over anhyd. Na_2SO_4 and evaporated to dryness. The residue was recrystallized from EtOH to give XVIII (7.2 g, 64.0%) as colorless prisms, mp 195—198°. *Anal.* Calcd. for $C_{11}H_{14}O_3N_4$: C, 52.79; H, 5.64; N, 22.39. Found: C, 53.10; H, 5.88; N, 21.96. UV λ_{max}^{MeOH} mμ (log ε): 273 (4.18). NMR (CD_3OD) ppm: 2.19, 2.41 (each 3H, two singlets, $2\times CH_3$), 4.01, 4.03 (each 3H, two singlets, $2\times OCH_3$), 6.50 (1H, singlet, pyrimidine-C_5–H).

1-(4-Methoxy-6-methyl-2-pyrimidinyl)-3-methyl-4-hydroxy-5-methoxypyrazole Sulfate (URM-1) and Its Ammonium Salt——a) Sulfamic acid (3.88 g) was added to a solution of XVIII (5.0 g) in pyridine (70 ml) and the mixture was heated at 90—100° with stirring for one hour. After cooling, insoluble material was removed by filtration and the filtrate was concentrated *in vacuo*. The residue was dissolved in H_2O and the solution was acidified with HCl. The resulting precipitate was collected by filtration and washed with EtOH. Recrystallization from H_2O gave 1-(4-methoxy-6-methyl-2-pyrimidinyl)-3-methyl-4-hydroxy-5-methoxypyrazole sulfate (4.2 g, 63.7%) as colorless needles, mp 135—145° (decomp.). *Anal.* Calcd. for $C_{11}H_{14}O_6N_4S$: C, 39.99; H, 4.27; N, 16.96; S, 9.71. Found: C, 39.75; H, 4.27; N, 16.60; S, 9.69.

The above compound URM-1 (4.2 g) was dissolved in 10% NH_4OH and the solution was concentrated to dryness *in vacuo*. The residue was recrystallized from MeOH–ether to give NH_4–salt of URM-1 (3.2 g, 46.0% based on XVIII) as a colorless powder, mp 204—207° (decomp.). *Anal.* Calcd. for $C_{11}H_{17}O_6N_5S$: C, 38.03; H, 4.93; N, 20.16; S, 9.23. Found: C, 37.77; H, 5.15; N, 19.91; S, 9.16. UV λ_{max}^{MeOH} mμ (log ε): 263 (4.29). NMR (CD_3OD) ppm: 2.31, 2.44 (each 3H, two singlets, $2\times CH_3$), 4.02, 4.23 (each 3H, two singlets, $2\times OCH_3$), 6.60 (1H, singlet, pyrimidine-C_5–H).

b) Chlorosulfonic acid (1.16 g) was added dropwise to a stirred ice-cold solution of XVIII (1.0 g) in pyridine (14 ml) during one hour. The mixture was warmed at 50—60° with stirring for one hour. After cooling, the reaction mixture was poured into H_2O and acidified with HCl. The solid separated was collected by filtration and dissolved in 10% NH_4OH. The solution was concentrated to dryness *in vacuo* and the

residue was recrystallized from MeOH–ether to give a colorless powder (0.64 g, 46.0%). The melting point and IR spectrum of this substance were identical with those of NH_4-salt of URM-1 described above.

1-(1,6-Dihydro-4-hydroxymethyl-6-oxo-2-pyrimidinyl)-3-methyl-3-pyrazolin-5-one (XX)——A suspension of 2-hydrazino-4-hydroxymethyl-6-pyrimidone[15] (7.8 g) and ethyl acetoacetate (7.8 g) in EtOH (150 ml) was refluxed for 3.5 hr with stirring. To the resulting solution, 1.2N NaOH (100 ml) was added. The mixture was stirred at 100° for one hour and evaporated *in vacuo* to syrup, which was dissolved in H_2O and neutralized with AcOH. The crude product which precipitated on standing in refrigerator overnight was filtered, washed with cold water and recrystallized from dimethyl sulfoxide to give XX (9.2 g, 82.9%) as colorless prisms, mp 199—200° (decomp.). *Anal.* Calcd. for $C_9H_{10}O_3N_4$: C, 48.65; H, 4.54; N, 25.22. Found: C, 48.75; H, 4.38; N, 25.38.

1-(4-Hydroxymethyl-6-methoxy-2-pyrimidinyl)-3-methyl-5-methoxypyrazole (UNM-4)——To a solution of XX (8.88 g) in MeOH (300 ml) was added a large excess of diazomethane–ether solution. The mixture was allowed to stand for 48 hr at room temperature and evaporated *in vacuo* to syrup. The reisdue was chromatographed on silica gel (200 g). The fraction eluted with $CHCl_3$–AcOEt (2:1) was recrystallized from AcOEt to give 1-(4-hydroxymethyl-6-methoxy-2-pyrimidinyl)-3-methyl-5-methoxypyrazole (1.66 g, 16.6%) as colorless needles, mp 155—157°. *Anal.* Calcd. for $C_{11}H_{14}O_3N_4$: C, 52.79; H, 5.64; N, 22.39. Found: C, 52.75; H, 5.68; N, 22.11. UV λ_{max}^{MeOH} mμ (log ε): 251 (4.27). NMR (CD_3OD) ppm: 2.24 (3H, singlet, CH_3), 3.92, 4.01 (each 3H, two singlets, $2\times OCH_3$), 4.60 (2H, singlet, $-CH_2-$), 5.65 (1H, singlet, pyrazole-C_4–H), 6.74 (1H, singlet, pyrimidine-C_5–H).

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