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Synthesis of 2-Substituted 2,6-Dihydro-3-hydroxy-7*H*-pyrazolo[4,3-*d*]pyrimidin-7-ones

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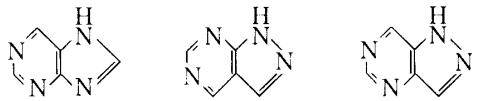
2-Substituted 2,6-dihydro-3-hydroxy-7*H*-pyrazolo[4,3-*d*]pyrimidin-7-ones bearing a methyl, phenyl, *p*-tolyl, *m*-tolyl or *p*-chlorophenyl group at the 2-position were synthesized by the reduction of ethyl 4-nitroso-5-hydroxy-1*H*-pyrazole-3-carboxylates and subsequent condensation of the resulting ethyl 4-amino-5-hydroxy-1*H*-pyrazole-3-carboxylates with formamide. Ethyl 4-nitroso-5-hydroxy-1*H*-pyrazole-3-carboxylates were prepared by nitrosation of ethyl 5-hydroxy-1*H*-pyrazole-3-carboxylates, which were derived from diethyl oxalacetate and monosubstituted hydrazines such as methyl-, phenyl-, *p*-tolyl-, *m*-tolyl-, and *p*-chlorophenylhydrazines.

Keywords——3-hydroxy-2*H*-pyrazolo[4,3-*d*]pyrimidine; 5-hydroxy-1*H*-pyrazole-3-carboxylate; 4-nitroso-5-hydroxy-1*H*-pyrazole-3-carboxylate; oxalacetate; oxalacetate hydrazone

Much attention has recently been paid to the chemical and biological properties of pyrazolopyrimidines, which are aza-deaza analogs of the purine nucleus.[1] Recent publications on the isolation[2,3] and characterization[4,5] of formycin and formycin B as C-nucleoside antibiotics, which were characterized as 7-amino- and 7-hydroxy-3-β-D-ribofuranosylpyrazolo-[4,3-*d*]pyrimidine, respectively, led us to investigate the chemistry of pyrazolo[4,3-*d*]pyrimidine derivatives.



(A) (B) (C)

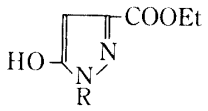
Chart 1

Structural analogy between 9*H*-purine (A) and 1*H*-pyrazolo[3,4-*d*]pyrimidine (B) and 1*H*-pyrazolo[4,3-*d*]pyrimidine (C)

Syntheses of pyrazolo[4,3-*d*]pyrimidine ring systems have been reported by several workers,[6] but only a few reports have appeared on the synthesis of this ring system with a hydroxyl group at the 3-position. Siewert[7] described the synthesis of 2-phenyl-3,5,7-trihydroxypyrazolo-[4,3-*d*]pyrimidine by the action of potassium cyanate on ethyl 4-amino-1-phenyl-5-hydroxy-1*H*-pyrazole-3-carboxylate. As a part of our investigation on the synthesis and tautomerism of 3-hydroxypyrazole derivatives,[8] we have now synthesized a condensed ring system, 2,6-dihydro-3-hydroxy-7*H*-pyrazolo[4,3-*d*]pyrimidin-7-one (**1a**) and the corresponding 2-substituted derivatives (**1b**—**e**,**g**). During our studies on this ring system,[9] Takei and his coworkers[10] reported on the formation of 3,7-dihydroxy-7*H*-pyrazolo[4,3-*d*]pyrimidine by treatment of ethyl 4-amino-5-hydroxy-1*H*-pyrazole-3-carboxylate hydrochloride with formamidine acetate. However, the absence of a synthesis of 2-substituted compounds and the paucity of spectral data in this report prompted us to continue our investigation. The available methods for the synthesis of pyrazolopyrimidines are (1) construction of fused pyrazole rings by diazotization of appropriate aminopyrimidines followed by an intramolecular coupling[11] and (2) cyclization of the pyrazole derivatives to the pyrazolopyrimidines.[12]

5-Hydroxy-1*H*-pyrazole-3-carboxylate was considered to be a convenient starting material to construct the ring system having a hydroxyl group at the 3-position and a substituent at the 2-position of pyrazolo[4,3-*d*]pyrimidine. As the key intermediate in the synthesis of 2,6-

TABLE I. Ethyl 5-Hydroxy-1*H*-pyrazole-3-carboxylates (**4**)



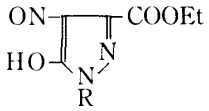
4	R	Recryst. solvent	Yield %	mp (°C)	Formula	Analysis % Calcd (Found) C	H	N
a	H	EtOH	72.6	167—168	$C_6H_8N_2O_3$	46.15 (46.32	5.16 5.08	17.94 17.78)
b	CH_3	H_2O	76.5	145—147	$C_7H_{10}N_2O_3$	49.40 (49.57	5.92 6.05	16.46 16.57)
c	C_6H_5	Benzene	83.2	179—180[a]	$C_{12}H_{12}N_2O_3$	62.06 (62.24	5.21 5.36	12.06 12.18)
d	*p*-$CH_3C_6H_4$	Benzene	85.5	187—189[b]	$C_{13}H_{14}N_2O_3$	63.40 (63.53	5.73 5.85	11.38 11.22)
e	*m*-$CH_3C_6H_4$	Benzene	83.8	179—180[c]	$C_{13}H_{14}N_2O_3$	63.40 (63.23	5.73 5.79	11.38 11.41)
f	*o*-$CH_3C_6H_4$	Benzene	87.5	170—171	$C_{13}H_{14}N_2O_3$	63.40 (63.61	5.73 5.77	11.38 11.46)
g	*p*-ClC_6H_4	Benzene	78.5	197—198[d]	$C_{12}H_{11}N_2O_3Cl$	54.04 (54.19	4.16 4.14	10.51 10.70)
h	*p*-$NO_2C_6H_4$	EtOH	76.2	237—239[e]	$C_{12}H_{11}N_3O_5$	51.99 (52.29	4.00 4.11	15.16 15.21)

4	IR (KBr) $\nu_{C=O}$ cm^{-1}	^{1}H-NMR (DMSO-d_6)[f] δ ppm
a	1730	1.28 (3H, t, *J*=7.3 Hz) 4.25 (2H, q, *J*=7.3 Hz) 5.92 (1H, s)
b	1740	1.26 (3H, t, *J*=7.3 Hz) 3.58 (3H, s) 4.20 (2H, q, *J*=7.3 Hz) 5.75 (1H, s) 11.32 (1H, s, D_2O-exchangeable)
c	1735	1.30 (3H, t, *J*=7.3 Hz) 4.27 (2H, q, *J*=7.3 Hz) 5.93 (1H, s) 7.34—7.79 (5H, m) 12.03 (1H, s, D_2O-exchangeable)
d	1740	1.29 (3H, t, *J*=7.3 Hz) 2.35 (3H, s) 4.26 (2H, q, *J*=7.3 Hz) 5.92 (1H, s) 7.28 (2H, d, *J*=8.8 Hz) 7.59 (2H, d, *J*=8.8 Hz) 11.93 (D_2O-exchangeable)
e	1740	1.30 (3H, t, *J*=7.3 Hz) 2.39 (3H, s) 4.27 (2H, q, *J*=7.3 Hz) 5.92 (1H, s,) 7.12—7.53 (4H, m) 11.94 (1H, s, D_2O-exchangeable)
f	1740	1.28 (3H, t, *J*=7.3 Hz) 2.07 (3H, s) 4.25 (2H, q, *J*=7.3 Hz) 5.90 (1H, s) 7.25—7.39 (4H, m) 11.60 (1H, s, D_2O-exchangeable)
g	1745	1.29 (3H, t, *J*=7.3 Hz) 4.27 (2H, q, *J*=7.3 Hz) 5.94 (1H, s) 7.54 (2H, d, *J*=8.8 Hz) 7.78 (2H, d, *J*=8.8 Hz) 12.25 (1H, br, D_2O-exchangeable)
h	1740	1.31 (3H, t, *J*=7.3 Hz) 4.30 (2H, q, *J*=7.3 Hz) 5.97 (1H, s, D_2O-exchangeable) 8.11 (2H, d, *J*=9.2 Hz) 8.38 (2H, d, *J*=9.2 Hz) 12.72 (1H, br, D_2O-exchangeable)

a) Lit.[14] 180.5 °C.
b) Lit.[14] 184—185 °C.
c) Lit.[14] 178—180 °C.
d) Lit.[14] 109.0—109.2 °C, which is very close to our value for the intermediate hydrazone (mp 111.5—112 °C).
e) Lit.[14] 227—232 °C.
f) The signals of NH and/or OH were not observed clearly. In general, the signals of NH and OH of 3-hydroxypyrazoles broaden and are not observed definitely due to rapid exchange of the protons between keto-enol tautomers.

dihydro-3-hydroxy-7*H*-pyrazolo[4,3-*d*]pyrimidin-7-ones (**1**), ethyl 5-hydroxy-1*H*-pyrazole-3-carboxylates (**4a**—**h**),[13] were prepared from commercially available starting materials through a slight modification of a previously reported method.[14] Sodium diethyl oxalacetate (**2**) was heated with an appropriate hydrazine hydrochloride (**3a**—**h**) in a mixture of benzene and acetic acid to give **4a**—**h** in high yields. When diethyl oxalacetate was treated with *p*-tolyl-, *p*-chlorophenyl-, or *p*-nitrophenylhydrazine in ethanol or in water at room temperature, the corresponding *N*-arylhydrazone (**5d, g, h**) separated in crystalline form. Heating of the hydrazones (**5d, g, h**) in acetic acid effected cyclization to afford the above-mentioned hydroxypyrazolecarboxylates (**4d, g, h**) in good yields.

TABLE II. Ethyl 4-Nitroso-5-hydroxy-1*H*-pyrazole-3-carboxylates (**6**)



6	R	Method	Recryst. solvent	Yield %	mp (°C)[a]	Formula	Analysis % Calcd (Found) C	H	N
a	H	A	H_2O	83.5	172—174	$C_6H_7N_3O_4$	38.92 (38.93	3.81 3.64	22.70 22.68)
b	CH_3	A	EtOH	80.4	164	$C_7H_9N_3O_4$	42.21 (42.33	4.55 4.41	21.10 21.31)
c	C_6H_5	B	EtOH	70.5	178	$C_{12}H_{11}N_3O_4$	55.17 (55.40	4.24 4.22	16.09 15.87)
d	*p*-$CH_3C_6H_4$	B	EtOH	82.3	201—203	$C_{13}H_{13}N_3O_4$	56.72 (56.71	4.76 4.79	15.27 15.54)
e	*m*-$CH_3C_6H_4$	B	EtOH	81.5	157	$C_{13}H_{13}N_3O_4$	56.72 (56.97	4.76 4.93	15.27 15.17)
f	*o*-$CH_3C_6H_4$	B	Benzene	65.0	168—170	$C_{13}H_{13}N_3O_4$	56.72 (56.85	4.76 4.81	15.27 15.[illegible])
g	*p*-ClC_6H_4	B	aq. EtOH	84.2	188—191	$C_{12}H_{10}N_3O_4Cl$	48.74 (48.62	3.41 3.63	14.21 14.42)
h	*p*-$NO_2C_6H_4$	B	EtOH	80.7	218—219	$C_{12}H_{10}N_4O_6$	47.06 (47.26	3.29 3.18	18.30 18.24)

6	IR (KBr) $\nu_{C=O}$ cm^{-1}		UV λ_{max}^{MeOH} nm (log ϵ)		^{1}H-NMR (DMSO-d_6)[b] δ ppm
a	1740	1720	264	(3.94)	1.29 (3H, t, *J*=7.5Hz) 4.28 (2H, q, *J*=7.5Hz) 12.38 (1H, D_2O-
	1620		374	(3.46)	exchangeable)
b	1735	1720	266	(3.95)	1.30 (3H, t, *J*=7Hz) 3.35 (3H, s) 4.32 (2H, q, *J*=7Hz)
	1620		371	(4.46)	
c	1740	1720	263	(4.33)	1.32 (3H, t, *J*=7Hz) 4.35 (2H, q, *J*=7Hz) 7.27—7.85 (5H, m)
	1620		390	(3.29)	
d	1730	1715	264	(4.33)	1.3 (3H, t, *J*=7Hz) 2.33 (3H, s) 4.35 (2H, q, *J*=7Hz) 7.28 (2H, d,
	1615		390	(3.25)	*J*=9Hz) 7.68 (2H, d, *J*=9Hz)
e	1715	1600	254	(4.40)	1.32 (3H, t, *J*=6.8Hz) 2.37 (3H, s) 4.36 (2H, q, *J*=7Hz)
			393	(3.23)	7.08—7.52 (4H, m)
f	1720	1700	256	(4.07)	1.30 (3H, t, *J*=7Hz) 2.19 (3H, s) 4.33 (2H, q) 7.36 (4H, m)
			370	(3.47)	15.16 (1H, br, D_2O-exchangeable)
g	1720	1710	265	(4.42)	1.32 (3H, t, *J*=7Hz) 4.36 (2H, q, *J*=7Hz) 7.54 (2H, d, *J*=9Hz)
	1610		390	(3.23)	7.80 (2H, d, *J*=9Hz)
h	1740	1710	222	(4.16)	1.34 (3H, t, *J*=7Hz) 4.39 (2H, q, *J*=7Hz) 8.09 (2H, d, *J*=9Hz)
	1610		286	(4.19)	8.38 (2H, d, *J*=9Hz)
			312	(4.29)	

a) All compounds decompose at the indicated temperature.
b) See footnote *f*) in Table I.

Treatment of a solution of the pyrazoles (**4a**—**h**) with sodium nitrite in hydrochloric acid resulted in the formation of ethyl 4-nitroso-5-hydroxy-1*H*-pyrazole-3-carboxylates (**6a**—**h**) in high yields.

The nitrosopyrazolecarboxylate **6a** was heated with conc. ammonium hydroxide to give dark-red needles (**7**). The ^{1}H-NMR spectrum did not show any ethyl signal of an ester function. The IR spectrum lacked an ester band (1740 cm^{-1}) but showed an amide carbonyl band (1670 cm^{-1}). These spectral data and the elemental analysis data ($C_4H_7N_5O_3$) indicated that **7** is the ammonium salt of 4-nitroso-5-hydroxy-1*H*-pyrazole-3-carboxamide (**8**). The free amide (**8**) was formed by the treatment of **7** with hydrochloric acid.

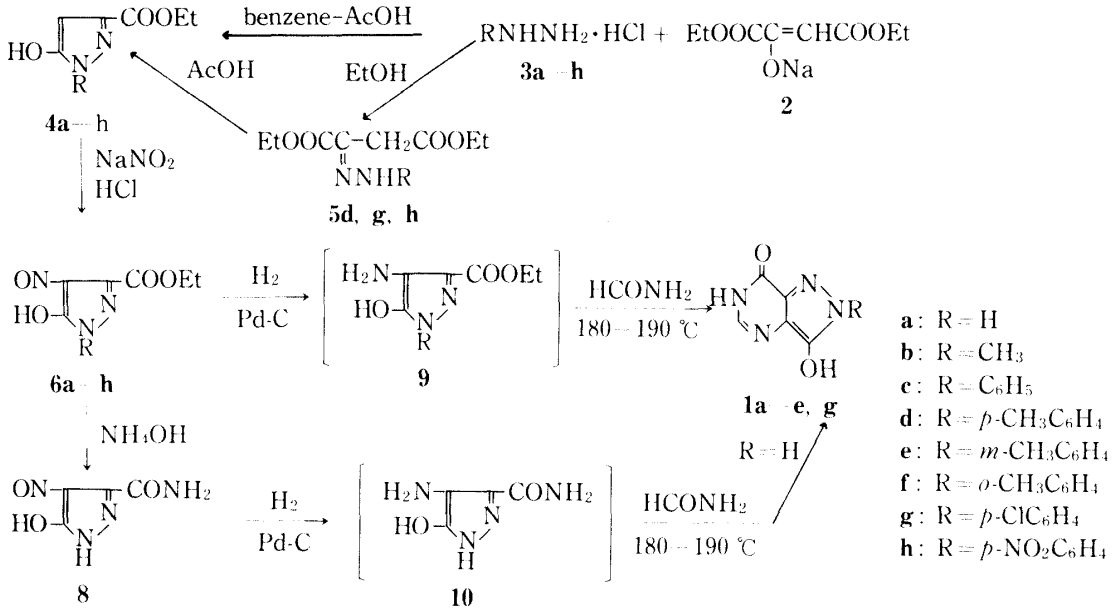
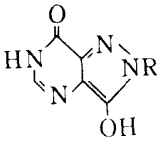


Chart 2

TABLE III. 2, 6-Dihydro-3-hydroxy-7*H*-pyrazolo [4,3-*d*] pyrimidin-7-ones (**1**)



Compd. **1**	R	Yield (%)	mp (°C)	Formula	Analysis % Calcd (Found)		
					C	H	N
a	H	87.0	360	$C_5H_4N_4O_2$	39.48 (39.76)	2.65 2.60	36.84 36.74)
b	CH_3	78.3	320—325[a]	$C_6H_6N_4O_2$	43.37 (43.58)	3.64 3.62	33.73 33.52)
c	C_6H_5	83.5	274—276[a]	$C_{11}H_8N_4O_2$	57.89 (57.47)	3.53 3.28	24.55 24.87)
d	*p*-$CH_3C_6H_4$	65.7	310[a]	$C_{12}H_{10}N_4O_2$	59.50 (59.78)	4.16 4.25	23.13 23.04)
e	*m*-$CH_3C_6H_4$	68.2	276—278	$C_{12}H_{10}N_4O_2$	59.50 (59.77)	4.16 4.34	23.13 23.17)
g	*p*-ClC_6H_4	66.8	341—344	$C_{11}H_7N_4O_2Cl$	50.30 (50.52)	2.69 2.52	21.33 21.42)

Compd. **1**	IR (KBr) $\nu_{C=O}$ cm^{-1}	UV λ_{max}^{MeOH} nm (log ϵ)			NMR (DMSO-d_6-D_2O) δ ppm
a	1680	230 (3.97)	288 (3.60)		7.72 (1H, s)
b	1720	227 (4.13)	231 (4.12)[c]	298 (3.73)	3.72 (3H, s) 7.58 (1H, s)
c	1690	248 (4.28)	304 (3.77)		7.38—7.88 (6H, m)
d	1690	249 (4.33)	305 (3.86)		2.37 (3H, s) 7.30 (2H, d, J=8.3Hz) 7.70 (1H, s) 7.73 (2H, d, J=8.3Hz)
e	1685	250 (4.26)	310 (3.77)		2.40 (3H, s) 7.12—7.65 (4H, m) 7.65 (1H, s)
g	1720	251 (4.35)	304 (3.81)		7.55 (2H, d, J=9Hz) 7.72 (1H, s) 7.95 (2H, d, J=9Hz)

a) Decomposition.
b) Several carbonyl bands were observed between 1680—1740cm^{-1} reflecting many hydrogen-bonding forms of compound **1**. The main peak in this region is shown in Table III.
c) Shoulder.

When the 4-nitrosopyrazole (**6a**) was hydrogenated in ethanol in the presence of 5% Pd–C, the color of the reaction solution changed from yellow to colorless after absorption of 2 mol eq of hydrogen, but this colorless solution became purple instantly on exposure to air to give a structurally unknown purple powder, the desired 4-amino-5-hydroxy-1*H*-pyrazole-3-carboxylate (**9**) not being isolated. Difficulty in isolation of the 4-aminopyrazole (**9**), led us to heat the reaction mixture at 180—190°C under a nitrogen atmosphere after hydrogenation of the nitrosopyrazole (**6a**) in formamide, without isolation of the 4-aminopyrazole (**9a**). Filtration and dilution of the solution with water afforded a colorless solid (**1a**). The ^{1}H-NMR spectrum of **1a** showed a proton signal at δ 7.72 which could be assigned to the C-5 proton of the pyrazolopyrimidine ring, and no ester proton signals were seen. The IR spectrum (KBr) exhibited carbonyl absorption at 1680 cm^{-1}. The elemental analysis and high resolution mass spectroscopic data were consistent with the molecular formula $C_5H_4N_4O_2$. The spectra and analytical data indicated **1a** to be 2,6-dihydro-3-hydroxy-7*H*-pyrazolo[4,3-*d*]pyrimidin-7-one.[15]

In a similar manner, 2-substituted 2,6-dihydro-3-hydroxy-7*H*-pyrazolo[4,3-*d*]pyrimidin-7-ones (**1b—e, g**)[15] were synthesized from appropriate 1-substituted 4-nitroso-5-hydroxy-1*H*-pyrazole-3-carboxylates (**6b—e, g**) by hydrogenation and subsequent cyclization. Likewise, 4-nitroso-5-hydroxy-1*H*-pyrazole-3-carboxamide (**8**) was cyclized into the pyrazolopyrimidine (**1a**) in good yield by hydrogenation and subsequent heating in formamide. The properties of compounds **1** were examined. These pyrazolopyrimidine (**1**) are stable in a hot aqueous solution of sodium hydroxide but decompose slowly in hot dilute sulfuric acid. They showed a coloration with alcoholic solution of ferric chloride.

The tautomerism and reactivity of these compounds will be discussed elsewhere.

Experimental

Melting points were determined on a Büchi melting point apparatus in open capillary tubes and are uncorrected. Infrared (IR) spectra were recorded on a JASCO A-102 spectrophotometer. ^{1}H-Nuclear magnetic resonance (NMR) spectra were taken on a Hitachi R-22 90 MHz spectrophotometer or FX-100 spectrophotometer, with tetramethylsilane as an internal reference. The abbreviations are as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; and br, broad. UV spectra were obtained on a Hitachi 340 spectrophotometer.

General Method for the Preparation of Ethyl 5-Hydroxy-1*H*-pyrazole-3-carboxylates (4a—h)——A solution of a hydrazine monohydrochloride (0.05 mol) in water (50 ml) was added dropwise to a mixture of sodium diethyl oxalacetat (10.5 g, 0.05 mol), acetic acid (100 ml), and benzene (50 ml) under stirring at room temperature. The mixture was heated under reflux with stirring for 3 h then concentrated *in vacuo*, and water was added to the residue. The separated crystals were collected by filtration, washed with cold water, dried, and recrystallized to give **4**. Physical constants of the compounds and their analytical data are summarized in Table I.

Diethyl Oxalacetate *p*-Tolylhydrazone (5d)——A solution of *p*-tolylhydrazine monohydrochloride (158 mg) in water (10 ml) was added dropwise to a stirred solution of sodium diethyl oxalacetate (210 mg) in water (10 ml) at room temperature. After being stirred for 2 h at room temperature, the reaction mixture was cooled in an ice-bath. The separated crystals were collected by filtration and recrystallized from hexane to give **5d**, as a colorless cotton, 185 mg (63.5%), mp 101—102°C. *Anal.* Calcd for $C_{15}H_{20}N_2O_4$: C, 61.63; H, 6.90; N, 9.58. Found: C, 61.43; H, 6.71; N, 9.55. IR ν_{max}^{KBr} cm^{-1}: 3300, 1720. ^{1}H-NMR ($CDCl_3$) δ ppm: 1.23 (3H, t, J=7.5 Hz), 1.36 (3H, t, J=7.5 Hz), 2.28 (3H, s), 3.71 (2H, s), 4.16 (2H, q, J=7.5 Hz), 4.32 (2H, q, J=7.5 Hz), 7.11 (4H, s), 9.18 (1H, br, D_2O-exchangeable).

Diethyl Oxalacetate *p*-Chlorophenylhydrazone (5g)——Sodium diethyl oxalacetate (210 mg) and *p*-chlorophenylhydrazine hydrochloride (181 mg) were treated as described in the procedure for **5d**. Recrystallization from hexane gave the hydrazone **5g**, as a colorless cotton, 198 mg (63.5%), mp 111.5—112°C. *Anal.* Calcd for $C_{14}H_{17}N_2O_4Cl$: C, 53.76; H, 5.48; N, 8.96. Found: C, 53.93; H, 5.46; N, 9.10. IR ν_{max}^{KBr} cm^{-1}: 3300, 1745, 1720. ^{1}H-NMR ($CDCl_3$) δ ppm: 1.27 (3H, t, J=7 Hz), 1.36 (3H, t, J=7 Hz), 3.72 (2H, s), 4.18 (2H, q, J=7 Hz), 4.33 (2H, q, J=7 Hz), 7.22 (4H, s), 9.35 (1H, br, D_2O-exchangeable).

Diethyl Oxalacetate *p*-Nitrophenylhydrazone (5h)——A solution of *p*-nitrophenylhydrazine (770 mg) in ethanol (40 ml) was added to a stirred solution of diethyl oxalacetate (940 mg) in ethanol (10 ml) at room temperature with stirring. Stirring was continued for 3 h at room temperature, then the solvent was evaporated off *in vacuo*, and the residure was recrystallized from a mixture of ethyl acetate and hexane (2: 1, v/v) to give yellow needles, 1132 mg (70.3%), mp 140—141.5°C. *Anal.* Calcd for $C_{14}H_{17}N_3O_6$: C, 52.01; H, 5.30;

N, 13.00. Found: C, 52.15; H, 5.30; N, 13.07. IR ν_{max}^{KBr} cm^{-1}: 3280, 1720, 1710. ^{1}H-NMR ($CDCl_3$) δ ppm: 1.28 (3H, t, J=6 Hz), 1.39 (3H, t, J=6 Hz), 3.30 (2H, s), 4.22 (2H, q, J=6 Hz), 4.35 (2H, q, J=6 Hz), 7.30 (2H, d, J=10 Hz), 8.32 (2H, d, J=10 Hz), 9.50 (1H, br, D_2O-exchangeable).

Cyclization of the Diethyl Oxalacetate Hydrazone (5)——A mixture of the appropriate hydrazone (**5**, 1.0 g) and acetic acid (10 ml) was heated under reflux for 1 h. The reaction mixture was concentrated *in vacuo*, and the residue was recrystallized from benzene to give the corresponding pyrazole (**4**).

i) **Ethyl 1-*p*-Tolyl-5-hydroxy-1*H*-pyrazole-3-carboxylate (4d)**——In the above procedure, 1.0 g of **5d** gave 0.72 g (85.5%) of **4d**, whose IR and ^{1}H-NMR spectral data were identical with those of the sample prepared by the general method described above.

ii) **Ethyl 1-*p*-Chlorophenyl-5-hydroxy-1*H*-pyrazole-3-carboxylate (4g)**——In the above procedure, 1.0 g of **5g** gave 0.61 g (76.5%) of **4g**, whose IR and ^{1}H-NMR spectral data were identical with those of the sample prepared by the general method described above.

iii) **Ethyl 1-*p*-Nitrophenyl-5-hydroxy-1*H*-pyrazole-3-carboxylate (4h)**——In the above procedure, 1.0 g of **5h** gave 0.70 g (87.2%) of **4h**, whose IR and ^{1}H-NMR spectral data were identical with those of the sample prepared by the general method described above.

General Method for the Preparation of Ethyl 4-Nitroso-5-hydroxy-1*H*-pyrazole-3-carboxylates (6)——Method A: A solution of sodium nitrite (10.0 g) in water (140 ml) was added dropwise to a stirred solution of **4** (0.1 mol) in 10% hydrochloric acid (250 ml) on an ice-bath. Stirring was continued for 1 h, then the separated precipitate was collected by filtration, washed with cold water, and recrystallized.

Method B: A solution of sodium nitrite (10 g) in water (50 ml) was added dropwise to a stirred mixture of **4** (0.1 mol), concd. hydrochloric acid (70 ml), and ethanol (150 ml) on an ice-bath. Stirring was continued for 1 h, then the reaction mixture was added to water (200 ml). The separated precipitate was collected by filtration, washed with cold water, and recrystallized.

The yields, physical constants, and analytical data of the products are summarized in Table II.

4-Nitroso-5-hydroxy-1*H*-pyrazole-3-carboxamide (8)——A mixture of **6a** (3.0 g) and 28% ammonium hydroxide (25 ml) was heated in a boiling water bath for 3 h in a sealed-tube, then cooled. The resultant precipitate was filtered off to give **7** (ammonium salt of **8**), 2.29 g (81.5%). Recrystallization from water gave dark-red needles, mp >230°C. *Anal.* Calcd for $C_4H_7N_5O_3$: C, 27.75; H, 4.07; N, 40.45. Found: C, 27.56; H, 3.90; N, 40.76. IR ν_{max}^{KBr} cm^{-1}: 1670.

A mixture of **7** described above (1.0 g) and 10% hydrochloric acid (10 ml) was stirred at room temperature for 0.5 h, then cooled. The resultant precipitate was collected by filtration and recrystallized from water to give **8** as yellow flakes, 0.77 g (85.5%), mp 260°C (dec.). *Anal.* Calcd for $C_4H_4N_4O_3$: C, 30.78; H, 2.58; N, 35.89. Found: C, 30.92; H, 2.76; N, 35.63. IR ν_{max}^{KBr} cm^{-1}: 1740, 1690.

General Method for the Preparation of 2-Substituted 2,6-Dihydro-3-hydroxy-7*H*-pyrazolo[4,3-*d*]pyrimidin-7-ones (1)——A solution of the nitrosopyrazole **6** (5.0 g) in formamide (50 ml) was hydrogenated on 5% Pd-C (100 mg) at atmospheric pressure of hydrogen. When two molar equivalents of hydrogen had been consumed, the mixture was heated at 180—190°C for 3 h under a nitrogen atomosphere. The catalyst was removed by filtration, and the filtrate was concentrated to a half volume *in vacuo*. Water (300 ml) was added to the residue, and the mixture was acidified with 10% hydrochloric acid. The separated crystals were collected by filtration, washed with cold water, and dried in a desiccator. The yields, physical constants, and analytical data of the products are summarized in Table III.

2,6-Dihydro-3-hydroxy-7*H*-pyrazolo[4,3-*d*]pyrimidin-7-one (1a)——i) In the general procedure, **6a** was treated as described above. Recrystallization of the product from 10% sodium carbonate gave the sodium salt of **1a** as colorless needles. The sodium salt was suspended in water, and the suspension was acidified with acetic acid to give **1a** as a colorless powder.

ii) Treatment of **8** according to the general procedure described above afforded a colorless powder. Recrystallization from 10% sodium carbonate gave the sodium salt of **1a** as colorless needles. The sodium salt was suspended in water, and the suspension was acidified with acetic acid to give **1a** as a colorless powder.

2,6-Dihydro-3-hydroxy-2-methyl-7*H*-pyrazolo[4,3-*d*]pyrimidin-7-one (1b)——In the general procedure, **6b** was treated as described above. Recrystallization of the product from water gave **1b** as a greenish-yellow powder.

2,6-Dihydro-3-hydroxy-2-phenyl-7*H*-pyrazolo[4,3-*d*]pyrimidin-7-one (1c)——In the general procedure, **6c** was treated as described above. Recrystallization of the product from methanol gave **1c** as colorless needles.

2,6-Dihydro-3-hydroxy-2-*p*-tolyl-7*H*-pyrazolo[4,3-*d*]pyrimidin-7-one (1d)——In the general procedure, **6d** was treated as described above. Recrystallization of the product from methanol gave **1d** as light brown granules.

2,6-Dihydro-3-hydroxy-2-*m*-tolyly-7*H*-pyrazolo[4,3-*d*]pyrimidin-7-one (1e)——In the general procedure, **6e** was treated as described above. Recrystallization of the product from methanol gave **1e** as colorless needles.

2-*p*-Chlorophenyl-2,6-dihydro-3-hydroxy-7*H*-pyrazolo[4,3-*d*]pyrimidin-7-one (1g)——In the general procedure, **6g** was treated as described above. Recrystallization of the product from methanol gave **1g** as yellow-brown needles.

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