[Chem. Pharm. Bull. 33(8)3113—3121(1985)]

Syntheses of 4-Methyl-*s*-triazolo[4,3-*a*]purin-9(4*H*)-ones and Tetrazolo-[1,5-*a*]purin-9(4*H*)-ones as Aza Analogs of "Y" Bases

TOMOHISA NAGAMATSU,[a] MASAYOSHI UKAI,[a] FUMIO YONEDA,*[,b] and DESMOND J. BROWN[c]

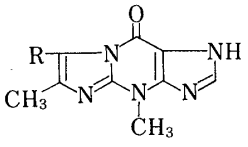
Faculty of Pharmaceutical Sciences, Kumamoto University,[a] 5–1, Oe-honmachi, Kumamoto 862, Japan, Faculty of Pharmaceutical Sciences, Kyoto University,[b] Yoshida, Sakyo-ku, Kyoto 606, Japan, and John Curtin School of Medical Research, The Australian National University,[c] Canberra City, A.C.T., Australia

(Received October 31, 1984)

4-Methyl-*s*-triazolo[4,3-*a*]purin-9(4*H*)-ones (IV) were synthesized by the condensation of 2-hydrazino-3-methylpurin-6(3*H*)-ones (III), which were derived from the reaction of 3-methyl-2-thioxanthines (II) with hydrazine hydrate, with appropriate ortho esters. 7-Aryl-4-methyl-*s*-triazolo[4,3-*a*]purin-9(4*H*)-ones (VI) were synthesized by the oxidative cyclization of 2-arylidene-hydrazino-3-methylpurin-6(3*H*)-ones (V), which were derived from the reaction of III with appropriate benzaldehydes, with diethyl azodicarboxylate (DAD) or with air in glacial acetic acid. 7-Mercapto-4-methyl-*s*-triazolo[4,3-*a*]purin-9(4*H*)-ones (VII) were also prepared in a manner similar to that used for III, but using carbon disulfide, and VII were further converted into the corresponding 7-alkylthio derivatives VIII by alkylation. The treatment of III with nitrous acid afforded the corresponding 4-methyltetrazolo[1,5-*a*]purin-9(4*H*)-ones (IX).

Keywords——4-methyl-*s*-triazolo[4,3-*a*]purin-9(4*H*)-one; 2-hydrazino-3-methylpurin-6(3*H*)-one; 3-methyl-2-thioxanthine; ortho ester; oxidative cyclization; 2-arylidenehydrazino-3-methylpurin-6(3*H*)-one; carbon disulfide; 4-methyltetrazolo[1,5-*a*]purin-9(4*H*)-one

Since RajBhandary *et al.*[1] first found an unusual fluorescent nucleoside Y in the phenylalanine transfer ribonucleic acid (tRNA) of baker's yeast, Y-like fluorescent bases have been successively isolated from various sources,[2–5] and the structures of the "Y" bases have been elucidated as tricyclic guanine derivatives (imidazo[1,2-*a*]purines) (Chart 1) by several workers.[6–11] It is interesting to note that tricyclic nucleosides similar in structure to the "Y" bases have been found to exhibit significant *in vivo* antitumor activity.[12] The above findings stimulated us to prepare several azolopurine derivatives, which are the 6-aza and 6,7-diaza analogs of the "Y" bases, since they might have some biological activities. We here report the syntheses of 4-methyl-*s*-triazolo[4,3-*a*]purin-9(4*H*)-ones (only one example[13] of this ring system has been reported previously) and tetrazolo[1,5-*a*]purin-9(4*H*)-ones (a new, stable ring system).



"Y" bases

wybutine: $R=CH_2-CH_2-\underset{\displaystyle COOCH_3}{\underset{|}{CH}}-NHCOOCH_3$

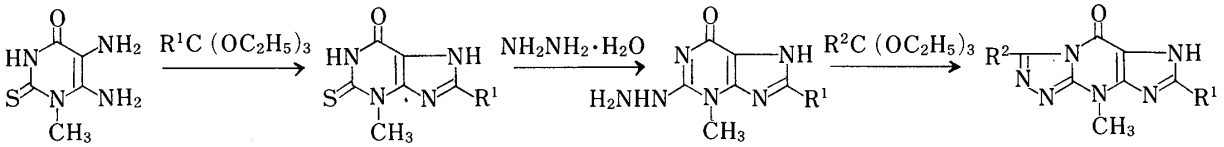
wybutoxine: $R=CH_2-\underset{\displaystyle OOH}{\underset{|}{CH}}-\underset{\displaystyle COOCH_3}{\underset{|}{CH}}-NHCOOCH_3$ or $CH_2-\underset{\displaystyle OH}{\underset{|}{CH}}-\underset{\displaystyle COOCH_3}{\underset{|}{CH}}-NHCOOCH_3$

wye: $R=H$

Chart 1

Synthesis of 4-Methyl-*s*-triazolo[4,3-*a*]purin-9(4*H*)-ones (IV)

The requisite starting materials, 3-methyl-2-thioxanthines (IIa—d), were prepared by the condensation of 5,6-diamino-1,2,3,4-tetrahydro-1-methyl-4-oxo-2-thiopyrimidine (I) with appropriate ortho esters according to the known procedure,[14] (Chart 2) (Table I). The treatment of II with 50% aqueous hydrazine hydrate afforded the 2-hydrazino-3-methylpurine-6(3*H*)-ones (IIIa—d). Heating the compounds III thus obtained with appropriate ortho esters gave the corresponding 4-methyl-*s*-triazolo[4,3-*a*]purin-9(4*H*)-ones (IVa—i) in good yields as indicated in Table II. Compounds IIa and IIb were idnetical with the known compounds in the literature.[15,16] The structural assignments of IIc, d, III, and IV were based on the results of elemental analyses and spectroscopic data including proton nuclear magnetic resonance (^{1}H-NMR) spectra (Table VII). The infrared (IR) spectra of IV had a band at 1695—1740 cm^{-1} (C=O absorption). In the ^{1}H-NMR spectra (in CF_3CO_2H) of IVa, the characteristic signal of the C^2 proton was located at 1.08 ppm higher field than that of the C^7 proton, and the signal of the C^2-Me protons in IVd was located at 0.34 ppm higher field than that of the C^7-Me protons. The ultraviolet (UV) absorption spectra of the purines IIIb, c (excluding the aryl derivative IIId from the discussion) may be classified into two groups of bands which are located approximately at 221 nm and at 275 nm in the π–π^* absorption region. On the other hand, the UV spectra of the triazolopurines IVa—h may be classified into three groups of bands which are located approximately at 220—225 nm, at 240—250 nm, and at 300—310 nm. Namely, the UV absorption maxima of IV at the longest wavelength showed a 25—30 nm bathochromic shift compared with those of the purines III owing to the extra triazole ring (Table VII).



I IIa—d IIIa—d IVa—i

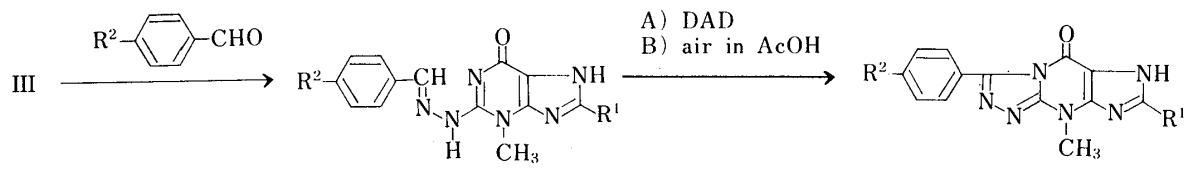
IIa—d: R^1=H, CH$_3$, C$_2$H$_5$, or C$_6$H$_5$

IVa—i: R^1=H, CH$_3$, C$_2$H$_5$, or C$_6$H$_5$; R^2=H, CH$_3$, or C$_2$H$_5$

Chart 2

Synthesis of 7-Aryl-4-methyl-*s*-triazolo[4,3-*a*]purin-9(4*H*)-ones (VI)

The desired 7-aryl derivatives VI of the triazolopurines were prepared by the oxidative cyclization of the 2-arylidenehydrazino-3-methylpurin-6(3*H*)-ones (Va—f) which were derived from the treatment of III with appropriate benzaldehydes in abs. EtOH (Chart 3) (Table III). Namely, heating the compounds V with diethyl azodicarboxylate (DAD) (method A) or in glacial acetic acid (method B) yielded the corresponding 7-aryl-4-methyl-*s*-triazolo[4,3-*a*]purin-9(4*H*)-ones (VIa—f) (Table IV). It should be noted that the UV absorption maxima of VI at the longest wavelength showed *ca.* 20 nm hypsochromic shift compared with those of the 2-arylidenehydrazinopurines (V) (Table VII).



III Va—f VIa—f

VIa—f: R^1=CH$_3$, C$_2$H$_5$, or C$_6$H$_5$; R^2=H, CH$_3$, Cl, or OCH$_3$

Chart 3

TABLE I. 8-Substituted 3-Methyl-2-thioxanthines (II) and 8-Substituted 2-Hydrazino-3-methylpurin-6(3*H*)-ones (III)

Compd. No.	R^1	Yield (%)	mp[a] (°C)	Formula	Analysis (%) Calcd (Found)		
					C	H	N
IIa[15]	H	77	>330	$C_6H_6N_4OS$	39.55 (39.68	3.32 3.33	30.75 30.73)
IIb[16]	CH_3	64	>330	$C_7H_8N_4OS$	42.85 (42.98	4.11 4.22	28.55 28.31)
IIc	C_2H_5	92	>330	$C_8H_{10}N_4OS$	45.70 (45.66	4.79 4.85	26.65 26.72)
IId	C_6H_5	98	>330	$C_{12}H_{10}N_4OS$	55.80 (55.96	3.90 3.91	21.69 21.73)
IIIa	H	55	>330	$C_6H_8N_6O$	40.00 (40.21	4.48 4.50	46.65 46.45)
IIIb	CH_3	70	>330	$C_7H_{10}N_6O$	43.29 (43.18	5.19 5.22	43.28 43.29)
IIIc	C_2H_5	92	295	$C_8H_{12}N_6O$	46.15 (46.01	5.81 5.98	40.36 40.49)
IIId	C_6H_5	62	298	$C_{12}H_{12}N_6O$	56.24 (56.41	4.72 4.79	32.79 32.65)

a) All compounds were recrystallized from *N*,*N*-dimethylformamide (DMF) and were obtained as colorless powders.

TABLE II. 2,7-Disubstituted 4-Methyl-*s*-triazolo[4,3-*a*]purin-9(4*H*)-ones (IV)

Compd. No.	R^1	R^2	Yield (%)	mp[a] (°C)	Formula	Analysis (%) Calcd (Found)		
						C	H	N
IVa	H	H	88	>330	$C_7H_6N_6O$	44.21 (44.41	3.18 3.20	44.19 44.02)
IVb	H	CH_3	62	>330	$C_8H_8N_6O$	47.06 (47.25	3.95 3.98	41.16 41.00)
IVc	CH_3	H	76	>330	$C_8H_8N_6O$	47.06 (47.00	3.95 3.99	41.16 41.25)
IVd	CH_3	CH_3	80	>330	$C_9H_{10}N_6O$	49.54 (49.41	4.62 4.53	38.51 38.71)
IVe	CH_3	C_2H_5	61	318	$C_{10}H_{12}N_6O$	51.72 (51.79	5.21 5.32	36.19 36.18)
IVf	C_2H_5	H	86	>330	$C_9H_{10}N_6O$	49.54 (49.81	4.62 4.51	38.51 38.66)
IVg	C_2H_5	CH_3	65	>330	$C_{10}H_{12}N_6O$	51.72 (51.91	5.21 5.20	36.19 36.08)
IVh	C_2H_5	C_2H_5	78	300	$C_{11}H_{14}N_6O$	53.65 (53.65	5.73 5.62	34.13 34.12)
IVi	C_6H_5	H	65	>330	$C_{13}H_{10}N_6O$	58.64 (58.60	3.79 3.85	31.56 31.59)

a) All compounds were recrystallized from DMF and were obtained as colorless needles.

Synthesis of 7-Mercapto- and 7-Alkylthio-4-methyl-*s*-triazolo[4,3-*a*]purin-9(4*H*)-ones (VII and VIII)

It was recently reported that the effective dose of phleomycin which is a wide-spectrum

TABLE III. 8-Substituted 2-Arylidenehydrazino-3-methylpurin-6(3*H*)-ones (V)

Compd. No.	R^1	R^2	Yield (%)	mp[a] (°C)	Formula	Analysis (%) Calcd (Found)		
						C	H	N
Va	CH_3	H	80	305	$C_{14}H_{14}N_6O$	59.56	5.00	29.77
						(59.71	5.21	29.58)
Vb	CH_3	CH_3	45	315	$C_{15}H_{16}N_6O$	60.80	5.44	28.36
						(60.83	5.49	28.29)
Vc	C_2H_5	Cl	88	312	$C_{15}H_{15}ClN_6O$	54.47	4.57	25.41
						(54.45	4.59	25.44)
Vd	C_2H_5	CH_3	68	320	$C_{16}H_{18}N_6O$	61.92	5.85	27.08
						(61.99	5.80	27.22)
Ve	C_2H_5	OCH_3	79	296	$C_{16}H_{18}N_6O_2$	58.88	5.56	25.75
						(58.69	5.59	25.88)
Vf	C_6H_5	H	84	>330	$C_{19}H_{16}N_6O$	66.27	4.68	24.40
						(66.25	4.65	24.58)

a) All compounds were recrystallized from *n*-butanol and were obtained as pale yellow powders.

TABLE IV. 7-Aryl-4-methyl-*s*-triazolo[4,3-*a*]purin-9(4*H*)-ones (VI)

Compd. No.	R^1	R^2	Yield[a] (%)	mp[b] (°C)	Formula	Analysis (%) Calcd (Found)		
						C	H	N
VIa	CH_3	H	20 (71)	>330	$C_{14}H_{12}N_6O$	59.99	4.32	29.98
						(59.87	4.39	30.05)
VIb	CH_3	CH_3	29 (65)	>330	$C_{15}H_{14}N_6O$	61.21	4.79	28.55
						(61.29	4.85	28.33)
VIc	C_2H_5	Cl	35 (76)	>330	$C_{15}H_{13}ClN_6O$	54.80	3.99	25.56
						(54.54	3.86	25.41)
VId	C_2H_5	CH_3	30 (64)	275—280	$C_{16}H_{16}N_6O$	62.32	5.23	27.26
						(62.38	5.26	27.18)
VIe	C_2H_5	OCH_3	30 (60)	283—285	$C_{16}H_{16}N_6O_2$	59.25	4.97	25.91
						(59.43	4.95	25.82)
VIf	C_6H_5	H	36 (70)	>330	$C_{19}H_{14}N_6O$	66.66	4.12	24.55
						(66.77	4.19	24.43)

a) Yields based on method B are given in parentheses. *b*) All compounds were recrystallized from DMF and were obtained as colorless needles.

antibiotic, could be reduced considerably by using it in conjunction with amplifying agents such as purines[17] or *s*-triazolopyrimidines,[18] and in particular, the alkylthio derivatives of purines[19] and *s*-triazolopyrimidines[18,19] were very effective as amplifiers of phleomycin. Therefore we planned to prepare the 7-alkylthio derivatives of *s*-triazolo[4,3-*a*]purin-9(4*H*)-ones, which contain both purine and *s*-triazolopyrimidine moieties in the molecules. First, the 7-mercapto-4-methyl-*s*-triazolo[4,3-*a*]purin-9(4*H*)-ones (VIIa, b) were synthesized by the heating of III with carbon disulfide in pyridine (Chart 4) (Table V). Then the alkylthio derivatives VIII were prepared by the alkylation of VII thus obtained using appropriate alkylating agents in a usual way. That is, the treatment of VII with dimethyl sulfate, ethyl iodide, or α-chloroacetamide in 1 N NaOH solution at room temperature afforded the corresponding 7-alkylthio derivatives VIIIa—f in good yields, as shown in Table V. The

structures of the products VIII were established by the satisfactory analytical and spectral data.

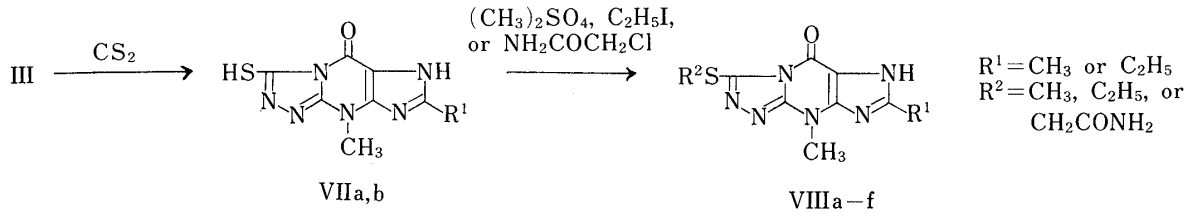


Chart 4

TABLE V. 7-Mercapto- and 7-Alkylthio-4-methyl-*s*-triazolo[4,3-*a*]purin-9(4*H*)-ones (VII and VIII)

Compd. No.	R^1	R^2	Yield (%)	mp[a] (°C)	Formula	Analysis (%) Calcd (Found)		
						C	H	N
VIIa	CH_3	H	75	318	$C_8H_8N_6OS$	40.67	3.41	35.57
						(40.78	3.52	35.33)
VIIb	C_2H_5	H	71	300 (dec.)	$C_9H_{10}N_6OS$	43.19	4.03	33.58
						(43.08	4.30	33.62)
VIIIa	CH_3	CH_3	68	>330	$C_9H_{10}N_6OS$	43.19	4.03	33.58
						(43.26	4.08	33.66)
VIIIb	C_2H_5	CH_3	75	310	$C_{10}H_{12}N_6OS$	45.44	4.58	31.80
						(45.68	4.47	31.87)
VIIIc	CH_3	C_2H_5	72	308	$C_{10}H_{12}N_6OS$	45.44	4.58	31.80
						(45.33	4.45	31.55)
VIIId	C_2H_5	C_2H_5	80	307	$C_{11}H_{14}N_6OS$	47.47	5.07	30.19
						(47.50	5.11	30.08)
VIIIe	CH_3	CH_2CONH_2	77	315—318	$C_{10}H_{11}N_7O_2S$	40.95	3.78	33.43
						(41.10	3.78	33.24)
VIIIf	C_2H_5	CH_2CONH_2	74	295	$C_{11}H_{13}N_7O_2S$	42.99	4.26	31.90
						(43.05	4.33	31.93)

a) All compounds were recrystallized from DMF and were obtained as colorless needles.

TABLE VI. Tetrazolo[1,5-*a*]purin-9(4*H*)-ones (IX)

Compd. No.	R^1	Yield (%)	mp[a] (°C)	Formula	Analysis (%) Calcd (Found)		
					C	H	N
IXa	H	53	>330	$C_6H_5N_7O$	37.70	2.64	51.30
					(37.81	2.66	51.22)
IXb	CH_3	57	310	$C_7H_7N_7O$	40.98	3.44	47.79
					(40.76	3.45	47.95)
IXc	C_2H_5	67	270	$C_8H_9N_7O$	43.83	4.14	44.73
					(43.77	4.00	44.63)
IXd	C_6H_5	89	>330	$C_{12}H_9N_7O$	53.93	3.39	36.69
					(53.90	3.37	36.75)

a) All compounds were recrystallized from DMF and were obtained as pale yellow powders.

TABLE VII. UV and ^{1}H-NMR Spectral Data for II—IX

Compd. No.	λ_{max}^{EtOH} nm (log ε)[a]	δ (CF_3COOH) ppm
IIa[b]	286.8 (——), 233.4 (——)	4.12 (3H, s, N^3-CH_3), 9.05 (1H, s, C^8-H)
IIb	287.8 (4.42), 233.0 (4.24)	2.95 (3H, s, C^8-CH_3), 4.03 (3H, s, N^3-CH_3)
IIc	287.8 (4.30), 233.1 (4.11)	1.63 (3H, t, J=7.6 Hz, C^8-$CH_2C\underline{H}_3$), 3.33 (2H, q, J=7.6 Hz, C^8-$C\underline{H}_2CH_3$), 4.07 (3H, s, N^3-CH_3)
IId	c)	Insoluble in TFA
IIIa	c)	4.00 (3H, s, N^3-CH_3), 8.67 (1H, s, C^8-H)
IIIb	274.0 (3.65), 221.2 (3.76)	2.90 (3H, s, C^8-CH_3), 3.98 (3H, s, N^3-CH_3)
IIIc	275.4 (3.96), 220.7 (4.07)	1.58 (3H, t, J=7.2 Hz, C^8-$CH_2C\underline{H}_3$), 3.20 (2H, q, J=7.2 Hz, C^8-$C\underline{H}_2CH_3$), 4.00 (3H, s, N^3-CH_3)
IIId[b]	307.4 (——), 230.6 (——)	4.05 (3H, s, N^3-CH_3), 7.70 (3H, m, C^8-Ph), 8.08 (2H, m, C^8-Ph)
IVa[b]	302.4 (——), 246.0 (——), 220.6 (——)	4.28 (3H, s, N^4-CH_3), 8.75 (1H, s, C^2-H), 9.83 (1H, s, C^7-H)
IVb	304.0 (4.11), 243.6 (3.80), 222.0 (4.48)	3.30 (3H, s, C^7-CH_3), 4.25 (3H, s, N^4-CH_3), 8.78 (1H, s, C^2-H)
IVc	302.8 (4.19), 243.4 (3.83), 223.4 (4.46)	2.96 (3H, s, C^2-CH_3), 4.23 (3H, s, N^4-CH_3), 9.93 (1H, s, C^7-H)
IVd	305.0 (3.63), 247.8 (3.49), 224.4 (4.05)	2.93 (3H, s, C^2-CH_3), 3.27 (3H, s, C^7-CH_3), 4.12 (3H, s, N^4-CH_3)
IVe	309.0 (4.41), 247.2 (4.13), 225.2 (4.65)	1.62 (3H, t, J=7.2 Hz, C^7-$CH_2C\underline{H}_3$), 2.95 (3H, s, C^2-CH_3), 3.72 (2H, q, J=7.2 Hz, C^7-$C\underline{H}_2CH_3$), 4.13 (3H, s, N^4-CH_3)
IVf	303.5 (3.70), 254.9 (3.45), 223.0 (3.99)	1.61 (3H, t, J=7.6 Hz, C^2-$CH_2C\underline{H}_3$), 3.33 (2H, q, J=7.6 Hz, C^2-$C\underline{H}_2CH_3$), 4.24 (3H, s, N^4-CH_3), 9.92 (1H, s, C^7-H)
IVg	304.5 (4.10), 245.4 (3.86), 223.9 (4.01)	1.58 (3H, t, J=8.0 Hz, C^2-$CH_2C\underline{H}_3$), 3.27 (3H, s, C^7-CH_3), 3.32 (2H, q, J=8.0 Hz, C^2-$C\underline{H}_2CH_3$), 4.12 (3H, s, N^4-CH_3)
IVh	305.0 (3.95), 247.8 (3.69), 224.9 (4.35)	1.63 (6H, t, J=8.0 Hz, C^2-$CH_2C\underline{H}_3$ and C^7-$CH_2C\underline{H}_3$), 3.35 (2H, q, J=8.0 Hz, C^2-$C\underline{H}_2CH_3$), 3.76 (2H, q, J=8.0 Hz, C^7-$C\underline{H}_2CH_3$), 4.16 (3H, s, N^4-CH_3)
IVi	c)	4.32 (3H, s, N^4-CH_3), 7.70 (3H, m, C^2-Ph), 8.13 (2H, m, C^2-Ph), 9.81 (1H, s, C^7-H)
Va	332.8 (4.24), 234.4 (4.19)	2.90 (3H, s, C^8-CH_3), 4.15 (3H, s, N^3-CH_3), 7.53 (3H, m, Ph), 7.97 (2H, m, Ph), 8.62 (1H, s, –CH=N–)
Vb	334.4 (4.48), 233.8 (4.38)	2.44 (3H, s, Ph-$C\underline{H}_3$), 2.89 (3H, s, C^8-CH_3), 4.17 (3H, s, N^3-CH_3), 7.33 (2H, d, J=8.0 Hz, $\underline{Ph}$-CH_3), 7.86 (2H, d, J=8.0 Hz, $\underline{Ph}$-CH_3), 8.53 (1H, s, –CH=N–)
Vc[b]	342.6 (——), 230.9 (——)	1.57 (3H, t, J=7.6 Hz, C^8-$CH_2C\underline{H}_3$), 3.26 (2H, q, J=7.6 Hz, C^8-$C\underline{H}_2CH_3$), 4.13 (3H, s, N^3-CH_3), 7.50 (2H, d, J=8.2 Hz, $\underline{Ph}$-Cl), 7.96 (2H, d, J=8.2 Hz, $\underline{Ph}$-Cl), 8.58 (1H, s, –CH=N–)
Vd	c)	1.57 (3H, t, J=7.6 Hz, C^8-$CH_2C\underline{H}_3$), 2.44 (3H, s, Ph-$C\underline{H}_3$), 3.26 (2H, q, J=7.6 Hz, C^8-$C\underline{H}_2CH_3$), 4.12 (3H, s, N^3-CH_3), 7.32 (2H, d, J=8.0 Hz, $\underline{Ph}$-CH_3), 7.85 (2H, d, J=8.0 Hz, $\underline{Ph}$-CH_3), 8.53 (1H, s, –CH=N–)
Ve	337.0 (4.37), 232.0 (4.19)	1.58 (3H, t, J=7.6 Hz, C^8-$CH_2C\underline{H}_3$), 3.28 (2H, q, J=7.6 Hz, C^8-$C\underline{H}_2CH_3$), 4.03 (3H, s, Ph-$OC\underline{H}_3$), 4.12 (3H, s, N^3-CH_3), 7.16 (2H, d, J=8.4 Hz, $\underline{Ph}$-OCH_3), 8.03 (2H, d, J=8.4 Hz, $\underline{Ph}$-OCH_3), 8.55 (1H, s, –CH=N–)

TABLE VII. (continued)

Compd. No.	λ_{max}^{EtOH} nm (log ε)[a]	δ (CF_3COOH) ppm
Vf	c)	4.20 (3H, s, N^3-CH_3), 7.60 (6H, m, C^8-Ph and Ph-CH=), 8.03 (4H, m, C^8-Ph and Ph-CH=), 8.62 (1H, s, –CH=N–)
VIa	310.4 (3.83), 242.8 (3.89), 220.4 (4.10)	2.96 (3H, s, C^2-CH_3), 4.23 (3H, s, N^4-CH_3), 7.78 (5H, br s, C^7-Ph)
VIb	311.8 (3.67), 240.8 (3.78), 220.7 (3.89)	2.55 (3H, s, C^7-Ph-CH_3), 2.97 (3H, s, C^2-CH_3), 4.20 (3H, s, N^4-CH_3), 7.47 (2H, d, J=9.0 Hz, C^7-Ph-CH_3), 7.72 (2H, d, J=9.0 Hz, C^7-Ph-CH_3)
VIc	312.0 (3.68), 241.8 (3.73), 223.4 (3.90)	1.59 (3H, t, J=7.4 Hz, C^2-CH_2CH_3), 3.32 (2H, q, J=7.4 Hz, C^2-CH_2CH_3), 4.20 (3H, s, N^4-CH_3), 7.71 (4H, br s, C^7-Ph-Cl)
VId	c)	1.58 (3H, t, J=7.0 Hz, C^2-CH_2CH_3), 2.52 (3H, s, C^7-Ph-CH_3), 3.28 (2H, q, J=7.0 Hz, C^2-CH_2CH_3), 4.18 (3H, s, N^4-CH_3), 7.30—7.82 (4H, br m, C^7-Ph-CH_3)
VIe	312.8 (3.81), 254.2 (4.01), 219.6 (4.04)	1.62 (3H, t, J=7.6 Hz, C^2-CH_2CH_3), 3.35 (2H, q, J=7.6 Hz, C^2-CH_2CH_3), 4.05 (3H, s, C^7-Ph-OCH_3), 4.22 (3H, s, N^4-CH_3), 7.26 (2H, d, J=9.0 Hz, C^7-Ph-OCH_3), 7.87 (2H, d, J=9.0 Hz, C^7-Ph-OCH_3)
VIf	c)	4.35 (3H, s, N^4-CH_3), 7.50—8.70 (10H, br m, C^2-Ph and C^7-Ph)
VIIa	c)	2.96 (3H, s, C^2-CH_3), 4.21 (3H, s, N^4-CH_3)
VIIb[b]	303.2 (——), 223.0 (——)	1.62 (3H, t, J=7.8 Hz, C^2-CH_2CH_3), 3.33 (2H, q, J=7.8 Hz, C^2-CH_2CH_3), 4.08 (3H, s, N^4-CH_3)
VIIIa	315.2 (3.69), 236.0 (4.06), 218.8 (3.91)	3.00 (6H, s, C^2-CH_3 and C^7-SCH_3), 4.15 (3H, s, N^4-CH_3)
VIIIb	315.2 (3.95), 237.0 (4.33), 219.0 (4.20)	1.61 (3H, s, J=7.6 Hz, C^2-CH_2CH_3), 2.97 (3H, s, C^7-SCH_3), 3.33 (2H, q, J=7.6 Hz, C^2-CH_2CH_3), 4.12 (3H, s, N^4-CH_3)
VIIIc	315.6 (4.05), 236.6 (4.46), 218.8 (4.33)	1.63 (3H, t, J=7.8 Hz, C^7-SCH_2CH_3), 2.94 (3H, s, C^2-CH_3), 3.49 (2H, q, J=7.8 Hz, C^7-SCH_2CH_3), 4.12 (3H, s, N^4-CH_3)
VIIId	316.4 (3.94), 237.6 (4.33), 219.0 (4.21)	1.60 (6H, t, J=7.8 Hz, C^7-SCH_2CH_3 and C^2-CH_2CH_3), 3.00—3.72 (4H, m, C^7-SCH_2CH_3 and C^2-CH_2CH_3), 4.08 (3H, s, N^4-CH_3)
VIIIe	c)	2.92 (3H, s, C^2-CH_3), 4.18 (3H, s, N^4-CH_3), 4.30 (2H, s, C^7-SCH_2CONH_2)
VIIIf	c)	1.57 (3H, t, J=7.6 Hz, C^2-CH_2CH_3), 3.24 (2H, q, J=7.6 Hz, C^2-CH_2CH_3), 4.19 (3H, s, N^4-CH_3), 4.30 (2H, s, C^7-SCH_2CONH_2)
IXa[b]	291.0 (——), 225.0 (——)	4.13 (3H, s, N^4-CH_3), 8.95 (1H, s, C^2-H)
IXb	295.0 (4.47), 225.0 (4.47)	2.96 (3H, s, C^2-CH_3), 4.03 (2H, s, N^4-CH_3)
IXc	294.4 (4.36), 247.0 (3.84), 225.3 (4.37)	1.62 (3H, t, J=8.0 Hz, C^2-CH_2CH_3), 3.33 (2H, q, J=8.0 Hz, C^2-CH_2CH_3), 4.03 (3H, s, N^4-CH_3)
IXd[b]	333.8 (——), 320.2 (——), 276.8 (——), 240.6 (——)	4.11 (3H, s, N^4-CH_3), 7.65 (3H, m, C^2-Ph), 8.14 (2H, m, C^2-Ph)

a) The underlined values refer to wavelengths at which shoulders or inflexions occur in the absorption. *b*) This compound was not sufficiently soluble in abs. ethanol for accurate determination of log ε values. *c*) This compound was insoluble in abs. EtOH. TFA = trifluoroacetic acid.

Synthesis of 4-Methyltetrazolo[1,5-*a*]purin-9(4*H*)-ones (IX)

The treatment of III with nitrous acid did not yield the corresponding 2-azido-3-methylpurin-6(3*H*)-ones (X) but 4-methyltetrazolo[1,5-*a*]purin-9(4*H*)-ones (IX). Namely, the

treatment of III with a saturated aqueous $NaNO_2$ in 5% aqueous HCl solution at room temperature afforded the corresponding tetrazolopurines IXa—d in the yields indicated in Table VI (Chart 5). The structures of IX were confirmed by the IR, ^{1}H-NMR, and UV spectra, and elemental analysis data (Table VII). An examination of the IR spectra of IX revealed the absence of the azide absorption in the region of 2120—2160 nm and showed the carbonyl absorption at 1705—1735 cm^{-1} with high intensity. Moreover, a comparison of the UV spectra among the tetrazolopurines IX, the purines III, and the *s*-triazolopurines IV offered further support for the structure of IX. The pattern of the UV absorption spectra of IX did not resemble that of III but that of IV, as indicated in Table VII. Therefore, it is probable that the characteristic UV absorption spectra of IX are a result of the modification of the purine nucleus through the formation of the tetrazole ring.

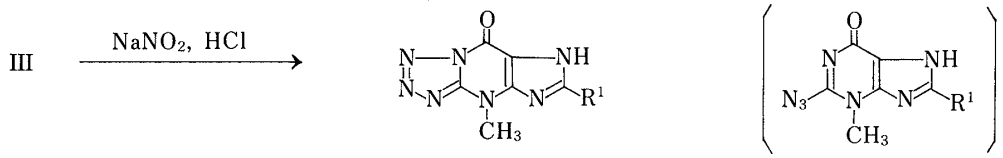


Chart 5

Experimental

All melting points were recorded on a Yanagimoto hot-stage apparatus, and are uncorrected. ^{1}H-NMR spectra were recorded on a Hitachi R-24B 60 MHz spectrometer, and all chemical shifts are given in ppm downfield from tetramethylsilane. The abbreviations used are as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad. UV spectra were obtained in abs. EtOH with a Hitachi 100-60 spectrophotometer.

8-Substituted 3-Methyl-2-thioxanthines (IIa—d)——General Procedure: A mixture of 5,6-diamino-1,2,3,4-tetrahydro-1-methyl-4-oxo-2-thiopyrimidine (I) (12 mmol) and an appropriate ortho ester (120—180 mmol) was heated under reflux for 5—15 h. Cooling of the solution gave the corresponding IIa—d (Table I).

8-Substituted 2-Hydrazino-3-methylpurin-6(3*H*)-ones (IIIa—d)——General Procedure: A mixture of II (2.4 mmol) and 50% aqueous hydrazine hydrate (24.0 mmol) was heated under reflux for 3—10 h. Cooling of the mixture and washing of the precipitated crystals with H_2O gave the corresponding IIIa—d (Table I).

2,7-Disubstituted 4-Methyl-*s*-triazolo[4,3-*a*]purin-9(4*H*)-ones (IVa—i)——General Procedure: A mixture of III (2.4 mmol) and an appropriate ortho ester (72.0 mmol) was heated under reflux for 20—25 h. Cooling of the solution and washing of the precipitated crystals with abs. EtOH gave the corresponding IVa—i (Table II).

8-Substituted 2-Arylidenehydrazino-3-methylpurin-6(3*H*)-ones (Va—f)——General Procedure: A mixture of III (2.4 mmol) and an appropriate aryl aldehyde (2.92 mmol) in abs. EtOH (10 ml) was heated under reflux for 2—5 h. Cooling of the mixture and washing of the crystals with abs. EtOH gave the corresponding Va—f (Table III).

7-Aryl-4-methyl-*s*-triazolo[4,3-*a*]purin-9(4*H*)-ones (VIa—f)——1) Oxidative Cyclization of V by DAD: Method A: General Procedure: A mixture of V (5.45 mmol) and DAD (2.0 ml) was fused at 180—200 °C for 10—30 min. After the reaction, dilution of the mixture with abs. EtOH gave the corresponding VIa—f (Table IV).

2) Oxidative Cyclization of V by Air in AcOH: Method B: General Procedure: A mixture of V (0.3 mmol) and glacial acetic acid (10 ml) was heated under reflux for 5 h. Concentration of the mixture *in vacuo* and dilution of the residue with abs. EtOH gave the corresponding VIa—f (Table IV).

7-Mercapto-4-methyl-*s*-triazolo[4,3-*a*]purin-9(4*H*)-ones (VIIa, b)——General Procedure: A mixture of III (2.4 mmol) and carbon disulfide (2.9 mmol) in pyridine (10 ml) was heated under reflux for 5 h. Concentration of the mixture to dryness *in vacuo* and treatment of the residue with abs. EtOH gave the corresponding VIIa, b (Table V).

4-Methyl-7-methylthio-*s*-triazolo[4,3-*a*]purin-9(4*H*)-ones (VIIIa, b)——General Procedure: Dimethyl sulfate (0.1 ml, 1.03 mmol) was added to a solution of VII (0.8 mmol) in 1 N aqueous NaOH solution (5 ml). The mixture was stirred at room temperature for 1 h, then neutralized with glacial acetic acid and the precipitated crystals were washed with H_2O to yield the corresponding VIIIa, b (Table V).

7-Ethylthio-4-methyl-*s*-triazolo[4,3-*a*]purin-9(4*H*)-ones (VIIIc, d)——General Procedure: Shaking of VII (1.2 mmol) with ethyl iodide (1.0 g, 6.41 mmol) in 1 N aqueous NaOH solution (8 ml) at room temperarure for 24 h and neutralization of the mixture with glacial acetic acid yielded the corresponding VIIIc, d (Table V). The crystals

were collected by filtration, washed with H_2O, and dried under reduced pressure.

2-(4,9-Dihydro-4-methyl-9-oxo-*s*-triazolo[4,3-*a*]purine-7-ylthio)acetamides (VIIIe, f)——General Procedure: A mixture of VII (0.8 mmol) and α-chloroacetamide (1.28 mmol) in 1 N aqueous NaOH solution (10 ml) was treated for 6 h as described above to afford the corresponding VIIIe, f (Table V).

2-Substituted 4-Methyltetrazolo[1,5-*a*]purin-9(4*H*)-ones (IXa—d)——General Procedure: A saturated aqueous $NaNO_2$ solution (7.25 mmol) was added dropwise to a solution of III (2.4 mmol) in 5% aqueous HCl solution (10 ml) under stirring at room temperature. The precipitate was collected by filtration, washed with H_2O, and dried under reduced pressure.

References

1) U. L. RajBhandary, S. H. Chang, A. Stuart, R. D. Faulkner, R. M. Hoskinson, and H. G. Khorana, *Proc. Natl. Acad. Sci. U.S.A.*, **57**, 751 (1967).
2) R. Thiebe and H. G. Zachau, *Eur. J. Biochem.*, **5**, 546 (1968).
3) L. M, Fink, T. Goto, F. Frankel, and I. B. Weinstein, *Biochem. Biophys. Res. Commun.*, **32**, 963 (1968).
4) B. S. Dudock, G. Katz, E. K. Taylor, and R. W. Holley, *Proc. Natl. Acad. Sci. U.S.A.*, **62**, 941 (1969).
5) G. Keith, F. Picand, J. Weissenbach, J. P. Ebel, G. Petrissant, and G. Dirheimer, *FEBS Lett.*, **31**, 345 (1973).
6) K. Nakanishi, N. Furutachi, M. Funamizu, D. Grunberger, and I. B. Weinstein, *J. Am. Chem. Soc.*, **92**, 7617 (1970).
7) H. Kasai, Z. Yamaizumi, Y. Kuchino, and S. Nishimura, *Nucleic Acids Res.*, **6**, 993 (1979).
8) H. Kasai, M. Goto, K. Ikeda, M. Zama, Y. Mizuno, S. Takemura, S. Matsuura, T. Sugimoto, and T. Goto, *Biochemistry*, **15**, 898 (1976).
9) S. H. Blobstein, D. Grunberger, I. B. Weinstein, and K. Nakanishi, *Biochemistry*, **12**, 188 (1973).
10) A. M. Feinberg, K. Nakanishi, J. Barciszewski, A. J. Rafalski, H. Augustyniak, and M. Wiewiórowski, *J. Am. Chem. Soc.*, **96**, 7797 (1974).
11) A. Mochizuki, Y. Omata, and Y. Miyazawa, *Bull. Chem. Soc. Jpn.*, **53**, 813 (1980).
12) L. B. Townsend, G. A. Bhat, F. L. Chung, K. H. Schram, R. P. Panzica, L. L. Wotring, and R. A. Earl, Third International Round Table on the Chemistry and Biology of Nucleosides and Nucleotides, Montpellier, October 1978; Colloq. Inst. Natl. Sante Rech. Med., 1978 (Pub. 1979), 81 (Nucleosides, Nucleotides Appl. Biol.), 37–81 [*Chem. Abstr.*, **92**, 51501*w* (1980)].
13) R. Marumoto, Y. Yoshioka, and M. Honjo, *Chem. Pharm. Bull.*, **22**, 342 (1974).
14) E. Richter, J. E. Loeffler, and E. C. Taylor, *J. Am. Chem. Soc.*, **82**, 3144 (1960).
15) G. B. Elion, *J. Org. Chem.*, **27**, 2478 (1962).
16) F. Bergmann and M. Tamari, *J. Chem. Soc.*, **1961**, 4468.
17) G. W. Grigg, M. J. Edwards, and D. J. Brown, *J. Bacteriol.*, **107**, 599 (1971).
18) D. J. Brown, W. C. Dunlap, G. W. Grigg, L. Danckwertz, and T. Nagamatsu, *Aust. J. Chem.*, **31**, 397 (1978).
19) D. J. Brown, G. W. Grigg, Y. Iwai, K. N. McAndrew, T. Nagamatsu, and R. van Heeswyck, *Aust. J. Chem.*, **32**, 2713 (1979).