FACILE AND GENERAL SYNTHESIS OF 8-SUBSTITUTED 2-METHYLTHIOPURIN-6-ONES

Tomohisa Nagamatsu* and Hiroo Yamasaki

Faculty of Pharmaceutical Sciences, Okayama University, Tsushima, Okayama 700, Japan

Fumio Yoneda*

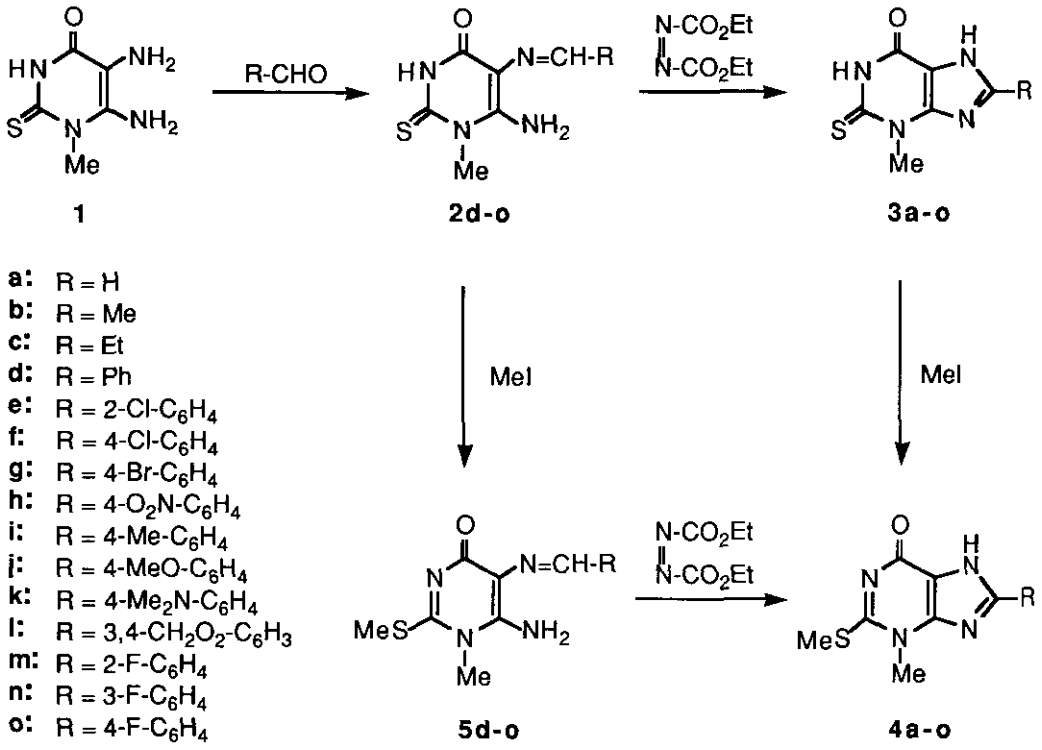
Faculty of Pharmaceutical Sciences, Kyoto University, Yoshida, Sakyo-ku, Kyoto 606, Japan

Abstract --- A variety of 3-methyl-6-oxo-2-thioxo-1,2,3,6-tetrahydropurine (**3a**) and its 8-substituted derivatives (**3b-o**) were synthesized by oxidative cyclization of the reaction product of 5,6-diamino-1-methyl-2-thiouracil (**1**) with an appropriate aldehyde or 6-amino-5-benzylideneamino-1-methyl-2-thiouracils (**2d-o**) in the presence of diethyl azodicarboxylate (DEAD). In addition, the oxidative cyclization of 4-amino-5-benzylideneamino-3-methyl-2-methylthiopyrimidin-6(3*H*)-ones (**5d-o**) in the presence of DEAD gave the corresponding 8-aryl-3-methyl-2-methylthio-6-oxo-3,6-dihydropurines (**4d-o**), which were identical with the compounds prepared by methylation of **3d-o**, respectively. 2-Methylthio-6-oxo-1,6-dihydropurine (**8a**) and its 8-alkyl and 8-aryl derivatives (**8b-h**) were synthesized from 4,5-diamino-2-methylthiopyrimidin-6(1*H*)-one (**6**) or 4-amino-5-benzylideneamino-2-methylthiopyrimidin-6(1*H*)-ones (**7d-h**) in a similar manner as above.

Studies on the synthesis of a number of purines structurally related to guanine and adenine

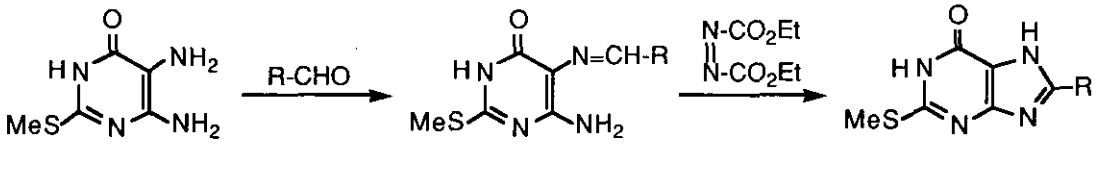
were undertaken in many laboratories in connection with investigation of the effects of structural modifications upon the activity of purine antagonists such as 6-mercaptopurine.[1,2] In addition, such thiopurines have long been interest for their potential biological activities. Actually, the findings that 6-thioguanine acts as an inhibitor of the growth of *Lactobacillus casei*,[1,3] embryonic tissue[4] and a number of neoplasms, *e.g.*, sarcoma 180[5] and leukemia L 1210[6,7] and 2-alkylthiopurines act as amplifiers of the antibiotic activity of phleomycin against *Escherichia coli* B,[8] have aroused interest to us to determine whether similar effects would be observed for 8-substituted 2-thioxantine derivatives.

2-Thioxanthine[9] and 3-methyl-2-thioxanthine[10] were previously prepared by the reaction of 5,6-diamino-2-thiouracil and 5,6-diamino-3-methyl-2-thiouracil with formamide, respectively. Such 5,6-diamino compounds should be useful as precursors for syntheses of a variety of thioxanthines and related compounds. However the 2-thioxanthine derivatives substituted by alkyl or aryl groups were little explored so far. This paper is concerned with the development of synthetic method for the preparation of the biologically interesting 8-substituted 3-methyl-2-methylthio-6-oxo-3,6-dihydropurines (**4b-o**) and 2-methylthio-6-oxo-1,6-dihydropurines (**8b-h**). That is, the key intermediates, 6-amino-5-benzylideneamino-1-methyl-2-thiouracils (**2d-o**), were prepared by treatment of 5,6-diamino-1-methyl-2-thiouracil (**1**)[11] with several aromatic aldehydes in dioxane at 80 °C (Scheme 1) (Table 1). The oxidative cyclization of the compounds (**2d-o**) thus obtained to the corresponding 8-aryl-3-methyl-6-oxo-2-thioxo-1,2,3,6-tetrahydropurines (**3d-o**) was performed by heating at 100 °C with DEAD in dimethylformamide (DMF) in excellent yields (Table 2). On the other hand, the 8-unsubstituted and 8-alkyl derivatives (**3a-c**) were synthesized by the reaction of the compound (**1**) in the presence of an appropriate aldehyde and DEAD without isolation of the intermediates (**2a-c**). The methylation of **3a-o** with methyl iodide in 1N potassium hydroxide aqueous solution afforded the corresponding 3-methyl-2-methylthio-6-oxo-3,6-dihydropurine (**4a**) and its 8-substituted derivatives (**4b-o**) in high yields, respectively (Table 3). Moreover, heating 4-amino-5-benzylideneamino-3-methyl-2-methylthiopyrimidin-6(3*H*)-ones (**5d-o**), which were derived from **2d-o** with methyl iodide in 1N potassium hydroxide aqueous solution (Table 4), with DEAD in DMF, yielded similarly the cyclized compounds (**4d-o**), respectively (Table 3).



Scheme 1

In a similar manner as above, the method was applied to the preparation of 2-methylthio-6-oxo-1,6-dihydropurine (**8a**) and its 8-substituted derivatives (**8b-h**) (Scheme 2). Namely, the compounds (**8a-c**) were synthesized by heating 4,5-diamino-2-methylthiopyrimidin-6(1*H*)-one (**6**) with an appropriate aldehyde and DEAD in dioxane at 80 - 90 °C, whereas the compounds (**8d-h**) were synthesized by heating 4-amino-5-benzylideneamino-2-methylthiopyrimidin-6(1*H*)-



Scheme 2

a: R = H, **b**: R = Me, **c**: R = Et, **d**: R = Ph, **e**: R = 4-Cl-C_6H_4, **f**: R = 4-O_2N-C_6H_4, **g**: R = 4-Me-C_6H_4, **h**: R = 4-F-C_6H_4

Table 1. Yields and Analytical Data for 6-Amino-5-benzylideneamino-1-methyl-2-thiouracils (**2d-o**)

Compd. No.	R	Yield (%)	Mp (°C)	Appearance[a]	Formula	Analysis (%) Calcd (Found) C	H	N
2d	Ph	92	280 - 282	yellow needles	$C_{12}H_{12}N_4OS$	55.36	4.64	21.52
						(55.63	4.68	21.60)
2e	2-Cl-C_6H_4	91	291 - 293 (decomp.)	yellow needles	$C_{12}H_{11}N_4OClS$	48.89	3.76	19.00
						(48.65	3.73	18.75)
2f	4-Cl-C_6H_4	94	278 - 280 (decomp.)	yellow powder	$C_{12}H_{11}N_4OClS$	48.89	3.76	19.00
						(48.98	3.76	19.00)
2g	4-Br-C_6H_4	92	277 - 279 (decomp.)	yellow prisms	$C_{12}H_{11}N_4OBrS$	42.48	3.26	16.51
						(42.23	3.20	16.37)
2h	4-O_2N-C_6H_4	92	> 330	red powder	$C_{12}H_{11}N_5O_3S$	47.20	3.63	22.93
						(47.45	3.71	22.72)
2i	4-Me-C_6H_4	93	269 - 271	yellow prisms	$C_{13}H_{14}N_4OS$	56.91	5.14	20.42
						(56.83	5.26	20.36)
2j	4-MeO-C_6H_4	93	252 - 254	yellow prisms	$C_{13}H_{14}N_4O_2S$	53.77	4.86	19.29
						(53.63	5.01	19.27)
2k	4-Me_2N-C_6H_4	91	> 260 (decomp.)	yellow powder	$C_{14}H_{17}N_5OS$	55.42	5.64	23.08
						(55.28	5.77	23.31)
2l	3,4-CH_2O_2-C_6H_3	93	273 - 275 (decomp.)	yellow needles	$C_{13}H_{12}N_4O_3S$	51.30	3.97	18.40
						(51.11	3.98	18.53)
2m	2-F-C_6H_4	94	276 - 278 (decomp.)	yellow needles	$C_{12}H_{11}N_4OFS$	51.78	3.98	20.13
						(51.66	3.90	20.04)
2n	3-F-C_6H_4	95	278 - 280 (decomp.)	yellow plates	$C_{12}H_{11}N_4OFS$	51.78	3.98	20.13
						(51.51	3.91	20.11)
2o	4-F-C_6H_4	94	279 - 281 (decomp.)	yellow needles	$C_{12}H_{11}N_4OFS$	51.78	3.98	20.13
						(51.73	3.88	19.95)

[a] All compounds were recrystallized from 2-ethoxyethanol.

ones (**7d-h**), which were prepared by the reaction of **6** and an appropriate aromatic aldehyde in dioxane, with DEAD at 80 °C in good yields, respectively (Tables 5 and 6). The structural assignments of **2d-o**, **3a-o**, **4a-o**, **5d-o**, **7d-h**, and **8a-h** were based on the results of elemental analyses and spectroscopic data (Table 7).

Thus, the present methodology constitutes facile and general means of preparing a variety of 2-thioxanthine and its 8-substituted derivatives by the dehydrogenative cyclization of their precursors such as the Schiff's bases **2d-o**, **5d-o**, and **7d-h** using DEAD. The dehydrogenative

Table 2. Yields and Analytical Data for 3-Methyl-6-oxo-2-thioxo-1,2,3,6-tetrahydropurine and Its 8-Alkyl and 8-Aryl Derivatives (**3a-o**)

Compd. No.	R	Yield (%)	Mp (°C)	Appearance (Recryst. solv.)	Formula	Analysis (%) Calcd (Found) C	H	N
3a[a]	H	72	> 330	colourless powder (water)	$C_6H_6N_4OS$			
3b[b]	Me	79	> 330	colourless powder (water)	$C_7H_8N_4OS$			
3c	Et	69	> 330	colourless leaves (water)	$C_8H_{10}N_4OS$	45.69 (45.55	4.79 4.90	26.64 26.82)
3d[c]	Ph	73	> 330	colourless powder (DMSO)	$C_{12}H_{10}N_4OS$			
3e	2-Cl-C_6H_4	65	> 330	colourless powder (DMSO)	$C_{12}H_9N_4OClS$	49.23 (49.18	3.09 3.21	19.13 19.31)
3f	4-Cl-C_6H_4	71	> 330	colourless powder (DMSO)	$C_{12}H_9N_4OClS$	49.23 (49.05	3.09 3.16	19.13 19.37)
3g	4-Br-C_6H_4	73	308 (decomp.)	colourless powder (DNSO)	$C_{12}H_9N_4OBrS$	42.74 (42.86	2.69 2.72	16.61 16.55)
3h	4-O_2N-C_6H_4	73	> 330	yellow powder (DMSO)	$C_{12}H_9N_5O_3S$	47.52 (47.38	2.99 2.75	23.09 23.31)
3i	4-Me-C_6H_4	79	> 330	colourless powder (DMSO)	$C_{13}H_{12}N_4OS$	57.33 (57.58	4.44 4.41	20.57 20.35)
3j	4-MeO-C_6H_4	79	> 330	colourless needles (DMSO)	$C_{13}H_{12}N_4O_2S$	54.15 (54.32	4.19 4.35	19.43 19.33)
3k	4-Me_2N-C_6H_4	71	> 330	grey powder (DMSO)	$C_{14}H_{15}N_5OS$	55.79 (55.81	5.01 5.00	23.23 23.42)
3l	3,4-CH_2O_2-C_6H_3	68	> 330	colourless powder (DMSO)	$C_{13}H_{10}N_4O_3S$	51.64 (51.88	3.33 3.09	18.53 18.55)
3m	2-F-C_6H_4	68	> 330	colourless powder (DMSO)	$C_{12}H_9N_4OFS$	52.16 (51.92	3.28 3.32	20.27 20.07)
3n	3-F-C_6H_4	75	> 330	colourless powder (DMSO)	$C_{12}H_9N_4OFS$	52.16 (52.31	3.28 3.33	20.27 20.17)
3o	4-F-C_6H_4	77	> 330	colourless powder (DMSO)	$C_{12}H_9N_4OFS$	52.16 (52.19	3.28 3.07	20.27 20.39)

[a]Ref. 10. [b]Ref. 12. [c]Ref. 13.

Table 3. Yields and Analytical Data for 3-Methyl-2-methylthio-6-oxo-3,6-dihydropurine and Its 8-Alkyl and 8-Aryl Derivatives (**4a-o**)

Compd. No.	R	Yield (%)[a] A	Yield (%)[a] B	Mp (°C)	Appearance[b] (Recryst. solv.)	Formula	Analysis (%) Calcd (Found) C	H	N
4a[c]	H	87		300 - 302	powder (water)	$C_7H_8N_4OS$			
4b[d]	Me	86		308 - 310	powder (water)	$C_8H_{10}N_4OS$			
4c	Et	85		280 - 282 (decomp.)	needles (water)	$C_9H_{12}N_4OS$	48.19 (48.20	5.39 5.42	24.98 24.76)
4d	Ph	89	74	323 - 325	leaves (DMF)	$C_{13}H_{12}N_4OS$	57.33 (57.29	4.44 4.36	20.57 20.44)
4e	2-Cl-C_6H_4	90	68	284 - 286	leaves (DMF)	$C_{13}H_{11}N_4OClS$	50.89 (50.88	3.61 3.82	18.26 18.38)
4f	4-Cl-C_6H_4	92	82	> 330	needles (DMF)	$C_{13}H_{11}N_4OClS$	50.89 (51.11	3.61 3.80	18.26 18.05)
4g	4-Br-C_6H_4	92	81	329 (decomp.)	needles (DNF)	$C_{13}H_{11}N_4OBrS$	44.45 (44.68	3.15 3.09	15.95 15.99)
4h	4-O_2N-C_6H_4	94	77	325 - 327 (decomp.)	powder (DMF)	$C_{13}H_{11}N_5O_3S$	49.20 (49.43	3.49 3.57	22.06 22.32)
4i	4-Me-C_6H_4	91	75	> 320 (decomp.)	leaves (DMF)	$C_{14}H_{14}N_4OS$	58.72 (58.44	4.92 4.86	19.56 19.27)
4j	4-MeO-C_6H_4	90	79	313 - 315 (decomp.)	leaves (DMF)	$C_{14}H_{14}N_4O_2S$	55.61 (55.33	4.66 4.61	18.53 18.32)
4k	4-Me_2N-C_6H_4	92	83	> 330	leaves (DMF)	$C_{15}H_{17}N_5OS$	57.12 (56.98	5.43 5.71	22.20 22.29)
4l	3,4-CH_2O_2-C_6H_3	88	72	> 330	powder (DMF)	$C_{14}H_{12}N_4O_3S$	53.15 (53.38	3.82 3.88	17.71 17.55)
4m	2-F-C_6H_4	92	69	279 - 281	plates (DMF)	$C_{13}H_{11}N_4OFS$	53.78 (53.78	3.81 3.77	19.29 19.50)
4n	3-F-C_6H_4	92	85	321 - 323 (decomp.)	leaves (DMF)	$C_{13}H_{11}N_4OFS$	53.78 (53.71	3.81 3.89	19.29 19.22)
4o	4-F-C_6H_4	93	89	> 330	needles (DMF)	$C_{13}H_{11}N_4OFS$	53.78 (53.85	3.81 3.59	19.29 19.43)

[a]See Experimental, A : Method A; B : Method B. [b]All compounds were obtained as colourless crystals without **4h** (yellow) and **4k** (pale yellow). [c]Ref. 14. [d]Ref. 12.

Table 4. Yields and Analytical Data for 4-Amino-5-benzylideneamino-3-methyl-2-methylthiopyrimidin-6(3*H*)-ones (**5d-o**)

Compd. No.	R	Yield (%)	Mp (°C)	Appearance[a]	Formula	Analysis (%) Calcd (Found) C	H	N
5d	Ph	80	274 - 276 (decomp.)	yellow prisms	$C_{13}H_{14}N_4OS$	56.91 (56.88)	5.14 5.29	20.42 20.34)
5e	2-Cl-C_6H_4	79	282 - 283	yellow powder	$C_{13}H_{13}N_4OClS$	50.56 (50.58)	4.24 4.25	18.14 18.18)
5f	4-Cl-C_6H_4	80	> 280 (decomp.)	yellow leaves	$C_{13}H_{13}N_4OClS$	50.56 (50.48)	4.24 4.28	18.14 18.04)
5g	4-Br-C_6H_4	83	279 - 280 (decomp.)	yellow leaves	$C_{13}H_{13}N_4OBrS$	44.20 (44.07)	3.70 3.68	15.86 15.66)
5h	4-O_2N-C_6H_4	82	309 (decomp.)	orange powder	$C_{13}H_{13}N_5O_3S$	48.89 (48.61)	4.10 4.04	21.93 21.76)
5i	4-Me-C_6H_4	84	258 (decomp.)	yellow needles	$C_{14}H_{16}N_4OS$	58.31 (58.32)	5.59 5.76	19.42 19.37)
5j	4-MeO-C_6H_4	82	273 - 275 (decomp.)	yellow leaves	$C_{14}H_{16}N_4O_2S$	55.24 (54.97)	5.29 5.33	18.40 18.47)
5k	4-Me_2N-C_6H_4	82	> 285 (decomp.)	yellow powder	$C_{15}H_{19}N_5OS$	56.76 (56.51)	6.03 6.20	22.06 21.87)
5l	3,4-CH_2O_2-C_6H_3	77	287 - 289 (decomp.)	yellow needles	$C_{14}H_{14}N_4O_3S$	52.81 (52.59)	4.43 4.36	17.59 17.46)
5m	2-F-C_6H_4	80	277 - 279	yellow leaves	$C_{13}H_{13}N_4OFS$	53.41 (53.48)	4.48 4.27	19.16 19.31)
5n	3-F-C_6H_4	82	> 284 (decomp.)	yellow powder	$C_{13}H_{13}N_4OFS$	53.41 (53.33)	4.48 4.50	19.16 19.16)
5o	4-F-C_6H_4	86	275 - 277 (decomp.)	yellow leaves	$C_{13}H_{13}N_4OFS$	53.41 (53.14)	4.48 4.40	19.16 19.37)

[a]All compounds were recrystallized from DMF.

cyclization of such Schiff's bases containing mercapto or alkylthio group using other oxidizing agents such as lead tetraacetate was quite difficult. There are two examples[18,19] for the preparation of xanthine derivatives by the similar method using DEAD so far.

EXPERIMENTAL

All melting points were taken using a Yanagimoto micro melting points apparatus and are uncorrected. Microanalyses were performed with a Yanagimoto MT-2 CHN elemental analyser.

Table 5. Yields and Analytical Data for 4-Amino-5-benzylideneamino-2-methylthio-pyrimidin-6(1*H*)-ones (**7d-h**)

Compd. No.	R	Yield (%)	Mp (°C)	Appearance[a]	Formula	Analysis (%) Calcd (Found) C	H	N
7d	Ph	91	257 - 259	pale yellow powder	$C_{12}H_{12}N_4OS$	55.36 (55.18	4.64 4.77	21.52 21.32)
7e	4-Cl-C_6H_4	93	266 - 268	yellow powder	$C_{12}H_{11}N_4OClS$	48.89 (48.78	3.76 3.70	19.00 19.23)
7f	4-O_2N-C_6H_4	95	295 - 297	orange powder	$C_{12}H_{11}N_5O_3S$	47.20 (47.18	3.63 3.81	22.93 23.12)
7g	4-Me-C_6H_4	89	258 - 260	pale yellow powder	$C_{13}H_{14}N_4OS$	56.91 (56.77	5.14 5.32	20.42 20.65)
7h	4-F-C_6H_4	91	267 - 269	pale yellow powder	$C_{12}H_{11}N_4OFS$	51.78 (51.99	3.98 4.12	20.13 20.02)

[a]All compounds were recrystallized from 2-ethoxyethanol.

Ir and ^{1}H-nmr spectra were measured with JASCO IRA-102 spectrophotometer and Hitachi R-1500 FT-NMR (60MHz) instrument with tetramethylsilane as an internal standard, respectively. The following abbreviations are used: s = singlet; d = doublet; t = triplet; q = quartet; m = multiplet; br = broad.

General Procedure for Preparation of 6-Amino-5-benzylideneamino-1-methyl-2-thiouracils (2d-o)

A mixture of 5,6-diamino-1-methyl-2-thiouracil (**1**) (2 g, 11.6 mmol) and an appropriate aryl aldehyde (15.1 mmol) in dioxane (30 ml) was heated at 80 °C with stirring for 2 h. After cooling, the resulting solid was collected by filtration, washed with ethanol, dried, and recrystallized from 2-ethoxyethanol to afford the corresponding pure products (**2d-o**) (Table 1).

General Procedure for Preparation of 3-Methyl-6-oxo-2-thioxo-1,2,3,6-tetrahydropurine and Its 8-Alkyl Derivatives (3a-c)

A mixture of 5,6-diamino-1-methyl-2-thiouracil (**1**) (2 g, 11.6 mmol) and an appropriate

Table 6. Yields and Analytical Data for 2-Methylthio-6-oxo-1,6-dihydropurine and Its 8-Alkyl and 8-Aryl Derivatives (**8a-h**)

Compd. No.	R	Yield (%)	Mp (°C)	Appearance[a]	Formula	Analysis (%) Calcd (Found) C	H	N
8a[b]	H	72	> 310	colourless powder	$C_6H_6N_4OS$			
8b[c]	Me	74	314 (decomp.)	colourless powder	$C_7H_8N_4OS$			
8 c	Et	67	279 - 281	colourless powder	$C_8H_{10}N_4OS$	45.69	4.79	26.64
						(45.77	4.61	26.55)
8 d	Ph	60	257 - 259	pale yellow powder	$C_{12}H_{10}N_4OS$	55.79	3.90	21.69
						(55.91	3.95	21.55)
8 e	4-Cl-C_6H_4	62	260 - 262 (decomp.)	pale brown powder	$C_{12}H_9N_4OClS$	49.23	3.09	19.13
						(49.41	3.10	19.43)
8 f	4-O_2N-C_6H_4	60	301 - 303 (decomp.)	pale orange powder	$C_{12}H_9N_5O_3S$	47.52	2.99	23.09
						(47.68	3.05	23.11)
8 g	4-Me-C_6H_4	64	304 - 306 (decomp.)	pale yellow powder	$C_{13}H_{12}N_4OS$	57.33	4.44	20.57
						(57.43	4.44	20.83)
8 h	4-F-C_6H_4	66	308 - 310	colourless powder	$C_{12}H_9N_4OFS$	52.16	3.28	20.27
						(52.32	3.08	20.43)

[a]All compounds were recrystallized from 2-ethoxyethanol. [b]Ref. 16. [c]Ref. 17.

formaldehyde, acetaldehyde, or propionaldehyde (17.4 mmol) in dioxane (30 ml) was stirred at room temperature for 1 h. Then, to a stirred mixture was added DEAD (2.6 g, 15.1 mmol) and the mixture was heated at 80 - 90 °C for 5 h. After cooling, the resulting solid was collected by filtration, washed with ethanol, dried, and recrystallized from water to afford the corresponding pure products (**3a-c**) (Table 2)

General Procedure for Preparation of 8-Aryl-3-methyl-6-oxo-2-thioxo-1,2,3,6-tetrahydropurines (3d-o)

A mixture of **2d-o** (4 mmol) and DEAD (0.9 g, 5.2 mmol) in DMF (30 ml) was heated at 100 °C with stirring for 0.5 - 2 h. After cooling, the resulting solid was collected by filtration, washed with

Table 7. Nmr and Ir Spectral Data for **2d-o**, **3a-o**, **4a-o**, **5d-o**, **7d-h**, and **8a-h**

Compd. No.	Ir ν_{KBr}^{max} cm^{-1}	^{1}H-Nmr (CF_3CO_2D / TMS)[a]: δ (ppm), J (Hz)
2d	3370 (NH_2) 3270 (NH_2) 1632 (CO) 1610 (δ NH_2)	3.84 (3H, s, NMe), 7.46 (5H, m, Ph-*m*,*p*H and D_2O exchangeable NH_2), 7.95 (2H, m, Ph-*o*H), 9.75 (1H, s, NCH), 12.15 (1H, br s, D_2O exchangeable SH)
2e	3400 (NH_2) 3290 (NH_2) 1638 (CO) 1602 (δ NH_2)	3.85 (3H, s, NMe), 7.44 (5H, m, Ar-*m*,*p*H and D_2O exchageable NH_2), 8.48 (1H, m, Ar-*o*H), 10.14 (1H, s, NCH), 12.22 (1H, br s, D_2O exchangeable SH)
2f	3400 (NH_2) 3280 (NH_2) 1632 (CO) 1604 (δ NH_2)	3.81 (3H, s, NMe), 6.97 (2H, d, J_{AB} = 8.76, Ar-*m*H), 7.36 (2H, br s, D_2O exchangeable NH_2), 7.88 (2H, d, J_{AB} = 8.76, Ar-*o*H), 9.68 (1H, s, NCH), 12.11 (1H, br s, D_2O exchangeable SH)
2g	3380 (NH_2) 3260 (NH_2) 1630 (CO) 1608 (δ NH_2)	3.83 (3H, s, NMe), 7.53 (2H, br s, D_2O exchangeable NH_2), 7.58 (2H, d, J_{AB} = 8.76, Ar-*m*H), 7.92 (2H, d, J_{AB} = 8.76, Ar-*o*H), 9.72 (1H, s, NCH), 12.16 (1H, s, D_2O excangeable SH)
2h	3450 (NH_2) 3340 (NH_2) 1630 (CO) 1608 (δ NH_2)	3.84 (3H, s, NMe), 7.69 (2H, br s, D_2O exchangeable NH_2), 8.21 (4H, s, Ar-H), 9.82 (1H, s, NCH), 12.23 (1H, br s, D_2O exchanbeable SH)
2i	3450 (NH_2) 3370 (NH_2) 1638 (CO) 1707 (δ NH_2)	2.35 (3H, s, CMe), 3.84 (3H, s, NMe), 7.23 (2H, d, J_{AB} = 8.22, Ar-*m*H), 7.40 (2H, br s, D_2O exchangeable NH_2), 7.82 (2H, d, J_{AB} = 8.22, Ar-*o*H), 9.71 (1H, s, NCH), 12.13 (1H, br s, D_2O exchangeable SH)
2j	3370 (NH_2) 3280 (NH_2) 1635 (CO) 1600 (δ NH_2)	3.57 (3H, s, OMe), 3.83 (3H, s, NMe), 7.45 (2H, d, J_{AB} = 8.82, Ar-*m*H), 7.52 (2H, br s, D_2O exchangeable NH_2), 7.98 (2H, d, J_{AB} = 8.82, Ar-*o*H), 9.73 (1H, s, NCH), 12.20 (1H, br s, D_2O exchangeable SH)
2k	3320 (NH_2) 3170 (NH_2) 1635 sh (CO) 1610 (δ NH_2)	2.99 (6H, s, NMe_2), 3.83 (3H, s, NMe)), 6.72 (2H, d, J_{AB} = 8.82, Ar-*m*H), 7.26 (2H, br s, D_2O exchangeable NH_2), 7.74 (2H, d, J_{AB} = 8.82, Ar-*o*H), 9.59 (1H, s, NCH), 12.06 (1H, br s, D_2O exchangeable SH)
2l	3350 (NH_2) 3250 (NH_2) 1630 sh (CO) 1603 (δ NH_2)	3.83 (3H, s, NMe), 6.07 (2H, s, OCH_2O), 6.92 (1H, d, $J_{5',6'}$ = 8.22, 5'-H), 7.22 (1H, dd, $J_{2',6'}$ = 1.80, $J_{5',6'}$ = 8.22, 6'-H), 7.44 (2H, br s, D_2O exchangeable NH_2), 7.82 (1H, d, $J_{2',6'}$ = 1.80, 2'-H), 9.65 (1H, s, NCH), 12.12 (1H, br s, D_2O exchangeable SH)
2m	3400 (NH_2) 3280 (NH_2) 1638 (CO) 1604 (δ NH_2)	3.85 (3H, s, NMe), 7.22 - 7.53 (5H, m, Ar-*m*,*p*H and D_2O exchangeable NH_2), 8.40 (1H, m, Ar-*o*H), 9.98 (1H, s, NCH), 12.19 (1H, br s, D_2O exchangeable SH)
2n	3380 (NH_2) 3270 (NH_2) 1636 (CO) 1614 (δ NH_2)	3.84 (3H, s, NMe), 7.16 - 7.68 (5H, m, Ar-H and D_2O exchangeable NH_2), 7.89 - 8.07 (1H, m, Ar-*o*H), 9.75 (1H, s, NCH), 12.18 (1H, s, D_2O exchangeable SH)
2o	3430 (NH_2) 3320 (NH_2) 1666 (CO) 1614 (δ NH_2)	3.84 (3H, s, NMe), 7.23 (2H, dd, $J_{H,H}$ = 8.82, $J_{H,F}$ = 8.76, Ar-*m*H), 7.47 2H, br s, D_2O exchangeable NH_2), 8.01 (2H, ddd, $J_{H,H}$ = 8.82, $J_{H,H}$ = 2.34, $J_{H,F}$ = 5.82, Ar-*o*H), 9.74 (1H, s, NCH), 12.16 (1H, br s, D_2O exchangeable SH)
3a	3130 (NH) 1680 (CO)	4.10 (3H, s, NMe), 8.97 (1H, s, 8-H)
3b	3060 (NH) 1680 (CO)	2.95 (3H, s, CMe), 4.03 (3H, s, NMe)

3 c	3080 (NH) 1710 (CO)	1.62 (3H, t, J = 7.02, CH_2Me), 3.31 (2H, q, J = 7.02, CH_2Me), 4.05 (3H, s, NMe)
3 d	3130 (NH) 1673 (CO)	b
3 e	3175 (NH) 1687 (CO)	4.12 (3H, s, NMe), 7.50 - 7.97 (5H, m, Ar-H)
3 f	3125 (NH) 1683 (CO)	b
3 g	3100 (NH) 1675 (CO)	b
3 h	3100 (NH) 1673 (CO)	b
3 i	3170 (NH) 1665 (CO)	2.56 (3H, s, CMe), 4.13 (3H, s, NMe), 7.57 (2H, d, J_{AB} = 8.76, Ar-*m*H), 8.01 (2H, d, J_{AB} = 8.76, Ar-*o*H)
3 j	3180 (NH) 1674 (CO)	4.04 (3H, s, OMe), 4.14 (3H, s, NMe), 7.29 (2H, d, J_{AB} = 8.76, Ar-*m*H), 8.13 (2H, d, J_{AB} = 8.76, Ar-*o*H)
3 k	3150 (NH) 1678 (CO)	3.56 (6H, s, NMe_2), 4.17 (3H, s, NMe), 7.96 (2H, d, J_{AB} = 8.76, Ar-*m*H), 8.45 (2H, d, J_{AB} = 8.76, Ar-*o*H)
3 l	3100 (NH) 1670 (CO)	4.12 (3H, s, NMe), 6.18 (2H, s, OCH_2O), 7.12 (1H, d, $J_{5',6'}$ = 8.22, 5'-H), 7.51 (1H, d, $J_{2',6'}$ =2.34, 2'-H), 7.73 (1H, dd, $J_{2',6'}$ = 2.34, $J_{5',6'}$ = 8.22, 6'-H)
3 m	3180 (NH) 1690 (CO)	b
3 n	3140 (NH) 1680 (CO)	b
3 o	3120 (NH) 1670 (CO)	b
4 a	3090 (NH) 1620 (CO)	3.10 (3H, s, SMe), 4.20 (3H, s, NMe), 8.62 (1H, s, 8-H)
4 b	3120 (NH) 1615 (CO)	2.87 (3H, s, 8-Me), 3.07 (3H, s, SMe), 3.19 (3H, s, NMe)
4 c	3120 (NH) 1628 (CO)	1.55 (3H, t, J = 7.62, CH_2Me), 3.04 (3H, s, SMe), 3.22 (2H, q, J = 7.62, CH_2Me), 4.18 (3H, s, NMe)
4 d	3050 (NH) 1618 (CO)	3.12 (3H, s, SMe), 4.28 (3H, s, NMe), 7.70 (3H, m, Ph-*m,p*H), 8.17 (2H, m, Ph-*o*H)
4 e	3030 (NH) 1612 (CO)	3.14 (3H, s, SMe), 4.28 (3H, s, NMe), 7.55 - 7.70 (3H, m, Ar-*m,p*H), 8.24 (1H, m, Ar-*o*H)
4 f	3050 (NH) 1620 (CO)	3.14 (3H, s, SMe), 4.28 (3H, s, NMe), 7.62 (2H, d, J_{AB} = 8.76, Ar-*m*H), 8.16 (2H, d, J_{AB} =8.76, Ar-*o*H)
4 g	3050 (NH) 1618 (CO)	3.13 (3H, s, SMe), 4.27 (3H, s, NMe), 7.79 (2H, d, J_{AB} =8.76, Ar-*m*H), 8.08 (2H, d, J_{AB} = 8.76, Ar-*o*H)
4 h	3040 (NH) 1605 (CO)	3.15 (3H, s, SMe), 4.30 (3H, s, NMe), 8.51 (4H, s, ArH)
4 i	3050 (NH) 1610 (CO)	2.52 (3H, s, CMe), 3.09 (3H, s, SMe), 4.27 (3H, s, NMe), 7.49 (2H, d, J_{AB} = 8.22, Ar-*m*H), 8.08 (2H, d, J_{AB} = 8.22, Ar-*o*H)
4 j	3070 (NH) 1630 (CO)	3.10 (3H, s, SMe), 4.06 (3H, s, OMe), 4.27 (3H, s, NMe), 7.25 (2H, d, J_{AB} = 8.76, Ar-*m*H), 8.21 (2H, d, J_{AB} = 8.76, Ar-*o*H)
4 k	3060 (NH) 1600 (CO)	3.15 (3H, s, SMe), 3.56 (6H, s, NMe_2), 4.29 (3H, s, NMe), 7.92 (2H, d, J_{AB} = 8.76, Ar-*m*H), 8.54 (2H, d, J_{AB} = 8.76, Ar-*o*H)
4 l	3080 (NH) 1585 (CO)	3.11 (3H, s, SMe), 4.26 (3H, s, NMe), 6.13 (2H, s, OCH_2O), 7.07 (1H, d, $J_{5',6'}$ = 8.22, 5'-H), 7.66 (1H, d, $J_{2',6'}$ = 1.80, 2'-H), 7.83 (1H, dd, $J_{2',6'}$ = 1.80, $J_{5',6'}$ = 8.22, 6'-H)
4 m	3050 (NH) 1615 (CO)	3.14 (3H, s, SMe), 4.30 (3H, s, NMe), 7.19 - 7.81 (3H, m, Ar-*m,p*H), 8.29 - 8.58 (1H, m, Ar-*o*H)
4 n	3050 (NH) 1620	3.17 (3H, s, SMe), 4.32 (3H, s, NMe)), 7.32 - 8.08 (4H, m, Ar-H)

4 o	3050 (NH) 1600 (CO)	3.14 (3H, s, SMe), 4.28 (3H, s, NMe), 7.32 (2H, dd, $J_{H,H}$ = 8.82, $J_{H,F}$ = 8.22, Ar-*m*H), 8.25 (2H, ddd, $J_{H,H}$ = 8.82, $J_{H,H}$ = 2.34, $J_{H,F}$ = 5.28, Ar-*o*H)
5 d	3420 (NH_2) 3250 (NH_2) 1622 (CO) 1603 (δ NH_2)	2.85 (3H, s, SMe), 3.95 (3H, s, NMe), 7.60 - 8.38 (5H, m, Ph-H), 9.19 (1H, s, NCH)
5 e	3420 (NH_2) 3270 (NH_2) 1623 (CO) 1600 (δ NH_2)	2.84 (3H, s, SMe), 3.93 (3H, s, NMe), 7.58 - 8.03 (3H, m, Ar-*m,p*H), 8.37 (1H, m, Ar-*o*H), 9.69 (1H, s, NCH)
5 f	3370 (NH_2) 3260 (NH_2) 1623 sh (CO) 1607 (δ NH_2)	2.84 (3H, s, SMe), 3.93 (3H, s, NMe), 7.80 (2H, d, J_{AB} = 8.76, Ar-*m*H), 8.25 (2H, d, J_{AB} = 8.76, Ar-*o*H), 9.17 (1H, s, NCH)
5 g	3370 (NH_2) 3250 (NH_2) 1622 (CO) 1603 (δ NH_2)	2.84 (3H, s, SMe), 3.93 (3H, s, NMe), 7.85 - 8.08 (4H, m, Ar-H), 9.17 (1H, s, NCH)
5 h	3380 (NH_2) 3250 (NH_2) 1624 (CO) 1608 (δ NH_2)	2.82 (3H, s, SMe), 3.94 (3H, s, NMe), 8.09 - 8.60 (4H, m, Ar-H), 9.55 (1H, s, NCH)
5 i	3420 (NH_2) 3250 (NH_2) 1624 (CO) 1602 (δ NH_2)	2.51 (3H, s, CMe), 2.84 (3H, s, SMe), 3.93 (3H, s, NMe), 7.67 (2H, d, J_{AB} = 8.22, Ar-*m*H), 8.18 (2H, d, J_{AB} =8.22, Ar-*o*H), 9.02 (1H, s, NCH)
5 j	3420 (NH_2) 3250 (NH_2) 1620 sh (CO) 1600 (δ NH_2)	2.83 (3H, s, SMe), 3.93 (3H, s, NMe), 4.14 (3H, s, OMe), 7.31 (2H, d, J_{AB} = 9.36, Ar-*m*H), 8.26 (2H, d, J_{AB} = 9.36, Ar-*o*H), 8.75 (1H, s, NCN)
5 k	3400 (NH_2) 3250 (NH_2) 1620 sh (CO) 1592 (δ NH_2)	2.81 (3H, s, SMe), 3.45 (6H, s, NMe_2), 3.91 (3H, s, NMe), 7.26 (2H, d, J_{AB} = 9.36, Ar-*m*H), 8.02 (2H, d, J_{AB} = 9.36, Ar-*o*H), 8.47 (1H, s, NCH)
5 l	3420 (NH_2) 3270 (NH_2) 1622 (CO) 1598 (δ NH_2)	2.82 (3H, s, SMe), 3.92 (3H, s, NMe), 6.32 (2H, s, OCH_2O), 7.20 (1H, d, $J_{5',6'}$ = 8.22, 5'-H), 7.74 (1H, d, $J_{2',6'}$ = 1.80, 2'-H), 7.90 (1H, dd, $J_{2',6'}$ = 1.80, $J_{5',6'}$ = 8.22, 6'-H), 8.72 (1H, s, NCH)
5 m	3420 (NH_2) 3280 (NH_2) 1632 (CO) 1608 (δ NH_2)	2.84 (3H, s, SMe), 3.93 (3H, s, NMe), 7.36 - 7.76 (2H, m, Ar-*m,p*H), 8.01 - 8.35 (2H, m, Ar-*o,m*H), 9.32 (1H, s, NCH)
5 n	3380 (NH_2) 3270 (NH_2) 1638 (CO) 1610 (δ NH_2)	2.85 (3H, s, SMe), 3.94 (3H, s, NMe), 7.62 - 8.07 (4H, m, Ar-H), 9.28 (1H, s, NCH)
5 o	3370 (NH_2) 3250 (NH_2) 1612 (CO) 1600 (δ NH_2)	2.84 (3H, s, SMe), 3.94 (3H, s, NMe), 7.52 (2H, dd, $J_{H,H}$ = 8.82, $J_{H,F}$ = 8.76, Ar-*m*H), 8.41 (2H, ddd, $H_{H,H}$ = 8.82, $J_{H,H}$ = 2.34, $J_{H,F}$ =5.28, Ar-*o*H), 9.15 (1H, s, NCH)
7 d	3450 (NH_2) 3260 (NH_2) 3120 (NH) 1600 (CO, δ NH_2)	2.78 (3H, s, SMe), 7.78 - 8.25 (5H, m, Ph-H), 9.30 (1H, s, NCH)

7 e	3440 (NH_2) 3260 (NH_2) 3120 (NH) 1598 (CO, δ NH_2)	2.76 (3H, s, SMe), 7.74 (2H, d, J_{AB} = 8.82, Ar-*m*H), 8.14 (2H, d, J_{AB} = 8.82, Ar-*o*H), 9.31 (1H, s, NCH)
7 f	3450 (NH_2) 3270 (NH_2) 3120 (NH) 1602 (CO, δ NH_2)	2.75 (3H, s, SMe), 8.17 - 8.60 (4H, m, Ar-H), 9.81 (1H, s, NCH)
7 g	3450 (NH_2) 3260 (NH_2) 3120 (NH) 1602 (CO, δ NH_2)	2.63 (3H, s, Me), 2.79 (3H, s, SMe), 7.62 (2H, d, J_{AB} = 8.22, Ar-mH), 8.10 (2H, d, J_{AB} = 8.22, Ar-*o*H), 9.12 (1H, s, NCH)
7 h	3460 (NH_2) 3270 (NH_2) 3130 (NH) 1601 (CO, δ NH_2)	2.78 (3H, s, SMe), 7.46 (2H, dd, $J_{H,H}$ = 8.82, $J_{H,F}$ = 8.22, Ar-*m*H), 8.31 (2H, ddd, $J_{H,H}$ = 8.82, $J_{H,H}$ = 1.74, $J_{H,F}$ = 5.22, Ar-*o*H), 9.27 (1H, s, NCH)
8 a	3120 (NH) 3050 (NH) 1702 (CO)	2.77 (3H, s, SMe), 9.14 (1H, s, 8-H)
8 b	3120 sh (NH) 3040 (NH) 1672 (CO)	2.75 (3H, s, SMe), 2.98 (3H, s, 8-Me)
8 c	3120 sh (NH) 3030 (NH) 1678 (CO)	1.63 (3H, t, J = 7.62, CH_2*Me*), 2.75 (3H, s, SMe), 3.33 (2H, q, J = 7.62, *C*H_2Me)
8 d	3140 (NH) 3110 (NH) 1674 (CO)	2.86 (3H, s, SMe), 7.73 (3H, m, Ph-H), 8.24 (2H, m, Ph-H)
8 e	3140 (NH) 3100 sh (NH) 1660 (CO)	2.85 (3H, s, SMe), 7.65 (2H, d, J_{AB} = 8.82, Ar-*m*H), 8.18 (2H, d, J_{AB} = 8.82, Ar-*o*H)
8 f	3150 (NH) 3100 (NH) 1680 (CO)	2.81 (3H, s, SMe), 8.42 (2H, d, J_{AB} = 9.36, Ar-*m*H), 8.67 (2H, d, J_{AB} = 9.36 , Ar-*o*H)
8 g	3160 sh (NH) 3140 (NH) 1660 (CO)	2.57 (3H, s, CMe), 2.79 (3H, s, SMe), 7.60 (2H, d, J_{AB} = 8.82, Ar-*m*H), 8.07 (2H, d, J_{AB} = 8.82, Ar-*o*H)
8 h	3140 (NH) 3098 (NH) 1662 (CO)	2.79 (3H, s, SMe), 7.48 (2H, dd, $J_{H,H}$ = 8.76, $J_{H,F}$ = 7.62, Ar-*m*H), 8.23 (2H, ddd, $J_{H,H}$ = 8.76, $J_{H,H}$ = 2.34, $J_{H,F}$ = 4.74, Ar-*o*H)

[a]Compounds (**2d-o**) were measured in DMSO-d_6. [b]This compound was not sufficiently soluble in any solvents at room temperature.

ethanol, dried, and recrystallized from dimethyl sulfoxide (DMSO) to afford the corresponding pure products (**3d-o**) (Table 2).

General Procedure for Preparation of 3-Methyl-2-methylthio-6-oxo-3,6-dihydropurine and Its 8-Alkyl and 8-Aryl Derivatives (4a-o)

Method A

A mixture of **3a-o** (2 mmol) and methyl iodide (0.85 g, 6 mmol) in 1N aqueous KOH (8 ml, 8 mmol) was stirred at 5 - 15 °C for 1.5 - 2 h. The resulting solution was neutralized with glacial acetic acid to afford the corresponding products (**4a-o**), which were washed with water, dried, and recrystallized from water or DMF (Table 3).

Method B

A mixture of **5d-o** (2 mmol) and DEAD (0.45 g, 2.6 mmol) in DMF (20 ml) was heated at 100 °C with stirring for 0.5 - 1.5 h. After cooling, the resulting solid was collected by filtration, washed with ethanol, dried, and recrystallized from DMF to afford the corresponding pure products (**4d-o**) (Table 3).

General Procedure for Preparation of 4-Amino-5-benzylideneamino-3-methyl-2-methylthiopyrimidin-6(3*H*)-ones (5d-o)

A mixture of **2d-o** (4 mmol) and methyl iodide (1.7 g, 12 mmol) in 1N aqueous KOH (12 ml, 12 mmol) was stirred at 5 - 15 °C for 1 - 1.5 h. The resulting solid was collected by filtration, washed with water, dried, and recrystallized from DMF to afford the corresponding pure products (**5d-o**) (Table 4).

General Procedure for Preparation of 4-Amino-5-benzylideneamino-2-methylthiopyrimidin-6(1*H*)-ones (7d-h)

A mixture of 4,5-diamino-2-methylthiopyrimidin-6(1*H*)-one (**6**) (2 g, 11.6 mmol) and an appropriate aryl aldehyde (17.4 mmol) in dioxane (30 ml) was heated at 80 °C with stirring for 2 h. After cooling, the resulting solid was collected by filtration, washed with ethanol, dried, and recrystallized from 2-ethoxyethanol to afford the corresponding pure products (**7d-h**) (Table 5).

General Procedure for Preparation of 2-Methylthio-6-oxo-1,6-dihydropurine and Its 8-Alkyl Derivatives (8a-c)

A mixture of 4,5-diamino-2-methylthiopyrimidin-6(1*H*)-one (**6**) (2 g, 11.6 mmol) and an appropriate formaldehyde, acetaldehyde, or propionaldehyde (17.4 mmol) in dioxane (30 ml) was stirred at room temperature for 1 h. Then, to a stirred mixture was added DEAD (2.6 g, 15 mmol)

and the mixture was heated at 80 - 90 °C for 8 h. After cooling, the resulting solid was collected by filtration, washed with ethanol, dried, and recrystallized from 2-ethoxyethanol to afford the corresponding pure products (**8a-c**) (Table 6).

General Procedure for Preparation of 8-Aryl-2-methylthio-6-oxo-1,6-dihydropurines (8d-h)

A mixture of **7d-h** (4 mmol) with DEAD (3.48 g, 20 mmol) was heated at 100 - 110 °C with stirring for 2 - 4 h. After cooling, the mixture was diluted with ethanol to get the solid, which was collected by filtration, washed with ethanol, dried, and recrystallized from 2-ethoxyethanol (Table 6).

REFERENCES

1. G. B. Elion, G. H. Hitchings, and H. VanderWerff, *J. Biol. Chem.*, 1951, **192**, 505.
2. D. A. Clarke, G. B. Elion, G. H. Hitchings, and C. C. Stock, *Cancer Res.*, 1958, **18**, 445.
3. G. B. Elion, S. Singer, G. H. Hitchings, M. E. Balis, and G. B. Brown, *J. Biol. Chem.*, 1953, **202**, 647.
4. S. Bieber, R. Bieber, and G. H. Hichings, *Ann, N. Y. Acad. Sci.*, 1954, **60**, 207.
5. D. A. Clarke, F. S. Philips, S. S. Sternberg, and C. C. Stock, *Ann, N. Y. Acad. Sci.*, 1954, **60**, 235.
6. L. W. Law, *Proc. Soc. Exptl. Biol. Med.*, 1953, **84**, 409.
7. L. W. Law, V. Taormina, and P. J. Boyle, *Ann, N. Y. Acad. Sci.*, 1954, **60**, 244.
8. A. M. Angyal, G. W. Grigg, R. J. Badger, D. J. Brown, and J. H. Lister, *J. Gen. Microbiol.*, 1974, **85**, 163.
9. R. K. Robins, K. J. Dille, C. H. Willits, and B. E. Christensen, *J. Am. Chem. Soc.*, 1953, **75**, 263.
10. F. Bergmann, G. Levin, A. Kalmus, and H. Kwietny-Govrin, *J. Org. Chem.*, 1961, **26**, 1504.
11. W. Traube and F. Winter, *Arch. Pharmazie* , 1906, **244**, 11.
12. F. Bergmann and M. Tamari, *J. Chem. Soc.*, 1961, 4468.
13. T. Nagamatsu, M. Ukai, F. Yoneda, and D. J. Brown, *Chem. Pharm. Bull.*, 1985, **33**, 3113
14. G. B. Elion, *J. Org. Chem.*, 1962, **27**, 2478.
15. C. O. Johns and E. J. Baumann, *J. Biol. Chem.*, 1913, **14**, 381.
16. G. B. Elion, W. H. Lange, and G. H. Hitchings, *J. Am. Chem. Soc.*, 1956, **78**, 217.

17. H. C. Koppel and R. K. Robins, *J. Org. Chem.*, 1958, **23**, 1457.

18. F. Yoneda, S. Matsumoto, and M. Higuchi, *J. Chem. Soc., Chem. Commun.*, 1975, 146.

19. R. H. Erickson, R. N. Hiner, S. W. Feeney, P. R. Blake, W. J. Rzeszotarski, R. P. Hicks, D. G. Costello, and M. E. Abreu, *J. Med. Chem.*, 1991, **34**, 1431.

Received, 11th November, 1991