Unequivocal Synthesis of 6-Arylpteridines by Intramolecular Cycloaddition of Azahexatrienes

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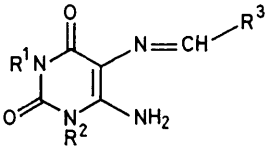
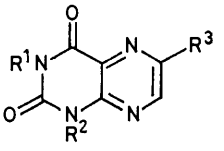
Treatment of 6-amino-5-benzylideneaminopyrimidines, readily prepared by condensation of 5,6-diaminopyrimidines with aromatic aldehydes, with an excess of triethyl orthoformate in dimethylformamide afforded the corresponding 6-ethoxymethyleneamino-derivatives, which underwent thermal cyclization through valence isomerization and subsequent aromatization by elimination of ethanol to give 6-arylpteridines. Treatment of 6-amino-5-benzylideneaminopyrimidines with dimethylformamide diethyl acetal gave the corresponding 6-dimethylaminomethyleneamino-derivatives, which on heating in tetramethylene sulphone also yielded 6-arylpteridines.

INTRAMOLECULAR cycloaddition of azahexatrienes has recently been shown to offer a useful route to heterocycles, *e.g.* purines [1] and pyrazolo[3,4-*d*]pyrimidines.[1,2] This paper describes a synthesis of 6-arylpteridines which is applicable, in principle, to the preparation of other 6-substituted pteridines. Although many selective syntheses of 6-substituted pteridines by condensation of 5,6-diaminopyrimidines with two-carbon sources have been devised, they appear involved, lengthy, and sometimes inefficient.[3] Our new route, which involves an intramolecular cycloaddition of a 2,5-diazahexatriene, is remarkable for its positional selectivity and for the simplicity of the procedure; it is applicable to a wide variety of aryl groups.



(1)



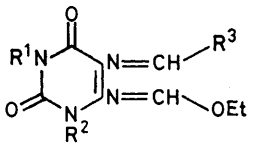
(2)

		M.p. (°C) of (1)	M.p. (°C); yield (%) of (2)
a;	R^1 = Me, R^2 = Me, R^3 = Ph	225 (decomp.)	258;[5,6] 88
b;	R^1 = Me, R^2 = Me, R^3 = 4-ClC_6H_4	220	250; 92
c;	R^1 = Me, R^2 = Me, R^3 = 3,4-$Cl_2C_6H_3$	249	285; 87
d;	R^1 = Me, R^2 = Me, R^3 = 3-NO_2·C_6H_4	300 (decomp.)	259; 78
e;	R^1 = Me, R^2 = Me, R^3 = 4-MeC_6H_4	233	233; 69
f;	R^1 = Me, R^2 = Me, R^3 = 4-MeO·C_6H_4	206	222; 70
g;	R^1 = Me, R^2 = Me, R^3 = 3,4-$(MeO)_2$·C_6H_3	235	251; 77
h;	R^1 = Me, R^2 = Me, R^3 = 3,4-$(CH_2O_2)C_6H_3$	280 (decomp.)	260; 85
i;	R^1 = Me, R^2 = Me, R^3 = 4-Me_2N·C_6H_4	248	243; 70
j;	R^1 = Me, R^2 = Me, R^3 = PhCH:CH	277 (decomp.)	189; 71
k;	R^1 = Me, R^2 = Me, R^3 = 2-pyridyl	259	246; 83
l;	R^1 = Me, R^2 = Me, R^3 = 3-pyridyl	278	221; 80
m;	R^1 = Me, R^2 = Me, R^3 = 2-thienyl	244	267; 77
n;	R^1 = H, R^2 = Me, R^3 = Ph	>340	327; 81
o;	R^1 = H, R^2 = Me, R^3 = 4-ClC_6H_4	>340	306; 84
p;	R^1 = H, R^2 = Me, R^3 = 3,4-$Cl_2C_6H_3$	>340	303; 81
q;	R^1 = H, R^2 = Me, R^3 = 4-NO_2·C_6H_4	>340	345; 80
r;	R^1 = H, R^2 = Me, R^3 = 3-NO_2·C_6H_4	>340	275; 87
s;	R^1 = H, R^2 = Me, R^3 = 4-MeC_6H_4	>340	313; 95
t;	R^1 = H, R^2 = Me, R^3 = 4-MeO·C_6H_4	>340	350; 92
u;	R^1 = H, R^2 = Me, R^3 = 3-MeO-4-OH·C_6H_3	>340	>360; 80
v;	R^1 = H, R^2 = Me, R^3 = 3,4-$(CH_2)_2C_6H_3$	>340	360 (decomp.); 97
w;	R^1 = H, R^2 = Me, R^3 = PhCH:CH	>340	>360; 62
x;	R^1 = H, R^2 = Me, R^3 = 2-pyridyl	290	352; 78
y;	R^1 = H, R^2 = Me, R^3 = 3-pyridyl	301	>360; 89
z;	R^1 = H, R^2 = Me, R^3 = 2-thienyl	264	330; 74
a';	R^1 = H, R^2 = H, R^3 = Ph	>340	>360;[6] 70
b';	R^1 = H, R^2 = H, R^3 = 4-ClC_6H_4	335	>360; 81
c';	R^1 = H, R^2 = H, R^3 = 3,4-$Cl_2C_6H_3$	340	>360; 65
d';	R^1 = H, R^2 = H, R^3 = 3-NO_2·C_6H_4	340 (decomp.)	>360; 68
e';	R^1 = H, R^2 = H, R^3 = 4-MeC_6H_4	>340	>360; 67
f';	R^1 = H, R^2 = H, R^3 = 4-MeO·C_6H_4	311	355; 65
g';	R^1 = H, R^2 = H, R^3 = 3,4-$(CH_2O_2)C_6H_3$	>340	350 (decomp.); 82
h';	R^1 = H, R^2 = H, R^3 = 2-pyridyl	>340	>360; 65
i';	R^1 = H, R^2 = H, R^3 = 3-pyridyl	>340	>360; 75

Refluxing 6-amino-5-benzylideneamino-1,3-dimethyluracil (1a) [4] with a large excess of triethyl orthoformate in dimethylformamide followed by cooling caused

[1] F. Yoneda, M. Higuchi, and T. Nagamatsu, *J. Amer. Chem. Soc.*, 1974, **96**, 5607.
[2] F. Yoneda, T. Nagamatsu, T. Nagamura, and K. Senga, *J.C.S. Perkin I*, 1977, 765.
[3] A. Rosowsky and K. K. N. Chen, *J. Org. Chem.*, 1973, **38**, 2073, and references cited therein.
[4] W. Traube and W. Nithak, *Ber.*, 1906, **39**, 227.

separation of 1,3-dimethyl-6-phenyl-lumazine (2a) [5,6] in high yield. Similarly, other anils (1b—i'), which were readily prepared by condensation of 5,6-diaminouracils and benzaldehydes in ethanol or dimethylformamide, gave the corresponding 6-aryl-lumazines (2b—i') under



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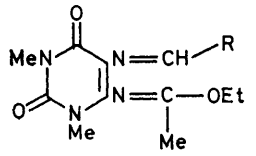
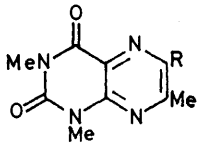
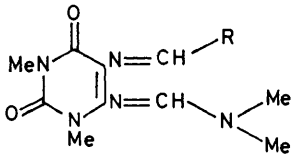


(4a); R = 4-MeO·C_6H_4
(4b); R = 3,4-$(MeO)_2$·C_6H_3



(5a); R = 4-MeO·C_6H_4
(5b); R = 3,4-$(MeO)_2$·C_6H_3



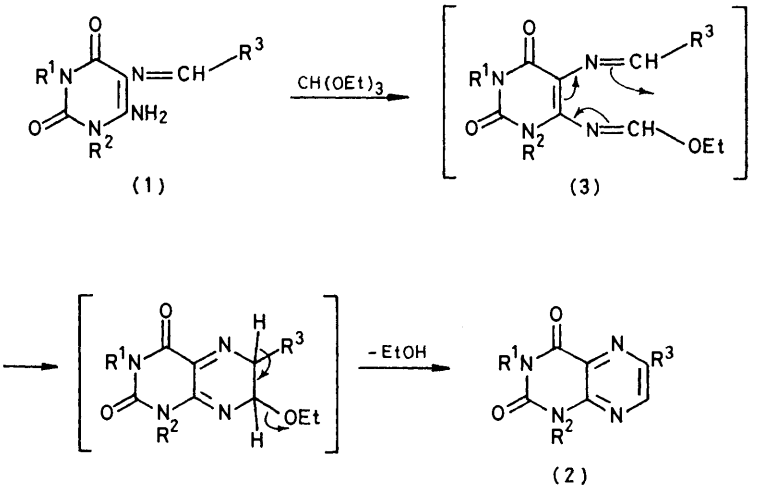
		M.p. (°C); yield (%)
(6) a;	R = Ph	170; 95
b;	R = 4-ClC_5H_4	185; 93
c;	R = 4-MeO·C_6H_4	176; 91
d;	R = 3,4-$(CH_2O_2)C_6H_3$	242; 82

the same conditions (Table 1).* Some of these lumazines could also be synthesized by refluxing the anils in triethyl orthoformate alone. The 1,3- and 3-unsubstituted lumazines thus obtained were converted into the respective 1,3-dimethyl-lumazines by methylation with methyl iodide and potassium carbonate in dimethylformamide for identification purposes.

The reaction presumably proceeds by initial formation of the 6-ethoxymethyleneamino compound (3), which possesses a 2,5-diazahexatriene-type structure. This could undergo thermal cyclization through valence isomerization and then aromatization by elimination of ethanol (Scheme 1). Although we did not detect the intermediates (3) condensation of some anils (1f and g) with triethyl orthoacetate in dimethylformamide gave high yields of the corresponding 2,5-diazahexatriene-type 6-(α-ethoxyethylideneamino)-intermediates (4a and b). Heating compounds (4) in tetramethylene sulphone led to the respective 6-aryl-1,3,7-trimethyl-lumazines (5a and b).

Pfleiderer and Blank [7] have reported an analogous intramolecular cycloaddition with subsequent oxidation of 5,6-dibenzylideneaminouracils, which were considered to be intermediates in the synthesis of 6,7-diaryl-lumazines by fusion of 5,6-diaminouracils or their 5-*N*-benzylidene derivatives with aromatic aldehydes. We have encountered oxidative cycloaddition of the similar 2,5-diazahexatriene-type intermediates in the disproportionation of 6-amino-5-benzylideneamino-1,3-dimethyluracils in formamide leading to 6,7-diaryl-1,3-dimethyl-lumazines and theophylline.[8] Padwa and his co-workers [9] suggested a similar cycloaddition of a 2,5-diazahexatriene intermediate (1,2-dibenzylideneamino-1,2-diphenylethylene) in the conversion of 1,3-diazabicyclo[3.1.0]hex-3-ene into pyrazine and related reactions.

In order to confirm this reaction mechanism, the intramolecular cycloaddition of some 5-benzylideneamino-6-dimethylaminomethyleneamino-1,3-dimethyluracils (6),[10] which are also compounds of the 2,5-diazahexatriene type, was studied. Compounds (6a—d) were readily prepared by condensation of 6-amino-5-benzyl-



(1) (3) (2)

SCHEME 1

* Tables 1—4 [analytical data for compounds (2) and (6)—(8); i.r. data for (2) and (8)] are available as Supplementary Publication No. SUP 22029 (6 pp.). For details see Notice to Authors No. 7, *J.C.S. Perkin I*, 1976, Index issue.

[5] G. P. C. Dick, H. C. S. Wood, and W. R. Logan, *J. Chem. Soc.*, 1956, 2131.

[6] R. B. Angier, *J. Org. Chem.*, 1963, **28**, 1398.

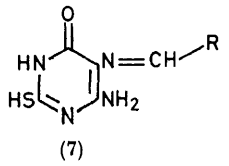
[7] W. Pfleiderer and H.-U. Blank, *Angew. Chem.*, 1968, **80**, 534.

[8] M. Higuchi, T. Nagamura, and F. Yoneda, *Heterocycles*, 1976, **4**, 977.

[9] A. Padwa, S. Clough, M. Dharan, J. Smolanoff, and S. I. Wetmore, *J. Amer. Chem. Soc.*, 1972, **94**, 1395.

[10] F. Yoneda, M. Higuchi, and M. Kawamura, *Heterocycles*, 1976, **4**, 1659.

ideneamino-1,3-dimethyluracils (1a, b, f, and h) with an excess of dimethylformamide diethyl acetal in ethanol (Table 4). Thermolysis of compounds (6) in tetramethylene sulphone gave the corresponding 1,3-dimethyl-lumazines (2a, b, f, and h) *via* intramolecular cycloaddition with subsequent aromatization by elimination of dimethylamine (evolution of which was observed), albeit in lower yields.



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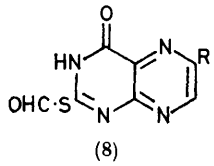
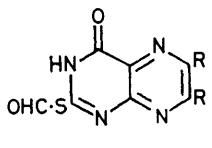
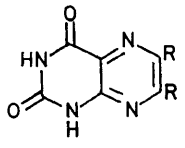


(8)

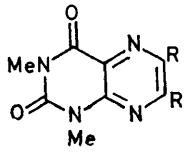
	M.p. (°C); yield (%) of (7)	M.p. (°C); yield (%) of (8)
a; R = Ph	350 (decomp.); 80	285; 73
b; R = 4-ClC_6H_4	281; 76	282; 82
c; R = 3,4-$Cl_2C_6H_3$	282; 78	246; 80
d; R = 4-MeC_6H_4	269 (decomp.); 88	271; 78
e; R = 4-MeO·C_6H_4	266; 80	258; 82
f; R = 3,4-$(CH_2O_2)C_6H_3$	273; 89	270; 70



(9)



(10)



(11)

a; R = 4-ClC_6H_4
b; R = 3,4-$Cl_2C_6H_3$
c; R = 3,4-$(CH_2O_2)C_6H_3$

The new synthesis of 6-arylpteridines appears to be general and is equally applicable to the 5-*N*-benzylidene derivatives of other 5,6-diaminopyrimidines. For example, 5,6-diamino-4-hydroxy-2-mercaptopyrimidine was condensed with aromatic aldehydes in dimethylformamide to give the corresponding 5-*N*-benzylidene derivatives (7a—f) (Table 2), which were likewise treated with triethyl orthoformate (*ca.* 10 equiv.) in dimethylformamide to give the respective 6-aryl-2-formylthio-4-hydroxypteridines (8a—f) (Table 3). Heating compounds (8a—f) with concentrated hydrochloric acid in ethanol or refluxing them in formic acid gave the corresponding 6-aryl-lumazines (2), identical with samples prepared as described above.

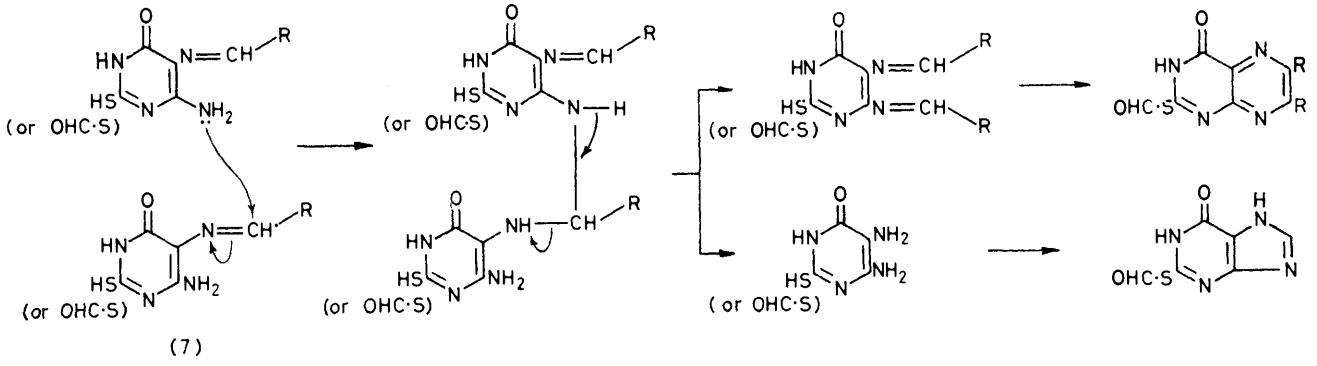
When a smaller excess of triethyl orthoformate (3 equiv.) was used in the above intramolecular cyclization of (7), the corresponding 6,7-diaryl-2-formylthio-4-hydroxypteridines (9) were obtained along with 2-formylthio-4-hydroxypurine. Hydrolysis of compounds (9a—c) with hydrochloric acid in ethanol gave the corresponding 6,7-diaryl-lumazines (10a—c). Methylation of (10a—c) with methyl iodide and potassium carbonate in dimethylformamide afforded the respective 6,7-diaryl-1,3-dimethyl-lumazines (11a—c), identical with authentic samples.[8] The formation of compounds (9) is rationalized in terms of initial nucleophilic attack of the 6-amino-group of (7) on the anil carbon atom of another molecule of (7). Subsequent nitrogen–carbon bond cleavage accompanying hydrogen transfer affords 5,6-bisbenzylideneamino- and 5,6-diamino-pyrimidines. The former could then be cyclized, dehydrogenated, and formylated to give 6,7-diaryl-2-formylthio-4-hydroxypteridines (9). The diaminopyrimidines should yield 2-formylthio-4-hydroxypurine with triethyl orthoformate. Analogous disproportionation has been observed in the reaction of 6-amino-5-benzylideneamino-1,3-dimethyluracils with formamide.[8]

EXPERIMENTAL

M.p.s were obtained with a Yanagimoto micro apparatus. N.m.r. spectra were determined with a JEOL JNM 3H-60 spectrometer (tetramethylsilane as internal standard), and i.r. spectra (KBr discs) with a JASCO DS-701 G spectrometer.

6-*Amino-5-benzylideneaminouracils* (1a—i'); *General Procedure*.—A suspension of a 5,6-diaminouracil (0.06 mol) and an aromatic aldehyde (0.07 mol) in ethanol (40 ml) or dimethylformamide (40 ml) was refluxed for 3—4 h. After cooling, the crystals were filtered off, washed with hot water, and recrystallized from ethanol [for (1a—m)] or dimethylformamide [for (1n—i')].

6-*Aryl-lumazines* (2a—i'); *General Procedure*.—To a solution of compound (1) (0.02 mol) in dimethylformamide (25 ml) was added triethyl orthoformate (15 g, 0.1 mol), and the mixture was refluxed for 10 h. After cooling, the crystals were filtered off and recrystallized from ethanol [for (2a—m)] or dimethylformamide [for (2n—i')]. The



SCHEME 2

n.m.r. spectra (trifluoroacetic acid) showed sharp singlets for the C-7 protons at δ 8.9—9.5. M.p.s and yields are indicated in Scheme 1.

Methylation of Compounds (2n—i'); *General Procedure.*—A mixture of the 6-aryl-lumazine (2) (0.001 mol), methyl iodide (1.4 g, 0.01 mol), and potassium carbonate (0.5 g) in dimethylformamide (10 ml) was refluxed for 2 h. Concentration to a small volume and dilution with water precipitated crystals, which were filtered off and recrystallized from ethanol to give the corresponding 1,3-dimethyl-lumazines in 80—90% yields.

5-(3,4-*Dimethoxybenzylideneamino*)-6-(α-*ethoxyethylideneamino*)-1,3-*dimethyluracil* (4b).—A mixture of compound (1g) (1.6 g, 0.005 mol) and triethyl orthoacetate (8 g, 0.05 mol) in dimethylformamide (10 ml) was refluxed for 8 h. The precipitate was filtered off and the filtrate was evaporated *in vacuo* to dryness; the residue was treated with ether to separate yellow crystals, which were filtered off. Recrystallization from ethanol gave pale yellow *needles* (1.61 g, 83%), m.p. 159° (Found: C, 58.6; H, 6.45; N, 14.2. $C_{19}H_{24}N_4O_5$ requires C, 58.75; H, 6.25; N, 14.45%).

6-(α-*Ethoxyethylideneamino*)-5-(4-*methoxybenzylideneamino*)-1,3-*dimethyluracil* (4a).—Similarly condensation of (1f) (1.4 g, 0.005 mol) and triethyl orthoacetate (8 g, 0.05 mol) in dimethylformamide (10 ml) gave the *product* (4a) as pale yellow needles (1.41 g, 79%), m.p. 153° (Found: C, 60.15; H, 6.3; N, 15.45. $C_{18}H_{22}N_4O_4$ requires C, 60.3; H, 6.2; N, 15.65%).

6-(3,4-*Dimethoxyphenyl*)-1,3,7-*trimethyl-lumazine* (5b).—A solution of compound (4b) (1 g, 0.002 6 mol) in tetramethylene sulphone (3 ml) was heated at 220 °C for 7 h. After cooling, the mixture was diluted with water and set aside overnight at room temperature. The crystals which separated were filtered off, washed with water, and dried. Recrystallization from dimethylformamide gave a pale yellow *powder* (0.51 g, 58%), m.p. 319°, M^+ 342, $\nu_{max.}$ (KBr) 1 691s, 1 636s, 1 598m, 1 560w, and 1 513s cm^{-1} (Found: C, 59.85; H, 5.15; N, 16.15. $C_{17}H_{18}N_4O_4$ requires C, 59.65; H, 5.3; N, 16.35%).

6-(4-*Methoxyphenyl*)-1,3,7-*trimethyl-lumazine* (5a).—This was similarly prepared by heating (4a) (1 g, 0.002 8 mol) in tetramethylene sulphone (3 ml). Recrystallization from dimethylformamide gave a pale yellow *powder* (0.6 g, 69%), m.p. 338°, M^+ 312, $\nu_{max.}$ (KBr) 1 688s, 1 639s, 1 603m, 1 572w, 1 545m, and 1 512m cm^{-1} (Found: C, 61.45; H, 5.0; N, 17.75. $C_{16}H_{16}N_4O_3$ requires C, 61.55; H, 5.15; N, 17.95%).

5-*Benzylideneamino*-6-*dimethylaminomethyleneamino*-1,3-*dimethyluracils* (6a—d); *General Procedure.*—A solution of compound (1) (0.005 mol) and dimethylformamide diethyl acetal (1.5 g, 0.01 mol) in ethanol (10 ml) was refluxed for 4 h and set aside overnight. The crystals which separated were filtered off and recrystallized from ethanol to give yellow needles. Compounds (6a—d) were thus prepared from (1a, b, f, and h).

Thermal Cyclization of Compounds (6) *to* 1,3-*Dimethyl-lumazines* (2); *General Procedure.*—A solution of compound (6a—d) (0.002 mol) in tetramethylene sulphone (3 ml) was heated at 200 °C for 3 h; dimethylamine was evolved. The mixture was diluted with water and set aside overnight. The crystals were filtered off, washed with water, and recrystallized from ethanol to give the corresponding 1,3-dimethyl-lumazines (2a, b, f, and h).

6-*Amino*-5-*benzylideneamino*-4-*hydroxy*-2-*mercaptopyrimidines* (7a—f); *General Procedure.*—A suspension of 5,6-diamino-4-hydroxy-2-mercaptopyrimidine (0.05 mol) and an aromatic aldehyde (0.06 mol) in dimethylformamide (30 ml) and acetic acid (10 ml) was refluxed for 3 h. After cooling, the crystals were filtered off, washed with hot water, and recrystallized from dimethylformamide to give complexes of the products (7) with dimethylformamide.

6-*Aryl*-2-*formylthio*-4-*hydroxypteridines* (8—f); *General Procedure.*—A mixture of compound (7a—f) (0.01 mol) in triethyl orthoformate (15 g, 0.1 mol) and dimethylformamide (25 ml) was refluxed for 10 h, then evaporated *in vacuo*, and the residue was crushed in water. The solid was filtered off and recrystallized from ethanol several times to give a yellow powder.

Hydrolysis of Compounds (8a—f) *to* 6-*Aryl-lumazines* (2); *General Procedure.*—A mixture of compound (8) (0.002 mol) and concentrated hydrochloric acid (3 ml) in ethanol (10 ml) was refluxed for 1 h, then evaporated to dryness. The residue was washed with water and dried. Recrystallization from dimethylformamide gave the corresponding 6-aryl-lumazine (2), identical with the authentic material described above.

6,7-*Diaryl*-2-*formylthio*-4-*hydroxypteridines* (9a—c); *General Procedure.*—A mixture of 6-amino-5-benzylideneamino-4-hydroxy-2-mercaptopyrimidine (7) (0.01 mol) and triethyl orthoformate (4.4 g, 0.03 mol) in dimethylformamide (25 ml) was refluxed for 10 h. The precipitate of 6-hydroxy-2-mercaptopurine and its formyl derivative were filtered off, the filtrate was evaporated into dryness, and the residue was crushed in water. The solid was filtered off and recrystallized from ethanol. By this method were obtained the 6,7-*bis*-(4-*chlorophenyl*) *derivative* (9a) [m.p. 215°; 40%; $\nu_{max.}$ (KBr) 1 686br,s, 1 595w, 1 564m, and 1 528w cm^{-1} (Found: C, 53.3; H, 2.3; N, 13.15. $C_{19}H_{10}Cl_2N_4O_2S$ requires C, 53.15; H, 2.35; N, 13.05%)]; the 6,7-*bis*-(3,4-*dichlorophenyl*) *derivative* (9b) [m.p. 260° (decomp.); 40%; $\nu_{max.}$ (KBr) 1 680br,s, 1 562m, 1 548m, and 1 533m cm^{-1} (Found: C, 45.65; H, 1.75; N, 10.95. $C_{19}H_8Cl_4N_4O_2S$ requires C, 45.8; H, 1.6; N, 11.25%)]; and the 6,7-*bis*-(3,4-*methylenedioxyphenyl*) *derivative* (9c) [m.p. 250° (decomp.); 42%; $\nu_{max.}$ (KBr) 1 690br,s, 1 562m, 1 547m, 1 523w, and 1 500m cm^{-1} (Found: C, 56.3; H, 2.85; N, 12.35. $C_{21}H_{12}N_4O_6S$ requires C, 56.25; H, 2.7; N, 12.5%)].

We thank Misses N. Kawano and J. Iwamoto for technical assistance, and Mrs. K. Shiraki, Mr. K. Takeda, and Miss Y. Kimura for microanalytical and spectral data. Financial support from the Ministry of Education of Japan is acknowledged.

[6/2307 *Received*, 20*th December*, 1976]