Synthesis of Purines by Cyclization of the Michael-type Adducts from 6-Aminopyrimidines and 4-Phenyl-1,2,4-triazoline-3,5-dione

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Treatment of 6-amino- and 6-alkylamino-uracils with 4-phenyl-1,2,4-triazoline-3,5-dione (PTAD) gave Michael-type adducts, *viz.* 6-amino- (1) and 6-alkylamino-5-(3,5-dioxo-4-phenyl-1,2,4-triazolin-1-yl)uracils (2). The oxidative cyclization of (2) with nitrobenzene gave the corresponding xanthine derivatives, which were also obtained by the condensation of (1) with the aromatic aldehydes. The Michael-type adducts from 2-methyl- and 2-phenyl-6-alkylamino-4-hydroxypyrimidines and PTAD gave the corresponding 9-alkylpurine-6,8(1*H*,7*H*)-diones, by direct cyclization upon treatment with nitrobenzene.

4-PHENYL-1,2,4-TRIAZOLINE-3,5-DIONE (PTAD) reacts readily with 6-anilinouracil derivatives to give the corresponding Michael-type adducts, *viz.* 6-anilino-5-(3,5-dioxo-4-phenyl-1,2,4-triazolin-1-yl)uracils.[1] These adducts are useful starting materials for the preparation of alloxazines.[2]

We now report a new synthetic route to purine derivatives, in which PTAD is also effective as a nitrogen source for N-7 of the purine ring.[3] Stirring 6-aminopyrimidines unsubstituted in position 5 with PTAD, in dioxan at room temperature, gave high yields of the corresponding Michael-type adducts. By this method, 6-amino- (1a and b) and 6-alkylamino-5-(3,5-dioxo-1,2,4-triazolin-1-yl)uracils (1c—g), and 2-methyl- and 2-phenyl-6-alkylamino-5-(3,5-dioxo-1,2,4-triazolin-1-yl)-4-hydroxypyrimidines (2a—e) were obtained (Tables 1 and 2.)†

The starting materials for the adducts (2a—e), *viz.* 2-methyl- and 2-phenyl-6-alkylamino-4-hydroxypyrimidines (6a—e), were prepared by condensation of 6-chloropyrimidines with alkylamines in n-butyl alcohol (Table 4).†

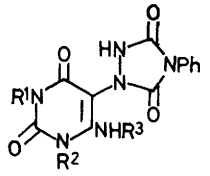
Treatment of compounds (1c and d) with nitrobenzene under gentle reflux caused oxidative cyclization to give the corresponding xanthines (3a and f) in 50 and 75% yields, respectively. Nitrobenzene probably abstracts two hydrogen atoms from the adducts to give the 6-anil intermediates (7), which could well cyclize to give the corresponding xanthine derivatives (3a and f).[4] However, compounds (1e—g) did not give the corresponding xanthines in nitrobenzene.

To support the above mechanism, we examined the condensation of 6-amino-5-(3,5-dioxo-4-phenyl-1,2,4-triazolin-1-yl)uracils with aromatic aldehydes, which would presumably give the anil intermediates (7). Thus, heating (1a and b) with several aromatic aldehydes under the conditions indicated in Table 3 yielded the respective xanthine derivatives (3a—h).[4,5]

† Tables 1, 2, and 4 [analytical data for compounds (1), (2), and (6); i.r. data for (1) and (2)] are available as Supplementary Publication No. SUP 22123 (4 pp.). For details of Supplementary Publications see Notice to Authors No. 7, *J.C.S. Perkin I*, 1976, Index issue.

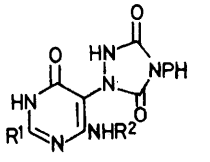
[1] F. Yoneda, S. Matsumoto, and Y. Sakuma, *Chem. and Pharm. Bull. (Japan)*, 1975, **23**, 2425.
[2] F. Yoneda, Y. Sakuma, T. Nagamatsu, and S. Mizumoto, *J.C.S. Perkin I*, 1976, 2398.
[3] Preliminary report, F. Yoneda, S. Matsumoto, and M. Higuchi, *J.C.S. Chem. Comm.*, 1974, 551.
[4] F. Yoneda and T. Nagamatsu, *J.C.S. Perkin I*, 1976, 1547.
[5] F. Yoneda, M. Higuchi, and T. Nagamatsu, *J. Amer. Chem. Soc.*, 1974, **96**, 5607.

Heating compounds (2c—e) in nitrobenzene gave the corresponding 9-alklypurine-6,8(1*H*,7*H*)-diones (4a—c);



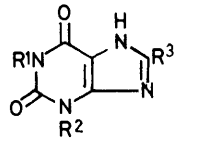
(1)

	M.p. (°C)	Yield (%)
a; $R^1 = R^2 = Me$, $R^3 = H$	241	91
b; $R^1 = R^3 = H$, $R^2 = Me$	244	89
c; $R^1 = R^2 = Me$, $R^3 = CH_2Ph$	248	90
d; $R^1 = H$, $R^2 = Me$, $R^3 = CH_2Ph$	260	74
e; $R^1 = R^3 = Me$, $R^2 = H$	215	77
f; $R^1 = Me$, $R^2 = H$, $R^3 = Pr^n$	214	88
g; $R^1 = Me$, $R^2 = H$, $R^3 = Bu^n$	267	70



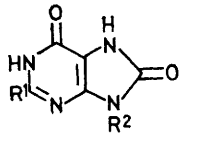
(2)

	M.p. (°C)	Yield (%)
a; $R^1 = Me$, $R^2 = Pr^n$	281	87
b; $R^1 = Me$, $R^2 = Bu^n$	251	70
c; $R^1 = Me$, $R^2 = CH_2Ph$	278	95
d; $R^1 = Me$, $R^2 = [CH_2]_2Ph$	270	85
e; $R^1 = Ph$, $R^2 = CH_2Ph$	330	94



(3)

a; $R^1 = R^2 = Me$, $R^3 = Ph$
b; $R^1 = R^2 = Me$, $R^3 = p\text{-}ClC_6H_4$
c; $R^1 = R^2 = Me$, $R^3 = 3,4\text{-}Cl_2C_6H_3$
d; $R^1 = R^2 = Me$, $R^3 = p\text{-}MeOC_6H_4$
e; $R^1 = R^2 = Me$, $R^3 = p\text{-}(Me)_2NC_6H_4$
f; $R^1 = H$, $R^2 = Me$, $R^3 = Ph$
g; $R^1 = H$, $R^2 = Me$, $R^3 = p\text{-}ClC_6H_4$
h; $R^1 = H$, $R^2 = Me$, $R^3 = 3,4\text{-}Cl_2C_6H_3$



(4)

a; $R^1 = Me$, $R^2 = CH_2Ph$
b; $R^1 = Me$, $R^2 = [CH_2]_2Ph$
c; $R^1 = Ph$, $R^2 = CH_2Ph$

in these cases PTAD becomes the amide source for the 7- and 8-positions of the final products. This implies that compounds of type (2) resist dehydrogenation with nitrobenzene to anil intermediates such as (7), and direct cyclization takes place predominantly.

TABLE 3

Xanthine formation by reaction of 6-amino-5-(3,5-dioxo-4-phenyl-1,2,4-triazolin-1-yl)uracils (Michael-type adducts) and aromatic aldehydes (RCHO)

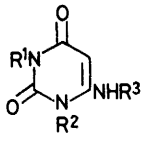
Adduct	R	Temp. (°C)	Time (h)	Product [a]	Yield (%)
(1a)	Ph	180	1	(3a)	70
(1a)	$p\text{-}ClC_6H_4$	180	1.5	(3b)	76
(1a)	$3,4\text{-}Cl_2C_6H_3$	180	0.5	(3c)	82
(1a)	$p\text{-}MeO\cdot C_6H_4$	180	1	(3d)	72
(1a)	$p\text{-}Me_2N\cdot C_6H_4$	140	3	(3e)	35
(1b)	Ph	230	3	(3f)	68
(1b)	$p\text{-}ClC_6H_4$	230	1	(3g)	75
(1b)	$3,4\text{-}Cl_2C_6H_3$	230	1	(3h)	78

[a] None of these compounds melted below 330 °C.

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 disc) with a JASCO IRA-1 spectrometer.

Starting 6-alkylaminouracils (5c—g) were prepared according to the literature.[6,7]



(5)

a; $R^1 = R^2 = Me$, $R^3 = H$
b; $R^1 = R^3 = H$, $R^2 = Me$
c; $R^1 = R^2 = Me$, $R^3 = CH_2Ph$
d; $R^1 = H$, $R^2 = Me$, $R^3 = CH_2Ph$
e; $R^1 = R^3 = Me$, $R^2 = H$
f; $R^1 = Me$, $R^2 = H$, $R^3 = Pr^n$
g; $R^1 = Me$, $R^2 = H$, $R^3 = Bu^n$

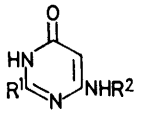
6-Amino-5-(3,5-dioxo-1,2,4-triazolin-1-yl)pyrimidines (1) *and* (2). *General Procedure.*—To a suspension of a 6-aminopyrimidine (0.01 mol) in dioxan (30 ml) was added PTAD [8,9] (0.01 mol), and the mixture was stirred at room temperature (the colour changed from red to white or pale yellow). After 1 h, the precipitate was filtered off, washed with hot water, and dried. Recrystallization from dimethylformamide gave white *crystals* (Tables 1 and 2).

6-Chloro-4-hydroxy-2-methylpyrimidine.[10]—To a mixture of concentrated hydrochloric acid (30 ml) and n-butyl alcohol (50 ml) was added 4,6-dichloro-2-methylpyrimidine (4.9 g, 0.03 mol) and the mixture was refluxed for 3 h. After cooling, the crystals were filtered off, washed with water, and dried. Recrystallization from ethanol gave *needles* (60%), m.p. 235°, M^+ 144 (Found: C, 41.35; H, 3.55; N, 19.2. $C_5H_5ClN_2O$ requires C, 41.55; H, 3.5; N, 19.4%).

6-Alkylamino-4-hydroxy-2-methylpyrimidines (6a—d). *General Procedure.*—A mixture of 6-chloro-4-hydroxy-2-methylpyrimidine (14.46 g, 0.1 mol) and an alkylamine

[6] H. Goldner, G. Dietz, and E. Carstens, *Annalen*, 1966, **691**, 142.
[7] F. Yoneda and T. Nagamatsu, *J.C.S. Perkin I*, 1976, 1547.
[8] R. Stollé, *Ber.*, 1912, **45**, 273.
[9] W. Ried and S. H. Lim, *Annalen*, 1973, 129.
[10] (*a*) F. R. Basford, F. H. S. Curd, and F. L. Rose, *J. Chem. Soc.*, 1946, 713; (*b*) H. R. Henze, W. J. Clegg, and C. W. Smart, *J. Org. Chem.*, 1952, **17**, 1320.

(0.22 mol) in n-butyl alcohol (100 ml) was refluxed for 4 h. After cooling, the crystalline material was collected by filtration, washed with water, and recrystallized from ethanol to give *needles* (Table 4).



(6)

	M.p. (°C)	Yield (%)
a; R^1 = Me, R^2 = Pr^n	198	81
b; R^1 = Me, R^2 = Bu^n	179	77
c; R^1 = Me, R^2 = CH_2Ph	243	76
d; R^1 = Me, R^2 = $[CH_2]_2Ph$	244	97
e; R^1 = Ph, R^2 = CH_2Ph	231	70

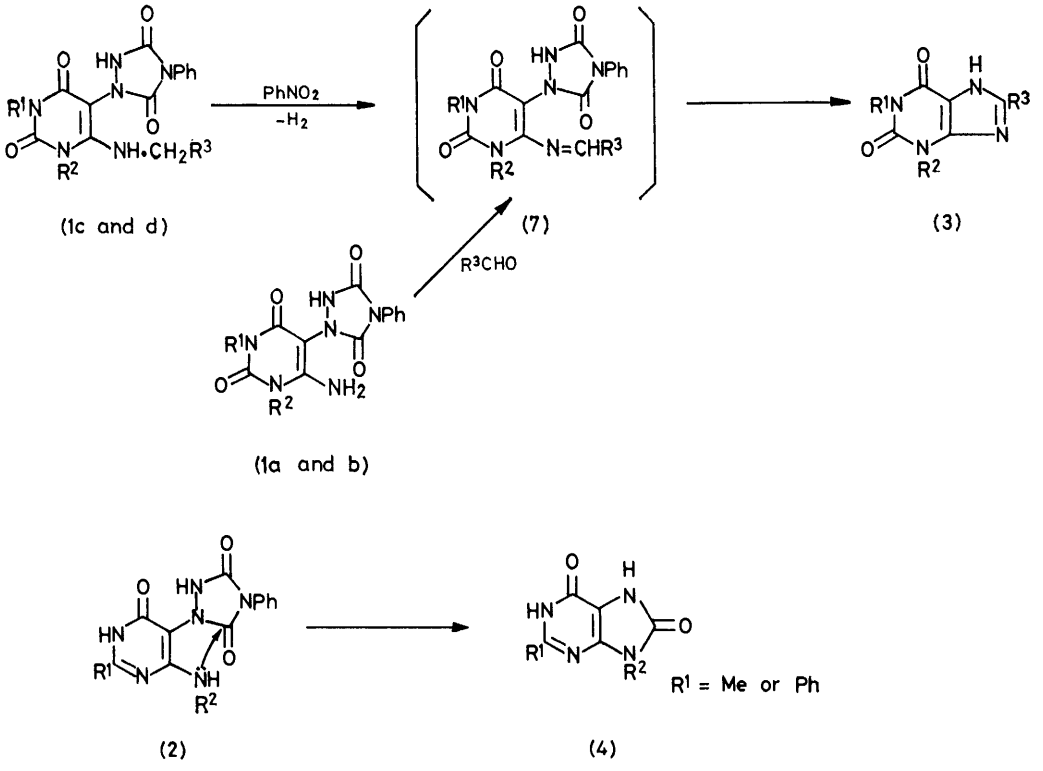
6-Benzylamino-4-hydroxy-2-phenylpyrimidine (6e).—6-Chloro-4-hydroxy-2-phenylpyrimidine [11] (3.7 g, 0.018 mol) and benzylamine (4.3 g, 0.04 mol) in n-butyl alcohol (20 ml) were refluxed for 4 h. The benzylamine hydrochloride was filtered off and the filtrate was diluted with water to precipitate the *benzylamino-derivative* (70%), m.p. 231° (from ethanol), M^+ 277 (Found: C, 73.5; H, 5.4; N, 14.9. $C_{17}H_{15}N_3O$ requires C, 73.65; H, 5.45; N, 15.15%).

Oxidative Cyclization of the Adducts (1c *and* d) *with Nitrobenzene to the Xanthines* (3a *and* f).—The adducts (1c and d) (0.005 mol) were heated in nitrobenzene (10 ml) or in a mixture of nitrobenzene (5 ml) and tetramethylene sulphone (5 ml) under mild reflux for 6 h. The mixture was concentrated to a small volume, diluted with ethanol, and set aside overnight. Recrystallization of the resulting crystals from dimethylformamide gave the xanthines (3a and f) in 50 and 75% yields, respectively.

Synthesis of Xanthines (3a—h) *by Condensation of the Adducts* (1a *and* b) *with Aromatic Aldehydes. General Procedure.*—A mixture of the adduct (1a or b) (0.01 mol) and the aldehyde (0.03 mol) was heated under the conditions indicated in Table 3 After cooling, the mixture was crushed in ethanol. The crystals which separated were filtered off and washed with ethanol. Recrystallization from dimethylformamide or ethanol gave the corresponding xanthines (3a—h).[4,5] By this method, 8-(p-*dimethylaminophenyl*)-*theophylline* (3e) was synthesized, M^+ 299 (Found: C, 60.5; H, 5.6; N, 23.45. $C_{15}H_{17}N_5O_2$ requires C, 60.2; H, 5.7; N, 23.4%).

9-Benzyl-2-phenylpurine-6,8(1H,7H)-dione (4c)—The adduct (2e) (1.36 g, 0.003 mol) in nitrobenzene (5 ml) and tetramethylene sulphone (5 ml) was heated under mild reflux for 3 h. The mixture was concentrated to a small volume, diluted with ethanol, and set aside overnight. Recrystallization of the resulting crystals from dimethylformamide gave the *purine*, m.p. >330°, $\nu_{max.}$ (Nujol) 1 719, 1 680, and 1 550 cm^{-1}, δ (CF_3CO_2H) 5.35 (benzylic H), M^+ 318 (Found: C, 67.75; H, 4.4; N, 17.55. $C_{18}H_{14}N_4O_2$ requires C, 67.9; H, 4.45; N, 17.6%).

9-Benzyl-2-methylpurine-6,8(1H,7H)-dione (4a)—The adduct (2c) (1.17 g, 0.003 mol) in nitrobenzene (5 ml) and tetramethyl sulphone (5 ml) was treated as above and the product recrystallized from dimethylformamide to give the *purine* (54%), m.p. >330°, $\nu_{max.}$ (Nujol) 1 720, 1 680, 1 660sh, and 1 580 cm^{-1}, M^+ 256 (Found: C, 61.05; H, 4.8; N, 21.65. $C_{13}H_{12}N_4O_2$ requires C, 60.95; H, 4.7; N, 21.85%).



[11] (*a*) F. Yoneda and T. Nagamatsu, *J.C.S. Perkin I*, 1976, 1550; (*b*) H. C. Carrington, F. H. S. Curd, and D. N. Richardson, *J. Chem. Soc.*, 1955, 1858.

2-*Methyl*-9-*phenethylpurine*-6,8(1H,7H)-*dione* (4b), similarly prepared (48%) had m.p. >330° (from dimethylformamide); $\nu_{max.}$ (Nujol) 1 709, 1 665, and 1 580 cm^{-1}, M^+ 270 (Found: C, 62.35; H, 5.25; N, 20.45. $C_{14}H_{14}N_4O_2$ requires C, 62.75; H, 5.2; N, 20.75%).

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