Purines, Pyrimidines, and Imidazoles. Part 61.[1] Reaction of 6-Alkylamino-4-chloro-5-nitropyrimidines with Diethyl Malonate, Ethyl Cyanoacetate, and Ethyl Acetoacetate and some derived Pyrrolo[3,2-*d*]pyrimidines related to the Cytokinins

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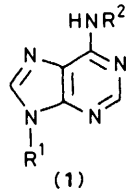
Reaction of 4-chloro-6-methylamino-5-nitropyrimidine (**3d**) with diethyl malonate and sodium hydroxide afforded diethyl 6-methylamino-5-nitropyrimidin-4-ylmalonate which was reduced to diethyl 5-amino-6-methylaminopyrimidin-4-ylmalonate and this, with sodium carbonate, produced ethyl 6,7-dihydro-4-methylamino-6-oxo-5*H*-pyrrolo[3,2-*d*]pyrimidine-7-carboxylate. Ethyl cyanoacetate and ethyl acetoacetate with (**3d**) and alkali similarly afforded ethyl 6-methylamino-5-nitropyrimidin-4-ylcyano (or aceto) acetate respectively. The latter compound when reduced afforded ethyl 5-amino-6-methylaminopyrimidin-4-ylacetate (**4e**) which was also obtained by treatment of ethyl α-(6-methylamino-5-nitropyrimidin-4-yl)acetoacetate with aqueous ammonia to give ethyl 6-methylamino-5-nitropyrimidin-4-ylacetate, followed by subsequent hydrogenation of this compound. Cyclisation of (**4e**) with phosphoryl trichloride and dimethylformamide gave, after hydrolysis, 4-methylamino-5*H*-pyrrolo[3,2-*d*]pyrimidine-7-carboxylic acid (**2g**). 4-[(*trans*)-4-t-Butoxy-3-methylbut-2-enylamino)-6-chloro-5-nitropyrimidine in a similar sequence of reactions gave the cytokinin analogue 4-(4-hydroxy-3-methylbutylamino)-5*H*-pyrrolo[3,2-*d*]pyrimidine-7-carboxylic acid (**2j**).

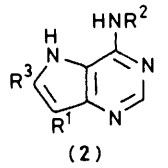
The cytokinins are a group of substances which stimulate cell division in plant tissues. They are largely 6-alkylaminopurines (**1**) and include several naturally occurring substances such as *trans*-zeatin (**1a**),[2–4] dihydrozeatin (**1b**),[5] and the related isopentenyl derivative (**1c**)[6] which also occur as 9-β-D-ribofuranosides such as zeatin riboside (**1d**).[4] In addition, several simple 6-alkylaminopurines have marked cytokinin activity[7] including 6-benzylamino-, 6-furfurylamino-, and 6-pentylamino-purines. As part of a programme designed to prepare compounds structurally related to the cytokinins with potential as anti-cytokinins we have been especially interested to synthesise specific pyrrolo[3,2-*d*]pyrimidines (**2**), which are 9-deaza derivatives of the cytokinins, by a method which would ultimately permit the synthesis of 7-substituted † glycosides (**2a**) which are isosteres of the naturally occurring cytokinin 9-substituted nucleosides. Recently, syntheses of the inosine,[8] adenosine,[9] and guanosine[10] analogues of compounds (**2**) have been recorded from pyrrole intermediates.

An early route[11] to the pyrrolo[3,2-*d*]pyrimidine structure involved the condensation of various 2,6-substituted 4-chloro-5-nitropyrimidines with diethyl malonate in the presence of sodium hydroxide followed by reduction of the resulting pyrimidinylmalonate to the corresponding aminopyrimidines [(**4**), R^3 = alkyl, R^2 = $CH(CO_2Et)_2$] and cyclisation of these to pyrrolo[3,2-*d*]pyrimidines. However, the compound we wished to use, namely 4,6-dichloro-5-nitropyrimidine (**3a**) with a free 2-position, was found[12] to behave anomalously with diethyl malonate and produced the 2-substituted pyrimidine (**4a**) in which the nitro group is reduced during the reaction. Similar reactions occurred with anions derived from ethyl acetoacetate and acetylacetone. The problem has been overcome in one example[13] by reaction of the dichloro derivative (**3a**) with ketene diethyl acetal to afford the 2,2-diethoxyvinyl derivative (**3b**) which, after hydrolysis, gave the ester (**3c**) which, after amination and reduction, produced the diaminopyrimidine (**4b**) which was in turn cyclised with phosphoryl trichloride in dimethylformamide (DMF) to the pyrrolo[3,2-*d*]pyrimidines (**2b**) or (**2c**).



(1)

a; R^1 = H, R^2 = *trans*-$CH_2CH{=}CMe{\cdot}CH_2OH$
b; R^1 = H, R^2 = $CH_2CH_2CHMe{\cdot}CH_2OH$
c; R^1 = H, R^2 = $CH_2CH{=}CMe_2$
d; R^1 = β-D-ribofuranosyl, R^2 = *trans*-$CH_2CH{=}CMe{\cdot}CH_2OH$

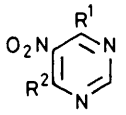


(2)

a; R^1 = glycosyl, R^2 = *trans*-$CH_2CH{=}CMe{\cdot}CH_2OH$, R^3 = H
b; R^1 = CO_2Et, R^2 = R^3 = H
c; R^1 = R^2 = H, R^3 = OH
d; R^1 = CO_2Et, R^2 = Me, R^3 = OH
e; R^1 = H, R^2 = Me, R^3 = OH
f; R^1 = CO_2Et, R^2 = Me, R^3 = H
g; R^1 = CO_2H, R^2 = Me, R^3 = H
h; R^1 = CO_2Et, R^2 = $CH_2C_6H_4OMe$-*p*, R^3 = H
i; R^1 = CO_2Et, R^2 = $CH_2CH_2CH(Me)CH_2OCMe_3$, R^3 = H
j; R^1 = CO_2H, R^2 = $CH_2CH_2CH(Me)CH_2OH$, R^3 = H

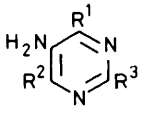
This route does not offer an obvious opportunity to introduce a glycosyl unit so we have re-examined the earlier route in the hope of introducing a malonate or similar residue into the desired 6-position which would ultimately permit *C*-

† Pyrrolo[3,2-*d*]pyrimidine systematic numbering.



(3)

a; $R^1 = R^2 = Cl$
b; $R^1 = Cl$, $R^2 = CH{=}C(OEt)_2$
c; $R^1 = Cl$, $R^2 = CH_2CO_2Et$
d; $R^1 = NHMe$, $R^2 = Cl$
e; $R^1 = NHMe$, $R^2 = CH(CO_2Et)_2$
f; $R^1 = NHMe$, $R^2 = CH(CN)CO_2Et$
g; $R^1 = NHMe$, $R^2 = CH(COMe)CO_2Et$
h; $R^1 = NHMe$, $R^2 = CH_2CO_2Et$
i; $R^1 = NHCH_2Ph$, $R^2 = CH_2CO_2Et$
j; $R^1 = NHCH_2C_6H_4OMe{-}p$, $R^2 = CH_2CO_2Et$
k; $R^1 = trans{-}NHCH_2CH{=}CMe\cdot CH_2OCMe_3$, $R^2 = Cl$
l; $R^1 = trans{-}NHCH_2CH{=}CMe\cdot CH_2OCMe_3$, $R^2 = CH(COMe)CO_2Et$
m; $R^1 = trans{-}NHCH_2CH{=}CMe\cdot CH_2OCMe_3$, $R^2 = CH_2CO_2Et$



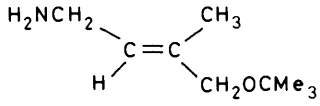
(4)

a; $R^1 = R^2 = Cl$, $R^3 = CH(CO_2Et)_2$
b; $R^1 = NH_2$, $R^2 = CH_2CO_2Et$, $R^3 = H$
c; $R^1 = NHMe$, $R^2 = CH(CO_2Et)_2$, $R^3 = H$
d; $R^1 = NHMe$, $R^2 = CH(CN)CO_2Et$, $R^3 = H$
e; $R^1 = NHMe$, $R^2 = CH_2CO_2Et$, $R^3 = H$
f; $R^1 = NHCH_2C_6H_4OMe{-}p$, $R^2 = CH_2CO_2Et$, $R^3 = H$
g; $R^1 = NHCH_2CH_2CH(Me)CH_2OCMe_3$, $R^2 = CH_2CO_2Et$, $R^3 = H$

glycosylation to be attained on the malonate residue at this position.

It should be possible to modify the anomalous reaction of (**3a**) with the diethyl malonate anion described earlier,[12] and to diminish the potential positive charge at the 2-position of (**3a**) by replacing one of the chlorine atoms by an alkylamino group of the type required in the final cytokinin analogue. Accordingly, in preliminary experiments we have explored the reaction of 4-chloro-6-methylamino-5-nitropyrimidine (**3d**),[14] prepared from the dichloropyrimidine (**3a**) and methylammonium acetate, with diethyl malonate in acetone and aqueous sodium hydroxide at room temperature when replacement of the chlorine by a malonate residue readily occurred and an excellent yield of the required crystalline malonate derivative (**3e**) was obtained. Similar reactions of (**3d**) with anions derived from ethyl cyanoacetate and ethyl acetoacetate gave good yields of the corresponding derivatives (**3f**) and (**3g**) respectively. Hydrogenation of the malonate (**3e**) and cyanoacetate (**3f**) derivatives in ethanol solution with a palladium catalyst gave the corresponding aminopyrimidines (**4c**) and (**4d**) respectively, whereas in contrast the keto ester (**3g**) gave the pyrimidinylacetate derivative (**4e**), the weakly basic solution produced during the hydrogenation clearly being sufficient to cause fission of the acetyl group. The same compound was also prepared by treatment of the nitro keto ester (**3g**) with aqueous ammonia, when acyl fission readily occurred to produce the nitro ester (**3h**) which, after hydrogenation, then gave the ester (**4e**). This is an especially useful route to this last type of compound. Similar compounds prepared by the same route include the benzylamino (**3i**) and *p*-methoxybenzylamino (**3j**) nitropyrimidines and hydrogenation of the latter produced the diaminopyrimidine derivative (**4f**).

When the malonate derivative (**4c**) was heated with aqueous sodium carbonate the pyrrolo[3,2-*d*]pyrimidinone (**2d**) was readily obtained and converted by hot hydrochloric acid into the decarboxylated derivative (**2e**) which could also be produced directly from the ester (**4e**) and 6M-hydrochloric acid. Alternatively, cyclisation of the pyrimidinyl ester (**4e**) with phosphoryl trichloride in DMF gave the pyrrolo[3,2-*d*]-pyrimidine (**2f**) which, with acid, produced the carboxylic acid (**2g**). The related pyrrolo[3,2-*d*]pyrimidine (**2h**) was prepared in a similar fashion.



(5)

Reaction of the dichloronitropyrimidine (**3a**) with *trans*-4-amino-1-t-butoxy-2-methylbut-2-ene (**5**)[1] at 0 °C during 30 min gave the pyrimidine (**3k**) which smoothly reacted with ethyl acetoacetate in acetone and aqueous sodium hydroxide to produce the ester (**3l**). This was treated immediately with aqueous ammonia to give the ester (**3m**) which, with palladium catalyst and hydrogen, afforded the aminopyrimidine (**4g**) in high (74%) yield. This readily cyclised with phosphoryl trichloride and DMF to give the pyrrolo[3,2-*d*]pyrimidine (**2i**) which, with acid, produced the deblocked carboxylic acid (**2j**).

Experimental

Evaporations were carried out with a Buchi rotary evaporator, under water-pump vacuum with a flask temperature <40 °C. U.v. Absorption spectra were measured with a Unicam SP 800 spectrophotometer, ^1H n.m.r. spectra with a JOEL-MH-100 spectrometer (tetramethylsilane as internal standard), and mass spectra with an A.E.I. MS 902 spectrometer. Silica gel (0.05—0.20 mm; 325—370 mesh; Machery Nagel and Co.) was used for column chromatography and silica gel $60F_{254}$ 0.25 mm precoated glass plates (Merck) were used for t.l.c. with (A) chloroform–methanol (9:1), (B) toluene–ethyl acetate (7:3), (C) ethyl acetate–n-propyl alcohol–water (7:2:1), (D) toluene–ethyl acetate (9:1), or (E) chloroform–methanol (3:1) as development systems. Light petroleum refers to the fraction boiling in the range 40—60 °C.

Reaction of 4-*Chloro*-6-*methylamino*-5-*nitropyrimidine* (**3d**) *with Diethyl Malonate, Ethyl Cyanoacetate, and Ethyl Acetoacetate and Hydrogenation of the Products.*—The ester (3.9 mmol) was added to a solution of 4-chloro-6-methylamino-5-nitropyrimidine (0.5 g, 2.6 mmol) in acetone (25 ml) at 0 °C; 11M-sodium hydroxide (0.8 ml) was then added dropwise to the stirred mixture during 20 min and the colour of the mixture changed from yellow to red. It was set aside at room temperature for 30 min.

(a) *Diethyl malonate and ethyl acetoacetate.* Water (50 ml) and acetic acid (to pH 8) were added and the resultant solution was extracted with ether. The combined extracts were dried (anhyd. Na_2SO_4) and evaporated to dryness. The residue was evaporated several times with toluene to produce a yellow solid.

(b) *Ethyl cyanoacetate.* Water (20 ml) was added and the solution was extracted with ether (3 × 50 ml). The extracts were discarded. The aqueous phase, on treatment with acetic acid, gave a solid yellow precipitate. Thus prepared were: *diethyl* 6-*methylamino*-5-*nitropyrimidin*-4-*ylmalonate* (**3e**) (0.58 g) [from

method (a)] which crystallised from light petroleum (b.p. 40—60 °C) as needles, m.p. 78 °C (Found: C, 46.3; H, 5.0; N, 17.7%; M^+, 312. $C_{12}H_{16}N_4O_6$ requires C, 46.5; H, 5.16; N, 17.94%; *M*, 312); *m/z* 266 (*M* − NO_2); *ethyl α-cyano-α-(6-methylamino-5-nitropyrimidin-4-yl)acetate* (**3f**) (0.54 g) [from method (b)] which crystallised from methanol as needles, m.p. 216 °C (Found: C, 45.7; H, 4.3; N, 26.0%; M^+, 265. $C_{10}H_{11}N_5O_4$ requires C, 45.3; H, 4.2; N, 26.4%; *M*, 265); and *ethyl α-(6-methylamino-5-nitropyrimidin-4-yl)acetoacetate* (**3g**) (0.48 g) [from method (a)] which crystallised from toluene as needles, m.p. 146 °C (Found: C, 46.75; H, 4.95; N, 19.95%; M^+, 282. $C_{11}H_{14}N_4O_5$ requires C, 46.8; H, 5.0; N, 19.85%; *M*, 282). Solutions of (**3e**) (0.5 g), (**3f**) (0.5 g), and (**3g**) (0.05 g) in ethanol (15, 200, and 50 ml respectively) with 10% palladium–carbon (0.025, 0.1, and 0.025 g respectively) were shaken in hydrogen for 8 h after which time the reaction was complete [2 h in the case of (**3g**)]. The mixtures were filtered through Celite and the filtrates were evaporated to dryness and the residues triturated with ether to produce solids. Thus prepared were *diethyl 5-amino-6-methylaminopyrimidin-4-ylmalonate* (**4c**) (0.38 g) which crystallised from toluene as needles, m.p. 162 °C (Found: C, 51.5; H, 6.5; N, 19.7%; M^+, 282. $C_{12}H_{18}N_4O_4$ requires C, 51.05; H, 6.43; N, 19.85%; *M*, 282); *ethyl α-cyano-α-(5-amino-6-methylaminopyrimidin-4-yl)acetate hemihydrate* (**4d**) (0.3 g) which crystallised from water as prisms, m.p. 253 °C (Found: C, 49.4; H, 5.5; N, 28.3%; M^+, 235. $C_{10}H_{13}N_5O_2 \cdot \frac{1}{2}H_2O$ requires C, 49.2; H, 5.75; N, 28.7%; *M*, 235); $\nu_{max.}$ 2 180 cm^{-1} (CN); and *ethyl 5-amino-6-methylaminopyrimidin-4-ylacetate* (**4e**) (0.033 g) which crystallised from benzene as prisms, m.p. 172 °C (Found: C, 51.4; H, 6.7; N, 26.2%; M^+, 210. $C_9H_{14}N_4O_2$ requires C, 51.42; H, 6.71; N, 26.65%; *M*, 210). The latter compound (0.1 g) in 98% formic acid (5 ml) was heated on a steam-bath for 45 min after which time starting material had been replaced by a product (R_F 0.52, System E). The solution was evaporated to afford a gum which was purified by silica gel chromatography with chloroform–methanol (3:1) as eluant. Fractions corresponding to the product were combined and evaporated to leave a solid. *Ethyl 5-formamido-6-methylaminopyrimidin-4-ylacetate* (0.06 g) crystallised from benzene as needles, m.p. 153 °C (Found: C, 50.25; H, 5.8; N, 23.6%; M^+, 238. $C_{10}H_{14}N_4O_3$ requires C, 50.4; H, 5.9; N, 23.5%; *M*, 238).

Ethyl 6-Methylamino-5-nitropyrimidin-4-ylacetate (**3h**).—A suspension of ethyl α-(6-methylamino-5-nitropyrimidin-4-yl)-acetoacetate (**3g**) (3.5 g) in 2M-ammonium hydroxide (75 ml) was shaken at room temperature for 5 h. The resulting solid precipitate was collected, washed with water, and dried. The *pyrimidine* (**3h**) (3.07 g) crystallised from toluene as needles, m.p. 152 °C (Found: C, 45.5; H, 5.2; N, 23.2%; M^+, 240. $C_9H_{12}N_4O_4$ requires C, 45.0; H, 5.05; N, 23.35%; *M*, 240); $\nu_{max.}$ 1 740 cm^{-1} (CO); δ($CDCl_3$) 1.32 (3 H, t, CH_2CH_3), 3.3 (3 H, d, CH_3N), 4.23 (2 H, m, CH_2CH_3), 4.35 (2 H, s, CH_2CO), and 8.2 (1 H, s, 2-H).

Catalytic hydrogenation of compound (**3h**) (0.2 g) with palladium–carbon was complete in 4 h and gave ethyl 5-amino-6-methylaminopyrimidin-4-ylacetate (**4e**) (0.12 g), m.p. 172 °C, identical [i.r., t.l.c. (System A), and mass spectral analysis] with the sample prepared above. Similarly prepared were *ethyl 6-benzylamino-5-nitropyrimidin-4-ylacetate* (**3i**) (64% yield) which crystallised from aqueous ethanol as needles, m.p. 114 °C (Found: C, 57.5; H, 5.1; N, 18.0%; M^+, 316. $C_{15}H_{16}N_4O_4$ requires C, 57.0; H, 5.1; N, 17.7%; *M*, 316); and *ethyl 6-(p-methoxybenzylamino)-5-nitropyrimidin-4-ylacetate* (**3j**) (52% yield) which crystallised from aqueous ethanol as needles, m.p. 130 °C (Found: C, 55.8; H, 5.5; N, 16.0%; M^+, 346. $C_{16}H_{18}N_4O_5$ requires C, 55.5; H, 5.25; N, 16.2%; *M*, 346). The latter compound after hydrogenation gave *ethyl 5-amino-6-(p-methoxybenzylamino)pyrimidin-4-ylacetate* (**4f**) (83% yield) which crystallised from benzene as prisms, m.p. 132 °C (Found: C, 60.7; H, 6.4; N, 17.7%; M^+, 316. $C_{16}H_{20}N_4O_3$ requires C, 60.74; H, 6.37; N, 17.71%; *M*, 316); δ($CDCl_3$) 1.3 (3 H, t, CH_2CH_3), 3.57 (3 H, s, OCH_3), 4.1 (2 H, m, CH_2CH_3). 4.55 (2 H, s, CH_2CO), 7.4 (4 H, m, C_6H_4), and 8.2 (1 H, s, CH=N). With 90% formic acid at 100 °C for 30 min, compound (**4f**) gave the *N-formyl derivative* which crystallised from benzene as prisms, m.p. 115 °C (Found: C, 59.15; H, 5.8; N, 15.9%; M^+, 344. $C_{17}H_{20}N_4O_4$ requires C, 59.3; H, 5.8; N, 16.28%; *M*, 344).

Ethyl 6,7-Dihydro-4-methylamino-6-oxo-5H-pyrrolo[3,2-d]-pyrimidine-7-carboxylate (**2d**).—A suspension of diethyl 5-amino-6-methylaminopyrimidin-4-ylmalonate (**4c**) (0.05 g, 0.18 mmol) and anhydrous sodium carbonate (0.6 g, 0.56 mmol) in water (5 ml) was heated on a steam-bath until all the solid dissolved; the solution changed from colourless to orange-yellow in colour. Addition of acetic acid (to pH 7) precipitated a solid which was collected by filtration, washed with water, and dried. The *pyrrolopyrimidine hydrate* (**2d**) (0.038 g) crystallised from water as needles, m.p. >230 °C (Found: C, 47.2; H, 5.6; N, 21.5%; M^+, 236. $C_{10}H_{12}N_4O_3 \cdot H_2O$ requires C, 47.25; H, 5.55; N, 22.05%; *M*, 236).

6,7-Dihydro-4-methylamino-5H-pyrrolo[3,2-d]pyrimidin-6-one (**2e**).—(a) A solution of ethyl 5-amino-6-methylamino-pyrimidin-4-ylacetate (**4e**) (0.02 g, 0.095 mmol) in 6M-hydrochloric acid (2 ml) was heated on a steam-bath for 15 min then evaporated to dryness. The residue, on treatment with ether, precipitated a solid which was collected by filtration, washed with ether, and dried *in vacuo*. The *pyrimidinone hydrochloride* (**2e**)·HCl (0.01 g) had m.p. 280 °C and was homogeneous on t.l.c. (Found: C, 41.85; H, 4.7; N, 28.2; Cl, 17.4%; M^+, 164. $C_7H_8N_4O \cdot HCl$ requires C, 41.9; H, 4.53; N, 27.95; Cl, 17.7%; *M*, 164).

(b) Ethyl 6,7-dihydro-4-methylamino-6-oxo-5*H*-pyrrolo[3,2-*d*]pyrimidine-7-carboxylate (**2d**) (0.1 g) and 6M-hydrochloric acid (10 ml) were heated together on a steam-bath for 1 h. The solution, on evaporation to dryness, gave the pyrimidinone hydrochloride (0.1 g), identical (i.r., m.p. and mixed m.p.) with the compound prepared under (a) above.

4-Methylamino-5H-pyrrolo[3,2-d]pyrimidine-7-carboxylic Acid (**2g**).—Phosphoryl trichloride (0.7 ml, 7 mmol) was added to a stirred, ice-cold solution of ethyl 5-amino-6-methylamino-pyrimidin-4-ylacetate (**4e**) (0.3 g, 1.4 mmol) in anhydrous DMF (20 ml). The reaction mixture was set aside at room temperature overnight, when t.l.c. examination (System E) revealed the absence of starting material and the presence of a single product at R_F 0.51. The solution was evaporated to dryness and water (20 ml) was added. The aqueous solution was set aside at 4 °C for 3 h then extracted with ethyl acetate (3 × 20 ml). The extract was dried (anhyd. Na_2SO_4) and evaporated to give ethyl 6,7-dihydro-4-methylamino-5*H*-pyrrolo[3,2-*d*]pyrimidine-7-carboxylate hydrochloride (0.155 g) as a glass which was homogeneous on t.l.c. (Found: M^+, 220. $C_{10}H_{12}N_4O_2$ requires *M*, 220).

A suspension of the foregoing ester (0.05 g, 0.23 mmol) in 6M-hydrochloric acid (2 ml) was heated on a steam-bath. T.l.c. examination (System E) revealed that after 30 min all the starting material had been replaced by a product (R_F 0.61). The mixture was heated with charcoal, filtered through Celite, and the filtrate was evaporated to afford a gum which, when triturated with ether, gave the *carboxylic acid hydrochloride* (**2g**)·HCl as a white solid (0.028 g) which was collected by filtration and dried *in vacuo*. It had m.p. >250 °C (Found: C, 41.95; H, 3.7; N, 24.0; Cl, 15.2%; M^+, 192. $C_8H_8N_4O_2 \cdot HCl$ requires C, 42.0; H, 3.95; N, 24.54; Cl, 15.55%; *M*, 192).

Similarly, *ethyl 4-(p-methoxybenzylamino)-5H-pyrrolo[3,2-d]pyrimidine-7-carboxylate hydrochloride* (**2h**)·HCl (60% yield)

was obtained as a hard glass (Found: C, 56.1; H, 5.5; N, 15.2; Cl, 9.9%; M^+, 326. $C_{17}H_{18}N_4O_3$·HCl requires C, 56.25; H, 5.3; N, 15.45; Cl, 9.8%; *M*, 326).

4-[(trans)-4-*t*-*Butoxy*-3-*methylbut*-2-*enylamino*]-6-*chloro*-5-*nitropyrimidine* (**3k**).—To an ice-cold solution of 4,6-dichloro-5-nitropyrimidine (**3a**) (1 g, 5 mmol) in n-butyl alcohol (70 ml) were added triethylamine (0.52 g, 5 mmol) and *trans*-4-amino-1-t-butoxy-2-methylbut-2-ene[1] (0.8 g, 5 mmol) (from the phthaloyl derivative and hydrazine). The mixture was stirred at 0 °C and after 30 min the starting material (R_F 0.62) (System B) had been replaced by a product (R_F 0.55). The solution was evaporated to dryness and ice-cold water (50 ml) was added to the residue which was immediately extracted with ethyl acetate (3 × 50 ml) and the combined extracts dried (anhyd. Na_2SO_4), filtered, and evaporated to afford a red gum which was applied to a silica gel column and eluted with toluene–ethyl acetate (7:3). Evaporation of the combined major u.v.-absorbing fraction afforded the *pyrimidine* (**3k**) (1.2 g, 76%) which crystallised from light petroleum as pale yellow plates, m.p. 52 °C (Found: C, 49.6; H, 6.1; N, 17.7; Cl, 11.4%; M^+, 314. $C_{13}H_{19}ClN_4O_3$ requires C, 49.6; H, 6.1; N, 17.8; Cl, 11.28%; *M*, 314); *m*/*z* 241 ($M - OC_4H_9$); δ($CDCl_3$) 1.2 (9 H, s, CMe_3), 1.65 (3 H, s, CH_3), 3.1—3.4 (2 H, m, CH_2NH), 3.76 (2 H, s, CH_2O), 5.5 (1 H, t, CH=C), 8.2 (1 H, s, 2-H).

Ethyl 6-[(trans)-4-*t*-*Butoxy*-3-*methylbut*-2-*enylamino*)-5-*nitropyrimidin*-4-*ylacetate* (**3m**).—Ethyl acetoacetate (0.22 g, 1.7 mmol) was added to an ice-cold solution of 4-[(*trans*)-4-t-butoxy-3-methylbut-2-enylamino]-6-chloro-5-nitropyrimidine (0.2 g, 0.5 mmol) in freshly distilled acetone (10 ml). The temperature was maintained at 0 °C whilst 11M-sodium hydroxide (0.3 ml) was added dropwise during 20 min. The mixture was stirred for 30 min, then water (20 ml) and acetic acid (to pH 7) were added. The mixture was extracted with chloroform (3 × 50 ml) and the extracts dried (anhyd. Na_2SO_4) and evaporated to afford a gum which was applied to a silica-gel column and eluted with toluene–ethyl acetate (7:3). Fractions corresponding to the acetoacetate product (**3l**) (R_F 0.31; System B) were collected and evaporated and the residue was dissolved in 2M-aqueous ammonium hydroxide (10 ml), the solution was shaken at room temperature for 30 min, and the resulting yellow solid precipitate was collected. The *pyrimidinylacetate hemihydrate* (**3m**) (0.186 g, 85%) crystallised from aqueous ethanol as needles, m.p. 108 °C (Found: C, 54.3; H, 7.0; N, 15.0%; M^+, 366. $C_{17}H_{26}N_4O_5 \cdot \frac{1}{2}H_2O$ requires C, 54.4; H, 7.2; N, 14.9%; *M*, 366); δ($CDCl_3$) 1.2 (9 H, s, CMe_3), 1.3 (3 H, t, CH_3CH_2), 1.65 (3 H, s, CH_3), 3.1—3.4 (2 H, m, CH_2OBu^t), 3.75 (2 H, s, CH_2N), 4.2 (2 H, m, CH_2CH_3), 4.35 (2 H, s, CH_2CO), 5.6 (1 H, t, CH=C), and 8.2 (1 H, s, 2-H).

Ethyl 5-*Amino*-6-(4-*t*-*butoxy*-3-*methylbutylamino*)*pyrimidin*-4-*ylacetate* (**4g**).—A solution of the foregoing nitropyrimidine (**3m**) (0.03 g, 0.08 mmol) in ethanol (30 ml) was shaken with palladium–carbon catalyst (10% Pd; 0.015 g) in an atmosphere of hydrogen for 3 h after which time the starting material (R_F 0.8) had been replaced by a product (R_F 0.66; System C). The filtered solution was evaporated, the residue was dissolved in ethanol (10 ml), and hydrogen chloride gas was passed into this solution for 1 min. After evaporation of the solvent to low volume, diethyl ether was added dropwise to give a white solid which was collected by filtration, washed with ether, and dried *in vacuo*. The *pyrimidine hydrochloride* (**4g**)·HCl (0.02 g) had m.p. 230 °C (Found: C, 54.3; H, 8.3; N, 14.7; Cl, 9.25%; M^+, 338. $C_{17}H_{30}N_4O_3$·HCl requires C, 54.46; 8.35; N, 14.94; Cl, 9.47%; *M*, 338) δ[$(CD_3)_2SO$] 1.17 (9 H, s, CMe_3), 1.22 (3 H, d, CH_3), 1.4 (3 H, t, CH_2CH_3), 1.9—2.2 (3 H, m, CH_2CH_2CH), 3.45 (2 H, d, CH_2OBu^t), 3.9 (2 H, m, CH_2N), 4.1 (2 H, m, CH_2CH_3), 4.3 (2 H, s, CH_2CO), and 8.4 (1 H, s, 2-H).

4-(4-*Hydroxy*-3-*methylbutylamino*)-5H-*pyrrolo*[3,2-d]*pyrimidine*-7-*carboxylic Acid* (**2j**).—Phosphoryl trichloride (0.5 ml, 5 mmol) was added slowly to a stirred, ice-cold solution of the foregoing *pyrimidine hydrochloride* (**4g**)·HCl (0.35 g, 1 mmol) in anhydrous DMF (20 ml). The reaction mixture was set aside at room temperature overnight. The excess of solvent was evaporated off, water (10 ml) was added to the cooled, stirred residue, the mixture was extracted with ethyl acetate (3 × 20 ml), and the extracts were dried (anhyd. Na_2SO_4) and evaporated to afford a glass which was homogeneous on t.l.c. (System A); ethyl 4-(4-t-butoxy-3-methylbutylamino)-5*H*-pyrrolo[3,2-*d*]pyrimidine-7-carboxylate (**2i**) was obtained as a glass (0.16 g) (Found: M^+, 348. $C_{18}H_{28}N_4O_3$ requires *M*, 348); *m*/*z* 291 ($M - CMe_3$).

A suspension of the ester (**2i**) (0.2 g, 0.57 mmol) in 6M-hydrochloric acid (10 ml) was heated on a steam-bath for 4 h. After evaporation of the mixture to low volume under reduced pressure the resulting solid was collected by filtration, washed with water, and dried *in vacuo*. The *pyrrolopyrimidine hydrochloride* (**2j**)·HCl (0.13 g, 86%) had m.p. 280 °C (Found: C, 47.95; H, 5.6; N, 18.8; Cl, 11.75%; M^+, 264. $C_{12}H_{16}N_4O_3$·HCl requires C, 47.9; H, 5.7; N, 18.65; Cl, 11.8%; *M*, 264); δ[$(CD_3)SO$] 0.9 (3 H, d, CH_3), 1.8—2.4 (3 H, m, CH_2CH_2CH), 3.3 (2 H, d, CH_2O), 3.8 (2 H, m, CH_2N), 5.1—6.4 (2 H, br, OH and NH, exch. with D_2O with difficulty), 8.4 (1 H, d, 6-H), 8.75 (1 H, s, 2-H), and carboxyl absorption obscured.

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