Structural Studies on Bio-active Compounds. Part 5.[1] Synthesis and Properties of 2,4-Diaminopyrimidine Dihydrofolate Reductase Inhibitors bearing Lipophilic Azido Groups

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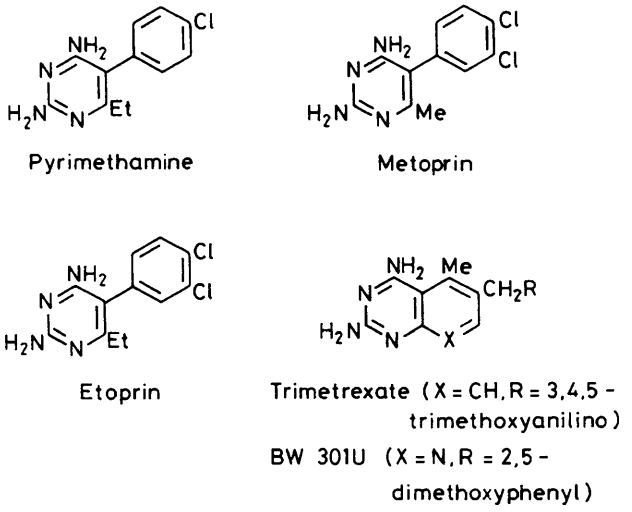
A series of 2,4-diamino-5-(azidoaryl)-6-alkylpyrimidines has been prepared. The azide (**36**) (MZP) can be reduced by thiol reagents to the corresponding amine (**28**) but reductive deazidation occurred when the series of azidophenyl derivatives was heated with hydrazine hydrate. Degradation of azide (**36**) in a trifluoroacetic acid–trifluoromethanesulphonic acid mixture at 0 °C affords a means of introducing the bulky trifluoromethylsulphonyloxy substituent into the hindered *ortho*-position of the 5-aryl substituent. The products formed from thermolysis and photolysis of the azide (**36**) and the planar analogue 2,4-diamino-6-azidoquinazoline (**70**) derive from the triplet nitrene reactive intermediates.

The azido compounds are potent inhibitors of rat liver dihydrofolate reductase although not as active as metoprin. The azide (**36**), as its ethanesulphonic acid salt, was selected for clinical trial on the basis of its ease of synthesis and suitable biological and pharmaceutical properties, and has a shorter biological half-life than compounds of comparable hydrophobicity.

Lipophilic 2,4-diaminopyrimidines which inhibit the enzyme dihydrofolate reductase (DHFR) have found a limited clinical role in the treatment of methotrexate-resistant malignancies[2] where the resistance is mediated by modification of the active process which transports the polar methotrexate (octanol–water Log *P* value −1.85)[3] into cells. Thus the lipophilic agents pyrimethamine (Log *P* 2.69), metoprin (2.82), and etoprin (3.19) achieve ingress to cells by passive diffusion and can accumulate in lipid compartments of the body (*e.g.* the brain).[3]

A lipophilic DHFR inhibitor should have potent inhibitory activity against mammalian DHFR but only weak (or no) inhibitory activity against the enzyme histamine *N*-methyltransferase. Inhibition of these two enzymes often runs in tandem in diaminopyrimidines[4] and suppression of histamine metabolism in brain tissue elicits neurotoxicity manifest as convulsions. Recently two new agents have entered clinical trial, trimetrexate and BW 301U, with properties of potent activity against DHFR but minimal effect on histamine metabolism.

Our approach to the design of novel antitumour diaminopyrimidines was to prepare compounds which are lipophilic, have a $pK_a \sim 7.3$ so that at physiological pH there is a balance between neutral (transportable) and protonated (bioactive) species, and are good inhibitors of DHFR but weak inhibitors of histamine *N*-methyltransferase. Crucially, these inhibitors incorporate the lipophilic aromatic group which can be biotransformed either metabolically (or chemically)[5] into the corresponding polar aromatic azido amino group. Implicit in the design of these compounds is the expectation that the lipophilic azides should have a relatively short biological half-life ($t_{\frac{1}{2}}$), being transformed into polar metabolites (or metabonates) devoid of biological activity. In summary, we set out to prepare some simple, lipophilic, biodegradable DHFR inhibitors with a plasma $t_{\frac{1}{2}}$ in humans comparable to that of methotrexate (10 ± 2 h)[6] in the expectation that such compounds would not exhibit the chronic toxicity of the prototype lipophilic antifolate metoprin (plasma $t_{\frac{1}{2}}$ 216 h).[3]



Structures of lipophilic antitumour dihydrofolate reductase inhibitors

Chemistry of 2,4-Diamino-6-alkyl-5-(substituted phenyl)-pyrimidines.—The starting materials required for the present work were prepared by the general route described by Russell and Hitchings.[7] Thus substituted phenylacetonitriles (**1**) were converted into the corresponding β-keto nitriles (**2**) with ethyl acetate or ethyl propionate in sodium ethoxide solution and thence to methoxyacrylonitriles (**3**) with ethereal diazomethane. Cyclisation of the methoxyacrylonitriles with guanidine in sodium ethoxide for 10—15 h afforded diaminopyrimidines (**4**)—(**10**) in good overall yield (see Scheme 1). Problems were encountered at the stage of the conversion of (2-chlorophenyl)-acetonitrile (**1**; R^1 = Cl, R^2 = R^3 = H) into the corresponding β-keto nitrile with ethyl propionate: only a 10% yield of the 2-chlorophenyl ketone (**2**; R^1 = Cl, R^2 = R^3 = H, R^4 = Et) was formed under optimum conditions although subsequent conversion into the diaminopyrimidine (**11**) proceeded smoothly. Efforts to prepare the methoxyphenylpyrimidine (**12**) were thwarted by the reluctance of (2-methoxyphenyl)acetonitrile (**1**; R^1 = OMe, R^2 = R^3 = H) to react with ethyl propionate even under forcing conditions.

Nitration of the phenylpyrimidine (**4**) with potassium nitrate–sulphuric acid has been reported to yield the 4′-nitrophenyl derivative (**13**) exclusively.[7] However, ^{1}H n.m.r. analysis of the

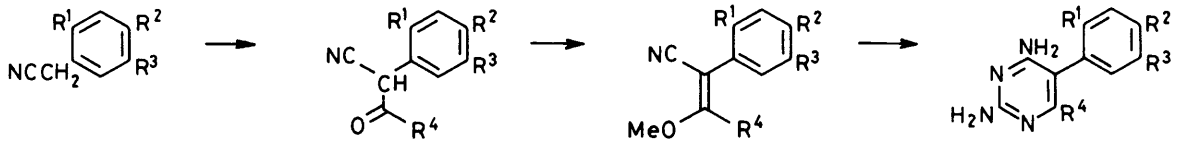
Table 1. ^{1}H N.m.r. spectra[a] (δ-values) of diaminopyrimidines

Compound	Solvent	Me[t]	CH_2q	2′-H	3′-H	4′-H	5′-H	6′-H	Other absorptions[b]
				(If not hydrogen, other substituent in parentheses)					
(7)[c]	A	0.96	2.12	*d*	*d*	(Cl)	*d*	*d*	5.62 (2 H, NH) 5.91 (2 H, NH)
(8)	A	0.95	2.08	*e*	*e*	(F)	*e*	*e*	5.56 (2 H, NH) 5.88 (2 H, NH)
(10)	A	0.97	2.11	*f*	(Cl)	*f*	*f*	*f*	5.70 (2 H, NH) 5.94 (2 H, NH)
(11)	B	1.05	2.21m	(Cl)	7.38m				4.43 (2 H, NH) 4.85 (2 H, NH)
(17)	A	1.88s		7.88d	(NO_2)	(Cl)	7.78d	7.52dd	5.94 (2 H, NH) 6.04 (2 H, NH)
(18)[c]	A	1.00	2.15	7.94d	(NO_2)	(Cl)	7.86d	7.59dd	6.01 (2 H, NH 6.10 (2 H, NH)
(19)	B	1.07	2.25	7.95dd	(NO_2)	(F)	7.39dd	7.53m	4.42 (2 H, NH) 4.80 (2 H, NH)
(20)	A	1.90s		7.60d	(Cl)	(NO_2)	8.10d	7.42dd	6.01 (2 H, NH 6.12 (2 H, NH)
(21)	C	1.20	2.50	7.35d	(Cl)	(NO_2)	8.08d	7.52dd	*g*
(22)	C	1.30	2.70	8.05d	(NO_2)	(OMe)	7.35m		4.15 (3 H, s, OMe)
(23)	C	1.30	2.65	8.02d	(NO_2)	(OEt)	7.55m		*g* 1.57 (3 H, t, OCH_2*Me*) 4.35 (2 H, q, OCH_2Me)
(24)	A	1.30[h]	2.20	*i*	(NO_2)	(OBu^n)	*i*	*i*	*g* 1.00 (3 H, m, Me) 1.65 (4 H, m, $[CH_2]_2$) 3.50 (2 H, q, OCH_2) 7.0 (2 H, NH) 7.5 (2 H, NH)
(26)	A	0.98	2.15	7.59d	(NO_2)	(NMe_2)	7.28d	7.36dd	2.53 (6 H, d, NMe_2) 5.71 (2 H, NH) 5.90 (2 H, NH)
(27)	C	2.25s		7.75d	(NH_2)	(Cl)	7.85d	7.50dd	*g*
(28)[c]	A	1.00	2.18	6.65d	(NH_2)	(Cl)	7.25d	6.38dd	5.35 (2 H, NH) 5.69 (2 H, NH) 5.90 (2 H, NH)
(29)	A	0.97	2.12	6.56dd	(NH_2)	(F)	7.01dd	6.30m	5.65 (2 H, NH) 5.90 (2 H, NH)
(30)	A	1.88s		6.96d	(Cl)	(NH_2)	6.83m		5.20 (2 H, NH) 5.90 (2 H, NH)
(31)	A	1.80	2.20	6.96d	(Cl)	(NH_2)	6.84m		5.31 (2 H, NH) 5.64 (2 H, NH) 5.77 (2 H, NH)
(32)	C	0.95	2.20	6.40d	(NH_2)	(OMe)	6.90d	6.70dd	4.12 (3 H, s, OMe)
(33)	C	1.00	2.15	6.30d	(NH_2)	(OEt)	6.90d	6.52dd	*g* 1.37 (3 H, t, OCH_2*Me*) 4.08 (2 H, q, OCH_2Me) 4.76 (2 H, NH) 5.60 (2 H, NH) 5.88 (2 H, NH)
(34)	A	0.98	2.15	6.48d	(NH_2)	(NMe_2)	6.94d	6.35dd	2.60 (6 H, s, NMe_2) 4.77 (2 H, NH) 5.45 (2 H, NH) 5.81 (2 H, NH)
(35)	C	2.35s		7.15 d	(N_3)	(Cl)	7.65d	7.10dd	*d*
(35) (ethane-sulphonate)	A	2.03s		7.45d	(N_3)	(Cl)	7.69d	7.17dd	7.06 (1 H. NH) 7.82 (2 H, NH) 8.18 (1 H, NH) *j*
(36)	A	1.00	2.18	7.19d	(N_3)	(Cl)	7.59d	7.00dd	5.84 (2 H, NH) 5.96 (2 H, NH)
(36) (ethane-sulphonate)	A	1.08	2.26	7.39d	(N_3)	(Cl)	7.65d	7.12dd	7.02 (1 H, NH) 7.85 (2 H, NH) 8.19 (1 H, NH) *j*
(36) (hydro-chloride)	A	1.08	2.30	7.39d	(N_3)	(Cl)	7.68d	7.13dd	7.48 (4 H, m, NH)
(37)	A	0.97	2.11	7.05dd	(N_3)	(F)	7.34dd	6.97m	5.80 (2 H, NH) 5.96 (2 H, NH)
(38)	C	2.35s		*k*	(Cl)	(N_3)	*k*	*k*	*g*

Table 1 (*continued*)

Compound	Solvent	Me[i]	CH_2q	2′-H	3′-H	4′-H	5′-H	6′-H	Other absorptions[b]
(**38**) (ethane-sulphonate)	A	2.00s		7.53d	(Cl)	(N_3)	7.63d	7.40dd	7.04 (1 H, NH) 7.83 (2 H, NH) 8.16 (1 H, NH) 12.56 (1 H, NH) *j*
(**39**)	A	0.96	2.10	7.29d	(Cl)	(N_3)	7.46d	7.21dd	5.68 (2 H, NH) 5.90 (2 H, NH)
(**39**) (ethane-sulphonate)	A	1.04	2.25	7.54d	(Cl)	(N_3)	7.63d	7.40dd	7.03 (1 H, NH) 7.83 (2 H, NH) 8.20 (1 H, NH) *j*
(**40**) (ethane-sulphonate)	A	1.05	2.23	7.03d	(N_3)	(OMe)	7.30d	7.12dd	3.94 (3 H, s, OMe) 6.88 (1 H, NH) 7.73 (2 H, NH) 8.15 (1 H, NH) *j*
(**41**) (ethane-sulphonate)	A	1.04	2.26	6.97d	(N_3)	(OEt)	7.27d	7.10dd	1.40 (3 H, t, OCH_2*Me*) 4.22 (2 H, q, OCH_2Me) 6.86 (1 H, NH) 7.72 (2 H, NH) 8.14 (1 H, NH) *j*
(**42**)	A	0.98	2.13	6.84d	(N_3)	(NMe_2)	7.07d	6.91dd	2.74 (6 H, s, NMe_2) 5.62 (2 H, NH) 5.86 (2 H, NH)
(**44**)	A	0.98	2.18	7.00d	(NHAc)	(Cl)	7.45d	7.00dd	2.12 (3 H, s, Ac) 5.70 (2 H, NH) 5.94 (2 H, NH) 9.50 (1 H, NH)
(**45**)	A	0.98	2.18	7.41d	($NCHNMe_2$)	(Cl)	6.81d	6.77d	3.01 (6 H, d, NMe_2) 5.58 (2 H, NH) 5.86 (2 H, NH) 7.77 (1 H, s, CH)
(**48**)	A	1.00	2.18	7.55d	($NNNMe_2$)	(Cl)	7.29d	7.00dd	3.25 (3 H, s, NMe) 3.56 (3 H, s, NMe) 5.85 (2 H, NH) 6.02 (2 H, NH)
(**49**)	A	0.98	2.17	7.54d	(NNNHMe)	(Cl)	7.20d	7.00dd	3.08 (3 H, d, *J* 5 Hz NH*Me*) 5.75 (2 H, NH) 5.96 (2 H, NH) 10.77 (1 H, q, NH)
(**55**)	A	0.95	2.10	*l*	*l*	(OMe)	*l*	*l*	3.78 (3 H, s, OMe) 5.39 (2 H, NH) 5.80 (2 H, NH)
(**56**)	C	1.25	2.55	*m*	*m*	(OEt)	*m*	*m*	1.50 (3 H, t, OCH_2*Me*) 4.25 (2 H, q, OCH_2Me) *g*
(**57**)	A	0.96	2.15	*n*	*n*	(NMe_2)	*n*	*n*	2.92 (6 H, s, NMe_2) 5.39 (2 H, NH) 5.73 (2 H, NH)
(**57**)	C	1.70	2.99	*o*	*o*	(NMe_2)	*o*	*o*	3.96 (6 H, s, NMe_2) 7.47 (1 H, s, NH) 8.68 (2 H, NH) 8.88 (1 H, NH) 10.27 (1 H, NH)
(**60**)[p]	A	1.03	2.09m	(CF_3SO_3)	7.30s	(Cl)	(NH_2)	6.71	1.17 (3 H, t, $MeCO_2CH_2$*Me*) 1.98 (3 H, s, *Me*CO_2Et) 4.02 (2 H, q, $MeCO_2CH_2$Me) 5.59 (4 H, NH) 5.95 (2 H, NH)
(**63**)	A	1.10	2.25m	(CF_3SO_3)	7.25s	(Cl)	(N_3)	7.43	5.76 (4 H, NH)

Solvents: A, [$^2H_6$]DMSO; B, $CDCl_3$; C, [^{2}H]TFA.
[a] Spectra were recorded either on a Perkin-Elmer R34 spectrometer (220 MHz) or a Bruker WH400 spectrometer (400 MHz). [b] All NH absorptions appeared as broad singlets, exchangeable with D_2O. [c] Ref. 2. [d] 7.25d and 7.53d (AA′BB′). [e] 7.71—7.26m. [f] 7.38m. [g] All NH protons fully exchanged. [h] Exact chemical shift not determined; absorption superimposable with Me protons of butoxy group. [i] 7.40m and 7.75m. [j] Excluding absorptions of ethanesulphonic acid. [k] 7.40 br s. [l] 6.99d and 7.09d (AA′BB′). [m] 7.25s. [n] 6.78d and 6.98d (AA′BB′). [o] 8.14d and 8.37d (AA′BB′). [p] Solvate with ethyl acetate.



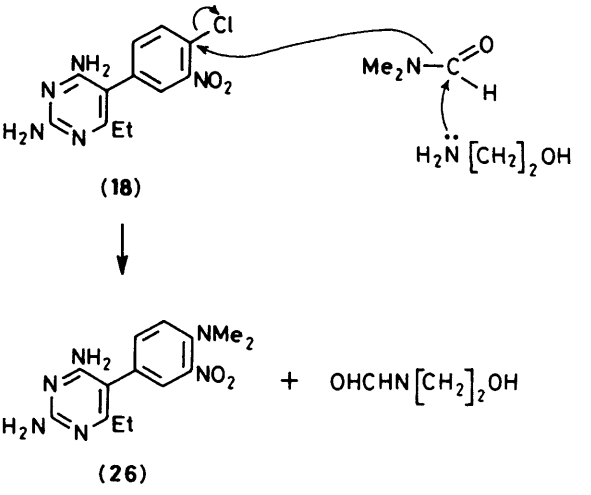
(1) (2) (3)

	R^1	R^2	R^3	R^4
(4)	H	H	H	Me
(5)	H	H	H	Et
(6)	H	Cl	H	Me
(7)	H	Cl	H	Et
(8)	H	F	H	Et
(9)	H	H	Cl	Me
(10)	H	H	Cl	Et
(11)	Cl	H	H	Et
(12)	OMe	H	H	Et
(13)	H	NO_2	H	Me
(14)	H	H	NO_2	Me
(15)	H	NO_2	H	Et
(16)	H	H	NO_2	Et
(17)	H	Cl	NO_2	Me
(18)	H	Cl	NO_2	Et
(19)	H	F	NO_2	Et
(20)	H	NO_2	Cl	Me
(21)	H	NO_2	Cl	Et
(22)	H	OMe	NO_2	Et
(23)	H	OEt	NO_2	Et
(24)	H	OBu^n	NO_2	Et
(25)	H	OH	NO_2	Et
(26)	H	NMe_2	NO_2	Et

	R^1	R^2	R^3	R^4
(27)	H	Cl	NH_2	Me
(28)	H	Cl	NH_2	Et
(29)	H	F	NH_2	Et
(30)	H	NH_2	Cl	Me
(31)	H	NH_2	Cl	Et
(32)	H	OMe	NH_2	Et
(33)	H	OEt	NH_2	Et
(34)	H	NMe_2	NH_2	Et
(35)	H	Cl	N_3	Me
(36)	H	Cl	N_3	Et
(37)	H	F	N_3	Et
(38)	H	N_3	Cl	Me
(39)	H	N_3	Cl	Et
(40)	H	OMe	N_3	Et
(41)	H	OEt	N_3	Et
(42)	H	NMe_2	N_3	Et
(43)	H	Cl	NHCHO	Et
(44)	H	Cl	NHAc	Et
(45)	H	Cl	N=CHNMe$_2$	Et
(46)	H	Cl	$N_2^+BF_4^-$	Et
(47)	H	Cl	F	Et
(48)	H	Cl	N=NNMe$_2$	Et
(49)	H	Cl	N=NNHMe	Et

Scheme 1.

products formed in the present work revealed the presence of an equal amount of the 3′-nitrophenyl isomer (**14**). Similarly, nitration of the pyrimidine (**5**) yielded a mixture of the 4′- (**15**) and 3′-nitrophenyl isomers (**16**) which could not be separated by chromatographic or crystallisation methods. In contrast, nitration of the halogeno-substituted pyrimidines (**6**)—(**10**) in concentrated nitric–sulphuric acids at 25 °C afforded nitro derivatives (**17**)—(**21**), respectively, which were characterised by the aromatic splitting patterns in their ^{1}H n.m.r. spectra (Table 1). The 4′-chloro group of compound (**18**) was sufficiently activated to undergo displacement by sodium alkoxides to yield the nitro ethers (**22**)—(**24**) although purification of the unstable butoxy derivative (**24**) required conversion into the corresponding ethanesulphonic acid salt. Efforts to prepare the nitrophenol (**25**) from the 4′-chloro-3′-nitropyrimidine (**18**) with boiling 2M- or 5M-sodium hydroxide or by demethylation of the methoxyphenylpyrimidine (**22**) with 45% hydrobromic acid in acetic acid, or recently developed methods using aluminium iodide[8] or sodium nitrite in dimethyl sulphoxide (DMSO),[9] led only to the recovery of starting material. Reaction of compound (**18**) and aqueous dimethylamine to form the dimethylaniline (**26**) was retarded by the poor solubility of compound (**18**) and the volatility of dimethylamine towards prolonged reflux. A more efficient route to the aniline (**26**) employed a mixture of dimethylformamide (DMF) and ethanolamine at 95 °C as the dimethylaminating agent. The mechanism of this reaction may involve ethanolamine serving as a formyl acceptor (Scheme 2) since the reaction does not occur in its absence. This convenient method of replacing activated chloro groups by a dimethylamino group obviates the necessity of using volatile dimethylamine and has wide practicability.[10]



(18) (26)

Scheme 2.

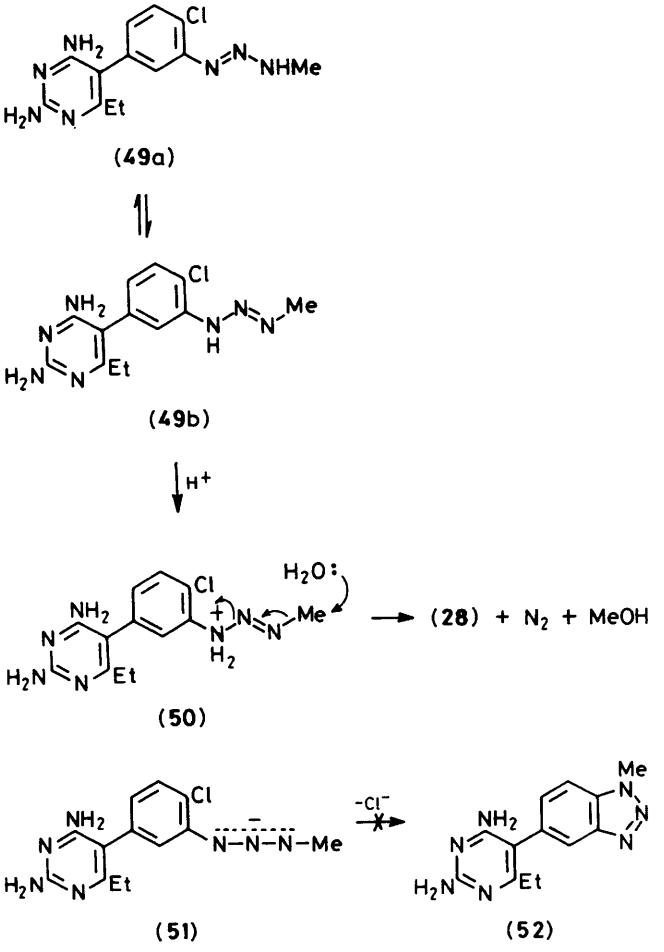
Reduction of appropriate nitro compounds to amines (**27**)—(**34**) was achieved by the use of either hydrazine–Raney nickel or tin(II) chloride in ethanol, and the amines were subsequently transformed into the target azides (**35**)—(**42**) by diazotisation and azidation.

The ^{1}H n.m.r. spectral data of all the compounds prepared in the course of this work are displayed in Table 1. These data serve to characterise certain compounds which gave unsatisfactory microanalytical results. In the case of the azide (**36**; '*m*-azidopyrimethamine'; MZP), which was selected as the

clinical candidate, a series of salts was prepared; the ethanesulphonic acid salt (MZPES) was chosen as the most pharmaceutically acceptable derivative.[11] Many other compounds were also converted into monoethanesulphonic acid salts to facilitate their biological evaluation (see later). The amine (**28**) formed a crystalline bis(ethanesulphonic acid) salt with two equivalents of the acid.

Interaction of amine (**28**) with formic acid at 95 °C and acetic anhydride–pyridine at 25 °C afforded monoformyl (**43**) and monoacetyl derivatives (**44**). When the latter reaction was conducted under more vigorous conditions the product was contaminated with di- and tri-acetylated derivatives. The methyl protons of the formamidine (**45**) synthesized from (**28**) and DMF dimethyl acetal at 95 °C absorbed as a doublet centred at δ 3.01 because of restricted rotation about the C–NMe_2 bond. Diazotisation of amine (**28**) in aqueous tetrafluoroboric acid yielded a stable diazonium tetrafluoroborate salt (**46**). The e.i. mass spectrum of this salt gave a molecular ion corresponding to $C_{12}H_{12}ClFN_4$, the Schiemann reaction product (**47**). The diazonium salt of (**28**), prepared in 3M-hydrochloric acid, coupled with excess of dimethylamine to yield the dimethyltriazene (**48**) and with methylamine to form the monomethyltriazene (**49**).

The ^1H n.m.r. spectrum of the triazene (**49**) in [$^2H_6$]DMSO at 35 °C showed the presence of methylamino tautomer (**49a**) exclusively. Thus the *N*-methyl resonance at δ 3.08 was split into a doublet ($J \sim 5$ Hz) by the NH proton: the doublet collapsed to a singlet on the addition of D_2O. The methyltriazene was surprisingly stable in protic solvents and could be crystallised unchanged from aqueous acetone, presumably because the preponderant tautomer is not susceptible to hydrolytic degradation. In the presence of cold 0.5M-hydrochloric acid, the triazene effervesced and the basified solution afforded the arylamine (**28**). In this case, tautomer (**49b**) is probably the species which becomes protonated to form a triazenium ion (**50**) which is ideally aligned for nucleophilic breakdown by water (Scheme 3). This methylation reaction is the molecular basis for the mutagenic and carcinogenic action of monomethyltriazenes,[12] and the triazene (**49**) can be considered as a potential active-site-directed irreversible inhibitor of DHFR.[13] It might be conjectured that in the case of the predominant tautomer (**49a**) the electron-withdrawing azo grouping might activate the chloro group to nucleophilic displacement (*cf.* corresponding nitro group). Sadly, when the methyltriazene was boiled in moist pyridine only the amine (**28**) was formed, in quantitative yield. Treatment of a solution of compound (**49**) in dry tetrahydrofuran (THF) with lithium bis(trimethylsilyl)amide gave a deep yellow colouration indicative of the formation of the anion (**51**), but no cyclisation to the benzotriazole (**52**) was detected (t.l.c.) when the mixture was refluxed. Presumably, the resonance-stabilised triazene anion (**51**) deactivates the chloro substituent towards intramolecular cyclisation.

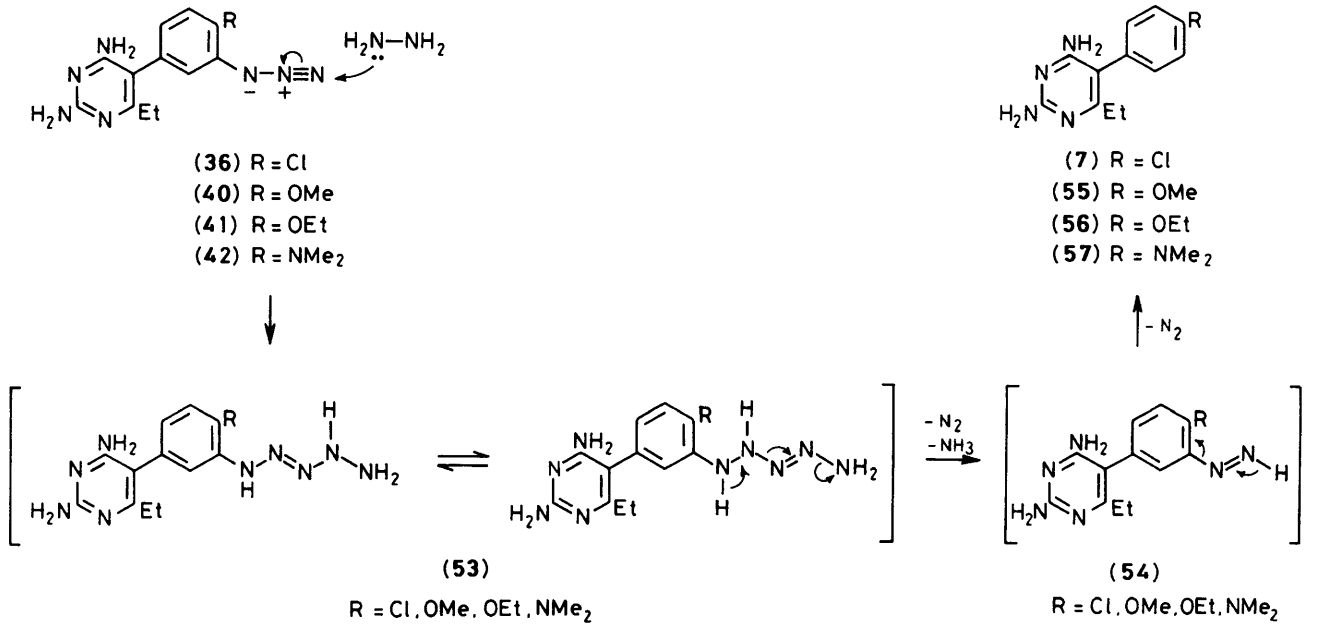


Scheme 3.

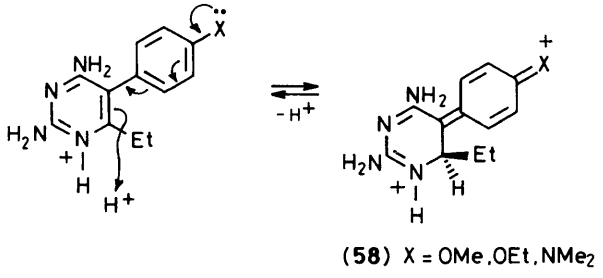
MZP (**36**) was reduced smoothly to the corresponding arylamine (**28**) by sodium hydrogen sulphide or 2-mercaptoethanol thus giving credence to our expectation that such azides might be chemically reduced *in vivo* by cellular thiols. Reduction of compound (**36**) in 98% hydrazine hydrate at 100 °C took a different course and the product was pyrimethamine (**7**). The methoxy- (**40**), ethoxy- (**41**), and dimethylamino- (**42**) substituted azides similarly underwent reductive deazidation to the corresponding disubstituted benzenes (**55**)—(**57**), respectively. The latter three examples illustrate the synthetic utility of this reaction whereby an unreactive aromatic chloro group [*e.g.* of (**7**)] can be replaced by oxygen and nitrogen nucleophiles in the following high yielding sequence:

(i) nitration *ortho* to the chloro group;
(ii) nucleophilic displacement of chloride;
(iii) reduction of nitro to amino;
(iv) diazotisation and azidation of the amine;
(v) deazidation in hydrazine hydrate.

The mechanism of the deazidation step probably involves intermediate pentazenes (**53**) which eliminate nitrogen and ammonia to form unstable diazenes (**54**), which then fragment to the corresponding arenes (Scheme 4). Whereas pyrimethamine (**7**) gives a colourless solution in hydrochloric acid, those 5-arylpyrimidines bearing powerful $+M$ substituents in the *para*-position (**55**)—(**57**) give deep red solutions in concentrated mineral acids. In the case of the methoxyphenyl analogue (**55**) the red colour was discharged on the addition of water or ethanol; addition of aqueous ammonia led to the recovery of the unchanged free base of (**55**). Colour formation was not observed in any of the other 5-arylpyrimidines described in this work. Crystal-structure determinations of several salts of 2,4-diamino-5-arylpyrimidines have confirmed that protonation occurs at N-1 and that the 5-aryl substituent is disposed essentially orthogonally with respect to the pyrimidine ring.[14] A ^1H and ^{13}C n.m.r. evaluation of protonation of similar compounds in the solution state is the subject of the following paper in this series. The species responsible for the red colours formed from pyrimidines (**55**)—(**57**) in strong acid must be extensively conjugated and we propose, tentatively, structures (**58**) to account for colour formation. If the second protonation in these unique pyrimidines is at C-6, coplanarity of the two rings can be achieved by virtue of the development of sp^3 geometry at C-6



Scheme 4.



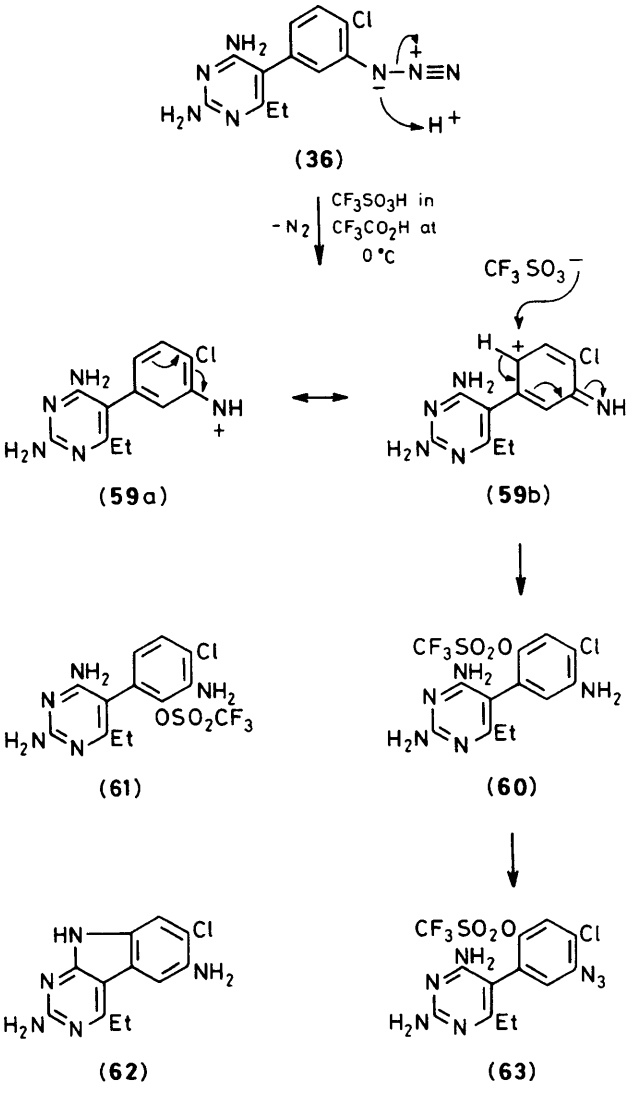
Scheme 5.

with the $+M$ substituent bearing the second positive charge (Scheme 5). Although similar, but less intense, colours were also formed in trifluoroacetic acid (TFA) we were unable to find evidence from high-field ^{1}H n.m.r. studies to confirm the presence of dications (**58**). For example, the ^{1}H n.m.r. spectrum of the dimethylaminophenylpyrimidine free base (**57**) in [$^2H_6$]DMSO shows a singlet for the methyl protons at δ 2.92 (Table 1); in TFA this signal moves downfield (to δ 3.96) but is not split into a doublet which would be expected of species (**58**; X = NMe_2). Additionally, no signal for the methine proton at C-6 could be detected in the TFA spectrum. If species (**58**) are indeed responsible for the red colour they are in too low concentrations to be detected spectroscopically, at least in TFA.

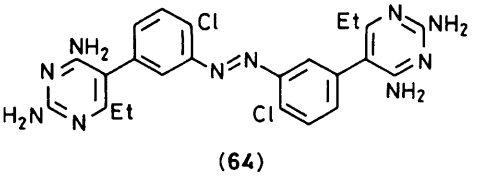
The azido compound (**36**) decomposed with violent effervescence in conc. sulphuric acid. In an effort to control the acidic decomposition the azide was stirred for 4 days at 25 °C in TFA; no change was observed in the ^{1}H n.m.r. spectrum. However, when the azide was added to a mixture of TFA–trifluoroacetic anhydride (TFAA) and trifluoromethanesulphonic acid (TFSA) at 0 °C a smooth evolution of nitrogen occurred. The generation of arylnitrenium species from azides with TFSA in TFA has been explored by Abramovitch* and others.[15] The mesomeric π-carbocations of these species can be trapped either by the trifluoromethanesulphonate anion or, more interestingly, by intramolecular cyclisation. The product in the present case was identified as the trifluoromethylsulphonyloxyphenylpyrimidine (**60**) because its ^{1}H n.m.r. spectrum showed the presence of a 1,2,4,5-tetrasubstituted phenyl group (two uncoupled singlets at δ 6.71 and 7.30) which excludes the isomeric 1,2,3,4-tetrasubstituted structure (**61**). Presumably, the possible product of intramolecular cyclisation, the tricycle (**62**), is not formed because the diaminopyrimidine moiety of intermediate (**59**) is protonated and non-nucleophilic. Diazotisation and azidation of the arylamino group of compound (**60**) led to the formation of the azide (**63**) (Scheme 6). Thus, this reaction is potentially valuable for the stepwise elaboration of an azidoarene into a substituted azidoarene and notable in the present example as a means of introducing a bulky substituent into the hindered *ortho*-position of the aryl group. Interestingly, the 400 MHz ^{1}H n.m.r. spectra of the (2′-chlorophenyl)pyrimidine (**11**) and the tetrasubstituted phenyl derivative (**60**) showed the methylene protons of the ethyl group to absorb as sixteen-line multiplets centred at δ 2.21 (Figure) and 2.09 respectively. In contrast, the ^{1}H n.m.r. spectra of all other compounds lacking a 2′-substituent studied in this work showed conventional quartets for the methylene absorptions (Table 1). The existence of restricted rotation about the aryl–pyrimidine C–C bond evidenced by the prochiral nature of the methylene group of compounds (**11**) and (**60**) raises the intriguing possibility that the enantiomers of these compounds might be separable by conventional resolution techniques.

No evidence for triplet-derived nitrene products was adduced in any of the aforementioned decompositions. However, thermolysis of azide (**36**) in boiling nitrobenzene afforded a maroon, gritty, high melting solid, presumably the azo compound (**64**) although its physical characteristics militated against further characterisation. The thermal and photochemical degradations of aqueous solutions of the azide selected for clinical development, the ethanesulphonic acid salt of (**36**) (MZPES), are complex. Preliminary results[16] show that the proportions of the principal degradation products, which derive from the triplet nitrene reactive intermediate, vary according to the oxygen tension of the solutions: in oxic conditions the nitrophenylpyrimidine (**18**) predominates whereas in hypoxic solutions the amine (**28**) and azo compounds (**64**) are more abundant.

* We thank Prof. R. A. Abramovitch for suggesting this reaction to us.



Scheme 6.



Chemistry of 2,4-*Diaminoquinazolines*.—2,4-Diamino-6-(substituted)quinazolines are also potent DHFR inhibitors.[17] Nitration and reduction of the diaminoquinazoline (**65**) afforded the 6-nitro- (**66**) and 6-amino-quinazoline (**67**), respectively. The e.i. mass spectrum of the diazonium tetrafluoroborate (**68**) derived from the amine gave a molecular ion corresponding to 2,4-diamino-6-fluoroquinazoline. The stable hydrochloride salt of the diazonium chloride (**69**) was converted into the 6-azidoquinazoline (**70**) by conventional azidation.

The pK_a of unsubstituted 2,4-diaminoquinazoline (**65**) is 8.06 ± 0.04 (determined spectroscopically at 340 nm). Attachment of an azido group at C-6 in compound (**70**) has a base-weakening effect (pK_a 7.53 ± 0.06 at 342 nm) and the molecule is protonated at N-1.[18] The base-weakening effect in the 5-(substituted phenyl)-2,4-diaminopyrimidine series is, as expected, much less, with the unconjugated azido group marginally lowering the pK_a of pyrimethamine (**7**) from 7.30 ± 0.16 to 7.19 ± 0.10 in MZP (**36**).

In other respects the chemistry of the azidodiaminoquinazoline (**70**) was very similar to that of the azidodiaminopyrimidine (**36**). When compound (**70**) was boiled in hydrazine hydrate (6 h) the azide-free product proved to be 2,4-dihydrazinoquinazoline (**71**). Examples of hydrazinolytic deazidation of azidoarenes have been described earlier in this paper and displacement of amino groups in a cyclic amidine arrangement in π-deficient heterocycles with hydrazine is a reaction with precedent.[19] 2,4-Diaminoquinazoline (**65**) also yielded the same dihydrazinoquinazoline (**71**) on prolonged boiling in hydrazine hydrate: shorter reaction time led to the isolation of a monohydrazinoquinazoline which was assigned structure (**72**) since its m.p. differed from that of the known 2-hydrazino isomer (**73**).

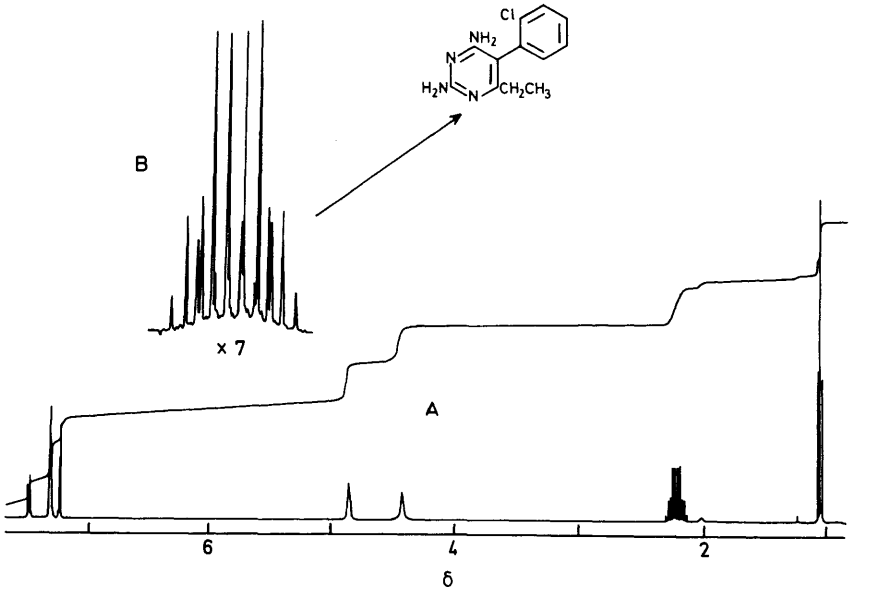
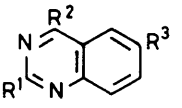


Figure. 400 MHz ^{1}H N.m.r. spectrum of A, 2,4-diamino-5-(2-chlorophenyl)-6-ethylpyrimidine (**11**) in deuteriochloroform; B, expanded methylene absorption centred at δ 2.21



	R^1	R^2	R^3
(65)	NH_2	NH_2	H
(66)	NH_2	NH_2	NO_2
(67)	NH_2	NH_2	NH_2
(68)	NH_2	NH_2	$N_2^+BF_4^-$ (as tetrafluoroborate salt)
(69)	NH_2	NH_2	$N_2^+Cl^-$ (as hydrochloride salt)
(70)	NH_2	NH_2	N_3
(71)	$NHNH_2$	$NHNH_2$	H
(72)	NH_2	$NHNH_2$	H
(73)	$NHNH_2$	NH_2	H
(74)	NH_2	NH_2	2,4-diaminoquinazolin-6-ylazo

The only products identified from photolysis or thermolysis of 2,4-diamino-6-azidoquinazoline (**70**) were derived from the triplet nitrene intermediate. Thus photolysis of the free base of (**70**) in methanol with a 100 W, unfiltered, medium-pressure lamp gave a 40% yield of the maroon azo-dye (**74**) in addition to the triamine (**67**) and unchanged azide. The azo-dye, which was characterised by its mass spectrum (molecular ion at *m/z* 346) and ease of reduction to triamine (**67**) with sodium dithionite, was formed more efficiently (95%) by thermolysis of the azide in boiling nitrobenzene. In contrast, thermolysis of compound (**70**) in decahydronaphthalene (decalin) afforded only the triamine (**67**). Photolysis of the hydrochloride salt of azide (**70**) in water or methanol gave the triamine as the major product.

Biological Properties of 2,4-*Diamino*-6-*alkyl*-5-(*substituted phenyl*)*pyrimidines*.—The ethanesulphonic acid salts of the azido compounds were screened against rat liver DHFR. I_{50} and K_i values are recorded in Table 2. All the azido compounds are approximately equiactive with pyrimethamine but an order of magnitude less active than metoprin. In the pairs of compounds (**35**) and (**36**) and (**38**) and (**39**), results show that an ethyl group is preferred at R^4 over methyl for maximum activity and that the 3′-azido-4′-chloro series (**35**) and (**36**) are less active than the isomeric 4′-azido-3′-chloro compounds (**38**) and (**39**) although the differences are relatively small.

Preliminary human pharmacokinetic studies on the ethanesulphonic acid salt of azide (**36**) (MZPES) indicate that the compound has a plasma $t_{\frac{1}{2}}$ of 30—35 h in humans (*cf.* 216 h for metoprin).[3]

Experimental

Ethanol refers to 95% ethanol; light petroleum refers to the fraction b.p. 60—80 °C. All m.p.s were measured on an electrothermal melting point apparatus and are uncorrected. I.r. spectra were recorded on a Unicam SP200 Infrared Spectrometer for potassium bromide discs. Mass spectra were recorded on a V.G. Micromass 12 instrument at 70 eV; source temperature 250—300 °C. The t.l.c. systems employed Kieselgel $60F_{254}$ (0.25 mm) as the adsorbent and either toluene–acetone (10:3) or toluene–acetone–ethanol (1:3:3) as the developing solvent.

Synthesis of 2,4-*Diamino*-6-*alkyl*-5-(*substituted*)*pyrimidines*.—The following compounds were prepared by a literature process: 2,4-diamino-6-methyl-5-phenylpyrimidine (**4**), m.p. 250—251 °C (lit.,[7] 249—250 °C); 2,4-diamino-6-ethyl-5-phenylpyrimidine (**5**), m.p. 243—244 °C (lit.,[7] 237—240 °C); 2,4-diamino-5-(4-chlorophenyl)-6-methylpyrimidine (**6**), m.p. 282—284 °C (lit.,[7] 264—265 °C); 2,4-diamino-6-ethyl-5-(4-fluorophenyl)pyrimidine (**8**), m.p. 268—270 °C (lit.,[7] 269 °C); 2,4-diamino-5-(3-chlorophenyl)-6-methylpyrimidine (**9**), m.p. 221—222 °C. 2,4-Diamino-5-(4-chlorophenyl)-6-ethylpyrimidine(pyrimethamine) (**7**) was obtained from the Wellcome Foundation Ltd, Dartford, Kent.

2,4-*Diamino*-5-(3-*chlorophenyl*)-6-*ethylpyrimidine* (**10**).—A solution of 3-chloro-α-propionylphenylacetonitrile (**2**; R^1 = R^2 = H, R^3 = Cl, R^4 = Et) (22 g) in diethyl ether (250 ml) was treated with a solution of diazomethane (10 g) in ether (500 ml) during 15 min. The mixture was stirred at 10 °C overnight. Excess of diazomethane was destroyed by the dropwise addition of acetic acid, and the ether was evaporated off to give the methoxyacrylonitrile (**3**; R^1 = R^2 = H, R^3 = Cl, R^4 = Et) (22.6 g) as a yellow syrup. A solution of sodium ethoxide [from sodium (4.0 g)] in ethanol (100 ml) and a solution of guanidine hydrochloride (16.0 g) in ethanol (50 ml) were mixed and stirred at 25 °C for 5 min and sodium chloride was removed. The ethanolic guanidine solution was refluxed with the acrylonitrile for 12 h. The cooled, concentrated solution furnished the *pyrimidine* (**10**) (40%) as crystals, m.p. 211—213 °C (from ethanol) (Found: C, 57.6; H, 5.2; N, 22.6%; M^+, 248 [250]. $C_{12}H_{13}ClN_4$ requires C, 58.0; H, 5.2; N, 22.5%; *M*, 248 [250]).

Similarly prepared, from 2-chloro-α-propionylphenylacetonitrile (**2**; R^1 = Cl, R^2 = R^3 = R^4 = Et), diazomethane, and guanidine, was 2,4-*diamino*-5-(2-*chlorophenyl*)-6-*ethylpyrimidine* (**11**) (40%), m.p. 200—201 °C (Found: C, 58.4; H, 5.3; N, 22.7%; M^+ 248 [250]).

Table 2. Activity of 2,4-diamino-5-(azidoaryl)-6-alkylpyrimidines against rat liver dihydrofolate reductase[a]

Compound	Solvent	R^1	R^2	R^3	R^4	I_{50} (μM)[b]	K_i (nM)[c]
Pyrimethamine (7)	A	H	Cl	H	Et	1.40	2.60 ± 0.31[d]
Metoprin	A	H	Cl	Cl	Me	0.10	0.12 ± 0.04
(35)[e]	B	H	Cl	N_3	Me	3.20	2.60 ± 0.76
(36)[e]	B	H	Cl	N_3	Et	1.30	1.60 ± 0.38
(38)[e]	B	H	N_3	Cl	Me	1.00	0.82 ± 0.01
(39)[e]	B	H	N_3	Cl	Et	0.34	0.38 ± 0.12
(40)[e]	B	H	OMe	N_3	Et	0.66	1.72 ± 0.34
(41)[e]	B	H	OEt	N_3	Et	1.60	1.73 ± 0.34
(42)[e]	B	H	NMe_2	N_3	Et	1.60	3.00 ± 0.22

Solvents: A, 0.1M-hydrochloric acid; B, water.
[a] Partially purified rat liver DHFR (E.C.1.5.1.3) was prepared by the method of Bertino and Fischer[21] and assayed spectrophotometrically by a previously published method.[22] [b] Defined as the final concentration of inhibitor in the assay system necessary to reduce the enzymatic reaction rate to 50% of the uninhibited rate. I_{50} values were determined by conducting inhibitory assays in duplicate at four inhibitor concentrations estimated to reduce DHFR activity by 20, 40, 60, and 80% of control values. [c] Inhibition constants were calculated by a Zone B analysis method described previously,[22] assuming a K_m value of 0.2 μM for dihydrofolate.[23] [d] 95% Confidence limits. [e] Ethanesulphonic acid salts.

2,4-*Diamino*-5-(4-*chloro*-3-*nitrophenyl*)-6-*ethylpyrimidine* (**18**).—Nitration of pyrimethamine (**7**) with nitric acid (*d* 1.42) and conc. sulphuric acid at 50 °C (1 h) afforded the nitrophenylpyrimidine (**18**) (95%), m.p. 204—205 °C (lit.,[20] 203—205 °C), as yellow rosettes from aqueous ethanol. The *ethanesulphonic acid salt*, prepared from the base and aqueous ethanesulphonic acid, crystallised as yellow rosettes, m.p. 260—262 °C (decomp.) (Found: C, 41.9; H, 4.5; N, 17.4. $C_{14}H_{18}ClN_5O_5S$ requires C, 41.6; H, 4.5; N, 17.3%); δ ([$^2H_6$]DMSO)* 1.03 (3 H, t, Me), 1.13 (3 H, t, $MeCH_2SO_3^-$), 2.25 (2 H, q, CH_2), 2.60 (2 H, q, $MeCH_2SO_3^-$), 7.5—7.7 (2 H, m, 5′- and 6′-H), 8.0 (1 H, d, 2′-H), 7.5—8.5 (4 H, NH).

Similarly prepared were the following. 2,4-*Diamino*-5-(4-*chloro*-3-*nitrophenyl*)-6-*methylpyrimidine* (**17**) (93%), m.p. 259—260 °C (Found: C, 47.3; H, 3.7; N, 25.3%; M^+, 279 [281]. $C_{11}H_{10}ClN_5O_2$ requires C, 47.2; H, 3.6; N, 25.0%; *M*, 279 [281]); 2,4-*diamino*-6-*ethyl*-5-(4-*fluoro*-3-*nitrophenyl*)*pyrimidine* (**19**) (98%), m.p. 218—219 °C (Found: C, 52.1; H, 4.4; N, 25.3. $C_{12}H_{12}FN_5O_2$ requires C, 52.0; H, 4.3; N, 25.3%).

2,4-*Diamino*-5-(3-*chloro*-4-*nitrophenyl*)-6-*methylpyrimidine* (**20**).—Nitration of 2,4-diamino-5-(3-chlorophenyl)-6-methylpyrimidine (**9**) (9.0 g) with nitric acid (*d* 1.42; 3.6 g) in conc. sulphuric acid at 25 °C (12 h) gave a yellow syrup, which was quenched with ice–aqueous ammonia. The *pyrimidine* (**20**) (83%) formed yellow crystals (from aqueous ethanol), m.p. 251—253 °C (Found: C, 47.2; H, 3.9; N, 25.0%; M^+, 279 [281]. $C_{11}H_{10}ClN_5O_2$ requires C, 47.2; H, 3.6; N, 25.0%; *M*, 279 [281]).

Similarly prepared was 2,4-*diamino*-5-(3-*chloro*-4-*nitrophenyl*)-6-*ethylpyrimidine* (**21**) (95%), m.p. 266—267 °C (decomp.) (Found: 49.1; H, 4.1; N, 23.9%; M^+, 293 [295]. $C_{12}H_{12}ClN_5O_2$ requires C, 49.1; H, 4.1; N, 23.9%; *M*, 293 [295]).

2,4-*Diamino*-6-*ethyl*-5-(4-*methoxy*-3-*nitrophenyl*)*pyrimidine* (**22**).—The nitropyrimidine (**18**) (2.0 g) was added to a solution of NaOMe [from sodium (1.0 g)] in dry methanol (50 ml) and the mixture was refluxed (18 h). The cooled, concentrated solution was diluted with water (50 ml) and the yellow *methoxynitrophenylpyrimidine* (**22**) was collected (92%). A pure sample was crystallised from DMF as yellow crystals, m.p. 277—278 °C (decomp.) (Found: C, 53.7; H, 5.1; N, 24.5%; M^+, 289. $C_{13}H_{15}N_5O_3$ requires C, 54.0; H, 5.2; N, 24.2%; *M*, 289).

Similarly prepared was 2,4-*diamino*-5-(4-*ethoxy*-3-*nitrophenyl*)-6-*ethylpyrimidine* (**23**) (82%), which was crystallised from aqueous ethanol as yellow crystals, m.p. 266—267 °C (Found: 55.1; H, 5.7; N, 22.6%; M^+, 303. $C_{14}H_{17}N_5O_3$ requires C, 55.4; H, 5.6; N, 23.1%; *M*, 303).

2,4-*Diamino*-5-(4-*butoxy*-3-*nitrophenyl*)-6-*ethylpyrimidine* (**24**) was prepared from the nitropyrimidine (**18**) (2.0 g) and sodium (0.17 g) in refluxing butan-1-ol (30 ml) for 1 h. Dilution of the green mixture with water (50 ml) afforded the crude pyrimidine (0.8 g, 35%), which gave a pure *ethanesulphonic acid salt*, m.p. 260—262 °C (decomp.) when crystallised from aqueous ethanesulphonic acid (Found: C, 49.0; H, 6.3; N, 15.9. $C_{18}H_{27}N_5O_6S$ requires C, 49.0; H, 6.1; N, 15.9%).

Attempted Preparation of 2,4-*Diamino*-6-*ethyl*-5-(4-*hydroxy*-3-*nitrophenyl*)*pyrimidine* (**25**).—(i) When the nitropyrimidine (**18**) was boiled in 2M- or 5M-sodium hydroxide for 4 h starting material (95 and 93% respectively) was recovered from the cooled solutions.

(ii) Attempted demethylation of the methoxyphenylpyrimidine (**22**) with 45% hydrobromic acid in refluxing acetic acid (3 h), or by aluminium iodide in acetonitrile,[8] or sodium nitrite in DMSO,[9] led to the recovery of starting material.

* Primed numbers refer to the aromatic ring.

2,4-*Diamino*-5-(4-*dimethylamino*-3-*nitrophenyl*)-6-*ethylpyrimidine* (**26**).—To a solution of the nitropyrimidine (**18**) (2.0 g) in DMF (10 ml) was added 2-aminoethanol (0.84 g) and the mixture was heated at 90 °C (16 h). The cooled solution, diluted with water (50 ml), afforded deep red crystals of the *dimethylaminopyrimidine* (**26**) (87%), which was crystallised from aqueous DMF with m.p. 256—257 °C (Found: C, 55.6; H, 5.9; N, 27.4%; M^+, 302. $C_{14}H_{18}N_6O_2$ requires C, 55.6; H, 5.9; N, 27.8%; *M*, 302).

The same product (68%) was formed when the nitropyrimidine (10 g) was boiled for 48 h with 40% aqueous dimethylamine (400 ml) added in 4 × 100 ml portions at 12-hourly intervals.

2,4-*Diamino*-5-(3-*amino*-4-*chlorophenyl*)-6-*ethylpyrimidine* (**28**).—This amine was prepared by reduction of the nitropyrimidine (**18**) with tin(II) chloride dihydrate in 10M-hydrochloric acid, tin(II) chloride dihydrate in refluxing ethanol, or by Raney nickel in ethanolic hydrazine hydrate at 60—65 °C. The amine was crystallised as the anhydrous base from 100% ethanol (lit.,[20] m.p. 215—217 °C) or as the amine hydrate from 50% aqueous ethanol (lit.,[20] 215—217 °C). The same amine (84 and 89% yield, respectively) was formed when 2,4-diamino-5-(3-azido-4-chlorophenyl)-6-ethylpyrimidine (**36**) was reduced with sodium hydrogen sulphide (5 mol equiv.) in water at 65 °C or by excess of 2-mercaptoethanol at 60 °C.

The amine base (2.64 g) in ethanol (20 ml) containing ethanesulphonic acid (2.4 g, 2.1 mol equiv.) gave a precipitate of the *diethanesulphonic acid salt* (4.0 g) which was crystallised as the *hemihydrate* from ethanol, white needles, m.p. 233—235 °C (Found: C, 38.8; H, 5.4; N, 14.2. $C_{16}H_{26}ClN_5O_6S_2 \cdot 0.5H_2O$ requires C, 39.0; H, 5.5; N, 14.2%).

Similarly prepared, from the appropriate nitropyrimidine, by reduction with tin(II) chloride in refluxing ethanol or Raney nickel and hydrazine in ethanol at 60—65 °C were the following. 2,4-*Diamino*-5-(3-*amino*-4-*chlorophenyl*)-6-*methylpyrimidine* (**27**) (84%), m.p. 242—244 °C (from aqueous ethanol) (Found: C, 52.5; H, 4.9; N, 28.0%; M^+, 249 [251]. $C_{11}H_{12}ClN_5$ requires C, 52.9; H, 4.8; N, 28.1%; *M*, 249 [251]); 2,4-*diamino*-5-(3-*amino*-4-*fluorophenyl*)-6-*ethylpyrimidine* (**29**) (92%), m.p. 260—262 °C (from aqueous ethanol) (Found: C, 58.5; H, 5.7; N, 28.4. $C_{12}H_{14}FN_5$ requires C, 58.3; H, 5.7; N, 28.3%); 2,4-*diamino*-5-(4-*amino*-3-*chlorophenyl*)-6-*methylpyrimidine* (**30**) (81%), m.p. 205—206 °C (from aqueous ethanol) (decomp.) (Found: C, 52.8; H, 4.8; N, 28.3%; M^+, 249 [251]. $C_{11}H_{12}ClN_5$ requires C, 52.8; H, 4.8; N, 28.1%; *M*, 249 [251]); 2,4-*diamino*-5-(4-*amino*-3-*chlorophenyl*)-6-*ethylpyrimidine* (**31**) (87%), m.p. 189—190 °C (from aqueous ethanol) (Found: C, 54.3; H, 5.2; N, 26.2%; M^+, 263 [265]. $C_{12}H_{14}ClN_5$ requires C, 54.7; H, 5.3; N, 26.6%; *M*, 263 [265]); 2,4-*diamino*-5-(3-*amino*-4-*methoxyphenyl*)-6-*ethylpyrimidine* (**32**) (95%), m.p. 264—265 °C (decomp.) (from DMF) (Found: C, 60.4; H, 6.0; N, 27.2%; M^+, 259. $C_{13}H_{17}N_5O$ requires C, 60.7; H, 5.8; N, 27.2%; *M*, 259); 2,4-*diamino*-5-(3-*amino*-4-*ethoxyphenyl*)-6-*ethylpyrimidine* (**33**) (78%), m.p. 176—177 °C (from aqueous ethanol) (Found: C, 61.2; H, 7.1; N, 25.5%; M^+, 273. $C_{14}H_{19}N_5O$ requires C, 61.5; H, 7.0; N, 25.6%; *M*, 273); 2,4-*diamino*-5-(3-*amino*-4-*dimethylaminophenyl*)-6-*ethylpyrimidine* (**34**) (89%), m.p. 188—189 °C (from aqueous ethanol) (Found: C, 61.4; H, 7.8; N, 31.1%; M^+, 272. $C_{14}H_{20}N_6$ requires C, 61.7; H, 7.4; N, 30.9%; *M*, 272).

2,4-*Diamino*-5-(3-*azido*-4-*chlorophenyl*)-6-*ethylpyrimidine* (**36**).—A fine suspension of 2,4-diamino-5-(3-amino-4-chlorophenyl)-6-ethylpyrimidine (**28**) (1.84 g) in 5M-hydrochloric acid (60 ml) was diazotised at 0 °C with sodium nitrite (0.6 g) in water (2 ml). To the suspension, at 0 °C, was added sodium azide (1.8 g) and the mixture was stirred for 2 h. The *azide* (**36**)

(1.82 g, 90%) was precipitated with conc. aqueous ammonia and was crystallised from ethanol as photosensitive cream prisms, m.p. 197—198 °C (decomp.); $\nu_{max.}$ 1 450, 1 564, 1 639, 2 150 (N_3), 3 140, 3 300, and 3 460 cm^{-1}; *m/z* 291 (15%), 289 (M^+, 40), 263 (21), 262 (39), 226 (66), and 65 (100) (Found: C, 49.9; H, 4.2; N, 33.3. $C_{12}H_{12}ClN_7$ requires C, 49.7; H, 4.2; N, 33.8%).

When a suspension of the azide (**36**) (1.0 g) and nitrobenzene (3 ml) was boiled (0.25 h) the azide dissolved with effervescence and a black solid precipitated. The black product, probably 2,2′-dichloro-5,5′-bis-(2,4-diamino-6-ethylpyrimidin-5-yl)azobenzene (**64**), (0.6 g) was insoluble in boiling ethanol or 2-ethoxyethanol and melted with decomposition in the range 250—350 °C. The *azide monohydrochloride*, m.p. 220—225 °C (decomp.) (from 3M-hydrochloric acid) had $\nu_{max.}$ 1 542, 1 575, 1 600, 1 642, 1 660, and 2 180 (N_3) cm^{-1} (Found: C, 44.3; H, 4.0; N, 30.3. $C_{12}H_{13}Cl_2N_7$ requires C, 44.2; H, 4.0; N, 30.0%); the *azide diacetate* from acetic acid, had m.p. 190—195 °C (decomp.) (Found: C, 46.5; H, 4.6. $C_{16}H_{20}ClN_7O_4$ requires C, 46.9; H, 4.9%); the *azide ethanesulphonic acid salt* (75%), from ethanesulphonic acid (1.1 mol equiv.) in water, had m.p. 191—192 °C (decomp.) (Found: C, 41.9; H, 4.6; N, 24.5. $C_{14}H_{18}ClN_7O_3S$ requires C, 42.1; H, 4.5; N, 24.5%).

Similarly prepared, from the corresponding amine, sodium nitrite, and sodium azide were the following azides. 2,4-*Diamino*-5-(3-*azido*-4-*chlorophenyl*)-6-*methylpyrimidine* (**35**) (92%), m.p. 198—200 °C (decomp.) (from aqueous ethanol) (Found: C, 47.9; H, 3.6; N, 35.4%; M^+, 275 [277]. $C_{11}H_{10}ClN_7$ requires C, 47.9; H, 3.6; N, 35.6%; *M*, 275 [277]) and the *ethanesulphonic acid salt* (52%), m.p. 202—203 °C (decomp.) (from water) (Found: C, 40.4; H, 4.1; N, 25.6. $C_{13}H_{16}ClN_7O_3S$ requires C, 40.5; H, 4.2; N, 25.4%); 2,4-*diamino*-5-(3-*azido*-4-*fluorophenyl*)-6-*ethylpyrimidine* (**37**) (91%), m.p. 178—180 °C (decomp.) (from aqueous ethanol) (Found: C, 52.9; H, 4.3; N, 35.3. $C_{12}H_{12}FN_7$ requires C, 52.75; H, 4.4; N, 35.9%); 2,4-*diamino*-5-(4-*azido*-3-*chlorophenyl*)-6-*methylpyrimidine* (**38**) (90%), m.p. 160—162 °C (decomp.) (from aqueous ethanol) (Found: C, 47.4; H, 3.5; N, 35.4%; M^+, 275 [277]. $C_{11}H_{10}ClN_7$ requires C, 47.9; H, 3.6; N, 35.6%; *M*, 275 [277]) and the *ethanesulphonic acid salt*, m.p. 184—185 °C (decomp.) (from water) (Found: C, 40.0; H, 4.1; N, 25.0. $C_{13}H_{16}ClN_7O_3S$ requires C, 40.5; H, 4.2; N, 25.4%); 2,4-*diamino*-5-(4-*azido*-3-*chlorophenyl*)-6-*ethylpyrimidine* (**39**) (88%), m.p. 186—187 °C (decomp.) (from aqueous ethanol) (Found: C, 49.7; H, 4.1; N, 33.7%; M^+, 289 [291]. $C_{12}H_{12}ClN_7$ requires C, 49.7; H, 4.2; N, 33.9%; *M*, 289 [291]) and the *ethanesulphonic acid salt* (63%), m.p. 196—197 °C (decomp.) (from water) (Found: C, 42.4; H, 4.4; N, 24.3. $C_{14}H_{18}ClN_7O_3S$ requires C, 42.0; H, 4.5; N, 24.5%); 2,4-*diamino*-5-(3-*azido*-4-*methoxyphenyl*)-6-*ethylpyrimidine* (**40**) (91%), m.p. 184—185 °C (decomp.) (from aqueous ethanol) (Found: C, 54.6; H, 5.3; N, 34.7%; M^+, 285. $C_{13}H_{15}N_7O$ requires C, 54.7; H, 5.3; N, 34.4%; *M*, 285) and its *ethanesulphonic acid salt* (43%), m.p. 272—274 °C (decomp.) (from water) (Found: C, 45.6; H, 4.9; N, 24.5. $C_{15}H_{21}N_7O_4S$ requires C, 45.6; H, 5.3; N, 24.8%); 2,4-*diamino*-5-(3-*azido*-4-*ethoxyphenyl*)-6-*ethylpyrimidine* (**41**) (90%), m.p. 182—183 °C (decomp.) (from aqueous ethanol) (Found: C, 56.3; H, 5.7; N, 32.4%; M^+ 299. $C_{14}H_{17}N_7O$ requires C, 56.2; H, 5.7; N, 32.8%; *M*, 299) and its *ethanesulphonic acid salt* (38%), m.p. 173—174 °C (decomp.) (from water) (Found: C, 47.4; H, 5.6; N, 23.7. $C_{16}H_{23}N_7O_4S$ requires C, 46.9; H, 5.6; N, 24.0%); 2,4-*diamino*-5-(3-*azido*-4-*dimethylaminophenyl*)-6-*ethylpyrimidine* (**42**) (91%), m.p. 158—159 °C (decomp.) (from aqueous ethanol) (Found: C, 56.4; H, 5.9; N, 37.8%; M^+, 298. $C_{14}H_{18}N_8$ requires C, 56.4; H, 6.0; N, 37.6%; *M*, 298).

2,4-*Diamino*-5-(4-*chloro*-3-*formylamino*)-6-*ethylpyrimidine* (**43**).—A sample of the aminophenylpyrimidine (**28**) (1.5 g) and formic acid (99—100%; 2 ml) was heated at 95 °C for 40 min. The cooled solution was diluted with water (10 ml) and basified with aqueous ammonia. The white formamide (**43**) (1.45 g) formed prisms, mp. 226—228 °C (from ethanol) (Found: M^+, 291 [293]. $C_{13}H_{14}ClN_5O$ requires *M*, 291 [293]); $\nu_{max.}$ 1 685 cm^{-1} (CO).

5-(3-*Acetylamino*-4-*chlorophenyl*)-2,4-*diamino*-6-*ethylpyrimidine* (**44**).—A mixture of the aminophenylpyrimidine (**28**) (2.64 g), acetyl chloride (1 ml), and pyridine (15 ml) was heated at 95 °C for 3 h and then cooled. Addition of conc. aqueous ammonia (10 ml) gave an amber solid after 8 h. The *acetamide* (**44**) (1.6 g; 52%) was crystallised from ethanol as amber microprisms, m.p. 257—259 °C (Found: C, 54.8; H, 5.2; N, 23.2%; M^+, 305.104 33. $C_{14}H_{16}ClN_5O$ requires C, 55.0; H, 5.2; N, 22.9%; *M*, 305.103 80); $\nu_{max.}$ 1 280, 1 450, 1 578, 1 618, 1 640, 1 670, 2 950, 3 180, 3 330, and 3 450 cm^{-1}. The *diacetyl derivative* (55%) from the aminophenylpyrimidine (**28**) and acetic anhydride–acetic acid (1:1) at 95 °C for 1.5 h was crystallised from ethanol as prisms, m.p. 243—244 °C (Found: C, 55.2; H, 5.1; N, 20.2%; M^+, 347.114 89. $C_{16}H_{18}ClN_5O_2$ requires C, 55.3; H, 5.2; N, 20.1%; *M*, 347.114 49); $\nu_{max.}$ 1 320, 1 575br, 1 660br, and 3 300br cm^{-1}. The *triacetyl derivative* (47%) from the amine (**28**) and refluxing acetic anhydride (1 h), followed by trituration with ice–water, and m.p. 174—176 °C (Found: C, 55.1; N, 18.1%; M^+ 389.125 57. $C_{18}H_{20}ClN_5O_3$ requires C, 55.5; H, 5.1; N, 18.0%; *M*, 389.125 52).

2,4-*Diamino*-5-(4-*chloro*-3-*dimethylaminomethyleneamino*)-6-*ethylpyrimidine* (**45**).—A mixture of the aminophenylpyrimidine (**28**) (5.27 g) and DMF dimethyl acetal (15 ml) was refluxed (4 h) and evaporated to yield a yellow gum. The gum was dissolved in a mixture of ethanol (10 ml) and 6M-hydrochloric acid (10 ml) and left for 4 weeks at 25 °C. The solution was basified with ice–conc. aqueous ammonia to yield the *dimethylaminomethyleneaminopyrimidine* (**45**) (4.9 g), which was crystallised from ethanol as prisms (4.4 g), m.p. 224—226 °C (Found: M^+, 317 [319]. $C_{15}H_{18}ClN_6$a requires *M*, 317 [319]; $\nu_{max.}$ 815, 1 052, 1 100, 1 385, 1 445, 1 580, 1 625, 3 150 (NH), 3 340, and 3 420 cm^{-1}.

2-*Chloro*-5-(2,4-*diamino*-6-*ethylpyrimidin*-5-*yl*)*benzenediazonium Tetrafluoroborate* (**46**).—The amine (**28**) (2.63 g) was dissolved in 20% aqueous tetrafluroboric acid (40 ml) and was diazotised at 0 °C with sodium nitrite (0.75 g) in water. The cream-coloured salt (3.4 g) was crystallised by being dissolved in acetonitrile (10 ml) and reprecipitated to afford the *diazonium tetrafluoroborate hydrotetrafluoroborate hemihydrate* as orange needles, m.p. 165 °C (decomp.) (Found: C, 31.3; H, 3.1; N, 18.5. $C_{12}H_{12}BClF_4N_6{\cdot}HBF_4{\cdot}0.5H_2O$ requires C, 31.4; H, 3.0; N, 18.3%); $\nu_{max.}$ 1 120—1 020 (BF) and 2 290 cm^{-1} (N_2^+). Careful thermolysis of the diazonium tetrafluoroborate (5 mg) at 200 °C gave a grey residue (Found: M^+, 266 [268]. $C_{12}H_{12}ClFN_4$ requires *M*, 266 [268]).

The diazonium tetrafluoroborate salt coupled with 2-naphthol in aqueous 2M-potassium hydroxide to afford a *naphtholazo dye* (95%), which was crystallised from DMF as red needles of the solvate, m.p. 300—302 °C (Found: C, 60.9; H, 5.3; N, 20.3. $C_{22}H_{19}ClN_6{\cdot}C_3H_7NO$ requires C, 61.0; H, 5.3; N, 19.9%).

2,4-*Diamino*-5-[4-*chloro*-3-(3,3-*dimethyltriazen*-1-*yl*)*phenyl*]-6-*ethylpyrimidine* (**48**).—A solution of the amine (**28**) (5.27 g) in 3M-hydrochloric acid (70 ml) was diazotised at 0 °C with a solution of sodium nitrite (1.5 g) in water (10 ml). A solution of 25—30% aqueous dimethylamine (10 ml) was added followed by sufficient sodium carbonate to adjust the pH to 10. The oily mixture was stirred at 0 °C for 2 h and the cream-coloured solid was collected. The dimethyltriazene (**48**) was crystallised from ethanol as cream-coloured prisms (1.75 g), m.p. 233—236 °C

(efferv.) (Found: M^+, 319 [321]. $C_{14}H_{18}ClN_7$ requires M, 319 [321]). CAUTION: this compound is a potential carcinogen.

Similarly prepared, from the diazotised amine (**28**) and excess of 25% aqueous methylamine at 0 °C, was 2,4-diamino-5-[4-chloro-3-(3-methyltriazen-1-yl)phenyl]-6-ethylpyrimidine (**49**) (85%), which was crystallised from aqueous acetone as a cream-coloured solid, m.p. 170—172 °C (efferv.) (Found: M^+, 305 [307]. $C_{13}H_{16}ClN_7$ requires M, 305 [307]). CAUTION: this compound is a potential carcinogen.

When the methyltriazene (**49**) was boiled in pyridine for 0.5 h and the solution diluted with water and cooled, the product was the amine (**28**) (65%). The same amine (95%) was isolated when triazene (**49**) was boiled in 0.5M-hydrochloric acid for 5 mins, cooled, and the solution basified with aqueous ammonia.

A solution of lithium bis(trimethylsilyl)amide (0.12 g) in dry THF (10 ml) was added to a stirred solution of the triazene (**49**) in dry THF at 25 °C. The yellow solution was stirred for 12 h and then refluxed (4 h). T.l.c. analysis of the mixture showed that no reaction had taken place.

2,4-*Diamino*-6-*ethyl*-5-(4-*methoxyphenyl*)*pyrimidine* (**55**).—A suspension of the methoxyazidopyrimidine (**40**) (0.5 g) in 98% hydrazine hydrate (20 ml) was boiled (0.5 h). The cooled solution was diluted with water (50 ml) and stored at 4 °C. The cream-coloured precipitate of the *methoxyphenylpyrimidine* (**55**) (0.31 g) was crystallised from aqueous 2-ethoxyethanol as pale yellow flakes, m.p. 267—269 °C (Found: C, 63.6; H, 6.8; N, 23.0%; M^+, 244. $C_{13}H_{16}N_4O$ requires C, 63.9; H, 6.6; N, 23.0%; M, 244).

The methoxyphenylpyrimidine (**55**) (0.2 g) was dissolved in 10M-hydrochloric acid (5 ml). The bright red solution was stirred at 25 °C for 5 days, diluted with water, and basified with aqueous ammonia. The precipitated cream-coloured solid (0.2 g) was identical (i.r., m.s., and t.l.c.) with the starting material.

The following 2,4-diamino-6-ethyl-5-(4-substituted-phenyl)-pyrimidines were prepared from the starting azides (**36**), (**41**), and (**42**) respectively: pyrimethamine (**7**) (85% after 0.25 h reflux); 2,4-*diamino*-6-*ethyl*-5-(4-*ethoxyphenyl*)*pyrimidine* (**56**) (40% after 5 h reflux), m.p. 251—253 °C (from aqueous 2-ethoxyethanol) (Found: C, 65.3; H, 7.3; N, 21.8%; M^+, 258. $C_{14}H_{18}N_4O$ requires C, 65.1; H, 7.0; N, 21.7%; M, 258); 2,4-*diamino*-5-(4-*dimethylaminophenyl*)-6-*ethylpyrimidine* (**57**) (78% after 0.5 h reflux), m.p 237—239 °C (Found: C, 65.4; H, 7.5; N, 27.5%; M^+, 257. $C_{14}H_{19}N_5$ requires C, 65.4; H, 7.4; N, 27.2%; M, 257).

2,4-*Diamino*-5-(5-*amino*-4-*chloro*-2-*trifluoromethylsulphonloxy*)-6-*ethylpyrimidine* (**60**).—To a stirred mixture of TFA (10 ml) and TFAA (1 ml) at 0 °C was added TFSA (3 ml). Solid azidophenylpyrimidine (**36**) (3.5 g) was added in portions during 2 h at 0 °C. The yellow solution was stirred overnight at 25 °C and basified with ice–aqueous ammonia. The cream-coloured product (3.8 g) was collected and crystallised from ethyl acetate–light petroleum to give pink microprisms of the *pyrimidine ethyl acetate solvate*, m.p. 177—178 °C (decomp.) (Found: C, 40.5; H, 4.1; N, 14.8. $C_{13}H_{13}ClF_3N_5O_3S{\cdot}C_4H_8O_2$ requires C, 40.8; H, 4.2; N, 14.0%).

2,4-*Diamino*-5-(5-*azido*-4-*chloro*-2-*trifluoromethylsulphonyloxy*)-6-*ethylpyrimidine* (**63**).—To a stirred solution of the amine (**60**) in 5M-hydrochloric acid (50 ml) at 0 °C was added a solution of sodium nitrite (0.27 g) in water (5 ml). The yellow solution was stirred at 0 °C (0.5 h) and solid sodium azide (0.9 g) was added in portions during 0.5 h. The suspension was stirred at 0 °C for a further 2 h and poured into ice–aqueous ammonia. The *azidophenylpyrimidine* (**63**) (0.9 g) was crystallised from aqueous ethanol as cream-coloured felted needles, m.p. 161—162 °C (decomp.) (Found: C, 35.7; H, 2.5; N, 22.4. $C_{13}H_{11}ClF_3N_7O_3S$ requires C, 36.0; H, 2.6; N, 22.2%); $\nu_{max.}$ 2 160 cm^{-1} (N_3).

2,4,6-*Triaminoquinazoline* (**67**).—Finely powdered 2,4-diamino-6-nitroquinazoline (**66**) (14.0 g) was added in portions to a stirred mixture of tin(II) chloride dihydrate (50.6 g) in 10M-hydrochloric acid (150 ml) at such a rate that the temperature was maintained below 30 °C. The mixture was kept at 4 °C (24 h) and the white triaminoquinazoline–tin(IV) complex was collected. A solution of the complex in boiling water (100 ml) was cooled to 36 °C and adjusted to pH 12 with 10M-sodium hydroxide. The precipitated product (**67**) (92%) was crystallised from water as amber prisms, m.p. 251—253 °C (lit.,[24] 255—258 °C).

The triamine (**67**) gave, in boiling acetic anhydride (0.5 h), a *triacetyl derivative*, which was crystallised from water as prisms, m.p. 278—280 °C (Found: C, 55.5; H, 5.0; N, 23.1. $C_{14}H_{15}N_5O_3$ requires C, 55.8; H, 5.0; N, 23.3%); $\nu_{max.}$ 1 680 cm^{-1} (C=O); m/z 301 (35%, M^+), 259 (100), 217 (100), and 175 (85); δ 2.10 (3 H, s, Ac), 2.25 (3 H, s, Ac), 2.35 (3 H, s, Ac), 7.78 (1 H, d, $J_{8,7}$ 9.2 Hz, 8-H), 8.12 (1 H, dd, $J_{7,8}$ 9.2, $J_{7,5}$ 2.2 Hz 7-H), 8.49 (1 H, d, $J_{5,7}$ 2.2 Hz, 5-H), 10.30 (1 H, s, NH), and 10.5 (1 H, br s, NH).

2,4-*Diaminoquinazoline*-6-*diazonium Tetrafluoroborate* (**68**).—A solution of 2,4,6-triaminoquinazoline (**67**) (1.1 g) in 50% aqueous tetrafluoroboric acid (2.5 ml) at 0—5 °C was diazotised by dropwise addition of a solution of sodium nitrite (0.48 g) in water (5 ml) during 1.5 h. The precipitate (82%) was shaken with cold acetonitrile (5 ml) and the buff solid was collected and washed with diethyl ether; the product, m.p. 197—200 °C (decomp.), analysed as the *diazonium tetrafluoroborate tetrafluoroboric acid salt* with acetonitrile of crystallisation (Found: C, 30.1; H, 2.7; N, 23.9. $C_8H_7N_6{\cdot}BF_4{\cdot}HBF_4{\cdot}C_2H_3N$ requires C, 29.8; H, 2.7; N, 24.3%); $\nu_{max.}$ 2 300 cm^{-1}.

A solution of 2-naphthol (0.5 g) in 1M-potassium hydroxide (25 ml) was mixed with a solution of the diazonium tetrafluoroborate (**68**) (0.54 g) in water (25 ml) at 4 °C. The precipitated 2,4-*diamino*-6-(2-*hydroxy*-1-*naphthylazo*)*quinazoline* crystallised from aqueous ethanol as red microneedles (25%) m.p. > 300 °C (Found: C, 60.3; H, 4.7; N, 22.9%; M^+, 330.122. $C_{18}H_{14}N_6O{\cdot}1.5H_2O$ requires C, 60.5; H, 4.8; N, 23.5%; M, 330.123); $\nu_{max.}$ 1 570, 1 620, and 3 400br cm^{-1}.

2,4-*Diaminoquinazoline*-6-*diazonium Chloride Hydrochloride* (**69**).—A stirred mixture of 2,4,6-triaminoquinazoline (**64**) (0.5 g) in 6M-hydrochloric acid (20 ml) deposited a crystalline hydrochloride salt which dissolved to give a yellow solution when sodium nitrite (0.3 g) in water (2 ml) was added at 0 °C during 1.5 h. The fine yellow precipitate which collected when the mixture was stirred at 0 °C for a further 1 h, was dissolved in DMSO (1 ml). Addition of chloroform (0.5 ml) followed by diethyl ether afforded the diazonium chloride (0.5 g), m.p. 160 °C (violent decomp.); $\nu_{max.}$ 2 300 cm^{-1} (N_2^+).

2,4-*Diamino*-6-*azidoquinazoline* (**70**).—A suspension of the diazonium chloride (**69**) [prepared from 2,4,6-triaminoquinazoline (**67**) (7.2 g) in 2M-hydrochloric acid (70 ml) following treatment with sodium nitrite (2.84 g) in water (15 ml) at 0 °C] was treated portionwise with sodium azide (2.68 g) in water (25 ml). The mixture was stirred at 0 °C for 2 h and basified with conc. aqueous ammonia. The precipitated *azide* (**70**) (98%) was crystallised from ethanol to form cream-coloured microneedles, m.p. 135 °C (decomp.) (Found: C, 47.7; H, 3.4; N, 48.7. $C_8H_7N_6$ requires C, 47.7; H, 3.5; N, 48.8%); $\nu_{max.}$ 2 140 cm^{-1} (N_3). Thermolysis of the azide free base (0.1 g) in refluxing decalin (3 ml) for 8 h gave an impure sample of 2,4,6-triaminoquinazoline (**70**) (0.6 g).

The azide free base (**70**) was crystallised from 2M-hydro-

chloric acid to form a *hydrochloride salt* (80%) as yellow flakes, m.p. 135 °C (decomp.) (Found: C, 40.4; H, 3.4; N, 41.4. $C_8H_7N_7$·HCl requires C, 40.4; H, 3.4; N, 41.3%); $\nu_{max.}$ 2 120 cm^{-1} (N_3).

2,4-*Dihydrazinoquinazoline* (**71**).—2,4-Diamino-6-azidoquinazoline (**70**) (1.25 g) was refluxed in hydrazine hydrate (15 ml) for 6 h and cooled. The yellow crystalline product (50%) was recrystallised from pyridine to yield green prisms of the *dihydrazinoquinazoline* (**71**), m.p. 226—229 °C (lit.,[25] 226—227 °C). The dihydrazinoquinazoline was formed (60%) when the diaminoquinazoline (**65**) was refluxed in hydrazine hydrate (6 h).

2-*Amino*-4-*hydrazinoquinazoline* (**72**).—2,4-Diaminoquinazoline (**65**) (1.25 g) was refluxed in hydrazine hydrate for 1.5 h. The cooled solution deposited yellow crystals of the *monohydrazinoquinazoline* (**72**) (40%), which was recrystallised from pyridine as prisms, m.p. 206—208 °C (Found: C, 54.8; H, 5.1; N, 40.6%; M^+, 175.085 79. $C_8H_9N_5$ requires C, 54.9; H, 5.1; N, 40.0%; M, 175.085 47); $\nu_{max.}$ 1 620, 1 640, 3 100br, 3 300, and 3 490 cm^{-1}.

The same (i.r. monohydrazinoquinazoline (**72**) (65%) was formed when 2,4-diamino-6-azidoquinazoline (**70**) (0.3 g) was refluxed in hydrazine hydrate (5 ml) for 1.5 h.

2,2′,4,4′-*Tetra-amino*-6,6′-*azoquinazoline* (**74**).—(i) A solution of 2,4-diamino-6-azidoquinaozline (**70**) (0.59 g) in nitrobenzene (15 ml) was refluxed in a light-protected vessel for 2 h. The cooled solution deposited purple microcrystals (0.49 g), which were purified by washing with ethanol. The pure *azoquinazoline* had m.p. >360 °C, and $\nu_{max.}$ 840, 1 140, 1 410, 1 500, 1 550, 1 620, 1 650, 3 180, and 3 350 cm^{-1}; $\lambda_{max.}$(water) 480 nm; M^+, 346. No consistent microanalytical data could be obtained for this compound. Reduction of a solution of the azo compound (0.1 g) in 2-ethoxyethanol (15 ml) with 10% aqueous sodium dithionite (15 ml) afforded the triamine (**67**) (0.055 g).

(ii) A solution of 2,4-diamino-6-azidoquinazoline (**70**) (1.33 g) in methanol (l l) was photolysed with an unfiltered 100 W, medium-pressure lamp in an Hanovia photochemical reactor for 10 h during which time nitrogen was evolved. At hourly intervals the quartz sleeve of the lamp was cleaned free of adhering maroon product. The methanol solution was concentrated to 25 ml and the maroon product (0.5 g), which was collected and washed repeatedly with hot water, was identical (i.r., u.v.) with a sample of the azo compound prepared above. T.l.c. examination of the photolysate confirmed the presence of unchanged starting material and 2,4,6-triaminoquinazoline (**67**).

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