The Synthesis of Heterocycles *via* Addition–Elimination Reactions of 4- and 5-Aminoimidazoles

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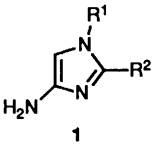
4-Aminoimidazoles **1** undergo addition–elimination reactions with the electrophilic reagents **5–12** to give exclusively *N*-adducts, which are useful intermediates for further synthetic transformations to novel heterocyclic systems. Diethyl ethoxymethylenemalonate **5** and 4-amino-1-benzylimidazole **1g** give the adduct **13g** and subsequent acid-catalysed cyclisation gives the imidazo[4,5-*b*]pyridine **25** and the heterocyclic mesomeric betaine **26** which undergoes 1,3-dipolar cycloaddition with dimethyl acetylenedicarboxylate to give two products **29** and **30**. When the 2-alkyl-4-aminoimidazoles **1b–d** are generated *in situ* in the presence of the reagent **5**, significant products are the 5,5′-diimidazoles **15** and a mechanism for this novel transformation is proposed. 4-Amino-3-cyanoimidazo[1,5-*a*]pyrimidines **40** and **41** are formed by cyclisation of the *N*-adducts prepared using ethoxymethylenemalononitriles **6** and **7**. Ethoxymethyleneurethane **9** gives the adducts **66** and cyclisation of the parent adduct **66a** gives the novel imidazo[1,5-*a*]-1,3,5-triazin-4-one **68a**, the potassium salt of which undergoes *N*-alkylation. The use of the reagents **10–12** leads to novel 4-aminoimidazo[1,5-*a*]-1,3,5-triazine derivatives **72** whose chemical reactions with both electrophilic and nucleophilic reagents are reported. 5-Aminoimidazoles **3** undergo addition–elimination reactions with the electrophilic reagents **5–12** to give *N*-adducts and/or *C*-adducts, depending upon the structure of the reagent. These stable addition–elimination products are usually obtained in good yield and are useful intermediates for further synthesis. Reaction of the amines **3** with diethyl ethoxymethylenemalonate **5** gives mainly *N*-adducts **17** which can be cyclised using phosphoryl chloride to give the versatile 7-chloroimidazo[4,5-*b*]pyridines **31**. With ethoxymethylenemalononitrile **6** the amines **3** give *C*-adducts **42**. Thermal cyclisation of these adducts **42** gives 5-amino-6-cyanoimidazo[4,5-*b*]pyridines **43** which are transformed into novel heterocyclic systems including the tricyclic imidazo[4′,5′:5,6]pyrido[2,3-*d*]pyrimidines **55**. Cyclisation of the adducts obtained using ethoxymethyleneurethane **9** and the *N*-cyano analogues **10** and **12** provides new synthetic routes to amino-purine derivatives **86** and **87** and hypoxanthines **70**. The preference of electrophilic reagents for *N*- or *C*-addition to 5-aminoimidazoles **3** is rationalised using Frontier Molecular Orbital theory.

In the preceding paper [1] we have described the *in situ* generation of 4- and 5-aminoimidazoles **1** and **3** by catalytic reduction of 4- and 5-nitroimidazoles **2** and **4**. We now report the condensation of these novel amines with electrophilic reagents **5–12** and the utilisation of the resulting products in heterocyclic synthesis. In most of this work we have found it convenient to generate the amines **1** *in situ* in the presence of the appropriate reagent. In a later section we discuss the factors which may control *C*-addition or *N*-addition of electrophilic reagents to 5-aminoimidazoles **3** in terms of a Frontier Molecular Orbital model.

Reactions Utilising Diethyl Ethoxymethylenemalonate **5**.— When 4-aminoimidazole **1a** or the 1-substituted derivatives **1e**, **g**, **i**, **j** were generated *in situ* in the presence of diethyl ethoxymethylenemalonate **5**, by catalytic reduction of ethanolic solutions of the appropriate 4-nitroimidazole **2**, the *N*-addition–elimination products **13a**, **e**, **g**, **i**, **j** were obtained. No other products were isolated and there was no evidence of formation of the *C*-addition–elimination products **14**. In contrast, when the 1-unsubstituted 2-alkyl-4-nitroimidazoles **2b–d** were reduced under similar conditions, in addition to the products **13b–d**, the 5,5′-diimidazole derivatives **15b–d** were obtained as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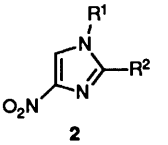
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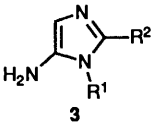
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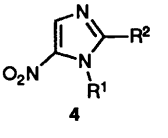
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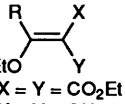
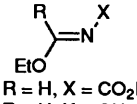
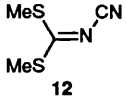
In formulae **1–33**, **38–43**, and **64–70** : **a** $R^1 = R^2 = H$; **b** $R^1 = H$, $R^2 =$, Me; **c** $R^1 = H$, $R^2 = Et$; **d** $R^1 = H$, $R^2 = Pr^i$; **e** $R^1 = R^2 = Me$; **f** $R^1 = Me$, $R^2 = Pr^i$; **g** $R^1 = CH_2Ph$, $R^2 = H$; **h** $R^1 = CH_2OCOMe$, $R^2 = H$; **i** $R^1 = CH_2OCOMe$, $R^2 = Me$; **j** $R^1 = SO_2NMe_2$, $R^2 = H$; **k** $R^1 = Me$, $R^2 = H$; **l** $R^1 = CH_2CH_2OH$, $R^2 = Me$; **m** $R^1 = Me$, $R^2 = CH_2CH_2Ph$; **n** $R^1 = CH_2CH_2OAc$, $R^2 = Me$; **o** $R^1 = Me$, $R^2 = CHCHPh$; **p** $R^1 = CH_2CH_2Cl$, $R^2 = Me$


5 R = H, X = Y = CO_2Et
6 R = H, X = Y = CN
7 R = Me, X = Y = CN
8 R = H, X = CO_2Et, Y = CN


9 R = H, X = CO_2Et
10 R = H, X = CN
11 R = Me, X = CN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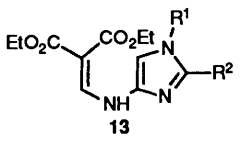
the major products. Table 1 shows the isolated yields of products **13** and **15** formed from various precursors. The product structures **13** and **15** were fully supported by their spectroscopic and chemical properties. Typically, compound **13b** shows a ^{1}H NMR signal at δ 6.57 which is attributable to the imidazole ring proton at position 5 and doublets at δ 8.68 and δ 10.90 due to the coupled (J 13 Hz) aminomethylene (NHCH=) protons. In the spectrum of the 5,5′-diimidazole **15b** a signal attributable to an imidazole ring proton is absent but the aminomethylene signals (δ 8.55 and 10.66) are still observed. Acid-catalysed cyclisation (conc. H_2SO_4 and acetic anhydride) of the 5,5′-diimidazoles **15** gives the 8,8′-diimidazo[3,4-*a*]pyrimidines **16**.

When 5-amino-1,2-dimethylimidazole **3e** was generated *in situ* in ethanol solution in the presence of diethyl ethoxymethylenemalonate **5**, by catalytic reduction of 1,2-dimethyl-5-nitroimidazole **4e**, three products were obtained. The major



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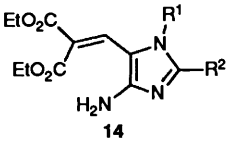

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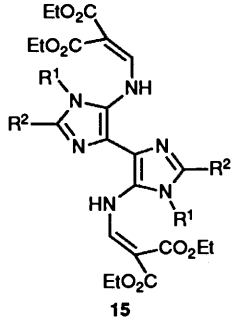

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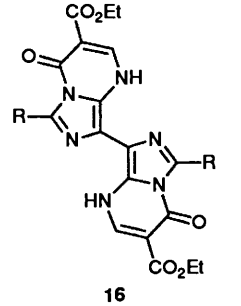

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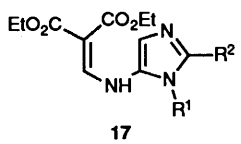

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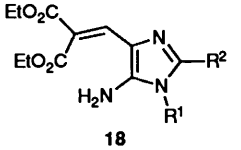

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product (65%) was the ethyleneamino derivative **17e** resulting from condensation of the reagent with the 5-amino group. A minor product (5%) was the isomer **18e** which is formed by reaction of the reagent at the 4-position of the imidazole ring. This pair of isomers could not be interconverted, **17e** ⇌ **18e**, and the assigned structures are fully supported by their chemical and spectroscopic properties. Particularly significant is the presence of an imidazole ring proton (δ 6.79, 4-H) in the ^{1}H NMR spectrum of compound **17e** whereas a similar proton signal is absent from the spectrum of the amine **18e**. The third product (1%) was shown to have the 5,5′-diimidazole structure **15e**. This structural assignment **15e** is fully supported by analytical and spectroscopic data. The ^{1}H NMR spectrum shows the absence of any imidazole ring protons together with a =CH–NH fragment (J 12 Hz), two methyl groups (C–CH_3 and N–CH_3) and two ethyl ester functions.

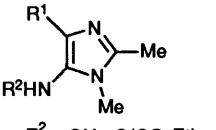
Using procedures similar to that described for compound **3e**, the amines **3f–m** were also allowed to react with diethyl ethoxymethylenemalonate **5** and the yields of the products isolated are shown in Table 1. The vinylamine **17** is the major product in all cases and, when isolated, the derivatives **18** and **15** are only minor products. When *in situ* formation and trapping of the amines **3e, l** was repeated using dioxane as solvent, the major products **17e, l** were formed in significantly greater yield (Table 1) and the by-products **15e, l** and **18e, l** were absent. This advantage of dioxane over ethanol as solvent led us to use

Table 1 Products formed by the reduction of 4- or 5-nitro-imidazoles **2** or **4** in the presence of diethyl ethoxymethylenemalonate **5**

Nitroimidazole	Solvent	Products (% yield)		
4-Nitroimidazoles		**13**	**14**	**15**
2a	Ethanol	45	—	—
2b	Ethanol	8	—	30
2c	Ethanol	—	—	32
2d	Ethanol	9	—	34
2e	Ethanol	36	—	—
2i	Ethanol	41	—	—
2j	Ethanol	14	—	—
5-Nitroimidazoles		**17**	**18**	**15**
4e	Ethanol	65	5	1
4e	Dioxane	86	—	—
4k	Ethanol	62	—	—
4l	Ethanol	32	—	0.4
4l	Dioxane	44	—	—
4f	Ethanol	64	4.5	1.6
4m	Ethanol	43	3	—

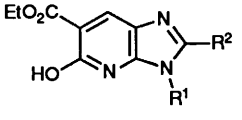
dioxane as the preferred solvent in all subsequent synthetic work using 4- or 5-aminoimidazoles **1** or **3**.

Further support for the structures of the amines **18** was provided by a study of the chemical properties of the derivative **18e**. Reaction with diethyl ethoxymethylenemalonate **5** gave the bis(diethoxycarbonylvinyl) derivative **19** (87%) and 3,4-dichlorophenyl isocyanate gave the urea **20** (34%), confirming the presence of the primary amino group. When compound **18e** was heated at reflux temperature in a solution of ethanol saturated with hydrogen chloride, cyclisation occurred to give the imidazo[4,5-*b*]pyridine **21e** (82%). Interestingly, when



19 $R^1 = R^2 = CH{=}C(CO_2Et)_2$

20 $R^1 = CH{=}C(CO_2Et)_2$, $R^2 = CONHC_6H_3Cl_2$–3,4



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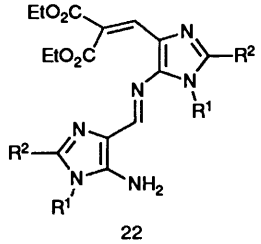

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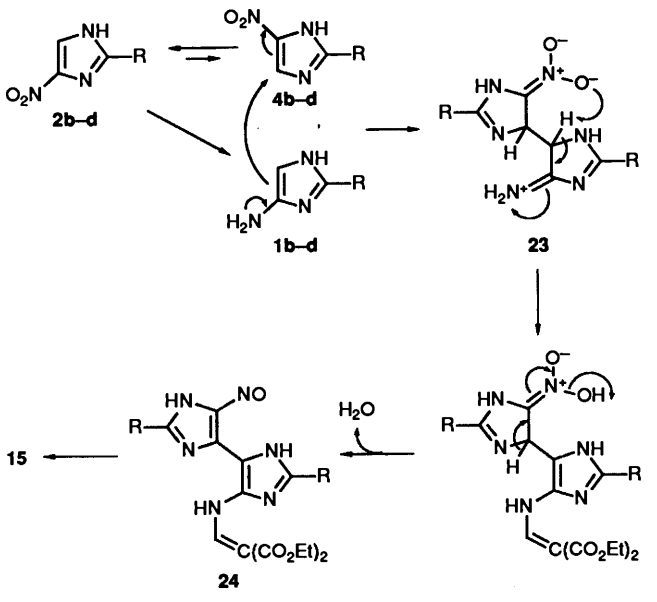
the same compound **18e** was heated under reflux in xylene an intermolecular condensation with elimination of diethyl malonate occurred to give the orange crystalline imine **22e** (56%).

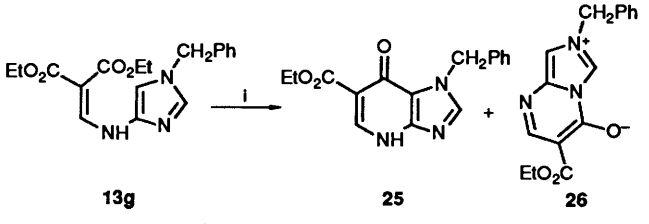
Formation of the diimidazole derivatives **15** was unexpected and it is of interest to consider reaction mechanisms which can account for: i, formation of diimidazoles in moderate yield using 1-unsubstituted 2-alkyl-4-nitroimidazoles **2b–d**; ii, formation of diimidazoles in very low yield using 5-nitroimidazoles; iii, no formation of diimidazoles using 4-nitroimidazole **2a** or 1-substituted 4-nitroimidazoles **2e, g, i, j**. We propose that formation of the products occurs *via* an initial electrophilic addition of the precursor nitroimidazole to its aminoimidazole reduction product. This mechanism is shown in Scheme 1. In particular, we suggest that it is a 5-nitroimidazole **4** which is the electrophile and that it is the opportunity for 4-nitroimidazoles **2b–d** to tautomerise to the 5-nitro isomers **4b–d** which enables



Scheme 1

them to participate in the reaction. Our preference for proposing a 5-nitroimidazole as the reaction species is based on the observation that 5-nitroimidazoles **4** are known to have significantly greater electron affinities than 4-nitroimidazoles **2** and can be expected to be more reactive towards electron-rich species.[1] This aspect of the mechanism is discussed in a later section where we discuss the relationship between the electronic structure and the reactivity and regioselectivity of aminoimidazoles towards electrophiles. The intermediate **23** (Scheme 1) may then undergo tautomerism and elimination of water to give the nitroso derivative **24** which is then reduced to the amine and reaction with diethyl ethoxymethylenemalonate **5** gives the observed product **15**. A similar mechanism can account for the formation of analogous products by 5-nitroimidazoles. The reason why 5-nitroimidazoles give only very low yields of 4,4′-diimidazole products is not clear but this is possibly due to either a restriction on the tautomeric opportunities during reaction or a greater reactivity towards 4-aminoimidazoles rather than 5-aminoimidazoles. It is surprising that 4(5)-nitroimidazole **2a** shows no evidence of diimidazole formation during reduction: it is possible that a 2-alkyl substituent is necessary to activate the aminoimidazole by elevating its HOMO energy.

Cyclisation of the 4-amino-1-benzylimidazole addition–elimination product **13g** using concentrated sulfuric acid in acetic anhydride gave a mixture of two products (Scheme 2)

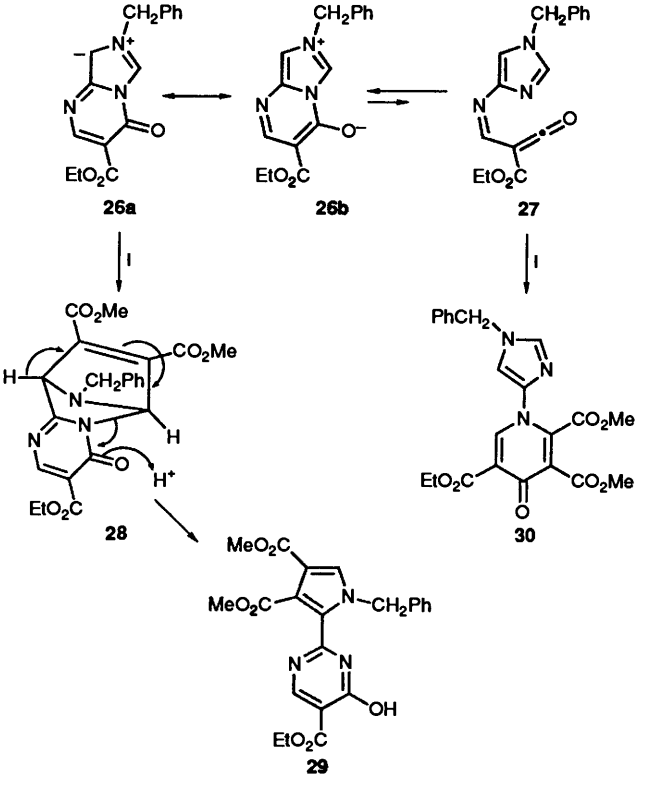


Scheme 2 *Reagents:* i, conc. H_2SO_4/Ac_2O

which were separated by pH-controlled selective precipitation and identified as the imidazo[4,5-*b*]pyridine **25** (11%) and the imidazo[3,4-*a*]pyrimidin-7-ium-4-olate **26** (29%). The structure of the first product **25**, which was isolated and characterised as its hydrogen sulfate salt, was fully supported by its ^{1}H NMR spectrum which showed two uncoupled heterocyclic ring protons at δ 8.40 (5-H) and δ 9.94 (2-H). The ^{1}H NMR spectrum of the conjugated heterocyclic mesomeric betaine **26** shows three heterocyclic ring protons. Signals at δ 7.73 (8-H) and δ 9.55 (6-H) appear as doublets (J 1 Hz), which is consistent with the structural assignment **26**, and the third signal at δ 8.46 (2-H) is a singlet.

Participation in 1,3-dipolar cycloadditions is a property of many conjugated heterocyclic mesomeric betaines[2,3] and we have investigated the reaction of compound **26** with dimethyl acetylenedicarboxylate. When this reagent was heated with the mesomeric betaine **26** in toluene solution of 100 °C, a mixture of two products was obtained. These were separated by chromatography and identified as the *N*-benzylpyrrole derivative **29** (32%) and the *N*-benzylimidazole derivative **30** (21%).

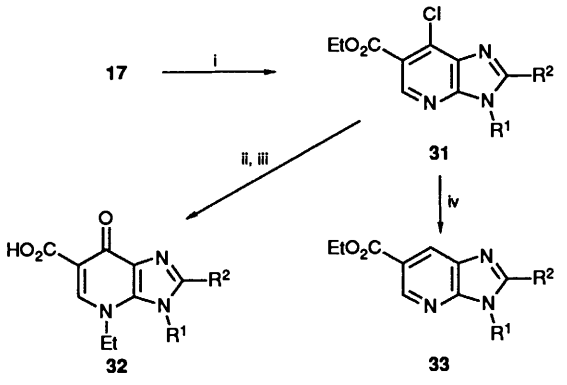
Product **29** was fully characterised by its analytical and spectroscopic properties. The ^{1}H NMR spectrum shows a pyrrole ring proton (δ 7.87), a pyrimidine ring proton (δ 8.64) and a very broad signal (δ 13.00) due to the acidic OH proton. We interpret the formation of this product **29** in terms of an initial 1,3-dipolar cycloaddition of dimethyl acetylenedicarboxylate to the azomethine ylide fragment of betaine **26a** (Scheme 3). The intermediate cycloadduct **28** may then undergo



Scheme 3 *Reagents:* i, $MeO_2C{\cdot}C{\equiv}C{\cdot}CO_2Me$

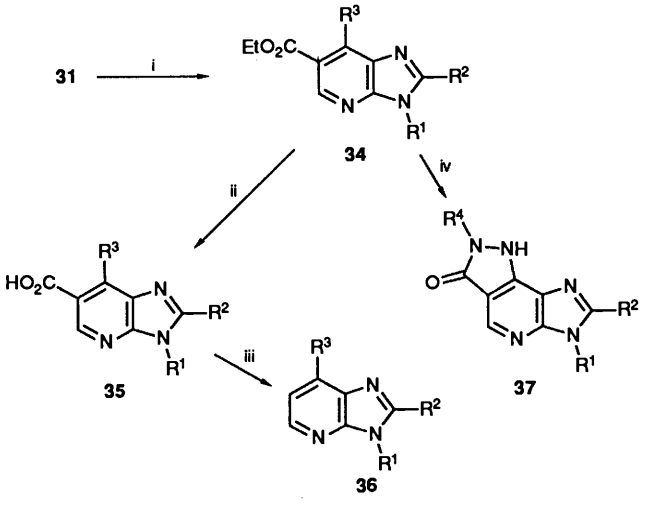
fragmentation in the manner shown in Scheme 3 to give the observed product **29**. The ^{1}H NMR spectrum of the second product showed coupling of the imidazole ring protons (J 1 Hz) at δ 7.65 (5-H) and δ 7.86 (2-H) together with a singlet at δ 8.35 which is attributable to the pyridone 2-H. The formation of the pyridone **30** can be rationalised in terms of a mechanism in which the betaine **26a**↔**26b** ring opens to the ketene intermediate **27** which then undergoes a hetero Diels–Alder reaction with dimethyl acetylenedicarboxylate to give the observed product **30** (Scheme 3).

Since the imidazole derivatives **17** are formed in good yield, they are attractive intermediates for further synthesis. They can be cyclised to the ethyl 7-chloroimidazo[4,5-*b*]pyridine-6-carboxylates **31** using phosphoryl chloride at reflux temperature and in this way the derivatives **31e**, **f**, **m**, **n**, **p** were prepared in good yield (Scheme 4). Cyclisation of the 1-(2-hydroxyethyl)-imidazole **17l** resulted in formation of the 3-(2-chloroethyl)



Scheme 4 *Reagents and conditions:* i, $POCl_3$, boil; ii, NaOH, H_2O, $EtO(CH_2)_2OH$, boil; 3 h; EtI, boil, 1 h; iii, EtOH, NaOH, H_2O, 0.5 h; iv, EtOH, Et_3N, Pd/C, H_2

derivative **31p**. If necessary, the 2-hydroxyethyl function can be protected by conversion into the 1-(2-acetoxyethyl)imidazole **17n** which undergoes cyclisation to the derivative **31n**. This preparation of ethyl 7-chloro-imidazo[4,5-*b*]pyridine-6-carboxylates **31** forms the basis of a new 1-deazapurine synthesis:[4] the reactive intermediates **31** can be transformed into a variety of structural analogues of systems of biological significance. The derivatives **31e, m** were transformed to the nalidixic acid[5]



Scheme 5 *Reagents and conditions:* i, R^3NH_2, EtOH, boil; ii, EtOH, NaOH, boil; HCl; iii, Dowtherm, boil; iv, NaOH, EtOH, boil

In formulae **34–37**;

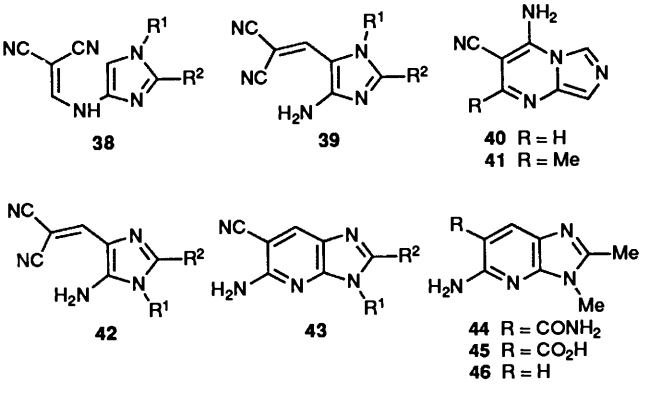
a $R^1 = R^2 = Me$, $R^3 = NHnBu$
b $R^1 = R^2 = Me$, $R^3 = NHCH_2Ph$
c $R^1 = R^2 = Me$, R^3 = morpholin-1-yl
d $R^1 = R^2 = Me$, $R^3 = NH(CH_2)_3NMe_2$
e $R^1 = R^2 = Me$, $R^3 = NHCH_2CH{=}CMe_2$
f $R^1 = R^2 = Me$, $R^3 = NH_2$
g $R^1 = R^2 = Me$, $R^3 = NHNH_2$
h $R^1 = R^2 = Me$, $R^3 = NHNHPh$
i $R^1 = R^2 = Me$, $R^3 = SCH_2Ph$
j $R^1 = R^2 = Me$, $R^3 = OEt$
k $R^1 = R^2 = Me$, $R^3 = OCH_2Ph$
l $R^1 = CH_2CH_2OH$, $R^2 = Me$, $R^3 = NHnBu$
m $R^1 = CH_2CH_2OH$, $R^2 = Me$, $R^3 = NHCH_2Ph$
n $R^1 = CH_2CH_2OH$, $R^2 = Me$, $R^3 = NH_2$
o $R^1 = CH_2CH_2OH$, $R^2 = Me$, $R^3 = NHNHPh$
p $R^1 = CH_2CH_2OH$, $R^2 = Me$, $R^3 = NHfurfuryl$
q $R^1 = CH_2CH_2OAc$, $R^2 = Me$, $R^3 = NHfurfuryl$
r $R^1 = Me$, $R^2 = Pr^i$, $R^3 = NHCH_2Ph$
s $R^1 = Me$, $R^2 = Pr^i$, $R^3 = NHCH_2CH{=}CMe_2$
t $R^1 = R^2 = Me$, $R^4 = H$
u $R^1 = R^2 = Me$, $R^4 = Ph$
v $R^1 = CH_2CH_2OH$, $R^2 = Me$, $R^4 = Ph$

analogues **32e, m** using the following procedure: i, hydrolysis with 10 mol dm^{-3} NaOH in hot ethoxyethanol solution; ii, alkylation by addition of ethyl iodide; and iii, saponification to give the carboxylic acid. The chlorine atom of the derivatives **31** can be removed by catalytic reduction giving, for example, the 2,3-dimethylimidazo[4,5-*b*]pyridine **33e** (58%) whose NMR spectrum shows *meta* coupled doublets (J 2 Hz) at δ 8.88 (5-H) and δ 8.40 (7-H). In this way, the derivatives **33f, n** were also prepared.

The chloro derivatives **31** readily undergo nucleophilic substitution and using nitrogen nucleophiles the derivatives **34a–h, l–s** were prepared (Scheme 5). These derivatives include compounds with amine substituents chosen to provide analogues of the cytokinins, which are naturally occurring purine derivatives having growth-regulating properties in plants.[6] In a similar manner using the appropriate alkoxide or thiolate the derivatives **34i–k** were made. Saponification of the esters **34a–e, k–n** gave the corresponding carboxylic acids **35** which in the case of the derivatives **35a–e, n** were decarboxylated thermally giving the 2,3,7-trisubstituted imidazo-[4,5-*b*]pyridines **36a–e, n**. In accord with expectation, cyclisation of the hydrazine derivatives **34g, h, o** occurred in hot ethanolic alkali giving the 1,2-dihydroimidazo[4,5-*b*]pyrazolo-[3,4-*d*]pyridin-3(6*H*)-ones **37t–v**. A table of yields, melting points, microanalytical data, and NMR spectra of the derivatives **34a–j, l–s, 35b–e, i, k–n**, and **36b–e, l, n** has been deposited as Supplementary Information [Suppl. Publ. no. 56895 (11 pp.)].*

Reactions Utilising Ethoxymethylenemalononitriles **6** *and* **7**.—Treatment of a dioxane solution of 4-aminoimidazole **1a** with ethoxymethylenemalononitrile **6** and subsequent concentration of the reaction solution gave a crystalline product which was identified by ^1H NMR spectroscopy as the *N*-addition–elimination product **38a** (82%). In particular, the weakly coupled (J 1 Hz) imidazole 2- and 5-protons are clearly observed at δ 7.50 and 6.75 and the olefinic proton appears as a singlet at δ 8.18. None of the alternative *C*-addition–elimination product **39a** was detected and this is an interesting difference to the 5-aminoimidazoles which give exclusively *C*-addition–elimination products with this reagent **6**.

Attempts to recrystallise compound **38a** resulted in cyclisation to 4-amino-3-cyanoimidazo[1,5-*a*]pyrimidine **40a** and we have found that this transformation **38a**→**40a** is best



achieved by crystallisation from hot water. The 2-methyl derivative **41** was prepared from 4-aminoimidazole **1a** and the reagent **7** using a similar procedure. The structures of the imidazo[1,5-*a*]-pyrimidines **40** and **41** were fully supported by their analytical and spectroscopic properties.

* For details of the deposition scheme see Instructions for Authors in *J. Chem. Soc., Perkin Trans. 1*, 1992, issue 1.

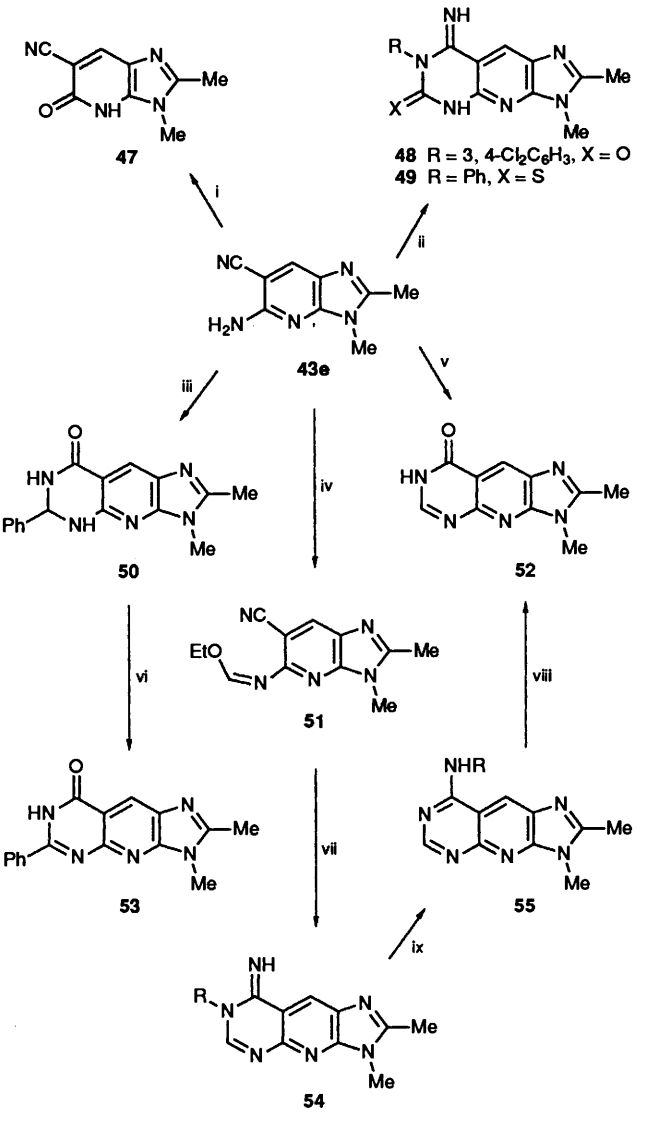
Reaction of the 1-substituted 4-aminoimidazoles **1e**, **f**, **k** with ethoxymethylenemalononitrile **6** gave the *N*-addition–elimination products **38e**, **f**, **k** and ^{1}H NMR spectroscopy (5-H δ 6.5–6.8) fully supported these structural assignments. However, it is interesting to note that amine **1i** gave a mixture of the *N*-addition–elimination product **38i** {δ_H([$^2H_6$]-DMSO) 2.08 (s, $COCH_3$), 2.35 (s, CCH_3), 5.35 (s, CH_2O), 6.92 (s, 5-H), 8.22 (s, HNC*H*) and 11.42 (br s, *H*NCH)} and the *C*-addition–elimination product **39i** {δ([$^2H_6$]-DMSO) 2.05 (s, $COCH_3$), 2.40 (s, CCH_3), 5.90 (s, CH_2O), 7.13 (br s, NH_2) and 7.73 (s, CH)}.[7] The factors which determine the regioselectivity of these addition–eliminations are clearly finely balanced.

In contrast to their reactions with diethyl ethoxymethylenemalonate **5**, 5-aminoimidazoles **3** react with ethoxymethylenemalononitrile **6** to give exclusively, and in high yield, the *C*-addition products, 5-amino-4-(2,2-dicyanovinyl)imidazoles **42**. The TLC examination of the reaction mixtures revealed no other products. Typically, the amine **3e** in dioxane solution was stirred with a dioxane solution of the reagent **6** and the product **42e** (84%) was precipitated as a yellow crystalline solid after several minutes. Analytical and spectroscopic data fully supported the structural assignments for compounds **42**. The ^{1}H NMR spectra showed the presence of broad singlets corresponding to the protons of the primary amino groups and, significantly, imidazole 4-H signals were absent. Chemical evidence for the structures **42** was provided by cyclisation. When heated at 90 °C in aqueous alcoholic sodium hydroxide the amines **42** cyclise in good yield to give 5-amino-6-cyanoimidazo[4,5-*b*]pyridines **43**. In this way, the derivatives **43e**, **f**, **l** were prepared. The ^{1}H NMR spectra of these derivatives **43** are characterised by a broad signal at δ 6.4–6.6 due to the primary amino groups at position 5 and a singlet in the region δ 8.0–8.1 due to the proton at position 7.

The imidazo[4,5-*b*]pyridine derivatives **43** are versatile synthetic intermediates[8] and their preparation in good overall yield from 5-nitroimidazoles **4** provides the opportunity of preparing a variety of novel 1-deazapurine analogues. Some transformations of the 2,3-dimethyl derivative **43e**, which are described below, illustrate the utility of these intermediates. The nitrile function of compound **43e** can be hydrolysed to the amide **44** using hot 0.2 mol dm^{-3} KOH or to the carboxylic acid **45** using hot 5 mol dm^{-3} NaOH. The latter product **45** readily undergoes thermal decarboxylation thus providing a novel route to 5-aminodeazapurines **46**. Treatment of the amine **43e** with nitrous acid gives the imidazo[4,5-*b*]pyridin-2-one **47**.

A feature of the intermediates **43** is the opportunity they provide for synthesising tricyclic heterocyclic systems which can be regarded as elongated purine derivatives. Leonard and Hiremath[9] have described such systems as 'stretched-out' purines and they have used them as dimensional probes to investigate the requirements of enzymic reactions. Their studies[9] mainly focused on the use of a benzene ring as a spacer group between the pyrimidine ring and the imidazole ring of purines. Using the dimethyl derivative **43e** we have prepared a number of 'stretched-out' purine analogues in which the spacer group is a pyridine ring (Scheme 6). Reaction of compound **43e** with triethyl orthoformate gave the imino ether **51** (53%) which upon treatment with primary amines in ethanol solution resulted in cyclocondensation giving the 8-iminoimidazo-[4′,5′:5,6]pyrido[2,3-*d*]pyrimidines **54**. Reaction of these compounds **54** with a further portion of the appropriate primary amine in glacial acetic acid gave the isomeric 8-aminoimidazo-[4′,5′:5,6]pyrido[2,3-*d*]pyrimidines **55** in good yields. This Dimroth rearrangement[10] **54**→**55** presumably occurs by acid-catalysed ring opening by the amine followed by recyclisation to the more stable isomer.

The parent 8-amino derivative **55a** was formed directly from the intermediate **51** by treatment with saturated ethanolic

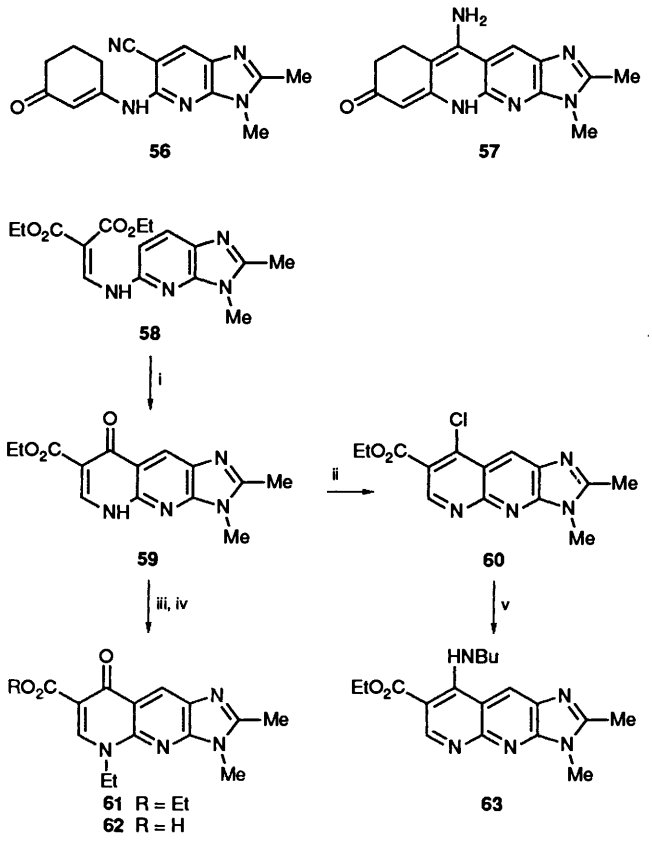


Scheme 6 *Reagents and conditions:* i, $NaNO_2$, $HCl_{(aq)}$, 20 °C, 0.5 h; ii, 3,4-Cl_2PhNCO or PhNCS, DMF, 100 °C, 6 h; iii, KOH, EtOH, PhCHO, 60 °C, 30 h; iv, $(EtO)_3CH$, tosic acid, reflux, 3 h; v, HCO_2H, 100 °C, 24 h; vi, $PhNO_2$, reflux, 5 h; vii, EtOH, RNH_2, 20 °C, 18 h; viii, $HCl_{(aq)}$, reflux, 2.5 h; ix, EtOH, AcOH, RNH_2, reflux, 2 h

In formulae **54** and **55**: **a**, R = H; **b**, R = Bu; **c**, R = CH_2Ph; **d**, R = morpholin-4-ylpropyl; **e**, R = 2-furylmethyl; **f**, R = 2-pyridylmethyl; **g**, R = CH_2CH_2OH; **h**, R = 4-methylpyrazin-1-ylpropyl; **i**, R = Ac.

ammonia; the imino tautomer **54a** if formed rapidly equilibrates with the more stable amino isomer **55a**. Hydrolysis of this amine **55a** using hot 2 mol dm^{-3} hydrochloric acid gave the 8-oxo derivative **52** which was also formed by the reaction of the 5-amino-6-cyanoimidazo[4,5-*b*]pyridine **43e** with hot 90% formic acid. With acetic anhydride, the amine **55a** gave the amide **55i**.

With phenyl isothiocyanate in DMF solution, compound **43e** gave, after heating at 100 °C, the tricyclic derivative **49** and a similar procedure using 3,4-dichlorophenyl isocyanate gave the derivative **48**. When treated with benzaldehyde and potassium hydroxide in hot ethanol the intermediate **43e** gave compound **50** which could be oxidised to the aromatic system **53** thermally in nitrobenzene. The tetracyclic system **57** was prepared by condensation of compound **43e** with cyclohexane-1,3-dione in hot toluene in the presence of toluene-*p*-sulfonic acid and cyclisation of the resulting intermediate **56** using zinc chloride in hot xylene.



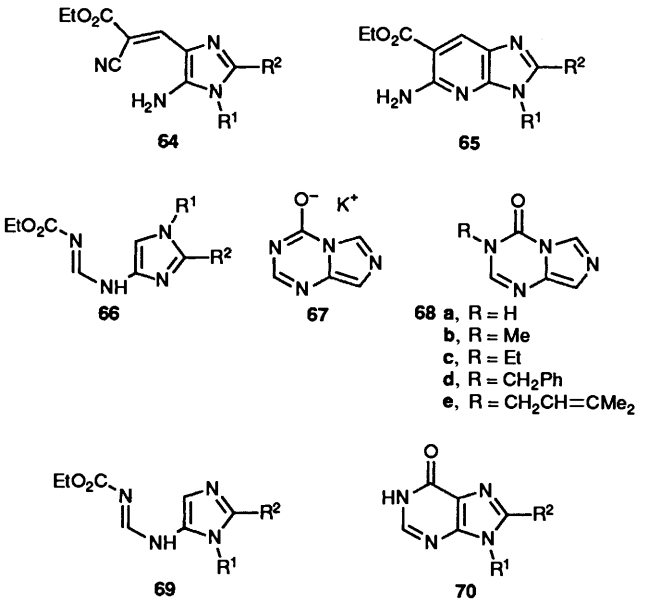
Scheme 7 *Reagents and conditions:* i, Dowtherm, reflux, 0.5 h; ii, $POCl_3$, reflux, 0.25 h; iii, DMF, K_2CO_3, EtI, 100 °C, 1.5 h; iv, $KOH_{(aq)}$, reflux, 18 h; v, $BuNH_2$, EtOH, reflux, 2 h

Further examples of novel tricyclic systems (Scheme 7) were prepared from compound **58** which was readily obtained by condensation of the amine **46** with diethyl ethoxymethylenemalonate **5**. Thermal cyclisation of compound **58** gave the compound **59** which with phosphoryl chloride gave the 8-chloro derivative **60**. Subsequent treatment with butylamine in ethanol gave the 8-butylamino derivative **63**. Alkylation of compound **59** using ethyl iodide and potassium carbonate gave the ester **61** which was converted into the novel nalidixic acid derivative **62** using 2 mol dm^{-3} potassium hydroxide.

Reactions Utilising Ethyl (Ethoxymethylene)cyanoacetate **8**.—When the 5-aminoimidazoles **3e, f, l** were allowed to react with ethyl (ethoxymethylene)cyanoacetate **8** in dioxane solution in a manner similar to that used for ethoxymethylenemalononitrile **6** the products were exclusively the 3-(5-aminoimidazol-4-yl)-2-cyanoacrylates **64** which are *C*-adducts. None of the isomers resulting from condensation on the amino group were detected. Typically, the amine **3e** gave the cyanoacrylate **64e** which had a ^1H NMR spectrum comparable to the analogues **18e** and **42e**. In compound **64e** only one set of ethyl signals was observed implying that a single geometric isomer is formed but this is not necessarily the *trans* ester structure depicted in structure **64e**.

Thermal cyclisation of compound **64e** gave the imidazo[4,5-*b*]pyridine **65e** (70%), m.p. 176–177 °C, which had a ^1H NMR spectrum similar to the closely related derivatives **43e**, **44**, **45** and **46**. The alternative cyclisation giving the 5-oxoimidazo-[4,5-*b*]pyridine **47**, m.p. >360 °C, was not observed. Chemical reactions of the esters **65** were not further explored since similar products were also accessible from the analogous nitriles **43** (*e.g.* Scheme 6).

Reactions Utilising Ethoxymethyleneurethane **9**.—*In situ* generation of the 4-aminoimidazoles **1a, e, h** in dioxane solution followed by addition of ethoxymethyleneurethane **9** gave the ethyl[(imidazol-4-yl)aminomethylene]carbamates **66a, e, h** in good yield. The structures **66** were fully supported by elemental analysis and their spectroscopic properties. In particular, ^1H NMR spectroscopy showed the presence of imidazole 5-H (δ 6.70–6.95), which, in the case of the derivatives **66a, h**, were coupled with 2-H, and also exchangeable protons (NH) in the region δ 10.35–10.50. This evidence confirms that the reagent **9** has condensed with the amino function of the 4-amino-imidazoles **1**.

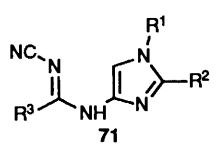


Cyclisation of the parent derivative **66a** in hot ethanol solution using potassium carbonate gave the potassium salt **67** (75%) which upon treatment with hot aqueous acetic acid was converted into imidazo[1,5-*a*]-1,3,5-triazin-4-one **68a** (66%). This novel heterocycle **68a** showed a carbonyl absorption at 1740 cm^{-1} in its IR spectrum. The ^1H NMR spectrum revealed doublets at δ 8.34 and 7.25 (*J* 1 Hz) corresponding to the 6- and 8-H together with a singlet at δ 7.76 attributable to 2-H and a broad exchangeable signal at δ 12.40 (NH). The UV spectrum showed a single absorption band at 255 nm (ε 7650).

Treatment of the potassium salt **67** with alkyl halides gave good yields of the *N*-alkyl derivatives **68**. For example, a suspension of the salt **67** in dimethylformamide was warmed with methyl iodide to give the 3-methyl derivative **68b** (80%) and compounds **68c–e** were obtained in a similar manner. The derivatives **68b–e** show a carbonyl absorption in the region 1720–1740 cm^{-1} thus providing strong evidence that *N*-alkylation has occurred.

Evidence that N-3 rather than N-1 or N-7 alkylation had occurred was provided using $^1H/^1H$ nuclear Overhauser enhancement (NOE) difference spectroscopy on compound **68e**. A nuclear Overhauser enhancement existed between the 2-H proton and the methylene group (CH_2) of the isopentenyl side chain but no enhancement was observed between 8-H and the isopentenyl CH_2 group. This observation infers that compound **68e** has the proposed structure. NOE experiments with compound **68c** showed a similar effect.

Reaction of the 5-aminoimidazoles **3e, k, l** with ethoxymethyleneurethane **9** in dioxane solution at ambient temperature was complete within 1 h and gave exclusively the ethyl *N*-[(imidazol-5-yl)aminomethylene]carbamates **69e, k, l**. There was no evidence, including that from the TLC examination of the mother liquors, of formation of *C*-addition–elimination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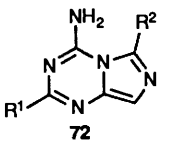
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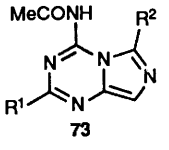
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In formula **71**: **a**, $R^1 = R^2 = R^3 = H$; **b**, $R^1 = R^3 = H$, $R^2 = Me$; **c**, $R^1 = CH_2OCOMe$, $R^2 = Me$, $R^3 = H$; **d**, $R^1 = R^2 = H$, $R^3 = Me$; **e**, $R^1 = R^3 = Me$, $R^2 = Pr^i$; **f**, $R^1 = R^2 = H$, $R^3 = SMe$

In formulae **72** and **73**: **a**, $R^1 = R^2 = H$; **b**, $R^1 = Me$, $R^2 = H$; **c**, $R^1 = H$, $R^2 = Me$; **d**, $R^1 = SMe$, $R^2 = H$

products analogous to those formed with other reagents. The product **69e** was obtained as a colourless solid and the structure was fully confirmed by analytical and spectroscopic data. The ^1H NMR spectrum clearly showed an imidazole 4-H at (δ 6.75) and there was only one exchangeable proton (δ 10.65) which was attributed to the NH of the aminomethylene fragment.

Thermal cyclisation of the derivatives **69e**, **l** gave the hypoxanthines **70e**, **l** in good yield. The ester carbonyl absorption (1730 cm^{-1}) of the precursors **69** was absent in the products **70** which were associated with a carbonyl absorption at 1680 cm^{-1}, indicating that these purines exist as the 6-oxo tautomers **70**.[11] These transformations (**3**→**69**→**70**) represent a new hypoxanthine synthesis which can be achieved in good yield and essentially in two steps from 5-nitroimidazoles **4**.

Reactions utilising Ethyl N-*Cyanoformimidate* **10**, *Ethyl* N-*Cyanoacetimidate* **11** *and* S,S′-*Dimethyl*-N-*Cyanodithioimino-carbonate* **12**.—Reaction of 4-aminoimidazole **1a** in dioxane solution with ethyl *N*-cyanoformimidate **10** gave a good yield of the *N*-cyano-*N*′-(imidazol-4-yl)formamidine **71a** (73%). Similar procedures gave the derivatives **71b**, **c** and with ethyl *N*-cyanoacetimidate **11** as condensing agent the derivatives **71d**, **e** were formed. Condensation of the amine **1a** with the dithio reagent **12** gave the 4-amino-2-methylthioimidazo[1,5-*a*]-1,3,5-triazine **72** (R^1 = SMe, R^2 = H) (81%). The acyclic intermediate **71f** was not encountered and probably cyclised under the reaction conditions. The derivatives **71a**, **b**, **d** were transformed into the corresponding 4-aminoimidazo[1,5-*a*]-1,3,5-triazines **72** during recrystallisation from hot water.

The structures of the imidazo[1,5-*a*]-1,3,5-triazines **72** and the isomeric amidine precursors **71** were fully supported by their spectroscopic properties. The IR spectra of the amidines all show a strong absorption in the nitrile stretch region (ν_{max} 2180–2200 cm^{-1}) which disappeared upon cyclisation. Furthermore, the ^1H NMR spectra of the amidines showed the presence of imidazole 5-H (δ 7.15–7.40) demonstrating that condensation had taken place on the amino function.

The ^1H NMR spectra of the 4-aminoimidazo[1,5-*a*]-1,3,5-triazines **72** show the amino group as a broad singlet in the region δ 7.75–8.60. A study of the spectra of the 2-methyl and 6-methyl derivatives **72b** and **72c** confirmed the following assignments of the ring protons in the parent heterocycle: δ 7.88 (2-H), 8.42 (6-H) and 7.26 (8-H). The amines **72** were obtained as high melting solids which underwent typical amine reactions with electrophilic reagents. Reaction of the parent amine **72a** with phenyl isocyanate gave the urea **74** (R = Ph) and reaction with benzoic anhydride at 180 °C gave the benzamide **76a**. A similar procedure yielded the urea **74** (R = 3,4-$Cl_2C_6H_3$) and the use of hot acetic anhydride gave the acetamide derivatives **73a–c**. Treatment of the parent amine **72a** with benzoyl chloride in dimethylformamide in the presence of potassium carbonate gave the *N*,*N*-dimethylformamidine **75** (R = H) and reaction with diethyl ethoxymethylene malonate **5** gave the novel tricyclic system **77**.

When the 2-methylthio derivative **72d** was allowed to react with primary amines an interesting and unexpected transformation took place (Scheme 8). We expected that the


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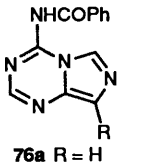
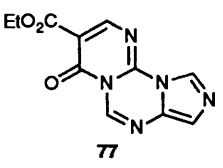

76a R = H
b R = Br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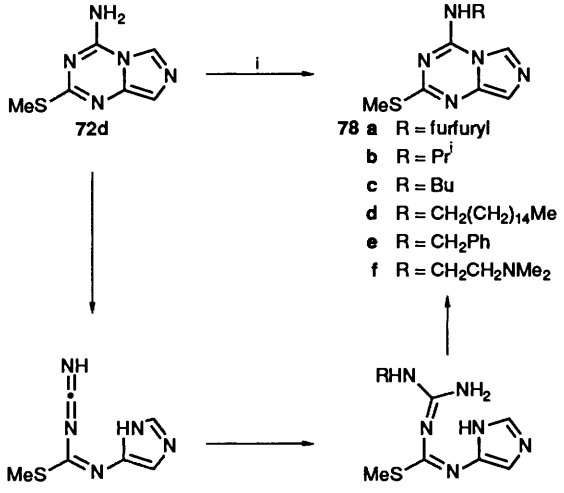
2-methylthio function would be displaced by the amine nucleophile but instead the 4-amino group was replaced. Typically, treatment of compound **72d** with furfurylamine in ethoxyethanol at reflux temperature gave the 4-furfurylamino derivative **78a** (39%) and a similar procedure with the appropriate primary amine gave the derivatives **78b–f** (Scheme 8). We interpret this reaction (**72d**→**78**) as proceeding *via* a



Scheme 8 *Reagents and conditions:* i, RNH_2, 2-ethoxyethanol, reflux, 40 h

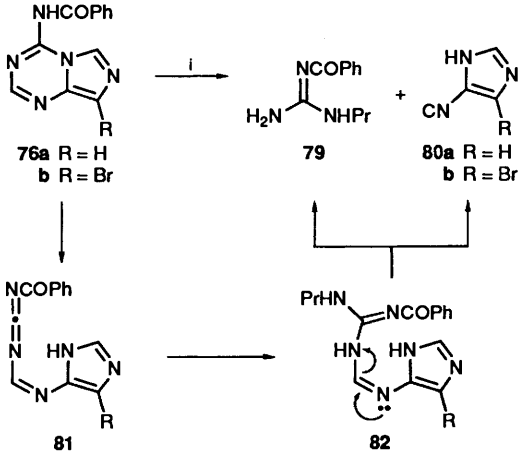
base-catalysed ring opening to a carbodiimide followed by addition of the primary amine to form an intermediate guanidine which can recyclise with elimination of ammonia to form the observed product. An attempted repeat of the reaction with 4-aminoimidazo[1,5-*a*]-1,3,5-triazine **72a** gave only a complex mixture of products.

Electrophilic substitution of the imidazo[1,5-*a*]-1,3,5-triazine system **72** was investigated using the benzamide derivative **76a**. Treatment of a suspension of compound **76a** in dimethylformamide solution with phosphoryl chloride and subsequent hydrolysis resulted in Vilsmeier–Haack formylation at position 8. Interestingly, the *N*-benzamido group was simultaneously transformed into an amidino group giving compound **75** (R = CHO) (41%) as the isolated product. The mechanism of formation of the amidino function presumably involves addition of the Vilsmeier reagent (Me_2N^+=CHOPO·Cl_2) to the amide nitrogen followed by elimination of benzoyl chloride. Evidence that formylation had occurred at the 8-position was provided by a comparison of the ^1H NMR spectrum of the product **75** (R = CHO) with that of the parent formamidine structure **75** (R = H). In particular, coupling between the aromatic protons was absent in the spectrum of the aldehyde and a signal at *ca.* δ 7.4, which had been attributed to 8-H in the parent molecule **75** (R = H), was also absent. In compound **75** (R = CHO) 2-H and 6-H (δ 8.30 and 8.55) were shifted downfield by *ca.* 0.3 ppm relative to the corresponding signals in the

parent compound (δ 8.00 and 8.28), which is consistent with the location of an electronegative formyl group at position 8.

Attempted bromination of the benzamide **76a** with *N*-bromosuccinimide in carbon tetrachloride solution was unsuccessful. A good yield (76%) of the 8-bromo derivative **76b** was obtained by treating a warm solution of the benzamide **76a** in a mixture of acetic and trifluoroacetic acids with bromine. The position of substitution was confirmed by comparison of the ^{1}H NMR spectrum of the bromo compound **76b** with that of the precursor **76a**. As in the case of the 8-formyl derivative **75** (R = CHO), the highfield aromatic proton δ 7.33 in the starting material **76a** was absent in the product **76b**.

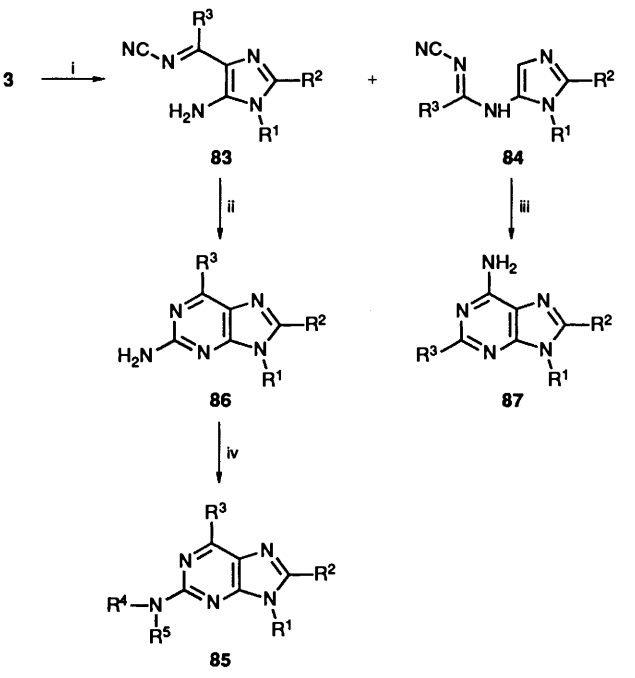
An unexpected fragmentation was discovered when we investigated the nucleophilic substitution of the 8-bromo derivative **76b** with amines. Treatment of a hot ethanol solution of compound **76b** with propylamine gave, after purification by chromatography, *N*-benzoyl-*N'*-propylguanidine **79** (44%) as pale orange crystals. We have rationalised the formation of this product by a mechanism (Scheme 9) similar to that proposed for the formation of the amines **78** (Scheme 8). Base-catalysed ring opening can give the carbodiimide **81** which with propylamine forms the guanidine intermediate **82** (Scheme 9).



Scheme 9 *Reagents and conditions:* i, $PrNH_2$, ethanol, reflux

In this reaction, however, instead of recyclisation (*cf.* Scheme 8) fragmentation leading to an isonitrile **80b** and the isolated product **79** can occur. Although not isolated, the strong characteristic odour of an isonitrile was produced during the reaction. According to the proposed mechanism (Scheme 9), formation of the guanidine **79** should take place irrespective of the substituent at position 8 of the benzamide. When the parent benzamide **76a** was treated with propylamine under the same conditions the guanidine **79** was again isolated and shown to be identical with the sample obtained from compound **76b**. A strong isonitrile odour was again detected in the reaction mixture and evidence for the formation of the isonitrile **80a** was obtained using FAB mass spectrometry on a freshly prepared sample of the reaction mixture. In addition to starting material **76a**, the major signals in the spectrum has masses consistent with the presence of the guanidine **79** and the isonitrile **80a**.

When 1 equiv. of ethyl *N*-cyanoformimidate **10** was added to a solution of each of the 5-aminoimidazoles **3e, f, k** in dioxane solution at ambient temperature, reaction was complete in a few minutes. The products were shown to be two component mixtures which were separated by chromatography and identified as the pairs of isomers **83a, b, d** and **84a, b, d** (Scheme 10). Table 2 shows the isolated yields. When the amine **31** was used, only a single product **83c** was obtained in very low yield (8%). The reason for this low yield is not clear since the amine **31** reacted

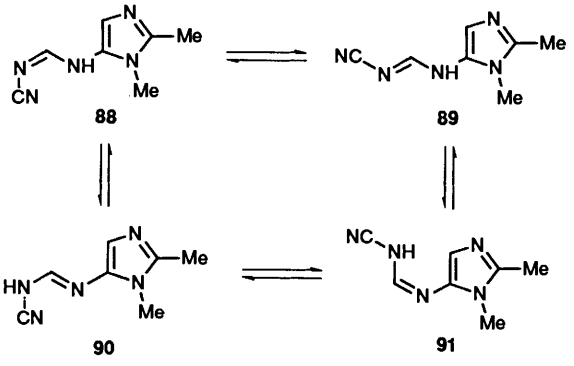


Scheme 10 *Reagents and conditions:* i, Dioxane, EtOCH=NCN, 25 °C, 1 h; ii, decalin, reflux, 1 min; iii, 200 °C, 1 min; iv, Ac_2O or Bz_2O heat, 10 min

In formulae **83–87**; **a**, $R^1 = R^2 = Me$, $R^3 = H$; **b**, $R^1 = Me$, $R^2 = R^3 = H$; **c**, $R^1 = CH_2CH_2OH$, $R^2 = Me$, $R^3 = H$; **d**, $R^1 = Me$, $R^2 = Pr^i$, $R^3 = H$; **e**, $R^1 = R^2 = Me$, $R^3 = SMe$; **f**, $R^1 = CH_2CH_2OH$, $R^2 = Me$, $R^3 = SMe$; **g**, $R^1 = Me$, $R^2 = H$, $R^3 = SMe$

with other reagents to give products in yields comparable to those given by other 5-aminoimidazoles **3**.

Analytical and spectroscopic data confirmed the structural assignments **83** and **84** but the complexity of the ^{1}H NMR spectra of the amidines **84a, b, d** required further examination. In [$^2H_6$]-DMSO solution at room temperature these compounds **84a, b, d** appeared to be mixtures of two isomers in the ratio of *ca.* 3:1. For compound **84a** at ambient temperature, there were six sharp signals appearing in pairs in the ratio of 3:1 at δ 2.37 and 2.30, 3.47 and 3.39 and 7.02 and 6.77. Upon the addition of D_2O a seventh signal at δ 8.18 separated into a pair of singlets and the NH signal, which was a very broad peak at δ 4.5, disappeared. When the ^{1}H NMR spectrum of compound **84a** was run at increasingly higher temperatures the pairs of signals collapsed with a coalescence temperature of 80–90 °C. At 100 °C the spectrum was consistent with a single structure with singlet signals observed at δ 2.33 (C–CH_3), 3.43 (N–CH_3), 4.5 (br, NH), 6.85 (4-H) and 8.17 (formamidine H). This phenomenon can be understood in terms of interconversion between four possible isomers (Scheme 11) which can inter-



Scheme 11

Table 2 Products formed from the reaction of 5-aminoimidazoles **3** with either ethyl *N*-cyanoformimidate **10** or *S,S'*-dimethyl-*N*-cyanodithioiminocarbonate **12**

Amine	Reagent	Product yields (%) 83	84
3e	**10**	23	26
3k	**10**	4	42
3l	**10**	8	—
3f	**10**	36	11
3e	**12**	47	—
3k	**12**	10	32
3l	**12**	10.5	—

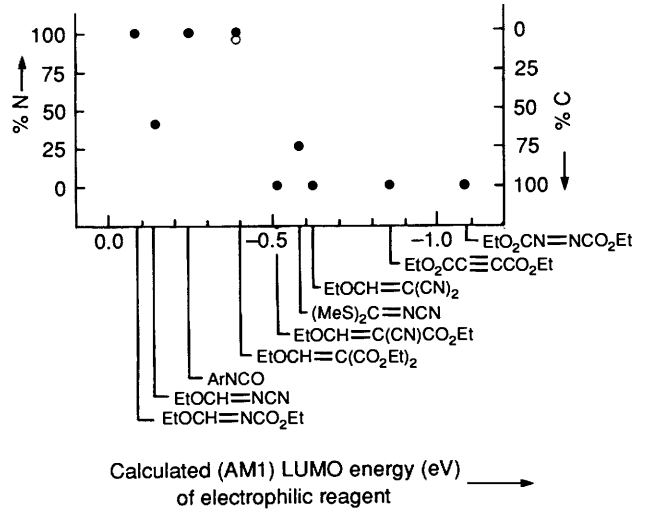


Fig. 1 Relative yields of *C*- and *N*-adducts from the reaction of 5-aminoimidazoles with various electrophilic reagents in dioxane (●) or ethanol (○)

convert either by a process of stereomutation (*e.g.* **88**⇌**89**) or [1,3]-prototropic shift (*e.g.* **88**⇌**90**). At room temperature the ^{1}H NMR spectrum shows a mixture of signals but only two of the four possible isomers (Scheme 11) are observed to be populated. It was not possible to make assignments to two particular isomers.

Bellora *et al.*[12] have reported the synthesis of a series of *N*-aryl-*N'*-cyanoformamidines (ArNHCH=NCN) together with details of their ^{1}H NMR spectra, which are complex but which were not rationalised by the authors. Using the published method,[12] we have resynthesised the *p*-methoxyphenyl derivative and examined its ^{1}H NMR spectrum. At ambient temperature in [$^2H_6$]-DMSO solution a complex spectrum was obtained. Upon increasing the temperature to 100 °C broadening of the peaks had occurred and at 160 °C coalescence of the signals took place. We conclude that a similar process to that observed for compound **84a** is taking place (*i.e.* stereomutation or [1,3]prototropic shift) and this appears to be a general property of this type of *N*-cyanoformamidine.

The ^{1}H NMR spectra of the amidines **71** (R^3 = H) formed from 4-aminoimidazoles **1** also showed evidence of the molecules existing in two isomeric forms which interconvert either by a process of [1,3]-prototropic shift or stereomutation. However, in these compounds **71** there was a much greater predominence of one isomer over the other (>10:1 by integration of signals) and only the signals of the major isomers were recorded.

Condensation of *S,S'*-dimethyl *N*-cyanodithioiminocarbonate **12** with the amines **3e**, **k**, **l** was achieved in dioxane. In each case TLC examination of the reaction mixture showed that a multicomponent mixture had been formed and condensation products were isolated either by crystallisation or medium pressure liquid chromatography. In each case the *C*-addition–elimination products **83** were obtained and the isolated yields are shown in Table 2. The ^{1}H NMR spectra of the derivatives **83e**, **f**, **g** showed the absence of imidazole 4-H. Only in the case of 5-amino-1-methylimidazole **3k** was an *N*-addition–elimination product (*i.e.* **84g**) isolated from the reaction mixture (Table 2).

Thermal cyclisation of the *N*-[(5-amino-1*H*-imidazol-4-yl)-methylene]cyanamides **83** provides a new route to 2-aminopurines **86**. Typically, compound **83a** was heated under reflux in decahydronaphthalene to give a single product which was identified as 2-amino-8,9-dimethyl-9*H*-purine **86a** (77%). In a similar manner, the 2-aminopurine derivatives **86b–g** were prepared from the precursors **83b–g** in 60–80% yield. This route to 2-aminopurines **86** from 5-nitroimidazoles **4** provides a useful alternative to the usual approach[13] which starts with pyrimidine derivatives. The amine **86d** when heated under reflux (10 min) with acetic anhydride, gave both the monoacetamide **85d** (R^4 = H, R^5 = Ac) (26%) and the diacetamide **85d** (R^4 = R^5 = Ac) (55%). With benzoic anhydride the benzamide **85d** (R^4 = H, R^5 = Bz) was formed (47%). The structures of all the purines **85** and **86a–g** were consistent with their analytical and spectroscopic data and provide further confirmation of the structures **83**.

Thermal cyclisation of the *N*-addition–elimination products **84** gives 9-substituted adenines **87**. Thus compound **84b** when heated at 200 °C without solvent cyclised to the 6-aminopurine **87b**. A similar procedure gave the derivative **87g** (m.p. 274–276 °C) which was previously obtained by Todd and co-workers[14] (m.p. 261–262 °C) by methylation of 2-methylthioadenine.

A Frontier Molecular Orbital (FMO) Analysis.—In the preceding paper[1] we have described a molecular orbital (MO) study of 4- and 5-aminoimidazoles **1** and **3** and 4- and 5-nitroimidazoles **2** and **4**. This analysis has led us to conclude that *C*-addition to aminoimidazoles is favoured by soft electrophiles whereas *N*-addition is favoured by hard electrophiles. We now describe the extension of our FMO analysis to the addition–elimination reactions of 5-aminoimidazoles **3** with the reagents **5–12**. MO calculations were carried out using the AM1 method. An introduction to our approach together with supporting data can be found in the preceding paper.[1]

Calculated properties of a series of electrophilic reagents, some of which we have allowed to react with 5-aminoimidazoles **3**,[1] are given in Table 3. These molecules are arranged in order of increasing softness as measured by the calculated LUMO energy. The relative yields of *N* and *C* addition–protonation or addition–elimination products obtained when simple 5-aminoimidazoles **3** were treated with a number of these reagents are summarised in Fig. 1. In particular, Fig. 1 shows a plot of the relative yields of *N* and *C* products *versus* the LUMO energies of specific reagents. Experimental details of these reactions are described here and in the preceding paper.[1] The relative yield for each reagent shown in Fig. 1 is the averaged value of the yields for all 5-aminoimidazole derivatives **3** which were treated with the reagent. We emphasise that our programme of work was directed towards synthetic targets and the yields discussed are isolated yields. Nevertheless, crude reaction mixtures were routinely monitored using TLC to determine the absence or presence of products and the yields of isolated products, often obtained using MPLC, are a reliable guide to the actual product ratios.

Inspection of Fig. 1 reveals an interesting trend in the mode of reaction of 5-aminoimidazoles **3** with electrophilic reagents and our experimental and theoretical studies have led us to make the following general observations. i, Reagents with a

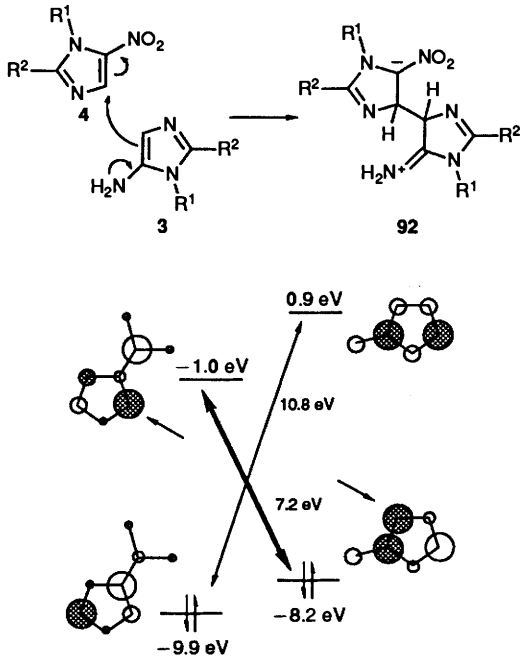


Fig. 2 Frontier orbital interactions for the proposed reaction between 5-nitroimidazoles **4** and 5-aminoimidazoles **3** to give diimidazoles *via* the intermediates **92**

calculated LUMO energy > 0.0 eV do not appear to readily undergo electrophilic addition reactions with the amines **3**. For example, ethyl propiolate did not react with 5-aminoimidazoles **3**. ii, Reagents with a calculated (AM1) LUMO energy in the range 0.0 eV > LUMO > −0.5 eV react predominantly on the exocyclic nitrogen atom. iii, Reagents with a calculated (AM1) LUMO energy < −0.5 eV react predominantly on C-4 of the imidazole. The calculations described in the preceding paper[1] demonstrate that 5-aminoimidazoles **3** can be expected to behave as soft nucleophiles and that soft electrophilic reagents should favour reaction on C-4. We, therefore, attribute the preference of reagents with a LUMO energy < −0.5 eV for reaction on carbon (Fig. 1) as due to the contribution of frontier orbital interactions to transition state stabilisation. Presumably, for reagents with higher LUMO energies reaction on carbon is less favoured due to smaller frontier orbital interactions.

Although the FMO analysis described above highlights an interesting trend in the reactions of 5-aminoimidazoles **3** with electrophilic reagents, there are two notable anomalies in the data which we have presented (Fig. 1). Whereas ethoxymethyleneurethane ($EtOCH{=}NCO_2Et$) gave exclusively *N*-addition–elimination products, ethyl *N*-cyanoformimidate ($EtOCH{=}NC{\equiv}N$) gives mixtures of *N*- and *C*-addition–elimination products of widely varying composition depending upon the nature of the ring substituents R^1 and R^2 in **3**. Since the calculated LUMO energies of these two reagents differ by only 0.06 eV, this suggests that, not surprisingly, other steric and electronic effects contribute to the outcome of the reaction. It is tempting to speculate on what these effects may be but we feel that any further analysis of the results would seriously risk over-interpretation of the data. It is noteworthy, however, that another reagent which shows a variation in product composition is *S,S'*-dimethyl *N*-cyanodithioiminocarbonate [$(MeS)_2C{=}NC{\equiv}N$] and this also contains the *N*-cyanoimino function ($C{=}NC{\equiv}N$).

We have suggested (Scheme 1) that diimidazole products **15** formed during the catalytic reduction of nitroimidazoles may be produced by reaction of the nitroimidazole with its aminoimidazole reduction product. Inspection of Table 3 reveals that 5-nitroimidazoles, exemplified by 2-methyl-5-nitroimidazole **4b**, have a very low energy LUMO and should be classified as soft electrophiles. Indeed, they are calculated to be softer than DMAD and, like DMAD, can be expected to be reactive towards the ring carbon atoms of 4- and 5-aminoimidazoles **1** and **3**. Fig. 2 shows the favourable frontier orbital mixing during formation of the proposed intermediate **92** from a 5-aminoimidazole **3** and a 5-nitroimidazole **4**. The calculated electronic properties are, therefore, consistent with the mechanism which we have proposed in an earlier section (Scheme 1) for the formation of diimidazoles.

We have suggested that the particularly high yields of diimidazole by-products **15** formed during the reduction of 1-unsubstituted 4-nitroimidazoles **2** (R^1 = H) are possibly due to the opportunity for these molecules to tautomerise to give a 5-nitroimidazole **4** (R^1 = H). Inspection of Table 3 reveals that 5-nitroimidazoles can be expected to be more reactive than 4-nitroimidazoles towards electron-rich species such as aminoimidazoles. We cannot rule out the possibility that it is the opportunity for the 4-aminoimidazole reduction products **1** (R^1 = H) to tautomerise to 5-aminoimidazoles **3** (R^1 = H) which is an essential step in the mechanism of formation of diimidazole products. The calculated properties[1] however, suggest that 4- and 5-aminoimidazoles should be equally reactive towards electrophiles.

We have observed that, in contrast to the 2-alkyl-4-nitroimidazoles **2** (R^1 = H, R^2 = alkyl), unsubstituted 4-nitroimidazole **2a** does not form a diimidazole by-product upon reduction. We have suggested that the reaction occurs for 2-alkyl derivatives because the alkyl substituent increases the HOMO energy thus enhancing reactivity towards electrophiles. This hypothesis is consistent with the calculated properties. Both 4-amino-2-methylimidazole **1b** and 5-amino-2-methylimidazole **3b** are calculated to have first ionisation potentials which are less than that calculated for 4(5)-aminoimidazole **1a**.

We conclude that 5-aminoimidazoles **3** are soft ambident nucleophiles that react with soft electrophiles. Very soft electrophiles favour reaction on carbon whereas less soft electrophiles react on the exocyclic nitrogen atom. Since nitrogen is the harder reaction centre, presumably Coulombic forces favour reaction on nitrogen if HOMO–LUMO interactions are not large enough to dominate. In contrast to the 5-aminoimidazoles **3**, we have found that for 4-aminoimidazoles **1** the only reagent which we investigated which reacted on carbon was dimethyl acetylenedicarboxylate. This presumably reflects the nature of the alternative transition states in the 4-amino series.

Experimental

General experimental directions are given in the preceding paper.[1]

Addition–Elimination Reactions of 4-*Aminoimidazoles* **1**.—(a) *With diethyl ethoxymethylenemalonate* **5**.[15] A mixture of 2-isopropyl-4-nitroimidazole **2d**[16] (4.65 g), compound **5** (6.6 g) and 5% Pd/C (2.3 g) in ethanol (300 cm^3) was vigorously shaken under an atmosphere of hydrogen until reduction was complete (*ca.* 1 h). After removal of the catalyst, the filtrate was evaporated to give a dark green oil (11 g) which was shaken with ethyl acetate (100 cm^3). The solid which separated was collected, washed with ethyl acetate, and recrystallised from ethyl acetate to give *tetraethyl* 2,2'-[2'',2'''-*diisopropyl*-5'',5'''-*biimidazole*-4'',4'''-*diylbis*(*aminomethylene*)]*dimalonate* **15d** (3.0 g, 34%), as a yellow solid, m.p. 236–238 °C (Found: C, 57.1; H, 6.81; N, 14.1. $C_{28}H_{40}N_6O_8$ requires C, 57.1; H, 6.85; N, 14.3%); ν_{max}/cm^{-1} 1235, 1410, 1640, 1715, 2980 and 3305; $\delta_H(CDCl_3)$ 1.0–1.45 [m, 4 OCH_2CH_3 and 2 $CH(CH_3)_2$], 2.88 [sept, *J* 7, 2 $CH(CH_3)_2$], 3.85–4.35 (m, 4 OCH_2CH_3), 8.72 (d,

Table 3 AM1 Calculated properties of some electrophilic reagents and related species

Species	LUMO energy (eV)	LUMO coefficient on reacting atom[a]	Total charge on reacting atom[a]
$HO\mathit{CO}_2^-$	8.54	0.79	+0.40
$(HO)_2\mathit{CO}$	1.06	0.80	+0.40
CO	0.94	0.86	+0.20
CO_2	0.85	0.80	+0.41
$EtO\mathit{CH}{=}CHCO_2Et$	0.18	0.67	+0.06
$H\mathit{C}{\equiv}CCO_2Et$	0.14	0.57	−0.10
$EtO\mathit{CH}{=}NCO_2Et$	−0.08	0.68	+0.12
$EtO\mathit{CH}{=}NCN$	−0.14	0.71	+0.11
$PhN\mathit{CO}$	−0.24	0.40	+0.33
$EtO\mathit{CH}{=}C(CO_2Et)_2$	−0.40	0.72	+0.13
$EtO\mathit{CH}{=}C(CN)CO_2Et$	−0.51	0.72	+0.11
2-Me-4-nitroimidazole	−0.57	0.59[b]	−0.06[b]
$(MeS)_2\mathit{C}{=}NCN$	−0.58	0.70	−0.22
$EtO\mathit{CH}{=}C(CN)_2$	−0.62	0.72	+0.09
$EtO_2C{\cdot}\mathit{C}{\equiv}C{\cdot}CO_2Et$	−0.85	0.42	−0.07
2-Me-5-nitroimidazole	−1.02	0.42[c]	−0.04[c]
$EtO_2C\mathit{N}{=}N{\cdot}CO_2Et$	−1.08	0.40	−0.01
$(HO)_2\mathit{C}{=}O^+H$	−6.30	0.82	+0.48

[a] The reacting atom is defined as that at which new bond formation occurs and is indicated in italics. [b] The reacting atom is the carbon at position 5. [c] The reacting atom is the carbon at position 4.

J 14, 2 C*H*NH), 10.70 (br d, *J* 14, 2 CHN*H*) and 10.73 (br s, 2 1-H).

The remaining filtrate and mother liquors were combined and evaporated and the residue purified by MPLC (1:1, ethyl acetate–Et_2O as eluent). The major fraction was collected and trituration with diethyl ether gave *diethyl* 2-[(2-*isopropylimidazol*-4-*yl*)*aminomethylene*]*malonate* **13d** (0.8 g, 9%) as a green solid, m.p. 123–125 °C (Found: C, 56.9; H, 7.1; N, 14.3. $C_{14}H_{21}N_3O_4$ requires C, 56.9; H, 7.2; N, 14.2%); ν_{max}/cm^{-1} 1275, 1385, 1425, 1610, 1630, 1665, 2980, 3230 and 3270; δ_H 1.05–1.40 [m, 2 OCH_2CH_3 and $CH(CH_3)_2$], 2.90 [sept. *J* 7, $CH(CH_3)_2$], 4.08 (q, *J* 7, OCH_2CH_3), 4.13 (q, *J* 7, OCH_2CH_3), 6.84 (s, 5-H), 8.57 (d, *J* 14, C*H*NH), 9.55 (br s, 1-H) and 10.70 (br d, *J* 14, CHN*H*).

In a similar manner the following compounds were prepared from 2-methyl-4-nitroimidazole **2b**[16] and 2-ethyl-4-nitroimidazole **2c**[16] respectively.

Tetraethyl 2,2′-[2″,2‴-*dimethyl*-5″,5‴-*biimidazole*-4″,4‴-*diylbis*(*aminomethylene*)]*dimalonate* **15b** (42 g, 30%) as a pale green solid, m.p. 188–190 °C (decomp.) (Found: C, 54.1; H, 6.11; N, 16.0. $C_{24}H_{32}N_6O_8$ requires C, 54.1; H, 6.06; N, 15.8%); ν_{max}/cm^{-1} 1245, 1300, 1380, 1410, 1615, 1640, 1705, 2980 and 3260; δ_H 1.20 (t, *J* 7, 2 OCH_2CH_3), 1.26 (t, *J* 7, 2 OCH_2CH_3), 2.35 (s, 2 CCH_3), 4.00 (q, *J* 7, 2 OCH_2CH_3), 4.10 (q, *J* 7, 2 OCH_2CH_3), 8.55 (d, *J* 13, 2 C*H*NH), 10.66 (br d, *J* 13, 2 CHN*H*) and 12.33 (vbr s, 2 NH) and *diethyl* 2-[(2-*methylimidazol*-4-*yl*)*aminomethylene*]*malonate* **13b** (17.0 g, 8%) as a pale green solid, m.p. 83 °C (Found: C, 54.2; H, 6.65; N, 15.9. $C_{12}H_{17}N_3O_4$ requires C, 53.92; H, 6.41; N, 15.7%); ν_{max}/cm^{-1} 1220, 1240, 1285, 1385, 1420, 1630, 1680, 1705, 2990, 3250 and 3320; δ_H 1.30 (t, *J* 7, OCH_2CH_3), 1.33 (t, *J* 7, OCH_2CH_3), 2.40 (s, CCH_3), 4.23 (q, *J* 7, OCH_2CH_3), 4.27 (q, *J* 7, OCH_2CH_3), 6.57 (s, 5-H), 8.68 (d, *J* 13, NHC*H*), 9.80 (br s, N*H*) and 10.90 (br d, *J* 13, N*H*CH).

Tetraethyl 2,2′-[2″,2‴-*diethyl*-5″,5‴-*biimidazole*-4″,4‴-*diylbis*-(*aminomethylene*)]*dimalonate* **15c** (4.5 g, 32%) as a green solid, m.p. 233–234 °C (decomp.) (Found: C, 55.7; H, 6.6; N, 15.1. $C_{26}H_{36}N_6O_8$ requires C, 55.7; H, 6.47; N, 15.0%); ν_{max}/cm^{-1} 1240, 1300, 1380, 1410, 1630, 1720, 2980 and 3300; δ_H 1.15 (t, *J* 7, 2 CH_2CH_3), 1.23 (t, *J* 7, 2 OCH_2CH_3), 1.27 (t, *J* 7, 2 OCH_2CH_3), 2.67 (q, *J* 7, 2 CH_2CH_3), 4.02 (q, *J* 7, 2 OCH_2CH_3), 4.12 (q, *J* 7, 2 OCH_2CH_3), 8.68 (d, *J* 13, 2 C*H*NH), 10.75 (br d, *J* 13, 2 CHN*H*) and 12.22 (br s, 2 NH).

Under similar conditions the 4-nitroimidazoles **2a**, **e**, **g**, **i**, **j**[16,17] gave the following derivatives. *Diethyl* 2-[(*imidazol*-4-*yl*)*aminomethylene*]*malonate* **13a** (10.1 g, 45%) as a pale blue crystalline solid, m.p. 180–182 °C (Found: C, 52.0; H, 5.91; N, 16.5. $C_{11}H_{15}N_3O_4$ requires C, 52.2; H, 5.97; N, 16.6%); ν_{max}/cm^{-1} 1235, 1270, 1310, 1385, 1420, 1620, 1685, 2680, 2910, 2980 and 3110; δ_H([$^2H_6$]-DMSO) 1.28 (t, *J* 7, CH_2CH_3), 1.30 (t, *J* 7, CH_2CH_3), 4.10 (q, *J* 7, CH_2CH_3), 4.20 (q, *J* 7, CH_2CH_3), 7.00 (d, *J* 1, 5-H), 7.50 (d, *J* 1, 2-H), 8.68 (d, *J* 14, C*H*NH), 10.80 (br d, *J* 14, CHN*H*) and 12.00 (vbr s, 1-H); *diethyl* 2-[(1,2-*dimethylimidazol*-4-*yl*)*aminomethylene*]*malonate* **13e** (4.0 g, 36%) as a crystalline solid, m.p. 125–126 °C (Found: C, 55.3; H, 6.8; N, 15.0. $C_{13}H_{19}N_3O_4$ requires C, 55.5; H, 6.81; N, 14.9%); ν_{max}/cm^{-1} 1230, 1255, 1385, 1425, 1610, 1670, 2910, 2990, 3160 and 3270; δ_H 1.30 (t, *J* 7, OCH_2CH_3), 1.35 (t, *J* 7, OCH_2CH_3), 2.32 (s, CCH_3), 3.51 (s, NCH_3), 4.18 (q, *J* 7, OCH_2CH_3), 4.30 (q, *J* 7, OCH_2CH_3), 6.48 (s, 5-H), 8.62 (d, *J* 14, C*H*NH) and 10.80 (br d, *J* 14, CHN*H*); *diethyl* 2-[(1-*acetoxymethyl*-2-*methylimidazol*-4-*yl*)*aminomethylene*]*malonate* **13i** (6.9 g, 41%) as a pale pink crystalline solid, m.p. 126–128 °C (Found: C, 52.8; H, 6.31; N, 12.4. $C_{15}H_{21}N_3O_6$ requires C, 53.1; H, 6.24; N, 12.4%); ν_{max}/cm^{-1} 1220, 1260, 1365, 1385, 1415, 1560, 1610, 1630, 1665, 1685, 1750, 2980, 3130 and 3260; δ_H 1.31 (t, *J* 7, CH_2CH_3), 1.34 (t, *J* 7, CH_2CH_3), 2.10 (s, $COCH_3$), 2.45 (s, CCH_3), 4.23 (q, *J* 7, CH_2CH_3), 4.30 (q, *J* 7, CH_2CH_3), 5.70 (s, NCH_2), 6.64 (s, 5-H), 8.60 (d, *J* 14, C*H*NH) and 10.8 (br d, *J* 14, CHN*H*); *diethyl*-2-[(1-N,N-*dimethylaminosulfonylimidazol*-4-*yl*)*aminomethylene*]*malonate* **13j** (1.2 g, 14%) as a crystalline solid, m.p. 118–119 °C (Found: C, 43.2; H, 5.6; N, 15.8; S, 8.9. $C_{13}H_{20}N_4O_6S$ requires C, 43.3; H, 5.6; N, 15.6; S, 8.9%); ν_{max}/cm^{-1} 1255, 1293, 1338, 1393, 1420, 1620, 1683, 2987 and 3115; δ_H 1.34 (t, *J* 7, CH_2CH_3), 1.4 (t, *J* 7, CH_2CH_3), 2.91 [s, $N(CH_3)_2$], 4.27 (q, *J* 7, CH_2CH_3), 4.33 (q, *J* 7, CH_2CH_3), 6.91 (s, 5-H), 7.75 (s, 2-*H*), 8.68 (d, *J* 13, NHC*H*) and 10.92 (br d, *J* 13, N*H*CH); *m*/*z*; 360 ($M^{\cdot+}$); diethyl 2-[(1-benzylimidazol-4-yl)aminomethylene]-malonate **13g** (crude yield, 21 g) obtained as a brown oil which was used without further purification.

(b) *With Ethoxymethylenemalononitrile* **6**.[18] A solution of 4-nitroimidazole **2a**[16] (11.3 g) in dioxane solution was reduced in the manner previously described.[1] Ethoxymethylenemalononitrile (12.2 g) in dioxane (100 cm^3) solution was added without stirring to the filtrate and after 1 h the solution was concentrated (80 cm^3). The solid which separated was collected, washed with ether and identified as the product **38a** (13.1 g, 82%) as a yellow–brown solid, m.p. 294–298 °C; δ_H([$^2H_6$]-DMSO) 6.75 (d, *J* 1,

5-H), 7.50 (d, *J* 1, 2-H), 8.18 (s, C=CH) and 12.0 (vbr s, 1-H and CHN*H*). Attempts to recrystallise this product resulted in cyclisation to compound **40** and the material was used without further purification.

By a similar procedure the following derivatives were prepared from the 4-nitroimidazoles **2k**, **2e** and **2f**[16,19] respectively.

4-(2,2-*Dicyanovinylamino*)-1-*methylimidazole* **38b** (4.0 g, 63%) as a buff solid, m.p. 225 °C (decomp.) (Found: C, 55.4; H, 3.9; N, 40.2. $C_8H_7N_5$ requires C, 55.5; H, 4.07; N, 44.4%); δ_H([$^2H_6$]-DMSO + $CDCl_3$) 3.67 (s, NCH_3), 6.75 (d, *J* 1, 5-H), 7.31 (d, *J* 1, 2-H), 8.17 (s, HNC*H*) and 11.10 (vbr s, *H*NCH); 4-(2,2-*dicyanovinylamino*)-1,2-*dimethylimidazole* **38c** (8.0 g, 74%) as a buff solid, m.p. 205–206 °C (Found: C, 57.3; H, 4.98; N, 37.0. $C_9H_9N_5$ requires C, 57.7; H, 4.85; N, 37.4%); δ_H([$^2H_6$]-DMSO + $CDCl_3$) 2.30 (s, CCH_3), 3.53 (s, NCH_3), 6.57 (s, 5-H), 8.08(s, HNC*H*) and 10.50 (vbr s, *H*NCH); δ_H($CDCl_3$ at −40 °C) 2.38 (s, CCH_3), 3.60 (s, NCH_3), 6.60 (s, 5-H), 8.17 (d, *J* 14, HNC*H*) and 10.18 (br d, *J* 14, *H*NCH); 4-(2,2-*dicyanovinylamino*)-2-*isopropyl*-1-*methylimidazole* **38d** (4.0 g, 66%) as pale yellow crystals, m.p. 212 °C (Found: C, 61.1; H, 6.15; N, 32.4. $C_{11}H_{13}N_5$ requires C, 61.4; H, 6.09; N, 32.5%); δ_H 1.27 [d, *J* 7, HC(CH_3)$_3$], 2.96 [sept, *J* 7, *H*C(CH_3)$_2$], 3.60 (s, NCH_3), 6.51 (s, 5-H), 8.28 (br s, HNC*H*) and 9.08 (vbr s, *H*NCH).

(c) *With* 3,3-*dicyano*-2-*ethoxyprop*-2-*ene* **7**.[20] A solution of 4-nitroimidazole **2a**[16] (11.3 g) in dioxane was reduced according to the method previously described.[1] Compound **7** (13.6 g) was added to the filtrate and, after 1 h, the solution was concentrated (50 cm^3) and the solid product collected, recrystallised from water and identified as 4-*amino*-3-*cyano*-2-*methylimidazo*[1,5-a]*pyrimidine* **41** (4.0 g, 23%) as needles, m.p. 323–325 °C (decomp.) (Found: C, 55.8; H, 3.87; N, 40.5. $C_8H_7N_5$ requires C, 55.5; H, 4.07; N, 40.4%); ν_{max}/cm^{-1} 1250, 1300, 1390, 1480, 1545, 1615, 1670, 2220, 3105 and 3330; δ_H([$^2H_6$]-DMSO) 2.44 (s, CCH_3), 7.21 (s, 8-H), 8.49 (s, 6-H) and 8.82 (br s, NH_2); *m*/*z* 173 ($M^{\cdot+}$).

(d) *With ethoxymethyleneurethane* **9**.[21] A solution of 4-nitroimidazole **2a**[16] (11.3 g) in dioxane (250 cm^3) was reduced. Reagent **9** (14.5 g) was added with stirring to the filtered solution and after 30 min at ambient temperature the solution was concentrated (to *ca.* 60 cm^3). The resulting solid product was collected, washed with ether and dried. Recrystallisation from tetrahydrofuran gave *ethyl* N-[(1-H-*imidazol*-4-*yl*)*aminomethylene*]*carbamate* **66a** (14.2 g, 78%) as needles, m.p. 179–182 °C (Found: C, 46.8; H, 5.6; N, 30.2. $C_7H_{10}N_4O_2$ requires C, 46.1; H, 5.53; N, 30.8%); δ_H([$^2H_6$]-DMSO) 1.25 (t, *J* 7, CH_2CH_3), 4.15 (q, *J* 7, CH_2CH_3), 6.80 (d, *J* 1, 5-H), 7.45 (d, *J* 1, 2-H), 8.80 (s, N=CH), 10.40 (br s, =CHN*H*) and 11.90 (br s, 1-H).

The following compounds were similarly prepared from 1,2-dimethyl-4-nitroimidazole **2e**[16] (7.05 g) and 1-acetoxymethyl-4-nitroimidazole **2h**[16] (9.25 g) respectively. *Ethyl* [(1,2-*dimethyl*-1H-*imidazol*-4-*yl*)*aminomethylene*]*carbamate* **66b** (6.9 g, 66%), prisms, m.p. 162–164 °C (Found: C, 51.3; H, 6.7; N, 26.3. $C_9H_{14}N_4O_2$ requires C, 51.4; H, 6.71; N, 26.7%); ν_{max}/cm^{-1} 1230, 1300, 1465, 1490, 1640, 1730 and 3180; δ_H([$^2H_6$]-DMSO) 1.20 (t, *J* 7, CH_2CH_3), 2.20 (s, CCH_3), 3.45 (s, NCH_3), 4.15 (q, *J* 7, CH_2CH_3), 6.70 (s, 5-H), 8.70 (s, N=CH) and 10.35 (br s, =CHN*H*); *m*/*z* 210 ($M^{\cdot+}$); *ethyl* [(1-*acetoxymethyl*-1H-*imidazol*-4-*yl*)*aminomethylene*]*carbamate* **66c** (6.6 g, 52%), prisms, m.p. 131–133 °C (Found: C, 47.2; H, 5.55; N, 22.2. $C_{10}H_{14}N_4O_4$ requires C, 47.2; H, 5.55; N, 22.0%); ν_{max}/cm^{-1} 1210, 1270, 1330, 1380, 1410, 1670, 1730, 2900, 3000, 3060 and 3150; δ_H([$^2H_6$]-DMSO) 1.20 (t, *J* 7, CH_2CH_3), 2.05 (s, $CH_2O_2CCH_3$), 4.15 (q, *J* 7, CH_2CH_3), 5.85 (s, NCH_2O), 6.95 (d, *J* 1, 5-H), 7.65 (d, *J* 1, 2-H), 8.75 (s, N=CH) and 10.50 (br s, =CHN*H*); *m*/*z* 254 ($M^{\cdot+}$).

(e) *With ethyl* N-*cyanoformimidate* **10**.[21] A solution of 4-nitroimidazole **2a**[16] (11.3 g) in dioxane was reduced and compound **10** (9.8 g) was added with stirring to the filtrate. After 15 min the solid product was collected, washed with ether and dried to give N-*cyano*-N^1-(*imidazol*-4-*yl*)*formamidine* **71a** (9.9 g, 73%) as a green solid, m.p. 297 °C (decomp.) (Found: C, 43.9; H, 3.6; N, 51.4. $C_5H_5N_5$ requires C, 44.4; H, 3.58; N, 51.8%); ν_{max}/cm^{-1} 1360, 1570, 1620, 2180, 2780 and 3340; δ_H([$^2H_6$]-DMSO) 7.31 (d, *J* 1, 5-H), 7.56 (d, *J* 1, 2-H), 8.32 (s, N=CH), 11.32 (br s, NH) and 12.16 (br s, 1-H); *m*/*z* 135 ($M^{\cdot+}$).

Similarly, the following compounds were prepared from 2-methyl-4-nitroimidazole **2b**[16] (12.7 g) and 1-acetoxymethyl-2-methyl-4-nitroimidazole **2i**[22] (9.95 g) respectively.

N-Cyano-*N*-(2-methylimidazol-4-yl)formamidine **71b** (4.1 g, 28%) as a light brown solid, m.p. 234–236 °C (decomp.); δ_H([$^2H_6$]-DMSO) 2.22 (s, CCH_3), 7.16 (s, 5-H), 8.25 (s, N=CH), 11.20 (br s, NH) and 11.80 (br s, 1-*H*). Attempts to recrystallise this compound resulted in cyclisation and it was used without further purification; N-(1-*acetoxymethyl*-2-*methylimidazol*-4-*yl*)-N-*cyanoformamidine* **71c** (1.6 g, 15%) as needles, m.p. 207–209 °C (Found: C, 48.8; H, 5.01; N, 31.8. $C_9H_{11}N_5O_2$ requires C, 48.9; H, 5.01; N, 31.7%); ν_{max}/cm^{-1} 1235, 1360, 1580, 1615, 1750, 2200 and 2800; δ_H([$^2H_6$]-DMSO) 2.05 (s, O_2CCH_3), 2.35 (s, CCH_3), 5.90 (s, CH_2), 7.40 (s, 5-H), 8.30 (s, N=CH) and 11.20 (br s, NH); *m*/*z* 221 ($M^{\cdot+}$).

(f) *With ethyl* N-*cyanoacetimidate* **11**.[21] A solution of 2-isopropyl-1-methyl-4-nitroimidazole **2f**[19] (8.45 g) in dioxane (125 cm^3) was reduced. Compound **9** (5.6 g) was then added with stirring to the filtrate and after 1 h the solution was evaporated. The residue was subjected to MPLC (9:1, $CHCl_3$–MeOH as eluent) and the major fraction (R_f 0.2) was collected and evaporated to give a buff solid. Recrystallisation from toluene gave N-*cyano*-N′-(2-*isopropyl*-1-*methylimidazol*-4-*yl*)-*acetamidine* **71e** (1.66 g, 16%) as a colourless solid, m.p. 150–151 °C (Found: C, 58.7; H, 7.35; N, 33.7. $C_{10}H_{15}N_5$ requires C, 58.5; H, 7.37; N, 34.1%); ν_{max}/cm^{-1} 1560, 2180, 2930, 2975, 3120 and 3220; δ_H([$^2H_6$]-DMSO) 1.23 [d, *J* 7, CH(CH_3)$_2$], 2.38 (s, CCH_3), 3.03 [sept, *J* 7, C*H*(CH_3)$_2$], 3.62 (s, NCH_3), 7.2 (s, 5-H) and 11.08 (br s, NH); *m*/*z* 205 ($M^{\cdot+}$).

Similarly, 4-nitroimidazole **2a**[16] (11.3 g) gave *N*-cyano-*N*-(imidazol-4-yl)acetamidine **71d** (8.1 g, 54%), m.p. 197–199 °C. δ_H([$^2H_6$]-DMSO) 2.38 (s, CCH_3), 7.30 (d, *J*, 5-H), 7.53 (d, *J* 1, 2-H), 11.12 (br s, CNH) and 12.08 (br s, 1-H). Attempts to recrystallise this material resulted in cyclisation and it was used without further purification.

(g) *With* S,S′-*dimethyl*-N-*cyanodithioiminocarbonate* **12**.[23] A solution of 4-nitroimidazole **2a**[16] (11.3 g) in dioxane (270 cm^3) was reduced and compound **12** (14.6 g) was added to the filtrate. After 1 h the solution was concentrated to 50 cm^3 and the solid product collected. Recrystallisation from water gave 4-*amino*-2-*methylthioimidazo*[1,5-a]-1,3,5-*triazine* **72d** (14.7 g, 81%) as colourless needles, m.p. 278–279 °C (Found: C, 39.8; H, 3.9; N, 39.0; S, 17.7. $C_6H_7N_5S$ requires C, 39.8; H, 3.89; N, 38.7; S, 17.7%); ν_{max}/cm^{-1} 1200, 1255, 1280, 1355, 1520, 1550, 1610, 1680, 3110 and 3260; δ_H([$^2H_6$]-DMSO) 2.42 (s, SCH_3), 7.02 (d, *J* 1, 8-H), 8.26 (d, *J* 1, 6-H) and 8.51 (br s, NH_2).

Cyclisation of Tetraethyl 2,2′[5″,5‴-*Biimidazole*-4″,4‴-*diylbis*-(*aminomethylene*)]*dimalonates* **15**.—Concentrated sulfuric acid (6.7 cm^3) was added quickly (over 1 min) to a stirred suspension of compound **15c** (6.7 g) in acetic anhydride (67 cm^3) to give an exothermic reaction (maximum temp. 95 °C). The resulting solution was cooled and poured onto water (500 cm^3) and the solid which separated was collected, recrystallised from acetic acid and identified as *diethyl* 4,4′-*dihydroxy*-6,6′-*diisopropylbi*(*imidazo*[3,4-a]*pyrimidine*)3,3′-*dicarboxylate* **16c** (3.0 g, 54%) as a yellow solid, m.p. 250 °C (decomp.) (Found: C, 58.1; H, 5.8; N, 16.9; $C_{24}H_{28}N_6O_6$ requires C, 58.05; H, 5.68; N, 16.9%); ν_{max}/cm^{-1} 1260, 1305, 1370, 1450, 1565, 1620, 1675, 1715, 2985 and 3335; δ_H([$^2H_6$]-DMSO + D_2O) 1.3 (t, *J* 7, 2 OCH_2CH_3),

1.36 [d, *J* 8, 2 $CH(CH_3)_2$], 3.75 [sept, *J* 8, 2 $CH(CH_3)_2$], 4.19 (q, *J* 7, 2 OCH_2CH_3) and 8.44 (s, 2 2-H).

Similarly, the following derivative was prepared from compound **15b**. *Diethyl* 4,4'-*dihydroxy*-6,6'-*dimethyl* 8,8-*bi*(*imidazo*[3,4-a]*pyrimidine*)-3,3'-*dicarboxylate* **16b** (3.8 g, 53%) as a yellow solid, m.p. 337–338 °C (decomp.) (Found: C, 54.3; H, 4.6; N, 19.2. $C_{20}H_{20}N_6O_6$ requires C, 54.5; H, 4.58; N, 19.1%); ν_{max}/cm^{-1} 1285, 1310, 1370, 1450, 1565, 1620, 1700, 1725, 2990, 3230 and 3320; $\delta_H([^2H_6]$-DMSO + $D_2O)$ 1.29 (t, *J* 7, 2 OCH_2CH_3), 2.88 (s, 2 CH_3), 4.22 (q, *J* 7, 2 OCH_2CH_3) and 8.41 (s, 2 2-H).

Cyclisation of Diethyl 2-[(1-*Benzylimidazol*-4-*yl*)*aminomethylene*]*malonate* **13g**.—A solution of a crude sample of compound **3g** (21 g) in acetic anhydride (200 cm^3) was treated with conc. H_2SO_4 (22.0 g), the temperature of the mixture rising to *ca.* 70 °C. The homogeneous mixture was then poured into water (200 cm^3) and the aqueous mixture extracted with CH_2Cl_2 (2 × 100 cm^3). The combined extracts were dried ($MgSO_4$) and evaporated to give a residue which was recrystallised from aqueous dimethylformamide and identified as the hydrogen sulfate salt of *ethyl* 1-*benzyl*-7-*hydroxyimidazo*[4,5-b]*pyridine*-6-*carboxylate* **25** (2.6 g, 11%), a colourless crystalline solid, m.p. 260–262 °C (Found: C, 48.6; H, 4.0; N, 10.5; S, 8.3. $C_{16}H_{15}N_3O_3 \cdot H_2SO_4$ requires C, 48.6; H, 4.3; N, 10.6; S, 8.1%); ν_{max}/cm^{-1} 1240, 1255, 1295, 1350, 1585, 1750, 3100, 3180, 3520 and 3620; $\delta_H([^2H_6]$-DMSO + $D_2O)$ 1.28 (t, *J* 7, OCH_2CH_3), 4.28 (q, *J* 7, OCH_2CH_3), 5.77 (s, CH_2Ph), 7.33–7.60 (m, C_6H_5), 8.40 (s, 5-H) and 9.94 (s, 2-H).

The aqueous phase was basified to pH 4 and the solid which separated was collected, recrystallised from ethanol and identified as 7-*benzyl*-3-*ethoxycarbonylimidazo*[3,4-a]*pyrimidin*-7-*ium*-4-*olate* **26** (5.2 g, 29%), a crystalline solid, m.p. 239 °C (Found: C, 64.3; H, 5.0; N, 14.2. $C_{16}H_{15}N_3O_3$ requires C, 64.6; H, 5.09; N, 14.1%); ν_{max}/cm^{-1} 1275, 1340, 1425, 1545, 1635, 1730, 2985, 3080 and 3125; δ_H 1.25 (t, *J* 7, OCH_2CH_3), 4.20 (q, *J* 7, OCH_2CH_3), 5.55 (s, CH_2Ph), 7.38–7.55 (m, C_6H_5), 7.73 (d, *J* 1, 8-H), 8.46 (s, 2-H) and 9.55 (d, *J* 1, 6-H).

Cycloaddition Reactions of 7-*Benzyl*-3-*ethoxycarbonylimidazo*[3,4-a]*pyrimidin*-7-*ium*-4-*olate* **26**.—A mixture of compound **26** (1.5 g) and dimethyl acetylenedicarboxylate (0.6 cm^3) in toluene (20 cm^3) was heated and stirred at 100 °C (22 h). The mixture was then filtered and evaporated to give a brown oil which was purified by MPLC (99:1, $CHCl_3$–MeOH as eluent). The first major component (R_f 0.5) was collected, recrystallised from ethyl acetate and identified as *ethyl* 2-(1-*benzyl*-3,4-*dimethoxycarbonylpyrrol*-2-*yl*)-4-*oxo*-3,4-*dihydropyrimidine*-5-*carboxylate* **29** (0.7 g, 32%), colourless crystals, m.p. 140–141 °C (Found: C, 60.1; H, 5.0; N, 9.4. $C_{22}H_{21}N_3O_7$ requires C, 60.1; H, 4.82; N, 9.6%); ν_{max}/cm^{-1} 1220, 1300, 1315, 1340, 1370, 1455, 1520, 1560, 1600, 1685, 1730, 2950 and 3130; δ_H 1.28 (t, *J* 7, OCH_2CH_3), 3.70 (s, OCH_3), 3.74 (s, OCH_3), 4.25 (q, *J* 7, OCH_2CH_3), 5.55 (s, CH_2Ph), 6.95–7.35 (m, C_6H_5), 7.87 (s, pyrrole 2-H), 8.64 (s, pyrimidine 6-H) and 13.00 (vbr s, OH).

The second major fraction (R_f 0.3) was collected, recrystallised from ethyl acetate and identified as 1-*benzyl*-4-(2,3-*dimethoxycarbonyl*-5-*ethoxycarbonyl*-4-*oxo*-1,4-*dihydro*-1-*pyridyl*)*imidazole* **30** (0.45 g, 21%), off-white solid, m.p. 73 °C (Found: C, 60.0; H, 4.65; N, 9.3. $C_{22}H_{21}N_3O_7$ requires C, 60.1; H, 4.82; N, 9.6%); ν_{max}/cm^{-1} 1280, 1435, 1560, 1630, 1705, 1740, 2960, 3120 and 3450br; δ_H 1.26 (t, *J* 7, OCH_2CH_3), 3.58 (s, OCH_3), 3.75 (s, OCH_3), 4.22 (q, *J* 7, OCH_2CH_3), 5.28 (s, CH_2Ph), 7.25–7.44 (m, C_6H_5), 7.65 (d, *J* 1, imidazole 5-H), 7.86 (d, *J* 1, imidazole 2-H) and 8.35 (s, pyridine 6-H).

4-*Amino*-3-*cyanoimidazo*[1,5-a]*pyrimidine* **40**.—Compound **38a** (13.1 g) was added with stirring to a suspension of charcoal (5.0 g) in boiling water (750 cm^3). Heating was continued (5 min) and the hot suspension was then filtered. The filtrate was concentrated to 150 cm^3 and the solid product which separated was collected, washed with cold ethanol and identified as the *title compound* **40** (5.1 g, 39%), colourless needles, m.p. 325 °C (decomp.) (Found: C, 52.4; H, 3.03; N, 43.5. $C_7H_5N_5$ requires C, 52.8; H, 3.17; N, 44.0%); ν_{max}/cm^{-1} 1570, 1600, 1685, 2210, 3000 and 3140; δ_H 7.36 (d, *J* 1, 8-H), 8.07 (s, 2-H), 8.56 (d, *J* 1, 6-H) and 8.97 (br s, NH_2); *m*/*z* 159 ($M^{\bullet+}$).

Imidazo[1,5-a]-1,3,5-*triazin*-4-*one* **68a**.—A mixture of compound **66a** (6.37 g) and potassium carbonate (4.83 g) in ethanol (300 cm^3) was heated under reflux (2 h). Charcoal was added and the hot solution filtered, cooled and concentrated to 60 cm^3. The solid product was collected, washed with ether and identified as *potassium imidazo*[1,5-a]-1,3,5-*triazin*-4-*olate* **67** (4.6 g, 75%), an off-white solid, m.p. >360 °C (Found: C, 34.1; H, 1.6; K, 22.6; N, 31.9. $C_5H_3KN_4O$ requires C, 34.5; H, 1.74; K, 22.4; N, 32.2%); ν_{max}/cm^{-1} 1210, 1250, 1310, 1360, 1390, 1510, 1560, 1640 and 3140; $\delta_H([^2H_6]$-DMSO) 6.75 (d, *J* 1, 8-H), 7.52 (s, 2-H) and 7.78 (d, *J* 1, 6-H).

A solution of compound **67** (2.5 g) in water (80 cm^3) was acidified to pH 5 (AcOH) and the resulting suspension heated under reflux (5 min), filtered and allowed to stand at 0 °C (1 h). The solid product was then collected, washed with EtOH (2 × 15 cm^3) and ether (3 × 15 cm^3) and identified as the *title compound* **68a** (1.3 g, 66%), colourless prisms, m.p. 270 °C (decomp.) (Found: C, 43.7; H, 2.7; N, 41.0. $C_5H_4N_4O$ requires C, 44.1; H, 2.96; N, 41.2%); λ_{max}(EtOH)/nm 255 (ε 7650); ν_{max}/cm^{-1} 1230, 1280, 1330, 1360, 1455, 1580, 1610, 1740 and 3100; $\delta_H([^2H_6]$-DMSO) 7.25 (d, *J* 1, 8-H), 7.76 (s, 2-H), 8.34 (d, *J* 1, 6-H) and 12.4 (br s, 3-H); *m*/*z* 136 ($M^{\bullet+}$).

Alkylation of Potassium Imidazo[1,5-a]-1,3,5-*triazin*-4-*olate* **67**.—Compound **67** (1.74 g) was stirred with a solution of methyl iodide (1.5 g) in DMF (50 cm^3). The mixture was warmed and when homogeneous (3 min) was evaporated. The residue was dissolved in water (50 cm^3) and extracted with chloroform (3 × 50 cm^3). The combined extracts were dried ($MgSO_4$), concentrated (*ca.* 40 cm^3) and diluted with ether. The product which crystallised was identified as 3-*methylimidazo*[1,5-a]-1,3,5-*triazin*-4-*one* **68b** (1.0 g, 67%), colourless crystals, m.p. 171–173 °C (Found: C, 47.5; H, 3.95; N, 37.3. $C_6H_6N_4O$ requires C, 48.0; H, 4.03; N, 37.3%); λ_{max}(EtOH)/nm 258 (ε 9310); ν_{max}/cm^{-1} 1275, 1340, 1430, 1455, 1610, 1720, 3070, 3105 and 3120; $\delta_H([^2H_6]$-DMSO) 3.45 (s, NCH_3), 7.22 (d, *J* 1, 8-H), 7.95 (s, 2-H) and 8.35 (d, *J* 1, 6-H); *m*/*z* 150 ($M^{\bullet+}$).

Similarly the following derivatives were prepared with ethyl iodide, benzyl bromide or 3,3-dimethylallyl bromide. 3-*Ethylimidazo*[1,5-a]-1,3,5-*triazin*-4-*one* **68c** (1.32 g, 81%), small lustrous plates, m.p. 156–159 °C (Found: C, 50.8; H, 4.75; N, 34.2. $C_7H_8N_4O$ requires C, 51.2; H, 4.91; N, 34.1%); ν_{max}/cm^{-1} 1245, 1270, 1360, 1380, 1470, 1610, 1725 and 3080; $\delta_H([^2H_6]$-DMSO) 1.3 (t, *J* 7, CH_2CH_3), 3.93 (q, *J* 7, CH_2CH_3), 7.25 (d, *J* 1, 8-H), 8.00 (s, 2-H) and 8.35 (d, *J* 1, 6-H); *m*/*z* 164 ($M^{\bullet+}$); 3-*benzylimidazo*[1,5-a]-1,3,5-*triazin*-4-*one* **68d** (1.34 g, 58%), colourless needles, m.p. 142–143 °C (Found: C, 63.3; H, 4.4; N, 24.9. $C_{12}H_{10}N_4O$ requires C, 63.7; H, 4.46; N, 24.8%); ν_{max}/cm^{-1} 1265, 1355, 1370, 1450, 1600 and 1740; δ_H 5.15 (s, CH_2), 7.30 (d, *J* 1, 8-H), 7.32–7.45 (m, C_6H_5), 8.16 (s, 2-H) and 8.38 (d, *J* 1, 6-H); *m*/*z* 226 ($M^{\bullet+}$); 3-(3-*methylbut*-3-*enyl*)*imidazo*[1,5-a]-1,3,5-*triazin*-4-*one* **68e** (0.35 g, 34%), lustrous plates, m.p. 92–94 °C (Found: C, 58.7; H, 5.9; N, 27.5. $C_{10}H_{12}N_4O$ requires C, 58.8; H, 5.92; N, 27.4%); ν_{max}/cm^{-1} 1250, 1270, 1360, 1370, 1460, 1610, 1730 and 3090; δ_H 1.72 (s, CH_3), 1.79 (s, CH_3), 4.52 (d, *J* 7, CH_2), 5.32 (t, t, *J* 7 and 1, $HCCH_2$), 7.26 (d, *J* 1, 8-H), 7.94 (s, 2-H) and 8.35 (d, *J* 1, 6-H); *m*/*z* 204 ($M^{\bullet+}$).

Preparation of 4-*Aminoimidazo*[1,5-a]-1,3,5-*triazines* **72**.—Compound **71a** (26.4 g) was added to a suspension of activated charcoal (10 g) in boiling water (4 dm^3). The hot solution was filtered and concentrated (*ca.* 500 cm^3). The solid which separated was collected, washed with cold ethanol (2 × 20 cm^3) and then ether (3 × 25 cm^3); it was identified as 4-*amino-imidazo*[1,5-a]-1,3,5-*triazine* **72a** (13 g, 49%), colourless crystals, m.p. 300 °C (decomp.) (Found: C, 44.3; H, 3.55; N, 51.6. $C_5H_5N_5$ requires C, 44.4; H, 3.73; N, 51.8%); λ_{max}(EtOH)/nm 215, 268 and 308 (ε 15 370, 7140 and 4230); ν_{max}/cm^{-1} 1300, 1355, 1375, 1465, 1540, 1610, 1690, 3030 and 3120; $\delta_H([^2H_6]$-DMSO) 7.26 (d, *J* 1, 8-H), 7.88 (s, 2-H), 8.42 (d, *J* 1, 6-H) and 8.56 (br s, NH_2); *m/z* 135 ($M^{\cdot+}$).

Similarly, the following derivatives were also prepared from compounds **71d** and **71b** respectively. 4-*Amino-2-methyl-imidazo*[1,5-a]-1,3,5-*triazine* **72b** (6.2 g, 76%), colourless crystals, m.p. 278–279 °C (Found: C, 48.1; H, 4.65; N, 47.2. $C_6H_7N_5$ requires C, 48.3; H, 4.73; N, 47.0%); ν_{max}/cm^{-1} 1220, 1270, 1295, 1395, 1470, 1550, 1615 and 1690; $\delta_H([^2H_6]$-DMSO) 2.30 (s, CCH_3), 7.00 (s, 8-H), 8.30 (s, 6-H) and 8.40 (br s, NH_2); *m/z* 149 ($M^{\cdot+}$); 4-*amino-6-methylimidazo*[1,5-a]-1,3,5-*triazine* **72c** (1.15 g, 8%), an off-white solid, m.p. 245–247 °C (Found: C, 48.0; H, 4.6; N, 47.1. $C_6H_7N_5$ requires C, 48.3; H, 4.73; N, 47.0%); ν_{max}/cm^{-1} 1210, 1285, 1370, 1530, 1600, 1655, 3020 and 3430; δ_H 2.84 (s, CCH_3), 6.94 (s, 8-H), 7.63 (s, 2-H) and 7.75 (br s, NH_2); *m/z* 149 ($M^{\cdot+}$).

Reactions of 4-*Aminoimidazo*[1,5-a]-1,3,5-*triazines* **72**.—(a) *With aryl isocyanates.* To a stirred solution of compound **72a** (2.7 g) in a mixture of 1 mol dm^{-3} aqueous NaOH (22.5 cm^3) and acetone (30 cm^3) was added a solution of phenyl isocyanate (2.62 g) in acetone (10 cm^3), the temperature being maintained below 10 °C during the addition. After being stirred at room temperature (30 min), the mixture was acidified (glacial AcOH, 2 cm^3). The solid product was collected, recrystallised from ethoxyethanol and identified as N-(*imidazo*[1,5-a]-1,3,5-*triazin-4-yl*)-N′-*phenylurea* **74** (R = Ph) (1.3 g, 26%), fine needles, m.p. 239 °C (decomp.) (Found: C, 56.3; H, 3.79; N, 33.2. $C_{12}H_{10}N_6O$ requires C, 56.7; H, 3.96; N, 33.1%); ν_{max}/cm^{-1} 1205, 1240, 1320, 1370, 1395, 1440, 1530, 1595, 1640, 1670, 3060 and 3150; $\delta_H([^2H_6]$-DMSO) 7.00–7.08 (m, 1 PhH), 7.26–7.36 (m, 2 PhH and 8-H), 7.64–7.74 (m, 2 PhH), 7.77 (s, 2-H), 8.32 (s, 6-H), 10.08 (br s, NH) and 12.47 (br s, NH); *m/z* 254 ($M^{\cdot+}$).

Similarly the following compound was prepared. N-(*Imidazo*-[1,5-a]-1,3,5-*triazin-4-yl*)-N′-3,4-*dichlorophenylurea* **74** (R = 3,4-$Cl_2C_6H_3$) (0.75 g, 12%), colourless crystals, m.p. 250 °C (decomp.) (Found: C, 44.4; H, 2.4; Cl, 21.7; N, 25.7. $C_{12}H_8Cl_2N_6O$ requires C, 44.6; H, 2.50; Cl, 21.9; N, 26.0%); ν_{max}/cm^{-1} 1210, 1240, 1300, 1320, 1385, 1480, 1530, 1590, 1665 and 3100; $\delta_H([^2H_6]$-DMSO) 7.32 (s, 8-H), 7.57 (br s, 2 ArH), 7.75 (s, 2-H), 8.10 (br s, 1 ArH), 8.29 (s, 6-H), 10.42 (br s, NH) and 12.56 (br s, NH); *m/z* 323 ($M^{\cdot+}$).

(b) *With benzoic anhydride.* Benzoic anhydride (67.8 g) was heated to 180 °C and compound **72a** (4.05 g) was added with stirring. The mixture became homogeneous followed by separation of a yellow–green solid. After cooling, toluene (100 cm^3) was added with stirring and the solid product collected. Recrystallisation from ethoxyethanol gave 4-*benzamidoimidazo*-[1,5-a]-1,3,5-*triazine* **76a** (6.6 g, 92%) as a buff solid, m.p. 294 °C (decomp.) (Found: C, 60.5; H, 3.65; N, 29.3. $C_{12}H_9N_5O$ requires C, 60.2; H, 3.79; N, 29.3%); ν_{max}/cm^{-1} 1200, 1270, 1305, 1315, 1330, 1370, 1390, 1425, 1450, 1605, 1675 and 3060; δ_H 7.33 (d, *J* 1, 8-H), 7.45–7.65 (m, 3 PhH), 7.82 (s, 2-H), 8.23–8.40 (m, 2 PhH), 8.60 (d, *J* 1, 6-H) and 12.40 (br s, NH); *m/z* 239 ($M^{\cdot+}$).

(c) *With acetic anhydride.* Compound **72a** (3.38 g) was added to boiling acetic anhydride (30 cm^3) and reflux was maintained (10 min). After cooling, the solid product which separated was collected, recrystallised from ethoxyethanol and identified as 4-*acetamidoimidazo*[1,5-a]-1,3,5-*triazine* **73a** (1.4 g, 32%), cream crystals, m.p. 224 °C (Found: C, 47.3; H, 3.85; N, 39.7. $C_7H_7N_5O$ requires C, 47.4; H, 3.98; N, 39.5%); ν_{max}/cm^{-1} 1240, 1285, 1360, 1390, 1415, 1600, 1675 and 3060; δ_H 2.38 (s, $COCH_3$), 7.43 (s, 8-H), 8.00 (s, 2-H), 8.51 (s, 6-H) and 11.87 (br s, NH); *m/z* 177 ($M^{\cdot+}$).

Similarly, the following compounds were prepared. 4-*Acetamido-6-methylimidazo*[1,5-a]-1,3,5-*triazine* **73c** (0.67 g, 23%), pale yellow needles, m.p. 196–197 °C (Found: C, 50.2; H, 4.7; N, 36.9. $C_8H_9N_5O$ requires C, 50.3; H, 4.75; N, 36.6%); ν_{max}/cm^{-1} 1225, 1310, 1370, 1600 and 3150; $\delta_H([^2H_6]$-DMSO) 2.24 (s, $COCH_3$), 2.84 (s, CCH_3), 7.10 (s, 8-H), 7.63 (s, 2-H) and 12.21 (br s, NH); *m/z* 191 ($M^{\cdot+}$); 4-*acetamido-2-methylimidazo*[1,5-a]-1,3,5-*triazine* **73b** (0.9 g, 35%), colourless solid, m.p. 134–136 °C (Found: C, 49.9; H, 4.8; N, 36.9. $C_8H_9N_5O$ requires C, 50.2; H, 4.75; N, 36.6%); ν_{max}/cm^{-1} 1220, 1260, 1275, 1370, 1385, 1610, 1670, 3120 and 3160; δ_H 2.40 (s, CCH_3 or $COCH_3$), 2.45 (s, $COCH_3$ or CCH_3), 7.25 (d, *J* 1, 8-H), 8.40 (d, *J* 1, 6-H) and 11.50 (br s, NH); *m/z* 191 ($M^{\cdot+}$).

(d) *With benzoyl chloride and dimethylformamide.* Benzoyl chloride (11.25 g) was added to a stirred solution of compound **72a** (5.4 g) and potassium carbonate (11.05 g) in dimethylformamide (250 cm^3). The orange solution was stirred at ambient temperature (30 min), filtered and evaporated. The residue was extracted with chloroform (3 × 50 cm^3) and the extract purified by MPLC (9:1, $CHCl_3$–MeOH as eluent). The major fraction (R_f 0.35) was collected and identified as N,N-*dimethyl*-N′-(*imidazo*[1,5-a]-1,3,5-*triazin-4-yl*)*formamidine* **75** (R = H) (1.8 g, 24%), yellow crystals, m.p. 167–168 °C (Found: C, 50.2; H, 5.2; N, 44.1. $C_8H_{10}N_6$ requires C, 50.5; H, 5.30; N, 44.2%); ν_{max}/cm^{-1} 1270, 1300, 1410, 1490, 1580, 1630, 3110 and 3300; δ_H 3.31 [s, $N(CH_3)_2$], 7.40 (d, *J* 1, 8-H), 8.00 (s, 2-H), 8.28 (d, *J* 1, 6-H) and 8.93 (s, N=CH); *m/z* 190 ($M^{\cdot+}$).

(e) *With diethyl ethoxymethylenemalonate* **5**. Compound **72a** (10.13 g) was added with stirring to boiling diethyl ethoxymethylenemalonate (100 cm^3). When the solution was clear (10 min) the mixture was allowed to cool and the solid which separated was collected, recrystallised from ethoxyethanol and identified as *ethyl* 4-*oxo*-4H-*imidazo*[3,4-c]*pyrimido*[1,2-a]-1,3,5-*triazine*-3-*carboxylate* **77** (10.7 g, 55%), buff plates, m.p. 244–246 °C (Found: C, 50.8; H, 3.35; N, 27.0. $C_{11}H_9N_5O_3$ requires C, 51.0; H, 3.50; N, 27.0%); λ_{max}(EtOH)/nm 209, 270 and 326 (ε 10 360, 13 680 and 9210); ν_{max}/cm^{-1} 1220, 1280, 1445, 1460, 1520, 1605, 1695, 1745, 3080 and 3120; δ_H 1.32 (t, *J* 7, CH_2CH_3), 4.32 (q, *J* 7, CH_2CH_3), 7.68 (d, *J* 1, 8-H), 8.72 (s, 6-H) and 8.86 (d, *J* 1, 10-H); *m/z* 259 ($M^{\cdot+}$).

(f) *With primary amines.* A mixture of compound **72d** (7.24 g), furfurylamine (11.6 g) and ethoxyethanol (130 cm^3) was heated under reflux (40 h). Charcoal was added and the solution was filtered, evaporated and the residue purified by MPLC (9:1, $CHCl_3$–MeOH as eluent). The major fraction (R_f 0.41) was collected, concentrated and the product which crystallised with time (12 h at 0 °C) was collected, washed with ether (2 × 15 cm^3) and identified as 4-*furfurylamino-2-methylthioimidazo*-[1,5-a]-1,3,5-*triazine* **78a** (4.1 g, 39%), pale pink crystals, m.p. 161–163 °C (Found: C, 50.5; H, 4.2; N, 27.0; S, 11.9. $C_{11}H_{11}N_5O_5S$ requires C, 50.6; H, 4.24; N, 26.8; S, 12.3%); ν_{max}/cm^{-1} 1250, 1295, 1350, 1490, 1590, 1620, 3130 and 3240; δ_H 2.56 (s, SCH_3), 4.84 (d, *J* 6, NCH_2), 6.32–6.41 (m, 3,4-furyl-H), 7.11 (s, 8-H), 7.38 (br s, 5-furyl-H), 7.88 (br, t, *J* 6, NH) and 8.11 (s, 6-H); *m/z* 261 ($M^{\cdot+}$).

Similarly the following compounds were also prepared. 2-*Methylthio-4-isopropylaminoimidazo*[1,5-a]-1,3,5-*triazine* **78b** (2.4 g, 22%), buff crystals, m.p. 193–195 °C (Found: C, 48.6; H, 5.7; N, 31.1. $C_9H_{13}N_5S$ requires C, 48.4; H, 5.87; N, 31.4%), ν_{max}/cm^{-1} 1245, 1350, 1365, 1485, 1575, 1610, 2980, 3120 and 3200; δ_H 1.28 [d, *J* 8, $HC(CH_3)_2$], 2.55 (s, SCH_3), 4.53 [d, sept, *J* 8 and 8, $HC(CH_3)_2$], 7.14 (d, *J* 1, 8-H), 7.21 (br d, *J* 8, NH) and 8.18 (d, *J* 1, 6-H); *m/z* 223 ($M^{\cdot+}$); 4-*butylamino*-2-

methylthioimidazo[1,5-a]-1,3,5-*triazine* **78c** (1.4 g, 30%), colourless crystals, m.p. 205–207 °C (Found: C, 50.3; H, 6.40; N, 29.3; S, 13.3. $C_{10}H_{15}N_5S$ requires C, 50.6; H, 6.37; N, 29.5; S, 13.5%); ν_{max}/cm^{-1} 1250, 1290, 1360, 1430, 1500, 1605, 1630, 2970, 3120 and 3260; δ_H 0.94 (t, *J* 7, CH_2CH_3), 1.42 (m, CH_2CH_3), 1.69 (m, $CH_2CH_2CH_2$), 2.55 (s, SCH_3), 3.66 (q, *J* 6, $HNCH_2CH_2$), 7.10 (d, *J* 1, 8-H), 8.35 (d, *J* 1, 6-H) and 8.70 (br t, *J* 6, NH); *m*/*z* 237 ($M^{\cdot+}$); 4-*hexadecylamino*-2-*methylthioimidazo*[1,5-a]-1,3,5-*triazine* **78d** (1.5 g, 25%), colourless plates, m.p. 102–103 °C (Found: C, 65.1; H, 10.0; N, 17.2; S, 7.7. $C_{22}H_{39}N_5S$ requires C, 65.1; H, 9.69; N, 17.3; S, 7.9%); ν_{max}/cm^{-1} 1250, 1360, 1370, 1490, 1590, 1620, 2860 and 2920; δ_H 0.88 (t, *J* 7, CH_2CH_3), 1.30 (m, 24 aliphatic H), 1.76 (m, $HNCH_2CH_2CH_2$), 1.86 (m, $HNCH_2CH_2CH_2$), 2.56 (s, SCH_3), 3.66 (q, *J* 7, $HNCH_2CH_2$), 7.13 (s, 8-H), 7.56 (br t, *J* 7, NH) and 8.19 (s, 6-H); *m*/*z* 405 ($M^{\cdot+}$); 4-*benzylamino*-2-*methylthioimidazo*[1,5-a]-1,3,5-*triazine* **78e** (0.95 g, 18%), colourless solid, m.p. 189–190 °C (Found: C, 57.7; H, 4.9; N, 25.9; S, 11.6. $C_{13}H_{13}N_5S$ requires C, 57.5; H, 4.83; N, 25.8; S, 11.8%); ν_{max}/cm^{-1} 1250, 1355, 1495, 1620, 3040, 3130 and 3240; δ_H 2.54 (s, SCH_3), 4.82 (d, *J* 6, $HNCH_2$), 6.93 (d, *J* 1, 8-H), 7.2–7.4 (m, C_6H_5), 8.10 (d, *J* 1, 6-H) and 8.30 (br t, *J* 6, NH); *m*/*z* 271 ($M^{\cdot+}$); 4-[2′-(N,N-*dimethylamino*)*ethylamino*]-2-*methylthioimidazo*[1,5-a]-1,3,5-*triazine* **78f** (1.7 g, 34%), colourless solid, m.p. 133–135 °C (Found: C, 47.4; H, 6.3; N, 33.0; S, 12.4. $C_{10}H_{16}N_6S$ requires C, 47.6; H, 6.39; N, 33.3; S, 12.7%); ν_{max}/cm^{-1} 1255, 1350, 1370, 1495, 1620 and 3120; δ_H 2.32 [s, $N(CH_3)_2$], 2.54 (s, SCH_3), 2.63 (t, *J* 6, $HNCH_2CH_2N$), 3.71 (t, *J* 6, $HNCH_2CH_2$), 7.16 (d, *J* 1, 8-*H*), 8.00 (d, *J* 1, 6-H) and 12.00 (vbr s, NH); *m*/*z* 252 ($M^{\cdot+}$).

Reactions of 4-*Benzamidoimidazo*[1,5-a]-1,3,5-*triazines* **76**.—(a) *With bromine*. Bromine (1.2 g) was added to a stirred solution of compound **76a** (1.2 g) in glacial acetic acid (95 cm^3) and trifluoroacetic acid (1 cm^3) maintained at 70 °C. The solid which separated was collected, recrystallised from DMF–methanol and identified as 4-*benzamido*-8-*bromoimidazo*[1,5-a]-1,3,5-*triazine* **76b** (1.5 g, 76%), a buff solid, m.p. 286 °C (decomp.) (Found: C, 45.2; H, 2.35; Br, 25.2; N, 22.1. $C_{12}H_8BrN_5O$ requires C, 45.3; H, 2.53; Br, 25.1; N, 22.0%); ν_{max}/cm^{-1} 1210, 1285, 1320, 1360, 1380, 1600, 1650, 3100 and 3140; δ_H([$^2H_6$]-DMSO) 7.50–7.70 (m, 3 PhH), 7.86 (s, 2-H), 8.30–8.36 (m, 2 PhH), 8.76 (s, 6-H) and 12.91 (br s, NH); *m*/*z* 318 ($M^{\cdot+}$).

(b) *With phosphoryl chloride and dimethylformamide*. Phosphoryl chloride (4.59 g) was slowly added with stirring to a slurry of compound **76a** (4.78 g) in dimethylformamide (40 cm^3). The slurry was then heated to 105 °C and allowed to cool whilst being stirred. After evaporation, water (50 cm^3) was added to the residue and the mixture stirred until homogeneous. This solution was then adjusted to pH 7 (saturated aq. $NaHCO_3$) and heated at 100 °C (30 min). The aqueous solution was then extracted with chloroform (3 × 200 cm^3) and the combined extracts were washed, dried (Na_2SO_4) and evaporated. The residue was purified by MPLC (19:1, $CHCl_3$–MeOH as eluent) and the major component (R_f 0.12) collected, recrystallised from dioxane and identified as N,N-*dimethyl*-N′-(8-*formylimidazo*[1,5-a]-1,3,5-*triazin*-4-*yl*)*formamidine* **75** (R = CHO) (1.8 g, 41%), orange-yellow prisms, m.p. 225–227 °C (Found: C, 49.7; H, 4.65; N, 39.0. $C_9H_{10}N_6O$ requires C, 49.5; H, 4.62; N, 38.5%); ν_{max}/cm^{-1} 1295, 1325, 1350, 1410, 1430, 1510, 1590, 1645, 1680, 3130 and 3170; δ_H([$^2H_6$]-DMSO) 3.35 [s, $N(CH_3)_2$], 8.30 (s, 2-H), 8.55 (s, 6-H), 9.10 (s, CH=N) and 10.00 (s, CH=O); *m*/*z* 218 ($M^{\cdot+}$).

(c) *With propylamine*. A suspension of compound **76b** (1.0 g) in ethanol (100 cm^3) was heated under reflux and propylamine (0.59 g) was added. The mixture became homogeneous and was then evaporated to give a brown oil which was purified by MPLC (9:1, $CHCl_3$–MeOH as eluent). The major component (R_f 0.24) was collected, crystallised from light petroleum (b.p. 80–100 °C) and identified as N-*benzoyl*-N′-*propylguanidine* **79** (0.3 g, 44%), pale orange crystals, m.p. 75–77 °C (Found: C, 64.6; H, 7.6; N, 20.4. $C_{11}H_{15}N_3O$ requires C, 64.4; H, 7.37; N, 20.5%); ν_{max}/cm^{-1} 1370, 1560, 1680, 2970 and 3330; δ_H 0.98 (t, *J* 7, CH_2CH_3), 1.63 (sextet, *J* 7, CH_2CH_3), 3.10 (m, $NHCH_2CH_2$), 6.20–8.00 (vbr s, NH and NH_2), 7.34–7.48 (m, 3 Ph*H*) and 8.11–8.19 (m, 2 Ph*H*); *m*/*z* 205 ($M^{\cdot+}$).

Addition–Elimination Reactions of 5-*Aminoimidazoles* **3**.—(a) *With diethyl ethoxymethylenemalonate* **5**. A mixture of 1,2-dimethyl-5-nitroimidazole[24] **4e** (100 g, 0.71 mol), diethyl ethoxymethylenemalonate **5** (153 g, 0.71 mol) and 5% Pd/C (25 g) in ethanol (4 dm^3) was vigorously shaken under an atmosphere of hydrogen until 3 mol equiv. of gas had been consumed. The catalyst was filtered off and evaporation of the filtrate gave a brown oil which was dissolved in 2 mol dm^{-3} HCl (1 dm^3). This solution was purified by pH gradient extraction with ethyl acetate at pH 5, 7 and 9. The extract at pH 5 was discarded.

The extract at pH 7 was dried ($MgSO_4$) and evaporated to give a brown oil (15 g) which was dissolved in a small volume of ethyl acetate and a little light petroleum (b.p. 40–60 °C) was added. The resulting solid was collected and recrystallisation from ethanol gave *diethyl* (5-*amino*-1,2-*dimethylimidazol*-4-*yl*)*methylenemalonate* **18e** (9.2 g, 5%), as yellow prisms, m.p. 195–196 °C (Found: C, 55.5; H, 6.8; N, 14.9. $C_{13}H_{19}N_3O_4$ requires C, 55.5; H, 6.81; N, 14.9%); λ_{max}(EtOH)/nm 211 (ε 6018), 240 (ε 6606) and 374 (ε 25 835); ν_{max}/cm^{-1} 1210, 1255, 1562, 1583, 1680, 1700, 2985, 3240 and 3360; δ_H([$^2H_6$]-DMSO + $CDCl_3$) 1.28 (t, *J* 7, OCH_2CH_3), 1.31 (t, *J* 7, OCH_2CH_3), 2.18 (s, CCH_3), 3.30 (s, NCH_3), 4.17 (q, *J* 7, OCH_2CH_3), 4.28 (q, *J* 7, OCH_2CH_3), 5.58 (br s, NH_2) and 7.6 (s, CH); *m*/*z* 281 ($M^{\cdot+}$).

The mother liquor from the pH 7 extraction was further diluted with ether to precipitate a second solid. This was collected and recrystallisation from ethyl acetate gave 4,4′-*bis*(5-*diethoxycarbonylethyleneamino*-1,2-*dimethylimidazole*) **15e** (2.0 g, 1%), as an off-white solid, m.p. 209–211 °C (Found: C, 55.9; H, 6.5; N, 15.0. $C_{26}H_{36}N_6O_8$ requires C, 55.7; H, 6.47; N, 15.0%); λ_{max}(EtOH)/nm 216 (ε 22 366), 277 (ε 20 024) and 310s (ε 17 377); ν_{max}/cm^{-1} 1220, 1260, 1370, 1417, 1600, 1642, 1686, 2980 and 3420; δ_H 1.27 (t, *J* 7, 2 OCH_2CH_3), 1.38 (t, *J* 7, 2 OCH_2CH_3), 2.30 (s, 2 CCH_3), 3.40 (s, 2 NCH_3), 4.10 (q, *J* 7, 2 OCH_2CH_3), 4.20 (q, *J* 7, 2 OCH_2CH_3), 8.03 (d, *J* 12, 2 HNC*H*) and 10.50 (d, *J* 12, 2 *H*NCH); *m*/*z* 560 ($M^{\cdot+}$).

The remainder of the mother liquor from the pH 7 extraction was combined with the pH 9 extract and evaporated to give a crude yield of the major product **10a** (130 g, 65%) which could be used without further purification. An analytical sample was obtained using MPLC (9:1, $CHCl_3$–MeOH as eluent). The product was washed with ether and identified as 5-*diethoxycarbonylethyleneamino*-1,2-*dimethylimidazole* **17e**, an amorphous solid, m.p. 60–63 °C (Found: C, 55.1; H, 6.7; N, 14.8. $C_{13}H_{19}N_3O_4$ requires C, 55.5; H, 6.81; N, 14.9%); λ_{max}(EtOH)/nm 217 (ε 10 188) and 291 (ε 12 698); ν_{max}/cm^{-1} 1230, 1617, 1660, 1710, 2980 and 3720; δ_H 1.28 (t, *J* 7, OCH_2CH_3), 1.37 (t, *J* 7, OCH_2CH_3), 2.36 (s, CCH_3), 3.42 (s, NCH_3), 4.18 (q, *J* 7, OCH_2CH_3), 4.30 (q, *J* 7, OCH_2CH_3), 6.79 (s, 4-H), 7.98 (d, *J* 12, HNC*H*) and 10.36 (d, *J* 12, *H*NCH).

The following compounds were similarly prepared from the appropriate 5-nitroimidazole **4**.

1-Methyl-5-nitroimidazole[25] **4k** (2.54 g) gave 5-*diethoxycarbonylethyleneamino*-1-*methylimidazole* **17k** (3.3 g, 62%), as a colourless solid, m.p. 97–98 °C (Found: C, 54.0; H, 6.45; N, 15.7. $C_{12}H_{17}N_3O_4$ requires C, 53.9; H, 6.41; N, 15.7%); ν_{max}/cm^{-1} 1230, 1265, 1380, 1605, 1645, 1690, 2990 and 3110; δ_H 1.3 (t, *J* 7, OCH_2CH_3), 1.35 (t, *J* 7, OCH_2CH_3), 3.55 (s, NCH_3), 4.17 (q, *J* 7, CH_2CH_3), 4.24 (q, *J* 7, OCH_2CH_3), 6.83 (s, 4-H), 7.28 (s, 2-H), 7.98 (d, *J* 12, HNC*H*) and 10.4 (br d, *J* 12, *H*NCH).

1-(2-Hydroxyethyl)-2-methyl-5-nitroimidazole[26] **4l** (200 g) gave 4,4′-bis[5-*diethoxycarbonylethyleneamino*-1-(2-*hydroxyethyl*)-2-*methylimidazole*] **15l** (1.2 g, 0.4%) as yellow prisms, m.p. 190–192 °C (Found: C, 54.0; H, 6.5; N, 13.6. $C_{28}H_{40}N_6O_{10}$ requires C, 54.2; H, 6.50; N, 13.5%); λ_{max}(EtOH)/nm 281 (ε 16 200) and 311 (ε 18 900); ν_{max}/cm^{-1} 1250, 1302, 1373, 1400, 1595, 1655, 1690, 2960, 3200 and 3460; δ_H 1.25 (t, *J* 7, 2 OCH_2CH_3), 1.30 (t, *J* 7, 2 OCH_2CH_3), 2.30 (s, 2 CCH_3), 3.80 (br s, 2 CH_2CH_2OH), 4.07 (q, *J* 7, 2 OCH_2CH_3), 4.18 (q, *J* 7, 2 OCH_2CH_3), 7.81 (d, *J* 13, 2 HNC*H*) and 10.50 (br d, *J* 13, 2 *H*NCH), and 5-*diethoxycarbonylethyleneamino*-1-(2-*hydroxyethyl*)-2-*methylimidazole* **17l** (117.6 g, 32%), a buff amorphous solid, m.p. 190–192 °C (Found: C, 54.1; H, 6.9; N, 13.7. $C_{14}H_{21}N_3O_5$ requires C, 54.0; H, 6.8; N, 13.5%); λ_{max}(EtOH)/nm 218 (ε 10 200) and 305 (ε 15 200); ν_{max}/cm^{-1} 1225, 1328, 1380, 1445, 1510, 1585, 1650, 1690 and 2650–3300; δ_H 1.25 (t, *J* 7, 2 OCH_2CH_3), 2.25 (s, CCH_3), 3.45–4.30 (m, CH_2CH_2OH and 2 OCH_2CH_3), 5.15 (vbr s, CH_2CH_2OH), 6.67 (s, 4-H), 7.80 (br s, HNC*H*) and 10.15 (vbr s, *H*NCH). 2-Isopropyl-1-methyl-5-nitroimidazole[27] **4f** (200 g) gave *diethyl* (5-*amino*-2-*isopropyl*-1-*methylimidazol*-4-*yl*)*methylenemalonate* **18f** (16.3, 4.5%) as yellow prisms, m.p. 161–162 °C (Found: C, 58.2; H, 7.3; N, 13.6. $C_{15}H_{23}N_3O_4$ requires C, 58.2; H, 7.49; N, 13.6%); ν_{max}/cm^{-1} 1210, 1245, 1600, 1680, 1710, 2980, 3240 and 3360; δ_H 1.20 [d, *J* 7, $CH(CH_3)_2$], 1.26 (t, *J* 7, OCH_2CH_3), 1.32 (t, *J* 7, OCH_2CH_3), 2.80 [sept, *J* 7, $CH(CH_3)_2$], 3.30 (s, NCH_3), 4.0 (br s, NH_2), 4.2 (q, *J* 7, OCH_2CH_3), 4.35 (q, *J* 7, OCH_2CH_3) and 7.25 (s, C*H*); 4,4′-*bis*(5-*diethoxycarbonylethyleneamino*-2-*isopropyl*-1-*methylimidazole*) **15f** (6.0 g, 1.6%), an amorphous solid, m.p. 172–173 °C (Found: C, 58.4; H, 7.5; N, 13.7. $C_{30}H_{44}N_6O_8$ requires C, 58.4; H, 7.19; N, 13.6%); ν_{max}/cm^{-1} 1240, 1375, 1420, 1595, 1630, 1680 and 2980; δ_H 1.2 (t, *J* 7, 2 OCH_2CH_3), 1.28 [d, *J* 7, 2 $CH(CH_3)_2$], 1.38 (t, *J* 7, 2 OCH_2CH_3), 2.88 [sept, *J* 7, 2 $CH(CH_3)_2$], 3.4 (s, 2 NCH_3), 4.07 (q, *J* 7, 2 OCH_2CH_3), 4.2 (q, *J* 7, 2 OCH_2CH_3), 8.15 (d, *J* 12, 2 HNC*H*) and 10.55 (d, *J* 12, 2 *H*NCH) and 5-diethoxycarbonylethyleneamino-2-isopropyl-1-methylimidazole **17f** as a brown impure oil which was used without further purification.

1-Methyl-5-nitro-2-styrylimidazole[28] **4o** (11.45 g) gave *diethyl* (5-*amino*-1-*methyl*-2-*phenylethylimidazol*-4-*yl*)*methylenemalonate* **18m** (0.6 g, 3%) as a yellow solid, m.p. 153–155 °C (Found: C, 64.2; H, 6.9; N, 11.2. $C_{20}H_{25}N_3O_4$ requires C, 64.7; H, 6.74; N, 11.3%); ν_{max}/cm^{-1} 1210, 1230, 1580, 1690, 2990, 3240, 3340 and 3410; δ_H 1.25 (t, *J* 7, OCH_2CH_3), 1.30 (t, *J* 7, OCH_2CH_3), 2.60–3.15 (m, CH_2CH_2 and NCH_3), 3.88 (br s, NH_2), 4.00–4.60 (m, 2 OCH_2CH_3), 7.17 (br s, C_6H_5) and 7.20 (s, CH); *m*/*z* 371 ($M^{\cdot+}$) and 5-*diethoxycarbonylethyleneamino*-1-*methyl*-2-*phenylethylimidazole* **17m** (8.0 g, 43%) a buff solid, m.p. 62–64 °C (Found: C, 63.2; H, 7.1; N, 11.0. $C_{20}H_{25}N_3O_4 \cdot 0.5H_2O$ requires C, 63.2; H, 6.84; N, 11.1%); ν_{max}/cm^{-1} 1220, 1260, 1380, 1595, 1650, 1695, 2990 and 3240; δ_H 1.27 (t, *J* 7, OCH_2CH_3), 1.32 (t, *J* 7, OCH_2CH_3), 2.10 (s, H_2O), 2.8–3.1 (m, CH_2CH_2), 3.17 (s, NCH_3), 4.19 (q, *J* 7, OCH_2CH_3), 4.25 (q, *J* 7, OCH_2CH_3), 6.80 (s, 4-*H*), 7.05–7.25 (m, C_6H_5), 7.95 (d, *J* 13, HNC*H*) and 10.30 (br d, *J* 13, *H*NCH).

(b) *With ethoxymethylenemalononitrile* **6**. A solution of 1,2-dimethyl-5-nitroimidazole[24] **4e** (6.0 g) in dioxane (250 cm^3) was reduced to give a solution of the amine according to the procedure described in the preceding paper.[1] After removal of the catalyst, ethoxymethylenemalononitrile **6** (6.5 g) was added with stirring to the filtrate and the mixture stirred (30 min). The solid product was collected and recrystallised from ethanol to give 5-*amino*-4-(2,2-*dicyanovinyl*)-1,2-*dimethylimidazole* **42e** (6.7 g, 84%) as a yellow solid, m.p. indistinct (due to cyclisation) (Found: C, 57.9; H, 4.65; N, 37.1. $C_9H_9N_5$ requires C, 57.7; H, 4.85; N, 37.4%); ν_{max}/cm^{-1} 1315, 1370, 1490, 1565, 1610, 1665, 2200, 2210, 3180, 3340 and 3380; δ_H 2.20 (s, CCH_3), 3.28 (s, NCH_3), 7.46 (br s, NH_2) and 7.60 (s, CH).

The following compounds were similarly prepared from 1-(2-hydroxyethyl)-2-methyl-5-nitroimidazole[26] **4l** (5.14 g) and 2-isopropyl-1-methyl-5- nitroimidazole[27] **4f** (8.45 g) respectively. 5-*Amino*-4-(2,2-*dicyanovinyl*)-1-(2-*hydroxyethyl*)-2-*methylimidazole* **42c** (4.7 g, 72%), yellow needles, m.p. 198–200 °C (Found: C, 55.0; H, 5.0; N, 32.2. $C_{10}H_{11}N_5O$ requires C, 55.3; H, 5.07; N, 32.3%); ν_{max}/cm^{-1} 1318, 1350, 1555, 1605, 1677, 2200, 2218, 3212, 3360 and 3458; δ_H 2.24 (s, CCH_3), 3.45–3.90 (m, CH_2CH_2OH), 5.00 (br t, *J* 6, CH_2CH_2OH), 7.42 (br s, NH_2) and 7.60 (s, CH); 5-*amino*-4-(2,2-*dicyanovinyl*)-2-*isopropyl*-1-*methylimidazole* **42d** (6.13 g, 57%), yellow prisms, m.p. 216–218 °C (Found: C, 61.2; H, 5.9; N, 32.8. $C_{11}H_{13}N_5$ requires C, 61.4; H, 6.09; N, 32.5%); ν_{max}/cm^{-1} 1235, 1270, 1340, 1395, 1460, 1550, 1600, 1660, 2210, 2940, 2980, 3220 and 3350; δ_H 1.19 [d, *J* 7, $CH(CH_3)_2$], 2.94 [sept, *J* 7, $CH(CH_3)_2$], 3.32 (s, NCH_3), 7.29 (br s, NH_2) and 7.64 (s, CH); *m*/*z* 215 ($M^{\cdot+}$).

(c) *With ethyl* (*ethoxymethylene*)*cyanoacetate* **8**. A solution of 1,2-dimethyl-5-nitroimidazole[24] **4e** (12.5 g) in dioxane (150 cm^3) was reduced to give a solution of the amine. After removal of the catalyst, a solution of ethyl (ethoxymethylene)cyanoacetate **8** (15 g) in dioxane (100 cm^3) was added and the mixture allowed to stand at ambient temperature (18 h). The resulting solid was collected and recrystallised from ethanol to give *ethyl* 3-(5-*amino*-1,2-*dimethylimidazol*-4-*yl*)-2-*cyanoprop*-2-*enoate* **64e** (9.5 g, 46%) as yellow crystals, m.p. 231–233 °C (Found: C, 56.6; H, 6.15; N, 23.6. $C_{11}H_{14}N_4O_2$ requires C, 56.4; H, 6.02; N, 23.9%); ν_{max}/cm^{-1} 1250, 1490, 1535, 1597, 1640, 1670, 2208, 3240, 3340 and 3405; δ_H 1.25 (t, *J* 7, OCH_2CH_3), 2.2 (s, CCH_3), 3.27 (NCH_3), 4.14 (q, *J* 7, OCH_2CH_3), 7.3 (br s, NH_2) and 7.98 (s, CH).

The following compounds were similarly prepared from 1-(2-hydroxyethyl)-2-methyl-5-nitroimidazole[26] **4l** (4.23 g) and 2-isopropyl-1-methyl-5-nitroimidazole[27] **4f** (6.76 g) respectively. *Ethyl* 3-[5-*amino*-1-(2-*hydroxyethyl*)-2-*methylimidazol*-4-*yl*]-2-*cyanoprop*-2-*enoate* **64l** (4.7 g, 72%), a yellow solid, m.p. 195–197 °C (Found: C, 54.5; H, 6.0; N, 21.1. $C_{12}H_{16}N_4O_3$ requires C, 54.55; H, 6.06; N, 21.2%); ν_{max}/cm^{-1} 1250, 1410, 1530, 1590, 1665, 2205, 3190, 3350 and 3480; δ_H 1.24 (t, *J* 7, OCH_2CH_3), 2.25 (s, CCH_3), 3.40–3.90 (m, CH_2CH_2OH), 4.15 (q, *J* 7, OCH_2CH_3), 5.00 (br t, *J* 6, CH_2CH_2OH), 7.27 (br s, NH_2) and 7.96 (s, CH); *ethyl* 3-(5-*amino*-2-*isopropyl*-1-*methylimidazol*-4-*yl*)-2-*cyanoprop*-2-*enoate* **64f** (7.0 g, 67%), a yellow solid, m.p. 183–184 °C (Found: C, 59.0; H, 7.0; N, 21.3. $C_{13}H_{18}N_4O_2$ requires C, 59.5; H, 6.92; N, 21.4%); ν_{max}/cm^{-1} 1240, 1290, 1400, 1530, 1585, 1655, 2210, 2980, 3205 and 3340; δ_H 1.20 [d, *J* 7, $CH(CH_3)_2$], 1.25 (t, *J* 7, OCH_2CH_3), 2.92 [sept, *J* 7, $CH(CH_3)_2$], 3.30 (s, NCH_3), 4.15 (q, *J* 7, OCH_2CH_3), 7.25 (br s, NH_2) and 8.00 (s, CH).

(d) *With ethoxymethyleneurethane*[21] **9**. A solution of 5-amino-1,2-dimethylimidazole **3e** (2.22 g) in dioxane (40 cm^3) was prepared by the method described in the preceding paper.[1] Ethoxymethyleneurethane[21] **9** (2.9 g) was added and the mixture warmed to 60 °C with stirring. The solution was then stirred at ambient temperature (30 min) and the buff solid which had formed was collected and identified as the product **69e** (2.05 g, 49%) which was used without further purification. Recrystallisation of a small sample from acetonitrile gave N-(1,2-*dimethylimidazol*-5-*yl*)-N′-*ethoxycarbonylformamidine* **69e** as colourless prisms, m.p. indistinct (due to cyclisation) (Found: C, 51.3; H, 6.7; N, 26.6. $C_9H_{14}N_4O_2$ requires C, 51.4; H, 6.71; N, 26.7%); ν_{max}/cm^{-1} 1240, 1290, 1540, 1645 and 1745; δ_H 1.25 (t, *J* 7, OCH_2CH_3), 2.25 (s, CCH_3), 3.45 (s, NCH_3), 4.25 (q, *J* 7, OCH_2CH_3), 6.75 (s, 4-H), 8.50 (s, HNC*H*) and 10.65 (br s, NH); *m*/*z* 210 ($M^{\cdot+}$).

The following compounds were similarly prepared from 1-methyl-5-nitroimidazole[25] **4k** (6.35 g) and 1-(2-hydroxyethyl)-2-methyl-5-nitroimidazole[26] **4l** (8.55 g), respectively. N-*Ethoxycarbonyl*-N′-(1-*methylimidazol*-5-*yl*)*formamidine* **69k**

(5.1 g, 52%) as colourless lustrous plates, m.p. 161–163 °C (Found: C, 48.6; H, 5.9; N, 29.0. $C_8H_{12}N_4O$ requires C, 49.0; H, 6.17; N, 28.6%); ν_{max}/cm^{-1} 1240, 1285, 1510, 1660, 1740, 2710 and 3130; δ_H 1.23 (t, *J* 7, OCH_2CH_3), 3.46 (s, CCH_3), 4.19 (q, *J* 7, OCH_2CH_3), 6.77 (d, *J* 1, 4-H), 7.45 (d, *J* 1, 2-H), 8.36 (d, *J* 10, HNC*H*) and 10.83 (br d, *J* 10, NH); *m*/*z* 196 ($M^{\bullet+}$); N-*ethoxycarbonyl*-N′-[1-(2-*hydroxyethyl*)-2-*methylimidazol*-5-*yl*]*formamidine* **69l** (2.3 g, 33%), colourless prisms, m.p. 172–173 °C (Found: C, 50.1; H, 6.6; N, 23.2. $C_{10}H_{16}N_4O_3$ requires C, 50.0; H, 6.71; N, 23.3%); ν_{max}/cm^{-1} 1220, 1240, 1420, 1645 and 1730; δ_H 1.24 (t, *J* 7, OCH_2CH_3), 2.26 (s, CCH_3), 3.52 (t, *J* 6, NCH_2CH_2OH), 3.86 (t, *J* 6, NCH_2CH_2OH), 4.19 (q, *J* 7, OCH_2CH_3), 4.78 (br s, OH), 6.57 (s, 4-H), 8.31 (s, HNC*H*) and 10.64 (br s, NH); *m*/*z* 240 ($M^{\bullet+}$).

(e) With *ethyl* N-*cyanoformimidate*[21] **10**. A solution of 1,2-dimethyl-5-nitroimidazole **4e** (7.05 g) in dioxane (250 cm^3) was reduced to the amine according to the previously described procedure. Ethyl *N*-cyanoformimidate[21] **10** (4.9 g) was added with stirring and the resulting solid was collected (5.3 g). Concentration of the filtrate under diminished pressure gave a second crop (1.75 g). Both crops were shown by TLC to be two-component mixtures and were combined. The mixture (7.05 g) was separated by MPLC (9:1 chloroform–methanol as eluent). The first component (R_f 0.17) was collected and concentration and trituration with ether gave 5-*amino*-4-N-*cyanoiminomethyl*-1,2-*dimethylimidazole* **83a** (1.88 g, 23%) as pale yellow crystals, m.p. 208 °C (Found: C, 51.2; H, 5.4; N, 43.2. $C_7H_9N_5$ requires C, 51.5; H, 5.56; N, 42.9%); ν_{max}/cm^{-1} 1295, 1310, 1410, 1520, 1610, 2170, 3150 and 3330; δ_H 2.2 (s, CCH_3), 3.35 (s, NCH_3), 7.55 (br s, NH_2) and 8.45 (s, CH); *m*/*z* 163 ($M^{\bullet+}$).

The second component (R_f 0.10) was collected and concentration and trituration with ether gave a solid which was recrystallised from acetonitrile to give N-*cyano*-N′-(1,2-*dimethylimidazol*-5-*yl*)*formamidine* **84a** (2.1 g, 26%) as tiny needles, m.p. 185–187 °C (Found: C, 51.6; H, 5.6; N, 43.0. $C_7H_9N_5$ requires C, 51.5; H, 5.56; N, 42.9%); ν_{max}/cm^{-1} 1320, 1365, 1400, 1510, 1640, 2165 and 2205; δ_H(at 100 °C) 2.30 (s, CCH_3), 3.40 (s, NCH_3), 4.5 (vbr s, HCN*H*), 6.85 (s, 4-H) and 8.15 (s, *H*CNH); *m*/*z* 163 ($M^{\bullet+}$).

The following compounds were similarly prepared from the appropriate 5-nitroimidazole **4**.

1-Methyl-5-nitroimidazole[25] **4k** (6.35 g) gave 5-*amino*-4-*cyanoiminomethyl*-1-*methylimidazole* **83b** (0.3 g, 4%), as a pale yellow solid, m.p. 184–186 °C (Found: C, 48.1; H, 4.6; N, 46.9. $C_6H_7N_5$ requires C, 48.3; H, 4.73; N, 47.0%); ν_{max}/cm^{-1} 1270, 1330, 1390, 1515, 1560, 1600, 2180, 3080 and 3340; δ_H 3.40 (s, NCH_3), 7.35 (s, 2-H), 7.50 (br s, NH_2) and 8.60 (s, CH); *m*/*z* 149 ($M^{\bullet+}$) and N-*cyano*-N′-(1-*methylimidazol*-5-*yl*)*formamidine* **84b** (3.1 g, 42%) as colourless plates, m.p. 178–180 °C (Found: C, 47.9; H, 4.8; N, 46.9. $C_6H_7N_5$ requires C, 48.3; H, 4.73; N, 47.0%); ν_{max}/cm^{-1} 1250, 1300, 1360, 1510, 1550, 1600, 2200 and 3220; δ_H([$^2H_6$]-DMSO at 100 °C) 3.55 (s, NCH_3), 6.90 (s, 4-H), 7.60 (s, 2-H), 8.35 (s, HNC*H*) and 10.90 (vbr s, NH); *m*/*z* 149 ($M^{\bullet+}$).

1-(2-Hydroxyethyl)-2-methyl-5-nitroimidazole[26] **4l** (17.1 g) gave 5-*amino*-4-*cyanoiminomethyl*-1-(2-*hydroxyethyl*)-2-*methylimidazole* **83c** (1.6 g, 8%) as a pale yellow solid, m.p. 183–184 °C (Found: C, 49.4; H, 5.6; N, 36.3. $C_8H_{11}N_5O$ requires C, 49.7; H, 5.74; N, 36.3%); ν_{max}/cm^{-1} 1240, 1310, 1380, 1410, 1530, 1600, 1650, 2150, 2960 and 3360; δ_H([$^2H_6$]-DMSO at 100 °C) 2.25 (s, CCH_3), 3.65 (t, *J* 5, CH_2CH_2OH), 3.90 (t, *J* 5, CH_2CH_2OH), 6.42 (br s, OH and NH_2) and 8.44 (s, CH); *m*/*z* 193 ($M^{\bullet+}$).

2-Isopropyl-1-methyl-5-nitroimidazole[27] **4f** (16.9 g) gave 5-*amino*-4-*cyanoiminomethyl*-2-*isopropyl*-1-*methylimidazole* **83d** (6.9 g, 36%) as pale yellow needles, m.p. 149–151 °C (Found: C, 56.3; H, 6.9; N, 37.0. $C_9H_{13}N_5$ requires C, 56.5; H, 6.85; N, 36.6%); ν_{max}/cm^{-1} 1270, 1310, 1400, 1520, 1600, 2170, 2970 and 3300; δ_H([$^2H_6$]-DMSO at 100 °C) 1.25 [d, *J* 7, $CH(CH_3)_2$], 2.8 [sept, *J* 7, $CH(CH_3)_2$], 3.4 (s, NCH_3), 7.3 (br s, NH_2) and 8.5 (s, CH); *m*/*z* 191 ($M^{\bullet+}$) and N-*cyano*-N′-(1-*methyl*-2-*isopropylimidazol*-5-*yl*)*formamidine* **84d** (2.1 g, 11%) as colourless needles, m.p. 145–146 °C (Found: C, 56.9; H, 6.9; N, 36.6. $C_9H_{13}N_5$ requires C, 56.5; H, 6.85; N, 36.6%); ν_{max}/cm^{-1} 1310, 1360, 1475, 1560, 1610, 2195 and 2970; δ_H([$^2H_6$]-DMSO at 100 °C) 1.25 [d, *J* 7, $CH(CH_3)_2$], 3.05 [sept, *J* 7, $CH(CH_3)_2$], 3.45 (s, NCH_3), 6.80 (s, 4-H), 8.20 (s, HNC*H*), NH not visible; *m*/*z* 191 ($M^{\bullet+}$).

(f) *With* S,S′-*dimethyl* N-*cyanodithioimidocarbonate* **12**. A solution of 1,2-dimethyl-5-nitroimidazole[24] **4e** (7.05 g) in dioxane (120 cm^3) was reduced to the amine. *S*,*S*′-Dimethyl N-cyanodithioimidocarbonate **12** (7.3 g) was added with stirring to the filtrate and after 1 h the solution was concentrated to give a crystalline product. Recrystallisation from ethanol gave 5-*amino*-4-*cyanoimino*(*thiomethyl*)*methyl*-1,2-*dimethylimidazole* **83e** (4.9 g, 47%) as buff needles, m.p. 202 °C (Found: C, 45.6; H, 5.25; N, 33.1; S, 15.2. $C_8H_{11}N_5S$ requires C, 45.9; H, 5.30; N, 33.5; S, 15.3%); ν_{max}/cm^{-1} 1330, 1450, 1480, 1575, 1630, 2170, 3100, 3220, 3280 and 3400; δ_H 2.20 (s, CCH_3), 2.85 (s, SCH_3), 3.30 (s, NCH_3) and 7.40 (br s, NH_2); *m*/*z* 209 ($M^{\bullet+}$).

Similarly 1-(2-hydroxyethyl)-2-methyl-5-nitroimidazole[26] **4l** (17.1 g) gave 5-*amino*-4-*cyanoimino*(*thiomethyl*)*methyl*-1-(2-*hydroxyethyl*)-2-*methylimidazole* **83f** (2.5 g, 10.5%) as yellow needles, m.p. 216 °C (with sintering at 170 °C) (Found: C, 45.4; H, 5.6; N, 29.4. $C_9H_{13}N_5OS$ requires C, 45.2; H, 5.48; N, 29.3%); ν_{max}/cm^{-1} 1320, 1370, 1480, 1585, 1625, 2160 and 3360; δ_H 2.25 (s, CCH_3), 2.85 (s, SCH_3), 3.55 (q, *J* 6, CH_2CH_2OH), 3.85 (t, *J* 6, NCH_2CH_2), 5.00 (t, *J* 6, OH) and 7.40 (br s, NH_2); *m*/*z* 239 ($M^{\bullet+}$).

The following procedure was followed using 5-amino-1-methylimidazole **3k**. A mixture of compound **3k** (776 mg) and *S*,*S*′-dimethyl *N*-cyanodithioimidocarbonate **12** (1.17 g) in dioxane (20 cm^3) was heated to 50 °C and stirred until homogeneous. The solution was then evaporated and shown by TLC to be a two-component mixture which was subjected to MPLC (4:1, chloroform–methanol as eluent). The first component (R_f 0.4) was collected and concentration and dilution with ether gave 5-*amino*-4-*cyanoimino*(*thiomethyl*)*methyl*-1-*methylimidazole* **83g** (150 mg, 10%) as tiny yellow squat needles, m.p. 167–168 °C (Found: C, 42.8; H, 4.45; N, 35.6. $C_7H_9N_5S$ requires C, 43.1; H, 4.65; N, 35.9%); ν_{max}/cm^{-1} 1310, 1390, 1490, 1545, 1580, 1640 and 2170; δ_H 2.90 (s, SCH_3), 3.40 (s, NCH_3), 7.35 (s, CH) and 7.40 (br s, NH_2); *m*/*z* 195 ($M^{\bullet+}$). The second component (R_f 0.2) was similarly collected and recrystallised from ethanol to give 3-*cyano*-1-(1-*methylimidazol*-5-*yl*)-2-*methylisothiourea* **84g** (500 mg, 32%) as tiny colourless prisms, m.p. 274–275 °C (with sintering at 220 °C) (Found: C, 43.0; H, 4.4; N, 35.7. $C_7H_9N_5S$ requires C, 43.1; H, 4.65; N, 35.9%); ν_{max}/cm^{-1} 1295, 1340, 1455, 1560, 2130, 2930 and 3170; δ_H 2.4 (s, SCH_3), 3.65 (s, NCH_3), 7.25 (d, *J* 1, 4-H), 8.55 (d, *J* 1, 2-H) and 12.2 (vbr s, NH); *m*/*z* 195 ($M^{\bullet+}$).

Reactions of Diethyl (5-*Amino*-1,2-*dimethylimidazol*-4-*ylmethylene*)*malonate* **18e**.—(a) *With diethyl ethoxymethylenemalonate* **5**. A mixture of compound **18e** (0.5 g), compound **5** (2.0 cm^3), toluene (40 cm^3) and ethanol (2 cm^3) was heated at 100 °C (8 h). The residue, after evaporation, was subjected to MPLC (25:1, CH_2Cl_2–MeOH as eluent) and the product (R_f 0.5) identified as 4-*diethoxycarbonylvinyl*-5-*diethoxycarbonylvinylamino*-1,2-*dimethylimidazole* **19a** (0.7 g, 87%), a pale yellow solid, m.p. 157–158 °C (Found: C, 56.0; H, 6.7; N, 9.3. $C_{21}H_{29}N_3O_8$ requires C, 55.9; H, 6.47; N, 9.3%); ν_{max}/cm^{-1} 1235, 1280, 1385, 1404, 1618, 1655, 1705, 2990 and 3250; δ_H 1.15–1.55 (m, 4 OCH_2CH_3), 2.33 (s, CCH_3), 3.40 (s, NCH_3), 4.0–4.55 (m, 4 OCH_2CH_3), 7.22 (s, C=CH), 7.9 (d, *J* 12, HNC*H*) and 10.4 (d, *J* 12, *H*NCH).

(b) *With* 3,4-*dichlorophenyl isocyanate*. A mixture of com-

pound **18e** (1.7 g) and 3,4-dichlorophenyl isocyanate (1.14 g) in dioxane (50 cm^3) was heated at 80 °C (2 h). Purification of the product by MPLC (19:1, CH_2Cl_2–MeOH as eluent) gave N-(3,4-*dichlorophenyl*)-N′-[4-(2,2-*diethoxycarbonylvinyl*)-1,2-*dimethylimidazol-5-yl*]*urea* **20** (0.95 g, 34%) as a colourless solid, m.p. 186–187 °C (Found: C, 50.6; H, 5.3; Cl, 15.2; N, 11.9. $C_{20}H_{22}Cl_2N_4O_5$ requires C, 51.2; H, 4.73; Cl, 15.1; N, 11.9%); δ_H 1.2 (t, *J* 7, OCH_2CH_3), 1.26 (t, *J* 7, OCH_2CH_3), 2.25 (s, CCH_3), 3.34 (s, NCH_3), 4.15 (q, *J* 7, OCH_2CH_3), 4.24 (q, *J* 7, OCH_2CH_3), 7.34 (s, C=CH), 7.38–7.50 (m, 2 ArH), 7.83 (d, *J* 2, 1 ArH), 8.7 (br s, NH) and 9.35 (br s, NH).

(c) *Acid-catalysed cyclisation.* A solution of compound **18e** (6.0 g) in HCl-saturated ethanol (240 cm^3) was heated under reflux (1 h). The cooled reaction was neutralised (aqueous $NaHCO_3$) and then evaporated. The residue was purified by MPLC (49:1, CH_2Cl_2–MeOH as eluent) and identified as 6-*ethoxycarbonyl*-2,3-*dimethylimidazo*[4,5-b]*pyridin*-5-*one* **21e** (4.1 g, 82%), a pale yellow solid, m.p. 157–159 °C (Found: C, 56.3; H, 5.6; N, 17.9. $C_{11}H_{13}N_3O_3$ requires C, 56.2; H, 5.57; N, 17.9%); ν_{max}/cm^{-1} 1240, 1283, 1360, 1500, 1630, 1685, 2300–2800 and 2990; δ_H 1.45 (t, *J* 7, OCH_2CH_3), 2.5 (s, CCH_3), 3.7 (s, NCH_3), 4.4 (q, *J* 7, OCH_2CH_3), 8.27 (s, CH) and 11.68 (s, OH).

(d) *Thermal self-condensation.* A mixture of compound **18e** (0.5 g) in xylene (24 cm^3) was heated at 150 °C (4 h). The mixture was then poured into light petroleum (b.p. 40–60 °C) (250 cm^3) and the resulting precipitate was collected, washed with a little Et_2O and purified by MPLC (9:5:1, ethyl acetate–chloroform–methanol as eluent). The major fraction was collected and identified as 5-(5-amino-1,2-dimethylimidazol-4-ylmethyleneamino)-4-(2,2-diethoxycarbonylvinyl)-1,2-dimethylimidazole **22e** (220 mg, 56%), an orange crystalline solid, m.p. 243–244 °C; δ_H 1.23 (t, *J* 8, OCH_2CH_3), 1.37 (t, *J* 8, OCH_2CH_3), 2.15 (s, CCH_3), 2.33 (s, CCH_3), 3.22 (s, NCH_3), 3.30 (s, NCH_3), 4.15 (q, *J* 8, OCH_2CH_3), 4.35 (q, *J* 8, OCH_2CH_3), 5.70 (br s, NH_2), 7.27 (s, CH) and 8.13 (s, CH); *m/z* 402 ($M^{\cdot+}$).

1-(2-*Acetoxyethyl*)-5-*diethoxycarbonylvinylamino*-2-*methylimidazole* **17n**.—A mixture of compound **17l** (160 g), pyridine (640 cm^3) and acetic anhydride (58 g) was heated at 100 °C (2 h). Evaporation gave a residue which was diluted with toluene (250 cm^3) and re-evaporated. The residue was then dissolved in $CHCl_3$ (300 cm^3), washed with water (2 × 400 cm^3), dried ($MgSO_4$) and evaporated. The product was dissolved in ether (500 cm^3) and light petroleum (b.p. 40–60 °C) (250 cm^3) was added whereupon gentle agitation resulted in crystallisation of the product **17n** as a buff solid (144 g, 79%) which was collected and used without further purification. An analytical sample was obtained by recrystallisation from ethyl acetate giving 1-(2-*acetoxyethyl*)-5-*diethoxycarbonylvinylamino*-2-*methylimidazole* **17n** as colourless crystals, m.p. 87–90 °C (Found: C, 54.4; H, 6.8; N, 11.8. $C_{16}H_{23}N_3O_6$ requires C, 54.4; H, 6.52; N, 11.9%); ν_{max}/cm^{-1} 1240, 1380, 1600, 1660, 1715, 1750, 2990 and 3240; δ_H 1.28 (t, *J* 7, OCH_2CH_3), 1.35 (t, *J* 7, OCH_2CH_3), 2.1 (s, $COCH_3$), 2.38 (s, CCH_3), 4.0–4.5 (m, 2 × OCH_2CH_3 and $CH_2CH_2OCOCH_3$), 6.75 (s, CH), 7.95 (d, *J* 13, HNC*H*) and 10.50 (br d, *J* 13, *H*NCH).

Ethyl 7-*Chloroimidazo*[4,5-b]*pyridine*-6-*carboxylates* **31**.—A suspension of compound **17n** (133.8 g) in phosphoryl chloride (700 cm^3) was heated under reflux (7 h). The dark solution was then evaporated and the residual oil poured into ice (2 dm^3) with vigorous stirring. The resulting mixture was extracted with $CHCl_3$ (3 × 400 cm^3) and the combined extracts were washed with water (2 × 400 cm^3), dried ($MgSO_4$) and evaporated. Recrystallisation of the residue from ether gave *ethyl* 3-(2-*acetoxyethyl*)-7-*chloro*-2-*methylimidazo*[4,5-b]*pyridine*-6-*carboxylate* **31n** (108 g, 87%) as a buff solid, m.p. 103–105 °C (Found: C, 51.1; H, 4.9; Cl, 10.9; N, 12.7. $C_{14}H_{16}ClN_3O_4$ requires C, 51.6; H, 4.9; Cl, 10.9; N, 12.9%); ν_{max}/cm^{-1} 1230, 1260, 1300, 1345, 1365, 1425, 1465, 1595, 1715, 1740 and 2990; δ_H 1.42 (t, *J* 7, OCH_2CH_3), 1.98 (s, $COCH_3$), 2.68 (s, CCH_3), 4.2–4.6 (m, OCH_2CH_3 and CH_2CH_2) and 8.75 (s, CH).

Similarly, the derivatives **31e**, **31f**, **31m** and **31p** were obtained from compounds **17e**, **17f**, **17m** and **17l** respectively and their analytical and spectral data has been deposited as a Supplementary Publication [SUP No: 56895 (pp. 11)].*

Reactions of Ethyl 7-*Chloroimidazo*[4,5-b]*pyridine*-6-*carboxylates* **31**.—(a) *Catalytic hydrogenation.* A mixture of compound **31n** (5.4 g), 5% Pd/C (1 g), triethylamine (2.5 cm^3) and ethanol (100 cm^3) was shaken under an atmosphere of hydrogen until 1 mol equiv. of hydrogen had been consumed. The catalyst was then filtered off and the filtrate evaporated to give a residue which was purified by MPLC (ethyl acetate as eluent). The major component (R_f 0.3) was collected and the residue after evaporation triturated with light petroleum (b.p. 40–60 °C) to give *ethyl* 3-(2-*acetoxyethyl*)-2-*methylimidazo*[4,5-b]*pyridine*-6-*carboxylate* **33n** (2.9 g, 60%) as colourless crystals, m.p. 70–73 °C (Found: C, 58.1; H, 5.95; N, 14.2. $C_{14}H_{17}N_3O_4$ requires C, 57.7; H, 5.84; N, 14.4%); ν_{max}/cm^{-1} 1240, 1305, 1380, 1425, 1613, 1720, 1750 and 2990; δ_H 1.40 (t, *J* 7, OCH_2CH_3), 2.00 (s, $COCH_3$), 2.68 (s, CCH_3), 4.40 (q, *J* 7, OCH_2CH_3), 4.48 (br s, CH_2CH_2), 8.48 (d, *J* 2, 7-H) and 8.90 (d, *J* 2, 5-H).

Similarly, the following derivatives were prepared from compounds **31e** and **31f** respectively. *Ethyl* 2,3-*dimethylimidazo*[4,5-b]*pyridine*-6-*carboxylate* **33e** (3.9 g, 58%), as buff crystals, m.p. 93–95 °C (Found: C, 60.3; H, 6.0; N, 19.2. $C_{11}H_{13}N_3O_2$ requires C, 60.3; H, 5.98; N, 19.2%); ν_{max}/cm^{-1} 1245, 1290, 1308, 1355, 1370, 1410, 1469, 1611, 1705 and 2980; δ_H 1.4 (t, *J* 7, OCH_2CH_3), 2.65 (s, CCH_3), 3.80 (s, NCH_3), 4.35 (q, *J* 7, OCH_2CH_3), 8.40 (d, *J* 2, 7-H) and 8.88 (d, *J* 2, 5-H); *ethyl* 2-*isopropyl*-3-*methylimidazo*[4,5-b]*pyridine*-6-*carboxylate* **33f** (6.8 g, 73%), a waxy yellow solid, m.p. 40–43 °C (Found: C, 62.8; H, 7.1; N, 16.7. $C_{13}H_{17}N_3O_2$ requires C, 63.1; H, 6.9; N, 17.0%); δ_H 1.40 (t, *J* 7, OCH_2CH_3), 1.50 [d, *J* 7, $CH(CH_3)_2$], 3.28 [sept, *J* 7, $CH(CH_3)_2$], 3.7 (s, NCH_3), 4.38 (q, *J* 7, OCH_2CH_3), 8.52 (d, *J* 2, 7-H) and 8.92 (d, *J* 2, 5-H).

(b) *With amines and hydrazines.* A solution of compound **31e** (3.0 g) and butylamine (2.6 g) in ethanol (45 cm^3) was heated under reflux (6 h). Evaporation gave a residue which was extracted with light petroleum (b.p. 40–60 °C) (3 × 100 cm^3). The combined extracts were evaporated and purified by MPLC (ethyl acetate as eluent). The product (R_f 0.5) was collected and identified as *ethyl* 7-*butylamino*-2,3-*dimethylimidazo*[4,5-b]-*pyridine*-6-*carboxylate* **34e** (2.5 g, 72%), a colourless solid, m.p. 84–85 °C (Found: C, 62.1; H, 7.6; N, 19.3. $C_{15}H_{22}N_4O_2$ requires C, 62.0; H, 7.64; N, 19.3%); ν_{max}/cm^{-1} 1260, 1276, 1309, 1530, 1590, 1670, 2940, 2960 and 3300; δ_H 0.98 [t, *J* 7, $(CH_2)_3CH_3$], 1.32 (t, *J* 7, OCH_2CH_3), 1.5–1.8 (m, 4-aliphatic H), 2.50 (s, CCH_3), 3.68 (s, NCH_3), 3.95–4.30 (m, $HNCH_2CH_2$), 4.30 (q, *J* 7, OCH_2CH_3), 8.56 (br s, NH) and 8.68 (s, 5-H). Similarly, compounds **34b–h** and **34l–s** were prepared {see Supplementary Publication [SUP No: 56895 (pp. 11)]}.*

(c) *With alkoxides.* A 60% suspension of sodium hydride in oil (0.96 g) was added to a solution of ethanol (1.5 cm^3) in DMF (50 cm^3) with stirring and under an argon atmosphere. Compound **31e** (5.1 g) was then added and the solution stirred at ambient temperature (3 h). Evaporation gave a residue which dissolved in 1 mol dm^{-3} HCl solution (50 cm^3) and was extracted with $CHCl_3$ (2 × 50 cm^3). The combined extracts were dried ($MgSO_4$) and evaporated to give a product which was purified by MPLC (49:1, CH_2Cl_2–MeOH as eluent). The

* For details of the deposition scheme see Instructions for Authors, *J. Chem. Soc., Perkin Trans. 1*, 1992, issue 1.

major fraction (R_f 0.5) was collected and identified as *ethyl* 2,3-*dimethyl*-7-*ethoxyimidazo*[4,5-b]*pyridine*-6-*carboxylate* **34j** (2.4 g, 46%), a buff solid, m.p. 83–88 °C (Found: C, 59.0; H, 6.6; N, 15.8. $C_{13}H_{17}N_3O_3$ requires C, 59.3; H, 6.51; N, 15.9%); ν_{max}/cm^{-1} 1265, 1295, 1350, 1600, 1720, 2940 and 2980; δ_H 1.28 (t, *J* 7, OCH_2CH_3), 1.33 (t, *J* 7, OCH_2CH_3), 2.46 (s, CCH_3), 3.63 (s, NCH_3), 4.19 (q, *J* 7, OCH_2CH_3), 4.90 (q, *J* 7, OCH_2CH_3) and 8.33 (s, 5-H). Compound **34k** was similarly prepared {Supplementary publication [SUP No: 56895 (pp. 11)]}.*

(d) *With toluene-α-thiol.* Compound **31e** (8.7 g) was added to a stirred suspension of potassium carbonate (11.0 g) and toluene-α-thiol (4.46 g) in DMF (85 cm^3) at ambient temperature. After being stirred (18 h) the mixture was filtered and the filtrate evaporated. The residue was subjected to MPLC ($CHCl_3$ as eluent) and the major component (R_f 0.2) collected, recrystallised from ethanol and identified as *ethyl* 7-*benzylthio*-2,3-*dimethylimidazo*[4,5-b]*pyridine*-6-*carboxylate* **34i** (5.6 g, 48%), as colourless prisms, m.p. 118–119 °C (Found: C, 63.1; H, 5.55; N, 12.2; S, 9.5. $C_{18}H_{19}N_3O_2S$ requires C, 63.3; H, 5.61; N, 12.3; S, 9.4%); ν_{max}/cm^{-1} 1275, 1300, 1330, 1570, 1700, 2940 and 2980; δ_H 1.38 (t, *J* 7, OCH_2CH_3), 2.55 (s, CCH_3), 3.72 (s, NCH_3), 4.37 (q, *J* 7, OCH_2CH_3), 5.1 (s, SCH_2), 7.1–7.5 (m, 5 ArH) and 8.27 (s, 5-H).

(e) *Hydrolytic alkylation.* A mixture of compound **31m** (2.6 g) and 10 mol dm^{-3} NaOH (15 cm^3) in ethoxyethanol (100 cm^3) was heated under reflux (3 h). Ethyl iodide (6 cm^3) was then added and heating continued (1 h). After cooling and evaporation of the mixture, the residue was dissolved in water (100 cm^3) and acidified to pH 5 (AcOH). The aqueous mixture was extracted with $CHCl_3$ (2 × 50 cm^3), dried ($MgSO_4$) and evaporated. The residue was dissolved in EtOH (25 cm^3), 2 mol dm^{-3} NaOH (10 cm^3) was added and the mixture heated under reflux (30 min). After cooling, the mixture was acidified to pH 5 (AcOH) and diluted with water (100 cm^3) to give a solid which was collected, recrystallised from methanol and identified as 4-*ethyl*-3-*methyl*-7-*oxo*-2-(2-*phenethyl*)*imidazo*[4,5-b]*pyridine*-6-*carboxylic acid* **32m** (0.55 g, 22%), colourless crystals, m.p. 160–162 °C (decomp.) (Found: C, 66.3; H, 5.9; N, 12.8. $C_{18}H_{19}N_3O_3$ requires C, 66.5; H, 5.85; N, 12.9%); ν_{max}/cm^{-1} 1250, 1290, 1360, 1490, 1580, 1597, 1707 and 2300–3100; δ_H($CDCl_3$ + D_2O) 1.55 (t, *J* 7, CH_2CH_3), 3.04 (s, CH_2CH_2), 3.50 (s, NCH_3), 5.20 (q, *J* 7, CH_2CH_3), 7.15 (br s, C_6H_5) and 8.85 (s, 5-H). The following compound was prepared similarly from the derivative **31e**: 4-*ethyl*-7-*oxo*-2,3-*dimethylimidazo*[4,5-b]*pyridine*-6-*carboxylic acid* **32e** (0.5 g, 25%), as a buff solid, m.p. 230 °C (decomp.) (Found: C, 55.8; H, 5.55; N, 18.0. $C_{11}H_{13}N_3O_3$ requires C, 56.2; H, 5.57; N, 17.9%); ν_{max}/cm^{-1} 1250, 1290, 1345, 1595, 1670, 1700 and 2400–3600; δ_H 1.37 (t, *J* 7, CH_2CH_3), 2.55 (s, CCH_3), 3.75 (s, NCH_3), 5.0 (q, *J* 7, CH_2CH_3), 8.5 (s, 5-H) and 11.5 (vbr s, CO_2H); *m*/*z* 235 ($M^{\cdot+}$).

Saponification of Ethyl Imidazo[4,5-b]*pyridine*-6-*carboxylates* **34**.—A solution of compound **34i** (2.2 g) in a mixture of ethanol (50 cm^3) and 2 mol dm^{-3} NaOH (7 cm^3) was allowed to stand at room temperature (3 h). Evaporation gave a residue which was dissolved in water (20 cm^3) and acidified (glacial acetic acid). The resulting solid was collected and identified as 7-*benzylthio*-2,3-*dimethylimidazo*[4,5-b]*pyridine*-6-*carboxylic acid* **35i** (1.6 g, 84%), a colourless solid, m.p. 262–263 °C (decomp.) (Found: C, 61.0; H, 4.6; N, 13.4; S, 10.4. $C_{16}H_{15}N_3O_2S$ requires C, 61.3; H, 4.82; N, 13.4; S, 10.2%); ν_{max}/cm^{-1} 1270, 1340, 1570, 1685 and 2300–3100br. Compounds **35b–e**, **k–n** were similarly prepared {see Supplementary publication [SUP No: 56895 (pp. 11)]}.*

Decarboxylation of Imidazo[4,5-b]*pyridine*-6-*carboxylic Acids* **35**.—A mixture of compound **35l** (7.2 g) in Dowtherm® [29] (120 cm^3) was boiled (10 min). After cooling the mixture was extracted with 2 mol dm^{-3} HCl (2 × 100 cm^3) and the combined extracts were basified to pH 11 (2 mol dm^{-3} NaOH) with ice cooling. The resulting solid was collected, dissolved in $CHCl_3$ (250 cm^3), dried ($MgSO_4$) and concentrated to *ca.* 10 cm^3. Trituration with light petroleum (b.p. 60–80 °C) gave a solid product which was identified as 7-*butylamino*-3-(2-*hydroxyethyl*)-2-*methylimidazo*[4,5-b]*pyridine* **36l** (4.4 g, 71%), a colourless solid, m.p. 98–100 °C (Found: C, 62.5; H, 8.3; N, 22.7. $C_{13}H_{20}N_4O$ requires C, 62.9; H, 8.06; N, 22.6%); ν_{max}/cm^{-1} 1290, 1350, 1390, 1425, 1470, 1510, 1620, 2865, 2920, 2960, 3150 and 3340; δ_H 0.8–1.1 (m, CH_2CH_3), 1.2–1.8 (m, $CH_2CH_2CH_3$), 2.47 (s, CCH_3), 3.29 (q, *J* 6, CH_2CH_2), 3.8–4.3 (m, $HNCH_2$ and CH_2CH_2), 5.23 (vbr s, *OH*), 6.20 (d, *J* 6, 6-H) and 7.80 (d, *J* 6, 5-H). Compounds **36b–e**, **n** were similarly prepared {Supplementary publication [SUP No: 56895 (pp. 11)]}.*

Preparation of 1,2-*Dihydroimidazo*[4,5-b]*pyrazolo*[3,4-d]*pyridin*-3(6H)-*ones* **37**.—A mixture of compound **34g** (3.0 g), ethanol (100 cm^3) and 2 mol dm^{-3} NaOH (50 cm^3) was heated under reflux (10 min). The solution was cooled, acidified to pH 5 (acetic acid) and the resulting solid collected. The product was recrystallised from acetic acid and identified as 1,2-*dihydro*-6,7-*dimethylimidazo*[4,5-b]*pyrazolo*[3,4-d]*pyridin*-3(6H)-*one* **37t** (1.7 g, 65%), colourless crystals, m.p. >360 °C (Found: C, 53.0; H, 4.2; N, 34.4. $C_9H_9N_5O$ requires C, 53.2; H, 4.46; N, 34.5%); ν_{max}/cm^{-1} 1225, 1405, 1442, 1520, 1625 and 2300–3200; δ_H([$^2H_6$]-DMSO + TFA) 3.00 (s, CCH_3), 4.15 (s, NCH_3) and 9.05 (s, 4-H); *m*/*z* 203 ($M^{\cdot+}$). The following compounds were similarly prepared from the derivatives **34h** and **34o** respectively: 1,2-*dihydro*-6,7-*dimethyl*-2-*phenylimidazo*[4,5-b]*pyrazolo*[3,4-d]*pyridin* 3(6H)-*one* **37u** (4.1 g, 75%), colourless crystals, m.p. 299–301 °C (Found: C, 64.7; H, 4.6; N, 25.4. $C_{15}H_{13}N_5O$ requires C, 64.5; H, 4.69; N, 25.1%); ν_{max}/cm^{-1} 1315, 1368, 1382, 1500, 1585, 1645, 1670 and 2400–2900; δ_H([$^2H_6$]-DMSO + D_2O) 2.58 (s, CCH_3), 3.78 (s, NCH_3), 7.0–8.0 (m, 5 ArH) and 8.50 (s, 4-H); 1,2-*dihydro*-6-(2-*hydroxyethyl*)-7-*methyl*-2-*phenylimidazo*[4,5-b]*pyrazolo*[3,4-d]*pyridin*-3(6H)-*one* **37v** (2.15 g, 62%), colourless crystals, m.p. 262–264 °C (Found: C, 61.9; H, 4.85; N, 22.8; $C_{16}H_{15}N_5O_2$ requires C, 62.1; H, 4.85; N, 22.7%); ν_{max}/cm^{-1} 1312, 1380, 1498, 1637, 1687 and 2700–3200; δ_H([$^2H_6$]-DMSO + D_2O) 2.60 (s, CCH_3), 3.6–3.9 (m, CH_2CH_2), 4.1–4.45 (m, CH_2CH_2), 6.9–7.6 (m, 3 ArH), 7.7–8.0 (m, 2 ArH) and 8.50 (s, 4-H).

Preparation of 5-*Amino*-6-*cyanoimidazo*[4,5-b]*pyridines* **43**.—A hot solution of compound **42e** (10.0 g) in MeOH (200 cm^3) was added to a hot (90 °C) solution of 50% (w/v) NaOH (15 cm^3) in water (450 cm^3) with stirring. The mixture was then chilled and the solid product collected, recrystallised from DMF and identified as 5-*amino*-6-*cyano*-2,3-*dimethylimidazo*-[4,5-b]*pyridine* **43e** (6.4 g, 64%), colourless plates, m.p. 320 °C (Found: C, 57.7; H, 4.75; N, 37.4. $C_9H_9N_5$ requires C, 57.7; H, 4.85; N, 37.4%); ν_{max}/cm^{-1} 1285, 1305, 1355, 1405, 1425, 1500, 1580, 1620, 2210, 3140, 3320 and 3420; δ_H 2.45 (s, CCH_3), 3.57 (s, NCH_3), 6.55 (br s, NH_2) and 8.05 (s, 7-H); *m*/*z* 187 ($M^{\cdot+}$).

The following compounds were similarly prepared from compounds **42l** and **42f** respectively; 5-*amino*-6-*cyano*-3-(2-*hydroxyethyl*)-2-*methylimidazo*[4,5-b]*pyridine* **43l** (3.0 g, 65%), colourless plates, m.p. 245–247 °C (Found: C, 55.6; H, 5.2; N, 32.7. $C_{10}H_{11}N_5O$ requires C, 55.3; H, 5.07; N, 32.3%); ν_{max}/cm^{-1} 1288, 1430, 1496, 1576, 1623, 1650, 2210, 3180, 3250, 3360 and 3430; δ_H 2.50 (s, CCH_3), 3.67 (q, *J* 6, CH_2CH_2OH), 4.08 (t, *J* 6, CH_2CH_2OH), 4.95 (br t, *J* 6, CH_2CH_2OH), 6.53 (br s, NH_2) and 8.00 (s, 7-H); 5-*amino*-6-*cyano*-2-*isopropyl*-3-*methylimidazo*[4,5-b]*pyridine* **43f** (2.4 g, 77%), colourless prisms, m.p.

* For details of the deposition scheme see Instructions for Authors, *J. Chem. Soc., Perkin Trans. 1*, 1992, issue 1.

254–255 °C (Found: C, 61.3; H, 5.9; N, 32.9. $C_{11}H_{13}N_5$ requires C, 61.4; H, 6.09; N, 32.5%); ν_{max}/cm^{-1} 1280, 1420, 1450, 1500, 1580, 1620, 1645, 2210, 2980, 3210, 3300 and 3340; $\delta_H([^2H_6]$-DMSO) 1.29 [d, *J* 7, $CH(CH_3)_2$], 3.22 [sept, *J* 7, $CH(CH_3)_2$], 3.62 (s, NCH_3), 6.39 (br s, NH_2) and 8.02 (s, 7-H); *m/z* 215 ($M^{\bullet+}$).

Reactions of 5-*Amino*-6-*cyano*-2,3-*dimethylimidazo*[4,5-b]-*pyridine* **43e**.—(a) *With* 0.2 mol dm^{-3} *potassium hydroxide*. A mixture of compound **43e** (3.7 g) and 0.2 mol dm^{-3} KOH solution (690 cm^3) was heated under reflux with vigorous stirring (40 min). The resulting solution was then chilled (10 °C) and the solid which separated was collected, washed with water and dried. Recrystallisation from DMF gave 5-*amino*-2,3-*dimethylimidazo*[4,5-b]*pyridine*-6-*carboxamide* **44** (2.2 g, 52%) as colourless crystals, m.p. 325–327 °C (Found: C, 52.7; H, 5.5; N, 34.2. $C_9H_{11}N_5O$ requires C, 52.7; H, 5.40; N, 34.1%); ν_{max}/cm^{-1} 1270, 1354, 1402, 1550, 1580, 1625, 1670, 3180, 3330 and 3490; δ_H 2.45 (s, CCH_3), 3.57 (s, NCH_3), 7.10 (br s, NH_2), 7.36 (vbr s, $CONH_2$) and 8.18 (s, 7-H).

(b) *With* 5 mol dm^{-3} *sodium hydroxide*. A suspension of compound **43e** (3.7 g) in 5 mol dm^{-3} NaOH solution (200 cm^3) was stirred and heated under reflux (5 h). The solution was then chilled (10 °C) and the solid product collected and dissolved in water (150 cm^3). This solution was adjusted to pH 5 (glacial acetic acid:dropwise with cooling) and the solid product collected, recrystallised from DMF and identified as 5-*amino*-2,3-*dimethylimidazo*[4,5-b]*pyridine*-6-*carboxylic acid* **45** (2.6 g, 64%), a colourless solid, m.p. 280 °C (decomp.) (Found: C, 52.3; H, 4.7; N, 27.3. $C_9H_{10}N_4O_2$ requires C, 52.4; H, 4.9; N, 27.2%); ν_{max}/cm^{-1} 1200, 1390, 1420, 1610, 1675, 2300–2600, 3295 and 3410; $\delta_H([^2H_6]$-DMSO + D_2O) 2.45 (s, CCH_3), 3.57 (s, NCH_3) and 8.15 (s, 7-H).

(c) *With* 90% *formic acid*. A suspension of compound **43e** (1.9 g) in 90% formic acid (50 cm^3) was heated at 100 °C (24 h) and then cooled and diluted with water (100 cm^3). This aqueous solution was adjusted to pH 3 by adding 50% (w/v) NaOH whilst maintaining the temperature below 30 °C. The solid product was collected and washed with water followed by EtOH. After drying, the product was identified as 3,5-*dihydro*-2,3-*dimethylimidazo*[4′,5′:5,6]*pyrido*[2,3-d]*pyrimidin*-6-*one* **52** (1.8 g, 82%), a yellow solid, m.p. 372 °C (decomp.) (Found: C, 55.4; H, 4.1; N, 32.3. $C_{10}H_9N_5O$ requires C, 55.8; H, 4.21; N, 32.5%); ν_{max}/cm^{-1} 1270, 1370, 1390, 1430, 1567, 1610, 1685 and 2500–2950; $\delta_H([^2H_6]$-DMSO + D_2O) 3.12 (s, CCH_3), 4.30 (s, NCH_3), 8.67 (s, 8-H) and 9.02 (s, 9-H).

(d) *With nitrous acid*. A solution of sodium nitrite (4.5 g) in water (100 cm^3) was added dropwise (20 min) to a stirred solution of compound **43e** (1.9 g) in 2 mol dm^{-3} HCl (180 cm^3) with the temperature being maintained in the range 20–25 °C. After further stirring (30 min) the mixture was chilled (10 °C) and treated with 50% (w/v) NaOH until pH 3 was achieved. Saturated aqueous $NaHCO_3$ was then added until the solution was mildly basic and the resulting solid was collected, recrystallised from DMF and identified as 6-*cyano*-4,5-*dihydro*-2,3-*dimethylimidazo*[4,5-b]*pyridine*-5-*one* **47** (1.0 g, 52%), tiny colourless plates, m.p. >360 °C (Found: C, 57.9; H, 4.3; N, 30.1. $C_9H_8N_4O$ requires C, 57.4; H, 4.28; N, 29.8%); ν_{max}/cm^{-1} 1275, 1360, 1390, 1435, 1455, 1623, 2235 and 3100; $\delta_H([^2H_6]$-DMSO + D_2O) 2.50 (s, CCH_3), 3.65 (s, NCH_3) and 8.15 (s, 7-H).

(e) *With triethyl orthoformate*. A mixture of compound **43e** (5.0 g), triethyl orthoformate (100 cm^3) and toluene-*p*-sulfonic acid hydrate (20 mg) was stirred and heated under reflux (3 h). Activated charcoal was then added and the hot mixture filtered. The filtrate was cooled and the solid which had separated was collected, washed with a little Et_2O and after drying identified as *ethyl* N-(6-*cyano*-2,3-*dimethylimidazo*[4,5-b]*pyridin*-5-*yl*)*formimidate* **51** (3.5 g, 53%), a colourless solid, m.p. 188–190 °C; ν_{max}/cm^{-1} 1251, 1270, 1378, 1410, 1610, 1630, 2225, 3000 and 3040; δ_H 1.42 (t, *J* 7, CH_2CH_3), 2.60 (s, CCH_3), 3.73 (s, NCH_3), 4.47 (q, *J* 7, CH_2CH_3), 8.00 (s, 7-H) and 8.43 (br s, CH).

(f) *With* 3,4-*dichlorophenyl isocyanate*. Compound **43e** (3.7 g) was added to a stirred solution of 3,4-dichlorophenyl isocyanate (3.8 g) in DMF (150 cm^3) at ambient temperature and the mixture was then heated at 100 °C (6 h). After 18 h at ambient temperature the solid product was collected, washed with ethanol, dried and identified as 7-(3,4-*dichlorophenyl*)-8-*imino*-2,3-*dimethyl*-3,5,7,8-*tetrahydroimidazo*[4′,5′:5,6]*pyrido*[2,3-d]-*pyrimidine*-6-*one* **48** (2.2 g, 29%), a yellow solid, m.p. >360 °C (Found: C, 51.4; H, 3.2; Cl, 18.3; N, 22.7. $C_{16}H_{12}Cl_2N_6O$ requires C, 51.2; H, 3.22; Cl, 18.9; N, 22.4%); ν_{max}/cm^{-1} 1225, 1263, 1390, 1470, 1610, 1710, 2700–3200 and 3318; $\delta_H([^2H]$-TFA) 3.15 (s, CCH_3), 4.20 (s, NCH_3), 7.42 (dd, *J* 3 and 8, ArH), 7.72 (d, *J* 3, ArH), 7.88 (d, *J* 8, ArH) and 9.52 (s, 9-H).

(g) *With phenyl isothiocyanate*. By a procedure analogous to that described in (f), compound **43e** (1.87 g) and phenyl isothiocyanate (1.35 g) gave 8-*imino*-2,3-*dimethyl*-7-*phenyl*-3,5,7,8-*tetrahydroimidazo*[4′,5′:5,6]*pyrido*[2,3-d]*pyrimidine*-6-*thione* **49** (0.4 g, 11%), a yellow solid, m.p. 314–316 °C (decomp.) (Found: C, 59.4; H, 4.55; N, 26.2; S, 9.3. $C_{16}H_{14}N_6S$ requires C, 59.6; H, 4.38; N, 26.7; S, 9.9%); ν_{max}/cm^{-1} 1307, 1434, 1451, 1530, 1580, 1630, 2800–3200 and 3300; $\delta_H([^2H_6]$-DMSO) 2.60 (s, CCH_3), 3.75 (s, NCH_3), 7.15–7.50 (m, 3 ArH), 7.8–8.0 (m, 2 ArH), 9.0 (s, 9-H), 9.85 (vbr s, NH) and 12.55 (vbr s, NH).

(h) *With benzaldehyde*. A stirred mixture of compound **43e** (9.4 g), KOH (1.1 g), benzaldehyde (5.8 g) and ethanol (100 cm^3) was heated (60 °C) under an inert atmosphere (30 h). The solid product was collected from the hot solution, washed with ether, dried and identified as 2,3-*dimethyl*-6-*phenyl*-3,5,6,7-*tetrahydroimidazo*[4′,5′:5,6]*pyrido*[2,3-d]*pyrimidin*-8-*one* **50** (5.8 g, 39%), a yellow solid, m.p. 380 °C (decomp.) (Found: C, 65.0; H, 5.4; N, 23.4. $C_{16}H_{15}N_5O$ requires C, 65.5; H, 5.15; N, 23.9%); ν_{max}/cm^{-1} 1298, 1352, 1405, 1461, 1550, 1621, 1660, 2935, 3050 and 3180; $\delta_H([^2H_6]$-DMSO) 2.46 (s, CCH_3), 3.58 (s, NCH_3), 5.74–5.81 (m, 5-H), 7.24–7.50 (m, C_6H_5), 7.64 (br s, NH), 8.02 (s, 9-H) and 8.29 (br s, NH); *m/z* 294 (MH^+).

(i) *With cyclohexane*-1,3-*dione*. A mixture of compound **43e** (5.6 g), cyclohexane-1,3-dione (6.7 g) and toluene-*p*-sulfonic acid (1.0 g) in toluene (600 cm^3) was stirred and heated under reflux (18 h) with azeotropic removal of water. The hot mixture was then filtered and evaporated to give a residue which was recrystallised from ethanol and identified as 3-(6-*cyano*-2,3-*dimethylimidazo*[4,5-b]*pyridin*-5-*ylamino*)*cyclohex*-2-*enone* **56** (4.6 g, 55%), yellow needles, m.p. 241–243 °C (Found: C, 64.1; H, 5.2; N, 25.3. $C_{15}H_{15}N_5O$ requires C, 64.0; H, 5.37; N, 24.9%); ν_{max}/cm^{-1} 1238, 1282, 1398, 1414, 1520, 1580, 1614, 2218, 2440 and 3390; δ_H 2.16 (quint, *J* 6, $CH_2CH_2CH_2$), 2.48 (t, *J* 6, CH_2CH_2), 2.6–2.7 (m, CH_2CH_2 and CCH_3), 3.82 (s, NCH_3), 6.97 (br s, NH), 7.24 (s, CH) and 8.08 (s, 7-H).

Decarboxylation of 5-*Amino*-2,3-*dimethylimidazo*[4,5-b]*pyridine*-6-*carboxylic Acid* **45**.—A mixture of compound **45** (29.0 g) and finely powdered copper bronze (4.0 g) in Dowtherm® [29] (500 cm^3) was heated under reflux (1 h). The mixture was filtered whilst hot and allowed to cool. Light petroleum (b.p. 60–80 °C) (1 dm^3) was then added and the solid product collected, recrystallised from acetonitrile and identified as 5-*amino*-2,3-*dimethylimidazo*[4,5-b]*pyridine* **46** (18.3 g, 81%), a buff solid, m.p. 212–214 °C (Found: C, 59.2; H, 6.2; N, 34.9. $C_8H_{10}N_4$ requires C, 59.2; H, 6.21; N, 34.5%); ν_{max}/cm^{-1} 1290, 1367, 1407, 1592, 1640, 3210, 3327 and 3380; $\delta_H(CDCl_3$ + $D_2O)$ 2.52 (s, CCH_3), 3.65 (s, NCH_3), 6.35 (d, *J* 8, 6-H) and 7.65 (d, *J* 8, 7-H).

5-*Diethoxycarbonylvinylamino*-2,3-*dimethylimidazo*[4,5-b]-*pyridine* **58**.—A solution of compound **46** (4.9 g), diethyl

ethoxymethylenemalonate **3** (7.1 g) and toluene (200 cm^3) was heated under reflux (90 min). After cooling and evaporation of the mixture the residue was extracted with boiling light petroleum (b.p. 80–100 °C) (3 × 250 cm^3) and the combined extracts were set aside at 0 °C (3 h). The crystalline product was collected, dried and identified as *compound* **58** (8.4 g, 84%), yellow crystals, m.p. 128–130 °C (Found: C, 57.7; H, 6.2; N, 16.9. $C_{16}H_{20}N_4O_4$ requires C, 57.8; H, 6.07; N, 16.9%); ν_{max}/cm^{-1} 1230, 1345, 1400, 1620, 1642, 1685 and 2983; δ_H 1.37 (t, *J* 7, CH_2CH_3), 1.40 (t, *J* 7, CH_2CH_3), 2.62 (CCH_3), 3.82 (s, NCH_3), 4.30 (q, *J* 7, CH_2CH_3), 4.35 (q, *J* 7, CH_2CH_3), 6.73 (d, *J* 8, 6-H), 7.86 (d, *J* 8, 7-H), 9.25 (d, *J* 13, NHCH) and 11.25 (d, *J* 13, NHCH).

Ethyl 2,3-*Dimethyl*-8-*oxo*-5,8-*dihydroimidazo*[4,5-b][1,8]-*naphthyridine*-7-*carboxylate* **59**.—A mixture of compound **58** (18.6 g) in Dowtherm® [29] (300 cm^3) was heated under reflux (30 min). The solution was cooled and the solid product collected, washed with light petroleum (b.p. 60–80 °C) and dried to give *compound* **59** (3.8 g, 24%) as a yellow solid, m.p. 322 °C (decomp.) (Found: C, 58.7; H, 4.9; N, 19.4. $C_{14}H_{14}N_4O_3$ requires C, 58.7; H, 4.93; N, 19.6%); ν_{max}/cm^{-1} 1310, 1400, 1430, 1525, 1570, 1620, 1685, 1720 and 2700–3300; $\delta_H([^2H_6]$-DMSO + $D_2O)$ 1.27 (t, *J* 7, CH_2CH_3), 2.60 (s, CCH_3), 3.75 (s, NCH_3), 4.22 (q, *J* 7, CH_2CH_3), 8.45 (s, 6- or 9-H) and 8.53 (s, 9- or 6-H).

Ethyl 8-*Chloro*-2,3-*dimethylimidazo*[4,5-b][1,8]*naphthyridine*-7-*carboxylate* **60**.—A mixture of compound **59** (1.0 g) and phosphoryl chloride (50 cm^3) was heated under reflux (15 min). After evaporation of the mixture the residue was poured onto ice (400 g) with stirring. The aqueous mixture was then extracted with $CHCl_3$ (2 × 200 cm^3) and the combined extracts were dried ($MgSO_4$) and evaporated. The residue was triturated with ether (20 cm^3), collected and dried to give *compound* **60** (260 mg, 25%) as a buff solid, m.p. 140–142 °C (Found: C, 55.0; H, 4.1; Cl, 11.5; N, 18.4. $C_{14}H_{13}ClN_4O_2$ requires C, 55.2; H, 4.30; Cl, 11.6; N, 18.4%); ν_{max}/cm^{-1} 1204, 1227, 1360, 1385, 1444, 1597 and 1730; δ_H 1.48 (t, *J* 7, CH_2CH_3), 2.78 (s, CCH_3), 3.98 (s, NCH_3), 4.55 (q, *J* 7, CH_2CH_3), 8.95 (s, 6- or 9-H) and 9.40 (s, 9- or 6-H).

Ethyl 8-*Butylamino*-2,3-*dimethylimidazo*[4,5-b][1,8]*naphthyridine*-7-*carboxylate* **63**.—A solution of compound **60** (2.4 g) and butylamine (1.7 g) in ethanol (100 cm^3) was heated under reflux (2 h). After cooling and evaporation of the reaction mixture, the residue was triturated with water (50 cm^3) and collected and dried. Recrystallisation from acetonitrile gave *compound* **63** (1.95 g, 72%) as a colourless solid, m.p. 183–184 °C (Found: C, 63.5; H, 6.95; N, 20.6. $C_{18}H_{23}N_5O_2$ requires C, 63.3; H, 6.79; N, 20.5%); ν_{max}/cm^{-1} 1205, 1265, 1590, 1600, 1670, 2880 and 2960; δ_H 0.98 (t, *J* 7, $CH_2CH_2CH_3$), 1.44 (t, *J* 7, OCH_2CH_3), 1.50–1.95 (m, $CH_2CH_2CH_3$), 2.70 (s, CCH_3), 3.7–4.0 (m, $HNCH_2$ and NCH_3), 4.39 (q, *J* 7, OCH_2CH_3), 8.85 (s, 6- or 9-H), 9.24 (s, 6- or 9-H) and 9.5 (br s, $HNCH_2$).

Ethyl 5-*Ethyl*-2,3-*dimethyl*-8-*oxoimidazo*[4,5-b][1,8]*naphthyridine*-7-*carboxylate* **61**.—A mixture of compound **59** (0.5 g), potassium carbonate (0.5 g), ethyl iodide (0.55 g) and DMF (50 cm^3) was heated at 100 °C with stirring (90 min). After filtration and evaporation of the mixture, the residue was triturated with ethyl acetate (10 cm^3) and the solid product subjected to MPLC (19:1, $CHCl_3$–MeOH as eluent). The major component was collected and identified as *compound* **61** (0.3 g, 55%), a yellow solid, m.p. 215–216 °C (Found: C, 60.9; H, 5.7; N, 17.8. $C_{16}H_{18}N_4O_3$ requires C, 61.1; H, 5.77; N, 17.8%); ν_{max}/cm^{-1} 1228, 1316, 1376, 1508, 1625, 1678, 1720, 2985 and 3060; δ_H 1.43 (t, *J* 7, OCH_2CH_3), 1.54 (t, *J* 7, NCH_2CH_3), 2.66 (s, CCH_3), 3.85 (s, NCH_3), 4.45 (q, *J* 7, CH_2CH_3), 4.54 (q, *J* 7, CH_2CH_3), 8.55 (s, 6- or 9-H) and 8.86 (s, 9- or 6-H).

5-*Ethyl*-2,3-*dimethyl*-8-*oxoimidazo*[4,5-b][1,8]*naphthyridine*-7-*carboxylic Acid* **62**.—A suspension of compound **61** (1.95 g) in 2 mol dm^{-3} KOH (35 cm^3) was heated at 100 °C (18 h). The hot solution was then filtered, cooled and acidified to pH 5 (acetic acid). The mixture was chilled (10 °C) and the solid product was collected, dried, and recrystallised from DMF to give *compound* **62** (0.8 g, 45%) as buff needles, m.p. 338–340 °C (decomp.) (Found: C, 59.0; H, 4.9; N, 19.5. $C_{14}H_{14}N_4O_3$ requires C, 58.7; H, 4.93; N, 19.6%); ν_{max}/cm^{-1} 1352, 1380, 1462, 1562, 1632, 1720 and 3060; $\delta_H([^2H_6]$-DMSO) 1.54 (t, *J* 7, NCH_2CH_3), 2.68 (s, CCH_3), 3.85 (s, NCH_3), 4.75 (q, *J* 7, NCH_2CH_3), 8.71 (s, 6- or 9-H), 9.02 (s, 9- or 6-H) and 14.95 (vbr s, CO_2H).

3,7-*Dihydro*-2,3-*dimethyl*-6-*phenylimidazo*[4′,5′:5,6]-*pyrido*[2,3-d]*pyrimidin*-8-*one* **53**.—A suspension of compound **50** (3.0 g) in nitrobenzene (150 cm^3) was heated under reflux (5 h). The solid which formed upon cooling was collected, recrystallised from DMF and identified as *compound* **53** (1.6 g, 56%), yellow solid, m.p. >360 °C (Found: C, 65.8; H, 4.5; N, 23.8. $C_{16}H_{13}N_5O$ requires C, 66.0; H, 4.50; N, 24.0%); ν_{max}/cm^{-1} 1290, 1375, 1470, 1560, 1600, 1620, 1658 and 2800–3200; $\delta_H([^2H_6]$-DMSO) 2.64 (s, CCH_3), 3.83 (s, NCH_3), 7.50–7.64 (m, 3 ArH), 8.22–8.30 (m, 2 ArH), 8.54 (s, 9-H) and 12.36 (br s, NH).

Preparation of 8-*Iminoimidazo*[4′,5′:5,6-]*pyrido*[2,3-d]-*pyrimidines* **54**.—A mixture of compound **51** (5.0 g), ethanol (300 cm^3) and butylamine (10 cm^3) was allowed to stand at ambient temperature (18 h). The solid which separated was collected, recrystallised fom ethyl acetate and identified as 7-*butyl*-7,8-*dihydro*-2,3-*dimethyl*-8-*iminoimidazo*[4′,5′:5,6]-*pyrido*[2,3-d]*pyrimidine* **54b** (3.0 g, 54%), buff crystals, m.p. 205–207 °C (Found: C, 62.3; H, 6.9; N, 31.3. $C_{14}H_{18}N_6$ requires C, 62.2; H, 6.67; N, 31.1%); ν_{max}/cm^{-1} 1380, 1408, 1600, 2850, 2910, 2940, 3040 and 3260; δ_H 0.98 (t, *J* 7, CH_2CH_3), 1.10–2.00 (m, $CH_2CH_2CH_3$), 2.68 (s, CCH_3), 3.85 (s, NCH_3), 3.88 (q, *J* 7, NCH_2CH_2), 7.85 (s, 6-H), 8.36 (s, 9-H) and 11.30 (vbr s, NH).

The derivatives **54c–h** were similarly prepared from compound **51** and the appropriate amine. Their analytical and spectral details have been deposited as a Supplementary Publication [SUP No: 56895 (pp. 11)].*

Preparation of 8-*Amino*-2,3-*dimethylimidazo*[4′,5′:5,6]*pyrido*[2,3-d]*pyrimidines* **55**.—(a) A mixture of compound **51** (2.0 g) and saturated ethanolic ammonia solution (400 cm^3) was stirred at ambient temperature (18 h). The solution was then concentrated (50 cm^3) and the solid product collected, washed with a little ether and dried to give 8-*amino*-2,3-*dimethylimidazo*[4′,5′:5,6]*pyrido*[2,3-d]*pyrimidine* **55a** (1.6 g, 93%) as a colourless solid, m.p. >360 °C (Found: C, 55.7; H, 4.9; N, 39.1. $C_{10}H_{10}N_6$ requires C, 56.1; H, 4.67; N, 39.25%); ν_{max}/cm^{-1} 1295, 1330, 1405, 1510, 1570, 1584, 1624, 1673, 2800–3250 and 3310; $\delta_H([^2H_6]$-DMSO + DCl) 2.60 (s, CCH_3), 3.97 (s, NCH_3), 8.90 (s, 6-H) and 9.75 (s, 9-H).

(b) A mixture of compound **54h** (1.4 g, 4 mmol), 1-(3-aminopropyl)-4-methylpiperazine (1.26 g, 8 mmol), ethanol (50 cm^3), and glacial acetic acid (0.48 g, 8 mmol) was heated under reflux (2 h). Evaporation of the mixture gave a residue which was recrystallised from acetonitrile to give 2,3-*dimethyl*-8-(4-*methylpiperazin*-1-*ylpropyl*)*imidazo*[4′,5′:5,6]*pyrido*[2,3-d]-*pyrimidine* **55h** (0.75 g, 54%) as a buff solid, m.p. 247–249 °C

* For details of the deposition scheme see Instructions for Authors, *J. Chem. Soc., Perkin Trans. 1*, 1992, issue 1.

(Found: C, 60.8; H, 7.5; N, 31.5. $C_{18}H_{26}N_8$ requires C, 61.0; H, 7.39; N, 31.6%); ν_{max}/cm^{-1} 1322, 1398, 1550, 1575, 1626, 2805, 2940 and 3350; δ_H 1.88 (quint, *J* 7, $CH_2CH_2CH_2$), 2.4 (s, CCH_3), 2.5–2.75 (m, 10 aliphatic H), 3.77 (q, *J* 7, $HNCH_2$), 3.85 (s, NCH_3), 8.45 (br t, *J* 7, $HNCH_2$), 8.50 (s, 6- or 9-H) and 8.70 (s, 9- or 6-H).

The derivatives **55b–g** were similarly prepared from the corresponding imine **54** and the appropriate primary amine. Their analytical and spectral details have been deposited as Supplementary publication [SUP No: 56895 (pp. 11)] *.

Reactions of 8-*Amino*-2,3-*dimethylimidazo*[4′,5′:5,6]-*pyrido*[2,3-d]*pyrimidine* **55a**.—(a) *Acid hydrolysis.* A stirred solution of compound **55a** (1.1 g) in 2 mol dm^{-3} HCl (100 cm^3) was heated under reflux (2.5 h). The resulting pale yellow solution was chilled, made alkaline (conc. aq ammonia solution) and after further storage (0 °C) the solid product was collected, washed (i, H_2O; ii, EtOH; iii, Et_2O), dried and identified as compound **52** (0.8 g, 74%), a buff solid, m.p. >360 °C; identical with a sample prepared from compound **43e** and formic acid (see above).

(b) *With acetic anhydride.* A suspension of compound **55a** (2.1 g) in acetic anhydride (50 cm^3) was heated under reflux (30 min). After the mixture had cooled the solid product was collected, washed with ether and recrystallised from DMF to give 8-*acetamido*-2,3-*dimethylimidazo*[4′,5′:5,6]*pyrido*[2,3-d]-*pyrimidine* **55i** (1.6 g, 63%) as buff needles, m.p. 311–313 °C (decomp.) (Found: C, 56.0; H, 4.7; N, 32.4. $C_{12}H_{12}N_6O$ requires C, 56.2; H, 4.72; N, 32.8%); ν_{max}/cm^{-1} 1255, 1335, 1490, 1585, 1600, 1635, 1700 and 2700–3250; δ_H 2.39 (s, CCH_3), 2.70 (s, $COCH_3$), 3.84 (s, NCH_3), 8.79 (s, 6- or 9-H), 8.97 (s, 9- or 6-H) and 10.70 (vbr s, NH).

10-*Amino*-2,3-*dimethyl*-6,7,8,9-*tetrahydroimidazo*[4′,5′:5,6]-*pyrido*[2,3-b]*quinolin*-9-*one* **57**.—A mixture of compound **56** (1.6 g) and zinc chloride (11.2 g) in xylene (100 cm^3) was stirred and heated under reflux (3 h). After the mixture had cooled it was evaporated and the solid residue triturated with water (400 cm^3). Saturated aqueous citric acid (100 cm^3) was added to give a clear solution which was treated with 2 mol dm^{-3} NaOH to give a solution of pH 11. The resulting solid product was collected, washed with water, dried and recrystallised from DMF to give *compound* **57** (0.8 g, 50%) as a buff solid, m.p. >360 °C (Found: C, 63.8; H, 5.6; N, 24.7. $C_{15}H_{15}N_5O$ requires C, 64.0; H, 5.37; N, 24.9%); ν_{max}/cm^{-1} 1264, 1410, 1514, 1553, 1588, 1620, 2958, 3158 and 3302; δ_H([$^2H_6$]-DMSO + D_2O) 2.04 (quint, *J* 6, $CH_2CH_2CH_2$), 2.62–2.70 (m, CH_2CH_2 and CCH_3), 3.02 (t, *J* 6, CH_2CH_2), 3.80 (s, NCH_3) and 8.92 (s, 11-H).

Ethyl 5-*Amino*-2,3-*dimethylimidazo*[4,5-b]*pyridine*-6-*carboxylate* **65e**.—A mixture of compound **64e** (10.0 g) in Dowtherm® [29] (200 cm^3) was heated under reflux (5 min). The mixture was then chilled, poured into light petroleum (b.p. 60–80 °C) (400 cm^3) and extracted with 2 mol dm^{-3} HCl (2 × 50 cm^3). The combined extracts were basified to pH 11 (50% w/v NaOH) and the solid which formed was collected, washed with water and dried. Purification by MPLC (49:1, $CHCl_3$–MeOH as eluent) gave *compound* **65e** (7.0 g, 70%) as pale yellow crystals, m.p. 176–177 °C (Found: C, 56.6; H, 6.4; N, 23.9. $C_{11}H_{14}N_4O_2$ requires C, 56.4; H, 6.02; N, 23.9%); ν_{max}/cm^{-1} 1205, 1260, 1290, 1400, 1420, 1570, 1600, 1620, 1680, 3360 and 3460; δ_H 1.35 (t, *J* 7, OCH_2CH_3), 2.50 (s, CCH_3), 3.61 (s, NCH_3), 4.33 (q, *J* 7, OCH_2CH_3), 7.15 (br s, NH_2) and 8.20 (s, 7-H).

Preparation of Hypoxanthines **70**.—Dowtherm® [29] (15 cm^3) was heated under reflux and compound **69e** (1.05 g) was added as a powder. Boiling was continued (1 min) and the solution was then allowed to cool. The resulting solid was collected, washed with ether and dried to give 8,9-*dimethyl*-1H,9H-*purin*-6-*one* **70e** (0.75 g, 91%), a buff solid, m.p. >360 °C (Found: C, 51.3; H, 4.85; N, 34.0. $C_7H_8N_4O$ requires C, 51.2; H, 4.91; N, 34.1%); ν_{max}/cm^{-1} 1200, 1265, 1340, 1370, 1395, 1550, 1595 and 1680; δ_H 2.44 (s, CCH_3), 3.63 (s, NCH_3), 7.92 (s, 2-H) and 12.0 (vbr s, 1-H); *m*/*z* 164 ($M^{\cdot+}$).

Similarly, compound **69l** (1.2 g) gave 9-(2-*hydroxyethyl*)-8-*methyl*-1H,9H-*purin*-6-*one* **70l** (0.6 g, 65%) as buff plates, m.p. >360 °C (Found: C, 49.2; H, 5.0; N, 29.0. $C_8H_{10}N_4O$ requires C, 49.5; H, 5.19; N, 28.9%); ν_{max}/cm^{-1} 1275, 1350, 1380, 1440, 1465, 1595, 1680 and 3440; δ_H 2.48 (s, CCH_3), 3.69 (t, *J* 6, CH_2CH_2OH), 4.14 (t, *J* 6, CH_2CH_2OH), 4.90 (br s, OH), 7.93 (s, 2-H) and 12.05 (vbr s, 1-H); *m*/*z* 194 ($M^{\cdot+}$).

Preparation of 2-*Amino*-9H-*purines* **86**.—A solution of compound **83a** (2.2 g) in decahydronaphthalene (25 cm^3) was boiled (1 min) and then allowed to cool. The solid which separated was collected, recrystallised from ethanol and identified as 2-*amino*-8,9-*dimethyl*-9H-*purine* **86a** (1.7 g, 77%), colourless crystals, m.p. 248–250 °C (Found: C, 51.6; H, 5.55; N, 42.8. $C_7H_9N_5$ requires C, 51.5; H, 5.56; N, 42.9%); ν_{max}/cm^{-1} 1270, 1340, 1370, 1420, 1455, 1500, 1585, 1620, 1655, 3170 and 3315; δ_H 2.45 (s, CCH_3), 3.55 (s, NCH_3), 6.34 (br s, NH_2) and 8.40 (s, 6-H); *m*/*z* 163 ($M^{\cdot+}$).

The following compounds were similarly prepared from the amines **83b–g**: 2-amino-9-methyl-9*H*-purine **86b** (111 mg, 59%), a colourless solid, m.p. 244–246 °C (lit.,[30] m.p. 242–243 °C) (Found: C, 48.7; H, 4.85; N, 46.8. Calc. for $C_6H_7N_5$: C, 48.3; H, 4.73; N, 47.0%); ν_{max}/cm^{-1} 1290, 1410, 1440, 1470, 1525, 1580, 1630, 3180, 3300 and 3390; δ_H([$^2H_6$]-DMSO) 3.63 (s, NCH_3), 6.50 (br s, NH_2), 8.00 (s, 8-H) and 8.55 (s, 6-H); *m*/*z* 149 ($M^{\cdot+}$); 2-*amino*-9-(2-*hydroxyethyl*)-8-*methyl*-9H-*purine* **86c** (0.54 g, 72%), buff crystals, m.p. 213–216 °C (Found: C, 50.1; H, 5.85; N, 36.1. $C_8H_{11}N_5O$ requires C, 49.7; H, 5.74; N, 36.3%); ν_{max}/cm^{-1} 1255, 1340, 1430, 1500, 1590, 1630, 1660, 3160, 3330 and 3380; δ_H 2.48 (s, CCH_3), 3.70 (q, *J* 6, CH_2CH_2OH), 4.08 (t, *J* 6, CH_2CH_2OH), 5.02 (br t, *J* 6, OH), 6.38 (br s, NH_2) and 8.40 (s, 6-*H*); *m*/*z* 193 ($M^{\cdot+}$); 2-*amino*-8-*isopropyl*-9-*methyl*-9H-*purine* **86d** (3.4 g, 79%), pale orange crystals, m.p. 186–188 °C (Found: C, 56.3; H, 6.95; N, 36.2. $C_9H_{13}N_5$ requires C, 56.5; H, 6.85; N, 36.6%); ν_{max}/cm^{-1} 1240, 1270, 1410, 1445, 1585, 1610, 2970, 3190, 3370 and 3470; δ_H([$^2H_6$]-DMSO) 1.30 [d, *J* 7, $CH(CH_3)_2$], 3.24 [sept, *J* 7, $CH(CH_3)_2$], 3.60 (s, NCH_3), 6.40 (br s, NH_2) and 8.44 (s, 6-H); *m*/*z* 191 ($M^{\cdot+}$); 2-*amino*-8,9-*dimethyl*-6-*methylthio*-9H-*purine* **86e** (1.2 g, 74%), tiny colourless needles, m.p. 235–237 °C (Found: C, 46.3; H, 5.42; N, 33.6; S, 15.1. $C_8H_{11}N_5S$ requires C, 45.9; H, 5.30; N, 33.5; S, 15.3%); ν_{max}/cm^{-1} 1270, 1290, 1340, 1400, 1460, 1490, 1570, 1595, 1625, 3180, 3300 and 3500; δ_H 2.40 (s, CCH_3), 2.55 (s, SCH_3), 3.50 (s, NCH_3) and 6.30 (br s, NH_2); *m*/*z* 209 ($M^{\cdot+}$); 2-*amino*-9-(2-*hydroxyethyl*)-8-*methyl*-6-*methylthio*-9H-*purine* **86f** (0.95 g, 66%), a colourless solid, m.p. 214–215 °C (Found: C, 45.2; H, 5.4; N, 28.9. $C_9H_{13}N_5OS$ requires C, 45.2; H, 5.48; N, 29.3%); ν_{max}/cm^{-1} 1280, 1300, 1355, 1420, 1490, 1580, 1600, 1650, 2930, 3200, 3340 and 3410; δ_H 2.55 (s, CCH_3), 2.65 (s, SCH_3), 3.70 (q, *J* 6, CH_2CH_2OH), 4.10 (t, *J* 6, CH_2CH_2OH), 5.10 (br t, *J* 6, OH) and 6.50 (br s, NH_2); *m*/*z* 239 ($M^{\cdot+}$); 2-amino-9-methyl-6-methylthio-9*H*-purine **86g** (90 mg, 62%), colourless crystals, m.p. 183–184 °C (lit.,[31] m.p. 190 °C) (Found: C, 43.3; H, 4.7; N, 35.5. Calc. for $C_7H_9N_5S$: C, 43.1; H, 4.65; N, 35.9%); ν_{max}/cm^{-1} 1310, 1390, 1460, 1510, 1565, 1590, 1630, 3200, 3320 and 3410; δ_H 2.57 (s, SCH_3), 3.60 (s, NCH_3), 6.50 (br s, NH_2) and 7.88 (s, 8-H); *m*/*z* 195 ($M^{\cdot+}$).

* For details of the deposition scheme see Instructions for Authors, *J. Chem. Soc., Perkin Trans. 1*, 1992, issue 1.

Preparation of 6-*Amino*-9H-*purines* **87**.—Compound **84b** (3.0 g) was heated at 200 °C (1 min). The melt was allowed to cool and solidify and was then powdered, recrystallised from ethanol and identified as 6-amino-9-methyl-9*H*-purine **87b** (0.3 g, 10%), colourless prisms, m.p. 302–304 °C (sealed tube) [lit.,[32] m.p. 301–302 °C (sealed tube)] (Found: C, 48.0; H, 4.65; N, 47.3. Calc. for $C_6H_7N_5$. C, 48.3; H, 4.73; N, 47.0%); ν_{max}/cm^{-1} 1230, 1325, 1410, 1480, 1575, 1600, 1670, 3100 and 3280; δ_H 3.72 (s, NCH_3), 7.18 (br s, NH_2), 8.08 (s, 8-H) and 8.16 (s, 2-H); *m/z* 196 (MH^+). Similarly, compound **84g** gave 6-amino-9-methyl-2-methylthio-9*H*-purine **87g** (180 mg, 61%) as colourless needles, m.p. 274–276 °C (lit.,[14] m.p. 261–262 °C) (Found: C, 43.2; H, 4.7; N, 35.8. Calc. for $C_7H_9N_5S$: C, 43.1; H, 4.65; N, 35.9%); ν_{max}/cm^{-1} 1240, 1305, 1320, 1420, 1450, 1580, 1630, 3170, 3300 and 3390; δ_H 2.48 (s, SCH_3), 3.66 (s, NCH_3), 7.26 (br s, NH_2) and 7.96 (s, 8-H); *m/z* 196 (MH^+).

Reactions of 2-*Amino*-8-*isopropyl*-9-*methyl*-9H-*purine* **86d**.—(a) *With acetic anhydride*. A mixture of compound **86d** (1.5 g) and acetic anhydride (15 cm^3) was boiled (10 min). The orange solution was evaporated and the residue shown (TLC) to be a two-component mixture which was separated by MPLC (19:1, $CHCl_3$–MeOH as eluent). The first component (R_f 0.32) was identified as 2-(N,N-*diacetamido*)-8-*isopropyl*-9-*methyl*-9H-*purine* **85** (R^4 = R^5 = AcO) (1.2 g, 55%), a colourless lustrous solid, m.p. 166–168 °C (Found: C, 56.9; H, 6.1; N, 25.3. $C_{13}H_{17}N_5O_2$ requires C, 56.7; H, 6.22; N, 25.4%); ν_{max}/cm^{-1} 1230, 1250, 1375, 1390, 1590, 1605, 1710, 2940 and 2980; δ_H 1.50 [d, *J* 7, $CH(CH_3)_2$], 2.33 (s, 2 × $COCH_3$), 3.32 [sept, *J* 7, $CH(CH_3)_2$], 3.86 (s, NCH_3) and 9.06 (s, 6-H); *m/z* 275 ($M^{\cdot+}$). The second component (R_f 0.12) was identified as 2-(*acetamido*-8-*isopropyl*-9-*methyl*-9H-*purine* **85** (R^4 = H, R^5 = AcO) (0.5 g, 26%), colourless crystals, m.p. 188–190 °C (Found: C, 56.2; H, 6.4; N, 30.2. $C_{11}H_{15}N_5O$ requires C, 56.6; H, 6.48; N, 30.0%); ν_{max}/cm^{-1} 1240, 1275, 1320, 1380, 1415, 1440, 1520, 1615, 1680, 2980, 3100, 3150 and 3220; δ_H 1.34 [d, *J* 7, $CH(CH_3)_2$], 2.22 (s, $COCH_3$), 3.32 [sept, *J* 7, $CH(CH_3)_2$], 3.72 (s, NCH_3), 8.76 (s, 6-H) and 10.19 (br s, NH); *m/z* 233 ($M^{\cdot+}$).

(b) *With benzoic anhydride*. Compound **86d** (1.5 g) was added with stirring to benzoic anhydride (18 g) at 150 °C and heating maintained (10 min). The orange solution was cooled and added with stirring to aqueous 2 mol dm^{-3} Na_2CO_3 (250 cm^3). After being stirred (30 min) the solution was extracted with CH_2Cl_2 (3 × 100 cm^3) and the combined extracts were dried (Na_2SO_4) and evaporated. The residue was purified by MPLC (19:1, $CHCl_3$–MeOH as eluent) to give 2-*benzamido*-8-*isopropyl*-9-*methyl*-9H-*purine* **85** (R^4 = H, R^5 = Bz) (1.1 g, 47%) as fine colourless needles, m.p. 186–187 °C (Found: C, 65.2; H, 5.8; N, 23.8. $C_{16}H_{17}N_5O$ requires C, 65.1; H, 5.80; N, 23.7%); ν_{max}/cm^{-1} 1230, 1300, 1410, 1430, 1510, 1605, 1700 and 3240; δ_H 1.36 [d, *J* 7, $CH(CH_3)_2$], 3.38 [sept, *J* 7, $CH(CH_3)_2$], 3.76 (s, NCH_3), 7.45–7.65 (m, 3 ArH), 7.98–8.04 (m, 2 ArH), 8.90 (s, 6-H) and 10.96 (br s, NH); *m/z* 296 ($M^{\cdot+}$).

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