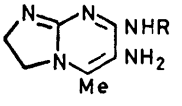
Heterocyclic Studies. Part 40.[1] Synthesis and Unusual Tautomerism of Some Dihydro-imidazo- and -pyrimido-[1,2-*a*]pyrimidines

By **Jim Clark*** and **Michael Curphey**, The Ramage Laboratories, Department of Chemistry and Applied Chemistry, University of Salford, Salford M5 4WT

Syntheses of a number of 7-(substituted amino)-2,3-dihydro-5-methyl-6-nitroimidazo[1,2-*a*]pyrimidine hydrochlorides and 8-(substituted amino)-3,4-dihydro-6-methyl-7-nitro-2*H*-pyrimido[1,2-*a*]pyrimidine hydrochlorides are described. Free bases obtained from these compounds exhibit unusual tautomerism. The imidazopyrimidines with a 7-(monosubstituted amino)-group exist as 7-(substituted amino)-1,2,3,5-tetrahydro-5-methylene-6-nitroimidazo[1,2-*a*]pyrimidines in several solvent systems; those with a 7-(disubstituted amino)-group show solvent-dependent equilibria between the 5-methyl and 1,5-dihydro-5-methylene tautomers. The behaviour of pyrimidopyrimidines closely follows that of analogous imidazopyrimidines. Other closely related imidazo-[1,2-*a*]- and -[1,2-*c*]-pyrimidines have normal methyl groups. ^{1}H N.m.r. spectra of many of the compounds are reported.

An earlier paper [2] described the synthesis of some 7-alkylamino-2,3-dihydro-5-methyl-6-nitroimidazo[1,2-*a*]pyrimidine hydrochlorides (4; R = H, X = NHR'). They were unusual in that their 5-methyl groups were exceptionally reactive as compared with typical pyrimidinium compounds.[3] Thus when attempts were made to measure ^{1}H n.m.r. spectra of the compounds in deuterium oxide the methyl group signals rapidly disappeared, and even with [$^2H_6$]dimethyl sulphoxide as solvent the methyl signals were removed easily by addition of a little deuterium oxide. Furthermore, the diamines (1) produced by reducing these compounds underwent certain reactions, including condensation with thionyl chloride to give imidazoisothiazolopyrimidines (2), in which the methyl group was involved in preference to the substituted amino-group.[4] The nature of the methyl groups in these and some new closely related compounds is now examined in more detail.

Synthesis of Imidazo- and Pyrimido-pyrimidine Hydrochlorides.—Known [2] 7-alkylaminoimidazopyrimidine hydrochlorides (4; R = H, X = NHMe, NHEt, NH·CH_2Ph, or NH·CH_2·CH_2·OH) were synthesised by treating 4-alkylamino-2-chloro-6-methyl-5-nitropyrimidines (3; X = NHR, Y = Cl) with 2-chloroethylamine or by treating appropriate 4-alkylamino-2-(2-hydroxyethylamino)-6-methyl-5-nitropyrimidines (3; X = NHR, Y = NH·CH_2·CH_2·OH) with phosphoryl chloride



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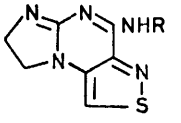


(2)

and cyclising the resulting chloroethylamino-derivatives (3; Y = NHCH_2·CH_2Cl). Some 7-(disubstituted amino)-derivatives (4; R = H, X = NMe_2, pyrrolidino, piperidino, or morpholino) were then synthesised *via* the appropriate 4-(disubstituted amino)-2-(2-hydroxyethylamino)-6-methyl-5-nitropyrimidines (3; X = NR_2, Y = NH·CH_2·CH_2·OH) but the latter compounds were treated

[1] Part 39, J. Clark, B. Parvizi, and R. Colman, *J.C.S. Perkin I*, 1976, 1004.
[2] J. Clark and T. Ramsden, *J. Chem. Soc.* (*C*), 1971, 679.
[3] T. J. Batterham, D. J. Brown, and M. N. Paddon-Row, *J. Chem. Soc.* (*B*), 1967, 171.
[4] J. Clark and T. Ramsden, *J. Chem. Soc.* (*C*), 1971, 1942.

with cold thionyl chloride to give the chloroethylamino-precursors (3; X = NR_2, Y = NH·CH_2·CH_2Cl) of the imidazopyrimidines (4; X = NR_2', R = H); treatment with phosphoryl chloride gave very low yields and intractable by-products. A 1-methyl analogue (4; R = Me, X = NMe_2) was similarly synthesised from a

Orientation of Substituents in Imidazo- and Pyrimido-pyrimidines.—It was necessary to prove the structures of the new compounds because all the synthetic procedures described above ended with cyclisation of a 2-(2-chloroethylamino- or 3-chloropropylamino-)pyrimidine which, in principle, could take place onto either pyrimidine ring

TABLE 1

^{1}H N.m.r. and ionisation data

Compound	Solvent	^{1}H N.m.r. τ Values [a] (*J* in Hz): Substituent CH_3 or CH_2 [c]	Ring CH_2	Substituted amino-group	Others [d]	pK_a Value [b]
(4; X = NHMe, R = H) [e]	$(CD_3)_2SO$	7.42 (3 H, s)	5.28—6.17 (4 H, m)	7.02 (3 H) [f]	0.83, −0.17	
(10; X = NH_2, R = H)	$(CD_3)_2SO$	5.97 (1 H, s), 4.40 (1 H, s)	6.27 (4 H) [g]		1.67, −0.17	8.63 ± 0.05
(10; X = NHMe, R = H)	$(CD_3)_2SO$	5.97 (1 H, s), 4.30 (1 H, s)	6.25 (4 H) [g]	7.02 (3 H) [f]	1.47, −1.0	8.74 ± 0.04
(10); X = NHEt, R = H)	$(CD_3)_2SO$	5.90 (1 H, s), 4.33 (1 H, s)	6.28 (4 H) [g]	8.87 (3 H, *t*, *J* 7) 6.50 (2 H, m) [h]		8.83 ± 0.02
(10; X = NH·CH_2Ph, R = H)	$(CD_3)_2SO$	5.88 (1 H, s), 4.28 (1 H, s)	6.23 (4 H) [g]	5.27 (2 H) [f] 2.68 (5 H)	1.45, −1.42	8.71 ± 0.04
(10; X = NH·CH_2·CH_2·OH, R = H	$(CD_3)_2SO$	5.92 (1 H, s), 4.32 (1 H, s)	6.23 (4 H) [g]	6.43 (4 H) [g]	1.52, −1.18, 5.13	8.60 ± 0.02
(4; X = NMe_2, R = H)	D_2O	7.48 (3 H, s)	5.30—6.23 (4 H, m)	6.87 (6 H, s)		
(4; X = pyrrolidino, R = H)	CD_3OD	7.50 (3 H, s)	5.20—6.30 (4 H, m)	6.68 (4 H, m), 8.30 (4 H, m)		
(4; X = piperidino, R = H)	D_2O	7.40 (3 H, s)	5.20—6.17 (4 H, m)	6.25 (4 H, m), 8.30 (6 H, m)		
(4; X = morpholino, R = H)	CD_3OD	7.45 (3 H, s)	5.30—6.17 (4 H, m)	6.29 (8 H, m)		
(10; X = NMe_2, R = H) / (9; X = NMe_2)	equil. mixt. [i] $CDCl_3$	4.57 (s), 5.85 (s)	6.17 [g]	6.88 (s)		
		7.55 (s)	6.01 [g]	7.00 (s)		
(10; X = NMe_2, R = H) / (9; X = NMe_2)	equil. mixt. [i] $(CD_3)_2SO$	4.67, 5.97 (s)	6.08 [g]	6.90 (s)		
		7.50 (s)	6.08 [g]	7.01 (s)		
(10; X = NMe_2, R = H)	$(CD_3)_2SO$	4.77 (1 H, s), 5.97 (1 H, s)	6.23 (4 H) [g]	6.97 (6 H, s)		
(10; X = NMe_2, R = Me)	$CDCl_3$	4.57 (1 H, s), 5.92 (1 H, s)	6.25 (4 H) [g]	6.85 (6 H, s)	7.00 (3 H, s) [j]	
(10; X = NHMe, R = Me)	$(CD_3)_2SO$	4.37 (1 H, s), 5.97 (1 H, s)	6.29 (4 H) [g]	7.00 (3 H) [f]	7.05 (3 H, s) [j]	*ca.* 9
(11)	$CDCl_3$	5.31 (2 H, q, *J* 7), 8.46 (3 H, d, *J* 7) [k]	6.26 (4 H) [g]	6.97 (3 H) [f]	6.97 (3 H, s) [j]	8.44 ± 0.06
(5; X = NH·CH_2·CH_2·OH	$(CD_3)_2SO$	7.33 (3 H, s)	5.93—6.70 (4 H, m), 7.60—8.10 (2 H, m)	*ca.* 6.0 [l]		
(14; X = NHMe)	$(CD_3)_2SO$	4.18 (1 H, s), 5.58 (1 H, s)	6.84 (4 H, m), 7.92—8.32 (2 H, m)	7.18 (3 H) [f]		
(14; X = NHEt)	$(CD_3)_2SO$	3.95 (1 H, s), 5.38 (1 H, s)	6.17—7.00 (4 H, m), 7.6—8.2 (2 H, m)	8.60 (3 H, t) [m]	0.85, 1.67	
(14; X = NMe_2) and 6-methyl tautomer	equil. mixt. $CDCl_3$	4.41 (s), 5.25 (s) 7.55 (s)	6.17—7.00 (4 H, m) [n] 7.63—8.20 (2 H, m) [n]	6.90 (s) 6.97 (s)		
(8; X = NHMe, Y = Me)	$(CD_3)_2SO$	7.58 (3 H, s) [p]	6.17 (4 H) [g]	7.05 (3 H) [f]		8.87 ± 0.02
(8; X = Me, Y = NHMe)	$(CD_3)_2SO$	7.80 (3 H, s) [p]	6.13 (4 H) [g]	7.05 (3 H) [f]		8.84 ± 0.02

[a] Tetramethylsilane as internal standard except for aqueous solutions, when sodium 3-trimethylsilylpropane-1-sulphonate was used. [b] H_2O; 20 °C. [c] Signals removed at various rates on addition of D_2O unless otherwise stated. [d] NH or OH signal unless otherwise stated. [e] Typical example of this system from ref. 2 for comparison. [f] Doublet, *J* 5, which becomes singlet on addition of D_2O. [g] Narrow multiplet. [h] Quartet, *J* 7, after addition of D_2O. [i] For proportions of tautomers see text. [j] 1-Methyl signal. [k] Signal for 5-ethylidene group. [l] Signals for NH·CH_2·CH_2·OH obscured by reduced pyrimidine ring signals. [m] Signals for CH_2 of ethyl group obscured by reduced pyrimidine ring signals. [n] Signals for both tautomeric forms. [p] Signal not removed by D_2O.

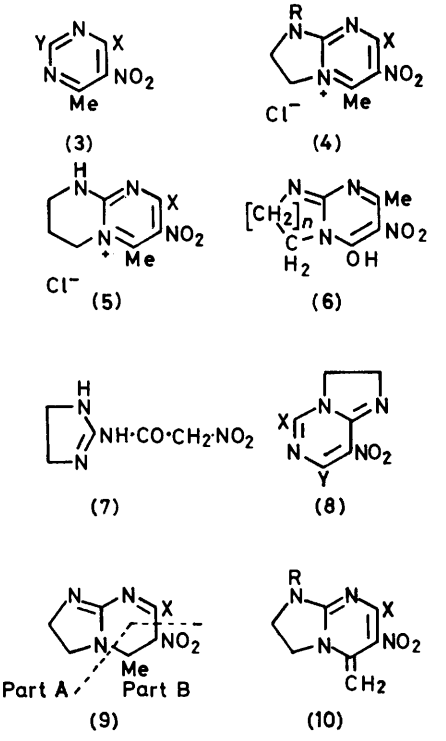
2-hydroxyethylmethylamino-compound (3; X = NMe_2, Y = NMe·CH_2·CH_2·OH), and a 5-ethyl derivative (5-ethyl-2,3-dihydro-1-methyl-7-methylamino-6-nitroimidazo[1,2-*a*]pyrimidinium chloride) was synthesised from 4-ethyl-5-nitrouracil. Several 3,4-dihydro-2*H*-pyrimido[1,2-*a*]pyrimidine hydrochlorides (5; X = NHMe, NHEt, NH·CH_2·CH_2·OH, or NMe_2) were made by routes analogous to those used for corresponding imidazopyrimidines.

nitrogen atom. 4-Alkylamino-2-(2-chloroethylamino)-6-methyl-5-nitropyrimidines had already been shown to cyclise exclusively to 5-methylimidazopyrimidines (4; R = H, X = NHR'),[2,4] and each of the new reactions similarly gave one product only. All the (disubstituted amino)-derivatives (4; R = H, X = NMe_2, pyrrolidino, piperidino, or morpholino) had very similar u.v. and ^{1}H n.m.r. spectra, so cyclisation must have occurred in the same sense in each case. (^{1}H N.m.r. spectra are recorded

in Table 1, but u.v. spectra will be dealt with in detail in a later paper on the unusual ionisation behaviour of these and related compounds.) Compound (4; X = NMe_2, R = H) was hydrolysed by concentrated hydrochloric acid to the hydrochloride of the corresponding 7-hydroxy-imidazopyrimidine (4; R = H, X = OH), which was different from that of the known [2] 5-hydroxy-isomer (6; n = 1). Both the hydroxy- (4; R = H, X = OH) and the dimethylamino-compound (4; R = H, X = NMe_2) gave 4,5-dihydo-2-(2-nitroacetylamino)imidazole (7) on treatment with alkali, and this compound was clearly derived from the 7- rather than the 5-hydroxy-imidazo-pyrimidine.

Similarly, cyclisations leading to pyrimidopyrimidines gave only one isomer in each case and the products (5; X = NHMe, NHEt, or NH·CH_2·CH_2·OH) had u.v. and ^{1}H n.m.r. spectra (Table 1) very similar to each other and to those of corresponding 7-(substituted amino)imidazo-[1,2-*a*]pyrimidines (4; R = H). The dimethylamino-pyrimidopyrimidine (5; X = NMe_2) was hydrolysed to the corresponding hydroxy-compound (5; X = OH), which was different from the hydroxy-compound pro-duced by cyclising 2-(3-chloropropylamino)-6-methyl-5-nitropyrimidin-4-ol (3; X = OH, Y = NH·CH_2·CH_2·CH_2Cl). The last reaction was considered to give the 5-hydroxy-derivative (6; n = 2) because 4-methyl-pyrimidin-6-ols with a variety of side-chains at position 2 cyclise to give 5-hydroxy- rather then 7-hydroxy-imidazo-pyrimidines.[5] This assignment was supported by the fact that the hydroxy-compounds assigned structures (6; n = 1) and (6; n = 2) had u.v. spectra which were similar to each other but appreciably different from those of compounds assigned structures (4; R = H, X = OH) and (5; X = OH) (see Experimental section).

Tautomerism of Free Bases.—Treatment of the first group of hydrochlorides, namely those of 7-alkylamino-2,3-dihydro-5-methyl-6-nitroimidazo[1,2-*a*]pyrimidines (4; R = H, X = NH_2, NHMe, NHEt, $NHCH_2Ph$, or NH·CH_2·CH_2·OH), with sodium hydroxide yielded stable free bases whose analytical data were consistent with the expected structures (9; X = NH_2, *etc.*). The pK_a values of 8.6—8.8 associated with base formation seemed unexceptional because they agreed well with those of closely related imidazo[1,2-*c*]pyrimidines. For example, the methylamino-compound, then considered to have the structure (4; X = NHMe, R = H), had a pK_a value of 8.74; *cf.* 8.87 and 8.84 for its isomers (8; X = NHMe, Y = Me) and (8; X = Me, Y = NHMe). However, ^{1}H n.m.r. spectra of the [1,2-*a*]-bases were clearly anomalous since they showed no 5-methyl signals but each had two unexpected olefinic proton signals. In a typical example these appeared at τ 5.97 and 4.30, values appropriate for $=CH_2$ near an anisotropic group such as nitro.[6] This indicated that the compounds have structures (10; R = H, X = NH_2, NHMe, NHEt, NH·CH_2Ph, or NH·CH_2·CH_2·OH). The 1-proton was shown not be removed during free base formation when the 1-methyl salts (4; R = Me, X = NHMe or NMe_2) also had pK_a values of *ca.* 9. These could not be measured precisely because the bases were unstable but they were clearly similar to those of 1-unsubstituted analogues even in the case of the dimethylamino-deriv-ative (4; R = Me, X = NMe_2) which has no obvious ionisable proton. Bases from both compounds gave the typical olefinic proton signals in their ^{1}H n.m.r. spectra. The olefinic signals were firmly assigned to the 5-sub-stituent when a 5-ethyl compound, pK_a *ca.* 8.5, gave a free base (11) showing signals for a $=CHMe$ group.



An apparent minor anomaly in the ^{1}H n.m.r. spectra of the methylene derivatives is the absence of geminal coupling in the $=CH_2$ signals. However, geminal coupling constants for vinyl derivatives generally have only small positive or negative values, and may be zero,[7] and those for 2-substituted [8] and 2,3-disubstituted propenes [9] are also very small.

^{1}H N.m.r. spectra of very closely related imidazo[1,2-*c*]-pyrimidines [*e.g.* (8; X = NHMe, Y = Me) and (8; X = Me, Y = NHMe)] (Table 1) had normal methyl signals at τ 7.6—7.8, and even the imidazo[1,2-*a*]pyrim-idine (12), which is identical with one of the present

[5] M. A. Prokof'ev, E. G. Antonovich, and Yu P. Shvachkin, *Doklady Akad. Nauk S.S.S.R.*, 1952, **87**, 783 (*Chem. Abs.*, 1954, **48**, 169); M. A. Prokof'ev, Z. A. Shabrova, and E. G. Antonovich, *Zhur. obshchei Khim.*, 1955, **25**, 397 (*Chem. Abs.*, 1955, **49**, 9660); S. C. Bell and W. T. Caldwell, *J. Amer. Chem. Soc.*, 1960, **82**, 1469; T. Pyl, S. Melde, and H. Beyer, *Annalen*, 1963, **663**, 108.

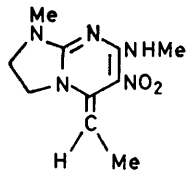
[6] T. J. Batterham in ' NMR Spectra of Simple Heterocycles,' Wiley–Interscience, New York, 1973, p. 521.

[7] T. Schaefer, *Canad. J. Chem.*, 1962, **40**, 1.

[8] E. B. Whipple, W. E. Stewart, G. S. Reddy, and J. H. Gold-stein, *J. Amer. Chem. Soc.*, 1960, **82**, 3010.

[9] E. B. Whipple, J. H. Goldstein, and G. R. McLure, *J. Amer. Chem. Soc.*, 1960, **82**, 3811.

compounds except for interchange of methyl and ethylamino-substituents, had a normal methyl group. Although there are occasional examples of complex



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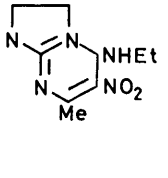

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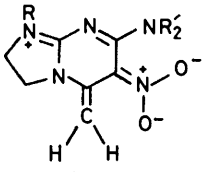

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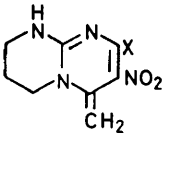

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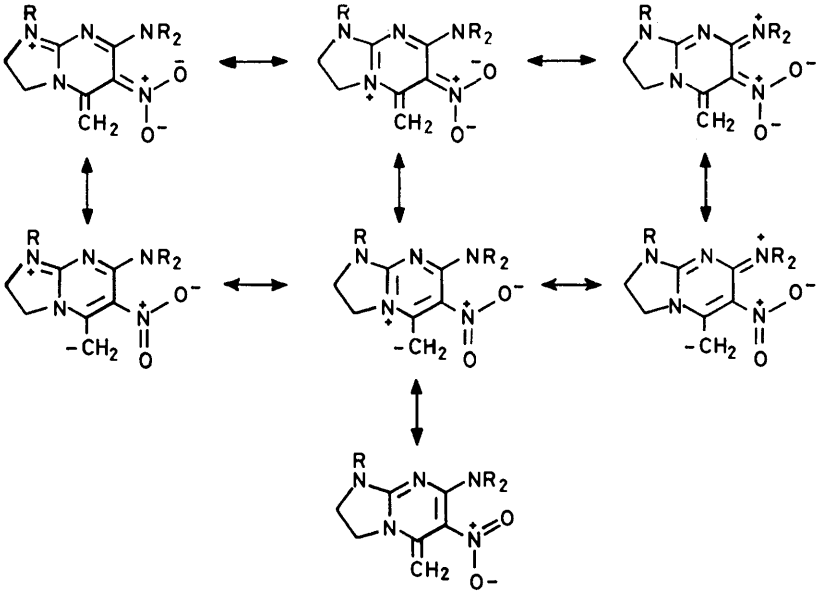
compounds where a ' methyl ' compound occurs in an unexpected tautomeric form,[10] the methylene tautomers (10) seem to be much more stable than typical examples,[11] so that there must be some factor which specially favours the methylene form in the present compounds. This seems to be the presence of essentially independent vinylogous guanidine (9; X = NHR, part A) and vinylogous nitroalkane (9; X = NHR, part B) systems. Since the former is highly basic [12] and the latter quite acidic,[13] the stable form of the base is the essentially zwitterionic, heavily resonance stabilised, methylene form (Scheme), to which the uncharged canonical form (10; R = H, X = NHR') probably makes a relatively minor contribution as compared with charged forms such as (13; R = H). Hydrogen bonding between the adjacent 6-nitro- and 7-alkylamino-groups helps to maintain the planarity essential for maximum resonance stabilisation. Corresponding methylene forms of the closely related imidazopyrimidines (12), (8; X = NHR, Y = Me), and (8; X = Me, Y = NHR), which do not show similar tautomerism, would each contain a less basic amidinium system combined with the vinylogous nitroalkane system, and hence would be less likely to exist in the zwitterionic form.

The concept of a highly polar resonance-stabilised system in the methylene tautomers received support from the behaviour of 7-(disubstituted amino)imidazopyrimidines, which proved to have less stable methylene forms because the absence of hydrogen bonding and the bulk of the 7-dialkylamino-group prevent the guanidinium system from adopting the planar configuration essential for maximum resonance stabilisation. These compounds, which were so unstable and hygroscopic that samples had to be freshly prepared for ^{1}H n.m.r. measurements, showed a solvent-dependent equilibrium between methylene forms (13; R = H, NR_2' = NMe_2, pyrrolidino, piperidino, or morpholino) and methyl forms (9; X = NMe_2, *etc.*). In a typical example the highly polar methylene form was present to the extent of almost 100% in the highly polar solvent [$^2H_6$]dimethyl sulphoxide, but only *ca.* 60% in [$^2H_6$]acetone and *ca.* 35% in [^{2}H]chloroform. The more stable 7-monoalkylamino-



SCHEME

[10] J. Elguero, C. Marzin, A. R. Katritzky, and P. Linda, ' The Tautomerism of Heterocycles,' Academic Press, New York, 1976, p. **179** *et seq.*; W. Pfleiderer, W. Mengel, and P. Hemmerich, *Chem. Ber.*, 1971, **104**, 2273; A. R. Katritzky and J. M. Lagowski, *Adv. Heterocyclic Chem.*, 1963, **1**, 339.

[11] E. N. Shaw in ' Pyridine and its Derivatives, Part 2,' ed. E. Klingsberg, Interscience, New York, 1961, p. 36 *et seq.*; F. M. Hamer, R. J. Rathbone, and B. S. Winton, *J. Chem. Soc.*, 1947, **954**; H. Decker, *Ber.*, 1905, **38**, 2496; O. Mumm and G. Hingst, *Ber.*, 1923, **56**, 2301.

[12] D. D. Perrin, ' Dissociation Constants of Organic Bases in Aqueous Solution,' Butterworths, London, 1965, p. **444**.

[13] A. T. Nielson in ' The Chemistry of the Nitro and Nitroso Groups, Part I,' ed. H. Feuer, Interscience, New York, 1969, p. 372.

compounds were almost exclusively in the methide form (**13**; R = H, NR_2' = NHMe, NHEt, $NH{\cdot}CH_2Ph$, or $NH{\cdot}CH_2{\cdot}CH_2{\cdot}OH$) in all the above solvents. The possibility that the solvent-dependent changes in spectra were due not to a tautomeric equilibrium, but to ring cleavage, was excluded when the 1-methyl-7-dimethylamino-derivative (**13**; R = Me, NR_2' = NMe_2), which is at least as likely to undergo cleavage but cannot tautomerise to a methyl form, showed only the methylene form signals in all the solvents.

The pyrimidopyrimidines fitted well into the general scheme described above: the monosubstituted amino-compounds (**5**; X = NHMe, NHEt, or $NH{\cdot}CH_2{\cdot}CH_2{\cdot}OH$) gave bases which preferred the methylene form (**14**) in the three solvents referred to above, but that from an 8-(disubstituted amino)-salt (**5**; X = NMe_2) exhibited a solvent-dependent equilibrium between methyl and methylene forms.

The completely different tautomeric behaviour of the 7-(substituted amino)imidazo- and 8-(substituted amino)-pyrimido-pyrimidines from that of other possible isomers confirms the correctness of the structural assignments made after the original cyclisations and provides a ready means of proving the orientation of new members of these series of compounds.

EXPERIMENTAL

Ionisation constants were measured by a rapid spectrophotometric method.[14] U.v. spectra were measured for solutions in aqueous buffer on a Unicam SP 800 spectrometer, and ^{1}H n.m.r. spectra on a Varian A60 A instrument at normal probe temperature with tetramethysilane as internal standard.

4-(Substituted amino)-2-chloro-6-methyl-5-nitropyrimidines (**3**; Y = Cl, X = *pyrrolidino, piperidino, or morpholino*).—A solution of the appropriate amine (0.02 mol) in chloroform (10 ml) was added during 20 min to a stirred solution of 2,4-dichloro-6-methyl-5-nitropyrimidine (0.01 mol) in chloroform (50 ml). After a further 1 h water (20 ml) was added and the chloroform layer was separated, washed with water, dried, and evaporated to dryness to yield the *amine*, which was crystallised from a suitable solvent. Details of the compounds are in Table 2.

4-(Substituted amino)-2-(2-hydroxyethylamino)-6-methyl-5-nitropyrimidines (**3**; X = NMe_2, *pyrrolidino, piperidino, or morpholino*).—The appropriate 4-(substituted amino)-2-chloro-6-methyl-5-nitropyrimidine (0.01 mol), 2-aminoethanol (0.02 mol), and ethanol (20 ml) were heated under reflux for 1 h. Water was added and the solution refrigerated until the *hydroxyethylamino-derivative* crystallised. Yields and properties of the compounds are given in Table 2.

4-(Substituted amino)-2-(2-chloroethylamino)-6-methyl-5-nitropyrimidines (**3**; X = NMe_2, *pyrrolidino, piperidino, or morpholino*).—The appropriate 4-(substituted amino)-2-(2-hydroxyethylamino)-6-methyl-5-nitropyrimidine (0.01 mol) was added in small portions to thionyl chloride (20 ml) and the solution kept for 18 h. The excess of thionyl chloride was evaporated off under reduced pressure with the minimum of heating, and the oily residue dissolved in cold water. The solution was made alkaline with dilute sodium hydroxide and the *chloroethylamino-compound* filtered off and crystallised from a suitable solvent. Yields and properties of the products are in Table 2.

7-(Substituted amino)-2,3-dihydro-5-methyl-6-nitroimidazo-[1,2-a]pyrimidine Hydrochlorides (**4**; R = H, X = NMe_2, *pyrrolidino, piperidino, or morpholino*).—The appropriate 4-(substituted amino)-2-(2-chlorethylamino)-5-nitropyrimidine (0.01 mol) was heated under reflux for 1 h in propan-2-ol. Ether was added to the cooled solution to the point of precipitation and the mixture refrigerated to yield the crystalline *imidazopyrimidine hydrochloride*. Yields and properties of the products are in Table 3. These compounds yielded free bases which were unstable and hydroscopic and could not be characterised conveniently. Fresh specimens were prepared for ^{1}H n.m.r. spectral measurements as follows. The appropriate hydrochloride (0.2 g) was dissolved in water (5 ml), made alkaline, and immediately extracted with chloroform (3 × 5 ml). The combined extracts were dried ($MgSO_4$) and evaporated and the residue was dissolved in the appropriate deuteriated solvent.

7-(Substituted amino)-1,2,3,5-tetrahydro-5-methylene-6-nitroimidazo[1,2-a]pyrimidines (**10**; R = H; X = NH_2, NHMe,

TABLE 2

4-(Substituted amino)-6-methyl-5-nitropyrimidines

Compound (3) X	Compound (3) Y	Yield (%)	M.p. (°C)	Cryst. solvent	Formula	Found (%) C	Found (%) H	Found (%) N	Required (%) C	Required (%) H	Required (%) N
Pyrrolidino	Cl	72	75—76	Pr^{n}OH	$C_9H_{11}ClN_4O_2$	44.3	4.7	23.1	44.5	4.6	23.1
Piperidino	Cl	74	96—97	MeOH–H_2O	$C_{10}H_{13}ClN_4O_2$	46.5	4.9	21.7	46.8	5.1	21.8
Morpholino	Cl	80	125—126	MeOH	$C_9H_{11}ClN_4O_3$	41.5	4.4	22.0	41.8	4.3	21.7
NMe_2	$NH{\cdot}CH_2{\cdot}CH_2{\cdot}OH$	76	100—101	EtOH–H_2O	$C_9H_{15}N_5O_3$	44.6	6.1		44.8	6.3	
Pyrrolidino	$NH{\cdot}CH_2{\cdot}CH_2{\cdot}OH$	93	147—148	EtOH–H_2O	$C_{11}H_{17}N_5O_3$	49.3	6.2		49.4	6.4	
Piperidino	$NH{\cdot}CH_2{\cdot}CH_2{\cdot}OH$	77	83—84	EtOH–H_2O	$C_{12}H_{19}N_5O_3$	51.3	6.8		51.2	6.8	
Morpholino	$NH{\cdot}CH_2{\cdot}CH_2{\cdot}OH$	88	158—159	EtOH–H_2O	$C_{11}H_{17}N_5O_4$	46.2	6.1		46.6	6.0	
NMe_2	$NH{\cdot}CH_2{\cdot}CH_2Cl$	78	98—99	MeOH	$C_9H_{14}ClN_5O_2$	41.4	5.4	26.8	41.6	5.4	27.0
Pyrrolidino	$NH{\cdot}CH_2{\cdot}CH_2Cl$	84	122—123	MeOH	$C_{11}H_{16}ClN_5O_2$	46.2	5.5	23.6	46.2	5.6	24.5
Piperidino	$NH{\cdot}CH_2{\cdot}CH_2Cl$	82	101—102	MeOH	$C_{12}H_{18}ClN_5O_2$	47.9	6.2	23.2	48.1	6.0	23.3
Morpholino	$NH{\cdot}CH_2{\cdot}CH_2Cl$	85	95—96	MeOH	$C_{11}H_{16}ClN_5O_3$	43.4	5.3	23.0	43.8	5.3	23.2
NHMe	$NH{\cdot}[CH_2]_3Cl$	76	99—101	Pr^{i}OH	$C_9H_{14}ClN_5O_2$	41.5	5.3	27.1	41.6	5.4	27.0
NHEt	$NH{\cdot}[CH_2]_3Cl$	72	97—98	Pr^{i}OH	$C_{10}H_{16}ClN_5O_2$	44.0	6.0	25.4	43.9	5.9	25.6
$NH{\cdot}CH_2{\cdot}CH_2{\cdot}OH$	$NH{\cdot}[CH_2]_3Cl$	63	108—109	Pr^{i}OH	$C_{10}H_{16}ClN_5O$	41.4	5.6	23.8	41.5	5.5	24.2
NHMe	$NMe{\cdot}CH_2{\cdot}CH_2{\cdot}OH$	50	107—108	EtOH–H_2O	$C_9H_{15}N_5O_3$	44.6	6.0	28.6	44.8	6.2	29.0
NMe_2	$NMe{\cdot}CH_2{\cdot}CH_2{\cdot}OH$	70	72—74	EtOH–H_2O	$C_{10}H_{17}N_5O_3$	47.3	6.6	27.0	47.0	6.7	27.4
NMe_2	$NH{\cdot}[CH_2]_3{\cdot}OH$	78	124—125	EtOH–H_2O	$C_{10}H_{17}N_5O_3$	46.9	6.8	27.0	47.0	6.7	27.4
NMe_2	$NH{\cdot}[CH_2]_3Cl$	65	109—110	MeOH	$C_{10}H_{16}ClN_5O_2$	43.6	5.7	25.4	43.9	5.9	25.6

[14] J. Clark and A. E. Cunliffe, *Chem. and Ind.*, 1973, 281.

NHEt, NH·CH_2Ph, *or* NH·CH_2·CH_2·OH).—(*a*) The appropriate 7-(substituted amino)-2,3-dihydro-5-methyl-6-nitroimidazo[1,2-*a*]pyrimidinium chloride (4) [2] (0.5 g) in water (10 ml) was made alkaline with dilute sodium hydroxide and the product filtered off and crystallised from methanol as yellow needles. Yields and properties of the products are in Table 4.

(*b*) Similar products were obtained by heating each hydrochloride (0.5 g) under reflux in ethanol (10 ml) with an excess of anhydrous sodium acetate.

4-(*Substituted amino*)-2-(3-*chloropropylamino*)-6-*methyl*-5-*nitropyrimidines* (3; Y = NH·$[CH_2]_3$Cl, X = NHMe, NHEt, *or* NH·CH_2·CH_2·OH).—The appropriate 4-(substituted amino)-2-chloro-6-methyl-5-nitropyrimidine (0.01 mol), 3-chloropropylamine hydrochloride (0.01 mol), and anhydrous sodium acetate (0.02 mol), were heated in propanol (30 ml), under reflux, with stirring for 1 h. The hot solution was filtered to remove inorganic matter and the filtrate refrigerated to yield the chloropropylamino-compound. Yields and properties of the products are in Table 2.

8-(*Substituted amino*)-3,4-*dihydro*-6-*methyl*-7-*nitro*-2H-*pyrimido*[1,2-a]*pyrimidine Hydrochlorides* (5; R = H, X = NHMe, NHEt, *or* NH·CH_2·CH_2·OH).—The appropriate 4-(substituted amino)-2-(3-chloropropylamino)-6-methyl-5-nitropyrimidine (1 g) in propan-2-ol (20 ml) was heated under reflux for 24 h. The solution was evaporated under reduced pressure and the resulting *pyrimidopyrimidine hydrochloride* was crystallised from ethanol. Yields and properties of the compounds are in Table 5.

8-(*Substituted amino*)-1,3,4,6-*tetrahydro*-6-*methylene*-7-*nitro*-2H-*pyrimido*[1,2-a]*pyrimidines* (14; X = NHMe *or* NHEt).—The appropriate hydrochloride (6; R = H, X = NHMe or NHEt) (0.5 g) in water (10 ml) was made alkaline with dilute sodium hydroxide solution and the *product* filtered off and crystallised from methanol as yellow needles. The 8-methylamino-derivative (55% yield) had m.p. 198—199° and the ethylamino-compound (61%), m.p. 189—190°.

4-*Ethyl*-2-[N-(2-*hydroxyethyl*)*methylamino*]-6-*methylamino*-5-*nitropyrimidine*.—Aqueous methylamine (25% w/v; 1.2 ml) was added during 10 min to a stirred solution of 2,4-dichloro-6-ethyl-5-nitropyrimidine (1.05 g) in dioxan (5 ml). After a further 1 h water (10 ml) was added and the resulting mixture extracted with chloroform. The extract was dried ($MgSO_4$) and evaporated to leave an oily residue, which was heated with ethanol (10 ml) and 2-methylaminoethanol (1.5 g) under reflux for 1 h. The solution was evaporated under reduced pressure and the residue triturated with water (10 ml). The *hydroxyethylmethylamino-compound* (0.9 g), m.p. 88—89°, was filtered off and crystallised from aqueous ethanol (Found: C, 46.6; H, 6.5. $C_{10}H_{17}N_5O_3$ requires C, 47.0; H, 6.7%).

5-*Ethylidene*-1,2,3,5-*tetrahydro*-1-*methyl*-7-*methylamino*-6-*nitroimidazo*[1,2-a]*pyrimidine* (11).—The above hydroxyethylmethylamino-compound (0.2 g) and phosphoryl chloride (5 ml) were heated under reflux for ½ h. The excess of phosphoryl chloride was evaporated off under reduced pressure and the oily residue was dissolved in cold water and made alkaline with dilute aqueous sodium hydroxide. The *imidazopyrimidine* (0.15 g), m.p. 178—179°, was filtered off and crystallised from propan-2-ol as yellow needles (Found: C, 50.6; H, 6.4; N, 29.2. $C_{10}H_{15}N_5O_2$ requires C, 50.6; H, 6.4; N, 29.5%).

2-(2-*Hydroxyethylmethylamino*)-4-*methyl*-6-*methylamino*-5-*nitropyrimidine* (3; X = NHMe, Y = NMe·CH_2·CH_2·OH).—2-Chloro-4-methyl-6-methylamino-5-nitropyrimidine (1.8 g), 2-methylaminoethanol (1.7 g), and ethanol (25 ml) were heated under reflux for 1 h. The solution was evaporated to dryness under reduced pressure and the oily residue

TABLE 3

7-(Substituted amino)-2,3-dihydro-5-methyl-6-nitromidazo[1,2-*a*]pyrimidine hydrochlorides

Compound (4)		Yield				Found (%)			Required (%)		
R	X	(%)	M.p. (°C)	Cryst. solvent	Formula	C	H	N	C	H	N
H	NMe_2	80	170 (decomp.)	Pr^iOH–H_2O	$C_9H_{13}N_5O_2$,HCl	41.6	5.4	26.8	41.6	5.4	27.0
H	Pyrrolidino	80	207 (decomp.)	Pr^iOH–H_2O	$C_{11}H_{15}N_5O_2$,HCl	46.1	5.4	24.6	46.2	5.6	24.5
H	Piperidino	90	144 (decomp.)	Pr^iOH–H_2O	$C_{12}H_{17}N_5O_2$,HCl	47.9	5.7	22.9	48.1	6.0	23.3
H	Morpholino	95	197 (decomp.)	Pr^iOH–H_2O	$C_{11}H_{15}N_5O_3$,HCl	43.4	5.3	23.0	43.8	5.3	23.2

TABLE 4

7-(Substituted amino)-1,2,3,5-tetrahydro-5-methylene-6-nitroimidazo[1,2-*a*]pyrimidines

Compound (10)		Yield		Cryst.		Found (%)			Required (%)		
R	X	(%)	M.p. (°C)	solvent	Formula	C	H	N	C	C	H
H	NH_2	65	228	MeOH	$C_7H_9N_5O_2$	43.2	4.7	35.6	43.0	4.6	35.9
H	NHMe	65	219	MeOH	$C_8H_{11}N_5O_2$	45.5	5.3	33.4	45.9	5.3	33.5
H	NHEt	63	188	MeOH	$C_9H_{13}N_5O_2$	48.2	5.8	30.9	48.4	5.9	31.4
H	$NHCH_2Ph$	72	147	MeOH	$C_{14}H_{15}N_5O_2$	58.9	5.3	25.0	58.9	5.3	24.5
H	NH·CH_2·CH_2·OH	55	164	MeOH	$C_9H_{13}N_5O_3$	44.8	5.3	28.9	45.2	5.5	29.3
Me	NHMe	76	222—227	Pr^iOH	$C_9H_{13}N_5O_2$	48.1	5.9	31.2	48.4	5.9	31.4

TABLE 5

8-(Substituted amino)-3,4-dihydro-6-methyl-7-nitro-2*H*-pyrimido[1,2-*a*]pyrimidine hydrochlorides

Compound (5)		Yield		Cryst.		Found (%)			Required (%)		
R	X	(%)	M.p. (°C)	solvent	Formula	C	H	N	C	H	N
H	NHMe	67	208—210	EtOH	$C_9H_{13}N_5O_2$,HCl	41.9	5.6	26.7	41.6	5.4	27.0
H	NHEt	75	226—227	EtOH	$C_{10}H_{15}N_5O_2$,HCl	43.6	6.0	25.3	43.9	5.9	25.6
H	NH·CH_2·CH_2·OH	60	250	EtOH	$C_{10}H_{15}N_5O_3$,HCl	41.0	5.4	24.6	41.5	5.6	24.2
H	NMe_2	70	176—177	Pr^iOH–Et_2O	$C_{10}H_{15}N_5O_2$,HCl	43.7	5.7	25.1	43.9	5.9	25.6

treated with water (10 ml). The *hydroxyethylmethylamino-compound* was filtered off and crystallised (yield and properties in Table 2).

1,2,3,5-*Tetrahydro*-1-*methyl*-5-*methylene*-7-*methylamino*-6-*nitroimidazo*[1,2-a]*pyrimidine* (10; X = NHMe, R = Me).—The foregoing hydroxyethylmethylamino-compound (1 g) and phosphoryl chloride (10 ml) were heated under reflux for 1 h and the solution was then evaporated under reduced pressure. The oily residue was dissolved in cold water and made alkaline with dilute aqueous sodium hydroxide. The *imidazopyrimidine*, was filtered off and crystallised as fine yellow needles (yield and properties in Table 4).

4-*Dimethylamino*-2-[N-(2-*hydroxyethyl*)*methylamino*]-6-*methyl*-5-*nitropyrimidine* (3; X = NMe_2, Y = $NMe{\cdot}CH_2{\cdot}CH_2{\cdot}OH$).—2-Chloro-4-dimethylamino-5-nitro-6-methylpyrimidine (0.01 mol), 2-methylaminoethanol (0.02 mol), and ethanol (25 ml) were heated under reflux for 1 h. Water was added and the solution was refrigerated to yield the *product* as yellow needles (yield and properties in Table 2).

2,3-*Dihydro*-1,5-*dimethyl*-7-*dimethylamino*-6-*nitroimidazo*-[1,2-a]*pyrimidinium Chloride* (4; X = NMe_2, R = Me).—The foregoing hydroxyethylmethylamino compound (1 g) was added in portions to thionyl chloride (10 ml), and the resulting solution was kept for 18 h. The excess of thionyl chloride was evaporated off under reduced pressure with the minimum of heating to give an oily residue which was dissolved in cold water and made alkaline with dilute aqueous sodium hydroxide. The 2-chloroethylmethylamino-compound was filtered off, dried, and heated with propan-2-ol (10 ml) for 1 h. The solvent was evaporated off under reduced pressure and the residue triturated with ethyl acetate to yield the crude *salt* (4; X = NMe_2, R = Me) (0.5 g), m.p. 44—46°. The compound was used without further purification for the preparation of samples of the base for ^1H n.m.r. measurements as described above for other 7-dialkylamino-imidazopyrimidines. The hydrochloride was characterised as its complex with thiourea, prepared by adding the compound (0.5 g) in propan-2-ol (5 ml) to thiourea (0.2 g) in ethanol (5 ml) and heating the mixture under reflux for ½ h. The *complex* (0.15 g), m.p. 143—145°, crystallised from the cooled solution as yellow needles (Found: C, 36.2; H, 6.1; N, 26.8. $C_{10}H_{16}ClN_5O_2,CH_4N_2S,H_2O$ requires C, 36.2; H, 6.0; N, 26.7%).

2-(3-*Hydroxypropylamino*)-4-*dimethylamino*-6-*methyl*-5-*nitropyrimidine* (3; X = NMe_2, Y = $NH{\cdot}CH_2{\cdot}CH_2{\cdot}OH$).—2-Chloro-4-dimethylamino-6-methyl-5-nitropyrimidine (6.5 g), 3-aminopropan-1-ol (4.5 g), and ethanol (75 ml) were heated under reflux for 1 h. Water was added and the solution was refrigerated to yield the 3-*hydroxypropylamine* derivative as yellow needles (yield and properties in Table 2).

2-(3-*Chloropropylamino*)-4-*dimethylamino*-6-*methyl*-5-*nitropyrimidine* was made by treating the foregoing hydroxypropylamino-compound with thionyl chloride as described for its hydroxyethylamino-analogue (yield and properties in Table 2).

8-*Dimethylamino*-3,4-*dihydro*-6-*methyl*-7-*nitro*-2H-*pyrimido*[1,2-a]*pyrimidine Hydrochloride* (5; X = NMe_2, R = H).—The foregoing chloropropylamino-derivative (0.01 mol) was heated under reflux with propan-2-ol (20 ml) for 8 h. The solution was cooled and ether added to the point of precipitation. On refrigeration the *pyrimidopyrimidine* crystallised (yield and properties in Table 5).

3,4-*Dihydro*-8-*methyl*-7-*nitro*-2H-*pyrimido*[1,2-a]*pyrimidin*-6-*ol* (6; *n* = 2).—2-Chloro-6-methyl-5-nitropyrimidin-4-ol (1.2 g), 3-chloropropylamine hydrochloride (0.65 g), anhydrous sodium acetate (1.6 g), and ethanol (40 ml) were heated under reflux for 3 h. Sodium chloride was filtered off and the filtrate evaporated to dryness under reduced pressure. The oily residue was dissolved in water and chilled to produce the yellow *pyrimidopyrimidine hydrochloride* (0.6 g), m.p. 186—187° [Found: C, 36.6; H, 5.0; N, 20.8%; M^+, 210. $C_8H_{10}N_4O_3,H_2O,HCl$ requires C, 36.2; H, 4.9; N, 21.2%; *M*, 210 (free base)], $\lambda_{max.}$ (H_2O; pH 5) 202 (log ε 4.04), 298 (3.40), and 349 nm (3.44).

3,4-*Dihydro*-6-*methyl*-7-*nitro*-2H-*pyrimido*[1,2-a]*pyrimidin*-8-*ol Hydrochloride* (5; X = OH).—3,4-Dihydro-8-dimethylamino-6-methyl-7-nitro-2*H*-pyrimido[1,2-*a*]pyrimidine hydrochloride (1.2 g) and concentrated hydrochloric acid (30 ml) were heated under reflux for 2.5 h. The mixture was evaporated to dryness under reduced pressure. The residue was washed with propan-2-ol and crystallised from methanol to yield the *pyrimidopyrimidinol hydrochloride* (0.4 g), m.p. 237—238° (decomp.) [Found: C, 35.9; H, 4.8%; M^+, 210. $C_8H_{10}N_4O_3,H_2O,HCl$ requires C, 36.2; H, 4.9%; *M*, 210 (free base)], $\lambda_{max.}$ (H_2O; pH 5) 257 (log ε 3.67) and 354 nm (3.11).

2,3-*Dihydro*-5-*methyl*-6-*nitroimidazo*[1,2-a]*pyrimidin*-7-*ol* (6; *n* = 1) was produced, as its *hydrochloride* (0.2 g), m.p. 296—297° (from water), when the corresponding 7-dimethylamino-derivative (4; X = NMe_2, R = H) (0.5 g) was similarly treated with concentrated hydrochloric acid (15 ml) [Found: C, 33.4; H, 4.4%; M^+, 196. $C_7H_8N_4O_3,H_2O,HCl$ requires C, 33.5; H, 4.4%; *M*, 196 (free base)], $\lambda_{max.}$ (H_2O; pH 5) 270 (log ε 3.69), 277 (3.68), and 350 nm (3.41). Its 5-hydroxy-7-methyl isomer (4; X = OH, R = H) had $\lambda_{max.}$ (H_2O; pH 5) 201 (log ε 4.05), 301 (3.45), and 343 nm (3.55).

4,5-*Dihydro*-2-(2-*nitroacetylamino*)*imidazole* (7).—(*a*) 2,3-Dihydro-7-dimethylamino-5-methyl-6-nitroimidazo[1,2-*a*]-pyrimidine hydrochloride (2 g) was dissolved in 2N-sodium hydroxide (15 ml)and the solution kept for 5 h. The pH was adjusted to 7 by addition of concentrated hydrochloric acid, and the precipitate was filtered off and crystallised from water to give the *imidazole* (0.9 g), m.p. 218—219° (Found: C, 34.8; H, 4.7%; M^+, 172. $C_5H_8N_4O_3$ requires C, 34.9; H, 4.7%; *M*, 172).

(*b*) 2,3-Dihydro-5-methyl-6-nitroimidazo[1,2-*a*]pyrimidine hydrochloride (0.25 g) in 2N-sodium hydroxide (2.5 ml) was kept for 2 h and the solution was then neutralised with concentrated hydrochloric acid. The precipitated product (0.07 g) was identical with that obtained by method (*a*).

[7/323 *Received*, 23*rd February*, 1977]