Heterocyclic Studies. Part XXXVII.[1] Ready Ring Cleavage and Decarbonylation of Pyrimidine-5-carbaldehydes

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Treatment of 4-chloro-6-dialkylaminopyrimidine-5-carbaldehydes (4) with boiling water or dilute acetic or hydrochloric acid gave corresponding 3-dialkylamino-3-iminopropiononitriles (11) by ring cleavage and deformylation. The acid-catalysed deformylations, which followed ring cleavage, proceeded under extremely mild conditions and the formyl groups were lost as formic acid. Mechanisms for the ring cleavages and deformylations are proposed.

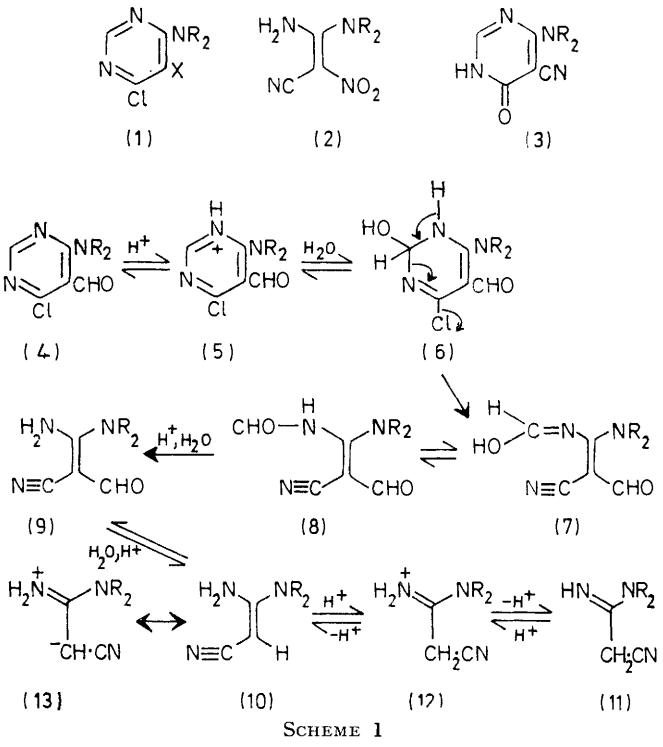
4-Chloro-6-monoalkylaminopyrimidine-5-carbaldehydes (16; X = CHO) under the same conditions underwent mainly simple hydrolysis of the chloro-substituent to give 6-alkylamino-5-formylpyrimidin-4(3*H*)-ones (17; X = CHO). Some other 4,6-disubstituted pyrimidine-5-carbaldehydes underwent deformylation without ring cleavage.

MANY pyrimidine derivatives undergo ring cleavage when treated with nucleophiles, but the severity of conditions necessary to achieve ring scission varies widely and depends on the substitution pattern. Electron-donating substituents tend to increase the resistance to ring cleavage by acids and bases,[2] whereas electron-withdrawing substituents tend to have the reverse effect.[3] Cleavage reactions are of interest because they often lead to compounds which are difficult to synthesise in other ways[4] or to interesting transformations into other heterocyclic systems.[5]

An earlier paper in this series showed that 4-chloro-6-dialkylamino-5-nitropyrimidines (1; X = NO_2) underwent ring cleavage under mild conditions to yield highly substituted olefins (2),[6] but the corresponding 5-cyanopyrimidines (1; X = CN) underwent simple hydrolysis of the chloro-substituent to give pyrimidones (3).[7] This paper deals with the related pyrimidine-5-carbaldehydes (4), whose behaviour under mildly acidic conditions was recently reported in preliminary form.[8]

A range of 4-(substituted amino)-6-chloropyrimidine-5-carbaldehydes was prepared by treating the appropriate amines with 4,6-dichloropyrimidine-5-carbaldehyde. Strongly basic secondary amines were best neutralised with acetic acid before treatment with the dichloro-compound 0.5 mol. equiv. Primary amines were advantageously condensed with the dichloro-compound (1 mol. equiv.) in the presence of triethylamine (1 mol. equiv.).

Treatment of the 4-chloro-6-dialkylaminopyrimidine-5-carbaldehydes (4; NR_2 = NMe_2, NEt_2, pyrrolidino, piperidino, morpholino, or perhydroazepin-1-yl) with boiling water for 1—3 h gave 60—70% yields of products which were hydrochlorides of strong bases. Similar results were obtained when the same pyrimidine derivatives (4) were heated with dilute acetic acid and when one of the compounds (4; NR_2 = pyrrolidino) was heated with dilute hydrochloric acid.



SCHEME 1

The i.r. spectrum of each product showed the presence of a cyano-group (ν_{CN} 2 160—2 200 cm^{-1}) and the absence of a formyl group. Each ^1H n.m.r. spectrum (Table 3) confirmed the lack of a formyl group and there was also

[1] Part XXXVI, J. Clark, M. R. Hughes, and I. W. Southon, *J.C.S. Perkin II*, 1974, 1277.

[2] See, for example, A. S. Jones, A. A. Mian, and R. T. Walker, *J. Chem. Soc.* (*C*), 1966, 1784; D. J. Brown, 'The Pyrimidines,' Interscience, New York and London, 1962, p. 10; D. J. Brown in 'Mechanisms of Molecular Migration,' ed. B. S. Thyagarajan, Wiley, New York and London, 1968, vol. 1, p. 217.

[3] See, for example, H. Bredereck, F. Effenberger, and W. Resemann, *Angew. Chem.*, 1962, **74**, 253; M. E. C. Biffin, D. J. Brown, and T. C. Lee, *J. Chem. Soc.* (*C*), 1967, 573; D. J. Brown in 'Mechanisms of Molecular Migrations,' ed. B. S. Thyagarajan, Wiley, New York, 1968, vol. 1, p. 218.

[4] See, for example, J. Clark, G. Neath, and C. Smith, *J. Chem. Soc.* (*C*), 1969, 1297; J. Clark and C. Smith, *ibid.*, 1971, 1948; E. C. Taylor, *J. Amer. Chem. Soc.*, 1952, **74**, 1651; J. Clark, M. Curphey, and I. W. Southon, *J.C.S. Perkin I*, 1974, 1611.

[5] H. C. van der Plas and H. Jongejan, *Rec. Trav. chim.*, 1968, **87**, 1065; H. W. van Meeteren and H. C. van der Plas, *Tetrahedron Letters*, 1966, 4517; H. C. van der Plas, B. Haase, B. Zuurdeeg, and M. C. Vollering, *Rec. Trav. chim.*, 1966, **85**, 1101 and later papers in the series; H. C. van der Plas and H. Jongejan, *ibid.*, 1970, **89**, 680; H. C. van der Plas, H. Jongejan, G. Guertsen, and M. C. Vollering, *ibid.*, 1971, **90**, 1246.

[6] J. Clark, I. Gelling, I. W. Southon, and M. S. Morton, *J. Chem. Soc.* (*C*), 1970, 494.

[7] M. S. Morton, Ph.D. Thesis, University of Salford 1972.

[8] J. Clark, B. Parvizi, and I. W. Southon, *Chem. and Ind.*, 1974, 661.

no signal for the 2-hydrogen atom of the pyrimidine ring. Measurement of the ionisation constants of representative examples showed that the compounds were bases with pK_a *ca.* 9.7, and their u.v. spectra showed no absorption maximum above 270 nm.

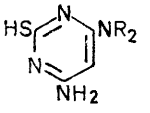
Ring cleavage and deformylation of the pyrimidines had occurred to give products which were assigned cyanoacetamidine structures (11). Molecular weights, determined by mass spectrometry, were in agreement with (and in two cases accurate mass measurements were made to confirm) the molecular formulae. Final confirmation of the structures was obtained when u.v. spectra and ionisation constants of some of the compounds were compared with those of specimens * synthesised by treating the hydrochloride of the iminoether $NC{\cdot}CH_2{\cdot}C(:NH){\cdot}OEt$ [9] with the appropriate secondary amines.

The compounds are written as cyanoacetamidine derivatives (11) for convenience although several alternative tautomeric forms are possible. ^1H N.m.r. spectra (Table 3) confirm the expected cyanoacetamidinium structures (12) for the salts initially isolated. Both ^1H and ^{13}C n.m.r. spectra rule out the uncharged aminoacrylaldehyde form (10) for the neutral molecules because there are no signals which could be attributed to a normal olefinic CH group. The ^{13}C n.m.r. spectrum of the pyrrolidino-compound in deuteriochloroform (chemical shifts in p.p.m. from tetramethylsilane; multiplicities in the off-resonance spectrum in parentheses) showed δ 25.4 (t) (pyrrolidino β-CH_2's), 47.1 (t) (pyrrolidino α-CH_2's), 39.0 (d) (*C*HCN), 124.5 (s), (*C*N), and 160.1 (s) $\{C(:NH_2){\cdot}N{\cdot}[CH_2]_4\}$. The chemical shift of C-2 (39 p.p.m.) clearly is not that of an olefinic carbon atom. However the fact that the signal appears as a doublet in the off-resonance spectrum shows that it is attached to only one hydrogen atom. These facts agree best with the zwitterionic form (13). This interpretation is supported by the ^1H n.m.r. spectrum (Table 3), which shows a very broad, one-proton peak at τ *ca.* 5.5, whereas the corresponding hydrochloride has a much sharper, two-proton peak at τ 5.5. Signals for NH_2 are not observed in any of the spectra of the neutral molecules, probably because they are extremely broad. The tautomerism of compounds (11) is being investigated in greater detail.

Protection of the aldehyde group by acetal formation did not prevent deformylation, for 4-chloro-5-(1,3-dioxolan-2-yl)-6-morpholinopyrimidine (14) also yielded a cyanoacetamidine (11; NR_2 = morpholino) when refluxed with water. In this, as in the other reactions, a little hydrogen chloride is probably formed by simple hydrolysis of the chloropyrimidine and this acid then catalyses ring cleavage, deacetalation, and deformylation.

One amidine (11; NR_2 = pyrrolidino) was condensed with thiourea to confirm its structure but the reaction yielded 4,6-diamino-2-mercaptopyrimidine (15; NR_2 = NH_2) rather than the hoped-for pyrrolidinopyrimidine (15; NR_2 = pyrrolidino).


(14)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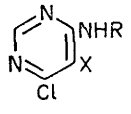
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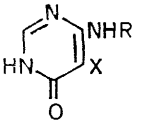

(17)

By contrast with the dialkylaminopyrimidine-5-carbaldehydes (4) the corresponding alkylamino-compounds (16; X = CHO) underwent mainly simple hydrolysis of the chloro-substituent to give pyrimidinones (17; X = CHO) when treated with boiling water. However some ring cleavage probably occurred: small amounts of oily material with an i.r. absorption in the CN stretching region (*ca.* 2 200 cm^{-1}) were produced. These results resemble previous ones from 5-nitro- (16; X = NO_2)[6] and 5-cyano-pyrimidines (1 or 16; X = CN) [7] and confirm that in acid-catalysed cleavages of this kind steric hindrance between the 5- and 6-substituents favours cleavage at the expense of 4-chloro-substituent hydrolysis.

It is proposed that the cyanoacetamidines (11) arise from the reaction sequence indicated in Scheme 1, but a variant of this scheme in which the cation of the covalent hydrate (6) undergoes cleavage to give the cation of (7) is also possible. Several steps were confirmed by isolating intermediates under mild conditions. Thus careful treatment of 4-chloro-6-piperidinopyrimidine-5-carbaldehyde (4; NR_2 = piperidino) with water at 25 °C for 24 h gave 2-formyl-3-formylamino-3-piperidinoacrylonitrile (8; NR_2 = piperidino), and the morpholinopyrimidine (4; NR_2 = morpholino) similarly gave the appropriate acrylonitrile (8; NR_2 = morpholino). The latter was *N*-deformylated with dilute acetic acid (or better sodium carbonate) to give the amino-formylmorpholinoacrylonitrile (9; NR_2 = morpholino), which lost its *C*-formyl group on treatment with refluxing dilute hydrochloric acid to give the final product (10) ⇌ (11).

The steps leading from the pyrimidine (4) to the olefin (9) are analogous to those undergone by the corresponding 5-nitro-derivatives (1; X = NO_2),[6] but the final decarbonylation step was unexpected. Acidic catalysis was clearly involved since the amino-formyl-acrylonitriles (9) were stable under neutral or alkaline conditions. The *C*-formyl group was shown to be expelled as formic acid when treatment of 3-amino-2-formyl-3-morpholino-

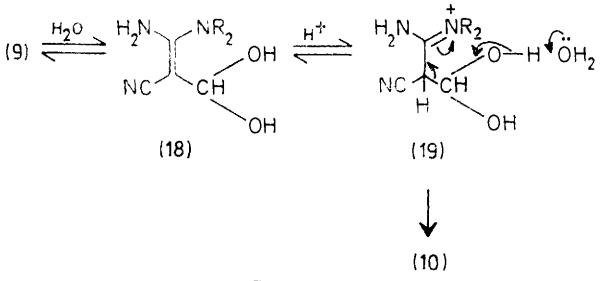
* These compounds were supplied by Dr. A. Krauss, Fachbereich Chemie, Universität Konstanz, West Germany.

[9] A. H. Cook, G. Harris, and A. L. Levy, *J. Chem. Soc.*, 1949, 3227.

acrylonitrile (9; NR_2 = morpholino) with hydrochloric acid gave, as well as the cyanoacetamidine (11; NR_2 = morpholino), 1 mol. equiv. of formic acid, isolated as its *S*-benzylthiouronium salt. Furthermore 4-chloro-6-pyrrolidinopyrimidine-5-carbaldehyde (4; NR_2 = pyrrolidino) similarly gave 2 mol. equiv. of formic acid and the cyanoacetamidine (11; NR_2 = pyrrolidino) but in this case, of course, half the formic acid originates from the pyrimidine 2-carbon atom.

The mechanism of deformylation is probably as indicated in Scheme 2. Formyl groups attached to electron-withdrawing systems are readily hydrated in aqueous solution,[10] so involvement of a hydrated carbonyl group (18) is likely. In addition, the compounds concerned (9) are enamino-aldehydes, so protonation of the carbon atom β to the amino-group is to be expected.[11] Loss of formic acid from the resulting cation (19) is probably assisted by a base such as water or a molecule of reactant or product. A similar mechanism has been proposed for the acid-catalysed decarbonylations of certain highly substituted benzaldehydes,[12] but these reactions required much more severe conditions than the present ones, which proceed under astonishingly mild conditions. For example one pyrimidine (4; $NR_2 = NMe_2$) underwent all the steps in Scheme 1 to yield the cyanoacetamidine (11; $NR_2 = NMe_2$) on stirring in water at 25 °C.

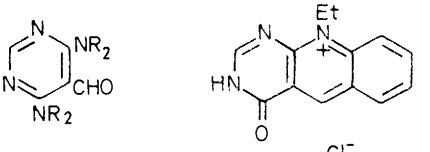
If the proposed mechanism for deformylation is correct then other compounds which may be regarded as enamino-aldehydes should behave similarly; this proved to be the case. Thus some diamines (20), prepared by replacing the chlorine atoms of 4,6-dichloropyrimidine-5-carbaldehyde successively with different substituted amino groups, readily underwent deformylation on heating in hydrochloric acid. Deformylation was confirmed by the absence of an aldehyde proton signal in the

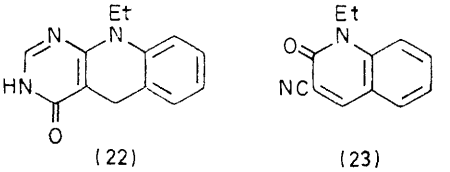


SCHEME 2

^{1}H n.m.r. spectra of the products and the presence of a signal due to a pyrimidine 5-proton. The introduction of both amino-groups under very mild conditions was possible because of the activating influence of the formyl group. Therefore this reaction sequence followed by the easy deformylation provides a route to 4,6-bis-(substituted amino)pyrimidines which avoids the use of the sealed tube reaction which is often necessary[13] to introduce the second amino-group if one starts from 4,6-dichloropyrimidine. Some other reactions of 4-(substituted amino)pyrimidine-5-carbaldehydes also involved deformylation. Thus treatment of 4-anilino-6-chloropyrimidine-5-carbaldehyde with ethanolic hydrogen chloride gave 4-anilino-6-ethoxypyrimidine or a mixture of the latter and 4-anilino-6-hydroxypyrimidine according to conditions.

When 4-chloro-6-*N*-ethylanilinopyrimidine-5-carbaldehyde (4; NR_2 = NEtPh) was heated under reflux with water, none of the expected cyanoacetamidine





(11; NR_2 = NEtPh) was produced. Instead the major product was a pyrimidoquinolinium chloride (21), which was accompanied by smaller quantities of a dihydropyrimidoquinoline (22) and a cyanoquinolone (23). These reactions will be dealt with in a subsequent paper.

EXPERIMENTAL

Ionisation constants were measured at 20 °C by a rapid spectrophotometric method,[14] and u.v. spectra for buffered aqueous solutions were measured with a Unicam SP 800 instrument, with the following results: 3-imino-3-pyrrolidinopropiononitrile, pK_a 9.80 ± 0.06, $\lambda_{max.}$ (neutral molecule; pH 12.0) 260 (log ε 4.27), (cation; pH 7.2) 210 (log ε 3.98); 3-imino-3-piperidinopropiononitrile, pK_a 9.64 ± 0.06, $\lambda_{max.}$ (neutral molecule; pH 12.0) 265 (log ε 4.21), (cation; pH 7.2) 214 (log ε 4.04). The ^{13}C n.m.r. spectrum was measured with a Varian CFT 20 instrument. Mass spectra were measured with an A.E.I. MS 902S spectrometer (source temperature *ca.* 200 °C). Accurate mass measurements were made at a resolving power of 10 000.

4-(Substituted amino)-6-chloropyrimidine-5-carbaldehydes.—*Method* (*a*). Glacial or 4N-acetic acid was added to the appropriate amine (0.022 mol) to adjust its pH value to 8 before it was added dropwise to a stirred solution of 4,6-dichloropyrimidine-5-carbaldehyde[15] (0.01 mol) in dioxan (50 ml) at 10—15 °C (dimethylamine was purchased and used as an aqueous 25% solution). After a further 3 h the mixture was poured into ice-cold water (150 ml) and

[10] Y. Ogata and A. Kawasaki, in 'The Chemistry of the Carbonyl Group,' vol. 2, ed. J. Zabicky, Interscience, London and New York, 1970, p. 3.
[11] J. Szmuszkovicz, *Adv. Org. Chem.*, 1963, **4**, 94.
[12] H. Burkett, W. M. Schubert, F. Schulz, R. B. Murphy, and R. Talbot, *J. Amer. Chem. Soc.*, 1959, **81**, 3923; H. Burkett, W. M. Schubert, W. Buddenbaum, R. Edminster, K. Kirk, and L. Nichols, *Amer. Chem. Soc. Div. Petrol. Chem. Reprints*, 1966, **11**, 179.
[13] D. J. Brown in 'The Pyrimidines,' ed. A. Weissberger, Interscience, London and New York, 1962, p. 190.
[14] J. Clark and A. E. Cunliffe, *Chem. and Ind.*, 1973, 281.
[15] W. Klötzer and M. Herberz, *Monatsh.*, 1965, **96**, 1567.

the product was filtered off, dried, and crystallised from propan-2-ol. Yields *etc.* are given in Table 1.

Method (*b*). A mixture of the appropriate amine (0.011 mol), and triethylamine (0.011 mol) was added dropwise to a stirred solution of 4,6-dichloropyrimidine-5-carbaldehyde (0.01 mol) in dry chloroform at 0 °C. Stirring was continued for a further 3 h before the mixture was washed with water, dried ($MgSO_4$), and evaporated. The product was crystallised from propan-2-ol (see Table 1).

15—20 °C. After a further 3 h, ice-cold water (100 ml) was added and the product was filtered off and crystallised from propan-2-ol (see Table 1).

Ring Opening and Deformylation of 4-(*Substituted amino*)-6-*chloropyrimidine-5-carbaldehydes.—Method* (*e*). The relevant pyrimidine (1 g) was heated under reflux with water (10 ml) for 3 h and the resulting solution evaporated to dryness. The residue was triturated with a little propan-2-ol, filtered off, and crystallised from a suitable solvent,

TABLE 1

4-(Substituted amino)-6-chloropyrimidine-5-carbaldehydes (4) and acetal (14)

NR_2	Method of prepn.*	Yield (%)	M.p. (°C)	Formula †	Found (%) C	H	N	Required (%) C	H	N
NMe_2	(*a*)	70	139—141 ‡	$C_7H_8ClN_3O$	45.6	4.0	22.6	45.3	4.3	22.6
Piperidino	(*a*)	72	78—79	$C_{10}H_{12}ClN_3O$	53.5	5.4	18.8	53.2	5.3	18.6
Pyrrolidino	(*a*)	72	111—112	$C_9H_{10}ClN_3O$	51.2	4.8	20.1	51.1	4.7	19.9
Morpholino	(*c*)	60	92—93	$C_9H_{10}ClN_3O_2$	47.5	4.6	18.7	47.5	4.4	18.5
Perhydroazepin-1-yl	(*a*)	71	109—110	$C_{11}H_{14}ClN_3O$	55.0	5.8	17.6	55.1	5.9	17.5
NH·CH_2Ph	(*b*)	82	69—70	$C_{12}H_{10}ClN_3O$	57.9	4.1	17.0	58.2	4.0	17.0
$NHCH_2$·CH:CH_2	(*b*)	76	50—51	$C_8H_8ClN_3O$	48.7	4.2	21.3	48.6	4.0	21.3
NHEt	(*b*)	70	76—77	$C_7H_8ClN_3O$	45.1	4.3	22.7	45.5	4.3	22.6
NEtPh	(*c*)	78	115—117	$C_{13}H_{12}ClN_3O$	59.4	4.8	16.2	59.7	4.6	16.1
	(*d*)	90	115—117							
NMePh	(*d*)	62	104—105	$C_{12}H_{10}ClN_3O$	58.0	4.3	17.2	58.2	4.0	17.0
(14)	(*c*) §	74	83—85	$C_{11}H_{14}ClN_3O$	48.3	4.9		48.6	5.2	

* See Experimental section. † All compounds gave appropriate molecular ions. ‡ Lit.,[17] 140—141°. § Starting from 4,6-dichloro-5-(1,3-dioxolan-2-yl)-6-morpholinopyrimidine (W. Klötzer and M. Herberz, *Monatsh.*, 1965, **96**, 1573).

TABLE 2

Ring cleavage and deformylation of 4-(substituted amino)-6-chloropyrimidine-5-carbaldehydes [a]

NR_2 in cyanoacetamidine (11) produced	Solvent for cleavage	Method of cleavage [a]	Yield (%)	M.p. (°C)	Cryst. solvent	Formua [b]	Found (%) C	H	N	Required (%) C	H	N
NMe_2, HCl	H_2O	(*e*)	45	177—178°	EtOH	$C_5H_9N_3$,HCl	40.6	6.8	28.5	40.7	6.8	28.5
NMe_2, HCl	AcOH–H_2O	(*g*)	57	177—178	EtOH							
NMe_2 [c]	H_2O	(*f*)	70	83—84	PhH	$C_5H_9N_3$	(M^+, 111.0799.			*M*, 111.0796)		
Pyrrolidino, HCl	H_2O	(*e*)	67	193—195	Pr^{i}OH	$C_7H_{11}N_3$,HCl	48.3	6.8	24.5	48.4	7.0	24.2
Pyrrolidino	H_2O	(*f*)	70	145—146	Pr^{i}OH	$C_7H_{11}N_3$	61.4	8.3	30.2	61.3	8.0	30.7
Pyrrolidino	AcOH–H_2O	(*h*)	52	145—146	Pr^{i}OH	$C_7H_{11}N_3$	(M^+, 137.0956.			*M*, 137.0953)		
Pyrrolidino	HCl–H_2O	(*i*)	62	193—195	Pr^{i}OH							
Piperidino, HCl	H_2O	(*e*)	56	165—166	Pr^{i}OH	$C_8H_{13}N_3$,HCl	51.3	7.4	22.2	51.2	7.5	22.4
Piperidino, HCl	AcOH–H_2O	(*g*)	54	165—166	Pr^{i}OH							
Morpholino, HCl	H_2O	(*e*)	64	198—200		$C_7H_{11}N_3O$,HCl	44.1	6.4	22.5	44.3	6.3	22.2
Morpholino	H_2O	(*f*)	70	103—104	Pr^{i}OH	$C_7H_{11}N_3O$	54.8	7.2	27.6	54.9	7.2	27.5
Morpholino	H_2O	(*f*) [d]	40	103—104	Pr^{i}OH							
NEt_2	AcOH–H_2O	(*j*) [e]	53	67—68	PhH–LP [f]	$C_7H_{13}N_3$	60.4	9.2	30.0	60.4	9.3	30.2
Perhydroazepin-1-yl	H_2O	(*f*)	44	108—109	PhH	$C_9H_{15}N_3$	65.8	9.1		65.4	9.2	

[a] See Experimental section. [b] All compounds gave appropriate molecular ions. [c] Soon decomposes as free base. [d] Starting from the ethylene acetal compound (14). [e] Starting from 4,6-dichloropyrimidine-5-carbaldehyde (see Experimental section). [f] Benzene–light petroleum (b.p. 60—80°).

Method (*c*). The appropriate amine (0.022 mol) was added dropwise to a stirred solution of 4,6-dichloropyrimidine-5-carbaldehyde (0.01 mol) in dioxan (50 ml) at 0—5 °C. After a further 3 h ice-cold water (120 ml) was added and the solution was extracted with chloroform (2 × 50 ml). The combined extracts were washed with water, dried, and evaporated to yield a residue which was crystallised from propan-2-ol without further treatment or after trituration with water and filtration (see Table 1).

Method (*d*). A mixture of the appropriate amine (0.055 mol; freshly distilled) and triethylamine (0.055 mol) was added dropwise to a stirred solution of 4,6-dichloropyrimidine-5-carbaldehyde (0.05 mol) in dioxan (50 ml) at if necessary, to yield the hydrochloride of the 3-dialkylamino-3-iminopropiononitrile derivative (11). Yields *etc.* are given in Table 2. (Reaction times as short as 20 min appear to give similar yields.)

Method (*f*). The relevant pyrimidine (1 g) was heated under reflux with water for ½—3 h and the resulting solution evaporated to dryness. A little water was added and the solution made alkaline with 2N-sodium hydroxide. The product was either filtered off or extracted with chloroform and crystallised from a suitable solvent (see Table 2).

Method (*g*). As method (*e*) except that the pyrimidine (1 g) was cleaved with a mixture of glacial acetic acid (3 ml) and water (5 ml) for 3 h under reflux (see Table 2).

Method (*h*). As method (*f*) except that the pyrimidine (1 g) was cleaved with a mixture of glacial acetic acid (3 ml) and water (5 ml) for 3 h under reflux (see Table 2).

Method (*i*). 4-Chloro-6-pyrrolidinopyrimidine-5-carbaldehyde (0.6 g) and N-hydrochloric acid (4 ml) were stirred at 20 °C for 24 h. The solution was then made alkaline with 2N-sodium hydroxide and resulting amidine filtered off (Table 2).

Method (*j*). 4,6-Dichloropyrimidine-5-carbaldehyde (2.66 g) in ether (75 ml) was stirred at 0 °C during the addition over 20 min of a solution of diethylamine (2.19 g) in ether (75 ml) and for a further 3 h. Diethylamine hydrochloride was filtered off and the filtrate washed with water, dried ($MgSO_4$), and evaporated. The residue was heated, under reflux, with glacial acetic acid (7.5 ml) and water (13.5 ml) for 3 h and the resulting solution was evaporated to dryness. The residue was dissolved in water (10 ml) and made alkaline with 2N-sodium hydroxide. The amidine (11; NR_2 = NEt_2) was filtered off, dried, and crystallised from benzene (see Table 2).

TABLE 3

^{1}H N.m.r. spectra of 3-dialkylamino-3-iminopropionitriles

	τ Values			
NR_2 in structure (11)	NR_2	CH or CH_2	NH and/or NH_2	Solvent
Piperidino,HCl	8.52—8.13 (6 H, m), 6.50—6.12 (4 H, m)	5.45 (s) *	0.08vbr (2 H)	$(CD_3)_2SO$
NMe_2	7.08 (6 H, s)	5.47br †		$CDCl_3$
NMe_2,HCl	6.80 (3 H, s), 6.68 (3 H, s)	5.47 (s) *	0.17vbr (2 H)	$(CD_3)_2SO$
Morpholino	6.95—6.57 (4 H, m), 6.37—6.12 (4 H, m)	5.48br †		$CDCl_3$
Morpholino,HCl	6.42—6.10 (8 H, m)	5.42 (s) *	−0.18vbr (2 H)	$(CD_3)_2SO$
Pyrrolidino	8.18—7.85 (4 H, m), 6.87—6.50 (4 H, m)	5.52br †		$CDCl_3$
Pyrrolidino,HCl	8.17—7.85 (4 H, m), 6.65—6.07 (4 H, m)	5.47 (s) *	0.65br (1 H), −0.17br, (1 H)	$(CD_3)_2SO$
NEt_2	8.83 (3 H, t, *J* 6.5 Hz), 6.77 (2 H, q, *J* 6.5 Hz)	5.72vbr †		$CDCl_3$
Perhydroazepin-1-yl	8.67—8.00 (8 H, m), 6.87—6.48 (4 H, m)	5.60vbr †		$CDCl_3$

* 2 H, rapidly removed on deuteriation. † 1 H, very broad signal removed on deuteriation at variable rates (see text for discussion of tautomerism).

Ring Cleavages under Mild Conditions.—(i) A suspension of 4-chloro-6-morpholinopyrimidine-5-carbaldehyde (1 g) in water (30 ml) was stirred at 20—25 °C for 21 h. *2-Formyl-3-formylamino-3-morpholinoacrylonitrile* (81%), m.p. 177—178° (from methanol) was filtered off (Found: C, 51.7; H, 5.0; N, 20.0. $C_9H_{11}N_3O_3$ requires C, 51.7; H, 5.3; N, 20.1%), τ [$(CD_3)_2SO$] 6.53—6.12 (8 H, m), 1.43 (1 H, s, NHC*H*O), 0.78 (1 H, s, CHO), and −1.15br (1 H, s, NH).

(ii) 4-Chloro-5-(1,3-dioxolan-2-yl)-6-morpholinopyrimidine (12) (1 g) when treated as in (i) also yielded 2-formyl-3-formylamino-3-morpholinoacrylonitrile (78%).

(iii) 4-Chloro-6-piperidinopyrimidine-5-carbaldehyde (0.3 g) was stirred with water (10 ml) at 20—25 °C for 24 h and *2-formyl-3-formylamino-3-piperidinoacrylonitrile* (29%), m.p. 154—155° (decomp.) was filtered off (Found: C, 58.0; H, 6.3. $C_{10}H_{13}N_3O_2$ requires C, 57.9; H, 6.3%), τ [$(CD_3)_2SO$] 8.55—8.17 (6 H, m), 6.57—6.28 (4 H, m), 1.45 (1 H, s, NHC*H*O), 0.78 (1 H, s, C*H*O), and −1.10br (1 H, s, NH).

(iv) 4-Chloro-6-dimethylaminopyrimidine-5-carbaldehyde (1 g) was stirred with water (45 ml) at 20—25 °C for 24 h. The solution was made alkaline and extracted with chloroform to yield the *NN*-dimethylacetamidine (11; R = Me) (54%), identical with that described above (Table 2).

Degradation of 2-Formyl-3-formylamino-3-morpholinoacrylonitrile.—(i) A mixture of the formylamino-compound (8; NR_2 = morpholino) (0.5 g), glacial acetic acid (3.6 ml), and water (3.6 ml) was stirred at 25 °C for 2 days. A little insoluble matter was filtered off and the filtrate was evaporated to dryness under reduced pressure. The residue was crystallised from ethanol to yield *3-amino-2-formyl-3-morpholinoacrylonitrile* (0.5 g), m.p. 210° (decomp.) (from ethanol) (Found: C, 52.7; H, 5.6; N, 22.8. $C_8H_{11}N_3O_2$ requires C, 53.0; H, 6.1; N, 23.2%), τ [$(CD_3)_2SO$] 6.85—6.12 (8 H, m), 2.18br (*ca.* 2 H, NH_2), and 0.98 and 1.14 (total 1 H, each s, CHO).

(ii) The formylamino-compound (8; NR_2 = morpholino) (0.2 g) and N-hydrochloric acid (3 ml) were heated under reflux for 1 h. The solution was evaporated to dryness and the residue triturated with propan-2-ol to yield the amidine (11; NR_2 = morpholino) (38%), identical with that described above (Table 2). 3-Amino-2-formyl-3-morpholinoacrylonitrile was similarly decarbonylated to yield the amidine.

Isolation of Formic Acid produced in Deformylations.—(i) 3-Amino-2-formyl-3-morpholinoacrylonitrile (1 g) and 2N-hydrochloric acid (10 ml) were heated under reflux for 20 min and the resulting solution was made just alkaline with 2N-sodium hydroxide. The amidine produced (11; NR_2 = morpholino) was extracted with chloroform and the aqueous layer was evaporated to half bulk, exactly neutralised, and treated with a freshly prepared solution of *S*-benzylthiouronium chloride (1 g) in water (5 ml). *S*-Benzylthiouronium formate (0.4 g), m.p. 150—151° (lit.,[16] 151°), was filtered off.

(ii) 4-Chloro-6-pyrrolidinopyrimidine-5-carbaldehyde (1 g) and water (15 ml) were heated in a sealed tube at 100 °C for 3 h. The solution was made just alkaline with sodium hydroxide and continuously extracted with benzene for 12 h. The aqueous layer was evaporated to half bulk and treated as in (i) to yield *S*-benzylthiouronium formate (1.2 g), m.p. 150—151°. A blank experiment with the expected amount of formic acid (0.44 g) also gave the salt (1.2 g).

6-Anilino-5-formylpyrimidin-4(3H)-one.—4-Anilino-6-chloropyrimidine-5-carbaldehyde [17] (2 g) and water (10 ml) were heated under reflux for 1.5 h. The solid which separated was filtered from the hot solution and crystallised from ethanol to yield *6-anilino-5-formylpyrimidin-4(3H)-one* (42%), m.p. 257° (decomp.) (Found: C, 61.6; H, 4.5; N, 19.4. $C_{11}H_9N_3O_2$ requires C, 61.4; H, 4.2; N, 19.5%).

6-Benzylamino-5-formylpyrimidin-4(3H)-one (65%), m.p.

[16] A. I. Vogel, 'A Text-book of Practical Organic Chemistry including Qualitative Organic Analysis,' Longmans Green, London, New York, and Toronto, 3rd edn., 1957, p. 365.

[17] H. Bredereck, G. Simchen, and A. A. Santos, *Chem. Ber.*, 1967, **100**, 1344.

238—239° (from aqueous dimethylformamide), was similarly obtained when the corresponding chloropyrimidine (1.5 g) was treated with boiling water (20 ml) (Found; 62.6; H, 4.7; N, 18.4. $C_{12}H_{11}N_3O_2$ requires C, 62.9; H, 4.8; N, 18.3%).

6-*Ethylamino*-5-*formylpyrimidin*-4(3H)-*one* (50%), m.p. 244—245° (decomp.) (from water), was similarly obtained when 4-chloro-6-ethylaminopyrimidine-5-carbaldehyde (0.9 g) was treated with boiling water (15 ml) (Found: C, 50.3; H, 5.3; N, 25.1. $C_7H_9N_3O_2$ requires C, 50.3; H, 5.4; N, 25.1%).

6-*Allylamino*-5-*formylpyrimidin*-4(3H)-*one* (60%), m.p. 194—195° (from aqueous ethanol), was similarly obtained when the corresponding chloropyrimidine (1.5 g) was treated with boiling water (20 ml) and ethanol (5 ml). Most of the solvent was evaporated off before the product was removed by filtration (Found: C, 53.6; H, 5.3; N, 23.4. $C_8H_9N_3O_2$ requires C, 53.6; H, 5.0; N. 23.5%).

4-*Amino*-6-*dimethylaminopyrimidine*-5-*carbaldehyde*.—A mixture of 4-amino-6-chloropyrimidine-5-carbaldehyde [17] (0.9 g), ethanol (15 ml), and dimethylamine (2 ml of ethanolic 33% solution) was heated under reflux for 1 h, and then cooled and filtered. The *product* (0.75 g) had m.p. 201—202° (from ethanol) (Found: C, 50.3; H, 5.9; N. 34.1. $C_7H_{10}N_4O$ requires C, 50.6; H, 6.0; N, 33.7%).

4-*Dimethylamino*-6-N-*ethylanilinopyrimidine*-5-*carbaldehyde*.—Dimethylamine (1.15 g of ethanolic 33% solution) was added dropwise to a solution of 4-chloro-6-*N*-ethylanilinopyrimidine-5-carbaldehyde (2.61 g) in toluene (50 ml). The resulting solution was stirred at 60 °C for 1 h and then evaporated. The residue was treated with water (5 ml) and extracted with chloroform. The chloroform layer was dried and evaporated to dryness and the residue was extracted with boiling light petroleum (b.p. 60—80°; 60 ml). The extract was evaporated to 20 ml; the *product* (70%) separated as crystals, m.p. 111° (Found: C, 66.3; H, 6.9; N, 20.4. $C_{15}H_{18}N_4O$ requires C, 66.6; H, 6.7; N, 20.7%).

4-*Morpholino*-6-*pyrrolidinopyrimidine*-5-*carbaldehyde*.—Morpholine (5.22 g) in benzene (48 ml) was added dropwise during 5 min to a stirred solution of 4-chloro-6-pyrrolidinopyrimidine-5-carbaldehyde (6.36 g) in benzene (48 ml). After 3 h morpholine hydrochloride was filtered off and the filtrate evaporated to dryness under reduced pressure. The residue was triturated with ether to produce a colourless solid which was extracted with boiling light petroleum (b.p. 60—80°). Insoluble matter was filtered from the hot solution and the filtrate was concentrated to yield the *morpholinopyrrolidinopyrimidine* (3.54 g), m.p. 97—98° (Found: C, 59.4; H, 6.6; N, 22.0. $C_{13}H_{18}N_4O_2$ requires C, 59.5; H, 6.9; N, 21.3%), τ ($CDCl_3$) 8.17—7.87 (4 H, m), 6.42—6.03 (12 H, m), 1.85 (1 H, s, 2-proton), and 0.37 (1 H, s, CHO).

Deformylation of 4,6-*Bis*-(*substituted amino*)*pyrimidine*-5-*carbaldehydes*.—4-Amino-6-dimethylaminopyrimidine-5-carbaldehyde (1 g) and 2N-hydrochloric acid (20 ml) were heated under reflux for 3 h. The solution was then evaporated to dryness under reduced pressure. The residue was dissolved in water (10 ml), basified with 2N-sodium hydroxide solution, and extracted with chloroform. The extract was washed with water, dried ($MgSO_4$), and evaporated to yield 4-*amino*-6-*dimethylaminopyrimidine* (0.6 g), m.p. 178° (decomp.) [from light petroleum (b.p. 100—120°)] (Found: C, 52.0; H, 7.5; N, 40.1. $C_6H_{10}N_4$ requires C, 52.2; H. 7.2; N, 40.6%).

4-Morpholino-6-pyrrolidinopyrimidine-5-carbaldehyde (1 g) similarly yielded 4-*morpholino*-6-*pyrrolidinopyrimidine* (0.45 g), m.p. 106—107° [from light petroleum (b.p. 80—100°)] (Found: C, 61.7; H, 7.7. $C_{12}H_{18}N_4O$ requires C, 61.5; H, 7.7%), τ ($CDCl_3$) 8.17—7.88 (4 H, m), 6.73—6.17 (12 H, m), 4.80 (1 H, s, 5-proton), and 1.95 (1 H, s, 2-proton).

4-Dimethylamino-6-*N*-ethylanilinopyrimidine-5-carbaldehyde (2 g) was similarly deformylated except that ethanolic hydrogen chloride (33%; 15 ml) was used. The product was 4-*dimethylamino*-6-N-*ethylanilinopyrimidine* (1.4 g), m.p. 105—106° [from light petroleum (b.p. 60—80°)] (Found: C, 69.4; H, 7.6; N. 23.1. $C_{14}H_{18}N_4$ requires C, 69.4; H, 7.4; N. 23.1%).

Deformylation of 4-*Anilino*-6-*chloropyrimidine*-5-*carbaldehyde*.—(i) The anilinopyrimidine (0.9 g) and ethanolic hydrogen chloride (30%; 20 ml) were heated under reflux for 3 h. The solution was evaporated to dryness under reduced pressure. Water (5 ml) was added and the resulting solid was filtered off and crystallised from propan-2-ol to yield 4-anilinopyrimidin-6(1*H*)-one (0.4 g), m.p. 248—250° (lit.,[18] 248—250°). The aqueous filtrate was basified with 2*N*-sodium hydroxide and a solid filtered off and crystallised from light petroleum (b.p. 60—80°) to yield 4-anilino-6-ethoxypyrimidine (0.2 g), m.p. 121—123° (lit.,[19] 122—123°).

(ii) 4-Anilino-6-chloropyrimidine-5-carbaldehyde (0.9 g) was treated with ethanolic hydrogen chloride (30%; 20 ml) at 20 °C for 2 weeks. The precipitate of 4-*anilino*-6-*ethoxypyrimidine hydrochloride* (0.5 g), m.p. 160—161°, was filtered off, washed with ethanol and dried (Found: C, 57.3; H, 5.6; N, 16.7. $C_{12}H_{14}ClN_3O$ requires C, 57.3; H, 5.6; N, 16.7%).

4,6-*Diamino*-2-*mercaptopyrimidine*.—Thiourea (0.76 g) and 3-imino-3-pyrrolidinopropiononitrile (1.37 g) were added to a solution of sodium (0.3 g) in absolute ethanol (15 ml) and the mixture was heated under reflux for 2½ h. The precipitated sodium salt was filtered off, dissolved in water (4 ml), and acidified with glacial acetic acid to yield the diaminopyrimidine (0.38 g), m.p. > 300°, identical with an authentic specimen.[20]

We thank Dr. O. Meth-Cohn for the ^{13}C n.m.r. spectrum and for discussion, Mrs. Ruth Maynard for mass spectral measurements, Mr. A. E. Cunliffe for pK_a values and u.v. spectra, and Miss S. Bogle for n.m.r. spectra. We also thank Allen and Hanburys Ltd. for financial support.

[5/1089—*Received*, 5*th June*, 1975]

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