Heterocyclic Studies. Part XXXIX.[1] Ring Cleavage of Some Pyrimidine Derivatives in Alkali

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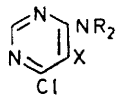
4-(Substituted amino)-6-chloropyrimidines bearing a mesomeric electron-withdrawing substituent such as NO_2, CN, CHO, or Ac at position 5 are cleaved by dilute sodium hydroxide, often at room temperature, to yield tetra-substituted olefins. Unlike acid-catalysed attacks on similar pyrimidines, the course of these basic reactions was not strongly influenced by steric interference between the 4(6)- and 5-substituents.

PREVIOUS papers [2-4] have described the ready ring cleavage of 5-substituted 4-chloro-6-dialkylaminopyrimidines (1) under acidic conditions. The ring-cleavage reactions, which gave highly substituted olefins (2), competed successfully with simple hydrolysis to pyrimidones (3) only if there was a bulky group at position 6(4) and a non-linear strongly electron-withdrawing group at position 5. For example high yields of complex olefins (2; X = NO_2, NR_2 = dialkylamino or cyclo-$N[CH_2]_n$) were obtained by treating 4-chloro-6-dialkylamino-5-nitropyrimidines (1; X = NO_2, NR_2 = dialkylamino or cyclo-$N[CH_2]_n$) with water, dilute acetic acid,



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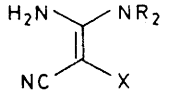

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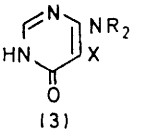

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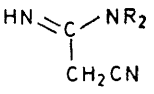

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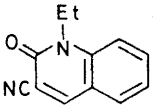

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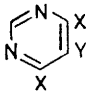

(6)

or dilute hydrochloric acid, but similar treatment of 6-chloro-4-alkylamino-5-nitropyrimidines (1; X = NO_2, NR_2 = NH-alkyl) gave mainly pyrimidones (3; X = NO_2, NR_2 = NH-alkyl). 5-Cyanopyrimidines (1; X = CN) gave pyrimidones (3; X = CN) whether the substituent was alkylamino or dialkylamino.[5]

We now show that many of the pyrimidines mentioned undergo ring cleavage under alkaline conditions, and that there are important differences in product patterns from those observed under acidic conditions.

4-Chloro-6-dialkylamino-5-nitropyrimidines (1; X = NO_2) were readily cleaved to olefins (2; X = NO_2) on stirring for 1—3 days at 25 °C with *ca.* 2 equiv. of dilute aqueous sodium hydroxide and, if necessary, a little ethanol or dioxan to aid dissolution. The products (Table) were identical with those obtained by cleavage under acidic conditions.[2] However the corresponding alkylaminopyrimidines (1; NR_2 = NH-alkyl, X = NO_2) and even the primary amino-compound (1; NR_2 = NH_2, X = NO_2) also gave the appropriate olefins (2) (Table) rather than the pyrimidones obtained under acidic conditions.[2]

It was clear that steric effects on the cleavages under basic conditions were different from those under acidic conditions, so the 5-cyanopyrimidines (1; X = CN), which had not given olefins under acidic conditions,[5] were treated with sodium hydroxide. Fairly good yields of a new series of dinitriles (2; X = CN) were obtained. The known [6] (diaminomethylene)malononitrile (2; X = CN, NR_2 = NH_2) was made in this way.

Ring cleavage under alkaline conditions also promised a route to formylolefins (2; X = CHO). Treatment of the appropriate dialkylaminopyrimidines (1; X = CHO) under acidic conditions did not give these compounds, except under special conditions, because they underwent such a ready acid-catalysed deformylation that cyanoacetamidine derivatives (4) were isolated instead.[3] We now report that, under alkaline conditions, the cleavages proceed readily to give good yields of formylolefins (2; X = CHO) without interference from deformylation. Furthermore the reactions succeed whether the 4(6)-substituent is dialkylamino, alkylamino, or amino. One useful compound obtained in this way was the *N*-ethylanilino-derivative (2; X = CHO, NR_2 = NEtPh). When treated with acid this olefin underwent deformylation, rather than cyclisation and hydrolysis to the quinolone (5), which had been one product of treatment of the parent pyrimidine (1; X = CHO, NR_2 = NEtPh) with acid.[1] This result rules out the possibility that the quinolone had been formed *via* the formylolefin (2; X = CHO, NR_2 = NEtPh).

Some 5-acetylpyrimidines (1; X = Ac, NR_2 = morpholino or NEtPh) were also synthesised and cleaved under alkaline conditions to the corresponding olefins (2; X = Ac, NR_2 = morpholino or NEtPh).

[1] Part XXXVIII, J. Clark and B. Parvizi, *J.C.S. Perkin I*, 1976, 131.
[2] J. Clark, I. Gelling, I. W. Southon, and M. S. Morton, *J. Chem. Soc.* (*C*), 1970, 494.
[3] J. Clark, B. Parvizi, and I. W. Southon, *J.C.S. Perkin I*, 1976, 125.
[4] J. Clark, M. Curphey, and I. W. Southon, *J.C.S. Perkin I*, 1974, 1611.
[5] M. S. Morton, Ph.D. Thesis, University of Salford, 1972.
[6] W. J. Middleton and U. A. Engelhardt, *J. Amer. Chem. Soc.*, 1958, **80**, 2788.

Few 5-acetylpyrimidines are known,[7] and the necessary intermediates *en route* to the desired compounds (1; X = Ac) proved troublesome to make. Treatment of 4,6-dihydroxypyrimidine with phosphoryl chloride and *NN*-dimethylacetamide, a method analogous to that used for 4,6-dichloropyrimidine-5-carbaldehyde [8] did not give 5-acetyl-4,6-dichloropyrimidine. Similarly 5-lithio-4,6-bismethylthiopyrimidine (6; X = SMe, Y = Li) did not yield a 5-acetyl derivative on treatment with *NN*-dimethylacetamide, although it had given a 5-formyl derivative (6; X = SMe, Y = CHO) with *NN*-dimethylformamide.[9] Finally 5-acetyl-4,6-dichloropyrimidine (6; X = Cl, Y = Ac) was synthesised by treating the corresponding formyl compound with methylmagnesium iodide and oxidising the resulting alcohol (6; X = Cl, Y = CHMe·OH) with manganese dioxide. The last step succeeded with manganese dioxide prepared by the method of Attenburrow *et al.*[10] but not with that prepared by the simpler method of Carpino.[11] The dichloro-compound was condensed with appropriate amines to give the desired pyrimidines (1; X = Ac, NR_2 = morpholino or NEtPh).

The mechanism of the alkaline ring cleavage reactions appears to be similar to that of acid-catalysed cleavages [2,3] except that it involves attack by a powerful nucleophile (OH^-) on a neutral molecule (Scheme), rather than attack by a weak nucleophile (*e.g.* H_2O) on a cation. The involvement of an anion is supported by the fact that a 5-substituent capable of accommodating a negative charge greatly assists the reaction. Thus 5-formyl, -acetyl, -nitro-, and -cyano-compounds which can form strongly resonance-stabilised anions [(7a) ⟷ (7b) ⟷ (7c)] were easily cleaved, but 5-chloro-, -bromo-, and -methyl compounds resisted cleavage even under much more severe conditions. The mechanism resembles that proposed for cleavage of some fused pyrimidine derivatives, for example 4-carboxymethylthio-6,7-diphenylpteridine, which also had features capable of stabilising an anion and a good leaving group in a suitable position.[12] A puzzling feature of the pyrimidine reactions is the fact that under acidic conditions the steric requirements of the 4(6)-amino-group and the 5-substituent are decisive in controlling the site of attack by the nucleophile water. As well as the hindered compounds we have described, the related enamine (8), which has considerable interaction between the 4(6)- and 5-substituents, underwent cleavage, under acidic conditions, to an olefin [(9) in that case], rather than hydrolysis to a pyrimidone.[13] Yet, in complete contrast, steric effects are relatively unimportant under

Ring cleavage of pyrimidines (1) to give olefins (2) *

NR_2 [in (1) and (2)]	X [in (1) and (2)]	Yield [of (2)]	M.p. (°C) [of (2)]	Isolation procedure *	Cryst. solvent	Found (%) for (2)			Required (%) for (2)			Lit. m.p. (°C) and ref.
						C	H	N	C	H	N	
NH_2	NO_2	77	>300 (decomp).	(a)	Pr^iOH	28.0	3.3	43.6	28.1	3.2	43.7	250 (decomp.) [2]
NHMe	NO_2	24	229—231	(b)	Pr^iOH							229—230 [2]
NHEt	NO_2	58	186—187	(a)	H_2O	38.5	5.4	35.6	38.5	5.1	35.9	166—168 [2]
Pyrrolidino	NO_2	50	177—178	(a)	H_2O							176—178 [2]
Piperidino	NO_2	62	193—194	(a)	Pr^iOH							184—186 [2]
Morpholino	NO_2	53	230—231	(a)	H_2O							230—231 [2]
NMe_2	NO_2	42	189—190	(b)	H_2O							190—191 [2]
NH_2	CHO	72	216 (decomp.)	(a)	H_2O	43.4	4.6	37.9	43.2	4.5	37.8	
NHMe	CHO	59	210—212	(a)	Pr^iOH	48.0	5.5	33.4	47.8	5.6	33.5	
NHEt	CHO	78	190—191	(a)	EtOH	51.6	6.6	30.6	51.8	6.5	30.2	
Pyrrolidino	CHO	63	162—163	(b)	EtOH–H_2O	58.3	6.2	24.3	58.2	6.7	24.5	
Piperidino	CHO	61	169—170	(a)	EtOH–H_2O	60.4	7.4	23.5	60.3	7.3	23.5	
Morpholino	CHO	63	214—216	(a)	Pr^iOH							210 (decomp.) [3]
NEtPh	CHO	95	188—189	(a)	EtOH	66.8	5.9	19.5	67.0	6.0	19.5	
NMe_2	CHO	77	114—115	(b)	LP†–EtOAc	51.9	6.4	30.4	51.8	6.5	30.2	
NHPh	CHO	71	149—150	(a)	EtOH–H_2O	64.3	4.6	22.4	64.2	4.8	22.6	
$NHCH_2Ph$	CHO	98	180—181	(a)	EtOH–H_2O	65.7	5.2	20.6	65.7	5.5	20.9	
$NHCH_2{\cdot}CH{:}CH_2$	CHO	60	102—103	(a)	EtOH–H_2O	55.6	5.9	27.8	55.6	6.0	27.8	
NH_2	CN	55	238—239	(a)	H_2O	44.6	3.7	51.6	44.4	3.7	51.9	236—238 [6]
Piperidino	CN	75	168—169	(a)	EtOH–H_2O	61.7	6.8	32.5	61.4	6.8	31.8	
NMe_2	CN	42	224—225	(c)	Pr^iOH	53.2	6.0	40.9	52.9	5.9	41.2	
Morpholino	Ac	93	132—133	(b)	LP†–EtOAc	55.3	6.4	21.8	55.4	6.7	21.5	
NEtPh	Ac	82	184—185	(a)	MeOH	68.3	6.6	18.4	68.1	6.6	18.3	

* See Experimental section. † Light petroleum (b.p. 60—80°).

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[8] W. Klötzer and M. Herberz, *Monatsh.*, 1965, **96**, 1567.
[9] M. P. L. Caton, M. S. Grant, D. L. Pain, and R. Slack, *J. Chem. Soc.*, 1965, 5467; M. S. Mehta, D. Miller, and E. F. Mooney, *ibid.*, p. 6695.
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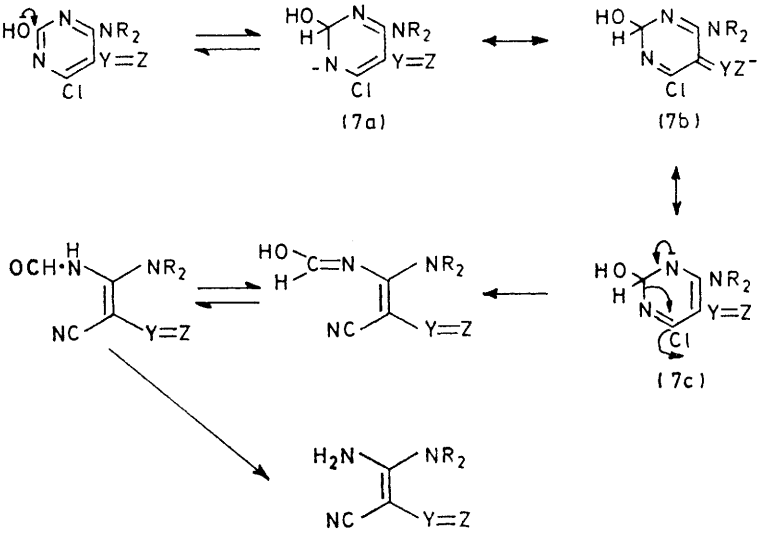
[11] L. A. Carpino, *J. Org. Chem.*, 1970, **35**, 3971.
[12] E. C. Taylor, R. J. Knopf, J. A. Cogliano, J. W. Barton, and W. Pfleiderer, *J. Amer. Chem. Soc.*, 1960, **82**, 6058; 1961, **83**, 2786.
[13] J. A. Montgomery and A. G. Laseter, *J. Heterocyclic Chem.*, 1972, **9**, 1077.

alkaline conditions. It seems that steric interactions may tilt the delicate balance between the competing cleavage and hydrolysis reactions under acidic conditions, when the nucleophile is water, by impeding formation of the Wheland intermediate which is essential for hydrolysis of the chloro-substituent.[2,3] However ring cleavage seems to be intrinsically favoured over hydrolysis of the chloro-substituent when the nucleophile is hydroxide ion. Examples of reactions of halogenopyrimidines with powerful nucleophiles at positions other than that occupied by the halogen atom are becoming more common. For example both 2- and 4-chloropyrimidines can give σ-complexes, *e.g.* (10)[14] and (11),[15] with amide ions in liquid ammonia, and many apparently simple substitution reactions of halogenopyrimidines also involve initial nucleophilic attack at an unsubstituted carbon atom.[16] Some ring cleavage also occasionally occurs.[17] Chloropteridines too can undergo nucleophilic attack at positions other than that occupied by the chlorine atom.[18]

One of the formylolefins (2; X = CHO, NR_2 = NMe_2) was treated with hydrazine to give a pyrazole (12), identical with an authentic specimen,[19] but on the whole the olefins were not very reactive.

The structures of the olefins (2) have been drawn in the geometrical form in which they would be expected to be produced by ring-cleavage. However, under the reaction conditions it is possible that they may adopt their most stable configurations which are not necessarily those shown.



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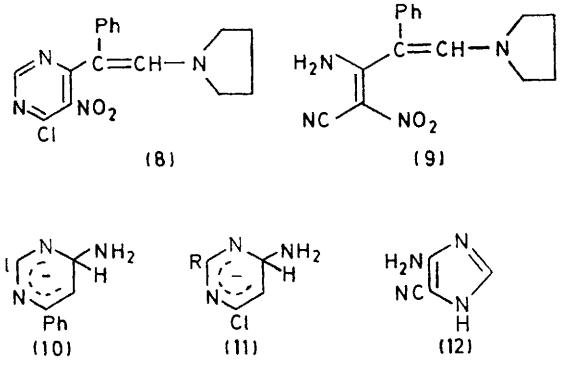

EXPERIMENTAL

4,6-Dichloro-5-(1-hydroxyethyl)pyrimidine.— 4,6-Dichloropyrimidine-5-carbaldehyde (22 g) in dry ether (200 ml) was added dropwise to a stirred solution of methylmagnesium iodide [from magnesium turnings (4.2 g) in dry ether (20 ml) and methyl iodide (22.4 g)] under nitrogen. After 2 h the mixture was filtered and the solid dissolved in aqueous 10% ammonium chloride. The solution was extracted with ether (2 × 100 ml) and the extract was washed twice with saturated aqueous sodium disulphite and then with water, dried ($MgSO_4$), and evaporated. The *product* (19.2 g) had m.p. 111—112° [from light petroleum (b.p. 60—80°)] (Found: C, 37.2; H, 3.2; N, 14.6. $C_6H_6Cl_2N_2O$ requires C, 37.3; H, 3.1; N, 14.5%).

5-Acetyl-4,6-dichloropyrimidine.— 4,6-Dichloro-5-(1-hydroxyethyl)pyrimidine (7 g), manganese dioxide (70 g), and methylene chloride (250 ml) were stirred for 3 days and then the mixture was filtered. The residue was thoroughly

[14] J. P. Geerts, H. C. Van der Plas, and A. Van Veldhuizen, *Rev. Trav. chim.*, 1973, **92**, 1232.
[15] P. J. Lont, H. C. Van der Plas, and A. Van Veldhuizen, *Rec. Trav. chim.*, 1973, **92**, 708.
[16] A. P. Kroon and H. C. Van der Plas, *Rec. Trav. chim.*, 1972, **91**, 1414; 1973, **92**, 145, 471, 1020; 1974, **93**, 227; J. de Valk, H. C. Van der Plas, and J. W. A. de Bode, *ibid.*, 1973, **92**, 442.
[17] H. C. Van der Plas and A. Koudijis, *Rev. Trav. chim.*, 1973, **92**, 711; J. de Valk and H. C. Van der Plas, *ibid.*, p. 471.
[18] J. Clark, *J. Chem. Soc.*, 1964, 4920.
[19] R. K. Robins, *J. Amer. Chem. Soc.*, 1956, **78**, 784.

extracted with methylene chloride and the combined filtrates were evaporated to yield the *product* (6.2 g), m.p. 90—91° [from light petroleum (b.p. 60—80°)] (Found: C, 37.6; H, 2.3; N, 14.6. $C_6H_4Cl_2N_2O$ requires C, 37.7; H, 2.1; N, 14.7%). The crude product, which contained a trace of starting material, was suitable for use in the following condensations.

5-Acetyl-4-chloro-6-morpholinopyrimidine.— Morpholine (0.46 g) was added to a solution of 5-acetyl-4,6-dichloropyrimidine (0.48 g) in dioxan (8 ml) and the mixture was stirred for 3 h. Water (3 ml) was added and the solution was extracted with chloroform (30 ml). The dried ($MgSO_4$) extract was evaporated under reduced pressure to yield the *product* (0.3 g), m.p. 79—80° [from light petroleum (b.p. 60—80°)] (Found: C, 50.0; H, 4.7; N, 17.6. $C_{10}H_{12}ClN_3O_2$ requires C, 49.7; H, 5.0; N, 17.4%).

5-Acetyl-4-chloro-6-N-ethylanilinopyrimidine.—5-Acetyl-4,6-dichloropyrimidine (3.84 g), benzene (30 ml), freshly distilled *N*-ethylaniline (2.42 g), and triethylamine (2.4 g) were heated under reflux for 5 h. The cooled mixture was washed with water, dried, and evaporated under reduced pressure to yield the *product* (4 g), m.p. 81—82° [from light petroleum (b.p. 60—80°)] (Found: C, 61.1; H, 4.8; N, 15.1. $C_{14}H_{14}ClN_3O$ requires C, 61.0; H, 5.1; N, 15.2%).

4-Amino-6-chloropyrimidine-5-carbonitrile.—Gaseous ammonia was passed through a solution of 4,6-dichloropyrimidine-5-carbonitrile (1.75 g) in benzene for 3 h, and the resulting precipitate was filtered off, washed with water, and crystallised from methanol to yield the *product* (1.2 g), m.p. 200° (decomp.) (Found: C, 38.6; H, 1.9; N, 36.3. $C_5H_3ClN_4$ requires C, 38.9; H, 1.9; N, 36.2%).

4-Chloro-6-piperidinopyrimidine-5-carbonitrile.— Piperidine (1 g) was adjusted to pH 8 with 4N-acetic acid and added dropwise to a stirred solution of 4,6-dichloropyrimidine-5-carbonitrile (1 g) in dioxan (10 ml) at 15—20 °C. After a further 3 h water (20 ml) was added and the resulting solid (1.05 g) was filtered off and crystallised from ethanol to yield the *product* (0.9 g), m.p. 54—55° (Found: C, 53.9; H, 4.6; N, 25.2. $C_{10}H_{11}ClN_4$ requires C, 53.9; H, 5.0; N, 25.2%).

4-Chloro-6-pyrrolidinopyrimidine-5-carbonitrile.— Pyrrolidine (0.41 g) was adjusted to pH 8 with glacial acetic acid and then added dropwise to a stirred solution of 4,6-dichloropyrimidine-5-carbonitrile (0.5 g) in dioxan (5 ml). After 4 h the mixture was poured onto crushed ice; the *product* was filtered off and crystallised from ethanol to give needles (0.5 g), m.p. 98—100° (Found: C, 52.0; H, 4.3; N, 27.2. $C_9H_9ClN_4$ requires C, 51.8; H, 4.3; N, 26.9%).

4-Chloro-6-dimethylaminopyrimidine-5-carbonitrile.— Aqueous dimethylamine (25%; 2.5 ml) was adjusted to pH 8 with glacial acetic acid and condensed with 4,6-dichloropyrimidine-5-carbonitrile by the procedure described in the previous preparation. The *product* (0.45 g) had m.p. 107—108° [from light petroleum (b.p. 60—80°)] (Found: C, 46.1; H, 3.9; N, 30.7. $C_7H_7ClN_4$ requires C, 46.1; H, 3.9; N, 30.7%).

Ring Cleavage of Pyrimidines.—The appropriate pyrimidine (1; X = CHO, Ac, NO_2, or CN) (0.01 mol. equiv.), water (20—30 ml), and 2N-sodium hydroxide (10 ml), together with a little dioxan or ethanol to aid partial dissolution if necessary, were stirred at *ca.* 25 °C for 18—72 h. In one case (I; X = CHO, NR_2 = NHMe) the mixture was heated to 60 °C for 2 h, but the lowest practicable temperature usually gave the best results. Each product was isolated by one of the following methods: (*a*) filtration and recrystallisation from a suitable solvent, (*b*) by extraction with chloroform, continuous if necessary, from the neutralised aqueous solution, (*c*) evaporation of the aqueous solution under reduced pressure and extraction of the residue with propan-2-ol. Details of the products are given in the Table.

4-Aminopyrazole-3-carbonitrile.— 3-Amino-3-dimethylamino-2-formylacrylonitrile (0.7 g), ethanol (15 ml), and hydrazine hydrate (0.25 g) were heated under reflux for 12 h. Insoluble matter was filtered off and the solution evaporated to dryness and triturated with water. The solid was filtered off and crystallised from water to give 4-aminopyrazole-3-carbonitrile (0.2 g), m.p. 173—174° (lit.,[19] 174—175°).

[5/2312 *Received*, 27*th November*, 1975]