Heterocyclic Studies. Part XXXI.[1] New Routes to Reduced Imidazole, Pyrimidine, and Pyridopyrimidine Derivatives

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Treatment of 4-(substituted amino)-6-chloro-5-nitropyrimidines (4-substituents *N*-ethylanilino, hexamethyleneamino, *N*-methyl-2-hydroxyethylamino, 2-hydroxyethylamino, allylamino, and benzylamino) with dilute acetic acid gave corresponding 3-(substituted amino)-3-amino-2-nitroacrylonitrile derivatives. Cyclisation of 4-(*N*-alkyl-2-chloroethylamino)-6-chloro-5-nitropyrimidines gave imidazopyrimidines which were immediately cleaved to give dihydroimidazoles with a 2-[cyano(nitro)methylene] substituent. Similarly 4-(*N*-alkyl-3-hydroxypropylamino)-pyrimidines gave pyrimidopyrimidines which were cleaved to give reduced pyrimidines. Hexahydropyridopyrimidines were obtained in analogous fashion from 4-[2-(2-hydroxyethyl)piperidino]pyrimidines. Mechanisms of the ring-cleavage reactions are discussed.

PYRIMIDINE ring-cleavage reactions are mechanistically interesting and also useful in synthesis. Such reactions may involve, for example, photolysis,[2] hydrogenolysis,[3] or nucleophilic attack.[4,5] Transformations of pyrimidines into pyrazoles,[6] imidazoles,[7] triazines,[8] triazoles,[9] and pyridines [10] have been observed.

The ready ring-cleavage of some 4-(substituted amino)-6-chloro-5-nitropyrimidines (1) to give substituted olefins (6) [4] has now been extended to throw more light on the mechanism and adapted to the synthesis of reduced

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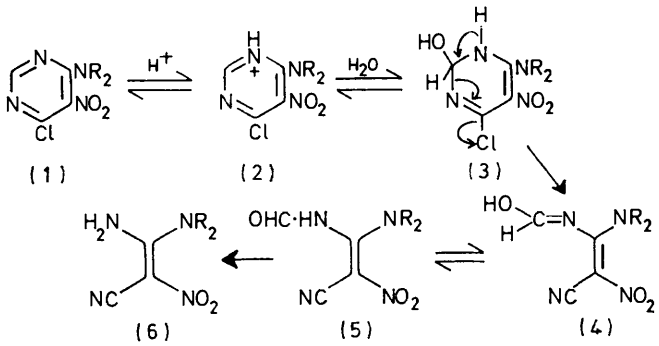
imidazoles (9) and (11), pyrimidines (12), and pyridopyrimidines (14).

4-Chloro-6-(*N*-ethylanilino)-5-nitropyrimidine (1; NR_2 = NEtPh) was readily cleaved under acidic conditions to give the novel arylaminoacrylonitrile (6; NR_2 = NEtPh). The corresponding benzylamino- and hexamethyleneamino-pyrimidines (1; NR_2 = $NHCH_2Ph$ or $[CH_2]_6N$) similarly gave the acrylonitriles (6; NR_2 = $NHCH_2Ph$ or $N[CH_2]_6$).

4,6-Dichloro-5-nitropyrimidine was condensed with 2-aminoethanol, 2-methylaminoethanol, and allylamine to give the pyrimidines (1; NR_2 = $NH{\cdot}[CH_2]_2{\cdot}OH$, $NMe{\cdot}[CH_2]_2{\cdot}OH$, or $NH{\cdot}CH_2{\cdot}CH{:}CH_2$), which were cleaved to give the corresponding acrylonitriles (6) containing additional functional groups suitable for further reactions. Those 4-(substituted amino)-6-chloro-5-nitropyrimidines (1) which are secondary amines normally give mixtures of acrylonitrile derivatives (6) and pyrimidones (7) on treatment with hot hydrochloric or acetic acid.[4] However, we have obtained acrylonitriles free from pyrimidones in one step from 4,6-dichloro-5-nitropyrimidine by treatment of the latter with the relevant amine in dioxan and then diluting the reaction mixture with water and leaving it in the cold for several days until the acrylonitrile (6; NR_2 = $NH{\cdot}[CH_2]_2{\cdot}OH$, $NH{\cdot}CH_2{\cdot}CH{:}CH_2$, or $NHCH_2Ph$) separated.

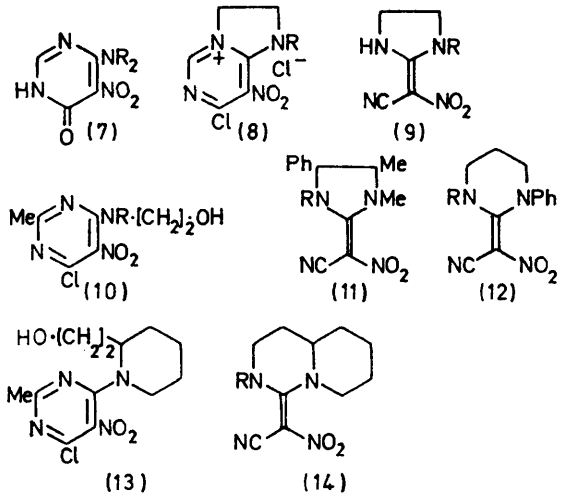
The suggested mechanism for the ring-cleavage reactions (Scheme) involves attack of a water molecule



SCHEME

on the cation (2) to give an intermediate (3) which cleaves to give a formylamino-compound [(4) ⇌ (5)].[4] We therefore expected that quaternisation of the 3-nitrogen atom of pyrimidines (1) would eliminate the need for acid catalysis and lead to compounds which would be very readily cleaved under neutral conditions. This proved to be the case and a method of producing novel reduced heterocycles was thus discovered.

For example, the reduced imidazole (9; R = Me) was prepared, presumably *via* the quaternary salt (8), by treating the 4-(*N*-methyl-2-hydroxyethylamino)-pyrimidine (1; NR_2 = $NMe{\cdot}[CH_2]_2{\cdot}OH$) with phosphoric trichloride, removing the solvent, and adding cold water. The occurrence of ring cleavage was revealed by the i.r. spectrum of the product, which showed $\nu_{max.}$ 2240 (CN) and 3350 cm^{-1} (NH) and the mass spectrum (M^+ 168; no chlorine isotope pattern). Cyclisation and cleavage proceeded so readily that a methyl group in the 2-position of the pyrimidine ring did not prevent the



latter reaction; consequently the imidazoles (9; R = Me or Ph) also resulted from treatment of the 2-methylpyrimidines (10; R = Me or Ph) with phosphoric trichloride.

The bischloroethylaminopyrimidine [1; NR_2 = $N(CH_2{\cdot}CH_2Cl)_2$] underwent cyclisation and ring cleavage to yield the imidazole (9; R = $CH_2{\cdot}CH_2Cl$). A low yield of the latter was obtained even when this cyclisation and cleavage was carried out in acetate buffer, a reagent which had prevented cleavage of simple dialkylaminopyrimidines (1) by preventing formation of the cations (2). This supports the suggestion that quaternisation to give a cation (8) obviates the need for acid catalysis. Further confirmation of the suggested reaction pathways was provided by the isolation of *N*-acylimidazole intermediates. Thus condensation of 4,6-dichloro-5-nitropyrimidine with ephedrine gave the expected pyrimidine (1; NR_2 = $NMe{\cdot}CHMe{\cdot}CHPh{\cdot}OH$) which, with phosphoric trichloride and then water, gave a formylimidazole (11; R = CHO). This confirmed that cleavage occurred at what had been the 1,2-bond in the original pyrimidine.

Treatment of an *N*-(3-hydroxypropyl)anilino-compound (1; NR_2 = $NPh{\cdot}[CH_2]_3{\cdot}OH$) with phosphoric trichloride and then water gave a hexahydropyrimidine (12; R = H) and its formyl derivative (12; R = CHO). In a similar fashion the hydroxyethylpiperidinopyrimidine (13) gave an octahydropyrido[1,2-*c*]pyrimidine (14; R = Ac).

Products [*e.g.* (14; R = Ac)] which still contained the original 2-carbon atom in a formyl or an acetyl group were so readily deacylated that they were only isolable when the acyl group was attached to a six-membered ring [*e.g.* in (12) or (14)] or had an adjacent substituent [*e.g.* in (11)]. Steric hindrance to hydrolysis may provide stability in these cases.

The examples studied show that 4-chloro-5-nitropyrimidines carrying a 6-hydroxyalkylamino-substituent

can be cyclised and readily cleaved to give a variety of reduced mono- and poly-cyclic heterocycles which may be difficult to synthesise in other ways.

EXPERIMENTAL

4-Chloro-6-N-ethylanilino-5-nitropyrimidine.—Freshly distilled *N*-ethylaniline (6 ml) was added dropwise to a stirred solution of 4,6-dichloro-5-nitropyrimidine (4·85 g) in dioxan (40 ml) at 15—20°. After a further 3 h water (120 ml) was added and the bright yellow *amine* (5·4 g), m.p. 119—120°, was filtered off and crystallised from propan-2-ol (Found: C, 51·7; H, 4·0; N, 20·1. $C_{12}H_{11}ClN_4O_2$ requires C, 51·7; H, 4·0; N, 20·1%).

4-Chloro-6-(N-2-hydroxyethylanilino)-2-methyl-5-nitropyrimidine.—4,6-Dichloro-2-methyl-5-nitropyrimidine (3·0 g) was similarly condensed with 2-anilinoethanol (4·1 g) in dioxan (25 ml) to yield the *amine* (4·7 g), m.p. 101—102° (from ethanol) (Found: C, 50·5; H, 4·5; N, 18·2. $C_{13}H_{13}ClN_4O_3$ requires C, 50·6; H, 4·2; N, 18·2%).

4-Chloro-6-hexamethyleneamino-5-nitropyrimidine.—Hexamethyleneamine (6·53 g) was neutralised with 5N-acetic acid and condensed with 4,6-dichloro-5-nitropyrimidine (5·28 g) in dioxan (35 ml) as described above. The *product* (7·24 g) had m.p. 91—92° (from propan-2-ol) (Found: C, 46·5; H, 5·0; N, 22·0. $C_{10}H_{13}ClN_4O_2$ requires C, 46·8; H, 5·1; N, 21·8%).

4-Chloro-6-(N-methyl-2-hydroxyethylamino)-5-nitropyrimidine.—2-Methylaminoethanol (8·8 ml) was neutralised with glacial acetic acid and condensed with 4,6-dichloro-5-nitropyrimidine (9·7 g) in dioxan (50 ml). The mixture was diluted with water (150 ml) and extracted with chloroform (3 × 45 ml). The dried extract was evaporated and the residue crystallised from benzene–light petroleum (b.p. 40—60°) to give the *amine* (8·9 g), m.p. 80—82° (Found: C, 36·2; H, 3·95; N, 24·6. $C_7H_9ClN_4O_3$ requires C, 36·1; H, 3·9; N, 24·1%).

4-Chloro-2-methyl-6-(N-methyl-2-hydroxyethylamino)-5-nitropyrimidine.—2-Methylaminoethanol (3·0 g) in water (5 ml) was neutralised with glacial acetic acid and added during 20 min to a stirred solution of 4,6-dichloro-2-methyl-5-nitropyrimidine (4·1 g) in dioxan (20 ml). After a further 2 h water (100 ml) was added and the *product* (3·3 g), m.p. 96—97° (from aqueous methanol), was filtered off (Found: C, 38·7; H, 4·7. $C_8H_{11}ClN_4O_3$ requires C, 38·95; H, 4·5%).

4-Chloro-6-(N-methyl-β-hydroxy-α-methylphenethylamino)-5-nitropyrimidine.—Ephedrine (1·75 g) in methanol (5 ml) was added during 20 min to a stirred solution of 4,6-dichloro-5-nitropyrimidine (0·97 g) in methanol (15 ml) which was kept at 0°. After a further 1 h water (30 ml) was added and the precipitate was filtered off, dried, and crystallised from benzene–light petroleum (b.p. 60—80°) to yield the *product*, m.p. 134—135° (Found: C, 51·9; H, 4·8; N, 17·8. $C_{14}H_{15}ClN_4O_3$ requires C, 52·1; H, 4·7; N, 17·4%).

4-Chloro-6-[2-(2-hydroxyethyl)piperidino]-2-methyl-5-nitropyrimidine.—A solution of 2-piperidinoethanol (0·65 g) and triethylamine (0·55 g) in ether (5 ml) was added, during 20 min, to a stirred solution of 4,6-dichloro-2-methyl-5-nitropyrimidine (1 g) in ether (15 ml). After a further 1 h the precipitate was filtered off and washed with water to yield the *product* (0·9 g), m.p. 145—146° (from propan-2-ol) (Found: C, 47·7; H, 5·6. $C_{12}H_{17}ClN_4O_3$ requires C, 47·9; H, 5·7%).

4-Chloro-6-[N-(3-hydroxypropyl)anilino]-5-nitropyrimidine.—3-Anilinopropan-1-ol (3 g) in ethanol (10 ml) was added during 20 min to a stirred solution of 4,6-dichloro-5-nitropyrimidine (1·95 g) in ether (20 ml). After a further 1 h, water (10 ml) was added and the ethereal layer was separated, dried ($MgSO_4$), and evaporated to dryness. The residue was crystallised from benzene–light petroleum (b.p. 60—80°) to yield the *amine* (1 g), m.p. 81—83° (Found: C, 50·8; H, 4·2; N, 17·9. $C_{13}H_{13}ClN_4O_3$ requires C, 50·6; H, 4·2; N, 18·15%).

4-(Bis-2-chloroethylamino)-6-chloro-5-nitropyrimidine.—Bis-2-chloroethylamine hydrochloride (1·8 g) in methanol (5 ml) was added during 20 min to a stirred solution of 4,6-dichloro-5-nitropyrimidine (1·9 g) and anhydrous sodium acetate (2 g) in methanol (25 ml). After a further 1 h water was gradually added to precipitate the amine (1·2 g), which was used without further purification.

Ring-cleavage of Simple Tertiary Amines.—The appropriate 4-(substituted amino)-6-chloro-5-nitropyrimidine was heated with glacial acetic acid and water for 3 h and the mixture was then evaporated to dryness. The residue was treated with water and the acrylonitrile derivative was filtered off and recrystallised if necessary. Reactants and results were as follows. Pyrimidine (1; NR_2 = NEtPh) (1 g), acetic acid (14 ml), and water (30 ml) gave *3-amino-3-N-ethylanilino-2-nitroacrylonitrile* (6; NR_2 = NEtPh) (0·59 g), m.p. 174° (Found: C, 56·8; H, 5·3; N, 24·1%; M^+, 232. $C_{11}H_{12}N_4O_2$ requires C, 56·9; H, 5·2; N, 24·1%; *M*, 232). Pyrimidine (1; NR_2 = $[CH_2]_6N$) (2·5 g), acetic acid (13·5 ml), and water (13·5 ml) gave *3-amino-3-hexamethyleneamino-2-nitroacrylonitrile* (1·55 g), m.p. 170—171° (from water) (Found: C, 51·8; H, 6·5; N, 26·4. $C_9H_{14}N_4O_2$ requires C, 51·4; H, 6·7; N, 26·65%). Pyrimidine (1; NR_2 = $NMe\cdot[CH_2]_2\cdot OH$) (0·9 g), acetic acid (2·5 ml), and water (4·5 ml) gave *3-amino-3-(N-methyl-2-hydroxyethylamino)-2-nitroacrylonitrile* (0·15 g), m.p. 126—127° (from propan-2-ol) (Found: C, 39·2; H, 5·5; N, 29·9. $C_6H_{10}N_4O_3$ requires C, 38·7; H, 5·4; N, 30·1%).

3-Amino-3-(2-hydroxyethylamino)-2-nitroacrylonitrile.— 2-Aminoethanol (0·67 g) was adjusted to pH 8 with 5N-acetic acid and added dropwise to a stirred solution of 4,6-dichloro-5-nitropyrimidine (0·97 g) in dioxan (15 ml) at 20°. After a further 4 h water (100 ml) was added and the mixture was kept for 7 days in an open vessel. The *acrylonitrile derivative* (0·3 g) which separated had m.p. 193—194° (from water) (Found: C, 34·7; H, 4·4; N, 31·8%; M^+, 172. $C_5H_8N_4O_3$ requires C, 34·9; H, 4·7; N, 32·55%; *M*, 172).

3-Allylamino-3-amino-2-nitroacrylonitrile.— Allylamine (1·42 g) was similarly neutralised and condensed with the dichloropyrimidine (1·94 g) in dioxan (35 ml) at 15—20°. Water (120 ml) was added, followed by sufficient dioxan to redissolve a little oil which had separated. After 3 days the volume was reduced to about one quarter under reduced pressure. After a further 3 days the *acrylonitrile derivative* (0·37 g), m.p. 136—138°, was filtered off (Found: C, 42·3; H, 4·5; N, 32·7%; M^+, 168. $C_6H_8N_4O_2$ requires C, 42·85; H, 4·8; N, 33·3%; *M*, 168).

3-Amino-3-benzylamino-2-nitroacrylonitrile.— 4-Benzylamino-6-chloro-5-nitropyrimidine (2 g) was dissolved in dioxan (*ca.* 105 ml) and water (*ca.* 105 ml) so that a clear solution was obtained. After 14 days the mixture was evaporated, under reduced pressure, to about 60 ml and the *acrylonitrile derivative* (1·05 g), m.p. 163—164° (from water), was filtered off. Dissolution of the material in 12 parts of 0·5N-sodium hydroxide and reprecipitation with glacial acetic acid did not increase the m.p. (Found: C, 55·6; H,

5·0%; M^+, 218. $C_{10}H_{10}N_4O_2$ requires C, 55·0; H, 4·6%; M, 218).

Chlorination, Cyclisation, and Ring-cleavage of 4-Chloro-6-(2-chloroethylamino)-5-nitropyrimidines.—The appropriate 4-chloro-6-(2-hydroxyethylamino)-derivative (2 g) was dissolved in phosphoric trichloride (15 ml) and kept at 20° for 18 h. The solvent was removed under reduced pressure and the residue dissolved in cold water. The *product* usually crystallised slowly; if not, it was isolated by chloroform extraction. In the case of 4-chloro-6-(*N*-3-hydroxypropylanilino)-5-nitropyrimidine the aqueous solution deposited some 1-formylpyrimidine (12; R = CHO) first and then, after several days, some deformylated compound (12; R = H); for products and yields see Table.

1-Cyano(nitro)methylene-2,3,4,4a,5,6,7,8-octahydro-1H-pyrido[1,2-c]pyrimidine (14; R = H) *Hydrochloride.*—2-Acetyl-1-cyano(nitro)methylene-2,3,4,4a,5,6,7,8-octahydro-1*H*-pyrido[1,2-*c*]pyrimidine (0·3 g) was heated under reflux with 5N-hydrochloric acid (5 ml) for 15 min. The solution was evaporated to dryness under reduced pressure and the residue triturated with propan-2-ol. The hydrochloride of the *deacetylated compound* (0·1 g) had m.p. 190—192° (from ethanol) (see Table for analysis).

1-(2-Chloroethyl)-2-cyano(nitro)methylene-2,3,4,5-tetrahydroimidazole.—(*a*) 4-Chloro-6-(bis-2-chloroethylamino)-5-nitropyrimidine (0·4 g) was heated under reflux with water (10 ml) for 5 min; the mixture was then cooled and filtered. The *imidazole* (0·15 g) was obtained as fine brown needles which gradually decomposed above 125°; m.p. 138—139° (Found: C, 38·7; H, 4·2; N, 25·6. $C_7H_9ClN_4O_2$ requires C, 38·8; H, 4·2; N, 25·9%).

(*b*) The same pyrimidine (0·7 g), anhydrous sodium acetate (1 g), glacial acetic acid (6 ml), and water (2 ml) were heated under reflux for 5 min. Insoluble matter was filtered off and the filtrate was evaporated to dryness. The residue was crystallised from water to yield the imidazole (0·054 g).

Chlorination, cyclisation, and ring-cleavage of 4-chloro-6-(2-hydroxyethylamino)pyrimidines *

	Product										
						Found (%)			Required (%)		
Starting pyrimidine	Structure	Yield (%)	M.p. (°C)	Cryst. solvent	Formula	C	H	N	C	H	N
(1; NR_2 = NMe·$[CH_2]_2$·OH)	(9; R = Me)	38	216—218	Me_2N·CHO–H_2O	$C_6H_8N_4O_2$	42·7	4·7	33·6	42·9	4·8	33·3
(10; R = Me)	(9; R = Me)	60	216—218	Me_2N·CHO–H_2O							
(10; R = Ph)	(9; R = Ph)	40	174—175	MeOH–H_2O	$C_{11}H_{10}N_4O_2$	57·7	4·7	24·2	57·4	4·4	24·3
(1; NR_2 = NPh·$[CH_2]_3$·OH)	(12; R = CHO)	69 †	209—210	Me_2N·CHO–H_2O	$C_{13}H_{12}N_4O_3$	57·2	4·8		57·3	4·4	
(1; NR_2 = NPh·$[CH_2]_3$·OH)	(12; R = H)	15 †	198—199		$C_{12}H_{12}N_4O_2$	58·5	5·0		59·0	5·0	
(1; NR_2 = NMe·CHMe·CHPh·OH)	(11; R = CHO)	68	170—172	EtOH	$C_{14}H_{14}N_4O_3$	58·2	4·9	19·6	58·7	4·9	19·6
(13; R = Me)	(14; R = Ac)	59	173—174		$C_{12}H_{16}N_4O_3$	54·2	5·9	20·9	54·5	6·1	21·2
	(14; R = H) ‡		190—192	EtOH	$C_{10}H_{14}N_4O_2$,HCl	46·4	6·2		46·4	5·8	

* See Experimental section for reaction conditions. † From the same experiment (see Experimental section). ‡ Hydrochloride. By hydrolysis of the acetyl derivative (see Experimental section).

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