Heterocyclic Studies. Part XXXIII.[1] Cleavage of 1,3-Dimethylpyrimido-[4,5-*d*]pyrimidine-2,4(1*H*,3*H*)-dione by Nucleophiles

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

Primary amines reacted with 1,3-dimethylpyrimido[4,5-*d*]pyrimidine-2,4(1*H*,3*H*)-dione to yield 5-alkyliminomethyl-6-amino-1,3-dimethyluracil derivatives. Hydrazine, 1,1-dimethylhydrazine, and hydroxylamine reacted in analogous fashion to give the hydrazone, dimethylhydrazone, and oxime, respectively, of 6-amino-5-formyl-1,3-dimethyluracil. Secondary and tertiary amines and methoxyamine failed to cleave the pyrimidopyrimidine.

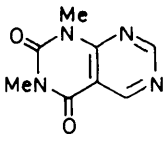
RING cleavage of bicyclic fused pyrimidine derivatives has been widely studied. It is of interest in connection with biologically significant systems such as pteridines [2] and purines [3] and in correlating the reactions of heterocyclic systems with their electronic structures. When compounds which have a pyrimidine ring fused to another cyclic system are attacked by nucleophiles it is usually the pyrimidine ring which is cleaved first, often at its highly polarised '3,4-bond'. For example pyrimidine ring cleavage by hydrazine occurs in quinazolines,[4] pteridines,[5] pyrazolopyrimidines,[6] thiadiazolopyrimidines,[7] triazolopyrimidines,[8] and pyridopyrimidines.[9] Less commonly nucleophilic attack opens the other ring, as in some pyranopyrimidines,[10] pyrimidooxazepines,[11] and purines,[12] and occasionally either ring may be cleaved, as has been shown for certain pteridines.[13]

We now describe the effect of nucleophiles on 1,3-dimethylpyrimido[4,5-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (1). The 1,3-dimethylpyrimidine-2,4-(1*H*,3*H*)-dione system is known to be susceptible to cleavage by nucleophiles, as in, for example, 1,3-dimethyl-lumazines [14] (2), and the unsubstituted pyrimidine ring can also be cleaved readily, as in, for example, pteridine.[15] It was of interest therefore to see which ring underwent cleavage in the pyrimidopyrimidine (1).

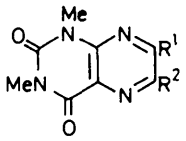
The pyrimidopyrimidine (1) did not react with refluxing ethanolic solutions of isopropylamine or butylamine during 2 days, but it was cleaved when heated, without solvent, with these or other amines (benzylamine, cyclohexylamine, or allylamine) at 100° for 24 h. The products (Table 1) were assigned structures (3) on the basis of ^{1}H n.m.r. spectra (Table 2), which showed that

[1] Part XXXII, J. Clark and I. W. Southon, preceding paper.
[2] *E.g.* H. Wieland, H. Metzger, C. Schöpf, and M. Bülow, *Annalen*, 1933, **507**, 226; C. Schöpf, E. Becker, and R. Reichert, *ibid.*, 1939, **539**, 156.
[3] *E.g.* H. Biltz and H. Rakett, *Ber.*, 1928, **61**, 1409; L. F. Cavalieri, J. F. Tinker, and G. B. Brown, *J. Amer. Chem. Soc.*, 1949, **71**, 3973; J. Liebig and F. Wöhler, *Annalen*, 1838, **26**, 285; E. Fischer, *Ber.*, 1897, **30**, 219.
[4] N. J. Leonard and D. Y. Curtin, *J. Org. Chem.*, 1947, **11**, 341; N. J. Leonard and W. V. Ruyle, *ibid.*, 1948, **13**, 903.
[5] E. C. Taylor in 'Chemistry and Biology of Pteridines,' eds. G. E. W. Wolstenholme and M. P. Cameron, Churchill, London, 1953, p. 2.
[6] H. Bredereck, F. Effenberger, and W. Resemann, *Angew. Chem.*, 1962, **74**, 253; B. M. Lynch and A. J. Robertson, *J. Heterocyclic Chem.*, 1965, **2**, 112.
[7] Y. F. Shealy and J. D. Clayton, *J. Org. Chem.*, 1963, **28**, 1491.
[8] F. Baumbach, H. G. Henning, and G. Hilgetag, *Z. Chem.*, 1962, **12**, 369; K. Shirakawa, *Yakugaku Zasshi*, 1958, **78**, 1395; H. Gehlen and B. Simon, *Arch Pharm.*, 1970, **303**, 513.
[9] M. Ridi and S. Checchi, *Ann. Chim. (Italy)*, 1957, **47**, 728; J. Biggs and P. Sykes, *J. Chem. Soc.*, 1959, 1849; W. J. Irwin and D. G. Wibberley, *ibid.*, 1965, 4240; I. R. Gelling and D. G. Wibberley, *Chem. Comm.*, 1969, 931.
[10] A. G. Ismail and D. G. Wibberley, *J. Chem. Soc.* (*C*), 1968, 2706.
[11] A. A. Santilli, D. H. Kim, and S. V. Wanser, *J. Heterocyclic Chem.*, 1972, **9**, 309.
[12] A. Albert and D. J. Brown, *J. Chem. Soc.*, 1954, 2060; W. Pfleiderer and F. Sagi, *J. Amer. Chem. Soc.*, 1958, **80**, 3899.
[13] J. Clark and G. Neath, *J. Chem. Soc.* (*C*), 1966, 1112; 1968, 919; J. Clark, C. Smith and G. Neath, *ibid.*, 1967, 1297.
[14] J. Clark and C. Smith, *J.C.S. Perkin I*, 1972, 247.
[15] A. Albert and H. Yamamoto, *J. Chem. Soc.* (*C*), 1968, 2289.

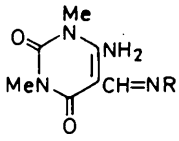
both methyl groups survived and the unsubstituted pyrimidine ring was destroyed. I.r. spectra showed ν_{NH} bands for the NH_2 groups at about 3300 cm^{-1} and



(1)

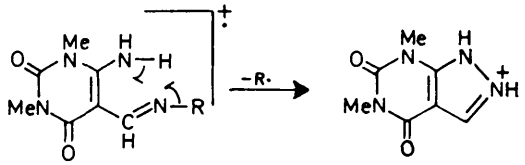


(2)



(3)

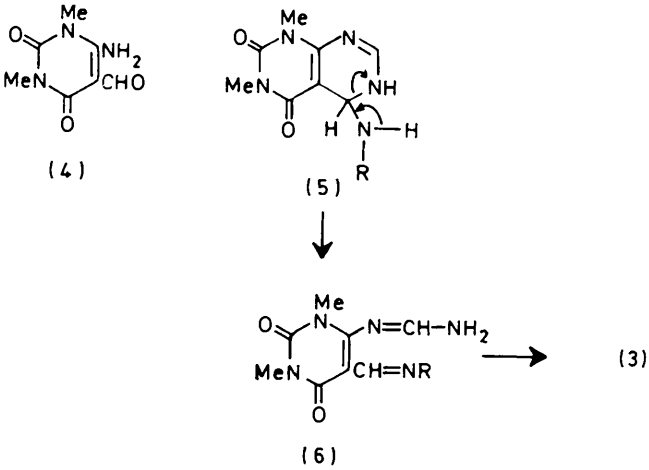
$\nu_{C=O}$ bonds at about 1710 and 1620 cm^{-1}. Mass spectra included appropriate molecular ions (*a*) and all showed a common important fragment ion at *m/e* 181 $[(M - R)^+]$ which probably has the pyrazolopyrimidine structure (*b*).



(*a*) (*b*)

Heating the pyrimidopyrimidine (1) with *aqueous* solutions of ethylamine or methylamine gave oily mixtures, probably because the primary products (3; R = Et or Me) are partly hydrolysed to the formyl derivative (4), which undergoes condensation reactions. The pyrimidopyrimidine (1) was much more stable towards secondary amines. For example it was unchanged after being heated with diethylamine at 100 °C for 24 h.

Final proof of the structures of the cleavage products (3; R = $[CH_2]_5CH{\cdot}NH$ or $PhCH_2{\cdot}NH$) was provided by



(4) (5) (6) (3)

synthesising them from 6-amino-5-formyl-1,3-dimethylpyrimidine-2,4(1*H*,3*H*)-dione (4) and the appropriate amine.

Hydrazine, which cleaves the dimethylpyrimidinedione ring of lumazines [*e.g.* (2; $R^1 = R^2 = H$)], attacked the unsubstituted ring of compound (1) at 20° to yield the hydrazone (3; R = NH_2) of a 5-formylpyrimidine. The presence of the free terminal NH_2 group of the hydrazone was demonstrated by treatment with acetone and benzaldehyde to give isopropylidene and benzylidene derivatives (3; R = N:CMe_2 or N:CHPh). 1,1-Dimethylhydrazine reacted less readily with the pyrimidopyrimidine (1) but after 48 h at reflux gave an analogous product (3; R = NMe_2) which did not react with acetone or benzaldehyde. The oxime (3; R = OH) was obtained by treating the pyrimidopyrimidine (1) with aqueous 2M-hydroxylamine at pH 6 and 70—80° for 5 days, but similar treatment with methoxyamine left the starting material (1) unchanged. The structure of the hydrazone (3; R = NH_2) was confirmed by synthesis from the formyl compound (4).

Thus the unsubstituted pyrimidine ring is much more susceptible to attack at its highly polarised 5,6-bond than is the substituted ring at its polarised 2- and 4-carbonyl groups. The mechanism obviously parallels those of similar cleavages [16] in giving an adduct (5) followed by an amidine (6) which is degraded to the final product (3). There was no evidence for cleavage of the dione system, consistent with the much milder conditions necessary for cleavage of the pyrimidopyrimidine (1) than of the dione system of the lumazine (2; $R^1 = R^2 = H$).[14]

EXPERIMENTAL

Ring Cleavage of 1,3-*Dimethylpyrimido*[4,5-d]*pyrimidine*-2,4(1H,3H)-*dione by Amines*.—The pyrimidopyrimidine (0·2 g) and the appropriate amine (5 ml) were heated in a sealed tube at 100° for 2 h. The mixture was evaporated to dryness under reduced pressure and the product crystallised from a suitable solvent (Table 1).

Alternatively the pyrimidopyrimidine and the amine were heated on a boiling water-bath for 24 h and the product was worked up similarly.

6-*Amino*-5-*benzyliminomethyl*-1,3-*dimethyluracil* (3; R = $PhCH_2$).—6-Amino-5-formyl-1,3-dimethyluracil [17] (0·5 g), benzylamine (1 g), and benzene (20 ml) were heated under reflux for 1 h. Insoluble matter was filtered from the hot solution and the azomethine (0·25 g), m.p. 167—168°, crystallised from the cooled solution. It was identical with that obtained previously (Table 1).

6-*Amino*-5-*cyclohexyliminomethyl*-1,3-*dimethyluracil* (3; R = $[CH_2]_5CH$).—The 5-formyluracil (0·5 g) and cyclohexylamine (1 g) were heated under reflux in ethanol (10 ml); the product (0·35 g), m.p. 171—173°, isolated as in the previous experiment, was identical with that obtained before (Table 1).

6-*Amino*-5-*formyl*-1,3-*dimethyluracil Hydrazone*(3; R = NH_2).—(*a*) The pyrimidopyrimidine (1) (0·4 g) was suspended in hydrazine hydrate (8 ml) and stirred at 20° for 24 h. The *product* (0·4 g), m.p. >300°, was filtered off and crystallised from ethanol (Found: C, 42·6; H, 5·6; N, 35·7%; M^+, 197. $C_7H_{11}N_5O_2$ requires C, 42·7; H, 5·6; N, 35·5%; *M*, 197).

(*b*) The pyrimidopyrimidine (1) (0·4 g) and hydrazine hydrate (8 ml) were heated on a steam-bath for 3 h to yield the hydrazone (0·22 g), m.p. >300°.

(*c*) 6-Amino-5-formyl-1,3-dimethyluracil (0·5 g), hydrazine hydrate (0·5 g), and ethanol (10 ml) were stirred at 20° for

[16] W. L. F. Armarego, *J. Chem. Soc.*, 1962, 4094.
[17] W. Pfleiderer and G. Strauss, *Annalen*, 1957, **612**, 173.

18 h. The hydrazone (0·42 g), m.p. >300° was filtered off and crystallised from ethanol; it was identical with the two specimens already described.

The hydrazone (0·1 g) was heated under reflux with acetone (10 ml) for 24 h. The solvent was removed and the residue crystallised from ethanol to yield the *isopropylidene derivative* (3; R = NCMe$_2$) (0·065 g), m.p. >300° (Found: C, 50·6; H, 6·3; N, 29·2%; M^+, 237. $C_{10}H_{15}N_5O_2$ requires C, 50·6; H, 6·4; N, 29·5%; *M*, 237). The *benzylidene derivative* (3; R = NCHPh) (0·015 g), m.p. 277°, was similarly prepared from the hydrazone (0·07 g), benzaldehyde (0·1 g), and ethanol (10 ml) (Found: C, 58·3; H, 5·4; N, 24·8%; M^+, 285. $C_{14}H_{15}N_5O_2$ requires C, 58·9; H, 5·3; N, 24·6%; *M*, 285).

6-*Amino*-5-*formyl*-1,3-*dimethyluracil Dimethylhydrazone* (3; R = NMe$_2$).—The pyrimidopyrimidine (1) (0·4 g) and 1,1-dimethylhydrazine (4 ml) were heated on a steam-bath for 48 h. The orange precipitate was filtered from the cooled solution and crystallised from propan-2-ol (charcoal) to give the *dimethylhydrazone* (0·13 g), m.p. 242—244° (Found: C, 47·7; H, 6·6; N, 30·7%; M^+, 225. $C_9H_{15}N_5O_2$ requires C, 48·0; H, 6·7; N, 31·1%; *M*, 225).

6-*Amino*-5-*formyl*-1,3-*dimethyluracil Oxime* (3; R = OH).—The pyrimidopyrimidine (0·4 g) and aqueous hydroxylamine (2M; pH 6; 10 ml) were stirred at 70—80° for 5 days. Insoluble matter was filtered from the hot solution; the oxime (0·3 g), m.p. 248—249° (from aqueous ethanol), separated on cooling (Found: C, 42·2; H, 5·0; N, 28·3%; M^+, 198. $C_7H_{10}N_4O_3$ requires C, 42·4; H, 5·1; N, 28·3%; *M*, 198).

TABLE 1

Cleavage of 1,3-dimethylpyrimido[4,5-*d*]pyrimidine-2,4(1*H*,3*H*)-dione with amines

Product	Yield (%)	M.p. (°C)	Cryst. solvent	Formula	M^+ (Found) *	*M* (Required)
(3; R = CHMe$_2$)	63	177—179	Pr^{i}OH	$C_{10}H_{16}N_4O_2$	224·1272	224·1773
(3; R = [CH$_2$]$_3$·CH$_3$)	44	161—163	EtOH–H$_2$O	$C_{11}H_{18}N_4O_2$	238·1432	238·1430
(3; R = CH$_2$Ph)	67	167—168	PhH	$C_{14}H_{16}N_4O_2$	272·1274	274·1273
(3; R = CH$_2$·CH:CH$_2$)	52	145—146	EtOH–H$_2$O	$C_{10}H_{14}N_4O_2$	222·1121	222·1117
(3; R = [CH$_2$]$_5$CH)	55	171—173	EtOH	$C_{13}H_{20}N_4O_2$	264·1592	264·1586

* Measured on an A.E.I. MS902S spectrometer at resolving power of *ca.* 10,000.

TABLE 2

^{1}H N.m.r. data [a]

		τ Values (*J* in Hz)				
		N-Me [b]				
Compound	Solvent			5-H [c]	R	6-NH$_2$ [d]
(3; R = CHMe$_2$)	(CD$_3$)$_2$SO	6·70	6·85	1·52	8·85 (6H, d, *J* 6·5)	
(3; R = [CH$_2$]$_3$·CH$_3$)	CD$_3$OD	6·65	6·77	1·52	9·27—8·33 (7H, m), 6·41—6·78 (2H, m)	
(3; R = CH$_2$Ph)	CDCl$_3$	6·68	6·73	1·42	5·39 (2H, s), 2·75 (5H, s)	
(3; R = CH$_2$·CH:CH$_2$)	CDCl$_3$	6·61	6·68	1·55	5·91 (2H, d, *J* 4), 4·92 (1H, m), 3·70 (2H, d, *J* 4)	
(3; R = [CH$_2$]$_5$CH)	CDCl$_3$	6·65	6·70	1·61	7·83—9·0 (10H, m), 6·51 (1H, m)	
(3; R = NH$_2$)	(CD$_3$)$_2$SO	6·64	6·82	1·86		
(3; R = NMe$_2$)	(CD$_3$)$_2$SO	6·69	6·85	2·28	7·30 (6H, s)	1·42
(3; R = OH)	(CD$_3$)$_2$SO	6·68	6·85	1·76	−0·04br (s) [e]	1·76

[a] Measured on a Varian A60 spectrometer at normal probe temperature. [b] Singlets (3H). [c] Singlet (1H). [d] Broad singlet (2H) removed on deuteriation. [e] Removed on deuteriation.

We thank I.C.I. (Pharmaceuticals) Ltd., Alderley Park, for financial support (for M. S. M.), Mrs. R. Maynard for mass spectra and accurate mass measurements, and Mr. D. Barraclough for ^{1}H n.m.r. spectra.

[4/354 *Received*, 22*nd February*, 1974]