The Dimroth Rearrangement. Part XVI.[1] A New General Synthesis and Rearrangement of *C*-Alkylated 1,6-Dihydro-6-imino-1-methylpyrimidines

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A new primary synthesis of 1,6-dihydro-6-imino-1-methylpyrimidine (3a) and its 2-, 4-, and/or 5-alkylated derivatives (3c—o) is described: a 3-aminoacrylonitrile (1) is converted by an orthoester into its 3-ethoxyalkylideneamino-analogue (2) which undergoes methylaminolysis and subsequent cyclization to the required imine (3); a similar route gives the bicyclic imines (6; n = 3 or 4). All the imines rearrange in alkaline media to the corresponding 6(4)-methylaminopyrimidines [(4) or (7)], but at widely differing rates which depend on the position, type, and number of *C*-alkyl substituents. The rearrangement rates, ionization constants, and some mass spectra are discussed.

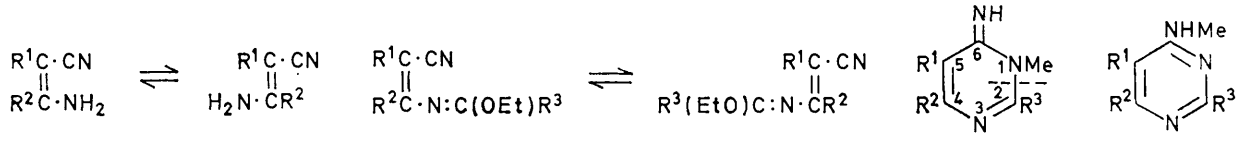
STUDIES on the Dimroth rearrangement of 4(6)-iminopyrimidines have been confined to 1,6-dihydro-6-imino-1-methylpyrimidine (3a) and its 2-methylthio derivative (3b),[2] mainly because of preparative difficulties. We now report a new and general route to *C*-alkylated derivatives of the imine (3a) and the rates for their rearrangement to the corresponding methylaminopyrimidines (4).

Syntheses.—Our general synthetic route to the imines (3) involved the initial formation of an enaminonitrile (1) which was converted into its ethoxyalkylidene derivative (2) using an appropriate orthoester. Subsequent methylaminolysis of the ethoxy-group in the

[1] Part XV, A. Albert, *J.C.S. Perkin I*, 1973, 2659.
[2] D. J. Brown and B. T. England, *J. Chem. Soc.* (*C*), 1971, 2507.

intermediate (2) was followed by spontaneous cyclization to give the imine (3), isolated conveniently as its hydriodide.

The enaminonitriles (1; R^1 = H or alkyl, R^2 = H) were best made by the method of Sieveking and Lüttke [3] involving lithium aluminium hydride reduction of malononitrile or an appropriate *C*-alkyl derivative

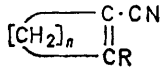


(1) (2) (3) (4)

	R^1	R^2	R^3
a;	H	H	H
b;	H	H	SMe
c;	Me	H	H
d;	Et	H	H
e;	Pr^i	H	H
f;	H	Me	H
g;	H	Pr^i	H
h;	Me	Me	H

	R^1	R^2	R^3
i;	Pr^i	Pr^i	H
j;	H	H	Me
k;	Me	H	Me
l;	H	Me	Me
m;	Me	Me	Me
n;	H	H	Et
o;	H	H	Pr^i

[$R^1CH(CN)_2$]. This reaction gave the known [3] products (1; R^1 = H or Me, R^2 = H) and their new homologues (1; R^1 = Et or Pr^i, R^2 = H), each as a mixture of its *cis*- and *trans*-isomer (^{1}H n.m.r. evidence: *cf.* ref. 3). The parent (1; $R^1 = R^2$ = H) was also obtained by aminolytic fission of isoxazole (*cf.* ref. 4) but the yield was poor. The other enaminonitriles (1; R^1 = H or alkyl, R^2 = alkyl) were made in high yield by condensation of two simple alkanonitriles in the presence of lithium diethylamide, a method outlined by Kulp [5] for converting pimelonitrile into the cyclic enaminonitrile (5; R = NH_2, n = 4). The products (1; R^1 = H or Me, R^2 = Me) had been made previously [6,7] by less effective methods. These and the homologues (1;

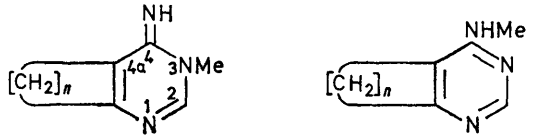


(5)

R = H or Pr, $R^2 = Pr^i$) were also obtained and subsequently used as mixtures of *cis*- and *trans*-isomers [*e.g.* the nitrile (1; R^1 = H, $R^2 = Pr^i$) had δ ($CDCl_3$) 1·08 (d, *J* 8 Hz, CMe_2), 2·40 (sept, *J* 8 Hz, CH of Pr^i), 3·72 (s, α-CH), and 6·4br (s, NH); plus 1·16 (d, *J* 8 Hz, CMe_2), 2·40 (sept, *J* 8 Hz, CH of Pr^i), 3·80 (s, α-CH), and 6·4br (s, NH)]. The cyclic analogue (5; R = NH_2, n = 3) was made [8] from adiponitrile.

Each enaminonitrile was then converted into the corresponding ethoxyalkylidene derivative (2) in which the substituent R^3 was determined by the orthoester used. Thus triethyl orthoformate gave the products (2a), (2c—i), and (5; R = N:CHOEt, n = 3 or 4); triethyl orthoacetate, the methyl homologues (2j—m); triethyl orthopropionate, an ethylated example (2n); and trimethyl orthoisobutyrate,[9] the corresponding isopropyl derivative (2o). The ^{1}H n.m.r. spectra for most of these compounds were too complicated for complete assignment but mixtures of geometric isomers were clearly indicated and elemental analyses confirmed the isomeric nature of the constituents of each product.

Treatment of each ethoxyalkylidene derivative (2) with ethanolic methylamine replaced the ethoxy- by a methylamino-group and brought about partial cyclization. This was completed during evaporation and subsequent dissolution of the residue in refluxing ethanol prior to addition of hydriodic acid to give the hydriodides of the iminopyrimidines (3a),[2] (3c—o), and (6; n = 3 or 4). Each was rearranged in warm alkali to give the methylaminopyrimidines (4a),[2] (4c—o), and (7; n = 3



(6) (7)

or 4) respectively. The spectra (Tables 1 and 2) confirm the structures [(3), (4), (6), and (7)].

Rearrangements.—The pK_a values and u.v. spectra (Table 1) of the imines (3) and (6) and their respective methylamino-isomers (4) and (7) indicated that each rearrangement could be followed spectrometrically at *p*H 13·0, where no more than 1% of cation was present. Thus at a given temperature, the spectrum of each imine changed progressively to that of the corresponding methylamine, with two perfect isosbestic points during >90% of the rearrangement. The change in optical density at 300 nm (or any other convenient wavelength) proved to be of the first-order: rates were expressed as $t_{\frac{1}{2}}$-values (Table 3).

It is evident that the rate of rearrangement varied widely with the nature, number, and position of the *C*-alkyl substituents (*cf.* the analogous behaviour of

[3] H. U. Sieveking and W. Lüttke, *Angew. Chem.*, 1969, **81**, 431.
[4] L. Claisen, *Ber.*, 1909, **42**, 59.
[5] S. S. Kulp, *Canad. J. Chem.*, 1967, **45**, 1981.
[6] H. Adkins and G. M. Whitman, *J. Amer. Chem. Soc.*, 1942, **64**, 151.
[7] A. Kotelko, H. Mikolajewska, and B. Zajaczkowska, *Acta Polon. Pharm.*, 1960, **17**, 361 (*Chem. Abs.*, 1961, **55**, 14,295).
[8] Q. E. Thompson, *J. Amer. Chem. Soc.*, 1958, **80**, 5483.
[9] S. M. McElvain and J. T. Venerable, *J. Amer. Chem. Soc.*, 1950, **72**, 1661.

TABLE 1

Ionization constants and u.v. spectra

Compd.	pK_a [a]	$\lambda_{max.}$/nm (log ε) [species] [b]
(3a) [c]	10·04	293 (3·39), *249* (3·77), 243 (3·93) [0]
		277 (3·48), 238 (3·59) [+]
(3c)	9·82 ± 0·06	295 (3·57), *250* (3·94), 244 (4·09) [0]
		274 (3·78), 235 (3·62) [+]
(3d)	9·86 ± 0·01	295 (3·48), *252* (3·85), 244 (3·96) [0]
		275 (3·68), 233 (3·70) [+]
(3e)	9·86 + 0·03	296 (3·55), *253* (3·90), 246 (4·04) [0]
		276 (3·76), 233 (3·89) [+]
(3f)	10·08 ± 0·04	284 (3·49), *253* (3·97), 245 (4·12) [0]
	(275)	270 (3·61), 239 (3·68) [+]
(3g)	10·56 ± 0·03	293 (3·32), *251* (4·00), 244 (4·13) [0]
		270 (3·68), 232 (3·87) [+]
(3h)	10·76 ± 0·04	293 (3·76), *253* (4·19), 249 (4·20) [0]
		274 (4·03), 244 (3·61) [+]
(3i)	10·35 ± 0·03	295 (3·58), *255* (3·97), 249 (4·03) [0]
		277 (3·81), 238 (3·75) [+]
(3j)	10·35 ± 0·03	299 (3·59), *251* (3·94), 242 (4·12) [0]
		275 (3·79), 229 (3·74) [+]
(3k)	10·14 ± 0·04	295 (3·66), *251* (3·88), 244 (3·99) [0]
		278 (3·86), 235 (3·59) [+]
(3l)	11·01 ± 0·04	294 (3·46), *251* (3·99), 245 (4·11) [0]
	(278)	273 (3·76), 233 (3·71) [+]
(3m)	10·88 ± 0·02	293 (3·62), *253* (3·97), 246 (4·05) [0]
	(275)	278 (3·87), 234 (3·71) [+]
(3n)	10·05 ± 0·06	299 (3·55), 238 (4·11) [0]
		277 (3·76), 228 (3·96) [+]
(3o)	10·32 ± 0·03	302 (3·48), 238 (4·04), [0]
		278 (3·71), 228 (3·94) [+]
(4a) [c]	6·12	276 (3·54), 242 (4·18) [0]
		254 (4·20) [+]
(4c)	6·56 ± 0·03	273 (3·61), 243 (4·03) [0]
		259 (4·12) [+]
(4d)	6·68 ± 0·02	273 (3·63), 244 (4·04) [0]
		259 (4·11) [+]
(4e)	6·76 ± 0·02	273 (3·64), 245 (4·05) [0]
		260 (4·13) [+]
(4f)	6·65 ± 0·01	270 (3·59), 243 (4·18) [0]
		257 (4·24) [+]
(4g)	6·48 ± 0·05	270 (3·55), 243 (4·10) [0]
		258 (4·11) [+]
(4h)	6·97 ± 0·01	*268* (3·78), 244 (4·09) [0]
		263 (4·18) [+]
(4i)	7·05 ± 0·02	*271* (3·70), 248 (3·97) [0]
		267 (4·18) [+]
(4j)	7·19 ± 0·01	279 (3·55), 241 (4·02) [0]
		252 (4·07) [+]
(4k)	7·61 ± 0·02	276 (3·78), 242 (4·05) [0]
		258 (4·14) [+]
(4l) [d]	7·57	275 (3·65), 242 (4·07) [0]
		255 (4·15) [+]
(4m)	8·14 ± 0·04	272 (3·78), 245 (3·98) [0]
		263 (4·11) [+]
(4n)	7·28 ± 0·05	279 (3·67), 240 (4·13) [0]
		253 (4·18) [+]
(4o)	7·41 ± 0·03	280 (3·65), 240 (4·11) [0]
		253 (4·15) [+]
(6;	10·45 ± 0·02	293 (3·53), *255* (4·03), 248 (4·12) [0]
$n = 3$)		274 (3·77), 239 (3·80) [+]
(6;	10·34 ± 0·05	288 (3·54), *251* (3·99), 246 (4·07) [0]
$n = 4$)		271 (3·73), 238 (3·70) [+]
(7;	6·50 ± 0·03	*270* (3·75), 250 (4·05) [0]
$n = 3$)		266 (4·14) [+]
(7;	7·20 ± 0·02	*265* (3·79), 247 (4·01) [0]
$n = 4$)		263 (4·11) [+]

[a] Except where indicated in parentheses, the analytical λ for the imines [(3) and (6)] was 305 nm; for the amines [(4) and (7)], it was the $\lambda_{max.}$ of each cation. [b] Inflexions and shoulders in italics; neutral molecules [0] of imines at pH 13·0 and cations [+] at pH 7·0; amines [0] at pH 10 and [+] at pH 4·0. [c] From ref. 2. [d] From ref. 20.

C-alkylated 1,2-dihydro-2-imino-1-methylpyrimidines [10]). Thus the addition of a 5-alkyl group caused a marked (25—190 fold) slowing of rearrangement: (3a ⟶ c), 75; (3a ⟶ d), 93; (3a ⟶ e), 190; (3g ⟶ i), 61; (3j ⟶ k), 24; and (3l ⟶ m), 41 fold. The relative effect of individual groups was 5-Pr^i > 5-Et > 5-Me. The addition of a 4- or 2-alkyl group caused much less (<6 fold) slowing: (3a ⟶ f), 1·6; (3a ⟶ g), 3·2; (3a ⟶ j), 5·2; (3a ⟶ n), 1·9; (3a ⟶ o), 3·3; (3c ⟶ h), 3·6; (3e ⟶ i), 1·6; (3f ⟶ l), 2·3; and (3k ⟶ m), 1·2 fold. In two cases, (3h ⟶ m) and (3j ⟶ l), there was a small increase in rate on adding a methyl group; moreover, the relative effects of methyl, ethyl, and isopropyl groups in the 2- or 4-position followed no fixed order.

We see the marked effect of a 5-alkyl group as due to a combination of (*a*) mesomeric electron-enrichment at C-2 which discourages OH^- attack, probably the first step [11] in Dimroth rearrangement; and (*b*) steric hindrance to the 180° rotation about the 5,6-bond (8a ⟶ 8b), a necessary preliminary to non-reversible recyclization to the aromatic pyrimidine (4). The importance of the latter factor is confirmed in appropriate

(8a) (8b)

molecular models and is consistent with the particularly large effect of an isopropyl group. The relatively minor effect of a 4-alkyl group on rearrangement appears to arise from minimal mesomeric and inductive effects on C-2 coupled with the lack of any steric factor. In contrast, the similarly minor effect of a 2-alkyl group seems to be the result of several competing factors: (*a*) inductive electron-enrichment at C-2; (*b*) steric hindrance to hydroxy approach; (*c*) 1,2-bond instability from crowding in the N-1/C-2 area following hydroxylation; and (*d*) steric accentuation of the required conformation (8b) in the equilibrium (8a ⇌ 8b).

The tetramethylene derivative (6; $n = 4$) rearranged at a rate comparable with that of the 4,5-dimethyl-analogue (3m) but the trimethylene derivative (6; $n = 3$) did so eight times faster. Molecular models indicated that two factors were probably involved: (*a*) the mild strain, introduced by annulation of the five (but not the six) membered ring, tended to elongate (destabilize) the 2,3-bond; and (*b*) after fission of the 2,3-bond, there was less steric hindrance to the necessary rotation about the 4,4a-bond in the intermediate from (6; $n = 3$) than in that from (6; $n = 4$).

Ionization and Mass Spectra.—The effect (Table 1) of added *C*-alkyl groups on the pK_a of 6-methylamino-pyrimidine (4a) followed a normal pattern: the 4-alkylations [(4a ⟶ f or g), (4c ⟶ h), (4e ⟶ i), (4j ⟶ l), and (4k ⟶ m)] increased the basic strength by 0·3—0·5 units; the 5-alkylations [(4a ⟶ c, d, or e), (4g ⟶

[10] D. J. Brown and J. S. Harper, *J. Chem. Soc.*, 1963, 1276; D. J. Brown and M. N. Paddon-Row, *J. Chem. Soc.* (*C*), 1967, 1928; D. J. Brown and B. T. England, *ibid.*, 1971, 250.

[11] D. D. Perrin and I. H. Pitman, *J. Chem. Soc.*, 1965, 7071.

i), (4j ⟶ k), and (4l ⟶ m)] did likewise by 0·4—0·65 units; and the 2-alkylations [(4a ⟶ j, n, or o), (4f ⟶ l), and (4h ⟶ m)] caused a larger increase of 0·9—1·3 units because the additional alkyl group was adjacent to both ring-nitrogen atoms. The basic strength of the imine (3a) was affected quite differently by added *C*-alkyl groups: the 2- or 4-alkylations [(3a ⟶ f, g, j, n, or o), (3c ⟶ h), (3e ⟶ i), (3f ⟶ l), (3h ⟶ m), (3j ⟶ l), and (3k ⟶ m)] caused apparently random increases in pK_a of 0·01—0·9 units; in contrast, all the 5-alkylations [(3a ⟶ c—e), (3g ⟶ i), (3j ⟶ k), and (3l ⟶ m)] *decreased* the basic strength by 0·13—0·22 units. We attribute this unusual phenomenon to a selective inductive strengthening of the imino-group as a basic centre in the non-aromatic pyrimidine (3): this would increase the tendency to form the non-aromatic cation (9a) at the expense of the highly stable aromatic cation (9b), the ready formation of which is the reason for the high basic strength of imines such as (3).

TABLE 2

^{1}H N.m.r. spectra

Compound	δ Values [a]
(3a)	8·90 (s, 2-H), 8·40 (d, *J* 8, 4-H), 7·12 (d, *J* 8, 5-H), 3·75 (s, Me)
(3c)	8·60 (s, 2-H), 8·15 (s, 4-H), 3·70 (s, NMe), 2·14 (s, 5-Me)
(3d)	8·81 (s, 2-H), 8·29 (s, 4-H), 3·78 (s, NMe), 2·65 (q, *J* 6, CH_2), 1·18 (t, *J* 6, CMe)
(3e)	8·70 (s, 2-H), 8·20 (s, 4-H), 3·72 (s, NMe), 3·07 (sept, *J* 6, CH), 1·21 (d, *J* 6, CMe_2)
(3f)	8·80 (s, 2-H), 6·90 (s, 5-H), 3·72 (s, NMe), 2·40 (s, 4-Me)
(3g)	8·83 (s, 2-H), 6·90 (s, 5-H), 3·70 (s, NMe), *ca.* 3·1 (m, CH),[b] 1·22 (d, *J* 6, CMe_2)
(3h)	8·65 (s, 2-H), 8·60br (s, NH),[c] 3·73 (s, NMe), 2·41 (s, 4-Me), 2·15 (s, 5-Me)
(3i)	8·80 (s, 2-H), 3·76 (s, NMe), *ca.* 3·2 (m, 2 × CH),[b] 1·33 (d, *J* 8, Me_2 of 2-Pr^i), 1·21 (d, *J* 8, Me_2 of 4-Pr^i)
(3j)	9·10br (s, NH),[c] 8·20 (d, *J* 6, 4-H), 6·95 (d, *J* 6, 5-H), 3·62 (s, NMe), 2·67 (s, 2-Me)
(3k)	8·85br (s, NH),[c] 8·20 (s, 4-H), 3·72 (s, NMe), 2·68 (s, 2-Me), 2·16 (s, 5-Me)
(3l)	6·78 (s, 5-H), 3·65 (s, NMe), 2·67 (s, 2-Me), 2·45 (s, 4-Me)
(3m)	8·50br (s, NH),[c] 3·65 (s, NMe), 2·63 (s, 2-Me), 2·40 (s, 4-Me). 2·15 (s, 5-Me)
(3n)	9·12br (s, NH),[c] 8·34 (d, *J* 6, 4-H), 7·02 (d, *J* 6, 5-H), 3·68 (s, NMe), 3·03 (q, *J* 7, CH_2), 1·25 (t, *J* 7, CMe)
(3o)	8·60 (d, *J* 8, 4-H), 7·02 (d, *J* 8, 5-H), 3·74 (s, NMe), 3·63 (sept, *J* 7, CH), 1·25 (d, *J* 7, CMe_2)
(4a)	8·54 (d, 2-H), 8·23 (d, *J* 6, 4-H), 6·37 (d, *J* 6, 5-H), 2·95 (d, *J* 5, NMe) [d]
(4c)	8·50 (s, 2-H), 8·00 (s, 4-H), 4·96br (s, NH),[c] 3·08 (d, *J* 5, NMe),[d] 2·01 (s, 5-Me)
(4d)	8·60 (s, 2-H), 8·20 (s, 4-H), 5·20br (s, NH),[c] 3·06 (d, *J* 5, NMe),[d] 2·42 (q, *J* 5, CH_2), 1·22 (t, *J* 5, CMe)
(4e)	8·61 (s, 2-H), 8·10 (s, 4-H), 5·35br (s, NH),[c] 3·08 (d, *J* 5, NMe),[d] 2·75 (m, CH),[b] 1·28 (d, *J* 7, CMe_2)
(4f)	8·52 (s, 2-H), 6·21 (s, 5-H), 5·81br (s, NH),[c] 2·94 (d, *J* 5, NMe),[d] 2·36 (s, 4-Me)
(4g)	8·50 (s, 2-H), 6·20 (s, 5-H), 5·60br (s, NH),[c] 2·93 (d, *J* 5, NMe),[d] 2·90 (sept, *J* 7, CH), 1·25 (d, *J* 7, CMe_2)
(4h)	8·46 (s, 2-H), 3·05 (d, *J* 5, NMe),[d] 2·35 (s, 4-Me), 1·99 (s, 5-Me)
(4i)	8·60 (s, 2-H), 4·70br (s, NH),[c] 3·03 (d, *J* 5, NMe),[d] *ca.* 3·0 (m, 2 × CH), 1·30 (d, *J* 8, 4-CMe_2), 1·20 (d, *J* 8, 2-CMe_2)
(4j)	8·20 (d, *J* 6, 4-H), 6·18 (d, *J* 6, 5-H), 5·50br (s, NH),[c] 2·93 (d, *J* 5, NMe),[d] 2·50 (s, 2-Me)
(4k)	7·91 (s, 4-H), 6·80br (s, NH),[c] 3·06 (d, *J* 5, NMe),[d] 2·52 (s, 2-Me), 1·98 (s, 5-Me)
(4l)	6·08 (s, 5-H), 5·55br (s, NH),[c] 2·95 (d, *J* 5, NMe),[d] 2·52 (s, 2-Me), 2·35 (s, 4-Me)
(4m)	5·08br (s, NH),[c] 3·02 (d, *J* 5, NMe),[d] 2·48 (s, 2-Me), 2·31 (s, 4-Me), 1·93 (s, 5-Me)
(4n)	8·22 (d, *J* 6, 4-H), 6·20 (d, *J* 6, 5-H), 5·75br (s, NH),[c] 2·93 (d, *J* 5, NMe),[d] 2·77 (q, *J* 8, CH_2), 1·31 (t, *J* 8, CMe)
(4o)	8·23 (d, *J* 6, 4-H), 6·19 (d, *J* 6, 5-H), 5·55br (s, NH),[c] 2·95 (d, *J* 5, NMe),[d] 2·94 (m, CH),[b] 1·30 (d, *J* 8, CMe_2)
(6; *n* = 3)	8·75 (s, 2-H), 3·76 (s, NMe), 2·95br (s, 5,7-$[CH_2]_2$), 2·20br (s, 6-CH_2)
(6; *n* = 4)	8·70 (s, 2-H), 3·75 (s, NMe), 2·70br (s, 5,8-$[CH_2]_2$), 1·80br (s, 6,7-$[CH_2]_2$)
(7; *n* = 3)	8·52 (s, 2-H), 5·20br (s, NH),[c] 3·06 (d, *J* 5, NMe),[d] 2·8br (s, 5,7-$[CH_2]_2$), 2·1br (s, 6-CH_2)
(7; *n* = 4)	8·51 (s, 2-H), 3·05 (d, *J* 5, NMe),[d] 3·15br (s, 5,8-$[CH_2]_2$), 1·80br (s, 6,7-$[CH_2]_2$]

[a] Hydriodides of the imines (3) and (6) in $(CD_3)_2SO$; amines (4) and (7) as bases in $CDCl_3$; *J* values in Hz. [b] Septet for CH of Pr^i poorly resolved. [c] Disappeared on adding D_2O. [d] Collapsed to singlet on adding D_2O.

TABLE 3

Rearrangement of 1,6-dihydro-6-imino-1-methylpyrimidines at pH 13

Imine	$t_{\frac{1}{2}}$ (20°)/min	$t_{\frac{1}{2}}$ (70°)/min
(3a)	29	
(3c)	2160	11·6
(3d)	2700	15
(3e)	5400 [a]	30
(3f)	45	
(3g)	94	
(3h)		42
(3i)	5880 [b]	49
(3j)	150	
(3k)	3600	30
(3l)	103	
(3m)	4200 [b]	35
(3n)	54	
(3o)	97	
(6; *n* = 3)	360	4·7
(6; *n* = 4)		36

[a] Approximate value derived by multiplying that at 70° by $t_{\frac{1}{2}}$ (20°)/$t_{\frac{1}{2}}$ (70°) for (3d). [b] Approximate value similarly derived using data for (3k).

(9a) (9b)

In contrast to the mass spectra of 6(4)-aminopyrimidines,[12] the initial fragmentation steps for 6-methylaminopyrimidines (Table 4) involved loss from the parent structure (10) of $HN{:}CH_2$ (composed of N-1 + *N*-CH_3) to give (11) which then lost R^3CN (R^3 + C-2 + N-3 of the original molecule) to give the fragment (12).

EXPERIMENTAL

Analyses were done by the Australian National University Analytical Services Unit. M.p.s are corrected.

[12] T. Nishiwaki, *Tetrahedron*, 1966, **22**, 3117; Q. N. Porter and J. Baldas, 'Mass Spectrometry of Heterocyclic Compounds,' Wiley, New York, 1971, p. 471 *et seq.*

Ionization constants were measured spectrometrically [13] at 20° and $<10^{-3}$M concentration in buffers [14] of 10^{-2}M ionic strength; thermodynamic corrections were not applied. ^{1}H N.m.r. spectra were measured at 60 MHz and 33° using Me_4Si as internal standard by Mr S. E. Brown; u.v. data were recorded on a Unicam SP 1800 followed by a manual check of peaks; mass spectra were done by Dr J. MacLeod using an A.E.I. MS9 instrument.

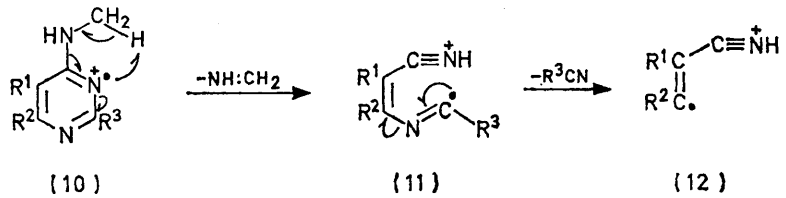
1,6-*Dihydro*-6-*imino*-1-*methylpyrimidine* (3a).—Malononitrile was reduced [3] by lithium aluminium hydride to give a mixture of *cis*- and *trans*-3-aminoacrylonitrile (1; $R^1 = R^2 = H$) (40%). Alternatively, isoxazole [15] (1 g) was heated with saturated ethanolic ammonia (20 ml) in a sealed tube at 70° for 24 h. The residue from evaporation was extracted with boiling chloroform. Passage of the extract through an alumina column followed by evaporation and distillation gave a mixed product (31%), similar in composition to that above. The crude 3-aminoacrylonitrile (3·4 g), triethyl orthoformate (25 ml), and acetic anhydride (25 ml) were heated under reflux for 15 min. Fractional distillation gave a mixture of *cis*- and *trans*-3-ethoxymethyleneaminoacrylonitrile (2a) (61%), b.p. 74° at 0·5 mmHg. This crude material (0·5 g) was added to ethanolic methylamine (33%; 5 ml). After 10 min at 25°, the solution was evaporated *in vacuo* to remove the excess of amine. The oily residue was diluted with ethanol (5 ml) and heated under reflux for 1 h to effect cyclization. The addition of a few drops of concentrated hydriodic acid followed by partial evaporation gave the iminopyrimidine hydriodide (70%), m.p. 220° (from ethanol) (lit.,[2] 218—220°), identical in u.v. and ^{1}H n.m.r. spectra with authentic material.[2]

1,6-*Dihydro*-6-*imino*-1,5-*dimethylpyrimidine* (3c).—Methylmalononitrile was reduced to 3-aminomethacrylonitrile (1; $R^1 = Me$, $R^2 = H$) (40%).[3] The mixture of isomers (1·1 g) was converted as above into crude 3-(ethoxymethyleneamino)methacrylonitrile (2c) (54%), b.p. 75—78° at 0·15 mmHg, and thence by methylamine (cyclization; 3 h) into 1,6-*dihydro*-6-*imino*-1,5-*dimethylpyrimidine hydriodide* (64%), m.p. 224° (from ethanol) (Found: C, 29·0; H, 4·3; N, 16·7. $C_6H_{10}IN_3$ requires C, 28·7; H, 4·0; N, 16·7%).

5-*Ethyl*-1,6-*dihydro*-6-*imino*-1-*methylpyrimidine* (3d).—Ethylmalononitrile [16] (8·1 g), dissolved in a mixture of ether (20 ml) and tetrahydrofuran (40 ml), was added in drops to a stirred solution of lithium aluminium hydride (5 g) in a mixture of ether (400 ml) and tetrahydrofuran (100 ml) at 20—25°. After stirring for a further 3 h, water (10 ml) was added carefully. The organic layer was then washed thoroughly with 5N-sodium hydroxide (10 ml) followed by water (30 ml). Filtration, dehydration (potassium carbonate), and fractional distillation gave crude 3-amino-2-ethylacrylonitrile (1; $R^1 = Et$, $R^2 = H$) (45%), b.p. 86—96° at 0·3 mmHg. This was converted (as the de-ethyl homologue above) into 3-ethoxymethyleneamino-2-ethylacrylonitrile (2d) (77%), b.p. 95—105° at 0·5 mmHg, and thence into the *5-ethyl-6-iminopyrimidine hydriodide* (78%), m.p. 240° (from ethanol) (Found: C, 31·9; H, 4·7; N, 15·7. $C_7H_{12}IN_3$ requires C, 31·7; H, 4·6; N, 15·8%).

TABLE 4

Mass spectra of 6-methylaminopyrimidines



(10) (11) (12)

			m/e				
R^1	R^2	R^3	[M^+]	[$NH{:}CH_2$]	(11)	[R^3CN]	(12)
H	H	H	109	29	80	27	53
Me	H	H	123	29	94	27	67
H	Me	H	123	29	94	27	67
H	H	Me	123	29	94	41	53
H	Me	Me	137	29	108	41	67
H	H	Et	137	29	108	55	53

1,6-*Dihydro*-6-*imino*-5-*isopropyl*-1-*methylpyrimidine* (3e).—Isopropylmalononitrile [17] was converted successively as above into 3-amino-2-isopropylacrylonitrile (1; $R^1 = Pr^i$, $R^2 = H$) (36%), b.p. *ca.* 90° at 0·3 mmHg, 3-ethoxymethyleneamino-2-isopropylacrylonitrile (2e) (89%), b.p. 105—115° at 0·5 mmHg (Found: C, 65·2; H, 8·6. Calc. for $C_9H_{14}N_2O$: C, 65·0; H, 8·5%), and the *imino-5-isopropylpyrimidine hydriodide* (66%), m.p. 222° (Found: C, 34·5; H, 4·9; N, 14·9. $C_8H_{14}IN_3$ requires C, 34·4; H, 5·1; N, 15·1%).

1,6-*Dihydro*-6-*imino*-1,4-*dimethylpyrimidine* (3f).—Lithium diethylamide (0·5 mol) was prepared [18] in ether (400 ml) from lithium (7·35 g), bromobenzene (79 g), and diethylamine (36·5 g). The solution was cooled in a solid carbon dioxide–acetone bath prior to the addition of acetonitrile (40·1 g) during 10 min. The mixture was then allowed to attain room temperature. After 12—16 h, water was added and the ethereal layer was separated, dehydrated (magnesium sulphate), and evaporated. The residue crystallized from ethanol to give 3-aminocrotononitrile (1; $R^1 = Me$, $R^2 = H$) (93%), m.p. 50° (*cf.* lit.: 37%,[6] m.p. 50—53° [19]). This nitrile (9 g), triethyl ortho-

[13] A. Albert and E. P. Serjeant, ' Determination of Ionization Constants,' Chapman and Hall, London, 1971.
[14] D. D. Perrin, *Austral. J. Chem.*, 1963, **16**, 572.
[15] P. J. Tarsio and L. Nicholl, *J. Org. Chem.*, 1957, **22**, 192.
[16] J. C. Hessler, *Amer. Chem. J.*, 1899. **22**, 169.
[17] P. Henry, *Bull. Acad. roy. Belg.*, 1889, [3], **18**, 670; *Ber.*, 1891, 24, *referate* p. 73.
[18] R. F. Brown and N. M. van Gulick, *J. Amer. Chem. Soc.*, 1955, **77**, 1083.
[19] E. von Meyer, *J. prakt. Chem.*, 1895, [2], **52**, 81; J. J. Conn and A. Taurins, *Canad. J. Chem.*, 1953, **31**, 1211.

formate (30 ml), and acetic anhydride (30 ml) were heated under reflux for 20 min. Fractional distillation of the mixture gave 3-*ethoxymethyleneaminocrotononitrile* (2f) (61%), b.p. 70° at 0·2 mmHg (Found: C, 61·1; H, 7·3; N, 20·4. $C_7H_{10}N_2O$ requires C, 60·9; H, 7·3; N, 20·3%), which was converted (as for the isomeric methacrylonitrile above) into the 6-*imino*-1,4-*dimethylpyrimidine hydriodide* (64%), m.p. 216° (from ethanol) (Found: C, 28·7; H, 4·0; N, 16·7. $C_6H_{10}IN_3$ requires C, 28·7; H, 4·0; N, 16·7%).

1,6-*Dihydro*-6-*imino*-4-*isopropyl*-1-*methylpyrimidine* (3g).—Treatment of lithium diethylamide with acetonitrile followed by isobutyronitrile (as for the 4-ethyl homologue above) gave 3-*amino*-4-*methylpent*-2-*enonitrile* (1; R^1 = H, R^2 = Pr^i) (91%), b.p. 92—94° at 0·35 mmHg (Found: C, 65·1; H, 8·9; N, 25·5. $C_6H_{10}N_2$ requires C, 65·4; H, 9·15; N, 25·4%), which was converted into 3-*ethoxymethyleneamino*-4-*methylpent*-2-*enonitrile* (2g) (85%), b.p. 88° at 0·1 mmHg (Found: C, 64·9; H, 8·3; N, 16·95. $C_9H_{14}N_2O$ requires C, 65·0; H, 8·5; N, 16·85%), and thence into the *imino*-4-*isopropylpyrimidine hydriodide* (71%), m.p. 216° (from ethanol) (Found: C, 34·7; H, 4·9; N, 14·8. $C_8H_{14}IN_3$ requires C, 34·4; H, 5·1; N, 15·1%).

1,6-*Dihydro*-6-*imino*-1,4,5-*trimethylpyrimidine* (3h).—3-Amino-2-methylcrotononitrile [7] (1; R^1 = R^2 = Me) was converted by triethyl orthoformate plus acetic anhydride into 3-*ethoxymethyleneamino*-2-*methylcrotononitrile* (2h) (60%), b.p. 64° at 0·3 mmHg (Found: C, 62·8; H, 7·7; N, 18·2. $C_8H_{12}N_2O$ requires C, 63·1; H, 7·95; N, 18·4%). This intermediate (0·76 g) and ethanolic methylamine (33%; 5 ml) were stirred for 3 h at 25° prior to concentration *in vacuo* to *ca.* 1·5 ml. Several drops of concentrated hydriodic acid were added and the solution was heated on a steam-bath for 2 h. Refrigeration and subsequent concentration gave two crops of the *imino*-1,4,5-*trimethylpyrimidine hydriodide* (70%), m.p. 244° (from ethanol) (Found: C, 31·9; H, 4·8; N, 15·8. $C_7H_{12}IN_3$ requires C, 31·7; H, 4·6; N, 15·8%).

1,6-*Dihydro*-6-*imino*-4,5-*di-isopropyl*-1-*methylpyrimidine* (3i).—Successive addition of isovaleronitrile and isobutyronitrile to ethereal lithium diethylamide (as above) gave a single solid product, 3-*amino*-2-*isopropyl*-4-*methylpent*-2-*enonitrile* (1; R^1 = R^2 = Pr^i) (90%), m.p. 93—94° (from ethanol) (Found: C, 71·4; H, 10·2; N, 18·1. $C_9H_{16}N_2$ requires C, 71·0; H, 10·6; N, 18·4%), which was converted into a single geometric isomer (^{1}H n.m.r. spectrum) of 3-*ethoxymethyleneamino*-2-*isopropyl*-4-*methylpent*-2-*enonitrile* (2i) (82%), b.p. 76—82° at 0·1 mmHg (Found: C, 69·3; H, 9·6; N, 13·3. $C_{12}H_{20}N_2O$ requires C, 69·2; H, 9·7; N, 13·45%) which reacted with methylamine [as for the parent imine (3a) but refluxing for 15 h to effect cyclization] to give the *imino*-4,5-*di-isopropylpyrimidine hydriodide* (50%), m.p. 252° (from ethanol) (Found: C, 41·2; H, 6·2; N, 12·8. $C_{11}H_{20}IN_3$ requires C, 41·1; H, 6·3; N, 13·1%).

1,6-*Dihydro*-6-*imino*-1,2-*dimethylpyrimidine* (3j).—3-Aminoacrylonitrile (4·0 g), triethyl orthoacetate (40 ml), and acetic anhydride (40 ml) were heated under reflux for 2 h. Fractional distillation gave 3-(1-ethoxyethylideneamino)acrylonitrile (2j) (75%), b.p. 70° at 0·4 mmHg, m.p. 84—85° (from light petroleum). The crude intermediate (1·5 g) and ethanolic methylamine (30%; 12 ml) were stirred at 25° for 16 h. Evaporation and addition of a little hydriodic acid gave the *imino*-1,2-*dimethylpyrimidine hydriodide* (80%), m.p. 246° (from ethanol) (Found: C, 28·9; H, 4·1; N, 16·4. $C_6H_{10}IN_3$ requires C, 28·7; H, 4·0; N, 16·7%).

1,6-*Dihydro*-6-*imino*-1,2,5-*trimethylpyrimidine* (3k).—3-Aminomethacrylonitrile, triethyl orthoacetate, and acetic anhydride similarly gave 3-(1-ethoxyethylideneamino)-methacrylonitrile (2k) (79%). The crude product was converted (as in the foregoing preparation) into the *imino*-1,2,5-*trimethylpyrimidine hydriodide* (83%), m.p. 244° (Found: C, 31·4; H, 4·9; N, 15·8. $C_7H_{12}IN_3$ requires C, 31·7; H, 4·6; N, 15·8%).

1,6-*Dihydro*-6-*imino*-1,2,4-*trimethylpyrimidine* (3l).—3-Aminocrotononitrile was treated as its isomer above to give successively a single geometric isomer of 3-(1-*ethoxyethylideneamino*)*crotononitrile* (2l) (94%), b.p. 76° at 0·6 mmHg (Found: C, 63·1; H, 7·7; N, 18·5. $C_8H_{12}N_2O$ requires C, 63·1; H, 7·95; N, 18·4%), and the *imino*-1,2,4-*trimethylpyrimidine hydriodide* (82%), m.p. 246° (from ethanol) (Found: C, 32·0; H, 4·6; N, 15·8. $C_7H_{12}IN_3$ requires C, 31·7; H, 4·6; N, 15·8%).

1,6-*Dihydro*-6-*imino*-1,2,4,5-*tetramethylpyrimidine* (3m).—3-Amino-2-methylcrotononitrile similarly gave 3-(1-*ethoxyethylideneamino*)-2-*methylcrotononitrile* (2m) (70%), b.p. 81—85° at 1 mmHg (Found: C, 65·1; H, 8·8; N, 16·7. $C_9H_{14}N_2O$ requires C, 65·0; H, 8·5; N, 16·85%), and thence the *iminotetramethylpyrimidine hydriodide* (71%), m.p. 249° (Found: C, 34·7; H, 5·0; N, 15·0. $C_8H_{14}IN_3$ requires C, 34·4; H, 5·1; N, 15·1%).

2-*Ethyl*-1,6-*dihydro*-6-*imino*-1-*methylpyrimidine* (3n).—3-Aminoacrylonitrile was treated with triethyl orthopropionate and acetic anhydride [as for the lower homologue (1n)] to give 3-(1-*ethoxypropylideneamino*)*acrylonitrile* (2n) (67%), b.p. 70° at 0·15 mmHg (Found: C, 63·3; H, 7·8; N, 18·4. $C_8H_{12}N_2O$ requires C, 63·1; H, 7·95; N, 18·4%), and thence the 2-*ethyl*-6-*iminopyrimidine hydriodide* (64%), m.p. 215° (from ethanol) (Found: C, 31·8; H, 4·7; N, 15·6. $C_7H_{12}IN_3$ requires C, 31·7; H, 4·6; N, 15·8%).

1,6-*Dihydro*-6-*imino*-2-*isopropyl*-1-*methylpyrimidine* (3o).—3-Aminoacrylonitrile was converted (as immediately above, but using trimethyl orthoisobutyrate [9]) into crude 3-(1-ethoxy-2-methylpropylideneamino)acrylonitrile (2o) (80%), and thence into the *imino*-2-*isopropylpyrimidine hydriodide* (72%), m.p. 204° (Found: C, 34·7; H, 5·0; N, 14·9. $C_8H_{14}IN_3$ requires C, 34·4; H, 5·1; N, 15·1%).

4,5,6,7-*Tetrahydro*-4-*imino*-3-*methyl*-3H-*cyclopenta*[d]*pyrimidine* (6; *n* = 3).—Adiponitrile was converted [8] by sodium t-butoxide into 2-aminocyclopentene-1-carbonitrile (5; R = NH_2, *n* = 3) in 78% yield. This material (4·1 g), triethyl orthoformate (50 ml), and acetic anhydride (50 ml) were heated under reflux for 30 min. The residue from evaporation gave a solid on prolonged refrigeration. This was filtered off and added to ethanolic methylamine (30%; 30 ml). After 20 min at room temperature, the solution was evaporated. The residue was diluted with ethanol (25 ml) prior to heating under reflux for 3—4 h. Hydriodic acid (5 ml) was added. Evaporation gave the *iminocyclopentapyrimidine hydriodide* (62%), m.p. 256—258° (Found: C, 34·3; H, 4·6; N, 15·4. $C_8H_{12}IN_3$ requires C, 34·7; H, 4·4; N, 15·2%).

3,4,5,6,7,8-*Hexahydro*-4-*imino*-3-*methylquinazoline* (6; *n* = 4).—2-Aminocyclohexene-1-carbonitrile (5; R = NH_2, *n* = 4) [5] was treated as the corresponding cyclopentene (foregoing preparation) to give the *hexahydro-iminoquinazoline hydriodide* (60%), m.p. 222° (from ethanol) (Found: C, 37·3; H, 5·0; N, 14·15. $C_9H_{14}IN_3$ requires C, 37·1; H, 4·85; N, 14·4%).

4(6)-*Methylaminopyrimidines* [(4) *and* (7)].—The hydriodide of each iminopyrimidine (3) (*ca.* 75 mg) and 2M-sodium hydroxide (5 ml) were heated under reflux on a water-bath at 80° for 3 h. The cooled solution was extracted with chloroform (10 × 5 ml). After dehydration (magnesium sulphate) of the extract, the chloroform was evaporated off at room temperature in a partial vacuum to give the appropriate methylaminopyrimidine (sometimes better converted into the hydrochloride by passing hydrogen chloride into an ethanolic solution): 5-*methyl*-4- (4c) (92%), m.p. 124° (Found: C, 58·3; H, 7·3; N, 34·2. $C_6H_9N_3$ requires C, 58·5; H, 7·4; N, 34·1%); 5-*ethyl*-4- (4d) (94%), m.p. 148° (Found: C, 61·6; H, 8·3; N, 30·5. $C_7H_{11}N_3$ requires C, 61·3; H, 8·1; N, 30·6%); 5-*isopropyl*-4- (4e) (91%), m.p. 121° (Found: C, 63·3; H, 9·1; N, 27·6. $C_8H_{13}N_3$ requires C, 63·55; H, 8·7; N, 27·8%); 4-*methyl*-6- (4f) (97%), m.p. 115° (Found: C, 58·4; H, 7·5; N, 34·0. $C_6H_9N_3$ requires C, 58·5; H, 7·4; N, 34·1%); *hydrochloride* of 4-*isopropyl*-6- (4g) (94%), m.p. 257° (Found: C, 51·6; H, 7·8; N, 22·4. $C_8H_{14}ClN_3$ requires C, 51·2; H, 7·5; N, 22·4%); 4,5-*dimethyl*-6- (4h) (96% after 12 h heating), m.p. 136° (Found: C, 61·3; H, 8·4; N, 30·7. $C_7H_{11}N_3$ requires C, 61·6; H, 8·1; N, 30·6%); 4,5-*di-isopropyl*-6- (4i) (95% after 12 h heating), m.p. 130° (Found: C, 68·5; H, 9·9; N, 21·6. $C_{11}H_{19}N_3$ requires C, 68·35; H, 9·9; N, 21·7%); 2-*methyl*-4- (4j) (95%), m.p. 90° (Found: C, 58·6; H, 7·4; N, 34·35. $C_6H_9N_3$ requires C, 58·5; H, 7·4; N, 34·1%); 2,5-*dimethyl*-4- (4k) (90% after 12 h heating), m.p. 114° (Found: C, 61·0; H, 8·1; N, 30·6. $C_7H_{11}N_3$ requires C, 61·3; H, 8·1; N, 30·6%); 4,5-dimethyl-6- (4l) (96% after 12 h heating), m.p. 127° (lit.,[20] 126°); 2,4,5-*trimethyl*-6- (4m) (91% after 12 h heating), m.p. 94—96° (Found: C, 63·6; H, 8·6. $C_8H_{13}N_3$ requires C, 63·55; H, 8·7%); *hydrochloride* of 2-*ethyl*-4- (4n) (93%), m.p. 247° (Found: C, 48·8; H, 6·9; N, 24·4. $C_7H_{12}ClN_3$ requires C, 48·4; H, 7·0; N, 24·2%); and the *hydrochloride* of 2-*isopropyl*-4-*methylaminopyrimidine* (4o) (93%), m.p. 195° (Found: C, 51·1; H, 7·2; N, 22·6. $C_8H_{14}ClN_3$ requires C, 51·2; H, 7·5; N, 22·4%). A similar procedure gave 4-methylaminopyrimidine (4a) (93%), m.p. 69—72° (lit.,[21] 69—75°); 6,7-*dihydro*-4-*methylamino*-5H-*cyclopenta*-[d]*pyrimidine* (7; $n = 3$) (96% after 12 h heating), m.p. 157—158° (Found: C, 64·4; H, 7·5; N, 28·4. $C_8H_{11}N_3$ requires C, 64·4; H, 7·4; N, 28·2%); and 5,6,7,8-*tetrahydro*-4-*methylaminoquinazoline* (7; $n = 4$) (91% after 10 h heating), m.p. 116° (Found: C, 66·4; H, 8·3; N, 25·4. $C_9H_{13}N_3$ requires C, 66·2; H, 8·0; N, 25·7%).

Rate Measurements.—A 2 × 10^{-4}M-solution of each imine hydriodide at 20° was diluted with 20·0% of its volume of 1M-potassium hydroxide, also at 20°, to give a final solution at pH 13; this was transferred to a spectrophotometer cell. The optical density of the mixture at 300 nm was read immediately and at intervals during 90% of the rearrangement; t_0 was obtained by extrapolation in the faster rearrangements. The cell was removed from the instrument (in a 20 ± 0·5° room) between readings. At t_∞ (24 h), the whole spectrum was almost indistinguishable from that of the corresponding authentic methylaminopyrimidine recorded under comparable conditions with an appropriate [I^-] in both cells. Plots of $\log[(D_0 - D_\infty)/(D - D_\infty)]$ *versus* time were rectilinear: $t_{\frac{1}{2}}$ values derived therefrom were repeatable within ±5%.

For slow rearrangements, an appropriately larger volume of mixture, made as above from individual solutions preheated to 70°, was maintained in a thermostat at 70 ± 0·2°. Samples, withdrawn at intervals, were rapidly cooled in ice–water before measurement of their optical density.

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