The Dimroth Rearrangement. Part XIII.[1] The Small Effect of *p*-Substitution on Rearrangement Rates for 1,2-Dihydro-2-imino-1-methyl-5-phenylpyrimidines

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Rates have been measured for the Dimroth rearrangements of 1,2-dihydro-2-imino-1-methyl-5-(*p*-substituted phenyl)pyrimidines. Although the mesomeric effects of the *p*-substituents are severely attenuated by the presence of a considerable interplanar angle between the benzene and pyrimidine rings, rearrangement rates decrease in the order NO_2 > F > Cl > Br > Me > OMe > NH_2 > NMe_2, following qualitatively the σ_p values for the groups. 1,2-Dihydro-2-imino-1,4,6-trimethyl-5-phenylpyrimidine and its *p*-nitro- and *p*-amino-derivatives, for which u.v. spectra and pK_a values indicate even less through-conjugation, behave similarly.

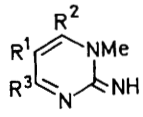
Syntheses are described for the three trimethylated imines and their products of rearrangement; for 1,2-dihydro-2-imino-1,6-dimethylpyrimidine, which rearranges more rapidly than its 1,4-dimethyl-isomer; and for 1,2-dihydro-2-imino-5-methoxy-1-methylpyrimidine, required for comparison of its rearrangement with that of the *p*-methoxyphenyl analogue and with those of quinazoline analogues. Structures were confirmed by ^{1}H n.m.r. spectra.

ALTHOUGH the profound effect of substitution on the rate of Dimroth rearrangement in 1,2-dihydro-2-imino-1-methylpyrimidines (1) has been studied in detail,[2] proximity effects have precluded quantitative correlation of rates with substituent constants. In an attempt to eliminate such secondary factors, we have prepared a series of 1,2-dihydro-2-imino-1-methyl-5-(*p*-substituted

[1] Part XII, A. Albert, *J. Chem. Soc.* (*C*), 1970, 230.

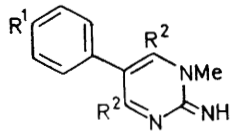
[2] D. J. Brown, in 'Mechanisms of Molecular Migrations,' ed. B. S. Thyagarajan, Interscience, New York, 1968, vol. 1, p. 209; also references therein.

phenyl)pyrimidines [3] (2; $R^2 = H$) and their 1,4,6-trimethyl homologues (2; $R^2 = Me$). In these, the steric environment of the 1,6-bond undergoing fission is maintained; each substituent exerts its electronic effect from the remote *para*-position. This approach has already led to a satisfactory correlation [3] of pK_a with



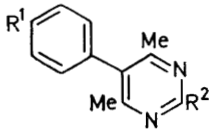
(1)

	R^1	R^2	R^3
a;	H	Me	H
b;	OMe	H	H
c;	H	Me	Cl
d;	H	H	Me
e;	Br	H	H
f;	H	H	H
g;	Cl	H	H
h;	I	H	H
i;	H	Me	Me
j;	Br	Me	Me



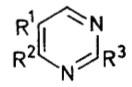
(2)

	R^1	R^2		R^1	R^2
a;	H	Me	g;	Cl	H
b;	NO_2	Me	h;	Br	H
c;	NH_2	Me	i;	Me	H
d;	H	H	j;	OMe	H
e;	NO_2	H	k;	NH_2	H
f;	F	H	l;	NMe_2	H



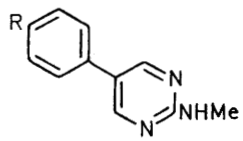
(3)

	R^1	R^2
a;	H	NH_2
b;	H	SH
c;	H	SMe
d;	H	SO_2Me
e;	H	NHMe
f;	H	OH
g;	NO_2	OH
h;	NO_2	Cl
i;	NO_2	NH_2
j;	NO_2	NHMe
k;	NH_2	NH_2
l;	NMe_2	NH_2
m;	NH_2	NHMe



(4)

	R^1	R^2	R^3
a;	H	Me	NH_2
b;	H	Me	NHMe
c;	OMe	H	NH_2
d;	Cl	H	NH_2
e;	OMe	H	NHMe
f;	OMe	Cl	SMe
g;	OMe	Cl	SO_2Me
h;	OMe	H	SO_2Me
i;	OMe	OH	SMe
j;	OMe	OH	NH_2
k;	OMe	Cl	NH_2



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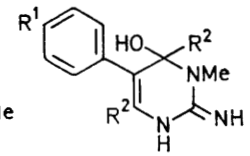

(6)

R = (a) H; (b) NO_2; (c) F; (d) Cl; (e) Br; (f) Me; (g) OMe; (h) NH_2; (i) NMe_2

σ values. In addition, we have prepared and rearranged the imines (1a and b) for comparison with similar studies of 1,2-dihydro-2-imino-1,4-dimethylpyrimidine [4] and 2,3-dihydro-2-imino-5(or 6 or 7)-methoxy-3-methylquinazolines,[5] respectively.

Preparations.—3-Phenylacetylacetone was prepared by an improved method: boron trifluoride–ether complex was used to facilitate acetylation of benzyl methyl ketone. It could be condensed directly with guanidine carbonate to give 2-amino-4,6-dimethyl-5-phenylpyrimidine (3a), but the yield was very poor. However, the same diketone was converted [6] by thiourea into the mercaptopyrimidine (3b) and thence by successive *S*-methylation, oxidation, and aminolysis into the phenylpyrimidines (3c, d, and a). *N*-Methylation of the amine (3a) gave the imine (2a), which rearranged in alkali to its isomer (3e), also prepared by methylaminolysis of the sulphone (3d). In contrast to the formation of 2-amino-5-*p*-nitrophenylpyrimidine,[3] nitration of the aminopyrimidine (3a) gave only 2-amino-4,6-dimethyl-5-*m*-nitrophenylpyrimidine and other unwanted products. However, nitration of the hydroxypyrimidine (3f) [6] gave its *p*-nitro-derivative (3g), which was converted *via* the chloro-compound (3h) into the required amine (3i). This underwent methylation to yield the imine (2b), and thence the isomer (3j), which was also made by aminolysis of its chloro-analogue (3h). The *p*-aminophenylimine (2c) was best made as its hydriodide by reduction of the corresponding nitro-imine (2b) with iron powder in the presence of hydriodic acid, but it was also made by reduction of the nitro-amine (3i) to the diamine (3k) followed by methylation; in the last step the main product was the *p*-dimethylamino-amine (3l), distinguished from possible isomeric products by its failure to diazotize and couple, by the lack of an n.m.r. doublet representing a 2-methylamino-group, and by the absence of a high pK_a value. Rearrangement of the imine (2c) and hydrogenation of the nitro-compound (3j) both gave the amino-methylamine (3m). An attempt to prepare the nitro-amine (3i) by a Gomberg reaction between *p*-nitrobenzenediazonium chloride and 2-amino-4,6-dimethylpyrimidine gave only 4,6-dimethyl-2-(*p*-nitrophenyldiazoamino)pyrimidine (*cf.* ref. 7). The structures of this and the other products mentioned were confirmed by ^1H n.m.r. spectra (Table 1).

2-Amino-4-chloro-6-methylpyrimidine, unlike the dechloro-analogue (4a), underwent methylation at the ring-nitrogen atom between the amino- and the methyl groups. The structure of the product (1c) was established by dechlorination to the imine (1a). This differed from the known [4] isomer (1d) but both gave the same methylaminopyrimidine (4b) [4] on rearrangement.

2-Amino-5-methoxypyrimidine (4c) was prepared by a rather unsatisfactory indirect method,[8,9] because a direct approach by attempted condensation of 1,1,2,3,3-pentamethoxypropane (made from its 2-bromo-analogue [10] by an improved method) with guanidine in ethanolic

[3] D. J. Brown and B. T. England, *J. Chem. Soc.* (*C*), in the press.

[4] D. J. Brown and M. N. Paddon-Row, *J. Chem. Soc.*, (*C*) 1967, 1928.

[5] D. J. Brown and B. T. England, *Austral. J. Chem.*, 1968, **21**, 2813.

[6] C. R. Hauser and R. M. Manyik, *J. Org. Chem.*, 1953, **18**, 588.

[7] B. Lythgoe and L. S. Rayner, *J. Chem. Soc.*, 1951, 2323; R. S. Karlinskaya and N. V. Khromov-Borisov, *J. Gen. Chem.* (*U.S.S.R.*), 1962, **32**, 1829.

[8] Z. Buděšínský, V. Bydžovský, J. Kopecký, A. Šváb, and J. Vavřina, *Cesk. Farm.*, 1961, **10**, 241.

[9] Z. Buděšínský, V. Bydžovský, J. Kopecký, J. Přikryl, and A. Šváb, *Cesk. Farm.*, 1961, **10**, 14.

[10] H. Bredereck, F. Effenberger, and E. H. Sweitzer, *Chem. Ber.*, 1962, **95**, 803.

TABLE 1

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

Compd. [a]		τ Values [b]
(1a)	A	*C*-Me: 7·42; *N*-Me: 6·37; 5-H: 2·66 (d, *J* 7); 4-H: 1·36 (d, *J* 7)
	B	*C*-Me: 7·09; *N*-Me: 6·08; 5-H: 1·90 (d, *J* 7); 4-H: 0·74 (d, *J* 7)
(1b)	B	OMe: 6·18; *N*-Me: 6·07; 6-H: 1·06 (d, J_m3); 4-H: 1·27 (d, J_m3)
(1c)	B	*C*-Me: 7·36; *N*-Me: 6·24; 5-H: 2·80
(1d)	A	*C*-Me: 7·63; *N*-Me: 6·21; 5-H: 3·08 (d, *J* 7); 6-H: 1·99 (d, *J* 7)
	B [c]	*C*-Me: 7·38; *N*-Me: 6·10; 5-H: 2·82 (d, *J* 7); 6-H: 1·64 (d, *J* 7)
(2a)	B	4,6-Me_2: 7·80, 7·68; *N*-Me: 6·25; Ph: 2·5(m)
(2b)	A	4,6-Me_2: 7·82, 7·72; *N*-Me: 6·30; C_6H_4: 2·31, 1·56 (A_2B_2)
(2c)	A	4,6-Me_2: 7·76, 7·65; *N*-Me: 6·30; C_6H_4: 3·24, 3·05 (A_2B_2)
(3a)	A	4- + 6-Me: 7·86; NH_2: 5·6br; Ph: 2·5br
(3b)	A	4- + 6-Me: 7·86; Ph: 2·5(m)
(3c)	C	4- + 6-Me: 7·80; SMe: 7·40; Ph: 2·6(m)
(3d)	C	4- + 6-Me: 7·76; SO_2Me: 6·43; Ph: 2·5(m)
(3e)	C	4- + 6-Me: 7·84; *N*-Me: 6·94(d); NH: 4·4br; Ph: 2·6(m)
(3g)	A	4- + 6-Me: 7·96; C_6H_4: 2·30, 1·62 (A_2B_2)
(3h)	C	4- + 6-Me: 7·73; C_6H_4: 2·48, 1·49 (A_2B_2)
(3i)	A	4- + 6-Me: 7·84; C_6H_4: 2·30, 1·61 (A_2B_2)
m-(3i) [d]	A	4- + 6-Me: 8·00; 6′-H: 3·41(m); 4′- + 5′-H: 2·20(m); 2′-H: 1·85
(3j)	A	4- + 6-Me: 7·82; *N*-Me: 6·90(d); C_6H_4: 2·28, 1·67 (A_2B_2)
(3k)	A	4- + 6-Me: 7·86; C_6H_4: 3·09, 2·96 (A_2B_2)
(3l)	B	4- + 6-Me: 7·66; NMe_2: 6·56; C_6H_4: 2·31, 2·10 (A_2B_2)
	C	4- + 6-Me: 7·82; NMe_2: 6·97; C_6H_4: 3·14, 2·95 (A_2B_2)
(3m)	C	4- + 6-Me: 7·88; *N*-Me: 6·98(d); NH_2: 6·0br; NH: 4·5br; C_6H_4: 3·18, 3·07 (A_2B_2)
(4c) [e]	C	OMe: 6·24; NH_2: 4·2br; 4- + 6-H: 1·78
(4d)	A	NH_2: 3·1br; 4- + 6-H: 1·71
(4e)	C	*N*-Me: 7·02; OMe: 6·19; 4- + 6-H: 1·84
(4f)	C	SMe: 7·49; OMe: 6·20; 6-H: 21·0
(4g)	C	OMe: 6·67; SO_2Me: 5·84; 6-H: 1·43
(4i)	A	SMe: 7·55; OMe: 6·27; 6-H: 2·45
(4j)	A	OMe: 6·32; 6-H: 2·29
(4k)	C	OMe: 6·06; NH_2: 2·3br; 6-H: 1·84
[f]	C	4- + 6-Me: 7·49; 5-H: 3·12; C_6H_4: 2·12, 1·66 (A_2B_2)
[g]	C	4- + 6-Me: 7·89; Ph: 2·6(m)

[a] In (A) $(CD_3)_2SO$, (B) 2N-DCl, or (C) $CDCl_3$; compounds (1a—2c) as hydriodides. [b] Singlets unless indicated otherwise; all A_2B_2 systems had J_o 9 Hz and doublets for NHMe had $J_{NH,Me}$ 5 Hz. [c] *Cf.* T. J. Batterham, D. J. Brown, and M. N. Paddon-Row, *J. Chem. Soc.* (*B*), 1967, 171. [d] *meta*-Isomer of (3i). [e] Crude sample. [f] 4,6-Dimethyl-2-*p*-nitrophenyldiazoaminopyrimidine. [g] $PhCAc_2.BF_2$.

hydrogen chloride gave only 2-amino-5-chloropyrimidine (4d). Methylation of the amine (4c) gave the required imine (1b), which rearranged to the methylaminopyrimidine (4e), also prepared from 4-chloro-5-methoxy-2-methylthiopyrimidine (4f) [8] *via* the intermediates (4g and h).

Rearrangement Rates.—The pK_a values and u.v. spectra (Table 2 and ref. 3) of the imines (2a—l) and their rearrangement products (3e, j, m; 5a—i) showed that each imine was >99% unprotonated at pH 13 and/or 14 and that its rearrangement at high pH could be followed spectrophotometrically. A final spectral comparison of each imine solution after the completion of rearrangement with that of the corresponding pure methylaminopyrimidine confirmed the virtual absence of by-products.

TABLE 2

Ionization and spectra

Pyrimidine	pK'_a [a]	$\lambda_{max.}$ (log ε) [b]	pH
(1a)	10·86 ± 0·05	340(3·47), 229(4·30)	13
	(300)	302(3·71), 223(4·32)	8
(1b)	11·44 ± 0·04	368(3·40), *250(4·08)*	14
	(250)	336(3·60)	8
(2a)	11·48 ± 0·02	343(3·54), *247(4·27)*	14
	(250)	305(3·74), 228(4·44)	8
(2b)	11·03 ± 0·04	*350(3·70)*, 320(3·94), *270(4·05)*	14
	(295)	*310(3·94)*, 276(4·08)	8
(2c)	11·71 ± 0·05	344(3·42), 249(4·35)	14
	3·64 ± 0·04	*300(3·76)*	8
	(260)	306(3·74)	1
(3a)	4·91 ± 0·03	293(3·59), 235(4·15)	7
	(315)	305(3·74), 231(4·23)	2
(3e)	5·12 ± 0·04	306(3·54), 244(4·21)	8
	(325)	316(3·69), 237(4·30)	2
(3i)	4·54 ± 0·03	*345(3·42)*, 290(4·11), 226(4·22)	8
	(265)	289(4·12), 224(4·27)	1
m-(3i) [c]	4·47 ± 0·05	*285(3·94)*, 234(4·18)	8
	(305)	297(3·90), 275(3·94), 229(4·30)	1
(3j)	4·41 ± 0·04	*350(3·52)*, 298(4·01), 239(4·25)	8
	(295)	*315(3·98)*, 276(4·04), 231(4·30)	1
(3k)	5·12, 3·71 [d]	*295(3·71)*, 235(4·24)	8
	(255)	304(3·75), 231(4·26)	1
(3l)	5·31, 3·86 [d]	*300(3·75)*, 257(4·24), 226(4·22)	8
	(260)	304(3·75), 231(4·27)	1
(3m)	5·29, 3·77 [d]	*310(3·57)*, 246(4·30)	8
	(260)	317(3·68), 238(4·31)	1
(4e)	3·44 ± 0·06	336(3·37), 238(4·15)	6
	(230)	361(3·73), 236(4·13)	1

[a] For method see Experimental Section; analytical wavelength (nm) in parentheses. [b] In nm.; inflexions in italics. [c] *meta*-Isomer of (3i). [d] Calculated with the aid of a computer programme (H. Kinns and D. D. Perrin, personal communication).

The first-order constants for the disappearance of imines (Table 3) were a measure of the rates of the ring-

TABLE 3

Rearrangement rates [a] of 1,2-dihydro-2-imino-1-methylpyrimidines

Imine	Analyt. λ (nm.)	20° and pH 13	30° and pH 13	40° and pH 13	40° and pH 14
(2d)	370	1·63, *424*	5·09, *136*	17·3, *40*	19·8, *35*
(2e)	370	2·30, *301*	8·77, *79*	23·9, *29*	27·7, *25*
(2f)	370	2·00, *346*	6·45, *108*	17·8, *39*	18·8, *37*
(2g)	370	1·86, *372*	5·97, *116*	15·7, *44*	17·8, *39*
(2h)	370	1·69, *410*	5·50, *126*	17·4, *40*	18·7, *37*
(2i)	370	1·61, *430*	5·37, *129*	16·5, *42*	17·4, *40*
(2j)	380	1·60, *431*	5·33, *130*	16·4, *43*	17·4, *40*
(2k)	370	1·58, *438*	5·25, *132*	14·4, *48*	13·5, *51*
(2l)	370	1·56, *444*	4·86, *143*	13·6, *51*	14·2, *49*
(2a)	350	2·69, *257* [b]	7·97, *87* [b]		21·1, *33*
(2b)	350	3·75, *185* [b]	11·0, *63* [b]		29·9, *23*
(2c)	350	1·80, *386* [b]	5·76, *120* [b]		12·2, *45*
(1a)	350	25·8, *27* [b]	60·3, *11·5* [b]		133, *5·2*
(1b)	384	9·18, *76* [b]	22·7, *31* [b]		47·4, *15*

[a] First-order constants (10^3k in min^{-1}); $t_{\frac{1}{2}}$ values (min.) in italics; estimated accuracy within ±5% for $t_{\frac{1}{2}}$ values above 100 min. and ±10% below 100 min. [b] At pH 14.

fission steps, known [11] to be rate-determining in such systems. It was evident that each substituent affected the rates far less when attached at the *para*-position of a 5-phenyl group than when attached directly to the

[11] D. D. Perrin, *J. Chem. Soc.*, 1963, 1284; D. D. Perrin and I. H. Pitman, *ibid.*, 1965, 7071.

pyrimidine ring: for example, the *p*-bromo-derivative (2h) rearranged only slightly more rapidly than its parent imine (2d) whereas the 5-bromo-derivative (1e) underwent ring fission [12] about 120 times as fast as its parent (1f); similarly, *p*-methoxylation [(2b) → (2j)] produced an almost insignificant slowing of rearrangement but 5-methoxylation [(1f) → (1b)] decreased the rate by 50%. The effect of *para*-substitution on rearrangement of the imines (2d—l) was so small because of reduced interannular transmission resulting from the considerable angle between the two rings. This phenomenon has been discussed already with reference to the ionization constants and spectra of the series (2d—l), (5a—i), and the corresponding 2-amino-analogues; [3] it was accentuated in the present context because the species actually undergoing the rate-determining ring-fission were not the imines (2) but almost certainly [11] the water-adducts (6), in which an even greater interplanar angle must exist, and which have a less satisfactory conjugation pathway for the transmission of resonance effects.

The addition of *C*-methyl groups at the 4- and 6-positions on such imines (2a—c) further reduced transmission of substituent effects as judged by the ionization constants: the difference between the pK_a values of the *p*-nitro- and *p*-amino-imines (2b and c) was appreciably less than that [3] between the values for the corresponding pair (2e and k) lacking *C*-methyl groups. On the other hand, no such effect was evident in the rearrangement rates, for example, in a comparison of ratio of $t_{\frac{1}{2}}$ values for the imines (2b and c) with the corresponding ratio for the lower homologues (2e and k). None of the rearrangements showed appreciable sensitivity to base catalysis.

TABLE 4

Approximate kinetic parameters [a]

Compounds	E_A(kcal.)	$\Delta S^\ddagger$ (e.u.)	$\Delta G^\ddagger$ (kcal.)
(1a)	15	−26	22
(1b)	15	−26	22
(1e, g, h) [b]	19 ± 0·1	+ 1 ± 0·4	17 ± 0·2
N-Et-(1e) [b,c]	19 ± 0·1	−1	18
(1f) [b]	25	+4	23
(1i) [d]	28	+15	23
(1j) [b]	20	−7	22
(2a—c)	19 ± 0·1	−15·5 ± 0·9	23 ± 0·2
(2d—l)	23 ± 0·3	−7·5 ± 0·7	25 ± 0·5

[a] For ring-fission reaction; spreads given where a series is involved. [b] Calculated from data in ref. 11. [c] *N*-Ethyl homologue of (1e). [d] Calculated from rather inadequate data in ref. 12.

The small spreads in kinetic parameters (Table 4) for the two series (2a—c) and (2d—l) emphasised the poor interannular transmission of substituent effects. Nevertheless, plots of log *k* against Berliner's substituent constants [13] showed approximate rectilinearity, although a truly quantitative relationship could not be claimed. This unsatisfactory outcome probably resulted from the decreased dominance of electronic control permitting minor factors to become relatively important in the measured rates. The calculated parameters indicated that the 4,6-dimethylated imines (2a—c) underwent ring fission (and subsequent steps) a little more rapidly than did their respective homologues (2d, e, and k) because of lower energies of activation (E_A) and despite a numerically higher negative entropy of activation ($\Delta S^\ddagger$) arising presumably from greater steric crowding in the transition state; the reverse order pertained in the rates for ring-fission of the simple imines (1f and i) on account of a lower E_A value for the former and despite a higher positive $\Delta S^\ddagger$ value for the latter. 5-Bromo-1-ethyl-1,2-dihydro-2-iminopyrimidine rearranged more slowly than its methyl homologue (1e) because of a negative probability factor occasioned by increased steric requirements in the transition state of the higher homologue. The free energy of activation ($\Delta G^\ddagger$) values are consistent with the rate constants.

1,2-Dihydro-2-imino-1,6-dimethylpyrimidine (1a) rearranged much more rapidly ($t_{\frac{1}{2}}$ *ca.* 20 min. at 25°) than its 1,4-dimethyl-isomer[(1d); $t_{\frac{1}{2}}$ >310 min.] or their homologues [(1f); $t_{\frac{1}{2}}$ = 114 min. and (1i); $t_{\frac{1}{2}}$ 166 min.] under the same conditions. These figures suggested that rearrangement of the imine (1f) was facilitated by a 6-methyl but retarded by a 4-methyl substituent and that the rate for the 4,6-dimethyl derivative (1i) was due to a combination of both effects. This hypothesis was consistent with the published [4] data for other 4-mono- and 4,6-di-methylated imines and with the kinetic parameters for the imines (1a, f, and i); we are unable to suggest a rational explanation.

The rearrangement rate for the 5-methoxy-imine (1b) was greater than that [12] for the parent imine (1f) and even approached those [14] for the 5-halogenated imines (1e, g, and h). This indicated an inductive electron-withdrawal from the reaction site in contrast to the mesomeric electron-donation as evinced both by the enhanced pK_a value of the methoxy-imine (11·4) compared with that [12] for its parent (1f) (pK_a 10·8), and by the rearrangement rates for the *p*-methoxyphenyl imine (2j) compared with those for its parent (2d). These results paralleled those [5] from the quinazoline series: insertion of a methoxy-group within inductive range of the reaction site increased the rearrangement rate, but at a greater distance it decreased the rate.

Ionization and Spectra.—The usual base-strengthening effect of two methyl groups (1—1·5 units) was evident in comparing ionization constants for the 4,6-dimethylpyrimidines (2a and b; 3a and i; 3e and j) with those [3] for their respective lower homologues (2d and e; 5a and b; and the 2-amino-analogues of the latter pair). However, these methyl groups had little or no effect on the *p*-amino-group of the imine (2c) (pK_a 11·7 and 3·6) because its lower constant was so close to that of the homologue (2k) (pK_a 11·0 and 3·4). Hence, in the diamine (3k) (pK_a 5·1 and 3·7), the higher value could

[12] D. J. Brown and J. S. Harper, *J. Chem. Soc.*, 1963, 1276.
[13] E. Berliner and E. A. Blommers, *J. Amer. Chem. Soc.*, 1951, **73**, 2479; E. Berliner and L. H. Liu, *ibid.*, 1953, **75**, 2417.
[14] D. J. Brown and M. N. Paddon-Row, *J. Chem. Soc.* (*C*), 1967, 903.

not be assigned to the *p*-amino-group, which in the homologous 2-amino-5-*p*-aminophenylpyrimidine [3] had a pK_a value of only 4·2, and it was allotted to the guanidine system of the pyrimidine; the remaining value (3·7) for the *p*-amino-group, was depressed by prior protonation in the pyrimidine, and therefore corresponded closely to the second constant (3·6) for the imine (2c). This assignment, the reverse of that [3] in the lower homologues (5h and i; and their 2-amino-analogues), was consistent with the changes in pK_a value resulting from additional methyl groups in the diamines (3l and m).

A comparison of the u.v. spectra for 5-phenylpyrimidines [3] with those for their respective 4,6-dimethyl derivatives (Table 2) confirmed the presence of a larger interplanar angle in the latter. For example, on 4,6-dimethylation the whole spectrum of the amine (5a) underwent a hypsochromic shift, *ca.* 20 nm. for the neutral molecule and *ca.* 30 nm. for the cation. Such shifts differed from the usual small bathochromic effects of *C*-methyl groups on spectra, and were interpreted as indicating sharply diminished conjugation between the rings on account of twisting by steric hindrance (*cf.* a similar spectral shift evident in comparing biphenyl and 2,2′-dimethylbiphenyl, which have interplanar angles of *ca.* 25° and 70° respectively; [15] when a measure of flatness is restored to such compounds by insertion of a 6,6′-methylene bridge,[16] a comparable bathochromic shift occurs).

EXPERIMENTAL

Analyses were done by Dr J. E. Fildes and her staff; ^{1}H n.m.r. spectra were measured by Mr S. E. Brown at 60 MHz and 33° with tetramethylsilane or sodium 3-trimethylsilylpropane-1-sulphonate as standard; and u.v. spectra were obtained with a Shimadzu recording spectrophotometer (positions of peaks were checked with an Optica manual instrument). The ionization constants were measured spectrometrically at 20° at concentrations below 10^{-4}M in buffers [17] of 10^{-2}M ionic strength. The methods are outlined by Albert and Serjeant; [18] thermodynamic corrections were not applied.

Rate Measurements.—A 4 × 10^{-4}M-solution of each imine hydriodide was brought to the required temperature in a thermostatted cell holder in the recording spectrophotometer. It was diluted with an equal volume of carbonate-free 0·17M- or 1·8M-potassium hydroxide already at the same temperature to produce a final pH value of 13 or 14. The first optical density reading at the chosen analytical wavelength was taken 30 sec. after mixing and thereafter at intervals during at least 80% of the reaction. The most suitable wavelength for following the disappearance of each imine during its rearrangement (Table 3) was predetermined by successive complete scans of the spectra of solutions prepared as described. 'Infinity' readings were recorded about 24 hr. after the initiation of each rearrangement. The k_1 values were derived from plots of log $(D_0 - D_\infty/D - D_\infty)$ against time (D = optical density), which all proved to be rectilinear; $t_{\frac{1}{2}}$ values were derived therefrom and checked by direct reference to the spectrophotometer record. These parameters were reproducible in successive runs to within ±1%.

3-*Phenylacetylacetone.*—Boron trifluoride–ether complex (B.D.H.) (56·4 g.) was added with stirring to a mixture of benzyl methyl ketone (26·8 g.), acetic anhydride (40·8 g.), and toluene-*p*-sulphonic acid (4·4 g.), precooled to below 10°. The mixture was stirred at 25° for 30 min., then heated under reflux (120° bath) for 2 hr. and set aside for 12 hr. Recrystallisation of the precipitate from light petroleum followed by sublimation (120°/0·3 mm.) gave 3-*phenylacetylacetone borofluoride* (90%), m.p. 163° (Found: C, 59·4; H, 5·2; F, 16·4. $C_{11}H_{11}BF_2O_2$ requires C, 59·0; H, 4·95; F, 16·9%). The crude complex (35 g.), sodium acetate (110 g.), and water (250 ml.) were boiled under reflux for 2 hr. The cooled mixture was extracted with light petroleum (b.p. 40—60°; 3 × 100 ml.). The extract was washed with saturated aqueous sodium hydrogen carbonate and evaporated to give 3-phenylacetylacetone (84%), m.p. 58—60° (lit.,[6] 58·5—59·5°).

4,6-*Dimethyl*-2-*methylthio*-5-*phenylpyrimidine.*— 2-Mercapto-4,6-dimethyl-5-phenylpyrimidine hydrochloride (5·0 g.) (prepared [6] from 3-phenylacetylacetone) was dissolved in N-sodium hydroxide (70 ml.). The solution was shaken with methyl iodide (2 × 5 ml.) for 30 min. at 25°. Extraction with chloroform and evaporation gave the *methylthiopyrimidine* (93%), m.p. 69° (from ethanol) (Found: C, 67·6; H, 6·1; N, 12·0. $C_{13}H_{14}N_4S$ requires C, 67·8; H, 6·1; N, 12·2%).

4,6-*Dimethyl*-2-*methylsulphonyl*-5-*phenylpyrimidine.*—The methylthiopyrimidine (4·6 g.) in chloroform (20 ml.) was added gradually to a cooled solution of *m*-chloroperbenzoic acid (75%; 8·4 g.) in chloroform (200 ml.). The mixture was set aside at room temperature overnight, then shaken with saturated aqueous sodium sulphite, N-sodium carbonate, and then water. Evaporation gave the *sulphone* (89%), m.p. 146° (from ethanol) (Found: C, 59·2; H, 5·5; N, 10·8. $C_{13}H_{14}N_2O_2S$ requires C, 59·5; H, 5·4; N, 10·7%).

4,6-*Dimethyl*-2-*methylamino*-5-*phenylpyrimidine.*—(*a*) The foregoing sulphone (0·7 g.) and ethanolic methylamine (33%; 5 ml.) were heated at 100° in a sealed tube for 2 hr. The residue from evaporation was recrystallised from ethanol and sublimed (110°/0·4 mm.) to give the *methylaminopyrimidine* (90%), m.p. 133° (Found: C, 72·95; H, 6·8; N, 19·6. $C_{13}H_{15}N_3$ requires C, 73·2; H, 7·1; N, 19·7%).

(*b*) 1,2-Dihydro-2-imino-1,4,6-trimethyl-5-phenylpyrimidine hydriodide (0·2 g.) was warmed in 2N-sodium hydroxide (20 ml.) for 4 hr. Extraction with chloroform and sublimation gave the methylaminopyrimidine (84%) identical with that obtained in (*a*).

2-*Amino*-4,6-*dimethyl*-5-*phenylpyrimidine.*—(*a*) The sulphone (0·5 g.), ammonium chloride (0·75 g.), and conc. aqueous ammonia (5 ml.) were heated in a sealed tube at 120° for 18 hr. The mixture was boiled for 10 min. to remove ammonia; cooling then gave the 2-aminopyrimidine (81%), m.p. 179° (after recrystallisation from ethanol and sublimation at 130°/0·2 mm.; *cf.* lit.,[6] m.p. 180—181°).

(*b*) 3-Phenylacetylacetone (1·0 g.) and guanidine carbonate (0·9 g.) were heated together at 150° for 15 hr. Ex-

[15] H. Suzuki, *Bull. Chem. Soc. Japan*, 1959, **32**, 1340, 1350, 1357.
[16] R. B. Sandin, R. Melby, A. S. Hay, R. N. Jones, E. C. Miller, and J. A. Miller, *J. Amer. Chem. Soc.*, 1952, **74**, 5073.
[17] D. D. Perrin, *Austral. J. Chem.*, 1963, **16**, 572.
[18] A. Albert and E. P. Serjeant, 'Ionization Constants of Acids and Bases,' Methuen, London, 1962.

traction with carbon tetrachloride and recrystallisation of the residue from ethanol gave the same amino-compound (18%) as in (*a*).

1,2-*Dihydro*-2-*imino*-1,4,6-*trimethyl*-5-*phenylpyrimidine Hydriodide*.— 2-Amino-4,6-dimethyl-5-phenylpyrimidine (0·2 g.) was heated at 115° with methyl iodide (2 ml.) for 2 hr. The *iminopyrimidine hydriodide* (71%) had m.p. 225° (from ethanol) (Found: C, 45·4; H, 4·75; N, 12·05. $C_{13}H_{16}IN_3$ requires C, 45·7; H, 4·7; N, 12·3%).

Nitration of 2-*Amino*-4,6-*dimethyl*-5-*phenylpyrimidine*.—(*a*) A solution of the aminopyrimidine (0·3 g.) in conc. sulphuric acid (7·0 ml.) was cooled to 5—10°. Potassium nitrate (0·4 g.) was added with stirring during 20 min. and after a further 30 min. at 25° the solution was poured on ice and adjusted to pH 4—5. The resulting solid was dried and extracted with boiling methanol (15 ml.). The residual 2-*amino*-4,6-*dimethyl*-5-m-*nitrophenylpyrimidine* (42%) had m.p. 205° (from 60% aqueous ethanol) (Found: C, 58·85; H, 4·9; N, 22·75. $C_{12}H_{12}N_4O_2$ requires C, 59·0; H, 4·95; N, 22·9%). Evaporation of the methanolic extract gave a solid, mainly the *p*-nitro-isomer (see later) (^{1}H n.m.r. evidence).

(*b*) The aminopyrimidine (0·4 g.) was added during 20 min. to polyphosphoric acid (8 g.) containing nitric acid (*d* 1·42; 5 g.) at 60°. After a further 3 hr. the mixture was poured on ice and adjusted to pH 4. The solid was identified as 2-hydroxy-4,6-dimethyl-5-*p*-nitrophenylpyrimidine (see later).

(*c*) Use of nitric acid–sulphuric acid gave a mixture of amino- and hydroxy-pyrimidines; nitric acid-glacial acetic acid had no effect; and acetyl nitrate gave intractable tars.

2-*Hydroxy*-4,6-*dimethyl*-5-p-*nitrophenylpyrimidine*.—Concentrated sulphuric acid (4·0 ml.) was added slowly to a solution of 2-hydroxy-4,6-dimethyl-5-phenylpyrimidine hydrochloride [6] in nitric acid (*d* 1·5; 4·0 ml.) at 0—5°. After a further 1 hr. at 25° the mixture was poured on ice and adjusted to pH 4. The dried solid was Soxhlet-extracted with methanol until the remaining solid was colourless. Repeated recrystallisation of this solid from boiling methanol gave the p-*nitrophenylpyrimidine* (24%), m.p. 286° (Found: C, 59·0; H, 4·7; N, 16·9. $C_{12}H_{11}N_3O_3$ requires C, 58·8; H, 4·5; N, 17·1%).

2-*Chloro*-4,6-*dimethyl*-5-p-*nitrophenylpyrimidine*.—The 2-hydroxypyrimidine (0·4 g.) was heated under reflux with phosphoryl chloride (12 ml.) for 12 hr. The residue from partial distillation was poured on ice, stirred for 20 min., and adjusted to pH 4. The *chloropyrimidine* (91%) had m.p. 278—280° (from ethanol) (Found: C, 54·45; H, 3·8; N, 16·0. $C_{12}H_{10}ClN_3O_2$ requires C, 54·7; H, 3·8; N, 15·9%).

2-*Amino*-4,6-*dimethyl*-5-p-*nitrophenylpyrimidine*.—Ethanolic 10N-ammonia (10 ml.) and the foregoing chloropyrimidine (1·0 g.) were heated for 17 hr. at 150°. The resulting *aminopyrimidine* (>90%) had m.p. 277° (from ethanol) (Found: C, 58·8; H, 4·8; N, 22·7. $C_{12}H_{12}N_4O_2$ requires C, 59·0; H, 4·9; N, 22·9%).

4,6-*Dimethyl*-2-*methylamino*-5-p-*nitrophenylpyrimidine*.—(*a*) Ethanolic methylamine (33%; 3 ml.) and the chloropyrimidine (0·3 g.) were heated for 17 hr. at 150°. The *methylaminopyrimidine* (>90%) had m.p. 248° (from propanol) (Found: C, 60·5; H, 5·6; N, 21·5. $C_{13}H_{14}N_4O_2$ requires C, 60·45; H, 5·5; N, 21·7%).

(*b*) 1,2-Dihydro-2-imino-1,4,6-trimethyl-5-p-nitrophenylpyrimidine hydriodide (0·2 g.) was warmed at 50° in 2N-sodium hydroxide (20 ml.) for 4 hr. Extraction with chloroform and sublimation gave the methylaminopyrimidine (78%) identical with that obtained in (*a*).

1,2-*Dihydro*-2-*imino*-1,4,6-*trimethyl*-5-p-*nitrophenylpyrimidine Hydriodide*.—2-Amino-4,6-dimethyl-5-*p*-nitrophenylpyrimidine (0·5 g.) was heated with methyl iodide (5 ml.) at 115° for 2 hr. The *iminopyrimidine hydriodide* (84%) had m.p. 246° (from methanol) (Found: C, 40·2; H, 3·6; N, 14·8. $C_{13}H_{15}IN_4O_2$ requires C, 40·4; H, 3·9; N, 14·5%).

2-*Amino*-5-p-*aminophenyl*-4,6-*dimethylpyrimidine*.— The 2-amino-4,6-dimethyl-5-*p*-nitrophenylpyrimidine (0·3 g.) and Raney nickel catalyst (2·0 g. wet) were shaken in methanol (180 ml.) under hydrogen at 25°. The catalyst was removed and the filtrate was evaporated to dryness. The residual 2-*amino*-5-p-*aminophenyl*-4,6-*dimethylpyrimidine* was reprecipitated from warm dilute hydrochloric acid by aqueous ammonia and recrystallised from water; yield 38%, m.p. 214° (Found: C, 67·5; H, 6·7; N, 26·0. $C_{12}H_{14}N_4$ requires C, 67·3; H, 6·6; N, 26·15%).

5-p-*Aminophenyl*-4,6-*dimethyl*-2-*methylaminopyrimidine*.—(*a*) 4,6-Dimethyl-2-methylamino-5-nitropyrimidine was hydrogenated like its 2-amino-homologue. The p-*aminophenylpyrimidine* (83%) had m.p. 107° (from ethanol) (Found: C, 68·6; H, 7·0; N, 24·1. $C_{13}H_{16}N_4$ requires C, 68·4; H, 7·1; N, 24·5%).

(*b*) 5-*p*-Aminophenyl-1,2-dihydro-2-imino-1,4,6-trimethylpyrimidine hydriodide (0·2 g.) was warmed in 2N-sodium hydroxide (20 ml.) for 4 hr. Extraction with chloroform and sublimation gave the methylamino-compound (81%) identical to that obtained in (*a*).

5-p-*Aminophenyl*-1,2-*dihydro*-2-*imino*-1,4,6-*trimethylpyrimidine Hydriodide*.—1,2-Dihydro-2-imino-1,4,6-trimethyl-5-*p*-nitrophenylpyrimidine (4·0 g.) was refluxed for 7 hr. in ethanol (300 ml.) with iron powder (20 g.), iron(II) sulphate (0·1 g.), and hydriodic acid (5 drops). Evaporation of the filtrate gave the *aminophenyliminopyrimidine hydriodide* (73%), m.p. 236° (from isobutyl alcohol containing a trace of hydriodic acid) (Found: C, 44·0; H, 4·9; N, 15·5. $C_{13}H_{17}IN_4$ requires C, 43·8; H, 4·8; N, 15·7%). Less satisfactory results were obtained by hydrogenation over nickel (48%) or palladium-charcoal (18%), or by reduction with zinc powder (31%).

N-*Methylation of* 2-*Amino*-5-p-*aminophenyl*-4,6-*dimethylpyrimidine*.—The aminopyrimidine (0·3 g.) was heated with methyl iodide (3 ml.) at 115° for 2 hr. Extraction of the crude solid with chloroform gave 2-*amino*-5-p-*dimethylaminophenyl*-4,6-*dimethylpyrimidine* (39%), m.p. 268—269° (from ethanol) (Found: C, 69·35; H, 7·6; N, 23·1. $C_{14}H_{18}N_4$ requires C, 69·4; H, 7·5; N, 23·1%). The residual solid was recrystallised from ethanol to give 5-p-*aminophenyl*-1,2-*dihydro*-2-*imino*-1,4,6-*trimethylpyrimidine dihydriodide ethanolate* (17%), m.p. 187—189°, identified by rearrangement and spectra (Found: C, 33·4; H, 4·5; I, 48·0; N, 10·6. $C_{15}H_{24}I_2N_4O$ requires C, 34·0; H, 4·5; I, 48·0; N, 10·6%).

4,6-*Dimethyl*-2-p-*nitrophenyldiazoaminopyrimidine*.— 2-Amino-4,6-dimethylpyrimidine (10·2 g.) was added to a solution of *p*-nitrobenzenediazonium chloride during 20 min. at room temperature and with stirring. After 1 hr. the suspension was diluted to 250 ml. with water. The precipitated *diazoaminopyrimidine* (87%) had m.p. 194° (from 60% aqueous ethanol) (Found: C, 53·3; H, 4·5; N, 30·5. $C_{12}H_{12}N_6O_2$ requires C, 52·9; H, 4·4; N, 30·9%).

4-Chloro-1,2-dihydro-2-imino-1,6-dimethylpyrimidine Hydriodide.—2-Amino-4-chloro-6-methylpyrimidine (2·5 g.) was heated at 125° for 3 hr. with methyl iodide (2·0 ml.). The *iminopyrimidine hydriodide* (72%) had m.p. 257° (from ethanol) (Found: C, 25·2; H, 3·0; N, 14·55. $C_6H_9ClIN_3$ requires C, 25·2; H, 3·2; N, 14·7%).

1,2-Dihydro-2-imino-1,6-dimethylpyrimidine Hydriodide.—The foregoing imine hydriodide (0·2 g.) and methanol (100 ml.) were shaken with palladium–charcoal (0·2 g.) under hydrogen. Removal of catalyst and solvent left *1,2-dihydro-2-imino-1,6-dimethylpyrimidine hydriodide* (23%), m.p. 220° (from propanol) (Found: C, 28·7; H, 4·2. $C_6H_{10}IN_3$ requires C, 28·7; H, 4·1%).

4-Methyl-2-methylaminopyrimidine.—(*a*) 1,2-Dihydro-2-imino-1,6-dimethylpyrimidine hydriodide (0·05 g.) was warmed at 40° with 2N-sodium hydroxide (5 ml.). Extraction with chloroform and sublimation (50°/0·2 mm.) gave the methylamino-compound (82%), identical with authentic material.[4]

(*b*) 2-Amino-4-methylpyrimidine (0·6 g.) (from its 6-chloro-derivative by dehalogenation with zinc), 2N-sodium hydroxide (10 ml.), and methyl iodide (5 ml.) were warmed at 60° for 16 hr. Extraction with chloroform and sublimation gave the methylamino-compound [4] (62%), identified by mixed m.p. and spectra.

2-Amino-5-chloropyrimidine.—2-Bromo-1,1,3,3-tetramethoxypropane [10] (7 g.) was added with stirring to methanolic sodium methoxide [from sodium (0·8 g.)]. The mixture was boiled under reflux for 3 hr., then cooled and poured into water (150 ml.). Extraction with ether and distillation gave 1,1,2,3,3-pentamethoxypropane (90%), b.p. 114—118°/12 mm. (lit.,[19] 65—66°/2 mm.; yield 40%). This intermediate (2·0 g.), guanidine hydrochloride or carbonate (2·0 g.), ethanol (30 ml.), and conc. hydrochloric acid (2 ml.) were heated under reflux for 12 hr. Evaporation and sublimation gave 2-amino-5-chloropyrimidine (60%), identified with authentic material [20] by mixed m.p. (232—234°) and spectra. No reaction occurred in the absence of acid, nor with urea, thiourea, or *S*-methylthiourea.

1,2-Dihydro-2-imino-5-methoxy-1-methylpyrimidine Hydriodide.—Crude 2-amino-5-methoxypyrimidine (*ca.* 0·2 g.) (obtained by catalytic dehalogenation of the corresponding 4-chloro-derivative,[9] prepared from 2-amino-4-hydroxy-5-methoxypyrimidine [21]) dissolved in methanol (10 ml.), and methyl iodide (3 ml.) were set aside in the dark at 25° for 3 days. Evaporation gave the *iminopyrimidine hydriodide* (0·2 g.), m.p. 190° (decomp.) (from ethanol) (Found: C, 26·7; H, 3·8; N, 15·9. $C_6H_{10}IN_3O$ requires C, 26·9; H, 3·8; N, 15·7%).

4-Chloro-5-methoxy-2-methylsulphonylpyrimidine.—4-Chloro-5-methoxy-2-methylthiopyrimidine [8] (3 g.), in chloroform (100 ml.) was gradually added to a solution of *m*-chloroperbenzoic acid (75%; 10 g.) in chloroform (500 ml.) at 0—10°. After 12 hr. at 25° the solution was shaken successively with saturated aqueous sodium sulphite (25 ml.), N-sodium carbonate (250 ml.), and water (100 ml.). Extraction with chloroform gave *4-chloro-5-methoxy-2-methylsulphonylpyrimidine* (73%), m.p. 148° (from ethanol) (Found: C, 32·3; H, 3·3; N, 12·4. $C_6H_7ClN_2O_3S$ requires C, 32·4; H, 3·2; N, 12·6%).

5-Methoxy-2-methylaminopyrimidine.—(*a*) The foregoing chloro-compound (1·0 g.) was hydrogenated over palladium–charcoal (0·5 g.) in methanol (100 ml.). Evaporation and recrystallisation gave 5-methoxy-2-methylsulphonylpyrimidine (76%) identified with authentic material [22] by mixed m.p. (119°) (Found: C, 38·5; H, 4·2; N, 14·8. Calc. for $C_6H_8N_2O_3S$: C, 38·3; H, 4·3; N, 14·9%). This material (0·5 g.) was heated at 90° for 2 hr. with ethanolic methylamine (33%; 5 ml.). Evaporation and sublimation (40°/0·2 mm.) gave the *methylaminopyrimidine* (90%), m.p. 96° (Found: C, 51·7; H, 6·7; N, 30·1. $C_6H_9N_3O$ requires C, 51·8; H, 6·5; N, 30·2%).

(*b*) 1,2-Dihydro-2-imino-5-methoxy-1-methylpyrimidine hydriodide was stirred in 2N-sodium hydroxide (10 parts) for 2 hr. at 40—45°. Extraction with chloroform and sublimation gave the same methylamino-compound.

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[19] V. T. Klimko, N. E. Chupriyanova, and A. P. Skoldinov, *Zhur. org. Khim.*, 1957, **3**, 2145.
[20] M. Yanagita, *J. Pharm. Soc. Japan*, 1952, **72**, 1383.
[21] E. A. Falco, P. B. Russell, and G. H. Hitchings, *J. Amer. Chem. Soc.*, 1951, **73**, 3753.
[22] Z. Buděšínský, J. Přikryl, and E. Svátek, *Coll. Czech. Chem. Comm.*, 1964, **29**, 2980.