Simple Pyrimidines. Part XII.[1] Synthesis and Methylation of Some 2-Amino-5-phenylpyrimidines

By **D. J. Brown** * and **B. T. England**, Department of Medical Chemistry, John Curtin School of Medical Research, Canberra, Australia, 2600

Syntheses of 2-amino-, 2-methylamino-, and 1,2-dihydro-2-imino-1-methyl- 5-phenylpyrimidines, and of their derivatives *para*-substituted by a methyl, chloro-, bromo-, fluoro-, methoxy-, dimethylamino-, nitro-, or amino-group, are described. The routes involve primary synthesis of appropriate 5-phenylpyrimidine-2-thiols followed by *S*-methylation, oxidation to the corresponding sulphones, and aminolysis. On methylation, the 2-amino-pyrimidines produced give the imines, which undergo Dimroth rearrangement to the methylamino-isomers, also made directly by methylaminolysis of the sulphones. 2-Amino- and 2-methylamino-5-*p*-nitrophenylpyrimidine are better made by nitration of the corresponding phenylpyrimidines or by nitration of 2-methylsulphonyl-5-phenyl-pyrimidine followed by aminolysis. Reduction of the appropriate nitro-compounds gives 2-amino-5-*p*-amino-phenylpyrimidine and its 2-methylamino-homologue.

Linear relationships exist between the ionisation constants of these 2-amino-, imino-, and methylamino-pyrimidines and Berliner's σ values for *para*-substituted-phenyl substituents. The existence of a considerable interplanar angle in such molecules is inferred from the reduced transmission of substituent effects, illustrated not only by pK_a values but also by u.v. and ^1H n.m.r. spectra.

In seeking a quantitative relationship between rate of Dimroth rearrangement [2] and substituent in 1,2-dihydro-2-imino-1-methylpyrimidines, we have prepared the 5-phenyl and a series of 5-(*para*-substituted phenyl) derivatives. The present paper reports the synthetic routes to these compounds and to the potential products of rearrangement, *viz.* the corresponding 5-(*para*-substituted phenyl)-2-methylaminopyrimidines, and also reports the pK_a values and spectral properties of the series.

Recent systematic development [3] of heterocyclic sulphoxides and sulphones as substrates for nucleophilic attack suggested that the required 2-amino- and 2-methylamino-pyrimidines might be prepared *via* their mercapto-, methylthio-, and methylsulphonyl-analogues. This sequence appeared to be marginally better than the use of known 2-chloropyrimidines [4] and proved to be much better than aminolysis [5] of 2-methoxypyrimidines, which produced pyridines as troublesome by-products.

Modification of existing procedures [4,6] were used to convert *p*-tolylacetonitrile into its α-formyl derivative and thence by hydrogenation into 3-imino-2-*p*-tolyl-propionaldehyde. This was condensed with thiourea in ethanolic hydrochloric acid to give 5-*p*-tolylpyrimidine-2-thiol (Ia; $R^2 = SH$) which underwent *S*-methylation to the sulphide (Ia; $R^2 = SMe$) followed by oxidation with *m*-chloroperoxybenzoic acid to the sulphone (Ia; $R^2 = SO_2Me$). Aminolysis with ammonia or methylamine gave 2-amino(or methylamino)-5-*p*-tolylpyrimidine (Ia; $R^2 = NH_2$ or NHMe), respectively. The aminopyrimidine was heated with methyl iodide to give the hydriodide of the imine (IIa; X = NH), which underwent Dimroth rearrangement in alkali to the methylamine (Ia; $R^2 = NHMe$), identical with that already prepared. The same general route was used to make the imines (IIb—g; X = NH) *via* the pyrimidinethiols (Ib—g; $R^2 = SH$), the sulphides (Ib—g; $R^2 = SMe$), the sulphones (Ib—g; $R^2 = SO_2Me$), and the amines (Ib—g; $R^2 = NH_2$); rearrangement of the imines gave the methylaminopyrimidines (Ib—g; $R^2 = NHMe$) which were also made by methylaminolysis of the sulphones. Of the required (*para*-substituted phenyl)-acetonitriles, only the *p*-dimethylamino-analogue was not available commercially. It was best made by complete *N*-methylation of *p*-aminophenylacetonitrile to give the *p*-trimethylammonio-iodide followed by partial demethylation in ethanolic sodium hydroxide.

2-Amino-5-*p*-nitrophenylpyrimidine (Ih; $R^2 = NH_2$) was made by nitration of 2-amino-5-phenylpyrimidine (Ib; $R^2 = NH_2$), or by nitration of the sulphone (Ib; $R^2 = SO_2Me$) followed by aminolysis; in each nitration, ^1H n.m.r. spectra (Table 1) revealed that only the *para*-isomer had been formed. The secondary amine (Ih; $R^2 = NHMe$) was made in three ways: by methylaminolysis of the same nitro-sulphone (Ih; $R^2 = SO_2Me$), by nitration of the amine (Ib; $R^2 = NHMe$), and by rearrangement of the imine (IIh; X = NH). The *para*-amino-analogues (Ii; $R^2 = NH_2$ or NHMe) were prepared by hydrogenation of the corresponding *para*-nitro-compounds (Ih; $R^2 = NH_2$ or NHMe); the secondary amine (Ii; $R^2 = NHMe$) was also made by rearrangement of the imine (IIi; X = NH).

In the four compounds (Ig and Ii; $R^2 = NHMe$ or NH_2) having two basic centres of comparable strength, the higher pK_a value is assigned to the *para*-amino-group because alkylation of the 2-amino-group affects only the lower ionisation constant. Protonation of the *para*-amino-group results in a lowering of the basic strength of the guanidine system of the pyrimidine ring to the extent of 0·5 unit, an effect similar to that produced (Table 2) by the *p*-nitro-substituent in (Ih; $R^2 = NHMe$ or NH_2) or in 4-amino-4′-nitrobiphenyl (pK_a 3·86; *cf.*

[1] Part XI, M. E. C. Biffin, D. J. Brown, and T.-C. Lee, *J. Chem. Soc.* (*C*), 1967, 573.

[2] M. Wahren, *Z. Chem.*, 1969, **9**, 241; D. J. Brown in 'Mechanisms of Molecular Migrations,' ed. B. S. Thyagarajan, Interscience, New York, 1968, vol. 1, p. 209.

[3] G. B. Barlin and W. V. Brown, *J. Chem. Soc.* (*C*), 1967, 2473; 1969, 921; D. J. Brown and P. W. Ford, *ibid.*, 1967, 568; 1969, 2620, 2720.

[4] D. J. Brown and T.-C. Lee, *J. Chem. Soc.* (*C*), 1970, 214.

[5] D. J. Brown and B. T. England, *Austral. J. Chem.*, 1970, **23**, 625.

[6] P. B. Russell and G. H. Hitchings, *J. Amer. Chem. Soc.*, 1951, **73**, 3763.

TABLE 1

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

Compound [a]	τ [b]
(Ia) R² = SH [c]	Me: 7·64(s); C_6H_4: 2·65,2·34(A_2B_2); 4- and 6-H: 0·88(s)
SMe	Me: 7·62(s); SMe: 7·41(s); C_6H_4: 2·72,2·63(A_2B_2); 4- and 6-H: 1·31(s)
SO_2Me	Me: 7·60(s); SO_2Me: 6·65(s); C_6H_4: 2·62,2·52(A_2B_2) 4- and 6-H: 0·93(s)
NHMe	Me: 7·64(s); NMe: 6·92(d); C_6H_4: 2·75,2·66(A_2B_2) 4- and 6-H: 1·43(s)
NH_2	Me: 7·63(s); NH_2: 4·75(s); C_6H_4: 2·75,2·66(A_2B_2) 4- and 6-H: 1·48(s)
(IIa) X = NH [c]	Me: 7·62(s); NMe: 6·11(s); C_6H_4: 2·60,2·25(A_2B_2); 6-H: 0·90(d); 4-H: 0·68(d)
(Ib) R² = SH [c]	Ph: 2·60(s); 4- and 6-H: 1·39(s)
SMe	SMe: 7·42(s); Ph: 2·54(s); 4- and 6-H: 1·29(s)
SO_2Me	SO_2Me: 6·41(s); Ph: 2·40(s); 4- and 6-H: 0·90(s)
NHMe	NMe: 6·89(d); Ph: 2·50(s); 4- and 6-H: 1·38(s)
NH_2	NH_2: 4·7(s); Ph: 2·66(s); 4- and 6-H: 1·48(s)
(IIb) X = NH [c]	NMe: 6·16(s); Ph: 2·3(m); 6-H: 0·93(d); 4-H: 0·66(d)
(Ic) R² = SH [c]	C_6H_4: 2·28,2·21(A_2B_2); 4- and 6-H: 1·32(s)
SMe	SMe: 7·40(s); C_6H_4: 2·53(s); 4- and 6-H: 1·31(s)
SO_2Me	SO_2Me: 6·60(s); C_6H_4: 2·43(s); 4- and 6-H: 0·92(s)
NHMe	NMe: 6·94(d); C_6H_4: 2·63(s); 4- and 6-H: 1·51(s)
NH_2	NH_2: 4·0(s); C_6H_4: 2·56(s); 4- and 6-H: 1·48(s)
(IIc) X = NH [c]	NMe: 6·12(s); C_6H_4: 2·32,2·11(A_2B_2); 6-H: 0·88(d); 4-H: 0·70(d)
O [c]	NMe: 6·18(s); C_6H_4: 2·33,2·13(A_2B_2); 4- and 6-H: 0·35(s)
(Id) R² = SH	C_6H_4: 2·37,2·22(A_2B_2); 4- and 6-H: 1·33(s)
SMe	SMe: 7·40(s); C_6H_4: 2·60,2·37(A_2B_2); 4- and 6-H: 1·28(s)
SO_2Me	SO_2Me: 6·60(s); C_6H_4: 2·50,2·28(A_2B_2); 4- and 6-H: 0·90(s)
NHMe	NMe: 6·92(d); C_6H_4: 2·64,2·44(A_2B_2); 4- and 6-H: 1·51(s)
NH_2	NH_2: 4·8(s); C_6H_4: 2·63,2·38(A_2B_2); 4- and 6-H: 1·48(s)
(IId) X = NH [c]	NMe: 6·18(s); C_6H_4: 2·35,2·08(A_2B_2); 6-H: 0·91(d); 4-H: 0·68(d)
(Ie) R² = SH [c]	C_6H_4: 2·76,2·21(A_2B_2); 4- and 6-H: 1·40(s)
SMe	SMe: 7·41(s); C_6H_4: 2·85,2·43(A_2B_2); 4- and 6-H: 1·26(s)
SO_2Me	SO_2Me: 6·62(s); C_6H_4: 2·77,2·37(A_2B_2); 4- and 6-H: 0·88(s)
NHMe	NMe: 6·93(d); C_6H_4: 2·88,2·51(A_2B_2); 4- and 6-H: 1·46(s)
NH_2	NH_2: 4·2(s); C_6H_4: 2·88,2·51(A_2B_2); 4- and 6-H: 1·46(s)
(IIe) X = NH [c]	NMe: 6·16(s); C_6H_4: 2·48,2·20(A_2B_2); 6-H: 0·94(d); 4-H: 0·68(d)
O [c]	NMe: 6·18(s); C_6H_4: 2·60,2·12(A_2B_2); 4- and 6-H: 0·34(s)
(If) R² = SH [c]	OMe: 6·20(s); C_6H_4: 2·91,2·31(A_2B_2); 4- and 6-H: 0·95(s)
(If) R² = SMe	SMe: 7·40(s); OMe: 6·14(s); C_6H_4: 2·92,2·54(A_2B_2); 4- and 6-H: 1·27(s)
SO_2Me	SO_2Me: 6·62(s); OMe: 6·12(s); C_6H_4: 2·90,2·44(A_2B_2) 4- and 6-H: 0·91(s)
NHMe [c]	NMe: 7·11(d); OMe: 6·20(s); C_6H_4: 2·92,2·54(A_2B_2); 4- and 6-H: 1·38(s)
NH_2	OMe: 6·14(s); C_6H_4: 2·98,2·57(A_2B_2); 4- and 6-H: 1·46(s)
(IIf) X = NH [c]	NMe: 6·20(s); OMe: 6·20(s); C_6H_4: 2·84,2·27(A_2B_2) 6-H: 1·01(d); 4-H: 0·70(d)
(Ig) R² = SH [d]	NMe_2: 6·63(s); C_6H_4: 2·08(s); 4- and 6-H: 0·82(s)
SMe	SMe: 7·41(s); NMe_2: 7·01(s); C_6H_4: 3·17,2·60(A_2B_2); 4-H and 6-H: 1·28(s)
SO_2Me	NMe_2: 6·94(s); SO_2Me: 6·62(s); C_6H_4: 3·08,2·43(A_2B_2); 4- and 6-H: 0·90(s)
NHMe	NMe_2: 6·98(s); NMe: 6·90(d); C_6H_4: 3·13,2·57(A_2B_2); 4- and 6-H: 1·39(s)
NH_2	NMe_2: 7·01(s); NH_2: 4·5(s); C_6H_4: 3·13,2·58(A_2B_2); 4- and 6-H: 1·43(s)
(IIg) X = NH [c]	NMe_2: 6·98(s); NMe: 6·18(s); C_6H_4: 2·47,2·18(A_2B_2); 6-H: 0·88(d); 4-H: 0·68(d)
(Ih) R² = SO_2Me	SO_2Me: 6·58(s); C_6H_4: 2·32,1·91(A_2B_2); 4- and 6-H: 0·72(s)
NHMe	NMe: 7·09(d); C_6H_4: 1·97,1·70(A_2B_2); 4- and 6-H: 1·16(s)
NH_2	NH_2: 2·95(s); C_6H_4: 2·03,1·76(A_2B_2); 4- and 6-H: 1·23(s)
(IIh) X = NH [c]	NMe: 6·12(s); C_6H_4: 1·88,1·62(A_2B_2); 6-H: 0·75(d); 4-H: 0·60(d)
O(HI) [c]	NMe: 6·22(s); C_6H_4: 1·98,1·58(A_2B_2); 4- and 6-H: 0·30(s)
$O(HI_3)$ [c]	NMe: 6·16(s); C_6H_4: 1·82,1·58(A_2B_2); 4- and 6-H: 0·14(s)
(Ii) R² = NHMe	NMe: 6·98(d); NH_2: 6·6(s); NH: 4·6(s); C_6H_4: 3·21,2·73(A_2B_2); 4- and 6-H: 1·58(s)
NH_2 [c]	$(NH_2)_2$: 5·45(s); C_6H_4: 3·31,2·74(A_2B_2); 4- and 6-H: 1·53(s)
(IIi) X = NH [c]	NMe: 6·18(s); C_6H_4: 3·29,2·52(A_2B_2); 6-H: 1·16(d); 4-H: 0·82(d)
Disulphide [c,e]	$(Ph)_2$: 2·53(s); 4- and 6-H: 1·20(s)
(IIIb) R² = NH_2 [d]	5-H: 2·70(t, J_{ortho} 5 Hz); 4- and 6-H: 1·14(d, J_{ortho} 5)
(IIIc) R² = NH_2 [d]	4- and 6-H: 1·26(s)
(IIId) R² = NH_2 [d]	4- and 6-H: 1·10(s)
(IIIh) R² = NH_2 [d]	4- and 6-H: 0·86(s)
(IIIb) R² = NHMe	NMe: 6·99(d); NH: 4·2(s); 5-H: 3·46 (t, J_{ortho} 5); 4- and 6-H: 1·66 (d, J_{ortho} 5)
(IIId) R² = NHMe	NMe: 7·25(d); NH: 2·6(s); 4- and 6-H: 1·58(s)
(IVb) [d]	NMe: 6·06(s); 5-H: 2·72(q, J_{ortho} 7 and 5): 6-H: 1·44(q, J_{ortho} 7, J_{meta} 2); 4-H: 1·04(q, J_{ortho} 5, J_{meta} 2)
(IVc) [d]	NMe: 6·10(s); 6-H: 1·28(d, J_{meta} 3); 4-H: 1·06(d, J_{meta} 3)
(IVd) [d]	NMe: 6·10(s); 6-H: 1·23(d, J_{meta} 3); 4-H: 1·02(d, J_{meta} 3)
(IVj) [d]	Me: 8·75(t, J 8); CH_2: 7·32(q, J 8); NMe: 6·11(s); 6-H: 1·66(d, J_{meta} 3); 4-H: 1·17(d, J_{meta} 3)

[a] In $CDCl_3$ unless otherwise indicated. For preparation of simple pyrimidines (III) and (IV) see ref. 12. [b] J values in Hz. Except where otherwise indicated, all A_2B_2 systems have J_{ortho} 9, doublets for Me in NHMe groups have J_{NH-Me} 5, and doublets for 4- or 6-H have J_{meta} 4. [c] In $(CD_3)_2SO$. [d] In 2N-DCl. [e] Bis-(5-phenylpyrimidin-2-yl) disulphide.

TABLE 2

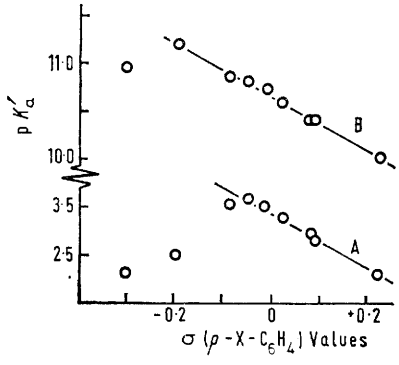
Ionization data and u.v. spectra

Compound	pK'_a [a]	pH	$\lambda_{max.}$ [b] (log ε)
(Ia) R² = NHMe	3·59 ± 0·05 (300)	7	320(3·37), 270(4·35)
		1	346(3·32), 264(4·35)
NH₂	3·32 ± 0·04 (345)	7	311(3·31), 263(4·27)
		1	335(3·26), 261(4·27)
(IIa) X = NH	10·82 ± 0·05 (290)	13	368(3·40), 273(4·50)
		8	338(3·43), 262(4·44)
(Ib) R² = NHMe	3·42 ± 0·03 (290)	7	322(3·46), 269(4·42)
		1	341(3·41), 271(4·41)
		c	322(3·47), 271(4·42)
NH₂	3·34 ± 0·05 (290)	7	*312*(3·46), 261(4·32)
		1	329(3·42), 256(4·37)
(IIb) X = NH	10·75 ± 0·05 (288)	13	366(3·19), 273(4·33)
		8	325(3·36), 256(4·31)
(Ic) R² = NHMe	3·26 ± 0·04 (300)	7	*325*(3·41), 273(4·41)
		1	340(3·37), 261(4·39)
NH₂	3·14 ± 0·04 (300)	7	*320*(3·29), 265(4·29)
		1	327(3·31), 261(4·31)
(IIc) X = NH	10·45 ± 0·01 (300)	13	365(2·94), 277(4·18)
		8	325(3·28), 264(4·21)
(Id) R² = NHMe	3·17 ± 0·03 (300)	7	330(3·30), 274(4·23)
		1	340(3·31), 267(4·27)
NH₂	3·06 ± 0·03 (295)	7	*315*(3·30), 267(4·27)
		1	325(3·30), 263(4·30)
(IId) X = NH	10·45 ± 0·03 (325)	13	366(3·03), 277(4·33)
		8	327(3·33), 267(4·32)
(Ie) R² = NHMe	3·39 ± 0·05 (293)	7	325(3·43), 262(4·41)
		1	343(3·45), 259(4·42)
		c	323(3·43), 269(4·42)
NH₂	3·25 ± 0·05 (285)	7	314(3·03), 257(3·87)
		1	330(3·03), 253(3·89)
(IIe) X = NH	10·62 ± 0·04 (293)	13	367(3·15), 268(4·29)
		1	327(3·34), 257(4·26)
(If) R² = NHMe	3·54 ± 0·04 (355)	7	324(3·41), 273(4·49)
		1	347(3·34), 272(4·44)
		c	320(3·41), 274(4·49)
NH₂	3·32 ± 0·03 (360)	7	*320*(3·36), 265(4·39)
		1	346(3·26), 268(4·37)
(IIf) X = NH	10·88 ± 0·04 (320)	13	372(3·27), 273(4·42)
		8	*350*(3·30), 272(4·36)
(Ig) R² = NHMe	4·72, 2·82 [d] (300)	7	*350*(3·09), 289(4·41)
		0	343(3·45), 262(4·41)
		c	*315*(4·37), 297(4·48)
NH₂	4·67, 2·48 [d] (295)	7	286(4·42)
		0	325(3·54), 259(4·41)
		c	297(4·38)
(IIg) X = NH	11·26 ± 0·05 (300)	13	283(4·36), 352(3·03)
	3·19 ± 0·05 (260)	8	321(3·35), 261(4·27)
		1	324(3·51), 258(4·41)
(Ih) R² = NHMe	2·81 ± 0·03 (300)	7	342(4·05), 243(4·00)
		0	*347*(3·81), 311(4·09), 236(3·98)
		c	344(4·30), 246(4·12)
NH₂	2·70 ± 0·03 (350)	7	*347*(4·03), 323(4·17), 232(4·11)
		0	*345*(3·69), 307(4·19), 230(4·09)
(IIh) X = NH	10·05 ± 0·05 (355)	13	350(4·09), *253*(4·15)
		8	306(4·11)
(Ii) R² = NHMe	4·25, 2·99 [d] (260)	7	345(3·24), 278(4·42)
		0	332(3·41), 261(4·41)
NH₂	4·21, 2·63 [d] (290)	7	273(4·40)
		0	324(3·53), 255(4·40)
		c	279(4·35), *290*(4·32)
(IIi) X = NH	10·97 ± 0·05 (325)	13	382(3·18), 279(4·34)
	3·41 ± 0·03 (290)	8	*358*(3·30), 286(4·26)
		1	323(3·48), 255(4·40)
(IVf) [e]	11·44 ± 0·04 (250)	14	368(3·40), *250*(4·08)
		8	336(3·60)
4-Amino-4′-nitrobiphenyl	3·86 ± 0·02 (305)	6	364(4·10), 243(3·98)
		0	305(4·11)

[a] Like other ionisation constants measured spectrometrically in this Department since 1963, these pK_a′ values are not thermodynamic but practical constants obtained at 20° from spectra in buffers of 0·01M ionic strength (D. D. Perrin, *Austral. J. Chem.*, 1963, **16**, 572) by methods outlined by Albert and Serjeant (ref. 8). Analytical wavelengths are in parentheses. [b] In nm; inflexions in italics. [c] In ethanol. [d] Calculated with the aid of a computer program (H. Kinns and D. D. Perrin, personal communication). [e] Prepn.: D. J. Brown and B. T. England, unpublished work.

4-aminobiphenyl,[7] 4·3). The ionisation constants of the imines (IIa—i; X = NH) are well separated and there is no doubt that initial protonation occurs at the guanidinium system. As a result the ionisation constant of the *para*-amino-group is depressed to a value comparable with the second constant[8] for 4,4′-diaminobiphenyl (pK_a 4·7 and 3·6).

Linear relationships exist (*e.g.* Figure) between the ionisation constants of the compounds (Ia—i; R² = NHMe or NH_2) and (IIa—i, X = NH) and the σ(*p*-X·C_6H_4) values derived by Berliner *et al.* from the closely analogous 4,4′-disubstituted biphenyl system in which the interplanar angle is apparently 20—30°.[9,10] Exceptions (*e.g.* Figure, plot A) occur naturally where the *para*-substituent is more strongly basic than the 2-substituent (see before), and for the usual reasons[11] in the amino-imine (plot B). Appropriate values for the *p*-dimethylaminophenyl and *p*-fluorophenyl substituents were obtained from the classical Hammett values[11] by assuming a reduction in transmission similar to that observed by Berliner[9] for other substituents. Such a reduced transmission of substituent effects is evident from the pK_a values and u.v. spectra of Table 2. In



Plots of pK_a′ values for 5-(*para*-substituted phenyl) derivatives of (A) 2-methylamino- and (B) 1,2-dihydro-2-imino-1-methylpyrimidine against Berliner's σ(*p*-X·C_6H_4) values where X (left to right) = NMe_2, NH_2, OMe, Me, H, F, Cl, Br, and NO_2

[7] F. Kieffer and P. Rumpf, *Compt. rend.*, 1950, **230**, 1874.

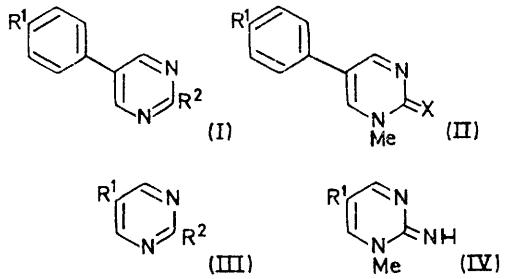
[8] A. Albert and E. P. Serjeant, 'Ionization Constants of Acids and Bases,' Methuen, London, 1962.

[9] E. Berliner and E. A. Blommers, *J. Amer. Chem. Soc.*, 1951, **73**, 2479; E. Berliner and L. H. Liu, *ibid.*, 1953, **75**, 2417.

[10] H. Suzuki, *Bull. Chem. Soc. Japan*, 1959, **32**, 1350; H. H. Jaffé and M. Orchin, 'Theory and Applications of Ultraviolet Spectroscopy,' Wiley, New York, 1962, pp. 400 *et seq.*

[11] H. H. Jaffé, *Chem. Rev.*, 1953, **53**, 191; J. Hine, 'Physical Organic Chemistry,' McGraw-Hill, New York, 1962, pp. 87 *et seq.*

these properties the simple pyrimidines [12] (IIIb; $R^2 = NH_2$), (IIIb; $R^2 = NHMe$), and (IVb) differ considerably (*cf.* refs. 6 and 13) from their respective 5-phenyl derivatives (Ib; $R^2 = NH_2$), (Ib; $R^2 = NHMe$), and (IIb; X = NH) but the latter are affected much less by *para*-substitution than are the former by 5-substitution. Thus a bromo- (or chloro-) substituent at the 5-position reduces the pK_a of 2-aminopyrimidine by *ca.* 2 units, and a nitro-substituent reduces it by 3·5 units; the same substituents in the *para*-position of 2-amino-5-phenylpyrimidine reduce its pK_a by only 0·2 and 0·6 unit respectively. Likewise, shifts of *ca.* 20 nm result from 5-substitution of 2-aminopyrimidine whereas *para*-substitution of 2-amino-5-phenylpyrimidine produces shifts of only 3—5 nm. Similar relationships in ΔpK_a and $\Delta\lambda_{max.}$ emerge on comparing (ref. 12 and Table 2) the change (IVb ⟶ f) with (IIb ⟶ f; X = NH) and the change (IIIb ⟶ j; $R^2 = NHMe$) with (Ib ⟶ a; $R^2 = NHMe$).



R¹ = (a) Me, (b) H, (c) Cl, (d) Br, (e) F, (f) OMe, (g) NMe_2, (h) NO_2, (i) NH_2, (j) Et

The ^1H n.m.r. spectra (Table 1) also reveal poor interannular transmission in the 5-phenylpyrimidine system. Thus the range of chemical shift for the 4- and 6-protons in the 2-aminopyrimidines (IIIb—d, h; $R^2 = NH_2$) is 0·4 p.p.m., whereas that for the corresponding 2-amino-5-phenylpyrimidines (Ib—d, h; $R^2 = NH_2$) is only 0·25 p.p.m.; these same protons in the simple imines (IVb—d, j) are apparently affected much more by the 5-substituents than are those in the phenyl-imines (IIa—i; X = NH) by the *para*-substituents.

EXPERIMENTAL

Analyses were done by Dr. J. E. Fildes and her staff, mass spectra were recorded by Dr. J. MacLeod on an A.E.I. MS9 instrument, 60 MHz ^1H n.m.r. spectra were obtained by Mr. S. E. Brown at 33° referred to tetramethylsilane or sodium 3-trimethylsilylpropane-1-sulphonate as appropriate, and u.v. spectra were measured with a Shimadzu recording spectrophotometer with peaks checked on an Optica manual instrument. Ionisation constants were measured spectrometrically at concentrations below 10^{-4}M.

2-Amino-5-p-tolylpyrimidine.—A mixture of *p*-tolylacetonitrile (35·1 g) and ethyl formate (22·2 g) was added during 1 h to a stirred suspension of sodium chips (6·9 g) in ether (500 ml). The suspension was stirred for 2 days; the solid was then filtered off and resuspended in water. Acidification to pH 1 converted the salt into the free α-formyl derivative which was hydrogenated at 80—90° and 3 atmos. in ethanol (250 ml) over Raney nickel (10 g). Evaporation gave 3-imino-2-*p*-tolylpropionaldehyde (35%), m.p. 130° (from benzene) (lit.,[4] 129—131°).

This aldehyde (12·0 g), thiourea (6·0 g), ethanol (150 ml), and 10N-hydrochloric acid (12·0 ml) were heated under reflux for 2 h. Refrigeration gave *5-p-tolylpyrimidine-2-thiol* (38%), m.p. 249° (from methoxyethanol) (Found: C, 65·2; H, 4·9. $C_{11}H_{10}N_2S$ requires C, 65·3; H, 5·0%). The thiol (4·9 g), N-sodium hydroxide (25 ml), and methyl iodide (4·5 g) were shaken at 25° for 90 min. Evaporation of a chloroform extract gave *2-methylthio-5-p-tolylpyrimidine* (82%), m.p. 106° (from ethanol) (Found: C, 66·3; H, 5·5; N, 12·9. $C_{12}H_{12}N_2S$ requires C, 66·65; H, 5·6; N, 13·0%). A solution of *m*-chloroperoxybenzoic acid (*ca.* 75%; 10·3 g) in chloroform (220 ml) was added slowly at 5—10° to the foregoing sulphide (3·25 g) in chloroform (25 ml). After 12 h the mixture was shaken in turn with saturated aqueous sodium sulphite (100 ml), N-sodium carbonate (100 ml), and water (100 ml). Removal of the chloroform gave *2-methylsulphonyl-5-p-tolylpyrimidine* (87%), m.p. 186° (from ethanol) (Found: C, 58·2; H, 4·6; N, 11·25. $C_{12}H_{12}N_2O_2S$ requires C, 58·1; H, 4·9; N, 11·3%).

The sulphone (0·5 g) and ethanolic ammonia (*ca.* 10%; 7·0 ml) were heated in a sealed tube at 90° for 2 h. Refrigeration gave *2-amino-5-tolylpyrimidine* (92%), m.p. 196° (from ethanol) (Found: C, 71·8; H, 5·7; N, 22·9. $C_{11}H_{11}N_3$ requires C, 71·3; H, 6·0; N, 22·7%).

2-Methylamino-5-p-tolylpyrimidine.—(*a*) The foregoing aminopyrimidine (0·2 g) and methyl iodide (0·2 g) were heated in a sealed tube at 130° for 3 h. The resulting *1,2-dihydro-2-imino-1-methyl-5-p-tolylpyrimidine hydriodide* (65%) had m.p. 261° (from ethanol) (Found: C, 44·4; H, 4·4; N, 12·6. $C_{12}H_{14}IN_3$ requires C, 44·05; H, 4·3; N, 12·8%). The hydriodide (0·1 g) and N-potassium hydroxide (10 ml) were stirred for 12 h at 25°. Evaporation of a chloroform extract gave the *methylaminopyrimidine* (81%), m.p. 164° (from ethanol) (Found: C, 72·65; H, 6·35; N, 21·4. $C_{12}H_{13}N_3$ requires C, 72·3; H, 6·6; N, 21·1%).

(*b*) 2-Methylsulphonyl-5-*p*-tolylpyrimidine reacted with ethanolic methylamine (as with ammonia) to give the 2-methylaminopyrimidine (90%), identified by mixed m.p.

2-Amino-5-phenylpyrimidine.—By analogy with the foregoing route to the tolyl analogue, purified α-formylbenzyl cyanide [6] was hydrogenated to give 3-imino-2-phenylpropionaldehyde (70%; *cf.* a method [4] needing 3 days). This was converted sequentially into 5-phenylpyrimidine-2-thiol (30%), m.p. 225—227° (lit.,[14] 225—228°) (Found: C, 63·7; H, 4·0; N, 14·9. Calc. for $C_{10}H_8N_2S$: C, 63·8; H, 4·3; N, 14·9%); *2-methylthio-5-phenylpyrimidine* (82%), m.p. 96° (from ethanol) (Found: C, 65·5; H, 5·3; N, 13·7. $C_{11}H_{10}N_2S$ requires C, 65·3; H, 5·0; N, 13·9%); *2-methylsulphonyl-5-phenylpyrimidine* (72%), m.p. 178° (Found: C, 56·6; H, 4·45; N, 12·3. $C_{11}H_{10}N_2O_2S$ requires C, 56·4; H, 4·3; N, 12·0%); and 2-amino-5-phenylpyrimidine (91%), m.p. 158° (lit.,[15] 161—163°) (Found: C, 70·1; H,

[12] D. J. Brown and L. N. Short, *J. Chem. Soc.*, 1953, 331; D. J. Brown and J. S. Harper, *ibid.*, 1963, 1276; D. J. Brown, B. T. England, and J. M. Lyall, *J. Chem. Soc.* (*C*), 1966, 226; D. J. Brown and M. N. Paddon-Row, *ibid.*, 1967, 903.

[13] A. Maggiolo and P. B. Russell, *J. Chem. Soc.*, 1951, 3297.

[14] L. Rylski, F. Šorm, and Z. Arnold, *Coll. Czech. Chem. Comm.*, 1959, **24**, 1667.

[15] T. V. Protopopova, V. T. Klimko, and A. P. Skoldinov, *Khim. Nauka i Prom.*, 1959, **4**, 805 (*Chem. Abs.*, 1960, **54**, 11,036).

5·5; N, 24·5. Calc. for $C_{10}H_9N_3$: C, 70·15; H, 5·3; N, 24·55%).

Bis-(5-phenylpyrimidin-2-yl) Disulphide.—(*a*) Potassium nitrate (0·22 g) was added during 30 min to a stirred mixture of 5-phenylpyrimidine-2-thiol (0·37 g) and 50% sulphuric acid (12 ml) at 20—25°. After a further 1 h, ice was added and the pH was adjusted to 4—5. The *disulphide* (73%) had m.p. 207° (from ethanol) (Found: C, 64·5; H, 3·95; N, 14·9. $C_{20}H_{14}N_4S$ requires C, 64·2; H, 3·8; N, 15·0%).

(*b*) A mixture of the pyrimidinethiol (0·2 g), N-sodium hydroxide (10 ml), M-potassium iodide (10 ml), and iodine (0·3 g) was shaken for 1 h. The insoluble product (58%) was identified as the foregoing disulphide by mixed m.p.

2-*Methylamino-5-phenylpyrimidine.*— 2-Amino-5-phenylpyrimidine (0·2 g), dimethyl sulphate (0·5 ml), and nitrobenzene (20 ml) were heated under reflux for 2 h. The cooled mixture was extracted with an equal volume of water. Sodium iodide was added to the extract and refrigeration gave 1,2-*dihydro*-2-*imino*-1-*methyl*-5-*phenylpyrimidine hydriodide* (62%), m.p. 262° (from ethanol) (Found: C, 42·1; H, 3·9; N, 13·5. $C_{11}H_{12}IN_3$ requires C, 42·4; H, 3·8; N, 13·4%), which gave 2-*methylamino*-5-*phenylpyrimidine* (74%), m.p. 124° (Found: C, 71·7; H, 5·9; N, 22·4. $C_{11}H_{11}N_3$ requires C, 71·3; H, 6·0; N, 22·7%) by a similar rearrangement to that of its tolyl analogue; it was also made (95%) by methylaminolysis of the corresponding sulphone.

2-*Amino*-5-p-*nitrophenylpyrimidine.*—(*a*) Potassium nitrate (0·12 g) was added during 10 min to a stirred solution of 2-amino-5-phenylpyrimidine (0·17 g) in conc. sulphuric acid (5 ml) at 35—40°. The mixture was warmed to 60° for 3 min, cooled, and poured on to crushed ice. After neutralisation with ammonia at $<10°$ the 2-*amino*-5-p-*nitrophenylpyrimidine* (80%), m.p. 262°, was filtered off and purified by dissolution in acid and reprecipitation with ammonia (Found: C, 55·6; H, 3·6; N, 26·2. $C_{10}H_8N_4O_2$ requires C, 55·55; H, 3·7; N, 25·9%).

(*b*) Potassium nitrate (0·5 g) was added slowly to 2-methylsulphonyl-5-phenylpyrimidine (1·0 g) in conc. sulphuric acid (10 ml) at $<10°$. The mixture was stirred for 1 h at 20—25°, then treated as in the previous preparation to give 2-*methylsulphonyl*-5-p-*nitrophenylpyrimidine* (82%), m.p. 223—225° (from ethanol) (Found: C, 47·0; H, 3·5; N, 14·8. $C_{11}H_9N_3O_4S$ requires C, 47·3; H, 3·25; N, 15·05%). This sulphone (0·17 g) was stirred in saturated ethanolic ammonia (20 ml) at 25° for 1 h. Evaporation to dryness and purification as before gave the amino-5-nitrophenylpyrimidine (98%).

2-*Methylamino*-5-p-*nitrophenylpyrimidine.*—(*a*) Aminolysis of the sulphone as before, but with ethanolic methylamine, gave the *methylaminonitrophenylpyrimidine* (87%), m.p. 195° (from ethanol or isobutyl methyl ketone) (Found: C, 57·1; H, 4·4; N, 24·5. $C_{11}H_{10}N_4O_2$ requires C, 57·4; H, 4·4; N, 24·3%) or m.p. 252° (Found: C, 57·5; H, 4·4; N, 24·3%). The lower-melting metastable form was easily converted into the stable form by seeding during recrystallisation, but the reverse interconversion was not achieved.

(*b*) Nitration of 2-methylamino-5-phenylpyrimidine, as for the 2-amino-homologue, gave the same product (92%), identified by mixed m.p.

(*c*) The reaction of 2-amino-5-*p*-nitrophenylpyrimidine with dimethyl sulphate, as for the corresponding phenylpyrimidine but with concentration of the mother liquors, gave eventually 1,2-*dihydro*-2-*imino*-1-*methyl*-5-p-*nitrophenylpyrimidine hydriodide* (60%), m.p. 253° (from methanol) (Found: C, 37·20; H, 3·3; N, 15·4. $C_{11}H_{11}IN_4O_2$ requires C, 36·9; H, 3·1; N, 15·6%). Rearrangement of a minute amount of the imine gave material identified by spectra and paper chromatography as the methylaminonitrophenylpyrimidine.

2-*Amino*-5-p-*aminophenylpyrimidine.*—Hydrogenation of a suspension of 2-amino-5-*p*-nitrophenylpyrimidine (0·6 g) in methanol (300 ml) over Raney nickel gave the *diamine* (75%), m.p. 176—178° (from water) (Found: C, 64·5; H, 5·4; N, 29·7. $C_{10}H_{10}N_4$ requires C, 64·5; H, 5·4; N, 30·1%).

5-p-*Aminophenyl*-2-*methylaminopyrimidine.*—(*a*) Similar hydrogenation of 2-methylamino-5-*p*-nitrophenylpyrimidine gave its para-*amino-analogue* (87%), m.p. 142° (after sublimation at 95° and 0·2 mmHg) (Found: C, 65·7; H, 6·2; N, 28·2. $C_{11}H_{12}N_4$ requires C, 66·0; H, 6·0; N, 28·0%).

(*b*) 1,2-Dihydro-2-imino-1-methyl-5-*p*-nitrophenylpyrimidine hydriodide (0·07 g), hydriodic acid (*ca.* 0·1 g), iron powder (0·2 g), iron(II) sulphate (*ca.* 0·01 g), and ethanol (7 ml) were stirred and heated under reflux for 7 h and immediately filtered. The residue from evaporation of the filtrate was recrystallised from ethanol to give 5-p-*aminophenyl*-1,2-*dihydro*-1-*imino*-1-*methylpyrimidine hydriodide* (91%), m.p. 251° (Found: C, 40·4; H, 4·0; N, 16·8. $C_{11}H_{13}IN_4$ requires C, 40·25; H, 4·0; N, 17·1%). The same imine was obtained in 60% yield by treatment of 2-amino-5-*p*-aminophenylpyrimidine with methyl iodide, as described for the *para*-tolyl analogue. Rearrangement in alkali gave the same product as in (*a*), identified by chromatography and spectra.

2-*Amino*-5-p-*halogenophenylpyrimidines.*—Appropriate *p*-halogenophenylacetonitriles were converted (as for the tolyl analogue) into the crude 2-*p*-halogenophenyl-3-iminoacetonitriles, and thence into: 5-p-*chlorophenylpyrimidine*-2-*thiol* (40%), m.p. 228° (from butanol) (Found: C, 54·4; H, 3·2; N, 12·85. $C_{10}H_7ClN_2S$ requires C, 53·9; H, 3·2; N, 12·6%); its *bromo-analogue* (38%), m.p. 243° (from methoxyethanol) (Found: C, 44·7; H, 2·5; N, 10·5. $C_{10}H_7BrN_2S$ requires C, 45·0; H, 2·6; N, 10·5%); and its *fluoro-analogue* (31%), m.p. 226° (from butanol) (Found: C, 58·6; H, 3·5; N, 13·3. $C_{10}H_7FN_2S$ requires C, 58·2; H, 3·4; N, 13·6%).

Methylation then gave: 5-p-*chlorophenyl*-2-*methylthiopyrimidine* (90%), m.p. 144° (from ethanol) (Found: C, 55·3; H, 3·6; N, 11·9. $C_{11}H_9ClN_2S$ requires C, 55·8; H, 3·8; N, 11·8%); its *bromo-analogue* (81%), m.p. 140° (after sublimation at 125° and 0·3 mmHg) (Found: C, 46·8; H, 3·3; N, 9·9. $C_{11}H_9BrN_2S$ requires C, 47·0; H, 3·2; N, 10·0%); and its *fluoro-analogue* (87%), m.p. 141° (from ethanol) (Found: C, 60·0; H, 4·2; N, 12·9. $C_{11}H_9FN_2S$ requires C, 60·0; H, 4·1; N, 12·7%).

These were converted by oxidation with *m*-chloroperoxybenzoic acid into: 5-p-*chlorophenyl*-2-*methylsulphonylpyrimidine* (90%), m.p. 228° (from ethanol) (Found: C, 49·3; H, 3·5; N, 10·2. $C_{11}H_9ClN_2O_2S$ requires C, 49·2; H, 3·4; N, 10·4%); its *bromo-analogue* (88%), m.p. 227° (from ethanol) (Found: C, 42·0; H, 3·0. $C_{11}H_9BrN_2O_2S$ requires C, 42·2; H, 2·9%); and its *fluoro-analogue* (85%), m.p. 229° (from ethanol) (Found: C, 52·2; H, 3·8; N, 10·9. $C_{11}H_9FN_2O_2S$ requires C, 52·4; H, 3·7; N, 11·1%).

Optimal conditions for avoidance of by-products in the aminolysis of these sulphones were as follows: ethanolic

ammonia at 5—10° for 6 h gave 2-*amino*-5-p-*chlorophenylpyrimidine* (92%), m.p. 198° (from ethanol) (Found: C, 58·4; H, 3·9; N, 20·6. $C_{10}H_8ClN_3$ requires C, 58·4; H, 3·9; N, 20·4%); ethanolic ammonia at 10° for 1 h and then at 25° for 12 h gave the *bromo-analogue* (95%), m.p. 206° (from ethanol) (Found: C, 47·8; H, 3·4; N, 16·6. $C_{10}H_8BrN_3$ requires C, 48·0; H, 3·2; N, 16·8%); and liquid ammonia in a sealed tube for 15 h gave the *fluoro-analogue* (>95%), m.p. 185—187° (from ethanol) (Found: C, 63·3; H, 4·2. $C_{10}H_8FN_3$ requires C, 63·4; H, 4·3%).

5-p-*Halogenophenyl*-2-*methylaminopyrimidines*.—(*a*) Each *p*-halogenophenyl sulphone underwent methylaminolysis as did its tolyl analogue to give: 5-p-*chlorophenyl*-2-*methylaminopyrimidine* (>95%), m.p. 183° (from ethanol) (Found: C, 60·4; H, 4·9. $C_{11}H_{10}ClN_3$ requires C, 60·15; H, 4·6%); its *bromo-analogue* (94%), m.p. 198° (from ethanol) (Found: C, 49·8; H, 3·95; N, 15·9. $C_{11}H_{10}BrN_3$ requires C, 50·0; H, 3·8; N, 15·9%); and its *fluoro-analogue* (>95%), m.p. 153° (from ethanol) (Found: C, 65·1; H, 5·05; N, 21·0. $C_{11}H_{10}FN_3$ requires C, 65·0; H, 5·0; N, 20·7%).

(*b*) Each 2-amino-5-*p*-halogenophenylpyrimidine was heated with methyl iodide (10 parts) at 140° for 2 h to give respectively 5-p-*chlorophenyl*-1,2-*dihydro*-2-*imino*-1-*methylpyrimidine hydriodide* (40%), m.p. 217° (from methanol) (Found: C, 37·85; H, 3·2; N, 11·9. $C_{11}H_{11}ClIN_3$ requires C, 38·0; H, 3·2; N, 12·1%); its *bromo-analogue* (38%), m.p. 251° (from ethanol) (Found: C, 33·6; H, 2·8; N, 10·7. $C_{11}H_{11}BrIN_3$ requires C, 33·7; H, 2·8; N, 10·7%); and its *fluoro-analogue* (47%), m.p. 231° (from isopropyl alcohol) (Found: C, 40·1; H, 3·5. $C_{11}H_{11}FIN_5$ requires C, 39·9; H, 3·3%).

Each imine rearranged in alkali to the corresponding 2-methylamino-base, identified with the appropriate product by chromatography and mixed m.p. or spectra.

2-*Amino*-5-p-*methoxyphenylpyrimidine*.—As for the tolyl analogue, 3-amino-2-*p*-methoxyphenylpropionaldehyde [4] was converted successively into: 5-p-*methoxyphenylpyrimidine*-2-*thiol* (*ca.* 40%), m.p. 218° (from propanol) (Found: C, 60·8; H, 4·3. $C_{11}H_{10}N_2OS$ requires C, 60·5; H, 4·6%); 5-p-*methoxyphenyl*-2-*methylthiopyrimidine* (63%), m.p. 96—98° (from ethanol) (Found: C, 62·1; H, 5·4; N, 11·9. $C_{12}H_{12}N_2OS$ requires C, 62·0; H, 5·2; N, 12·1%); 5-p-*methoxyphenyl*-2-*methylsulphonylpyrimidine* (91%), m.p. 182° (from ethanol) (Found: C, 54·4; H, 4·4. $C_{12}H_{12}N_2SO_3$ requires C, 54·5; H, 4·6%); and 2-*amino*-5-p-*methoxyphenylpyrimidine* (89%), m.p. 182° (from ethanol) (Found: C, 65·6; H, 5·5; N, 20·5. $C_{11}H_{11}N_3O$ requires C, 65·7; H, 5·5; N, 20·9%).

5-p-*Methoxyphenyl*-2-*methylaminopyrimidine*.—(*a*) Methylaminolysis of the foregoing sulphone (90°; 2 h) gave the *methylaminopyrimidine* (93%), m.p. 126° (from ethanol) (Found: C, 67·3; H, 6·35; N, 19·7. $C_{12}H_{13}N_3O$ requires C, 67·0; H, 6·1; N, 19·5%).

(*b*) Treatment of 2-amino-5-*p*-methoxyphenylpyrimidine with methyl iodide (as for the *p*-halogenophenyl analogues) gave 1,2-*dihydro*-2-*imino*-5-p-*methoxyphenyl*-1-*methylpyrimidine hydriodide* (37%), m.p. 254° (from ethanol) (Found: C, 42·0; H, 4·2; N, 12·1. $C_{12}H_{14}IN_3O$ requires C, 42·0; H, 4·1; N, 12·25%), which rearranged to give the aforementioned methylaminopyrimidine (*ca.* 80%), identified by mixed m.p.

2-*Amino*-5-p-*dimethylaminophenylpyrimidine*.—*p*-Aminophenylacetonitrile [16] (32 g) in 2N-sodium hydroxide (400 ml) was shaken vigorously at room temperature for 20 min with methyl iodide (32 g). An equal amount of methyl iodide was then added and the mixture was shaken for a further 40 min. The solution was extracted with chloroform (200 ml) whereupon a solid began to be deposited from the aqueous phase. Refrigeration and filtration gave (p-*cyanomethylphenyl*)*trimethylammonium iodide* (26 g), m.p. 170° (from ethanol) (Found: C, 44·2; H, 5·2; N, 9·3. $C_{11}H_{15}IN_2$ requires C, 43·7; H, 5·0; N, 9·3%). Evaporation of the chloroform extract gave *p*-dimethylaminophenylacetonitrile (*ca.* 20 g) which proved difficult to purify. It was better obtained from the foregoing quaternary amine; the iodide (15 g), silver acetate (10 g), and water (200 ml) were shaken for 2 h. The filtered solution was evaporated to dryness. The residue was boiled for 3 h under reflux in benzene (400 ml) containing acetonitrile (10 ml). Evaporation gave the dimethylamino-compound (85%), m.p. 49—50° (lit.,[16] 49—51°). Demethylation also occurred under alkaline conditions. The iodide (3·0 g) was heated under reflux in ethanolic sodium ethoxide [from sodium (0·23 g) and ethanol (15 ml)] for 50 min; evaporation and extraction with ether gave the dimethylamino-derivative (37%). When sodium hydroxide in 95% ethanol was used similarly, the product was mainly p-*dimethylaminophenylacetamide* (72%), m.p. 172° (from ethyl acetate) (Found: C, 67·7; H, 8·1; N, 15·6. $C_{10}H_{14}N_2O$ requires C, 67·4; H, 7·9; N, 15·7%).

p-Dimethylaminophenylacetonitrile was converted [4] into 2-*p*-dimethylaminophenyl-3-iminopropionaldehyde and thence by the usual route into: 5-p-*dimethylaminophenylpyrimidine*-2-*thiol* (40%), m.p. 212—215° (from propanol) (Found: C, 62·0; H, 5·7; N, 17·9. $C_{12}H_{13}N_3S$ requires C, 62·3; H, 5·7; N, 18·2%); the 2-*methylthio-analogue* (78%), m.p. 144° (from ethanol) (Found: C, 64·0; H, 6·4; N, 16·9. $C_{13}H_{15}N_3S$ requires C, 63·7; H, 6·2; N, 17·1%); and the 2-*methylsulphonyl analogue* (45%), m.p. 191° (from ethanol) (Found: C, 56·2; H, 5·6; N, 15·1. $C_{13}H_{15}N_3O_2S$ requires C, 56·3; H, 5·45; N, 15·2%). The sulphone (0·5 g) was stirred magnetically in liquid ammonia (10 ml) within a sealed tube for 15 h at *ca.* 25°. Evaporation gave 2-*amino*-5-p-*dimethylaminophenylpyrimidine* (>95%), m.p. 193° (from ethanol) (Found: C, 66·6; H, 6·8; N, 26·1. $C_{12}H_{14}N_4$ requires C, 67·25; H, 6·6; N, 26·15%).

5-p-*Dimethylaminophenyl*-2-*methylaminopyrimidine*.—(*a*) Methylaminolysis of the foregoing sulphone (as for the tolyl analogue) gave the *methylaminopyrimidine* (>95%), m.p. 196° (from ethanol) (Found: C, 68·2; H, 7·5; N, 24·1. $C_{13}H_{16}N_4$ requires C, 68·4; H, 7·1; N, 24·5%).

(*b*) Treatment of the 2-amino-compound with methyl iodide (as for the *p*-halogenophenyl analogues) gave 5-p-*dimethylaminophenyl*-1,2-*dihydro*-2-*imino*-1-*methylpyrimidine hydriodide* (44%), m.p. 251° (from ethanol) (Found: C, 43·3; H, 4·6; N, 15·9. $C_{13}H_{17}IN_4$ requires C, 43·8; H, 4·8; N, 15·7%). Rearrangement gave the aforementioned methylamino-base, identified by chromatography and spectra.

5-(para-*Substituted Phenyl*)-1,2-*dihydro*-1-*methyl*-2-*oxopyrimidines*.—Methylation of crude samples of 2-amino-5-(*para*-substituted phenyl)pyrimidines gave not only the imines already described but also the corresponding oxopyrimidines.

When 2-amino-5-*p*-nitrophenylpyrimidine containing some of the 2-hydroxy-analogue was heated at 140° with methyl iodide two by-products were obtained: red-brown

[16] M. Borovička, Z. Šedivý, J. O. Jílek, and M. Protiva, *Coll. Czech. Chem. Comm.*, 1955, **20**, 437.

methanol-insoluble crystals of 1,2-*dihydro*-1-*methyl*-5-p-*nitrophenyl*-2-*oxopyrimidinium tri-iodide*, m.p. 219° (from isopropyl alcohol) (Found: C, 21·7; H, 1·8; N, 6·4. $C_{11}H_{10}I_3N_3O_3$ requires C, 21·55; H, 1·6; N, 6·85%); and the corresponding methanol-soluble yellow *monoiodide*, m.p. 234° (from aqueous ethanol) (Found: C, 36·9; H, 2·95; N, 11·3. $C_{11}H_{10}IN_3O_3$ requires C, 36·8; H, 2·8; N, 11·7%). The latter iodide was identified (mixed m.p.; i.r. spectra) with material made from the known [4] base.

Aminolysis of 5-*p*-chlorophenyl-2-methylsulphonylpyrimidine by warm ethanolic ammonia gave the 2-amino-analogue contaminated with the 2-ethoxy-analogue (*cf.* ref. 3). Methylation of the crude material as before gave 5-p-*chlorophenyl*-1-*methylpyrimidine*-2(1H)-*one hydriodide* as a by-product arising from the ethoxy-compound by a Hilbert–Johnson reaction.[17] It had m.p. 269° (from methoxyethanol) (Found: C, 37·6; H, 3·0; N, 8·1. $C_{11}H_{10}ClIN_2O$ requires C, 37·9; H, 2·5; N, 8·0%) and was identical with material made from the authentic [4] base.

[17] J. Pliml and M. Prystaš, *Adv. Heterocyclic Chem.*, 1967, **8**, 115.

Similar reactions gave 5-p-*fluorophenyl*-1-*methylpyrimidine*-2(1H)-*one hydriodide*, m.p. 263° (from isopropyl alcohol) (Found: C, 39·95; H, 3·1; N, 8·6. $C_{11}H_{10}FIN_2O$ requires C, 39·8; H, 3·0; N, 8·4%) and its 5-p-*dimethylaminophenyl-analogue*, m.p. 215—217° (from methanol containing a trace of sodium thiosulphate) (Found: C, 44·3; H, 4·4; N, 11·9. $C_{13}H_{16}IN_3O$ requires C, 44·7; H, 4·5; N, 11·8%), identified as before.

4-*Amino*-4′-*nitrobiphenyl*.—This was made by nitration [18] of 4-benzylideneaminobiphenyl. After purification [19] and recrystallisation from methanol, the product (27%) had m.p. 204° (lit.,[19] 203·5—204°).

We thank Professor Adrien Albert for suggestions, Mr D. T. Light for measuring some pK_a values, and the Australian National University for supporting B. T. E. as a scholar.

[0/476 *Received*, *March* 26*th*, 1970]

[18] F. Bell and J. Kenyon, *J. Chem. Soc.*, 1926, 2705.
[19] D. W. Sherwood and M. Calvin, *J. Amer. Chem. Soc.*, 1942, **64**, 1350.