Simple Pyrimidines. Part XIV.[1] The Formation and Reactions of Some Derivatives of Simple Pyrimidinesulphonic Acids

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Appropriate pyrimidine-2-thiones react with chlorine in the presence of potassium hydrogen difluoride to give pyrimidine-2-sulphonyl fluoride (2; R = H, X = F) and its 4-methyl, 5-methyl, and 4,6-dimethyl derivatives. Under mild conditions, these react with ammonia to give the corresponding sulphonamides and with amines to give, for example, *N*(2)-ethyl-4,6-dimethylpyrimidine-2-sulphonamide (2; R = Me, X = NHEt); also the analogous *NN*-diethyl-sulphonamide, 2-sulphonomorpholide, *NN*-di-isopropylsulphonamide, and sulphonohydrazide (converted into its *N*-isopropylidene derivative). Under more vigorous conditions, the whole sulphur-containing group is displaced to yield, for example, 2-hydrazino-, 2-diethylamino-, 2-azido-, and 2-methoxy-4,6-dimethylpyrimidine; also 2-hydrazino- and 2-azido-5-methylpyrimidine. The reaction rate for each sulphonyl fluoride with methoxide ion depends on the number and position of the *C*-methyl substituents. 4,6-Dimethylpyrimidine-2-thione (1; R = Me) is oxidized by chloramine to a separable mixture of the corresponding sulphenamide (3; R = S·NH_2) and disulphide; and by aqueous permanganate to the potassium sulphonate. This latter improved method also yields potassium 5-methylpyrimidine-2-sulphonate and the isomeric 4-methylpyrimidine-6-sulphonate. Appropriate sulphonates and sulphonamides react with hydrazine to give 2-hydrazino-4,6- and 4-hydrazino-2,6-dimethylpyrimidine (4). U.v. and ^{1}H n.m.r. spectra were used to confirm structures and to follow reactions.

APART from some pioneering work in connection with carbonic anhydrase inhibitors,[2] derivatives of simple pyrimidinesulphonic acids (lacking other functional substituents) have been neglected.[3] We now describe the preparation of some simple pyrimidine-2-sulphonyl fluorides and their conversion into sulphonamides and sulphonohydrazides; an improved method (*cf.* ref. 1) for making potassium pyrimidinesulphonates, involving

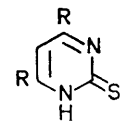
[1] Part XIII, D. J. Brown and J. A. Hoskins, *J. Chem. Soc.* (*B*), 1971, 2214.

[2] R. O. Roblin and J. W. Clapp, *J. Amer. Chem. Soc.*, 1950, **72**, 4890.

[3] D. J. Brown, 'The Pyrimidines,' Wiley, New York, 1962, p. 295 *et seq.*; 'The Pyrimidines: Supplement I,' 1970, p. 221 *et seq.*

oxidation of pyrimidinethiones; the displacement of such S^{VI}-groups by appropriate nucleophiles to give the corresponding amino-, hydrazino-, azido-, hydroxy-, and methoxy-pyrimidines; and the formation of a simple pyrimidinesulphenamide and some hitherto unknown disulphides.

The experience of Beaman and Robins [4] in the purine series suggested that simple pyrimidinesulphonyl fluorides might prove to be more amenable than the corresponding chlorides, which were known [2] to be highly unstable. Accordingly, a well cooled solution of the pyrimidinethione (1; R = Me) containing potassium hydrogen difluoride was treated with a stream of chlorine. The sulphonyl fluoride (2; R = Me, X = F) which resulted in good yield, was a low-melting solid,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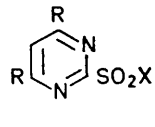
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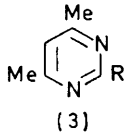
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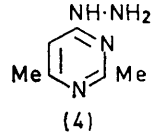
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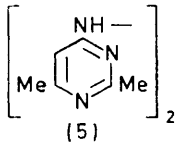
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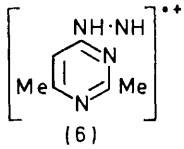
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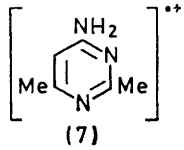
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stable to recrystallization from boiling ethanol, and had not decomposed after a year. Other thiones were oxidized similarly to give, for example, pyrimidine-2-sulphonyl fluoride (2; R = H, X = F) and its 4- and 5-methyl derivatives, but attempts to prepare 2,4-dimethylpyrimidine-6-sulphonyl fluoride by this method failed on account of the instability of the product. The ^1H n.m.r. and u.v. spectra of the sulphonyl fluorides and some derived or related pyrimidines are given in Tables 1 and 2; characteristic i.r. absorptions are recorded in the Experimental section.

On dissolution in liquid ammonia, the sulphonyl fluoride (2; R = Me, X = F) was converted rapidly into the sulphonamide (2; R = Me, X = NH_2), identical with a specimen prepared by modification of the known [2] procedure; pyrimidine-2-sulphonamide (2; R = H, X = NH_2) and its 4- and 5-methyl derivatives were made similarly. The fluoride (2; R = Me, X = F) also reacted under mild conditions with appropriate amines to give the *N*(2)-substituted 4,6-dimethylpyrimidine-2-sulphonamides [2; R = Me; X = NHEt, NEt_2, NPr^i_2, $N(CH_2{\cdot}CH_2)_2O$, or $NH{\cdot}NH_2$]; the last of these was characterized additionally as its isopropylidene derivative (2; R = Me, X = $NH{\cdot}N{:}CMe_2$). Under more vigorous conditions, the whole 2-substituent of 5-methylpyrimidine-2-sulphonyl fluoride or of the pyrimidines (2; R = Me, X = F, NH_2, or $NH{\cdot}NH_2$) underwent nucleophilic displacement by amines to give,

[4] A. G. Beaman and R. K. Robins, *J. Amer. Chem. Soc.*, 1961, **83**, 4038.

TABLE 1

^1H N.m.r. spectra

Pyrimidine [a]	δ [b]
2-SO_2F (A)	5-H: 7·85(t, *J* 5); 4-H and 6-H: 9·20 (d, *J* 5)
2-SO_2F-4-Me (A)	4-Me: 2·76; 5-H: 7·78 (d, *J* 5); 6-H: 8·99 (d, *J* 5)
2-SO_2F-5-Me (A)	5-Me: 2·60; 4-H and 6-H: 8·99
2-SO_2F-4,6-Me_2 (B)	4-Me and 6-Me: 2·61; 5-H: 7·85
2-$SO_2{\cdot}NH_2$-4-Me (C)	4-Me: 2·80; 5-H: 7·87 (d, *J* 6); 6-H: 9·05 (d, *J* 6)
2-$SO_2{\cdot}NH_2$-4,6-Me_2 (B)	4-Me and 6-Me: 2·54; 5-H: 7·53
2-$SO_2{\cdot}NHEt$-4,6-Me_2 (A)	Et: 1·20 (t, *J* 7), 3·35 (q, *J* 7); 4-Me and 6-Me: 2·60; NH: 4·96br (t, *J ca.* 6); 5-H: 7·25
2-$SO_2{\cdot}NEt_2$-4,6-Me_2 (A)	Et: 1·20 (t, *J* 7), 3·48 (q, *J* 7); 4-Me and 6-Me: 2·58; 5-H: 7·24
2-$SO_2{\cdot}NPr^i_2$-4,6-Me_2 (C)	Pr^i: 1·34 (d, *J* 6·8), 3·61 (m); 4-Me and 6-Me: 2·62; 5-H: 7·75
2-$SO_2{\cdot}NH{\cdot}NH_2$-4,6-Me_2 (A)	4-Me and 6-Me: 2·61; NH_2: *ca.* 3·9br; 5-H: 7·28
2-$SO_2{\cdot}NH{\cdot}N{:}CMe_2$-4,6-$Me_2$ (A)	CMe_2: 1·93; 4-Me and 6-Me: 2·56; 5-H: 7·22
2-$NH{\cdot}NH_2$-5-Me (A)	5-Me: 2·21; NH_2: 4·0br; NH: 6·95br; 4-H and 6-H: 8·51
4-$NH{\cdot}NH_2$-2,6-Me_2 (C)	2-Me and 6-Me: 2·27, 2·38; 5-H: 6·44
(D)	2-Me and 6-Me: 2·55, 2·71; 5-H: 6·98
2-N_3-5-Me (B) [c]	5-Me: 2·55; 2-H and 4-H: 9·37 (d, *J* 2), 9·94br (d, *J* 2)
(E)	5-Me: 2·65; 2-H and 4-H: 9·20
2-$S{\cdot}NH_2$-4,6-Me_2 (B)	4-Me and 6-Me: 2·39; NH_2: 3·96br; 5-H: 6·95
2-SH-4-Me (B)	4-Me: 2·30; 5-H: 6·77 (d, *J* 6); 6-H: 8·15 (d, *J* 6)
2-SH-5-Me (B)	5-Me: 2·07; 4-H and 6-H: 8·20
2-SH-4,6-Me_2 (B)	4-Me and 6-Me: 2·29; 5-H: 6·68
2-S·S-2′ (B)	5-H: 7·41 (t, *J* 5); 4-H and 6-H: 8·78 (d, *J* 5)
4,4′-Me_2-2-S·S-2′ (B)	4-Me: 2·39; 5-H: 7·25 (d, *J* 5); 6-H: 8·61 (d, *J* 5)
5,5′-Me_2-2-S·S-2′ (B)	5-Me: 2·19; 4-H and 6-H: 8·61
4,4′,6,6′-Me_4-2-S·S-2′ (B)	4-Me and 6-Me: 2·35; 5-H: 7·11
(A)	4-Me and 6-Me: 2·39; 5-H: 6·81

[a] Solvents: (A), $CDCl_3$; (B), $(CD_3)_2SO$; (C), D_2O; (D), 2M-D_2SO_4–D_2O; (E), $F_3C{\cdot}CO_2H$; pyrimidinethiones are designated mercaptopyrimidines for convenience. [b] Measured in p.p.m. at 60 MHz against Me_4Si or $Me_3Si{\cdot}[CH_2]_3{\cdot}SO_3Na$ as internal standard; singlet peaks unless indicated otherwise; *J* in Hz. [c] Present in this solvent as the tautomer, 6-methyltetrazolo-[1,5-*a*]pyrimidine (*cf.* ref. 10).

TABLE 2

U.v. spectra

Pyrimidine [a]	$\lambda_{max.}$/nm (log ε) [b]
2-SO_2F	238 (3·18), 243 (3·19), *248* (3·05)
2-SO_2F-4-Me	245 (3·33), 247 (3·33), *252* (3·22)
2-SO_2F-5-Me	243 (3·39), 248 (3·37), *256* (3·24)
2-SO_2F-4,6-Me	245 (3·38), *253* (3·25)
2-$SO_2{\cdot}NH_2$-4,6-Me_2 [c]	248 (3·52)
2-$SO_2{\cdot}NEt_2$-4,6-Me_2	247 (3·67)
2-$SO_2{\cdot}NPr^i_2$-4,6-Me_2	248 (3·45)
2-$SO_2{\cdot}N{\cdot}(CH_2{\cdot}CH_2)_2{\cdot}O$-4,6-$Me_2$	246 (3·64)
2-$SO_2{\cdot}NH{\cdot}NH_2$-4,6-Me_2	247 (4·45)
2-$S{\cdot}NH_2$-4,6-Me_2	251 (4·04), *282* (3·51)
4,4′,6,6′-Me_4-2-S·S-2′	241 (4·30), *268* (3·93)

[a] In methanol. [b] Inflections and shoulders in italics. [c] In water.

respectively, 2-hydrazino-5-methylpyrimidine and the known 2-hydrazino-[5] or 2-diethylamino-4,6-dimethylpyrimidine[6] (3; R = NH·NH_2 or NEt_2); the sulphonate groups were displaced similarly by hydrazine from the potassium salt (2; R = Me, X = OK) and its isomer, potassium 2,4-dimethylpyrimidine-6-sulphonate,[1] to give the amines (3; R = NH·NH_2)[5] and (4),[7] respectively. When the concentration of free hydrazine was restricted during the preparation of the amine (4), in the unrealized hope of detecting an intermediate sulphonohydrazide, the dipyrimidin-6-ylhydrazine (5) was obtained as a by-product. The structure (5), analogous to that of a homologue described by Miller and Rose,[8] was consistent with the mass spectrum {*m/e* 244·14372 (M^+, 100%), 137·08261 [33%, ion (6) (metastable peak at *m/e* 77)], and 123·07950 [9%, ion (7)]}.

Complete displacement of the sulphonyl fluoride group also occurred on warming 5-methylpyrimidine-2-sulphonyl fluoride or its analogue (2; R = Me, X = F) with methanolic sodium azide to give, respectively, 2-azido-5-methylpyrimidine or the known[9] azide (3; R = N_3); the latter contained initially a little of the corresponding sulphonamide (2; R = Me, X = NH_2). The foregoing azidopyrimidines are in tautomeric equilibrium[10] with 6-methyl- and 5,7-dimethyl-tetrazolo[1,5-*a*]pyrimidine, respectively (see Table 1). On boiling in water the sulphonyl fluoride (2; R = Me, X = F) gave 4,6-dimethylpyrimidin-2-one; in methanolic sodium methoxide it gave the methoxypyrimidine (3; R = OMe). The rates for the latter and for three analogous reactions were measured spectrometrically: the results in Table 3

TABLE 3

Formation rates of 2-methoxypyrimidines from pyrimidine-2-sulphonyl fluorides in an excess of methanolic 0·051M-sodium methoxide at 25°

Pyrimidine	$10^3 \times k_1/s^{-1}$	$t_{\frac{1}{2}}$/s	Analyt. λ/nm
2-SO_2F	46·9	15	265
4-Me-2-SO_2F	11·7	59	265
5-Me-2-SO_2F	3·57	194	272
4,6-Me_2-2-SO_2F	3·58	193	265

suggest that a 4- or 6-methyl group decreases the reaction rate 3—4-fold, and a 5-methyl group about 12-fold. This is broadly parallel to the effect of *C*-methyl groups on the alkaline hydrolysis of potassium pyrimidine-2-sulphonates.[1]

In seeking another route to simple pyrimidinesulphonamides by oxidation of sulphenamides (*cf.* ref. 11), the thione (1; R = Me) was treated with chloramine to give the sulphenamide (3; R = S·NH_2), which was separated from any remaining intermediate[12] disulphide by sublimation. The sulphenamide was unchanged on mild treatment with 3% hydrogen peroxide, *m*-chloroperoxybenzoic acid in chloroform, or potassium permanganate in acetone; treatment with 30% hydrogen peroxide in acetone or acetic acid followed by neutralization with ammonia gave a crude product clearly containing ammonium 4,6-dimethylpyrimidine-2-sulphonate (i.r. spectra[1]) but no sulphonamide was obtained. Treatment of the thione (1; R = Me) with diethylchloramine gave only bis-(4,6-dimethylpyrimidin-2-yl) disulphide, also prepared unambiguously by oxidation of the same thione with iodine or potassium permanganate in acetone; dipyrimidin-2-yl disulphide and its 4- and 5-methyl derivatives were prepared likewise for comparison. The mass spectrum of dipyrimidin-2-yl disulphide [M^+ 222 (93%)] showed an initial loss of S_2 to give a fragment of *m/e* 158 (100%), corresponding to a bipyrimidinyl; this transition was confirmed by a metastable peak at *m/e* 112·5. The subsequent breakdown pattern included not only all the peaks obtained from authentic 2,2′-bipyrimidinyl[13] but also another set: this suggested that the initial product might be a mixture of bipyrimidinyls. Bis-(4,6-dimethylpyrimidin-2-yl) disulphide behaved similarly.

In the course of this work it was found that simple potassium pyrimidinesulphonates could be prepared conveniently by the addition of aqueous potassium permanganate to appropriate pyrimidinethiones in aqueous ethanol until colouration persisted. The process was a marked improvement over treatment of a chloropyrimidine with potassium sulphite, a method[1] which gave sulphonates contaminated with potassium chloride, difficult or impossible to remove. The oxidative method was tested in typical preparations of the following: potassium 5-methylpyrimidine-2-sulphonate, the analogue (2; R = Me, X = OK), potassium 4-methylpyrimidine-6-sulphonate, and potassium pyrimidine-2(and 4)-sulphonates (both of which were unattainable by the previous method[1]).

EXPERIMENTAL

The i.r. absorptions recorded (cm^{-1}) for Nujol mulls are those associated with the $-SO_2-$ grouping;[14] they are the most intense bands in each spectrum.

Bis-(4,6-dimethylpyrimidin-2-yl) Disulphide.—4,6-Dimethylpyrimidine-2(1*H*)-thione[15] (0·25 g) in 0·2M-sodium hydroxide (10 ml) was shaken for 2 min with a solution of iodine (0·3 g) in M-potassium iodide (10 ml). The precipitate was filtered off and washed with water at 0°. The *disulphide* (96%) (from methanol) had m.p. 150—155° (according to the rate of heating) (Found: C, 51·6; H, 5·1; N, 20·1; S, 23·05. $C_{12}H_{14}N_4S_2$ requires C, 51·5; H, 5·2; N, 20·3; S, 22·7%).

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Bis-(4-methylpyrimidin-2-yl) Disulphide.—A solution of 4-methylpyrimidine-2(1*H*)-thione hydrochloride [16] (0·25 g) in water (5 ml) was adjusted to pH 7 with saturated aqueous sodium hydrogen carbonate. A 3% solution of iodine in M-potassium iodide was added dropwise with stirring until a colouration persisted for 10—15 s. Filtration gave the disulphide (73%), m.p. 104° (from methanol) (Found: N, 22·15; S, 25·8. $C_{10}H_{10}N_4S_2$ requires N, 22·4; S, 25·6%).

Bis-(5-methylpyrimidin-2-yl) Disulphide.—Treatment of 5-methylpyrimidine-2(1*H*)-thione [17] like its 4-methyl isomer gave the *disulphide* (88%), m.p. 178—179° (from ethanol) (Found: C, 47·7; H, 3·8; N, 22·6; S, 25·5. $C_{10}H_{10}N_4S_2$ requires C, 48·0; H, 4·0; N, 22·4; S, 25·6%).

Dipyrimidin-2-yl Disulphide.—Similar oxidation of pyrimidine-2(1*H*)-thione gave this *disulphide* (85%), m.p. 136° (from methanol; *cf.* ref. 18) (Found: C, 43·45; H, 2·55; N, 24·9; S, 28·65. $C_8H_6N_4S_2$ requires C, 43·2; H, 2·7; N, 25·2; S, 28·9%).

4,6-Dimethylpyrimidine-2-sulphonyl Fluoride.—A steady stream of chlorine was passed for *ca.* 30 min into a stirred mixture of 4,6-dimethylpyrimidine-2-thione [15] (7·0 g), potassium hydrogen difluoride (39 g), water (25 ml), and methanol (25 ml) maintained in a polypropylene flask at $< -10°$. The end of the reaction was confirmed by a lack of tendency for the temperature to rise and by immediate bleaching of litmus paper by a drop of the mixture. The slurry was added immediately to crushed ice (*ca.* 150 g). The solid was filtered off and washed with water at 0° until the washings were pH >3. Dried *in vacuo*, the *sulphonyl fluoride* (78%) had m.p. 58° (from diethyl ether), $\nu_{max.}$ 1195 (Found: C, 38·05; H, 3·9; S, 17·0. $C_6H_7FN_2O_2S$ requires C, 37·9; H, 3·7; S, 16·9%).

Other Sulphonyl Fluorides.—Pyrimidine-2-thione and its 4- and 5-methyl derivatives were each treated as above up to the stage of addition to crushed ice. Each suspension was then extracted with ether. The extract was washed with a little aqueous sodium hydrogen carbonate, dehydrated, and evaporated to give, respectively, *pyrimidine-2-sulphonyl fluoride* (90%), m.p. 57° (from ethanol), $\nu_{max.}$ 1158 and 1250 (Found: N, 17·0; S, 19·9. $C_4H_3FN_2O_2S$ requires N, 17·25; S, 19·8%); *4-methylpyrimidine-2-sulphonyl fluoride* (75%), b.p. 101—102° at 0·3 mmHg, $\nu_{max.}$ 1168 and 1204 (Found: C, 34·3; H, 2·6; S, 18·6. $C_5H_5FN_2O_2S$ requires C, 34·4; H, 2·85; S, 18·2%); and *5-methylpyrimidine-2-sulphonyl fluoride* (>95%), m.p. 76—77° (from ethanol), $\nu_{max.}$ 1145 and 1220 (Found: C, 34·5; H, 2·9; S, 18·5%).

4,6-Dimethylpyrimidine-2-sulphonamide.—(*a*) 4,6-Dimethylpyrimidine-2-sulphonyl fluoride (0·5 g) was added to liquid ammonia (*ca.* 5 ml). After 5 min, the mixture was filtered and allowed to evaporate. The residual sulphonamide (82%) had m.p. 198—199° (from aqueous methanol) (lit.,[2] 200°), $\nu_{max.}$ 1158 (Found: N, 22·5. Calc. for $C_6H_9N_3O_2S$: N, 22·45%).

(*b*) 4,6-Dimethylpyrimidine-2-thione [15] (1·4 g) in M-potassium hydroxide (10 ml) was maintained at *ca.* −10° while a stream of chlorine was passed in for 35 min. The solid was filtered off immediately, washed with cold water, and added in portions to liquid ammonia (*ca.* 10 ml). A small amount of undissolved disulphide (identified by mixed m.p.) was filtered off. The residue from evaporation was recrystallized from water to give the same sulphonamide (44%) as in (*a*).

Other Sulphonamides.—Using method (*a*), pyrimidine-2-sulphonyl fluoride and its 4- and 5-methyl derivatives were converted respectively into pyrimidine-2-sulphonamide, m.p. 181° (lit.,[2] 181°); *4-methylpyrimidine-2-sulphonamide* (79%), m.p. 163° (from aqueous ethanol) (Found: C, 35·05; H, 4·1; N, 24·0; S, 18·2. $C_5H_7N_3O_2S$ requires C, 35·0; H, 4·1; N, 24·3; S, 18·5%) [from some batches, another crystalline form (which melted at 151°, resolidified, and remelted at 163°) was isolated (Found: N, 24·3; S, 18·6%)]; and *5-methylpyrimidine-2-sulphonamide*, m.p. 151—152°, $\nu_{max.}$ 1120 and 1185 (Found: C, 34·9; H, 4·2; N, 24·0; S, 18·6%).

4,6-Dimethylpyrimidine-2-sulphonyl fluoride (0·5 g) was added to ethanolic 30% ethylamine (5 ml). After 5 min, the solution was evaporated. The residue was triturated with a little cold water and recrystallized from aqueous ethanol to give N(2)-*ethyl*-4,6-*dimethylpyrimidine-2-sulphonamide* (*ca.* 10%), m.p. 130—131° (Found: C, 44·9; H, 6·3; S, 14·9. $C_8H_{13}N_3O_2S$ requires C, 44·5; H, 6·1; S, 14·9%). The same substrate (0·5 g) and neat diethylamine (5 ml) were boiled under reflux for 5 min. Filtration and evaporation gave N(2)N(2)-*diethyl*-4,6-*dimethylpyrimidine-2-sulphonamide* (>90%), m.p. 60° (from aqueous ethanol), $\nu_{max.}$ 1145, 1170, and 1195 (Found: C, 49·5; H, 7·4; N, 17·3; S, 13·3. $C_{10}H_{17}N_3O_2S$ requires C, 49·4; H, 7·0; N, 17·3; S, 13·2%). Similar treatment of the fluoride with morpholine (100° for ½ h) or di-isopropylamine (80° for 4 h) gave respectively 4,6-*dimethylpyrimidine-2-sulphonomorpholide* (93%), m.p. 159—160° (from diethyl ether), $\nu_{max.}$ 1110 and 1150 (Found: C, 46·6; H, 6·0; N, 16·3; S, 12·5. $C_{10}H_{15}N_3O_3S$ requires C, 46·7; H, 5·9; N, 16·3; S, 12·5%); and N(2)N(2)-*di-isopropyl*-4,6-*dimethylpyrimidine-2-sulphonamide* [40% directly and a further 44% by elution of the mother liquor contents from a silica column first with chloroform (rejected) and then with ethanol (retained)], m.p. 235° (decomp.) (from aqueous ethanol), $\nu_{max.}$ 1160, 1185, and 1230 [Found (for material dried at 25°): C, 49·6; H, 8·3; N, 14·45. $C_{12}H_{21}N_3O_2S,H_2O$ requires C, 49·8; H, 8·0; N, 14·5%].

4,6-Dimethylpyrimidine-2-sulphonohydrazide.—Hydrazine hydrate (0·5 ml) in methanol (1 ml) was added in drops to an agitated solution of 4,6-dimethylpyrimidine-2-sulphonyl fluoride (1·0 g) in methanol (5 ml) maintained at −10 to −15°. The mixture was filtered at once. [The filtrate contained 2-hydrazino-4,6-dimethylpyrimidine which increased in amount if the reaction was prolonged.] The solid, dissolved in chloroform, was washed with a little water. The chloroform layer was dried and evaporated to give the *sulphonohydrazide* (40%), m.p. 124—125° (from ethanol), $\nu_{max.}$ 1160 (Found: C, 35·7; H, 5·2; S, 15·8. $C_6H_{10}N_4O_2S$ requires C, 35·6; H, 5·0; S, 15·9%). This material (0·05 g) was boiled under reflux in acetone (2 ml) for 5 min. Filtration and evaporation gave a solid, which was dissolved in chloroform, washed with water, and recovered by evaporation. Recrystallized from ethanol, N(2)-*isopropylidene*-4,6-*dimethylpyrimidine-2-sulphonohydrazide* (92%) had m.p. 171°, $\nu_{max.}$ 1160 (Found: C, 44·8; H, 6·25; N, 22·75; S, 13·2. $C_9H_{14}N_4O_2S$ requires C, 44·6; H, 5·85; N, 23·1; S, 13·25%).

2-Hydrazino-4,6-dimethylpyrimidine.—(*a*) A mixture of

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4,6-dimethylpyrimidine-2-sulphonohydrazide, -sulphonamide, or -sulphonyl fluoride (0·5 g) with hydrazine hydrate (2 ml) in methanol (10 ml) was boiled under reflux for 1 h. The residue from evaporation was mixed with water (25 ml) and extracted with chloroform (4 × 15 ml). Evaporation of the extract and sublimation (100° at 0·2 mmHg) gave the 2-hydrazino-dimethylpyrimidine (>95%), m.p. 162° (lit.,[5] 165°) (Found: C, 52·3; H, 7·65; N, 40·5. Calc. for $C_6H_{10}N_4$: C, 52·2; H, 7·25; N, 40·6%).

(*b*) Potassium 4,6-dimethylpyrimidine-2-sulphonate [1] was treated with hydrazine as in (*a*) but with 50% aqueous ethanol as solvent. The sublimed product (41%) was identified with that in (*a*) by mixed m.p.

4-Hydrazino-2,6-dimethylpyrimidine.—(*a*) Potassium 2,4-dimethylpyrimidine-6-sulphonate [1] underwent hydrazinolysis like its isomer to give the 4-hydrazinodimethylpyrimidine (56%), m.p. 186—187° (lit.,[7] 186—187°) (Found: C, 52·5; H, 7·5; N, 40·05. Calc. for $C_6H_{10}N_4$: C, 52·5; H, 7·25; N, 40·6%).

(*b*) A solution of the same sulphonate (0·5 g) and hydrazine sulphate (0·5 g) in 50% aqueous ethanol (10 ml) was adjusted to pH 7 by addition of hydrazine hydrate. After boiling under reflux for 45 min, water (25 ml) was added, and the mixture was extracted with chloroform. Evaporation of the extract and sublimation gave the same product (41%) as in (*a*). The unsublimed residue crystallized from ethanol to give a little *NN'-bis-2,4-dimethylpyrimidin-6-ylhydrazine*, m.p. 255—256°, M^+, 244·14372 ($C_{12}H_{16}N_6$ requires *M*, 244·14364), $\lambda_{max.}$ (MeOH) 235 (log ε 4·23) and 272 nm (4·08) [*cf.* 2-propyl-homologue,[8] 228 (4·15) and 273 (4·05)].

2-Diethylamino-4,6-dimethylpyrimidine.— 4,6-Dimethylpyrimidine-2-sulphonyl fluoride (1·0 g) and diethylamine (10 ml) were heated in a sealed tube at 150° for 4 h. Evaporation and sublimation (25° at 0·2 mmHg) of the residue gave the diethylaminodimethylpyrimidine (60%), identified with authentic material [6] by mixed m.p., t.l.c., and i.r. spectra.

2-Hydrazino-5-methylpyrimidine.—Hydrazine hydrate (2·5 ml) was added to 5-methylpyrimidine-2-sulphonyl fluoride (0·18 g) in methanol (2·5 ml). After the vigorous reaction, the mixture was boiled under reflux for 30 min. The residue from partial evaporation was added to water (10 ml) and the solution was adjusted to pH 8 with hydrochloric acid. Extraction with chloroform, evaporation of the extract, and sublimation (80° at 0·1 mmHg) gave the *hydrazinomethylpyrimidine* (>90%), m.p. 143—144° (Found: C, 48·5; H, 6·5; N, 45·2. $C_5H_8N_4$ requires C, 48·4; H, 6·5; N, 45·1%).

2-Azido-5-methylpyrimidine.— 5-Methylpyrimidine-2-sulphonyl fluoride (0·18 g) in methanol (0·5 ml) was added to sodium azide (0·07 g) in water (0·3 ml). After 24 h the mixture was evaporated to dryness and extracted with anhydrous methanol. Evaporation to small bulk followed by preparative t.l.c. on silica (chloroform–5% methanol) separated two compounds: the *azidomethylpyrimidine* (55%), m.p. 123° (Found: C, 44·0; H, 3·8; N, 51·85. $C_5H_5N_5$ requires C, 44·4; H, 3·7; N, 51·8%), and a minor unidentified product.

2-Azido-4,6-dimethylpyrimidine.— 4,6-Dimethylpyrimidine-2-sulphonyl fluoride (0·19 g) in methanol (0·5 g) was stirred at 50° for 1 h with sodium azide (0·07 g) in water (0·3 ml). After 24 h, the residue from evaporating the mixture was extracted with anhydrous methanol, and the extract was again reduced to dryness. Recrystallization (with concentration) from ethanol–water (1 : 2) gave the bulk of the product; submission of the residual solution to preparative t.l.c. (silica; chloroform–5% methanol) separated a little more product from a by-product. The azidopyrimidine (69%), had the same m.p. (154—155°) and i.r. spectrum as authentic material; [9,10] the by-product (14%) was shown to be 4,6-dimethylpyrimidine-2-sulphonamide by mixed m.p. and i.r. spectra.

4,6-Dimethylpyrimidin-2(1H)-one.— 4,6-Dimethylpyrimidine-2-sulphonyl fluoride (0·25 g) and water (2·5 ml) were boiled under reflux until the mixture was homogeneous (*ca.* 45 min). The solution was adjusted to pH 2 with sodium hydroxide and evaporated to dryness, using azeotropic distillation with chloroform to remove the last traces of water. The solid was extracted in a Soxhlet apparatus by ethyl acetate. Evaporation of the extract and recrystallization from ethanol gave the pyrimidinone (47%), identified with authentic material [19] by mixed m.p. (199°) and i.r. spectra.

2-Methoxy-4,6-dimethylpyrimidine.— 4,6-Dimethylpyrimidine-2-sulphonyl fluoride (0·5 g) and methanolic sodium methoxide [from sodium (0·1 g) and methanol (25 ml)] were boiled under reflux for 1·5 h. The residue from removal of solvent was diluted with water (10 ml) and extracted with chloroform (5 × 15 ml). The oil obtained on evaporation of the extract was triturated with aqueous sodium hydrogen carbonate and re-extracted into ether. Evaporation gave the methoxypyrimidine (60%), identified with authentic material [20] by i.r. spectra and as its picrate, m.p. 137—138° (lit.,[21] 137—138°). The sulphonyl fluoride was recovered unchanged after being boiled with anhydrous methanol under reflux for 5 h.

Rate Measurements.—Rates for the reactions of four pyrimidine-2-sulphonyl fluorides with methanolic sodium methoxide were measured as follows. Equal volumes of a methanolic 2—3 × 10^{-4}M-solution of the sulphonyl fluoride and of methanolic 0·103M-sodium methoxide were mixed in an all-polytetrafluoroethylene stopped-flow rapid-reaction apparatus [22] thermostatted at 25 ± 0·1° and attached to a Shimadzu RS27 spectrophotometer recording optical density (at a predetermined wavelength: Table 3) against time. Rates for these pseudo-first-order reactions were calculated from the general equation, $k = 1/t \times \ln[a/(a - x)]$, and expressed as first order constants (s^{-1}) under the defined conditions. Each reaction was followed at least from 15 to 75% completion, in which range the standard deviation was <3%. The whole u.v. spectrum of each solution, recorded after *ca.* 5 × $t_{\frac{1}{2}}$, closely resembled that of the expected product: 2-methoxypyrimidine [23] or its 4-methyl-,[24] 5-methyl-,[25] or 4,6-dimethyl-derivative.[26]

4,6-Dimethylpyrimidine-2-sulphenamide.— Commercial 1·4M-sodium hypochlorite solution (15 ml) was cooled to <0° and added to similarly cooled 1·4M-ammonia (40 ml). The resulting solution of chloramine was mixed with a solution of 4,6-dimethylpyrimidine-2-thione [15] (1·4 g) in

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2M-potassium hydroxide (5 ml), also at <0°. The mixture was stirred until it had warmed to room temperature (*ca.* 15 min). The crystalline solid was filtered off and washed with a little ice-cold water. Dried at 25° *in vacuo*, the *sulphenamide* (25%) had m.p. 99—100° [after sublimation (90° and 1 mmHg)] (Found: C, 46·4; H, 6·15; N, 27·0; S, 20·95. $C_6H_9N_3S$ requires C, 46·45; H, 5·85; N, 27·1; S, 20·65%). When 5M-ammonia was substituted for potassium hydroxide the crude product gave the sulphenamide (11%) by sublimation; the residue was bis-(4,6-dimethylpyrimidin-2-yl) disulphide (59%), identified by i.r. spectra and mixed m.p. with authentic material.

Potassium Pyrimidinesulphonates.—The oxidation of pyrimidinethiones is a better method to make potassium pyrimidinesulphonates free of inorganic salts than is the recently described [1] treatment of chloropyrimidines with potassium sulphite.

Aqueous 0·05M-potassium permanganate was added in drops to a shaken slurry of 4,6-dimethylpyrimidine-2-thione [15] (0·7 g) in 50% aqueous ethanol (20 ml) until a pink colour persisted for 10—15 s. After 10 min the manganese dioxide was filtered off and washed with aqueous ethanol. The combined filtrate and washings were evaporated and the last traces of water were removed by co-distillation with chloroform. The residue, which was completely soluble in boiling anhydrous methanol, was recrystallized from aqueous ethanol to give potassium 4,6-dimethylpyrimidine-2-sulphonate (65%), m.p. 295° (decomp.), identified with authentic material [1] by i.r. spectra and m.p. (Found: C, 31·65; H, 3·1; K, 17·4; S, 13·9. Calc. for $C_6H_7KN_2O_3S$: C, 31·8; H, 3·1; K, 17·3; S, 14·1%).

Similar oxidation of 5-methylpyrimidine-2-thione [17] (0·63 g) gave a crude product containing some disulphide. This was removed by dissolution of the sulphonate in water (12 ml) and filtering. Evaporation of the aqueous filtrate and recrystallization gave *potassium 5-methylpyrimidine-2-sulphonate* (76%), decomposing above 310° and identical in i.r. spectra with the salt-containing specimen previously described [1] (Found: C, 28·1; H, 2·2; S,15·1. $C_5H_5KN_2O_3S$ requires C, 28·3; H, 2·4; S, 15·1%).

In a similar way, 4-methylpyrimidine-6-thione [24] gave *potassium 4-methylpyrimidine-6-sulphonate* (>90%), m.p. 259—260° (Found: K, 18·6; S, 14·8. $C_5H_5KN_2O_3S$ requires K, 18·4; S, 15·1%); pyrimidine-2-thione gave [oxidized at *ca.* 5°; disulphide removed from crude product by extraction with chloroform] *potassium pyrimidine-2-sulphonate* (74%), m.p. 328° (decomp.), $\nu_{max.}$ 1032, 1205, and 1250 (*cf.* ref. 1), and $\lambda_{max.}$ (H_2O) 243·5sh (log ε 3·30) and 246 nm (3·33) (*cf.* ref. 1) (Found: C, 23·9; H, 1·4; K, 19·9; N, 13·8; S, 15·9. $C_4H_3KN_2O_3S$ requires C, 24·2; H, 1·5; K, 19·7; N, 14·1; S, 16·2%); pyrimidine-4-thione [27] gave [like its isomer; oxidized at *ca.* 5°] *potassium pyrimidine-4-sulphonate* (>90%), m.p. 330° (decomp.), $\nu_{max.}$ 1044, 1215, and 1230, pK'_a −0·53 ± 0·02 (analyt. λ 255 nm) (*cf.* predicted [1] value −0·4), $\lambda_{max.}$ (H_2O) 245·5sh (log ε 3·60), 250·5 (3·65), and 256sh nm (3·51), δ (D_2O) 8·11 (q $J_{5,6}$ 5, $J_{2,5}$ 1·3 Hz, 5-H), 9·18 (d, $J_{5,6}$ 5 Hz, 6-H), and 9·41br p.p.m. (2-H) (Found: C, 24·5; H, 1·6; K, 19·5; N, 14·1; S, 15·9%). The rate of alkaline hydrolysis of potassium pyrimidine-4-sulphonate as a *ca.* 1×10^{-4}M-soln. in N-NaOH was determined spectrophotometrically at 232 nm (see ref. 1 for details).

T/°C	$k \times 10^{-5}$/s^{-1} [a]	$t_{\frac{1}{2}}$/min
40	275 (*ca.* 100)	4·2
25	77·9 (91)	14·8

[a] Reaction followed from <10% to % in parentheses.

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