1016. *Reactions of Pyrimidin-5-yl-lithium Compounds*

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Pyrimidin-5-yl-lithium compounds, mostly having alkoxy-substituents, reacted with carbon dioxide, dimethylformamide, and sulphur, forming respectively carboxylic acids, aldehydes, and polysulphides. The last were reduced and converted *in situ* into (pyrimidin-5-ylthio)alkanoic acids. Preparations of pyrimidin-5-ylacetic acids and of 5-bromo-2-formylpyrimidine are also described.

The synthetic application of pyrimidin-5-yl-lithium compounds has not been investigated in detail. Langley[1] prepared 2,4-dimethoxypyrimidine-5-carboxylic acid by carbonation of the lithium derivative from 5-bromo-2,4-dimethoxypyrimidine, and other pyrimidine-5-carboxylic acids prepared by this method have been mentioned in the patent literature.[2] Rajkumar and Binkley [3] prepared a series of 5-arylhydroxymethyl-2,4-diethoxypyrimidines from 2,4-diethoxypyrimidin-5-yl-lithium and aromatic aldehydes. This Paper describes the synthesis of a number of pyrimidine-5-carboxylic acids (see Table); the lithium compounds with dimethylformamide gave aldehydes and, with sulphur, polysulphides which on reduction with sodium dithionite gave mercapto-compounds, isolated by conversion

[1] B. W. Langley, *J. Amer. Chem. Soc.*, 1956, **78**, 2136.
[2] F. P. Doyle and H. C. Nayler (Beecham Research Labs. Ltd.), B.P. 905,778.
[3] T. B. Rajkumar and S. B. Binkley, *J. Medicin. Chem.*, 1963, **6**, 550.

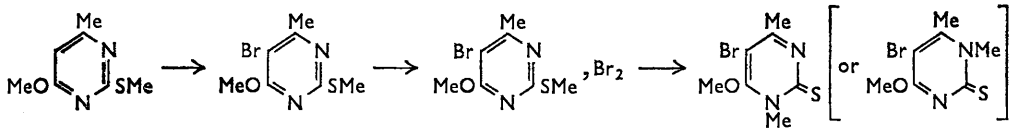
Pyrimidine-5-carboxylic acids

Substituent at position				Yield		Found (%)			Reqd. (%)		
2	4	6	M. p.	(%)	Formula	C	H	N	C	H	N
H	MeO	MeO	196—197°	57	$C_7H_8N_2O_4$ [2]	45·8	4·5	15·4	45·7	4·4	15·2
Me	MeO	MeO	209—210	41	$C_8H_{10}N_2O_4$	48·3	5·1	14·1	48·5	5·1	14·1
Et	MeO	MeO	148—151	5	$C_9H_{12}N_2O_4$	50·9	5·8	12·9	50·9	5·7	13·2
$PhCH_2$	MeO	MeO	154—155	10	$C_{14}H_{14}N_2O_4$	61·6	5·4	9·9	61·3	5·1	10·2
Ph	MeO	MeO	183—185	64	$C_{13}H_{12}N_2O_4$	59·7	4·7	11·0	60·0	4·6	10·8
MeO	MeO	MeO	207—209	89	$C_8H_{10}N_2O_5$	45·2	4·9	12·8	44·9	4·7	13·1
H	EtO	EtO	107—109	24	$C_9H_{12}N_2O_4$	51·0	5·9	13·2	50·9	5·7	13·2
EtO	EtO	EtO	138—140	56	$C_{11}H_{16}N_2O_5$	51·8	6·4	11·1	51·6	6·3	10·9
PrO	PrO	PrO	87—88	21	$C_{14}H_{22}N_2O_5$	56·7	7·6	9·4	56·4	7·4	9·4
H	MeS	MeS	229—230	25	$C_7H_8N_2O_2S_2$ [a]	39·2	4·0	12·7	38·9	3·7	13·0
H	Cl	MeO	140—141	1	$C_6H_5ClN_2O_3$ [b] [2]	—	—	14·5	—	—	14·9
Ph	Cl	MeO	177—178	34	$C_{12}H_9ClN_2O_3$ [c]	54·2	3·5	—	54·4	3·4	—

[a] From 5-bromo-4,6-dimethylthiopyrimidine, H. C. Koppel, R. H. Springer, R. K. Robins, and C. C. Cheng, *J. Org. Chem.*, 1961, **26**, 792. [b] Found: Cl, 19·2. Reqd: Cl, 18·8%. [c] Found: Cl, 13·8. Reqd: Cl, 13·4%.

with chloroacetic acid into pyrimidinethioacetic acids. The lithiations were in all cases conducted at −70° under nitrogen. The ease of lithiation, as estimated by the yield of carboxylic acid, is dependent on the nature of the substituents in the pyrimidine ring. The available data suggest that, in general, the reaction is successful only for those compounds which possess at least two methoxy-groups or other substituents with equivalent electron-releasing characteristics. Thus, whereas 5-bromo-2,4,6-trimethoxypyrimidine gave the highest yield, 5-bromo-4-chloro-6-methoxypyrimidine gave only a 1% yield, and no acid at all was isolated from 5-bromo-4-methoxy- or 5-bromo-4-methoxy-6-methylpyrimidine. 5-Chloropyrimidines were unsuitable for this work; 5-chloro-2,4,6-trimethoxypyrimidine, for example, gave no carbonation product.

The required alkoxy-5-bromopyrimidines were obtained by bromination of alkoxypyrimidines with *N*-bromosuccinimide in glacial acetic acid. Alternatively, the corresponding hydroxy-5-bromopyrimidines were treated with phosphoryl chloride and the resulting chloro-5-bromopyrimidines allowed to react with the required sodium alkoxide. The second method, however, often failed to give a pure product, but the impure materials could be used to prepare pure carboxylic acids. When bromination of alkoxypyrimidines was carried out with bromine in glacial acetic acid at 100°, *e.g.*, the bromination of 4-methoxy-6-methyl-2-methylthiopyrimidine, migration of one of the methyl groups to a ring nitrogen atom occurred. The same reaction at 20° gave a low yield of 5-bromo-4-methoxy-6-methyl-2-methylthiopyrimidine, together with a tribromo-compound containing the equivalent of two methoxy-groups, which was converted into the above *N*-methyl compound when heated. Since migration only occurred when elementary bromine was used, the following sequence is suggested:



4,6-Dimethoxy- and 2,4,6-trimethoxy-pyrimidine-5-carboxylic acids were converted into the corresponding pyrimidin-5-ylacetic acids by the Arndt–Eistert procedure. 4,6-Dimethoxypyrimidine-5-carboxylic acid was converted successively into the amide and nitrile, but the latter failed to form a thioamide on reaction with hydrogen sulphide, probably for steric reasons.

5-Bromo-2-formylpyrimidine was prepared by Hammick's method,[4] a reaction that does not hitherto appear to have been applied successfully to the pyrimidine series.

[4] D. L. Hammick, *J.*, 1926, 1302.

5-Bromo-2-tribromomethylpyrimidine [5] with tin and hydrochloric acid gave 5-bromo-2-dibromomethylpyrimidine, which on hydrolysis gave the aldehyde, isolated as the thiosemicarbazone and dinitrophenylhydrazone.

Experimental

2-Benzyl-4,6-dihydroxypyrimidine.—Phenylacetamidine hydrochloride (17 g.) was added to sodium ethoxide solution (from 5 g. of sodium and 100 ml. of dry ethanol) followed by diethyl malonate (16 g.), and the mixture was boiled under reflux for 3 hr. and left overnight. The solid which separated was collected, dissolved in water, and acidified with concentrated hydrochloric acid. The crude product (10·4 g., 51%) was collected and washed with water, and a sample was crystallised from dilute acetic acid to give *2-benzyl-4,6-dihydroxypyrimidine*, m. p. >250° (Found: C, 65·3; H, 5·2; N, 13·5. $C_{11}H_{10}N_2O_2$ requires C, 65·3; H, 5·0; N, 13·9%).

5-Bromo-2-ethyl-4,6-dihydroxypyrimidine.—Bromine (36 ml.) in glacial acetic acid (360 ml.) was added dropwise with stirring to 2-ethyl-4,6-dihydroxypyrimidine [6] (84 g.) in glacial acetic acid (600 ml.) at room temperature and the mixture was left overnight. The solid (119 g., 91%) was collected and washed with water, and a sample was recrystallised from dilute acetic acid to give *5-bromo-2-ethyl-4,6-dihydroxypyrimidine*, m. p. 223—224° (decomp.) (Found: C, 33·0; H, 3·4; Br, 36·4; N, 12·6. $C_6H_7BrN_2O_2$ requires C, 32·9; H, 3·2; Br, 36·5; N, 12·8%).

Similarly were prepared: *2-benzyl-5-bromo-3,6-dihydroxypyrimidine* (81%), decomp. >200° (Found: C, 47·2; H, 3·0; N, 9·8. $C_{11}H_9BrN_2O_2$ requires C, 47·0; H, 3·2; N, 10·0%); *5-bromo-4-hydroxy-6-methylpyrimidine* (42%), m. p. 227—229° from 4-hydroxy-6-methylpyrimidine [7] (Found: C, 31·8; H, 2·8; N, 14·4. $C_5H_5BrN_2O$ requires C, 31·8; H, 2·7; N, 14·8%); and 5-bromo-4,6-dihydroxy-2-methylpyrimidine which could not be obtained pure by this method.

5-Bromo-4,6-dihydroxy-2-methylpyrimidine.—4,6-Dihydroxy-2-methylpyrimidine [8] (10 g.) in glacial acetic acid (60 ml.) was heated at 100° for 10 min. with acetic anhydride (12 ml.). 1,3-Dibromo-5,5-dimethylhydantoin (21·5 g.) was added and heating was continued for a further 3 hr. The mixture was cooled and the solid (8·5 g., 52%) was collected and thoroughly washed with water to give *5-bromo-4,6-dihydroxy-2-methylpyrimidine*, decomp. *ca.* 240° (Found: Br, 38·8; N, 13·0. $C_5H_5BrN_2O_2$ requires Br, 38·8; N, 13·6%).

5-Chloro-4,6-dihydroxy-2-phenylpyrimidine.—4,6-Dihydroxy-2-phenylpyrimidine [9] (4·7 g.) was heated at 100° for 1 hr. with chlorine (1·95 g.) in glacial acetic acid (45 ml.) and cooled. The solid was collected, washed with water, and recrystallised from aqueous dimethylformamide to give 5-chloro-4,6-dihydroxy-2-phenylpyrimidine (2·3 g., 50%) as a pale yellow solid, m. p. 331—332° (decomp.) (lit.,[10] >320°) (Found: C, 53·5; H, 3·4; N, 12·7. Calc. for $C_{10}H_7ClN_2O_2$: C, 54·0; H, 3·2; N, 12·6%). An excess of chlorine passed into a suspension of 4,6-dihydroxy-2-phenylpyrimidine in glacial acetic acid yielded a *trichloro-derivative* (from ethanol), m. p. 127—128° (decomp.) (Found: Cl, 36·9; O, 11·1. $C_{10}H_5Cl_3N_2O_2$ requires Cl, 36·5; O, 11·0%).

2-Benzyl-5-bromo-4,6-dichloropyrimidine.—2-Benzyl-5-bromo-4,6-dihydroxypyrimidine (90 g.) and phosphoryl chloride (900 ml.) were heated under reflux for 2 hr. Most of the excess of phosphoryl chloride was removed *in vacuo*, the cooled residue was poured on to ice, and the mixture was extracted with ether. The extract was shaken with sodium hydrogen carbonate solution, dried ($MgSO_4$), and evaporated. The residue was recrystallised from light petroleum (b. p. 40—60°) to give *2-benzyl-5-bromo-4,6-dichloropyrimidine* (26·4 g., 37%), m. p. 84—87° (Found: C, 42·0; H, 2·7; N, 8·7. $C_{11}H_7BrCl_2N_2$ requires C, 41·5; H, 2·7; N, 8·8%).

Similarly were prepared: 5-bromo-4,6-dichloro-2-methylpyrimidine and 5-bromo-4,6-dichloro-2-ethylpyrimidine, which were not obtained pure, but which were converted directly into the 2-alkyl-5-bromo-4,6-dimethoxypyrimidines (see below); *5-bromo-4-chloro-6-methylpyrimidine* (78%), m. p. 56—57° (Found: C, 28·6; H, 1·5; N, 14·0. $C_5H_4BrClN_2$ requires C, 28·9; H, 2·0; N, 13·5%); and *5-bromo-4,6-dichloro-2-phenylpyrimidine* (43%), m. p. 118—119°, from 5-bromo-4,6-dihydroxy-2-phenylpyrimidine [9] (Found: N, 8·7; AgX, 156·3. $C_{10}H_5BrCl_2N_2$ requires N, 9·2; AgX, 156·1%).

4-Chloro-6-methoxy-2-phenylpyrimidine and 4,6-Dimethoxy-2-phenylpyrimidine.—A solution of

[5] A. Holland and R. Slack, *Chem. and Ind.*, 1954, 1203.
[6] H. R. Henze and J. L. McPherson, *J. Org. Chem.*, 1953, **18**, 653.
[7] H. M. Foster and H. R. Snyder, *Org. Synth.*, 1955, **35**, 80.
[8] L. P. Ferris and A. R. Ronzio, *J. Amer. Chem. Soc.*, 1940, **62**, 606.
[9] E. L. Pinner, *Ber.*, 1908, **41**, 3517.
[10] S. Ruhemann, *J.*, 1903, 379.

sodium methoxide (from 1·84 g. of sodium and 30 ml. of dry methanol) was added dropwise with stirring to 4,6-dichloro-2-phenylpyrimidine [11] (4·5 g.) in dry methanol (50 ml.), below 30°. Stirring was continued for a further 1 hr. and the mixture was poured into water (150 ml.) at 10°. The solid was collected and extracted with hot light petroleum (b. p. 40—60°), and the extract was concentrated and cooled to give *4-chloro-6-methoxy-2-phenylpyrimidine* (4·1 g., 95%), m. p. 70—71° (Found: C, 60·1; H, 4·1; N, 12·4; MeO, 14·1. $C_{11}H_9ClN_2O$ requires C, 59·9; H, 4·1; N, 12·7; MeO, 14·1%). The same mixture was heated at 100° for 30 min. and the product was recrystallised from methanol to give *4,6-dimethoxy-2-phenylpyrimidine* (92%), m. p. 56—58° (Found: C, 66·4; H, 5·7; N, 12·7. $C_{12}H_{12}N_2O_2$ requires C, 66·7; H, 5·6; N, 13·0%).

2,4,6-Tripropoxypyrimidine.—Sodium (7·5 g.) was dissolved in dry propanol (150 ml.). Dry xylene (150 ml.) and 2,4,6-trichloropyrimidine [12] (18·2 g.) were added and the excess of propanol was distilled off during 3 hr. (bath temp. 140°). Benzene (100 ml.) and water (200 ml.) were added to the cooled mixture, and the aqueous layer was extracted with benzene. The combined organic solutions were dried (Na_2SO_4) and evaporated, and the residue was distilled to give *2,4,6-tripropoxypyrimidine* (16·6 g., 65%), b. p. 178—180°/20 mm. (Found: C, 61·9; H, 8·8; N, 11·1. $C_{13}H_{22}N_2O_3$ requires C, 61·4; H, 8·7; N, 11·0%).

Bromination of 4-Methoxy-6-methyl-2-methylthiopyrimidine.—(*a*) *With bromine–acetic acid at* 100°. Bromine (10·8 g.) in glacial acetic acid (50 ml.) was added during 45 min. with stirring to 4-methoxy-6-methyl-2-methylthiopyrimidine [13] (11·5 g.) in glacial acetic acid (50 ml.) at 100°. Heating and stirring were continued for a further 105 min. and the mixture was left overnight. The solid was collected, washed with water, and crystallised from ethanol (400 ml.) to give *5-bromo-6-methoxy-1,4-dimethylpyrimidine-2-thione* (or an isomer; 8·8 g., 53%) as a colourless solid, m. p. 237—238° (decomp.) (Found: Br, 31·9; N, 11·5; S, 12·8; Zeisel calc. as MeO, 12·3. $C_7H_9BrN_2OS$ requires Br, 32·1; N, 11·3; S, 12·9; one MeO or MeS calc. as MeO, 12·5%).

(*b*) *With bromine–acetic acid at* 20°. The experiment described in (*a*) was repeated without heating. An orange solid (52%) was obtained which was crystallised from glacial acetic acid to give *5-bromo-4-methoxy-6-methyl-2-methylthiopyrimidine dibromide* as orange needles, m. p. 135° (rapid heating) (Found: C, 20·1; H, 2·7; Br, 60·4; N, 6·7; S, 7·3; Zeisel calc. as MeO, 12·8. $C_7H_9Br_3N_2OS$ requires C, 20·6; H, 2·2; Br, 58·6; N, 6·9; S, 7·8; Zeisel calc. as 2MeO, 15·2%). After melting, the compound resolidified to give a colourless solid, m. p. 240° (decomp.) (cf. (*a*)). The filtrate from the reaction mixture was concentrated *in vacuo*, and the solid obtained was crystallised from aqueous ethanol to give *5-bromo-4-methoxy-6-methyl-2-methylthiopyrimidine* (12%) as colourless needles, m. p. 70—71° (Found: C, 33·8; H, 3·9; Br, 31·8; N, 11·6; S, 12·9; Zeisel, calc. as MeO, 23·6. $C_7H_9BrN_2OS$ requires C, 33·8; H, 3·6; Br, 32·1; N, 11·3; S, 12·9; Zeisel, calc. as 2MeO, 24·9%).

(*c*) *With N-bromosuccinimide.* 4-Methoxy-6-methyl-2-methylthiopyrimidine was brominated with *N*-bromosuccinimide as described below [method (*a*)] to give 5-bromo-4-methoxy-6-methyl-2-methylthiopyrimidine (50%), identical with that obtained in method (*b*) (above).

Alkoxy-5-halogenopyrimidines.—*Method* (*a*). *5-Bromo-4,6-dimethoxypyrimidine.* 4,6-Dimethoxypyrimidine [14] (197·7 g.) in glacial acetic acid (850 ml.) was heated at 100° for 10 min. with acetic anhydride (170 ml.). *N*-Bromosuccinimide (314 g.) was added and heating was continued for a further 3 hr., and the mixture was cooled. The solid was collected and a further crop was obtained by pouring the filtrate into ice–water. The combined solids (294·5 g., 95%) were washed with light petroleum (b. p. 60—80°) and a sample was crystallised from light petroleum (b. p. 60—80°) to give *5-bromo-4,6-dimethoxypyrimidine*, m. p. 149—151° (Found: C, 32·8; H, 3·5; Br, 36·7; N, 12·8. $C_6H_7BrN_2O_2$ requires C, 32·9; H, 3·2; Br, 36·5; N, 12·8%).

Similarly were prepared: *5-bromo-2,4,6-trimethoxypyrimidine* (89%), m. p. 144—145° from 2,4,6-trimethoxypyrimidine [15] (Found: C, 34·0; H, 3·6; Br, 32·3; MeO, 37·8. $C_7H_9BrN_2O_3$ requires C, 33·8; H, 3·6; Br, 32·1; MeO, 37·4%); *5-bromo-2,4,6-triethoxypyrimidine* (68%), m. p. 52—54° from 2,4,6-triethoxypyrimidine [16] (Found: Br, 27·9; N, 9·5. $C_{10}H_{15}BrN_2O_3$

[11] J. A. Hendry and R. F. Homer, *J.*, 1952, 328.
[12] J. Baddiley and A. Topham, *J.*, 1944, 678.
[13] J. F. W. McOmie, E. R. Sayer, and J. Chesterfield, *J.*, 1957, 1830.
[14] D. J. Brown and J. S. Harper, *J.*, 1961, 1298.
[15] E. Büttner, *Ber.*, 1903, **36**, 2227.
[16] W. Winklemann, *J. prakt. Chem.*, 1927, **115**, 292.

requires Br, 27·4; N, 9·6%); *5-bromo-2,4,6-tripropoxypyrimidine* (86%), b. p. 130—140°/0·1 mm. (Found: C, 46·8; H, 6·5; Br, 24·3; N, 8·4. $C_{13}H_{21}BrN_2O_3$ requires C, 46·9; H, 6·4; Br, 24·0; N, 8·4%); *5-bromo-4,6-dimethoxy-2-phenylpyrimidine* (65%), m. p. 103° (Found: Br, 26·8; N, 9·2. $C_{12}H_{11}BrN_2O_2$ requires Br, 27·1; N, 9·5%); and 5-bromo-4-chloro-6-methoxy-2-phenylpyrimidine (68%), identical with that prepared by method (*c*) (below).

Method (*b*). *5-Bromo-4,6-dimethoxypyrimidine.* A cooled, stirred suspension of 5-bromo-4,6-dichloropyrimidine [17] (8·5 g.) in methanol (100 ml.) was treated with sodium methoxide solution (from 3·1 g. of sodium and 60 ml. of methanol) below 30°. The solid was collected and extracted with hot light petroleum (b. p. 60—80°), and the extract was concentrated and cooled to give the product, m. p. 148—150°. A further quantity was obtained by evaporation of the methanol filtrate. Total yield 6·6 g. (81%).

Similarly were prepared: *5-bromo-4,6-dimethoxy-2-methylpyrimidine* (52%), m. p. 116—119° (Found: C, 35·8; H, 3·7; N, 12·3. $C_7H_9BrN_2O_2$ requires C, 36·1; H, 3·9; N, 12·0%); *5-bromo-2-ethyl-4,6-dimethoxypyrimidine* (56%), m. p. 67—69° (Found: C, 38·5; H, 5·0. $C_8H_{11}BrN_2O_2$ requires C, 38·9; H, 4·5%); *2-benzyl-5-bromo-4,6-dimethoxypyrimidine* (66%), m. p. 114—115° (Found: C, 51·0; H, 4·5; N, 9·0. $C_{13}H_{13}BrN_2O_2$ requires C, 50·5; H, 4·2; N, 9·1%); 5-bromo-4,6-dimethoxy-2-phenylpyrimidine (83%), identical with that prepared by method (*a*); *5-bromo-4-methoxypyrimidine* (85%), m. p. 72—74°, from 5-bromo-4-chloropyrimidine [17] (Found: C, 32·0; H, 3·0; N, 14·7. $C_5H_5BrN_2O$ requires C, 31·8; H, 2·7; N, 14·8%); *5-bromo-4-methoxy-6-methylpyrimidine* (64%), m. p. 79—80° (Found: C, 35·3; H, 3·4; N, 13·5. $C_6H_7BrN_2O$ requires C, 35·5; H, 3·5; N, 13·8%); *5-bromo-4-chloro-6-methoxypyrimidine* (87%), m. p. 67—70°, from 5-bromo-4,6-dichloropyrimidine using only one mol. of sodium methoxide (Found: C, 26·7; H, 2·1; N, 12·3. $C_5H_4BrClN_2O$ requires C, 26·9; H, 1·8; N, 12·5%); *5-chloro-2,4,6-trimethoxypyrimidine* (57%), m. p. 130—132°, from 2,4,5,6-tetrachloropyrimidine [18] (Found: C, 40·8; H, 4·4; Cl, 17·4; N, 13·3. $C_7H_9ClN_2O_3$ requires C, 41·1; H, 4·4; Cl, 17·3; N, 13·7%); *5-bromo-4,6-diethoxypyrimidine* (61%), m. p. 34—35° (Found: N, 11·6. $C_8H_{11}BrN_2O_2$ requires N, 11·3%); and *5-chloro-2,4,6-triethoxypyrimidine* (42%), m. p. 44—48° (Found: Cl, 14·6; EtO, 53·2. $C_{10}H_{15}ClN_2O_3$ requires Cl, 14·4; EtO, 54·8%).

Method (*c*). *5-Bromo-4-chloro-6-methoxy-2-phenylpyrimidine.* 5-Bromo-4,6-dichloro-2-phenylpyrimidine (6·08 g.) was boiled under reflux for 3 hr. with sodium methoxide (from 0·5 g. of sodium) in dry toluene (50 ml.) and left overnight. The sodium chloride was removed, the filtrate was evaporated *in vacuo*, and the residue was recrystallised from light petroleum (b. p. 60—80°) to give *5-bromo-4-chloro-6-methoxy-2-phenylpyrimidine* (5·45 g., 92%), m. p. 91—93° (Found: C, 43·5; H, 3·0; Halogen, expressed as Br, 53·6; N, 9·6. $C_{11}H_8BrClN_2O$ requires C, 44·1; H, 2·7; Halogen, expressed as Br, 53·4; N, 9·4%).

Pyrimidine-5-carboxylic Acids (See Table).—A solution [in dry ether or 15% w/w in n-hexane (Foote Mineral Co., Johnsonville, Tenn.)] of n-butyl-lithium (0·11 mole) was added with stirring to a solution of the appropriate 5-bromopyrimidine (0·1 mole) in dry tetrahydrofuran (300 ml.) at −70° in an atmosphere of nitrogen at such a rate that the temperature did not rise above −60°. After a further 15 min. at −60° to −70°, an excess of dry, powdered carbon dioxide was added. The mixture was allowed to attain room temperature and was acidified with 2N-hydrochloric acid. The aqueous layer was extracted twice with ether and the combined tetrahydrofuran and ether solutions were dried ($MgSO_4$) and evaporated *in vacuo*. The resulting crude acid was crystallised from water or ethyl acetate, or was reprecipitated from sodium hydrogen carbonate solution by hydrochloric acid.

5-Formyl-2,4,6-trimethoxypyrimidine.—Dry dimethylformamide (9 ml.) was added all at once to a solution of 2,4,6-trimethoxypyrimidin-5-yl-lithium (from 25 g. of 5-bromo-2,4,6-trimethoxypyrimidine) in dry tetrahydrofuran (250 ml.) at −65° in an atmosphere of nitrogen. The mixture was stirred for 1 hr. at −65°, allowed to warm to 0°, and treated with an excess of 2N-hydrochloric acid. The aqueous layer was extracted twice with ether, the combined tetrahydrofuran and ether solutions were dried ($MgSO_4$) and evaporated, and the residue was crystallised from light petroleum (b. p. 60—80°) to give the *aldehyde* (12·9 g., 65%), m. p. 130—133° (Found: C, 48·1; H, 5·3; N, 14·4. $C_8H_{10}N_2O_4$ requires C, 48·5; H, 5·1; N, 14·1%) [*thiosemicarbazone*, m. p. 221—223° (Found: C, 40·0; H, 5·1; N, 26·0. $C_9H_{13}N_5O_3S$ requires C, 39·8; H, 4·8; N, 25·8%)]. Similarly were prepared: *5-formyl-4,6-dimethoxypyrimidine* (39%), m. p. 135—137° (Found: C, 49·9; H, 4·6; N, 16·5. $C_7H_8N_2O_3$ requires C, 50·0; H,

[17] J. Chesterfield, J. F. W. McOmie, and E. R. Sayer, *J.*, 1955, 3478.
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4·8; N, 16·7%) [*thiosemicarbazone*, m. p. 221—223° (decomp.) (Found: C, 39·6; H, 4·7; N, 29·2. $C_8H_{11}N_5O_2S$ requires C, 39·8; H, 4·6; N, 29·0%)]; and 5-formyl-4,6-dimethoxy-2-phenylpyrimidine (not obtained pure) [*thiosemicarbazone*, m. p. 210—212° (Found: C, 53·1; H, 5·0; N, 22·2. $C_{14}H_{15}N_5O_2S$ requires C, 53·0; H, 4·8; N, 22·1%)].

(4,6-*Dimethoxypyrimidin-5-ylthio*)*acetic Acid*.—4,6-Dimethoxypyrimidin-5-yl-lithium (from 5·2 g. of 5-bromo-4,6-dimethoxypyrimidine) in tetrahydrofuran at −65° was treated with sulphur (0·75 g.) and the mixture was left at room temperature overnight. It was acidified with 2N-hydrochloric acid, the aqueous layer was extracted with ether, and the combined organic solutions were dried (Na_2SO_4) and evaporated. Trituration of the residue with light petroleum (b. p. 40—60°) gave crude 4,6-dimethoxypyrimidin-5-yl polysulphide (2 g.), which was heated under reflux for 1 hr. with sodium dithionite (2 g.) and sodium hydroxide (0·5 g.) in ethanol (25 ml.) and water (25 ml.). Sodium chloroacetate (3 g.) was added and heating was continued for a further 1·5 hr. The ethanol was removed, the aqueous solution was filtered, brought to pH 2, and kept at 0° overnight, to give the *acid* (0·25 g., 4·5%), m. p. 123—125° (Found: C, 41·9; H, 4·4; N, 12·4; S, 13·6. $C_8H_{10}N_2O_4S$ requires C, 41·7; H, 4·4; N, 12·2; S, 13·9%). Similarly were prepared: (2,4,6-*trimethoxypyrimidin-5-ylthio*)*acetic acid* (33%), m. p. 148—150° (decomp.) (Found: C, 42·3; H, 5·1; N, 10·7; S, 12·4. $C_9H_{12}N_2O_5S$ requires C, 41·5; H, 4·6; N, 10·8; S, 12·3%); and α-(2,4,6-*trimethoxypyrimidin-5-ylthio*)*propionic acid* (33%), m. p. 153—155° (Found: N, 10·3; S, 11·5. $C_{10}H_{14}N_2O_5S$ requires N, 10·2; S, 11·7%).

4,6-*Dimethoxypyrimidine-5-carbonyldiazomethane*.—4,6-Dimethoxypyrimidine-5-carboxylic acid (3·2 g.) was heated under reflux with thionyl chloride (32 ml.) for 40 min. and the excess of thionyl chloride was removed *in vacuo* through a short column. A solution of the residue in dry ether (50 ml.) was added dropwise to an ethereal solution of diazomethane (from 20 g. of *N*-methyl-*N*-nitrosourea) at 0°, and the mixture was left at room temp. for 40 hr. The solvent was removed *in vacuo* and the residue was crystallised from cyclohexane to give the *diazoketone* (2·2 g., 61%) as a pale yellow solid, m. p. 110—111° (decomp.) (Found: C, 46·5; H, 4·2; N, 26·6. $C_8H_8N_4O_3$ requires C, 46·2; H, 3·9; N, 26·9%).

2,4,6-*Trimethoxypyrimidine-5-carbonyldiazomethane* was prepared similarly. It was crystallised from light petroleum (b. p. 60—80°) to give pale yellow crystals (37%), m. p. 93—95° (decomp.) (Found: C, 46·3; H, 4·9; N, 21·4. $C_9H_{10}N_4O_4$ requires C, 45·4; H, 4·2; N, 23·5%).

4,6-*Dimethoxypyrimidin-5-ylacetic Acid*.—4,6-Dimethoxypyrimidine-5-carbonyldiazomethane (8 g.) in dioxan (60 ml.) was added with stirring during 10 min. to silver oxide (1 g.), sodium thiosulphate (1·6 g. of pentahydrate), and sodium carbonate (2·5 g.) in water (100 ml.) at 50—60°, and the mixture was stirred at 90—95° for 1 hr. and cooled. The solid was removed and the filtrate was acidified with 2N-nitric acid and concentrated *in vacuo*. The solid was collected and crystallised from ethanol to give the *acid* (3·6 g., 47%), m. p. 177—179° (Found: C, 48·7; H, 5·2; N, 14·1. $C_8H_{10}N_2O_4$ requires C, 48·5; H, 5·1; N, 14·1%).

2,4,6-*Trimethoxypyrimidin-5-ylacetic acid* was prepared similarly. It was crystallised from aqueous ethanol to give a yellow solid (58%), m. p. 161—163° (Found: C, 47·7; H, 5·3; N, 12·3. $C_9H_{12}N_2O_5$ requires C, 47·4; H, 5·3; N, 12·3%).

4,6-*Dimethoxypyrimidine-5-carbonamide*.—4,6-Dimethoxypyrimidine-5-carbonyl chloride (from 5 g. of the corresponding acid) in dry acetone (50 ml.) was added slowly to an excess of ice-cold aqueous ammonia (*d* 0·9). The solid was collected and crystallised from water to give the *amide* (3·8 g., 76%) as colourless needles, m. p. 242—244° (Found: C, 46·1; H, 5·2; N, 22·4. $C_7H_9N_3O_3$ requires C, 45·9; H, 5·0; N, 23·0%).

5-*Cyano*-4,6-*dimethoxypyrimidine*.—4,6-Dimethoxypyrimidine-5-carbonamide (2 g.) and phosphoric oxide (1·15 g.) were heated at 175° for 4 hr. and the product was extracted with hot methylene chloride (6 × 40 ml.). The extract was evaporated and the residue was crystallised from ethanol to give the *nitrile* (0·5 g., 28%) as colourless blades, m. p. 208—210° (sublimes) (Found: C, 50·7; H, 4·4; O, 19·4. $C_7H_7N_3O_2$ requires C, 50·9; H, 4·3; O, 19·4%).

5-*Bromo*-2-*dibromomethylpyrimidine*.—5-Bromo-2-tribromomethylpyrimidine [5] (20·5 g.) in acetone (140 ml.) was added to tin (6 g.) in concentrated hydrochloric acid (30 ml.) and the mixture was heated under reflux for 1 hr. The acetone was removed *in vacuo* and the residue was treated with water (80 ml.). 5-*Bromo*-2-*dibromomethylpyrimidine* (5·9 g., 36%) separated on cooling. A sample recrystallised from light petroleum (b. p. 40—60°) had m. p. 66—68° (Found: C, 18·3; H, 1·0. $C_5H_3Br_3N_2$ requires C, 18·2; H, 0·9%).

5-*Bromo*-2-*formylpyrimidine*.—Silver nitrate (1·25 g.) in water (4 ml.) was added to 5-bromo-2-dibromomethylpyrimidine (1·26 g.) in ethanol (10 ml.) and the mixture was heated under

reflux for 6·5 hr. The hot mixture was filtered, cooled, acidified with 2N-hydrochloric acid, filtered, and continuously extracted with ether. Evaporation of the extract gave crude 5-bromo-2-formylpyrimidine, which was converted directly into the *thiosemicarbazone hydrate* (0·47 g., 47%), m. p. 229—230° (decomp.) (Found: C, 25·8; H, 3·0; S, 11·4; H_2O, 6·3. $C_6H_6BrN_5S,H_2O$ requires C, 25·9; H, 2·9; S, 11·5; H_2O, 6·5%) [*2,4-dinitrophenylhydrazone*, m. p. 225—227° (Found: C, 35·8; H, 1·9; N, 22·7. $C_{11}H_7BrN_6O_4$ requires C, 36·0; H, 1·9; N, 22·9%)].

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