1243. *The Preparation of Some 4,6-Disubstituted Pyrimidine-5-carboxylic Acids*

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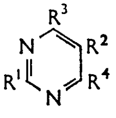
4,6-Disubstituted pyrimidine-5-carboxylic acids have been prepared from 5-bromopyrimidines through the halogen–metal interconversion with n-butyl-lithium. When bromine and chlorine were both present in the pyrimidine nucleus, only the former underwent the interconversion reaction. Most of the acids were converted into derivatives through their acid chlorides. The reaction of 4,6 dimethoxypyrimidine with n-butyl-lithium gave a 2,5-dihydropyrimidine whose n.m.r. spectrum showed coupling between the C-2 and C-5 protons with the unusually large coupling constant of 5·5 c./sec. This is discussed.

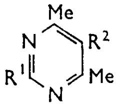
This work was carried out in order to prepare hindered 5-carboxypyrimidines substituted with groups such as alkyl, alkoxy, alkylthio, halogen, or phenyl. Pyrimidinecarboxylic acids have usually been prepared by hydrolysis of esters, amides, or nitriles, or by oxidation of alkyl or formyl derivatives.[1a] These intermediates are themselves normally prepared by primary synthesis from two simpler fragments.



(I)

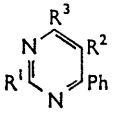
	R^1	R^2	R^2	R^4
(a)	SH	H	OH	OH
(b)	SH	H	OH	Me
(c)	OEt	H	OEt	Li
(d)	OMe	Li	OMe	H
(e)	H	Br	Cl	OMe
(f)	H	Br	Cl	Cl

	R^1	R^2	R^3	R^4
(g)	H	Br	Cl	OMe
(h)	H	Br	OMe	OMe
(i)	H	Br	SH	SH
(j)	H	Br	SMe	SMe
(k)	H	H	OMe	OMe



(II)

	R^1	R^2
(a)	Cl	Br
(b)	OMe	CO_2H
(c)	OH	Br
(d)	NEt_2	Br
(e)	OMe	Br
(f)	Cl	CO_2H



(III)

	R^1	R^2	R^3
(a)	H	Br	Cl
(b)	SH	H	OH
(c)	H	H	OH
(d)	H	Br	OH
(e)	H	Br	OMe

Several unsuccessful attempts were made to form a pyrimidine nucleus containing a 5-ethoxycarbonyl group by condensing thiourea with appropriately substituted esters. Triethoxycarbonylmethane and thiourea in the presence of sodium ethoxide gave only 2-mercaptobarbituric acid (Ia),[2] whilst ethyl diacetylacetate under the same conditions gave 4-hydroxy-2-mercapto-6-methylpyrimidine (Ib).[3] In view of these results, it was decided to utilise the halogen–metal interconversion reaction between appropriately substituted 5-bromopyrimidines and n-butyl-lithium, followed by carbonation of the resulting pyrimidinyl-lithium, to give 5-carboxylic acids directly; this method is simple and the 5-bromopyrimidines are readily available. Several workers have carried out bromine–lithium interconversions on pyrimidines[4] although, only Langley[4a] carbonated the intermediate 2,4-diethoxy-6-pyrimidinyl-lithium (Ic), in a synthesis of orotic acid. He found the 6-pyrimidinyl-lithium to be extremely unstable even at the low temperature of the reaction (−80°), whilst 2,4-dimethoxy-5-pyrimidinyl-lithium (Id) was much more stable. Our acids (Table 2) have been prepared in generally good yields (50—87%)

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[1] D. J. Brown, in " The Pyrimidines," Wiley, New York, 1962, (*a*) p. 389; (*b*) p. 168.

[2] A. W. Dox and G. P. Plaisance, *J. Amer. Chem. Soc.*, 1916, **38**, 2156.

[3] H. L. Wheeler and D. F. McFarland, *Amer. Chem. J.*, 1909, **42**, 101.

[4] (*a*) B. W. Langley, *J. Amer. Chem. Soc.*, 1956, **78**, 2136; (*b*) T. K. Liao, E. G. Podrebarac, and C. C. Cheng, *ibid.*, 1964, **86**, 1869; (*c*) R. Shapiro and R. W. Chambers, *ibid.*, 1961, **83**, 3920; (*d*) T. V. Ulbricht, *Tetrahedron*, 1959, **6**, 225; (*e*) G. M. Kosolapoff and C. H. Roy, *J. Org. Chem.*, 1961, **26**, 1895; (*f*) T. V. Rajkumar and S. B. Binkley, *J. Medicin. Chem.*, 1963, **6**, 550.

using a modified procedure at —35 to —45°. Of greatest interest were the halogen–metal interconversions carried out on bromochloropyrimidines, *viz.*, 5-bromo-4-chloro-6-methoxy- (Ie), 5-bromo-2-chloro-4,6-dimethyl- (IIa), and 5-bromo-4-chloro-6-phenyl-pyrimidine (IIIa). In these cases, only the bromine atoms were replaced, giving finally the appropriate carboxychloropyrimidines.

These results were predictable on the theory[4d,5] that interconversion involves preferential attack by the anion of the organolithium compound on the more electropositive bromine atom, to give in the above cases the more stable 5-pyrimidinyl anion. They are also analogous to the findings of Gilman and Spatz[6] who observed no reaction between 2-chloroquinoline and n-butyl-lithium, even though the chlorine atom in this compound is reactive in a similar manner to those in the 2- and 4-positions of the pyrimidine nucleus. All the acids were crystalline solids which melted with decomposition. Most reacted with thionyl chloride in the presence of dimethylformamide, and the intermediate acid chlorides were converted into amides or, in one case, an anilide. The 2-chloro- and 2-methoxy-4,6-dimethylpyrimidine-5-carboxylic acids (IIf) and (IIb) were very sensitive to thionyl chloride, but the methoxy-compound (IIb) with this reagent at low temperature, in the presence of excess triethylamine, gave the acid chloride or some other reactive species, as shown by its subsequent conversion into amide. After similar treatemnt, the chloro-compound (IIf) failed to give any amide. The acids reacted through their acid chlorides with 6-aminopenicillanic acid, to form new penicillins as described elsewhere.[7]

The intermediate 5-bromopyrimidines were prepared by standard procedures. Reaction of 5-bromo-4,6-dichloropyrimidine (If) with one or two equivalents of sodium methoxide in methanol resulted in displacement of chlorine to give the monomethoxy- (Ig) and dimethoxy-pyrimidine (Ih), respectively. The latter compound had been reported[8] but no details were given. Treatment of the 4,6-dichloro-compound (If) with thiourea in boiling ethanol rapidly gave a bisisothiouronium salt which was hydrolysed with dilute sodium hydroxide to 5-bromo-4,6-dimercaptopyrimidine (Ii). Methylation with dimethyl sulphate gave the 4,6-bismethylthio-derivative (Ij). These compounds, prepared by a slightly different route, were described subsequent to this work.[9] The starting material for the 4,6-dimethyl compounds (II) was 5-bromo-2-hydroxy-4,6-dimethylpyrimidine (IIc) which, with phosphorus oxychloride, gave the 2-chloro-derivative (IIa). Chlorine was readily displaced by diethylamine or alkoxide ion to give 5-bromo-2-diethylamino- (IId) and 5-bromo-2-methoxy-4,6-dimethylpyrimidine (IIe), respectively.

Desulphuration of 4-hydroxy-2-mercapto-6-phenylpyrimidine (IIIb), with Raney nickel in aqueous solution,[10] gave 4-hydroxy-6-phenylpyrimidine (IIIc).[11] Bromination of this compound with bromine in glacial acetic acid at 70° gave the 5-bromo-derivative (IIId) whose structure is unambiguous since the same compound was obtained on bromination with sodium hypobromite solution, a reagent known to brominate hydroxypyrimidines in the 5-position.[1b] With phosphorus oxychloride the bromo-derivative (IIId) gave 5-bromo-4-chloro-6-phenylpyrimidine (IIIa) which, with sodium methoxide, was converted into the 4-methoxy-compound (IIIe).
activating effect of two methoxy-groups would be sufficient to promote hydrogen–lithium exchange in the 5-position. The only reaction observed which took place rapidly at *ca.* —40° was addition of n-butyl-lithium to the 1,2-azomethine linkage to give 2-n-butyl-2,5-dihydro-4,6-dimethoxypyrimidine (IV) which was a single compound as shown by

In addition to the bromine–lithium interconversions described above, a reaction was carried out between n-butyl-lithium and 4,6-dimethoxypyrimidine (Ik), to see if the

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[5] S. V. Sunthankar and H. Gilman, *J. Org. Chem.*, 1951, **16**, 8.

[6] H. Gilman and S. M. Spatz, *J. Amer. Chem. Soc.*, 1941, **63**, 1553.

[7] F. P. Doyle and J. H. C. Nayler, B.P. spec. 905,778/1962.

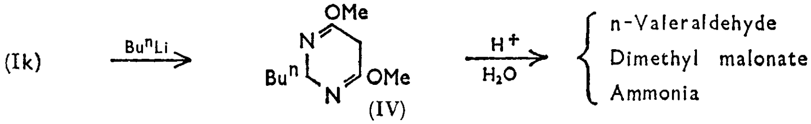
[8] A. Cardon, *Ind. chim. belge*, 1961, **26** (1), 50.

[9] H. C. Koppel, R. H. Springer, R. K. Robins, and C. C. Cheng, *J. Org. Chem.*, 1961, **26**, 792.

[10] Cf. M. Robba and R. Moreau, *Bull. Soc. chim. France*, 1960, 1648.

[11] (*a*) O. Seide, *Ber.*, 1925, **58**, 352; (*b*) G. Shaw and G. Sugowdz, *J.*, 1954, 665.

gas chromatography. This result parallels previous findings that the pyrimidine ring is too electron-deficient to undergo hydrogen–metal exchange, but readily undergoes the addition reaction with both organolithium [12] and Grignard reagents.[12a] The structure of (IV) was confirmed by infrared and n.m.r. spectroscopy. There was no absorption in the 3600—3000 cm.$^{-1}$ region (absence of N–H) but there were strong bands at 1725 and 1675 cm.$^{-1}$. In spite of their high value, these bands must be attributed to the imino-ether system in order to be compatible with the n.m.r. findings. The dihydropyrimidine (IV) was stable at room temperature, only darkening slightly after several months. In dilute aqueous hydrochloric acid, however, decomposition was rapid, as evidenced by the immediate odour of n-valeraldehyde. Gas chromatography of the decomposition products, after extraction into ether, showed the presence of n-valeraldehyde (30·0%), dimethyl malonate (51·4%), and an unidentified component (14·0%). The aqueous solution after the decomposition was made alkaline, and the liberated ammonia determined as ammonium chloride (78·5%).



The Nuclear Magnetic Resonance Spectrum of 2-*n-Butyl*-2,5-*dihydro*-4,6-*dimethoxypyrimidine*.—The spectrum consisted of a number of sets of signals. The chemical shifts, and the numbers of protons (in parentheses) giving rise to these signals, are shown in Table 1.

TABLE 1

MeO	6·32 τ (6)	Singlet
=C–CH$_2$–C=	7·45 τ (2)	Doublet, J = 5·5 c./sec.
=N–CH–N=	4·92 τ (1)	Quintet, J = 5·5 c./sec.
[CH$_2$]$_3$ of Bu^{n}	Approx. 8·6 τ (6)	Multiplet
ω-CH$_3$ of Bu^{n}	9·1 τ (3)	Triplet

That long-range coupling between the C-5 methylene and the C-2 methine groups occurs, to give doublet and quintet resonance signals, respectively, was demonstrated by double-resonance experiments. Saturating the C-5 methylene group at 7·45 τ caused the quintet at 4·92 τ to collapse to a triplet, owing to coupling with the α-methylene of the n-butyl group, with J = 5 c./sec. Similarly, saturation of the C-2 methine quintet at 4·92 τ resulted in collapse of the C-5 methylene doublet to a singlet. The ^{1}H spectrum of this compound is thus consistent with the dihydropyrimidine structure (IV), although the magnitude of the long range C-2 and C-5 proton coupling is unexpected.

Since, on double resonance, the C-5 methylene signal collapses to a simple A$_2$ spectrum, it may be considered that the dihydropyrimidine ring is essentially planar. If it were not, the C-5 methylene resonance would be an AB spectrum due to the two configurations of the C-5–H bonds. Since the dihydropyrimidine (IV) possesses highly nucleophilic groups or atoms, namely Me–$\underset{\cdot\cdot}{\ddot{\text{O}}}$– and =$\ddot{\text{N}}$–, it is possible to draw up a number of charged canonical structures involving delocalisation of σ-electrons. Whilst the exact mechanism of long-range coupling remains open to speculation, but has usually been related to extended π-electron conjugation,[13] the observation [14] that increased delocalisation of σ-electrons is accompanied by increased long-range coupling is relevant to the present work.

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[12] (*a*) H. Bredereck, R. Gompper, and H. Herlinger, *Ber.*, 1958, **91**, 2832; (*b*) T. D. Heyes and J. C. Roberts, *J.*, 1951, 328.

[13] M. Karplus, *J. Chem. Phys.*, 1960, **33**, 1842; H. S. Gutowsky and A. L. Porte, *ibid.*, 1961, **35**, 839; R. A. Hoffmann and S. Gronowitz, *J. Amer. Chem. Soc.*, 1961, **83**, 3910.

[14] P. N. Gates and E. F. Mooney, *J.*, 1964, 4648.

The parent pyrimidine shows[15] long-range coupling across the ring with $J_{2,5} = 1{\cdot}4$ c./sec., so the extraordinary magnitude of the long-range coupling found in the dihydropyrimidine studied in the present work may be due to the presence of the methoxy-groups. Long-range coupling over five bonds, as in the present case, is usually small, *e.g.*, indene $J_{3,7} = 0{\cdot}7$ c./sec.,[16] benzofuran $J_{3,7} = 0{\cdot}9$ c./sec.,[16] and quinoline $J_{4,8} = 0{\cdot}8$ c./sec.[17] The coupling found in the dihydropyrimidine (IV) approaches that of allene $J_{1,3} = 7$ c./sec.[18] which is only over four bonds.

EXPERIMENTAL

The ^1H spectra were recorded on a Perkin-Elmer R.10. n.m.r. spectrometer operating at 60 Mc./sec., using 10 or 20% solutions in carbon tetrachloride, and tetramethylsilane as internal standard. The Perkin-Elmer ^1H decoupling unit was used for the double-resonance experiments together with an external audio-oscillator to record the frequency swept spectra.

Substituted Pyrimidine-5-carboxylic Acids and their Derivatives.—(a) 4-*Chloro*-6-*methoxypyrimidine*-5-*carboxylic acid.* (i) 5-Bromo-4-chloro-6-methoxypyrimidine (2·93 g.) in dry ether (55 ml.) was added during 6 min. to a stirred ethereal solution of n-butyl-lithium (11·05 ml. of a 1·36N-solution diluted to 31 ml.) in an atmosphere of nitrogen at an internal temperature of −36 to −40°. After stirring at −45° for 8 min., the reaction mixture was carbonated by the addition of excess solid carbon dioxide, and allowed to warm to 0°. Water was added, keeping the temperature about 0°, the aqueous layer was separated, and the ether solution was extracted twice with saturated sodium hydrogen carbonate solution. The combined aqueous solutions were acidified (5N-hydrochloric acid) and exhaustively extracted with chloroform. Removal of solvent after drying (Na_2SO_4) gave a slightly gummy acid which solidified [(1·51 g., 53%) m. p. 145° (decomp.)] on trituration with light petroleum (b. p. 40—60°). Crystallisation from chloroform–light petroleum (b. p. 80—100°) afforded the *product* (0·87 g.). (ii) The acid (0·5 g.), thionyl chloride (5 ml.), and dimethylformamide (2 drops), were allowed to stand at room temperature for 1 hr. Removal of excess thionyl chloride *in vacuo* gave the crude acid chloride which, on treatment with aqueous ammonia (*d* 0·88), gave the 5-*carboxyamide* (0·2 g.).

(b) 2-*Methoxy*-4,6-*dimethylpyrimidine*-5-*carboxylic acid.* (i) 5-Bromo-2-methoxy-4,6-dimethylpyrimidine (10·85 g.) in dry ether (100 ml.) was added during 15 min. to a stirred ethereal solution of n-butyl-lithium (41 ml. of a 1·34N-solution diluted to 81 ml.) in an atmosphere of nitrogen at an internal temperature of −35 to −40°. Ether (50 ml.) was now added, and, after stirring at −40° for a further 15 min., the reaction mixture was carbonated and worked up as in (a), to give the crude acid (5·11 g.). Recrystallisation (charcoal) gave the *product* (4·63 g.) as needles. (ii) Thionyl chloride (0·22 ml.) was added rapidly to a stirred solution of the acid (0·5 g.) and triethylamine (0·83 ml.) in methylene chloride (4·5 ml.) at −35 to −40°. After stirring for 30 min. at −25°, ammonia gas was passed in for 5 min., and water and saturated sodium hydrogen carbonate solution were added. After evaporation to dryness *in vacuo*, the residue was extracted with boiling chloroform (2 × 30 ml.) which on evaporation gave the brown solid amide (0·47 g.). Recrystallisation gave the 5-*carboxyamide*.

(*c*) Other *pyrimidine*-5-*carboxylic acids* and *derivatives* listed in Table 2, were prepared similarly. Tetrahydrofuran or ether–toluene mixtures could also be used as solvents for the 5-bromopyrimidines in the halogen–metal exchange reaction if their solubilities in ether were low.

Reaction of n-Butyl-lithium with 4,6-*Dimethoxypyrimidine.*—4,6-Dimethoxypyrimidine[19] (4·0 g.) in ether (45 ml.) was added during 10 min. to an ethereal solution of n-butyl-lithium (23 ml. of a 1·3N-solution diluted to 43 ml.) under nitrogen at −35 to −40°. After stirring for a further 25 min. at −43°, the mixture was carbonated and allowed to warm to room temperature. After extraction with saturated sodium hydrogen carbonate solution and drying (Na_2SO_4), removal of solvent gave an almost colourless oil (5·6 g.) which, on distillation afforded 2-*n-butyl*-2,5-*dihydro*-4,6-*dimethoxypyrimidine* (3·9 g., 69%), b. p. 81°/0·8 mm., n_D^{20} 1·4640 (Found: C,

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[15] S. Gronowitz and R. A. Hoffmann, *Arkiv Kemi*, 1960, **16**, 459.

[16] J. A. Elvidge and R. G. Foster, *J.*, 1963, 590.

[17] F. A. L. Anet, *J. Chem. Phys.*, 1960, **32**, 1274.

[18] E. B. Whipple, J. H. Goldstein, and W. E. Stewart, *J. Amer. Chem. Soc.*, 1959, **81**, 4761.

[19] R. G. Shepherd, W. E. Taft, and H. M. Krazinski, *J. Org. Chem.*, 1961, **26**, 2764.

60·5; H, 9·0; N, 13·7; OMe, 30·4. $C_{10}H_{18}N_2O_2$ requires C, 60·6; H, 9·1; N, 14·1; OMe, 31·3%). Treatment of the sodium hydrogen carbonate extracts as in the previous experiments failed to give any acidic material.

TABLE 2

Pyrimidine-5-carboxylic acids and derivatives

	Subst. at position						
	2	4	5	6	M. p.*	Cryst. from †	Yield (%)
1	—	OMe	CO_2H	OMe	200—201°	MeOH	58
2	—	OMe	$CONH_2$	OMe	242	EtOH	73
3	—	Cl	CO_2H	OMe	145·5	$CHCl_3$–pet	53
4	—	Cl	$CONH_2$	OMe	181	$CHCl_3$–pet	40
5	—	SMe	CO_2H	SMe	225	MeOH	64
6	—	SMe	$CONH_2$	SMe	214—215	EtOH	73
7	Cl	Me	CO_2H	Me	152	$CHCl_3$–pet	65
8	OMe	Me	CO_2H	Me	152·5—153	C_6H_6	51
9	OMe	Me	$CONH_2$	Me	237·5—238 ‡	EtOAc	94
10	NEt_2	Me	CO_2H	Me §	146	pet	60
11	NEt_2	Me	CO·NHPh	Me	173—174	pet	76
12	—	OMe	CO_2H	Ph	189—190	MeOH–H_2O	87
13	—	OMe	$CONH_2$	Ph	230—231	EtOH	84
14	—	Cl	CO_2H	Ph	136	C_6H_6	56

	Found (%)						Required (%)				
	C	H	Hal	N	S	Formula	C	H	Hal	N	S
1	45·6	4·3		15·3		$C_7H_8N_2O_4$	45·7	4·4		15·2	
2	45·9	4·9		22·9		$C_7H_9N_3O_3$	45·9	4·9		23·0	
3	37·8	2·9	18·5	14·6		$C_6H_5ClN_2O_3$	38·2	2·6	18·8	14·9	
4	38·3	3·5	18·35	22·2		$C_6H_6ClN_3O_2$	38·4	3·2	18·9	22·4	
5	38·9	3·9		13·3	29·4	$C_7H_8N_2O_2S_2$	38·9	3·7		13·0	29·6
6	39·0	4·5		20·2	29·5	$C_7H_9N_3OS_2$	39·1	4·2		19·5	29·8
7	45·1	4·1	19·1	15·1		$C_7H_7ClN_2O_2$	45·0	3·75	19·0	15·0	
8	52·6	5·6		15·6		$C_8H_{10}N_2O_3$	52·75	5·5		15·4	
9	52·9	5·9		23·15		$C_8H_{11}N_3O_2$	53·0	6·1		23·2	
10	59·5	7·8		18·8		$C_{11}H_{17}N_3O_2$	59·2	7·6		18·8	
11	68·5	7·4		18·8		$C_{17}H_{22}N_4O$	68·5	7·4		18·8	
12	62·3	4·5		12·5		$C_{12}H_{10}N_2O_3$	62·6	4·35		12·2	
13	62·8	5·1		18·2		$C_{12}H_{11}N_3O_2$	62·9	4·8		18·3	
14	56·4	3·4	15·3	12·0		$C_{11}H_7ClN_2O_2$	56·3	3·0	15·1	11·9	

* All the acids melted with decomposition. † pet = light petroleum. ‡ Melts with charring. § Precipitated from aqueous solution at pH 3—4.

Decomposition of 2-*n-Butyl*-2,5-*dihydro*-4,6-*dimethoxypyrimidine*.—The dihydropyrimidine (1·0 g.) was dissolved in 12% aqueous hydrochloric acid (6 ml.) and stirred with ether (10 ml.) for 6 hr. The ether solution was separated, and the aqueous layer stirred with more ether (10 ml.) for 16 hr. After separation and further extraction of the aqueous solution with ether (2 × 5 ml.), the combined ethereal solutions were dried ($MgSO_4$) and evaporated, to give an almost colourless oil (0·7 g.). This was shown by gas chromatography to contain n-valeraldehyde (30·0%; 70°, 10% polyethylene glycol adipate on 80—100 mesh firebrick), dimethyl malonate (51·4%; 160°, same column), and an unknown component (14%; 85°, 0·5% polyethylene glycol adipate on micro glass beads column). n-Valeraldehyde was also identified by the formation of its 2,4-dinitrophenylhydrazone, m. p. and mixed m. p. 105—106°. The aqueous solution was refluxed for 5 hr. with 40% aqueous sodium hydroxide solution (6 ml.) while nitrogen was passed through the reaction mixture into an excess of 18% aqueous hydrochloric acid in methanol. Evaporation of this solution left an almost colourless residue of ammonium chloride (0·42 g., 78·5%), identified by infrared spectroscopy.

5-*Bromo*-4,6-*dimethoxypyrimidine*.—5-Bromo-4,6-dichloropyrimidine [20] (8·9 g.) in dry methanol (75 ml.) was added rapidly (exothermic reaction) to a stirred solution of sodium methoxide in methanol (5·0 g. of sodium in 75 ml. of methanol). After refluxing, with stirring,

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[20] J. Chesterfield, J. F. W. McOmie, and E. R. Sayer, *J.*, 1955, 3478.

for 30 min. and allowing to cool, the precipitated solid was filtered off and washed exhaustively with ether (500 ml.). The methanol filtrate was treated with carbon dioxide to remove strong alkali and evaporated. Water was added to the residue, the insoluble material extracted into ether (3 × 200 ml.), and the combined ether solutions were dried (Na_2SO_4). Removal of solvent gave the *product* (7·7 g., 89%), m. p. 146—149°. Recrystallisation from ethanol or ethyl acetate afforded plates, m. p. 149—150° (Found: C, 35·3; H, 3·4; Br, 36·7; N, 13·1. $C_6H_7BrN_2O_2$ requires C, 32·9; H, 3·2; Br, 36·5; N, 12·8%). Repeated recrystallisation and sublimation failed to raise the m. p. or improve the carbon analysis.

5-*Bromo*-4-*chloro*-6-*methoxypyrimidine*.—5-Bromo-4,6-dichloropyrimidine (4·56 g.) in dry methanol (50 ml.) was stirred and treated dropwise with a solution of sodium methoxide in methanol (0·46 g. of sodium in 25 ml. of methanol). When addition was complete, the reaction mixture was cooled and the precipitated sodium chloride filtered off. The filtrate was evaporated *in vacuo* and the residue dissolved in ether. More sodium chloride was filtered off and the ether evaporated, to give a colourless solid (4·0 g., 88%), m. p. 72—73°. Recrystallisation from light petroleum (b. p. 60—80°) afforded the *product*, m. p. 77°, as rosettes of needles (Found: C, 27·0; H, 1·9; Br, 37·0; Cl, 16·4; N, 12·8. $C_5H_4BrClN_2O$ requires C, 26·8; H, 1·8; Br, 35·8; Cl, 15·9; N, 12·5%).

5-*Bromo*-4,6-*dimethylthiopyrimidine*.—5-Bromo-4,6-dichloropyrimidine (2·0 g.) and thiourea (1·5 g.) were refluxed in dry ethanol (16 ml.) for 15 min. After cooling, the pale yellow bisisothiouronium salt was filtered off and dried (3·08 g.), m. p. >260°. This material was hydrolysed by refluxing for 1 hr. with 10% aqueous sodium hydroxide solution (25 ml.); acidification with glacial acetic acid precipitated 5-bromo-4,6-dimercaptopyrimidine (1·69 g.), m. p. >290° [lit.,[9] 213° (decomp.)] as a yellow solid. A stirred solution of the dimercaptopyrimidine in 10% aqueous sodium hydroxide solution (25 ml.) was treated at room temperature with dimethyl sulphate (2·0 ml.) during 1 min. After stirring for 30 min. and setting aside overnight, the precipitated solid was extracted into ether and the solution dried (Na_2SO_4). Evaporation of solvent *in vacuo* left a pale yellow crystalline solid (1·44 g.), m. p. 145—148°. Recrystallisation from ethanol afforded colourless needles of 5-bromo-4,6-dimethylthiopyrimidine (1·1 g., 50%), m. p. 155·5° (lit.,[9] 155°) (Found: C, 28·7; H, 3·0; Br, 31·6; N, 11·4; S, 25·5. Calc. for $C_6H_7BrN_2S_2$: C, 28·7; H, 2·8; Br, 31·9; N, 11·2; S, 25·5%).

5-*Bromo*-2-*chloro*-4,6-*dimethylpyrimidine*.—5-Bromo-2-hydroxy-4,6-dimethylpyrimidine[21] (20 g.), phosphorus oxychloride (200 ml.), and diethylaniline (10 ml.) were heated under reflux for 3 hr. Excess phosphorus oxychloride was removed *in vacuo* and the residual oil poured on to crushed ice. The precipitated solid was extracted with ether (350 ml.) and the solution dried (Na_2SO_4). Evaporation of solvent gave the *product* (19·5 g., 89%), m. p. 80—83° which crystallised from methanol (charcoal) as needles, m. p. 80—81·5° (Found: C, 32·8; H, 2·6; Br, 36·9; Cl, 16·4; N, 12·9. $C_6H_6BrClN_2$ requires C, 32·5; H, 2·7; Br, 36·1; Cl, 16·0; N, 12·6%).

5-*Bromo*-4,6-*dimethyl*-2-*methoxypyrimidine*.—5-Bromo-2-chloro-4,6-dimethylpyrimidine (16·0 g.) slurried in methanol (140 ml.) was added rapidly to a warm stirred solution of sodium methoxide in methanol (6·25 g. of sodium in 100 ml. of methanol). After refluxing for 50 min. and setting aside overnight, excess sodium methoxide was decomposed by the passage of carbon dioxide, and methanol was removed *in vacuo*. Inorganic material was dissolved by the addition of water, and the remaining solid was extracted into ether (500 ml.) and the solution dried (Na_2SO_4). Removal of solvent gave the *product* (13·0 g., 81%), m. p. 60—61°, which crystallised from light petroleum (b. p. 40—60°) as prisms, m. p. 61—62° (Found: C, 38·4; H, 4·3; Br, 36·6; N, 13·1. $C_7H_9BrN_2O$ requires, C, 38·7; H, 4·2; Br, 36·9; N, 12·9%).

5-*Bromo*-2-*diethylamino*-4,6-*dimethylpyrimidine*.—5-Bromo-2-chloro-4,6-dimethylpyrimidine (5·0 g.), diethylamine (20 ml.), and ethanol (50 ml.) were refluxed overnight. Ethanol was removed *in vacuo*, water added, and the insoluble oil extracted into ether (150 ml.). Removal of solvent after drying (Na_2SO_4) gave a pale yellow oil (5·12 g.) which on distillation afforded the *product* (4·2 g., 72%), b. p. 109—110°/0·6 mm., n_D^{20} 1·5492 (Found: C, 46·6; H, 6·6; Br, 31·1; N, 16·5. $C_{10}H_{16}BrN_3$ requires C, 46·5; H, 6·2; Br, 31·0; N, 16·3%). In a larger scale experiment, the yield was 82%.

4-*Hydroxy*-6-*phenylpyrimidine*.—4-Hydroxy-2-mercapto-6-phenylpyrimidine[22] (3·5 g.) in dilute aqueous ammonia solution (6·0 ml. of *d* 0·88 ammonia solution in 72 ml. of water) was

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[21] O. Stark, *Annalen*, 1911, **381**, 143.

[22] T. B. Johnson and E. H. Hemingway, *J. Amer. Chem. Soc.*, 1915, **37**, 378.

refluxed, with stirring, for 1 hr. in the presence of Raney nickel (8 g.). The nickel was filtered off, washed with 3 portions of boiling dilute aqueous ammonia solution, and the combined aqueous solutions were evaporated until crystals commenced to form. Refrigeration overnight gave gave 4-hydroxy-6-phenylpyrimidine (2·17 g., 73%), m. p. 269—271° (lit.,[11a] 267°), as plates.

Bromination of 4-Hydroxy-6-phenylpyrimidine.—(a) *With bromine.* Bromine (37·3 g.) in glacial acetic acid (230 ml.) was added during 90 min. to a stirred solution of 4-hydroxy-6-phenylpyrimidine (40 g.) in glacial acetic acid (700 ml.) maintained at 70°. After setting aside overnight, acetic acid was removed *in vacuo* and the residual oil poured into water. The precipitated white solid was filtered off, washed, and dried, to give the *5-bromo-compound* (38·4 g., 66%), m. p. 240—242°. A sample crystallised from ethanol as needles, m. p. 243·5° (Found: C, 47·2; H, 3·1; Br, 31·8; N, 11·4. $C_{10}H_7BrN_2O$ requires, C, 47·8; H, 2·8; Br, 31·9; N, 11·15%).

(b) *With sodium hypobromite.* A solution of sodium hypobromite was prepared from bromine (0·5 ml.) and 10% sodium hydroxide solution (20 ml.) at 0—5°. To this was added 4-hydroxy-6-phenylpyrimidine (0·45 g.) in sodium hydroxide solution (10 ml.). After standing at 0—5° for 2½ hr., excess hypobromite was decomposed with sodium hydrogen sulphite solution and the reaction mixture acidified to give needles of the *5-bromo-compound* (0·32 g., 48%), m. p. 239—241° undepressed on admixture with the product from (a).

5-Bromo-4-chloro-6-phenylpyrimidine.—5-Bromo-4-hydroxy-6-phenylpyrimidine (37 g.) was heated under reflux for 1 hr. with phosphorus oxychloride (400 ml.) and diethylaniline (20 ml.). After working up as described previously, the *product* (39·6 g., 100%), m. p. 83—84°, was obtained. Recrystallisation from light petroleum (b. p. 60—80°) (charcoal) gave plates, m. p. 86° (Found: C, 44·7; H, 2·5; Br, 30·6; Cl, 13·55; N, 10·2. $C_{10}H_6BrClN_2$ requires C, 44·5; H, 2·2; Br, 29·7; Cl, 13·2; N, 10·4%).

5-Bromo-4-methoxy-6-phenylpyrimidine.—A solution of 5-bromo-4-chloro-6-phenylpyrimidine (16·7 g.) in warm methanol (200 ml.) was stirred and treated dropwise with a solution of sodium methoxide in methanol (from 2·76 g. of sodium and 75 ml. of methanol). After refluxing for 1 hr. and setting aside overnight, working up as previously described gave the *product* (15·2 g., 92%), m. p. 88—89°, which crystallised fom methanol as needles, m. p. 87·5—89° (Found: C, 49·7; H, 3·4; Br, 30·0; N, 10·5. $C_{11}H_9BrN_2O$ requires C, 49·8; H, 3·4; Br, 30·2; N, 10·6%).

Condensation of Thiourea with Triethoxycarbonylmethane.—Thiourea (15·2 g.) was dissolved in a solution of sodium ethoxide in dry ethanol (from 9·2 g. of sodium and 380 ml. of ethanol). Triethoxycarbonylmethane [23] (46·2 g.) in ethanol (50 ml.) was added quickly to the stirred solution and the reaction mixture refluxed for 2 hr. and set aside overnight. The precipitated material was filtered off, dissolved in water (250 ml.), and acidified (10N-hydrochloric acid), whereupon a cream solid was precipitated (28 g.). Recrystallisation from glacial acetic acid gave 2-mercaptobarbituric acid (15 g., 52%), m. p. *ca.* 245° (decomp.), identified by analysis and comparison of its infrared spectrum with that of an authentic sample [2] (Found: C, 33·8; H, 2·5; N, 19·4; S, 22·0. Calc. for $C_4H_4N_2O_2S$: C, 33·4; H, 2·8; N, 19·4; S, 22·2%). The same compound was obtained (78%) when, instead of refluxing, the reaction mixture was allowed to stand at room temperature for 60 hr.

Condensation of Thiourea with Ethyl Diacetylacetate.—Thiourea (5·33 g.) and ethyl diacetylacetate [24] (8·6 g.) were condensed together in ethanolic sodium ethoxide solution (from 2·3 g. of sodium and 50 ml. of ethanol) by refluxing for 8 hr. Working up as described above gave 4-hydroxy-2-mercapto-6-methylpyrimidine (5·3 g., 75%), m. p. and mixed m. p. 330° [3] (Found: C, 42·7; H, 4·5; N, 19·8; S, 22·5. Calc. for $C_5H_6N_2OS$: C, 42·25; H, 4·2; N, 19·7; S, 22·5%).

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[23] H. Lund and A. Voigt, *Org. Synth.*, Coll. Vol. II, 594.

[24] A. Spassow, *Org. Synth.*, Coll. Vol. III, 390.