Heterocyclic Studies. Part XXXII.[1] Some 5*H*-Pyrimido[4,5-*b*][1,4]thiazin-6(7*H*)-ones

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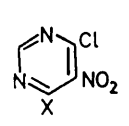
Condensation of 6-(substituted amino)-5-aminopyrimidine-4(3*H*)-thiones with chloroacetic acid (or its ethyl ester), ethyl bromomalonate, or ethyl α-bromopropionate yielded 4-(substituted amino)-5*H*-pyrimido[4,5-*b*][1,4]-thiazin-6(7*H*)-ones with no substituent, an ethoxycarbonyl group, or a methyl group, respectively, in the 7-position. Some of the compounds were converted into 5-methyl, 5-benzyl, or 5-allyl derivatives. ^{1}H N.m.r., u.v., and i.r. spectroscopy showed that the pyrimidothiazines were 5*H*-6(7*H*)-ones rather than other possible tautomers. Ionisation of the compounds is discussed and mass spectra are recorded and discussed.

PYRIMIDO[4,5-*b*][1,4]THIAZINES are interesting because of their structural relationship with the biologically important pteridines. A recent patent [2] disclosed that certain 5-alkylpyrimido[4,5-*b*][1,4]thiazines exhibit pharmacological activity. However relatively few pyrimidothiazines have been made and little is known of their properties. Safanova and Keremov have prepared several 5*H*-pyrimido[4,5-*b*][1,4]thiazin-6(7*H*)-ones by condensation of 5-amino-6-chloropyrimidines with thioglycolic acid,[3] and Safanova and Nemeryuk used 5-aminopyrimidine-4(3*H*)-thiones and α-halogeno-acids to prepare similar compounds.[4] Isolated examples of syntheses of such compounds have been reported by other workers.[5-8]

This paper describes the synthesis of a range of new 5*H*-pyrimido[4,5-*b*][1,4]thiazin-6(7*H*)-ones and their alkylation reactions. Their ionisation, tautomerism, and mass spectrometric fragmentations have also been investigated.

(a) 4-(*Substituted amino*)-5H-*pyrimido*[4,5-b][1,4]-*thiazin*-6(7H)-*ones*.—4,6-Dichloro-5-nitropyrimidine was condensed with primary and secondary amines to yield monochloro-compounds (1), which reacted with sodium hydrogen sulphide to give the 5-aminopyrimidine-4(3*H*)-thiones (2) (Table 1). Heating the thiones with chloroacetic acid in aqueous alkaline solution followed by acidification with 5N-hydrochloric acid gave the 4-(substituted amino)pyrimido[4,5-*b*][1,4]thiazin-6(7*H*)-ones (3) (Table 2). The more basic compounds [*e.g.* (3; X = NMe_2, $R^1 = R^2 = H$)] were obtained as their sparingly soluble hydrochlorides; the less basic ones [*e.g.* (3; X = NPhEt or $N{\cdot}[CH_2]_2{\cdot}O{\cdot}[CH_2]_2$, $R^1 = R^2 = H$)] were isolated as free bases. Some of the pyrimidothiazinones were also made by condensing the appropriate thiones (2) with ethyl chloroacetate.

Some 7-ethoxycarbonyl derivatives (3; $R^1 = H$, $R^2 = CO_2Et$) were made by condensing the thiones (2) with ethyl bromomalonate. This reagent, which had not been used previously in such condensations, gave poor yields, but bromomalonic acid was even worse and gave none of the expected 7-carboxylic acids (3; $R^1 = H$, $R^2 = CO_2H$). The products in this case were 7-unsubstituted (3; $R^1 = R^2 = H$); probably partly because bromomalonic acid underwent decarboxylation under the reaction conditions and partly because the expected products are readily decarboxylated. Some 7-methyl compounds (3; $R^1 = H$, $R^2 = Me$) were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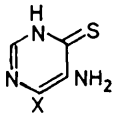
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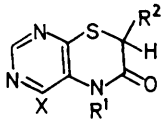
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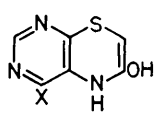
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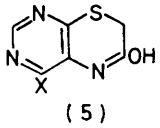

(5)


(6)


(7)

synthesised from the thiones (2) and ethyl α-bromopropionate.

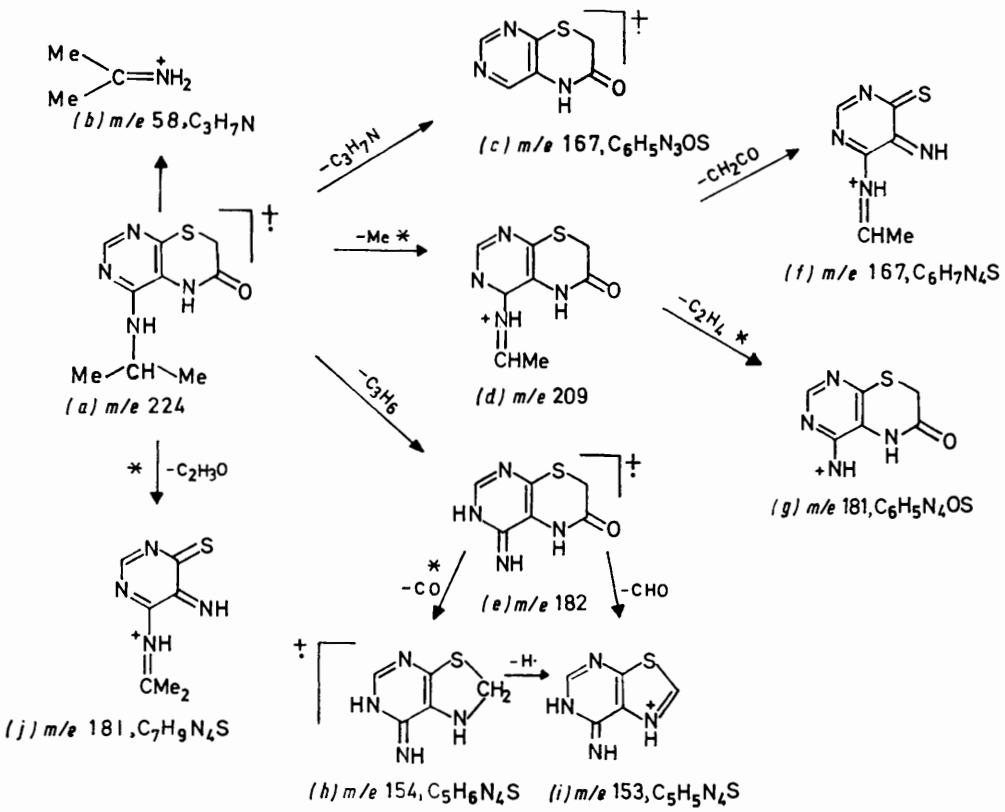
(b) 5-*Alkyl*-4-(*substituted amino*)-5H-*pyrimido*[4,5-b]-[1,4]*thiazin*-6(7H)-*ones*.—Representative examples of the thiazinones (3; $R^1 = H$) reacted readily with methyl iodide, benzyl chloride, or allyl bromide, in the presence of sodium hydroxide, to give 5-methyl, benzyl, or allyl derivatives (3; $R^1 = Me$, CH_2Ph, or $CH_2{\cdot}CH{:}CH_2$), respectively (Table 2). A single product was obtained from each reaction and ^{1}H n.m.r. spectra of the products (Table 3) showed that they were *N*-alkyl rather than *O*- or *C*-alkyl derivatives.

(c) *Tautomerism*.— 5*H*-Pyrimido[4,5-*b*][1,4]thiazin-6(7*H*)-ones have usually been assumed to have the keto-structures (3) rather than the alternative enol forms

[1] Part XXXI, J. Clark, M. Curphey, and I. Southon, *J.C.S. Perkin I*, 1974, 1611.
[2] Abbott Laboratories, B.P. 1,165,260/1969.
[3] T. S. Safonova and A. F. Keremov, U.S.S.R.P. 239,962/1969 (*Chem. Abs.*, 1969, **71**, 49,964).
[4] T. S. Safonova and M. P. Nemeryuk, *Khim. geterotsikl. Soedinenii*, 1966, 714.
[5] F. L. Rose, *J. Chem. Soc.*, 1952, 3448.
[6] M. Ishidate and H. Yuki, *Chem. and Pharm. Bull.* (*Japan*), 1960, **8**, 131.
[7] E. C. Taylor and E. E. Garcia, *J. Org. Chem.*, 1964, **29**, 2121.
[8] J. R. Piper and T. P. Johnston, *J. Org. Chem.*, 1965, **30**, 1247.

(4) and (5). This was proved to be the case in the present examples. ^{1}H N.m.r. spectra of 7-unsubstituted compounds show the 7-proton signal as a two-proton singlet in each case, whereas spectra of the 7-substituted compounds (3; R^1 = Me or CO_2Et) show a signal for CHR^1 (Table 3). This evidence rules out structures (4).

(pK_a 9·66 at 20°) is similar to that of succinimide (9·62 at 25°);[9] the other 5-unsubstituted analogues with tertiary 4-substituents were slightly weaker acids. The loss of acidic properties on 5-alkylation showed that the N(5)H group was the acidic centre. The open-chain analogue (6) (pK_a 2·84) had a basic strength similar to



SCHEME 1

Quoted ion compositions are based on accurate mass measurements which agree within 5 p.p.m. Details of multiplets: *m/e* 181 doublet, $C_7H_9N_4S$ and $C_6H_5N_4OS$, *ca.* 1 : 1; *m/e* 167, doublet $C_6H_7N_4S$ and $C_6H_5N_3OS$, *ca.* 3 : 1

The very close similarity between the u.v. spectra of the neutral molecules of pyrimidothiazinones [*e.g.* (3; X = NH·CH_2Ph or N·$[CH_2]_2$·O·$[CH_2]_2$, $R^1 = R^2$ = H)] and their 5-methyl derivatives (R^1 = Me) strongly suggests that the compounds are in the cyclic amide form, and this is confirmed by strong carbonyl stretching absorptions at about 1680 cm^{-1} in the i.r. spectra of all the compounds. This rules out the structure (5).

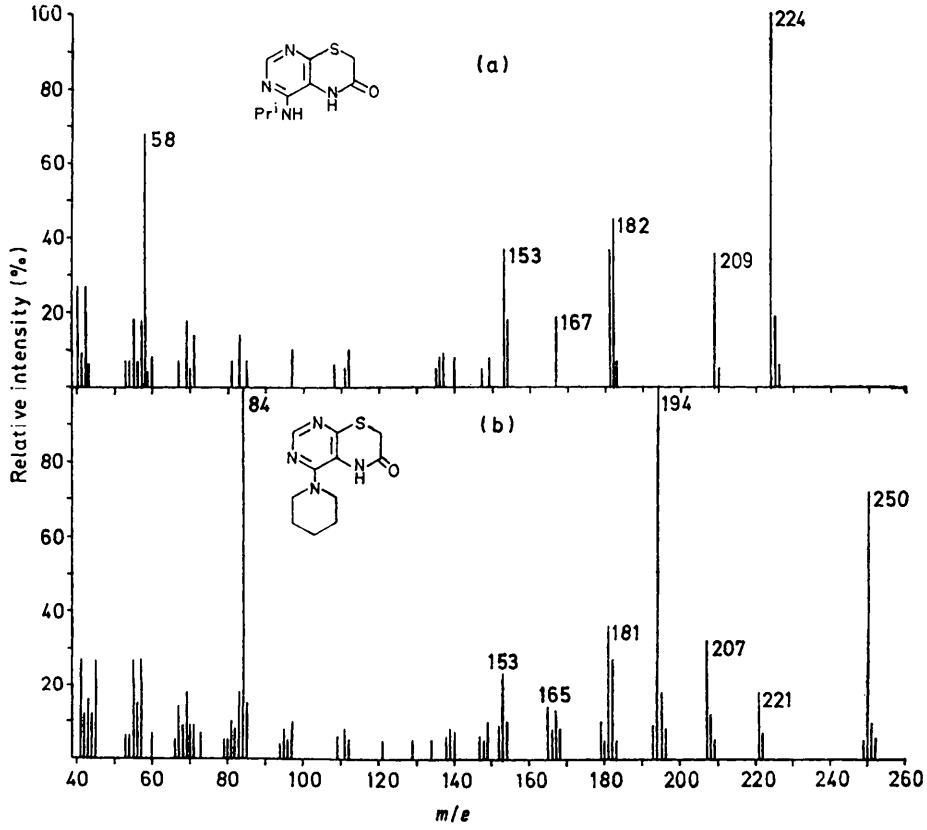
(d) *Ionisation.*—The 5-unsubstituted pyrimidothiazinones (3; R^1 = H) were freely soluble in cold sodium hydroxide and were reprecipitated on neutralisation. The compounds are essentially cyclic analogues of acylated heterocyclic amines and were not expected to be appreciably acidic. Indeed an open-chain analogue (6) was synthesised and shown to be alkali-insoluble. pK_a Values (Table 4) show that the 5-unsubstituted pyrimidothiazinones (3; R^1 = H) are weak acids and weak bases, whereas the 5-alkyl derivatives (3; R^1 = Me) are only weak bases. The acidity of the benzylamino-derivative (3; X = NH·CH_2Ph, $R^1 = R^2$ = H) that of its cyclic counterpart (3; X = NH·CH_2Ph, $R^1 = R^2$ = H) (pK_a 2·65) but it was a very much weaker acid (pK_a 12·89) than the cyclic compound (pK_a 9·66). The higher acidity of the cyclic compounds is probably largely due to more efficient solvation of the cyclic anions (7).

(e) *Mass Spectra.*—No mass spectral data for pyrimido[4,5-*b*][1,4]thiazines have been published previously. The present compounds gave moderately abundant molecular ions and a variety of fragment ions. It was apparent from the low resolution spectra (Figure and Experimental section) that there was no strongly favoured fragmentation pathway applicable to the compounds as a group. High resolution measurements revealed that the situation was very complex: many of the peaks proved to be multiplets. For example the peak at *m/e* 207 in the spectrum of the piperidino-compound (3; X = $[CH_2]_5$N, $R^1 = R^2$ = H) was a

[9] G. B. Barlin and D. D. Perrin, *Quart. Rev.*, 1966, **20**, 100; H. F. Walton and A. A. Schilt, *J. Amer. Chem. Soc.*, 1952, **74**, 4995.

triplet consisting of the ions $(M - C_3H_7)^+$, $(M - C_2H_5N)^+$, and $(M - C_2H_3O)^+$ ions. Schemes 1 and 2 illustrate the breakdown of typical compounds with a 4-alkylamino- and a 4-(cyclic amino)-substituent, respectively. The pathways suggested are based on data from low resolution spectra, metastable peaks, accurate mass measurements, and the effects of introducing a 7-methyl substituent or deuteriating the NH group(s).

4-*Isopropylamino*-5H-*pyrimido*[4,5-b][1,4]*thiazin*-6(7-H)-*one* [Scheme 1; Figure (a)]. The 4-isopropylamino-group is lost either as an ion (*b*) (*m/e* 58, 68%) or less readily as a radical to give the ion (*c*) (*m/e* 167, 19%). A series of peaks results from partial loss of the 4-substituent. [Scheme 2; Figure (b)]. Loss of the 4-substituent as an ion (*l*) (*m/e* 84) is again strongly favoured. (In almost all the compounds examined this type of fragmentation is responsible for the base peak or at least a very intense peak. Thus all piperidino-compounds give a large *m/e* 84 peak, pyrrolidino-compounds an *m/e* 70 peak, and morpholino-compounds an *m/e* 86 peak.) Partial breakdown of the piperidino-group of the molecular ion (*k*) is signified by loss of $C_2H_5^{\bullet}$, C_3H_6, $C_3H_7^{\bullet}$, C_5H_8, and $C_5H_9^{\bullet}$ to give ions which probably have structures (*m*), (*n*), (*o*), (*p*), and (*q*). The losses of $C_2H_5^{\bullet}$ and C_3H_6 are also prominent to the mass spectrum of piperidine itself [11] but the ions (*m'*) and (*n'*), which are analogous to



Mass spectra of (a) 4-isopropylamino-5*H*-pyrimido[4,5-*b*][1,4]thiazin-6(7*H*)-one, and (b) 4-piperidino-5*H*-pyrimido-[4,5-*b*][1,4]thiazin-6(7*H*)-one

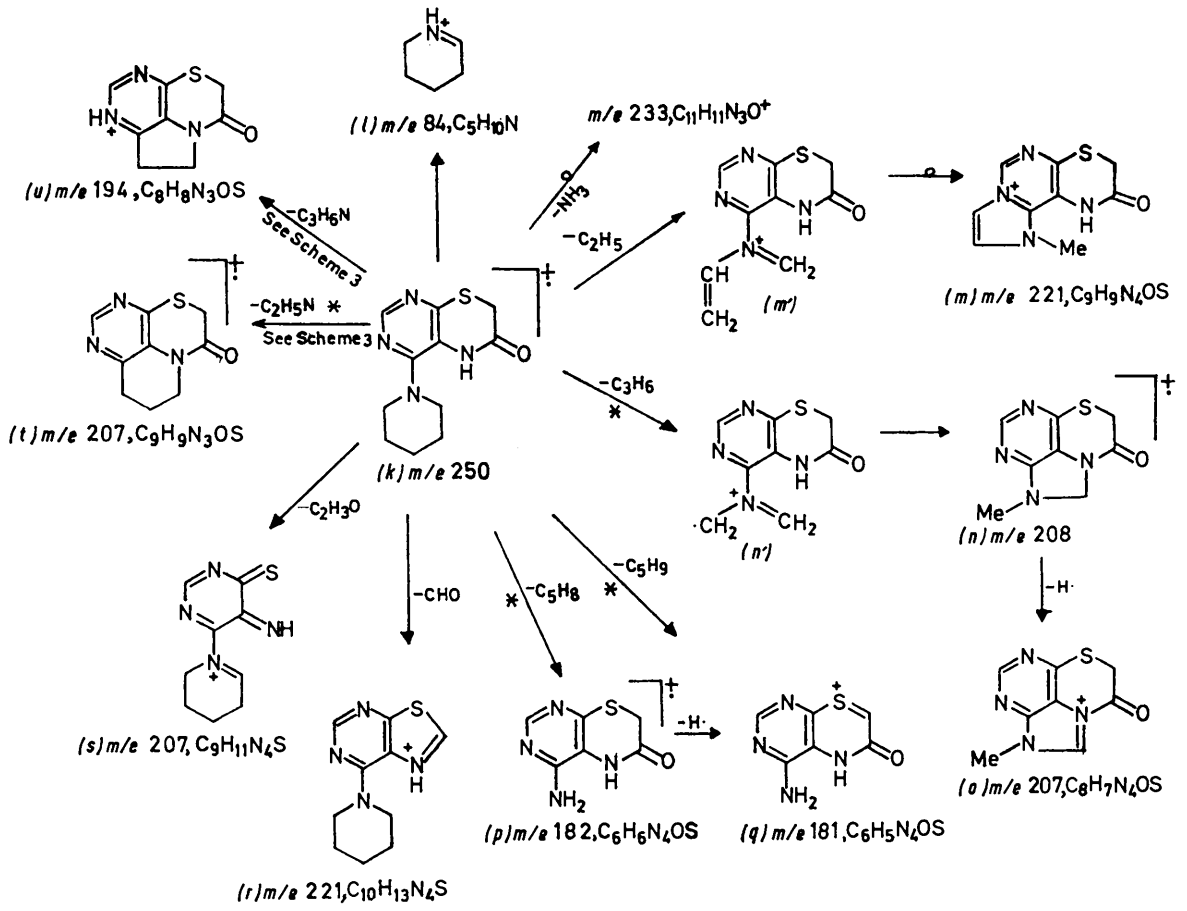
Loss of CH_3, a typical α-cleavage of an amine, gives the ion (*d*) which, in turn, probably fragments to give the ions (*f*) and (*g*). Loss of C_3H_6 from the molecular ion (*a*) to give the ion (*e*) is a McLafferty rearrangement similar to those of, for example, 6-alkylaminopurines.[10] The ion (*e*) then fragments by loss of ·CHO or CO and H· to yield the ions (*h*) and (*i*). A cleavage of the thiazinone ring similar to that which gives the ion (*f*) may also precede degradation of the 4-substituent to give the ion (*j*) (*m/e* 181).

4-*Piperidino*-5H-*pyrimido*[4,5-b][1,4]*thiazin*-6(7H)-*one* those formed from piperidine, can, in the present compound, form more stable cyclic ions, (*m*) and (*n*).

Breakdown of the thiazinone ring of the molecular ion occurs to a small extent. Losses of ·CHO and $\cdot C_2H_3O$ give the ions (*r*) and (*s*) which contribute to peaks at *m/e* 221 and 207. Analogues of all the ions mentioned appear 14 mass units higher in the spectrum of the 7-methyl derivative (3; X = $[CH_2]_5N$, R^1 = H, R^2 = Me), except (*l*) and that part of the *m/e* 207 peak due to (*s*), which are unchanged.

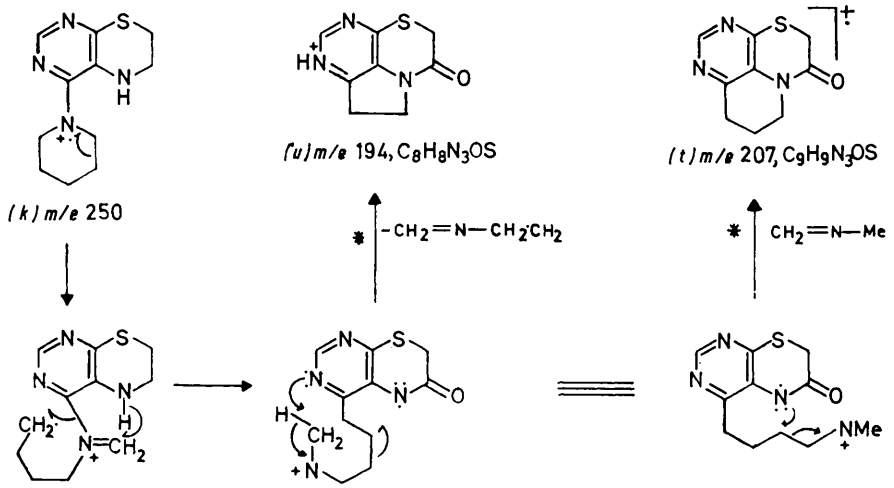
[10] H. Budzikiewicz, C. Djerassi, and D. H. Williams, 'Mass Spectrometry of Organic Compounds,' Holden-Day, San Francisco, 1967, p. 593.

[11] A. M. Duffield, H. Budzikiewicz, and C. Djerassi, *J. Amer. Chem. Soc.*, 1965, **87**, 810; R. A. Saunders and A. E. Williams in 'Advances in Mass Spectrometry,' ed. M. L. Mead, The Institute of Petroleum, London, 1966, vol. 3, p. 681.



SCHEME 2

Quoted ion compositions are based on accurate mass measurements which agree within 5 p.p.m. Details of multiplets: *m/e* 221, doublet, $C_9H_9N_4OS$ and $C_{10}H_{13}N_4S$, *ca.* 1 : 1; *m/e* 207, triplet, $C_8H_7N_3OS$, $C_9H_9N_3OS$, and $C_9H_{11}N_4S$, *ca.* 1 : 2 : 1



SCHEME 3

Losses of C_2H_5N and $C_3H_6N\cdot$ are less easy to rationalise but they are important fragmentations. The $(M - C_3H_6N)^+$ peak (*u*) is the joint base peak (*m/e* 194) in the spectrum of the piperidino-compound, and its analogue (*m/e* 208, 93%) is an important peak in the spectrum of the 7-methyl compound (3; X = $[CH_2]_5N$, R^1 = H, R^2 = Me). The 4-substituent must be involved and suggested mechanisms for the losses and structures of the ions are given in Scheme 3. The peaks at *m/e* 194 in the spectra of the 4-morpholino- and 4-pyrrolidino-

compounds and those at *m/e* 208 in the spectra of the 7-methyl-4-morpholino- and 7-methyl-4-pyrrolidino-compounds can be similarly explained.

The peak at *m/e* 233 is due to loss of NH_3, which must involve a rearrangement. Several other compounds showed losses of NH_3 and one lost OH as well but the mechanisms have not been established.

Representative examples of the compounds in Table 2 were tested as antimicrobial agents but they showed only slight or negligible activity.

EXPERIMENTAL

pK_a Values were measured by a rapid spectrophotometric method.[12] U.v. spectra were measured, in buffered aqueous solution, with a Unicam SP 800 instrument, and i.r. spectra for Nujol mulls with a Perkin-Elmer 257 instrument.

Mass Spectra of 5H-*Pyrimido*[4,5-b][1,4]*thiazin*-6(7H)-*ones*.—These were measured with an A.E.I. MS-902S spectrometer (ionising voltage 70 eV). Samples were introduced by a direct insertion probe into a source maintained at about 200°. Accurate mass measurements were made at a resolving power of 10,000. Spectra given in the Figure are not recorded here. Where an accurate mass measurement was made the relevant ion composition is given. Peaks recorded had *m/e* ⩾40 and relative abundance ⩾8%.

5-Methyl-4-piperidino-, *m/e* 264 (32%), 84 (100), and 43 (13); 5,7-*dimethyl*-4-*pyrrolidino*-, *m/e* 264 (41%), 220 (10), 138 (9), 71 (27), 70 (100), and 41 (8); 4-ethylamino-, *m/e* 211 (14%), 210 (100), 195 (14), 182 (23), 181 (14), 178 (8), 177 (14), 154 (8), 153 (36), 112 (9), 83 (8), 71 (9), 69 (9), 58 (27), 57 (9), 55 (14), 54 (7), 53 (9), 44 (41), 43 (63), and 41 (11); 7-methyl-4-piperidino-, *m/e* 265 (14%), 264 (79), 235 (10), 231 (14), 222 (18), 221 (29), 209 (14), 208 (93), 207 (11), 204 (11), 196 (11), 195 (26), 181 (11), 179 (10), 176 (14), 167 (10), 163 (10), 153 (10), 148 (8), 147 (8), 85 (10), 84 (100), 83 (8), 69 (12), 57 (10), 56 (10), 55 (14), 45 (11), 43 (8), 42 (12), and 41 (29); 4-morpholino-, *m/e* 253 (18%), 252 (100), 251 (9), 224 (23) ($C_8H_8N_4O_2S$), 221 (11), 209 (12), 208 (23), 207 (63) ($C_8H_7N_4OS$), 196 (12), 195 (63) ($C_7H_7N_4OS$), 194 (72) ($C_8H_8N_3OS$), 193 (23), 182 (14), 181 (14), 180 (14), 179 (18), 168 (8), 167 (23), 166 (18), 165 (32), 153 (11), 152 (23), 139 (11), 125 (12), 111 (8), 97 (8), 86 (45) (C_4H_8NO), 83 (8), 71 (12), 69 (12), 68 (9), 67 (8), 66 (8), 57 (15), 56 (12), 55 (16), 53 (8), 45 (13), 43 (15), 42 (13), and 41 (18); 4-pyrrolidino-, *m/e* 237 (15%), 236 (100), 219 (12) (doublet, $C_{10}H_{11}N_4S$ and $C_{10}H_9N_3OS$, *ca.* 1 : 1), 208 (27) ($C_8H_8N_4OS$), 207 (12) (doublet, $C_8H_7N_4OS$ and $C_9H_{11}N_4S$, *ca.* 1 : 1), 195 (10), 194 (63) ($C_8H_8N_3O$), 193 (45) ($C_7H_5N_4OS$), 181 (41) ($C_7H_7N_3OS$), 180 (13), 179 (11), 167 (11), 166 (23), 165 (36) ($C_6H_5N_4S$), 148 (12), 147 (8), 81 (8), 80 (9), 71 (10), 70 (100), 69 (9), 68 (8), 57 (9), 56 (9), 55 (18), 54 (8), 53 (8), 45 (8), 44 (100), 43 (18), 42 (9), and 41 (23); 7-methyl-4-pyrrolidino-, *m/e* 251 (16%), 250 (100), 233 (11), 222 (20), 221 (11), 217 (12), 209 (11), 208 (63), 207 (45), 195 (36), 194 (21), 193 (11), 190 (10), 189 (10), 181 (9), 179 (27), 166 (18), 165 (11), 162 (30), 161 (15), 149 (15), 147 (10), 134 (9), 129 (9), 111 (8), 109 (9), 97 (16), 95 (12), 85 (12), 84 (13), 83 (20), 82 (13), 81 (15), 73 (14), 71 (24), 70 (81), 69 (26), 68 (10), 67 (12), 60 (12), 57 (27), 56 (15), 55 (36), 54 (9), 45 (36), 44 (23), 43 (29), 42 (10), and 41 (35); 4-*ethylamino*-7-*methyl*-, *m/e* 225 (14%), 224 (100), 209 (13), 196 (18), 195 (15), 191 (12), 182 (11) ($C_6H_6N_4OS$), 181 (23) ($C_7H_9N_4S$), 168 (10) (triplet, $C_7H_{10}N_3S$, $C_6H_6N_3OS$, and $C_6H_8N_4S$), 167 (16), 164 (11), 163 (11), 153 (36), 136 (9), 121 (9), 112 (9), 73 (8), 71 (8), 69 (9), 60 (10), 57 (13), 55 (12), 45 (14), 44 (32), 43 (11), and 41 (11); 5-methyl-4-morpholino-, *m/e* 267 (18%), 266 (100), 265 (8), 238 (9), 235 (9), 223 (36), 222 (25), 221 (54), 210 (10), 209 (63), 208 (39), 207 (13), 195 (11), 193 (14), 182 (8), 181 (24) ($C_7H_9N_4S$), 180 (10), 179 (39), 167 (14) ($C_6H_7N_4S$), 166 (13), 165 (18), 153 (11) ($C_5H_5N_4S$), 152 (22), 139 (26), 138 (48), 125 (10), 112 (9), 111 (10), 87 (11), 86 (23), 84 (20), 71 (12), 70 (26), 69 (9), 67 (22), 56 (14), 55 (10), 54 (8), 42 (15), and 41 (12).

TABLE 1

6-(Substituted amino)-5-aminopyrimidine-4(3*H*)-thiones (2)

Structure (2)	Method of preparation *	Method of purification †	M.p. (°C)	Yield (%)	Formula	Found (%) C	H	N	Required (%) C	H	N
R = NMe_2	(*a*)	A	181—182	71	$C_6H_{10}N_4S$	42·9	5·8	33·0	42·4	5·9	32·9
R = $[CH_2]_5N$	(*b*)	B	214—215	73	$C_9H_{14}N_4S$	51·3	6·6	26·8	51·5	6·7	26·7
R = $[CH_2]_4N$	(*a*)	B	269—270	60	$C_8H_{12}N_4S$	48·7	6·1	28·9	49·0	6·1	28·6
R = NPhMe	(*a*)	B	*ca.* 207 (decomp.)	52	$C_{11}H_{12}N_4S$	56·7	4·7	24·6	56·9	5·2	24·2
R = NPhEt	(*a*)	B	178—179	49	$C_{12}H_{14}N_4S$	57·5	5·6	22·2	58·5	5·7	22·7
R = $N{\cdot}[CH_2]_2{\cdot}O{\cdot}[CH_2]_2$	(*a*)	B	238—239	69	$C_8H_{12}N_4OS$	45·5	5·8	26·6	45·2	5·7	26·4
R = NHEt	(*a*)	C	213—214	80	$C_6H_{10}N_4S$	42·7	5·8	33·4	42·4	5·9	32·9
R = NHPr^i	(*b*)	B	*ca.* 205 (decomp.)	36	$C_7H_{12}N_4S$	45·4	6·3	30·7	45·6	6·5	30·4
R = $NH{\cdot}CH_2Ph$	(*a*)	B	194—195	67	$C_{11}H_{12}N_4S$	56·6	5·0	24·1	56·9	5·2	24·2
R = $[CH_2]_5CH{\cdot}NH$	(*b*)	A	203—205	63	$C_{10}H_{16}N_4S$	52·8	6·9	24·8	53·5	7·2	25·0

* See Experimental section. † A = reprecipitated from alkali; B = recrystallised from aqueous dimethylformamide; C = recrystallised from ethanol.

6-(*Substituted amino*)-5-*aminopyrimidine*-4(3H)-*thiones* (2; X = subst. amino).—(*a*) The appropriate aminopyrimidine (1; X = subst. amino) (1 equiv.) and aqueous N-sodium hydrogen sulphide (5 equiv.) were stirred under reflux for 3 h. The cooled solution was acidified with glacial acetic acid and the resulting *solid* was purified by reprecipitation with acetic acid from solution in dilute aqueous sodium hydroxide (see Table 1).

(*b*) The appropriate aminopyrimidine (1; X = subst. amino) was stirred with aqueous N-sodium hydrogen sulphide at about 10° below its m.p. for 18 h and then purified as in (*a*) (see Table 1).

4-(*Substituted amino*)-5H-*pyrimido*[4,5-b][1,4]*thiazin*-6(7H)-*ones*.—(*a*) The appropriate thione (2) (1 equiv.), chloroacetic acid (1·1 equiv.), and 0·5N-sodium hydroxide

[12] J. Clark and A. E. Cunliffe, *Chem. and Ind.*, 1973, 281.

(2·2 equiv.) were heated at 90—95° for 1 h. The mixture was then acidified with 5N-hydrochloric acid. Products which contained a secondary amino-group separated as colourless *hydrochlorides* (Table 2). Products with a tertiary amino-group were isolated by evaporation under reduced pressure, extraction of the residue with hot ethanol, filtration and concentration of the resulting solution, to yield the *pyrimidothiazinone* hydrochloride (Table 2).

4-(Substituted amino)-5*H*-pyrimido[4,5-*b*][1,4]thiazin-6(7*H*)-ones were obtained as free bases in the following reactions.

(*b*) The appropriate hydrochloride prepared in (*a*) (1 equiv.) and 0·5N-sodium hydroxide solution (3·5 equiv.) were stirred for 15 min, and the solution was acidified with glacial acetic acid. The *free base* was crystallised from a suitable solvent (Table 2).

(*c*) The appropriate thione (2) (1 equiv.), chloroacetic acid (1·1 equiv.), and 0·5N-sodium hydroxide (2·2 equiv.) were heated together at 90—95° for 1 h. The cooled solution was acidified with 5N-hydrochloric acid and evaporated to dryness under reduced pressure. The residue was extracted with boiling ethanol and, after filtration, the *pyrimidothiazinone* crystallised from the cooled solution (Table 2).

TABLE 2

4-(Substituted amino)-5*H*-pyrimido[4,5-*b*][1,4]thiazin-6(7*H*)-ones (3)

Structure (3)			Method of prepn. (see exptl.)	Yield (%)	Cryst. solvent	M.p. (°C)	Formula	Found (%)			Required (%)		
R^1	R^2	X						C	H	N	C	H	N
H	H	NMe_2,HCl	(*a*)	54		238	$C_8H_{10}N_4OS$,HCl	38·9	4·5	22·6	38·9	4·5	22·7
H	H	$[CH_2]_4N$,HCl	(*a*)	29		233 (decomp.)	$C_{10}H_{12}N_4OS$,HCl	44·2	4·8	20·2	44·0	4·8	20·5
H	H	$[CH_2]_4N$	(*a*) + (*b*)	79 *	MeOH	215—216	$C_{10}H_{12}N_4OS$	50·4	5·1	24·0	50·85	5·1	23·7
H	H	NHEt,HCl	(*a*)	54		252	$C_8H_{10}N_4OS$,HCl	39·3	4·2	22·4	38·9	4·5	22·7
H	H	NHEt	(*a*) + (*b*)	82 *	†	268 (decomp.)	$C_8H_{10}N_4OS$	45·6	4·8	27·3	45·7	4·6	26·7
H	H	$NHPr^i$,HCl	(*a*)	38		249 (decomp.)	$C_9H_{12}N_4OS$,HCl	41·5	5·0	21·8	41·5	5·0	21·5
H	H	$NHPr^i$	(*d*)	18	†	260	$C_9H_{12}N_4OS$	48·0	5·1	24·6	48·3	5·35	25·0
H	H	$NH{\cdot}CH_2Ph$,HCl	(*a*)	42		*ca.* 240 (decomp.)	$C_{13}H_{12}N_4OS$,HCl	50·4	4·3	18·4	50·5	4·2	18·3
H	H	$NH{\cdot}CH_2Ph$	(*d*)	48	EtOH	240 (decomp.)	$C_{13}H_{12}N_4OS$	57·3	4·4	20·1	57·35	4·4	20·6
H	H	$NH{\cdot}CH[CH_2]_5$,HCl	(*a*)	37		288 (decomp.)	$C_{12}H_{16}N_4OS$,HCl	47·9	5·8	18·9	47·9	5·7	18·6
H	H	$NH{\cdot}CH[CH_2]_5$	(*a*) + (*b*)	68 *	MeOH	286 (decomp.)	$C_{12}H_{16}N_4OS$	54·1	5·9	21·0	54·5	6·1	21·2
H	H	$[CH_2]_5N$	(*d*)	46	Pr^nOH	174—175	$C_{11}H_{14}N_4OS$	52·7	5·8	22·6	52·8	5·6	22·4
H	H	$N{\cdot}[CH_2]_2{\cdot}O{\cdot}[CH_2]_2$	(*c*)	30	EtOH	275—276	$C_{10}H_{12}N_4O_2S$	47·6	4·6	22·4	47·6	4·7	22·2
H	H	NEtPh	(*c*)	20	EtOH	157—158	$C_{14}H_{14}N_4OS$	58·4	5·1	19·7	58·75	4·9	19·6
H	CO_2Et	$N{\cdot}[CH_2]_2{\cdot}O{\cdot}[CH_2]_2$	(*e*)	5	C_6H_6–LP ‡	213 (decomp.)	$C_{13}H_{16}N_4O_4S$	48·4	5·1	16·9	48·2	4·9	17·3
H	CO_2Et	$[CH_2]_5N$	(*f*)	30	H_2O–DMF §	197—199	$C_{14}H_{18}N_4O_3S$	51·9	5·7	17·3	52·2	5·6	17·4
H	CO_2Et	$[CH_2]_4N$	(*f*)	30	H_2O–DMF §	223 decomp.	$C_{13}H_{16}N_4O_3S$	49·4	5·2	17·8	50·6	5·2	18·2
H	CO_2Et	$NH{\cdot}CH_2Ph$	(*e*)	12	C_6H_6–LP	155—157	$C_{16}H_{16}N_4O_3S$	55·1	4·6	15·9	55·8	4·65	16·3
H	Me	$[CH_2]_5N$	(*d*)	10	Pr^nOH	159—160	$C_{12}H_{16}N_4OS$	55·1	5·9	20·8	54·5	6·1	21·2
H	Me	$[CH_2]_4N$	(*d*)	52	¶	217—218	$C_{11}H_{14}N_4OS$	53·2	5·8	22·1	52·8	5·6	22·4
H	Me	NHEt	(*d*)	31	Pr^nOH	249—250	$C_9H_{12}N_4OS$	48·2	5·6	25·5	48·2	5·4	25·0
Me	H	$N{\cdot}[CH_2]_2{\cdot}O{\cdot}[CH_2]_2$	(*g*)	43	H_2O	179—180	$C_{11}H_{14}N_4O_2S$,0·5 H_2O	47·8	5·4	20·5	48·0	5·45	20·4
$CH_2{:}CH{\cdot}CH_2$	H	$N{\cdot}[CH_2]_2{\cdot}O{\cdot}[CH_2]_2$	(*g*)	75	H_2O	139	$C_{13}H_{16}N_4O_2S$	53·5	5·6	19·3	53·4	5·5	19·2
CH_2Ph	H	$N{\cdot}[CH_2]_2{\cdot}O{\cdot}[CH_2]_2$	(*g*)	57	EtOH	194—195	$C_{17}H_{18}N_4O_2S$	60·1	5·3	16·5	59·6	5·3	16·4
Me	H	$[CH_2]_5N$	(*g*)	61	EtOH–H_2O	145—146	$C_{12}H_{16}N_4OS$	54·7	6·3	21·2	54·5	6·1	21·2
$CH_2{:}CH{\cdot}CH_2$	H	$[CH_2]_5N$	(*g*)	59	EtOH	162—163	$C_{14}H_{18}N_4OS$	57·9	6·3	19·2	57·9	6·2	19·3
CH_2Ph	H	$[CH_2]_5N$	(*g*)	42	EtOH	169—170	$C_{18}H_{20}N_4OS$	62·9	6·0	16·4	63·5	5·9	16·5
$CH_2{:}CH{\cdot}CH_2$	H	$[CH_2]_4N$	(*g*)	76	EtOH–H_2O	165—166	$C_{13}H_{16}N_4OS$	56·3	5·7	20·2	56·5	5·8	20·3
CH_2Ph	H	$[CH_2]_4N$	(*g*)	92	MeOH–H_2O	168—169	$C_{17}H_{18}N_4OS$	62·6	5·6	17·3	62·6	5·5	17·2
Me	Me	$[CH_2]_4N$	(*g*)	39	Pr^iOH–H_2O	119—120	$C_{12}H_{16}N_4OS$	54·1	6·3	21·2	54·5	6·1	21·2
$CH_2{:}CH{\cdot}CH_2$	Me	$[CH_2]_4N$	(*g*)	65	Pr^iOH	146—147	$C_{14}H_{18}N_4OS$	57·4	6·4	20·0	57·9	6·2	19·3
CH_2Ph	Me	$[CH_2]_4N$	(*g*)	29	EtOH	174—175	$C_{18}H_{20}N_4OS$	63·8	6·0	16·6	63·5	5·9	16·5

* Yield in 2nd step. † Crystallised from reaction mixture in a pure state. ‡ Benzene–light petroleum (b.p. 60—80°). § Aqueous dimethylformamide. ¶ Reprecipitated from alkaline solution.

TABLE 3

^{1}H N.m.r. data [a]

Compound (3)	τ Values (J inH z) 2-H [b]	7-Substituent	4-Substituent	5-Substituent
$R^1 = R^2 = H$, X = NMe_2,HCl	1·79	6·35 (2H, s)	6·88 (6H, s)	−0·26 (1H) [c]
$R^1 = R^2 = H$, X = NHEt,HCl	1·48	6·23 (2H, s)	8·77 (3H, t *J* 7), 6·40 (2H, q, *J* 7), 2·15 (1H)	−0·72 (1H) [c]
$R^1 = R^2 = H$, X = NH·CH_2Ph,HCl	1·53	6·23 (2H, s)	5·22 (2H, d, *J* 4), 2·50—2·60 (5H, m)	−0·60 (1H) [c]
$R^1 = R^2 = H$, X = $[CH_2]_4$N,HCl	1·59	*d*	6·11—6·43 (6H, m), [e] 7·91—8·24 (4H, m)	
$R^1 = R^2 = H$, X = O·$[CH_2]_2$·N·$[CH_2]_2$	1·88	*d*	6·20—6·75 (10H, m)	
R^1 = H, R^2 = Me, X = $[CH_2]_4$N	1·91	6·22 (1H, q, *J* 7), 8·63 (3H, d, *J* 7)	8·01—8·28 (4H, m), 6·30—6·56 (4H, m)	0·12 (1H) [c]
R^1 = H, R^2 = Me, X = NHEt [f]	1·97	6·45 (1H, q, *J* 7), 8·76 (3H, d, *J* 7)	8·76 (3H, t, *J* 7), 6·57 (2H, q, *J* 7), [g] 3·5 (1H) [c]	0·32 (1H) [c]
R^1 = Me, R^2 = H, X = $[CH_2]_5$N	1·78	6·35 (2H, s)	8·45br (6H, s), 6·62br (4H, s)	7·0 (3H, s)
R^1 = H, R^2 = CO_2Et, X = $[CH_2]_5$N [h]	1·63	6·33 (1H, s), 8·77 (3H, t, *J* 7) 5·78 (2H, q, *J* 7)	8·28br (6H, s), 6·6br (4H, s)	1·95 (1H) [c]
R^1 = CH_2Ph, R^2 = H, X = O·$[CH_2]_2$·N·$[CH_2]_2$	1·75	*d*	5·94—6·61 (12H, m)	2·54—2·98 (5H, m)
R^1 = CH_2·CH·CH_2, R^2 = Me, X = $[CH_2]_4$N	1·88	8·43 (3H, d, *J* 7·5) [j]	7·80—8·28 (4H, m), 6·10—6·95 (5H, m) [k]	4·13—5·43 (5H, m)
$R^1 = R^2$ = Me, X = $[CH_2]_4$N	1·87	8·42 (3H, d, *J* 7) [j]	7·83—8·23 (4H, m), 6·47—6·70 (5H, m) [k]	6·89 (3H, s)

[a] Measured on a Varian A60A spectrometer at normal probe temperature with $(CD_3)_2SO$ as solvent and tetramethylsilane as internal standard. [b] Singlet (1H). [c] Signal removed on deuteriation. [d] Obscured by signal due to 4-substituent. [e] Includes signal due to 7-H_2. [f] Measured on Varian EM-360 spectrometer in $CDCl_3$ with a little $(CD_3)_2SO$ if necessary. [g] Quartet only after deuteriation. [h] In $CDCl_3$. [i] Includes signals due to 7-H_2 and benzylic CH_2. [j] Signal for 7-H obscured by that due to 4-substituent. [k] Includes 7-H.

TABLE 4

U.v. spectra and ionisation constants

Compound (3)	Ionisation [a] (H_2O; 20°) pK_a and spread	Spectroscopy [b] pH	Species [c]	$\lambda_{max.}$/nm				log $\varepsilon_{max.}$			
$R^1 = R^2 = H$, X = $[CH_2]_5$N	2·67 ± 0·01	−0·4 [d]	C	232	266	307		4·04	3·93	4·08	
	10·63 ± 0·03	5·0	NM	*245*	265	293	*315*	*3·91*	4·17	4·00	*3·76*
		13·0	A	238	305	*333*		4·14	4·10	*3·80*	
R^1 = Me, R^2 = H, X = $[CH_2]_5$N	2·51 ± 0·05	−0·3 [d]	C	238	264	305		4·10	3·97	4·11	
		5·0	NM	241	265	288	*315*	4·07	4·25	4·02	*3·70*
R^1 = H, R^2 = Me, X = $[CH_2]_5$N	2·77 ± 0·05	−0·3 [d]	C	232	265	308		4·06	3·96	4·12	
	10·76 ± 0·02	4·9	NM	*245*	263	293	*315*	*4·01*	4·20	4·03	*3·81*
		13·0	A	239	304	*335*		4·18	4·15	*3·83*	
R^1 = H, R^2 = CO_2Et, X = $[CH_2]_5$N	2·04 ± 0·03	−0·3 [d]	C	233	263	304		4·08	3·94	4·14	
	9·30 ± 0·04	5·0	NM	238	265	292	*320*	4·06	4·15	4·08	*3·72*
		11·4	A	238	304	*337*		4·19	4·13	*3·74*	
$R^1 = R^2 = H$, X = NH·CH_2Ph	2·65 ± 0·02	0·4	C	224	264	291		3·93	3·78	3·90	
	9·66 ± 0·03	7·62	NM	225	258	*279*	310	4·22	4·39	*3·83*	3·72
		12·0	A	225	259	293	*312*	4·24	4·12	4·05	*3·83*
(6)	2·84 ± 0·03	0·4	C	244	295			4·21	4·25		
	12·89 ± 0·04	5·1	NM	243	284			4·47	3·83		
$R^1 = R^2 = H$, X = N·$[CH_2]_2$·O·$[CH_2]_2$	2·07 ± 0·04	−0·1 [d]	C	231	263	318		4·04	4·00	4·11	
	10·37 ± 0·04	8·2	NM	*238*	262	292		*4·05*	4·23	3·99	
		13·0	A	237	*250*	304		4·17	*4·14*	4·11	
R^1 = Me, R^2 = H, X = N·$[CH_2]_2$·O·$[CH_2]_2$	Not determined	8·2	NM	*245*	262	288		*4·13*	4·29	3·96	

[a] Measured spectrophotometrically.[12] [b] In aqueous solution; inflections and shoulders in italics. [c] C = cation, NM = neutral molecule, A = anion. [d] H_0 Value (M. A. Paul and F. A. Long, *Chem. Rev.*, 1957, **57**, 12).

(*d*) The appropriate thione (2) was similarly condensed with ethyl chloroacetate (or ethyl α-bromopropionate for 7-methyl derivatives) except that the reaction mixture was not acidified (Table 2). In most cases the solution was simply cooled and filtered to yield the pyrimidothiazinone.

(*e*) An alkaline solution of the appropriate thione (2) (1 equiv.) was shaken with diethyl bromomalonate (1·1 equiv.) for 30 min and the mixture was then heated on a water-bath for 15 min. The brown oil was separated and extracted with hot benzene. The hot extract was filtered (charcoal), dried ($MgSO_4$), and concentrated to small bulk. Light petroleum (b.p. 60—80°) was added and the *product* was allowed to crystallise over several days.

(*f*) The appropriate thione (2) (1 equiv.) was dissolved in N-sodium hydroxide and heated on a water-bath with diethyl bromomalonate (1·1 equiv.) for 2 h. After cooling,

the aqueous layer was decanted off and the black semi-solid residue was washed several times with benzene to leave the pale yellow crystalline *product* (Table 2).

(*g*) *Alkylation of* 4-(*substituted amino*)-5H-*pyrimido*[4,5-b]-[1,4]*thiazin*-7(5H)-*ones*. The appropriate pyrimidothiazine (3; R^1 = H) (1 equiv.), the appropriate halide (methyl iodide, allyl bromide, or benzyl chloride) (1·1 equiv.), and N-sodium hydroxide (1·1 equiv.) were shaken together for 3 h. The solid which separated was filtered off and crystallised from a suitable solvent (Table 2).

5-*Amino*-4-*benzylamino*-6-*methylthiopyrimidine*.—A mixture of 5-amino-6-benzylaminopyrimidine-4(3*H*)-thione (1·16 g), 0·5N-sodium hydroxide (12 ml), and methyl iodide (0·37 ml) was vigorously shaken for 1 h. The *methylthio-derivative* (1·0 g) was filtered off and crystallised from aqueous dimethylformamide; m.p. 138° (Found: C, 58·3; H, 5·7; N, 22·9. $C_{12}H_{14}N_4S$ requires C, 58·5; H, 5·7; N, 22·8%).

5-*Acetamido*-4-*benzylamino*-6-*methylthiopyrimidine*.— A solution of the foregoing methylthio-compound (0·9 g) in pyridine (10 ml) and acetic anhydride (10 ml) was stirred at 20° for 18 h. The solvents were removed under reduced pressure and residue was treated with water (5 ml) and taken to dryness three times. The solid was triturated with benzene, filtered off, and crystallised from propan-2-ol to yield the *acetamido-derivative* (0·5 g), m.p. 178—179° (Found: C, 58·1; H, 5·8; N, 19·0. $C_{14}H_{16}N_4OS$ requires C, 58·3; H, 5·6; N, 19·45%).

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