Heterocyclic Studies. Part XXXIV.[1] Some 5*H*-Pyrimido[4,5-*b*][1,4]thiazine-6(7*H*)-ones, -4,6(3*H*,7*H*)-diones and -2,4,6(1*H*,3*H*,7*H*)-triones

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Condensation of several 6-substituted 5-aminopyrimidine-4(3*H*)-thiones (1; X= Cl, OEt, SH, or OMe) with chloroacetic acid and of the methoxy-compound with various α-bromo-esters gave corresponding 4-substituted 5*H*-pyrimido[4,5-*b*][1,4]thiazin-6(7*H*)-ones. The 4,6(3*H*,7*H*)-diones were made by acidic hydrolysis of the corresponding 4-methoxy-6(7*H*)-ones. Alkylation before or both before and after hydrolysis furnished 5- or 3,5-dialkyl derivatives of the diones. 3-Methyl- and 1,3-dimethyl-5*H*-pyrimido[4,5-*b*][1,4]thiazine-2,4,6(1*H*,3*H*,7*H*)-trione were made from the appropriate pyrimidinethiones and chloroacetic acid.

In Part XXXII [2] we described the synthesis of some 4-(substituted amino)-5*H*-pyrimido[4,5-*b*][1,4]thiazin-6(7*H*)-ones as potential pharmaceutical agents. The work has now been extended to include several more thiazinones together with some diones and triones and certain alkyl derivatives of these compounds.

[1] Part XXXIII, J. Clark and M. S. Morton, preceding paper.
[2] J. Clark and I. W. Southon, *J.C.S. Perkin I*, 1974, 1805.

(a) 4-*Substituted* 5H-*Pyrimido*[4,5-b][1,4]*thiazin*-6(7H)-*ones*.—Treatment of 4-chloro-6-ethoxy-5-nitropyrimidine with sodium hydrogen sulphide gave the amino-ethoxy-thione (1; X = OEt). This and its known chloro-, methoxy-, and mercapto-analogues (1; X = Cl, OMe, or SH) were condensed with chloroacetic acid to yield pyrimidothiazinones (2; R^1 = R^2 = R^3 = H, X = OEt, Cl, OMe, or SH) (Table 1). The last compound was produced by treatment of the thione (1; X = SH) with only 1 mol. equiv. of chloroacetic acid; treatment with an excess of chloroacetic acid is known to give the carboxymethylthiopyrimidothiazinone [3] (2; R^1 = R^2 = R^3 = H, X = $S{\cdot}CH_2{\cdot}CO_2H$).

The methoxy-thione (1; X = OMe) was also condensed with bromosuccinic acid, ethyl α-bromopropionate, and ethyl α-bromoisobutyrate to produce the 7-carboxymethyl- (2; X = OMe, R^1 = R^3 = H, R^2 = $CH_2{\cdot}CO_2H$), 7-methyl (2; X = OMe, R^1 = R^3 = H, R^2 = Me), and 7,7-dimethyl- (2; X = OMe, R^1 = R^2 = Me, R^3 = H) pyrimidothiazinones (Table 1), identified by ^{1}H n.m.r. spectroscopy (Table 2) as 5*H*-6(7*H*)-ones (2). The fact that the u.v. spectra of the 7,7-dimethyl and 7-unsubstituted compounds are almost identical, for both neutral molecules and anions, confirmed that the compounds exist in the 7*H*-tautomeric form in aqueous solution whether ionised or not (for u.v. spectra see Experimental section).

(b) 5H-*Pyrimido*[4,5-b][1,4]*thiazine*-4,6(3H,7H)-*diones*.—The foregoing 4-methoxy-5*H*-pyrimidothiazin-6(7*H*)-ones, two of which had been prepared previously,[4a] were converted into the corresponding 5*H*-pyrimidothiazine-4,6(3*H*,7*H*)-diones (3; R^3 = R^4 = H) by acidic hydrolysis. This route was preferred to one in which the first step was hydrolysis of 5-amino-4,6-dichloropyrimidine to 5-amino-6-chloropyrimidin-4(3*H*)-one (4). Treatment of the latter with thioglycolic acid and related compounds was expected to give pyrimidothiazine-4,6-diones [4b] but the yield in the first step was too low to make the route practicable.

A range of 5-alkyl-5*H*-pyrimidothiazine-4,6(3*H*,7*H*)-diones (3; R^3 = alkyl, R^4 = H) was obtained by alkylating the 4-methoxy-6(7*H*)-ones (2; X = OMe) with methyl iodide, benzyl chloride, or allyl bromide before

TABLE 1

5*H*-Pyrimido[4,5-*b*][1,4]thiazin-6(7*H*)-ones

Compound (2) X	R^1	R^2	R^3	Method of prepn.*	Yield (%)	Cryst. solvent	M.p. (°C)	Formula	Found (%) C	H	N	Required (%) C	H	N
OEt	H	H	H	(*a*)	36		198—200	$C_8H_9N_3O_2S$	44·8	4·3	19·7	44·5	4·3	19·9
Cl	H	H	H	(*a*)	17		157 (decomp.)	$C_6H_4ClN_3OS$	34·7	2·3	20·5	35·7	2·0	20·8
SH	H	H	H	(*a*)	53		273—274	$C_6H_5N_3OS_2$	36·5	2·7		36·2	2·5	
OMe	H	H	H	(*a*)	69	EtOH	192—193 †							
OMe	Me	H	H	(*b*)	22	Pr^{i}OH	173—174 ‡							
OMe	Me	Me	H	(*b*)	25	Pr^{i}OH	186—187	$C_9H_{11}N_3O_2S$	48·0	5·0	19·1	48·0	4·9	18·7
OMe	$CH_2{\cdot}CO_2H$	H	H	(*b*)	28	H_2O–$Me_2N{\cdot}CHO$	230—232	$C_9H_9N_3O_4S$	42·8	3·7	16·5	42·3	3·55	16·4
OMe	H	H	Me	(*c*)	47		125—126	$C_8H_9N_3O_2S$	45·1	4·2	19·7	45·5	4·3	19·9
OMe	H	H	$CH_2{\cdot}CH{:}CH_2$	(*c*)	81	Pr^{i}OH–H_2O	64—65	$C_{10}H_{11}N_3O_2S$	49·9	4·9	17·5	50·6	4·7	17·7
OMe	Me	H	Me	(*c*)	73	Pr^{i}OH	154—156	$C_9H_{11}N_3O_2S$	47·9	5·1	19·0	48·0	4·9	18·7
OMe	Me	H	$CH_2{\cdot}CH{:}CH_2$	(*c*)	48	Pr^{i}OH–H_2O	71—72	$C_{11}H_{13}N_3O_2S$	53·2	5·5	16·8	52·6	5·2	16·7
OMe	Me	Me	Me	(*c*)	18		123—124	$C_{10}H_{13}N_3O_2S$	50·2	5·5	17·7	50·2	5·5	17·6

* See Experimental section. † Lit.,[4] 191—193°; E. C. Taylor and E. E. Garcia (*J. Org. Chem.*, 1964, **29**, 2121) quote m.p. 190—191°. ‡ Lit.,[4] 175—176·5.

TABLE 2

^{1}H N.m.r. data for 4-methoxy-5*H*-pyrimido[4,5-*b*][1,4]thiazin-6(7*H*)-ones [a]

Compound (2) X	R^1	R^2	R^3	τ Values (*J* in Hz) 2-H	OMe	7-Substituent	5-Substituent	Solvent
OMe	H	H	H	1·67	6·05	6·34 (2H, s)	−0·23br (1H, s) [b]	$(CD_3)_2SO$
OMe	Me	Me	H	1·53	5·88	8·45 (6H, s)	1·73br (1H, s) [b]	$CDCl_3$
OMe	$CH_2{\cdot}CO_2H$	H	H	1·67	6·03	5·89 (1H, t, *J* 7), 7·18 (2H, d, *J* 7)	−0·35br (1H, s) [b]	$(CD_3)_2SO$
OMe	H	H	Me	1·57	5·98	6·34 (2H, s)	6·79 (3H, s)	$(CD_3)_2SO$
OMe	Me	H	Me	1·54	5·88	6·40 (1H, q, *J* 7) 8·47 (3H, d, *J* 7)	6·63 (3H, s)	$CDCl_3$
OMe	Me	Me	Me	1·61	5·91	8·54 (6H, s)	6·64 (3H, s)	$CDCl_3$
OMe	H	H	$CH_2{\cdot}CH{:}CH_2$	1·79	6·04	6·64 (2H, s)	5·48 (2H, d, *J* 6) 4·26—4·64 (1H, m), 4·92—5·10 (2H, m)	$CDCl_3$ [c]
OMe	Me	H	$CH_2{\cdot}CH{:}CH_2$	1·78	6·04	6·55 (1H, q, *J* 7), 8·53 (3H, d, *J* 7)	5·23—5·72 (2H, m), 4·24—4·62 (1H, m), 4·92—5·08 (2H, m)	$CDCl_3$ [c]
OEt	H	H	H	1·69	*d*	6·34 (2H)	−0·23br (1H, s) [b]	

[a] Measured on a Varian A60A spectrometer at normal probe temperature with tetramethylsilane as internal standard. [b] Removed on deuteriation. [c] Measured on a Varian HA-100 spectrometer. [d] Ethoxy-signal τ 5·58 (2H, q, *J* 7), 8·68 (3H, t, *J* 7).

[3] M. Ishidate and H. Yuki, *Chem. and Pharm. Bull.* (*Japan*), 1960, **8**, 131.

[4] T. S. Safonova and M. P. Nemeryuk, *Khim. geterotsikl. Soedinenii*, (*a*) 1966, **5**, 714; (*b*) 1971, **1**, 73.

TABLE 3

5*H*-Pyrimido[4,5-*b*][1,4]thiazine-4,6(3*H*,7*H*)-diones

Compound (3)				Method of prepn.*	Yield (%)	M.p. (°C)	Formula	Found (%)			Required (%)		
R^1	R^2	R^3	R^4					C	H	N	C	H	N
H	$CH_2{\cdot}CO_2H$	H	H	(*d*)	66	275—277	$C_8H_7N_3O_4S$	39·5	3·0	17·1	39·8	2·9	17·4
Me	Me	H	H	(*d*)	42	273	$C_8H_9N_3O_2S$	45·4	4·5	19·8	45·5	4·3	19·9
H	H	Me	H	(*d*)	53	225—227	$C_7H_7N_3O_2S$	42·4	3·7	21·4	42·6	3·6	21·3
H	H	$CH_2{\cdot}CH{:}CH_2$	H	(*d*)	49	146—148	$C_9H_9N_3O_2S$	48·3	4·2	18·8	48·4	4·1	18·8
H	Me	$CH_2{\cdot}CH{:}CH_2$	H	(*d*)	55	203—204	$C_{10}H_{11}N_3O_2S$	50·0	4·9	17·4	50·6	4·7	17·7
H	Me	Me	H	(*d*)	53	250—251	$C_8H_9N_3O_2S$	45·3	4·3	19·5	45·5	4·3	19·9
Me	Me	Me	H	(*d*)	40	197—199	$C_9H_{11}N_3O_2S$	47·9	5·0	18·7	48·0	4·9	18·7
H	H	$CH_2{\cdot}CH{:}CH_2$	Me	(*e*)	45	128—129	$C_{10}H_{11}N_3O_2S$	50·1	4·7	17·7	50·6	4·7	17·7
H	H	Me	Me	(*e*)	37	239—241	$C_8H_9N_3O_2S$	46·2	4·6	19·8	45·5	4·3	19·9
H	Me	Me	Me	(*e*)	43	180—181	$C_9H_{11}N_3O_2S$	48·7	5·2	19·3	48·0	4·9	18·7

* See Experimental section.

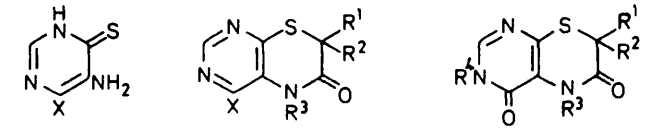
TABLE 4

^{1}H N.m.r. data for 5*H*-pyrimido[4,5-*b*][1,4]thiazine-4,6(3*H*,7*H*)-diones [a]

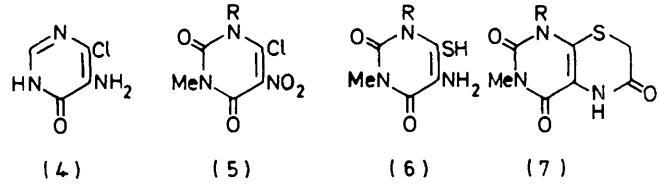
Compound (3)				τ Values (*J* in Hz)				
R^1	R^2	R^3	R^4	2-H	3-Substituent	5-Substituent	7-Substituents	Solvent
H	H	Me	H	2·00		6·78 (3H, s)	6·43 (2H, s)	$(CD_3)_2SO$
Me	Me	H	H	2·01		−0·17br (1H, s) [b]	8·58 (6H, s)	$(CD_3)_2SO$
Me	Me	Me	H	2·05		6·53 (3H, s)	8·50 (6H, s)	$CDCl_3$
Me	H	Me	H	1·98		6·72 (3H, s)	6·20 (1H, q, *J* 7), 8·63 (3H, d, *J* 7)	$(CD_3)_2SO$
Me	H	Me	Me	2·07	6·45 (3H, s)	6·60 (3H, s)	6·30 (1H, q, *J* 7), 8·48 (3H, d, *J* 7)	$CDCl_3$
H	H	$CH_2{\cdot}CH{:}CH_2$	H	2·22		5·27 (2H, d, *J* 6), 4·16—4·53 (1H, m), 4·89—5·06(2H, m)	6·60 (2H, s)	$CDCl_3$ [c]
H	H	$CH_2{\cdot}CH{:}CH_2$	Me	2·25	6·57 (3H, s)	5·30 (2H, d, *J* 6), 4·18—4·55 (1H, m), 4·90—5·09 (2H, m),	6·66 (2H, s)	$CDCl_3$ [c]
H	$CH_2{\cdot}CO_2H$	H	H	2·07		0·07 (1H, s) [b]	5·98 (1H, t, *J* 7), 7·19 (2H, d, *J* 7)	$(CD_3)_2SO$

[a] Measured on a Varian A60A spectrometer at normal probe temperature with tetramethylsilane as internal standard. [b] Removed on deuteriation. [c] Measured on a Varian HA100 spectrometer.

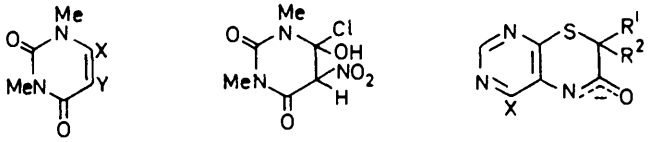
hydrolysis of the 4-methoxy-group. 3,5-Dialkyl derivatives (3; R^3 and R^4 = alkyl) were prepared by



(1) (2) (3)



(4) (5) (6) (7)



(8) (9) (10)

further alkylation of the 5-alkyl compounds (Table 3). Structures of the various alkyl derivatives were confirmed by ^{1}H n.m.r. spectroscopy (Table 4).

[5] C. C. Cheng and T. K. Liao, *J. Heterocyclic Chem.*, 1964, **1**, 212.

(c) 5H-*Pyrimido*[4,5-b][1,4]*thiazine*-2,4,6(1H,3H,7H)-*triones*.—The amino-mercapto-compound (6; R = H), which was derived from the chloro-nitro-compound (5; R = H), was condensed with chloroacetic acid to furnish a 3-methylpyrimidothiazinetrione (7; R = H). The 1,3-dimethyl analogue of the latter was similarly synthesised from 6-chloro-1,3-dimethyl-5-nitropyrimidine-2,4(1*H*,3*H*)-dione (5; R = Me). The last named pyrimidinedione (5; R = Me) has recently been reported by two groups of workers,[5,6] who (respectively) give its m.p. as 65—68 and 80—83°. It may be obtained more pure (m.p. 85—87°) when prepared under milder nitration conditions than those published. Thus, whereas nitration of the precursor (8; X = Cl, Y = H) with mixed nitric and sulphuric acids at 10—15°, as in ref. 6, gave an impure product, carrying out the reaction at 0—5° gave pure material. Above 15° appreciable hydrolysis to 1,3-dimethyl-5-nitrobarbituric acid (8; X = OH, Y = NO_2) occurred, and some of this was isolated and identified by comparison with an authentic specimen.[7] When we treated the chloropyrimidine (8; X = Cl, Y = H) with fuming nitric acid and glacial acetic acid at 20—23°, or with nitric acid and acetic anhydride at 0—5°, or with fuming nitric acid alone at 10°, we obtained a different com-

[6] W. Pfleiderer and E. Bühler, *Chem. Ber.*, 1966, **99**, 2997.
[7] H. Biltz and K. Sedlatschek, *Ber.*, 1924, **57**, 339.

pound, m.p. 286—287°, which was assigned a 5,6-dihydropyrimidine structure (9). This assignment was based on microanalytical results, the absence of a normal 5-proton signal in the ^1H n.m.r. spectrum, and the mass spectrum. No molecular ion peak was observed but the base peak at *m/e* 190·0145 (Cl isotope pattern), due to $C_6H_7{}^{35}ClN_2O_3$ ions, and another intense peak at *m/e* 156·0535, due to $C_6H_8N_2O_3$ ions, may be attributed to reasonable losses of HNO_2 and NO_2Cl, respectively, from the absent molecular ion. The occurrence of addition reactions at the 5,6-bond of pyrimidines, particularly uracil derivatives, is well established and may involve, for example, addition of the elements of nitric acid,[8,9] hypobromous acid,[10] hypochlorous acid,[8] or water.[11]

It has been noted previously [2] that 4-(substituted-amino-5*H*-pyrimido[4,5-*b*][1,4]thiazin-6(7*H*)-ones (2; X = NHR or NR_2) are acidic, although they are essentially cyclic analogues of acyl derivatives of 4-aminopyrimidines. The present compounds (2; X = OMe, Cl, or OEt) are also freely soluble in sodium hydroxide solution and are reprecipitated on acidification. The 4-methoxy-compound (2; X = OMe, $R^1 = R^2 = H$) and its 7,7-dimethyl derivative (2; X = OMe, $R^1 = R^2 = Me$), for example had pK_a values of 11·00 and 11·28, respectively, and showed very similar spectral changes on ionisation. The fact that the 7,7-dimethyl derivative behaved like the other compounds confirms that it is ionisation of the 5-NH group which is responsible for the acidity of the compounds, and that dissociation of a 7-proton is not involved. Open chain analogues (5-acylaminopyrimidines) are not appreciably ionised even at pH 14. Perhaps the cyclic anions (10) are more effectively solvated than anions from simple acylamino-groups.

Representative examples of compounds in Tables 1 and 3 showed slight or negligible activity as antimicrobial agents.

EXPERIMENTAL

pK_a Values were measured by a rapid spectrophotometric method.[12] U.v. spectra were recorded on a Unicam SP 800 spectrometer for buffered aqueous solutions. 4-Methoxy-5*H*-pyrimido[4,5-*b*][1,4]thiazin-6(7*H*)-one (pK_a 11·00 ± 0·02) showed $\lambda_{max.}$ (neutral molecule at pH 8·9) 296 (log ε 3·74), 288infl (3·73), and 244 nm (4·21); $\lambda_{max.}$ (anion at pH 13·3) 309infl (3·80), 293 (3·89), and 254 (4·12). Its 7,7-dimethyl derivative (pK_a 11·28 ± 0·02) showed $\lambda_{max.}$ (neutral molecule at pH 9·0) 292 (log ε 3·76), 287infl (3·75), and 243 nm (4·21); $\lambda_{max.}$ (anion at pH 13·3) 311infl (3·82), 293 (3·95), and 253 (4·09).

5-Amino-6-ethoxypyrimidine-4(3H)*-thione*.— 4-Chloro-6-ethoxy-5-nitropyrimidine (0·8 g) and aqueous N-sodium hydrogen sulphide (20 ml) were stirred at 20° until a clear solution was obtained (*ca.* 45 min), and then at 60—65° for a further 16 h. The solution was acidified with glacial acetic acid and the resulting solid filtered off and reprecipitated from 0·5N-sodium hydroxide (10·8 ml). The *ethoxypyrimidinethione* had m.p. 193—195° (from ethanol) (Found: C, 41·6; H, 5·1; N, 25·1. $C_6H_9N_3OS$ requires C, 42·1; H, 5·3; N, 25·4%).

5H-Pyrimido[4,5-b][1,4]*thiazin-6*(7H)*-ones*.—(a) *4-Substituted derivatives*. The appropriate aminopyrimidinethione (1 equiv.), chloroacetic acid (1·1 equiv.) and N-sodium hydroxide solution (2·2 equiv.) were heated at 90—95° for 1 h. The cooled solution was adjusted to pH 1 with 5N-hydrochloric acid and the pure pyrimidothiazinone (2; $R^1 = R^2 = H$) was filtered off (Table 1).

(b) *7-Substituted 4-methoxy-derivatives*. 5-Amino-6-methoxypyrimidine-4(3*H*)-thione (1·57 g), N-sodium hydroxide (12 ml), and ethyl α-bromopropionate (1·54 ml) were shaken together vigorously for 5 min before being heated at 90—95° for 1 h. The *7-methyl compound* (0·46 g) separated from the cooled solution (Table 1). The same pyrimidine (1·1 g), N-sodium hydroxide solution (8·4 ml), and ethyl α-bromoisobutyrate (1·23 ml) were similarly condensed together, but for 3 h, to yield the *7,7-dimethyl derivative* (0·37 g) (Table 1). The pyrimidine (0·63 g), N-sodium hydroxide (8·8 ml), and bromosuccinic acid (0·94 g) were heated at 90—95° for 1 h. The cooled solution, on acidification to pH 1 with 5N-hydrochloric acid, yielded the *7-carboxymethyl derivative* (0·37 g) (Table 1).

(c) *5-Alkyl-4-methoxy-derivatives*. The appropriate thiazinone (1 equiv.), methyl iodide (or allyl bromide) (1·1 equiv.), and N-sodium hydroxide (1·1 equiv.) were shaken for a suitable time (24—48 h). The *products* were filtered off and washed with a little water (methyl derivatives) or propan-2-ol (allyl derivatives) before recrystallisation from a suitable solvent (Table 1).

5H-Pyrimido[4,5-b][1,4]*thiazine-4,6*(3H,7H)*-diones*.— (d) *3-Unsubstituted derivatives*. The 4-methoxypyrimidothiazinone (2; X = OMe) (0·3 g) and 2N-hydrochloric acid (3 ml) were stirred under reflux until a clear solution was obtained and for a further 2 h. The *product* crystallised from the cooled solution in an analytically pure state (Table 3).

(e) *3,5-Dialkyl derivatives*. The relevant 5-alkyl compound (0·4 g) in 0·5N-sodium hydroxide (4·8 ml) was vigorously shaken with methyl iodide (0·15 ml) for 24—36 h. The *product* was filtered off and crystallised from a suitable solvent (Table 3).

5-Amino-6-chloropyrimidin-4(3H)*-one*.—A mixture of 5-amino-4,6-dichloropyrimidine (1·63 g) and 6N-hydrochloric acid (15 ml) was heated under reflux for 1 h and evaporated to dryness under reduced pressure. The residue was suspended in water (3 ml) and pH adjusted to 4 with N-sodium hydroxide. The *pyrimidone* was filtered off and crystallised from water as buff crystals (0·6 g), m.p. 241° (Found: C, 33·2; H, 2·8; N, 29·1. $C_4H_4ClN_3O$ requires C, 33·0; H, 2·8; N, 28·9%).

5-Amino-6-mercapto-3-methylpyrimidine-2,4(1H,3H)*-dione* (6; R = H).—6-Chloro-3-methyl-5-nitropyrimidine-2,4(1*H*,3*H*)-dione (3·6 g) was heated under reflux for 3 h with a solution of sodium hydrogen sulphide prepared by saturating 2N-sodium hydroxide (53 ml) with hydrogen sulphide. The solution was acidified with glacial acetic acid and filtered. The *mercapto-compound*, purified by

[8] T. B. Johnson, *Amer. Chem. J.*, 1908, **40**, 19.
[9] T. B. Johnson, *J. Biol. Chem.*, 1908, **4**, 407.
[10] O. Baudisch and D. Davidson, *Ber.*, 1925, **58**, 1680; *J. Biol. Chem.*, 1925, **64**, 234; S. Y. Wong, *J. Org. Chem.*, 1959, **24**, 11; J. R. Piper and T. P. Johnston, *ibid.*, 1965, **30**, 1247.
[11] A. M. Moore, *Canad. J. Chem.*, 1958, **36**, 281; A. M. Moore and C. H. Thompson, *ibid.*, 1957, **35**, 163; *Science*, 1955, **122**, 594.
[12] J. Clark and A. E. Cunliffe, *Chem. and Ind.*, 1973, 281.

reprecipitation from 2N-sodium hydroxide after alkali-insoluble matter had been filtered off, had m.p. >300° (Found: C, 34·0; H, 3·7; N, 23·7. $C_5H_7N_3O_2S$ requires C, 34·7; H, 4·1; N, 24·3%).

3-*Methyl*-5H-*pyrimido*[4,5-b][1,4]*thiazine*-2,4,6(1H,3H,-7H)-*trione* (7; R = H).—The foregoing mercapto-compound (0·5 g) and chloroacetic acid (1·5 g) were heated at 140° for 5 min and cooled. The excess of chloroacetic acid was extracted with water (20 ml) and the residue boiled with dimethylformamide (20 ml). The insoluble *pyrimidothiazinetrione* (0·2 g), m.p. >300°, was filtered off as a buff solid (Found: C, 39·4; H, 3·4; N, 19·7. $C_7H_7N_3O_3S$ requires C, 39·4; H, 3·3; N, 19·7%).

6-*Chloro*-1,3-*dimethyl*-5-*nitrouracil*.— 6-Chloro-1,3-dimethyluracil (8·5 g) was added in portions to stirred concentrated sulphuric acid (25 ml), kept below 15° by cooling in ice. Fuming nitric acid (8·4 ml) was added slowly, the temperature being maintained at 0—5°, and the solution was then poured onto ice (100 g) with stirring. The product was at once extracted into chloroform (2 × 100 ml) and the extract was dried ($MgSO_4$) and quickly evaporated to afford a yellow crystalline solid (5·4 g), m.p. 85—87° (lit.,[4b] 65—68°; lit.,[5] 80—83°).

1,3-*Dimethyl*-5H-*pyrimido*[4,5-b][1,4]*thiazine*-2,4,6(1H,-3H,7H)-*trione*.—The foregoing chloro-compound (3·29 g) and aqueous 2N-sodium hydrogen sulphide solution (38 ml) were stirred under reflux for 3 h, acidified with glacial acetic acid, and filtered. The solid was reprecipitated from 2N-sodium hydroxide after removal of alkali-insoluble matter and heated with chloroacetic acid (0·69 g) and 0·5N-sodium hydroxide (14·5 ml) at 90—95° for 1 h. The *pyrimidothiazinetrione* (0·42 g), m.p. 250°, separated from the cooled solution (Found: C, 41·8; H, 3·8; N, 18·1. $C_8H_9N_3O_3S$ requires C, 42·3; H, 4·0; N, 18·5%).

A solution of the compound (0·38 g) in N-sodium hydroxide (2 ml) gradually deposited the sodium salt (0·27 g).

5-*Benzyl*-1,3-*dimethyl*-5H-*pyrimido*[4,5-b][1,4]*thiazine*-2,4,6(1H,3H,7H)-*trione*.—The foregoing sodium salt (0·27 g), water (3 ml), ethanol (3 ml), and benzyl chloride (0·15 ml) were heated under reflux for 1 h and evaporated to dryness under reduced pressure. Water (2 ml) was added to the residue and the *benzyl derivative* (0·062 g), m.p. 181—182° (from aqueous ethanol), was filtered off (Found: C, 55·8; H, 4·8; N, 13·5. $C_{15}H_{15}N_3O_3S$ requires C, 56·8; 4·8; N, 13·2%).

6-*Chloro*-5,6-*dihydro*-1,3-*dimethyl*-6-*hydroxy*-5-*nitrouracil* (9).—(*a*) 6-Chloro-1,3-dimethyluracil (10·5 g) was added in portions to a stirred mixture of glacial acetic acid (21·6 ml) and fuming nitric acid (7·8 ml) maintained at 20—23°. The solution was stirred for a further 0·5 h, then poured onto ice, evaporated to small bulk, cooled, and treated with water (60 ml). The *hydroxy-nitro-compound* (5·1 g) which separated had m.p. 286—287° [from light petroleum (b.p. 80—100°) or methanol] (Found: C, 30·8; H, 2·9; N, 17·6. $C_6H_8ClN_3O_5$ requires C, 30·3; H, 3·4; N, 17·7%).

(*b*) 6-Chloro-1,3-dimethyluracil (1·75 g) was added in portions during 15 min to stirred fuming nitric acid (5 ml) kept at 10°. The solution was stirred at 20° for a further 0·5 h, then poured onto ice, and the product (1·1 g), m.p. 286—287° (from ethanol), was isolated as in (*a*).

(*c*) The same product was obtained by treating 6-chloro-1,3-dimethyluracil (1·75 g) in acetic anhydride (8 ml) at 0° with a mixture of fuming nitric acid (1·3 ml) and acetic anhydride (8 ml). After 0·5 h at 0—5° and 0·5 h at 20° the mixture was poured onto ice and treated as in (*a*) [yield 0·76 g; m.p. 286—187° (from methanol)].

We thank the S.R.C. for a Co-operative Award in Pure Science (to I. W. S.) and Messrs Allen and Hanburys Ltd., who co-operated in the work and carried out the pharmaceutical testing. We also thank Mr. A. E. Cunliffe for pK_a values and u.v. spectra, Mrs. R. Maynard for mass spectra, and Mr. D. J. Barraclough for n.m.r. spectra.

[4/353 *Received*, 22*nd February*, 1974]