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Azoles. Part 10.[1] Thiazolo[4',5';4,5]thieno[3,2-*d*]pyrimidine, a New Heterocyclic Ring System

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Dedicated to Professor C.W. Rees, F.R.S., Hofmann Professor of Organic Chemistry, Imperial College, London, on the occasion of his 65th birthday.

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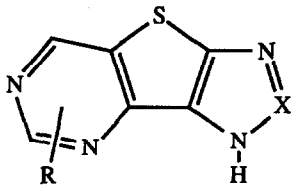
Key words: 4-chlorothiazole-5-carbaldehydes; 4-chlorothiazole-5-carbonitriles; thieno[2,3-*d*]thiazoles; thiazolo[4',5';4,5]thieno[3,2-*d*]pyrimidines; cytokinin analogues.

Abstract: Thieno[2,3-*d*]thiazoles were prepared by reaction of 4-chlorothiazole-5-carbaldehydes or 4-chlorothiazole-5-carbonitriles with either ethyl 2-mercaptoacetate or 2-mercaptoacetamide. The 6-aminothieno[2,3-*d*]thiazole-5-carboxamides obtained were converted into the corresponding thiazolo[4',5';4,5]thieno[3,2-*d*]pyrimidin-5(6*H*)-one by treatment with triethyl orthoformate in acetic anhydride. With phosphoryl chloride these gave the 5-chloro-derivative, which underwent displacement of the chlorine-atom when allowed to react with various amines. Reductive dechlorination of 5-chlorothiazolo[4',5';4,5]thieno[3,2-*d*]-pyrimidine gave the parent heterocycle.

Leonard's group[2] have synthesised "stretched (or extended) purines" as dimensional probes of enzyme-co-enzyme binding sites. "*Lin*"-extended purines are active, providing that the pyrimidine and imidazole rings are separated by only one other ring (the "spacer unit"), whilst "angular"-extended purines are inactive. As far as we are aware "stretched purines" in which the "spacer unit" is a heterocyclic ring have not been extensively investigated. Indeed, Leonard[2] considers that systems in which the "spacer unit" is a thiophene ring are "good candidates for an analysis of deaminase and oxidase activities". Such systems are neither "linear" nor fully "angular" but "bent" in shape.

With this background in mind and because purine analogues are of interest also as potential anticancer and antiviral agents, several years ago we set ourselves the target of synthesising molecules with the general structure **1** (X = CH or N).[3] Progress to date has resulted in the synthesis of several 4-bromoimidazole-5-carbaldehydes[4,5] and their conversion into thieno[2,3-*d*]imidazoles.[6] We have experienced difficulties in

converting these compounds into the target molecules **1** (X = CH). However, in a parallel investigation, which we now describe, we have succeeded in synthesising the novel thiazole analogues **2** - **12**.



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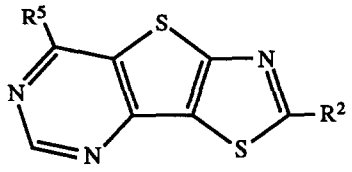


2 $R^2 = R^5 = H$

3 $R^2 = H$, $R^5 = Cl$

4 $R^2 = H$, $R^5 = NH_2$

5 $R^2 = H$, $R^5 = NHCH_2Ph$

6 $R^2 = H$, $R^5 = NHCH_2$(2-furyl)

7 $R^2 = H$, $R^5 = NMe_2$

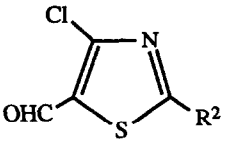
8 $R^2 = SMe$, $R^5 = Cl$

9 $R^2 = SMe$, $R^5 = NH_2$

10 $R^2 = SMe$, $R^5 = NHCH_2Ph$

11 $R^2 = SMe$, $R^5 = NHCH_2$(2-furyl)

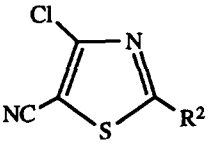
12 $R^2 = SMe$, $R^5 = NMe_2$



13 $R^2 = H$

14 $R^2 = Cl$

15 $R^2 = SMe$



16 $R^2 = H$

17 $R^2 = Cl$

18 $R^2 = SMe$

19 $R^2 = NH_2$

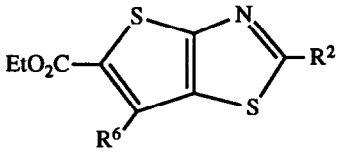
20 $R^2 = SCH_2CONH_2$

21 $R^2 = OPr\text{-}i$

2,4-Dichlorothiazole-5-carbaldehyde **14** is readily synthesised by subjecting commercially available thiazolidine-2,4-dione to a Vilsmeier reaction.[1,7] Its dechlorination at position-2 followed by reaction of the product with ethyl 2-mercaptoacetate in ethanol in the presence of sodium ethoxide gives ethyl thieno[2,3-*d*]-thiazole-5-carboxylate **22**.[1]

We converted 4-chloro- **13**,[1] 2,4-dichloro- **14**,[1,7] and 4-chloro-2-methylthio-thiazole-5-carbaldehyde **15**[1] into the corresponding 5-carbonitriles, **16** (67% yield from the oxime), **17** (75%),[7] and **18** (73%), respectively, through dehydration of their oximes with acetic anhydride. Attempts to convert 2,4-dichloro-thiazole-5-carbonitrile **17** into 4-chlorothiazole-5-carbonitrile **16** by its irradiation[8] in ether, tetrahydrofuran, hexane, or ethanol failed; starting material was recovered quantitatively in each case. However, when compound **17** was irradiated in isopropanol, it gave 4-chloro-2-isopropoxythiazole-5-carbonitrile **21** (53% yield).

Nitriles **16** and **17** were each allowed to react with ethyl 2-mercaptoacetate[6,9-11] which gave the corresponding thieno[2,3-*d*]thiazole, **23** (53% yield) or **25** (74%), respectively. However, on being heated in formamide for 8 h at 200 °C,[9,12,13] thieno[2,3-*d*]thiazoles **23** and **25** failed to cyclise to the desired thiazolo[4',5';4,5]thieno[3,2-*d*]pyrimidin-5(6*H*)-one, **31** and **32**, respectively; these reactions afforded a black intractable residue. In an alternative strategy, we converted the aminothieno[2,3-*d*]thiazole **23** into its *N*-formyl derivative **24** (71% yield) which was heated in formamide in the presence of ammonium formate.[11] Again, a black intractable residue was obtained. A similar result was obtained when the same *N*-formyl derivative **24** was heated with formamide in dimethyl sulfoxide in the presence of sodium ethoxide.[11]

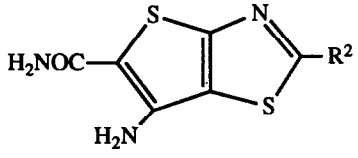


22 $R^2 = R^6 = H$

23 $R^2 = H$, $R^6 = NH_2$

24 $R^2 = H$, $R^6 = NHCHO$

25 $R^2 = Cl$, $R^6 = NH_2$



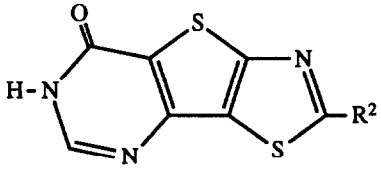
26 $R^2 = H$

27 $R^2 = Cl$

28 $R^2 = SMe$

29 $R^2 = NH_2$

30 $R^2 = OPr\text{-}i$



31 $R^2 = H$

32 $R^2 = Cl$

33 $R^2 = SMe$

34 $R^2 = OPr\text{-}i$

Compounds **16**, **18** and **21** were allowed to react with freshly prepared 2-mercaptoacetamide[14] in ethanol in the presence of sodium ethoxide, which gave the 6-aminothieno[2,3-*d*]thiazole-5-carboxamides **26** (50% yield), **28** (40%), and **30** (48%), respectively.[9] Treatment of the amino-ester **23** with ammonia (see details in Experimental section) failed to convert it into the 6-aminothieno[2,3-*d*]thiazole-5-carboxamide **26**, whilst treatment of 2,4-dichlorothiazole-5-carbonitrile **17** with 2-mercaptoacetamide[14] resulted in displacement of the 2-chlorine atom, which gave compound **20** (46% yield), and not the 4-chlorine atom, which would have yielded 6-amino-2-chlorothieno[2,3-*d*]thiazole-5-carboxamide **27**. With ammonia, 2,4-dichlorothiazole-5-carbonitrile **17** likewise gave 2-amino-4-chlorothiazole-5-carbonitrile **19** (78.5%). The reactions of 2,4-dichlorothiazole-5-carbonitrile **17** with 2-mercaptoacetamide and ammonia are, by contrast with its reaction with ethyl 2-mercaptoacetate (*loc cit*), in keeping with the usual reactivity pattern of dihalogenothiazoles.[15]

Treatment of 2-amino-4-chlorothiazole-5-carbonitrile **19** with freshly prepared 2-mercaptoacetamide[14] in ethanol in the presence of sodium ethoxide appeared to give 2,6-diaminothieno[2,3-*d*]thiazole-5-carboxamide **29** (52% yield) but this compound was extremely difficult to purify.

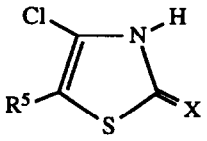
The 6-aminothieno[2,3-*d*]thiazole-5-carboxamides **26** and **28** were allowed to react with triethyl orthoformate in acetic anhydride[12,16] which gave the corresponding thiazolo[4',5';4,5]thieno[3,2-*d*]-pyrimidin-5(6*H*)-one, **31** (61% yield) or **33** (62%), respectively. For the synthesis of thiazolo[4',5';4,5]-thieno[3,2-*d*]pyrimidin-5(6*H*)-one **34** (19% yield) the 6-aminothieno[2,3-*d*]thiazole-5-carboxamide **30** was treated with triethyl orthoformate in ethanol in the presence of sodium ethoxide. Compounds **31** and **33** were converted into the corresponding 5-chloro-derivative, **3** (62%) and **8** (58%), with phosphoryl chloride.[9,11,13] Catalytic hydrodechlorination of compound **3** with ammonium formate in methanol in the presence of palladium-charcoal[9,17] gave the parent heterocycle **2** as a yellow compound in 35% yield, m.p. 168-170 °C. In its ^{1}H NMR spectrum this compound displayed a singlet for 2-H at δ 9.71 and two doublets at δ 9.21and 9.58, for 5-H and 7-H, respectively.

The 5-chloro-derivatives **3** and **8** were allowed to react with various amines in refluxing *n*-butanol, to give the 5-amino-derivatives **4-7** (63-77%) and **9-12** (32-78%).[18] Compounds **4** and **9** are related to adenine whilst compounds **5-7** and **10-12** are related to the cytokinins, plant growth hormones which promote cell division and inhibit senescence.[18,19] An appropriately substituted methylthio-group enhances the biological activity of cytokinin analogues.[20]

This is the first report of the thiazolo[4',5';4,5]thieno[3,2-*d*]pyrimidine ring system.

In an alternative approach to the synthesis of 4-chloro-2-methylthiothiazole-5-carbonitrile **18**, we prepared 4-chloro-5-formylthiazol-2(3*H*)-one **35** (44% yield) by treatment of thiazolidine-2,4-dione with a mixture of phosphoryl chloride and *N,N*-dimethylformamide (Vilsmeier conditions),[21] converted it into the corresponding nitrile **36** (89%) by dehydration of the oxime with phosphoryl chloride, and allowed nitrile **36** to react with phosphorus pentasulfide in pyridine. The last reaction afforded only starting material and none of the desired thione **37** and this route was not investigated further.

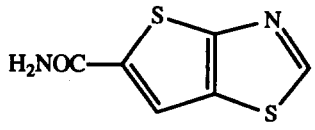
With 2-mercaptoacetamide[14] 4-chlorothiazole-5-carbaldehyde **13** gave thieno[2,3-*d*]thiazole-5-carboxamide **38** (60% yield) but attempts to convert this compound into the corresponding 5-amino-derivative by subjecting it to the Hofmann reaction[22,23] failed.



35 X = O, R^5 = CHO

36 X = O, R^5 = CN

37 X = S, R^5 = CN



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Experimental

The instruments used and the general experimental procedures were the same as those already described.[24]

4-Chloro- **13**,[1] 2,4-dichloro- **14**,[1,7] and 4-chloro-2-methylthio-thiazole-5-carbaldehyde **15**[1] were prepared as described previously. 2-Mercaptoacetamide (prepared fresh prior to its use) (80%), m.p. 53-55 °C (lit., 96% and b.p. 49-51 °C at 16 mmHg[14] and m.p. 54-56 °C[25]), 4-chloro-5-formylthiazol-2(3*H*)-one **35** (44%), m.p. 218 °C (from ethanol) [lit., m.p. 219 °C (with decomp.)[21]], 2,4-dichlorothiazole-5-carbaldehyde **14** oxime (99%), m.p. 159-160 °C (lit., 99% and m.p. 160 °C[7]), and 2,4-dichlorothiazole-5-carbonitrile **17** (75%), m.p. 34-35 °C (sublimed at 120 °C/12 mmHg) (lit., 76% and m.p. 33-35 °C[7]) were prepared by literature procedures.

Yields, m.p.'s, and analytical data for new compounds are given in Table 1 and IR and ^{1}H NMR data in Table 2.

4-Chloro-2-isopropoxythiazole-5-carbonitrile **21**. - A solution of 2,4-dichlorothiazole-5-carbonitrile **17** (5.0 g, 28.0 mmol) in isopropanol (30 cm^3) was irradiated overnight at ambient temperature in a borax glass tube using UV light of λ 300 nm, then the solvent was removed under reduced pressure to give the product as a yellow oil which solidified (3.0 g, 53%).

4-Chlorothiazole-5-carbaldehyde **13** Oxime. - Hydroxylamine hydrochloride (3.3 g, 47.5 mmol) was added portionwise to a stirred solution of sodium hydrogen carbonate (4.0 g, 47.5 mmol) in water (150 cm^3) at ambient temperature, then a solution of 4-chlorothiazole-5-carbaldehyde **13** (7.0 g, 47.5 mmol) in ethanol (15 cm^3) was added. Stirring was continued for a further 1 h, then the colourless precipitate was filtered off, washed with water, and dried, to give 4-chlorothiazole-5-carbaldehyde **13** oxime (5.0 g, 65%).

4-Chloro-2-methylthiazole-5-carbaldehyde **15** oxime (93%) and 4-chloro-5-formylthiazole-2(3*H*)-one **35** oxime (72%) were prepared similarly.

4-Chlorothiazole-5-carbonitrile **16**. - A solution of 4-chlorothiazole-5-carbaldehyde **13** oxime (5.0 g, 31.0 mmol) in acetic anhydride (25 cm^3) was heated under reflux for 4 h, then the excess of acetic anhydride was removed by distillation under reduced pressure, to give the product **16** (3.0 g, 67%).

4-Chloro-2-methylthiothiazole-5-carbonitrile **18** was prepared similarly.

4-Chlorothiazole-2(3*H*)-one-5-carbonitrile **36**. - A mixture of 4-chloro-5-formylthiazole-2(3*H*)-one **35** oxime (10.0 g, 56.0 mmol) and phosphoryl chloride (50 cm^3) was heated under reflux for 30 min. The resulting mixture was cooled and poured onto ice-water (500 cm^3) and the precipitate was filtered off, washed with water, and crystallised from ethanol, to yield 4-chlorothiazol-2(3*H*)-one-5-carbonitrile **36** (8.0 g, 89%).

2-(4-Chloro-5-cyanothiazol-2-ylthio)acetamide **20**. - 2-Mercaptoacetamide (0.25 g, 2.79 mmol) was added slowly to a stirred solution of sodium ethoxide in ethanol [prepared by addition of sodium (0.064 g, 2.79 mmol) to ethanol (10 cm^3)] at ambient temperature, then a solution of 2,4-dichlorothiazole-5-carbonitrile **17** (0.5 g, 2.79 mmol) in ethanol (10 cm^3) was added, and the resulting mixture was stirred overnight at ambient temperature. Then the mixture was heated under reflux for 4 h. The solvent was removed under reduced pressure and water (20 cm^3) was added to the residue. Extraction with ethyl acetate (3 x 100 cm^3) gave 2-(4-chloro-5-cyanothiazol-2-ylthio)acetamide **20** as yellow crystals (0.3 g, 46%).

2-Amino-4-chlorothiazole-5-carbonitrile **19**. - Gaseous ammonia was bubbled through a solution of 2,4-dichlorothiazole-5-carbonitrile **17** (10.0 g, 55.9 mmol) in ethanol (100 cm^3) for 3 h during which time a precipitate formed. Then the reaction mixture was heated at 50 °C for 1 h. Distillation of the solvent under reduced pressure gave 2-amino-4-chlorothiazole-5-carbonitrile **19** (7.0 g, 78.5%).

Ethyl 6-Amino-2-chlorothieno[2,3-*d*]thiazole-5-carboxylate **25**. - A solution of ethyl 2-mercapto-acetate (2.0 g, 17.0 mmol) in ethanol (10 cm^3) was added dropwise during 1 h to a stirred solution of sodium ethoxide in ethanol [prepared by addition of sodium (0.4 g, 17.0 mmol) to ethanol (10 cm^3)] at ambient temperature, then a solution of 2,4-dichlorothiazole-5-carbonitrile **17** (3.0 g, 17.0 mmol) in ethanol (15 cm^3) was added, and the resulting mixture was heated under reflux for 5 h. Removal of the solvent under reduced pressure, addition of water (20 cm^3) to the residue, and extraction with ethyl acetate (3 x 100 cm^3) gave the product **25** as yellow crystals (3.25 g, 74%).

Ethyl 6-Aminothieno[2,3-*d*]thiazole-5-carboxylate **23** was prepared similarly from nitrile **16**.

Ethyl 6-N-Formylaminothieno[2,3-*d*]thiazole-5-carboxylate **24**. - A mixture of formic acid (20 cm^3, large excess), ethyl 6-aminothieno[2,3-*d*]thiazole-5-carboxylate **23** (0.5 g, 2.19 mmol), and sodium acetate (0.18 g, 2.19 mmol) was heated under reflux for 1 h, then the excess of formic acid was distilled off under reduced pressure. The solid residue was triturated with water (10 cm^3), then filtered and dried, to give ethyl 6-N-formylaminothieno[2,3-*d*]thiazole-5-carboxylate **24** as yellow crystals (0.4 g, 71%).

6-Aminothieno[2,3-*d*]thiazole-5-carboxamide **26**. - 2-Mercaptoacetamide (1.82 g, 20.0 mmol) was added slowly to a stirred solution of sodium ethoxide in ethanol [prepared by addition of sodium (0.46 g, 20.0 mmol) in ethanol (20 cm^3)] at ambient temperature, then a solution of 4-chlorothiazole-5-carbonitrile **16** (2.89 g, 20.0 mmol) in ethanol (10 cm^3) was added and the mixture was stirred overnight. Then it was heated under reflux for a further 4 h. Distillation of the solvent under reduced pressure, additon of water (50 cm^3) to

the residue, and extraction of the product with ethyl acetate (4 x 50 cm^3) gave 6-aminothieno[2,3-*d*]thiazole-5-carboxamide **26** (2.0 g, 50%) as yellow crystals.

Compounds **28** and **30** were prepared similarly.

Reactions of Ethyl 6-Aminothieno[2,3-*d*]thiazole-5-carboxylate **23** with Ammonia. - (a) A mixture of the thienothiazole **23** (0.5 g, 2.2 mmol) and aqueous ammonia (25 cm^3; s.g. 880) was stirred at 0 °C for 20 h, then the ammonia was evaporated off under reduced pressure. Extraction of the residue with ethyl acetate gave starting material (0.4 g, 80% recovery), identified by its m.p. and ^1H NMR spectrum.

(b) Gaseous ammonia was bubbled through a solution of the thienothiazole **23** (0.5 g, 2.2 mmol) in ethanol (10 cm^3) for 3 h, then the solution was heated at 50 °C for a further 2 h. Distillation of the solvent under reduced pressure and crystallisation of the residue from ethanol gave starting material (0.4 g, 80% recovery), identical (m.p. and IR and ^1H NMR spectra) with an authentic sample.

(c) A solution of the thienothiazole **23** (0.5 g, 2.2 mmol) in liquid ammonia (25 cm^3) was heated in an autoclave at 100 °C overnight, then the ammonia was evaporated off to leave a black intractable residue.

Thiazolo[4',5';4,5]thieno[3,2-*d*]pyrimidin-5(6*H*)-one **31**. - A mixture of 6-aminothieno[2,3-*d*]-thiazole-5-carboxamide **26** (0.5 g, 2.51 mmol), triethyl orthoformate (10 cm^3; large excess), and acetic anhydride (10 cm^3) was heated under reflux for 4 h, then cooled and poured into iced-water (50 cm^3). The precipitate was filtered off, washed with water, and crystallised from ethanol, to give the product **31** (0.32 g, 61%) as colourless crystals.

Compound **33** was prepared similarly.

2-Isopropoxythiazolo[4',5';4,5]thieno[3,2-*d*]pyrimidin-5(6*H*)-one **34**. - 6-Amino-2-isopropoxythieno[2,3-*d*]thiazole-5-carboxamide **30** (0.5 g, 1.95 mmol) was added to a stirred solution of sodium ethoxide in ethanol [prepared by addition of sodium (0.22 g, 9.6 mmol) to ethanol (20 cm^3)] at ambient temperature followed by triethyl orthoformate (0.71 g, 9.6 mmol) and the resulting mixture was heated under reflux for 3 h, then diluted by addition of water (50 cm^3). Extraction with ethyl acetate (4 x 100 cm^3) gave brown crystals which, on crystallisation from *n*-butanol, gave the product **34** (0.1 g, 19%).

Attempted Synthesis of Thiazolo[4',5';4,5]thieno[3,2-*d*]pyrimidin-5(6*H*)-one **31**. - (a) A solution of ethyl 6-aminothieno[2,3-*d*]thiazole-5-carboxylate **23** (0.5 g, 2.20 mmol) in formamide (6 cm^3, large excess) was heated under reflux at 200 °C for 8 h, then cooled to ambient temperature and diluted with water (10 cm^3). A black material precipitated which was isolated and shown by TLC to be a complex mixture. It was not examined further.

(b) A mixture of ethyl 6-*N*-formylaminothieno[2,3-*d*]thiazole-5-carboxylate **24** (0.3 g, 1.17 mmol) and sodium ethoxide (0.08 g, 1.17 mmol) in dimethyl sulfoxide (10 cm^3) was added to formamide (0.15 g, 3.33 mmol) at ambient temperature and the resulting mixture was heated at 90 °C for 1 h, then cooled and poured into water (20 cm^3). Acidification of the resulting solution with acetic acid caused a black precipitate to form. This was isolated and shown by TLC to be a complex mixture which was not examined further.

Table 1

Yields, M.p.'s, and Analytical Data

Compound	Yield (%)	M.p. (°C)[a]	Found (%) C	H	N	Found[b] M^+	Formula	Required (%) C	H	N	Required *M*
2	35	168-170 (A)				193.9845 (CI)[c]	$C_7H_3N_3S_2$				193.9847[c]
3	62	190-191 (A)	37.1	0.8	18.0	227	$C_7H_2ClN_3S_2$	36.9	0.9	18.4	227
4	65	240-243 (B)				207.9878	$C_7H_4N_4S_2$				207.9877
5	64	202-203 (A)				298.0353 (CI)	$C_{14}H_{10}N_4S_2$				298.0347
6	71	240-242 (B)				288.0127	$C_{12}H_8N_4OS_2$				288.0140
7	77	223-224 (B)	45.4	3.6		237.0248 (CI)[c]	$C_9H_8N_4S_2$	45.7	3.4		237.0269[c]
8	58	165-167 (A)	35.8	1.3	14.9	275.9309[c,d]	$C_8H_4ClN_3S_3$	35.1	1.5	15.3	275.9305[c,d]
9	32	214-217 (B)				253.9763	$C_8H_6N_4S_3$				253.9755
10	64	185-187 (A)	51.8	3.6	15.9	344.0220	$C_{15}H_{12}N_4S_3$	52.3	3.5	16.3	344.0224
11	65	240-241 (A)	46.5	2.6	16.5	334.0014	$C_{13}H_{10}N_4OS_3$	46.7	3.0	16.8	334.0016
12	78	211-212 (B)	42.3	3.8	19.2	282	$C_{10}H_{10}N_4S_3$	42.55	3.57	19.9	282
13 (oxime)	65	211-212 (B)	29.9	1.8	16.7	162	$C_4H_3ClN_2OS$	29.55	1.9	17.2	162
15 (oxime)	93	180-181 (B)				208.9611[c]	$C_5H_5ClN_2OS_2$				208.9610[c]
16	67	76-77 (C)[e]	33.5	0.85	19.3	144	C_4HClN_2S	33.2	0.7	19.4	144
18	73	90-91 (C)	31.2	1.3	14.5	189.9424	$C_5H_3ClN_2S_2$	31.5	1.6	14.7	189.9426

19	78.5	177-178 (B)	30.4	1.3	26.2	158.9658	$C_4H_2ClN_3S$	30.1	1.3	26.3	158.9667
20	46	115-117 (A)				232.9489	$C_6H_4ClN_3OS_2$				232.9484
21	53	70-71 (A)	41.6	3.1	13.6	202	$C_7H_7ClN_2OS$	41.5	3.5	13.8	202
23	53	159-160 (A)	42.4	3.4	12.2	228 (CI)	$C_8H_8N_2O_2S_2$	42.1	3.5	12.3	228
24	71	147-148 (A)				255.9971	$C_9H_8N_2O_3S_2$				255.9976
25	74	181-182 (A)	36.6	2.6	10.55	262	$C_8H_7ClN_2O_2S_2$	36.6	2.7	10.7	262
26	50	134-135 (A)	36.1	2.2	20.8	199.9942 (CI)[c]	$C_6H_5N_3OS_2$	36.2	2.5	21.0	199.9952[c]
28	40	235-236 (B)	33.85	2.6	16.5	244.9753	$C_7H_7N_3OS_3$	34.2	2.9	17.1	244.9751
30	48	106-107 (A)				257.0285	$C_9H_{11}N_3O_2S_2$				257.0293
31	61	335-337 (A)				209.9785 (CI)[c]	$C_7H_3N_3OS_2$				209.9796[c]
33	62	352-353 (A) (with decomp)				254.9600	$C_8H_5N_3OS_3$				254.9595
34	19	305-306 (D)				267.0140	$C_{10}H_9N_3O_2S_2$				267.0136
35 (oxime)	72	190-191 (B)				195.9940 (CI)[f]	$C_4H_3ClN_2O_2S$				195.9947[f]
36	89	132-133 (A)	30.3	0.6	17.2	159.9498	C_4HClN_2OS	29.9	0.6	17.45	159.9496
38	60	236-237 (A)	38.6	2.2	14.9	183.9761	$C_6H_4N_2OS_2$	39.1	2.2	15.2	183.9765

[a] Solvent of crystallisation in parentheses: A, ethanol; B, aqueous ethanol; C, hexane; D, *n*-butanol. [b] By electron impact unless stated otherwise (by CI in parentheses). [c] $M^+ + 1$ and $M + 1$ values, respectively. [d] ^{37}Cl peak measured. [e] B.p. 152°C 3.0 mmHg. [f] $M^+ + 18$ and $M + 18$ values, respectively.

Table 2

IR and NMR Spectroscopic Date

Compound	$\nu_{max.}$/cm^{-1} (Assignment)[a]	^{1}H and ^{13}C NMR data (δ-value)[b]
2		9.21 (1 H, d, $J_{5,7}$ 0.8, 5-H), 9.58 (1 H, d, $J_{7,5}$ 0.8, 7-H) and 9.71 (1 H, s, 2-H)
3		9.03 (1 H, s, 7-H) and 9.27 (1 H, s, 2-H) ($CDCl_3$ - [$^2H_6$]-DMSO)
4	3200 and 3371 (NH_2)	8.66 br (2 H, s, exchangeable, NH_2), 8.98 (1 H, s, 7-H) and 9.71 (1 H, s, 2-H)
5		4.76 (2 H, d, J 6.0, CH_2), 7.30-7.50 (5 H, m, ArH), 8.53 (1 H, s, 7-H), 8.74 (1 H, t, J 6.0, NH) and 9.61 (1 H, s, 2-H)
6		4.75 (2 H, d, J 5.5, CH_2), 6.33 (1 H, m, furyl-H), 6.39 (1 H, m, furyl-H), 7.59 (1 H, m, furyl-H), 8.58 (1 H, s, 7-H), 8.61 (1 H, t, J 5.5, NH) and 9.61 (1 H, s, 2-H)
7		3.38 (6 H, s, NMe_2), 8.48 (1 H, s, 7-H) and 9.60 (1 H, s, 2-H)
8		3.33 (3 H, s, SMe) and 9.08 (1 H, s, 7-H)
9	3282 and 3366 (NH_2)	3.36 (3 H, s, SMe), 7.55 (2 H, s, exchangeable, NH_2) and 8.60 (1 H, s, 7-H)
10		3.92 (3 H, s, SMe), 4.74 (2 H, d, J 6.0, CH_2), 7.30-7.45 (5 H, m, ArH), 8.49 (1 H, s, 7-H) and 8.66 (1 H, t, J 6.0, NH)
11		3.35 (3 H, s, SMe), 4.73 (2 H, d, J 5.5, CH_2), 6.32 (1 H, m, furyl-H), 6.39 (1 H, m, furyl-H), 7.58 (1 H, m, furyl-H) and 8.53 (2 H, overlapping s + m, 7-H and NH)
12		3.35 (3 H, s, SMe), 3.36 (6 H, s, NMe_2) and 8.44 (1 H, s, 7-H)
13 (oxime)	1687 (C=N)	
15 (oxime)	1642 (C=N)	
16	2229 (CN)	8.91 (1 H, s, 2-H) ($CDCl_3$)
18	2219 (CN)	2.73 (3 H, s, SMe) ($CDCl_3$)
19	2216 (CN) and 3275 and 3349 (NH_2)	8.83 br (2 H, s, NH_2)

20	1683 (CO), 2223 (CN) and 3264 and 3357 (NH_2)	
21	2225 (CN)	δ_C 30.22 (q, Me_2), 75.50 (d, $\underline{C}H$), 101.23 (s, 5-C), 110.76 (s, 2-C), 148.46 (s, 4-C) and 185.61 (s, $\underline{C}N$) ($CDCl_3$)
23	1660 (CO) and 3280 and 3426 (NH_2)	1.36 (3 H, t, *J* 7.0, Me), 4.32 (2 H, q, *J* 7.0, CH_2), 5.70 br (2 H, s, exchangeable, NH_2) and 8.95 (1 H, s, 2-H) ($CDCl_3$)
24	1683 (CO)	
25	1660 (CO) and 3278 and 3315 (NH_2)	1.28 (3 H, t, *J* 7.0, Me), 4.06 (2 H, s, exchangeable, NH_2) and 4.23 (2 H, q, *J* 7.0, CH_2) ($CDCl_3$)
26	1643 (CO) and 3187, 3281 and 3367 (NH_2)	6.99 br (2 H, s, exchangeable, NH_2), 7.02 br (2 H, s, exchangeable, NH_2) and 8.94 (1 H, s, 2-H).
28	1642 (CO) and 3158, 3272 and 3406 (NH_2)	δ_H 3.36 (3 H, s, SMe), 6.99 br (2 H, s, exchangeable, NH_2) and 7.09 br (2 H, s, exchangeable, NH_2) δ_C 16.11 (q, SMe), 98.69 (s, 2-C), 122.10 (s, 6a-C), 144.10 (s, 3a-C), 153.66 (s, 5-C), 167.02 (s, 6-C) and 172.49 (s, CO)
30	1650 (CO) and 3188 and 3371 (NH_2)	1.20 (6 H, s, 2 x Me), 1.24 (1 H, m, $C\underline{H}Me_2$), 6.84 br (2 H, s, exchangeable, NH_2) and 7.29 br (2 H, s, exchangeable, NH_2)
31	1701 (CO)	3.41br (1 H, s, NH), 8.32 (1 H, s, 7-H) and 9.61 (1 H, s, 2-H)
33	1690 (CO)	2.75 (1 H, s, SMe), 7.37 br (1 H, s, NH) and 7.59 (1 H, s, 7-H)[c]
34	1690 (CO)	δ_C 30.50 (q, Me_2), 72.78 (d, $O\underline{C}HMe_2$), 122.42, 127.51, 147.88 149.39, 157.60, 157.81 and 190.22 (s, CO)
35 (oxime)	1634 (C=N) and 1692 (CO)	
36	1697 (CO) and 2225 (CN)	
39	1655 (CO) and 3150 and 3380 (NH_2)	7.65 (1 H, s, 6-H), 8.12 br (2 H, s, exchangeable, NH_2) and 9.37 (1 H, s, 2-H)

[a] Nujol mulls. [b] Solvents in parentheses; in $[^2H_6]$-DMSO unless stated otherwise; *J* values in Hz. [c] In $[^2H_6]$-Me_2CO.

5-Chlorothiazolo[4',5';4,5]thieno[3,2-*d*]pyrimidine **3**. - A mixture of thiazolo[4',5';4,5]thieno[3,2-*d*]pyrimidin-5(6*H*)-one **31** (0.3 g, 1.44 mmol) and phosphoryl chloride (10 cm^3, large excess) was heated under reflux for 3 h, then cooled to ambient temperature and poured into iced-water (50 cm^3). The precipitate was filtered off and crystallised from ethanol to give the 5-chloro-derivative **3** (0.20 g, 62%).

Compound **8** was prepared similarly.

5-Aminothiazolo[4',5';4,5]thieno[3,2-*d*]pyrimidines: General Procedure.[18] - A mixture of 5-chlorothiazolo[4',5';4,5]thieno[3,2-*d*]pyrimidine **3** (0.5 g, 2.2 mmol), benzylamine (0.3 g, 2.8 mmol), and triethylamine (0.5 cm^3) in *n*-butanol (15 cm^3) was heated under reflux for 3 h, then cooled to ambient temperature and the solvent distilled off under reduced pressure. The pale yellow crystals obtained were crystallised from ethanol to give 5-benzylaminothiazolo[4',5';4,5]thieno[3,2-*d*]pyrimidine **5** (0.42 g, 64%).

Compounds **6**, **7** (using a 33% aqueous solution of Me_2NH; Et_3N excluded) **10**, **11**, and **12** (using a 33% aqueous solution of Me_2NH; Et_3N excluded) were prepared similarly.

5-Aminothiazolo[4',5';4,5]thieno[3,2-*d*]pyrimidine **4**. - Gaseous ammonia was bubbled through a solution of 5-chlorothiazolo[4',5';4,5]thieno[3,2-*d*]pyrimidine **3** (0.5 g, 2.2 mmol) in *n*-butanol (20 cm^3) for 3 h at ambient temperature, then the reaction mixture was heated under reflux for 3 h. Distillation of the solvent and crystallisation of the residue from ethanol gave the 5-amino-compound **4** (0.30 g, 65%).

5-Amino-2-methylthiothiazolo[4',5';4,5]thieno[3,2-*d*]pyrimidine **9** was prepared similarly.

Thiazolo[4',5';4,5]thieno[3,2-*d*]pyrimidine **2**. - A mixture of 5-chlorothiazolo[4',5';4,5]thieno-[3,2-*d*]pyrimidine **3** (0.5 g, 2.2 mmol), ammonium formate (0.55 g, 8.7 mmol), and 10% palladium-charcoal (50 mg) in methanol (15 cm^3) was heated under reflux for 5 h, then cooled and filtered. Distillation of the solvent from the filtrate under reduced pressure gave the crude product which was crystallised from ethanol, to give thiazolo[4',5';4,5]thieno[3,2-*d*]pyrimidine **2** (0.15 g, 35%).

Attempted Synthesis of 4-Chloro-5-cyanothiazol-2(3*H*)-thione **37**. - A mixture of 4-chloro-5-cyano-thiazol-2(3*H*)-one **36** (0.2 g, 1.25 mmol), phosphorus pentasulfide (0.36 g, 1.62 mmol), and pyridine (10 cm^3) was heated under reflux for 13 h, then the mixture was poured into hot water (20 cm^3). The precipitate which formed was filtered off and identified by m.p., TLC and IR spectroscopy as starting material (0.15 g, 75% recovery).

Thieno[2,3-*d*]thiazole-5-carboxamide **38**. - 2-Mercaptoacetamide (0.25 g, 2.78 mmol) was added portionwise to a stirred solution of sodium ethoxide [prepared by addition of sodium (0.06 g, 2.75 mmol) to ethanol (10 cm^3)] in ethanol at ambient temperature followed by a solution of 4-chlorothiazole-5-carbaldehyde **13** (0.4 g, 2.78 mmol) in ethanol (10 cm^3) and the resulting mixture was stirred overnight at ambient temperature, then heated under reflux for 4 h. Distillation of the solvent under reduced pressure, addition of water (20 cm^3) to the residue, and extraction with ethyl acetate (5 x 100 cm^3) gave thieno[2,3-*d*]thiazole-5-carboxamide **38** as colourless crystals (0.3 g, 60%).

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