Heterocyclic Studies. Part 43.[1] Thieno[2,3-*d*:4,5-*d'*]dipyrimidines

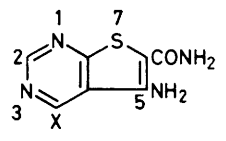
Jim Clark and George Hitiris*
The Ramage Laboratories, Department of Chemistry and Applied Chemistry, University of Salford, Salford M5 4WT

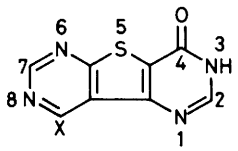
5-Aminothieno[2,3-*d*]pyrimidine-6-carboxamides or -6-carboxylic esters have been converted into thieno[2,3-*d*:4,5-*d'*]dipyrimidines with the reagents formamide, triethyl orthoformate, urea, methyl isothiocyanate, phenyl isocyanate, and guanidine.

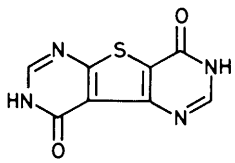
A 5-aminothieno[2,3-*d*]pyrimidine-6-carboxamide gave, on treatment with nitrous acid, the first pyrimido[5',4'-4,5]thieno[3,2-*d*]-1,2,3-triazine.

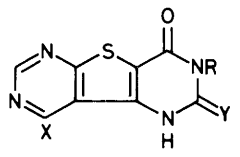
Many compounds containing the thienopyrimidine ring system have interesting pharmacological properties. Biological activity is exhibited by the simple thienopyrimidine system (see, for example, refs. 2—8) and by tri- and tetra-cyclic compounds containing a thienopyrimidine system (see, for example, refs. 9—11). This paper describes syntheses of a number of thienodipyrimidines, the work on which was prompted by a report that some compounds of this type had central nervous system activity and low toxicity.[1,2]

The readily prepared 5-amino-4-carbamoylmethylthiothieno[2,3-*d*]pyrimidine-6-carboxamide (**1**; X = SCH_2CONH_2)[13] was initially used as the starting material since it has suitable substituents for building on a second pyrimidine ring. Using the compound directly gave disappointing results because the carbamoylmethylthio group was too labile and the vigorous conditions needed to synthesize the pyrimidine system led to serious side-reactions. Several other thienopyrimidines (**1**; X = OMe, NHMe, or NMe_2), made from the carbamoylmethylthio compound were examined as alternatives. The 4-methoxy derivative reacted with formamide to give a mixture of the dione (**3**) and the desired product (**2**; X = OMe) but with triethyl orthoformate and acetic anhydride both the methoxy and dimethylamino compounds (**1**; X = OMe or NMe_2) gave good yields of thienodipyrimidinones (**2**; X = OMe or NMe_2).

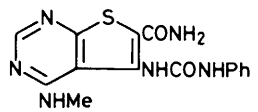

(1)

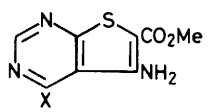

(2)

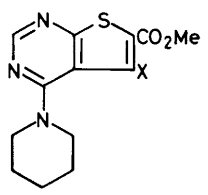

(3)

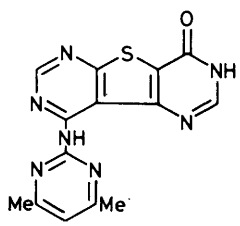

(4)

The 4-methylamino derivative (**1**; X = NHMe) reacted with triethyl orthoformate–acetic anhydride to yield the expected thienodipyrimidinone (**2**; X = NHMe), with urea to give the thienodipyrimidinedione (**4**; R = H, X = NHMe, Y = O), and with methyl isothiocyanate to yield the thione (**4**; R = Me, X = NHMe, Y = S). Reaction of the same thienopyrimidine (**1**; X = NHMe) with phenyl isocyanate took an unexpected course and gave the dione (**4**; R = H, X = NHMe, Y = O) rather than the *N*-phenyl derivative (**4**; R = Ph, X = NHMe, Y = O). Presumably the intermediate (**5**) cyclised with loss of aniline rather than ammonia although similar reactions had previously given *N*-phenyl compounds.[14]


(5)


(6)


(7)


(8)

As alternatives to the rather disappointing carbamoyl compounds, some esters (**6**) were prepared as intermediates for thienodipyrimidine syntheses. Methyl 5-amino-4-(methoxycarbonylmethylthio)thieno[2,3-*d*]pyrimidine-6-carboxylate (**6**; X = SCH_2CO_2Me), prepared by condensing 4,6-dichloropyrimidine-5-carbonitrile with methyl thioglycolate,[13] reacted with alkyl- or aryl-amines to yield the corresponding 4-substituted-amino derivatives (**6**; X = NHMe, NHPh, NHC_6H_4Cl-*p*, or NHC_6H_4Me-*p*). These amino compounds reacted with formamide to yield the corresponding thienodipyrimidines (**2**). Curiously, the tertiary amines (**6**; X = NMe_2, piperidino, or morpholino), also prepared from the methoxycarbonylmethylthio compound (**6**; X = SCH_2CO_2Me) and appropriate amines, all gave the primary amino compound (**2**; X = NH_2) on treatment with formamide. Presumably ammonia produced by decomposition of formamide displaced the 4-substituent in each case.

Treatment of the amino ester (**6**; X = piperidino) with trifluoroacetic anhydride gave the trifluoroacetylamino compound (**7**; X = $NHCOCF_3$) and also the bis(trifluoroacetyl)-amino derivative [**7**; X = $N(COCF_3)_2$] which readily lost one acetyl group on recrystallisation. The trifluoroacetylamino compound could not be cyclised to a thienodipyrimidine by heating with 14M-methanolic ammonia under pressure.

The methoxycarbonylmethylthio compound (**6**; X = SCH_2CO_2Me) and its piperidino analogue again showed the remarkable reactivity of certain substituents at the 4-position of such compounds, by reacting with guanidine to give the 4-

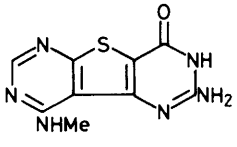
Table.

Compound	Solvent	^{1}H N.m.r. [a]	Assignment	Infrared (cm^{-1})
(**2**; X = NHMe)	CF_3CO_2D	3.55 s(3 H)	$NHCH_3$	3 360, 3 330 (NH);
		8.65 s(1 H)	2-H	1 675 (CO)
		8.9 s(1 H)	7-H	
(**4**; R = H, X = NHMe, Y = O)	CF_3CO_2D	3.63 s(3 H)	$NHCH_3$	3 440 (NH);
		8.84 s(1 H)	7-H	1 740 and 1 680 (CO)
(**4**; R = Me, X = NHMe, Y = S)	CF_3CO_2D	2.45 s(3 H)	N-CH_3	3 340 (NH) (br);
		3.52 s(3 H)	$NHCH_3$	1 670 (CO)
		8.84 s(1 H)	7-H	
(**10**)	CF_3CO_2D	3.6 s(3 H)	$NHCH_3$	3 330 (NH);
		8.96 s(1 H)	7-H	1 660 (CO)
(**6**; X = NHC_6H_4Cl-*p*)	CF_3CO_2D	3.96 s(3 H)	CO_2CH_3	3 330 (NH);
		7.35—7.65 m(4 H)	Ph	1 712 (CO)
		8.61 s(1 H)	2-H	
(**2**; X = NHPh)	CF_3CO_2D	7.64 s(5 H)	Ph	3 330 (NH);
		8.72 s(1 H)	2-H	1 680 (CO)
		8.83 s(1 H)	7-H	
(**2**; X = NMe_2)	$(CD_3)_2SO$	3.32 s(6 H)	$N(CH_3)_2$	1 660 (CO)
		8.34 s(1 H)	2,7-H	
		8.5 s(1 H)	2,7-H	
(**6**; X = 4,6-dimethylpyrimidin-2-ylamino)	$(CD_3)_2SO$	2.45—2.5 m(6 H)	$C_4HN_2(CH_3)_2$	3 500, 3 280 (NH);
		3.8 s(3 H)	CO_2CH_3	1 690 (CO)
		6.9 s(1 H)	$C_4HN_2(CH_3)_2$	
		7.7 s(1 H)	NH	
		8.46 s(1 H)	2-H	
(**9**)	CF_3CO_2D	3.5 s(3 H)	$NHCH_3$	3 350, 3 400 (NH);
		8.84 s(1 H)	7-H	1 690 (CO)

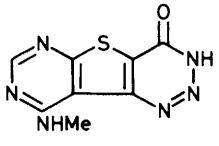
[a] Signals are given in the form: chemical shift (δ), multiplicity (s = singlet, m = multiplet), and number of protons.

guanidino derivative [**6**; X = $NHC(NH_2)$:NH], rather than the expected 6-guanidinocarbonyl derivatives. The alkylamino compound, (**6**; X = NHMe), again behaved differently from the dialkylamino derivative by condensing with guanidine at the ester group to give a 6-guanidinocarbonyl compound, which cyclised in boiling acetic acid to produce the 2-aminothienodipyrimidinone (**9**). The 4-guanidino compound [**6**; X = $NHC(NH_2)$:NH] reacted with acetylacetone to produce the 4-(4,6-dimethylpyrimidin-2-ylamino) derivative which, in turn, was condensed with formamide to give the appropriate pyrimidinylaminothienodipyrimidine (**8**).

A single example of a new heterocyclic system was made by treating the carboxamide (**1**; X = NHMe) with nitrous acid at low temperature to produce the thienopyrimidotriazine (**10**).



(**9**)



(**10**)

Experimental

^{1}H N.m.r. spectra were measured on a Perkin-Elmer R32 spectrometer at normal probe temperature, unless otherwise specified, using tetramethylsilane as internal standard. Infrared spectra were recorded as Nujol mulls using a Perkin-Elmer 297 spectrometer. Spectroscopic details for some of the compounds are given in the Table. Mass spectra were recorded on an AEI MS 902S instrument, using an ionising energy of 70 eV and introduction by direct insertion probe. Microanalyses were performed by Butterworth Laboratories Ltd.

9-*Methoxythieno*[2,3-d:4,5-d′]*dipyrimidin*-4(3H)-*one* (**2**; X = OMe).—5-Amino-4-methoxythieno[2,3-*d*]pyrimidine-6-carboxamide (**1**; X = OMe) (20.4 g) was stirred under reflux for 3 h in a 1:1 mixture of triethyl orthoformate and acetic anhydride (212 ml). The reaction mixture was then allowed to cool to room temperature and the precipitated solid was filtered off and washed with water and methanol. The filtrate was evaporated and the remaining solid was washed with water and methanol, dried by suction, and re-treated with a 1:1 mixture of triethyl orthoformate and acetic anhydride (60 ml), as described above, to give a further crop of product. The combined solids constituted the *title compound* (19.2 g, 90%), m.p. 287—290 °C (from aqueous dimethyl sulphoxide) [Found: C, 45.9; H, 2.75; N, 23.7%; M^+ (mass spectrum), 234. $C_9H_6N_4O_2S$ requires C, 46.15; H, 2.6; N, 23.9%; *M*, 234].

9-*Methylaminothieno*[2,3-d:4,5-d′]*dipyrimidine*-4(3H)-*one* (**2**; X = NHMe).—(a) 5-Amino-4-methylaminothieno[2,3-*d*]-pyrimidine-6-carboxamide (**1**; X = NHMe) (2.02 g) was heated under reflux in a 1:1 mixture of triethyl orthoformate and acetic anhydride (60 ml) for 20 h. The volume of the reaction mixture was reduced, under reduced pressure by 20 ml and the remaining solution was kept overnight. The precipitated solid was filtered off to give the *title compound* (1.2 g, 57%), m.p. > 350 °C (from aqueous methanol) [Found: C, 46.6; H, 3.0; N, 29.8%; M^+ (mass spectrum), 233. $C_9H_7N_5OS$ requires C, 46.3; H, 3.0; N, 30.0%; *M*, 233].

(b) A mixture of methyl 5-amino-4-methylaminothieno[2,3-*d*]pyrimidine-6-carboxylate (**6**; X = NHMe) (1.0 g) and formamide (15 ml) was stirred at 155 °C for 5 h. The precipitated solid was filtered off, washed with water, and dried to yield a product (0.7 g, 71%), m.p. > 350 °C, identical with that from method (a).

9-*Methylaminothieno*[2,3-d:4,5-d′]*dipyrimidine*-2,4(1H,3H)-*dione* (**4**; R = H, X = NHMe, Y = O).—(a) A mixture of urea, 5-amino-4-methylaminothieno[2,3-*d*]pyrimidine-6-carboxamide (**1**; X = NHMe) (1.0 g), and 3-methylpyridine (15 ml) was stirred at 145 °C for 30 h and then cooled. The precipitated

solid was filtered off and washed with water and methanol to give the *title compound* (0.15 g, 13%), m.p. > 360 °C (from aqueous dimethyl sulphoxide) [Found: C, 43.2; H, 2.9; N, 28.1%; M^+ (mass spectrum), 249. $C_9H_7N_5O_2S$ requires C, 43.4; H, 2.8; N, 28.1%; *M*, 249].

(b) 5-Amino-4-methylaminothieno[2,3-*d*]pyrimidine-6-carboxamide (**1**; X = NHMe) (0.5 g) was stirred with phenyl isocyanate (7 ml) at 130 °C for 3 days. The cooled mixture was filtered and the solid so collected was washed with water and boiling methanol to give a product (0.26 g, 58%), m.p. > 360 °C, identical with that from method (a).

3-*Methyl*-9-*methylamino*-2-*thioxo*-1,2-*dihydrothieno*[2,3-d:4,5-d']*dipyrimidine*-4(3H)-*one* (**4**; R = Me, X = NHMe, Y = S).—5-Amino-4-methylaminothieno[2,3-*d*]pyrimidine-6-carboxamide (**1**; X = NHMe) (1.8 g) was dissolved in pyridine (30 ml). Methyl isothiocyanate (1.8 g) was addded and the mixture was heated under reflux for 3 days. It was kept at room temperature overnight and the precipitated solid was filtered off, washed with water and methanol, and dried. Water was added to the filtrate and the mixture was cooled in ice for 12 h. The new precipitate was filtered off, washed, dried, and the two solids were combined to give the *title compound* (1.8 g, 80%), m.p. 266—268 °C (from aqueous dimethyl sulphoxide) [Found: C, 42.8; H, 3.5; N, 24.8%; M^+ (mass spectrum), 279. $C_{10}H_9N_5OS_2$ requires C, 43.0; H, 3.25; N, 25.1%; *M*, 279].

5-*Amino*-4-*dimethylaminothieno*[2,3-d]*pyrimidine*-6-*carboxamide* (**1**; X = NMe_2).—5-Amino-4-carbamoylmethylthiothieno[2,3-*d*]pyrimidine-6-carboxamide (**1**; X = SCH_2CONH_2) (14.3 g) was stirred in methanol (200 ml). A 26% solution of dimethylamine in water (80 ml) was added with stirring, the mixture was heated under reflux for 2 h and then kept in ice overnight. The precipitated solid was filtered off, washed with water, and dried to give the *title compound* (9.76 g, 81%), m.p. 189—192 °C (from water) [Found: C, 45.5; H, 4.55; N, 29.6%; M^+ (mass spectrum), 237. $C_9H_{11}N_5OS$ requires C, 45.6; H, 4.7; N, 29.5%; *M*, 237].

9-*Dimethylaminothieno*[2,3-d:4,5-d']*dipyrimidine*-4(3H)-*one* (**2**; X = NMe_2).—5-Amino-4-dimethylaminothieno[2,3-*d*]pyrimidine-6-carboxamide (**1**; X = NMe_2) (7.9 g) was heated under reflux in a 1:1 mixture of triethyl orthoformate and acetic anhydride (200 ml) for 2 h. The solution was evaporated until its volume was reduced by 50 ml and then refrigerated overnight. The precipitated solid was filtered off, washed with water and a small amount of cold methanol, and dried by suction to give the *title compound* (4.8 g, 58%), m.p. 296—299 °C (from aqueous dimethyl sulphoxide) [Found: C, 45.5; H, 3.65; N, 26.2%; M^+ (mass spectrum), 247. $C_{10}H_9N_5OS{\cdot}H_2O$ requires C, 45.3; H, 4.2; N, 26.4%; *M*, 247].

Methyl 5-*Amino*-4-*anilinothieno*[2,3-d]*pyrimidine*-6-*carboxylate* (**6**; X = NHPh).—Methyl 5-amino-4-(methoxycarbonylmethylthio)thieno[2,3-*d*]pyrimidine-6-carboxylate (**6**; X = SCH_2CO_2Me) (2.65 g) was stirred in aniline (10 ml) at 80 °C for 3 h. The precipitated solid was filtered off, washed with water, and dried to give the *title compound* (1.95 g, 77%), m.p. 159—160 °C (from methanol) (Found: C, 55.8; H, 4.1; N, 18.6. $C_{14}H_{12}N_4O_2S$ requires C, 56.0; H, 4.0; N, 18.6%).

Methyl 5-*Amino*-4-(p-*chloroanilino*)*thieno*[2,3-d]*pyrimidine*-6-*carboxylate* (**6**; X = NHC_6H_4Cl-p).—Methyl 5-amino-4-(methoxycarbonylmethylthio)thieno[2,3-*d*]pyrimidine-6-carboxylate (**6**; X = SCH_2CO_2Me) (1.0 g) was added to a solution of *p*-chloroaniline (4.0 g) in ethanol (15 ml), and the mixture was heated under reflux for 5 h. It was cooled to room temperature and the precipitated solid was washed with 0.5M-hydrochloric acid, water, and a small amount of cold methanol to give the *title compound* (0.9 g, 84%), m.p. 162—163 °C (from methanol) [Found: C, 50.1; H, 3.4; N, 16.9%; M^+ (mass spectrum), 334. $C_{14}H_{11}ClN_4O_2S$ requires C, 50.2; H, 3.3; N, 16.7%; *M*, 334].

Methyl 5-*Amino*-4-(p-*toluidino*)*thieno*[2,3-d]*pyrimidine*-6-*carboxylate* (**6**; X = NHC_6H_4Me-p).—Methyl 5-amino-4-(methoxycarbonylmethylthio)thieno[2,3-*d*]-pyrimidine-6-carboxylate (**6**; X = SCH_2CO_2Me) (2.0 g) was added to a solution of *p*-toluidine (6.8 g) in methanol (20 ml). The mixture was heated under reflux for 2 h and treated as its *p*-chloroanilino homologue above to give the *title compound* (1.75 g, 87%), m.p. 163—164 °C (from methanol) [Found: C, 57.2; H, 4.4; N, 18.0%; M^+ (mass spectrum), 314. $C_{15}H_{14}N_4O_2S$ requires C, 57.3; H, 4.5; N, 17.8%; *M*, 314].

9-*Anilinothieno*[2,3-d:4,5-d']*dipyrimidine*-4(3H)-*one* (**2**; X = NHPh).—Methyl 5-amino-4-anilinothieno[2,3-*d*]pyrimidine-6-carboxylate (**6**; X = NHPh) (0.6 g) was stirred in formamide (10 ml) at 160 °C for 4 h. The reaction mixture was cooled to room temperature and the precipitated solid was filtered off and washed with water and methanol to give the *title compound* (0.45 g, 76%), m.p. > 330 °C (from aqueous dimethylformamide) (Found: C, 56.9; H, 3.2; N, 23.7. $C_{14}H_9N_5OS$ requires C, 56.9; H, 3.1; N, 23.7%).

9-(*p*-*Chloroanilino*)*thieno*[2,3-d:4,5-d']*dipyrimidine*-4(3H)-*one* (**2**; X = NHC_6H_4Cl-p).—Methyl 5-amino-4-(*p*-chloroanilino)thieno[2,3-*d*]pyrimidine-6-carboxylate (**6**; X = NHC_6H_4Cl-*p*) (0.35 g) was stirred in formamide (6 ml) at 175 °C for 6 h. The mixture was treated as its 9-anilino homologue above to give the *title compound* (0.3 g, 87%), m.p. 350 °C (decomp) (from acetic acid) (Found: C, 50.8; H, 2.4; N, 21.4. $C_{14}H_8ClN_5OS$ requries C, 51.0; H, 2.45; N, 21.2%).

9-(p-*Toluidino*)*thieno*[2,3-d:4,5-d']*dipyrimidine*-4(3H)-*one* (**2**; X = NHC_6H_4Me-p).—Methyl 5-amino-4-(*p*-toluidino)-thieno[2,3-*d*]pyrimidine-6-carboxylate (**6**; X = NHC_6H_4Me-p) (0.95 g) was stirred in formamide (15 ml) at 150 °C for 24 h. The mixture was treated as its 9-anilino homologue to give the *title compound* (0.77 g, 82%), m.p. 323 °C (decomp.) (from methanol) (Found: C, 58.2; H, 3.6; N, 22.5. $C_{15}H_{11}N_5OS$ requires C, 58.2; H, 3.6; N, 22.6%).

Methyl 5-*Amino*-4-*dimethylaminothieno*[2,3-d]*pyrimidine*-6-*carboxylate* (**6**; X = NMe_2).—A 26% solution of dimethylamine in water (17 ml) was added to a solution of methyl 5-amino-4-(methoxycarbonylmethylthio)thieno[2,3-*d*]pyrimidine-6-carboxylate (**6**; X = SCH_2CO_2Me) (2 g) in methanol (10 ml), and the mixture was refluxed for 1 h. It was allowed to cool to room temperature and the precipitated solid was filtered off and washed with water and cold methanol to give the *title compound* (0.8 g, 50%), m.p. 194—197 °C (from aqueous ethanol) [Found: C, 47.3; H, 4.9; N, 21.6%; M^+ (mass spectrum), 252. $C_{10}H_{12}N_4O_2S$ requires C, 47.6; H, 4.8; N, 22.2%; *M*, 252].

Methyl 5-*Amino*-4-*morpholinothieno*[2,3-d]*pyrimidine*-6-*carboxylate* (**6**; X = *morpholino*).—Morpholine (12 ml) was added to a solution of methyl 5-amino-4-(methoxycarbonylmethylthio)thieno[2,3-*d*]pyrimidine-6-carboxylate (**6**; X = SCH_2CO_2Me) (2.04 g) in methanol (20 ml), and the mixture was heated under reflux for 3 h. Water (*ca.* 20 ml) was added dropwise and the mixture was kept at room temperature overnight. The separated solid was filtered off and washed with water and dried to give the *title compound* (1.36 g, 72%), m.p. 202—203 °C (from methanol) [Found: C, 49.2; H, 4.7; N, 19.1%;

M^+ (mass spectrum), 294. $C_{12}H_{14}N_4O_3S$ requires C, 49.0; H, 4.8; N, 19.0%; *M*, 294].

9-*Aminothieno*[2,3-d:4,5-d′]*dipyrimidine*-4(3H)-*one* (**2**; X = NH_2).—(a) Methyl 5-amino-4-piperidinothieno[2,3-*d*]pyrimidine-6-carboxylate (**6**; X = piperidino) (0.5 g) was stirred in formamide (10 ml) at 160 °C for 10 h. The precipitated solid was filtered off and washed with water and methanol to give the *title compound* (0.1 g, 27%), m.p. > 360 °C (from dimethyl sulphoxide) [Found: C, 43.6; H, 2.3; N, 31.7%; M^+ (mass spectrum), 219. $C_8H_5N_5OS$ requires C, 43.8; H, 2.3; N, 31.9%; *M*, 219].

(b) A similar experiment, in which methyl 5-amino-4-morpholinothieno[2,3-*d*]pyrimidine-6-carboxylate (**6**; X = morpholino) (0.5 g) was stirred in formamide (10 ml) at 140 °C for 24 h, afforded a product (0.2 g, 54%), identical with that obtained by method (a).

(c) A similar experiment but with methyl 5-amino-4-dimethylaminothieno[2,3-*d*]pyrimidine-6-carboxylate (**6**; X = NMe_2) also gave the same product.

Methyl 4-*Piperidino*-5-(*trifluoroacetylamino*)*thieno*[2,3-d]*pyrimidine*-6-*carboxylate* (**7**; X = $NHCOCF_3$).—Methyl 5-amino-4-piperidinothieno[2,3-*d*]pyrimidine-6-carboxylate (**6**; X = piperidino) (0.9 g) was heated under reflux in trifluoroacetic anhydride (8 ml) for 1 h. The reaction mixture was cooled to room temperature and the precipitated solid was filtered off and washed with water to give the *title compound* (1.2 g, 100%), m.p. 161—163 °C (from aqueous methanol) [Found: C, 46.6; H, 4.0; N, 14.6%; M^+ (mass spectrum), 388. $C_{15}H_{15}F_3N_4O_3S$ requires C, 46.4; H, 3.9; N, 14.4%; *M*, 388].

Methyl 5-*Amino*-4-*guanidinothieno*[2,3-d]*pyrimidine*-6-*carboxylate* [**6**; X = $NHC(NH_2):NH$].—Guanidine hydrochloride (2.0 g) was stirred with a solution of sodium (0.48 g) in methanol (40 ml) for 10 min. The precipitated salt was filtered off and methyl 5-amino-4-(methoxycarbonylmethylthio)thieno-[2,3-*d*]pyrimidine-6-carboxylate (**6**; X = SCH_2CO_2Me) (5.2 g) was added to the filtrate. The mixture was stirred for 2 h at 50 °C, then for 16 h at room temperature. The separated solid was filtered off and washed with water to give the *title compound* (4.38 g, 99%), m.p. 260 °C (decomp.) (from methanol) (Found: C, 40.8; H, 3.9; N, 31.3. $C_9H_{10}N_6O_2S$ requires C, 40.6; H, 3.9; N, 31.6%).

Methyl 5-*Amino*-4-(4,6-*dimethylpyrimidin*-2-*ylamino*)*thieno*-[2,3-d]*pyrimidine*-6-*carboxylate* (**6**; X = 4,6-*dimethylpyrimidin*-2-*ylamino*).—Methyl 5-amino-4-guanidinothieno[2,3-*d*]pyrimidine-6-carboxylate [**6**; X = $NHC(NH_2):NH$] (0.6 g) was heated in acetylacetone (10 ml) under reflux for 4 h, and kept for 24 h before the yellow precipitate was filtered off and washed with water and methanol to give the *title compound* (0.55 g, 74%), m.p. 276 °C (decomp.) (from glacial acetic acid) [Found: C, 50.9; H, 4.4; N, 25.4; M^+ (mass spectrum), 330. $C_{14}H_{14}N_6O_2S$ requires C, 50.9; H, 4.3; N, 25.4%; *M*, 330].

9-(4,6-*Dimethylpyrimidin*-2-*ylamino*)*thieno*[2,3-d:4,5-d′]-*dipyrimidin*-4(3H)-*one* (**8**).—Methyl 5-amino-4-(4,6-dimethylpyrimidin-2-ylamino)thieno[2,3-*d*]pyrimidine-6-carboxylate (**6**; X = 4,6-dimethylpyrimidin-2-ylamino) (0.3 g) was heated under reflux with formamide (5 ml) for 8 h. The reaction mixture was cooled and the precipitated solid was filtered off and washed with water and methanol to give the *title compound* (0.12 g, 40%), m.p. > 350 °C (from aqueous dimethyl sulphoxide) [Found: M^+ (mass spectrum), 325.0729. $C_{14}H_{11}N_7OS$ requires *M*, 325.0745].

5-*Amino*-6-*guanidinocarbonyl*-4-*methylaminothieno*[2,3-d]-*pyrimidine*.—Guanidine hydrochloride (0.8 g) was added to a 1M solution of sodium methoxide in methanol (30 ml) and stirred for 30 min. It was then filtered from the precipitated salt and to the filtrate methyl 5-amino-4-methylaminothieno[2,3-*d*]pyrimidine-6-carboxylate (**6**; X = NHMe) (2 g) was added. The mixture was heated under reflux for 20 h and treated as its dimethylpyrimidinylamino homologue above to give the *title compound* (1.55 g, 74%), m.p. 260 °C (decomp.) after reprecipitation from an alkaline solution with acetic acid [Found: C, 40.9; H, 3.9; N, 36.7%; M^+ (mass spectrum), 265. $C_9H_{11}N_7OS$ requires C, 40.75; H, 4.2; N, 37.0%; *M*, 265].

2-*Amino*-9-*methylaminothieno*[2,3-d:4,5-d′]*dipyrimidin*-4(3H)-*one* (**9**).—A solution of 5-amino-6-guanidinocarbonyl-4-methylaminothieno[2,3-*d*]pyrimidine (2 g) in glacial acetic acid (40 ml) was heated at 140 °C under reflux for 6 h. The precipitated solid was filtered off and washed with water and methanol to give the *title compound* (1.2 g, 64%), m.p. > 350 °C after reprecipitation from an acidic solution with 4M-sodium hydroxide [Found: C, 43.7; H, 3.4; N, 33.4%; M^+ (mass spectrum), 248. $C_9H_8N_6OS$ requires C, 43.5; H, 3.2; N, 33.8%; *M*, 248].

9-*Methylaminopyrimido*[5′,4′-4,5]*thieno*[3,2-d]-1,2,3-*triazine*-4(3H)-*one* (**10**).—5-Amino-4-methylaminothieno[2,3-*d*]-pyrimidine-6-carboxamide (**1**; X = NHMe) (0.3 g) was dissolved in warm 3M-hydrochloric acid. The solution was cooled in ice and a solution of sodium nitrite (0.35 g) in water (1 ml) was added dropwise with stirring, while the temperature of the mixture was maintained at 0 °C. The mixture was stirred for 10 min more and the precipitated solid was filtered off and washed with water and methanol to give the *title compound* (0.25 g, 79%), m.p. 253 °C (decomp.) (from aqueous dimethyl sulphoxide) [Found: C, 40.9; H, 2.7; N, 35.65%; M^+ (mass spectrum), 234. $C_8H_6N_6OS$ requires C, 41.0; H, 2.6; N, 35.9%; *M*, 234].

References

1 Part 42, J. Clark and G. Varvounis, *J. Chem. Soc., Perkin Trans. 1*, 1984, 1475.
2 D. L. Temple, Jr., *U.S.P.* 4,054,656, 18th October, 1977.
3 V. Darvias, M. P. Fernandez-Tome, R. Madronero, J. Del Rio, and A. Vila-Coro, *Chim. Ther.*, 1972, **7**, 224 (*Chem. Abstr.*, 1972, **77**, 139960w).
4 F. Sauter, *Ger. Offen.* 2,104,435, 26th August 1971.
5 A. Rosowski, M. Chaykowski, K. K. N. Chen, M. Lin, and E. J. Modest, *J. Med. Chem.*, 1973, **16**, 185.
6 A. Rosowski, K. K. N. Chen, and M. Lin, *J. Med. Chem.*, 1973, **16**, 192.
7 V. J. Ram, *Arch. Pharm.*, 1979, **312**, 19.
8 F. Sauter, *Fr. Demande* 2,128,348, 23rd February 1972; 2,166,363, 17th August 1973.
9 P. Schmidt, E. Eichenberger, and E. Schweizer, *Ger. Offen.* 1,908,497, 18th September 1969; 2,060,968, 24th June 1971.
10 P. Blaszkiewitz, H. Vorbrüggen, and H. J. Kessler, *Ger. Offen.* 2,411,274, 18th September 1975.
11 I. Wellings, *U.S.P.* 3,681,351, 1st August 1972.
12 A. A. Santilli and D. H. Kim, *U.S.P.* 3,635,965, 18th January 1972.
13 M. S. Shahhet, Ph.D. Thesis, University of Salford, 1976.
14 F. Sauter and W. Deinhammer, *Monatsh. Chem.*, 1973, **104**, 1593; S. M. Khripak, A. A. Dobosh, and N. Smolanka, *Khim. Geterotsikl. Soedin., Engl. Edn.*, 1973, **9**, 525.

Received 18*th November* 1983; *Paper* 3/2058