Heterocyclic Studies. Part 42.[1] Pyrimido[5,4-*d*][1,2,3]triazines and some Related Tricyclic Compounds

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Nitrous acid treatment of 2,4-disubstituted 6-methyl-5-nitropyrimidines gave the corresponding pyrimido[5,4-*d*][1,2,3]triazine 3-oxides. The latter reacted with thionyl chloride to give 4-chloro derivatives which were then converted into other 4-substituted pyrimidotriazines, two of which were further converted into the novel heterocyclic systems, imidazo- and pyrimido-[1′,2′-*c*]pyrimido[4,5-*e*]-[1,2,3]triazine.

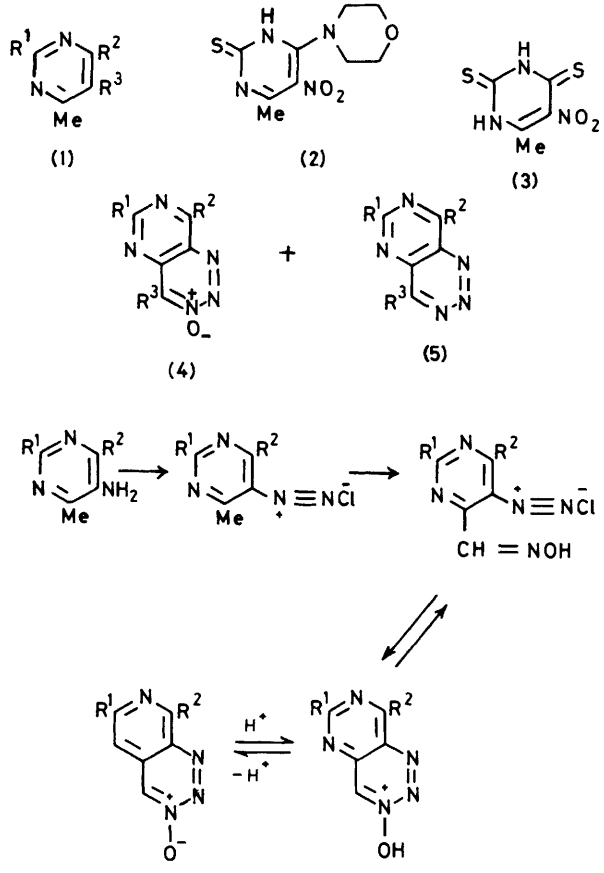
Measurements of ^{1}H n.m.r. spectra included variable temperature studies of some bis(dimethylamino) compounds. These showed that the extent to which a dimethylamino group is conjugated with the heterocyclic system, and the energy barrier to its rotation, vary substantially with its position in the pyrimidotriazine system.

There was a wave of interest in pyrimido[5,4-*d*][1,2,3]triazines during the early 1960s when a number of reports on their synthesis and biological activity appeared.[2–7] The publications included reports of anti-inflammatory, antibacterial, cardiovascular, and spasmolytic activity in compounds of this class. Since then little work on this type of compound has been reported and relatively little is known of their chemistry.

Recently a colleague of ours synthesised a few pyrimido-[5,4-*d*][1,2,3]triazines,[8] but we now report the synthesis of a substantial number of such compounds and related pyrimido[5,4-*d*][1,2,3]triazine 3-oxides. Some novel heterocyclic systems containing an extra ring fused to the pyrimidotriazine unit are also described. The twin objects of this work were to produce pharmacologically active compounds and to extend our knowledge of the chemistry of the pyrimido[5,4-*d*][1,2,3]-triazine system.

The established route to pyrimido[5,4-*d*][1,2,3]triazines is by diazotisation of 5-amino-4(6)-methylpyrimidines.[2–4,7,8] Compounds of the latter type were now synthesised from 2,4-dichloro-6-methyl-5-nitropyrimidine (**1**; $R^1 = R^2 = Cl$, $R^3 = NO_2$), the chlorine atoms of which were replaced by two similar or two different substituents. Stepwise replacement always involved the 4-chlorine atom first. Introduction of a substituted amino group required treatment with two equivalents of the appropriate amine per chlorine to be replaced. Thione groups were introduced by treatment of the appropriate mono- or di-chloro compound with sodium sulphide nonahydrate or sodium hydrogen sulphide, while methylthio compounds were obtained by treating the resulting mono- or di-thione (**2**) or (**3**) with methyl iodide and base. The resulting pyrimidines (**1**; $R^3 = NO_2$), some of which had been described previously, were reduced catalytically to 5-amino compounds (**1**; $R^3 = NH_2$) which were used for the next stage without purification. This stepwise procedure gave a much better yield of 5-amino-2,4-bis(methylthio)-6-methylpyrimidine (**1**; $R^1 = R^2 = SMe$, $R^3 = NH_2$) than the published method.[9]

Diazotisation of the 5-amino compounds (**1**; $R^3 = NH_2$) with isopentyl nitrite in ethanolic hydrogen chloride, with the exclusion of light, gave moderate yields of the corresponding 6,8-disubstituted pyrimido[5,4-*d*][1,2,3]triazine 3-oxides (**4**; $R^3 = H$). That cyclisation had taken place was indicated by the disappearance of the 6-methyl signal in the ^{1}H n.m.r. spectrum of each compound and its replacement by a characteristic one proton signal at about δ 8.5. The mechanism of cyclisation probably involves initial diazotisation of the 5-amino group,



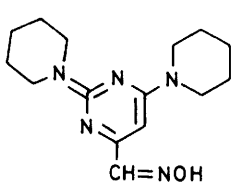
Scheme.

nitrosation of the adjacent methyl group, now strongly activated by the diazonium group, and then cyclisation to a protonated version of the *N*-oxide (Scheme). In agreement with this scheme, 5-amino-2,4-bis(dimethylamino)-6-ethylpyrimidine reacted to give a 4-methylpyrimidotriazine 3-oxide (**4**; $R^1 = R^2 = NMe_2$, $R^3 = Me$).

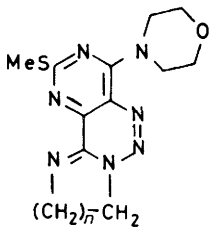
The ^{1}H n.m.r. spectra of the two 6,8-bis(dimethylamino)-pyrimidotriazine 3-oxides (**4**; $R^1 = R^2 = NMe_2$, $R^3 = H$ or Me) and those of two 4-substituted 6,8-bis(dimethylamino)-

pyrimidotriazines (**5**; $R^1 = R^2 = NMe_2$, $R^3 = NHNHCH_2CH_2OH$ or SCH_2COCH_3), whose preparations are described below, were interesting in that the signals due to the two dimethylamino groups in each compound had similar chemical shifts but quite different peak shapes. At normal probe temperature, in deuteriochloroform solution, one group normally gave a relatively sharp peak and the other a broad one. It seemed likely that closer study would give information on the extent to which the dimethylamino groups conjugate with the pyrimidotriazine system, in their different positions, and hence the ways in which they might influence the chemistry of the system.

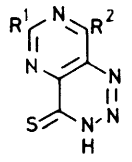
The effects of varying the temperature on the signals are illustrated for the hydroxyethylhydrazinopyrimidotriazine (**5**; $R^1 = R^2 = NMe_2$, $R^3 = NHNHCH_2CH_2OH$). At 20 °C the two dimethylamino-group signals appeared as two singlets (I) and (II) at δ 3.55 and 3.14, but at −40 °C the former had split into two widely spaced peaks (IA) and (IB) and the latter into two more closely spaced peaks (IIA) and (IIB). As the temperature was raised from −40 °C, the peaks (IIA) and (IIB) gradually broadened and coalesced as the rate of rotation of the relevant dimethylamino group increased. A coalescence temperature of −7 °C was observed. Similarly, signals (IA) and (IB) coalesced near 0 °C. This behaviour, which is analogous to that of *N,N*-dimethylamides,[10] is due to the restricted rotation of the dimethylamino groups as a result of the partial double bond character of the CN linkages attaching them to the pyrimidine ring (**6**).



(**7**)

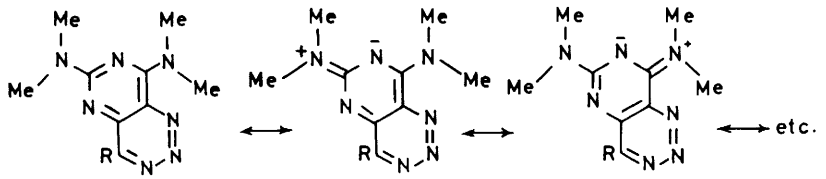


(**8**)



(**9**)

are not readily applicable to the pyrimidotriazine analogues. Reactions with benzoyl chloride and potassium cyanide,[12] ethanolic hydrogen chloride,[13] methyl iodide,[14] dimethyl sulphate,[14] and triethyloxonium tetrafluoroborate[15] failed to give electrophilic addition products. The anomalous behaviour of the pyrimidotriazine 3-oxides may be due to the very electron deficient nature of the system and a ready reversal of the ring closure step (Scheme) under acidic conditions.



(**6** a) (**6** b) (**6** c)

The variable temperature data enable the free energy of activation for the transition of each dimethylamino group from one conformation to another to be calculated. Gutowsky and Holm's equation, $K_c = \pi\Delta_{AB}/2^{\frac{1}{2}}$, gives the exchange rate (K_c) at the coalescence temperature (T_c) for the transfer of magnetisation between the methyl groups whose chemical shift difference, in the absence of exchange, is Δ_{AB}.[11] The free energy of activation is then given by:

$$K_c = \frac{kT_c}{h} \exp\left(\frac{-\Delta G^{\ddagger}}{RT_c}\right)$$

Data for three compounds examined are given in Table 1. In each compound, the dimethylamino group which is shown to be in a rather symmetrical environment by the small value of Δ_{AB}, may confidently be assigned to position 6, and the group with a large Δ_{AB} to the less symmetrically situated 8-position, where the lone pair on N-1 can affect one methyl group much more than the other. The energy barrier to rotation was always higher (Table 1) for the 6-dimethylamino group which can more readily adopt a coplanar configuration and therefore has more double bond character in the bond joining it to the ring. It is more highly conjugated with the heterocyclic system than the 8-dimethylamino group which is more sterically crowded in the planar configuration.

Some reactions of the *N*-oxides (**4**) were explored to compare their behaviour with those of simple pyridine *N*-oxides. It soon transpired that many characteristic pyridine *N*-oxide reactions

Some pyrimidotriazine 3-oxides have been reported to undergo ring contraction reactions, to give isoxazolo- and pyrazolo-[4,3-*d*]pyrimidines,[2,3,16] but no such products were isolated from similar treatment of our compounds. However, reduction with stannous chloride of the piperidino compound (**4**; $R^1 = R^2$ = piperidino, R^3 = H) gave the oxime (**7**).

One typical pyridine *N*-oxide reaction which worked well with the pyrimidotriazine analogues was treatment with thionyl chloride, which yielded 4-chloropyrimido[5,4-*d*][1,2,3]triazines (**5**; R^3 = Cl). The chlorine atoms in such compounds proved to be very reactive indeed, so the chloro compounds provided a route to many 4,6,8-trisubstituted pyrimido[5,4-*d*][1,2,3]-triazines. The reagents used to introduce the appropriate substituent into the 4-position included benzylamine, diethylamine, dimethylamine, 2-hydroxyethylamine, 2-hydroxyethylhydrazine, 3-hydroxypropylamine, and pyrrolidine. The high reactivity of a 4-chlorine atom in this system is illustrated by the fact that the one in the bis(methylthio) compound (**5**; $R^1 = R^2$ = SMe, R^3 = Cl) can be displaced without interference from the simultaneous displacement of the very reactive 8-methylthio group.

The hydroxyethylamino and hydroxypropylamino compounds [**5**; R^1 = SMe, R^2 = morpholino, R^3 = $NH(CH_2)_2OH$ or $NH(CH_2)_3OH$] were used to prepare examples of the novel tricyclic heterocyclic systems imidazo- and pyrimido-[1′,2′-*c*]pyrimido[4,5-*e*][1,2,3]triazine (**8**; $n = 1$ or 2). These resulted from treatment of the appropriate precursors, with thionyl chloride and phosphorous trichloride, respectively,

Table 1. Variable temperature data

Compound			δ (frozen conformation)		Δ_{AB} (Hz)		K_c (s^{-1})		T_c (K)		$\Delta G^{\ddagger}$ (kJ mol^{-1})	
	R^1 and R^2	R^3	6-NMe_2	8-NMe_2	6-NMe_2	8-NMe_2	6-NMe_2	8-NMe_2	6-NMe_2	8-NMe_2	6-NMe_2	8-NMe_2
(4)	NMe_2	Me	3.24, 3.29	3.36, 3.82	4.5	41.4	10.0	92.0	291	288	65.7	59.7
(5)	NMe_2	$NHNHCH_2CH_2OH$	3.08, 3.18	3.24, 3.79	9.0	45.0	20.0	100.0	266	273	58.3	56.25
(5)	NMe_2	SCH_2COMe	3.21, 3.29	3.33, 3.93	7.2	54.0	16.0	120.0	298	292	66.2	59.9

and cyclisation of the resulting chloroethylamino and chloropropylamino intermediates.

The thiones (**9**) which resulted from treatment of appropriate 4-chloro compounds (**5**; R^3 = Cl) with sodium hydrogen sulphide, reacted with α-halogeno-ketones or -esters (chloroacetone, phenacyl halides, or ethyl chloroacetate) to yield the corresponding acyl thiols (**5**; R^3 = SCH_2COMe, SCH_2COPh, or SCH_2CO_2Et) which are potential intermediates for further new tricyclic heterocycles.

Experimental

M.p.s are uncorrected. I.r. spectra were recorded as Nujol mulls on a Perkin-Elmer 297 spectrometer. ^1H N.m.r. spectra were measured for $CDCl_3$ or $(CD_3)_2SO$ solutions on a Perkin-Elmer R32 instrument. Microanalyses were performed by Butterworth Laboratories Ltd., Teddington, Middlesex.

2-(3-*Hydroxypropylamino*)-6-*methyl*-4-*morpholino*-5-*nitropyrimidine* [**1**; R^1 = $NH(CH_2)_3OH$, R^2 = morpholino, R^3 = NO_2].—3-Hydroxypropylamine (6 g) was added to a stirred suspension of 2-chloro-4-methyl-6-morpholino-5-nitropyrimidine (**1**; R^1 = Cl, R^2 = morpholino, R^3 = NO_2) (10 g) in ethanol (100 ml) and the mixture heated under reflux for 1 h. The solvent was removed under reduced pressure and the residue dissolved in chloroform. The solution was washed with water, dried ($MgSO_4$), and evaporated. The residual oil was triturated with light petroleum (b.p. 40—60 °C) and the solid filtered off and crystallised from toluene to yield the title *product* (10.5 g), m.p. 94—95 °C (Found: C, 48.5; H, 6.4; N, 23.6. $C_{12}H_{19}N_5O_4$ requires C, 48.5; H, 6.4; N, 23.6%).

4-*Methyl*-6-*morpholino*-5-*nitropyrimidine*-2(1H)-*thione* (**2**).—(*a*) A solution of sodium sulphide nonahydrate (30 g) in methanol (150 ml) was kept below 20 °C during the addition of glacial acetic acid (7.5 g) in methanol (25 ml). The resulting mixture was gradually added to a stirred solution of 2-chloro-4-methyl-6-morpholino-5-nitropyrimidine (**1**; R^1 = Cl, R^2 = morpholino, R^3 = NO_2) (14 g) in methanol (200 ml) at 50 °C. The temperature was raised to 65 °C for 15 min before the mixture was evaporated to 100 ml under reduced pressure, treated with water (50 ml), and acidified with glacial acetic acid. The solid was collected and suspended in 4M-ammonium hydroxide, the insoluble material (3.5 g, see below) was filtered off, and the filtrate acidified to pH 6 to precipitate the *product* (**2**) (10.5 g), m.p. 194—196 °C, $\nu_{max.}$ 3 160 cm^{-1} (SH); M^+ (mass spectrum), 256 (Found: C, 42.2; H, 4.8; N, 22.0. $C_9H_{12}N_4O_3S$ requires C, 42.2; H, 4.7; N, 21.9%).

(*b*) 2-Chloro-4-methyl-6-morpholino-5-nitropyrimidine (**1**; R^1 = Cl, R^2 = morpholino, R^3 = NO_2) (15 g) was added in portions to a warmed, stirred solution of sodium hydrogen sulphide (9.2 g) in methanol (300 ml). The solution was warmed gently until dissolution occurred, and then stirred at 20 °C for 3 h. Sodium chloride was filtered off and the filtrate was evaporated to dryness under reduced pressure. Water (100 ml) was added to the residue, the insoluble material (3 g, see below) was filtered off, and the filtrate acidified to pH 6 to precipitate the product (7.5 g), identical with that obtained by method (*a*).

The alkali-insoluble matter produced by each of the above methods was washed with water and then methanol, dried, and crystallised from toluene to yield *bis*(4-*methyl*-6-*morpholino*-5-*nitropyrimidin*-2-*yl*) *disulphide*, m.p. 201—202 °C [Found: M^+ (mass spectrum), 510.1102. $C_{18}H_{22}N_8O_6S_2$ requires *M*, 510.1102].

4-*Methyl*-2-*methylthio*-6-*morpholino*-5-*nitropyrimidine* (**1**; R^1 = SMe, R^2 = morpholino, R^3 = NO_2).—4-Methyl-6-morpholino-5-nitropyrimidine-2(1*H*)-thione (**2**) (15 g), water (100 ml), and sodium carbonate (3 g) were stirred at 70 °C and then cooled to 20 °C. Methyl iodide (14.2 g) was added and the mixture was stirred rapidly for 16 h. The solid was filtered off and crystallised from light petroleum (b.p. 40—60 °C) to yield the required *product* (10.5 g), m.p. 81—83 °C (Found: C, 44.5; H, 5.3; N, 20.7. $C_{10}H_{14}N_4O_3S$ requires C, 44.4; H, 5.2; N, 20.7%).

6-*Methyl*-5-*nitropyrimidine*-2,4(1H,3H)-*dithione* (**3**).—Finely ground 2,4-dichloro-6-methyl-5-nitropyrimidine (25 g) was added in portions to a stirred solution of sodium hydrogen sulphide (25 g) in methanol (450 ml). The mixture was stirred at 20 °C for 16 h, filtered to remove sodium chloride, and evaporated to dryness under reduced pressure. The residue was treated with 4M-sodium hydroxide, filtered to remove the insoluble material, and acidified to pH 5 with glacial acetic acid. The product was purified by dissolution in aqueous sodium hydroxide and reprecipitation with acid several times to give pure material (22 g), m.p. 241 °C (decomp.) [lit.,[17] 240 °C (decomp.)].

4-*Methyl*-2,6-*bis*(*methylthio*)-5-*nitropyrimidine* (**1**; R^1 = R^2 = SMe, R^3 = NO_2).—The above dithione (**3**) (20 g), water (150 ml), and sodium carbonate (10.6 g) were stirred at 70 °C, cooled to 20 °C, and treated with methyl iodide (35.5 g) as described for the morpholino-thione (**2**) above. The product (19.5 g) had m.p. 84—85 °C (from methanol) (Found: C, 36.3; H, 3.8; N, 18.7. $C_7H_9N_3O_2S_2$ requires C, 36.4; H, 3.9; N, 18.2%).

2,4-*Bis*(*dimethylamino*)-6-*ethyl*-5-*nitropyrimidine*.—Dimethylamine (72 g of 25% solution in ethanol) was added during 15 min to dioxane (100 ml). The mixture was stirred for 16 h before water (40 ml) was added to precipitate the title *product* (22.1 g), m.p. 74—75 °C [from light petroleum (b.p. 40—60 °C)] (Found: C, 50.4; H, 7.2; N, 29.3. $C_{10}H_{17}N_5O_2$ requires C, 50.2; H, 7.2; N, 29.3%).

6,8-*Disubstituted Pyrimido*[5,4-d][1,2,3]*triazine* 3-*Oxides* (**4**; R^3 = H).—*General method A*. The appropriate 2,4-disubstituted 6-methyl-5-nitropyrimidine (0.04 mol) was suspended in methanol (300 ml) and shaken with Raney nickel (8 g settled suspension) under hydrogen until the theoretical uptake was observed. Charcoal was added and the mixture heated under reflux for 5 min before being filtered. The insoluble material was washed with hot methanol (100 ml) and the combined filtrates were evaporated under reduced pressure to give an oil. The latter was triturated with light petroleum (b.p. 40—60 °C), which was decanted off, to leave the 5-amino compound as a

Table 2. Pyrimido[5,4-*d*][1,2,3]triazines

	Compound *				Crystallisation	Yield	M.p.	Found (%)			Required (%)			δ (p.p.m.)
	R^1	R^2	R^3	Method †	solvent ‡	(%)	(°C)	C	H	N	C	H	N	
(4)	SMe	SMe	H	A	MeOH	48	171—173 (decomp.)	34.8	2.9	28.9	34.8	2.9	29.0	2.67 (s, 6 H, 2 × SMe), 8.79 (s, 1 H, 4-H)
(4)	SMe	Mor	H	A	Toluene	40	191 (decomp.)	43.1	4.3	30.0	42.9	4.3	29.9	2.52 (s, 3 H, SMe), 3.65—3.85 (m, 4 H, CH_2NCH_2), 4.15—4.50 (m, 4 H, $CH_2OCH_2CH_2$), 8.15 (s, 1 H, 4-H)
(4)	NMe_2	NMe_2	H	A	Propan-2-ol	57	192 (decomp.)	45.9	5.6	41.6	46.0	5.6	41.7	3.10 (s, 6 H, NMe_2), 3.41 (s, 6 H, NMe_2), 7.89 (s, 1 H, 4-H)
(4)	Pip	Pip	H	A	MeOH	72	183—184	57.3	6.5	31.1	57.1	6.7	31.1	1.72 (s, 12 H, piperidino H), 3.85 (br, s, 4 H, CH_2NCH_2), 4.27 (br, s, 4 H, CH_2NCH_2), 7.90 (s, 1 H, 4-H)
(4)	NMe_2	NMe_2	Me	A	MeOH	67	122—123	48.0	6.2	39.4	48.2	6.1	39.3	2.55 (s, 3 H, Me), 3.25 s, 6 H, NMe_2), 3.85 (br, s, 6 H, NMe_2)
(5)	NHMe	Mor	Cl	B		90	143—144 (decomp.)							
(5)	SMe	Mor	Cl	B	LP	66	158—160 (decomp.)	40.9	3.9	28.7	40.2	3.7	28.1	
(5)	NMe_2	NMe_2	Cl	B	Toluene	78	133 (decomp.)	42.8	4.8	38.7	42.6	4.8	38.7	
(5)	NMe_2	NMe_2	$NHNH(CH_2)_2OH$	D	$EtOH–H_2O$	93	140	45.0	6.4	43.0	45.0	6.5	43.0	3.18 (s, 6 H, NMe_2), 3.59 (s, 6 H, NMe_2), 4.07 (m, 2 H, $NHCH_2$), 4.40 (m, 2 H, CH_2OH), 4.70 (br, s, 1 H, OH); NH signals were not observed
(5)	SMe	SMe	Cl	B	LP	51	179—180 (decomp.)	33.3	2.6	26.7	32.4	2.3	27.0	
(5)	NMe_2	NMe_2	$NHCH_2Ph$	E	MeOH	56	172—174	59.9	6.2	34.5	59.2	6.2	34.5	3.16 (s, 6 H, NMe_2), 3.62 (br, s, 6 H, NMe_2), 4.9 (d, 2 H, CH_2), 6.55 (br, s, 1 H, NH), 7.20—7.50 (m, 5 H, Ph)
(5)	SMe	SMe	NEt_2	C	Propan-2-ol	64	126	44.4	5.3	28.4	44.6	5.4	28.4	1.15—1.45 (t, 6 H, 2 × Me), 2.57 (s, 6 H, 2 × SMe), 3.90—4.30 (q, 4 H, 2 × CH_2)
(5)	SMe	SMe	Pyr	C	Toluene	73	186—187	44.7	5.0	28.7	44.9	4.8	28.6	1.80—2.15 (m, 4 H, CH_2CH_2), 2.57 (d, 6 H, 2 × SMe), 3.60—4.50 (m, 4 H, CH_2NCH_2)
(5)	SMe	SMe	$NH(CH_2)_2OH$	D	Toluene	86	172—174	38.0	4.2	29.5	38.0	4.3	29.6	2.62 (d, 6 H, 2 × SMe), 3.80—4.00 (m, 4 H, $NHCH_2$-CH_2OH), 2.25 (br s, 1 H, NH), 6.90 (br s, 1 H, OH)
(5)	SMe	SMe	$NH(CH_2)_3OH$	D	$MeOH–H_2O$	87	179—181	40.3	4.6	28.2	40.3	4.7	28.2	1.87 (q, 2 H, CH_2), 2.66 (d, 6 H, 2 × SMe), 3.47—3.90 (m, 4 H, NCH_2 and CH_2OH), 4.61 (t, 1 H, OH), 8.45 (t, 1 H, NH)
(5)	SMe	Mor	NMe_2	C	MeOH	78	112—113	47.0	5.4	32.4	46.9	5.6	31.9	2.52 (s, 3 H, SMe), 3.62 (s, 6 H, NMe_2), 3.86 (m, 4 H, CH_2NCH_2), 4.67 (m, 4 H, CH_2OCH_2)

Table 2. (*cont.*)

	Compound*			Method†	Crystallisation solvent‡	Yield (%)	M.p. (°C)	Found (%)			Required (%)			δ (p.p.m.)
	R^1	R^2	R^3					C	H	N	C	H	N	
(5)	SMe	Mor	Pyr	C	Propan-2-ol	81	119—121	50.5	5.7	29.6	50.4	5.7	29.4	2.15 (m, 4 H, CH_2CH_2), 2.55 (s, 3 H, SMe), 3.63—4.80 (m, 12 H, CH_2OCH_2, CH_2NCH_2, and CH_2NCH_2)
(5)	SMe	Mor	$NH(CH_2)_2OH$	D	MeOH	55	180—182	44.4	5.3	30.2	44.6	5.3	30.3	2.42 (s, 3 H, SMe), 3.3—3.8 (m, 12 H, morph + $NHCH_2$-CH_2OH)
(5)	SMe	Mor	$NH(CH_2)_3OH$	D	Propan-2-ol	71	177—178	46.2	5.7	29.3	46.3	5.7	29.1	1.95 (q, 2 H, CH_2), 2.54 (s, 3 H, SMe), 3.18 (br, s, 1 H, OH), 3.60—4.00 (m, 8 H, CH_2NCH_2, CH_2OH, and CH_2NH) 4.57 (br, s, 4 H, CH_2OCH_2), 6.91 (br, s, 1 H, NH)
(9)	NHMe	Mor		F	Rep	93	207—208	43.0	4.7	35.1	43.0	4.7	35.1	2.88 (d, 3 H, Me), 3.66—4.00 (m, 4 H, CH_2NCH_2), 4.10—4.50 (m, 4 H, CH_2OCH_2), 7.90 (br, s, 1 H, NH), 10.50 (br, s, 1 H, *SH*)
(9)	NMe_2	NMe_2		F	Rep	85	204 (decomp.)	43.1	5.4	39.0	43.0	5.2	39.0	3.40 (s, 6 H, NMe_2), 3.61 (br, s, 6 H, NMe_2), 10.55 (br, s, 1 H, SH)
(9)	SMe	Mor		F	Rep	57	193—194 (decomp.)							
(5)	NHMe	Mor	SCH_2COMe	G	Propan-1-ol	93	205—206	46.4	5.1	29.4	46.6	5.1	29.2	2.11 (s, 3 H, MeCO), 2.50 (d, 3 H, NHMe), 3.70—4.00 (m, 4 H, CH_2NCH_2), 4.17 (s, 2 H, $COCH_2S$), 4.30—4.60 (m, 4 H, CH_2OCH_2)
(5)	NHMe	Mor	SCH_2COPh	H	Toluene	82	177—179	54.4	4.9	24.6	54.5	4.8	24.7	3.00 (d, 3 H, NM*Me*), 3.66—4.00 (m, 4 H, CH_2NCH_2), 4.30—4.70 (m, 4 H, CH_2OCH_2), 4.88 (s, 2 H, $COCH_2S$), 7.37—7.67 (m, 3 H, C_3H_3), 8.00—8.20 (m, 2 H, C_3H_2)
(5)	SMe	Mor	SCH_2COMe	G	MeOH	76	184—185	44.3	4.6	23.8	44.3	4.5	23.8	2.41 (s, 3 H, MeCO), 2.58 (s, 3 H, SMe), 3.70—4.00 (m, 8 H, morpholino H), 4.25 (s, 2 H, $COCH_2S$)
(5)	NMe_2	NMe_2	SCH_2COMe	H	Propan-2-ol	78	187—188	47.0	5.7	31.9	46.9	5.6	31.9	2.40 (s, 3 H, MeCO), 3.23 (s, 6 H, NMe_2), 3.63 (br, s, 6 H, NMe_2), 4.20 (s, 2 H, $COCH_2S$)
(5)	NMe_2	NMe_2	SCH_2COPh	H	EtOH	72	193—195	55.3	5.2	26.4	55.3	5.1	26.5	3.43 (s, 6 H, NMe_2), 3.64 (br s, 6 H, NMe_2), 4.90 (s, 2 H, $COCH_2S$), 7.40—7.65 (m, 3 H, C_3H_3), 8.03—8.35 (m, 2 H, C_3H_2)

Table 2. (*cont.*)

	Compound *			Method †	Crystallisation solvent ‡	Yield (%)	M.p. (°C)	Found (%)			Required (%)			δ (p.p.m.)
	R^1	R^2	R^3					C	H	N	C	H	N	
(5)	NHMe	Mor	SCH_2CO_2Et	H	EtOH	73	160—161	46.0	5.2	26.8	45.9	5.4	26.8	1.01 (t, 3 H, Me), 4.22 (q, 2 H, CH_2), 3.06 (d, 3 H, NHMe), 3.75—4.06 (m, 4 H, CH_2NCH_2), 4.30—4.70 (m, 4 H, CH_2OCH_2), 5.60 (br s, 1 H, NH)

* Mor = morpholino, Pip = piperidino, Pyr = pyrrolidino. † See Experimental section. ‡ LP = light petroleum (b.p. 100—200 °C), Rep = reprecipitation by acid from alkaline solution.

solid. Ethanol (150 ml) was added and the resulting suspension was adjusted to pH 3 by the dropwise addition of concentrated hydrochloric acid. The stirred mixture was cooled in ice and a solution of isopentyl nitrite (16 ml) in ethanol (20 ml) was added during 30 min. Light was excluded while the mixture was stirred for a further 16 h without cooling, neutralised with 4M-ammonium hydroxide, and chilled in ice for 2 h. The *product* was filtered off, dried, and crystallised from a suitable solvent (data in Table 2).

6,8-*Disubstituted* 4-*Chloropyrimido*[5,4-d][1,2,3]*triazines* (**5**; R^3 = Cl).—*General method B.* The appropriate pyrimidotriazine 3-oxide (**4**) (0.02 mol) was added in portions to stirred thionyl chloride (25 ml) at 0—5 °C and the resulting solution stirred for a further 16 h without cooling. The excess of thionyl chloride was removed under reduced pressure at < 50 °C and the residue crystallised from a suitable dried solvent (data in Table 2).

4,6,8-*Trisubstituted Pyrimido*[5,4-d][1,2,3]*triazines* (**5**).—*General method C.* The appropriate secondary amine (0.001 mol), and the appropriate 4-chloropyrimidotriazine (**5**; R^3 = Cl) (0.001 mol) were stirred in chloroform (20 ml) for 12 h. The suspension was washed with water (2 × 5 ml) and the chloroform layer separated, dried ($MgSO_4$), and evaporated. The product was crystallised from a suitable solvent (data in Table 2).

General method D. The appropriate amine (0.004 mol) and the appropriate 4-chloropyrimidotriazine (**5**; R^3 = Cl) (0.002 mol) were dissolved in warm ethanol (20 ml) and then stirred for 2 h. Water (10 ml) was added and the mixture cooled in ice. The *product* was filtered off, dried, and crystallised from a suitable solvent (data in Table 2).

General method E. The appropriate amine (0.006 mol), the appropriate 4-chloropyrimidotriazine (**5**; R^3 = Cl) (0.003 mol), and ethanol (25 ml) were heated under reflux for 1 h. The product separated on cooling and was crystallised from a suitable solvent (data in Table 2).

2,4-*Dipiperidinopyrimidine*-6-*carbaldehyde Oxime* (**7**).—6,8-Dipiperidinopyrimido[5,4-*d*][1,2,3]triazine 3-oxide (**4**; R^1 = R^2 = piperidino, R^3 = H) (0.63 g), ethanol (50 ml), and 10% palladium-on-charcoal catalyst were shaken with hydrogen at 20 °C until no more hydrogen was absorbed. The catalyst was filtered off and washed with ethanol and the combined filtrates evaporated. The product was applied to a preparative scale silica t.l.c. plate which was developed with 1:1 ethyl acetate–toluene mixture to give four bands, the major one of which was separated to yield the *oxime* (**7**) (0.3 g), m.p. 283—284 °C [Found: C, 62.3; H, 8.1; N, 24.3%; M^+ (mass spectrum), 289.1931. $C_{15}H_{23}N_5O$ requires C, 62.3; H, 8.0; N, 24.2%; *M*, 289.1903]. $\nu_{max.}$ 3 350 (OH) and 1 658 cm^{-1} (C=N); δ($CDCl_3$) 7.91 (s, 1 H, HON=C*H*), 6.23 (s, 1 H, 5-H), 3.70 and 1.65 (both m, 8 H and 12 H, piperidino H).

6,8-*Disubstituted Pyrimido*[5,3-d][1,2,3]*triazine*-4(3H)-*thiones* (**9**).—*General method F.* The appropriate 6,8-disubstituted 4-chloropyrimido[5,4-*d*][1,2,3]triazine (**5**; R = Cl) (2 g) was added in portions to a hot, stirred solution of sodium hydrogen sulphide (2 g) in methanol (100 ml), and the mixture was stirred for 16 h without further heating. The solvent was removed under reduced pressure and the residue taken up in 4M-sodium or -ammonium hydroxide, filtered to remove the insoluble material, and then acidified with acetic acid. The *product* was filtered off, washed with water, and dried (data in Table 2).

6,8-*Disubstituted* 4-*Acylmethylthiopyrimido*[5,4-d][1,2,3]-*triazines.*—*General method G.* The appropriate 6,8-disubstituted pyrimido[5,4-*d*][1,2,3]triazine-4(3*H*)-thione (**9**) (0.004 mol) was dissolved in a warm solution of potassium carbonate (0.004 mol) in water (20 ml). The solution was filtered to remove the insoluble material, chloroacetone (0.004 mol) was added, and the mixture was stirred for 30 min. The product was extracted with chloroform and the extracts were washed with water, dried (Na_2SO_4), and evaporated to yield a crude solid which was crystallised from a suitable solvent (data in Table 2).

General method H. The appropriate 6,8-disubstituted pyrimido[5,4-*d*][1,2,3]triazine-4(3*H*)-thione (**9**) (0.004 mol) was dissolved in a warm solution of potassium carbonate (0.004 mol) in water (20 ml). Any insoluble matter was filtered off and the solution was stirred during the dropwise addition of the appropriate halogeno-ketone or -ester (0.004 mol) in ethanol (5 ml) and for a further 30 min. The mixture was thoroughly chilled and the precipitated solid filtered off, washed with water, dried, and crystallised from a suitable solvent (data in Table 2).

2,3-*Dihydro*-9-*methylthio*-7-*morpholinoimidazo*[1′,2′-c]-*pyrimido*[4,5-e][1,2,3]*triazine* (**8**; *n* = 1).—4-(2-Hydroxyethylamino)-6-methylthio-8-morpholinopyrimido[4,5-*e*][1,2,3]triazine (0.001 mol) was added in portions to stirred thionyl chloride and the resulting mixture was stirred for a further 16 h with exclusion of moisture. The volatile material was removed under reduced pressure, water (10 ml) was added, and the solution made alkaline with 4M-sodium hydroxide. The mixture was extracted with dichloromethane (3 × 10 ml) and the combined extracts were dried ($MgSO_4$) and evaporated. Crystallisation of the residue from ethanol gave the *tricyclic compound* (**8**; *n* = 1) as yellow microcrystals (0.2 g), m.p. 230—231 °C [Found: C, 47.3; H, 4.8; N, 32.1%; M^+ (mass spectrum),

305. $C_{12}H_{15}N_7OS$ requires C, 47.2; H, 5.0; N, 32.1; *M*, 305]; δ($CDCl_3$) 2.56 (s, 3 H, SMe), 3.90—3.70 (m, 4 H, CH_2NCH_2), and 4.55—4.10 (m, 8 H, CH_2OCH_2 and NCH_2CH_2N).

9,10-*Dihydro*-2-*methylthio*-4-*morpholino*-8H-*pyrimido*-[1′,2′-c]*pyrimido*[4,5-e][1,2,3]*triazine* (**8**; *n* = 2).—4-(3-Hydroxypropylamino)-6-methylthio-8-morpholinopyrimido-[4,5-e][1,2,3]triazine (0.001 mol) was added in portions to stirred phosphorus trichloride (5 ml) at 5 °C and the solution was allowed to warm to 20 °C and stirred for a further 16 h with exclusion of moisture. The product was isolated in a similar manner to the previous tricyclic compound and crystallised from methanol as yellow *needles* (0.18 g), m.p. 182—183 °C (Found: C, 48.9; H, 5.4; N, 30.7. $C_{13}H_{17}N_7OS$ requires C, 48.9; H, 5.4; N, 30.7%); δ($CDCl_3$) 1.85—2.30 (m, 2 H, $3CH_2$), 2.53 (s, 3 H, SMe), 3.50—4.00 (m, 8 H, $8CH_2$, $10CH_2$, and CH_2NCH_2), and 4.42—4.50 (m, 4 H, CH_2OCH_2).

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References

1 Part 41, J. Clark and M. Bakavoli, *J. Chem. Soc., Perkin Trans. 1*, 1977, 1966.
2 V. Papesch and R. M. Dodson, U.S. Pat. 1962, 3 056 783 (*Chem. Abstr.*, 1963, **58**, 5703); *J. Org. Chem.*, 1963, **28**, 1329.
3 V. Papesch, U.S. Pat. 1962, 3 056 781 (*Chem. Abstr.*, 1963, **58**, 5702).
4 V. Papesch, U.S. Pat. 1962, 3 056 782 (*Chem. Abstr.*, 1963, **58**, 5703).
5 K. Thomae, Brit. Pat. 1964, 971 166 (*Chem. Abstr.*, 1965, **62**, 1676).
6 J. Roch, U.S. Pat. 1965, 3 213 090 (*Chem. Abstr.*, 1966, **64**, 17618).
7 J. C. Davies, H. H. Balard, and J. W. Jones, *J. Heterocycl. Chem.*, 1970, **7**, 405.
8 M. Bakavolid, Ph.D. Thesis, University of Salford, 1980.
9 F. L. Rose, *J. Chem. Soc.*, 1954, 4116.
10 W. D. Phillips, *J. Chem. Phys.*, 1955, **23**, 1363; A. Calzolari, F. Conti, and C. Franconi, *J. Chem. Soc. B*, 1970, 555.
11 H. S. Gutowsky and C. H. Holm, *J. Chem. Phys.*, 1956, **25**, 1228.
12 A. Reissert, *Ber.*, 1905, 1603.
13 J. F. Vozza, *J. Org. Chem.*, 1962, **27**, 3856.
14 A. R. Hand and A. R. Katritzky, *J. Chem. Soc.*, 1958, 1754.
15 C. Reichardt, *Chem. Ber.*, 1966, **99**, 1769.
16 R. Behrend, *Ann. Chem.*, 1888, **245**, 213.
17 M. Polonovski and H. Schmitt, *Bull. Soc. Chim. Fr.*, 1950, 616; M. Polonovski and H. Schmitt, *C.R. Acad. Sci.*, 1950, **230**, 754.

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