# Heterocyclic Studies. Part 44.[1] Novel Tricyclic Compounds containing the Pyrimido[5,4-*d*]-1,2,3-triazine System

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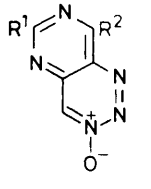
Treatment of methyl 8-amino-5-chloro-2,3-dihydroimidazo[1,2-*c*]pyrimidine-7-carboxylate with suitable amines and then nitrous acid gave derivatives (**4**) of the novel heterocyclic system imidazo[1′,2′:1,6]pyrimido[5,4-*d*][1,2,3]triazine. The same heterocyclic system in the form of an 8-oxide derivative (**5**) resulted from nitrous acid treatment of 8-amino-5-methylamino-7-methyl-2,3-dihydroimidazo[1,2-*c*]pyrimidine hydrochloride. In a similar way nitrous acid treatment of suitable imidazo- and pyrimido-[1,2-*a*]pyrimidine hydrochlorides (**6**; $n$ = 1 or 2) yielded examples of the new heterocyclic systems imidazo- and pyrimido-[2′,1′:2,3]pyrimido[5,4-*d*][1,2,3]triazine (**7**; $n$ = 1 or 2).

The synthesis of some triazolo-[4,3-*a*]- and -[1,5-*a*]-pyrimidines is described and one of these was converted into the 5-morpholino-8-oxide derivative of the novel [1,2,4]triazolo[3′,4′:2,3]pyrimido-[5,4-*d*][1,2,3]triazine system, compound (**14**). Acylation of 4-hydrazino-6,8-bisdimethylamino-pyrimido[5,4-*d*]-1,2,3-triazine (**15**; $R^1 = R^2 = NMe_2$, $R^3 = NHNH_2$) and cyclisation of the products gave derivatives of the new pyrimido[4,5-*e*]-1,2,4-triazolo[4,3-*c*][1,2,3]triazine system (**16**; R = H, Me, Et, $CHCl_2$, or $NH_2$). However, the benzoylhydrazino compound failed to cyclise in polyphosphoric acid and gave, instead, an oxadiazolyl pyrimidine (**18**; Scheme 2). The hydrazino compound (**15**; $R^1 = R^2 = NMe_2$, $R^3 = NHNH_2$) gave a pyrimidotetrazolotriazine (**22**) on treatment with nitrous acid, and a novel pyrimido[4,5-*e*][1,2,4]triazino[4,3-*c*][1,2,3]triazine (**23**) on treatment with pyruvic acid.

An earlier paper in this series[2] described the synthesis of some pyrimido[5,4-*d*]-1,2,3-triazines and their 3-oxides which were of interest as potential pharmaceuticals. Two new heterocyclic systems, imidazo- and pyrimido-[1,2-*c*]pyrimido[4,5-*e*][1,2,3]-triazine were also described. By an unfortunate oversight the earliest example of one of these systems, which was prepared by M. Bakavoli,[3] co-author of this paper, was omitted. The synthesis of that compound, 2,3-dihydro-7,9-dimorpholino-imidazo[1,2-*c*]pyrimido[4,5-*e*][1,2,3]triazine (**2**), is given in the Experimental section of this paper together with synthesis, by the same worker, of some additional pyrimido[5,4-*d*]-1,2,3-triazines (**1**; $R^1$ = NHMe or morpholino, $R^2$ = morpholino) and (**15**; $R^1 = R^2$ = morpholino, $R^3$ = NHMe, $NHCH_2CH_2OH$, or $NHCH_2CH_2Cl$).

Further work has now extended the range of tricyclic compounds which incorporate the pyrimido[5,4-*d*]-1,2,3-triazine system but as well as successful syntheses of several novel systems some reactions which led to unexpected products are reported.



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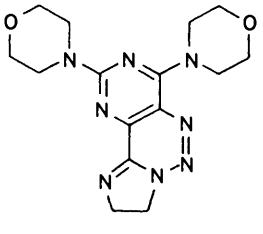

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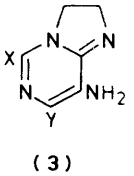

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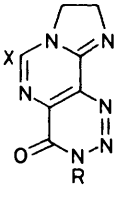

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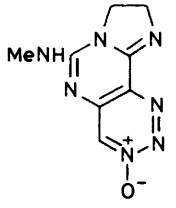
*Imidazo*[1′,2′:1,6]*pyrimido*[5,4-d][1,2,3]*triazines*.—Imidazopyrimidotriazines (**4**) were shown to be readily prepared by treatment of methyl 8-amino-5-chloroimidazo[1,2-*c*]-pyrimidine-7-carboxylate[4] (**3**; X = Cl, Y = $CO_2Me$) with suitable amines and then nitrous acid. In a typical synthesis the ester was treated with benzylamine to yield its 5-benzylamino-7-benzylaminocarbonyl analogue (**3**; X = $NHCH_2Ph$, Y = $CONHCH_2Ph$) which, after treatment with nitrous acid, gave 8-benzyl-5-benzylaminoimidazo[1′,2′:1,6]pyrimido[5,4-*d*]-[1,2,3]triazin-7(8*H*)-one (**4**; X = $NHCH_2Ph$, R = $CH_2Ph$), an example of a new heterocyclic system. Other examples of this system, in the form of 8-oxide derivatives, could be made from 8-amino-7-methylimidazo[1,2-*c*]pyrimidines. For example, nitrous acid treatment of the methylamino compound (**3**; X = NHMe, Y = Me) gave the imidazopyrimidotriazine-8-oxide (**5**).

*Imidazo- and Pyrimido*-[2′,1′:2,3]*pyrimido*[5,4-d][1,2,3]*triazines*.—Representatives of another new imidazopyrimidotriazine system were synthesised in a similar way to the last mentioned compounds by treatment of 6-amino-5-methyldihydroimidazo[1,2-*a*]pyrimidine hydrochlorides (**6**; $n$ = 1, X = morpholino or piperidino, Y = $NH_2$) with nitrous acid to yield hydrochlorides of corresponding 1,2-dihydroimidazo-



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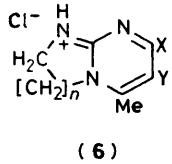

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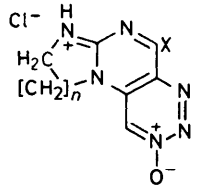


(7)

**Table 1.** Ionisation and u.v. spectroscopy

| Compound | Ionisation[a] $pK_a$ ($H_2O$; 20 °C) | Spectroscopy: Solvent | Species[b] | $\lambda_{max.}$/nm[c] | | | log ε | | |
|---|---|---|---|---|---|---|---|---|---|
| (**9**) | 4.35 ± 0.05 | $H_2O$; pH 7.2 | NM | 304 | *288* | 235 | 3.99 | 4.31 | 4.32 |
| | | $H_2O$; pH 2.0 | C | 319 | *302* | 203 | 4.04 | 3.98 | 4.36 |
| (**12**; R = Et, X = $NH_2$) | 3.88 ± 0.06 | $H_2O$; pH 5.8 | NM | 325 | *250* | 206 | 3.89 | 3.82 | 4.69 |
| | 7.73 ± 0.04 | $H_2O$; pH 9.9 | A | 340 | 264 | 227 | 3.92 | 3.71 | 4.21 |
| | | $H_2O$; pH 1.1 | C | 307 | 300 | 250 | 3.95 | 3.97 | 3.66 |
| | | | | 253 | 207 | | 3.76 | 4.19 | |
| (**13**; R = Et, X = H) | 6.60 ± 0.06 | $H_2O$; pH 4.0 | NM | 271 | 216 | | 4.02 | 4.28 | |
| | | $H_2O$; pH 9.9 | A | 280 | 254 | 212 | 4.06 | 3.78 | 4.47 |
| (**13**; R = Et, X = $NH_2$) | 3.25 ± 0.06 | $H_2O$; pH 5.2 | NM | 302 | 258 | 221 | 3.80 | 3.60 | 4.35 |
| | 7.03 ± 0.04 | $H_2O$; pH 9.9 | A | 306 | 263 | 223 | 3.95 | 3.72 | 4.40 |
| | | $H_2O$; pH 1.0 | C | 277 | 235 | 208 | 3.94 | 3.36 | 4.39 |
| (**13**; R = X = H) | 6.45 ± 0.06 | $H_2O$; pH 4.0 | NM | 271 | 212 | | 3.71 | 3.80 | |
| | | $H_2O$; pH 9.9 | A | 280 | 255 | 209 | 4.06 | 3.77 | 4.04 |

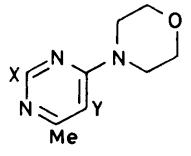
[a] Measured by a rapid spectrophotometric method, J. Clark and A. E. Suncliffe, *Chem. Ind. (London)*, 1973, 281. [b] NM = neutral molecule, C = cation, A = anion. [c] Shoulders and inflections in italics.

[2′,1′:2,3]pyrimido[5,4-*d*][1,2,3]triazine-8-oxides (**7**; *n* = 1). Yet another new system resulted from similar treatment of a pyrimido[1,2-*a*]pyrimidine (**6**; *n* = 2, X = morpholino, Y = $NH_2$), made from the corresponding 7-nitro compound,[5] which yielded the hydrochloride of 9,10-dihydro-5-morpholino-8H-pyrimido[2′,1′:2,3]pyrimido[5,4-*d*][1,2,3]triazine-2-oxide (**7**; *n* = 2, X = morpholino).

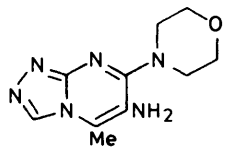
None of the imidazo- or pyrimido-pyrimidotriazine oxides described above behaved like normal heterocyclic *N*-oxides since they could not be converted, as could similar pyrimidotriazine 3-oxides,[2] into 3-chloro compounds by treatment with thionyl chloride. Other reagents which have been used on a variety of *N*-oxides[6] also failed to effect the conversion.

*Triazolopyrimidines and* [1,2,4]*Triazolo*[3′,4′:2,3]*pyrimido*-[5,4-d][1,2,3]*triazines.*—Routes to triazolopyrimidotriazines were also explored. First a 4-morpholino-2-hydrazinopyrimidine (**8**; X = $NHNH_2$, Y = $NO_2$) was converted into a range of hydrazides by treatment with formic acid, acetic and propionic anhydrides, and benzoyl chloride. These hydrazides failed to cyclise to the corresponding triazolopyrimidines on prolonged heating in toluene or xylene in the presence of toluene-*p*-sulphonic or polyphosphoric acid. However, after reduction of the nitro group, which was expected to facilitate cyclisation, one member of the series (**8**; X = NHNHCHO; Y = $NH_2$) gave a triazolopyrimidine (**9**) or (**10**) on heating with polyphosphoric acid. Less predictably a second amine (**8**; X = NHNHCOEt, Y = $NH_2$) cyclised to give a triazolopyrimidinone (**11** or **12**; R = Et, X = $NH_2$). It is clear that the unsymmetrical 2,2′-acylhydrazinopyrimidines could cyclise in two ways so it was necessary to prove the structures (**9**) and (**12**; R = Et, X = $NH_2$) which were eventually assigned to the products, especially as the assignments indicated opposite modes of cyclisation in the two cases. Other workers have noted the delicate balance between two possible cyclisations in similar cases.[7]

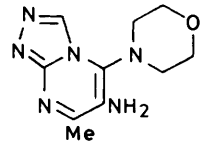
Fairly close analogues (**11** and **12**; R = X = H) of the two possible structures for the triazolopyrimidinone were already known. The u.v. spectra of these known isomeric 1,2,4-triazolo-[4,3-*a*]pyrimidines differ markedly from each other in that the 7-one derivative (**11**; R = X = H) shows two bands (at 210 and 248 nm) while the 5-one isomer shows three bands (at 210, 246, and 294 nm).[8] After making allowances for a small shift due to the ethyl group and a larger bathochromic shift due to the 6-amino group, the u.v. spectrum of our compound, which shows



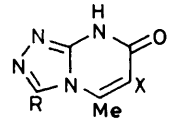
(**8**)



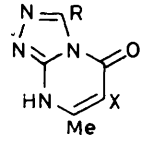
(**9**)



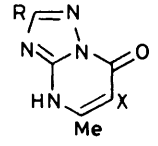
(**10**)



(**11**)



(**12**)



(**13**)

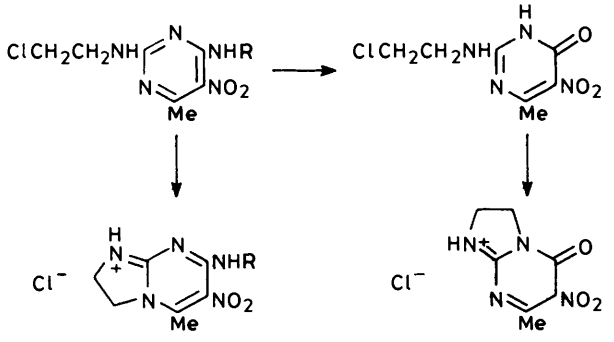
three bands (at 220, 250, and 325 nm) (Table 1) is clearly compatible with the 5-one structure (**12**; R = Et, X = $NH_2$) but not the 7-one structure (**11**; R = Et, X = $NH_2$). Support for this assignment came from comparisons of the compound's u.v. spectra with those of an isomeric triazolo[1,5-*a*]pyrimidine (**13**; R = Et, X = $NH_2$). The spectra of the cation, neutral molecule, and anion species of the two compounds (Table 1) show a close similarity except that for each species the longest wavelength band of our compound (**12**; R = Et, X = $NH_2$) is at about 20—30 nm longer wavelength than that of the [1,5-*a*] isomer. This is just the relationship expected by analogy with published spectra of the simpler isomeric pairs of triazolopyrimidines (**12** and **13**; R = X = H).[8]

The reference compound used here (**13**; R = Et, X = $NH_2$) was synthesised by condensation of the known 3-amino-5-ethyl-1,2,4-triazole[9] with ethyl acetoacetate to give the new [1,2,4]-triazolo[1,5-*a*]pyrimidin-7-one (**13**; R = Et, X = H) which was then nitrated and reduced. The 7-one structure of the compounds was expected from experience with similar syntheses[9] and was confirmed by comparison of the ionisation constant

and u.v. spectra of the new compound (**13**; R = Et, X = H) with those of its known 2-unsubstituted analogue (**13**; X = R = H).[10] The u.v. spectra of the neutral molecule and anionic species were virtually identical while the small difference in their $pK_a$ values (Table 1) merely illustrated the slight acid-weakening effect of an ethyl group.

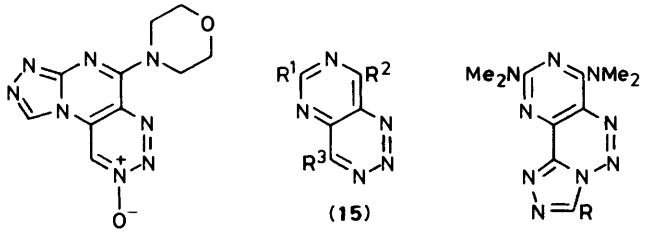
The structure of our other 1,2,4-triazolo[4,3-*a*]pyrimidine, the morpholino compound (**9**), also followed from u.v. studies. It is well known[11,12] that replacing an amino or substituted-amino group in an aromatic or heterocyclic system by $O^-$ has little effect on the u.v. spectrum. Therefore, if our compound had been the 5-morpholino derivative (**10**) its spectrum (Table 1) would have resembled that of the anion of the 5-one derivative but it was quite different and instead resembled that of the anion of the 7-one (**11**; R = X = H) but modified, as predicted from the presence of the 6-amino group.

The results of the orientation studies described above fitted perfectly with those on the formation of some other bicyclic compounds from pyrimidines with a side-chain in the 2-position which could cyclise onto either pyrimidine ring nitrogen atom. In the case of 2-chloroethylamino compounds with an amino or substituted-amino group in the 4-position cyclisation also occurred away from the amino group, but with 4-ones cyclisation occurred in the reverse direction[5,13] (Scheme 1).



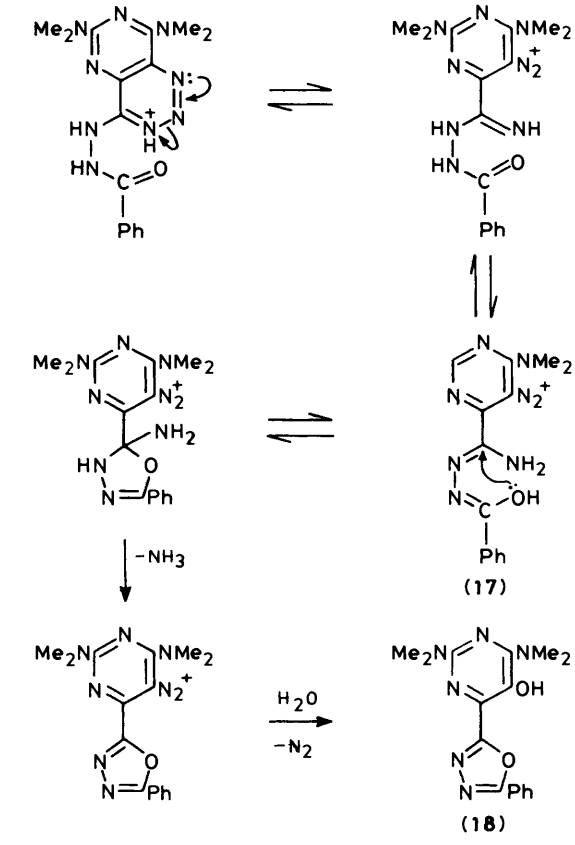
Scheme 1.

As expected, treatment of the bicyclic compound (**9**) with nitrous acid gave a [1,2,4]triazolo[3′,4′:2,3]pyrimido[5,4-*d*]-[1,2,3]triazine-8-oxide (**14**) but the yield of 20% was disappointing in view of the fact that the large number of nitrogen atoms in the triazolopyrimidine was expected to enhance reactivity of the 5-methyl group.



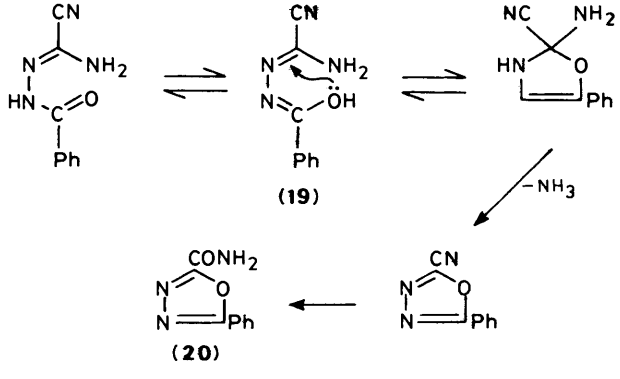
(**14**) (**15**) (**16**)

*Pyrimido*[4,5-e]-1,2,3-*triazolo*[4,3-c][1,2,3]*triazines*.—Triazolotriazines have frequently been made from hydrazino-1,2,4-triazines[14] but rarely from hydrazino-1,2,3-triazines[15] but nevertheless a close relative of the latter system, 6,8-bisdimethylamino-4-hydrazinopyrimido[5,4-*d*]-1,2,3-triazine (**15**; $R^1$ = $R^2$ = $NMe_2$, $R^3$ = $NHNH_2$), was readily converted into 3-substituted-7,9-bisdimethylaminopyrimido[4,5-*e*]-1,2,4-triazolo[4,3-*c*][1,2,3]*triazines* (**16**; R = H, Me, Et, $CHCl_2$, or $NH_2$) by condensation with formic acid, acetic, propionic, or dichloroacetic anhydride, or cyanogen bromide respectively. However, the benzoyl derivative (**15**; $R^1$ = $R^2$ = $NMe_2$, $R^3$ = NHNHCOPh) did not cyclise readily and in polyphosphoric acid at 120—140 °C gave an oxadiazolylpyrimidine (**18**; Scheme 2) whose structure followed from elemental analysis and n.m.r. spectroscopy. A suggested mechanism is given (Scheme 2) and this is supported by the fact that reversible ring-openings, with transient formation of diazonium compounds, are common in fused 1,2,3-triazines[16] and have been postulated in, for example, the hydrolysis of pyrazolo[2,3-*c*][1,2,3]benzotriazines[17] and 4-amino-1,2,3-benzotriazines.[18] Part of the suggested diazonium intermediate (**17**; Scheme 2) has a very similar structure to the benzoyl derivative of 1-cyanoformimidic acid hydrazide, (**19**; Scheme 3), which undergoes an analogous cyclisation[19] to give an oxadiazole (**20**; Scheme 3).



(**17**) (**18**)

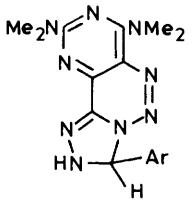
Scheme 2.



(**19**) (**20**)

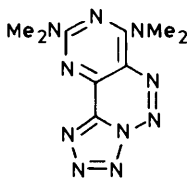
Scheme 3.

Heating the hydrazine (**15**; $R^1 = R^2 = NMe_2$, $R^3 = NHNH_2$) with benzaldehyde or *p*-methoxybenzaldehyde gave hydrazones (**15**; $R^1 = R^2 = NMe_2$, $R^3 = NHN{=}CHAr$) rather than the hoped for isomeric dihydrotriazolopyrimidotriazines (**21**). The failure to cyclise was shown by the $^1H$ and $^{13}C$ n.m.r. spectra of the products.



(**21**)

*Pyrimido*[4,5-e]*tetrazolo*[1,5-c][1,2,3]*triazines*.—Application of one published method for the conversion of a hydrazino into an azide group[15] failed with the hydrazinopyrimidotriazine (**15**; $R^1 = R^2 = NMe_2$, $R^3 = NHNH_2$). Instead of the desired product a high yield of the corresponding amine (**15**; $R^1 = R^2 = NMe_2$, $R^3 = NH_2$) was obtained. Perhaps the desired azide was formed but decomposed in the acetic acid medium, although strongly acidic media are usually necessary for the conversion of azides into amines.[20] A change of solvent to ethanol, to avoid acidic conditions, led to a product which analysed for the desired pyrimidotetrazolotriazine (**22**), but a weak azide band in its i.r. spectrum suggested that the compound (**22**) may be in equilibrium with some of the bicyclic azide from (**15**; $R^1 = R^2 = NMe_2$, $R^3 = N_3$). Solubility problems prevented the sort of detailed n.m.r. and i.r. studies which have been used to demonstrate similar equilibria for several fused tetrazoles.[21] Only one example of a tetrazole ring annelated to a 1,2,3-triazine system is known.[22]



(**22**)

(**23**)

*Pyrimido*[4,5-e][1,2,4]*triazino*[4,3-c][1,2,3]*triazines*.—A pyrimidotriazinotriazine (**23**) was obtained by heating the hydrazine (**15**; $R^1 = R^2 = NMe_2$, $R^3 = NHNH_2$) with ethyl pyruvate in ethanol or by prolonged treatment with neat pyruvic acid at room temperature. This is the first representative of the pyrimido[4,5-*e*][1,2,4]triazino[4,3-*c*][1,2,3]triazine system.

## 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. $^{13}C$ N.m.r. spectra were measured on a Varian CFT 20 instrument. Microanalyses were performed by Butterworth Laboratories Ltd., Teddington, Middlesex. Mass spectra were recorded on a Kratos MS 30 spectrometer using a direct-insertion probe.

6,8-*Dimorpholinopyrimido*[5,4-d]-1,2,3-*triazine* 3-*Oxide* (**1**; $R^1 = R^2$ = morpholino).—5-Amino-6-methyl-2,4-dimorpholinopyrimidine (2.5 g) was dissolved in ethanol (50 ml) containing conc. hydrochloric acid (1 ml) and the mixture was stirred at 0 °C during the addition, during 30 min, of a solution of isopentyl nitrite (3.6 ml) in ethanol (10 ml). The mixture was stirred, with exclusion of light, at 20 °C for 12 h before the solid was filtered off, washed with diethyl ether, and crystallised from toluene as yellow microcrystals (1.3 g), m.p. 210—212 °C (decomp.) [Found: C, 48.8; H, 5.5; N, 30.7%; $M^+$ (mass spectrum), 319. $C_{13}H_{17}N_7O_3$ requires C, 48.9; H, 5.4; N, 30.7%; *M*, 319] (n.m.r., Table 2).

6-*Methylamino*-8-*morpholinopyrimido*[5,4-d]-1,2,3-*triazine*-3-*oxide* (**1**; $R^1$ = NHMe, $R^2$ = morpholino).—5-Amino-6-methyl-2-methylamino-4-morpholinopyrimidine (1.99 g) was treated with isopentyl nitrite as in the previous experiment. The solid product was washed successively with ethanol and then aqueous sodium hydrogen carbonate before being crystallised from toluene to yield the *title compound* as a white solid (2.2 g), m.p. 190 °C (decomp.) [Found: C, 45.6; H, 4.9; N, 37.2%; $M^+$ (mass spectrum), 263. $C_{10}H_{13}N_7O_2$ requires C, 45.6; H, 5.0; N, 37.2%; *M*, 263].

4-*Methylamino*-6,8-*dimorpholinopyrimido*[5,4-d]-1,2,3-*triazine* (**15**; $R^1 = R^2$ = morpholino, $R^3$ = methylamino).—A solution of 4-chloro-6,8-dimorpholinopyrimido[4,5-d]-1,2,3-triazine[23] (0.34 g) in chloroform (30 ml) was heated under reflux with a solution of methylamine (33% w/w) in ethanol (0.2 g) for 1 h. The solution was washed with water, dried ($MgSO_4$), and evaporated. The product was crystallised from methanol as pale yellow prisms (0.3 g), m.p. 270 °C (decomp.) (Found: C, 50.4; H, 6.1; N, 33.7. $C_{14}H_{20}N_8O_2$ requires C, 50.6; H, 6.1; N, 33.7%).

4-(2-*Hydroxethylamino*)-6,8-*dimorpholinopyrimido*[5,4-d]-1,2,3-*triazine* (**15**; $R^1 = R^2$ = morpholino, $R^3 = NHCH_2CH_2OH$).—A solution of 4-chloro-6,8-dimorpholinopyrimido-[5,4-*d*]-1,2,3-triazine[23] (0.34 g), ethanol (80 ml), and ethanolamine (0.25 g) was heated under reflux for 1 h. Water (50 ml) was added and the mixture was refrigerated for 12 h before the solid was filtered off, dried, and crystallised from toluene to yield the *title compound* (0.22 g), m.p. 250—252 °C [Found: C, 49.7; H, 6.2; N, 30.9%; $M^+$ (mass spectrum), 362. $C_{15}H_{22}N_8O_3$ requires C, 49.7; H, 6.1; N, 30.9%; *M*, 362].

4-(2-*Chloroethylamino*)-6,8-*dimorpholinopyrimido*[5,4-d]-1,2,3-*triazine* (**15**; $R^1 = R^2$ = morpholino, $R^3 = CH_2CH_2Cl$).—The previous product (0.9 g) was stirred for 18 h in thionyl chloride (50 ml) before the excess of reagent was removed under reduced pressure below 50 °C. The residue was dissolved in water, and the solution was made alkaline with 4M-ammonium hydroxide and filtered. Reprecipitation afforded the *title compound* (0.8 g), m.p. 224—226 °C (Found: C, 47.2; H, 5.4; N, 29.3. $C_{15}H_{21}ClN_8O_2$ requires C, 47.3; H, 5.6; N, 29.4%).

2,3-*Dihydro*-7,9-*dimorpholinoimidazo*[1,2-c]*pyrimido*[4,5-e]-[1,2,3]*triazine* (**2**).—The previous product (0.9 g) was heated under reflux for 2 h in propan-2-ol (30 ml). The mixture was partly evaporated and cooled before diethyl ether was added to the point of precipitation. On refrigeration the *hydrochloride* of the title compound separated as a yellow powder (0.4 g), m.p. 218—220 °C [Found: C, 45.8; H, 5.5; N, 28.3%; $M^+$ (mass spectrum), 344. $C_{15}H_{20}N_8O_2{\cdot}HCl{\cdot}H_2O$ requires C, 45.2; H, 5.8; N, 28.1%; *M*, 344] (n.m.r., Table 3).

The *title compound* was obtained by dissolving the hydrochloride (0.4 g) in water (5 ml) and making the solution alkaline with 4M-sodium hydroxide. The product crystallised from water as yellow needles (0.3 g), m.p. 180 °C (decomp.) (Found: C, 52.2; H, 5.4; N, 32.1. $C_{15}H_{20}N_8O_2$ requires C, 52.3; H, 5.8; N, 32.5%).

**Table 2.**

| Product | Method | Reaction time (h) | Crystallisation solvent | M.p. | Yield (%) | Found C | Found H | Found N | Found $M^+$ | Required C | Required H | Required N | Required $M^+$ |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| (3; X = NHNHMe, Y = CONHNHMe) | A1 | 20 | EtOH | 224—226 | 69 | 42.8 | 6.2 | 44.5 | | 42.9 | 6.4 | 44.4 | |
| (3; X = $NHCH_2CH_2OH$, Y = $CONHCH_2CH_2OH$) | A2 | 5 | propan-2-ol | 212—213 | 57 | 46.9 | 6.5 | 29.9 | 282 | 46.8 | 6.4 | 29.8 | 282 |
| (3; X = NHcyclohexyl, Y = CONHcyclohexyl) | A3 | 6 | toluene | 205—207 | 62 | 63.9 | 8.5 | 23.6 | 258 | 63.7 | 8.4 | 23.4 | 358 |
| (3; X = $NHCH_2PH$, Y = $CONHCH_2Ph$) | A3 | 16 | toluene | 199—201 | 58 | 67.5 | 6.0 | 22.5 | 374 | 67.4 | 5.9 | 22.4 | 374 |
| (4; R = cyclohexyl, X = NHcyclohexyl) | B | 16 | EtOH | 227—228 | 68 | 61.8 | 7.4 | 26.7 | 369 | 61.8 | 7.4 | 26.5 | 369 |
| (4; R = $CH_2Ph$, X = $NHCH_2Ph$) | B | 16 | EtOH | 246—249 | 78 | 61.6 | 5.2 | 24.2 | 385 | 62.5 | 5.3 | 24.3 | 385 |
| (5) | see Exptl. | 16 | Aq. $Me_2SO$ | 235 (decomp.) | 50 | 43.9 | 4.1 | 44.8 | 219 | 43.8 | 4.1 | 44.7 | 219 |
| (6; *n* = 1, X = morpholino, Y = $NH_2$) | C | | $MeOH–Et_2O$ | 241—242 | 47 | 48.4 | 6.6 | 25.6 | | 48.6 | 6.6 | 25.8 | |
| (6; *n* = 1, X = piperidino, Y = $NH_2$) | C | | $MeOH–Et_2O$ | 250 | 39 | 53.2 | 7.3 | 25.7 | | 53.4 | 7.5 | 26.0 | |
| (7; *n* = 1, X = morpholino) | D | | $EtOH–H_2O$ | 234—235 (decomp.) | 87 | 42.5 | 4.7 | 31.4 | | 42.4 | 4.5 | 31.5 | |
| (7; *n* = 1, X = piperidino) | D | | $EtOH–H_2O$ | 228 (decomp.) | 75 | 46.7 | 4.8 | 31.5 | | 46.5 | 5.2 | 31.6 | |
| (8; X = NHNHCHO, Y = $NO_2$) | E1 | | toluene | 138—140 | 85 | 42.6 | 5.0 | 29.8 | | 42.4 | 4.9 | 29.7 | |
| (8; X = NHNHCOMe, Y = $NO_2$) | E2 | | toluene | 182—183 | 60 | 44.6 | 5.4 | 28.5 | | 44.6 | 5.4 | 28.4 | |
| (8; X = NHNHCOEt, Y = $NO_2$) | E2 | | toluene | 195—196 | 71 | 46.5 | 6.0 | 27.1 | | 46.5 | 5.6 | 27.1 | |
| (8; X = NHNHCOPh, Y = $NO_2$) | E2 | | toluene | 180—181 | 95 | 53.6 | 5.1 | 23.4 | | 53.6 | 5.1 | 23.5 | |
| (8; X = NHNHCHO, Y = $NH_2$) | F | | EtOH | 176—178 | 67 | 47.5 | 6.4 | 33.3 | | 47.6 | 6.4 | 33.3 | |
| (8; X = NHNHCOMe, Y = $NH_2$) | F | | toluene | 198—200 | 89 | 49.7 | 7.0 | 31.4 | | 49.6 | 6.8 | 31.6 | |
| (8; X = NHNHCOEt, Y = $NH_2$) | F | | toluene | 195—196 | 71 | 46.5 | 6.0 | 27.1 | | 46.5 | 5.6 | 27.1 | |
| (8; X = NHNHCOPh, Y = $NH_2$) | F | | toluene | 144—145 | 62 | 58.4 | 6.2 | 25.5 | | 58.5 | 6.1 | 25.6 | |
| (14) | F | 16 | $Bu^nOH$ | 215—217 | 20 | 44.1 | 3.8 | 40.9 | | 43.8 | 3.7 | 40.9 | |
| (15; $R^1$ = $R^2$ = $NMe_2$, $R^3$ = NHN=CHPh) | H | 48 | EtOH | 218 (decomp.) | 84 | 57.1 | 5.7 | 37.5 | | 57.0 | 5.7 | 37.4 | |
| [15; $R^1$ = $R^2$ = $NMe_2$, $R^3$ = $NHN=C_6H_4OMe(p)$] | H | 48 | EtOH | 191—192 | 86 | 55.6 | 5.8 | 34.3 | | 55.6 | 5.8 | 34.3 | |
| (16; R = H) | G1 | 5 | MeOH | 257 (decomp.) | 84 | 46.5 | 5.2 | 48.7 | 259 | 46.3 | 5.1 | 48.6 | 259 |
| (16; R = Me) | G2 | 48 | toluene | 266 (decomp.) | 85 | 48.3 | 5.6 | 46.2 | 273 | 48.3 | 5.5 | 46.1 | 273 |
| (16; R = Et) | G2 | 48 | propan-2-ol | 196—197 | 78 | 50.1 | 5.9 | 43.9 | 287 | 50.2 | 6.0 | 43.9 | 287 |
| (16; R = $CHCl_2$) | G3 | 48 | propan-2-ol | 216 (decomp.) | 82 | 38.7 | 4.0 | 36.8 | | 38.6 | 3.8 | 36.8 | |
| (16; R = $NH_2$) | G4 | 2 | $HO[CH_2]_2OEt$ | 238 (decomp.) | 59 | 43.8 | 5.2 | 51.3 | 274 | 43.8 | 5.1 | 51.2 | 274 |

8-*Amino*-2,3-*dihydro*-5-(*substituted amino*)-7-(*substituted aminocarbonyl*)*imidazo*[1,2-c]*pyrimidines* (**3**).—*General method A.* Methyl 8-amino-5-chloro-2,3-dihydroimidazo[1,2-*c*]pyrimidine-7-carboxylate (0.5 g) and the relevant amine or hydrazine (5 ml) were heated under reflux (160 °C for benzylamine) for a suitable period. The product was filtered (method A1), or treated with propan-2-ol and refrigerated (method A2), or treated with water and extracted with methylene dichloride (method A3). Crystallisation from a suitable solvent gave the *title compounds* (data in Tables 2 and 3).

2,3-*Dihydro*-8-*substituted*-5-(*substituted amino*)*imidazo*-[1′,2′:1,6]*pyrimido*[5,4-d][1,2,3]*triazin*-7(8H)-*ones* (**4**).—*General method B.* The relevant amide, prepared by method A above (0.5 g), was dissolved in ethanol (5 ml) and the solution was adjusted to pH 3 by addition of conc. hydrochloric acid. The solution was cooled to 0 °C and a solution of isopentyl nitrite (0.55 ml) in ethanol (5 ml) was added during 10 min. The mixture was stirred for 16 h, neutralised with 4M-ammonium hydroxide, and chilled in ice for 3 h. The solid was collected, washed successively with water then ethanol, and crystallised to give the desired *tricyclic compound* (data in Tables 2 and 3).

2,3-*Dihydro*-5-*methylaminoimidazo*[1′,2′:1,6]*pyrimido*-[5,4-d][1,2,3]*triazine* 3-*Oxide* (**5**).—2,3-Dihydro-5-methylamino-7-methyl-8-nitroimidazo[1,2-*c*]pyrimidine hydrochloride[13] (1 g) was suspended in methanol (100 ml) containing 5% palladium–carbon (0.25 g) and shaken in an atmosphere of hydrogen until the theoretical uptake was observed. The catalyst was filtered off and washed with hot methanol (30 ml). The combined filtrates were evaporated under reduced pressure and the residue was triturated with light petroleum (b.p. 40—60 °C) which was then decanted off. The residue was treated with ethanol (30 ml), isopentyl nitrite (2 g), and hydrochloric acid as in general method B above (data in Tables 2 and 3).

6-*Amino*-2,3-*dihydro*-5-*methyl*-7-(*substituted amino*)*imidazo*-[1,2-a]*pyrimidine Hydrochlorides* (**6**; *n* = 1, X = morpholino or piperidino, Y = $NH_2$).—*General method C.* The appropriate nitro compound (**6**; *n* = 1, Y = $NO_2$)[5] (1 g) was dissolved in methanol (50 ml) and shaken with Raney nickel (5 g settled suspension) in an atmosphere of hydrogen until the theoretical uptake was achieved. After 2 min reflux the catalyst was filtered off and the volume of the filtrate was reduced, by evaporation, to 10 ml. Diethyl ether was added to the point of precipitation and the mixture was refrigerated to produce crystals of the *title compounds* (data in Table 2).

1,2-*Dihydro*-5-(*substituted amino*)*imidazo*[2′,1′:2,3]*pyrimido*-[5,4-d][1,2,3]*triazine* 8-*Oxide Hydrochlorides* (**7**; *n* = 1, X =

**Table 3.** $^1$H N.m.r. spectroscopy

| Compound | Solvent[a] | $\delta_H$, multiplicity, integration, and assignment |
|---|---|---|
| (1; $R^1 = R^2$ = morpholino) | A | 3.90 (m, 8 H, 6-morpholino), 3.75 (m, 4 H) and 4.37 (br s, 4 H) (8-morpholino), 7.92 (s, 1 H, 4-H) |
| (1; $R^1$ = NHMe, $R^2$ = morpholino) | A | 2.95 (s, 3 H, Me), 3.85 (m, 4 H) and 4.35 (br s, 4 H) (8-morpholino), 7.95 (br s, 1 H, NH), 9.47 (s, 1 H, 4-H) |
| (2) Hydrochloride | A | 3.70 (m, 8 H, 9-morpholino), 3.7 (m, 4 H) and 4.30 (br s, 4 H) (7-morpholino), 4.05 (m, 2 H) and 4.10 (m, 2 H) ($CH_2CH_2$) |
| (3; X = $NHCH_2CH_2OH$, Y = $CONHCH_2CH_2OH$) | A | 3.12—3.70 (m, 8 H, 2 × $CH_2CH_2O$), 3.91 (s, 4 H, 2- and 3-$H_2$), 4.67 (br s, 2 H, 2 × OH), 5.67 (br s, 2 H, $NH_2$), 6.02 (t, 1 H, NH), 8.03 (t, 1 H, CONH) |
| (3; X = NHNHMe, Y = CONHNHMe) | B | 2.52 (s, 3 H, Me), 2.91 (s, 3 H, Me), 3.35 (br s, 2 H, 2 × NH), 3.82—4.50 (m, 4 H, $CH_2CH_2$), 5.96 (br s, 2 H, $NH_2$), 8.77 (s, 1 H, NH), 9.03 (s 1 H, NH) |
| (3; X = NHcyclohexyl, Y = CONHcyclohexyl) | C | 0.90—2.40 (m, 22 H, 2 × $C_6H_{11}$), 3.62 (br s, 2 H, 2 × NH), 3.40—4.30 (m, 4 H, $CH_2CH_2$), 5.55 (br s, 2 H, $NH_2$) |
| (3; X = $NHCH_2Ph$, Y = $CONHCH_2PH$) | B | 3.85—4.10 (m, 4 H, $CH_2CH_2$), 4.35 (d, 2 H, $NHCH_2$), 4.45 (d, 2 H, $NHCH_2$), 5.45 (br s, 4 H, 2 × NH and $NH_2$), 7.10—7.40 (m, 10 H, 2 × Ph) |
| (4; R = cyclohexyl, X = NHcyclohexyl) | A | 1.05—2.30 (m, 22 H, 2 × $C_6H_{11}$), 3.80—4.40 (m, 4 H, $CH_2CH_2$), 7.20 (d, 1 H, NH) |
| (4; R = $CH_2Ph$, X = $NHCH_2Ph$) | A | 4.62—4.64 (m, 4 H, $CH_2CH_2$), 4.75 (d, 2 H, $NHCH_2$), 5.48 (s, 2 H, $NCH_2$), 7.20—7.60 (m, 10 H, 2 × Ph) |
| (5) | D | 2.86 (s, 3 H, Me), 3.60—4.20 (m, 4 H, $CH_2CH_2$), 7.80 (s, 1 H, 4-H) |
| (7; $n$ = 1, X = morpholino) | A | 3.95 (m, 2 H) and 5.73 (m, 2 H) ($CH_2CH_2$), 3.85 (m, 4 H) and 4.40 (br s, 4 H) (morpholino), 8.95 (s, 1 H, 9-H) |
| (7; $n$ = 2, X = morpholino) | A | 2.80—4.80 (m, 14 H, morpholino + $CH_2CH_2CH_2$), 9.13 (1 H, 1-H) |
| (8; X = $NHCH_2CH_2CH_2Cl$, Y = $NO_2$) | C | 2.05 (q, 2 H, middle $CH_2$), 2.40 (s, 3 H, Me), 3.30—3.80 (m, 12 H, morpholino + $CH_2Cl$ and $CH_2NH$), 5.54 (br s, 1 H, NH) |
| (8; X = $NHNH_2$, Y = $NO_2$) | B | 2.36 (s, 3 H, Me), 3.20—3.80 (m, 8 H, morpholino), 4.2 (br s, 2 H, $NH_2$), 8.38 (br s, 1 H, NH) |
| (8; X = NHNHCHO, Y = $NO_2$) | B | 2.38 (s, 3 H, Me), 3.34—3.54 (m, 4 H) and 3.56—3.80 (m, 4 H) (morpholino), 8.05 (d, 1 H, CHO), 9.25 (br s, 1 H, NH), 9.81 (br s, 1 H, NH) |
| (8; X = NHNHCOMe, Y = $NO_2$) | C | 2.00 (s, 3 H, Me), 2.63 (s, 3 H, COMe), 3.2—3.85 (m, 8 H, morpholino), 8.25 (br s, 1 H, NH), 9.26 (br s, 1 H, NH) |
| (8; X = NHNHCOEt, Y = $NO_2$) | B | 1.14 (t, 3 H, $MeCH_2$), 2.25 (q, 2 H, $MeCH_2$), 2.64 (s, 3 H, Me), 3.30—3.55 (m, 4 H) and 3.60—3.90 (m, 4 H) (morpholino), 8.75 (br s, 1 H, NH), 9.48 (br s, 1 H, NH) |
| (8; X = NHNHCOPh, Y = $NO_2$) | B | 2.36 (s, 3 H, Me), 3.20—3.80 (m, 8 H, morpholino), 7.30—8.05 (m, 5 H, Ph), 8.30 (br s, 1 H, NH), 9.72 (br s, 1 H, NH) |
| (8; X = NHNHCHO, Y = $NH_2$) | A | 2.19 (s, 3 H, Me), 3.05—3.35 (m, 4 H) and 3.60—3.92 (m, 4 H) (morpholino), 7.67 (br s, 1 H, NH), 8.03 (d, 1 H, CHO), 9.53 (br s, 1 H, NH) |
| (8; X = NHNHCOMe, Y = $NH_2$) | A | 1.94 (s, 3 H, MeCO), 2.22 (s, 3 H, Me), 3.10—3.40 (m, 4 H), and 3.65—3.95 (m, 4 H) (morpholino), 3.50 (br s, 2 H, $NH_2$), 7.11 (br s, 1 H, NH), 9.40 (br s, 1 H, NH) |
| (8; X = NHNHCOEt, Y = $NH_2$) | B | 1.14 (t, 3 H, $MeCH_2$), 2.25 (q, 2 H, $MeCH_2$), 2.37 (s, 3 H, Me), 3.30—3.55 (m, 4 H) and 3.60—3.90 (m, 4 H) (morpholino), 8.75 (br s, 1 H, NH), 9.48 (br s, 1 H, NH) |
| (8; X = NHNHCOPh, Y = $NH_2$) | C | 2.35 (s, 3 H, Me), 3.17 (br s, 2 H, $NH_2$), 3.30—3.50 (m, 4 H) and 3.75—4.00 (m, 4 H) (morpholino), 7.13 (br s, 2 H, 2 × NH), 7.25—8.10 (m, 5 H, Ph) |
| (9) | A | 2.50 (s, 3 H, Me), 3.15—3.55 (m, 4 H) and 3.65—3.95 (m, 4 H) (morpholino), 4.58 (br s, 2 H, $NH_2$), 8.83 (s, 1 H, 3-H), 2.29 (s, 3 H, Me) |
| (12; R = Et, X = $NH_2$) | B | 1.64 (t, 3 H, $CH_2Me$), 2.29 (s, 3 H, Me), 3.30 (q, 2 H, $MeCH_2$), 5.75 (br s, 2 H, $NH_2$) |
| (13; R = Et, X = H) | B | 1.31 (t, 3 H, $CH_2Me$), 2.33 (s, 3 H, Me), 2.77 (q, 2 H, $MeCH_2$), 5.71 (s, 1 H, 6-H) |
| (13; R = Et, X = $NO_2$) | B | 1.38 (t, 3 H, $CH_2Me$), 2.52 (s, 3 H, Me), 2.87 (q, 2 H, $CH_2Me$), 14.95 (br s, 1 H, NH) |
| (14) | A | 2.65—3.95 (m, 4 H) and 4.14—4.50 (m, 4 H) (morpholino), 8.80 (s, 1 H, 1-H), 8.65 (s, 1 H, 9-H) |
| (15; $R^1 = R^2$ = $NMe_2$, $R^3$ = $NHNH_2$) | B | 3.13 (s, 6 H, $NMe_2$), 3.52 (s, 6 H, $NMe_2$), 4.52 (br s, 1 H, $NH_2$), 8.05 (br s, 1 H, NH) |
| (15; $R^1 = R^2$ = $NMe_2$, $R^3$ = NHNHCOPh) | B | 3.60 (s, 6 H, $NMe_2$), 4.10 (s, 6 H, $NMe_2$), 7.75—8.65 (m, 5 H, Ph) |
| (15; $R^1 = R^2$ = $NMe_2$, $R^3$ = NHN=CHPh) | E | 3.17 (s, 6 H, $NMe_2$), 3.52 (s, 6 H, $NMe_2$), 3.85 (br s, 1 H, NH), 7.30—7.90 (m, 5 H, Ph), 8.53 (s, 1 H, N=CH) |
| [15; $R^1 = R^2$ = $NMe_2$, $R^3$ = $NHN{=}CHC_6H_4OMe(p)$][b] | C | 3.20 (s, 6 H, $NMe_2$), 3.60 (s, 6 H, $NMe_2$), 3.82 (s, 3 H, OMe), 6.92 (d, 2 H) and 7.78 (d, 2 H) (aromatics), 8.18 (s, 1 H, N=CH) |
| (16; R = H) | B | 3.25 (s, 6 H, $NMe_2$), 3.60 (br s, 6 H, $NMe_2$), 8.50 (s, 1 H, 3-H) |
| (16; R = Me) | B | 2.65 (s, 3 H, Me), 3.02 (s, 6 H, $NMe_2$), 3.32 (s, 6 H, $NMe_2$) |
| (16; R = Et) | C | 2.50 (t, 3 H, Me), 3.00 (q, 2 H, $CH_2$), 3.20 (d, 12 H; 2 × $NMe_2$) |
| (16; R = $CHCl_2$) | B | 3.25 (s, 6 H, $NMe_2$), 3.39 (s, 6 H, $NMe_2$), 7.50 (s, 1 H, $CHCl_2$) |
| (16; R = $NH_2$) | D | 3.17 (s, 6 H, $NMe_2$), 3.50 (s, 6 H, $NMe_2$), 5.85 (br s, 2 H, $NH_2$) |
| (18) | C | 3.13 (s, 6 H, $NMe_2$), 3.28 (s, 6 H, $NMe_2$), 7.40—8.30 (m, 5 H, Ph), 9.58 (br s, 1 H, OH) |
| (23) | A | 3.51 (s, 6 H, $NMe_2$), 3.54 (s, 6 H, $NMe_2$), 3.80 (s, 3 H, Me) |

[a] Solvent: A = $(CD_3)_2SO$, B = $(CD_3)_2SO$–$CDCl_3$, C = $CDCl_3$, D = $(CD_3)_2SO$ at 140 °C, E = $(CD_3)_2SO$ at 105 °C. [b] $^{13}$C N.m.r. spectrum in solvent B showed peak at $\delta_C$ 147.32 p.p.m. (–N=CH–).

morpholino or piperidino).—*General method D.* The appropriate imidazopyrimidine (previous experiment) (0.2 g) 4M-hydrochloric acid (1 ml), and water (4 ml) were stirred at 0 °C during the addition of a solution of sodium nitrite (0.1 g) in water (1 ml). The mixture was then heated on a water-bath for 5 min, treated with ethanol 3 ml, and refrigerated to yield the *title product* as pale yellow needles (data in Tables 2 and 3).

2-(3-*Chloropropylamino*)-4-*methyl*-6-*morpholino*-5-*nitropyrimidine* (**8**; X = $NHCH_2CH_2CH_2Cl$, Y = $NO_2$).—The corresponding hydroxypropylamino compound (**8**; X = $NHCH_2CH_2CH_2OH$, Y = $NO_2$) (3 g) was added portionwise to stirred thionyl chloride and the resulting solution was stirred for a further 12 h. The excess of reagent was removed under reduced pressure at 50 °C and the oily residue was dissolved in water and basified with 4M-ammonium hydroxide. The solid was filtered off, washed with water, and crystallised from ethanol to give the *title compound* (2.2 g) as yellow needles, m.p. 102—103 °C [Found: C, 45.8; H, 5.85; N, 22.1%; $M^+$ (mass spectrum), 315.1097. $C_{12}H_{18}ClN_5O_3$ requires C, 45.6; H, 5.7; N, 22.2%; *M*, 315.1097].

3,4-*Dihydro*-6-*methyl*-8-*morpholino*-7-*nitro*-2H-*pyrimido*[1,2-a]*pyrimidine Hydrochloride* (**6**; *n* = 2, X = morpholino, Y = $NO_2$).—The product from the previous experiment (2 g) was heated under reflux in propan-2-ol for 24 h and the solution was then evaporated to 20 ml. Diethyl ether was added to the cooled solution and the solid was filtered off and crystallised from propan-2-ol–diethyl ether as a yellow powder (2.6 g), m.p. 187—188 °C [Found: C, 45.6; H, 5.8; N, 22.0%; $M^+$ (mass spectrum), 315. $C_{12}H_{18}ClN_5O_3$ requires C, 45.6; H, 5.7; N, 22.2%; *M*, 315].

9,10-*Dihydro*-5-*morpholino*-8H-*pyrimido*[2′,1′:2,3]*pyrimido*[5,4-d][1,2,3]*triazine* 2-*Oxide Hydrochloride* (**7**; *n* = 2, X = morpholino).—The product of the previous experiment (2 g) was reduced by general method C (above). The resulting solid was dissolved in ethanol (30 ml), adjusted to pH 3 by dropwise addition of conc. hydrochloric acid, and then stirred at 0 °C, during the addition (15 min) of a solution of isopentyl nitrite (6 ml) in ethanol (15 ml) and then for a further 2 h. The solid was collected, washed with diethyl ether, and crystallised from methanol to give the *title compound* (1.4 g), m.p. 244 °C (decomp.) (Found: C, 44.3; H, 5.1; N, 30.2. $C_{12}H_{16}ClN_7O_2$ requires C, 44.2; H, 5.0; N, 30.1%) (n.m.r., Table 3).

2-*Hydrazino*-4-*methyl*-6-*morpholino*-5-*nitropyrimidine* (**8**; X = $NHNH_2$, Y = $NO_2$).—A solution of hydrazine hydrate (1.6 g) and triethylamine (3.2 g) and *NN*-dimethylformamide (DMF) (30 ml) was added during 30 min to a warm, stirred solution of 2-chloro-4-methyl-6-morpholino-5-nitropyrimidine (8 g) in DMF (30 ml). The mixture was stirred at 20 °C for a further 12 h and the solid was filtered off. A second crop was obtained by addition of water (50 ml) to the filtrate and the combined solids were washed with water, dried, and crystallised from propan-2-ol to give the yellow *title compound* (5.44 g), m.p. 162—163 °C [Found: C, 42.6; H, 5.5; N, 33.1%; $M^+$ (mass spectrum), 254. $C_9H_{14}N_6O_3$ requires C, 42.5; H, 5.6; N, 33.1%; *M*, 254].

2-(2-*Acylhydrazino*)-4-*methyl*-6-*morpholino*-5-*nitropyrimidines* (**8**; X = NHNHCOR, Y = $NO_2$).—*Method E*1. 2-Hydrazino-4-methyl-6-morpholino-5-nitropyrimidine (2 g) and formic acid (30 ml) were heated under reflux for 50 min. Most of the solvent was removed under reduced pressure, and water (20 ml) was added to the residue. The suspension was made alkaline with sodium hydrogen carbonate and extracted with methylene dichloride (3 × 5 ml). The combined extracts were dried ($MgSO_4$) and evaporated to yield the 2-*formylhydrazino* compound which was crystallised from toluene (data in Tables 2 and 3).

*General method E*2. 2-Hydrazino-4-methyl-6-morpholino-5-nitropyrimidine (1.5 g) was added in portions to the appropriate acid anhydride (9 ml) in dry diethyl ether (20 ml). The mixture was stirred for a further 15 min before the solid was filtered off, washed with diethyl ether, dried, and crystallised (data in Tables 2 and 3).

*Method E*3. Benzoyl chloride (0.9 g) in dry pyridine (5 ml) was added dropwise to a stirred solution of 2-hydrazino-4-methyl-6-morpholino-5-nitropyrimidine (1.5 g) in dry pyridine (20 ml). The resulting mixture was heated on a steam-bath for 5 min, and then evaporated under reduced pressure. The residue was triturated with water and the solid was collected, dried, and crystallised to yield the 2-*benzoylhydrazino* derivative (data in Tables 2 and 3).

2-(2-*Acylhydrazino*)-5-*amino*-4-*methyl*-6-*morpholinopyrimidines* (**8**; X = acylhydrazino, Y = $NH_2$).—*General method F.* The appropriate nitro compound (prepared by method E above) (1 g) was suspended in water (150 ml) and the mixture was shaken with 5% palladium–carbon in an atmosphere of hydrogen until the theoretical uptake was observed. Charcoal was added and the mixture heated, under reflux, for 2 min, and filtered. The residue was washed with hot water (50 ml) and the combined filtrates were evaporated under reduced pressure. The residual oil was triturated with diethyl ether and the solid was filtered off, dried, and crystallised (data in Tables 2 and 3).

6-*Amino*-5-*methyl*-7-*morpholino*-1,2,3-*triazolo*[4,3-a]*pyrimidine* (**9**).—5-Amino-2-(2-formylhydrazino)-6-methyl-4-morpholinopyrimidine (1.5 g) and polyphosphoric acid (15 ml) were heated at 125—135 °C for 5 h and then cooled before ice (50 g) was added. After its pH value had been adjusted to 8 with 4M-ammonium hydroxide the solution was continuously extracted with methylene dichloride for 48 h. The extract was dried and evaporated and the residue was crystallised from methanol to give the *title compound* (0.8 g), m.p. 270 °C (decomp.) [Found: C, 51.3; H, 6.1; N, 36.0%; $M^+$ (mass spectrum), 234. $C_{10}H_{14}N_6O$ requires C, 51.3; H, 6.0; N, 35.9%; *M*, 234] (n.m.r., Table 3).

6-*Amino*-3-*ethyl*-7-*methyl*-1,2,4-*triazolo*[4,3-a]*pyrimidin*-5(8H)-*one* (**12**; R = Et, X = $NH_2$).—5-Amino-4-methyl-6-morpholino-2-(2-propionylhydrazino)pyrimidine (1.3 g) and polyphosphoric acid (15 ml) were heated at 130 °C for 5 h and then cooled before ice (50 g) was added. The solution was neutralised with sodium hydrogen carbonate and extracted as described in the previous experiment. The title compound (0.7 g), m.p. 225—230 °C, crystallised from methanol [Found: C, 49.8; H, 5.8; N, 36.3%; $M^+$ (mass spectrum), 193. $C_8H_{11}N_5O$ requires C, 49.7; H, 5.7; N, 36.3%; *M*, 193] (n.m.r., Table 3).

2-*Ethyl*-5-*methyl*[1,2,4]*triazolo*[1,5-a]*pyrimidin*-7(4H)-*one* (**13**; R = Et, X = H).—A mixture of 3-amino-5-ethyl-1H-1,2,4-triazole[9] (3 g), ethyl acetoacetate (3.6 g), and glacial acetic acid (15 ml) was heated under reflux for 6 h and then evaporated to dryness under reduced pressure. The residue was washed with ether, dried, and crystallised from methanol to yield the *title compound* (2.4 g), m.p. 236—238 °C [Found: $M^+$ (mass spectrum), 178.0853. $C_8H_{10}N_4O$ requires *M*, 178.0854] (n.m.r., Table 3).

2-*Ethyl*-5-*methyl*-6-*nitro*[1,2,4]*triazolo*[1,5-a]*pyrimidin*-7(4H)-*one* (**13**; R = Et, X = $NO_2$). —The product of the previous reaction (2 g) was added in portions to a stirred

mixture of conc. sulphuric acid (4 ml) and fuming nitric acid (4 ml) at 7—10 °C. The mixture was stirred at *ca.* 10 °C for 1 h and then poured onto ice (20 g). The precipitated solid was filtered off, washed with water, dried, and crystallised from ethanol to give the *title compound* as yellow needles (1.5 g), m.p. 234—236 °C [Found: $M^+$ (mass spectrum), 223.0703. $C_8H_9N_5O_3$ requires *M*, 223.0705] (n.m.r., Table 3).

6-*Amino*-2-*ethyl*-5-*methyl*[1,2,4]*triazolo*[1,5-a]*pyrimidin*-7(4H)-*one* (**13**; R = Et, X = $NH_2$).—The product of the previous reaction (0.5 g), methanol (30 ml), and Raney nickel (1 g settled suspension) were shaken in an atmosphere of hydrogen until the theoretical uptake was achieved. The catalyst was filtered off and the filtrate was evaporated to low volume. The solid was filtered off and crystallised from methanol to yield the *title compound* (0.35 g), m.p. 225 °C (Found: C, 49.8; H, 5.8; N, 36.3. $C_8H_{11}N_5O$ requires C, 49.7; H, 5.7; N, 36.3%).

5-*Morpholino*[1,2,4]*triazolo*[3′,4′:2,3]*pyrimido*[5,4-d]-[1,2,3]*triazine* 8-*Oxide* (**14**).—A suspension of 6-amino-5-methyl-7-morpholino-1,2,4-triazolo[4.3-a]*pyrimidine* (**9**) (0.4 g) in ethanol (15 ml) was treated by general method B to yield the title compound (data in Tables 2 and 3).

6,8-*Bisdimethylamino*-4-*hydrazinopyrimido*[5,4-d]-1,2,3-*triazine* (**15**; $R^1 = R^2 = NMe_2$, $R^3 = NHNH_2$).—A mixture of 6,8-bisdimethylamino-4-chloropyrimido[5,4-d]-1,2,3-triazine[2] (1.5 g), triethylamine (0.6 g), and 98% hydrazine hydrate (0.3 g) in ethanol (30 ml) was stirred for 16 h and the resulting solid was filtered off, washed successively with water and methanol, and crystallised from methanol to yield the *title product* (1.26 g), m.p. 201—202 °C [Found: C, 43.4; H, 6.0; N, 50.6%; $M^+$ (mass spectrum), 249. $C_9H_{15}N_9$ requires C, 43.4; H, 6.1; N, 50.6%; *M*, 249].

7,9-*Bisdimethylaminopyrimido*[4,5-e]-1,2,4-*triazolo*[4,3-c]-[1,2,3]*triazines* (**16**).—The hydrazine from the previous reaction was treated by one of the following methods.

*Method G*1. The hydrazine (0.4 g) was heated under reflux with formic acid (10 ml) for 5 h. The solution was cooled and neutralised with sodium hydrogen carbonate before the *product* was filtered off, washed successively with water and methanol, dried, and crystallised (data in Tables 2 and 3).

*Method G*2. The hydrazine (0.4 g) was stirred with the appropriate anhydride (4 ml acetic anhydride or 8 ml propionic anhydride) for 48 h and the *product* was filtered off, washed with a little diethyl ether, and crystallised (data in Tables 2 and 3).

*Method G*3. The hydrazine (0.4 g), dry benzene (25 ml), and dichloroacetic anhydride (1.6 g) were stirred together for 48 h. The solvent was removed under reduced pressure and the residual oil was titurated with diethyl ether. The *product* was filtered off and crystallised (data in Tables 2 and 3).

*Method G*4. The hydrazine (0.4 g), methanol (30 ml), and cyanogen bromide (0.16 g) were heated under reflux for 2 h, then cooled and treated with triethylamine (0.16 g). The *solid* was collected, washed successively with water and methanol, dried, and crystallised (data in Tables 2 and 3).

4-(2-*Benzoylhydrazino*)-6,8-*bisdimethylaminopyrimido*-[5,4-d]-1,2,3-*triazine* (**15**; $R^1 = R^2 = NMe_2$, $R^3$ = NHNHCOPh).—A solution of benzoyl chloride (0.2 g) in dry pyridine (5 ml) was added during 15 min to a stirred solution of 6,8-bisdimethylamino-4-hydrazinopyrimido[5,4-*d*]-1,2,3-triazine (0.4 g), and the mixture was stirred for a further 30 min, then evaporated under reduced pressure and the residue was triturated with water to give a solid which was collected, washed with water, dried, and crystallised from propan-2-ol to yield the *title compound* (0.4 g), m.p. 222 °C (decomp.) (Found: C, 54.4; H, 5.4; N, 35.7. $C_{16}H_{19}N_9O$ requires C, 54.5; H, 5.4; N, 35.7%) (n.m.r., Table 3).

2,4-*Bisdimethylamino*-5-*hydroxy*-6-(5-*phenyl*-1,3,4-*oxadiazol*-2-*yl*)*pyrimidine* (**18**).—The product of the previous reaction (0.3 g) was heated with polyphosphoric acid (2 ml) at 135 °C for 2 h; the mixture was then cooled, treated with ice (20 g), and neutralised with sodium hydrogen carbonate. The solid was filtered off, washed with water, dried, and crystallised from ethanol to yield the *title compound* (0.23 g), m.p. 163—164 °C [Found: C, 59.0; H, 5.6; N, 25.8%; $M^+$ (mass spectrum), 326.1489. $C_{16}H_{18}N_6O_2$ requires C, 58.9; H, 5.6; N, 25.8%; *M*, 326.1490] (n.m.r., Table 3).

4-*Arylidenehydrazino*-6,8-*bisdimethylaminopyrimido*[5,4-d]-1,2,3-*triazines* (**15**; $R^1 = R^2 = NMe_2$, $R^3$ = NHN=CHAr).—*General method H.* The appropriate aldehyde (0.0012 mol), 6,8-bisdimethylaminopyrimido[5,4-*d*]-1,2,3-triazine (**15**; $R^1 = R^2 = NMe_2$, $R^3$ = H) (0.0012 mol), and ethanol (20 ml) were heated under reflux for 48 h and then the mixture was cooled and filtered. The *residue* was washed with ethanol, dried, and crystallised (data in Tables 2 and 3).

4-*Amino*-6,8-*bisdimethylaminopyrimido*[5,4-d]-1,2,3-*triazine* (**15**; $R^1 = R^2 = NMe_2$, $R^3 = NH_2$).—Isopentyl nitrite (0.32 ml) was added dropwise to a stirred suspension of 6,8-bisdimethylamino-4-hydrazinopyrimido[5,4-*d*]-1,2,3-triazine (**15**; $R^1 = R^2 = NMe_2$, $R^3 = NHNH_2$) (0.2 g) in glacial acetic acid (2 ml) at 0—5 °C. The mixture was stirred for a further 1 h at 0—5 °C, then kept at that temperature for 15 h. The solid was filtered off, washed with diethyl ether, and crystallised from methanol to give the *title compound* (0.12 g), m.p. 268—269 °C (decomp.) [Found: C, 46.3; H, 6.1; N, 47.7%; $M^+$ (mass spectrum), 234.1339. $C_9H_{14}N_8$ requires C, 46.1; H, 6.0; N, 47.8%; *M*, 234.1340].

7,9-*Bisdimethylaminopyrimido*[4,5-e]*tetrazolo*[1,5-c][1,2,3]-*triazine* (**22**).—The pH value of a solution of 6,8-bisdimethylamino-4-hydrazinopyrimido[5,4-*d*]-1,2,3-triazine (**15**; $R^1 = R^2 = NMe_2$, $R^3 = NHNH_2$) (0.2 g) in ethanol (10 ml) was adjusted to 3 by the addition of conc. hydrochloric acid. The resulting solution was stirred at 0 °C during the addition (15 min) of a solution of isopentyl nitrite (0.32 g) in ethanol (2 ml), and then for a further 1 h. The solid was filtered off, washed with diethyl ether, and crystallised from ethanol to give the *title compound* as yellow needles (0.18 g), m.p. 159—160 °C [Found: C, 41.7; H, 4.7; N, 53.9%; $M^+$ (mass spectrum), 234. $C_9H_{12}N_{10}$ requires C, 41.5; H, 4.7; N, 53.8%; *M*, 234].

8,10-*Bisdimethylamino*-3-*methylpyrimido*[4,5-e][1,2,4]*triazino*[4,3-c][1,2,3]*triazine*-4-*one* (**23**).—(*a*) 6,8-Bisdimethylamino-4-hydrazinopyrimido[5,4-*d*]-1,2,3-triazine (**15**; $R^1 = R^2 = NMe_2$, $R^3 = NHNH_2$) (0.5 g), ethyl pyruvate (0.46 g), glacial acetic acid (0.2 ml), and ethanol (25 ml) were stirred together at 20 °C for 2 h, then heated under reflux for 2 h. The solid was filtered from the cooled mixture, washed with ethanol, dried, and crystallised from aqueous dimethyl sulphoxide to yield the *title compound* (0.38 g), m.p. 246—248 °C [Found: C, 47.7; H, 5.1; N, 41.9%; $M^+$ (mass spectrum), 301. $C_{12}H_{15}N_9O$ requires C, 47.8; H, 5.0; N, 41.8%; *M*, 301].

(*b*) An identical product (0.18 g) was obtained by stirring the same hydrazine (0.2 g) with pyruvic acid (3 ml) at 25 °C for 12 h. The solid was filtered off and crystallised as in (*a*).

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