Tricyclic Heteroaromatic Systems Containing a Bridgehead Nitrogen Atom. Part 3.[1] [1,2,4]Triazolo[3',4':3,2]pyrazolo[3,4-*d*]pyrimidines, Tetrazolo[1',5':1,5]pyrazolo[3,4-*d*]pyrimidines and Pyrimido-[5',4':4,5]pyrazolo[3,2-*c*][1,2,4]triazines

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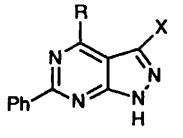
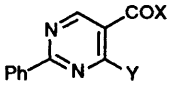
6-Phenyl-1*H*-pyrazolo[3,4-*d*]pyrimidin-3(2*H*)-one **16** has been prepared and converted into its 3-chloro **6**, 3-thioxo **17** and 3-methylthio derivatives **9**. Each of these could be converted into the 3-hydrazino derivative **3**, cyclisation of which with carbon disulfide or triethyl orthoformate generated the fused 1,2,4-triazoles **23** and **20**, respectively. Alternatively, the hydrazino derivative **3** gave a substituted hydrazide **26** or thiosemicarbazide **25**, from which the 1,2,4-triazoles **21** and **22** respectively were obtained. The equilibrium between 3-azido-6-phenyl-1*H*-pyrazolo[3,4-*d*]-pyrimidine **5** and 2-phenyl-9*H*-tetrazolo[1'5':1,5]pyrazolo[3,4-*d*]pyrimidine **27** was studied.

3-Diazo-4-methyl-6-phenyl-1*H*-pyrazolo[3,4-*d*]pyrimidine **29** was prepared by diazotisation of the corresponding amine **1** and converted into the 3-azido compound **4**, which could not be cyclised to form a tetrazole. Finally, the diazo compound **29** readily formed the pyrimido[5'4':4,5]pyrazolo-[3,2-*c*][1,2,4]triazine derivatives **32** and **33**, when treated with pentane-2,4-dione and ethyl acetoacetate respectively.

In earlier papers[1,2] we have described the preparation of tricyclic purine analogues of the type ABC, in which ring A = pyrimidine, ring B = pyrazole or isothazole, ring C = imidazole or pyrimidine, and in which rings B and C share a common bridgehead nitrogen atom. We now report similarly fused compounds in which ring A = pyrimidine, ring B = pyrazole, and ring C = 1,2,4-triazole **20**–**23**, 1,2,4-triazine **32** and **33** and tetrazole **27**.

Previously we had used 3-amino-4-methyl-6-phenyl-1*H*-pyrazolo[3,4-*d*]pyrimidine **1** as a convenient starting material,





1 X = NH_2, R = Me
2 X = N_2^+, R = Me
3 X = $NHNH_2$, R = H
4 X = N_3, R = Me
5 X = N_3, R = H
6 X = Cl, R = H
7 X = NMe_2, R = H
8 X = $NHCH_2C_6H_4Cl$-*p*, R = H
9 X = SMe, R = H
10 X = SCH_2Ac

11 X = OEt, Y = OH
12 X = OEt, Y = Cl
13 X = OEt, Y = $NHNH_2$
14 X = Y = Cl

but for the present work we required a 3-substituent containing two (or three) nitrogen atoms. Diazotisation of **1** would give such a compound **2**, but initially we aimed to prepare the 3-hydrazino derivative **3**. Both **2** and **3** should then yield the azido compounds **4** and **5** (required to prepare the fused tetrazoles **27** and **28**).

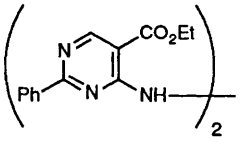
First we obtained ethyl 4-hydroxy-2-phenylpyrimidine-5-carboxylate **11**[3] by an improved procedure, then converted it into the corresponding 4-chloro compound **12**. Heating **12** with an excess of hydrazine hydrate gave, not the expected 3-oxopyrazolo[3,4-*d*]pyrimidine **16**, but ethyl 4-hydrazino-2-phenylpyrimidine-5-carboxylate **13** (76%). Use of an equimolar amount of hydrazine hydrate gave the *N*,*N*'-disubstituted hydrazine **15** (67%), together with some **13**. Surprisingly, our attempts to cyclise the hydrazine **13** to the 3-oxo compound **16** were unsuccessful. However, treatment of 4-chloro-2-phenylpyrimidine-5-carbonyl chloride **14** [obtained (50%) by reaction of the corresponding 4-hydroxy-5-carboxylic acid[5] with PCl_5] with hydrazine hydrate in 1,4-dioxane gave the required pyrazolo[3,4-*d*]pyrimidin-3-one **16** in 54% yield.

We expected that the 3-oxo compound **16** would be easily converted into its 3-chloro derivative **6** by reaction with phosphoryl trichloride, since a similar reaction had readily been achieved with the analogous compound, 3-oxo-5,6-benzindazole.[6] However, no reaction took place, either with $POCl_3$ alone, or in the presence of an organic base. Thionyl chloride alone was likewise ineffective, but the use of thionyl chloride and dimethylformamide (DMF) gave the required chloro compound **6**, albeit in only 31% yield. The 3-dimethylamino compound **7** was always obtained as a by-product from this reaction; the proportion of **7** increased as the amount of DMF increased (*cf.* ref. 7). The 3-chloro compound **6** was unstable, but was characterised as its 3-*p*-chlorobenzylamino derivative **8**, which was readily formed by reaction with *p*-chlorobenzylamine. The yield of 3-chloro compound **6** was increased slightly (to 40 and 46% respectively) by use of a mixture of thionyl chloride and methanesulfonyl chloride[8] or chlorosulfonyl isocyanate.[9] The chlorine atom in **6** was readily replaced by hydrazine, to give the 3-hydrazino compound **3**; the *N*,*N*'-disubstituted hydrazine **18** was always obtained as a by-product.

In view of the low yield and the instability of the chloro compound **6**, it was more convenient to convert the 3-oxo compound **16** into the corresponding thione **17** {either with phosphorus pentasulfide or Lawesson's reagent [2,4-bis(4-methoxyphenyl)-1,3-dithia-2,4-diphosphetane 2,4-disulfide]}. The thione **17** was difficult to purify, but was readily *S*-methylated, to give the easily crystallised 3-methylthio compound **9**. Subsequent nucleophilic displacements could then be carried out, either on the thione **17** (with elimination of H_2S) or, more readily, on the methylthio compound **9** (with elimination of methanethiol). As a diversion from our main programme, we

alkylated the thione **17** with chloroacetone, then cyclised the product **10** with phosphoryl trichloride, to give what we believe to be the thiazolopyrazolopyrimidine **19**.

The 3-hydrazino compound **3** was readily obtained (56 and 74% respectively) by heating either the thione **17** or its *S*-methyl derivative **9** with hydrazine hydrate. It was then cyclised by heating with triethyl orthoformate to 2-phenyl-9*H*-[1,2,4]triazolo[3′,4′:3,2]pyrazolo[3,4-*d*]pyrimidine **20** (43%).



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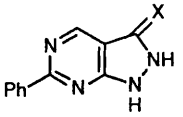
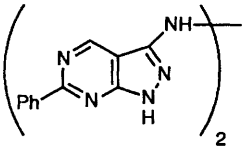


16 X = O
17 X = S



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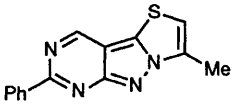

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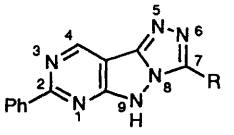
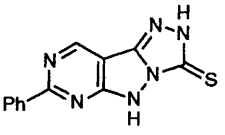


20 R = H
21 R = C_6H_4Cl-*p*
22 R = NHC_6H_4Cl-*p*



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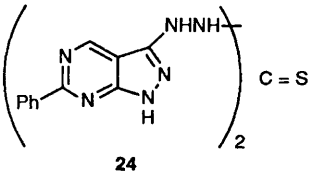
Treatment of the hydrazine derivative **3** with carbon disulfide in the presence of alkali gave the tricyclic thione **23** (32%); a by-product from the reaction is believed to be the thiocarbohydrazide derivative **24**. Heating hydrazine derivatives of the type **3** with aryl isothiocyanates is said[10] to proceed with loss of arylamine, to give thiones of type **23**. Heating **3** with ethanolic *p*-chlorophenyl isothiocyanate gave the thiosemicarbazide **25**, which resisted cyclisation under these conditions. However, cyclohydrodesulfurisation of **25** with dicyclohexylcarbodiimide[11] gave the 7-arylamino derivative **22** (29%).

We next prepared the substituted hydrazide **26** either by aroylation of the hydrazine **3** with *p*-chlorobenzoyl chloride [in contrast to some previous reports (*e.g.* ref. 10), polyaroylation was not a problem], or by reaction of the methylthio compound **9** with *p*-chlorobenzenecarbohydrazide. This was then cyclised with polyphoshoric acid or phosphoryl trichloride, to give the 7-substituted tricycle **21** (51% and 42% respectively). Mainly out of curiosity, we also carried out the cyclisation with triphenylphosphine in tetrachloromethane, which has been used successfully on related systems,[12] but the yield of **21** was disappointing (17%).

We next investigated the preparation of the azide **5** and its cyclisation into the tetrazolo compound **27**. The azide–tetrazole equilibrium has been widely studied in related systems, and the results are often confusing.[13] The present work proved no exception to this generalisation: we obtained conflicting results, several of which could not be reproduced satisfactorily, probably because of the sensitivity of this equilibrium to changes in solvent, temperature *etc.* The results which we now report have been obtained consistently. Treatment of the hydrazine derivative **3** with nitrous acid gave the azide **5** (63%), which existed almost entirely in this form in the solid phase (ν_{max} 2135 cm^{-1}). However, in solution in dimethyl sulfoxide (DMSO), whilst the azido form **5** predominated (*ca.* 80%), it was clear that some of the isomeric fused tetrazole **27** was also present. The azide **5** and the tetrazole **27** were distinguished by their ^1H NMR spectra in DMSO solution: the former showed a singlet peak at δ_H 8.65 (4-H); the latter showed a singlet at δ_H 8.81 (4-H). The mixture of solid products, as recovered from the DMSO solution, could not be separated chromatographically (but two spots were evident on TLC), but vacuum sublimation of the mixture gave almost pure azide **5**. The pure tetrazole could be obtained treating the azide with sodium methoxide, then acidifying the resulting sodium salt. This method has been used successfully by Tisler[14] on related systems, and depends on the presence of the acidic NH proton in **5** and **27**. In DMSO solution, the tetrazole gave the same equilibrium mixture as before; when sublimed, the tetrazole gave back the azide **5**. In an alternative approach to **5** and **27**, the 3-chloro compound **6** was treated with sodium azide in ethanolic DMF (*Note:* the nucleophilic displacement of the chloride ion did not take place in ethanol alone). This procedure gave a mixture of the azide and the tetrazole (*ca.* 1:1; the proportions in the solid phase were estimated by IR spectroscopy).

Next we diazotised 3-amino-4-methyl-6-phenyl-1*H*-pyrazolo-[3,4-*d*]pyrimidine **1**, in the hope that the resulting diazonium salt **2** might be deprotonated to give a stable 3-diazopyrazolo[3,4-*d*]pyrimidine **29**. An analogous product has



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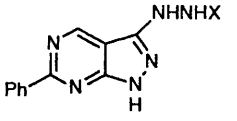
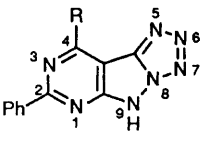
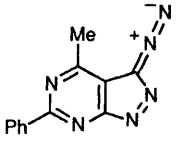


25 X = $CSNHC_6H_4Cl$-*p*
26 X = COC_6H_4Cl-*p*



27 R = H
28 R = Me



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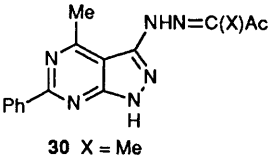
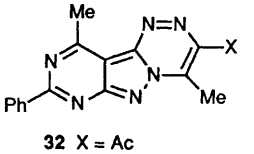


30 X = Me
31 X = CO_2Et



32 X = Ac
33 X = CO_2Et

previously been obtained[14] in the pyrazolo[3,4-*d*]pyridine series by careful diazotisation of the appropriate amine in aqueous tetrafluoroboric acid, followed by basification of the resulting diazonium salt. Surprisingly, we found that the 3-diazo compound **29** was obtained by diazotisation of the amine **1** under ordinary conditions, when it separated from the reaction mixture (83%) without the need for basification.

In view of the work already described, we aimed first to prepare the fused tetrazole **28**, by cyclisation of the corresponding azido compound **4**. We treated the diazo compound **29** with ethanolic hydroxylamine and satisfactorily obtained the azide **4** (56%), but it proved quite resistant to cyclisation. This marked contrast with the behaviour of the azide **5** is surprising: in view of its weak electron releasing effect and its relatively small size, the 4-methyl group was not expected to alter the course of the reaction so significantly.

Finally, we treated the 3-diazo compound **29** with pentane-2,4-dione or ethyl acetoacetate, in the expectation that the respective hydrazones **30** and **31** would be formed (*cf.* ref. 14), and that they could subsequently be cyclised. In practice, **30**

and **31** cyclised spontaneously, to yield directly the target pyrimidopyrazolo-1,2,4-triazines, **32** and **33** respectively (53 and 60%). It should be noted that **33** had been formed by cyclisation involving the acetyl group of the hydrazone **31**, rather than the ethoxycarbonyl group; this is perhaps surprising since cyclisation *via* the latter would have preserved the aromaticity of ring A.

Experimental

General experimental details are given in Parts 1 and 2.[1,2] Many of the compounds described in the present work have ill-defined, high m.p.s (often with decomposition), and have low solubilities in common solvents. Their purity was usually assessed by HPLC and combustion analysis. ^{1}H NMR data refer, unless stated otherwise, to solutions in $(CD_3)_2SO$, *J*-values are given in Hz. Signals due to NH protons were often not observed. Mass spectral data for chlorine containing compounds refer to the ^{35}Cl isotope.

Ethyl 4-*Hydrazino*-2-*phenylpyrimidine*-5-*carboxylate* **13**.—A rapidly stirred mixture of benzamidine hydrochloride (2 g, 0.013 mol), sodium hydroxide (1.1 g, 0.027 mol), and ethyl ethoxymethylenemalonate (2.8 g, 0.013 mol) was kept at room temperature for 1 h. The mixture was acidified with concentrated hydrochloric acid, then the precipitate was filtered off and recrystallised from aqueous ethanol, to give ethyl 4-hydroxy-2-phenylpyrimidine-5-carboxylate **11** as colourless needles (1.98 g, 62%), m.p. 215–218 °C (lit.,[3] 214–215 °C). This was converted into ethyl 4-chloro-2-phenylpyrimidine-5-carboxylate **12** by heating it with thionyl chloride.[4]

A stirred mixture of the 4-chloro compound **12** (1 g, 0.0038 mol), hydrazine hydrate (98% w/w; 1 g), and ethanol (10 cm^3) was heated under reflux for 1.5 h, then evaporated to dryness. The residue was washed, then recrystallised from aqueous ethanol, to give pale yellow *needles* (0.75 g, 76%), m.p. 105–106 °C (Found: C, 60.6; H, 5.5; N, 21.75%; M$^+$, 258. $C_{13}H_{14}N_4O_2$ requires C, 60.45; H, 5.45; N, 21.7%, *M*, 258); ν_{max}/cm^{-1} 3380, 3320 ($NHNH_2$) and 1690 (ester C=O); δ_H 1.33 (3 H, t, CH_2*Me*), 4.33 (2 H, q, CH_2Me), 4.93 (2 H, br, NHNH_2), 8.83 (1 H, s, 6-H) and 9.03 (1 H, br, N*H*NH$_2$).

1,2-*Bis*(5-*ethoxycarbonyl*-2-*phenylpyrimid*-4-*yl*)*hydrazine* **15**.—A stirred mixture of ethyl 4-chloro-2-phenylpyrimidine-5-carboxylate **12** (1 g, 0.0038 mol), hydrazine hydrate (98% w/w; 0.22 g, 0.004 mol) and ethanol (10 cm^3) was heated under reflux for 8 h, then cooled. The solid which separated formed yellow *needles* (0.62 g, 67%), m.p. 210 °C (from chloroform–ethanol) (Found: C, 64.15; H, 5.0; N, 17.35%; M$^+$, 484. $C_{26}H_{24}N_6O$ requires C, 64.45; H, 5.0; N, 17.35%; *M*, 484); ν_{max}/cm^{-1} 3310 (NH) and 1685 (ester C=O); δ_H(CDCl$_3$) 1.43 (3 H, t, CH_2*Me*), 4.46 (2 H, q, CH_2Me), 8.93 (1 H, s, 6-H) and 11.26 (1 H, br, NH).

Evaporation of the ethanolic mother liquor from the reaction gave the hydrazine derivative **13** (0.15 g), identical with that just described.

4-*Chloro*-2-*phenylpyrimidine*-5-*carbonyl Chloride* **14**.—The hydroxy ester **11** was hydrolysed with aqueous potassium hydroxide to the corresponding carboxylic acid (70%), m.p. 267–270 °C (lit.,[5] 265 °C). A stirred mixture of the carboxylic acid (4.45 g, 0.02 mol) and phosphorus pentachloride (24 g) was kept at 130 °C (bath) for 1 h, then cooled. The resulting solid mass was broken up and extracted with warm, dry ether (200 cm^3). The ethereal solution was evaporated until a precipitate began to form, then it was cooled and the precipitate was filtered off and recrystallised from light petroleum (b.p. 80–100 °C), to give *needles* (2.5 g, 50%), m.p. 118–119 °C (Found: C, 52.05; H, 2.45; N, 11.2%; M$^+$, 252. $C_{11}H_6Cl_2N_2O$ requires C, 52.2; H, 2.4; N, 11.05%; *M*, 252); ν_{max}/cm^{-1} 1780 (C=O); δ_H(CDCl$_3$) 9.33 (1 H, s, 6-H).

6-*Phenyl*-1H-*pyrazolo*[3,4-d]*pyrimidin*-3(2H)-*one* **16**.—Hydrazine hydrate (98% w/w; 14 cm^3) was added to a rapidly stirred solution of 4-chloro-2-phenylpyrimidine-5-carbonyl chloride **14** (3.5 g, 0.014 mol) in 1,4-dioxane (30 cm^3). The resulting mixture was kept at 120 °C (bath) for 5 min, then cooled. The precipitate was collected, washed with ethanol, and recrystallised from acetic acid, to give yellow *needles* (1.6 g, 54%), m.p. >300 °C (Found: C, 62.4; H, 3.95; N, 26.15%; M$^+$, 212. $C_{11}H_8N_4O$ requires C, 62.25; H, 3.8; N, 26.4%; *M*, 212); ν_{max}/cm^{-1} 3600br (NH and OH) and 1630br (C=O); δ_H 7.42 (3 H, m, Ph), 8.32 (2 H, m, Ph), 9.05 (1 H, s, 4-H) and 12.0 (1 H, br, NH).

3-*Chloro*-6-*phenyl*-1H-*pyrazolo*[3,4-d]*pyrimidine* **6**.—*Method 1*. Thionyl chloride (5 cm^3) was added dropwise to an ice-cold, stirred suspension of 6-phenyl-1*H*-pyrazolo[3,4-*d*]-pyrimidin-3(2*H*)-one **16** (2.12 g, 0.01 mol) in chloroform (30 cm^3) and DMF (5 cm^3). The mixture was stirred at 0 °C for 0.5 h, heated under reflux for 3 h, then evaporated to half volume at 30 °C (bath) under reduced pressure. Aqueous 10% sodium hydrogen carbonate (50 cm^3) was added and organic material was extracted into chloroform in the usual way. The solvent was removed from the dried extracts at 30 °C (bath) until a solid started to separate. An equal volume of ether was then added and the resulting dark solid (0.71 g, 31%) was filtered off (Found: M$^+$, 230. $C_{11}H_7ClN_4$ requires *M*, 230). The chloro compound **6** was unstable, and was best stored in the deep freeze under nitrogen.

The mother liquors were filtered through silica gel. Elution with ether gave 3-dimethylamino-6-phenyl-1*H*-pyrazolo-[3,4-*d*]pyrimidine **7** (120 mg, 5%), which formed pale yellow *needles* (from chloroform–light petroleum), m.p. 211–214 °C (Found: C, 65.15; H, 5.45; N, 29.2%; M$^+$, 239. $C_{13}H_{13}N_5$ requires: C, 65.25; H, 5.5; N, 29.25%; *M*, 239); δ_H(CDCl$_3$) 2.88 (6 H, s, NMe$_2$), 8.82 (1 H, s, 4-H) and 9.8 (1 H, br, NH).

Repetition of the experiment using equal volumes of chloroform and DMF in the chlorination reaction caused extensive decomposition, and none of the 3-chloro derivative **6** could be isolated. However, chromatography of the black product by the method just described afforded the dimethylamino compound **7** (24%). The amine **7** could also be obtained (*ca.* 60%) by keeping a solution of the crude chloro compound **6** in ethanol–DMF (10:1) with dimethylamine at 50 °C for 2 h.

Method 2. (*Cf.* ref. 8) A mixture of the 3-oxo compound **16** (2.12 g, 0.01 mol), thionyl chloride (7.1 g, 0.06 mol), methanesulfonyl chloride (3.45 g, 0.03 mol) and chloroform (20 cm^3) was heated under reflux overnight, then evaporated under reduced pressure. Isolation of the product as in Method 1 gave a brown solid (0.92 g, 40%), identical with that already described.

Method 3. (*Cf.* ref. 9) A mixture of the 3-oxo compound **16** (2.12 g, 0.01 mol), chlorosulfonyl isocyanate (1.41 g, 0.01 mol) and chloroform (20 cm^3) was stirred under reflux for 3 h, then kept overnight at room temperature. The product **6** (1.06 g, 46%) was isolated as before.

3-(p-*Chlorobenzyl*)*amino*-6-*phenyl*-1H-*pyrazolo*[3,4-d]-*pyrimidine* **8**.—A mixture of the crude 3-chloro compound **6** (1.25 g, *ca.* 5 mmol) and *p*-chlorobenzylamine (1.41 g, 0.01 mol) was heated under reflux for 0.5 h in ethanol (25 cm^3), containing a few drops of DMF. Crystals soon separated and were filtered off from the cooled solution, to give pale yellow *plates* (1.37 g, 82%), m.p. 254–255 °C (from chloroform–light petroleum) (Found: C, 64.5; H, 4.15; N, 20.9%; M$^+$, 335. $C_{18}H_{14}ClN_5$ requires C, 64.4; H, 4.2; N, 20.85%; *M*, 335); ν_{max}/cm^{-1} 3310

and 3350 (NH); $\delta_H(CDCl_3)$ 3.75 (2 H, s, NCH_2), 3.5 (1 H, br, NH), 9.7 (1 H, br, ring NH) and 8.97 (1 H, s, 4-H).

(6-*Phenyl*-1H-*pyrazolo*[3,4-d]*pyrimidin*-3-*yl*)*hydrazine* **3**.—A mixture of the crude 3-chloro compound **6** (3 g, 0.013 mol), hydrazine hydrate (98% w/w; 4 cm^3) and ethanol (50 cm^3) was heated under reflux for 5 h. The mixture was then filtered hot, and the filtrate was evaporated to half volume. Cooling gave *needles* (1.53 g, 52%), m.p. 288–291 °C (decomp.) (from ethanol) (Found: C, 58.7; H, 4.5; N, 36.95%; M^+, 226. $C_{11}H_{10}N_6$ requires C, 58.4; H, 4.45; N, 37.15%; *M*, 226); ν_{max}/cm^{-1} 3380 and 3330 ($NHNH_2$); δ_H 5.3 (2 H, br, NH_2), 8.85 (1 H, s, 4-H) and 10.2 (2 H, br, 2 × NH).

The residue from the filtration was N,N′-*bis*(6-*phenyl*-1H-*pyrazolo*[3,4-d]*pyrimidin*-3-*yl*)*hydrazine* **18** (200 mg, 4%), m.p. >300 °C (from DMF) (Found: C, 62.55; H, 3.95; N, 33.05%; M^+, 420. $C_{22}H_{16}N_{10}$ requires C, 62.85; H, 3.85; N, 33.3%; *M*, 420); ν_{max}/cm^{-1} 3350 (NH); δ_H 8.88 (s, 4- and 4′-H).

6-*Phenyl*-1H-*pyrazolo*[3,4-d]*pyrimidine*-3(2H)-*thione* **17**.—*Method 1*. A mixture of the 3-oxo compound **16** (6.35 g, 0.03 mol), phosphorus pentasulfide (3.0 g), and dry pyridine (20 cm^3) was heated under reflux for 6 h, then evaporated to dryness. The resulting black semi-solid was extracted continuously with chloroform (Soxhlet), then the ethanolic extract was evaporated. The resulting brown solid (4 g, 60%) (*ca.* 88% pure; HPLC), m.p. >300 °C (decomp.) could not be purified. However, it showed M^+, 228 ($C_{11}H_8N_4S$ requires *M*, 228).

Method 2. A mixture of the 3-oxo compound **16** (6.35 g, 0.03 mol), Lawesson's reagent (6 g) and toluene (150 cm^3) was heated under reflux overnight, by which time most of the starting material had gone into solution. Insoluble material was filtered off and the filtrate was evaporated, to give a brown solid, which was digested with boiling carbon disulfide (3 × 50 cm^3). The material which remained (4.5 g, 66%) was identical with that obtained by Method 1.

3-*Methylthio*-6-*phenyl*-1H-*pyrazolo*[3,4-d]*pyrimidine* **9**.—Iodomethane (1.7 g, 0.011 mol) was added dropwise to a stirred solution of the foregoing thione **17** (2.4 g, *ca.* 0.01 mol) in methanolic sodium methoxide [from sodium (0.25 g, 0.011 mol) and methanol (20 cm^3)]. Stirring was continued until all of the starting material had reacted (*ca.* 3 h) (TLC), then the solvent was removed. Addition of water gave solid material, which formed large, pale yellow, lustrous *plates* (1.62 g, 67%), m.p. 263–264 °C (from ethyl acetate–light petroleum) (Found: C, 59.65; H, 4.2; N, 23.15%; M^+, 242. $C_{12}H_{10}N_4S$ requires C, 59.5; H, 4.15; N, 23.1%; *M*, 242); $\delta_H(CDCl_3)$ 2.66 (3 H, s, SMe), 8.95 (1 H, s, 4-H) and 10.15 (1 H, br s, NH).

Heating the thioxo compound **17** or the methylthio compound **9** with ethanolic hydrazine hydrate gave the hydrazine derivative **3**, identical with that obtained earlier (56% and 74%; heating times 4 h and 1.5 h, respectively).

{(6-*Phenyl*-1H-*pyrazolo*[3,4-d]*pyrimidin*-3-*yl*)*thio*}*propanone* **10**.—A mixture of the thione **17** (2.4 g, *ca.* 0.01 mol), redistilled chloroacetone (1 g, 0.011 mol), and ethanol (100 cm^3) was heated under reflux for 4 h, then evaporated to low volume. An excess of aqueous sodium hydrogen carbonate was added, and the resulting sticky solid was extracted into chloroform. The usual work-up gave *needles* (1.9 g, 67%), m.p. 273–275 °C (from a large volume of ethanol) (Found: C, 59.1; H, 4.35; N, 19.77%; M^+, 284. $C_{14}H_{12}N_4OS$ requires C, 59.15; H, 4.25; N, 19.7%; *M*, 284); ν_{max}/cm^{-1} 1720 (C=O); $\delta_H(CDCl_3)$ 2.15 (3 H, s, Me), 3.45 (2 H, s, CH_2), 8.90 (1 H, s, 4-H) and 9.8 (1 H, br s, NH).

Cyclisation of the Ketone **10**.—A mixture of the ketone **10** (1 g, 3.5 mmol), phosphoryl trichloride (2 g) and xylene (25 cm^3) was heated under reflux for 8 h. Most of the solvent was removed under reduced pressure, then chloroform (100 cm^3) was added. Aqueous sodium hydrogen carbonate was added, some insoluble material was filtered off, then the chloroform solution was washed, dried and evaporated. The residue was filtered in chloroform through silica gel, to give the thiazolopyrazolopyrimidine **19**, which formed pale yellow *needles* (0.35 g, 38%), m.p. 263–265 °C (decomp.) (from ethanol) (Found: C, 63.05; H, 3.75; N, 20.95%; M^+, 266. $C_{14}H_{10}N_4S$ requires C, 63.15; H, 3.8; N, 21.05%; *M*, 266); δ_H 2.52 (3 H, d, *J* 1.5, 7-Me), 6.55 (1 H, q, 6-H) and 8.62 (1 H, s, 4-H); no NH signal.

2-*Phenyl*-9H-[1,2,4]*triazolo*[3′,4′:3,2]*pyrazolo*[3,4-d]*pyrimidine* **20**.—A mixture of the 3-hydrazino compound **3** (2.25 g, 0.01 mol), triethyl orthoformate (3 g, 0.02 mol), and DMF (30 cm^3) was kept at 120 °C for 8 h, during which time low boiling material was distilled off (Dean–Stark). Addition of water to the cooled solution gave the product, which formed *needles* (1 g, 43%), m.p. 245–247 °C (from DMF–water) (Found: C, 61.15; H, 3.35; N, 35.6%; M^+, 236. $C_{12}H_8N_6$ requires C, 61.0; H, 3.4; N, 35.5%; *M*, 236); ν_{max}/cm^{-1} 3250 (NH); δ_H 9.17 and 8.85 (each 1 H, s, 4-H and 7-H).

2-*Phenyl*-9H-[1,2,4]*triazolo*[3′,4′:3,2]*pyrazolo*[3,4-d]*pyrimidine*-7(6H)-*thione* **23**.—A mixture of the hydrazino compound **3** (2.25 g, 0.01 mol), pyridine (50 cm^3), water (50 cm^3) and carbon disulfide (1 g, 13 mmol) was heated under reflux for 6 h, then more carbon disulfide (1 g) was added and heating was continued until the evolution of hydrogen sulfide had ceased (*ca.* 12 h in total). The yellow solid (300 mg) which separated was filtered off and washed with ethanol and carbon disulfide. It had m.p. >300 °C and could not be obtained quite pure. It is believed to be the thiocarbohydrazide derivative **24** [Found: C, 55.3; H, 3.5; N, 33.7%; M^+ (weak), 494. $C_{23}H_{18}N_{12}S$ requires C, 55.85; H, 3.65; N, 34.0%; *M*, 494]; ν_{max}/cm^{-1} 1340w (C=S).

The filtrate was concentrated under reduced pressure, then water was added. The resulting yellow solid crystallised from chloroform, to give **23** as fine *needles* (0.86 g, 32%) (Found: C, 53.7; H, 3.5; N, 31.25%; M^+, 268. $C_{12}H_8N_6S$ requires C, 53.75; H, 3.0; N, 31.35%; *M*, 268); ν_{max}/cm^{-1} 1350 (C=S); δ_H 10.0 (2 H, br, 2 × NH) and 8.92 (1 H, s, 4-H).

Thiosemicarbazide Derivative **25**.—The hydrazine derivative **3** (2.25 g, 0.01 mol) was dissolved in the minimum volume of boiling ethanol, then *p*-chlorophenyl isothiocyanate (1.7 g, 0.01 mol) was added. Heating was continued for 0.5 h, then the product **25** was filtered off. It formed *needles* (3.8 g, 96%), m.p. >300 °C (from DMF–ethanol) (Found: C, 54.65; H, 3.5; N, 24.75%; M^+, 395. $C_{18}H_{14}ClN_7S$ requires C, 54.6; H, 3.55; N, 24.75%; *M*, 395); the IR and NMR spectra were complex, and gave little useful information.

7-(p-*Chlorophenylamino*)-2-*phenyl*-9H-[1,2,4]*triazolo*[3′,4′:3,2]*pyrazolo*[3,4-d]*pyrimidine* **22**.—A stirred suspension of the thiosemicarbazide derivative **25** (1.98 g, 5 mmol) and 1,3-dicyclohexylcarbodiimide (1.03 g, 0.005 mol) in ethanol (50 cm^3) was heated under reflux overnight, by which time a clear solution had resulted. The solvent was removed and the residue was shaken with a mixture of dilute hydrochloric acid (50 cm^3) and chloroform (50 cm^3) until all of the solid had dissolved. The acid layer was then removed, and basified with sodium hydrogen carbonate. The product was filtered off and crystallised from ethanol, to give *needles* (0.52 g, 29%), m.p. 198–200 °C (Found: C, 59.85; H, 3.25; N, 27.2%; M, 361. $C_{18}H_{12}ClN_7$ requires C, 59.75; H, 3.35; N, 27.1%; *M*, 361); δ_H 8.83 (1 H, s, 4-H) and 7.6 (2 H, br, 2 × NH).

2-(6-*Phenyl*-1H-*pyrazolo*[3,4-d]*pyrimidin*-3-*yl*)-p-*chlorobenzenecarbohydrazide* **26**.—*Method 1*. A solution of the hydrazine derivative **3** (2.25 g, 0.01 mol) in pyridine (25 cm^3) was treated dropwise at 0 °C with *p*-chlorobenzoyl chloride (1.75 g, 0.01 mol), then the solution was kept at 0 °C overnight. Addition of water and crystallisation of the product from DMF–ethanol gave *needles* (2.2 g, 61%), m.p. 288–289 °C (Found: C, 59.15; H, 3.55; N, 23.1%; M, 364. $C_{18}H_{13}ClN_6O$ requires C, 59.25; H, 3.6; N, 23.05; *M*, 364); ν_{max}/cm^{-1} 1660 (C=O); δ_H 8.84 (1 H, s, 4-H).

Method 2. A mixture of the methylthio compound **9** (2.42 g, 0.01 mol), *p*-chlorobenzenecarbohydrazide (1.70 g, 0.01 mol) (from ethyl *p*-chlorobenzoate and hot ethanolic hydrazine hydrate), ethanol (50 cm^3) and a few drops of DMF was heated under reflux for 4 h, then cooled. The resulting crystals (2.4 g, 66%) were filtered off, and were identical with those obtained by Method 1.

7-(p-*Chlorophenyl*)-2-*phenyl*-9H-[1,2,4]*triazolo*-[3′,4′:3,2]*pyrazolo*[3,4-d]*pyrimidine* **21**.—*Method 1*. A stirred mixture of the hydrazide **26** (1.82 g, 0.005 mol) and polyphosphoric acid (10 g) was kept at 130–135 °C for 2 h, then cooled and treated with ice–water. Neutralisation with sodium hydrogen carbonate gave the product, which formed small *flakes* (0.88 g, 51%), m.p. 286–288 °C (from DMF–ethanol) (Found: C, 62.45; H, 3.2; N, 24.1%; M, 346. $C_{18}H_{11}ClN_6$ requires C, 62.35; H, 3.2; N, 24.25%; *M*, 346); δ_H 8.96 (1 H, s, 4-H) and 10.05 (1 H, br s, NH).

Method 2. The hydrazide **26** was cyclised with phosphoryl trichloride using the method described for **19**, except that there was no need to purify the product (42%) by chromatography.

Method 3. Carbon tetrachloride (0.23 g, 5 mmol) was added to a stirred suspension of the hydrazide **26** (0.55 g, 1.5 mmol) and triphenylphosphine (0.5 g, 1.8 mmol) in dry acetonitrile (5 cm^3). After 7 d water was added and the product (88 mg, 17%; difficult to purify) was filtered off.

3-*Azido*-6-*phenyl*-1H-*pyrazolo*[3,4-d]*pyrimidine* **5**.—*Method 1*. A solution of sodium nitrite (2.9 g, 0.042 mol) in water (10 cm^3) was added to an ice-cold, stirred solution of the 3-hydrazino compound **3** (2.25 g, 0.01 mol) in HCl (2 mol dm^{-3}; 50 cm^3). Stirring was continued at room temperature for 3 h, then the precipitate was filtered off and crystallised from DMF–ethanol, to give the azide as yellow *needles* (1.49 g, 63%), m.p. 256–259 °C (decomp.) (Found: C, 55.55; H, 2.9; N, 41.55. $C_{11}H_7N_7$ requires C, 55.7; H, 2.95; N, 41.35%); ν_{max}/cm^{-1} 2135 (N_3); δ_H(see text); *m/z* 209 (*M* − N_2) (no M^+).

Addition of water to a solution of the azide in DMSO gave material which contained the azide **5** (*ca.* 80%) and the isomeric tetrazole **27**. Sublimation at 150 °C (bath) and 0.1 mmHg gave almost pure azide.

Method 2. Sodium azide (0.71 g, 0.011 mol) was added portionwise to a stirred solution of 3-chloro-6-phenyl-1*H*-pyrazolo[3,4-*d*]-pyrimidine **6** (2.3 g, 0.01 mol) in DMF (20 cm^3) and ethanol (5 cm^3), then the mixture was stirred at 50–60 °C for 2 h. Dilution with water gave material (1.6 g) which contained the azide **5** and the tetrazole **27** (*ca.* 1:1).

2-*Phenyl*-9H-*tetrazolo*[1′,5′:1,5]*pyrazolo*[3,4-d]*pyrimidine* **27**.—A suspension of the azide **5** (1.18 g, 5 mmol) in methanolic sodium methoxide [from sodium (0.115 g, 5 mmol) and methanol (20 cm^3)] was stirred at 45–50 °C until all of the solid had dissolved (*ca.* 1 h). The mixture was then evaporated to dryness, water (10 cm^3) was added, and the solution was neutralised at 0 °C with dilute acetic acid. The resulting solid was washed with methanol, then dried at 25 °C, to give the *tetrazole* **27** (0.85 g) (Found: C, 55.6; H, 2.75; N, 42.5%); no azide absorption in the IR; δ_H 8.81 (1 H, s, 4-H).

3-*Diazo*-4-*methyl*-6-*phenyl*-1H-*pyrazolo*[3,4-d]*pyrimidine* **29**.—Concentrated hydrochloric acid (1.4 g) was added to a stirred suspension of the 3-amino compound **1** (2 g, 8.8 mmol) in water (40 cm^3), to give a suspension of the hydrochloride. The mixture was cooled to 0 °C, then a solution of sodium nitrite (0.82 g, 0.012 mol) in water (10 cm^3) was added dropwise during 0.5 h, whilst maintaining the temperature at 0 °C, and adding water to ensure even mixing. The mixture was then kept at room temperature for 0.5 h and the yellow precipitate was collected. It was dissolved in chloroform, then the solution was washed well, dried, and evaporated until crystals started to appear. Cooling in ice gave yellow *needles* (1.72 g, 83%), m.p. *ca.* 150 °C [decomp. (with explosion)] (Found: C, 61.05; H, 3.3; N, 35.4%; M^+, 236. $C_{12}H_8N_6$ requires C, 61.0; H, 3.4; N, 35.55%; *M*, 236); ν_{max}/cm^{-1} 2160 (diazo); $\delta_H(CDCl_3)$ 2.92 (3 H, s, 4-Me).

3-*Azido*-4-*methyl*-6-*phenyl*-1H-*pyrazolo*[3,4-d]*pyrimidine* **4**.—A stirred mixture of the 3-diazo compound **29** (0.24 g, 1 mmol), water (10 cm^3), ethanol (5 cm^3), and hydroxylamine hydrochloride (0.25 g, 3.5 mmol) was kept at 0 °C for 2 h, allowed to attain room temperature, then neutralised with aqueous sodium hydrogen carbonate. The resulting precipitate formed *needles* (0.14 g, 56%), m.p. 184–185 °C [from ethanol (charcoal)] (Found: C, 57.45; H, 3.65; N, 38.9%: M^+, 251. $C_{12}H_9N_7$ requires C, 57.35; H, 3.6; N, 39.05%; *M*, 251); ν_{max}/cm^{-1} 3400 (br, NH) and 2120 (N_3); δ_H 3.26 (3 H, s, 4-Me) and 13.9 (1 H, br, NH).

7-*Acetyl*-4,8-*dimethyl*-2-*phenylpyrimido*[5′4′:4,5]*pyrazolo*-[3,2-*c*][1,2,4]*triazine* **32**.—A stirred mixture of the 3-diazo compound **29** (0.25 g, 0.001 mol), pentane-2,4-dione (0.11 g, 1.1 mmol) and ethanol (10 cm^3) was kept at room temperature for 2 h. The resulting precipitate was collected and crystallised from acetone, to give fawn *needles* (0.17 g, 53%), m.p. 270 °C (decomp.) (Found: C, 64.0; H, 4.5; N, 26.6%; M^+, 318. $C_{17}H_{14}N_6O$ requires C, 64.15; H, 4.45; N, 26.4%; *M*, 318); ν_{max}/cm^{-1} 1700 (C=O); $\delta_H(CDCl_3)$ 3.06 (3 H, s, Ac) and 3.46 (6 H, 4-Me and 8-Me).

Ethyl 4,8-*Dimethyl*-2-*phenylpyrimido*[5′4′:4,5]*pyrazolo*[3,2-c][1,2,4]*triazine*-7-*carboxylate* **33**.—A stirred mixture of the 3-diazo compound **29** (0.25 g 1 mmol), ethyl acetoacetate (0.15 g, 1.2 mmol) and ethanol (10 cm^3) was kept at room temperature for 17 h. The resulting precipitate gave pink *needles* (0.21 g, 60%), m.p. 210–212 °C [from acetone (charcoal)] (Found: C, 61.95; H, 4.55; N, 23.95%; M^+, 348. $C_{18}H_{16}N_6O_2$ requires C, 62.05; H, 4.65; N, 24.15%; *M*, 348); ν_{max}/cm^{-1} 1730 (ester C=O); δ_H 1.56 (3 H, t, CH_2Me), 3.40 (6 H, br s, 4-Me and 8-Me) and 4.72 (2 H, q, CH_2Me).

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