# Regioselective Deacylation of 2,4-Diacylaminopyrimidine Derivatives by Lewis Acids and Crystal Structures of Two Products

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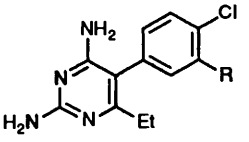
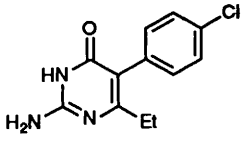
Deacylation of 2,4-diacylamino derivatives of pyrimethamine and related diaminopyrimidines with tin(II) chloride or zinc chloride, in ethanol or propan-2-ol, affords 2-acyl-4-aminopyrimidines exclusively. Regioselective 4-deacylation was observed by $^1$H NMR spectroscopy and established by crystallographic analysis of the 2,4-dipropionylpyrimidine **11** and the corresponding 4-amino-2-propionylpyrimidine deacylation product **17**. The latter exists in the solid state as an unusual base-pair dimer linked by two pairs of equivalent hydrogen bonds.

An earlier paper[1] describes the results of studies on the hydrolysis with hydrochloric acid and deamination by nitrous acid, of the antimalarial 2,4-diaminopyrimidine pyrimethamine **1**, to furnish the 2-aminopyrimidin-4-one **2** and the isomeric 4-aminopyrimidin-2-one **3**. As part of our continuing studies to



**1** R = H
**4** R = $NO_2$
**8** R = $NH_2$
**9** R = NHAc
**22** R = $N_3$



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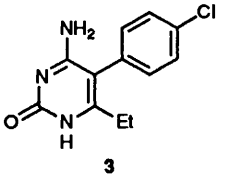

**3**

elucidate the influence of structural modification upon the biological activity of 2,4-diaminopyrimidine antifolates, with a view to identifying novel anti-proliferative and anti-infective agents, the effect on activity of modifying the amino substituents by acylation was investigated. The superior antimalarial activity and reduced toxicity of several diacylamino analogues of pyrimethamine over the parent drug has been reported previously.[2] Since, for diaminopyrimidine antifolates, a 2,4-diamino-*meta*-diazine pharmacophore is a prerequisite for inhibition of dihydrofolate reductase (DHFR), the target enzyme,[3] this implies that the diacylated analogues are either acting at an alternative site, or more probably, are serving as pyrimethamine prodrugs and undergoing subsequent reconversion into the parent antifolate. The obvious deleterious effect of diacylation upon aqueous solubility, and the requirement for hydrolysis of both acyl substituents to occur for DHFR-inhibitory activity to be restored led us to consider the possibility of preparing monoacylated diaminopyrimidine derivatives. Here, we report the preparation of a series of 2,4-diacylamino analogues of pyrimethamine and several derivatives, and the subsequent regioselective deacylation by Lewis acids to furnish a series of hitherto unreported 2-acylamino-4-aminopyrimidines. The structures of one of the monoacylated derivatives and its diacylamino counterpart have been determined unambiguously by X-ray crystallography, and the unusual duplex arrangement of the monoacyl derivative is described.

## Results and Discussion

The reaction of 2,4-diamino-5-(4-chloro-3-nitrophenyl)-6-ethylpyrimidine, 'nitropyrimethamine'[1] **4** with boiling acetic anhydride gave only a complex mixture of products (TLC), while similar treatment with a 1:1 mixture of acetic anhydride and acetic acid furnished the 2,4-diacetamido derivative **5** in excellent yield. The stability of the nitro group to such vigorous reaction conditions was confirmed by the treatment of compound **5** with ethanol–hydrochloric acid at 60 °C, whereupon reconversion into the starting material **4** was observed. Surprisingly, the subsequent reaction of compound **5** with tin(II) chloride in ethanol, purportedly a highly selective method for the reduction of aromatic nitro substituents,[4] did not furnish the expected diacetamidopyrimidine **6** or a rearrangement product thereof. Instead the compound **7** obtained was characterised by $^1$H NMR and mass spectrometry as a monoacetyl derivative of 2,4-diamino-5-(3-amino-4-chlorophenyl)-6-ethylpyrimidine, 'aminopyrimethamine' **8** suggesting that reduction of the nitro substituent was accompanied by loss of a single acetyl function (Scheme 1). Although the exact position of the acetamido group could not be assigned at this time, treatment of compound **7** with ethanol–hydrochloric acid at 60 °C gave the aminopyrimethamine **8**, which was identical with an authentic sample prepared previously by reduction of compound **4** with hydrazine–Raney nickel.[1] This confirmed that the acetyl substituent must have resided at the 2-amino **7a** or 4-amino position **7b** of the diaminopyrimidine, since an authentic sample of 2,4-diamino-5-(3-acetamido-4-chlorophenyl)-6-ethylpyrimidine **9**[5] proved resistant to deacylation under identical conditions.

These observations prompted us to investigate further the suitability of this deacylation reaction for the preparation of novel therapeutic diaminopyrimidines, and also for the protection, under mild conditions, of amino substituents on nitrogen heterocycles. Previous approaches utilising acetylation for the protection of pyrimidine amino groups in the synthesis of

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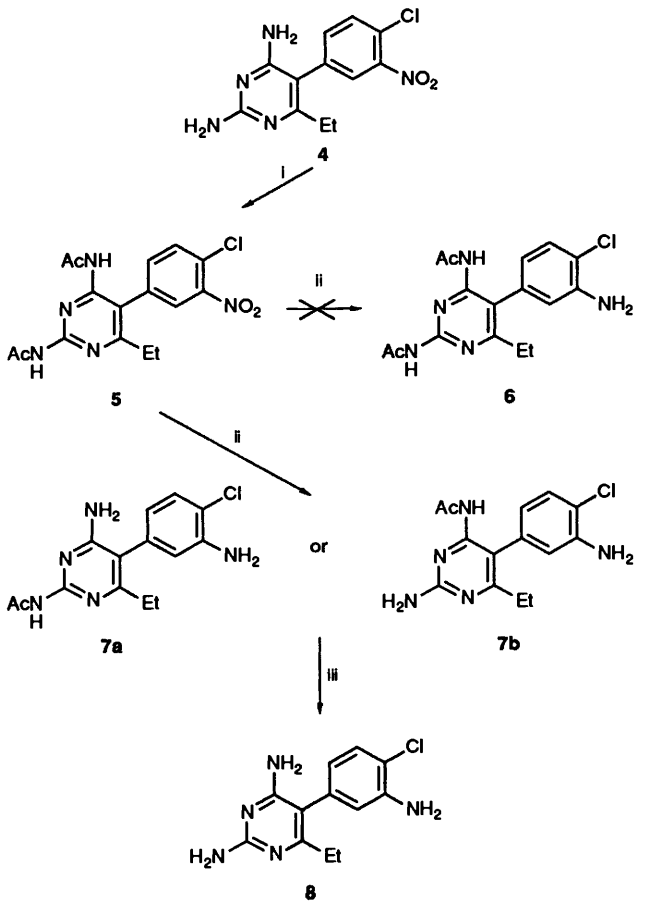
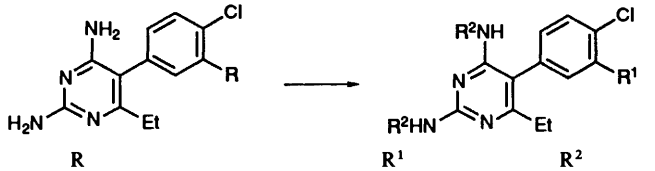


**Scheme 1** *Reagents and conditions:* i, AcOH–$Ac_2O$, reflux; ii, $SnCl_2$–EtOH, 70 °C; iii, EtOH–HCl, 60 °C

8-deazahomofolic acid derivatives[6] and diaminopyrimidine alkylating agents,[7] have necessitated the use of refluxing ethanol–hydrochloric acid for the ultimate deacylation step, and although we have demonstrated that deacylation may be achieved under milder conditions (60 °C), no regioselectivity was apparent. Pyrimethamine **1** was used for these studies and reacted smoothly with anhydrides at 100 °C or under reflux conditions to furnish the appropriate diacylaminopyrimidine derivatives **10–15** in good yield. Details of the synthesis, physical properties, and chemical structures of the compounds prepared in this study are summarised in Table 1 and Scheme 2. Treatment of compound **1** with acetyl chloride in dry pyridine, containing 4-dimethylaminopyridine as catalyst, at room temperature also furnished the diacetamido derivative **10**, although analogous reactions using trimethylacetyl chloride or benzoyl chloride proved less satisfactory, giving mixtures in each case. The diacetylation of a single amino group has been observed for a limited number of aminopyrimidines under vigorous reaction conditions (boiling acetic anhydride in pyridine).[8] However, no evidence was adduced to support an analogous reaction in this study, the 300 MHz $^1$H NMR spectra of compounds **10–15** exhibiting two broad singlets each corresponding to an RCON*H* resonance integrating as a single proton, and exchanging only slowly on deuteriation. In contrast the $NH_2$ protons of diaminopyrimidines invariably appear as a broad singlet (2 H) and are rapidly exchanged upon deuteriation. Moreover, derivatives of this type are reportedly highly labile, readily losing an acetyl group in ethanol or water, and this is contrary to our observations where compounds **10–15** crystallised unchanged from boiling ethanol–water, and compound **10** was stable to protracted boiling in ethanol.

The 300 MHz $^1$H NMR spectra of the diacylaminopyrimethamine derivatives **10–15** revealed considerable differences in shift ($\Delta\delta$) between the 2-and 4-acylamino substituents, this being particularly evident for the group adjacent to the amide carbonyl function (Table 2). For example, the methyl groups of the 2- and 4-acetamido substituents of compound **10** appeared as singlets at $\delta$ 2.60 and 2.35, while the methylene groups of the 2- and 4-propionamido substituents of the dipropionamidopyrimethamine **11** appeared as quartets centred at $\delta$ 2.92 and 2.71. A similar shift difference was also observed for the *tert*-butyl substituents of the bis(trimethylacetamido)pyrimidine **14** which appeared as singlets (9 H) at $\delta$ 1.32 and 0.98. These differences possibly arise as a consequence of the C-4 substituent falling within the shielding cone of the adjacent 5-phenyl ring and thus resonating upfield of the C-2 group. Alternatively, differences in the positioning of the 2- and 4-substituents relative to the electron-withdrawing pyrimidine ring nitrogens, the C-2 group being in the di-*ortho* position, may account for 2-acyl substituents experiencing a greater deshielding effect than those in the C-4 position.

*Deacylation of Diacylaminopyrimidines with Lewis Acids.*— Treatment of diacetamidopyrimethamine **10** with a 5 molar excess of tin(II) chloride in ethanol at room temperature resulted in complete consumption of the starting material **10** after 12 h (TLC), to furnish a single compound of polarity intermediate between pyrimethamine **1** and the parent diacylaminopyrimidine **10**, and with a molecular ion in the mass spectrum (EI) corresponding to $C_{14}H_{15}ClN_4O$, the mono-acetylation product. Analysis by $^1$H NMR spectroscopy confirmed the loss of a single acetyl group to afford the expected monoacetamidopyrimidine **16**, the acetamido methyl appearing as a singlet at $\delta$



| R | | R$^1$ | R$^2$ | R$^1$ | R$^2$ |
|---|---|---|---|---|---|
| **1** | H | **5** | $NO_2$ | MeCO | **7** $NH_2$ | MeCO |
| **4** | $NO_2$ | **6** | $NH_2$ | MeCO | **16** H | MeCO |
| **8** | $NH_2$ | **10** | H | MeCO | **17** H | EtCO |
| **9** | NHCOMe | **11** | H | EtCO | **18** H | PrCO |
| **27** | NHCOBu$^t$ | **12** | H | PrCO | **19** H | BuCO |
| | | **13** | H | BuCO | **20** H | Bu$^t$CO |
| | | **14** | H | Bu$^t$CO | **21** H | PhCO |
| | | **15** | H | PhCO | **24** NHCOMe | MeCO |
| | | **23** | NHCOMe | MeCO | **26** NHCOBu$^t$ | Bu$^t$CO |
| | | **25** | NHCOBu$^t$ | Bu$^t$CO | | |

**Scheme 2**

**Table 1** Preparative, physical and analytical data for diaminopyrimidine derivatives

| Compd. | Method | Yield (%) | M.p. (°C) | Formula | *M* | % Found (Required) C | H | N |
|---|---|---|---|---|---|---|---|---|
| **5** | A | 93 | 168–171 | $C_{16}H_{16}ClN_5O_4$ | 377/379 | 50.85 (50.86) | 4.2 (4.24) | 18.5 (18.54) |
| **7** | — | 87 | <40[a] | $C_{14}H_{16}ClN_5O$ | 305/307 | 54.00 (55.00) | 5.5 (5.24) | 22.7 (22.91) |
| **10** | A | 89 | 173–174[b] | $C_{16}H_{17}ClN_4O_2$ | 332/334 | — | — | — |
| **11** | A | 83 | 142–145[c] | $C_{18}H_{21}ClN_4O_2$ | 360/362 | 59.8 (59.92) | 5.89 (5.87) | 15.7 (15.53) |
| **12** | A | 77 | 119–121 | $C_{20}H_{25}ClN_4O_2$ | 388/390 | 61.5 (61.77) | 6.5 (6.48) | 14.5 (14.41) |
| **13** | A | 88 | 88–95 | $C_{22}H_{29}ClN_4O_2$ | 416/418 | 62.9 (63.38) | 7.5 (7.01) | 13.4 (13.44) |
| **14** | A | 62 | 180–181 | $C_{22}H_{29}ClN_4O_2$ | 416/418 | 63.0 (63.39) | 7.3 (6.96) | 13.3 (13.45) |
| **15** | A | 76 | 88–89 | $C_{26}H_{21}ClN_4O_2$ | 456/458 | 68.3 (68.35) | 4.55 (4.60) | 12.4 (12.27) |
| **16** | B | 69 | 206–208 | $C_{14}H_{15}ClN_4O$ | 290/292 | 56.9 (56.83) | 5.1 (5.16) | 19.6 (19.28) |
| **17** | B | 83 | 187–188 | $C_{15}H_{17}ClN_4O$ | 304/306 | 58.9 (59.11) | 5.7 (5.62) | 18.5 (18.38) |
| **18** | B | 82 | 155–156 | $C_{16}H_{19}ClN_4O$ | 319/321 | 60.0 (60.28) | 6.05 (6.01) | 17.6 (17.57) |
| **19** | B | 56 | 140–142 | $C_{17}H_{21}ClN_4O$ | 332/334 | 61.3 (61.35) | 6.4 (6.36) | 16.8 (16.83) |
| **20** | C | 100 | 168–171 | $C_{17}H_{21}ClN_4O$ | 332/334 | 61.6 (61.35) | 6.3 (6.32) | 16.8 (16.84) |
| **21** | C | 58 | 93–95 | $C_{19}H_{17}ClN_4O$ | 352/354 | 64.5 (64.68) | 4.8 (4.82) | 15.9 (15.90) |
| **23** | A | 58 | 187 | $C_{18}H_{20}ClN_5O_3$ | 389/391 | 55.6 (55.46) | 5.2 (5.23) | 18.05 (17.97) |
| **24** | — | 78 | 112–114 | $C_{16}H_{18}ClN_5O_2$ | 347/349 | 55.65 (55.26) | 4.9 (5.18) | 20.45 (20.14) |
| **25** | — | 61 | 114–115 | $C_{27}H_{38}ClN_5O_3$ | 515/517 | 62.7 (62.85) | 7.4 (7.37) | 13.6 (13.58) |
| **26** | B | 55 | 135–136 | $C_{22}H_{30}ClN_5O_2$ | 431/433 | 61.2 (61.18) | 7.0 (6.95) | 16.3 (16.22) |
| **27** | — | 95 | 161–163[b] | $C_{17}H_{22}ClN_5O$ | 347/349 | 59.1 (58.71) | 6.05 (6.33) | 20.5 (20.14) |

[a] Low melting glass. [b] Lit. m.p. 172 °C.[19] [c] Sinters.

2.62. This corresponded to the observed shift value for the most deshielded acetamido substituent ($\delta$ 2.60) of the diacetamido derivative **10**, previously provisionally assigned as in the C-2 position, implying that deacylation occurred with loss of the 4-acetyl group. Similar reactions conducted with the dipropionamido, dibutyramido and dihexanamidopyrimethamine derivatives **11–13** afforded the appropriate monoacylaminopyrimidines **17–19** in good yield, and in all cases deacylation was accompanied by a disappearance in the $^1$H NMR spectrum, of signals corresponding to acyl groups located on the more shielded of the amino functions on the pyrimidine ring, provisionally assigned as the 4-position. Treatment of the bis(trimethylacetamido)pyrimidine **14** or dibenzamidopyrimidine **15** with tin(II) chloride under identical conditions gave only starting materials after 12 h as monitored by TLC, and prolonged reactions (1 week) afforded a mixture of compounds.

In order to further investigate the nature of this unusual regioselective deacylation the initial reaction conditions adopted for the diacetamidopyrimidine **10** were modified; thus quantitative conversion (TLC) of **10** to the monoacetamido derivative **16** was achieved with precisely 1 mol equivalent of tin(II) chloride although reaction times were extended (24 h). Ethanol or a similar alcohol appears to be essential since deacylation was not apparent when ethyl acetate or tetrahydrofuran was utilised as solvent, and while the reaction proceeded smoothly in propan-1-ol, only starting materials were recovered when propan-2-ol was adopted as solvent, presumably due to steric factors. Under forcing conditions (reflux) removal of both acetyl substituents occurred without exception, regardless of the alcohol employed, to afford pyrimethamine **1** as the only product, Replacement of tin(II) chloride with zinc chloride in ethanol at room temperature resulted in deacylation at both the C-2 and C-4 positions to give a near quantitative yield of compound **1** and, interestingly, the reactivity of zinc chloride was attenuated when propan-2-ol was adopted as solvent, reaction with compound **10** at room temperature giving the monoacetamidopyrimidine **16**. Prolonged boiling (24 h) of the diacetamidoaminopyrimidine **10** in ethanol alone was without effect underlying the importance of the Lewis acid in the deacylation reaction.

The enhanced reactivity of zinc chloride over tin(II) chloride was exploited as a possible strategy for the regioselective deacylation of the bis(trimethylacetamido)- and dibenzamidopyrimethamine derivatives **14** and **15**, which reacted sluggishly with tin(II) chloride. Thus conversion into the required 2-trimethylacetamido **20** and 2-benzamido derivatives **21** was achieved in moderate yield following treatment with zinc chloride in ethanol, although longer reaction times (24 h) proved necessary. Allowing the reactions to proceed for an extended time period (1 week) resulted in further deacylation of compound **20** to afford pyrimethamine **1**, although no further debenzoylation of compound **21** was observed. The high resolution $^1$H NMR spectrum of compound **20** again showed that the most shielded of the two singlets at $\delta$ 0.98 and 1.32

**Table 2** $^1$H NMR spectra[a] of 2,4-diaminopyrimidine derivatives

| Compd. | Me(t) | $CH_2$(q) | 5-Phenyl | 2-NHCOC$H_2$ | 4-NHCOC$H_2$ | Other signals[b] |
|---|---|---|---|---|---|---|
| **5** | 1.07 | 2.48 | 7.58 (dd), 7.74 (d), 8.01 (d) | — | — | 2.04 (3 H, s, 4-NHCOC$H_3$), 2.23 (3 H, s, 2-NHCOC$H_3$), 9.80 (1 H, CONH), 10.53 (1 H, CONH) |
| **7** | 0.95 | 2.47 | 6.63 (d), 6.41 (dd), 7.22 (d) | — | — | 2.26 (3 H, s, 2-NHCOC$H_3$), 6.25 (2 H, CONH), 6.50 (2 H, CONH), 9.74 (1 H, CONH) |
| **10** | 1.14 | 2.50 | 7.15 (d), 7.46 (d) | — | — | 2.35 (3 H, s, 4-NHCOC$H_3$), 2.60 (3 H, s, 2-NHCOC$H_3$), 8.10 (1 H, CONH), 9.08 (1 H, CONH) |
| **11** | 107 | 2.45 | 7.15 (d), 7.45 (d) | 2.92 (q) | 2.71 (q) | 1.11 (3 H, t, $CH_3$), 1.24 (3H, t, $CH_3$), 7.84 (1 H, CONH), 8.67 (1 H, CONH) |
| **12** | 1.03 | 2.50 | 7.16 (d), 7.46 | 3.0 (t) | 2.45 (t) | 0.80–1.30 (6 H, m, 2 × $CH_3$), 1.40–2.00 (4 H, m, 2 × $CH_2$), 8.76 (1 H, CONH), 9.50 (1 H, CONH) |
| **13** | 1.10 | 2.50 | 7.13 (d), 7.43 (d) | 2.95 (t) | 2.3–2.6 (m) | 0.7–2.0 (6 H, m, 2 × $CH_3$), 0.7–2.0 (8 H, m, 4 × $CH_2$), 8.54 (1 H, CONH), 9.38 (1 H, CONH) |
| **14** | 1.11 | 2.50 | 7.16 (d), 7.46 (d) | — | — | 0.98 [9 H, s, 4-NHCOC($CH_3$)$_3$], 1.32 [9 H, s, 2-NHCOC($CH_3$)$_3$], 7.62 (1 H, CONH), 8.57 (1 H, NH) |
| **15** | 1.17 | 2.57 | 7.27 (d), 7.38 (d) | — | — | 7.24–7.59 (5 H, m, 4-NHCOC$_6H_5$), 7.24–7.59 (3 H, m, 2-NHCOC$_6H_3$), 7.98 (2 H, dd, 2-NHCOC$_6H_2$, 2-H, 6-H), 8.20 (1 H, NH), 9.09 (1 H, NH) |
| **16** | 1.09 | 2.32 | 7.17 (d), 7.44 (d) | — | — | 2.62 (3 H, s, 2-NHCOC$H_3$), 6.00 (2 H, NH), 10.26 (1 H, CONH) |
| **17** | 1.09 | 2.32 | 7.17 (d), 7.44 (d) | 3.06 (q) | — | 1.18 (3 H, t, $CH_3$), 6.40 (2 H, NH), 10.06 (1 H, CONH) |
| **18** | 1.06 | 2.27 | 7.10 (d); 7.40 (d) | 3.01 (t) | — | 0.93 (3 H, t, $CH_3$), 1.66 (2 H, q, $CH_2$), 6.05 (2 H, NH), 10.25 (1 H, CONH) |
| **19** | 1.30 | 2.32 | 7.12 (d), 7.42 (d) | 3.10 (t) | — | 0.7–1.9 (4 H, m, 2 × $CH_2$), 0.7–1.9 (3 H, m, $CH_3$), 6.1 (2 H, NH), 10.20 (1 H, CONH) |
| **20** | 1.05 | 2.32 | 7.16 (d), 7.44 (d) | — | — | 1.30 [9 H, s, 2-NHCOC($CH_3$)$_3$], 4.88 (2 H, NH), 7.87 (1 H, CONH) |
| **21** | 1.09 | 2.36 | 7.19 (d), 7.46 (d) | — | — | 5.20 (2 H, NH), 7.39–7.60 (3 H, m, 2-NHCOC$_6H_3$), 7.39–7.60 (1 H, NH), 7.95 (2 H, dd, 2-NHCOC$_6H_2$, 2-H, 6-H) |
| **23** | 1.06 | 2.45 | 7.0 (dd), 7.54 (d), 7.6 (d) | — | — | 2.04 (3 H, s, ArNHCOC$H_3$), 2.09 (3 H, s, 4-NHCOC$H_3$), 2.22 (3 H, s, 2-NHCOC$H_3$), 9.29 (1 H, CONH), 9.58 (1 H, CONH), 10.49 (1 H, CONH) |
| **24** | 1.00 | 2.37 | 7.00 (dd), 7.54 (d), 7.65 (d) | — | — | 2.10 (3 H, s, ArNHCOC$H_3$), 2.21 (3 H, s, 2-NHCOC$H_3$), 6.15 (2 H, NH), 9.54 (1 H, CONH), 9.79 (1 H, CONH) |
| **25** | 1.04 | 2.50 | 7.02 (dd), 7.38 (d), 7.52 (d) | — | — | 0.89 [9 H, s, 4-NHCO($CH_3$)$_3$], 1.23 [9 H, s, 2-NHCO($CH_3$)$_3$], 1.23 [9 H, s, ArNHCO($CH_3$)$_3$], 9.02 (1 H, CONH), 9.57 (1 H, CONH), 10.10 (1 H, CONH) |
| **26** | 1.07 | 2.33 | 6.88 (dd), 7.45 (d), 8.30 (d) | — | — | 1.31 [9 H, s, 2-NHCO($CH_3$)$_3$], 1.33 [9 H, s, ArNHCO($CH_3$)$_3$], 4.89 (2 H, NH), 7.86 (1 H, CONH), 8.02 (1 H, CONH) |
| **27** | 0.96 | 2.14 | 7.02 (dd), 7.39 (d), 7.53 (dd) | — | — | 1.23 [9 H, s, ArNHCO($CH_3$)$_3$], 5.54 (2 H, NH), 5.92 (2 H, NH), 8.94 (1 H, CONH) |

[a] Spectra were recorded on a Perkin-Elmer R34 spectrometer (220 MHz) or a Bruker WH400 spectrometer (400 MHz) using tetramethylsilane as an internal standard. All spectra were recorded in [$^2H_6$]DMSO as solvent (t = triplet, s = singlet, q = quartet, d = doublet, dd = double doublet, m = multiplet). [b] All NH absorptions appeared as broad singlets and both NH and CONH absorptions were exchangeable with $D_2O$.

emanating from the methyl protons of each trimethylacetamido group in derivative **14** was clearly absent, consistent with deacylation at the 4-position. Considerable signal overlap prevented unambiguous assignment of the aromatic protons of each of the benzamido substituents of compound **15**. However, a two proton signal centred at $\delta$ 7.98 (dd), and arising from the 2-H and 6-H aromatic protons of the benzoyl group, was also observed ($\delta$ 7.95) for the monoacylaminopyrimidine **21** following debenzoylation, in keeping with the predicted retention of the most deshielded C-2 benzamido substituent (Table 2).

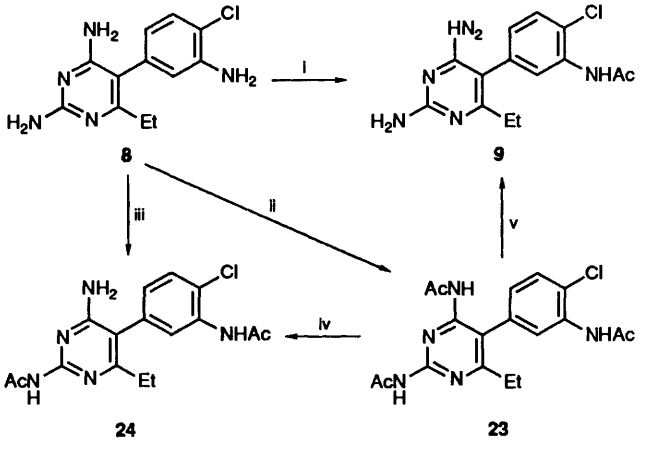
In order to confirm $^1$H NMR evidence that deacylation by Lewis acids does indeed proceed regioselectively to furnish 2-acylaminopyrimidines, the X-ray crystal structures of the 4-amino-2-propionamidopyrimidine **17** and its 2,-4-dipropionamido counterpart **11** were determined.

The synthetic utility of these reactions as a strategy for the protection and sequential deprotection of 2,4-diaminopyrimidines in high yields is evident. Thus, initial diacylation with the appropriate anhydride to introduce the requisite acyl protecting groups enables subsequent regioselective deprotection of the 4-amino substituent, or removal of both acyl protecting groups as required, depending upon the choice of protecting group, the combination of Lewis acid and alcohol utilised, and the reaction time and temperature employed.

These reactivity differences proved useful for the characterisation of a diacetylated derivative of the aforementioned *m*-aminopyrimethamine (MAP; **8**), a metabolite of the investigational antitumour drug *m*-azidopyrimethamine (MZP; **22**).[9] Reaction of MAP with acetic anhydride–pyridine at 25 °C to afford the acetanilide derivative **9**, a prospective metabolite of MZP, has been reported previously, and acetylation at the 3-amino group of the phenyl ring was confirmed by $^1$H NMR spectroscopy, the acetamido substituent ($CH_3$, $\delta$ 2.12, s) imparting a deshielding influence upon the adjacent 2-aromatic

proton ($\delta$ 7.00, d) compared to that of the parent amine ($\delta$ 6.65, d).[5] Bliss[10] found that while acetylation of MAP in refluxing acetic anhydride afforded the expected triacetylated pyrimidine **23**, treatment with acetic anhydride–acetic acid at 100 °C gave a diacetamido derivative **24**, and although acetylation of the 3-amino group was established by NMR analysis, the site of acylation on the exocyclic amino group of the pyrimidine ring could not be identified. Re-examination of this reaction and the $^1$H NMR spectrum of compound **24** revealed two singlets (3 H), one centred at $\delta$ 2.10 corresponding to the 3-acetamido substituent, and the second at $\delta$ 2.21 consistent with an acetamido group sited at the C-2 position on the pyrimidine ring. Moreover, the triacetamidopyrimidine **23** exhibited an additional signal at $\delta$ 2.02 attributable to the C-4 acetamido substituent absent from compound **24**.

Confirmation that the second acetyl group of the diacetamido derivative resided at C-2 came from chemical studies; thus treatment of compound **24** with tin(II) chloride in ethanol was without effect as expected, whereas hydrolysis with ethanol-hydrochloric acid or deacylation with zinc chloride in ethanol afforded the known 3-acetamido-MAP **9**. As expected compound **9** was isolated unchanged following treatment with tin(II) chloride or zinc chloride in ethanol, thus demonstrating that the deacylation of 2,4-diacylaminopyrimidines may be conducted in the presence of an acetanilide without detrimental effect upon the latter (Scheme 3).




**Scheme 3** *Reagents and conditions:* i, AcCl–pyridine, 25 °C; ii, $Ac_2O$, reflux; iii, $Ac_2O$–AcOH, 100 °C; iv, $SnCl_2$–EtOH, 25 °C; v, $ZnCl_2$–EtOH, 25 °C

The structure of compound **24** was also confirmed by comparison with an authentic sample prepared by the direct regioselective deacylation of the triacetamidopyrimidine **23**. Thus treatment of the pyrimidine **23** with tin(II) chloride in ethanol in the usual manner afforded 2-acetamido-5-(3-acetamido-4-chlorophenyl)-4-amino-6-ethylpyrimidine which proved identical (NMR, MS, TLC) with compound **24** prepared as described above. In keeping with the established reactivity characteristics of diacylaminopyrimidines, the triacetamidopyrimidine **23** was also smoothly converted to compound **9** upon treatment with zinc chloride in ethanol. Characterisation of the 'monoacetylated' product **7** formed from the initial reaction of diacetamidonitropyrimethamine **5** with tin(II) chloride was now possible; thus the $^1$H NMR spectrum of compound **7** exhibits a singlet at $\delta$ 2.26 clearly correlating with an acetamido group residing at the more deshielded C-2 position as expected.

The successful protection–stepwise deprotection of the three amino functions of compound **8** was also achieved using trimethylacetylation; thus reaction of compound **8** with trimethylacetic anhydride at 100 °C furnished the tristrimethylacetamido derivative **25** in good yield. Subsequent treatment with zinc chloride in ethanol at room temperature afforded the bistrimethylacetamidopyrimidine **26**, while heating the reaction mixture under reflux resulted in removal of the 2-trimethylacetyl substituent to give 2,4-diamino-5-(4-chloro-3-trimethylacetamidophenyl)-6-ethylpyrimidine **27** in good yield. The $^1$H NMR spectra of each compound again confirmed the position of substitution of each trimethylacetyl substituent. The structure of the pyrimidine **27** was also established by comparison (NMR, TLC) with an authentic sample prepared by acylation of the 3-amino group of compound **8** with trimethylacetyl chloride in pyridine containing 4-dimethylaminopyridine as catalyst.

*The Reaction Mechanism.*—Differences in the reactivity of amino substituents on a pyrimidine ring are well established; thus the more nucleophilic 5-amino group acylates in preference to those in the 2-, 4-, or 6-position.[11] Trattner and colleagues[12] found that the 4-amino group of pyrimethamine and several planar fused-ring diaminopyrimidines was more susceptible to acid or alkaline hydrolysis than the 2-amino group. However, we subsequently demonstrated the acid hydrolysis of pyrimethamine to be an exception, the shielding effect of the hydrophobic 4-chlorophenyl group of the diprotonated species reducing nucleophilic attack by water at C-4 and thus favouring attack at the C-2 position.[1]

4-Aminopyrimidine is a stronger base ($pK_a$ = 5.71) than 2-aminopyrimidine ($pK_a$ = 3.54), this being attributable to the former adopting the more favourable *p*-quinonoid resonance structure upon protonation thereby stabilising the cation.[11] Thus, the 4-amino and to a lesser degree the 2-amino substituents of diaminopyrimidines, while existing predominantly in the amino form, exhibit considerable imidic character, and this would be expected to render the corresponding 4-acylamino group more susceptible to nucleophilic attack than the 2-acylamino group. It is proposed that association of tin(II) chloride with the carbonyl oxygen of either amide group of the diacylaminopyrimidine occurs in the role of an acid catalyst, and that nucleophilic attack by the alcohol then proceeds at the most electrophilic carbon, notably that of the 4-acylamino carbonyl group, to furnish the 2-acylamino-4-aminopyrimidine and an ester. Presumably, further hydrolysis of the 2-acylamino derivative is precluded by the deactivating effect of the now available electron-donating 4-amino group. In contrast, zinc chloride, being a stronger Lewis acid than tin(II) chloride, renders both acylamino groups susceptible to attack by alcohol resulting in deacylation at both the 2- and 4-positions. The need to employ zinc chloride for the deacylation of the dibenzamidopyrimidine **15** is not surprising in view of the greater stability to hydrolysis of aromatic amides.

An alternative mechanism for the reaction may involve additional coordination of the Lewis acid with a pyrimidine ring nitrogen in a manner analogous to that observed by Hori and colleagues[13] for the regioselective de-*O*-benzylation of polyols, but evidence to support this possibility has not been adduced, and attempts to produce a crystal of the pyrimidine–Lewis acid complex suitable for crystallographic analysis have proven unsuccessful. Studies regarding the biological activity and mechanism of action of the compounds prepared in this study are in progress, and will be reported elsewhere.

*X-Ray Crystallography.*—Positional parameters for the structure of compound **11** are shown in Table 3. The corresponding data for the structure of compound **17** are reported in Table 4.*

* Bond lengths, angles, H-atom coordinates and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre. For details, see 'Instructions for Authors, 1992,' *J. Chem. Soc., Perkin Trans. 1*, 1992, issue 1.

**Table 3** Positional parameters (fractional coordinates × $10^4$) for compound **11** (estimated standard deviation)

| Atom | *x* | *y* | *z* |
|---|---|---|---|
| Cl(1) | −7038(1) | 6075(1) | −62(1) |
| N(1) | 152(3) | 6031(2) | 4120(2) |
| C(2) | 1336(2) | 5487(2) | 3985(2) |
| N(3) | 1416(3) | 4972(2) | 3287(1) |
| C(4) | 120(3) | 5021(2) | 2657(2) |
| C(5) | −120(3) | 5588(2) | 2707(2) |
| C(6) | −1130(4) | 6082(2) | 3467(2) |
| C(1P) | −2620(4) | 5627(2) | 1979(2) |
| C(2P) | −2336(5) | 6012(2) | 1139(2) |
| C(3P) | −3685(5) | 6134(2) | 496(3) |
| C(4P) | −5308(5) | 5886(3) | 708(3) |
| C(5P) | −5616(5) | 5516(2) | 1511(3) |
| C(6P) | −4279(4) | 5396(2) | 2152(3) |
| N(21) | 2735(3) | 5420(2) | 4615(2) |
| C(22) | 3126(4) | 5817(2) | 5416(2) |
| O(23) | 4438(2) | 5618(1) | 5856(1) |
| C(23) | 1997(5) | 6470(3) | 5750(3) |
| C(24) | 2530(5) | 6818(2) | 6659(3) |
| N(41) | 120(3) | 4491(2) | 1922(2) |
| C(42) | 972(4) | 3780(2) | 1776(3) |
| O(43) | 709(3) | 3450(2) | 1040(2) |
| C(43) | 2148(5) | 3425(2) | 2520(3) |
| C(44) | 2612(6) | 2570(2) | 2320(4) |
| C(61) | −2437(5) | 6746(3) | 3641(3) |
| C(62) | −3535(5) | 6657(3) | 3172(3) |

**Table 4** Positional parameters (fractional coordinates × $10^4$) for compound **17** (estimated standard deviation)

| Atom | *x* | *y* | *z* |
|---|---|---|---|
| Cl(1) | −1 416(1) | 14 529(1) | 3 183(1) |
| N(1) | 2 037(2) | 8 126(2) | 1 147(1) |
| C(2) | 1 267(2) | 7 075(3) | 719(2) |
| N(3) | 134(2) | 6 953(2) | 647(1) |
| C(4) | −267(2) | 8 087(3) | 1 057(2) |
| C(5) | 464(2) | 9 334(3) | 1 515(2) |
| C(6) | 1 620(2) | 9 275(3) | 1 550(2) |
| C(1P) | −22(2) | 10 604(3) | 1 928(2) |
| C(2P) | 405(3) | 10 314(3) | 2 629(2) |
| C(3P) | −805(3) | 11 508(4) | 3 016(2) |
| C(4P) | −899(2) | 13 011(3) | 2 689(2) |
| C(5P) | −530(3) | 13 339(3) | 2 000(2) |
| C(6P) | −98(3) | 12 145(3) | 1 607(2) |
| N(21) | 1 664(2) | 5 883(3) | 280(1) |
| C(22) | 2 613(2) | 5 863(3) | −4(2) |
| C(23) | 2 818(2) | 4 660(2) | −345(2) |
| C(23) | 3 351(3) | 7 319(4) | 52(2) |
| C(24) | 4 194(4) | 7 162(4) | −462(3) |
| N(41) | −1 393(2) | 8 012(3) | 1 004(2) |
| C(61) | 2 534(3) | 10 444(4) | 2 050(2) |
| C(62) | 3 038(6) | 11 388(7) | 1 485(4) |

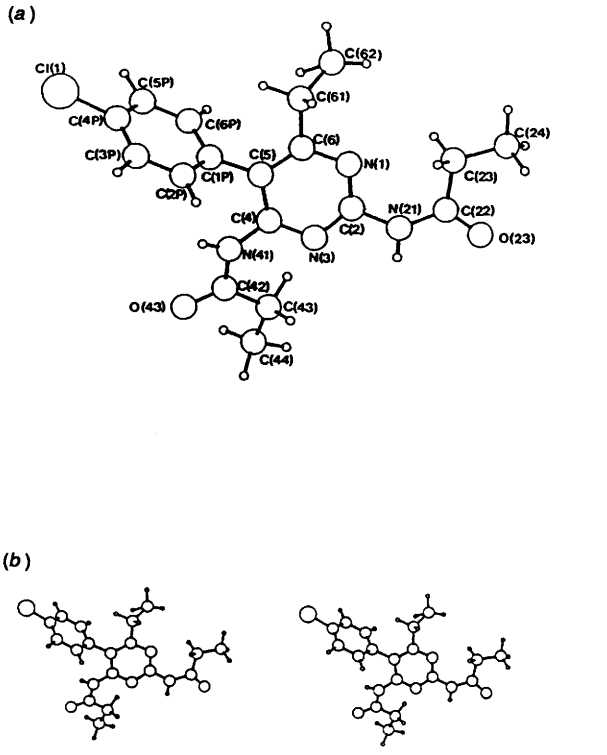



**Fig. 1** PLUTO[14] drawing of (*a*) Numbering scheme for atoms in **11** (*b*) Stereo plot of **11**

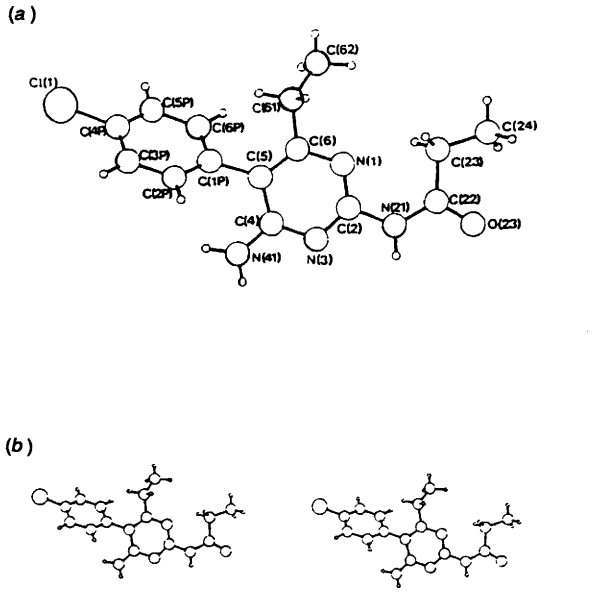



**Fig. 2** PLUTO[14] drawing of (*a*) Numbering scheme for atoms in **17** (*b*) Stereo plot of **17**

The crystal structure determinations confirm the structures of the pyrimidines **11** and **17** proposed on evidence from $^1$H NMR studies; the crystallographic numbering schemes used are shown in Figs. 1 and 2.

In the solid state, compound **17**, exists as a base pair dimer linked by N(21)–H(21)···N(3) hydrogen bonds [3.261(8) Å] about a centre of symmetry. Such a conformation is quite common in pyrimidine and related structures.[16] However, the propionamido group at C(2) allows additional hydrogen bonding, N(41)–H(41)···O(23) [2.838(7) Å] to produce a quadruply hydrogen-bonded base pair consisting of two equivalent pairs of hydrogen bonds (Fig. 3). The remaining proton on N(41) forms a weak interaction with Cl(1) [3.551(8) Å], *via* the symmetry operation $-0.5 - x, 0.5 + y, 1.5 - z$.

In order to accommodate all four hydrogen bonds, the N(21)–H(21)···N(3) interaction appears weaker than that found in similar compounds; typically this value is less than 3.2 Å as found in the structure of 2,4,6-triaminopyrimidine.[17] The interaction is further accommodated by O(23) rotating out of the plane of the pyrimidine ring, principally about the C(2)–N(21) bond; N(1)–C(2)–N(21)–C(22) torsion angle of 22.2°.

In the 2,4-dipropionamido compound **11** the orientation of the 4-propionamido substituent inhibits hydrogen bonding at the N(3) position of the pyrimidine ring, and dimerisation about a centre of symmetry is achieved by N(21)–H(21)···O(23) hydrogen bonds [2.894(8) Å] on the 2-propionamido group.

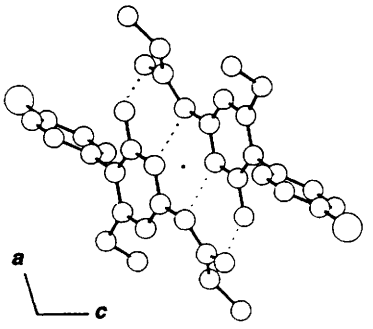



Fig. 3 PLUTO[14] drawing of base-pair dimerisation in **17**

Without the additional hydrogen bonding constraints of compound **17**, this group attains a more planar conformation with the pyrimidine ring with the torsion angle being 1.2°.

The geometry of the two ring systems is quite typical of substituted pyrimethamine derivatives[18] with the angle between the least squares plane through the pyrimidine and benzene rings being 75° and 67° for compounds **11** and **17**. It is not surprising, however, that the former angle is somewhat larger being adjacent to the bulky 4-propionamido group, albeit that this rotates out of the plane of the pyrimidine ring; N(3)–C(4)–N(41)–C(42) torsion angle of 17.3°.

The bond lengths in the pyrimidine rings in the two compounds are almost identical with the exception of N(3)–C(4) and C(4)–C(5) which are shorter in compound **11** by at least $3\sigma$ in both cases. This can be accounted for by the pronounced double bond nature of the C(4)–N(41) bond in compound **17** [1.332(4) Å] suggesting considerable electron donation by the N(41) amino group and an associated lengthening of the two adjacent bonds in the pyrimidine ring. With respect to the 2-propionamido group in the two compounds, the N(21)–C(22) bond is shorter than the C(2)–N(21) bond by 0.034 Å and 0.044 Å for compounds **11** and **17** respectively. This is due largely to the electron-withdrawing effect of O(23), which may also explain the additional double bond nature of the C(4)–N(41) bond in compound **17** over and above an average value of 1.35 Å for related 2,4-diaminopyrimidines as determined by Schwalbe and Cody.[16] Presumably, the electron-withdrawing group at the 2-position significantly enhances the electron-donating effect of the 4-amino nitrogen.

## Experimental

Ethanol refers to 95% ethanol; light petroleum refers to the fraction b.p. 60–80 °C. All m.p.s were measured on an electrothermal melting point apparatus and are uncorrected. IR spectra were recorded on a Unicam SP200 Infrared Spectrometer as potassium bromide discs. Mass spectra were recorded on a V.G. Micromass 12 instrument at 70 eV; source temperature 250–300 °C. The TLC systems employed Kieselgel $60F_{254}$ (0.25 mm) as the adsorbent and either chloroform–methanol (4:1) or toluene–ethanol–acetone (7:5:3) as the developing solvent. The physical and analytical data for compounds prepared in this study are summarised in Tables 1 and 2.

2,4-*Diacetamido*-5-(4-*chloro*-3-*nitrophenyl*)-6-*ethylpyrimidine* **5**.—A solution of nitropyrimethamine[1] **4** (1 g) in acetic acid (8 $cm^3$) and acetic anhydride (8 $cm^3$) was refluxed for 0.5 h. The dark mixture was cooled, poured into water (50 $cm^3$) and the solution was basified with concentrated aqueous ammonia. The oil which separated was extracted with ethyl acetate (2 × 50 $cm^3$) and the extract after being washed with saturated aqueous sodium hydrogen carbonate (2 × 50 $cm^3$) and water (100 $cm^3$), dried ($Na_2SO_4$), and evaporated afforded the diacetamidopyrimidine **5**; this crystallised from ethyl acetate–light petroleum as cream microcrystals.

A solution of compound **5** (0.2 g) in a mixture of ethanol (25 $cm^3$) and hydrochloric acid (0.1 mol $dm^{-3}$, 25 $cm^3$) was stirred at 60 °C for 12 h. Removal of solvents gave a white solid which was dissolved in warm water (20 $cm^3$) and basified with sodium hydrogen carbonate to give a yellow solid which was collected, washed with water and dried. Recrystallisation of this from ethanol afforded yellow microrosettes identical (NMR, TLC) with an authentic sample of compound **4**.[1]

2-*Acetamido*-4-*amino*-5-(3-*amino*-4-*chlorophenyl*)-6-*ethylpyrimidine* **7**.—Tin(II) chloride (4 g) was added in portions over 15 min to a solution of the diacetamidopyrimidine **5** (1 g) in ethanol (50 $cm^3$), and the mixture was stirred at 70 °C overnight. After cooling, the solvent was evaporated to leave a yellow syrup which was redissolved in hot water. The solution was cooled, basified to pH 12 with aqueous sodium hydroxide (10 mol $dm^{-3}$), and the resulting precipitate was collected, washed thoroughly with water and dried. Recrystallisation from aqueous ethanol afforded the title compound **7** as pale yellow flakes.

A solution of compound **7** (0.3 g) in a mixture of ethanol (25 $cm^3$) and hydrochloric acid (0.1 mol $dm^{-3}$; 25 $cm^3$) was stirred at 60 °C for 12 h. Ethanol was removed under reduced pressure and the residue was dissolved in water (20 $cm^3$) and basified with sodium hydrogen carbonate, whereupon a cream solid was deposited and collected, washed with water and dried. Recrystallisation from ethanol afforded a white amorphous solid identical (NMR, TLC) with an authentic sample of the aminopyrimethamine **8**.[5]

*Acylaminopyrimidines.—General method A.* In a typical reaction a suspension of pyrimethamine **1** (5 g) in acetic anhydride (25 $cm^3$) was boiled for 2 h and the yellow solution was cooled and poured into water (200 $cm^3$). The mixture was carefully basified with concentrated aqueous ammonia and extracted with ethyl acetate (2 × 50 $cm^3$). The combined ethyl acetate layers were washed with saturated aqueous sodium hydrogen carbonate (2 × 50 $cm^3$), followed by water (50 $cm^3$), and dried ($Na_2SO_4$). Evaporation of the solvent furnished the required diacetamidopyrimidine **10** which crystallised from ethanol–water as colourless prisms. Analogous reactions conducted with pyrimethamine and the appropriate anhydride gave the required diacylaminopyrimidines **11**–**15**.

The diacetamidopyrimethamine **10** was also prepared as follows. Pyrimethamine **1** (1 g) was dissolved in pyridine (20 $cm^3$) with warming and 4-dimethylaminopyridine (50 mg) was added. The solution was cooled to 0 °C and acetyl chloride (1.14 g) was added dropwise over 30 min. After stirring at room temperature for 12 h the mixture was poured into water (100 $cm^3$), stirred for 30 min and the resultant oil was extracted with ethyl acetate (2 × 100 $cm^3$). The organic layer was washed with water (100 $cm^3$), dried ($Na_2SO_4$) and the solvent was evaporated to give a pale yellow oil which slowly crystallised on standing. Recrystallisation twice from ethanol–water gave a cream solid identical (NMR, TLC) to **10** above. Analogous reactions conducted with compound **1** and either trimethylacetyl chloride or benzoyl chloride gave intractable mixtures in both cases.

*General method B.* Typically, to a solution of 2,4-diacetamidopyrimethamine **10**, (1 g) in ethanol (30 $cm^3$) was added tin(II) chloride (3 g) and the solution was stirred at room temperature overnight. Evaporation of the solvent afforded a yellow syrup which was redissolved in ethyl acetate (100 $cm^3$) and shaken with saturated aqueous sodium hydrogen carbonate (2 × 100 $cm^3$). The organic layer was washed thoroughly with water (2 × 100 $cm^3$), dried ($Na_2SO_4$), and evaporated to furnish the

monoacetamidopyrimidine **16** which was recrystallised from ethanol–water to afford colourless needles. Similarly prepared from the corresponding diacylaminopyrimidines **11**–**14** were the monoacylaminopyrimidines **17**–**20**.

The 2-acetamido-4-aminopyrimidine **16** was also formed (70%) when compound **10** (0.2 g) was treated with 1 mol equiv. of tin(II) chloride in ethanol (30 $cm^3$) as above (24 h).

*General method C.* The bis(trimethylacetamido)pyrimidine **14** (1 g) was dissolved in ethanol (50 $cm^3$) and anhydrous zinc chloride (3 g) was added in a single portion. The mixture was stirred for 2 h at room temperature when dissolution was complete and all starting materials were consumed (TLC). Following evaporation of the ethanol the remaining syrup was redissolved in ethyl acetate (100 $cm^3$) and the solution was shaken thoroughly with saturated aqueous sodium hydrogen carbonate (2 × 100 $cm^3$), washed with water (100 $cm^3$), and dried ($Na_2SO_4$). Removal of the solvent and recrystallisation of the cream solid from ethanol–water gave the 2-trimethylacetamidopyrimidine **20** as colourless microcrystals. Similarly prepared from the dibenzamidopyrimidine **15** was the 2-benzamido derivative **21**.

The above reactions were repeated over a prolonged period (1 week) and also under reflux conditions (2 h). While complete deacylation of **14** was observed (TLC) in both cases to give pyrimethamine as the only product, analogous debenzoylation of **15** was apparent only after prolonged boiling (6 h) of the reaction mixture. Treatment of the diacetamidopyrimidine **10** (0.2 g) with zinc chloride (1.0 g) in ethanol (30 $cm^3$) at room temperature (2 h), gave only compound **1** (TLC), while the reaction with propan-2-ol (20 $cm^3$) as solvent afforded, after work-up, colourless flakes (0.13 g) identical (NMR, TLC) with the 2-acetamido-4-aminopyrimidine **16** prepared by method B above.

*2-Acetamido-5-(3-acetamido-4-chlorophenyl)-4-amino-6-ethylpyrimidine* **24**.—To a solution of the triacetamidopyrimidine **23**[10] (0.3 g) in ethanol (30 $cm^3$) was added tin(II) chloride (1 g) and the mixture was stirred overnight at room temperature. Following evaporation of solvent and work-up as described for method B above, the pale yellow powder (0.21 g) was crystallised from ethanol–water to give the title compound **24** as colourless prisms.

The same product was formed (80%) when a solution of the 3-aminophenylpyrimidine **8** (4 g) in a mixture of acetic anhydride (23 $cm^3$) and acetic acid (23 $cm^3$) was stirred at 100 °C for 1 h. After cooling and adding water (40 $cm^3$), the mixture was basified with concentrated aqueous ammonia solution and the resulting white precipitate was collected, washed with water and dried. Recrystallisation from ethanol–water furnished compound **24** as pale yellow needles.

Treatment of the di- or tri-acetamidopyrimidines **23** and **24** (0.3 g) with zinc chloride (1 g) in ethanol (30 $cm^3$) as described for method C above afforded a white powder (0.1 g) identical (NMR, TLC) to an authentic sample of the 3-acetamidophenylpyrimidine **9**.[5]

*2,4-Bistrimethylacetamido-5-(4-chloro-3-trimethylacetamidophenyl)-6-ethylpyrimidine* **25**.—A suspension of 2,4-diamino-5-(3-amino-4-chlorophenyl)-6-ethylpyrimidine **8** (1 g) in trimethylacetic anhydride (8 $cm^3$) was boiled for 1 h, cooled and poured into water (50 $cm^3$). The oil that separated upon basification with concentrated aqueous ammonia was extracted into ethyl acetate (2 × 100 $cm^3$), and the combined extracts were washed with saturated aqueous sodium hydrogen carbonate (2 × 100 $cm^3$) followed by water (100 $cm^3$), and dried ($Na_2SO_4$). Evaporation of solvent afforded a yellow oil (3.5 g) which upon trituration with ether and storage at 4 °C overnight gave a white precipitate which was collected. Recrystallisation of this twice from ethyl acetate–light petroleum gave the tris(trimethylacetamido)pyrimidine **25** as colourless microprisms.

*4-Amino-5-(4-chloro-3-trimethylacetamidophenyl)-6-ethyl-2-trimethylacetamidopyrimidine* **26**.—Zinc chloride (1 g) was added to a solution of the tristrimethylacetylpyrimidine **25** (0.2 g) in ethanol (15 $cm^3$) and the mixture was stirred overnight at room temperature. Evaporation of solvent afforded a pale yellow syrup which was redissolved in ethyl acetate (50 $cm^3$) and the solution washed thoroughly with saturated aqueous sodium hydrogen carbonate (2 × 100 $cm^3$). After being washed with water (100 $cm^3$) and dried ($Na_2SO_4$) the organic phase was evaporated to give the title compound **26** as a white amorphous solid which crystallised from ethyl acetate–light petroleum as cream microprisms.

*2,4-Diamino-5-(4-chloro-3-trimethylacetamidophenyl)-6-ethylpyrimidine* **27**.—The aminopyrimethamine **8** (1.0 g) was dissolved in dry pyridine (20 $cm^3$) with gentle warming and 4-dimethylaminopyridine (0.05 g) was added to the solution. This was stirred at room temperature whilst trimethylacetyl chloride (0.55 g) was added dropwise over 30 min. The solution was stirred for a further 2 h, poured onto ice–water (100 $cm^3$) and the mixture was extracted with ethyl acetate (2 × 100 $cm^3$). The combined ethyl acetate fractions were washed with water (100 $cm^3$), dried ($Na_2SO_4$), and evaporated to give the title compound **27** as a cream solid which crystallised from ethyl acetate–light petroleum as colourless microprisms.

*Crystal Structure of the 2,4-Dipropionamidopyrimidine* **11**.—The numbering scheme used in the crystallographic determination is shown in Fig. 1.

*Crystal Data.* 2,4-Dipropionamidopyrimidine **11**, $C_{18}H_{21}ClN_4O_2$, $M$ = 360.843. Monoclinic, $a$ = 7.753(4), $b$ = 16.677(3), $c$ = 14.510(3) Å, $\beta$ = 92.13(3)°, $V$ = 1874.6(9) $Å^3$ (by least squares refinement on diffractometer angles for 25 automatically centred reflections, $\lambda$ = 0.710 69 Å), space group $P2_1/n$, $Z$ = 4, $D_x$ = 1.279 g $cm^{-3}$, crystal dimensions = 0.65 × 0.50 × 0.4 mm, $\mu$(Mo-K$\alpha$) = 1.81 $cm^{-1}$.

*Crystal Structure of the 4-Amino-2-propionamidopyrimidine* **17**.—The numbering scheme used in the crystallographic determination is shown in Fig. 2.

*Crystal Data.* 4-Amino-2-propionamidopyrimidine **17**, $C_{15}H_{17}ClN_4O$, $M$ = 304.780. Monoclinic, $a$ = 12.037(2), $b$ = 8.499(6), $c$ = 16.201(2) Å, $\beta$ = 108.97(1)°, $V$ = 1567.3(7) $Å^3$ (by least squares refinement on diffractometer angles for 25 automatically centred reflections, $\lambda$ = 0.710 69 Å), space group $P2_1/n$, $Z$ = 4, $D_x$ = 1.290 g $cm^{-3}$, crystal dimensions = 0.75 × 0.30 × 0.15 mm, $\mu$(Mo-K$\alpha$) = 2.06 $cm^{-1}$.

*Collection and Processing of Data.*—Enraf–Nonius CAD4 diffractometer, $\omega$-2$\theta$ mode with scan width = 1.0 + 0.35 tan $\theta$ (11) and 0.90 + 0.35 tan $\theta$ (17), scan speed 0.9 to 5.0° $min^{-1}$ (11) and 0.6 to 3.3° $min^{-1}$ (17), graphite monochromated Mo-K$\alpha$ radiation. For compound **11** 3289 unique reflections were measured (merging $R$ = 0.021) between $2° \leqslant \theta < 25°$ for $\pm h$, $\pm k$, $+l$ giving 2287 with $|F_o| > 3\sigma(F_o)$. For compound **17** 2750 unique reflections were measured (merging $R$ = 0.079) between $2° \leqslant \theta < 25°$ for $+h$, $\pm k$, $\pm l$ giving 2017 with $|F_o| > 3\sigma(F_o)$. No decomposition or movement of the crystals was detected during data collection and no correction was made for extinction or absorption during refinement.

*Structure Analysis and Refinement.*—The structure of 2,4-dipropionamidopyrimidine **11** was solved using SHELX.[15] Hydrogen positions for the 6-ethyl group and the terminal methyls of the 2- and 4-propionamido-groups were calculated;

all others were determined by a difference electron density synthesis. Final full matrix least squares refinement of coordinates and anisotropic thermal parameters for non-hydrogen atoms, and coordinates and isotropic temperature factors for hydrogen atoms (terminal methyls refined as rigid groups) reduced $R = \Sigma|[F_o] - [F_c]|/\Sigma|F_o|$ and $R_w = \Sigma w^{\frac{1}{2}}|[F_o] - [F_c]|/\Sigma w^{\frac{1}{2}}$ ($|F_o|$ to 0.059 and 0.061 respectively). In the final stages of refinement, reflections were weighted according to $w = k/\sigma^2(F_o)$ where $k$ converged at 2.612 and $\sigma(F_o)$ was obtained from counting statistics and an allowance for instability of the instrument. Refinement was terminated when no positional parameter shifted by more than 0.053 esd at which point a difference electron density map showed no feature greater than $\pm 0.35$ e Å$^{-3}$.

The structure of 4-amino-2-propionamidopyrimidine **17** was also solved and subsequently refined using SHELX.[15] All hydrogen atoms were located from a difference electron density synthesis. Final full matrix least squares refinement as for compound **11**, but without constraints on the methyl hydrogen atoms, reduced $R$ and $R_w$ to 0.045 and 0.042 respectively. In the final stages reflections were weighted according to $w = k/\sigma^2(F_o)$ and $k$ converged at 1.915. The refinement was terminated when no positional parameter shifted by more than 0.004 esd at which point a difference electron density map showed no feature greater than $\pm 0.17$ e Å$^{-3}$.

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