# Purine Studies. Part XVI.[1] Occurrence of *syn*- and *anti*-Isomers † in 4-Amino-5-formamidopyrimidine Derivatives

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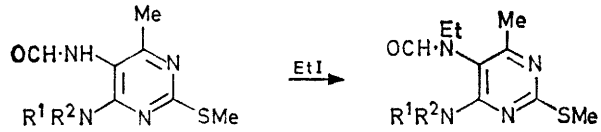
The multiple nature of the resonances in the $^1$H n.m.r. spectra of a series of derivatives of 4-amino-5-formamido-6-methyl-2-methylthiopyrimidines, with special reference to those due to the formyl and *C*-methyl groups, is attributed to the presence of *syn*- and *anti*-isomers. The isomeric ratio, which varies with the solvent employed, almost always has the *syn*-conformer as the equal or predominant species. Following ethylation the resulting 5-(*N*-ethylformamido)pyrimidines also show two isomeric modifications but in these derivatives the *anti*-form is the major one present. While some analogies can be drawn between the spectra of the above derivatives and those of formanilide analogues, significant differences are found also. Thus, the reversal of the positions of the *syn*- and *anti*-formyl resonances is taken to reflect the essentially planar conformation of the amide group with the ring plane in the case of the simple formanilides compared with the orthogonal position assumed by this group in the formamidopyrimidines.

ONE aspect of previous studies [2,3] with acetylated and trifluoracetylated derivatives of 4,5-diamino-6-methyl-2-methylthiopyrimidines was an examination of their $^1$H n.m.r. spectra to ascertain if cyclic adducts [*i.e.* 7,8(8,9)-dihydropurines], such as have been claimed [4,5] to be formed with some acetylated 4,5-diaminopyrimidines, were present, possibly in equilibrium with the acylamidopyrimidines. Although evidence for such cyclic forms was lacking several features of diagnostic value in structure elucidation were obtained from the $^1$H n.m.r. data.

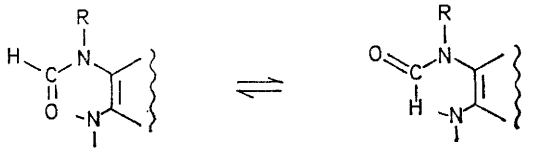
In the present work the results of a similar spectral examination of the corresponding series of 5-formamidopyrimidines and related *N*-ethylated homologues are reported. A significant observation was that in all cases multiplet, rather than singlet, character was a feature of most of the group resonances, this being most pronounced in the formyl and *C*-methyl group shifts.

(a) 4-*Amino-5-formamidopyrimidines.*—With the 4-amino- (1a) and 4-ethylamino-5-formamidopyrimidines (1b) the formyl resonances can be resolved into two doublets, the one at higher field having a much larger coupling constant ($J$ 12 Hz) than the other ($J$ 1.2 Hz).




(1) (2)

a; $R^1 = R^2 = H$
b; $R^1 = H$, $R^2 = Et$
c; $R^1 = R^2 = Me$




*syn* *anti*

(3) (4)

On changing the solvent from dimethyl sulphoxide to chloroform both sets of signals moved slightly downfield,

† The terms *syn* and *anti* are used here to denote the conformation of the amide nitrogen substituent (whether hydrogen or ethyl) relative to the formyl hydrogen atom.

[1] Part XV, W. Pendergast, *J.C.S. Perkin I*, 1975, 2240.
[2] M. D. Fenn and J. H. Lister, *J.C.S. Perkin I*, 1975, 1300.
[3] M. D. Fenn and J. H. Lister, *J.C.S. Perkin I*, 1975, 485.
[4] H. Bredereck, I. Hennig, W. Pfleiderer, and G. Weber, *Chem. Ber.*, 1953, **86**, 333.
[5] H. Biltz and W. Schmidt, *Annalen*, 1923, **431**, 70.

with no alteration in the coupling constant values. A change, however, is observed in the intensity of the peak heights; the shift of larger $J$ value increases with a corresponding decrease in height of the smaller $J$ value shift. The reversible nature of this effect is shown by the fact that on stepwise addition of an excess of one of the above solvents to a solution of the formyl derivative in the other one a transformation of the original spectrum to that of the amide in the other (diluting) solvent occurs. By analogy with the results of like studies [6] with formanilides the presence of *syn*- and *anti*-isomers is inferred. Splitting of the formyl signal in both modifications, which arises from vicinal coupling with the amide proton, can be obviated by the addition of deuterium oxide. As the smaller coupling ($J$ 1.2 Hz) is shown by the *syn*-form [6,7] (**3**; R = H) an assessment of the isomer ratios present in a particular solvent is therefore possible from comparison of peak heights and peak areas (Table).

no longer in the plane of the ring but is rotated about the ring carbon–amide nitrogen bond to a position near-perpendicular to the ring plane. Conformations of this type have been reported with other aromatic formamide derivatives.[8] It has been demonstrated [9] that while the *anti*-formyl proton is the more deshielded one when in a planar conformation the reverse holds on rotation of the amide group to the orthogonal position. In this case the *anti*-formyl proton is now positioned above the plane of the ring. These findings are in agreement with those obtained from *ortho*-substituted formanilides [10] in which a similar transposing of *syn*- and *anti*-formyl resonances is reported due to the out-of-plane conformation induced by the steric effects of the *ortho*-substituents. Molecular model studies of the amidopyrimidines support the orthogonal conformation, this affording the least sterically hindered form. The spectral similarity of (1a—c) points to the same conformation being adopted in all three cases. This, therefore, suggests that no significant

$^1$H N.m.r. spectra of *syn*- and *anti* [a]-4-amino-5-formamidopyrimidines (δ values)

| 6-Methyl-2-methylthio-pyrimidine | Solvent [b,c] | 2-SMe | 6-Me | 4-$NH_2$ | 5-$NH_2$ | $CH_2$·$CH_3$ | $CH_2$·$CH_3$ | CHO [d] | *syn* : *anti* (%) |
|---|---|---|---|---|---|---|---|---|---|
| 4-$NMe_2$-5-$NH_2$ | A | 2.40 | 2.22 | 2.80 [i] | 4.40 | | | | |
| | C | 2.52 | 2.30 | 2.88 [i] | 3.10 | | | | |
| 4-$NH_2$-5-NH·CHO | A | 2.38 | 2.08, *2.17* | 6.70 | 8.50 | | | 8.18, [f] *7.87* [g] | 90 : 10 |
| | B | 2.45 | 2.17, *2.23* | Exch. | Exch. | | | 8.30, [f] *8.00* [g] | 75 : 25 |
| 4-NHEt-5-NH·CHO [h] | A | 2.35 | 2.02, *2.10* | 6.90 | 9.00 | 1.07 | 3.25 | 8.13, [f] *7.78* [g] | 85 : 15 |
| | C | 2.50 | 2.23, *2.28* | 5.20 | 6.80 | 1.22 | 3.42 | 8.37, [f] *7.93* [g] | 50 : 50 |
| 4-$NMe_2$-5-NH·CHO | A | 2.43 | 2.12 | 3.02, *3.05* [i] | 9.50 | | | 8.20, [f] 7.83 [g] | 85 : 15 |
| | C | 2.50, *2.48* | 2.20, *2.29* | 3.10, *3.13* [i] | 7.50 | | | 8.33, [f] 7.92 [g] | 60 : 40 |
| 4-$NH_2$-5-NEt·CHO [j] | A | 2.40 | 2.05, *2.12* | 6.90, 7.00 [k] | | 1.00, 1.05 | 3.47, 3.52 | 8.18, *7.92* | 50 : 50 |
| | C | 2.50 | 2.23, *2.25* | 5.20, *5.50* | | 1.20, 1.17 | 3.62, 3.65 | 8.32, *7.97* | 20 : 80 |
| 4-NHEt-5-NEt·CHO | A | 2.37 | 1.97, *2.03* | 7.20 | | 0.93, 0.98, 1.03 | 3.3br | 8.18, *7.87* | 50 : 50 |
| | C | 2.52 | 2.20, *2.22* | 5.00 | | 1.15, 1.22, 1.22 | 3.60 [l] | 8.33, *7.93* | 20 : 80 |
| | D | 2.47 | 2.10, *2.13* | 7.20 | | 1.05, 1.13, 1.17 | 3.57 [l] | 8.32, *8.00* | 40 : 60 |
| 4-$NMe_2$-5-NEt·CHO | A | 2.47 | 2.07, *2.15* | 3.02, *2.97* [i] | | 0.95, 1.00 | 3.63 [l] | 8.32, *8.18* | 70 : 30 |
| | B | 2.50 | 2.15, *2.22* | 3.12, *3.07* [i] | | 1.11 | 3.63 | 8.35, *8.22* | 75 : 25 |
| | C | 2.50 | 2.20, *2.27* | 3.08, *3.02* [j] | | 1.07, 1.12 | 3.67 [l] | 8.30, *8.13* | 50 : 50 |
| | D | 2.50 | 2.15, *2.22* | 3.10, *3.05* [i] | | 1.08 | 3.68 [l] | 8.40, *8.25* | 70 : 30 |

[a] *anti*-Shifts in italics. [b] A = $(CD_3)_2SO$, B = $CD_3OD$, C = $CDCl_3$, D = $DCON(CD_3)_2$. [c] Concentrations are 35—40% w/v. [d] Formyl shifts are independent of concentration. [e] Compound not soluble in $CDCl_3$. [f] Doublet, $J$ 1.2 Hz. [g] Doublet, $J$ 12 Hz. [h] Ref. 3. [i] Singlet, NMe. [j] Ref. 2. [k] Unassigned. [l] Multiplet.

Comparisons of the formamidopyrimidine spectra with those of simple formanilides show a reversal in the positions of the *syn*- and *anti*-formyl resonances, the *syn*-form now showing the most deshielding. A translocation of this nature is explicable by assuming that in the case of the formamidopyrimidines the amide group is

degree of internal hydrogen bonding would be expected to exist in any of these derivatives and seems to be borne out by the fact that the *anti*-formyl resonances of the 4-aminopyrimidine (1a) and the 4-dimethylamino-analogue (1c), in which bonding is precluded, are near identical (δ 7.83 and 7.87 respectively).

[6] A. J. R. Bourn, D. G. Gillies, and E. W. Randall, *Tetrahedron*, 1964, **20**, 1811.

[7] E. W. Randall and J. D. Baldschwieler, *J. Mol. Spectroscopy*, 1962, **8**, 365.

[8] W. E. Stewart and T. H. Siddall, *Chem. Rev.*, 1970, **70**, 517.

[9] C. E. Johnson and F. A. Bovey, *J. Chem. Phys.*, 1958, **29**, 1012.

[10] I. D. Rae, *Canad. J. Chem.*, 1966, **44**, 1334.

(b) *4-Amino-5-(N-ethylformamido)pyrimidines.*— The occurrence of *syn-* and *anti*-conformers (relative to the *N*-ethyl group) is shown by the presence of two formyl singlets and two *C*-methyl singlets. Because of the absence of splitting assignment of the formyl resonances to the appropriate isomer was made by matching the shift of major intensity with the corresponding major *C*-methyl shift. By making the assumption that in these isomers the *C*-methyl resonances were comparable in intensity and shift with those of the isomers of the 5-formamidopyridine precursors, which have been unambiguously assigned, the conformer ratios were identified and quantified (Table).

In both the 5-formamidopyrimidines (1a—c) and the *N*-ethylated homologues (2a—c) the formyl shifts of the *syn-* forms occur at lower fields. In this respect a further contrast is seen with the formanilide analogues which show the *anti*-resonance in this position.[11] Following ethylation of the formamidopyrimidines a change in isomeric preference is found in all solvents employed. Thus, the predominance of the *syn*-form (3; R = H) is lost on alkylation and the *anti*-conformer (4; R = Et) now becomes an equal or major component of the mixture. An exception to this, however, is the 4-dimethylamino-derivative (2c) which, in four solvents, retains the *syn*-conformation for the main isomer.

The shift data, taken together with the results from model studies, indicate that while an orthogonal disposition of the amide group is retained there is, due to the bulk effect of the 5-*N*-ethyl group, the probability that some inclination of the amide group towards the 4-amino-substituent occurs.

## EXPERIMENTAL

$^1$H N.m.r. spectra were recorded at 35° on a Varian T60A instrument, with tetramethylsilane as standard.

*4-Ethylamino-5-(N-ethylformamido)-6-methyl-2-methylthiopyrimidine* (2b).—A solution of 4-ethylamino-5-formamido-6-methyl-2-methylthiopyrimidine [3] (0.3 g) in dimethylformamide (4 ml) containing dried potassium carbonate (0.35 g) was treated with iodoethane (0.4 g) and stirred for 24 h. After removal of inorganic salts by filtration the solution was diluted three-fold with water and evaporated to dryness. Extraction of the residue with chloroform and evaporation of the dried ($Na_2SO_4$) extracts gave the *5-(N-ethylformamido)pyrimidine* (0.3 g), m.p. 122—123° (from aqueous methanol) (Found: C, 51.9; H, 7.3; N, 22.1. $C_{11}H_{18}N_4OS$ requires C, 51.9; H, 7.1; N, 22.0%).

*5-Amino-4-dimethylamino-6-methylpyrimidine-2-thione and 5-Amino-4-dimethylamino-6-methyl-2-methylthiopyrimidine.*— 2-Chloro-4-dimethylamino-6-methyl-5-nitropyrimidine [12] (6.3 g) and thiourea (5.8 g) in ethanol (50 ml) were heated under reflux for 3 h. The yellow crystalline adduct which formed on cooling (5.6 g) was removed and taken up in N-sodium hydroxide and the resulting solution acidified with acetic acid. The thiopyrimidine which precipitated was redissolved in N-sodium hydroxide (30 ml), heated to 60° and sodium hydrosulphite (11 g) added slowly. On cooling *5-amino-4-dimethylamino-6-methylpyrimidine-2-thione* (1.0 g), m.p. 250° (decomp.) emerged (Found: C, 45.2; H, 6.7; N, 30.2. $C_7H_{12}N_4S$ requires C, 45.6; H, 6.6; N, 30.4%). On dissolving the thione in N-sodium hydroxide (7 ml) and water (5 ml) and treating the solution with iodomethane (0.5 ml) the required 2-methylthiopyrimidine (0.8 g) was obtained, m.p. 71—72° (lit.,[12] 70°) [from light petroleum (b.p. 80—100°)].

*4-Dimethylamino-5-formamido-6-methyl-2-methylthiopyrimidine* (1c).—The 5-amino-4-dimethylaminopyrimidine (0.65 g) in formic acid (98%, 3 ml) was heated (steam-bath) for 3 h. Trituration of the oil remaining after evaporation with ammonia solution gave a solid from which the *5-formamidopyrimidine* (0.4 g), m.p. 179—181°, was obtained in crystalline form from ethanol (Found: C, 47.8; H, 6.1; N, 24.9. $C_9H_{14}N_4OS$ requires C, 47.8; H, 6.2; N, 24.8%).

*4-Dimethylamino-5-(N-ethylformamido)-6-methyl-2-methylthiopyrimidine* (2c).—The above 5-formamidopyrimidine (0.3 g), iodoethane (0.5 g), and potassium carbonate (0.4 g) in dimethylformamide (4 ml) were stirred for 26 h. After removal of the potassium salts by filtration, the filtrate was diluted with water (20 ml) and taken to dryness. The residue was extracted with hot chloroform and the extracts then evaporated to give the *5-(N-ethylformamido)-derivative* (0.4 g), m.p. 109—110° (from aqueous methanol) (Found: C, 52.0; H, 7.2; N, 21.9. $C_{11}H_{18}N_4OS$ requires C, 52.0; H, 7.1; N, 22.0%).

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