Novel 4-Substituted 4,5-Dihydro-3*H*-(8-amino-6-oxo)pyrrolo[3,4-*f*][1,3,5]triazepines from (*Z*)-*N*^{2}-(2-Amino-1,2-dicyano)formamidine and Carbonyl Compounds

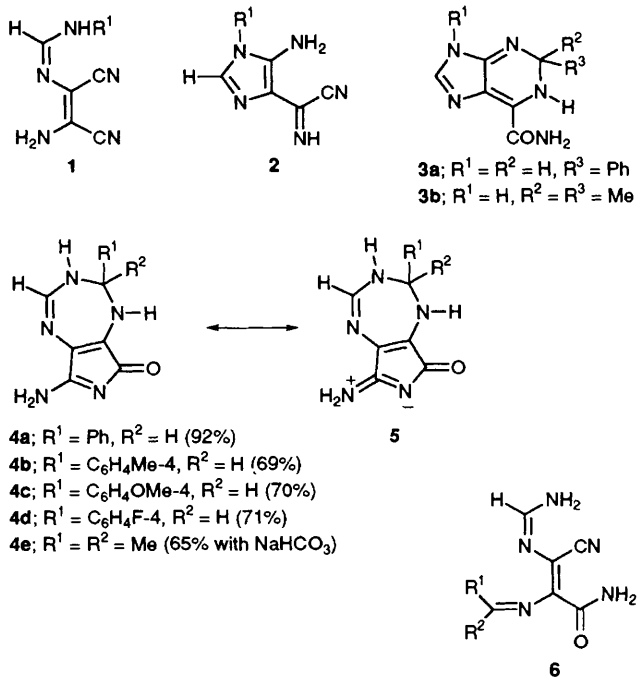
M. José Alves,[b] Brian L. Booth,*[a] Paul Eastwood,[a] Robin Pritchard[a] and M. Fernanda J. R. P. Proença[b]

[a] *Department of Chemistry, University of Manchester Institute of Science and Technology, Manchester, UK M60 1QD*
[b] *Department of Chemistry, University of Minho, Braga, Portugal*

The title formamidine reacts with ArCHO (where Ar = Ph, 4-MeC$_6$H$_4$, 4-MeOC$_6$H$_4$, 4-FC$_6$H$_4$) and acetone in the presence of a base to give products, shown by X-ray crystallography (Ar = Ph), to be the title compounds **4a–e**.

Previous work by our groups[1–4] has shown that (*Z*)-*N*^{2}-(2-amino-1,2-dicyanovinyl)formamidine **1** (R^1 = H) and its derivatives cyclize under the influence of a base to form 5-amino-4-(cyanoformimidoyl)imidazoles of type **2**. These compounds, which can be difficult to isolate in a pure state,[4] react slowly with aldehydes and ketones to afford 6-carbamoyl-1,2-dihydropurines **3**, usually in high yield. As part of this investigation we were interested to establish whether the compounds **3** could be obtained directly from **1** by treatment with a base and a large excess of an aldehyde or ketone, without the need to isolate the compounds **2**.

The reaction between **1** (R^1 = H)[2] and benzaldehyde with a few drops of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) at room temperature gave an immediate exothermic reaction



and the precipitation of an orange solid in high yield;† no reaction occurs in the absence of DBU. Microanalysis and FAB mass spectrometry established a molecular formula of $C_{12}H_{11}N_5O$ as expected for the 1,2-dihydropurine **3a** ($R^1 = R^2 = H$, $R^3 = Ph$). However, when an authentic sample of **3a** was prepared in 72% yield as an orange solid by treatment of **2** ($R^1 = H$) with benzaldehyde in methanol, it was apparent that these two products had different structures. Both compounds show a strong carbonyl stretching vibration in the 1670–1680 cm^{-1} region of the IR spectrum and the ^1H NMR spectra were similar‡ except that the spectrum of **3a** showed four NH bands (integration 1:1:1:1), while that of the unknown showed only three (integration 1:1:2). The major difference appeared in the ^{13}C NMR spectra,‡ where the spectrum of **3a** had a band for C-5 at δ 114.2, which was absent from that of the unknown compound. Instead, the latter spectrum showed a band at δ 170.6 attributable to an *N*–C=N group. A single crystal X-ray structure determination (see Fig. 1)§ established that the unknown compound was the novel 4-phenyl-4,5-dihydro-3*H*-(8-amino-6-oxo)pyrrolo[3,4-*f*][1,3,5]triazepine

† In a typical procedure DBU (0.05 cm^3, 0.33 mmol) was added to a stirred suspension of the amidine (180 mg, 1.3 mmol) in a large excess of benzaldehyde (2.0 cm^3, 2.08 g, 19.6 mmol). An immediate exothermic reaction occurred and the amidine dissolved. After a few minutes a precipitate appeared and this was filtered off, washed with diethyl ether and then with acetone to give the product as a pale-orange solid (280 mg, 1.2 mmol, 92%). Needle crystals suitable for X-ray analysis were obtained by recrystallisation from a 1:1 mixture of methanol–light petroleum (b.r. 30–40 °C).

‡ *NMR data* [$(CD_3)SO$] for δ_H 5.8 (d, 1H, *J* 4.5 Hz), 6.5 (d, 1H, *J* 4.5 Hz, NH), 7.4 (m, 3H, Ph), 7.55 (s, 1H), 7.65 (s, 1H, NH), 7.7 (m, 2H, Ph), 7.9 (s, 1H, NH), 12.2 (s, 1H, NH); δ_C 77.5, 114.2, 132.6, 133.1, 133.4, 144.5, 147.5, 154.8, 160.6, 171.7. For **4a**: δ_H 5.5 (s, 1H), 7.05 (s, 1H, NH), 7.3–7.5 (m, 6H, Ph + 2-H), 8.5 (br s, 2H, NH), 9.7–10.0 (br s, 1H, NH); δ_C 72.5, 121.9, 130.1, 132.4, 133.0, 134.6, 146.2, 153.1, 170.6, 174.2.

§ *Crystal data*: $C_{12}H_{11}N_5O$, triclinic, space group $P\bar{1}$, a = 8.141(5), b = 10.179(5), c = 7.203(3) Å, α = 93.56(3), β = 100.72(3), γ = 102.39(2)°, Z = 2, 736 reflections with $I > 2\sigma(I)$ used in refinement, R = 0.051, R_w = 0.054. Atomic coordinates, bond lengths and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre. See Notice to Authors, Issue No. 1.

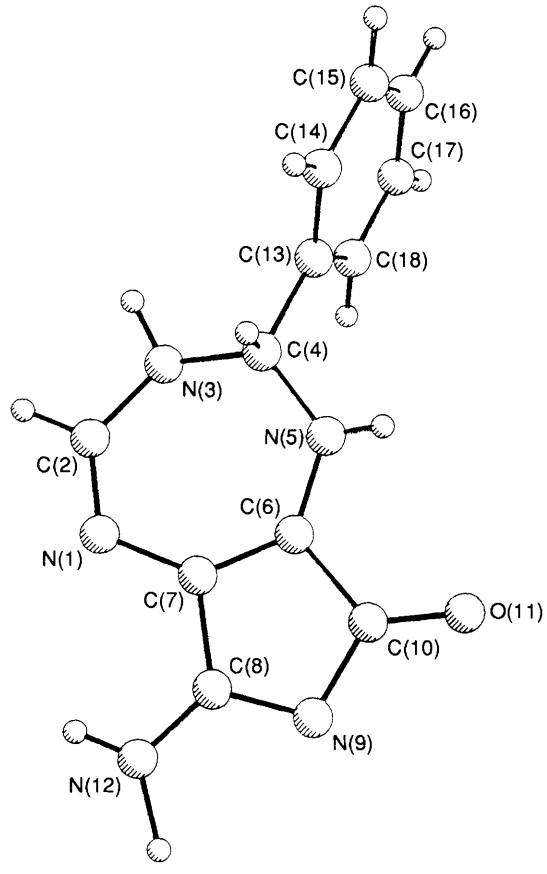


Fig. 1 X-Ray crystal structure of 4-phenyl-4,5-dihydro-3*H*-(8-amino-6-oxo)pyrrolo[3,4-*f*][1,3,5]triazepine

4a. From the crystal structure it is apparent that from N(3) through C(2) to N(5) the ring is almost planar as expected, but puckered at C(4). The C(2)–N(1) bond is short (1.287 Å), as is the C(7)–C(6) bond (1.359 Å), indicative of double bond character. The N(3)–C(2), N(1)–C(7) and C(6)–N(5) bonds are longer (1.355, 1.385 and 1.339 Å, respectively), but there is obviously electron delocalisation around these six atoms. The lone pair electrons on the N(12) (the exocyclic amino group) are also delocalised into the pyrrole ring to the extent that the N(12)–C(8) bond has double bond character (1.301 Å) and the structure is more accurately described by the canonical form **5**. In the solid state the compound exists as a dimer with strong hydrogen bonds between a hydrogen on N(12) and N(9′) of a second molecule and *vice versa* (see Fig. 2). This weakens and lengthens the N(12)–H bond considerably [1.198 Å; *cf.* 0.81 Å for the other N(12)–H bond] to the extent that this H atom appears to be oscillating between N(12) and N(9′).

Under similar conditions reaction between **1** and *p*-tolualdehyde, 4-methoxybenzaldehyde and 4-fluorobenzaldehyde gave **4b–d** in the yields shown, indicating that the reaction is of general applicability for aromatic aldehydes.

Triazepine formation appears to depend critically upon the rate of cyclization of **1** to **2**. Formamidine **1** (R^1 = H), which forms the 1,3,5-triazepines in good yields, cyclizes only slowly to the imidazole **2** (R^1 = H) in the presence of DBU and the imidazole has to be prepared using the stronger base $Ba(OH)_2$.[2] In contrast, formidines where R^1 = Ar, which cyclise rapidly to **2** in the presence of DBU, do not give 1,3,5-triazepines under the conditions described above, but instead afford 1,2-dihydropurines and other products arising from intermediate **2**. Reaction between **1** (R^1 = H) and aliphatic ketones is so slow that cyclization to **2** followed by formation of the 1,2-dihydropurine **3** starts to compete under

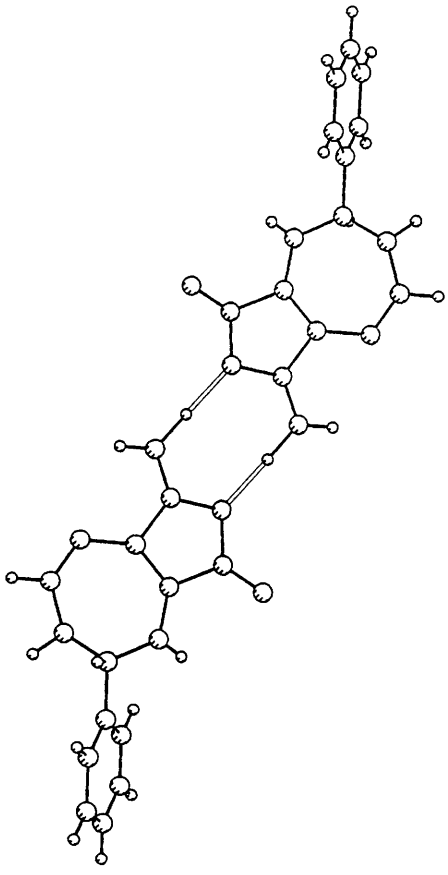


Fig. 2 Illustration of dimeric structure and H-bonding interactions

certain conditions with 1,3,5-triazepine formation. So, for example, reaction between **1** (R^1 = H) and acetone in the presence of a saturated solution of $NaHCO_3$ in aqueous methanol takes 8 days at room temperature to give the triazepine **4e** together with a trace of the dihydropurine **3b**. In acetone with DBU reaction takes 19 h to give **4e** in 76% yield. Compound **3b** has been prepared from **2** (R^1 = H) and acetone in 87% yield as reported previously.[2]

The oxygen atom in **4** can only arise from the aldehyde and we believe that initial reaction occurs by a base-catalysed addition of the 2-amino group of **1** to the aldehyde to form an aminomethanol, followed by intramolecular hydrolysis of the 2-cyano group giving an intermediate **6**, which cyclizes by attack of the 5-amino group at the carbon atom of the imine group.

As a class of compounds the 1,3,5-triazepines have been little explored.[5] Fully unsaturated monocyclic 1,3,5-triazepines have been prepared by the photolytic ring expansion of 2-azidopyrazines and 4-azidopyrimidines as first described in 1990.[6] There have also been a few accounts of bicyclic and tricyclic 1,3,5-triazepines,[7] but to our knowledge these are the first examples of 4,5-dihydro-3*H*-pyrrolo[3,4-*f*][1,3,5]triazepines.

Thanks are due to the SERC for a studentship to one of us (P. E.).

Received, 9th February 1993; Com. 3/00793F

References

1 B. L. Booth and M. F. Proença, *J. Chem. Soc., Chem. Commun.*, 1981, 788.
2 M. J. Alves, B. L. Booth and M. F. J. R. P. Proença, *J. Chem. Soc., Perkin Trans. 1*, 1990, 1705.
3 M. J. Alves, B. L. Booth, A. P. Freitas and M. F. J. R. P. Proença, *J. Chem. Soc., Perkin Trans. 1*, 1992, 913.
4 B. L. Booth, A. M. Dias and M. F. J. R. P. Proença, *J. Chem. Soc., Perkin Trans. 1*, 1992, 2119.
5 N. P. Peet, *Azepines*, ed. A. Rosowsky, *The Chemistry of Heterocyclic compounds*, Wiley, New York, 1984, vol. 43, part 2, p. 734.
6 H. Sawanishi and T. Tsuchiya, *J. Chem. Soc., Chem. Commun.*, 1990, 723.
7 P. R. Birkett, C. B. Chapleo and G. Mackenzie, *Synthesis*, 1991, 823; B. Agai, Gy. Hornyak, K. Lempert and Gy. Simig, *Periodica Polytechnica Chem. Eng.*, 1982, **26**, 211; *Tetrahedron*, 1976, **32**, 839; R. R. Wittekind, T. Capiris, J. Fahey and J. Shavel, *J. Org. Chem.*, 1973, **38**, 1641.