A RE-EXAMINATION OF THE HYDROLYSIS OF THE ANTIMALARIAL DRUG PYRIMETHAMINE

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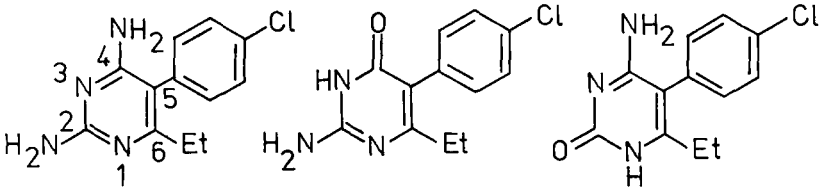
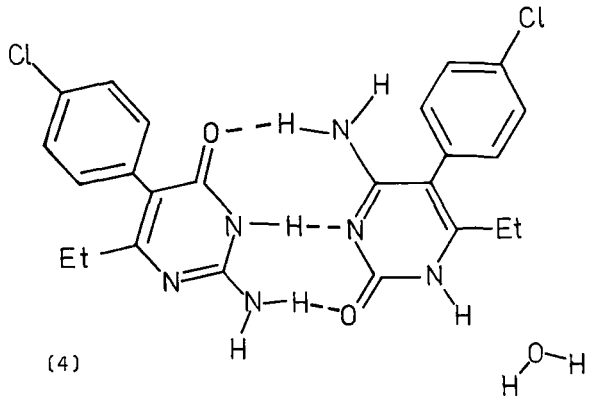
Pyrimethamine (1) is a potent inhibitor of protozoal dihydrofolate reductase and its affinity for the target enzyme is largely dictated by the diaminopyrimidine moeity. Hydrolysis of (1) in 6N-hydrochloric acid has been reported to yield the biologically inactive 2-aminopyrimidin-4(3H)-one (2) in 95% yield (Trattner *et al* 1964).

When this hydrolysis was repeated under the same conditions a different result was obtained: the acid hydrolysate initially deposited colourless flakes of the hydrochloride salt of the 2-aminopyrimidinone (2) (m.p. 290-305° decomp.) followed by colourless prisms of the hydrochloride salt of the isomeric 4-amino-pyrimidin-2(1H)-one (3) (m.p. > 310°). Analysis of the mixture by 220 MHz ^{1}H n.m.r. spectroscopy confirmed the presence of (2) and (3) in the ratio 1:3.



(1) (2) (3)

Crystallisation of a mixture of the free bases of (2) and (3) from 95% ethanol furnished colourless prisms which were shown by X-ray crystallographic analysis to be a hydrated equimolar complex (4) with the respective amino- and oxo-groups linked by three hydrogen bonds in the manner of a Watson-Crick cytosine: guanine base pair.



(4)

Protonation of pyrimethamine involves the N(1) position (Phillips & Bryan 1969) and it is logical to expect that the adjacent amino group at C(2) would be the substituent most labile to acid hydrolysis, as observed in the present work. Moreover, the chlorophenyl- and pyrimidinyl-groups of pyrimethamine are considerably twisted from coplanarily (angle $\tau = 67^{\circ}$) and the hydrophobic chloro-phenyl group would be expected to repel approach of the hydronium ion at C(4).

Trattner, R.B. *et al* (1964) *J. Org. Chem.* 29: 2674-2677
Phillips, T., Bryan, R.F. (1969) *Acta Cryst.* A25: S200

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