Electrophilic Substitution at C-5 in 1-Methyl-5,6-dihydrocytosine

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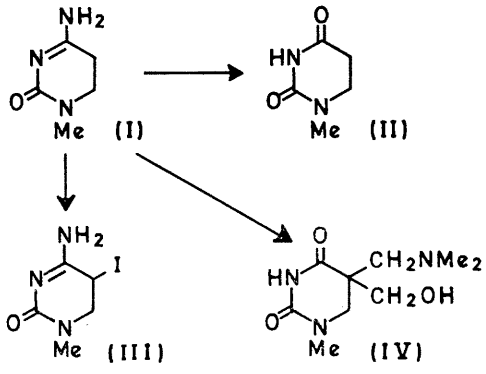
Summary 1-Methyl-5,6-dihydrocytosine is rapidly deuteriated at C-5 at neutral pD's, treatment with iodine affords the 5-iodo-compound, and aminomethylation gives an unusual 5,5-disubstituted product (IV).

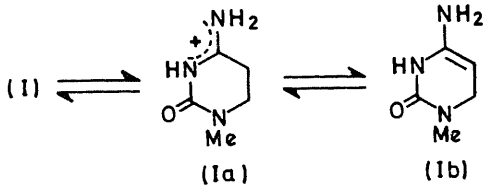
DURING the hydrolysis of 1-methyl-5,6-dihydrocytosine (I) in D_2O the resulting 1-methyl-5,6-dihydrouracil was fully deuteriated at C-5.[1] The product (II) did not exchange under these conditions, so that exchange had occurred prior to hydrolysis.

We have studied the exchange of the C-5 protons of (I) in D_2O (0·2M-phosphate, 38°) at the pD values indicated. The approximate half-lives are < 15 s (6·8), 0·25 h (7·2), and 2·5 h (8·0): n.m.r. τ 7·56 (t, 5-H), 7·06 (s, N-CH_3), and 6·58 (t, 6-H). As exchange proceeds the C-5 triplet disappears and the C-6 protons collapse to a broad singlet. At higher pD values the rate of hydrolysis becomes comparable with the rate of exchange. As the pD is lowered there is a sharp



increase in the exchange rate. The pK_a of (I) is 6·6,[1] and we suggest that the species (Ia) undergoes proton exchange

through reversible formation of the enamine-type intermediate (Ib).



Compound (I) reacts rapidly with one equivalent of iodine (pH 6·2, 38°) in aqueous ethanol with the formation of a yellow, insoluble, compound which decomposes above 100°. The n.m.r. spectrum is consistent with 1-methyl-5-iodo-5,6-dihydrocytosine (III), τ ($CD_3{\cdot}CO_2D$), 6·93 (s, CH_3), 6·68 (q, J *ca.* 2Hz, 15Hz, 1H), 6·16 (q, J 3·5Hz, 15Hz, 1*H*), 5·06 (t, J *ca.* 2Hz, 3·5Hz, 1H). The low coupling constant of 2Hz suggests that the iodine is axial.[2,3] No exchange of the C-5 proton was observed in $CD_3{\cdot}CO_2D$ at room temperature. Compound (III) rapidly decomposes on exposure to light.

Reaction of (I) with excess CH_2O–Me_2NH at pH 8 (38°) for 5 min followed by hydrolysis (pH 2) at 60° for 30 min gave a basic oil (IV) (crystalline hydrochloride, m.p. 220° and *O*-acetate hydrochloride m.p. 185—187°). The n.m.r. spectrum of the free amine (D_2O) shows the C-6 protons at τ 6·28 and 6·40 coupled only to each other (J 11 Hz), the CH_2–N protons appear as non-equivalent at τ 7·10 and 7·40 (J 14 Hz), due to hindered rotation about the Me_2NC–C(5) bond; 6·49 (s, OCH_2), 6·97 (s, N–CH_3), 7·74 [s, $N(CH_3)_2$], *m/e* 215.

It has been suggested that the enzymatic catalysis of alkylation of the pyrimidine nucleus at C-5 may involve reversible addition of a nucleophile at C-6 followed by electrophilic attack at C-5.[4] The very rapid exchange reaction of (I) compared with that of (II) ($t_{\frac{1}{2}}$ 10 h at 70° and pD 7) suggests that the former may be useful in model enzymatic studies.

All compounds described had satisfactory elemental analyses.

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