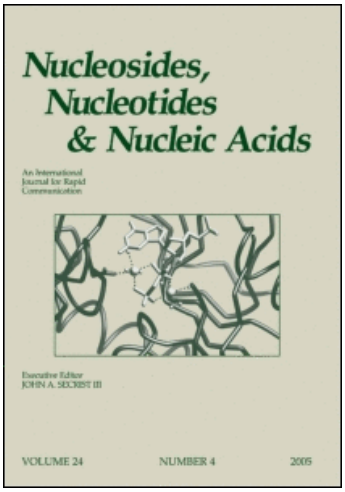

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Base Analogues Related to N^4-Hydroxicytosine

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BASE ANALOGUES RELATED TO N^4-HYDROXYCYTOSINE

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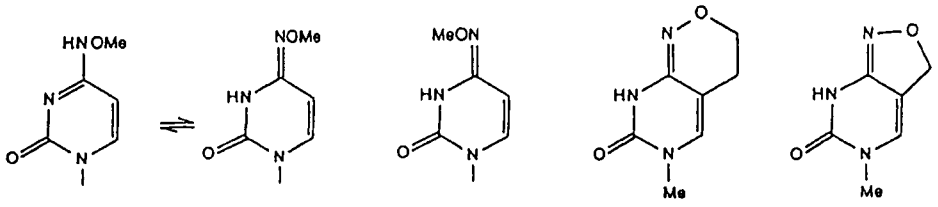
Abstract. Syntheses directed to the bicyclic derivatives (3) and (4) related to N^4-hydroxycytosine are discussed.

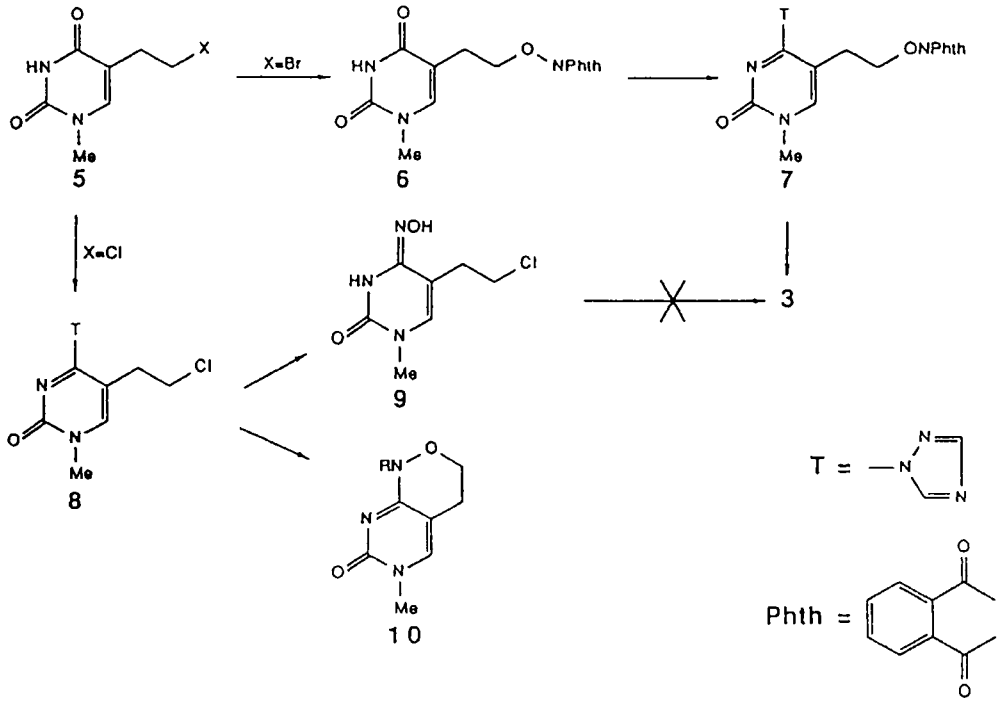
In earlier work an oligodeoxyribonucleotide was synthesised containing an N^4-methoxycytosine residue (1) and its base-pairing potential with A and G compared by T_m and T_d measurements. It was clear that duplexes containing these base-pairs were of comparable stability.[1] Our expectation that this would be so derived from the fact that the tautomeric constants (K_T) of N^1-alkyl derivatives of (1) and of N^4-hydroxycytosine were much closer to unity (~10) than the normal bases (~10^4).[2] Hence we felt that they would form Watson-Crick pairs with A and



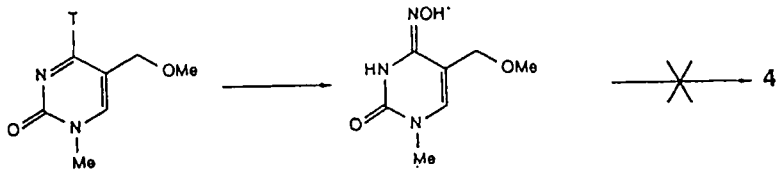
1a 1b 2 3 4

G, the requisite tautomeric form mimicking T or C in each case. However in later experiments it was found that two or more N^4-methoxycytosine residues in an oligomer led to lowered T_D values.[3] This is probably in part due to the fact that the more uracil-like tautomer (1b) is predominant but since it was also held[4] that the syn conformer (2) is favoured over the anti (1b) progressive destabilisation could result; only the latter (anti) conformer can base-pair. The synthesis of the ring systems (3) and (4) was therefore initiated so that their tautomeric and hydrogen-bonding properties could be investigated; only the synthetic experiments are described here.

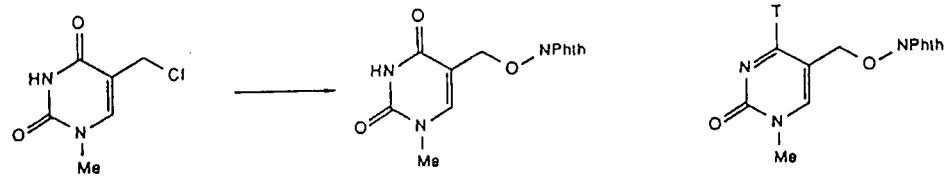
The readily available 5-(2-hydroxyethyl)uracil[5] gave access to the bromo- and chloro-ethyluracils (5). 5(X = Br) gave the phthaloyl-protected oxyamine (6) and thence the 4-triazolo derivative (7) using the mild conditions described by Webb and Matteuci.[6] The phthaloyl group is removed from its N-alkoxy derivatives very readily and conveniently by ammonia[7] and in this instance (7) with ammonia in dry dioxan at 80° gave directly the ring closed product (3) quantitatively.



In looking at an alternative route, 5(R = Cl) was converted to the triazolo derivative (8), and then to the N^4-hydroxycytosine (9). The latter, however, could not be induced to undergo base-catalysed cyclisation. It is likely that this was due to the preferred dissociation of the N^3-proton inhibiting formation of the oxy-anion. Consistent with this was the observation that (8) with N-alkylhydroxylamines in pyridine rapidly gave the ring closed products (10; R = Me, $PhCH_2$).



11 12



13 14 15

5-Hydroxymethyluracil was considered to be a convenient starting material for the synthesis of the bicyclic system in (4), particularly as the C-5 methylene group shows very marked allylic reactivity.[8] Conversion to 1-methyl 5-methoxymethyluracil by conventional methods[9] and triazolylation gave (11), from which the N^4-hydroxycytosine derivative (12) was obtained, each step in high yield. However, treatment with dry HCl in dioxan gave only its hydrochloride, no conversion to the 5-chloromethyl derivative occurring. Clearly protonation of the basic ring system obliterates any allylic reactivity. By contrast the 5-methoxymethyluracil readily gave rise to the chloromethyl derivative (13) and this was converted to the protected oxyamine (14). The low solubility of (14) has precluded its conversion to the 4-triazolo derivative and further routes to (15) are being investigated.

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