Conversion of 2'-Deoxyuridine into Thymidine and Related Studies

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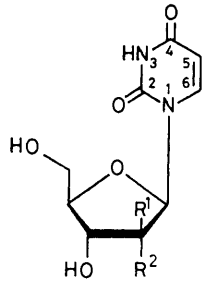
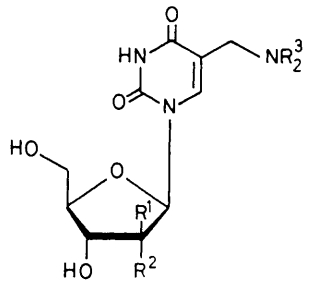
Unprotected 2'-deoxyuridine is converted into thymidine in three steps by a procedure which is equally effective for the 5-methylation of uridine and even more effective for the conversion of 1-β-D-arabinofuranosyluracil into its 5-methyl derivative.

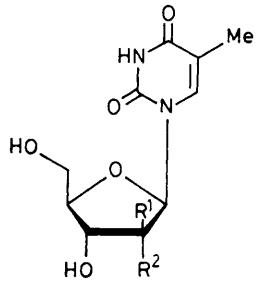
The biosynthesis of thymidine 5'-phosphate involves[1] the thymidylate synthetase promoted methylation of 2'-deoxyuridine 5'-phosphate. Although the detailed mechanism of this process has not yet been elucidated, it is believed to proceed *via* the reduction (possibly involving an internal redox reaction)[2] of a Mannich base derived from a 6-substituted 5,6-dihydrouridine 5'-phosphate and 5,10-methylene-5,6,7,8-tetrahydrofolate.[1] We now report a simple three-step conver-



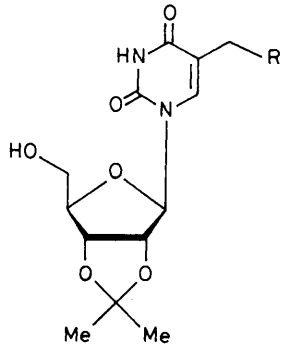
(1)



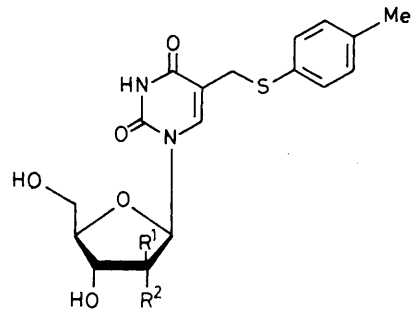
(2)



(3)



(4)

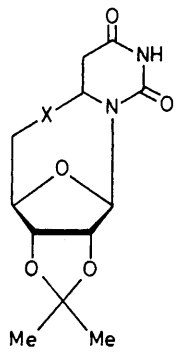


(5)

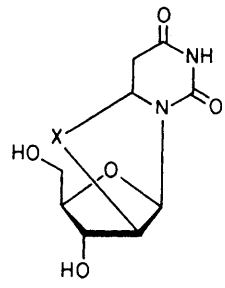
a; $R^1 = R^2 = H$;
b; $R^1 = H$, $R^2 = OH$;
c; $R^1 = OH$, $R^2 = H$.

sion of 2′-deoxyuridine (**1a**) into thymidine (**3a**) by a procedure also involving an intermediate Mannich base (**2a**; $R_2^3 = -[CH_2]_4-$).

A number of years ago, it was reported[3] that uridine (**1b**) was converted into its 5-diethylaminomethyl derivative (**2b**; R^3 = Et) by heating it with an excess both of diethylamine and formaldehyde in aqueous solution at 100 °C. 2′,3′-*O*-Isopropylideneuridine has similarly been converted into corresponding Mannich bases (**4**; R = NMe_2 and pyrrolidin-1-yl)[4,5] under milder reaction conditions. The Mannich base (**2b**; R^3 = Et) was further converted[3] into 5-methyluridine (**3b**) by hydrogenolysis in the presence of platinum oxide and the methiodide of (**4**; R = NMe_2) was converted[4] into 2′,3′-*O*-isopropylidene-5-methyluridine (**4**; R = H) by reduction with sodium borohydride.† However, we recently reported[5] that



(6)



(7)

a; X = O
b; X = S

(**4**; R = pyrrolidin-1-yl) could be converted into (**4**; R = H) by what we believe to be a more convenient procedure involving an intermediate 5-(*p*-tolylthiomethyl) derivative.

In the present study, we found that when 2′-deoxyuridine (**1a**) was heated, under gentle reflux, for 16 h with a tenfold excess each of formaldehyde and pyrrolidine in aqueous solution, it was completely consumed and the corresponding Mannich base (**2a**; $R_2^3 = -[CH_2]_4-$) was obtained. The latter compound was not isolated but the crude products were heated, under reflux, with a twofold excess of toluene-*p*-thiol in ethanol for 16 h to give the 5-(*p*-tolylthiomethyl) derivative (**5a**)‡ as a crystalline solid, m.p. 160—161 °C, in 30% isolated overall yield. The latter compound was converted into thymidine (**3a**), m.p. 185—186 °C; 66% isolated yield, by heating it with Raney nickel in ethanol, under reflux, for 4 h.

Uridine (**1b**) was converted into its 5-(*p*-tolylthiomethyl) derivative (**5b**), m.p. 176 °C; isolated crystalline yield 33%, by the same two-step procedure under virtually identical contions. Raney nickel reduction of the intermediate (**5b**) gave 5-methyluridine (**3b**) as a crystalline solid, m.p. 175 °C, in 65% isolated yield. Both steps of the conversion of 1-β-D-arabinofuranosyluracil (araU), (**1c**) into its 5-(*p*-tolylthiomethyl) derivative (**5c**) proceeded much more readily. When (**1c**) was heated, under gentle reflux, with a fivefold excess each of formaldehyde and pyrrolidine, it was completely consumed after only 15 min. The crude Mannich base was then heated, under reflux, with a twofold excess of toluene-*p*-thiol in ethanol for 15 min to give (**5c**) as a crystalline solid, m.p. 195 °C, in 65% isolated overall yield. The latter compound was converted into 1-β-D-arabinofuranosylthymine (**3c**), m.p. 242 °C; 66% isolated yield, by treating it with Raney nickel under the conditions described above. Preliminary experiments suggest that 1-β-D-xylofuranosyluracil reacts with formaldehyde and pyrrolidine at least as slowly as does uridine, and that the conversion of the intermediate Mannich base into the corresponding 5-(*p*-tolylthiomethyl) derivative again occurs relatively slowly.

The facility with which 2′,3′-*O*-isopropylideneuridine and 1-β-D-arabinofuranosyluracil (**1a**) undergo both steps of their conversions into the corresponding 5-(*p*-tolylthiomethyl) derivatives (**4**; R = 4-MeC_6H_4S) and (**5c**), respectively, correlates well with the rates at which the two compounds undergo[6] base catalysed exchange of H-5. The exchange reactions, the formation of the Mannich bases, and their conversion into 5-(*p*-tolylthiomethyl) derivatives all seem likely to involve tetra- and tri-cyclic intermediates [such as (**6a**) and

† In our hands (ref. 5) treatment of the methiodide of (**4**; R = pyrrolidin-1-yl) appeared to lead to over-reduction.

‡ Satisfactory spectroscopic and microanalytical data have been obtained for all crystalline compounds described.

(**7a**), respectively]. As expected from the H-5 exchange data,[6] 1-β-D-arabinofuranosyluracil (**1c**) appears to be the best of the present substrates; when it is heated, under reflux, with a fivefold excess each of pyrrolidine and formaldehyde in aqueous solution, the half-times of its conversion into the corresponding Mannich base (**2c**; $R_2^3 = -[CH_2]_4-$) are *ca.* 3 and 20 min at pH 10.3 and 7.0, respectively.

5′-Deoxy-5′-mercapto-2′,3′-*O*-isopropylideneuridine and 1-β-D-(2-deoxy-2-mercaptoarabinofuranosyl)uracil have been shown[7,8] to exist in their tetra- and tri-cyclic tautomeric forms, (**6b**) and (**7b**) respectively, except in alkaline solution. Evidence supporting the relationship[4] between the electron-withdrawing character of the 6-substituent in a 5,6-dihydrouridine system and the ease of Mannich base formation was provided by our lack of success in converting either (**6b**) or (**7b**) into the corresponding Mannich base. This result is of particular interest in that it has been suggested[9] that *in vivo* thymidylate synthetase promoted methylation of 2′-deoxyuridine 5′-phosphate involves an intermediate 6-alkylthio substituted 5,6-dihydrouracil derivative.

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References

1 S. J. Benkovic, *Acc. Chem. Res.*, 1978, **11**, 314.
2 P. A. Charlton and D. W. Young, *J. Chem. Soc., Perkin Trans.* 1, 1982, 1363.
3 E. I. Budowsky, V. N. Shibaev, and G. I. Eliseeva in 'Synthetic Procedures in Nucleic Acid Chemistry,' eds. W. W. Zorbach and R. S. Tipson, Interscience, New York, 1968, pp. 436—438.
4 S. A. Salisbury and D. M. Brown, *J. Chem. Soc., Chem. Commun.*, 1979, 656.
5 S. S. Jones, C. B. Reese, and A. Ubasawa, *Synthesis*, 1982, 259.
6 D. V. Santi and C. F. Brewer, *Biochemistry*, 1973, **12**, 2416.
7 R. W. Chambers and V. Kurkov, *J. Am. Chem. Soc.*, 1963, **85**, 2160.
8 M. Imazawa, T. Ueda, and T. Ukita, *Chem. Pharm. Bull.*, 1975, **23**, 604.
9 P. V. Danenburg, R. J. Langenback, and C. Heidelberger, *Biochemistry*, 1974, **13**, 926.