A method for the rapid preparation of 5-vinyluracil in high yield

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ABSTRACT

A method for the rapid preparation of the thymine analogue, 5-vinyluracil, in 83% yield from 5-(1-hydroxyethyl)uracil via the methanesulphonyl ester is reported.

INTRODUCTION

5-Vinyluracil (I) has been prepared by several methods.¹⁻³ The compound may be of use as a thymine analogue which may confer radiation sensitivity to nucleic acids which contain it^{2,4} and when polymerised, 5-vinyluracil could also be useful as a chromatographic medium which is selective for polynucleotides containing poly A sequences.¹ It has already been shown that a thymine-requiring mutant of Escherichia coli will incorporate 5-vinyluracil into its DNA when grown on a thymine-deficient medium.⁴

However both of the methods of preparation of 5-vinyluracil initially described^{1,2} gave very low yields (<20%) and the most recent preparation has the sole advantage that the starting materials are very cheap and hence the preparation can be done on a large scale but the overall yield is lower (<10%) and involves the fractionation of materials at one stage on a spinning band column.³

The low yield in our previous preparation² was due to the acidic conditions needed to eliminate water from 5-(1-hydroxyethyl)uracil (II) which also encouraged dimerisation of the product to take place. We thus decided to investigate the production of 5-vinyluracil by means of an ester elimination under basic conditions as we knew that 5-vinyluracil was stable in alkali.² Attempts at the preparation of 5-vinyluracil by this method had previously been reported¹ using 5-(2-hydroxyethyl)uracil (III) as the starting material. However the methanesulphonyl ester of III under basic conditions either cyclised to give 2H,3H,5(7)H-furano [2,3d]pyrimidin-6-one (IV) in the presence of collidine or potassium t-butoxide or gave 5-(2-pyridiniummethyl)uracil methanesulphonate (V) when heated in pyridine solution.

IV

- I R = CH₂=CH-
 II R = CH₂-CHOH-
 III R = CH₂OH-CH₂-

DISCUSSION

It is sterically improbable that starting with 5-(1-hydroxyethyl)uracil a bicyclic product similar to IV could be produced, but all attempts to form the methanesulphonyl ester (VI) of 5-(1-hydroxyethyl)uracil in pyridine solution failed and the product of the reaction was tentatively identified by NMR as 5-(1-pyridiniummethyl)uracil methanesulphonate (VII), arising not from the desired elimination reaction but by a nucleophilic substitution reaction. The replacement of pyridine by 2,6-lutidine resulted in the identification by tlc of some 5-vinyluracil in the solution but this could not be isolated.

However when 5-(1-hydroxyethyl)uracil was dissolved in dry dimethylformamide and the methanesulphonyl ester produced by adding one mole of *N*-methylmorpholine and one mole of methanesulphonyl chloride and allowing the solution to stand at 4° overnight, further addition of a mole of *N*-methylmorpholine resulted in the production of 5-vinyluracil when the solution was heated under reflux. To isolate the product the conditions had to be kept alkaline otherwise the 5-vinyluracil dimer previously reported² was produced. All attempts to isolate the presumed intermediate VI in the reaction were unsuccessful. Either the conditions used were too mild and little reaction occurred or too drastic and much 5-vinyluracil was present. Attempts to

separate the mixtures so produced failed, as the ester appeared to decompose to 5-vinyluracil during the fractionation procedures.

Thus 5-vinyluracil can now be prepared from readily available starting materials (diketene and urethane) which give 5-acetyluracil (VIII) in 50% yield which can be quantitatively converted into 5-(1-hydroxyethyluracil) from which 5-vinyluracil can be produced in > 80% yield. As previously reported, this method allows the compounds to be radioactively labelled using either tritiated water or tritiated sodium borohydride as the source of tritium.

EXPERIMENTAL

5-Acetyluracil was prepared by the method of Shaw and coworkers,^{5,6} 5-(1-hydroxyethyl)uracil was prepared as previously described.² 5-(1-Hydroxyethyl)uracil (0.52g, 3.3 mmoles) was dissolved in dry dimethylformamide (10ml), *N*-methylmorpholine (0.36ml, 3.6 mmoles) and methansulphonyl chloride (0.26ml, 3.3 mmoles) added and the solution allowed to stand at 4° for 22 hours. A further 3.3 mmoles of *N*-methylmorpholine was then added, the solution was heated at 100° for 30 minutes, cooled, NaOH solution (0.1N, 25ml) added and the solution evaporated to a small volume. A further 10ml of NaOH (0.1N) was added and the solution evaporated to dryness to yield a yellow solid which was added to water (20ml) and the resulting white solid was filtered off, washed with a little cold water and dried (Yield 385mg, 83%, Found: C, 52.2; H, 4.65; N, 20.3. Calc. for C₆H₆N₂O₂: C, 52.2; H, 4.39; N, 20.3%). The NMR and UV spectral data were identical to those previously reported.²

If, after heating the solution at 100° for 30 minutes, the solution was not made alkaline but was cooled and evaporated to dryness, added to water and the product isolated (350mg, 76% yield), NMR showed it to consist of the 5-vinyluracil dimer previously reported² contaminated with a trace of *N*-methylmorpholinium methanesulphonate.

REFERENCES

- 1 Fissekis, J. D. and Sweet, F. (1973) *J. Org. Chem.*, **38**, 264-269
- 2 Evans, C. H., Jones, A. S. and Walker, R. T. (1973) *Tetrahedron* **29**, 1611-1614
- 3 Fissekis, J. D. and Sweet, F. (1973) *J. Org. Chem.* **38**, 1963-1970
- 4 Chelton, E. T. J., Evans, C. H., Jones, A. S. and Walker, R. T. (1973) *Biochim. Biophys. Acta* **312**, 38-44
- 5 Ralph, R. K., Shaw, G. and Naylor, R. N. (1959) *J. Chem. Soc.* 1169-1178
- 6 Dewar, J. H. and Shaw, G. (1961) *J. Chem. Soc.* 3254-3260