

Synthesis of Fluorinated Carbocyclic Nucleosides: Preparation of Carbocyclic 1-(2'-Deoxy-6'-fluororibofuranosyl)-5-iodouracils

Keith Biggadike,^a Alan D. Borthwick,^a Anne M. Exall,^a Barrie E. Kirk,^a Stanley M. Roberts,^{a†} Peter Youds,^a Alexandra M. Z. Slawin^b, and David J. Williams^b

^a Department of Microbiological Chemistry, Glaxo Group Research, Greenford, Middlesex UB6 0HE, U.K.

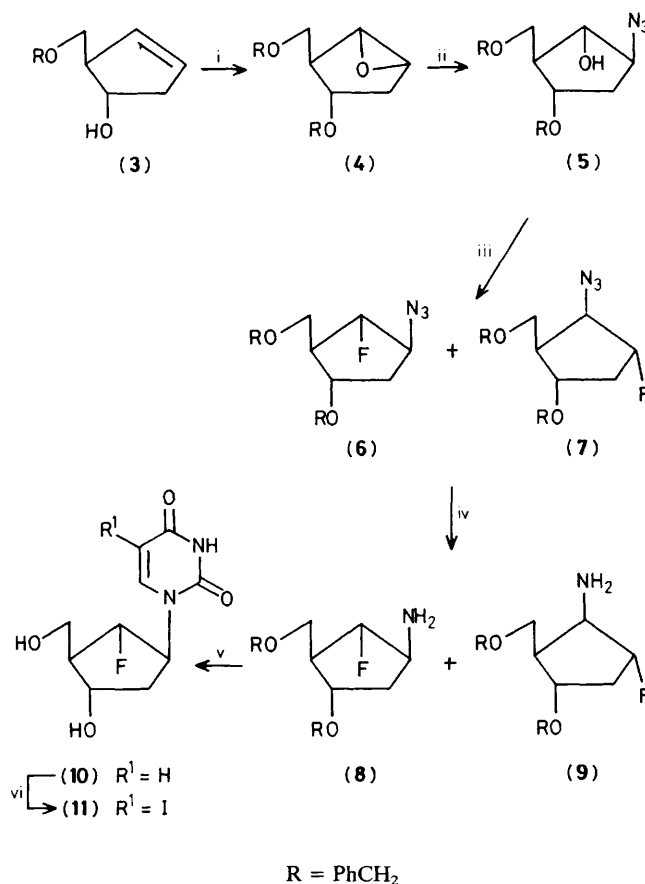
^b Department of Chemistry, Imperial College of Science and Technology, South Kensington, London SW7 2AY, U.K.

The epoxide (**4**) was opened regioselectively using azide ion and fluoride ion to give the alcohols (**5**) and (**13**) respectively as the major products; azido alcohol (**5**) was converted into the anti-viral carbocyclic 2'-deoxy-6'-fluorouridines (**11**) and (**16**) [crystal data were obtained on compound (**15**)].

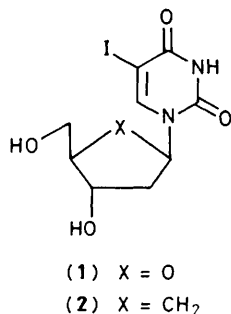
There has been considerable interest in modified nucleosides such as 5-iodo-2'-deoxyuridine (IDU) (**1**) and the corresponding carbocyclic compounds, for example carbocyclic-IDU (**2**).¹ Compounds from both series exhibit interesting and useful anti-viral properties.^{1,2} The replacement of the heterocyclic oxygen atom of the sugar by a methylene group is a drastic change in terms of the stereoelectronic effect on the rest of the molecule. A more subtle change involves replacement of the oxygen atom by a fluoromethylene group; the isosteric relationship of an oxygen atom and a fluoromethylene group has been noted previously.³ We describe herein the preparation and anti-herpes activity of two carbocyclic 2'-deoxy-6'-fluorouridines.⁴

Conversion of cyclopentadiene into the optically active alcohol (**3**) (enantiomeric excess, e.e., >98%) was accomplished in 38% yield using an asymmetric hydroboration procedure.⁵ Oxidation of the cyclopentene derivative (**3**) under Sharpless' conditions followed by protection of the hydroxy group gave the oxirane (**4**) (Scheme 1). Reaction of (**4**) with azide ion gave the required azido alcohol (**5**) in 85% yield. Treatment of the alcohol (**5**) with diethylaminosulphur trifluoride (DAST) gave a mixture of the fluoro-compounds (**6**) and (**7**) in the ratio 2:3. Participation of a neighbouring azido group in a reaction employing DAST (resulting in replacement of the hydroxy group by a fluorine atom with retention of configuration and partial or total migration of the azido-group) has been reported previously.⁶ Reduction of the mixture of (**6**) and (**7**) gave the amines (**8**) and (**9**) which were separated by chromatography. The amine (**8**) was readily converted into the uracil derivative (**10**) in three steps (overall yield 60%). Carbocyclic 1-(2'-deoxy-6'- α -fluororibofuranosyl)-5-iodouracil (**11**), [α]_D²² 37° (c 0.5, Me₂SO), was obtained from (**10**) in 51% yield.

Not surprisingly, opening of the epoxide in compound (**4**) by potassium hydrogen difluoride was highly regioselective in the wrong sense (in terms of providing a route to the second



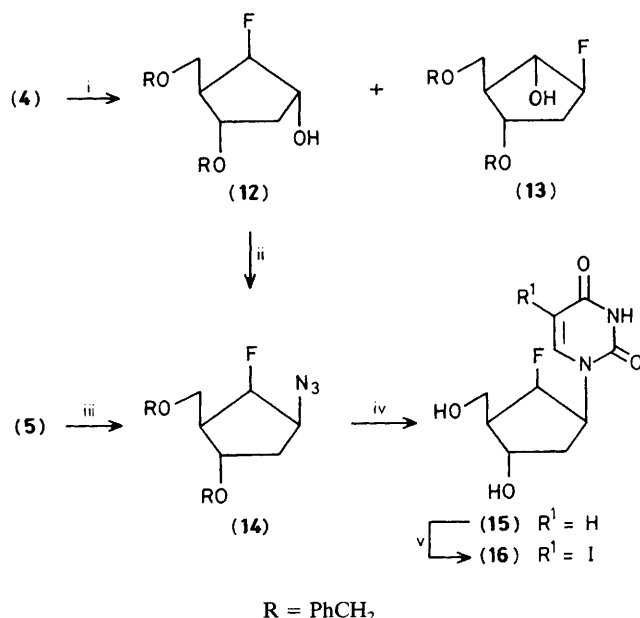
Scheme 1. Reagents: i, Bu^tOOH, vanadyl acetylacetonate, then NaH, PhCH₂Br, Bu₄N⁺I⁻(cat.); ii, NaN₃, NH₄Cl, aq. EtOH, heat; iii, DAST, CH₂Cl₂; iv, H₂, Lindlar cat.; v, EtOCH=CHCONCO, C₆H₆, 5°C, then 0.5 M-H₂SO₄, aq. dioxane, heat, then H₂, Pd/C, aq. EtOH, H⁺ (cat.); vi, I₂, HNO₃, CHCl₃, heat.



objective) affording the required alcohol (**12**) (7%) and the isomeric fluorohydrin (**13**) (61%) (Scheme 2). The alcohol (**12**) was transformed into the azide (**14**) in two steps.† A far better route to the azide (**14**) involved activation of the hydroxy group in compound (**5**) by formation of the trifluoromethanesulphonate derivative and displacement of the latter moiety by fluoride ion.⁷ The azide (**14**) was converted into the uracil derivative (**15**) (52%) and the configuration of the fluorine atom in this compound was confirmed by X-ray

† Present address: Department of Chemistry, University of Exeter, Exeter EX4 4QD, U.K.

‡ A small quantity of 3-fluoro-4-benzyloxymethylcyclopent-1-ene was obtained as a side-product in this conversion.



Scheme 2. Reagents: i, KHF₂, MeO[CH₂]₂OH, heat; ii, *p*-MeC₆H₄-SO₂Cl, 4-*N,N*-dimethylaminopyridine (DMAP), NEt₃, CH₂Cl₂ then NaN₃, dimethylformamide (DMF), heat; iii, CF₃SO₂Cl, DMAP, NEt₃, CH₂Cl₂ then BuN₄F, tetrahydrofuran (THF); iv, H₂, Lindlar cat., then EtOCH=CHCONCO, C₆H₆, 5°C then 0.5 M-H₂SO₄, aq. dioxane, heat, then H₂, Pd/C, aq. EtOH, H⁺ (cat.); v, I₂, HNO₃, CHCl₃, heat.

crystallography (Figure 1).§ The required carbocyclic 1-(2'-deoxy-6'-β-fluororibofuranosyl)-5-iodouracil (16) (49%) was produced from (15) in the usual manner.

Interestingly, the 6'-α-fluoro-compound (11) was highly active against herpes simplex virus type 1 (HSV-1) infected cells in the microtitre assay (*ca.* one half the activity of acyclovir) while the 6'-β-fluoro-compound (16) was at least two orders of magnitude less active.

§ *Crystal data:* 1-(*c*-2-fluoro-*t*-4-hydroxy-*c*-3-hydroxymethyl-*r*-1-cyclopentyl)uracil (15), C₁₀H₁₃FO₄N₂, *M* = 244.2, monoclinic, *a* = 9.670(5), *b* = 10.685(4), *c* = 10.696(7) Å, β = 98.85(5)°, *U* = 1092 Å³, space-group *P*2₁, *Z* = 4 (2 crystallographically independent molecules), *D*_c = 1.48 g cm⁻³, μ(Cu-Kα) = 10 cm⁻¹. Data were measured on a Nicolet R3m diffractometer with Cu-Kα radiation (graphite monochromator) using ω-scans. The structure was solved by direct methods and refined anisotropically to give *R* = 0.055, *R*_w = 0.054 for 1501 independent observed reflections [|*F*_o| > 3σ(|*F*_o|), θ < 58°]. Atomic co-ordinates, bond lengths and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre. See Notice to Authors, Issue No. 1.

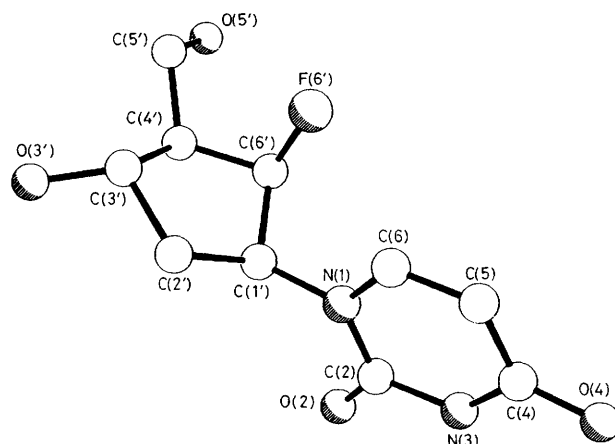


Figure 1. The molecular structure of (15) (there are no major differences between the conformations of the two independent molecules). In both molecules, A and B, the hydroxy groups are involved in intermolecular hydrogen bonds; molecule A: O(3') ··· O(5') 2.88, H ··· O(5') 1.91 Å, angle at H 172°; O(5') ··· O(4) 2.78, H ··· O(4) 1.80 Å, angle at H 175°; molecule B: O(3*) ··· O(5*) 2.86, H ··· O(5*) 1.95 Å, angle at H 153°; O(5*) ··· O(4*) 2.76, H ··· O(4*) 1.79 Å, angle at H 174°. There are no hydrogen-bonding interactions between molecules A and B.

We thank Mr. D. J. Knight and Dr. J. A. V. Coates for the biological results; further data will be presented elsewhere.

Received, 7th October 1986; Com. 1418

References

- 1 Y. F. Shealy, C. A. O'Dell, W. M. Shannon, and G. Arnett, *J. Med. Chem.*, 1983, **26**, 156.
- 2 K. G. Nicholson, *The Lancet*, 1984, **2**, 503.
- 3 G. M. Blackburn and D. E. Kent, *J. Chem. Soc., Perkin Trans. 1*, 1986, 913.
- 4 The numbering of the carbocyclic nucleosides is in accord with the system used by G. V. Madhavan and J. C. Martin, *J. Org. Chem.*, 1986, **51**, 1287.
- 5 Cf. J. J. Partridge, N. K. Chadha, and M. R. Uskokovic, *J. Am. Chem. Soc.*, 1973, **95**, 532.
- 6 S. Castillon, A. Dessinges, R. Faghih, G. Lukacs, A. Olesker, and T. T. Thang, *J. Org. Chem.*, 1985, **50**, 4913; K. C. Nicolaou, T. Ladduwahetty, J. L. Randall, and A. Chucholowski, *J. Am. Chem. Soc.*, 1986, **108**, 2466; cf. A. Hasegawa, M. Goto, and M. Kiso, *J. Carbohydr. Chem.*, 1985, **4**, 627.
- 7 Cf. D. O. Kiesewetter, J. A. Katzenellenbogen, M. R. Kilbourn, and M. J. Welch, *J. Org. Chem.*, 1984, **49**, 4900; T. Haradahira, M. Maeda, Y. Kai, and M. Kojima, *J. Chem. Soc., Chem. Commun.*, 1985, 364.