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# An Unexpected Synthesis of a Dihydropyrrolo-[1,2-*c*]pyrimidinedione Nucleoside Analogue from 5-Fluorouracil†

**Géraldine Grangier-McMath,[a] David J. Aitken,*[a] Dominique Guillaume,[a] Angèle Chiaroni,[b] Claude Riche[b] and Henri-Philippe Husson[a]**

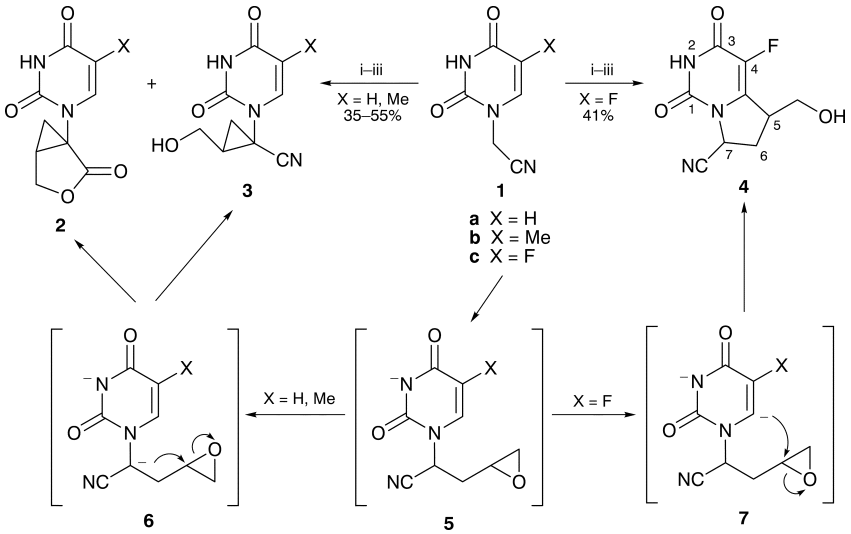
[a]*Laboratoire de Chimie Thérapeutique associé au CNRS, Faculté des Sciences Pharmaceutiques et Biologiques, Université René Descartes (Paris V), 4 Avenue de l'Observatoire, 75270 Paris cedex 06, France*
[b]*Laboratoire de Cristallochimie, Institut de Chimie des Substances Naturelles du CNRS, Avenue de la Terrasse, 91198 Gif-sur-Yvette cedex, France*

In the presence of an excess of LDA, the tandem deprotonation–alkylation reaction of 1-cyanomethyl-5-fluorouracil with epibromohydrin gives the novel dihydropyrrolo[1,2-*c*]pyrimidinedione **4** as a mixture of diastereoisomers.

In the search for new nucleoside analogues having anti-viral or anti-tumour activity, structures in which carbocyclic or acyclic residues have replaced the ribose moiety have received considerable attention.[1] We have carried out some studies on original synthetic approaches towards such compounds,[2,3] and in one particular investigation[2] we observed that the 1-cyanomethyl derivatives of uracil and thymine, **1a** and **1b**, underwent sequential double deprotonation–alkylation reactions with racemic epibromohydrin in the presence of an excess of strong base, leading to the novel cyclopropane nucleoside analogues **2** and **3** (Scheme 1). Here we report that the same reaction conditions, when applied to the 5-fluorouracil derivative **1c**, do not produce a cyclopropane compound, but give instead a single product **4** having an unusual 6,7-dihydropyrrolo-[1,2-*c*]pyrimidine-1,3-dione skeleton.

The starting material 1-cyanomethyl-5-fluorouracil **1c** was prepared in 58% yield by alkylation of the bis(trimethylsilyl) derivative of 5-fluorouracil using bromoacetonitrile. Treatment of a THF solution of **1c** at −70 °C with an excess (5 equiv.) of LDA–HMPA followed by racemic epibromohydrin gave, in addition to unreacted **1c**, a 1:1 mixture of *cis* and *trans* isomers of compound **4** in 41% yield. Separation of the isomeric forms could be achieved on a small scale by repeated column chromatography, and was aided by the fact that one isomer could be crystallized. The relative configuration of each isomer was deduced from NMR spectral data; diagnostic apparent double triplets at $\delta$ 2.60 ($J$ = 13.8 and 2.7 Hz) and $\delta$ 2.93 ($J$ = 13.8 and 9.9 Hz) in the $^1$H NMR spectrum of the *cis* isomer were attributed to *syn*-H(6) and *anti*-H(6) respectively. The structure of the *cis*-**4** isomer was confirmed by an X-ray diffraction study (Fig. 1). In the crystal, the pyrimidinedione ring is virtually planar, while the five-membered ring is in a chair conformation with atoms C(5) and C(6) deviating by 0.173(3) and −0.245(3) Å respectively from the plane of the other three atoms.

The formation of **4** probably proceeds *via* the same mono-alkylated intermediate that one would expect in the formation of **2** and **3**, *i.e.* an oxiranylmethyl derivative **5** (Scheme 1). Whereas uracil and thymine derivatives **5a** and **5b** are deprotonated again on the carbon $\alpha$ to the nitrile, giving dianions **6** which are set up for cyclopropane formation, the electron withdrawing effect of the 5-fluoro substituent in **5c** induces preferred deprotonation at the pyrimidinedione C(6) centre,[4] giving dianion **7** which undergoes a 5-*exo*-*tet* cyclization to give **4**.




**Scheme 1** *Reagents and conditions*: i, LDA–HMPA (5 equiv.), THF, −70 °C; ii, (±)-epibromohydrin; iii, satd. aq. $NH_4Cl$

*To receive any correspondence.
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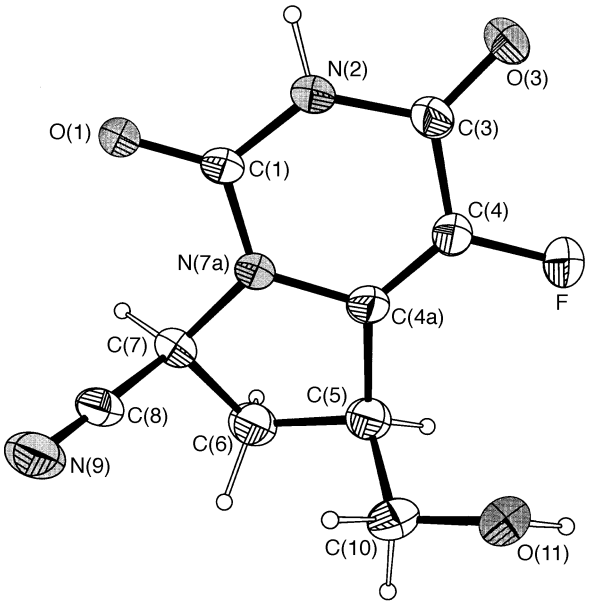


**Fig. 1** ORTEP drawing of compound *cis*-**4**. The structure shows the hydroxy group oxygen atom in the more abundant of its two possible positions; the bonded hydrogen atom is suggested, not located

The pyrrolo[1,2-*c*]pyrimidinedione ring system has generated interest recently as a structural unit of rigidified spiro-anomeric nucleosides.[5] A particular interest arises from the 5-hydroxymethyl derivative described here, since examination of molecular models of **4** indicates that the nucleic base plane and the primary hydroxy group can be superimposed upon the corresponding functions of one conformation of a 5-fluorouridine molecule, suggesting that compounds of this type may be interesting leads in the search for new nucleoside analogues.

## Experimental

1-*Cyanomethyl*-5-*fluorouracil* **1c**.—A suspension of 5-fluorouracil (10.0 g, 76.9 mmol) and ammonium sulfate (50 mg) in hexamethyldisilazane (150 ml) was refluxed under nitrogen for 4 h. Volatiles were distilled at atmospheric pressure to leave the crude bis(trimethylsilyl) derivative as an oily residue, which was dissolved in 1,2-dichloroethane (100 ml). Bromoacetonitrile (5.9 ml, 84.7 mmol) was added and the mixture refluxed under nitrogen for 18 h. After cooling, ethanol (5 ml) was added and the precipitate was collected by filtration then crystallized from methanol, yield 7.50 g (58%); mp 220 °C (MeOH); $\delta_H(CD_3OD)$ 4.84 (2 H, s), 7.98 (1 H, d, *J* 6.1); $\delta_C(CDCl_3)$ 46.7, 125.5, 139.1 (d, *J* 34), 150.1 (d, *J* 231), 159.4, 167.8 (d, *J* 27); *m*/*z* 187 $[M + H + NH_3]^+$, 170 $[M + H]^+$.

7-*Cyano*-4-*fluoro*-5-*hydroxymethyl*-6,7-*dihydropyrrolo*[1,2-*c*]-*pyrimidine*-1,3(2H,5H)-*dione* **4**.—A solution of **1c** (3.00 g, 17.8 mmol) and HPA (15.5 ml, 89.1 mmol) in THF (15 ml) was added slowly to a solution of LDA [prepared by addition of 2.5 M butyllithium solution in hexane (35.6 ml, 89.0 mmol) to a solution of diisopropylamine (12.5 ml, 89.1 mmol) in THF (100 ml)] under nitrogen at −70 °C. After 15 min, epibromohydrin (1.7 ml, 19.8 mmol) was added dropwise and the reaction mixture stirred at −70 °C for 3 h. A saturated aqueous solution of ammonium chloride (100 ml) was added and the mixture warmed to room temperature. The resulting thick liquid mass was extracted with dichloromethane (3 × 75 ml). The combined extracts were dried over magnesium sulfate and evaporated, and the residue subjected to flash chromatography using EtOAc–cyclohexane (8:2) to give the product as a *cis*/*trans* mixture (*ca.* 1:1), yield 1.64 g (41%). After careful repeated chromatography, a sample of the *cis* isomer was obtained sufficiently pure to be crystallized from methanol. For *cis*-**4**, mp 209 °C (MeOH) (Found: C, 48.08; H, 4.02; N, 18.01%. $C_9H_8FN_3O_3$ requires C, 48.01; H, 3.58; N, 18.66%); $\delta_H(CD_3OD)$ 2.60 (1 H, dt, *J* 2.7 and 13.8), 2.93 (1 H, dt, *J* 9.9 and 13.8), 3.81 (1 H, m), 3.91 (1 H, dd, *J* 4.1 and 11.1), 4.02 (1 H, dd, *J* 5.2 and 11.1), 5.30 (1 H, dd, *J* 2.7 and 10.0); $\delta_C(CDCl_3)$ 31.2, 44.7, 49.6, 62.5, 117.9, 138.1 (d, *J* 230), 143.8 (d, *J* 28), 149.0, 160.4; *m*/*z* 243 $[M + H + NH_3]^+$, 226 $[M + H]^+$. For *trans*-**4**, oil; $\delta_H(CD_3OD/[^2H_6]$benzene) 2.29 (1 H, m), 2.43 (1 H, m), 3.31 (1 H, m), 3.72 (1 H, dd, *J* .1 and 11.0), 3.86 (1 H, dd, *J* 4.5 and 11.0), 4.94 (1 H, dd, *J* 4.8 and 9.1); $\delta_C(CDCl_3)$ 32.1, 44.7, 49.6, 61.5, 117.5, 138.3 (d, *J* 228), 142.9 (d, *J* 28), 148.9, 160.4; *m*/*z* 243 $[M + H + NH_3]^+$, 226 $[M + H]^+$.

*X-Ray Crystallography*.—A crystal of *cis*-**4** (dimensions 0.50 × 0.50 × 0.30 mm) was grown from methanol solution. $C_9H_8FN_3O_3$, $M_W = 225.18$, triclinic, space group $P\bar{1}$, $Z = 2$, $a = 6.577(10)$, $b = 7.867(12)$, $c = 9.786(16)$ Å, $\alpha = 97.94(10)$, $\beta = 83.99(11)$, $\gamma = 107.28(8)°$, $V = 478$ Å$^3$, $d_c = 1.57$ g cm$^{-3}$, $F(000) = 32$, $\lambda(CuK\alpha) = 1.5418$ Å, $\mu = 1.15$ mm$^{-1}$; 1774 intensities measured of which 1666 unique ($R_{int} = 0.036$). No intensity decay. Intensity data were measured on an Enraf-Nonius Cad-4 diffractometer using the ($\omega$–2$\theta$) scan technique up to $\theta = 66°$. The structure was solved by direct methods using SHELXS86 and refined by full-matrix least-squares based upon unique $F_o^2$ with SHELXL93. The hydroxy group was disordered with two positions O(11) and O(11′) of respective occupancy 2/3:1/3, each allowing hydrogen bonding with the nearest molecules [O(11′) deduced from O(11) by a rotation of 120° around the C(5)—C(10) bond]. Given the short intermolecular distances, the H atom of the hydroxy group in the site O(11) can be directed either towards the oxygen O(11′) of the molecule $(1 - x, 1 - y, 1 - z)$ [distance O(11) · · · O(11′) = 2.724(4) Å] or towards the oxygen O(11) of the molecule $(2 - x, 1 - y, 1 - z)$ [distance O(11) · · · O(11) = 2.883(4) Å], with equal weighting. In the site O(11′), the hydrogen bond is established with the nitrogen atom N(9) of the molecule $(1 - x, 2 - y, 1 - z)$ [distance O(11′) · · · N(9) = 3.018(7) Å] With the exception of the hydroxy group hydrogen, all the hydrogen atoms were located in a difference Fourier map and fitted in idealized positions (C—H = 1.00 Å). All hydrogen atoms were assigned an isotropic displacement parameter equivalent to that of the bonded C atom, plus 10%. Thus, refinement of 149 variables converged to $R_1(F) = 0.0871$ [for 1509 $F_o$ with $F_o \geq 4\ \sigma(F_o)$] and $wR_2(F^2) = 0.2464$ (for all the 1666 data with goodness-of-fit $S = 1.175$). The residual electron density was found between −0.34 and 0.49 e Å$^{-3}$ in the final difference map. Full crystallographic details, excluding structure factors, have been deposited at the Cambridge Crystallographic Data Centre (CCDC). See Instructions for Authors, *J. Chem. Research (S)*, 1998, Issue 1. Any request to the CCDC for this material should quote the full literature citation and the reference number 423/7.

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