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PATENT SPECIFICATION

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(19)

(54) PREPARATION OF 5-FLUOROPYRIMIDINES AND NOVEL INTERMEDIATE THEREFROM

(71) We, RESEARCH INSTITUTE FOR MEDICINE AND CHEMISTRY INC., a corporation organised under the laws of the Commonwealth of Massachusetts, United States of America, of 49 Amherst Street, Cambridge, Massachusetts 02142, United States of America, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention relates to a process for the fluorination of uracil and related pyrimidines.

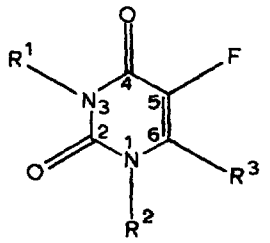
5-Fluorouracil, 5-fluorouridine and various related 5-fluorinated pyrimidines have been found to possess cytotoxic properties of use in the management of certain types of cancer and some types of viral infections. Previously, these have been prepared by total synthesis involving several reaction stages and relatively low overall yield. We have now found that uracil and related pyrimidines more particularly set out below, may be fluorinated in the 5-position using certain electrophilic fluorinating agents.

This is in contrast to previous attempts to halogenate uracil, for example, chlorination, when further elimination and addition of halogen occurs to yield products from which 5-chloropyrimidines cannot readily be obtained.

Although uracil and related pyrimidines are virtually inert to the known fluorinating agent perchloryl fluoride, we have found that reaction with a hypofluorite, the fluoroxy group of which is covalently bonded to an inert electron attracting group, introduces fluorine smoothly at the 5-position. A related reagent which we have found suitable is elemental fluorine diluted with an inert gas.

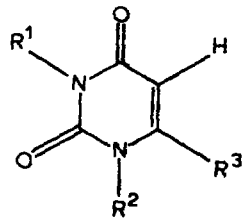
While we do not wish to be bound by theoretical considerations, it is believed that initially fluorine adds electrophilically at the 5-position forming a carbonium ion with a positive charge at the 6-position which then combines with a nucleophile present in the reaction medium to form a 6-substituted 5-fluoro- 5,6-dihydro pyrimidine; this can readily be made to eliminate the 6-substituent, together with the 5-hydrogen, e.g. by heating, to form the desired 5,6-dehydro-product.

According to the present invention therefore, we provide a process for the preparation of compounds of the formula



I

(where R^1 and R^3, which may be the same or different, are alkyl groups or hydrogen atoms; and
R^2 is an alkyl group, a hydrogen atom or a sugar residue) comprising reacting a compound of the formula



II

(where R^1, R^2 and R^3 have the above meanings) with a hypofluorite, the fluoroxy group of which is covalently bonded to an inert electron attracting group, or with elemental fluorine diluted with an inert gas, to introduce a fluorine atom at the 5-position and an atom or group at the 6-position, and thereafter eliminating said atom or group at the 6-position together with the hydrogen atom at the 5-position to yield the required 5,6-double bond.

In formulae I and II, alkyl groups in positions R^1, R^2 and R^3 preferably have 1—6 carbon atoms, as in methyl, ethyl, butyl or hexyl

groups. Where R^2 is a sugar residue, this may, for example, be a 1-ribosyl, 1-(2-deoxyribosyl) or arabinosyl residue. The nucleophile present may, for example, comprise hydroxyl ions from water, alkoxyl ions from alkanols, carboxylate ions from a carboxylic acid or halide ions, in particular fluoride ions from the fluorinating reagent. We have found that such 6-substituted products are relatively stable and since they do not possess a 5,6-double bond they are relatively free from attack by further reagent. Consequently, it is advantageous to effect the reaction in the presence of a nucleophile in order to enhance the formation of the 6-substituted-5-fluoro-5,6-dihydropyrimidine intermediate.

The reaction is preferably carried out in a solvent for the pyrimidine, advantageously a polar solvent such as water, a hydrate of a perfluoroketone such as hexafluoroacetone, or trifluoroacetic acid. Water is preferred. Co-solvents which may be present include, for example, alkanols, preferably C_{1-5}, such as methanol or ethanol; aliphatic acids (preferably C_{1-5}) e.g. an alkanoic acid such as acetic or propionic acid; or esters of phosphoric or phosphonic acids. Most of the above solvent systems will contain nucleophiles suitable to form the above stable 6-substituted derivatives. In addition, it will be noted that where F_2 is used as reagent, F^- ions may also act as nucleophiles; where a hypofluorite reagent is used and this includes a perfluoroalkyl group as in trifluoromethyl hypofluorite, decomposition of perfluoroalkoxy anions liberated in the reaction also yields F^-. Thus, in general, if the reaction is carried out in water, the initial reaction product will be predominantly a 5 - fluoro - 6 - hydroxy - 5,6 - dihydropyrimidine containing, however, a proportion (e.g. 5—10%) of 5,6-difluoro-5,6-dihydropyrimidine. Both these 6-substituted products, however, can readily be converted into the desired 5-fluoro-pyrimidine, for example by heating, in the case of the simpler heat-stable pyrimidines such as uracil itself, where heating *in vacuo* yields 5-fluorouracil as a sublimate, or in the case of more complex and heat sensitive substrates, by heating the initial product in a solvent with a hydrogen fluoride and/or water scavenger, for example a molecular sieve, ethylene oxide, sodium or potassium fluoride or sodium or potassium acetate. The formation of substantially the same products by both the hypofluorite reagent and elemental fluorine indicates that the same reaction mechanism is concerned.

The hypofluorite reagents are preferably fluoroalkyl hyperfluorites and while the alkyl group may carry one or more hydrogen atoms, it preferably carries at least 2 fluorine atoms per carbon atom. Preferred reagents of this type are trifluoromethyl, perfluoro-n-propyl, perfluoroisopropyl, perfluoro-*t*-butyl, monochlorohexafluoro - n - propyl, monochlorohexafluoroisopropyl or perfluoro - *t*-pentyl hypofluorite and 1,2-difluoroxytetrafluoroethanes and 1,1-difluoroxydifluoromethane. The most preferred reagent is trifluoromethyl hypofluorite.

Where the fluorinating agent is a volatile liquid, it may conveniently be passed into the reaction mixture in gaseous form or may be dissolved in an inert liquid such as chlorotrifluoromethane or other fluorinated hydrocarbons, which advantageously also carry a chlorine substituent.

The reaction temperature is preferably kept relatively low, for example in the range −78° to +40° C. Reaction at room temperatures is rapid and smooth. The reaction may, for example, be monitored by n.m.r. spectroscopy or thin layer chromatography.

Where elemental fluorine is used as fluorinating agent, the gas should be diluted with an inert gas such as nitrogen or argon, the concentration of fluorine in the gas being preferably 1 to 50% by volume; in general lower reaction temperatures will be used than those optimal for hypofluorite reagents, but the reaction is controllable at room temperature.

The intermediate 5-fluoro-6-hydroxy-5,6-dihydrouracil which may be obtained in the process of the invention, a sample of which is characterised by an Rf value of 0.3 for thin layer chromatography on silica gel using methanol: chloroform (20:80) as eluant, an infra red spectrum with absorption maxima (KBr disc) at 3300, 1720, 1475, 1250, 1140, 1080, 880 and 800 cm^{-1}, a PMR spectrum comprising a complex pattern of resonances from 5—6 ppm which is characteristic of the AB pattern of an ABX system, and an FMR spectrum comprising a signal at Ø+207.6 ppm which is a broad doublet with J=45 Hz, is a new compound and comprises a further feature of the present invention.

The following Examples are given by way of illustration only; all melting points were taken on the Kofler hot stage and are reported uncorrected, PMR spectra were obtained at 60M Hz using a Varian T—60 spectrometer and are reported as shifts downfield from internal tetramethyl silane. FMR spectra were obtained at 56.4M Hz on the above instrument and are reported as shifts from internal $CFCL_3$. CF_3OF is a powerful oxidant and while we have experienced no difficulty with its use certain precautions are indicated; all reactions should be conducted with adequate shielding, accumulation of the reagent in the presence of oxidizable substances should be avoided, material for handling of the reagent should consist of glass, Teflon, Kel-F, or passivated metal; *on no account should PVC, rubber, polyethylene or similar substances be used.* I.R. spectra were obtained with a Perkin-Elmer model 137

spectrometer. Solutions of CF_3OF were prepared by passing the gaseous reagent into $CFCl_3$ at −78°; aliquots were treated with an excess of aqueous KI and the concentration of CF_3OF estimated by titration of the I_2 liberated;

$$CF_3OF + 2KI + H_2O \rightarrow I_2 + 2KF + 2HF + CO_2$$

Example 1.

Fluorination of Uracil with CF_3OF

Uracil (0.336 g., 3 m.mole) in a mixture of trifluoroacetic acid (6 cc) and water (20 cc) was added to a solution of trifluoromethyl hypofluorite (4.5 m.mole) in $CFCl_3$ (50 cc) at −78° C in a pressure bottle. The precipitated uracil redissolved in the aqueous layer when the mixture was warmed up to room temperature. The mixture was vigorously stirred for 15 hours. The excess CF_3OF was removed with nitrogen and the solvent was removed under reduced pressure. The solid residue was sublimed at 210—230° C under reduced pressure (0.5 mm Hg) to give crude 5-fluorouracil (0.365 g., 94%) m.p. 260—70°. Recrystallization from methanol-ether gave pure 5-fluorouracil (0.33 g., 85%) m.p. 282—3° C, mixed m.p. (with authentic 5-fluorouracil) 282—3° C. PMR, FMR, IR, and U.V. spectra were identical to those of authentic 5-fluorouracil.

In a companion fluorination as above, the crude products were not subjected to heat, but instead separated by preparative t.l.c. (silica gel GF 254, methanol: chloroform, 20:80) into a fraction having R_f 0.5 (5-fluorouracil) and a fraction having R_f 0.3 (which on heating was quantitatively converted to 5-fluorouracil):

KBr

ν

cm^{-1}

3300(s), 1720(s), 1475(m), 1250(m), 1140(m), 1080(m), 880(m), 800(m). The proton NMR showed a complex pattern of resonances from 5—6 ppm (AB pattern of an ABX system). The FMR had $\emptyset = +207.6$ ppm (broad doublet $J = 45$ Hz). The mass spectrum had molecular ion at m/e 148^+; accurate mass, m/e 148.0291 (cal. for $C_4H_5FN_2O_3$, m/e 148.0284). This product was 5 - fluoro - 6 - hydroxy - 5,6 - dihydrouracil.

Analysis: $C_4H_5FN_2O_3$

Requires:

C, 32.45% H, 3.40%; N, 18.92% F, 12.83%

Found:

C, 32.26% H, 3.5%, N, 18.90% F, 13.84%

Example 2.

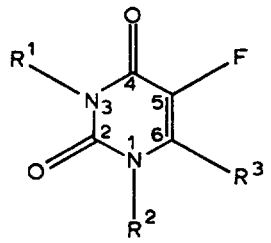
Fluorination of Uracil with Fluorine

Fluorine gas diluted liberally with nitrogen was passed at room temperature into a vigorously stirred solution of uracil (150 mg., 1.34 m.mole) in water (50 cc). After the disappearance of starting material (NMR control; ca. 2.5 m.mole F_2) the solvent was removed under reduced pressure and the residue sublimed to give 5-fluorouracil (95 mg., 0.74 m.mole, 55% yield) identified by comparison with authentic 5-fluorouracil.

In Patent Specification No. 1,323,785, which was published after the filing date of this application and which has a priority date earlier than the priority date of this application, there is claimed in claim 1 a method of producing 5-fluorouracil, comprising fluorinating uracil with a gaseous mixture of elementary fluorine diluted with an inert gas, in a glacial acetic acid medium under a hydrodynamic condition of Reynold's number within the range from 35,000 to 45,000 and at a temperature of from 15 to 35° C to form 5 - fluoro - 6 - acetoxydihydrouracil and thereafter heating the reaction mixture at a temperature of from 90 to 95° C. We make no claim to the process claimed in claim 1 of the said Patent Specification No. 1,323,785.

Subject to the foregoing disclaimer, WHAT WE CLAIM IS:—

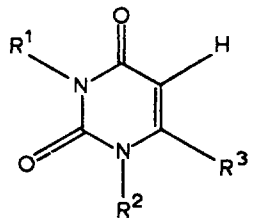
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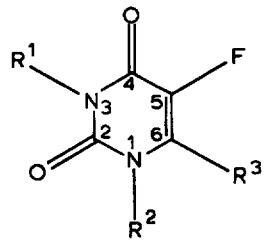
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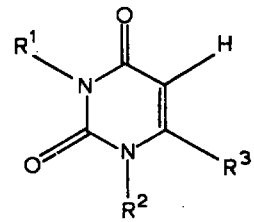
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* C L M S *

or group at the 6-position, and thereafter eliminating said atom or group at the 6-position together with the hydrogen atom at the 5-position to yield the required 5,6-double bond.

2. A process as claimed in claim 1 in which the hypofluorite reagent is trifluoromethyl hypofluorite.

3. A process as claimed in claim 1 in which the fluorinating agent is elemental fluorine diluted with nitrogen.

4. A process as claimed in any of claims 1—3 in which elimination of the said atom or group at the 6-position together with the hydrogen atom at the 5-position, is effected by heating.

5. A process as claimed in any of the preceding claims in which the fluorination is effected in the presence of a polar solvent.

6. A process as claimed in claim 5 in which the solvent is water, a hydrate of a perfluoroketone or trifluoroacetic acid.

7. A process as claimed in claim 5 or claim 6 in which an alkanol, an alkanoic acid or an ester of a phosphoric or phosphonic acid is used as a cosolvent.

8. A process as claimed in any of the preceding claims in which a nucleophile is added to the reaction system to enhance formation of the 6-substituted-5-fluoro-5,6-dihydropyrimidine intermediate.

9. A process as claimed in claim 8 in which the nucleophile is hydroxyl ion, alkoxy ion, carboxylate ion or halide ion.

10. A process as claimed in any of the preceding claims in which the fluorination is effected at −78° to +40° C.

11. A process for the fluorination of pyrimidines according to claim 1 substantially as herein described.

12. A process for the fluorination of pyrimidines substantially as herein described with reference to the Examples.

13. 5-Fluoropyrimidines whenever produced by a process as claimed in any of the preceding claims.

14. 5 - Fluoro - 6 - hydroxy - 5,6 - dihydrouracil whereof a sample is characterised by an Rf value of 0.3 for thin layer chromatography on silica gel using methanol: chloroform (20:80) as eluant, an infra red spectrum with absorption maxima (KBr disc) at 3300, 1720, 1475, 1250, 1140, 1080, 880 and 800 cm^{-1}, a PMR spectrum comprising a complex pattern of resonances from 5—6 ppm which is characteristic of the AB pattern of an ABX system, and an FMR spectrum comprising a signal at Ø +207.6 ppm which is a broad doublet with J=45 Hz.

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