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(54) METHOD OF PRODUCING 5-FLUOROURACIL DERIVATIVES

(71) We, TAKEDA YAKUMIN KOGYO KABUSHIKI KAISHA (also known as Takeda Chemical Industries Ltd.), a Japanese Company of 27, Doshomachi 2-Chome, Higashi-Ku, Osaka, Japan, 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 novel and industrially useful method of producing 1-(tetrahydro-2-furyl)-5-fluorouracil (may be abbreviated as mono-compound), 1,3-bis-(tetrahydro-2-furyl)-5-fluorouracil (may be abbreviated as bis-compound) or a mixture of them. These compounds are of value as anticancer agents. The bis-compound is also useful as an intermediate for the synthesis of the mono-compound.

As a representative prior art method for the production of the mono- or bis-compound, there is known a process comprising reacting 5-fluorouracil with 2-chlorotetrahydrofuran. However, the starting material 2-chlorotetrahydrofuran has industrially been produced by the addition of hydrogen chloride to 2,3-dihydrofuran.

Under the circumstances as above, the present inventors have made extensive studies to produce the present compounds with the use of 2,3-dihydrofuran as a starting material. The studies led to an unexpected finding that when 5-fluorouracil and 2,3-dihydrofuran are heated together at an elevated pressure, the mono- or bis-compound or their mixture is produced in unusually high yield.

The present inventors found also that the bis-compound, which is produced as above and may be a mixture with the mono-compound, is converted to the mono-compound by solvolysis under non-acidic conditions.

An object of the present invention is to provide an industrially simple and practical method of producing the mono- or bis-compound or their mixtures. Another object

of the invention is to provide a method for producing the mono-compound by subjecting the bis-compound, which is produced as above and may be a mixture with the mono-compound, to solvolysis under non-acidic conditions.

The present invention is directed to a method for producing the mono- or bis-compound or a mixture thereof which comprises heating 5-fluorouracil with 2,3-dihydrofuran under superatmospheric pressure, suitably in a closed vessel.

A part of this invention is directed to a method of producing the mono-compound which comprises subjecting the bis-compound as produced above to solvolysis under non-acidic conditions.

According to the present invention the mono- or bis-compound or a mixture thereof is produced by reacting 5-fluorouracil with 2,3-dihydrofuran at an elevated temperature under superatmospheric pressure, suitably in a closed vessel.

The heating temperature is normally within the range of 100° to 250°C. The preferable temperature to form the mono-compound is between 150° and 200°C and more preferably between 165° and 185°C. The bis-compound is formed preferably at a temperature between 125° and 180°C and more preferably between 135° and 165°C.

Production of the mono-compound generally tends to increase at a temperature higher than about 180°C, and at a lower temperature, that of the bis-compound tends to rise.

The reaction temperature may be selected from the above ranges according to the kind of solvent, scale of the reaction, reaction time and other conditions, trial runs being used with advantage for selecting the optimum temperature.

As the closed reaction vessel, an autoclave may be used.

This reaction may be carried out in the presence of a solvent. While one of the starting materials, i.e. 2,3-dihydrofuran, may be

used as the solvent as well, it is possible to employ another suitable solvent which is free of active hydrogen, such as amides (e.g. dimethylformamide, dimethylacetamide, or hexamethylphosphoramide), ethers (e.g. tetrahydrofuran or dioxane), tertiary amines (e.g. pyridine, or triethylamine), esters (e.g. ethyl formate, or ethyl acetate) and a suitable mixture of such solvents.

10 In general, it is preferable to carry out the reaction using a molar excess of 2,3-dihydrofuran over 5-fluorouracil.

For the purpose of producing predominantly the mono-compound, the molar ratio of 2,3-dihydrofuran to 5-fluorouracil may be selected from the range of 2 to 8 and, preferably, from the range of 4 to 6.

15 In order to produce mainly the bis-compound, it is advantageous to charge the solvent with both 5-fluorouracil and 2,3-dihydrofuran in high concentration. For example, the solvent may be employed in a proportion not exceeding about 15 times (v/w), preferably 8-1.5 times (v/w) the amount of 5-fluorouracil, 2,3-Dihydrofuran may be employed in an amount generally not less than 3 equivalents, preferably 3.5-10 equivalents, based on 5-fluorouracil. It is preferable to increase the ratio of 2,3-dihydrofuran to 5-fluorouracil when a large amount of solvent is employed.

20 Such a ratio as mentioned above may be selected experimentally in consideration of the kind and amount of solvent, reaction temperature and other conditions.

35 Provided that the reaction time is sufficient and the reaction temperature is between 135° and 165°C, the higher the concentration of 2,3-dihydrofuran the better is the yield of the bis-compound. The formation rate of the mono-compound to bis-compound varies with reaction time.

40 In the case of producing the mono-compound directly from 5 fluorouracil, it is preferable to stop the reaction as soon as the bis-compound is detected by thin-layer chromatography on silica gel.

45 To produce the bis-compound a prolonged reaction time, for example, more than 4 hours is preferable at about 150°C. In shorter reaction periods the production of the bis-compound is rather small. Especially when a solvent is employed in a rather small amount, a longer reaction time is preferable.

50 The desired compound thus obtained can easily be separated from the reaction mixture in a conventional manner.

55 For example, the desired compound may be separated by the procedure of concentrating the reaction mixture to dryness under reduced pressure, extracting the residue with a solvent and removing the solvent by distillation. As a solvent of recrystallization for the mono-compound ethanol is prefer-

able and petroleum ether is preferable for the bis-compound.

60 In order to produce the mono-compound, even where the reaction product mixture contains not only the bis-compound but also the mono-compound, it is possible to subject the reaction mixture to solvolysis under non-acidic conditions without separating the mono-compound. The bis-compound may be subjected to solvolysis after it has been isolated or, without prior isolation, as the resultant reaction mixture *per se*. This procedure may be accomplished merely by heating the bis-compound with water or a water-containing solvent (such as aqueous methanol, ethanol, pyridine, dioxane, tetrahydrofuran, or acetone) under non-acidic conditions.

65 In the presence of an acid, fixing of the reaction condition is difficult, because solvolysis of the bis-compound to the mono-compound and subsequent solvolysis of the mono-compound to 5-fluorouracil proceed so rapidly that it is extremely difficult to control the solvolysis so as to suppress the production of 5-fluorouracil. The acid may be an impurity in the product of the mono-compound. Therefore, addition of an acid into the reaction mixture is generally disadvantageous and solvolysis under neutral or basic condition is favourable.

70 Generally the solvolysis proceeds well under heating (e.g. at 40°-80°C). For example, while an aqueous alcohol is employed, the reaction temperature is desirably within the range of 50°C to the reflux temperature of the reaction system. But, the reaction may occasionally proceed without heating.

75 Preferably the water-containing solvents contain not more than 50% (v/v) of water, though more water may occasionally be useful. For example, the aqueous alcohol preferably contains 40 to 80 percent (v/v) of alcohol.

80 The present solvolysis proceeds under non-acidic conditions as mentioned above and so produces the desired mono-compound of high purity in a good yield in a simple and convenient procedure. The mono-compound produced in the above manner may be separated by conventional means, for instance, by distilling off solvent from the resultant reaction mixture.

85 The bis-compound produced in the present process is not only of value as an intermediate for producing the mono-compound, but also as an anticancer agent, having an effect on prolonging survival time of p-388 leukemia bearing mice.

90 The method according to this invention has the following technical advantages:

- (1) The contemplated compound can be produced in good yield and high purity.
- (2) Industrial production of 2-chloro-

tetrahydrofuran, a starting material for the aforesaid prior art process, has been produced by reacting 2,3-dihydrofuran, which is a starting material for this invention, with hydrogen chloride. Therefore, compared with the above known process, the method according to this invention has more advantage of substantially fewer reaction steps and lower cost as well.

(3) Whereas 2-chlorotetrahydrofuran, which is employed in the known process, is chemically unstable, 2,3-dihydrofuran to be employed according to this invention is chemically stable. Therefore, the method according to this invention employing the latter compound is more advantageous in respect of reaction procedure.

(4) Whereas, in the above prior art method the contemplated compound tends to be decomposed by the hydrochloric acid by-product no such decomposition of the contemplated compound takes place in the method of this invention.

(5) Since the amount of by-product is small as compared with the known process, the contemplated compound can be more easily isolated by the present process.

In the following examples, yields may be improved by repeating the experiments.

EXAMPLE 1

To 30 ml of pyridine, was added 1.3 g of 5-fluorouracil together with 2.8 g of 2,3-dihydrofuran and, in a closed tubular reactor, the resultant mixture was heated at 185°C for 8 hours. After cooling, the reaction mixture was concentrated to dryness under reduced pressure and the residue was recrystallized from 5 ml of ethanol. By the above procedure was obtained 1.3 g colorless needles of 1-(tetrahydro-2-furyl)-5-fluorouracil, melting point: 164–168°C.

In thin-layer chromatography on silica gel (solvent system: methanol-chloroform = 1:9), this product gave a single U.V. spot. The I.R. NMR and UV spectra of this product were also measured and agreed with the corresponding spectra of an authentic sample.

Elemental analysis:

Calcd. for $C_8H_9O_3N_2F$

C, 47.99; H, 4.50; N, 14.00

Found C, 47.55; H, 4.83; N, 13.82

EXAMPLE 2

To 20 ml of N,N-dimethylformamide, was added 0.5 g of 5-fluorouracil together with 2.3 g of 2,3-dihydrofuran and, in a closed tubular reactor, the mixture was heated at 185°C for 4 hours. After cooling, the reaction mixture was concentrated to dryness under reduced pressure and the residue was recrystallized from ethanol. By the above procedure was obtained 0.4 g

colorless crystals of 1-(tetrahydro-2-furyl)-5-fluorouracil, melting point: 164–168°C.

EXAMPLE 3

To 30 ml of pyridine was added 1.0 g of 5-fluorouracil together with 2.69 g of 2,3-dihydrofuran and, in a closed tubular reactor, the mixture was heated at 170°C for 10 hours. Thereafter, the reaction mixture was treated in the same manner as the foregoing examples to obtain 0.984 g colorless needles of the desired product. If thin layer chromatography on silica gel, this product gave a single spot at the same R_f as did an authentic sample.

EXAMPLE 4

In a closed tubular reactor, 1.3 g of 5-fluorouracil, 6.5 ml of pyridine and 7.0 g of 2,3-dihydrofuran were heated together at 200°C for 6 hours. After cooling, the reaction mixture was concentrated to dryness under reduced pressure and the residue was suspended in 10 ml of ethyl ether. The suspension was stirred for a while, after which the insolubles were filtered off.

The ethereal mother liquor was concentrated to about 5 ml and, then, 50 ml of petroleum ether was added dropwise, whereupon 1.5 g of 1,3-bis-(tetrahydro-2-furyl)-5-fluorouracil was obtained as a precipitate, melting point: 98°C.

Elemental analysis:

Calcd. for $C_{12}H_{13}FN_2O_4$

C, 53.33; H, 5.59; N, 10.36; F, 7.03

Found C, 53.42; H, 5.89; N, 9.98; F, 7.01

Ultraviolet absorption spectrum: $\max$ MeOH 274 $m\mu$

NMR absorption spectrum: (60 Mc, $CDCl_3$: δ 7.33, 1H, (d, $J=6$ Hz), δ 6.58, 1H, t, δ 5.97, 1H, m, δ 3.67–4.50, 4H, m, δ 1.67–2.67, 8H, m.

EXAMPLE 5

In a closed tubular reactor, 1.3 g of 5-fluorouracil, 5 ml of benzene and 14 g of 2,3-dihydrofuran were heated together at 200°C for 6 hours. After cooling, the reaction mixture was concentrated to dryness under reduced pressure and the residue was separated and purified by column chromatography on 25 g silica gel. From the chloroform eluate, the fractions rich in the desired compound were collected. The solvent was distilled off and the residue was recrystallized from petroleum ether. By the above procedure was obtained 1.3 g of 1,3-bis-(tetrahydro-2-furyl)-5-fluorouracil.

EXAMPLE 6

In an autoclave, 520 g of 5-fluorouracil, 1400 g of 2,3-dihydrofuran and 1.56 l of pyridine were heated together at 185°C for 130

3 hours. After cooling, the reaction mixture was concentrated to dryness under reduced pressure and the residue was dissolved in 6 l of ethanol-water (1:1). The solution was heated at 70°C for 2 hours, after which it was treated with activated charcoal. After filtration, the solution was concentrated under reduced pressure to about one-half of its original volume. After cooling, the resultant crystals were recovered by filtration and dried. By the above procedure was obtained 7880 g of 1-(tetrahydro-2-furyl)-5-fluorouracil. If necessary, this product may be recrystallized from ethanol. Recrystallization yielded 600 g of colorless needles, melting point: 167.5°C.

Elemental analysis:

Calcd. for $C_8H_8FN_2O_3$

C, 48.00; H, 4.53; N, 13.99

Found C, 47.93; H, 4.52; N, 13.85

EXAMPLE 7

Synthesis of 1,3-bis-(tetrahydro-2-furyl)-5-fluorouracil

In 20.8 ml of pyridine were dissolved 5.2 g (40 m mol) of 5-fluorouracil and 14 g (200 m mol) of 2,3-dihydrofuran. The solution was heated at about 150°C in a closed tubular reactor under agitation for 6 hours. After the reaction, the reaction mixture was concentrated to dryness under reduced pressure. The residue was dissolved in chloroform and the solution was passed through a column of silica gel. The column was eluted with chloroform and the effluent was concentrated to dryness under reduced pressure. The residue was washed with a small amount of petroleum ether to give the above-mentioned compound as colorless crystals. Yield, 9.2 g (85%), melting point: 89°C.

EXAMPLE 8

Synthesis of 1,3-bis-(tetrahydro-2-furyl)-5-fluorouracil

In 20.8 ml of pyridine were dissolved 5.2 g (40 m mol) of 5-fluorouracil and 9.8 g (140 m mol) of 2,3-dihydrofuran. The solution was heated at about 160°C in a closed tubular reactor under agitation for 5 hours. The resultant reaction mixture was treated similarly to Example 7 to give the above-mentioned compound.

Yield, 7.67 g (71%), melting point: 98°C.

EXAMPLE 9

Synthesis of 1-(tetrahydro-2-furyl)-5-fluorouracil

In 20.8 ml of pyridine were dissolved 5.2 g (40 m mol) of 5-fluorouracil and 9.8 g (140 m mol) of 2,3-dihydrofuran. The solution was heated at about 150°C in a closed tubular reaction under agitation for 6 hours. The resultant reaction mixture was concentrated to dryness under reduced pressure.

The residue was dissolved in 50% aqueous ethanol and heated at 70°C. After the reaction, the solution was concentrated to dryness under reduced pressure. Recrystallization of the residue from 90% ethanol gives 6.56 g of colorless crystals. Yield, 82%, melting point: 168°C.

WHAT WE CLAIM IS:—

1. A method for producing 1-(tetrahydro-2-furyl)-5-fluorouracil, which comprises heating 5-fluorouracil with 2,3-dihydrofuran under superatmospheric pressure to yield 1-(tetrahydro-2-furyl)-5-fluorouracil.

2. A method as claimed in Claim 1 wherein the said reactants are heated in a closed vessel.

3. A method as claimed in Claim 1 or Claim 2 wherein the reaction temperature is between 100° and 250°C.

4. A method as claimed in Claim 3 wherein the reaction temperature is between 150° and 200°C.

5. A method as claimed in Claim 4 wherein the reaction temperature is in the range 165° to 185°C.

6. A method as claimed in any one of the preceding claims wherein the reaction is carried out with a molar excess of 2,3-dihydrofuran over 5-fluorouracil.

7. A method as claimed in Claim 6 wherein the molar ratio of 2,3-dihydrofuran to 5-fluorouracil is in the range 2:1 to 8:1.

8. A method as claimed in Claim 7 wherein said ratio is in the range 4:1 to 6:1.

9. A method as claimed in any one of the preceding claims wherein the reaction is carried out in the presence of a solvent.

10. A method as claimed in Claim 9 wherein the solvent is an amide, ether, tertiary amine, ester or a mixture of two or more of said solvents.

11. A method as claimed in Claim 10 wherein the solvent is pyridine or N,N-dimethylformamide.

12. A method as claimed in any one of the preceding claims wherein the reaction between the said reactants is stopped as soon as 1,3-bis-(tetrahydro-2-furyl)-5-fluorouracil is detected by thin layer chromatography on silica gel.

13. A method as claimed in Claim 1 and substantially as hereinbefore described with reference to any one of Examples 1, 2 and 3.

14. A method as claimed in any one of Claims 1 to 12 wherein the 1-(tetrahydro-2-furyl)-5-fluorouracil is in admixture with 1,3-bis-(tetrahydro-2-furyl)-5-fluorouracil.

15. 1-(tetrahydro-2-furyl)-5-fluorouracil whenever prepared by a method as claimed in any one of the preceding claims.



3 hours. After cooling, the reaction mixture was concentrated to dryness under reduced pressure and the residue was dissolved in 5 l of ethanol-water (1:1). The solution was heated at 70°C for 2 hours, after which it was treated with activated charcoal. After filtration, the solution was concentrated under reduced pressure to about one-half of its original volume. After cooling, the resultant crystals were recovered by filtration and dried. By the above procedure was obtained 7880 g of 1-(tetrahydro-2-furyl)-5-fluorouracil. If necessary, this product may be recrystallized from ethanol. Recrystallization yielded 600 g of colorless needles, melting point: 167.5°C.

Elemental analysis:

Calcd. for $C_8H_8FN_2O_3$
C, 48.00; H, 4.53; N, 13.99
Found C, 47.93; H, 4.52; N, 13.85

EXAMPLE 7

Synthesis of 1,3-bis-(tetrahydro-2-furyl)-5-fluorouracil

In 20.8 ml of pyridine were dissolved 5.2 g (40 m mol) of 5-fluorouracil and 14 g (200 m mol) of 2,3-dihydrofuran. The solution was heated at about 150°C in a closed tubular reactor under agitation for 6 hours. After the reaction, the reaction mixture was concentrated to dryness under reduced pressure. The residue was dissolved in chloroform and the solution was passed through a column of silica gel. The column was eluted with chloroform and the effluent was concentrated to dryness under reduced pressure. The residue was washed with a small amount of petroleum ether to give the above-mentioned compound as colorless crystals. Yield, 9.2 g (85%), melting point: 89°C.

EXAMPLE 8

Synthesis of 1,3-bis-(tetrahydro-2-furyl)-5-fluorouracil

In 20.8 ml of pyridine were dissolved 5.2 g (40 m mol) of 5-fluorouracil and 9.8 g (140 m mol) of 2,3-dihydrofuran. The solution was heated at about 160°C in a closed tubular reactor under agitation for 5 hours. The resultant reaction mixture was treated similarly to Example 7 to give the above-mentioned compound. Yield, 7.67 g (71%), melting point: 98°C.

EXAMPLE 9

Synthesis of 1-(tetrahydro-2-furyl)-5-fluorouracil

In 20.8 ml of pyridine were dissolved 5.2 g (40 m mol) of 5-fluorouracil and 9.8 g (140 m mol) of 2,3-dihydrofuran. The solution was heated at about 150°C in a closed tubular reaction under agitation for 6 hours. The resultant reaction mixture was concentrated to dryness under reduced pressure.

The residue was dissolved in 50% aqueous ethanol and heated at 70°C. After the reaction, the solution was concentrated to dryness under reduced pressure. Recrystallization of the residue from 90% ethanol gives 6.56 g of colorless crystals. Yield, 82%, melting point: 168°C.

WHAT WE CLAIM IS:—

1. A method for producing 1-(tetrahydro-2-furyl)-5-fluorouracil, which comprises heating 5-fluorouracil with 2,3-dihydrofuran under superatmospheric pressure to yield 1-(tetrahydro-2-furyl)-5-fluorouracil.
2. A method as claimed in Claim 1 wherein the said reactants are heated in a closed vessel.
3. A method as claimed in Claim 1 or Claim 2 wherein the reaction temperature is between 100° and 250°C.
4. A method as claimed in Claim 3 wherein the reaction temperature is between 150° and 200°C.
5. A method as claimed in Claim 4 wherein the reaction temperature is in the range 165° to 185°C.
6. A method as claimed in any one of the preceding claims wherein the reaction is carried out with a molar excess of 2,3-dihydrofuran over 5-fluorouracil.
7. A method as claimed in Claim 6 wherein the molar ratio of 2,3-dihydrofuran to 5-fluorouracil is in the range 2:1 to 8:1.
8. A method as claimed in Claim 7 wherein said ratio is in the range 4:1 to 100:1.
9. A method as claimed in any one of the preceding claims wherein the reaction is carried out in the presence of a solvent.
10. A method as claimed in Claim 9 wherein the solvent is an amide, ether, tertiary amine, ester or a mixture of two or more of said solvents.
11. A method as claimed in Claim 10 wherein the solvent is pyridine or N,N-dimethylformamide.
12. A method as claimed in any one of the preceding claims wherein the reaction between the said reactants is stopped as soon as 1,3-bis-(tetrahydro-2-furyl)-5-fluorouracil is detected by thin layer chromatography on silica gel.
13. A method as claimed in Claim 1 and substantially as hereinbefore described with reference to any one of Examples 1, 2 and 3.
14. A method as claimed in any one of Claims 1 to 12 wherein the 1-(tetrahydro-2-furyl)-5-fluorouracil is in admixture with 1,3-bis-(tetrahydro-2-furyl)-5-fluorouracil.
15. 1-(tetrahydro-2-furyl)-5-fluorouracil whenever prepared by a method as claimed in any one of the preceding claims.



16. A method for producing 1,3-bis-(tetrahydro-2-furyl)-5-fluorouracil which comprises heating 5-fluorouracil with 2,3-dihydrofuran under superatmospheric pressure to yield 1,3-bis-(tetrahydro-2-furyl)-5-fluorouracil.
17. A method as claimed in Claim 16 wherein the reaction temperature is between 150° and 250°C.
18. A method as claimed in Claim 16 or Claim 17 wherein the reaction is carried out in the presence of a solvent.
19. A method as claimed in Claim 18 wherein the solvent is pyridine or N,N-dimethylformamide.
20. A method as claimed in either of Claims 18 and 19 wherein the solvent is employed in a proportion not exceeding 10 times (v/w) the amount of 5-fluorouracil.
21. A method as claimed in any one of Claims 16 to 20 wherein the 2,3-dihydrofuran is present in an amount of not less than 5 equivalents per equivalent of 5-fluorouracil.
22. A method as claimed in Claim 21 wherein the 2,3-dihydrofuran is present in an amount of 5 to 10 equivalents per equivalent of 5-fluorouracil.
23. A method as claimed in any one of Claims 16 to 21 wherein the said reactants are heated in a closed vessel.
24. A method as claimed in Claim 23 and substantially as described in any one of Examples 4, 5 and 6.
25. A method as claimed in any one of Claims 16 to 22 wherein the 1,3-bis-(tetrahydro-2-furyl)-5-fluorouracil is in admixture with 1-(tetrahydro-2-furyl)-5-fluorouracil.
26. A method as claimed in Claim 23 wherein the 1,3-bis-(tetrahydro-2-furyl)-5-fluorouracil is in admixture with 1-(tetrahydro-2-furyl)-5-fluorouracil.
27. 1,3-Bis-(tetrahydro-2-furyl)-5-fluorouracil whenever prepared by a method as claimed in any one of Claims 16 to 22 and 25.
28. 1,3-Bis-(tetrahydro-2-furyl)-5-fluorouracil whenever prepared by a method as claimed in any one of Claims 23, 24 and 26.
29. A method of producing 1-(tetrahydro-2-furyl)-5-fluorouracil which comprises subjecting 1,3-bis-(tetrahydro-2-furyl)-5-fluorouracil as claimed in Claim 27 to solvolysis under non-acidic conditions.
30. A method as claimed in Claim 29 wherein the reaction product of a method as claimed in any one of Claims 16 to 22 and 25 is subjected to solvolysis without separation of any 1-(tetrahydro-2-furyl)-5-fluorouracil.
31. A method as claimed in Claim 29 or Claim 30 wherein the solvolysis is carried out by heating with water.
32. A method as claimed in Claim 29 or 30 wherein the solvolysis is carried out by heating with a water-containing solvent.
33. A method as claimed in Claim 32 wherein the solvent is aqueous alcohol.
34. A method as claimed in Claim 33 wherein the aqueous alcohol contains 40 to 80% (v/v) alcohol and the solvolysis is carried out at a temperature from 50°C to the reflux temperature of the reaction system.
35. 1-(tetrahydro-2-furyl)-5-fluorouracil whenever prepared by a process as claimed in either of Claims 29 and 30.
36. A method of producing 1-(tetrahydro-2-furyl)-5-fluorouracil which comprises subjecting 1,3-bis-(tetrahydro-2-furyl)-5-fluorouracil as claimed in Claim 28 to solvolysis under non-acidic conditions.
37. A method as claimed in Claim 36 wherein the resultant product of a method as claimed in any one of Claims 23, 24 and 26 is subjected to solvolysis without separation of any 1-(tetrahydro-2-furyl)-5-fluorouracil.
38. A method as claimed in Claim 36 or Claim 37 wherein the solvolysis is carried out by heating with water.
39. A method as claimed in Claim 36 or Claim 37 wherein the solvolysis is carried out by heating with a water-containing solvent.
40. A method as claimed in Claim 39 wherein the solvent is aqueous alcohol.
41. A method as claimed in Claim 40 wherein the aqueous alcohol contains 40 to 80% (v/v) alcohol and the solvolysis is carried out at a temperature from 50°C to the reflux temperature of the reaction system.
42. A method as claimed in Claim 36 and substantially as described in Example 6.
43. 1-(tetrahydro-2-furyl)-5-fluorouracil whenever prepared by a process as claimed in either of Claims 36 and 37.
44. A method as claimed in Claim 16 wherein the reaction temperature is between 125° and 180°C.
45. A method as claimed in Claim 44 wherein the reaction temperature is in the range 135° to 165°C.
46. A method as claimed in Claim 44 or Claim 45, wherein the reaction is carried out in the presence of an organic solvent which is free of active hydrogen.
47. A method as claimed in Claim 46 wherein the solvent is pyridine or N,N-dimethylformamide.
48. A method as claimed in either of Claims 46 and 47 wherein the solvent is employed in a proportion not exceeding 15 times the amount of 5-fluorouracil.
49. A method as claimed in Claim 48 wherein the solvent is employed in a proportion of 8—1.5 times (v/w) the amount of 5-fluorouracil.
50. A method as claimed in any one of 130

14



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6

Claims 44 to 49 wherein the 2,3-dihydrofuran is present in an amount of not less than 3 equivalents per equivalent of 5-fluorouracil.

51. A method as claimed in Claim 50 wherein the 2,3-dihydrofuran is present in an amount of 3.5 to 10 equivalents per equivalent of 5-fluorouracil.

52. A method as claimed in any one of Claims 44 to 51 wherein the said reactants are heated in a closed vessel.

53. A method as claimed in Claim 52 and substantially as described in any one of Examples 7, 8 and 9.

54. A method as claimed in any one of Claims 44 to 51 wherein the 1,3-bis-(tetrahydro-2-furyl)-5-fluorouracil is in admixture with 1-(tetrahydro-2-furyl)-5-fluorouracil.

55. A method as claimed in Claim 52 wherein the 1,3-bis-(tetrahydro-2-furyl)-5-fluorouracil is in admixture with 1-(tetrahydro-2-furyl)-5-fluorouracil.

56. 1,3 - Bis - (tetrahydro - 2 - furyl)-5-fluorouracil whenever prepared as claimed in any one of Claims 44 to 51 and 54.

57. 1,3 - Bis - (tetrahydro - 2 - furyl)-5-fluorouracil whenever prepared by a method as claimed in any one of Claims 52, 53 and 55.

58. A method of producing 1 - (tetrahydro-2-furyl)-5-fluorouracil which comprises subjecting 1,3-bis-(tetrahydro-2-furyl)-5-fluorouracil as claimed in Claim 56 to solvolysis under non-acidic conditions.

59. A method as claimed in Claim 58 wherein the reaction product of a method as claimed in any one of Claims 44 to 51 and 54 is subjected to solvolysis without separation of any 1-(tetrahydro-2-furyl)-5-fluorouracil.

60. A method as claimed in Claim 58 or Claim 59 wherein the solvolysis is carried out by heating with water.

61. A method as claimed in Claim 58 or Claim 59 wherein the solvolysis is carried out by heating with a water-containing solvent.

62. A method as claimed in Claim 61 wherein the solvent is aqueous alcohol.

63. A method as claimed in any one of Claims 58 to 62 wherein the solvolysis is carried out at 40° to 80°C.

64. 1 - (Tetrahydro - 2 - furyl) - 5-fluorouracil whenever prepared by a process as claimed in any one of Claims 58 to 63.

65. A method of producing 1-(tetrahydro-2-furyl)-5-fluorouracil which comprises subjecting 1,3-bis-(tetrahydro-2-furyl)-5-fluorouracil as claimed in Claim 57 to solvolysis under non-acidic conditions.

66. A method as claimed in Claim 65 wherein the reaction product of a method as claimed in any one of Claims 52, 53 and 55 is subjected to solvolysis without separation of any 1-(tetrahydro-2-furyl)-5-fluorouracil.

tion of any 1-(tetrahydro-2-furyl)-5-fluorouracil.

67. A method as claimed in Claim 65 or Claim 66 wherein the solvolysis is carried out by heating with water.

68. A method as claimed in Claim 65 or Claim 66 wherein the solvolysis is carried out by heating with a water-containing solvent.

69. A method as claimed in Claim 68 wherein the solvent is aqueous alcohol.

70. A method as claimed in any one of Claims 65 to 69 wherein the solvolysis is carried out at 40° to 80°C.

71. A method as claimed in Claim 65 and substantially as described in Example 9.

72. 1 - (Tetrahydro - 2 - furyl) - 5-fluorouracil whenever prepared by a process as claimed in any one of Claims 65 to 71.

73. 1 - (Tetrahydro - 2 - furyl) - 5-fluorouracil whenever prepared by a process as claimed in any one of Claims 31 to 34.

74. 1 - (Tetrahydro - 2 - furyl) - 5-fluorouracil whenever prepared by a process as claimed in any one of Claims 38 to 42.

75. A method as claimed in any one of Claims 16, 18 to 23, 25 and 26 wherein the reaction temperature is between 100° and 150°C.

76. 1,3 - Bis (Tetrahydro - furyl) - 5-fluorouracil whenever prepared by a method as claimed in Claim 75.

77. A method as claimed in any one of Claims 29 to 34 wherein the 1,3-bis-(tetrahydro-2-furyl)-5-fluorouracil is as claimed in Claim 76.

78. A method as claimed in any one of Claims 16, 18, 19, 21, 22, 23, 25, 26 and 75 wherein the reaction is carried out in the presence of an amount of solvent not exceeding 15 (times (v/w) the amount of 5-fluorouracil.

79. A method as claimed in Claim 81 wherein the said proportion is 8 to 1.5 times the amount of 5-fluorouracil.

80. 1,3 - Bis - (tetrahydro - 2 - furyl)-5-fluorouracil whenever prepared by a method as claimed in Claim 78 or 79.

81. A method as claimed in any one of Claims 29 to 34 wherein the 1,3-bis-(tetrahydro-2-furyl)-5-fluorouracil is as claimed in Claim 80.

82. A method as claimed in any one of Claims 16 to 20, 23, 25, 26, 75 and 78 wherein the 2,3-dihydrofuran is present in an amount of not less than 3 equivalents per equivalent of 5-fluorouracil.

83. 1,3 - Bis - (tetrahydro - 2 - furyl)-5-fluorouracil whenever prepared by a method as claimed in Claim 82.

84. A method as claimed in any one of Claims 29 to 34 wherein the 1,3-bis-(tetrahydro-2-furyl)-5-fluorouracil is as claimed in Claim 80.

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hydro-2-furyl)-5-fluorouracil is as claimed in Claim 83.

5 85. A method as claimed in any one of Claims 16 to 21, 23, 25, 26, 75, 78 and 82 wherein the 2,3-dihydrofuran is present in an amount of 3.5 to 10 equivalents per equivalent of 5 fluorouracil.

10 86. 1,3 - Bis - (tetrahydro - 2 - furyl)-5-fluorouracil whenever prepared by a method as claimed in Claim 85.

87. A method as claimed in any one of Claims 29 to 34 wherein the 1,3-bis-(tetrahydro-2-furyl)-5-fluorouracil is as claimed in Claim 86.

15 88. A method as claimed in any one of Claims 29 to 33 and 36 to 40 wherein the solvolysis is carried out at 40° to 80°C.

20 89. 1 - (Tetrahydro - 2 - furyl) - 5-fluorouracil whenever prepared by a method as claimed in any one of Claims 77, 81, 84, 87 to 88.

90. A process for preparation of 1-(2-tetrahydrofuryl)-5-fluorouracil which com-

prises reacting 5-fluorouracil with 2,3-dihydrofuran at a temperature up to 200°C and under superatmospheric pressure. 25

91. A process as claimed in Claim 90 wherein 2,3-dihydrofuran is used in an amount of up to 4.0 mols per mol of 5-fluorouracil. 30

92. A process as claimed in Claim 90 or Claim 91 wherein the reaction is carried out in a polar solvent selected from dimethylformamide, dimethylacetamide, hexamethylphosphoramide, pyridine, triethylamine, tetrahydrofuran, dioxane or mixtures thereof. 35

93. 1 - (2 - Tetrahydrofuryl) - 5 - fluoro-uracil whenever prepared by a process as claimed in any one of Claims 90 to 92. 40

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