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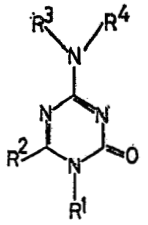
(54) A PROCESS FOR PREPARING 1-GLYCOSYL-5-AZACYTOSINES

(71) We, CESKOSLOVENSKA AKADEMIE VED, a Corporation organised and existing under the laws of Czechoslovakia of No. 3 Narodni, Prague 1, Czechoslovakia, 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 preparing 1 - glycosyl - 5 - azacytosines.

More particularly this invention relates to a process for preparing 1 - glycosyl - 5 - azacytosines of the general formula I:



(1)

wherein R^1 designates a glycosyl residue, R^2 designates a hydrogen atom or an alkyl group having from 1 to 4 carbon atoms and R^3 and R^4, which are identical or different, designate hydrocarbon atoms, alkyl groups having from 1 to 4 carbon atoms or aralkyl groups having from 7 to 10 carbon atoms.

Two compounds of the above type show significant biological effects, namely, 1 - β - D - ribofuranosyl - 4 - amino - 1, 2 - dihydro - 1, 3, 5 - triazin - 2 - one (or 5 - azacytidine) and 1 - (2 - deoxy - β - D - ribofuranosyl) - 4 - amino - 1, 2 - dihydro - 1, 3, 5 - triazine - 2 - one (or 5 - aza - 2' - deoxycytidine). 5 - Azacytidine, a pyrimidine antimetabolite, in low concentrations inhibits bacterial growth and exhibits a high antileukemic effect with mice. In the case of *V. faba meristem*, 5-azacytidine causes a mitosal inhibition and chromosomal aberrations. A mutagenic effect of 5 - azacytidine has been reported. Furthermore, 5 - azacytidine suppresses the formation of inductive enzymes in mammalian cells and regeneration of rat liver after heptatectomy and, on the other hand, protects mice against the effects of X-rays.

5 - Aza - 2' - deoxycytidine, similarly to 5 - azacytidine, suppresses considerably the formation of experimental leukemia and shows, even at low concentrations, significant bacteriostatic properties.

A similar biological activity can be expected also with some further 1 - glycosyl - 5 - azacytosines.

The preparation of 1 - glycosyl - 5 - azacytosines was previously reported in British patent specifications Nos. 1,046,181 and 1,050,899. Per-acylglycosyl isocyanates are added to O - alkylisoureas or S - alkyl - isothioureas to produce the corresponding peracylglycosylisobiurets or peracylglycosyliso - thiobiurets. Condensation of the latter compounds with ortho-esters of aliphatic acids affords 1 - per - acylglycosyl - 4 - alkoxy - 1, 2 - dihydro - 1, 3, 5 - triazin - 2 - ones or 1 - per - acylglycosyl - 4 - alkylthio - 1, 2 - dihydro - 1, 3, 5 - triazin - 2 - ones, the treatment of which with ammonia or amines in alcohols produces the 1 - glycosyl - 5 - azacytosines. One disadvantage of this procedure is that the reaction of ammonia or amines with 1 - per - acylglycosyl - 4 - alkoxy (or alkylthio) - 1, 2 - dihydro - 1, 3, 5 - triazine - 2 - ones usually produces the required 1 - glycosyl - 5 - azacytosines in very low yields because of the instability of the aforementioned intermediates under amination conditions. Furthermore, the 4 - alkylthio derivatives are less stable than the corresponding 4-alkoxy derivatives and their reactivity towards ammonia or amines is very low.

An object of the present invention is to

[*Price 25p*]

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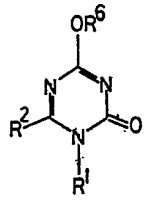
obviate or mitigate the aforesaid disadvantages.

We have discovered that the free 1 - glycosyl - 4 - alkoxy - 1, 2 - dihydro - 1, 3, 5 - triazine - 2 - ones are much more stable than their per-acyl derivatives. The amination of 1 - glycosyl - 4 - alkoxy - 1, 2 - dihydro - 1, 3, 5 - triazine - 2 - ones is very rapid and affords high yields of the required 1 - glycosyl - 5 - azacytosines.

The free 1 - glycosyl - 4 - alkoxy - 1, 2 - dihydro - 1, 3, 5 - triazine - 2 - ones are readily accessible by alcoholysis of the corresponding per-acyl derivatives as well as by alcoholysis of 1 - per - acylglycosyl - 4 - alkylthio - 1, 2 - dihydro - 1, 3, 5 - triazin - 2 - ones which, in this special case, is accompanied by a conversion of the 4 - alkylthio group to the 4 - alkoxy group.

According to the present invention there is provided a process for preparing a 1 - glycosyl - 5 - azacytosine of the general formula I defined above comprising effecting reaction of a 1 - glycosyl - 4 - alkoxy - 1, 2 - dihydro - 1, 3, 5 - triazin - 2 - one of the general formula III



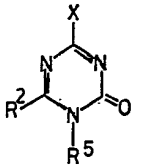
(3)

wherein R^1 and R^2 are as defined for general formula I and R^6 is an alkyl group having from 1 to 6 carbon atoms, with ammonia or an amine of the general formula IV

$$R^3—NH—R^4 \qquad IV$$

wherein R^3 and R^4 are as defined for general formula I.

The alkoxytriazinone of the general formula III may be prepared by effecting reaction of an alkali metal alkoxide having from 1 to 6 carbon atoms with a compound of the general formula II

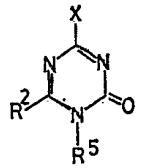


(2)

wherein R^2 is as defined for general formula I, R^5 is a peracylglycosyl group wherein the acyl group has from 2 to 10 carbon atoms and X is an alkoxy or alkylthio group having from 1 to 4 carbon atoms.

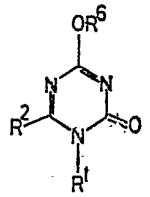
Conversion of the alkoxytriazinone or the alkylthiotriazinone of the general formula II to the 1 - glycosyl - 5 - azacytosine of the general formula I preferably is performed without isolation of the alkoxytriazinone of the general formula III.

Hence further according to the present invention there is provided a process for the preparation of a 1 - glycosyl - 5 - aza - cytosine of the general formula I, comprising effecting reaction of a compound of the general formula II



(2)

wherein R^2 is as defined for general formula I, R^5 designates a per - acylglycosyl residue wherein the acyl group has from 2 to 10 carbon atoms and X designates an alkoxy or alkylthio group having from 1 to 4 carbon atoms, with an alkali metal alkoxide having from 1 to 6 carbon atoms, preferably in methanol, thus effecting the formation of a 1 - glycosyl - 4 - alkoxy - 1,2 - dihydro - 1,3,5 - triazin - 2 - one of the general formula III



(3)

wherein R^1 and R^2 are as defined for general formula I and R^5 designates an alkyl group having from 1 to 6 carbon atoms, and effecting reaction of the alkoxytriazinone of the general formula III with ammonia or an amine of the general formula IV

$$R^3—NH—R^4 \qquad IV$$

wherein R^3 and R^4 are as defined above for general formula I.

The reaction of compounds of the general formula II with the alkali metal alkoxide preferably is performed at room temperature, preferably in an alkanol containing from 1 to 6 carbon atoms, and more preferably in methanol. This reaction preferably is carried out in the absence of atmospheric moisture. In the case of alkylthio derivatives, optimum yields are obtained with the use of 1.2 moles of the alkoxide per 1 mole of the starting compound.

The reaction of the alkoxytriazinone of the general formula III with ammonia or an amine of the general formula IV preferably is performed at room temperature, preferably in the medium of an alkanol containing

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from 1 to 6 carbon atoms, and more preferably in methanol.

The conversion of the compound of the general formula II to the 1 - glycosyl - 5 - azacytosine of the general formula I may be performed in one step, namely, by the simultaneous action of the alkali metal alkoxide and of an alkanol solution of ammonia or an amine of the general formula IV.

The invention will be illustrated further by the following examples, although it is not limited thereto.

5 - Azacytidine
(1 - β - D - Ribofuranosyl - 4 - amino - 1, 2 - dihydro - 1, 3, 5 - triazin - 2 - one)

EXAMPLE 1

A mixture of 1 - (2, 3, 5 - tri - O - benzoyl - β - D - ribofuranosyl) - 4 - methylthio - 1, 2 - dihydro - 1, 3, 5 - triazin - 2 - one 0.5875 g), absolute methanol (5 ml) and a normal methanolic sodium methoxide solution (1.2 ml) is stirred at room temperature with the exclusion of atmospheric moisture (a guard tube filled with potassium hydroxide pellets is fitted to the reaction vessel). The starting compound passes into solution in the course of 5 minutes. The resulting solution is allowed to stand at room temperature for 45 minutes and then the cations are removed by passage of the solution through a column packed with 10 ml of a weakly acidic cation exchange resin in the H^+ form prewashed with water and methanol. The methanolic effluent (60 ml) is evaporated under reduced pressure at 30° C, the residue is dissolved in methanol (20 ml) and the solution once again is evaporated. The residual crude crystalline 1 - β - D - ribo - furanosyl - 4 - methoxy - 1, 2 - dihydro - 1, 3, 5 - triazin - 2 - one is dissolved (without any additional purification) in a 10% solution of dry ammonia in absolute methanol (4 ml) and the whole reaction mixture is allowed to stand in a stoppered flask for 30 minutes at room temperature (the product begins to deposit in the course of 5 minutes) and for 12 hours in a refrigerator at −10° C. The resulting 5 - azacytidine is collected with suction, washed with methanol and dried under reduced pressure. A yield of 0.216 g (88.6%) of 5 - azacytidine, m.p. 232—234° C (decomposition), is obtained.

EXAMPLE 2

A mixture of 1 - (2, 3, 5 - tri - O - benzoyl - β - D - ribofuranosyl) - 4 - methyl - thio - 1, 2 - dihydro - 1, 3, 5 - triazin - 2 - one (0.5875 g), a 10% solution of dry ammonia in methanol 4 ml) and a normal methanolic sodium methoxide solution (1.2 ml) is stirred at room temperature with the exclusion of atmospheric moisture (a guard tube filled with potassium hydroxide pellets is fitted to the reaction vessel) until the starting compound dissolves (3 minutes). The resulting solution is allowed to stand for 45 minutes at room temperature after 30 minutes, the product begins to deposit) and for 12 hours in a refrigerator at −10° C. The crystals are collected with suction, washed with methanol and dried under reduced pressure. A yield of 0.162 g (66.4%) of 5 - aza - cytidine, m.p. 232—234° C (decomposition), is obtained.

EXAMPLE 3

A mixture of 1 - (2, 3, 5 - tri - O - benzoyl - β - D - ribofuranosyl) - 4 - methoxy - 1, 2 - dihydro - 1, 3, 5 - triazin - 2 - one (0.5715 g), absolute methanol (5 ml) and a normal methanolic sodium methoxide solution (1 ml) is stirred at room temperature with the exclusion of atmospheric moisture (a guard tube filled with potassium hydroxide pellets is fitted to the reaction vessel) until the starting compound dissolves (5 minutes), and the resulting solution is allowed to stand for one hour at room temperature and then is processed as in Example 1. A yield of 0.219 g (89.7%) of 5 - azacytidine, m.p. 232—234° C (decomposition), is obtained.

EXAMPLE 4

A mixture of 1 - (2, 3, 5 - tri - O - benzoyl - β - D - ribofuranosyl) - 4 - meth - oxy - 1, 2 - dihydro - 1, 3, 5 - triazin - 2 - one (0.5715 g), at 10% solution of dry ammonia in methanol (4 ml) and a normal methanolic sodium methoxide solution (1 ml) is stirred at room temperature with the exclusion of atmospheric moisture (a guard tube filled with potassium hydroxide pellets is fitted to the reaction vessel) until the starting compound dissolves (5 minutes). Work-up of the resulting solution is performed as in Example 2. A yield of 0.174 g (71.3%) of 5 - azacytidine, m.p. 232—234° C (decomposition), is obtained.

5 - Aza - 2′ - deoxycytidine
1 - (2 - Deoxy - β - D - ribofuranosyl) - 4 - amino - 1, 2 - dihydro - 1, 3, 5 - triazine - 2 - one

EXAMPLE 5

A mixture of 1 - (3, 5 - di - O - *p* - toluyl - 2 - deoxy - β - D - ribofuranosyl) - 4 - methylthio - 1, 2 - dihydro - 1, 3, 5 - triazin - 2 - one (0.4956 g), absolute methanol (10 ml) and a normal methanolic sodium methoxide solution (1.2 ml) is stirred magnetically at room temperature with the exclusion of atmospheric moisture (a guard tube filled with potassium hydroxide pellets is fitted to the reaction vessel) for 2 hours and 45 minutes (after 2 hours, the starting compound dissolves). The cations are then removed by passing the resulting solution

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through a column of a weakly acidic cation exchange resin (10 ml) in the H^+ form (prewashed with water and methanol). The methanolic effluent is evaporated under reduced pressure at 30° C, the residue is dissolved in methanol (10 ml) and the solution once more is evaporated. The resulting crude viscous 1 - (2 - deoxy - β - D - ribofuranosyl) - 4 - methoxy - 1, 2 - dihydro - 1, 3, 5 - triazine - 2 - one is dissolved in a 10% solution of dry ammonia in methanol (2 ml) and the resulting reaction mixture is allowed to stand in a stoppered flask for 30 minutes at room temperature (after 15 minutes, the crystalline product begins to separate) and for 12 hours in a regrigerator at −10° C. The crystals are collected, washed with methanol and dried under reduced pressure. A yield of 0.180 g (79%) of 5 - aza - 2′ - deoxycytidine, m.p. 196—198° C (resolidification), is obtained.

EXAMPLE 6

A mixture of 1 - (3, 5 - di - O - *p* - toluyl - 2 - deoxy - β - D - ribofuranosyl) - 4 - methylthio - 1, 2 - dihydro - 1, 3, 5 - triazine - 2 - one (0.4956 g), a 10% solution of dry ammonia in methanol (4 ml) and a normal methanolic sodium methoxide solution (1.2 ml) is stirred magnetically at room temperature with the exclusion of atmospheric moisture (a guard tube filled with potassium hydroxide pellets is fitted to the reaction vessel) until the starting compound dissolves (45 minutes). The resulting solution is allowed to stand at room temperature for 1 hour (during this period of time, the crystalline product begins to separate) and then in a refrigerator at −10° for an additional 12 hours. The crystals are collected with suction, washed with methanol and dried under reduced pressure. A yield of 0.132 g (58%) of 5 - aza - 2′ - deoxycytidine, m.p. 198—199° C (resolidification), is obtained.

EXAMPLE 7

A mixture of 1 - (3, 5 - di - O - p - toluyl - 2 - deoxy - β - D - ribofuranosyl) - 4 - methoxy - 1, 2 - dihydro - 1, 3, 5 - triazine - 2 - one (0.4796 g), absolute methanol (10 ml) and a normal methanolic sodium methoxide solution (1 ml) is stirred magnetically at room temperautre with the exclusion of atmospheric moisture (a guard tube filled with potassium hydroxide pellets is fitted to the reaction vessel) until the starting compound dissolves (45 minutes). The reaction mixture then is processed as described in Example 6. A yield of 0.120 g (52.7%) of 5 - azo - 2′ - deoxycytidine, m.p. 198—199° C (resolidification), is obtained.

EXAMPLE 8

A mixture of 1 - (3, 5 - di - O - *p* - toluyl - 2 - deoxy - β - D - ribofuranosyl - 4 - methoxy - 1, 2 - dihydro - 1, 3, 5 - triazine - 2 - one (0.4796 g) a 10% solution of dry ammonia in methanol (4 ml) and a normal methanolic sodium methoxide solution (1.0 ml) is stirred magnetically at room temperature with the exclusion of atmospheric moisture (a guard tube filled with potassium hydroxide pellets is fitted to the reaction vessel) until the starting compound dissolves (45 minutes). The reaction mixture then is processed as described in Example 6. A yield of 0.120 g (52.7%) of 5 - aza - 2′ - deoxy - cytidine, m.p. 198—199° C (resolidification), is obtained.

1 - β - D - Ribofuranosyl - 4 - methoxy - 1, 2 - dihydro - 1, 3, 5 - triazine - 2 - one

EXAMPLE 9

A mixture of 1 - (2, 3, 5 - tri - O - benzoyl - β - D - ribofuranosyl) - 4 - methyl - thio - 1, 2 - dihydro - 1, 3, 5 - triazine - 2 - one (0.5875 g), absolute methanol (5 ml) and a normal methanolic sodium methoxide solution (1.2 ml) is stirred at room temperature with the exclusion of atmospheric moisture (a guard tube filled with potassium hydroxide pellets is fitted to the reaction vessel) until the starting compound dissolves (5 minutes). The resulting solution is allowed to stand at room temperature for an additional 40 minutes and is processed as described in Example 1. The crude crystalline product is recrystallised from absolute methanol. A yield of 0.210 g (81%) of 1 - β - D - ribofuranosyl - 4 - methoxy - 1, 2 - dihydro - 1, 3, 5 - triazin - 2 - one, m.p. 177—179° C, is obtained.

1 - β - D - Ribofuranosyl - 4 - methylamino - 1, 2 - dihydro - 1, 3, 5 - triazin - 2 - one

EXAMPLE 10

A mixture of 1 - β - D - ribofuranosyl - 4 - methoxy - 1, 2 - dihydro - 1, 3, 5 - triazin - 2 - one (0.259 g) and a 7% solution of dry methylamine in absolute methanol (2 ml) is stirred at room temperature with the exclusion of atmospheric moisture (a guard tube filled with potassium hydroxide pellets is fitted to the reaction vessel) for 5 minutes, kept at room temperature for an additional 10 minutes and finally in a refrigerator at −10° C for 15 minutes. The crystals are collected with suction, washed with ice-cool methanol and dried under reduced pressure. A yield of 0.210 g (81.4%) of 1 - β - D - ribofuranosyl - 4 - methylamino - 1, 2 - dihydro - 1, 3, 5 - triazine - 2 - one, m.p. 148—150° C., is obtained.

1 - β - D - Ribofuranosyl - 4 - dimethyl - amino - 1, 2 - dihydro - 1, 3, 5 - triazine - 2 - one

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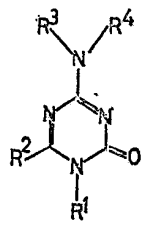
EXAMPLE 11

A mixture of 1 - β - D - ribofuranosyl - 4 - methoxy - 1, 2 - dihydro - 1, 3, 5 - triazin - 2 - one (0.259 g) and a 7% solution of dry dimethylamine in absolute methanol (2 ml) is stirred at room temperature with the exclusion of atmospheric moisture (potassium hydroxide guard tube) for 5 minutes, kept at the same temperature for additional 15 minutes and evaporated under reduced pressure at 30° C. The residue is coevaporated with absolute methanol (5 ml) and finally dissolved in absolute ethanol (1 ml). The solution is cooled and stirred with a sharp edged rod to deposit crystals which are kept in a refrigerator at —10° C overnight, collected with suction, washed with ethanol and dried under reduced pressure. A yield of 0.216 g (79.4%) of 1 - β - D - ribofuranosyl - 4 - dimethyl - amino - 1, 2 - dihydro - 1, 3, 5 - triazin - 2 - one, m.p. 128—130° C, is obtained.

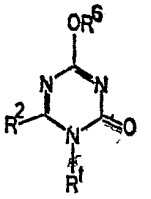
WHAT WE CLAIM IS:—

1. A process for preparing 1 - glycosyl - 5 - azacytosine of the general formula I



(1)

wherein R^1 designates a glycosyl residue, R^2 designates a hydrogen atom or an alkyl group having from 1 to 4 carbon atoms and R^3 and R^4, which are identical or different, designate hydrogen atoms, alkyl groups having from 1 to 4 carbon atoms or aralkyl groups having from 7 to 10 carbon atoms, comprising effecting reaction of a 1 - glycosyl - 4 - alkoxy - 1, 2 - dihydro - 1, 3, 5 - triazin - 2 - one of the general formula III



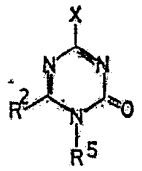
(3)

wherein R^1 and R^2 are as defined for general formula I and R^6 is an alkyl group having from 1 to 6 carbon atoms, with ammonia or an amine of the general formula IV

$$R^3—NH—R^4 \qquad IV$$

wherein R^3 and R^4 are as defined for general formula I.

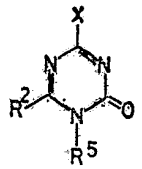
2. A process as claimed in claim 1, wherein the alkoxytriazinone of the general formula III is prepared by effecting reaction of an alkali metal alkoxide having from 1 to 6 carbon atoms with a compound of the general formula II



(2)

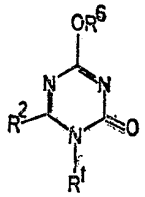
wherein R^2 is as defined for general formula I, R^5 is a per-acylglycosyl group wherein the acyl group has from 2 to 10 carbon atoms and X is an alkoxy or alkylthio group having from 1 to 4 carbon atoms.

3. A process for the preparation of a 1 - glycosyl - 5 - azacytosine of the general formula I defined in claim 1, comprising effecting reaction of a compound of the general formula II



(2)

wherein R^2 is as defined in claim 1 for general formula I, R^5 designates a per-acylglycosyl residue wherein the acyl group has from 2 to 10 carbon atoms and X designates an alkoxy or alkylthio group having from 1 to 4 carbon atoms, with an alkali metal alkoxide having from 1 to 6 carbon atoms, thus effecting the formation of a 1 - glycosyl - 4 - alkoxy - 1, 2 - dihydro - 1, 3, 5 - triazin - 2 - one of the general formula III



(3)

wherein R^1 and R^2 are as defined in claim 1 for general formula I and R^6 designates an alkyl group having from 1 to 6 carbon atoms, and effecting reaction of the alkoxytriazinone of the general formula III with ammonia or an amine of the general formula formula IV

$$R^3—NH—R^4 \qquad IV$$

wherein R^3 and R^4 are as defined in claim 1 for general formula I.

4. A process as claimed in Claim 2 or

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claim 3 wherein the reaction between the compound of general formula II and the alkali metal alkoxide is carried out in a medium of an alkanol having from 1 to 6 carbon atoms.

5. A process as claimed in any one of claims 1 to 4 wherein the reaction of the alkoxytriazinone of general formula III with the ammonia or amine of general formula IV is carried out in a medium of an alkanol having from 1 to 6 carbon atoms.

6. A process as claimed in claim 4 or claim 5, wherein the alkanol is methanol.

7. A process as claimed in any one of claims 2, 3 and 4 or in claim 5 or claim 6 as appendant to any one of claims 2, 3 and 4, wherein in the compound of general formula II X is an alkylthio group and the molar ratio of the compound of the general formula II to the alkali metal alkoxide is 1:1.2.

8. A process as claimed in any one of the preceding claims, wherein the reaction of the alkoxytriazinone of general formula III with the ammonia or amine of general formula IV is performed at room temperature.

9. A process as claimed in any one of claims 2, 3 and 4, or in any one of claims 5 to 8 as appendant to any one of claims 2, 3 and 4, wherein the reaction of the compound of the general formula II with the alkali metal alkoxide is carried out at room temperature.

10. A process as claimed in claim 9, wherein the reaction of the compound of the general formula II with the alkali metal alkoxide is carried out in the absence of atmospheric moisture.

11. A process as claimed in any one of claims 2, 3 and 4, or in any one of the claims 5 to 10 as as appendant to any one of the claims 2, 3 and 4, wherein conversion of the compound of general formula II to the 1 - glycosyl - 5 - azacytosine of general formula I is carried out in one step by the simultaneous action of the alkali metal alkoxide and an alkanol solution of the ammonia or amine of general formula IV.

12. A process for preparing a 1 - glycosyl - 5 - azacytosine according to claim 1, substantially as hereinbefore described.

13. A process for preparing a 1 - glycosyl - 5 - azacytosine according to claim 3, substantially as hereinbefore described.

14. A process for the preparation of a 1 - glycosyl - 5 - azacytosine as described in any one of the Examples 1 to 9.

15. A process for the preparation of a 1 - glycosyl - 5 - azacytosine according to Example 10 or Example 11.

16. A 1 - glycosyl - 5 - azacytosine whenever prepared by the process claimed in any one of Claims 1 to 15.

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