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For two-letter codes and other abbreviations, refer to the “Guidance Notes on Codes and Abbreviations” appearing at the beginning of each regular issue of the PCT Gazette.

Title: PROCESS FOR THE PREPARATION OF RIBAVIRIN

Abstract: A process for the preparation of ribavirin on an industrial scale is described which comprises the reaction of glycosylation of 3-substituted triazoles in the presence of a Lewis acid. Said process comprises: (a) the reaction of a triazole of the formula (I) (see enclosed paper copy) with a protected ribofuranose of the formula (II) (see enclosed paper copy); (b) the removal of the Pg groups and, optionally, the conversion into a carboxyamide group of the R2 group of the compound obtained of the formula (III) (see enclosed paper copy).
PROCESS FOR THE PREPARATION OF RIBAVIRIN

Ribavirin, or 1-β-D-ribofuranosyl-1H-1,2,4-triazole-3-carboxyamide, is a known antiviral agent which is normally administered in association with alpha-2b interferon for treating patients affected by chronic hepatitis C.

TECHNICAL FIELD OF THE INVENTION

Ribavirin, (Merck Index 11th edition), the structure formula of which is given below,

\[
\begin{array}{c}
\text{HO} \\
\text{N} \\
\text{O} \\
\text{N} \\
\text{N} \\
\text{NH}_2 \\
\text{OH} \\
\text{OH}
\end{array}
\]

is generally prepared synthetically or fermentatively.

Particularly important among the processes for the synthetic preparation of ribavirin are the reactions of coupling of the preformed triazole nucleus with protected derivatives of sugar.

Such processes customarily provide for the activation of the preselected triazole nucleus with silylating agents and the subsequent reaction of the intermediate silyltriazole with the appropriate protected ribofuranose, according to the following general scheme:

25
SCHEME 1

wherein $R^1$ usually represents an O-acetyl group or a halogen, Pg is a group protecting the hydroxyl function, such as for example acetyl or benzoyl, $R^2$ is preferably a carboxymethoxy group and R represents alkyl, preferably methyl.

Ribavirin is then customarily obtained from the intermediate product III by de-protection of the sugar and conversion of the ester group into amide.

The sequence given above is described, for example, in J. Med. Chem. (1972), 15, 1150-1154.

However, the process has some drawbacks which make it of little applicative interest. In fact, in the glycosylation reaction in question there is obtained a raw product consisting of a 1:1 mixture of the desired product III, glycosylate on the triazole nitrogen in position 1, and of the glycosylate regioisomer on the nitrogen in position 2.

Consequently, not only is the final reaction yield significantly less than theory but, above all, the presence of large amounts of by-product necessitates the purification of the intermediate product IV by chromatography, with all the problems that said technique involves, especially in the case of industrial application.
Subsequently, the method of synthesis of ribavirin described above was the subject of numerous studies, from which different variants resulted, consisting essentially in the preparation in situ of the silylating agent \[\text{Rev. Roum. Chim.} \ (1987), \ 32, \ 329-333\], or in the use of a suitable acid catalyst. The latter reaction of silylation-glycosylation in the presence of acid catalysts, in particular Friedel-Crafts catalysts or Lewis acids, represents a standard methodology for preparing nucleosides \[\text{Chem. Ber.} \ (1981), \ 114, \ 1256-1268\] and, in various cases, this was applied specifically to the preparation of ribavirin.

To this end, Vorbrüggen et al., in \text{Chem. Ber.} \ (1981), \ 114, \ 1234-1255, studied the catalytic effect of silyltriflates with respect to the more conventional Lewis acids, such as, for example, SnCl\(_4\) in the condensation of trimethylsilyltriazoles to give ribavirin precursors.

Another example of specific application of said synthetic procedure, catalysed by HgBr\(_2\), is reported in \text{Nucl. Acid. Chem.} \ (1978), \ 1, \ 255-260.

Subsequently, an analogous synthesis of ribavirin, conducted in the presence of particular acid catalysts (CF\(_3\)CF\(_2\)OCF\(_3\)CF\(_2\)SO\(_3\)SiMe\(_3\)), was presented at a symposium \[\text{Nucleosides Nucleotides} \ (1991), \ 10, \ 619-20\].

From a general evaluation of the literature pertaining to the above-mentioned synthesis of ribavirin, starting from the first work in 1972 up to the more recent work of 1991, the teaching clearly emerges that, in order to prepare ribavirin through glycosylation of the triazole, it is necessary to carry out preliminary activation thereof by silylation.

In fact, the publications mentioned above are characterised by the constant use of the silyltriazole for the specific reaction of glycosylation in question while experimental activity was directed to evaluating the influence of the acid catalysis on the reaction yield and on the composition of the final raw product. Apart from the reaction of silylation-glycosylation discussed hitherto, the synthesis of ribavirin may be conducted according to an alternative, rather drastic, fusion procedure. For example, the same article cited previously \[\text{J. Med. Chem.} \ (1972), \ 15, \ 1150-1154\] describes the preparation of ribavirin by fusion at 160-165°C of a 1:1 mixture of 3-carbomethoxytriazole and tetra-acetyltrisibose, in the presence of bis(p-nitrophenyl)phosphate. This process, however, the condensation yield of which is remarkably around 78% after crystallisa-
tion, is difficultly usable on an industrial level because of the rather critical conditions, such as the absence of solvent and the high temperature.

A new process has now been found for the preparation of ribavirin on an industrial scale, under particularly simple conditions and with high yields.

With respect to the procedures described in the prior art, the present invention makes it possible to prepare the intermediate product of the formula IV advantageously without the preliminary silylation of the triazole system and with a purity such as to permit the direct use of the raw reaction product in the subsequent stages, thus avoiding tedious purification processes.

Moreover, the rather mild reaction conditions make the present process particularly suitable for industrial application.

**DESCRIPTION OF THE INVENTION**

The subject of the present invention is therefore a process for the preparation of ribavirin which comprises:

a) the reaction of a triazole of the formula

\[
\text{NH} \quad \text{N} \quad \text{NH} \\
\text{N} \quad \text{R}_2
\]

(I)

wherein \( R_2 \) represents a \( C_1-C_4 \) alkoxycarbonyl, arylalkoxycarbonyl, carboxyl, cyano, carboxyamide group with a protected ribofuranose of the formula

\[
\text{OPg} \quad \text{O} \quad \text{OPg} \\
\text{OPg} \quad \text{OPg} \\
\text{R}_1
\]

(II)
wherein Pg represents a group protecting the hydroxyl function and R₁ represents a leaving group selected from among C₁-C₄ acyloxy, aryloxy and halogen;

in the presence of a Lewis acid (IV); and

b) the removal of the Pg groups and, optionally, the conversion into a carboxyamide group of the R₂ group of the compound obtained of the formula

\[
\begin{align*}
\text{PgO} & \quad \text{N} \\
\text{OPg} & \quad \text{OPg} \\
\text{N} & \quad \text{N} \\
\text{R₂} &
\end{align*}
\]

wherein Pg and R₂ have the meanings given above, to give ribavirin

\[
\begin{align*}
\text{HO} & \quad \text{N} \\
\text{OH} & \quad \text{NH₂} \\
\text{O} & \quad \text{O} \\
\text{OH} &
\end{align*}
\]

The starting triazole of the formula I can generally be prepared according to known procedures, for example as described in US Patent 3798209. Preferred compounds of the formula I are those in which R₂ represents a C₁-C₄ alkoxy carbonyl group, particularly those in which R₂ represents a carbomethoxy group.

The protected ribofuranose of the formula II can be prepared from ribose according to conventional techniques for protection of sugars or is commercially available.

According to the present invention, Pg represents a group protecting the hydroxyl function. Suitable protecting groups are generally ethers, esters, ketals and all the
groups commonly used in the field of carbohydrate chemistry. See for example the
groups described by T. Green and P. Wuts in "Protecting Groups in Organic
Synthesis", chapter 2, page 17, 3rd Ed. (1999). Preferred protecting groups are acetyl,
benzoyl and benzyl groups. In this context, the acetyl group is particularly preferred.

The R₁ group of the compound of the formula II represents a leaving group selected
from among C₁₋₄ acyloxy, aryloxy and halogen, preferably chlorine, bromine and
C₁₋₄ acyloxy, and even more preferably acetoxy.

The present coupling reaction is conducted in the presence of a Lewis acid. For a
definition of the term "Lewis acid" see, for example, J. March in "Advanced Organic
Chemistry", page 227, 3rd Ed. (1985). According to the present invention, preferred
Lewis acids are AlCl₃, SbCl₅, BF₄, SnCl₄ and FeCl₃; SnCl₄ has proved particularly
advantageous.

Solvents usable in the present coupling reaction are generally halogenated hydro-
carbons, ethers or aromatic hydrocarbons. Halogenated hydrocarbons such as di-
chloromethane, chloroform, trichloroethane and higher homologues are preferred.
Dichloromethane is particularly preferred.

In the present invention, the triazole (I), the protected ribofuranose (II) and the Lewis
acid (IV) are generally used in a molar ratio of 1-2 moles of I and 1-1.5 moles of IV, for
every mole of II. The molar reaction ratios preferably used in the present process
provide for 1-1.2 moles of I and 1-1.1 moles of IV for every mole of II.

The coupling reaction according to the present invention is generally conducted at a
temperature of between -10°C and the reflux temperature of the solvent. Preferably,
the reaction mixture is cooled to a temperature of between +5 and +20°C during the
addition of the Lewis acid and is afterwards heated to reflux.

The product of the coupling reaction of formula III is customarily isolated according to
conventional procedures, known to an expert in the field, such as, for example, extrac-
tion with suitable solvents, concentration of the organic phase by evaporation and
filtration of the raw product thus precipitated. The raw product is preferably used as
such in the subsequent stages or, alternatively, it can be purified, for example through
crystallisation or chromatography.
The process for the preparation of ribavirin according to the present invention finally provides for the removal of the Pg protecting groups and, optionally, the conversion of the R₂ group, of the intermediate product of the formula III, into a carboxyamide group.

5 The removal of the Pg protecting groups is performed under standard conditions, which vary depending on the chemical nature of the group itself. In general, see the removal conditions described by T. Green and P. Wuts in the text cited above, "Protecting Groups in Organic Synthesis", chapter 2, page 17, 3rd Ed. (1999).

10 For example in the case where the protecting group is an ester, its removal will be effected by alcoholsysis in basic catalysis conditions. In particular, when Pg represents an acetyl group, de-protection is preferably performed with methanol in the presence of sodium methyate.

15 Finally, if R₂ is different from CONH₂, the synthesis of ribavirin will be completed through conversion of the R₂ group of the intermediate product of formula III already de-protected on the sugar, into a carboxyamide group.

20 Said conversion will be conducted under different conditions based on the meaning of R₂ and in any case through reactions well known to an expert in the field and not binding for the purposes of the present invention. By way of example there may be cited the reactions of preparation of amides reported by J. March in "Advanced Organic Chemistry", page 1152, 3rd Ed. (1985).

25 In particular, when R₂ represents carbethoxy, it is preferred to perform the aforesaid transformation of the de-protected intermediate product III by treatment with ammonia in methanol. This reaction of ammonolysis may be conducted at a pressure of between 1 and 4 atmospheres, preferably at 1.9-2.5 atm.

30 Alternatively, it is possible to proceed at the same time with the de-protection of the sugar and with the conversion of the R₂ group of the compound of formula III into a carboxyamide group, to give ribavirin directly.

35 For example, ribavirin may be prepared directly by treatment of the intermediate product III, in which Pg represents acetyl and R₂ represents carbethoxy, with

According to a preferred embodiment, to the pre-cooled suspension of the triazole of formula I and of the protected ribose of formula II in the preselected solvent, the Lewis acid IV is added while stirring and in an inert atmosphere, maintaining the temperature below 20°C.

When the addition is finished, the reaction is brought to reflux until completed. The reaction is terminated by the addition of acidified water, checking that the temperature does not exceed 20°C. The phases are separated, the organic phase is washed again with acidified water and the aqueous phases are extracted several times with organic solvent. The organic phases are concentrated under vacuum and the raw product IV is isolated through precipitation by the addition of a co-solvent, partial evaporation and filtration of the solid.

The solid thus obtained is taken up with the preselected alcohol and de-protected, according to conventional techniques, preferably by alcoholysis in the presence of the corresponding sodium alcoholate, and then converted into ribavirin, by ammonolysis in an alcoholic medium. The ribavirin is then isolated by crystallisation, preferably from aqueous methanol; according to the best embodiment of the invention, said crystallisation is carried out at a temperature below 50°C and using from 2 to 5 volumes of methanol per volume of water.

As will be seen from the following examples, which should not be regarded as limiting the invention, the present process makes it possible to prepare ribavirin with high yields and purities without having recourse to any preliminary stage of activation of the triazole ring, with obvious advantages in terms of time, purity and raw materials.

The process of the present invention further makes it possible to prepare ribavirin as a single polymorphous form, as required by the health authorities. Ribavirin in fact exists in two distinct polymorphous forms; the first, obtained by crystallisation from aqueous ethanol, has a melting point of 166-168°C; the second, obtained by crystallisation from ethanol, has a melting point of 174-176°C (Merck Index 11th edition). With the process according to the present invention, ribavirin is obtained exclusively in the first form (or that having a melting point of 166-168°C), without any trace of the second.
EXAMPLES

Synthesis of the methyl ester of 1-(2,3,5-tri-O-acetyl-β-D-ribofuranosyl)-1H-1,2,4-triazole-3-carboxylic acid

(triacetylarabinosir, 3-carbomethoxy, TARC, IV, PG=CH₂CO, R₂=COOCH₃)

In a 6000 ml, 4-neck anhydrous reactor equipped with thermometer, condenser and mechanical stirrer, there are placed, while stirring and with a flow of nitrogen, 1680 ml of dichloromethane, 400 g of tetra-acetylribose (Fluka) and 185.2 g of 3-carbo-

methoxytriazole. The mixture is cooled to about 5°C and 360 g of tin tetrachloride are added to the suspension in a thin stream while stirring. The exothermy of the reaction is controlled by cooling with an ice bath so that the temperature does not exceed 15-

20°C and, when the addition is finished, the reaction mixture is heated to reflux for 2 hours. It is cooled to 20°C with a water and ice bath in 15 minutes. Then 30% hydro-

chloric acid (176.7 ml) and water (1503.3 ml) are added at a temperature below +20°C and stirring is carried out for 45 minutes; the mixture is left to dephase for 15 minutes, then the upper aqueous phase is separated from the rich organic phase which is sub-

sequently treated with 30% hydrochloric acid (176.7 ml) and water (1503.3 ml). After 45 minutes' stirring, the mixture is left to dephase for 15 minutes and the upper

aqueous phase is separated from the rich organic phase, which is subsequently treated with 30% hydrochloric acid (176.7 ml) and water (1503.3 ml). After 45 minutes' stirring, the mixture is left to dephase for 15 minutes and the phases are separated: the organic phase is distilled at atmospheric pressure (internal T approx. 45°C), and to the oily residue 3000 ml of toluene are added and the mixture is distilled under vacuum at about 200 mbar of residual pressure to a stirrable moist paste. It is cooled to 5-10°C for 2 hours and filtered over a Buchner filter while washing with toluene. 524 g of moist product are obtained, equal to 392 g dry product.

Synthesis of the methyl ester of 1-β-D-ribofuranosyl-1H-1,2,4-triazole-3-carboxylic acid

(methyl ester of ribavirin, RIBEST, IV, Pg=H, R₂=COOCH₃)

To the moist solid residue thus obtained, 2000 ml of methanol are added and it is checked that the moisture content is below 0.2%. The mixture is cooled to 10°C and 34g of sodium methoxide in 30% methanol are added in 30 minutes. A clear yellow solution is obtained which is maintained while stirring in an inert atmosphere for 3

hours at 10°C. Then 11.4 g of glacial acetic acid are added and the mixture is distilled
under vacuum (from 300 mbar to 50 mbar) at 30-35°C to an oily residue. The residue is taken up again with methanol, distilling under vacuum to an oily residue.

**Synthesis of ribavirin (I)**

To the residue thus obtained, 1000 ml of methanol and 64 g of gaseous ammonia are added and the mixture left for 4 hours at 20°C while stirring; there is precipitation of product in the course of the reaction. Distillation under reduced pressure (200 mmHg; internal T 40°C) is carried out to about half volume and 200 ml of water are added; heating to 60°-70°C is carried out until dissolved and 400 ml of methanol are added. The mixture is cooled to 0°-5°C for 4 hours and the solid is filtered over a Buchner filter while washing with methanol; 300 g of moist raw Ribavirin are obtained and this is crystallised without desiccation.

**Crystallisation**

200 ml of water are placed in a 1000 ml reactor equipped with stirrer and condenser and are heated to 40°-50°C while adding, a little at a time, 300 g of moist ribavirin (equal to 206 g dry product), heating to a maximum temperature of 60°C while stirring until dissolved. Then 500 ml of methanol are added; the resultant pH is equal to 7-8. Cooling to around 40°-45°C is carried out, bringing about the precipitation of the product and this is left to crystallise for one hour while stirring at ambient temperature: formation of abundant precipitate. Cooling to 5°C is carried out for 2 hours and the product is filtered over a Buchner filter, while washing with 200 ml of methanol. 300 g of moist crystallised Ribavirin are obtained which are dried at 60°C under vacuum overnight to give 197.5 g of dry product.

**Analytical data:**

- Appearance: crystalline white monomorphous powder,
- \([\alpha]_D(10 \text{ mg/ml; H}_2\text{O}): -35.6^\circ\]
- Melting point: 166-168°C
- HPLC purity: 99.8%
- NMR (Brucker 300MHz, d₆-DMSO): the \(^1\text{H}\) and \(^{13}\text{C}\) NMR spectra confirm the structure of the ribavirin.
The NOESY spectrum excludes the presence of α anomer and demonstrates that the regioisomer obtained is that in which position 1 of the ribose is bonded to the nitrogen atom in 1 of the triazole ring. DSC analysis finally confirms the total absence of other polymorphous forms (even traces).
CLAIMS

1. A process for the preparation of ribavirin which comprises:
   a) the reaction of a triazole of the formula

\[
\text{(I)}
\]

wherein \( R_2 \) represents a \( C_1-C_4 \) alkoxy carbonyl, arylalkoxy carbonyl, carboxyl, cyano, carboxyamide group with a protected ribofuranose of the formula

\[
\text{(II)}
\]

wherein \( \text{Pg} \) represents a group protecting the hydroxyl function and \( R_1 \) represents a leaving group selected from among \( C_1-C_4 \) acyloxy, aryloxy and halogen;

in the presence of a Lewis acid (V); and

b) the removal of the \( \text{Pg} \) groups and, optionally, the conversion of the \( R_2 \) group of the compound obtained of the formula

\[
\text{(III)}
\]
wherein Pg and R₂ have the meanings given above, into a carboxamide group, to give ribavirin.

2. A process according to claim 1, wherein R₂ represents a C₁-C₄ alkoxy carbonyl group, preferably carbomethoxy group.

3. A process according to claim 1, wherein Pg represents acetyl, benzoyl or benzyl, preferably acetyl.

4. A process according to claim 1, wherein R₁ represents a group selected from among chlorine, bromine and C₁-C₄ acyloxy, preferably acetox.

5. A process according to claim 1, wherein the Lewis acid (IV) is selected from among AlCl₃, SbCl₅, BF₄, SnCl₄ and FeCl₃, preferably SnCl₄.

6. A process according to claim 1, wherein the solvent used in stage a) is a halogenated hydrocarbon, preferably dichloromethane.

7. A process according to claim 1, wherein the reagents in stage a) are used in a molar ratio of 1-2 moles of I and 1-1.5 moles of IV to every mole of II, preferably 1-1.2 moles of I and 1-1.1 moles of IV to every mole of II.

8. A process according to claim 1, wherein the reaction temperature in stage a) is between -10°C and the reflux temperature of the solvent.

9. A process according to claim 1, wherein ribavirin is isolated by crystallisation from aqueous methanol.

10. A process according to claim 9, wherein said crystallisation is carried out at a temperature below 50°C and using from 2 to 5 volumes of methanol per volume of water.
INTERNATIONAL SEARCH REPORT

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07H19/056 C07H1/00 A61K31/7056 A61P31/12

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED
Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07H A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
PAJ, EPO-Internal, WPI Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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<td>PATENT ABSTRACTS OF JAPAN vol. 005, no. 035 (C-046), 5 March 1981 (1981-03-05) &amp; JP 55 160793 A (MICROBIAL CHEM RES FOUND), 13 December 1980 (1980-12-13) abstract</td>
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Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

Date of the actual completion of the international search
25 October 2002

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