Note: Within nine months from the publication of the mention of the grant of the European patent, any person may give notice to the European Patent Office of opposition to the European patent granted. Notice of opposition shall be filed in a written reasoned statement. It shall not be deemed to have been filed until the opposition fee has been paid. (Art. 99(1) European Patent Convention).
This invention relates to a process for the preparation of pharmaceutical compounds. The compound 2-amino-6-chloropurine (ACP) of formula: is a useful intermediate in the preparation of nucleoside analogue antiviral agents, such as penciclovir (previously known as BRL 39123) and famciclovir (previously known as BRL 42810), described in EP-A-141927 (Example 1) and EP-A-182024 (Example 2), respectively. The intermediate is 9-substituted with an appropriate side chain precursor, followed by conversion of the 6-chloro moiety to a hydroxy (a guanine) or hydrogen (a 2-aminopurine). A process from ACP is generally described in EP-A-302644 and US Patent No 5175288 and an improved process over the process specifically described in this publication has now been discovered. The process for the preparation of penciclovir/famciclovir from ACP comprises the process from ACP as described in EP-A-302644, characterised in that the 6-chloro substituent is removed subsequent to the decarboxylation and hydrolysis steps. The key difference is that in the original process the chlorine group in the 6-position of the purine molecule is removed early in the process (see reaction Scheme 1). Significant yield and processing advantages are obtained by retaining the 6-chloro substituent in the molecule through the process, removing it only at the final step (see reaction Scheme 2). With streamlining of the process stages and removal of the column chromatography steps, which would have rendered the route disadvantageous as a production process, overall yields have been increased from 10.6% to 41%.

Accordingly, the present invention provides a process for the preparation of a compound of formula (A):

wherein X is hydrogen or hydroxy; and R_a and R_b are hydrogen, or acyl or phosphate derivatives thereof, which process comprises:

(i) the preparation of a compound of formula (I):
wherein $R_1$ is $C_{1-6}$ alkyl, or phenyl $C_{1-6}$ alkyl; and $R_3$ is an amino group or a protected amino group, which preparation comprises the reaction of a compound of formula (II):

$$\text{(II)}$$

wherein $R_3$ is as defined for formula (I) with a compound of formula (V):

$$\text{(V)}$$

wherein $L$ is a leaving group and $R_1$ is as defined for formula (I), to give a compound of formula (VI):

$$\text{(VI)}$$
and thereafter converting the intermediate compound of formula (VI) to a compound of formula (I) via decarboxylation, and, as necessary or desired, interconverting variables R₁ to further values of R₁;

(ii) the conversion of the resulting compound of formula (I) to a compound of formula (A) by deprotecting variable R₃ where necessary, reducing the ester groups CO₂R₁ to CH₂OH and optionally forming acyl or phosphate derivatives thereof, and converting the Cl substituent in the compound of formula (I) to variable X in the compound of formula (A).

[0005] The process preferably comprises the reaction of a compound of formula (II) wherein R₃ is as defined above with a compound of formula (V) wherein R₁ is C₁₋₄ alkyl and L is halogen, followed by decarboxylation of the resulting compound of formula (VI), and, as necessary or desired, interconverting R₁ in the resulting compound of formula (I) to further values of R₁ as defined for formula (I).

[0006] The process may be used for the production of 9-(4-acetoxy-3-acetoxymethylbut-1-yl)-2-aminopurine (famciclovir) and 9-(4-hydroxy-3-hydroxymethylbut-1-yl)guanine (penciclovir).

[0007] As no aqueous dilution is used to precipitate the product at the coupling step there is large capacity advantage, and the dimethylformamide is more easily recovered as it does not have to be separated from a large volume of water.

[0008] There are greater overall volume efficiencies in the process.

[0009] Several of the compounds of formula (I) are novel, thus according to a further aspect of the invention there is provided a compound of formula (I) or a salt thereof:

![Chemical structure](image)

(I)

wherein R₁ is methyl or ethyl and R₃ is amino; e.g. 2-amino-6-chloro-9-(methyl 2-carbomethoxybutanoate-4-yl)purine.

[0010] The following Examples illustrate the invention.

**EXAMPLE 1**

(Stage 1 Product)

**Preparation of 2-amino-6-chloro-9-(methyl 2-carbomethoxybutanoate-4-yl)purine**

[0011] A mixture of 2-amino-6-chloropurine (9.18g, 53.1 mmole), triethyl 3-bromopropane-1,1,1-tricarboxylate (20.33g, 57.3 mmole), potassium carbonate (11.1g, 80.3 mmole) and dimethylformamide (190ml) were stirred together at 60°C to 63°C for 22h. After this time the reaction mixture was filtered hot through a celite bed and the cake washed with dimethylformamide (30ml). The filtrate and washing were combined and the solvent removed under high vacuum distillation to leave a crude reddish brown oil. This was dissolved in methanol (140ml), cooled to 20°C and then a solution of sodium methoxide (1.2g) in methanol (40ml) was added with stirring. After ca 20 minutes a precipitate formed and the stirring was continued for a total of 1 hour. The reaction mixture was then cooled to 15°C and held at this temperature for 30 minutes. The product was filtered off and washed with methanol (10ml) and dried at 40°C for 16h under vacuum.

Yield: 12.0g of 95% purity material.
EXAMPLE 2

(Stage 2 product)

Preparation of 9-(4-acetoxy-3-acetoxymethylbut-1-yl)-2-amino-6-chloropurine

[0012] A mixture of 2-amino-6-chloro-9-(methyl 2-carbomethoxybutanoate-4-yl) purine (32.7g, 0.1 mole), sodium borohydride (11.5g, 0.3 mole) and methylene dichloride (125ml) were stirred at 20°C. Methanol (75ml) was added dropwise over 2.0 hour period while the reaction temperature was maintained at 20-22°C with cooling. The reaction mixture was left to stir for a further 1.5h. Water (100ml) was added followed by the dropwise addition of concentrated hydrochloric acid (20-22ml) to pH 6.7 to 7.0 keeping the reaction temperature at 20°-22°C. Methylene dichloride and methanol were removed under vacuum until a reaction volume of 150ml was obtained. The reaction mixture was cooled to 5°C and stirred at this temperature for 30 minutes. The resulting precipitate was filtered off and the product cake washed with cold water (20ml). The resulting damp solid (40-50g) was stirred with triethylamine (15ml), 4-dimethylaminopyridine (1.0g) in methylene dichloride (250ml). Acetic anhydride (75ml, 0.79 mole) was added dropwise over 20 to 30 minutes at such a rate to control the reflux. The reaction mixture was heated under reflux for a further 1.5 hours. The reaction was cooled to 20°C and neutralised with 20% w/w sodium hydroxide solution to pH 6.4-6.5. The methylene dichloride layer was separated and the aqueous phase extracted with methylene dichloride (100ml). The combined methylene dichloride phases were evaporated to dryness. The crude damp solid was recrystallised from 3:1 methanol:water (75ml), cooling the precipitate to -5°C for 1h before filtration. The product was washed with cold 3:1 methanol:water (0°C) and dried at 40°C for 16h in a vacuum oven.

Yield: 23g of 97% to 98% purity material

EXAMPLE 3

(Stage 3 Product)

a) Preparation of 9-(4-acetoxy-3-acetoxymethylbut-1-yl)-2-aminopurine-famiclovir

[0013] A mixture of 9-(4-acetoxy-3-acetoxymethylbut-1-yl)-2-amino-6-chloropurine (15.4g, 43 mmole), 5% palladium on carbon (6.16g), triethylamine (6.6ml, 47 mmole) and ethyl acetate (77ml) was stirred at 50°C under a hydrogen atmosphere at 1 bar pressure in an autoclave for 3 to 5 hours. After completion of the reaction the mixture was removed from the autoclave which was washed out with ethyl acetate (30ml) keeping the washings at 50°C. The main reaction mixture was filtered through a celite bed followed by the washings and finally with ethyl acetate (30ml). Water (46ml) was added to the combined ethyl acetate filtrate plus washings. The ethyl acetate was evaporated to dryness to leave a crude white solid. This was recrystallised from n-butanol (62ml), stirring the cooled solution at 0 to 5°C for 3h before filtration. The product was filtered off and washed with the mother liquors. The solid was reslurried in n-heptane (50ml) stirred for 30 minutes and filtered. The product was dried at 40°C for 16h under vacuum.

Yield: 11-11.3g

b) Preparation of 9-(4-hydroxy-3-hydroxymethylbut-1-yl) guanine - penciclovir

[0014] A mixture of 9-(4-acetoxy-3-acetoxymethylbut-1-yl)-2-amino-6-chloropurine (10g, 28.1mmole), formic acid (96%, 6.3ml) and water (55ml) was stirred and heated to reflux for about 4 hours. After cooling the solution was basified by mixing with sodium hydroxide solution (12.5M, 27ml) and the resulting solution was stirred for 1.5 hrs. The solution was neutralised by the addition of formic acid. The resultant slurry was heated to reflux (ca 105°C) then cooled to 40-45°C and stirred for about 3 hours. The crude product was then isolated and washed with water (20ml). The isolated product was dissolved in sodium hydroxide solution (3M, 80ml). Carbon (ca 1.5g) was added and the slurry stirred for about 1 hr then the carbon was removed by filtration and washed with water (20ml). The solution was neutralised by the addition of formic acid and the resultant precipitate was redissolved by heating to ca 100°C and was then cooled. The precipitated product was stirred for about 3 hrs then isolated and washed with water (2 x 20ml) before being dried.

Yield 5.3 - 5.5g.
(Scheme 1)
Process of the Invention

70% yield
(b) Acetic anhydride
(c) NaBH₄

90% yield

H₂/Pd

3 Steps

OVERALL YIELD

41%
Claims

1. A process for the preparation of a compound of formula (A):

   \[
   \text{(A)}
   \]

   wherein \(X\) is hydrogen or hydroxy and \(R_a\) and \(R_b\) are hydrogen, or acyl or phosphate derivatives thereof, which process comprises:

   (i) the preparation of a compound of formula (I):

   \[
   \text{(I)}
   \]

   wherein \(R_1\) is \(C_{1-6}\) alkyl, or phenyl \(C_{1-6}\) alkyl; and \(R_3\) is an amino group or a protected amino group, which preparation comprises the reaction of a compound of formula (II):

   \[
   \text{(II)}
   \]

   wherein \(R_3\) is as defined for formula (I) with a compound of formula (V):
wherein L is a leaving group and R₁ is as defined for formula (I), to give a compound of formula (VI):

and thereafter converting the intermediate compound of formula (VI) to a compound of formula (I) via decarboxylation, and, as necessary or desired, interconverting variables R₁ to further values of R₁:

(ii) the conversion of the resulting compound of formula (I) to a compound of formula (A) by deprotecting variable R₃ where necessary, reducing the ester groups CO₂R₁ to CH₂OH and optionally forming acyl or phosphate derivatives thereof, and converting the Cl substituent in the compound of formula (I) to variable X in the compound of formula (A).

2. A process for the preparation of a compound of formula (I) as defined in claim 1, which process comprises the reaction of a compound of formula (II) wherein R₃ is as defined in claim 1 with a compound of formula (V) wherein R₁ is C₁₋₄ alkyl and L is halogen, followed by decarboxylation of the resulting intermediate compound of formula (VI), and, as necessary or desired, interconverting variables R₁ in the resulting compound of formula (I) to further values of R₁ as defined for formula (I) in claim 1.

3. A compound of formula (I), or a salt thereof:
wherein $R_1$ is methyl or ethyl and $R_3$ is amino.

4. 2-Amino-6-chloro-9-(methyl 2-carbomethoxybutanoate-4-yl)purine.

5. A process according to claim 1 or 2 for the preparation of 9-(4-acetoxy-3-acetoxymethylbut-1-yl)-2-aminopurine (famciclovir).

6. A process according to claim 1 or 2 for the preparation of 9-(4-hydroxy-3-hydroxymethylbut-1-yl)guanine (penciclovir).

**Patentansprüche**

1. Verfahren zur Herstellung einer Verbindung der Formel (A):

   in der $X$ ein Wasserstoffatom oder eine Hydroxygruppe bedeutet und $R_a$ und $R_b$ Wasserstoffatome darstellen, oder Acyl- oder Phosphatderivate davon, wobei das Verfahren umfaßt:

   (i) die Herstellung einer Verbindung der Formel (I):
in der R₃ einen C₆₆-Alkyl- oder Phenyl-C₆₆-alkylrest bedeutet und R₃ eine Aminogruppe oder eine geschützte Aminogruppe darstellt, wobei die Herstellung die Umsetzung einer Verbindung der Formel (II):

in der L eine Abgangsgruppe bedeutet und R₁ wie für Formel (I) definiert ist, wobei eine Verbindung der Formel (VI) erhalten wird:

und anschließend Umwandeln der Zwischenverbindung der Formel (VI) über eine Decarboxylierung in eine
Verbindung der Formel (I) und, falls notwendig oder erwünscht, wechselseitiges Umwandeln der Variablen $R_1$ in weitere Werte von $R_1$ umfaßt;

(ii) die Umwandlung der erhaltenen Verbindung der Formel (I) in eine Verbindung der Formel (A) durch Schutzgruppenabspaltung aus der Variablen $R_3$, wo es notwendig ist, Reduzieren der Estergruppen $CO_2R_1$ zu $CH_2OH$ und gegebenenfalls Bilden von Acyl- oder Phosphatderivaten davon, und Umwandeln des Cl-Substituenten in der Verbindung der Formel (I) in die Variable $X$ in der Verbindung der Formel (A).

2. Verfahren zur Herstellung einer Verbindung der Formel (I) nach Anspruch 1, wobei das Verfahren die Umsetzung einer Verbindung der Formel (II), in der $R_3$ wie in Anspruch 1 definiert ist, mit einer Verbindung der Formel (V), in der $R_1$ einen C$_{1-4}$-Alkylrest bedeutet und $L$ ein Halogenatom darstellt, gefolgt von einer Decarboxylierung der erhaltenen Zwischenverbindung der Formel (VI) und, falls notwendig oder erwünscht, wechselseitiges Umwandeln der Variablen $R_1$ in der erhaltenen Verbindung der Formel (I) in weitere Werte von $R_1$, wie für Formel (I) in Anspruch 1 definiert, umfaßt.

3. Verbindung der Formel (I) oder ein Salz davon:

\[
\begin{align*}
\text{Cl} \\
\text{N} \text{N} \\
\text{N} \\
\text{N} \\
\text{R}_3 \\
\text{(CH}_2\text{)}_2 \\
\text{R}_1\text{O}_2\text{C} - \text{CH} - \text{CO}_2\text{R}_1
\end{align*}
\]

in der $R_1$ eine Methyl- oder Ethylgruppe bedeutet und $R_3$ eine Aminogruppe darstellt.

4. 2-Amino-6-chlor-9-(methyl-2-carbomethoxybutanoat-4-yl)purin.

5. Verfahren nach Anspruch 1 oder 2 zur Herstellung von 9-(4-Acetoxy-3-acetoxymethylbut-1-yl)-2-aminopurin (Famciclovir).

6. Verfahren nach Anspruch 1 oder 2 zur Herstellung von 9-(4-Hydroxy-3-hydroxymethylbut-1-yl)guanin (Penciclovir).

Reverdissons

1. Procédé pour la préparation d’un composé de formule (A) :

\[
\begin{align*}
\text{X} \\
\text{H}_2\text{N} \\
\text{N} \text{N} \\
\text{N} \\
\text{N} \\
\text{(CH}_2\text{)}_2 \\
\text{R}_a\text{O}\text{-CH}_2\text{-CH}-\text{CH}_2\text{-OR}_b
\end{align*}
\]
dans laquelle X est un atome d'hydrogène ou un groupe hydroxy ; et R_a et R_b sont un atome d'hydrogène, ou des dérivés acyle ou phosphate de celui-ci, lequel procédé comprend :

(i) la préparation d'un composé de formule (1):

\[
\text{Cl} \quad \text{(I)}
\]

\[
R_1O_2C - \text{CH} - \text{CO}_2R_1
\]

dans laquelle R_1 est un groupe alkyle en C_{1-6} ou phényl-alkyle en C_{1-6} ; et R_3 est un groupe amino ou un groupe amino protégé, laquelle préparation comprend la réaction d'un composé de formule (II) :

\[
\text{Cl} \quad \text{(II)}
\]

dans laquelle R_3 est tel que défini pour la formule (I), avec un composé de formule (V):

\[
L - (\text{CH}_2)_2 - \text{C} - \text{CO}_2R_1
\]

\[
\text{CO}_2R_1
\]

dans laquelle L est un groupe mobile et R_1 est tel que défini pour la formule (I), pour donner un composé de formule (VI) :

\[
\]
et ensuite la conversion du composé intermédiaire de formule (VI) en un composé de formule (I) par décarboxylation, et selon ce qui est nécessaire ou désiré, l'interconversion des variables R₁ en d'autres valeurs de R₁ ;

(ii) la conversion du composé résultant de formule (I) en un composé de formule (A) par déprotection de la variable R₃ lorsque cela est nécessaire, la réduction des groupes ester CO₂R₁ en CH₂OH et la formation éventuelle de leurs dérivés acyle ou phosphate, et la conversion du substituant Cl dans le composé de formule (I) en une variable X dans le composé de formule (A).

2. Procédé pour la préparation d'un composé de formule (I) tel que défini dans la revendication 1, lequel procédé comprend la réaction d'un composé de formule (II) dans laquelle R₁ est tel que défini dans la revendication 1, avec un composé de formule (V) dans laquelle R₃ est un groupe alkyle en C₁-₄ et L est un atome d'halogène, suivie de la décarboxylation du composé intermédiaire résultant de formule (VI), et selon ce qui est nécessaire ou désiré, l'interconversion des variables R₁ dans le composé résultant de formule (I) en d'autres valeurs de R₁ tel que défini pour la formule (I) dans la revendication 1.

3. Composé de formule (I) ou sel de celui-ci :

4. 2-Amino-6-chloro-9-(méthyl-2-carbométhoxybutanoate-4-yl)-purine.

5. Procédé suivant les revendications 1 ou 2 pour la préparation de la 9-(4-acétoxy-3-acétoxyméthylbut-1-yl)-2-amino-purine (famciclovir).

6. Procédé suivant les revendications 1 ou 2 pour la préparation de la 9-(4-hydroxy-3-hydroxyméthylbut-1-yl)guanine (penciclovir).