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Janssen et al.

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[54] **3-PIPERIDINYL-1,2-BENZISOXAZOLES**
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[52] U.S. Cl. **514/258; 544/282**
[58] Field of Search **544/282; 514/258**

[73] Assignee: **Janssen Pharmaceutica N.V., Beerse, Belgium**

[56] **References Cited**

[*] Notice: **The portion of the term of this patent subsequent to Oct. 27, 2009 has been disclaimed.**

U.S. PATENT DOCUMENTS

[21] Appl. No.: **932,142**

4,804,663 2/1989 Kennis **544/282**
5,151,424 9/1992 Janssens **544/282**
5,158,952 10/1992 Janssen **544/282**

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Attorney, Agent, or Firm—**Charles J. Metz**

Related U.S. Application Data

[60] Division of Ser. No. 422,847, Oct. 17, 1989, Pat. No. 5,158,952, which is a continuation-in-part of Ser. No. 267,857, Nov. 7, 1988, abandoned.

[57] **ABSTRACT**

[51] Int. Cl.⁵ **C07D 487/04; C07D 413/04; A61K 31/505**

The invention relates to C₂₋₂₀alkanoic acid esters of 3-[2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]ethyl]-6, 7,8,9-tetrahydro-9-hydroxy-2 -methyl-4H-pyrido[1,2-a]pyrimidin-4-one, pharmaceutically acceptable acid addition salts thereof, and enantiomeric forms thereof, which are useful in the treatment of warm-blooded animals suffering from psychotic diseases.

6 Claims, No Drawings

3-PIPERIDINYL-1,2-BENZISOXAZOLES

This application is a division of our copending application Ser. No. 422,847, filed Oct. 17, 1989, now U.S. Pat. No. [5,158,952], which in turn was a continuation-in-part of application Ser. No. 267,857, filed Nov. 7, 1988, now abandoned.

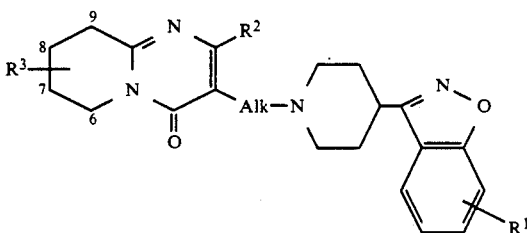
BACKGROUND OF THE INVENTION

In EP-A-0,196,132 there are described a number of 3-piperidinyl-1,2-benzisoxazoles having antipsychotic activity.

The compounds of the present invention differ therefrom by the specific substitution on the (2-C₁₋₄alkyl-6,7,8,9-tetrahydro-4-oxo-4H-pyrido[1,2-a]-pyrimidin-3-yl)alkyl substituent at the 1 position of the piperidinyl moiety.

DESCRIPTION OF THE INVENTION

The present invention is concerned with novel 3-piperidinyl-1,2-benzisoxazoles having the formula



the pharmaceutically acceptable acid addition salts thereof, and the stereochemically isomeric forms thereof, wherein

Alk is C₁₋₄alkanediyl;

R¹ is hydrogen, C₁₋₄alkyl or halo;

R² is C₁₋₄alkyl;

R³ is hydroxy or R⁴-C(=O)O-; and

R⁴ is C₁₋₁₉alkyl.

In the foregoing definitions C₁₋₄alkanediyl defines bivalent straight and branch chained alkanediyl radicals having from 1 to 4 carbon atoms such as, for example, methylene, 1,2-ethanediyl, 1,3-propanediyl, 1,4-butanediyl and the branched isomers thereof; C₁₋₄alkyl defines straight and branch chained saturated hydrocarbon radicals having from 1 to 4 carbon atoms such as, for example, methyl, ethyl, propyl, 1-methylethyl, butyl, 1-methylpropyl, 2-methylpropyl and 1,1-dimethylethyl; C₁₋₁₉alkyl defines C₁₋₄alkyl radicals as defined hereinabove and the higher homologs thereof having from 5 to 19 carbon atoms such as, for example, pentyl, hexyl, heptyl, octyl, nonyl, decyl, undecyl, dodecyl, tridecyl, tetradecyl, pentadecyl, hexadecyl, heptadecyl, octadecyl, nonadecyl and the like; halo is generic to fluoro, chloro, bromo and iodo. R³ as defined hereinabove may be substituted on any of the 6,7,8 or 9 positions of the 6,7,8,9-tetrahydro-2-C₁₋₄alkyl-4H-pyrido[1,2-a]pyrimidin-4-one moiety.

Particular compounds are those compounds of formula (I) wherein R³ is substituted on the 9 position of the 6,7,8,9-tetrahydro-2-C₁₋₄alkyl-4H-pyrido[1,2-a]pyrimidin-4-one moiety.

More particular compounds within the invention are those particular compounds wherein Alk is ethanediyl;

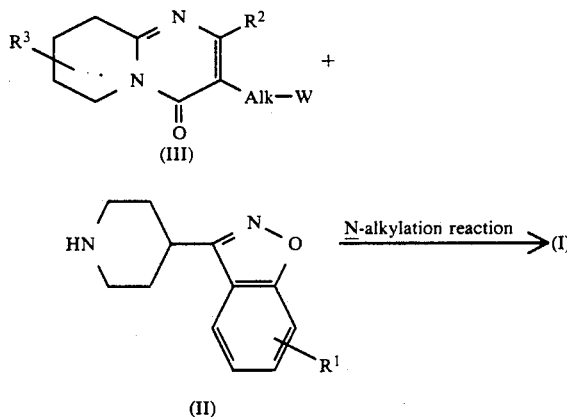
and/or R¹ is halo, in particular fluoro and more in particular 6-fluoro; and/or R² is methyl.

Among the above defined groups of compounds of formula (I) those compounds wherein R⁴ is C₇₋₁₃alkyl, in particular heptyl, nonyl, undecyl or tridecyl are of particular interest.

The most interesting compounds within the invention are selected from the group consisting of 3-[2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]ethyl]-6,7,8,9-tetrahydro-9-hydroxy-2-methyl-4H-pyrido[1,2-a]pyrimidin-4-one, the pharmaceutically acceptable acid addition salt forms and the enantiomeric forms thereof.

From formula (I) it is evident that the compounds of this invention have at least one asymmetric carbon atom in their structure, namely the carbon atom bearing the R³ substituent. The absolute configuration of this centre may be indicated by the stereochemical descriptors R and S, this R and S notation corresponding to the rules described in Pure Appl. Chem. 1976, 45, 11-30. Unless otherwise mentioned or indicated, the chemical designation of compounds denotes the mixture of all possible stereochemically isomeric forms, said mixtures containing all diastereomers and enantiomers of the basic molecular structure. Stereochemically isomeric forms of the compounds of formula (I) are obviously intended to be embraced within the scope of the invention.

The compounds of formula (I) can generally be prepared by N-alkylating a 3-piperidinyl-1,2-benzisoxazole of formula (II) with an alkylating reagent of formula (III) following art-known N-alkylation procedures.



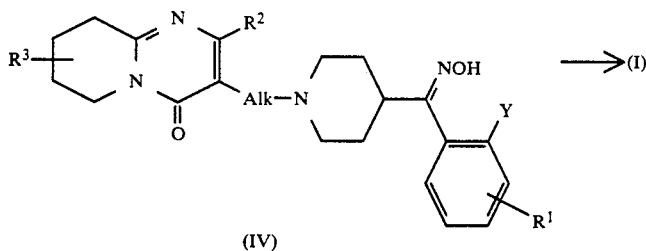
In formula (III) W represents an appropriate reactive leaving group such as, for example, halo, e.g. chloro, bromo or iodo; sulfonyloxy, e.g. methanesulfonyloxy, trifluoromethanesulfonyloxy, benzenesulfonyloxy, 4-methylbenzenesulfonyloxy and the like leaving groups. Said N-alkylation reaction can conveniently be carried out by mixing the reactants, optionally in a reaction-inert solvent such as, for example, water, an aromatic solvent, e.g. benzene, methylbenzene, dimethylbenzene, chlorobenzene, methoxybenzene and the like; a C₁₋₆alkanol, e.g. methanol, ethanol, 1-butanol and the like; a ketone, e.g. 2-propanone, 4-methyl-2-pentanone and the like; an ester, e.g. ethyl acetate, γ -butyrolactone and the like; an ether, e.g. 1,1'-oxybisethane, tetrahydrofuran, 1,4-dioxane and the like; a dipolar aprotic solvent, e.g. N,N-dimethylformamide, N,N-dimethylacetamide, dimethylsulfoxide, pyridine, 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone, 1,3-dimethyl-2-imidazolidi-

none, 1,1,3,3-tetramethylurea, 1-methyl-2-pyrrolidinone, nitrobenzene, acetonitrile and the like; or a mixture of such solvents. The addition of an appropriate base such as, for example, an alkali metal or an earth alkaline metal carbonate, hydrogen carbonate, hydroxide, oxide, carboxylate, alkoxide, hydride or amide, e.g. sodium carbonate, sodium hydrogen carbonate, potassium carbonate, sodium hydroxide, calcium oxide, sodium acetate, sodium methoxide, sodium hydride, sodium amide and the like, or an organic base such as, for example, a tertiary amine, e.g. N,N-diethylethanamine, N-(1-methylethyl)-2-propanamine, 4-ethylmorpholine, 1,4-diazabicyclo[2.2.2]octane, pyridine and the like, may optionally be used to pick up the acid which is formed during the course of the reaction. In some instances the addition of an iodide salt, preferably an alkali metal iodide, or a crown ether, e.g. 1,4,7,10,13,16-hexaoxa-cyclooctadecane and the like, may be appropriate. Stirring and somewhat elevated temperatures may enhance the rate of the reaction; more in particular the reaction may be conducted at the reflux temperature of the reaction mixture. Additionally, it may be advantageous to conduct said N-alkylation under an inert atmosphere such as, for example, oxygen-free argon or nitrogen gas.

Alternatively, said N-alkylation may be carried out by applying art-known conditions of phase transfer catalysis reactions. Said conditions comprise stirring the reactants, with an appropriate base and optionally under an inert atmosphere as defined hereinabove, in the presence of a suitable phase transfer catalyst such as, for example, a trialkylphenylmethylammonium, tetraalkylammonium, tetraalkylphosphonium, tetraarylphosphonium halide, hydroxide, hydrogen sulfate and the like catalysts. Somewhat elevated temperatures may be appropriate to enhance the rate of the reaction.

In this and the following preparations, the reaction products may be isolated from the medium and, if necessary, further purified according to methodologies generally known in the art such as, for example, extraction, crystallization, trituration and chromatography.

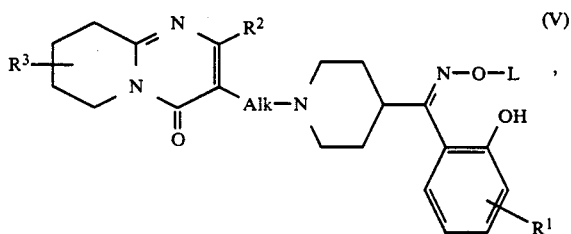
The compounds of formula (I) can also be obtained by the cyclization of an oxime of formula (IV), wherein Y is a reactive leaving group such as, for example, halo or nitro. Preferably Y is a halo group and more particularly fluoro.



Said cyclization reaction of the oxime of formula (IV) may conveniently be conducted by treatment with an appropriate base, preferably in a suitable reaction-inert solvent at temperatures in the range of 20° to 200° C., preferably at 50° to 150° C., and in particular at the reflux temperature of the reaction mixture. Or, if desirable, said base may first be added, preferably at room temperature, whereupon the thus formed oxime salt is cyclized, preferably at an increased temperature and more preferably at the reflux temperature of the reaction mixture. Appropriate bases for said cyclization are,

for example, alkali and earth alkaline metal carbonates, hydrogen carbonates, hydroxides, alkoxides or hydrides, e.g. sodium carbonate, sodium hydrogen carbonate, potassium carbonate, sodium hydroxide, sodium methoxide, sodium hydride or organic bases such as amines, e.g. N,N-diethylethanamine, 4-ethylmorpholine and the like bases. Suitable solvents are, for example, water; aromatic hydrocarbons, e.g. benzene, methylbenzene, dimethylbenzene and the like; halogenated hydrocarbons, e.g. dichloromethane, trichloromethane, 1,2-dichloroethane and the like; lower alkanols, e.g. methanol, ethanol, 1-butanol and the like; ketones, e.g. 2-propanone, 4-methyl-2-pentanone and the like; ethers, e.g. 1,4-dioxane, tetrahydrofuran and the like; dipolar aprotic solvents, e.g. N,N-dimethylformamide, N,N-dimethylacetamide, dimethylsulfoxide, 1-methyl-2-pyrrolidinone and the like, or mixtures of such solvents.

The compounds of formula (I) can also be obtained by cyclizing an activated oxime derivative of formula



wherein L is an acid residue and more particularly is formyl, (C₁₋₆alkyl or aryl)-carbonyl, e.g. acetyl, propionyl, benzoyl and the like; (C₁₋₆alkyl or aryl)oxycarbonyl, e.g. methoxycarbonyl, ethoxycarbonyl, (1,1-dimethyl)ethoxycarbonyl, phenyloxycarbonyl and the like; (C₁₋₆alkyl or aryl)sulfonyl, e.g. methanesulfonyl, benzenesulfonyl, 4-methylbenzenesulfonyl, 2-naphthalenesulfonyl and the like; N-acylaminocarbonyl, e.g. trichloromethylcarbonylaminocarbonyl and the like. Said cyclization reaction of the activated oxime derivative of formula (V) may conveniently be conducted by treatment with an appropriate base, preferably in a suitable reaction-inert solvent, at temperatures in the range from 20° to 200° C., particularly from 50° to 150° C. and preferably at the reflux temperature of the reaction mixture. In some instances however, it may be advanta-

geous not to add a base to the reaction mixture and to remove the acid liberated during the reaction by distillation at normal pressure or, if desired, at reduced pressure. Alternatively, said cyclization may also be effected by heating the oxime derivative (V) in vacuo without a solvent. Appropriate bases are for example, alkali and earth alkaline metal carbonates, hydrogen carbonates and organic amines, e.g. sodium carbonate, potassium carbonate, sodium hydrogen carbonate, N,N-

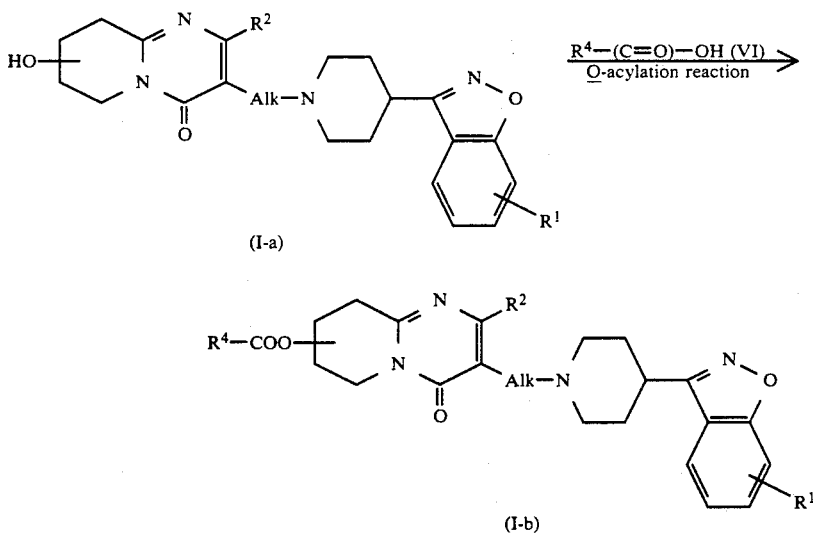
diethylethanamine, 4-ethylmorpholine, 1,4-diazabicyclo[2.2.2]octane, pyridine and the like bases. Suitable solvents for said cyclization are, for example, aromatic hydrocarbons, e.g. benzene, methylbenzene, dimethylbenzene and the like; ethers, e.g. 1,1'-oxybisethane, 1,1'-oxybisbutane, tetrahydrofuran, 1,4-dioxane, 1,1'-oxybis[2-methoxyethane], 2,5,8,11-tetraoxadodecane and the like; dipolar aprotic solvents, e.g. N,N-dimethylformamide, N,N-dimethylacetamide, 1-methyl-2-pyrrolidinone, hexamethylphosphoric triamide, pyridine, acetic anhydride and the like; halogenated hydrocarbons, e.g. trichloromethane, tetrachloromethane, 1,2-dichloroethane, chlorobenzene and the like solvents.

The compounds of formula (I) wherein R^3 is $R^4-(C=O)-O-$, said compounds being represented by formula (I-b), can be obtained by the O-acylation reaction of a compound of formula (I-a) wherein R^3 is hydroxy, with a carboxylic acid of formula (VI) or a suitable reactive functional derivative thereof such as, for example, an acyl halide, symmetric or mixed anhydride, ester or amide, acyl azide and the like derivatives. Said functional derivatives may be prepared following art-known methods, for example, by reacting the carboxylic acid of formula (VI) with a halogenating reagent such as, for example, thionyl chloride, phosphorous trichloride, phosphoryl chloride, oxalyl chloride and the like, or by reacting said carboxylic acid (VI) with an acyl halide such as acetyl chloride and the like. Said derivatives may be generated in situ, or if desired, be isolated and further purified before reacting them with the compound of formula (I-a).

pyridinium iodide, phosphorus pentoxide, 1,1'-carbonylbis[1H-imidazole], 1,1'-sulfonyl bis[1H-imidazole] and the like reagents.

Said O-acylation reactions can conveniently be carried out by stirring the reactants optionally in a suitable reaction-inert solvent such as, for example, a halogenated hydrocarbon, e.g. dichloromethane, trichloromethane and the like; an aromatic hydrocarbon, e.g. benzene, methylbenzene and the like; an ether, e.g. 1,1'-oxybisethane, tetrahydrofuran and the like; or a dipolar aprotic solvent, e.g. N,N-dimethylformamide, N,N-dimethylacetamide, or pyridine and the like. In some instances it may be appropriate to employ an excess of one of the reagents as solvent. The water, acid, alcohol or amine which is liberated during the course of the reaction may be removed from the reaction mixture by art-known procedures such as, for example, azeotropic distillation, complexation, salt formation and the like methods. In some instances particularly the addition of a suitable base such as, for example, a tertiary amine, e.g. N,N-diethyl-ethanamine, 4-ethylmorpholine, pyridine or N,N-dimethyl-4-aminopyridine, may be appropriate. Further, in order to enhance the rate of the reaction, said acylation reaction may advantageously be conducted at a somewhat elevated temperature, and in particular instances at the reflux temperature of the reaction mixture.

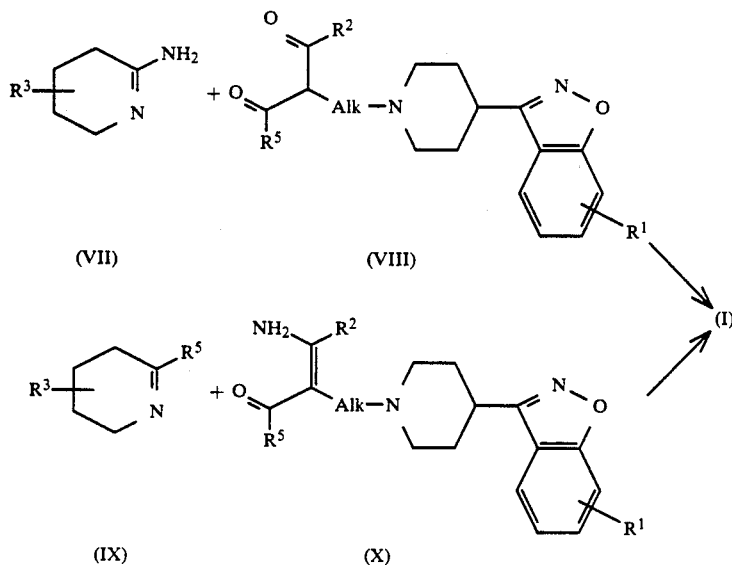
The compounds of formula (I) can also be prepared following art-known cyclization procedures for preparing pyrimidin-4-ones such as, for example, by reacting an amidine of formula (VII) with a β -dicarbonyl intermediate of formula (VIII), or by cyclizing a reagent of



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Alternatively, the compound of formula (I-a) and the carboxylic acid of formula (VI) may also be esterified in the presence of a suitable reagent capable of forming esters such as, for example, a dehydrating reagent, e.g. dicyclohexylcarbodiimide, 2-chloro-1-methyl-

formula (IX) with an enamine of formula (X). In formulae (VIII), (IX) and (X) R^5 represents an appropriate leaving group such as, for example, C_{1-6} alkyloxy, hydroxy, halo, amino, mono- or di- $(C_{1-6}$ alkyl)amino and the like.



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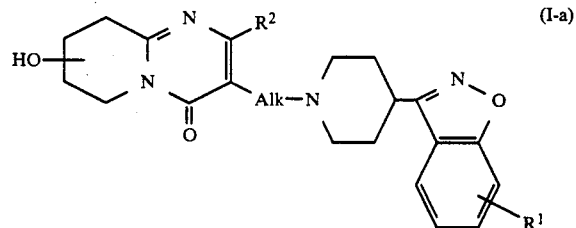
Said cyclization reactions may generally be carried out by stirring the reactants, optionally in the presence of a suitable reaction-inert solvent such as, for example, an aliphatic, alicyclic or aromatic hydrocarbon, e.g. hexane, cyclohexane, benzene and the like; pyridine, N,N-dimethylformamide and the like dipolar aprotic solvents. In order to enhance the rate of the reaction it may be appropriate to increase the temperature, more particularly, it may be recommendable to carry out the reaction at the reflux temperature of the reaction mixture.

The compounds of formula (I) have basic properties and, consequently, they may be converted to their therapeutically active non-toxic acid addition salt forms by treatment with appropriate acids, such as, for example, inorganic acids, such as hydrohalic acid, e.g. hydrochloric, hydrobromic acid and the like, sulfuric acid, nitric acid, phosphoric acid and the like; or organic acids, such as, for example, acetic, propanoic, hydroxyacetic, 2-hydroxypropanoic, 2-oxopropanoic, ethanedioic, propanedioic, butanedioic, (Z)-2-butenedioic, (E)-2-butenedioic, 2-hydroxybutanedioic, 2,3-dihydroxybutanedioic, 2-hydroxy-1,2,3-propanetricarboxylic, methanesulfonic, ethanesulfonic, benzenesulfonic, 4-methylbenzenesulfonic, cyclohexanesulfamic, 2-hydroxybenzoic, 4-amino-2-hydroxybenzoic and the like acids. Conversely the salt form can be converted into the free base form by treatment with alkali.

The term acid addition salt as used hereinabove also comprises the solvates which the compounds of formula (I) are able to form and said solvates are meant to be included within the scope of the present invention. Examples of such solvates are e.g., the hydrates, alcoholates and the like.

Enantiomeric forms of the compounds of formula (I-a)

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(I-a)

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can be obtained by converting the racemic mixtures of the compounds of formula (I-a) with a suitable resolving reagent such as, for example, a chiral acid, e.g. tartaric, malic and mandelic acids, campher sulfonic acid, 4,5-dihydro-1H-2-benzopyran-2-carboxylic acid and the like, or the reactive functional derivatives thereof, e.g. the acyl halides, to a mixture of diastereomeric salts or compounds, particularly esters; physically separating said mixtures of diastereomeric salts or compounds by, for example, selective crystallization or chromatographic techniques, e.g. liquid chromatography and the like methods; and finally converting said separated diastereomeric salts or compounds into the corresponding enantiomeric forms of the compounds of formula (I-a) by hydrolysis in an acidic or basic aqueous medium, optionally at an elevated temperature.

Some of the intermediates and starting materials for use in the foregoing preparations are known compounds, while others are novel. The intermediates of formula (II) and methods of preparing them are known from EP-A-0,196,132. The alkylating reagents of formula (III) are novel and can be prepared according to art-known methodologies of preparing similar compounds and will be described hereinafter in more detail.

By condensing an optionally protected 2-aminopyridine derivative (XI) with an α-acyl lactone (XII) in the presence of an activating reagent in a suitable reaction-inert solvent, an intermediate of formula (XIII) can be obtained.

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