Improved process for the preparation of dihydro-1H-pyrrolizine-3,5-(2H,6H)-dione.

Priority: 21.03.86 US 842702
Date of publication of application: 23.09.87 Bulletin 87/39
Publication of the grant of the patent: 31.10.90 Bulletin 90/44
Designated Contracting States: AT BE CH DE ES FR GB GR IT LI LU NL SE
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EP-A-0 164 652

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The file contains technical information submitted after the application was filed and not included in this specification

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Description

The present invention relates to chemical processes. More particularly, the present invention is concerned with an improved process for preparing dihydro-1H-pyrrolizine-3,5-(2H,6H)-dione Dihydro-1H-
pyrrolizine-3,5-(2H,6H)-dione possesses useful pharmacological properties for enhancing memory and
reversing the effects of amnesia caused by electroconvulsive shock. (See United States Patent 4 372
966).

The prior art discloses several alternative routes to dihydro-1H-pyrrolizine-3,5-(2H,6H)-dione start-
ing with one or another derivative of heptanolidic acid, generally a 4-substituted-heptanolidic acid
such as the 4-nitro-, 4-amino-, 4-oxo-, or 4-hydroxyiminoderviative. However, most of these process-
es involve numerous steps or produce low overall yields of the desired end-product, typically on the or-
der of 50% or less. Consequently, there is a need for an improved method of preparing this pharmaco-
logically useful agent.

United States Patent 4 372 966 to Butler discloses a method whereby dimethyl 4-nitro-heptanolidoate
is catalytically reduced by the action of hydrogen in the presence of palladium to produce a mixture of
methyl 5-oxo-2-pyrrolidinepropanoate and the corresponding free acid. The mixture is next treated with
base and then acidified to convert the ester in the mixture to the free acid. In a final step, the 5-oxo-2-
pyrrolidinepropanoate is esterified by the action of acetic anhydride to dihydro-1H-pyrrolizine-3,5-
(2H,6H)-dione. The reported overall yield for this synthetic sequence is about 48%.

Lukes et al., Coll. Czech. Chem. Comm., 12: 278-279 (1947) disclose a method by which diethyl 4-
(hydroxyiminino)heptanolidoate is catalytically reduced by the action of platinum oxide in the presence of
ferrous chloride to produce a mixture of ethyl 5-oxo-2-pyrrolidinepropanoate and 4-oxo-heptanolidic
acid. The yield of the pyrrolidine derivative is reported as 40%.

Linnert et al., J. Am. Chem. Soc., 68: 690-692 (1947) disclose a method of preparing dihydro-1H-pyr-
rolizine-3,5-(2H,6H)-dione comprising catalytically reducing dimethyl 4-nitro-heptanolidoate by the ac-
tion of hydrogen in the presence of platinum oxide to methyl 5-oxo-2-pyrrolidinepropanoate in 55% yield.
This material is subsequently cyclized in 60% yield to dihydro-1H-pyrrolizine-3,5-(2H,6H)-dione by heat-
ing for 30 hours under hydrogen at 250-300 atmospheres (2.5 × 10^4 – 3.0 × 10^4 kPascal) in the presence
of copper chromate.

Michael et al., Ann. chem., 581: 225-237 (1953) disclose the preparation of dihydro-1H-pyrrolizine-
3,5-(2H,6H)-dione by first converting 4-aminoheptanolidic acid to the "half lactam" (i.e., 5-oxo-2-pyrro-
lidinepropanoic acid) and then cyclizing this material to the dione by the action of acetic anhydride.

Michael et al., Chem. Ber., 88: 509-510 (1955) disclose a method of preparing dihydro-1H-pyrrolizine-
3,5-(2H,6H)-dione in 56% yield by the reduction of 4-oxo-heptanolidic acid, followed by the treatment of
the 5-oxo-2-pyrrolidinepropanoic acid thus formed with acetyl chloride in acetic acid.

In Chem. Abstr., 86: 94-232g (1976) a process for the preparation of 2-(3-pyridyl)pyrrolidine is de-
scribed. This compound is prepared from γ-(3-pyridyl)-γ-hydroxyiminobutyrate esters by reduction with
Flaney-nickel cyclisatation to a pyrrolidone. This process does not use rhodium/alumina catalysts and is not
carried out in the presence of a tertiary amine.

In accordance with the present invention an improved process for preparing dihydro-1H-pyrrolizine-
3,5-(2H,6H)-dione comprises the steps of first catalytically hydrogenating a mono straight or branched
(1 to 3 C-alkyl) ester of 4-(hydroxyiminino) heptanolidic acid in the presence of a tertiary lower alkyl amine
containing from three to nine carbon atoms to produce 4-(hydroxyiminino) 5-oxo-2-pyrrolidinepropanoic acid, and there-
thereafter heating the 5-oxo-2-pyrrolidinepropanoic acid in the presence of an acid anhydride, 2,2,6-trimethyl-
1,3-dioxen-4-one or diketene as a cyclizing agent to form dihydro-1H-pyrrolizine-3,5-(2H,6H)-dione.

By "straight or branched (1 to 3 C-alkyl)" used throughout this specification and appended claims is
meant branched or unbranched alkyl groups of one to three carbon atoms such as methyl, ethyl, propyl,
and isopropyl.

The method of the present invention provides dihydro-1H-pyrrolizine-3,5-(2H,6H)-dione in overall
yields from the starting mono straight or branched (1 to 3 C-alkyl) ester of 4-(hydroxyiminino)heptanolidic
acid which regularly exceed 80%, considerably higher than yields obtained from prior art methods. The
improvements in the present method lie in the combined use of said ester of 4-(hydroxyiminino)
heptanolidic acid, and the catalytic hydrogenation in the presence of an acid anhydride, 2,2,6-trimethyl-
1,3-dioxen-4-one or diketene and a tertiary amine.

Following the step of reducing the starting hydroxylimino compound to 5-oxo-2-pyrrolidinepropanoic
acid, the acid is cyclized to the desired final product, dihydro-1H-pyrrolizine-3,5-(2H,6H)-dienes, by
heating the acid in the presence of an acid anhydride, 2,2,6-trimethyl-1,3-dioxen-4-one (TKO), or diket-
etene as a cyclizing agent. Preferred cyclizing agents for this step of the process include acid anhy-
drides, with acetic anhydride being most preferred.

Referring to the accompanying Reaction Scheme, the starting material, 4-(hydroxyiminino)heptanolidic
acid, monoalkyl ester, is prepared from the alkali metal salt of the monoalkyl ester, 2. This ester-salt, 2,
is readily prepared by treatment of the spirodilactone 1 with any suitable lower alcohol in the presence of a base such as sodium carbonate, potassium carbonate and the like. The preparation of the spirodilactone 1 and its conversion to the alkali metal salt monoester 2 are disclosed by Paniza et al., Synthetic Communications, 13(3): 243–254 (1983). Preferred alcohols for this conversion are methyl and ethyl alcohol on the basis of cost, with methyl alcohol being most preferred.

The alkali metal salt 2 is converted to 4-(hydroxylimino)heptanedioic acid, mono straight or branched (1 to 3 C-alkyl) ester 3 in high yield by heating the salt 2 in aqueous solution at temperatures between about 20–50°C with hydroxylamine hydrochloride for a period of from about 15 minutes to about one hour.

The principle contribution of the process of the present invention to improved yields of dihydro-1H-pyrazoline-3,5-(2H,6H)-dione lies in the next step indicated in the Reaction Scheme where the hydroxyimino monoester 3 is catalytically hydrogenated using a rhodium/alumina catalyst to produce...
Reaction Scheme

1

\[ \text{Na}_2\text{CO}_3 \quad \text{CH}_3\text{OH} \]

2

\[ \text{NH}_2\text{OH} \cdot \text{HCl} \quad \text{H}_2\text{O} \]

3

\[ \text{Et}_3\text{N} \quad \text{H}_2, \text{Rh/Al}_2\text{O}_3 \]

4

\[ (\text{CH}_3\text{CO})_2\text{O} \]

5
5-oxo-2-pyrrolidinopropionic acid 4. As can be seen by Example 1 below, when the reduction of 3 is carried out over said rhodium/alumina catalyst in the presence of a tertiary alkyl amine containing from three to nine carbon atoms such as triethylamine, in accordance with the method of this invention, very high yields of 5-oxo-2-pyrrolidinopropionic acid are realized, with the product being substantially free of contaminating starting material.

These results are to be contrasted with those in Example 2 where the same reduction in the absence of a tertiary lower alkyl amine yielded a roughly 3:1 molar ratio of 5-oxo-2-pyrrolidinopropionic acid and the corresponding methyl ester. This mixed material must be subjected to the further step of hydrolyzing the ester contained in the mixture in order to obtain the acid prior to the subsequent step of cyclizing to the desired end-product, dihydro-1H-pyrrolizine-3,5-(2H,6H)-dione.

Further, as can be seen by reference to Example 3, catalytic reduction of an alkali metal salt of 4-(hydroxyimino)heptanedioic acid results in yields of the desired intermediate, 5-oxo-2-pyrrolidinopropionic acid but in yields of only about 70%.

The following examples are provided to enable one skilled in the art to practice the present invention.

EXAMPLE 1

Catalytic Reduction of 4-(Hydroxyimino)heptanedioic Acid, Methyl Ester in the Presence of Triethylamine

Preparation of 4-(Hydroxyimino)heptanedioic Acid, Monomethyl ester

To a solution of 114.3 g (0.45 mol) of the crude sodium salt of 4-oxoheptanedioic acid, monomethyl ester (containing about 17% mixed carbonates of sodium) in 400 ml of water was gradually added a solution of 56.9 g (0.33 mol) of hydroxylamine hydrochloride in 45 ml of water.

The mixture was warmed to 40°C for 15 minutes, then cooled to 0–5°C while the pH was adjusted to 3.0 with 37% hydrochloric acid. The product was extracted four times with 250-ml portions of ethyl acetate. The organic layer was separated and dried over magnesium sulfate. The mixture was filtered and the solvent removed to yield 83.6 g (91%) of white crystalline 4-(hydroxyimino)heptanedioic acid, monomethyl ester mp 89–91°C, which was found to be 98.9% pure by high pressure liquid chromatographic (HPLC) analysis.

Reduction of 4-(Hydroxyimino)heptanedioic acid, Monomethyl ester

Monomethyl 4-(hydroxyimino)heptanedioate (15.7 g, 0.077 mol) was placed in a 500-ml hydrogenation bottle together with 300 ml of isopropyl alcohol, 7.8 g of triethylamine, and 2.27 g of 5% rhodium/alumina catalyst. The mixture was shaken for 16 hours under a hydrogen atmosphere at 50 psig (345 kPascal) while being heated at a temperature of 60°C.

At the end of this period, the catalyst was removed by filtration and the solvent and amine was removed under vacuum to yield 12.2 g (0.077 mol, 100%) of 5-oxo-2-pyrrolidinopropionic acid.

EXAMPLE 2

Catalytic Reduction of 4-(Hydroxyimino)heptanedioic Acid, Methyl Ester in the Absence of Amine

Monomethyl 4-(hydroxyimino)heptanedioate (16.7 g, 0.082 mol) was placed in a 500-ml hydrogenation bottle together with 300 ml of methyl alcohol and 2.4 g of 5% rhodium/alumina catalyst. The mixture was shaken for 16 hours under a hydrogen atmosphere at 50 psig (345 kPascal) while being heated at a temperature of 60°C.

The catalyst was removed by filtration under nitrogen, and the filter cake was washed with 50 ml of methanol. The solvent was removed from the filtrate under vacuum to yield a colorless oil. This material was heated at 90°C for 9 hours under a vacuum of 3 Torr (0.4 kPascal) to remove any remaining solvent.

A sample of this material was analyzed by nuclear magnetic resonance spectroscopy which showed the presence of methyl ester in the material, indicating incomplete cyclization of the starting ester to 5-oxo-2-pyrrolidinopropionic acid.

The material was heated at 110°C for an additional 5 hours under a vacuum of 3 Torr (0.4 kPascal). Upon cooling, there was obtained 9.5 g of a solid product which showed by nuclear magnetic resonance spectroscopy to be a roughly 3:1 molar ratio of 5-oxo-2-pyrrolidinopropionic acid and methyl 5-oxo-2-pyrrolidinepropanoate.

EXAMPLE 3

Catalytic Reduction of Sodium 4-(Hydroxyimino)heptanedioate in the Absence of Amine

Sodium 4-(hydroxyimino)heptanedioate (11.9 g, 0.052 mol) was placed in a 500-ml hydrogenation bottle together with 285 ml of methyl alcohol and 2.2 g of 5% rhodium/alumina catalyst. The mixture was shaken
for 1 hour under a hydrogen atmosphere at 50 psig (345 kPascal) at 60°C after which time the uptake of hydrogen ceased at 30% of the theoretical amount. The catalyst was removed by filtration and replaced with 2.2 g of fresh 5% rhodium/alumina catalyst was added. Hydrogenation at 50 psig (345 kPascal) and 60°C was continued for an additional 24 hours at which point the theoretical amount of hydrogen had been consumed.

The solvent was removed by filtration under nitrogen and the filter cake was washed with 50 ml of methanol. The solvent was removed from the filtrate under vacuum to yield 12.1 g of a semi-solid residue. This material was acidified with aqueous hydrochloric acid. Analysis of the material by high pressure liquid chromatographic (HPLC) methods indicated it to contain 68.8% 5-oxo-2-pyrrolidinepropanoic acid, 17.6% methyl 5-oxo-2-pyrrolidinepropanoic.

EXAMPLE 4

Cyclization of 5-Oxo-2-pyrrolidinepropanoic Acid to dihydro-1H-pyrrolizine-3,5-(2H,6H)dione

5-Oxo-2-pyrrolidinepropanoic acid (15.7 g, 0.1 mol) was added to 45 ml of acetic anhydride and the mixture was heated slowly to 50°C and held at that temperature for six hours. The mixture was cooled and the volatile materials stripped off at a temperature of 60°C under vacuum. The residue (14.2 g) was dissolved in 230 ml of isopropyl alcohol, the solution decolorized, filtered, and concentrated to 30 ml. This solution was cooled 0–5°C for two hours, and the solid which separated was collected by filtration, washed twice with 25-ml portions of isopropyl alcohol to yield 12.5 g (89.9%) of dihydro-1H-pyrrolizine-3,5-(2H,6H)-dione, mp 180.2–181.8°C, which was found to be 99.5% pure by high pressure liquid chromatographic (HPLC) analysis.

Claims

1. A process for preparing dihydro-1H-pyrrolizine-3,5-(2H,6H)-dione by catalytically hydrogenating an ester of 4-(hydroxymino)heptanediolic acid and subsequently cyclizing the resulting product to dihydro-1H-pyrrolizine-3,5-(2H,6H)-dione, characterized by hydrogenating a mono straight or branched (1 to 3 C-alkyl) ester of 4-(hydroxymino)heptanediolic acid in the presence of a rhodium/alumina catalyst and of a tertiary alkyl amine containing from three to nine carbon atoms to produce 5-oxo-2-pyrrolidinepropanoic acid; and thereafter heating said 5-oxo-2-pyrrolidinepropanoic acid in the presence of an acid anhydride, 2,2,6-trimethyl-1,3-dioxen-4-one or diltetane as a cyclizing agent.

2. The process as defined in Claim 1 wherein said tertiary lower alkyl amine is triethyl amine.

3. The process as defined in Claim 1 wherein said cyclizing agent is acetic anhydride.

4. The process as defined in Claim 3 wherein said mono-(lower alkyl) ester of heptanediolic acid is monomethyl heptanedioc.

Patentansprüche

1. Verfahren zur Herstellung von Dihydro-1H-pyrrolizin-3,5-(2H,6H)-diön durch katalytische Hydrierung eines Ester einer 4-(Hydroxymino)heptandisäure und nachfolgende Cyclisierung des erhaltenen Produktes zu Dihydro-1H-pyrrolizin-3,5-(2H,6H)-diön, dadurch gekennzeichnet, daß man einen Mono-(C₁-C₆)-alkylaldehyd mit gerader oder verzweigter Kette von 4-(Hydroxymino)heptandisäure in Gegenwart eines Rhodium/Aluminiumoxydxkatalysators und eines tertiären Alkylamins mit drei bis neun Kohlenstoffatomen hydriert, um 5-Oxo-2-pyrrolidinpropionsäure herzustellen, und danach die 5-Oxo-2-pyrrolidinpropionsäure in Gegenwart eines Säureanhydrids oder von 2,2,6-Trimethyl-1,3-dioxen-4-on oder Di-lketen als Cyclisierungsmittel erwärmt.

2. Verfahren nach Anspruch 1, darin gekennzeichnet, daß das tertiäre Niederalkylamin Triethylamin ist.

3. Verfahren nach Anspruch 1, darin gekennzeichnet, daß das Cyclisierungsmittel Essigsäure-anhydrid ist.


Revendications

1. Un procédé pour préparer la dihydro-1H-pyrrolizin-3,5-(2H,6H)-dione par hydrogénation catalytique d'un ester d'acide 4-(hydroxymino)-heptanédioïlique, puis cyclisation ultérieure du produit resultant en dihydro-1H-pyrrolizin-3,5-(2H,6H)-dione, caractérisé par l’hydrogénation d’un monoéster alkyle à chaîne droite ou ramifiée ayant 1 à 3 atomes de carbone d'acide 4-(hydroxymino)-heptanédioïlique en présence d'un catalyseur au rhodium/alumine et d’une amine alkylamine tertiaire contenant de trois à neuf atomes de carbone pour produire l'acide 5-oxo-2-pyrrolidinépropanoïque, et ensuite le chauffage de cet acide 5-oxo-2-pyrrolidinépropanoïque en présence d’anhydride d’acide, de 2,2,6-triméthyl-1,3-dioxé-4-on ou de dicétène comme agent de cyclisation.
2. Un procédé suivant la revendication 1, caractérisé en ce que cette alkyldiméthylamine tertiaire est la triéthylamine.
3. Un procédé suivant la revendication 1, caractérisé en ce que cet agent de cyclisation est l’anhydride acétique.
4. Un procédé suivant la revendication 3, caractérisé en ce que ce monoester alkyle de l’acide heptanedioïque est l’heptanédioate de monométhyle.