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(54) Title: A NEW METHOD OF MANUFACTURING 2-(6-(4-CHLOROPHENYL)-2,2-DIMETHYL-7'-PHENYL-2,3-DIHYDRO-L-/PYRROLIZINE-5-YL)ACE H C ACID (LICOF ELONE)

(57) Abstract: A method of manufacturing 2-(6-(4-chlorophenyl)-2,2-dimethyl-7'-phenyl-2,3-dihydro-l/-pyrrolizine-5-yl)acetic acid of formula I, wherein 6-(4-chlorophenyl)-2,2-dimethyl-7'-phenyl-2,3-dihydro-l/-pyrrolizine of formula II is alkylated with a iodo derivative of formula VII, wherein A is either the cyano group CN or an ester group COOR, wherein R is an (un)branched C1-C6 alkyl group, with the use of the Fenton reagent in the presence of a sulfoxide of formula R1-SO-R2, wherein R1 is an (un)branched C1-C12 alkyl group, R2 is either an (un)branched C1-C12 alkyl group, an aryl group or a substituted aryl group, or wherein R1, R2 are independently (CH2)nX(CH2)nX, wherein X = CH2, O, S, NR, m = 1-3, n = 1-3 and R is either an (un)branched C1-C12 alkyl group, an aryl group or a substituted aryl group, the reaction being carried out in the environment of the sulfoxide used or in its mixture with suitable solvents at a temperature of 0°C to 80°C, preferably at temperatures in the range of 10 to 40°C, and the resulting ester of formula IV or nitrile of formula VIII is hydrolyzed to the desired product of formula I either directly or in the case of the nitrile via the amide of formula (IX).
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A new method of manufacturing 2-(6-(4-chlorophenyl)-2,2-dimethyl-7-phenyl-2,3-dihydro-1\(H\)-pyrrolizine-5-yl)acetic acid (licofelone)

Technical Field

The invention deals with a new method of the production of 2-(6-(4-chlorophenyl)-2,2-dimethyl-7-phenyl-2,3-dihydro-1\(H\)-pyrrolizine-5-yl)acetic acid of formula I.

![Chemical Structure Image]

Licofelone (I) was developed by Merckle as an anti-inflammatory drug that can also be used as an anti-arthritic medicament.

Background Art

Most described methods of producing licofelone (I) uses, as the key intermediate, 6-(4-chlorophenyl)-2,2-dimethyl-7-phenyl-2,3-dihydro-1\(H\)-pyrrolizine (II), which can be obtained by several methods described in the corresponding patents (US 5260451, US 7078535, WO 98/17666), as well as in scientific literature (J. Org. Chem. 1997, 62, 7900; Tetrahedron 1999, 55, 5145).

In the method described in patents nos. US 5260451 and US 7078535 the pyrrolizine intermediate (II) is transformed via a reaction with oxalyl chloride in the THF environment to the substance (III), which is subsequently reduced by the Wolff-Kishner reduction with
hydrazine in an alkaline environment. Under the reaction conditions used the acid chloride is at the same time transformed to the free carboxylic acid I (licofelone). A disadvantage of the above mentioned method is the necessity to reduce the oxo group by the Wolff-Kishner reaction, which proceeds under harsh conditions and uses toxic hydrazine.

In the basic US patent 5260451 and the subsequent publication (J. Med. Chem. 1994, 37, 1894-1897) the reaction of 6-(4-chlorophenyl)-2,2-dimethyl-7-phenyl-2,3-dihydro-1H-pyrrolizine (II) with ethyl diazoacetate in the presence of metallic copper is described leading to the ethyl ester (IV), which is in the next step subject to alkaline saponification to obtain the desired product (I) (licofelone). A disadvantage of the above mentioned method is the use of ethyl diazoacetate, the utilization of which is not possible in the industrial scale.

A newer method (WO 98/17666; J. Org. Chem. 1997, 62, 7900; Tetrahedron 1999, 55, 5145), not using 6-(4-chlorophenyl)-2,2-dimethyl-7-phenyl-2,3-dihydro-1H-pyrrolizine (II) as the intermediate, is based on Suzuki’s cross-coupling of the triflate (V) with 4-chlorophenylboronic acid. The resulting intermediate (VI) is converted to the corresponding tosyl hydrazone, which via the reduction with sodium cyanoborohydride provides the ester (IVa). A disadvantage of this method is difficult attainability of the substance (V), which will not be commercially available unlike 6-(4-chlorophenyl)-2,2-dimethyl-7-phenyl-2,3-dihydro-1H-pyrrolizine (II).
The Fenton reagent is a solution of hydrogen peroxide and iron (II) sulfate; in this solution Fe\(^{2+}\) is oxidized to Fe\(^{3+}\) while the hydroxyl anion OH\(^-\) and the hydroxyl radical OH\(^-\) are produced. The Fe\(^{3+}\) cation is then reduced back to Fe\(^{2+}\), the peroxide radical OOH\(^-\) and proton H\(^+\). The high reactivity of this reagent can be e.g. used for decomposition of organic substances, including chlorinated compounds such as trichloroethylene or tetrachloroethylene, e.g. in wastewater.

\[
(1) \text{Fe}^{2+} + \text{H}_2\text{O}_2 \rightarrow \text{Fe}^{3+} + \text{OH}^- + \text{OH}^-
\]

\[
(2) \text{Fe}^{3+} + \text{H}_2\text{O}_2 \rightarrow \text{Fe}^{2+} + \text{OOH}^- + \text{H}^+
\]


\[
(3) \text{OH}^- + \text{Me-S(O)-Me} \rightarrow \text{Me}^- + \text{MeSO}_2\text{H}
\]

Minisci et al. (J. Org. Chem. 1989, 54, 5224) and Bacciochi et al. (J. Org. Chem. 1992, 57, 6817; Tetrahedron Lett. 1993, 34, 3799; Tetrahedron Lett. 1993, 34, 5015) have found that if during a reaction of the Fenton type in the presence of dimethylsulfoxide a suitable iodo derivative is added, the corresponding radical is generated, which, in the presence of reactive derivatives of pyrrole, indole, thiophene or furan, alkylates these reactive substrates.

\[
(4) \text{Me}^- + \text{R-I} \rightarrow \text{R}^- + \text{MeI}
\]

As the iodo derivatives in the case of very highly reactive substrates esters of iodoacetic acid or iodoacetonitrile can be used. In the case of using of these highly reactive substrates such as pyrrole and its simpler derivatives a high excess of this substrate (15-20 fold) has been used.

After unsuccessful attempts at alkylation of 6-(4-chlorophenyl)-2,2-dimethyl-7-phenyl-2,3-dihydro-1\(H\)-pyrrolizine (II) using ethyl bromoacetate and ethyl iodoacetate with the use of
various bases (NaH, BuLi, LDA) and Lewis acids (BF$_3$-Et$_2$O, MgBr$_2$, AlCl$_3$) we focused on various types of radical reactions. Attempts at radical alkylations using ethyl iodoacetate in the presence of AIBN and tributyltin hydride, tris(trimethylsilyl)silane or N-ethylpiperidine hypophosphite have not lead to the desired product (IVa).

Disclosure of Invention

We have surprisingly found out that the use of the Fenton reagent in the presence of dimethylsulfoxide and ethyl iodoacetate provides good yields of the desired product (IVa).

Therefore, we have extended our study to the use of other alkyl iodoacetates by the methyl, tert-butyl and hexyl esters and by the use of iodoacetonitrile. Although the best results have been achieved with the use of dimethylsulfoxide, the reaction has proved to be feasible also with other sulfoxides (dibutyl sulfoxide, tetrahydrothiophene oxide, methyldodecyl sulfoxide, thioanisole-S-oxide) while having turned out that the reaction can either be carried out in the corresponding sulfoxide as the reaction medium or its mixtures with suitable solvents (acetonitrile, dimethylformamide, ethanol) can be used. It has also turned out that although the reaction cannot be performed with the corresponding chloro and bromo derivatives, these derivatives can be first converted, by reaction with alkaline iodides in a suitable solvent, to the corresponding iodides and these resulting iodides can be used without isolation for the reaction with the Fenton reagent in the presence of a suitable sulfoxide.

The object of the invention consists in a new method of manufacturing 2-(6-(4-chlorophenyl)-2,2-dimethyl-7-phenyl-2,3-dihydro-l H-pyrrolizine-5-yl)acetic acid (licofelone), based on homolytic substitution of 6-(4-chlorophenyl)-2,2-dimethyl-7-phenyl-2,3-dihydro-l H-pyrrolizine with alkyl iodoacetate or iodoacetonitrile and subsequent hydrolysis of the corresponding ester or nitrile to licofelone. This whole invention is based on the surprising finding that although 6-(4-chlorophenyl)-2,2-dimethyl-7-phenyl-2,3-dihydro-l H-pyrrolizine (II) cannot be directly alkylated in position 5 with esters or nitriles of haloacetic acids with the use of nucleophilic, electrophilic or standard radical conditions, under homolytic conditions using electrophilic C-centered radicals generated under the conditions of a Fenton type reaction the substance (II) can be alkylated by means of iodo derivatives (VII) containing electron-attracting substituents A, wherein A is COOR or CN, resulting in the corresponding esters (IV) or nitrile (VIII). These derivatives of licofelone can be further hydrolyzed to
licofelone (I); esters (IV) provide licofelone (I) by hydrolysis, the nitrile (VIII) can be hydrolyzed to licofelone (I) via the amide (IX).

The essence of the method of manufacturing 2-(6-(4-chlorophenyl)-2,2-dimethyl-7-phenyl-2,3-dihydro-1H-pyrrolizine-5-yl)acetic acid of formula I

according to the present invention consists in alkylation of 6-(4-chlorophenyl)-2,2-dimethyl-7-phenyl-2,3-dihydro-1H-pyrrolizine of formula II

with a iodo derivative of formula VII

wherein A is either the cyano group CN or an ester group COOR, wherein R is an (un)branched C\textsubscript{1}-C\textsubscript{6} alkyl group.
with the use of the Fenton reagent in the presence of a sulfoxide of formula R₁-SO-R²,
wherein R₁ is a C₁-C₁₂ (un)branched alkyl group, R² is either an (un)branched Ci-Ci₂ alkyl
group, an aryl group or a substituted aryl group, or wherein R₁, R² are independently

(\text{CH}_2)_mX(\text{CH}_2)_n, wherein X = CH₂, O, S, NR³, m = 1-3, n = 1-3 and R³ is either an
(un)branched Ci-Ci₂ alkyl group, an aryl group or a substituted aryl group,

the reaction being carried out in the environment of the sulfoxide used or of its mixture with
suitable solvents at a temperature of 0 °C to 80 °C, advantageously at temperatures in the
range between 10 and 40 °C and the resulting ester of formula IV or nitrile of formula VIII is
hydrolyzed to the desired product of formula I either directly, or in the case of the nitrile via
the amide of formula IX.

\[ \text{A} = \text{COOR} \]
\[ \text{B} = \text{CN} \]
\[ \text{C} = \text{CONH}_2 \]

A detailed description of the invention follows:

In a usual embodiment the respective iodo derivative and then iron (II) sulfate hemihydratate
were added at the laboratory temperature to a solution of the starting 6-(4-chlorophenyl)-2,2-
dimethyl-7-phenyl-2,3-dihydro-1H-pyrrozine (II) in the corresponding sulfoxide or a mixture
of the sulfoxide and a suitable solvent. After thorough stirring the mixture was cooled down to
the initial temperature (0-20 °C) and the used hydrogen peroxide was added dropwise under
continuous cooling. After the addition the reaction was monitored by means of TLC and after
completion of the reaction the mixture was poured into brine while being stirred. The mixture
obtained this way was extracted with a suitable solvent (ether, dichloromethane, ethyl acetate).

The combined extracts were then gradually washed with a solution of a base (sodium
hydrogencarbonate, sodium carbonate, sodium acetate), with a solution for removing the
excess of hydrogen peroxide (sodium hydrogen sulfite, sodium sulfite, sodium pyrosulfite,
sodium thiosulfate, iron (II) sulfate) and finally with brine. The removal of the excess of
hydrogen peroxide can also be achieved by addition of a suitable agent, e.g. sodium hydrogen
sulfite, directly to the mixture obtained by pouring the reaction mixture to brine. After drying of the processed extract with a suitable desiccant (magnesium sulfate, sodium sulfate, molecular sieves) and after evaporation of the solvent the crude ester (IV) or nitrile (VIII) is obtained, which, after crystallization, provides the pure substance in the yields of 60-80%. In case of using other sulfoxides than dimethylsulfoxide it was usually necessary to perform chromatographic purification and the achieved yield was generally lower.

The subsequent hydrolysis of the esters (IV) can be carried out under various conditions; in the usual embodiment alkaline hydrolysis with an aqueous or aqueous-alcoholic solution of sodium hydroxide at temperatures from the laboratory temperature to the boiling point was used, preferably in the range of 20 to 100 °C. Similar alkaline hydrolysis of the nitrile (VIII) at temperatures of e.g. 50 to 100 °C provided high yields of the respective amide (IX) and its subsequent hydrolysis with sulfuric acid then provided licofelone (I).

The intermediates used, methyl 2-(6-(4-chlorophenyl)-2,2-dimethyl-7-phenyl-2,3-dihydro-1H-pyrrolizine-5-yl)acetate, hexyl 2-(6-(4-chlorophenyl)-2,2-dimethyl-7-phenyl-2,3-dihydro-1H-pyrrolizine-5-yl)acetate, 2-(6-(4-chlorophenyl)-2,2-dimethyl-7-phenyl-2,3-dihydro-1H-pyrrolizine-5-yl)acetonitrile and 2-(6-(4-chlorophenyl)-2,2-dimethyl-7-phenyl-2,3-dihydro-1H-pyrrolizine-5-yl)acetamide, are compounds not hitherto described in the literature.

The invention is elucidated in a more detailed way in the following examples. These examples, which illustrate the improvement of the procedure according to the invention, have a purely illustrative character and do not limit the scope of the invention in any respect.

**Examples**

**Example 1**

Ethyl 2-(6-(4-chlorophenyl)-2,2-dimethyl-7-phenyl-2,3-dihydro-1H-pyrrolizine-5-yl)acetate (IVa)

To the stirred mixture of 6-(4-chlorophenyl)-2,2-dimethyl-7-phenyl-2,3-dihydro-1H-pyrrolizine (III) (1 g, 3.1 mmol), ethyl iodoacetate (0.8 g, 3.7 mmol), iron (II) sulfate
heptahydrate (0.2 g, 0.75 mmol) and dimethylsulfoxide (20 ml) a solution of 30% hydrogen peroxide (2.1 ml) and dimethylsulfoxide (5 ml) was added dropwise under cooling in a cold water bath within 15 minutes. The temperature of the reaction mixture rose from the initial temperature of 10 °C to 20 °C. The reaction mixture was poured into brine (150 ml) and the resulting mixture was extracted with ether (3 x 50 ml). The organic layer was gradually washed with a saturated solution of sodium hydrogencarbonate (25 ml), a saturated solution of sodium sulfite (25 ml) and brine (2 x 25 ml) and dried with magnesium sulfate. After evaporation 1.4 g of the evaporation residue was obtained whose crystallization from ethanol provided 0.9 g (71%) of crystals with the melting temp. of 77-79 °C. 1H-NMR spectrum (CDCl₃): 1.28 t, J=7.1, 2H (CH₂); 1.29 s, 6H (2xCH₃); 2.85 s, 2H (CH₂); 3.51 s, 2H (CH₂); 3.75 s, 2H (CH₂); 4.18 q, J=7.1, 2H (CH₂); 7.02-7.27 m, 9H Ar.

Example 2

Ethyl 2-(6-(4-chlorophenyl)-2,2-dimethyl-7-phenyl-2,3-dihydro-1 H-pyrrolizine-5-yl)acetate (IVa)

To the stirred mixture of 6-(4-chlorophenyl)-2,2-dimethyl-7-phenyl-2,3-dihydro-1 H-pyrrolizine (III) (1 g, 3.1 mmol), ethyl iodoacetate (0.8 g, 3.7 mmol), iron (II) sulfate heptahydrate (0.2 g, 0.75 mmol), dimethylsulfoxide (2 ml) and acetonitrile (20 ml) a solution of 30% hydrogen peroxide (2.1 ml) and dimethylsulfoxide (2 ml) was added dropwise under cooling in a cold water bath within 15 minutes. The temperature of the reaction mixture rose from the initial temperature of 5 °C to 18 °C. The reaction mixture was poured into brine (150 ml) and the resulting solution was extracted with ether (3 x 50 ml). The organic layer was gradually washed with a saturated solution of sodium hydrogencarbonate (25 ml), saturated solution of sodium sulfite (25 ml) and brine (2 x 25 ml) and dried with magnesium sulfate. After evaporation 1.1 g of the evaporation residue was obtained whose crystallization from ethanol produced 0.75 g (59%) of crystals with the melting temp. of T₁=79 °C.
Example 3

Ethyl 2-(6-(4-chlorophenyl)-2,2-dimethyl-7-phenyl-2,3-dihydro-1 \( H \)-pyrrolizine-5-yl)acetate (IVa)

Carrying out the procedure described in example 2 and subsequent chromatographic separation (Cyclograph, hexane-ethyl acetate) using a dimethylsulfoxide-ethanol mixture, 38% of the desired product (IVa) were obtained besides 24% of the starting 6-(4-chlorophenyl)-2,2-dimethyl-7-phenyl-2,3-dihydro-1 \( H \)-pyrrolizine (III).

Example 4

Ethyl 2-(6-(4-chlorophenyl)-2,2-dimethyl-7-phenyl-2,3-dihydro-1 \( H \)-pyrrolizine-5-yl)acetate (IVa)

To the stirred mixture of 6-(4-chlorophenyl)-2,2-dimethyl-7-phenyl-2,3-dihydro-1 \( H \)-pyrrolizine (III) (1 g, 3.1 mmol), ethyl iodoacetate (0.8 g, 3.7 mmol), iron (II) sulfate heptahydrate (0.2 g, 0.75 mmol), dodecylmethylsulfoxide (2 ml) and acetonitrile (20 ml) a solution of 30% hydrogen peroxide (2.1 ml) and dimethylsulfoxide (2 ml) was added dropwise under cooling in a cold water bath within 15 minutes. The mixture was stirred at the laboratory temperature for 15 minutes, cooled to the temperature of 10 °C and a solution of 30% hydrogen peroxide (1 ml) and dimethylsulfoxide (1 ml) was added dropwise under cooling in a cold water bath within 15 minutes and the mixture was stirred at the laboratory temperature for another 15 minutes. The reaction mixture was poured into brine (150 ml) and the resulting solution was extracted with ether (3 x 50 ml). The organic layer was gradually washed with a saturated solution of sodium hydrogencarbonate (25 ml), a saturated solution of sodium sulfite (25 ml) and brine (2 x 25 ml) and dried with magnesium sulfate. The obtained evaporation residue was purified by chromatography on silica gel in the toluene/ethanol system (95:5).

After crystallization of the fractions containing the desired product from ethanol 0.45 g (35 %) of the desired substance was obtained.
Example 5

Ethyl 2-(6-(4-chlorophenyl)-2,2-dimethyl-7-phenyl-2,3-dihydro-1H-pyrrolizin-5-yl)acetate (IVa)

Carrying out the procedure described in example 4 using phenylmethylsulfoxide (thioanisole-S-oxide) as the sulfoxide provided 24% yield of the desired product.

Example 6

Ethyl 2-(6-(4-chlorophenyl)-2,2-dimethyl-7-phenyl-2,3-dihydro-1H-pyrrolizine-5-yl)acetate (IVa)

Carrying out the procedure described in example 4 using dibutylsulfoxide as the sulfoxide provided 43% yield of the desired product.

Example 7

Ethyl 2-(6-(4-chlorophenyl)-2,2-dimethyl-7-phenyl-2,3-dihydro-1H-pyrrolizine-5-yl)acetate (IVa)

Carrying out the procedure described in example 4 using tetrahydrothiofenoxide as the sulfoxide provided 43% yield of the desired product.
Example 8

Ethyl 2-(6-(4-chlorophenyl)-2,2-dimethyl-7-phenyl-2,3-dihydro-1H-pyrrolizine-5-yl)acetate (IVa)

To a solution of 0.72 g (4.7 mmol) of sodium iodide in 10 ml of acetonitrile, 0.72 g (4.7 mmol) of ethyl bromoacetate was added under stirring; then the mixture was stirred at the laboratory temperature for 1 hour. Subsequently, the solids were filtered off and the filtrate was evaporated in a rotatory vacuum evaporator. The evaporation residue of crude ethyl iodoacetate was added to a mixture of 6-(4-chlorophenyl)-2,2-dimethyl-7-phenyl-2,3-dihydro-1H-pyrrolizine (III) (1 g, 3.1 mmol), iron (II) sulfate heptahydrate (0.2 g, 0.75 mmol) in dimethylsulfoxide (24 ml). The mixture was cooled to the temperature of 10°C and 30% hydrogen peroxide (2.2 ml) was added dropwise under cooling in a cold water bath within 20 minutes and the mixture was stirred at the laboratory temperature for another 90 minutes. The reaction mixture was poured into brine (150 ml) and the resulting solution was extracted with ether (3 x 50 ml). The organic layer was gradually washed with a saturated solution of sodium hydrogen carbonate (25 ml), a saturated solution of sodium sulfite (25 ml) and brine (2 x 25 ml) and dried with magnesium sulfate. The obtained evaporation residue was re-crystallized from ethanol, yielding 0.64 g (51%) of the desired substance.

Example 9

Ethyl 2-(6-(4-chlorophenyl)-2,2-dimethyl-7-phenyl-2,3-dihydro-1H-pyrrolizine-5-yl)acetate (IVa)

To the stirred solution of 0.72 g (4.7 mmol) of sodium iodide in 10 ml of acetonitrile, 0.72 g (4.7 mmol) of ethyl bromoacetate was added under stirring; the mixture was then stirred at the laboratory temperature for 1 hour. Subsequently, the solids were filtered off and the filtrate was added to a mixture of 6-(4-chlorophenyl)-2,2-dimethyl-7-phenyl-2,3-dihydro-1H-pyrrolizine (III) (1 g, 3.1 mmol) and iron (II) sulfate heptahydrate (0.2 g, 0.75 mmol) in dimethylsulfoxide (24 ml). The mixture was cooled to the temperature of 10°C and 30% hydrogen peroxide (2.2 ml) was added dropwise under cooling in a cold water bath within 30
minutes and the mixture was stirred at the laboratory temperature for another 90 minutes. The reaction mixture was poured into brine (200 ml) and the resulting solution was extracted with ether (3 x 50 ml). The organic layer was gradually washed with a saturated solution of sodium hydrogen carbonate (25 ml), a saturated solution of sodium bisulfite (25 ml) and brine (2 x 25 ml) and dried with magnesium sulfate. The obtained evaporation residue was re-crystallized from ethanol, yielding 0.70 g (55 %) of the desired substance.

Example 10

Ethyl 2-(6-(4-chlorophenyl)-2,2-dimethyl-7-phenyl-2,3-dihydro-1H-pyrrolizine-5-yl)acetate (IVa)

To the stirred mixture of 6-(4-chlorophenyl)-2,2-dimethyl-7-phenyl-2,3-dihydro-1H-pyrrolizine (III) (1 g, 3.1 mmol), ethyl bromoacetate (0.8 g, 4.6 mmol), sodium iodide (0.7 g, 4.6 mmol), iron (II) sulfate heptahydrate (0.2 g, 0.75 mmol) and dimethylsulfoxide (25 ml) a solution of 30% hydrogen peroxide (2.1 ml) and dimethylsulfoxide (5 ml) was added dropwise under cooling in a cold water bath within 20 minutes. The temperature of the reaction mixture rose from the initial temperature of 10 °C to 20 °C. The reaction mixture was poured into brine (200 ml) and the resulting mixture was extracted with ether (3 x 50 ml). The organic layer was gradually washed with a saturated solution of sodium hydrogen carbonate (25 ml), a saturated solution of sodium sulfite (25 ml) and brine (2 x 25 ml) and dried with magnesium sulfate. After evaporation 1.4 g of the evaporation residue was obtained whose crystallization from ethanol provided 0.6 g (47 %) of crystals with the melting temp. of 74-76 °C.

Example 11

Methyl 2-(6-(4-chlorophenyl)-2,2-dimethyl-7-phenyl-2,3-dihydro-1H-pyrrolizine-5-yl)acetate (IVb)

Carrying out the procedure described in example 1 using methyl iodoacetate provided the desired product (IVb) in 78% yield, melting temp. 166-168 °C. 1H-NMR spectrum (CDCl₃):
Example 12

Methyl 2-(6-(4-chlorophenyl)-2,2-dimethyl-7-phenyl-2,3-dihydro-1H-pyrrolizine-5-yl)acetate (IVb)

To the stirred mixture of 6-(4-chlorophenyl)-2,2-dimethyl-7-phenyl-2,3-dihydro-1H-pyrrolizine (III) (1 g, 3.1 mmol), methyl bromoacetate (0.7 g, 4.6 mmol), sodium iodide (0.7 g, 4.6 mmol), iron (II) sulfate heptahydrate (0.2 g, 0.75 mmol) and dimethylsulfoxide (25 ml) a solution of 30% hydrogen peroxide (2.1 ml) and dimethylsulfoxide (5 ml) was added dropwise under cooling in a cold water bath within 20 minutes. The temperature of the reaction mixture rose from the initial temperature of 10 °C to 20 °C. The reaction mixture was poured into brine (200 ml) and the resulting mixture was extracted with ether (3 x 50 ml). The organic layer was gradually washed with a saturated solution of sodium hydrogen carbonate (25 ml), saturated solution of sodium sulfite (25 ml) and brine (2 x 25 ml) and dried with magnesium sulfate. After evaporation 1.4 g of the evaporation residue was obtained whose crystallization from ethanol provided 0.5 g (45%) of crystals with the melting point of 165-167 °C.

Example 13

7-tert-Butyl 2-(6-(4-chlorophenyl)-2,2-dimethyl-7-phenyl-2,3-dihydro-1H-pyrrolizine-5-yl)acetate (IVc)

Carrying out the procedure described in example 1 using tert-butyl iodoacetate the desired product (IVc) was obtained in the yield of 78%, melting temp. 165-167 °C. 1H-NMR spectrum (CDCl₃): 1.29s, 6H (2xCH₃); 1.46s, 9H (t-Bu); 2.84s, 2H (CH₂); 3.41s, 2H (CH₂); 3.75s, 2H (CH₂); 7.03-7.26m, 9H Ar.
Example 14

_Tert-Butyl 2-(6-(4-chlorophenyl)-2,2-dimethyl-7-phenyl-2,3-dihydro-1 H-pyrrolizine-5-yl)acetate (IVc)_

Carrying out the procedure described in example 9 using tert-butyl bromoacetate the desired product (IVc) was obtained in the yield of 60%, melting temp. 166-168 °C.

Example 15

_Hexyl 2-(6-(4-chlorophenyl)-2,2-dimethyl-7-phenyl-2,3-dihydro-1 H-pyrrolizine-5-yl)acetate (IVd)_

Carrying out the procedure described in example 1 using hexyl iodoacetate the desired product (IVd) was obtained in the yield of 73%.

Example 16

_2-(6-(4-Chlorophenyl)-2,2-dimethyl-7-phenyl-2,3-dihydro-1 H-pyrrolizine-5-yl)acetonitrile (VIII)_

Carrying out the procedure described in example 1 using iodoacetonitrile the desired product (VIII) was obtained in the yield of 65%, melting temp. 144-146 °C. 

_J_H-NMR spectrum (CDCl₃): 1.33s, 6H (2xCH₃); 2.85s, 2H (CH₂); 3.62s, 2H (CH₂); 3.84s, 2H (CH₂); 7.00-7.31m, 9H Ar._
Example 17

2-(6-(4-Chlorophenyl)-2,2-dimethyl-7-phenyl-2,3-dihydro-1\textsubscript{H}-pyrrolizine-5-yl)acetic acid (I)

The mixture of the ester (IVa) (0.5 g, 1.2 mmol), ethanol (3 ml) and 10 % of NaOH (1 ml) was stirred under slight reflux for 30 minutes. Then the mixture was poured into diluted hydrochloric acid (10 ml) and extracted with ether (3x5 ml). The combined extracts were evaporated until dryness and the evaporation residue was re-crystallized from ethanol. The desired product (I) was obtained in the yield of 64%, melting temp. 164-166 °C. \textsuperscript{1}H-NMR spectrum (CDCl\textsubscript{3}): 1.30s, 6H (2xCH\textsubscript{3}); 2.85s, 2H (CH\textsubscript{2}); 3.57s, 2H (CH\textsubscript{2}); 3.75s, 2H (CH\textsubscript{2}); 7.02-7.27m, 9H\textsubscript{Ar}.

Example 18

2-(6-(4-Chlorophenyl)-2,2-dimethyl-7-phenyl-2,3-dihydro-1\textsubscript{H}-pyrrolizine-5-yl)acetic acid (I)

Carrying out the procedure described in example 17 using the ester (IVb) the desired product (I) was obtained in the yield of 71%.

Example 19

2-(6-(4-Chlorophenyl)-2,2-dimethyl-7-phenyl-2,3-dihydro-1\textsubscript{H}-pyrrolizine-5-yl)acetic acid (I)

The mixture of the ester (IVc) (0.5 g, 1.2 mmol), ethanol (5 ml) and 50% NaOH (1 ml) was stirred under slight reflux for 8 hours. Then the mixture was poured into diluted hydrochloric acid (25 ml) and extracted with (3x5 ml). The combined extracts were dried with magnesium sulfate, evaporated until dryness and the evaporation residue was re-crystallized from ethanol. The desired product (I) was obtained in the yield of 60%.
Example 20

2-(6-(4-Chlorophenyl)-2,2-dimethyl-7-phenyl-2,3-dihydro-1H-pyrrolizine-5-yl)acetamide (IX)

The mixture of the nitrite (VIII) (0.5 g, 1.4 mmol), ethanol (50 ml) and 2N NaOH (5 ml) was stirred under slight reflux for 2 hours. Then the mixture was poured into water (500 ml), acidified with concentrated hydrochloric acid (10 ml) and extracted with ether (3x50 ml). The combined extracts were evaporated until dryness and the evaporation residue was re-crystallized from ethanol. The desired product (IX) was obtained in the yield of 48%, melting temp. 230-232 °C. 1H-NMR spectrum (CDCl₃): 1.29s, 6H (2xCH₃); 2.85s, 2H (CH₂); 3.49s, 2H (CH₂); 3.71s, 2H (CH₂); 5.64 brd, J=61,5 Hz, 2H (CONH₂); 7.02-7.28m, 9H Ar.

Example 21

2-(6-(4-Chlorophenyl)-2,2-dimethyl-7-phenyl-2,3-dihydro-1H-pyrrolizine-5-yl)acetic acid (I)

To the solution of the amide (IX) (0.2 g, 0.52 mmol) in methanol (20 ml), heated up to slight reflux, 0.2 ml of sulfuric acid was added and the mixture was refluxed for 4 hours. Subsequently, 40% aqueous solution of sodium hydroxide (2 ml) was added to the reaction mixture and the mixture was further refluxed for 4 hours. Then, the reaction mixture was poured into diluted hydrochloric acid (50 ml) and extracted with ether (3x10 ml). The combined extracts were dried with magnesium sulfate, evaporated until dryness and the evaporation residue was re-crystallized from ethanol. The desired product (I) was obtained in 50% yield.
CLAIMS

1. A method of manufacturing 2-(6-(4-chlorophenyl)-2,2-dimethyl-7-phenyl-2,3-dihydro-
   \(1H\)-pyrrolizine-5-yl)acetic acid of formula I

\[
\text{(I)}
\]

characterized in that 6-(4-chlorophenyl)-2,2-dimethyl-7-phenyl-2,3-dihydro-\(1H\)-pyrrolizine of formula II

\[
\text{(II)}
\]

is alkylated with a iodo derivative of formula VII

\[
\text{ICH}_2A
\]

(VII),

wherein A is either the cyano group CN or an ester group COOR, wherein R is an
(un)branched Q-C\(_6\) alkyl group,

with the use of the Fenton reagent in the presence of a sulfoxide of formula \(R^1\)-SO-\(R^2\),
wherein \(R^1\) is an (un)branched Ci-Ci\(_2\) alkyl group, \(R^2\) is either an (un)branched Ci-Ci\(_2\) alkyl group, an aryl group or a substituted aryl group, or wherein \(R^1, R^2\) are
independently \((\text{CH}_2)_mX(\text{CH}_2)_n\), wherein \(X = \text{CH}_2, O, S, NR^3, m = 1-3, n = 1-3, \) and \(R^3\)
is either an (un)branched Ci-Ci\(_2\) alkyl group, an aryl group or a substituted aryl group,
the reaction being carried out in the environment of the sulfoxide used or in its mixture with suitable solvents at a temperature of 0 °C to 80 °C, preferably at temperatures in the range of 10 to 40 °C, and the resulting ester of formula IV or nitrile of formula VIII is hydrolyzed to the desired product of formula I either directly or in the case of the nitrile via the amide of formula IX.

2. The method according to claim 1, characterized in that ethyl iodoacetate is used as the iodo derivative of formula VII for the alkylation.

3. The method according to claim 1, characterized in that methyl iodoacetate is used as the iodo derivative of formula VII for the alkylation.

4. The method according to claim 1, characterized in that tert-butyl iodoacetate is used as the iodo derivative of formula VII for the alkylation.

5. The method according to claim 1, characterized in that hexyl iodoacetate is used as the iodo derivative of formula VII for the alkylation.

6. The method according to claim 1, characterized in that iodoacetonitrile is used as the iodo derivative of formula VII for the alkylation.

7. The method according to claim 1, characterized in that a iodo derivative of formula ICH₂A (VII) is used, obtained from the corresponding chloro derivative ClCH₂A or bromo derivative BrCH₂A, wherein A is as defined in claim 1, by reaction with a suitable inorganic, ammonium, or quaternary ammonium iodide in a suitable solvent from the group of dialkylketones of formula R⁴-CO-R⁵, wherein R⁴ and R⁵ are branched or unbranched Ci-C₅ alkyl groups, or from the group of polar aprotic solvents.
including acetonitrile, dimethylformamide, or dimethylsulfoxide, and the subsequent reaction is carried out without isolation of the resulting iodo derivative.

8. The method according to claim 7, characterized in that sodium iodide is used as the iodide and acetone is used as the solvent.

9. The method according to claim 7, characterized in that sodium iodide is used as the iodide and acetonitrile is used as the solvent.

10. The method according to claim 7, characterized in that sodium iodide is used as the iodide and dimethylsulfoxide is used as the solvent.

11. The method according to claim 1, characterized in that the sulfoxide used is also used as the reaction medium.

12. The method according to claim 1, characterized in that a solution of the sulfoxide used in admixture with a suitable polar aprotic solvent, such as acetonitrile or dimethylformamide, or a mixture thereof with a suitable chlorinated solvent, such as dichloromethane, is used as the reaction medium.

13. The method according to any one of claims 1, 7, 11 and 12, characterized in that dimethylsulfoxide is used as the sulfoxide component.

14. The method according to any one of claims 1, 7, 11 and 12, characterized in that dibutyl sulfoxide is used as the sulfoxide component.

15. The method according to any one of claims 1, 7, 11 and 12, characterized in that tetrahydrothiophene oxide is used as the sulfoxide component.

16. The method according to any one of claims 1, 7, 11 and 12, characterized in that methyl dodecyl sulfoxide is used as the sulfoxide component.
17. The method according to any one of claims 1, 7, 11 and 12, characterized in that methyl phenyl sulfoxide (thioanisole oxide) is used as the sulfoxide component.

18. The method according to claim 1, characterized in that the alkylation of the compound of formula II is a radical alkylation at a temperature in the range of 10 to 40 °C.

19. The method according to claim 1, characterized in that the hydrolysis of the ester of formula IV is carried out with a solution of an alkali hydroxide at temperatures in the range of 20 °C to 100 °C.

20. The method according to claim 1, characterized in that the hydrolysis of the nitrile of formula IV is carried out with a solution of an alkali hydroxide at temperatures in the range of 50 °C to 100 °C and the resulting amide of formula IX is further transformed to licofelone of formula I.

21. Methyl 2-(6-(4-chlorophenyl)-2,2-dimethyl-7-phenyl-2,3-dihydro-1H-pyrrolizine-5-yl)acetate.

22. Hexyl 2-(6-(4-chlorophenyl)-2,2-dimethyl-7-phenyl-2,3-dihydro-1H-pyrrolizine-5-yl)acetate.

23. 2-(6-(4-Chlorophenyl)-2,2-dimethyl-7-phenyl-2,3-dihydro-l H-pyrrolizine-5-yl)acetonitrile.

24. 2-(6-(4-Chlorophenyl)-2,2-dimethyl-7-phenyl-2,3-dihydro-l H-pyrrolizine-5-yl)acetamide.