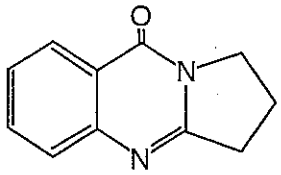
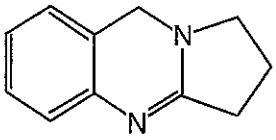
Processes for the production of chinazoline alkaloids

The invention refers to processes for the production of chinazoline alkaloids of the following formulas (I) and (III).



(I)



(III)

Compound (III) is 1,2,3,9-tetrahydropyrrolo[2,1-b]chinazoline. This compound is also known under the trivial name of deoxypeganine and occurs in plants of the Zygophyllaceae family. Because of its pharmacological properties, deoxypeganine is regarded as a member of the group of reversibly active cholinesterase inhibitors.
Apart from this, it also acts as a monoamine oxidase inhibitor. Deoxypeganine is taken into consideration as a medicinal agent for therapeutic purposes, e.g. for treating drug addiction and drug dependence (DE-A 199 06 978), for the therapy of Alzheimer's dementia (DE-A 199 06 975), or for the therapy of nicotine dependence (DE-A 199 06 979).

Compound (I), known under the designation of pegen-(9)-one-(8), is an important intermediate product in the synthesis of deoxypeganine and other chinazoline alkaloids of this type. The synthesis of pegen-(9)-one-(8) (short: pegenone) can be performed according to SPÄTH and PLATZER (Ber. 68 (1935), 2221-2224) by converting isatoic acid anhydride with an equimolar amount of pyrrolidone. Subsequently, a high-vacuum distillation at 140 to 160 °C must be carried through in order to separate the reaction byproducts. This method is suitable only for small amounts (in the gram range), but not for production on a larger scale.

According to MORRIS, HANFORD and ADAMS (J. Amer. Chem. Soc. 57 (1935), 951-954), pegenone (2,3-trimethylene-4-chinazolone) can be obtained (i) by oxidation of deoxyvasicine by means of hydrogen peroxide. Deoxyvasicine is identical with deoxypeganine. Alternatively, (ii), pegenone can be obtained by multistage synthesis, with γ-phenoxybutyryl chloride being reacted with o-aminobenzamide to the corresponding amide. After ring closure under heating, the phenoxyl group is replaced by bromine, and subsequently, through a further ring closure, 2,3-trimethylene-4-chinazolone (= pegenone) is obtained.

If pegenone is required as a starting compound for the production of deoxypeganine, the only method that could be taken into consideration - apart from the method according to SPÄTH and PLATZER mentioned above - is, if at all, the synthesis method (ii) proposed by Morris et al. This method, however, is uneconomical due to the number of reaction steps.

Deoxypeganine is preferably obtained by isolation from Syrian rue (Peganum harmala), or by synthesis.

MORRIS, HANFORD and ADAMS (loc cit., p. 953) describe the production of deoxyvasicine (= deoxypeganine) by reduction of 2,3-(α-hydroxytrimethylene)-4-chinazolone or 2,3-(α-chlorotrimethylene)-4-chinazolone, using glacial acetic acid and zinc dust (reaction type: Clemmensen reduction). Following chloroform extraction, the product was isolated by crystallisation from petroleum ether. It is disadvantageous here that the starting compounds (2,3-(α-hydroxytrimethylene)-4-chinazolone or 2,3-(α-chlorotrimethylene)-4-chinazolone) have to be synthesized starting from peganine (= vasicine).

According to SARGAZAKOV et al. (Khim. Prir. Soedin. 4 (1990), 506-507), deoxypeganine hydrochloride can be obtained by cyclocondensation of anthranilic acid with 2-pyrrolidone to give deoxyvasicinone hydrochloride (= pegenone hydrochloride) and subsequent Clemmensen reduction of this intermediate product to give deoxypeganine hydrochloride. The cyclocondensation reaction is performed in the presence of phosphorus trichloride, with toluene being used as solvent. Both after the first step (cyclocondensation) and after the second step (reduction), multiple chloroform extractions are necessary. Altogether, the production of 2 kg of deoxypeganine hydrochloride requires approx. 50 l of toluene and 80 l of chloroform.

The synthesis method described by SARGAZAKOV et al. is disadvantageous for several reasons. The yield amounts to only approx. 50%, the product obtained (deoxypeganine hydrochloride) being of a purity of 94-95%. This method requires large amounts of organic solvents, especially toluene and chloroform, as well as phosphorus trichloride. This is disadvantageous for reasons of ecology, but also for reasons of safety and cost. In addition, this method requires great expenditure of time and work since several chloroform extraction steps have to be carried through in order to achieve the aforementioned degree of purity. With a view to the use of deoxypeganine as medicinal agent it is especially disadvantageous that chlorohydrocarbons are used.

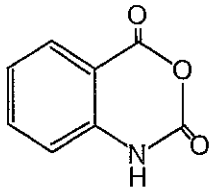
In the above-mentioned known synthesis methods, it is furthermore of disadvantage that due to the high proportion of reaction byproducts, isolation of the products by crystallisation methods is not possible and can instead be attained only by costly extraction steps or high-vacuum distillation.

It was therefore the object of the invention described herein to indicate synthesizing processes for the production of chinazoline alkaloids of the above-indicated formulas (I) and (III) which

- enable yields and degrees of product purity which at least correspond to those of known processes, or which surpass them;
- enable the production of deoxypeganine (III) for use in the manufacture of medicaments;
- largely do without the use of substances which are damaging to the environment or to health, especially organic solvents;
- have a good raw material balance;
- substantially produce only such byproducts as can be readily recycled;
- can be carried through using cost-effective starting materials;
- altogether enable a simpler and more cost-effective production of the above mentioned compounds on an industrial scale.

These and other objects are surprisingly achieved by methods according to the independent claims 1, 9, 18 and 20, as well as by the further embodiments described in the dependent claims.

According to claim 1, in a process according to the invention, a compound of formula (II) (= isatoic acid anhydride)



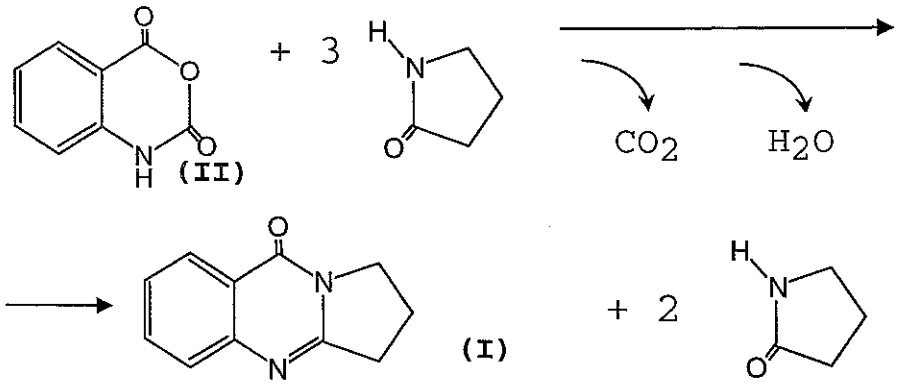
(II)

is reacted with 2-pyrrolidone (= pyrrolidinone) to obtain a compound of formula (I). In this reaction, an excess of

2-pyrrolidone is used, relative to the amount of compound (II) used. This means that the amount of pyrrolidone used is larger than the equimolar amount. Preferably, 1.5 to 5 mol, especially 2 to 4 mol, and most preferably 2.5 to 3.5 mol, of pyrrolidone are used, each of these values relating to the amount of compound (II) used.

This surprisingly has as a consequence that the formation of unfavourable reaction products is reduced and that the nascent product (I) can be readily crystallized. In addition, it is possible to obtain high yields (70%), with purity at approx. 99% (NMR). Thanks to the excellent crystallizability, it is possible to dispense with expensive purification methods, such as high-vacuum distillation.
Since purification of the product can be achieved in a simple manner by crystallization, the process can also be carried through on a larger scale without any problems.

The process is based on the following reaction equation, presented by way of example:



The reaction is performed under addition of heat, preferably at temperatures in the range of 50 to 200 °C. It is preferred that initially a temperature in the range of 70 to 130 °C, and subsequently a temperature in the range of 140 to 200 °C be maintained; with particular preference,

the temperature is initially 80 to 120 °C, and later 150 to 190 °C.

The aforementioned initial temperature is preferably maintained for a period of 0.5 to 2h, especially 1 to 1.5 h, after the start of the reaction. The aforementioned subsequent temperature is preferably maintained for a period of 1 to 8 h, especially 2 to 5 h.

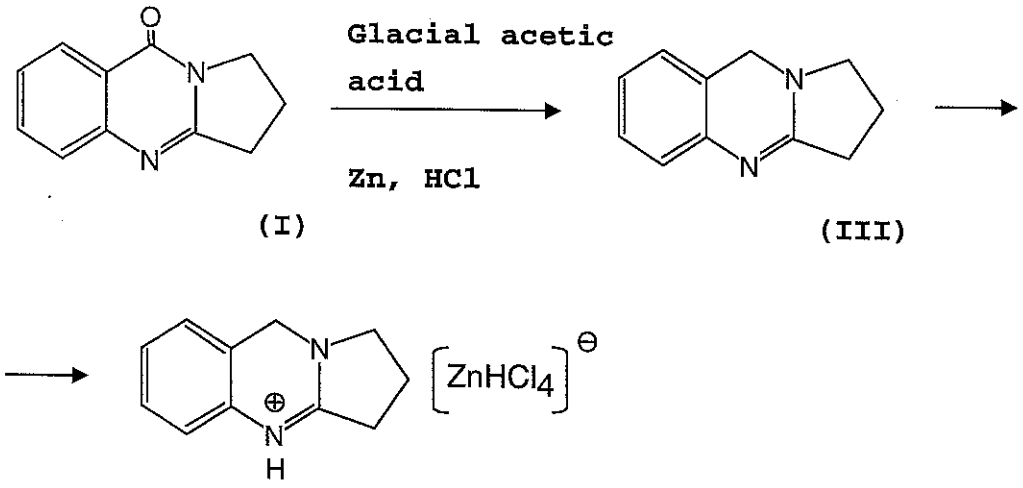
The process is preferably carried through by providing pyrrolidone and thereafter adding thereto the compound (II) in portions.

It is particularly advantageous to isolate product (I) directly from the reaction mixture by crystallisation. To crystallize compound (I), the reaction mixture is left to cool and is seeded with seed crystals. Crystallization is carried through at room temperature, preferably at least 25 °C, with preference 30 to 70 °C, most preferably 40 to 60 °C, whereby the course of the crystallization is accelerated. The crystallization process takes approx. 24 h to 7 days, preferably approx. 50 h to 100 h. The resultant crystals contain pyrrolidone.

The present invention further relates to processes for the production of deoxypeganine (compound according to formula III). The processes substantially comprise three steps:

(A) Producing compound (I) according to a process according to any one of claims 1 to 8;
(B) reduction reaction, giving compound (III) in salt form;
(C) liberating compound (III) from the salt.

The course of the reduction reaction (Clemmensen reaction) can be indicated, by way of example, as follows:

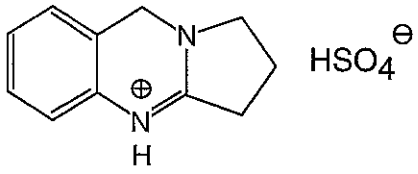


Compound (III) is here obtained in the form of a salt; in the case presented above by way of example, tetrachlorozincate salt is obtained if the reduction reaction is carried through in the presence of glacial acetic acid, zinc, and hydrochloric acid.

With particular preference, the starting compound (I) used is a reaction product isolated by crystallisation, this reaction product can be obtained by the above-described processes.

According to a preferred embodiment of the invention, the reduction reaction is performed using glacial acetic acid, zinc (zinc dust) and hydrochloric acid, this is preferably done by initially dissolving compound (I) in glacial acetic acid and subsequently adding zinc and hydrochloric acid.

According to a further preferred embodiment, the reduction reaction is performed under addition of zinc (as zinc dust) and sulfuric acid, without use of glacial acetic acid. This yields the hydrogen sulfate of compound (III):



The reaction is preferably carried through at temperatures of approx. 50 to 90 °C, especially 70 to 80 °C; generally, the reaction has quantitatively terminated after about 2 to 3 h. After termination of the reaction, the excess zinc is removed by known methods, e.g. by colation.

The salt of compound (III) thus obtained can be isolated in a simple and efficient manner by crystallisation from the reaction mixture. For this purpose the reaction mixture is seeded with seed crystals. When the crystallisation has taken place, the remaining mother liquor is separated by methods known to those skilled in the art (e.g. decanting).

In the above-mentioned step (C) of the inventive processes for the production of a compound of formula (III), the salt obtained in step (B) is then converted to the free base (III).

This is generally done by adding a base, preferably NaOH, to an aqueous solution of the salt.

According to a particularly preferred embodiment, this step is carried out in such a manner that the liberated base is obtained in molten form. This is achieved by carrying through the reaction at a temperature that is higher than the melting point (86 °C) of the free base (III) (= deoxypeganine), preferably at temperatures in the range of from 90 to 100 °C. The base present in molten form can be separated in a simple manner, possibly after freezing, from the reaction mixture; methods suitable for this purpose are known to those skilled in the art.

According to a further, especially preferred embodiment, the molten base (III) is thereafter cooled down and left to freeze. The frozen product is dissolved to obtain a satu-

rated solution; preferably, water is used as the solvent. From this saturated solution, which is adjusted so as to be alkaline by addition of a base (preferably NaOH), the final product deoxypeganine can be isolated in high-purity form through the subsequent crystallisation process.

The invention thus extends to processes for the production of deoxypeganine (compound of formula (III)) which contain a step wherein said compound is separated from the reaction mixture in liquid form. More particularly, the invention encompasses production processes of the kind mentioned which contain the following process steps:

- reducing the mentioned compound (I) to compound (III), whereby compound (III) is formed in salt form;
- adding of a base, whereby compound (III) is liberated from the salt and separates out in liquid form.

The inventive processes enable a simple and economical manufacture of the mentioned compounds (I, III) in a quantity and purity required in the production of medicaments. It is of particular advantage here that the use of organic solvents can be dispensed with.

The processes according to the invention will in the following be illustrated by examples.

Example 1 (Comparison example)

Preparation of pegen-9-(one)-(8) (identical with formula (I)) by converting pyrrolidone with an equimolar amount of isatoic acid anhydride according to SPÄTH and PLATZER (loc cit., p. 2221) and 2224.

Two litres of pyrrolidone were heated with 4 kg of isatoic acid anhydride (molar quantity ratio 1:1.07), in a chrome steel vessel (receptivity: 10 l), under vigorous stirring,

to 120 °C until incipient gas formation. This was followed by heating for 10 min to 160 °C and subsequently for 30 to 190 °C. Of this reaction mixture, 558 g (= 3 mol) was transferred, in still hot-liquid state, into a 1-litre flask (NS 29). The residue remaining in the steel vessel froze to a black, glassy mass which is not suitable for isolation of pegenone.

From the reaction mixture (558 g) transferred into the flask, up to 117 g of pegenone could be distilled by high-vacuum distillation using a distillation condenser that was heated to 120 °C; this corresponds to a yield of 21%. After recrystallization from ether, a melting point of 111 °C was determined.

Example 2:

Synthesis of pegenone (Compound according to formula (I))

One mole of isatoic acid anhydride (formula (II)) was converted with 3 mol of pyrrolidone. To this end, pyrrolidone was placed in a heatable chrome steel drum (30 l) and heated to approx. 100 °C, subsequently isatoic acid anhydride was added in portions while stirring continuously. After approx. 1 h, the entire amount of isatoic acid anhydride was dissolved in pyrrolidone. This was followed by heating for 5 h up to 155 to 160 °C (during this process, CO_2 and H_2O was formed; see above) and finally by heating for a short time up to 170 to 180 °C.

After cooling to approx. 50 °C, the mass thus obtained was seeded with pegenone crystals and left to crystallise for approx. 50 to 100 h at room temperature. By increasing the temperature (at least 25 °C), the crystallisation process could be accelerated (duration only approx. 2 to 3 days).

The "mother liquor" was separated from the crystals by decanting.

Altogether, more than 90% of the starting compounds used were converted to pegenone. The yield of crystallised pegenone was 40%; the remaining portion of the pegenone is dissolved in pyrrolidone. The pegenone crystals obtained still have a content of 30%-mol of pyrrolidone, according to NMR; the purity of the pegenone is approx. 99 % according to NMR.

In a modification of this process, the starting compounds were used in a quantity ratio of 1:2.5 (isatoic acid anhydride:pyrrolidone). The proportion of the crystallised pegenone could thereby be increased to approx. 55 %, at a purity of approx. 99%.

Example 3:

a) Clemmensen reduction of compound (I)

The pegenone crystals prepared according to Example 2 (2.5 kg; with a content of 15%-wt of pyrrolidone; this corresponds to 1.83 kg or 9.81 mol of pure pegenone) were dissolved at approx. 50 °C in 6.1 l (= 100.4 mol) of glacial acetic acid and transferred into a chrome steel vessel (50 l). Subsequently, 3.7 kg (= 56.4 mol) of zinc dust was added in small portions, during which process the temperature of the reaction mixture was kept at approx. 60°C. After approx. 1 h, 4 x 3 l of concentrated HCl (32%; corresponding to 121.74 mol) were added, in small portions, within 2 h while stirring continuously. Thereafter (after approx. 4 to 5 h) the excess zinc dust was removed from the reaction mixture by colation. After seeding with seed crystals, approx. 66% of the deoxypeganine salt could be separated by crystallization. The remaining mother liquor was

narrowed down by evaporation, whereupon 66% of the deoxypeganine salt again crystallized. Altogether, approx. 90% of the deoxypeganine salt could be obtained in crystalline form.

b) Liberation of deoxypeganine base (compound (III))

Crystals (2.5 kg) obtained in this manner were dissolved in hot water (approx. 11 l). Subsequently, NaOH was added under stirring (approx. 8 kg rotulae), while heating the mixture to 95 to 100 °C. This yielded deoxypeganine in molten form, and this was separated from the reaction mixture. After freezing, the product was again dissolved in heated water to obtain a saturated solution, which solution was adjusted with NaOH so as to be alkaline. From this saturated alkaline solution, deoxypeganine was isolated by crystallisation.

The deoxypeganine yield, relative to the deoxypeganine salt, was more than 90%, with a purity of 99.9% (NMR).

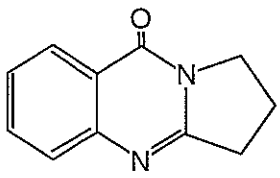
Example 4:
Clemmensen reduction of compound (I)
(alternative method)

175 g pegenone crystals (containing 30%-mol of pyrrolidone; this corresponds to 150 g of pegenone; see Example 2) were mixed with 750 ml of (20%) H_2SO_4 and heated (approx. 85 °C) for approx. 30 min while stirring.
Subsequently, 260 g of zinc dust was gradually added (duration: approx. 2 h). After approx. 1 h, H_2SO_4 was added again (375 ml, 40%). After a total of approx. 3 h, the reaction had terminated, and the excess zinc was separated by colation.

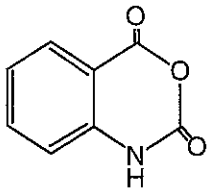
As described under Example 3 a), the deoxypeganine salt obtained was separated from the reaction mixture by crystallisation. The liberation of the base was carried through according to the method described under Example 3 b).

CLAIMS

1. Process for the production of a compound of the following formula (I)



(I)



(II)

by converting a compound of formula (II) with 2-pyrrolidone, characterized in that an excess of 2-pyrrolidone is used, relative to compound (II),

2. Process according to claim 1, characterized in that in a subsequent step the reaction product (I) is isolated directly from the reaction mixture by crystallisation.

3. Process according to claim 1 or 2, characterized in that 1.5 to 5 mol, preferably 2 to 4 mol, especially preferably 2.5 to 3.5 mol, of 2-pyrrolidone are used, each value relative to the amount of compound (II).

4. Process according to any one of the preceding claims, characterized in that the conversion is performed at 50 to 200 °C.

5. Process according to claim 4, characterized in that the temperature of the reaction mixture is initially heated to 70 to 130 °C, preferably to 80 to 120 °C, and subsequently to 140 to 200 °C, preferably 150 to 190 °C.

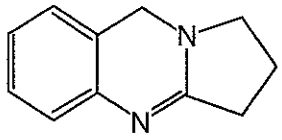
6. Process according to claim 5, characterized in that the said initial temperature is maintained for a period of 0.5 to 2 h, preferably 1 to 1.5 h, and the said subsequent

temperature is maintained for a period of 1 to 8 h, preferably from 2 to 5 h.

7. Process according to claim 6, characterized in that the reaction mixture is, after cooling, seeded with seed crystals of compound (I), and is maintained at room temperature, preferably at least 25 °C, for a period of 24 h to 7 days, preferably 50 to 100 h, to enable crystallisation.

8. Process according to claim 7, characterized in that the crystallisation is carried through at 30 to 70 °C, preferably at 40 to 60 °C.

9. Process for the production of a compound of the following formula (III), comprising the following steps:



(III)

(A) Preparing compound (I) according to a process according to any one of claims 1 to 8;
(B) reduction reaction, giving compound (III) in salt form;
(C) liberating compound (III) from the salt.

10. Process according to claim 9, characterized in that a reaction product isolated by crystallisation according to any one of claims 1 to 8 is used as compound (I).

11. Process according to claim 9 or 10, characterized in that the reduction reaction (step B) is performed in the presence of zinc and acid.

12. Process according to claim 11, characterized in that compound (I), preferably in crystallised form, is initially dissolved in glacial acetic acid and that subsequently zinc and hydrochloric acid are added.

13. Process according to claim 12, characterized in that the reduction reaction is performed in the presence of aqueous sulfuric acid and zinc dust.

14. Process according to any one of claims 9 to 13, characterized in that subsequent to step (B), compound (III) is isolated as a salt by crystallisation from the reaction mixture.

15. Process according to any one of claims 9 to 14, characterized in that in step (C) the compound (III) is liberated from the salt by addition of a base, preferably by addition of NaOH.

16. Process according to claim 15, characterized in that step (C) is carried through under heating, with the compound (III), which is liberated from the salt, being obtained in molten form.

17. Process according to claim 16, characterized in that the compound (III) present in molten form is cooled down and, after freezing, is crystallised from aqueous alkaline solution.

18. Process for the production of compound (III), starting from a salt of said compound, characterized in that compound (III) is liberated and isolated from the salt as a free base in molten form.

19. Process according to claim 18, characterized in that the compound (III) present in molten form is cooled down

and, after freezing, is crystallised from aqueous alkaline solution.

20. Process for the production of a compound of formula (III) as indicated, characterized in that it contains a step wherein this compound is separated from the reaction mixture in liquid form.

21. Process for the production of a compound of formula (III) as indicated, according to claim 20, characterized in that said process comprises the following steps:

- reducing the aforementioned compound (I) to compound (III), which gives compound (III) in salt form;
- adding a base, whereby compound (III) is liberated from the salt and separates out in liquid form.

22. Use of a compound of formula (I), produced according to a process according to any one of claims 1 to 9, for the production of a compound of formula (III) as a free base or in the form of a salt.