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The invention relates to a process for preparing 3-amino-9,13b-dihydro-1H-dibenz[c,f]imidazo[1,5-a]azepine hydrochloride.

This compound belongs to the group comprising the 2-aminoimidazolines and is a therapeutically effective substance which is particularly characterised by its antiallergic and antihistaminergic effect (EP 35749).

Large numbers of 2-aminoimidazolines are known. In order to synthesise them, diamines are reacted with cyclising reagents such as O-alkylisoureas and S-alkylisothioureas, particularly N-acylated or N-carbalkoxylated O-alkylisoureas and S-alkylisothioureas. However, this method of synthesis involves numerous steps and requires laborious purifying procedures. It comprises the acylation or alkoxylation of the alkyliso(thio)ureas, condensation with the diamine, the cyclisation reaction and saponification of the acyl group.

Another disadvantage is the emission of equimolar quantities of alkylmercaptans which occurs when S-alkylisothioureas are used.

The cyclisation reaction using alkali metal cyanates leads to similar problems.

However, the cyclisation reaction to produce 2-aminoimidazolines with bromocyanogen occurs in a single reaction step.

A process of this kind for synthesising 3-amino-9,13b-dihydro-1H-dibenz[c,f]imidazo[1,5-a]azepine hydrochloride is known from EP 35749. The reaction steps are described as follows:

6-chloro-11H-dibenz[b,e]azepine is reacted with sodium cyanide, the resulting nitrile is reduced with lithium aluminium hydride and reacted with bromocyanogen to form the corresponding 2-aminoimidazoline base which is finally precipitated in the form of the hydrochloride

from a methanolic suspension and then isolated. The yield is 41.8%.

However, within the scope of synthesis on an industrial scale, it is important not only to achieve high yields but also to obtain maximum possible throughput with the minimum technical expenditure.

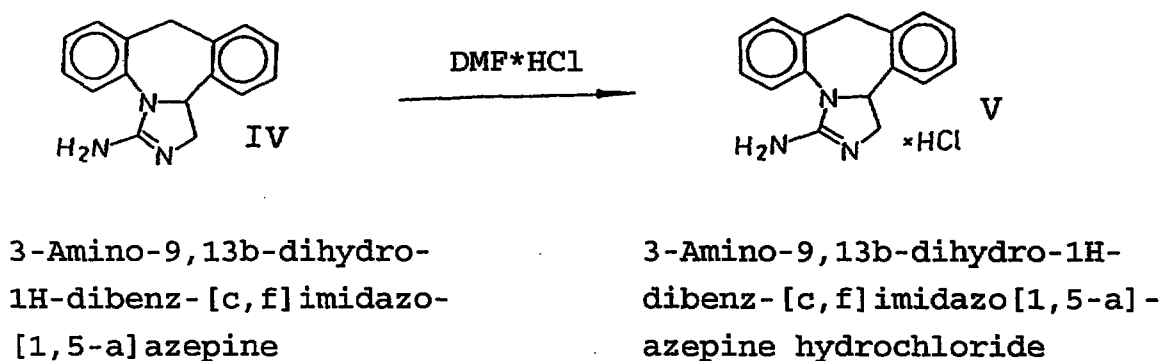
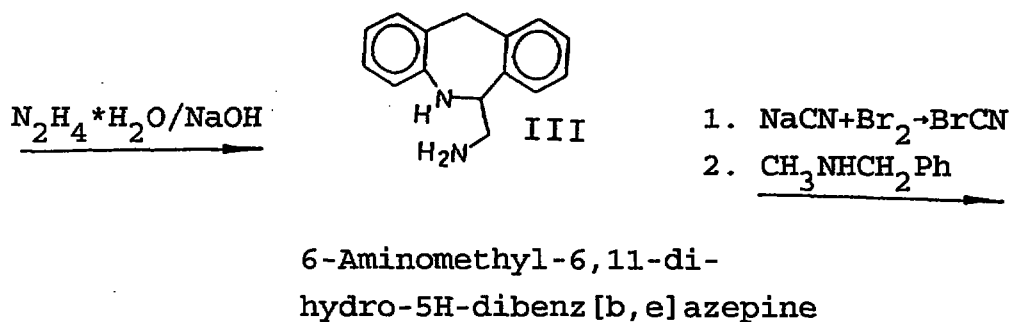
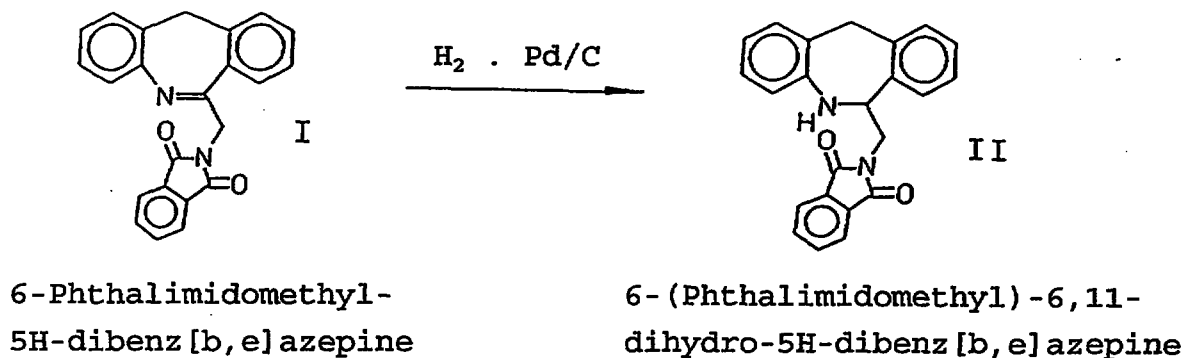
This is not possible, however, with the process proposed in EP 35749, because the reaction volumes cannot be increased without complex security measures, on account of the use of bromocyanogen, for example, which is a highly volatile, toxic substance. Moreover, each step of the reaction is followed by a purifying procedure, resulting in substantial losses of yield.

A further disadvantage is the reaction of the base to form the hydrochloride. The use of alcohols in the precipitation process as proposed in EP 35749 results in a loss of quality caused by gradual decomposition of the product.

A procedure of this kind is complicated, uneconomic and wasteful and is therefore not suitable for industrial production.

The aim of the present invention is to provide an industrial process which does not have the disadvantages of the prior art described above and makes it possible, in particular, to achieve a throughput of larger quantities of substance, whilst improving the quality of the end product.

It has now been found, surprisingly, that by hydrogenation of 6-phthalimidomethyl-5H-dibenz[b,e]-azepine (I), subsequent alkaline hydrazinolysis, reaction with bromocyanogen prepared in situ and precipitation of the resulting base (IV) in the form of the hydrochloride, the synthesis of 3-amino-9,13b-dihydro-1H-dibenz[c,f]imidazo(1,5-a)azepine hydrochloride (V) can be carried out so advantageously that industrial production is possible. Moreover, the process according to the invention involves a substantial increase in yield.



For the hydrogenation, 6-phthalimidomethyl-5H-dibenz-[b,e]azepine (I), which is obtainable by known methods, is reacted in dimethylformamide (if formic acid is used) or dimethylacetamide (if acetic acid is used) with hydrogen in a pressure range from 1 to 10 bar, preferably 6 to 8 bar, more particularly 7 bar, with palladium/charcoal catalyst, at a temperature of 40 to 100°C, preferably 60-80°C, more especially 70°C. 0.5 to 5 mol/mol, preferably 1 to 3 mol/mol, and more especially 2 mol/mol of acetic or formic acid is added to the reaction mixture. If hydrogenation were carried

out in pure organic acids, the reaction product would be precipitated and would then require laborious separation from the catalyst.

This effect advantageously permits a throughput of larger quantities of the substance. Moreover, the hydrogenation product need not be separated from the catalyst by additional extraction. After the hydrogenation reaction, the catalyst can be filtered off and, after some of the solvent has been distilled off, the product can be precipitated in a 90% yield by the addition of acetone.

In the process according to the invention, the hydrogenation product is subjected to an alkaline hydrazinolysis reaction, and the extracts from the reaction are reacted directly with bromocyanogen prepared in situ. For this purpose, 6-(phthalimido-methyl)-6,11-dihydro-5H-dibenz[b,e]azepine (II) is reacted with hydrazine hydrate in an alkaline mixture of water and a high-boiling liquid which is, however, immiscible with chlorohydrocarbons, e.g. ethyleneglycol, propyleneglycol, glycerol, preferably ethyleneglycol, for 2 hours at 100 to 150°C, preferably at 110-120°C. An alkali metal hydroxide solution, preferably sodium hydroxide solution, is used as the base.

Alkaline hydrolysis after a hydrazinolysis reaction is known (Gibson, M.S. and Bradshaw, R.W., *Angew. Chem.* 80, 986-996 (1968)), but direct reaction with hydrazine in an alkaline solution, thus enabling direct extraction of the resulting amine (III), is not known.

In addition, the hydrazinolysis under alkaline conditions advantageously enables the quantity of hydrazine used to be reduced to stoichiometric amounts, thus making it considerably easier to handle this carcinogenic substance.

The process according to the invention, by using water-miscible, high boiling liquids such as glycols, makes it possible to increase the reaction temperature

and thereby shorten the reaction times. In this way it is also possible to achieve direct extraction of the clean product with chlorohydrocarbons for the subsequent reaction with bromocyanogen. All impurities, e.g. the sodium salt of phthalic hydrazide which is produced during the reaction, remain in the aqueous phase, so that no separate purifying procedures are required.

Extraction is carried out at 15°C using a chlorinated hydrocarbon which is immiscible with the reaction mixture of the hydrazinolysis and which has a greater density; examples include chloroform, carbon tetrachloride, 1,2-dichloroethane, preferably dichloromethane.

For the reaction with bromocyanogen, the extraction phase is added to an aqueous solution formed from an aqueous sodium bromide solution which has been reacted with bromine at 5 to 25°C, preferably at 10 to 15°C, and then reacted with an aqueous sodium cyanide solution at 10 to 15°C. The mixture is stirred at 5 to 35°C, preferably at 15 to 25°C. The bromocyanogen formed in situ thus reacts with the amine. Consequently, there is no direct handling of large quantities of bromocyanogen.

After the reaction has ended, a non-volatile base, the reaction product of which with bromocyanogen is soluble in water or in benzene, toluene, xylene or halobenzene, is added in order to destroy the excess bromocyanogen. Examples of such bases include secondary monoamines such as N,N-dibenzylamine, N,N-dibutylamine, diethanolamine, diisopropylamine, as well as N-ethylbenzylamine, sarcosine-Na salt and preferably N-methylbenzylamine. After the base has been added, the mixture is refluxed for 15 minutes.

The handling of bromocyanogen on an industrial scale requires extensive safety procedures. Because the bromocyanogen in this case is produced in situ, it is possible to perform the reaction safely even on an industrial scale and at the same time to isolate the

product in clean form without complex purification: for the selective precipitation of 3-amino-9,13b-dihydro-1H-dibenz[c,f]imidazo[1,5-a]azepine (IV) the organic solvent is distilled off, mixed with benzene or xylene or a halobenzene, but preferably with toluene, and the base is precipitated by the addition of sodium hydroxide solution. The resulting amine (IV) is obtained with a high degree of purity and in a yield of 76%.

The use of alcohols such as methanol as solvent for preparing the hydrochloride, as described in EP 35749, leads to a gradual decomposition of the compound. Surprisingly, it has been found that 3-amino-9,13b-dihydro-1H-dibenz[c,f]imidazo[1,5-a]azepine can be precipitated from dimethylformamide in the form of the hydrochloride (V) in a virtually quantitative yield and with good stability.

To achieve this, the amine is dissolved, with heating, in dimethylformamide containing dissolved hydrochloric acid gas in a concentration ranging from 2.0 to 7.0 wt.-%, preferably 4.7 wt.-% and after filtration and partial distillation of the solvent the mixture is cooled. The hydrochloride is thus precipitated. After centrifuging, washing and drying, a yield of 90% is achieved.

The total yield of this process is 61.6%, compared with 41.8% for the process described in EP 35749.

The process according to the invention thus represents a significant improvement over the processes of the prior art. This applies both to the throughput, which is increased in particular by the improved solubility of the hydrogenation product, and also to the reduction in the number of synthetic stages and purifying procedures required. Moreover, the reaction yield has been significantly improved.

The Examples which follow serve to illustrate the invention.

Example 1: Preparation of 6-(phthalimidomethyl)-6,11-dihydro-5H-dibenz[b,e]azepine (II)

A suspension of 110.0 kg of 6-phthalimidomethyl-5H-dibenz[b,e]azepine in 911.4 litres of dimethylformamide, 28.7 kg of formic acid and a suspension of 12.5 kg of 10% palladium charcoal in 25 litres of dimethylformamide is fed into a 1200 litre VA-propulsive jet loop reactor. The reaction mixture is heated to 70°C and hydrogenated under 7 bar of absolute hydrogen pressure. After the catalyst has been filtered off and the reaction equipment and catalyst have been washed with 80 litres of dimethylformamide, 960 litres of dimethylformamide are distilled off from the combined filtrates at 70 to 80°C. After cooling to 50°C, 150 litres of acetone are added, then after further cooling to 15°C the precipitated crystals are centrifuged, washed with acetone and dried.

Yield: 99.5 kg of 6-(phthalimidomethyl)-6,11-dihydro-5H-dibenz[b,e]azepine (90% of theory)

Example 2: Preparation of 3-amino-9,13b-dihydro-1H-dibenz[c,f]imidazo[1,5-a]azepine (IV)

62.3 kg of 6-(phthalimidomethyl)-6,11-dihydro-5H-dibenz[b,e]azepine, 176 litres of glycol, 9 kg of hydrazine hydrate and 10.8 litres of 45% sodium hydroxide solution are introduced successively into a 1000 litre VA stirred apparatus and heated for 2 hours to 110°C (solution 1).

Meanwhile, in a 500 litre enamel apparatus, 19.9 kg of anhydrous sodium bromide are dissolved in 88 litres of water and 29.6 kg of bromine are metered in at 10 to 15°C. Then, at 10 to 15°C, a mixture of 34.0 kg of 26.5% sodium cyanide solution and 35.2 litres of water are added (solution 2).

Solution 1 is cooled to 15°C, 315 litres of water are added and extraction is carried out with 140.8 litres of dichloromethane. The dichloromethane phase is mixed with solution 2 at 15 to 20°C. The extraction of solution 1 with 95 litres and 10 litres of dichloromethane is repeated twice and the extracts are also added to solution 2. The two-phase mixture is stirred overnight at 20 to 25°C, then 10.7 kg of N-methylbenzylamine are added and the mixture is refluxed for 15 minutes.

After the organic solvent has been distilled off, 88 litres of toluene and 39.6 litres of 45% sodium hydroxide solution are added at 60°C, then after 30 minutes the mixture is cooled to 5°C and stirred for 30 minutes. The precipitate is centrifuged, washed and dried.

Yield: 33.3 kg of 3-amino-9,13b-dihydro-1H-dibenz[c,f]-imidazo[1,5-a]azepine
(76% of theory)

Example 3: Preparation of 3-amino-9,13b-dihydro-1H-dibenz[c,f]imidazo[1,5-a]azepine hydrochloride (V)

In a 250 litre enamel apparatus, 60 kg of 6-(phthalimidomethyl)-6,11-dihydro-5H-dibenz[b,e]azepine, 157.9 litres of dimethylformamide and 48.4 kg of a 20% hydrochloric acid gas solution in dimethylformamide are introduced. After heating to 120°C the solution is filtered and, after the apparatus has been washed with 23.6 litres of dimethylformamide, 75 to 80 litres of solvent are distilled off and the contents of the reaction apparatus are cooled to 5°C. The crystals obtained are removed by centrifuging, washed and dried.

Yield: 61.9 kg of 3-amino-9,13b-dihydro-1H-dibenz[c,f]-imidazo[1,5-a]azepine hydrochloride
(90% of theory)



Patent claims

1. Process for preparing 3-amino-9,13b-dihydro-1H-dibenz[c,f]imidazo[1,5-a]azepine hydrochloride, characterised in that 6-phthalimidomethyl-5H-dibenz[b,e]azepine is hydrogenated in dimethylformamide with the addition of formic acid or in dimethylacetamide with the addition of acetic acid, the molar ratio of the compound which is to be hydrogenated to the particular acid being 1 : 0.5 to 1 : 5, with hydrogen in the presence of palladium/charcoal as catalyst at a hydrogen pressure of 1 to 10 bar and at a temperature of 40 to 100°C, the hydrogenation product is subjected to hydrazinolysis in alkaline solution with the addition of a higher boiling, water-miscible solvent at 100 to 150°C, extracted with a chlorinated hydrocarbon in order to separate off the hydrazinolysis product, the extract is reacted with bromocyanogen prepared in situ at 5 to 35°C and after destruction of the excess bromocyanogen by the addition of a less volatile base and after the organic solvent has been distilled off the 3-aminoazepine is finally isolated as the hydrochloride after reaction with hydrogen chloride.

2. Hydrogenation of 6-phthalimidomethyl-5H-dibenz[b,e]azepine according to claim 1, characterised in that the hydrogenation is carried out in dimethylformamide with the addition of formic acid in a concentration range of from 1 to 3 mol of acid per mol of azepine, preferably 2 mol/mol, using palladium/charcoal as catalyst at 6 to 8 bar, preferably 7 bar of hydrogen pressure and at a temperature of 60 to 80°C, preferably 70°C.

3. Hydrazinolysis of 6-(phthalimidomethyl)-6,11-dihydro-5H-dibenz[b,e]azepine according to claim 1, characterised in that the hydrazinolysis is carried out in an alkaline mixture of water and a high-boiling



liquid which is immiscible with chlorinated hydrocarbons.

4. Hydrazinolysis of 6-(phthalimidomethyl)-6,11-dihydro-5H-dibenz[b,e]azepine according to claim 1, characterised in that

- a) the reaction is carried out with hydrazine hydrate in an alkaline solution at between 100 and 150°C, preferably at 110 to 120°C,
- b) the base used is an alkali metal hydroxide solution, preferably sodium hydroxide solution,
- c) the work is done in higher-boiling water-miscible solvents, preferably ethylene glycol, propylene glycol, glycerol, most preferably ethylene glycol and
- d) in order to isolate the hydrazinolysis product, extraction is carried out with a chlorinated hydrocarbon, preferably chloroform, carbon tetrachloride, 1,2-dichloroethane, most preferably dichloromethane.

5. Reaction of 6-aminomethyl-6,11-dihydro-5H-dibenz[b,e]azepine with bromocyanogen according to claim 1, characterised in that

- a) sodium bromide in aqueous solution is reacted with bromine at 5 to 25°C, preferably 10 to 15°C, and then with sodium cyanide at 10 to 15°C and
- b) this solution is stirred at 5 to 35°C, preferably at 15 to 25°C, with the extraction phase which contains the hydrazinolysis product and then
- c) a base is added, preferably N,N-dibenzylamine, N,N-dibutylamine, diethanolamine, diisopropylamine, N-ethylbenzylamine, sarcosine Na salt and especially N-methylbenzylamine and
- d) the resulting 3-amino-9,13b-dihydro-1H-dibenz[c,f]-imidazo[1,5-a]azepine is taken up in benzene, xylene or a halobenzene, preferably toluene, and precipitated by the addition of sodium hydroxide



solution.

6. Preparation of the hydrochloride according to claim 1, characterised in that the base is dissolved, with heating, in dimethylformamide which contains dissolved hydrochloric acid gas in a concentration range from 2.0 to 7.0 wt.-%, preferably 4.7 wt.-%, and after filtration and distillation of about one third of the solvent, the mixture is cooled, whereupon 3-amino-9,13b-dihydro-1H-dibenz[c,f]imidazo[1,5-a]azepine hydrochloride is precipitated.