

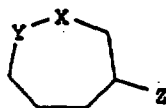
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The title of the invention is:

**Improved method for the preparation of hexahydroazepinones
and hexahydroazepinoles**

Improved method for the preparation of hexahydroazepinones and hexahydroazepinoles

The present invention relates to an improved method for the preparation of hexahydroazepinones and hexahydroazepinoles of the general formula I



10

wherein

X signifies N-R, CH₂, S, O

Y signifies N-R, N-CH₃, or signifies N-CH₂-CH₂-C₆H₅ and

15 Z signifies O, -OH, wherein in each case R represents H, alkyl, cycloalkyl, aralkyl, aryl and the addition salts thereof.

Heterocyclic ketones having seven-membered rings are important intermediate products for the synthesis of pharmacologically active substances. These include structures of the azelastine type (INN) and the flezelastine type (INN), which have active antiasthmatic and antiallergic properties (for example, DE-OS 3634942/Drugs Of The Future 12 (3), 283 (1987/EP 488209), as well as structures for the treatment of disorders of the central nervous system such as Parkinsonism, hyperprolactinaemia and schizophrenia or for the treatment of cardiovascular diseases (for example, DE-OS 3820775).

30

Fungicidally active substances containing a heterocyclic seven-ringed structural element are also known.

Moreover, derivatives of the phospholipid type containing a heterocyclic seven-ringed structural element in the main component display antineoplastic activity.

35

Prior art

A comprehensive survey of the Dieckmann condensation is found in Org. Reactions, Vol. 15, 1-203 (1967) and in the
5 references cited there.

Three criteria are invariably emphasised in the synthesis of seven-membered and higher-membered rings:

- 10 1. high dilution in order to promote the intramolecular as against the intermolecular reaction
2. long reaction times (slow dropwise addition of the dicarboxylic ester in order to promote the intramolecular reaction)
- 15 3. large excesses of the base employed.

The greatly varying yields are also noticeable, even in the preparation of identical products by different working groups.

20

Alternative methods of preparation such as

- Friedel-Crafts acylation (J. Chem. Soc., Perkin Trans. I 1992, 445)
 - ring enlargement using diazomethane (Bull. Chem. Soc., Japan, 31, 418 (1958); Coll. Czech. Chem. Commun., 51, 2034 (1986))
 - ozonolysis of cyclohexenone followed by a reductive amino cyclisation (Synth. Commun., 21 (7), 881 (1991))
- do not lead to satisfactory yields of the desired products,
25 quite apart from the technical achievement of ozonolysis or
30 the handling of diazomethane.

The object of the invention is to develop a method for the large-scale preparation of heterocyclic ketones having
35 seven-membered rings, based on the well-known Dieckmann condensation reaction.

The invention relates to the preparation of salts of heterocyclic ketones having seven-membered rings by means of Dieckmann condensation.

- 5 The operation is such that a 1,8-dicarboxylic ester obtainable in a known manner is reacted with strong bases in an inert solvent. Following acid hydrolysis of the cyclic β -enolate carboxylic ester formed, the ester is saponified without being isolated and thermally
- 10 decarboxylated. The resulting heterocyclic ketone having a seven-membered ring is subsequently separated from the reaction mixture in the form of its acid addition salt and isolated in pure form.
- 15 Surprisingly, it was found that the parameters of long reaction time, large excess of bases and high dilution do not (as hitherto assumed) influence the amount of the yield in a particular way. At reaction times of from 1 to 6 hours, preferably 1 to 3 hours, and excesses of base of
- 20 from 0% to a maximum of 20%, it was possible to establish technical conditions for carrying out the dilution without resorting to large quantities of solvent and hence greatly to increase the production output.
- 25 To this end two methods were developed.
1. The base, which is dissolved in an inert solvent, is circulated. A jet nozzle is positioned in the circulation system, similar to the principle of the water-jet pump. The
 - 30 dicarboxylic ester is introduced undiluted into the side inlet of the nozzle (see Figure 1).
 2. The ascending vapour along a packed column is used to dilute the dicarboxylic ester introduced in undiluted form,
 - 35 which is charged at the top of the column. A practical side-effect is that the diester is thereby brought to the reaction temperature and, by means of a suitable solvent,

can also be dissolved in the column and freed from highly volatile by-products, such as residual solvents. The concentrations in the two methods described above range between 0.1 and 1.5 mol/l, preferably between 0.3 and 0.9 mol/l (dicarboxylic ester to solvent initially employed). At the same time as the dicarboxylic ester is added, an azeotropic solvent mixture is separated off at the top of the column, and corresponds in fact to as much as 1 to 3 times the quantitative volume of the dicarboxylic ester introduced.

Suitable solvents are:

aliphatic ethers such as, for example

- diethyl ether
- tetrahydrofuran
- dioxane

aromatic hydrocarbons such as, for example

- benzene
- toluene
- o-xylene
- m-xylene
- p-xylene
- xylene (mixture of isomers)
- mesitylene

The bases which can be employed are:

- alkali and alkaline-earth hydrides
- alkali and alkaline-earth amides
- alkali and alkaline-earth alcoholates

Suitable alcohol components for the 1,8-dicarboxylic esters are

- alkyl alcohols
- isoalkyl alcohols
- cycloalkyl alcohols

as well as aralkyl or aryl alcohols.

The present invention is illustrated in more detail by the following examples.

5

Example 1

A side stream of 245.3 g of ethyl 4-(2-carbethoxyethyl-methylamino)butyrate is charged evenly under nitrogen over
10 a period of 2 hours into a solution of 123.4 g of potassium tert-butyrate in 1.3 l of boiling xylene pumped round a circulation system and the mixture is allowed to react for a further 0.5 hours. 750 ml of distillate is withdrawn. The reaction mixture is hydrolysed at 50 to 80°C by rapid
15 addition to a mixture of 300 ml of concentrated (37%) hydrochloric acid and 500 g of ice cubes. The organic phase separated off is washed twice, each time with 150 ml of semi-concentrated hydrochloric acid. The combined aqueous extracts are heated for 2 hours under vigorous reflux and
20 then evaporated to dryness in a vacuum. The residue is dissolved in 700 ml of isopropanol, filtered off hot from the undissolved potassium chloride and crystallised at 0 to -5°C. The residue filtered off is dried to constant weight in a vacuum at elevated temperature. A second fraction can
25 be obtained by concentrating the mother liquor to a volume of approximately 100 ml. 141.6 g (86.6%) of 1-methyl-perhydroazepin-4-one HCl is obtained.

Melting point: 167°C (decomposition)

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Example 2

A side stream of 245.3 g of ethyl 4-(2-carbethoxyethyl-methylamino)butyrate dissolved in 900 ml of xylene is
35 charged evenly under nitrogen over a period of 3 hours into a solution of 123.4 g of potassium tert-butyrate in 1.3 l of boiling xylene pumped around a circulation system and

the mixture is allowed to react for a further 1.5 hours. 1500 ml of distillate is withdrawn. The reaction mixture is hydrolysed at 50 to 80°C by rapid addition to a mixture of 300 ml of concentrated (37%) hydrochloric acid and 500 g of ice cubes. The organic phase separated off is washed twice, each time with 150 ml of semi-concentrated hydrochloric acid. The combined aqueous extracts are heated for 2 hours under vigorous reflux and then evaporated to dryness in a vacuum. The residue is dissolved in 700 ml of isopropanol, filtered off hot from the undissolved potassium chloride and crystallised at 0 to -5°C. The residue filtered off is dried to constant weight in a vacuum at elevated temperature. A second fraction can be obtained by concentrating the mother liquor to a volume of approximately 100 ml. 145.9 g (89.2%) of 1-methylperhydroazepin-4-one HCl is obtained.

Melting point: 163-164°C (decomposition)

Example 3

A side stream of 100 g of ethyl 4-(2-carbethoxyethylbenzylamino)butyrate dissolved in 780 ml of xylene is charged evenly under nitrogen over a period of 3 hours into a solution of 43.6 g of potassium tert-butyrate in 1.65 l of boiling xylene pumped round a circulation system and the mixture is allowed to react for a further 1.5 hours. 800 ml of distillate is withdrawn. The reaction mixture is hydrolysed at 50 to 80°C by rapid addition to a mixture of 200 ml of concentrated (37%) hydrochloric acid and 500 g of ice cubes. The organic phase separated off is washed twice, each time with 100 ml of semi-concentrated hydrochloric acid. The combined aqueous extracts are heated for 2 hours under vigorous reflux and then evaporated to dryness in a vacuum. The residue is exhaustively extracted from isopropanol and crystallised. The residue filtered off is dried to constant weight in a vacuum at elevated

temperature. A second fraction can be obtained by concentrating the mother liquor to a volume of approximately 100 ml. 60.3 g (80.8%) of 1-benzylperhydroazepin-4-one HCl is obtained.

5

Melting point: 191 to 193°C (decomposition)

Example 4

- 10 90.0 kg of ethyl 4-(2-carbethoxyethylmethylamino)butyrate is charged evenly under nitrogen over a period of 2 to 3 hours at the top of the column into a solution of 50.0 kg of potassium tert-butyrate in 400 ml of boiling xylene and the mixture is allowed to react for a further 1 to
- 15 1.5 hours. Approximately 160 l of distillate is withdrawn. The reaction mixture is hydrolysed at 50 to 80°C by rapid addition to a mixture of 80 l of concentrated (37%) hydrochloric acid and 100 g of ice cubes. The organic phase separated off is washed twice, each time with 50 l of semi-
- 20 concentrated hydrochloric acid. The combined aqueous extracts are heated for 2 hours under vigorous reflux and then evaporated to dryness in a vacuum. The residue is dissolved in 400 l of isopropanol, filtered off hot from the undissolved potassium chloride and crystallised at 0 to
- 25 -5°C. The residue filtered off is dried to constant weight in a vacuum at elevated temperature. 43.2 kg (72.0%) of 1-methylperhydroazepin-4-one HCl is obtained.

Melting point: 162-165°C (decomposition)

30

Example 5

- 168.8 g of ethyl 4-(2-carbethoxyethyl(2-phenyl-ethyl)amino)butyrate (content: 94%) is charged evenly,
- 35 together with nitrogen, over a period of 2 to 3 hours at the top of a packed column into a solution of 61.7 g of potassium tert-butyrate in 1.5 l of boiling

xylylene and the mixture is allowed to react for a further 1 to 1.5 hours. Approximately 500 ml of distillate is withdrawn. The reaction mixture is hydrolysed at 50 to 80°C by rapid addition to a mixture of 200 ml of concentrated
5 (37%) hydrochloric acid and 300 g of ice cubes. The organic phase separated off is washed twice, each time with 100 ml of semi-concentrated hydrochloric acid. The combined aqueous extracts are heated for 2 hours under vigorous reflux and then evaporated to dryness in a vacuum. The
10 residue is suspended hot in 250 ml of isopropanol and crystallised in the cold. The crystallisate is exhaustively extracted from isopropanol and crystallised. The residue filtered off is dried to constant weight in a vacuum at elevated temperature. A second fraction can be obtained by
15 concentrating the mother liquor to a volume of approximately 100 ml. 107.7 g (89.7%) of 1-(2-phenylethyl)perhydroazepin-4-one HCl is obtained.

Melting point: 196-198°C (decomposition)

20

Example 6

84.5 kg of ethyl 4-(2-carbethoxyethyl(2-phenylethyl)amino)butyrate (content: 92.2%) is charged evenly
25 under nitrogen, over a period of 2 to 3 hours at the top of a packed column into a solution of 30.0 kg of potassium tert-butyrate in 400 l of boiling xylene and the mixture is allowed to react for a further 1 to 1.5 hours. Approximately 150 l of distillate is withdrawn. The
30 reaction mixture is hydrolysed at 50 to 80°C by rapid addition to a mixture of 60 l of concentrated (37%) hydrochloric acid and 60 g of ice cubes. The organic phase separated off is washed twice, each time with 30 l of semi-concentrated hydrochloric acid. The combined aqueous
35 extracts are heated for 2 hours under vigorous reflux and then evaporated to dryness in a vacuum. The residue is

exhaustively extracted from isopropanol and crystallised. The residue filtered off is dried to constant weight in a vacuum at elevated temperature. 40.0 kg (67.8%) of 1-(2-phenylethyl)perhydroazepin-4-one HCl is obtained.

5

Melting point: 196-198°C (decomposition)

Elemental analysis: calculated: C 66.26 H 7.95 N 5.52

found: C 66.24 H 7.94 N 5.43

Content (Cl-): 100.28%

10

Example 7

100 ml of 1 N sodium hydroxide solution is added to a solution of 18.9 g of sodium borohydride in 100 ml of
15 water. A solution of 163.6 g of 1-methylperhydroazepin-4-one HCl in 100 ml of water is added dropwise at an internal temperature of 0 to 5°C. The mixture is stirred for 2 hours at 0 to 5°C and then for 2 hours at room temperature. The pH value is adjusted to 2 to 3 by addition of semi-
20 concentrated hydrochloric acid. The mixture is evaporated to dryness in a vacuum, the residue is taken up in 600 ml of isopropanol, the inorganic salts are separated off at 60 to 75°C and the product is crystallised out in the cold. The product is filtered under suction and dried to constant
25 weight in a vacuum at elevated temperature. 149 g (90%) of 1-methylperhydroazepin-4-ol HCl is obtained.

Melting point: 156-158°C

30

Example 8

34.0 kg of ethyl 4-(2-carbethoxyethylmethylamino)butyrate dissolved in 400 l of xylene is charged evenly under nitrogen over a period of 2 to 3 hours into a suspension of
35 5.0 kg of sodium hydride (80% in white mineral oil) in 200 l of boiling xylene and allowed to react for a further 0.5 hours. Approximately 400 l of distillate is withdrawn.

The reaction mixture is hydrolysed at 50 to 80°C by rapid addition to a mixture of 35 l of concentrated (37%) hydrochloric acid and 60 g of ice cubes. The organic phase separated off is washed twice, each time with 30 l of semi-
5 concentrated hydrochloric acid. The combined aqueous extracts are heated for 2 hours under vigorous reflux and then evaporated to dryness in a vacuum. The residue is dissolved in 100 l of isopropanol, filtered off hot from the undissolved potassium chloride and crystallised at 0 to
10 -5°C. The residue filtered off is dried to constant weight in a vacuum at elevated temperature. 11.7 kg (52.0%) of 1-methyl-perhydroazepin-4-one HCl is obtained.

Melting point: 162-164°C

15

Example 9

245.3 g of ethyl 4-(2-carbethoxyethylmethylamino)butyrate is charged evenly, together with nitrogen, over a period of
20 1.75 hours into a solution of 39.0 g of sodium hydride (80% in white mineral oil) and 75 ml of ethanol in 1.3 l of boiling xylene and allowed to react for a further 0.5 hours. Approximately 700 l of distillate is withdrawn. The reaction mixture is hydrolysed at 80 to 100°C by rapid
25 addition to a mixture of 300 ml of concentrated (37%) hydrochloric acid and 500 g of ice cubes. The organic phase separated off is washed twice, each time with 150 ml of semi-concentrated hydrochloric acid. The combined aqueous extracts are heated for 2 hours under vigorous reflux and
30 then evaporated to dryness in a vacuum. The residue is extracted hot from 600 ml of isopropanol and crystallised. The residue filtered off is dried to constant weight in a vacuum at elevated temperature. A second fraction can be obtained by concentrating the mother liquor to a volume of
35 approximately 100 ml. 44.3 g (27.1%) of 1-methyl-perhydroazepin-4-one HCl is obtained.

Melting point: 159-161°C (decomposition)

Example 10

5 181.8 g of n-butyl 4-(2-carbethoxyethyl(2-phenyl-ethyl)amino)butyrate (content: 93%) is charged evenly, together with nitrogen, over a period of 2 to 3 hours at the top of a packed column into a solution of 61.7 g of potassium tert-butyrate in 1.5 l of boiling
10 xylene and the mixture is allowed to react for a further 1 to 1.5 hours. Approximately 500 ml of distillate is withdrawn. The reaction mixture is hydrolysed at 50 to 80°C by rapid addition to a mixture of 200 ml of concentrated (37%) hydrochloric acid and 300 g of ice cubes. The organic
15 phase separated off is washed twice, each time with 100 ml of semi-concentrated hydrochloric acid. The combined aqueous extracts are heated for 2 hours under vigorous reflux and then evaporated to dryness in a vacuum. The residue is suspended hot in 250 ml of isopropanol and
20 crystallised in the cold. The crystallisate is exhaustively extracted from isopropanol and crystallised. The residue filtered off is dried to constant weight in a vacuum at elevated temperature. 95.4 g (80.8%) of 1-(2-phenylethyl)-perhydroazepin-4-one HCl is obtained.

25

Melting point: 196-197°C (decomposition)

Example 11

30 153.7 g of methyl 4-(2-carbomethoxyethyl(2-phenyl-ethyl)amino)butyrate (content: 96%) is charged evenly, together with nitrogen, over a period of 2 to 3 hours at the top of a packed column into a solution of 61.7 g of potassium tert-butyrate in 1.5 l of boiling
35 xylene. In the course of this a precipitate is formed which is difficult to stir, which dissolves completely during the subsequent reaction time and is allowed to react for a

further 1 to 1.5 hours. Approximately 500 l of distillate is withdrawn. The reaction mixture is hydrolysed at 50 to 80°C by rapid addition to a mixture of 200 ml of concentrated (37%) hydrochloric acid and 300 g of ice
5 cubes. The organic phase separated off is washed twice, each time with 100 ml of semi-concentrated hydrochloric acid. The combined aqueous extracts are heated for 2 hours under vigorous reflux and then evaporated to dryness in a vacuum. The residue is exhaustively extracted from
10 isopropanol and crystallised. The residue filtered off is dried to constant weight in a vacuum at elevated temperature. A second fraction can be obtained by concentrating the mother liquor to a volume of approximately 100 ml. 105.4 g (86.5%) of
15 1-(2-phenylethyl)perhydroazepin-4-one HCl is obtained.

Melting point: 196-198°C (decomposition)

Example 12

20 245.3 g of ethyl 4-(2-carbethoxyethylmethylamino)butyrate is added over a period of 3 minutes, together with nitrogen, to a solution of 123.4 g of potassium tert-butylate in 1.3 l of boiling xylene, with 300 ml of solvent
25 being rapidly distilled off, and the mixture is allowed to react for a further 0.5 hours. A further 350 ml of distillate is withdrawn. The reaction mixture is hydrolysed at 80 to 100°C by rapid addition to a mixture of 300 ml of concentrated (37%) hydrochloric acid and 500 g of ice
30 cubes. The organic phase separated off is washed twice, each time with 150 ml of semi-concentrated hydrochloric acid. The combined aqueous extracts are heated for 2 hours under vigorous reflux and then evaporated to dryness in a vacuum. The residue is extracted hot from 600 ml of
35 isopropanol and crystallised. The residue filtered off is dried to constant weight in a vacuum at elevated temperature. A second fraction can be obtained by

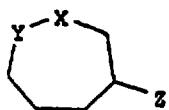
concentrating the mother liquor to a volume of approximately 100 ml. 78.3 g (47.9%) of 1-methyl-perhydroazepin-4-one HCl is obtained.

5 Melting point: 164-165°C (decomposition)



Claims

1. Improved method for the preparation of
hexahydroazepinones and hexahydroazepinoles of the
general formula I



- wherein
X signifies N-R, CH₂, S, O
Y signifies N-R, N-CH₃, or signifies N-CH₂-CH₂-C₆H₅ and
Z signifies O, -OH
wherein in each case R represents H, alkyl,
cycloalkyl, aralkyl, aryl and the salts thereof, by
means of the Dieckmann condensation using strong bases
in inert solvents, characterised by the following
features:
- that an excess of up to a maximum of 20% of
strong bases is used
 - that the condensation reaction is carried out
over reaction times of from 1 to 6 hours,
preferably from 1 to 3 hours
 - that the operation is conducted using
concentrations of from 0.1 to 1.5 mol, preferably
0.3 to 0.9 mol, of the undiluted dicarboxylic
ester flowing in to be condensed, per litre of
solvent
 - that, avoiding the conventional dilution
technique, either
- the reaction is carried out in a closed device,
with the dissolved base being circulated and the





undiluted dicarboxylic ester being charged into the circulation system by means of a jet nozzle, or

5 that the ascending condensate formed is used simultaneously in a packed column for the dilution and heating of the undiluted dicarboxylic ester introduced at the top of the column.

10

2. Preparation and isolation of hexahydroazepinoles and the salts thereof through reduction of the hexahydroazepinones according to claim 1 by means of complex hydrides or hydrogen, on contact with which
15 hydrogenolysis occurs, in water or alcohols.

15

3. Method for the preparation of azelastine hydrochloride, characterised in that the compound I, wherein X signifies CH_2 , Y signifies N-CH_2 , and Z
20 signifies O, in the form of its acid addition salt with hydrochloric acid

20

a) is reacted in organic solution with benzoylhydrazine and the intermediate compound is
25 reduced, without being isolated, to form a benzoylazepine hydrazine and

25

b) the latter compound, following acidic splitting-off of the benzoyl radical in water or organic solvent, by means of 2-(4-chlorophenacetyl)-benzoic acid is converted into azelastine and isolated in the form of an acid addition salt by
30 means of acid.

30

35 4. Method for the preparation of flezelastine hydrochloride, characterised in that the compound I, wherein X signifies CH_2 , Y signifies $\text{N-CH}_2\text{CH}_2\text{-C}_6\text{H}_5$, and Z





signifies O, in the form of its acid addition salt
with acid

5 a) is reacted in organic solution with
benzoylhydrazine and the intermediate compound is
reduced, without being isolated, to form a
benzoylazepine hydrazine

10 b) the latter compound, following acidic splitting-
off of the benzoyl radical in water or organic
solvents, by means of 2-(4-fluorophenacetyl)-
benzoic acid is converted into flezelastine and
isolated in the form of an acid addition salt by
means of acid.

15

This Sheet Has Been Replaced

