(12) PATENT
(19) AUSTRALIAN PATENT OFFICE

(11) Application No. AU 199718772 B2
(10) Patent No. 717720

(54) Title

Process for preparing 1,4,7,10-tetraazacyclododecane and its derivatives

(51)[6] International Patent Classification(s)
C07D 257/02

(21) Application No: 199718772

(22) Application Date: 1997.02.26

(87) WIPO No: WO97/31905

(30) Priority Data

(31) Number	(32) Date	(33) Country
19608307	1996.02.26	DE

(43) Publication Date : 1997.09.16
(43) Publication Journal Date : 1997.11.13
(44) Accepted Journal Date : 2000.03.30

(71) Applicant(s)

Schering Aktiengesellschaft

(72) Inventor(s)

Orlin Petrov; Annette Prelle; Klaus Graske; Klaus Nickisch; Bernd Raduchel; Johannes Platzek

(74) Agent/Attorney

DAVIES COLLISON CAVE,GPO Box 3876,SYDNEY NSW 2001

OPI DATE 16/09/97 APPLN. ID 18772/97
AOJP DATE 13/11/97 PCT NUMBER PCT/EP97/00927

AU9718772

(51) Internationale Patentklassifikation 6 :
C07D 257/02

A1

(11) Internationale Veröffentlichungsnummer: WO 97/31905

(43) Internationales Veröffentlichungsdatum: 4. September 1997 (04.09.97)

(21) Internationales Aktenzeichen: PCT/EP97/00927

(22) Internationales Anmeldedatum: 26. Februar 1997 (26.02.97)

(30) Prioritätsdaten:
196 08 307.9 26. Februar 1996 (26.02.96) DE

(71) Anmelder *(für alle Bestimmungsstaaten ausser US)*: SCHERING AKTIENGESELLSCHAFT [DE/DE]; Müllerstrasse 178, D-13353 Berlin (DE).

(72) Erfinder; und
(75) Erfinder/Anmelder *(nur für US)*: PETROV, Orlin [BU/DE]; Friedrichshaller Strasse 7b, D-14999 Berlin (DE). PRELLE, Annette [DE/DE]; Friedrich-Franz-Strasse 45, D-12103 Berlin (DE). GRASKE, Klaus [DE/DE]; Schlangenbader Strasse 41, D-14197 Berlin (DE). NICKISCH, Klaus [DE/DE]; Zescher Strasse 14, D-12307 Berlin (DE). RADÜCHEL, Bernd [DE/DE]; Gollanczstrasse 132, D-13465 Berlin (DE). PLATZEK, Johannes [DE/DE]; Grottkauer Strasse 55, D-12621 Berlin (DE).

(81) Bestimmungsstaaten: AL, AM, AU, AZ, BB, BG, BR, BY, CA, CN, CZ, EE, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, RO, RU, SD, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, europäisches Patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).

Veröffentlicht
Mit internationalem Recherchenbericht.
Vor Ablauf der für Änderungen der Ansprüche zugelassenen Frist. Veröffentlichung wird wiederholt falls Änderungen eintreffen.

(54) Title: PROCESS FOR PREPARING 1,4,7,10-TETRAAZACYCLODODECANE AND ITS DERIVATIVES

(54) Bezeichnung: VERFAHREN ZUR HERSTELLUNG VON 1,4,7,10-TETRAAZACYCLODODECAN UND DESSEN DERIVATEN

(57) Abstract

The invention concerns a process for preparing 1,4,7,10-tetraazacyclododecane (cyclene) and its derivatives on an industrial scale by the cyclotetramerization of benzylaziridine prepared in situ.

(57) Zusammenfassung

Die Erfindung betrifft ein Verfahren zur Herstellung von 1,4,7,10-Tetraazacyclododecan (Cyclen) und dessen Derivaten in technischem Maßstab durch Cyclotetramerisierung von in situ hergestellten Benzylaziridin.

The cyclotetramerization of N-substituted aziridines offers a method for the production of 1,4,7,10-tetraazacyclododecane that appears to be basically simpler. Various variants of this reaction are described in the literature. In this case, the corresponding N-substituted aziridine is first produced from benzylethanolamine and isolated. Aziridine is then cyclotetramerized at low yield in the presence of Brönsted acids, such as, e.g., p-TsOH (J. Heterocyclic Chem. 1968, 305) or Lewis acids, such as trialkylaluminum (US Pat. 3,828,023) or BF_3-etherate (Tetrahedron Letters, 1970, 1367). Although the process can be implemented only for the production of small amounts (< 5 g), it is still the state of the art 16 years after the first publication (WO 95/31444).

All previously described cyclotetramerization reactions require the use of pure aziridines, which, as is generally known, have strong mutagenic and carcinogenic action (Roth, Giftliste, VCH Weinheim). For this reason, the cyclotetramerization of aziridines, which seems to be the simplest method for the production of 1,4,7,10-tetraazacyclododecane, is virtually unused on an industrial scale. There is therefore a great deal of interest in a technically practicable process for the production of 1,4,7,10-tetraazacyclododecane that is basically environmentally benign and largely safe.

The object of this invention is therefore to provide a practicable process for the production of 1,4,7,10-tetraazacyclododecane on an industrial scale, which process overcomes the above drawbacks and in particular avoids the threat

to humans posed by mutagenic and carcinogenic aziridine intermediate stages.

This object is achieved by the process according to the invention, as it is characterized in the claims.

In this case, this is a process for the production of cyclene derivatives by cyclotetramerization of benzylaziridine derivatives, characterized in that the benzylaziridine derivative is produced in situ and is tetramerized without isolation into a tetrabenyzlcyclene derivative with the addition of a strong acid, and finally the benzyl groups are removed by hydrogenation.

Within the framework of this invention, the term cyclene derivatives is intended to comprise both 1,4,7,10-tetraazacyclododecane and those derivatives in which the ethylene bridges have alkyl substituents. The term cyclene derivative thus also relates to, for example, the compounds [2S-(2α,5α,8α,11α)]-2,5,8,11-tetramethyl-1,4,7,10-tetraazacyclododecane and [2S-(2α,5α,8α,11α)]-2,5,8,11-tetraethyl-1,4,7,10-tetraazacyclododecane.

Analogously, the term tetrabenzylcyclene derivatives within the framework of this invention is intended to comprise both 1,4,7,10-tetrabenzyl-1,4,7,10-tetraazacyclododecane and those derivatives in which the ethylene bridges have alkyl substituents. The term benzylaziridine derivative within the framework of this invention is intended to comprise benzylaziridine and those derivatives in which the aziridine ring has alkyl substituents. The term benzylaziridine derivative thus

also relates to, for example, the compounds (S)-1-benzyl-2-methyl-aziridine and (S)-1-benzyl-2-ethyl-aziridine.

The invention therefore relates to a process for the production of optionally substituted 1,4,7,10-tetraazacyclododecane derivatives by tetramerization of corresponding educts. The invention preferably relates to the production of 1,4,7,10-tetraazacyclododecane.

A preferred embodiment of the process starts from readily accessible benzylethanolamine, which is converted by heating (80-150°C, preferably 90-110°C) with 1-1.4 equivalents of concentrated sulfuric acid in an organic solvent (e.g., toluene, cyclohexane, heptane, i.a., concentration: 10-20%) and azeotropic distillation of the water that is produced in this case into the corresponding sulfuric acid ester. The reaction time in this case is 2-10 hours. The latter is heated with 2-5 equivalents of an aqueous alkaline solution (e.g., NaOH, KOH), and the benzylaziridine that is produced in this case in a second reaction vessel, which together with the first forms a closed system, is continuously azeotropically distilled off with water. The aqueous benzylaziridine emulsion that is thus formed can, after dilution with an organic solvent (e.g., ethanol, methanol, THF), be reacted surprisingly completely to form tetrabenzylcyclene by continuous addition of at least 0.25-0.4 mol (preferably 0.25-0.35 mol) of a strong acid per mol of benzylaziridine (i.e., equivalent amount of acid relative to the product). As an organic solvent, e.g., ethanol, methanol, or tetrahydrofuran (THF) can be used. As a strong acid, for

example, para-toluenesulfonic acid (p-TsoH), methanesulfonic acid (MsOH), sulfuric acid, or BF_3-etherate can be used. After the reaction mixture is alkalized (0.2-0.5 equivalent of base, e.g., NaOH, KOH), the product is obtained by crystallization from polar solvents (e.g., THF, ethanol, acetone, isopropanol, diethyl ether, ethyl acetate, furan, dioxane, water or their mixtures) and is then hydrogenated in an organic solvent (ethanol, methanol, isopropanol, THF) with the aid of a catalyst (Pd/C, amount 5-20% relative to the tetrabenzylcyclene derivative, pressure: 1-20 bar). After the catalyst is filtered and the solvent is distilled off, 1,4,7,10-tetraazacyclododecane is obtained at a yield of 45-60% of the theoretical total yield.

Analogously to this synthesis, alkyl-substituted benzylethanolamine can also be used, e.g., L-2-benzylaminopropanol or L-2-benzylaminobutanol, to obtain cyclene derivatives that have branches in the ethylene bridges. In a preferred embodiment of this synthesis, (S)-1-benzyl-2-methyl-aziridine is produced analogously to the above-described process from L-2-benzylaminopropanol and is reacted without isolation to form [2S-(2α,5α,8α,11α)]-2,5,8,11-tetramethyl-1,4,7,10-tetrakis(benzyl)-1,4,7,10-tetraazacyclododecane by tetramerization, from which (2S-(2α,5α,8α,11α)]-2,5,8,11-tetramethyl-1,4,7,10-tetraazacyclododecane is obtained by hydrogenation.

The process of cyclotetramerizing the benzylaziridine derivatives according to the invention differs from the process that is known in the prior art in that no isolation of the

aziridine in pure form is necessary. The procedure described thus makes it possible to carry out the process in a closed system and thus to avoid the threat posed to humans and the environment by aziridine, which is carcinogenic.

In contrast to the process for cyclotetramerizing benzylaziridine that is known in the prior art, a stoichiometric amount (0.25-0.35 mol relative to one mol of benzylaziridine) is used instead of a catalytic amount of an acid (p-TsOH, MsOH, sulfuric acid, BF_3-etherate or trialkylaluminum). In tests to scale up the known process and to be able to produce large amounts of 1,4,7,10-tetraazacyclododecane in this process, only 12-25% of theoretical yield was achieved using catalytic amounts of p-TsOH in the reaction of the benzylaziridine emulsion that is produced in situ. It has now been found, surprisingly enough, that by continuously adding 0.25 to 0.35 equivalent of p-TsOH (relative to the benzylaziridine) to the azeotropically distilled-off benzylaziridine emulsion at 60-78°C within 6-9 hours, the yield of 1,4,7,10-tetrabenzyl-1,4,7,10-tetraazacyclododecane can be improved to 60-65% of the theoretic yield.

Other advantages of this process are the high overall yield and small amounts of waste (Na-sulfate in the case of aziridine production and toluene in the case of hydrogenation) in contrast to known processes.

Embodiments:

The following examples are to explain the subject of the invention without intending that they be limited to this subject.

Example 1

53 ml of concentrated sulfuric acid is added to a solution of 95 ml of benzylethanolamine in 690 ml of toluene. The suspension that is produced is heated to boiling for 2 hours. The water that is produced in this case (14 ml) is separated with the aid of a water separator. After cooling to 20°C, the reaction mixture is mixed with 1300 ml of water and absorptively precipitated for 10 minutes, and the organic phase is separated. Then, the aqueous phase is quickly added to a solution of 92.2 g of NaOH in 95 ml of water that is introduced into a second reaction vessel. The reaction mixture is heated to boiling. 880 g of water-N-benzylaziridine emulsion in a third reaction vessel is distilled off through a distillation bridge. The emulsion is mixed with 880 ml of ethanol and heated to 60°C. To this end, a solution of 38.0 g of p-TsOH in 19 ml of water is added within 8 hours via a metering pump. After the addition is completed, it is refluxed for two hours. Then, the reaction mixture is mixed with a solution of 12.0 g of NaOH in 20 ml of water. The precipitated product is filtered and recrystallized from 600 ml of 2:1 ethanol-THF mixture. The tetrabenzylcyclene (53 g) thus obtained is dissolved in 500 ml of isopropanol and hydrogenated

with 10 g of Pd/C (10%) at 80°C and 20 bar of H_2 pressure. After the catalyst is filtered off, the reaction solution is concentrated by evaporation, and the product is recrystallized from toluene. 15.9 g (55% of theory) of cyclene is obtained as colorless crystals. Melting point 110-112°C.

Example 2

95 ml of benzylethanolamine is reacted with sulfuric acid and then with NaOH, as described in Example 1. The aqueous N-benzylaziridine emulsion that is obtained is mixed with 2.6 l of ethanol and heated to 50°C. To this end, a solution of 29.3 g of p-TsOH in 15 ml of water is added within 8 hours via a metering pump. After the addition is completed, it is refluxed for two hours. Then, the reaction mixture is mixed with a solution of 9.5 g of NaOH in 20 ml of water. The precipitated product is filtered and recrystallized from 600 ml of 2:1 ethanol-THF mixture. The tetrabenzylcyclene thus obtained (55.7 g) is dissolved in 500 ml of isopropanol and hydrogenated with 10 g of Pd/C (10%) at 80°C and 20 bar of H_2 pressure. After the catalyst is filtered off, the reaction solution is concentrated by evaporation, and the product is recrystallized from toluene. 15.9 g (58% of theory) of cyclene is obtained as colorless crystals. Melting point 111-113°C.

Example 3

Like Example 1, only the tetramerization is carried out with 0.33 equivalent of methanesulfonic acid. Yield 52% cyclene. Melting point 110-112°C.

Table 1: Comparative Table on Conditions and Yields of Cyclene Synthesis by Cyclotetramerization of Benzylaziridine

Conditions	**Yield**
0.03 eq. of p-TsOH, 95% EtOH, Rfl. (analogously to Lit. 1*)	12-25%
0.33 eq. of p-TsOH, 50% EtOH, 60-80°C (Example 1)	55%
0.25 eq. of p-TsOH, 75% EtOH, 50-80°C (Example 2)	58%
0.33 eq. of MsOH, 50% EtOH, 70°C (Example 3)	52%

* Lit. 1: J. Heterocyclic Chem. 1968, 305.

Claims

1. Process for the production of optionally alkyl-substituted cyclene derivatives by cyclotetramerization of optionally alkyl-substituted benzylaziridine derivatives, characterized in that the benzylaziridine derivative is produced from an optionally alkyl-substituted benzylethanolamine derivative in situ by reaction with sulfuric acid and subsequent reaction of the corresponding sulfuric acid ester with aqueous alkaline solution,
the latter is tetramerized without isolation of the benzylaziridine derivative into a tetrabenzylcyclene derivative with the addition of 0.25-0.35 mol of a strong acid per mol of benzylaziridine derivative, and
finally the benzyl groups are removed by catalytic hydrogenation.

2. Process according to claim 1, wherein the optionally alkyl-substituted cyclene derivative is 1,4,7,10-tetraazacyclododecane.

3. Process for the production of optionally alkyl-substituted tetrabenzylcyclene derivatives by cyclotetramerization of optionally alkyl-substituted benzylaziridine derivatives, wherein
the benzylaziridine derivative is produced from a benzylethanolamine derivative in situ by reaction with sulfuric acid and subsequent reaction of the corresponding sulfuric acid ester with aqueous alkaline solution, and

the latter is tetramerized without isolation of the benzylaziridine derivative into a tetrabenzylcyclene derivative with the addition of 0.25-0.35 mol of a strong acid per mol of benzylaziridine derivative.

4. Process according to claim 1, wherein the cyclene derivative is [2S-(2α,5α,8α,11α)]-2,5,8,11-tetramethyl-1,4,7,10-tetraazacyclododecane.

5. Process according to claim 1 or 3, wherein the acid that is used is para-toluenesulfonic acid, methanesulfonic acid, or sulfuric acid.

Dated this 24th day of January 2000

Schering Aktiengesellschaft

By its Patent Attorneys of

Davies Collison Cave