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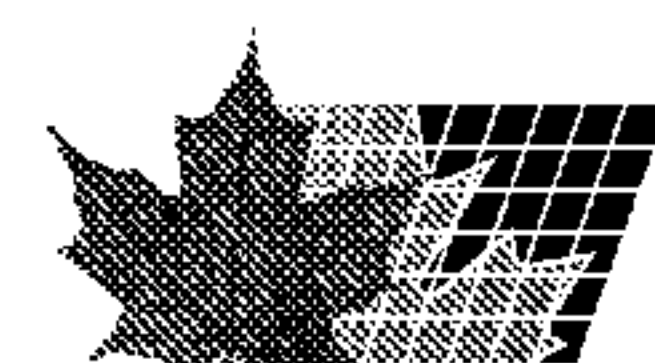
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(54) Titre : PROCEDE DE PRODUCTION D'ENDOTROPINE

(54) Title: PROCESS FOR THE PRODUCTION OF ENDOTROPINE

(57) **Abrégé/Abstract:**

The invention relates to a process for the production of endotropine by reducing tropanone with hydrogen catalytically activated by Raney nickel or Raney copper. The prior art processes known from US patents 2,366,760 and 2,746,976 use an overpressure and organic solvents, so that there is a high fire and explosion risk when working up the reaction batch. This problem is obviated by the invention in that the tropanone, in aqueous solution with hydrogen, in a closed system, at atmospheric pressure and ambient temperature, is subject to turbulent action at 1000 to 1500 r.p.m. The process according to the invention leads to average yields of 94%.



ABSTRACT

The invention relates to a process for the production of endotropine by reducing tropanone with hydrogen catalytically activated by Raney nickel or Raney copper. The prior art processes known from US patents 2,366,760 and 2,746,976 use an overpressure and organic solvents, so that there is a high fire and explosion risk when working up the reaction batch. This problem is obviated by the invention in that the tropanone, in aqueous solution with hydrogen, in a closed system, at atmospheric pressure and ambient temperature, is subject to turbulent action at 1000 to 1500 r.p.m. The process according to the invention leads to average yields of 94%.

Process for the Production of Endotropine

The invention relates to a process for the production of endotropine by the reduction of tropanone with hydrogen catalytically activated by Raney nickelTM or Raney copper catalyst. Other standard names for tropine are: 3 α -tropanol, 3 α -hydroxytropane, 1 α H, 5 α H-tropan-3 α -ol, 8-methyl-8-azabicyclo-[3,2,1]-nonan-3 α -ol (CAS [120-29-6]).

Endotropine is an important substance for the production of nortropine by oxidative methylation, which is in turn used for the production of important azoniaspironortropanol esters, which are used as pharmaceuticals, particularly spasmolytics (cf. German patent 1 194 42).

The situation regarding the prior art is as follows. The 1945 US patent 2,366,760 describes the preparation of tropine from tropanone by catalytic reduction with hydrogen activated by a Raney nickel catalyst, without giving the yield. The reaction is performed under pressure and in an organic solvent, preferably ethanol, giving a quantitative yield.

This procedure involves high apparatus expenditure with pressure vessels or autoclaves. Through the use of organic solvents in conjunction with Raney nickel catalysts there is a higher fire or explosion risk when working up the reaction batch. Corresponding accidents are well known from practical experience.

The 1956 US patent 2,746,976 describes in its example 12 the preparation of tropine, using an autoclave as the reaction vessel and an organic solvent, at an operating pressure of 60 atmospheres overpressure. The aforementioned disadvantages once again arise.

Chemical Abstract 99 (15), 122, 721a describes a catalytic hydrogenation of tropanone in the presence of a rhodium-phosphine complex.

The prior art discloses further processes, in which endotropine is produced by the hydrogenation of tropanone in the presence of a Raney nickel catalyst (Chemical Abstract 97 (23), 198, 428q, Chemical Abstract 93 (13), 132 665a and Chemical Abstract 83 (23), 193 561d). In the first-mentioned literature reference, a yield of 92% is given.

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Thus, the hitherto known processes only make it possible to produce tropine in the presence of organic solvents and when using a higher pressure.

It has now surprisingly been found that it is possible to reduce tropanone selectively and with good yields without using a higher pressure and without using organic solvents so as to give tropine, in that the mixture, in aqueous solution, is subject to turbulent action at atmospheric pressure and ambient temperatures at 1000 to 1500 r.p.m. It could not be foreseen on the basis of the hitherto known processes that this reaction would take place smoothly and also stereoselectively supplies the desired endo-compound.

In accordance with one aspect of the present invention there is provided a process for the production of endotropine which comprises the reduction of tropanone with hydrogen catalytically activated by Raney nickel or Raney copper, characterized in that the tropanone, in aqueous solution with hydrogen, in a closed system, at atmospheric pressure and ambient temperature is subject to turbulent action at 1000 to 1500 r.p.m. Preferably the turbulent action takes place at 1300 r.p.m. Preferably the turbulent action is produced using a high-speed stirrer.

Examples:

The starting product is 100 ml of Raney nickel catalyst, in ready to use form, i.e. with an approximately 10% solids fraction, in aqueous suspension and in it are dissolved, accompanied by stirring, 14 g of tropanone. The complete mixture in a closed system is then subject to turbulent action in a hydrogen atmosphere and in pressureless form (i.e. without executing any pressure) at ambient temperature with approximately 1300 r.p.m., until the taking up of hydrogen is ended.

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The tropanone is then substantially completely reacted and in the gas chromatogram there are at least 98% by area tropine and max 2% by area pseudotropine. The catalyst is separated by filtration and the clear, aqueous filtrate is mixed portionwise with 14 g of sodium hydroxide and then extracted with three 20 ml dichloromethane portions. The extracts are combined and concentrated. 13.5 g of colourless, thick oil are left behind as residue and completely crystallize after standing briefly. The white crystals melt at approximately 60°C.

CLAIMS

1. A process for the production of endotropine which comprises the reduction of tropanone with hydrogen catalytically activated by Raney nickel or Raney copper, characterized in that the tropanone, in aqueous solution with hydrogen, in a closed system, at atmospheric pressure and ambient temperature is subject to turbulent action at 1000 to 1500 r.p.m.
2. The process according to claim 1, wherein the turbulent action takes place at 1300 r.p.m.
3. The process according to claim 1, wherein the turbulent action is produced using a high-speed stirrer.