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(71) Applicant: 000000354
Ishihara Sangyō KK
Ōsaka-fu, Ōsaka-shi, Nishi-ku,
Edobori 1-chome 3-ban 15-gō

(72) Inventor: Shigehara Itaru
Mie-ken, Yokkaichi-shi,
Ishihara-chō, 1-banchi,
Ishihara Sangyō KK
Yokkaichi Business Center

(72) Inventor: Sawaki Masahiko
Mie-ken, Yokkaichi-shi,
Ishihara-chō, 1-banchi,
Ishihara Sangyō KK
Yokkaichi Business Center

(54) **[Title of Invention]** **Method to Prepare Spiro(oxirane-2,3')quinuclidine**

(57) [Summary]

[Object] the present invention relates to methods of preparing spiro(oxirane-2,3')quinuclidine which are useful intermediates for medications to treat diseases of the mammalian central nervous system, a method of preparation having economically feasible raw materials which are suitable for use in an industrial process.

[Composition] spiro(oxirane-2,3')quinuclidine is produced by reacting quinuclidin-3-one with a basic substance and trimethylsulfoxonium methylsulfate or trimethylsulfonium methylsulfate.

[Claims]

[Claim 1] The method of producing spiro(oxirane-2,3')quinuclidine wherein quinuclidin-3-one, a basic substance, and trimethylsulfoxonium methylsulfate or trimethylsulfonium methylsulfate are caused to react.

[Claim 2] The method of producing spiro(oxirane-2,3')quinuclidine of [Claim 1] wherein quinuclidin-3-one, a basic substance, and trimethylsulfoxonium methylsulfate are caused to react.

[Claim 3] The method of producing spiro(oxirane-2,3')quinuclidine of [Claim 1] wherein quinuclidin-3-one, a basic substance, and trimethylsulfonium methylsulfate are caused to react.

[Claim 4] The method of producing spiro(oxirane-2,3')quinuclidine of [Claim 1] wherein 1 mole of quinuclidin-3-one, and 1-5 moles of a basic substance together with 1-5 moles of trimethylsulfoxonium methylsulfate or trimethylsulfonium methylsulfate are caused to react.

[Claim 5] The method of producing spiro(oxirane-2,3')quinuclidine of [Claim 1] wherein trimethylsulfoxonium methylsulfate or trimethylsulfonium methylsulfate are produced by causing dimethyl sulfate and dimethylsulfoxide or dimethylsulfide to react, which is subsequently cause to react with quinuclidin-3-one and a basic substance.

[Claim 6] The method of producing spiro(oxirane-2,3')quinuclidine of [Claim 1] wherein the reaction is carried out in a solvent under conditions of 0~200 ℃.

[Claim 7] Trimethylsulfoxonium methylsulfate

[Description of Invention]
[0001]
[Field of Industrial Utility] The present invention concerns an advantageous industrial method for the preparation of spiro(oxirane-2,3')quinuclidine (abbreviated below as QE), which is a useful intermediate for medications to treat diseases of the mammalian central nervous system, especially diseases arising from cholinergic hyperactivity, and furthermore the autoimmune disease known as Sjogren’s syndrome, etc., and other medicines.

[0002]
[Prior Art] Regarding the abovementioned QE, an example is mentioned in the patent JP 1986 280491, specifically with respect to a method of producing quinuclidin-3-one (abbreviated below as QO), a preparative method is mentioned for the epoxide formation from QO to give QE from the reaction of trimethylsulfoxonium iodide and sodium hydroxide, followed by addition of dimethylsulfoxide (abbreviated below as DMSO) as solvent.

[0003]
[Problem to be Solved by the Invention] Regarding the preparation method for the abovementioned QE, because of the particularly high price of the trimethylsulfoxonium iodide used as a raw material and the attendant increase in manufacturing cost of QE, a simple

preparation method was sought which would employ a raw material that could be procured cheaply in large quantities, and moreover would minimize the reaction handling aspects of the chemical manufacturing process.

[0004]
[Means to Solve the Problem] In the course of pursuing various earlier investigations in connection with the problem mentioned above, the present inventors found it was possible to shorten the reaction process with QO epoxide as the starting material when trimethylsulfoxonium iodide was substituted, with no detriment in yield for the chemical reaction, having been led to use this specific compound on the basis of its ready commercial availability in large quantity and at low cost, they were able to achieve an economically advantageous process for QE, and moreover they were easily led to discover the aforementioned medicinal agent 2-methylspiro(1,3-oxathiolane-5,3-quinuclidine (below abbreviated as MSOQ), which completed the present invention.

[0005] Accordingly the present invention comprises a method for preparing spiro(oxirane-2,3')quinuclidine, in which quinuclidin-3-one, a basic substance, and trimethylsulfoxonium methylsulfate or trimethylsulfonium methylsulfate are caused to react together.

[0006] The raw material QO used in the method of the present invention can be prepared by various methods. For example, as reported in Organic Syntheses Collected Volume 5, pp 989-991, 1-carbethoxymethyl-4-carbethoxide[1] can be cyclized in the presence of potassium ethoxide, and the 2-carbethoxy-3-oxoquinuclidine can be extracted from the reaction product obtained can be subsequently decarboxylated, making possible the preparation of QO.

[0007] For example, it is possible to prepare the the trimethylsulfoxonium methylsulfate or trimethylsulfonium methylsulfate (abbreviated below as TMSOMS and TMSMS, resp.) of the present invention under conditions where dimethyl sulfate and either DMSO or dimethylsulfide are caused to react in approximately equimolar quantities under heating to 0~200 °C, and moreover TMSOMS is preferable to TMSMS. Dimethyl sulfate, DMSO or dimethylsulfide can be procured readily in that they are sold commercially in large quantities and inexpensively.

[0008] Furthermore, TMSOMS is a colorless, transparent, oily substance.
IR analytical values: 1400 cm^{-1}; 1230 cm^{-1} SO_2 stretching vibration; 1050 cm^{-1} SO stretching vibration.
NMR analytical values (DMSO) in ppm units: the δ 3.2 ppm CH_3 signal from $(CH_3)_3SO$ is recognized.

[0009] Without limiting the range of applicable amounts of trimethylsulfoxonium methylsulfate or trimethylsulfonium methylsulfate to employ under different reaction conditions, usually for one mole of the aforementioned QO 1-5 moles, and more preferably 1-2 moles should be used.

[0010] Regarding the basic substance employed in the method of the present invention, various things can be utilized, concrete examples of which are alkali metals, alkali metal hydroxide

[1] *Translator's Note:* reference to this original source shows that the compound is misidentified in the patent, and its full name should be '1-carbethoxymethyl-4-carbethoxypiperidine.'

compounds, alkali metal alkoxides, alkali metal alkyls, and the like, and more definite examples being sodium hydroxide, sodium methoxide, potassium t-butoxide, sodium metal, n-butyllithium and the like can be envisioned, and from this group sodium hydroxide, sodium methoxide, and potassium t-butoxide are preferred.

[0011] Moreover, without limiting the range of applicable amounts of applicable amounts of the basic substance employed, usually for one mole of the aforementioned QO 1-5 moles, and more preferably 1-2 moles of the basic substance should be used. Furthermore, regarding the solvent employed in the method of the present invention, various types can be utilized, for example chloroform, dimethylsulfoxide, toluene, acetonitrile and solvent mixtures can also be employed.

[0012] Regarding the production of QE by epoxide formation from QO with the method of the present invention, which involves the reaction of QO, and TMSOMS or TMSMS, and a basic substance, there are several methods by which this can be carried out. For example, a reaction vessel is charged with TMSOMS or TMSMS and a basic substance together with a solvent, or TMSOMS or TMSMS is produced in the reaction system in a prior step by the addition of dimethylsulfate and either DMSO or dimethylsulfide to the reaction vessel and heating at 0~200 °C, after which the basic substance together with the solvent are added. Next, after the DMSO or other solvent is added with stirring and the TMSOMS or TMSMS has formed an ylide, the QO is added and caused to react for the recommended length of time, thus enabling the preparation of QE by epoxide formation from QO.

[0013] In the same way, without limiting the range of reactions belonging to the method of the present invention, usually the reaction is carried out at 0~200 °C, preferably 90~150 °C, further it is preferable to maintain the reaction system under an inert atmosphere such as nitrogen. After the termination of the reaction, the reaction product containing the desired QE is purified by the usual methods, and a separation process is performed. For example, the organic layer with the reaction product is separated, then the aqueous layer is extracted with an organic solvent such as chloroform or the like, the organic layer is combined with this extract, the solvent is removed at reduced pressure, and the desired QE is thus obtained.

[0014]
[Working Example] Into a 1 L 4-neck flask equipped with a stirring motor, thermometer and calcium chloride tube, 39 g of dimethylsulfoxide (DMSO) (0.5 mol) was added, followed by addition of 63 g of dimethyl sulfate (0.5 mol), and after stirring for 30 m, reaction mixture was heated to 100 °C for 40 m with continued stirring to produce trimethylsulfoxonium methylsulfate (TMSOMS). After this the flask was cooled to 20 °C, and then 80 g of toluene was added. The flask was stirred under nitrogen atmosphere, and 20 g of 60% solution (weight) of sodium hydroxide (0.5 mol) was added dropwise, then 150 g of DMSO was added in one portion, and after 3 h stirring, 100 g of a 50% (weight) toluene solution of quinuclidin-3-one (0.4 mol) was added dropwise.

[0015] After the contents of the flask had been stirred for another 17 h, the reaction mixture was poured into 140 g of water and this was extracted with chloroform, the chloroform solution was dried over anhydrous sodium sulfate, the sodium sulfate was removed by filtration, and then the solvent was removed by distillation to yield 39 g of spiro(oxirane-2,3')quinuclidine. This was

analyzed by gas chromatography, and the spectra appeared the same as that for a sample of spiro(oxirane-2,3')quinuclidine obtained by substituting trimethylsulfoxonium iodide for TMSOMS.

[0016]
[Effect of the Invention] According to the present invention, quinuclidin-3-one (QO) and a basic substance and trimethylsulfoxonium methylsulfate (TMSOMS) or trimethylsulfonium methylsulfate (TMSMS) can be utilized as starting materials to make possible an advantageous industrial method for the preparation of spiro(oxirane-2,3')quinuclidine (QE), which is a useful intermediate for medications, medicines, and the like. Accordingly, specific comparisons with the reaction process, reaction handling procedures, and the conditions involved in the addition which accompany the traditional methods, the possibility of inexpensive procurement in large quantities leads to the use of TMSOMS or TMSMS as a way to derive QE.

Technical Translation by
Matthew F. Schlecht, PhD.
Word Alchemy