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- (21) Application No. 8593/77 (22) Filed 1 March 1977
 (31) Convention Application No. G0 1331
 (32) Filed 2 March 1976 in (33) Hungary (HU)
 (44) Complete Specification published 20 Aug. 1980
 (51) INT. CL.³ C07C 93/06 119/18
 (52) Index at acceptance

C2C 20Y 220 227 22Y 29X 29Y 302 30Y 313 31Y 322
 328 32Y 338 360 362 364 36Y 452 45X 45Y 502
 50Y 620 623 624 650 652 662 748 802 80Y AA
 AB LFMG

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(54) - PROCESS FOR PREPARING PROPANOL DERIVATIVES

(71) We, RICHTER GEDEON VEGYESZETI GYAR RT., a body corporate organized under the laws of Hungary, of 19-21, Gyomroi ut, Budapest X., Hungary, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

10 The invention relates to a process for preparing 1 - tert. - butylamino - 3 - (2, 5 - dichlorophenoxy) - 2 - propanol, its acid addition salts and enantiomers.

British patent specification No. 1,337,921 describes the preparation of 1 - tert. - butylamino - 3 - (2, 5 - dichlorophenoxy) - 2 - propanol, its acid addition salts and its enantiomers by the following processes:

a) 1, 2 - epoxy - 3 - (2, 5 - dichlorophenoxy) - propane is reacted with tert. - butylamine;

b) 1 - chloro - 3 - (2, 5 - dichlorophenoxy) - 2 - propanol is reacted with tert. - butylamine;

25 c) sodium salt of 2, 5 - dichlorophenol is reacted with a 1 - tert. - butylamino - 3 - halo - 2 - propanol;

d) 2, 5 - dichlorophenol is reacted with 1 - tert. - butylamino - 2, 3 - epoxypropane.

30 whereafter the base obtained is converted, if desired, into a salt or resolved.

From the above-listed processes only processes a) and b) are practicable under industrial conditions because the starting materials of processes c) and d) can be prepared only in a very cumbersome way, by means of a reaction entailing explosion hazards (see Chem. and Ind. 1971, 994). The main disadvantages of the use of processes a) and b) are as follows:

40 - the cleavage of the epoxide ring by tert. - butylamine is not selective,
 - when using tert. - butylamine the end product is capable of reacting with another molecule of the starting substance, whereby

not only the yield decreases but also various by-products are formed from which the desired product can be separated only by further steps of purification;

- a long reaction period is required for the completion of the reaction;

- the temperature required for the reaction is higher than the boiling point of tert. - butylamine used as reagent;

- tert. - butylamine used as reagent is a toxic and inflammable substance, and these noxious properties are aggravated because the boiling point of the compound is rather low (44-45°C);

- the noxious tert. - butylamine must be used in a large excess.

The aim of our invention is to develop, by elimination or mitigation of the above-mentioned drawbacks, a novel process by the aid of which the desired product can be prepared in a simple way and in good yield.

Now it has been found that this aim can be attained by allowing 1, 2 - epoxy - 3 - (2, 5 - dichlorophenoxy) - propane to react with N - tert. - butylformimidate esters. These latter compounds were hitherto unknown in the literature, with the exception of methyl N - tert. - butylformimidate [see: J. Org. Chem. 39, 3855 (1974)]. The ethyl ester is particularly suitable for carrying out the reaction according to the invention.

Accordingly, racemic and optically active 1 - tert. - butylamino - 3 - (2, 5 - dichlorophenoxy) - 2 - propanol and its acid-addition salts are prepared by reacting racemic or optically active 1, 2 - epoxy - 3 - (2, 5 - dichlorophenoxy) - propane in a liquid medium, preferably in an apolar organic solvent e.g. dichloromethane, in the presence of a Lewis acid catalyst, preferably tin (IV)-chloride, with an alkyl (preferably lower alkyl of 1-4 carbon atoms) N - tert. - butylformimidate ester, more preferably with the ethyl ester, and optionally converting the product to an acid addition salt

thereof. An acid addition salt of the desired product may simply be formed in the reaction mixture by adding an acid thereto. For example, on addition of an alkanol containing hydrochloric acid, preferably ethanol, the hydrochloride of the desired product precipitates which, if desired, is converted into another acid addition salt or into the free base, or the optical antipodes are separated from each other.

The above-described cleavage of the epoxide ring represents a novel type of cleavage. It is surprising to a person skilled in the art that the reaction according to the invention can be carried out only with N-substituted formimide esters. Namely, under the conditions of the process according to the invention neither N-tert. - butyl-formamide nor any other N - tert. butylimidic acid ester is reactive. Thus, for the reaction according to the invention the formimide esters are entirely specific.

The N - tert. - butyl - formimide esters used as starting materials can be prepared e.g. by O-alkylating N - tert. butylformamide with a dialkyl sulphate or an alkyl chloroformate and liberating the alkyl N - tert. - butyl - formimide ester with a base from the salt so formed of N - tert. - butyl-formimide ester.

The racemic product obtained by the process according to the invention is, if desired, decomposed to its optical antipodes by subjecting the diastereoisomer salt pair obtainable by treatment with (+)- or (-) - dibenzoyl - tartaric acid to fractional crystallization.

According to our investigations on the physiological effects of 1 - tert. - butylamino - 3 - (2, 5 - dichlorophenoxy) - 2 - propanol hydrochloride, the dose effective to inhibit an ouabain-induced arrhythmia is 3.8 times lower and the corresponding doses of the (+) - and (-) - enantiomers are 7 times lower than those of Propranolol.

According to clinical investigations which we have carried out, 1 - tert. - butylamino - 3 - (2, 5 - dichlorophenoxy) - 2 - propanol hydrochloride possesses biological effects which both in qualitative and quantitative aspects offer some advantages over the beta-adrenergic blocking agents available at present in the market. Thus:

- it shows in essential circulatory hyperkinesis, even after a single oral dose of 2.5 mg, a surprisingly strong negative chronotropic effect (decreasing cardiac frequency) and substantially prolongs the circulatory period. In contrast to that, its negative inotropic (myocardium-weakening) effect is not appreciable. The favourable change in the parameters characterizing the disease is denoted also by the fact that the complaints of the treated patients are thus alleviated:

- surprisingly, 1 - tert. - butylamino - 3 -

(2, 5 - dichlorophenoxy) - 2 - propanol hydrochloride proved to be efficient also in case of patients suffering from cardiac arrhythmia who exhibited complete resistance against other beta-adrenergic blocking agents (Propranolol, Pindolol etc.). The compound was efficient not only in sinus tachycardia, supraventricular paroxysmal tachycardia, auricular vibration, tachycardiac forms of arrhythmia absoluta (in these conditions the therapy was virtually 100% efficient) but also in case of ventricular extrasystolia where in 50% of the cases complete healing or an at least 50% decrease of the number of extrasystoles was observed. (As generally known, the beta-adrenergic blocking agents hitherto available on the market are in general unsuitable for the treatment of ventricular rhythmic disturbances);

- 1 - tert. - butylamino - 3 - (2, 5 - dichlorophenoxy) - 2 - propanol hydrochloride, in contrast to the beta - adrenergic blocking agents already on the market, is capable of substantially decreasing the blood pressure of patients suffering from moderately severe hypertonia even in a relatively small dose (on average: 30.3 mg./day);

- according to observations made on patients suffering from anginal complaints, the compound not only decreases the number of anginal spasms but suspends also the pathological deviations characteristic of the disease and detectable by electrocardiography.

It should be emphasized that during the clinical application of the compound its surprisingly strong therapeutic effect was not accompanied by any specific side effects (such as cardiodepressive or respiratory-depressant activity) generally characterizing the beta-adrenergic blocking agents, or by any aspecific side effects (on the hematopoietic system, liver function, kidneys, metabolism etc.), or any side effects characteristic of some beta-adrenergic blocking agents (such as the detrimental action of Practolol on the eye, fibrous peritonitis, alterations of the type of lupus erythematoïden).

The process according to the invention offers a number of advantages over the processes known thus far. The main advantages are as follows:—

a) The reaction is selective, and thus the end product is of relatively good purity.

b) In the formimide ester reagent the amino moiety is protected; thus few by-products are formed during the reaction.

c) The reaction of a completely novel type gives high yields (e.g. about 80%).

d) The formimide ester reagent employed is not dangerously toxic, is non-inflammable and is not excessively volatile.

e) The reactants can be used in nearly

stoichiometric amounts.

f) The reaction takes place very rapidly, almost instantaneously.

9) The reaction can be carried out at 5 room temperature; no heating for long periods is required.

10) At the termination of the reaction, a hydrochloride salt suitable directly for therapeutic application can be formed and separated from the reaction mixture by simple filtration.

By the process according to the invention not only racemic but also optically active compounds can be prepared when an adequate, optically active epoxide is used as starting material or by resolving the racemic product.

Optically active 1,2 - epoxy - 3 - (2,5 - dichlorophenoxy) - propane serving as starting compound can be prepared, similarly to the corresponding racemic compounds (see British patent specification No. 1,337,921) from the sodium salt of 2,5 - dichlorophenol and optically active epi - halo - hydrin [see Ber. 47, 1856, 2884 (1914) and 48, 1863 (1915)].

The starting substance (-) - 1,2 - epoxy - 3 - (2,5 - dichlorophenoxy) - propane can be prepared also by allowing (+) - 1 - (2,5 - dichlorophenoxy) - 3 - (4 - toluenesulphonyloxy) - 2 - propanol to react with a base [see J. Med. Chem. 16, 168 (1973)]. In case of a racemic end product resolution is carried out with (+) - or (-) - dibenzoyltartaric acid in the way described in British Patent Specification No. 1,337,921.

The process according to the invention is further illustrated by the aid of the following Examples.

40 Example 1

4.4 g. of 1,2 - epoxy - 3 - (2,5 - dichlorophenoxy) - propane are dissolved in 40 ml. of anhydrous dichloromethane under stirring, then 3.4 g. of ethyl N - tert. - butyl - formimidate ester are added to the mixture. The solution is kept at 25°C by cooling with cold water, then a solution of 3.5 g. of tin(IV) - chloride in 15 ml. of anhydrous dichloromethane is dropwise added in 30 minutes. A white, crystalline precipitate is formed instantaneously. The suspension is stirred for 30 minutes, then 10 ml. of 25% ethanol containing hydrochloric acid are added, stirring is continued for further 30 minutes, the crude product filtered, washed with dichloromethane and dried *in vacuo*. The product weighing 7.30 g. is boiled with 70 ml. of water, the insoluble inorganic part filtered off while hot and washed with some hot water. The pure 1 - tert. - butylamino - 3 - (2,5 - dichlorophenoxy) - 2 - propanol hydrochloride precipitating from the filtrate is cooled and filtered, then washed with some water and dried *in vacuo*. Yield: 5.15 g. (78.5%); m.p. 211-212°C.

Example 2

One proceeds according to Example 1, with the difference that 4.4 g. of (+) - 1,2 - epoxy - 3 - (2,5 - dichlorophenoxy) - propane are used as starting material, affording 70 as product 4.95 g. (75%) of (-) - 1 - tert. - butyl - amino - 3 - (2,5 - dichlorophenoxy) - 2 - propanol hydrochloride; m.p. 211-212°C; $(\alpha)_D = -3.93^\circ$ (1% aqueous solution).

Example 3

One proceeds as described in Example 1, with the difference that 4.4 g. of (-) - 1,2 - epoxy - 3 - (2,5 - dichlorophenoxy) - propane are used as starting material, affording 80 as product 5.05 g. (77%) of (+) - 1 - tert. - butyl - amino - 3 - (2,5 - dichlorophenoxy) - 2 - propanol hydrochloride; m.p. 211-212°C; $(\alpha)_D = +3.90^\circ$ (1% aqueous solution).

Example 4

a) 10 g. of 1 - tert. - butylamino - 3 - (2,5 - dichlorophenoxy) - 2 - propanol hydrochloride are dissolved in 200 ml of water, then 45 ml. of a 10% solution of sodium hydrogen carbonate are added. An oil separates which crystallizes on standing. The suspension is filtered, washed with water and dried *in vacuo*. Yield: 8.8 g. of 1 - tert. - butylamino - 3 - (2,5 - dichlorophenoxy) - 2 - propanol; m.p. 83-84°C.

b) 10 g. of 1 - tert. - butylamino - 3 - (2,5 - dichlorophenoxy) - 2 - propanol are dissolved in 100 ml. of ethanol, then 50 ml. of 48% aqueous hydrogen bromide are added. The precipitated crystals are filtered, washed with ethanol and dried. Yield: 1.15 g. of 1 - tert. - butylamino - 3 - (2,5 - dichlorophenoxy) - 2 - propanol hydrobromide; m.p. 172-173°C.

c) 10 g. of 1 - tert. - butylamino - 3 - (2,5 - dichlorophenoxy) - 2 - propanol are dissolved in 50 ml. of ethanol, then 5.5 g. of (+) - tartaric acid are added. The precipitated crystals are filtered, washed with ethanol and dried. Yield: 1.25 g. of 1 - tert. - butylamino - 3 - (2,5 - dichlorophenoxy) - 2 - propanol - (+) - tartrate with a decomposition point of 213-214°C.

d) 9.70 g. (-) - dibenzoyl tartaric acid monohydrate and 7.45 g. of 1 - tert. - butylamino - 3 - (2,5 - dichlorophenoxy) - 2 - propanol are dissolved in 50 ml. of anhydrous ethanol, then the solution is allowed to stand overnight at 45-50°C. The precipitated ld-salt weighs 6.67 g.; m.p. 165-167°C (with decomposition); $(\alpha)_D = -54.1^\circ$ (1% ethanolic solution). The ld-salt is dissolved in 15 ml. of ethanol. 3 ml. of ethanol containing hydrochloric acid are added. The precipitated crystals are filtered and recrystallized twice from 10 ml. of water. Yield: 1.20 g. of (+) - tert. - butylamino - 3 - (2,5 - dichlorophenoxy) - 2 - propanol hydrochloride; m.p. 211-212°C; 130

$(\alpha)_D = +3.90^\circ$ (1% aqueous solution).

From the mother liquor of the ld-salt the ll-salt of a weight of 9.45 g. is obtained. On crystallization from ether: 7.02 g.; m.p. 152-153°C (with decomposition); $(\alpha)_D = -65.3^\circ$ (1% ethanolic solution). The crystals are dissolved in 20 ml. of ethanol, the solution is allowed to stand overnight at room temperature, and the precipitated racemic salt filtered off, then the mother liquor evaporated to dryness *in vacuo*. The residue is treated with ether, then subjected to suction. Yield: 5.25 g.; m.p. 156-157°C (with decomposition); $(\alpha)_D = -66.1^\circ$ (1% ethanolic solution). The crystals are dissolved in 15 ml. of ethanol, then 5 ml. of ethanol containing hydrochloric acid added, the precipitated crystals filtered and twice recrystallized from 20 ml. of water. Yield: 2.10 g. of (-) - 1 - tert. - butylamino - 3 - (2,5 - dichlorophenoxy) - 2 - propanol hydrochloride; m.p. 211-212°C; $(\alpha)_D = 3.93^\circ$ (1% aqueous solution).

WHAT WE CLAIM IS:

1. A process for the preparation of racemic or optically active 1 - tert. - butylamino - 3 - (2,5 - dichlorophenoxy) - 2 - propanol and acid addition salts thereof which comprises reacting racemic or optically active 1,2 - epoxy - 3 - (2,5 - dichlorophenoxy) - propane with an alkyl N-tert. - butylformimide in a liquid medium in the presence of a Lewis acid catalyst and optionally converting the product to an acid addition salt thereof.
2. A process according to claim 1 wherein said Lewis acid catalyst comprises stannic chloride.
3. A process according to claim 1 or 2 wherein said liquid medium is an apolar organic solvent.
4. A process according to claim 3 wherein said apolar organic solvent is dichloromethane.
5. A process according to any of the preceding claims wherein a lower alkyl N-tert. - butylformimide is employed.
6. A process according to claim 5 wherein ethyl N - tert. - butylformimide is employed.
7. A process according to any of the

preceding claims wherein an acid addition salt of the desired product is formed in the reaction mixture by adding an acid thereto.

8. A process according to claim 7 wherein an alkanol containing hydrogen chloride is added to the reaction mixture.

9. A process according to claim 8 wherein ethanol containing hydrochloric acid is added to the reaction mixture.

10. A process for the preparation of racemic or optically active 1-tert. - butylamino - 3 - (2,5 - dichlorophenoxy) - 2 - propanol and its acid addition salts, wherein racemic or optically active 1,2 - epoxy - 3 - (2,5 - dichlorophenoxy) - propane is reacted in an apolar medium, in the presence of stannic chloride, with an alkyl N - tert. - butylformimide, then an alkanol containing hydrochloric acid is added to the reaction mixture, and, if desired, the base is liberated from the hydrochloride salt so obtained or the hydrochloride is converted into another acid addition salt or the racemic compound is separated into its enantiomers.

11. A process according to any of the preceding claims wherein optically active 1,2 - epoxy - 3 - (2,5 - dichlorophenoxy) - propane is employed.

12. A process according to any of claims 1-10 wherein a racemic product is resolved by fractional crystallization of its acid addition salt with (+) or (-) - dibenzoyltartaric acid.

13. A process according to claim 1, substantially as illustrated in any one of Examples 1-3.

14. A process according to claim 1, substantially as illustrated in Examples 1-3 and 4.

15. Racemic or optically active 1-tert. - butylamino - 3 - (2,5 - dichlorophenoxy) - 2 - propanol and acid addition salts thereof whenever made by the process of any of claims 1-14.

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(α)_D = +3.90° (1% aqueous solution).

From the mother liquor of the 1d-salt the 1l-salt of a weight of 9.45 g. is obtained. On crystallization from ether: 7.02 g.; m.p. 152-153°C (with decomposition); (α)_D = -65.3° (1% ethanolic solution). The crystals are dissolved in 20 ml. of ethanol, the solution is allowed to stand overnight at room temperature, and the precipitated racemic salt filtered off, then the mother liquor evaporated to dryness *in vacuo*. The residue is treated with ether, then subjected to suction. Yield: 5.25 g.; m.p. 156-157°C (with decomposition); (α)_D = -66.1° (1% ethanolic solution). The crystals are dissolved in 15 ml. of ethanol, then 5 ml. of ethanol containing hydrochloric acid added, the precipitated crystals filtered and twice recrystallized from 20 ml. of water. Yield: 2.10 g. of (-) - 1 - tert. - butylamino - 3 - (2,5 - dichlorophenoxy) - 2 - propanol hydrochloride; m.p. 211-212°C; (α)_D = 3.93° (1% aqueous solution).

WHAT WE CLAIM IS:

1. A process for the preparation of racemic or optically active 1 - tert. - butylamino - 3 - (2,5 - dichlorophenoxy) - 2 - propanol and acid addition salts thereof which comprises reacting racemic or optically active 1,2 - epoxy - 3 - (2,5 - dichlorophenoxy) - propane with an alkyl N-tert. - butylformimide in a liquid medium in the presence of a Lewis acid catalyst and optionally converting the product to an acid addition salt thereof.
2. A process according to claim 1 wherein said Lewis acid catalyst comprises stannic chloride.
3. A process according to claim 1 or 2 wherein said liquid medium is an apolar organic solvent.
4. A process according to claim 3 wherein said apolar organic solvent is dichloromethane.
5. A process according to any of the preceding claims wherein a lower alkyl N-tert. - butylformimide is employed.
6. A process according to claim 5 wherein ethyl N - tert. - butylformimide is employed.
7. A process according to any of the

preceding claims wherein an acid addition salt of the desired product is formed in the reaction mixture by adding an acid thereto.

8. A process according to claim 7 wherein an alkanol containing hydrogen chloride is added to the reaction mixture.

9. A process according to claim 8 wherein ethanol containing hydrochloric acid is added to the reaction mixture.

10. A process for the preparation of racemic or optically active 1-tert. - butylamino - 3 - (2,5 - dichlorophenoxy) - 2 - propanol and its acid addition salts, wherein racemic or optically active 1,2 - epoxy - 3 - (2,5 - dichlorophenoxy) - propane is reacted in an apolar medium, in the presence of stannic chloride, with an alkyl N - tert. - butylformimide, then an alkanol containing hydrochloric acid is added to the reaction mixture, and, if desired, the base is liberated from the hydrochloride salt so obtained or the hydrochloride is converted into another acid addition salt or the racemic compound is separated into its enantiomers.

11. A process according to any of the preceding claims wherein optically active 1,2 - epoxy - 3 - (2,5 - dichlorophenoxy) - propane is employed.

12. A process according to any of claims 1-10 wherein a racemic product is resolved by fractional crystallization of its acid addition salt with (+) or (-) - dibenzoyltartaric acid.

13. A process according to claim 1, substantially as illustrated in any one of Examples 1-3.

14. A process according to claim 1, substantially as illustrated in Examples 1-3 and 4.

15. Racemic or optically active 1-tert. - butylamino - 3 - (2,5 - dichlorophenoxy) - 2 - propanol and acid addition salts thereof whenever made by the process of any of claims 1-14.

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