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(72) Inventors GILBERT LAVIELLE and CHRISTIAN HERISSON

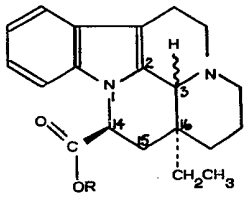
(19)

(54) 14-ALKOXYCARBONYL-3,4-DEHYDRO-14,15-DIHYDRO-14α,16β-EBURNAMENINE PERCHLORATES AND THEIR USE TO PREPARE STEREOISOMERS OF DIHYDRO APOVINCAMINIC ACID ESTERS

(71) I, ANDRE BUZAS, of 25, Rue L. Mignotte a 91470 Bievres, France, a French citizen, do hereby declare the invention for which I pray that a patent may be granted to me and the method by which it is to be performed to be particularly described in and by the following statement:—

This invention relates to processes for the stereospecific synthesis of stereoisomers of dihydro apovincaminic acid esters, which are of interest in the field of cerebro-vascular therapy, to new intermediates for such processes, and to a process for the preparation of the intermediates.

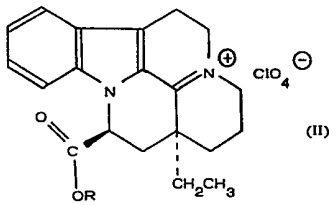
The above dihydro apovincaminic ester compounds are compounds of the general formula I



I

wherein R stands for a lower alkyl group containing up to 5 carbon atoms.

The invention provides new intermediates for the synthesis of the above compounds: 14 - alkoxycarbonyl - 3,4 - dehydro - 14,15 - dihydro - 14α,16β - eburnamenine perchlorates which have the general formula II



(II)

wherein R has the above meaning.

The intermediates II may be obtained according to this invention by reacting 1 - ethyl - 1,2,3,4,5,6,7 - hexahydro - 12H - indolo[2,3 - α]quinolizine in solution, for example in dichloromethane, with an appropriate alkyl α-chloro acrylate in the presence of alcohols and/or phenols, and forming the perchlorate salt of the product.

The intermediates II can be converted into the final apovincaminic ester compounds I according to this invention by two alternative processes, the choice of which depends on the stereoisomer of I that is required. To obtain isomers of the esters I in which the 3- position hydrogen is in the α configuration (above the plane of the paper as the general formula is written in this Specification) the intermediate II is dissolved in a mixture of methanol and dichloromethane, cooled and treated with sodium borohydride.

To obtain isomers of the esters I in which the 3- position hydrogen is in the β configuration (below the plane of the paper as the general formula is written in this Speci-

fication) the intermediate II is treated with zinc powder and acetic acid at room temperature.

This invention is illustrated by the following examples.

Example 1.

14 - methoxycarbonyl - 3,4 - dehydro - 14,15 - dihydro - 14α,16β - eburnamenine perchlorate:

In a 0.5 litre reactor fitted with warming, cooling and stirring means there were poured 7.15 g (28.4 millimols) of 1 - ethyl - 1,2,3,4,5,6,7 - hexahydro - 12H - indolo[2,3 - *a*]quinolizine dissolved in 0.2 litres of dichloromethane, 3.2 g (34 millimols) of phenol and 8 g (66.7 millimols) of methyl α-chloro-acrylate.

The reaction mixture was stirred at room temperature for 4 hours, then the solution was concentrated by warming and there were added 40 ml of a mixture containing equal parts by volume of ethanol and ethyl acetate, plus 5 ml of 70% perchloric acid. There were thus obtained, after separation, 9.2 g of a compound melting at 245°C (yield 74%), analysis of which showed good conformity with the formula $C_{21}H_{25}N_2O_2.ClO_4$.

Example 2.

14 - ethoxycarbonyl - 3,4 - dehydro - 14,15 - dihydro - 14α,16β - eburnamenine perchlorate:

This compound was prepared as described in Example 1, using 1.1 g (4.35 millimols) of 1 - ethyl - 1,2,3,4,5,6,7 - hexahydro - 12H - indolo[2,3 - *a*]quinolizine, 40 ml of dichloromethane, 0.4 g (4.25 millimols) of phenol and 1 g (7.45 millimols) of ethyl α-chloro-acrylate, with only 1 ml of perchloric acid.

There were obtained 1.50 g (yield 80%) of a product melting at 240°C, analysis of which showed good conformity with the formula $C_{22}H_{27}N_2O_2.ClO_4$.

Example 3.

14 - methoxycarbonyl - 14,15 - dihydro - 3α,14α,16β - eburnamenine:

This compound was prepared in the same kind of reactor as that used in the previous Examples.

1 g (2.28 millimols) of 14 - methoxycarbonyl - 3,4 - dehydro - 14,15 - dihydro - 14α,16β - eburnamenine perchlorate was dissolved in a mixture of 30 ml of methanol and 10 ml of dichloromethane. The mixture was iced and there were slowly added 600 mg of sodium borohydride. The mixture was then stirred for 10 hours at room temperature and concentrated, then treated with 50 ml of water and extracted three times with 50 ml of dichloromethane. After drying and evaporation there was obtained an oily product which led readily to a white crystalline product (700 mg, yield 90%), melting at 185°C and presenting Bohlman's bands. Analysis of the crystalline product corresponded to the formula $C_{21}H_{26}N_2O_2$.

Example 4.

14 - ethoxycarbonyl - 14,15 - dihydro - 3α,14α,16β - eburnamenine:

0.7 g (1.55 millimols) of 14 - ethoxycarbonyl - 3,4 - dehydro - 14,15 - dihydro - 14α,16β - eburnamenine perchlorate was treated as in Example 3 after dissolution in a mixture of 100 ml of methanol and 30 ml of dichloromethane, except that there were used 500 mg of sodium borohydride. There were finally obtained 450 mg (yield 90%) of an oily product leading readily to a white crystalline product melting at 152°C and presenting Bohlman's bands. Analysis of the crystalline product corresponded to the formula $C_{22}H_{28}N_2O_2$.

NMR analysis ($CDCl_3$ internal TMS) indicated at 4.95 PPM, one proton, C_{14}, doublet of doublet, $J_1 = 1.33$ Hz and $J_2 = 8.7$ Hz.

Example 5.

14 - methoxycarbonyl - 14,15 - dihydro - 3β,14α,16β - eburnamenine:

In the same kind of reactor as that used in the previous Examples there were poured 1.5 g (3.42 millimols) of 14 - methoxycarbonyl - 3,4 - dehydro - 14,15 - dihydro - 14α,16β - eburnamenine perchlorate, 40 ml of acetic acid, 80 ml of water and 5 g of zinc powder. The mixture was stirred for 20 hours at room temperature. The zinc was eliminated by filtration and the product was washed with dichloromethane and with water. The washing liquids were collected and made alkaline by an ammonia solution. After drying and evaporation there was thus obtained an oily product which was separated by chromatography on a silica column, the eluant being diethyl ether. The product obtained after evaporation of the eluant was a white crystalline product (yield 800 ml or 69%) melting at 155°C and presenting an absence of Bohlman's bands. Analysis showed a good correspondence with the formula $C_{21}H_{26}N_2O_2$.

NMR analysis ($CDCl_3$ internal TMS) indicated at 4.7 PPM, one proton, C_{14}, doublet of doublet, $J_1 = 5.6$ Hz and $J_2 = 12$ Hz.

Example 6.

14 - ethoxycarbonyl - 14,15 - dihydro - 3β,14α,16β - eburnamenine:

By the same method as that described in Example 5, but using 0.6 g (1.33 millimols) of 14 - ethoxycarbonyl - 3,4 - dehydro -

14,15 - dihydro - 14α,16β - eburnamenine perchlorate, 5 ml of acetic acid, 8 ml of water and 3 g of zinc powder, there was obtained 0.4 g (yield 70%) of a white crystalline product melting at 138°C and presenting an absence of Bohlman's bands. Analysis showed a good correspondence with the formula $C_{22}H_{28}N_2O_2$.

NMR analysis ($CDCl_3$ internal TMS) indicated at 4.7 PPM, one proton, C_{14}, doublet of doublet, $J_1 = 5.35$ Hz and $J_2 = 12$ Hz.

WHAT I CLAIM IS:—

1. A 14 - alkoxycarbonyl - 3,4 - dehydro - 14,15 - dihydro - 14α,16β - eburnamenine perchlorate of the general formula II herein.

2. A process for preparing a stereoisomer of a dihydro apovincaminic ester compound of the general formula I herein in which the 3-position hydrogen is in the α configuration, which comprises dissolving a compound according to claim 1 in a mixture of methanol and dichloromethane, cooling the solution and reducing it with sodium borohydride.

3. A process for preparing a stereoisomer of a dihydro apovincaminic ester compound of the general formula I herein in which the 3- position hydrogen is in the β configuration, which comprises reducing a compound according to claim 1 with zinc powder and acetic acid at room temperature.

4. A process for preparing a compound according to claim 1 which comprises reacting 1 - ethyl - 1,2,3,4,5,6,7 - hexahydro - 12H - indolo[2,3 - α]quinolizine in solution with an appropriate alkyl α-chloro-acrylate in the presence of an alcohol and/or a phenol, and forming the perchlorate salt of the product.

5. A process according to claim 2 or claim 3, wherein the compound II has been prepared by a process according to claim 4.

6. A 14,15 - dihydro - eburnamenine perchlorate substantially as disclosed in either of Examples 1 and 2 herein.

7. A process for the preparation of a 14,15 - dihydro - eburnamenine compound substantially as disclosed in any of the Examples herein.

SERJEANTS,
Chartered Patent Agents,
25 The Cresecent,
Leicester

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