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(54) **PROCEDE DE PREPARATION D'UN DERIVE D'INDOLE**
(54) **PROCESS FOR THE PREPARATION OF AN INDOLE DERIVATIVE**

(57) L'invention concerne un procédé de préparation 2-(3-chloropropoxy)-indole-3-carboxylate de méthyle. Ce procédé consiste à faire réagir un composé 3-chloro-3-carboxlyate indole avec du 3-chloropropanol en présence d'un acide présentant un pKa compris entre 0 et 2.

(57) A process for the preparation of methyl 2-(3-chloropropoxy)-indole-3-carboxylate, which comprises reacting a 3-chloro-3-carboxylate indole compound with 3-chloropropanol in the presence of an acid having a pKa of from 0 to 2.

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(54) Title: PROCESS FOR THE PREPARATION OF AN INDOLE DERIVATE

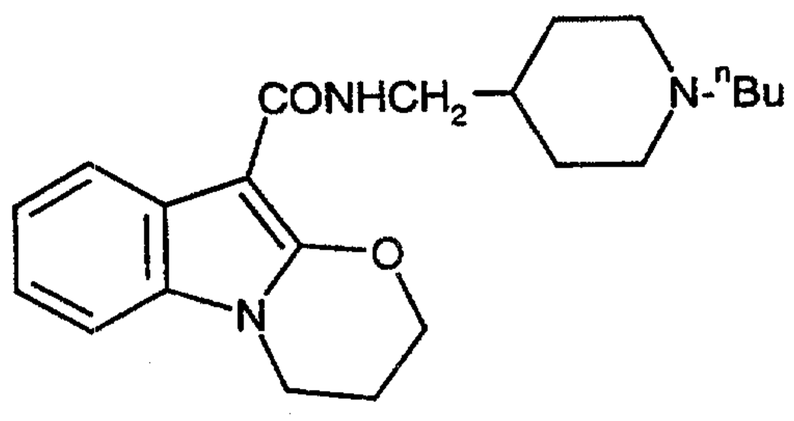
(57) Abstract

A process for the preparation of methyl 2–(3–chloropropoxy)–indole–3–carboxylate, which comprises reacting a 3–chloro–3–carboxylate indole compound with 3–chloropropanol in the presence of an acid having a pKa of from 0 to 2.

PROCESS FOR THE PREPARATION OF AN INDOLE DERIVATIVE

This invention relates to a new synthetic process to a compound having pharmacological activity.

WO 93/18036 (SmithKline Beecham plc) describes certain indole compounds having 5-HT_4 receptor antagonist activity including the compound of formula (I)

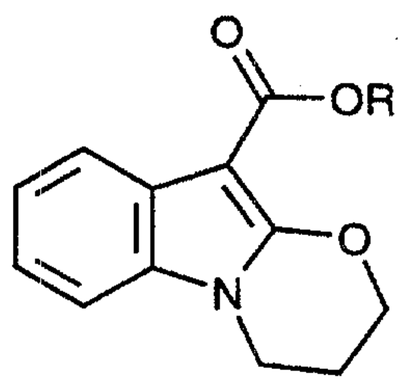


(I)

and its pharmaceutically acceptable salts. This compound is N-[(1-^{n}butyl-4-piperidyl)methyl]-3,4-dihydro-2H-[1,3]oxazino[3,2-a]indole-10-carboxamide, referred to herein by its code number SB-207266, (the hydrochloride salt is SB-207266-A), which is being developed by SmithKline Beecham plc as the active ingredient in a medicament for treatment of irritable bowel syndrome.

Example 3 of WO 93/18036 describes a method of preparation of SB-207266-A from N-[(1-^{n}butyl-4-piperidyl)methyl]indole-3-carboxamide (i.e. the compound corresponding to SB-207266, without the oxazino moiety), by reacting with N-chlorosuccinimide and 3-bromo-1-propanol, followed by treatment with sodium carbonate. N-[(1-^{n}butyl-4-piperidyl)methyl]indole-3-carboxamide is prepared by coupling N-(1-^{n}butyl-4-piperidyl)methylamine with a indole-3-carboxylic acid.

WO 98/07728 (SmithKline Beecham plc) describes a process for preparing SB-207266-A which involves the use of the N-(1-^{n}butyl-4-piperidyl)methylamine intermediate at a later stage in the process thus resulting in an increased yield of SB-207266-A relative to the amount of this intermediate, which is relatively expensive to produce. In particular, the alternative process comprises the reaction of of N-(1-^{n}butyl-4-piperidyl)methylamine with a compound of formula (A):

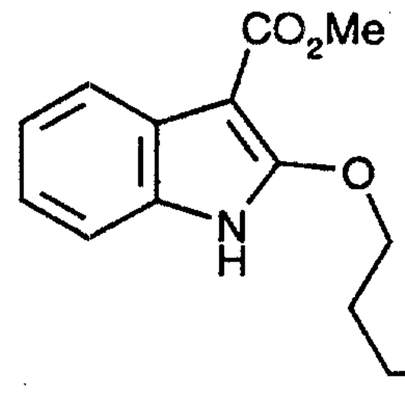


(A)

wherein R is alkyl, such as methyl or ethyl.

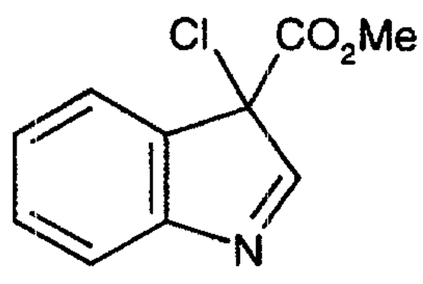
The compound of formula (A) wherein R is methyl is methyl 3,4-dihydro-2*H*-[1,3]-oxazino[3,2-*a*]indole-10-carboxylate.

WO98/07728 also describes the preparation of the oxazinoindole compound of the formula (A) from the corresponding indole by reaction with N-chlorosuccinimide and a 3-halo-propanol, such as 3-chloropropanol or 3-bromopropanol followed by cyclisation of the intermediate (B) by treatment with base in a suitable solvent.



(B)

The Description in the latter specification describes in more detail the the preparation of compound (B) from the corresponding methyl indole-3-carboxylate by reaction of the latter with N-chlorosuccinimide in the presence of 1,4-diazabicyclo[2.2.2]octane (DABCO) to form an intermediate of formula (C):



(C)

and subsequent reaction of (C) with 3-chloropropanol in the presence of

methanesulphonic acid.

We have now found that the use of an acid having a pKa of from 0 to 2, especially trichloroacetic acid, in place of methanesulphonic acid results in significant advantages for the commercial operation of the process.

According to a feature of the present invention we provide a process for the preparation of the compound of formula (B) above, namely methyl 2-(3-chloropropyl-1-oxy)-indole-3-carboxylate, which comprises reacting a compound of formula (C) with 3-chloropropan-1-ol in the presence of an acid having a pKa of from 0 to 2, especially trichloroacetic acid.

Other acids which may be used in accordance with the invention in addition to trichloroacetic acid include dichloroacetic acid and trifluoroacetic acid.

The use of the above-defined acid such as trichloroacetic acid in place of methanesulphonic acid has been found to increase significantly the overall yield of the process. The former acid also has the advantage over the latter that its use results in the formation of lower levels of the corresponding 2-methoxy compound, as an impurity.

The reaction is conveniently effected in an organic solvent such as dichloromethane or chloroform, at a temperature in the range -20°C to +10°C , for example using a catalytic amount of the acid. The resulting product of formula (B) can be used for the next stage in the synthesis of SB-207266 e.g as described in WO 98/07728.

The following Example illustrates the invention.

Example

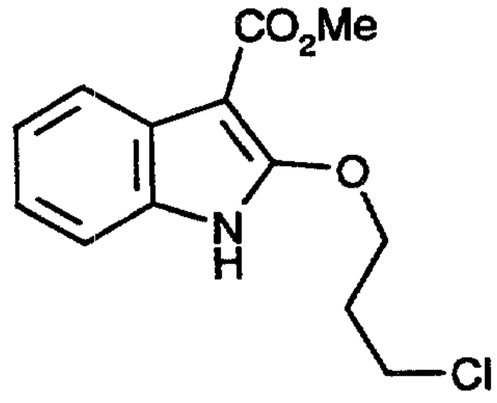
Methyl 2-(3-chloropropyl-1-oxy)-indole-3-carboxylate (formula (B))

A mixture of methyl indole-3-carboxylate and dichloromethane is cooled to 0° C. 1,4-dimethylpiperazine (0.55eq.) and N-chlorosuccinimide (1.1 eq) are added and the mixture left to stir for two hours to give a slurry containing the compound of formula (C) above. The resulting slurry is added to a solution of 3-chloropropan-1-ol (1.1 eq) and trichloroacetic acid (0.12 eq) in dichloromethane, maintaining the temperature below 0° C. The reaction mixture is left to stir for half an hour, then washed with 10% aqueous sodium carbonate, 0.5 M hydrochloric acid and water. The organic solution is dried over sodium sulphate, filtered and the solvent evaporated. Toluene is added

and the mixture stirred at 0-5° C for one hour. The product is then filtered, washed with toluene and dried to give the title product in 83 % yield.

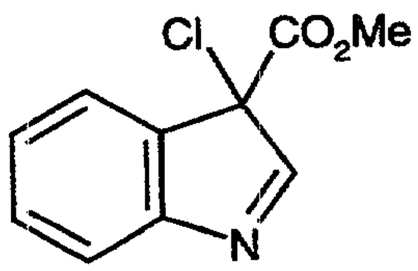
Claims

1. A process for the preparation of methyl 2-(3-chloropropyl-1-oxy)-indole-3-carboxylate, i.e. the compound of formula (B):



(B)

which process comprises reacting a compound of formula (C)



(C)

with 3-chloropropan-1-ol in the presence of an acid having a pKa of from 0 to 2.

2. A process as claimed in claim 1 in which the acid is trichloroacetic acid, dichloroacetic acid and/or trifluoroacetic acid.

3. A process as claimed in claim 1 in which the acid is trichloroacetic acid.

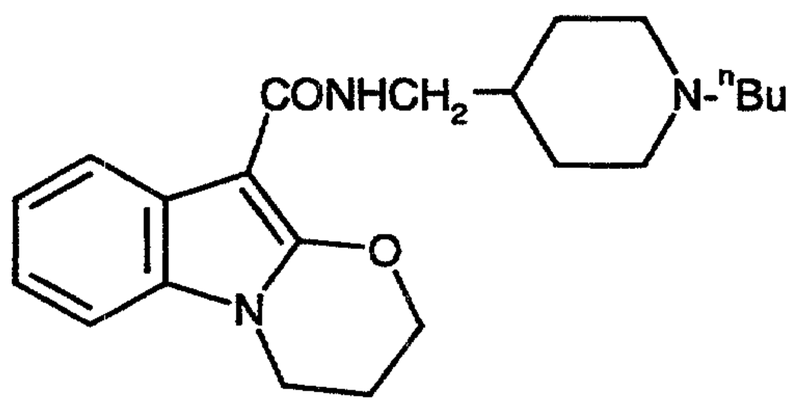
4. A process as claimed in claim 1, 2 or 3 in which the reaction is effected in an organic solvent at a temperature in the range -20°C to +10°C.

5. A process as claimed in claim 4 in which the organic solvent is dichloromethane or chloroform.

6. A process as claimed in claim 4 or 5 wherein the reaction is effected using a catalytic amount of the acid.

7. A process for preparing methyl 3,4-dihydro-2*H*-[1,3]-oxazino[3,2-*a*]indole-10-carboxylate, comprising performing a process as defined in any one of claims 1 to 6 and cyclising the resulting methyl 2-(3-chloropropyl-1-oxy)-indole-3-carboxylate by treatment with base in a suitable solvent.

8. A process for preparing N-[(1-^{n}butyl-4-piperidyl)methyl]-3,4-dihydro-2H-[1,3]oxazino[3,2-a]indole-10-carboxamide, i.e. the compound of Formula (I):



(I)

or a pharmaceutically acceptable salt thereof, comprising performing a process as defined in any one of claims 1 to 6 and using the resulting methyl 2-(3-chloropropyl-1-oxy)-indole-3-carboxylate in the synthesis of N-[(1-^{n}butyl-4-piperidyl)methyl]-3,4-dihydro-2H-[1,3]oxazino[3,2-a]indole-10-carboxamide or said salt.

9. A process as claimed in claim 8 comprising cyclising the resulting methyl 2-(3-chloropropyl-1-oxy)-indole-3-carboxylate by treatment with base in a suitable solvent to prepare methyl 3,4-dihydro-2*H*-[1,3]-oxazino[3,2-*a*]indole-10-carboxylate.

10. A process as claimed in claim 8 or 9, comprising

(i) preparing methyl 3,4-dihydro-2*H*-[1,3]-oxazino[3,2-*a*]indole-10-carboxylate from the methyl 2-(3-chloropropyl-1-oxy)-indole-3-carboxylate,

(ii) reacting the methyl 3,4-dihydro-2*H*-[1,3]-oxazino[3,2-*a*]indole-10-carboxylate with N-(1-n-butyl-4-piperidyl)methylamine to form N-[(1-^{n}butyl-4-piperidyl)methyl]-3,4-dihydro-2H-[1,3]oxazino[3,2-a]indole-10-carboxamide, and

(iii) optionally forming a pharmaceutically acceptable salt of N-[(1-^{n}butyl-4-piperidyl)methyl]-3,4-dihydro-2H-[1,3]oxazino[3,2-a]indole-10-carboxamide.