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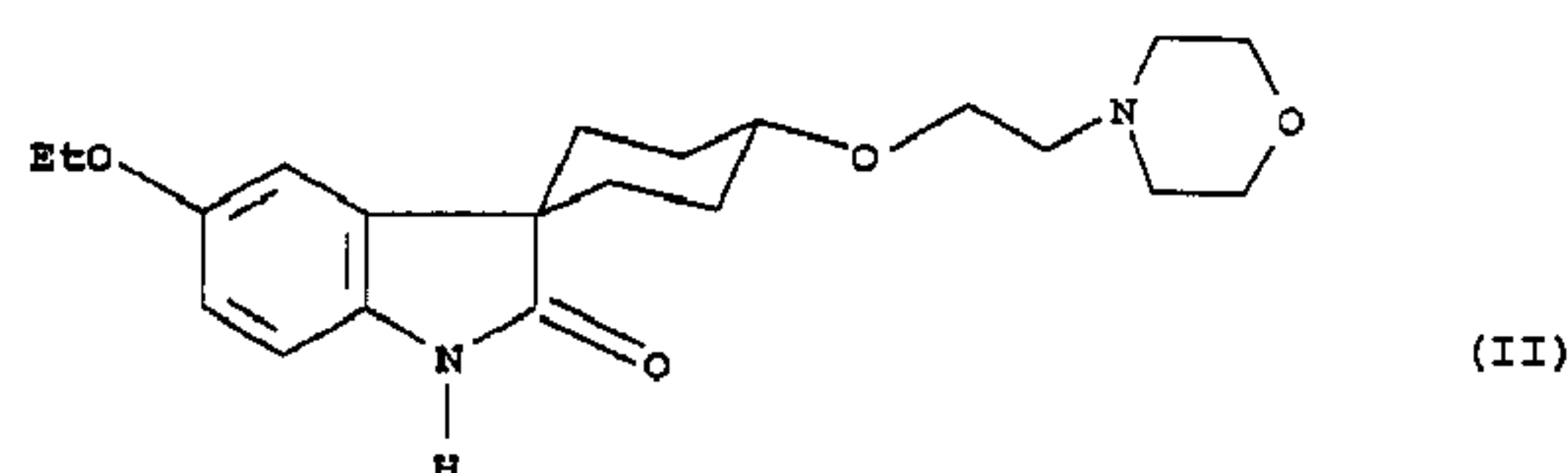
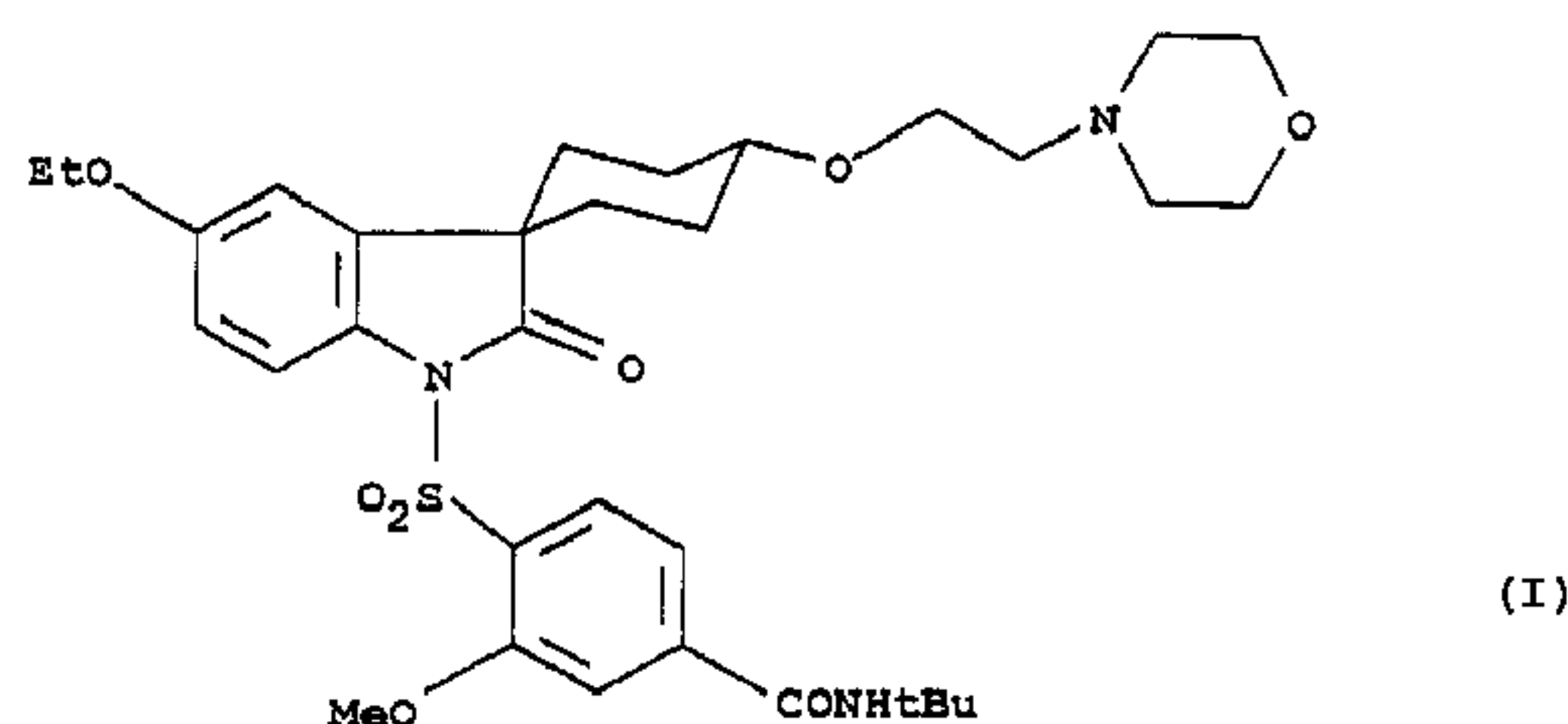
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(54) Title: NEW PROCESS FOR THE PREPARATION OF N-(1,1-DIMETHYLETHYL)-4-[[5'-ETHOXY-4-CIS-[2-(4-MORFOLINO)ETHOXY]-2'-OXOSPIRO[CYCLOHEXAN-1,3'-[H]INDOL]-1'(2'H)-YL]-SULFONYL]-3-METHOXYBENZAMIDE AND ITS SALTS



(57) Abrégé/Abstract:

The invention relates to a process for the preparation of a compound of formula (I) and the salts thereof by reacting the compound of formula (II) with the compound of formula (III), which comprises carrying out the reaction in dimethyl sulfoxide, at a

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temperature between 10 °C and 40 °C, preferably at room temperature and transforming the resulting base of formula (I), if desired, into its salt by a method known per se.

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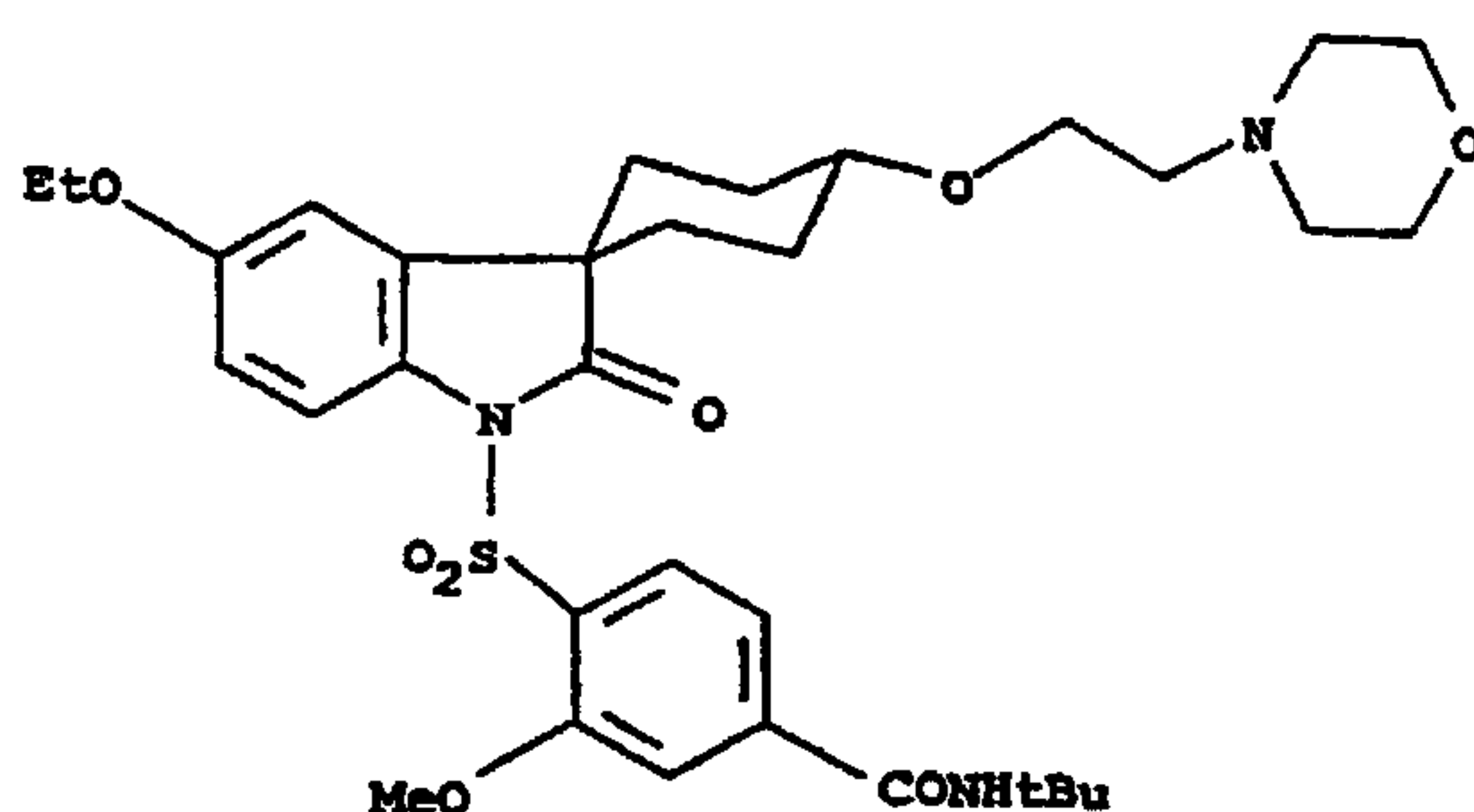
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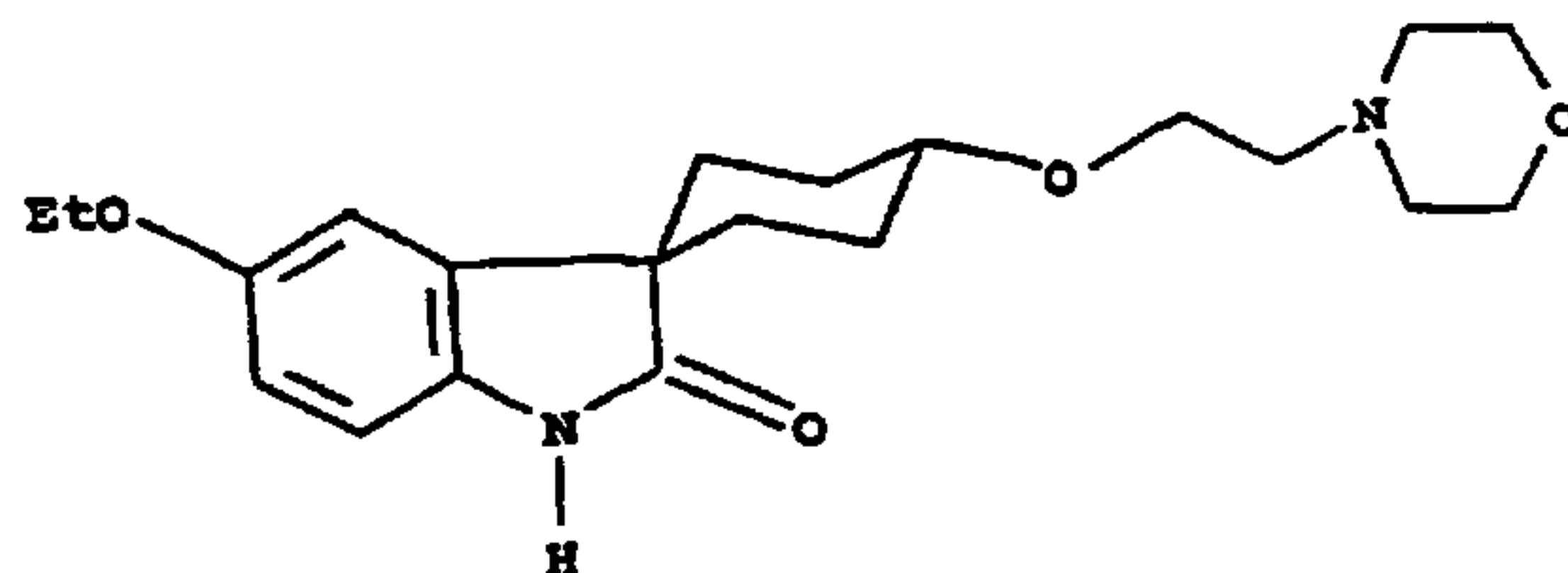
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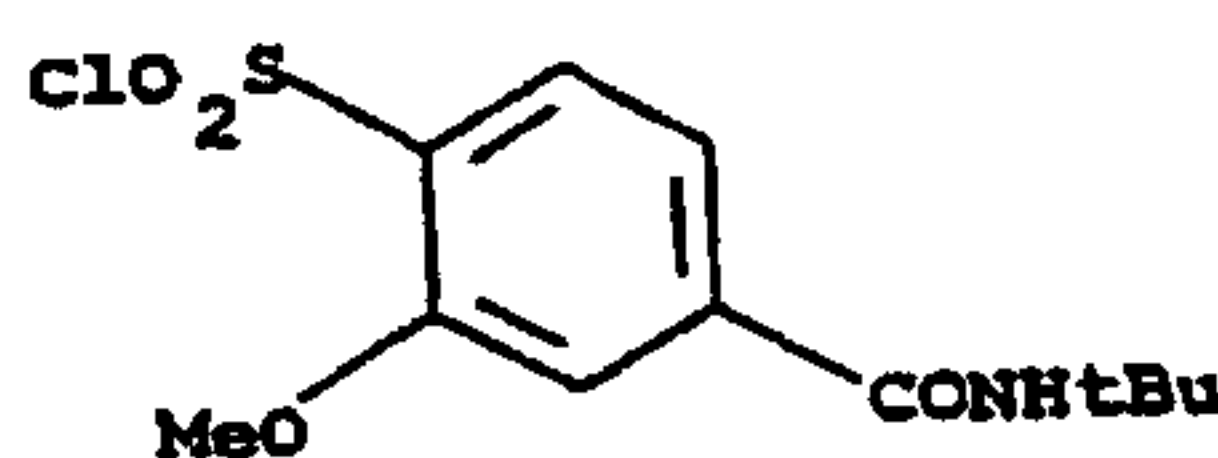
(54) Title: NEW PROCESS FOR THE PREPARATION OF N-(1,1-DIMETHYLETHYL)-4-[[5'-ETHOXY-4-*cis*-[2-(4-MOR-
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AND ITS SALTS



(I)



(II)



(III)

(57) Abstract: The invention relates to a process for the preparation of a compound of formula (I) and the salts thereof by reacting the compound of formula (II) with the compound of formula (III), which comprises carrying out the reaction in dimethyl sulfoxide, at a temperature between 10 °C and 40 °C, preferably at room temperature and transforming the resulting base of formula (I), if desired, into its salt by a method known per se.

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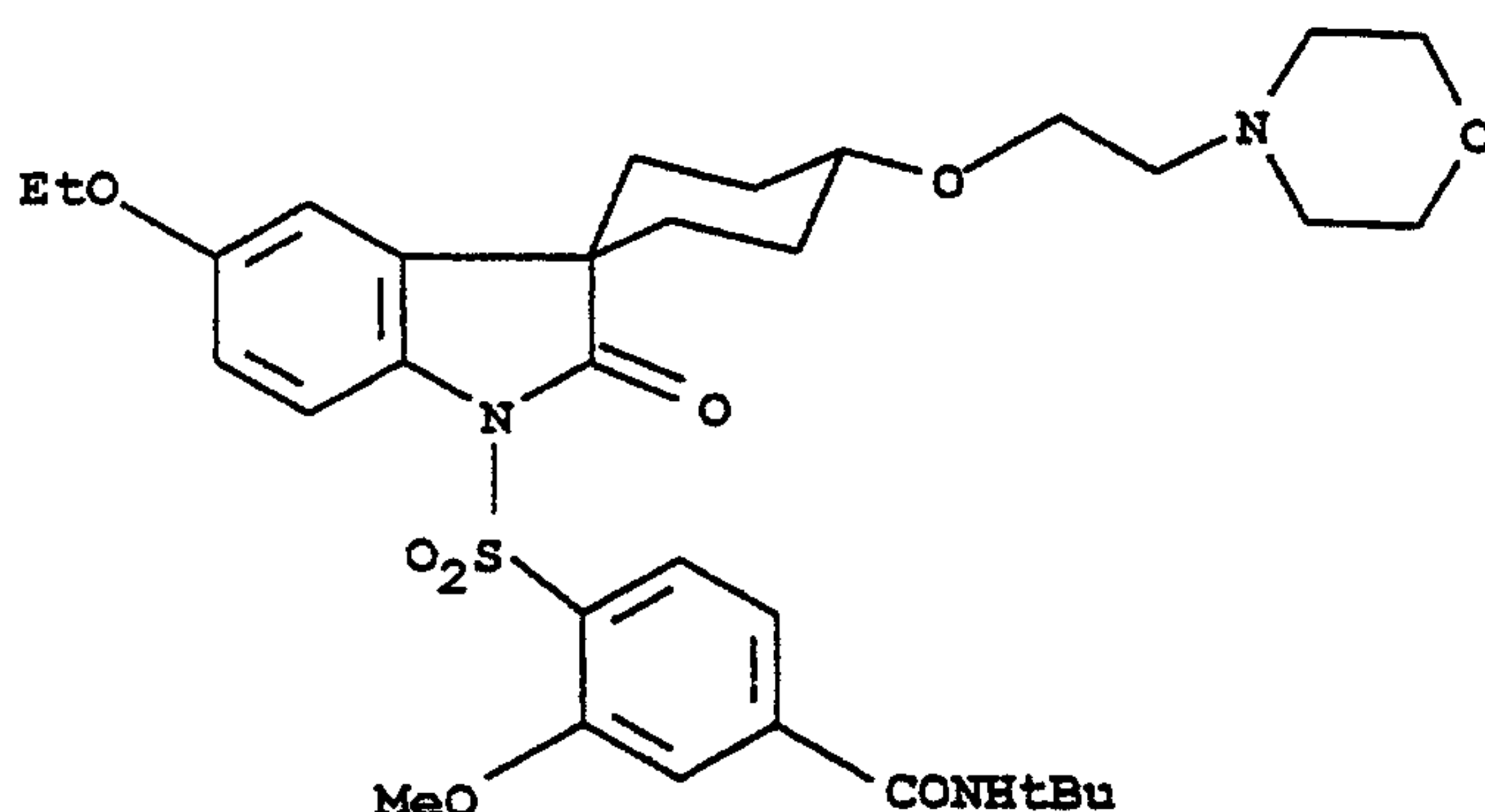
Enclosure

PCT/HU00/00078

New process for the preparation of N-(1,1-dimethylethyl)-4-[[5'-ethoxy-4-cis-[2-(4-morfolino)ethoxy]-2'-oxospiro[cyclohexan-1,3'-[3H]indol]-1'(2'H)-yl]-sulfonyl]-3-methoxybenzamide and its salts

- 5 The subject of the present invention is a process for the preparation of N-(1,1-dimethylethyl)-4-[[5'-ethoxy-4-cis-[2-(4-morfolino)ethoxy]-2'-oxospiro[cyclohexan-1,3'-[3H]indol]-1'(2'H)-yl]-sulfonyl]-3-methoxybenzamide (SR 121463) of formula I

10



I.

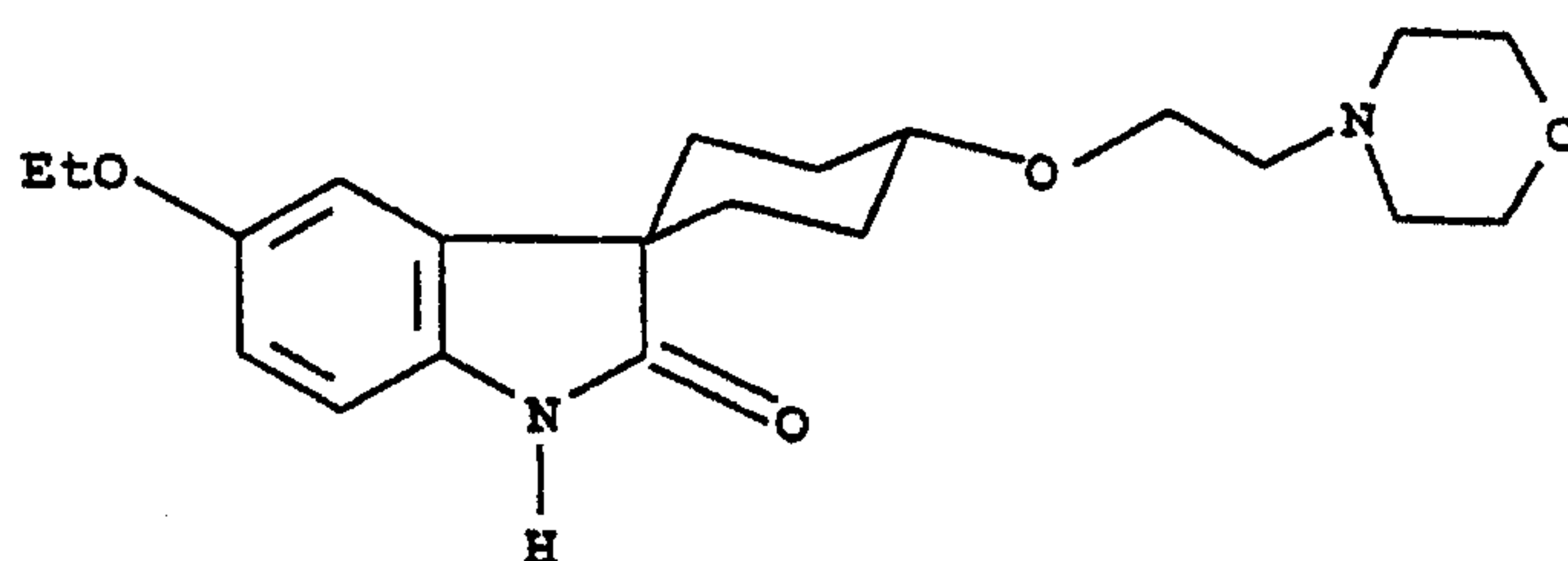
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and its salts, compounds having vasopressine V₂ antagonistic effect.

According to patent application WO 9715556 the compound of formula I

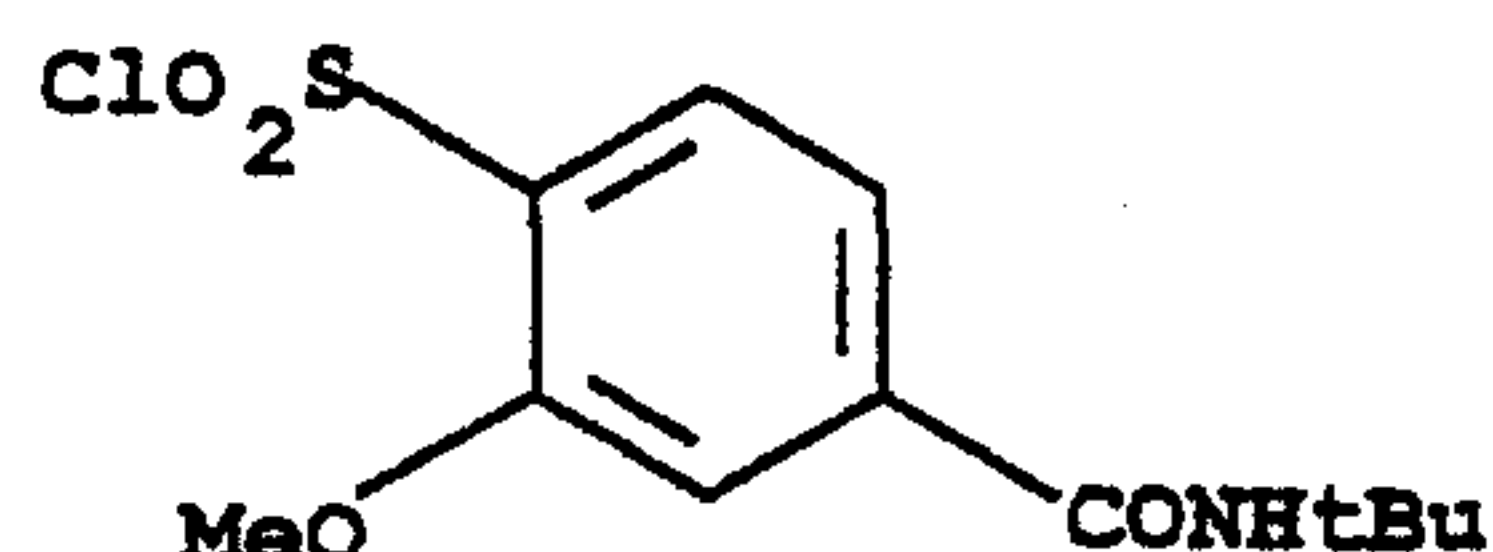
is prepared by reacting the spiro/cis-4-(beta-morfolino-ethyloxy)cyclohexan-1,3'-(5'-ethoxy)-[3H]indol-2'[1'H]one of formula II

20



II.

with the 2-methoxy-4-(N-t-butylaminocarbonyl)benzenesulfonyl chloride of formula III



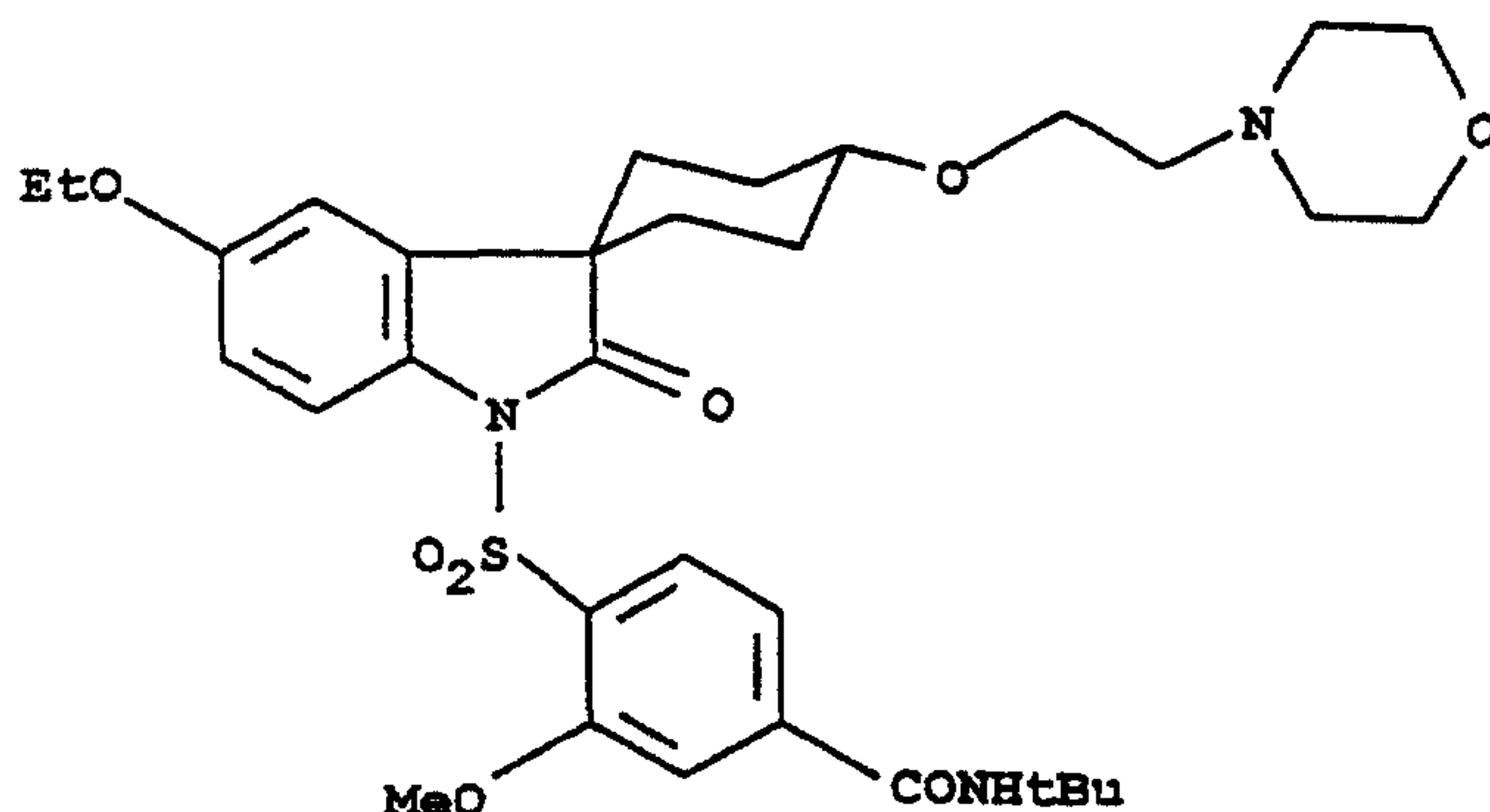
III.

using potassium-*t*-butylate in tetrahydrofuran.

Because of the applied solvent (tetrahydrofuran) and reaction temperature (between -60 °C and 40 °C) it is not easy to carry out the process under industrial conditions, the yield is low, the product is contaminated, its purification requires repeated crystallization.

To our surprise, we have found that by stirring in dimethyl sulfoxide at room temperature the reaction proceeds in very good yield (85 - 92%). The work-up procedure is simple, while in the original process the product is obtained by extraction, in the present process the base precipitates on diluting the reaction mixture with water, and it can be filtered off. The purity of the resulting base is 93-96% and the salt formed from it is appropriately pure.

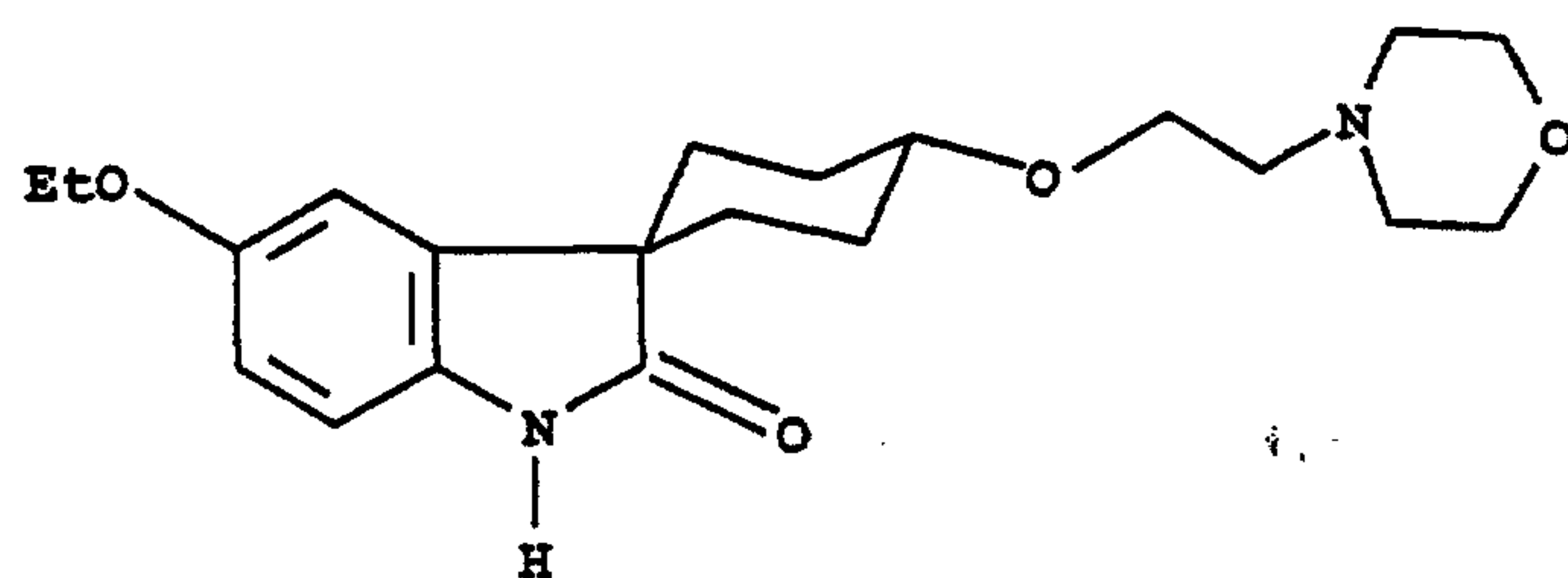
In accordance with the above, the subject of the invention is a process for the preparation of the compound of the formula I



I.

and the salts thereof, by reacting the compounds of the formula II

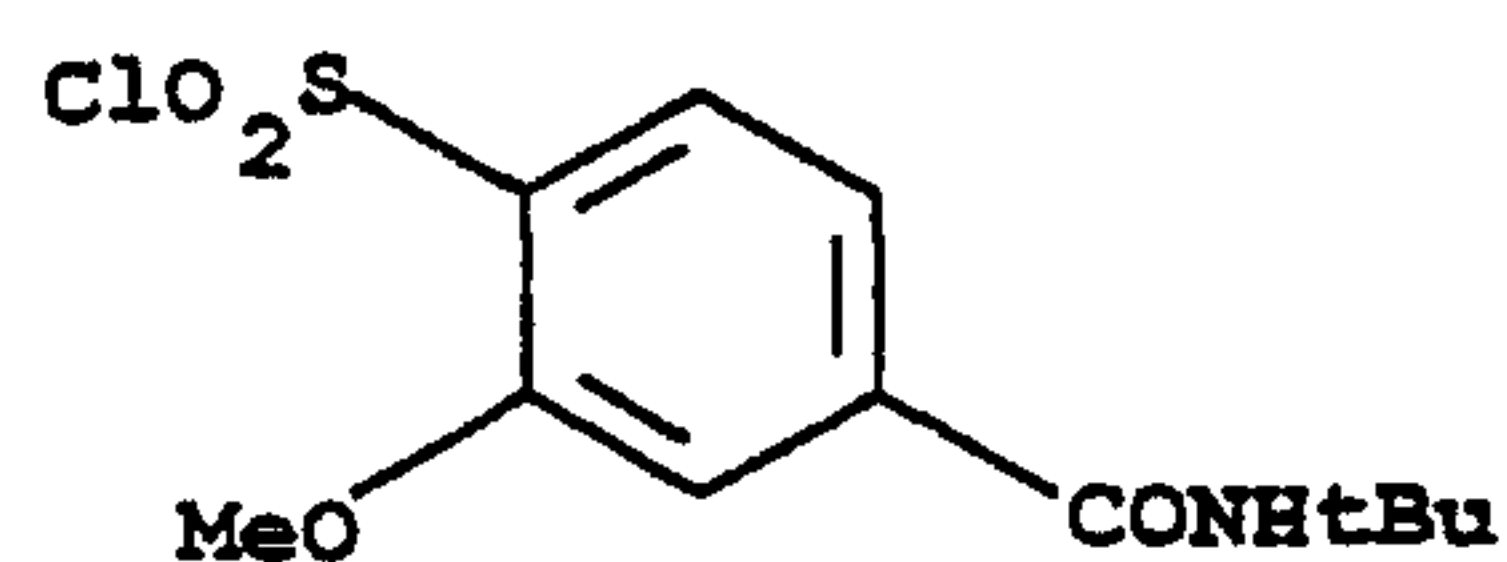
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II.

5

and III,



III.

- 10 which comprises carrying out the reaction in dimethyl sulfoxide at a temperature between 10°C and 40°C, preferably at room temperature and transforming the resulting base of formula I into its salt by a method known per se.

15

The process according to the invention is illustrated by the following examples:

Example 1.

In 180 ml of dimethyl sulfoxide 26,7 g of potassium *t*-butylate is dissolved. After 10
5 minutes of stirring 74,9 g of compound II is added to the mixture, at 20 - 25 °C, and
the mixture is stirred until complete dissolution. Then rapidly, keeping the temperature
below 25 °C, the compound of formula III is added to the mixture. The resulting
light-brown suspension is stirred at 25 °C for 1.5 hours, then it is decomposed with
700 ml of ice-water. After 1 hour of stirring the precipitate is filtered off, suspended
10 and washed with 2x500 ml of water, thoroughly sucked and washed with 2x 100 ml of
96 % ethanol. 117 g of compound of formula I is obtained, assay (by HPLC): 95,2 %.
Yield: 90,8 %.

Example 2.

15 1 mol of the base of compound I is suspended in 3-5-fold amount of ethanol and to
the mixture 0.5-1 mol of acid is added. After dissolution the solution is clarified by
active carbon and filtered. On cooling the salt precipitates, it is filtered off, washed
with a small amount of cold ethanol and dried. Yield ranges between 87-95% .

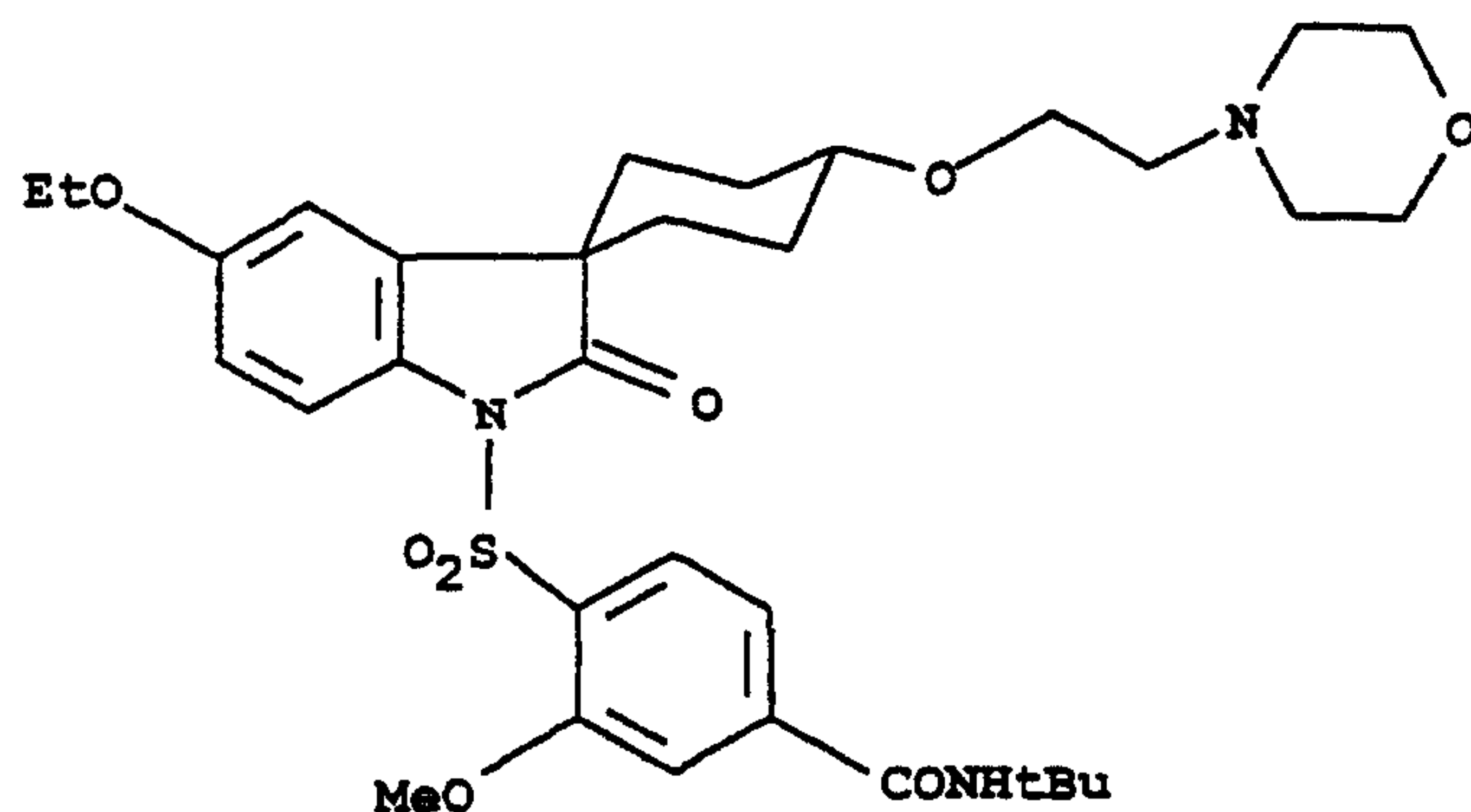
Dihydrogenphosphate monohydrate salt: mp.: 164.5°C

20 Hydrogen maleate salt: mp.: 184-185°C

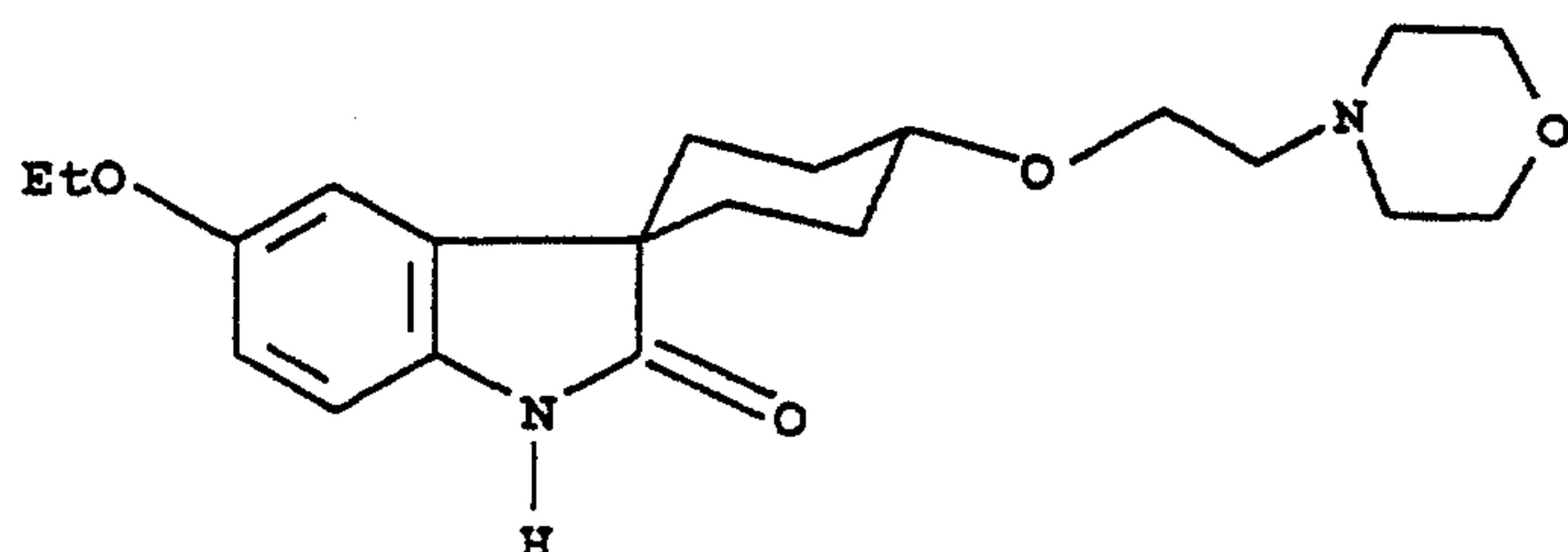
Hydrogen fumarate salt: mp.: 182-183°C

What we claim is:

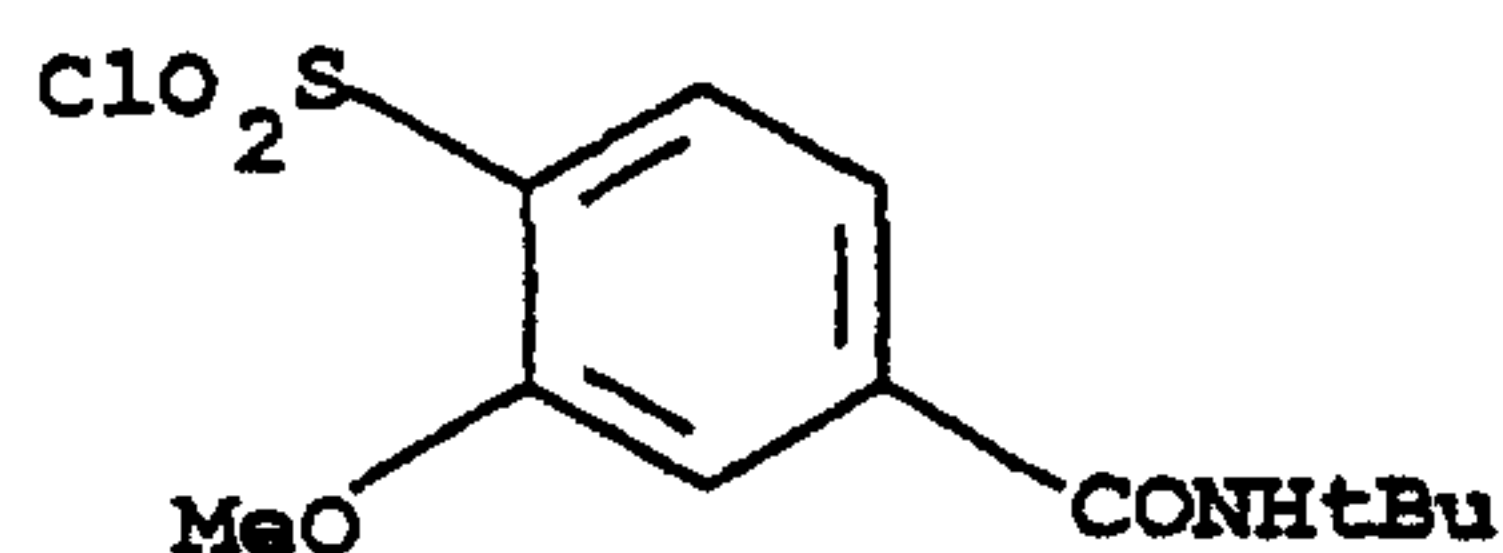
Process for the preparation of a compound of formula I



10 and the salts thereof by reacting the compound of formula II



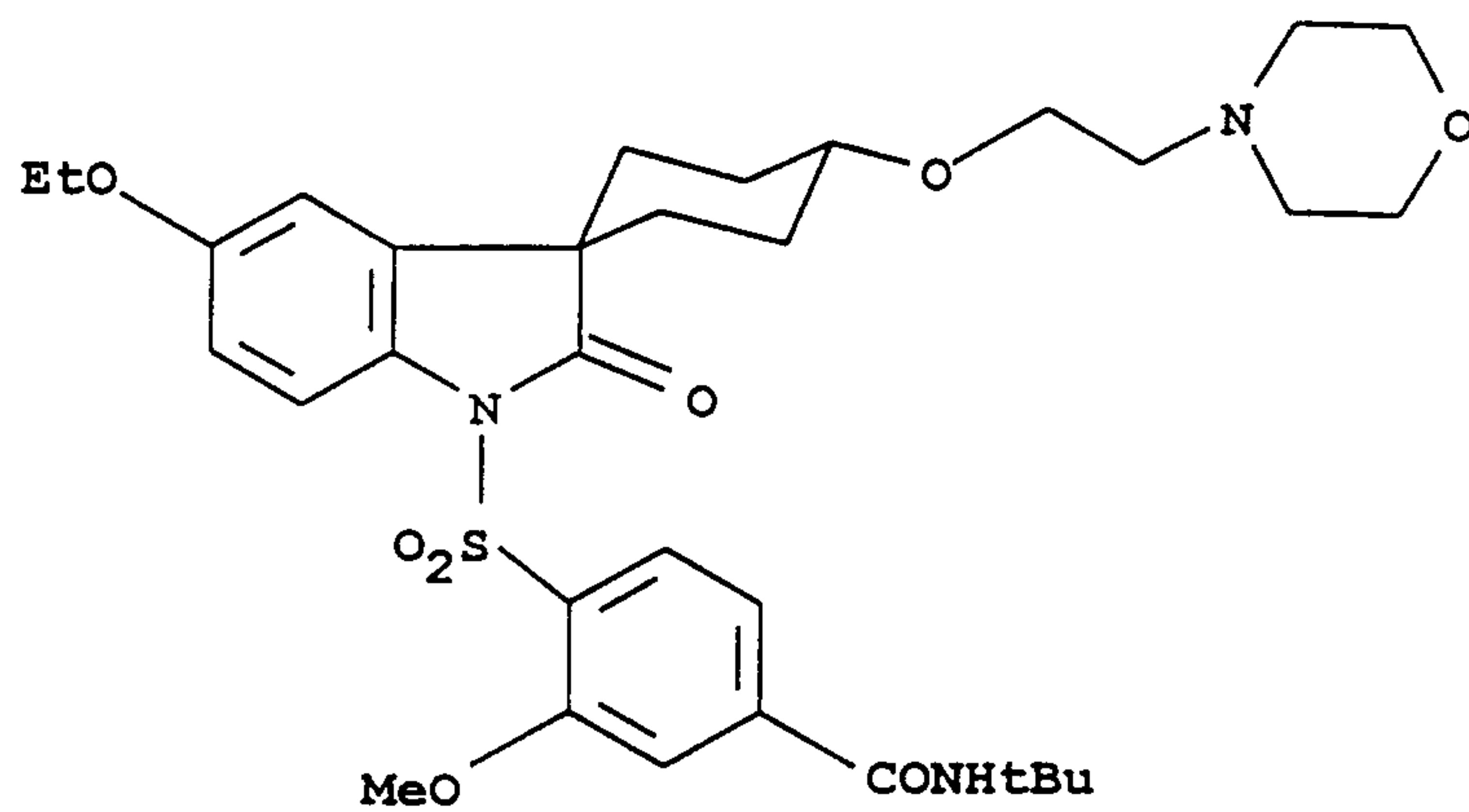
20 with the compound of formula III,



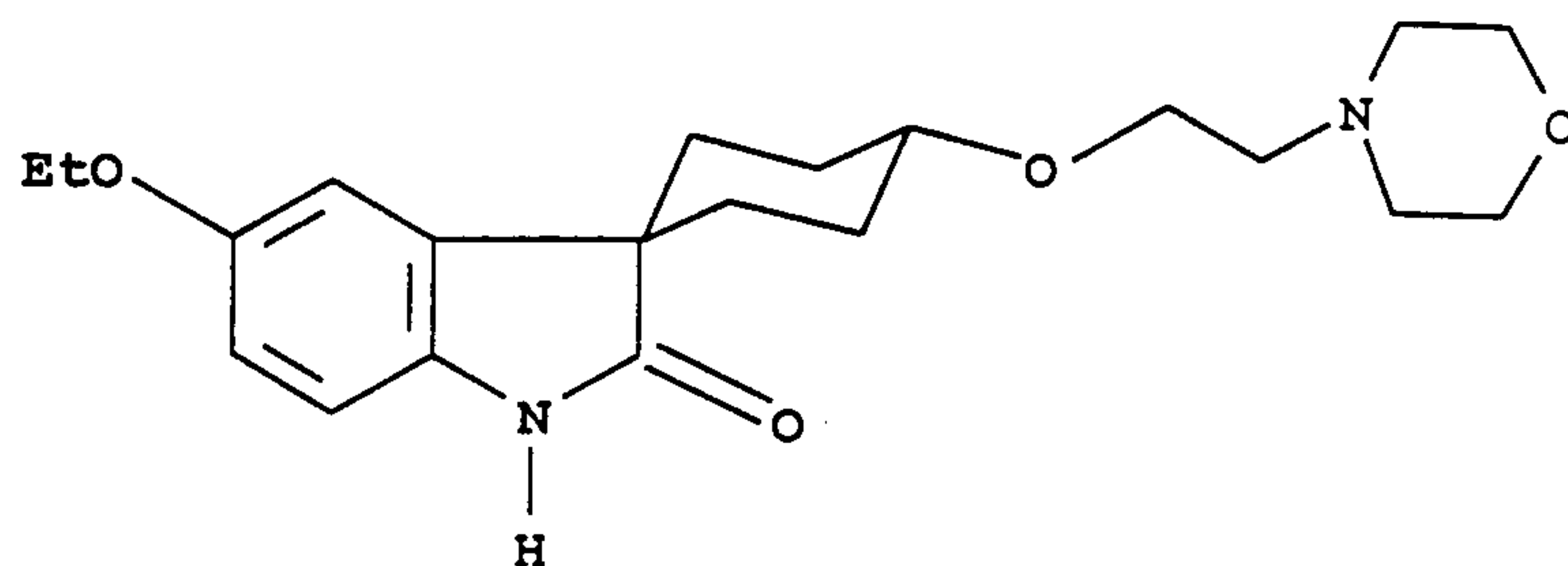
which comprises carrying out the reaction in dimethyl sulfoxide, at a temperature between 10°C and 40°C, preferably at room temperature and transforming the resulting base of formula I, if desired, into its salt by a method known per se.

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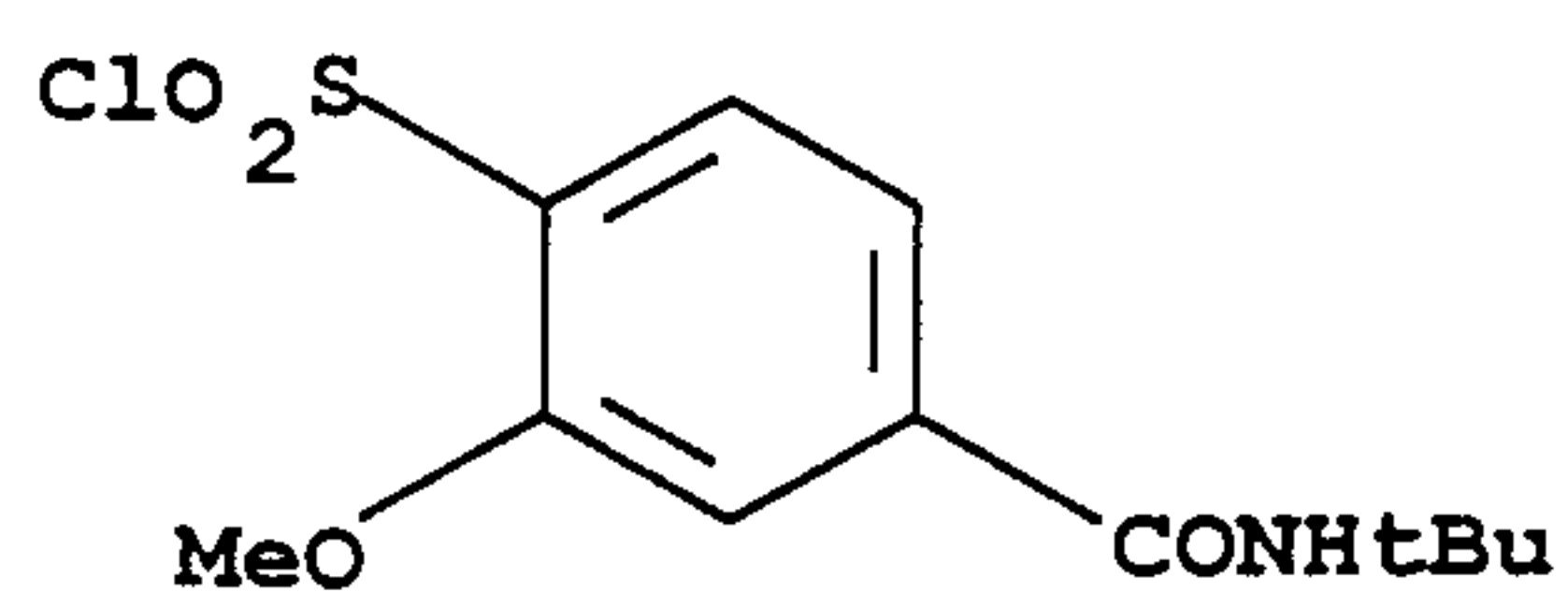
Figure 1



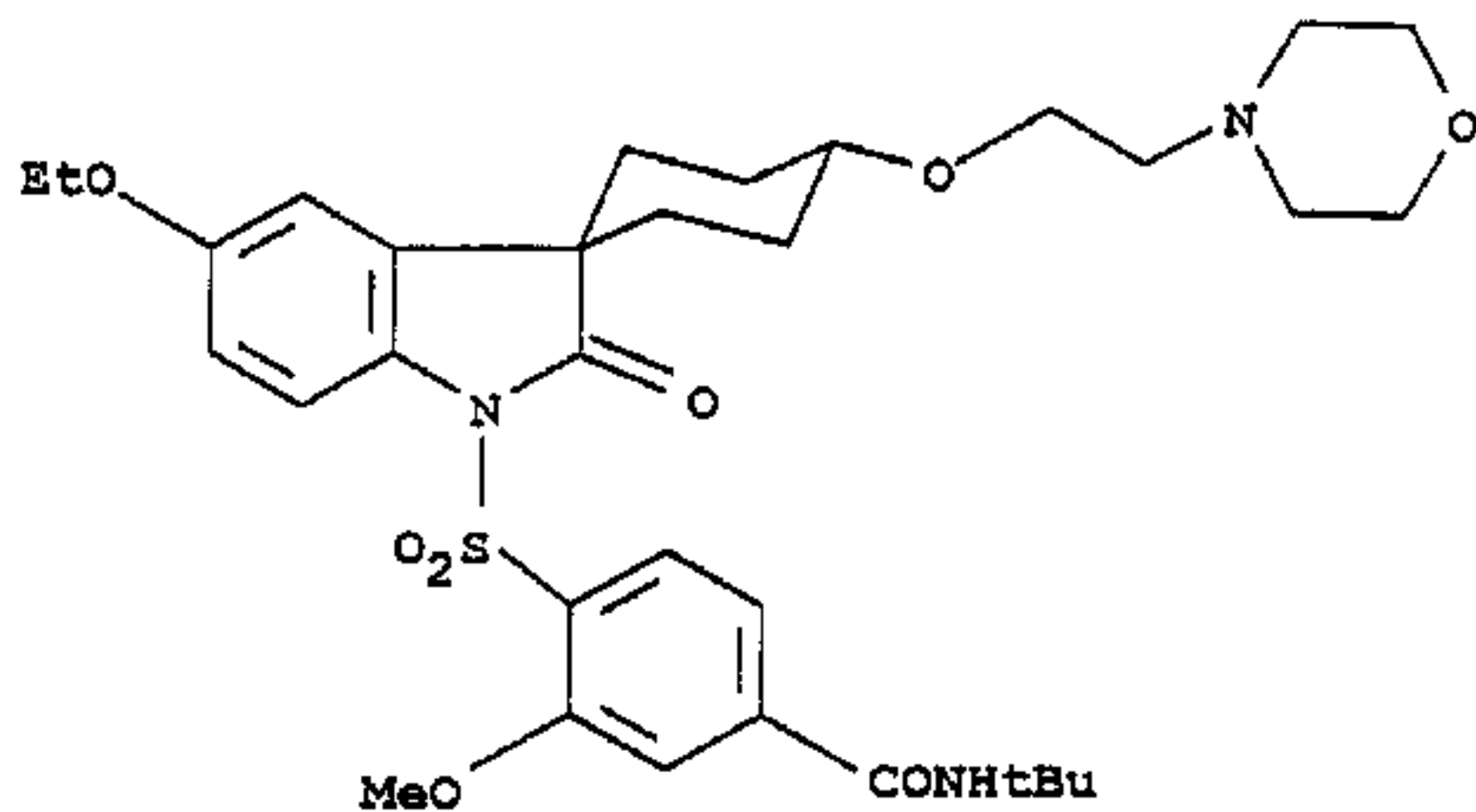
I.



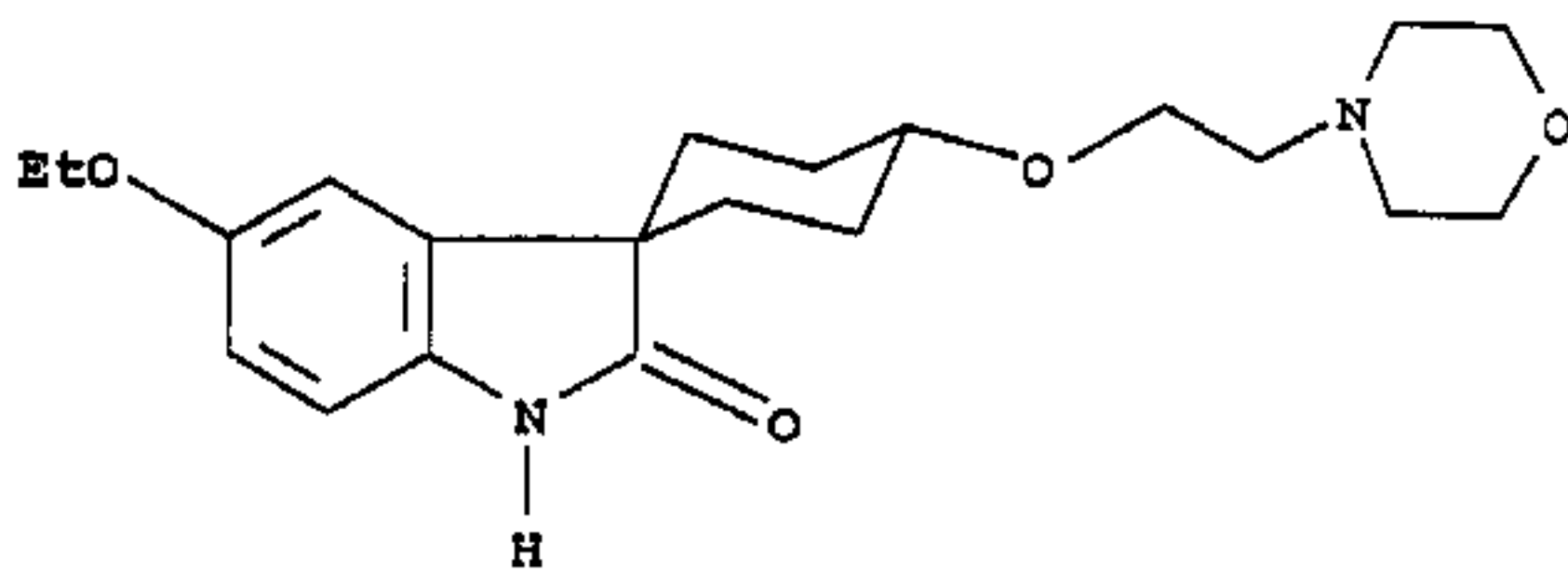
II.



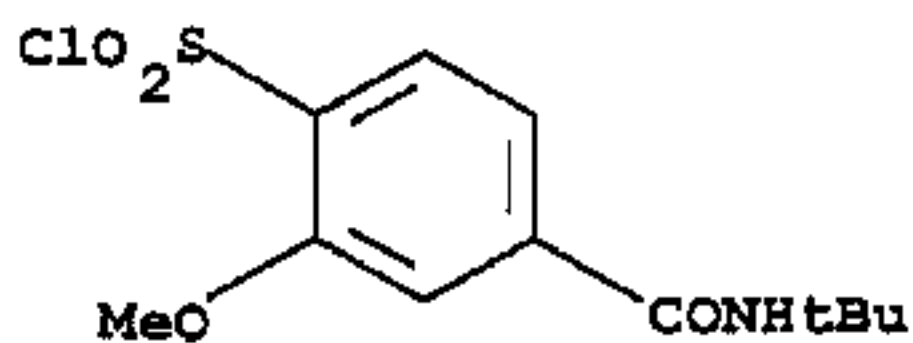
III.



(I)



(II)



(III)