PROCESS FOR THE PREPARATION OF 2-[(2-PYRIDINYL)METHYL]SULFONYL]-1H-BENZIMIDAZOLES AND NOVEL COMPOUNDS OF USE FOR SUCH PURPOSE

A process for the preparation of 2-[(2-pyridinyl)methyl]sulfonfyl]-1H-benzimidazole derivatives of general formula (I), wherein R^2 represents H, OCH_3, OCHF_2 or CF_3; R^3 represents H, CH_3 or OCH_3; R^4 represents H, OCH_3, OCH_2CF_3, or halo, such as Cl, Br or F; and R^5 represents H, CH_3 or OCH_3, or salts thereof, comprising reducing a compound of general formula (II) or a salt thereof wherein R^2, R^3, R^4 and R^5 are as defined above, in an alcoholic solvent, the reduction being carried out using a thiobisamine as reducing agent in the presence of a mineral acid, and, if desired, converting a compound obtained in free form into a salt thereof, or vice versa, and novel intermediates of formula (II) are described. The compounds of formula (I) are biologically active and/or may be of use as intermediates in the synthesis of biologically active compounds.

![Chemical Structures](image-url)
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Process for the preparation of 2-[[2-pyridinyl)methyl]sulfinyl]-1H-benzimidazoles and novel compounds of use for such purpose.

The present invention relates to a process for the preparation of 2-[[2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole derivatives of the general formula I

![Chemical Structure](image)

wherein

R² represents H, OCH₃, OCHF₂ or CF₃,
R³ represents H, CH₃ or OCH₃,
R⁴ represents H, OCH₃, OCH₂CF₃ or halo, such as Cl, Br or F, and
R⁵ represents H, CH₃ or OCH₃,
and salts thereof.

Furthermore, the invention relates to novel compounds of use for such purpose.

The above mentioned compounds of formula I are biologically active and/or may be of use as intermediates in the synthesis of biologically active compounds.

The compounds, 5-methoxy-2-[[4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole (omeprazole), 2-[[4-(2,2,2-trifluoroethoxy)-3-methyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole (lansoprazole), 2-[[2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole (timoprazole) and 5-difluoromethoxy-2-[[3,4-dimethoxy-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole (pantoprazole), being known as gastric acid secretion inhibiting agents, are examples of biologically active
compounds of the general formula I.

Basically, compounds of formula I has been prepared by oxidation of the corresponding thioether into the sulfinyl compound using suitable oxidation agents such as m-chloroperbenzoic acid. E.g. the compound 5-methoxy-2-([(4-methoxy-3,5-dimethyl-2-pyridinyl)mer-
yl]sulfinyl]-1H-benimidazole (omeprazole) and its preparation from 5-methoxy-2-([(4-methoxy-3,5-dimethyl-
2-pyridinyl)methyl]thio]-1H-benimidazole by oxidation

with m-chloroperbenzoic acid has been described in EP 0 005 129 B1. Similarly the compound 2-([(4-(2,2,2-
trifluoroethoxy)-3-methyl-2-pyridinyl)methyl]sulfinyl]-
1H-benimidazole (lansoprazole) and its preparation by oxidation of 2-([(4-(2,2,2-trifluoroethoxy)-3-methyl-2-
pyridinyl)methyl]thio]-1H-benimidazole with m-chloro-
perbenzoic acid has been described in EP 0 174 726 B1.

However, the oxidation process has been reported to be associated with certain disadvantages, one of these being that the final product is unstable under the acidic conditions at issue. Another disadvantage having been reported is that the starting thioether is an oil under ordinary conditions of temperature and pressure and thus difficult to purify. Furthermore discoloration of the final product made by oxidation of the thioether has been reported to occur.

In order to overcome these disadvantages PCT-
/CA94/00452 (WO 95/12590) suggests a process for the preparation of omeprazole and lansoprazole, wherein the oxidation is carried out on an amide analogue of the thioether, which is a crystalline compound, after which the resulting corresponding sulfinyl compound is hydrolysed in an alkaline medium to give the correspon-
ding carboxylic acid salt which can be decarboxylated to omeprazole or lansoprazole, as the case may be.

PCT/SE91/00402 (WO 91/18895) is directed to an
improved method for the synthesis of omeprazole by oxidation of the thioether with m-chloroperbenzoic acid aiming at eliminating the drawbacks of previously known methods. For that purpose, the reaction with m-chloroperbenzoic acid is carried out in a methylene chloride solution at a substantially constant pH of about 8.0 to 8.6; the reaction is extracted with aqueous NaOH; the aqueous phase is separated from the organic phase; and an alkyl formate is added to the aqueous phase, resulting in crystallization of omeprazole.

The present invention is directed to a basically different process for the preparation of the compounds of formula I whereby the compounds of formula I are prepared by reduction rather than by oxidation, the above mentioned disadvantages by the oxidation process thereby being eliminated.

Thus the present invention provides a new process for the preparation of 2-[[2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole derivatives of the general formula I

![Chemical Structure](image)

wherein

- \(R^2\) represents H, OCH\(_3\), OCHF\(_2\) or CF\(_3\),
- \(R^3\) represents H, CH\(_3\) or OCH\(_3\),
- \(R^4\) represents H, OCH\(_3\), OCH\(_2\)CF\(_3\) or halo, such as Cl, Br or F, and
- \(R^5\) represents H, CH\(_3\) or OCH\(_3\),

and salts thereof,

which process comprises reducing a compound of the
general formula II or a salt thereof

wherein R², R³, R⁴ and R⁵ are as defined above, in an alcoholic solvent, the reduction being carried out using a thiobisamine as reducing agent in the presence of a mineral acid, and, if desired, converting a compound obtained in free form into a salt thereof, or vice versa.

The compounds of formula II, most of which are novel compounds, may e.g. be prepared as described in our copending patent application (Danish patent application No. 0250/97, International patent application No. PCT/DK98/ ) being directed to a new synthesis for the preparation of these compounds which proceeds in three steps via novel cyclic intermediates and provides the compounds in excellent yield. The three steps may even be carried out in situ as a one-pot process.

The unsubstituted compound of formula II, i.e. the compound 2-[[(1-oxido-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole, is described in FR 2 567 123 A1, Example 13. No conversion of the compound to the corresponding 2-[[(2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole is described.

The compound of formula II wherein R³ and R⁵ represent CH₃, and R² and R⁴ represent OCH₃, i.e. the compound, 5-methoxy-2-[[4-methoxy-3,5-dimethyl-1-oxido-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole (omeprazole-N-oxide), has been reported as having been found as a metabolite of omeprazole in rats, CA 124:-
306394, Yakubutsu Dotai, 11(1), 45-56 (Japanese) 1996.

The compound of formula II wherein R² and R⁵ are hydrogen, R³ is methyl and R⁴ is 2,2,2-trifluoroethoxy, i.e. the compound 2-[[4-(2,2,2-trifluoroethoxy)-3-
5 methyl-1-oxido-2-pyridinyl]methyl]sulfinyl]-1H-benzi-
dazole (lansoprazole-N-oxide), is described in ES 2 063
705 B1 as being obtained as an impurity when the compound 2-[[4-(2,2,2-trifluoroethoxy)-3-methyl-2-
pyridinyl]methyl]thio]-1H-benimidazole is oxidized
into 2-[[4-(2,2,2-trifluoroethoxy)-3-methyl-2-pyridi-
nyl]methyl]sulfinyl]-1H-benimidazole (lansoprazole),
using m-chloroperbenzoic acid or hydrogen peroxide
in the presence of vanadium compounds as oxidation agent. There is no mentioning of the N-oxide being isolated or
converted into lansoprazole.

Actually, ES 2 063 705 does describe an N-oxide
which is converted into lansoprazol. However, this N-
oxide is not lansoprazole-N-oxide, but the compound 2-
[[4-(2,2,2-trifluoroethoxy)-3-methyl-1-oxido-2-pyridi-
nyl]methyl]thio]-1H-benimidazole and it is not con-
verted directly into lansoprazol. On the contrary, it
is reduced into the compound 2-[[4-(2,2,2-trifluoro-
ethoxy)-3-methyl-2-pyridinyl]methyl]thio]-1H-benzi-
dazole which is then oxidized into 2-[[4-(2,2,2-tri-
fluoroethoxy)-3-methyl-2-pyridinyl]methyl]sulfinyl]-1H-
benimidazole, i.e. lansoprazole, the last step thus
concerning to the oxidation described in the above

By the process according to the invention, the 2-
30 [[(2-pyridinyl)methyl]sulfinyl]-1H-benimidazole
derivatives of the formula I can be obtained in high
yield by reduction of the corresponding N-oxides using
thiobisamines as reducing agent under particular
reaction conditions.

Many reducing agents have been suggested for use
in the reduction of pyridine-N-oxides into pyridines, cf. e.g. the survey given in Houben-Weyl, "Methoden der Organischen Chemie", Vol. E7b, Part 2, (1992), pp. 543 - 557. However, as far as we know, thiobisamines have not hitherto been suggested for use in the reduction of pyridine-N-oxides into pyridines.

The thiobisamines allow for selective reduction of the N-oxide group in the compounds of formula II when the reduction is carried out in an alcoholic solvent in the presence of a mineral acid. Hereby the compounds of formula I may be obtained in an almost quantitative yield.

As a further advantage, the reaction takes place under mild conditions. Thus, the reduction is carried out in an alcoholic solvent, such as in a methanolic and/or ethanolic solvent. Furthermore, the reaction will usually be carried out at a temperature in the range from -10°C - 40°C, although, in principle, there is no hindrance to using temperatures outside this range, such as temperatures in the ranges from -50°C - -10°C and from 40°C - 70°C.

The reduction is carried out in the presence of a mineral acid, such as hydrochloric acid and/or sulphuric acid. The hydrochloric acid may be added as a solution of hydrogen chloride in water, e.g. as concentrated hydrochloric acid or as a solution of hydrogen chloride in a solvent, preferably an alcoholic solvent, such as a solution in methanol and/or ethanol. Also a solution of hydrogen bromide, e.g. in an alcohol as mentioned above, may be used. As will be appreciated from the above, the alcoholic solvent does not need to be anhydrous, but may include some water. However, it will also be appreciated that an anhydrous alcoholic solvent may be used.

The thiobisamine used in the process according to
the invention is preferably a compound of the general formula III

\[ R'(R'') - N - S - N - (R''')R''' \]  

III

wherein \( R', R'', R''', \) and \( R'''', \) which may be the same or different, represent hydrogen, \( C_1-C_8 \) alkyl or \( C_1-C_8 \) cycloalkyl, at least one of \( R' \) and \( R'' \) and at least one of \( R''' \) and \( R'''', \) being other than hydrogen, or the groups \( R' \) and \( R'' \), respectively the groups \( R''' \) and \( R'''', \), may be joined so as to form a 5- or 6-membered heterocyclic ring together with the nitrogen atom to which they are bound, which heterocyclic ring may optionally contain one or two additional hetero atoms selected from oxygen, sulphur and nitrogen.

As examples of the \( C_1-C_8 \) alkyl groups, linear and branched alkyl groups like methyl, ethyl, propyl, incl. n-propyl and i-propyl, butyl, incl. n-butyl, sec.-butyl and tert.-butyl, pentyl, incl. n-pentyl, and tert.-pentyl, hexyl, heptyl and octyl may be mentioned, and as examples of the \( C_1-C_8 \) alkyl groups cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl and cyclooctyl may be mentioned.

The thiobisamines used as reducing agents in the process according to the invention may be symmetrical or asymmetrical, and they may be primary or secondary or mixed primary and secondary amines.

In an embodiment being particularly preferred at present, the reduction is carried out in a methanolic and/or ethanolic solvent in the presence of hydrogen chloride under substantially anhydrous conditions using thiobismorpholine or thiobispiperidine as reducing agent.

Usually, the thiobisamine is used in at least an equimolar ratio to the compound of formula II, although
the reaction may proceed at lower ratios such as at ratios of about 0.8. There is no specific upper limit, but for economical reasons molar ratios above 5.0 will normally be avoided. Typically, the molar ratio will not exceed 2.5 and in most cases the molar ratio will be in the range from 1.0 to 1.5.

The thiobisdiamines used as reducing agents by the process according to the invention may e.g. be prepared by the process described by John L. Rice et al., J. Org. Chem. 1991, 56, 5235-5236. They are stable compounds which can be synthesized by a simple process using easily available starting materials and several of them are crystalline. The crystalline compounds are preferred for ease of handling, although it does not mean that liquid thiobisamines cannot be used as reducing agents by the process according to the invention. Thiobismorpholine and thiobispiperidine are examples of the crystalline compounds and as such represent preferred reducing agents.

Other methods for the preparation of thiobisamines (diaminosulfanes) have e.g. been described in Houben-Weyl, "Methoden der organischen Chemie", Vol. El1, pp. 15-21, (1985).

The invention will now be further illustrated by specific examples which, however, should not be regarded as any limitation of the scope of the invention.
EXAMPLES.

Preparation of starting materials.

**Example A.** N-Cyclohexyl-2,3-dihydro-5-methoxy-2-thioxo-1H-benzimidazole-1-carboxamide (from 4-methoxy-2-nitroaniline).

**N-Cyclohexyl-N’-(4-methoxy-2-nitrophenyl)urea.**

4-Methoxy-2-nitroaniline (150 g, 892 mmol), cyclohexylisocyanate (112 g, 892 mmol) og pyridine (45 mL) were dissolved in DMF (dimethylformamide) (1.5 L) and heated to 80°C for 8 h. The formed suspension was cooled to room temperature and ethanol (0.5 L) was added. After cooling on an ice bath, the precipitate was filtered off and washed with ethanol. Drying at 50°C afforded 227 g (87%) of the title compound as a yellow product. Mp. 233-35°C.

**N-Cyclohexyl-N’-(2-amino-4-methoxyphenyl)urea.**

N-Cyclohexyl-N’-(4-methoxy-2-nitrophenyl)urea (50.0 g, 170 mmol) was suspended in ethanol (1.5 L) and 10% Palladium on Carbon (5.0 g) was added. The mixture was reduced with hydrogen at 1 atm. and room temperature overnight. Then the reaction mixture was heated to 70°C and the catalyst filtered off. The filtrate was evaporated to 400 mL and cooled to -20°C. The precipitate was filtered off, washed with ethanol and dried at 50°C to give 39.8 g (89%) of the title compound as a white crystalline product. Mp. 187-88°C.

**N-Cyclohexyl-2,3-dihydro-5-methoxy-2-thioxo-1H-benzimidazole-1-carboxamide.**

N-Cyclohexyl-N’-(2-amino-4-methoxyphenyl)urea (104.4 g, 397 mmol) and carbondisulfide (66.4 g, 874
mmol) were heated in dry DMF (400 mL) for 41 h at 50°C. The resulting solution was cooled to room temperature and added to water (1250 mL) over 1½ h. After further stirring for 2 h the precipitate was filtered off, washed with water and dried at 60°C to give 118.6 g (98 %) of the title compound as a white crystalline product. Mp. 188-90°C. Recrystallisation from acetone raised the melting point to 198-201°C.

Example B. N-Cyclohexyl-2,3-dihydro-2-thioxo-1H-benzimidazole-1-carboxamide.

The title compound was synthesized from 2-mercaptobenzimidazole and cyclohexylisocyanate essentially following the procedure described by E. Dyer et al., J. Heterocyclic Chem. 6 (1969) 23-28.


A. 2-Cyclohexyl-7-methoxy-1,2,4-thiadiazolo[4,5-al]benzimidazole-3(2H)-one.

N-Cyclohexyl-2,3-dihydro-5-methoxy-2-thioxo-1H-benzimidazole-1-carboxamide (91.6 g, 300 mmol) (Ex. A) was suspended in chloroform (1.1 L) at room temperature. Bromine (47.9 g, 300 mmol) in chloroform (150 mL) was added over 70 min. at room temperature. Triethylamine (60.6 g, 600 mmol) was added. The formed solution was allowed to cool to room temperature over 1 h and then washed with water (2x1 L). The organic phase was dried over anhydrous sodium sulfate and evaporated in vacuum into a fat crystalline suspension. Ethanol (1.0 L) was added. After cooling to 0°C the precipitate was filtered off, washed with ethanol and
dried in vacuum at 35°C to give 87.0 g (96%) of the title compound as an off-white product. Mp. 181-4°C. Calc. for C<sub>15</sub>H<sub>14</sub>N<sub>3</sub>O<sub>2</sub>S: C:59.4%; H:5.7%; N:13.9%; S:10.6%. Found: C:59.2%; H:5.8%; N:13.6%; S:10.6%.

B. 2-Cyclohexyl-7-methoxy-1,2,4-thiadiazolo[4,5-a]benzimidazole-3(2H)-one-1-oxide.

2-Cyclohexyl-7-methoxy-1,2,4-thiadiazolo[4,5-a]benzimidazole-3(2H)-one (24.3 g, 80 mmol) (Ex. C-A) was suspended in chloroform (160 mL) and cooled on an ice bath. 99% m-CPBA (m-chloroperbenzoic acid) (13.8 g, 80 mmol) was added in small portions over 45 min. at 2-5°C. Then the ice bath was replaced with a 2-propanol-ice bath. After further stirring for 20 min. cold t-butylmethylether (480 mL) was added over 15 min. After cooling to -9°C the precipitate was filtered off and washed with t-butylmethylether. Drying in vacuum at room temperature gave 20.6 g (81%) of the title compound as a white product. Mp. 155-60°C. Calc. for C<sub>15</sub>H<sub>14</sub>N<sub>3</sub>O<sub>2</sub>S: C:56.4%; H:5.4%; N:13.2%; S:10.0%. Found: C:55.9%; H:5.4%; N:12.8%; S:9.8%.

C. 5-Methoxy-2-[(4-methoxy-3,5-dimethyl-1-oxido2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole (Omepra-zole-N-oxide).

2-Cyclohexyl-7-methoxy-1,2,4-thiadiazolo[4,5-a]benzimidazole-3(2H)-one-1-oxide (19.2 g, 60 mmol) (Ex. C-B) was suspended in dry tetrahydrofuran (200 mL) and cooled on an ice bath. Potassium-t-butoxide (20.2 g, 180 mmol) was added in portions over 30 min. After further stirring for 5 min., 4-methoxy-2,3,5-trimethylpyridine-N-oxide (8.0 g, 48 mmol) was added. The dark green reaction mixture was stirred for 20 min., whereupon acetic acid (7.2 g, 120 mmol) was added. The suspension was evaporated in vacuum to about 100 mL,
and the formed residue was dissolved in 1-butanol-toluene (1:4) (100 mL) - water (250 mL). After adjusting the pH to 12 with 1N sodium hydroxide the phases were separated. The water phase was slowly neutralized to pH 7.5 with acetic acid, whereby the title compound precipitated. After cooling to 0°C the precipitate was filtered off, washed with water and dried to give 12.8 g of crude omeprazole-N-oxide. The crude product was stirred with methanol (150 mL) for 20 min. at room temperature and then cooled to -20°C. The precipitate was filtered off and dried at 60°C to give 11.1 g (64%) of omeprazole-N-oxide as a white product. Mp. 177-8°C (dec).

Calc. for C17H12N3O4S: C: 56.5%; H: 5.3%; N: 11.6%; S: 8.9%.

Found: C: 56.2%; H: 5.4%; N: 11.7%; S: 9.2%.

**Example D.** 2-Cyclohexyl-1,2,4-thiadiazol-4,5-albenzimidazole-3(2H)-one-1-oxide (2 steps in situ).

N-Cyclohexyl-2,3-dihydro-2-thioxo-1H-benzimidazole-1-carboxamide (68.8 g, 250 mmol) (Ex. B) was suspended in chloroform (1.0 L) at room temperature. Bromine (40.0 g, 250 mmol) was added over 30 min. at 23-30°C. Triethylamine (50.5 g, 500 mmol) was added. The formed solution was cooled to room temperature and stirred for 1 h and then washed with water (2x500 mL). The organic phase was dried over anhydrous sodium sulfate.

The above solution was cooled on an ice bath. 98% m-CPBA (43.3 g, 250 mmol) dissolved in chloroform (200 mL) was added over 30 min. at 3-8°C. After further stirring for 30 min. chloroform was distilled off in vacuum (bath 40°C) until a fat suspension (about 250 mL) was obtained. t-Butylmethyl ether (1 L) was added. After cooling on an ice bath the precipitate was
filtered off and washed with t-butylmethyl ether. Drying at 30°C in vacuum gave 61.2 g (85% over 2 steps) of the title compound as an off-white product. Mp. 155-7°C.

Calc. for C_{14}H_{15}N_{3}O_{2}S: C: 58.1%; H: 5.2%; N: 14.5%; S: 11.1%.
Found: C: 58.6%; H: 5.4%; N: 14.4%; S: 11.2%.

**Example E.** 2-[[3-methyl-4-(2,2,2-trifluoroethoxy)-1-oxido-2-pyridinyl]methyl][sulfinyl]-1H-benzimidazole (Lansoprazole-N-oxide).

2-Cyclohexyl-1,2,4-thiadiazolo[4,5-a]benzimidazole-3(2H)-one-1-oxide (28.9 g, 100 mmol) (Ex. D) was dissolved in dry tetrahydrofuran (300 mL) and cooled on an ice bath. Potassium-t-butylate (28.0 g, 250 mmol) was added in portions over 40 min. After further stirring for 10 min. 2,3-dimethyl-4-(2,2,2-trifluoroethoxy)pyridine-N-oxide (13.3 g, 60 mmol) was added. The reaction mixture was stirred for 15 min, whereupon acetic acid (9.0 g, 150 mmol) was added. The mixture was evaporated in vacuum, and the formed residue was dissolved in 1-butanol-toluene (2:3) (250 mL) - water (250 mL) and acetic acid was added until a pH of 7.0 was obtained. The phases were separated and the organic phase was evaporated. The formed fat suspension was taken up in methanol (200 mL) and cooled on an ice bath. The precipitate was filtered off and washed with methanol followed by water. Drying at 50°C gave 7.9 g of crude lansoprazole-N-oxide. The product was shortly heated to reflux in chloroform (100 mL) and then cooled to room temperature. The crystals were filtered off, washed with chloroform and dried to give 5.3 g (23%) of lansoprazole-N-oxide as an off-white crystalline product. Mp. 183-3¾°C (dec.).

Calc. for C_{16}H_{14}F_{3}N_{3}O_{2}S: C: 49.9%; H: 3.7%; N: 10.9%; S: 8.3%
Example F. 2-[[4-methoxy-3,5-dimethyl-1-oxido-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole.

2-Cyclohexyl-1,2,4-thiadiazolo[4,5-a]benzimidazole-3(2H)-one-1-oxide (11.6 g, 40 mmol) (Ex. D) was suspended in dry tetrahydrofuran (150 mL) and cooled on an ice bath. Potassium-t-butylate (13.4 g, 120 mmol) was added in portions over 25 min. After further stirring for 5 min., 4-methoxy-2,3,5-trimethylpyridine-N-oxide (5.4 g, 24 mmol) was added. The dark green solution was stirred for 30 min., whereupon acetic acid (4.8 g, 80 mmol) was added. The reaction mixture was evaporated in vacuum to a fat suspension (about 50 mL) and then 1-butanol-toluene (1:3) (80 mL) and water (150 mL) were added. The pH was adjusted to 12 with 11N sodium hydroxide. The water phase was washed with further 1-butanol-toluene (1:3) (80 mL) and then adjusted to pH 7.7 by slowly addition of acetic acid. The resulting suspension was cooled on an ice bath. The precipitate was filtered off and washed with water. Drying at 50°C gave 7.0 g of the crude title compound. The product was shortly stirred with methanol (80 mL) at room temperature and then cooled to -20°C. The product was filtered off, washed with methanol and dried at 50°C to give 6.3 g (59 %) of the title compound as an off-white powder. Mp. 183-4° (dec.).

Calc. for C₁₆H₁₇N₃O₃S: C: 58.0%; H: 5.2%; N: 12.7%; S: 9.7%.

Found: C: 57.9%; H: 5.4%; N: 12.8%; S: 9.8%.
Examples illustrating the process according to the invention.

Example 1. 5-Methoxy-2-[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole (Omeprazole).

Pulverized omeprazole-N-oxide (3.61 g, 10.0 mmol) (Ex. C) and 4,4'-thiobismorpholine (2.65 g, 13.0 mmol) (synthesized from sodium thiosulfate pentahydrate, bromine and morpholine as described by J. L. Kice et al, J. Org. Chem. 56 (1991) 5235-6) were suspended in methanol (70 mL) and cooled on an ice bath. 2.83 N hydrogen chloride in ethanol (7.4 mL, 21.0 mmol) was added. After stirring for 20 min., a clear yellowish solution was obtained. 1N sodium hydroxide (20 mL) was added and the resulting solution was evaporated in vacuum to about 25 mL. To the residue was added water (100 mL) and t-butylmethylether (50 mL). The pH was adjusted to 12 with 1N sodium hydroxide. After stirring for 20 min. at pH 12, the phases were separated and acetic acid was added slowly to the water phase until a pH 7.8 was obtained. After stirring at room temperature the precipitate was filtered off, washed with water and dried at 50°C to give 3.24 g (94 %) of omeprazole as a beige coloured powder. Mp. 153-4°C (dec.). The FTIR-spectra of the product and an authentic sample were identical.

Calc. for C_{15}H_{19}N_{2}O_{3}S: C:59.1%; H:5.6%; N:12.2%; S:9.3%.

Found: C:59.1%; H:5.6%; N:12.1%; S:9.6%.

Preparation of Omeprazole sodium salt.

Omeprazole (3.45 g, 10.0 mmol) was suspended in methanol (15 mL). Sodium methoxide (540 mg, 10.0 mmol) was added, whereby a new precipitate was formed. After
addition of t-butylmethyl ether (50 mL) the precipitate was filtered off, washed with t-butylmethyl ether and dried to give 3.7 g of omeprazole sodium salt as a white product.

Example 2. 5-Methoxy-2-{
[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole (Omeprazone).

Example 1 was repeated, but using 1,1'-thiobis-piperidine (synthesized from sodium thiosulfate pentahydrate, bromine and piperidine as described by J. L. Kice et al, J. Org. Chem. 56 (1991) 5235-6) as the reducing agent. Yield 91%. Mp. 154-5°C (dec.).

Calc. for C₁₅H₁₈N₂O₃S: C:59.1%; H:5.6%; N:12.2%; S:9.3%. Found: C:59.1%; H:5.6%; N:12.2%; S:9.5%.

Example 3. 2-{
[(3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole (Lansoprazole).

Lansoprazole-N-oxide (3.85 g, 10.0 mmol) (Ex. E) and 4,4'-thiobismorpholine (2.85 g, 14.0 mmol) (synthesized from sodium thiosulfate pentahydrate, bromine and morpholine as described by J. L. Kice et al, J. Org. Chem. 56 (1991) 5235-6) were suspended in methanol (80 mL) at room temperature. 2.85 N hydrogen chloride in ethanol (8.4 mL, 24 mmol) was added over 3 min. After stirring for 90 min. the formed solution was evaporated in vacuum to about 25 mL and water (100 mL) was added slowly. The pH was adjusted to 7.5 with 1N sodium hydroxide. After stirring at room temperature the formed precipitate was filtered off and washed with water. Drying at 40°C gave 3.57 g (97%) of a 94% pure lansoprazole. Mp. 169-70°C (dec.). Recrystallization
from acetone gave analytically pure lansoprazole as a white crystalline product. Mp. 176-7°C (dec.). The FTIR-spectra of the product and an authentic sample were identical.

Calc. for C_{16}H_{14}F_{1}N_{5}O_{2}S: C: 52.0%; H: 3.8%; N: 11.4%; S: 8.7%
Found: C: 52.2%; H: 4.0%; N: 11.1%; S: 8.8%.

**Example 4.** 2-[[4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole.

2-[[4-Methoxy-3,5-dimethyl-1-oxido-2-pyridinyl]-methyl]sulfinyl]-1H-benzimidazole (3.31 g, 10.0 mmol) (Ex. F) and 4,4'-thiobismorpholine (2.86 g, 14.0 mmol) (synthesized from sodium thiosulfate pentahydrate, bromine and morpholine as described by J. L. Kice et al., J. Org. Chem. 56 (1991) 5235-6) were suspended in methanol (75 mL) and cooled on an ice bath. 2.83 N hydrogen chloride in ethanol (7.4 mL, 21.0 mmol) was added. The reaction was monitored by HPLC. After stirring for 1½ h and 2½ h further thiobismorpholine (0.82 g and 0.41 g) and 2.83 N hydrogen chloride in ethanol (2.8 mL and 1.4 mL) was added. After further stirring for 30 min., 1N sodium hydroxide (33 mL) was added. The reaction mixture was evaporated in vacuum to about 35 mL and then water (100 mL) and t-butyldimethyl-ether (50 mL) were added. The pH was adjusted to 12 with 1N sodium hydroxide. After stirring at pH 12.0 for 5 min., the phases were separated. The water phase was washed with t-butyldimethyl ether (50 mL) and then acetic acid was added slowly until pH 8.0. The formed suspension was extracted with 1-butanol-toluene (1:1) (120 mL) at 30°C. The organic phase was dried over anhydrous sodium sulfate and then evaporated in vacuum to about 35 mL. Cooling to 5°C, filtration, washing with 1-35 butanol and drying at 50°C gave 2.41 g (77%) of the
title compound as a white crystalline product. Mp. 164-5°C (dec.).
Calc. for C₁₅H₁₇N₃O₂S: C:60.9%; H:5.4%; N:13.3%; S:10.2%
Found: C:61.1%; H:5.6%; N:13.3%; S:10.0%.

Another crop 0.21 g (7%) of the title compound (96% purity) could be obtained from the mother liquor.

In the preceding the invention has been described by means of specific examples of preferred embodiments.

However, it will be appreciated by a person skilled in the art that various modifications can be made without deviating from the spirit and scope of the invention.
PATENT CLAIMS

1. A process for the preparation of 2-[(2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole derivatives of the general formula I

\[
\begin{align*}
R^2 &\text{ represents H, OCH}_3, \text{ OCHF}_2 \text{ or CF}_3, \\
R^3 &\text{ represents H, CH}_3 \text{ or OCH}_3, \\
R^4 &\text{ represents H, OCH}_3, \text{ OCH}_2\text{CF}_3 \text{ or halo, such as Cl, Br or F, and} \\
R^5 &\text{ represents H, CH}_3 \text{ or OCH}_3, \\
\end{align*}
\]

wherein or salts thereof, characterized in reducing a compound of the general formula II or a salt thereof

\[
\begin{align*}
R^2 &\text{ represents H, OCH}_3, \text{ OCHF}_2 \text{ or CF}_3, \\
R^3 &\text{ represents H, CH}_3 \text{ or OCH}_3, \\
R^4 &\text{ represents H, OCH}_3, \text{ OCH}_2\text{CF}_3 \text{ or halo, such as Cl, Br or F, and} \\
R^5 &\text{ represents H, CH}_3 \text{ or OCH}_3, \\
\end{align*}
\]

wherein \( R^2, R^3, R^4 \) and \( R^5 \) are as defined above, in an alcoholic solvent, the reduction being carried out using a thiobisamine as reducing agent in the presence of a mineral acid, and, if desired, converting a compound obtained in free form into a salt thereof, or vice versa.

2. A process according to claim 1, wherein the thiobisamine is a compound of the general formula III

\[ R'(R'')-N-S-N-(R''')R'''' \]
wherein R', R'', R''' and R'''', which may be the same or different, represent hydrogen, C₁-C₈ alkyl or C₃-C₈ cycloalkyl, at least one of R' and R'' and at least one of R''' and R'''' being other than hydrogen, or the groups R' and R'', respectively the groups R''' and R'''', may be joined so as to form a 5- or 6-membered heterocyclic ring together with the nitrogen atom to which they are bound, which heterocyclic ring may optionally contain one or two additional hetero atoms selected from oxygen, sulphur and nitrogen.

3. A process according to claim 2, wherein the thiobisamine is thiobismorpholine or thiobispiperidine.

4. A process according to one or more of the preceding claims, wherein the thiobisamine is used in a molar ratio to the compound of formula (II) of 0.8 - 5.0, particularly in a molar ratio of 1.0 - 2.5 and preferably in a molar ratio of 1.0 - 1.5.

5. A process according to one or more of the preceding claims, wherein the reduction is carried out in a methanolic and/or ethanolic solvent.

6. A process according to one or more of the preceding claims, wherein the reduction is carried out in the presence of hydrochloric acid and/or sulphuric acid.

7. A process according to one or more of the preceding claims, wherein the reduction is carried out at a temperature in the range from -50°C - 70°C, preferably in the range from -10°C - 40°C.

8. A compound of the general formula (II)
wherein R², R³, R⁴ and R⁵ are as defined above, or a salt thereof, with the provisos that R², R³, R⁴ and R⁵ are not all hydrogen, that when R³ is methyl and R⁴ is 2,2,2-trifluoroethoxy, then R² and R⁵ are not both hydrogen, and that when R³ and R⁵ are both CH₃, then R² and R⁴ are not both OCH₃.

9. A compound according to claim 8, wherein R² represents OCHF₂, R³ and R⁴ represent OCH₃, and R⁵ represents H.
C. DOCUMENTS CONSIDERED TO BE RELEVANT

<table>
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<tr>
<th>Category</th>
<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
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<tr>
<td>A</td>
<td>EP 0 484 265 A (GENESIS PARA LA INVESTIGACION; ESTEVE QUIMICA SA (ES)) 6 May 1992 * see the whole document; in particular page 24 - page 25, examples 9 and 10 *</td>
<td>1-9</td>
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<tr>
<td>A</td>
<td>H. KAGAMI ET AL.: &quot;Deoxygenation of Amine N-Oxides or C-Nitroso Compounds by Dialkyl Sulfoxylates&quot; JOURNAL OF ORGANIC CHEMISTRY, vol. 43, no. 6, 17 March 1978, EASTON US, pages 1267-1268, XP002039565 see the whole document</td>
<td>1-7</td>
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Further documents are listed in the continuation of box C. Patent family members are listed in annex.

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