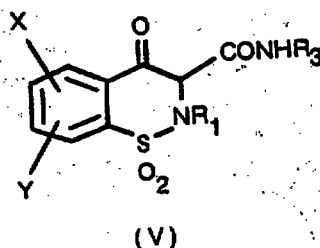


Description

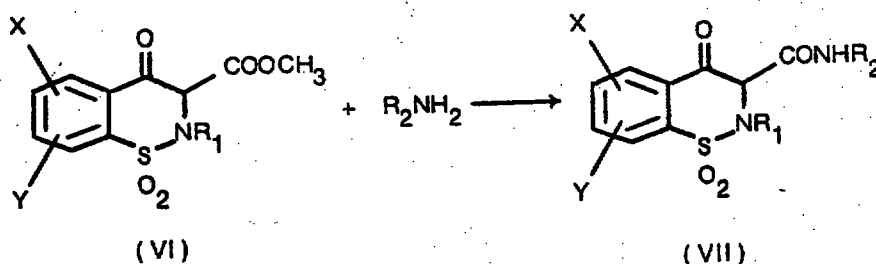
The invention relates to a novel class of compounds of empirical formula $C_9H_7N_2O_5SRR^1Z$ which are useful as intermediates in an improved process for production of benzothiazine carboxamide anti-inflammatory agents.

Two methods for synthesis of N-substituted benzothiazine carboxamide anti-inflammatory agents are disclosed in U.S. 3,591,584. The first of these is used to prepare carboxamides in which the N-substituent is not an heterocyclic moiety. It comprises contacting an organic isocyanate, R_3NCO , wherein R_3 is, e.g. certain alkyl, phenyl or naphthyl groups, with a 4-oxo (or 3-oxo)1,2-benzothiazine to produce e.g., the compound of the formula



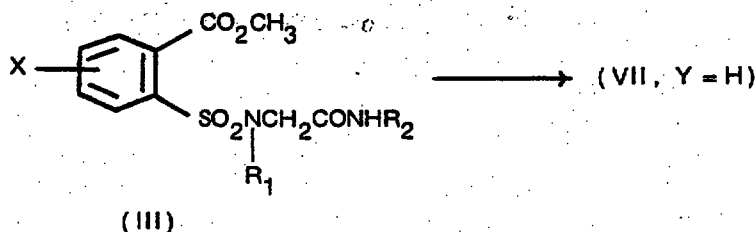
or the corresponding 3-oxo-4-carboxamide.

A second method is preferred for the preparation of those amides wherein the N-substituent is an heterocyclic moiety; it involves reaction of the corresponding carboxylic acid ester with the appropriate amine, R_2NH_2 , where R_2 is a heterocyclic group, to produce the desired benzothiazine carboxamide, e.g.,



In U.S. 3,891,637 a process is disclosed whereby the N-heterocyclic amides of formula (VII) are obtained from the corresponding N-phenyl amides by a transamidation process.

U.S. 3,853,862 discloses a process for production of 4-oxo-1,2-benzothiazine-3-carboxamides of formula (VII) by cyclization of a benzenesulfonylglycineamide (III) in the presence of a metal hydride, e.g.,



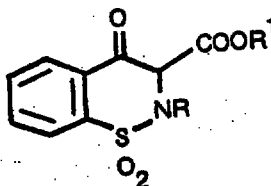
U.S. 4,289,879 issued September 15, 1981, discloses a method for preparing piroxicam [4-hydroxy-2-methyl-N-(2-pyridyl)-2H-1,2-benzothiazine-3-carboxamide 1,1-dioxide] via the corresponding 3-(2-methoxyethyl) ester.

In accordance with the present invention, it has now been found that a novel class of compounds of the empirical formula



(II)

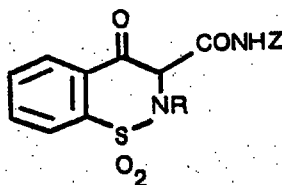
is obtained by reacting an ester of formula



(II)

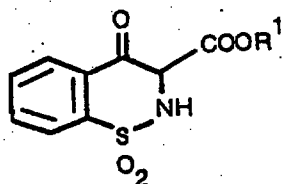
with an equimolar amount of an amine of the formula ZNH_2 in the presence of reaction inert organic solvent at a temperature of from about 0 to 110°C, wherein R is hydrogen, benzyl or alkyl having from one to three carbon atoms; R¹ is benzyl or alkyl having from one to four carbon atoms; and Z is 2-pyridyl, alkyl substituted-2-pyridyl, 2-thiazolyl, 2-thiazolyl-substituted by one or two alkyl groups, or 5-alkyl-3-isoxazolyl, each alkyl having from one to four carbon atoms, can be prepared and isolated in good yield. The compounds of formula (I) are of as yet undefined structure.

The present invention also provides a novel process for production of 4-oxo-1,2-benzothiazine-3-carboxamide-1,1-dioxide anti-inflammatory agents of the formula (IV), said process having significant advantages over prior art methods.



(IV)

wherein R and Z are as defined above, which comprises the steps of
(a) reacting a 4-oxo-1,2-benzothiazine-3-carboxylic acid ester of the formula



(I)

with an equimolar amount of an amine of the formula ZNH_2 in the presence of a reaction inert organic solvent and at a temperature of from 0 to 110°C to provide an intermediate of empirical formula



(I)

(b) heating the intermediate obtained in (a) in the presence of a reaction inert organic solvent at a temperature of from about 120 to 200°C to eliminate R^1OH where R¹ is as defined above.

In the compounds of the invention of formula (I) and in the process of the invention particularly preferred values for substituents R, R¹ and Z are:

R is alkyl having from one to three carbon atoms,

R¹ is alkyl having from one to four carbon atoms, and Z is 2-pyridyl, 2-thiazolyl, 5-methyl-3-isoxazolyl, 6-methyl-2-pyridyl or 4,5-dimethyl-2-thiazolyl.

More particularly preferred values for the above substituents are:

R is methyl,

R¹ is methyl or ethyl, and

Z is 2-pyridyl, 2-thiazolyl or 5-methyl-3-isoxazolyl. The most particularly preferred compound of the invention is of formula (I) where R and R¹ are each methyl and Z is 2-pyridyl. The corresponding anti-inflammatory agent of formula (IV) provided by the invention process is known generically as "piroxicam".

See, e.g., Wiseman, Roy. Soc. Med. Int. Cong. Symp. Ser. 7, 11-23 (1978).

The invention process has advantages of improved yield and increased productivity which affords a significantly greater weight of product of formula (IV) per volume of solvent. The product of formula (IV) obtained by the invention process is also of improved purity. A further advantage of the invention process is that the mother liquors can be recycled repeatedly to the next batch with good results.

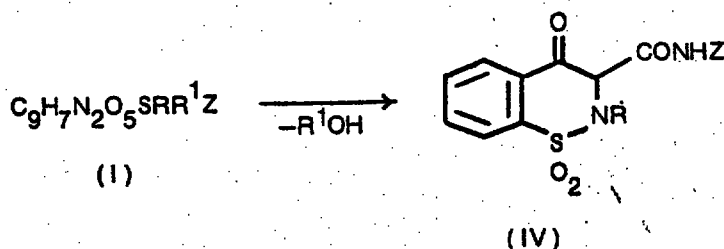
Isolation of the intermediate of formula (I) in the process of the invention affords an additional purification, not possible in the prior art process. Thus, in the instant process, one may use starting materials of lesser purity since they are purified by isolation of the intermediate compound (I). This is a distinct advantage since an impure amine ZNH_2 can be employed without reduction of purity of the anti-inflammatory agent (IV). Furthermore, it is known in the art that amines, of the formula ZNH_2 as defined above are difficult to purify by prior art methods.

The compounds of the invention of the formula (I) are obtained by contacting approximately equimolar amounts of 4-oxo-1,2-benzothiazine-3-carboxylic acid ester of formula (II) and the appropriate amine, ZNH_2 , where Z is as previously defined. The reaction is carried out in the presence of a reaction inert organic solvent at a temperature of from about 0 to 110°C and a reaction time of up to twenty-four hours. An especially preferred range of temperature for this reaction is from about 20 to 90°C, at which temperature the reaction is ordinarily complete in from a few minutes to a few hours, for example, 15 minutes to about four hours. The product of formula (I) is then isolated, if desired, e.g., by cooling the reaction mixture to room temperature or below, filtering to collect the precipitated solid, and drying.

A reaction inert organic solvent as defined herein is one that does not react appreciably with either the starting materials or the products of the reaction under the reaction conditions employed, and is capable of dissolving at least a substantial portion of the starting materials at or below the reaction temperature. Further, said solvent is one from which the desired product is readily recoverable by standard techniques known to one of skill in the art. Examples of reaction inert organic solvents which can be employed in preparing the desired compounds of formula (I) are hydrocarbons such as benzene, toluene, the xylenes, ethylbenzene, tetralin and decalin; halogenated hydrocarbons such as chloroform, methylene dichloride, ethylene dichloride, ethyl bromide and ethylene dibromide; ketones such as acetone and methyl-ethylketone, ethers such as ethyl ether, tetrahydrofuran, 1,2-dimethoxyethane and diethyleneglycol dimethylether; dialkylamides such as dimethylformamide, dimethylacetamide and N-methyl-2-pyrrolidinone; dimethylsulfoxide and acetonitrile. Particularly preferred are the above solvents having an atmospheric boiling point at least as high as the maximum reaction temperature employed. Especially preferred is commercial mixed xylenes for reasons of economy and efficiency.

Initial studies on the products of formula (I) suggested covalent bonding between the amine and ester to form a structure analogous to the classical (unstable) intermediate for such reactions. However, the results of further investigation strongly suggest that a 1:1 molar adduct is a more accurate representation of the structure of the compounds of empirical formula (I). The ^{13}C -NMR and ^1H -NMR spectral evidence and the presence of two carbonyl bands in the infrared spectrum, particularly, are consistent with such an adduct.

As mentioned above, the compounds of formula (I) are useful as intermediates in production of anti-inflammatory agents of the formula (IV) by elimination of R^1OH .



The above reaction is also carried out in the presence of one of the particularly preferred reaction inert organic solvents, defined above, but at an elevated temperature in order to drive out the alcohol generated in the reaction. A preferred temperature for this reaction is from about 120 to 200°C and especially preferred is about 135 to 145°C.

The reaction inert organic solvents that can be used in production of compounds of formula (IV) by the above reaction are the same as those given above for the production of the invention compounds of formula (I), except those which boil at a temperature substantially below the preferred range of temperature, and would thus require the use of high pressure equipment. Especially preferred solvents for this reaction are toluene, the xylenes, ethylbenzene, tetralin and decalin; and most especially preferred is mixed xylenes for reasons of economy and efficiency. Of course, as one of skill in the art will recognize, the mixed xylenes also have the advantage of having a boiling point within the especially preferred range of temperature, a feature which facilitates temperature regulation and removal of by-product alcohol, R^1OH .

In the first step of the invention process the formation of a solid intermediate product of formula (I) provides a purification method not possible with the prior art process in which the ester (II) and amine ZNH_2 are reacted to form (IV) directly. Thus, relatively impure starting materials of formula (II) and ZNH_2 can be employed in the instant process and purification effected by isolation of the novel intermediate of formula (I) prior to its conversion to the anti-inflammatory agent, (IV).

A further advantage of the present process is that the desired product (IV) can be obtained in improved yield and with greater throughput than is possible with the most favorable prior art process, i.e., the method of U.S. 3,591,584 described above for production of benzothiazine-3-carboxamides via the corresponding 3-carboxylic acid ester and a heterocyclic amine such as ZNH_2 , where Z is as defined herein. In the prior art method when total concentration of reactants greater than about 3 g per 100 ml of solvent are employed, the reaction mixture produces relatively high levels of decomposition products and color bodies, which makes isolation of the desired product of formula (IV) difficult and renders an impure product not suitable for pharmaceutical use without further costly purification steps.

The present process, however, can be carried out in such a manner that the throughput can be increased in Step (b) to 6—8 grams per 100 ml, or higher, without sacrificing yield of product or its purity. This is accomplished by isolating the novel intermediate compound of formula (I) obtained in Step (a) and adding it in portions to the heated solvent mixture employed in Step (b) to eliminate the elements of R'OH and form the product (IV) in high yield and purity.

Yet another advantage that can be demonstrated with the invention process is that the mother liquors can be recycled repeatedly to the next reaction run. High yield and high purity of product is observed after repeated recycling of mother liquors in the instant process, thus avoiding loss of product retained in the mother liquor. By contrast, when recycling is carried out with the prior art process, accumulation of impurities becomes so great after a few recycles of mother liquor that the desired product can not be isolated or can only be isolated with great difficulty.

The following Examples are illustrative of the claimed invention. The following abbreviations are used for NMR peak multiplicity: s, singlet; d, doublet; t, triplet; d of t, doublet or triplets; q, quartet; m, multiplet.

Example 1

Crystalline Compound of Formula (I), $R = R' = CH_3$, $Z = 2$ -pyridyl

Under a nitrogen atmosphere to a solution of 120 g (0.446 mole) methyl 3,4-dihydro-2-methyl-4-oxo-2H-1,2-benzothiazine-3-carboxylate-1,1-dioxide in 300 ml xylene is added 48 g (0.510 mole) 2-amino-pyridine. The mixture is heated to 80°C with vigorous stirring, held at this temperature for two hours, cooled to room temperature, filtered and dried to obtain 158.6 g (98%) of the desired complex as yellow crystals, m.p. 132—133°C.

Titration of a sample with 0.50 N hydrochloric acid in 2:1 (by volume) methanol/water gave a neutralization equivalent of 367.6 (theory 363). Mass spectrum (m/e) parent peak at 331. Infrared spectrum (KBr) cm^{-1} : strong carbonyl absorption at 1675 and 1600 cm^{-1} .

Analysis:

Calc'd for $C_{16}H_{17}N_3O_5S$:	C, 52.89;	H, 4.72;	N, 11.56.
Found:	C, 52.88;	H, 4.77;	N, 11.66.

250 MHz 1H -NMR ($CDCl_3$) ppm (delta):

ppm	Multiplicity	Integral
8.05	m	2
7.88	m	1
7.73	m	2
7.44	d of t	1
6.60	d of t	1
6.52	d	1
3.97	s	3
2.96	s	3

(13)

¹³C—NMR (DMSO):

	Line	ppm	Multiplicity
5	1	167,988	s
	2	158,917	s
10	3	158,449	s
	4	146,076	d
	5	137,673	d
15	6	134,902	302 s
	7	133,005	de d
20	8	132,743	d
	9	128,662	s
	10	126,557	d
25	11	123,381	d
	12	111,736	d
30	13	109,330	s
	14	108,609	d
	15	52,458	q
35	16	38,489	q

For comparison with ¹³C—NMR spectra of piroxicam and methyl 3,4-dihydro-2-methyl-4-oxo-2H-1,2-benzothiazine-3-carboxylate 1,1-dioxide, see Whipple, *Organic Magnetic Resonance*, 10, 23 (1977).

Addition of 1.0 equivalent of methyl 3,4-dihydro-2-methyl-4-oxo-2H-1,2-benzothiazine-3-carboxylate 1,1-dioxide to a sample of the above product in dimethylsulfoxide produced an increase in 11 of the lines of the ¹³C—NMR spectrum, with slight changes in chemical shift. This clearly shows that in solution there is a rapid exchange during the NMR time scale.

Example 2

To 13 ml acetone is added 2.69 g (0.01 mole) methyl 3,4-dihydro-2-methyl-4-oxo-2H-1,2-benzothiazine-3-carboxylate-1,1-dioxide and 0.94 g (0.01 mole) 2-aminopyridine and the mixture warmed to affect solution. The yellow solution is refrigerated until precipitation is complete, filtered and the yellow crystals dried to afford the compound (I), R = R' = CH₃, Z = 2-pyridyl, m.p. 132—133°C, in 84% yield.

The above procedure is repeated on the same scale, but employing a wide variety of reaction inert organic solvents in place of acetone. The results are summarized in the table, below.

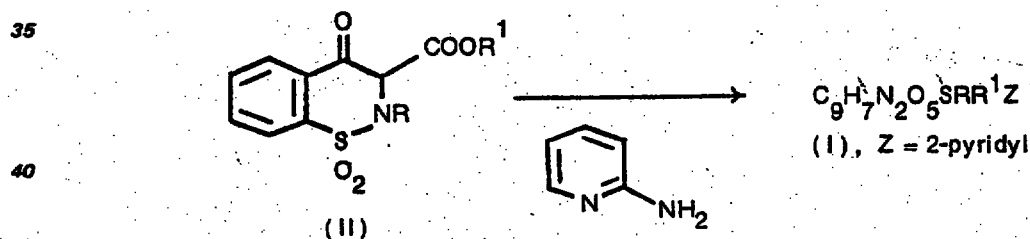
	<u>Solvent</u>	<u>Volume, ml</u>	<u>Reaction Temp., °C</u>	<u>% Yield</u>	<u>Comment</u>
5	CH ₂ Cl ₂	50	30°	98	crystals washed with hexane
	CHCl ₃	20	warm to dissolve	81	crystals washed with hexane
10	CH ₃ CO ₂ C ₂ H ₅	20	"	88	—
	CH ₃ CN	10	"	89	crystals washed with hexane
15	tetrahydrofuran	15	"	80	—
	CH ₃ COCH ₃	(15)	reflux (56°)	94	product precipitated with hexane
20					

When the above reaction is repeated in acetone as solvent, but with a molar excess of either the methyl ester or 2-aminopyridine reactant, the same is obtained as yellow crystals, m.p. 132—134°C. When the ester reactant (II) is used in excess, it sometimes forms as white crystals adhering to the sides of the flask which are readily separated from the yellow crystals of formula (I).

When the procedure is repeated in tetrahydrofuran at 0°C or in toluene at 110°C, the results are substantially the same.

Example 3

30 When the procedures of Examples 1 or 2 are repeated but the methyl 3,4-dihydro-2-methyl-4-oxo-2H-1,2-benzothiazine-3-carboxylate 1,1-dioxide is replaced with an appropriate compound of formula (II), the corresponding compound of formula (I) where Z is 2-pyridyl is obtained.



	R	R'
45	CH ₃	C ₂ H ₅
	CH ₃	<i>n</i> -C ₃ H ₇
50	C ₂ H ₅	<i>i</i> -C ₃ H ₇
	C ₆ H ₅ CH ₂	<i>n</i> -C ₄ H ₉
55	CH ₃	<i>i</i> -C ₄ H ₉
	<i>i</i> -C ₃ H ₇	<i>n</i> -C ₄ H ₉
	<i>n</i> -C ₃ H ₇	<i>sec</i> -C ₄ H ₉
60	C ₆ H ₅ CH ₂	CH ₃
	H	<i>n</i> -C ₄ H ₉
65	H	C ₂ H ₅

Example 4

Crystalline Compound of Formula (I), $R = R' = \text{CH}_3$, $Z = 2\text{-thiazolyl}$

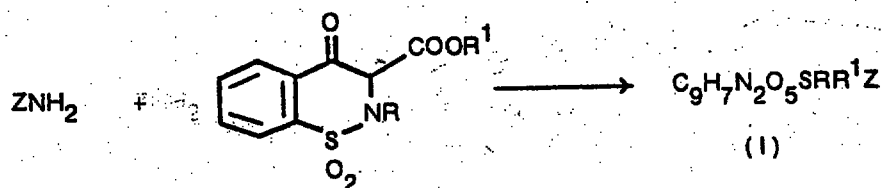
To a mixture of 2.69 g (10 mmole) methyl 3,4-dihydro-2-methyl-4-oxo-2H-1,2-benzothiazine-3-carboxylate-1,1-dioxide and 50 ml xylene stirred under nitrogen is added 1.05 g (10.5 mmole) 2-aminothiazole. The mixture is heated at 85–90°C for 3 hours, cooled to room temperature, filtered and the brown, crystalline product dried *in vacuo* to obtain the title compound, 2.3 g (62.3%), m.p. 131–142°C.

The crystalline product is dissolved in 20 ml of methylene chloride, decolorized by addition of activated charcoal and then filtered. Addition of the filtrate to hexane with good stirring, granulating for one hour and then filtering gave a white crystalline product; m.p. 140–145°C; 1.35 g.

When the above procedure is repeated but employing acetone, methylene chloride, ethyl ether, ethylene dibromide, 1,2-dimethoxyethane, benzene, dimethylformamide, dimethylacetamide, ethylbenzene, toluene or decalin as solvent at a temperature of from 0–110°C for 2–24 hours, the desired product of formula (I) is similarly obtained.

Example 5

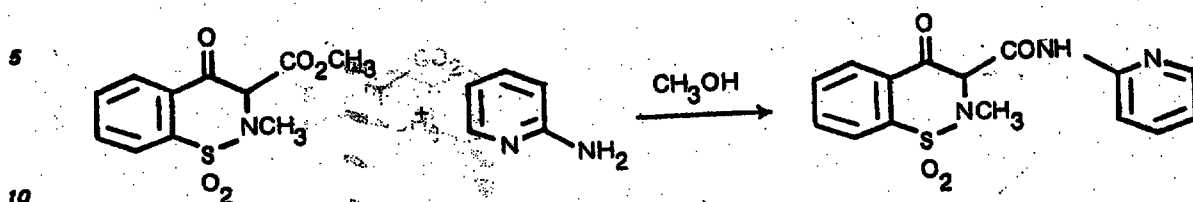
The following compounds of formula (I) are obtained by the procedures of Examples 1–4 by employing the appropriate starting materials of formula (II) and ZNH_2 .



R	R'	Z
CH ₃	C ₆ H ₅ CH ₂	C ₆ H ₅
C ₂ H ₅	<i>n</i> -C ₃ H ₇	2-pyridyl
<i>n</i> -C ₃ H ₇	<i>n</i> -C ₄ H ₉	2-thiazolyl
<i>n</i> -C ₄ H ₉	C ₆ H ₅ CH ₂	5-methyl-2-thiazolyl
CH ₃	<i>i</i> -C ₃ H ₇	4-ethyl-2-thiazolyl
C ₆ H ₅ CH ₂	CH ₃	5- <i>n</i> -butyl-2-thiazolyl
CH ₃	CH ₃	5-methyl-3-isoxazolyl
C ₂ H ₅	CH ₃	5-methyl-2-pyridyl
CH ₃	CH ₃	4-methyl-2-pyridyl
CH ₃	CH ₃	6-methyl-2-pyridyl
CH ₃	C ₂ H ₅	6- <i>n</i> -propyl-2-pyridyl
CH ₃	CH ₃	6- <i>i</i> -butyl-2-pyridyl
C ₂ H ₅	CH ₃	5-ethyl-3-isoxazolyl
C ₂ H ₅	CH ₃	5-isopropyl-3-isoxazolyl
H	CH ₃	5- <i>n</i> -butyl-3-isoxazolyl
H	CH ₃	4-methyl-2-thiazolyl
CH ₃	CH ₃	4,5-dimethyl-2-thiazolyl
CH ₃	CH ₃	4,5-di- <i>n</i> -butyl-2-thiazolyl

Example 6

Standard Method for Preparation of Piroxicam



To a five liter flask equipped with thermometer, packed distillation column, condenser, and stirrer, under a nitrogen atmosphere is added 3300 ml mixed xylenes, 80 g (0.297 mole) methyl 3,4-dihydro-2-methyl-4-oxo-2H-1,2-benzothiazine-3-carboxylate-1,1-dioxide, 32 g (0.340 mole) 2-aminopyridine and 8 g of activated carbon (Darco G-60* or Darco KBB*). The mixture is heated at reflux (ca. 140°C) for 28 hours while slowly distilling off methanol and xylene at a rate of about 25 ml per hour for the first 8 hours, then at a rate of 5–10 ml per hour for the remaining reflux period, while adding fresh xylene to maintain a reaction volume of about 3500 ml. After 28 hours, the reaction mixture is cooled slightly (~100°C) and filtered to remove carbon. The carbon cake was washed with warm xylene (100 ml), the filtrate and washings cooled slowly under a nitrogen atmosphere with rapid stirring to 25–50°C. Stirring was continued for one hour to allow for complete crystallization. The crystals were collected by filtration, the mother liquor concentrated to about 1500 ml, cooled under nitrogen to 0–5°C, filtered, the cake washed with 100 ml cold xylene and the crystals dried under vacuum below 60°C for several hours. The yield is 76.7–84.6 g (78–86% of theory). Average throughput 24.4 g/liter of solvent.

Example 7

Improved Piroxicam Process Employing the Intermediate (I, R = R' = CH₃, Z = 2-pyridyl)

A. To a one liter flask purged with nitrogen is added 300 ml mixed xylenes, 120 g (0.446 mole) methyl 3,4-dihydro-2-methyl-4-oxo-2H-1,2-benzothiazine-3-carboxylate-1,1-dioxide and 48 g (0.510 mole) 2-aminopyridine. The mixture is heated to 90°C, stirred rapidly at this temperature for one hour and allowed to cool under a nitrogen atmosphere.

To a five liter flask containing 3300 ml xylene is added 12 g of activated carbon (Darco G-60) and the mixture heated at reflux while collecting xylene/water in a separator/decanter. To this is added one half of the above xylene slurry of the intermediate compound of formula (I) obtained above. The mixture is brought to reflux and methanol/xylene distilled off at a rate of 25 ml per hour while adding fresh xylene to maintain a reaction volume of about 3500 ml. After four hours, one third of remaining slurry of the intermediate compound is added and methanol/xylene distillation resumed at the same rate. The remaining portions (one third or remainder) of intermediate are added at 8 hours and 12 hours, respectively, and the distillation continued at 25 ml/hour for a total of 16 hours. After 16 hours the distillation rate is decreased to 12.5 ml per hour for a total of 34 hours.

The reaction mixture is cooled to about 100°C, and filtered to remove carbon, washing the carbon cake with 100 ml warm xylene. The filtrate is purged with nitrogen, cooled to 25–50°C with rapid stirring. Stirring is continued for one hour to allow for complete crystallization. The crystals are collected by filtration, the mother liquor concentrated to about 1500 ml, cooled under nitrogen to 0–5°C, filtered, the cake is washed with 100 ml cold xylene and the crystalline product dried under vacuum below 60°C. The yield of piroxicam is 121–132.8 g (82–90% of theory). Average throughput, 38.5 g/liter of solvent.

B. The above procedure is repeated but with the following modifications:

To 600 ml of mixed xylene, under a nitrogen atmosphere is added 160 g (0.594 mole) methyl 3,4-dihydro-2-methyl-4-oxo-2H-1,2-benzothiazine-3-carboxylate-1,1-dioxide and 60 g (0.637 mole) technical grade 2-aminopyridine. The mixture is heated at 85–90°C for two hours, cooled to 20–25°C and stirred at this temperature for 2 hours. The resulting crystalline intermediate is collected by filtration and washed with 100 ml cold xylene. A weighed sample of the solvent-wet crystals was dried *in vacuo*. Differential scanning colorimetry of the dry sample gave a single sharp peak at 132.9°C. From the weight of dried sample it is determined that the yield of intermediate of formula (I), R = R' = CH₃, Z = 2-pyridyl is 215.9 g (98%).

To 3300 ml of mixed xylenes is added 3 g of 2-aminopyridine, 8 g of activated carbon (Darco KBB), the mixture is heated to a gentle reflux while collecting xylene/water until system is devoid of moisture. Then 81 g (dry weight basis) (0.223 mole) of the above crystalline intermediate mixed with 50 ml xylene is added. The reaction mixture is heated at reflux while separating methanol/xylene at a rate of 25 ml/hour. Every two hours an additional 17 g intermediate is added until all of the 215.9 g obtained above is consumed. This requires about 16 hours. Refluxing at 25 ml/hour is continued until the 20 hour mark at which time the reflux rate is reduced to 12–13 ml/hour. The total reaction volume is maintained between 3.3 and 3.7 liters

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by addition of xylene as required. After a total reaction time of 34 hours, the mixture is cooled and the product isolated as in Part A, above to provide 165.3 g (84%) of piroxicam. Throughput, 50 g/liter of solvent.

Example 8

5 Comparison of Standard and Improved Piroxicam Processes Employing Recycling of Mother Liquors

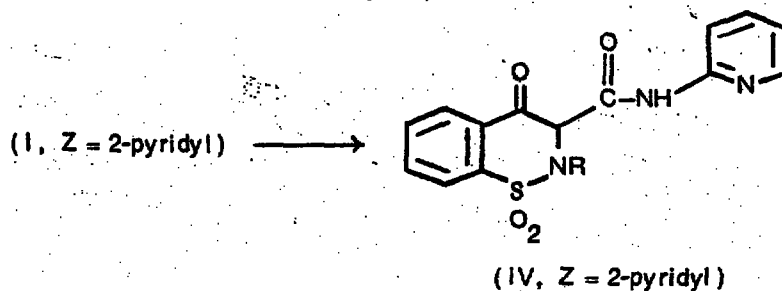
The Standard Method (Example 6) and the Improved Method (Example 7) were each repeated four times with recycling of the mother liquor from the previous run in each of the 2nd, 3rd and 4th runs. Results are summarized below.

Run No.	% Yield	% Yield
	Standard Method with Recycle	Improved Method with Recycle
1	81	83
2	90	87
3	93	96
4	None	93
Av. over 4 Runs	66	90

At each stage of this recycle experiment the batches employing the Standard Method had higher color levels, which became progressively more marked. In the fourth run by the Standard Method only a syrup was obtained which could not be induced to crystallize. The Improved Method, by contrast, gave a 93% yield in the fourth run. The experiment was terminated at this point because the Standard Method afforded no product. After the fourth run by the Improved Method the mother liquor was still clear and, it is assumed, could be used in further runs to good advantage.

Example 9

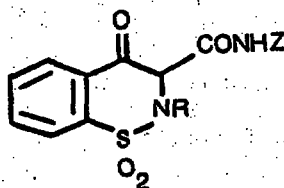
When the procedures of Examples 7 and 8 are repeated but employing the appropriate compound of formula (I), provided in Example 3, as intermediate, the following products of formula (IV) are also obtained in improved yield and throughput.



where R and R' are as defined in Example 3.

Example 10

Employing the compounds of formula (I) provided in Examples 4 and 5 as starting material in the procedure of Example 7 and in the recycling procedure of Example 8, the following products of formula (IV) are also obtained in improved yield and throughput.



where R and Z are as defined in Examples 4 and 5.

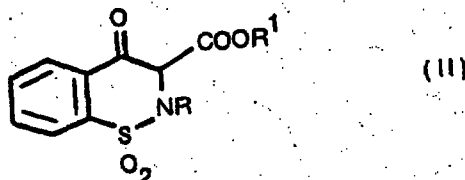
Example 11

Improved Sudoxicam Process Employing Intermediate (I, $R = R' = CH_3$, $Z = 2$ -thiazolyl)

A flask containing 30 ml xylene and 0.5 g of the crystalline 2-thiazolyl intermediate of formula (I), obtained previously, is slowly distilled at the rate of 5 ml per 2.5 hours. Xylene (5 ml) and 0.25 g of intermediate are then added and the distillation repeated as above. It is then repeated one more time after which the mixture is subjected to total reflux for 7 hours. The mixture is then stirred at ambient temperature over the weekend (~ 60 hours) and filtered to remove the product Sudoxicam, the 2-thiazolyl analog of Piroxicam, in 65% yield (590 mg), m.p. 245–247°C (dec).

10 Claims for the Contracting States: BE CH DE FR GB IT LI LU NL SE

1. A compound of empirical formula $C_9H_7N_2O_5SRR^1Z$ produced by reacting an ester of the formula



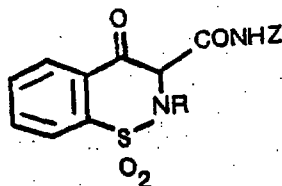
20 with an equimolar amount of an amine of the formula ZNH_2 in the presence of reaction inert organic solvent at a temperature of from 0° to 110°C, wherein R is hydrogen, benzyl or alkyl having from one to three carbon atoms;

25 R¹ is benzyl or alkyl having from one to four carbon atoms; and Z is 2-pyridyl, alkyl substituted 2-pyridyl, 2-thiazolyl, 2-thiazolyl substituted by one or two alkyl groups, or 5-alkyl-3-isoxazolyl, each alkyl having from one to four carbon atoms.

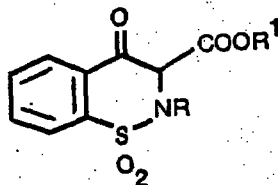
30 2. A compound according to claim 1 wherein R is methyl, R¹ is methyl or ethyl and Z is 2-pyridyl, 2-thiazolyl, 5-methyl-3-isoxazolyl, 6-methyl-2-pyridyl or 4,5-dimethyl-2-thiazolyl.

3. A compound according to claim 2 wherein R¹ is methyl and Z is 2-pyridyl.

4. A process for production of a 3,4-dihydro-2H-1,2-benzothiazine-3-carboxamide-1,1-dioxide of the formula



40 wherein R is hydrogen, benzyl or alkyl having from one to three carbon atoms; and Z is 2-pyridyl, alkyl substituted-2-pyridyl, 2-thiazolyl, 2-thiazolyl substituted by one or two alkyl groups, or 5-alkyl-3-isoxazolyl, each alkyl having from one to four carbon atoms; from an ester of the formula



50 wherein R¹ is benzyl or alkyl having from one to four carbon atoms, and an amine of the formula ZNH_2 , characterized by:

(a) reacting equimolar amounts of the ester and the amine in the presence of a reaction inert organic solvent at a temperature of from 0 to 110°C, to provide an intermediate compound of the empirical formula



60 (b) heating said intermediate in the presence of reaction inert organic solvent at a temperature of from 120 to 200°C.

5. A process according to claim 4 wherein R is methyl, R¹ is methyl or ethyl and Z is 2-pyridyl, 2-thiazolyl, 5-methyl-3-isoxazolyl, 6-methyl-2-pyridyl or 4,5-dimethyl-2-thiazolyl.

6. A process according to claim 5 wherein Z is 2-pyridyl and R¹ is methyl.



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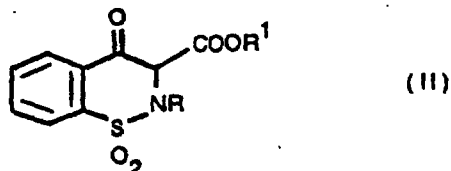
Example 11

Improved Sudoxicam Process Employing Intermediate (I), $R = R' = CH_3$, $Z = 2$ -thiazolyl)

A flask containing 30 ml xylene and 0.5 g of the crystalline 2-thiazolyl intermediate of formula (I), obtained previously, is slowly distilled at the rate of 5 ml per 2.5 hours. Xylene (5 ml) and 0.25 g of intermediate are then added and the distillation repeated as above. It is then repeated one more time after which the mixture is subjected to total reflux for 7 hours. The mixture is then stirred at ambient temperature over the weekend (~ 60 hours) and filtered to remove the product Sudoxicam, the 2-thiazolyl analog of Piroxicam, in 65% yield (590 mg), m.p. 245–247°C (dec).

10 Claims for the Contracting States: BE CH DE FR GB IT LI LU NL SE

1. A compound of empirical formula $C_9H_7N_2O_5SRR^1Z$ produced by reacting an ester of the formula



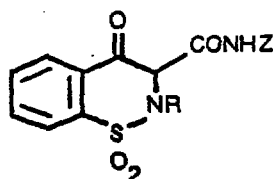
with an equimolar amount of an amine of the formula ZNH_2 in the presence of reaction inert organic solvent at a temperature of from 0° to 110°C, wherein R is hydrogen, benzyl or alkyl having from one to three carbon atoms;

25 R^1 is benzyl or alkyl having from one to four carbon atoms; and Z is 2-pyridyl, alkyl substituted 2-pyridyl, 2-thiazolyl, 2-thiazolyl substituted by one or two alkyl groups, or 5-alkyl-3-isoxazolyl, each alkyl having from one to four carbon atoms.

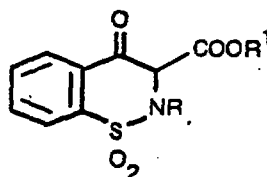
30 2. A compound according to claim 1 wherein R is methyl, R^1 is methyl or ethyl and Z is 2-pyridyl, 2-thiazolyl, 5-methyl-3-isoxazolyl, 6-methyl-2-pyridyl or 4,5-dimethyl-2-thiazolyl.

3. A compound according to claim 2 wherein R^1 is methyl and Z is 2-pyridyl.

4. A process for production of a 3,4-dihydro-2H-1,2-benzothiazine-3-carboxamide-1,1-dioxide of the formula



wherein R is hydrogen, benzyl or alkyl having from one to three carbon atoms; and Z is 2-pyridyl, alkyl substituted-2-pyridyl, 2-thiazolyl, 2-thiazolyl substituted by one or two alkyl groups, or 5-alkyl-3-isoxazolyl, each alkyl having from one to four carbon atoms; from an ester of the formula



wherein R^1 is benzyl or alkyl having from one to four carbon atoms, and an amine of the formula ZNH_2 , characterized by:

55 (a) reacting equimolar amounts of the ester and the amine in the presence of a reaction inert organic solvent at a temperature of from 0 to 110°C, to provide an intermediate compound of the empirical formula



60 (b) heating said intermediate in the presence of reaction inert organic solvent at a temperature of from 120 to 200°C.

5. A process according to claim 4 wherein R is methyl, R^1 is methyl or ethyl and Z is 2-pyridyl, 2-thiazolyl, 5-methyl-3-isoxazolyl, 6-methyl-2-pyridyl or 4,5-dimethyl-2-thiazolyl.

6. A process according to claim 5 wherein Z is 2-pyridyl and R^1 is methyl.

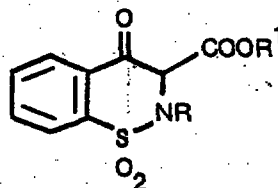


(19)

7. A process according to claim 4 wherein in step (a) said contacting is carried out at 20 to 90°C and in step (b) said temperature is from 135 to 145°C.
8. A process according to claim 4 wherein in step (a) said intermediate is isolated.
9. A process according to claim 4 wherein the product of step (b) is isolated and the mother liquor is recycled.
10. A process according to claim 4 wherein said reaction inert organic solvent is xylene.

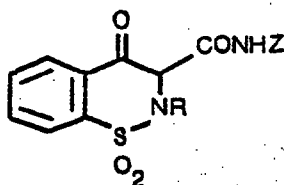
Claims for the Contracting State: AT

1. A process for the production of a compound of empirical formula $C_8H_7N_2O_5SRR^1Z$, wherein R is hydrogen, benzyl or alkyl having from one to three carbon atoms; R^1 is benzyl or alkyl having from one to four carbon atoms; and Z is 2-pyridyl, alkyl substituted-2-pyridyl, 2-thiazolyl, 2-thiazolyl substituted by one or two alkyl groups, or 5-alkyl-3-isoxazolyl, each alkyl having from one to four carbon atoms; which comprises reacting an ester of the formula

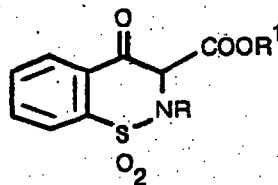


- with an equimolar amount of an amine of formula ZNH_2 , where R, R^1 and Z are as previously defined, in the presence of a reaction inert organic solvent at a temperature of from 0 to 110°C.

2. A process according to claim 1 wherein R is methyl, R^1 is methyl or ethyl and Z is 2-pyridyl, 2-thiazolyl, 5-methyl-3-isoxazolyl, 6-methyl-2-pyridyl or 4,5-dimethyl-2-thiazolyl.
3. A process according to claim 2 wherein R^1 is methyl and Z is 2-pyridyl.
4. A process for production of a 3,4-dihydro-2H-1,2-benzothiazine-3-carboxamide-1,1-dioxide of the formula



- wherein R is hydrogen, benzyl or alkyl having from one to three carbon atoms; and Z is 2-pyridyl, alkyl substituted-2-pyridyl, 2-thiazolyl, 2-thiazolyl substituted by one or two alkyl groups, or 5-alkyl-3-isoxazolyl, each alkyl having from one to four carbon atoms; from an ester of the formula



- wherein R^1 is benzyl or alkyl having from one to four carbon atoms, and an amine of the formula ZNH_2 , characterised by:

- (a) reacting equimolar amounts of the ester and the amine in the presence of reaction inert organic solvent at a temperature of from 0 to 110°C., to provide an intermediate compound of the empirical formula $C_8H_7N_2O_5SRR^1Z$; and

- (b) heating said intermediate in the presence of a reaction inert organic solvent at a temperature of from 120 to 200°C.

5. A process according to claim 4 wherein R is methyl, R^1 is methyl or ethyl and Z is 2-pyridyl, 2-thiazolyl, 5-methyl-3-isoxazolyl, 6-methyl-2-pyridyl or 4,5-dimethyl-2-thiazolyl.

6. A process according to claim 5 wherein Z is 2-pyridyl and R^1 is methyl.

7. A process according to claim 4 wherein in Step (a) said contacting is carried out at 20 to 90°C. and in Step (b) said temperature is from 135 to 145°C.

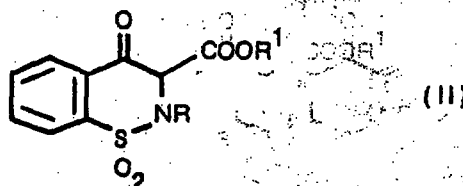
8. A process according to claim 4 wherein in Step (a) said intermediate is isolated.

9. A process according to claim 4 wherein the product of step (b) is isolated and the mother liquor is recycled.

10. A process according to claim 4 wherein said reaction inert organic solvent is xylene.

Patentansprüche für die Vertragsstaaten: BE CH DE FR GB IT LI LU NL SE

1. Verbindung der empirischen Formel $C_9H_7N_2O_5SRR^1Z$, hergestellt durch Umsetzen eines Esters der Formel



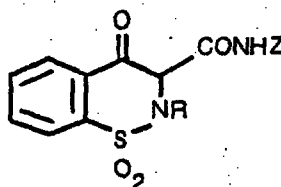
mit einer äquimolaren Menge einesamins der Formel ZNH_2 in Gegenwart eines reaktionsinerten organischen Lösungsmittels bei einer Temperatur von 0 bis 110°C, worin R Wasserstoff, Benzyl oder Alkyl mit 1 bis 3 Kohlenstoffatomen ist,

R^1 Benzyl oder Alkyl mit 1 bis 4 Kohlenstoffatomen ist und Z 2-Pyridyl, alkylsubstituiertes 2-Pyridyl, 2-Thiazolyl, 2-Thiazolyl substituiert durch eine oder zwei Alkylgruppen, oder 5-Alkyl-3-isoxazolyl ist, wobei jedes Alkyl 1 bis 4 Kohlenstoffatome hat:

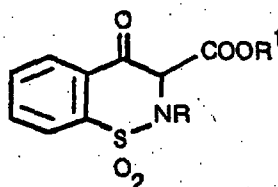
2. Verbindung nach Anspruch 1, worin R Methyl, R^1 Methyl oder Äthyl und Z 2-Pyridyl, 2-Thiazolyl, 5-Methyl-3-isoxazolyl, 6-Methyl-2-pyridyl oder 4,5-Dimethyl-2-thiazolyl ist.

3. Verbindung nach Anspruch 1, worin R^1 Methyl und Z 2-Pyridyl ist.

4. Verfahren zur Herstellung eines 3,4-Dihydro-2H-1,2-benzothiazin-3-carboxamid-1,1-dioxids der Formel



worin R Wasserstoff, Benzyl oder Alkyl mit 1 bis 3 Kohlenstoffatomen und Z 2-Pyridyl, alkylsubstituiertes 2-Pyridyl, 2-Thiazolyl, 2-Thiazolyl substituiert durch eine oder zwei Alkylgruppen, oder 5-Alkyl-3-isoxazolyl ist, wobei jedes Alkyl 1 bis 4 Kohlenstoffatome hat, aus einem Ester der Formel



worin R^1 Benzyl oder Alkyl mit 1 bis 4 Kohlenstoffatomen ist, und einem Amin der Formel ZNH_2 , gekennzeichnet durch:

(a) Umsetzen äquimolarer Mengen des Esters und des Amins in Gegenwart eines reaktionsinerten organischen Lösungsmittels bei einer Temperatur von 0 bis 110°C zu einer Zwischenstufenverbindung der empirischen Formel



(b) Erwärmen der Zwischenstufe in Gegenwart eines reaktionsinerten organischen Lösungsmittels auf eine Temperatur von 120 bis 200°C.

5. Verfahren nach Anspruch 4, bei dem R Methyl, R^1 Methyl oder Äthyl und Z 2-Pyridyl, 2-Thiazolyl, 5-Methyl-3-isoxazolyl, 6-Methyl-2-pyridyl oder 4,5-Dimethyl-2-thiazolyl ist.

6. Verfahren nach Anspruch 5, bei dem Z 2-Pyridyl und R^1 Methyl ist.

7. Verfahren nach Anspruch 4, bei dem in Stufe (a) bei 20 bis 90°C zusammengebracht wird und in Stufe (b) die Temperatur 135 bis 145°C ist.

8. Verfahren nach Anspruch 4, bei dem in Stufe (a) die Zwischenstufe isoliert wird.

9. Verfahren nach Anspruch 4, bei dem das Produkt der Stufe (b) isoliert und die Mutterlauge rückgeführt wird.

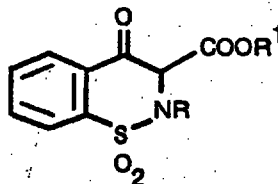
10. Verfahren nach Anspruch 4, bei dem das reaktionsinerte organische Lösungsmittel Xylol ist.



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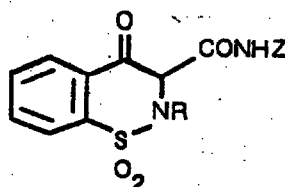
Patentansprüche für den Vertragsstaat: AT

1. Verfahren zur Herstellung einer Verbindung der empirischen Formel $C_9H_7N_2O_5SRR^1Z$, worin R Wasserstoff, Benzyl oder Alkyl mit 1 bis 3 Kohlenstoffatomen ist, R^1 Benzyl oder Alkyl mit 1 bis 4 Kohlenstoffatomen ist und Z 2-Pyridyl, alkylsubstituiertes 2-Pyridyl, 2-Thiazolyl, 2-Thiazolyl substituiert durch eine oder zwei Alkylgruppen, oder 5-Alkyl-3-isoxazolyl ist, wobei jedes Alkyl 1 bis 4 Kohlenstoffatome hat, das das Umsetzen eines Esters der Formel



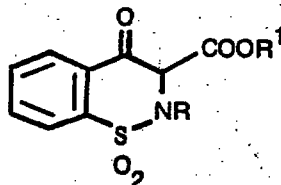
mit einer äquimolaren Menge eines Amins der Formel ZNH_2 , worin R, R^1 und Z wie zuvor definiert sind, in Gegenwart eines reaktionsinerten organischen Lösungsmittels bei einer Temperatur von 0 bis 110°C umfaßt.

2. Verfahren nach Anspruch 1, bei dem R Methyl, R^1 Methyl oder Äthyl und Z 2-Pyridyl, 2-Thiazolyl, 5-Methyl-3-isoxazolyl, 6-Methyl-2-pyridyl oder 4,5-Dimethyl-2-thiazolyl ist.
 3. Verfahren nach Anspruch 2, worin R^1 Methyl und Z 2-Pyridyl ist.
 4. Verfahren zur Herstellung eines 3,4-Dihydro-2H-1,2-benzothiazin-3-carboxamid-1,1-dioxids der Formel



worin R Wasserstoff, Benzyl oder Alkyl mit 1 bis 3 Kohlenstoffatomen

und Z 2-Pyridyl, alkylsubstituiertes 2-Pyridyl, 2-Thiazolyl, 2-Thiazolyl substituiert durch eine oder zwei Alkylgruppen, oder 5-Alkyl-3-isoxazolyl ist, wobei jedes Alkyl 1 bis 4 Kohlenstoffatome hat, aus einem Ester der Formel



worin R^1 Benzyl oder Alkyl mit 1 bis 4 Kohlenstoffatomen ist, und einem Amin der Formel ZNH_2 gekennzeichnet durch:

(a) Umsetzen äquimolarer Mengen des Esters und des Amins in Gegenwart eines reaktionsinerten organischen Lösungsmittels bei einer Temperatur von 0 bis 110°C zu einer Zwischenstufenverbindung der empirischen Formel



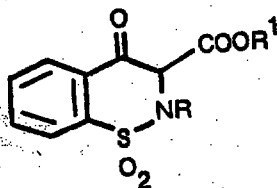
(b) Erwärmen der Zwischenstufe in Gegenwart eines reaktionsinerten organischen Lösungsmittels auf eine Temperatur von 120 bis 200°C.

5. Verfahren nach Anspruch 4, bei dem R Methyl, R^1 Methyl oder Äthyl und Z 2-Pyridyl, 2-Thiazolyl, 5-Methyl-3-isoxazolyl, 6-Methyl-2-pyridyl oder 4,5-Dimethyl-2-thiazolyl ist.
 6. Verfahren nach Anspruch 5, bei dem Z 2-Pyridyl und R^1 Methyl ist.
 7. Verfahren nach Anspruch 4, bei dem in Stufe (a) bei 20 bis 90°C zusammengebracht wird und in Stufe (b) die Temperatur 135 bis 145°C ist.
 8. Verfahren nach Anspruch 4, bei dem in Stufe (a) die Zwischenstufe isoliert wird.
 9. Verfahren nach Anspruch 4, bei dem das Produkt der Stufe (b) isoliert und die Mutterlauge rückgeführt wird.
 10. Verfahren nach Anspruch 4, bei dem das reaktionsinerte organische Lösungsmittel Xylol ist.



Revendications pour les Etats contractants: BE CH DE FR GB IT LI LU NL SE

1. Composé de formule brute $C_9H_7N_2O_5SRR^1Z$ obtenu par réaction d'un ester de formule



avec une quantité équimolaire d'une amine de formule ZNH_2 en présence d'un solvant organique inerte vis-à-vis de la réaction, à une température de 0 à 110°C, R représentant l'hydrogène, le groupe benzyle ou un groupe alkyle ayant 1 à 3 atomes de carbone;

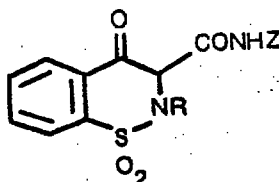
R^1 est un groupe benzyle ou un groupe alkyle ayant 1 à 4 atomes de carbone; et

Z est un groupe 2-pyridyle, 2-pyridyle à substituant alkyle, 2-thiazolyle, 2-thiazolyle substitué par un ou deux groupes alkyle, ou 5-alkyl-3-isoxazolyle, chaque groupe alkyle ayant 1 à 4 atomes de carbone.

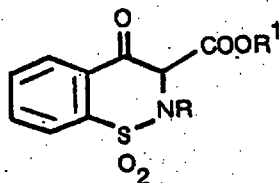
2. Composé suivant la revendication 1, dans lequel R est le groupe méthyle, R^1 est le groupe méthyle ou éthyle et Z est un groupe 2-pyridyle, 2-thiazolyle, 5-méthyl-3-isoxazolyle, 6-méthyl-2-pyridyle ou 4,5-diméthyl-2-thiazolyle.

3. Composé suivant la revendication 2, dans lequel R^1 est le groupe méthyle et Z est un groupe 2-pyridyle.

4. Procédé de production d'un 1,1-dioxyde de 3,4-dihydro-2H-1,2-benzothiazine-3-carboxamide de formule



dans laquelle R est l'hydrogène, le groupe benzyle ou un groupe alkyle ayant 1 à 3 atomes de carbone; et Z est le groupe 2-pyridyle, un groupe 2-pyridyle à substituant alkyle, le groupe 2-thiazolyle, un groupe 2-thiazolyle substitué par un ou deux groupes alkyle, ou un groupe 5-alkyl-3-isoxazolyle, chaque groupe alkyle ayant 1 à 4 atomes de carbone; à partir d'un ester de formule



dans laquelle R^1 est le groupe benzyle ou un groupe alkyle ayant 1 à 4 atomes de carbone, et d'une amine de formule ZNH_2 , caractérisé par:

(a) la réaction de quantités équimolaires de l'ester et de l'amine en présence d'un solvant organique inerte vis-à-vis de la réaction à une température de 0 à 110°C pour former un composé intermédiaire de formule brute



(b) le chauffage dudit composé intermédiaire en présence d'un solvant organique inerte vis-à-vis de la réaction à une température de 120 à 200°C.

5. Procédé suivant la revendication 4, dans lequel R est le groupe méthyle, R^1 est le groupe méthyle ou éthyle et Z est le groupe 2-pyridyle, 2-thiazolyle, 5-méthyl-3-isoxazolyle, 6-méthyl-2-pyridyle ou 4,5-diméthyl-2-thiazolyle.

6. Procédé suivant la revendication 5, dans lequel Z est le groupe 2-pyridyle et R^1 est le groupe méthyle.

7. Procédé suivant la revendication 4, dans lequel la mise en contact dans l'étape (a) est effectuée à 20—90°C et la température dans l'étape (b) va de 135 à 145°C.

8. Procédé suivant la revendication 4, dans l'étape (a) duquel ledit composé intermédiaire est isolé.

9. Procédé suivant la revendication 4, dans lequel le produit de l'étape (b) est isolé et la liqueur-mère est recyclée.

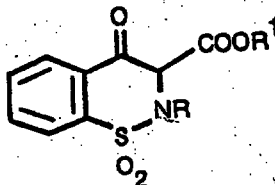


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10. Procédé suivant la revendication 4, dans lequel ledit solvant organique inerte vis-à-vis de la réaction est le xylène.

Revendications pour l'Etat contractant: AT

- 5 1. Procédé de production d'un composé de formule brute $C_9H_7N_2O_5SRR^1Z$, dans laquelle R est l'hydrogène, le groupe benzyle ou un groupe alkyle ayant 1 à 3 atomes de carbone; R¹ est le groupe benzyle ou un groupe alkyle ayant 1 à 4 atomes de carbone; et Z est le groupe 2-pyridyle, un groupe 2-pyridyle à substituant alkyle, le groupe 2-thiazolyle, un groupe 2-thiazolyle substitué par un ou deux groupes alkyle, ou un groupe 5-alkyl-3-isoxazolyle, chaque groupe alkyle ayant 1 à 4 atomes de carbone; qui consiste à faire réagir un ester de formule

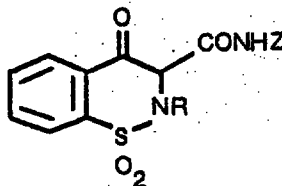


- 15 20 avec une quantité équimolaire d'une amine de formule ZNH_2 où R, R¹ ont les définitions données ci-dessus, en présence d'un solvant organique inerte vis-à-vis de la réaction, à une température de 0 à 110°C.

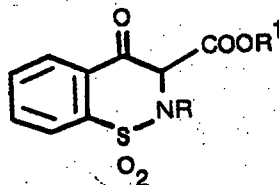
2. Procédé suivant la revendication 1, dans lequel R est le groupe méthyle, R¹ est le groupe méthyle ou éthyle et Z est le groupe 2-pyridyle, 2-thiazolyle, 5-méthyl-3-isoxazolyle, 6-méthyl-2-pyridyle ou 4,5-diméthyl-2-thiazolyle.

- 25 3. Procédé suivant la revendication 2, dans lequel R¹ est le groupe méthyle et Z est le groupe 2-pyridyle.

4. Procédé de production d'un 1,1-dioxyde de 3,4-dihydro-2H-1,2-benzothiazine-3-carboxamide de formule



- 30 35 dans laquelle R est l'hydrogène, le groupe benzyle ou un groupe alkyle ayant 1 à 3 atomes de carbone; et Z est le groupe 2-pyridyle, un groupe 2-pyridyle à substituant alkyle, le groupe 2-thiazolyle, un groupe 2-thiazolyle substitué par un ou deux groupes alkyle, ou un groupe 5-alkyl-3-isoxazolyle, chaque groupe alkyle ayant 1 à 4 atomes de carbone, à partir d'un ester de formule



40 45 dans laquelle R¹ est le groupe benzyle ou un groupe alkyle ayant 1 à 4 atomes de carbone, et d'une amine de formule ZNH_2 , caractérisé par:

- 50 (a) la réaction de quantités équimolaires de l'ester et de l'amine en présence d'un solvant organique inerte vis-à-vis de la réaction, à une température de 0 à 110°C, pour former un composé intermédiaire de formule brute $C_9H_7N_2O_5SRR^1Z$; et

(b) le chauffage dudit composé intermédiaire en présence d'un solvant organique inerte vis-à-vis de la réaction à une température de 120 à 200°C.

- 55 5. Procédé suivant la revendication 4, dans lequel R est le groupe méthyle, R¹ est le groupe méthyle ou éthyle et Z est un groupe 2-pyridyle, 2-thiazolyle, 5-méthyl-3-isoxazolyle, 6-méthyl-2-pyridyle ou 4,5-diméthyl-2-thiazolyle.

6. Procédé suivant la revendication 5, dans lequel Z est le groupe 2-pyridyle et R¹ est le groupe méthyle.

- 60 7. Procédé suivant la revendication 4, dans lequel la mise en contact dans l'étape (a) est effectuée à 20-90°C et la température dans l'étape (b) va de 135 à 145°C.

8. Procédé suivant la revendication 4, dans l'étape (a) duquel ledit composé intermédiaire est isolé.

9. Procédé suivant la revendication 4, dans lequel le produit de l'étape (b) est isolé et la liqueur-mère est recyclée.

- 65 10. Procédé suivant la revendication 4, dans lequel ledit solvant organique inerte vis-à-vis de la réaction est le xylène.