

Description

This invention relates to the use of acetazolamide-related compounds having inhibiting activity on carbonic anhydrase in the topical treatment of glaucoma. More particularly, this invention relates to the use of agents capable of inhibiting carbonic anhydrase, which agents are characterized in that they can be well absorbed locally, so that they are particularly suitable for topical administration.

The term glaucoma commonly means a variety of clinical conditions which are characterized by a progressive increase in intraocular pressure, a condition which gives rise to severe defects in the eye structures, up to optical atrophy. Various kinds of primary and secondary glaucoma are known, but all forms show a common feature, i.e. the increase of aqueous humour in the anterior chamber of the eye (camera anterior bulbi).

Various drugs are known that are capable of reducing the intraocular pressure, so that they could be employed for treating glaucoma, but their efficiency is variable and all of them show more or less serious side effects. Among such drugs, there are compounds showing cholinergic action (acetylcholine, pilocarpine and eserine), having a short-lasting action, compounds showing anticholinergic action, with remarkable side effects (atropine), compounds with adrenergic action (adrenalin), which are effective but painful, and compounds with antiadrenergic action (adrenergic beta-blocking agents).

These last compounds are the most commonly employed: thymolole, an adrenergic beta-blocking agent, is the most diffused product presently on the market in many countries; however, this class of drugs is also affected by undesired side effects, such as fits of asthma and cardiac troubles.

An additional class of compounds capable of reducing intraocular pressure, and therefore potentially useful for treating glaucoma, is the class of carbonic anhydrase inhibitors, the best known among them being acetazolamide. These compounds, though remarkably efficient, cannot be absorbed topically, so that they are to be administered systemically, and in particular through the oral route.

Systemic administration of such drugs, and, in particular, of acetazolamide, is however affected by a number of side effects, such as a feeling of weariness, gastrointestinal troubles and anorexia, due to the diuretic action of such drugs. Their effects are so severe, especially at the kidney level, that their employment for treating glaucoma is impossible as a matter of fact.

J. Pharmacol. Exper. Therap., vol. 218, 1981, p. 600-607 concerns macromolecular (more specifically, dextran-bound) inhibitors of carbonic anhydrase and mentions acetazolamide (ACTZ) as a well-known carbonic anhydrase inhibitor. The paper discloses the synthesis of 2-succinylamido-1,3,4-thiadiazole-5-sulfonamide (STZ) by direct acylation of the corresponding amino derivative. STZ is then coupled to dextran (AED) in order to obtain a dextran-bound inhibitor (DBI) which does not enter the proximal tubular cells of rat kidneys, clearly in view of a systemic use of such inhibitor. The article also gives the *in vitro* activity of STZ as a carbonic anhydrase inhibitor.

Quant. Struct. - Activ. Relat. in Pharmacol. Chem. and Biol., vol. 6, 1987, P. 51-53, as well as J. Org. Chem., vol. 21, 1956, p. 700-701, report about the *in vitro* activity of some heterocyclic sulfonamides as carbonic anhydrase inhibitors. Amongst the others, both references mention 5-aminoacetamido-2-sulfonamido-1,3,4-thiadiazole, while the second one also mentions 5-(2-carboxybenzamido)2-sulfonamido-1,3,4-thiadiazole.

Egyptian J. Pharm. Sci., vol. 21, 1980, p. 189-198, corresponding to Chem. Abs., vol. 98, 1983, abstract 107 226d, describes some acetazolamide derivatives which are modified in the sulfonamide group, and one which is modified in the acetamide group, i.e. 5-(ethylmalonylamino)-1,3,4-thiadiazole-2-sulfonamide. The said compounds are disclosed as hypoglycemic agents.

The US-A-4 483 864 discloses acetazolamide derivatives modified in the sulfonamide group, and explains that carbonic anhydrase inhibitors are known to be effective for reducing the intraocular pressure, and therefore for treating glaucoma, but they can only be employed for oral use, with severe side effects. In order to provide a medicament for the therapy of glaucoma which can be absorbed topically, the above-referenced document proposes a prodrug of acetazolamide, which is not active *in vitro* as carbonic anhydrase inhibitor, but gives rise to the active compound once metabolized in the eye.

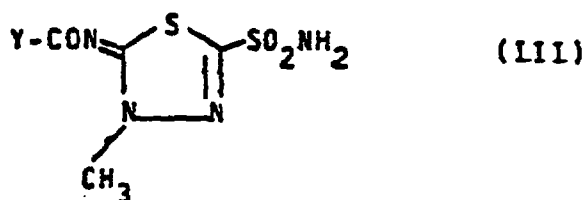
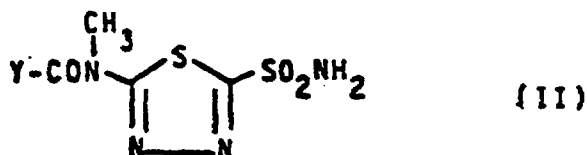
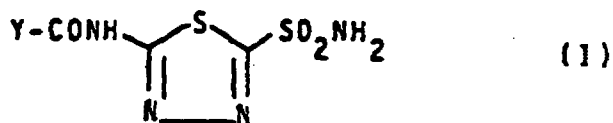
The object of the present invention is to provide compounds capable of inhibiting carbonic anhydrase, which compounds, in addition to showing an activity comparable to that of acetazolamide, also are characterized by being well absorbed locally, so that they can be employed by administration through the topical route. It is quite clear that topical administration allows to obtain a therapeutic action without the noxious side effects given by the drug itself when it is administered through the systemic route.

Accordingly, we have devised to modify the molecule of acetazolamide so as to increase both their water solubility and their lipophilic character. As a matter of fact, acetazolamide is practically insoluble and lacks lipophilic groups, its poor absorption when instilled in the eye being ascribable to both such factors.

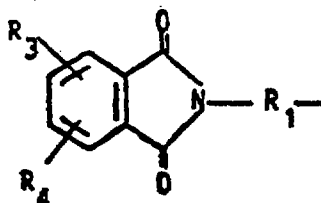
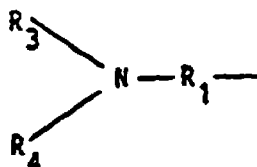
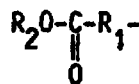
The present invention provides some compounds related to acetazolamide or to its N-methyl derivatives, which contain a lipophilic acyclic chain bearing at its other end an esterified or unesterified carboxylic group, an

amino group or a phthalimido group, for use in the topical treatment of glaucoma.

Accordingly, the present invention specifically provides the use of compounds related to acetazolamide or to its N-methyl derivatives, capable of inhibiting carbonic anhydrase, said compounds having the formula:



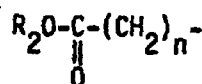
wherein Y is one of the following groups:



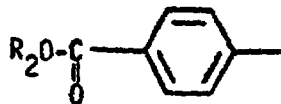
wherein R₁ is a straight or branched alkylene or arylalkylene or a Phenylene group, R₂ is hydrogen or a straight or branched alkyl optionally substituted with halogen, R₃ and R₄, which are the same or different from one another, are hydrogen or a straight or branched alkyl, as well as the physiologically acceptable salts thereof, for the manufacture of a medicament for the topical treatment of glaucoma.

More particularly, the present invention provides the use for glaucoma treatment of compounds having the

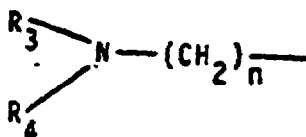
formulas (I), (II), or (III) wherein Y has one the following structures:



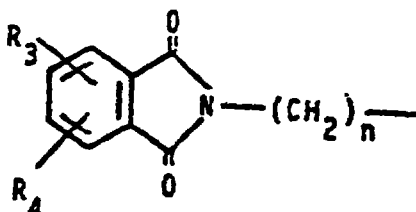
wherein R_2 is hydrogen or a straight or branched alkyl having 1-20 carbon atoms and optionally substituted with halogen, n being an integer between 1 and 10; or:



wherein R_2 has the same meaning as above; or:



wherein R_3 and R_4 , which are the same or different from one another, are hydrogen or a lower alkyl of 1-6 carbon atoms, n being an integer between 1 and 10; or:

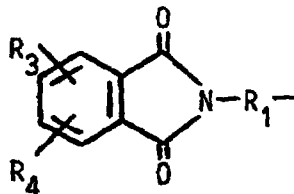


wherein both R_3 and R_4 , as well as n , have the same meanings as above.

The compounds disclosed above can also be in the form of their physiologically acceptable salts, both of bases and of acid, either organic or inorganic.

Some of the compounds listed above are also new per se, and therefore the present invention also provides the N-methyl derivatives of acetazolamide of the formulae (II) and (III) wherein Y has the same meanings as in the main claim.

Further, the invention provides compounds related to acetazolamide and its N-methyl derivatives having the formulae (I), (II) and (III) wherein Y is:



and R_1 , R_3 and R_4 have the same meanings as in the main claim.

The preferred compounds of the latter group are those in which R_1 is $-(CH_2)_n-$, n is an integer between 1 and 10 and R_3 and R_4 , which can be the same or different from each other, are hydrogen or lower alkyl of 1-6 carbon atoms.

Examples of suitable bases are sodium hydroxide, potassium hydroxide, calcium, barium and ammonium hydroxides.

Hydrogen halides, sulfonic acid, phosphoric, nitric, perchloric acid, and aliphatic, cycloaliphatic, aromatic

or heterocyclic carboxylic and sulfonic organic acids such as formic, acetic, propionic, succinic, glycolic, lactic, malic, tartaric, citric, ascorbic, maleic, hydroxymaleic, piruvic, phenylacetic, benzoic, paraaminobenzoic, anthranilic, p-hydroxybenzoic, salicylic, p-aminosalicylic, pantoic, methanesulfonic, ethanesulfonic, hydroxyethanesulfonic, ethylenesulfonic, halogenobenzenesulfonic, toluenesulfonic, naphthalenesulfonic, and sulfonylic acid are particularly suitable to form salts for pharmaceutical employment.

The novel active compounds of the present invention keep the property of enzymic inhibitor typical of acetazolamide, and, at the same time, they are more soluble and more lipophilic with respect to acetazolamide because of the presence in their structures of the modifier group Y. Therefore, they are much more absorbable topically.

Moreover, among such compounds those which have in their chain an esterified carboxyl group have a further feature that makes them particularly interesting for topical treatment of glaucoma: due to the action of esterases that are present in the ocular tissue, they give rise to a principal metabolite with a free carboxyl group. The latter, as a result of its physicochemical characteristics, has a poor tendency to pass into the plasma and to spread throughout the organism. This contributes to reduce the possibility that the novel compounds exert a systemic action and hence this contributes to reduce the possibility of occurrence of side effects.

The following table 1 reports some results of *in vitro* activity tests of the compounds of the present invention; beside the solubility in a buffer at pH = 7.6, there is shown the value of the molar concentration that gives a 50 % reduction of enzymic activity (I_{50}): as can be clearly seen, the *in vitro* activity of the compounds of the present invention is comparable to or better than that of acetazolamide.

TABLE 1

COMPOUND

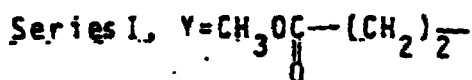
Solubility in
buffer pH
7.6 (mg/ml) I_{50}
 $\times 10^{-7}$

ACETAZOLAMIDE

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4.4

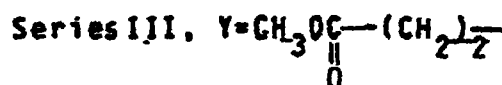
RENDE 023



0.74

5.5

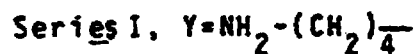
RENDE 024



2.25

4.5

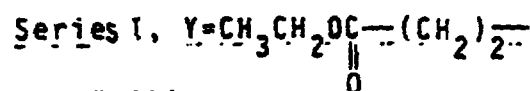
RENDE 027



0.208

4.4

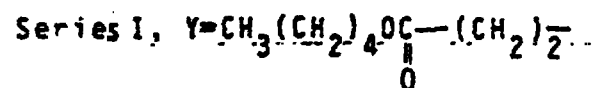
RENDE 029



2.76

7.3

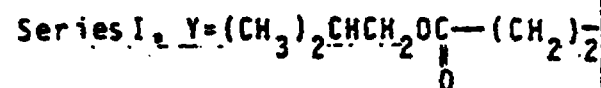
RENDE 032



0.47

3.9

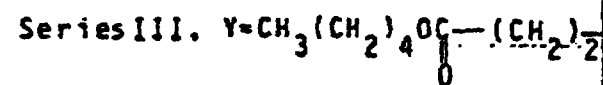
RENDE 034



1.24

3.7

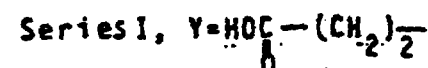
RENDE 035



0.535

3.07

RENDE 037



28.7

5.5

For determining the *in vitro* activities, samples were employed at molar concentrations of 10^{-7} , 3×10^{-7} , 6×10^{-7} , and 10^{-6} , and the results given in Table 1 were obtained by CO_2 -electrode potentiometric analysis.

In vivo experiments were carried out on the compounds of the present invention, and, amongst the others, those experiments whose results are reported in the following Table 2, concerning the decrease in the ocular pressure in rabbit.

For determining such results a transient ocular hypertension model was employed, said hypertension being obtained in rabbit through rapid venous infusion of suitable volumes (20 ml/kg) of 5 % glucose solution.

Albino rabbits from the same farm in New Zealand were employed, whose weights were between 2,500 g

3,000 g. Each treatment was carried out on a group of six animals.

The drug was prepared in a phosphate buffer water solution at pH 7.5. The solution was made isotonic with sodium chloride and the possibility of microbial contamination was prevented through the addition of benzalkonium chloride. In case of compounds of low solubility, a dispersing suspension of the finely divided compound in methyl cellulose was prepared. The solution (or the suspension) was instilled into the right eye of each animal in the amount of 2 drops of 2 % solution, at an interval of 2 minutes from one another. The left eye was treated with an equal volume of diluent.

The measurements of pressure were performed while animals were in superficial local anaesthesia (0.4 % benoxinate), by means of a McKay-Marg electronic pressure gage, at the times -30', 0', 10', 20', 40'.

The following table reports the endocular pressure measured after 10, 20, and 40 minutes both in the right and in the left eye: the higher the difference in the ocular pressure between the treated eye and the untreated eye, the higher the efficiency of the drug considered.

TABLE 2

Compound	mmHg					
	10'		20'		40'	
	OD	OS	OD	OS	OD	OS
RENDE 023	25.33	25.5	19.5	20.17	16.5	16.67
RENDE 024	24.67	25.83	20.33	21.5	17.33	17.83
RENDE 027	24.0	26.17	20.83	21.5	16.83	17.33
RENDE 029	20.33	25.67	17.33	20.67	15.67	17.67
RENDE 032	22.67	24.5	20.0	21.33	17.83	18.83
RENDE 034	21.5	25.67	19.0	21.17	16.67	17.17
RENDE 035	24	25.17	20.67	22.0	17.83	18.0
RENDE 037	19.33	26.0	17.17	21.67	15.67	19.0

The derivatives proposed by the present invention can be employed for pharmaceutical purposes and can be administered topically as such or in the form of salts.

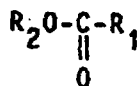
The products of the present invention and their salts can be employed in the form of pharmaceutical preparations with liquid or solid, organic or inorganic excipients, which are suitable for the topical administration. Suitable excipients are pharmaceutically acceptable compounds that do not interfere with the activity of the compounds of this invention, such as water, cellulose, surface active agents, gelatins, lactose, talc, starch, magnesium stearate.

Moreover, the pharmaceutical preparations, which can be collyria, tablets, capsules, pills, solutions, suspensions, emulsions, ointments, creams and suppositories, can also contain preserving agents, as well as stabilizing, wetting, emulsifying, solubilizing agents and salts for adjusting the osmotic pressure and the pH value.

The compounds disclosed hereinbefore may be prepared according to one of the following methods.

A first group comprises methods which, although different in some details depending on the structure of the product to prepare, all start from the 5-amino-2 mercapto-1,3,4-thiadiazole and comprise three fundamental steps: the acylation step of the amino group of the starting compound, the oxidation step of the mercapto group to the corresponding sulfonyl, and the reaction step with ammonia to obtain the corresponding sulfonamide.

The specific method of this group for preparing the compounds of the series I wherein Y is the group



5 is disclosed with its variants in the following scheme A: 5-amino-2-mercapto-1,3,4-thiadiazole is subjected to acylation (step a), employing as acylating agents the hemiesters of bicarboxylic acids of the formula:



or the acid halides of said esters having the formula:



20 wherein X is a halogen atom, or asymmetric diesters of the formula



or the anhydrides of the hemiesters as above, of the formula:

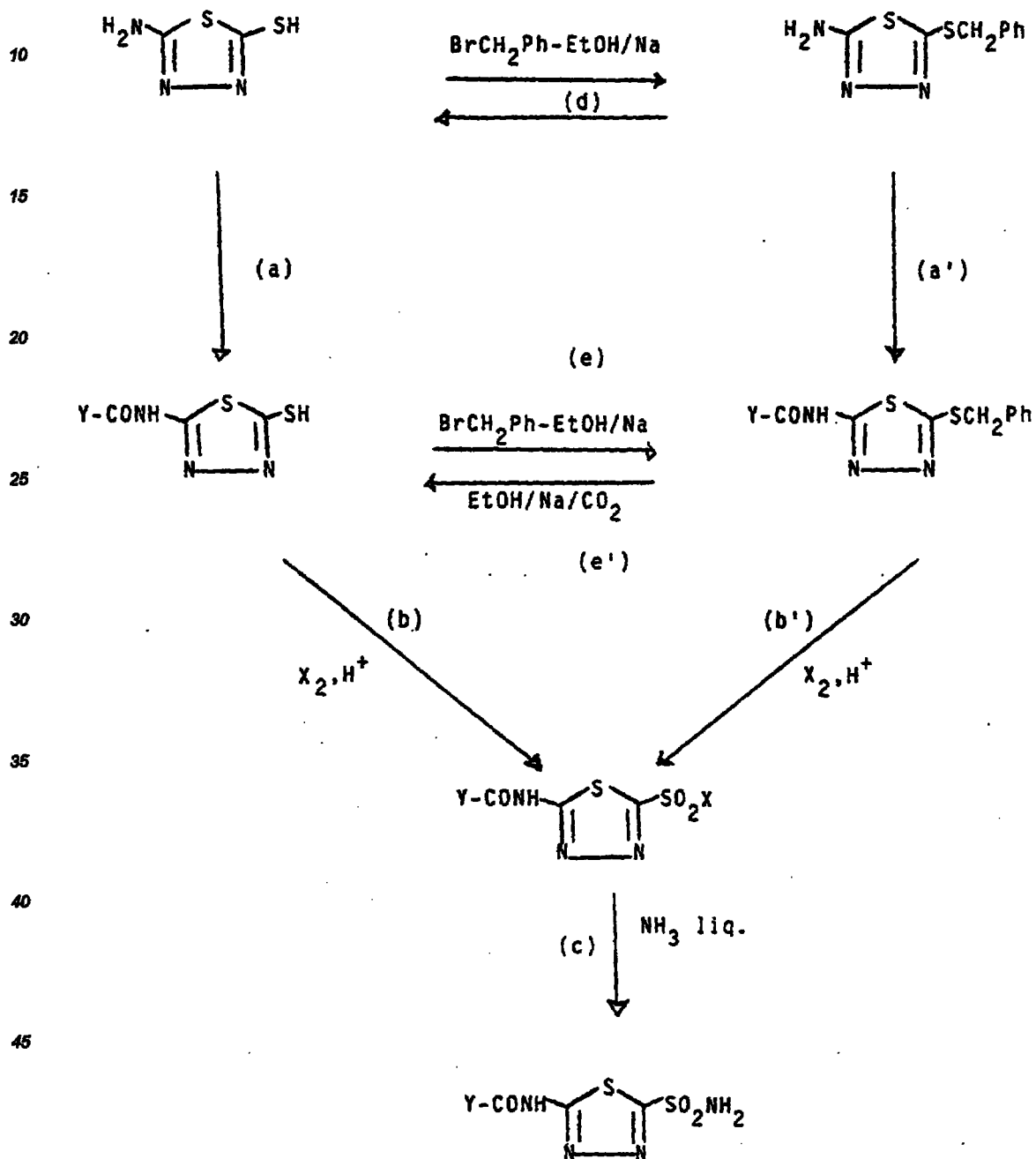


or the cyclic anhydrides of the bicarboxylic acid, of the formula:



45 In the formulas reported above, R_2 is different from hydrogen. In the particular instance in which the final desired product has $R_2=H$, any esterified acylating agent can be employed, and the terminal carboxylic group is liberated at the end of the process, through saponification by prolonged treatment with a strong alkali. In particular, the compound is treated with NaOH for at least 2 hours at room temperature.

SCHEME A



The acylation reaction a) can be carried out in a suitable organic solvent, preferably in anhydrous tetrahydrofuran (THF) or methylene chloride, under nitrogen at room temperature and employing as a catalyst an

organic base, generally triethylamine with small amounts of 4-dimethylaminopyridine (DMAP).

The oxidation of the mercapto group (step b) is performed preferably with a gaseous halide (X_2) in acetic acid at low temperature, generally at 0°C ; under these conditions, the sulfonyl halide is formed directly. Such compound, after extraction with an organic solvent or filtration in case it is a solid, is reacted with liquid ammonia (step c).

The reaction step c) is carried out at a very low temperature, preferably at -78°C , under nitrogen.

The reaction product is purified through direct crystallization or through dissolution in a weak basic medium and successive precipitation with an acid, preferably with hydrochloric acid at pH 4.

In alternative to the process consisting of the steps a), b) and c), it is possible to protect the mercapto group through benzylation (step d) before performing the acylation of the amino group. Such operation can be carried out, for instance, by reacting the starting compound with benzyl bromide (BrCH_2Ph) in ethanol in the presence of elemental sodium.

After acylation (step a'), the benzyl group can be removed by treatment with elemental sodium in anhydrous ethyl alcohol and bubbling CO_2 (step e'). In that case, the preparation process is completed through the steps b) and c).

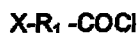
Alternatively, the benzyl derivative is subjected directly to the oxidation of the substituted mercapto group to sulfonyl halide (step b') under conditions similar to those disclosed for the oxidation step b); the process ends with the step c).

A further route of synthesis according to the scheme A consists in subjecting the starting compound to acylation (step a), and then performing the benzylation of the mercapto group (step e) followed by the oxidation (step b') and the treatment with ammonia (step c).

The specific process for preparing the compounds of the series I wherein Y is the group

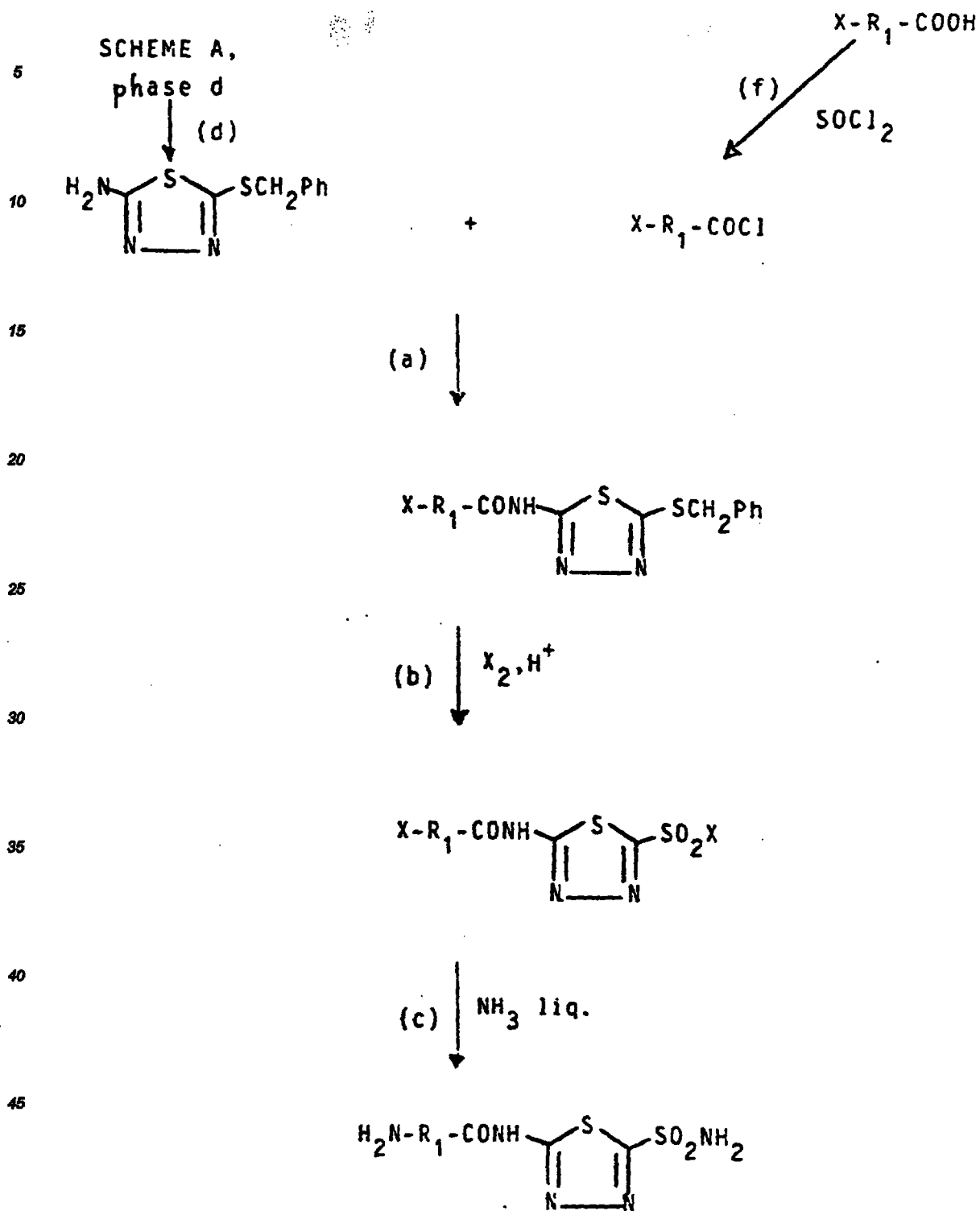


wherein R_1 is a straight or branched alkylene or arylalkylene, or a phenylene, is disclosed in the following scheme B: the 5-amino-2-mercapto-1,3,4-thiadiazole is first benzylated in the mercapto group as in the reaction step d) of the preceding scheme, and then it is subjected to acylation of the amino group with the halogenated carboxylic acid chloride of the formula:



wherein X is a halogen atom and R_1 is the chain desired to be present in the final group Y.

SCHEME E

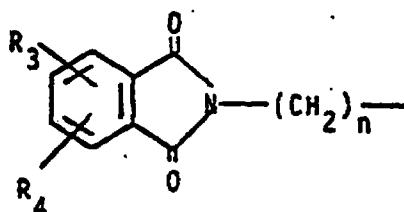


The acylating agent $\text{X}-\text{R}_1\text{COCl}$ can be obtained according to the preparation step f) by reacting the corresponding halogenated carboxylic acid with thionyl chloride (SOCl_2).

After the acylation step a) of the benzylated starting compound, which is carried out according to the same operational modes as those employed in steps a) and a') of the scheme A, the oxidation step of the mercapto group (step b) is performed, which step is similar to the step b) of the scheme A.

The compound so obtained, treated with liquid ammonia (step c) as in the step c) of the scheme A, is subjected to the substitution, both of the halogen atom in the sulfonyl halide group and of the halogen atom bound to R_1 , with two amino groups.

The present invention also relates to a specific process for producing the compounds of the series I wherein Y is the group



wherein R_1 , R_3 , and R_4 have the meanings already known, which is illustrated with its variants in the following scheme C.

A possible route of synthesis is that of proceeding in the same way as that shown in the scheme B, steps d), f) and a), thus obtaining a benzyl mercaptan which is acylated in the amino group with the chain $X-R_1-CO-$, and, in a second step, of introducing the phthalimido group as the terminal group in said chain through the reaction with the desired potassium phthalimide (step h).

SCHEME C

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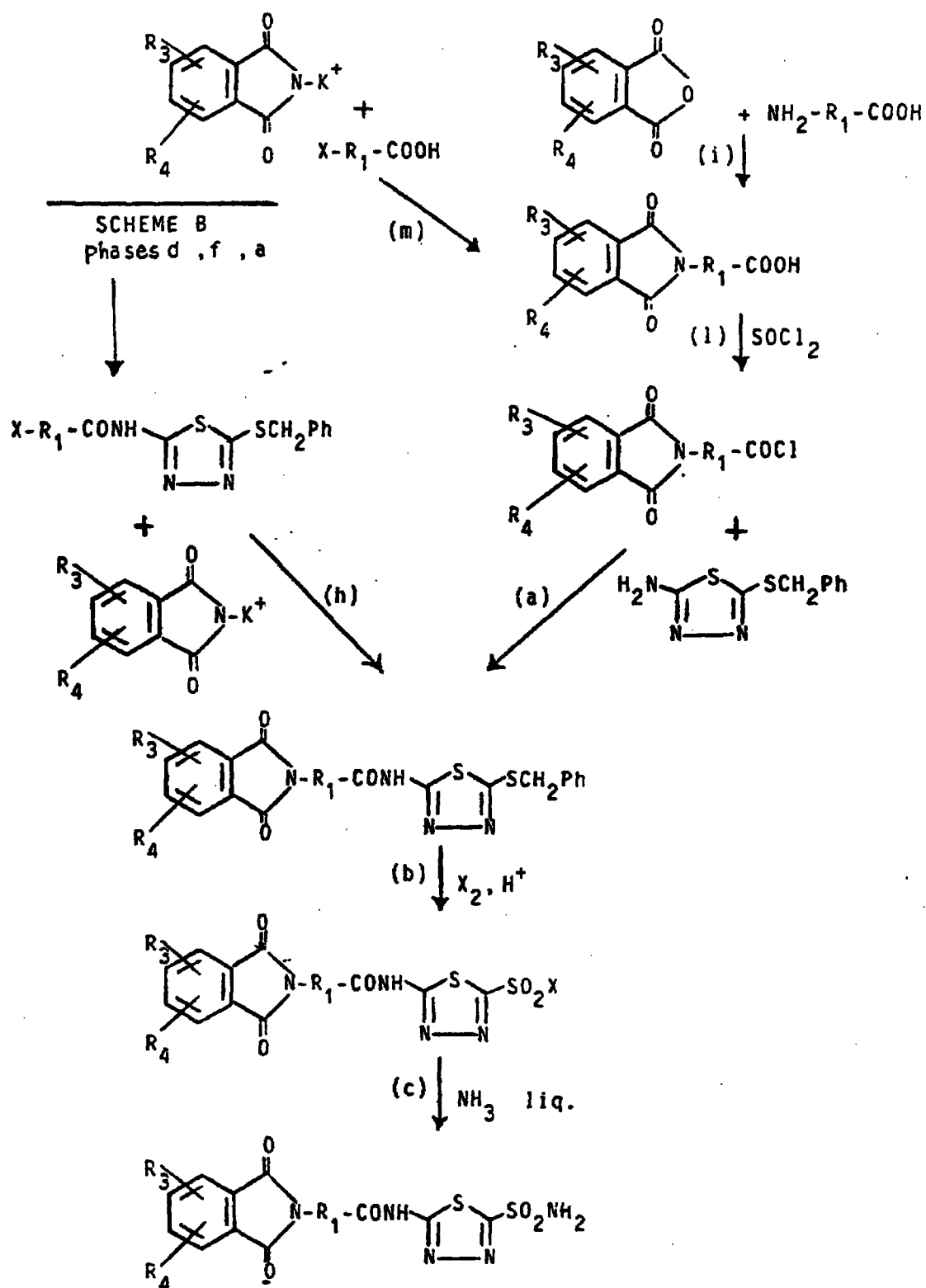
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Starting from that point, the oxidation of the benzylmercaptan group and the treatment with ammonia are similar to the steps of the preceding schemes (steps b) and c).

Alternatively, the phthalimido group can already be present in the initial acylating agent, so that the acylation of the amino nitrogen of the 5-amino-2-benzylmercapto-1,3,4-thiadiazole (step b) is performed according to ways similar to the steps a) and a') of the preceding schemes.

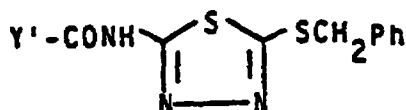
The acylating agent of the step a), which is the phthalimidocarboxylic acid chloride, corresponding to the desired group Y, is obtained (step 1) through treatment of the corresponding carboxylic acid with thionyl chloride; the phthalimidocarboxylic acid can be in turn prepared according to two different ways (step m and step i): either by reaction of potassium phthalimide with a halogenated carboxylic acid of the formula



or by reaction of phthalic anhydride with an amino acid of the formula NH_2-R_1-COOH .

After the acylation step a), the synthesis proceeds through the same steps as those of the preceding case (steps b and c).

According to a specific embodiment of this invention, the compounds of the series II and III (the N-methyl derivatives), may be prepared by carrying out first of all the acylation of the 5-amino-2-benzylmercapto-1,3,4-thiadiazole (obtained through benzylation according to the step d) of the Scheme A). According to the desired meaning of the group Y, the scheme A, steps d) and a'), or a) and e), the scheme B, steps d) and a) the scheme C, step h) or step a) are followed. The product obtained from such operations can be represented by the following formula:



wherein Y' is Y in case the terminal group is an ester or an acid (scheme A) and in case the terminal group is a phthalimido group (scheme C). In case the terminal group is an amino group (scheme B), Y' is $X-R_1-$ (wherein X is a halogen), as the amino group will be introduced at the end by means of treatment with ammonia.

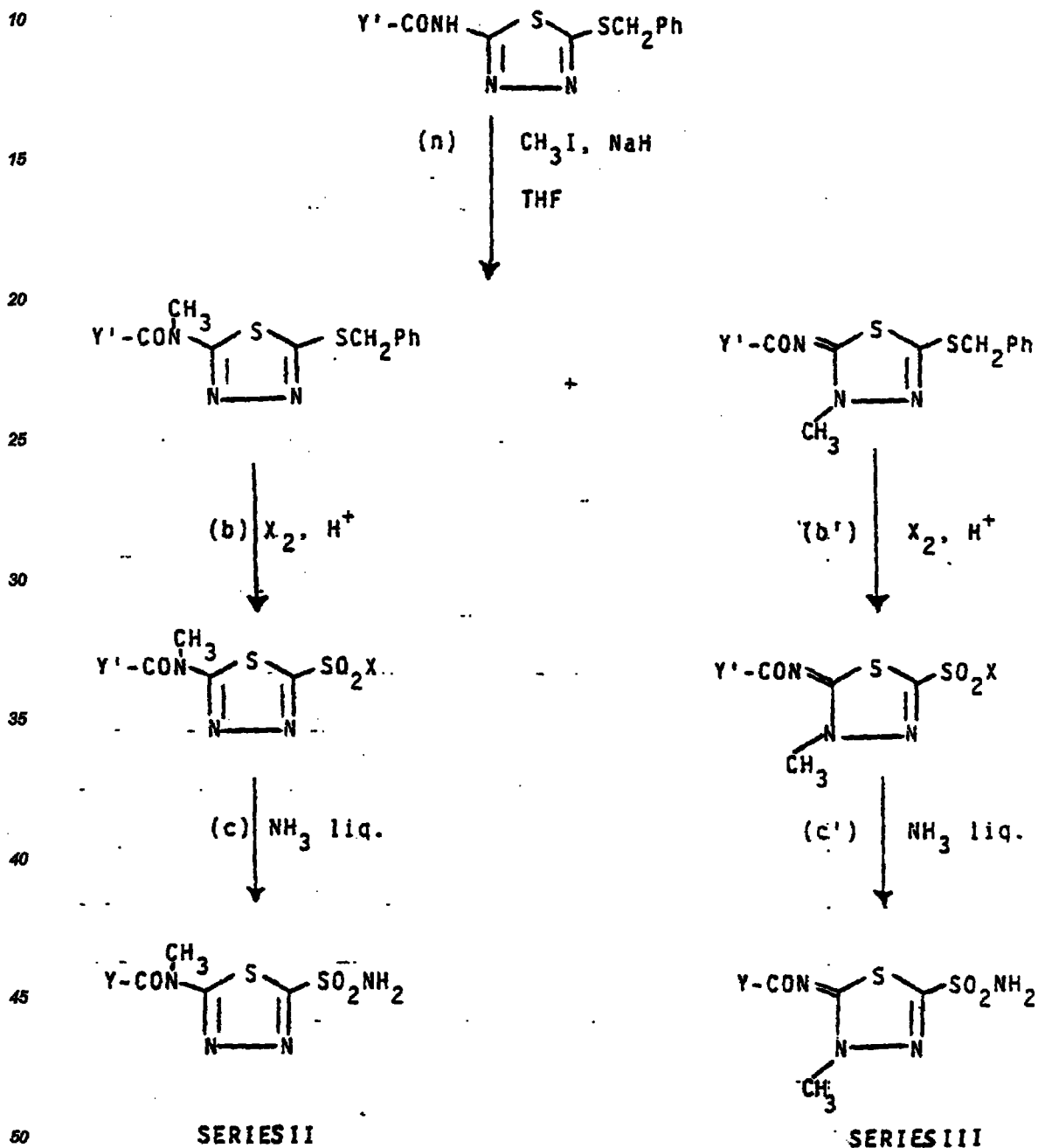
The compound of the preceding formula is subjected to a methylation reaction which is pointed out by "n" in the scheme D illustrated below.

SCHEME D

Scheme A, steps d and a' or steps a and e

Scheme B, step a

Scheme C, steps a or h



The methylation reaction is performed by dissolving the compound in an anhydrous organic solvent, generally THF, containing sodium hydride in a slight stoichiometric excess.

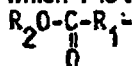
Then methyl iodide is added while keeping the mixture stirred under nitrogen. After completion of the reac-

tion, the two methyl derivatives are separated by column chromatography.

The two methyl derivatives are then oxidized and transformed into sulfonamide under the same conditions disclosed for the derivatives of the series I (steps b and c, or steps b' and c').

Alternatively, the compounds of series I in which Y is the group

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can be prepared by making use of acetazolamide as a starting material, instead of 5-amino-2-mercapto-1,3,4-thiadiazole. In this case acetazolamide is first of all hydrolyzed so as to eliminate the amide group bound in the 5th position and to leave, in place thereof, an amine group. The resulting compound is then acylated in its aminic group, while no transformation is required for the group bound in the and position, which is already the one desired.

The above method is illustrated in the following scheme E: acetazolamide (5-acetamido-2-sulfonamido-1,3,4-thiadiazole) is subjected to acid hydrolysis (step o), followed by neutralization of the resulting acid solution up to precipitation of 5-amino-2-sulfonamido-1,3,4-thiadiazole (step p).

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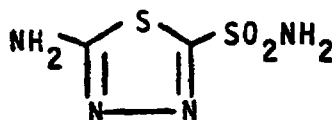
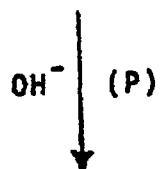
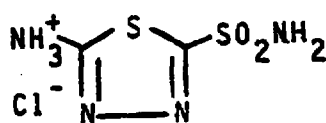
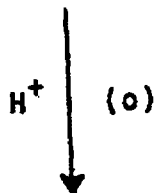
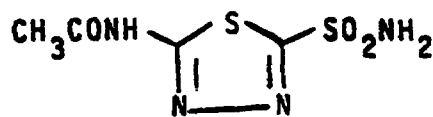
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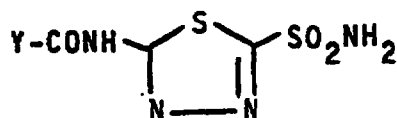
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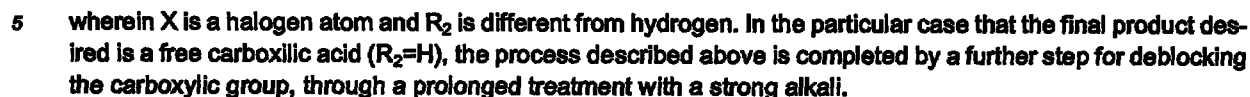
55

SCHEME E



$$\begin{array}{c} \downarrow \\ (\text{q}) \end{array}$$


Thereafter, 5-amino-2-sulfonamido-1,3,4-thiadiazole is acylated (step q) by means of a hemiester hemialde of the bicarboxylic acid corresponding to the desired group, i.e.



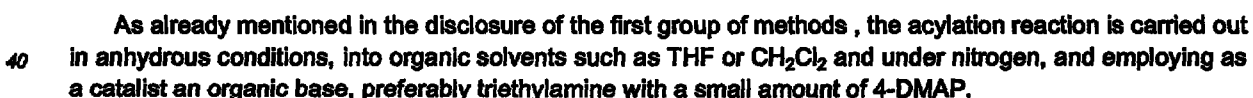
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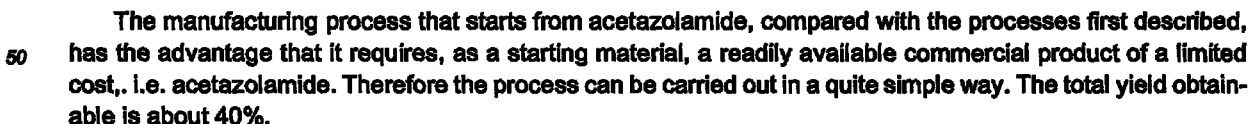
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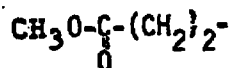
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55

5-methylsuccinoglamino-2-sulfonamido-1, 3,4-thiadiazole,

(Rende 023) Series I, Y =



5

SCHEME A, route steps (a), (b), (c)

(a) Preparation of 5-methylsuccinoylamino-2-mercapto-1, 3, 4-thiadiazole

10

5 g of 5-amino-2-mercapto-1,3,4-thiadiazole (0.037 mole) is suspended in 30 ml of CH_2Cl_2 , under nitrogen at room temperature and with stirring. Then 6 ml of Et_3N (0.043 mole), 5.6 ml (0.037 mole) of succinoyl chloride monomethyl ether and 100 mg of 4-dimethylaminopyridine (4-DMAP) are added. The reaction is checked by thin layer chromatography (TLC) on silica gel (10 % methanol in chloroform) and it shows to be complete after 3 hours.

15

To obtain the purified product, a double volume (about 100 ml) of 30 % NH_4OH is added to the mixture, then it is diluted with methylene chloride and the water phase, after separation, is acidified to pH 4 with concentrated hydrochloric acid without heating.

20

The precipitate so formed is filtered off and crystallized from ethanol, yielding 7 g of the product with melting point 183-186°C; yield 76 %.

$^1\text{H-NMR}$ 60 MHz (Py): $\delta = 2,8$ (m, 4H, $-\text{CH}_2\text{CH}_2-$); 3,62 (s, 3H, OCH_3)

IR(KBr) : $\nu_{\text{max}} = 3225, 2920, 1695, 1580, 1365, 990, 730 \text{ cm}^{-1}$

(b) Preparation of 5-methylsuccinoylamino-2-sulfonylchloride-1,3,4-thiadiazole

25

Gaseous chlorine is bubbled through a suspension of 2 g of 5-methylsuccinoylamino-2-mercapto-1,3,4-thiadiazole in 25 ml of a water solution of 33 % acetic acid, while the mixture is kept stirred at 0°C for 2 hours.

The sulfonyl chloride that is precipitated is filtered, then washed with ice-cold water and then dried under vacuum.

30

2.3 g of sulfonyl chloride is obtained, which is immediately employed for the preparation of the sulfonamide.

(c) Preparation of 5-methylsuccinoylamino-2-sulfonamido-1,3,4-thiadiazole (Rende 023)

35

2.3 g of methylsuccinoylamino-2-sulfonylchloride-1,3,4-thiadiazole is slowly added under nitrogen to 50 ml of freshly condensed liquid NH_3 at -78°C.

When the addition is complete, ammonia is removed keeping the reaction vessel at room temperature, and the residue is dried in vacuum. The raw product of sulfonamide is then purified through solubilization in 2N NH_4OH and subsequent precipitation by addition of concentrated HCl up to pH 4.

40

After filtering and drying, 1.5 g of the product with melting point 173-175°C is obtained, the yield being 60% as calculated starting from 5-methylsuccinoylamino-2-mercapto-1,3,4-thiadiazole.

$^1\text{H-NMR}$ 300 MHz ($\text{DMSO}-d_6$): $\delta = 2,76$ (m, 4H, $-\text{CH}_2\text{CH}_2-$); 3,59 (s, 3H, OCH_3); 8,29 (s, 2H, SO_2NH_2)

$^{13}\text{C-NMR}$ ($\text{DMSO}-d_6$): 27,8 (C-9), 29,7 (C-8), 51,5 (CH_3), 161 (C-5), 164,2 (CSO_2NH_2), 171,7 (CONH), 172,8 (CO)

IR (KBr) : $\nu_{\text{max}} = 3320, 3220, 1718, 1700, 1360, 1355, 1160, 925 \text{ cm}^{-1}$

45

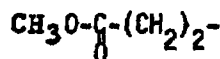
Analysis ($\text{C}_7\text{H}_{10}\text{NO}_5\text{S}_2$) calcd.: C, 28.56; H, 3.42; N, 19.04; found: C, 28.23; H, 3.45; N, 18.79; S, 21.45

EXAMPLE 2

5-methylsuccinoylamino-2-sulfonamido-1,3,4-thiadiazole (Rende 023)

50

Series I, Y =



SCHEME A, route steps (d), (a'), (b'), (c)

55

(d) Preparation of 5-amino-2-benzylmercapto-1,3,4-thiadiazole

10 g of 5-amino-2-benzylmercapto-1,3,4-thiadiazole is added to 300 ml of 95 % ethanol into which 1.7 g

of sodium had been dissolved. After dissolution of the product, 9 ml of benzyl bromide is added with stirring and at room temperature (molar ratio 1/1). Stirring is ended after 15 minutes, during which period the formation of a white precipitate is observed; the mixture is left standing overnight.

The mixture is then diluted with water and the solid matter is separated by filtration and washed with water.
 5 After crystallization from 95% ethanol, 10 g of the product with melting point 158-161°C is obtained, the yield being 60%.

(a') Preparation of 5-methylsuccinoylamino-2-benzylmercapto-1,3,4-thiadiazole

10 2.7 g (27 mmole) of Et₃N, 2.7 g (18 mmole) of succinoyl chloride monomethyl ester and 100 mg of 4-DMAP are successively added to 4 g of 5-amino-2-benzylmercapto-1,3,4-thiadiazole (18 mmole) suspended in 20 ml of anhydrous methyl chloride.

The reaction mixture is kept stirred under nitrogen and is checked by TLC (10 % methanol in chloroform); the reaction shows to be complete after 4 hours. The reaction mixture is then diluted with 2N HCl and extracted
 15 three times with CH₂Cl₂. The organic extracts are washed with water till neutral reaction and dried over Na₂SO₄.

The raw product obtained gives after crystallization from ethanol 4.2 g of the product with melting point 156-161 °C; yield = 70%.

¹ H-NMR 60 MHz (CDCl₃): δ=2.85 (dt, 4H, -CH₂CH₂-); 3.65 (s, 3H, OCH₃); 4.4 (s, 2H, CH₂benzyl); 7.6, 3 (s, 5H, aryl).

20 IR (CHCl₃): ν_{max} 3400, 3170, 2920, 1740, 1700 cm⁻¹

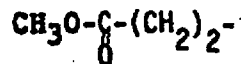
(b') and (c) Preparation of 5-methylsuccinoylamino-2-sulfonamido-1,3,4-thiadiazole (Rende 023)

The oxidation with gaseous chlorine and the subsequent formation of 5-methylsuccinoylamino-2-sulfonamid-1,3,4-thiadiazole are carried out like those performed in Example 1, steps (b) and (c).
 25

EXAMPLE 3

5-methylsuccinoylamino-2-sulfonamido-1,3,4-thiadiazole (Rende 023)

30 Series I, Y =



35

SCHEME A, route steps (a), (e), (b'), (c)

(a) Preparation of 5-methylsuccinoylamino-2-mercapto-1,3,4-thiadiazole

40 The preparation is carried out as disclosed in Example 1, step (a).

(e) Preparation of 5-methylsuccinoylamino-2-benzylmercapto-1,3,4-thiadiazole

45 4 g of 5-methylsuccinoylamino-2-mercapto-1,3,4-thiadiazole is added to 420 mg of sodium dissolved in 80 ml of 95 % ethanol. After dissolution of the product, 22 ml of benzyl bromide is added with stirring at room temperature. The reaction mixture is kept in such conditions for 15 minutes, during which time the formation of a white precipitate is observed. Stirring is then stopped and the mixture is kept reacting overnight. Then the same is diluted with water, filtered and washed with water. The solid product so obtained is purified through crystallization from ethanol so as to obtain 5.2 g of benzylate; yield = 86 %.

50

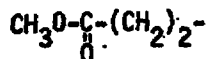
(b) and (c) Preparation of the 5-methylsuccinoylamino-2-sulfonamido-1,3,4-thiadiazole (Rende 023)

The process is carried out according to the steps (b') and (c) of the preceding Example.

55 EXAMPLE 4

5-methylsuccinoylamino-2-sulfonamido-1,3,4-thiadiazole (Rende 023)

Series I, Y =



SCHEME A, route steps (d), (a'), (e'), (b), (c) (d) and (a') Preparation of 5-methylsuccinoylamino-2-benzylmercapto-1,3,4-thiadiazole

5 The process is carried out according to steps (d) and (a') of Example 2.

(e') Debenzylation of 5-methylsuccinoylamino-2-benzylmercapto-1,3,4-thiadiazole

10 1 g of the benzylate dissolved in 100 ml of absolute EtOH is added to 7.5 g of sodium. The mixture is kept under reflux till complete dissolution of sodium. A further volume of 300 ml of ethanol is then added, and CO₂ is bubbled for 1-2 hours. Sodium carbonate so formed is filtered off and repeatedly washed with ethanol.

Washing and filtering waters are collected and then concentrated in vacuum under CO₂, and the residue is extracted three times with ethyl acetate.

15 After solvent removal, the raw product so obtained is crystallized from ethanol yielding 440 mg of 5-methylsuccinoylamino-2-mercapto-1,3,4-thiadiazole; yield = 70%.

(b) and (c) Preparation of 5-methylsuccinoylamino-2-sulfonamido-1,3,4-thiadiazole (Rende 023)

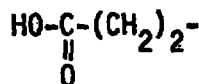
The process is carried out according to the steps (b) and (c) of Example 1.

20 EXAMPLE 5

5-succinoylamino-2-sulfonamido-1,3,4-thiadiazolic acid (Rende 037)

Series I, Y =

25



30 SCHEME A

Preparation of 5-methylsuccinoylamino-2-sulfonamid - 1,3,4-thiadiazole (Rende 023)

The preparation is carried out according to the procedures disclosed in any one of the preceding examples. Preparation of 5-succinoylamino-2-sulfonamido-1,3,4-thiadiazolic acid (Rende 037)

35 5 g of 5-methylsuccinoylamino-2-sulfonamido-1,3,4-thiadiazole is dissolved into 20 ml of 5N NaOH and kept standing for 2 hours at room temperature. The solution is acidified to pH 4 by adding concentrated HCl. The solid so formed is filtered off, washed with cold water and then dried. 3.3 g of the acid is obtained with melting point 196-198°C and yield of 70 %.

¹H-NMR 300 MHz (DMSO-d₆): δ= 2,68 (dt, 4H, -CH₂CH₂-); 8,3 (s, 2H, SO₂NH₂); 12,7 (s', 1H, OH)

¹³C-NMR (DMSO-d₆): 27,8(C-9), 2,95(C-8); 160,6(C-5); 163,7(CSO₂NH₂); 171(CONH); 172,9(CO)

40 IR (KBr): ν_{max} 3520, 3220, 1732, 1723, 1370, 1170 cm⁻¹

Elemental analysis (C₆H₈N₄O₅S₂) Calcd.: C, 25.7; H, 2.9, N, 19.98; S, 22.88; Found: C, 25.3; H, 3.15, N, 19.62; S, 22.50.

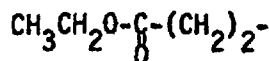
EXAMPLE 6

45

5-Ethylsuccinoylamino-2-sulfonamido-1,3,4-thiadiazole (Rende 029)

Series I, Y =

50



SCHEME A, route steps (d), (a'), (b'), (c)

Preparation of succinoyl chloride monoethyl ester (the acylating agent)

55 35 ml of absolute ethanol and a catalytic amount (0.05 ml) of concentrated sulfuric acid are added to 5 g of succinic anhydride. The reaction mixture is kept under reflux for 30 minutes, then it is stirred for 20 minutes at room temperature and again for 30 minutes by heating.

The excess ethanol is evaporated and the solution is diluted with water and then extracted with acetate.

The organic extracts are washed with brine, then dried over Na_2SO_4 so giving, after solvent evaporation an amount of 6.3 g of succinic acid monoethyl ester.

6.3 g of the acid is kept under reflux for 3 hours at 60°C with 4.7 ml of SOCl_2 (molar ratio 1:1.5).

The solution is distilled under reduced pressure (18 mm Hg) so obtaining 4.4 g of the product (boiling point $=93^\circ\text{C}$, 18 mm Hg).

(d) Preparation of 5-amino-2-benzylmercapto-1,3,4-thiadiazole

The process is carried out according to the step (d) of Example 2.

(a') Preparation of 5-ethylsuccinoylamino-2-benzylmercapto-1,3,4-thiadiazole

4.4 ml (30 mmole) of triethylamine, 3.3 g of succinoyl chloride monoethyl ester (20 mmole) and 100 mg of 4-dimethylaminopyridine are successively added to 4.5 g of 5-amino-2-benzylmercapto-1,3,4-thiadiazole (20 mmole) suspended in 10 ml of anhydrous methylene chloride. The reaction mixture is kept stirred under a nitrogen and a TLC is performed to follow the reaction course (5 % methanol in chloroform), said reaction showing to be complete in 6 hours. The mixture is then filtered, diluted with 0.2 N HCl and extracted three times with methylene chloride. The organic extracts are then collected, washed with water till neutrality and finally dried over anhydrous sodium sulfate. The raw product so obtained is purified by crystallization from ethanol so giving 4.9 g of the product with melting point $140-143^\circ\text{C}$ and yield of 70 %.

$^1\text{H-NMR}$ 60MHz (DCl_3): $\delta = 1,2$ (t, 3H, CH_3); 2,88 (m, 4H, $-\text{CH}_2\text{CH}_2-$); 4,1 (q, 2H, OCH_2); 4,5 (s, 2H, CH_2 benzyl); 7,34 (s, 5H, aryl)

IR (CHCl_3): ν_{max} 3165, 2920, 1735, 1700, 1555, 1310, 1160 cm^{-1}

(b') Preparation of 5-ethylsuccinoylamino-2-sulfonylchloride-1,3,4-thiadiazole

4 g of 5-ethylsuccinoylamino-2-benzylmercapto-1,3,4-thiadiazole is suspended in 70 ml of a 33 % water solution of acetic acid. The mixture is kept stirred at 10°C under chlorine for three hours and a half.

The solid chloride so formed is filtered off in vacuo and then washed with cold water and set aside to dry. 3.4 g of the raw product is thus obtained, and it is immediately employed for the next reaction.

(c) Preparation of 5-ethylsuccinoylamino-2-sulfonamide-1,3,4-thiadiazole (Rende 029)

3.4 g of 5-ethylsuccinoylamino-2-sulfonylchloride-1,3,4-thiadiazole is added at -78°C under nitrogen atmosphere to 80 ml of freshly condensed liquid ammonia. The reaction vessel is then placed in a water bath and ammonia is thus removed with a nitrogen stream.

The solid residue is purified by direct crystallization with 95 % ethanol (checks performed through TLC with 6% methanol in chloroform, RF about 0.4). 1.7 g of the product is obtained with melting point $192-197^\circ\text{C}$ and 50 % yield starting from 5-ethylsuccinoylamino-2-benzylmercapto-1,3,4-thiadiazole.

$^1\text{H-NMR}$ 300 MHz ($\text{DMSO}-d_6$): $\delta = 1,15$ (t, 3H, CH_3); 2,68 (t, 2H, CH_2); 2,79 (t, 2H, CH_2); 4,05 (q, 2H, OCH_2); 8,35 (s, 2H, SO_2NH_2)

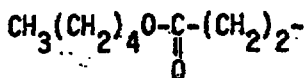
$^{13}\text{C-NMR}$ ($\text{DMSO}-d_6$): 14(CH_3); 28,1(C-9); 29,7(C-8); 60(C-11); 161(C-5); 164,2(CSO_2NH_2); 171,2(CONH); 171,8(C-10)

IR (KBr): ν_{max} 3330, 1720, 1555, 1340, 1170, 930 cm^{-1}

Elemental analysis ($\text{C}_8\text{H}_{12}\text{N}_4\text{O}_6\text{S}_2$) Calcd.: C, 31.16, H, 3.92, N, 18.07, S, 20.79; Found: C, 31.51, H, 4.1, N, 17.94, S, 20.44.

EXAMPLE 7

5-Pentylsuccinoylamino-2-sulfonamido-1,3,4-thiadiazole (Rende 032)
Series I, Y =



SCHEME A, route steps (d), (a'), (b'), (c)

Preparation of succinoyl chloride monopentyl ester (the acylating agent)

5.4 ml of 1-pentanol (molar ratio 1:1) and 0.1 ml of concentrated sulfuric acid are added to 5 g of succinic anhydride. The reaction mixture is kept under reflux at 70°C for 15 minutes, then it is stirred at room temperature for 15 minutes and it is heated again for 30 minutes.

The excess alcohol is evaporated in vacuo and the reaction mixture is then diluted with water and extracted with ethyl acetate. The organic extracts, after drying over anhydrous sodium sulfate and evaporation, yield 7.2 g of the succinic acid monopentyl ester.

The hemiester so obtained is chlorinated by treatment with 4.1 ml of SOCl_2 (molar ratio 1:1.5) under reflux at 70°C for 5 hours.

The chloride so formed is then distilled under reduced pressure and 6.7 of the chloride is collected.

(d) Preparation of 5-amino-2-benzylmercapto-1,3,4-thiadiazole

The preparation is carried out according to the step (d) of Example 2.

(a') Preparation of 5-pentylsuccinoylamino-2-benzylmercapto-1,3,4-thiadiazole

4.6 ml (34 mmole) of triethylamine, 4.6 ml of succinoyl chloride monopentyl ester and 150 mg of 4-DMAP are successively added to 5 g of 5-amino-2-benzylmercapto-1,3,4-thiadiazole (22 mmole) suspended in 30 ml of anhydrous CH_2Cl_2 .

The mixture is kept stirred at room temperature under inert gas atmosphere for 5 hours and the reaction is checked through TLC (6 % methanol in chloroform).

The reaction mixture is neutralized with 2N HCl and is extracted three times with methylene chloride; the organic extracts are washed with water and then they are dried over anhydrous sodium sulfate.

The raw product so obtained is purified by crystallization from ethanol so giving 5.3 g of the product with melting point 128-130°C and yield of 60 %.

$^1\text{H-NMR}$ 60MHz (CDCl_3): δ = 0,83 (t,3H, CH_3); 1,32 [m,6H,(CH_2)₃]; 2,84 (m,4H,- CH_2CH_2 -); 4,01 (t,2H, OCH_2); 4,35 (s,2H, CH_2 benzyl); 7,32 (s,5H,aryl)

IR (CHCl_3): ν_{max} 3160, 2925, 1730, 1700, 1505, 1300, 1160 cm^{-1}

(b') Preparation of 5-pentylsuccinoylamino-2-sulfonylchloride-1,3,4-thiadiazole

5 g of 5-pentylsuccinoylamino-2-benzylmercapto-1,3,4-thiadiazole is suspended in 80 ml of a 33 % water solution of acetic acid. The mixture is kept stirred at 0°C with a constant chlorine flow for 4 hours. The solid chloride so formed is filtered off, washed with cold water and then set aside to dry.

3.5 g of the sulfonyl chloride is so obtained, and it is immediately employed for preparing the sulfonamide.

(c) Preparation of 5-pentylsuccinoylamino-2-sulfonamido-1,3,4-thiadiazole (Rende 032)

3.5 g of 5-pentylsuccinoylamino-2-sulfonylchloride-1,3,4-thiadiazole is added at -78°C under nitrogen to 80 ml of freshly condensed liquid ammonia.

The ammonia is removed with a nitrogen stream by dipping the flask into a water bath, and the residue is purified through solubilization into 2N NH_4OH (pH 8) and then through precipitation of the product by adding concentrated HCl till reaching a pH 4. After filtration and drying, 2.2 g of the sulfonamide is obtained with melting point 201-203°C and 48 % yield starting from 5-pentylsuccinoyl amino-2-benzylmercapto-1,3,4-thiadiazole.

$^1\text{H-NMR}$ 300MHz (DMSO-d_6): δ = 0,80 (t,3H, CH_3); 1,2 (s,4H,(CH_2)₂pent); 1,55 (t,2H, $\text{OCH}_2\text{-CH}_2$); 2,75(dt,4H,- CH_2CH_2 -); 4,0 (t,2H, OCH_2); 8,4 (s,2H, SO_2NH_2)

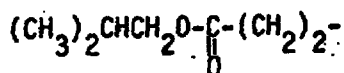
$^{13}\text{C-NMR}$ (DMSO-d_6): 13,7(CH_3), 21,7(C-14), 27,5(C-12), 28(C-9), 28,1(C-13), 29,8(C-8), 64(C-11), 161(C-5), 164,2(CSO_2NH_2), 171,2(CONH), 171,8(CO)

Elemental analysis ($\text{C}_{11}\text{H}_{18}\text{N}_4\text{O}_5\text{S}_2$) Calcd.: C, 37.7; H, 5.18; N, 15.99; S, 18.3; Found: C, 38.05; H, 5.27; N, 16.01; S, 18.10.

IR (KBr): ν_{max} 3340, 3240, 1720, 1710, 1550, 1365, 1165, 930 cm^{-1}

EXAMPLE 8**5-Isobutylsuccinoylamino-2-sulfonamido-1,3,4-thiadiazole (Rende 034)**

Series I, Y =



5 SCHEME A, route steps (d), (a'), (b'), (c)

Preparation of succinoyl chloride monoisobutyl ester (the acylating agent)

5.5 ml of isobutyl alcohol is added to 5 g of succinic anhydride (molar ratio 1:1.2) together with 0.05 ml of concentrated sulfuric acid.

10 The reaction mixture is kept under reflux at 60°C for 30 minutes and then it is stirred at room temperature for 20' and then again under reflux for a further time of 30 minutes. The excess alcohol is removed in vacuo and the mixture is diluted with water and extracted with ethyl acetate. The organic phase after drying over sodium sulfate gives 6.5 g of succinic acid monoisobutyl ester that is kept then under reflux with 4 ml of SOCl₂ at 60°C.

The mixture yields, after distillation under reduced pressure, 6-4 g of the product.

15

(d) Preparation of 5-amino-2-benzylmercapto-1,3,4-thiadiazole

The process is carried out according to the step (d) of Example 2

20

(a') Preparation of 5-isobutylsuccinoylamino-2-benzylmercapto-1,3,4-thiadiazole

2.9 ml (22 mmole) of Et₃N, 2.8 g (14 mmole) of succinoyl chloride monoisobutyl ester and 90 mg of 4-DMAP are successively added to 3.2 g (14 mmole) of 5-amino-2-benzylmercapto-1,3,4-thiadiazole suspended in 10 ml of anhydrous CH₂Cl₂.

25

The reaction mixture is kept under nitrogen and the reaction course is checked through TLC (6 % methanol in chloroform); the reaction shows complete in 5 hours.

The mixture is then neutralized with 0.1 N HCl (5 ml) and is extracted twice with 50 ml portions of CH₂Cl₂. The organic extracts are then washed with water and dried over sodium sulfate.

30

After crystallization from ethanol, 2.7 g of the product is obtained with melting point 133-136°C and 50 % yield.

¹H-NMR 60 MHz (CDCl₃): δ = 0,85 (d, 6H, CH₃); 1,9 (m, 1H, CH); 2,9 (m, 4H, -CH₂CH₂-); 3,8 (d, 2H, OCH₂); 4,35 (s, 2H, CH₂benzyl); 7,3 (s, 5H, aryl)

IR (CHCl₃): ν_{max} 3400, 3160, 2940, 1730, 1700, 1555, 1305, 1160 cm⁻¹

35

(b') Preparation of 5-isobutylsuccinoylamino-2-sulfonylchloride-1,3,4-thiadiazole

2 g of 5-isobutylsuccinoylamino-2-benzylmercapto-1,3,4-thiadiazole suspended in 20 ml of a 33% water solution of acetic acid is kept stirred at 0°C under chlorine for 3 hours.

40

The sulfonyl chloride product so formed is then filtered off, washed with water and set aside to dry in vacuo. 1.74 g of the product is thus obtained which is employed for the next reaction.

(c) Preparation of 5-isobutylsuccinoylamino-2-sulfonamide-1,3,4-thiadiazole (Rende 034)

45

1.74 g of 5-isobutylsuccinoylamino-2-sulfonylchloride 1,3,4-thiadiazole is slowly added under nitrogen to 35ml of freshly condensed liquid ammonia at -78°C.

When the addition has been completed, the ammonia is removed keeping the reaction flask at room temperature and keeping the nitrogen flow. The raw product so obtained is purified by solubilization in 2N NH₄OH at pH 8.5 and subsequent precipitation of sulfonamide by addition of concentrated HCl till reaching pH 4.

50

After filtration and drying, 1.5 g of the product is obtained with melting point 201-203°C and 85 % yield starting from the benzylated compound.

¹H-NMR (300MHz) (DMSO-d₆): δ = 0,85 (d, 6H, CH₃); 1,85 (m, 1H, CH); 2,7 (t, 2H, CH₂); 2,82 (t, 2H, CH₂); 3,81 (d, 2H, OCH₂)

¹³C (DMSO-d₆): 18,7(2CH₃); 27,1(C-12); 28,1(C-9); 29,8(C-8); 69,8(C-11), 161(C-5); 164,2(CSO₂NH₂); 171,2(CONH); 171,7(CO)

55

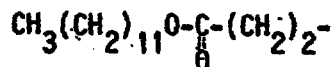
Elemental analysis (C₁₀H₁₆N₄O₅S₂) Calcd.: C, 35.7; H, 4.79; N, 16.65; S, 19.06; Found: C, 35.84; H, 4.86; N, 16.80; S, 18.98.

Ir (KBr): ν_{max} 3315, 3225, 2980, 1740, 1700, 1555, 1370, 1175, 920 cm⁻¹

EXAMPLE 9

5-Dodecylsuccinoylamino-2-sulfonamido-1,3,4-thiadiazole (Rende 033)
Series I, Y =

5



10 SCHEME A, route steps, (d), (a'), (b'), (c)

Preparation of succinoyl chloride monododecyl ester (the acylating agent)

11.2 ml of 1-dodecyl alcohol is added to 5 g of succinic anhydride (molar ratio 1:1) together with 0.05 ml of concentrated sulfuric acid. The reaction mixture is kept under reflux at 70°C for 15 minutes, then it is stirred at room temperature for 15 minutes and again heated for 30 minutes.

15 The excess alcohol is removed by evaporation in vacuum and the mixture is diluted with water and extracted with ethyl acetate.

The organic extracts, after drying over anhydrous sodium sulfate and removal of the solvent through evaporation, yield 9.7 g of the succinic acid monododecyl ester.

20 The monoester product so obtained is then reacted with 3.7 ml of SOCl_2 (molar ratio 1:1.5) under reflux at 65°C for 4 hours.

The excess unreacted SOCl_2 is removed by distillation from the solution so obtained under reduced pressure, and the amount of 8.2 g of the residue is made up of the solid succinoyl chloride monododecyl ester with melting point 104-106°C; the yield of the whole process is 54 %.

25 (d) Preparation of 5-aminobenzylmercapto-1,3,4-thiadiazole

The process is carried out according to the step (d) of Example 2.

(a') Preparation of 5-dodecylsuccinoylamino-2-benzylmercapto-1,3,4-thiadiazole

30

3.4 ml (25 mmole) of Et_3N , 5 g (16 mmole) of succinoyl chloride monododecyl ester and 80 mg of 4-DMAP are successively added to 3.7 g (16 mmole) of 5-amino-2-benzylmercapto-1,3,4-thiadiazole suspended in 25 ml of anhydrous methylene chloride.

35 The mixture is kept stirred under nitrogen atmosphere and the reaction course is checked through TLC (5 % methanol in chloroform) and the reaction shows to be complete in 6 hours.

The reaction mixture is neutralized with 2 N HCl and extracted twice with CH_2Cl_2 . The organic extracts are then washed with water and dried over anhydrous sodium sulfate.

The raw product so obtained, after crystallization from ethanol, gives 4.4 g of the product with melting point 130-133°C, and 55 % yield.

40 $^1\text{H-NMR}$ 60MHz (CDCl_3): δ = 0.85 (t, 3H, CH_3); 1.3 (s, 20H, $(\text{CH}_2)_{10}$); 2.9 (m, 4H, $-\text{CH}_2\text{CH}_2-$); 4.1 (t, 2H, OCH_2); 4.35 (s, 2H, CH_2 benzyl); 7.25 (s, 5H, aryl)

IR (CHCl_3): ν_{max} 3400, 3165, 2920, 1732, 1700 cm^{-1}

(b') Preparation of 5-dodecylsuccinoylamino-2-sulfonylchloride-1,3,4-thiadiazole

45

Chlorine is bubbled through a suspension of 4 g of 5-dodecylsuccinoylamino-2-benzylmercapto-1,3,4-thiadiazole in 40 ml of a 33 % acetic acid solution, while the mixture is kept stirred at 5°C for 2 hours.

The solid sulfonyl chloride is filtered off, washed with ice-cold water and then dried in vacuo.

3.5 g of the product is obtained which is immediately employed for preparing sulfonamide.

50

(c) Preparation of 5-dodecylsuccinoylamino-2-sulfonamido-1,3,4-thiadiazole (Rende 033).

3.5 g of 5-dodecylsuccinoylamino-2-sulfonylchloride-1,3,4-thiadiazole is slowly added under nitrogen atmosphere to 60 ml of freshly condensed liquid NH_3 .

55 When the addition is complete, ammonia is removed by leaving the reaction vessel at room temperature and bubbling through the mixture a stream of nitrogen, and the raw product is checked through TLC (8 % methanol in chloroform). Sulfonamide is directly crystallized from ethanol, so yielding 2.5 g of a product with melting point 184-186°C and 70 % yield starting from 5-dodecylsuccinoylamino-2-benzylmercapto-1,3,4-thia-

diazole.

$^1\text{H-NMR}$ 300MHz (DMSO- d_6): δ = 0,85 (t,3H,CH₃); 1,25 (m,20H,(CH₂)₁₀); 2,65 (t,2H,-CH₂CO); 2,8 (t,2H,-COCH₂); 4,0 (t,2H,OCH₂); 8,32 (s',2H,SO₂NH₂)

$^{13}\text{C-NMR}$ (DMSO- d_6): 13,3(CH₃); 28,1(C-9); 29,8(C-8); 64(C-11); 161(C-5), 164,2(CSO₂NH₂); 171,2(CONH); 171,8(CO)

Analysis (C₁₈H₃₂N₄O₆S₂) calcd.: C, 48.19; H, 7.19; N, 12.49; S, 14.29; found: C, 49.07; H, 7.6; N, 12.02; S, 15.67.

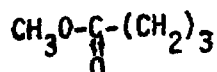
IR (KBr): ν_{max} 3325, 3240, 2920, 1740, 1720, 1470, 1175, 940 cm⁻¹

10 EXAMPLE 10

5-Methylglutaroylamino-2-sulfonamido-1,3,4-thiadiazole (Rende 030)

Series I, Y =

15



20

SCHEME A, route steps (d), (a'), (b'), (c)

(d) Preparation of 5-amino 2-benzylmercapto-1,3,4-thiadiazole

25

The process is carried out according to step (d) of Example 2.

(a') Preparation of 5-methylglutaroylamino-2-benzylmercapto-1,3,4-thiadiazole

30

1.9 ml (13 mmole) of Et₃N, 1.26 ml (9 mmole) of glutaroyl chloride monomethyl ester and 100 mg of 4-DMAP are successively added to 2 g (9 mmole) of 5-amino-2-benzylmercapto-1,3,4-thiadiazole suspended in 12 ml of anhydrous CH₂Cl₂. The mixture is kept stirred at room temperature under an inert.

The reaction is checked through TLC (6 % methanol in chloroform) and it shows complete within 2 hours. The reaction mixture is then neutralized with 2N HCl and extracted twice with CH₂Cl₂; the organic extracts are then washed with water and dried over anhydrous sodium sulfate.

35

The raw product so obtained is purified through crystallization from ethanol so yielding 3.02 g of the product with melting point 121-123°C and 96 % yield.

$^1\text{H-NMR}$ 60MHz (CDCl₃): δ = 1,9 (m,2H,-CH₂-); 2,5 (m,4H,(CH₂)₂); 3,5 (s,3H,OCH₃); 4,3 (s,2H,CH₂benzyl); 7,3 (s,5H,aryl)

IR (CHCl₃): ν_{max} 3400, 3160, 2950, 1735, 1700, 1555, 1300 cm⁻¹

40

(b') Preparation of 5-methylglutaroylamino-2-sulfonylchloride-1,3,4-thiadiazole

3 g of 5-methylglutaroylamino-2-benzylmercapto-1,3,4-thiadiazole is suspended in 50 ml of a 33 % water solution of acetic acid, and the mixture is kept stirred at 0°C with bubbling a constant stream of chlorine.

45

The disappearance of the starting product is checked through TLC (4 % methanol in chloroform) and it is shown complete within 2 hours.

The chloride so formed is filtered off, washed with cold water and dried in vacuo.

2.4 g of sulfonyl chloride is obtained which is immediately employed for the preparation of sulfonamide.

50

(c) Preparation of 5-methylglutaroylamino-2-sulfonamido 1,3,4-thiadiazole (Rende 030)

2.4 g of sulfonyl chloride is slowly added under nitrogen atmosphere into 50 ml of freshly condensed liquid ammonia, at -78°C. When the addition is complete, ammonia is removed by leaving the reaction flask at room temperature, and the residue is dried in vacuo.

55

The raw sulfonamide is purified through dissolution in 2N NH₄OH at pH 8, and successive precipitation by addition of conc. HCl till pH 4.

After filtering and drying, 1.85 g of sulfonamide is obtained with melting point 181-184°C and 70 % yield starting from benzylthiol.

¹H-NMR 300MHz (DMSO-d₆): δ = 1,85 (m,2H,CH₂-); 2,4 (t,2H,CH₂); 2,55 (t,2H,CH₂); 3,6 (s,3H,OCH₃); 8,3 (s,2H,SO₂NH₂)

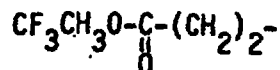
¹³C-NMR (DMSO-D₆): 19,6(C-9); 32,3(C-10); 33,7(C-8); 51,2(C-12); 161(C-5); 164,2(CSO₂NH₂); 171,6(CONH); 172,8(CO)

Analysis (C₈H₁₂N₄O₅S₂) calcd. C, 31.16; H, 3.92; N, 18.07; S, 20.79; Found: C, 31.36; H, 3.99; N, 18.43; S, 20.51.

IR (KBr): ν_{max} 3400, 3145, 2920, 1735, 1680, 1380, 1300, 1170 cm⁻¹

EXAMPLE 11

5-Trifluoroethylsuccinoylamino-sulfonamido-1,3,4-thiadiazole (Rende 039)
Series I, Y =



SCHEME A, route steps (d), (a'), (b'), (c)

Preparation of succinoyl chloride monotrifluoroethyl ester (the acylating agent)

3.59 ml of CF₃CH₂OH and 0.05 ml of conc. sulfuric acid are added to 5 g of succinic anhydride.

The reaction mixture is kept under reflux at 70°C for 30 minutes, then for 20 minutes under stirring at room temperature, and again heated for 30 minutes.

The excess alcohol is evaporated and the solution is diluted with water and extracted with acetate.

The organic extracts are then washed with brine, and then dried over sodium sulfate so giving, after evaporation of the solvent, 7.3 g of the succinic acid monotrifluoroethyl ester.

7.3 g of the acid is then treated under reflux for 5 hours at 70°C with 4 ml of SOCl₂ (molar ratio 1/1.5).

The solution is distilled under reduced pressure so giving 5.5 g of the product.

(d) Preparation of 5-amino-2-benzylmercapto-1,3,4-thiadiazole

The process is carried out according to step (d) of Example 2.

(a') Preparation of 5-trifluoromethylsuccinoylamino-2-benzylmercapto-1,3,4-thiadiazole

5.26 ml (38 mmole) of triethylamine, 5.5 g of succinoyl chloride monotrifluoroethyl ester (25 mmole) and 120 mg of 4-DMAP are successively added to 5.6 g of 5-amino-2-benzylmercapto-1,3,4-thiadiazole (25 mmole) suspended in 37 ml of anhydrous CH₂Cl₂.

The reaction mixture is kept stirred under nitrogen atmosphere and the reaction course is checked through TLC (5 % methanol in chloroform), the reaction being complete within 4 hours.

The reaction mixture is filtered, then diluted with 0.2 N HCl and extracted three times with methylene chloride. The organic extracts are then collected together and washed with water, and then they are dried over anhydrous sodium sulfate. The raw product so obtained is purified through crystallization from ethanol so giving 7.46 g of the product with melting point 169-173°C and 73 % yield.

¹H-NMR 80 MHz (DMSO-d₆): δ = 2,6 (s,4H,-CH₂CH₂-); 4,4 (s,2H,CH₂benzyl); 4,7 (q,2H,OCH₂); 7,4(s,5H,aryl)

IR (CHCl₃): ν_{max} 3160, 2950, 1730, 1710, 1300, 1150 cm⁻¹

(b') Preparation of 5-trifluoroethylsuccinoylamino-2-sulfonylchloride-1,3,4-thiadiazole

5 g of 5-trifluoroethylsuccinoylamino-2-benzylmercapto-1,3,4-thiadiazole is suspended in 70 ml of a 33 % acetic acid water solution. The mixture is kept stirred at 5°C under chlorine atmosphere for 4 hours. The solid chloride so formed is filtered in vacuo, washed with cold water and dried. 2.6 g of the raw product is obtained which is immediately employed for the subsequent reaction.

(c) Preparation of 5-trifluoroethylsuccinoylamino-2-sulfonamido-1,3,4-thiadiazole (Rende 039)

2.6 g of 5-trifluoroethylsuccinoylamino-2-sulfonylchloride-1,3,4-thiadiazole is added to 60 ml of freshly condensed liquid ammonia at -78°C under nitrogen atmosphere. When the addition is complete, ammonia is

removed with a nitrogen stream while the reaction vessel is kept within a water bath.

The residue so obtained is not identified as the compound shows to be very unstable and becomes very easily hydrolysed.

5 EXAMPLE 12

5-(5-Aminovaleroylamino)-2-sulfonamido-1,3,4-thiadiazole (Rende 027)

Series I, Y = NH₂(CH₂)₄-

SCHEME B

10

(c) Preparation of 5-chlorovaleroylamino-2-benzylmercapto-1,3,4-thiadiazole

1.5 ml (13 mmole) of Et₃N, 1.38 g of 5-chlorovaleryl chloride and 80 ml of 4-DMAP are successively added to 2 g of 5-amino-2-benzylmercapto-1,3,4-thiadiazole (8.9 mmole) suspended in 5 ml of anhydrous methylene chloride at room temperature with stirring and under nitrogen atmosphere. The reaction is checked by TLC (10 % methanol in chloroform) and it is complete after 3 hours. The solid product so formed is filtered, washed with water and purified by crystallization from ethanol. 2.7 g of 5-chlorovaleroylamino-2-benzylmercapto-1,3,4-thiadiazole is obtained with melting point 145-148°C and 90 % yield.

¹H-NMR 60MHz (CDCl₃): δ = 1,9 (m, 4H, -CH₂CH₂-); 2,78 (t, 2H, CH₂CO); 3,69 (t, 2H, CH₂Cl); 4,5 (s, 2H, CH₂benzyl); 7,36 (s, 5H, aryl).

IR (CDCl₃): ν_{max} 3.160, 1700, 1555, 1305 cm⁻¹

(b) and (c) Preparation of 5-(5-aminovaleroylamino)-2-sulfonamide-1,3,4-thiadiazole (Rende 027)

25 The preparation of 5-(5-aminovaleroylamino)-2-sulfonamide-1,3,4-thiadiazole is performed starting from 2 g of 5-chlorovaleroylamino-2-benzylmercapto-1,3,4-thiadiazole and it follows the synthesis route already disclosed in example 1 through the formation, with chlorine in acid medium, of the corresponding sulfonyl chloride and subsequent reaction with liquid ammonia. The raw product so obtained is crystallized directly from 95 % ethanol so yielding 750 mg of the product with melting point 209-212°C and 45 % yield.

30 ¹H-NMR 80MHz (DMSO-d₆) δ = 1,7 (m, 4H, -CH₂CH₂-); 2,5 (t, 2H, -CH₂CO); 3,6 (t, 2H, CH₂NH₂); 8,3 (s, 2H, SO₂NH₂).

IR (KBr): ν_{max} 3360, 3200, 3100, 1690, 1565, 1380, 1175, 910 cm⁻¹

Analysis (C₇H₁₃N₅O₃S₂) Calcd.: C, 30.09; H, 4.69; N, 25.07; S, 22.96; Found: C, 29.74; H, 4.29; N, 22.17; S, 21.90.

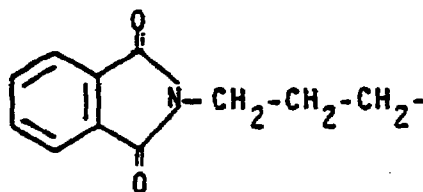
35

EXAMPLE 13

5-Phthalimidobutyrylamino-2-sulfonamido-1,3,4-thiadiazole (Rende 031)

Series I Y =

40



45

SCHEME C, route steps (i), (e), (a), (b), (c)

50

(i) Preparation of gamma-phthalimidobutyric acid

2g of gamma-aminobutyric acid is reacted with an equimolar amount (2.87 g) of phthalic anhydride by dry melting at 150°C. The reaction product is crystallized from ethanol/water (1/2) so yielding 4 g of gamma-phthalimidobutyric acid with melting point 120-123°C and 88 % yield.

55

(l) Preparation of 5-phthalimidobutyryl chloride

1 g of gamma-phthalimidobutyric acid is reacted with 0.45 ml of thionyl chloride (1/1.5 molar ratio) at 70°C for 5 hours. The excess thionyl chloride is then removed in vacuo and the residue is purified by crystallization from xylene/petroleum ether 30-50°C (1/2 ratio). 950 mg of phthalimidobutyryl chloride is obtained with 77 % yield.

(a) Preparation of 5-phthalimidobutyrylamino-2-benzylmercapto-1,3,4-thiadiazole

0.8 ml (5.7 mmole) of triethylamine, 950 mg (3.8 mmole) of 5-phthalimidobutyryl chloride and 100 mg of 4-DMAP are added under nitrogen atmosphere to 845 mg (3.8 mmole) of 5-amino-2-benzylmercapto-1,3,4-thiadiazole suspended in 10 ml of CH₂Cl₂.

The reaction mixture is neutralized with 0.1 N HCl after 3 hours and then it is extracted with CH₂Cl₂. The organic extracts are then washed with water and dried over sodium sulfate. After removal of the solvent, the raw product is crystallized from ethanol so yielding 660 mg of 5-phthalimidobutyrylamino-2-benzylmercapto-1,3,4-thiadiazole with melting point 128-131°C and 40 % yield. 420 mg of 5-amino-2-benzylmercapto-1,3,4-thiadiazole (50 %) is recovered from crystallization waters.

¹H-NMR (80 MHz) (CDCl₃): δ = 2,25 (m, 2H, CH₂); 2,7 (t, 2H, CH₂CO); 4,18 (t, 2H, NCH₂); 4,5 (s, 2H, CH₂benzyl); 7,3 (d, 5H, aryl); 7,8 (m, 4H, phthalimide)

(b) Preparation of 5-phthalimidobutyrylamino-2-sulfonylchloride-1,3,4-thiadiazole

A suspension of 600 mg of 5-phthalimidobutyrylamino-2-benzylmercapto-1,3,4-thiadiazole in 12 ml of acetic acid (33 % water solution) is kept at 0°C under chlorine atmosphere for 3 hours. During that period changes are observed in the appearance of the solid; the excess chlorine present in the reaction medium is then removed and the solid is filtered off and washed with cold water. 550 mg of raw sulfonyl chloride is obtained which is employed for the next reaction.

(c) Preparation of 5-phthalimidobutyrylamino-2-sulfonamido-1,3,4-thiadiazole (Rende 031)

550 mg of sulfonyl chloride is added slowly and under nitrogen atmosphere into 20 ml of freshly condensed liquid ammonia at -78°C. When the addition is complete, ammonia is removed putting the reaction flask into a water bath at room temperature.

The raw sulfonamide so obtained is purified through dissolution of the residue in 2N NH₄OH and subsequent acidification to pH 4 by addition of conc. HCl until reaching pH 4.

After filtering and drying the precipitate, 100 mg of the product is obtained with melting point 226-229°C and 31 % yield starting from the corresponding benzyl compound.

¹H-NMR 300 MHz (DMSO-d₆): δ = 2,2 (q, 2H, CH₂); 2,7 (t, 2H, CH₂CO); 4,1 (t, 2H, NCH₂); 7,8 (m, 4H, phthalim); 8,4 (s, 2H, SO₂NH₂)

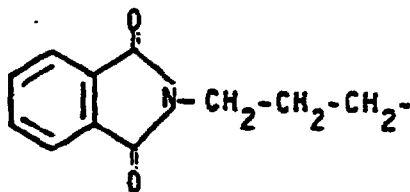
IR (KBr): ν_{max} 3250, 2930, 1690, 1360, 1170 cm⁻¹

Analysis (C₁₄H₁₃N₅O₆S₂) Calcd.: C, 42.52; H, 3.31; N, 17.71; S, 16.22; Found: C, 42.75; H, 3.47; N, 18.98; S, 17.51.

EXAMPLE 14

5-Phthalimidobutyrylamino-2-sulfonamido-1,3,4-thiadiazole (Rende 031)

Series I Y =



SCHEME C, route steps (m), (l), (a), (b), (c) (m) Preparation of gamma-phthalimidobutyric acid

3 g of 4-chlorobutyric acid is reacted with 4.5 g (molar ratio 1/1) of potassium phthalimide in 60 ml of DMF with stirring and at room temperature.

The reaction mixture is then treated after 2 hours by adding water and filtering the precipitate so formed. After crystallization from ethanol, 4.6 g of phthalimido butyric acid is obtained with 80 % yield.

- 5 (l), (a), (b) and (c) Preparation of 5-phthalimidobutyroylamino-2-sulfonamido-1,3,4-thiadiazole (Rende 031)
The same steps are followed that correspond to those of the preceding example.

EXAMPLE 15

- 10 5-Methylsuccinoylamino-4-methyl-2-sulfonamido-1,3,4-thiadiazole (Rende 024)

Series III, Y =



SCHEME D, route steps (n), (b'), (c')

- 20 (n) Methylation reaction of 5-methylsuccinoylamino-2-benzylmercapto-1,3,4-thiadiazole

600 mg (13 mmole) of a 50 % sodium hydride oil suspension is added to 3 g (9 mmole) of 5-methylsuccinoylamino-2)benzylmercapto-1,3,4-thiadiazole (obtained according to the Example 2, steps (d) and (d'), or
25 according to the Example 3, steps (a) and (e)) dissolved into 90 ml of anhydrous THF.

8 ml of CH_3I (molar ratio 10/1) is slowly added to the mixture with stirring under nitrogen while checking the reaction through TLC(5 % methanol in chloroform).

The reaction mixture is neutralized with 2N HCl after 3 hours and then extracted three times with ether; the organic phase is washed with water and dried. The raw product is made up of a mixture which is purified
30 through silica gel column chromatography eluting with ethyl acetate/petroleum ether 40/60.

1.86 g of 5-methylsuccinoylamino-4-methyl-2-benzylmercapto-1,3,4-thiadiazole (A) is obtained from such separation, with melting point 76-78°C (60 % yield) and 800 mg of 5-methylsuccinoyl-N-methylamino-2-benzylmercapto-1,3,4-thiadiazole (B) (26 % yield).

(A) $^1\text{H-NMR}$ 60 MHz (CDCl_3): δ = 2,8 (dt,4H,- CH_2CH_2 -); 3,6 (s,3H, OCH_3); 3,8 (s,3H, CH_3); 4,3
35 (s,2H, CH_2benzyl) 7,2 (s,5H,aryl)

IR (CHCl_3): ν_{max} 2960, 1740, 1620 cm^{-1}

(B) $^1\text{H-NMR}$ 60 MHz (CDCl_3): δ = 2,8 (dt,4H,- CH_2CH_2 -);3,63 (s,3H, OCH_3); 3,7 (s,3H, CH_3); 4,4
(s,2H, CH_2benzyl) 7,25 (s,5H,aryl)

IR (CHCl_3): ν_{max} 2970, 1735, 1675, 1410 cm^{-1}

- 40 (b') Preparation of 5-methylsuccinoylamino-4-methyl-2-sulfonylchloride-1,3,4-thiadiazole

Chlorine is bubbled through a suspension of 1 g of 5-methylsuccinoylamino-4-methyl-2-benzylmercapto-1,3,4-thiadiazole in 15 ml of a 33 % acetic acid water solution while the mixture is kept under stirring at 0°C.

45 The reaction is checked through TLC (40 % acetate in petroleum ether) and it is shown to be complete within 2 hours. The chloride so formed is extracted with methylene chloride, the organic phase is washed at 0°C with a NaHCO_3 saturated solution and next with water until it is neutral and finally dried over sodium sulfate. 920 mg of the product is obtained which is immediately employed for the subsequent reaction.

As already discussed in the preceding disclosure, a particular care is to be taken in checking the temperature during preparation, because of the instability of sulfonyl chloride in compounds of the series II and III.

- 50 (c') Preparation of 5-methylsuccinoylamino-4-methyl-2-sulfonamido-1,3,4-thiadiazole (Rende 024)

900 mg of 5-methylsuccinoylamino-4-methyl-2-sulfonylchloride-1,3,4-thiadiazole dissolved in 5 ml of
55 anhydrous THF is slowly added under nitrogen to 25 ml of freshly condensed liquid ammonia at -78°C. Ammonia is removed by leaving the reaction vessel at room temperature. The residue is purified by dissolution into 2N NH_4OH and filtration of the insoluble residue.

Waters are acidified with conc. HCl up to pH 4 and the precipitate so formed yields 320 mg of 5-methyl-

succinoylamino-4-methyl-2-sulfonamido-1,3,4-thiadiazole, melting point 135-137°C; yield = 38%.

$^1\text{H-NMR}$ 300 MHz (DMSO- d_6): δ = 2,62 (t, 2H, CH_2); 2,81 (t, 2H, CH_2); 3,6 (s, 3H, OCH_3); 3,97 (s, 3H, CH_3); 8,23 (s', 2H, SO_2NH_2)

IR (KBr): ν_{max} 3318, 3220, 3120, 1715, 1642, 1330, 1180 cm^{-1}

$^{13}\text{C-NMR}$ (DMSO- d_6): 28,7(C-9) 33,7(C-8) 38,1(NCH_3) 51,2(C-11) 157,6(C-5) 164,2(CSO_2NH_2) 172,7(CO) 180,9(CONH)

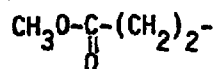
Analysis ($\text{C}_8\text{H}_{12}\text{N}_4\text{O}_5\text{S}_2$) Calc.: C, 31.16; H, 3.92; N, 18.07; S, 20.79; Found: C, 31.70; H, 3.86; N, 18.09; S, 20.55.

10 EXAMPLE 16

5-Methylsuccinoyl-N-methylamino-2-sulfonamido-1,3,4-thiadiazole (Rende 026)

Series II, Y =

15



SCHEME D, route steps (n), (b), (c)

20

(n) Methylation reaction of 5-methylsuccinoylamino-2-benzylmercapto-1,3,4-thiadiazole

The procedure is the same as that followed in the preceding example.

25

(b) Preparation of 5-methylsuccinoyl-N-methylamino-2-sulfonylchloride-1,3,4-thiadiazole

Chlorine gas is bubbled through a suspension of 800 mg of 5-methylsuccinoyl-N-methylamino-2-benzylmercapto-1,3,4-thiadiazole in 10 ml of a 33 % acetic acid water solution, while the mixture is kept stirred at 0°C.

30

The reaction is stopped after 3 hours and the reaction mixture is treated by methylene chloride extraction. The organic extracts are then washed with a NaHCO_3 saturated solution at 0°C and then with water up to neutrality and finally dried over anhydrous sodium sulfate.

670 mg of an oily compound is obtained which is employed in the raw state for the formation of the corresponding sulfonamide.

35

(c) Preparation of 5-methylsuccinoyl-N-methylamino-2-sulfonamido-1,3,4-thiadiazole (Rende 026)

670 mg of 5-methylsuccinoyl-N-methylamino-2-sulfonylchloride-1,3,4-thiadiazole, dissolved into 3 ml of anhydrous THF, is slowly added into 25 ml of freshly condensed liquid ammonia at -78°C under nitrogen.

40

When the addition has been completed, ammonia is removed by putting the reaction vessel into a water bath at room temperature, and the residue is dissolved into 2N NH_3 at pH 8 and next precipitated by addition of conc. HCl up to pH 4.

The precipitate so formed is filtered and dried so that 250 mg of the product is obtained, with melting point 120-124°C and 35 % yield starting from 5-methylsuccinoyl-N-methylamino-2-benzylmercapto-1,3,4-thiadiazole

45

$^1\text{H-NMR}$ (80 MHz (DMSO - d_6): δ = 2,8 (dt, 4H, $-\text{CH}_2\text{CH}_2-$); 3,6 (s, 3H, OCH_3); 3,72 (s, 3H, CH_3); 8,2 (s', 2H, SO_2NH_2)

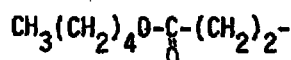
IR (KBr): ν_{max} 3300, 3250, 1750, 1660, 1350, 1175 cm^{-1}

EXAMPLE 17

50

5-Pentylsuccinoylamino-4-methyl-2-sulfonamido-1,3,4-thiadiazole (Rende 035)

Series III, Y =



55

SCHEME d, route steps (n), (b'), (c')

(n) Methylation reaction of 5-pentylsuccinoylamino-2-benzylmercapto-1,3,4-thiadiazole

500 mg (10,5 mmole) of a 50 % sodium iodide oil suspension is added to 3 g (7.8 mmole) of 5-pentylsuccinoyl amino-2-benzylmercapto-1,3,4-thiadiazole (obtained for example according to the Example 4, steps (d) and (a')), dissolved into 100 ml of anhydrous THF.

10 ml of CH_3I is slowly added to the mixture (molar ratio 10/1) with stirring under nitrogen (check performed through TCL, 2 % acetone in chloroform).

The reaction is shown to be complete in 3 hours. The reaction mixture is then diluted with 200 ml of acetate and washed first with acidified water and then with water up to neutrality; the organic extracts are then dried and the raw product is purified through silica gel column chromatography.

1.94 g of 5-pentylsuccinoylamino-4-methyl-2-benzylmercapto-1,3,4-thiadiazole (A) is obtained from such separation with 62 % yield, as well as 870 mg of 5-pentylsuccinoyl-N-methylamino-2-benzylmercapto-1,3,4-thiadiazole (B) with 27 % yield.

(A) $^1\text{H-NMR}$ 60MHz (CDCl_3): $\delta = 0,85$ (t,3H, CH_3), 1,4 (m,6H,(CH_2)₃); 2,8 (m,4H,- CH_2CH_2 -); 3,85 (s,3H, CH_3); 4,1 (t,2H, OCH_2); 4,3 (s,2H, CH_2 benzyl); 7,3 (s,5H,aryl)

IR (CHCl_3): ν_{max} 2925, 1730, 1620, 1380, 975 cm^{-1}

(B) $^1\text{H-NMR}$ 60MHz (CDCl_3): $\delta = 0,9$ (t,3H, CH_3), 1,4 (m,6H,(CH_2)₃); 2,85 (m,4H,- CH_2CH_2 -); 3,79 (s,3H, CH_3); 4,2 (t,2H, OCH_2); 4,5 (s,2H, CH_2 benzyl); 7,35 (s,5H,aryl)

IR (CHCl_3): ν_{max} 2925, 1730, 1670, 1310, 1115 cm^{-1}

(b') Preparation of 5-pentylsuccinoylamino-4-methyl-2-sulfonylchloride-1,3,4-thiadiazole

Chlorine is bubbled through a suspension of 1.94 g of 5-methylsuccinoylamino-4-methyl-2-benzylmercapto-1,3,4-thiadiazole in 30 ml of a 33 % acetic acid water solution, while the mixture is kept stirred at 0°C.

The disappearance of the starting product is controlled through TLC (5 % methanol in chloroform) and it shows complete within 2 hours.

The chloride so formed is extracted by means of CH_2Cl_2 , the organic phase is washed at 0°C with a saturated solution of NaHCO_3 , then with water up to neutrality and finally it is dried over anhydrous sodium sulfate.

The cold evaporation of the organic solvent yields 1.7 g of the product which is immediately employed for the next reaction.

(c') Preparation of 5-pentylsuccinoylamino-4-methyl-2-sulfonamido-1,3,4-thiadiazole (Rende 035)

1.7 g of 5-pentylsuccinoylamino-4-methyl-2-sulfonyl-chloride-1,3,4-thiadiazole dissolved into 6 ml of anhydrous THF is slowly added to 40 ml of freshly condensed liquid ammonia at -78°C and under nitrogen atmosphere. When the addition has been completed, ammonia is removed by dipping the reaction flask into a water bath. The residue is dissolved with a 2N NH_4OH water solution and then acidified to pH 4 with conc. HCl.

An oily product is separated that is extracted twice with ethyl acetate. The organic extracts are then collected together, washed with brine, dried over anhydrous sodium sulfate and the solvent is evaporated off. Purification of the raw sulfonamide is performed by means of silica gel column chromatography, eluting with 5 % methanol in chloroform. 1.12 g of the product is obtained with melting point 95-97°C and 64 % yield starting from the benzyl product.

$^1\text{H-NMR}$ 300 MHz (DMSO-d_6): $\delta = 0,85$ (t,3H, CH_3); 1,27 (m,4H,- CH_2CH_2 -); 1,55 (m,2H, CH_2); 2,65 (t,2H, CH_2CO); 2,82 (t,2H, COCH_2); 3,92 (s,3H, CH_3); 4,0 (t,2H, OCH_2); 8,26 (s,2H, SO_2NH_2)

$^{13}\text{C-NMR}$ (DMSO-d_6): 13,7(CH_3); 21,6(C-14); 27,4(C-12); 27,7(C-13); 29,1(C-9); 33,7(C-8); 38,1(C-4); 63,7(C-11); 157,6(C-5); 164,2(CSO_2NH_2); 172,2(CO); 181(CON)

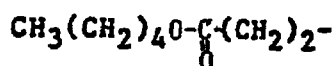
IR (CHCl_3): ν_{max} 3425, 3345, 2925, 1730, 1625, 1375, 1160 cm^{-1}

Analysis ($\text{C}_{12}\text{H}_{20}\text{N}_4\text{O}_5\text{S}_2$) Calcd.: C, 39.55; H, 5.53; N, 15.37; S, 17.59; Found: C, 39.33; H, 5.65; N, 15.16; S, 17.49.

EXAMPLE 18

5-Pentylsuccinoyl-N-methylamino-2-sulfonamido-1,3,4-thiadiazole (Rende 038)

Series II, Y =



SCHEME D, route steps (n), (b), (c)

(n) Methylation reaction of 5-pentylsuccinoylamino-2-benzylmercapto-1,3,4-thiadiazole

5 The procedure is the same as that followed in the preceding example.

(b) Preparation of 5-pentylsuccinoyl-N-methylamino-2-sulfonylchloride-1,3,4-thiadiazole

10 Chlorine is bubbled through a suspension of 800 mg of 5-pentylsuccinoyl-N-methylamino-2-benzylmercapto-1,3,4-thiadiazole in 15 ml of a 33 % acetic acid water solution, while the mixture is kept under stirring at 0°C. The reaction is checked through TLC (2 % acetone in chloroform) and is complete in 4 hours.

The chloride so formed is extracted with methylene chloride, the organic phase is washed with a saturated solution of NaHCO₃ at 0°C, and subsequently with ice-cold water up to neutrality, and finally it is dried over anhydrous sodium sulfate.

15 750 mg of the raw product is obtained that is employed for the successive reaction.

(c) Preparation of 5-pentylsuccinoyl-N-methylamino-2-sulfonamide-1,3,4-thiadiazole (Rende 038)

20 750 mg of sulfonyl chloride dissolved into 3 ml of anhydrous THF is slowly added into 20 ml of freshly condensed liquid ammonia at -78°C and under nitrogen atmosphere.

Ammonia is removed at room temperature and the residue is dissolved into 2N NH₄OH.

The solution, acidified with conc. HCl up to pH 4, is extracted twice with ethyl acetate and the organic phase is dried over anhydrous sodium sulfate.

25 The purification of the sulfonamide is carried out through silica gel column chromatography, eluting with 2% acetone in chloroform.

145 mg of the product is obtained with melting point 83-87°C and 20 % yield starting from 5-pentylsuccinoyl-N-methylamino-2-benzylmercapto-1,3,4-thiadiazole.

EXAMPLE 19

30 5-methylsuccinoylamino-2-sulfonamido-1,3,4-thiadiazole (Rende 023)
Series I,



SCHEME E

40 (o) and (P) Preparation of 5-amino-2-sulfonamido-1,3,4-thiadiazole

17 g of acetazolamide (purchased from Aldrich) is hydrolyzed with 150 ml 10 % HCl. The reaction is kept under reflux and stirred, and is monitored by means of TLC (20 % methanol in chloroform). After 5 hours the reaction shows to be complete.

45 The reaction mixture is cooled to room temperature and neutralized with NaOH up to pH 6. After precipitation and filtration under vacuum 12 g of 5-amino-2-sulfonamido-1,3,4-thiadiazole is obtained, with yield of 87 %.

50 (q) Preparation of 5-methylsuccinoylamino-2-sulfonamido-1,3,4-thiadiazole

12 g of 5-amino-2-sulfonamido-1,3,4-thiadiazole is suspended in 60 ml of anhydrous CH₂Cl₂; 8.7 ml of Et₃N, 170 mg of 5-DMAP and, slowly, 6.5 ml of succinoylchloride monomethyl (3-carbomethoxy-propionylchloride) are then added to such suspension.

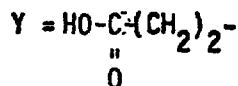
55 The reaction, kept under nitrogen, is followed through TLC (20 % methanol in chloroform) and shows to be complete after 5 hours.

In order to obtain the purified product, 40 ml of 25 % NH₄OH is added to the reaction mixture and after separation, the aqueous phase is acidified with 37 % HCl up to pH 4.

The precipitate so formed is filtered and crystallized from water. 13 g of the final product is obtained, with a yield of 66 %.

EXAMPLE 20

5-succinoylamino-2-sulfonamido-1,3,4-thiadiazole (Rende 037)
Series I,



SCHEME E

Preparation of 5-methylsuccinoylamino-2-sulfonamido-1,3,4-thiadiazole (Rende 023)

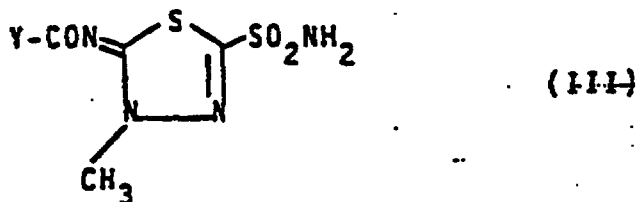
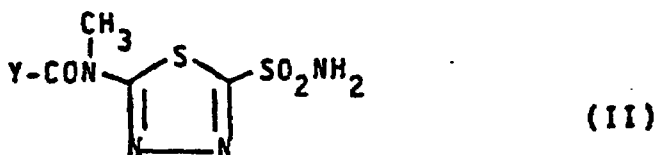
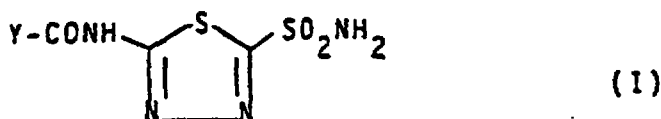
The preparation is carried out according to example 19. Preparation of 5-succinoylamino-2-sulfonamido-1,3,4-thiadiazole (Rende 037)

13 g of 5-methylsuccinoylamino-2-sulfonamido-1,3,4-thiadiazole is dissolved in 150 ml of 5 % NaOH. The reaction is kept under stirring at 60°C for 1 hour and 30 min. and is followed by means of TLC (40 % methanol in chloroform).

The reaction mixture is then cooled and acidified with 5N HCl up to precipitation of the product. The solid so formed is filtered, washed with water and dried. 8.6 g of the final product is obtained, with a yield of 70 %.

Claims

1. Use of compounds related to acetazolamide or to its N-methyl derivatives, having inhibiting activity of carbonic anhydrase, of the formulae:

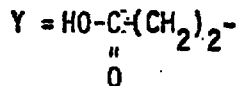


wherein Y is one of the following groups

The precipitate so formed is filtered and crystallized from water. 13 g of the final product is obtained, with a yield of 66 %.

EXAMPLE 20

5-succinoylamino-2-sulfonamido-1,3,4-thiadiazole acid (Rende 037)
Series I,



SCHEME E

Preparation of 5-methylsuccinoylamino-2-sulfonamido-1,3,4-thiadiazole (Rende 023)

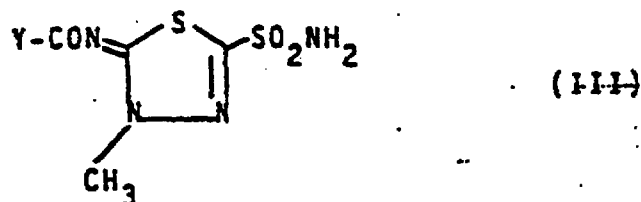
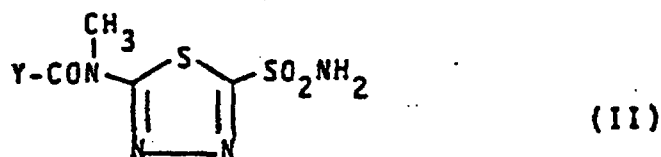
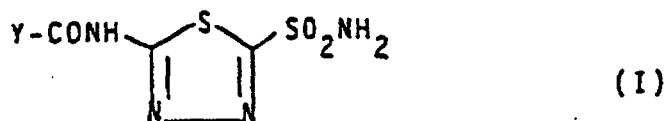
The preparation is carried out according to example 19. Preparation of 5-succinoylamino-2-sulfonamido-1,3,4-thiadiazole acid (Rende 037)

13 g of 5-methylsuccinoylamino-2-sulfonamido-1,3,4-thiadiazole is dissolved in 150 ml of 5 % NaOH. The reaction is kept under stirring at 60°C for 1 hour and 30 min. and is followed by means of TLC (40 % methanol in chloroform).

The reaction mixture is then cooled and acidified with 5N HCl up to precipitation of the product. The solid so formed is filtered, washed with water and dried. 8.6 g of the final product is obtained, with a yield of 70 %.

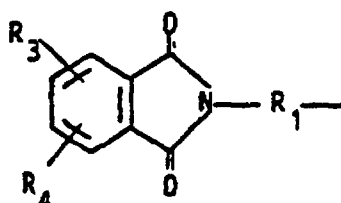
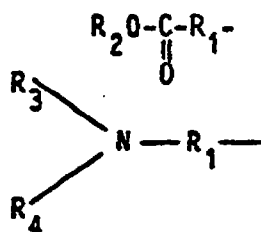
Claims

1. Use of compounds related to acetazolamide or to its N-methyl derivatives, having inhibiting activity of carbonic anhydrase, of the formulae:



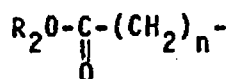
wherein Y is one of the following groups





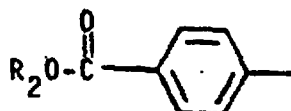
wherein R_1 is a straight or branched alkylene or arylalkylene, or a phenylene, R_2 is hydrogen or a straight or branched alkyl possibly substituted with halogen, R_3 and R_4 , which can be the same or different from each other, are hydrogen or straight or branched alkyl, and the physiologically acceptable salts thereof, for the manufacture of a medicament for the topical treatment of glaucoma.

2. Use according to claim 1, wherein Y is the group:



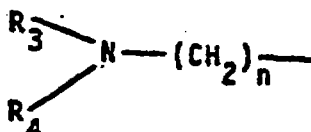
wherein R_2 is hydrogen or a straight or branched alkyl having 1-20 carbon atoms and possibly substituted with halogen, and n is an integer between 1 and 10.

3. Use according to claim 1, wherein Y is the group:



wherein R_2 is hydrogen or a straight or branched alkyl having 1-20 carbon atoms.

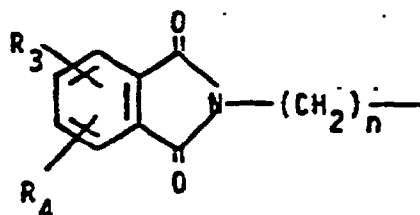
4. Use according to claim 1, wherein Y is the group of the formula:



wherein R_3 and R_4 , which can be the same or different from each other, are hydrogen or a lower alkyl of 1-6 carbon atoms, and n is an integer between 1 and 10.

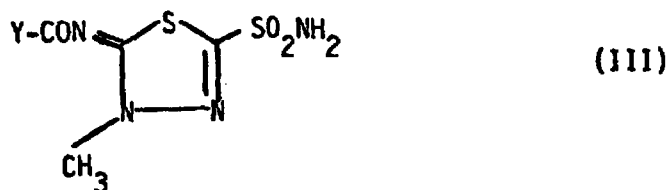
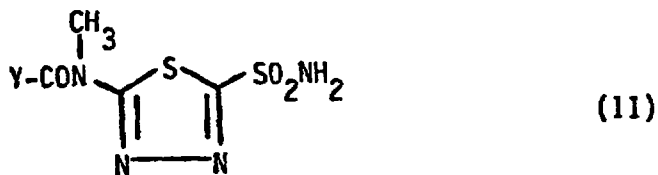
5. Use according to claim 1, wherein Y is the group:



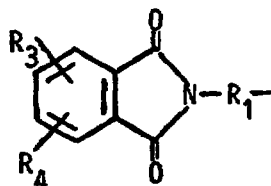
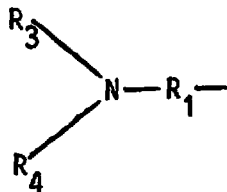
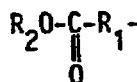


wherein R_3 and R_4 , which can be the same or different from each other, are hydrogen or a lower alkyl of 1-6 carbon atoms and n is an integer between 1 and 10.

6. Compounds related to the N-methyl derivatives of acetazolamide, having inhibiting activity of carbonic anhydrase, of the formulae



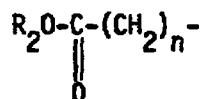
wherein Y is one of the following groups



wherein R_1 is a straight or branched alkylene or arylalkylene, or a phenylene, R_2 is hydrogen or a straight or branched alkyl possibly substituted with halogen, R_3 and R_4 , which can be the same or different from each other, are hydrogen or straight or branched alkyl, and the physiologically acceptable salts thereof.

7. Compounds according to claim 6, wherein Y is the group:



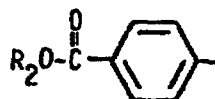


5

wherein R_2 is hydrogen or a straight or branched alkyl having 1-20 carbon atoms and possibly substituted with halogen, and n is an integer between 1 and 10.

8. Compounds according to claim 6, wherein Y is the group:

10

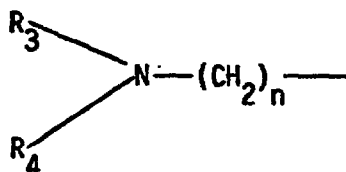


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wherein R_2 is hydrogen or a straight or branched alkyl having 1-20 carbon atoms.

9. Compounds according to claim 6, wherein Y is the group of the formula:

20

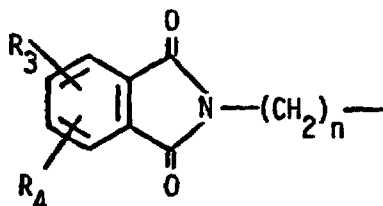


25

wherein R_3 and R_4 , which can be the same or different from each other, are hydrogen or a lower alkyl of 1-6 carbon atoms, and n is an integer between 1 and 10.

10. Compounds according to claim 6, wherein Y is the group:

30



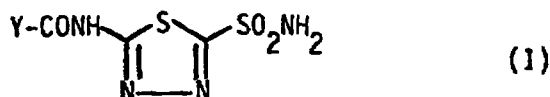
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wherein R_3 and R_4 , which can be the same or different from each other, are hydrogen or a lower alkyl of 1-6 carbon atoms and n is an integer between 1 and 10.

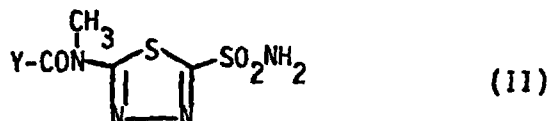
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11. Compounds related to acetazolamide or to its N-methyl derivatives, having inhibiting activity of carbonic anhydrase, of the formulae:

45

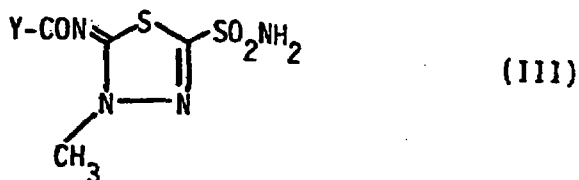


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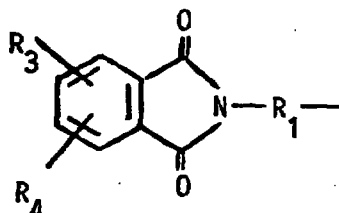


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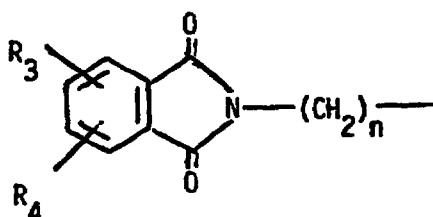


wherein Y is:



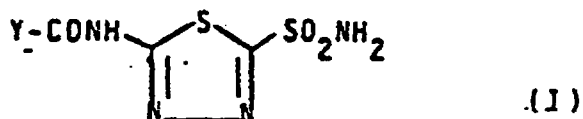
wherein R_1 is a straight or branched alkylene or arylalkylene, or a phenylene, R_2 is hydrogen or a straight or branched alkyl possibly substituted with halogen, R_3 and R_4 , which can be the same or different from each other, and hydrogen or straight or branched alkyl, and the physiologically acceptable salts thereof.

12. The compounds according to claim 11, where in Y is the group:

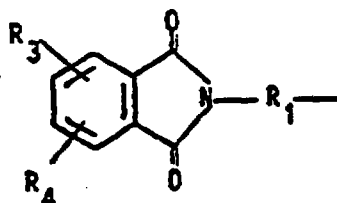


wherein R_3 and R_4 , which can be the same or different from each other, are hydrogen or a lower alkyl of 1-6 carbon atoms and n is an integer between 1 and 10.

13. A process for the production of the compounds of the formula:



wherein Y is the group:



wherein R_1 is a straight or branched alkylene or arylalkylene or a phenylene, and R_3 and R_4 , which can be the same or different from one another, are hydrogen or a straight or branched, said process comprising the steps of:

- d) benzylating the mercapto group of 5-amino-2-mercapto-1,3,4-thiadiazole;
- a) acylating the amino group of the compound so obtained with the halogenated carboxylic acid chloride



of the formula $X-R_1-COCl$, wherein R_1 corresponds to that of the desired group Y;

h) reacting the compound so obtained with potassium phthalimide corresponding to the desired group Y in order to introduce the terminal phthalimido group:

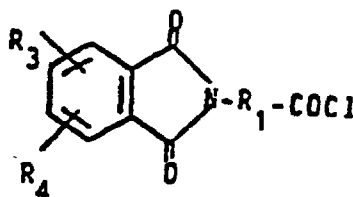
b) oxidizing the benzylmercapto group of the compound so obtained to sulfonyl halide with gaseous halogen in an acid medium;

c) treating the compound so obtained with liquid ammonia in order to transform the sulfonyl halide group into sulfonamide.

14. A process for the production of the compounds claimed in claim 13, said process comprising the steps of:

d) benzylating the mercapto group of 5-amino-2-mercapto-1,3,4-thiadiazole;

a) acylating the amino group of the compound so obtained with phthalimidocarboxylic acid chloride of the formula:



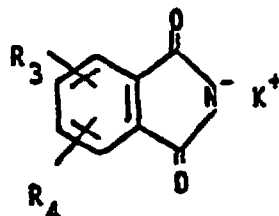
wherein R_1 , R_3 and R_4 correspond to those of the desired group Y;

b) oxidizing the benzylmercapto group of the compound so obtained to sulfonyl halide by means of gaseous halogen in an acid medium;

c) treating the compound so obtained with liquid ammonia in order to change the sulfonyl halide group into sulfonamide.

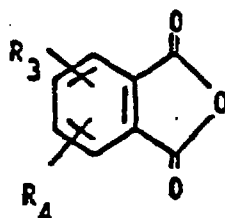
15. A process according to claim 14, wherein said phthalimidocarboxylic acid chloride is obtained by means of a step 1) consisting in treating the corresponding phthalimidocarboxylic acid with thionyl chloride.

16. A process according to claim 15, wherein said phthalimidocarboxylic acid is obtained by means of a step m) consisting in reacting potassium phthalimide of the formula



with the halogenated carboxylic acid of the formula $X-R_1-COOH$.

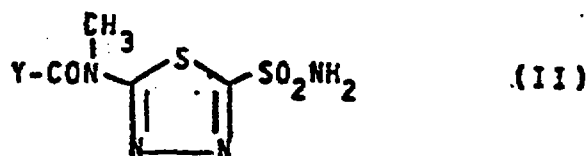
17. A process according to claim 15, wherein said phthalimido carboxylic acid is obtained by means of a step i) consisting in reacting phthalic anhydride of the formula



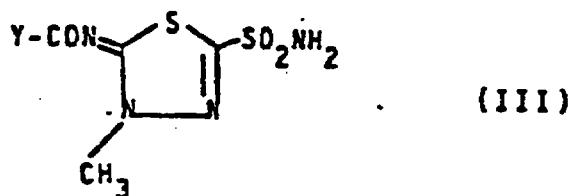
with the amino acid of the formula NH_2-R_1-COOH .

18. A process for the production of the compounds of the formula:

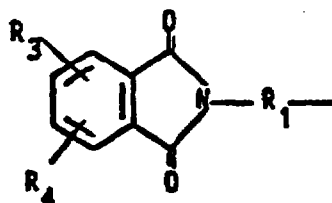
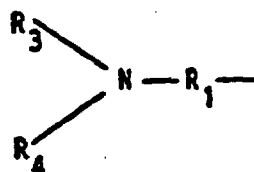
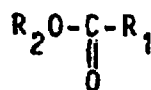




and



wherein Y is one of the following groups



wherein R_1 is a straight or branched alkylene or arylalkylene, or a phenylene, R_2 is hydrogen or a straight or branched alkyl possibly substituted with halogen, R_3 and R_4 , which can be same or different from each other are hydrogen or straight or branched alkyl, in which process, after the steps of benzylating and acylating 5-amino-2-mercapto-1,3,4-thiadiazole, the compound so obtained is subjected to the steps of:

n) methylation through treatment with methyl iodide to obtain the two corresponding N-methyl substituted compounds;

n') separation of said two methyl derivatives so obtained, by means of chromatography;

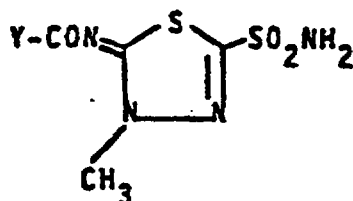
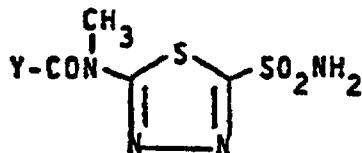
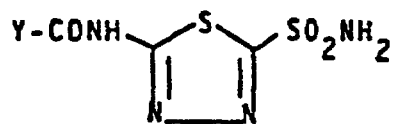
b) or b') oxidation of the mercapto group of each one of said two compounds so obtained to yield the sulfonyl halide with gaseous halogen in an acid medium;

c) or c') treating each one of the two compounds so obtained with liquid ammonia.

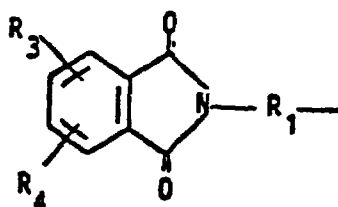
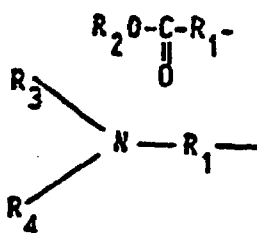
Patentansprüche

1. Verwendung von mit Acetazolamid oder N-Methyl-Derivaten verwandten Verbindungen, die eine Hemmwirkung auf die carbonische Anhydrase ausüben, der Formel:



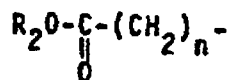


in den Y eine der folgenden Gruppen ist:



in den R1 ein lineares oder verzweigtes Alkyl oder Arylalkyl, oder ein Phenyl, R2 Wasserstoff oder ein lineares oder verzweigtes, gegebenenfalls mit Halogen ersetztes Alkyl ist, R3 und R4, die untereinander gleich oder unterschiedlich sein können, Wasserstoff oder lineares oder verzweigtes Alkyl sind, und deren physiologisch verträgliche Salze, für die Vorbereitung eines Arzneimittels zur topischen Behandlung von Glaukom.

2. Verwendung nach Anspruch 1, worin Y die Gruppe:



ist, in der R2 Wasserstoff oder ein lineares oder verzweigtes, gegebenenfalls mit Halogen ersetztes Alkyl mit 1 bis 20 Kohlenstoffatomen ist und n eine ganze Zahl von 1 bis 10 ist.

3. Verwendung nach Anspruch 1, worin Y die Gruppe



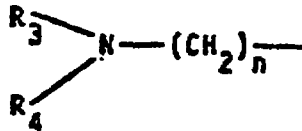


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ist, in der R₂ Wasserstoff oder ein lineares oder verzweigtes Alkyl mit 1 bis 20 Kohlenstoffatomen ist.

4. Verwendung nach Anspruch 1, worin Y die Gruppe der Formel:

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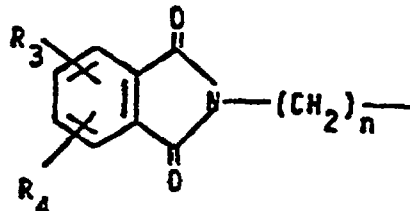


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ist, in der R₃ und R₄, die untereinander gleich oder unterschiedlich sein koennen, Wasserstoff oder ein niedrigeres Alkyl mit 1 bis 6 Kohlenstoffatomen sind und n eine ganze Zahl zwischen 1 und 10 ist.

5. Verwendung nach Anspruch 1, worin Y die Gruppe

20



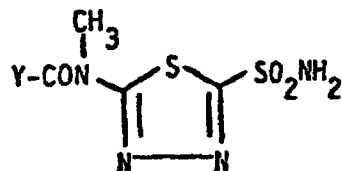
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ist, in der R₃ und R₄, die untereinander gleich oder unterschiedlich sein koennen, Wasserstoff oder ein niedrigeres Alkyl mit 1 bis 6 Kohlenstoffatomen sind und n eine ganze Zahl zwischen 1 und 10 ist.

30

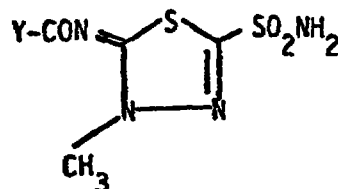
6. Mit N-Methyl-Derivaten von Acetazolamid verwandte Verbindungen, die eine Hemmwirkung auf die carbonische Anhydrase ausueben, der Formel:

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(II)

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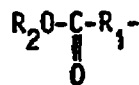
(III)

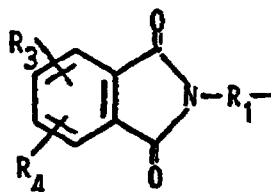
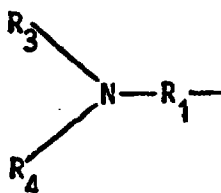
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in der Y eine von den folgenden Gruppen ist:

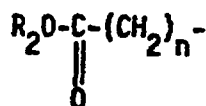
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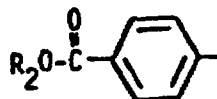
In der R1 ein lineares oder verzweigtes Alkyl oder Arylalkyl oder Phenyl ist, R2 Wasserstoff oder ein lineares oder verzweigtes, gegebenenfalls mit Halogen ersetztes Alkyl ist, R3 und R4, die untereinander gleich oder unterschiedlich sein koennen, wasserstoff oder ein lineares oder verzweigtes Alkyl sind, und deren physiologisch vertraegliche Salze.

7. Verbindungen nach Anspruch 6, worin Y die Gruppe



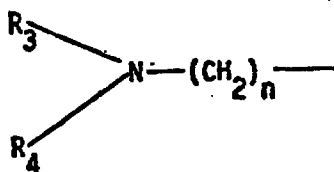
ist, in der R2 Wasserstoff oder ein lineares oder verzweigtes, gegebenenfalls mit Halogen ersetztes Alkyl mit 1 bis 20 Kohlenstoffatomen ist.

8. Verbindungen nach Anspruch 6, worin Y die Gruppe



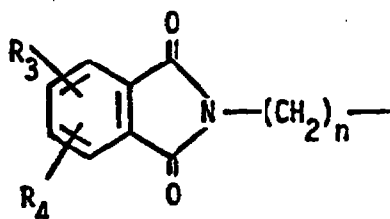
ist, in der R2 Wasserstoff oder lineares oder verzweigtes Alkyl mit 1 bis 20 Kohlenstoffatomen ist.

9. Verbindungen nach Anspruch 6, wobei Y die Gruppe der Formel:



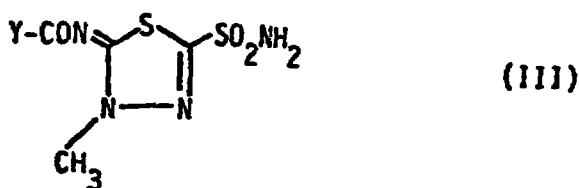
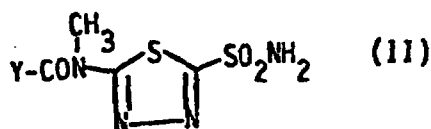
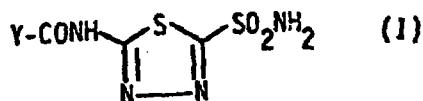
ist, in der R3 und R4, die untereinander gleich oder unterschiedlich sein koennen, Wasserstoff oder ein niedrigeres Alkyl mit 1 bis 6 Kohlenstoffatomen sind und n eine ganze Zahl zwischen 1 und 10 ist.

10. Verbindungen nach Anspruch 6, worin Y die Gruppe

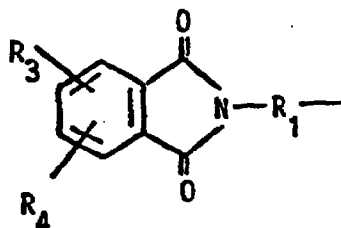


ist, in der R3 und R4, die untereinander gleich oder unterschiedlich sein koennen, Wasserstoff oder ein lineares oder verzweigtes niedrigeres Alkyl mit 1 bis 6 Kohlenstoffatomen sind und n eine ganze Zahl zwischen 1 und 10 ist.

11. Mit Acetazolamide oder N-Methyl-Derivaten verwandte Verbindungen, die eine Hemmwirkung auf carbonische Anhydrase aufweisen, der Formel:

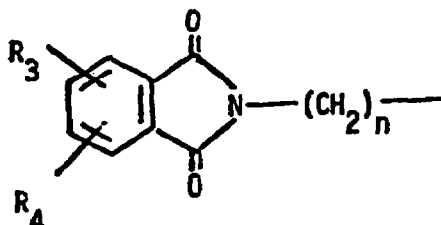


In den Y die Gruppe der Formel:



ist, in der R1 ein lineares oder verzweigtes Alkylen oder Arylalkylen, oder ein Phenylen ist, R2 Wasserstoff oder ein lineares oder verzweigtes, gegebenenfalls mit Halogen ersetztes Alkyl ist, R3 und R4, die untereinander gleich oder unterschiedlich sein koennen, Wasserstoff oder ein lineares oder verzweigtes Alkyl sind, und deren physiologisch vertraegbare Salze.

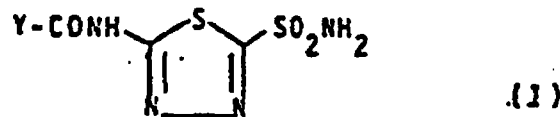
12. Verbindungen nach Anspruch 11, worin Y die Gruppe



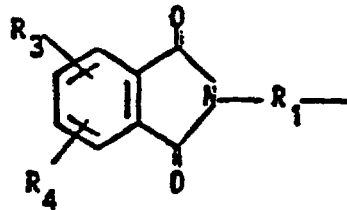
ist, in der R3 und R4, die untereinander gleich oder unterschiedlich sein koennen, Wasserstoff oder ein niedrigeres Alkyl mit 1 bis 6 Kohlenstoffatomen sind und n eine ganze Zahl zwischen 1 und 10 ist.

13. Verfahren zur Herstellung der Verbindungen der Formel:





in der Y die Gruppe



ist, in der R1 ein lineares oder verzweigtes Alkyl oder Arylalkyl, oder ein Phenyl ist und R3 und R4, die untereinander gleich oder unterschiedlich sein koennen, Wasserstoff oder ein lineares oder verzweigtes Alkyl, welches Verfahren die folgenden Verfahrensschritte umfasst:

d) Benzilylierung der Mercaptogruppe von 5-Amino-2-Mercapto-1,3,4-Thiadiazol;

a) Acylierung der Amino-Gruppe der so erhaltenen Verbindungen mit halogeniertem Carbonsaure - Chlorid der Formel $\text{X-R}_1\text{-COCl}$, in der R1 der gewünschten Y-Gruppe entspricht,

h) die so erhaltene Verbindung mit dem der gewünschten Y-Gruppe entsprechenden Kalium - Phthalimid reagieren lassen, um die Phthalimido-Endgruppe einzufuehren;

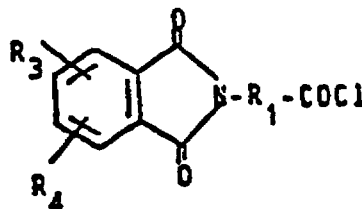
b) Oxydation der Mercapto-Gruppe der so erhaltenen Verbindungen zum Sulphonyl- Halogenid mit gasfoermigem Halogen in einem Saeuremittel;

c) Behandlung der so erhaltenen Verbindung mit fluessigem Ammonium um die Sulphonyl-Halogenid-Gruppe in Sulphonamid umzuwandeln.

14. Verfahren zur Herstellung der im Anspruch 13 beanspruchten Verbindungen, das die folgenden Verfahrensschritte umfasst:

d) Benzilylierung der Mercapto-Gruppe von 5-Amino-2-Mercapto-1,3,4-Thiadiazol,

a) Acylierung der Amino-Gruppe der so erhaltenen Verbindung mit dem Phthalimido-Carbonsaure-Chlorid der Formel:



in der R1, R3 und R4 denjenigen der gewünschten Y-Gruppe entsprechen;

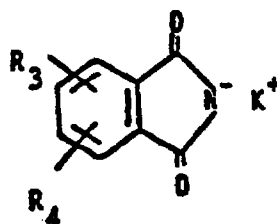
b) Oxydation der Benzylmercapto-Gruppe der so erhaltenen Verbindung mit gasfoermigem Halogen in einem Saeuremittel;

c) Behandlung der so erhaltenen Verbindung mit fluessigem Ammonium zur Umwandlung der Sulonyl-Halogenid-Gruppe in Sulphonamid.

15. Verfahren nach Anspruch 14, worin das genannte Phthalimido-Carbonsaure-Chlorid durch einen Verfahrensschritt 1) erhalten wird, der darin besteht, dass die entsprechende Phthalimid-Carbonsaure mit Thionyl-Chlorid behandelt wird.

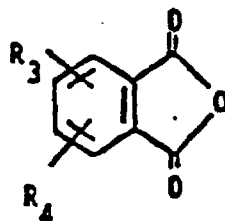
16. Verfahren nach Anspruch 15, worin die genannte Phthalimido-Carbonsaure durch einen Verfahrensschritt m) erhalten wird, der darin besteht, dass Kalium-Phthalimid der Formel:





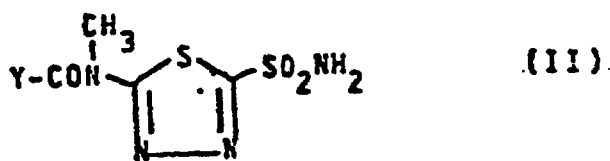
10 mit der halogenierten Carbonsäure der Formel X-R1-COOH zur Reaktion gebracht wird.

17. Verfahren nach Anspruch 15, worin die genannte Phthalimido-Carbonsäure durch einen Verfahrensschritt i) erhalten wird, der darin besteht, dass Phthalanhydrid der Formel:

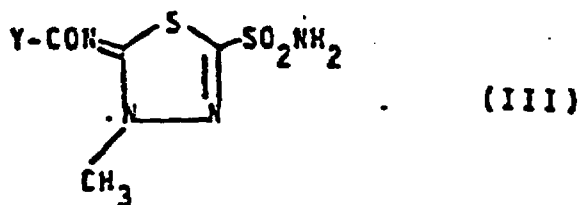


mit der Amino-Säure der Formel NH2-R1-COOH zur Reaktion gebracht wird.

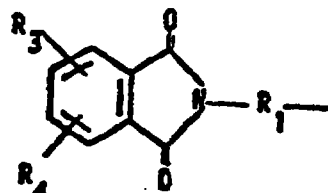
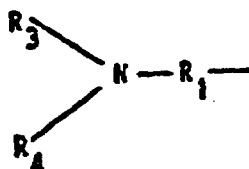
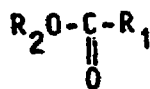
18. Verfahren fuer die Herstellung der Verbindungen der Formel:



und



in den Y eine der folgende Gruppen



55 ist, in den R1 ein lineares oder verzweigtes Alkyl oder Arylalkyl, oder Phenyl ist, R2 Wasserstoff oder ein lineares oder verzweigtes, gegebenenfalls mit Halogen ersetztes Alkyl ist, R3 und R4, die untereinander gleich oder unterschiedlich sein koennen, Wasserstoff oder lineares oder gezwertes Alkyl sind, in welchem Verfahren nach der Benzylierung und Acylierung vom 5-Amino-2-Mercapto-1,3,4-Thiadiazol, die so erhaltene Verbindung den folgenden Verfahrensschritten unterworfen wird:

n) Methylierung durch eine Behandlung mit Methyl-Iodid zur Erhaltung von zwei entsprechenden N-Methyl



ersetzen Verbindungen;

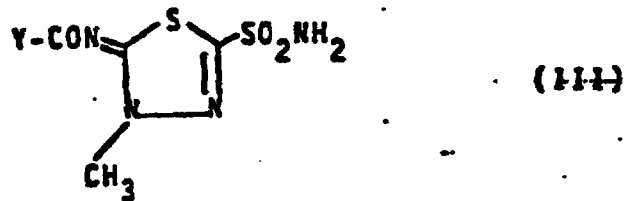
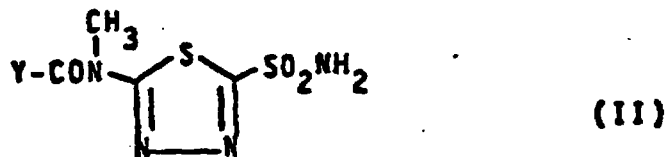
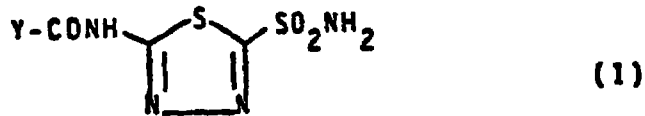
n') Abscheidung der so erhaltenen, genannten Methyl Derivate durch Chromatographie;

b) oder b') Oxydation der Mercapto-Gruppe einer jeden der so erhaltenen zwei Verbindungen zur Erzielung des Sulphonyl-Halogenids mit gasförmigem Halogen in einem Säuremittel;

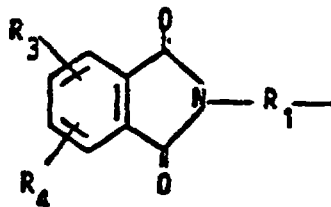
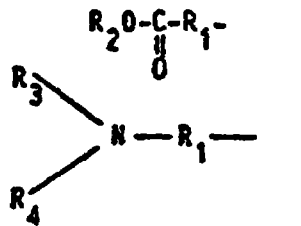
c) oder c') Behandlung einer jeden der so erhaltenen zwei Verbindungen mit flüssigem Ammonium.

Revendications

1. Application des composés apparentés à l'acétazolamide ou à ses dérivés N-méthylliques, ayant une activité d'inhibition de l'anhydrase carbonique, de la formule:



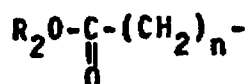
dans lesquels Y est un des groupes suivants:



où R1 est un alcoyle ou arylalcoyle linéaire ou ramifié ou un phényle éventuellement substitué avec halogène, R3 et R4, qui peuvent être égaux ou différents entre eux, sont hydrogène ou un alcoyle linéaire ou ramifié et leur sels physiologiquement acceptables, pour la production d'un médicament pour le traitement topique du glaucome.

2. Application selon la revendication 1, dans laquelle Y est le groupe:



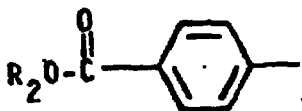


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où R₂ est hydrogène ou un alcoyl linéaire ou ramifié ayant 1-2 atomes de carbone et éventuellement substitué avec halogène et n est un nombre entier entre 1 et 10.

3. Application selon la revendication 1, dans laquelle Y est le groupe:

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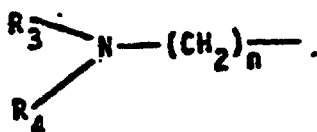


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où R₂ est hydrogène ou un alcoyl linéaire ou ramifié ayant 1-20 atomes de carbone.

4. Application selon la revendication 1, dans laquelle Y est le groupe de formule:

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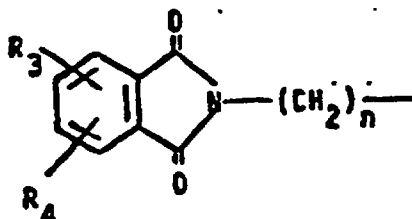


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où R₃ et R₄, qui peuvent être égaux ou différents entre eux, sont hydrogène ou un alcoyle inférieur avec 1-6 atomes de carbone et n est un nombre entier entre 1 et 10.

5. Application selon la revendication 1, dans laquelle Y est le groupe:

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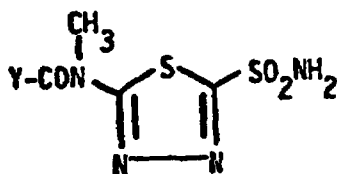
35

où R₃ et R₄, qui peuvent être égaux ou différents entre eux, sont hydrogène ou un alcoyle inférieur avec 1-6 atomes de carbone et n est un nombre entier entre 1 et 10.

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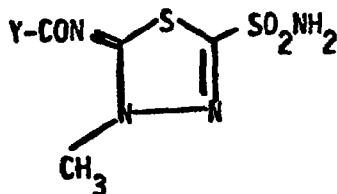
6. Composés apparentés aux dérivés N-méthyliques de l'acetazolamide ayant une activité d'inhibition de l'anhydrase carbonique, de formule:

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(II)

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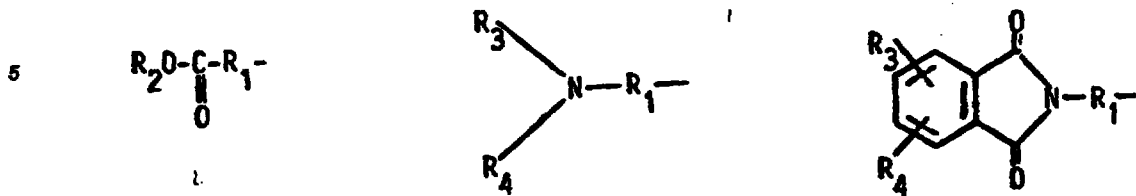


(III)

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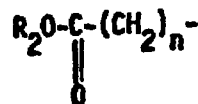
dans lesquels Y est un des groupes suivants:



où R1 est un alcoyle ou arylalcoyle linéaire ou ramifié, ou un phenyle, R2 est hydrogène ou un alcoyl linéaire ou ramifié, éventuellement substitué avec halogène, R3 et R4, qui peuvent être égaux ou différents entre eux, sont hydrogène ou un alcoyle linéaire ou ramifié, et leur sels physiologiquement acceptables.

7. Composés selon la revendication 6, dans lesquels Y est le groupe:

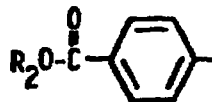
15



où R2 est hydrogène ou un alcoyle linéaire ou ramifié ayant 1-20 atomes de carbone, éventuellement substitué avec halogène et n est un nombre entier entre 1 et 10.

8. Composés selon la revendication 6, dans lesquels Y est le groupe:

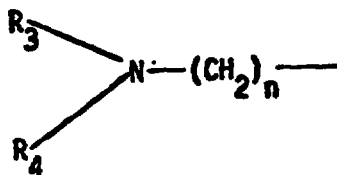
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où R2 est hydrogène ou un alcoyle linéaire ou ramifié ayant 1-20 atomes de carbone.

9. Composés selon la revendication 6, dans lesquels Y est le groupe de formule:

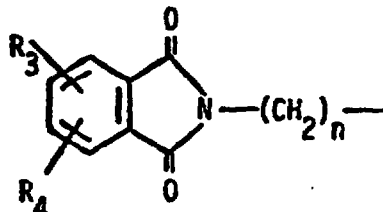
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où R3 et R4, qui peuvent être égaux ou différents entre eux, sont hydrogène ou un alcoyle inférieur avec 1-6 atomes de carbone et n est un nombre entier entre 1 et 10.

10. Composés selon la revendication 6, dans lesquels Y est le groupe:

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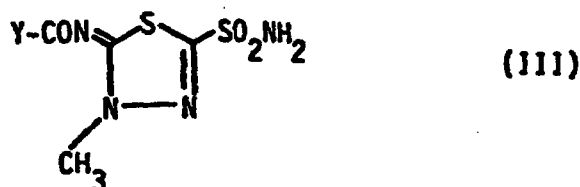
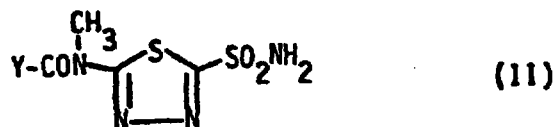
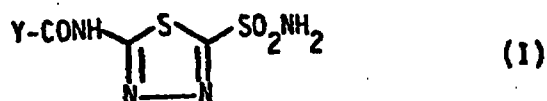


où R3 et R4, qui peuvent être égaux ou différents entre eux, sont hydrogène ou un alcoyle inférieur avec 1-6 atomes de carbone et n est un nombre entier entre 1 et 10.

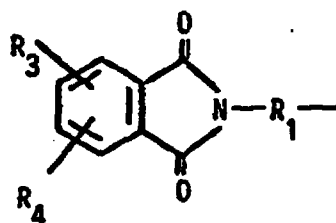
11. Composés apparentés à l'acétazolamide ou à ses dérivés N-méthyliques, ayant une activité d'inhibition de l'anhydrase carbonique, de formule:

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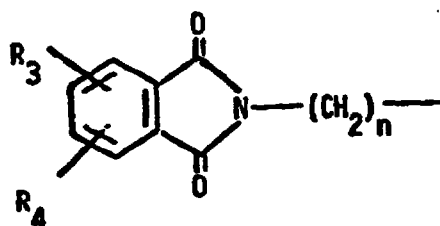


20 dans lesquels Y est:



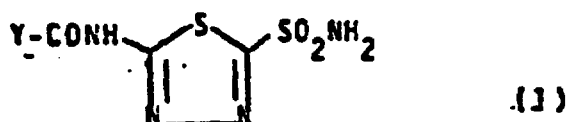
où R1 est un alcoyle ou arylcoyle linéaire ou ramifié ou un phényle, R2 est hydrogène ou un alcoyle linéaire ou ramifié, éventuellement substitué avec halogène, R3 et R4, qui peuvent être égaux ou différents entre eux, sont hydrogène ou un alcoyle linéaire ou ramifié, et leur sels physiologiquement acceptables.

12. Composés selon la revendication 11, dans lesquels Y est le groupe:



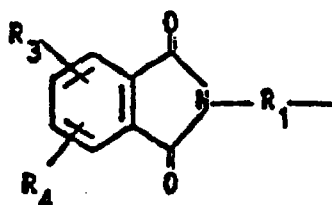
où R3 et R4, qui peuvent être égaux ou différents entre eux, sont hydrogène ou un alcoyle inférieur avec 1-6 atomes de carbone et n est un nombre entier entre 1 et 10.

13. Procédé pour la production des composés de la formule:



où Y est le groupe:



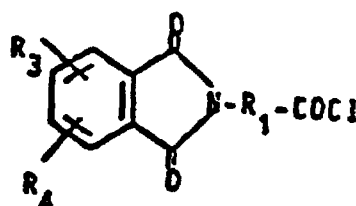


où R1 est un alcoyle ou arylalcoyle linéaire ou ramifié, ou un phényle et R3 et R4, qui peuvent être égaux ou différents entre eux, sont hydrogène ou un alcoyle linéaire ou ramifié, ledit procédé comprenant les phases de:

- d) benzylation du groupe mercapto du 5-amino-2-mercapto-1,3,4-thiadiazole;
- a) acylation du groupe aminique du composé ainsi obtenu avec le chlorure d'acide carboxylique halogéné de la formule X-R1-COCl, où R1 correspond à celui du group Y désiré;
- h) réaction du composé ainsi obtenu avec la phtalimide de potassium correspondant au groupe Y désiré pour introduire le groupe phtalimido terminal;
- b) oxydation du groupe benzylmercapto du composé ainsi obtenu avec l'halogène gazeux dans un milieu acide, à donner le sulfonyl halogénure;
- c) traitement du composé ainsi obtenu avec de l'ammoniaque pour transformer le groupe sulfonyl halogénure en sulfonamide.

14. Procédé pour la production des composés revendiqués par la revendication 13, ledit procédé comprenant les phases de:

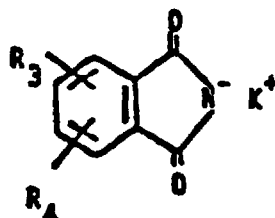
- d) benzylation du groupe mercapto du 5-amino-2-mercapto-1,3,4-thiadiazole;
- a) acylation du groupe aminique du composé ainsi obtenu avec le chlorure d'acide phtalimidocarboxylique de formule



- où R1, R3 et R4 correspondent au group Y désiré;
- b) oxydation du groupe benzylmercapto du composé ainsi obtenu pour changer le groupe sulfonyl-halogénure en sulfonamide;
- c) traitement du composé ainsi obtenu avec de l'ammoniaque pour transformer le groupe sulfonyl-halogénure en sulfonamide.

15. Procédé selon la revendication 14, dans lequel ledit chlorure d'acide phtalimidocarboxylique est obtenu au moyen d'une phase 1) consistante en traiter l'acide phtalimidocarboxylique correspondant avec le chlorure de thionyle.

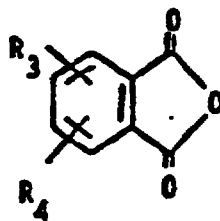
16. Procédé selon la revendication 15, dans lequel ledit acide phtalimidocarboxylique est obtenu au moyen d'une phase m) consistante en faire réagir la phtalimide de potassium de formule:



avec l'acide carboxylique halogéné de formule X-R1-COOH.

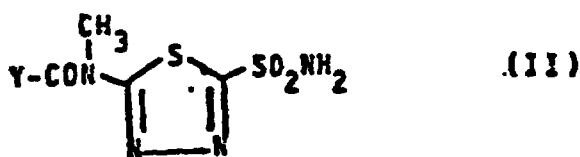
17. Procédé selon la revendication 15, dans lequel ledit acide phtalimido-carboxylique est obtenu au moyen d'une phase i) consistante en faire réagir l'anhydride phtalique de formule



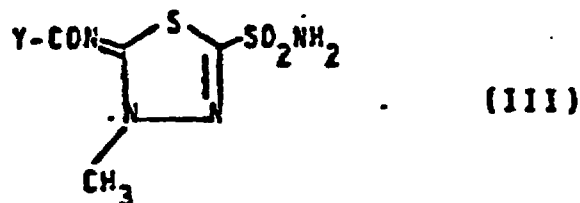


avec l'ammino-acide de formule $\text{NH}_2\text{-R}_1\text{-COOH}$.

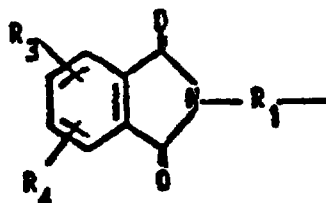
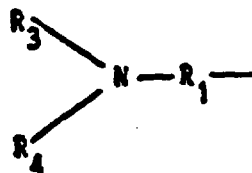
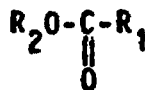
18. Procédé pour la production des composés de formule:



et



où Y est un des groupes suivants:



où R1 est un alcoyle ou arylalcoyle linéaire ou ramifié, ou un phényle, R2 est hydrogène ou un alcoyle linéaire ou ramifié, éventuellement substitué avec halogène, R3 et R4, qui peuvent être égaux ou différents entre eux, sont hydrogène ou un alcoyle linéaire ou ramifié, procédé dans lequel, après les phases de benzylation et d'acylation du 5-amino-2-mercapto-1,3,4-thiadiazole, le composé ainsi obtenu est soumis aux phases suivantes:

n) méthylation au moyen d'un traitement avec iodure de méthyle pour obtenir les deux composés N-méthyle substitués ;



n') séparation desdits deux dérivés méthylés ainsi obtenus par chromatographie,
b) ou b') oxydation du groupe mercapto de chacun desdits deux composés ainsi obtenus avec de l'halogène gazeux dans un milieu acide à donner le sulfonyl halogénure;
c) ou c') traitement de chacun des deux composés ainsi obtenus avec de l'ammoniaque.

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