United States Patent Office

3,210,347
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3,210,347

BENZOTHIADIAZINE-1,1-DIOXIDES

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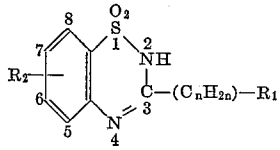
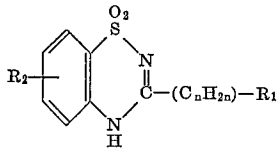
5 Claims. (Cl. 260—243)

The present invention concerns 3-carbocyclic aryl-lower alkyl-1,2,4-benzothiadiazine-1,1-dioxides. More particularly, it relates to compounds having one of the formulae:



and



in which the letter *n* stands for one of the whole numbers 1, 2, 3 and 4, R represents monocyclic carbocyclic aryl, and R_2 stands for hydrogen, halogeno, lower alkyl, trifluoromethyl and nitro, or salts of such compounds, as well as process for the preparation thereof.

The letter *n* stands primarily for 1, but may also represent one of the numbers 2, 3 and 4. The group of the formula $—(C_nH_{2n})—$ may, therefore, represent lower alkylene having from one to four carbon atoms, primarily methylene, as well as 1,1-ethylene, 1,2-ethylene, 1,1-propylene, 1,2-propylene, 2,2-propylene, 2,3-propylene, 1,3-propylene, 1,1-butylene, 1,4-butylene and the like.

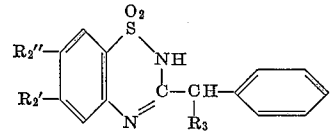
The monocyclic carbocyclic aryl portion R_1 represents primarily phenyl; it may also stand for substituted phenyl, such as lower alkyl-phenyl, e.g. 4-methyl-phenyl, 3,4-dimethyl-phenyl, 2-ethyl-phenyl, 4-isopropyl-phenyl and the like, etherified hydroxy-phenyl, particularly lower alkoxy-phenyl, e.g. 4-methoxy- phenyl, 3,4,5-trimethoxy-phenyl, 3-ethoxy-phenyl, 4-secondary butyloxy-phenyl and the like, halogeno-phenyl, e.g. 4-fluoro-phenyl, 4-chloro-phenyl, 2,5-dichloro-phenyl, 3-bromo-phenyl and the like, trifluoromethyl-phenyl, e.g. 4-trifluoromethyl-phenyl and the like, or any other suitably substituted phenyl group.

The group R_2, which is preferably attached to the 6-position or the 7-position of the 1,2-4-benzothiadiazine-1,1-dioxide nucleus, may represent hydrogen, nitro or lower alkyl having from one to four carbon atoms, e.g. methyl, ethyl, n-propyl, isopropyl, n-butyl, secondary butyl, tertiary butyl and the like. However, R_2 represents primarily trifluoromethyl or halogeno, especially halogeno having an atomic weight between 35 and 80, i.e. chloro or bromo, as well as fluoro and the like.

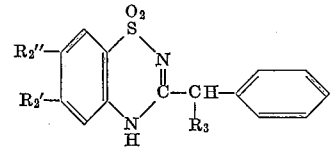
Salts of the compounds of this invention are primarily alkali metal, e.g. sodium, potassium and the like, or alkaline earth metal, e.g. magnesium, calcium and the like, salts thereof.

The compounds of this invention counteract the effect of physiological pressure agents, such as epinephrine, norepinephrine or hypertensive polypeptides, e.g. angiotensin-II-amide and the like, and thus cause a lowering of the blood pressure. They can, therefore, be used as antihypertensive agents to relieve hypertensive conditions, such as renal hypertension, essential hypertension, malignant hypertension and the like.

Particularly useful are the compounds having one of the formulae:



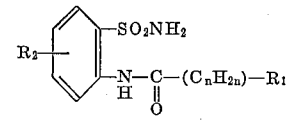
or



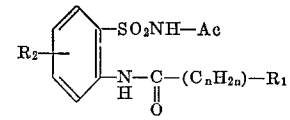
in which one of the groups R_2' and R_2'' represents chloro, bromo or trifluoromethyl, and the other stands for hydrogen or methyl, or the alkali metal, e.g. sodium, potassium and the like, salts thereof.

The new compounds of this invention may be used in the form of pharmaceutical preparations, which contain the new 3-carbocyclic aryl-lower alkyl-1,2,4-benzothiadiazine-1,1-dioxides or salts thereof in admixture with a pharmaceutical organic or inorganic, solid or liquid carrier suitable for enteral or parenteral administration. For making up the preparations there can be employed substances which do not react with the new compounds, such as water, gelatine, lactose, starches, stearic acid, magnesium stearate, stearyl alcohol, talc, vegetable oils, benzyl alcohols, gums, waxes, propylene glycol, polyalkylene glycols or any other known carrier used for pharmaceutical preparations. The latter may be in solid form, for example, as capsules, tablets, dragees and the like or in liquid form, for example, as solutions, suspensions, emulsions and the like. If necessary, these compositions may contain auxiliary substances, such as preserving, stabilizing, wetting, emulsifying agents and the like, as well as salts for varying the osmotic pressure, buffers, etc. They may also contain, in combination, other useful substances, particularly antihypertensive agents, such as Rauwolfia alkaloids, e.g. reserpine, deserpidine, rescinnamine and the like, semisynthetic Rauwolfia alkaloids, e.g. syrosingopine and the like, veratrum alkaloids, e.g. protoveratine A, protoveratine B and the like, synthetic antihypertensive drugs, e.g. hydralazine, dihydralazine, guanethidine and the like, ganglionic blockers, e.g. chlorisondamine and the like, or any other useful substances, such as potassium chloride and the like.

The compounds of this invention are prepared according to methods known per se, for example, by cyclizing a 2-sulfamyl-N-(carbocyclic aryl-lower alkanoyl)-aniline, particularly a compound of the formula:

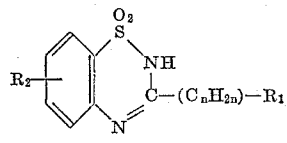


or a 2-(N-acyl-sulfamyl) - N - (carbocyclic aryl-lower alkanoyl)-aniline, particularly a compound of the formula:

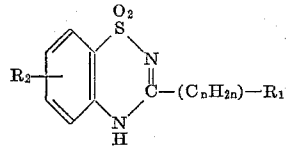


in which *n*, R_1 and R_2 have the previously-given meaning, and acyl, particularly the acyl radical of the formula Ac, stands for the acyl radical of an organic carboxylic acid, to form the desired 3-(carbocyclic aryl-lower alkyl)-

1,2,4-benzothiadiazine - 1,1 - dioxide compound, particularly a compound having one of the formulae:



or

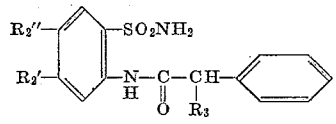


in which n, R_1 and R_2 have the previously-given meaning, and, if desired, converting a resulting salt into the free compound, and/or, if desired, converting a resulting compound into a salt thereof.

The acyl radical of an organic carboxylic acid, which substitutes the sulfamyl group, and which is represented in the above formula by the radical Ac, is, for example, the acyl radical of a carbocyclic aryl carboxylic acid and has more especially the formula $-CO-(C_nH_{2n})-R_1$, in which n and R_1 have the previously-given meaning. However, it may also stand for the acyl radical of any other suitable organic carboxylic acid, such as a lower alkanoic acid, e.g. acetic, propionic acid and the like.

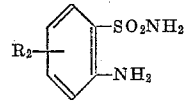
Cyclization of the 2-sulfamyl-N-(carbocyclic aryl-lower alkanoyl)-aniline is carried out at an elevated temperature, preferably at a temperature between 75° and 200°. The cyclization may take place in the absence or in the presence of an inert solvent, such as, for example, ethanol, propanol, diethyleneglycol dimethyl ether, N,N-dimethylformamide and the like, if necessary, in a closed vessel under pressure, and/or in the atmosphere of an inert gas, e.g. nitrogen and the like.

The starting materials used in the above procedure are new and are intended to be included within the scope of this invention. Particularly useful as starting materials are the compounds of the formula:

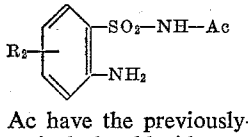


in which R_2', R_2'' and R_3 have the previously-given meaning.

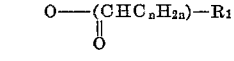
The starting materials may be prepared, for example, by reacting a 2-sulfamyl-aniline, especially a compound of the formula:



or a 2-(N-acyl-sulfamyl)-aniline, particularly a compound of the formula:



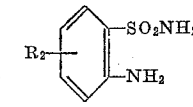
in which R_2 and Ac have the previously-given meaning, with the halide, particularly chloride, or anhydride of a carbocyclic aryl carboxylic acid, particularly an acid of the formula:



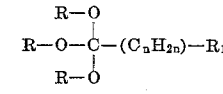
in which n and R_1 have the previously-given meaning.

The acylation of the sulfamyl-nitrogen may take place simultaneously with the desired acylation of the aniline-nitrogen. Whenever the treatment with the acylating reagent is carried out in the presence of an inert, slightly polar to non-polar organic solvent, such as an aromatic hydrocarbon, an ether and the like, the mono-acylated product, in which the aniline-nitrogen is acylated, is obtained. Any acid generated during the acylation reaction may be neutralized by adding a suitable reagent, e.g. sodium acetate and the like. Di-acylation occurs whenever the acylation is used in an excess amount and in the presence of a base, such as a tertiary amine, e.g. N,N,N-triethylamine and the like, or a heterocyclic base, e.g. pyridine and the like.

The compounds of this invention may also be prepared by reacting a 2-sulfamyl-aniline compound, particularly a compound of the formula:



in which R_2 has the previously-given meaning, with an ortho-ester, especially a lower alkyl ortho-ester, of a carbocyclic aryl-lower alkanoic acid, particularly an ortho-ester of the formula:



in which n and R_1 have the previously-given meaning, and R represents lower alkyl, and, if desired, carrying out the optional steps.

As mentioned hereinbefore, an ortho-ester of a carbocyclic aryl-lower alkanoic acid is preferably a lower alkyl ortho-ester, in which lower alkyl (represented in the above formula by R) has from one to four carbon atoms and stands for methyl, ethyl, n-propyl, isopropyl, n-butyl and the like; ethyl ortho-esters are the preferred reagents. The above reaction is preferably carried out at an elevated temperature, and in the presence of an inert organic solvent; if necesary, it may be performed in a closed vessel under pressure, and/or in the atmosphere of an inert gas, e.g. nitrogen and the like.

The resulting product may be obtained in the form of the free compound or as a salt thereof. A resulting meal, such as an alkali metal, salt may be converted into the free compound by treatment with an acidic reagent, such as an aqueous mineral acid, e.g. hydrochloric, sulfuric acid and the like. A resulting free compound may be converted into a metal, particularly into an alkali metal salt, for example, by treatment with an alkali metal hydroxide, e.g. sodium hydroxide, potassium hydroxide and the like, in the presence of a suitable inert solvent, such as in a lower alkanol, e.g. methanol, ethanol and the like, or in water and evaporating the solvent, or by reacting the free compound, for example, in an ether, e.g. p-dioxane, diethyleneglycol dimethyl-ether and the like, solution, with a metal, particularly an alkali metal, hydride or a metal, particularly an alkali metal, amide, e.g. sodium hydride, potassium hydride, sodium amide, potassium amide and the like.

The invention also comprises any modification of the process wherein a compound obtainable as an intermediate at any state of the process is used as starting material and the remaining step(s) of the process is (are) carried out, as well as any new intermediates.

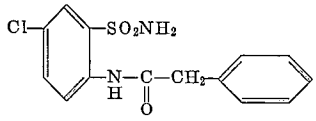
In the process of this invention such starting materials are preferably used which lead to final products mentioned in the beginning as preferred embodiments of the invention.

The following examples illustrate the invention; they are not to be construed as being limitations thereon. Temperatures are given in degrees centigrade.

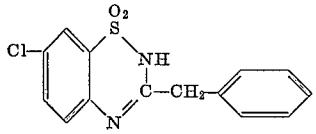
Example 1

A mixture of 5.0 g. of 4-chloro-2-sulfamyl-aniline and 3.45 g. of phenyl-acetic acid chloride in benzene contain-

ing 2.2 g. of sodium acetate is heated on the steam bath. The precipitate is filtered off, and the benzene solution is evaporated to yield the desired 4-chloro-N-phenylacetyl-2-sulfamyl-aniline of the formula:



The latter is dissolved in N,N-dimethylformamide and the solution is refluxed for one hour. Water is added, and, upon chilling, the desired 3-benzyl-7-chloro-1,2,4-benzothiadiazine-1,1-dioxide having one of the formulae:



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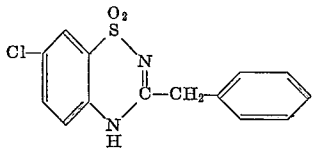
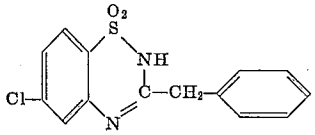


precipitates, is collected and recrystallized from ethanol.

Example 2

A mixture of 4.0 g. of 5-chloro-2-sulfamyl-aniline and 2.78 g. of phenyl acetic acid chloride in a benzene solution containing 1.75 g. of sodium acetate, when reacted as shown in Example 1, yields the 5-chloro-N-phenylacetyl-2-sulfamyl-aniline, which is ring-closed to the desired benzyl-6-chloro-1,2,4-benzothiadiazine-1,1-dioxide having one of the formulae:



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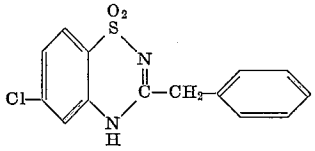


by refluxing an N,N-dimethylformamide solution thereof.

Other compounds, such as, for example, the

7-chloro-3-(1-phenylethyl)-1,2,4-benzothiadiazine-1,1-dioxide,
7-chloro-3-(2-phenylethyl)-1,2,4-benzothiadiazine-1,1-dioxide,
7-bromo-3-benzyl-1,2,4-benzothiadiazine-1,1-dioxide,
3-benzyl-7-nitro-1,2,4-benzothiadiazine-1,1-dioxide,
3-benzyl-1,2,4-benzothiadiazine-1,1-dioxide,
3-benzyl-6-trifluoromethyl-1,2,4-benzothiadiazine-1,1-dioxide,
3-benzyl-7-trifluoromethyl-1,2,4-benzothiadiazine-1,1-dioxide,
3-benzyl-6-methyl-1,2,4-benzothiadiazine-1,1-dioxide,
3-benzyl-7-methyl-1,2,4-benzothiadiazine-1,1-dioxide,
6-chloro-3-(4-methyl-benzyl)-1,2,4-benzothiadiazine-1,1-dioxide,
7-chloro-3-(4-chloro-benzyl)-1,2,4-benzothiadiazine-1,1-dioxide,
6-bromo-3-(4-trifluoromethyl-benzyl)-1,2,4-benzothiadiazine-1,1-dioxide,
3-(3,4,5-trimethoxy-benzyl)-6-trifluoromethyl-1,2,4-benzothiadiazine-1,1-dioxide,

3-[1,(4-isopropyl-phenyl)-ethyl]-7-trifluoromethyl-1,2,4-benzothiadiazine-1,1-dioxide,
7-chloro-3-[1-(4-ethoxy-phenyl)-ethyl]-1,2,4-benzothiadiazine-1,1-dioxide and the like,

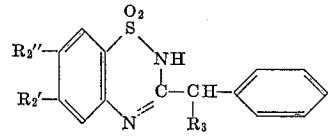
are prepared according to the previously-outlined procedure illustrated in the above examples.

Example 3

An aqueous solution of the sodium salt of 3-benzyl-7-chloro-1,2,4-benzothiadiazine-1,1-dioxide is prepared by dissolving 0.5 g. of 3-benzyl-7-chloro-1,2,4-benzothiadiazine-1,1-dioxide in a solution of an equivalent amount of sodium hydroxide in water.

What is claimed is:

1. A compound having one of the formulae:



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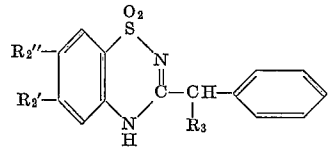
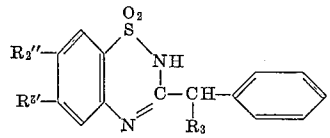
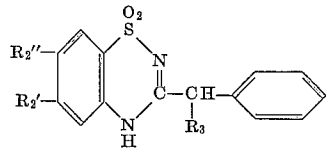


in which one of the groups R_2' and R_2'' represents a member selected from the group consisting of chloro, bromo and trifluoromethyl, and the other stands for hydrogen, and R_3 represents a member selected from the group consisting of hydrogen and methyl.

2. An alkali metal salt of a compound having one of the formulae:



and

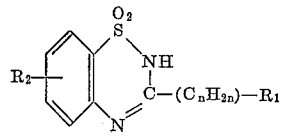


in which one of the groups R_2' and R_2'' represents a member selected from the group consisting of chloro, bromo and trifluoromethyl, and the other stands for hydrogen, and R_3 represents a member selected from the group consisting of hydrogen and methyl.

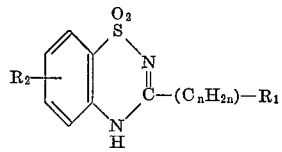
3. 3-benzyl-7-chloro-1,2,4-benzothiadiazine-1,1-dioxide.

4. 3-benzyl-6-chloro-1,2,4-benzothiadiazine-1,1-dioxide.

5. A pharmaceutical preparation, which contains as the essential ingredient a pharmacologically effective amount of a compound having one of the formulae:



and



in which the letter *n* stands for an integer from 1 to 4, both inclusive R_1 represents a member selected from the group consisting of phenyl, and R_2 represents hydrogen, halogeno, lower alkyl, trifluoromethyl and nitro, and an alkali metal salt thereof, together with an inert carrier.

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NICHOLAS S. RIZZO, *Primary Examiner.*

UNITED STATES PATENT OFFICE

CERTIFICATE OF CORRECTION

Patent No. 3,210,347 October 5, 1965

Lincoln Harvey Werner et al.

It is hereby certified that error appears in the above numbered patent requiring correction and that the said Letters Patent should read as corrected below.

Column 7, lines 2 and 3, for "both inclusive R_1 represents a member selected from the group consisting of phenyl, and R_2 represents hydrogen," read -- both inclusive, R_1 represents phenyl, and R_2 represents a member selected from the group consisting of hydrogen, --.

Signed and sealed this 19th day of July 1966.

(SEAL)
Attest:

ERNEST W. SWIDER
Attesting Officer

EDWARD J. BRENNER
Commissioner of Patents