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PATENT SPECIFICATION

NO DRAWINGS

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Int. Cl.:—C 07 d 93/32

COMPLETE SPECIFICATION

Novel 1,2,4-Benzothiadiazine-1,1-Dioxides and Process for their Manufacture

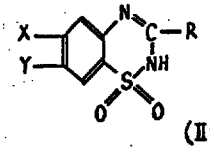
We, SCHERICO LTD., of Topfarstrasse 5, Lucerne, Switzerland, a body corporate constituted under the laws of Switzerland, do hereby declare the invention for which we pray that a patent may be granted to us and the method by which it is to be performed, to be particularly described in and by the following statement:—

The invention relates to novel 1,2,4-benzothiadiazine-1,1-dioxides and processes for their manufacture.

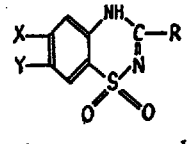
The novel compounds of the present invention are 3 - cyclopentenyl - 2H - 1,2,4 - benzothiadiazine - 1,1 - dioxides having a chloro, bromo, trifluoromethyl, nitro or methyl substituent in each of the 6- and 7-positions thereof, with the proviso that when one of the said positions is substituted by nitro or methyl the other is substituted by chloro, bromo or trifluoromethyl, and their tautomers and non-toxic salts, especially their alkali metal salts.

As used in the present specification and claims the term "cyclopentenyl" means those cyclopentenyl radicals which contain a double bond not in conjugation with the 1,2,4 - benzothiadiazine - 1,1 - dioxide nucleus, that is a 2-cyclopentenyl or a 3-cyclopentenyl radical. Apart from the cyclopentenyl radical in position 3 the present compounds are unsubstituted in the heterocyclic portion of the nucleus.

The compounds according to the present invention include those having one of the following general formulae:



(II^{I})



(II^{II})

in which X and Y independently represent chloro, bromo, trifluoromethyl, nitro or methyl, with the proviso that when one of X and Y represents nitro or methyl the other represents chloro, bromo or trifluoromethyl, and R is a cyclopentenyl radical and their non-toxic alkali metal salts and other non-toxic salts. Especially preferred are 3-(3-cyclopentenyl)-6, - 7 - dichloro - 2H - 1,2,4 - benzothiadiazine - 1,1 - dioxide, 3 - (3 - cyclopentenyl - 6 - trifluoromethyl - 7 - chloro - 2H - 1,2,4 - benzothiadiazine - 1,1 - dioxide and 3 - (3 - cyclopentenyl) - 6 - chloro - 7 - trifluoromethyl - 2H - 1,2,4 - benzothiadiazine - 1,1 - dioxide.

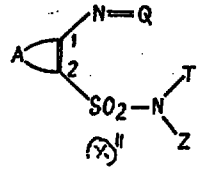
The present compounds may be used in the treatment of hypertension. They are high melting, white crystalline solids which are substantially insoluble in water. They

are, however, soluble in aqueous alkali and in other polar solvents, such as lower aliphatic alcohols. Examination of compounds produced according to the hereinafter described processes reveals, upon ultraviolet and infrared spectrographic analysis, spectral data confirming the molecular structure hereinbefore set forth. For example, the C=N frequency characteristic of the cyclized nucleus is evident. The aforementioned physical characteristics, taken together with the nature of the starting materials and the mode of synthesis, positively confirm the structure of the compounds.

It is known that a 1,2,4-benzothiadiazine-1,1-dioxide may exist in either one or both of the two tautomeric forms which are shown in the formulae above. In one form the double bond is between the 3- and 4-positions atoms, while in the other form the double bond is between the 2- and 3-position atoms. Either or both tautomeric structures are contemplated as within the scope of the instant invention.

The present invention provides a process for the production of 3 - cyclopentenyl - 6X - 7Y - 2H - 1,2,4 - benzothiadiazine - 1,1 - dioxides and tautomers thereof, wherein X and Y are as defined above, which process includes the step of subjecting a compound which differs from the desired compound only in that the thiadiazine ring is broken at one point only and that at least one of the atoms adjacent the break bears a reactive group to an intramolecular condensation so as to cyclise the compound to form the thiadiazine ring.

Thus the process may be carried out by subjecting a substance having the general formula:



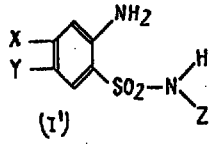
(X)

wherein A together with the C—C-double bond shown represents a phenylene radical having in the 5-position thereof a substituent X and in the 4-position thereof a substituent Y, X and Y being as defined above; Q is (H,H), (H,RCO), (RCO,RCO) or RCOR', wherein R is cyclopentenyl and R' is alkyl, preferably lower alkyl; T is hydrogen or RCO, wherein R has the above meaning (provided that when Q is (H,H) T is RCO); and Z is hydrogen, benzyl, cyclopentenyl or alkyl, preferably lower alkyl; to a condensation reaction by heating, whereby a 3-R -6-X -7-Y -2H-1,2,4-benzothiadiazine-1,1-dioxide is formed. Preferably in the above formula Q represents (H,H), T represents RCO and Z represents hydrogen.

If desired, the 2H - 1,2,4 - benzothiadiazine - 1,1 - dioxide obtained may be converted into a non-toxic salt thereof, preferably an alkali metal salt.

The present novel compounds are weakly acidic in character and their salts may be prepared therefore by methods well known in the art for the preparation of a strong base with a weak acid. Although the alkali metal salt may be obtained on evaporation of an alkaline solution of a compound of this invention, it is preferred to employ non-aqueous media. For example, by mixing together an alcoholic solution of a compound of the present invention with an alcoholic solution containing a stoichiometric quantity of an alkali metal alkoxide and after evaporating the solvent, there is obtained the corresponding alkali metal salt.

Another process for the production of the 3-R -6X -7Y-2H-1,2,4-benzothiadiazine-1,1-dioxides of the invention and their tautomers comprises condensing a 3X-4Y-6-sulphamyl-aniline compound, preferably having the formula



(I')

wherein X, Y, and Z have the above meaning, (Z preferably being hydrogen), with a second reactant of the general formula R—C≡B, wherein R is as defined above and B represents from one to three functional groups or atoms which, in the course of condensation, are split off together with three of the four atoms or groups attached to the two nitrogen atoms shown in the above formula.

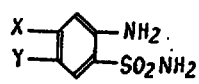
The said second reactant is very conveniently a carboxylic acid of the formula RCOOH or a derivative thereof, such as an alkali metal salt, an ester, for example a simple lower alkyl ester or an ortho ester of the formula $RC(OR')_3$, an acid halide, an anhydride or an amide or a compound convertible into the acid or one of its derivatives. For each of these reactants, R is representative of the cyclopentenyl radical in the 3-position of the 1,2,4-benzothiadiazine-1,1-dioxide nucleus and R' represents a lower alkyl group.

As will be obvious to a person skilled in the art, by slight variation of the conditions of the above reaction with the second reactant, R—C≡B, intermediates of the above formula (X''), wherein at least one of the substituents represented by Q and T is other than hydrogen, are formed. These intermediates may be condensed to benzothiadiazine-1,1-dioxides according to the present invention, such as by heating them to a temperature which preferably does not differ more than about 30°C upwards from their melting points. Although these intermediates are preferably prepared by the above described reaction it is to be understood that they may also be prepared by any other convenient and known process, such as by a process of the type as described in reaction schemes C and D hereinbelow.

The aforementioned reactions utilizing a second reactant of the formula R—C≡B are usually carried out at above room temperature (i.e. 18°C) and below 150°C. In the absence of a solvent, the temperature range is preferably from about 40°C to the boiling point of the particular second reactant applied. A temperature range of about 80°C—130°C is particularly preferred. If the reaction is effected in the presence of an inert organic solvent, the temperature is usually maintained at about the reflux temperature of the reaction mixture. Solvents such as dioxan, benzene, dimethylene glycol and dimethyl ether are preferred, but other suitable non-reactive solvents may also be used.

In particular when the reactant R—C≡B is a carboxylic acid, acid halide or acid anhydride, a catalyst may be used in order to facilitate the direct obtention of the desired 1,2,4-benzothiadiazine-1,1-dioxide. When used, the catalyst may be a basic substance, such as the alkali metal hydroxides, carbonates or bicarbonates or ammonium hydroxide, an acidic substance, such as perchloric acid, or a tertiary amine, such as pyridine, picoline or lutidine.

In the preferred embodiments of the present process the substance to be reacted with the reactant R_1—C≡B is an *o*-sulfamylaniline of the general formula I:

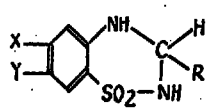


(I)

wherein X and Y are chloro, bromo, trifluoromethyl, nitro or methyl, with the proviso that, when one of X and Y is nitro or methyl the other is chloro, bromo or trifluoromethyl.

The 3 - R - 6X - 7Y - 2H - 1,2,4 - benzothiadiazine - 1,1 - dioxides and their tautomers may also be prepared by introducing into the corresponding 3,4 - dihydro - 1,2,4 - benzothiadiazine - 1,1 - dioxide a double bond between the atoms in positions 3 and 4.

For example, a compound of the general formula



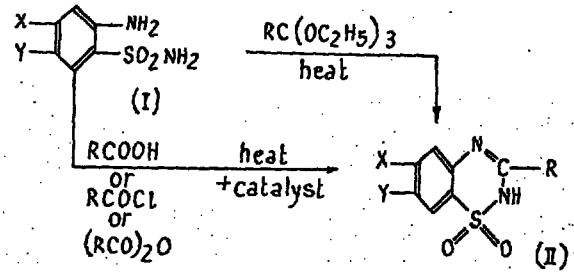
wherein X, Y and R have the above meaning, may be converted into the corresponding 1,2,4 - benzothiadiazine - 1,1 - dioxide by treatment with a dehydrogenation agent, for example potassium permanganate.

In another embodiment of this process a compound of the immediately preceding formula having W instead of R_1 in position 3 (wherein W represents cyclopentenyl

with a halogen atom attached to the α-position thereof) is treated with known dehydrohalogenation means whereby the corresponding 1,2,4-benzothiadiazine-1,1-dioxide is formed.

The aforementioned preferred reactions are illustrated as follows in reaction schemes A—E. It is to be understood that these schemes as well as the description clarifying them are not intended and should not be construed in any way to limit the scope of the present invention.

A



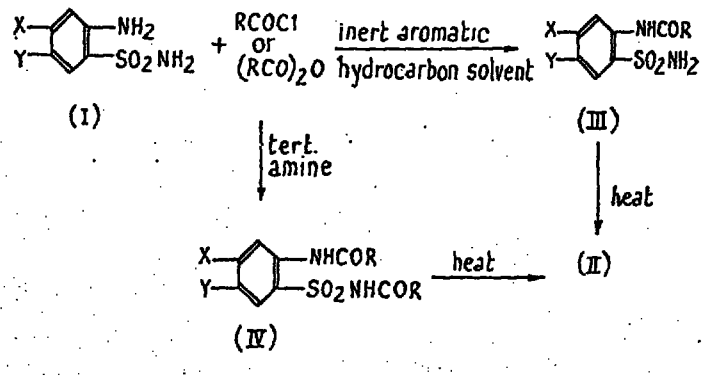
wherein X and Y are chloro, bromo or trifluoromethyl and R is cyclopentenyl.

Although the ortho ester reactant $RC(OC_2H_5)_3$ is shown as being an ethyl ester, it will be apparent that other esters may be similarly employed without changing the final product, since the concerned alkoxy groups are eliminated during the reaction.

The immediately preceding description is of reactants and reactions which in essentially one step produce an X,X - substituted - 3 - R - 2 H- 1,2,4 - benzothiadiazine - 1,1 - dioxide (II). By slight variations in conditions, various intermediates are producible which themselves can be converted to one final product. For example, if the catalyst is omitted during the reaction between the *o*-sulfamylaniline starting material (I), and the acid halide or acid anhydride, there is produced the correspondingly N-acylated-*o*-sulfamylaniline intermediate (III). This reaction is generally effected in an inert aromatic hydrocarbon solvent such as benzene, toluene or xylene, preferably at reflux temperatures. Other solvents such as di-alkyl ethers, and cyclic ethers may also be used. The acylated intermediate may be isolated and heated above its melting point whereupon cyclization occurs forming the appropriate 1,2,4-benzothiadiazine-1,1-dioxide (II). An example of the foregoing is the reaction of 2-sulfamyl-4,5-dichloroaniline with 2-cyclopentene-1-carboxylic acid chloride or 2-cyclopentene-1-carboxylic acid anhydride in refluxing toluene whereupon there is produced 2-sulfamyl-4,5-dichloro-2'-cyclopentenanilide. Upon heating this intermediate above its melting point, there is produced 3-(2-cyclopentenyl)-6,7-dichloro-2H-1,2,4-benzothiadiazine-1,1-dioxide. It is apparent that by varying the *o*-sulfamyl starting material or the acylating agent, the various final compounds falling within the scope of this invention may be readily prepared.

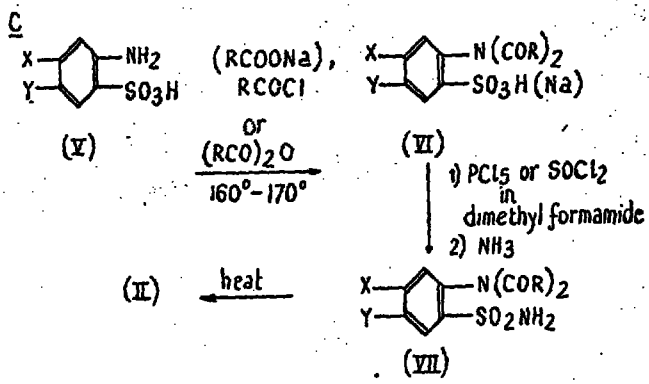
By changing the solvent in the foregoing to a tertiary amine such as a pyridine, a diacylated intermediate (IV) is produced; one acyl group being on the aniline nitrogen atom, and the other on the sulfamyl nitrogen atom. This diacylated intermediate may be cyclized to the 1,2,4-benzothiadiazine-1,1-dioxide in like manner simply by heating above its melting point. Those reactions may be illustrated as follows in Reaction Scheme B:

B



An equivalent reaction involving a modification of the starting material is that shown in Reaction Scheme C:

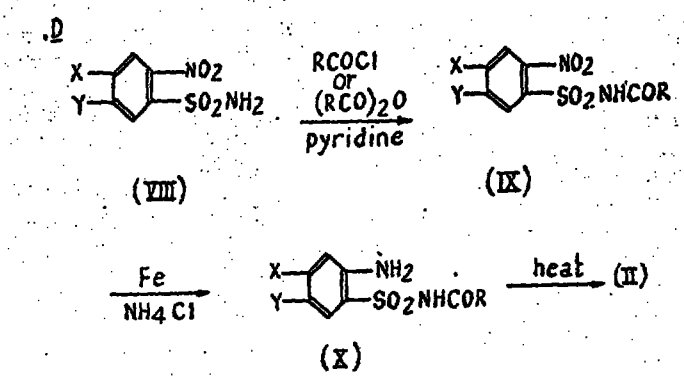
C



In this reaction an X,Y-substituted orthanilic acid (V) is employed as starting material and transformed as above. Diacylation produces (VI) (in the form of its sodium salt when RCOONa has been used.) Compound (VI) can be transformed by known methods to the N,N-di-acyl-sulfonamide (VII), which may spontaneously cyclize to (II) or be converted by heating to the cyclized products of this invention (II), depending on the nature of the substituents X, Y and R.

Reaction Schemes A, B and C all employ an aniline derivative as starting material. Under some circumstances it may be desirable to utilize precursors of the aniline compounds such as sulfamyl-nitrobenzenes (VIII). These substances are convertible to the novel end products (II) by reactions chemically equivalent to A, B and C but providing different intermediates. Such a transformation is shown in Reaction Scheme D:

D

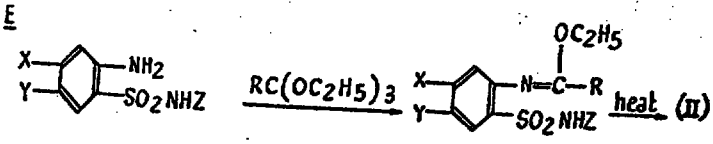


In this reaction scheme acylation of the sulfonamide group is first effected to yield (IX) which upon reduction forms the acylated intermediate (X). It is to be noted that (X) is an isomer of (III), scheme B, and can be similarly converted to the end product (II) by heating.

In reaction schemes C and D, sulfonamide intermediates have been shown (formulae (VII and VIII) which (as illustrated at the example of formula VII) may be prepared by reacting the respective sulfonyl chlorides with ammonia. Equivalent to these N-unsubstituted sulfonamides are the respective N-alkyl- and N-aralkyl-substituted sulfonamides. These may be produced by amination of the respective sulfonyl chlorides with a primary alkyl amine or aralkyl amine, preferably benzylamine. Their corresponding transformation products will carry this substituent which is eliminated during the conversion to the 1,2,4-benzothiadiazine-1,1-dioxide (II). For example, if benzylamine is used, the starting material (I) in scheme B would possess a benzyl substituent on the sulfamyl nitrogen atom. This substance can be acylated as described and during the heating of the acylated product the benzyl group is eliminated and (II) is formed. An analogous reaction occurs in schemes C, D and in that part A pertaining to the reaction with carboxylic acids or derivatives thereof.

In reaction scheme E the ortho ester reaction of scheme A is shown for a starting material containing a benzyl or cyclopentenyl substituent on the sulfamyl nitrogen atom. The reaction then proceeds in two steps with the formation of an intermediate (XII) which upon heating forms (II).

E



(XI) (XII)

Z = benzyl or cyclopentenyl.

The following examples will serve to further exemplify and illustrate the preferred method of preparation of the compounds of this invention.

The manner of using the present compounds will now be described.

It is well known that certain 1,2,4-benzothiadiazine-1,1-dioxides in their action upon the peripheral vasculature exhibit significant anti-hypertensive effects. Indeed, at one time it was thought that such compounds would enjoy a wide range of application in the alleviation and control of, for example, essential hypertension, malignant hypertension, Buerger's Disease and Raynauds' Disease. Unfortunately, however, such compounds have also exhibited electrolyte retention and hyperglycemic properties which have seriously impaired their general usefulness in the alleviation and control of hypertension. In contrast to these prior art 1,2,4-benzothiadiazine-1,1-dioxides, the compounds of this invention exhibit more potent anti-hypertensive effects without concomitant electrolyte retention and hyperglycemic effects.

Various pharmacological procedures are carried out to ascertain the hypotensive, electrolyte retention, and hyperglycemic properties of the compounds of this invention. For example, the hypotensive potency of the compounds is first evaluated by administering a wide range of doses to groups of hypertensive rats (prepared by implantation of desoxycorticosterone acetate pellets, plus maintainence on saline). From statistical evaluations of the effects of this series of doses, the minimum effective dose (MED) for anti-hypertensive efficacy is determined. On the basis of this test, as well as other standard evaluative procedures such as the standard in vitro aortic strip test, it is determined that the compounds of this invention exhibit enhanced potency values relative to the heretofore mentioned prior art compounds. Similarly, when evaluated according to acceptable pharmacological techniques it is also determined that the compounds of this invention exhibit significantly lowered electrolyte retention and hyperglycemic properties when compared with the prior art 1,2,4-benzothiadiazine-1,1-dioxides. Thus, from an analysis of the pharmacological test results, it is seen that the compounds of this invention represent a significant improvement in the alleviation and control of hypertension. Quite unexpectedly, it is also found that the 3-cyclopentenyl-1,2,4-benzothiadiazine-1,1-dioxides of this invention exhibit hypotensive effects which are significantly longer in duration and of greater potency than the corresponding 3-cyclopentyl-1,2,4-benzothiadiazine-1,1-dioxides.

It is determined that 3-cyclopentenyl-1,2,4-benzothiadiazine-1,1-dioxides having a nitro or a methyl substituent in place of one of the 6- or 7-position chloro, bromo and trifluoromethyl substituents will result in compounds in which the pharmacological profile is not materially affected. Such modified compounds, as for example, 3 - (3 - cyclopentenyl) - 6 - chloro - 7 - methyl - 1,2,4 - benzothiadiazine - 1,1 - dioxide, 3 - (3 - cyclopentenyl) - 6 - nitro - 7 - chloro - 1,2,4 - benzothiadiazine - 1,1 - dioxide are therefore also embraced within the concepts of this application.

The effective dosage of the compounds of this invention depends upon the severity, the stage and the individual characteristics of each case and will be determined by an attending diagnostician. Generally a dosage range of from 0.03 to about 1 mg. per kg. of body weight per day constitutes the overall range, for the instant class of compounds.

The novel compounds of our invention may be used in the form of pharmaceutical preparations which contain the active ingredient in admixture with a pharmaceutical carrier suitable for enteral or parenteral administration. Such preparations may be in solid forms, as for example, tablets, capsules and suppositories, or in liquid forms, as for example, elixirs, emulsions and injectables.

In the formulation of pharmaceutical preparations there can be employed such substances which do not react with the active substances, as for example, water gelatin,

lactose, starches, magnesium stearate, calcium carbonate, talc, vegetable oils, benzyl alcohols, gums, polyalkylene glycols, and petroleum jelly. The active ingredient is preferably present in the preparation in such proportions by weight that the proportion by weight of active ingredient in the formulation to be administered lies between 0.1% and 50%.

Representative preparations are illustrated below with the preparations administerable once to several times per day.

TABLET FORMULATION

The following formulation provides for the manufacture of 1000 tablets:

(1)	3-(3-cyclopentenyl)-6,7-dichloro-2H-1,2,4-benzothiadiazine-1,1-dioxide	25 g
(2)	Lactose, U.S.P.	181 g
(3)	Corn starch, U.S.P.	92.5 g
(4)	Magnesium stearate	1.5 g

Thoroughly granulate a mixture of 72.5 g. of corn starch and the lactose with a paste prepared by dissolving 20 gm. of corn starch in 100 ml. of hot distilled water. Dry the resulting granulation at 40—45°C. and pass it through a No. 16 mesh screen. To the dried, screened granulation add a blended mixture of the active ingredient (1) and the magnesium stearate. Thoroughly blend and then press into tablets of 300 mg. each.

CAPSULE FORMULATION

The following formulation provides for the manufacture of 1000 capsules:

(1)	3-(3-cyclopentenyl)-6,7-dichloro-2H-1,2,4-benzothiadiazine-1,1-dioxide	25 g
(2)	Lactose	273.5 g
(3)	Magnesium stearate	1.5 g

Mix active ingredients (1) with the lactose and blend in the magnesium stearate. Fill hard gelatin capsules with 300 mg. each of the blended mixture to produce capsules containing 25 mg. of 3 - (3 - cyclopentenyl) - 6,7 - dichloro - 2H - 1,2,4 - benzothiadiazine - 1,1 - dioxide.

PARENTERAL FORMULATION

The following formulation provides for the manufacture of 1000 vials each containing 100 mg. of active ingredient, as its sodium salt:

(1)	3-(3-cyclopentenyl)-6,7-dichloro-2H-1,2,4-benzothiadiazine-1,1-dioxide sodium salt	10.95 g
(2)	Monobasic potassium phosphate	6.0 g
(3)	Water for injection, U.S.P.q.s.	1.0 litre

Dissolve ingredients (1) and (2) in approximately 80 percent of the volume of the water (3) and filter the resulting solution. Add to the filtrate sufficient water to make a 1000 ml. volume. Sterile-filter the solution and aseptically fill one milliliter portions of the so-prepared solution into two milliliter vials, then lyophilize. After the lyophilized cake is dry aseptically stopper the vials with rubber plugs and seal.

It is to be understood that instead of the exemplified active ingredient any other of the active compounds of the present invention may be used in the above formulation examples.

EXAMPLE 1

3-(3-Cyclopentenyl)-6,7-dichloro-2H-1,2,4-benzothiadiazine-1,1-dioxide

And 12.7 g. of oxalyl chloride to a solution of 11.2 g. of 3 - cyclopentene - 1 - carboxylic acid in 10 ml. of benzene. After 15 minutes at room temperature heat on a steam bath for 30 minutes. Dilute with 300 ml. of benzene, added 24.1 g of 2-amino-4,5-dichlorobenzenesulfonamide and reflux the resulting mixture for 6 hrs. Cool and filter off the resulting 2 - (3 - cyclopentene - 1 - carboxamido) - 4,5 - dichlorobenzenesulfonamide. Add this material to 1500 ml. of 28% aqueous ammonium hydroxide

solution and reflux for 1.5 hrs. Cool, filter off the crude product and recrystallize from methanol-acetone to give the product of this example. (m.p. = 344—346°C). By substituting equivalent quantities of 2 - amino - 4 - chloro - 5 - trifluoromethyl - benzenesulfonamide, 2 - amino - 4 - bromo - 5 - trifluoromethyl - benzenesulfonamide, 2 - amino - 4 - trifluoromethyl - 5 - chlorobenzenesulfonamide, 2 - amino - 4,5 - dibromo - benzenesulfonamide, or 2 - amino - 4,5 - ditrifluoromethyl - benzenesulfonamide in place of the 2 - amino - 4,5 - dichloro - benzenesulfonamide, and by following substantially the same reaction procedure of this example, there are produced 3 - (3 - cyclopentenyl) - 6 - chloro - 7 - trifluoromethyl - 2H - 1,2,4 - benzothiadiazine - 1,1 - dioxide, 3 - (3 - cyclopentenyl) - 6 - bromo - 7 - trifluoromethyl - 2H - 1,2,4 - benzothiadiazine - 1,1 - dioxide, 3 - (3 - cyclopentenyl) - 6 - trifluoromethyl - 7 - chloro - 2H - 1,2,4 - benzothiadiazine - 1,1 - dioxide, 3 - (3 - cyclopentenyl) - 6,7 - dibromo - 2H - 1,2,4 - benzothiadiazine - 1,1 - dioxide and 3 - (3 - cyclopentenyl) - 6,7 - di-(trifluoromethyl) - 2H - 1,2,4 - benzothiadiazine - 1,1 - dioxide, respectively.

Example 2
3-(2-Cyclopentenyl)-6,7-dichloro-2H-1,2,4-benzothiadiazine-1,1-dioxide

Add 12.7 g. of oxalyl chloride to a solution of 11.2 g. of 2 - cyclopentene - 1 - carboxylic acid in 10 ml. of benzene. After 15 minutes at room temperature heat on a steam bath for 30 minutes. Dilute with 300 ml of benzene, add 24.1 g of 2 - amino - 4,5 - dichloro - benzenesulfonamide and reflux the resulting mixture for 6 hrs. Cool and filter the resulting 2 - (2 - cyclopentene - 1 - carboxamido) - 4,5 - dichlorobenzenesulfonamide. Add this material to 1500 ml. of 28% aqueous ammonium hydroxide solution and reflux for 1.5 hrs. Cool, filter off the crude product and recrystallize from methanol-acetone to give the product of this example.

By substituting equivalent quantities of 2 - amino - 4 - chloro - 5 - trifluoromethyl-benzenesulfonamide, 2 - amino - 4 - bromo - 5 - trifluoromethyl - benzenesulfonamide, 2 - amino - 4 - trifluoromethyl - 5 - chloro - benzenesulfonamide, 2 - amino - 4,5 - dibromo - benzenesulfonamide, or 2 - amino - 4,5 - ditrifluoromethyl - benzenesulfonamide in place of the 2 - amino - 4,5 - dichlorobenzenesulfonamide, and by following substantially the same reaction procedure of this example, there are produced 3 - (2 - cyclopentenyl) - 6 - chloro - 7 - trifluoromethyl - 2H - 1,2,4 - benzothiadiazine - 1,1 - dioxide, 3 - (2 - cyclopentenyl) - 6 - bromo - 7 - trifluoromethyl - 2H - 1,2,4 - benzothiadiazine - 1,1 - dioxide, 3 - (2 - cyclopentenyl) - 6 - trifluoromethyl - 7 - chloro - 2H - 1,2,4 - benzothiadiazine - 1,1 - dioxide, 3 - (2 - cyclopentenyl) - 6,7 - dibromo - 2H - 1,2,4 - benzothiadiazine - 1,1 - dioxide and 3 - (2 - cyclopentenyl) - 6,7 - di(trifluoromethyl) - 2H - 1,2,4 - benzothiadiazine - 1,1 - dioxide, respectively.

The following example is illustrative of an alternative method for the preparation of the compositions of this invention:

Example 3
3-(3-Cyclopentenyl)-6,7-dichloro-2H-1,2,4-benzothiadiazine-1,1-dioxide

A: Ethyl ortho-3-cyclopentene-1-carboxylate.

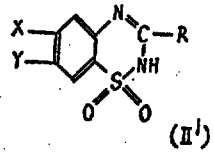
Add 50 g. of 3 - cyclopentene - 1 - carbonyl chloride dropwise, with stirring, to 1 l. of 28% aqueous ammonium hydroxide solution cooled in an ice bath. After 1 hr. filter off the 3-cyclopentene-1-carbonamide, washed with water and air-dry. Heat an intimate mixture of 40 g. of the dry powdered amide and 80 g. of phosphorus pentoxide at 100—250°C., and distil out 3 - cyclopentene - 1 - cyanide from the reaction mixture under vacuum. Dissolve 25 g. of the cyanide in 50 ml. of absolute ethanol and bubble 10 g. of hydrogen chloride gas into the solution at 0°C. Keep the solution at this temperature for 7 days. Add 500 ml. of anhydrous ether to the solution and allow to stand at room temperature overnight. Cool the reaction mixture to −40°C. and filter off rapidly the solid imino ester hydrochloride. Dissolve the latter in 100 ml. of absolute ethanol by stirring at room temperature and dilute the solution with 200 ml. of anhydrous ether. Reflux for 16 hr., cool, filter off the precipitated ammonium chloride, remove the solvent and distil the residue under vacuum to obtain ethyl ortho - 3 - cyclopentene - 1 - carboxylate.

B: Heat a mixture of 5 g. of 2 - amino - 4,5 - dichlorobenzenesulfonamide and 15 ml. of ethyl ortho - 3 - cyclopentene - 1 - carboxylate at 100—110°C for 1.5 hrs. Cool and filter the solids, recrystallize the desired product from methanol-acetone to yield 3 - (3 - cyclopentenyl) - 6,7 - dichloro - 2H - 1,2,4 - benzothiadiazine - 1,1 - dioxide, (m.p. = 344—346°C).

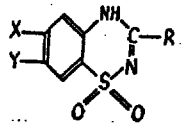
WHAT WE CLAIM IS:—

1. 3 - Cyclopentenyl - 6X - 7Y - 2H - 1,2,4 - benzothiadiazine - 1,1 - dioxides, and tautomers and non-toxic salts thereof, in which X and Y independently represent chloro, bromo, trifluoromethyl, nitro or methyl, with the proviso that when one of X and Y represents nitro or methyl the other must represent chloro, bromo or trifluoromethyl.

2. 3 - Cyclopentenyl - 6X - 7Y - 2H - 1,2,4 - benzothiadiazine - 1,1 - dioxides, and non-toxic salts thereof, having one of the following general formulae:



(II')



(II")

in which X and Y have the same significance as in claim 1, and R is a cyclopentenyl radical.

3. Compounds as claimed in claim 1 or 2 in which both X and Y represent chloro.

4. Compounds as claimed in claim 1 or 2 in which X represents chloro and Y represents trifluoromethyl, or X represents trifluoromethyl and Y represents chloro.

5. 3 - (3 - Cyclopentenyl) - 6,7 - dichloro - 2H - 1,2,4 - benzothiadiazine - 1,1 - dioxide.

6. 3 - (2 - Cyclopentenyl) - 6,7 - dichloro - 2H - 1,2,4 - benzothiadiazine - 1,1 - dioxide.

7. 3 - (3 - Cyclopentenyl) - 6 - trifluoromethyl - 7 - chloro - 2H - 1,2,4 - benzothiadiazine - 1,1 - dioxide.

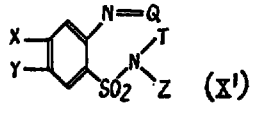
8. 3 - (3 - Cyclopentenyl) - 6 - chloro - 7 - trifluoromethyl - 2H - 1,2,4 - benzothiadiazine - 1,1 - dioxide.

9. Alkali metal salts of the compounds claimed in any one of the preceding claims.

10. 3 - Cyclopentenyl - 6X - 7Y - 1,2,4 - benzothiadiazine - 1,1 - dioxides, and tautomers and non-toxic salts thereof, in which X and Y have the same significance as in claim 1, substantially as hereinbefore described.

11. Process for preparing 3 - cyclopentenyl - 6X - 7Y - 1,2,4 - benzothiadiazine - 1,1 - dioxides and tautomers thereof, wherein X and Y have the same significance as in claim 1, which process includes the step of subjecting a compound which differs from the desired compound only in that the thiadiazine ring is broken at one point only and that at least one of the atoms adjacent the break bears a reactive group to an intramolecular condensation so as to cyclise the compound to form the thiadiazine ring.

12. Process as claimed in claim 11, in which a compound of the formula:



(X')

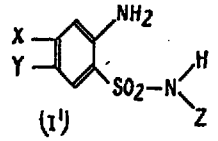
wherein X and Y have the same significance as in claim 11, Q represents (H,H), (H,RCO), (RCO,RCO) or (RCOR), T represents hydrogen or RCO, except that Q and T cannot both represent hydrogen, with R representing cyclopentenyl and R' representing alkyl, and Z represents hydrogen, benzyl, cyclopentenyl or alkyl, is heated to effect the intramolecular condensation.

13. Process as claimed in claim 12, in which in the compound of formula (X') Q represents (H,H), T represents RCO and Z represents hydrogen.

* C L M S *

14. Process for preparing 3R - 6X - 7Y - 2H - 1,2,4 - benzothiadiazine - 1,1 - dioxides, and tautomers thereof, which comprises condensing together a 3X - 4Y - 6 - sulphamyl - aniline compound and a compound of the formula R—C≡B, wherein R represents cyclopentenyl, X and Y have the same significance as in claim 1 and B represents from one to three functional groups or atoms which, in the course of the condensation, are split off together with three of the atoms or groups attached to the two nitrogen atoms in the aniline and sulphamyl groups in the sulphamyl-aniline compound.

15. Process as claimed in claim 14, in which the sulphamyl-aniline compound has the formula



(I')

wherein X and Y have the same significance as in claim 1, and Z has the same significance as in claim 12.

16. Process as claimed in claim 15, in which Z in the compound of formula I' represents hydrogen.

17. Process as claimed in any one of claim 14—16, in which the reactant R—C≡B is a carboxylic acid of the general formula R—COOH or an ester, including ortho esters, anhydride, amide or acid halide thereof.

18. Process as claimed in any of claims 14—17, in which the condensation is carried out at a temperature above room temperature and below 150°C.

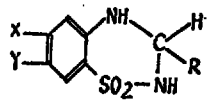
19. Process as claimed in claim 18, in which the condensation is carried out at a temperature of between 80 and 130°C.

20. Process as claimed in any one of claims 14—19, in which the condensation is carried out in the presence of a catalyst.

21. Process as claimed in any one of claims 14—20, in which the condensation is carried out in the presence of an inert organic solvent.

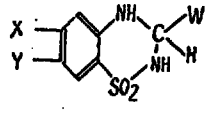
22. Process for preparing 3R - 6X - 7Y - 2H - 1,2,4 - benzothiadiazine - 1,1 - dioxides, and tautomers thereof, wherein R represents cyclopentenyl and X and Y have the same significance as in claim 1 which comprises introducing into a 3,4-dihydro - 1,2,4 - benzothiadiazine - 1,1 - dioxide a double bond between the atoms in positions 3 and 4.

23. Process as claimed in claim 22, in which the 3,4 - dihydro - 1,2,4 - benzothiadiazine - 1,1 - dioxide has the formula:



wherein R, X and Y have the same significance as in claim 22, and the introduction of the double bond is effected by treating it with a dehydrogenation agent.

24. Process as claimed in claim 22, in which the 3,4 - dihydro - 1,2,4 - benzothiadiazine - 1,1 - dioxide has the formula:



wherein X and Y have the same significance as in claim 22, and wherein W represents cyclopentenyl with a halogen atom attached to the α-position thereof, and the introduction of the double bond is effected by dehydrohalogenation.

25. Process as claimed in any of claims 11—24, in which the 2H - 1,2,4 - benzothiadiazine - 1,1 - dioxide so-obtained is transformed into a non-toxic salt thereof.

26. Process as claimed in claim 25 in which the 2H - 1,2,4 - benzothiadiazine - 1,1 - dioxide so-obtained is transformed into an alkali metal salt thereof.

27. Process for the preparation of a 3 - cyclopentyl - 6X - 7Y - 2H - 1,2,4 - benzothiadiazine - 1,1 - dioxide claimed in any one of claims 1 to 10, substantially as described with particular reference to any one of the foregoing examples.

* C L M S *

28. 3 - cyclopentyl - 6X - 7Y - 2H - 1,2,4 - benzothiadiazine - 1,1 - dioxides and tautomers and non-toxic salts thereof whenever prepared by a process as claimed in any one of claims 1—27.

29. A pharmaceutical composition which comprises, as an active ingredient, a 3 - cyclopentenyl - 6 - X - 7 - Y - 2H - 1,2,4 - benzothiadiazine - 1,1 - dioxide, or a tautomer or non-toxic salt thereof, in which X and Y have the same significance as in claim 1 and, in association therewith, a pharmaceutically acceptable carrier.

30. Process for the preparation of a pharmaceutical composition as claimed in claim 29, wherein the active ingredient is admixed with a pharmaceutically acceptable carrier.

31. A pharmaceutical composition whenever prepared by a process as claimed in claim 30.

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