PATENT SPECIFICATION

NO DRAWINGS

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863,474

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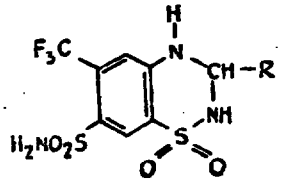
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COMPLETE SPECIFICATION

Benzothiadiazine Derivatives and their preparation

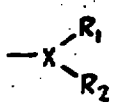
I, KNUD ABILDGAARD, a Danish Subject, trading as LØVENS KEMISKE FABRIK ved A. Kongsted, of 11, Ballerup Byvej, Denmark (formerly of 19, Bronshøjvej, Copenhagen, Denmark), do hereby declare the invention for which I pray that a patent may be granted to me, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention relates to 6-trifluoromethyl-7 - sulfamyl - 3,4 - dihydro - 1,2,4 - benzothiadiazine - 1,1 - dioxide and derivatives thereof, which compounds have the general formula:



(I)

in which R is a hydrogen atom; or a cyclohexyl, phenyl, benzoyl, furyl, or pyridyl group; or a group having the general formula:



(II)

in which X is a straight or branched hydrocarbon group, which may contain a carbon-to-carbon double bond; R_1 is a hydrogen atom, a phenyl group, or a lower carbalkoxy group containing not more than 6 carbon atoms; and R_2 is a hydrogen, fluorine, chlorine, or bromine atom; a hydroxyl group optionally etherified with a lower alkyl group containing from 1 to 5 carbon atoms, a lower acyl group containing from 2 to 8 carbon atoms, or a lower carbalkoxy group containing from 2 to 6 carbon atoms; a nitro group; a phenyl group optionally substituted with a fluorine, chlorine, or bromine atom, or with a lower alkyl or lower alkoxy group containing from 1 to 5 carbon atoms; a phenoxy group optionally substituted with one or more fluorine, chlorine, or bromine atoms, or a nitro, or an amino group; or a benzyl mercapto group.

The said compounds are hitherto unknown substances, and it has been found that they are capable of exerting strongly saluretic effects when administered orally or parenterally to human beings. In table II the saluretic activity of a number of the compounds is indicated as found in tests with rats.

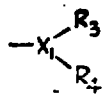
Among the derivatives hereinbefore defined the members of the following sub-groups have proved to possess particularly high saluretic activity in tests with rats. After the definition of each sub-group are indicated some of the members of the sub-group which in tests with rats have been found to possess the same or a higher saluretic activity than 6-trifluoromethyl-7 - sulfamyl - 3,4 - dihydro - 1,2,4 - benzothiadiazine-1,1-dioxide:

(A) Compounds comprised by formula (1) in which R is an alkyl group which contains from one to six carbon atoms, and which may be substituted with a fluorine, chlorine, or bromine atom, or a nitro group.

[*Price 3s. 6d.*]

3 - *n* - Butyl - 6 - trifluoromethyl - 7-sulfamyl - 3,4 - dihydro - 1,2,4 - benzothiadiazine - 1,1 - dioxide (example 14).
3 - n - Pentyl - 6 - trifluoromethyl - 7-sulfamyl - 3,4 - dihydro - 1,2,4 - benzothiadiazine - 1,1 - dioxide (ex. 16).
3 - Bromomethyl - 6 - trifluoromethyl-7 - sulfamyl - 3,4 - dihydro - 1,2,4-benzothiadiazine-1,1-dioxide (ex. 10).

(B) Compounds comprised by formula (I) in which R is a group having the general formula:



in which X_1 is an aliphatic hydrocarbon group, R_3 is a hydrogen atom, or a phenyl group, and R_4 is a phenyl group; which may be substituted with a fluorine, chlorine or bromine atom or a lower alkyl group containing from 1 to 5 carbon atoms.

3 - Benzyl - 6 - trifluoromethyl - 7-sulfamyl - 3,4 - dihydro - 1,2,4 - benzothiadiazine-1,1-dioxide (exs. 24 and 25).
3 - *β* - Phenylethyl - 6 - trifluoromethyl - 7 - sulfamyl - 3,4 - dihydro-1,2,4 - benzothiadiazine - 1,1 - dioxide (ex. 26).
3 - p - Chlorobenzyl - 6 - trifluoromethyl - 7 - sulfamyl - 3,4 - dihydro-1,2,4 - benzothiadiazine - 1,1 - dioxide (ex. 28).

(C) Compounds comprised by formula (I) in which R is an alkoxyalkyl group containing not more than five carbon atoms.

3 - *β* - Methoxyethyl - 6 - trifluoromethyl - 7 - sulfamyl - 3,4 - dihydro-1,2,4 - benzothiadiazine - 1,1 - dioxide (ex. 19).

(D) Compounds comprised by formula (I) in which R is a phenoxyalkyl or phenylalkoxyalkyl group, in which groups the phenyl radical may be substituted with a fluorine, chlorine, bromine atom, or a nitro, or an amino group, which radicals do not contain more than ten carbon atoms.

3 - Benzyloxymethyl - 6 - trifluoromethyl - 7 - sulfamyl - 3,4 - dihydro-1,2,4 - benzothiadiazine - 1,1 - dioxide (ex. 29).
3 - *β* - Benzylmercaptoethyl - 6 - trifluoromethyl - 7 - sulfamyl - 3,4-dihydro - 1,2,4 - benzothiadiazine - 1,1-dioxide (ex. 36).

(E) Compounds comprised by formula (I) in which R is a carbalkoxyalkyl group, the alkyl radical of said group containing one or two carbon atoms.

The compounds comprised by formula (I) can be produced by reacting 5-trifluoromethyl-2,4-disulfamylaniline with an aldehyde having the general formula RCHO, in which R has the same meaning as in formula (I). The said aldhehyde may be replaced by a reactive derivative of the same, such as an acetal, a *α*-halogenalkylether, a vinylester, a vinylether, or a 1,1-diiodo-alkane (which is capable of reacting in a manner analogous to an aldehyde), or a polymer, a hydrosulphite or a cyanhydrin of the aldehyde.

The reaction of the aniline with the aldehyde can be accelerated by adding a catalytic amount of an acid, preferably of a strong acid, such as hydrochloric acid, sulphuric acid or toluenesulphonic acid. In the cases where the 3-position is substituted with a substituent containing a nitro-group, the nitro-group may be reduced to the corresponding amino-group by means of a catalytic hydrogenation.

The invention will now be illustrated by the following Examples.

EXAMPLE 1

6-Trifluoromethyl-7-sulfamyl-3,4-dihydro-1,2,4-benzothiadiazine-1,1-dioxide.

3.2 g. of 5-trifluoromethyl-2,4-disulfamylaniline was added to a solution of 0.33 g. of paraformaldehyde in 25 ml. of 2-ethoxyethanol together with a catalytic amount of *p*-toluenesulphonic acid, and the mixture was boiled with reflux for 5 hours. Thereafter, the solvent was distilled off in vacuo, and the residue was triturated with 30 ml. of ethyl acetate. Thereby the reaction product crystallized out. By recrystallization from methanol/water the desired substance was obtained with a m.p. of 272—273° C.

EXAMPLE 2

6-Trifluoromethyl-7-sulfamyl-3,4-dihydro-1,2,4-benzothiadiazine-1,1-dioxide.

3.2 g. of 5-trifluoromethyl-2,4-disulfamylaniline was dissolved in a mixture of 25 ml. of 99% ethanol and 10 ml. of ethylal. A catalytic amount of *p*-toluenesulphonic acid was added and the solution was boiled with reflux overnight. The solvent was removed in vacuo. By recrystallisation of the crude residue from methanol/water, the desired substance was obtained with a m.p. of 271—272° C.

EXAMPLE 3

6-Trifluoromethyl-7-sulfamyl-3,4-dihydro-1,2,4-benzothiadiazine-1,1-dioxide.

To a solution of 3.2 g. of 5-trifluoromethyl-2,4-disulfamylaniline in 50 ml. of 99% ethanol was added 3 g. of sodium formaldehyde sulphoxylate, and the resulting suspension was boiled with reflux while stirring for 16 hours. After cooling, 100 ml. of water was added, and most of the ethanol was removed in vacuo. The precipitate thereby formed was filtered off and washed with water. By recrystallization from methanol/water the desired substance was obtained with a m.p. of 270—271.5° C.

EXAMPLE 4

6-Trifluoromethyl-7-sulfamyl-3,4-dihydro-1,2,4-benzothiadiazine-1,1-dioxide.

To a solution of 16 g. of sodium hydroxide in 1200 ml. of water was added 128 g. of 5-trifluoromethyl-2,4-disulfamylaniline. The mixture was heated to the boiling point, and to the clear solution thus obtained 33.5 ml. of a 36% aqueous formaldehyde solution was added. The mixture was boiled with reflux for 4 hours, and cooled to 55° C. 20% aqueous sulphuric acid was then added while stirring until a pH of 5—6 had been reached. The resulting suspension was filtered, the filter cake was washed with water, and the resulting product was dried at 90—100° C. The desired product was obtained with a m.p. of 272—273° C.

EXAMPLE 5

6-Trifluoromethyl-7-sulfamyl-3,4-dihydro-1,2,4-benzothiadiazine-1,1-dioxide.

A mixture of 1.0 g. of 5-trifluoromethyl-2,4-disulfamylaniline, 0.25 g. of 35% aqueous formaldehyde solution and 100 ml. of water was boiled with reflux for 18 hours. After cooling, the crystals were filtered off, washed on the filter with 2 × 5 ml. of water and dried at 100° C. Thereby the desired substance was obtained with a m.p. of 271—273° C. This reaction can also be carried out in aqueous 1 N HCl as the reaction medium.

EXAMPLE 6

3-Methyl-6-trifluoromethyl-7-sulfamyl-3,4-dihydro-1,2,4-benzothiadiazine-1,1-dioxide.

3.2 g. of 5-trifluoromethyl-2,4-disulfamylaniline was suspended in a mixture of 25 ml. of ethanol and 10 ml. of ethylvinylether. A catalytic amount of *p*-toluenesulphonic acid was added and the mixture was boiled with reflux for 30 minutes. The solvent was removed in vacuo, and the oily residue crystallized by addition of ethylacetate and hexane. By recrystallization from methanol/water the desired substance was obtained with a m.p. of 240—240.5° C.

EXAMPLE 7

3-Methyl-6-trifluoromethyl-7-sulfamyl-3,4-dihydro-1,2,4-benzothiadiazine-1,1-dioxide.

3.2 g. of 5-trifluoromethyl-2,4-disulfamylaniline and 0.95 g. of vinylacetate were dissolved in 25 ml. of dioxane. A catalytic amount of *p*-toluenesulphonic acid was added, and the mixture was boiled with reflux for 5 hours. The reaction mixture was evaporated to dryness in vacuo, and the residue was dissolved in methanol and precipitated by addition of water. The desired substance was thereby obtained in pure form with a m.p. of 245—246° C.

EXAMPLE 8

3-Methyl-6-trifluoromethyl-7-sulfamyl-3,4-dihydro-1,2,4-benzothiadiazine-1,1-dioxide.

3.2 g. of 5-trifluoromethyl-2,4-disulfamylaniline and 1.2 g. of α-chloroethyl ethyl ether were dissolved in 20 ml. of dioxane. A catalytic amount of *p*-toluenesulphonic acid was added, and the mixture was boiled with reflux overnight. The reaction mixture was evaporated to dryness in vacuo, the residue dissolved in methanol and crystallized by addition of water. The desired substance was thereby obtained with a m.p. of 240—243° C.

EXAMPLE 9

3 - Chloromethyl - 6 - trifluoromethyl - 7-sulfamyl - 3,4 - dihydro - 1,2,4 - benzothiadiazine - 1,1 - dioxide.

To a solution of 3.2 g. of 5-trifluoromethyl-2,4-disulfamylaniline in 50 ml. of dioxane was added a catalytic amount of *p*-toluenesulphonic acid followed by 4 ml. of a 40% aqueous solution of chloroacetaldehyde. The mixture was boiled with reflux for 4 hours, whereupon the solvent was removed by distillation in vacuo. The residue was triturated with chloroform, and the crystalline product thus obtained was recrystallized from ethylacetate/hexane. Thereby the desired substance was obtained with a m.p. of 245—245.5° C. (decomposition).

EXAMPLE 10

3 - Bromomethyl - 6 - trifluoromethyl - 7-sulfamyl - 3,4 - dihydro - 1,2,4 - benzothiadiazine - 1,1 - dioxide.

3.2 g. of 5-trifluoromethyl-2,4-disulfamylaniline and 2.2 g. of bromoacetaldehyde diethyl acetal were dissolved in 30 ml. of dioxane. A catalytic amount of *p*-toluenesulphonic acid was added, and the mixture was boiled with reflux overnight. After cooling, the reaction product was precipitated by addition of methylene chloride and hexane. By recrystallization from methanol/water the desired substance was obtained with a m.p. of 209.5—210° C.

EXAMPLE 11

3 - Ethyl - 6 - trifluoromethyl - 7 - sulfamyl-3,4 - dihydro - 1,2,4 - benzothiadiazine-1,1 - dioxide.

3.2 g. of 5-trifluoromethyl-2,4-disulfamylaniline was added to a solution of 0.79 ml. of propionaldehyde in 30 ml. of 99% ethanol, and the mixture was boiled with reflux for 4½ hours. Already after 2 hours crystals began to separate out. After cooling, the crystals were filtered off and washed with 99% ethanol. The substance was purified by dissolving it in 24 ml. of boiling 2-methoxy-ethanol and precipitating with 10 ml. of water. Thereby the desired substance was obtained with a m.p. of 255.5—256° C.

EXAMPLE 12

3 - *n* - Propyl - 6 - trifluoromethyl - 7-sulfamyl - 3,4 - dihydro - 1,2,4 - benzothiadiazine - 1,1 - dioxide.

3.2 g. of 5-trifluoromethyl-2,4-disulfamylaniline was added to a solution of 0.89 ml. of *n*-butyraldehyde in 20 ml. of 99% ethanol together with a catalytic amount of *p*-toluenesulphonic acid, and the mixture was boiled with reflux overnight. Thereafter, the ethanol

was distilled off in vacuo to dryness, and the residue was recrystallized from methanol/water. Thereby the desired substance was obtained with a m.p. of 232—233° C.

EXAMPLE 13

3 - Isopropyl - 6 - trifluoromethyl - 7-sulfamyl - 3,4 - dihydro - 1,2,4 - benzothiadiazine - 1,1 - dioxide.

3.2 g. of 5-trifluoromethyl-2,4-disulfamylaniline and 2 drops of piperidine were added to a solution of 1.0 ml. of isobutyraldehyde in 20 ml. of 99% ethanol, and the mixture was boiled with reflux for 5 hours. Thereafter the reaction mixture was poured into 200 ml. of water, the solution was left standing overnight in an ice-box, and the precipitate thereby formed was filtered off. By recrystallization from ethanol the desired substance was obtained with a m.p. of 244—245° C.

EXAMPLE 14

3 - *n* - Butyl - 6 - trifluoromethyl - 7-sulfamyl - 3,4 - dihydro - 1,2,4 - benzothiadiazine - 1,1 - dioxide.

3.2 g. of 5-trifluoromethyl-2,4-disulfamylaniline and 1.15 ml. of *n*-valeraldehyde were dissolved in 20 ml. of dioxane. A catalytic amount of *p*-toluenesulphonic acid was added, and the mixture was boiled with reflux for 5 hours. After cooling, the reaction product was precipitated by addition of water and filtered off. By recrystallization from ethyl acetate/hexane and subsequently from methanol/water, the desired substance was obtained with a m.p. of 216.5—217.5° C.

EXAMPLE 15

3 - δ - Hydroxybutyl - 6 - trifluoromethyl - 7-sulfamyl - 3,4 - dihydro - 1,2,4 - benzothiadiazine - 1,1 - dioxide.

6.4 g. of 5-trifluoromethyl-2,4-disulfamylaniline and 2.25 g. of δ-hydroxypentanal were dissolved in 30 ml. of dimethylformamide. A catalytic amount of *p*-toluenesulphonic acid was added, and the mixture was heated to 70° C. for 7 hours. Thereupon the dimethylformamide was distilled off in vacuo. The residue was dissolved in methyl isobutyl ketone and precipitated by addition of methylene chloride and hexane. By recrystallization from acetone/hexane the desired substance was obtained with a m.p. of 175—175.5° C.

EXAMPLE 16

3 - *n* - Pentyl - 6 - trifluoromethyl - 7-sulfamyl - 3,4 - dihydro - 1,2,4 - benzothiadiazine - 1,1 - dioxide.

3.2 g. of 5-trifluoromethyl-2,4-disulfamylaniline and 1.35 ml. of capronaldehyde were dissolved in 20 ml. of dioxane. A catalytic amount of *p*-toluenesulphonic acid was added, and the mixture was boiled with reflux for 5 hours. After cooling, the reaction product crystallized out. By three recrystallizations from methanol/water the desired substance was obtained with a m.p. of 190—191.5° C.

EXAMPLE 17

3 - (γ - Nitropentyl) - 6 - trifluoromethyl - 7-sulfamyl - 3,4 - dihydro - 1,2,4 - benzothiadiazine - 1,1 - dioxide.

3.2 g. of 5-trifluoromethyl-2,4-disulfamylaniline and 1.5 g. of γ-nitrocaproaldehyde was dissolved in 30 ml. of dioxane. A catalytic amount of *p*-toluenesulphonic acid was added, and the mixture was boiled with reflux overnight. After cooling, the reaction product was precipitated by addition of water. By recrystallization of the residue from methanol/water, the desired substance was obtained with a m.p. of 234.5—235° C.

EXAMPLE 18

3 - Acetonyl - 6 - trifluoromethyl - 7 - sulfamyl - 3,4 - dihydro - 1,2,4 - benzothiadiazine - 1,1 - dioxide.

A mixture of 3.2 g. of 5-trifluoromethyl-2,4-disulfamylaniline, 2.65 g. of acetoacetaldehyde diethyl acetal, a catalytic amount of *p*-toluenesulphonic acid and 30 ml. of dioxane was boiled with reflux for 16 hours. The solvent was removed by distillation in vacuo, and the residue was recrystallized by dissolving it in a mixture of *n*-propanol and methylene chloride and precipitating by addition of hexane. The desired substance was thereby obtained with a m.p. of 208—209° C. (decomposition).

EXAMPLE 19

3 - (β - Methoxyethyl) - 6 - trifluoromethyl-7 - sulfamyl - 3,4 - dihydro - 1,2,4-benzothiadiazine - 1,1 - dioxide.

3.2 g. of 5-trifluoromethyl-2,4-disulfamylaniline and 1.76 g. of β-methoxypropionaldehyde were dissolved in 50 ml. of methanol. A catalytic amount of *p*-toluenesulphonic acid was added, and the mixture was boiled with reflux for 7 hours. Thereupon the methanol was distilled off in vacuo, and the residue was dissolved in a mixture of dioxane and methylene chloride and precipitated by addition of hexane. After repeating this procedure once more, the precipitate was recrystallized from isopropanol, and the desired substance was obtained with a m.p. of 188—190° C.

EXAMPLE 20

3 - Dicarbethoxymethyl - 6 - trifluoromethyl-7 - sulfamyl - 3,4 - dihydro - 1,2,4-benzothiadiazine - 1,1 - dioxide.

3.2 g. of 5-trifluoromethyl-2,4-disulfamylaniline and 10 ml. of diethyl ethoxymethylene malonate were dissolved in 25 ml. of dioxane. A catalytic amount of *p*-toluenesulphonic acid was added, and the mixture was boiled with reflux for 5 hours. Thereupon the dioxane was distilled off, and the residue was triturated with methylene chloride. After recrystallization from dioxane/hexane the desired substance was obtained with a m.p. of 232—233° C.

EXAMPLE 21

3 - Phenyl - 6 - trifluoromethyl - 7 - sulfamyl-3,4 - dihydro - 1,2,4 - benzothiadazine-1,1 - dioxide.

2.8 g. of 5-trifluoromethyl-2,4-disulfamylaniline was dissolved in a mixture of 15 ml. of 2-methoxyethanol and 2.2 ml. of benzaldehyde. A catalytic amount of *p*-toluenesulphonic acid was added, and the mixture was boiled with reflux for 16 hours. After cooling, the precipitate was filtered off and recrystallized from ethanol/hexane, whereby the desired substance was obtained with a m.p. of 218.5—219.5° C.

EXAMPLE 22

3 - Diphenylmethyl - 6 - trifluoromethyl - 7-sulfamyl - 3,4 - dihydro - 1,2,4-benzothiadiazine - 1,1 - dioxide.

3.2 g. of 5-trifluoromethyl-2,4-disulfamylaniline and 2.1 g. of diphenylacetaldehyde were dissolved in 30 ml. of dioxane. A catalytic amount of *p*-toluenesulphonic acid was added and the mixture was boiled with reflux for 5 hours. After cooling, the reaction product was preciptated by addition of a mixture of methylene chloride and hexane. By recrystallization twice from ethanol/water the desired substance was obtained with a m.p. of 261—262.5° C.

EXAMPLE 23

3 - (β - (p - Methoxyphenyl) - ethyl) - 6-trifluoromethyl - 7 - sulfamyl - 3,4 - dihydro - 1,2,4 - benzothiadiazine - 1,1-dioxide.

3.2 g. of 5-trifluoromethyl-2,4-disulfamylaniline and 2.6 g. of β-(*p*-methoxyphenyl)-propionaldehyde diethyl acetal were dissolved in 25 ml. of dioxane. A catalytic amount of *p*-toluenesulphonic acid was added, and the mixture was boiled with reflux overnight. After cooling, the reaction product was precipitated by addition of water. By recrystallization from methanol/water the desired substance was obtained with a m.p. of 250.5—251.5° C.

EXAMPLE 24

3 - Benzyl - 6 - trifluoromethyl - 7 - sulfamyl-3,4 - dihydro - 1,2,4 - benzothiadiazine-1,1 - dioxide.

6.4 g. of 5-trifluoromethyl-2,4-disulfamylaniline was dissolved in 12 ml. of dioxane. 2.7 ml. of phenylacetaldehyde and a catalytic amount of *p*-toluenesulphonic acid were added. After boiling for a short time with reflux, the reaction mixture crystallized, and, after filtration and recrystallization from dioxane, the desired substance was obtained with a m.p. of 224.5—225.5° C.

EXAMPLE 25

3 - Benzyl - 6 - trifluoromethyl - 7 - sulfamyl-3,4 - dihydro - 1,2,4 - benzothiadiazine-1,1 - dioxide.

9.6 g. of 5-trifluoromethyl-2,4-disulfamylaniline and 4.9 g. of ω-ethoxystyrene were dissolved in 35 ml. of *n*-butanol. 0.5 g. of *p*-toluenesulphonic acid was added, and the mixture was heated on a steam bath while stirring. When the solution was clear, 55 ml. of hexane was added, whereafter the mixture was heated for further 1½ hour. After cooling, the desired substance was filtered off and had a m.p. of 222—223° C.

EXAMPLE 26

3 - (β - Phenylethyl) - 6 - trifluoromethyl - 7-sulfamyl - 3,4 - dihydro - 1,2,4 - benzothiadiazine - 1,1 - dioxide.

A mixture of 9.6 g. of 5-trifluoromethyl-2,4-disulfamylaniline, 3.6 ml. of β-phenylpropionaldehyde, a catalytic amount of *p*-toluenesulphonic acid and 40 ml. of ethanol was boiled with reflux overnight. After cooling, 20 ml. of water was added, and the crystalline product thereby obtained was filtered off and dissolved in 40 ml. of ethanol. 20 ml. of water was added, and the precipitate formed was filtered off and dried. Thereby the desired substance was obtained with a m.p. of 235—236° C.

EXAMPLE 27

3 - (α - Phenylethyl) - 6 - trifluoromethyl - 7-sulfamyl - 3,4 - dihydro - 1,2,4 - benzothiazine - 1,1 - dioxide.

3.2 g. of 5-trifluoromethyl-2,4-disulfamylaniline and 1.48 g. of hydratropaldehyde (α-phenylpropionaldehyde) were dissolved in 50 ml. of 99% ethanol. A catalytic amount of *p*-toluenesulphonic acid was added, and the mixture was boiled with reflux for 5 hours. After cooling, the reaction product was precipitated by addition of water. By recrystallization from methanol/water the desired substance was obtained with a m.p. of 242—243.5° C.

EXAMPLE 28

3 - *p* - Chlorobenzyl - 6 - trifluoromethyl - 7-sulfamyl - 3,4 - dihydro - 1,2,4 - benzothiadiazine - 1,1 - dioxide.

3.2 g. of 5-trifluoromethyl - 2,4 - disulfamylaniline and 2.5 g. of *p*-chlorophenylacetaldehyde diethyl acetal were dissolved in 25 ml. of dioxane. A catalytic amount of *p*-toluenesulphonic acid was added, and the mixture was boiled with reflux overnight. After cooling, the reaction product was precipitated by addition of water. By recrystallization from methanol/water the desired substance was obtained with a m.p. of 243.5—244.5° C.

EXAMPLE 29

3 - Benzyloxymethyl - 6 - trifluoromethyl - 7-sulfamyl - 3,4 - dihydro - 1,2,4 - benzothiadiazine - 1,1 - dioxide.

3.2 g. of 5-trifluoromethyl-2,4-disulfamylaniline and 2.5 g. of benzyloxyacetaldehyde diethyl acetal were dissolved in 30 ml. of dioxane. A catalytic amount of *p*-toluenesulphonic acid was added, and the mixture was boiled with reflux overnight. Thereupon the dioxane was distilled off in vacuo, and the residue was dissolved in isopropanol. The reaction product was precipitated by addition of water. By recrystallization from isopro-

propanol/water the desired substance was obtained with a m.p. of 221—221.5° C.

EXAMPLE 30

3 - Phenoxymethyl - 6 - trifluoromethyl - 7-sulfamyl - 3,4 - dihydro - 1,2,4 - benzothiadiazine - 1,1 - dioxide.

3.2 g. of 5-trifluoromethyl-2,4-disulfamylaniline and 2.3 g. of phenoxyacetaldehyde diethyl acetal were dissolved in 30 ml. of dioxane. A catalytic amount of *p*-toluenesulphonic acid was added, and the mixture was boiled with reflux overnight. The reaction product was precipitated by addition of a mixture of methylene chloride and hexane. By recrystallization from methanol/water the desired substance was obtained with a m.p. of 244.5—246°C. (decomposition).

EXAMPLE 31

3 - *p* - Nitrophenoxymethyl - 6 - trifluoromethyl - 7 - sulfamyl - 3,4 - dihydro-1,2,4 - benzothiadiazine - 1,1 - dioxide.

3.2 g. of 5-trifluoromethyl-2,4-disulfamylaniline and 3.0 g. of *p*-nitrophenoxyacetaldehyde diethyl acetal were dissolved in 25 ml. of dioxane. A catalytic amount of *p*-toluenesulphonic acid was added, and the mixture was boiled with reflux overnight. After cooling, the reaction product was precipitated by addition of water. By recrystallization from dimethylformamide/water the desired substance was obtained with a m.p. of 261.5—262° C.

EXAMPLE 32

3 - (*p* - Aminophenoxymethyl) - 6 -trifluoromethyl - 7 - sulfamyl - 3,4 - dihydro-1,2,4 - benzothiadiazine - 1,1 - dioxide.

2.4 g. of 3 - (*p* - nitrophenoxymethyl) - 6-trifluoromethyl - 7 - sulfamyl - 3,4 - dihydro-1,2,4 - benzothiadiazine - 1,1 - dioxide was dissolved in 15 ml. of dimethylformamide and 200 mg. of PtO_2-catalyst was added. The mixture was shaken with hydrogen at atmospheric pressure until the theoretical amount of hydrogen had been absorbed. The catalyst was filtered off, and the dimethylformamide distilled off in vacuo. The residue was dissolved in methyl isobutyl ketone, and the reaction product precipitated by addition of methylene chloride. The precipitate was dissolved in methanol and precipitated again by addition of a mixture of methylene chloride and hexane. By recrystallization from methanol/water the desired substance was obtained with a m.p. of 193—194° C.

EXAMPLE 33

3 - (2^1,4^1 - Dichlorophenoxymethyl) - 6-trifluoromethyl - 7 - sulfamyl - 3,4-dihydro - 1,2,4 - benzothiadiazine - 1,1-dioxide.

3.2 g. of 5-trifluoromethyl-2,4-disulfamylaniline and 2.8 g. of 2,4-dichlorophenoxyacetaldehyde diethyl acetal were dissolved in 25 ml. of dioxane. A catalytic amount of *p*-toluenesulphonic acid was added, and the mixture was boiled with reflux overnight. After cooling, the reaction product was precipitated by addition of methylene chloride and hexane. By recrystallization from methanol/water the desired substance was obtained with a m.p. of 230.5—231° C.

EXAMPLE 34

3 - Benzoyl - 6 - trifluoromethyl - 7 -sulfamyl-3,4 - dihydro - 1,2,4 - benzothiadiazine-1,1 - dioxide.

A mixture of 3.2 g. of 5-trifluoromethyl-2,4-disulfamylaniline, 2.7 g. of phenylglyoxal and 50 ml. of absolute ethanol containing a catalytic amount of *p*-toluenesulphonic acid was boiled with reflux for 16 hours. The ethanol was removed by distillation in vacuo, and the residue was recrystallized from ethylacetate. The desired substance was obtained with a m.p. of 261.5—262.5° C.

EXAMPLE 35

3 - Benzylmercaptomethyl - 6 - trifluoromethyl - 7 - sulfamyl - 3,4 - dihydro-1,2,4 - benzothiadiazine - 1,1 - dioxide.

3.2 g. of 5-trifluoromethyl-2,4-disulfamylaniline and 2.6 g. of benzylmercaptoacetaldehyde diethyl acetal were dissolved in 20 ml. of dioxane. A catalytic amount of *p*-toluenesulphonic acid was added, and the mixture was boiled with reflux overnight. After cooling, the reaction product was precipitated by addition of a mixture of methylene chloride and hexane. By recrystallization from methanol/water the desired substance was obtained with a m.p. of 202-203.5° C.

EXAMPLE 36

3 - (β - Benzylmercaptoethyl) - 6 - trifluoromethyl - 7 - sulfamyl - 3,4 - dihydro-1,2,4 - benzothiadiazine - 1,1 - dioxide.

6.4 g. of 5-trifluoromethyl-2,4-disulfamylaniline and 3.6 g. of β - benzyl - mercaptopropionaldehyde were dissolved in 50 ml. of dioxane. The mixture was boiled with reflux for 17 hours. The dioxane was distilled off. The residue was dissolved in a mixture of equal amounts of dioxane and methylene chloride, and the product was precipitated by addition of hexane. This recrystallization was repeated twice and the desired substance was thereby obtained with a m.p. of 134—~~146~~° C.

EXAMPLE 37

3 - (2^1 - Pyridyl) - 6 - trifluoromethyl - 7-sulfamyl - 3,4 - dihydro - 1,2,4 - benzothiadiazine - 1,1 - dioxide.

3.2 g. of 5-trifluoromethyl-2,4-disulfamylaniline and 1.2 g. of pyridine-2-aldehyde were dissolved in 20 ml. of 99.9 % ethanol. The mixture was boiled with reflux for 48 hours and, after cooling, poured into 300 ml. of water, whereby the reaction product precipitated out. By recrystallization from methanol/water the desired substance was obtained with a m.p. of 304—306° C. (decomposition).

EXAMPLE 38

3 - (2¹ - Furyl) - 6 - trifluoromethyl - 7-sulfamyl - 3,4 - dihydro - 1,2,4 - benzothiadiazine - 1,1 - dioxide.

3.2 g. of 5-trifluoromethyl-2,4-disulfamylaniline and 1.06 g. of freshly distilled furfural were dissolved in 20 ml. of 99.9% ethanol. The mixture was boiled with reflux for 48 hours, and after cooling poured into 150 ml. of water. The precipitate thereby formed was filtered off and recrystallized from methanol/water. The desired substance was then obtained with a m.p. of 190—192° C.

EXAMPLE 39

3 - Cyclohexyl - 6 - trifluoromethyl - 7 - sulfamyl - 3,4 - dihydro - 1,2,4 - benzothiadiazine - 1,1 - dioxide.

A mixture of 3.2 g. of 5 - trifluoromethyl-2,4 - disulfamylaniline and 2.05 g. of hexahydrobenzaldehyde diethyl acetal was dissolved in 25 ml. of dioxane, a catalytic amount of *p* - toluenesulphonic acid was added, and the solution was boiled with reflux overnight. After cooling, a mixture of methylene chloride and hexane was added, and the precipitate was recrystallized twice from methanol/water, whereby the desired substance was obtained with a m.p. of 258—259.5° C.

EXAMPLES 40—44

Following the procedure of the aforementioned examples, but using the aldehyde reactants indicated in the table I, the following 3 - R - 6 - trifluoromethyl - 7 - sulfamyl - 3,4-dihydro - 1,2,4 - benzothiadiazine - 1,1-dioxide derivatives were prepared:

TABLE I

Example No.	R	Aldehyde Reactant	m.p. °C.	Recrystallized from:
40	1¹-Propenyl	Crotonaldehyde	213.5—215	Ethylacetate/Hexane
41	*n*-Hexyl	Enanthaldehyde	178—179	Dioxane/Hexane
42	*n*-Tridecyl	Myristaldehyde	no m.p.	Dioxane/Hexane
43	3¹-Pyridyl	Pyridine-3-aldehyde	240—241	Ethanol
44	Styryl	Cinnamaldehyde	167—169 (dec.)	Ethanol

EXAMPLE 45

6 - Trifluoromethyl - 7 - sulfamyl - 3,4-dihydro - 1,2,4 - benzothiadiazine - 1,1-dioxide.

3.2 g. of 5-trifluoromethyl-2,4-disulfamylaniline, 1.21 ml. of methylene iodide and 2.8 ml. of triethylamine were dissolved in 25 ml. of dioxane, and the solution was boiled with reflux for 5 hours. The reaction mixture was evaporated to dryness in vacuo, and the residue was dissolved in methanol and precipitated by addition of water. The precipitate thereby formed was boiled with a little quantity of ethyl acetate and filtered off. The precipitate was recrystallized from methanol/water, whereby the desired substance was obtained with a m.p. of 260—263° C. There was no depression of the m.p. by mixing this substance with an equal amount of the substance produced by Example 1.

In a series of tests with rats the saluretic effects of some of the compounds of the invention were determined. The results are given in table II.

Each animal received a single oral dose of a solution of the test substance as indicated in the second column of table II. The excretion of urine from a number of groups of rats (each group consisting of three rats) was measured during the first 6 hours after administration of the test substance, and the contents of sodium, potassium and chloride ions were determined. From these figures average values were calculated for the total excretions of the said three ions during 6 hours in micro-equivalents per group of three animals.

TABLE II

Example No.	Dose mg./kg.	Number of groups	Excretions in micro-equivalents of: Na+	K+	Cl-
Control		6	120	271	85
»		6	165	260	140
»		12	100	229	76
»			165	248	135
Average value			138	252	109
1	5.00		871	459	1077
	10.00		1177	679	1486
6	1.25	6	546	404	514
9	1.25	6	701	397	776
	5.00	6	1068	576	1315
10	0.078	6	286	342	206
	0.625	6	845	396	1035
11	5.00		979	477	1281
12	5.00		761	438	997
13	5.00		918	423	1157
14	0.156	6	533	436	741
16	0.078	6	548	372	540
	0.156	6	577	320	680
	0.313	6	649	421	862
17	1.25	6	654	499	796
19	1.25	3	773	383	810
23	0.625	6	637	352	638+)
24	0.078	6	420	341	437
	0.156	6	634	419	718
	0.313	6	803	524	1025
	0.625	6	982	590	1143
26	0.078	6	516	417	534
	0.156	6	714	395	961
	0.313	6	836	396	936

TABLE II—*continued*

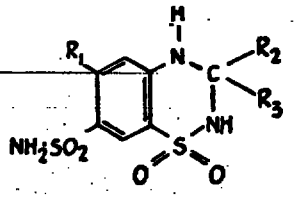
Example No.	Dose mg./kg.	Number of groups	Excretions in micro-equivalents of: Na+	K+	Cl−
27	0.078	6	321	263	203
	0.156	6	505	361	575
28	0.978	6	486	285	469
29	0.078	6	245	325	233
30	0.156	6	367	292	390+)
31	0.313	6	270	255	373
32	0.156	6	201	256	171
35	0.156	6	413	364	318
36	0.078	6	226	262	232
	0.156	6	486	380	452
38	0.625	6	295	254	218
39	0.625	6	759	444	905
41	1.25	6	566	517	729

+) number of groups = 3.

PATENT OFFICE

By repeated tests with groups of ten healthy persons under conventional experimental condition it was found that 2.0 mg. of 3-benzyl-6-trifluoromethyl - 7 - sulfamyl - 3,4 - dihydro-1,2,4 - benzothiadiazine - 1,1 - dioxide had the same natriuretic and chlorouretic effects as 20 mg. of 3-benzyl-6-chloro-7-sulfamyl-3,4-dihydro-1,2,4-benzothiadiazine-1,1-dioxide.

This invention also relates to 3,3-disubstituted derivatives of 7-sulfamyl-3,4-dihydro-1,2,4 - benzothiadiazine - 1,1 - dioxide of the general formula:

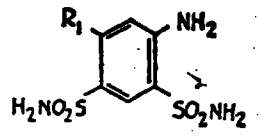


(IV)

in which R_1 is a hydrogen, fluorine, chlorine, or bromine atom, or a trifluoromethyl, methyl, methoxy, or nitro group; R_2 is a methyl group; and R_3 is an alkyl, halogenalkyl, acyl, carbalkoxy or carbalkoxymethyl group, the alkyl or alkylene radical of said groups containing not more than two carbon atoms; or R_3 forms together with R_2 a spirocyclic polymethylene group optionally substituted with fluorine, chlorine or bromine atom, or with a lower alkyl group containing from 1 to 5 carbon atoms.

The said compounds are hitherto unknown substances, and it has been found that they are capable of exerting strongly saluretic effects when administered orally or parenterally to human beings. In table III the saluretic activity of a number of the compounds is indicated as found in tests with rats.

The compounds comprised by formula (IV) can be produced by reacting a 2,4-disulfamylaniline of the general formula:



(V)

with a ketone of the general formula $R_2—CO—R_3$, in which two formulas R_1, R_2

and R_1 have the meaning hereinbefore defined in connection with formula IV.

The said ketone may be replaced by a reactive, functional derivative of the same, such as a ketal or an enol-ether, or by the hydrosulphite or cyanhydrin of the ketone.

The invention will now be illustrated by the following further Examples.

EXAMPLE 1a

3,3 - Dimethyl - 6 - trifluoromethyl - 7-sulfamyl - 3,4 - dihydro - 1,2,4 - benzothiadiazine - 1,1 - dioxide.

3.2 g. of 5-trifluoromethyl-2,4-disulfamylaniline was dissolved in 50 ml. of acetone, a catalytic amount of *p*-toluenesulphonic acid was added, and the solution was boiled with reflux overnight. Thereafter the main part of the acetone was distilled off, and to the concentrated solution water was added. The desired substance was precipitated as a crystalline substance, which was subsequently recrystallized from ethanol/water. The recrystallized substance had a m.p. of 222.5—223.5° C.

By substituting 10 ml. of 2-methoxy-1-propylene and 20 ml. of dioxane for the acetone and using the aforementioned procedure the same substance was obtained.

EXAMPLE 2a

3,3 - Dimethyl - 6 - nitro - 7 - sulfamyl-3,4 - dihydro - 1,2,4 - benzothiadiazine-1,1 - dioxide.

3.0 g. of 5-nitro-2,4-disulfamylaniline was dissolved in 50 ml. of acetone. A catalytic amount of *p*-toluenesulphonic acid was added, and the mixture was boiled with reflux overnight. After cooling, the reaction product was precipitated by addition of water and filtered off. By recrystallization from methanol/water the desired substance was obtained with a m.p. of 233—233.5° C.

EXAMPLES 3a—7a

Following the procedure of the aforementioned examples 1a and 2a, but using the 2,4-disulfamylaniline reactant indicated in table Ia, the following 3,3-dimethyl-6-X-7-sulfamyl - 3,4 - dihydro - 1,2,4 - benzothiadiazine - 1,1 - dioxide derivatives were obtained:

TABLE 1a

Example No.	X	Disulfamylaniline Reactant	m.p. °C.	Recrystallized from:
3a	Cl	5-Chloro-2,4-disulfamylaniline	230—231	Acetone, Water
4a	Br	5-Bromo-2,4-disulfamylaniline	228—229	Acetone, Hexane
5a	CH_3O	5-Methoxy-2,4-disulfamylaniline	240—240.5	Methanol
6a	CH_3	5-Methyl-2,4-disulfamylaniline	243—244	Acetone, Ether
7a	H	2,4-Disulfamylaniline	242—242.5	Methanol/Water

EXAMPLE 8a

3 - Methyl - 3 - ethyl - 6 - chloro - 7-sulfamyl - 3,4 - dihydro - 1,2,4, - benzothiadiazine - 1,1 - dioxide.

2.9 g. of 5-Chloro-2,4-disulfamylaniline was dissolved in 75 ml. of methyl ethyl ketone. A catalytic amount of *p*-toluenesulphonic acid was added, and the mixture was boiled with reflux overnight. The reaction mixture was evaporated to dryness in vacuo. By recrystallization from methanol/water the desired substance was obtained with a m.p. of 231.5—233° C.

EXAMPLE 9a

3 - Methyl - 3 - ethyl - 6 - trifluoromethyl-7 - sulfamyl - 3,4 - dihydro - 1,2,4-benzothiadiazine - 1,1 - dioxide.

Following the procedure of Example 8a, but substituting the 5-trifluoromethyl-2,4-disulfamylaniline for the 5-chloro-2,4-disulfamylaniline, the desired substance was obtained with a m.p. of 212—213° C.

EXAMPLE 10a

3 - Methyl - 3 - chloromethyl - 6 - trifluoromethyl - 7 - sulfamyl - 3,4 - dihydro-1,2,4 - benzothiadiazine - 1,1 - dioxide.

To a solution of 3.2 g. of 5-trifluoromethyl-2,4-disulfamylaniline in 25 ml. of dioxane was added a catalytic amount of *p*-toluenesulphonic acid and 5 ml. of chloroacetone. The mixture was boiled with reflux overnight. After cooling, a mixture of methylene chloride and hexane was added, and the precipitate thereby formed was recrystallized twice from methanol/water, whereby the desired substance was obtained with a m.p. of 227—227.5° C. (decomposition).

EXAMPLE 11a

3 - Methyl - 3 - chloromethyl - 6 - nitro - 7-sulfamyl - 3,4 - dihydro - 1,2,4 - benzothiadiazine - 1,1 - dioxide.

3.0 g. of 5-nitro-2,4-disulfamylaniline and 5 ml. of chloroacetone were dissolved in 35 ml. of dioxane. A catalytic amount of *p*-toluenesulphonic acid was added, and the mixture was boiled with reflux overnight. The reaction mixture was evaporated to dryness in vacuo. The residue was dissolved in ethyl acetate and precipitated by addition of a mixture of methylene chlorine and hexane. The precipitate thereby formed was filtered off and the filtrate was evaporated to dryness. The residue was dissolved in methanol, and by addition of water the desired substance was obtained with a m.p. of 238.5—239.5° C.

EXAMPLE 12a

3 - Methyl - 3 - carbethoxy - 6 - trifluoromethyl - 7 - sulfamyl - 3,4 - dihydro-1,2,4 - benzothiadiazine - 1,1 - dioxide.

A solution of 3.2 g. of 5-trifluoromethyl-2,4-disulfamylaniline, 5 ml. of ethyl pyruvate and a catalytic amount of *p*-toluenesulphonic acid in 25 ml. of dioxane was boiled with reflux overnight. The dioxane was removed by distillation in vacuo, and the residue was triturated with chloroform. The substance was collected and recrystallized from ethyl acetate/hexane. The desired substance was obtained with a m.p. of 191—194° C.

EXAMPLE 13a

3 - Methyl - 3 - carbethoxymethyl - 6-trifluoromethyl - 7 - sulfamyl - 3,4-dihydro - 1,2,4 - benzothiadiazine - 1,1-dioxide.

A mixture of 3.2 g. of 5-trifluoromethyl-2,4-disulfamylaniline, a catalytic amount of *p*-toluenesulphonic acid and 50 ml. of ethyl acetoacetate was heated on a steam bath overnight. The excess of ethyl acetoacetate was removed by distillation in vacuo, and the residue was triturated with methylene chloride. The crystalline substance thus obtained was recrystallized from dioxane/chloroform/hexane, whereby the desired substance was obtained with a m.p. of 150—152° C.

EXAMPLE 14a

3 - Methyl - 3 - carbethoxymethyl - 6 - nitro-7 - sulfamyl - 3,4 - dihydro - 1,2,4-benzothiadiazine - 1,1 - dioxide.

5.9 g. of 5-nitro-2,4-disulfamylaniline was dissolved in 50 ml. of ethyl acetoacetate. A catalytic amount of *p*-toluenesulphonic acid was added, and the mixture was boiled with reflux overnight. The reaction mixture was thereafter evaporated to dryness in vacuo. The residue was treated with methylene chloride and hexane and was recrystallized from 99% ethanol. By a further recrystallization from methanol/water the desired substance was obtained with a m.p. of 218—219° C.

EXAMPLE 15a

Cyclopentane - 1',3 - spiro - 6 - trifluoromethyl - 7 - sulfamyl - 3,4 - dihydro-1,2,4 - benzothiadiazine - 1,1 - dioxide.

3.2 g. of 5-trifluoromethyl-2,4-disulfamylaniline and a few crystals of *p*-toluenesulphonic acid were dissolved in 20 ml. of cyclopentanone, and the mixture was boiled with reflux for 24 hours. After cooling, the reaction mixture was poured into 150 ml. of petroleum ether (boiling range 105—120° C.) The oily substance which thereby separated out crystallized after stirring for a while. The crystals were separated from the solution and washed with petroleum ether. The dark coloured crystalline product was purified by suspension in 15 ml. of ethanol and filtering off the undissolved substance, which subsequently was recrystallized from ethanol. Thereby the desired substance was obtained with a m.p. of 232.5—234° C.

EXAMPLE 16a

Cyclopentane - 1',3 - spiro - 6 - chloro - 7-sulfamyl - 3,4 - dihydro - 1,2,4 - benzothiadiazine - 1,1 - dioxide.

4 g. of 5-chloro-2,4-disulfamylaniline was dissolved in 35 ml. of cyclopentanone. A catalytic amount of *p*-toluenesulphonic acid was added and the mixture was boiled with reflux for 6 hours. After cooling, a mixture of methylene chloride and hexane was added, whereby the reaction product precipitated out. The precipitate was dissolved in hot dioxane, and after cooling precipitated by addition of a mixture of methylene chloride and hexane. By recrystallization from 99% ethanol the desired substance was obtained with a m.p. of 234° C.

EXAMPLE 17a

Cyclohexane - 1',3 - spiro - 6 - bromo - 7-sulfamyl - 3,4 - dihydro - 1,2,4 - benzothiadiazine - 1,1 - dioxide.

5.0 g. of 5-bromo-2,4-disulfamylaniline and 30 ml. of cyclohexanone were boiled with reflux for 24 hours. After cooling, the reaction product crystallized out. After filtration the precipitate was washed with ether and dried. By recrystallization from methanol the desired

substance was obtained with a m.p. of 281—283° C.

EXAMPLES 18a—22a

Following the procedure of Example 17a, but using the 5-substituted 2,4-disulfamylaniline reactant indicated in table IIa instead of the 5-bromo-2,4-disulfamylaniline and recrystallizing from the solvent indicated the following cyclohexane - 1',3 - spiro - 6 - X - 7-sulfamyl - 3,4 - dihydro - 1,2,4 - benzothiadiazine - 1,1 - dioxide derivatives were obtained:

TABLE IIa

Example No.	X	2,4-Disulfamylaniline Reactant	m.p. °C.	Recrystallized from:
18a	CF_3	5-Trifluoromethyl-2,4-disulfamylaniline	261—262	Ethanol
19a	Cl	5-Chloro-2,4-disulfamylaniline	283.5—285	Ethanol
20a	CH_3	5-Methyl-2,4-disulfamylaniline	261.5—263	Ethanol/Hexane
21a	CH_3O	5-Methoxy-2,4-disulfamylaniline	268.5—269.5	Dimethylformamide/Water
22a	NO_2	5-Nitro-2,4-disulfamylaniline	261.5	Formamide/Water

EXAMPLE 23a

2' - Methylcyclohexane - 1',3 - spiro - 6-trifluoromethyl - 7 - sulfamyl - 3,4-dihydro - 1,2,4 - benzothiadiazine - 1,1-dioxide.

4.0 g. of 5-Trifluoromethyl-2,4-disulfamylaniline was dissolved in 20 ml. of 2-methylcyclohexanone. A catalytic amount of *p*-toluenesulphonic acid was added, and the mixture was boiled with reflux for 24 hours. After cooling, the reaction product was precipitated by addition of 200 ml. of hexane. The precipitate was dissolved in 25 ml. of *n*-propanol. By evaporation a first fraction crystallized out containing unreacted starting material. By further evaporation the desired substance crystallized out. By recrystallization from methanol the pure substance was obtained with a m.p. of 232—234° C.

EXAMPLE 24a

2' - Methylcyclohexane - 1',3 - spiro - 6-bromo - 7 - sulfamyl - 3,4 - dihydro-1,2,4 - benzothiadiazine - 1,1 - dioxide.

4 g. of 5-Bromo-2,4-disulfamylaniline was dissolved in 20 ml. of 2-methylcyclohexanone. A catalytic amount of *p*-toluenesulphonic acid was added, and the mixture was boiled with reflux overnight. After cooling, the unreacted 5-bromo-2,4-disulfamylaniline was filtered off, and to the filtrate hexane was added until the reaction product was precipitated out. The precipitate was dissolved in *n*-propanol and reprecipitated by addition of a mixture of methylene chloride and hexane. By recrystallization from methanol/water the desired substance was obtained with a m.p. of 231—233° C.

EXAMPLE 25a

2' - Chlorocyclohexane - 1',3 - spiro - 6 - trifluoromethyl - 7 - sulfamyl - 3,4-dihydro - 1,2,4 - benzothiadiazine - 1,1-dioxide.

6.4 g. of 5-Trifluoromethyl-2,4-disulfamylaniline and 4.6 g. of 1,1-diethoxy-2-chlorocyclohexane were dissolved in 20 ml. of dioxane. A catalytic amount of *p*-toluenesulphonic acid was added, and the mixture was boiled with reflux for 24 hours. After cooling, the reaction mixture was poured into 200 ml. of hexane and the precipitate thereby formed was recrystallized twice from methanol/water. The desired substance was obtained with a m.p. of 218—219° C. (decomposition).

EXAMPLE 26a

2' - Chlorocyclohexane -1',3 - spiro - 6-chloro - 7 - sulfamyl - 3,4 - dihydro-1,2,4 - benzothiadiazine - 1,1 - dioxide.

5.8 g. of 5-Chloro-2,4-disulfamylaniline and 4.6 g. of 1-chloro-2-diethoxy-cyclohexane were dissolved in 50 ml. of dioxane. A catalytic amount of *p*-toluenesulphonic acid was added, and the mixture was boiled with reflux overnight. After cooling, the reaction mixture was precipitated by addition of hexane. The precipitate was dissolved in methanol and by addition of water the desired substance crystallized out, and by recrystallization from dimethylformamide/water it was obtained with a m.p. of 223—225° C.

EXAMPLE 27a

4¹ - Chlorocyclohexane - 1¹,3 - spiro - 6-trifluoromethyl - 7 - sulfamyl - 3,4-dihydro - 1,2,4 - benzothiadiazine - 1,1-dioxide.

6.4 g. of 4-Trifluoromethyl-2,4-disulfamylaniline and 2.9 g. of 4-chlorocyclohexanone were dissolved in 20 ml. of dioxane. A catalytic amount of *p*-toluenesulphonic acid was added, and the mixture was boiled with reflux for 20 hours. After cooling, the reaction mixture was poured into 300 ml. of hexane. The precipitate thereby formed was recrystallized from methanol/methylene chloride/hexane and thereafter from methanol/water. Thereby the desired substance was obtained with a m.p. of 217—218° C. (decomposition).

EXAMPLE 28a

4¹ - Chlorocyclohexane - 1¹,3 - spiro - 6-chloro - 7 - sulfamyl - 3,4 - dihydro-1,2,4 - benzothiadiazine - 1,1 - dioxide.

5.8 g. of 5-Chloro-2,4-disulfamylaniline and 2.9 g. of 4-chlorocyclohexanone were dissolved in 50 ml. of diethylene glycol dimethyl ether. A catalytic amount of *p*-toluenesulphonic acid was added, and the mixture was heated to 125° C. overnight. After cooling, the reaction product was precipitated by addition of hexane. The precipitate was dissolved in methanol and reprecipitated by addition of a mixture of methylene chloride and hexane. By recrystallization from methanol/water the desired substance was obtained with a m.p. of 219.5—220.5° C.

EXAMPLE 29a

3 - Methyl - 3 - acetyl - 6 - chloro - 7-sulfamyl - 3,4 - dihydro - 1,2,4 - benzothiadiazine - 1,1 - dioxide.

5.8 g. of 5-Chloro-2,4-disulfamylaniline and 15 ml. of diacetyl were dissolved in 50 ml. of dioxane. A catalytic amount of *p*-toluenesulphonic acid was added, and the mixture was boiled with reflux for 5 hours. The reaction mixture was evaporated to dryness in vacuo, and the residue was dissolved in ethyl acetate and precipitated by addition of hexane. By recrystallization from methanol/water the desired substance was obtained with a m.p. of 246—247° C. (decomposition).

In a series of tests with rats, the saluretic effects of some of the compounds of the invention were determined. The results are given in table IIIa.

Each animal received a single oral dose of a solution of the test substance as indicated in the second column of table IIIa. The excretion of urine from a number of groups of rats (each group consisting of three rats) was measured during the first 6 hours after administration of the test substance, and the contents of sodium, potassium and chloride ions were determined. From these figures average values were calculated for the total excretions of the said three ions during 6 hours in micro-equivalents per group of three animals.

TABLE IIIa

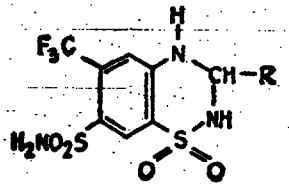
o.	Dose mg./kg.	Number of groups	Excretions in micro-equivalents of: Na+	K+	Cl−
			120	271	85
			165	248	135
		12	100	229	76
		3	188	268	236
Average values of the controls.			151	248	149
1a	5.00		766	438	1016
2a	1.25	6	469	334	671+)
3a	5.00		615	432	690
4a	1.25	6	325	278	322
	5.00	6	453	384	~~527~~ 537
9a	5.00		663	504	921
10a	0.625	6	445	368	380
13a	1.25	6	458	313	432
	5.00	6	777	463	921
15a	5.00		734	455	1043
17a	0.078	3	313	230	262
18a	1.25	6	883	535	1105
19a	1.25	6	1105	511	1358
20a	1.25	3	688	526	938
22a	1.25	6	697	485	873
23a	0.313	6	348	308	400
	0.625	6	675	471	733
25a	0.625	6	468	367	372
27a	0.156	6	511	607	563

+) number of groups = 3.

PATENT OFFICE

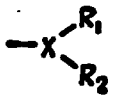
WHAT I CLAIM IS:—

1. 6 - Trifluoromethyl - 7 - sulfamyl - 3,4-dihydro - 1,2,4 - benzothiadiazine - 1,1-oxide and derivatives thereof, which compounds have the general formula:



(I)

in which R is a hydrogen atom or a cyclohexyl, phenyl, benzoyl, furyl, or pyridyl group; or a group having the general formula:

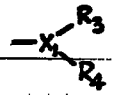


(II)

in which X is a straight or branched hydrocarbon group, which may contain a carbon-to-carbon double bond; R_1 is a hydrogen atom, a phenyl group, or a lower carbalkoxy group containing not more than 6 carbon atoms; and R_2 is a hydrogen, fluorine, chlorine, or bromine atom; a hydroxyl group optionally etherified with a lower alkyl group containing from 1 to 5 carbon atoms; a lower acyl group containing from 2 to 8 carbon atoms; or a lower carbalkoxy group containing from 2 to 6 carbon atoms; a nitro group; a phenyl group optionally substituted with a fluorine, chlorine, or bromine atom, or with a lower alkyl or lower alkoxy group containing from 1 to 5 carbon atoms; a phenoxy group optionally substituted with one or more fluorine, chlorine, or bromine atoms, or a nitro, or an amino group; or a benzyl mercapto group.

2. Compounds comprised by formula (I) in which R is an alkyl group which contains from one to six carbon atoms, and which may be substituted with fluorine, chlorine, bromine or a nitro group.

3. Compounds comprised by formula (I) in claim 1, in which formula R is a group having the general formula:



(III)

in which X_1 is an aliphatic hydrocarbon group, R_3 is a hydrogen atom, or a phenyl group, and R_4 is a phenyl group, which may be substituted with a fluorine, chlorine, or bromine atom, or a lower alkyl group containing from 1 to 5 carbon atoms.

4. Compounds comprised by formula (I) in claim 1, in which formula R is an alkoxyalkyl group containing not more than five carbon atoms.

5. Compounds comprised by formula (I) in claim 1, in which formula R is a phenoxyalkyl or phenylalkoxyalkyl group, in which groups the phenyl radical may be substituted with fluorine, chlorine, or bromine atoms, or a nitro, or an amino group, which phenyl-containing groups each do not contain more than ten carbon atoms.

6. Compounds comprised by formula (I) in claim 1, in which formula R is a carbalkoxyalkyl group, the alkyl radical of said group containing one or two carbon atoms.

7. 6 - Trifluoromethyl - 7 - sulfamyl - 3,4-dihydro - 1,2,4 - benzothiadiazine - 1,1-dioxide.

8. 3 - Bromomethyl - 6 - trifluoromethyl-7 - sulfamyl - 3,4 - dihydro - 1,2,4 - benzothiadiazine - 1,1 - dioxide.

9. 3 - *n* - Butyl - 6 - trifluoromethyl - 7-sulfamyl - 3,4 - dihydro - 1,2,4 - benzothiadiazine - 1,1 - dioxide.

10. 3 - *n* - Pentyl - 6 - trifluoromethyl - 7-sulfamyl - 3,4 - dihydro - 1,2,4 - benzothiadiazine - 1,1 - dioxide.

11. 3 - β - Methoxyethyl - 6 - trifluoromethyl - 7 - sulfamyl - 3,4 - dihydro - 1,2,4-benzothiadiazine - 1,1 - dioxide.

12. 3 - Benzyl - 6 - trifluoromethyl - 7-sulfamyl - 3,4 - dihydro - 1,2,4 - benzothiadiazine - 1,1 - dioxide.

13. 3 - β - Phenylethyl - 6 - trifluoromethyl - 7 - sulfamyl - 3,4 - dihydro - 1,2,4-benzothiadiazine - 1,1 - dioxide.

14. 3 - *p* - Chlorobenzyl - 6 - trifluoromethyl - 7 - sulfamyl - 3,4 - dihydro - 1,2,4-benzothiadiazine - 1,1 - dioxide.

15. 3 - Benzyloxymethyl - 6 - trifluoromethyl - 7 - sulfamyl - 3,4 - dihydro - 1,2,4-benzothiadiazine - 1,1 - dioxide.

16. 3 - β - Benzylmercaptoethyl - 6 - trifluoromethyl - 7 - sulfamyl - 3,4 - dihydro-1,2,4 - benzothiadiazine - 1,1 - dioxide.

17. 3 - Cyclohexyl - 6 - trifluoromethyl-7 - sulfamyl - 3,4 - dihydro - 1,2,4 - benzothiadiazine - 1,1 - dioxide.

18. A method for the production of the compounds according to claim 1, characterized in that 5-trifluoromethyl-2,4-disulfamylaniline is reacted (I) with an aldehyde having the general formula RCHO, in which R has the same meaning as hereinbefore, or (II) with a reactive derivative of such an aldehyde; whereafter, in case it is desired that a nitro group be transformed to an amino group, the nitro compound is reduced to the corresponding amino compound.

19. A method according to claim 18, characterized in that the reaction with the aldehyde is performed in the presence of an acid.

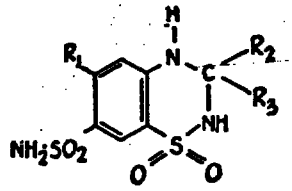
20. A 6 - trifluoromethyl - 7 - sulfamyl-3,4 - dihydro - 1,2,4 - benzothiadiazine - 1,1-dioxide or derivative thereof as described in any one of Examples 1 to 45 of the foregoing Examples.

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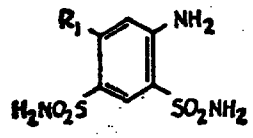
21. A method for the production of a 6 - trifluoromethyl - 7 - sulfamyl - 3,4-dihydro - 1,2,4 - benzothiadiazine substantially as hereinbefore described in any one of Examples 1 to 45 of the foregoing Examples.

22. 3,3 - Disubstituted derivatives of 7-sulfamyl - 3,4 - dihydro - 1,2,4 - benzothiadiazine - 1,1 - dioxide of the general formula:



in which R_1 is a hydrogen, fluorine, chlorine, or bromine atom, or a trifluoromethyl, methyl, methoxy, or nitro group; R_2 is a methyl group, and R_3 is an alkyl, halogenalkyl, acyl, carbalkoxy, or carbalkoxymethyl group, the alkyl or alkylene radical of said groups containing not more than two carbon atoms; or R_3 forms together with R_2 a spirocyclic polymethylene group optionally substituted with a fluorine, chlorine, or bromine atom, or with a lower alkyl group containing from 1 to 5 carbon atoms.

23. A method for the production of the compounds according to claim 22, characterized in that a 2,4-disulfamylaniline of the general formula:



is reacted with a ketone of the general formula $R_2—CO—R_3$, or a reactive, functional derivative of such a ketone, the substituents R_1, R_2 and R_3 in the two formulas having the same meaning as in the formula defined in claim 22.

24. A 3,3-disubstituted derivative of 7 - sulfamyl - 3,4 - dihydro - 1,2,4 - benzothiadiazine - 1,1 - dioxide as described in any one of Examples 1a to 29a of the foregoing Examples.

25. A method for the production of a 3,3-disubstituted derivative of 7-sulfamyl-3,4-dihydro-1,2,4-benzothiadiazine substantially as hereinbefore described in any one of Examples 1a to 29a of the foregoing Examples.

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PROVISIONAL SPECIFICATION

No. 26063 A.D. 1958

Benzothiadiazine Derivatives and their preparation

I, KNUD ABILDGAARD, a Danish Subject, trading as LØVENS KEMISKE FABRIK ved A. Kongsted, of 19, Brønshøjvej, Copenhagen, Denmark, do hereby declare this invention to be described in the following statement:—

This invention relates to 7-sulfamyl-3,4-dihydro - 1,2,4 - benzothiadiazine - 1,1-dioxide and derivatives thereof containing further substituents at the atoms in the ring system, particularly at the carbon atoms 3,5 and 6. Thus, one or both of the hydrogen atoms in the 3-position may be substituted by an alkyl group, or one of the said hydrogen atoms may be substituted by a mononuclear aryl or aralkyl group. Furthermore, one or both of the hydrogen atoms in the 5- and 6-positions may be substituted by a fluorine, a chlorine or a bromine atom, or by a trifluoromethyl group or an alkyl or alkoxy group. The invention also relates to salts of the said compounds, especially the alkali metal salts.

The compounds of the invention are hitherto unknown substances which are therapeutically useful agents because they are capable of exerting strongly saliuretic and/or diuretic effects.

In a series of tests with rats the diuretic effects of three of the compounds of the invention were compared with the saliuretic effects of two widely applied diuretic agents. The results of these tests are given in Table I, in which the three compounds of the invention are designated as A, B and C, and the two known agents are designated as D and E.

The five substances are:

A. 6 - Trifluoromethyl - 7 - sulfamyl - 3,4-dihydro - 1,2,4 - zothiadiazine - 1,1-dioxide.

B. 3 - n - Propyl - 6 - trifluoromethyl - 7-sulfamyl - 3,4 - dihydro - 1,2,4 - benzothiadiazine - 1,1 - dioxide.

C. 3,3 - Dimethyl - 6 - trifluoromethyl - 7-sulfamyl - 3,4 - dihydro - 1,2,4 - benzothiadiazine - 1,1 - dioxide.

D. 6 - Chloro - 7 - sulfamyl - 1,2,4 - benzothiadiazine - 1,1 - dioxide.

E. 2 - Acetamido - 1,3,4 - thiadiazol - 5-sulfamide.

Each animal received a single oral dose of a solution of the test substance, as indicated in the first column of the Table. The amounts of urine were measured, and the contents of sodium, potassium and chlorine ions were determined 6 hours after administering the test substance. From these figures average values for the total excretions of the said three ions during 6 hours were calculated in micro-equivalents per group of three animals.

Test Substance	Dose mg/kg	Excretions in micro-equivalents of: Na+	K+	Cl÷
Control	0	165	248	135
A	5.0	871	459	1077
A	10.0	1177	679	1486
B	5.0	761	438	997
C	5.0	766	438	1016
D	5.0	243	345	414
E	5.0	1084	769	179

From the foregoing Table it appears that A, B and C are considerably more active in respect to Na^+- and $Cl^÷$ - excretion than the known agent D, whereas the K^+-excretion is not increased in the same proportion. Furthermore, the effects of A, B and C differ from those of the other known agent E in that their activities in respect to $Cl^÷$ - excretion are several times higher than those of E, whereas their activities in respect of K^+-excretion are lower. Finally, it has been found that the compounds of the invention are less toxic than D. These differences offer distinct therapeutical advantages over the known agents.

The compounds of the invention can be produced by reacting an aldehyde or a ketone, or a reactive derivative of such a compound, with 2,4-disulfamyl-aniline or a derivative thereof having such further substituents as may be desired in the compound to be produced.

The invention will be illustrated by the following Examples:—

EXAMPLE 1.

6-Trifluoromethyl-7-sulfamyl-3,4-dihydro-1,2,4-benzothiadiazine-1,1-dioxide.

113 ml. chlorosulphonic acid were cooled in an ice-bath, and to the acid were added dropwise while stirring 26.6 g. α,α,α-trifluoro-m-toluidine. 105 g. sodium chloride were added during 1—2 hours, whereafter the temperature of the reaction mixture was raised slowly to 150—160° C., which temperature was maintained during 3 hours. After cooling the mixture, ice-cooled water was added, whereby 5 - trifluoromethyl - aniline - 2,4 - disulphonyl chloride separated out from the mixture. This substance was taken up in ether, and the ether solution was dried with magnesium sulphate.

The ether was removed from the solution by distillation, the residue was cooled to 0° C. and 60 ml. ice-cooled, concentrated ammonia water were added while stirring. Thereafter, the solution was heated for 1 hour on a steam bath, and subsequently evaporated in vacuo to crystallisation. The crystallised product was 5 - trifluoromethyl - 2,4 - disulphamylaniline, which was filtered off, washed with water and dried in a vacuum-exsiccator over phosphorus pentoxide. After recrystallisation from a mixture of 30% ethanol and 70% water to the compound had m.p. 247—248° C. 3.2 g. of the compound thus obtained were added to a solution of 0.33 g. para-formaldehyde in 25 ml. 2-ethoxy-ethanol together with a catalytical amount of *p*-toluene-sulphonic acid, and the mixture was boiled with reflux for 5 hours. Thereafter, the solvent was distilled off in vacuo, and the residue was triturated with 30 ml. ethyl acetate. Thereby, 6-trifluoromethyl - 7 - sulfamyl - 3,4 - dihydro - 1,2,4-benzothiadiazine-1,1-dioxide crystallised out. After recrystallisation from methanol/water, the substance had m.p. 272—273° C.

EXAMPLE 2.

3 - n - Propyl - 6 - trifluoromethyl - 7-sulfamyl - 3,4 - dihydro - 1,2,4 - benzothiadiazine - 1,1 - dioxide.

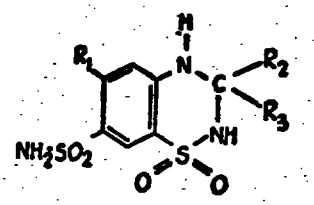
3.2 g. 5 - trifluoromethyl - 2,4 - disulfamyl-aniline prepared as described in Example 1 were added to a solution of 0.89 ml. *n*-butyraldehyde in 20 ml. 99% ethanol together with a catalytical amount of *p*-toluene-sulphonic acid, and the mixture was boiled with reflux overnight. Thereafter, the ethanol was distilled off in vacuo to dryness, and the residue was crystallised from methanol/water. Thereby the desired substance was obtained with m.p. 232—233° C.

EXAMPLE 3.

3,3 - Dimethyl - 6 - trifluoromethyl - 7-sulfamyl - 3,4 - dihydro - 1,2,4 - benzothiadiazine - 1,1 - dioxide.

3.2 g. 5 - trifluoromethyl - 2,4 - disulfamylaniline, prepared as described in Example 1, were dissolved in 50 ml. acetone, a catalytical amount of p-toluene-sulphonic acid was added, and the solution was boiled with reflux overnight. Thereafter, the main part of the acetone was distilled off, and to the concentrated solution water was added. The desired substance was precipitated as a crystalline substance, which was subsequently recrystallised from ethanol/water. The recrystallised product had m.p. 222.5—223.5° C.

By substantially the same method as that described in the foregoing Examples, a series of other compounds of the invention were also produced. These compounds were members of a group having the following general formula:



In the following Table the melting points of the said compounds are indicated. The formula of each of the compounds has been given by means of the three substituents R_1, R_2 and R_3 in the general formula.

R_1	R_2	R_3	Melting point (°C.)
CF_3	C_2H_5	H	255.5 — 256
»	$CH(CH_3)_2$	H	244 — 245
»	CH_3	C_2H_5	212 — 213
Cl	H	H	270 — 271.5
»	n—C_3H_7	H	250 — 251
»	CH_3	CH_3	230 — 231

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PROVISIONAL SPECIFICATION
No. 28199 A.D. 1958

Benzothiadiazine Derivatives and their preparation

I, KNUD ABILDGAARD, a Danish Subject, trading as LØVENS KEMISKE FABRIK ved A. Kongsted, of 19, Bronshøjvej, Copenhagen, Denmark, do hereby declare this invention to be described in the following statement:—

This invention, which is complementary to that described in the Provisional Specification of my copending Application No. 26063/1958, relates to 7-sulfamyl-3,4-dihydro-1.2,4-benzothiadiazine-1,1-dioxide and derivatives thereof containing further substituents at the atoms in the ring system, particularly at the carbon atoms 3, 5 and 6. Thus, one or both of the hydrogen atoms in the 3-position may be substituted by an alkyl group, or one of the said hydrogen atoms may be substituted by a mononuclear aryl or aralkyl group. Furthermore, one or both of the hydrogen atoms in the 5- or 6-position may be substituted by a fluorine, a chlorine or a bromine atom, or by a trifluoromethyl group or an alkyl or alkoxy group. The invention also relates to salts of the said compounds, especially the alkali metal salts.

It has been found that the compounds belonging to the said groups, except those having two substituents in the 3-position, can be produced by reduction or by catalytic hydrogenation of the corresponding compounds having a double bond between the carbon atoms in the 3-position and the nitrogen atom in the 4-position. These compounds can be produced by the method described in Specification No. 826,923. By the reduction of a complex alkali metal hydride, for example sodium borohydride or lithium aluminium hydride, can be used as the reducing agent. By the hydrogenation a platinum catalyst has

been found satisfactory. It should be noted that by using such a catalyst, a halogen atom, present for example, in the 6-position, will be removed. Thereby, the halogen-free 3,4-dihydro-compounds can be produced from the 6-halogen-compounds, which conveniently can be produced by the method described in Specification No. 826,923 or by the method described in the Specification of my aforementioned Application No. 20063/1958.

The reduction or hydrogenation of the compounds having a 3,4-double bond is illustrated by the following Examples.

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EXAMPLE 1.

6-Trifluoromethyl-7-sulfamyl-3,4-dihydro-1,2,4-benzothiadiazine-1,1-dioxide.

To a solution of 1.97 g. 6-trifluoromethyl-7-sulfamyl-1,2,4-benzothiadiazine-1,1-dioxide in 20 ml. methanol was added dropwise while stirring a solution of 750 mg. sodium borohydride in 10 ml. water, and the mixture was boiled with reflux for one hour. After cooling, the mixture was acidified with acetic acid and the reaction product precipitated by addition of 150 ml. water. The precipitate was filtered off, washed with a solution of sodium bicarbonate and thereafter with water, and dried. By recrystallisation from methanol/water the desired compound was obtained with m.p. 271—272° C.

EXAMPLE 2.

6-Trifluoromethyl-7-sulfamyl-3,4-dihydro-1,2,4-benzothiadiazine-1,1-dioxide.

658 mg. 6-trifluoromethyl-7-sulfamyl-1,2,4-benzothiadiazine-1,1-dioxide were dissolved in 8 ml. 2-methoxyethanol and hydrogenated at room temperature and atmospheric pressure in the presence of 65 mg. of a platinum oxide catalyst. When one mol of hydrogen per mol of the starting substance had been absorbed, the catalyst was filtered off and the reaction product precipitated from the filtrate by addition of water. The precipitate was filtered off, washed with a solution of sodium bicarbonate and thereafter with water and dried. Thereby, the desired compound was obtained with m.p. 269—270° C. By recrystallisation from methanol/water the m.p. was raised to 271—272° C.

EXAMPLE 3.

6-Chloro-7-sulfamyl-3,4-dihydro-1,2,4-benzothiadiazine-1,1-dioxide.

To a solution of 2.96 g. 6-chloro-7-sulfamyl-1,2,4-benzothiadiazine-1,1-dioxide in 80 ml. 0.25-N sodium hydroxide was added dropwise while stirring, a solution of 2.0 g. sodium borohydride in 25 ml. water. The mixture was heated on a steam bath for 15 minutes, cooled to room temperature and acidified with acetic acid. After standing for 2 hours the precipitate was filtered off, washed with a solution of sodium bicarbonate and thereafter with water, and dried. By recrystallisation from a mixture of equal volumes of ethanol and water the desired compound was obtained with m.p. 269—270° C.

The following Example illustrates the method by which a halogen atom in the 6-position is removed by hydrogenation.

EXAMPLE 4.

7-Sulfamyl-3,4-dihydro-1,2,4-benzothiadiazine-1,1-dioxide.

300 mg. 6-chloro-7-sulfamyl-3,4-dihydro-1,2,4-benzothiadiazine-1,1-dioxide were dissolved in 12 ml. 0.25-N sodium hydroxide and hydrogenated at room temperature and atmospheric pressure in the presence of 300 mg. of a catalyst containing 5% palladium on calcium carbonate. When one mol of hydrogen per mol of the starting substance had been absorbed, the catalyst was filtered off and the filtrate acidified with acetic acid and left standing for 2 hours. The precipitate thereby formed was filtered off, washed with water and dried. By recrystallisation of the crude product from water the desired compound was obtained with m.p. 325—330° C.

The following Examples relate to the production of further compounds of the group by the method described in the Specification of my aforementioned Application No. 26063/1958.

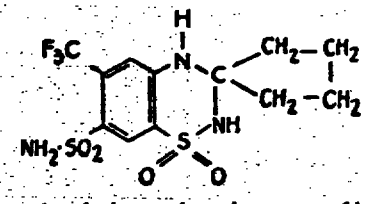
EXAMPLE 5.

6-Methyl-7-sulfamyl-3,4-dihydro-1,2,4-benzothiadiazine-1,1-dioxide.

A mixture of 2.65 g. 3-methyl-4,6-disulfamylaniline, 0.33 g. paraformaldehyde, a catalytical amount of p-toluene-sulphonic acid and 25 ml. ethyleneglycolmonoethylether was boiled with reflux for 16 hours. Thereafter, the mixture was evaporated to dryness in vacuo, and the residue was crystallised from methanol/water. By a further recrystallisation from a mixture of 30 volumes ethanol and 70 volumes water the desired compound was obtained with m.p. 257.5—258.5° C.

EXAMPLE 6.

3.2 g. 5-trifluoromethyl-2,4-disulfamylaniline and a few crystals of p-toluenesulphonic acid were dissolved in 20 ml. cyclopentanone, and the mixture was boiled with reflux for 24 hours. After cooling, the reaction mixture was poured into 150 ml. petroleum ether (boiling range 105—120° C.). The oily substance which thereby separated out crystallised after stirring for a while. The crystals were separated from the solution and washed with petroleum ether. Thereby, 3.7 g. of the reaction product were obtained with m.p. 200—210° C. (decomposition). The dark coloured crystalline product was purified by suspension in 15 ml. ethanol and filtering off the undissolved substance, which subsequently was recrystallised from 20 ml. ethanol. Thereby, the desired reaction product was obtained with m.p. 232.5—234° C. The reaction product is represented by the following formula:



It may be designated cyclopentane-1',3-spiro-6 - trifluoromethyl - 7 - sulfamyl - 3,4-dihydro-benzothiadiazine-1,1-dioxide.

EXAMPLE 7.

3 - Isopropyl - 6 - trifluoromethyl - 7-sulfamyl - 3,4 - dihydro - 1,2,4 - benzothiadiazine - 1,1 - dioxide.

3.2 g. 5 - trifluoromethyl - 2,4 - disulfamyl-aniline prepared as described in Example 1 of Application No. 26063/1958 and 2 drops of piperidine were added to a solution of 1.0 ml. iso-butyraldehyde in 20 ml. 99% ethanol, and the mixture was boiled with reflux for 5 hours. Thereafter the reaction mixture was poured into 200 ml. water, the mixture was left standing overnight in an ice-box, and the precipitate was filtered off. By recrystallisation from 45 ml. ethanol the desired substance was obtained with m.p. 244—245° C.

EXAMPLE 8.

3 - Ethyl - 6 - trifluoromethyl - 7 - sulfamyl-3,4 - dihydro - 1,2,4 - benzothiadiazine-1,1 - dioxide.

3.2 g. 5 - trifluoromethyl - 2,4 - disulfamyl-aniline were added to a solution of 0.79 ml. propionaldehyde in 30 ml. 99% ethanol, and the mixture was boiled with reflux for 4½ hours. Already after 2 hours crystals began to separate out. After cooling the crystals were filtered off and washed with 99% ethanol. The substance was purified by dissolving it in 24 ml. boiling 2-methoxy-ethanol and precipitation with 10 ml. water. The purified product had m.p. 255.5—256° C.

In tests with rats the saliuretic effects of 8 of the compounds of the invention (in addition to the three compounds for which the results of such tests were given in the Specification of my Application No. 26063/1958) have been determined and compared with the effects of two widely applied diuretic agents. The results of these tests are given in Table II in which the 8 compounds of the invention are designated A—H, and the two known agents are designated I and J.

The 10 substances are listed in Table I in which the letters R_1, R_2 and R_3 refer to the following formula:

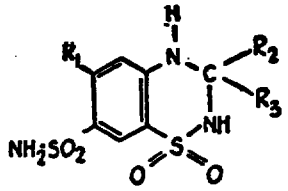


TABLE I

	R_1	R_2	R_3
A	CF_3	CH_3	C_2H_5
B	Cl	H	H
C	CF_3	$CH(CH_3)_2$	H
D	Cl	CH_3	CH_3
E	CF_3	C_2H_5	H
F	Cl	n—C_3H_7	H
G	CF_3	spiro-cyclopentane	
H	CH_3	H	H

I = 6-chloro-7-sulfamyl-1,2,4-benzothiadiazine-1,1-dioxide

J = 2-acetamidol,3,4-thiadiazol-5-sulfamide.

Each animal received a single oral dose of a solution of the test substance corresponding to 5.0 mg. per kg. body weight. The amounts of urine were measured, and the contents of dium, potassium and chlorine ions were determined 6 hours after administration of the test substance. From these figures average values were calculated for the total excretions of the said ions during 6 hours in microgram-equivalents per group of 3 animals.

TABLE II

Test Substance	Excretion in microgram-equivalents of		
	Na^+	K^+	Cl^-
Control	165	248	135
A	663	504	921
B	782	449	1138
C	918	423	1157
D	615	432	690
E	979	477	1281
F	931	570	1283
G	734	455	1043
H	653	525	1009
I	243	345	414
J	1084	769	179

It appears from the Table that the compounds A—H are all considerably more active in respect to excretion of Na^+ and Cl^- than the known agent I, whereas the excretion of K^+ is not increased in the same proportion. Moreover, the effects of A—H differ from those of the other known agent J in that their activities in respect to excretion of Cl^- are several times higher than that of J, whereas their activities in respect to excretion of K^+ are lower. These differences offer distinct therapeutical advantages over the known agents.

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PROVISIONAL SPECIFICATION
No. 30897 A.D. 1958

Therapeutically Active Compounds and method for their production

I, KNUD ABILDGAARD, a Danish Subject, trading as LØVENS KEMISKE FABRIK ved A. Kongsted, of 19, Brønshøjvej, Copenhagen, Denmark, do hereby declare this invention to be described in the following statement:—

This invention, which is complementary to that described in the Provisional Specifications of my co-pending Application No. 26063/1958 and of my co-pending Application No. 28199/1958, relates to 7-sulfamyl-3,4 - dihydro - 1,2,4 - benzothiadiazine - 1,1-dioxide and derivatives thereof containing further substituents at the atoms in the ring system, particularly at the nitrogen atom in the 2-position and the carbon atoms in the position 3, 5 and 6. Thus, the hydrogen atom in the 2-position may be substituted by an alkyl group. One or both of the hydrogen atoms in the 3-position may be substituted by an alkyl group, both of them may be substituted with alkylene groups to form a spirocyclopentyl or spirocyclohexyl derivative, or one of the said hydrogen atoms may be substituted by a mononuclear aryl or aralkyl group. Furthermore,

one or both of the hydrogen atoms in the 5- or 6-position may be substituted by a fluorine, a chlorine or a bromine atom, or by a trifluoromethyl group or an alkyl or alkoxy group. The invention also relates to salts of the said compounds, especially the alkali metal salts.

The compounds of the invention can be produced by the method described in the Specification of the aforementioned Application No. 26063/1958 by reacting an aldehyde or a ketone, or a reactive derivative of such a compound, with 2,4 - disulfamylaniline or a derivative thereof having such further substituents as may be desired in the compound to be produced, or they can be produced, except those having two substituents in the 3-position, as described in the Specification of the aforementioned Application No. 28199/1958 by reduction or catalytic hydrogenation of the corresponding compounds having a double bond between the carbon atom in the 3-position and the nitrogen atom in the 4-position. These compounds can be produced by the method described in United States Specification No. 2,809,194.

The following Examples are intended to provide further supplement to the aforementioned Applications.

EXAMPLE 1.

3-Phenyl-6-methoxy-7-sulfamyl-3,4-dihydro-1,2,4-benzothiadiazine-1,1-dioxide.

2.8 g. 5-Methoxy-2,4-disulfamylaniline were dissolved in a mixture of 15 ml. 2-methoxyethanol and 2.2 ml. benzaldehyde. A catalytical amount of p-toluene-sulphonic acid was added, and the mixture was boiled with reflux for 16 hours. After cooling, the precipitate was filtered off and recrystallised from dimethylformamide/water to give the desired substance with m.p. 261.5—262° C.

EXAMPLE 2.

2-Methyl-6-trifluoromethyl-7-sulfamyl-3,4-dihydro-1,2,4-benzothiadiazine-1,1-dioxide.

22 g. 6-Trifluoromethyl-7-sulfamyl-1,2,4-benzothiadiazine-1,1-dioxide were dissolved in a mixture of 100 ml. 96% ethanol, 15 ml. water and 2.4 g. sodium hydroxide. 6.5 ml. methyliodide were added and the mixture was boiled with reflux overnight. After cooling, the precipitate was filtered off. By recrystallisation from methanol/water 2 - methyl - 6 - trifluoromethyl - 7 - sulfamyl - 1,2,4 - benzothiadiazine-1,1-dioxide was obtained with m.p. 264—264.5° C.

To a solution of 2.06 g. 2-methyl-6-trifluoromethyl - 7 - sulfamyl - 1,2,4 - benzothiadiazine - 1,1 - dioxide in 40 ml. 0,25-N sodium hydroxide was added dropwise while stirring, a solution of 1.2 g. sodium borohydride in 15 ml. water. The mixture was heated on the steam bath for 15 minutes, cooled to room temperature and acidified with acetic acid. After standing for two hours the precipitate was filtered off, washed with water and dried. By recrystallisation from methanol/water the desired compound was obtained with m.p. 227.5—228° C.

EXAMPLE 3.

3 - Methyl - 6 - trifluoromethyl - 7 - sulfamyl-3,4 - dihydro - 1,2,4 - benzothiadiazine-1,1 - dioxide.

3.2 g. 5 - Trifluoromethyl - 2,4 - disulfamylaniline were suspended in a mixture of 25 ml. ethanol and 10 ml. ethylvinylether. A catalytical amount of p-toluenesulphonic acid was added and the mixture was boiled with reflux for 30 minutes. The solvent was removed in vacuo and the oil residue was crystallised from ethylacetate/hexane. By recrystallisation from methanol/water the desired substance was obtained with m.p. 240—240.5° C.

EXAMPLE 4.

6-Trifluoromethyl-7-sulfamyl-3,4-dihydro-1,2,4-benzothiadiazine-1,1-dioxide.

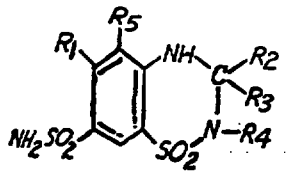
3.2 g. 5 - Trifluoromethyl - 2,4 - disulfamylaniline were dissolved in a mixture of 25 ml. 99% ethanol and 10 ml. ethylal. A catalytical amount of p-toluenesulphonic acid was added and the solution was boiled with reflux overnight. The solvent was removed in vacuo. By recrystallisation of the crude residue from methanol/water the desired substance was obtained with m.p. 271—272° C.

EXAMPLE 5.

6-Trifluoromethyl-7-sulfamyl-3,4-dihydro-1,2,4-benzothiadiazine-1,1-dioxide.

To a solution of 3.2 g. 5-trifluoromethyl-2,4-disulfamylaniline in 50 ml. 99% ethanol were added 3 g. sodium formaldehyde sulphoxylate (Rongalite C), and the resulting suspension was boiled with reflux while stirring for 16 hours. After cooling, 100 ml. water were added and most of the ethanol was removed in vacuo. The precipitate thereby formed was filtered off and washed with water. By recrystallisation from methanol/water the desired substance was obtained with m.p. 270—271.5° C.

Further Examples are listed in Table 1 in which the letters R_1, R_2, R_3, R_4 and R_5 refer to the following formula:



The letters referred to in column 8 denote denote that the compounds are produced in the following manner:

A: as Example 4 in the Specification of Application No. 28199/1958
B: as Example 3 in the Specification of Application No. 26063/1958
C: as Example 2 in the Specification of Application No. 26063/1958
D: as Example 1 in the present Specification.

TABLE 1

No.	R_1	R_2	R_3	R_4	R_5	M.P.	Method	Recrystallised from
1	H	CH_3	CH_3	H	H	242 — 242.5°	A	Methanol — water
2	H	H	C_3H_7	H	H	243 — 244°	A	Methanol — water
3	H	H	C_6H_5	H	H	330°	A	Dimethylformamide — water
4	H	CH_3	CH_3	H	CH_3	267.5—268°	B	
5	H	H	C_3H_7	H	CH_3	288 — 288.5°	C	Dimethylformamide — ether
6	H	H	C_3H_7	H	Cl	270 — 271°	C	Dioxane — hexane
7	Cl	H	C_6H_5	H	H	238 — 240°	D	Acetone — hexane
8	Cl	H	$C_6H_5CH_2$	H	H	249 — 250°	C	Acetone — hexane
9	Cl	Spiro-cyclohexan		H	H	283.5—285°	B	Ethanol
10	CH_3O	H	H	H	H	246 — 248°	C	Acetone — hexane
11	CH_3O	CH_3	CH_3	H	H	240 — 240.5°	B	Methanol
12	CF_3	H	C_6H_{11}	H	H	178 — 179°	C	Dioxane — hexane
13	CF_3	H	C_6H_5	H	H	218.5—219.5°	D	Ethanol — hexane
14	CF_3	Spiro-cyclohexan		H	H	261 — 262°	B	Ethanol
15	CH_3	CH_3	CH_3	H	H	243 — 244°	B	Acetone — ether

These hitherto unknown compounds are therapeutically useful agents, because they are capable of exerting strongly saliuretic and/or diuretic effects. The diuretic effect of two of the compounds of the invention have been determined in test with rats, as described in the aforementioned Applications. The results are listed in Table 2.

TABLE 2

No. Table 1	mg/kg	Number of groups	Excretion in microgram-equivalent		
			Na^+	K^+	Cl^-
Control		3	188	268	236
14	1;25	6	883	535	1105
9	1;25	3	805	375	1010

Both substances are highly active in respect to urinary excretion of Na^+ and Cl^-, while the K^+ excretion is intensified to a much lesser degree.

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PATENT OFFICE

PROVISIONAL SPECIFICATION

No. 36437 A.D. 1958

Benzothiadiazine Derivatives and their preparation

I, KNUD ABILDGAARD, a Danish Subject, trading as LØVENS KEMISKE FABRIK ved A. Kongsted, of 19, Brønshøjvej, Copenhagen, Denmark, do hereby declare this invention to be described in the following statement:—

This invention, which is complementary to that described in the Provisional Specifications of my co-pending Applications Nos. 26,063/1958, 28,199/1958 and 30,897/1958, relates to 7 - sulfamyl - 3,4 - dihydro - 1,2,4-benzothiadiazine - 1,1 - dioxide derivatives containing further substituents on the atoms in the ring system, particularly on the carbon atoms in the positions 3, 5 and 6. Thus, one or both of the hydrogen atoms in the 3-position may be substituted by a saturated or unsaturated, straight or branched hydrocarbon group, both of them may be substituted with alkylene groups to form a spirocyclopentyl or spirocyclohexyl derivative, or one of the said hydrogen atoms may be substituted by a mononuclear aryl, aralkyl or aralkenyl group or by a heterocyclic group. Furthermore, one or both of the hydrogen atoms in the 5- or 6-position may be substituted by a fluorine, a chlorine or a bromine atom, or by a trifluoromethyl group or an alkyl or alkoxy group, or by a nitro or an amino group. The invention also relates to salts of the said compounds, especially the alkali metal salts.

The nitro compounds of the invention can be produced by the method described in the aforementioned Application No. 26,063/1958 by reacting an aldehyde or a ketone or a reactive functional derivative of one of the said compounds with 5-nitro or 6-nitro-2,4-disulfamylaniline. Furthermore, the nitro compounds of the invention can be obtained from the corresponding nitro - 7 - sulfamyl - 1,2,4-benzothiadiazine - 1,1 - dioxide, produced by the method described in Specification No. 826,923, by reduction with a complex alkali metal hydride, such as sodium borohydride or lithium aluminium hydride as described in the aforementioned Application No. 28,199/1958. By this method only the double bond between the carbon atom in the 3-position and the nitrogen atom in the 4-position is hydrogenated.

Supplementary to the hydrogenation methods described in Application No. 28,199/1958 it has been found that compounds of the invention, except those having two substituents in the 3-position, can be produced by electrolytical reduction of the corresponding compounds having a double bond between the carbon atom in the 3-position and the nitrogen atom in the 4-position. By this method a nitro group in the 5- or 6-position will be reduced to an amino group, a bromine atom in one of these positions will be removed, while a chlorine atom and other substituents in one of these positions will resist the hydrogenation.

The amino compounds of the invention can be produced by reduction of the corresponding nitro derivatives obtained by one of the aforementioned methods. The reduction can be performed as a catalytic hydrogenation, using "Raney" Nickel ("Raney" is a Registered Trade Mark), PtO_2 or Pd as a catalyst.

The compounds described in the following Examples and Table I have been synthesised by one of the methods described in this or one of the aforementioned Applications.

The compounds of the invention are hitherto unknown substances which are therapeutically useful agents because they are capable of exerting strongly saliuretic, respectively diuretic effects. The saliuretic effect of the compounds has been determined by tests with rats as described in the aforementioned Applications. The results are given in Table II.

The invention is further illustrated by the following Examples.

EXAMPLE 1.

6-Nitro-7-sulfamyl-3,4-dihydro-1,2,4-benzothiadiazine-1,1-dioxide.

41.4 g. of *m*-nitroaniline were added dropwise over a period of 30 minutes to a mixture of 220 ml. of chlorosulfonic acid and 200 ml. of tetrachloroethane cooled in an ice-bath. 210 g. of sodium chloride were added portionwise over one hour, and the mixture was then heated in an oil bath at 150° C. for 3 hours. After cooling in an ice-bath, the reaction mixture was treated with 1 litre of ice water. The product was taken up in ether, and the ethereal solution washed with water and dried. After concentration in vacuum, a crystalline reaction product separated, which was filtered off, washed with ether and dried. This substance was suspended in concentrated aqueous ammonia and heated to about 60° C., whereupon a vigorous reaction took place. When the initial reaction had subsided, the mixture was heated on a steam bath for 1 hour. After cooling, the precipitate was collected on a filter. Recrystallisation from water yielded 5-nitro-2,4-disulfamylaniline as yellow crystals with m.p. 170.5—171.5° C.

1.48 g. of 5-nitro-2,4-disulfamylaniline were dissolved in 10 ml. of hot 2-methoxyethanol. 150 mg. of paraformaldehyde and a catalytic amount of p-toluenesulphonic acid were added, and the mixture was boiled under reflux for 16 hours. The solvent was removed in vacuum, and the residue was crystallised by treatment with ethyl acetate. By recrystallisation from water yellow crystals of the desired com-

PATENT OFFICE

pound with m.p. 274—275° C, were obtained.

EXAMPLE 2.

6-Amino-7-sulfamyl-3,4-dihydro-1,2,4-benzothiadiazine-1,1-dioxide.

A solution of 1.6 g. of 6-nitro-7-sulfamyl-3,4 - dihydro - 1,2,4 - benzothiadiazine - 1,1-dioxide in 30 ml. of 2-methoxy ethanol was hydrogenated over 100 mg. of platinum catalyst at room temperature with hydrogen at a pressure of one atmosphere. When the theoretical amount of hydrogen had been absorbed, 3 ml. of 2 N sodium hydroxide solution were added, and the catalyst was filtered off. The reaction product was precipitated from the filtrate by acidification with acetic acid. By recrystallisation from aqueous sodium hydroxide/acetic acid, colourless crystals of the desired substance with m.p. 265—267° C. (with decomposition) were obtained.

EXAMPLE 3.

6-Chloro-7-sulfamyl-2,4-dihydro-1,2,4-benzothiadiazine-1,1-dioxide.

A solution of 1.0 g. 6-chloro-7-sulfamyl-1,2,4-benzothiadiazine-1,1-dioxide in a mixture of 150 ml. of a 5% aqueous solution of sodium bicarbonate and 30 ml. ethanol was saturated with CO_2 and thereafter reduced electrolytically in a cell equipped with a carbon anode, a diaphragm of sintered glass and a mercury cathode. The electrolysis was carried out at room temperature and during the electrolysis gaseous CO_2 was continuously led through the cathode compartment, and a cathode potential of 1.65 volts, measured against a saturated calomel electrode, was maintained. As the reduction proceeded, the desired substance crystallised from the solution. After an amount of electricity corresponding to 2 Faradays per mol of the starting compound had been passed through the solution, the electrolysis was stopped, and the crystals filtered off. The infra-red spectrum of the substance thus obtained was identical with that of an authentic specimen of 6-chloro-7 - sulfamyl - 3,4 - dihydro - 1,2,4 - benzothiadiazine - 1,1 - dioxide.

EXAMPLE 4.

6-Trifluoromethyl-7-sulfamyl-3,4-dihydro-1,2,4-benzothiadiazine-1,1-dioxide.

A mixture of 1.0 g. of 5-trifluoromethyl-2,4-disulfamylaniline, 0.25 g. of 35% aqueous formaldehyde solution and 100 ml. water was boiled with reflux for 18 hours. After cooling, the crystals were filtered off, washed on the filter with 2 × 5 ml. of water and dried at 100° C. The product thus obtained had m.p. 271—273° C.

This reaction can also be carried out in aqueous 1 N HCl as the reaction medium.

Further examples are listed in Table I in which R_1, R_2, R_3, R_4 and R_5 refer to substituents in the following formula:

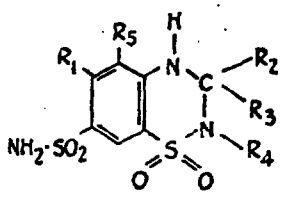
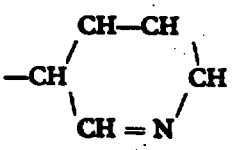


TABLE I

No.	R_1	R_2	R_3	R_4	R_5	M.p. °C.	Recrystallised from
1	H	H	$-CH_2C_6H_5$	H	H	235—237	Acetone/Hexane
2	H	H	$-CH_2C_6H_5$	H	CH_3	272—272.5	Dimethylformamide/Water
3	CH_3	$-(CH_2)_5-$		H	H	261.5—263	Ethanol/Hexane
4	CH_3O	$-(CH_2)_5-$		H	H	268.5—269.5	Dimethylformamide/Water
5	H	$-(CH_2)_5-$		H	Cl	262.5—263.5	2-Ethoxyethanol/Hexane
6	H	H	$-CH_2C_6H_5$	H	Cl	259.5—260	Ethanol
7	H	CH_3	CH_3	H	Cl	249.5—250.5	Acetone/Hexane
8	Br	H	H	H	H	279.5—281	Acetone/Hexane
9	Br	H	n-C_3H_7	H	H	257.5—258	Acetone/Hexane
10	Br	H	C_6H_5	H	H	228—230	Ethylacetate/Hexane
11	Br	CH_3	CH_3	H	H	228—229	Acetone/Hexane
12	Cl	H	n-C_3H_7	H	CH_3	280—281	Dimethylformamide/Water
13	Cl	H	H	H	CH_3	296.5—298	Dimethylformamide/Water
14	Cl	H	$-CH_2C_6H_5$	H	CH_3	271.5—272	2-Methoxyethanol/Benzene/Hexane
15	NO_2	$-(CH_2)_5-$		H	H	261.5	Formamide/Water
16	F_3C	H	$-CH=CH-CH_3$	H	H	213.5—215	Ethylacetate/Hexane
17	F_3C	H	n-$C_{13}H_{27}$	H	H	no m.p.	Dioxane/Hexane
18	F_3C	H		H	H	240—241	Ethanol
19	F_3C	H	$-CH_2C_6H_5$	H	H	220.5—222	Dioxane
20	F_3C	H	$-CH=CH-C_6H_5$	H	H	167—169 (dec.)	Ethanol

The compounds Nos. 1 and 2 of Table I were produced by catalytic hydrogenation of the corresponding 6-halogen compounds as described in the aforementioned Application No. 28,199/1958.

All the other compounds of the Table I were produced by reacting an aldehyde or ketone or a reactive functional derivative of one of the said compounds with a 2,4-disulfamylaniline or a derivative thereof having such further substituents as may be desired in the compound to be produced as described in the aforementioned Application No. 26,063/1958.

In Table II below, the saliuretic effects of several of the compounds of the invention are listed. The figures in the first column correspond to the figures in the first column of Table I.

TABLE II

No. in Table I	Dose mg/kg	Number of groups	Excretion in micro-equivalents Na+	K+	Cl-
Control		12	100	229	76
Compound of Example 1	1.25	6	346	423	440
3	1.25	3	688	526	938
5	5	6	397	358	360
6	5	6	358	286	345
8	1.25	6	776	380	882
9	1.25	6	730	449	800
10	5	6	370	355	439
11	1.25	6	325	278	322
11	5	6	453	384	537
12	5	6	336	316	344
15	1.25	6	697	485	873

Each animal received a single oral dose of a solution of the test substance as indicated in the second column of the Table. The excretion of urine from a number of groups of rats (each group including three rats) was measured during the first 6 hours after administration of the test substance, and the contents of sodium, potassium and chlorine ions were determined. From these figures average values were calculated for the total excretions of the said three ions during 6 hours in micro-equivalents per group of three animals.

The saliuretic effects of some of the compounds described in the specification of the co-pending Application No. 30,897/1958 have been determined by the same method. The results are listed in Table III, in which the numbers in the first column correspond to those in the first column of Table I in the Specification of Application No. 30,897/1958.

TABLE III

Substance	Dose mg/kg	Number of groups	Excretion in micro-equivalents Na+	K+	Cl-
Control		12	100	229	76
Compound of Example 3	1.25	6	546	404	514
2	5	6	351	224	274
8	1.25	6	1103	544	1403
12	1.25	6	566	517	729
13	5	6	357	345	361
15	5	6	284	309	192

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PROVISIONAL SPECIFICATION
No. 37997 A.D. 1958

Benzothiadiazine Derivatives and their preparation

I, KNUD ABILDGAARD, a Danish Subject, trading as LØVENS KEMISKE FABRIK ved A. Kongsted, of 19, Brønshøjvej, Copenhagen, Denmark, do hereby declare this invention to be described in the following statement:—

This invention, which is complementary to that described in the Provisional Specification of my co-pending Patent Applications Nos. 26,063/1958, 28,199/1958, 30,897/1958 and 36,437/1958, relates to 7-sulfamyl-3,4-dihydro-1,2,4-benzothiadiazine-1,1-dioxide derivatives containing further substituents on the atoms in the ring system, particularly on the carbon atoms in the positions 3, 5 and 6. Thus, one of the hydrogen atoms in the 3-position may be substituted by an alkyl group, while the other hydrogen atom in the 3-position may be substituted by a group which, besides carbon and hydrogen, contains one or more halogen atoms and/or one or more oxygen atoms. Furthermore, one or both of the hydrogen atoms in the 5- or 6-position may be substituted by a fluorine, a chlorine or a bromine atom, or by a trifluoromethyl, alkyl, alkoxy, nitro, or amino group. The invention also relates to salts of the said compounds, especially the alkali metal salts.

The compounds of the invention can be produced by the method described in the Provisional Specification of the aforementioned Application No. 26,063/1958 by reacting an aldehyde or a ketone or a reactive functional derivative of one of the said compounds with a derivative of 2,4-disulfamylaniline.

The compounds of the invention are hitherto unknown substances which are therapeutically useful agents because they are capable of exerting strongly saliuretic, respectively diuretic effects. The saliuretic effect of some of the compounds has been determined by tests with rats. The results are given in the following Table.

EXAMPLE 1.

3-Benzoyl-6-trifluoromethyl-7-sulfamyl-3,4-dihydro-1,2,4-benzothiadiazine-1,1-dioxide.

A mixture of 3.2 g. of 5-trifluoromethyl-2,4-disulfamylaniline, 2.7 g. of phenylglyoxal and 50 ml. of absolute ethanol containing a catalytic amount of *p*-toluenesulphonic acid was boiled under reflux for 16 hours. The ethanol was removed by distillation *in vacuo*, and the residue was recrystallised from ethylacetate. The product had m.p. 261.5—262.5° C.

EXAMPLE 2.

3-Acetonyl-6-trifluoromethyl-7-sulfamyl-3,4-dihydro-1,2,4-benzothiadiazine-1,1-dioxide.

A mixture of 3.2 g. of 5-trifluoromethyl-2,4-disulfamylaniline, 2.65 g. of acetoacetaldehyde diethylacetal, a catalytic amount of *p*-toluenesulphonic acid and 30 ml. of dioxane was boiled under reflux for 16 hours. The solvent was removed by distillation *in vacuo*, and the residue was recrystallised from *n*-propanol-methylene chloride/hexane. The product had m.p. 208—209° C. (decomposition).

EXAMPLE 3.

3-Methyl-3-carbethoxymethyl-6-trifluoromethyl-7-sulfamyl-3,4-dihydro-1,2,4-benzothiadiazine-1,1-dioxide.

A mixture of 3.2 g. of 5-trifluoromethyl-2,4-disulfamylaniline, a catalytic amount of *p*-toluenesulphonic acid and 50 ml. of ethyl acetoacetate was heated on a steam bath overnight. The excess ethyl acetoacetate was removed by distillation *in vacuo*, and the residue was triturated with methylene chloride. The crystalline product thus obtained was recrystallised from dioxane/chloroform/hexane. The product had m.p. 150—152° C.

EXAMPLE 4.

3-Chloromethyl-6-trifluoromethyl-7-sulfamyl-3,4-dihydro-1,2,4-benzothiadiazine-1,1-dioxide.

To a solution of 3.2 g. of 5-trifluoromethyl-2,4-disulfamylaniline in 50 ml. of dioxane was added a catalytic amount of *p*-toluenesulphonic acid followed by 4 ml. of a 40% aqueous solution of chloroacetaldehyde. The mixture was boiled under reflux for 4 hours, whereupon the solvent was removed by distillation *in vacuo*. The residue was triturated with chloroform, and the crystalline product thus obtained was recrystallised from ethylacetate/hexane. The product had m.p. 245—245.5° C. (decomposition).

EXAMPLE 5.

3-Methyl-3-carbethoxy-6-trifluoromethyl-7-sulfamyl-3,4-dihydro-1,2,4-benzothiadiazine-1,1-dioxide.

A solution of 3.2 g. of 5-trifluoromethyl-2,4-disulfamylaniline, 5 ml. of ethyl pyruvate and a catalytic amount of *p*-toluenesulphonic acid in 25 ml. of dioxane was boiled under reflux overnight. The dioxane was removed by distillation *in vacuo*, and the residue was

triturated with chloroform. The product thus obtained was recrystallised from ethyl acetate/hexane. The recrystallised product had m.p. 191—194° C.

The following Table illustrates the saliuretic effect of some of the foregoing compounds on rats.

TABLE

Substance of Example No.	Dose mg/kg	Number of groups	Excretion in micro-equivalents		
			Na^+	K^+	Cl^+
Control		12	100	229	76
2	1.25	6	298	284	318
	5.0	6	722	524	916
3	1.25	3	367	249	355
	5.0	6	777	463	921
4	1.25	3	626	395	705
	5.0	6	1068	576	1315

Each animal received a single oral dose of a solution of the test substance as indicated in the second column of the Table. The excretion of urine from a number of groups of rats (each group consisting of three rats) was measured during the first 6 hours after administration of the test substance, and the contents of sodium, potassium and chlorine ions were determined. From these figures average values were calculated for the total excretions of the said three ions during 6 hours in micro-equivalents per group of three animals.

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PROVISIONAL SPECIFICATION
No. 2314 A.D. 1959

Benzothiadiazine Derivatives and their preparation

I, KNUD ABILDGAARD, a Danish Subject, trading as LØVENS KEMISKE FABRIK ved A. Kongsted, of 19, Brønshøvej, Copenhagen, Denmark, do hereby declare this invention to be described in the following statement:—

This invention, which is complementary to that described in the Provisional Specifications of my co-pending Applications Nos. 26,063/1958; 28,199/1958; 30,897/1958; 36,437/1958 and 37,997/1958, relates to 7-sulfamyl-3,4-dihydro-1,2,4-benzothiadiazine-1,1-dioxide derivatives containing further substituents on the carbon atoms in the ring system, particularly on the carbon atoms in the 3-, 5-, and 6-positions. Thus, one of the hydrogen atoms in the 3-position may be substituted by an alkyl group, while the other hydrogen atom in the 3-position may be substituted by a group which, besides hydrogen and carbon contains one or more halogen atoms and/or one or more oxygen or sulphur atoms. Furthermore, one or both of the hydrogen atoms in the 5- or 6-position may be substituted by a fluorine, chlorine or bromine atom or by a trifluoromethyl, alkyl, alkoxy, nitro or amino group. The invention also relates to salts of the said compounds, especially the alkali metal salts.

The compounds of the invention can be produced by the method described in the Provisional Specification of my aforementioned Application No. 26,063/1958 by reacting an aldehyde or a ketone or a reactive functional derivative of one of the said compounds with a derivative of 2,4-disulfamylaniline.

The compounds of the invention are hitherto unknown substances which are therapeutically useful agents because they are capable of exerting strongly saliuretic, or diuretic effects. The saliuretic effect of some of the compounds has been determined by tests with rats. The results are given in the Table II.

The invention will now be illustrated by the following Examples:

EXAMPLE 1.

3 - Diphenylmethyl - 6 - trifluoromethyl - 7-sulfamyl - 3,4 - dihydro - 1,2,4 - benzothiadiazine - 1,1 - dioxide.

3.2 g. of 5-trifluoromethyl-2,4-disulfamylaniline and 2.1 g. of diphenylacetaldehyde were dissolved in 30 ml. of dioxane. A catalytic amount of *p*-toluenesulphonic acid was added and the mixture was boiled under reflux for 5 hours. After cooling, the reaction product was precipitated by the addition of methylene chloride/hexane. By recrystallisation twice from ethanol/water the desired substance was obtained with m.p. 261—262.5° C.

EXAMPLE 2.

3 - (β - methoxyethyl) - 6 - trifluoromethyl-7 - sulfamyl - 3,4 - dihydro - 1,2,4-benzothiadiazine - 1,1 - dioxide.

3.2 g. of 5-trifluoromethyl-2,4-disulfamylaniline and 1.76 g. of β-methoxypropionaldehyde were dissolved in 50 ml. of methanol. A catalytic amount of *p*-toluenesulphonic acid was added and the mixture was boiled under reflux for 7 hours. Thereupon the methanol was distilled off *in vacuo*, and the residue was dissolved in a mixture of equal parts of dioxane and methylene chloride and precipitated by addition of hexane. After repeating this procedure once more, the precipitate was recrystallised from isopropanol, and the desired substance was obtained with m.p. 188—190° C.

EXAMPLE 3.

3 - Chloromethyl - 6 - chloro - 7 - sulfamyl-3,4 - dihydro - 1,2,4 - benzothiadiazine-1,1 - dioxide.

2.9 g. of 5-chloro-2,4-disulfamylaniline and 2.2 ml. of a 40—45% aqueous solution of chloroacetaldehyde were dissolved in 30 ml. of dioxane. A catalytic amount of *p*-toluenesulphonic acid was added, and the mixture was boiled overnight under reflux. Thereupon the dioxane was distilled off *in vacuo*, and the residue was triturated with *n*-propanol. By recrystallisation from *n*-propanol the desired compound was obtained with m.p. 239.5—240° C.

EXAMPLE 4.

3 - Dicarbethoxymethyl - 6 - trifluoromethyl-7 - sulfamyl - 3,4 - dihydro - 1,2,4-benzothiadiazine - 1,1 - dioxide.

3.2 g. of 5-trifluoromethyl-2,4-disulfamylaniline and 10 ml. of diethyl ethoxymethylene malonate were dissolved in 25 ml. of dioxane. A catalytic amount of *p*-toluenesulphonic acid was added, and the mixture was boiled under reflux for 5 hours. Thereupon the dioxane was distilled off, and the residue was triturated with methylene chloride. After recrystallisation from dioxane/hexane the desired compound was obtained with m.p. 232—233° C.

EXAMPLE 5.

3 - (β - benzylmercaptoethyl) - 6 - trifluoromethyl - 7 - sulfamyl - 3,4 - dihydro-1,2,4 - benzothiadiazine - 1,1 - dioxide.

6.4 g. of 5-trifluoromethyl-2,4-disulfamylaniline and 3.6 g. of β-benzylmercaptopropionaldehyde were dissolved in 50 ml. of dioxane. The mixture was boiled under reflux for 17 hours. The dioxane was distilled off. The residue was dissolved in a mixture of equal amounts of dioxane and methylene chloride, and the product was precipitated by the addition of hexane. This recrystallisation was repeated twice and the desired product was thereby obtained and had m.p. 134—136° C.

EXAMPLE 6.

6 - Trifluoromethyl - 7 - sulfamyl - 3 - (β-phenylethyl) - 3,4 - dihydro - 1,2,4-benzothiadiazine - 1,1 - dioxide.

A mixture of 9.6 g. of 5-trifluoromethyl-2,4-disulfamylaniline, 3.6 ml. of β-phenylpropionaldehyde, a catalytic amount of *p*-toluenesulphonic acid and 40 ml. of methanol was boiled overnight under reflux. After cooling, 20 ml. of water were added, and the crystalline product thereby obtained was filtered off and dissolved in 40 ml. of ethanol. 20 ml. of water were added, whereby, after filtration and drying, the desired product was obtained with m.p. 235—236° C.

EXAMPLE 7.

3 - Benzyl - 6 - trifluoromethyl - 7 - sulfamyl-3,4 - dihydro - 1,2,4 - benzothiadiazine-1,1 - dioxide.

6.4 g. of 5-trifluoromethyl-2,4-disulfamylaniline were dissolved in 12 ml. of dioxane. 2.7 ml. of phenylacetaldehyde and a catalytic amount of *p*-toluenesulphonic acid were added. After boiling for a short time under reflux, the reaction mixture crystallised, and, after filtration and recrystallisation from dioxane, the desired product was obtained with m.p. 224.5—225.5° C.

EXAMPLE 8.

3-Benzyl-6-nitro-7-sulfamyl-3,4-dihydro-1,2,4-benzothiadiazine-1,1-dioxide.

This compound was synthesised by the same method as the compounds described in Example 1. After recrystallisation from dioxane/hexane the desired product was obtained with m.p. 226—227° C.

EXAMPLE 9.

6-Trifluoromethyl-7-sulfamyl-3,4-dihydro-1,2,4-benzothiadiazine-1,1-dioxide.

To a solution of 16 g. of sodium hydroxide in 1200 ml. of water were added 128 g. of 5-trifluoromethyl-2,4-disulfamylaniline. The mixture was heated to the boiling point, and to the clear solution thus obtained 33.5 ml. of a 36% aqueous formaldehyde solution were added. The mixture was boiled under reflux

for 4 hours, and cooled to 55° C. 20% aqueous sulphuric acid was then added with stirring until a pH of 5—6 had been reached. The resulting suspension was filtered, the filter cake was washed with water, and the resulting product was dried at 90—100° C. The 6 - trifluoromethyl - 7 - sulfamyl - 3,4-dihydro - 1,2,4 - benzothiadiazine - 1,1-dioxide thus obtained had a m.p. of 272—273° C.

In the following Table I the compounds mentioned in the Examples of this invention are listed as are the compounds mentioned in Table II showing the biological effects of some of the compounds. The letters R_1, R_2, R_3 and R_5 refer to the following formula:

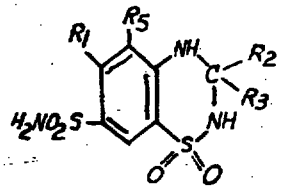


TABLE I

No.	R_1	R_2	R_3	R_5	M.p. °C.	Recrystallised from
1	CF_3	H	$-CH(C_6H_5)_2$	H	261—262.5	Ethanol/Water
2	CF_3	H	$-CH_2CH_2OCH_3$	H	188—190	Isopropanol
3	Cl	H	$-CH_2Cl$	H	239.5—240	*n*-Propanol
4	CF_3	H	$-CH(COOC_2H_5)_2$	H	232—233	Dioxane/Hexane
5	CF_3	H	$-CH_2CH_2SCH_2C_6H_5$	H	134—136	Dioxane/Methylene chloride/Hexane
6	CF_3	H	$-CH_2CH_2C_6H_5$	H	235—236	Methanol/Water
7	CF_3	H	$-CH_2C_6H_5$	H	224.5—225.5	Dioxane
8	NO_2	H	$-CH_2C_6H_5$	H	226—227	Dioxane/Hexane
9	Cl	H	$-CH_2C_6H_5$	CH_3	271.5—272	2-Methoxyethanol/Benzene/Hexane
10	Cl	H	$-CH_2C_6H_5$	H	249—250	Acetone/Hexane
11	CF_3	H	H	H	272—273	

TABLE II

No. in Table I	Dose mg/kg	Number of groups	Excretions in micro-equivalents		
			Na^+	K^+	Cl^-
Control		6	120	271	85
1	0.156	3	298	350	205
2	1.25	3	773	383	810
7	0.078	6	420	341	437
	0.156	6	634	419	718
	0.313	6	803	524	1025
	0.625	6	982	590	1143
9	1.25	6	723	482	736
	0.313	6	345	316	323

Each animal received a single oral dose of a solution of the test substance as indicated in the second column of the Table. The excretion of urine from a number of groups of rats (each group consisting of three rats) was measured during the first 6 hours after administration of the test substance, and the contents of sodium, potassium and chloride ions were determined. From these figures average values were calculated for the total excretions of the said three ions during 6 hours in micro-equivalents per group of three animals.

The compounds Nos. 7 and 9 have already been disclosed in Table I of the specification of my co-pending Application No. 36,437/1958, where they have the numbers 19 and 14, respectively.

As will be seen from the above Table II the compound No. 7 (3-benzyl-6-trifluoromethyl - 7 - sulfamyl - 3,4 - dihydro - 1,2,4-benzothiadiazine - 1,1 - dioxide) has a high activity giving rise to very high sodium excretions even in small dosages. Similar high activities are obtained with the compound No. 8 (3 - benzyl - 6 - nitro - 7 - sulfamyl - 3,4-dihydro - 1,2,4 - benzothiadiazine - 1,1-dioxide) and compound No. 10 (3 - benzyl-6 - chloro - 7 - sulfamyl - 3,4 - dihydro-1,2,4 - benzothiadiazine - 1,1 - dioxide).

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No. 21027 A.D. 1959

Benzothiadiazine Derivatives and their preparation

I, KNUD ABILDGAARD, a Danish Subject, trading as LØVENS KEMISKE FABRIK ved A. Kongsted, of 11, Ballerup Byvej, Ballerup, Denmark, do hereby declare this invention to be described in the following statement:—

This invention, which is complementary to that described in the Provisional Specifications of my co-pending Applications Nos. 26,063/1958; 28,199/1958; 30,897/1958; 36,437/1958; 37,997/1958 and 2,314/1959, relates to 7 - sulfamyl - 3,4 - dihydro - 1,2,4 - benzothiadiazine - 1,1 - dioxide derivatives containing further substituents on the carbon atoms in the ring system, particularly on the carbon atoms in the 3- and 6-positions. Thus, one of the hydrogen atoms in the 3-position may be substituted by an alkyl group, while the other hydrogen atom in the 3-position may be unsubstituted or substituted by a group which, besides hydrogen and carbon, contains one or more halogen atoms and/or one or more oxygen and/or sulphur or nitrogen atoms. Both of the hydrogen atoms in the 3-position may be substituted by alkylene groups to form a spirocyclopentyl or a spirocyclohexyl group, in which one or more of the hydrogen atoms may be substituted by one or more halogen atoms. Furthermore, the hydrogen atom in the 6-position may be substituted by a chlorine atom, a trifluoromethyl group or a nitro group. The invention also relates to salts of the said compounds, especially the alkali metal salts.

The compounds of the invention can be produced by the method described in the Specification of the aforementioned Application No. 26,063/1958 by reacting an aldehyde or a ketone or a reactive functional derivative of one of the said compounds with a derivative of 2,4-disulfamylaniline.

The compounds of the invention are hitherto unknown substances which are therapeutically useful agents since they are capable of exerting strongly saliuretic effects. The saliuretic effects of some of the compounds have been determined by tests with rats. The results are given hereafter in Table II.

The invention will now be illustrated by the following Examples:

EXAMPLE 1

3 - δ - Hydroxybutyl - 6 - trifluoromethyl-7 - sulfamyl - 3,4 - dihydro - 1,2,4-benzothiadiazine - 1,1 - dioxide.

6.4 g. of 5-trifluoromethyl-2,4-disulfamylaniline and 2.25 g. of δ-hydroxypentanal were dissolved in 30 ml. of dimethylformamide. A catalytic amount of *p*-toluenesulphonic acid was added, and the mixture was heated to 70° C. for 7 hours. Thereupon the dimethylformamide was distilled off in vacuo. The residue was dissolved in methyl-isobutylketone and precipitated by the addition of a methylene chloride/hexane mixture. By two re-crystallisations from an acetone/hexane mixture the desired substance was obtained, and had a melting point of 175—175.5° C.

EXAMPLE 2

3 - (β - (*p* - Methoxyphenyl) - ethyl) - 6-trifluoromethyl - 7 - sulfamyl - 3,4-dihydro - 1,2,4 - benzothiadiazine - 1,1-dioxide.

3.2 g. of 5-trifluoromethyl-2,4-disulfamylaniline and 2.6 g. of β-(*p*-methoxyphenyl)-propionaldehyde diethyl acetal were dissolved in 25 ml. of dioxane. A catalytic amount of *p*-toluenesulphonic acid was added, and the mixture was boiled under reflux overnight. After cooling, the reaction product was precipitated by the addition of water. By recrystallisation from a methanol/water mixture the desired substance was obtained and had a melting point of 250.5—251.5° C.

EXAMPLE 3

3 - Phenoxymethyl - 6 - trifluoromethyl - 7-sulfamyl - 3,4 - dihydro - 1,2,4 - benzothiadiazine - 1,1 - dioxide.

3.2 g. of 5-trifluoromethyl-2,4-disulfamylaniline and 2.3 g. of phenoxyacetaldehyde diethyl acetal were dissolved in 30 ml. of dioxane. A catalytic amount of *p*-toluenesulphonic acid was added, and the mixture was boiled under reflux overnight. The reaction product was precipitated by addition of a methylene chloride/hexane mixture. By recrystallisation from a methanol/water mixture the desired substance was obtained, and had a melting point (with decomposition) of 244.5—246° C.

EXAMPLE 4

3 - Benzyloxymethyl - 6 - trifluoromethyl - 7-sulfamyl -3,4 - dihydro - 1,2,4 - benzothiadiazine - 1,1 - dioxide.

3.2 g. of 5-trifluoromethyl-2,4-disulfamylaniline and 2.5 g. of benzyloxyacetaldehyde diethyl acetal were dissolved in 30 ml. of dioxane. A catalytic amount of *p*-toluenesulphonic acid was added, and the mixture was boiled with reflux overnight. Thereupon the dioxane was distilled off in vacuo, and the residue was dissolved in isopropanol. The reaction product was precipitated by the addition of water. By recrystallisation from an isopropanol/water mixture the desired substance was obtained, and had a melting point of 221—221.5° C.

EXAMPLE 5

3 - *p* - Nitrophenoxymethyl - 6 - trifluoromethyl - 7 - sulfamyl - 3,4 - dihydro-1,2,4 - benzothiadiazine - 1,1 - dioxide.

3.2 g. of 5-trifluoromethyl-2,4-disulfamylaniline and 3.0 g. of *p*-nitrophenoxyacetaldehyde diethyl acetal were dissolved in 25 ml. of dioxane. A catalytic amount of *p*-toluenesulphonic acid was added, and the mixture was boiled under reflux overnight. After cooling, the reaction product was precipitated by the addition of water. By recrystallisation from a dimethylformamide/water mixture the desired substance was obtained, and had a melting point of 261.5—262° C.

EXAMPLE 6

3 - (2^1,4^1 - Dichlorophenoxymethyl) - 6-trifluoromethyl - 7 - sulfamyl - 3,4-dihydro - 1,2,4 - benzothiadiazine - 1,1-dioxide.

3.2 g. of 5-trifluoromethyl-2,4-disulfamylaniline and 2.8 g. of 2,4-dichlorophenoxyacetaldehyde diethyl acetal were dissolved in 25 ml. of dioxane. A catalytic amount of *p*-toluenesulphonic acid was added, and the mixture was boiled under reflux overnight. After cooling, the reaction product was precipitated by the addition of a methylene chloride/hexane mixture. By recrystallisation from an ethanol/water mixture the desired substance was obtained, and had a melting point of 230.5—231° C.

EXAMPLE 7

3 - Bromomethyl - 6 - trifluoromethyl - 7-sulfamyl - 3,4 - dihydro - 1,2,4 - benzothiadiazine - 1,1 - dioxide.

3.2 g. of 5-trifluoromethyl-2,4-disulfamylaniline and 2.2 g. of bromoacetaldehyde diethyl acetal were dissolved in 30 ml. of dioxane. A catalytic amount of *p*-toluenesulphonic acid was added, and the mixture was boiled under reflux overnight. After cooling, the reaction product was precipitated by the addition of a methylene chloride/hexane mixture. By recrystallisation from a methanol/water mixture the desired substance was obtained, and had a melting point of 209.5—210° C.

EXAMPLE 8

3 - *p* - Chlorobenzyl - 6 - trifluoromethyl - 7-sulfamyl - 3,4 - dihydro - 1,2,4 - benzothiadiazine - 1,1 - dioxide.

3.2 g. of 5-trifluoromethyl-2,4-disulfamylaniline and 2.5 g. of *p*-chlorophenylacetaldehyde diethyl acetal were dissolved in 25 ml. of dioxane. A catalytic amount of *p*-toluenesulphonic acid was added, and the mixture was boiled under reflux overnight. After cooling, the reaction product was precipitated by the addition of water. By recrystallisation from a methanol/water mixture the desired substance was obtained, and had a melting point of 243.5—244.5° C.

EXAMPLE 9

2^1 - Chlorocyclohexane - 1^1,3 - spiro - 6-trifluoromethyl - 7 - sulfamyl - 3,4-dihydro - 1,2,4 - benzothiadiazine - 1,1-dioxide.

6.4 g. of 5-trifluoromethyl-2,4-disulfamylaniline and 4.6 g. of 1,1-diethoxy-2-chlorocyclohexane were dissolved in 20 ml. of dioxane. A catalytic amount of *p*-toluenesulphonic acid was added, and the mixture was boiled under reflux for 24 hours. After cooling, the reaction mixture was poured into 200 ml. of hexane and the precipitate thereby formed was recrystallised twice from a methanol/water mixture. The desired substance was obtained and had a melting point (with decomposition) of 218—219° C.

EXAMPLE 10

4^1 - Chlorocyclohexane - 1^1,3 - spiro - 6-trifluoromethyl - 7 - sulfamyl - 3,4-dihydro - 1,2,4 - benzothiadiazine - 1,1-dioxide.

6.4 g. of 5-trifluoromethyl-2,4-disulfamylaniline and 2.9 g. of 4-chlorocyclohexanone were dissolved in 20 ml. dioxane. A catalytic amount of *p*-toluenesulphonic acid was added, and the mixture was boiled under reflux for 20 hours. After cooling, the reaction mixture was poured into 300 ml. of hexane. The precipitate thereby formed was recrystallised from a methanol/methylene chloride/hexane mixture and thereafter from a methanol/water mixture. The desired substance was obtained, and had a melting point (with decomposition) of 217—218° C.

EXAMPLE 11

3 - (2¹ - Furyl) - 6 - trifluoromethyl - 7-sulfamyl - 3,4 - dihydro - 1,2,4 - benzothiadiazine - 1,1 - dioxide.

3.2 g. of 5-trifluoromethyl-2,4-disulfamylaniline and 1.06 g. of freshly distilled furfural were dissolved in 20 ml. of 99.9% ethanol. The mixture was boiled under reflux for 48 hours, and, after cooling, was poured into 150 ml. of water. The precipitate thereby formed was filtered off and recrystallised from a methanol/water mixture. The desired substance was obtained, and had a melting point of 190—192° C.

EXAMPLE 12

3 - (2¹ - Pyridyl) - 6 -trifluoromethyl - 7-sulfamyl - 3,4 - dihydro - 1,2,4 - benzothiadiazine - 1,1 - dioxide.

3.2 g. of 5-trifluoromethyl-2,4-disulfamylaniline and 1.2 g. of pyridine-2-aldehyde were dissolved in 20 ml. of 99.9% ethanol. The mixture was boiled under reflux for 48 hours, and, after cooling, was poured into 300 ml. of water, whereby the reaction product precipitated out. By recrystallisation from a methanol/water mixture the desired substance was obtained and had a melting point (with decomposition) of 304—306° C.

EXAMPLE 13

3 - *n* - Butyl - 6 - trifluoromethyl - 7 - sulfamyl - 3,4 - dihydro - 1,2,4 - benzothiadiazine - 1,1 - dioxide.

3.2 g. of 5-trifluoromethyl-2,4-disulfamylaniline and 1.15 ml. of *n*-valeraldehyde were dissolved in 20 ml. of dioxane. A catalytic amount of *p*-toluenesulphonic acid was added, and the mixture was boiled under reflux for 5 hours. After cooling, the reaction product was precipitated by the addition of water, and the precipitate was filtered off. By recrystallisation from a methanol/water mixture the desired substance was obtained, and had a melting point of 216.5—217.5° C.

EXAMPLE 14

3,3 - Dimethyl - 6 - nitro - 7 - sulfamyl - 3,4-dihydro - 1,2,4 - benzothiadiazine - 1,1-dioxide.

3.0 g. of 5-nitro-2,4-disulfamylaniline was dissolved in 50 ml. of acetone. A catalytic amount of *p*-toluenesulphonic acid was added, and the mixture was boiled under reflux overnight. After cooling, the reaction product was precipitated by the addition of water, and the precipitate was filtered off. By recrystallisation from a methanol/water mixture the desired substance was obtained, and had a melting point of 233—233.5° C.

EXAMPLE 15

3 - (γ - Nitropentyl) - 6 - trifluoromethyl - 7-sulfamyl - 3,4 - dihydro - 1,2,4 - benzothiadiazine - 1,1 - dioxide.

3.2 g. of 5-trifluoromethyl-2,4-disulfamylaniline and 1.5 g. of γ-nitrocaproaldehyde was dissolved in 30 ml. of dioxane. A catalytic amount of *p*-toluenesulphonic acid was added and the mixture was boiled under reflux overnight. After cooling, the reaction product was precipitated by the addition of water. By recrystallisation of the residue from a methanol/water mixture the desired substance was obtained, and had a melting point of 234.5—235° C.

In the following Table I the compounds described in Examples 1 to 15 are listed under the numbers 1—15. The Table also includes some compounds (numbered 16 to 18) which have been disclosed in the Specification of my co-pending Application No. 2,314/1959. Furthermore, the Table includes some compounds (numbered 19 to 24), the biological effects of which have proved to be very strong giving rise to high sodium excretions even in small dosages, as will be seen from the following Table II.

TABLE I

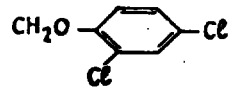
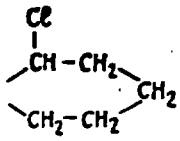
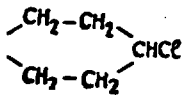
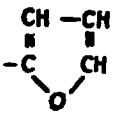
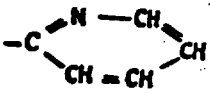
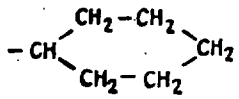
No.	R_1	R_2	R_3	m.p. °C.	Recrystallised from:
1	CF_3	H	$CH_2CH_2CH_2CH_2OH$	175—175.5	Acetone/Hexane
2	CF_3	H		250.5—251.5	Methanol/Water
3	CF_3	H	$CH_2OC_6H_5$	244.5—246	Methanol/Water
4	CF_3	H	$CH_2OCH_2C_6H_5$	221—221.5	Isopropanol/Water
5	CF_3	H		261.5—262	Dimethylformamide/ Water
6	CF_3	H		230.5—231	Methanol/Water
7	CF_3	H	CH_2Br	209.5—210	Methanol/Water
8	CF_3	H		243.5—244.5	Methanol/Water
9	CF_3			218—219	Methanol/Water
10	CF_3			217—218	Methanol/Water
11	CF_3	H		190—192	Methanol/Water
12	CF_3	H		304—306	Methanol/Water
13	CF_3	H	C_6H_5	216.5—217.5	Methanol/Water
14	NO_2	CH_3	CH_3	233—233.5	Methanol/Water
15	CF_3	H	$-CH_2CH_2CH(NO_2)CH_2CH_3$	234.5—235	Methanol/Water
16	CF_3	H	$-CH_2CH_2SCH_2C_6H_5$	134—136	

TABLE I

No.	R_1	R_2	R_3	m.p. °C.	Recrystallised from:
17	CF_3	H	$-CH_2CH_2C_6H_5$	235—236	
18	Cl	H	CH_2Cl	239.6—240	
19	CF_3	H	$-CH(CH_3)-C_6H_5$	242—243.5	
20	Cl	H	$-CH_2CH_2C_6H_5$	224—225	
21	CF_3	H	C_6H_{11}	190—191.5	
22	CF_3	H		258—259.5	
23	CF_3	CH_3	CH_2Cl	227—227.5	
24	Cl	H	C_4H_9	213—215	

In a series of tests with rats, the saliuretic effects of some of the compounds of Table I were determined. The results are given in Table II.

TABLE II

No. in Table I	Dose mg/kg	Number of groups	Excretion in micro-equivalents of Na^+	K^+	Cl^-
2	0.625	3	676	536	779
7	0.625	3	801	377	915
8	0.156	3	449	361	478
13	0.156	6	533	436	741
16	0.156	6	486	380	452
17	0.078	6	516	417	534
	0.156	6	714	395	961
	0.313	6	836	396	936
18	0.156	6	432	385	485
	0.625	6	846	547	1107
19	0.156	6	505	361	575
20	0.156	6	745	529	1060
21	0.156	6	577	320	680
	0.313	6	649	421	862
22	0.625	6	759	444	905
23	0.625	6	582	415	730
24	0.078	6	589	448	873
	0.625	6	1053	544	1228
Control		6	165	260	140

Each animal received a single oral dose of a solution of the test substance as indicated in the second column of Table II. The excretion of urine from a number of groups of rats (each group consisting of three rats) was measured during the first 6 hours after administration of the test substance, and the contents of sodium, potassium and chloride ions were determined. From these figures average values were calculated for the total excretions of the said three ions during 6 hours in micro-equivalents per group of three animals.

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