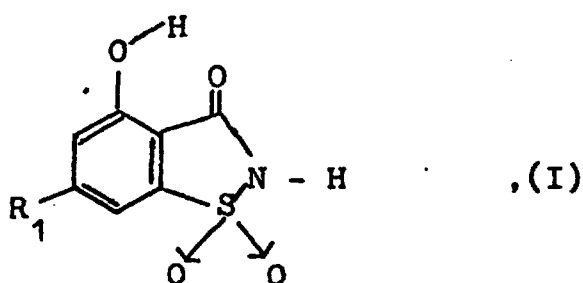


**4-Hydroxy-1,2-benzisothiazol-3(2H)-one-1,1-dioxides,
their salts, their preparation and use**

This invention describes as new compounds 4-hydroxy-1,2-benzo-
isothiazol-3(2H)-one-1,1-dioxides of general formula I



wherein R₁ represents a hydrogen atom or the hydroxy group,
their physiologically compatible salts with inorganic or
organic bases, processes for the preparation of these com-
pounds, preparations containing these compounds, and their
use as sweetening agents.

As salts of the 4-hydroxy-1,2-benzothiazol-3(2H)-one-1,1-dioxides all physiologically compatible alkali and alkaline earth metal salts may be used. Particular salts which may be mentioned are the alkali metal salts, e.g. the sodium, potassium or ammonium salts, especially the sodium salt, and the alkaline earth metal salts, e.g. the calcium salt.

In general the following demands are made on sweetening agents:

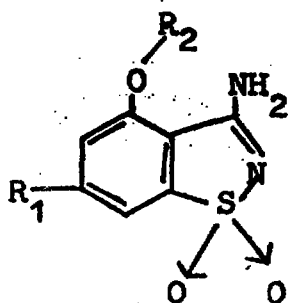
- a) as an additive to foodstuffs the sweetening agent must be absolutely safe, i.e. showing no toxic or pharmacological effects;
- b) it must have unobjectionable qualities of taste, taking the properties of sucrose as an example; the sweetening agent must not produce any smack or aftertaste, the sweet taste must begin immediately and must disappear rapidly;
- c) it must be sufficiently water-soluble, temperature-resistant in hot beverages and acid-stable in acidic juices.

None of the sweetening agents known up to now comes up to the above-mentioned expectations. Thus the use of cyclamate and saccharine as sweetening agents is not without objection since these compounds have shown some toxicological effects when administered in higher dosages. Sweetening agents with a dipeptide structure are not sufficiently temperature- and acid-stable, while oxathiazinone derivatives cannot produce a satisfactory taste. Higher molecular natural substances show a lack of sufficient stability, and owing to their long-lasting after-taste they are only of limited worth.

We have now found that the 4-hydroxy-1,2-benzisothiazol-3(2H)-one-1,1-dioxides of general formula I and their physiologically compatible salts with inorganic or organic bases possess a sweetening power at least equal to the sweetening agents used hitherto as well as exhibiting an unobjectionable quality of taste without any smack or after-taste. They are highly water-soluble and moreover they are temperature- and acid-stable. Furthermore, the compounds show absolutely no toxic or pharmacological effects, which makes them absolutely safe to use.

According to the invention the compounds of general formula I may be prepared as follows:

1. By alkaline saponification of 3-amino-1,2-benzisothiazol-1,1-dioxides of general formula II



wherein

- R_2 represents a hydrogen atom; an alkyl or aralkyl group, preferably an alkyl group with 1 to 6 carbon atoms; or the benzyl or phenylethyl group; and
- R_{21} represents a hydrogen atom; a hydroxy group; an alkoxy group, preferably with 1 to 6 carbon atoms; or an aralkoxy group, preferably the benzyloxy or phenylethyloxy group.

If R_2 represents a hydrogen atom, and R_{21} represents a hydrogen atom or a hydroxy group, immediately after saponification of this 3-amino compound the end-product of general formula I or its salt is obtained. If, however, R_2 represents an alkyl or aralkyl group; and/or R_{21} represents an

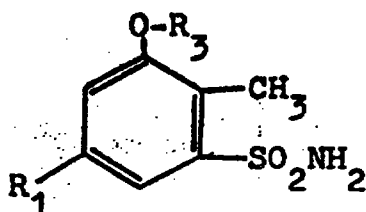
alkoxy group; or an aralkoxy group, these alkyl or aralkyl groups are subsequently separated by ether splitting.

The saponification of a compound of general formula II is carried out with bases. Thus, an aqueous solution of a compound of general formula II is treated with an inorganic base, e.g. with an alkali hydroxide such as sodium or potassium hydroxide, at temperatures between 50°C and the boiling point of the solution. If R_2 in the compound of general formula II represents a hydrogen atom, or R_{21} represents a hydroxy group, at least 2 equivalents of a base are necessary; if, however, R_2 represents a hydrogen atom and R_{21} represents a hydroxy group, at least 3 equivalents of a base are necessary, otherwise one equivalent or a slight excess of base is sufficient. After saponification, the solution is acidified, and, if the product does not precipitate by itself, the aqueous medium is extracted with an extracting agent such as ethyl acetate.

The subsequent ether splitting of a compound thus obtained, which in 4- and/or 6-position also contains an alkoxy or aralkoxy radical, is effected with acidic or alkaline methods. The acidic method comprises the use of Lewis acids such as boron halides, aluminium halides or pyridine hydrochloride. Using boron halides, e.g. boron tribromide or boron trichloride, the work is carried out in aprotic solvents, e.g. in halogenated hydrocarbons at temperatures up to the boiling point of the reaction mixture. It is of advantage to use the boron halide in a molar excess. If the reaction is carried out with aluminium halides, e.g. with anhydrous aluminium chloride, carbon disulfide, nitrobenzene or toluene may advantageously serve as aprotic solvents. The ether splitting with pyridine-hydrochloride is preferably carried out without a solvent in a melt.

In the alkaline method polar aprotic solvents may be used. Suitable solvents may be dimethyl sulfoxide; this method comprises the use of halides or pseudo-halides, which are used in molar amounts or in a 5- to 10-fold molar excess. The necessary reaction temperatures are between 120 to 200°C, preferably, however, between 150 and 180°C. Preferred halides may be for example alkali halides such as lithium iodide, lithium bromide, lithium chloride, sodium chloride, sodium bromide, sodium iodide, potassium chloride, potassium bromide, potassium iodide, but especially potassium bromide. Alkali pseudo halides may be the corresponding cyanides or rhodanides, but in particular sodium and potassium cyanide or potassium rhodanide.

2. By oxidation of o-sulfamoyl-toluenes of general formula III



, (III)

wherein

- R₃ represents an alkyl or aralkyl group, preferably an alkyl group with 1 to 6 carbon atoms or the benzyl or phenylethyl group and
- R₃₁ represents a hydrogen atom; or an alkoxy group, preferably with 1 to 6 carbon atoms; or an aralkoxy group, which preferably represents a benzyloxy or phenylethyloxy group; and subsequent cleavage of phenol ether.

Suitable oxidising agents are the usual inorganic oxidising agents such as for example potassium permanganate, potassium chromate or potassium dichromate. For example, an alkaline permanganate solution, e.g. a solution of potassium permanganate and sodium bicarbonate in water, or a solution of

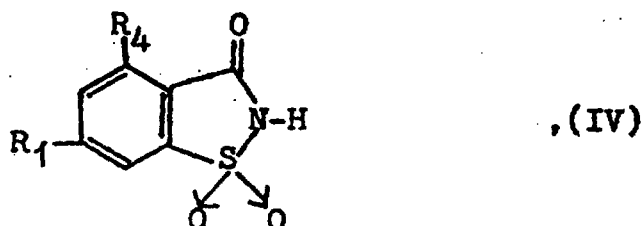
potassium dichromate in an aqueous acid, e.g. in sulfuric acid, may be used.

The oxidation is carried out at temperatures between room temperature and the boiling temperature of the reaction mixture; with potassium permanganate for example between 60 and 90°C.

The subsequent ether splitting, i.e. the cleavage of the radical R_3 , and the cleavage of the radical R_{31} , if it represents an alkoxy or aralkoxy group, is carried out according to the methods mentioned in process 1.

Thus a compound of general formula I is formed.

3. By nucleophilic substitution of the radical R_4 in a 1,2-benzisothiazol-3(2H)-one-1,1-dioxide of general formula IV



wherein

R_{31} is defined as mentioned before and

R_4 represents a nucleophilically exchangeable leaving group and subsequently, if R_{31} represents an alkoxy or aralkoxy group, by cleavage of the phenol ether grouping R_{31} .

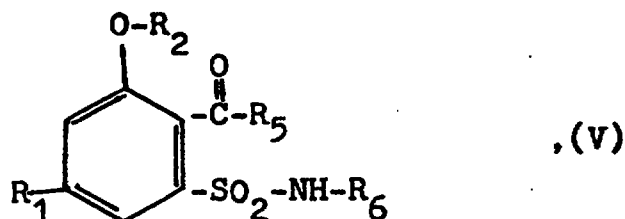
Suitable nucleophilically exchangeable leaving groups may be halogen, pseudo-halogen or a diazonium cation.

While from the diazonium compounds of general formula IV the compounds of general formula I can be prepared in a simple way by heating up to boiling point in aqueous or in acidic aqueous solution, e.g. in dilute sulfuric acid, the exchange of a halogen atom or a pseudo-halogen in 4-position of formula IV is made in the presence of ca-

talysts. Suitable catalysts are above all copper powder, copper(I) or copper(II) salts in the presence of alkalis, e.g. in the presence of sodium or potassium carbonate. Preferably, mixtures of copper powder with copper salts are used, e.g. copper powder with copper(II)chloride. The exchange of a halogen atom or a pseudo-halogen, such as for example a cyano or rhodanide group is carried out in the presence of water at temperatures between 120 and 160°C. The reaction is carried out in a pressure autoclave. After the reaction the reaction mixture is filtered off from the catalyst, the filtrate is evaporated, acidified and extracted, for example with ether.

If it is desired to obtain substances of general formula I, wherein R represents a hydroxy group, additionally a cleavage of phenol ether analogously to the methods mentioned in process 1 must be carried out.

4. A 2-sulfamoyl-3-carboxylic acid derivative of general formula V



wherein

R_2 and R_{21} are defined as mentioned before,

R_6 represents a hydrogen atom or a tert.-alkyl radical with 4 to 19 carbon atoms and

R_5 represents a nucleophilically exchangeable group such as the hydroxy group; an alkoxy group with 1 to 10 carbon atoms; an aryloxy group, wherein the aryl radical represents a phenyl or naphthyl group; a phenyl or naphthylalkoxy group with 1 to 3 carbon atoms in the alkylene part or a halogen atom, is treated at temperatures between 0°C and 100°C, preferably 50 to 70°C, with acids such as phosphoric acid, polyphosphoric acid, sulfuric acid or with mixtures of such acids, whereupon cyclisation

sets in. The end-product formed hereby is isolated by conventional methods, e.g. by addition of ice and purification of the resultant precipitate. The reaction can also be carried out in the absence of a mineral acid by merely heating at temperatures of from 100 to 250°C, for example also in the presence of a solvent, such as o-dichlorobenzene or toluene, or cyclisation may be effected under basic conditions, e.g. by means of sodium methoxide. If in the starting compound R_2 represents an alkyl or aralkyl group or R_{21} represents an alkoxy or aralkoxy group, the resultant compound is subsequently subjected to ether splitting to obtain a product of general formula I. The ether cleavage is carried out according to the conditions mentioned in process 1.

The starting compounds of general formula II may be obtained by refluxing a 2-nitro-6-alkoxy- (or 6-aralkoxy-)benzonitrile, optionally substituted in 4-position with an alkoxy or aralkoxy group, with tin and hydrochloric acid in the presence of tin(II)-chloride to the corresponding 2-amino-6-alkoxy- (or 6-aralkoxy-)benzonitrile, optionally substituted in 4-position with an alkoxy or aralkoxy group, and subsequently diazotizing this compound in the presence of glacial acetic acid and hydrochloric acid by means of sodium nitrite. At 20°C the reaction mixture is added to a solution of sulfur dioxide in glacial acetic acid and an aqueous solution of copper(II)-chloride is added dropwise. A sulfochloride is obtained, which is dissolved in dioxan and mixed with ethanol and aqueous conc. ammonia. Cyclisation to the 3-amino-4-alkoxy- (or 4-aralkoxy-)1,2-benzoisothiazol-1,1-dioxide, optionally substituted in 4-position with an alkoxy or aralkoxy group, is finished by heating up to 40°C. If in the last step an alkali halide or alkali pseudohalide (e.g. in dimethylsulfoxide) such as potassium cyanide is added, the 3-amino-4-hydroxy-1,2-benzoisothiazol-1,1-dioxide, or the 3-amino-4,6-dihydroxy-1,2-benzoisothiazol-1,1-dioxide is obtained directly.

The starting compound of general formula III, wherein R_{31} represents a hydrogen atom, may be obtained from the corresponding o-alkoxy (or o-aralkoxy)-o'-nitro-toluene, whereby this compound, which is dissolved in an alcohol, e.g. in ethanol, is hydrated with Raney nickel at 100 bar up to the absorption of the calculated amount of hydrogen, whereby the corresponding 3-alkoxy- (or 3-aralkoxy)-2-methylaniline is formed. The latter compound is subsequently dissolved in 50 % acetic acid saturated with gaseous hydrochloric acid and diazotized with sodium nitrite. The resultant diazonium salt solution is mixed with magnesium sulfate and subsequently poured on glacial acetic acid, which is saturated with sulfur dioxide and which contains some copper-(I)-chloride. After stirring for 4 hours at room temperature, water is added and the reaction mixture is extracted with methylene chloride. After removing the extracting agent, the extract is distilled in vacuo and the resultant pure sulfonic acid chloride, dissolved in ethanol, is mixed with conc. aqueous ammonia. Thus the corresponding 3-alkoxy or (3-aralkoxy)-2-methyl-benzene sulfonamide of general formula III is formed. The preparation of the starting compounds of general formula III, wherein R_{31} represents an alkoxy or an aralkoxy group, is carried out analogously to the method described from the corresponding p-alkoxy (or p-aralkoxy)-o-alkoxy (or -o-aralkoxy)-o'-nitro-toluenes.

The starting compounds of general formula IV may be obtained for example from 2-nitro-toluene, substituted in 6-position by a nucleophilically exchangeable radical (e.g. by a chlorine atom), by hydration with Raney-Nickel in the presence of a solvent, such as alcohol. Thus the 2-methyl-aniline, substituted in 3-position, may be obtained, which is subsequently diazotized in conc. hydrochloric acid by means of sodium nitrite at -7° to -3°C .

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The filtrate is poured in a thin stream into a suspension of copper(II) chloride in a 30% solution of sulfur dioxide in glacial acetic acid. Heating takes place up to approx. 40°C with strong development of gas. After stirring for approx. 1 hour at 20°C and for a further hour at 35°C, the reaction mixture is mixed with ice. The resultant 2-methylbenzene sulfonic acid chloride, substituted in 3-position, is subsequently dissolved in dioxan and reacted with an ethanolic ammonia solution at temperatures between 50°C and 80°C to the corresponding 2-methyl-benzene sulfonamide, substituted in 3-position. This sulfonamide is refluxed together with potassium carbonate and potassium permanganate in water for 1 hour. The reaction mixture is hot filtered and the residue is washed with hot water. The combined filtrates are acidified with hydrochloric acid and cooled. The 1,2-benzisothiazol-3(2H)-one-1,1-dioxide, substituted in 4-position, of general formula IV is obtained.

The starting compounds of general formula V may be prepared as follows: Diazotizing a m-alkoxy- (or aralkoxy)-aniline, dissolved in a polar solvent, e.g. in glacial acetic acid, by adding hydrochloric acid and sodium nitrite. The reaction mixture is slowly poured into a mixture consisting of copper(II)-chloride and copper(I)-chloride in a 30 % solution of sulfur dioxide in glacial acetic acid. The temperature rises to approx. 40°C with strong formation of gas, and the reaction mixture is kept for 1 hour at this temperature. After diluting with ice water, the benzene-sulfonic acid chloride, substituted in 3-position, is isolated from the organic phase, dissolved in tetrahydrofuran and reacted with tert.-butylamine (approx. 7 hours at 60°C). From the reaction mixture the N-tert.-butyl-3-alkoxy- (or 3-aralkoxy)-benzene sulfonamide is isolated. Other radicals R₆ may be prepared analogously by reaction with other amines of formula R₆-NH₂. The benzene-

sulfonamides obtained are subsequently dissolved in anhydrous tetrahydrofuran and reacted with lithiumdiisopropylamide or n-butyllithium at -80 to -50°C. After stirring for approx. 1 hour at 0°C, the reaction mixture is cooled to -70 to -50°C and treated with carbon dioxide gas. At room temperature the reaction is finished and from the reaction mixture the 2-(N-tert.butyl)-sulfamoyl-6-(alkoxy or aralkoxy)-benzoic acid of general formula V is isolated, whereby in this case R₅ represents the hydroxy group and R₆ represents the tert.butyl group. Using other amines of formula R₆-NH₂, the sulfamoyl benzoic acids, substituted in 2-position, are obtained. These benzoic acids may be esterified according to conventional methods.

As already mentioned before, the compounds of general formula I and their physiologically compatible salts possess sweetening properties:

For example the compounds

4-Hydroxy-1,2-benzisothiazol-3(2H)-one-1,1-dioxide = A

Sodium salt of 4-hydroxy-1,2-benzisothiazol-3(2H)-one-1,1-dioxide = B

4,6-Dihydroxy-1,2-benzisothiazol-3(2H)-one-1,1-dioxide = C

were tested in comparison with the known sweeteners

Cyclamate = X

Saccharine = Y

and in comparison with the compound

6-Hydroxy-1,2-benzisothiazole-3(2H)-one-1,1-dioxide = Z,

known from the literature.

A. Determination of the sweetening properties:

1. Determination of the threshold concentration:

From the test compounds A, B and C and from the comparison compounds X, Y and Z aqueous solutions having concentrations of 1:12500, 1:25000, 1:50000, 1:100000 and 1:200000 were prepared and each valued by 5 taste examiners according to the following scoring system: Very sweet (= 3 points), medium sweet (= 2 points), slightly sweet (= 1 point), and not sweet (= 0 point). The tests were carried out according to the rules given by H.G. Schutz and F.J. Pilgrim (Food Research 22, 206 (1957)). The dilution perceptible as sweet was defined as the concentration at which the average value reached the points 1.0 or more.

The following table shows the results obtained.

Table 1:

Test compound	concentration	average value of the points	Dilution perceptible as sweet
A	1:25000	2.4	1:50000
	1:50000	1.0	
	1:100000	0.2	
B	1:25000	2.6	1:50000
	1:50000	1.2	
	1:100000	0.0	
C	1:25000	1.8	1:50000
	1:50000	1.0	
	1:100000	0.0	
Comparison substances			
X	1:12500	0.6	>1:12500
	1:25000	0.2	
	1:50000	0.0	
Y	1:25000	2.4	1:50000
	1:50000	1.2	
	1:100000	0.4	
Z	1:25000	1.4	1:25000
	1:50000	0.6	
	1:10000	0.0	

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2. Determination of the relative sweetening power in comparison with sucrose

The relative sweetening power (often also defined as degree of sweetness) of sweetening agents in comparison with sucrose (cane sugar) varies considerably with concentrations. Thus in the usual concentrations (i.e. a 2 - 10% solution of saccharose) the relative sweetening power of saccharine varies from 200 to 700. Therefore, for the determination of the relative sweetening power of the above mentioned compounds a 3 % aqueous solution of sucrose was always used for comparison.

The determination of the relative sweetening power was carried out according to the statements of R. Pauli (Chemiker-Zeitung 44, 744 (1920)) and T. Paul (Chemiker-Zeitung 45, 38 (1921)). Each test solution was tested by 5 taste-examiners.

The results obtained with substances A, B and C and comparison substances X and Z are given in the following table:

Table 2:

Test compound	Relative sweetening power (sucrose = 1)
A	210
B	210
C	180
Comparison substances	
X	45
Z	140

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3. Determination of the taste quality:

Besides the absolute sweetening power of a sweetening agent the taste quality is of great importance. Thus, the sweetening power of saccharine and cyclamate is much greater than that of sucrose, but they do not have the taste quality of sucrose. Thus, the metallic-bitter after-taste and the bitter smack of saccharine can easily be demonstrated in taste-examinations. As the main demand on a sweetening agent is a taste which is equivalent to that of sucrose, a determination of the taste-qualities was carried out:

The tests were performed in accordance with the method of DuBois, G.A. Crosby, R.A. Stephanson and R.E. Wingard Jr., (J. Agric. Food Chem. 25, 763 (1977)). The test-compounds were used as aqueous solutions in a concentration which corresponds to an approx. 5% sucrose solution. As comparison compound sucrose was used. The tests were carried out under identical conditions. Only the characterization of the taste was judged, because the intensity had already been determined in previous experiments. The following judgements were determined by each examiner: percentage sweet to percentage bitter to percentage of other taste qualities. Furthermore, the presence or absence of an after-taste of the single test-compounds was tested. Each substance was tested twice with regard to five different measurements.

The results are given in the following table.

Table 3:

Test compound	Concentration	Number of determinations	Parts in %			After-taste
			sweet	bitter	others	
A	1:10000	10	94	2	4	3
B	1:10000	10	96	2	2	5
C	1:10000	10	86	3	11	8
Comparison substances						
Y	1:10000	10	72	21	7	80
Z	1:10000	10	81	7	12	29
sucrose	1:20	10	98	0	2	4

From the table it is clear that the ideal profile of sucrose is not attained by the comparison substances Y and Z by a long way. However, the substances A to C are to a large extent free of after-taste, which is surprising for sweetening agents. Moreover, the purity of the taste (94 - 96 %) for the substances A and B and 86 % for the substance C is excellent for sweeteners.

4. Determination of the solubility and the acid-stability:

A further demand on a sweetener is good water-solubility and stability in an acidic medium. It was found that substance B is easily soluble in water (solubility $\gg 1$ g/10 ml of water).

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For the stability-test the substance B in a concentration of 1 % was dissolved in 0.1 N hydrochloric acid and kept at room temperature for 27 days. No alteration could be detected. The solid substance was also tested daylight and at 60°C in the absence and in the presence of light for 4 weeks. Here again, no alteration could be found.

B. Testing for possible pharmacological effects:

The substance B was tested with regard to possible pharmacological and toxicological effects.

The individual tests and the results are given hereinafter:

1. Sedative and stimulant effect:

Influence on motility of mice

Method:

Eight female Chbb:NMRI-mice (SPF) having a body weight from 20 to 26 g were tested in light-beam cages after oral administration of a suspension of 1 % tylose. 30, 90 and 150 minutes after administration of the substance, their motility was measured for 5 minutes each; a control group received only the suspension agent (tylose:carboxymethyl cellulose). The change in motility given in percent with regard to that of the control group was determined.

Result:

Table 1: Motility of mice, contacts/animal $\pm$ SD

Treatment	N	minutes after application		
		30 - 35	90 - 95	150 - 155
Control	8	90 $\pm$ 35	83 $\pm$ 22	68 $\pm$ 23
Substance B 200 mg/kg p.o.	8	92 $\pm$ 21	84 $\pm$ 28	49 $\pm$ 17
Substance B % motility		102	101	72

N = number of animals

In the large dose of 200 mg/kg p.o. the substance B did not influence the motility of mice.

2. Sedative or stimulant effect:

Influence on motility of rats

Method:

According to the method described by FÜHRER and FELDHOFFEN (Arzneim.-Forsch. 11, 1027, 1961) substance B was tested in 6 female Chbb:THOM-rats (SPF) having a body weight of 160 - 190 g, after administration of 100 mg/kg p.o. in a suspension of 1 % tylose. The motility of the rats in cages was measured for 30 minutes 1 hour after administration of the test compound; A control group received only tylose. The change in motility given in percent with regard to that of the control group was determined.

Result:

Table 2: Motility of rats, contacts/animal $\pm$ SD

Treatment	N	minutes after application
		60 - 90
Control	6	208 $\pm$ 49
Substance B 100 mg/kg p.o.	6	235 $\pm$ 58
Substance B % motility		113

N = number of animals

It was found that substance B does not influence the motility of the rats.

3. Muscle-relaxant and/or ataxic effect:

Influence on the ability of mice to stay upright in rotating cylinders

Method:

According to the method described by YOUNG and LEWIS (Science 105, 368, (1947)), 10 female Chbb:NMRI-mice (SPF) having a weight of 20 - 26 g were tested as to whether they were able to stay upright in rotating cylinders after oral administration of 400 mg/kg of substance in aqua dist. The measurements were carried out 30 - 60, 90 - 120, 210 - 240 and 270-300 minutes after administration.

Result:

Table 3: Influence on the ability of mice to stay upright:

Treatment	N	animals which fell out, min. after applic.			
		30 - 60	90 - 120	210 - 240	270 - 300
Substance B 400 mg/kg p.o.	10	2	2	1	0

N = number of animals

Even at dosages of 400 mg/kg p.o. substance B does not influence the standing power of mice. The substance did not act as a muscle-relaxant or coordination inhibitor.

4. Barbiturate-intensifying effect:

Influence on the duration of hexobarbital narcosis in mice

Method:

According to WINTER (J. Pharmacol. exp. Ther. 94, 7, (1948)), 100 mg/kg of the substance B in a suspension of 1% tylose were administered orally to 10 male Chbb:NMRI-mice (SPF) having a body weight of 20 to 26 g. A control group received the suspension agent. After 1 hour all animals were given 80 mg/kg of hexobarbital by i.p. injection. The mice were put on a metal plate at 37°C and the time from the beginning of the loss of the righting reflex to the return of this reflex was measured as the duration of the narcosis. This time-difference was calculated in percent with regard to that of the control group.

Results:

Table 4: Influence on the duration of hexobarbital narcosis in mice.

Treatment	duration of narcosis	
	minutes $\bar{x}$ SD	%
Substance B 100 mg/kg p.o.	15.65 $\pm$ 6.32	106
Control	14.70 $\pm$ 3.62	100

At dosages of 100 mg/kg p.o. in mice substance B does not show any influence on the duration of hexobarbital narcosis.

5. Anticonvulsive effect:

Influence on the maximum electric shock convulsions in mice

Method:

According to SWINYARD, BROWN and GOODMAN (J. Pharmacol. exp. Ther. 106, 319 (1952)), 200 mg/kg of substance B in aqua dist. solution were administered orally to 10 male Chbb:NMRI-mice (SPF). After 30, 150 and 300 minutes tonic extensor spasms were induced by alternating current via head-electrodes (50 mA, 50 Hz, 2 sec duration). Tonic extensor spasms of the extremities cannot be observed in the treatment with substances having an anticonvulsive activity.

Results:

Table 5: Influence on the maximum electroshock convulsions in mice

Treatment	N	number of the protected animals		
		30	150	300 min after administration
Substance B 200 mg/kg p.o.	10	0	0	0

N = number of animals

At a dosage of 200 mg/kg p.o. in mice substance B does not show an anticonvulsive activity.

6. Antidepressant effect:

Influence on the reserpine hypothermia in mice

Method:

According to ASKEW (Life Sci. 2, 275, (1963)) hypothermia was induced by s.c. administration of 3 mg/kg of reserpine in male Chbb:NMRI-mice (SPF) having a weight of 20 - 26 g. After 17 hours the lowered body temperature was measured and substance B was administered orally to 10 animals at a dosage of 40 and 100mg/kg in aqua dist. solution. A control group received the solvent p.o.; 1 to 4 hours after administration the temperature was measured every hour. The values given in the table are the average temperature values $\pm$ SD.

Results:

Table 6: Behaviour of body temperature in comparison with controls; $^{\circ}\text{C} \pm \text{SD}$

Treatment	N	before admin.	hours after administration			
			1	2	3	4
Control	10	22.6 ± 0.2	24.6 ± 1.3	25.7 ± 1.9	26.2 ± 2.1	26.5 ± 1.9
Substance B 40 mg/kg p.o.	10	22.7 ± 0.3	24.0 ± 1.4	24.7 ± 1.7	25.3 ± 1.7	25.9 ± 1.4
Substance B 100 mg/kg p.o.	10	23.3 ± 0.5	26.0 ± 1.7	26.7 ± 1.4	26.6 ± 1.2	26.8 ± 1.4

N = number of animals

At dosages of 40 and 100 mg/kg p.o. Substance B does not show any influence on hypothermia in mice caused by reserpine.

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7. Antiexsudative effect:

Influence on kaolin oedema in rats:

Method:

According to HILLEBRECHT (Arzneim.-Forsch. 4, 607, (1954)) an oedema was induced in Chbb:THOM-rats (SPF) of both sexes having a weight of 125 - 150 g by subplantar injection of 0.05 ml of a 10 % kaolin suspension in the back paw.

30 minutes before, substance B was orally administered to the 10 animals in a dosage of 100 mg/kg as aqua dist. solution. 10 control animals received the solvent. The thickness of the paws was measured before the administration of the test compound and 5 hours after administration. The oedema-altering effect was assessed as a percentage of the average degree of swelling of the control animals.

Results:

Table 7: Effect against kaolin oedema in rats

Treatment	N	average degree of swelling	inhibition in %
Substance B 100 mg/kg p.o.	10	239.0	13.7
Control	10	277,0	

N = number of animals.

At a dosage of 100 mg/kg p.o. substance B does not show an antiexsudative effect in rats.

8. Ulcerogenic effect in rats:

Method:

Substance B in a dosage of 200 mg/kg in 1% tylose suspension was administered orally to 10 male and female (1:1) Chbb:THOM-rats (SPF) having an approx. body weight of 200 g. A control group received the suspension agent. After 4 hours all animals were killed, the stomach was dissected and inspected with regard to lesions of the mucosa.

Results:

Table 8: Ulcerogenic effect in rats

Treatment	N	animals having stomach lesions
Substance B 200 mg/kg p.o.	10	0
Control	10	0

N = number of animals

At dosages of 200 mg/kg p.o. substance B does not show an ulcerogenic effect in rats.

9. Influence on choleresis in rats

Method:

Into the ductus choledochus of anaesthetised fasting male Chbb:THOM-rats (SPF) having a body weight of 180 - 220 g, a cannula was bound and the bile liquid was recorded using a drop counter. Substance B with 100 or 200 mg/kg in aqua dist. solution was administered intraduodenal groups of 10 animals. A control group received the solvent. The number of drops obtained within 1 hour before the treatment was compared with the number of the drops obtained 1 - 5 hours after treatment.

Results:

Table 9: Choleresis in rats, average number of drops/h $\pm$ SD

Treatment	N	value before treatment	hours after treatment				
			1	2	3	4	5
Control	10	62.6 ± 4.8	57.1 ± 4.8	55.8 ± 5.1	56.3 ± 6.0	56.6 ± 6.9	58.1 ± 10.0
Substance B 100 mg/kg i.d.	10	55.1 ± 9.1	53.3 ± 10.1	51.7 ± 9.2	50.7 ± 9.3	49.9 ± 9.2	49.5 ± 9.1
Substance B 200 mg/kg i.d.	10	47.1 ± 11.5	44.1 ± 9.8	43.1 ± 10.3	43.1 ± 8.2	43.5 ± 8.2	44.4 ± 8.0

N = number of animals.

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In table 10 the average number of drops 1 - 5 hours after treatment was shown in percent, compared with the values before treatment.

Table 10: Choleresis in rats in % compared with the values before treatment

Treatment	N	value before treatment	hours after treatment				
			1	2	3	4	5
Control	10	100	91	89	90	90	93
Substance B 100 mg/kg i.d.	10	100	97	94	92	91	90
Substance B 200 mg/kg i.d.	10	100	94	92	92	92	94

N = number of animals

As tables 9 and 10 show, at dosages of 100 and 200 mg/kg substance B does not show an intraduodenal influence on choleresis in rats.

10. Circulatory effect:

Influence on the circulation in anaesthetised cats

Method:

In 3 adult anaesthetised cats the following parameters were measured:

the arterial blood-pressure in the carotid artery by means of a Statham pressure transducer ;

the heart frequency by means of a Grass Tachograph;

The respiratory frequency by means of a Fleisch Pneumotachograph;

10 mg/kg of substance B as solution in aqua dist. were administered i.v.

Results:

Table 11: Blood-pressure, heart frequency and respiratory frequency of narcotized cats, alteration compared with values before the administration of the substance in %

Treatment	N	alteration in %		respiratory f.
		blood-pressure	heart f.	
Substance B 10 mg/kg i.v.	3	+1	-1	-2

N = number of animals

At dosages of 10 mg/kg i.v. substance B does not show any influence on the arterial blood-pressure, the heart frequency and the respiratory frequency in anaesthetised cats.

11. Influence on the thrombocyte aggregation:

Method:

The thrombocyte aggregation was measured according to BORN and CROSS (J. Physiol. 170, 397 (1964)) in platelet-rich plasma of human citrate blood. The parameters were the alteration in the maximum aggregation velocity measured in % compared with a control, and also the alteration in the "optical density".

The aggregation was induced by collagen.

Results:

Table 12: Effect on the thrombocyte aggregation caused by collagen.

Treatment	alteration in %	
	max. aggregation velocity	optical density
Substance B 10^{-4} mol/l	± 0	± 0

At dosages of 1×10^{-4} mol/l substance B does not show any influence on the thrombocyte aggregation caused by collagen.

12. Bacteriostasis and fungistasis :

Methods:

Substance B was tested with regard to its bacteria- and fungi-inhibiting effect in a serial dilution test and agar diffusion test.

Results:

In the serial dilution test 320 µg/ml of substance B did not show any effect on *Staphylococcus aureus* SG 511, *Streptococcus* Aronson, *Sc. pyogenes* ATCC 8668, *Escherichia coli* ATCC 9637, *Pseudomonas aeruginosa* Hbg., *Serratia marcescens* ATCC 13880, *Candida albicans* ATCC 10231, *Trychophyton mentagrophytes* ATCC 9129 and *Aspergillus niger*.

Also in the agar diffusion test 1600 µg/ml of substance B did not show any effect against the same germs.

13. Diuretic effect:

Influence on the diuresis in rats:

Method:

Male Chbb:THOM-rats (SPF) having a body weight of 180 - 210 g, were kept away from food with free access to water 24 hours before the test. Substance B at dosages of 50, 100 and 200 mg/kg in aqua dist. solution was administered orally as 1 ml/100 g of body weight to 6 animals/dose. Additionally 4 ml water/100 g of body weight were administered orally. A control group received the solvent and the same amount of water.

5 hours after treatment the volume of the urine of each group was measured and the concentration of Na^+ , K^+ , and Cl^- was determined photometrically and complexometrically.

Results:

Table 13: Diuresis in water-laden rats

Treatment	N	Microval/kg			urine ml/kg
		Na^+	K^+	Cl^-	
Substance B					
50 mg/kg p.o.	6	456.6	456.6	616.4	45.7
100 mg/kg p.o.	6	401.9	321.5	325.5	40.2
200 mg/kg p.o.	6	467.6	425.1	535.7	42.5
Control	6	274.9	471.2	353.4	39.3

N = number of animals

At dosages of 50, 100 and 200 mg/kg p.o. substance B does not show an influence on the diuresis in rats. All found values are within the confidence limit ($p \leq 0.05$) of 50 average control values.

Na⁺: 154.3 - 660.9 μ Val/kg
K⁺: 146.3 - 550.0 μ Val/kg
Cl⁻: 189.9 - 673.1 μ Val/kg
Volume: 37.1 - 49.3 ml/kg

14. Mucosa-compatibility:

Local compatibility with the eye of the rabbit

Method:

Groups of 4 rabbits of both sexes were given 1 drop of a 1% sol. of substance B in aqua dist. into the conjunctival sac of the eye. 15, 30, 60, 90, 120 minutes and 24 hours after treatment the eyes of the rabbits were studied for any irritation of the conjunctiva (redness, secretion etc.) and for any alteration of the pupil. The second eye of each animal served as control.

Results:

Table 14: Local compatibility, eye of the rabbit

Treatment	N	result
Substance B		
1 %	4	no irritation of conjunctiva, no alteration of the pupil
10 %	4	no irritation of the conjunctiva, no alteration of the pupil

N = number of animals

Substance B does not show any incompatibility when dropped into the eye of the rabbit.

C. Examination with regard to possible acute, subacute, toxic and mutagenic effects

1. Examination on acute toxicity:

The acute toxicity was determined after oral administration of substance B to male and female mice, rats and dogs. The substance was administered to mice and rats in the form of a suspension in tylose and to dogs in the form of a solution in water. The following table shows the number of the animals which died within 1, 7 and 14 days after treatment.

Kind of animal	Dose	Number of animals	animals died within the observation time		
			1 day	7 days	14 days
Mouse	10 g/kg	10	0	0	0
Rat	10 g/kg	6	0	0	0
Dog	5 g/kg	2	0	0	0

During the observation time no animals died. Moreover, no toxic symptoms could be observed. All animals survived and showed completely normal behaviour.

2. Examination on subacute toxicity:

The subacute toxicity of substance B was tested in rats and dogs.

Test in the rat:

The test was carried out on 10 male and 10 female Chbb:THOM-rats. During a period of 5 weeks 750 mg/kg of substance B were administered to the animals daily. During the test period the animals showed normal behaviour. No spontaneous deaths were observed. After the 5 weeks the animals were killed and the following organs were dissected for histological examination: heart, lungs, liver, spleen, suprarenals, brain, kidney, and pancreas.

The histological examination of these organs did not show any pathological results which could be connected with the administration of the substance.

Test in the dog:

The test was carried out on 3 male and 3 female beagles. Over a period of 5 weeks 750 mg/kg of substance B were administered orally. The animals did not show any abnormal behaviour. No spontaneous deaths were observed.

After the test period of 5 weeks the animals were killed and the same organs were taken for histological examination.

No findings were observed which could be connected with the administration of the substance.

3. Test for mutagenic effects

The most important requisite for a sweetening agent is that it must be harmless to health. Most sweetening agents, however, do not satisfy this demand. Thus, for example, the saccharine shows a mutagenic effect (R.P. Batzinger, S.-Y.L. On and E. Bueding. Science 198, 944 (1977)), which calls into question its use as a sweetener.

Compound B was tested according to the AMES-system (Mutation Research 31, 347-364 (1975)) for mutagenic properties. In order to show the whole spectrum of induced molecular DNA-damage (base substitutions, frame-shift mutations, deletions) the auxotrophic bacterial strains *Salmonella typhimurium* TA 98, TA 100, TA 1535, TA 1537 and TA 1538 were used as genetic indicators.

The tests for all germs were carried out so that the influence of the test compounds on a microsomal enzyme system together with the corresponding co-factors could be tested and furthermore to find out the effect on enzyme induction. The tests were performed without an activating system and in the presence of an activating system. For the in-vitro activation S-9 supernatants (fractions of the endoplasmatic reticulum) of normal, i.e. not pre-treated rats and of rats induced by aroclor 1254 (500 mg/kg) were used. For the S-9 induced fraction, 3 different concentrations were tested.

Compound B was tested in concentrations of 0.25, 2.5, 5 and 10 mg/plate. In a preceding serial dilution test the highest dosage used showed no inhibition of the germs.

In no strain tested did compound B lead to an increase in the spontaneous mutation rate. No influence on enzyme induction and by the activating fraction on the reversion rate was detected. The colonies counted on the test plates showed the normal spontaneous range for each test strain.

The experiments showed that compound B does not induce base substitutions (*S. typhimurium* TA 1535, TA 100) or frame-shift mutations (*S. typhimurium* TA 1537, TA 1538, TA 98), thus indicating that the compound is not mutagenic.

The following examples serve to illustrate the invention.

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Example 1

4-Hydroxy-1,2-benzisothiazol-3(2H)-one-1,1-dioxide

5 g (25.2 m mol) of 3-amino-4-hydroxy-1,2-benzisothiazol-1,1-dioxide and 2.02 g (50.5 m mol) of sodium hydroxide were refluxed in 15 ml of water for 6.5 hours. Subsequently the solution was treated with activated charcoal at 60°C and filtered. At 60°C the filtrate was acidified with conc. aqueous hydrochloric acid (approx. 5 ml, approx. 0.06 mol). The resultant precipitate was filtered off, dried and recrystallized from water. 4.62 g (92 % of theory) of 4-hydroxy-1,2-benzisothiazole-3(2H)-one-1,1-dioxide were obtained.

M.p.: 228°C.

IR (CH₂Cl₂): 3320 (NH, OH assoc.); 1720 (CO); 1335 and 1140 cm⁻¹ (SO₂)

MS: 199 (M+), 136, 119 and 108 m/e.

C₇H₅NO₄S (199.19)

Calc.: C 42.20 H 2.53 N 7.03 S 16.10

Found: 42.23 2.60 6.97 16.10

The starting compound 3-amino-4-hydroxy-1,2-benzisothiazol-1,1-dioxide was prepared, starting from the 2-nitro-6-methoxy-benzonitrile (A. Russel and W.G. Tebbens, Org. Synthesis, Coll. Vol. III, page 293) in the following way:

2-Amino-6-methoxy-benzonitrile

10 g (56.1 m mol) of 2-nitro-6-methoxy-benzonitrile, 26.6 g (220 m mol) of tin and 12.7 g (56.1 m mol) of tin(II)-chloride were refluxed in 160 ml of semi-conc. hydrochloric acid for 1.5 hours. After cooling the reaction mixture to 60°C, a solution of 40 g of sodium hydroxide in 10 ml of water was added dropwise. After addition of sodium hydroxide solution (pH: approx. 4), the reaction mixture was adjusted to pH 9 by means of sodium carbonate and the resultant precipitate was suction fil-

tered. The filtration residue was refluxed with 0.2 l of ethanol for 20 minutes and filtered. The filtrate was evaporated and 9 g of crude product were obtained. Extraction of the tin hydroxide product mixture was repeated and approx. 0.5 g of crude product were obtained additionally.

The crude product from ethanol was recrystallized using activated charcoal. By evaporation of the mother liquor a second fraction of the same purity was obtained.

Yield: 7.5 g (90 % of theory) of 2-amino-6-methoxy-benzonitrile of m.p. 145°C.

3-Amino-4-methoxy-1,2-benzisothiazol-1,1-dioxide

10 g (67.5 mmol) of 2-amino-6-methoxy-benzonitrile were dissolved in 80 ml of glacial acetic acid at 60°C and the solution was mixed with 80 ml of conc. aqueous hydrochloric acid. The reaction mixture was cooled to -5°C and diazotized at this temperature by dropwise addition of a solution of 4 g of sodium nitrite in 18.5 ml of water. After stirring for 30 minutes (the temperature rose to 0°C), the reaction mixture was added in batches

to a prepared mixture of 94 ml consisting of a 30 % sulfur dioxide solution in glacial acetic acid and of a solution of 1.7 g of copper(II)-chloride in 4 ml of water. The temperature of the mixture was 20°C and at this temperature the diazonium salt solution was added. Subsequently the reaction mixture was stirred for 3 hours, whereby the colour changed from red to yellow-green and a part of the sulfochloride separated. The sulfochloride was filtered off, thoroughly washed with ice-water and dried (sulfochloride: 1st fraction). The filtrate was evaporated to a quarter of its volume and mixed with the 5-fold amount of ice-water. The resultant sulfochloride crystals were filtered off, washed with ice-water and dried (2nd fraction). Both sulfochloride fractions were dissolved in 40 ml of dioxan and warmed up to 40°C.

At this temperature a mixture consisting of 20 ml of ethanol and 20 ml of conc. aqueous ammonia was added dropwise and the reaction mixture was stirred for 1 hour at 40°C. After refluxing for 2 hours, the reaction mixture was cooled and filtered off from the 1st fraction, which was washed with water. The filtrate was evaporated in vacuo to dryness. The residue was suspended in water, filtered off and washed with water and a little cold ethanol (2nd fraction). After drying 10 g (70 % of theory) of 3-amino-4-methoxy-1,2-benzothiazole-1,1-dioxide were obtained.
M.p.: 273 - 276°C.

3-Amino-4-hydroxy-1,2-benzothiazol-1,1-dioxide

A mixture of 5 g of 3-amino-4-methoxy-1,2-benzothiazol-1,1-dioxide and 1.63 g of potassium cyanide in 15 ml of dimethylsulfoxide was heated up to 130 - 140°C (bath temperature 160°C) and kept at this temperature for 1.5 hours. After cooling the reaction mixture was stirred into 250 ml of methylene chloride and the resultant precipitate was filtered off, dried and dissolved in 30 ml of water. At 60°C the solution was treated with charcoal and not filtered. The hot filtrate was adjusted to pH 1 by means of conc. aqueous hydrochloric acid. After cooling the resultant crystals were suction filtered, washed with a little ice-water and dried in vacuo.

Yield: 43 g (92 % of theory) of 3-amino-4-hydroxy-1,2-benz^{is}othiazole-1,1-dioxide,
M.p.: 305°C (decomp.).

Example 2

Sodium salt of 4-hydroxy-1,2-benzisothiazol-3(2H)-one-1,1-dioxide

10 g of 4-hydroxy-1,2-benzisothiazol-3(2H)-one-1,1-dioxide were dissolved in isopropanol at 60°C. At this temperature a stoichiometrical amount of sodium hydroxide solution (2.0 g in 6 ml of water) was added. After cooling the sodium salt of the 4-hydroxy-1,2-benzisothiazol-3(2H)-one-1,1-dioxide was filtered off, washed with isopropanol and ether and dried. Yield: 10.8 g (96 % of theory),

M.p.: > 350°C.

IR (KBr): 3320 (NH and OH assoc.), 1730 (CO), 1330 and 1140 cm⁻¹ (SO₂).

¹H-NMR (DMSO-d₆): δ = 10.6 (s, 1, OH, exchangeable with CD₃OD); 7.55 (dd, 1H, J=4Hz, 6-H); 7.20 and 7.05 (two d, each 1H, J = 4 Hz, 5-H and 7-H)

C₇H₄NNaO₄S x H₂O (239.19)

Calc.:	C 35.15	H 2.52	N 5.85	S 13.41
Found:	35.36	2.40	5.88	13.45

Example 3

4,6-Dihydroxy-1,2-benzisothiazol-3(2H)-one-1,1-dioxide

1.5 g (4.7 m mol) of 2-(N-tert.-butyl)-sulfamoyl-4,6-dimethoxybenzoic acid were added to 25 ml of polyphosphoric acid warmed to 60°C and stirred for 1 hour at 80°C. The reaction mixture was poured on ice and the resultant precipitate was filtered off. The filtrate was extracted 3 times with ethyl acetate and the organic phase was dried and evaporated. The residue and the above obtained precipitate were recrystallized from methanol and 0.74 g (65 % of theory) of 4,6-dimethoxy-1,2-benzisothiazole-3(2H)-one-1,1-dioxide were obtained.

M.p.: 258°C.

$C_9H_9NO_5S$ (243.25)

Calc.:	C 44.44	H 3.93	N 5.76	S 13.18
Found:	44.70	3.75	5.97	13.32

The resultant 4,6-dimethoxy derivative was taken up in 25 ml of ethylene chloride and mixed with 3.05 g (12.2 mmol) of boron tribromide. After refluxing for 3 hours, a further 3.05 g of boron tribromide were added and the reaction mixture was again refluxed for 3 hours. The reaction mixture was added to methanol and several times evaporated to dryness with repeated addition of methanol. The residue was taken up in aqueous sodium bicarbonate solution. This solution was washed with ethyl acetate, acidified with hydrochloric acid and extracted with ethyl acetate. The extract was dried and evaporated. The remaining residue, which was recrystallized from ethylene chloride, was obtained in a yield of 0.31 g (48 % of theory) of 4,6-dihydroxy-1,2-benzisothiazol-3(2H)-one-1,1-dioxide

M.p.: 286°C.

IR (KBr): 3420, 3260 (OH, NH), 1700 (CO), 1330 and 1145 cm^{-1} (SO_2).

1H -NMR ($CDCl_3 + CD_3OD$): δ = 6.8 (d, 1H, $J=1.5Hz$) and 6.57 (d, each 1H, $J=1.5Hz$, 3-H and 5-H).

$C_7H_5NO_5S$ (215.19)

Calc.:	C 39.07	H 2.34	N 6.51	S 14.90
Found:	39.15	2.60	6.58	14.95

The starting compound 2-(N-tert.butyl)-sulfamoyl-4,6-dimethoxy-1,2-benzoic acid was prepared, starting from 3,5-dimethoxyaniline, in the following way:

3,5-Dimethoxybenzene sulfonic acid chloride

50 ml of conc. aqueous hydrochloric acid were added with cooling to a solution of 26.6 g (0.174 mol) of 3,5-dimethoxyaniline in 100 ml of glacial acetic acid (reaction temperature: max. +20°C). Within 35 minutes a solution of 12 g (0.174 mol) of sodium nitrite in 25 ml of water was added at -8 to -3°C with cooling. After stirring for 1 hour in the cold bath the reac-

tion mixture was filtered and the dark-brown filtrate was poured at 20 - 25°C into a stirred suspension of 10.2 g (60 m mol) of copper(II)-chloride and 2 g (20 m mol) of copper(I)-chloride in 120 ml of a 30 % solution of sulfur dioxide in glacial acetic acid. The reaction temperature initially rose to 40°C and after it had fallen the reaction mixture was heated to 40°C for further 90 minutes. After partial evaporation the reaction product was poured into 2 l of ice-water. After three extractions with ether, the organic extracts were washed with water, sodium bicarbonate solution and again with water.

The ether phase was dried, treated with charcoal and evaporated.

Yield: 19.8 g (48.5 %) of 3,5-dimethoxy-benzene sulfonic acid chloride. A sample was purified by recrystallization from cyclohexane.

M.p.: 74°C.

N-tert.-Butyl-3,5-dimethoxy-benzene sulfonamide

A solution of 7.3 g (0.1 mol) of tert.-butylamine in 20 ml of dioxan was added dropwise to a solution of 10.0 g (42 m mole) of 3,5-dimethoxy-benzene sulfonic acid chloride in 100 ml of dioxan at 40°C within 15 minutes. After the reaction temperature dropped the reaction mixture was heated to 45°C for 1.5 hours and to 60°C for 2 hours. After cooling and filtering, the filtrate was evaporated in vacuo. The residue was recrystallized from cyclohexane.

Yield: 7.5 g (64 % of theory) of N-tert.-butyl-3,5-dimethoxy-benzene sulfonamide.

M.p.: 140°C (from ethanol).

$C_{12}H_{19}NO_4S$ (273.36)

Calc.: C 52.73 H 7.01 N 5.12 S 11.73

Found: 53.00 6.93 5.05 11.70

2-(N-tert.-Butyl)-sulfamoyl-4,6-dimethoxy-benzoic acid

15.3 ml of a 15 % solution of n-butyllithium in hexane (25 m mol) were added dropwise to a solution of 2.5 g (25 m mol) of newly dist. diisopropylamine in 40 ml of anhydrous tetrahydrofuran at -10 to $-3^{\circ}C$ within 10 minutes. After stirring for 20 minutes, the reaction mixture was cooled to $-70^{\circ}C$ and at this temperature 1.7 g (6.2 m mol) of N-tert.-butyl-3,5-dimethoxy-benzene sulfonamide, dissolved in 50 ml of tetrahydrofuran, were added dropwise within 40 minutes. After the addition was completed the reaction mixture was left until room temperature was reached and stirred for 1 hour.

After cooling to $-70^{\circ}C$ a current of carbon dioxide was passed through the reaction mixture. When the reaction was finished, carbon dioxide was passed through the reaction mixture again, and the mixture thus obtained was heated to room temperature. The reaction mixture was evaporated in vacuo and the solid residue was distributed between water and ether. The organic phase was washed with water and evaporated and 1.1 g of the starting compound were obtained, which was again reacted. The aqueous phase was acidified with hydrochloric acid. The resultant precipitate was recrystallized from benzene and 0.5 g (86 % of yield, calculated from the reacted starting material) of 2-(N-tert.-butyl)-sulfamoyl-4,6-dimethoxy-benzoic acid were obtained.

M.p.: $209^{\circ}C$ (decomp.).

IR (KBr): 1730, 1710 (CO), 1320 and 1140 cm^{-1} (SO_2)
 $^1\text{H-NMR}$ ($\text{DMSO}-d_6 + \text{CD}_3\text{OD}$): δ = 7.15 (d, 1H, $J=1.5\text{Hz}$) and
 6.90 (d, 1H, $J=1.5\text{Hz}$, 3-H and 5-H); 4.05 (s, 3H) and 4.08
 (s, 3H; 4- OCH_3 and 6- OCH_3); 1.18 (s, 9H, $\text{C}(\text{CH}_3)_3$).
 $\text{C}_{13}\text{H}_{19}\text{NO}_6\text{S}$ (317.37)

Calc.:	C 49.20	H 6.04	N 4.41	S 10.10
Found:	48.96	6.07	4.35	9.95

Example 4

4-Hydroxy-1,2-benzisothiazol-3(2H)-one-1,1-dioxide

2.5 g (11.8 m mol) of 3-amino-4-methoxy-1,2-benzisothiazol-1,1-dioxide were refluxed for 3 hours in a solution of 0.47 g (11.8 m mol) of sodium hydroxide in 300 ml of water. The reaction mixture was filtered hot and acidified with hydrochloric acid. The resultant precipitate was filtered off, dried and recrystallized from benzene/ethyl acetate. 2.0 g (9.4 m mol) of 4-methoxy-1,2-benzisothiazol-3(2H)-one-1,1-dioxide (m.p.: 224°C) were obtained, these were dissolved in 500 ml of ethylene chloride and the solution was mixed with 10 g (40 mmol) of boron tribromide. The reaction mixture was slowly heated and refluxed for 1 hour. The reaction mixture was evaporated in vacuo and several times evaporated by addition of ethanol. The obtained product was recrystallized from water and 1.6 g (68 % of theory) of 4-hydroxy-1,2-benzisothiazole-3(2H)-one-1,1-dioxide were obtained.

M.p.: 228°C .

$\text{C}_7\text{H}_5\text{NO}_4\text{S}$ (199.19)

Calc.:	C 42.20	H 2.53	N 7.03	S 16.10
Found:	41.95	2.50	7.04	16.08.

Example 5

4-Hydroxy-1,2-benzisothiazol-3(2H)-one-1,1-dioxide

2.5 g (11.8 m mol) of 3-amino-4-methoxy-1,2-benzisothiazole-1,1-dioxide were reacted with sodium hydroxide analogously to Example 4. The reaction mixture was acidified, whereby the 4-methoxy-1,2-benzisothiazole-3(2H)-one-1,1-dioxide was obtained, which was subsequently heated up to 200 - 205°C with 20 g of pyridine-hydrochloride. After cooling the reaction mixture was several times extracted with benzene. The residue was dissolved in water and the solution was again extracted with benzene. The combined benzene phases were dried and evaporated in vacuo. The residue was recrystallized from water and 1.35 g (57.5 % of theory) of 4-hydroxy-1,2-benzisothiazol-3(2H)-one-1,1-dioxide were obtained.

M.p.: 228°C

$C_7H_5NO_4S$ (199.19)

Calc.:	C 42.20	H 2.53	N 7.03	S 16.10
Found:	41.90	2.45	7.18	16.30

Example 6

4-Hydroxy-1,2-benzisothiazol-3(2H)-one-1,1-dioxide

2.5 g (11.8 m mol) of 3-amino-4-methoxy-1,2-benzisothiazole-1,1-dioxide were reacted with sodium hydroxide analogously to Example 5 and by subsequent acidifying, converted to the 4-methoxy-1,2-benzisothiazol-3(2H)-one-1,1-dioxide. The compound obtained together with 650 mg (10 m mol) of potassium cyanide in dimethylsulfoxide was heated up to 180°C for 3 hours. After addition of petroleum ether the potassium salt of the product was precipitated and the precipitate was dissolved in water. After acidifying with aqueous hydrochloric acid, filtering off and recrystallizing 1.46 g (62 % of theory) of 4-hydroxy-1,2-benzisothiazol-3(2H)-one-1,1-dioxide were obtained.

M.p.: 228°C (from water).

$C_7H_5NO_4S$ (199.19)

Calc.: C 42.20 H 2.53 N 7.03 S 16.10

Found: 42.18 2.58 7.06 16.18

Example 7

4-Hydroxy-1,2-benzisothiazol-3(2H)-one-1,1-dioxide

2.5 g (11.8 m mol) of 3-amino-4-methoxy-1,2-benzisothiazole-1,1-dioxide were reacted analogously to Example 6. Instead of potassium cyanide, potassium bromide was used.

Yield: 1.05 g (45 % of theory) of 4-hydroxy-1,2-benzisothiazole-3(2H)-one-1,1-dioxide

M.p.: 228°C (from water)

$C_7H_5NO_4S$ (199.19)

Calc.: C 42.20 H 2.53 N 7.03 S 16.10

Found: 42.00 2.61 7.09 16.21

Example 8

4-Hydroxy-1,2-benzisothiazole-3(2H)-one-1,1-dioxide

8.1 g (40 m mol) of 3-methoxy-2-methyl-benzene sulfonamide and 5.5 g (52 m mol) of anhydrous sodium carbonate were diluted with 300 ml of water and a solution of 15.9 g (500 m mol) of potassium permanganate in 400 ml of water was added dropwise at 70 - 80°C. The reaction mixture was refluxed (approx. 1 to 2 hours) until decolorization and filtered hot. The filtrate was evaporated in vacuo to half its volume and acidified with conc. aqueous hydrochloric acid. A small quantity of the starting compound was obtained in crystals and after standing over night the resultant crystals of the 4-methoxy-1,2-benzisothiazole-3(2H)-one-1,1-dioxide were filtered off.

A further quantity of the product could be obtained by extracting the aqueous mother liquor with ether. After recrystallization from benzene/ethyl acetate 4.8 g (56 % of theory) of 4-methoxy-1,2-benzisothiazole-3(2H)-one-1,1-dioxide (m.p.: 225°C) were obtained. The obtained product was dissolved in 1000 ml of ethylene chloride and mixed with 11.3 g (45 mmol) of boron tribromide at -10°C. Subsequently the reaction mixture was stirred for 30 minutes at room temperature and refluxed for 1 hour. After evaporating in vacuo, the residue was heated for 15 minutes with 150 ml of 70 % ethanol and several times evaporated in vacuo by addition of ethanol.

Yield: 3.4 g (75 % of theory) of 4-hydroxy-1,2-benzisothiazol-3(2H)-one-1,1-dioxide

M. p.: 228°C (from water)

$C_7H_5NO_4S$ (199.19)

Calc.: C 42.20 H 2.53 N 7.03 S 16.10

Found: 42.10 2.59 7.06 16.20

The starting compound was obtained from 2-methoxy-6-nitro-toluene according to the following method:

3-Methoxy-2-methyl-aniline

200 g (1.19 mol) of 2-methoxy-6-nitro-toluene were hydrogenated in 2.5 l of ethanol in the presence of 25 g of Raney nickel at 100 bar until the absorption of the calculated amount of hydrogen. The reaction mixture was filtered and evaporated in vacuo. After distillation 158.3 g (97 % of theory) of 3-methoxy-2-methylaniline were obtained.

B.p.: 126°C at 16.25 mbar

3-Methoxy-2-methyl-benzene sulfonamide

10.0 g (73 mmol) of 3-methoxy-2-methyl-aniline were dissolved in 50 ml of 50 % aqueous acetic acid, which was saturated with gaseous hydrochloric acid and the solution was diazotized with 5.5 g (80 mmol) of sodium nitrite (dissolved in 10 ml of water).

A slight excess of nitrite was removed with urea. The diazonium salt solution was mixed with 6 g of magnesium sulfate and subsequently poured on 60 ml of glacial acetic acid, which was saturated with sulfur dioxide. Before using the glacial acetic acid, it was mixed with 3 g of copper(I)-chloride.

The reaction mixture was slowly heated to room temperature and stirred for 4 hours. After addition of 500 ml of water the crude product was extracted with methylene chloride. The organic phases were washed with water, sodium bicarbonate solution and again with water. After drying and evaporating the residue was distilled in vacuo. The product obtained at a pressure of 19.5 mbar and at a boiling point of 110 to 135°C (sulfonic acid chloride) was taken up in 50 ml of ethanol and mixed with conc. aqueous ammonia. The reaction mixture was stirred for 15 minutes and evaporated in vacuo. The residue was recrystallized from methanol/water and 4.6 g (31 % of theory) of 3-methoxy-2-methyl-benzene sulfonamide were obtained. M.p.: 193°C.

Example 9

4-Hydroxy-1,2-benzisothiazol -3(2H)-one-1,1-dioxide

6.6 g (30 m mol) of 4-chloro-1,2-benzisothiazol -3(2H)-one-1,1-dioxide, 12.3 g (90 m mol) of potassium carbonate, 0.6 g of copper powder and 1.5 g of copper(II)-chloride in 110 ml of water were heated for 12 hours up to 150°C in a glass autoclave. The reaction mixture was diluted with water, heated and filtered hot. The filtrate was acidified with hydrochloric acid and extracted with ether. The ether extracts were evaporated and the residue obtained was recrystallized from water. Yield: 4.3 g (72 % of theory) of 4-hydroxy-1,2-benzisothiazole-

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3(2H)-one-1,1-dioxide.

M.p.: 228°C

$C_7H_5NO_4S$ (199.19)

Calc.: C 42.20 H 2.53 N 7.03 S 16.10

Found: 42.10 2.59 7.06 16.20

Starting from the 2-chloro-6-nitro-toluene the preparation of the starting compound 4-chloro-1,2-benzisothiazole-3(2H)-one-1,1-dioxide was carried out according to one of the following processes:

Method A:

3-Chloro-2-methyl-aniline

100 g (0.583 mol) of 2-chloro-6-nitro-toluene were hydrogenated in a suspension of 10 g of Raney-Nickel in 1 l of ethanol. When the calculated amount of hydrogen was taken up, the reaction mixture was filtered and the filtrate was evaporated in vacuo.

The residue was distilled in a vacuum of 14 mbar. The compound obtained at 134 - 140°C was the 3-chloro-2-methyl-aniline.

Yield: 72 g (87 % of theory).

B.p.: 140°C / 14.3 mbar.

3-Chloro-2-methyl-benzene sulfonic acid chloride

30 g (0.212 mol) of 3-chloro-2-methyl-aniline were mixed with 50 ml of conc. aqueous hydrochloric acid. The reaction mixture was cooled to -7 to -3°C and at this temperature a solution of 14.6 g (0.212 mol) of sodium nitrite in 50 ml of water was added dropwise within 1 hour. After stirring for a further hour at 0°C, 20.3 g (0.1 mol) of magnesium chloride hexahydrate were added and the reaction mixture was stirred for 10 minutes and then filtered. The filtrate was poured in a thin stream into a suspension of

12 g (71 m mol) of copper(II)-chloride in 250 ml of a 30 % solution of sulfur dioxide in glacial acetic acid. During the addition the reaction mixture reached a temperature of 20 to 40°C, whereby a strong formation of gas took place. After stirring for 60 minutes at room temperature and for 60 minutes at 35°C, 500 g of ice were added. The mixture was stirred until the ice was thawed, then filtered. Yield: 38.2 g (80 % of theory) of 3-chloro-2-methyl-benzene-sulfonic acid chloride. The product obtained could be used directly in the subsequent reaction.

3-Chloro-2-methyl-benzene sulfonamide

38.2 g (0.17 mol) of 3-chloro-2-methyl-benzene sulfonic acid chloride were dissolved in 200 ml of dioxan and heated up to 40°C. Within 15 minutes a mixture of 100 ml of conc. aqueous ammonia and 100 ml of ethanol was added dropwise, whereby the reaction mixture reached a temperature of 55°C.

Subsequently the reaction mixture was heated to 70°C for 2 hours, then cooled and filtered. (The residue consisted of 3,3'-dichloro-2,2'-dimethyl-diphenyl disulfide). The filtrate was evaporated in vacuo and mixed with ice-water. The precipitate was suction filtered and washed with ice water. After recrystallization from ethanol/water 24 g (69 % of theory) of 3-chloro-2-methyl-benzene sulfonamide were obtained.

M.p.: 179°C

$C_7H_8ClNO_2S$ (205.67)

Calc.:	C 40.88	H 3.92	Cl 17.24	N 6.81	S 15.59
Found:	40.90	3.85	17.33	6.71	15.63

3-Chloro-2-methyl-benzene sulfinic acid was obtained by acidifying the filtrate with conc. aqueous hydrochloric acid.

M.p.: 112°C

Yield: 7.0 g ($\approx$ 22 % of theory).

The sulfinic acid was converted with copper(II)-chloride in formic acid to the 3-chloro-2-methyl-sulfonic acid chloride by heating for 1 hour at 40°C and reacting with conc. aqueous hydrochloric acid in ice.

Yield: 88 %.

The sulfonic acid chloride was converted subsequently into the 3-chloro-2-methyl-benzene sulfonamide.

Total yield: 85 % of theory.

4-Chloro-1,2-benzisothiazole-3(2H)-one-1,1-dioxide

16.4 g (80 m mol) of 3-chloro-2-methyl-benzene sulfonamide, 14 g (100 m mol) of potassium carbonate and 33.2 g (210 m mol) of potassium permanganate were refluxed for 1 hour in 350 ml of water. The reaction mixture was filtered hot and the filtration residue was washed with hot water. The combined filtrates were acidified with conc. aqueous hydrochloric acid and cooled. The crystals were suction filtered, washed with water and dried.

Yield: 12.6 g (72.5 % of theory) of 4-chloro-1,2-benzisothiazole-3(2H)-one-1,1-dioxide.

M.p.: 210°C (from water).

IR (KBr): 3420 (NH), 1730 (CO), 1330 and 1180 cm^{-1} (SO_2)

$\text{C}_7\text{H}_4\text{ClNO}_3\text{S}$ (217.64)

Calc.:	C 38.63	H 1.85	Cl 16.29	N 6.44	S 14.74
Found:	38.70	1.80	15.90	6.70	14.85

Method B:

2-Chloro-6-nitro-benzoic acid

A mixture of 77.7 g (0.453 mol) of 2-chloro-6-nitro-toluene, 190 g (1.2 mol) of potassium permanganate, 500 ml of 1 N potassium hydroxide solution and 4 l of water was heated for 8.5 hours

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up to 100°C. After standing over night, 25 g (0.16 mol) of potassium permanganate were added and the reaction mixture was heated for a further 2.5 hours to 100°C. The unreacted starting material was distilled off by steam distillation. The remaining reaction solution was filtered, the residue was washed with hot water and the filtrates were evaporated to approx. 750 ml. After acidifying with hydrochloric acid a precipitate was obtained, which was filtered off and dried. Yield: 45.9 g (50 % of theory) of 2-chloro-6-nitro-benzoic acid.

M.p.: 166°C (from ethylene chloride).

2-Chloro-6-nitro-benzoic acid chloride

1 ml of dimethyl formamide and 17.9 g (0.15 mol) of thionyl chloride were added to a suspension of 20.1 g (0.1 mol) of 2-chloro-6-nitro-benzoic acid in 150 ml of anhydrous benzene. The reaction mixture was stirred for 30 minutes and heated to reflux temperature. After 3 hours, a further 17.9g (0.15 mol) of thionyl chloride were added. The reaction mixture was further refluxed for 3 hours. After cooling the mixture was filtered and the filtrate was evaporated in vacuo.

Yield: 18.9 g (85.9 % of theory) of 2-chloro-6-nitro-benzoic acid. The product obtained was an oil.

Methyl 2-chloro-6-nitro-benzoate

18.9 g (86 m mol) of 2-chloro-6-nitro-benzoic acid chloride were added dropwise within 10 minutes to 100 ml of methanol. The reaction mixture was refluxed for 4 hours, then evaporated in vacuo. The residue was treated with a little ice-cold methanol and filtered off.

Yield: 12.3 g (66 % of theory) of methyl 2-chloro-6-nitrobenzoate

M.p.: 98°C (from cyclohexane).

Methyl 6-chloro-anthranilate

4.5 g (0.212 mol) of methyl 6-chloro-2-nitro-benzoate in 1.8 l of methanol were hydrogenated with Raney nickel until the calculated amount of hydrogen was taken up. The filtered reaction mixture was evaporated in vacuo and the residue was distilled in vacuo.

Yield: 34.6 g (88% of theory) of methyl 6-chloro-anthranilate
B.p.: 158°C at 14.3 mbar.

Methyl 6-chloro-2-chlorosulfonyl-benzoate

34.6 g (0.186 mol) of methyl 6-chloroanthranilate were added to 70 ml of conc. aqueous hydrochloric acid whilst stirring and cooling. At 0 to +10°C the reaction mixture was diazotized with a solution of 12.8 g (0.186 mol) of sodium nitrite in 30 ml of water. After stirring at 0°C for 45 minutes, the reaction mixture was poured into a stirred suspension of 2 g of copper(I)-chloride and 17 g of copper(II)-chloride in 160 ml of a 30 % solution of sulfur dioxide in glacial acetic acid. After the formation of nitrogen was finished, the reaction mixture was stirred for 2 hours at room temperature. After extraction with ether, the organic extracts were washed, dried and evaporated.

Yield: 38.2 g (76 % of theory) of methyl 6-chloro-2-chloro-sulfonyl-benzoate.

4-Chloro-1,2-benzisothiazol -3(2H)-one-1,1-dioxide

150 ml of ethanol saturated with ammonia, were added dropwise within 30 min. to a solution of 38.2 g (0.141 mol) of methyl 6-chloro-2-chlorosulfonyl-benzoate in 150 ml of dioxan at 30 - 50°C. Subsequently the reaction mixture was heated for 2 hours to 40°C and for 2 further hours up to 60°C. After cooling the reaction was evaporated, treated with ether and filtered.

The filtration residue was boiled with water, filtered hot and the filtrate was acidified with hydrochloric acid.

Yield: 19.8 g (64.5 % of theory) of 4-chloro-1,2-benzoisothiazol-3(2H)-one-1,1-dioxide.

M.p.: 210°C.

$C_7H_4ClNO_3S$ (217.64)

Calc.:	C 38.63	H 1.85	Cl 16.29	N 6.44	S 14.73
Found:	38.65	1.98	16.20	6.41	14.75

Example 10

4-Hydroxy-1,2-benzisothiazole-3(2H)-one-1,1-dioxide

3.4 g (12 mmol) of 2-(N-tert.-butyl)-sulfamoyl-6-methoxybenzoic acid were added to 50 g of polyphosphoric acid, warmed up to 60°C, within 5 minutes. Subsequently, the reaction mixture was heated for 20 minutes up to 70°C and ice was added thereto. The resultant precipitate was filtered off and recrystallized from water (1.6 g; m.p.: 224°C; $C_8H_7NO_4S$: 4-methoxy-1,2-benzisothiazol-3(2H)-one-1,1-dioxide).

The crystals were reacted with 24 ml (25 mmol) of boron tribromide in 400 ml of ethylene chloride for 1 hour at room temperature and for 2 hours at reflux temperature. Subsequently, the reaction mixture was evaporated and the residue was treated several times with methanol and evaporated. After recrystallization from isopropanol 1.4 g (58 % of theory) of 4-hydroxy-1,2-benzisothiazol-3(2H)-one-1,1-dioxide were obtained.

M.p.: 224°C.

$C_7H_5NO_4S$ (199.19)

Calc.:	C 42.20	H 2.53	N 7.09	S 16.10
Found:	42.16	2.57	6.99	16.01

Starting from m-anisidine the starting compound 2-(N-tert.-butyl)-sulfamoyl-6-methoxy-benzoic acid was prepared according to the following method:

3-Methoxy-benzene sulfonic acid chloride

61.6 g (0.5 mol) of m-anisidine were dissolved in 50 ml of glacial acetic acid and 110 ml of conc. aqueous hydrochloric acid were added dropwise. The mixture was cooled to 0°C and diazotized with a solution of 38 g (0.551 mol) of sodium nitrite in 75 ml of water. After stirring for 10 - 15 minutes, the reaction mixture was poured slowly into a mixture of 24 g (0.14 mol) of copper(II)-chloride and 5 g of copper(I)-chloride in 300 ml of a 30 % solution of sulfur dioxide in glacial acetic acid and 450 ml of benzene, whereby a strong formation of gas and an increase in the temperature up to 40°C could be observed. When the reaction temperature dropped, the mixture was heated further for 1 hour up to 40°C. After cooling, the reaction mixture was diluted with 2.5 l of ice-water, filtered and the organic phase was separated. The organic phase was washed with water and sodium bicarbonate solution and evaporated. Yield: 84.5 g (82 % of theory) of 3-methoxy-benzene sulfonic acid chloride.

N-tert.-Butyl-3-methoxy-benzene sulfonamide

49.5 g (0.24 mol) of 3-methoxy-benzene sulfonic acid chloride were dissolved in 50 ml of tetrahydrofuran and the solution was added dropwise within 25 minutes to a solution of 40 g (0.55 mol) of tert.-butylamine in 200 ml of tetrahydrofuran. After stirring for 1 hour at room temperature and for 7 hours at 60°C, the reaction mixture was filtered and the filtrate was evaporated in vacuo. The residue obtained was treated with cyclohexane and 54.1 g (92.6 % of theory) of N-tert.-butyl-3-methoxy-sulfonamide were obtained.
M.p.: 100°C.

2-(N-tert.-butyl)-sulfamoyl-6-methoxy-benzoic acid

A solution of 3.3 g (14 m mol) of N-tert.-butyl-3-methoxy-benzene sulfonamide in 70 ml of anhydrous tetrahydrofuran was mixed dropwise with 19 ml of a 15 % solution of n-butyl-lithium in hexane (31 m mol) under nitrogen within 15 minutes at -60 to -50°C. The reaction mixture was subsequently stirred for 1 hour at 0°C and after repeated cooling to -70 - -50°C a current carbon dioxide was passed through. The treatment with carbon dioxide was continued for 1 hour at room temperature after the exothermic reaction was finished. The reaction mixture was evaporated in vacuo and the residue was distributed between ice-water and ether. The aqueous layer was washed with ether and acidified with hydrochloric acid. The precipitate was filtered off and 3.6 g (87 % of theory) of 2-(N-tert.-butyl)-sulfamoyl-6-methoxy-benzoic acid were obtained.

Example 11

4-Hydroxy-1,2-benzisothiazol-3(2H)-one,1,1-dioxide

A solution of 1,2-benzisothiazol-3(2H)-one-1,1-dioxide 4-diazonium chloride, which was prepared by diazotisation of 1.98 g (10 m mol) of 4-amino-1,2-benzisothiazol-3(2H)-one-1,1-dioxide with sodium nitrite in dilute hydrochloric acid, was reacted with 150 ml of 10 % aqueous sulfuric acid and the reaction mixture was heated over a water bath until the formation of nitrogen was completed. After cooling the reaction mixture was strongly acidified with conc. aqueous hydrochloric acid and extracted with ether. The organic phase was evaporated, the residue was dissolved in a little sodium hydroxide solution, filtered and again acidified with hydrochloric acid. The crystals formed were recrystallized from water and 98 g (40 % of theory) of 4-hydroxy-1,2-benzisothiazole-3(2H)-one-1,1-dioxide were obtained.

M.p.: 228°C.

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$C_7H_5NO_4S$ (199.19)

Calc.: C 42.20 H 2.53 N 7.03 S 16.10

Found: 42.14 2.57 7.09 15.98

The starting compound of 1,2-benzisothiazole-3(2H)-one-1,1-dioxide was prepared according to the following method:

2-Methyl-3-nitro-benzene sulfonamide

7.5 g (49 m mol) of 2-amino-6-nitro-toluene were dissolved in a mixture of 27.5 g of conc. sulfuric acid and 250 ml of water and diazotized with a solution of 3.75 g (54 m mol) of sodium nitrite in 7.5 ml of water at 0 to 5°C. After 2 hours the reaction mixture was added in batches to a prepared mixture of 90 ml of a 30 % sulfur dioxide solution in glacial acetic acid and a solution of 1.5 g of copper(II)-chloride in 4 ml of water at 20°C. The further treatment and the reaction with ammonia was carried out analogously to the method described for the preparation of the 3-methoxy-2-methyl-benzene sulfonamide (Example 8). Yield: 8.2 g (77 % of theory) of 2-methyl-3-nitro-benzene sulfonamide.

$C_7H_8N_2O_4S$ (216.21)

Calc.: C 38.89 H 3.73 N 12.95 S 14.83

Found: 38.67 3.79 12.72 14.81

4-Nitro-1,2-benzisothiazol-3(2H)-one-1,1-dioxide

8.0 g (37 m mol) of 2-methyl-3-nitro-benzene sulfonamide were oxidized with potassium permanganate in water analogously to Example 8. After extraction with ether, evaporation and recrystallization from water 3.8 g (45 % of theory) of the nitro compound were obtained.

M.p.: 239°C.

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4-Amino-1,2-benzisothiazol-3(2H)-one-1,1-dioxide

3.0 g (13 m mol) of 4-nitro-1,2-benzisothiazol-3(2H)-one-1,1-dioxide were dissolved in 100 ml of ethanol. The solution was hydrogenated via hydrogen using a palladium/animal charcoal catalyst. After filtration, evaporation and recrystallization from ethanol 2.3 g (89.5 % of theory) of the amino compound were obtained.

M.p.: 244 - 245°C.

$C_7H_6N_2O_3S$ (198.19)

Calc.:	C 42.42	H 3.05	N 14.13	S 16.18
Found:	42.31	3.12	14.01	16.18

1,2-Benzisothiazol-3(2H)-one-1,1-dioxide-4-diazonium chloride

1.98 g (10 m mol) of 4-amino-1,2-benzisothiazole-3(2H)-one-1,1-dioxide were dissolved in water with the addition of sodium carbonate and the solution was precipitated with conc. aqueous hydrochloric acid. At 0 to 5°C a solution of 700 mg of sodium nitrite in 3 ml of water was added dropwise to this suspension and the reaction mixture was stirred for 2 hours at 5°C. The diazonium salt solution thus obtained was used directly for the further reactions without isolation of the diazonium salt.

The compounds of general formula I or their salts may be incorporated in conventional manner into pharmaceutical preparations such as tablets, powders or solutions. The following examples serve to illustrate this:

Example I

Solution of sweetening agent containing 50 mg of sodium salt of the 4-hydroxy-1,2-benzisothiazol-3(2H)-one-1,1-dioxide in 1 ml

The following substances were successively dissolved in 100 ml of dist. water at a temperature of 60°C whilst stirring:

0.1 g of sorbic acid
1.2 g of citric acid
1.5 g of disodium phosphate
5.0 g of sodium salt of the sweetening agent

1 ml (approx. 25 drops) contains 50 mg of the above mentioned sweetening agent and has a sweetening power approximately equivalent to 3 lumps of sugar.

Example II

Tablets for sweetening containing 20 mg of 4-hydroxy-1,2-benzo-
isothiazol-3(2H)-one-1,1-dioxide

Composition of tablet:

Sweetening agent	20 mg
Sodium hydrogen carbonate	5 mg
Powdered sorbitol	25 mg

The sweetening agent was mixed with the sodium hydrogen carbonate and the sorbitol and compressed to form tablets at a maximum relative humidity of 60%.

1 tablet has a sweetening force approximately equivalent to 1 lump of sugar.

Example III

Tablets for sweetening containing 20 mg of sodium salt of
4-hydroxy-1,2-benzoisothiazol-3(2H)-one-1,1-dioxide

Composition of a tablet:

Sodium salt of the sweetening agent	20 mg
Sorbitol	30 mg

The sweetening agent was mixed with the sorbitol and compressed to form tablets.

1 tablet has the sweetening power approximately equivalent to 1 lump of sugar.