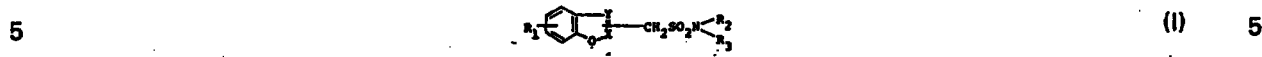


SPECIFICATION

Methane sulfonamide derivatives

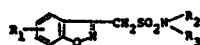
The present invention relates to novel methane-sulfonamide derivatives. The present invention provides a compound of the formula:



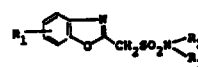
wherein R₁ is a hydrogen or halogen atom, R₂ and R₃ are each independently a hydrogen atom or an alkyl group having from 1 to 3 carbon atoms, and one of X and Y is a carbon atom and the other is a nitrogen atom, provided that the group: —CH₂SO₂NR₂R₃ is bonded to the carbon atom of either of X and Y, or an alkali metal salt thereof.

10 The term "halogen atom" denotes fluorine, chlorine and bromine atoms, and the term "alkyl" denotes a straight or branched alkyl group having 1 to 3 carbon atoms, such as methyl, ethyl, propyl or isopropyl. The term "alkali metal salt" includes sodium and potassium salts. 10

The compounds of formula (I) include the following two types of compounds:



(I')



(I'')

15 In the course of intensive studies on sulfamoyl-alkyl derivatives of various benzazoles it has been found that when the sulfamoylmethyl group is introduced at the 3-position of 1,2-benzisoxazoles or at the 2-position of benzoxazoles, the resulting compounds possess excellent anticonvulsant activity. 15

20 Although some 3-sulfamoylmethylindole derivatives are disclosed in United States Patent Specification No. 3,833,608, the compounds of formula (I) of the present invention are clearly different from the indole derivatives disclosed in this patent specification both in their chemical structure and pharmacological properties. 20

25 Preferred compounds of the present invention are the compounds of the formula (I) wherein R₁ is hydrogen atom or a halogen atom at the 5- or 6-position of the ring and R₂ and R₃ are each independently a hydrogen atom or a methyl group. Particularly preferred compounds are the compounds of formula (I) wherein R₁ is a hydrogen atom or a 5- or 6-halogen atom and R₂ and R₃ are both hydrogen atoms. Examples are as follows, of which the first three compounds are particularly preferred. 25

- 3-Sulfamoylmethyl-1,2-benzisoxazole
- 5-Fluoro-3-sulfamoylmethyl-1,2-benzisoxazole
- 30 2-Sulfamoylmethylbenzoxazole
- 5-Chloro-3-sulfamoylmethyl-1,2-benzisoxazole
- 5-Bromo-3-sulfamoylmethyl-1,2-benzisoxazole
- 6-Fluoro-3-sulfamoylmethyl-1,2-benzisoxazole

The compounds of the formula (I) may be prepared by reacting a compound of the formula:



wherein R₁, X and Y are as defined above, and Z is a halogen atom (e.g. chlorine or bromine), with an amine of the formula:



wherein R₂ and R₃ are as defined above.

40 The reaction of the compound of the formula (II) with the amine of the formula (III) may be carried out in the absence of a solvent, but may preferably be carried out in the presence of an inert solvent. The inert solvent may be water, an alcohol (e.g. ethanol or isopropanol), an aromatic hydrocarbon (e.g. toluene or xylene), an ether (e.g. diethyl ether, tetrahydrofuran or dioxane), an ester (e.g. ethyl acetate), or a mixture of two or more thereof. Preferred solvents are ethers and esters.

45 The reaction is preferably carried out in the presence of a base as a dehydrohalogenating agent. The base may be, for example, an alkali metal bicarbonate (e.g. sodium bicarbonate or potassium 45

bicarbonate), an alkali metal carbonate (e.g. sodium carbonate or potassium carbonate), or an organic amine (e.g. triethylamine). Instead of using a specific base, an excess amount of the amine of formula (III) may be used, this amine acting as a reactant and also as a dehydrohalogenating agent.

The amine of the formula (III) is usually used in an amount of from 1 to 4 moles to 1 mole of the compound of the formula (II), but may be used in a large excess amount. The reaction temperature is not critical, but the reaction is usually carried out at a temperature in the range of from 0°C to 35°C. The desired compound of the formula (I) can be isolated from the reaction mixture and purified in a conventional manner.

The starting compound of the formula (II) is prepared by reacting a halogenomethyl derivative of the formula:



wherein R₁, X and Y are as defined above, and Hal is a halogen atom (e.g. chlorine, bromine or iodine), which is prepared by the similar process to that disclosed in Chem. Pharm. Bull. (Tokyo), Vol. 24, page 632 (1976) and Belgian Patent No. 624,463, with sodium sulfite in an inert solvent (e.g. aqueous methanol or aqueous ethanol) at a temperature of from 40°C to 80°C to give a sodium methanesulfonate of the formula:



wherein R₁, X and Y are as defined above, and then reacting the resulting sodium methanesulfonate of the formula (V) with a halogenating agent (e.g. phosphorus oxychloride or phosphorus oxybromide).

The compound of the formula (I) wherein either one or both of R₂ and R₃ are hydrogen atoms may be reacted with an alkali metal compound in a conventional manner to give an alkali metal salt of the compound of the formula (I). The alkali metal compound may be, for example, an alkali metal hydroxide (e.g. sodium hydroxide or potassium hydroxide) or an alkali metal alcoholate (e.g. sodium ethylate).

The compounds of formula (I) and their alkali metal salts of the present invention possess good anticonvulsant activity. Pharmacological test data for representative compounds of the present invention are given below together with the data for commercially available anticonvulsants.

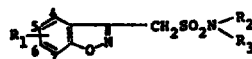
(1) anti-maximal electroshock seizure activity in mice

Male mice of STD—ddY strain were used. The test compounds were orally administered to the test animals (each group: 10 mice) in the form of a homogeneous suspension in a 0.5% tragacanth solution.

Maximal electroshock seizures (MES) were induced by the method of Swinyard [cf. J. Amer. Pharm. Assoc., Vol. 38, page 201 (1949)]. The animals were subjected to 60 Hz current of 25 mA for 0.2 second delivered through corneal electrodes after administration of the test compounds. Median effective dose (ED₅₀), i.e. the dose which prevents hindlimb tonic extensor components of seizures in 50% of animals, was calculated by the method of Litchfield and Wilcoxon [cf. J. Pharmacol. Exp. Ther., Vol. 96, page 99 (1947)].

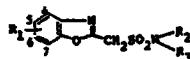
The ED₅₀ at peak effect time of the compounds is shown in Tables 1a and 1b.

TABLE 1a



Test compound				ED ₅₀ (mg/kg, p.o.)
No.	R ₁	R ₂	R ₃	
1	H	H	H	19.6
2	H	H	CH ₃	22.3
3	H	H	C ₂ H ₅	38.9
4	H	H	CH(CH ₃) ₂	56.0
5	H	CH ₃	CH ₃	37.2
6	5-Cl	H	H	14.2
7	5-Cl	H	CH ₃	ca. 20
8	5-Cl	H	C ₂ H ₅	21.3
9	5-Cl	CH ₃	CH ₃	56.2
10	5-F	H	H	14.5
11	5-F	H	CH ₃	34.5
12	5-F	H	C ₂ H ₅	31.6
13	5-F	CH ₃	CH ₃	32.0
14	5-Br	H	H	13.5
15	5-Br	H	CH ₃	15.0
16	5-Br	H	C ₂ H ₅	18.3
17	5-Br	H	CH(CH ₃) ₂	22.3
18	6-F	H	H	18.9

TABLE 1b



Test compound				ED ₅₀ (mg/kg, p.o.)
No.	R ₁	R ₂	R ₃	
19	H	H	H	12.0
20	H	H	CH ₃	17.2
21	H	CH ₃	CH ₃	34.0
22	H	H	(CH ₂) ₂ CH ₃	31.2
23	5-Cl	H	H	30.3
Diphenylhydantoin				7.6
Carbamazepine				13.2
Primidone				21.7
Phenacemide				61.2

[Note] :

Diphenylhydantoin : 5,5-diphenyl-2,4-imidazolidinedione

Carbamazepine : 5H-dibenz[b,f]azepine-5-carboxamide

Primidone : 5-ethyl-5-phenylhexahydropyrimidine-4,6-dione

Phenacemide : phenylacetylurea

The anti-MES activities of the compounds of this invention were more potent than that of phenacemide, while less than that of diphenylhydantoin. The activities of some compounds of this invention were almost equal to or more potent than those of carbamazepine and primidone.

5 (2) Effect on coordinated motor movements in mice

Mice trained to continue coordinated motor movements for 100 seconds or more on a rotarod apparatus (2.5 cm in diameter at 11 RPM) were used [J. Amer. Pharm. Assoc., Sci. Ed., Vol 46, page 208 (1957)]. Impairment of coordinated motor movements was defined as the inability of the animals to stay on the rotarod for a 100 second test period. After oral administration of the test compounds the rotarod performance was tested at intervals of 1 hour for 6 hours. The median neurotoxic dose (NTD₅₀), i.e. the dose which caused 50% of the animals to fall from the rotarod was calculated by the method of Litchfield and Wilcoxon.

The NTD₅₀ at peak effect time of the test compounds is shown in Table 2. The protective indices (NTD₅₀/ED₅₀ of anti-MES) of the test compounds were calculated and are also shown in the same table.

TABLE 2

Test compound *1	NTD ₅₀ (mg/kg, p.o.)	Protective index
1	292 (2) *2	14.9
10	154 (2)	10.6
19	168 (2)	14.0
Diphenylhydantoin	72 (6)	9.5
Carbamazepine	141 (1)	10.7

[Note] :

*1) The test compounds 1, 10 and 19 are as defined in Tables 1a and 1b.

*2) Figures in parentheses represent peak effect time in hours.

The neurotoxic effects of the compounds of this invention were about one-half to about one-quarter as potent as that induced by diphenylhydantoin. The protective indices of the compounds of this invention were higher than that of diphenylhydantoin and were almost equal to or higher than that of carbamazepine. Therefore, the compounds of this invention have a wide separation of therapeutic effects from acute neurotoxic effects.

(3) Acute toxicity in mice

Male mice of STD—ddY strain weighing 20—22 g were used. The test compounds were orally administered to the test animals (each group: 10 mice) in the form of a homogeneous suspension in 0.5% tragacanth solution. The mortality was observed for 7 days. The median lethal dose (LD₅₀), i.e. the dose which causes death in 50% of animals, was calculated by Probit method.

The LD₅₀ of the test compounds is shown in Table 3. The safety index (LD₅₀/ED₅₀ of anti-MES) of each compound was calculated and is also shown in the same table.

TABLE 3

Test compound *	LD ₅₀ (mg/kg, p.o.)	Safety index
1	1829	93.3
10	1257	86.7
19	ca. 1800	—
Diphenylhydantoin	363	47.8
Carbamazepine	1700	129

[Note] :

*) The test compounds 1, 10 and 19 are as defined in Tables 1a and 1b.

The acute lethal toxicities of the compounds of this invention were fairly weak compared with that of diphenylhydantoin. The safety indices of the compounds of this invention were about twice as high as that of diphenylhydantoin, while their indices were somewhat lower than that of carbamazepine. The compounds of this invention have large safety margins as compared to di-phenylhydantoin.

As is clear from the above test results, the compounds of the formula (I) and their alkali metal salts

of the present invention possess good anticonvulsant activity and have a low toxicity, and hence, these compounds are useful as anticonvulsants for controlling convulsions and seizures in patients with epilepsy.

The compounds of the present invention can be administered by an oral, parenteral or intrarectal route. The dosage of these compounds may vary in accordance with the particular compound, the administration route, the age of the patient and the degree of the therapeutic effect desired, but is usually in the range of 1 to 100 mg/kg/day, preferably 3 to 50 mg/kg/day, which may be administered in a single dose or in divided doses.

The compounds of the present invention are usually administered in the form of a pharmaceutical composition which contains them in admixture with a pharmaceutical carrier. The pharmaceutical composition may be in dosage forms such as tablets, capsules, granules, fine granules, powders, syrups, suppositories or injections. These preparations can be prepared by conventional methods.

The carriers useful for these preparations include all organic or inorganic carrier materials which are usually used for pharmaceutical preparations and are inert to the active ingredient. Examples of carriers suitable for the preparation of tablets, capsules, granules and fine granules are diluents such as lactose, starch, sucrose, D-mannitol, calcium sulfate, or microcrystalline cellulose; disintegrants such as sodium carboxymethylcellulose, modified starch, or calcium carboxymethylcellulose; binders such as methylcellulose, gelatin, acacia, ethylcellulose, hydroxypropylcellulose, or polyvinylpyrrolidone; lubricants such as light anhydrous silicic acid, magnesium stearate, talc, or hydrogenated oil. When formed into tablets, they may be coated in a conventional manner by using the conventional coating agents such as calcium phosphate, carnauba wax, hydroxypropyl methylcellulose, macrogol, hydroxypropyl methylphthalate, cellulose acetate phthalate, titanium dioxide or sorbitan fatty acid ester.

Examples of carriers suitable for the preparation of syrups are sweetening agents such as sucrose, glucose, fructose, or D-sorbitol; suspending agents such as acacia, tragacanth, sodium carboxymethylcellulose, methylcellulose, sodium alginate, microcrystalline cellulose or Veegum (Registered Trade Mark); dispersing agents such as sorbitan fatty acid ester, sodium lauryl sulfate, or polysorbate 80. When formed into syrups, conventional flavoring agents, aromatic substances or preservatives may optionally be added thereto. The syrups may be in the form of a dry syrup which is dissolved or suspended before use.

Examples of bases used for the preparation of suppositories are cacao butter, glycerin saturated fatty acid ester, glycerogelatin or macrogol.

When formed into suppositories, conventional surface active agents or preservatives optionally be admixed therewith.

When prepared for injection, the alkali metal salt of the compound is dissolved in distilled water for injection, to which may optionally be added conventional solubilizers, buffering or pH adjusting agents, isotonic agents preservatives and other suitable substances. The compositions may be in the form of solid dry preparations which are dissolved before injection.

The pharmaceutical compositions usually contain the compounds of formula (I) or their alkali metal salts as the active ingredient in an amount of 0.5% by weight or more, preferably 10 to 70% by weight, based on the total weight of the composition. These compositions may optionally contain other therapeutically active compounds.

The present invention is illustrated by the following Examples, but is not limited thereto. In Examples, the compounds were identified by elementary analysis, mass spectrum, IR spectrum, NMR spectrum, or the like.

45 EXAMPLE 1

1,2-Benzisoxazole-3-methanesulfonyl chloride:

To a solution of 8.0 g of 3-bromomethyl-1,2-benzisoxazole (m.p. 64—66°C) in 130 ml of methanol was added a solution of 8.1 g of sodium sulfite in 130 ml of water. The mixture was heated with stirring at 50°C for 4 hours and concentrated under reduced pressure. The crystalline residue was dissolved in 250 ml of methanol with warming and the insoluble material was filtered off. The filtrate was concentrated under reduced pressure and the crystalline residue was washed with diethyl ether to give crude sodium 1,2-benzisoxazole-3-methanesulfonate (10.5 g).

To 100 ml of phosphorus oxychloride was added 10.5 g of the above-mentioned sodium salt and the mixture was heated under reflux for 3 hours. The excess of phosphorus oxychloride was distilled off under reduced pressure. The residue was dissolved in 200 ml of ethyl acetate and the removal of the insoluble material by filtration gave the solution of the desired product.

EXAMPLE 2

The following compounds were prepared in substantially the same manner as in Example 1:

- 60 5-Fluoro-1,2-benzisoxazole-3-methanesulfonyl chloride;
- 5-Chloro-1,2-benzisoxazole-3-methanesulfonyl chloride;
- 5-Bromo-1,2-benzisoxazole-3-methanesulfonyl chloride;
- 6-Fluoro-1,2-benzisoxazole-3-methanesulfonyl chloride.

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EXAMPLE 3**3-Sulfamoylmethyl-1,2-benzisoxazole:**

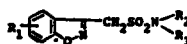
The solution of 1,2-benzisoxazole-3-methanesulfonyl chloride in ethyl acetate, which was prepared in Example 1, was cooled on an ice bath, saturated with dry ammonia gas, and allowed to stand at room temperature for one hour. After the removal of the insoluble material by filtration, the filtrate was concentrated to yield a crystalline solid, which was washed with a small amount of ethyl acetate and recrystallized from ethyl acetate to give the desired product (5.2 g), m.p. 160—163°C.

EXAMPLE 4**5-Fluoro-3-sulfamoylmethyl-1,2-benzisoxazole:**

Sixty six grams of sodium 5-fluoro-1,2-benzisoxazole-3-sulfonate, which was prepared in substantially the same manner as described in the first paragraph of Example 1, was dissolved in 500 ml of phosphorus oxychloride and the solution was heated under reflux for 4 hours. After the removal of the remaining phosphorus oxychloride by distillation, the residue was dissolved in 500 ml of benzene and then filtered. The filtrate was concentrated under reduced pressure and the residue was dissolved in 500 ml of diethyl ether. The resulting solution was saturated with dry ammonia gas under cooling on an ice bath and allowed to stand at room temperature for 30 minutes. The solvent was evaporated under reduced pressure and the residue was extracted with ethyl acetate. The ethyl acetate layer was concentrated to a volume of about 100 ml under reduced pressure. The crystalline precipitate was collected and washed with benzene to give the desired product (32 g), m.p. 182—185°C.

EXAMPLE 5

Various compounds of the formula:



as listed in the following Table 4 were prepared in substantially the same manner as in Examples 3 and 4.

TABLE 4

R ₁	R ₂	R ₃	Melting point (°C)
H	H	CH ₃	113 – 115
H	H	C ₂ H ₅	76 – 78
H	H	(CH ₂) ₂ CH ₃	86 – 88
H	H	CH(CH ₃) ₂	114 – 117
H	CH ₃	CH ₃	105 – 107
5-F	H	CH ₃	141 – 144
5-F	H	C ₂ H ₅	114 – 117
5-F	H	CH(CH ₃) ₂	127 – 130
5-F	CH ₃	CH ₃	145 – 148
6-F	H	H	187 – 190
5-Cl	H	H	192 – 195
5-Cl	H	CH ₃	148 – 151
5-Cl	H	C ₂ H ₅	150 – 152
5-Cl	H	CH(CH ₃) ₂	114 – 116
5-Cl	CH ₃	CH ₃	176 – 179
5-Br	H	H	221 – 225
5-Br	H	CH ₃	152 – 154
5-Br	H	C ₂ H ₅	144 – 147
5-Br	H	CH(CH ₃) ₂	95 – 97
5-Br	CH ₃	CH ₃	183 – 185

EXAMPLE 6**Benzoxazole-2-methanesulfonyl chloride:**

To a solution of 3.0 g of 2-bromomethylbenzoxazole [prepared according to the procedures described in Belgian Patent No. 624,463] in 40 ml of methanol was added a solution of 1.9 g of sodium sulfite in 40 ml of water. The mixture was heated with stirring at 60°C for 6 hours and concentrated under reduced pressure to give crude sodium benzoxazole-2-methanesulfonate (4.5 g). To the sodium salt was added 15 ml of phosphorus oxychloride and the mixture was heated under reflux for one hour. The removal of the remaining phosphorus oxychloride by distillation under reduced pressure gave the desired product as an oil.

EXAMPLE 7**2-Sulfamoylmethylbenzoxazole:**

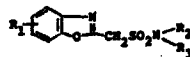
The benzoxazole-2-methanesulfonyl chloride, which was prepared in Example 6, was dissolved in 100 ml of ethyl acetate, saturated with dry ammonia gas under cooling on an ice bath, and allowed to stand at room temperature for 30 minutes. Evaporation of the solvent under reduced pressure gave an oily residue, which was chromatographed on silica gel with 3% methanol-chloroform as eluent. The eluate was concentrated to dryness and the crystalline residue was recrystallized from ethyl acetate to give the desired product (0.4 g), m.p. 166–169°C.

EXAMPLE 8

5-Chlorobenzoxazole-2-methanesulfonyl chloride was prepared in substantially the same manner as in Example 6.

EXAMPLE 9

5 Various compounds of the formula:



as listed in the following Table 5 were prepared in substantially the same manner as in Example 7.

TABLE 5

R ₁	R ₂	R ₃	Melting point (°C)
H	H	CH ₃	139 - 142
H	CH ₃	CH ₃	109 - 111
H	H	(CH ₂) ₂ CH ₃	146 - 149
5-Cl	H	H	188 - 191

EXAMPLE 10

10 Sodium salt of 3-sulfamoylmethyl-1,2-benzisoxazole:

To a solution of 7.0 g of 3-sulfamoylmethyl-1,2-benzisoxazole in 300 ml of ethanol was added a solution of sodium ethylate which was prepared from 0.76 g of sodium and 40 ml of ethanol. The mixture was allowed to stand at room temperature for a while and evaporated to one-fifth of its original volume under reduced pressure. The concentrated solution was cooled and the crystalline precipitate was collected, washed with ethanol and dried to give the desired product (6.5 g), m.p. 225—230°C (decomposition).

EXAMPLE 11

The following compounds were prepared in substantially the same manner as in Example 10:

20 Sodium salt of 5-fluoro-3-sulfamoylmethyl-1,2-benzisoxazole, m.p. 240—243°C (decomposition);

Sodium salt of 2-sulfamoylmethylbenzoxazole, m.p. 265—267°C (decomposition).

EXAMPLE 12

		per 1,000 tablets	
	3-Sulfamoylmethyl-1,2-benzisoxazole	100 g	
25	Lactose	35 g	25
	Corn starch	17 g	
	Microcrystalline cellulose	40 g	
	Polyvinylpyrrolidone	6 g	
	Light anhydrous silicic acid	1 g	
30	Magnesium stearate	1 g	30

The above components were blended, granulated and made into tablets by a conventional method. 1,000 tablets each weight 200 mg were formed.

EXAMPLE 13

	3-Sulfamoylmethyl-1,2-benzisoxazole	200 g	
	Lactose	779 g	
	Hydroxypropylcellulose	20 g	
5	Light anhydrous silicic acid	1 g	5

The above components were blended and made into fine granules by a conventional method.

EXAMPLE 14

The same procedures as in Examples 12 and 13 were repeated except that 5-fluoro-3-sulfamoylmethyl-1,2-benzisoxazole or 2-sulfamoylmethylbenzoxazole was used instead of 3-sulfamoylmethyl-1,2-benzisoxazole. Thus, tablets and fine granules of each compound were prepared respectively.

CLAIMS

1. A compound of the formula:



15 wherein R_1 is a hydrogen or halogen atom, R_2 and R_3 are each independently a hydrogen atom or an alkyl group having from 1 to 3 carbon atoms, and one of X and Y is a carbon atom and the other is a nitrogen atom, provided that the group: $-\text{CH}_2\text{SO}_2\text{NR}_2\text{R}_3$ is bonded to the carbon atom of either of X and Y, or an alkali metal salt thereof.

2. A compound of the formula:



wherein R_1 is a hydrogen or halogen atom, and R_2 and R_3 are each independently a hydrogen atom or an alkyl group having from 1 to 3 carbon atoms, or an alkali metal salt thereof.

3. A compound of the formula:



25 wherein R_1 is a hydrogen or halogen atom, and R_2 and R_3 are each independently a hydrogen atom or an alkyl group having from 1 to 3 carbon atoms, or an alkali metal salt thereof.

4. A compound as claimed in any one of the preceding claims wherein R_1 is a hydrogen atom or a halogen atom at the 5- or 6-position of the ring, or an alkali metal salt thereof.

5. A compound as claimed in claim 4, wherein R_2 and R_3 are each independently a hydrogen atom or a methyl group, or an alkali metal salt thereof.

6. A compound as claimed in claim 5, wherein R_2 and R_3 are both hydrogen atoms, or an alkali metal salt thereof.

7. 3-Sulfamoylmethyl-1,2-benzisoxazole or an alkali metal salt thereof.

8. 5-Fluoro-3-sulfamoylmethyl-1,2-benzisoxazole or an alkali metal salt thereof.

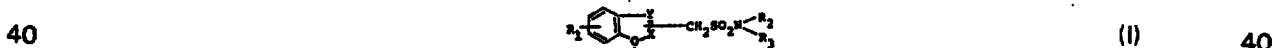
35 9. 5-Chloro-3-sulfamoylmethyl-1,2-benzisoxazole or an alkali metal salt thereof.

10. 5-Bromo-3-sulfamoylmethyl-1,2-benzisoxazole or an alkali metal salt thereof.

11. 6-Fluoro-3-sulfamoylmethyl-1,2-benzisoxazole or an alkali metal salt thereof.

12. 2-Sulfamoylmethylbenzoxazole or an alkali metal salt thereof.

13. A process for the preparation of a compound of the formula:



wherein R_1 , R_2 , R_3 , X and Y are as defined in claim 1, which process comprises reacting a compound of the formula:





EXAMPLE 13

	3-Sulfamoylmethyl-1,2-benzisoxazole	200 g	
	Lactose	779 g	
	Hydroxypropylcellulose	20 g	
5	Light anhydrous silicic acid	1 g	5

The above components were blended and made into fine granules by a conventional method.

EXAMPLE 14

The same procedures as in Examples 12 and 13 were repeated except that 5-fluoro-3-sulfamoylmethyl-1,2-benzisoxazole or 2-sulfamoylmethylbenzoxazole was used instead of 3-sulfamoylmethyl-1,2-benzisoxazole. Thus, tablets and fine granules of each compound were prepared respectively.

CLAIMS

1. A compound of the formula:



15 wherein R_1 is a hydrogen or halogen atom, R_2 and R_3 are each independently a hydrogen atom or an alkyl group having from 1 to 3 carbon atoms, and one of X and Y is a carbon atom and the other is a nitrogen atom, provided that the group: $-\text{CH}_2\text{SO}_2\text{NR}_2\text{R}_3$ is bonded to the carbon atom of either of X and Y, or an alkali metal salt thereof.

2. A compound of the formula:



wherein R_1 is a hydrogen or halogen atom, and R_2 and R_3 are each independently a hydrogen atom or an alkyl group having from 1 to 3 carbon atoms, or an alkali metal salt thereof.

3. A compound of the formula:



25 wherein R_1 is a hydrogen or halogen atom, and R_2 and R_3 are each independently a hydrogen atom or an alkyl group having from 1 to 3 carbon atoms, or an alkali metal salt thereof.

4. A compound as claimed in any one of the preceding claims wherein R_1 is a hydrogen atom or a halogen atom at the 5- or 6-position of the ring, or an alkali metal salt thereof.

5. A compound as claimed in claim 4, wherein R_2 and R_3 are each independently a hydrogen atom or a methyl group, or an alkali metal salt thereof.

6. A compound as claimed in claim 5, wherein R_2 and R_3 are both hydrogen atoms, or an alkali metal salt thereof.

7. 3-Sulfamoylmethyl-1,2-benzisoxazole or an alkali metal salt thereof.

8. 5-Fluoro-3-sulfamoylmethyl-1,2-benzisoxazole or an alkali metal salt thereof.

35 9. 5-Chloro-3-sulfamoylmethyl-1,2-benzisoxazole or an alkali metal salt thereof.

10. 5-Bromo-3-sulfamoylmethyl-1,2-benzisoxazole or an alkali metal salt thereof.

11. 6-Fluoro-3-sulfamoylmethyl-1,2-benzisoxazole or an alkali metal salt thereof.

12. 2-Sulfamoylmethylbenzoxazole or an alkali metal salt thereof.

13. A process for the preparation of a compound of the formula:



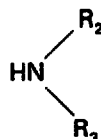
wherein R_1 , R_2 , R_3 , X and Y are as defined in claim 1, which process comprises reacting a compound of the formula:





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wherein R_1 , X and Y are as defined above and Z is a halogen atom, with an amine of the formula



wherein R_2 and R_3 are as defined above, and when either or both of R_2 and R_3 are hydrogen atoms, optionally converting the resulting compound into an alkali metal salt thereof.

5 14. A process as claimed in claim 13 wherein the group Z in formula (II) is a chlorine or bromine atom. 5

15. A process as claimed in claim 13 substantially as hereinbefore described with reference to any one of the foregoing Examples.

10 16. A compound as claimed in claim 1 whenever prepared by a process as claimed in any one of claims 13 to 15. 10

17. A pharmaceutical composition comprising as an active ingredient a compound of the formula:



as claimed in any one of claims 1 to 12, or claim 16 or an alkali metal salt thereof and a pharmaceutically acceptable carrier.