936,075

PATENT SPECIFICATION

NO DRAWINGS

936,075

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COMPLETE SPECIFICATION

Therapeutic Hypotensive Compositions comprising Phenylalanine Derivatives and Benzothiadiazine-1,1-Dioxide Derivatives

We, MERCK & CO., INC., a corporation duly organised and existing under the laws of the State of New Jersey, United States of America, of Rahway, New Jersey, United States of America, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention is concerned with pharmaceutical compositions for antihypertensive therapy, and is more particularly concerned with pharmaceutical preparations containing a novel mixture of coacting antihypertensive and diuretic pharmacotherapeutic agents.

Certain α-alkyl-phenylalanine derivatives are now being used in the treatment of hypertension, especially α-methyl-β-(3,4-dihydroxyphenyl)-alanine and some of its derivatives, homologues, analogues and isomers. Certain other compounds belonging to a broad class of benzothiadiazine dioxides are widely used as diuretics.

It has been found that a mixture of members of each of these classes results in an antihypertensive preparation of extraordinary utility. It is an advantage of these combinations that the required dosage of the α-alkyl-phenylalanine compounds is reduced, and that the active ingredients co-operate so as to enhance one or more characteristics of the individual agents. It is a further advantage that a combination dosage form is provided for use in α-alkyl-phenylalanine therapy of hypertensive patients which may be administered effectively in unit dosage that are so small that the α-alkyl-phenylalanine dosage level is below that at which the α-alkyl-phenylalanine compound alone would exhibit hypotensive properties.

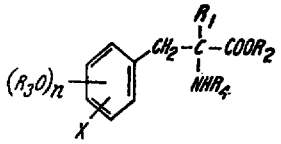
It has now been discovered that by administering a combined dosage of a hypotensive preparation for therapeutic administration comprising, preferably in unit-dosage form, such as a capsule or tablet (1) a compound selected from α-methyl-3,4-dihydroxyphenylalanine and its therapeutically active derivatives, homologues, isomers and analogues and having Formula I below (50—500 parts by weight) and (2) a sulphamoyl-substituted - 1,2,4 - benzothiadiazine - 1,1-dioxide (about 100—1000 parts by weight) or a sulphamoyl - 3,4 - dihydro - substituted-1,2,4 - benzothiadiazine - 1,1 - dioxide (about 10—100 parts by weight) having one of the formulæ 2, 3 and 4 below to hypertensive patients, a greatly increased hypotensive effect is brought about which in turn permits a lowered α-alkyl-phenylalanine dosage and a corresponding lessening of undesirable side-effects.

In addition to the effects set forth above, diuretic and other therapeutic effects, e.g., hypotensive effects of the benzothiadiazine or dihydrobenzothiadiazine compound are realized. The effects caused by the concurrent administration of an α-alkyl-phenylalanine and a benzothiadiazine or a dihydrobenzothiadiaziine is attributed to either a potentiation or synergistic effect. The antihypertensive effect of the α-alkyl-phenylalanine compound is potentiated by the benzothiadiazine or the dihydrobenzothiadiazine compound, which in some individuals has negligible or no effect of its own relative to anti-hypertension therapy. The mixture of an α-methyl-phenylalanine derivative and a benzothiadiazine or a dihydrobenzothiadiazine produces a hypotensive effect in excess of those predicted on the basis of the simple additive effects of the drugs used alone. Where treatment with the benzothiadiazine or the dihydrobenzothiadiazine compound alone does not produce a hypotensive effect, a potentiation of the hypotensive effect of the α-alkyl-phenylalanine is observed when the compositions of this invention are used. Where the benzothiadiazine or the dihydrobenzothiadiazine compounds do

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produce a hypotensive effect, a "true" synergism or therapeutic synergism is observed when therapy with the mixed compounds is practised in accordance with this invention.

The α-alkyl-phenylalanine derivatives which are used as one of the ingredients in the mixture of this invention have the general formula:



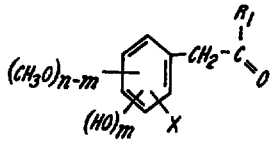
(Formula 1)

in which R_1 is a C_{1-5} alkyl radical, R_2 is a hydrogen atom or an alkyl radical, each of R_3 and R_4 is a hydrogen atom or a C_{1-6} alkanoyl radical, X is a hydrogen or halogen atom or an alkyl or trifluoromethyl radical, X being in a position para to the amino acid side chain when it is other than hydrogen, and *n* is 1, 2 or 3, the compound being a racemic mixture or having the *L* spatial configuration at the α-carbon atom. The optically active forms having the *L* or sinister absolute spatial configuration (i.e., the same spatial configuration as *L*-dihydroxyphenylalanine) possess the therapeutic anti-hypertensive activity and the *D* or rectus enantiomorphs, while inactive therapeutically, have the same toxicity level as the *L* compounds. Consequently, although its racemic form can be used quite conveniently, the phenylalanine ingredient in the compositions of this invention is preferably in the form of the *L*-enantiomorph substantially free of the *D*-enantiomorph. The acids among these compounds, whether racemic or optically active, are used as such or as their non-toxic therapeutically acceptable salts. Similarly, the esters can be used as acid-addition salts or as the free esters.

Some of the simpler compounds of the above class are disclosed and claimed in U.S. Patent 2,868,818. The preparation of the various homologues, analogues, derivatives and isomers useful in the compositions of the present invention, and the resolution of the racemic mixtures, together with the *L* isomers *per se*, are described and claimed in the specification of our copending Application No. 35724/60 (Serial No. 936,074).

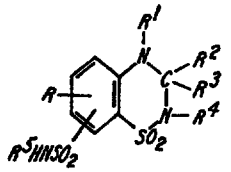
The preferred phenylalanine ingredients for the compositions of this invention are α-methyl - β - (3,4 - dihydroxyphenyl) alanine, its ethyl ester and its acetyl derivatives (both diacetyl and triacetyl) and their mineral acid-addition salts, both in the racemic form and in the optically active *L* or sinister spatial configuration form. In the case of the above phenylalanine derivative, the lævo-rotatory or *l*-form has the *L* or sinister absolute configuration. The same is also true of α-methyl-*m*-tyrosine, as well as many of the other phenylalanines within this class.

As disclosed in the above-mentioned U.K. specification and U.S. patent, the phenylalanine ingredients in the compositions of this invention are prepared by the reaction of a ketone of the formula:



in which *m* is 0 or 1 and the other symbols have the above meanings, with a water-soluble cyanide salt and ammonium carbonate to form a hydantoin derivative, which, on treatment with an aqueous hydrohalic acid, forms the amino acid by cleavage of the hydantoin ring and demethylation of the methoxyls. The amino acids can also be prepared by the reaction of the above ketones with a water-soluble cyanide salt and ammonium chloride to form an amino nitrile which is hydrolysed to the amino acid, the methoxyls then being split to form free hydroxyls. The various esters can be prepared by esterification of the carboxy group with an alcohol or by acylation of the hydroxyls by standard methods.

The dihydrobenzothiadiazine compounds and their alkali metal salts used in the compositions of this invention are 3,4-dihydro-1,2,4 - benzothiadiazine - 1,1 - dioxide compounds having the following structural formula



(Formula 2)

where R is a hydrogen or halogen atom, such as chlorine, bromine or fluorine, a trihalomethyl radical, e.g., trifluoromethyl, a C_{1-5} alkyl radical, a C_{1-5} alkoxy radical or a nitro or amino radical; each of R_1, R_4, and R_5 is a hydrogen atom or a C_{1-5} alkyl radical; R_2 is a hydrogen atom, an alkyl radical preferably having from 1 to 11 carbon atoms, a phenyl or halophenyl radical, for example chlorophenyl, or a benzyl or halobenzyl radical, for example chlorobenzyl, or a styryl radical; R_3 is a hydrogen atom or a C_{1-5} alkyl radical that may be unsubstituted or halogen-substituted, e.g., trichloromethyl; or R_2 and R_3 are alkyl groups joined together to form with the carbon atoms to which they

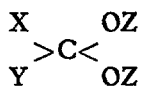
are attached a cycloaliphatic structure preferably having 5 or 6 carbon atoms, such as the 3,3-pentamethylene radical. The alkyl radicals represented by R_4 and R_5 can be hydroxy-substituted. Preferably, when R_2 and R_3 are both alkyl groups, each of R_1 and R_4 is hydrogen. Certain of the compounds are claimed in Patent No. 847,064.

Dihydrobenzothiadiazine compounds of this class can be prepared as disclosed in that patent or by analogous methods, which involve reacting a disulphamoylaniline compound having at least one sulphamoyl group in ortho position to the amino group with an aldehyde, acetal, ketone or ketal thus forming a sulphamoyl - 3,4 - dihydro - 1,2,4 - benzothiadiazine-1,1-dioxide.

Alternatively, a 3,4-dihydro-1,2,4-benzothiadiazine-1,1-dioxide can be halosulphonated by reaction with a halosulphonating such as chlorosulphonic acid or fluorosulphonic acid and the halosulphonyl-3,4-dihydro-1,2,4-benzothiadiazine-1,1-dioxide obtained then can be amidated with ammonia or a primary amine to form the sulphamoyl - 3,4-dihydro - 1,2,4 - benzothiadiazine-1,1-dioxide. The starting material in this reaction can be prepared by reacting an *ortho*-sulphamoylaniline compound with an aldehyde, acetal, ketone or ketal. The disulphamoylaniline or monosulphamoylaniline compound preferably is reacted with at least one molecular equivalent of aldehyde, acetal, ketone or ketal, although an excess of these reactants can be used if desired. Reaction with aldehydes or ketones can be conducted in either an acidic or basic medium. When acetals or ketals are used, reaction is carried out in an acidic medium. In all instances, reaction is advantageously carried out in the presence of a solvent, and either at room temperature or at elevated temperatures up to about 150° C.

Aldehydes or compounds which upon acid hydrolysis are converted to aldehydes, such as formaldehyde, paraformaldehyde, trioxane, paraldehyde and the like, or other aldehydes as chloral, acetaldehyde, propionaldehyde and the like having up to 12 carbon atoms as isobutyraldehyde, caproaldehyde, nonaldehyde, and lauraldehyde, can be used in the preparation of the hydrochlorothiazide.

Acetals or ketals, as methylal, 1,1-diethoxyethane, 3,3-diethoxypentane or other acetals or ketals having the general structural formula:

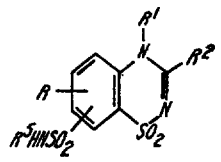


where each of X and Y is a hydrogen atom or an alkyl, preferably C_{1-5} alkyl, radical, and Z is a C_{1-5} alkyl radical, can also be used in the preparation of the compounds. Ketones also can be used and these may be symmetrical or unsymmetrical ketones such as acetone, diethyl ketone, dipropyl ketone, dibutyl ketone, methylethyl ketone, methylpropyl ketone, methylisopropyl ketone, cyclopentanone, and cyclohexanone.

The 3,4 - dihydro - 1,2,4 - benzothiadiazine - 1,1 - dioxides can be halosulphonated advantageously by reacting the compound with an excess of a molar equivalent of chlorosulphonic acid or fluorosulphonic acid and by heating the reaction mixture between about 100—165° C. The sulphonyl halide derivative thus prepared is reacted with ammonia or a primary amine to form the desired sulphamoyl-3,4-dihydro-1,2,4 - benzothiadiazine - 1,1 - dioxide. The ammonia or the amine is used in excess of that required to convert the sulphonyl halide group to the sulphamoyl group. Preferably, at least two molar equivalents of ammonia or the amine are used. Ammonia can be added in the form of aqueous or alcoholic ammonium hydroxide or liquid ammonia, or by dissolving the sulphonyl halide derivative in an organic solvent and bubbling ammonia gas into the solution to form the corresponding sulphamoyl compound. If a primary amine is used, this reactant preferably is a mono-lower alkylamine.

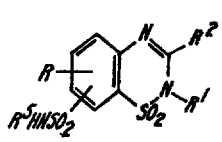
The above-described 3,4-dihydro-1,2,4-benzothiadiazine - 1,1 - dioxide compounds are useful pharmacotherapeutic agents principally because of their diuretic, natriuretic and/or saluretic properties. These compounds are particularly useful in the treatment of congestive heart failure and other abnormalities which produce an oedematous condition in the body or which produce an imbalance in the electrolyte condition in the body, as, for example, those in which abnormal retention of sodium occurs.

Certain of the 1,2,4-benzothiadiazine-1,1-dioxide compounds useful in compositions of the present invention are described and claimed in our prior Patents Nos. 826,921 and 826,923. Compounds having one of the general structural formulæ



(Formula 3)

and



(Formula 4)

and their non-toxic alkali metal salts, where R, R^1, R^2 and R^5 are as defined above for the 3,4 - dihydro - 1,2,4 - benzothiadiazine-1,1-dioxide compounds, are used in the compositions of this invention.

The specific compounds disclosed in the Examples contained in the aforementioned Patent No. 826,921 are all useful in the practice of this invention, when mixed with an α-methyl-phenylalanine derivative in proper dosages, all as particularized hereinafter.

Particularly useful and effective benzothiadiazine compounds for use in the compositions of this invention are 6-chloro-7-sulphamoyl - 1,2,4 - benzothiadiazine - 1,1-dioxide and its saturated analogue, 6-chloro-7 - sulphamoyl - 3,4 - dihydro - 1,2,4-benzothiadiazine - 1,1 - dioxide, as well as 6 - trifluoromethyl - 7 - sulphamoyl - 1,2,4-benzothiadiazine - 1,1 - dioxide and its saturated analogue, 6 - trifluoromethyl - 7-sulphamoyl - 3,4 - dihydro - 1,2,4 - benzothiadiazine-1,1-dioxide.

The following examples illustrate the preparation of tablets and capsules for use in oral administration of the combined agents according to this invention. In the examples, all parts are by weight and mesh sizes are U.S. Standard Sieve numbers.

Examples 1—2

Capsules of *DL*-α-methyl-3,4-dihydroxyphenylalanine with 6-chloro-7-sulphamoyl-1,2,4-benzothiadiazine-1,1-dioxide

Formulation:	Amounts per Capsule	
Ingredients	Capsule I	Capsule II
DL-α-methyl-3,4-dihydroxyphenylalanine	250 mg.	125 mg.
6-chloro-7-sulphamoyl-1,2,4-benzothiadiazine-1,1-dioxide	250 mg.	250 mg.

Directions:

1. Mix the *DL*-α-methyl-3,4-dihydroxyphenylalanine and 6 - chloro - 7 - sulphamoyl - 1,2,4 - benzothiadiazine - 1,1 - dioxide together.
2. Reduce to a fine powder and remix.
3. Encapsulate, filling 500 mg./capsule for Capsule I and 375 mg./capsule for Capsule II into No. 0 capsules.

Capsule I contains 1 part 6-chloro-7-sulphamoyl - 1,2,4 - benzothiadiazine - 1,1-dioxide to 1 part *DL* - α - methyl - 3,4-dihydroxyphenylalanine.

Capsule II contains 2 parts 6-chloro-7-sulphamoyl - 1,2,4 - benzothiadiazine - 1,1-dioxide to 1 part *DL* - α - methyl - 3,4-dihydroxyphenylalanine.

The above formulations are examples of the preparation of capsules containing suitable dosages of *DL*-α-methyl-3,4-dihydroxyphenylalanine and 6 - chloro - 7 - sulphamoyl-1,2,4-benzothiadiazine-1,1-dioxide.

Examples 3—4

Tablets *DL*-α-methyl-3,4-dihydroxyphenylalanine with 6-chloro-7-sulphamoyl-1,2,4-benzothiadiazine-1,1-dioxide

Formulation:	Amounts per Tablet	
Ingredients	Tablet I	Tablet II
DL-α-methyl-3,4-dihydroxyphenylalanine	250 mg.	250 mg.
6-chloro-7-sulphamoyl-1,2,4-benzothiadiazine-1,1-dioxide	250 mg.	500 mg.
Ethylene diamine tetraacetic acid disodium salt	0.075 mg.	0.075 mg.
Ethyl cellulose (as 5% solution in alcohol)	12.425 mg.	15.925 mg.
Corn starch	35.0 mg.	31.0 mg.
Magnesium Stearate	2.5 mg.	3.0 mg.

Directions:

1. Mix the *DL* - α - methyl - 3,4 - dihydroxyphenylalanine, the disodium salt of ethylene diamine tetraacetic acid, and 6-chloro-7 - sulphamoyl - 1,2,4 - benzothiadiazine-1,1-dioxide together.

2. Reduce to a fine powder and remix.

3. Granulate with the ethyl cellulose solution and pass the wetted mass through No. 10 mesh screen.

4. Heat dry at 120° F. for 12 hours.

5. Grind the dried granulation to No. 20 mesh.

6. Incorporate the corn starch and magnesium stearate.

7. Compress into tablets weighing 550 mg./tablet for Tablet I and 800 mg./tablet for Tablet II.

Tablet I contains 1 part 6-chloro-7-sulphamoyl - 1,2,4 - benzothiadiazine - 1,1-dioxide to 1 part *DL* - α - methyl - 3,4-dihydroxyphenylalanine.

Tablet II contains 2 parts 6-chloro-7-sulphamoyl - 1,2,4 - benzothiadiazine - 1,1-dioxide to 1 part *DL* - α - methyl - 3,4-dihydroxyphenylalanine.

The above formulations are examples of the preparation of tablets containing suitable dosages of *DL* - α - methyl - 3,4 - dihydroxyphenylalanine and 6 - chloro - 7-sulphamoyl - 1,2,4 - benzothiadiazine - 1,1-dioxide.

EXAMPLES 5—6

Capsules *L*-α-methyl-3,4-dihydroxyphenylalanine with 6-trifluoro-methyl-7-sulphamoyl-3,4-dihydro-1,2,4-benzothiadiazine-1,1-dioxide

Formulation:	Amounts per Capsule	
Ingredients	Capsule I	Capsule II
L-α-methyl-3,4-dihydroxyphenylalanine	250 mg.	250 mg.
6-trifluoromethyl-7-sulphamoyl-3,4-dihydro-1,2,4-benzothiadiazine-1,1-dioxide	25 mg.	50 mg.

Directions:

1. Mix the *L*-α-methyl-3,4-dihydroxyphenylalanine and 6 - trifluoromethyl - 7-sulphamoyl - 3,4 - dihydro - 1,2,4 - benzothiadiazine-1,1-dioxide together.

2. Reduce to a fine powder and remix.

3. Encapsulate, filling 275 mg./capsule for Capsule I and 300 mg./capsule for Capsule II into No. 0 capsules.

Capsule I contains 1 part 6-trifluoromethyl-7 - sulphamoyl - 3,4 - dihydro - 1,2,4 - benzothiadiazine-1,1-dioxide to 10 parts *L*-α-methyl-3,4-dihydroxyphenylalanine.

Capsule II contains 1 part 6-trifluoromethyl - 7 - sulphamoyl - 3,4 - dihydro-1,2,4 - benzothiadiazine - 1,1 - dioxide to 5 parts *L* - α - methyl - 3,4 - dihydroxyphenylalanine.

The above formulations are examples of the preparation of capsules comprising suitable dosages of *L* - α - methyl - 3,4-dihydroxyphenylalanine and 6 - trifluoromethyl - 7 - sulphamoyl - 3,4 - dihydro-1,2,4-benzothiadiazine-1,1-dioxide.

EXAMPLES 7—8

Tablets *DL*-α-methyl-3,4-dihydroxyphenylalanine with 6-chloro-7-Sulphamoyl-3,4-dihydro-1,2,4-benzothiadiazine-1,1-dioxide

Formulation:	Amount per Tablet	
Ingredients	Tablet I	Tablet II
DL-α-methyl-3,4-dihydroxyphenylalanine	250 mg.	250 mg.
6-chloro-7-sulphamoyl-3,4-dihydro-1,2,4-1,2,4-benzothiadiazine-1,1-dioxide	25 mg.	25 mg.
Ethylene diamine tetraacetic acid disodium salt	0.075 mg.	0.075 mg.
Ethyl cellulose (as 5% solution in alcohol)	7.925 mg.	8.425 mg.
Corn Starch	26 mg.	25 mg.
Magnesium Stearate	1 mg.	1 mg.

Directions:

1. Mix the *DL*-α-methyl-3,4-dihydroxyphenylalanine, the disodium salt of ethylene diamine tetraacetic acid and 6-chloro-7-sulphamoyl - 3,4 - dihydroxy - 1,2,4 - benzothiadiazine-1,1-dioxide together
2. Reduce to a fine powder and remix.
3. Granulate with the ethyl cellulose solution and pass the wetted mass through No. 10 mesh screen.
4. Heat dry at 120° F. for 12 hours.
5. Grind the dried granulation to No. 20 mesh.
6. Incorporate the corn starch and magnesium stearate.
7. Compress into tablets weighing 310 mg./tablet for Tablet I and 335 mg./tablet for Tablet II.

Tablet I contains 1 part 6-chloro-7-sulphamoyl - 3,4 - dihydro - 1,2,4 - benzothiadiazine - 1,1 - dioxide to 10 parts *DL* - α - methyl - 3,4 - dihydroxyphenylalanine.

Tablet II contains 1 part 6-chloro-7-sulphamoyl - 3,4 - dihydro - 1,2,4 - benzothiadiazine -1,1 - dioxide to 5 parts *DL* - α - methyl - 3,4 - dihydroxyphenylalanine.

The above formulations are examples of the preparation of tablets comprising suitable dosages of *DL* - α - methyl - 3,4 - dihydroxyphenylalanine and 6 - chloro - 7-sulphamoyl - 3,4 - dihydro - 1,2,4 - benzothiadiazine-1,1-dioxide.

EXAMPLES 9—23

By similar procedures to that followed in Examples 1 and 2 capsules containing the following compositions are prepared, parts being expressed in milligrams.

6-chloro-7-sulphamoyl-1,2,4-benzothiadiazine-1,1-dioxide	1000	100	250	500	100
DL-α-methyl-3,4-dihydroxy-phenylalanine	500	50	100	200	100
6-chloro-7-sulphamoyl-1,2,4-benzothiadiazine-1,1-dioxide	200	900	750	800	150
DL-α-methyl-3,4-dihydroxy-phenylalanine	400	400	350	250	100
6-chloro-7-sulphamoyl-1,2,4-benzothiadiazine-1,1-dioxide	100	1000	250	500	500
DL-α-methyl-3,4-dihydroxy phenylalanine	500	250	300	100	400

EXAMPLES 24—38

By procedures similar to those followed in Examples 5 and 6, capsules having the following compositions are prepared, parts being expressed in milligrams.

6-chloro-7-sulphamoyl-3,4-dihydro-1,2,4-benzothiadiazine-1,1-dioxide	100	10	25	50	10
DL-α-methyl-3,4-dihydroxy-phenyl-phenylalanine	500	50	100	200	100
6-chloro-7-sulphamoyl-3,4-dihydro-1,2,4-benzothiadiazine-1,1-dioxide	20	90	75	80	15
DL-α-methyl-3,4-dihydroxyphenyl-alanine	400	400	350	250	100
6-chloro-7-sulphamoyl-3,4-dihydro-1,2,4-benzothiadiazine-1,1-dioxide	10	100	25	50	50
DL-α-methyl-3,4-dihydroxyphenyl-alanine	500	250	300	100	400

EXAMPLES 39—40

The following compositions which can be put up in capsule form have been found particularly effective for use:

	Composition 1	Composition 2
6-chloro-7-sulphamoyl-3,4-dihydro-1,2,4-benzothiadiazine-1,1-dioxide	25 mg.	50 mg.
DL-α-methyl-3,4-dihydroxyphenylalanine	250 mg.	125 mg.
Potassium (in water soluble salt)	300 mg.	300 mg.

EXAMPLES 41—42

The following mixtures which can be put up in capsule form provide excellent results according to this invention:

6-chloro-7-sulphamoyl-3,4-dihydro-1,2,4-benzothiadiazine-1,1-dioxide	25 mg.	50 mg.
DL-α-methyl-meta-tyrosine	50 mg.	250 mg.

EXAMPLES 43—44

The following mixtures which can be put up in capsule form provide excellent results according to this invention:

6-trifluoromethyl-7-sulphamoyl-3,4-dihydro-1,2,4-benzothiadiazine-1,1-dioxide	25 mg.	50 mg.
Ethyl ester of *DL*-α-methyl-3,4-dihydroxy phenylalanine hydrochloride	125 mg.	250 mg.

EXAMPLES 45—46

The following mixtures which can be put up in capsule form provide excellent results according to this invention:

4-nitro-6-chloro-7-sulphamoyl-3,4-dihydro 1,2,4-benzothiadiazine-1,1-dioxide	25 mg.	50 mg.
L-α-methyl-3,4-dihydroxyphenylalanine	125 mg.	250 mg.

EXAMPLES 47—48

The following mixtures which can be put up in capsule form provide excellent results according to this invention:

3,3-diethyl-6-nitro-7-sulphamoyl-3,4-dihydro-1,2,4-benzothiadiazine-1,1-dioxide	25 mg.	50 mg.
L-α-methyl-3,4-dihydroxyphenylalanine	125 mg.	250 mg.

EXAMPLES 49—50

The following mixtures which can be put in capsule form provide excellent results according to this invention:

3-methyl-6-propoxy-7-sulphamoyl-3,4-dihydro-1,2,4-benzothiadiazine-1,1-dioxide	25 mg.	50 mg.
L-α-methyl-3,4-dihydroxyphenylalanine	100 mg.	500 mg.

The following mixtures which can be put up in capsule or tablet form in the dosage ranges given above are illustrative of those falling within the scope of this invention:

Dihydrobenzothiadiazine Compound	Phenylalanine
6-chloro-7-(hydroxymethylsulphamoyl)-3,4-dihydro-1,2,4-benzothiadiazine-1,1-dioxide	*DL*-α-methyl-3,4-dihydroxyphenylalanine
6-trifluoromethyl-7-sulphamoyl-3,4-dihydro-1,2,4-benzothiadiazine-1,1-dioxide	*L*-α-methyl-3,4-dihydroxyphenylalanine
6-trifluoromethyl-7-sulphamoyl-3,4-dihydro-1,2,4-benzothiadiazine-1,1-dioxide	*DL*-α-methyl-meta-tyrosine
3-methyl-6-chloro-7-sulphamoyl-3,4-dihydro-1,2,4-benzothiadiazine-1,1-dioxide	*DL*-α-methyl-3,4-dihydroxyphenylalanine
6-chloro-3-ethyl-7-sulphamoyl-3,4-dihydro-1,2,4-benzothiadiazine-1,1-dioxide	*L*-α-methyl-3,4-dihydroxyphenylalanine
3-(p-chlorophenyl)-6-chloro-7-sulphamoyl-3,4-dihydro-1,2,4-benzothiadiazine-1,1-dioxide	*L*-α-methyl-3,4-dihydroxyphenylalanine
6-chloro-3,3-pentamethylene-7-sulphamoyl-3,4-dihydro-1,2,4-benzothiadiazine-1,1-dioxide	*DL*-α-methyl-3,4-dihydroxyphenylalanine
3-methyl-3-isopropyl-6-bromo-7-sulphamoyl-3,4-dihydro-1,2,4-benzothiadiazine-1,1-dioxide	*L*-α-methyl-3,4-dihydroxyphenylalanine
6-fluoro-7-sulphamoyl-3,4-dihydro-1,2,4-benzothiadiazine-1,1-dioxide	*L*-α-methyl-3,4-dihydroxyphenylalanine
5-chloro-7-sulphamoyl-3,4-dihydro-1,2,4-benzothiadiazine-1,1-dioxide	ethyl ester of *l*-α-methyl-3,4-dihydroxyphenylalanine hydrochloride

The following mixtures which can be put up in capsule or tablet form in the dosage ranges given above are illustrative of various combinations that are useful in accordance with this invention:

Benzothiadiazine Compound	Phenylalanine
6-chloro-7-sulphamoyl-1,2,4-benzothiadiazine-1,1-dioxide	*DL*-α-methyl-*meta*-tyrosine
6-bromo-7-sulphamoyl-1,2,4-benzothiadiazine-1,1-dioxide	*DL*-α-methyl-3,4-dihydroxyphenylalanine
6-methyl-7-sulphamoyl-1,2,4-benzothiadiazine-1,1-dioxide	*L*-α-methyl-3,4-dihydroxyphenylalanine
7-chloro-6-sulphamoyl-1,2,4-benzothiadiazine-1,1-dioxide	ethyl ester of *l*-α-methyl-3,4-dihydroxyphenylalanine hydrochloride
6-trifluoromethyl-7-sulphamoyl-1,2,4-benzothiadiazine-1,1-dioxide	*L*-α-methyl-3,4-dihydroxyphenylalanine
6-methoxy-7-sulphamoyl-1,2,4-benzothiadiazine-1,1-dioxide	*L*-α-methyl-3,4-dihydroxyphenylalanine
6-chloro-3-methyl-7-sulphamoyl-1,2,4-benzothiadiazine-1,1-dioxide	*DL*-α-methyl-3,4-dihydroxyphenylalanine
Sodium salt of 6-chloro-7-sulphamoyl-1,2,4-benzothiadiazine-1,1-dioxide	*L*-α-methyl-3,4-dihydroxyphenylalanine

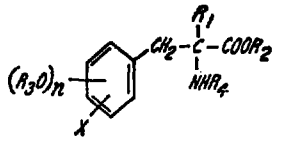
When, in any of the mixtures shown above, any of the indicated phenylalanine compounds is replaced by one of the following phenylalanine compounds, proportions being modified when necessary to allow for the relative activities of the compounds, there is obtained a new mixture also within the scope of this invention:

DL - α - ethyl - β - (3,4 - dihydroxyphenyl)alanine
DL - α - propyl - β - (3,4 - dihydroxyphenyl)alanine
DL - α - butyl - β - (3,4 - dihydroxyphenyl)alanine
DL - α - methyl - β - (2,3 - dihydroxyphenyl)alanine
DL - α - ethyl - β - (2,3 - dihydroxyphenyl)alanine
DL - α - methyl - β - (3,5 - dihydroxyphenyl)alanine
DL - α - methyl - β - (3,4,5 - trihydroxyphenyl)alanine
DL - α - methyl - β - (2,4,5 - dihydroxyphenyl)alanine
DL - α - methyl - β - (2,3,5 - trihydroxyphenyl)alanine
DL - α - methyl - β - (2,3,4 - trihydroxyphenyl)alanine
DL - α - methyl - *p* - chloro - *m* - tyrosine
DL - α - methyl - *p* - methyl - *m* - tyrosine
DL - α - methyl - *p* - fluoro - *m* - tyrosine
DL - α - methyl - *p* - trifluoromethyl - *m*-tyrosine
DL - α - methyl - β - (3,4 - diacetoxyphenyl)alanine
DL - N - acetyl - α - methyl - β - (3,4-diacetoxyphenyl)alanine
DL - N - formyl - α - methyl - β - (3,4-diformyloxyphenyl)alanine
L - α - methyl - β - (3,4,5 - trihydroxyphenyl)alanine
L - α - methyl - β - (3,5 - dihydroxyphenyl)alanine
L - α - methyl - *p* - chloro - *m* - tyrosine
L - α - methyl - *p* - trifluoromethyl - *m*-tyrosine
L - α - methyl - β - (3,4 - diacetoxyphenyl)alanine.

Although orally administrable pharmaceutical compositions have been particularly described, it is to be understood that liquid compositions suitable for injection, particularly intraperitoneally, can also be prepared.

WHAT WE CLAIM IS:—

1. A hypotensive pharmaceutical composition comprising a mixture of 50—500 parts by weight of a first compound having the formula:



The following mixtures which can be put up in capsule or tablet form in the dosage ranges given above are illustrative of various combinations that are useful in accordance with this invention:

Benzothiadiazine Compound	Phenylalanine
6-chloro-7-sulphamoyl-1,2,4-benzothiadiazine-1,1-dioxide	*DL*-α-methyl-*meta*-tyrosine
6-bromo-7-sulphamoyl-1,2,4-benzothiadiazine-1,1-dioxide	*DL*-α-methyl-3,4-dihydroxyphenylalanine
6-methyl-7-sulphamoyl-1,2,4-benzothiadiazine-1,1-dioxide	*L*-α-methyl-3,4-dihydroxyphenylalanine
7-chloro-6-sulphamoyl-1,2,4-benzothiadiazine-1,1-dioxide	ethyl ester of *l*-α-methyl-3,4-dihydroxyphenylalanine hydrochloride
6-trifluoromethyl-7-sulphamoyl-1,2,4-benzothiadiazine-1,1-dioxide	*L*-α-methyl-3,4-dihydroxyphenylalanine
6-methoxy-7-sulphamoyl-1,2,4-benzothiadiazine-1,1-dioxide	*L*-α-methyl-3,4-dihydroxyphenylalanine
6-chloro-3-methyl-7-sulphamoyl-1,2,4-benzothiadiazine-1,1-dioxide	*DL*-α-methyl-3,4-dihydroxyphenylalanine
Sodium salt of 6-chloro-7-sulphamoyl-1,2,4-benzothiadiazine-1,1-dioxide	*L*-α-methyl-3,4-dihydroxyphenylalanine

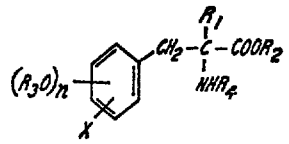
When, in any of the mixtures shown above, any of the indicated phenylalanine compounds is replaced by one of the following phenylalanine compounds, proportions being modified when necessary to allow for the relative activities of the compounds, there is obtained a new mixture also within the scope of this invention:

DL - α - ethyl - β - (3,4 - dihydroxyphenyl)alanine
DL - α - propyl - β - (3,4 - dihydroxyphenyl)alanine
DL - α - butyl - β - (3,4 - dihydroxyphenyl)alanine
DL - α - methyl - β - (2,3 - dihydroxyphenyl)alanine
DL - α - ethyl - β - (2,3 - dihydroxyphenyl)alanine
DL - α - methyl - β - (3,5 - dihydroxyphenyl)alanine
DL - α - methyl - β - (3,4,5 - trihydroxyphenyl)alanine
DL - α - methyl - β - (2,4,5 - dihydroxyphenyl)alanine
DL - α - methyl - β - (2,3,5 - trihydroxyphenyl)alanine
DL - α - methyl - β - (2,3,4 - trihydroxyphenyl)alanine
DL - α - methyl - *p* - chloro - *m* - tyrosine
DL - α - methyl - *p* - methyl - *m* - tyrosine
DL - α - methyl - *p* - fluoro - *m* - tyrosine
DL - α - methyl - *p* - trifluoromethyl - *m*-tyrosine
DL - α - methyl - β - (3,4 - diacetoxyphenyl)alanine
DL - N - acetyl - α - methyl - β - (3,4-diacetoxyphenyl)alanine
DL - N - formyl - α - methyl - β - (3,4-diformyloxyphenyl)alanine
L - α - methyl - β - (3,4,5 - trihydroxyphenyl)alanine
L - α - methyl - β - (3,5 - dihydroxyphenyl)alanine
L - α - methyl - *p* - chloro - *m* - tyrosine
L - α - methyl - *p* - trifluoromethyl - *m*-tyrosine
L - α - methyl - β - (3,4 - diacetoxyphenyl)alanine.

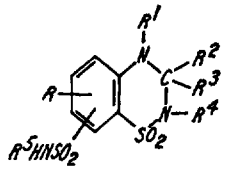
Although orally administrable pharmaceutical compositions have been particularly described, it is to be understood that liquid compositions suitable for injection, particularly intraperitoneally, can also be prepared.

WHAT WE CLAIM IS:—

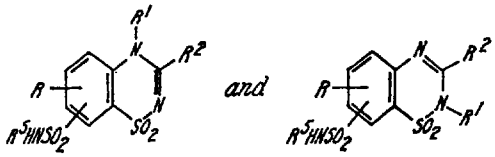
1. A hypotensive pharmaceutical composition comprising a mixture of 50—500 parts by weight of a first compound having the formula:



in which R_1 is a C_{1-5} alkyl group, R_2 is a hydrogen atom or alkyl group, each of R_3 and R_4 is a hydrogen atom or C_{1-6} alkanoyl group, X is a hydrogen or halogen atom or an alkyl or trifluoromethyl group, X being in a position *para* to the amino acid side chain when it is other than hydrogen, and *n* is a positive whole number less than 4, the compound being a racemic mixture or having the *L* absolute spatial configuration at the α-carbon atom, or salt of such a compound; with a second compound selected from sulphamoyl - 3,4 - dihydro - 1,2,4 - benzothiadiazine-1,1-dioxide compounds having the general formula:



or alkali metal salts of such compounds, in which R is a hydrogen or halogen atom or a C_{1-5} alkyl, C_{1-5} alkoxy, nitro, trihalomethyl or amino radical; R^1 is a hydrogen atom or a C_{1-5} alkyl radical; R^2 is a hydrogen atom or an alkyl, phenyl, halophenyl, benzyl or halobenzyl radical; R^3 is a hydrogen atom or a C_{1-5} alkyl or halogen-substituted C_{1-5} alkyl radical; or R^2 and R^3 are alkyl groups joined so as to form a cycloaliphatic ring; and each of R^4 and R^5 is a hydrogen atom or a C_{1-5} alkyl or C_{1-5} hydroxy-substituted alkyl radical; and sulphamoyl - 1,2,4 - benzothiadiazine-1,1-dioxide compounds having the general formula:



in which R, R^1, R^2 and R^3 are as defined for the formula of the sulphamoyl-3,4-dihydro-1,2,4 - benzothiadiazine - 1,1 - dioxide compounds, the sulphamoyl - 1,2,4 - benzothiadiazine-1,1-dioxide compounds being present in an amount of 100—1000 parts by weight and the sulphamoyl-3,4-dihydro-1,2,4-benzothiadiazine-1,1-dioxide compounds being present in an amount of 10—100 parts by weight.

2. A composition as claimed in Claim 1, in which the first compound is α-methyl-3,4-dihydroxyphenylalanine and the second compound is 6 - chloro - 7 - sulphamoyl - 3,4-dihydro - 1,2,4 - benzothiadiazine - 1,1 - dioxide.

3. A composition as claimed in Claim 1, in which the first compound is *L*-α-methyl-3,4-dihydroxyphenylalanine.

4. A composition as claimed in Claim 1, in which the first compound is *L*-α-methyl-3,4-dihydroxyphenylalanine and the second compound is 6 - chloro - 7 - sulphamoyl-1,2,4-benzothiadiazine-1,1-dioxide.

5. A composition as claimed in Claim 1, in which the first compound is α-methyl-metatyrosine and the second compound is 6-chloro - 7 - sulphamoyl - 3,4 - dihydro - 1,2,4-benzothiadiazine-1,1-dioxide.

6. A composition as claimed in Claim 1, in which the first compound is α-methyl-metatyrosine and the second compound is 6-chloro-7 - sulphamoyl - 1,2,4 - benzothiadiazine-1,1-dioxide.

7. A composition as claimed in any preceding claim, in unit dosage form.

8. A composition as claimed in any preceding claim, in the form of a capsule or tablet.

9. A composition as claimed in Claim 1, substantially as hereinbefore described with reference to the foregoing Examples.

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