

[54] **NOVEL METHOD FOR LOWERING BLOOD PRESSURE IN MAMMALS**

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[63] Continuation-in-part of Ser. No. 151,155, June 8, 1971, abandoned.

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[58] Field of Search **424/250**

[56]

References Cited

UNITED STATES PATENTS

3,475,431 10/1969 Bachmann et al. 260/250

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[57]

ABSTRACT

This disclosure describes a method of lowering blood pressure in mammals by the administration of compositions containing as the active component certain 6-(substituted-phenyl)-5-methyl-4,5-dihydro-3(2H)-pyridazinones.

4 Claims, No Drawings

NOVEL METHOD FOR LOWERING BLOOD PRESSURE IN MAMMALS

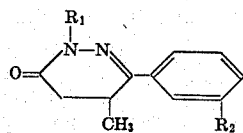
CROSS REFERENCE TO RELATED APPLICATION

This application is a continuation-in-part of my co-pending application Ser. No. 151,155, filed June 8, 1971, now abandoned.

BRIEF SUMMARY OF THE INVENTION

This invention relates to new compositions of matter for lowering blood pressure. More particularly, it relates to therapeutic compositions containing certain 6-(substituted-phenyl)-5-methyl-4,5-dihydro-3(2H)-pyridazinones which operate to reduce blood pressure in mammals. The invention includes the new compositions of matter and methods of lowering blood pressure therewith.

The invention is based upon the discovery that certain 6-(substituted-phenyl)-5-methyl-4,5-dihydro-3(2H)-pyridazinones are potent hypotensive agents. The 6-(substituted-phenyl)-5-methyl-4,5-dihydro-3(2H)-pyridazinones of the present invention may be represented by the following general formula:



wherein R₁ is hydrogen or methyl and R₂ is nitro, amino, or lower alkanoylamino. Suitable lower alkanoylamino groups contemplated by the present invention are those having up to four carbon atoms such as formylamino, acetylamino, propionylamino, n-butylamino and isobutylamino. The novel compounds of the present invention wherein R₂ is amino are organic bases and thus are capable of forming acid-addition salts with a variety of non-toxic organic and inorganic salt-forming reagents. Thus, acid-addition salts, formed by admixture of the organic free base with an acid, suitably in a neutral solvent, are formed with such acids as sulfuric, phosphoric, hydrochloric, hydrobromic, sulfamic, citric, lactic, malic, succinic, tartaric, acetic, benzoic, gluconic, ascorbic, and related acids. For purposes of this invention these free bases are equivalent to their non-toxic acid-addition salts.

DETAILED DESCRIPTION OF THE INVENTION

The 6-(substituted-phenyl)-5-methyl-4,5-dihydro-3(2H)-pyridazinones of the present invention may be administered either orally or parenterally. The amount of a single dose or of a daily dose to be given will vary but should be such as to give a proportionate dosage of from about 1 mg. to about 15 mg. per kilogram of body weight per day. Thus, such dosage units are employed that a total of from about 50 mg. to about 1.0 g. for a subject of about 70 kg. body weight are administered in a 24 hour period. This dosage regimen may be adjusted to provide the optimum therapeutic response, for example, several doses of 25-250 mg. may be administered daily or the dose may be proportionately re-

duced as indicated by the exigencies of the therapeutic situation.

The 6-(substituted-phenyl)-5-methyl-4,5-dihydro-3(2H)-pyridazinones may be orally administered, for example, with an inert diluent or with an assimilable edible carrier, or they may be enclosed in hard or soft shell gelatin capsules, or they may be compressed into tablets, or they may be incorporated directly with the food of the diet. For oral therapeutic administration, the active compounds of this invention may be incorporated with excipients and used in the form of tablets, troches, capsules, elixirs, suspensions, syrups, wafers, and the like. Such compositions and preparations should contain at least 0.1 percent of active compound. The percentage in the composition and preparations may, of course, be varied and may conveniently be between about 5 percent to about 75 percent or more of the weight of the unit. The amount of active compound in such therapeutically useful compositions or preparations is such that a suitable dosage will be obtained. Preferred compositions or preparations according to the present invention are prepared so that an oral dosage unit form contains between about 25 and 250 milligrams of active compound.

The tablets, troches, pills, capsules and the like may also contain the following: a binder such as gum tragacanth, acacia, corn starch or gelatin; an excipient such as dicalcium phosphate; a disintegrating agent such as corn starch, potato starch, alginic acid and the like; a lubricant such as magnesium stearate; and a sweetening agent such as sucrose, lactose, or saccharin may be added or a flavoring agent such as peppermint, oil of wintergreen, or cherry flavoring. When the dosage unit form is a capsule, it may contain in addition to materials of the above type a liquid carrier such as a fatty oil. Various other materials may be present as coatings or to otherwise modify the physical form of the dosage unit, for instance, tablets, pills or capsules may be coated with shellac, sugar, or both. A syrup or elixir may contain the active compounds, sucrose as a sweetening agent, methyl and propyl parabens as preservatives, a dye and a flavoring such as cherry or orange flavor. Of course, any material used in preparing any dosage unit form should be pharmaceutically pure and substantially non-toxic in the amounts employed.

Compositions having the desired clarity, stability, and adaptability for parenteral use are obtained by dissolving from 0.10 percent to 10.0 percent by weight of a 6-(substituted-phenyl)-5-methyl-4,5-dihydro-3(2H)-pyridazinone in a vehicle consisting of a mixture of non-volatile, normally liquid polyethylene glycols which are soluble in both water and organic liquids and which have molecular weights of from about 200 to about 1,500. Such mixtures of polyethylene glycols are commercially available and are usually obtained by condensing glycol with ethylene oxide. Although the amount of 6-(substituted-phenyl)-5-methyl-4,5-dihydro-3(2H)-pyridazinone dissolved in the above vehicle may vary from 0.10 percent to 10.0 percent by weight, it is preferred that the amount employed be from about 3.0 percent to about 9.0 percent by weight. Although various mixtures of the aforementioned nonvolatile polyethylene glycols may be employed, it is preferred to use a mixture of non-volatile polyethylene glycols having an average molecular weight of about 400. Such a mixture is usually referred to as polyethylene glycol 400. A preferred embodiment comprises a clear solu-

tion of from about 3.0 percent to about 9.0 percent by weight of the 6-(substituted-phenyl)-5-methyl-4,5-dihydro-3(2H)-pyridazinone dissolved in an aqueous solution of polyethylene glycol 400. In addition to the 6-(substituted-phenyl)-5-methyl-4,5-dihydro-3(2H)-pyridazinone, the parenteral solutions may also contain various preservatives which may be used to prevent bacterial and fungal contamination or chemical degradation.

The novel compounds of the present invention possess an asymmetric carbon atom at the 5-position and hence may exist in more than one stereoisomeric form. It is to be understood that the present invention includes within its scope all such stereoisomeric forms.

The following examples illustrate the preparation and hypotensive effect of the novel compositions of the present invention and the method of administering them.

EXAMPLE 1

Preparation of 6-(m-nitrophenyl)-5-methyl-4,5-dihydro-3(2H)-pyridazinone

3-Benzoylbutyric acid [Lutz et al., J.A.C.S. 75, 5039 (1953)] was dissolved in 20 ml. of conc. nitric acid, cooled, and 20 ml. of conc. sulfuric acid was added over 30 min. with stirring. The mixture was then stirred at room temperature for 1.5 hours, and then poured onto ice. The resulting gum was extracted with chloroform which was washed with saturated salt solution, then dried (MgSO₄). Evaporation of the chloroform gave an amber oil which resisted crystallization.

The above oil was refluxed for one hour in 20 ml. of ethanol containing 1.0 ml. of hydrazine hydrate, treated with Norit, and filtered. The filtrate deposited crystals of 6-(m-nitrophenyl)-5-methyl-4,5-dihydro-3(2H)-pyridazinone; m.p. 189°-192° C. The product was recrystallized from ethanol to afford light yellow crystals; m.p. 191°-194° C.

EXAMPLE 2

Preparation of 6-(m-aminophenyl)-5-methyl-4,5-dihydro-3(2H)-pyridazinone

A mixture of 1.2 g. of 6-(m-nitrophenyl)-5-methyl-4,5-dihydro-3(2H)-pyridazinone, 0.25 g. of 10 percent palladium on carbon, 20 ml. of ethanol, and 10 ml. of cyclohexene was refluxed for 18 hours, filtered, and evaporated to give an oil which crystallized. Recrystallization from ethyl acetate-hexane, followed by ethanol, afforded the 6-(m-aminophenyl)-5-methyl-4,5-dihydro-3(2H)-pyridazinone; m.p. 143°-145° C.

EXAMPLE 3

Preparation of 6-(m-formamidophenyl)-5-methyl-4,5-dihydro-3(2H)-pyridazinone

A mixture of 10 g. of 6-(m-aminophenyl)-5-methyl-4,5-dihydro-3(2H)-pyridazinone in 100 ml. of toluene containing 10 ml. of formic acid is refluxed for one hour while removing water azeotropically in a Dean-Stark trap. Evaporation of the solvent in vacuo affords the 6-(m-formamidophenyl)-5-methyl-4,5-dihydro-3(2H)-pyridazinone.

EXAMPLE 4

Preparation of 6-(m-acetamidophenyl)-5-methyl-4,5-dihydro-3(2H)-pyridazinone

A mixture of 0.25 g. of 6-(m-aminophenyl)-5-methyl-4,5-dihydro-3(2H)-pyridazinone in 1.0 ml. of acetic anhydride was heated on a steam bath for 5 minutes. White crystals of the 6-(m-acetamidophenyl)-5-methyl-4,5-dihydro-3(2H)-pyridazinone, m.p. 216°-219° C., were obtained upon cooling and filtration.

EXAMPLE 5

Preparation of 6-(m-propionamidophenyl)-5-methyl-4,5-dihydro-3(2H)-pyridazinone

By replacing the acetic anhydride employed in Example 4 with an equimolecular quantity of propionic anhydride and following substantially the same procedure described in Example 4, there is obtained the 6-(m-propionamidophenyl)-5-methyl-4,5-dihydro-3(2H)-pyridazinone.

EXAMPLE 6

Preparation of 6-[m-(n-butyramido)phenyl]-5-methyl-4,5-dihydro-3(2H)-pyridazinone

The procedure of Example 4 is repeated, substituting an equimolecular amount of n-butyric anhydride for the acetic anhydride employed in that example. There is thus obtained the 6-[m-(n-butyramido)phenyl]-5-methyl-4,5-dihydro-3(2H)-pyridazinone.

EXAMPLE 7

Preparation of 6-[m-(iso-butyramido)phenyl]-5-methyl-4,5-dihydro-3(2H)-pyridazinone

In place of the acetic anhydride of Example 4 there is employed an equimolecular quantity of isobutyric anhydride whereby the 6-[m-(iso-butyramido)phenyl]-5-methyl-4,5-dihydro-3(2H)-pyridazinone is obtained in equally good yield.

EXAMPLE 8

Hypotensive activity of 6-(substituted-phenyl)-5-methyl-4,5-dihydro-3(2H)-pyridazinones in normotensive rats

Conscious male albino Sherman strain rats were fastened to rat boards in a supine position by means of canvas vests and limb ties. The femoral areas were anesthetized by subcutaneous infiltration of lidocaine. The left or right common iliac arteries were exposed and clamped off proximally by an artery clamp and distally with thread. Incisions were made near the tie and short nylon catheters were inserted and tied in place. The other end of the catheters were fitted with 24 gauge hubless needles attached to thick-walled polyethylene tubes. The 6-(substituted-phenyl)-5-methyl-4,5-dihydro-3(2H)-pyridazinones were administered to the animals orally by stomach tube. The compounds were suspended in 2 percent aqueous starch solution, 1 ml. of which gave, per 100 g. of body weight, the desired dose. Volume was usually 2.5 ml. since the rats average 250 g. in weight. Mean arterial blood pressure was measured 4 hours after administration of the compounds. Comparisons were then made to the mean con-

trol pressure of 121 ± 7 mm. of mercury. Blood pressure measurements were made with four Statham P23 Db strain gauges attached to a Sanborn Polyviso Recorder. The recorder is equipped with four strain gauge preamplifiers with averaging circuits for measuring mean arterial pressure. Table I below summarizes the effects on mean blood pressure (MBP) of typical 6-(substituted-phenyl)-5-methyl-4,5-dihydro-3(2H)-pyridazinones of the present invention, 4 hours after administration to a series of rats. Under the conditions of this experiment, the 6-(substituted-phenyl)-5-methyl-4,5-dihydro-3(2H)-pyridazinones of the present invention demonstrate hypotensive activity.

TABLE I

Compound	Oral Dose mg./kg. of body weight	No. of rats	MBP mm. Hg
Controls		50	121 ± 7
6-(m-nitrophenyl)-5-methyl-4,5-dihydro-3(2H)-pyridazinone	100	3	79
6-(m-aminophenyl)-5-methyl-4,5-dihydro-3(2H)-pyridazinone	100	2	86
6-(m-acetamidophenyl)-5-methyl-4,5-dihydro-3(2H)-pyridazinone	100	2	82
6-(m-nitrophenyl)-2,5-dimethyl-4,5-dihydro-3(2H)-pyridazinone	100	2	66

EXAMPLE 9

Preparation of Tablet Formulation

Ingredient	Per Tablet (g.)	For 10,000 Tablets (g.)
Active ingredient: 6-(m-nitrophenyl)-5-methyl-4,5-dihydro-3(2H)-pyridazinone	0.0500	500
Lactose	0.0800	800
Corn Starch (for mix)	0.0150	150
Corn Starch (for paste)	0.0100	100
	0.1550	1,550
Magnesium Stearate (1%)	0.0013	12.5
	0.1563	1,562.5

The active ingredient, lactose and corn starch (for mix) are blended together. The corn starch (for paste) is suspended in 800 milliliters of water and heated with stirring, to form a paste. This paste is then used to granulate the mixed powders. Additional water is used, if necessary. The wet granules are passed through a No. 8 hand screen and dried at 120°F . The dry granules are then passed through a No. 16 screen. The mixture is lubricated with 1 percent magnesium stearate and compressed into tablets in a suitable tableting machine.

EXAMPLE 10

Preparation of Oral Syrup Formulation

Ingredient	Amount
Active ingredient: 6-(m-acetamidophenyl)-2,5-dimethyl-4,5-dihydro-3(2H)-pyridazinone	1000 mg.
Sorbitol solution (70% N.F.)	40 ml.
Sodium benzoate	150 mg.
Sucaryl	90 mg.
Saccharin	10 mg.
Red dye (F.D. & C. No. 2)	10 mg.

EXAMPLE 10-Continued

Preparation of Oral Syrup Formulation

Ingredient	Amount
Cherry flavor	50 mg.
Distilled water, q.s. ad	100 ml.

The sorbitol solution is added to 40 ml. of distilled water and the active ingredient is suspended therein. The sucaryl, saccharin, sodium benzoate, flavor and dye are added and dissolved in the above solution. The volume is adjusted to 100 ml. with distilled water.

Other ingredients may replace those listed in the above formulation. For example, a suspending agent such as bentonite magma, tragacanth, carboxymethylcellulose or methylcellulose may be used. Phosphates, citrates or tartrates may be added as buffers. Preservatives may include the parabens, sorbic acid and the like and other flavors and dyes may be used in place of those listed above.

EXAMPLE 11

Preparation of Parenteral Formulation

In a solution of 119 ml. of propylene glycol and 30 ml. of distilled water was dissolved 8.5 g. of 6-(m-aminophenyl)-5-methyl-4,5-dihydro-3(2H)-pyridazinone hydrochloride, with stirring. After dissolution was complete, a solution of 850 mg. of sodium formaldehyde sulfoxylate in 3.0 ml. of distilled water was then added to the formulation. The pH of this solution was then adjusted to 7.0 with ethanolamine and the volume was made up to 170 ml. with distilled water. The formulation was filtered through a fine sintered glass filter, filled into 5.0 ml. ampoules each containing 2.0 ml., and sealed under nitrogen.

EXAMPLE 12

Preparation of 6-(m-formamidophenyl)-2,5-dimethyl-4,5-dihydro-3(2H)-pyridazinone

A mixture of 10 g. of 6-(m-aminophenyl)-2,5-dimethyl-4,5-dihydro-3(2H)-pyridazinone in 100 ml. of toluene containing 10 ml. of formic acid is refluxed for one hour while removing water azeotropically in a Dean-Stark trap. Evaporation of the solvent in vacuo affords the 6-(m-formamidophenyl)-2,5-dimethyl-4,5-dihydro-3(2H)-pyridazinone.

EXAMPLE 13

Preparation of 6-(m-acetamidophenyl)-2,5-dimethyl-4,5-dihydro-3(2H)-pyridazinone

A mixture of 0.25 g. of 6-(m-aminophenyl)-2,5-dimethyl-4,5-dihydro-3(2H)-pyridazinone in 1.0 ml. of acetic anhydride is heated on a steam bath for 5 minutes. White crystals of the 6-(m-acetamidophenyl)-2,5-dimethyl-4,5-dihydro-3(2H)-pyridazinone are obtained upon cooling and filtration.

EXAMPLE 14

Preparation of 6-(m-propionamidophenyl)-2,5-dimethyl-4,5-dihydro-3(2H)-pyridazinone

By replacing the acetic anhydride employed in Example 13 with an equimolecular quantity of propionic anhydride and following substantially the same procedure

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described in Example 13, there is obtained the 6-(m-propionamidophenyl)-2,5-dimethyl-4,5-dihydro-3(2H)-pyridazinone.

EXAMPLE 15

Preparation of 6-[m-(n-butyramido)phenyl]-2,5-dimethyl-4,5-dihydro-3(2H)-pyridazinone

The procedure of Example 13 is repeated, substituting an equimolecular amount of n-butyric anhydride for the acetic anhydride employed in that example. There is thus obtained the 6-[m-(n-butyramido)phenyl]-2,5-dimethyl-4,5-dihydro-3(2H)-pyridazinone.

EXAMPLE 16

Preparation of 6-[m-(iso-butyramido)phenyl]-2,5-dimethyl-4,5-dihydro-3(2H)-pyridazinone

In place of the acetic anhydride of Example 13 there is employed an equimolecular quantity of isobutyric anhydride whereby the 6-[m-(iso-butyramido)phenyl]-2,5-dimethyl-4,5-dihydro-3(2H)-pyridazinone is obtained in equally good yield.

EXAMPLE 17

Preparation of 6-(m-nitrophenyl)-2,5-dimethyl-4,5-dihydro-3(2H)-pyridazinone

A solution of 4.47 g. of 3-(m-nitrobenzoyl)butyric acid and 2.4 ml. of methylhydrazine in 20 ml. of ethanol is heated at reflux temperature for 3 hours. The solution is cooled to give a solid which is recrystallized from dilute methanol to furnish 3.23 g. of white crystals, m.p. 94°-96° C.

EXAMPLE 18

Preparation of 6-(m-aminophenyl)-2,5-dimethyl-4,5-dihydro-3(2H)-pyridazinone

A mixture of 2.56 g. of 4,5-dihydro-2,5-dimethyl-6-

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(m-nitrophenyl)-3(2H)-pyridazinone and 250 mg. of 10 percent palladium-on-carbon in 50 ml. of ethanol is shaken under hydrogen in a Parr apparatus until the pressure is constant (13 minutes). The mixture is filtered and the filtrate is evaporated to give an oil that crystallizes from ether-petroleum ether to give 2.10 g. of crystals, m.p. 120°-122° C.

I claim:

1. A therapeutic composition in dosage unit form useful for lowering blood pressure in mammals comprising from about 50 mg. to about 1.0 gram per daily dosage unit of 6-(m-nitrophenyl)-5-methyl-4,5-dihydro-3(2H)-pyridazinone, and a pharmaceutical carrier.

2. A therapeutic composition in dosage unit form useful for lowering blood pressure in mammals comprising from about 50 mg. to about 1.0 gram per daily dosage unit of 6-(m-nitrophenyl)-2,5-dimethyl-4,5-dihydro-3(2H)-pyridazinone, and a pharmaceutical carrier.

3. The method of lowering blood pressure in a mammal which comprises administering internally to said mammal an effective amount of 6-(m-nitrophenyl)-5-methyl-4,5-dihydro-3(2H)-pyridazinone, in association with a pharmaceutical carrier to provide a daily dosage of from about 1 mg. to about 15 mg. per kilogram of body weight of said mammal.

4. The method of lowering blood pressure in a mammal which comprises administering internally to said mammal an effective amount of 6-(m-nitrophenyl)-2,5-dimethyl-4,5-dihydro-3(2H)-pyridazinone, in association with a pharmaceutical carrier to provide a daily dosage of from about 1 mg. to about 15 mg. per kilogram of body weight of said mammal.

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