United States Patent Office 3,441,648 Patented Apr. 29, 1969

3,441,648

COMPOSITIONS AND METHODS FOR LOWERING BLOOD PRESSURE WITH 1,4-DIHYDROPYRIDINES

Bernard Loev, Broomall, Pa., and Ralph E. Tedeschi, Cherry Hill, N.J., assignors to Smith Kline & French Laboratories, Philadelphia, Pa., a corporation of Pennsylvania

No Drawing. Filed Feb. 7, 1967, Ser. No. 614,393
Int. Cl. A61k 27/00; C07d 29/40
U.S. Cl. 424—263 10 Claims

ABSTRACT OF THE DISCLOSURE

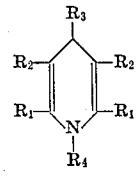
Hypotensive compositions containing 4-aryl, 4-aralkyl, 4-aralkenyl or 4-heteroaryl-1,4-dihydropyridines and methods of lowering blood pressure. 1,4-dihydro-4-(2-trifluoromethylphenyl)pyridines which have hypotensive activity are prepared by reacting a 2-trifluoromethylbenzaldehyde with two equivalents of a keto compound and ammonia, with two equivalents of an unsaturated amino compound or with one equivalent of a keto compound and one equivalent of an unsaturated amino compound.

This invention relates to new hypotensive compositions containing 1,4-dihydropyridines and to methods of lowering blood pressure by administering these compositions. In addition, this invention relates to 1,4-dihydro-4-(2-trifluoromethylphenyl)pyridines which are new compounds having hypotensive activity.

Some of the 1,4-dihydropyridine compounds of the hypotensive compositions of this invention are known to the art, for example, as reported in Beilstein, Handbuch der Organischen Chemie, 27: 327, III, 389; 22: 172; 27: I, 383 and Hinkel et al., J. Chem. Soc., 750 (1929), and 1835 (1931). The present invention resides in the finding of hypotensive activity using a series of 4-aryl, 4-aralkyl, 4-aralkenyl or 4-heteroaryl-1,4-dihydropyridines and in certain new 1,4-dihydro-4-(2-trifluoromethylphenyl)pyridine compounds which have hypotensive activity. The nature of the 4-substituent on the 1,4-dihydropyridines is apparently not critical as compounds having a variety of 4-substituents chosen from aryl, aralkyl, aralkenyl or heteroaryl groups have hypotensive activity. In the 4-aryl series, compounds having substituents on the ortho positions of the aryl nuclei have particularly advantageous therapeutic properties as will be noted hereinafter.

The hypotensive compositions of this invention, in dosage unit form, contain an effective but nontoxic amount of a 1,4-dihydropyridine of the formula:

FORMULA I



in which:

R_1 is lower alkyl having 1–6 carbon atoms;
R_2 is COOR' or COR";
R_3 is phenyl, halophenyl, dihalophenyl, lower alkylphenyl, di-lower alkylphenyl, tri-lower alkylphenyl, lower alkoxyphenyl, di-lower alkoxyphenyl, tri-lower alkoxyphenyl, trifluoromethylphenyl, benzyl, styryl, furyl, thienyl, pyridyl, or pyrrolyl, said lower alkyl and lower alkoxy groups having 1–4 carbon atoms;

R_4 is hydrogen or lower alkyl having 1–6 carbon atoms and
R' and R" are lower alkyl having 1–6 carbon atoms.

Preferred hypotensive compositions of this invention which have advantageous oral activity contain, as the active ingredient, a 1,4-dihydropyridine of Formula I in which R_1 is methyl; R_2 is carbomethoxy or carbethoxy; R_3 is chlorophenyl, preferably o-chlorophenyl, tolyl, preferably o-tolyl, trimethylphenyl, preferably 2,4,6-trimethylphenyl, trifluoromethylphenyl, preferably o-trifluoromethylphenyl, furyl, preferably 2-furyl, pyridyl, preferably 2- or 3-pyridyl, or pyrrolyl, preferably 2-pyrrolyl; and R_4 is hydrogen.

A particularly advantageous composition of this invention consists of, in a dosage unit, a pharmaceutical carrier and 3,5-dicarbethoxy-1,4-dihydro-2,6-dimethyl-4-(2-trifluoromethylphenyl)pyridine.

The compositions of this invention contain a 1,4-dihydropyridine of Formula I in an amount of from about 5 mg. to about 500 mg., preferably from about 25 mg. to about 250 mg., per dosage unit.

One skilled in the art will recognize that in determining the amounts of the active ingredient in the claimed dosage unit compositions, the activity of the chemical ingredient as well as the size of the host animal must be considered. On a mg./kg. basis the amount of the active ingredient in the claimed compositions will be from about 0.1 mg./kg. to about 10 mg./kg., preferably from about 0.5 mg./kg. to about 5 mg./kg.

Generally, the active ingredients in dosage unit form will be combined with a pharmaceutical carrier. The pharmaceutical carrier may be, for example, either a solid or a liquid. Exemplary of solid carriers are lactose, magnesium stearate, terra alba, sucrose, talc, stearic acid, gelatin, agar, pectin or acacia. Exemplary of liquid carriers are peanut oil, olive oil or sesame oil. Similarly, the carrier or diluent may include a time delay material such as glyceryl monostearate or glyceryl distearate alone or with a wax.

A wide vriety of pharmaceutical forms can be employed. Thus, if a solid carrier is used, the preparation can be tabletted, placed in a hard gelatin capsule or in the form of a troche or lozenge. The amount of solid carrier will vary widely but preferably will be from about 25 mg. to about 1 gm. If a liquid carrier is used, the preparation may be in the form of a soft gelatin capsule, a liquid suspension, or a sterile suspension or solution for parenteral use.

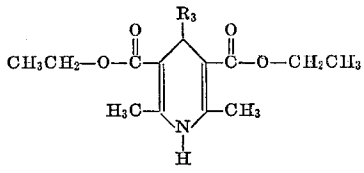
A method of lowering blood pressure in accordance with this invention comprises administering internally to animals an effective but nontoxic amount of a 1,4-dihydropyridine of Formula I. The active ingredient will preferably be administered in dosage unit form as described above. The route of administration will be orally and/or parenterally. Advantageously, the active ingredient will be administered in a total daily dosage of from about 5 mg. to about 2000 mg., preferably from about 50 mg. to about 1000 mg. When the administration is carried out as described above, hypotensive activity is produced.

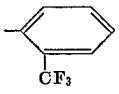
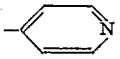
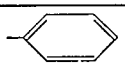
The dosage units or dosage ranges presented herein are designed for a hypertensive subject of about 50 kg.

The hypotensive activity of the 1,4-dihydropyridines of Formula I is demonstrated by standard procedures, that is, by intravenous administration to anesthetized dogs or cats and, for compounds which are orally active, in particular the active ingredients of the preferred hypotensive compositions indicated hereabove, by oral administration to neurogenic, hypertensive dogs or to normotensive dogs.

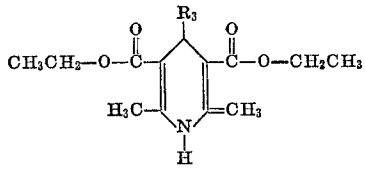
The following results were obtained by administering intravenously the following 1,4-dihydropyridines to dogs

anesthetized with pentobarbital and recording the blood pressure response:

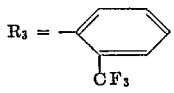


Compound	Dose (mg./kg.)	Blood Pressure Response (mm. Hg)	Duration (minutes)
R_3 = 	0.05 0.1	−65 −98	>60 >60
R_3 = 	0.5 1.0 5.0	−76 −84 −109	5 7 >20
R_3 = 	0.1 0.5 1.0	−55 −50 −72	3 4 >4
Using Cats Anesthetized With Ether-chloralose			
R_3 = 	0.5	−66	8

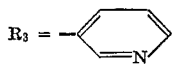
Administering the following 1,4-dihydropyridines orally to neurogenic, hypertensive dogs produced significant lowering of blood pressure at the doses indicated:



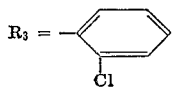
Compound

R_3 = 

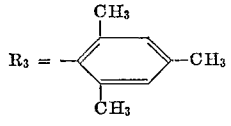
(Dose: 10 mg./kg.)

R_3 = 

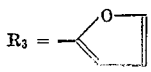
(Dose: 5, 10 and 20 mg./kg.)

R_3 = 

Dose: 2.5 b.i.d., mg./kg.)

R_3 = 

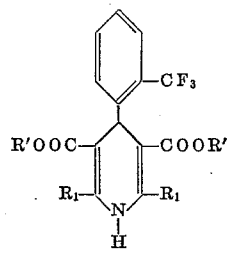
(Dose: 20 and 30 mg./kg.)

R_3 = 

(Dose: 5 and 10 mg./kg.)

The new 1,4-dihydro-4-(2-trifluoromethylphenyl)-pyridines which are also objects of this invention are represented by the following formula:

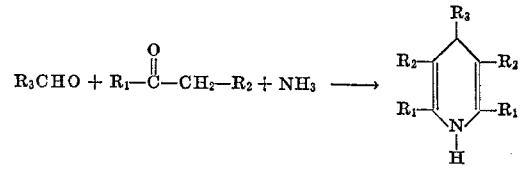
FORMULA II

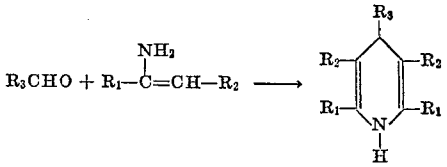


in which R_1 and R' are lower alkyl having 1–6 carbon atoms.

A preferred compound of Formula II is the compound in which R_1 is methyl and R' is ethyl, i.e. 3,5-dicarbethoxy - 1,4 - dihydro - 2,6 - dimethyl-4-(2-trifluoromethylphenyl)pyridine, which has particularly advantageous activity, that is, potent hypotensive activity of relatively long duration on oral administration.

1,4-dihydropyridines of Formula I in which R_4 is hydrogen are prepared by methods generally known to the art such as the following:

I. 

II. 

The terms R_1, R_2 and R_3 are as defined above.

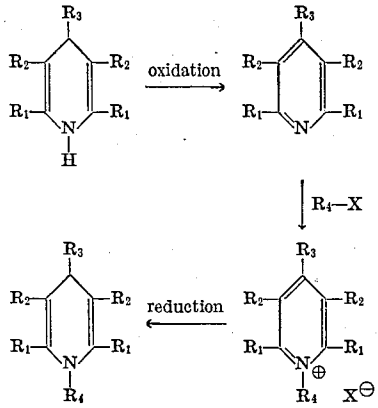
According to procedure I, one molar equivalent of an aldehyde is reacted with two molar equivalents of the keto compound and an excess of ammonia. The reaction is preferably carried out in a solvent, such as a lower alkanol or dioxane, at elevated temperature, conveniently at reflux temperature, for about 1 to 4 hours.

According to procedure II, one molar equivalent of an aldehyde is reacted with two molar equivalents of the unsaturated amino compound. Preferably, the reaction is carried out in a solvent, such as a lower alkanol or dioxane, at elevated temperature, conveniently at reflux temperature.

Also, compounds of Formula I are prepared by reacting one molar equivalent of an aldehyde with one molar equivalent of the keto compound used in procedure I and one molar equilavent of the unsaturated amino compound used in procedure II. The reaction is carried out at elevated temperature.

Compounds of Formula I in which R_4 is lower alkyl

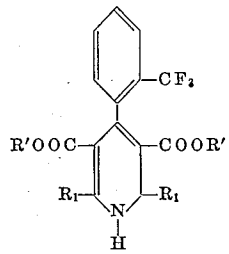
are prepared from the compounds in which R_4 is hydrogen by the following procedure:



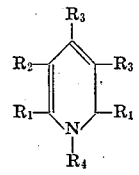
The terms R_1 to R_4 are as defined above and X is an anion.

In the above reaction, the oxidation of the dihydropyridine is carried out with an oxidizing agent such as a nitrous oxide, nitrous acid, hydroxylamine, hydrogen peroxide, oxygen, etc. The resulting pyridine compound is quaternized by using any suitable alkyl ester such as methyl iodide, ethyl sulfate, butyl methane sulfonate and the like. The resulting quaternary salt is reduced by catalytic hydrogenation or by using a chemical reducing agent such as sulfur dioxide or sodium hydrosulfite to give principally the 1,4-dihydropyridine or sodium borohydride to give principally the 1,2-dihydropyridine.

Although the 2-trifluoromethylphenyl-dihydropyridines of this invention and the dihydropyridines which are the active ingredients of the compositions are drawn as having the 1,4-dihydropyridine structure, the positions of the double bonds are not known with certainty in all instances and thus it is understood that some of these compounds may have the following 1,2-dihydro structures, respectively:



and



The terms R_1 to R_4 and R' are as defined above.

The following examples are not limiting but are illustrative of this invention.

Example 1

Twelve grams of the diethylacetal of o-trifluoromethylbenzaladehyde is mixed and refluxed with 50 ml. of 6 N hydrochloric acid for three hours under nitrogen. The mixture is cooled and the oil and aqueous layers are separated. The aqueous layer is washed with about 25 ml. of methylene chloride. To the combined oil and extract is added 12.6 g. of ethyl acetoacetate followed by 25 ml. of ethanol and 5.0 ml. of concentrated ammonium hydroxide. The resulting mixture is refluxed for 19 hours, then is chilled and poured onto about 500 ml. of ice water. Filtering and recrystallizing from isopropyl ether gives 3,5-dicarbethoxy - 1,4-dihydro-2,6-dimethyl-4-(2-trifluoromethylphenyl)pyridine.

Example 2

Twelve grams of the diethylacetal of m-trifluoromethylbenzaldehyde is mixed and refluxed with 50 ml. of 6 N hydrochloric acid for three hours under nitrogen. The mixture is then cooled and the oil and aqueous layers are separated. The aqueous layer is washed with methylene chloride. The oil layer and extract are combined and treated with 12.6 g. of ethyl acetoacetate followed by 25 ml. of ethanol and 45.0 ml. of concentrated ammonium hydroxide. The resulting mixture is heated at reflux for one hour, allowed to stand overnight at room temperature, then refluxed for two hours, cooled and poured into 500 ml. of ice water. Filtering and recrystallizing from isopropyl ether gives 3,5-dicarbethoxy-1,4-dihydro-2,6-dimethyl-4-(3-trifluoromethylphenyl)pyridine.

Example 3

A mixture of 20 g. of p-trifluoromethylbenzaldehyde oxime and 100 ml. of 20% sulfuric acid is heated for two hours on a steam bath. Extracting with ether, then removing the ether from the extract in vacuo gives p-trifluoromethylbenzaldehyde.

To 18.4 g. of p-trifluoromethylbenzaldehyde in 150 ml. of ethanol is added 27.6 g. of ethyl acetoacetate and 10 ml. of ammonium hydroxide. The resulting mixture is heated at reflux for five hours, then is poured into water. Methylene chloride is added. The organic layer is dried and concentrated. The resulting oil is dissolved in isopropyl ether. The resulting solution is cooled and filtered. The solid material is sublimed in vacuo to give 3,5-dicarbethoxy - 1,4-dihydro-2,6 - dimethyl - 4-(4-trifluoromethylphenyl)pyridine.

Example 4

A mixture of 17.5 g. of 2,6-dichlorobenzaldehyde, 26 g. of ethyl acetoacetate, 60 ml. of ethanol and 10 ml. of concentrated ammonium hydroxide is heated at reflux for 14 hours, then is poured into water. The gum which forms is filtered off and heated with petroleum ether. The petroleum ether layer is decanted and the resulting oil is crystallized from methylcyclohexane to give 3,5-dicarbethoxy-4-(2,4-dichlorophenyl)-1,4-dihydro - 2,6-dimethylpyridine.

Example 5

A mixture of 20 g. of 2,4,6-trimethylbenzaldehyde, 35.1 g. of ethyl acetoacetate, 80 ml. of ethanol and 13.5 ml. of ammonium hydroxide is heated at reflux for six hours, then poured into water. The resulting material which consists of two layers is heated to 150° C. at 0.3 mm. to remove volatile materials. The residue is heated with petroleum ether and the petroleum ether layer is removed. The remaining material is recrystallized from methylcyclohexane to give 3,5-dicarbethoxy-1,4-dihydro-2,6-dimethyl-4-(2,4,6-trimethylphenyl)pyridine.

Example 6

A mixture of 100 g. of t-butyl acetoacetate, 33.6 g. of benzaldehyde and 40 ml. of ammonium hydroxide is heated at reflux for 45 minutes, 20 ml. of ammonium hydroxide is added and the resulting mixture is refluxed for 30 minutes. The mixture is concentrated and methanol is added. The solution is cooled; the precipitate is filtered off and recrystallized from cyclohexane to give 3,5-di-t-butoxycarbonyl - 1,4 - dihydro - 2,6-dimethyl-4-phenylpyridine.

Example 7

Sodium nitrite (20 g.) is added portionwise with stirring to a mixture of 22 g. of 3,5-dicarbethoxy-1,4-dihydro-2,6-dimethyl-4-(2 - trifluoromethylphenyl)pyridine (prepared as in Example 1) in 250 ml. of acetic acid. The resulting mixture is heated until the evolution of nitrogen oxide fumes ceases, then is poured into 1.5 l. of water.

The oil which separates is extracted with ether. The extract is rinsed with dilute base and then with water, then dried and concentrated to give 3,5-dicarbethoxy-2,6-dimethyl-4-(2-trifluoromethylphenyl)pyridine.

A mixture of 10.0 g. of the above prepared pyridine and 7.6 g. of dimethyl sulfate is heated on a steam bath for 15 hours. The mixture is cooled, stirred with ether and filtered to give the corresponding N-methyl pyridinium sulfate.

Five grams of the above prepared quaternary salt in a concentrated aqueous solution is added to a solution of 12 g. of sodium hydrosulfite and 15 g. of sodium carbonate in 100 ml. of water. The mixture is stirred under nitrogen for two hours. The mixture is extracted with ether, washed with water, dried and concentrated. The residue is recrystallized from methanol to give 3,5-dicarbethoxy-1,4-dihydro-1,2,6-trimethyl-4-(2 - trifluoromethylphenyl)pyridine. Alternatively, dissolving 5 g. of the quaternary salt in 50 ml. of 40% ethanol, adding 5 g. of sodium carbonate and 1 g. of sodium borohydride gives a mixture containing 3,5-dicarbethoxy-1,4-dihydro-1,2,6-trimethyl-4-(2-trifluoromethylphenyl)pyridine and, principally, the corresponding 1,2-dihydro compound.

Similarly, using in place of dimethyl sulfate, 6.5 g. of ethyl bromide, 7.4 g. of n-propyl bromide or 8.2 g. of n-butyl bromide in the above procedure using sodium hydrosulfite to reduce the quaternary salt the following products, respectively, are obtained:

3,5-dicarbethoxy-1-ethyl-1,4-dihydro-2,6 - dimethyl-4-(2-trifluoromethylphenyl)pyridine,
3,5-dicarbethoxy-1,4-dihydro-2,6-dimethyl - 1-(n-propyl)-4-(2-trifluoromethylphenyl)pyridine and
1-(n-butyl)-3,5-dicarbethoxy-1,4-dihydro-2,6 - dimethyl-4-(2-trifluoromethylphenyl)pyridine.

Example 8

Ingredients:	Amounts, mg.
3,5-dicarbethoxy - 1,4 - dihydro-2,6-dimethyl-4-(2-trifluoromethylphenyl)pyridine	100
Sucrose	25
Starch	15
Talc	5
Stearic acid	3

The active ingredient is mixed with the sucrose and the resulting mixture is granulated with 10% gelatin solution. The wet granules are screened, dried and then mixed with the starch, talc and stearic acid, screen and compressed into a tablet.

A tablet prepared as described above is administered several times daily to a hypertensive subject.

Example 9

A tablet is made as described in Example 8 using, as the active ingredient, 3,5-dicarbethoxy-4-(2-chlorophenyl)-1,4-dihydro-2,6-dimethylpyridine.

Example 10

Ingredients:	Amounts, mg.
3,5-dicarbethoxy - 1,4 - dihydro-2,6-dimethyl-4-(2-pyrrolyl)pyridine	150
Lactose	75

The ingredients are mixed, screened and filled into a hard gelatin capsule.

A capsule, prepared as described above, is administered three times per day to a hypertensive subject.

Example 11

Ingredients:	Amounts, mg.
3,5-dicarbethoxy - 1,4 - dihydro-2,6-dimethyl-4-(3-pyridyl)pyridine	100
Lactose	150

The ingredients are screened, mixed and filled into a hard gelatin capsule.

Example 12

Ingredients:	Amounts, mg.
3,5-dicarbethoxy - 1,4 - dihydro-2,6-dimethyl-4-(4-pyridyl)pyridine	75
Lactose	100
Magnesium stearate	5

The ingredients are mixed, screened and filled into a hard gelatin capsule.

Example 13

Ingredients:	Amounts, mg.
3,5-dicarbethoxy-4-(2-furyl) - 1,4 - dihydro-2,6-dimethylpyridine	50
Lactose	150

The ingredients are screened, mixed and filled into a hard gelatin capsule.

Example 14

Ingredients:	
3,5-dicarbethoxy - 1,4 - dihydro - 2,6 - dimethyl-4-phenylpyridine	mg. 5
N,N-dimethylacetamide (50% aqueous solution)	ml. 2

The ingredients are sterilized, mixed to form a solution and filled into a sterile ampule.

Example 15

Ingredients:	
3,5-dicarbethoxy - 1,4 - dihydro - 2,6 - dimethyl-4-(2-thienyl)pyridine	mg. 5
N,N-dimethylacetamide (50% aqueous solution)	ml. 2

The ingredients are sterilized, mixed to form a solution and filled into a sterile ampule.

Example 16

Ingredients:	
3,5-dicarbethoxy - 1,4 - dihydro - 2,6 - dimethyl-4-styrylpyridine	mg. 20
N,N-dimethylacetamide (50% aqueous solution)	ml. 2

The ingredients are sterilized, mixed to form a solution and filled into a sterile ampule.

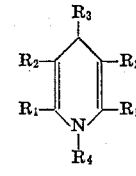
Example 17

Ingredients:	
4 - benzyl - 3,5 - dicarbethoxy - 1,4 - dihydro-2,6-dimethylpyridine	mg. 25
N,N-dimethylacetamide (50% aqueous solution)	ml. 2

The ingredients are sterilized, mixed to form a solution and filled into a sterile ampule.

What is claimed is:

1. A pharmaceutical dosage unit in the form of a tablet, capsule, troche, lozenge, liquid parenteral suspension or parenteral solution for internal administration to produce hypotensive activity comprising a pharmaceutical carrier and from about 5 mg. to about 500 mg. of a dihydropyridine of the formula:



in which:

R_1 is lower alkyl having 1–6 carbon atoms;

R_2 is COOR' or COR";

R_3 is phenyl, halophenyl, dihalophenyl, lower alkylphenyl, di-lower alkylphenyl, tri-lower alkylphenyl, lower alkoxyphenyl, di-lower alkoxyphenyl, tri-lower alkoxyphenyl, trifluoromethylphenyl, benzyl, styryl, furyl, thienyl, pyridyl or pyrrolyl, said lower alkyl and lower alkoxy groups having 1–4 carbon atoms;

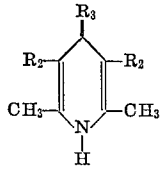
R_4 is hydrogen or lower alkyl having 1–6 carbon atoms; and

R′ and R″ are lower alkyl having 1–6 carbon atoms.

2. The pharamceutical dosage unit of claim **1** in which R_1 is methyl, R_2 is $COOCH_2CH_3$, R_3 is 2-trifluoromethyl and R_4 is hydrogen.

3. The pharmaceutical dosage unit of claim **1** in which R_1 is methyl, R_2 is $COOCH_2CH_3$, R_3 is 2-chlorophenyl and R_4 is hydrogen.

4. The pharmaceutical dosage unit of claim **1** in a solid form for oral administration in the form of a tablet, capsule, troche or lozenge to produce hypotensive activity comprising a pharmaceutical carrier and from about 5 mg. to about 500 mg. of a dihydropyridine of the formula:



in which:

R_2 is carbomethoxy or carbethoxy and

R_3 is chlorophenyl, tolyl, trimethylphenyl, trifluoromethylphenyl, furyl, pyridyl or pyrrolyl.

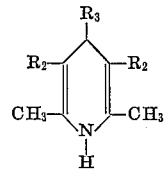
5. The pharmaceutical dosage unit of claim **2** in which the dihydropyridine is present in an amount of from about 25 to about 250 mg.

6. The method of lowering blood pressure in animals which comprises administering internally to animals a 1,4-dihydropyridine of the formula of claim **1** in a daily dosage of from about 5 mg. to about 2000 mg.

7. The method of claim **6** in which R_1 is methyl, R_2 is $COOCH_2CH_3$, R_3 is 2-trifluoromethylphenyl and R_4 is hydrogen.

8. The method of claim **6** in which R_1 is methyl, R_2 is $COOCH_2CH_3$, R_3 is 2-chlorophenyl and R_4 is hydrogen.

9. The method of claim **6** which comprises administering internally to animals a 1,4-dihydropyridine of the formula:



in which:

R_2 is carbomethoxy or carbethoxy and

R_3 is chlorophenyl, tolyl, trimethylphenyl, trifluoromethylphenyl, furyl, pyridyl or pyrrolyl in a daily dosage of from about 5 mg. to about 2000 mg.

10. The method of claim **9** in which the 1,4-dihydropyridine is administered orally.

References Cited

UNITED STATES PATENTS

3,221,017	11/1965	Biel	167—65 X
3,325,505	6/1967	Loev	167—65 X

ALBERT T. MEYERS, *Primary Examiner.*

S. FRIEDMAN, *Assistant Examiner.*

U.S. Cl. X.R.

260—295.5