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3,150,148

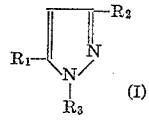
1,3,5-TRISUBSTITUTED PYRAZOLES

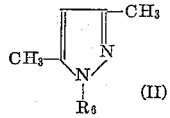
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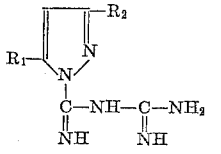
No Drawing. Filed June 5, 1961, Ser. No. 114,670
2 Claims. (Cl. 260—310)

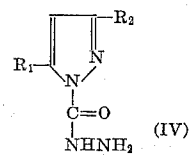
This invention relates to pyrazole derivatives and methods for their preparation and to therapeutic compositions containing such compounds and methods for their use.

The primary active ingredients of the novel compositions of this invention are represented by the formulas:

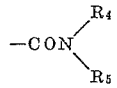

(I)


(II)


(III)


(IV)

wherein R_1 and R_2 are lower alkyls having 1 through 4 carbon atoms, R_3 is (1) —COOR in which R is hydrogen, lower alkyl having 1 through 7 carbon atoms, or alkali metal, or (2)



in which R_4 and R_5 are hydrogen, lower alkyl having 1 through 7 carbon atoms, or aryl, and R_6 is hydrogen or lower alkyl having 1 through 4 carbon atoms. Also included are the pharmaceutically acceptable acid addition salts of the foregoing basic compounds.

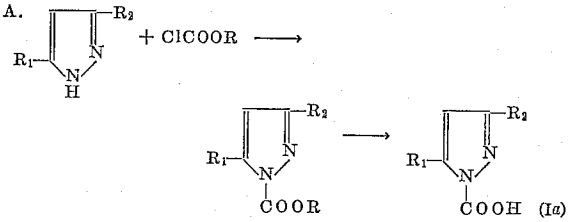
Representative compounds of those disclosed herein have been unexpectedly found to possess many times the hypoglycemic activity of tolbutamide, the most widely used oral antidiabetic in the world today. This pronounced activity, coupled with a low order of toxicity, makes the compositions incorporating such compounds outstandingly useful in reducing the blood sugar content in hyperglycemic subjects such as mammals, and in particular for administration by the preferred oral route or by injection in the management of human diabetes. In addition, these compounds possess potent diuretic activity, rendering them likewise useful in the treatment of edematous conditions.

The preparation of the active ingredients follow procedures of which those below are illustrative:

PREPARATION 1

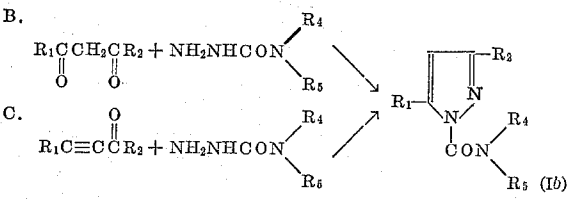
The 3,5-dialkylpyrazoles of Formula I above are prepared according to the following reactions:

A.

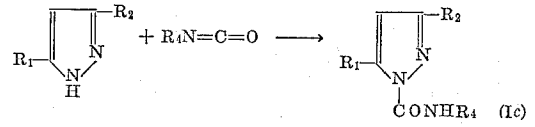

(Ia)

B.

C.


(Ib)

D.


(Ic)

wherein R is a lower alkyl having 1 through 7 carbon atoms, R_1 and R_2 are lower alkyls having 1 through 4 carbon atoms, R_4 and R_5 are hydrogen, lower alkyls having 1 through 7 carbon atoms, or aryl. In reactions A and B, where R_1 and R_2 in the reactants are different alkyl groups, the 3,5-dialkyl product is a mixture of $3R_1$, $5R_2$- and $3R_2$, $5R_1$-pyrazoles, the individual compounds being readily separable by conventional procedures. Reaction of the carboxylic acid Ia with the desired alkali metal hydroxide, such as sodium or potassium hydroxide, gives the corresponding alkali metal salt.

The following procedures exemplify the preparation of the foregoing compounds:

3,5-Dimethylpyrazole-1-Carboxylic Acid

A mixture of ethyl 3,5-dimethylpyrazole-1-carboxylate in 5% aqueous sodium hydroxide solution is heated under reflux for 15 minutes. The mixture is allowed to cool, and the excess sodium hydroxide is neutralized by the addition of acetic acid with ice-bath cooling. The resulting solid 3,5-dimethylpyrazole-1-carboxylic acid is removed by filtration and purified by recrystallization.

Alternately, the compound is prepared by the addition of solid carbon dioxide to an ethereal solution of the Grignard complex with 3,5-dimethylpyrazole, obtained by adding an ethereal solution of 3,5-dimethylpyrazole to an ethereal solution of ethyl magnesium bromide.

Ethyl 3,5-Dimethylpyrazole-1-Carboxylate

A mixture of equimolar amounts of 3,5-dimethylpyrazole, ethylchlorocarbonate, and finely ground potassium carbonate in anhydrous ether is stirred and heated under reflux for 24 hours. The mixture is filtered, the ether removed from the filtrate and the residue subjected to distillation in vacuo. The ethyl 3,5-dimethylpyrazole-1-carboxylate product is obtained as an essential colorless liquid.

N-Butyl-3,5-Dimethylpyrazole-1-Carboxamide

To 9.6 gm. (0.1 mole) of 3,5-dimethylpyrazole was added 19.8 gm. (0.2 mole) of n-butylisocyanate. The mixture was heated on the steam bath for 1 hour. The solution was cooled and 25 ml. of ether was added. The ether solution was washed with 25 ml. of aqueous 5% sodium carbonate solution and 25 ml. of water. The ether layer was dried and concentrated in vacuo. There was obtained 21 gm. (101% of theoretical) of N-butyl-3,5-dimethylpyrazole-1-carboxamide as an essentially colorless liquid which solidified upon stirring in an ice bath and which melted at 34.5–36° C.

Analysis.—Calcd. for $C_{10}H_{17}N_3O$: C, 61.51; H, 8.78; N, 21.52. Found C, 61.54; H, 8.45; N, 21.63.

Infrared spectrum supports the structure.

N-Phenyl-3,5-Dimethylpyrazole-1-Carboxamide

To a solution of 16.7 gm. (0.11 mole) of 4-phenylsemicarbazide in ethanol and water was added a solution of 10.0 gm. (0.1 mole) of acetylacetone in ethanol. A high melting solid was removed by filtration, water was added to the filtrate and more high melting material was obtained. The aqueous filtrate was extracted with ether, the ether layer dried and concentrated in vacuo. The crystals obtained were recrystallized from Skellysolve B (hexane hydrocarbons) to give N-phenyl-3,5-dimethylpyrazole-1-carboxamide which melted at 69–71° C.

Analysis.—Calcd. for $C_{12}H_{13}N_3O$: C, 66.95; H, 6.09; N, 19.52. Found: C, 66.97; H, 5.96; N, 19.24.

Infrared spectrum supports the structure.

Substitution of an equivalent amount of 4,4-diphenylsemicarbazide for the 4-phenylsemicarbazide above gives N,N-diphenyl-3,5-dimethylpyrazole-1-carboxamide.

3,5-Diethylpyrazole-1-Carboxamide

To a cooled solution of 11.2 gm. (0.1 mole) of semicarbazide hydrochloride in 30 ml. of water was added a solution of 12.8 gm. (0.1 mole) of 3,5-heptadione in ethyl alcohol over a period of 10 minutes with stirring. The mixture was stirred for 4 hours. The crystals were separated and recrystallized from benzene-Skellysolve B (hexane hydrocarbons). There was obtained 10.5 gm. (63%) of 3,5-diethylpyrazole-1-carboxamide as white crystals which melted at 69–72.5° C.

Analysis.—Calcd. for $C_8H_{13}N_3O$: C, 57.46; H, 7.84; N, 25.13. Found: C, 57.53; H, 7.52; N, 25.09.

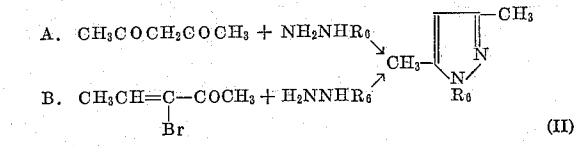
Infrared spectrum supports the structure.

N,N-Dimethyl-3,5-Dimethylpyrazole-1-Carboxamide

A solution of 9.6 gm. (0.1 mole) of 3,5-dimethylpyrazole in 75 ml. of dry benzene is added slowly to 3.9 gm. (0.1 mole) of sodamide. The solution is stirred at room temperature for ½ hour. Then a solution of 10.7 gm. (0.1 mole) of dimethylcarbamyl chloride in 25 ml. of dry benzene is added over a period of 15 minutes. The mixture is stirred for ½ hour, the insoluble salts filtered and the benzene solution concentrated in vacuo. Distilling at 1 mm. pressure gives essentially pure N,N-dimethyl-3,5-dimethylpyrazole-1-carboxamide.

PREPARATION 2

The 3,5-dimethylpyrazoles of Formula II above are prepared according to the following reactions:



(II)

wherein R_6 is hydrogen or lower alkyl having 1 through 4 carbon atoms. The acid addition salts, such as the hydrochlorides, hydrobromides, sulfates, nitrates, phosphates, benzoates, p-toluenesulfonates, salicylates, acetates, propionates, tartrates, citrates, lactates, succinates and the like are prepared by contacting the free base with the appropriate acid and purifying the product by conventional means.

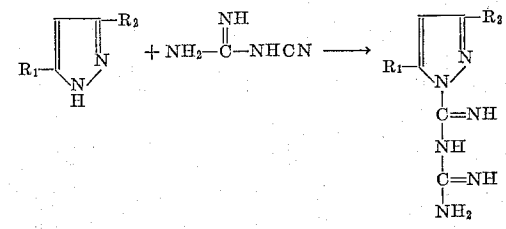
The following procedure exemplifies the preparation of the foregoing compounds:

3,5-Dimethylpyrazole Hydrochloride

To a solution of 13 gm. of hydrazine sulfate in 75 ml. of an aqueous 10% sodium hydroxide solution is added 12.8 gm. of 2,4-pentadione over a 15-minute period. The temperature of the reaction is maintained between 7–15° C. The reaction is stirred for 1 hour at this temperature, and 50 ml. of water is then added. An oil is separated and the water layer extracted 4 times with 25 ml. ether. The combined organic layer is washed with 25 ml. of sodium chloride solution, dried and concentrated in vacuo. Then, 75 ml. of a 1.4 N ethereal-hydrochloric acid solution is added. The resulting 3,5-dimethylpyrazole hydrochloride crystals are filtered and washed with ether and dried in vacuo.

PREPARATION 3

The novel 3,5-dialkylpyrazole guanidines of Formula III above are prepared according to the following reaction:



(III)

wherein R_1 and R_2 are lower alkyls having 1 through 4 carbon atoms. Acid addition salts, such as the hydrochlorides, hydrobromides, sulfates, nitrates, phosphates, benzoates, p-toluenesulfonates, salicylates, acetates, propionates, tartrates, citrates, succinates and the like are prepared by contacting the free base with the appropriate acid and purifying in the usual manner. Neutralization of the acid salts and purification by conventional procedures gives the basic guanidine product.

The following procedure exemplifies the preparation of the foregoing compounds:

1-(3,5-Dimethylpyrazole-1-Carboximidoyl) Guanidine Hydrochloride

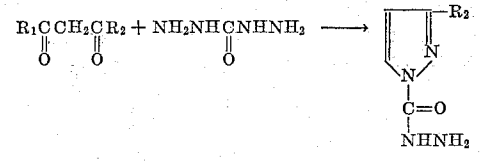
A mixture of 9.61 gm. (0.1 mole) of 3,5-dimethylpyrazole, 8.40 gm. (0.1 mole) of cyanoguanidine and 33.3 ml. (0.1 mole) of 3 N hydrochloric acid was heated under reflux for 3 hours. The solution was evaporated to dryness in vacuo on a steam bath and the residue triturated with acetone. There was obtained 11.30 gm. of 1-(3,5-dimethylpyrazole-1-carboximidoyl)guanidine hydrochloride melting at 125–128° C.

Analysis.—Calcd. for $C_7H_{13}ClN_6$: N, 38.79; Cl, 16.37. Found: N, 38.99; Cl, 16.85.

Omission of the hydrochloric acid and substitution of equivalent amounts of other 3,5-dialkylpyrazoles for the 3,5-dimethylpyrazole above, the alkyl groups being the same or mixed and having 1 through 4 carbon atoms, gives the corresponding basic 3,5-dialkyl products, such as 1-(3,5-diethylpyrazole-1-carboximidoyl)guanidine, 1-(3,5-dipropylpyrazole-1-carboximidoyl)guanidine, 1-(3,5-dibutylpyrazole-1-carboximidoyl)guanidine or mixed dialkyl products (e.g., the 3-methyl-5-propyl, 3-ethyl-5-butyl, and the like). Inclusion of hydrochloric acid as above, or other acids such as hydrobromic, sulfuric, nitric, phosphoric, benzoic, p-toluenesulfonic, salicylic, acetic, propionic, tartaric, citric, lactic, succinic and the like, gives the corresponding acid addition salts.

PREPARATION 4

The novel 3,5-dialkylpyrazole hydrazides of Formula IV above are prepared according to the following novel reaction:



wherein R_1 and R_2 are lower alkyls having 1 through 4 carbon atoms. The 1,3-dialkyl-1,3-propanedione dissolved in an organic solvent such as ethanol, ether, benzene, chloroform and the like is reacted with a solution of carbohydrazide in a suitable solvent such as water, ether and the like. The temperature can vary over a wide range, room temperature or slightly below being preferred. Reaction time varies with concentration of the reactants and temperature. Acid addition salts, such

as the hydrochlorides, hydrobromides, sulfates, nitrates, phosphates, benzoates, p-toluenesulfonates, salicylates, acetates, propionates, tartrates, citrates, lactates, succinates and the like are prepared by contacting the free base with the appropriate acid and purifying in the usual manner.

The following procedure exemplifies the preparation of the foregoing compounds:

3,5-Dimethylpyrazole-1-Carboxylic Acid Hydrazide

To a solution of 9.0 gm. (0.1 mole) of carbohydrazide in 35 ml. of water, previously cooled to 15° C. in an ice bath, was added a solution of 10.0 gm. (0.1 mole) of acetylacetone in 5 ml. of 95% ethanol over a period of 20 minutes, keeping the temperature between 10–15° C. The cloudy solution was stirred at room temperature for 4 hours. The reaction mixture was extracted 3 times with 10 ml. of ether. The water layer was allowed to stand overnight, filtered, and the cake washed with cold water and ether to give 13 gm. of white crystals melting at 99.5–100.5° C. Recrystallization from hot ether gave 9.5 gm. (62% of theoretical) of 3,5-dimethylpyrazole-1-carboxylic acid hydrazide melting at 110–111° C.

Analysis.—Calcd. for $C_6H_{10}N_4O$: C, 46.74; H, 6.54; N, 36.34. Found: C, 47.05; H, 6.50; N, 36.01.

Infrared spectrum supports the structure.

Substitution of equivalent amounts of other 1,3-dialkyl-1,3-propanediones for the acetylacetone above, the alkyl groups being the same or mixed and having 1 through 4 carbon atoms, gives the corresponding 3,5-dialkyl products, such as 3,5-diethylpyrazole-1-carboxylic acid hydrazide, 3,5-dipropylpyrazole-1-carboxylic acid hydrazide, 3,5-dibutylpyrazole-1-carboxylic acid hydrazide or 3,5-mixed-dialkylpyrazole-1-carboxylic acid hydrazides (e.g., the 3-methyl-5-propyl, 3-ethyl-5-butyl products and the like). Treatment of the foregoing compounds in the usual manner with such acids as hydrochloric, hydrobromic, sulfuric, nitric, phosphoric, benzoic, p-toluenesulfonic, salicylic, acetic, propionic, tartaric, citric, lactic, succinic, and the like, followed by conventional purification, gives the corresponding acid addition salts.

The dosage of the said primary active ingredients of the compositions of this invention in humans and animals for the purposes described herein is determined individually according to the subject's age, weight, response to the medication and severity of the condition being treated. Total daily doses range from about 10 to about 750 mg., given in single or divided doses. Each dosage unit can contain from about 10 to about 750 mg. of primary active ingredient.

In addition to the foregoing compounds as sole active ingredients, other complementary ingredients can be included to secure advantageous combinations of properties specially adapted to individual situations. Thus, other hypoglycemic agents such as tolbutamide, chlorpropamide, phenformin hydrochloride and mesoxalic acid can be combined with the forenamed ingredients in amounts not exceeding and preferably less than those normally employed in single unit doses where such added ingredients are employed singly. Utilizable potassium salts such as potassium chloride can be included in pyrazole formulations to offset possible potassium losses which may occur during therapy.

In adapting the active ingredients for use in animals, including humans, the novel compositions are suitably presented for administration in unit dosage form as tablets, pills, capsules, powders, wafers, cachets, granules, oral aqueous or oil dispersions, including elixirs, and the like.

For preparing solid compositions such as tablets, the active ingredient is mixed with a conventional non-sugar tableting component such as cornstarch, dicalcium phosphate, terra alba (calcium sulfate), talc, stearic acid, calcium stearate, gums, and functionally similar materials constituting pharmaceutical diluents or carriers. The

tablets or pills can be laminated or otherwise compounded to provide a dosage form affording the advantage of prolonged or delayed action or of predetermined successive action of the enclosed medication. For example, the tablet or pill can comprise as inner dosage and outer dosage component, the latter being in the form of an envelope over the former. The two components can be separated by an enteric layer which serves to resist disintegration in the stomach and permits the inner component to pass intact into the duodenum or to be delayed in release. A variety of materials can be used for such enteric layers or coatings, such materials including a number of polymeric acids or mixtures of polymeric acids with such materials as shellac, shellac and cetyl alcohol, cellulose acetate phthalate and the like. A particularly advantageous sustained release coating comprises a styrene maleic acid copolymer.

The liquid form in which the novel compositions of this invention can be incorporated include aqueous sugar-free solutions or suspensions, emulsions or suspensions with edible oils such as cottonseed oil, sesame oil, coconut oil, peanut oil and the like, as well as elixirs and similar pharmaceutical vehicles. Suitable dispersing or suspending agents for aqueous suspensions include the synthetic and natural gums such as tragacanth, acacia, alginate, dextran, methylcellulose, polyvinylpyrrolidone, gelatin and the like.

The term "unit dosage form" as used in the specification and claims herein refers to physically discrete units suitable as unitary dosages for human subjects, each unit containing a predetermined quantity of active material calculated to produce the desired therapeutic effect in association with the required pharmaceutical diluent, carrier or vehicle. The specification for the novel unit dosage forms of this invention are dictated by and directly dependent on (*a*) the unique characteristics of the active material and the particular therapeutic effect to be achieved and (*b*) the limitations inherent in the art of compounding such an active material for therapeutic use in humans, as disclosed in detail in this specification, these being features of the present invention. Examples of suitable unit dosage forms, as heretofore described, are tablets, capsules, pills, powder packets, wafers, cachets, teaspoonfuls, tablespoonfuls, dropperfuls, and segregated multiples of any of the foregoing, and other forms alluded to herein.

The following examples illustrate the best mode contemplated by the inventors for carrying out the invention but are not to be construed as limiting the scope thereof.

EXAMPLE 1

Compressed Tablets

A lot of 10,000 compressed tablets, each containing 10 mg. of 3,5-dimethylpyrazole, is prepared from the following ingredients:

3,5-dimethylpyrazole	gm.	100
Terra alba (calcium sulfate)	gm.	2500
Methylcellulose, U.S.P. (15 cps.)	gm.	65
Talc, bolted	gm.	450
Calcium stearate, fine powder	gm.	35

The 3,5-dimethylpyrazole and terra alba are mixed well, granulated with 7.5% solution of methylcellulose in water, passed through a No. 8 screen and dried at 120° F. The dried granules are passed through a No. 12 screen, mixed thoroughly with the talc and stearate and compressed into tablets.

One tablet is given three times daily in the oral treatment of diabetes in adult humans.

Substitution of the pharmaceutically acceptable acid addition salts of the above active ingredient, such as the preferred hydrochloride and the hydrobromide, sulfate, nitrate, phosphate, benzoate, p-toluenesulfonate, salicylate, acetate, propionate, tartrate, citrate, lactate, succinate, and the like, can be employed in the same manner.

EXAMPLE 2

Hard Gelatin Capsules

A lot of 10,000 two-piece hard gelatin capsules for oral use, each containing 400 mg. of 1,3,5-trimethylpyrazole is prepared from the following materials:

1,3,5-trimethylpyrazole	gm.	4000
Potassium chloride	gm.	1000
Mineral oil, U.S.P.	gm.	129.6
Magnesium stearate, powder	gm.	162
Talc, U.S.P.	gm.	162
Corn starch	gm.	1616

The powdered 1,3-5-trimethylpyrazole is mixed thoroughly with the rest of the powdered ingredients and then encapsulated.

One capsule daily is given in the treatment of human diabetes.

Similarly, other 1-lower-alkyl-3,5-dimethylpyrazoles, such as 1-ethyl, 1-propyl, or 1-butyl-3,5-dimethylpyrazoles, can be substituted for the active ingredient above.

As in Example 1, the pharmaceutically acceptable acid addition salts of the above active ingredients can be employed in the formulation and similarly administered. Likewise, other 1-lower-alkyl-3,5-dimethylpyrazoles, where the lower alkyl group contains 2–4 carbon atoms, or the acid addition salts thereof, can replace the 1,3,5-trimethylpyrazole above.

EXAMPLE 3

Oil Suspension

An oil suspension for oral use, each 5 ml. containing 100 mg. of 3,5-dimethylpyrazole-1-carboxylic acid, is prepared from the following materials:

Saccharin sodium	gm.	10
Cyclamate sodium (sodium cyclohexylsulfamate)	gm.	2.5
3,5-dimethylpyrazole-1-carboxylic acid	gm.	200
Benzoic acid, powder	gm.	10
Methylparaben	gm.	10
Butylated hydroxyanisole	gm.	1
Oil of orange	ml.	25
Aluminum monostearate-corn oil gel, q.s.	ml.	10,000

One teaspoonful (5 ml.) is given twice daily in the treatment of diabetes.

Substitution of carboxylic acid esters having 1 through 7 carbon atoms, such as the ethyl ester, or the sodium or potassium salt, for the carboxylic acid ingredient above gives a composition similarly useful in the treatment of diabetes.

EXAMPLE 4

Tablet

A lot of 10,000 oral tablets, each containing 50 mg. of 3,5-dimethylpyrazole-1-carboxamide, is prepared from the following materials:

3,5-dimethylpyrazole-1-carboxamide	gm.	500
Dicalcium phosphate	gm.	3050
Starch	gm.	65
Talc, bolted	gm.	450
Calcium stearate, fine powder	gm.	35

The finely powdered 3,5-dimethylpyrazole-1-carboxamide, dicalcium phosphate, starch, talc and calcium stearate are mixed well and slugged. The slugs are forced through a No. 8 screen and the granules slugged again. These are forced through a No. 12 screen and the resulting granules compressed into tablets containing 50 mg. of the active material per tablet.

One tablet is given twice daily in the treatment of diabetes.

EXAMPLE 5

Soft Gelatin Capsules

A batch of 1,000 soft gelatin capsules, each containing 100 mg. of N-phenyl-3,5-dimethylpyrazole-1-carboxamide and 250 mg. of tolbutamide in corn oil, is prepared from the following materials:

N-phenyl-3,5-dimethylpyrazole-1-carboxamide	gm.	100
Tolbutamide	gm.	250
Corn oil, q.s.		

A uniform dispersion of the active ingredient in the corn oil is prepared and the dispersion filled into soft gelatin capsules by conventional means.

One capsule is given twice a day in the treatment of diabetes in humans.

Substitution of other aryl or diaryl-3,5-dimethylpyrazole-1-carboxamides, such as N,N-diphenyl-3,5-dimethylpyrazone-1-carboxamide or the mono-or di- tolyl and salicyl derivatives, for the active ingredients above, gives a similarly useful formulation.

EXAMPLE 6

Aqueous Oral Suspension

An aqueous oral suspension containing, in each 5 ml., 250 mg. of N-butyl-3,5-dimethylpyrazole-1-carboxamide is prepared from the following materials:

N - butyl - 3,5 - dimethylpyrazole - 1 - carboxamide	gm.	500
Methylparaben, U.S.P.	gm.	7.5
Propylparaben, U.S.P.	gm.	2.5
Saccharin sodium	gm.	12.5
Cyclamate sodium	gm.	2.5
Glycerin	ml.	3000
Tragacanth powder	gm.	100
Orange oil flavor	gm.	10
F. D. and C. orange dye	gm.	7.5
Deionized water, q.s.	ml.	10,000

One teaspoonful (5 ml.) daily is employed in the treatment of human diabetes.

Substitution of other N-alkyl mono-substituted 3,5-dimethylpyrazole-1-carboxamides, where the alkyl group contains 1–7 carbon atoms, gives similarly useful compositions.

EXAMPLE 7

Aqueous Liquid

A sugar-free aqueous liquid for oral use containing, in each 5 ml., 750 mg. of N,N-dimethyl-3,5-dimethylpyrazole-1-carboxamide is prepared from the following materials:

N,N - dimethyl - 3,5 - dimethylpyrazole-1-carboxamide	gm.	1500
Methylparaben, U.S.P.	gm.	3
Sorbic acid	gm.	3
Sweetening agent	gm.	18
Flavoring	ml.	3
Glycerin	ml.	1500
Deionized water, q.s.	ml.	10,000

A dose of one teaspoonful (5 ml.) is given daily in the treatment of diabetes.

Substitution of other N,N-dialkyl substituted 3,5-dimethylpyrazole-1-carboxamides, where the alkyl groups are the same or mixed and contain 1 through 7 carbon atoms, for the active ingredient above gives a similarly useful formulation.

EXAMPLE 8

Compressed Tablets

A lot of 10,000 tablets for oral use, each containing 150 mg. of 1-(3,5-dimethylpyrazole-1-carboximidoyl)-guanidine hydrochloride, is prepared from the following materials:

1 - (3,5 - dimethylpyrazole - 1 - carboximidoyl)-guanidine hydrochloride	gm.	1500
Terra alba (calcium sulfate)	gm.	600
Talc	gm.	150
Methylcellulose, U.S.P. (15 cps.)	gm.	175
Starch	gm.	375
Magnesium stearate	gm.	10

All of the ingredients, except the last two, are mixed well and granulated with water. To the dried granules is added the lubrication mixture of starch and stearate, and the resulting mixture is then compressed into tablets.

One tablet is given daily in the treatment of diabetes.

The basic guanidine and other pharmaceutically acceptable acid addition salts of the above active ingredient, such as those in Example 1, can be employed in place of the hydrochloride and the resulting formulations similarly administered.

EXAMPLE 9

Hard Gelatin Capsules

A lot of 10,000 two-piece hard gelatin capsules for oral use, each containing 250 mg. of 3,5-dimethylpyrazole-1-carboxylic acid hydrazide, is prepared from the following materials:

3,5-dimethylpyrazole-1-carboxylic acid hydrazide	gm..	2500
Magnesium stearate, powder	gm..	250
Talc, U.S.P.	gm..	250

The powdered 3,5-dimethylpyrazole-1-carboxylic acid hydrazide is mixed thoroughly with the rest of the ingredients and then encapsulated.

One capsule is given daily in the treatment of diabetes.

The pharmaceutically acceptable acid addition salts of the above active ingredient, such as those of Example 1, can be employed instead of the basic hydrazide and the resulting compositions similarly administered.

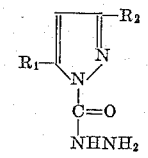
EXAMPLE 10

In each of the foregoing Examples 3 through 9, the 3,5-dimethylpyrazole ingredient can be replaced by other 3,5-lower alkyl pyrazole derivatives in which the lower alkyl groups contain from 2 through 4 carbon atoms,

e.g., the 3,5-diethyl, 3,5-dipropyl and 3,5-dibutyl, as well as mixed lower alkyl groups containing from 1 through 4 carbon atoms, e.g., the 3-methyl-5-ethyl, 3-ethyl-5-propyl, 3-propyl-5-butyl, 3-ethyl-5-methyl, and the like.

What is claimed is:

1. A compound selected from the group consisting of (1) a pyrazole of the formula:



wherein R_1 and R_2 are lower alkyl having 1 through 4 carbon atoms, and (2) the pharmaceutically acceptable acid addition salts thereof.

2. 3,5-dimethylpyrazole-1-carboxylic acid hydrazide.

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