

SPECIFICATION

4-Aroylimidazol-2-ones

U.S. Patent Specifications Nos. 2,514,380 and 2,441,933; Duschinsky *et al*, J.A.C.S, 68, 2350-55 (1946), 70, 657-62 (1948) and 67, 2079-84 (1945); and Rozin *et al*, *Khim. Geterotsikl. Soedin.*, 4(4), 698-701 (1968) disclose the preparation and chemical intermediate utility of the following compounds:

4-benzoyl-1, 3-dihydro-2*H*-imidazol-2-one;

4-benzoyl-1, 3-dihydro-2*H*-imidazol-2-one 1,3-diacetate;

4-benzoyl-1, 3-dihydro-5-(lower alkyl)-2*H*-imidazol-2-ones;

4-benzoyl-1, 3-dihydro-5-methyl-2*H*-imidazol-2-one 1, 3-diacetate;

1,3-dihydro-4-(3,4-dimethylbenzoyl)-2*H*-imidazol-2-one 1,3-diacetate;

1,3-dihydro-4-(hydroxybenzoyl)-2*H*-imidazol-2-one;

1,3-dihydro-4-(hydroxybenzoyl)-5-(lower alkyl)-2*H*-imidazol-2-ones;

1,3-dihydro-4-(3,4-dihydroxybenzoyl)-2*H*-imidazol-2-one;

1,3-dihydro-4-(4-nitrobenzoyl)-2*H*-imidazol-2-one;

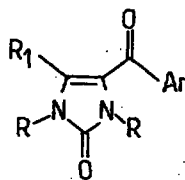
1,3-dihydro-4-methyl-5-(4-nitrobenzoyl)-2*H*-imidazol-2-one;

4-(3-aminobenzoyl)-1,3-dihydro-2*H*-imidazol-2-one;

4-(4-aminobenzoyl)-1,3-dihydro-2*H*-imidazol-2-one; and

4-(4-aminobenzoyl)-1,3-dihydro-5-methyl-2*H*-imidazol-2-one.

We have now discovered that compounds of formula 1, below, can have antihypertensive, cardiotonic and/or antithrombotic activity. These compounds have the formula



wherein R is hydrogen, C₁₋₄ alkyl, (C₁₋₄alkyl)carbonyl or benzoyl;

R₁ is hydrogen or C₁₋₄ alkyl; and

Ar is 2-furyl; 2-thienyl; phenyl; phenyl monosubstituted by halogen, hydroxy, C₁₋₄ alkyl, C₁₋₄ alkoxy, C₁₋₄ alkylthio, trifluoromethyl, -SO₂N(R₂)₂, NR₃R₄, pyrrolidino, piperidino, morpholino, piperazino or N'-

alkylpiperazino, in which R₂, R₃ and R₄ are independently selected from hydrogen and C₁₋₄ alkyl;

disubstituted phenyl in which one substituent is at the para position and the substituents are independently selected from halogen, hydroxy, C₁₋₄ alkyl and C₁₋₄ alkoxy; or 3,4-methylenedioxyphenyl in which the methylene group is optionally substituted by one or two methyl groups,

and include the pharmaceutically acceptable salts thereof.

Those compounds of formula I which are novel, particularly those of formula I in which Ar is not phenyl, mono- or di-hydroxyphenyl, aminophenyl or dimethylphenyl, form a further aspect of this invention.

A pharmaceutical composition according to the invention comprises a compound of formula I in association with a physiologically acceptable excipient (which is a solid or a sterile liquid when the compound is known).

Examples of C₁₋₄ alkyl are methyl, ethyl, *n*-propyl, isopropyl, *n*-butyl and isobutyl. Examples of C₁₋₄ alkoxy are methoxy, ethoxy, *n*-propoxy, isopropoxy, *n*-butoxy and isobutoxy. Examples of C₁₋₄ alkylthio are methylthio etc.

The term "halogen" means fluorine, chlorine, bromine or iodine, and "halide" means fluoride, chloride, bromide or iodide.

Methylenedioxy optionally substituted by one or two methyl groups means methylenedioxy, ethylene-dioxy or isopropylidenedioxy.

The substituent on Ar as monosubstituted phenyl will hereinafter be referred to as X₁. The substituents on Ar as disubstituted phenyl (including methylenedioxyphenyl) will hereinafter be referred to as X₂ and X₃, X₂ being at the para position.

Preferred compounds of this invention are those compounds of formula I wherein R is hydrogen and X₁ is piperidino, pyrrolidino, morpholino, piperazino, N'-alkyl-piperazino, C₁₋₄ alkoxy or C₁₋₄ alkylthio. Other preferred compounds of this invention are those wherein Ar is unsubstituted phenyl and where X₂ and X₃ are C₁₋₄ alkoxy, or (together) methylenedioxy. It is particularly preferred that R₁ is hydrogen, methyl or ethyl, especially methyl. X₁ is preferably at the para position, and is most preferably methoxy or methylthio. X₃ is preferably at the meta position and is most preferably methoxy.

Particularly preferred compounds of formula I are the following:

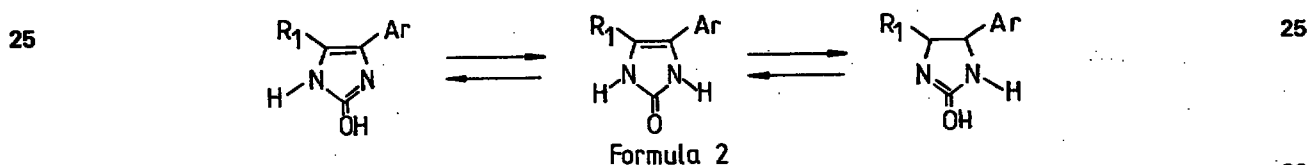
4-benzoyl-1,3-dihydro-5-methyl-2*H*-imidazol-2-one;

1,3-dihydro-4-methyl-5-(2-thienoyl)-2*H*-imidazol-2-one;

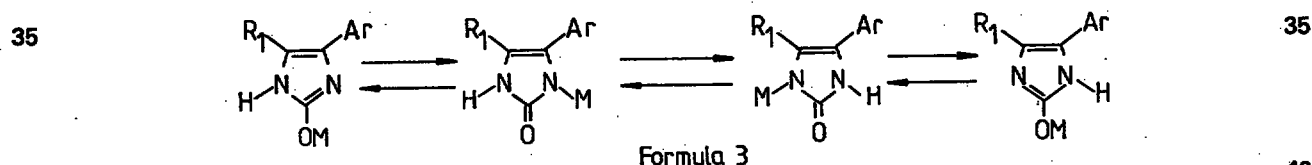
1,3-dihydro-4-methyl-5-(3,4-methylenedioxybenzoyl)-2*H*-imidazol-2-one;

1,3-dimethyl-4-benzoyl-2*H*-imidazol-2-one;

- 1,3-dihydro-4-(4-methoxybenzoyl)-5-methyl-2H-imidazol-2-one;
 4-benzoyl-1,3-dihydro-5-methyl-2H-imidazol-2-one, 1,3-diacetate;
 1,3-dihydro-4-(3,4-dimethoxybenzoyl)-5-methyl-2H-imidazol-2-one;
 1,3-dihydro-4-(2-furanoyl)-5-methyl-2H-imidazol-2-one;
 5 1,3-dihydro-4-ethyl-5-(4-methoxybenzoyl)-2H-imidazol-2-one;
 1,3-dihydro-4-ethyl-5-(4-methylthiobenzoyl)-2H-imidazol-2-one;
 1,3-dihydro-4-(2-thienoyl)-2H-imidazol-2-one,
 4-benzoyl-1,3-dihydro-2H-imidazol-2-one,
 1,3-dihydro-4-(2-furanoyl)-2H-imidazol-2-one,
 10 1,3-dihydro-4-(4-methoxybenzoyl)-2H-imidazol-2-one,
 1,3-dihydro-4-(4-fluorobenzoyl)-5-methyl-2H-imidazol-2-one,
 4-(2-chlorobenzoyl)-1,3-dihydro-5-methyl-2H-imidazol-2-one,
 1,3-dihydro-4-(2-hydroxybenzoyl)-5-methyl-2H-imidazol-2-one,
 4-(4-chlorobenzoyl)-1,3-dihydro-5-methyl-2H-imidazol-2-one,
 15 1,3-dihydro-4-methyl-5-(4-piperidinobenzoyl)-2H-imidazol-2-one,
 1,3-dihydro-4-methyl-5-(4-morpholinobenzoyl)-2H-imidazol-2-one,
 1,3-dihydro-4-methyl-5-(4-pyrrolidinobenzoyl)-2H-imidazol-2-one,
 1,3-dihydro-4-(4-dimethylaminobenzoyl)-5-methyl-2H-imidazol-2-one,
 1,3-dihydro-4-methyl-5-[4-(4-methylpiperazinobenzoyl)]-2H-imidazol-2-one,
 20 1,3-dihydro-4-(4-hydroxybenzoyl)-5-methyl-2H-imidazol-2-one, and
 1,3-dihydro-4-methyl-5-[4-(methylthio)benzoyl]-2H-imidazol-2-one,
 When R is hydrogen in Formula 1 compounds, the several tautomeric forms of general Formula 2 are possible;



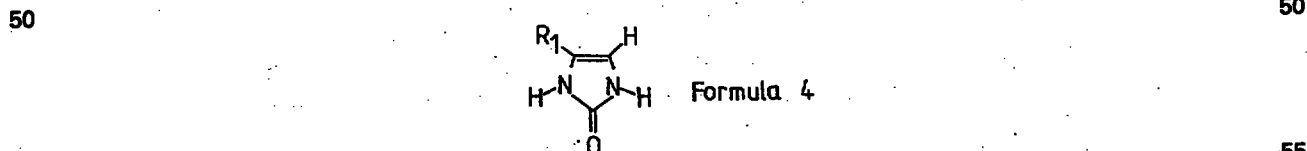
wherein R₁ and Ar are as defined in Formula 1. These acidic tautomers may form pharmaceutically active salts of general Formula 3



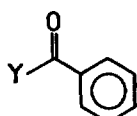
wherein R₁ and Ar are as defined in Formula 1, and M is a pharmaceutically acceptable alkali metal, such as sodium or potassium; alkaline earth metal, such as calcium or magnesium; transition metal, such as zinc or iron; main group metal; ammonium or organic ammonium ion, such as tetramethylammonium ion.

- 45 Throughout this disclosure the term imidazol-2-one shall be taken to mean any of the tautomers of Formula 2 and a pharmaceutically acceptable salt of an imidazol-2-one shall be taken to mean any tautomer of Formula 3.

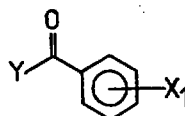
The 4-arylimidazol-2-ones of this invention wherein R is hydrogen may be prepared by a Friedel-Crafts acylation of an imidazol-2-one of Formula 4:



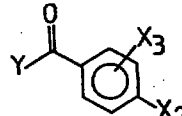
- 55 wherein R₁ is as defined in Formula 1. The acylating agent may be a 2-furanoyl halide, preferably 2-furanoyl chloride, a 2-thienoyl halide, preferably 2-thienoyl chloride, or a benzoyl halide, preferably a benzoyl chloride, of Formulas 5a, 5b or 5c



Formula 5a



Formula 5b



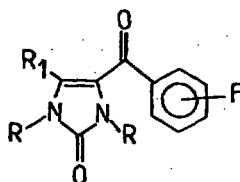
Formula 5c

wherein Y is a halogen and X_1 , X_2 and X_3 are as defined in Formula 1 or may additionally be any group which can be converted to the desired X_1 , X_2 or X_3 substituent subsequent to the Friedel-Crafts reaction such as a blocking group or a nitro group which can be converted, via the diazonium ion, to a variety of other substituents by chemistry generally known in the art. Furthermore, the Friedel-Crafts reaction may be performed on the free acid or its corresponding acid anhydride instead of the aroyl halides mentioned hereinabove employing essentially identical reaction conditions. These alternate reactions are more fully described in Olah, "Friedel-Crafts and Related Reactions," Vol. 111, Part 1, Interscience Publications, John Wiley and Sons, New York, 1964.

The Friedel-Crafts reactions of this invention are performed by premixing about 1 molar equivalent of the appropriate imidazol-2-one with about 1 molar equivalent to about 10 molar equivalents, preferably about 2 molar equivalents, of a Lewis acid catalyst in a suitable solvent, for example, petroleum ethers; a chlorinated hydrocarbon, such as carbon tetrachloride, ethylene chloride, methylene chloride or chloroform; a chlorinated aromatic, such as 1,2,4-trichlorobenzene or *o*-dichlorobenzene; carbon disulfide; or preferably nitrobenzene. About 1 molar equivalent to about 10 molar equivalents, preferably about 1.1 molar equivalents of the appropriate aroyl compound is added, preferably dropwise, to the mixture of imidazol-2-one, Lewis acid, and solvent and the reaction is allowed to proceed for about 1/2 hour to about 100 hours, preferably from about 1 hour to about 10 hours depending on the reactants, the solvent, and the temperature which can be from about -78° to about 150°C , preferably about 0° to about 100°C , most preferably about 60°C . The resulting aroylimidazol-2-one may be isolated from the reaction mixture by any suitable art-known procedure, preferably by quenching the reaction mixture with ice water and subsequently removing the product by filtration or extraction and solvent removal.

Lewis acid catalysts suitable for use in the Friedel-Crafts reactions described herein are, for example, a metal, such as aluminum, cerium, copper, iron, molybdenum, tungsten or zinc; a Bronstead acid, such as a phosphoric acid, sulfuric acid, sulfonic acid, or a hydrohalo acid, such as hydrochloric or hydrobromic acid; halogen substituted acetic acids, such as chloroacetic or trifluoroacetic acids; or a metallic halide, such as a boron halide, zinc chloride, zinc bromide, beryll chloride, copper chloride, iron(III) bromide, iron(III) chloride, mercury(II) chloride, mercury(I) chloride, antimony bromide, antimony chloride, titanium(IV) bromide, titanium(IV) chloride, titanium(III) chloride, aluminum bromide or preferably aluminum chloride.

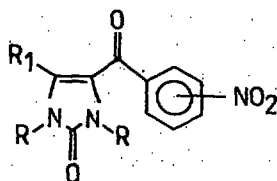
The compounds of Formula 1 wherein X_1 is at the ortho or para position and is a pyrrolidino, piperidino, morpholino, piperazino, *N'*-alkyl-piperazino and NR_3R_4 may be prepared as hereinabove described or may be prepared from a suitable fluorobenzoylimidazol-2-one of Formula 6



Formula 6

wherein R and R_1 are as defined above in Formula 1 and the fluorine atom is at either the ortho or para position. The appropriate compound of Formula 6 is allowed to react with from about 1 to about 10 molar equivalents of pyrrolidine, piperidine, morpholine, piperazine or *N'*-alkyl-piperazine, as appropriate. This reaction may be performed with or without a solvent, preferably, the amine is the solvent as well as the reactant. Suitable solvents, if desired, for this reaction are, for example, dimethylformamide; dimethylsulfoxide; petroleum ethers; chlorinated hydrocarbons, such as chloroform, methylene chloride, or carbon tetrachloride; carbon disulfide; ethereal solvents, such as diethyl ether, tetrahydrofuran or *p* dioxan; aromatic solvents such as benzene, toluene or xylene; or alcoholic solvents, such as ethanol. The reaction is allowed to proceed for about 1/2 hour to about 48 hours, preferably about 24 hours, depending on the reactants, the solvent if any, and the temperature which can be from about 0° to about 150°C .

The compounds of Formula 1 wherein X_1 is an amino group of the formula, $\text{-NR}_3\text{R}_4$, and wherein R_3 and R_4 are as defined in Formula 1, may alternatively be prepared from the corresponding nitro substituted benzoylimidazol-2-ones of Formula 7



Formula 7

wherein R and R₁ are as defined in Formula 1. The compounds of Formula 7 are either known in the prior art or may be prepared by Friedel-Crafts acylation of an imidazol-2-one of Formula 4 with a nitro substituted benzoyl halide, preferably a nitro substituted benzoyl chloride by procedures analogous to those outlined above. The nitro group is reduced to the unsubstituted amino group by any suitable art-known procedure and subsequently, if desired, the unsubstituted amino may be alkylated by any appropriate art known method.

The nitrobenzoylimidazol-2-ones may suitably be converted to the corresponding aminobenzoylimidazol-2-ones by reduction with tin, zinc, iron or other suitable active metal in concentrated hydrochloric acid solution. About 1 molar equivalent to about 10 molar equivalents of the metal is used and the reaction is allowed to proceed for about 1/2 hour to about 10 hours, preferably about 2 or 3 hours depending upon the reactants and the temperature which can be from about 25° to about 150°C, preferably about 100°C. Alternatively, the nitrobenzoylimidazol-2-ones may be reduced catalytically with nickel, platinum, palladium, or other similar suitable metals and molecular hydrogen. Such reactions are typically performed in an alcoholic solvent, preferably ethanol, but any nonreactive solvent may be used and the amount of metal catalyst may vary from about 0.001 molar equivalents to about 0.1 molar equivalents. The reaction is allowed to proceed for about 1 minute to about 1 hour, preferably about 10 minutes depending upon the reactants, the solvent and the temperature which can be from about 0° to about 100°C, preferably about 25°C. And alternatively, the nitrobenzoylimidazol-2-ones may be reduced with ammonium bisulfide (NH₄SH) in aqueous ammonia. About 1 to about 10 molar equivalents, preferably about 3 molar equivalents, of the bisulfide is allowed to react for about 1/2 hour to about 10 hours, preferably about 2 hours, depending upon the reactants and the temperature which may be from about 0° to about 150°C, preferably about 50°C. Finally, the nitrobenzoylimidazol-2-ones may be reduced to the corresponding amino compounds by any other appropriate art-known procedure.

The alkylation of the unsubstituted aminobenzoylimidazol-2-ones may be accomplished, for example, by reaction with one or more equivalents of an appropriate alkyl halide of the formulas R₃X and R₄X wherein R₃ and R₄ are as defined in Formula 1 and X is a halide. Typically these reactions are performed in a solvent such as petroleum ethers; chlorinated hydrocarbons such as carbon tetrachloride, chloroform or methylene chloride; chlorinated aromatics such as 1,2,4-trichlorobenzene, *o*-dichlorobenzene or chlorobenzene; carbon disulfide; nitrobenzene; dimethylformamide; dimethylsulfoxide; ethereal solvents such as diethyl ether, tetrahydrofuran or *p*-dioxan; aromatic solvents such as benzene, toluene or xylene, alcohols such as methanol, ethanol or propanol; and aqueous alcohols such as aqueous ethanol. These alkylations are preferably performed in the presence of one or more equivalents of a "proton sponge" such as triethylamine, pyridine, sodium hydroxide, calcium hydroxide or potassium hydroxide to neutralize any hydrohalide as it is formed. Alternatively, the unsubstituted aminobenzoylimidazol-2-ones may be alkylated by any other appropriate art-known procedure such as reaction with formic acid and formaldehyde to form a dimethylamine compound. Furthermore, a variety of other substituents such as halogen and hydroxy may be prepared from the nitro substituted benzoylimidazol-2-ones of Formula 7 via the diazonium ion by procedures well known in the art.

The compounds of Formula 1 wherein X₁ or X₂ and X₃ are hydroxy may be prepared as hereinabove described or preferably may be prepared from a suitable alkoxy, preferably methoxy, substituted benzoylimidazol-2-one wherein the alkoxy group is at the position of desired hydroxy substitution. The alkoxy compound is cleaved to form the corresponding hydroxybenzoylimidazol-2-one by any suitable art-known procedure such as are taught by R. L. Burwell, "The Cleavage of Ethers," *Chem. Rev.* 54, 615-85 (1954) whose contents are hereby expressly incorporated by reference.

The X₁, X₂ and X₃ substituents may be protected as necessary in order to improve the stability of the Formula 5b and 5c reactants or to allow for the acylation of the imidazol-2-one ring nitrogen atoms as described herein without concurrent acylation of any reactive X groups. For example, where X₁, X₂ or X₃ is hydroxy, an amino group of the formula -NHR₃ or -SO₂NH₂, a benzyl group may be employed to block the otherwise reactive hydroxy or amino groups. The benzyl group may be removed subsequently by, for example, hydrogenolysis with hydrogen over a palladium catalyst or with sodium in liquid ammonia.

When desired, one or both of the nitrogen atoms of the imidazol-2-one ring may be substituted with an alkyl group by any art-known procedure. Such methods include reacting the appropriate N-unsubstituted aroylimidazol-2-one of this invention with a base and an alkylating agent in presence of an unreactive solvent. Suitable bases for this reaction can be, for example, a hydride such as sodium hydride or calcium hydride; a carbonate or bicarbonate such as sodium carbonate or sodium bicarbonate; a phenoxide such as sodium phenoxide; an alkoxide such as sodium ethoxide; or preferably a hydroxide such as sodium hydroxide. Suitable alkylating agents for this reaction are, for example, an alkyl halide such as methyl chloride, methyl bromide, or methyl iodide; or a dialkylsulfate such as dimethylsulfate. Suitable unreactive solvents are, for example, petroleum ethers; chlorinated hydrocarbons such as carbon tetrachloride, chloroform, or methylene chloride; chlorinated aromatics such as 1,2,4-trichlorobenzene, *o*-dichlorobenzene, or chlorobenzene; carbon disulfide; nitrobenzene; ethereal solvents such as diethyl ether, tetrahydrofuran or *p*-dioxan; aromatic solvents such as benzene, toluene or xylene; or preferably the polar aprotic solvents such as dimethylformamide (DMF) or dimethylsulfoxide (DMSO). The reaction is allowed to proceed from about 1 minute to about 1 hour and the temperature may be from about 0°C to about 100°C, preferably about 25°C. When it is desired that only one of the imidazol-2-one nitrogen atoms be substituted

with an alkyl group, the appropriate imidazol-2-one is reacted with from about 1 molar equivalent to about 10 molar equivalents of a base, preferably about 1 molar equivalent and with about 1 molar equivalent of an alkylating agent. Utilizing this procedure, both possible monoalkylated nitrogen isomers result. These isomers are separable by conventional art-known procedures such as fractional crystallization, fractional distillation, or chromatography. When it is desired that both nitrogen atoms of the imidazol-2-one ring be alkyl substituted, the appropriate imidazol-2-one is reacted with from about 2 molar equivalents to about 10 molar equivalents of a base, preferably about 2 molar equivalents and from about 2 molar equivalents to about 10 molar equivalents of an alkylating agent, preferably about 2 molar equivalents. Finally, any reactive substituents on the aroyl rings, if present, may become alkylated concurrently. That is, the following X groups, X=OH, -NHR₃, SO₂NH₂ and unsubstituted piperazino, are alkylated under identical reaction conditions. If desired, the alkylation of the aroyl ring substituents may be avoided by the use of suitable protecting groups well-known in the art, for example, X=OH or -NHR₃ may be benzylated and later deblocked by hydrogenolysis.

When desired, the nitrogen atoms of the imidazol-2-one ring may be substituted with an alkylcarbonyl group by any suitable art-known procedure. Such methods include reacting the N-unsubstituted aroylimidazol-2-ones of this invention with an acyl halide, preferably an acyl chloride such as acetyl chloride, *n*-propanoyl chloride, isopropanoyl chloride or butanoyl chloride. Normally, acylation reactions utilizing acyl halides employ an acid sponge such as trimethylamine or pyridine to remove any hydrohalide as it is formed. Furthermore, the corresponding free acid anhydride may be employed instead of the acyl halides. Acylation reactions are generally run without added solvent but may be performed using any nonreactive solvent, for example, petroleum ethers; chlorinated hydrocarbons such as chloroform, methylene chloride or carbon tetrachloride; carbon disulfide; ethereal solvents, such as diethylether, tetrahydrofuran or *p*-dioxan or aromatic solvents such as benzene, toluene or xylene. The reactions are allowed to proceed for about 1 minute to about 100 hours, preferably from about 1 hour to about 10 hours and the temperature may be from about -78° to about 150°C preferably from 0° to 100°C. Finally, any reactive substituents on the aroyl rings, if present, will become acylated concurrently. That is, the following X groups, X=OH, -NHR₃, -SO₂NH₂ and unsubstituted piperazino, are acylated under identical reaction conditions. If desired, the acylation of the benzoyl ring substituents may be avoided by the use of suitable protecting groups well-known in the art, for example X=OH or -NHR₃ may be benzylated and later deblocked by hydrogenolysis.

The alkali metal, alkaline earth metal, transition metal, main group metal, ammonium or organic ammonium salts of the aroylimidazol-2-ones of this invention may be prepared from a corresponding metal or ammonium basic salt for example an alkoxide, such as sodium methoxide or sodium ethoxide, a phenoxide, such as sodium phenoxide; hydroxides, such as sodium hydroxide or potassium hydroxide; or a carbonate, such as sodium carbonate, potassium carbonate, zinc carbonate, magnesium carbonate or sodium hydrogen carbonate. These reactions may be performed with or without a solvent. Suitable solvents are, for example, lower alcohols, such as methanol, ethanol, isopropanol, *n*-propanol or *n*-butanol; aromatic solvents, such as benzene, toluene or xylene; ethereal solvents, such as diethyl ether, tetrahydrofuran or *p*-dioxan; and halogenated hydrocarbon solvents, such as chloroform, methylene chloride or carbon tetrachloride. The aroylimidazol-2-one and base are allowed to react for about 1 minute to about 24 hours depending on the reactants and the temperature which can be from about -78° to about 150°C, preferably from about 0° to about 25°C.

The aroyl chlorides of their corresponding carboxylic acids, which are required for the Friedel-Crafts acylation of this invention, are either generally available in the art or may be prepared by analogous procedures. The imidazol-2-one starting materials of Formula 4 may be prepared as described by or adapted from R. Duschinsky and L. A. Dolan, *J. Am. Chem. Soc.* 67, 2079 (1945), R. Duschinsky and L. A. Dolan, *J. Am. Chem. Soc.* 68, 2350 (1945) or U.S. patent 2,441,933.

The compounds of general Formula 1 may be used in the treatment of cardiac failure including congestive heart failure, backward heart failure, forward heart failure, left ventricular heart failure, or right ventricular heart failure or in the treatment of any other condition which requires the strengthening of heart action with a cardiotonic. In many respects these compounds possess digitalis-like action. The compounds of general Formula 1 may also be used in the treatment of hypertension including primary or essential hypertension, hormonally induced hypertension, renal hypertension and chemically induced hypertension. Finally, the compounds of general Formula 1 may be used as antithrombotics. They affect the coagulation of blood by preventing the aggregation of blood platelets, which play a dominant role in thrombotic conditions both in the initial event and at the occlusive stage. Arterial thrombosis, particularly in arteries supplying the heart muscle and brain, is a leading cause of death and disability.

The compounds may be administered in various manners to achieve the desired effect. The compounds may be administered alone or in the form of pharmaceutical preparations to the patient being treated either orally or parenterally, that is, intravenously or intramuscularly. The amount of compound administered will vary with the severity of the hypertension, cardiac failure or blood clotting and the mode of administration. For oral administration the antihypertensively effective amount of compound is from about 0.1 mg/kg (milligrams per kilograms) of patient body weight per day to about 500 mg/kg of patient body weight per day and preferably from about 50 mg/kg of patient body weight per day to about 150 mg/kg patient body weight per day.

For parenteral administration the antihypertensively effective amount of compound is from about

0.01 mg/kg of patient body weight per day up to about 150 mg/kg of patient body weight per day and preferably from about 1.0 mg/kg of patient body weight per day up to about 10.0 mg/kg of patient body weight per day. For oral or parenteral administration the cardiotonically effective amount of compound is from about 0.1 mg/kg patient body weight per day up to about 500 mg/kg of patient body weight per day and preferably from about 0.1 mg/kg of patient body weight per day up to about 10.0 mg/kg of patient body weight per day. For oral or parenteral administration the anticoagulant effective amount of compound is from about 0.1 mg/kg of patient body weight per day up to about 1000 mg/kg of patient body weight per day and preferably from about 1 mg/kg of patient body weight per day up to about 100 mg/kg of patient body weight per day.

For oral administration a unit dosage may contain, for example, from 10 to 100 mg of the active ingredient. For parenteral administration a unit dosage may contain, for example, from 5 to 50 mg of the active ingredient. Repetitive daily administration of the compounds may be desired and will vary with the condition of the patient and the mode of administration.

As used herein the term patient is taken to mean a warm blooded animal, for example, birds, such as chickens and turkeys, and mammals, such as primates, humans, sheep, horses, bovine cows and bulls, pigs, dogs, cats, rats and mice.

For oral administration the compounds can be formulated into solid or liquid preparations such as capsules, pills, tablets, troches, powders, solutions, suspensions or emulsions. The solid unit dosage forms can be a capsule which can be of the ordinary gelative type containing, for example, lubricants and inert filler, such as lactose, sucrose, and cornstarch. In another embodiment the compounds of general Formula 1 can be tableted with conventional tablet bases such as lactose, sucrose, and cornstarch in combination with binders, such as acacia, cornstarch or gelatin, disintegrating agents such as potato starch or alginic acid, and a lubricant such as stearic acid or magnesium stearate.

For parenteral administration the compounds may be administered as injectable dosages of a solution or suspension of the compound in a physiologically acceptable diluent with a pharmaceutical carrier which can be a sterile liquid such as water and oils with or without the addition of a surfactant and other pharmaceutically acceptable adjuvants. Illustrative of oils which can be employed in these preparations are those of petroleum, animal, vegetable, or synthetic origin, for example, peanut oil, soybean oil, and mineral oil. In general, water, saline, aqueous dextrose and related sugar solutions, ethanol and glycols such as propylene glycol or polyethylene glycol are preferred liquid carriers, particularly for injectable solutions.

The compounds can be administered in the form of a depot injection or implant preparation which may be formulated in such a manner as to permit a sustained release of the active ingredient. The active ingredient can be compressed into pellets or small cylinders and implanted subcutaneously or intramuscularly as depot injections or implants. Implants may employ inert materials such as biodegradable polymers or synthetic silicones, for example, Silastic (RTM), silicone rubber manufactured by the Dow-Corning Corporation.

Following are illustrative pharmaceutical formulations which may be employed in practicing the present invention:

Preparation of a tablet formulation

		Per Tablet	
40	a)	1,3-Dihydro-4-(4-methoxybenzoyl)-5-methyl-2H-imidazol-2-one	100 mg
	b)	Cornstarch	15 mg
45	c)	Lactose	33.5 mg
	d)	Magnesium stearate	1.5 mg

Preparation of a parenteral formulation

50	a)	1,3-Dihydro-4-(4-methoxybenzoyl)-5-methyl-2H-imidazol-2-one	1.000 g	50
	b)	Polyoxyethylene sorbitan monooleate	2.000 g	
	c)	Sodium chloride	0.128 g	
	d)	Water for injection qs ad	20.000 ml	

The following are examples of the use of the compounds of this invention as antihypertensives, cardiotonics and anticoagulants.

EXAMPLE A

Use of 1,3-dihydro-4-(4-methoxybenzoyl)-5-methyl-2H-imidazol-2-one as an antihypertensive

100 mg/kg of the title compound is administered orally to six spontaneously hypertensive rats. This dose results in a 40% decrease, on the average, in the blood pressure within 15 minutes of administration.

EXAMPLE B

Use of 1,3-dihydro-4-(4-methoxybenzoyl)-5-methyl-2H-imidazol-2-one as a cardiotonic

Heart failure is induced in a dog by administering sodium pentobarbitol (20 mg/kg) or propranolol hydrochloride (3 mg/kg) to the blood perfusing the heart. Following administration of either of these cardiac depressants the right atrial pressure increased dramatically and cardiac output is severely depressed. Administration of the title compound (1 mg/kg) reverses the failure as indicated by reversal of the right atrial pressure and cardiac output to near pretreatment levels.

EXAMPLE C

10 Use of 1,3-dihydro-4-(4-methoxybenzoyl)-5-methyl-2H-imidazol-2-one as an antithrombotic

When adenosine diphosphate is added to citrated platelet rich human plasma a typical aggregation of blood platelet occurs. However, if the title compound is added to the citrated platelet rich human plasma in concentrations of 3, 10, 30 and 100 µg/ml and subsequently adenosine diphosphate is added, the aggregation of blood platelets is inhibited 33, 49, 82 and 98%, respectively.

15 The following specific examples further illustrate the preparation of compounds employed in the instant invention.

EXAMPLE 1

1,3-Dihydro-4-(4-fluorobenzoyl)-5-methyl-2H-imidazol-2-one

20 To a stirred mixture of 98.1 g (1 mole) of 1,3-dihydro-4-methyl-2H-imidazol-2-one, 266.7 g (2 mole) of anhydrous aluminum chloride and 500 ml of nitrobenzene is added dropwise over 10 minutes, 158.6 g (1 mole) of *p*-fluorobenzoyl chloride. The mixture is stirred at 60-65°C for 6 hours, then poured on 2 kg of ice. The resulting precipitate is washed with diethyl ether and water and is recrystallized from 1.2 liters of dimethylformamide to give 131 g of the title compound. M.P. 289-292°C.

EXAMPLE 2

1,3-Dihydro-4-methyl-5-[4-(1-piperidiny)benzoyl]-2H-imidazol-2-one

A suspension of 11.0 g (0.05 mole) of 1,3-dihydro-4-(4-fluorobenzoyl)-5-methyl-2H-imidazol-2-one in 30 ml of piperidine is stirred at reflux temperature for 24 hours. Excess piperidine is evaporated under reduced pressure and the residue is recrystallized twice from a mixture of isopropanol and water to give 11.9 g of the title compound. M.P. 260-263°C.

EXAMPLE 3

1,3-Dihydro-4-methyl-5-[4-(4-morpholinyl)benzoyl]-2H-imidazol-2-one

35 Following the procedure of Example 2 but substituting morpholine for piperidine, the title compound is obtained. M.P. 283-286°C.

EXAMPLE 4

1,3-Dihydro-4-[4-(dimethylamino)benzoyl]-5-methyl-2H-imidazol-2-one

40 A mixture of 11.0 g (0.05 mole) of 1,3-dihydro-4-(4-fluorobenzoyl)-5-methyl-2H-imidazol-2-one, 100 ml of 30% aqueous solution of dimethylamine and 200 ml of ethanol is heated in a pressure bomb at 130-135°C for 22 hours. The mixture is cooled, the solid is collected and recrystallized from isopropanol-water to give the title compound. M.P. >310°C. λ(max)(methanol) 364 nm (ε = 23,300).

EXAMPLE 5

1,3-Dihydro-4-(4-hydroxybenzoyl)-5-methyl-2H-imidazol-2-one

To a melt of 26 g (0.23 mole) of pyridine hydrochloride at 200-205°C is added 5.3 g (0.023 mole) of 1,3-dihydro-4-(4-methoxybenzoyl)-5-methyl-2H-imidazol-2-one and the mixture is stirred mechanically for 30 minutes. The reaction mixture is poured on ice-2N HCl. The resulting precipitate is washed with water and recrystallized from isopropanol-water to give the title compound. M.P. >300°C. λ(max)(methanol) 320 nm (ε = 13,200).

EXAMPLE 6

1,3-Dihydro-4-methyl-5-[4-(methylthio)benzoyl]-2H-imidazol-2-one

55 A solution of 25.0 g of 4-(methylthio)-benzoic acid and 22 ml of thionyl chloride in 50 ml of benzene is refluxed for 4 hours. Excess reagent and solvent is evaporated and the residue is azeotroped 3 times with benzene to remove all thionyl chloride. The residue is added dropwise to a mixture of 11.8 g of 1,3-dihydro-4-methyl-2H-imidazol-2-one, 40.0 g of anhydrous aluminum chloride and 100 ml of nitrobenzene. The resulting mixture is stirred at 60-65°C for 5 hours, poured on ice and the precipitate that forms is collected, washed with ethyl ether and water, and recrystallized from isopropanol-water to give the title compound. M.P. 255-258°C. (dec.).

EXAMPLE 7

1,3-Dihydro-4-(4-methoxybenzoyl)-5-methyl-2H-imidazol-2-one

65 To 19.6 g of 1,3-dihydro-4-methyl-2H-imidazol-2-one and 53.2 g of anhydrous aluminum chloride in 150 ml

of nitrobenzene is added dropwise 34.2 g of *p*-methoxybenzoyl chloride and the mixture is poured on 500 ml of 2*N*-HCl and ice, washed 3 times with ethyl ether, the resulting solid is recrystallized from isopropanol-water to give the title compound. M.P. 257-258°C (dec.).

5 EXAMPLE 8

1,3-Dihydro-4-(4-methoxybenzoyl)-5-methyl-2H-imidazol-2-one, sodium salt

To 7.0 g of 1,3-dihydro-4-(4-methoxybenzoyl)-5-methyl-2*H*-imidazol-2-one in 100 ml of methanol is added 1.6 g of sodium methoxide. The mixture is heated on a steam bath until homogeneous, filtered and evaporated to dryness. The solid residue is recrystallized from isopropanol to give the title compound. M.P. 280-282°C (dec.).

EXAMPLE 9

4-Benzoyl-1,3-dihydro-5-methylimidazol-2-one

To a solution of 3.0 g of 4-methylimidazol-2-one and 8.0 g of aluminum chloride in 50 ml of nitrobenzene is added dropwise 4.6 g of benzoyl chloride. The solution is warmed at 60°C for 4 hours, poured over ice water, slurried with ether and the resulting solids filtered and dried to yield the title compound. M.P. 250-54°C.

EXAMPLE 10

1,3-Dihydro-4-methyl-5-thienoyl-2H-imidazol-2-one

To a solution of 7.3 g of 4-methylimidazol-2-one and 10.8 g of aluminum chloride in 150 ml of nitrobenzene is added 12.0 g of 2-thienoyl chloride. The mixture is stirred at 60°C for 3 hours, cooled and poured over ice water. The organic portion is extracted into ethyl acetate, dried and the organic solvent evaporated to give the title compound. M.P. 212-215°C.

25 EXAMPLE 11

1,3-Dihydro-4-(3,4-dimethoxybenzoyl)-2H-imidazol-2-one

To a solution of 6.5 g of 1,3-dihydro-4-methyl-2*H*-imidazol-2-one and 14.6 g of aluminum chloride in 65 ml of nitrobenzene is added 17.6 g of 3,4-dimethoxybenzoyl chloride in portions. The mixture is stirred for 3 hours at 60°C, cooled and poured over ice water. The gummy solids are filtered and recrystallized twice from ethyl alcohol-water to afford the title compound. M.P. 257-259°C.

EXAMPLE 12

1,3-Dihydro-4-(2-furanoyl)-5-methyl-2H-imidazol-2-one

To a slurry of 8.9 g of 1,3-dihydro-4-methyl-2*H*-imidazol-2-one and 24.0 g of aluminum chloride in 135 ml of nitrobenzene is added 12.9 g of furanoyl chloride in a dropwise manner. The mixture is stirred at 60°C for 3 hours, cooled and poured over ice water. The solid is then filtered and recrystallized twice from methyl alcohol to afford the title compound. M.P. 214-216°C.

EXAMPLE 13

1,3-Dihydro-4-(2-thienoyl)-2H-imidazol-2-one

In 50 ml of nitrobenzene is combined 13.3 g of aluminum chloride, 4.2 g of 1,3-dihydro-2*H*-imidazol-2-one and 8.1 g of thienoyl chloride. The mixture is stirred at 60°C for 3 hours and poured over ice water. The solids are filtered, washed with ether and recrystallized twice from ethanol-water to afford the title compound. M.P. 339-42°C.

EXAMPLE 14

4-Benzoyl-1,3-dihydro-2H-imidazol-2-one

To 51 ml of nitrobenzene is added 1.68 g of 1,3-dihydro-2*H*-imidazol-2-one, 5.3 g of aluminum chloride and 3.1 g of benzoyl chloride. The mixture is stirred for 3 hours at 60°C and poured into ice water. The solids are filtered, washed with ether and recrystallized twice from methyl alcohol-water to afford the title compound. M.P. 329-30°C.

EXAMPLE 15

1,3-Dihydro-4-furanoyl-2H-imidazol-2-one

To 50 ml of nitrobenzene is added 4.2 g of 1,3-dihydro-2*H*-imidazol-2-one, 13.3 g of aluminum chloride and 7.2 g of furanoyl chloride. The mixture is stirred at 60°C for 3 hours and poured over ice water. The solids are filtered, washed with ether and recrystallized twice from ethanol-water to afford the title compounds. M.P. 318-321°C.

60 EXAMPLE 16

1,3-Dihydro-4-(3,4-methylenedioxybenzoyl)-5-methyl-2H-imidazol-2-one

To 5.13 g. of 1,3-dihydro-4-methyl-2*H*-imidazol-2-one and 7.98 g. of anhydrous aluminum chloride in 80 ml. of nitrobenzene is added dropwise 10.60 g. of 3,4-methylenedioxybenzoyl chloride and the mixture is poured on 500 ml. of 2*N*-HCl and ice, washed 3 times with ethyl ether, the resulting solid is collected to give the title compound. M.P. 293-296°C (dec.).

EXAMPLE 17**1,3-Dihydro-4-(4-methoxybenzoyl)-1,3,5-trimethyl-2H-imidazol-2-one**

In 120 ml of DMSO is placed 15.2 g of powdered potassium hydroxide, 8.0 g of 1,3-dihydro-4-(4-methoxybenzoyl)-5-methyl-2H-imidazol-2-one, sodium salt and 19.5 g of methyl iodide. The mixture is stirred at room temperature for 60 minutes and then poured into 800 ml of water. Extraction with methylene chloride gives a solid, which is crystallized from ether. M.p. 109-111°C. NMR: N-CH₃ (6 protons) at 3.3 ppm.

EXAMPLE 18**1,3-Dihydro-(1 or 3),5-dimethyl-4-(4-methoxybenzoyl)-2H-imidazol-2-one**

To 2.0 g of 1,3-dihydro-4-(4-methoxybenzoyl)-5-methyl-2H-imidazol-2-one in 30 ml of DMSO is added 0.288 g of sodium hydride and 1.22 g of methyl iodide. The mixture is stirred at 22°C for 30 minutes, poured into methylene chloride and washed with water. The solvent is dried and evaporated to give an oil which when triturated with chloroform gives a solid. The solid is crystallized from methanol; m.p. 225-228°C.

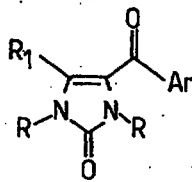
Anal. calcd. for C₁₂H₁₄N₂O₃: C, 63.40; H, 5.73; N, 11.39.;

Found: C, 63.34; H, 5.85; N, 11.21;

NMR: N-Methyl; Singlet at 3.2 ppm.

CLAIMS

1. A compound for use in the alleviation of hypertension or the treatment of cardiac failure, having the formula



wherein R is hydrogen, C₁₋₄ alkyl, (C₁₋₄alkyl)carbonyl or benzoyl;

R₁ is hydrogen or C₁₋₄ alkyl; and

- Ar is 2-furyl; 2-thienyl; phenyl; phenyl monosubstituted by halogen, hydroxy, C₁₋₄ alkyl, C₁₋₄ alkoxy, C₁₋₄ alkylthio, trifluoromethyl, -SO₂N(R₂)₂, NR₃R₄, pyrrolidino, piperidino, morpholino, piperazino or N'-alkylpiperazino, in which R₂, R₃ and R₄ are independently selected from hydrogen and C₁₋₄ alkyl; disubstituted phenyl in which one substituent is at the para position and the substituents are independently selected from halogen, hydroxy, C₁₋₄ alkyl and C₁₋₄ alkoxy; or 3,4-methylenedioxyphenyl in which the methylene group is optionally substituted by one or two methyl groups;

or a pharmaceutically acceptable salt thereof.

2. A compound having the formula defined in claim 1, with the provisos that Ar is not phenyl, mono- or di-hydroxyphenyl, aminophenyl or dimethylphenyl.

3. A compound as claimed in claim 1 wherein Ar is phenyl.

4. A compound as claimed in claim 1 or claim 2 wherein Ar is monosubstituted phenyl.

5. A compound as claimed in claim 4 wherein the substituent is C₁₋₄ alkoxy or C₁₋₄ alkylthio.

6. A compound as claimed in claim 4 wherein the substituent is methoxy.

7. A compound as claimed in claim 4 wherein the substituent is methylthio.

8. A compound as claimed in any of claims 4 to 7 wherein the substituent is at the para position.

9. A compound as claimed in any of claims 1 to 3 wherein Ar is disubstituted phenyl.

10. A compound as claimed in claim 9 wherein the substituents are each C₁₋₄ alkoxy.

11. A compound as claimed in claim 10 wherein the substituents are each methoxy.

12. A compound as claimed in any of claims 9 to 11 wherein the substituents are at the meta and para positions.

13. A compound as claimed in any of claims 1 to 3 wherein Ar is 3,4-methylenedioxyphenyl in which the methylene group is optionally substituted by one or two methyl groups.

14. A compound as claimed in any preceding claim wherein R is hydrogen and R₁ is hydrogen or C₁₋₄ alkyl.

15. A compound as claimed in any preceding claim wherein R₁ is hydrogen, methyl or ethyl.

16. A compound as claimed in claim 15 wherein R₁ is methyl.

17. 1,3-Dihydro-4-methyl-5-[4-(methylthio)benzoyl]-2H-imidazol-2-one or a pharmaceutically acceptable salt thereof.

18. A compound as claimed in claim 1 substantially as described in any of Examples 1 to 18.

19. A pharmaceutical composition comprising a compound as claimed in any preceding claim in association with a physiologically acceptable excipient.

20. A pharmaceutical composition comprising a compound having the formula defined in claim 1 in association with a physiologically acceptable excipient which is a solid or a sterile liquid.

21. A composition according to claim 19 substantially as herein described.

**EXAMPLE 17****1,3-Dihydro-4-(4-methoxybenzoyl)-1,3,5-trimethyl-2H-imidazol-2-one**

In 120 ml of DMSO is placed 15.2 g of powdered potassium hydroxide, 8.0 g of 1,3-dihydro-4-(4-methoxybenzoyl)-5-methyl-2H-imidazol-2-one, sodium salt and 19.5 g of methyl iodide. The mixture is stirred at room temperature for 60 minutes and then poured into 800 ml of water. Extraction with methylene chloride gives a solid, which is crystallized from ether. M.p. 109-111°C. NMR: N-CH₃ (6 protons) at 3.3 ppm.

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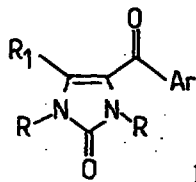
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2. A compound having the formula defined in claim 1, with the provisos that Ar is not phenyl, mono- or di-hydroxyphenyl, aminophenyl or dimethylphenyl.

3. A compound as claimed in claim 1 wherein Ar is phenyl.

4. A compound as claimed in claim 1 or claim 2 wherein Ar is monosubstituted phenyl.

5. A compound as claimed in claim 4 wherein the substituent is C₁₋₄ alkoxy or C₁₋₄ alkylthio.

6. A compound as claimed in claim 4 wherein the substituent is methoxy.

7. A compound as claimed in claim 4 wherein the substituent is methylthio.

8. A compound as claimed in any of claims 4 to 7 wherein the substituent is at the para position.

9. A compound as claimed in any of claims 1 to 3 wherein Ar is disubstituted phenyl.

10. A compound as claimed in claim 9 wherein the substituents are each C₁₋₄ alkoxy.

11. A compound as claimed in claim 10 wherein the substituents are each methoxy.

12. A compound as claimed in any of claims 9 to 11 wherein the substituents are at the meta and para positions.

13. A compound as claimed in any of claims 1 to 3 wherein Ar is 3,4-methylenedioxyphenyl in which the methylene group is optionally substituted by one or two methyl groups.

14. A compound as claimed in any preceding claim wherein R is hydrogen and R₁ is hydrogen or C₁₋₄ alkyl.

15. A compound as claimed in any preceding claim wherein R₁ is hydrogen, methyl or ethyl.

16. A compound as claimed in claim 15 wherein R₁ is methyl.

17. 1,3-Dihydro-4-methyl-5-[4-(methylthio)benzoyl]-2H-imidazol-2-one or a pharmaceutically acceptable salt thereof.

18. A compound as claimed in claim 1 substantially as described in any of Examples 1 to 18.

19. A pharmaceutical composition comprising a compound as claimed in any preceding claim in association with a physiologically acceptable excipient.

20. A pharmaceutical composition comprising a compound having the formula defined in claim 1 in association with a physiologically acceptable excipient which is a solid or a sterile liquid.

21. A composition according to claim 19 substantially as herein described.