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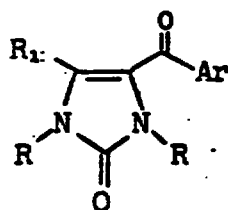
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4-AROYLIMIDAZOL-2-ONES

This invention relates to novel 4-arylimidazol-2-ones which can have utility as anti-hypertensive, cardio-tonic and anti-thrombotic agents.

4-Arylimidazol-2-ones are disclosed in US Patent
5 Specifications Nos. 2,514,380 and 2,441,933, as well as in
R. Duschinsky and L.A. Dolan, J. Am. Chem. Soc. 68, 2350-55
(1964); ibid. 70, 657-62 (1948); ibid. 67, 2079-84 (1945);
and Y.A. Rozin, E.P. Dorienko and Z.V. Pushkareva, Khim.
Geterotsikl. Soedin., 4(4), 698-701 (1968). These references
10 disclose the preparation and chemical utility of 4-benzoyl-
1,3-dihydro-2H-imidazol-2-one and related compounds.

British Patent Specification No. 2,055,364A
discloses and claims compounds of formula I



15 wherein R is hydrogen, C₁₋₄ alkyl, (C₁₋₄ alkyl)carbonyl or
benzoyl; R₁ is hydrogen or C₁₋₄ alkyl; and Ar is aryl, e.g.
mono-substituted phenyl. These compounds are disclosed as
having utility in the alleviation of hypotension and the
treatment of cardiac failure.

20 Novel compounds according to the invention are of
formula I, in which R and R₁ are as defined above, and in
which Ar is phenyl, mono-substituted at the ortho, meta or
para position, with a (C₁₋₄ alkyl)sulfinyl or (C₁₋₄ alkyl)-
sulfonyl group, and include the pharmaceutically acceptable
25 salts thereof. These compounds can have utility as anti-
hypertensive, cardiotonic and anti-thrombotic agents.

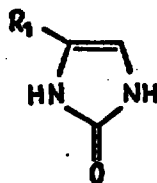
Each C₁₋₄ alkyl group which may be present is
straight or branched and may be, for example, methyl, ethyl,
propyl, isopropyl, butyl or isobutyl.

30 R is preferably hydrogen, in which case it is
preferred that R₁ is hydrogen, methyl or ethyl. R₂ is

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preferably methyl. The alkylsulfinyl or alkylsulfonyl group is preferably at the para position of the benzene ring of the Ar group.

When R is hydrogen, the compounds of the invention can exist in a number of tautomeric forms. These acidic tautomers may form pharmaceutically active salts with, for example, pharmaceutically acceptable alkali metals such as sodium or potassium, alkaline earth metals such as calcium or magnesium, transition metals such as zinc or iron, main group metals, or ammonium or organic ammonium ions such as the tetramethylammonium ion. The invention comprehends such tautomers and salts.

Compounds of the invention wherein R is hydrogen may be prepared by a Friedel-Crafts acylation of an imidazol-2-one of the formula



wherein R₁ is as defined above, with the appropriate aroyl halide, e.g. fluoride, chloride, bromide or iodide. If desired, instead of the halide, the corresponding free acid or acid anhydride may be used, under similar reaction conditions. These alternative reactions are more fully described in Olah, "Friedel-Crafts and Related Reactions," Vol. III, Part 1, Interscience Publications, John Wiley and Sons, New York, 1964.

25 The Friedel-Crafts reaction is performed by pre-mixing the appropriate imidazol-2-one with 1 to 10, preferably about 2, molar equivalents, of a Lewis acid catalyst in a solvent. Suitable solvents are, for example, petroleum ethers, chlorinated hydrocarbons such as carbon tetrachloride, ethylene chloride, methylene chloride or 30 chloroform, chlorinated aromatics such as 1,2,4-trichlorobenzene or *o*-dichlorobenzene, carbon disulfide and, preferably, nitrobenzene. From 1 to 10, preferably about 1.1, molar equivalents of the appropriate aroyl compound is

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added, preferably dropwise, to the mixture of imidazol-2-one, Lewis acid and solvent, and the reaction is allowed to proceed for 1 to 100 hours, preferably 1 to 10 hours, depending on the conditions. The temperature can be from 5 -78° to 150°C, preferably 0 to 100°C, and most preferably about 60°C. The resulting aroylimidazol-2-one may be isolated from the reaction mixture by any suitable procedure, preferably by quenching the reaction mixture with ice-water and subsequently removing the product by filtration or 10 extraction and solvent removal.

Suitable Lewis acid catalysts are, for example, metals such as aluminium, cerium, copper, iron, molybdenum, tungsten or zinc, Bronsted acids such as phosphoric, sulfuric, sulfonic or hydrohalo, e.g. hydrochloric or 15 hydrobromic, acid, halogen-substituted acetic acids such as chloroacetic or trifluoroacetic acid, and metallic halides such as boron halides, zinc chloride, zinc bromide, beryllium chloride, copper chloride, iron(III) bromide, iron(III) chloride, mercury(II) chloride, mercury(I) chloride, 20 antimony bromide, antimony chloride, titanium(IV) bromide, titanium(IV) chloride, titanium(III) chloride, aluminium bromide or, preferably, aluminium chloride.

Alternatively, compounds of the invention may be prepared by selectively oxidising a compound of formula I 25 in which Ar is phenyl substituted by a C₁₋₄ alkylthio group. Selective oxidation to produce a sulfoxide or a sulfone of the invention, respectively, can be accomplished by reaction with 1, or 2 or more, respectively, equivalents of hydrogen peroxide.

30 If it is desired to convert a compound of the invention in which R is hydrogen to a compound in which R is other than hydrogen, suitable reaction procedures are described on pages 4 and 5 of British Patent Specification No. 2,055,364A. That specification also describes suitable 35 methods for preparing salts of compounds of the invention, and the preparation of starting materials for the reactions described herein.

The utilities described for the compounds of

British Patent Specification No. 2,055,364A apply to the compounds of the present invention, and reference to the earlier specification should be made for the description of suitable uses, compositions, modes of administration and dosages. The contents of the earlier specification are incorporated herein, as appropriate, by way of reference. A pharmaceutical composition according to the present invention comprises a compound of the invention in association with a physiologically acceptable excipient.

10 The following Examples illustrate how compounds of the present invention may be prepared.

Example 1

1,3-Dihydro-4-ethyl-5-(4-methylsulfonylbenzoyl)-2H-imidazol-2-one

15 In 100 g polyphosphoric acid are placed 2.0 g 4-(methylsulfonyl)benzoic acid and 1.12 g 1,3-dihydro-4-ethyl-2H-imidazol-2-one. The mixture is heated to 150°C for 5 hours, cooled and quenched with 1000 ml of water. The title compound, which separates as a solid, is collected and washed with water.

By substituting 4-(methylsulfinyl)benzoic acid for 4-(methylsulfonyl)benzoic acid in the above procedure, the compound 1,3-dihydro-4-ethyl-5-(4-methylsulfinylbenzoyl)-2H-imidazol-2-one is obtained.

25 Example 2

1,3-Dihydro-4-Methyl-5-(4-methylsulfinylbenzoyl)-2H-imidazol-2-one

To 20 g of 1,3-dihydro-4-methyl-5-[4-(methylthio)benzoyl]-2H-imidazol-2-one in glacial acetic acid are added 11.3 g (1.25 equivalents) of 30% hydrogen peroxide. The solution is warmed at 50°C for 2½ hours and then allowed to cool overnight. Acetic acid is removed in vacuo to leave the title compound, m.p. 276-278°C (dec).

Example 3

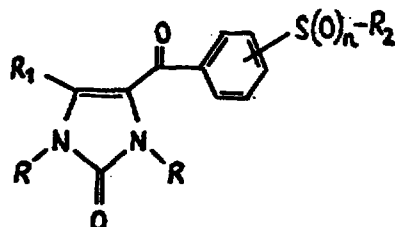
35 1,3-Dihydro-4-Methyl-5-(4-methylsulfonylbenzoyl)-2H-imidazol-2-one

To 25 g of 1,3-dihydro-4-methyl-5-[4-(methylthio)benzoyl]-2H-imidazol-2-one in glacial acetic acid are added

34 g (3 equivalents) of 30% hydrogen peroxide. The solution is warmed at 50°C for 20 hours. Acetic acid is removed in vacuo to leave the title compound, m.p. 315-318°C (dec).

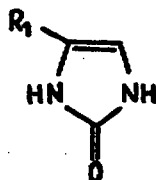
CLAIMS

1. A compound of the formula



wherein R is hydrogen, C₁₋₄ alkyl, (C₁₋₄ alkyl)carbonyl or benzoyl; R₁ is hydrogen or C₁₋₄ alkyl; R₂ is C₁₋₄ alkyl; and n is 1 or 2; or a pharmaceutically acceptable salt thereof.

2. A compound as claimed in claim 1 wherein R is hydrogen.
3. A compound as claimed in claim 2 wherein R₁ is hydrogen, methyl or ethyl.
4. A compound as claimed in any preceding claim, wherein the R₂S(O)_n- group is at the 4-position.
5. A compound as claimed in any preceding claim, wherein R₂ is methyl.
6. 1,3-Dihydro-4-methyl-5-(4-methylsulfinylbenzoyl)-2H-imidazol-2-one.
7. 1,3-Dihydro-4-methyl-5-(4-methylsulfonylbenzoyl)-2H-imidazol-2-one.
8. A compound as claimed in claim 1, substantially as described in any of the Examples.
9. A process for preparing a compound as claimed in claim 2, which comprises reacting a compound of the formula



wherein R₁ is as defined in claim 1, with 1 to 10 molar equivalents of a (C₁₋₄ alkylsulfinyl)benzoyl halide or (C₁₋₄ alkylsulfonyl)benzoyl halide, or the corresponding free acid or acid anhydride, in the presence of 1 to

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10 molar equivalents of a Lewis acid catalyst, in a solvent, at from 0 to 100°C for 1 to 10 hours.

10. A process for preparing a compound as claimed in claim 1, which comprises selectively oxidising a compound of the formula given in claim 1 but in which n is zero.

11. A pharmaceutical composition comprising a compound as claimed in any of claims 1 to 8, in association with a physiologically acceptable excipient.

