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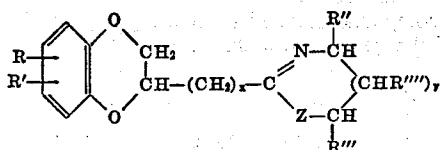
2,979,511

CERTAIN 1,4-BENZODIOXANYL IMIDAZOLINES AND CORRESPONDING PYRIMIDINES AND PROCESS

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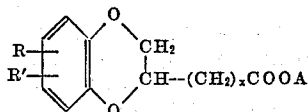
This invention relates to new heterocyclic derivatives of benzodioxane and more particularly to compounds of the general formula



and acid-addition salts of those compounds which contain a basic nitrogen atom, wherein R and R' are the same or different and represent hydrogen, hydroxy, halogen, trifluoromethyl, nitro, lower alkyl, lower alkenyl or lower alkoxy; R'', R''' and R'''' are the same or different and represent hydrogen or lower alkyl; x is zero or one, y is zero or one, and Z is —NH—, or —N(lower alkyl)—. Particularly preferred are compounds wherein R, R', R'', R''' and R'''' are hydrogen, y is zero, and Z is —NH—.

The compounds of this invention are physiologically active substances which are useful as peripheral vasodilators. Thus, they may be used instead of known peripheral vasodilators, such as Priscoline, in the treatment of peripheral vascular diseases, for which purpose they are administered perorally or parenterally with concentration and dosage adjusted for the activity of the particular compound. Furthermore, the compounds of this invention also possess adrenergic blocking and hypotensive action, and thus may be used instead of known agents such as Dibenamine in the treatment of hypertension.

The compounds of this invention are prepared by the process of this invention which comprises heating a compound of the general formula



wherein R, R', and x are as hereinbefore defined, and A is hydrogen or lower alkyl (preferably methyl), with a compound of the general formula:



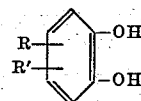
wherein R'', R''', R'''', y and Z are as hereinbefore defined.

Suitable benzodioxane reactants include the following carboxylic acids, as well as the lower alkanol esters thereof: 1,4-benzodioxane-2-carboxylic acid; hydroxy-1,4-benzodioxane-2-carboxylic acids, such as 6-hydroxy-1,4-benzodioxane-2-carboxylic acid and 8-hydroxy-1,4-benzodioxane-2-carboxylic acid; dihydroxy-1,4-benzodioxane-2-carboxylic acids, such as 6,8-dihydroxy-1,4-benzodioxane-2-carboxylic acid; halo-1,4-benzodioxane-2-carboxylic acids, such as 7-chloro-1,4-benzodioxane-2-carboxylic acid and 7-bromo-1,4-benzodioxane-2-carboxylic acid; dihalo-1,4-benzodioxane-2-carboxylic acids; trifluoromethyl-1,4-benzodioxane-2-carboxylic acids, such as 7-trifluoromethyl-1,4-benzodioxane-2-carboxylic acid; nitro-1,4-benzodioxane-2-carboxylic acids, such as 7-nitro-1,4-benzodioxane-2-carboxylic acid; lower alkyl-1,4-benzodioxane-2-carboxylic acids, such as 6-methyl-1,4-benzodioxane-2-

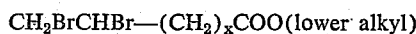
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carboxylic acid, 8-ethyl-1,4-benzodioxane-2-carboxylic acid, and 7-n-propyl-1,4-benzodioxane-2-carboxylic acid; di-(lower alkyl)-1,4-benzodioxane-2-carboxylic acids, such as 6,8-dimethyl-1,4-benzodioxane-2-carboxylic acid and 7,8-diethyl-1,4-benzodioxane-2-carboxylic acid; lower alkoxy-1,4-benzodioxane-2-carboxylic acids, such as 6-methoxy-1,4-benzodioxane-2-carboxylic acid and 8-ethoxy-1,4-benzodioxane-2-carboxylic acid; di-(lower alkoxy)-1,4-benzodioxane-2-carboxylic acids; lower alkyl-lower alkoxy-1,4-benzodioxane-2-carboxylic acids, such as 6-methyl-8-ethoxy-1,4-benzodioxane-2-carboxylic acid; (lower alkenyl)-1,4-benzodioxane-2-carboxylic acid, such as 6-allyl-1,4-benzodioxane-2-carboxylic acid; 1,4-benzodioxane-2-acetic acid; and the hydroxy, halo, trifluoromethyl, nitro, lower alkyl, lower alkenyl, and lower alkoxy derivatives of the last.

In those cases where the 1,4-benzodioxane-2-carboxylic acids (and the corresponding lower alkyl esters) are new compounds, they can be prepared by reacting a pyrocatechol of the formula



wherein R and R' are as hereinbefore defined, with a dibromoalkanoic acid ester of the formula:



wherein x is as hereinbefore defined, and if desired hydrolyzing the resultant ester to the corresponding acid. Those compounds wherein x is one can also be obtained from the corresponding 1,4-benzodioxane-2-carboxylic acid derivative by a series of steps including: (1) treating the acid with lithium aluminum hydride to yield the corresponding carbinol derivative; (2) reacting the carbinol with thionyl chloride in pyridine to yield the corresponding methyl chloride derivative; (3) reacting the methyl chloride derivative with sodium cyanide to yield the corresponding methyl nitrile derivative; and (4) hydrolyzing the nitrile to a carboxyl radical, thereby covering the original carboxylic acid radical to an acetic acid radical. (The pyrocatechols can be obtained by reduction of the correspondingly substituted o-nitrophenol to the o-amino-phenol, followed by diazotization to the pyrocatechols.)

Suitable amine reactants include lower alkylene diamines, such as ethylene diamine, trimethylene diamine, isopropylene diamine, 2,3-butylenediamine, 2,4-pentylene diamine, 2,3-hexylene diamine, and 2,4-octylene diamine; and N-(lower alkyl)-lower alkylene diamines, such as N-(lower alkyl)-ethylenediamines (e.g. N-ethyl-ethylenediamine), N-(lower alkyl)-trimethylenediamines (e.g. N-methyl-1,3-propanediamine), and N-(lower alkyl)-isopropylene diamines.

The compound formed, if it contains a basic nitrogen atom, can then be converted to its acid addition salt in the usual manner by treatment with the desired acid. The preferred acids are those which are non-toxic and include inorganic acids, such as the hydrohalic acids (e.g. hydrochloric acid), sulfuric acid, phosphoric acid, and nitric acid; and organic acids, such as tartaric acid, citric acid, oxalic acid, acetic acid, succinic acid, maleic acid and lactic acid.

The following examples illustrate the invention (all temperatures being in centigrade):

EXAMPLE 1

2-[2-(1,4-benzodioxanyl)]-2-imidazoline hydrochloride

(a) Preparation of 2-[2-(1,4-benzodioxanyl)]-2-imidazoline.—A mixture of 25.0 g. of 1,4-benzodioxane-2-carboxylic acid and 40 g. of ethylenediamine is refluxed for sixteen hours. At this point, about 10 ml. of distil-

late are collected to remove water and 10 ml. of ethylenediamine are added. The mixture is then refluxed for an additional eight hours and then concentrated by distillation. The residue is fractionated to give about 13.1 g. of nearly colorless product; B.P. about 155–165° (0.1 mm. mercury).

(b) *Preparation of 2-[2-(1,4-benzodioxanyl)]-2-imidazoline hydrochloride*.—12.8 g. of the 2-[2-(1,4-benzodioxanyl)]-2-imidazoline, obtained in step (a) is dissolved in 25 ml. of ethanol. The solution is treated with 12.8 ml. of 4.9 N alcoholic hydrogen chloride, followed by dilution with ether to yield a semisolid which solidifies on trituration with acetonitrile to a crystalline material melting at about 235–240° (dec.). After recrystallization from isopropyl alcohol, the colorless hydrochloride salt melts at about 241–243° (dec.).

EXAMPLE 2

Following the procedure of Example 1, step (a) but substituting 27.0 g. of methyl 1,4-benzodioxane-2-carboxylate for the 1,4-benzodioxane-2-carboxylic acid, the same product is obtained.

EXAMPLE 3

2-[2-(8-ethoxy-1,4-benzodioxanyl)]-2-imidazoline oxalate

Following the procedure of Example 1, step (a) but substituting 25 g. of 8-ethoxy-1,4-benzodioxane-2-carboxylic acid, for the 1,4-benzodioxane-2-carboxylic acid, there is obtained 2-[2-(8-ethoxy-1,4-benzodioxanyl)]-2-imidazoline, which upon treatment with an alcoholic solution of oxalic acid by the procedure of Example 1, step (b) yields the oxalate salt.

EXAMPLE 4

2-[2-(1,4-benzodioxanyl)]-1-methyl-1,4,5,6-tetrahydropyrimidine hydrochloride

Following the procedure of Example 1, but substituting 50 g. of N-methyl-1,3-propanediamine for the ethylene diamine in step (a), there is obtained 2-[2-(1,4-benzodioxanyl)]-1-methyl-1,4,5,6-tetrahydropyrimidine hydrochloride.

EXAMPLE 5

2-[2-(1,4-benzodioxanyl)-methyl]-2-imidazoline hydrochloride

Following the procedure of Example 1, but substituting 26 g. of 1,4-benzodioxane-2-acetic acid for the 1,4-benzodioxane-2-carboxylic acid, there is obtained 2-[2-(1,4-benzodioxanyl)methyl]-2-imidazoline hydrochloride.

EXAMPLE 6

2-[2-(7-chloro-1,4-benzodioxanyl)]-2-imidazoline

Interaction of 30 g. of 7-chloro-1,4-benzodioxane-2-carboxylic acid (prepared by reacting 4-chloropyrocatechol with ethyl α,β -dibromopropionate) with ethylenediamine in the same manner as Example 1, step (a) gives 2-[2-(7-chloro-1,4-benzodioxanyl)]-2-imidazoline.

EXAMPLE 7

2-[2-(6-trifluoromethyl-1,4-benzodioxanyl)]-2-imidazoline

Interaction of 28 g. of 6-trifluoromethyl-1,4-benzodioxane-2-carboxylic acid with ethylenediamine in the same manner as Example 1, step (a) gives 2-[2-(6-trifluoromethyl-1,4-benzodioxanyl)]-2-imidazoline.

EXAMPLE 8

2-[2-(6-allyl-1,4-benzodioxanyl)]-2-imidazoline

Interaction of 30 g. of 6-allyl-1,4-benzodioxane-2-carboxylic acid with ethylenediamine in the same manner as Example 1, step (a) gives 2-[2-(6-allyl-1,4-benzodioxanyl)]-2-imidazoline.

EXAMPLE 9

2-[2-(7-nitro-1,4-benzodioxanyl)]-2-imidazoline

Interaction of 25 g. of 7-nitro-1,4-benzodioxane-2-carboxylic acid with ethylenediamine in the same manner as Example 1, step (a) gives 2-[2-(7-nitro-1,4-benzodioxanyl)]-2-imidazoline.

EXAMPLE 10

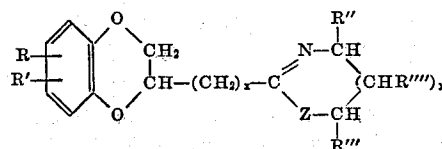
2-[2-(7-butyl-1,4-benzodioxanyl)]-2-imidazoline

Interaction of 25 g. of 7-butyl-1,4-benzodioxane-2-carboxylic acid with ethylenediamine in the same manner as Example 1, step (a) gives 2-[2-(7-butyl-1,4-benzodioxanyl)]-2-imidazoline.

The invention may be variously otherwise embodied within the scope of the appended claims.

What is claimed is:

1. A compound selected from the group consisting of bases of the general formula



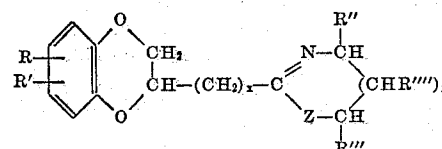
and the non-toxic acid addition salts thereof, wherein R and R' are each selected from the group consisting of hydrogen, hydroxy, halogen, trifluoromethyl, nitro, lower alkyl, lower alkenyl and lower alkoxy, R'', R''' and R'''' are each selected from the group consisting of hydrogen and lower alkyl, x is an integer from zero to one, y is an integer from zero to one, and Z is selected from the group consisting of —NH— and —N(lower alkyl)—.

2. 2-[2-(1,4-benzodioxanyl)]-2-imidazoline.

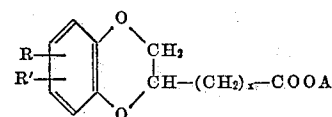
3. A non-toxic acid addition salts of 2-[2-(1,4-benzodioxanyl)]-2-imidazoline.

4. 2-[2-(1,4-benzodioxanyl)]-2-imidazoline hydrochloride.

5. A process for preparing a compound of the general formula



wherein R and R' are each selected from the group consisting of hydrogen, hydroxy, halogen, trifluoromethyl, nitro, lower alkyl, lower alkenyl, and lower alkoxy, R'', R''' and R'''' are each selected from the group consisting of hydrogen, and lower alkyl, x is an integer from zero to one, y is an integer from zero to one, and Z is selected from the group consisting of —NH— and —N(lower alkyl)—, which comprises heating a compound of the general formula



wherein R, R' and x are as above defined and A is selected from the group consisting of hydrogen and lower alkyl, with a compound of the general formula:



wherein R'', R''', R''', y and Z are as above defined.

6. A process for preparing 2-[2-(1,4-benzodioxanyl)]-2-imidazoline which comprises heating 1,4-benzodioxane-2-carboxylic acid with ethylenediamine.

References Cited in the file of this patent

Koo et al.: J. Am. Chem. Soc., vol. 77, pages 5373–4 (1955).