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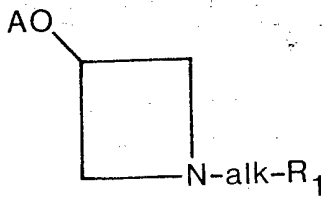
(54) SUBSTITUTED AZETIDINOLS

(71) We, BOEHRINGER INGELHEIM GmbH, a body corporate organised under the laws of the Federal Republic of Germany of Ingelheim am Rhein, Federal Republic of Germany, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

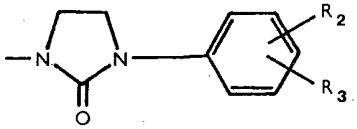
This invention relates to novel substituted azetidinol compounds suitable for use as intermediates in the preparation of pharmacologically active 1 - aryloxy - 2 - hydroxy - 3 - alkyleneamino - propanes and acid addition salts thereof.

According to one feature of the present invention there are provided compounds of general formula



(I)

(wherein A represents a hydrogen atom, an acyl group, or a group of the formula —CONH—alkyl, —CO—N(alkyl)$_2$, —CONH—NH$_2$, —CH$_2$SO$_2$CH$_3$ or —CONHOH; alk represents a C_1 to C_{12} straight-chained or branched alkylene group; and R_1 represents a heterocyclic group of the formula



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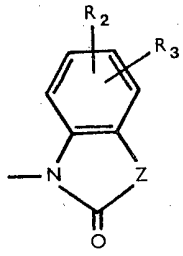


[in which R_2 and R_3, which may be the same or different, each represents a hydrogen or halogen atom, a C_1 to C_4 straight-chained or branched alkyl or alkoxy group, a trifluoromethyl or carboxamido group or a divalent group having the formula

$$—O—(CH_2)_y—O—$$

(wherein y is 1 or 2) bonded with the two free bonds in the *ortho*-position relative to each other; and Z represents a divalent group of the formula

(in which R_4 represents a hydrogen atom or a C_1 to C_6 alkyl, alkenyl, alkynyl, cycloalkyl or optionally substituted aryl group), a group $—OCH_2—$ (wherein the oxygen atom is attached to the phenyl nucleus), or a group $—(CH_2)_2—$] and acid addition salts thereof.

Examples of acyl groups for the group A in compounds according to the invention include acetyl, propionyl, butyryl or isobutyryl groups, or phenacetyl, benzoyl or naphthoyl groups optionally substituted in the aromatic nucleus by one or more halogen atoms, or C_1 to C_6 alkyl, nitro, cyano or carboxyl groups.

The group alk may, for example, be an ethylene, trimethylene, tetramethylene, hexamethylene, dodecamethylene, 1-methylethylene, 2-methylethylene, 1,1-dimethylethylene, 1,1-dimethylpropylene, 1,1-dimethylbutylene or 1,1,4,4-tetramethylbutylene group.

Acid addition salts of the compounds according to the invention may be conveniently formed from acids such as, for example, hydrochloric acid, hydrobromic acid, phosphoric acid or sulphuric acid, or from organic acids such as, for example, methanesulphonic acid, maleic acid, acetic acid, oxalic acid, lactic acid, tartaric acid, 8-chloro-theophylline, salicylic acid, citric acid, β-naphthoic acid, adipic acid, 1,1-methylene-bis-(2-hydroxy-3-naphthoic)acid or from an acidic synthetic resin, such as, for example, from a sulphonated polystyrene resin.

Compounds of general formula I according to the present invention may be useful as starting materials or intermediates in the preparation of pharmacologically active 1 - aryloxy - 2 - hydroxy - 3 - alkyleneaminopropanes and acid addition salts thereof. The use of the compounds in such processes is described in our copending patent application No. 41251/77 (Patent Specification No. 1592975).

According to a further feature of the present invention there is provided a process for the preparation of the compounds according to the invention (in which A represents a hydrogen atom) which comprises reacting an amino compound of formula

(II)

(wherein R_1 and alk are as hereinbefore defined, and R_5 represents a hydrogen atom, a C_1 to C_5 alkyl group or an optionally substituted C_7 to C_{14} aralkyl group) with epichlorohydrin.

Compounds of formula I in which A represents an acyl group may be prepared from corresponding compounds in which A represents a hydrogen atom in conventional manner.

Certain compounds of formula II used in the above process are themselves novel and, together with processes for their preparation, are described and claimed in our copending patent application No. 7941737 (Patent Specification No. 1592976).

The following Example serves to illustrate the preparation of compounds of formula I:—

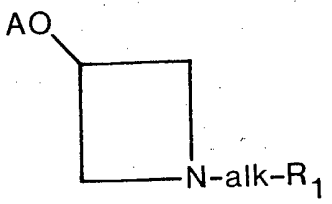
Example

N-(1,1-Dimethyl-2-benzimidazolonyl-ethyl)-azetidinol

3.1 g of N - (1 - amino - 2,2 - dimethylethyl) - benzimidazolone are dissolved in 30 ml of acetonitrile and 1.4 g of epichlorohydrin are added. The mixture is refluxed for 6 hours. After cooling it is evaporated *in vacuo*. The residue is dissolved in water and shaken with ethyl acetate. The aqueous phase is made alkaline with NaOH and extracted with ethyl acetate. The organic phase is dried, and the ethyl acetate distilled off. 1.4 g of N - (1,1 - dimethyl - 2 - benzimidazolonyl - ethyl) - azetidinol are obtained.

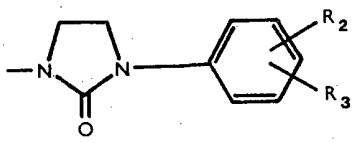
WHAT WE CLAIM IS:—

1. Compounds of general formula



(I)

(wherein A represents a hydrogen atom, an acyl group or a group of the formula —CONH—alkyl, —CON(alkyl)$_2$, —CONHNH$_2$, —CH$_2$SO$_2$CH$_3$ or —CONHOH; alk represents a C_1 to C_{12} straight-chained or branched alkylene group; and R_1 represents a heterocyclic group of the formula



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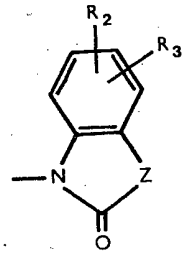
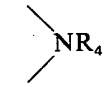


[in which R_2 and R_3, which may be the same or different, each represents a hydrogen or halogen atom, a C_1 to C_4 straight-chained or branched alkyl or alkoxy group, a trifluoromethyl or carboxamido group or a divalent group having the formula

$$—O—(CH_2)_y—O—$$

(wherein y is 1 or 2) bonded with the two free bonds in the *ortho*-position relative to each other; and Z represents a divalent group of the formula

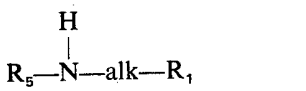


(in which R_4 represents a hydrogen atom or a C_1 to C_6 alkyl, alkenyl, alkynyl, cycloalkyl or optionally substituted aryl group), a group —OCH$_2$— (wherein the oxygen atom is attached to the phenyl nucleus), or a group —(CH$_2$)$_2$—] and acid addition salts thereof.

2. Compounds as claimed in claim 1 wherein alk represents an ethylene, trimethylene, tetramethylene, hexamethylene, dodecamethylene, 1-methylethylene, 2-methylethylene, 1,1-dimethylethylene, 1,1-dimethylpropylene, 1,1-dimethylbutylene or a 1,1,4,4-tetramethylbutylene group.

3. N - (1,1 - Dimethyl - 2 - benzimidazolonyl - ethyl) - azetidinol.

4. A process for the preparation of compounds as claimed in claim 1 (in which A represents a hydrogen atom) which comprises reacting a compound of formula



(II)

[wherein R_1 and alk are as defined in claim 1, and R_5 represents a hydrogen atom, a C_1 to C_5 alkyl group or an optionally substituted C_7 to C_{14} aralkyl group] with epichlorohydrin.

5. A process as claimed in claim 4 substantially as herein described in the Example.

6. Compounds of general formula I as claimed in claim 1 whenever prepared by a process as claimed in claim 4 or claim 5.

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