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3,637,850  
**SUBSTITUTED BENZYLIDENEAMINO  
 GUANIDINES**

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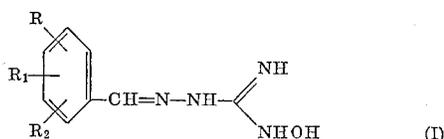
U.S. Cl. 260—564 F

2 Claims

**ABSTRACT OF THE DISCLOSURE**

Substituted benzylideneamino - 3 - hydroxy guanidines, e.g., 1-(m-trifluoromethylbenzylideneamino)-3 - hydroxyguanidine hydrochloride, are useful as hypoglycemics-antihyperglycemics.

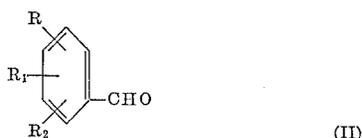
This invention relates to benzylideneamino guanidines, acid addition salts thereof, and to methods for their preparation. The substituted benzylideneamino guanidines of this invention may be represented by the following structural formula:



where each of R, R<sub>1</sub> and R<sub>2</sub> represents hydrogen, halo having an atomic weight of about 19-36, alkyl having from 1 to 4 carbon atoms, alkoxy having from 1 to 4 carbon atoms or trifluoromethyl; provided

- (1) when one of R, R<sub>1</sub> and R<sub>2</sub> is hydrogen the others are other than halo or 2,6-dimethyl;
- (2) when two of R, R<sub>1</sub> and R<sub>2</sub> are hydrogen, the other is not halo; and
- (3) when at least two of R, R<sub>1</sub> and R<sub>2</sub> are trifluoromethyl, they are not ortho to one another.

The compounds of Formula I may be prepared by treating in solvent an aldehyde of the formula:



wherein R, R<sub>1</sub> and R<sub>2</sub> are as defined above, with 1-amino-3-hydroxy-guanidine (III).

In accordance with the above process, the compounds of Formula I are prepared by treating the aldehydes of Formula II with 1-amino-3-hydroxyguanidine (III) or an acid addition salt thereof in lower alkanol solvent, e.g., methanol, ethanol or isopropanol. The reaction may be conducted at a temperature of from about 20-70° C., preferably 25-45° C. The resulting product (I) is recovered by conventional techniques such as recrystallization and filtration.

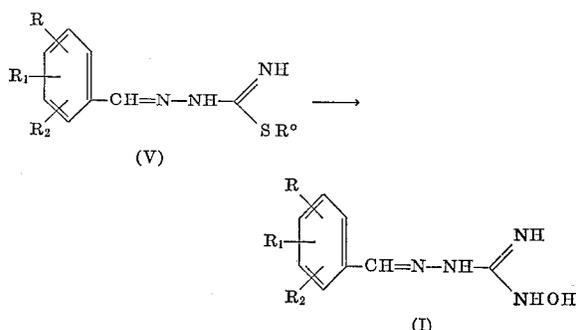
When an acid addition salt of 1-amino-3-hydroxyguanidine is utilized, the resulting product (I) is obtained as the corresponding acid addition salt. Such salt may be converted to the free base by conventional techniques. When an acid addition salt of the compound of Formula I is desired, it may be obtained by salifying the free base.

Certain of the aldehydes of Formula II are known and may be prepared according to methods disclosed in the literature. Those other aldehydes (II) not specifically disclosed may be prepared by analogous methods from known materials.

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The 1-amino-3-hydroxyguanidine (III) is prepared by treating in solvent and in the presence of base an acid addition salt of an S-lower alkyl or S-benzylisothiosemicarbazide (IV), preferably S-methylisothiosemicarbazide, with an acid addition salt (e.g., hydrohalide) of hydroxylamine. The acid addition salts of (IV) useful according to this procedure include strong mineral acid addition salts such as the hydrohalide salts, e.g., the hydrochloride salts and the hydroiodide salts, the lower alkyl sulfate salts such as the methyl sulfate salts, and the like. Alkali and alkaline earth metal hydroxides, preferably sodium hydroxide and potassium hydroxide are useful as the base present. About 1 molar equivalent of the base should be used to obtain good conversion to the 1-amino-3-hydroxyguanidine (III). The reaction is conducted at a temperature of about 20°-60° C., preferably about 25°-35° C. It is performed in aqueous solvent such as water either alone or in admixture with lower alkanol such as ethanol and isopropanol, and the like. The guanidine (III) may be recovered according to conventional techniques and converted to acid addition salts such as those mentioned above by salification.

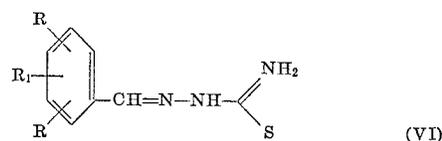
The compounds of Formula I may alternatively be prepared by treating a substituted benzaldehyde S-lower alkylisothiosemicarbazone (V) with hydroxylamine (the latter preferably as an acid addition salt, e.g., a hydrohalide such as the hydrochloride). The reaction may be represented as follows:



wherein R, R<sub>1</sub> and R<sub>2</sub> are as previously defined and R' represents lower alkyl, i.e., alkyl having 1-4 carbon atoms such as methyl, ethyl, isopropyl and the like.

The isothiosemicarbazone (V) is treated with the hydroxylamine in a solvent which dissolves both reactants, such as water in admixture with a lower alkanol, e.g., methanol or ethanol, or a tetrahydrofuran-water mixture, and the like. The reaction may be carried out at a temperature of about 10° C. to reflux temperature, preferably at about 20° C.-50° C. The particular solvent and temperature used is not critical in obtaining the compounds (I). In a manner similar to that earlier described respecting the process for preparing the compounds (I), use of an acid addition salt of hydroxylamine provides a corresponding salt of the benzylideneamino guanidine (I).

The S-lower alkylisothiosemicarbazones (V) are prepared by treating a substituted benzaldehydethiosemicarbazone of the formula:



wherein R, R<sub>1</sub> and R<sub>2</sub> are as earlier defined, in solvent with a loweralkyl halide, preferably the bromide or iodide, such as methyl iodide, methyl bromide, ethyl iodide and the like. This reaction may be conducted in solvent such