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2,801,243

IMIDAZOLE SALTS OF PENICILLIN

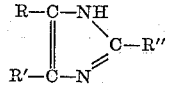
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2 Claims. (Cl. 260—239.1)

This invention relates to imidazole derivatives, particularly to relatively high molecular weight, ring-substituted imidazole salts and, more particularly, to penicillin salts thereof.

The compounds of the invention involve imidazole derivatives falling within the scope of the general formula:



or its equivalent, tautomeric forms wherein R and R′ each represent phenyl or substituted phenyl radicals while R″ represents hydrogen, or an aromatic radical; preferably phenyl or substituted phenyl.

The substituents that have been mentioned hereinabove, which may be on the aryl ring, may comprise from one to three alkyl, alkoxy, halogen, nitro, cyano or dialkylamino substituents. Because of the method of making the compounds of the invention, amino and hydroxy substituents should not be present but, once the diazaheterocyclic bases are formed, these substituents would not interfere with the formation of the penicillin salts. In forming salts of the bases and particularly penicillin salts, the only substituents that must be excluded are those having an oxidizing action or strong acid groups and, with these exceptions, no substituent has been found that interferes with the reaction to form penicillin salts.

The imidazole compounds of the invention are preferably of relatively high molecular weight since it has been found that the higher molecular weight compounds form substantially water-insoluble or at least sparingly water-soluble penicillin salts. An important feature of the invention is the formation of these penicillin salts.

It has been discovered that the substantially water-insoluble, relatively high molecular weight diaza-heterocyclic bases of the invention, specifically those having from about 15 to 27 carbon atoms, with a total molecular weight over about 200, or selected salts of such bases, are capable of combining with penicillin to form especially valuable penicillin salts. Probably because of the high molecular weight, these penicillin salts are all substantially water-insoluble or, at most, only sparingly water-soluble.

The non-toxic substantially insoluble or sparingly water-soluble salts of penicillin have been found valuable from a pharmacological aspect. In contact with body fluids, these salts slowly release penicillin for utilization in combatting bacterial infections. A prolonged antibiotic effect can thus be achieved without difficulty. By the use of these new penicillin salts, one greatly reduces the number of injections required to sustain the desired blood level concentration of penicillin.

A characteristic of imidazole salts of penicillin is that they are stable under mild acid conditions whereas with imidazolidine compounds, the ring opens in an acidic environment. This characteristic of imidazole salts is an advantage if the product is to be utilized with acid materials or in an acidic environment.

If the bases are to be used for the preparation of penicillin compounds, they are best used as salts rather than in the form of a free base to avoid the possibility of inactivating the penicillin. The salts may be formed from the free bases by dissolving the latter in a solvent, such as water or ether, to which is added the proper acid depending on the particular salt desired.

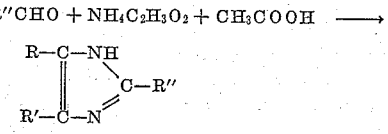
Inorganic or organic acids may be used in forming the salts from the free bases. The most common inorganic acids are hydrochloric, sulfuric, phosphoric, nitric, or hydrobromic acids. Organic acids which are deemed useful are the lower aliphatic carboxylic acids of the monocarboxylic, di-carboxylic, and tri-carboxylic classes. Lower alkyl, mono-hydroxy lower alkyl, and di-hydroxy lower alkyl carboxylic acids are deemed useful as well as halogen-substituted compounds and unsaturated aliphatic acids. As specific examples of organic acids, there may be mentioned the acids of 1 to 6 carbon atoms of the mono-carboxylic class such as formic, acetic, propionic, butyric, isovaleric, glycolic, lactic, gluconic, chloracetic, and crotonic acids. Examples of the di-carboxylic class found to be particularly useful are the acids of 3 to 6 carbon atoms such as malonic, succinic, glutaric, adipic, malic, tartaric, glutamic, maleic, and fumaric acids. In the class of the tri-carboxylic acids, citric, isocitric, and aconitic acids are also deemed useful.

It has been found highly advantageous to prepare and use those salts of the bases which are water-soluble when seeking to make penicillin salts of these bases. The reason for this lies in the fact that it is desirable to obtain the penicillin salts as a precipitated solid from a substantially aqueous medium. The desired salt may then be easily separated, as by filtration, and purified by washing. Thus, the selected water-soluble imidazole salt is dissolved in water and reacted with a water-soluble salt of penicillin. The desired penicillin salt, being either substantially water-insoluble or only sparingly water-soluble, precipitates from the aqueous medium and is separated therefrom. Where relatively water-soluble base salts are used in preparing penicillin salts therefrom, less liquid volume need be handled and therefore losses are likely to be less than if relatively insoluble salts are used.

In speaking of water-soluble, sparingly water-soluble, and substantially water-insoluble salts, the generally accepted meaning is intended. However, in order to avoid any question as to meaning, it is preferred to consider a water-soluble salt to be one which will dissolve in water to the extent of at least about 5% by weight per unit of liquid volume at 30° C. A sparingly water-soluble salt would be one whose solubility in water would range from just below this figure to about 1% by weight, while a substantially water-insoluble salt would be one having a solubility less than about 1% by weight per unit of liquid volume at 30° C.

Any of the known soluble penicillin salts may be combined with the poly-substituted imidazole bases. Thus, one may use the alkali or alkaline earth metal salts or amine salts of penicillin G, dihydro F, X, K or penicillin V for combination with the selected salts of imidazoles. However, the more preferred penicillin salts are the sodium or potassium salts of penicillin G.

Substituted imidazole bases may be prepared by heating at refluxing temperatures an aromatic diketone with either hexamethylenetetramine or an aliphatic, alicyclic, heterocyclic, or aromatic aldehyde in the presence of ammonium acetate and glacial acetic acid. The illustrated reaction is shown as follows:



where R, R', and R'' have the meanings as disclosed earlier.

It should be noted that where the 2-position on the ring is to remain unsubstituted (R''=H), hexamethylenetetramine should be used instead of an aldehyde since the former releases formaldehyde slowly. In carrying out the reaction, refluxing is continued for about an hour, the reaction products are then diluted with a small amount of water to precipitate impurities which are removed. The filtrate is then further diluted with a relatively large amount of water thereby causing the precipitation of the desired base.

The following examples will illustrate the invention in greater detail. It should be understood, however, that the examples are merely for illustrative purposes and are not to be considered limitative of the invention.

EXAMPLE 1

Preparation of 4,5-diphenylimidazole and a salt thereof

Benzil (10.5 gm.) (0.05 M); hexamethylene tetramine (1.3 gm.) (0.01 M) and ammonium acetate (30.0 gm.) (0.4 M) are added to 250 cc. of glacial acetic acid. The mixture is refluxed for one hour and then diluted to 2500 cc. with water. The slight turbidity is removed with charcoal. The filtered solution is chilled and dry ammonia gas is passed into the solution to precipitate 4,5-diphenylimidazole. The material is dissolved in ether and then dry hydrogen chloride gas is passed into the solution to precipitate the imidazole-hydrochloride. Filter and dry. M. P. 135° C.

EXAMPLE 2

Preparation of 2,4,5-triphenylimidazole and a salt thereof

Benzil (10.5 gm.) (0.05 M) and ammonium acetate (50.0 gm.) (0.65 M) are added to 250 cc. of glacial acetic acid. The mixture is refluxed for one hour and diluted then with 200 cc. of water; collecting a white precipitate. The filtrate is further diluted with water to 2500 cc. volume causing the precipitate of the product which is crystallized from hot pyridine by the addition of an equal volume of water. Filter and dry. M. P. 273–274° C. The 2,4,5-triphenylimidazole is dissolved in small volume of ethanol and then dry hydrogen chloride gas is passed into the solution. Add ether to precipitate the hydrochloride salt. Filter and dry. M. P. 155° C.

EXAMPLE 3

Preparation of 2,4,5-tri-(p-methoxyphenyl)imidazole and a salt thereof

Anisil (10.5 gm.) (0.04 M) and ammonium acetate (50.0 gm.) (0.65 M) are added to 250 cc. of glacial acetic acid. The mixture is refluxed for one hour and diluted with 200 cc. of water. The solution is filtered and further diluted with water to a volume of 2500 cc. The white precipitate is filtered and dried. M. P. 82° C. This product is dissolved in ethanol and then dry hydrogen chloride gas is passed into the solution. Upon concentrating the solution a white crystalline solid remains. M. P. 136–138° C.

EXAMPLE 4

Preparation of 2-(2-furyl)-4,5-diphenylimidazole and a salt thereof

Benzil (21.0 gm.) (0.2 M), furfural (19.2 gm.) (0.2 M) and ammonium acetate (60.0 gm.) (0.77 M) are added to 500 cc. of glacial acetic acid. The mixture is refluxed for one hour and then diluted with 200 cc. of water. Filter and the filtrate is added to 2000 cc. of water to precipitate the imidazole. Filter and dry. M. P. 188–189° C. The imidazole compound is dissolved in ethanol and dry hydrogen chloride gas is passed into the solution. Then distill off the ethanol by vacuum leaving an oil which upon the addition of acetone causes crystallization. M. P. 153–154° C.

The following examples illustrate the preparation of penicillin salts from the corresponding imidazoles.

EXAMPLE 5

Preparation of 4,5-diphenylimidazole-penicillin-G

4,5-diphenylimidazole-hydrochloride (2.59 gm.) (0.01 M) is dissolved in 75 cc. of water to which is added, with stirring, potassium-penicillin-G (3.74 gm.) (0.01 M) dissolved in 25 cc. of water. The white precipitate is filtered, washed with water and then dried. M. P. 96–97° C. Analysis: Sulfur calc. 5.74%. Found 5.7%.

EXAMPLE 6

Preparation of 2,4,5-triphenylimidazole-penicillin-G

2,4,5-triphenylimidazole-hydrochloride (3.3 gm.) (0.01 M) is dissolved in 60 cc. of water containing 20 cc. of ethanol to which is added potassium-penicillin-G (3.74 gm.) (0.01 M) dissolved in 15 cc. of water. The white precipitate is filtered, washed with water and then dried. M. P. 112–113° C. Analysis: Sulfur calc. 5.1%. Found 4.5%.

EXAMPLE 7

Preparation of 2,4,5-tri-(p-methoxyphenyl)imidazole-penicillin-G

2,4,5 - tri-(p - methoxyphenyl)imidazole - hydrochloride (4.2 gm.) (0.01 M) is dissolved in 15 cc. of acetone to which is added with stirring, potassium-penicillin-G (3.74 gm.) (0.01 M) dissolved in 75 cc. of water. The precipitate is filtered, washed with water and then dried. M. P. 94° C. Analysis: Nitrogen calc. 4.45%. Found 4.89%.

EXAMPLE 8

Preparation of 2-(2-furyl)-4,5-diphenylimidazole-penicillin-G

2 - (2 - furyl) - 4,5 - diphenylimidazole - hydrochloride (2.0 gm.) (0.0062 M) is dissolved in 20 cc. of ethanol to which is added, with stirring, potassium penicillin-G (2.3 gm.) (0.0061 M) dissolved in 100 cc. of water. The precipitate is filtered, washed with water and then dried. M. P. 97–98° C. Analysis: Nitrogen calc. 9.0%. Found 8.4%.

All of the penicillin salts of the imidazole bases may be cleaved to recover active penicillin if so desired. Since the higher molecular weight penicillin compounds are substantially water-insoluble or at least only sparingly water-soluble, the water-soluble salts of these bases are useful for freeing penicillin from other water-soluble, non-acidic substances that are relatively inert. On the other hand, when they are utilized for their therapeutic effect, their range from sparingly water-soluble to relative insolubility permits wide variation in obtaining long lasting blood levels. The physician is therefore given a choice of penicillin products varying in their blood level effects.

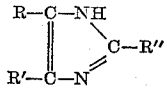
It is also obvious that therapeutic compositions may include a mixture of penicillin salts combining quick acting with long acting penicillin compounds. Likewise, one may include various suspending agents such as sodium-carboxymethylcellulose, gelatines, various gums, etc., where water is the medium to be used, or aluminum monostearate in oil. For all practical purposes, one may use a selected penicillin compound of the invention as one would use the well-known procaine-penicillin-G.

Many modifications and changes within the skill of the art will be readily apparent and are contemplated as falling within the scope of the invention as defined in the appended claims.

This application is a continuation-in-part of application Serial No. 313,374, filed October 6, 1952, now U. S. 2,750,379.

We claim:

1. A penicillin salt of an imidazole having the formula



wherein R and R′ represent a member of the group consisting of phenyl and lower-alkoxyphenyl while R″ stands for a member of the group consisting of hydrogen and phenyl.

2. A penicillin salt of 4,5-diphenyl imidazole.

No references cited.