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DIPHENYLETHYLENEDIAMINE-PENICILLIN SALT

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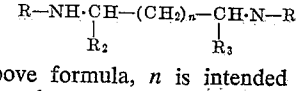
4 Claims. (Cl. 260—239.1)

This invention relates to polybasic compounds, particularly to ethylenediamine derivatives and salts thereof and more particularly to penicillin salts of alpha-substituted ethylenediamines.

An object of the invention is to prepare salts of alkylene diamine derivatives. A further object is to prepare water-soluble salts of α-substituted ethylenediamines. An important object of the invention involves the production of sparingly water-soluble to substantially water-insoluble salts of penicillin. A further important object of invention is to produce penicillin compositions for oral or parenteral use utilizing, as at least one active ingredient, ethylenediamine salts of penicillin. Other objects will become apparent from the general disclosure of the invention.

The compounds of the invention involve salts of ethylenediamine derivatives wherein the latter fall within the scope of the general formula



In the above formula, *n* is intended to represent a whole number from 0 to 10 while R and R_1 represent either hydrogen or aliphatic, alicyclic, aromatic or heterocyclic radicals, with or without substituents on a ring or alkyl chain, as taught by the Szabo et al. Patent No. 2,627,491, dated February 3, 1953. The radicals R_2 and R_3 are intended to represent aromatic radicals with or without substituents, with R_3 also capable of standing for hydrogen.

Where the radicals R and R_1 represent an aliphatic radical, straight- or branched-chain alkyl, alkene or alkyne radicals are contemplated.

When R and R_1 represent alicyclic or heterocyclic radicals, 5- or 6-membered rings are contemplated and, insofar as the heterocyclic nucleus is concerned, these will be of the saturated type. The ring elements in the heterocyclic nucleus may involve oxygen, sulfur or nitrogen atoms in addition to carbon. The aromatic radical for either R, R_1, R_2 or R_3 may involve either mono-, di- or tri-nuclear benzene rings with aryl, mono-arylalkyl, diarylalkyl and naphthyl radicals specifically deemed important.

Substitutents on a ring or alkyl chain in the above formula may comprise either alkyl, alkoxy, cyano, halogen, oxo, hydroxy, nitro, acylamino, mono- or dialkylamino groups with 3 or less of such substituents contemplated, particularly where they increase the solubility of the final product unduly. In forming salts from the ethylenediamine bases and particularly penicillin salts, the only substituents that must be excluded are strong acid groups, such as sulfonic acid radicals, and those having an oxidizing action as, for example, peroxides. With these two exceptions, no substituent has been found that interferes with the reaction to form penicillin salts.

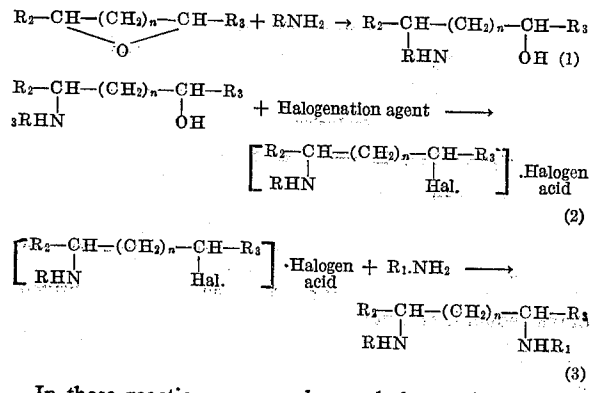
In general, the greater the molecular weight or the more complex the substituent or substituents on the ethylenediamine molecule, the more water-insoluble becomes the

penicillin salt thereof. Since such salts are desirable for reasons as will be more fully described below, the major bar to the more complex molecular structure is an economic one.

Turning to the procedures for preparing the compounds of the invention, the following method teaches one way for preparing the α-substituted ethylenediamines of the invention.

A compound containing an alkylene oxide structure is reacted with a primary or secondary amine thereby aminating the compound and changing the oxide to a hydroxy amine compound. By a halogenation step, a halogen atom replaces the hydroxyl radical and, finally, the halogen group is itself replaced by an amino radical by reacting the halogenated compound either with ammonia or a primary or secondary amine. The method is illustrated by the following reactions:

METHOD A



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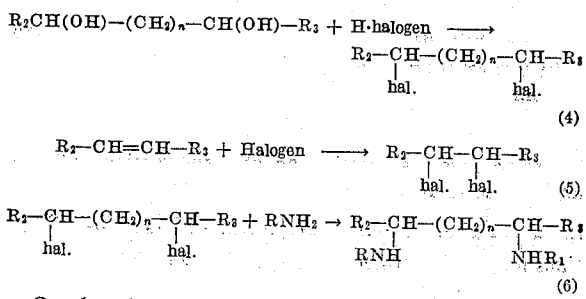
In these reactions, *n* may be a whole number from 0 to 10, while R, R_1, R_2, and R_3 are intended to have the same meanings as previously indicated.

A method for preparing C-polysubstitution alkylene diamine bases may be illustrated by the reaction of a glycol or olefin with a halide or halogen acid to form the di-halo substitution compound. The latter is then reacted with an appropriate primary or secondary amine to form the desired alklene diamine. This procedure may be illustrated by the following reactions:

METHOD B



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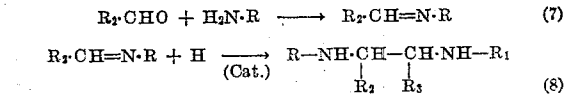
On the above reactions, *n* may stand for a number from 0 to 10. Reaction 4 may be carried out either with HCl or HBr, the latter being preferred. For Reaction 5, Br_2 is the preferred halide; and the product obtained may then be reacted with an amine as disclosed by Reaction 6. The radicals R, R_1, R_2 and R_3 have the same meanings as previously mentioned, with R_1 being similar to R.

In accordance with a preferred method of preparing the α,α′-disubstituted ethylenediamine bases, an aldehyde is condensed with an amine to form a Schiff's base with the release of water. The Schiff's base is then reduced using either aluminum or magnesium amalgam in ether and the mixture is heated at refluxing for some hours. The reaction may be illustrated as follows:

METHOD C



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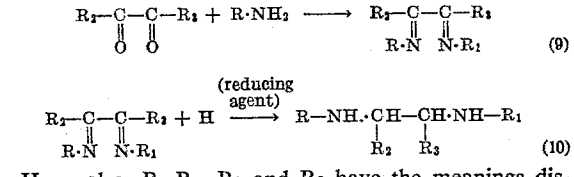
In the above reactions, R and R_2 are the same as indicated originally with R_1 being similar to R, and R_3 being similar to R_2. It will be noted that the α,α'-substituents will be identical by this procedure. But by using a different aldehyde to give a new Schiff's base, the latter when mixed in equimolal proportions with the product of reaction 7 will yield on bimolecular reduction an ethylenediamine in which the α and α' substituents are different.

Still another method for making the ethylenediamine bases permits the α,α'-radicals (R_2 and R_3) to be either similar or dissimilar to each other as in the case of Methods A and B. This method involves condensing a diketone with an amine which also forms a Schiff's base with the release of water. The Schiff's base is then reduced using a hydrogenation catalyst. This procedure may be illustrated as follows:

METHOD D



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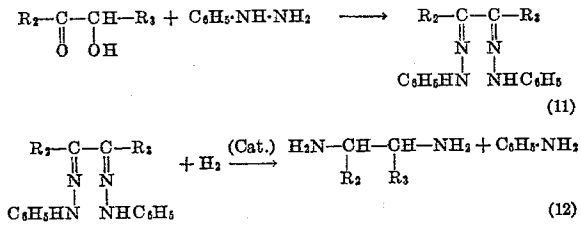
Here, also, R, R_1, R_2 and R_3 have the meanings disclosed originally with R and R_1 representing similar radicals.

A special procedure for preparing α,α'-disubstituted ethylenediamines where the amino groups are unsubstituted involves the reaction of a hydroxy-keto compound with phenylhydrazine to form an osazone. The latter is then hydrogenated catalytically to form the desired C-substituted ethylenediamine, the following reactions illustrating this procedure:

METHOD E



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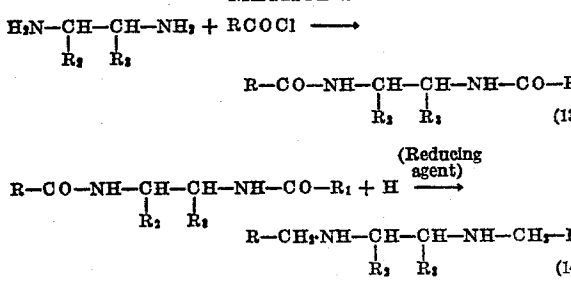
In this reaction R_2 and R_3 have the originally assigned meanings.

A broad and general method for preparing ethylenediamines including those falling within the scope of the invention involves reacting an ethylenediamine with an acyl halide to form a di-amido compound. In a second reaction, the di-amido compound is reduced with a reducing agent such as lithium aluminum hydride. The reactions may be illustrated more specifically as follows:

METHOD F



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In the reactions illustrated, R, R_1, R_2 and R_3 have the meanings previously assigned, with R and R_1 being similar radicals. This reaction is also flexible enough for preparing many of the compounds mentioned in the Szabo et al. patent, previously identified. While the preferred reducing agent is lithium aluminum hydride, one may also use in this reaction lithium borohydride, sodium borohydride or potassium borohydride. The reduction is carried out in diethyl ether or dioxane under refluxing conditions. When the reaction is complete, the products are cooled and the agent decomposed with water. The solvent may then be removed by distillation and the product treated with concentrated alkali metal hydroxide. The desired diamine base may then be reacted with an acid to form the corresponding salt.

Salts of the ethylenediamine derivatives may be prepared from the free bases by dissolving the latter in a solvent, such as ether, to which is added the proper acid, depending on the particular salt desired. Another method for making a selected salt of the base is by reacting a salt of the base with the desired acid or a salt thereof. Where penicillin salts of the ethylenediamines are desired, the second method, involving the double decomposition of salts, is preferred since it avoids the possibility of inactivating the penicillin.

The salts formed may be either mono-salts or di-salts, depending on the amounts of base and acid used. Thus, if one mol. equivalent each of acid and base were used, the mono-salt would be formed. On the other hand, if two mol. equivalents or an excess of acid are used with one mol. of the diamine, the di-salt would be formed. For making penicillin salts from the diamines, one would generally desire the double salt instead of the mono-salt since two mols. of penicillin would be combined when using the former whereas only one mol. of penicillin combines with the mono-salt.

Organic or inorganic acids may be used in forming salts of the ethylenediamines involved in this invention. The most common inorganic acids are hydrochloric, sulfuric, phosphoric, nitric or hydrobromic acids; and, of these, the ones preferred are the acids which form substantially water-soluble salts. With regard to salts of organic acids, the aliphatic carboxylic acids are particularly preferred because, in general, they have also been found to form water-soluble salts.

Organic acids which are deemed useful are the lower aliphatic carboxylic acids of the mono-carboxylic, 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 chloro-substituted compounds and unsaturated aliphatic acids. As specific examples of organic acids there may be mentioned the acids of 1 to 6 carbon atoms as formic, acetic, propionic, butyric, isovaleric, glycolic, lactic, gluconic, chloracetic, and crotonic acids as examples of the mono-carboxylic type. Examples of the di-carboxylic class found to be particularly useful are the acids of 3 to 6 carbon atoms 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 the water-soluble salts of the ethylenediamines when seeking to make penicillin salts of these bases. The reason for this lies in the fact that the penicillin salts of the diamines are substantially all water-insoluble, or, at the most, only sparingly water-soluble. 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 ethylenediamine salt is dissolved in an aqueous medium 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 were 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 penicillin salts may be combined with the poly-substituted diamines. Thus, one may use the alkali or alkaline earth metal salts of penicillin G, dihydro F, X, or penicillin K for combination with the selected diamine or salt thereof. However, the more preferred penicillin salts are the sodium or potassium salts of penicillin G. One or two molecules of any penicillin above indicated will unite with one molecule of the diamine, depending on the use of the mono- or the di-salt.

The diamine bases disclosed herein that form sparingly water-soluble or substantially water-insoluble penicillin salts are highly useful in that they can be used to isolate penicillin from a largely aqueous medium by reacting with this antibiotic and precipitating out as a penicillin salt. After isolation of the salt, one may easily cleave the salt in any known manner, as by treatment with an acid. This use not only permits isolation of the penicillin from an aqueous medium but is a means for purifying the penicillin from non-acidic impurities.

Additionally, the sparingly water-insoluble penicillin salts are stable in the dry state and may be kept for long periods of time without appreciable decomposition. The water-soluble salts of penicillin, on the other hand, decompose quickly in a humid environment. It is possible, therefore, to convert the unstable penicillin salts to the sparingly water-soluble salts of the invention for purposes of long storage and then cleave the penicillin at any subsequent time, when and if desired.

As an additional discovery, many of these substantially insoluble or sparingly water-soluble salts of penicillin have been found valuable from a pharmacological aspect since they are relatively non-toxic and, when in contact with body fluids, slowly release penicillin for utilization in combating 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.

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

EXAMPLE 1

Preparation of N,N'-diethyl-α-phenyl-ethylenediamine and salts thereof

60 grams styrene oxide and 45 grams ethylamine were dissolved in 200 cc. of absolute ethanol and held in a stoppered flask for 32 hours at room temperature. The solvent and excess amine were removed by concentration on the steam-bath. The residue was cooled, stirred with 100 cc. n-hexane; the precipitate, N-ethyl-β-hydroxy-β-phenethylamine, was filtered, washed with hexane and dried. M. P. 80–81° C.

0.2 mole (33 grams) of the above compound was dissolved in 200 cc. cold $HCCl_3$. To this solution was added, with stirring and cooling, 35 cc. $SOCl_2$ (0.3 mole). The mixture was stirred for one hour with cooling (ice bath); a precipitate forms. The suspension was transferred to a flask fitted with a reflux condenser, protected by a $CaCl_2$ tube and refluxed gently for one hour. Cool, filter, wash with chloroform, dry. The product, N-ethyl-β-chloro-β-phenethylamine-Hydrochloride, had a melting point of 183–4° C.

0.15 mole (33 grams) N-ethyl-β-chloro-β-phenethylamine Hydrochloride was suspended in 200 cc. refluxing isopropanol, stirred vigorously, while a solution of 30 grams ethylamine in 100 cc. isopropanol was dripped in over a 2-hour period. Refluxed an additional 2 hours. The solvent was removed under vacuum, cooled. The solid residue was taken up in a minimum of hot ethanol and pH adjusted to 6 with alcoholic HCl. The product, N,N'-diethyl-α-phenyl-ethylenediamine-2 HCl, was obtained after cooling. The product was filtered, dried and recrystallized from ethanol. M. P. 252–3° C.

3.8 grams N,N'-diethyl-α-phenyl-ethylenediamine-2 HCl was dissolved in 10 cc. warm water (<50° C.) To this was added 5.3 grams K penicillinate in 5 cc. water. Mixture chilled, supernatant decanted off. The residue was pressed as dry as possible, then dried overnight at 0.1 mm. and recrystallized from acetone. M. P. 108–9° C.

EXAMPLE 2

Preparation of N-ethyl-β-amino-β-phenethylamine and salts thereof

10 grams N-ethyl-β-chloro-β-phenethylamine Hydrochloride was suspended in 75 cc. absolute ethanol containing 12 grams anhydrous ammonia. Sealed in pressure bottle and heated to 80–90° for 6 hours; cooled and filtered off ammonium chloride. The filtrate was concentrated to 40 cc., made acidic with ethanolic HCl and concentrated to an oil identified as N-ethyl-β-amino-β-phenethylamine dihydrochloride.

The above compound was taken up in a minimum of water, made alkaline (40% NaOH) and ether extracted. The extract was dried over NaOH and filtered. The pH adjusted to 6–6.5 with glacial acetic acid and the ether removed under vacuum. The residue was dissolved in 5 cc. H_2O. To this was added 15 grams K penicillin in 30 cc. H_2O. Cooled. 100 cc. cold water added. A solid precipitated. This was separated, pressed dry, and vacuum dried. The dipenicillin salt of N-ethyl-β-amino-β-phenethylamine was dissolved in acetone, bone-blacked, filtered and solvent evaporated off under vacuum. M. P. 85–90° C.

EXAMPLE 3

Preparation of α,α'-diphenylethylenediamine and salts thereof

Benzil (50 grams) (0.238 M) and hydroxylamine hydrochloride (45 grams) (0.65 M) are dissolved in 400 cc. of ethanol to which is added five drops of concentrated hydrochloric acid. This solution is heated on the steam-bath for two hours, then cooled and the dioxime filtered and dried. M. P. 237° C.

Benzil dioxime (20 grams) (0.083 M) is added to 200 cc. of ethanol to which is added in small portions 70 grams of sodium. To prevent solidification additional ethanol is added to keep the mass fluid. After all the sodium is added, water is added until the solution is clear; and then concentrated hydrochloric acid is added until the solution is slightly acid. The ethanol is removed by vacuum distillation. The residue is chilled; concentrated aqueous sodium hydroxide is added to free the amine which is ether extracted. The ethereal solution is dried and then hydrogen chloride gas is passed into the solution which is filtered and the product, α,α'-diphenyl - ethylenediamine - dihydrochloride - dihydrate, dried. M. P. 248–9° C.

α,α'-Diphenylethylenediamine - dihydrochloride - dihydrate (3.21 grams) (0.01 M) is dissolved in 50 cc. of water to which is added potassium penicillin G (7.48 grams) (0.02 M) dissolved in 25 cc. of water. The precipitate is filtered, water washed and dried. M. P. 154° C.

Analysis: Calcd.: Nitrogen 9.55%; Found: Nitrogen 9.7%.

EXAMPLE 4

Preparation of N,N'-dimethyl-α,α'-diphenylethylenediamine and salts thereof

Benzil (21.0 grams) (0.1 M) is added to cold 100 cc. ethanol to which is added methylamine until the solution is clear. This solution is then subjected to catalytic hydrogenation using palladium on charcoal as a catalyst. After reduction has ceased, the solution is filtered and half the volume of ethanol removed by vacuum distillation. The residue is filtered; washed with cold ether and dried. M. P. 135–6° C. The free base is dissolved in ether and dry hydrogen chloride is passed into the solution to precipitate the diamine-dihydrochloride. M. P. 252–3° C.

α,α'-Diphenyl-N,N'-dimethylethylenediamine-dihydrochloride (1.62 grams) (0.005 M) is dissolved in 100 cc. of water to which is added potassium penicillin G (3.74 grams) (0.01 M) dissolved in 50 cc. of water. The precipitate is filtered, water washed and dried. M. P. 177° C. Analysis: Calcd.: Nitrogen 9.2%; Found: Nitrogen 8.6%.

EXAMPLE 5

Preparation of N,N'-di(2-heptyl)-α,α'-diphenylethylenediamine and salts thereof

Benzaldehyde (53.0 grams) (0.5 M) is added with rapid stirring to 2-heptylamine (57.5 grams) (0.5 M). After a few seconds a reaction occurs with evolution of heat and separation of water. The mixture is allowed to stand until cool, and then is added to 250 cc. of ether. The ether layer is removed leaving as residue 8.5 cc. of water.

The ether solution containing the benzal-2-heptylamine (105.5 grams) (0.5 M) is added to 250 cc. of ether containing aluminum amalgam (27.0 grams). The mixture is allowed to react at room temperature and then refluxed on the steam-bath for five hours. Upon cooling and filtering the spent aluminum the ether is removed by vacuum. The oily residue is dissolved in methanol to which is added dropwise sulfuric acid to precipitate the amine-sulfate salt. Filter and dry. M. P. 256–7° C.

α,α'-Diphenyl - N,N'-di(2-heptyl)ethylenediamine - sulfate (5.1 grams) (0.01 M) is dissolved in 35 cc. of distilled water which is then added to potassium penicillin G (7.44 grams) (0.02 M) dissolved in 15 cc. of distilled water. The white precipitated salt of penicillin G is filtered, water washed and dried. Analysis: Sulfur: Theory 6.0%; Found 7.0%.

EXAMPLE 6

Preparation of N,N'-di(n-decyl)-α,α'-diphenylethylenediamine and salts thereof

α,α'-Diphenylethylenediamine (25 grams) (0.118 M) is added to toluene (80 cc.) containing n-decyl chloride (41.8 grams) (0.236 M) and refluxed on the steam-bath for four hours. The solution is cooled and filtered to remove the α,α'-diphenyl-ethylenediamine dihydrochloride. To the clear toluene solution is added hydrogen chloride gas to precipitate the di-n-decyl diphenylethylenediamine-dihydrochloride as a wax-like solid.

α,α'-Diphenyl-N,N'-di-n-decylethylenediamine-dihydrochloride (1.4 grams) (0.0025 M) is dissolved in 15 cc. of water to which is added potassium penicillin G (1.87 grams) (0.005 M) dissolved in 5 cc. of water. The precipitate is filtered, water washed and dried. M. P. 118° C. Analysis: Calcd.: Sulfur 5.5%; Found: Sulfur 5.7%.

EXAMPLE 7

Preparation of N,N'-diphenyl-α,α'-diphenylethylenediamine and salts thereof

Benzalaniline (80.0 grams) (0.44 M) is added to 500 cc. dry ether containing aluminum amalgam (27.0 grams). The mixture is allowed to react at room temperature and then refluxed on the steam-bath for five hours. Upon cooling and filtering off the spent aluminum the ether is removed by vacuum. The oily residue is dissolved in methanol to which is added dropwise sulfuric acid to precipitate the amine-sulfate salt. Filter and dry. M. P. 215–216° C.

α,α'-Diphenyl - N,N'-diphenylethylenediamine - sulfate (4.62 grams) (0.01 M) is dissolved in 40 cc. of distilled water which is then added to potassium penicillin G (7.44 grams) (0.02 M) dissolved in 10 cc. of distilled water. The white precipitated salt of penicillin G is filtered, water washed and dried. Anaylsis: Sulfur: Theory 6.2%; Found 6.56%.

EXAMPLE 8

Preparation of N,N'-dibenzyl-α,α'-diphenylethylenediamine and salts thereof

Benzalbenzylamine (87.5 grams) (0.5 M) is added to 500 cc. of dry ether containing aluminum amalgam (27.0 grams). The mixture is allowed to react at room temperature and then refluxed on the steam-bath for five hours. Upon cooling and filtering the spent aluminum the ether is removed by vacuum. The oily residue is dissolved in methanol to which is added dropwise sulfuric acid to precipitate the amine-sulfate salt. Filter and dry. M. P. 251° C.

α,α'-Diphenyl - N,N'- dibenzylethylenediamine sulfate (5.60 grams) (0.01 M) is dissolved in 15 cc. of distilled water which is then added to potassium penicillin G (7.44 grams) (0.02 M) dissolved in 10 cc. of distilled water. The white precipitated salt of penicillin G is filtered, water washed and dried. Analysis: Nitrogen: Theory 8.0%; Found 8.7%.

EXAMPLE 9

Preparation og N,N'-diethyl-α,α'-di(p-methoxyphenyl)-ethylenediamine and salts thereof

50 grams anisaldehyde was dissolved in 250 cc. ether and ethylamine bubbled through the solution for about 2 hours, at a rapid rate. The reaction mixture was dried briefly over sodium sulfate, filtered, and concentrated to 170 cc. One-half of this was further concentrated and vacuum distilled, yielding (p-methoxy)-benzalethylamine, B. P. 120–25/.2 mm.

85 cc. of crude ethereal (p-methoxy)-benzalethylamine was added dropwise, with stirring and gentle heating, to 11 grams of clean, ether washed, aluminum filings, previously activated with ½ gram of mercuric chloride. After a 6 hour refluxing period the excess aluminum and a greenish "mud" were filtered off. The filtrate was concentrated under vacuum to remove excess ethylamine. The residue was added to an ethereal solution of oxalic acid. The precipitate, yellow, was bone-blacked and recrystallized from isopropanol (aqueous). M. P. 204–5° C. (white). It was converted to the free base as follows: 2.3 grams of the oxalate was dissolved in 50 cc. of hot water and 5% ammonia added dropwise. Cool, stir. The free base separates as white crystals. M. P. 91–92° C. The free base was dissolved in 20 cc. ether and the aqeuous filtrate extracted with two 20 cc. portions of ether. 0.5 cc. glacial acetic acid added. The ether was removed on the steam-bath and the residue taken up in 4 cc. of water. To this was added 2.6 grams of sodium penicillin in 3 cc. water. A solid product separated out, the aqueous phase decanted off and the residue vacuum dried over phosphorus pentoxide. M. P. 90–110° C.

EXAMPLE 10

Preparation of N,N'-diethyl-α,α'-di(p-hydroxyphenyl)-ethylenediamine and salts thereof

12 grams N,N'-diethyl-α,α'-di-p-methoxyphenyl-ethylenediamine dioxalate was suspended in 170 cc. of 48% hydrobromic acid and refluxed for 4 hours. Cooled. The

hydrobromide salt was filtered off and pressed dry (14 grams). The salt was redissolved in 200 cc. hot water and the pH adjusted to 8 with 5% ammonium hydroxide. The free base precipitated; this was filtered off, washed with water, then dilute methanol, and dried. Recrystallized from aqueous dimethyl formamide. M. P. 155–6° C. Analysis: Calcd.: Nitrogen 9.34; Found: Nitrogen 9.26.

2 grams N,N'-diethyl-α,α'-di(p-hydroxyphenyl)ethylenediamine was dissolved in a minimum of water acidified with 1 cc. acetic acid. To this was added 4.5 grams potassium penicillin. A solid product resulted. This was separated by decantation and dried under vacuum. The supernatant was chilled overnight. Additional crystals were obtained. The product was filtered and dried. M. P. 145-48° C.

EXAMPLE 11

Preparation of N,N'-dimethyl-α,α'-dibenzyl-ethylenediamine and salts thereof

A reaction is carried out in similar manner to the procedure of Method C and Example 5, utilizing phenylacetaldehyde and methylamine, both dissolved in an ether solution. The product is then reduced with aluminum metal previously activated with mercuric chloride in ether solution. Following the reaction, the isolated base is then reacted with pencillin, or a salt is first formed by reaction with an acid and the acid-addition salt is reacted with a salt of penicillin to yield the corresponding ethylenediamine dipenicillin salt.

EXAMPLE 12

Preparation of α-phenyl-ethylenediamine and salts thereof

Phenyl glyoxime (16.4 grams) (0.1 M) is added portionwise to 250 cc. of dry ether containing lithium aluminum hydride (19.9 grams) (0.5 M) so that gentle refluxing results. After complete addition of the glyoxime the mass is refluxed on the steam-bath for four hours. Upon cooling, 25 cc. of water is added slowly to decompose the excess lithium aluminum hydride; then an excess of 30% aqueous sodium hydroxide to liberate the free diamine which is in the ether layer. The ether solution is dried over magnesium sulfate and α-phenylethylenediamine is finally precipitated as the oxalate. M. P. 149° C.

Mono-α-phenylethylenediamine-oxalate (2.25 grams) (0.01 M) is dissolved in 60 cc. of water to which is added potassium pencillin G (7.48 grams) (0.02 M) dissolved in 15 cc. of water. The gummy solid is allowed to stand for crystallization. The yield is almost quantitative. M. P. 112–3° C. Analysis: Sulfur: Calcd. 7.97%; Found 7.54%. Nitrogen: Calcd. 10.4%; Found 10.03%.

EXAMPLE 13

Preparation of N,N'-difurfuryl-α,α'-diphenyl-ethylenediamine and salts thereof

α,α'-Diphenylethylenediamine (21.2 grams) is dissolved in trimethylamine and 2-furoyl chloride (27 grams) is added dropwise until the diamine is reacted, the reaction taking place at room temperature. After completion of the reaction, water is added, and the desired product, N,N'-di-(2-furoyl)-α,α'-diphenylethylenediamine hydrochloride, is precipitated. The free base is obtained by reacting the product with strong alkali, as, for example, sodium hydroxide solution.

Dry N,N'-di-(2-furoyl)-α,α'-diphenylethylenediamine (20 grams) is dissolved in 150 cc. of anhydrous ether containing lithium aluminum hydride (3.8 grams) and then heated on a steam-bath to gentle reflux for 5 hours. The mixture is chilled and sufficient water is added slowly to the mixture to decompose any lithium aluminum hydride and salts present. The ether is removed by vacuum and to the residue is added concentrated sodium hydroxide solution. The product is reacted with glacial acetic acid and the diacetate salt is isolated. The latter is then reacted with potassium penicillin G in an aqueous medium to form the dipenicillin salt of N,N'-di-furfuryl-α,α'-diphenylethylenediamine.

As mentioned before, the preceding method is quite flexible and provides a highly satisfactory method of making many substituted alkylene diamine salts including the penicillin salts. Thus, if one desired to make N,N'-dibenzylethylenediamine in high yields and of excellent purity, one merely reacts ethylenediamine with benzoyl chloride in the aforesaid manner and then reduces the benzoyl diamine compound to N, N'-dibenzylethylenediamine. Many other compounds of the ethylenediamine series may be prepared by the above disclosed procedures and further specific examples would merely be repetitive.

The penicillin salts of the invention are useful for therapeutic purposes and may be compounded in the same way as with other well-known penicillin salts. Thus, they may be used orally either in the form of a suspension in an aqueous vehicle, or in the form of a tablet compounded in the usual way with carriers, extenders, binders, etc.

The salts may likewise be utilized in parenteral compositions containing either hyaluronidase or other spreading agents, or substances to slow-up the absorption of the salt, such as beeswax or aluminum mono-stearate or alumina gel. Suspending or carrier agents utilizable with the salts are such non-toxic synthetic hydrophilic agents as sodium carboxymethyl cellulose, polyvinylpyrrolidone, dextran, methyl cellulose, hydroxyethyl cellulose, sodium cellulose sulfate, etc.; or naturally occurring, non-toxic hydrophilic substances may be used such as various gums, for example, acacia or tragacanth, agar, pectin, gelatine, etc. The composition may be in the form of a dry admixture to be combined with liquid at the time of use, or may be in the form of a liquid suspension.

Additional substances may likewise be present in the compositions. Thus, where it is desired to obtain an immediate penicillin effect combined with a long-acting effect, different penicillin salts with different degrees of water-solubility may be combined. These could involve either different alkylene diamine salts of penicillin or one or more of such salts combined with procaine penicillin or an alkali-metal salt of penicillin. Likewise, other active therapeutic substances not necessarily penicillin salts may be combined with the alkylene diamine penicillin salts of the invention, as, for example, one or more therapeutically active sulfonamides.

Many modifications and changes within the skill of the art are contemplated without departing from the scope of the invention as defined in the appended claims.

We claim:

1. The penicillin salt of N,N'-dimethyl-α,α'-diphenylethylenediamine.

2. The penicillin salt of α,α'-diphenyl-ethylenediamine.

3. The penicillin salt of N,N'-di(2-heptyl)-α,α'-diphenyl-ethylenediamine.

4. A penicillin salt of a compound having the formula

$$R{-}NH{-}\underset{\displaystyle R_2}{\underset{|}{CH}}{-}\underset{\displaystyle R_3}{\underset{|}{CH}}{-}NH{-}R_1$$

wherein R and R_1 each stand for a member of the group consisting of hydrogen and lower alkyl, with R_2 and R_3 each representing a member of the group consisting of phenyl and hydroxyphenyl.

References Cited in the file of this patent

UNITED STATES PATENTS

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