

UNITED STATES PATENT OFFICE

2,557,762

LONG CHAIN TERTIARY ALKYL AMINE-
PENICILLIN SALTS AND PREPARATION
THEREOF

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12 Claims. (Cl. 260—239.1)

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The invention relates to a new class of tertiary amine salts of penicillin and to methods for obtaining the same. More particularly, the invention relates to a class of penicillin amine salts possessing novel and highly useful repository characteristics.

This application is a continuation-in-part of our copending application, Serial 731,408, filed February 27, 1947, now abandoned.

The salts of penicillin in general use at the present time for therapeutic purposes are those containing a metal ion such as sodium, potassium and calcium. It has been found that these salts when administered in aqueous solutions produce a relatively transitory effective concentration of penicillin in the blood. For this reason it is necessary to inject such solutions at frequent intervals, e. g. at two to three hour intervals, in order to maintain therapeutic blood levels of penicillin. A number of lower molecular weight tertiary amine salts of penicillin have been prepared primarily for the purpose of aiding in the purification and recrystallization of penicillin. These salts resemble the metal salts of penicillin in their production of therapeutic blood levels of penicillin.

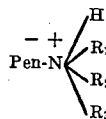
In an attempt to overcome the need for frequent injections of the known penicillin salts, it has been the practice to suspend or mix the inorganic salts of penicillin in vegetable oils or vegetable oil-wax mixtures. In this manner the penicillin is introduced into the body in the form of an oily "pool" from which it is only slowly extracted by the aqueous body fluids. By the use of plain oil suspensions instead of aqueous solutions the number of injections required per day for effective therapy is reduced to about one half. The incorporation of a wax in these oil suspensions further decreases the need for frequent injections and for this reason the suspensions of the vegetable oil-wax type are the most widely used at the present time. While these preparations give therapeutic blood levels of penicillin which persist for as long as twelve hours, they are so viscous and hard that they are extremely difficult to administer even after warming. Moreover, it has been found that due to the large amount of wax present in these preparations they produce irritation and undesirable reactions upon parenteral administration. Perhaps one of the most disagreeable characteristics of these oil-wax preparations is that the vehicle used to retard the absorption of the penicillin is only slowly absorbed by the body with the result that a hard lump of the vehicle remains at the site of the injection.

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We have made the surprising discovery that a certain class of higher tertiary amine salts of penicillin are water-soluble and that these salts, in aqueous solution, produce prolonged therapeutic blood levels of penicillin when administered parenterally. While this repository-like effect varies slightly with the different salts within the class, it, in general, is equal to or approaches that of the well known and widely used suspensions of the inorganic penicillin salts in vegetable oil-wax mixtures. Thus it is apparent that the amine salts of the present invention make it possible for the first time to produce prolonged therapeutic blood levels of penicillin without the use of an oil or oil-wax vehicle. Use of the aqueous solutions of these amine salts eliminates the irritation and undesirable reactions inherent in the commonly used oil-wax preparations. It also eliminates the mechanical difficulties which attend the injection of these oil-wax suspensions of the inorganic penicillin salts.

We have also found that vegetable oil preparations containing these amine salts in partial solution and suspension produce therapeutic levels of penicillin in the blood which persist even beyond those obtained using the aqueous solutions. Such vegetable oil preparations are unique in that they are very fluid at room temperature even though they contain high concentrations of the dissolved and suspended amine salts. Moreover, they do not exhibit the irritating and undesirable properties inherent in the oil-wax preparations in common use.

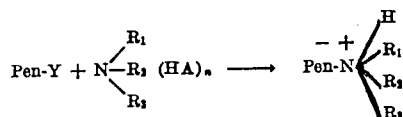
The class of amine salts of our invention may be represented by the following formula



where Pen- represents an anion of a penicillin acid, R₁ and R₂ are the same or different lower alkyl radicals and R₃ is an alkyl radical containing 6 to 18 carbon atoms inclusive. These compounds, in addition to the unique properties set forth above, possess unique solubility characteristics. They are soluble in both vegetable oils and water, the oil solubility increasing and the water solubility decreasing as the molecular weight of the amine residue increases. They are, in general, non-toxic and non-irritating. However, we have observed that some of the salts wherein the R₃ carbon chain contains more than about 12 carbon atoms are slightly irritating when injected intramuscularly. The preferred com-

pounds of the invention are, therefore, those in which R_1 and R_2 are the same or different lower alkyl radicals and R_3 is an alkyl radical containing 6 to 12 carbon atoms inclusive. This particular group of compounds possesses the maximum degree of repository-like action and water solubility coupled with appreciable oil solubility and the minimum toxic and irritating properties.

The penicillin amine salts of the present invention may be prepared by direct salt formation, i. e. by direct neutralization of the penicillin acid by the amine base, or by double decomposition of substantially chemically equivalent amounts of a penicillin metal salt and a mineral acid salt of the appropriate amine. This may be illustrated in the following manner:

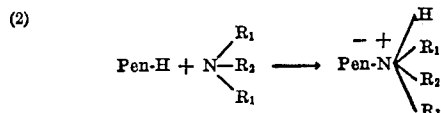
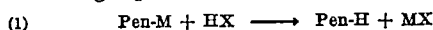


where Y is hydrogen, an alkali metal or one equivalent of an alkaline earth metal, $(\text{HA})_n$ represents n equivalents of a mineral acid, HA, where n is zero or one, n being zero when Y is hydrogen and Pen, R_1 , R_2 and R_3 have the same significance as given above.

In order to prepare the new tertiary amine salts of penicillin by direct neutralization, we react the free penicillin acid with an appropriate tertiary amine in a substantially anhydrous, water-immiscible, inert organic solvent at a temperature below about 10°C . The crude salt is recovered from the reaction mixture and purified, for example, as described hereinafter. Some of the solvents which may be used for the reaction are halogenated aliphatic hydrocarbons such as chloroform, methylene dichloride and ethylene dichloride, ethers such as diethyl ether, aromatic hydrocarbons such as benzene, and esters such as amyl acetate.

Since the free penicillin acids are very unstable in solution and in the solid form, they must be prepared in solution just prior to use from an inorganic penicillin salt. This may be accomplished very simply by dissolving the inorganic penicillin salt in water, adding the theoretical quantity of dilute mineral acid necessary to liberate the penicillin acid from the salt and extracting the free-acid with the water-immiscible organic solvent to be used in the subsequent step of the process. After drying, the solution of the penicillin acid is ready for use. Of course, all of the foregoing operations must be carried out within a reasonably short time and below about 5°C . in order to prevent the decomposition of the free penicillin acid.

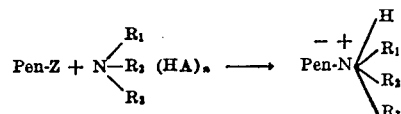
The chemical transformations taking place in the complete process may be represented by the following equations:



where Pen-, R_1 , R_2 and R_3 have the same significance as given above, M is one cation equivalent of an alkali or alkaline earth metal and X is one anion equivalent of an inorganic mineral acid.

As stated above, the amine salt formation may be accomplished by a double decomposition type of reaction wherein an alkali or alkaline

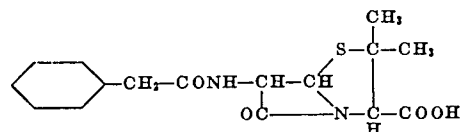
earth metal salt of a penicillin acid is allowed to react with a substantially equivalent amount of a mineral acid salt of an appropriate tertiary amine in the presence of water and a water-immiscible, inert organic solvent, such as chloroform, methylene dichloride and ethylene dichloride. In such case the amine salt of the penicillin acid is preferentially soluble in the inert organic solvent and may be isolated by separation, drying and evaporating said solvent. The transformation may be diagrammatically illustrated as follows:



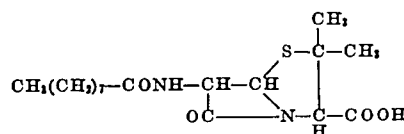
where Z is an alkali metal or one equivalent of an alkaline earth metal, $(\text{HA})_n$ represents n equivalents of a mineral acid, HA, n has the value of one and Pen, R_1 , R_2 and R_3 have the same significance as given above.

The crude salts obtained by either of the above described processes may be purified by recrystallization from a mixture consisting of the tertiary amine corresponding to the salt and a lower aliphatic ketone such as acetone. Any crystallization solvent adhering to the salt is removed by washing the salt with a substantially anhydrous, water-immiscible, inert, organic solvent in which the salt is insoluble. Some examples of such solvents are petroleum ether, benzene, toluene, ether and the like. The crystalline amine salts of penicillin which have been purified in this manner are practically non-hygroscopic and stable for at least a year at room temperature.

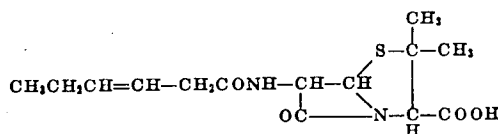
The preferred penicillin salts of the present invention are those derived from penicillin-G or a mixture of penicillins which is predominately composed of penicillin-G. The latter penicillins are the well known non-crystalline sodium and calcium penicillins of commerce which consist of approximately 85 to 90% penicillin-G, 5 to 10% penicillin-K and up to 5% penicillin-F and dihydro penicillin-F. Penicillins containing penicillin-X can also be used in the practice of our invention although at the present time such penicillins are not as readily available as those consisting of penicillins-G, K, F and dihydro-F due to the loss of the penicillin-X during the commonly used commercial isolation procedures. The structure of the various penicillin acids may be represented by the following formulae,



Penicillin-G

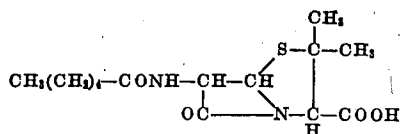


Penicillin-K

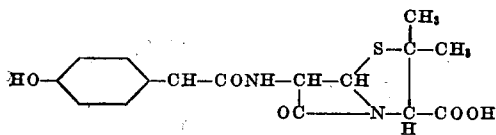


Penicillin-F

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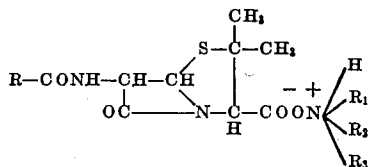


Dihydro penicillin-F



Penicillin-X

and the new tertiary amine salts of these acids by the general formula



where R is a benzyl, p-hydroxybenzyl, n-heptyl, n-amyl or pentene-2 radical and R₁, R₂ and R₃ have the same significance as given above.

The invention is illustrated by the following examples.

Example 1

3 g. of commercial calcium penicillin (1100 Oxford units/mg. and consisting of a mixture of about 90% penicillin-G and 10% penicillin-K) is dissolved in 90 cc. of distilled water. 75 cc. of ethylene dichloride is added and the exact amount of 1 N hydrochloric acid necessary to liberate the free penicillin acid added dropwise with stirring. The layers are separated and the aqueous solution extracted with a fresh portion (45 cc.) of ethylene dichloride. The ethylene dichloride extracts are combined, dried over magnesium sulfate and the drying agent removed by filtration. During all the foregoing operations the temperature of the solutions is not allowed to rise above about 2 or 3° C.

1.087 g. of dimethyl-n-hexyl-amine in a small amount of ethylene dichloride is added with stirring to the cold ethylene dichloride solution of the free penicillin acid and the solution allowed to stand for a few minutes. The solvent is evaporated off under reduced pressure (15 mm. of Hg) without the application of external heat and the last traces of solvent removed under high vacuo. The resulting orange-yellow, crystalline n-hexyl-dimethyl-amine salt of penicillin may be purified by recrystallization from a mixture of acetone and n-hexyl-dimethyl-amine. The pure crystalline product is freed from any adhering crystallization solvent by washing with petroleum ether and then dried in vacuo. The purified salt is practically non-hygroscopic, soluble in water and slightly soluble in vegetable oils. Biological assay of this purified salt shows it to have a potency of about 1200 Oxford units/mg. Aqueous solutions of this salt when injected intramuscularly produce therapeutic blood levels of penicillin which persist over a period of up to eight hours.

Example 2

4 g. of non-crystalline, commercial sodium penicillin (1200 Oxford units/mg. and consisting of about 90% penicillin-G and 10% penicillin-K) is dissolved in 120 cc. of distilled water. An equal volume of methylene dichloride is added and

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then the theoretical amount of 1 N hydrochloric acid necessary to liberate the free penicillin acid is added dropwise with rapid stirring. After thorough mixing the layers are separated and the aqueous phase extracted with a fresh portion of methylene dichloride. The methylene dichloride extracts are dried over magnesium sulfate and the drying agent removed by filtration. All of the foregoing operations are carried out below about 3° C. to prevent decomposition of the penicillin acid.

1.78 g. of 2-ethylhexyl-dimethyl-amine dissolved in a small amount of methylene dichloride is added dropwise to the methylene dichloride extracts containing the free penicillin acid and after mixing the solution allowed to stand for a few minutes. The methylene dichloride is distilled off in vacuo without the application of external heat to obtain the desired 2-ethylhexyl-dimethyl-amine salt of penicillin as a slightly waxy, crystalline residue. The crude yellowish-white salt is purified by recrystallization from a mixture of 2-ethylhexyl-dimethyl-amine and acetone and the crystallization solvent removed from the purified product by washing with petroleum ether. The crystalline salt so obtained is white in color, soluble in water, chloroform and methylene dichloride. It is slightly soluble in vegetable oils, practically non-hygroscopic and stable in the solid form indefinitely at room temperature. Biological assay of this crystalline material shows it to contain about 1160 Oxford units/mg. of penicillin activity. On standing in methyl or ethyl alcohol the salt loses its antibiotic activity due to the formation of the a-penicilloate esters.

Example 3

(a) 2 g. of commercial calcium penicillin (1100 Oxford units/mg. and consisting of a mixture of about 90% penicillin-G and 10% penicillin-K) is dissolved in 60 cc. of distilled water at 2 to 3° C. 60 cc. of chloroform is added and the exact quantity of 1 N hydrochloric acid necessary to liberate the free penicillin acid added with stirring. After thorough mixing, the chloroform layer is removed and the aqueous solution extracted with a fresh 30 cc. portion of chloroform. The chloroform extracts are combined, dried over magnesium sulfate and the drying agent removed by filtration. All the foregoing operations are carried out at a temperature of about 2 to 3° C. to prevent decomposition of the penicillin.

0.89 g. of n-octyl-dimethyl-amine in 12 cc. of chloroform is added with stirring to the dried chloroform extracts. After standing for a few minutes, the solvent is allowed to evaporate under reduced pressure and the last traces removed under high vacuo. The residual yellow-orange crystalline material consists of the crude n-octyl-dimethyl-amine salt of penicillin. This crude salt which assays about 900 Oxford units/mg. may be purified by first recrystallizing it from a mixture of n-octyl-dimethyl-amine and acetone and then washing the recrystallized salt with petroleum ether to remove any adhering crystallization solvent. The purified salt is very soluble in water, slightly soluble in vegetable oils, practically non-hygroscopic and stable in the solid form at room temperature over long periods of time. It is also soluble in organic solvents such as chloroform and methylene dichloride. Aqueous solutions of this salt on parenteral administration produce therapeutic blood levels of penicillin which persist several times as long as

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those produced by aqueous solutions of either calcium or sodium penicillin.

(b) 17.98 g. of crystalline sodium penicillin-G (1600 Oxford units/mg.) is dissolved in 450 cc. of distilled water. 540 cc. of ether is added and the exact quantity (54 cc. of 1.038 N) of hydrochloric acid necessary to liberate the free penicillin acid is added dropwise with stirring. After mixing, the layers are separated and the aqueous solution extracted with 270 cc. of ether. The ether extracts are combined, dried over anhydrous magnesium sulfate and the drying agent removed by filtration. All the foregoing operations are carried out at about 0 to 3° C.

8.89 g. of n-octyl-dimethyl-amine dissolved in a small amount of ether is added with stirring to the dried ether extracts containing the free penicillin acid. The amine salt of penicillin-G separates from the reaction mixture as a pale yellow oil immediately upon mixing of the reactants. The ether is removed as completely as possible by decantation and the last traces removed by storing the oil over phosphorus pentoxide in vacuo. The oil is dissolved in 38 cc. of acetone, the solution warmed to 45° C. and an equal volume of warm n-octyl-dimethyl-amine added with stirring. On cooling, the desired n-octyl-dimethyl-amine salt of penicillin-G separates in pure crystalline form. The salt is collected and washed well with petroleum ether. The yield of the white crystalline salt is 17 g. assaying 1200 Oxford units/mg. and melting at 114-5° C. This salt is soluble in water and slightly soluble in vegetable oils. It is also soluble in chloroform and methylene dichloride. It is practically non-hygroscopic and stable for long periods of time in the solid form at room temperature. Aqueous solutions of this salt produce, on parenteral administration, satisfactory therapeutic blood levels of penicillin persisting up to ten hours or better. These preparations are no more irritating than aqueous solutions of sodium penicillin-G. Vegetable oil suspensions of this salt are fluid at room temperature and produce even more prolonged therapeutic blood levels of penicillin on parenteral administration than those obtained by the use of the aqueous solutions of the salt.

Example 4

3.5 g. of non-crystalline, commercial sodium penicillin (1100 Oxford units/mg. and consisting of about 90% penicillin-G, 7% penicillin-K and 3% penicillin-F and dihydro-penicillin-F) is dissolved in 100 cc. of distilled water and an equal volume of amyl acetate added to the solution. The theoretical quantity of 1 N hydrochloric acid necessary to liberate the free penicillin acid from the salt is added dropwise with stirring and after thorough mixing the layers separated. The aqueous phase is extracted with 50 cc. amyl acetate and the combined amyl acetate extracts dried over magnesium sulfate. All the foregoing operations are carried out at a temperature below about 3° C.

1.84 g. of non-octyl-diethyl-amine dissolved in a small amount of amyl acetate is added to the amyl acetate extracts and the mixture allowed to stand for a few minutes. The amyl acetate is distilled off in vacuo without heating the material in the flask over about 5° C. to obtain the desired n-octyl-diethyl-amine salt of penicillin. The yellow-colored crude salt may be purified by recrystallizing from n-octyl-diethyl-amine-acetone mixture and washing

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with petroleum ether. The purified, white, crystalline salt is soluble in water, slightly soluble in vegetable oils and is practically non-hygroscopic. Biological assay of this salt shows it to possess about 1100 Oxford units/mg. of penicillin activity. Aqueous solutions of this salt exhibit a prolonged repository-like effect when injected intramuscularly.

Example 5

3 g. of commercial calcium penicillin (1150 Oxford units/mg. and consisting of about 90% penicillin-G, 10% penicillin-K and minor amounts of penicillin-F) is dissolved in 90 cc. of distilled water. 100 cc. of chloroform is added and then the theoretical quantity of 1 N sulfuric acid necessary to liberate the free penicillin acid from the salt added dropwise with stirring. The chloroform layer is separated and the aqueous solution extracted with a fresh portion of chloroform (50 cc.). The combined chloroform extracts are dried over magnesium sulfate and drying agent removed by filtration. During all the foregoing operations the temperature of the solutions is maintained at about 2 to 3° C.

1.57 g. of n-octyl-n-propyl-methyl-amine in a small amount of chloroform is added with stirring to the chloroform solution of the free penicillin acid and the mixture allowed to stand for a few minutes. The chloroform is removed under vacuo without allowing the temperature of the distilling mixture to rise over about 5° C. to obtain the desired n-octyl-n-propyl-methyl-amine salt of penicillin as a light orange colored, crystalline solid. The crude salt thus obtained is purified by first recrystallizing it from a mixture consisting of n-octyl-n-propyl-methyl-amine and acetone and then washing the crystalline salt with petroleum ether. The light colored purified salt is soluble in water, slightly soluble in vegetable oils and is stable in the solid form over long periods of time.

Example 6

2.5 g. of crystalline sodium penicillin-G (1400 Oxford units/mg.) is dissolved in 75 cc. of distilled water and an equal volume of chloroform added to the solution. The theoretical quantity of 1 N hydrochloric acid necessary to liberate the free penicillin acid is added dropwise with stirring and after thorough mixing the chloroform layer removed. The aqueous phase is extracted with 50 cc. of fresh chloroform, the extract added to the original chloroform extract and the mixture dried over magnesium sulfate. The temperature during all the foregoing operations is maintained at about 2 to 3° C.

1.3 g. of n-nonyl-ethyl-methyl-amine dissolved in a small quantity of chloroform is added to the chloroform extracts containing the free penicillin acid and the mixture allowed to stand for a few minutes. The chloroform is evaporated in vacuo without allowing the temperature of the mixture to rise above about 5° C. The crystalline residue which is pale yellow in color consists of the desired n-nonyl-ethyl-methyl-amine salt of penicillin-G. The crude salt is purified by recrystallizing from a mixture consisting of acetone and n-nonyl-ethyl-methyl-amine and washing with petroleum ether. The pure, white, crystalline salt is soluble in water and slightly soluble in vegetable oils. It is also soluble in chloroform and methylene dichloride. It is practically non-hygroscopic and is stable over long periods of time at room temperature.

This salt which assays about 1100 Oxford units/mg. when injected in aqueous solution produces therapeutic blood levels of penicillin which persist up to about ten hours.

By substituting 1.24 g. of n-nonyl-dimethylamine for the n-nonyl-ethyl-methylamine used in the above procedure one obtains the n-nonyl-dimethylamine salt of penicillin-G. This salt possesses about the same properties as those exhibited by the n-nonyl-methyl-ethylamine salt. This white, crystalline salt, in aqueous solution, produces remarkably prolonged therapeutic blood levels of penicillin but is no more irritating than the sodium salt of penicillin-G.

Example 7

2 g. of commercial calcium penicillin (1100 Oxford units/mg. and consisting of about 90% penicillin-G and 10% penicillin-K) is dissolved in 60 cc. of distilled water. 60 cc. of chloroform is added and then the theoretical quantity of 1 N hydrochloric acid necessary to liberate the free penicillin acid added dropwise with stirring. The chloroform layer is removed, the aqueous phase extracted with 30 cc. of chloroform and the combined chloroform extracts dried over magnesium sulfate. All of the foregoing operations are carried out at a temperature close to 0° C. in order to prevent the decomposition of the free penicillin acid.

1.05 g. of n-decyl-dimethylamine in about 10 cc. of chloroform is added to the cold chloroform solution of the free penicillin acid and after standing for a few minutes the chloroform is removed from the solution under reduced pressure. During the evaporation of the chloroform the material should not be allowed to rise above about 5° C. although toward the end of the evaporation the material can be allowed to come to room temperature. The orange-yellow, crystalline residue consists of the desired n-decyl-dimethylamine salt of penicillin. The crude salt is purified by first recrystallizing it from n-decyl-dimethylamine-acetone mixture and then washing it with petroleum ether. The crystalline salt thus obtained is soluble in water, chloroform and methylene dichloride. It is appreciably soluble in vegetable oils and is practically non-hygroscopic. Aqueous solutions of this salt on parenteral administration produce therapeutic blood levels of penicillin which persist for at least ten hours. Biological assay of the crystalline salt shows it to possess about 1125 Oxford units/mg. of penicillin activity.

If desired, an equivalent quantity of the pure sodium salt of penicillin-G may be substituted for the calcium salt used in the above procedure.

Example 8

2 g. of commercial calcium penicillin (1100 Oxford units/mg. and consisting of about 90% penicillin-G and 10% penicillin-K with minor amounts of penicillin-F) is converted to the free penicillin acids as described in Example 7 and the resulting chloroform solution treated with 1.13 g. of undecyl-dimethylamine in 15 cc. of chloroform. The chloroform is evaporated in vacuo to obtain the desired undecyl-dimethylamine salt of penicillin as an orange colored, crystalline residue. The crude salt may be purified by first recrystallizing it from a mixture of undecyl-dimethylamine and acetone and then washing it with petroleum ether to remove any adhering crystallization solvent. This salt assays about 1100 Oxford units/mg. of penicillin activity. It

is soluble in water, chloroform and methylene dichloride. It is also appreciably soluble in vegetable oils and practically non-hygroscopic. It is also stable in the solid form at room temperature over long periods of time.

Example 9

5 g. of commercial calcium penicillin (1150 Oxford units/mg. and consisting of about 90% penicillin-G and 10% penicillin-K) is converted to the free penicillin acid as described in Example 7. 3.02 g. of n-dodecyl-dimethylamine in 15 cc. of chloroform is added with stirring to the cold chloroform extract containing the free penicillin acid and the chloroform evaporated from the solution under reduced pressure while keeping the temperature of the mixture below about 5° C. The last traces of chloroform are removed from the residue under high vacuo at room temperature to obtain the desired crystalline n-dodecyl-dimethylamine salt of penicillin. This crude orange-yellow salt may be purified by recrystallizing from n-dodecyl-dimethylamine-acetone mixture and washing with petroleum ether. The purified crystalline salt thus obtained possesses physical and physiological properties similar to the salt of the preceding example.

Example 10

4 g. of commercial calcium penicillin (1200 Oxford units/mg. and consisting of about 90% penicillin-G, 8 to 10% penicillin-K and small amounts of penicillin-F and dihydro penicillin-F) is converted to the free penicillin acid in accordance with the procedure described in Example 7 and the cold chloroform solution containing the free penicillin acid treated with 3.05 g. of n-dodecyl-di-n-propylamine in 15 cc. of chloroform. The chloroform is evaporated from the solution under reduced pressure while maintaining the temperature of the solution below about 5° C. After almost all of the chloroform has been evaporated the mixture is allowed to come to room temperature and the last traces of chloroform removed under high vacuo. The residual, orange-colored, waxy, crystalline material consists of the desired n-dodecyl-di-n-propylamine salt of penicillin. The crude salt may be purified by recrystallization from n-dodecyl-di-n-propylamine-acetone mixture. The crystalline salt is washed well with petroleum ether to remove any adhering crystallization solvent and the last traces of petroleum ether removed in vacuo. The purified salt is soluble in water, chloroform, methylene dichloride and ethylene dichloride. It is also appreciably soluble in vegetable oils and practically non-hygroscopic. It is stable for long periods of time in the solid form. Aqueous solutions of this salt, as well as vegetable oil suspensions of the same, produce therapeutic blood levels of penicillin which persist several times longer than those obtainable by the administration of the corresponding sodium or calcium penicillin salt preparation.

Example 11

4 g. of commercial, crystalline sodium penicillin-G (1400 Oxford units/mg.) is dissolved in 120 cc. of distilled water and a chloroform solution of the free penicillin acid prepared as described in Example 6. 2.89 g. of n-pentadecyl-dimethylamine dissolved in 15 cc. of chloroform is added to the cold chloroform solution of the penicillin acid and the mixture allowed to stand for a short time. The chloroform is evaporated from

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the solution under reduced pressure and the last traces removed at room temperature under high vacuo. The light yellow colored, crystalline residue consists of the desired n-pentadecyl-dimethyl-amine salt of penicillin-G. The crude salt may be purified by first recrystallizing it from a mixture consisting of n-pentadecyl-dimethyl-amine and acetone and then washing it with petroleum ether. The pure, white, crystalline salt thus obtained is relatively soluble in water and appreciably soluble in vegetable oils. It is also soluble in chloroform, methylene dichloride and ethylene dichloride. Preparations containing this purified salt exhibit the same physiological properties as those of the previous example.

Example 12

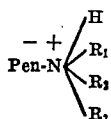
2 g. of commercial calcium penicillin (1175 Oxford units/mg. and consisting of about 90% penicillin-G and 10% penicillin-K and -F) is dissolved in 60 cc. of distilled water and a chloroform solution of the free penicillin acid prepared as described in Example 7. A solution of 1.43 g. of n-octadecyl-dimethyl-amine in 12 cc. of chloroform is added to the cold chloroform solution of the penicillin acid and the mixture allowed to stand for a few minutes. The chloroform is evaporated under reduced pressure without allowing the temperature to rise above about 5° C. until most of the chloroform has been removed. The last traces of chloroform are removed under high vacuo at room temperature. The orange colored, crystalline residue consists of the n-octadecyl-dimethyl-amine salt of penicillin. This crude salt may be purified by recrystallizing it from n-octadecyl-dimethyl-amine and acetone mixture and washing it with petroleum ether. The purified crystalline salt is appreciably soluble in water, more soluble in vegetable oils than the salts of the foregoing examples and practically non-hygroscopic. It is also soluble in chloroform and stable in the solid form over long periods of time.

Example 13

3 g. of commercial calcium penicillin (1170 Oxford units/mg. and consisting of about 90% penicillin-G, 5 to 7% of penicillin-K, 3 to 5% penicillin-F and dihydro penicillin-F) is dissolved in 30 cc. of cold distilled water and the solution stirred vigorously with 30 cc. of methylene dichloride. 2.48 g. of n-octyl-dimethyl-amine hydrochloride in 25 cc. of water is added with stirring to the well-stirred emulsion and stirring continued for about ten minutes. The layers are separated and the aqueous layer extracted with two additional 30 cc. portions of methylene dichloride. The combined extracts are washed with 25 cc. of distilled water, the methylene dichloride solution dried with magnesium sulfate, filtered and the filtrate evaporated to dryness at a temperature below 35° C. The yellow residual n-octyl-dimethyl-amine salt of penicillin has an antibiotic activity of about 700 Oxford units/mg. It may be recrystallized and washed as described in Example 3 (a) above in order to obtain the purified salt. The salt thus obtained possesses the same properties as the salt obtained in Example 3 (a).

What we claim as our invention is:

1. A penicillin salt having the formula



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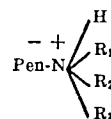
where Pen- is the anion of penicillin-G, R₁ and R₂ are lower alkyl radicals and R₃ is an alkyl radical containing 6 to 18 carbon atoms inclusive.

2. The n-octyl-dimethyl-amine salt of penicillin-G.

3. The n-nonyl-dimethyl-amine salt of penicillin-G.

4. The n-decyl-dimethyl-amine salt of penicillin-G.

5. Process for obtaining a penicillin salt of the formula



which comprises reacting penicillin-G with a tertiary amine of the formula



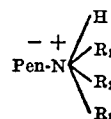
in a substantially anhydrous, water-immiscible, inert organic solvent at a temperature below about 10° C., recrystallizing the crude tertiary amine salt so obtained from a solvent mixture consisting of the corresponding tertiary amine and a lower aliphatic ketone and washing the recrystallized salt with a substantially anhydrous, water-immiscible, inert organic solvent, where Pen- is the anion of penicillin-G, R₁ and R₂ are lower alkyl radicals and R₃ is an alkyl radical containing 6 to 18 carbon atoms inclusive.

6. Process for obtaining the n-octyl-dimethyl-amine salt of penicillin-G which comprises reacting penicillin-G with n-octyl-dimethyl-amine in a substantially anhydrous, water-immiscible, inert organic solvent at a temperature below about 10° C., recrystallizing the crude tertiary amine salt so obtained from a solvent mixture consisting of n-octyl-dimethyl-amine and a lower aliphatic ketone and washing the recrystallized salt with a substantially anhydrous, water-immiscible, inert organic solvent.

7. Process for obtaining the n-nonyl-dimethyl-amine salt of penicillin-G which comprises reacting penicillin-G with n-nonyl-dimethyl-amine in a substantially anhydrous, water-immiscible, inert organic solvent at a temperature below about 10° C., recrystallizing the crude tertiary amine salt so obtained from a solvent mixture consisting of n-nonyl-dimethyl-amine and a lower aliphatic ketone and washing the recrystallized salt with a substantially anhydrous, water-immiscible, inert organic solvent.

8. Process for obtaining the n-decyl-dimethyl-amine salt of penicillin-G which comprises reacting penicillin-G with n-decyl-dimethyl-amine in a substantially anhydrous, water-immiscible, inert organic solvent at a temperature below about 10° C., recrystallizing the crude tertiary amine salt so obtained from a solvent mixture consisting of n-decyl-dimethyl-amine and a lower aliphatic ketone and washing the recrystallized salt with a substantially anhydrous, water-immiscible, inert organic solvent.

9. In a process for obtaining a penicillin salt of the formula



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the steps which comprise recrystallizing a crude tertiary amine salt of the above formula from a solvent mixture consisting of the corresponding tertiary amine and a lower aliphatic ketone and washing the recrystallized salt with a substantially anhydrous, water-immiscible, inert, organic solvent, where Pen- is the anion of penicillin-G, R₁ and R₂ are lower alkyl radicals and R₃ is an alkyl radical containing 6 to 18 carbon atoms inclusive.

10. In a process for obtaining the n-octyl-dimethyl-amine salt of penicillin-G, the steps which comprise recrystallizing the crude n-octyl-dimethyl-amine salt of penicillin-G from a solvent mixture consisting of n-octyl-dimethyl-amine and a lower aliphatic ketone and washing the recrystallized salt with a substantially anhydrous, water-immiscible, inert, organic solvent.

11. In a process for obtaining the n-nonyl-dimethyl-amine salt of penicillin-G, the steps which comprise recrystallizing the crude n-nonyl-dimethyl-amine salt of penicillin-G from a solvent mixture consisting of n-nonyl-dimethyl-amine and a lower aliphatic ketone and washing the recrystallized salt with a substantially anhydrous, water-immiscible, inert, organic solvent.

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12. In a process for obtaining the n-decyl-dimethyl-amine salt of penicillin-G, the steps which comprise recrystallizing the crude n-decyl-dimethyl-amine salt of penicillin-G from a solvent mixture consisting of n-decyl-dimethyl-amine and a lower aliphatic ketone and washing the recrystallized salt with a substantially anhydrous, water-immiscible, inert, organic solvent.

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