

PATENT SPECIFICATION

790,135



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COMPLETE SPECIFICATION

New Salts of Penicillin with Organic Bases and Processes for preparing them

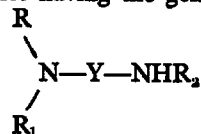
We, AMERICAN HOME PRODUCTS CORPORATION, a Corporation organised and existing under the laws of the State of Delaware, United States of America, of 22, East 40th Street, New York 16, New York, United States of America, (Assignee of Biochemie Gesellschaft mit beschränkter Haftung), do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

The present invention relates to new salts of penicillin with organic bases, and to processes for preparing them. The invention is particularly concerned with such new salts as are no more than sparingly soluble in water and suitable particularly for oral therapy.

It is known to prepare crystalline salts of penicillin G with organic nitrogen bases, such as *p*-aminobenzoyl-diethylaminoethanol-penicillin G or quinine-penicillin G, which are either used directly in therapy or as in the case of N-ethylpiperidine-penicillin G or triethylamine-penicillin G, represent intermediates in the preparation of pure alkali metal or alkaline earth metal salts of penicillin. According to a known procedure these base salts of penicillin, which are generally no more than slightly soluble in water, may be prepared by reacting alkali metal or alkaline earth metal salts of penicillin with inorganic or organic acid salts of the organic nitrogen bases, e.g. *p*-aminobenzoyl-diethylaminoethanol hydrochloride, in an aqueous or aqueous-alcoholic solution. In another procedure, which may be adopted also for preparing water-soluble base salts of penicillin, the free organic nitrogen base is caused to act in anhydrous organic solvent on the penicillin present as free acid. Another known process, which is useful for making organic nitrogen base salts of penicillin which are very slightly soluble or practically insoluble in water, comprises the reaction of organic nitrogen base salts of penicillin with

certain organic nitrogen base salts of inorganic or organic acids, whose base is different from the base of the penicillin salt employed; the penicillin base salts obtained by that process are less soluble in the reaction medium than the penicillin base salts used as starting materials.

In Specification No. 716,556 we have described and claimed new salts of penicillin and N-substituted diamines, said N-substituted diamines having the general formula:—



wherein R represents an aliphatic, alicyclic, araliphatic, aromatic or heterocyclic group which may or may not have substituents,

R₁ represents a hydrogen atom or an aliphatic, alicyclic, araliphatic, aromatic or heterocyclic group which may or may not have substituents,

R₂ represents a hydrogen atom or, where R₁ is hydrogen, an aliphatic, araliphatic, aromatic or heterocyclic group which may or may not have substituents, and

Y represents an alkylene radical having from 2 to 12 carbon atoms.

The penicillins named in Specification No. 716,556 are penicillin G, dihydro F, X and penicillin K.

In Specification No. 719,887 we have described and claimed a biologically active salt of penicillin with an organic base, said organic base having the formula:—



wherein R and R¹ are each different, and each represent a phenyl radical or a hydroxy- and/or alkoxy-substituted phenyl radical.

The term "penicillin" is stated in Specification No. 719,887 to be used therein to denote one or more of several variants of this antibiotic which are biologically active, such as the most common penicillin G, penicillin

F, penicillin X and also the various biosynthetic penicillins which are formed by fermentation in media containing specific precursors, one example of the latter being penicillin O, which is formed by the growth of a suitable penicillin-producing micro-organism in media containing allylmercaptoacetic acid or a suitable derivative thereof as described in the Journal of Biological Chemistry, Vol. 175, p. 803 (1948).

All previously known penicillins and penicillin salts, including organic nitrogen base salts of penicillin, have the disadvantage that their stability is low owing to the high susceptibility of these penicillins to acid; for this reason their oral administration involves great difficulties. Since the free acid in the stomach causes a considerable destruction of the antibiotic, the quantities of penicillin previously required to achieve such a penicillin content in the blood as will safely ensure a therapeutic effect were at least five to six times as large as those required for similar effects upon parenteral application. Besides it was possible to take the penicillin salts only on an empty stomach. Progress in this field was achieved only by the introduction of acid-resistant penicillins, which are applied as free acids. These acid-resistant penicillins, which are preferably administered in the form of lozenges, gave practically the same results as preparations for injection; they require the penicillin to be used in quantities which are only about 1.5 times as large as in the case of penicillin for injection and the emptiness of the stomach is of less importance in this connection. On the other hand, it has hitherto been possible to apply acid-resistant penicillins only in solid form e.g. as lozenges or dragées, not in liquid form, e.g. as an aqueous solution or suspension, for instance in the form of fruit syrups so popular in paediatrics, or in similar form. An aqueous suspension of acid-resistant penicillins (pH approximately 3) is durable only for less than the required period of one year or two; even with higher pH values (pH 5 to 7), when the acid-resistant penicillins are present as water-soluble salts, the durability is poor just as with solutions of salts of penicillin G. It has also been found that the administration of aqueous solutions of the freely water-soluble alkali metal salts of acid-resistant penicillins will lead to a higher penicillin content of the blood than an application of the same quantity of alkali metal salts of penicillin G, but to a lower content than that which results after a taking of the same quantity of acid-resistant penicillin in the form of free acid. This may be due to the fact that the free acid is liberated by the gastric acid also from the alkali metal salts of the acid-resistant penicillins but remains for some time in a supersaturated solution. In a supersaturated solution, however, the free acids of the acid-resistant penicillins are stabler than

the free acid of penicillin G, whereas they are less resistant to acid than the crystalline free acids of the acid-resistant penicillins.

It is an object of the invention to prepare salts of penicillins, which are no more than sparingly water-soluble, are not substantially reduced in activity in a neutral, slightly acid or acid medium and which can be used in preparing durable aqueous suspensions which are suitable particularly for oral therapy. The expressions "water-soluble", "freely water-soluble", "sparingly water-soluble", "slightly water-soluble" and "very slightly water-soluble" are used with their conventional meaning, as explained in Hackh's Chemical Dictionary (see 3rd Edition, page 787).

The process according to the invention for preparing novel salts of penicillin with organic bases, comprises essentially a reaction of an acid-resistant penicillin with an organic nitrogen base, with which it forms a salt which is no more than sparingly water-soluble such as diphenylethylamine, benzylphenylethylamine or dibenzylethylenediamine, to form a base salt of the penicillin which is highly stable in an aqueous suspension and does not suffer an appreciable decrease in penicillin activity in an acid medium. Other organic nitrogen bases which may be used are dibenzylamine, phenylethylbenzylamine, diphenylmethylamine, quinine, benzyl- β -phenylethylamine and alkylenediamines of the general formulæ $R_3-NH(CH_2)_m-NH_2$, $R_3NH-(CH_2)_m-NH-R_4$ and $R_3R_4N(CH_2)_mNH_2$ where R_3 and R_4 are aliphatic, aromatic, alicyclic or heterocyclic radicals with or without substituents on the rings and m represents a numeral from 1 to 12. Example of alkylenediamines characterised by the formulæ just given above are:—

di-(benzyl)-ethylenediamine,
di-(benzylamino)-propane,
di-(benzylamino)-pentane,
di-(benzylamino)-decane,
di-(cyclohexyl)-ethylenediamine,
di-(*p*-chlorobenzyl)-ethylenediamine,
di-(2,4-dichlorobenzyl)-ethylenediamine
mono-(*p*-hydroxybenzyl)-ethylenediamine
di-(*p*-aminobenzyl)-ethylenediamine,
di-(*p*-methoxybenzyl)-ethylenediamine,
di-(*p*-methylbenzyl)-ethylenediamine,
di-(*p*-hydroxybenzyl)-ethylenediamine,
di-(4-methyl-2-pentyl)-ethylenediamine,
di-(3,5,5-trimethyl-hexyl)-ethylenediamine,
di-(2-heptyl)-ethylenediamine,
di-(2-thenyl)-ethylenediamine,
di-(furfuryl)-ethylenediamine,
di-(piperonyl)-ethylenediamine, and
di-(γ -phenylpropyl)-ethylenediamine.

By the term "acid-resistant penicillin" when used in this specification, we mean a penicillin of the general formula: $C_8H_{10}O_3NS-NHCO-CH_2-X-R$, where in R represents a substituted or unsubstituted aromatic radical, especially an alkyl-, hydroxy-

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or nitro-substituted phenyl radical, and X represents oxygen or sulphur). The characteristics of these acid-resistant penicillins are typically different from those of the normal penicillins G, X, F and K. Examples of such acid-resistant penicillins are phenoxymethylpenicillin, *p*-cresoxymethyl-penicillin, *p*-hydroxyphenoxymethyl-penicillin, *p*-nitrophenoxymethyl-penicillin, and phenylmercaptomethyl-penicillin.

In a particularly suitable embodiment of the invention the novel organic nitrogen base salts of penicillin may be prepared by reacting the free acids of acid-resistant penicillins with the free organic nitrogen bases in organic solvents, such as butylacetate, amylacetate, ether, chloroform or acetone. Solid crystalline phenoxymethyl penicillin acid and a process for producing it are described and claimed in Specification No. 734,232. Alternatively acid-resistant penicillins may be reacted in the form of their salts, preferably of their alkali metal or alkaline earth metal salts, with salts of organic nitrogen bases in an aqueous solution, to which water-miscible organic solvents, e.g. aliphatic amides, such as formamide or acetamide may be added. Furthermore, the preparation of the organic nitrogen base salts of acid-resistant penicillins according to the invention is possible with a good yield also if organic nitrogen base salts of acid-resistant penicillins are reacted with those organic nitrogen base salts of inorganic or organic acids whose bases are different from the bases of the penicillin base salts employed and whereby organic nitrogen base salts are formed which are less soluble in the reaction medium than the starting penicillin base salts; the base salts of inorganic or organic acid may be suspended in solvents. The reactions described may be performed at normal or elevated temperature.

The solubility characteristics of organic nitrogen base salts of acid-resistant penicillins differ in many cases from the solubility characteristics of the corresponding organic nitrogen base salts of penicillin G. For instance, *p*-aminobenzoyldiethylaminoethanol penicillin G, the best known organic nitrogen base salt of penicillin G, has at room temperature a solubility of only about 0.5% in water whereas *p*-aminobenzoyldiethylaminoethanol-phenoxymethyl-penicillin has at the same temperature a solubility of about 6%, which is many times higher. This salt, being more than sparingly water-soluble, is not within the scope of the present invention.

Losses of activity as can be observed with alkali metal and alkaline earth metal salts of acid-stable penicillins, though to a much lower degree than with salts of penicillin G will not substantially occur as the novel organic nitrogen base salts of acid-resistant penicillins according to the invention pass through the stomach. This may be due to the fact that the solid phase of the base penicillin forms nuclei

for the crystallisation of the free acids of the acid-resistant penicillins so that a supersaturation, which is responsible for the loss in activity of the alkali metal and alkaline earth metal salts of acid-resistant penicillins in oral therapy, is eliminated. Organic nitrogen base salts particularly suitable for the preparation of durable aqueous suspensions are those having a solubility of less than 0.4% in water, preferably those having a solubility of less than 0.2% in water; a particularly desirable range of solubility in water lies between 0.03 and 0.1%.

Since the milligram activities are about 800 to 1000 units owing to the fact that the molecular weights are not very different, the saturated aqueous solutions will have activities in an order of about 1000 units per cubic centimetre. Organic nitrogen base salts of acid-resistant penicillins whose solubility characteristics correspond to the above conditions are, e.g., dibenzyl-ethylenediamine-phenoxymethylpenicillin, phenylethylbenzylamine-phenoxymethylpenicillin, dibenzylaminephenoxymethylpenicillin, dibenzylethylenediamine-*p*-cresoxymethylpenicillin, phenylethylbenzylamine-*p*-cresoxymethylpenicillin, diphenylethylamine-*p*-cresoxymethylpenicillin and dibenzylamine-*p*-cresoxymethylpenicillin. If such durable suspensions of organic nitrogen base salts of acid-resistant penicillins, which are only slightly or very slightly-soluble in water, are administered orally, the gastric juice will cause a reaction whereby the hydrochloride of the base and the acid-resistant penicillin in the form of the free acid is formed. Owing to the acid-resistance of the free acid of these penicillin salts their application in about the same quantities as are usually taken of the free acids of acid-resistant penicillins will lead to similar penicillin contents in the blood as in the latter case.

The solubility in water of dibenzylethylenediamine-phenoxymethylpenicillin is appreciable higher than that of the corresponding salt of penicillin G (0.03% compared to 0.01% at room temperature). This has certain advantages if the compound is administered parenterally. For instance, a penicillin content can be found in the blood after many days, in some cases even after one week or two, after a single injection of dibenzylethylenediamine-penicillin G. For this reason that preparation will be used to advantage wherever a prolonged presence of penicillin in the blood is desirable. A consideration of the blood content curves obtained upon a therapeutical application of that salt of penicillin G will show that beginning from the second or third day after the injection the content in the blood lies about 0.06 to 0.12 Oxford units per cubic centimetre of serum and may remain in that range for many days.

After an injection of, e.g., 300,000 units of dibenzylethylenediamine - phenoxymethyl

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penicillin its content in the blood after two or three days will also be about 0.1 Oxford unit per cubic centimetre but owing to the higher solubility in water of that penicillin salt that content will drop more rapidly than the penicillin contents in the blood resulting from an application of dibenzylethylenediamine-penicillin G. This is of special advantage for many applications. For instance, where the novel penicillin salts are used much fewer injections are required than in the case of penicillin salts of alkali metals. On the other hand the treatment of the patient may be discontinued within a relatively short time if necessary.

Dibenzylethylenediamine - phenoxymethylpenicillin appears to constitute a salt of optimum solubility for depot preparations to be administered parenterally because its solubility lies between that of *p*-aminobenzoylethylenediamine-penicillin G and of dibenzylethylenediamine-penicillin G.

EXAMPLE 1.

3.2 grams of dibenzylethylenediaminehydrochloride dissolved in 200 cubic centimetres water were added to a solution of 7.44 grams sodium-phenoxymethylpenicillin, having 1600 units per milligram in 200 cubic centimetres water. A deposit of dibenzylethylenediamine - phenoxymethylpenicillin was formed immediately and was sucked off, washed with water and dried. Yield: 9.1 grams dibenzylethylenediamine - phenoxymethylpenicillin having 1160 units per milligram (iodometric test) = 87.7% of theory.

When dried to constant weight the substance has a melting point of 105—100 deg. C. and a solubility of 0.4% in water at 24 deg. C.

EXAMPLE 2.

4.22 grams *N*- β -phenylethyl-(*N*-benzyl)amine base dissolved in 200 cubic centimetres butylacetate were added to 200 cubic centimetres butyl acetate phase containing phenoxymethylpenicillin (59,500 units per cubic centimetre—iodometric test). The deposit of *N*- β -phenylethyl-(*N*-benzyl)amine phenoxymethylpenicillin separating after several hours standing was sucked off, washed with ether and finally dried. The yield was 10.6 grams of *N*- β -phenylethyl-(*N*-benzyl)amine-phenoxymethylpenicillin having 1016 units per milligram (iodometric test) = 90.5% of theory. The solubility in water was 0.09% at 24 deg. C.

EXAMPLE 3.

1.1 gram of *N*- β -phenylethyl-(*N*-benzyl)amine-phenoxymethylpenicillin having 1050 units per milligram were suspended in a solution of 0.45 gram dibenzylethylenediaminediacetate in 30 cubic centimetres water. The suspension was shaken for many hours at room temperature on a shaking machine and was then allowed to stand for about 24 hours

at a temperature of 4 deg. C. This procedure gave 0.90 gram dibenzylethylenediamine-phenoxymethylpenicillin having 1150 units per milligram (iodometric test), corresponding to a yield of 90% of theory. The solubility in water was 0.04% at 24 deg. C.

EXAMPLE 4.

3.20 grams dibenzylethylenediaminehydrochloride dissolved in 200 millilitres water are added to a solution in water of 7.40 grams *Ca*-phenoxymethyl-penicillin having 1600 units per milligram (iodometric test). A deposit of dibenzylethylenediamine - phenoxymethyl - penicillin will form immediately and is sucked off, washed with water, and dried.

Yield: 88.7% of theory; dibenzylethylenediamine-phenoxymethyl-penicillin having 1160 units per milligram (iodometric test).

EXAMPLE 5.

4.22 grams *N*-benzyl- β -phenylethylamine base dissolved in 200 millilitres ether are added to a solution of 7.02 grams phenoxymethyl-penicillin, in the form of free acid having 1695 units per milligram (iodometric test), in 200 millilitres butylacetate. After a short time the phenoxymethyl-penicillin salt of *N*-benzyl- β -phenylethylamine separates from the solution and is filtered off, washed with ether and dried.

Yield: 10.6 grams *N*-benzyl- β -phenylethylaminophenoxy-methyl-penicillin having 1016 units per milligram (iodometric test) = 90.5% of theory.

The water solubility was 0.135 gram per 100 millilitres at 24 deg. C.

EXAMPLE 6.

A solution of 0.794 gram quinine hydrochloride in 100 millilitres of water is added to a solution of 0.744 gram *Na*-phenoxymethyl-penicillin having 1600 units per milligram, in 100 millilitres water. The quinine-phenoxymethyl-penicillin separating initially in oily form crystallises after a short time and is washed with some cold water and dried.

Yield: 1.27 gram quinine-phenoxymethylpenicillin having 802 units per milligram (iodometric test) = 86.0% of theory. The solubility in water is 0.173% at 24 deg. C.

EXAMPLE 7.

1.2 gram dibenzylamine base dissolved in 80 millilitres water are added to a solution of 1.75 gram phenoxymethyl-penicillin, in the form of free acid having 1695 units per milligram, in 12 millilitres acetone. The separated deposit is filtered off after standing for several hours and is washed with ether and dried.

Yield: 2.58 grams dibenzylamine-phenoxymethyl-penicillin having 1043 units per milligram = 90.7% of theory.

The solubility in water is 0.24% at 24 deg. C.

EXAMPLE 8.

A solution of 0.597 gram N,N^1 -bis-(dehydroabietyl)-ethylene diamine base in 50 millilitres ether is added to a solution of 0.701 gram phenoxymethyl-penicillin in the form of free acid in 30 millilitres acetone. The deposit separating soon is removed, washed with ether and dried.

Yield: 1.21 gram N,N^1 -bis-(dehydroabietyl) - ethylenediamine - phenoxymethyl - penicillin having 900 units per milligram (iodometric test)=91.7% of theory.

The solubility in water is 0.01% at 24 deg. C.

EXAMPLE 9.

2.20 grams (diphenylmethyl)aminehydrochloride dissolved in 50 millilitres water are added to a solution of 3.88 grams K-phenoxymethyl-penicillin, having 1520 units per milligram, in 50 millilitres water. The separated deposit is removed after standing for three hours and is washed with water and dried.

Yield: 4.97 grams (diphenylmethyl)-amine-phenoxymethyl-penicillin having 1080 units per milligram (iodometric test)=91% in of theory.

The solubility in water is 0.38% at 24 deg. C.

EXAMPLE 10.

1.1 gram N-benzyl- β -phenylethylamine-phenoxymethyl-penicillin having 1050 units per milligram and 0.45 gram dibenzylethylenediamine-diacetate are suspended in 30 millilitres water and shaken for some hours at 45 deg. C. The transformation product is removed, washed and dried.

Yield: 0.90 gram dibenzylethylenediamine-phenoxymethyl-penicillin having 1150 units per milligram (iodometric test)=90% of theory.

$N_{\text{found}} = 9.07\%$ (anhydrous product)

$N_{\text{in theory}} = 8.92\%$.

EXAMPLE 11.

0.36 gram dibenzylethylenediamine-diacetate dissolved in 200 millilitres water are added under stirring to a solution of 0.77 gram Na-salt of *p*-cresoxy-methyl-penicillin, having 1510 units per milligram, in 200 millilitres water. The separated deposit is filtered off, washed with cold water and dried.

Yield: 0.96 gram dibenzylethylenediamine salt of *p*-cresoxy-methyl-penicillin having 1120 units per milligram (iodometric test)=92.5% of theory.

$N_{\text{in theory}} = 8.67\%$

$N_{\text{found}} = 8.74\%$ (considering, that the water contents were 4.90%—determined by the method of Karl Fischer=K.F.M.).

The solubility in water is 0.039% at 24 deg. C.

EXAMPLE 12.

A solution of dibenzylamine in ether (prepared by extracting 1.16 gram dibenzylamine-hydrochloride with 60 millilitres ether at pH

=12) is added to a solution of 0.91 gram *p*-cresoxymethyl-penicillin, in the form of the free acid having 1610 units per milligram, in 6 millilitre acetone. The crystalline deposit separating soon is removed, washed with ether and dried.

Yield: 1.30 gram dibenzylamine salt of *p*-cresoxymethyl-penicillin having 1000 units per milligram (iodometric test)=88.7% of theory.

$N_{\text{in theory}} = 7.50\%$

$N_{\text{found}} = 7.59\%$ (considering, that the water contents were 3.06%—determined by K.F.M.).

The solubility in water is 0.16% at 24 deg. C.

EXAMPLE 13.

A solubility of quinine in ether (prepared by extracting 3.98 grams quinine hydrochloride. $2H_2O$ with 200 millilitres ether at pH 12) is added to a solution of 3.64 gram *p*-cresoxymethyl-penicillin, in the form of the free acid having 1610 units per milligram in 25 millilitres acetone. The quinine-*p*-cresoxymethyl-penicillin separating initially in oily form crystallises after standing for several hours under cooling. The salt is isolated, washed with ether and dried.

Yield: 6.09 grams quinine salt of *p*-cresoxymethyl-penicillin (hygroscopic), having 770 units per milligram (iodometric test)=80.0% of theory.

$N_{\text{in theory}} = 8.13\%$

$N_{\text{found}} = 8.66\%$ (considering that the water contents were 3.96%—determined by K.F.M.).

The water solubility is 0.16% at 24 deg. C.

EXAMPLE 14.

To 3.86 grams *p*-cresoxymethyl-penicillin-sodium having 1500 units per milligram (iodometric test) dissolved in 100 millilitres water was added a solution of 2.73 grams N-benzyl- β -phenylethylenediamine-diacetate in 100 millilitres water. The deposit was filtered off after standing for several hours and was washed with cold water and dried.

Yield: 5.15 grams N-benzyl- β -phenylethylenediamine salt of *p*-cresoxymethyl-penicillin, having 980 units per milligram (iodometric test)=87.2% of theory.

$N_{\text{in theory}} = 7.30\%$

$N_{\text{found}} = 7.46\%$ (considering, that the water contents were 2.54%, determined by K.F.M.).

The water solubility is 0.08% at 24 deg. C.

EXAMPLE 15.

0.22 gram dibenzylethylenediamine-diacetate are added to a suspension in water of 0.55 gram (diphenylmethyl)amine salt of *p*-cresoxymethyl-penicillin, having 1030 units per milligram. (The solubility in water of (diphenylmethyl)amine-*p*-cresoxymethyl-penicillin was 0.21% at 24 deg. C.

$N_{\text{in theory}} = 7.67\%$.

$N_{\text{found}} = 7.95\%$, considering that the water contents were 3.36% —determined by K.F.M.) The suspension is shaken for many hours at 45°C . This procedure gives 0.47 gram dibenzylethylenediamine salt of *p*-cresoxymethyl-penicillin, having 1100 units per milligram (iodometric test) $= 91.2\%$ of theory.

$N_{\text{in theory}} = 8.67\%$
 $N_{\text{found}} = 8.85\%$ (considering, that the water contents were 4.81% determined by K.F.M.).

EXAMPLE 16.

A solution of 1.80 grams dibenzylethylenediamine-diacetate in 200 millilitres water is added to a solution in water of 4.04 grams potassium - phenylmercaptomethyl - penicillin having 1450 units per milligram. The separated crystalline deposit is removed, washed with water and dried.

Yield: 4.60 grams dibenzylethylenediamine salt of phenylmercaptomethyl-penicillin having 1150 units per milligram (iodometric test) $= 90.5\%$ of theory.

The solubility in water is 0.046% at 24°C .

EXAMPLE 17.

7.00 grams phenoxymethyl penicillin-acid of 1690 U/mg (iodometric test) are dissolved in 200 ml butyl acetate and 4.45 grams β -phenylethylamine base, dissolved in 200 ml ether are added to this solution. After a short time the phenoxymethyl-penicillin salt of the β -phenylethylamine is separated from the solution which is filtered off, washed and dried. Yield: 10.7 grams. di-(β -phenylethyl)aminephenoxymethyl-penicillin of 1000 U/mg (iodometric test) equals 90.4% .

What we claim is:—

1. A salt which is no more than sparingly water-soluble of an acid-resistant penicillin of the general formula $C_8H_{10}O_3NSNHCO-CH_2-X-R$ (wherein R represents a substituted or unsubstituted aromatic radical and X represents oxygen or sulphur) with an organic nitrogen base.

2. A salt of an acid-resistant penicillin as claimed in Claim 1, wherein R represents an alkyl-substituted phenyl group and X represents oxygen.

3. A salt which is no more than sparingly

water-soluble of phenoxy-methyl penicillin with an organic nitrogen base.

4. A salt which is no more than sparingly water-soluble of *p*-cresoxy-methyl penicillin with an organic nitrogen base.

5. A salt as claimed in any of Claims 1 to 4 having a solubility in water of less than 0.2% .

6. A salt as claimed in Claim 5 having a solubility in water of between 0.03 and 0.1% .

7. The phenoxy-methyl penicillin salt of di-(β -phenylethyl)amine.

8. The phenoxy-methyl penicillin salt of benzyl- β -phenylethylamine.

9. The phenoxy-methyl penicillin salt of N,N' -dibenzylethylenediamine.

10. Process of preparing a new salt of penicillin as claimed in any of the preceding claims which comprises reacting the free acid-resistant penicillin with the free organic nitrogen base.

11. Process as claimed in Claim 10 carried out in solution in an organic solvent.

12. Process of preparing a new salt of penicillin as claimed in any of Claims 1 to 9 which comprises reacting a water-soluble salt of the acid-resistant penicillin with a salt of the organic nitrogen base, in aqueous solution.

13. Process as claimed in Claim 12 in which an alkali metal or alkaline earth metal salt of the acid-resistant penicillin is used.

14. Process as claimed in Claim 12 or 13 in which the aqueous solution contains water miscible organic solvent.

15. Process of preparing a new salt of penicillin as claimed in any of Claims 1 to 9 which comprises reacting an organic nitrogen base salt of the acid-resistant penicillin with an organic nitrogen base salt of an inorganic or organic acid suspended in a liquid reaction medium, the base of which is different from the base of the base salt of penicillin used and forms a base salt of the acid-resistant penicillin which is more difficultly soluble in the reaction medium than the base salt of the penicillin used as starting material.

16. The processes of preparing new salts of acid-resistant penicillins of the general formula given in Claim 1 and the salts so prepared, substantially as herein described.

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- $N_{\text{found}} = 7.95\%$, considering that the water contents were 3.36% —determined by K.F.M.) The suspension is shaken for many hours at 45°C . This procedure gives 0.47 gram dibenzylethylenediamine salt of *p*-cresoxymethyl-penicillin, having 1100 units per milligram (iodometric test) $= 91.2\%$ of theory.
- $N_{\text{in theory}} = 8.67\%$
- 10 $N_{\text{found}} = 8.85\%$ (considering, that the water contents were 4.81% determined by K.F.M.).

EXAMPLE 16.

- A solution of 1.80 grams dibenzylethylenediamine-diacetate in 200 millilitres water is added to a solution in water of 4.04 grams potassium - phenylmercaptomethyl - penicillin having 1450 units per milligram. The separated crystalline deposit is removed, washed with water and dried.
- 20 Yield: 4.60 grams dibenzylethylenediamine salt of phenylmercaptomethyl-penicillin having 1150 units per milligram (iodometric test) $= 90.5\%$ of theory.
- 25 The solubility in water is 0.046% at 24°C .

EXAMPLE 17.

- 7.00 grams phenoxymethyl penicillin-acid of 1690 U/mg (iodometric test) are dissolved in 200 ml butyl acetate and 4.45 grams β -phenylethylamine base, dissolved in 200 ml ether are added to this solution. After a short time the phenoxymethyl-penicillin salt of the β -phenylethylamine is separated from the solution which is filtered off, washed and dried. Yield: 10.7 grams. di- $(\beta$ -phenylethyl)aminephenoxymethyl-penicillin of 1000 U/mg (iodometric test) equals 90.4% .

What we claim is:—

- 40 1. A salt which is no more than sparingly water-soluble of an acid-resistant penicillin of the general formula $\text{C}_8\text{H}_{10}\text{O}_3\text{NSNHCO}-\text{CH}_2-\text{X}-\text{R}$ (wherein R represents a substituted or unsubstituted aromatic radical and X represents oxygen or sulphur) with an organic nitrogen base.
- 45 2. A salt of an acid-resistant penicillin as claimed in Claim 1, wherein R represents an alkyl-substituted phenyl group and X represents oxygen.
- 50 3. A salt which is no more than sparingly

water-soluble of phenoxy-methyl penicillin with an organic nitrogen base.

4. A salt which is no more than sparingly water-soluble of *p*-cresoxy-methyl penicillin with an organic nitrogen base. 55

5. A salt as claimed in any of Claims 1 to 4 having a solubility in water of less than 0.2% .

6. A salt as claimed in Claim 5 having a solubility in water of between 0.03 and 0.1% . 60

7. The phenoxy-methyl penicillin salt of di- $(\beta$ -phenylethyl)amine.

8. The phenoxy-methyl penicillin salt of benzyl- β -phenylethylamine.

9. The phenoxy-methyl penicillin salt of N,N' -dibenzylethylenediamine. 65

10. Process of preparing a new salt of penicillin as claimed in any of the preceding claims which comprises reacting the free acid-resistant penicillin with the free organic nitrogen base. 70

11. Process as claimed in Claim 10 carried out in solution in an organic solvent.

12. Process of preparing a new salt of penicillin as claimed in any of Claims 1 to 9 which comprises reacting a water-soluble salt of the acid-resistant penicillin with a salt of the organic nitrogen base, in aqueous solution. 75

13. Process as claimed in Claim 12 in which an alkali metal or alkaline earth metal salt of the acid-resistant penicillin is used. 80

14. Process as claimed in Claim 12 or 13 in which the aqueous solution contains water miscible organic solvent.

15. Process of preparing a new salt of penicillin as claimed in any of Claims 1 to 9 which comprises reacting an organic nitrogen base salt of the acid-resistant penicillin with an organic nitrogen base salt of an inorganic or organic acid suspended in a liquid reaction medium, the base of which is different from the base of the base salt of penicillin used and forms a base salt of the acid-resistant penicillin which is more difficulty soluble in the reaction medium than the base salt of the penicillin used as starting material. 85

16. The processes of preparing new salts of acid-resistant penicillins of the general formula given in Claim 1 and the salts so prepared, substantially as herein described. 90

17. The processes of preparing new salts of acid-resistant penicillins of the general formula given in Claim 1 and the salts so prepared, substantially as herein described. 95

18. The processes of preparing new salts of acid-resistant penicillins of the general formula given in Claim 1 and the salts so prepared, substantially as herein described. 100

19. The processes of preparing new salts of acid-resistant penicillins of the general formula given in Claim 1 and the salts so prepared, substantially as herein described.

20. The processes of preparing new salts of acid-resistant penicillins of the general formula given in Claim 1 and the salts so prepared, substantially as herein described.

21. The processes of preparing new salts of acid-resistant penicillins of the general formula given in Claim 1 and the salts so prepared, substantially as herein described.

22. The processes of preparing new salts of acid-resistant penicillins of the general formula given in Claim 1 and the salts so prepared, substantially as herein described.

23. The processes of preparing new salts of acid-resistant penicillins of the general formula given in Claim 1 and the salts so prepared, substantially as herein described.

24. The processes of preparing new salts of acid-resistant penicillins of the general formula given in Claim 1 and the salts so prepared, substantially as herein described.

25. The processes of preparing new salts of acid-resistant penicillins of the general formula given in Claim 1 and the salts so prepared, substantially as herein described.

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