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HYDROIODIDES OF AMINO ESTERS OF PENICILLIN AND OIL COMPOSITION THEREOF

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This invention relates to difficulty soluble hydroiodides of amino esters of penicillin and to injectable and other compositions comprising particles of the said salts in suspension in a suitable carrier.

This application is a continuation-in-part of our copending applications Serial Nos. 168,384 filed June 15, 1950, and 246,148, filed September 11, 1951 (now abandoned), the latter application being a continuation-in-part of the former.

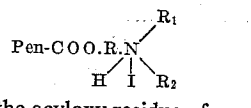
One object of the present invention is to provide novel penicillin compounds which possess advantageous antibiotic properties. Being difficulty soluble these compounds are advantageous in that a protracted penicillin effect is obtained. Furthermore, in the use of the esters of the invention penicillin accumulates in certain of the body tissues and fluids, for example in the lungs, brain and spinal fluid. Such accumulation provides a high concentration of penicillin which is effective therapeutically in the treatment of the infected portion of the body. The compounds are, furthermore, advantageous in the treatment of patients who cannot stand the action of metal salts (certain heart diseases) and who cannot, therefore, stand treatment with, for instance, sodium penicillin.

Another object of the invention is to provide for an injectable composition comprising a difficulty soluble hydroiodide of a dialkylaminoalkyl ester of penicillin in a vegetable or animal oil, to which a small amount, say 1 to 3 per cent, of a salt, particularly a basic salt, of aluminium and a lipophilic acid, such as stearic acid, may be added. Thereby the penicillin effect can be further protracted.

Further objects of the invention will appear from the following, where a more detailed description of our invention is given together with results of clinical tests with compounds of the invention and further the invention is illustrated by examples showing a convenient method of preparing said compounds, but we wish it to be understood that our invention is not to be considered limited thereby.

Some of the salts of the invention form crystals, while others form amorphous bodies, but in either case the salts have a full antibacterial effect corresponding to that of the content of penicillin.

The compounds of the present invention are the hydroiodide salts of aminoalcohol esters of penicillin represented by the following formula:



where Pen-COO is the acyloxy residue of penicillin; where R is an alkylene bridge of 2 to 8 carbon atoms in which there are attached to the carbon atoms thereof, in addition to Pen-COO and N, radicals selected from the group consisting of hydrogen and alkyl groups, the total carbon atoms in R not exceeding 14; and where R_1 and R_2 are alkyl groups containing from 1 to 12 carbon atoms. Generally, the total number of carbon atoms in R, R_1 and R_2 will not exceed 28, and in most instances, it will be preferred to limit the total number of carbon atoms in R to 10 with a total of carbon atoms in R, R_1 and R_2 not in excess of 28.

It has been found that when the alkylene bridge contains from 2 to 5 carbon atoms with not more than 4 carbon atoms in the alkyl substituents attached to the carbon atoms of the bridge and when the total number of

carbon atoms in R, R_1 and R_2 does not exceed 18, compounds of greater therapeutic value, as compared to the other compounds of the invention, result.

Because of their superior therapeutic properties, the preferred compounds of the present invention are those in which R is an alkylene bridge of 2 to 4 carbon atoms in which there are attached to the carbon atoms thereof, in addition to Pen-COO and N, radicals selected from the group consisting of hydrogen and alkyl groups, the number of carbon atoms in such alkyl groups not exceeding 4, preferably not exceeding 2, and in which R_1 and R_2 contain from 1 to 8 carbon atoms. In such compounds where R_1 and R_2 contain from 1 to 4 carbon atoms, an increase in desirable properties of the compounds has been noted.

The compounds of the present invention which are characterised by the greatest ability to provide high antibiotic properties and high accumulation in the lungs are those in which R is an unsubstituted alkylene bridge containing 2 to 3 carbon atoms and where R_1 and R_2 are alkyl groups containing from 1 to 3 carbon atoms; for example, the dimethyl-, methylethyl- and diethyl-aminoethyl ester; the di-propyl (either n- or iso-) aminoethyl ester; the methylpropyl or ethylpropyl (either n- or iso-) aminoethyl ester and the corresponding aminopropyl esters, such as dimethylaminopropyl ester and the diethylaminopropyl ester etc.

It will be noted that in the above formula the above bridges are connected at the left with the acyloxy residue of the penicillin and at the right with the nitrogen atom; thus the carbon atom at the left of the ethylene bridge is designated as 2 and the one at the right as 1; whereas in the octylene bridge the carbon atoms reading from left to right are designated 8, 7, . . . 2, 1, respectively, and the same is true of the other bridges.

From the above formula, it will be noted that in the particular compounds, the R_1 and R_2 groups may be the same or different and that these groups may be present in compounds having the various bridges defined by R.

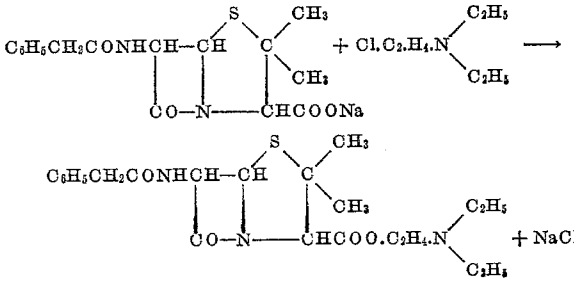
While the preferred esters will be the esters of benzylpenicillin (penicillin G) and such esters will be more specifically referred to herein, the penicillin residue in the compound may, if desired, be that of any other penicillin, for example, penicillin O, K, F, dihydro-F and X, as well as mixtures of various penicillins, for example, a mixture obtained by submersed cultivation.

Typical compounds of the invention are those in which the bridge is ethylene, propylene, butylene, pentylene, hexylene, heptylene or octylene, either unsubstituted or containing substituents as defined in the formula, where the total carbon atoms in R do not exceed 14, for example, methylethylene, dihexylethylene, methyloctylene or di-n-propyloctylene; and those in which the R_1 and R_2 groups vary from methyl to dodecyl, for example, dimethyl, butyloctyl, di-dodecyl. The typical compounds are also illustrated by the specific examples.

The compounds of the invention may be prepared by any suitable method. Advantageously, when the alkylene bridge contains 2 to 4 carbon atoms, where the carbon atom next to oxygen has at least one unsubstituted hydrogen atom, the esters are prepared by reacting a penicillin salt and a halide of the trialkylamine corresponding to the ester desired, such halide being prepared, if desired, from the corresponding aminoalcohol by well-known procedures. For example, a penicillin salt is suspended or dissolved in a suitable diluting agent in which the ester formed is soluble, such as one of the lower alcohols, for instance methanol, ethanol or isopropanol; a ketone such as acetone, methylethyl ketone, di-isopropyl ketone and acetylacetone; and hydrocarbon such as benzene, toluene, xylene; chlorinated hydrocarbons such as chloroform and carbon tetrachloride; dimethyl- and diethylacetamide, or tetrahydrofuran and the like. The halide may then be added, preferably in excess, for example 5–10 per cent excess, after which the mixture is allowed to react under agitation by stirring or shaking, if desired. The temperature at which the reaction takes place may be varied as desired, so long as it is not sufficiently high to cause decomposition of the penicillin salt or the penicillin ester formed. Generally, the reaction will be conducted between about room temperature, although it may be lower, and about

80° C. to 90° C. Preferably, the reaction is conducted under reflux at a temperature between about 40° C. and about 70° C., under which conditions good yields of the product will generally be obtained in from ½ to 5 hours.

The reaction may be illustrated by the following reaction using sodium penicillin and diethylaminoethyl chloride as typical:



The sodium chloride or other salt formed by the reaction is removed by filtration or other suitable means. The hydroiodide may be formed directly by adding an alcoholic solution of hydroiodic acid. The hydroiodide is then precipitated, preferably by adding water. Preferably, however, the solution of the ester is treated with an acid which forms a water-soluble salt of the ester, preferably an alcoholic solution of hydrochloric acid. Thereafter, an aqueous solution of a water-soluble iodide is added to the solution of the soluble salt of the ester which may previously have been diluted with water. The difficultly water-soluble hydroiodide of the penicillin ester precipitates and is removed from the solution by filtering, decanting, centrifuging or the like. Examples of soluble iodides are potassium, sodium, ammonium and calcium iodides.

In place of the sodium salt of penicillin given as an example in the above equation any soluble or insoluble penicillin salt may be employed for example the potassium, ammonium, calcium, barium, silver, procaine, triethylamine or N-ethyl-piperidine salt. Instead of employing the chloride of the tertiary amine, the other halides may be used, particularly the bromide.

The above method for producing the penicillin esters is not claimed herein, but is the subject matter of our co-pending application Serial No. 258,513, filed November 27, 1951.

Furthermore, certain of the penicillin esters and the soluble salts thereof form the subject matter of our co-pending application Serial No. 258,512, filed November 27, 1951.

In place of reacting the penicillin salt with the halide of the tertiary amine, the compounds of the present invention may be produced by reacting penicillin anhydride or a mixed anhydride of penicillin and acetic acid directly with the aminoalcohol corresponding to the ester desired. The mixed anhydride is prepared by reacting a penicillin salt in a suitable organic solvent with acetyl chloride at room temperature or slightly lower, for instance 5°C. to 10° C. The mixed anhydride in the solution is then reacted with aminolacohol at about the same temperature, the solution is evaporated to form a syrup, the residue is washed with petroleum ether, for example, and then extracted with a solvent, such as absolute ethanol. After removal of the chloride (formed by the cation of the penicillin salt and chlorine from the acetyl chloride) by filtration or in any other suitable manner, the ester is converted into a water-soluble salt such as the hydrochloride or citrate, and this again is converted to the difficultly soluble hydroiodide by the methods described above in connection with the production of the hydroiodides from the salt of penicillin and the halide of the tertiary amine. The method involving the use of penicillin anhydride is described in J. A. C. S. 70, pages 2964–2966 (1948).

Important properties characteristic of the new substances of the present invention are illustrated by the following biological tests which were carried out with penicillin-diethylaminoethyl ester-hydroiodide suspended in an aqueous carboxymethyl cellulose-phosphate mixture (called Preparation A hereinafter).

300,000 units of Preparation A were injected subcutaneously in 10 persons and 300,000 units of procaine-penicillin were injected in 10 other persons and in each case the concentration of penicillin in the blood in units per cc. was determined after 2, 12 and 24 hours. The results of these determinations are given in Table I.

TABLE I

Preparation A

Concentration in blood	2 hours	12 hours	24 hours
1st person	0.52	0.02	0
2d person	0.17	0.18	0.02
3d person	0.42	0.15	0
4th person	0.29	0.12	0.02
5th person	0.52	0.15	0.08
6th person	0.44	0.27	0.1
7th person	0.30	0.08	0.02
8th person	0.28	0.04	0.02
9th person	0.44	0.26	0
10th person	0.39	0.04	0
Average	0.38	0.13	0.026

Procaine-penicillin

Concentration in blood	2 hours	12 hours	24 hours
1st person	0.15	0.10	0.02
2d person	0.4	0.13	0.02
3d person	0.36	0.16	0.07
4th person	0.48	0.25	0.1
5th person	0.18	0.16	0.13
6th person	0.61	0.23	0.06
7th person	0.80	0.13	0.05
8th person	0.46	0.29	0.17
9th person	0.75	0.11	0.02
10th person	0.72	0.28	0.08
Average	0.49	0.18	0.07

The concentrations given are about 20 per cent below the actual concentrations, due to the restrictive effect of serum on the effect of penicillin.

It will be seen from the tables that after 2 and 12 as well as after 24 hours, Preparation A gives a concentration in the blood not much lower than the corresponding dose of procaine-penicillin and thus much in excess of that obtained with sodium penicillin. In order to ascertain whether this could possibly be due to the concentration in the blood being particularly high immediately after injection, the concentration was determined ½ hour and 1 hour after subcutaneous injection of 300,000 units of Preparation A in 5 persons. The results are given in Table II.

TABLE II

Preparation A

Concentration in blood	1/2 hour	1 hour
1st person	0.13	0.41
2d person	0.07	0.13
3d person	0.07	0.21
4th person	0.14	0.23
5th person	0.21	0.33
Average	0.12	0.26

These tests show that Preparation A has a fairly good protracted effect.

On the other hand further biological determinations of the penicillin concentration in various tissues show that in certain respects Preparation A is very superior to the hitherto known penicillin preparations, because it accumulates particularly in the lung tissue. This is demonstrated by the following.

25,000 units of Preparation A are dissolved in 2.5 ccs. of saline solution, and the solution was injected into a guinea-pig. In another guinea-pig 25,000 units of sodium benzylpenicillin in 2.5 ccs. of saline solution were injected. Both animals were killed ½ hour later, and the concentrations of penicillin were determined in the blood, the liver, the spleen and the lungs. The results are given in Table III.

TABLE III

	Preparation A		Sodium benzyl-penicillin	
	units	Ratio, organ/blood	units	Ratio, organ/blood
Blood	13	1	28.5	1
Lung	52.8	4.05	10.4	0.36
Liver	3.12	0.24	8.8	0.31
Spleen	1.44	0.11	2.25	0.08

This shows that Preparation A gives a lower concentration in the blood after ½ hour than sodium benzylpenicillin, but a five times higher concentration in the lungs. This accumulation in the lungs is very important in the treatment of lung infections and is further shown in the following experiments, where Preparation A is compared with procaine-penicillin.

The experiments were carried out with preparations giving a slight as well as a pronounced depot effect. The results are given in Tables IV and V.

TABLE IV

Slight depot effect

[100,000 units of Preparation A suspended in 4 ccs. of saline solution injected subcutaneously.]

	½ hour		1 hour		2 hours	
	units	ratio	units	ratio	units	ratio
Blood	24	1.0	28.6	1.0	18.5	1.0
Lungs	124	5.2	118	4.1	31.0	1.7
Liver	7.1	0.3	11.2	0.39	6.08	0.33
Spleen	3.3	0.14	3.9	0.13	2.2	0.12

[100,000 units of procaine-penicillin suspended in 4 ccs. of saline solution injected subcutaneously.]

	½ hour		1 hour		2 hours	
	units	ratio	units	ratio	units	ratio
Blood	45	1.0	30.8	1.0	22	1.0
Lungs	16	0.35	14.4	0.43	8.8	0.40
Liver	9.7	0.22	19.6	0.63	7.2	0.33
Spleen	2.2	0.05	2.72	0.09	1.44	0.05

TABLE V

Prolonged depot effect

[100,000 units of Preparation A suspended in 0.5 cc. of saline solution, subcutaneously.]

	1 hour		6 hours		9 hours	
	units	ratio	units	ratio	units	ratio
Blood	4.0	1.0	7.52	1.0	6.4	1.0
Lungs	7.08	1.77	9.0	1.19	4.95	0.78
Liver	1.77	0.44	1.65	0.22	0.84	0.13
Spleen	0.54	0.14	0.6	0.08	0.24	0.04

[100,000 units of procaine-penicillin suspended in 0.5 cc. of saline solution, subcutaneously.]

	1 hour		6 hours		9 hours	
	units	ratio	units	ratio	units	ratio
Blood	6.56	1.0	8.8	1.0	10.56	1.0
Lungs	2.56	0.39	2.13	0.24	3.02	0.28
Liver	2.01	0.31	2.4	0.27	1.56	0.15
Spleen	0.69	0.11	0.39	0.04	0.36	0.03

These experiments show that Preparation A accumulates in the lungs both when given under conditions where a slight depot effect is obtained and under conditions where a prolonged depot effect is obtained.

In order to try if the same effect is found in human beings the following experiments were carried out.

In patients with chronic bronchitis with abundant expectoration 600,000 units of either procaine-penicillin or Preparation A suspended in 1.8 ccs. of saline solution were injected subcutaneously, and the expectoration was collected in the periods 0–2 hours, 2–4 hours, 4–6 hours and 6–8 hours. The contents of penicillin in the expectoration are given in Table VI.

TABLE VI

Preparation A

	0–2 hours	2–4 hours	4–6 hours	6–8 hours
patient 1	0.34	0.88		
patient 2	0.30	0.61		
patient 3	0.32	0.63	0.49	0.28
patient 4	0.31	0.22	0.24	0.22

Procaine-penicillin

	0–2 hours	2–4 hours	4–6 hours	6–8 hours
patient 1	<0.1	0.1		
patient 2	<0.1	<0.1		
patient 3	<0.1	<0.1	<0.1	<0.1
patient 4	<0.1	<0.1	<0.1	<0.1

These experiments show that the accumulation of Preparation A takes place in the lungs of human beings just as in the case of animals since by injection of Preparation A much more penicillin is excreted through the lungs than in the case of procaine-penicillin.

Further tests have been made using rats weighing 200 g. each as test animals; the results of such tests are given in Table VII in which C_B is the concentration of penicillin in the blood (in units per cc.) one hour after 25,000 units of penicillin has been injected intramuscularly in the form of the compounds mentioned in the table; C_O is the concentration of penicillin in the lung tissue (units per g.) found when the animal was killed one hour after such injection.

TABLE VII

Compound (injected as the hydroiodide)	C_B	C_O	$\frac{C_O}{C_B}$
Benzylpenicillinester of 1-dimethylamino-ethanol-(2)	19	90	4.7
Benzylpenicillinester of 1-diethylamino-ethanol-(2)	21	113	5.4
Benzylpenicillinester of 1-methylethanol-aminoethanol-(2)	12	24	2.0
Benzylpenicillinester of 1-di-n-propylamino-ethanol-(2)	3.5	14	4.0
Benzylpenicillinester of 1-di-n-butylamino-ethanol-(2)	2.0	4.8	2.4
Benzylpenicillinester of 1-di-n-octylamino-ethanol-(2)	<0.1	1.0	
Benzylpenicillinester of 1-methyl-dodecyl-aminoethanol-(2)	0.5	1.0	2.0
Benzylpenicillinester of 1-di-dodecylamino-ethanol-(2)	<0.1	1.4	
Benzylpenicillinester of 1-diethylamino-n-propanol-(3)	1.0	10	10
Benzylpenicillinester of 1-diethylamino-4-methylbutanol-(4)	0.1	2.9	
Benzylpenicillinester of 1-diethylamino-2,2-dimethylethanol-(2)	1.3	9.2	7.1
Benzylpenicillinester of 1-diethylamino-2-methylethanol-(2)	8.4	37	4.4
Benzylpenicillinester of 1-diethylamino-n-octanol-(8)	<0.1	3.8	
Allylmercaptomethylpenicillinester[1] of 1-diethylaminoethanol-(2)	20	105	5.0
Sodium salt of benzylpenicillin	30	11	0.4

[1] Ester of penicillin O.

We have found that by suspending our new hydroiodides of the amino esters of penicillin in a vegetable or animal oil in which is dissolved a quantity, for example 1 to 3 per cent, of a salt of aluminium and a lipophilic acid, particularly a basic salt, such as aluminum monostearate or aluminium distearate, we can obtain compositions having a more enduring protracted effect than that obtained by injection of said hydroiodides suspended in saline.

Instead of stearates other salts of fatty acids having 12 to 22 carbon atoms in the molecule may be used. Examples of a suitable vegetable oil are peanut oil, cottonseed oil, soya oil, sesame oil and olive oil.

The preparations thus obtained have retained the ability of accumulating penicillin in the lungs, which is shown by the following tests.

25 rabbits weighing 2 kilograms each are injected intramuscularly with 45,000 units of a preparation of the above kind containing the hydroiodide of diethylaminoethyl ester of benzylpenicillin, whereafter the concentration of penicillin in the blood is determined after various periods following such injection.

As control a mixture of the same composition excepting the aluminium monostearate is injected on 25 rabbits weighing about 2 kilograms each.

The results appear from the following table:

Hours after injection	With monostearate—average blood level, units per cc.	Without monostearate—average blood level, units per cc.
½	0.43	0.60
1	0.72	1.05
2	0.58	0.75
4	0.51	0.40
8	0.20	0.08
16	0.10	0
20	0.08	0
24	0.05	0

The invention will be further illustrated by way of the following examples.

EXAMPLE 1.—BENZYLPENICILLIN-β-DIETHYLAMINOETHYL ESTER-HYDROIODIDE

7.44 kilograms of the potassium salt of penicillin are suspended in 40 liters of acetone (water content 1 to 1.7 per cent). 3 liters of diethylaminoethyl chloride are added, and the mixture is refluxed for ½ hour.

After cooling precipitated potassium chloride is removed by filtration, and the filtrate is evaporated in vacuum (70 to 80 mm. of mercury) until the temperature in the distillation vessel has raised to 30 to 35° C. Then the residue is poured into a mixture of 20 liters of water, 10 kilograms of ice and 1.28 liters of .85 per cent phosphoric acid.

Thereby a pale-yellow solution is obtained which is filtered under sterile conditions and cooled to 0° C. During 2–3 hours 40 liters of a sterile 20 per cent solution of potassium iodide are added with stirring. After addition the stirring is continued for another ½ hour at 0° C.

The crystalline precipitate of benzyl-penicillin-β-diethylaminoethyl ester-hydroiodide is separated from the liquid by filtration, washed with 10 liters of cold, sterile water and dried in vacuum at 40° C. The yield is from 9.5 to 10 kilograms.

EXAMPLE 2.—BENZYLPENICILLIN-DIMETHYLAMINOETHYL ESTER-HYDROIODIDE

35.6 grams of the sodium salt of penicillin are suspended in 250 cc. of dry boiling acetone and 6.45 grams of dimethylaminoethyl chloride are added.

After refluxing for ½ hour a further 3.2 grams of dimethylaminoethyl chloride are added and another 3.2 grams are added after 2 hours' refluxing. This method is employed because the dimethylaminoethyl chloride polymerizes very easily.

After refluxing for 8 hours (total) the mixture is filtered, and the filtrate is evaporated in vacuum to a syrup.

The residue is triturated with petrol ether to remove excess of dimethylaminoethyl chloride and after this treatment it is dissolved in 200 cc. of anhydrous ethanol.

After addition of an alcoholic solution of hydrochloric acid (until a sample diluted with water shows pH=5) and 100 cc. of dry ether, the solution stands at 0° C. over night. On dilution of the solution with water and addition of 20 per cent more than the calculated amount of a potassium iodide solution the hydroiodide is obtained in a yield of 67 per cent and with M. P. 185–186° C.

EXAMPLE 3.—BENZYLPENICILLIN-METHYLETHYLAMINOETHYL ESTER-HYDROIODIDE

7.4 grams of the potassium salt of benzylpenicillin are suspended in 40 cc. of acetone and 11.5 cc. of a solution of methylethylaminoethyl chloride in benzol containing 1.75 moles per liter are added. The mixture is refluxed for 3 hours. During this time potassium chloride separates which after refluxing of the mixture is removed by filtration. Then a solution of 4.2 grams of the monohydrate of citric acid in 100 cc. acetone is added to the filtrate from the potassium chloride. The mixture is left standing at 0° C. for 2 hours, whereby benzylpenicillin-methylethylaminoethyl ester-citrate crystallizes therefrom. The yield of this substance will be 8.75 grams corresponding to 73.5 per cent of the theoretically possible yield. The melting point of the citrate recovered in this manner is 76 to 79° C. 6.1 grams of the benzylpenicillin-methylethylaminoethyl ester-citrate are dissolved in 50 cc. of water and 17 cc. of a 10 per cent solution of potassium iodide in water are added. The mixture is left standing at 0° C. for 2 hours during which time the hydroiodide of benzylpenicillin-methylethylaminoethyl ester will crystallize. The crystallization product is recovered by filtration. The melting point of the benzylpenicillin-methylethylaminoethyl ester-hydroiodide recovered in this way is 180.5 to 181.5° C.

EXAMPLE 4.—BENZYLPENICILLIN-DI-N-PROPYLAMINOETHYL ESTER-HYDROIODIDE

7.4 grams of the potassium salt of penicillin are suspended in 40 cc. acetone and 3.3 grams di-n-propylaminoethyl chloride are added after which the mixture is refluxed for 2 hours. The potassium chloride formed in the refluxed mixture is then removed from the solution by filtration. Then a solution of 4.2 grams of the monohydrate of citric acid in 20 cc. acetone is added to the filtrate and the solution thus formed is diluted by 150 cc. of water. To the diluted solution 33 cc. of a 10 per cent aqueous solution of potassium iodide are added. The mixture is left standing for 12 hours at 0° C. and the crystalline benzylpenicillin-di-n-propylaminoethyl ester-hydroiodide formed in the solution is then removed by filtration. The yield of the hydroiodide amounts to 8.15 grams which corresponds to 69 per cent of the theoretically possible yield. The melting point of the hydroiodide is 142 to 144° C.

EXAMPLE 5.—BENZYLPENICILLIN-DI-N-BUTYLAMINOETHYL ESTER-HYDROIODIDE

7.4 grams of the potassium salt of benzylpenicillin are suspended in 40 cc. of acetone and 3.8 grams di-n-butylaminoethyl chloride are added to the suspension. The mixture formed is then refluxed for 2 hours. After that it is subjected to distillation in vacuum in order to remove 20 cc. of the acetone contained in the mixture and the remainder is poured into 150 cc. of a mixture of ice and water, at the same time adding to the mixture such a quantity of 50 per cent phosphoric acid that the pH-value of the resulting solution will be 4.5. To the solution 40 cc. of a 10 per cent aqueous solution of potassium iodide are added and the mixture is left standing for 12 hours at 0° C. The benzylpenicillin-di-n-butylaminoethyl ester-hydroiodide thereby formed in the solution is removed therefrom by filtration, whereby a yield of 9.2 grams of this substance is recovered. This yield corresponds to 75 per cent of the yield theoretically possible. The melting point of benzylpenicillin-di-n-butylaminoethyl ester-hydroiodide is 61° C.

EXAMPLE 6.—BENZYLPENICILLIN-DI-N-OCTYLAMINOETHYL ESTER-HYDROIODIDE

A suspension of 7.4 grams of the potassium salt of benzylpenicillin in 40 cc. acetone is mixed with a solution of 6.1 grams of di-n-octylaminoethyl chloride in 20 cc. benzol. The mixture is refluxed for 2 hours, whereby the penicillin salt and the organic chloride dissolve and potassium chloride separates which is then removed by filtration, whereafter the filtrate is evaporated in vacuo to form a syrup. This syrup is dissolved in 40 cc. of methanol and the equivalent amount of ethanolic hydrogen chloride is added to the solution which at the same time is subjected to cooling. A clear solution results to which 40 cc. of water are added and then 33 cc. of a 10 per cent solution of potassium iodide in water are also added. The mixture is left standing at 0° C. for 2 hours, whereby crystalline benzylpenicillin-di-n-octylaminoethyl ester-hydroiodide is formed therein. The crystals are removed from the solution by filtration. The yield of the ester-hydroiodide thereby obtained amounts to 8.75 grams which corresponds 60 per cent of the yield theoretically possible. The melting point of the ester-hydroiodide is 150–152° C.

EXAMPLE 7.—BENZYLPENICILLIN-DI-N-DODECYL-AMINOETHYL ESTER-HYDROIODIDE

By the same procedure as described in Example 6, using di-n-dodecylaminoethyl chloride in place of di-n-octyl-aminoethyl chloride as a starting material, benzylpenicillin-di-n-dodecylaminoethyl ester-hydroiodide will be obtained in a yield of 48 per cent of the yield theoretically possible. The melting point of this ester-hydroiodide is 170 to 173° C.

EXAMPLE 8.—BENZYLPENICILLIN-METHYL-N-DODECYLAMINOETHYL ESTER-HYDROIODIDE

7.4 grams of the potassium salt of benzylpenicillin are suspended in 40 cc. of acetone and a solution of 5.2 grams methyl-n-dodecylaminoethyl chloride in 43.5 cc. benzol is added to the suspension, whereafter the mixture thus formed is refluxed for 3½ hours. During the reaction thereby effected the potassium salt of penicillin dissolves and potassium chloride separates from the solution, which potassium chloride is removed by filtration, whereafter the clear solution obtained by the filtration is evaporated in vacuo to form a syrup. This syrup is dissolved in 40 cc. acetone and a solution of 4.2 grams of the monohydrate of citric acid in 20 cc. acetone is added. A clear solution results, which is diluted by 60 cc. of water, after which 40 cc. of a 10 per cent solution of potassium iodide in water are added. The mixture is left standing at 0° C. for 4 hours whereby benzylpenicillin-methyl-n-dodecylaminoethyl ester-hydroiodide crystallizes from the solution and is recovered by filtration. The yield is 8.9 grams which corresponds to 65 per cent of the yield theoretically possible. The melting point of the ester-hydroiodide is 67 to 70° C.

EXAMPLE 9.—BENZYLPENICILLIN-DIETHYLAMINO-N-PROPYLESTER-HYDROIODIDE

The suspension formed by adding 28.8 grams of the potassium salt of penzylpenicillin and 12 grams diethyl-amino-n-propyl chloride to 160 cc. of acetone is refluxed for 12 hours. The reaction product thereby obtained is cooled and the cooled product contains potassium chloride separated during the reaction which is then removed by filtration. A solution of 16.8 grams of the monohydrate of citric acid in 200 cc. of acetone is added to the filtrate which is then left standing for 3 hours at 0° C. During this time benzylpenicillin-diethylamino-n-propyl ester-citrate crystallizes from the solution and is recovered by filtration, the yield being 42.7 grams which corresponds to 86 per cent of the yield theoretically possible. The melting point of this citrate is 86 to 88° C.

6.4 grams of the benzylpenicillin-diethylamino-n-propyl ester-citrate are dissolved in 100 cc. of water and 17 cc. of a 10 per cent solution of potassium iodide in water are added. The mixture is left to stand at 0° C. until the benzylpenicillin-diethylamino-n-propyl ester-hydroiodide, which forms from the two constituents of the solution, has separated, after which the said ester-hydroiodide is recovered by filtration. The yield of this substance will be 4.8 grams and the melting point is 142 to 143° C.

EXAMPLE 10.—BENZYLPENICILLIN-DIETHYLAMINO-N-OCTYLESTER-HYDROIODIDE

13.06 grams of the triethylamine salt of benzylpenicillin are dissolved in 200 cc. of dry chloroform. A solution of 1.09 cc. of thionyl chloride in 20 cc. of dry chloroform is added dropwise to the former solution during agitation and cooling in a refrigerating mixture in such a manner that the temperature of the reaction mixture will be maintained within the temperature limits of −10 to −8° C. The addition having been completed, the resulting product is left to stand at the said temperature for 1 hour after which a solution of 3.02 grams of diethylamino-n-octanol in 20 cc. of dry chloroform is added to the reaction product and the mixture is left standing for 12 hours, the temperature being allowed to increase to 20° C. The mixture thus obtained is then subjected to extraction by 440 cc. of an aqueous solution containing 2 per cent of sodium carbonate and sodium bicarbonate. The chloroform phase is cooled by a solution of Dry Ice in acetone and the ice thereby formed is removed by filtration. The chloroform solution thus deprived of its water content is then evaporated in vacuo to dryness whereby a syrup remains which is dissolved in 30 cc. of acetone. A solution of 3.0 grams of the monohydrate of citric acid in 15 cc. of acetone is then added to the syrup and the mixture thereby formed is diluted by 90 cc. of water after which 8 cc. of a solution containing 10 per cent potassium iodide are added. The mixture is left to stand at 0° C. for 2 hours whereby benzylpenicillin-diethylamino-n-octylester-hydroiodide separates and is finally removed by filtration. The yield of this substance amounts to 4.35 grams corresponding to 45 per cent of the yield theoretically possible. The melting point of the said ester-hydroiodide is 108 to 109° C.

EXAMPLE 11.—BENZYLPENICILLIN-1-DIETHYLAMINO-2-METHYLETHYL ESTER-HYDROIODIDE

7.4 grams of the potassium salt of benzylpenicillin and 3 grams 1-diethylamino-2-methylethyl chloride are added to 40 cc. of acetone and the mixture formed is refluxed for 3 hours. During the refluxing time the components dissolve and potassium chloride separates which is then removed by filtration after which the filtrate is evaporated to dryness in vacuo. The remainder is dissolved in 50 cc. of ethanol and filtrated with alcoholic hydrogen chloride until a sample of the reaction product on dilution with water has the pH-value of 5. Then 200 cc. of ether are added to the main portion whereby amorphous benzylpenicillin-1-diethylamino-2-methylethyl ester-hydrochloride separates. By dissolving a portion of the said ester-hydrochloride in water and adding the calculated amount of potassium iodide increased by 10 per cent, the corresponding hydroiodide separates from the solution.

EXAMPLE 12.—BENZYLPENICILLIN-1-DIETHYLAMINO-2,2-DIMETHYLETHYL ESTER-HYDROIODIDE

7.4 grams of the potassium salt of benzylpenicillin are suspended in 100 cc. of acetone and a solution of 1.42 cc. of acetyl chloride in 25 cc. of acetone is added dropwise to the said suspension with agitation. When the addition has been completed, 2.9 grams 1-diethylamino-2,2-dimethylethanol-(2) are added to the resulting product. The mixture is then refluxed for 15 minutes and cooled. Potassium chloride is then removed by filtration. The filtrate is evaporated to 25 cc. and a solution of 4.0 grams of the monohydrate of citric acid in 20 cc. of acetone is added to the remainder. Now, 200 cc. of ether are added whereby the citrate of benzylpenicillin-1-diethylamino-2,2-dimethylethyl ester separates as an amorphous substance, which is removed from the solution by filtration and washed with ether.

6.5 grams of the amorphous benzylpenicillin-1-diethylamino-2,2-dimethylethyl ester-citrate are dissolved in 50 cc. of water and 15 cc. of a solution of potassium iodide containing 10 per cent potassium iodide are added. The mixture is left standing at 0° C. for 4 hours whereby benzylpenicillin-1-diethylamino - 2,2 - dimethylethyl ester-hydroiodide separates in the crystalline form. The crystals are removed from the solution by filtration and the yield of the crystalline product amounts to 4.2 grams which corresponds to 72 per cent of the yield that is theoretically possible in the reaction. The melting point of the said ester-hydroiodide is 153 to 154° C.

EXAMPLE 13.—BENZYLPENICILLIN-DIETHYLAMINO-2,2-DIMETHYLPROPYL ESTER-HYDROIODIDE

By using an equivalent amount of diethylamino-2,2-dimethylpropyl chloride in place of the 12 grams diethyl-amino-n-propyl chloride used in the procedure described in the above Example 9 and using the same procedure in all other respects, benzylpenicillin-diethylamino-2,2-dimethylpropyl ester-hydroiodide will be obtained.

EXAMPLE 14.—BENZYLPENICILLIN-1-DIETHYLAMINO-4-METHYLBUTYL ESTER-HYDROIODIDE

7.4 grams potassium salt of benzylpenicillin are suspended in 100 cc. of dry acetone and a solution of 1.42 cc. acetyl chloride in 25 cc. acetone is added dropwise to the suspension with agitation. A reaction takes place resulting in a solution of mixed anhydride of benzylpenicillin and acetic acid. 3.2 grams 1-diethylamino-4-methyl-butanol are added to this solution after which the mixture is left standing at 20° C. for 2 hours. The amount of potassium chloride separated is removed by filtration whereafter a solution of 4.0 grams of the monohydrate of citric acid in 20 cc. of acetone is added to the filtrate. The mixture is left standing at 0° C. for 2 hours whereby benzylpenicillin - 1 - diethylamino - 4 - methylbutyl ester-citrate separates which is recovered by filtration. The said citrate is dissolved in 50 cc. of water and 14 cc. of an aqueous 10 per cent solution of potassium iodide are

added. Thereby benzylpenicillin - 1 - diethylamino - 4 - methylbutyl ester-hydroiodide crystallizes from the solution and is recovered by filtration. The melting point of the ester-hydroiodide obtained is 160 to 161° C.

EXAMPLE 15.—BENZYLPENICILLIN-1-DIETHYLAMINO-1-METHYL-2-ETHYLPROPL ESTER-HYDROIODIDE

This substance is produced by using the general procedure described in the above Example 9, thereby replacing the 12 grams diethylamino-n-propyl chloride used as a starting material according to Example 9 by the equivalent amount of 1-diethylamino-1-methyl-2-ethylpropyl chloride.

EXAMPLE 16.—BENZYLPENICILLIN-1-DIETHYLAMINO-2,3-DIETHYLBUTYL-(4) ESTER-HYDROIODIDE

This compound is obtained by using the procedure described in Example 14 when in place of 3.2 grams 1-diethylamino-4-methylbutanol an equivalent amount of 1-diethylamino-2,3-diethylbutanol-(4) is employed.

EXAMPLE 17.—BENZYLPENICILLIN-1-DI-N-BUTYLAMINO-2,3-DIETHYLBUTYL-(4) ESTER-HYDROIODIDE

This compound is obtained by using the procedure described in the above Example 14 when in place of 3.2 grams 1-diethylamino-4-methylbutanol, an equivalent amount of 1-di-n-butylamino-2,3-diethylbutanol-(4) is employed.

EXAMPLE 18.—BENZYLPENICILLIN-1-METHYLOCTYLAMINO-5-BUTYLPENTYL-(5) ESTER-HYDROIODIDE

This compound is produced by using the procedure described in the above Example 12 when in place of 2.9 grams 1 - diethylamino - 2,2 - dimethylethanol - (2), an equivalent amount of 1-methyloctylamino-5-butylpentanol-(5) is employed.

EXAMPLE 19.—BENZYLPENICILLIN-4-DIDODECYLAMINO-4,5-DI-N-PROPYLOCTYL-(5) ESTER-HYDROIODIDE

This product is obtained by using the procedure described in the above Example 12 when in place of 2.9 grams 1 - diethylamino - 2,2 - dimethylethanol - (2), an equivalent amount of 4-didodecylamino-4,5-di-n-propyloctanol-(5) is employed.

EXAMPLE 20.—BENZYLPENICILLIN-1-HEXYLDODECYLAMINO-2,6-DIMETHYLOCTYL-(8) ESTER-HYDROIODIDE

This product is obtained by using the procedure described in Example 10 when in place of 3.02 grams diethylamino-n-octanol, the equivalent amount of 1-hexyldodecylamino-2,6-dimethyloctanol-(8) is employed.

EXAMPLE 21.—BENZYLPENICILLIN-DIETHYLAMINO-2,6-DIMETHYLOCTYL-(8) ESTER-HYDROIODIDE

This product is obtained by using the procedure described in Example 10 when in place of 3.02 grams diethylamino-n-octanol, the equivalent amount of diethylamino-2,6-dimethyloctanol-(8) is employed.

EXAMPLE 22.—BENZYLPENICILLIN-1-DI-DODECYLAMINO-2-ETHYL-ETHYL ESTER-HYDROIODIDE

This product is obtained by using the procedure described in Example 9 when in place of 12 grams diethylamino-n-propyl chloride, an equivalent amount of 1-di-dodecylamino-2-ethylethyl chloride is employed.

EXAMPLE 23.—BENZYLPENICILLIN-1-DIETHYLAMINO-2-HEXYLETHYL ESTER-HYDROIODIDE

This compound is obtained by using the procedure described in Example 14 when in place of 3.2 grams 1-diethylamino-4-methylbutanol, the equivalent amount of 1-diethylamino-2-hexylethanol is employed.

EXAMPLE 24.—ALLYLMERCAPTOMETHYLPENICILLIN-DIETHYLAMINOETHYL ESTER-HYDROIODIDE (PENICILLIN-O DIETHYLAMINOETHYL ESTER-HYDROIODIDE)

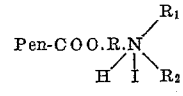
15 grams of the potassium salt of allylmercaptomethylpenicillin are suspended in 75 cc. acetone (containing 0.2 per cent of water) and 8.5 grams of diethylaminoethyl chloride are added to the suspension after which the mixture is refluxed for one hour. On cooling, potassium chloride separates which is then removed by filtration after which the filtrate is evaporated in vacuo to form a syrup to which then 50 cc. of ice water are added. Now, such an amount of a 10 per cent phosphoric acid is added that the solution takes a pH-value of 4. A solution of 8.9 grams sodium iodide in 17 cc. of water is added dropwise to the acidified solution with agitation. The addition having been completed, the solution is left standing at 0° C. for 15 minutes, whereby allylmercaptomethylpenicillin - diethylaminoethyl ester-hydroiodide separates. It is then recovered by filtration, washed with 15 cc. of ice water and dried in vacuo. The yield amounts to 20 grams and the melting point of the ester-hydroiodide is 116 to 119° C. This melting point, however, can be increased to 128 to 129° C. by recrystallizing the hydroiodide first produced from a mixture of acetone and ether.

EXAMPLE 25.—SUSPENSION OF BENZYLPENICILLIN-DIETHYLAMINOETHYL ESTER-HYDROIODIDE IN OIL

To 1 litre of peanut oil are added 20 grams of aluminum monostearate, and the mixture is heated slowly with stirring until a clear solution is obtained. The heating is continued until the solution has reached a temperature of 135° C. at which temperature it is kept for ½–1 hour and thereafter cooled at 25° C. Then 390 grams of the hydroiodide of the diethylaminoethyl ester of penicillin G having a particle size of 2 to 5μ and a strength of 1000 units per mg. are added. The said units are determined by assaying the preparation against *staphylococcus aureaus,* using sodium penicillin as a standard. The final mixture contains 300, 000 international units per cc.

We claim:

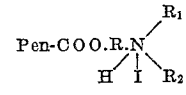
1. The hydroiodide salts of aminoalcohol esters of penicillin represented by the formula:



where Pen-COO represents penicillin with the hydrogen atom removed from the carboxyl group; where R is alkylene containing 2 to 8 carbon atoms in a straight chain, and containing no substituent groups other than alkyl, the total number of carbon atoms in R not exceeding 14; and where R_1 and R_2 are alkyl groups containing from 1 to 12 carbon atoms.

2. The compounds of claim 1, wherein the penicillin is benzylpenicillin.

3. The hydroiodide salts of aminoalcohol esters of penicillin represented by the formula:



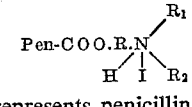
where Pen-COO represents penicillin with the hydrogen atom removed from the carboxyl group; where R is alkylene containing 2 to 4 carbon atoms in a straight chain, and containing no substituent groups other than alkyl, the total number of carbon atoms in such alkyl groups not exceeding 4; and where R_1 and R_2 are alkyl groups containing from 1 to 8 carbon atoms.

4. The compound of claim 3, wherein the penicillin is benzylpenicillin.

5. The compound of claim 3, wherein R_1 and R_2 are alkyl groups containing from 1 to 4 carbon atoms.

6. The compound of claim 5, wherein the penicillin is benzylpenicillin.

7. The hydroiodide salts of aminoalcohol esters of penicillin represented by the formula:



where Pen-COO represents penicillin with the hydrogen atom removed from the carboxyl group; where R is an unsubstituted alkylene of from 2 to 3 carbon atoms; and where R_1 and R_2 are alkyl groups containing from 1 to 3 carbon atoms.

8. The compound of claim 7, wherein the penicillin is benzylpenicillin.

9. The hydroiodide salt of the dimethylaminoethyl ester of benzylpenicillin.

10. The hydroiodide salt of the methylethylaminoethyl ester of benzylpenicillin.

11. The hydroiodide salt of the diethylaminoethyl ester of benezylpenicillin.

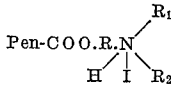
12. The hydroiodide salt of a methylpropylaminoethyl ester of benzylpenicillin.

13. The hydroiodide salt of an ethylpropylaminoethyl ester of benzylpenicillin.

14. An injectible therapeutic composition comprising solid particles of the compound of claim 1 suspended in an oil selected from the group consisting of vegetable and animal oils having dissolved therein a quantity of a basic salt of aluminum with a fatty acid having from 12 to 22 carbon atoms in its molecule.

15. An injectible therapeutic composition comprising solid particles of the compound of claim 7 suspended in an oil selected from the group consisting of vegetable and animal oils having dissolved therein a quantity of a basic salt of aluminum with a fatty acid having from 12 to 22 carbon atoms in its molecule.

16. The hydroiodide salts of amino alcohol esters of penicillin represented by the formula



where Pen-COO represents penicillin with the hydrogen atom removed from the carboxyl group; where R is alkylene containing 2 to 3 carbon atoms in a straight chain and containing no substituent groups other than alkyl, the total number of carbon atoms in R not exceeding 3; and where R_1 and R_2 are alkyl groups containing 1 to 4 carbon atoms, the total number of carbon atoms in R, R_1, and R_2 not exceeding 10.

17. The compounds of claim 16, wherein the penicillin is benzyl penicillin.

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