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PATENT SPECIFICATION (11) 1 400 584

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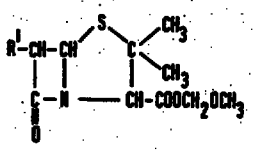
(54) ANTIBACTERIAL AGENTS

(71) We, BRISTOL-MYERS COMPANY, a Corporation organised and existing under the laws of the State of Delaware, United States of America, of 345 Park Avenue, New York State of New York, United States of America, 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:—

This invention relates to antibacterial agents and to a process for the preparation thereof. More particularly, the invention is directed to the methoxymethyl esters of ampicillin and hetacillin, which are themselves valuable antibiotic drugs.

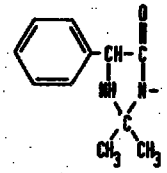
Hetacillin is a penicillin derivative known in the acid form as 6(2,2-dimethyl-5-oxo-4-phenyl-1-imidazolidinyl)penicillanic acid. This compound and many closely related compounds and the preparation thereof are disclosed in United States Patent 3,198,804. Esters of benzylpenicillins are disclosed in British Patent 1,003,479 and United States Patent 2,650,218 and acyloxymethyl esters of ampicillin are discussed by W.v. Daehne *et al.* in J. Med. Chem., 13, (4), 607—612, (1970). This publication also refers to early publications on the hydrolysis of esters. The pivaloyloxymethyl ester of ampicillin is also disclosed in South African Patent 68/5952. Various penicillin esters are also disclosed in United States Patent 3,528,965.

According to the present invention there is provided a compound having the formula:



Formula I

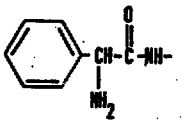
wherein R^1 is the group



Formula II

In general, the methoxymethyl ester of hetacillin can be prepared by reacting hetacillin with a suitable esterifying derivative of methyl ether, such as a halomethyl ether. The hetacillin ester can also be prepared from a basic fermentation-produced penicillin, such as phenoxymethyl penicillin, by a series of reactions in which the phenoxymethyl penicillin ester is deacylated by known procedures to provide the corresponding methoxymethyl ester of 6-aminopenicillanic acid. The 6-APA ester can then be converted to the methoxymethylester of ampicillin which may then be reacted with acetone to form the corresponding hetacillin ester.

The 6-APA ester can be acylated by known procedures to provide the methoxymethyl ester of ampicillin, i.e. the compound of Formula I wherein R^1 is the group:



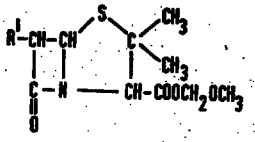
Either the free acid or its equivalent can be employed to acylate the free amino group of the 6-APA ester. Such acylating agents include the free acid and the corresponding carboxylic acid halides, e.g., the chlorides and bromides; the acid anhydrides, including mixed anhydrides and particularly the mixed anhydrides prepared from stronger acids such as the lower aliphatic monoesters of carbonic acid, of alkyl and aryl sulfonic acid and of more hindered acids, such as diphenylacetic

acid. In addition, an acid azide or an active ester or thioester (e.g., with p-nitrophenol, 2,4-dinitrophenol, thiophenol, thioacetic acid) may be used or the free acid itself may be coupled with 6-aminopenicillanic acid after first reacting said free acid with N,N'-dimethylchloroformiminium chloride [cf. Great Britain 1,008,170 and Novak and Weichet, Experientia XXI/6, 360 (1965)] or by the use of enzymes or of an N,N'-carbonyldiimidazole or an N,N'-carbonylditriazole [cf. South African Patent specification 63/2,684] of a carbodiimide reagent [especially N,N-dicyclohexylcarbodiimide, N,N'-diisopropylcarbodiimide or N-cyclohexyl-N'-(2-morpholinoethyl)carbodiimide; cf. Sheehan and Hess, *J. Amer. Chem. Soc., 77,* 1067, (1955)], or of alkynylamine reagent [cf. R. Buijle and H. G. Viehe, *Angew, Chem. International Edition, 3,* 582 (1964)], or of a ketenimine reagent [cf. C. L. Stevens and M. E. Monk, *J. Amer. Chem. Soc., 80,* 4065 (1958)] or of an isoxazolium salt reagent [cf. R. B. Woodward, R. A. Olofson and H. Mayer, *J. Amer. Chem. Soc., 83,* 1010 (1961)]. Another equivalent of the acid chloride is a corresponding azolide, i.e., an amide of the corresponding acid the amide nitrogen of which is a member of a quasi-aromatic five-membered ring containing at least two nitrogen atoms, i.e., imidazole, pyrazole, the triazoles, benzimidazole, benzotriazole, and their substituted derivatives. As an example of the general method for the preparation of an azolide, N,N'-carbonyldiimidazole is reacted with a carboxylic acid in equimolar proportions at room temperature in tetrahydrofuran, chloroform, dimethylformamide or a similar inert solvent to form the carboxylic acid imidazolide in practically quantitative yield with liberation of carbon dioxide and one mole of imidazole. Dicarboxylic acids yield diimidazolides. The by-product, imidazole, precipitates and may be separated and the imidizolide isolated, but this is not essential. The methods for carrying out these reactions to produce a penicillin and the methods used to isolate the penicillin so produced are well known in the art (cf. U.S. Patent Nos. 3,079,314, 3,117,126 and 3,129,224 and British patent Nos. 932,644, 957,570 and 959,054).

It is usually preferred, however, to use phenylglycyl chloride hydrochloride as the acylating agent.

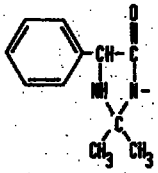
The resulting penicillin ester, i.e., the methoxymethyl ester of ampicillin can be reacted with acetone to form the hetacillin ester in accordance with the procedure disclosed in United States patent 3,198,804.

Thus, the invention includes a process for preparing a compound having the formula



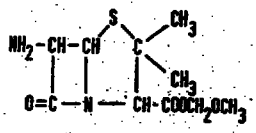
Formula I

wherein R^1 is the group



Formula II

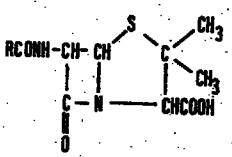
which process comprises acylating methoxymethyl 6-aminopenicillinate having the formula



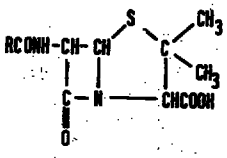
Formula IV

to form the methoxymethyl ester of ampicillin and reacting said ampicillin ester with acetone to form the methoxymethyl ester of hetacillin.

According to one embodiment, the process of this invention involves the formation of the methoxy methyl ester of a penicillin having the formula



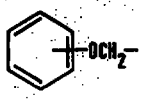
wherein R. is an organic radical to form a penicillin ester having the formula:



Formula V

The methoxymethyl 6-aminopenicillinate which is acylated in accordance with the process of the present invention may be prepared by the deacylation of the compound of Formula V.

The organic radical R may be the acyl group of any of the well known penicillins. A particularly preferred side chain is the phenoxymethyl radical,



and other examples include the benzyl, furylmethyl, thienylmethyl and isoxazoly radicals. As is well known, the various organic radicals may be substituted, if desired.

Further specific examples of aliphatic, carbocyclic-including and heterocyclic-including radicals defining the R group in the penicillin starting materials are the vinyl, ethoxy, cyclopentenyl, cyclohexyl, 2,4-dichlorobenzyl, 3,4-dichlorobenzyl, m-bromobenzyl, o-bromobenzyl, p-bromobenzyl, m-chlorobenzyl, o-chlorobenzyl, p-chlorobenzyl, m-fluorobenzyl, o-fluorobenzyl, p-fluorobenzyl, p-iodobenzyl, p-nitrobenzyl, p-chlorophenoxymethyl, m-nitrobenzyl, o-nitrobenzyl, 3-chloro-4-bromobenzyl, m-trifluoromethylbenzyl, m-trifluoromethylphenoxymethyl, p-tolylmethyl, o-methylbenzyl, m-methylbenzyl, phenylmercaptobenzyl, p-methylmercaptobenzyl, o-methoxybenzyl, m-methoxybenzyl, o-methylphenoxymethyl, p-methoxyphenoxymethyl, p-cyanobenzyl, styryl, 3,4-dimethylbenzyl, beta-phenyl-butyryl, p-carbethoxyhydroxybenzyl, beta-naphthylmethyl, beta-naphthoxymethyl, 1 - bromo - 2 - naphthylmethyl, 6 - bromo - 2 - naphthylmethyl, 2-chloro - 3 - naphthylmethyl, 6 - fluoro - 2-naphthylmethyl, 1 - nitro - 2 - naphthylmethyl, beta - naphthylmercaptomethyl, 6-methoxy - 2 - naphthylmethyl, p - phenoxybenzyl, p - biphenylylmethyl, p-isopropylbenzyl, and p-benzyloxybenzyl radicals.

More particularly, in the process of this invention a salt of phenoxymethyl penicillin in a suitable reaction medium may be reacted with chloromethyl methyl ether at a temperature from 0° C. to 50° C. and preferably from 0° C to 30° C. A preferred reaction medium is methylene chloride to which may be added some dimethylformamide generally in a ratio of 1 to 2 ml. per 150 ml. of methylene chloride. Dimethylformamide can also be used as a reaction medium. The reaction product can be recovered by conventional methods.

The recovered ester of phenoxymethyl penicillin can then be deacylated, either enzymatically or chemically. Enzymatic production of 6-APA is disclosed in United States Patent 3,014,846. The preferred method of chemical cleavage is carried out by forming an imino halide by reaction with a halogenating agent, such as phosphorous pentachloride. The ester is dissolved in a non-aqueous solvent, such as methylene chloride, benzene, or chloroform, to which there has been added a suitable amount of an acid-binding agent, such as dimethylaniline, pyridine, quinoline, or lutidine. The amount of acid-binding agent should be sufficient to take up the acid formed by the cleavage reaction. The chlorination reaction temperature should be maintained from −50° C. to 0° C. to provide complete chlorination of the ester. The imino chloride is then treated with an alcohol under acid conditions whereby an imino ether is formed under anhydrous conditions. Water is then added to the reaction mixture to hydrolyze the ether. The imino ether can conveniently be formed at temperatures of from −70° C. to −30° C.

The general procedure for this series of reactions is disclosed in United States Patent 3,499,909, along with various halogenating agents, acid-binding agents, alcohols, and solvents all of which are generally applicable to the herein disclosed methoxymethyl esters.

Alternatively, the 6-APA ester can be prepared directly from 6-aminopenicillanic acid by a process in which 6-APA is slurried at about 25° C. in methylene chloride and dissolved therein as the triethylamine salt. The reaction mixture is then cooled to about 0° C. and esterified with chloromethylmethyl ether. The 6-APA ester can be isolated from the reaction mixture as the free base or as an acid addition salt. The p-toluene-sulfonate salt of the 6-APA ester has been described in the literature by Jackson et al., *Chemical Communications*, 14, 1970.

Acylation of the 6-APA ester to provide the methoxymethyl ester of ampicillin can be achieved following known procedures, such as those disclosed in United States Patents 2,985,648 and 3,140,282.

The above-mentioned toluenesulfonate salt of the 6-APA ester can be contacted with an acylating agent, such as 2-phenylglycyl chloride hydrochloride, in an acidic aqueous medium at low temperature. Broadly, the acylating agent is employed in amounts of 1 to 3 moles per mole of 6-APA, and the temperature should be from −10° C. to +20° C. The pH of the reaction medium should be below 4 and preferably from 1.5 to 3.0, usually from 2.0 to 2.8. The reaction medium is preferably a mixture of water and organic solvents such as acetone, methylene chloride, or tetrahydrofuran. The acylated ester can be recovered by raising the pH of the reaction medium to about 4 or above, e.g., from 4 to 7. Any solids can be removed by filtration to provide a solution of the ampicillin ester.

In a preferred procedure, the ester is dissolved in methylene chloride-acetone mixture at ice bath temperatures generally from 0° C. to 5° C. A small amount of water, about 2.5% based on the volume of the organic solvent, is then added. The resulting admixture is maintained at about 0° C. until the acid chloride has dissolved. The reaction product can then be recovered by standard methods. This reaction can be run under anhydrous conditions.

The ampicillin methoxymethyl ester can be

converted to the corresponding hetacillin ester in reaction with aqueous acetone at a pH of from 6.5 to 9.5. In general, this step of the process can be carried out at a temperature from −10° C. to 15° C., although it is generally preferred to employ temperatures of 0° C. to 5° C. The pH and temperature should be maintained for a period of time which is sufficient to provide substantial conversion to hetacillin, e.g., from 12 to 170 hours, depending on the other conditions. After the reaction period, the hetacillin methoxymethyl ester can be recovered by adjusting the pH of the reaction mixture to from 1.5 to 2.0 with an acid such as hydrochloric acid and extracting with a suitable solvent such as methylene chloride. The hetacillin ester is recovered from the organic phase in the usual manner.

The hetacillin ester can be conveniently converted to hetacillin by hydrolysis of the ester group under acidic or mildly alkaline conditions. The ester can be hydrolyzed in hydrochloric acid having a strength of from 1 to 6 normal at temperatures from 0° C. to 40° C. In concentrated hydrochloric acid, the product is recovered as a hydrochloride salt which can easily be redissolved in a suitable solvent, such as water or a mixture of water and an organic liquid, such as acetone or methyl isobutyl ketone, and then reprecipitated by bringing the pH to the isoelectric point for hetacillin-free acid, i.e., about 2.5. Precipitation of the hydrochloride salt can be aided by the use of suitable solute, such as ammonium chloride.

The α-carbon of the acyl side chain is an asymmetric carbon atom, and the compounds of this invention can, therefore, exist in optically active isomeric forms as well as in a racemic form which is a mixture of the two optically active forms. All such optical isomers and mixtures thereof are included within the scope of this invention.

The invention also includes a pharmaceutical composition, which composition comprises a compound of the above formula I and a pharmaceutically acceptable excipient or carrier.

Following is a description by way of example of the preparation of the compounds of the invention.

Example 1.

Methoxymethyl Ester of Penicillin V. Potassium phenoxymethylpenicillinate (38.8 grams) was slurried in 150 ml. of methylene chloride and the mixture cooled to about 5° C. by means of a cooling bath, and 9.5 grams (0.118 mole) of chloromethylmethyl ether and 0.5 ml. of dimethylformamide was added. The cooling bath was removed and the mixture stirred for about 1.5 hours while allowing the mixture to come to room temperature. The methylene chloride solution was washed four times with 200 ml. portions of water and then dried and stripped to give 33.5 grams of a yellowish oil. The yield was about 84%.

Example 2.

6-Aminopenicillanic Acid Methoxymethyl Ester. To a solution of 12 grams (0.0304 mole) of Penicillin V methoxymethyl ester in 100 ml. of methylene chloride cooled to −55° C., there was added 4.8 ml. (4.6 grams, 0.038 mole) of dimethylaniline and this followed directly by 7.0 grams (0.0337 mole) of phosphorous pentachloride dissolved in 100 ml. of methylene chloride.

The mixture was held at −40° C. to −50° C. for about 2 hours. Thin layer chromatography indicated complete chlorination of the Penicillin V ester. The mixture was then cooled to −70° C. and 47 ml. of methanol, precooled to −50° C., was added rapidly. The mixture was then held for 2 hours at −50° C to −40° C. To the resulting yellow solution, 100 ml. of water was added with vigorous agitation. The temperature of the reaction mixture rose to about 0° C., and the pH of the mixture was 0.6 to 1.0. After holding the mixture for 10 to 15 minutes at this temperature and pH range, the pH was brought to 6.5 to 6.8 with dilute sodium hydroxide. The layers were separated and the methylene chloride layer was washed with water, carbon treated, and dried. Thin-layer chromatography showed dimethylaniline, methylphenoxy acetate, and 6-APA methoxymethyl ester.

Example 3.

Methoxymethyl-α-Aminobenzylpenicillinate. A methylene chloride solution containing methoxymethyl ester of 6-aminopenicillanic acid prepared from 0.04 mole of methoxymethyl phenoxymethyl penicillinate as in Example 2 was diluted with 100 ml. of acetone. After cooling the resulting mixture to 0° C. to 5° C., 5 ml. of water and 0.04 mole (4.8 grams) of dimethylaniline was added to the solution. Eight grams (0.039 mole) of phenylglycyl chloride hydrochloride was then added to the solution with vigorous stirring. The mixture was stirred for about one hour at 0° C. by which time all the acid chloride had dissolved. The yield of methoxymethyl ester of α-aminobenzylpenicillin was 42%, as determined by bio-assay of the reaction product mixture.

Example 4.

Methoxymethyl Ester of Hetacillin. An acylation reaction, as described in Example 3, was carried out using 13.0 grams (0.05 mole) of 6-aminopenicillanic acid ester and 20.6 grams (0.10 mole) of phenylglycyl chloride hydrochloride. After filtering off any undissolved phenylglycyl chloride hydrochloride, the pH of the solution was adjusted to 8.5 with 10% by weight sodium hydroxide

and the mixture aged at 8° C. for about 90 hours. Bioassay showed a yield of about 60%. The pH of the aged mixture was then adjusted to 1.8 with 6 *N* hydrochloric acid and the mixture extracted with methylene chloride. The methylene chloride layer was washed with water, dried, and stripped to yield about 14.4 grams of product.

Example 5.

Hetacillin.

(a) Five grams of methoxymethyl ester of hetacillin was slurried in 50 ml. of 3 *N* hydrochloric acid at 25° C. for about 20 minutes with vigorous stirring. The mixture was cooled by a water bath to 0° C. to 5° C., and the pH was adjusted to 3.1 with 20% by weight sodium hydroxide. After crystallization, the solid was separated by filtration and washed with acetone. The yield was 2.05 grams of hetacillin having a potency of 913 mcg./mg.

(b) Hetacillin methoxymethyl ester, one gram, was added to 20 ml. of 6 *N* HCl stirred for two minutes, seeded with hetacillin hydrochloride crystals and cooled to 0° C. to 5° C. After about 10 minutes of additional crystallization, hetacillin hydrochloride was filtered off. The yield was 64% of material with spectral properties (IR and NMR) and TLC comparable to hetacillin hydrochloride.

Example 6.

Hetacillin Methoxymethyl Ester. To 38.9 grams (0.1 mole) of hetacillin in 200 ml. of dry methylene chloride at 25° C. was added 10.1 grams (0.1 mole) of triethylamine. The clear solution was cooled to 0° C. and 8.05 grams (8 ml., 0.1 mole) of chloromethyl methyl ether dissolved in 50 ml. of methylene chloride was added over 10 minutes. After stirring one hour at 0° C., the reaction mixture was polish filtered and concentrated under reduced pressure to an oil which was taken up in acetone, polish filtered and again concentrated to an oil. This oil was taken up in methylene chloride and washed with water at pH 2 then twice with water at pH 7. After drying, the methylene chloride was removed under vacuum to give an amorphous, frothy solid, 40 grams or 93% yield. This material was homogeneous on TLC, and IR and NMR spectra were consistent with structure of the desired product.

A 2.0 gram (4.6 mmole) sample was dissolved in 25 ml. acetone, and 0.75 gram (6.3 mmoles) of p-toluenesulfonic acid monohydrate was added to the solution. On adding 25 ml. of diethyl ether, crystallization started. After 15 minutes at 0° C., the white crystals were filtered and washed with ether and dried to yield 1.9 grams of the toluenesulphonate salt of hetacillin methoxymethyl ester.

$C_{28}H_{35}N_3S_2O_8$ Calculated: C: 55.45; H: 5.82; N: 6.92%; Found: C: 55.75; H: 6.12; N: 6.92%.

In a similar preparation, 20 grams (0.046 mole) of hetacillin ester was stirred in 70 ml. of tetrahydrofuran and 3 ml. of concentrated hydrochloric acid at 25° C. for 20 minutes and then at 0° C. to 5° C. for 30 minutes. The resulting white precipitate was filtered and washed with 100 ml. of acetone in portions. There was obtained 16 grams of white crystalline hetacillin ester hydrochloride. Spectra were consistent with the desired structure. Bioassay showed activity of 764 mcg/mg vs. hetacillin.

$C_{21}H_{28}N_3O_5HCl$. Calculated: C: 53.65; H: 6.00; N: 8.94; CL: 7.54%. Found: C: 53.44; H: 5.95; N: 8.74; Cl: 7.72%.

Example 7.

Acylation of p-toluenesulfonate Salt of Methoxymethyl 6-aminopenicillinate. Three millimoles (1.3 grams) of p-toluenesulfonate salt of methoxymethyl 6-aminopenicillinate was admixed with 40 ml. of acetone and 10 ml. of water. The mixture was cooled to from 0° C to 5° C. To the cooled mixture there was added six millimoles (1.2 grams) of phenylglycyl chloride hydrochloride with vigorous stirring. The pH of the reaction mixture was maintained from 2.0 to 2.8 by addition of 10% by weight sodium hydroxide, as needed. After the reaction was complete, the pH was adjusted to from 6.5 to 7.0 and the mixture was filtered and diluted to 200 ml. with acetone to give a solution of the methoxymethyl ester of ampicillin.

Example 8.

Ampicillin Methoxymethyl Ester Hydrochloride. At 25° C. in 150 ml. of dimethylacetamide there was dissolved 37.1 grams (0.1 mole) of sodium ampicillin. The solution was cooled to 0° C. to 5° C. and 8.0 ml. (0.1 mole) of chloromethylmethyl ether added. After one hour of stirring, thin-layer chromotography showed no sodium ampicillin remaining. The mixture was poured into 200 ml. of cold pH 7 buffer and extracted three times with 100 ml. portions of methylene chloride. The methylene chloride extracts were added to about 150 ml. cold water and the pH adjusted to 1.6 hydrochloric acid. The water layer was separated and adjusted to pH 6.8 with dilute sodium hydroxide and extracted three times with 100 ml. portions of methylene chloride. The methylene chloride layers were dried over sodium sulfate and concentrated under reduced pressure to give a colorless oil showing one zone on thin-layer chromatogram. The oil was dissolved in 2-propanol, cooled, and HCl in 2-propanol added. This solution was then added to 700 ml. of cold, well-stirred ether. A white ppt. was formed which after 15 minutes of stirring was filtered and washed with cold ether. There was ob-

tained 12 grams of white solid soluble in water. IR and NMR spectra were consistent with structure for the hydrochloride salt of the methoxymethyl ester of ampicillin. Bio potency as ampicillin showed activity of 682 mcg/mg.

A useful embodiment of the process of this invention is a continuous series of reactions carried out without isolation or recovery of intermediates. For example, the potassium salt of phenoxymethyl penicillin is esterified with chloromethylmethyl ether in methylene chloride at a temperature from 0° C. to 30° C. The methylene chloride solution of the ester is then successively treated with phosphorous pentachloride, methyl alcohol, and water to complete removal of the phenoxymethyl side chain and provide a methylene chloride solution containing the methoxymethyl ester of 6-APA. This solution is then carried forward and used in the acylation reaction in which phenylglycyl chloride hydrochloride is added to the solution to give a methylene chloride solution of the ampicillin ester. In the final step, the solution of ampicillin ester is treated with acetone at pH 7.5 to 8.5 and held until hetacillin ester formation has proceeded. Hetacillin itself is recovered from the organic phase by treatment thereof with a strong acid and water, e.g., three normal hydrochloric acid. The hetacillin is insoluble in the liquid phase and crystallizes.

Oral absorption of the hetacillin ester was evaluated and compared to ampicillin and hetacillin, as shown in Table I, below. In each case, the antibiotic was administered orally in equivalent amounts to a group of eight male mice. The blood levels were determined by plate assay on *Bacillus subtilus* and reported as micrograms per milliliter of ampicillin.

The data indicate that the hetacillin ester absorption in mice is more rapidly absorbed into the mouse blood than either hetacillin or ampicillin, thus providing for early attainment of peak levels of the antibiotic in the blood.

TABLE I

Blood Levels after Oral Administration to Mice

Compound	Dose (mg./kg.)	Blood Levels (μg/ml) 0.5 Hours after Administration	1	2	3.5
Ester[1]	126	8.49	3.49	1.43	0.42
Hetacillin[1]	115	4.30	5.00	2.10	0.38
Ampicillin[1]	100	5.79	5.34	1.91	0.44
Ester[2]	126	10.20	4.48	1.53	0.42
Ampicillin[2]	100	5.35	3.67	1.45	0.51
Hetacillin[2]	115	2.52	2.81	1.46	0.52

[1] Administered in 5% sodium bicarbonate
[2] Administered in distilled water

Excretion and additional absorption data were obtained from studies on rat urine shown in Table II, below. The compounds were administered in 0.0001 M. phosphate buffer, and the amount of antibiotic recovered reported as ampicillin.

TABLE II

Urinary Recovery of Methoxymethyl Ester of Hetacillin After Oral Administration to Rats

Compound	Dose (mg/kg)	No. of Animals	Percent Recovered Hours After Administration 0–6	6–24	0–24
Ester	63	5	17.09	0.56	17.65
Hetacillin	57.5	5	4.42	0.52	4.94
Ampicillin	50	5	6.13	0.36	6.49

A rapid appearance of antibiotic in the urine indicates a suitability for treatment of urinary tract infections.

In addition to being a useful intermediate in a process for preparing hetacillin, the methoxymethyl ester of hetacillin has significant antibiotic properties. This compound also has value as an antibiotic because of its ability to give more rapid peak blood serum levels as compared to sodium ampicillin. When tested in beagle dogs, the methoxymethyl ester of hetacillin was found to give peak blood levels 15 to 20 minutes after administration. Peak levels for sodium ampicillin occur about one hour after administration under comparable conditions.

One of the factors in antibiotic evaluation is the biological half-life of the antibiotic. In beagle dogs, the methoxymethyl ester of hetacillin was found to have a half-life of about 1.2 hours. Under comparable conditions, sodium ampicillin was found to have a half-life of only 30 to 40 minutes. In these tests, the concentration of antibiotic was measured by bioassay.

Further studies have indicated that the methoxymethyl ester of hetacillin is more favorably distributed throughout the body tissue. Tests carried out in beagle dogs have shown that the ester has a significantly lower apparent volume of distribution, i.e., the drug seems to be dissolved in a larger fluid volume, as compared to sodium ampicillin. Preliminary estimates are that the ester is about twice as widely distributed than is sodium ampicillin.

Table III, below, shows data on the therapeutic activity of methoxymethyl esters of hetacillin and ampicillin in terms of the dose necessary to protect fifty percent of a mouse population challenged by exposure to a test organism. It can be seen that the ester is generally equivalent to known established antibiotics against a sensitive organism.

TABLE III

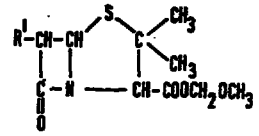
Chemotherapeutic Activity of Ampicillin, Hetacillin, and the Methoxymethyl Esters of Hetacillin and Ampicillin Following Oral Administration to Mice Infected with Escherichia coli

Compound	Vehicle	Oral PD_{50} mg/kg* E. coli Test 1	A15119 Test 2
(1) Ampicillin	H_2O	70	80
(2) Hetacillin	H_2O	70	76
(3) Hetacillin Ester	H_2O	70	50
(4) Ampicillin Ester	H_3PO_4 Buffer	50	54

* All compounds were administered orally at equimolar concentrations to mice at 1 hour post-challenge.
PD_{50}=Protective dose, 50%

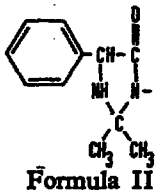
WHAT WE CLAIM IS:—

1. A compound having the formula



Formula I

wherein R^1 is the group



Formula II

2. The methoxymethyl ester of hetacillin.

3. A process for preparing a compound having the formula I defined in claim 1, which

A rapid appearance of antibiotic in the urine indicates a suitability for treatment of urinary tract infections.

In addition to being a useful intermediate in a process for preparing hetacillin, the methoxymethyl ester of hetacillin has significant antibiotic properties. This compound also has value as an antibiotic because of its ability to give more rapid peak blood serum levels as compared to sodium ampicillin. When tested in beagle dogs, the methoxymethyl ester of hetacillin was found to give peak blood levels 15 to 20 minutes after administration. Peak levels for sodium ampicillin occur about one hour after administration under comparable conditions.

One of the factors in antibiotic evaluation is the biological half-life of the antibiotic. In beagle dogs, the methoxymethyl ester of hetacillin was found to have a half-life of about 1.2 hours. Under comparable conditions, sodium ampicillin was found to have a half-life of only 30 to 40 minutes. In these tests, the concentration of antibiotic was measured by bioassay.

Further studies have indicated that the methoxymethyl ester of hetacillin is more favorably distributed throughout the body tissue. Tests carried out in beagle dogs have shown that the ester has a significantly lower apparent volume of distribution, i.e., the drug seems to be dissolved in a larger fluid volume, as compared to sodium ampicillin. Preliminary estimates are that the ester is about twice as widely distributed than is sodium ampicillin.

Table III, below, shows data on the therapeutic activity of methoxymethyl esters of hetacillin and ampicillin in terms of the dose necessary to protect fifty percent of a mouse population challenged by exposure to a test organism. It can be seen that the ester is generally equivalent to known established antibiotics against a sensitive organism.

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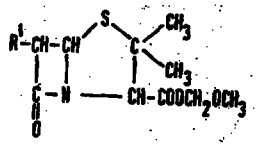
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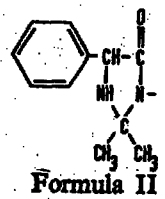
WHAT WE CLAIM IS:—

1. A compound having the formula



Formula I

wherein R^1 is the group



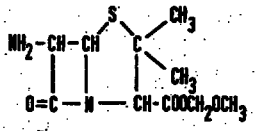
Formula II

2. The methoxymethyl ester of hetacillin.

3. A process for preparing a compound having the formula I defined in claim 1, which

* C L M S *

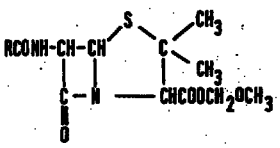
process comprises acylating methoxymethyl 6-aminopenicillinate having the formula



Formula IV

to form the methoxymethyl ester of ampicillin and reacting said ampicillin ester with acetone to form the methoxymethyl ester of hetacillin.

4. A process as claimed in claim 3, wherein the methoxymethyl 6-aminopenicillinate is prepared by deacylating a penicillin ester having the formula



Formula V

wherein R is an organic radical.

5. A process as claimed in claim 4, wherein R is phenoxymethyl.

6. A process as claimed in claim 3 substantially as hereinbefore described.

7. A process as claimed in claim 3 substantially as hereinbefore described with reference to Example 4.

8. A compound of the formula I defined in claim 1 when prepared by a process as claimed in any one of claims 3 to 7.

9. A pharmaceutical composition, which composition comprises a compound as claimed in claim 1, claim 2 or claim 8 and a pharmaceutically acceptable excipient or carrier.

10. Hetacillin or a pharmaceutically acceptable non-toxic salt thereof when produced from the methoxymethyl ester of hetacillin by hydrolysis under acidic or mildly alkaline conditions.

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